CNC.IBILI

2016 ANNUAL REPORT

INDEX

Funded by FEDER funds through the Operational Programme Factors Competitiveness - COMPETE 2020 and by National Funds through FCT - Foundation for Science and Technology under the Strategic Project: COMPETE: POCI-01-0145-FEDER-007440 *(UID / NEU / 04539/2013)*

INTRODUCTION

CNC.IBILI is a multidisciplinary research consortium created at the University of Coimbra, 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 2016 Annual Report is the second report of activities of the CNC.IBILI Research Consortium, which highlights the main achievements resulting from the development of its research strategic plan.

In 2016, CNC.IBILI research Consortium 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 (COMPETE-2020) operational programs (Portugal 2020), Santa Casa da Misericordia de Lisboa, JANSSEN Prize in Neurosciences and INFARMED, or international level, ERA-Nets EURONANOMED II and Joint Programming for Neurodegenerative Disease Research-JPND.

The scientific productivity of CNC.IBILI is demonstrated by an annual rate of publication of 614 scientific papers in peer reviewed journals in the last two years, an effort supported by 112 grant projects achieved in competitive calls. In 2016, 299 scientific papers were published and 48 new research projects were financed (36 FCT projects, 3 national projects and 9 international projects).

Post-graduate education is a major goal at CNC.IBILI. The research environment created at the consortium fosters creative reasoning, which is crucial to run In-house masters and PhD Programs and international training networks coordinated by CNC.IBILI.

The 2016 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 (2016)

RESEARCH STAFF

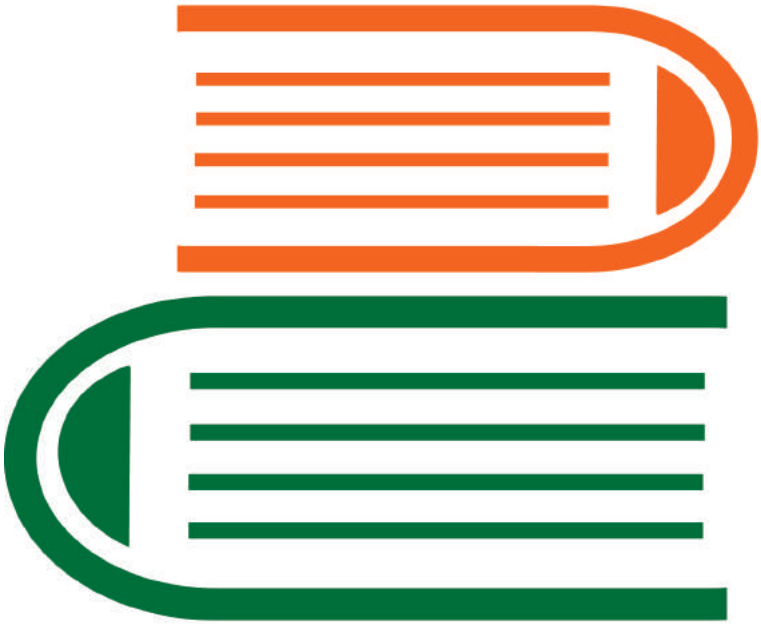
*Integrated Members holding Ph.D.	183 + (102 Post Doctoral Fellows)
Ph.D.Students	158
MSc Students	38

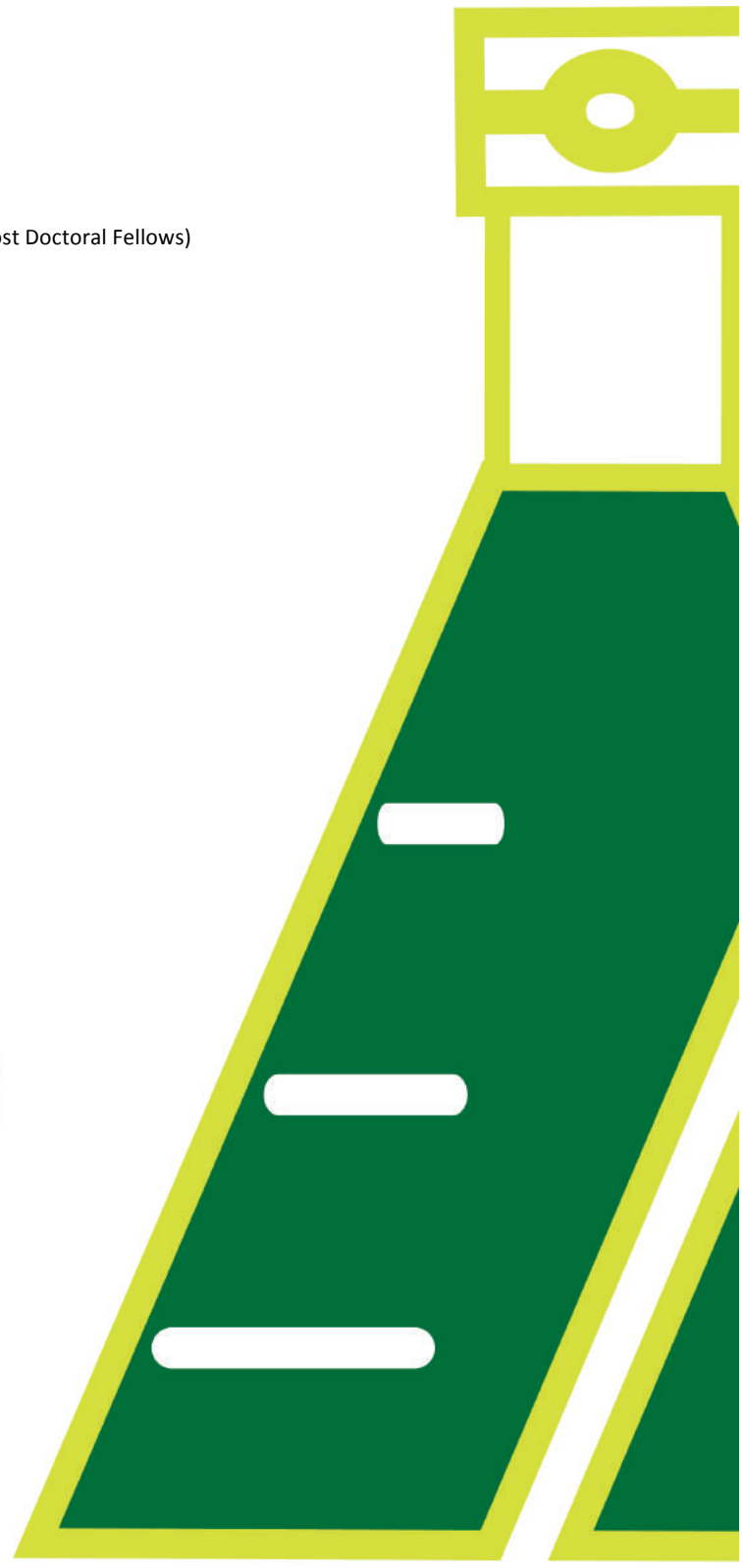
PUBLICATIONS

Scientific papers published	299
Scientific papers *In Press*	60

THESIS CONCLUDED

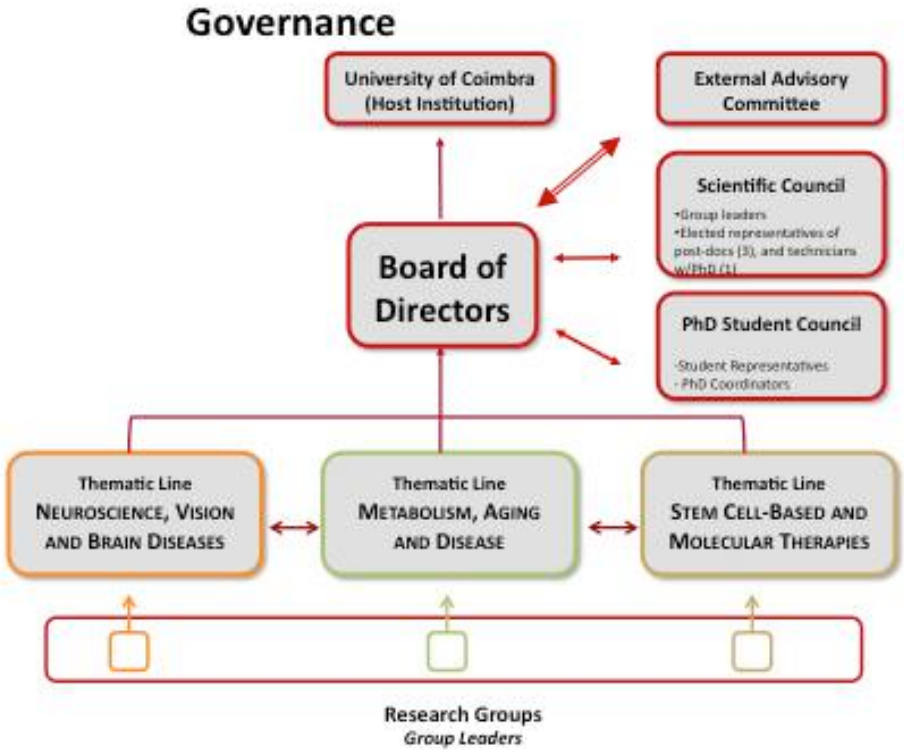
Ph.D. thesis	50
MSc thesis	102





* With more then 30% of dedication (11 PhD with less then 30% of dedication)

Organization of CNC.IBILI



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

SCIENTIFIC AREAS AND RESEARCH GROUPS

At present, research programmes and projects are organized in 3 research scientific areas, each coordinated by a senior scientist. The programme for each area is implemented by small research groups each headed by a research leader in his field of study. In 2016, the research groups for Thematic Strand can be identified, according to the following organization:

Neuroscience, Vision and Brain Diseases | *Ana Luísa Carvalho*

Synapse Biology Group *(Head: Carlos B. Duarte*)

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

Neuroendocrinology and Aging Group (*Head: Claudia Cavadas*)

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

Purines in brain diseases (*Head: Rodrigo Cunha*)

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

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

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

Metabolism Aging, and Disease | *João Ramalho Santos*

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

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

Metabolic Control Group *(Head: John Grifith Jones)*

Stem Cell-Based and Molecular Therapies | *Luis Pereira de Almeida*

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

Stem cell biotechnology Group (*Head: Lino Ferreira*)

Systems and Computational Biology Group (*Head: Armindo Salvador)*

Medical Microbiology Group (*Head: Teresa Gonçalves*)

Molecular Mycobacteriology Group (Head: Nuno Empadinhas)

Medicinal Chemistry & Drug Discovery Group (*Head: Maria Luísa Sá e Melo*)

Pharmacometrics Group (*Head: Amílcar Falcão*)

Biotechnology

Microbiology of Extreme Environments Group (*Head: Milton Costa*)

Molecular Biotechnology Group (*Head: Carlos Faro)*

NEUROSCIENCE, VISION AND BRAIN DISEASES

Coordinator: Ana Luísa Carvalho

GENERAL OBJECTIVES

The research line on Neuroscience, Vision and Brain Diseases (NVBD) aims to address fundamental questions about brain function and to unravel mechanisms of brain diseases using animal models and human patients. The NVBD research line brings together 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.

One hallmark of the research carried out at the NVBD line is the focus on understanding synaptic processes and brain metabolism, both towards addressing two key aspects of brain function and because dysfunction of either of these processes underlies many brain and retina diseases. The combination of mechanistic studies with behavioral analysis and brain imaging provides the opportunity to translate in vitro findings to animal models of disease and to design novel therapeutic strategies.

MAIN ACHIEVEMENTS

Research groups in the NVBD research line have identified new mechanisms of presynaptic differentiation that involve the proteasome (Pinto et al., J Cell Biol), and made significant progress in understanding the role of adenosine A2A receptors (A2AR) in brain function and in disease pathogenesis. For example, A2AR were shown to control amygdala synaptic plasticity and contextual fear memory (Simões et al., Neuropsychoparmacol), to regulate microglia remodeling in a model of chronic anxiety (Caetano et al., Mol Psych), and to participate in early synaptic deficits in a mouse models of Alzheimer's disease (Viana da Silva et al., Nature Comm). Caffeine, an A2AR antagonist, was found to be protective in an animal model of glaucoma (Madeira et al., Sci Rep). Together with other studies from several NVBD groups, these reports ascertain a role for A2AR in brain disease pathophysiology.

Several groups are interested in disease mechanisms underlying neurodegenerative polyQ disorders [such as Huntington's disease (HD) and Machado-Joseph disease (MJD)] and Alzheimer's disease (AD). Naia and colleagues (Mol Neurobiol) found that resveratrol and nicotinamide have mitochondria-dependent protective effects in HD models. Caloric restriction was found to block neuropathology and motor deficits in MJD (Cunha-Santos et al., Nature Comm), and expanded ataxin-3, the causative protein in MJD, was shown to trigger dendritic and synaptic defects which can be prevented by ataxin-3 phosphorylation (Matos et al., J Cell Biol). Rocha and colleagues (Neurobiol Aging) found age-dependent alterations in the glutamate-nitric oxide pathway associated to AD, whereas in blood-derived monocytes and macrophages from AD patients, chemotaxis and phagocytosis were found to be impaired, through an epigenetic mechanism (Guedes et al., Alzeimers Dement). Genetic studies in patients with frontotemporal lobar degeneration have yielded important results (*Almeida et al., Neurobiol Aging*).

Acute neurological diseases, such as cerebral ischemia, are a leading cause of death and disability. NVBD groups have further uncovered roles for glutamate NMDA receptors (Vieira et al., Neurobiol Dis) and $GABA_A$ receptors (Costa et al., Mol Neurobiol) in the pathogenesis of these disorders.
Understanding neuropsychiatric disorders is the focus of different NVBD groups, with a significant contribution in 2016 from Violante and colleagues (Neurology), who employed multimodal imaging and spectroscopy measures to uncover abnormalities in the GABA system in neurofibromatosis type 1 patients.

Researchers in the NVBD line organized the prestigious 7th ISN conference 'Synaptic function and dysfunction in brain diseases', and the International JPND course on 'Biological Markers in Neurological Diseases – Present and Future Approaches', which were held in Coimbra in June 2016.

FUTURE PLANS

the study of synaptic and postsynaptic density proteins implicated in autism and schizophrenia in specific cell-types and neuronal circuits.NVBD groups are developing novel tools and methodologies, including the use of novel animal models, brain-region specific approaches and newly designed biosensors, which will allow tackling in a fine manner questions about the role of particular proteins and processes in neuronal physiology, brain circuits and brain diseases. 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. For example the collaboration between groups at NVBD and the ICNAS bioimaging facility has been important in establishing a molecules to man strategy and in translating in vitro finding to patients. Important scientific contributions will arise from these recent developments in the NVBD line of research.

SYNAPSE BIOLOGY GROUP

Carlos Jorge B. Duarte	PhD *(Head of Group)*
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
Joana Fernandes	Post Doctoral Fellow
Joana Guedes	Post Doctoral Fellow
Joana Pedro	Post Doctoral Fellow
Miranda Mele	Post Doctoral Fellow
Rui Miguel Oliveira da Costa	Post Doctoral Fellow
Susana Louros	Post Doctoral Fellow
Tatiana Andreia Catarino	Post Doctoral Fellow
António Gomes	PhD Student
Diana Sequeira	PhD Student
Ivan Salazar	PhD Student
Susana Sampaio	PhD Student
Dominique Fernandes	PhD Student
Mariline Silva	PhD Student
Jeannette Schmidt	PhD Student
Gladys Caldeira	PhD Student
Lara Franco	PhD Student
Luís Martins	PhD Student
Mohamed Hussien	PhD Student
João Calmeiro Pereira	PhD Student
Mário Carvalho	PhD Student
António Pimenta	MSc Student
Bárbara Correia	MSc Student
Inês Santos	MSc Student
José Almeida	MSc Student
Tiago Rondão	MSc Student
Beatriz Rodrigues	Grant Technician
Débora Serrenho	Grant Technician
Marina Rodrigues	Grant Technician

REDOX BIOLOGY AND BRAIN SENSING GROUP

João António Laranjinha	PhD *(Head of Group)*
Rui Manuel Silva Barbosa	PhD
Leonor Martins de Almeida	PhD
Teresa do Carmo Dinis Silva	PhD
Ana Margarida da Cruz Ledo	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 *(Head of Group)*
Joana Rosmaninho Salgado	PhD
Ana Rita Álvaro	Post Doctoral Fellow
António Pedro Gomes	Post Doctoral Fellow
Célia Alexandra Aveleira	Post Doctoral Fellow
Ligia de Sousa Ferreira	Post Doctoral Fellow
Magda Santana	Post Doctoral Fellow
Mariana Botelho Rocha	Post Doctoral Fellow
Ana Patrícia Marques	PhD Student
Dina Pereira	PhD Student
Janete Santos	PhD Student
Marisa Marques	PhD Student
Sara Silva	PhD Student
Laetitia Gaspar	MSc Student
Ana dos Santos Carvalho	Collaborator
André Carvalho	MSc Student
Ana Rita Samões	MSc Student
Marta Quatorze	MSc Student
Patrick Silva	MSc Student
Joana Pereira	MSc Student
Patrícia Valério	MSc Student

VISION, BRAIN IMAGING AND COGNITIVE NEUROSCIENCE

Miguel Castelo-Branco	PhD *(Head of Group)*
Aldina Conceição Pires Reis	PhD
Antero Afonso de Abrunhosa	PhD
António Gonçalves Freire	PhD
António Morgado	PhD
Bárbara dos Santos Oliveiros	PhD
Eduardo José Silva	PhD
Francisco Cerqueira Alves	PhD
Francisco Caramelo	PhD
Francisco Oliveira	PhD
Guiomar Gonçalves Oliveira	PhD
Inês Bernardino	PhD
Inês Ribeiro Violante	PhD
João Miguel Castelhano	PhD
Joao Pereira Figueira	PhD
Joaquim Carlos Neto Murta	PhD
Jorge de Andrade Saraiva	PhD
José Paulo Domingues	PhD
José Vítor Oliveira Sereno	PhD
Luís Filipe Caseiro Alves	PhD
Mª Conceição da Fonseca	PhD
Mª Cristina Januário Santos	PhD
Mª João Vidigal	PhD
MªLuisa Ribeiro	PhD
Miguel Patrício	PhD
Nuno David Ferreira	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 Teixeira de Almeida	Post Doctoral Fellow
Joana Teresa Gonçalves	Post Doctoral Fellow
João Valente Duarte	Post Doctoral Fellow
Lorena Itatí Petrella	Post Doctoral Fellow
Mª Fatima Loureiro da Silva	Post Doctoral Fellow
Mª José Braga Ribeiro	Post Doctoral Fellow
Monika Intaite	Post Doctoral Fellow
Ana Cruz Dionísio	PhD Student
Ana Isabel Rodrigues	PhD Student
Ana Maria Batista	PhD Student
Andreia Martins Rosa	PhD Student
Carlos Manuel Amaral	PhD Student
Filipa Lima Júlio	PhD Student
Marco António Simões	PhD Student
Marta Cristina Teixeira	PhD Student
Otília d'Almeida	PhD Student
Pedro Luís s Fonseca	PhD Student
Sulaiman I S Abuhaiba	PhD Student
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Susana Isabel Simão Mouga	PhD Student
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Ana Rita Barreiros	Grant Technician
Andreia Sofia Pereira	Grant Technician
Ângela Sofia Miranda	Grant Technician
Carlos Daniel Ferreira	Grant Technician
Carlos Manuel Pereira	Grant Technician
Carolina César Alves	Grant Technician
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Gilberto Silva	Grant Technician
Hélio Jorge Gonçalves	Grant Technician
Hugo AlexandreQuental	Grant Technician
Isabel Catarina Duarte	Grant Technician
João André Pereira	Grant Technician
Lília Pereira Jorge	Grant Technician
Margarida Maria Marques	MD
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Ricardo José Martins	Grant Technician
Vítor Hugo Alves	Grant Technician

PURINES IN BRAIN DISEASES GROUP

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Henrique Silva	PhD
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Joana Marques	Post Doctoral Fellow
João Pedro Lopes	Post Doctoral Fellow
Nélio Gonçalves	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
Nuno Machado	PhD Student
Patrícia Sofia Alçada Morais	PhD Student
Sofia Ferreira	PhD Student
Xinli Xu	PhD Student
Tiago Alfaro	PhD Student
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Marlene Pereira	MSc Student
Patrícia Santos	MSc Student
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Sara Fernandes	Grant Technician
Sara Reis	Grant Technician
Vanessa Henriques	Grant Technician

MITOCHONDRIAL DYSFUNCTION AND SIGNALING IN NEURODEGENERATION GROUP

Ana Cristina Carvalho Rego	PhD *(Head of Group)*
Carla Lopes	Post Doctoral Fellow
Elisabete Baptista Ferreiro	Post Doctoral Fellow
Ildete Luisa Araujo Ferreira	Post Doctoral Fellow
Sandra Mota	Post Doctoral Fellow
Luana Naia	PhD Student
Carina Maranga	Grant Technician
Filipa Almeida	Grant Technician
Lígia Fão	Grant Technician
Nuno Piedade	Grant Technician

AGING AND BRAIN DISEASES: ADVANCED DIAGNOSIS AND BIOMARKERS GROUP

Catarina Resende de Oliveira	PhD *(Head of Group)*
Ana Telma Pereira	PhD
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
Mª Isabel Santana	PhD
Mª Joana Barbosa de Melo	PhD
Mª Rosário Almeida	PhD
Helena Carvalheiro	Post Doctoral Fellow
Sandra Freitas	Post Doctoral Fellow
Cátia Santa	PhD Student
Joana Pinto	PhD Student
Mafalda Bacalhau	PhD Student
Margarida Coelho	PhD Student
Mª João Leitão	PhD Student
Mª João Leitão	PhD Student
Ruben Salvado	PhD Student
Sandra Anjo	PhD Student
Ana Dias	MSc Student
Ana Coelho	MSc Student
Ana Sofia Morais	MD Collaborator
Ana Valado	Collaborator

António Gabriel	Collaborator
Carolina Roque	MD Collaborator
Célia Gomes	PhD 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)*

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

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

OBJECTIVES

Research in the 'Synapse Biology' group aims at understanding the presynaptic mechanisms contributing to synaptogenesis (i), as well as the postsynaptic molecular pathways controlling the activity of glutamatergic synapses under normal physiological conditions (ii). How dysregulation of glutamatergic and GABAergic synapses contribute to psychiatric (iii) and acute (iv) 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 (v).

(i) Local proteasome regulation in neuronal development (PI: Ramiro Almeida)

Control of protein turnover by the ubiquitin–proteasome system (UPS) has been shown to act locally at synapses (Segref and Hoppe, 2009). Moreover, the presynaptic ubiquitinated proteome includes both structural and signaling proteins as well as proteins with known roles in synaptogenesis (Franco et al., 2011; Na et al., 2012). Despite the wealth of knowledge on UPS degradation at the synapse, the physiological significance of such a complex presynaptic ubiquitinated proteome is far from being understood. One goal of our research is to determine the role of the UPS in axons. Particularly, if the UPS acts locally to regulate the axonal proteome controlling the assembly of new presynapses.

(ii & iii) Synapse function and dysfunction in brain disorders (PIs: Ana Luísa Carvalho and João Peça)

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.

(iv) GABAergic synapse dysfunction and neuronal death in brain ischemia (PI: Carlos Duarte)

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 synases following brain ischemia, and their impact in neuronal demise. In particular, studies have been performed to investigate the alterations in the subcellular distribution of $GABA_A$ receptors.

v) Structural characterization of protein-based interactions in dopamine receptor activity (PI: Irina Moreira)

Our aim is the development of new computational approaches for protein-based interfacial hot-spots detection. In particular, we aim to significantly expand both the number of studied complexes and the number of 3D complex structure-based features used for prediction including features that take into account the co-evolution of protein complexes. We apply our new approaches to a relevant biological system: the dopamine receptor family, which are Class A GPCRs involved in many cognitive, emotional and motor functions. For this particular target we aim to understand both the receptor dynamics and their interactions with the binding partners (Arrestins and G-proteins).

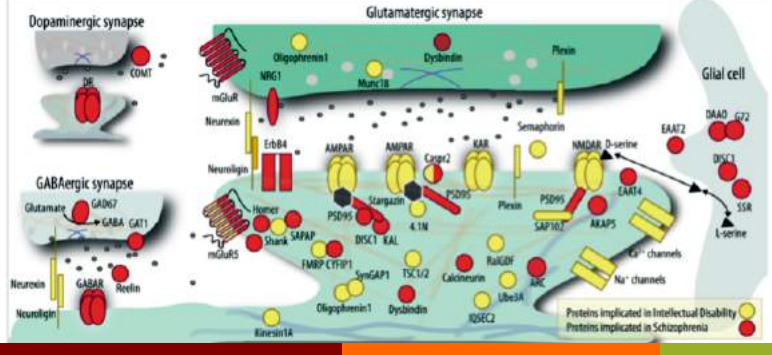


Fig.1. Synaptic proteins involved in SCZ and ID. Genes encoding for glutamatergic synapse proteins have been implicated in the development of SCZ. Many of those genes overlap in different psychiatric disorders, including ASD and ID. The figure represents a dopaminergic, a GABAergic and a glutamatergic synapse where some proteins implicated in SCZ (red) and ID (yellow) are depicted (Figure design by Gladys Caldeira).

MAIN ACHIEVEMENTS

(i) Local proteasome regulation in neuronal development (PI: Ramiro Almeida)

To understand the axonal intrinsic processes underlying formation of presynaptic clusters, we relied on microfluidic devices for the isolation of axons. We used this platform to specifically inhibit the proteasome in axons. We observed that axonal proteome inhibition increases the number of presynaptic sites. Importantly these new presynaptic boutons are functional since they are able to recycle FM-dyes. We also show a localized decrease in proteasome activity at the presynapse during the formation of axo-dendritic synapses. Finally we demonstrated that formation of presynaptic clusters is triggered by an on-site accumulation of polyubiquitinated proteins which in turn functions as a nesting platform for the clustering of presynaptic material and subsequently, presynaptic differentiation. This work was recently published in *The Journal of Cell Biology*.

(ii) Synapse function and dysfunction in brain disorders

PI: Ana Luísa Carvalho

1. We characterized molecular domains in the NMDAR GluN2B subunit which are required for neuronal death following ischemia, namely a C-terminal motif in GluN2B that mediates interaction with CaMKII (Vieira et al., 2016). This interaction is potentially interesting as a therapeutical target.
2. We characterized neuronal dendritic and synaptic defects triggered by the expanded form of ataxin-3 implicated in spinocerebellar ataxia type 3, and identified a phosphorylation event in ataxin-3 which is protective of the neuronal defects induced by expanded ataxin-3 (Matos et al., 2016).
3. 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, its function in mediating AMPA receptor traffic and homeostatic plasticity, and affects dendritic arborization and excitatory/inhibitory balance. Knock-in mice expressing an intellectual disability-associated mutation in *CACNG2* were generated in our lab, and present alterations in cognitive and social behavior (Caldeira et al., in preparation), implicating stargazin in the pathogenesis of neuropsychiatric disorders.
4. 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).
5. We analyzed the pathogenic effects of CASPR2 autoantibodies from synaptic encephalitis patients and identified crucial effects in synaptic function (Fernandes et al., in preparation).

PI: João Peça

1. We characterized the GPRASP2 conditional knockout mouse line as a model for autism spectrum disorders (Edfawi et al, in preparation).
2. We identified early life stress as trigger for subordinate behavior in adulthood and pinpointed a small group of genes that directly correlate with an animal dominance behavioral profile. We also implemented optogenetic manipulations to change animal behavior within a social hierarchy (Franco et al, in preparation).
3. We determined that social dominant behavior predicts activity in the medial prefrontal cortex in social behavior setting and that social subordinance is linked to enhanced performance in detecting social cues (Renato Sousa, Master Thesis)

(iv) GABAergic synapse dysfunction and neuronal death in brain ischemia (PI: Carlos Duarte)

1. Calpain-mediated cleavage of gephyrin was observed in in vitro and in vivo models of brain ischemia (OGD in cultured neurons and MCAO in rats, respectively). The formation of stable gephyrin cleavage products was found to contribute to the disassembly of the gephyrin lattice in GABAergic synapses with a consequent downregulation of the synaptic expression of $GABA_A$ receptors. The consequent decrease in inhibitory activity was shown plays a role in neuronal death in in vitro ischemia (Costa et al. 2016).

2. In the 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 $GABA_AR$ receptors contributes to neuronal death following OGD (Mele et al. 2017).
3. A disassembly of the proteasome was observed in cortical neurons subjected to OGD, in accordance with the reported results in in vivo models of brain ischemia. The impairment of the ubiquitin-proteasome system contributes to neuronal demise in brain ischemia. We are currently investigating the molecular mechanisms involved in the dysregulation of the proteasome in the ischemic brain.

v) Structural characterization of protein-based interactions in dopamine receptor activity (PI: Irina Moreira)

We have elucidated the allosteric mechanism underlying activation of arrestin, and identified functionally critical regions on arrestin structure that can be targeted with drugs or chemical tools for functional modulation(Sensoy *et al.* 2016, Sensoy et al. 2017). A variety of computational methods were also applied to investigate the putative interfaces between all members of the dopamine receptor family (D_1R-D_5R) and their binding partners (Arr-2, Arr-3, G-protein: G_q, G_z, G_{t2}, G_{i1}, G_{i2}, G_{i3}, $G_{s(sh)}$, G_o, G_{slong}) in order to determine various chemical, biological, and physical characteristics that could mediate their coupling. Complexes were analysed to assess the energetic determinants important for the affinity and the specificity of the receptor. We are currently assembling a web-server for easy access to this information (http://45.32.153.74/gpcr/, *Preto et al. 2017* – In preparation).

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

OBJECTIVES

(a) To study the molecular mechanisms inherent in neuromodulation and aging that critically involve nitric oxide (NO) in the brain, deciphering the mechanisms that support its role as a neuromodulator and as the mediator of neurovascular and neurometabolic coupling in vivo in anesthetized and in freely moving animals; (b) To study the mechanisms of action of plant-derived dietary phenolic compounds in terms of protection against vascular endothelial dysfunction, anti-inflammatory properties, as well as their impact on nitrite-driven regulatory processes along the nitrate: nitrite: nitric oxide pathway.

MAIN ACHIEVEMENTS

The main achievements incorporate both, technological and scientific components.

Technological developments:

1. Project, construction, development and application of a microbiosensor for the measurement of glucose in the brain in vivo in a real-time fashion. This biosensor, a ceramic-based microelectrode array, endowed with minimal oxygen, pH and temperature dependencies was used to study rapid local glucose changes in the hippocampus of anesthetized rats in connection with blood flow changes upon glutamatergic stimulation. It was established a closed temporal correlation of glucose increase with the change of cerebral change upon local glutamate stimulation.

It can be envisage that the use of this tool in vivo will permit to study the neurometabolism in the brain with high spatial and temporal resolution and shed light on controversial unsolved issues, namely aerobic glycolysis.

Scientific achievements:

1. Dysfunction along the axis Glutamate-Nitric oxide signaling pathway in the brain has been linked to the etiology of Alzheimer's disease (AD). We have revealed in the triple transgenic mice model of AD that aging is associated with a combination of both, synaptic and metabolic function changes. The earliest and most significant change in AD model is an increase in Glutamate NMDAr-evoked nitric oxide production, which then results in increased local change towards a more oxidant environment and is associated with a decline in mitochondrial oxidative phosphorylation and loss of sparing capacity. Revealing earlier derailment of neurometabolic and synaptic pathways in AD, before obvious signs of the classical amyloidopathy, is of utmost relevance to prevent the progression of the disease.

2. We have proposed a bidirectional interaction of dietary nitrate and polyphenols with gut microbiota as a novel pathway that it is determinant in connection with local and systemic inflammatory events. This proposal may pose as a novel strategy to tackle inflammatory cascades that, among other situations, underline neurodegenerative disorders.

3. In connection with the previous point we have revealed molecular mechanisms underlying the anti-inflammatory action of polyphenols from red wine extract, operating at complementary levels via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) and Nuclear factor- erythroid 2-related factor-2 (Nrf2) pathways.

In particular, cyaniding-3-glucoside and resveratrol were effective anti-inflammatory in human intestinal cells via modulation of Nrf2 and PPAR-g pathways.

We have also ascertained the role of dietary nitrate in the post-translational modifications of proteins with physiological impact. One example is the nitration of occludin in tight junctions.

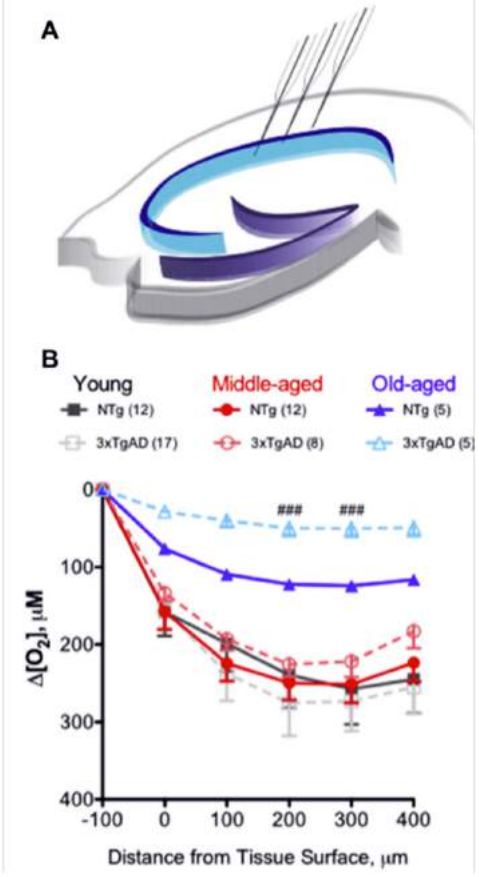


Fig. 1. Changes in interstitial O2 concentration in the CA1 subregion of hippocampal slices along tissue depth in the triple transgenic mice model of Alzeimer´s disease as compared to control mice.

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. In this context the group focuses the research on the following scientific questions:

I) How aging and aging related disease change hypothalamus?

II) 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?

III) Which targets in the hypothalamus could we manipulate to reduce obesity and insulin resistance?

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

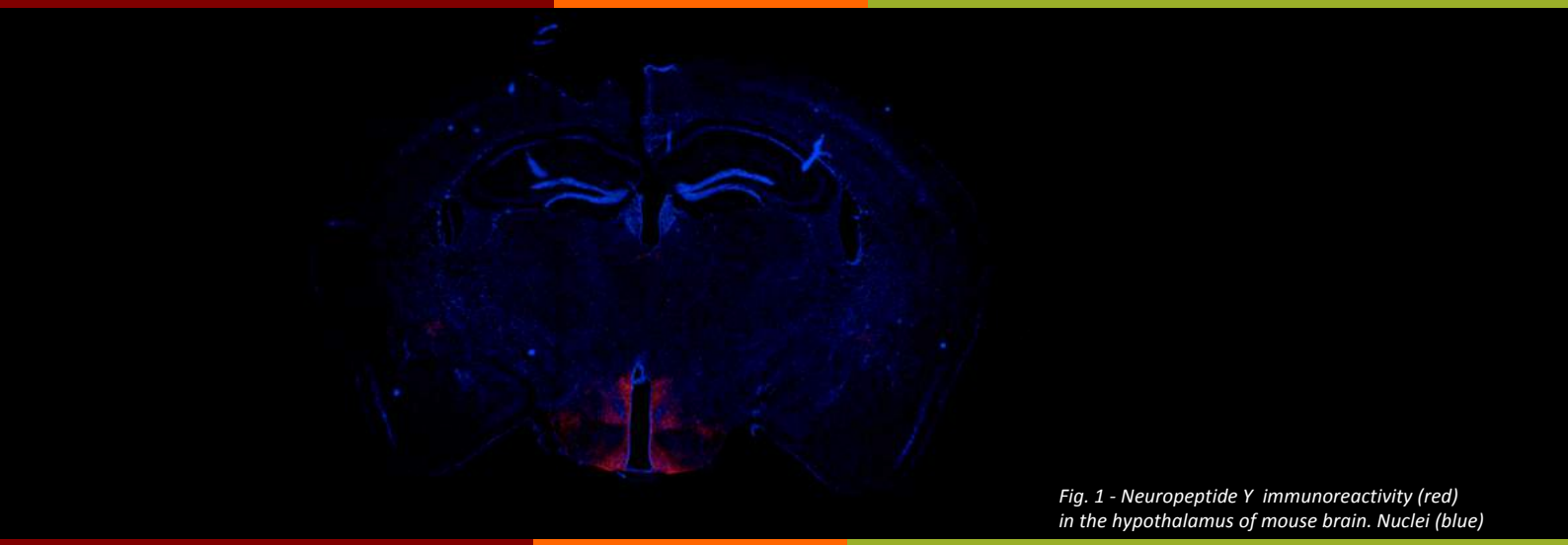


Fig. 1 - Neuropeptide Y immunoreactivity (red) in the hypothalamus of mouse brain. Nuclei (blue)

MAIN ACHIEVEMENTS

a) We investigated the involvement of NPY and ghrelin in caloric restriction induced autophagy. We observed that a caloric restriction mimetic cell culture medium stimulates autophagy in rat cortical neurons and NPY or ghrelin receptor antagonists blocked this effect. On the other hand, exogenous NPY or ghrelin stimulate autophagy in rat cortical neurons. Moreover, NPY mediates the stimulatory effect of ghrelin on autophagy in rat cortical neurons. Since autophagy impairment occurs in aging and age-related neurodegenerative diseases, NPY and ghrelin synergistic effect on autophagy stimulation may suggest a new strategy to delay aging process.

b) We investigated the role of NPY and ghrelin in rescuing the aging phenotype in human dermal fibroblasts of Hutchinson-Gilford Progeria Syndrome (HSPS). The results obtained show that NPY and also ghrelin decrease cellular hallmarks of premature aging of progeria fibroblasts, such as enhanced progerin clearance, autophagy stimulation, rescued nuclear abnormalities, increased cell proliferative capacity and delayed cellular senescence of HGPS cells. These results support that these peptides can be considered a promising strategy to delay or block the premature aging of HGPS.

c) 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.

d) 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.

e) Machado-Joseph disease (MJD) is a fatal dominantly inherited neurodegenerative disorder associated with an expanded polyglutamine tract within the ataxin-3 protein, and characterized by progressive impairment of motor coordination, with neurodegeneration of specific brain regions including cerebellum and striatum. We find that caloric restriction dramatically rescued the motor incoordination, imbalance and the associated neuropathology in transgenic MJD mice. We further show that caloric restriction rescued SIRT1 levels in transgenic MJD mice, whereas silencing SIRT1 is sufficient to prevent the beneficial effects on MJD pathology. In addition, the re-establishment of SIRT1 levels in MJD mouse model, through the gene delivery approach, significantly ameliorated neuropathology, reducing neuroinflammation and activating autophagy. Furthermore, the pharmacological activation of SIRT1 with resveratrol significantly reduced motor incoordination of MJD mice. The pharmacological SIRT1 activation could provide important benefits to treat MJD patients.

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

Objectives

As in the previous years, 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 thourough 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 define novel models of visual neuroplasticity (paper in Neuroimage Clinical).

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.

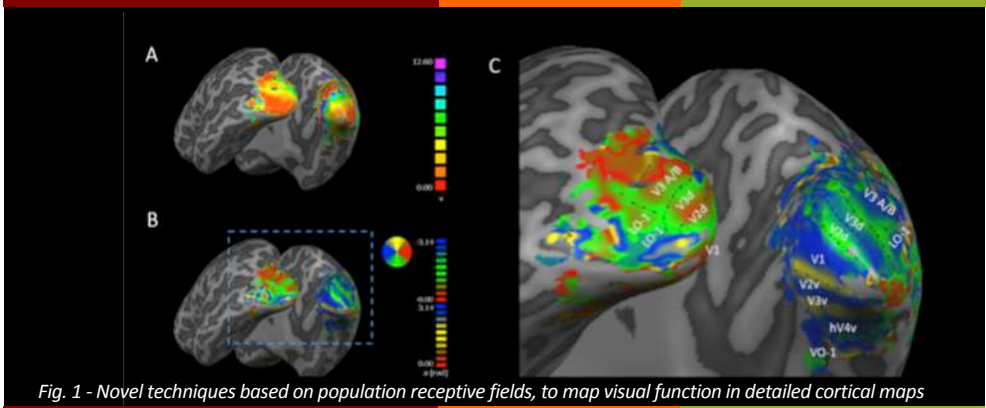


Fig. 1 - Novel techniques based on population receptive fields, to map visual function in detailed cortical maps

Main Achievements

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 being submitted. This led to mores 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 a landmark publication 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. 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. 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.

PURINES IN BRAIN DISEASES | *(Head: Rodrigo Cunha)*

Objectives

The general objective of the group is to identify modulation systems that can be targeted to interfere with the evolution of neurodegenerative diseases, with a central focus on purines (adenosine and ATP). We 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 (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 Rodrigues). 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 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- We established a role for A2AR in the amygdala in the control of fear in rodents.

2- We defined that A2AR overfunctioning is sufficient to trigger the dysfunction of synaptic plasticity and memory performance in an animal model early Alzheimer's disease

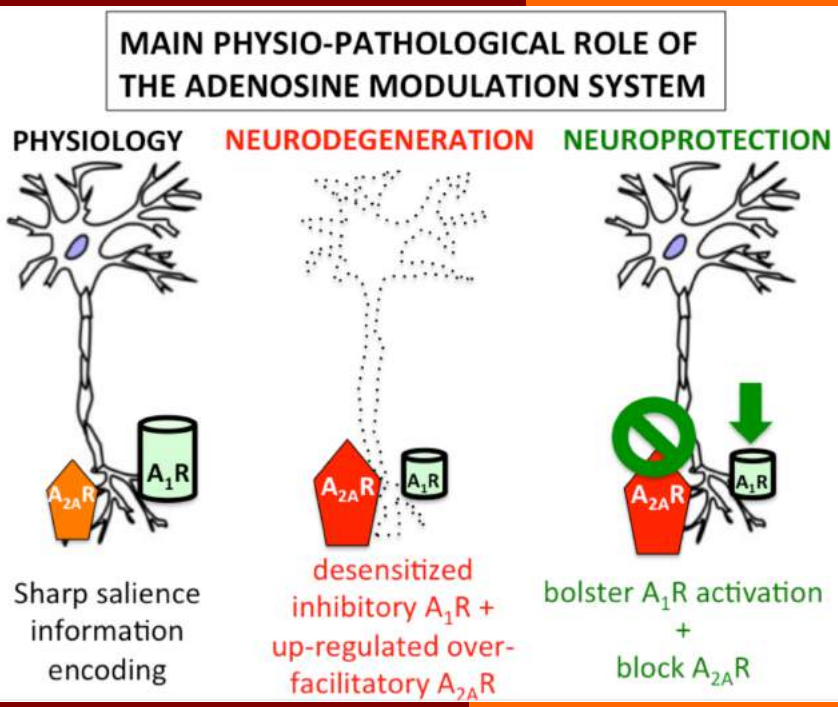
3- We revealed a novel general glucoregulatory role for cannabinoid CB2 receptors in the brain.

4- We found that the density of amyloid precursor protein decreases with aging in the human brain.

5- We found that ATP receptors heteromerize with nicotinic receptors to control neurotransmitter release in the brain.

6- We established that caffeine has gender-dependent effects in adolescent rats

7- We uncovered a role for purines in the control by microglia of synaptic transmission in the brain.



MITOCHONDRIAL DYSFUNCTION AND SIGNALING IN NEURODEGENERATION | *(Head: A. Cristina Rego)*

OBJECTIVES

Brain neurodegenerative diseases are chronic and debilitating disorders of the central nervous system, characterized by selective cerebral neurodegeneration and cognitive decline. There are several mechanisms by which neurons degenerate, but the initial triggers of neuronal dysfunction are largely unknown for each disorder. In this perspective, our current goal is focused on understanding how modified, misfolded or mutant proteins affect mitochondrial function and intracellular signaling pathways. By investigating mitochondrial dysfunction, oxidative stress, glutamate postsynaptic dysfunction, and modified neurogenesis and interrelated signaling pathways in distinct neurodegenerative disorders, namely in Alzheimer's disease (AD) and Huntington's disease (HD), our research aims to characterize molecular targets for therapeutic intervention, as recently reviewed by us (**Figure 1**) (Naia et al., 2017, *Biochem. Biophys. Res. Commun).*

During 2016, the research developed by our group has focused mainly in studying HD pathogenesis and treatment strategies. HD is an autosomal dominant disease caused by an expansion of CAG repeats in the *HTT* gene, encoding for the huntingtin protein (HTT), and the most prevalent polyglutamine expansion disorder, selectively affecting the striatum and cortex. Mitochondrial dysfunction associated with bioenergetic dysfunction, energy failure and oxidative stress play an important role in this untreated pathology. Unfortunately, there is no cure or neuroprotective treatment for HD.

Treatment paradigms aimed to ameliorate energy deficits appear to be suitable candidates in HD. In previous studies we observed protective effects of insulin growth factor-1 (IGF-1) in YAC128 and R6/2 mice, two HD mouse models, whereas IGF-1 and/or insulin halted mitochondrial-driven oxidative stress in mutant striatal cells and mitochondrial dysfunction in HD human lymphoblasts. Thus, we analysed the effect of IGF-1 *versus* insulin on energy metabolic parameters using striatal cells derived from HD knock-in mice and primary cortical cultures from YAC128 mice (Naia et al., 2016, *Neuropeptides*).

Sirtuin modulators are compounds with a protective role in several neurodegenerative processes. Sirtuin 1 (SIRT1), in particular, is a nicotinamide adenine dinucleotide (NAD+)-dependent lysine deacetylase that regulates longevity and enhances mitochondrial metabolism. Both activation and inhibition of SIRT1 were previously shown to ameliorate neuropathological mechanisms in HD. Thus, we tested the influence of resveratrol (RESV, a SIRT1 activator) *versus* nicotinamide (NAM, a SIRT1 inhibitor) in counteracting mitochondrial dysfunction in HD models, namely striatal and cortical neurons isolated from YAC128 transgenic mice embryos, HD human lymphoblasts and an in vivo HD model (Naia et al., 2016, *Mol. Neurobiol.*).

Finally, mutations of the *HTT* gene underlie both adult-onset and juvenile forms of HD; HTT modulates mitotic spindle orientation and cell fate in mouse cortical progenitors from the ventricular zone. Using human embryonic stem cells (hESC) characterized as carrying mutations associated with adult onset disease during pre-implantation genetic diagnosis, we investigated the influence of human HTT and of an adult-onset HD mutation on mitotic spindle orientation in human neural stem cells (NSCs) derived from control hESCs. We combined the use of neural derivatives of wild-type (WT) and adult-onset HD-hESCs and SNP-targeting HTT allele-specific mRNA interference to investigate the role of human HTT in the division of neural progenitors and to determine whether an adult-onset HD mutation affects this function (Lopes et al., 2016, *PLoS One*).

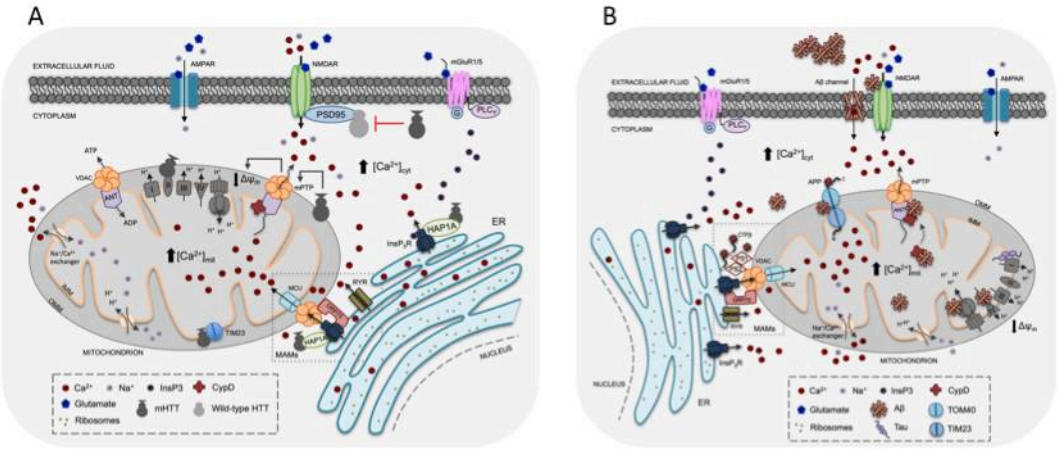


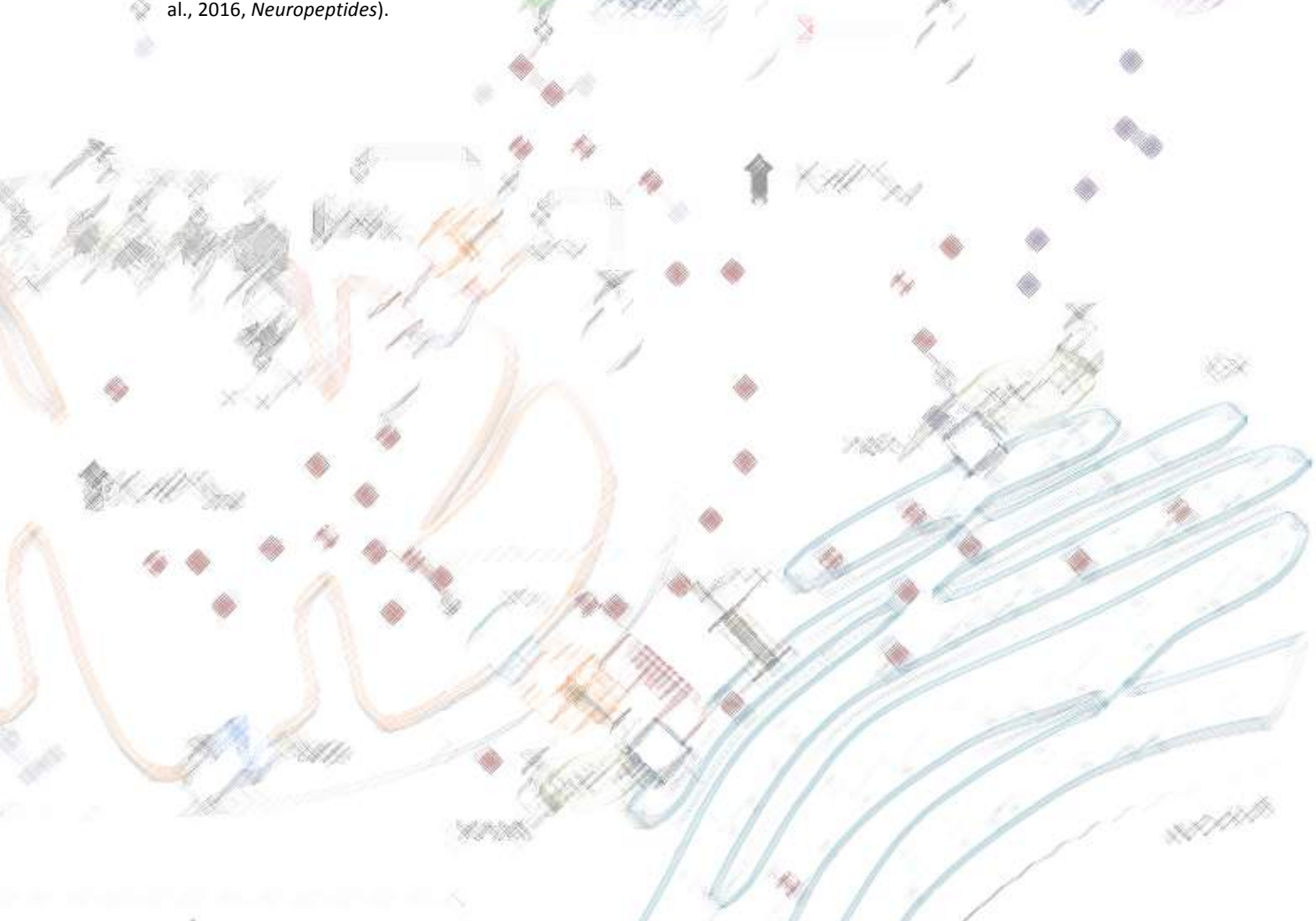
Fig. 1- Mutant huntingtin (mHTT, in A) and amyloid-beta peptide (Aß, in B) alter calcium buffering capacity by association with mitochondria and along the ER-mitochondrial axis (based on Naia et al., 2017, Biochem. Biophys. Res. Commun).

MAIN ACHIEVEMENTS

In the article published in *Neuropeptides* (Naia et al., 2016), STHdh$^{Q111/Q111}$ cells exhibited decreased ATP/ADP ratio and increased phosphocreatine levels. Moreover, pyruvate levels were increased in mutant cells, most probably in consequence of a decrease in pyruvate dehydrogenase (PDH) protein expression and increased PDH phosphorylation, reflecting its inactivation. Insulin and IGF-1 treatment significantly decreased phosphocreatine levels, whereas IGF-1 only decreased pyruvate levels in mutant cells. Primary cortical cultures derived from YAC128 mice also displayed energetic abnormalities. We observed a decrease in both ATP/ADP and phosphocreatine levels, which were prevented following exposure to insulin or IGF-1. Furthermore, decreased lactate levels in YAC128 cultures occurred concomitantly with a decline in lactate dehydrogenase activity, which was ameliorated with both insulin and IGF-1. These data demonstrated differential HD-associated metabolic dysfunction in striatal cell lines and primary cortical cultures, both of which being alleviated by insulin and IGF-1 (Naia et al., 2016, *Neuropeptides*).

HD cell models displayed a deregulation in mitochondrial membrane potential and respiration, implicating a decline in mitochondrial function (Naia et al., 2016, *Mol. Neurobiol.*). Further studies revealed decreased PGC-1alpha and TFAM protein levels, linked to mitochondrial DNA loss in HD lymphoblasts. Remarkably, RESV completely restored these parameters, while NAM increased NAD^+ levels, providing a positive add on mitochondrial function in in vitro HD models. In general, RESV decreased while NAM increased H3 acetylation at lysine 9. In agreement with in vitro data, continuous RESV treatment for 28 days significantly 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 indicated that activation of deacetylase activity by RESV improved gene transcription associated to mitochondrial function in HD, which may partially control HD-related motor disturbances (Naia et al., 2016, *Mol. Neurobiol.*)

In the paper published in *PLoS One* (Lopes et al., 2016) RNAi-mediated silencing of both HTT alleles in neural stem cells derived from hESCs disrupted spindle orientation and led to the mislocalization of dynein, the p150^{Glued} subunit of dynactin and the large nuclear mitotic apparatus (NuMA) protein. We also investigated the effect of the adult-onset HD mutation on the role of HTT during spindle orientation in NSCs derived from HD-hESCs. By combining SNP-targeting allele-specific silencing and gain-of-function approaches, we showed that a 46-glutamine expansion in human HTT was sufficient for a dominant-negative effect on spindle orientation and changes in the distribution within the spindle pole and the cell cortex of dynein, p150^{Glued} and NuMA in neural cells. Thus, neural derivatives of disease-specific human pluripotent stem cells constitute a relevant biological resource for exploring the impact of adult-onset HD mutations of the HTT gene on the division of neural progenitors, with potential applications in HD drug discovery targeting HTT-dynein-p150^{Glued} complex interactions (Lopes et al., 2016, *PLoS One*).



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

OBJECTIVES:

In 2016 our group has pursued its main objective, namely the identification and validation of biomarkers of aging and brain diseases fulfilling the most recent international criteria for early diagnosis and patient – tailored preventive therapeutic interventions. This involves a close interaction with clinicians and has allowed for interdisciplinary translational research and interventions in neurodegenerative disorders for which aging is the main risk factor, either Alzheimer's and Parkinson´s diseases and Frontotemporal Lobar Degeneration or neuropsychiatric disorders, particularly schizophrenia and bipolar disease.

An additional interest of the group is focused on the development of "OMICS" methodologies that have been applied, in a translational perspective, to the study of brain disorders, bigenomic disorders and in the characterization of cancer biomarkers.

Overall, the research developed in the group relies on collaborative efforts with the Coimbra University Hospital (CHUC) for access to human biological samples and clinical data, including clinical and neuropsychological evaluation, and on the team's integration in international consortia (Joint Programing in neurodegenerative Disorders- JPND- and Early Alzheimer's Disease Consortium – EADC) that define standard methodologies for sample collection, data analysis and information storage, establishing the link between fundamental and pre-clinical research and research performed in a clinical setting.

This capacity to perform collaborative research, both at national and international level, has led, in the last years, to publications in high impact scientific journals and to the organization of international courses, namely the 'Biological markers in Neurological diseases – Present and Future approaches' International JPND course, which was hold in Coimbra in 2016.

MAIN ACHIEVEMENTS:

According to the objectives of the group, the following main achievements have been reached:

1. Biomarkers of Neurodegenerative Diseases

Concerning Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), we have studied the relationship between the Butirylcholinesterase (BuChE)-K variant with Alzheimer's Disease (AD) risk, and also with the activity of the enzyme in CSF and ApoE genotype. We have established that, in our population, the BuChE-K variant does not seem to confer risk for AD or to influence the activity of the enzyme in CSF. However, we demonstrated an association between BuChE activity, ApoE-ε4 genotype and CSF Aβ42 levels, highlighting the importance of assessing BuChE activity as a possible modulator of Aβ load in the brain.

Furthermore, we have been involved in a large multicenter study aimed at investigating the prevalence of vascular, psychiatric, and lifestyle risk factors in prodromal AD/MCI due to AD and at examining whether the presence of these risk factors influences cognitive decline and in particular progression to AD-type dementia. We have shown that individuals with prodromal AD or high-AD-likelihood had a lower prevalence of depression, hypercholesterolemia, hypertension and obesity than those without prodromal AD or low-AD-likelihood. Apart from smoking, none of the risk factors increased the risk of cognitive decline in prodromal AD.

The genetic characterization of clinical diagnosed patients with Alzheimer's disease (AD), Frontotemporal Lobar Degeneration (FTLD), Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS), aiming to unveil novel and/or known variants, as well as the presence of double mutations carriers, to further elucidate mutations penetrance and clinical expressivity was also one of our research objectives.

For this purpose, the out- and in-patients followed in the Dementia Clinic of CHUC during 2016 were genetically characterized, mainly those who showed a positive family history and/or with early-onset of the disease. For the clinical diagnosed AD patients, the mutation analysis has been carried out in the entire coding region of the *PSEN1, PSEN2,* and for exons 16 and 17 of the *APP* gene, since these are the three genes associated with the disease. For the FTLD and ALS patients, the mutation analysis encompasses the entire coding region of the known causative genes such as, MAPT, PGRN and SQSTM1, by direct sequencing and combined this with repeat-primed PCR assessment for C9orf72 hexanucleotide expansions. To the PD patients, the Park2 and LRRK2 genes have been screened to the juvenile and adult forms of the disease, respectively.

Demyelinating diseases that can be associated to cognitive impairment, are a new line of research of the group. We have investigated the presence of the metalloproteinase-9 (MMP-9) -1562 C/T polymorphism in a Portuguese population of Multiple Sclerosis (MS) patients and assessed its impact in susceptibility and clinical course of the disease. The relation of MMP-9 serum levels with the polymorphism and with clinical and therapeutic factors was also assessed.

A significant increase in MMP-9 -1562 T-allele frequency was found in female MS patients, but not in the total patient population. No association between the presence of the polymorphism and disease progression was found. MMP-9 serum concentrations were increased in patients, and although not influenced by the -1562 C/T polymorphism, were modified by INF-beta therapy.

2. Diagnosis Strategies in Neuropsychiatric Disorders

In 2016 there were important goals achieved as a consequence of long-term investment in the proteomics/metabolomics field. We initiated the first integrative clinical project heavily engaged with these two screening approaches to identify new biomarkers for schizophrenia (PTDC/NEU-SCC/7051/2014). As a consequence, the research team was invited to join a PAC proposal to extend our biomarkers research approaches to

Parkinson's disease, Autism and Aging. This project was approved with starting date of February 2017 (SAICTPAC/0010/2015).

Several collaborative publications on the secretome analysis of stem cells allowed us to extend these approaches to translational research on biomarkers identification. This proved to have great potential by identifying new neurodegenerative biomarkers in the blood of Parkinson's disease animal models and the development of new approaches to monitor protein oxidative state. Moreover, our publications on quantitative Protein-Protein interactomics have gained special attention from the community with several invitations both for advanced training courses and a special invitation for a comprehensive tutorial to be published in 2017.

The diagnostic tools methodologies, based in biological markers, were developed in order to validate the diagnostic categories and improve its boundaries and discrimination among psychiatric disorders, namely, psychotic disorders.

Risk factors for the development of psychiatric disorders in certain developmental stages or life-cycle circumstances, such as perinatal anxiety/depression, were identified. The instruments to evaluate the identified risk factors and to analyze their reliability and validity (psychometric and operative characteristics), in the screening for psychiatric disorders, were developed or adapted.

The efficacy of prevention and/or early intervention programs designed to diminish the effect of the risk factors identified in our research (e.g. for perinatal distress; psychosis), based in cognitive-behavioral therapy and third generation cognitive therapies, was tested.

3. Diagnosis of Early Life Cognitive Dysfunction

The characterization of new biomarkers of neurodevelopment disorders associated with cognitive impairment continued to be one of the research objectives of the group.

Under this scope, as iodine deficit has been claimed to be involved in early age cognitive impairment, we participated in the evaluation of the iodine nutrition status and thyroid nodular pathology of the general population from the inland region in Portugal, providing data to identify treatment strategies (Santos et al, 2016), and also in the assessment of the urinary metabolite signature of prematurity in newborns (*Diaz et al., 2016*).

In a collaborative intra-institutional project, we helped to characterize Machado Joseph disease fibroblasts, which are an important resource for the study of this neurodegenerative disease, contributing for the understanding of mutant ataxin-3 biology and its molecular consequences (*Onofre et al., 2016*).

Additionally, we used several genomic tools for the assessment of new biomarkers in different pathologies, namely in cancer, and contributed to identify a specific set of genes as epigenetic diagnostic and prognostic biomarkers in oral cancer (Ribeiro et al., 2016a). The current knowledge of oral cancer was re-analyzed and the potential role of omics approaches to identify molecular biomarkers in the improvement of early diagnosis, treatment and prognosis was evaluated (*Ribeiro et al, 2016b*).

Furthermore, different chromosomal rearrangements and CNVs were shown to be related with acute lymphoblastic leukemia and to be associated with high rates of submicroscopic aberrations (*Alhourani et al., 2016; Othman et al, 2016)*.

4. Biomedical Research in Bigenomic Disorders and Personalized Medicine

Bigenomic investigation of disorders, aims to find genetic risk factors, in mitochondrial genome and nuclear genes associated with mitochondrial genomics/biogenesis/function/integrity/ proteomics/metabolomics, which will contribute to identify new tools for early diagnosis. The group has accomplished the latest developments in molecular genetics, including the Next Generation Sequencing (NGS) technique, and new methodological assays were developed to support functional genomics. These developments have made possible the functional studies for pathogenicity investigation of novel mutations identified in patients, which are more frequent with the application of the recent NGS technologies.

Two cases of Leigh syndrome (LS) likely caused by *SURF1* gene variants, a 39-year-old male patient with a novel homozygous deletion, and a case of a 6-year-old boy with the same deletion and a nonsense mutation, both in heterozygosity were studied with a focus in mitochondria functionality. In these patients, Blue native PAGE (BN-PAGE) showed absence of assembled complex IV. This was the first report of a variant that may abolish the *SURF1* gene initiation codon in two LS patients (*Ribeiro et al., Mitochondrion. 2016; 31:84-88*).

Functional studies conducted in patients with clinical diagnosis of MRC diseases and also in lysosomal storage disorders (LSD), comprising MRC enzymatic activity and relative quantification of complexes subunits and transcripts evaluation, together with the analysis of mitochondrial membrane potential ($\Delta_{\psi m}$), ROS levels, cellular ultrastructural morphology by transmission electron microscopy (TEM) and determination of defects in MRC complexes assembly by BN-PAGE have been essential to confirm/elucidate the pathogenicity of novel genetic variants.

Regarding the pharmacogenomics studies, the identification of genetic alterations and copy number variation that determine the metabolic profile or targeting depending on genetics, have been performed aiming to provide tools for more rationale treatments, managing risks and preventing drug adverse reactions.

Presently, a pharmacogenomic and metabolic study is ongoing, focused on drug addicts undergoing drug withdrawal with methadone therapy, aiming to understand the genetic factors underlying heterogeneity in detoxification fulfillment and diversity in response to treatment. So far, the genes *COMT* and *OPRM* and the predicted *CYP2D6* metabolic profile have been studied in 138 patients for further analysis and correlation with clinical data. Regarding *COMT* gene, the Met genotype is associated with higher risk of developing paranoid ideation. The frequencies of theoretical *CYP2D6* metabolic profiles were calculated and, as expected, the extensive and intermediate metabolizers profiles are more frequent, but the percentage of poor and ultra-rapid metabolizers is relevant, being statistically significant in the female group. Furthermore, analysis of MRC activity in 24 patients showed a significant reduction of energy production capacity. We believe this study will contribute to the development of new therapeutic strategies helping the reintegration of these individuals in the society, with direct impact in public health and in society.

NEW TARGETS AND THERAPEUTICS FOR CHRONIC DISEASES | *(Head: António Francisco Ambrósio)*

OBJECTIVES

The Group has been mainly focused in chronic disorders that affect brain and retina, but also affecting other organs and tissues as heart, kidney, bladder and bone. In many of those pathologies, age is a strong risk factor.

Since many therapies for chronic disorders are not satisfactory and the development of improved therapies is needed, we kept pursuing the following goals:

- elucidate the molecular and cellular mechanisms underlying the pathogenesis of chronic disorders affecting brain and retina, and other organs;

- elucidate the mechanisms of action of some drugs already used in pharmacotherapy and mechanisms underlying drug toxicity;

- identify new potential drug targets and more efficient therapeutic options (conventional drugs, and molecular and cellular therapies) for the treatment of chronic disorders affecting those organs, and evaluate the response to therapy.

Additionally, 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 disease 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, which include adenosine and neuropeptide Y. These systems can exert both neuroprotective and anti-inflammatory effects. We are also exploring the potential of using drugs already in the market for other purposes.

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. We are also assessing cold atmospheric plasma as a therapeutic option for retinoblastoma.

Neuroscience and Blood-Brain Barrier

Psychostimulants like methamphetamine (METH) cause significant brain damage leading to neurological and psychiatric anomalies. Moreover, methylphenidate is the most frequently prescribed drug for the symptomatic treatment of attention deficit hyperactivity disorder. We intended to clarify the impact of METH and methylphenidate on the brain, given a particular attention to blood-brain barrier (BBB) dysfunction, neuroinflammation, mood behavior, metabolism and immune system.

Diabetic encephalopathy is characterized by cognitive and memory impairments and hippocampus is particularly affected. We have been exploring how neuroinflammation can impair axonal transport in hippocampal neurons and how this impairment can affect memory performance. Moreover, we have been characterizing brain alterations in prediabetes.

We are also trying to understand how microglia respond to immune challenges, namely during brain development, and the way this response impact on brain circuits and mental health, as well as to pinpoint the role of the innate immune system in neurodegenerative diseases including Parkinson´s disease.

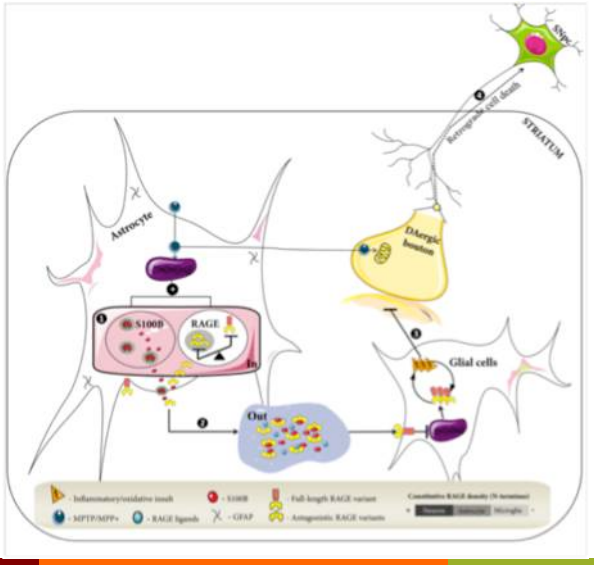


Fig. 1 - Increased antagonistic RAGE variants paralleling S100B up-regulation in early stages of MPTP-induced astrogliosis dynamics prior to astrocytes hypertrophy (1). We propose that selective RAGE regulation reflects a self-protective mechanism to maintain low levels of RAGE ligands (2), preventing long-term inflammation and oxidative stress arising from sustained ligands/flRAGE activation (3). Understanding loss of RAGE protective response to stress may provide new therapeutic options to halt or slow down dopaminergic axonopathy and, ultimately, neuronal death (4). Astrocyte-RAGE dynamic duo may be a putative therapeutic target in PD that needs to be further explored (In Viana Phd thesis 2016)

Stem Cells

We are investigating the molecular mechanisms underlying the development of chemoresistance mediated by Cancer Stem Cells (CSC) in solid tumors, and their role in tumor progression, with the perspective of designing more effective anticancer therapeutic strategies.

Experimental Therapeutics

Our group has been mainly focused on clinical and experimental studies related to pharmacological and therapeutic options (including diet and physical exercise) in cardiometabolic and cardiorenal disorders, such as type 2 diabetes and its vascular complications (namely nephropathy), dyslipidemia and chronic renal failure/aging. Additionally, we also intend to evaluate how GLP-1 analogue Liraglutide improves adipose tissue angiogenesis.

We are also evaluating the efficacy of novel photosensitizers for the treatment of cancer.

MAIN ACHIEVEMENTS

The blockade of A2A receptors prevents microglia-mediated neuroinflammation in the retina and protects retinal cells against injury. Madeira et al. Transl. Res. 2016, 169:112-128.

GLP-1 analog protects the retina against ischemia-reperfusion injury by reducing neuroinflammation. Gonçalves et al., Invest. Ophthalmol. Vis. Sci. 2016, 57:2584-2592.

Caffeine is protective in an animal model of glaucoma. Madeira et al. Sci. Rep. 2016, 6:27532.

Adenosine A2A receptor regulates microglia morphological remodeling in a model of chronic anxiety, and this is affected by gender. Caetano et al. 2016 Mol. Psychiatry.

Recombinant human erythropoietin-induced erythropoiesis regulates hepcidin expression over iron status.

Impaired renal endothelial nitric oxide synthase and reticulocyte production are the main modulators of hypertension induced by rHuEPO recombinant human erythropoietin.

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

High sucrose consumption induces memory impairment in rats which is not associated with metabolic changes in the hippocampus.

Development of new therapeutic approaches for retinoblastoma (confidential data).

Upregulation of RAGE inhibitory variants in striatal astrocytes at an early stage of experimental Parkinson's disease.

Extended-access to METH self-administration followed by forced abstinence increases BBB permeability in hippocampus and striatum.

Rats trained to self-administer METH present a neuroinflammatory profile in the brain.

METH interferes with AQP4 protein levels causing BBB breakdown and brain edema, culminating in locomotor and motivational impairment.

Methylphenidate regulates the macromolecular flux through human brain endothelial cells (ECs), increasing transcytosis without affecting paracellular permeability.

Conventional chemotherapeutics induce a phenotypic cell transition towards a stem-like phenotype in osteosarcoma through activation of the self-renewal Wnt/β-catenin pathway, that ultimately leads to therapy failure. Targeting Wnt/β-catenin pathway might be an effective approach to overcome the stemness plasticity that non-stem cells might acquire after cancer treatment.

A cell-based immunotherapeutic approach using allogenic Natural Killer cells from healthy donors are highly effective in the eradication of bladder Cancer Stem Cells, viewed as major precursors of muscle-invasive forms, by direct killing and by generation of differentiated cells vulnerable to conventional therapies.

Novel photosensitizers (galactodendritic porphyrin and chlorin) have a remarkable photodynamic efficiency in vitro system and in an animal model of bladder cancer.

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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 noted that the ImmunoMetabolic Pharmacology Group is no longer part of the CNC.IBILI Consortium, and was removed from the current report. Before or during 2016 group members joined other Institutes, or other CNC.IBILI groups (notably Metabolic Control, where immunology-based research is also carried out) and the PI asked for a 3-year unpaid leave of absence. Given that this was the smallest group in the strand, and the only one with no competitive funding, this change is not predicted to affect consortium productivity.

MAIN ACHIEVEMENTS

One of the main achievements was the pro-active involvement of the Strand in 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.

In terms of specific scientific goals Middle-aged diabetic females and males were found to present distinct susceptibility to Alzheimer's Disease (AD)-like pathology, and differential sex steroid hormone profiles/action may play a pivotal role in brain in type 2 diabetes (T2D) progression. Mitochondrial impairments were found to cause the loss of microtubule network leading to disturbances in the autophagic-lysosomal pathway in Alzheimers and Parkinson's disease. Furthermore, in the context of aging-related cachexia, our findings suggest that autophagy is operating at its full capacity in elderly individuals and can maintain a correct muscle fibers physiology in normal weight people. However, the autophagic response is not able to fulfill the requirements of muscle fibers from overweight people.

The stand has also continued to develop Mitochondrial-based therapeutics: showing that alterations in mitochondrial biogenesis, dynamics and autophagy markers induced by exercise may contribute to the observed protective brain cortex and cerebellum mitochondrial phenotype, more resistant to oxidative damage and apoptotic signaling in doxorubicin (DOX)-treated animals. Furthermore, antioxidant molecules which target mitochondria decreased damage in isolated fractions and cultured cells treated with stressors, which may also be extended towards targeting mitochondria in cancer.

Finally, we successfully deployed a NMR-based methodology of liver triglyceride ^{2}H and ^{13}C enrichments in naturally feeding mice, finding 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.

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.

For example our finding that new BACE1 inhibitors we are developing decrease insoluble Aβ40/42 brain levels in 3xTg-Alzheimer mice submitted to a chronic treatment suggesting that these compounds have the potential to be a disease-modifying therapy will be extended to preclinical models. 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 followed up will be our heart failure (HF) data in patients with and without diabetes given that epicardial adipocytes may be a possible therapeutic target for HF treatment.

In terms of targeting mitochondria this will 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. 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.

CELL METABOLISM AND QUALITY CONTROL GROUP

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MITOCHONDRIA, METABOLISM AND DISEASE GROUP

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João Silva	PhD Student
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CELL METABOLISM AND QUALITY CONTROL | (*Head: Paula Moreira*)

OBJECTIVES

We aimed to clarify the involvement of mitochondria, inflammation, quality control mechanisms and microbiome in aging and age-related neurodegenerative pathologies, namely Alzheimer´s disease (AD) and Parkinson´s disease (PD), as well as in other age-related diseases such as osteoarthritis. The mechanisms underlying diabetes-associated central and peripheral damage as well as their role as risk factors for several diseases were also studied. We also investigated the role of sex in the development of AD-like pathology. We intended to clarify the mechanisms involved in mitochondrial trafficking and signaling pathways and the crosstalk with other organelles such as the endoplasmic reticulum (ER) in the aforesaid diseases. The mechanisms of protein quality control present in these organelles and in the cytosol, and their role in inflammation, were another focus of our research. In addition, we aimed to explore the role of autophagy and intercellular communication in the maintenance of the cardiovascular system homeostasis. Another research interest was the identification and validation of biomarkers and of new drugs of natural origin. Ultimately, our goal was to identify novel therapeutic targets, to develop efficient treatment strategies and propose new uses for approved drugs (repurposing drugs).

Specific objectives:

To elucidate the role of mitochondrial metabolism signaling in the regulation of ubiquitin proteasomal system and autophagic lysosomal pathway in sporadic AD and PD;

To determine the role of gut microbiota on PD and AD etiology;

To develop a disease-modifying treatment for AD based on BACE1 inhibition;

To test the efficacy of anti-diabetic agents in AD and diabetes-associated neurodegeneration;

To clarify the role of sex in diabetes-associated neurodegeneration;

To establish the contribution of exosome-mediated intercellular communication to the heart pathophysiology;

To elucidate the mechanisms involved in the regulation of the intracellular trafficking of gap junction protein Cx43;

To unveil the signaling pathways underlying the development of pulmonary arterial hypertension;

To explore the therapeutic potential of exosomes, as drug-carrying systems;

To elucidate the mechanisms by which diabetes favours the development and progression of osteoarthritis;

To identify new compounds of natural origin with potential activity in chronic inflammation;

To develop and validate new anisotropic constructs for articular cartilage tissue engineering;

To develop in vitro and in silico non-animal cell-based approaches to detect skin and respiratory allergens;

Screening of lead molecules with anti-inflammatory and anti-tumoral properties obtained from medicinal plants;

To explore inflammasome activation in dendritic cells.

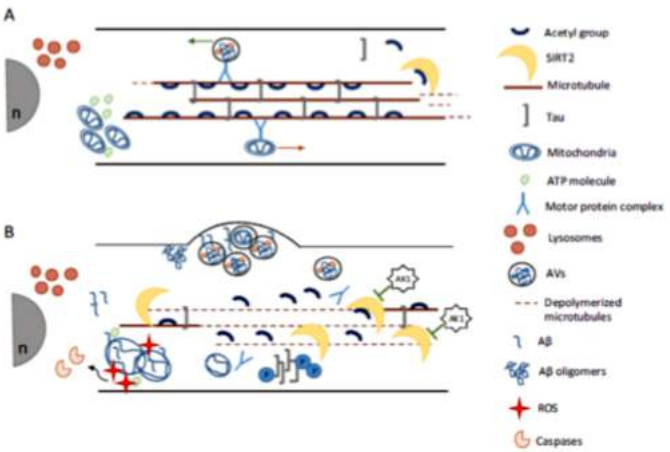


Fig. 1 - Proposed mechanism of sirtuin 2 (SIRT2) microtubule acetylation regulation. A) In healthy neurons, mitochondrial metabolism is optimal. Microtubules are dynamically stabilized by acetylation and Tau binding. SIRT2 may have a role in regulating this process in basal conditions. Cargos are transported along microtubules (retrograde and anterograde transport). Autophagic vesicles (AVs) are transported toward the cell body where lysosomes are mostly located, allowing the digestion of the wasting materials. B) In a disease state, mitochondrial metabolism fails, mitochondria are producing less ATP and more reactive oxygen species (ROS). These metabolic changes and SIRT2 upregulation drive microtubule dynamics impairment. SIRT2 deacetylates α-tubulin destabilizing microtubules. Tau dissociates from microtubules, is phosphorylated, and forms aggregates. Intracellular transport along microtubules is no longer efficient and AVs accumulate within the cell, impairing autophagic flux. The accumulation of AVs favors amyloid ß (Aß) production and oligomerization. Aß is imported by mitochondria aggravating cellular energy crisis. Ultimately, caspases are activated initiating cell death pathways. AK1, a SIRT2 inhibitor, partially reverts AD pathology hallmarks representing a good candidate as AD-modifying therapy.

MAIN ACHIEVEMENTS

Mitochondrial impairments cause the loss of microtubule network leading to disturbances in the autophagic-lysosomal pathway in AD and PD. Also, mitochondrial metabolism regulates NAD+/NADH ratio, impacting SIRT2 activation.

The new BACE1 inhibitors we are developing decrease insoluble Aβ40/42 brain levels in 3xTg-AD mice submitted to a

chronic treatment suggesting that these compounds have the potential to be a disease-modifying therapy.

Middle-aged diabetic females and males present distinct susceptibility to AD-like pathology. Differential sex steroid hormone profiles/action may play a pivotal role in brain over type 2 diabetes (T2D) progression reinforcing the need to establish sex-specific preventive and/or therapeutic approaches and an appropriate time window for the efficient treatment against T2D and AD.

Hyperglycemia and hyperinsulinemia are either one sufficient to impair autophagy and activate inflammatory pathways in human chondrocytes that drive cartilage degradation.

Structure-activity relationships of carvone derivatives of natural origin were established both relative to cytotoxicity and to anti-inflammatory activity.

Fig. 2. Schematic representation of the different roles played by Cx43 in intercellular communication. Cx43 forms hemi-channels that, when at the plasma membrane, allow the exchange of small molecules between the cytoplasm and the extracellular milieu, mediating a paracrine response. The docking of Cx43 hemi-channel ensures the electrical and metabolic coupling between adjacent cells. Cx43 at the membrane of microvesicles and exosomes may facilitate/ promote the interaction of these vesicles with target cells, allowing a more rapid and selective release of the vesicle content into the recipient cell (cell-vesicle coupling). Additionally, Cx43 presence in tunneling nanotubes (TNTs) permits electrical coupling and transfer of RNAs molecules (small interference RNA) transfer at long-distance in a controlled manner.

The skin sensitizer 1-fluoro-2,4-dinitrobenzene (DNFB), the respiratory allergen hexamethylene diisocyanate (HDI), and the irritant methyl salicylate (MESA) cause both specific and common alterations at phospholipidome levels. The common effects observed at phospholipids level might be related to unspecific cell cytotoxic mechanisms that nevertheless may contribute to the elicitation of specific immune responses.

Ubiquitin acts a selective sorting signal to incorporate Cx43 into exosomes.

Exosomes constitutes a valuable therapeutic vehicle to deliver the anti-tumor drug doxorubicin and the presence of Cx43 in exosomes-containing doxorubicin reduces cardiotoxicity.

Exosomes released by cardiomyocytes subjected to ischemia promote the formation of new vessels in the heart.

. EHD modulate the cardiomyocyte Cx43 remodeling associated with heart ischemia.

miRNA-424(322) is a new marker of disease progression in pulmonary arterial hypertension; miRNA-424(322) released by pulmonary endothelial cells contributes for right ventricular hypertrophy by targeting SMURF1.

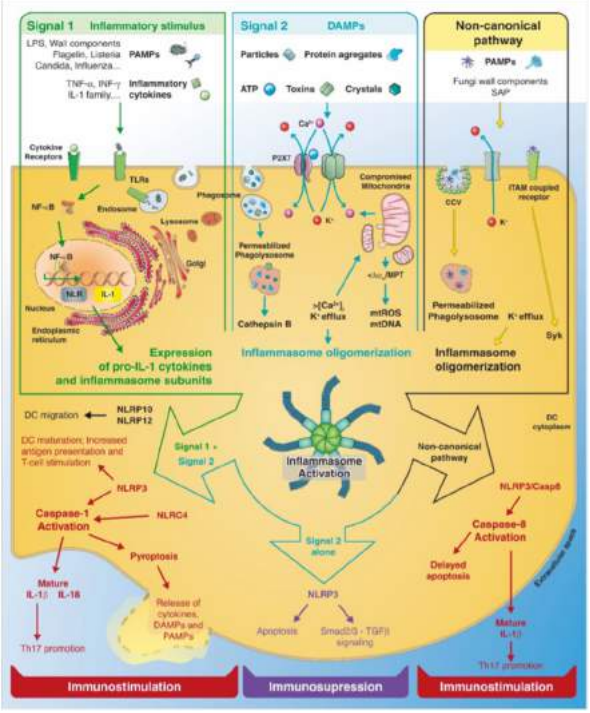


Fig. 3. Overview of the known mechanisms of inflammasome activation and its consequences to dendritic cells (DC) function in the regulation of immune responses. Inflammasomes are cytoplasmic multimeric protein complexes formed by the assembly of sensor (NLRs), adaptor (ASC) and effector (caspases) proteins. The assembly, and hence activation, of the NLRP3 inflammasome, the inflammasome best studied so far, may proceed though a canonical two stepwise process or through a non-canonical pathway. In the canonical pathway the first step is triggered by the activation of Toll like receptors (TLRs) by pathogen associated molecular patterns (PAMPs), either on the cell surface or in endosomes, or by the activation of cell surface specific cytokine receptors that sense pro-inflammatory cytokines. The activation of these receptors is coupled to the activation and nuclear translocation of transcription factors, such as NF-kB, which increase the transcription of NLRP3 and pro-IL-1b. The second signal consists of danger associated molecular patterns (DAMPs) that, through still incompletely characterized mechanisms (e.g. potassium efflux, alteration of calcium homeostasis, cathepsin B leakage from destabilized (phago)lysosomes or mitochondrial reactive oxygen species (mtROS) and DNA (mtDNA) release), lead to the oligomerization of inflammasomes. When these two signals are present inflammasomes catalyze the activation of pro-Caspase 1 (pro-Casp-1) which proteolytically activates IL-1b and Il-18 and induces pyroptosis, conferring immunostimulatory properties to DC. When oligomerization of inflammasomes stimulated by signal 2 occurs in the absence of the priming signal 1, they promote apoptosis and phosphorylation of Smad2/3 involved in TGFb signaling, turning DC immunosuppressive. More recently a non-canonical pathway of inflammasome activation triggered by fungi wall components and secreted aspartic proteases (SAP) has been described. Destabilization of phagolysosomes, potassium efflux and signaling mediated by the spleen tyrosine kinase (Syk) have been implied in the oligomerization of NLRP3 inflammasomes that leads to the activation of caspase 8. The proteolytically activation of IL-1b and the promotion of delayed apoptosis by casp-8 render DC immunostimulants.

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

OBJECTIVES

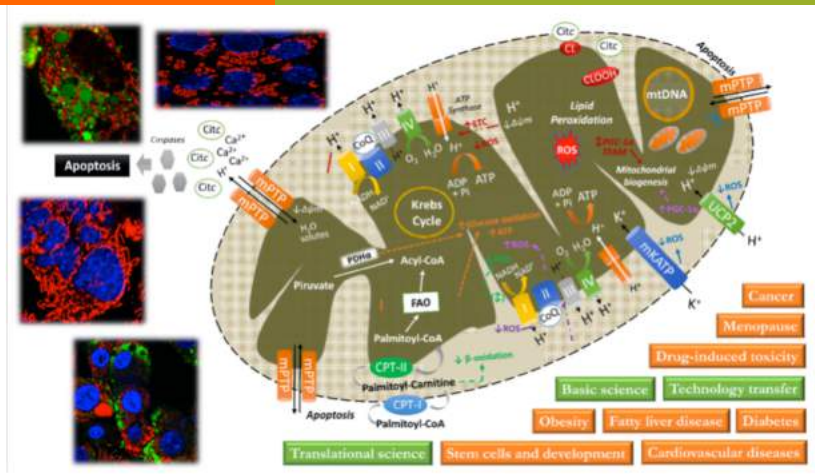
Mitochondria are critical organelles for cell physiology and survival. Mitochondria are the cell energy powerplants, producing most of the chemical energy for cell metabolism, and playing an important role in cell death and quality control processes. Since mitochondria are also active players in cellular redox and calcium homeostasis, as well as in intermediate metabolism, the general objective of our research group is to provide insights into the role of mitochondria in cellular metabolism, redox signaling and stress responses associated with chemical toxicology, cancer, cardiovascular and hepatic diseases, aging, and stem cell differentiation. The group has a multiple-prong approach to the main scientific question, focusing in various research lines:

1) Mitochondrial Therapeutics: Investigate whether intrinsic, pharmacological, or non-pharmacological (exercise or diet) regulation of mitochondrial biogenesis/metabolism and quality control reduces organ injury during disease or chemical toxicity. Design and testing novel mitochondrial-directed antioxidants based on dietary components in models for human diseases (cardiovascular/hepatic) as well as the development of new pharmacological conditioning strategies, resulting in the reduction of morbidity and mortality of liver resection surgery.

2) Mitochondrial Toxicology, Aging, Disease and Stress Responses: Unravel mechanism of mitochondrial dysfunction caused by different xenobiotics, including drug-induced injury (e.g. anthracyclines) and nanoparticles. Evaluate the impact of sestrin and sirtuin modulation as inducers of mitohormesis: preservation of mitochondrial function under pathologic stress. Identify molecular mechanisms responsible for miRNA regulation in several biological and disease processes, particularly the miRNAs acting in mitochondria or in mitochondria-related mechanisms. Evaluate cellular mechanisms behind overweight- and age-related muscle wasting during aging, as well as oxidative stress and endoplasmic reticulum stress markers and signaling, and their relationship with mitochondrial function alterations. Develop high-throughput methods to investigate mitochondrial function in the context of drug discovery or safety assessment of molecules of human interest.

3) Mitochondrial Physiology in Tumor Physiology and (Cancer) Stem Cells: Identify mitochondrial remodeling steps and mechanisms during cancer stem cell differentiation and carcinogenesis; investigate the role of autophagy for the differentiation of stem cells and their resistance to cell death. Investigate the 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. Evaluate exosomes' involvement in cytokines' release and the 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. Identify new strategies to block cancer stem cells formation and to modulate stromal cells phenotype to improve therapy's efficacy and consequently, patients care and welfare.

4) Osteoporosis and Menopause: Characterize the 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. Identify phytoestrogens (PE) with low toxicological effects and high therapeutic potential for menopausal-associated symptoms that could be safely included as additives in certain aliments that compose the diet of the Western population.



MAIN ACHIEVEMENTS

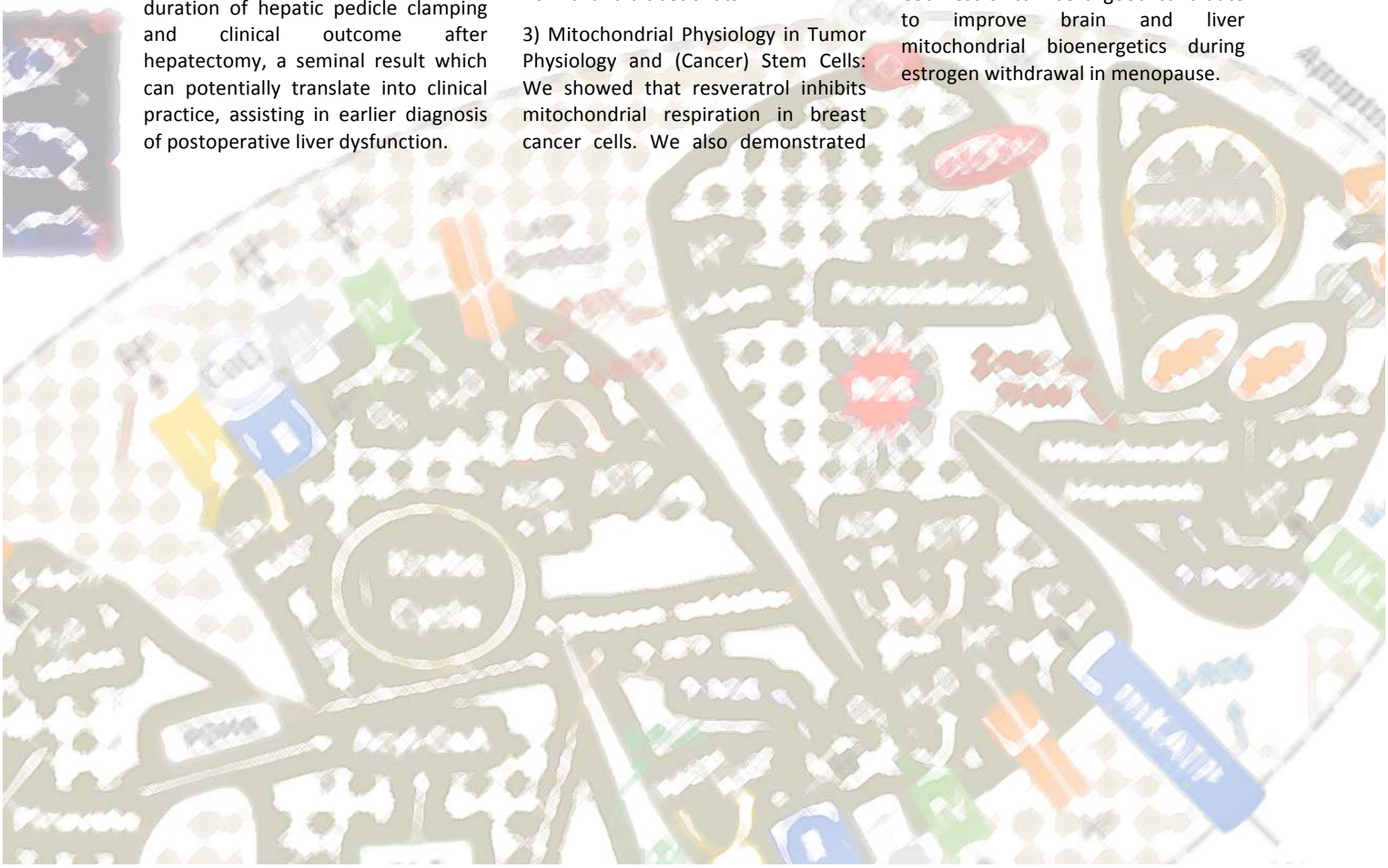
In the context of the different research lines, we produced different important contributions:

1) Mitochondrial Therapeutics: In collaboration with the University of Porto (UP), we obtained evidence that the alterations in mitochondrial biogenesis, dynamics and autophagy markers induced by exercise performed before and during DOX treatment may contribute to the observed protective brain cortex and cerebellum mitochondrial phenotype, more resistant to oxidative damage and apoptotic signaling in doxorubicin (DOX)-treated animals. Also in collaboration with the UP, we tested two families of antioxidant molecules which target mitochondria and decreased damage in isolated fractions and cultured cells treated with stressors. The mitochondrial protective agent, carvedilol was tested in an animal model of hyperglycemia showing activation of antioxidant defenses. Obesity-focused work demonstrated that chenodeoxycholic acid-induced metabolic alterations occur in white and brown adipocytes and are not totally dependent on endocrine/nervous system signaling. We also demonstrated a relationship between mitochondrial function, duration of hepatic pedicle clamping and clinical outcome after hepatectomy, a seminal result which can potentially translate into clinical practice, assisting in earlier diagnosis of postoperative liver dysfunction.

2) Mitochondrial Toxicology, Aging, Disease, and Stress Responses: Focusing on anthracycline DOX toxicity, we propose that loss of cytochrome c and cardiolipin is responsible for the depressed mitochondrial respiration observed after chronic DOX treatment. By using an in vitro cell model, our results suggested that DOX treatment induces p66Shc protein up-regulation in H9c2 cardiomyoblasts and that knock-down of this protein decreases the toxicity. In the context of aging-related cachexia, our findings suggest that autophagy is operating at its full capacity in elderly individuals and can maintain a correct muscle fibers physiology in normal weight people. However, the autophagic response is not able to fulfill the requirements of muscle fibers from overweight people, leading to a progressive accumulation of alterations. We also performed studies to investigate the role of mitochondria in the toxicity of nefazone, an anti-depressant withdrawn from the market, silver nanoparticles (showing toxicity for low concentrations), brominated flame retardants, including polybrominated diphenyl ethers, and chitin-derived glucosamine biopolymer chitosan in normal and diabetic rats.

3) Mitochondrial Physiology in Tumor Physiology and (Cancer) Stem Cells: We showed that resveratrol inhibits mitochondrial respiration in breast cancer cells. We also demonstrated here for the first time that resveratrol cytotoxic effects on breast cancer cells were modulated by SIRT1 and also involved mitochondrial complex I inhibition. Importantly, we also demonstrated that resveratrol reduced the pool of breast cancer cells with stemness markers through a SIRT1-dependent mechanism. Regarding cancer stem cell physiology, we demonstrated the individual role of cytokines in cell dedifferentiation process, as well accessed the involvement of exosomes as transport vehicle. We demonstrated that whenever exosomes' release was blocked, dedifferentiation was abrogated, further proving the role of critical cytokines and of exosomes in the dedifferentiation process. We also proved that ECM was not only a mere bystander in the overall process of dedifferentiation since, besides its role in cellular anchorage, it worked as a "signal reservoir" for the exosomes carrying IL-6 and Activin A.

4) Osteoporosis and Menopause: We obtained evidence that Coumestrol improves mitochondrial function in the brain of Wistar-Han rats after E2 withdrawal, without causing any associated mitochondrial or systemic toxicity. We concluded that Coumestrol can be a good candidate to improve brain and liver mitochondrial bioenergetics during estrogen withdrawal in menopause.



METABOLIC CONTROL GROUP | *(Head: John Grifith Jones)*

OBJECTIVES

Increased fructose consumption is implicated in the surge of Type 2 diabetes and fatty liver disease in Western societies. Our group pursued the following objectives for improving our understanding about the effects of elevated fructose consumption on lipid and glucose metabolism.

a) To develop stable-isotope methodologies for quantifying liver and adipose tissue fatty acid and glycerol biosynthesis from specific precursors using a combination of deuterated water and ^{13}C-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.

b) To measure the contribution of different proportions of ingested glucose and fructose mixtures to glycemic excursions in healthy and diabetic individuals in order to determine the threshold between the beneficial and adverse effects of fructose ingestion on glycemic control.

1. One of the main objectives of the past year was to assess the metabolic phenotype of epicardial adipose tissue (EAT). 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 glucose and lipid metabolism in EAT explants from heart failure patients, with and without diabetes.

2. Moreover, new onset diabetes after transplantation (NODAT) is a metabolic disorder that affects 40% of patients on immunosuppressive agent (IA) treatment, such as rapamycin (also known as sirolimus). IAs negatively modulate insulin action in peripheral tissues including skeletal muscle, liver and white fat. However, the effects of IAs on insulin sensitivity and thermogenesis in brown adipose tissue (BAT) have not been investigated. We have analyzed the impact of rapamycin on insulin signaling, thermogenic gene-expression and mitochondrial respiration in BAT.

3. In addition, we evaluated the involvement of Mast cells (MCs) in wound healing. Diabetic foot ulceration is a severe complication of diabetes that lacks effective treatment. MCs contribute to wound healing, but their role in diabetes skin complications is poorly understood. Here we show that the number of degranulated MCs is increased in unwounded forearm and foot skin of patients with diabetes and in unwounded dorsal skin of diabetic mice. Conversely, post-wounding MC degranulation increases in nondiabetic mice, but not in diabetic mice.

MAIN ACHIEVEMENTS

1) We were able to successfully deploy a combination of deuterated water and [U-^{13}C]glucose tracers coupled with ^{2}H and ^{13}C NMR resolution of liver triglyceride ^{2}H and ^{13}C 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.

2) Insulin-stimulated 14C-glucose uptake and isoproterenol-stimulated lipolysis were carried out for the first time ever in epicardial adipocytes (EA) from heart failure (HF) patients with and without diabetes. Not only was insulin-stimulated 14C-glucose uptake impaired in EA cells but lipolysis was greatly decreased compared to subcutaneous adipocytes (SA) of these patients. We identified significant metabolic differences between EA and SA, highlighting EA as a possible therapeutic target for HF treatment.

3) In vivo treatment of rats with rapamycin for three weeks abolished insulin-mediated Akt phosphorylation in BAT. Rapamycin also inhibited norepinephrine (NE)-induced lipolysis, the expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and uncoupling protein (UCP)-1 in brown adipocytes. Importantly, basal mitochondrial respiration, proton leak and maximal respiratory capacity were significantly decreased in brown adipocytes treated with rapamycin. In conclusion, we demonstrate, for the first time the important role of brown adipocytes as target cells of rapamycin, suggesting that insulin resistance in BAT might play a major role in NODAT development.

4) Pretreatment with the MC degranulation inhibitor disodium cromoglycate rescues diabetes-associated wound-healing impairment in mice and shifts macrophages to the regenerative M2 phenotype. Nevertheless, nondiabetic and diabetic mice deficient in MCs have delayed wound healing compared with their wild-type (WT) controls, implying that some MC mediator is needed for proper healing. MCs are a major source of vascular endothelial growth factor (VEGF) in mouse skin, but the level of VEGF is reduced in diabetic mouse skin, and its release from human MCs is reduced in hyperglycemic conditions. Topical treatment with the MC trigger substance P does not affect wound healing in MC-deficient mice, but improves it in WT mice. In conclusion, the presence of nondegranulated MCs in unwounded skin is required for proper wound healing, and therapies inhibiting MC degranulation could improve wound healing in diabetes.

PUBLICATIONS

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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 four research groups/labs devoted to structural biotechnology and more generic biotechnological applications of microbiology, proteolytic enzymes and siRNA/miRNA.

Researchers in this strand are taking advantage of stem cells and of molecular therapy approaches in order to i) establish disease models to study molecular mechanisms of targeted diseases, ii) investigate new advanced nucleic acid-based therapies and viral and non-viral delivery vectors, iii) devise stem cell-based therapies for the ischemia treatment and wound healing, iv) develop novel methods for cell reprogramming and stem cell modulation/ differentiation and v) create stem cell-based assays and *in silico* approaches for drug screening.

MAIN ACHIEVEMENTS

During 2016, the groups in this strand were particularly successful in attracting competitive funding from several framework/ operational programmes, namely Horizon2020, ERDF regional (CENTRO-2020) and national (COMPETE-2020) operational programmes (within Portugal 2020), Santa Casa da Misericórdia de Lisboa and INFARMED; other funding sources include the ERA-Nets Euronanomed II and JPND-Joint Programme on Neurodegenerative Disease Research, besides the French Muscular Dystrophy Association (AFM, France), the National Ataxia Foundation (NAF, USA) and the BioBlast Pharma (Israel). Several funded projects include partnerships with Hospitals/SMEs/companies (e.g., Hospital Rovisco Pais, Hospital Centre of the University of Coimbra) and other non-academic entities. The strand counts with 5 FCT Investigator awardees and an on-going ERC grant, the PI of which was recently appointed as ERA Chair (a H2020-WIDENING scheme).

Overall, research efforts originated more than 100 publications in peer-reviewed international journals (2016 issues), the majority resulting from fruitful collaborations with nearly a hundred different institutions (academic and otherwise) from over a dozen different countries. Of those, many involved the University Hospitals (CHUC) and counted with the participation of Portuguese institutions (including companies) other than those affiliated with the University of Coimbra. As for the international collaborations, Brazil and Spain feature the largest co-authorships, followed by the USA, UK, Italy, Germany and Canada. The majority of the publications are Q1, of which several papers in high-impact journals (IF>5), including Nature Communications, Brain, Annals of Neurology, Development Cell, Acta Biomaterialia, Biomaterials, Biochim Biophys Acta, Neuropsychopharmacology, Scientific Reports, Neurobiol Dis, Journal of Controlled Release, Brain Behavior and Immunity, Cardiovascular Research, Cell Death and Differentiation, Oncotarget or Journal of Antimicrobial Chemotherapy which put in evidence not only the quality but also the diversity of addressed subjects and multidisciplinary nature of the ongoing research.

Other performance indicators include the request for and/or concession of IPR protection: a US patent on *Use of umbilical cord blood derived exosomes for tissue repair*, an international patent on *Processes for production of acylated intermediates of essential microbial polysacharides*, and two provisional patent applications on *Compositions for reprogramming cells into dendritic cells or antigen presenting cells* and a *New method for efficient production and purification of maltose-1-phosphate (M1P) and related compounds*. Translation and knowledge transfer in this research line has already given rise to the spin offs Exo-T (Exogenus Therapeutics), BRT (Blood Reprogramming Technologies) e NoMicro.

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 one mandatory and one elective module of the 2016 edition of this programme. Also worth mentioning is one FP7 Marie-Curie Training Network (ITN) (*CAFFEIN)* running in 2016 featuring groups of this strand as participants.

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.

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Maria José Gonçalves	PhD
Maria Teresa Batista	PhD
Nuno Ricardo Mendonça	PhD
Renato Pires	PhD
Célia Cabral	Post Doctoral Fellow
Ana Alexandra Miranda	PhD Student
Mª Manuel Mendes	PhD Student

BIOTECHNOLOGY

MICROBIOLOGY OF EXTREME ENVIRONMENTS GROUP

Milton Simões da Costa	PhD (*Head of Group*)
Ana Rita Polónia	Post Doctoral Fellow
Rita Severino	PhD Student

MOLECULAR BIOTECHNOLOGY GROUP

Carlos José Costa Faro	PhD (*Head of Group*)
Euclides Pires	PhD
Isaura Simões	PhD
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VECTORS AND GENE THERAPY | *(Head: M. Conceição Pedroso Lima)*

OBJECTIVES

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

Our studies on non-viral vectors have been mainly focused on the evaluation of the potential of novel lipid-based nanosystems and polymeric nanoparticles in gene therapy strategies for the treatment of both cancer and neurodegenerative disorders, and for the development of vaccines.

Non-viral vectors, such as cationic liposomes, stable nucleic acid lipid particles and cell-penetrating peptides have been explored as carrier systems to deliver nucleic acids, including plasmid DNA encoding therapeutic proteins, as well as antisense oligonucleotides, siRNAs and anti-miRNA locked nucleic acids, aiming at promoting silencing of known oncogene proteins and both cancer-related and pro-inflammatory miRNAs. The group is interested in investigating the anti-tumoral effect of gene therapy strategies, either *per se* or in combination with chemotherapeutic agents, both *in vitro* and in animal models for different types of cancer. A lipidomic approach to cancer has been developed using RNA interference to unravel the role of membrane lipids in cancer cell signaling and chemoresistance. In addition, non-viral vectors are currently being developed to study the role of miRNAs in neuroinflammation, aiming at promoting neuronal survival by targeting inflammatory and neurodegenerative pathways.

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

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

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

The group also addresses a therapeutic vaccine for hepatitis B (oral and sc) using antigens (protein or DNA) encapsulated in polymeric nanovectors, to target the lymphoid structures of the mucosal immune system. In this regard, new glucan-based delivery systems able to encapsulate hepatitis B antigen have been developed and tested (*in vitro* and *in vivo*).

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 metastic 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 Aβ 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-alfa and *in vivo* the NPs revealed to be an excellent HBsAg adjuvant.

STEM CELL BIOTECHNOLOGY | *(Head: Lino Ferreira)*

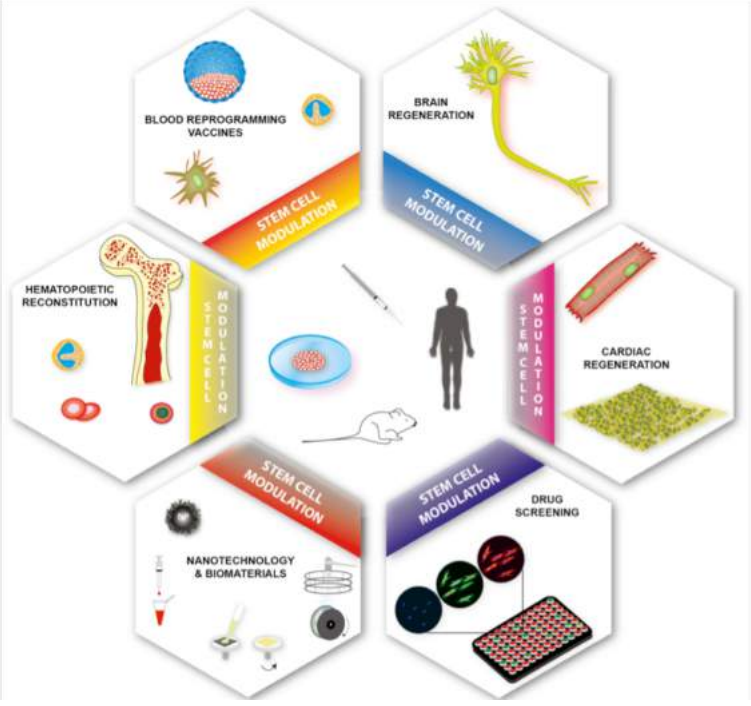
OBJECTIVES

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.



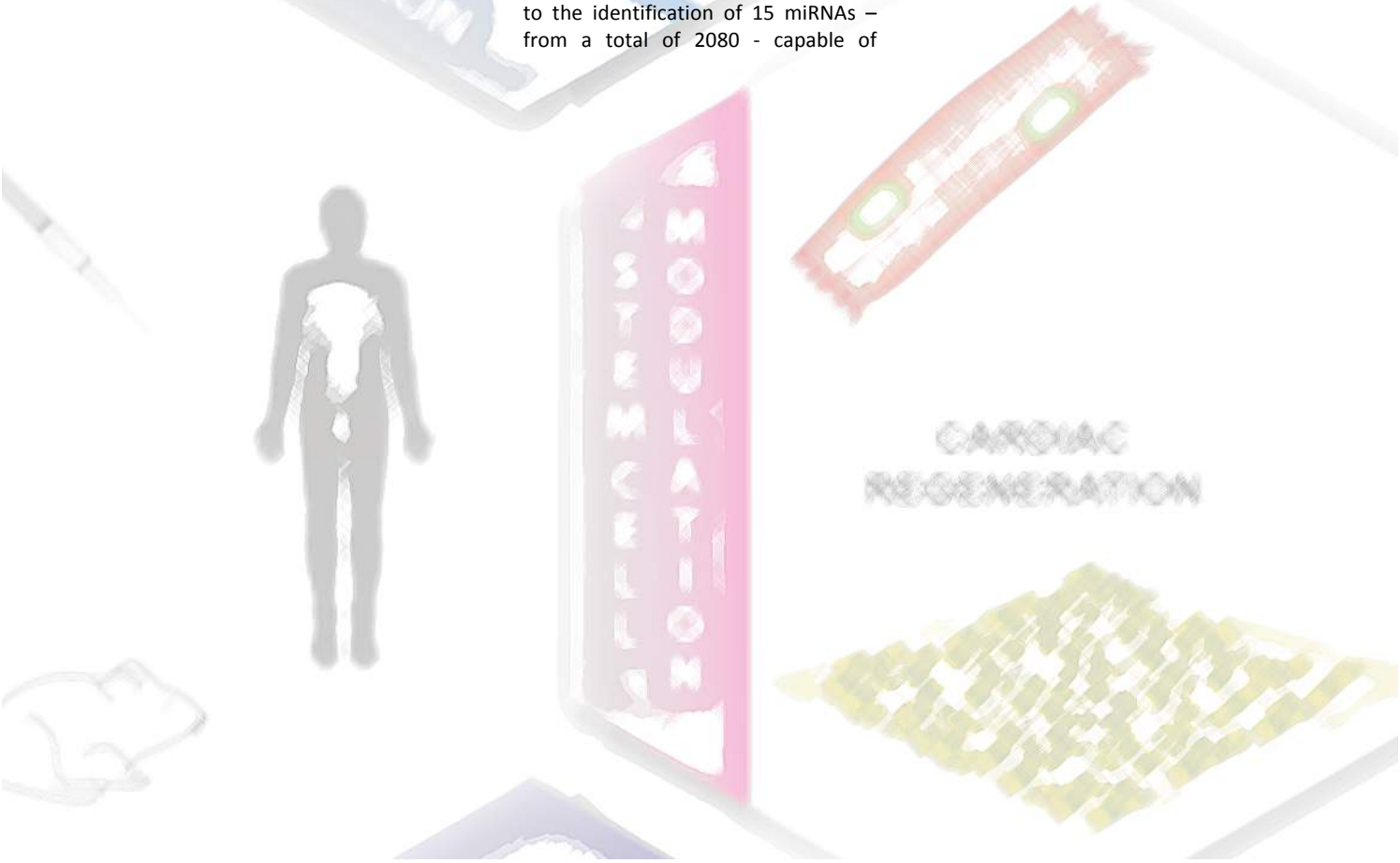
MAIN ACHIEVEMENTS

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 drug screening? (ii) can we modulate stem cell niche by nanomaterials? what are the miRNAs involved in (stem) cell survival after transplantation to ischemic sites?**

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. Progeria is a rare, progressive aging disease in children that leads to premature death. 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 in preparation). 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.

To tackle the second question we have synthesized new advanced nanomaterials to release proteins within cells. Intracellular delivery of proteins is extremely useful for the manipulation of cellular processes and cell reprogramming. However, protein transduction has been hindered by the poor membrane permeability of most of the proteins. In the past decade, different nanoformulations have been developed for the delivery of proteins to cells. However most of these strategies are based on the passive diffusion of the protein from the nanocarrier or on the enzymatic degradation of the nanoformulation. Despite the successful intracellular delivery of functional proteins reported in different studies, so far no formulation has the capacity to orchestrate the intracellular delivery of multiple proteins with remote control. This is an important issue in many biological applications such as cell reprogramming. Recently, we have developed a formulation able to orchestrate the release of 2 or more proteins within the cell from the same nanocarrier using a single trigger (Manuscript in preparation).

To tackle the third question 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 explored the use of nanoformulations to deliver both miRNAs to the cell of interest and showed that we can deliver very efficiently both miRNAs and, more importantly, we can do so using light-responsive nanoparticles, endowing us with the capacity to deliver them on-demand. We are currently preparing the in vivo studies to demonstrate the pro-survival effect of the two microRNAs in collaboration with the group of Seppo Herttuala (Finland) using adeno-associated virus to deliver the miRNA (Finland), Perpétua-Pinto-do-Ó (University Porto) using the above mentioned nanoparticles for delivery and Eugénia Carvalho using direct administration of the miRNAs.



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

OBJECTIVES

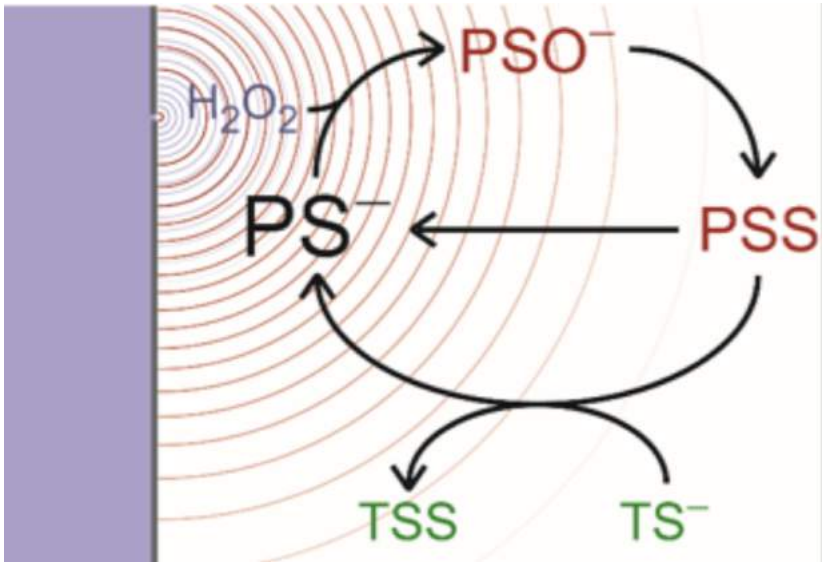
Research at the Computational & Systems Biology Group is distributed by the following three research lines:

1. Organization principles of biochemical systems. The main goal of this research line is to discover, understand and exploit generic rules (organization principles) that hold across processes, cell types and organisms. We are focusing on (a) rules relating the design (i.e. naturally evolved molecular mechanisms) of biochemical networks to their function, and (b) explaining generic phenomena of cell physiology (e.g. growth laws, stress responses, hormesis) from fundamental principles of physical chemistry and evolution. We envisage that the network-structure / function relationships in (a) will play in biomedicine and bioengineering a role analogous to that of QSAR in pharmacology. With regards to (b) we are finding that some apparently complex phenomena represent optimal cellular responses under physical-chemical constraints that apply universally. Importantly, these phenomena can be predicted without a detailed knowledge of mechanisms, supporting the application of coarse-grained constraint-based models to help understand the considerations and trade-offs that shape cell fates.

Main objects of interest in this research line are stress responses and redox signaling. 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, and that bioaccumulation may be limited by several distinct steps in the permeation pathway. 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 very fundamental computer-science methods that vastly 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

Hydrogen peroxide (H_2O_2) signaling through the peroxiredoxin (Prx) / thioredoxin (Trx) / Trx reductase system (PTTRS) is important in cell proliferation, neuroprotection, angiogenesis and tumorigenesis. However, the fundamental questions presented below remain unclear.

A. What are the physiologically relevant H_2O_2 concentrations?

To address the first question we used wound-generated inflammation in the zebra fish as a model for physiological H_2O_2 generation. We injected the tail-wounded fish larvae with an engineered *Escherichia coli* strain containing a synthetic gene circuit [Rubens *et al.* (2016) *Nat. Commun.* 7:11658] that retains memory of the maximal extracellular H_2O_2 concentration to which the bacterial lineage was exposed and reports it as a fluorescence color code. Fluorescence microscopy imaging of the emergence of fluorescence in the living animal revealed that extracellular H_2O_2 concentrations in excess of 20 mM are attained near the wound margins. Experiments were carried out at Dr. Miguel Godinho Ferreira's lab (IGC). Studies towards the development of methodologies to determine absolute basal *intracellular* H_2O_2 concentrations are ongoing.

B. How are H_2O_2 signals transduced in the cytoplasm of eukaryotic cells?

We used reaction-diffusion mathematical models to examine if the leading hypotheses to answer this question are consistent with the properties of the PTTRS' proteins. The study [Travasso et al. (2017) *Redox Biol.* 12:233-245] falsified two of the hypotheses and supported a signaling mode through spatially localized redox relays, whereby Prs act as the H_2O_2 sensors, maintain strong gradients, and relay the signal to effector proteins (Figure).

C. Are the responses of the PTTRS to H_2O_2 supply reproducible over cell types, and what are the underpinnings of eventual differences?

Based on a collection of quantitative proteomics datasets we predicted the responses for erythrocytes, hepatocytes, eleven human cell lines, and *Saccharomyces cerevisiae* [Selvaggio, Coelho & Salvador, submitted]. Erythrocytes, hepatocytes and the hepatoma-derived cell line show a response where both Prx and Trx accumulate in disulfide form over a wide range of intermediate H_2O_2 supply rates (v_{sup}). Remarkably, all other 10 cell lines show a stereotypic response where at a critical v_{sup} the Prx become hyperoxidized, and near-maximal Prx oxidation to disulfide occurs only over a narrow v_{sup} range. This response optimizes a trade-off between redox-relay signaling and Prx-mediated proteostasis. It ensues when the TrxR activity and/or the maximal Prx-SS reduction rate approach the maximal Prx-SS production rate. Strong correlations among the concentrations of several proteins over cell lines maintain this balance despite considerable composition heterogeneity. The response predictions for erythrocytes and HEK293 cells are supported by experimental observations. The yeast shows a distinct response, where the Prx Tsa1 accumulates in sulfenate form over a wide range of intermediate v_{sup} . This is due to an exceptional stability of Tsa1's sulfenate. Altogether, the results provide a framework to understand how the PTTRS integrates multiple modes of signaling and antioxidant protection, and how it fails to do so in disease.

We are applying a combination of molecular dynamics and kinetic modeling to help connecting drugs' molecular features to (passive) membrane permeability to ability to cross the blood-brain barrier. Work over 2016 focused in the development of methods to estimate permeation rate constants from molecular dynamics (MD) simulations. We performed a systematic comparison of alternative approaches to the quantitative assessment of translocation rate constants across lipid bilayers by MD based on umbrella sampling simulations. The best approach devised uses pre-exponential A factors calculated using frequencies obtained from relaxation simulations where the solute is initially placed in the position of maximal free energy along the translocation path.

MEDICAL MICROBIOLOGY | (*Head: Teresa Gonçalves*)

OBJECTIVES: MEDICAL MICROBIOLOGY:

A. Characterisation of melanin synthesis, and identification of melanin synthesis inhibitors as antifungal candidates

B. Purines and purinergic receptors impact in fungal gut colonization.

C. Identification of bioactive compounds in algal extracts

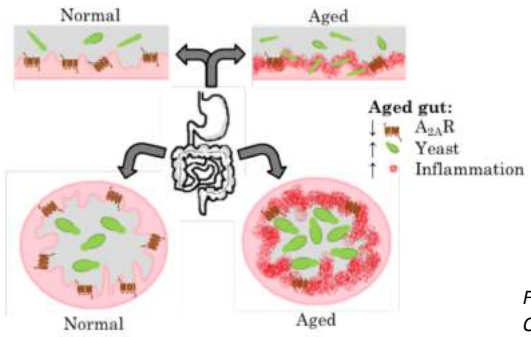


Fig. 1 - Graphical Abstract - Rodrigues et al., 20. Oncotarget. doi: 10.18632/oncotarget.11760.

MAIN ACHIEVEMENTS: MEDICAL MICROBIOLOGY

A. Before we proved that the production of melanin is a salvage mechanism against antifungals. During 2016, it was characterized the forms of melanin produced by several species in filamentous fungi and we identified one compound that inhibits the synthesis of melanin and can be used as an antifungal (manuscript in preparation) (2 papers)

B. An in vivo murine model of gut infection by *C. albicans* was implemented. With this we proved that the elderly are less able to deal with gut microrganism overgrowth due to a lower density of adenosine A2A receptors (one PhD thesis, 2 MSc thesis, two papers).

C. It was identified the compounds in one of the bioactive algal extracts with a possible inhibitory effect over MMD-Chs enzymes, essential for filamentous fungi growth and infection (two papers).

OBJECTIVES: MOLECULAR MYCOBACTERIOLOGY AND MICROBIOME

Research at the Molecular Mycobacteriology and Microbiome Group evolved beyond the study of metabolic pathways of mycobacterial pathogens, to an area focused on the intersection of the human microbiome and chronic diseases. In addition to the 1) identification of novel enzyme activities in mycobacterial pathogens, other important goals are 2) to associate specific gut microbiota to the onset of Parkinson's Disease (PD) and 3) to unravel specific microbial signatures linked to the progression of chronic diabetic foot ulcers. For the successful implementation of these recent projects we have established collaborations with groups at CNC.IBILI focused on these pathologies, which allowed us to secure important funding from INFARMED, Santa Casa da Misericórdia and from Centro2020/FEDER, which will help us decipher microbial biomarkers associated to these chronic diseases and to find the way to new preventive and therapeutic approaches.

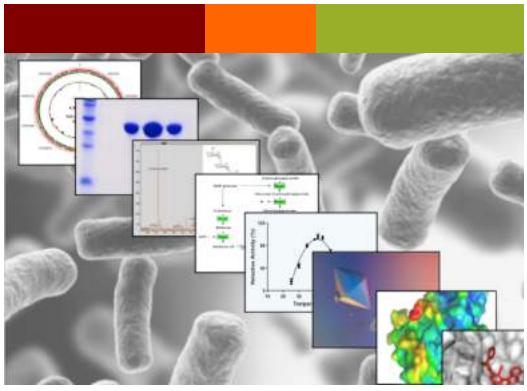
1) New mycobacterial targets

2) Parkinson's gut microbiome – neurotoxin-producing microbiota

3) Diabetic wound healing - ulcer microbiome dynamics

MAIN ACHIEVEMENTS: MOLECULAR MYCOBACTERIOLOGY AND MICROBIOME

The Molecular Mycobacteriology and Microbiome Group deciphered the functions of genes for the biosynthesis of polymethylated polysaccharides of Mycobacterium tuberculosis and of nontuberculous mycobacteria, where they modulate fatty acids biosynthesis and cell envelope assembly. In light of the proposed essential roles of these enzymes for mycobacterial survival, we characterized their functions and structures, laying experimental foundations for drug design. To find answers to several long-lasting questions about these polysaccharides' structures in vivo and immune responses to their presence, as well as about their potential use as tools for early diagnosis of mycobacterial disease, we assembled a multidisciplinary team of molecular microbiologists, biochemists, crystallographers and immunologists to unravel their biological roles and possible applications, which will now allow training of our students in three different Institutes and on different subjects. In a different line of research in collaboration with the Obesity Diabetes and Complications Group at CNC, we designed a strategy to underpin microbial signatures associated to the progression of chronic diabetic foot ulcers in diabetic patients. This proposal allowed us to secure important funding by INFARMED - Fundo para a Investigação em Saúde, crucial for the comprehensive characterization of microbial populations during wound progression. In the scope of a recently established collaboration with the Mitochondrial Regulation of Molecular Mechanisms of Cellular Degeneration Group at CNC we were able to detect a subset of neurotoxin-producing bacteria in the gut microbiota of Parkinson's patients. These exciting preliminary results allowed us to propose a new hypothesis for the etiology of PD, which was the basis for a grant proposal selected as the winner of the Mantero Belard Prize in Neuroscience 2016 by Santa Casa da Misericórdia.



MEDICINAL CHEMISTRY & DRUG DISCOVERY | *(Head: Maria Luísa Sá e Melo)*

OBJECTIVES

1. Steroids comprise a wide range of structurally related compounds with important functions *in vivo* and have shown a great therapeutic value due to anticancer, antiviral, antimicrobial and anticonvulsant activities. Following our work on steroids, with the objective to use new anti-convulsant drugs, acting at the $GABA_A$ receptor and mimicking the key endogenous allopreganolone, to avoid the well- known secondary effects of the classical drugs to treat epilepsy, a new library has been planned, as well as in vitro and in vivo biological experiments.

2. Pentacyclic triterpenoids are a class of pharmacologically active and structurally rich natural products with privileged motifs for further modifications and SAR analyses. We focused on the anticancer activity of the semisynthetic ursane triterpenoids derivatives of ursolic and asiatic acid.

3. 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 aim.

4. Loss of antibiotic effectiveness resulting from bacterial resistance is a global threat. New antibacterial molecules are sorely needed to fight the pan-resistant bacteria that are increasingly emerging. Our objectives are: to characterize resistance mechanisms and to assess their molecular epidemiology; to develop new molecules with potential antimicrobial activity and reduced toxicity.

5. Additionaly, we also focused on the anti-Leishmania activity of semisynthetic lupane triterpenoids derivatives of betulin and betulinic acid. Effects on the cell cycle, apoptosis/necrosis events, morphology and DNA integrity were also planned.

MAIN ACHIEVEMENTS

1. A library of new 21- derivatives of pregnanes, having in common two alternative functionalities on ring A, an olefin and an oxirane, each of them in different positions, has been synthesised and evaluated in vitro and in vivo. These experiments have put in evidence a novel structural modification in ring A. Indeed, a pregnane with a 2alpha,3alpha-epoxy ring revealed ability to bind the GABAAR, rendering this novel structural modification interesting for the search of neuroactive steroids. *In vivo* results of the epoxides show, however, that they are metabolised in the body within 2 h, which desserves a further investigation towards more drug-like compounds.

2. A series of novel fluorinated asiatic acid (AA) derivatives were successfully synthesized, tested for their antiproliferative activity against HeLa and HT-29 cell lines, and their structure activity relationships were evaluated. The great majority of fluorinated derivatives showed stronger antiproliferative activity than AA in a concentration dependent manner (Eur J Med Chem, 2016). A series of new A-ring cleaved UA derivatives were prepared and evaluated for their antiproliferative activity in non-small cell lung cancer (NSCLC) cell lines using 2D and 3D culture models.

3. 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)

4. The results obtained were a continuation of the previous studies on antimicrobial resistance The main achievements were: 1. Multidrug resistant bacteria carrying carbapenemases determinants with potential for dissemination were found in community patients that never were hospitalized; 2. We discovered for the first time in Portugal colistin resistance associated to the plasmidic gene *mcr-1* in Salmonella enterica strains isolated from food producing-animals, an threat for human health since colistin is one of the last therapeutic options in infections caused by extremely resistant bacteria; 3. Antimicrobial resistance and virulence were characterized in Salmonella spp. and Escherichia coli from isolates collected form food producing animal smaples; 4. *Streptacidiphilus jiangxiensis* did not show antimicrobial activity in the tested conditions and our hypothesis that it might synthesize a macrolide-like compound was not validated.

5. The anti-*Leishmania* activity of new semisynthetic lupane triterpenoids derivatives of betulin and betulinic acid were evaluated. The analysis of structure/activity relationship (SAR) allowed identifying the chemical modifications on betulin and betulinic acid derivatives that impact on biological activity against *Leishmania infantum*. In the derivatives of betulin, it was found that carbamates triazoles in C3 and/or C28 positions increased anti-*Leishmania* activity; also the modifications in the C20 and C29 positions had a positive impact on the anti-*Leishmania* activity; and that the acetylation of the position C3 and/or C28 decreased the activity of the derivatives. In relation to betulinic acid derivatives it was showed that oxidation of the hydroxyl group at C3, as well as dehydrogenation C1 / C2 increase the leishmanicidal activity of the derivatives. We also showed that combined-therapy including efavirenz and miltefosine could be alternative options for treating Leishmaniasis and Leishmania/HIV co-infections.

PHARMACOMETRICS | (*Head: Amílcar Falcão*)

OBJECTIVES

The Paharmacometrics 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 and their therapeutic and toxic effects.

Thus, Pharmacometrics Group early predicts kinetic and dynamic behaviors of drug candidates employing a wide methodological approach including *in silico* and *in vitro* models previously herein developed. Presently, we carry out these techniques to estimate drug human fraction absorption, the plasma protein binding and the ability of the compounds to reach the brain; we can also identify substrates, inhibitors and inductors of multi-drug resistance proteins (including P-glycoprotein and breast cancer resistant proteins) that compromise the disposition of a compound in the body and consequently their pharmacological effects and interaction potential. Resorting to non-clinical *in vivo* studies, the team members characterize the bioavailability and biodisposition of new therapeutic drugs, evaluating their concentrations in plasma and tissues (including liver, kidney, brain, etc).

Furthermore, our scientific breakthroughs have also been translated into novel therapeutics for clinical evaluation in patients. In fact, Pharmacometrics Group intends to correlate demographic, physiologic, pharmacological and genetic with administered doses and corresponding plasma drug concentration and pharmacodynamics prfiles, in order to develop and validate new practical technological tool to select the best therapy and/or treatment posology based on a patient's to minimize harmful side effects and ensure a more successful clinical outcome, coupled to lower costs compared with a "trial-and-error" approach.

The Pharmacometrics group focus not only on new chemical drug candidates, but also on bioactive fractions and new compounds extracted from plant sources. Indeed, we characterize and isolate extracts, bioactive fractions and new compounds from plant sources to further evaluate *in vitro*/*in vivo* their biological activities, citotoxicity and pharmacokinetics. Besides testing this natural drug discovery approach as a new preventive and therapeutic strategy, we also develop new pharmaceutical formulations and investigate new drug administration strategies, namely the intranasal administration of drugs to directly deliver therapeutic agents into the brain. Thus we assessed *in vivo* the pharmacokinetics of antiepileptic drugs, carbamazepine and lamotrigine, after intranasal and intravenous administrations in order to investigate whether a direct transport of the drug from nose to brain may be involved.

Briefly:

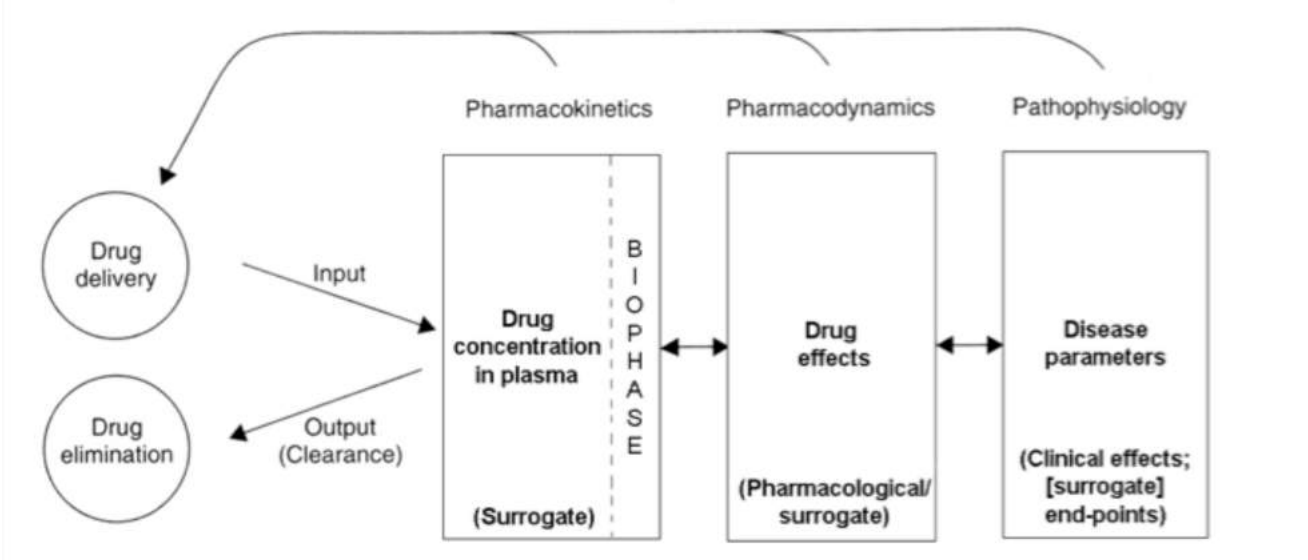
- HTS methods that estimate drug human fraction absorption, plasma protein binding, ability to cross BBB;

- MTS methods to identify substrates and inhibitors of efflux proteins;

- Development of *in vivo* pharmacokinetic studies;

- Characterize and isolate extracts, bioactive fractions and new compounds from plant sources;

- Develop new pharmaceutical formulations and investigate new drug administration strategies.



MAIN ACHIEVEMENTS

- To complement the in vitro technique of PAMPA presented in the previous report, during 2016, cellular models were developed and validated in order to predict the mediated transported of new chemical entities through the blood-brain barrier. These techniques have been well succeeded to a wide variety of compounds (including drugs for Parkinson Disease, antiepileptic drugs and anti-leishmania, among others).

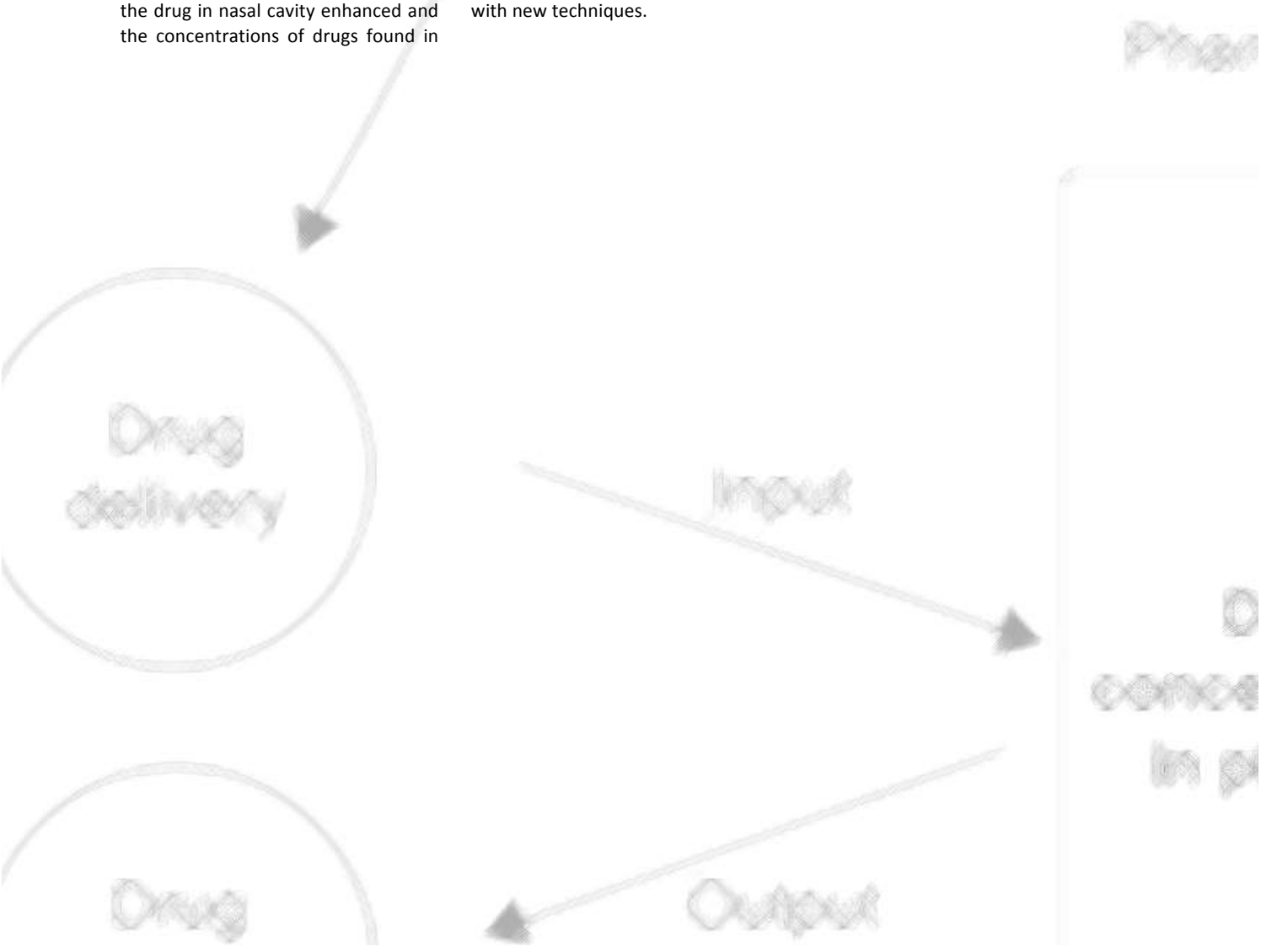
- To assess the potential of intranasal administration of ciprofloxacin to treat chronic rhinosinusitis, the pharmacokinetic parameters of the drug following intranasal and intravenous administrations to rats in plasma, olfactory bulb and nasal mucosa of anterior and posterior nasal regions were compared. Results were very promissory as after the intranasal administration of a thermoreversible in situ gel loading ciprofloxacin, the residence time of the drug in nasal cavity enhanced and the concentrations of drugs found in the site of infection was considerably higher than after intravenous administration. Moreover, the systemic absorption and lateral effects were negligible.

- Pharmacokinetics of opicapone, a third-generation COMT inhibitor recently approved for Parkinson's disease, was analysed after single and multiple oral administration at higher doses than those recurrently used with no evident accumulation after multiple dosing.

- In parallel, our internationally well-recognized know-how on developing and full validating bioanalytical methodologies to quantify distinct compounds (drugs, metabolites and other substances) in complex biological and samples (plasma, erythrocytes, brain, liver, macroalgae…) by liquid chromatography coupled to different detectors (e.g. UV-VIS, MS/MS…) after sample pre-treatment still increasing with new techniques.

- Researches of this group demonstrated that several plant extracts and compounds obtained from aromatic and medicinal plants, particularly essential oil´s terpenoids and phenolic compounds inhibited nitric oxide (NO) production, through modulation of MAPK and NF-κB signaling, suggesting their potential as source of compounds with anti-inflammatory properties. As inflammation is pointed out in preclinical studies as a major mechanism in the pathogenesis of chronic diseases, namely diabetes, hypertension and cancer, these results allowed the establishment of multiple research possibilities.

- Overall, significant antioxidant and antimicrobial (antifungal and antibacterial) properties were verified for different extracts, fractions and compounds, suggesting their potential application for pharmaceutical, cosmetic or alimentary industries.



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. The study the biodiversity of the brine and brine-seawater interface of Lake Medee, with high sodium and chloride levels to obtain enzymes of biotechnology value.

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 achaea from extreme environments with the purpose of finding new organisms that have some biotechnological potential. These organisms have different origens that also contribute to our knowledge of microbial diversity and their metabolic and biosynthetic processes.

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: Carlos Faro)*

OBJECTIVES

Our group has a main interest on proteolytic enzymes and their role in regulating complex and highly dynamic protein networks, in addition to their degradative function and biotechnological potential. We have also been interested on the structural/biophysical characterization of neuronal proteins involved in human brain diseases. Also, activities have been developed on characterization of pollen proteases and their role on inflammatory and immunological response. An emerging research line concerns the exploitation of different rickettsial survival strategies - particularly, proliferation in professional phagocytes - and correlation with rickettsial pathogenesis. Our activities are subdivided into 5 focus areas:

Biochemistry, biology and biotechnology potential of plant aspartic proteases (APs)

Proteases exert critical roles in different plant developmental processes as well as stress responses. Our work focuses on APs, the second largest class of plant proteases. Recent studies implicate APs as important players in developmental processes/stress responses. Based on the huge potential of system-wide proteomic approaches, our goal is to generate an integrated platform on proteases, their substrates, and their function - thereby enabling the elucidation of the biological roles of APs in plants.

Biochemistry and biology of prokaryotic aspartic proteases (APs) and their role as potential therapeutic targets in pathogenic Bacteria

The relevance of proteolytic events for bacterial pathogenicity and the progressive increase in antibiotic resistance among pathogenic bacteria contribute to positioning proteases as potential candidate targets for the development of alternative antibacterial strategies. Our work has provided the first unequivocal documentation of pepsin and retropepsin-type of proteases in prokaryotes. Our goal is to generate an integrated platform for the discovery, characterization (biochemical/structural/functional) and evaluation of "targetability" of APs from different (pathogenic) bacteria.

Structural and biophysical characterization of neuronal proteins involved in human brain diseases

Through the study of the structure and the dynamics of interaction of neuronal proteins with either protein- (PPI) or carbohydrate-interactors (PCI), we aim at unravelling the role of these PPIs and PCIs on the molecular mechanisms underlying different neuronal diseases and further explore if/how these interactions can be eventually modulated to ameliorate disease states. Our focus is on the structural /biophysical characterization of the interaction of laforin (a human phosphatase) and carbohydrates, as this protein is involved in Lafora disease; as well as on the detailed structural/interactomics' characterization of SAPAP3, a scaffolding protein, suggested to be involved in OCD.

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

The underlying mechanisms governing differences in pathogenicity by different species of Rickettsia are still to be understood. In this research line we aim to investigate novel mechanisms underlying rickettsiae-macrophage tropic and non-tropic interactions and their correlation with rickettsial pathogenesis.

The role of pollen proteases in allergic respiratory disorders.

Pollens are important triggers for allergic disorders. We have established that pollen grains, with distinct allergenic abilities, release proteases that are able to compromise epithelium barrier integrity by disruption of transmembrane adhesion protein. On-going activities include purification and functional characterization of proteases to evaluate their contribution on immunologic and inflammatory response.

MAIN ACHIEVEMENTS

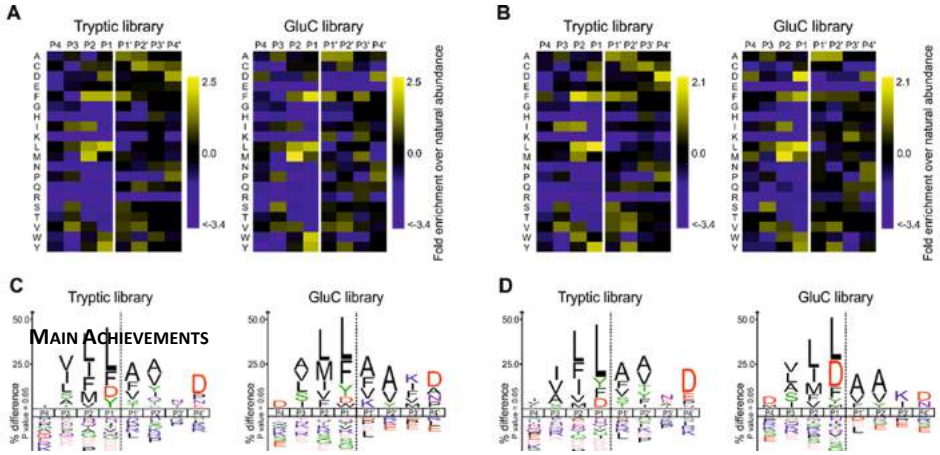


Fig. 1 – Shewasin D and shewasin A specify preferences profiled by PICS. Graphical representation of shewasin D (A and C) and shewasin A (B an D) specificity profiles by Heatmaps and IceLogos. Results are from Tryptic and GluC peptides libraries derived from a Homo sapiens proteome (THP1 cells) incubated with recombinant shewasin D or shewasin A at a ratio of 1:40 (enzyme/library). Leal e tal. 2016. Scientific Reports. 6:23869. DOI:

1. Biochemistry, biology and biotechnology potential of plant APs

The structure of synthetic cardosin produced in K. lactis was obtained and comparative specificity profiling performed (using PICS). (Manuscript in preparation).

We pursued with the functional characterization of 2 atypical APs from Arabidopsis. Our results suggest that these genes may be involved in two different regulatory mechanisms of lateral root formation. These results unveil a new role for APs in the regulation and adaptation of root development in Arabidopsis under normal growth conditions as well as under abiotic stresses. High-throughput proteomics studies were performed to understand the biological role of both proteases. This work is part of the PhD Dissertation Thesis of André Soares, submitted for defense. (Manuscript in preparation).

2. Biochemistry & biology of prokaryotic APs and their role as potential therapeutic targets in pathogenic Bacteria

We determined the first specificity analysis on prokaryotic pepsin-like proteases as well as evidences that they are expressed in vivo. Both shewasin D and shewasin A showed remarkable similarities with eukaryotic pepsins, in particular with BACE-1, thereby confirming their phylogenetic proximity. (Leal A.R., *et al* (2016) Scientific Reports, 6:23869, DOI: 10.1038/srep23869; Q1 Multidisciplinary Sciences).

3. Structural & biophysical characterization of neuronal proteins involved in human brain diseases

Laforin is a human dual-specificity phosphatase (DSP) involved in glycogen metabolism regulation containing a carbohydrate-binding module (CBM). We reported a thorough biophysical characterization of laforin-carbohydrate interaction using soluble glycans. (Dias D.M., *et al* (2016). Biochemical J. 473, 335–345., DOI 10.1042/BJ20141555; Q2 Biochemistry & Molecular Biology).

Regarding SAPAP3, and to help in the elucidation of the molecular mechanisms that associate SAPAP3 with OCD and schizophrenia, a functional characterization was performed, by the analysis of SAPAP3 domain 19 interactome, along with the interactome from two SAPAP3 mutants. Results from these analysis revealed an association between SAPAP3 and mitochondria-related components. This is the first study presenting a novel role for SAPAP3 through the identified interaction with mitochondria components. (This work is part of the PhD dissertation: "Biochemical and interactomic characterization of SAPAP3 - a scaffolding protein involved in obsessive-compulsive disorder", defended by Ana Sofia Lourenço).

4. 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 are interested in understanding in detail the role of macrophages in rickettsial pathogenesis and, so far, we have been able to demonstrate that there is a dramatic difference in the intracellular fate of a pathogenic member of the Spotted Fever Group Rickettsia (Rickettsia conorii) versus a non-virulent member (Rickettsia montanensis) to proliferate in THP-1 macrophage-like cells. (Curto P., *et al* (2016) Front. Cell. Infect. Microbiol. 6:80, doi: 10.3389/fcimb.2016.00080. (Q1 Immunology & Microbiology).

5. ETW 2018 -2The role of pollen proteases in allergic respiratory disorders.

Serine and metalloproteases isolated from *C. album*, *P.judaica* and *P.sylvestris* were tested on Calu-3 cells grown in an air-liquid interface system. The disruption of intercellular complexes was identified using immunoblotting and immunofluorescence assays. PAR- 2 activation and subsequent interleukin release were monitored using single-cell imaging and flow cytometry, respectively. These proteases disrupted the several transmembrane adhesion proteins. Pollen proteases from *C. album* and *P.sylvestris* were capable of activating PAR-2. Additionally, all proteases increased the release of IL-6 and IL-8.

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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.

PUBLICATION

Domingues P, Tablas MG, Otero A, Pascual D, Ruiz L, Miranda D, Sousa P, Gonçalves JM, Lopes MC, Orfao A and Tabernero MD. (2016) Tumor infiltrating immune cells in gliomas and meningiomas. *Brain Behavior and Immunity, vol. 53: 1-15.*

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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), Alexandra Amaral (CNC), Renata Tavares (CNC), Alexandra Carvalho (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 in 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.

There 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 in order to identify more functional populations of sperm.

Two 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.

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).

PUBLICATIONS

Amaral S, Tavares RS, Baptista M, Sousa MI, Silva A, Escada-Rebelo S, Paiva C & Ramalho-Santos J. (2016) Mitochondrial functionality and chemical compound action on sperm function. *Current Medicinal Chemistry* 23:3575-3606.

Tavares RS, Escada-Rebelo S, Correia M & Ramalho-Santos J. (2016) The non-genomic effects of endocrine-disrupting chemicals on mammalian sperm. *Reproduction* 151:R1-R13.

INTERNACIONALIZATION

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

PROJECTS IN COLLABORATION

NEUROSCIENCE, VISION AND BRAIN DISEASES STRAND

Synapse Biology Group

Participation in the European Neuroscience Campus joint PhD program. Ana Luisa Carvalho supervises Blanka Kellermayer who is a student in the program (Co-supervied by Laurent Groc, University of Bordeaux).

Collaborative publications with international groups:

Vieira MM, Schmidt J, Ferreira JS, She K, Oku S, Mele M, Santos AE, Duarte CB, Craig AM, Carvalho AL (2016) Multiple domains in the C-terminus of NMDA receptor GluN2B subunit contribute to neuronal death following in vitro ischemia. *Neurobiol Dis* 2016, 89:223-234.

Pinto MJ, Alves PL, Martins L, Pedro JR, Ryu HR, Jeon NL, Taylor AM, Almeida RD (2016) The proteasome controls presynaptic differentiation through modulation of an on-site pool of polyubiquitinated conjugates. *J Cell Biol* 2016 Mar 28;212(7):789-801.

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Sensoy O, Moreira IS, Morra G (2016) Understanding the differential selectivity of arrestins toward the phosphorylation state of the receptor. *ACS Chem Neurosci* 7 (9): 1212–1224.

Torsello M, Pimenta AC, Wolters LP, Moreira IS, Orian L, Polimero A (2016) General amber force field parameters for diphenyldiselenides and diphenylditellurides. *J Phys Chem* A, 120, 4389-400.

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Mollereau B, Rzechorzek NM, Roussel BD, Sedru M, Van denBrink D, Bailly-Maitre B, Palladino F, Medinas DB, Domingos PM, Hunot S, Chandran S, Birman S, Baron T, Vivien D, Duarte CB, Ryoo HD, Steller H, Urano F, Chevet E, Kroemer G, Ciechanover A, Calabrese EJ, Kaufman RJ, Hetz C (2016) Adaptive Preconditioning in Neurological Diseases Therapeutic Insights from Proteostatic Perturbations. *Brain Res.* 1648(Pt B):603-616.

JT Costa, M Mele, MS Baptista, JR Gomes, K Ruscher, RJ Nobre, LP de Almeida, T Wieloch, CB Duarte (2016) Gephyrin Cleavage in In Vitro Brain Ischemia Decreases $GABA_A$ Receptor Clustering and Contributes to Neuronal Death. *Mol Neurobiol.* 53, 3513-3527.

Redox Biology and Brain Sensing

Barbara S Rocha, Rui M Barbosa, Jon M Lundberg, Rafael Radi, and João Laranjinha (2016) Role of nitrite, urate and pepsin in the gastroprotective effects of saliva. *Redox Biology* 8, 407-414.

This paper resulted from a solid collaboration we have had along the years with Rafael Radi (Montevideo, Uruguay) in teh área of biochemistry of free radicals and Jon Lundebrg (Stockholm, Sweden) in the área of Nitrite Biology. These collaborations have been fruitful in terms of scientific publications and student exchange.

Cátia F. Lourenço, Ana Ledo, João Laranjinha, Greg A. Gerhardt and Rui M. Barbosa (2016) Microelectrode array biosensor for high-resolution measurements of extracellular glucose in the brain *Sensors and Actuators B: Chemical* 237, 298-307.

This paper 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.

Neuroendocrinology and Aging

Carlos Lopez Otin (Collaborative Research & Graduate training)
Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain.

David Sinclair (Collaborative Research)
Harvard Medical School, USA

Leonard Guarente (Collaborative Research & Publication)
Glenn Laboratory for the Science of Aging, Massachusetts Institute of Technology, Cambridge, USA.

Licio Velloso (Collaborative Publication)
University of Campinas, Brazil

Ruben Nogueiras (Collaborative Research)
CIMUS, University of Santiago de Compostela, Spain

Xavier Nissan (Collaborative Research & Graduate training)
I-Stem, Paris, France

Vision, Brain Imaging and Cognitive Neuroscience

Papers (international collaboration)

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.

Violante IR, Patricio M, Bernardino I, Rebola J, Abrunhosa AJ, Ferreira N, Castelo-Branco M. GABA deficiency in NF1: A multimodal [11C]-flumazenil and spectroscopy study. Neurology. 2016 Aug 30;87(9):897-904. doi: 10.1212/WNL.0000000000003044. Epub 2016 Jul 29. PubMed PMID: 27473134; PubMed Central PMCID: PMC5035153.

Petrella LI, Cai Y, Sereno JV, Gonçalves SI, Silva AJ, Castelo-Branco M. Brain and behaviour phenotyping of a mouse model of neurofibromatosis type-1: an MRI/DTI study on social cognition. Genes Brain Behav. 2016 Sep;15(7):637-46. doi: 10.1111/gbb.12305. Epub 2016 Jul 5. PubMed PMID: 27283753.

Castelhano J, Bernardino I, Rebola J, Rodriguez E, Castelo-Branco M. Oscillations or Synchrony? Disruption of Neural Synchrony despite Enhanced Gamma Oscillations in a Model of Disrupted Perceptual Coherence. J Cogn Neurosci. 2015 Dec;27(12):2416-26. doi: 10.1162/jocn_a_00863. Epub 2015 Aug 18. PubMed PMID: 26284991.

Lemos R, Santana I, Caetano G, Bernardino I, Morais R, Farivar R, Castelo-Branco M. Three-Dimensional Face Recognition in Mild Cognitive Impairment: A Psychophysical and Structural MR Study. J Int Neuropsychol Soc. 2016 Aug;22(7):744-54. doi: 10.1017/S135561771600059X. Epub 2016 Jul 13. PubMed PMID: 27406061.

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Scientific collaborations

Serge Picaud, Institut de La Vision, Paris, France

Reza Farivar, Harvard University, US and McGill University, Canada

Rainer Goebel, University of Maastricht

Agneta Nordberg, Karolinska Institute

Michael Wibral, University of Frankfurt

Eugenio Rodriguez, University of Chile

Alcino Silva, University of California at Los Angeles

Fred Ullen, Karolinska Institute

Valerie Voon, University of Cambridge

Richard Edden, John Hopkins University

Post-graduation and post-docs interchange

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

Networking

Coordination of the National Brain Imaging Network

Participation in EuroBioimaging (European infrastructure)

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

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

Member of InnoSTARS, EIT Health Knowledge Innovation Community

Participation in European Projects (FP7 and H2020): BrainTrain, INfradev, Marie Curie Actions, STIPED

Purines in brain diseases

Networks:

Member of the Steering Committee of the European Neuroscience Campus (with Univ. Amsterdan, The Netherlands; Univ. Bordeaux, France; Univ. Zurich, Switzerland; Univ. Gottingen, Germany)

Member of the European Network of Neurosciences Institutes (ENI-Net)

Member of the Association for Science and Information on Coffee

Research grants:

CAPES-FCT program with Rui Prediger (Univ. Federal Santa Catarina, Brazil)

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

Graduate training:

Co-supervision of a 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-supervison 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)

Mitochondrial Dysfunction and Signaling in Neurodegeneration Group

Organization of an international PhD course:

"Neuroscience and Mental Health - a Clinical and Molecular Perspective" course, University of Coimbra, Portugal (9-13th May, 2016).

Participation in international meetings:

- Brain With]out[Borders - 1st Int. Symposium, Nov. 18-19 2016, Coimbra, Portugal (1 abstract)
- Meeting of the COST Action BM1402, Nov. 14-15 2016, Vienna, Austria (1 abstract)
- Neuroscience/SfN 2016 Annual Meeting, Nov. 12-16 2016, San Diego, USA (2 abstracts)
- 10th FENS meeting, Jul. 2-6 2016, Copenhagen, Denmark (1 abstract)
- 7th ISN Special Neurochemistry Conference, Jun 1-4 2016, Coimbra, Portugal (3 abstracts)
- Meeting of the COST Action BM1402, Apr 11-13 2016, Madrid, Spain (1 abstract)

Invited speaker in international meeting:

- Ferreiro E et al (2016) *Meeting of the COST Action BM1402*, Nov. 14-15, 2016, Vienna, Austria.
- Rego AC (2016) *16th IUBMB Conference*, Jul. 17-21, 2016, Vancouver, Canada.
- Ferreiro E et al (2016) *Meeting of the COST Action BM1402*, Apr. 11-13, 2016, Madrid, Spain.

Research collaboration with:

- George Daley (MD, PhD), Boston Children's Hospital and Harvard Medical School, Boston, USA
- Sandrine Humbert (PhD), Grenoble Institut des Neurosciences, Grenoble, France
- Michael Hayden (MD, PhD), University of British Columbia, Vancouver, Canada
- Tiago Fleming Outeiro (PhD), University Medizin Goettingen, Goettingen, Germany

Collaborative publications:

- Naia et al. (2016) *Mol. Neurobiol.* [Epub ahead of print]
- Naia et al. (2016) *Neuropeptides* 58, 73-81.
- Lopes et al. (2016) *PLoS One* 11, e0148680.
- Figueira et al. (2016) *Mech Ageing Dev.* 160, 69-92.

Aging and Brain diseases: advanced diagnosis and biomarkers

Collaborative publications:

Validation of 14-3-3 Protein as a Marker in Sporadic Creutzfeldt-Jakob Disease Diagnostic. Matthias Schmitz, Elisabeth Ebert, Katharina Stoeck, Andre Karch, Steve Collins, Miguel Calero, Theodor Sklaviadis, Jean-Louis Laplanche, Ewa Golanska, Ines Baldeiras, Katsuya Satoh, Raquel Sanchez-Valle, Anna Ladogana, Anders Skinningsrud, Anna-Lena Hammarin, Eva Mitrova, Franc Llorens, Yong Sun Kim, Alison Green, Inga Zerr. Mol Neurobiol. 2016; 53(4):2189-99. doi: 10.1007/s12035-015-9167-5.

Comparison of Different Matrices as Potential Quality Control Samples for Neurochemical Dementia Diagnostics. Lelental N, Brandner S, Kofanova O, Blennow K, Zetterberg H, Andreasson U, Engelborghs S, Mroczko B, Gabryelewicz T, Teunissen C, Mollenhauer B, Parnetti L, Chiasserini D, Molinuevo JL, Perret-Liaudet A, Verbeek MM, Andreasen N, Brosseron F, Bahl JM, Herukka SK, Hausner L, Frölich L, Labonte A, Poirier J, Miller AM, Zilka N, Kovacech B, Urbani A, Suardi S, Oliveira C, Baldeiras I, Dubois B, Rot U, Lehmann S, Skinningsrud A, Betsou F, Wiltfang J, Gkatzima O, Winblad B, Buchfelder M, Kornhuber J, Lewczuk P. J Alzheimers Dis. 2016; 52(1):51-64. doi: 10.3233/JAD-150883.

Enzymatic properties, evidence for in vivo expression, and intracellular localization of shewasin D, the pepsin homolog from Shewanella denitrifican Ana Rita Leal, Rui Cruz, Daniel Bur, Pitter F Huesgen, Rosário Faro, Bruno Manadas, Alexander Wlodawer, Carlos Faro, Isaura Simões, Nature Scientific Reports 2016; 6: 23869, doi: 10.1038/srep23869, IF 5.58, Q1.

Oral communication in the JPND BIOMARKAPD course:
The quest for new protein and metabolite biomarkers" Bruno Manadas Advanced course "JPND BIOMARKAPD course: Biological markers in neurological diseases: present and future approaches" 23rd June 2016;

The group has several international collaborations aiming to bring new developments to the research performed in the group, namely at the Baylor College of Medicine (Houston, USA) – Lee-Jun wong and 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 CICAB Clinical Research Centre Extremadura University Hospital and Medical School, (Badajoz, Spain) – Adrián Lerena.

New Targets and Therapeutics for Chronic Diseases

Collaborative research:

Universidade de Utrecht. Netherlands

Universidade de S. Francisco. Bragança Paulista. Brasil

Universidade de Rio Preto. Rio Preto. Brasil

Universidade de Campinas. Brasil

David Antonetti, University of Michigan Kellogg Eye Center, Ann Arbor, Michigan, E.U.A.
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, Múrcia, Espanha.

Juan Corral, Universidad Complutense de Madrid, Espanha.

Thomas Langmann, University of Cologne, Alemanha.

Collaborative publications

Guest edition of a Special Issue for the Journal "Oxidative Medicine and Cellular Longevity" (IF=4.492).

mTOR signaling in cardiometabolic disease, cancer and aging" Guest Editors: Anindita Das, Flávio Reis, Yasuhiro Maejima, Zhiyou Cai, and Jun Ren. https://www.hindawi.com/journals/omcl/si/280327/

García-Casarrubios E, de Moura C, Arroba AI, Pescador N, Calderon-Dominguez M, Garcia L, Herrero L, Serra D, Cadenas S, Reis F, Carvalho E, Obregon MJ, Valverde ÁM. Rapamycin negatively impacts insulin signaling, glucose uptake and uncoupling protein-1 in brown adipocytes. Biochim Biophys Acta. 2016; 1861(12 Pt A): 1929-1941. (IF=4.779; Q1)

Matheus FC, Rial D, Real JI, Lemos C, Ben J, Guaita GO, Pita IR, Sequeira AC, Pereira FC, Walz R, Takahashi RN, Bertoglio LJ, Cunha CD, Cunha RA, Prediger RD (2016). Decreased synaptic plasticity in the medial prefrontal cortex underlies short-term memory deficits in 6-OHDA-lesioned rats. Behav Brain Res. 301:43-54. (IF=3.002)

Lemos C, Rial D, Gonçalves FQ, Pires J, Silva HB, Matheus FC, da Silva AC, Marques JM, Rodrigues RJ, Jarak I, Prediger RD, Reis F, Carvalho RA, Pereira FC, Cunha RA (2016). High sucrose consumption induces memory impairment in rats associated with electrophysiological modifications but not with metabolic changes in the hippocampus. Neuroscience. 19;315: 196-205. (IF 3.357)

Viana SD, Fernandes RC, Canas PM, Silva AM, Carvalho F, Ali SF, Fontes Ribeiro CA, Pereira FC (2016). Presymptomatic MPTP mice show neurotrophic S100B/mRAGE striatal levels. CNS Neuroscience and Therapeutics. 22(5):396-403.(IF 4.019)

Viana SD, Valero J, Rodrigues-Santos P, Couceiro P, Silva AM, Carvalho F, Ali SF, Fontes-Ribeiro CA, Pereira FC (2016). Regulation of striatal astrocytic receptor for advanced glycation end-products variants in an early stage of experimental Parkinson's disease. J Neurochem. 138(4):598-609. (IF 3.842)

Maria H. Madeira, Arturo Ortin-Martinez, Francisco Nadal-Nícolas, António F. Ambrósio, Manuel Vidal-Sanz, Marta Agudo-Barriuso, Ana Raquel Santiago. Caffeine administration prevents retinal neuroinflammation and loss of retinal ganglion cells in an animal model of glaucoma. Sci Rep. 2016 Jun 8;6:27532. doi: 10.1038/srep27532. (IF: 5.228)

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.

Coelho-Santos V, Socodato R, Portugal C, Leitão RA, Rito M, Barbosa M, Couraud PO, Romero IA, Weksler B, Minshall RD, Fontes-Ribeiro C, Summavielle T, Relvas JB, Silva AP. Methylphenidate-triggered ROS generation promotes caveolae-mediated transcytosis via Rac1 signaling and c-Src-dependent caveolin-1 phosphorylation in human brain endothelial cells. Cell Mol Life Sci. 2016; 73(24):4701-4716.

A. Gonçalves, C.M. Lin, A. Muthusamy, C. Fontes-Ribeiro, A.F. Ambrósio, S.F. Abcouwer, R. Fernandes and D.A. Antonetti. Protective effect of a GLP-1 analog on ischemia-reperfusion induced blood-retinal barrier breakdown and inflammation. Invest. Ophthalmol. Vis. Sci. 2016, 57:2584-2592. doi: 10.1167/iovs.15-19006. PMID: 27163772. (IF: 3,404)

Networks

Coordination of Ageing@Coimbra, European Innovation Partnership on Active and Healthy Ageing Reference Site (3 stars)

Coordination of the thematic group “Demographic Changes and Ageing” at RESOE (Centro, Norte of Portugal, Galiza, Castilla y Leon, Asturias)

Member of the Interim board of Reference Site Collaborative Network (ESCN)

Research Exchange Programs

Short-term visits of PhD students: European Project of Marie Curie Actions

Joana Teles Ferreira (June – October 2016)

Wioleta Borzęcka (October 2016)

Tutorship of medical students: Research Exchange Programme

Miroslav Kucera (July 2016)

METABOLISM, AGING AND DISEASE STRAND

Cell Metabolism and Quality Control

- Arsénio Fernández-López. Universidad de Léon, Spain. Collaborative Project (Rationally designed lipids and neurotrophins in the therapy of central nervous system pathologies; funded by Ministerio de Economia y Competitividad, Gobierno de Espana).

- Carmen García-Rodriguez, Institute of Biology and Molecular Genetic. CSIC-University of Valladolid, Spain. Co-supervision of 1 PhD student.

- Cesare Patrone from Karolinska Institutet, Sweden. Co-supervision of 1 PhD student.

- 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.

- David Busija from Tulane University School of Medicine, USA. Collaborative publication, research and co-supervision of 1 postdoc fellow.

- Francisco Blanco, Instituto de Investigación Biomédica de A Coruña (INIBIC), Centro Hospitalario Universitario de A Coruña (CHUAC), Spain. Co-supervision of 1 PhD student.

- George Perry from College of Sciences, University of Texas at San Antonio, USA. Collaborative publication, research and co-supervision of 1 postdoc fellow.

- Marcia Haigis, Harvard Medical School, USA. Co-supervison of 1 PhD student.

- Maria Björkqvist from Lund Medical School, Lund, Sweden. Collaborative publication and research

- Maurício Sforcin, Departamento de Microbiologia e Imunologia, Instituto de Biociências, UNESP,18618-970, Botucatu, SP, Brasil. Collaborative Projects (Própolis: Modulação da apresentação antigénica e ativação diferencial de linfócitos T; funded by FAPESP, Brasil).

- Oreste Gualillo, NEIRID Lab, NeuroEndocrine Interactions in Rheumatology and Inflammatory Diseases, SERGAS, Santiago University Clinical Hospital, IDIS: Instituto de Investigación Sanitaria de Santiago, Spain. Co-edition of a special issue of Frontiers in Physiology.

- Patrik Verstreken, VIB Center for the Biology of Disease, Belgium. Co-supervision of 1 postdoc fellow.

- PROTEOSTASIS COST Action. Exchange of Students with the Laboratories lead by Michael Clague (University of Liverpool), Viktor Korolchuk (University of Newcastle), Joost Sluijter (University of Utrecht), Manuel Rodriguez (University of Toulouse).

Mitochondria Metabolism and Disease Group

Visiting researchers

Giulia Vecchione (2016), University of Genoa, Italy

Collaborations

Albert Rizvanov, Kazan Federal University, Russia (P. Oliveira)

Anatoly Zhitkovich, Brown University, USA (C. Alpoim)

Anika Hartz, Bjorn Bauer, University of Kentucky, USA (V. Sardão)

Clemens Steegborn, University of Bayreuth, Germany (C. Palmeira, A. Rolo)

Daniel Dorta, University of São Paulo, Brazil

David Sinclair, Harvard Medical School, USA (C. Palmeira/A. Rolo)

Edward Perkins, Mercer University, USA (P. Oliveira)

Faustino Mollinedo, CSIC, Spain (P. Oliveira)

Ignacio Vega-Naredo, University of Oviedo, Spain (P. Oliveira)

Jan Kopecky, Academy of Sciences, Czech Republic (C. Palmeira, A. Rolo)

Jiiri Neuzil, Griffith University, Australia (P. Oliveira)

Joan Rosselo, CSIC, Spain (C. Palmeira, A. Rolo)

John Wise, University of Louisville, Louisville, USA (C. Alpoim)

Kendall Wallace, University of Minnesota, USA (A. Rolo, C. Palmeira, P. Oliveira)

Louise Torp Dalgaard, Department of Science, Systems and Models, Denmark (C. Palmeira, A. Rolo)

Maria Almeida, University of Arkansas, USA (V. Sardão)

Maria Felice Brizzi, Università degli Studi di Torino, Italy (C. Palmeira, A. Rolo)

Mariusz Wieckowski, Nenki Institute, Poland (P. Oliveira)

Mark Nijland, Laura Cox, University of Texas Health Science Center, USA (P. Oliveira)

Michael Sack, NHLBI, National Institutes of Health, USA (P. Oliveira)

Nika Danial, Dana-Farber Cancer Institute, USA (C. Palmeira)

Patricia Scott, Jon Holy, Pavel Krasutsky, University of Minnesota, USA (P. Oliveira)

Peter Nathanielsz, University of Wyoming, USA (P. Oliveira)

Piero Portincasa, University of Bari, Italy (P. Oliveira)

Saber Hussain, Wright State University, USA (C. Palmeira)

Metabolic Control Group

Collaboration with Prof. Adrian Vella at Mayo Clinic:

Varghese, R.T., Man, C.D., Sharma, A., Viegas, I., Barosa, C., Marques, C., Shah, M., Miles, J.M., Rizza, R.A., Jones, J.G., Cobelli, C. and Vella, A., 2016. Mechanisms underlying the pathogenesis of isolated impaired glucose tolerance in humans. *J. Clin. Endocrinol & Metab.* 101*,* 4816-4824.

Varghese, R.T., Viegas, I., Barosa, C., Marques, C., Shah, M., Rizza, R.A., Jones, J.G. and Vella, A. 2016. Diabetes-associated variation in TCF7L2 is not associated with hepatic or extrahepatic insulin resistance. *Diabetes* 65*,* 887-892.

Herrero L, Serra D, Cadenas S, Reis F, Carvalho E*, Obregón M, ValverdeA*. Rapamycin negatively impacts insulin signaling, glucose uptake and uncoupling protein-1 in brown adipocytes. Biochim Biophys Acta. 2016 Sep 26;1861(12 Pt A):1929-1941. (*share corresponding authorship)

Tellechea A, Leal EC, Kafanas A, Ostrovsky Y, Tecilazich F, Carvalho E, Zabolotny JM, Weng Z, Petra A, Patel A, Panagiotidou S, Pradhan Nabzdyk L, Theoharides TC, Veves A. Role of Mast Cells in Impaired Diabetic Wound Healing. Diabetes 2016 Jul;65(7):2006-19.

Collaboration with S. Schlatt (Univ. Munster, Germany)

Escada-Rebelo S, Silva AF, Amaral S, Tavares RS, Paiva C, Schlatt S, Ramalho-Santos J, Mota PC. Spermatogonial stem cell organization in felid testis as revealed by Dolichos biflorus lectin. Andrology. 2016 Nov;4(6):1159-1168. doi: 10.1111/andr.12223. Epub 2016 Jun 17.

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 treatmen*t, (A03/2016)

Projeto ao abrigo do Programa de Ações Integradas Luso-Alemãs. 2016-2018

Collaborative Publications:

I.V. Nieto, D. Brites, N. Karagianni, S. Ortolano, S. Georgopoulos, A.L. Cardoso, S. Novella, G. Lepperdinger, A.U. Trendelenburg, T.V. Zglinicki, R. Van Os, "Frailty in mouse aging: a conceptual approach", Mechanisms of Ageing and Development, 2016, S0047-6374(16)30109-9.

Adriana P. Gerola, Danielle C. Silva, Alan F.Y.Matsushita, Olga Borges, Adley F. Rubira, Edvani C. Muniz, Artur J. M. Valente; The effect of methacrylation on the behavior of gum arabic as pH-responsive matrix for colon-specific Drug DeliveryEur Polymer J., 2016, 78, 326-339.

P.C. Filho, A.L. Cardoso, M.I. Pereira, A.P. Ramos, F. Hallwass, M.M. Castro, C. Geraldes, B. Santos, M.C. Pedroso de Lima, G. Pereira and A. Fontes, CdTe quantum dots as fluorescent probes to study transferrin receptors in glioblastoma cells, BBA – General Subjects, 2016, 1860, 28-35.

Nélio Gonçalves, Ana T. Simões, Rui S. Prediger, Hirokazu Hirai, Rodrigo A. Cunha, Luís Pereira de Almeida. Caffeine alleviates progressive motor deficits in a transgenic mouse model of spinocerebellar ataxia. Annals of Neurology. 2016 Dec 29. doi: 10.1002/ana.24867.

Simões AP, Machado NJ, Gonçalves N, Kaster MP, Simões AT, Nunes A, de Almeida LP, Goosens KA, Rial D, Cunha RA. Adenosine A2A receptors in the amygdala control synaptic plasticity and contextual fear memory. Neuropsychopharmacology. 2016 Jun 17. doi: 10.1038/npp.2016.98.

Janete Cunha-Santos, Joana Duarte-Neves, Vitor Carmona, Leonard Guarente, Luís Pereira de Almeida* & Cláudia Cavadas* Caloric Restriction blocks neuropathology and motor deficits in Machado-Joseph Disease mouse models through activation of the SIRT1 pathway. Nature Communications. 2016 May 11;7:11445. doi: 10.1038/ncomms11445. (2016) *Equal contribution.
Mariana Conceição, Liliana Mendonça, Clévio Nóbrega, Célia Gomes, Pedro Costa, Hirokazu Hirai, João Nuno Moreira, Maria C. Lima, N. Manjunath, Luís Pereira de Almeida. Safety profile of the intravenous administration of brain-targeted stable nucleic acid lipid particles. Data in Brief. 2016 Jan 20;6:700-5. doi: 10.1016/j.dib.2016.01.017. eCollection 2016. Conceição M, Mendonça L, Nóbrega C, Gomes C, Costa P, Hirai H, Moreira JN, Lima MC, Manjunath N, Pereira de Almeida L. Intravenous administration of brain-targeted stable nucleic acid lipid particles alleviates Machado-Joseph disease neurological phenotype. Biomaterials. 2016 Mar; 82:124-37. doi: 10.1016/j.biomaterials.2015.12.021.

Stem Cell Biotechnology

Participation at the international program MIT-Portugal, focus area of bioengineering. Lino Ferreira, Ricardo Neves, Hugo Fernandes and Filipe Pereira are contributing 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 2016, 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 Blersh (CNC, Portugal), Michela Comune (CNC, Portugal), Veronique Preat (University of Louvain, Belgique), Klaus Liedl (University of Insbruck, Austria), Lino Ferreira (CNC, Portugal).

-Nanomaterials to modulate stem cells. Magdalena Gotz (Munichen Institute), Catarina Rebelo (CNC, Portugal), Sónia Pinho (CNC, Portugal), Carolyn Carr (University of Oxford), Lino Ferreira (CNC, Portugal).

- Cell reprogramming/stem cell modulation. Tariq Enver (University College of London, UK), Carlos Boto (CNC, Portugal), Emanuel Quartin (CNC, Portugal), Ricardo Neves (CNC, Portugal), DengLi (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. Christine Mummery/Robert Passier (University of Leiden, Netherlands), 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), 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)

- 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 Nimejgen, 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

Massachusetts Institute of Technology (U.S.A.)

Researchers: Timothy Lu

Project: Developing a synthetic biology *E. coli*-based H_2O_2 sensor with memory

University of Heidelberg (Germany) and Technical University of Kaiserslautern (Germany):

Researchers: Tobias Dick (UH) and Bruce Morgan (TUK)

Project: Development of method to determine absolute intracellular hydrogen peroxide concentrations

University of Otago (New Zealand):

Researchers: Christine Winterbourn

Project: Characterizing the operation of the Prx2/Trx1/TrxR system in human erythrocytes.

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 O_2-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

MOLECULAR MYCOBACTERIOLOGY & MICROBIOME:

Nunes-Costa D, Alarico S, Dalcolmo MP, Correia-Neves M, Empadinhas N (2016) The looming tide of nontuberculous mycobacterial infections in Portugal and Brazil. Tuberculosis 96:107-19.

Medicinal Chemistry & Drug Discovery

Collaborative publications

Kasal, A. and Budešínský, M. and Mareš, P. and Krištofíková, Z. and Leitão, A.J. and Sá e Melo, M.L. and Silva, M.M.C. Neurosteroids: Can a 2alpha,3alpha-epoxy ring make up for the 3alpha-hydroxyl group? Steroids, 2016, 105, 12-18.http://dx.doi.org/10.1016/j.steroids.2015.11.007

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

Mendes, V. I. S., Bartholomeusz, G. A., Ayres, M., Gandhi, V., Salvador, J. A. R. Synthesis and cytotoxic activity of novel A-ring cleaved ursolic acid derivatives in human non-small cell lung cancer cells. EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY 2016 Volume: 123 Pag. 317-331 DOI: 10.1016/j.ejmech.2016.07.045

Goncalves, Bruno M. F.; Salvador, Jorge A. R.; Marin, Silvia; Cascante, M.Synthesis and anticancer activity of novel fluorinated asiatic acid derivatives EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY 2016, Volume: 114, Pag. 101-117 DOI: 10.1016/j.ejmech.2016.02.057

Goncalves, Bruno M. F.; Salvador, Jorge A. R.; Santos, Diana S. M.; https://apps.webofknowledge.com/DaisyOneClickSearch.do?product=WOS&search_mode=DaisyOneClickSearch&colName=WOS&SID=Q11GPgbTgTD6uGClF5K&author_name=Marin,S&dais_id=21218366&excludeEventConfig=ExcludeIfFromFullRe

cPageMarin, Silvia; Cascante, Marta. Design, synthesis, and biological evaluation of novel asiatic acid derivatives as potential anticancer agents RSC ADVANCES 2016, Volume: 6 Ed 45 Pag. 39296-39309 DOI: 10.1039/c6ra04597a

Goncalves, Bruno M. F.; Salvador, Jorge A. R.; Marin, Silvia; Cascante, Marta. Synthesis and biological evaluation of novel asiatic acid derivatives with anticancer activity RSC ADVANCES 2016, Volume: 6 Ed 5 Pag. 3967-3985 DOI: 10.1039/c5ra19120c

Figueiredo R, Card RM, Nunez J, Pomba C, Mendonça N, Anjum MF, Da Silva GJ. Detection of a *mcr-1*-encoding plasmid mediating colistin resistance in *Salmonella enterica* from retail meat in Portugal. J Antimicrob Chemother.,2016, 71 (8):2338-40. doi: 10.1093/jac/dkw240

Anastácio S, Pimenta L, Simões J, Alegria N, Rabiço A, Sidi-Boumedine K, da Silva GJ. *Coxiella burnetii* is present in milk from dairy cattle herds in the Northwest Portugal. Experimental Pathology and Health Sciences, 2016, 8 (1): 13-14.

Mendonça N., Figueiredo R., Mendes C., Card RM., Anjum MF, da Silva GJ. Microarray evaluation of antimicrobial resistance and virulence of *Escherichia coli* isolates from Portuguese poultry. , 2016, 13; 5: 1-9.

Clarissa Perez Faria; Graziela Maria Zanini; Gisele Silva Dias; Sidnei da Silva; Maria do Céu Sousa Molecular Characterization of *Giardia lamblia*: First Report of Assemblage B in Human Isolates from Rio de Janeiro (Brazil). *Plos One*, 2016. DOI: 10.1371/journal.pone.0160762/journal. Pone. e0160762

Jorge M. Vieira, María L. Flores-López, Diana Jasso de Rodríguez, Maria C. Sousa, António A. Vicente, Joana T. Martin, Effect of chitosan–*Aloe vera* coating on postharvest quality of blueberry (Vaccinium corymbosum) fruit. *Postharvest Biology and Technology* , 2016, 11688–97.

Domingues S, Nielsen KM. Horizontal gene transfer: Uptake of extracellular DNA by bacteria. Reference Module in Biomedical Sciences. Elsevier. 2016. http://dx.doi.org/10.1016/B978-0-12-801238-3.99485-6

Graduate Training Networks

Grant: Programa Ciências Sem Fronteiras (CONCF)

Doutorado Sanduiche no Exterior – SWE. Doutorado do Programa de Pós Graduação em Ciências Farmacêuticas, Universidade Estadual de Maringá – UEM, Brasil.

Ref: 203183/2015-0

Name: Hélito Volpato

Duration: 1 year (February 2016 to February 2017)

Project: "Encapsulation of natural compounds and activity studies on *Leishmania* species"

Local: FFUC

Supervisors: Maria do Céu Sousa and Olga Borges

Grant: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) - PROJETOS MEC/MCTI/CAPES/CNPQ/FAPS.

Bolsa Pesquisador Visitante Especial- PVE 2014. Doutorado do Programa de Pós Graduação em Ciências Farmacêuticas, Universidade Estadual de Maringá – UEM, Brasil.

Name: Débora Botura Scariot

Duration: 1year (February 2016 to February 2017)

Project:"Mechanism of action on *Leishmania infantum* and Vectorization of Sugiol Diterpene"

Local: FFUC

Supervisors: Maria do Céu Sousa and Olga Borges

Grant: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) –

PROJETOS MEC/MCTI/CAPES/CNPQ/FAPS.

Bolsa de Pesquisador visitante Especial- PVE 2014. Doutorado do Programa de Pós Graduação em Ciências Farmacêuticas, Universidade Estadual de Maringá – UEM, Brasil.

Name: Maria do Céu Sousa

Duration: 1 month, 2016

Area: Ciências Biomédicas e da Saúde

Cooperation: Actividades do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade Estadual de Maringá, Brasil.

Cooperation: Projecto financiado pelo Instituto Nacional de Ciência, Tecnologia para a Inovação Farmacêutica INCT_if , chamada INCT-MCTI/CNPq/Capes/Faps nº 16/2014.

Title: "Composição química e actividade de plantas aromáticas da reserva florestal Adolpho Ducke-manaus-Amazonas contra protozoários flagelados dos genêros *Leishmania* e *Trypanosoma "*

Coordinators: Ivan da Rocha Pitta, Universidade Federal de Pernambuco (UFPE) and Norberto Peporine Lopes, Faculdade de Ciências Farmacêuticas de Ribeirão Preto (USP), Brasil.

Name: Maria do Céu Rodrigues de Sousa

Duration: 2016-2020

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

Cooperation: Cooperação Acadêmico-Científico no âmbito dos Estudos em Saúde Urbana, entre o Grupo de Investigação da Geografia da Sáude, Faculdade de Farmácia da Universidade de Coimbra e da Fundação Oswaldo Cruz FIOCRUZ.

Coordinators: Paula Santana (GIGS/FLUC/Portugal); Maria do Céu Rodrigues de Sousa (FFUC, Portugal); Marcelo Bessa de Freitas (ENSP/Fiocruz/Brasil);Graziela Zanini (INI/Fiocruz/Brasil).

Duration: 2015-2019

Visitor PhD student: Hadhemi Ben Chikh (from the Laboratory of Contagious Disease and Biologically Active Substances LR99-ES27 at Monastir's Pharmacy Faculty, Tunisia)

Duration: September - December 2016

Project: "Molecular characterization of carbapenemases of *Acinetobacter* spp. and *Enterobacteriaceae* clinical isolates from Tunisia"

Local: Laboratory of Microbiology, Faculty of Pharmacy, University of Coimbra

Supervisors: Gabriela Jorge da Silva

Pharmacometrics

M.S. Abu-Darwisha, C. Cabral, M.J. Gonçalves, C. Cavaleiro, M.T. Cruz, M. Paoli, F. Tomi, T. Efferth , L. Salgueiro. *Ziziphora tenuior* L. essential oil from Dana Biosphere Reserve (Southern Jordan); Chemical characterization and assessment of biological activities. Journal of Ethnopharmacology (2016) on-line http://dx.doi.org/10.1016/j.jep.2016.10.076

C Cabral (2016). A Prática Interdisciplinar na Interface Saúde e Ambiente. III Simpósio Interdisciplinar em Saúde e Ambiente (SISA2016), Universidade Tiradentes, Aracajú, Sergipe, Brasil

Molecular Biotechnology Group

Publications:

Curto P., Simões I., Riley S.P., Martinez J.J. (2016) Differences in intracellular fate of two spotted fever group Rickettsia species in macrophage-like cells. Front. Cell. Infect. Microbiol. 6:80, doi: 10.3389/fcimb.2016.00080

Leal A.R., Cruz R., Bur D., Huesgen P.F., Faro, R., Manadas B., Wlodawer A., Faro C., Simões, I.** (2016) Enzymatic properties, evidence for in vivo expression, and intracellular localization of shewasin D, the pepsin homolog from Shewanella denitrificans. Scientific Reports, 6:23869, DOI: 10.1038/srep23869

Gustchina, Mi Li, R. Cruz, M. Simões, P. Curto, J. Martinez, C. Faro, I. Simões and A. Wlodawer (2016) Crystal structure of the soluble domain of RC1339/APRc from Rickettsia conorii, a retropepsin-like aspartic protease Acta Cryst. (2016). A72, s217

Dias D.M., Furtado J., Wasielewski E., Cruz R., Costello B., Cole L., Faria T. Q., Baaske P., Brito R.M.M., Ciulli A., Simões I., Macedo-Ribeiro S., Faro C., Geraldes C. F. G. C., Castanheira P. (2016). Biophysical characterization of laforin-carbohydrate interaction. Biochemical J. 473, 335–345., DOI 10.1042/BJ20141555

Research:

Isaura Simões had an appointment as a Visiting Assistant Professor in Dr. Juan Martinez' lab at the Department of Pathobiological Sciences, Louisiana State University, Baton Rouge, USA (Jan 2016-Dec 2016), working under the context of a R21-NIH Grant approved as a follow-up of a project previously funded by FCT, Portugal (PI Isaura Simões). PhD Student Pedro Curto spent the year in the same laboratory, as part of his training (Grant SFRH/BD/96769/2013).

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), ForschungszentrumJülich, Germany

PARTICIPATION IN THE ORGANIZATION OF SCIENTIFIC MEETINGS

January 2016

Organizing of the 5º Congresso do CIMAGO *(Centro Hospitalar e Universitário de Coimbra, Coimbra)*
Date: January 27-28, 2016
CNC.IBILI members involved in the organization: Isabel Marques Carreira

March 2016

Organizing Opening Session of the International BAW_Brain Awareness Week "Brain and Music" Cérebro e Música. *(Exploratório Centro Ciência Viva de Coimbra, Coimbra)*
Date: March 13, 2016
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing Symposium "Machado-Joseph Disease: Where do we stand?" *(Lisbon*)
Date: March 17-20, 2016
CNC.IBILI members involved in the organization: Luis Pereira de Almeida

Organizing Workshop: "Os sinaptossomas como modelo da disfunção pré-sináptica em patologias do cérebro - o papel da mitocôndria". *XIX Encontro Nacional de Estudantes de Biologia.*
Date: March 21, 2016
CNC.IBILI members involved in the organization: Ana Cristina Rego

April 2016

Organizing Seminar "Aging is normal: reflections of a gerontologist" by Jose Vinha *(Univ. Valencia, Spain)*
Date: April 4, 2016
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing MIA Summer School "Biology of Ageing: from cell to society", Alvor
Date: April 25-30, 2016
CNC.IBILI members involved in the organization: Francisco Ambrosio

Organizing Workshop "Mitochondrial Biology and Medicine", part of the Annual Meeting of the European Society of Clinical Investigation, *(Paris, France)*
Date: April 27-29, 2016
CNC.IBILI members involved in the organization: Paulo Oliveira and Carlos Palmeira

May 2016

Organizing Seminar "Targeting the kynurenine pathway in neurodegenerative disease" by Dr. Flaviano Giorgini *(University of. Leicester, United Kingdom)*
Date: May 12, 2016
CNC.IBILI members involved in the organization: Ana Critina Rego

Organizing Seminar "Tauopathies and tau-based therapeutic strategies" by Dr. Miguel Medina *(CiberNed, Madrid, Spain)*
Date: May 13, 2016
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing Seminar "New advances in the therapy of multiple sclerosis" by Dr. Lucienne Costa Frossar *(Hospital Ramon y Cajal, Madrid, Spain)*
Date: May 13, 2016
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing Committee: 6º International Congress on Aromatic and Medicinal Plants (CIPAM 2016), (*Hotel Vila Galé, Coimbra, Portugal)*
Date: May 29-June 1, 2016
CNC.IBILI members involved in the organization: Líga Salgueiro, Carlos Cavaleiro, Célia Cabral

June 2016

Organizing 7th Special ISN meeting - Synaptic function & dysfunction in brain diseases, *(Coimbra)*
Date: June 1-4, 2016
CNC.IBILI members involved in the organization: Carlos Duarte

Organizing 18th Conference of the European Society for Clinical Hemorheology and Microcirculation *(Lisbon)*
Date: 5-8, June 2016
CNC.IBILI members involved in the organization: Francisco Ambrosio

Scientific and Organizing Committee, 5th International Iberian Biophysics Congress
Date: June 15-17, 2016
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the International JPND course 'Biological markers in Neurological diseases – Present and Future approaches'
Date: June 23-24, 2016
CNC.IBILI members involved in the organization: Catarina R. Oliveira, Inês Baldeiras

July 2016

Organizing Workshop Cardiostem Project: Engineered cardiac tissues and stem cell-based therapies for cardiovascular applications, 9th Lisbon Summer Meeting, *(Santa Marta)*
Date: July 2, 2016
CNC.IBILI members involved in the organization: Lino Ferreira

Organizing Committee of the 5th National Meeting of History of Science and Technology/2nd International Congress of Interdisciplinary History of Health
Date: July 13-15, 2016
CNC.IBILI members involved in the organization: Ana Pereira, Célia Cabral, João Pita, Pedro Fonseca, Victoria Bell

Organizing of the IV Cell Culture and Tissue Training Course *(Faculdade de Medicina da Universidade de Coimbra, Coimbra)*
Date: July 18-22, 2016
CNC.IBILI members involved in the organization: Isabel Marques Carreira

September 2016

Coordination of 2016 Summer School on Computational Biology, *(Coimbra)*
Date: September 5-15, 2016
CNC.IBILI members involved in the organization: Armindo Salvador

Member of the Scientific Comittee of the the ENOR 6Th Symposium of the European Network for Oxysterols Research, *(Université Paris Décartes, Paris, France)*
Date: September 29-30, 2016
CNC.IBILI members involved in the organization: Maria Luisa Sá e Melo

Organizing 1st Symposium on Aging Research @CNC – Molecular Mechanisms of Aging and Age-Related Diseases
Date: September 30, 2016
CNC.IBILI members involved in the organization: Claudia Cavadas, Luis Pereira de Almeida

October 2016

Part of the Retiro Anual do Programa de Doutoramento Interuniversitário em Envelhecimento e Doenças Crónicas, *(IBILI-FMUC)*
Date: October, 2016
CNC.IBILI members involved in the organization: Paula Moreira

Organizing Seminar "Mitochondria and neuroinflammation in the pathogenesis of Alzheimer's disease: modulation by hormesis and nutritional mushroom" by Dr. Vittorio Calabrese *(School of Medicine - Department of Biomedical and Biotechnological Sciences, University of Catania, Italy)*
Date: October 21, 2016
CNC.IBILI members involved in the organization: Ana cristina Rego

November 2016

Organizing Seminar "Agent-based modeling of complex systems", by Tiago Baptista *(ECOS, CISUC, Coimbra)*
Date: November 2, 2016
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the 20 ª Reunião Anual da Sociedade Portuguesa de Genética Humana, *(Fundação Bissaya Barreto, Coimbra)*
Date: November 10 - 12, 2016
CNC.IBILI members involved in the organization: Joana Barbosa de Melo

Organizing Meeting "Brain Without Borders" *(Coimbra)*
Date: November 18-19, 2016
CNC.IBILI members involved in the organization: Luis Pereira de Almeida

December 2016

Organizing Seminar "Chronic stress in the continuum between depression and dementia: from neuroplasticity to neurodegeneration" by Dr. João Bessa (ICVS, School of Health Sciences, University of Minho, Braga, Portugal)
Date: December 9, 2016
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing of the first "Conferência Nacional de Bioquímica". Professor Arsélio Pato de Carvalho *(Guimarães)*
Date: December 10, 2016
CNC.IBILI members involved in the organization: João Laranjinha

Organizing Seminar "Gold nanoparticles functionalized with antimicrobial peptides - a computational approach" by Pedro Simões *(FCTUC, Coimbra)*
Date: December 14, 2016
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the National meeting of the Portuguese Biochemical Society *(Guimarães)*
Date: December, 2016
CNC.IBILI members involved in the organization: João Laranjinha

GRADUATE STUDIES PROGRAMME

During 2016 CNC.IBILI organized 12 Advanced Courses (inserted at the Doctoral Programme in Experimental Biology and Biomedicine - PDBEB at CNC) and hosted 64 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 50 Ph.D. and 102 M.Sc. theses were concluded.

Advanced Courses 2016

Computational Tools in Biology: a hands on course
January 11-15, 2016
Rui Travasso, Physics Department, UC

Molecular Biology of Aging (*In articulation with FMUC*)
February 1-12, 2016
Henrique Girão/João Malva

Molecular and Cellular Neuroscience
February 15-19, 2016
Ana Luísa Carvalho

Neurodevelopment and Neurodevelopmental disorders
March 14-18, 2016
Carlos B Duarte & João Peça

Neuronal circuits and behavior *(together with the MIT-Portugal PD Bioengineering Neuroscience course)*
April 22-29, 2016
João Peça

Neuroscience and Mental Health: a clinical and molecular perspective
May 9-13, 2016
Ana Cristina Rego

Metabolism, Aging and Disease
April 4-8, 2016
João Ramalho-Santos & Paulo Oliveira

Cell Respirometry: Basics and Applications
April 11-15, 2016
Vilma Sardão

Advanced Therapies Course
June 13-16, 2016
Luís Pereira de Almeida e Lino Ferreira

Principles and Practice in Drug Development | MIT-PORTUGAL Program
April 4-15, 2016
João Nuno Moreira, Luís Pereira de Almeida, Sérgio Simões, Stan Finkelstein

Soft skills for PhD students in Biomedical Research
16-18 May 2016
Cláudia Cavadas, Adalberto Fernandes, Sara Amaral

CNC Cores Course
October 10 - 21, 2016
CNC Cores

CNC.IBILI Seminars

January-December 2016

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

Internal communication: Ana Maranha, 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

Portable in-vitro diagnostics
2016.01.06
João Pereira
Magnomics, Cantanhede

Oxysterols in health and disease
2016.01.15
Maria Manuel Silva
CNC and FFUC, Coimbra

Optimization Methods for Biological and Biomedical Sciences
2016.01.20
Francisco Pereira
ISEC and CISUC, Coimbra

Using yeast to dissect molecular basis of synucleinopathies
2016.01.22
Paula Ludovico
ICVS, School of Health Sciences, University of Minho, Braga

Synaptic network dysfunction in social stress and autism
2016.01.29
João Peça
CNC, Coimbra

FEBRUARY

The role of telomeres in cancer and ageing in the zebrafish
2016.02.03
Miguel Ferreira
IGC, Lisboa

Protein-protein interaction networks and sperm 'omics'
2016.02.05
Odete Cruz e Silva
iBiMED, Departamento de Ciências Médicas, University of Aveiro

Targeting adenosine receptors as protective strategies in retinal degenerative diseases
2016.02.12
Raquel Santiago
IBILI, FMUC, Coimbra

Dissociating voice from speech – a neuropsychological approach
2016.02.15
Cyril pernet
University of Edingburg, Scotland

Obesitility - Obesity and Male fertility
2016.02.17
Marco Alves
UBI, Covilhã

Bioengineering approaches for scalable production of human cells: applications in cell therapy and in the development of advanced 3D in vitro models for pre-clinical research
2016.02.19
Paula Alves
Animal Cell Technology Unit, ITQB, NOVA and IBET, Oeiras

Modulating polyglutamine toxicity through phosphorylation: the example of ataxin-3, the protein involved in Machado-Joseph disease
2016-02.26
Carlos Matos
CNC, Coimbra

MARCH

AMD: a multifactorial genetic disease
2016.03.01
Thomas Langmann
University of Cologne, Germany

Role of the NT3/TrkC system in the formation and extinction of (pathological) fear memories
2016.03.04
Mónica Santos
Genetics and Molecular Neurobiology, Institute of Biology, Otto von Guericke University, Germany

Physiopathology of the NMDA receptor in neurodevelopmental diseases with intellectual disability
2016.03.11
Xavier Altafaj
Unit of Neuropharmacology and Pain, Bellvitge Biomedical Resarch Institute (IDIBELL), Barcelona, Spain

Mechanistic insights into Xist lncRNA-mediated recruitment of chromatin modifiers during X-chromosome inactivation
2016.03.16
Simão Teixeira da Rocha
IMM/FMUL, Lisboa

Strategies to engineer skin: how far did we go?
2016.03.18
Alexandra P. Marques
3B's, Biomaterials, Biodegradables and Biomimetics, Department of Polymer Engineering, University of Minho

Adult restoration of Shank3 expression rescues selective autistic-like phenotypes
2016.03.18
Patrícia Monteiro
ICVS, Braga

Tracing fructose metabolism: the good, the bad and the ugly
2016.03.30
John Jones
CNC, Coimbra

APRIL

Cancer Stem Cells: a central question in tumor biology
2016.04.08
Célia Gomes
IBILI, FMUC, Coimbra

Dynamic epithelial cell-cell interactions in cancer
2016.04.13
Joana Paredes
IPATIMUP, Porto

Understanding the mechanisms and emergence of antimicrobial resistance
2016.04.15
Gabriela J. Silva
CNC and FFUC, Coimbra

From gene discovery to gene therapy for an inherited retinopathy in 20 years
2016.04.22
Miguel Seabra
CEDOC - Centro de Estudos de Doenças Crónicas, NOVA Medical School, Universidade Nova de Lisboa

Enhancement of hERG channel activity by scFv antibody fragments targeted to the PAS domain
2016.04.27
Carol Harley
IBMC/i3S, Porto

Dissecting the Molecular Mechanisms Governing the Alternative Pluripotent States
2016.04.28
Miguel Fidalgo
Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela, Spain

Turning a neuropeptide into a drug: Overcoming the blood-brain barrier in analgesia and neuroprotection
2016.04.29
Miguel Castanho
IMM, University of Lisbon Medical School

MAY

Epicardial adipose tissue metabolism in heart failure patients, with and without diabetes
2016.05.06
Ana Burgeiro
CNC, Coimbra

Lean on body neurons
2016.05.11
Ana Domingos
IGC, Lisboa

Cancer Therapeutics Using Molecular response and Image-Guided Optical Nanotechnology
2016.05.11
Tayyaba Hasan
Wellman Center for Photomedicine, Harvard Medical School (HMS) and Health Sciences and Technology (Harvard-MIT)

Meet the Industry: New opportunity for innovation with Janssen-Cilag
2016.05.12
José Antunes
(Janssen-Cilag)

Metabolic alterations in thyroid cancer
2016.05.13
Valdemar Máximo
IPATIMUP, I3S and FMUP, Porto

Aquaporins in membranes: novel targets for drug discovery
2016.05.20
Graça Soveral
Research Institute for Medicines, iMed.ULisboa

ATP as a multi-target danger signal in the brain
2016.05.27
Ricardo Rodrigues
CNC, Coimbra

JUNE

Navigating in the sea of genes in Multiple sclerosis – what do we find?
2016.06.06
Margareta Jernås
University of Gothenburg, Sweden

Programming of fetal cardiac mitochondria by maternal nutrition
2016.06.08
Susana Pereira
CNC, Coimbra

Innate immunity and cardiovascular physiopathology
2016.06.14
Carmen García-Rodríguez
Instituto de Biología y Genética Molecular, CSIC, Valladolid-Spain

Treating diabetes: is carotic body the new nirvana?
2016.06.17
Silvia Conde
CEDOC - Centro de Estudos de Doenças Crónicas, NOVA Medical School, Universidade Nova de Lisboa

Microglial response to optic nerve axotomy
2016.06.21
Marta Agudo-Barriuso
Departamento de Oftalmología, Facultad de Medicina, Universidad de Murcia &Instituto Murciano de Investigacion Biosanitaria Virgen de la Arrixaca (IMIB-Arrixaca), Spain

From molecules to target therapeutics in haematological neoplasia
2016.06.22
Ana Bela Sarmento
FMUC/CHUC/CIMAGO/CNC.IBILI, Coimbra

Immunomodulation during development - behaviour, synchrony and microglia sequelae
2016.06.24
Catarina Gomes
IBILI, Coimbra

Lipids under stress
2016.06.30
Tiago Gil Oliveira
ICVS, University of Minho

JULY

From rural Portugal to a career as a research scientist: a woman's journey into science
2016.07.06
Eugénia Carvalho
CNC, Coimbra

Metabolic reprogramming in macrophages: A role in cancer and inflammation
2016.07.06
Ricardo Silvestre
ICVS, Braga

Anti-inflammatory and blood-retinal barrier-preserving effects of GLP-1-based therapies in retinal degenerative diseases
2016.07.08
Rosa Fernandes
IBILI, Coimbra

High-Throughput screening facility @ UC-Biotech
2016.07.13
Sandra Pinto
CNC/UC-Biotech

Pharmacology of New Chemical Entities
2016.07.13
Nuno Pires
Bial

Translational approaches to the neurobiology of psychiatric disorders: a focus on neuroplasticity
2016.07.14
João Bessa
Instituto de Investigação em Ciências da Vida e Saúde (ICVS), University of Minho, Braga

Spatial Epidemiology: An application to hip fracture in Portugal
2016.07.15
Sandra Alves
INEB and ESTSP - Instituto Politécnico do Porto

Driving apoptosis machinery to improve neurogenesis
2016.07.20
Susana Sola
FFUL, Lisboa

SEPTEMBER

Nitric oxide and injury-induced neurogenesis: a role for S-nitrosylation
2016.09.09
Inês Araújo
Department of Biomedical Sciences and Medicine, University of Algarve

Examples of translational research: from stem cells to nanotechnologies
2016.09.16
Lino Ferreira
CNC/UC-Biotech

Imaging Methodologies: Current and Future perspectives
2016.09.23
Luísa Cortes
CNC, Coimbra

The hallmarks of aging: lessons from progeria
2016.09.30
Carlos López-Otín
Department of Biochemistry and Molecular Biology, University of Oviedo, Spain

OCTOBER

Ghrelin: a novel strategy to rescue the senescent phenotype of Progeria, a premature aging disease
2016.10.07
Célia Aveleira
CNC, Coimbra

High-content screening identifies pro-survival microRNAs
2017.10.14
Hugo Fernandes
CNC/UC-Biotech

Natural approaches in food processing
2017.10.21
Isabel C.F.R. Ferreira
Polytechnic Institute of Bragança, Mountain Research Centre, School of Agriculture

Targeting adenosine A_{2A} receptors in the amygdala: implications for fear memory and mood disorders
2016.10.28
Ana Patrícia Simões
CNC, Coimbra

NOVEMBER

Manipulating cell migration and invasion to impair cancer progression
2016.11.11
Duarte Barral
CEDOC, NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa

Meta"bone"lomics of post-menopausal osteoporosis: the orchestration of bone remodeling in presence and absence of estrogen-like molecules
2016.11.18
Vilma Sardão
CNC, Coimbra

Regulation of Large Dense Core Vesicle exocytosis by an upstream, dual-action calcium sensor
2016.11.25
Paulo Pinheiro
CNC, Coimbra

DECEMBER

Calcium deregulation in Alzheimer´s disease
2016.12.02
Ildete Ferreira
CNC, Coimbra

Role of SUMO proteins in cardiovascular diseases
2016.12.02
Elisa Ferrada
IBILI, UC

Analysis of the neural circuit underlying the detection of visual motion in Drosophila melanogaster
2016.12.14
Étienne Serbe
Dept. Circuits-Computation-Models , Max-Planck-Institute of Neurobiology , Martinsried, Germany

Decoding thiol redox signaling
2016.12.16
Armindo Salvador
CNC/UC-Biotech

PHD THESIS CONCLUDED IN 2016

Amanda Braga de Figueiredo
Recrutamento do receptor de adenosina A2B e ativação da via de AMPc-PI3K-ERK1/2 inibem a resposta de células dendríticas infectadas por Leishmania amazonensis.
March 3, 2016
Supervisors: Rodrigo Cunha

Ana Cristina Figueiredo de Lemos
Metabolic modifications associated with memory deficits.
July 22, 2016
Supervisors: Rodrigo Cunha

Ana Cristina Leal Gregório
Meeting the needs of breast cancer: a nucleolin's perspective.
July 14, 2016
Supervisors: João Nuno Moreira

Ana Francisca Silva de Lima
Biophysical modulation of cell fate through chromatin remodelling.
2016
Supervisors: Lino Ferreira

Ana Isabel Azevedo Serralheiro
Intranasal Delivery of Antiepileptic Drugs: Non-clinical Evaluation of Pharmacokinetics and Brain Biodistribution.
January 7, 2016
Supervisors: Amílcar Falcão

Ana Isabel Plácido Fernandes
Role of endoplasmic reticulum stress in Alzheimer's disease-associated neuronal and endothelial dysfunction.
February 26, 2016
Supervisors: Paula Moreira, Cláudia Pereira

Ana Margarida Ferreira Teixeira
Natural Killer cell-based immunotherapy: a new approach for targeting CSCs in bladder cancer.
July 2016
Supervisors: Francisco Ambrosio

Ana Sofia Tremoceiro Lourenço
Biochemical and interactomic characterization of SAPAP3 - a scaffolding protein involved in obsessive-compulsive disorder.
March 2, 2016
Supervisors: Euclides Pires

André Alexandre Lobo Lopes de Castro
Determinação de Ácido γ-hidroxibutírico (GHB) em sangue, urina e cabelo por GC/MS/MS.Avaliação de níveis endógenos e exógenos e sua aplicação nas áreas da Clínica e Patologia Forense.
September 2016
Supervisors: Francisco Ambrosio

Andreia Fernandes Dâmaso Gonçalves
Can DPP-IV inhibitors or GLP-1 analogs be tomorrow´s therapy for diabetic retinopathy?
September 30, 2016
Supervisors: Francisco Ambrosio

Ângela Crespo
Characterization of KIR2DS1+ decidual Natural Killer cells.
2016
Supervisor: João Ramalho-Santos

Ângela Filipa Valério Fernandes
Targeting nucleolin in lung cancer: towards a personalized therapy.
2016
Supervisors: João Nuno Moreira

Bruno Miguel Ferreira Gonçalves
Preparation and preclinical evaluation of new triterpenoid compounds.
November 24, 2016
Supervisors: Mª Luísa Sá e Melo

Cristina Susana Barcia
Proteasas de polen de Acacia caven y su importancia en alergias.
2016
Supervisors: Carlos Faro

Diana Jurado Serra
Modulation of intestinal inflammation by dietary polyphenols in comparison with 5-aminosalicylic acid: an in vitro approach. April 5, 2016
Supervisors: Teresa Dinis, Leonor Almeida

Elsa Teresa Santos Rodrigues
Occurrence, Fate and Effects of Azoxystrobin in Aquatic Ecosystems.
June 1, 2016
Supervisors: Fernando Ramos

Fernando Dobrachinski
Avaliação do efeito neuroprotetor da guanosina em ratos submetidos a trauma crânio encefálico: envolvimento do sistema glutamatérgico e adenosinérgico.
December 18, 2016
Supervisors: Rodrigo Cunha

Fernando José Figueiredo Agostinho D`Abreu Mendes
Caracterização Celular e Molecular dos Efeitos da Radiação em Neoplasias - Estudo experimental em Linfoma e Carcinoma de Pequenas Células do Pulmão.
2016
Supervisors: Francisco Ambrosio

Filipa Carvalhal Marques
Mechanisms of aging: neuronal orchestration of stress resistance and protein homeostasis in the nematode Caenorhabditis elegans.
May 4, 2016
Supervisors: Henrique Girão

Gianluca Selvaggio
Seeking general principles in the design of defense systems against hydrogen peroxide.
2016
Supervisors: Armindo Salvador

Isabel Maria dos Santos Onofre
Dissecting the pathogenesis of Machado-Joseph Disease in a new human disease model derived from induced pluripotent stem cells.
2016
Supervisors: Luis Pereira de Almeida

Jimmy George
Purines control neuron-glia interaction during neuroinflammation.
January 21, 2016
Supervisors: Rodrigo Cunha

Joana Catarina Reis Pedro
Intra-axonal translation of beta-actin mRNA underlies presynaptic differentiation.
February 2016
Supervisors: Ramiro Almeida

Joana Filipa Duarte das Neves
Neuropeptide Y gene transfer for neuroprotection in Machado- Joseph disease.
February 2016
Supervisors: Claudia Cavadas and Luis Pereira de Almeida

Joana Torres Liberal
Discovery of new anti-inflammatory drugs from natural products through bio-guided assays.
June 14, 2016
Supervisors: Mª Teresa Rosete

João Lemos
Neurobiologia dos Movimentos Oculares.
2016
Supervisors: Miguel Castelo-Branco

Katia A. Mesquita
Role of mitochondria and DNA damage responses in cancer stem cells resistance to chemotherapy.
January 2016
Supervisors: Ignacio Vega Naredo and Emilia Duarte

Lisa Catarina Oliveira Rodrigues
Candida-host interaction: role of purines and adenosine A_{2A} receptors.
January 29, 2016
Supervisors: Teresa Gonçalves, Rodrigo Cunha

Marcelo José Marques Correia
Mechanisms underlying metabolic shift in pluripotent stem cells.
January 27, 2016
Supervisor: João Ramalho-Santos

Margarida Teixeira
Role of NK Cells in tumorigenesis and therapy response of bladder cancer using a humanized CSC-based animal model.
2016
Supervisors: Francisco Ambrosio

Maria Helena Bica Madeira
Controlling neuroinflammation in the retina through $A_{2A}R$ modulation: potential therapeutic implication in glaucoma.
June 2016
Supervisors: Francisco Ambrosio

Maria João da Silva Fernandes Leal Carvalho
Cancro do endométrio: caracterização da célula tumoral, perfil proteómico sérico e implicações na disseminação metastática in vivo.
Supervisors: Francisco Ambrosio

Mariana Botelho da Rocha
Neuropeptide Y regulates autophagy in hypothalamus: a mechanism in life-span increase.
March 2016
Supervisors: Claudia Cavadas and Luis Pereira de Almeida

Mariana Oliveira Conceição
Non-viral silencing of Machado-Joseph disease through the systemic route.
February 16, 2016
Supervisors: Luis Pereira de Almeida, Conceição P. Lima

Michela Comune
Wound healing and pro-angiogenic properties of LL37-conjugated nanoparticles.
September 22, 2016
Supervisors: Lino Ferreira

Patrícia Manuela Ribeiro Pereira
Galactose-conjugated photosensitizers for targeted cancer photodynamic therapy
October 28, 2016
Supervisors: Francisco Ambrosio

Patrícia Raquel Pinheiro Pitrez Pereira
Bioengineering Platforms to Modulate the Activity of Smooth Muscle Cells Derived from Progeria-Induced Pluripotent Stem Cells.
2016
Supervisors: Lino Ferreira

Pedro João Madeira Afonso
Regulation of local translation by BDNF: effects on NMDA receptor trafficking.
May 20, 2016
Supervisors: Armanda Santos and Carlos Duarte

Pedro José Azeredo de São Bento Gouveia
Cardiac tissue constructs for drug screening.
June 2, 2016
Supervisors: Lino Ferreira, Ricardo Neves

Raquel Oliveira
Verbal Memory and Visual Perception in early Alzheimer's disease: Contribution of new diagnostic tools for new classification criteria.
March 22, 2016
Supervisors: Isabel Santana, Mário Simões and Miguel Castelo-Branco

Rui Baptista
Identification of the biological pathways and molecular players involved in pulmonary hypertension associated with mir-424.
2016
Supervisors: Henrique Girão

Rui Filipe Ramos Figueiredo
Microarray-based detection of antibiotic resistance and virulence factors genes of Salmonella spp. isolated from food-producing animals and processed food.
May 5, 2016
Supervisors: Mª Luísa Sá e Melo

Rui Manuel Vicente Benfeitas
Active and passive defenses against oxidative stress: a computational study.
December 9, 2016
Supervisors: Armindo Salvador

Rui Vasco Quintais Gradiz
A radioterapia metabólica no tratamento do adenocarcinoma pancreático.
2016
Supervisors: Francisco Ambrósio

Sandra Cristina Campos de Jesus
Adjuvant nanocarriers for hepatitis B vaccine: formulation design and mechanistic studies.
2016
Supervisors: Olga Borges

Sandra Patrícia Nunes Ribeiro
Anemia and high therapeutic doses of recombinant human erythropoietin in chronic kidney disease – a linkage of risk?
Abril 2016
Supervisors: Francisco Ambrósio

Sara Tavares de Sousa Melo Lima
Induction of different types of cell death by the ether lipid edelfosine in glioblastoma: signalling cross-talk controlling cell death commitment.
May 20, 2016
Supervisors: Mª Celeste Lopes

Sofia Andreia Domingues Viana
Modulação da função dos receptores dos produtos de glicação avançada na Doença de Parkinson.
2016
Supervisors: Francisco Ambrosio

Tiago Alexandre Ramos Teixeira de Sousa Santos
Therapeutic potential of reinoic acid-loaded nanoparticles for brain repair.
March 15, 2016
Supervisors: Emília Duarte

Vanessa Isabel da Silva Mendes
Preparation and Pre-Clinical Evaluation of New Pentacyclic Triterpenoids.
November 24, 2016
Supervisors: Mª Luísa Sá e Melo

MASTER THESIS

Adelaide Carina Rodrigues
Detection of Giardia lamblia e Cryptosporidium in ready-to-eat salads.
Date: September 29, 2016
Supervisor: Maria do Céu Sousa

Adele Ferragamo
Growth of Mycobacterium hassiacum under stress conditions.
2016
Supervisor: Nuno Empadinhas

Ágata Lourenço
The interaction of Giardia lamblia with macrophage cells: the action of parasite proteases on iNOS, COX-2 and p65RelA inflammatory proteins.
September 8, 2016
Supervisor: Maria do Céu Sousa

Alexandra Abrunheiro
Envolvimento do complexo Candida parapsilosis na microbiota de mastites em ovelhas
June 2016
Supervisor: Teresa Gonçalves

Alexandra Fernandes Carvalho
Avaliação histológica, funcional e ultra estrutural de tecido ovárico humano criopreservado.
2016
Supervisor: João Ramalho-Santos

Alexandre Nuno de Morais Sayal Abreu Campos
Brain Connectivity Analysis for real-time fMRI Neurofeedback Experiments.
2016
Supervisor: Miguel Castelo Branco

Allyson Trevino Garcia
Clarifying the Mechanism of Action of Trehalose on Alleviating Machado-Joseph Disease
2016

Amadeu Manuel Rodrigues Carvalho
O papel do farmacêutico na dispensa de suplementos alimentares e dispositivos médicos na farmácia comunitária em Portugal e no Brasil.
2016
Supervisor: Henrique Girão

Ana Alhinho
The Role of NEP-TC in the somatic embryogenesis of tamarillo (Solanum betaceum Cav.).
2016
Supervisor: Paula Verissimo

Ana Catarina Carrêlo
Alterações da motilidade gástrica na Diabetes Mellitus tipo II: o efeito dos agonistas do recetor do glucagon-like peptide I (GLP-1RA).
September 2016
Supervisor: Francisco Ambrosio

Ana Catarina Maltez Xavier
Potenciais efeitos protetores do pré-condicionamento por hipoxia na doença de Alzheimer - ênfase nas vias de sinalização da insulina, dinâmica mitocondrial e autofagia.
2016
Supervisor: Paula Moreira

Ana Catarina Silva Monteiro
Colesterol Oxidase, Hormonas Sexuais e Suscetibilidade à Tuberculose: um Estudo Exploratório.
September, 2016
Supervisor: Nuno Miguel da Silva Empadinhas, Maria Manuel Cruz Silva

Ana Luísa Vieira da Natividade Faria João
The incretin system ABC's in health and disease – Novel approaches for obesity and diabetes treatment.
April 30, 2016
Supervisor: Francisco Ambrosio

Ana Maria Alves
Derivados semissintéticos de compostos naturais monoterpénicos: preparação e avaliação da citotoxicidade.
2016
Supervisor: Alcino Jorge Lopes Leitão, Alexandrina Mendes

Ana Monteiro
Colesterol Oxidase, Hormonas Sexuais e Suscetibilidade à Tuberculose: Um estudo exploratório.
2016
Supervisor: Nuno Empadinhas

Ana Rafaela Oliveira
MiRNAs and risk gene interactions in Alzheimer's disease: from mechanisms to therapeutics.
2016
Supervisor: Ana Luísa Cardoso and Maria Amália Jurado

Ana Raquel Pinho
Desenvolvimento de uma técnica de HPLC para a quantificação de Colistina em plasma humano e a sua monitorização sérica em doentes internados no CHUC.
September 2016
Supervisor: Ana Fortuna

Ana Rita Marques Neves
Terapia fotodinâmica combinada com oxigenoterapia: uma abordagem no retinoblastoma?
2016
Supervisor: Francisco Ambrosio

Ana Rita Samões
MicroRNA-based therapeutic approaches for obesity.
September 2016
Supervisor: Claudia Cavadas

Ana Sofia Alberto Silva
A BACE1 como alvo terapêutico na doença de Alzheimer.
September 2016
Supervisor: Armanda Santos

Ana Sofia Marques Leal
Strategies to reverse cellular senescence and enhance progerin clearance in Hutchinson-Gilford progeria syndrome cells.
September 2016
Supervisor: Claudia Cavadas

Andreia Alves
Estudo da potencial utilização da membrana amniótica como opção terapêutica contra o cancro.
2016
Supervisor: Francisco Ambrosio

Andreia Camila Monteiro Oliveira
Development of a non-invasive approach for oral squamous cell carcinoma diagnosis.
2016
Supervisor: Isabel Marques Carreira

Andreia Ferreira
Oxidoreductase protein family interaction with DJ-1 and oxidative stress-induced modulation of HADHA interactome
2016
Supervisor: Bruno Manadas and Carlos Duarte

Andreia Freixo
Domain-specific functional organization: neurocognitive characterization of a case of hemi-prosopometamorphopsia.
2016
Supervisor: Mª Isabel Santana

Bárbara Marques
Avaliação do potencial terapêutico dos Inibidores das integrinas no tratamento de neoplasias hematológicas.
2016
Supervisor: Ana Bela Sarmento Ribeiro

Beatriz Figueiredo Rodrigues
miRNAs in the regulation of synaptic function.
September 2016
Supervisor: Ana Luísa Carvalho

Bruno Fradique Lopes Ribeiro
Experimental design and analysis in the neuroscience of decision making: a neuroimaging approach.
2016
Supervisor: Miguel Castelo Branco

Carina Sofia Barradas Maranga
Early mitochondrial modifications in YAC128 transgenic model of Huntington's disease.
September 13, 2016
Supervisor: Cristina Rego

Carmen Isabel Pereira Gonçalves
Influência da Função Renal na Otimização da Terapêutica da Amicacina.
July 2016
Supervisor: Ana Fortuna

Carolina Cesário Jordão
Estudo da Doença de Machado Joseph em modelo animal transgénico através de um equipamento de Ressonância Magnética de 9,4T.
2016
Supervisor: Miguel Castelo Branco

Carolina Santos
Identification of microRNAs to promote cell survival for the treatment of ischemic diseases.
2016
Supervisor: Lino Ferreira

Cristina Isabel da Silva Martins
Evaluation of the antimicrobial potential and synthesis of glucosilglicerate in Streptacidiphilus jiangxiensis under different stress conditions.
September 28, 2016
Supervisor: Gabriela Jorge da Silva, Nuno Empadinhas

Daniela Alexandra Dinis Costa
Endothelial cell's response to proteostatic dysregulation: pursuing the protective action of ghrelin.
2016
Supervisor: Cláudia Pereira

Débora Vanessa Lourenço Serrenho
Ghrelin receptor activation regulates hippocampal spine dynamics.
September 2016
Supervisors: Sandra Santos & Ana Luísa Carvalho

Diogo Fonseca
The anti-dermatomycotic properties of caffeine.
September 2016
Supervisor: Teresa Gonçalves

Diogo Miguel Monteiro Canhoto
Effect of chronic hyperglycaemia on beta-catenin levels of hippocampal immature neurons from an Alzheimer's disease mouse model.
November 25, 2016
Supervisor: Cristina Rego

Estela Sílvia Pedreiro
Análise in silico de impurezas provenientes da Síntese de fármacos. Pesquisa de estruturas de alerta de genotoxicidade, mutagenicidade e carcinogenicidade.
October 21, 2016
Supervisor: Maria Luisa Sá e Melo

Eurico da Silva Serrano
Tracking of the intracellular cytokines' transduced signals.
September 2016
Supervisors: Carmen Alpoim and Carlos Rodrigues

Fábio Fiúza Rosa
Direct Reprogramming of Fibroblasts to Dendritic Cells for Immunotherapy.
2016
Supervisor: Carlos Filipe Pereira

Filipa Luísa Lourenço de Almeida
Characterization of mitochondrial function and dynamics in models of Machado-Joseph disease.
September 9, 2016
Supervisor: Cristina Rego

Francisca Mora
Avaliação das Espécies Reativas de Oxigénio e Nitrogénio em Espermatozoides Humanos e sua Aplicação em Técnicas de Procriação Medicamente Assistida.
2016
Supervisor: João Ramalho-Santos

Gonçalo Fernandes Coelho
Strong Vs Weak Teams And Brand Love: Neural Correlates of Decision-Making in Football Fans.
2016
Supervisor: Miguel Castelo Branco

Gonçalo Filipe Moura Ferreira
Butirato e radioterapia no cancro colorretal.
2016
Supervisor: Francisco Ambrosio

Gonçalo Gil Chaves Figueira
A ladder paradigm for studying locomotor coordination in mice.
2016
Supervisor: Miguel Castelo Branco

Gonçalo Sousa Brites
Terapia Fotodinâmica combinação com a quimioterapia: uma opção no osteossarcoma.
2016
Supervisor: Francisco Ambrosio

Helena Alexandra Ribeiro de Carvalho Pinheiro
Gender-specific effects of glucocorticoids in the developing brain: a road to anxiety – focus on microglia.
2016
Supervisor: Francisco Ambrosio

Inês Marques
Rádio-223 no tratamento do carcinoma da próstata.
September 2016
Supervisor: João Nuno Moreira, Ana Abrantes

Inês Veríssimo
IAV vírus modulation of mitochondrial dynamics.
2016
Supervisor: Paula Moreira

Iris Lameiro Lopes
Lipid profile and lipogenic capacity of the seaweed Ulva lactuca (Chlorophyta) - use as potential ingredient for fish aquaculture.
2016
Supervisors: John Jones

Joana de Freitas Fresco Rodrigues Costa
Scale for mapping the brain: the role of stargazin in regulating dendritic spine morphology.
September 2016
Supervisors: Luísa Cortes & Ana Luísa Carvalho

Joana Fernandes
Potencial Terapêutico do Sirolimus e da Metforimina em células de Leucemia Linfoblástica Aguda.
2016
Supervisor: Ana Bela Sarmento Ribeiro

Joana Filipa Costa Pereira
Neuropeptide Y: A Novel Strategy To Delay Aging.
September 2016
Supervisor: Claudia Cavadas

Joana Manuela Tenreiro Pinto
A retrospective analysis of the efficacy of treatment of neuropathic peripheral pain.
2016
Supervisor: Francisco Ambrosio

Joana Margarida Morgado Menoita
Perfil genómico do carcinoma da cabeça e pescoço: existem preditores para as diferentes taxas de sobrevivência?
September 2016
Supervisor: Joana Barbosa de Melo

João Manuel Facas Martins
Correlation between sleep efficiency, memory impairment and amyloid Beta in the spectrum of Alzheimer Disease.
2016
Supervisor: Inês Baldeiras

João Nuno Ramos
Dimensions of the olfactory bulb and sulcus and their relation with olfactory cortical regions in usher syndrome.
June 2016
Supervisor: Miguel Castelo Branco

João Santos
Alterações genéticas em Leucemias Mieloblásticas Agudas – Implicações no prognóstico e terapêutica.
2016
Supervisor: Ana Bela Sarmento Ribeiro

Jorge Simão
Chip e controlo de qualidade proteico durante o envelhecimento
February 2016
Supervisor: Henrique Girão

José Carlos Pereira
Cytoskeleton regulation in bladder cancer cells after photodynamic treatment
December 21, 2016
Supervisor: Francisco Ambrosio

José Miguel Cunha de Alarcão
Perfeccionismo e regulação emocional – uma prespectiva transgeracional.
March 2016
Supervisor: António Macedo, Ana Telma Pereira

Joselina Reis Antunes
Avaliação do polimorfismo NFE2L2 na leucemia linfocítica crónica.
2016
Supervisor: Ana Bela Sarmento Ribeiro and Ana Cristina Gonçalves

Josiane Magalhães Barbosa
Preparação e avaliação da actividade anti-inflamatória de novos derivados polifenólicos glicosilados.
September, 2016
Supervisor: Maria Manuel Cruz Silva e Teresa Cruz Rosete

Judite Raquel Martins Coimbra
Alvos Terapêuticos na doença de Alzheimer- relevância da BACE1 e o desenvolvimento de inibidores desta secretase.
2016
Supervisor: Paula Moreira

Letícia Balanco
Polymorphisms in XRCC5, XRCC4, NFKB2, and BIRC5 genes: Influence in risk and Prognosis of Monoclonal Gammopathies.
2016
Supervisor: Ana Bela Sarmento Ribeiro

Laetitia Gaspar
Clock genes profile as disease biomarkers.
September 2016
Supervisor: Claudia Cavadas

Lígia Vanessa Rocha Fão
Amyloid-beta peptide-evoked Src signaling and redox changes in hippocampal cells.
September 21, 2016
Supervisor: Cristina Rego

Luísa Maria Pais Esteves
Análise in silico do perfil genómico do carcinoma da cabeça e do pescoço para determinação de preditores para as diferentes taxas de sobrevivência.
September 2016
Supervisor: Joana Barbosa de Melo

Madalena Guilherme Sousa
MiRNA-based metabolic modulation in glioblastoma cells: a strategy to surpass tumor chemoresistance
2016
Supervisor: Ana Maria Cardoso, Maria Amália Jurado

Mafalda Melo
MSH3 and BLM gene variants influence myelodysplastic syndrome susceptibility and prognosis, respectively, in a Portuguese population group.
2016
Supervisor: Ana Bela Sarmento Ribeiro

Mafalda Vaz
Impact of formulation and process variables, in technological features of dosage forms for skin delivery.
2016
Supervisor: Carla Vitorino

Márcia Catarina Resende de Oliveira Caroço
Modulation of adenosine in the persistence of Candida albicans inside macrophages
September 2016
Supervisor: Teresa Gonçalves

Marco António Rodrigues Ferreira
PERK inhibition role in Spinocerebellar ataxias.
September 2016
Supervisor: Clévio Nobrega and Luis Pereira de Almeida

Marco Rafael Lopes da Cunha
The importance of cytokines-mediated communication in CSCs' formation
September 2016
Supervisors: Carmen Alpoim and Carlos Rodrigues

Maria Eduarda Sequeira Machado
Perfeccionismo e sintomatologia obsessivo-compulsivos – uma prespectiva transgeracional.
Supervisor: António Macedo and Ana Telma Pereira

Maria Inês Fonseca
Functional investigation of OXPHOS assembly factors in Leber's Hereditary Optic Neuropathy.
September 6, 2016
Supervisor: Manuela Grazina

Maria Manuel Feliciano da Costa Mendes
Lipid nanoparticles as a versatile system for drug delivery.
June 2016
Supervisor: Carla Vitorino

Marina Alexandra Moreira Couto
Role of microglia-mediated neuroinflammation in dysfunction of blood brain barrier in glioblastoma.
2016
Supervisor: Francisco Ambrósio

Mariana Jorge de Oliveira Costa
Comportamento de procura de ajuda e de doença e personalidade.
February 2016
Supervisor: António Macedo and Ana Telma Pereira

Mariana Santos Vidal Tomás
Copy number variations analysis in retinal angiomatous proliferation.
Supervisor: Isabel Marques Carreira

Marina Manuela Ventura Rodrigues
The interactome of stargazin: relevance in neuropsychiatric disorders.
September 2016
Supervisor: Ana Luisa Carvalho

Marta Quatorze Correia
Unraveling the Role of Sirtuin 2 in Metabolic Homeostasis.
July 2016
Supervisor: Claudia Cavadas

Melanie Ribau da Costa
Perfeccionismo e perturbação psicológica – uma prespectiva transgeracional.
February 2016
Supervisor: António Macedo, Ana Telma Pereira

Miguel Neves Correia da Silva
Estudos de adaptação e aplicação de uma Escala de Gravidade da Afasia de causa vascular.
January 2016
Supervisor: Isabel Santana

Nicole Sónia Neto Pedro
Cachexia in patients with head and neck cancer undergoing radiotherapy or concurrent chemoradiotherapy: Characterization, molecular mechanisms and relationships.
September 2016
Supervisor: Luis Pereira de Almeida and Isabel Carreira

Nuno Alexandre Catalão Pina de Almeida
Terapia Fotodinâmica em combinação com ácido acetilsalicílico.
2016
Supervisor: Francisco Ambrósio

Nuno Costa
Inibidores da via da PI3K – Papel no tratamento de neoplasias hematológicas.
2016
Supervisor: Ana Bela Sarmento Ribeiro

Pasqualino de Luca
Regulation of synaptic transmission by BDNF: effects on NMDA receptor-mediated mEPSCs.
September 2016
Supervisors: Carlos B. Duarte and Miranda Mele

Patrícia Corredeira
Avaliação dos mecanismos moleculares de resistência aos moduladores epigenéticos em Leucemia Mielóide Aguda.
2016
Supervisor: Ana Bela Sarmento Ribeiro and Ana Cristina Gonçalves

Raquel Vaz Maia Monteiro
BCI applications regarding the perception of emotions in healthy individuals and autismo.
2016
Supervisor: Miguel Castelo Branco

Renato Sousa
Dissection of hierarchy formation in mice: behavioral and molecular correlates of dominance.
September 2016
Supervisor: João Peça

Rita Gaspar Fonseca
Interacções celulares de enxertos ósseos à base de fosfatos de cálcio.
2016
Supervisor: Francisco Ambrosio

Rita Machado
Visual cortical atrophy in retinitis pigmentosa patients with partially preserved vision: a voxel-based morphometry study.
June 2016
Supervisor: Miguel Castelo Branco

Sahana Srinivasan
Exploring alterations in metabolism and mitochondrial dynamics in a stem cell model of Huntington's disease.
July 8, 2016
Supervisor: Cristina Rego

Sandra Manuela Santos
Perceived causes for changes in sleep pattern in postpartum women.
March 2016
Supervisor: Ana Telma Pereira

Sara Carolina Henriques
Caracterização de um modelo animal de esclerose múltipla – aspectos comportamentais e bioquímicos da intoxicação por cuprizona.
September 7, 2016
Supervisor: Francisco Ambrosio

Sara Raquel Almeida Ferreira
Studying Alpha-Synuclein pathology in mouse striatal synaptosomes and primary neuronal cultures.
2016
Supervisor: Paula Moreira

Simona Zarcone
Attività antiossidante e anti-Acetilcolinesterasi di una frazione ricca in antocianine da mirtillo coltivato in Portogallo (Vaccinium corymbosum L.): uno studio in vitro.
June 2016
Supervisor: João Laranjinha

Sylvie Gonçalves
New therapeutic strategies for osteoarthritis: injective cell therapy.
2016
Supervisor: Paula Moreira

Tomás José Rodrigues de Freitas Meneses Osório
Colangiocarcinoma: Análise clínica e molecular de uma série.
2016
Supervisor: Francisco Ambrosio

Vanessa Jorge Henriques
Astrocytic A2A receptors: novel targets to manage brain disorders.
September
Supervisor: Rodrigo Cunha

Vitor César Arantes Pinheiro
Impact of Methamphetamine on Blood-Brain Barrier: Role of Exercise.
2016
Supervisor: Francisco Ambrósio

TECHNOLOGY TRANFER

Translational research and technology transfer have been progressively developed in CNC leading to a promising interaction with Industry and local authorities.

The main contribution of CNC for that goal was the creation of a technology transfer unit, Biocant, in collaboration with Cantanhede Municipal Council. This unit became the anchor of Biocant Park, a Biotechnology Park that is rapidly growing by atracting new Biotechnology companies.

BIOCANT

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

Companies operating in Biocant Park

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

SCIENCE COMMUNICATION AND OUTREACH

Coordinator: Cláudia Cavadas, PhD
Team: Adalberto Fernandes | Graduate Technician
Inês Braga | Student
Sara Varela Amaral | PhD

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 order to construct a truly scientific citizenship and a more knowledgeable society;

To consolidate CNC institutional image for the national and international scientific system, national and regional political decision-makers, public and private funders, and different types of publics;

To inspire and engage scientist in science communication initiatives, give them tools that improve the public engagement;

To evaluate our science communication strategies in order to improve and understand the best practices to engage community in science and scientific themes;

To establish strategies that contributes to a better communication and team spirit inside the research center.

Our partnerships – Ciência Viva, Science Museum of the University of Coimbra, University of Coimbra, Maratona da Saúde, Instituto de Educação e Cidadania, Jornal Público, Dana Foundation, Federation of European Neuroscience Societies, between others – are crucial to strategically target different publics. The outreach efforts have the enthusiastic involvement of the Center's research staff, graduate and undergraduate students.

SCIENCE IN THE MEDIA

Responsible: Adalberto Fernandes

CNC in the Media

The Science Communication Office is in charge of the public relations process, communicating science with news-values in the context of different agenda-settings, preserving the accuracy of scientific knowledge, and successfully liaising researchers with journalists. In 2016, CNC was in the news 1136 times with an advertising value of 2.545.544 euros, reaching a total number of 33.899.955 audiences. Some examples are available in CNC website *(http://www.cnbc.pt/outreach/outreach00.asp#divNews).* The numbers relating to the type of media and geographical impact are presented in the graphics below (Figures 1, 2 and 3).

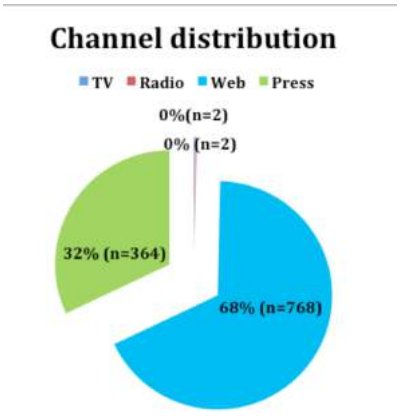


Fig. 1. News about CNC in the media in 2016 – Channel distribution.

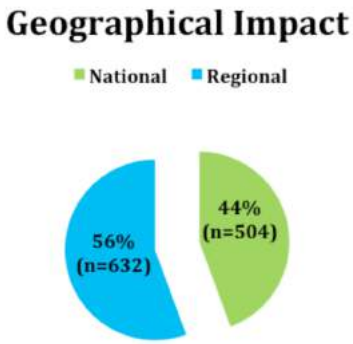


Fig. 2. News about CNC in the media in 2016 – Geographical impact

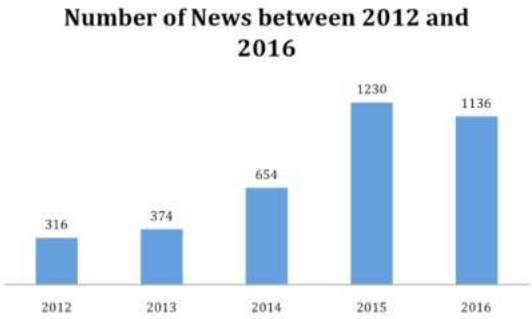


Fig. 3. News about CNC in the media between 2012 and 2016.

CNC in the Social Media

The importance of social media in building strong relationships between scientists and society is visible in the results of the communication strategy for the CNC Facebook page, with 4832 page 'likes' in 2016 (Figure 4), an increase compared to 2015 (3704 "likes"). Moreover, 465 posts were added and it had 973.426 visits in 2016. In 2016 was launched the LinkedIn account for CNC, in order to meet the professional needs of CNC researchers about professional networking.

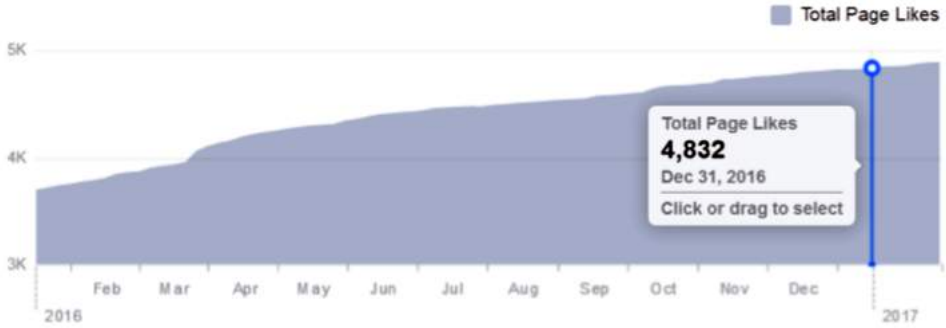


Fig. 4. Total Facebook page 'likes' in 2016.

PUBLIC ENGAGEMENT IN SCIENCE

Responsible: Sara Varela Amaral

Brain Awareness Week (BAW) **|** March 2016

Fig. 5. Program of activities of Brain Awareness Week (BAW) organized by the Science Communication Office - CNC. Funded by FENS.

The Brain Awareness Week (BAW) 2016 organized by by the Science Communication Office – CNC happened in Coimbra between 6th and 26th of March. The activities involved **55** researchers and reached **1121** people from different publics. Our BAW included the following activities:

1. Brain Myths, Facts and Research - radio and movies: Radio contents to explain or demystify myths about the brain and communicate scientific messages. The produced contents were transmitted by RUC every day during BAW and were shared in social networks of CNC and RUC. During BAW, RUC produced and transmitted a program about neuroscience with participation of neuroscientists. The podcast of the program is available on CNC website. Additionally, small videos, that we call "*selfie papers*", were developed where the scientist explains in an informal way his/her last published paper. We produced the following *"selfie papers"*: "The race of the monocyte to the brain" – Joana Guedes, "Building synapses" – Maria Joana Guimarães, "Phosphorylate to disaggregate" – Carlos Matos and "Can we delay the aging?" – Mariana Botelho. The videos and radio contents were shared on *CNC youtube channel* and *facebook page*. All the contents are on *CNC webpage*.

Numbers (*)

Views of publications on CNC´s Facebook page: 105799

Shares of publications on CNC´s Facebook page: 306

Likes on publications on CNC´s Facebook page: 1734

Researchers involved: 17

(*) data collected on 31th March 2016

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

Numbers

Participants: 882

Number of schools and institutions: 13

Researchers involved: 40

***Fig. 6**. Photos of the activity "Brains at the Schools" in schools and associations during BAW.*

3. Lab visits: CNC's research groups organized visits to their laboratories and gave talks about their research work.

Numbers

Participants: 129

Number of schools and institutions: 3

Researchers involved: 14

4. Neuroquiz: Public quiz in an informal environment (Aqui Base Tango, pub), organized by QUIZ SHOW Coimbra in collaboration with neuroscientists. The event happened in a local coffee shop and challenged the participants to explore brain-related issues like neurodegenerative diseases and brain function and to relate these topics with music, cinema and general knowledge. The room was full – 50 participants.

5. Brainyevent: CNC researchers participated in a event organized by a Portuguese fundraising project dedicated to the awareness of the society about the importance of biomedical research (*Maratona da Saúde*) with the collaboration of the Science Center Exploratório. The main objectives of this event were to engage publics in scientific research and to contribute to fundraising for science. Specifically, the fundraising

activities aim collecting funds to the research on neurodegenerative diseases. The hands-on activities, games and interactive modules of the exhibition about brain will trigger the debate between researchers and society. The event had 60 participants. The event resulted in the production of a *small TV content* by the national TV public channel (RTP).

Fig. 7. Photos of "Brainy Event" at Exploratório

Evaluation:

We performed evaluation of the impact of BAW activities organized by CNC (Fig.8) . These results work were presented, in poster format, at the international conference - FENS Forum for Neuroscience (July 2016, Denmark) - and also at the national science communication conference – SciCom PT (May 2016, Lisbon). The Figure 8 it is presented an example of the collected results.

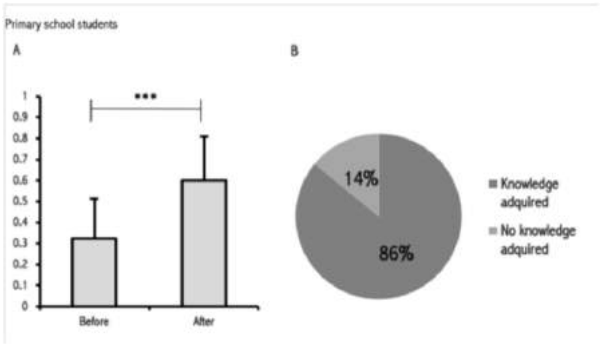


*Fig. 8. Example of result of the impact evaluation of BAW. Knowledge score. (A) Knowledge index before and after BAW activities. Repeated-measures ANOVA were performed to explore the differences between the two evaluation moments, "***" p<0,001 (n=100, primary school students). (B) Percentage of the population that acquired and that did not acquire knowledge after the activities (n=100, primary school students). SOURCE: Varela Amaral S, Braga I, Fernandes A, Cavadas C (2016) Brains Facts and Research 4evervone. Fens Forum 2016.*

Immunology day | April 2016

Portuguese Society of Immunology (SPI) promoted the Immunology Day for the first time in our country. The "Cell reprogramming and developmental hematopoiesis" group organized at UC-Biotech a set of activities tailored to high-school students during Immunology Day. The event targeted about 30 students.

Da célula à escola | April 2016 – May 2016

Project promoted by MITOX lab (PI: Paulo Oliveira) and Science Communication Office with a primary school in Coimbra (Escola Básica da Solum). The main goal of this project was to teach basic concepts of cell biology exploring questions as: What is a cell?; Where can I find cells?; What is inside the cell?; How cells work?; How do cells get energy to function?. The project involved more than 100 children (6-10 years-old).

Fig. 9. Image of an educational content produced during the project "Da Célula à Escola"

Science in the Holidays | July 2016

Science in the Holidays 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 2016 CNC received 12 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 12 positions offered in 2016 were the following:

Title	Nº students	PI
Análise morfológica de neurónios em desenvolvimento	1	Ricardo Rodrigues
A Energia da Vida: As Folias Mitocondriais	2	Paulo Oliveira
Neurónios, apetite, obesidade e envelhecimento	3	Cláudia Cavadas
MitoFitness: à procura de um programa de treino mitocondrial	4	Anabela Rolo
Reprogramação Celular e as Células Estaminais do Sangue	1	Carlos Filipe Pereira
Investigação e Diagnóstico no Laboratório de Bioquímica Genética	1	Manuela Grazina

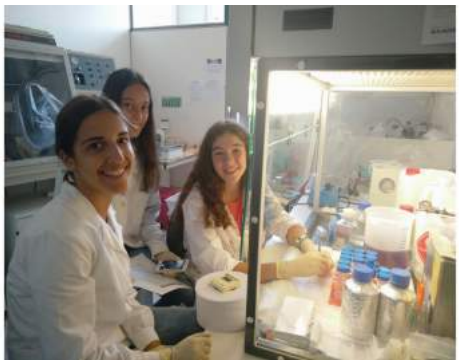


Fig. 10. Photos of Science in the Holidays project

Science in the Summer | July and September 2016

During one month (week-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.

Fig. 11. Photos of Science in the Summer project.

European Researchers´Night (ERN) | September 2016

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 2016 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 activities during ERN 2016.

Fig. 12. Photos of ERN.

Maratona da Saúde | January 2016 – July 2016

Fig. 13. Participation of CNC.IBILI researchers in Maratona da Saúde TV show at National TV RTP.

Maratona da Saúde, a novel initiative in Portugal, is a fundraising project through science communication events aiming at raising awareness of the public and promoting biomedical research. Biomedical research is a unique subject with the potential to bring hope to people and to make disease prevention and treatment possible. The innovative aspect of this initiative lies on joining entertainment to science communication, either through comedy, music or acting. This strategy has proven success in other countries, and it's an original way to bring information and hope to people, and to serve the society. *Maratona da Saúde* is committed to have the Portuguese population's confidence and trust, and gathered the support of key partners, namely the public radio and television station (RTP), several national research centers. In 2016 *Maratona da Saúde* was dedicated to awareness and fundraise to neurodegenerative disorders. CNC have been involved during all the edition of Maratona da Saúde: organization of a public event (Brainy Event), collaboration with MSc students in the creation of a movie to fundraise *(https://www.youtube.com/watch?v=2ei0F0_NOhM&feature=share),* development and participation of science communication activities (music festival NOS Alive) and participation on TV shows and in the final show (March 2016).

Science & Technology Week | November 2016

During Science & Technology Week CNC.IBILI researchers promoted several science communication initiatives in different venues:

- *Cafés Scientifique*: We organized informal conversations in coffee shops and pubs. The events occurred in the hometown of the researcher responsible of each event;

- Open Labs: We received visits from high-school students and associations in our labs;

- Public event: Science communication conference "Brain without borders and stem cells" to general public included in the program of the scientific symposium "Brain without Borders".

Overall, our activities engage about 500 people.

Fig. 14. Program of Science & Technology Week.

Art and Science | December 2016

Science Communication Office promoted the "Out of the Box" projects, an initiative that involved researchers that are also artists. The performances were presented at 1st meeting in biomedical research @ UC:

Concert with music and dance, presented during the dinner of the meeting;

Theater Play – O Ponto que nos Une – produced by Marionet and CNC.IBILI researchers (see here: *https://www.youtube.com/watch?v=6risgecX1PQ&t=145s*);

Fig. 15. Out of the Box projects of 1st meeting in biomedical research @ UC.

ORGANIZATION OF ADVANCED COURSES

Organizers: Cláudia Cavadas, Adalberto Fernandes & Sara Varela Amaral

Advanced Course – Soft Skills for PhD students in Biomedical Research | May 2016

Give tools and inspire scientists to communicate is crucial and requires knowledge not only of science, but of information technologies, journalism, visual communication and public engagement. Science Communication Office organized an advanced course, integrated in PhD programme in experimental biology and biomedicine, in order to help scientists to engage the public in different environments (PROGRAM: *http://beb.cnbc.pt/det_courses.asp?id=767*).

Fig. 16. Participants and lecturers of Advanced Course in Soft Skills for PhD students in biomedical research.

High School Teachers training | September-December 2016

Science Communication Office established a collaboration with teacher training centers of Coimbra region - Nova Ágora and Minerva – in order to promote training actions in neuroscience and cell biology that target high-school teachers.

In 2016 we promote the following actions:

Title	**Researchers involved**	**Duration**	**Nº participants**
A aprendizagem das células: Biologia reprodutiva e células estaminais	João Ramalho-Santos e Sara Varela Amaral	4 hours	26 (limit de participation: 30)
Neuroquestões	Cláudia Cavadas e Ana Rita Álvaro	3 hours	55 (limit of participation: 60)

SCIENCE COMMUNICATION WITH PEERS

1st meeting in Biomedical research @ UC | December 2016, Universidade de Coimbra (FMUC, polo III)

Coordination of the activity: Ana Luísa Carvalho

The **1st 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. A diversified program provided inspiration for asking novel questions, planning future projects and fostering collaborations: *http://www.meetingcncibili2016.cnc.uc.pt/Programme.html*. 363

Fig. 17. Moments of 1st meeting in biomedical research @ UC.

CNC.IBILI Retreat | November 2016, Inatel – Foz do Arelho

Coordination of the activity: Catarina Resende de Oliveira

CNC.IBILI retreat was a moment of encounter and exchange of ideas by all doctorate members of the consortium. In 2016 a program (2 days) was organized with the several themes as:

- Future strategy of the consortium;

- Ice break and team building (theatre strategies to help communication);

- Core facilities at CNC.IBILI;

- Future of science in Portugal (with the participation of Doutor Miguel Castanho from FCT);

- Ideas to grow and innovate (ideas contest to the consortium).

About 100 researchers participated.

BEB Symposium | September 2016, Museu da Ciência da Universidade de Coimbra / Teatro da Cerca de São Bernardo

Coordination of the activity: BEB students 2016 – Ana Raquel Coelho, Cláudia Deus, João Amorim, Marcos Gomes, Maria Inês Martins e Luís Martins

The 12th Edition of the Doctoral Programme of Experimental Biology and Biomedicine (PDBEB) of the Center for Neuroscience and Cell Biology (CNC) — University of Coimbra, organized the third edition of the BEB Symposium. The meeting had as its motto "*scientia potentia est*" (Knowledge is power) that guided the epilogue of a scientifically enriched day with a brainstorming session in the evening, opened to the entire academic community, under the baton of the inverted question: Is Knowledge Power?

The organizers invited world-renowned neuroscientists working on different fields of neuroscience, to share the state-of-the-art and the future of neuroscience research. To address the different core areas of CNC — Neuroscience and Behaviour; Stem Cell Research; Cellular and Molecular Biology; Immunology — PDBEB *alumni* were invited to share the course of their professional life after their PhD and talk about their current work. The evening debate had a panel composed of notable figures of Portuguese and international scientific, cultural and political society that will mirror a spectrum of scientific sensibilities and non-scientific relevant to the subject. This part of the event was also broadcasted live via Rádio Universidade de Coimbra (RUC). This edition also features the BEB Award, that awarded a candidate the opportunity to travel and present their work in an International Scientific Meeting, sponsored by Bluepharma. 120 people of scientific community participated on 3rd BEB Symposium.

Fig. 18. Moments at 3rd BEB symposium.

Beer for Thought | Since December 2016 (every month)

Coordination of the activity: Sara Varela Amaral

Science Communication Office and PDBEB students hosted the 1st Beer for Thought, a moment to promote networking between CNC members. The activity was launched in December and will be repeated every month.

Fig. 19. Organizers of 1st Beer for Thought.

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 husbrandy, 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.

The Animal House contains a barrier maintained facility, with 8 positive pressurised rooms, which are kept at 22ºC with a relative humidity of 55%. The rodents are breed 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)

Animal room – IVC cages (type I)

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.

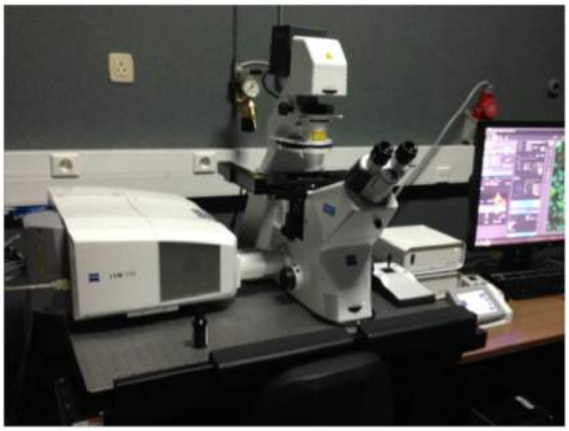
The unit provides training to inexperienced researchers and organizes annual flow cytometry seminars with the purpose to make this powerful technology known and available to all CNC researchers.

FACSAria™ III (Becton Dickinson) – 12 colours

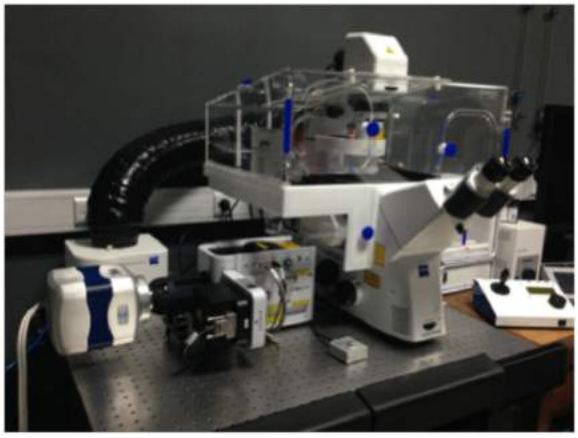
FACSCalibur (Becton Dickinson) - 4 colours

MICROSCOPY IMAGING CENTER OF COIMBRA - CNC

Head of Unit: Luísa Cortes



Confocal LSM 710 (34 channels)



Confocal Cell Observer Spinning-Disk

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 2016, the MICC facility supported 120 users from 58 research groups, three of them from outside the CNC.IBILI Unit.

In 2016, scientific collaborations with a CNC.IBILI research group, and an external research group from University of Beira Interior, resulted in two publications in which Cortes L is co-author (PMID: 27590517, IF 5.008; and PMID: 27260166, IF 4.667, respectively).

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. Caldeira MV and Cortes L organized the "II Quantitative Fluorescence Microscopy Course" (CNC, Nov 28th-Dec 2nd), and the JPND BIOMARKAPD Couse: "Biological Markers in Neurological Diseases – Present and Future Approaches" (CNC, June 24th-26th). Cortes L lectured at the "EMBO Practical Course: 3D developmental imaging" (IGC, July 1st-9th), and at the BEB and Health Science Doctoral Programmes.

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 RNIE roadmap, Cortes L being the Coordinator for the Mondego & Beiras Pole. MICC-CNC also participates in the EuroBioImaging network, which is an ESFRI initiative.

Team:

Luísa Cortes, PhD

Margarida Vaz Caldeira, PhD

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.

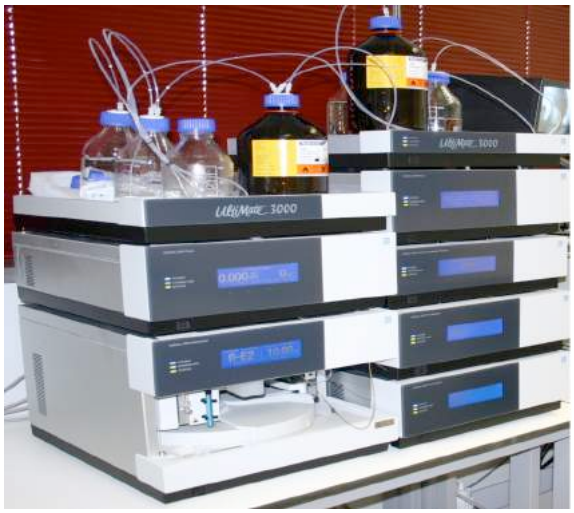
Presently, the Mass Spectrometry Unit is equipped with state of the art technology, namely: a 4000 QTRAP mass spectrometer (Applied Biosystems/MDS Sciex), hybrid triple quadrupole/ion-trap mass spectrometer with capacity of MS3, and a two-dimensional liquid chromatography system Ultimate 3000 (Dionex/LCPackings). 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 (June 2016-present): Carolina Ribeiro

Certification NP EN ISO 9001:2008. The transition to NP EN ISO 9001:2015 was successful achieved.

The Coordinator 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, only one sample of amniocytes was received for genetic prenatal testing, due to a pregnancy in a family affected with Leigh syndrome due to a mtDNA pathogenic mutation. Several fibroblast samples were used for further analyses.

BIOCHEMICAL ANALYSIS

Mitochondrial Respiratory Chain (MRC) and Krebs cycle enzymes

Biochemical assays related to mitochondrial respiratory chain biogenesis, functioning and maintenance are essential for achieving the probable diagnosis of Mitochondrial Respiratory Chain and Krebs Cycle Diseases.

A total of 28 patients suspected of Mitochondrial Cytopathy were studied, corresponding to the analysis of 29 samples, in 290 assays, including lymphocytes isolated of peripheral blood (18), muscular (10) and liver (1) biopsies. A MRC deficiency was detected in 3 patients (11%).

Krebs cycle enzymes (fumarase, aconitase, alfa-ketoglutarate, malate and isocitrate dehydrogenases) analysis was performed in one patient sample of blood cells, corresponding to 7 assays. There was not any deficiency concerning these activities. These tests represent an important set up for improving diagnostic of mitochondrial bioenergetics' defects.

GENETIC ANALYSIS

Genetic screening is the only available tool for reaching 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.

***Mitochondrial DNA (mtDNA) and nuclear (nDNA) genomes studies*:** 44 samples (blood - 32, muscle – 10, liver – 1 and amniocytes - 1) were received for DNA extraction.

Molecular differential analysis of mitochondrial cytopathies, as a high throughput screening, has been performed by sequencing analysis, of 11 mtDNA regions, covering a total of 424 mtDNA sequence variations that include 31 confirmed pathogenic mutations associated to MRC associated diseases. We have continued to screen deletions by flanking PCR of 6 hot-spot regions. Gene panel analysis was also performed in selected samples, according to clinic manifestations and results from previous biochemical and/or genetic screening. To follow the advances in genetic, during the last year, we have implemented total mtDNA sequencing analysis by NGS. Using this assay, we have already analysed 20 samples in the last year.

Forty-four patients, suspected of Mitochondrial Cytopathy, were studied, allowing detection of 701 mtDNA alterations. Pathogenic mutations were found in 2 patients and in blood and amniocytes samples of a family member of one index case, previously diagnosed in our laboratory.

Mitochondrial DNA depletion syndrome (MDS) is caused by defects in intergenomic communication and comprises a heterogeneous group of diseases, namely due to nuclear genes mutations leading to severe reduction of mtDNA content, with energy failure. Copy number (mtDNA) assays are part of the genetic mitochondrial genome screening.

Concerning the screening of nDNA defects causative of MRCD, we have screened **14** samples, comprising a total of 1,688 assays.

POLG1 gene was screening in 12 samples of 12 patients, in 1,560 assays, allowing the detection of 72 sequence variations.

Screening of ***TK2*** gene (2 samples of 2 patients, 128 assays) did not show any alteration, but it was relevant for genetic diagnosis and genetic counselling.

LABORATORY OF NEUROCHEMISTRY

Coordinators: Catarina Resende Oliveira, Inês Baldeiras

The Neurochemistry Unit is integrated in the Neurology Department of the University Hospitals of Coimbra (CHUC) and develops its activity in essentially two areas: laboratorial support of diagnosis and follow-up of neurological and metabolic diseases and clinical research of neurodegenerative disorders.

In what concerns the immediate support to the patient, the Neurochemistry Unit provides several test that help in the diagnosis and control of progression of neurodegenerative, demielinizing, neuromuscular, metabolic and vascular disorders:

- Cerebrospinal Fluid (CSF) cell count and chemical analysis
- Electrophoresis of CSF/serum proteins
- Detection of Immunoglobulin G Oligoclonal Bands in CSF/serum by Isoelectrical Focusing
- Determination of plasmatic Vitamin A and E levels by high-performance-liquid chromatography (HPLC)
- Evaluation of plasma and CSF redox status
- Quantification of urinary levels of purines and pyrimidines by HPLC
- Quantification of CSF levels of 5-Methyltetrahydrofolate (5-MTHF) by HPLC
- Seric evaluation of anti-neuronal antibodies in patients with polineuropathies
- Quantification of serum levels of antiepileptic drugs in patients under therapy
- Evaluation of the activity of Adenosine Deaminase (ADA) isoenzymes

Early and differential diagnosis of dementias is a particular important area of work of this laboratory. The Neurochemistry unit is, in the framework of the Portuguese Epidemiological Surveillance Program for Human Prion Diseases, the national reference laboratory for Cerebrospinal Fluid (CSF) analysis, and it performs:

- Quantification of CSF levels of total-Tau protein, phosphorylated-Tau protein and β-amyloid1-42 peptide for dementia diagnosis
- Detection of 14-3-3 protein in CSF in suspected cases of Creutzfeldt-Jakob Disease (CJD)
- Immunodetection of Prion protein isoforms in brain extracts of CJD patients

Characterization of oxidative status in neurodegenerative disorders is also a specific interest of this unit. In this context, we perform, either in patient's blood or in several cellular extracts, the:

- Evaluation of plasma and cellular oxidative stress

This includes the determination of a broad spectrum of non-enzymatic (uric acid, vitamin E, oxidized and reduced glutathione) and enzymatic antioxidants (glutathione reductase and peroxidase), nitrogen oxidative species and lipid (malondialdehyde) and protein (carbonyls) oxidation markers.

During first half of 2016, the Neurochemistry Unit has received around 400 blood and 250 CSF samples and has performed the following analysis:

	Blood (Serum/Plasma)	**CSF**	**Urine**	**Brain extracts**
Cytochemistry and electrophoresis	181	181		
IgG Oligoclonal bands	125	125		
Vitamin A/E	155			
Redox Satus	15	3		
Purines & Pyrimidines			2	
Anti-neuronal antibodies	17			
Antiepileptic drugs	1			
ADA2 activity in serum/plasma	30			
CSF levels of 5-MTHF		10		
CSF Tau, p-Tau and Aβ42		134		
CSF 14-3-3 protein		49		
Prion protein isoforms				1
Oxidative Stress	144			

LABORATORY OF NEUROGENETICS

Coordinator: Maria do Rosário Almeida

Molecular testing of Neurodegenerative diseases

The Neurogenetics Laboratory continues to provide the molecular diagnostic tests for several Neurodegenerative diseases such as: Frontotemporal Lobar degeneration (FTLD), Amyotrophic lateral sclerosis (ALS), Familial Alzheimer Disease (AD) and Parkinson´s Disease (PD). The genetic analysis included known causative genes, *PSEN1* and PSEN*2*, *APP, MAPT*, *PGRN*, *C9orf72*, *SQSTM, Parkin* and *LRRK2* as well as the known susceptibility risk gene for AD and PD, *APOE* and *GBA,* respectively. In addition, during 2016, the determination of the serum progranulin level has been performed a pre-screen procedure to identify patients harboring null PGRN mutations prior to direct sequencing to be performed. This year there was a slightly increase in the number of referrals for FTLD and ALS. Regarding the genetic tests available for PD, several requests were also arrived in the laboratory, not only to study the most common causative-genes for the dominant and recessive forms of PD such as: LRRK2 and Parkin but also to the susceptibility factor for this diseasse, GBA, particularly in cases with cognitive impairment. The group was aware that the next step to improve the molecular diagnosis of these neurodegenerative diseases requires the implementation of next generation sequencing technology (NGS), already set up in different international reference laboratories, therefore, the team members were also involved in setting up this methodology in the laboratory involving the design of custom gene Panels.

LABORATORY OF CELL BIOLOGY

Coordinator: Mário Grãos

Staff: Catarina Domingues | PhD Student
Tânia Lourenço | PhD Student
Heloísa Gerardo | Technician
Inês Caramelo | Student

The Laboratory of Cell Biology develops its activity between research projects and service providing.

In terms of research, in 2016 two international peer-reviewed publications were produced (1 research article and 1 review) with the PI as corresponding author, and 1 proceeding of scientific meeting. In terms of competitive funding, the laboratory participates in a project funded by the National Multiple Sclerosis Society, USA (2016-2019).

The laboratory continues efforts to provide advanced training. The PI was co-supervisor of 1 PhD student and supervisor of 1 MSc student, 2 research fellows, 1 technician and 1 internship student, as well as several lab rotation students from the Master in Molecular and Cell Biology (MBCM) organized by the Department of Life Sciences of the Faculty of Sciences and Technology of the University of Coimbra and other Master programmes.

In terms of advanced courses, the PI taught in 2 courses of MBCM, 1 course of PDBEB PhD Programme, was invited speaker at the I Portuguese Glial Network symposium and at the II Biotechnology Meeting at ESAC (Escola Superior Agrária de Coimbra), Coimbra.

Several outreach activities were carried out. The PI was invited speaker at various courses and events organized by IEC (Instituto de Educação e Cidadania) and lab members participated in 'Semana do Cérebro' organized by the CNC.

Concerning service providing, the laboratory continues its 2 services. One service supplies the determination of bio-molecules using the multiplex xMAP technology (Bio-Plex) and during 2016, 46 analytes were determined. Since each kit uses a 96-well plate format, this represents approximately 3400 sample data points. Another service is related to testing the viability of cryopreserved tissues samples. During the year of 2016, a total of approximately 4800 samples were tested (37% increase compared with the year 2015).

In 2016 the lab updated its certification for *Cell and tissue culture* to the ISO 9001-2015 and established a new certified service related with cell differentiation.

LABORATORY OF IMMUNOLOGY AND ONCOLOGY

Coordinator: Paulo Rodrigues Santos

Scope

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:

BCR-ABL1, qualitative, RT-PCR

BCR-ABL1, quantification, real-time quantitative PCR

ABL KD, mutation screening, High-resolution melting (HRM) real-time PCR

ABL KD, mutation identification, Next-generation sequencing (NGS)

BCR-ABL1^{+} leukemic stem cells, Fluorescence-activated cell sorting (FACS)/RT-qPCR

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

Service activity

The laboratory established during the last six years a robust and sustainable service, increasing its capacity to provide specialized tests to the community.

Development and Innovation

During 2016, our laboratory developed new tests for characterisation of cancer stem cells and immune monitoring of cancer and infection diseases.

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 Růžičková, Clinical Hematology Service, Coimbra Hospital and Universitary Centre, Coimbra, Portugal.

José Manuel Casanova, Locomotor Apparatus Tumour Unit, Coimbra Hospital and Universitary 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 Sarmento, 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 Fernando Mendes, Biophysics and Biomathematics Institute, IBILI-Faculty of Medicine, University of Coimbra; CIMAGO, FMUC-Faculty of Medicine, University of Coimbra; Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School, Department Biomedical Laboratory Sciences, Coimbra, Portugal.

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

Paulo Oliveira and Vilma Sardão, Metabolism, Aging and Disease Group and MitoXT: Mitochondrial Toxicology and Experimental Therapeutics, Center for Neuroscience and Cell Biology, Coimbra, Portugal.

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

Publications

1. Ferreira-Teixeira M, Paiva-Oliveira D, Parada B, Alves V, Sousa V, Chijioke O, Münz C, Reis F, Rodrigues-Santos P, Gomes C. Natural killer cell-based adoptive immunotherapy eradicates and drives differentiation of chemoresistant bladder cancer stem-like cells.
2. Viana SD, Valero J, Rodrigues-Santos P, Couceiro P, Silva AM, Carvalho F, Ali SF, Fontes-Ribeiro CA, Pereira FC. Regulation of striatal astrocytic receptor for advanced glycation end-products variants in an early stage of experimental Parkinson's disease.
3. Mendes F, Domingues C, Rodrigues-Santos P, Abrantes AM, Gonçalves AC, Estrela J, Encarnação J, Pires AS, Laranjo M, Alves V, Teixo RJ; Sarmento-Ribeiro AB, Botelho MF, Santos-Rosa M. *The role of immune system exhaustion on cancer cells escape and anti-tumor immune induction after irradiation.*
4. Monophosphoryl Lipid-A: A Promising Tool for Alzheimer's Disease Toll. Rego Â, Viana SD, Ribeiro CA, Rodrigues-Santos P, Pereira FC.
5. Mazini PS, Alves HV, Reis PG, Lopes AP, Sell AM, Santos-Rosa M, Visentainer JEL and Rodrigues-Santos P Gene Association with Leprosy: A Review of Published Data.
6. Areia A, Vale-Pereira S, Alves V, Rodrigues-Santos P, Santos-Rosa M, Moura P, Mota-Pinto A. *Can membrane progesterone receptor alpha on T regulatory cells explain the ensuing human labour?*
7. Areia AL, Vale-Pereira S, Vaz-Ambrósio A, Alves V, Rodrigues-Santos P, Santos Rosa M, Moura P, Mota-Pinto A. Does progesterone administration in preterm labor influence Treg cells?

Team: *Patrícia Couceiro, Jani Sofia Almeida, José Rui Simplício*

Genome Sequencing Biology

Coordinator: Conceição Egas

Staff: Cristina Barroso | Graduate Technician

The Genome Sequencing laboratory - 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 to R&D groups and companies. The Unit has a multidisciplinary team of experts in sequencing, genotyping and bioinformatics, delivering personalized solutions, from consultancy in experimental design to large scale data analysis with user-friendly outputs.

Services available at Genoinseq:

Small genome sequencing and annotation

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

Genoinseq provided a total of 37 sequencing or/and data analysis services in biodiversity of environmental communities (18), small genome sequencing (10) and exome or genotyping for clinical research (9).

The Laboratory initiated its participation in the H2020 project Metafluidics: Advanced toolbox for rapid and cost-effective functional metagenomic screening - microbiology meets microfluidics. H2020-LEIT-BIO-2015-1; ref. 685474-2. 2016-2020.

Genoinseq also participated in the Phase IIa Clinical Trial of the company Gene PreDiT. GPD-01-01 “Influence of single nucleotide polymorphisms of GP0044 gene on body weight and fat mass reduction by GPP846 in obese subjects. The phase II, multicenter, double-blind study is the first trial that aimed to validate a genotype-directed therapy based on a potential predictive biomarker of response to Perindopril to body weight and fat mass reduction. Team members received the Good Clinical Practice for Clinical Investigators and Trial Sites, by Abbvie, Inc.

The research activities of the unit resulted in the publication of 3 papers in peer-reviewed journals. On the other hand, the results of sequencing and/or bioinformatics analysis to clients resulted in 19 publications in peer-reviewed journals.

The Laboratory was granted the ISO 9001:2015 certification by APCER in next generation sequencing of nucleic acids and bioinformatics tools for DNA and RNA analysis.

Research papers:

Cardoso JMS, Anjo SI, Fonseca L, Egas C, Manadas B & Abrantes I. (2016). *Bursaphelenchus xylophilus* and *B. mucronatus* secretomes: a comparative proteomic analysis. Scientific Reports 6, Article number: 39007. doi:10.1038/srep39007.

Jones-Dias D, Clemente L, Egas C, Froufe H, Sampaio DA, Vieira L, Fookes M, Thomson NR, Manageiro V and Caniça M. (2016) *Salmonella Enteritidis* Isolate Harboring Multiple Efflux Pumps and Pathogenicity Factors, Shows Absence of O Antigen Polymerase Gene. Front. Microbiol. 7:1130. doi: 10.3389/fmicb.2016.01130.

Simões MJ, Carmona S, Roberts R, Wainwright G, Faro C, Silva E and Egas C. (2016). *CYP1B1* mutational screening in a Portuguese cohort of primary congenital glaucoma patients. Ophthalmic Genet. 2016 7:1-3. DOI: 10.1080/13816810.2016.1188121.

MitoXT Services Laboratory

Coordinator: Vilma Oliveira

Certification NP EN ISO 9001:2008

During drug development, the road towards a successful clinical trial also depends on whether toxicity to tissues is averted. During pre-clinical studies, it is critical to understand whether a drug candidate presents cellular and mitochondrial liability which may jeopardize its future use in the clinical market. Since mitochondria are known as the cell powerhouses and responsible for many critical tasks in cell metabolism, molecules that are toxic to that intracellular organelle lead to a bioenergetic disruption of the cell and organ failure. It is at this point that a line is drawn between a very promising compound and one that needs to be re-designed.

Our mission

The main objective of MitoXT service platform is to support companies or individual research groups in predicting the toxicity of single or mixtures molecules 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 enviorment 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 Extraflux Analyzer; Cytation 3 Multiplate Reader, CETICS TOXXs analyzer, MBIO AquaSpec mid-infrared spectroscopy analyzer

R&D:
Developing new screening methods and identifying biomarkers of disease and drug-induced toxicity.

Team: Vilma Oliveira (coordenador), Paulo Oliveira, Teresa Oliveira

Life Sciences Mass Spectrometry – LSMS

Coordinator: Bruno Manadas

During 2016 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 increase in the number and impact of the publications of the group, along with the beginning of an FCT project and approval 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 certified research mass spectrometry lab in Portugal).

The impact of our research in the community has raised quite significantly as the number of publications, projects, and services provided clearly show. However, we also believe that the invitations to: i) perform collaborative projects, ii) write book chapters and tutorials, and iii) disseminate our research through advanced courses and seminars, shows the influence of the research being performed in the group. Our strong technological capabilities, developed over the last years, are now resulting in higher biological impact research papers and demonstrating their potential to be transposed to biomarker research mainly in association with translational approaches. These indicators have contributed to increase the clinician's perception regarding the potential of the technology existent in the lab which resulted in the establishment of integrative screening projects for the search of new biomarkers for several diseases.

SERVICES AND CORES AT IBILI

ANIMAL 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

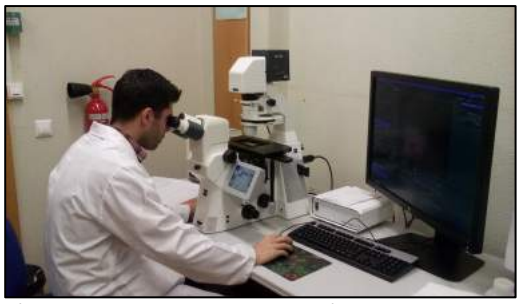
Head of Unit: Henrique Girão (*hmgirao@fmed.uc.pt*)

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.

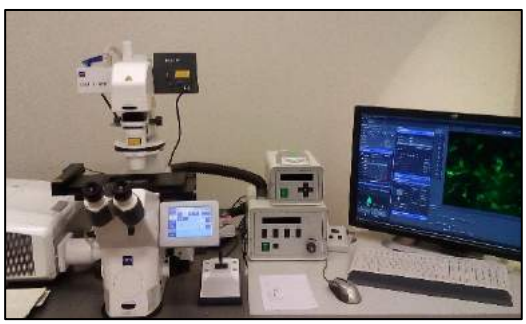
Equipment:

Leica ultramicrotome with a cryo unit (EM UC6 and EM



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

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 acessories

High-density array caps of electrodes, that come in different sizes (children to adult) and render possible faster subject preparation for simultaneous recordings with many electrodes. This is an absolute requirement for high-density recordings. Acessories include rechloriding equipment and electrodes

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

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

Visual and auditory stimulation software and hardware

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

Eye Tracker to integrate with visual stimulation

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

Digitizer for 3D localization of electrodes and fiduciary head landmarks

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

Reservation and Contact

Conditions for the Utilization of the Equipment:

For Researchers of the Participating Institutions: The time allocation of usage will be managed by the members of the Visual Psychophysiology Lab (IBILI – Fac. of Medicine). This lab will provide technical support for the running of experiments by all groups that will involved in collaborative research (see list above), but each group is responsible for experimental design and costs with materials required for the experiments.

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

Prices

175 € + IVA 20% per hour including technician.

Contact:

Prof. Miguel Castelo-Branco

Tel: +351 239480200

Email: *mcbranco@fmed.uc.pt*

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

LABORATORY OF BIOSTATISTICS AND MEDICAL INFORMATICS

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

Services

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

Courses

We currently offer a number of courses, see the full list here (in Portuguese). In this page only courses in English are listed. We are open to organising courses upon request.

Staff

Scientific Coordinator:

Miguel Castelo-Branco, MD. Ph.D

Teaching and Research Staff and collaborators:

Bárbara Oliveiros, Ph.D.

Francisco Caramelo, Ph.D.

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

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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 2015 funding of "Laboratório Associado – Centro de Neurociências e Biologia Celular" ascended the amount of 6.410.656,91€.

The main financing contribution was made by "Fundação para a Ciência e Tecnologia (FCT)", concerning global institution programs and national projects, namely amount of 3.459.419,21€ distribuited as follows:

Strategical Project_ UID/NEU/04539/2013	1.780.921,50€
Projects:	1.322.015,43€
Science Program:	356.482,29€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2016.

Besides Center for Neuroscience is financed by other national and international agencies. In 2016 Center for Neuroscience received the amount of 216.108,29€ concerning other national projects and 1.108.401,45€ concerning international projects.

Services is another important vector of our institution which ascends 1.376.955,44€

The amount of other resting funds, which are not listed, attains an amount of 249.772,52€.

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

Note: Financing values are based on expenditure values 2016

ONGOING PROJECTS

Title	Financing Agency	Duration	Budget (CNC)	Expenditure 2016
National Projects:				
"Rede Nacional de Espectrometria de Massa" Coordinator: Euclides Pires	FCT Refª: REDE/1506/REM/2005	01/01/2009 to 30/12/2016	19.430,11€	19.430,11€
"BaiTS-Dendrímeros biodegradáveis para o desenho de terapias neuroprotectoras direccionadas para o tratamento de acidentes vasculares cerebrais." Coordinator: Carlos Jorge A. Bandeira Duarte Proponent: INEB	FCT Refª: 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 Refª: PTDC/BIM-MEC/6911/2014	31/03/2016 to 30/03/2019	199.260,00€	31.822,86€
"Estratégias de reparação e repressão génica para tratar a doença de Machado-Joseph" Coordinator: Luís Pereira de Almeida	FCT Refª: PTDC/NEU-NMC/0084/2014	01/04/2016 to 31/03/2019	199.998,00€	39.323,38€
"Iniciativa Europeia para a doença de Machado-Joseph / Ataxia spinocerebelosa do tipo 3" Coordinator: Luís Pereira de Almeida	FCT Refª: JPCOFUND/0001/2015	01/05/2016 to 30/04/2019	175.000,00€	5.885,76€
"Modelos avançados de doenças de poliglutaminas" Coordinator: Luís Pereira de Almeida	FCT Refª: JPCOFUND/0005/2015	01/04/2016 to 31/03/2019	275.000,00€	22.421,47€
"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 Refª: PTDC/BIM-MET/4265/2014	01/07/2016 to 30/06/2019	39.576,00€	15.450,94€
"Previsão da diabetes e feridas em familiares em primeiro grau de diabéticos tipo 2" Coordinator: John Jones Proponent: Associação Protectora dos Diabéticos de Portugal (APDP)	FCT Refª: EXCL/DTP-PIC/0069/2012	01/06/2013 to 30/11/2016	173.264,00€	52.477,43€

"MitoBOOST: Uma Terapeutica de Nova Geração para a Doença de Fígado Gordo Não Alcoólico Baseado na Entrega Inteligente de Antioxidantes à Mitocôndria" Coordinator: Paulo Jorge G. Simões Oliveira	FCT Refª: PTDC/DTP-FTO/2433/2014	01/04/2016 to 31/03/2019	134.052,00€	40.583,57€
"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€	12.938,19€
"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€	29.692,47€
"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€	3.979,25€
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 30/11/2017	405.316,00€	143.763,61€
"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€	61.976,38€
"Red2Discovery-As macroalgas vermelhas Sphoerococcus 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€	4.559,52€
"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€	55.618,70€

"Co-encapsulação em transportadores lipidos 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€	18.699,37€
"Doença de Machado-Joseph, agregação e degradação proteicas, biologia de células estaminais, proteostase, neurodegeneração." Coordinator: Luís Pereira de Almeida	FCT Refª: E-RARE4/0003/2012	01/03/2013 to 31/12/2016	141.581,00€	41.184,03€
"Direcionamento multicelular mediado pela nucleolina de combinação sinergística 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€	17.737,76€
"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€	1.206,97€
"EXERCITANDO O FUTURO: Exercício Voluntário Durante Diabetes Gestacional com uma Estratégia para Melhorar a Função Mitocondrial na Descendência." Coordinator: António Joaquim M. Moreno Participant: Universidade do Porto	FCT Refª: PTDC/DTP-DES/1082/2014	01/04/ 2016 to 31/03/ 2019	128.088,00€	42.110,19 €
"Glicerol como ingrediente alternativo para rações de peixe - potencial para aquaculture." Coordinator: Ivan Daniel S. Martins Viegas Participant: CIIMAR	FCT Refª: PTDC/CVT-NUT/2851/2014	31/03/2016 To 30/03/ 2019	170.244,00€	37.601,44€
"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€	0,00€
"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€	46.444,84€
"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€	0,00€

“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€	18.118,03€
“Visualização da terapia génica do sistema nervoso central.” Coordinator: Luisa Maria O. Pinheiro L. Cortes	FCT Refª PTDC/BBB-NAN/0932/2014	01/06/2016 to 31/05/ 2019	199.999,00€	4.238,22€
“Identificação e caracterização funcional de microRNAs reguladores de dano cardíaco por isquemia-reperfusão.” Coordinator: Miguel Luís Cunha Mano	FCT Refª PTDC/BIM-MEC/2968/2014	01/04/ 2016 to 31/03/ 2019	177.540,00€	39.617,60€
“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€	14.702,94€
“Proteostasia da huntingtina e mitocôndria: alvos para prevenir a disfunção neuronal na doença de Huntington.” Coordinator: Paula Paula Isabel S. Moreira Proponent: ICETA Universidade do Porto	FCT Refª PTDC/NEU-NMC/0412/2014	01/06/ 2016 to 31/05/ 2019	36.000,00€	373,21€
“FishFree: Uma contribuição para a validação de um ensaio alternativo ao teste letal com peixes.” Coordinator: Paulo Jorge G. Simões Oliveira Proponent: Universidade de Coimbra	FCT Refª PTDC/AAG-TEC/4966/2014	01/07/ 2016 to 30/06/2019	25.680,00€	3.219,86€
“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€	168.634,84€
“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€	70.224,39€
‘‘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 Refª IF/00812/2012/CPO151/CT0001	01/07/2013 To 30/06/2018	50.000,00€	7.902,73€
‘‘Projeto de investigação Exploratória” Coordinator: Ricardo Pires	FCT Refª IF/00123/2013/CP1175/CT0003	15/12 2013 to 14/12/ 2018	50.000,00€	10.960,10€
Programa MIT Coordinator: Catarina Oliveira, Lino Ferreira	FCT Refª: MIT-Portugal 2016	01/01/2016 to 31/12/2016	13.571,25€	13.570,87€
‘‘Projeto de investigação Exploratória’’ Coordinator: Miguel Mano	FCT Refª: IF/00694/2013/CP1175/CT0002	01/07/2014 to 30/06/2019	50.000,00€	13.386,75€

‘‘Projeto de investigação Exploratória’’ Role of distinct synaptotagmin isoforms in exocytosys and neuronal function Coordinator: Paulo Pinheiro	FCT Refª: IF/01302/2012/CP0151/CT0002	01/10/ 2013 to 30/09/ 2018	50.000,00€	11.074,84€
‘‘Projeto de investigação Exploratória’’ Coordinator: Ignacio Vega Naredo	FCT Refª: IF/01316/2014/CP1258/CT0003	26/06/2015 to 25/06/2020	50.000,00€	42.121,38€
‘‘Projeto de investigação Exploratória’’ Coordinator: Irina Moreira	FCT Refª: IF/00578/2014/CP1258/CT0002	15/01/2015 to 14/01/2020	50.000,00€	8.302,26€
“Papel e mecanismos da propagação da sinucleina e da ataxina-3 nas doenças de Parkinson e Machado-Joseph” Coordinator:Luís Almeida	FCT Refª: JPND-CD/0001/2013	01/03/2015 to 28/02/2018	150.000,00€	112.285,48€
'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 Refª: Infect-ERA/0001/2014	01/04/2015 to 31/03/2018	124.980,00€	38.373,69€
Sub – Total FCT				**1.322.015,43€**
Other National Projects				
“Prémio FLAD Life SCience 2020” Coordinator:Ana Cristina Rego	Fundação Luso-Americana	01/01/2015 to 31/12/2017	300.000,00€	61.108,80€
“Engenharia Epigenética para reverter o Fonótipo Celular da Doença de Parkinson” Coordinator: Paulo Oliveira	Fundação Montepio	01/06/2014 To 31/05/2016	57.630,00€	3.737,88€
“Engenharia Epigenética para reverter o Fonótipo Celular da Doença de Parkinson” Coordinator: André Valente	Fundação Montepio	01/06/2014 To 31/05/2016	48.320,00€	9.456,33€
“Evaluation of oxidative stress and mitochondrial dysfunction in animal models and patients of Huntington`s disease using Cu(II)-ATSM PET Coordinator: Ana Cristina Carvalho Rego	Santa Casa da Misericórdia de Lisboa: “Prémio Mantero Belard´2013"	01/01/2014 to 31/12/2016	99.072,00€	41.267,85€
“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€	92.830,22€
“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€	7.707,21€
Sub – Total Other				**216.108,29€**

Total National Projects				**1.538.123,72€**
International Projects:				
"Cellular and Synaptic Dissection of the Neuronal Circuits of Social and Autistic Behavior" Coordinator: João Peça Silvestre	Brain & Behavior Research Foundation: "2013 Narsad Young Investigator Grant"	15/01/2014 to 14/07/2016	45.000€	2.937,36€
"Silencing Machado-Joseph Disease/ Spinocerebellar ataxia type 3 through the systemic route" Coordinator: Rui Nobre Jorge	National Ataxia Foundation	01/01/2014 to 31/12/2016	10.823,71€	2.634,05€
"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€	697,30€
"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€	35.392,30€
"The effect of TCF7L2 on Glucose Metabolism" Coordinator: John Jones	Mayo Clinic 5Ro1DK078646-08	01/08/2014 To 31/12/2016	17.395,53€	4.951,78€
"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 31/07/2015	110.000,00€	19.898,76€
"New Treatments for Stress-induced Dysregulation of Circuits Regulating Reward, Fear, and Habit Learning". Coordinator: Rodrigo Cunha	Massachusetts Institute of Technology Ref.ª: DARPA-BAA-009-68	01/04/2010 to 30/06/2016	944.680,00€	15,00€
"CAFFEIN-Cancer Associated Fibroblasts (CAF) Function in Tumor Expansion and Invasion". Coordinator: João Nuno Moreira	Marie Curie grant 316610 Refª FP7-People-2012-ITN	01/10/2012 to 30/09/2016	209.781,00€	53.605,59€
"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€	285.723,78€
"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 31/12/2016	11.186,27€	0€
"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 31/12/2016	10.823,71€	483,54€

"Mitochondrial Trafficking In Alzheimer Disease: Revealing the Role of Hummr." Coordinator: Paula Moreira	Alzheimer Association NIRG-13-282387	01/11/2013 to 30/12/2016	71.495,56€	28.073,93€
"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€	5.892,70€
"Ghrelin: a novel therapeutic intervention to rescue the phenotype of Hutchinson-Gilford progeria syndrome" Coordinator: Célia Aveleira	Progeria Research Foundation	01/04/2015 To 01/04/2017	61.718,64€	20.347,89€
"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€	97.235,26€
"EFSD – Combination therapy synergistically accelerates diabetic wound closure" Coordinator: Eugénia Carvalho	European Foundation for the Study of Diabetes	09/11/2015 to 31/12/2016	70.000€	31.872,41€
"Collaborative research project INBT" Coordinator: Tânia Perestrelo	John Hopkins University, Institute for NanoBIO Technology	01/07/2016 to 30/06/2017	11.500€	5.477,63€
"Advanced Induced Pluripotent Stem Cell – based Models of Machado-Joseph disease" Coordinator: Magda Santana	National Ataxia Foundation	01/01/2016 to 31.12.2016	31.920€	29.698,82€
"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€	18.026,59€
''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 31-12-2016	10.823,71€	2.397,65€
''ENC Network Cycle 4-2013 - PT - 04 -Amber Kerkhofs'' Coordinator: Rodrigo Cunha	European Neuroscience Campus Network Cycle	01/10/2013 to 30/09/2016	121.900,00€	39.548,66€
''159302-1-2009-1-NL-ERA MUNDUS-EMJD – Blanka Kellermay'' Coordinator: Ana Luísa Carvalho	European Neuroscience Campus Network	15-09-2014 to 14-09-2017	121.900,00€	40.526,93€
''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 14-09-2016	87.302,26€	20.904,27€
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€	7.441,65€

‘‘ENC Network Cycle 4-2013 - PT - 07 - Xin-Li Xu’’ Coordinator: Rodrigo Cunha	European Neuroscience Campus Network	01/10/2013 to 30/09/2016	126.400,00€	25.026,11€
"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€	35.721,07€
“AFM: Ataxin-2 as a new molecular target in Machado-Joseph disease: from translation regulation to disease alleviation” Coordinator: Clévio Nobrega	Association Française Myopathies Télethon"	01/03/2015 to 31/12/2017	37.000,00€	21.338,90€
“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€	53.632,49€
“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€	49.636,54€
“Mechanisms underlying hemogenic induction in human fibrobalsts” Coordinator: Carlos Filipe R. Lemos Pereira	Marie Curie FP7-People-2013-IIF PIIF-GA-2013-628761	18/02/2015 to 17/02/2017	202.630,00€	103.449,08€
“The transplantation of induced pluripotent stem cells (IPSC) - derived neural sem cells (NSC) in Machado-Joseph disease (MJD)” Coordinator: Liliana Mendonça	National Ataxia Foundation	01/01/2016 to 31/12/2017	13.673,78€	8.331,98€
Does the Transplantation of mutant ataxin-3-depleted patient-derived NSC alleviates Machado Joseph disease (MJD) Coordinator: Liliana Mendonça	Association Française Myopathies Télethon"	02/05/2016 To 01/05/2017	49.000,00€	5.831,56€
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€	51.649,87€
Total International Projects				**1.108.401,45€**
TOTAL				**2.646.525,16€**

FUNDING AT IBILI

Title	Financing Agency	Principal Investigator	Starting Date	Ending Date	Budget (IBILI)	Expenditure 2016
Age-related macular degeneration - can metabolomic profile distinguish progressors?	FCT HMSP - ICJ/0006/2013	Inês Laíns	01/07/2014	30/06/2016	46.525,00 €	80,24€
Protocolo Delta - FMUC	DELTA Proj. Cafeína e Glaucoma	Ana Raquel Santiago	29/01/2014	28/01/2016	4.900,00 €	1.536,00€
CNC.IBILI	FCT UID/04538/2015	Miguel Castelo-Branco	01/01/2015	31/12/2017	1.833.000,00 €	465.216,72€
RG-4539-2262 Neuro 4 - Brain Imaging	FCT UID/04538/2015	Miguel Castelo-Branco	01/01/2015	31/12/2017	1.008.150,00 €	233.192,04 €
RG-4539-2264 Neuro 8 - Chronic Diseases	FCT UID/04538/2015	Francisco Ambrósio	01/01/2015	31/12/2017	824.850,00 €	232.024,68 €
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 €	8.268,32 €
Crosstalk between perivascular adipose tissue and blood vessels in obesity and vascular dysfunction	PTDC/BIM-MET/4447/2014	Cristina Sena	01/06/2016	31/05/2018	199.512,00 €	23.389,31 €
Functional Neuroimaging in newborns with perinatal asphyxia predicting neurodevelopmental outcome	FCT PTDC/DTP-PIC/6032/2014	Guiomar Oliveira	01/06/2016	31/05/2018	115.416,00 €	12.878,12 €
Engineered Biodegradable Drug Delivery System for the Release of 2-Cl-IB-MECA for the treatment of glaucoma	PTDC/NEU-OSD/3123/2014	Raquel Santiago	01/06/2016	31/05/2018	142.476,00 €	6.858,98 €
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 €	15.476,25 €
Novartis	NOVARTIS	Francisco Ambrósio	-	-	30.000,00 €	17.547,18 €
The changing brain in AD: is the retina a reliable mirror of disease onset progression?	SANTA CASA MISERICORDIA MB-1049-2015	Francisco Ambrósio	01/01/2016	31/12/2018	154.608,00 €	78.060,93 €
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 €	2.367,06€
European young Investigators network for Usher Syndrome	EU-FCT	Eduardo Silva	01/05/2013	30/04/2016	183.284,00 €	24.201,06 €
Taking imaging into the therapeutic domain: self-regulation of brain systems for mental disorders	EU – FP7 BRAINTRAIN	Miguel Castelo-Branco	01/11/2013	30/10/2017	638.000,00 €	98.249,51€.
Euro-BioImaging Preparatory Phase II - Project	H2020 - Excellent Science	Miguel Castelo-Branco	01/01/2016	31/12/2017	15.302,50 €	6.612,14 €
Managing inflammation in diabetic retinopathy	Bayer Healthcare - Global Ophthalmology Awards Program	Ana Raquel Santiago	01/12/2015	30/11/2016	44.341,00 €	22 146,07 €

STAFF LIST

		Time % at CNC.IBILI
SERVICE STAFF		
Ana Carina Dias	(Graduate Technician, CNC)	100
Ana Cristina Franco dos Santos	(Graduate Technician, CNC)	100
Ana Margarida Ferreira	(Graduate Technician, CNC)	100
António José Azinhaga Teles Grilo	(Graduate Technician, CNC)	100
Catarina João Marques Simões	(Graduate Technician, CNC)	100
Carlos Pinto	(Technician, CNC)	100
Diana Patrícia Dias Vitória	(Graduate Technician, CNC)	100
Mª Conceição Egas	(PhD, Graduate Technician, CNC)	100
Maria João Ferreira Canas dos Santos	(Graduate Technician, CNC)	100
Mário Grãos	(PhD, Graduate Technician, CNC)	100
Marta Sofia Marques Simões	(Graduate Technician, CNC)	100
TECHNICAL STAFF		
Ana Filipa Oliveira	(Technician, CNC)	100
Anabela Marisa Azul	(PhD, Graduated Studies, CNC)	100
Cândida Elsa Frias Mendes	(Graduate Technician, CNC)	100
Carla Margarida dos Santos Veríssimo	(Graduate Technician, CNC)	100
Cármen Lídia Graça Semião	(Graduate Technician, CNC)	100
Diana dos Santos Simões Graça	(Technician, CNC)	100
Elsa Henriques	(PhD, Science Manager, CNC)	100
Fátima Cristina dos S. Carvalho Graça	(Technician, CNC)	100
Isabel Conceição Calado Esteves Costa	(Technician, CNC)	100
Isabel Nunes Correia	(PhD, Graduate Technician, CNC)	100
Isabel Dantas Fernandes	(Graduate Technician, CNC)	100
João Miguel Pratas	(Graduate Technician, CNC)	100
Luciana C. Albuquerque Pinto	(Graduate Technician, CNC)	100
Luisa Leitão Cortes	(PhD, Graduate Technician, CNC)	100
Margarida Caldeira	(PhD, Graduate Technician, CNC)	100
Maria do Céu Mendes Gomes	(Technician, CNC)	100
Maria Eugénia A. Silva Lopes Campos	(Technician, CNC)	100
Maria Fátima Moreira	(Graduate Technician, CNC)	100
Maria Isabel Gonçalves	(Technician, CNC)	100
Maria do Rosário da Costa Faro	(Graduate Technician, CNC)	100
Mónica Alexandra V. Serrano	(Graduate Technician, CNC)	100
Odete Pereira Cabanelas	(Graduate Technician, CNC)	100
Sandra Manuela Domingues dos Santos	(PhD, Graduate Technician, CNC)	10
Sara da Costa Jordão A. Lopes	(Technician, CNC)	100
Sandra Freire	(Graduate Technician, CNC)	100
Tânia Ribeiro	(Graduate Technician, CNC)	100
Vera Mendes	(Graduate Technician, CNC)	100
Vítor José Lopes Nunes	(Technician, CNC)	100
ADMINISTRATIVE STAFF		
Alda Gonçalves	(Administrative Assistant, IBILI)	100
Ana Claudia Caridade	(Administrative Assistant, IBILI)	50
Celia Valente	(Graduate Administrative, IBILI)	20
Joana Cipriano	(Graduate Administrative, IBILI)	100
Paula Miranda	(Administrative Assistant, IBILI)	20
Carla Lopes	(Administrative Assistant, CNC)	100
Catarina Alexandra Ferreira Gomes	(Graduate Administrative, CNC)	100
Heidi Maria da Silva Lopes Gonçalves	(Graduate Administrative, CNC)	100
Lia da Costa Jordão Aparício Lopes	(Graduate Administrative, CNC)	100
Mª Leonor Jesus	(Administrative Assistant, CNC)	100
Mª Luísa R. Caldeira Bonito	(Graduate Administrative, CNC)	100
Mónica Alexandra Rodrigues Morais	(Graduate Administrative, CNC)	100
Nilza Clara F. Marques Manadas	(Administrative Assistant, CNC)	100
Rosa Alexandra Folhas Fernandes	(Graduate Administrative, CNC)	100
Sandra Cristina Santos Luís	(Graduate Administrative, CNC)	100
Sílvia Marisa Esteves de Sousa	(Graduate Administrative, CNC)	100
Susana Adelaide Rocha da Silva	(Administrative Assistant, CNC)	100
Tatiana de Azevedo Paula	(Graduate Administrative, CNC)	100

RESEARCH STAFF AND STUDENTS / SCIENTIFIC RESEARCH LINE

NEUROSCIENCE, VISION AND BRAIN DISEASES | *ANA LUISA CARVALHO*

MEMBERS HOLDING PHD		TIME % AT CNC.IBILI
Aldina Conceição Pires Reis	(Assistant Professor)	30
Ana Cristina Rego	(Assistant Prof., FMUC)	60
Ana Filipa Marques Brito	(Investigator)	30
Ana Ledo	(Investigator)	100
Ana Luísa Carvalho	(Assistant Prof., FCTUC)	80
Ana Margarida Abrantes	(Assistant Professor)	50
Ana Paula Silva Martins	(Assistant Investigator)	80
Ana Santos Carvalho	(Assistant Inv., IEC)	Collaborator
Ana Telma Pereira	(Assistant Inv., FMUC)	30
Anabela Mota Pinto	(Full Prof., FMUC)	30
Ângelo Tomé	(Assistant Prof., FCTUC)	30
Antero Afonso de Abrunhosa	(Assistant Investigator)	30
António Gonçalves Freire	(Assistant Professor)	30
António Francisco Ambrósio	(Principal Investigator)	80
António Macedo Santos	(Assistant Prof., FMUC)	30
António Morgado	(Assistant Prof., FMUC)	70
Attila Köfalvi	(Assistant Inv., CNC)	100
Bárbara dos Santos Oliveiros	(Assistant Professor)	80
Belmiro Ataíde Parada	(MD)	40
Bruno Oliveira Manadas	(Assistant Inv., CNC)	100
Carlos Alberto F. Ribeiro	(Full Professor)	50
Catarina A. Reis Gomes	(Assistant Professor)	70
Carla Nunes	(Assistant Prof., FFUC)	50
Carlos B. Duarte	(Associate Prof., FCTUC)	80
Carlos Matias	(Investigator, UTAD)	60
Catarina R. Oliveira	Emeritus Prof., FMUC)	60
Célia Gomes	(Assistant Prof., IPC-UC)	Collaborator
Célia Maria Freitas Gomes	(Assist. Investigator)	100
Cláudia Cavadas	(Assistant Prof., FFUC)	70
Diana Serra	(Assistant Professor)	50
Eduardo José Silva	(Assistant Professor)	30
Emília P. Duarte	(Assistant Prof., FCTUC)	80
Eunice Virgínia Carrilho	(Full Professor)	30
Fernando Aidos	(Assistant Professor, FCTUC)	30
Fernando José Mendes	(Professor)	60
Flávio Nelson Reis	(Assistant Investigator)	80
Francisco Cerqueira Alves	(Assistant Investigator)	30
Francisco Caramelo	(Assistant Professor)	80
Francisco Oliveira	(Assistant Investigator)	80
Frederico G. Pereira	(Assistant Professor)	50
Guiomar Gonçalves Oliveira	(Associate Professor)	30
Inês Bernardino	(Investigator)	100

Inês Esteves Baldeiras	(Investigator, FMUC)	30
Inês Ribeiro Violante	(Professor)	30
Irina Moreira	(Assistant Inv., CNC)	100
Isabel Maria Marques Carreira	(Assistant Prof., FMUC)	30
Isabel Santos Pereira	(Assistant Professor)	40
Joana Rosmaninho-Salgado	(MD, CHUC)	Collaborator
João José Oliveira Malva	(Principal Investigator)	100
João Laranjinha	(Full Prof., FFUC)	60
João Miguel Santos Pereira	(Investigator)	30
João Miguel Castelhano	(Graduate Technician)	80
João Peça-Silvestre	(Assistant Inv., CNC)	100
João Pereira Figueira	(Assistant Prof. FFUC)	30
Joaquim Carlos Neto Murta	(Full Professor)	30
Joaquim Cerejeira	(Assistant Prof., CHUC)	Collaborator
Jorge de Andrade Saraiva	(Full Professor)	30
José Dionísio	(Assistant Prof. FFUC)	50
José Guilherme Tralhão	(Aux. Professor)	30
José Paulo Domingues	(Assistant Professor)	30
José Vítor Oliveira Sereno	(Investigator)	90
Leonor Almeida	(Full Prof., FFUC)	30
Luís Filipe Caseiro Alves	(Full Professor)	30
Luis Martinho do Rosário	(Associate Prof., FCTUC)	40
Manuel Marques Ferreira	(Assistant Professor)	30
Manuel Teixeira Veríssimo	(Assistant Professor)	30
Mª Conceição da Fonseca	(Associate Professor)	30
Mª Cristina Januário Santos	(Assistant Professor)	30
Mª do Rosário Almeida	(Assistant Inv., CNC)	100
Mª Dulce Ferreira Cotrim	(Associate, Professor)	30
Mª Emília Quinta-Ferreira	(Associate Prof., FCTUC)	40
Mª Filomena Botelho	(Full Professor)	50
Mª Isabel J. Santana	(Investigator, CHUC)	30
Mª Joana Barbosa de Melo	(Assistant Prof., FMUC)	30
Mª João Carvalho	MD)	30
Mª João Vidigal	(Professor)	30
Mª Luísa Ribeiro	(MD)	30
Mª Manuela Monteiro Grazina	(Assistant Prof., FMUC)	60
Mª Margarida Caramona	(Full Professor)	30
Miguel Castelo-Branco	(Associate Professor)	90
Miguel Patrício	(Assistant Investigator)	100
Natália António	(Assist. Professor)	30
Nuno David Ferreira	(Assistant Professor)	30
Paula G. Agostinho	(Investigator, FMUC)	60
Paulo Pinheiro	(Assistant Inv., CNC)	100
Paulo Fernando Santos	(Assistant Professor)	50
Paula Cristina Vaz Tavares	(Assistant Professor)	30
Pedro Miguel Serranho	(Assistant Professor)	30
Ramiro Almeida	(Assistant Prof., Inst. Pol. Porto)	80
Ricardo Rodrigues	(Assistant Inv., CNC)	100

Rodrigo A. Cunha	(Associate Prof., FMUC)	75
Rosa Cristina Fernandes	(Principal Investigator)	100
Rosa M. Santos	(Assistant Prof., FCTUC)	40
Rui Barbosa	(Assistant Prof., FFUC)	60
Rufino Martins da Silva	(Assistant Professor)	40
Rui Manuel Bernardes	(Assistant Professor)	60
Sergio José Do Carmo	(Investigator)	30
Sofia Andreia Viana	(Professor)	50
Sônia Alexandra Santos	(Assistant Professor)	50
Teresa Dinis Silva	(Associate Prof., FFUC)	60

POST-DOC MEMBERS	**TIME % AT CNC.IBILI**
Ana Patrícia Simões	100
Ana Raquel Santiago	100
Ana Rita Álvaro	100
António Pedro Gomes	100
Barbara da Silva Rocha	100
Bruno Miguel Leitão	100
Carla Nunes Lopes	100
Cátia Filipa Marques	100
Célia Aveleira	100
Elisa Regina Campos	100
Elisabete Baptista Ferreiro	100
Filipa Isabel Baptista	100
Filipa Solange Cardoso	100
Gabriel Ferreira da Costa	100
Helena Carvalheiro	100
Ildete Luísa Ferreira	100
Inês Teixeira de Almeida	100
Joana Fernandes	100
Joana Guedes	100
Joana Pedro	100
Joana Marques	100
Joana Teresa Gonçalves	100
João Filipe da Costa Martins	100
João Pedro Lopes	100
João Valente Duarte	100
Ligia de Sousa Ferreira	100
Lorena Itatí Petrella	100
Mafalda Sofia Cândido	100
Magda Santana	100
Mª Helena Madeira	100
Mª Fatima Loureiro da Silva	100
Mª José Braga Ribeiro	100
Mariana Botelho Rocha	100
Miranda Mele	100
Monika Intaite	100
Nélio Gonçalves	100

Paula Canas	100
Rui Miguel Oliveira da Costa	100
Samira Ferreira	100
Sandra Freitas	30
Sandra Mota	100
Susana Louros	35
Tatiana Andreia Catarino	100

PHD STUDENTS	**TIME % AT CNC.IBILI**
Amber Kerkhofs	100
Ana Cruz Dionísio	100
Ana Esmeralda Costa	20
Ana Isabel Rodrigues	100
Ana Maria Batista	100
Ana Patrícia Marques	100
Ana Salomé Pires	100
Ana Sofia Pais	100
Ana Rita Gaspar	100
Andreia Martins Rosa	100
Anna Pliássova	100
António Campos Figueiredo	25
António José Gomes	100
Cândida Dias	100
Carlos Manuel Amaral	100
Carlos Marto	30
Cátia Santa	100
Diana Sequeira	100
David Castelo	30
Dina Pereira	100
Diogo André Fonseca	100
Dominique Fernandes	100
Edgar Silva	30
Eurico Miguel Fial Ribeiro	80
Fátima Bastos	60
Filipa Lima Júlio	100
Filipe Palavra	50
Francisco Queiroz Gonçalves	100
Gladys Caldeira	100
Inês Amaral	100
Ivan Salazar	100
Janete Santos	100
Jeannette Schmidt	100
Joana Pinto	100
João Calmeiro	100
Lara Franco	100
João Eduardo Lopes	30
Leonor Barroso	30
Luana Naia	100

Luís Martins	100
Mafalda Bacalhau	100
Marco António Simões	100
Margarida Coelho	100
Marta Teixeira	100
Mª João Leitão	100
Mariline Silva	100
Marisa Marques	100
Mário Carvalho	100
Mohamed Hussien	100
Nuno Machado	100
Otília d'Almeida	100
Patrícia Sofia Alçada Morais	100
Pedro Luís Fonseca	30
Raquel Sofia Freitas Bóia	100
Ruben Salvado	100
Ricardo Jorge Martins	30
Ricardo Alexande Leitão	100
Rui Miguel Martins	30
Rui Pedro Oliveira	30
Samuel Filipe Chiquita	100
Sara Raquel Martins Neves	100
Sara Raquel Nunes	100
Sara Silva	100
Sofia Ferreira	100
Sónia Pereira	100
Sulaiman I S Abuhaiba	100
Susana Figueiredo e Silva	100
Susana Isabel Simão Mouga	100
Susana Sampaio	100
Sandra Anjo	100
Teresa Maria da Silva Sousa	100
Tiago Alfaro	30
Vânia Leal	20
Vanessa Filipa Santos	100
Xinli Xu	100

MSc Students	**Time % at CNC.IBILI**
Ana Dias	100
Ana Rita Samões	100
André Carvalho	100
António Pimenta	100
Bárbara Correira	100
Beatriz Martins	100
Carla Henriques	100
Carlota Nóbrega	100
Daniela Madeira	100
Fábio Sousa	100

Inês Santos		100
Joana Martins		100
Joana Coelho		100
Joana Pereira		100
João Pereira		100
José Almeida		100
Luciana Fernandes		100
Miguel Pinheiro		100
Laetitia Gaspar		100
Marlene Pereira		10
Marta Quatrorze Correia		100
Rafael Carecho		100
Patrícia Santos		100
Patrícia Valério		100
Patrick Silva		100
Tiago Rondão		100

TECHNICIANS / OTHERS		**TIME % AT CNC.IBILI**
Alexandra Campos		100
Alexandre Marques		40
Ana Catarina Neves		100
Ana Cruz Dionísio		100
Ana Mafalda Teixeira	(Grant Technician)	100
Ana Margarida Henriques		100
Ana Rita Barreiros		100
Andreia Sofia Pereira	(Grant Technician)	100
Ângela Sofia Miranda	(Grant Technician)	100
Beatriz Rodrigues		100
Carina Maranga		100
Filipa Almeida		100
Lígia Fão		100
Nuno Piedade		100
Carlos Daniel Ferreira	(Technician)	100
Carlos Manuel Pereira	(Grant Technician)	100
Carolina César Alves	(Grant Technician)	100
César Alejandro Nunes	(MD)	30
Daniela Isabel Oliveira	(Grant Technician)	100
Débora Serrenho		100
Frederico Duque		30
Henrique Silva		100
Diliana Rebelo Santos	(Grant Technician)	100
Gilberto Silva		100
Hélio Jorge Gonçalves	(Grant Technician)	100
Hugo Alexandre Quental	(Grant Technician)	100
Inês Roque Antunes Pita	(Grant Technician)	100
Inês Sofia Dinis Aires		100
Isabel Catarina Duarte	(Technician)	90

Lília Pereira Jorge	(Grant Technician)	100
Margarida Maria Marques	(MD)	30
Marina Rodrigues		100
Nádia Canário		100
Sara Beatriz Fernandes		100
Sara Reis		100
Vanessa Henriques		100
Ricardo José Martins	(Grant Technician)	100
Ricardo Jorge Teixo	(Grant Technician)	100
Vítor Hugo Alves	(Grant Technician)	100

METABOLISM AGING, AND DISEASE | *JOÃO RAMALHO SANTOS*

MEMBERS HOLDING PHD		**TIME % AT CNC.IBILI**
Alexandrina F. Mendes	(Assistant Prof., FFUC)	80
Américo Manuel Figueiredo	(Full Professor)	30
Ana Paula Marques de Sousa	(Investigator, CHUC)	50
Ana Teresa Almeida Santos	(Assistant Prof., FCTUC)	30
Ana Teresa Rufino	(Assistant. Prof. ESECVP)	80
Anabela P. Rolo	(Assistant Prof., FCTUC)	80
António Manuel Pires	(Investigator)	30
António Moreno	(Associate Professor, FCTUC)	80
Armanda Santos	(Assistant. Prof. FFUC)	80
Carla Isabel Marques	(Graduate Technician)	100
Carlos M. Palmeira	(Full Professor., FCTUC)	80
Cláudia M. F. Pereira	(Investigator, FMUC)	60
Cristina Maria Tristão Sena	(Assistant Professor)	90
Elizabete Jorge	(MD, CHUC)	40
Eugénia Carvalho	(Associate Inv., CNC)	100
Fernando Judas	(Associate Professor, FMUC)	30
Hans Eickhoff	(MD, CHUC	30
Henrique Manuel Girão	(Assistant Investigator)	100
João Moura Alves	(Assistant Prof., Inst Pol. Viana Castelo)	40
João Ramalho Santos	(Associate Prof., FCTUC)	80
João Vasco Ferreira	(Assistant Investigator)	100
John Jones	(Principal Inv., CNC)	100
Liliana Montezinho	(Assistant Prof., Univ Vasco Gama)	50
Lino Manuel Gonçalves	(Associate Professor)	40
Mª Carmen Alpoim	(Associate Prof., FCTUC)	60
Mª Margarida Souto-Carneiro	(Assistant Inv., CNC)	100
Maria S. Santos	(Principal Inv., FCTUC)	100
Maria Teresa Cruz	(Assistant Prof. FFUC)	80
Marina Pinto	(Assistant Prof.)	20
Paula Isabel Moreira	(Assistant Prof., FMUC)	60
Paulo J. Oliveira	(Princial Inv., CNC)	100

Paulo Pereira	(Investigator)	Collaborator
Raquel Maria Fino Seiça	(Full Professor)	60
Rui Baptista	(MD, CHUC)	40
Rui Travasso	(Assistant Professor)	30
Sandra Isabel M. Cardoso	(Assistant Prof., FMUC)	60
Vilma Sardão Oliveira	(Assistant Inv., CNC)	100

POST-DOC MEMBERS	**TIME % AT CNC.IBILI**
Ana Burgeiro	100
Ana Catarina Fonseca	100
Ana Duarte	100
Ana Raquel Esteves	100
Ana Silva	20
Ana Sofia Rodrigues	100
Cristina Barosa	100
Cristina Carvalho	100
Diana Silva	100
Elisa Aida da Silva Ferrada	100
Ermelindo Leal	100
Ivan Viegas	50
Joana Crisóstomo Silva	100
João Paulo Teodoro	100
Ludgero Tavares	100
Mª Alexandra B. Amaral	30
Mª Teresa Cunha-Oliveira	100
Monika Zuzarte	100
Patrícia Seraphim	100
Paula Mota	100
Paulo Nuno Centeio Matafome	100
Renata Tavares	100
Rosa Resende	100
Sandra Catarina G. Amaral	100
Sandro Pereira	100
Sonia Correia	100
Steve Mendes Catarino	100
Susana Cardoso	100
Susana Pereira	100

PHD STUDENTS	**TIME % AT CNC.IBILI**
Alexandra Carvalho	100
Ana Mª Silva	100
Ana Raquel Coelho	100
Ana Rita Moreira	100
Cátia Santos	100
Cátia Sousa	100
Cláudia Deus	100

Daniel Santos	100
Daniela Almeida	100
Emanuel Candeias	100
Eurico Serrano	100
Fernanda Carrilho	30
Guida Bento	100
Isabel Ferreira	100
Joana Liberal	100
João Amorim	100
João Demétrio B. Martins	100
João Rito	50
João Silva	80
Jorge Silva	100
Liliana Rita Velindo Letra	30
Luciana Ferreira	100
Mª Inês Almeida Sousa	100
Mª Madalena Ribeiro	100
Paula Cristina Martins	30
Ricardo Jorge Pereira	30
Rui Simões	100
Sara Rebelo	100
Tânia Perestrelo	100
Tânia Sofia Marques	100
Teresa Rodrigues	100
Tiago Daniel Rodrigues	30

MSc Students	**Time % at CNC.IBILI**
Bibiana Silva	100
Diogo Verde	100
Mª Inês Alves	100
Tiffany Pinto	100

Technicians /Others		**Time % at CNC.IBILI**
Carlos Rodrigues	(Grant Technician, CNC)	50
Caroline Veloso	(Grant Technician, CNC)	100
José Teixeira		Collaborator
Mónica Abreu		100

STEM CELL-BASED AND MOLECULAR THERAPIES | *LUIS PEREIRA DE ALMEIDA*

MEMBERS HOLDING PHD		TIME % AT CNC.IBILI
Alcino Jorge Lopes Leitão	(Assistant Prof., FFUC)	50
Amílcar Falcão	(Full Prof., FFUC)	50
Ana Catarina Gomes	(Executive Director, CNC)	100
Ana Cristina Fortuna	(Assistant Prof., FFUC)	30
Ana Bela Sarmento Ribeiro	(Assistant Prof., FMUC)	40
Ana Gregório	(Assist. Investigation)	Collaborator
Anália do Carmo	(Assistant Prof., FFUC)	35
André Xavier C. Negrão Valente	(Assistant Inv., CNC)	100
Armindo J. Alves S. Salvador	(Assistant Inv., CNC)	100
Bruno Gonçalves		100
Bruno Miguel Neves	(Assistant Prof. FFUC)	50
Carla Vitorino	(Assistant Prof, FFUC)	30
Carlos Cavaleiro	(Assistant Prof, FFUC)	50
Carlos Faro	(Associate Prof., FCTUC)	100
Carlos Filipe Pereira	(Investigator, CNC)	100
Célia Nogueira	(Assistant Prof, FMUC)	40
Cristiana Paulo		Collaborator
Euclides Pires	(Associate Prof., FCTUC)	40
Fernando Ramos	(Associate Prof, FFUC)	40
Gabriela Silva	(Assistant Prof., FFUC)	60
Henrique Faneca	(Assistant Inv., CNC)	100
Isabel Andrade Ramalho	(Professor, Private Sector)	Collaborator
Isaura Simões	(Assistant Inv., CNC)	100
João Nuno Moreira	(Assistant Prof., FFUC)	80
Jorge António R. Salvador	(Full Prof, FFUC)	60
Lígia Salgueiro	(Full Professor, FFUC)	50
Lino Ferreira	(Investigator, CNC)	100
Luís Loura	(Associate Prof., FCTUC)	Collaborator
Luís Pereira Almeida	(Assistant Prof., FFUC)	80
Mª Amália Jurado	(Assistant Prof., FCTUC)	80
Mª Celeste Lopes	(Full Prof., FFUC)	80
Mª Céu Rodrigues Sousa	(Assistant Prof. FFUC)	60
Mª Conceição Pedroso de Lima	(Emeritus Prof., FCTUC)	80
Mª João Silvestre	(Assistant Prof., FCTUC)	Collaborator
Mª José Gonçalves	(Assistant Prof., FFUC)	50
Mª Luísa Sá e Melo	(Emeritus Prof., FFUC)	50
Mª Manuel da Cruz Silva	(Assistant Prof., FFUC)	60
Mª Teresa Batista	(Emeritus Prof., FFUC)	40
Mariana Bexiga	(Investigator)	100
Miguel Mano	(Assistant Investigator, CNC)	100
Milton Simões da Costa	(Full Prof., FCTUC)	100
Nuno Empadinhas	(Assistant Inv., CNC)	100
Nuno Fonseca	(Associate Director, Treat U)	100
Olga Maria F. Borges Ribeiro	(Assistant Prof., FFUC)	60

Paula Veríssimo Pires	(Assistant Prof., FCTUC)	40
Raghu Kalluri	(Investigator, HMS)	35
Renato Pires	(Investigator, Univ Açores)	50
Ricardo Neves	(Assistant Inv., CNC)	100
Ricardo Pires	(Assistant Inv., CNC)	100
Sara Domigues	(Assistant Prof., FFUC)	60
Sérgio Simões	(Associate Prof., FFUC)	80
Sónia Pereira	(Professor, Private Sector)	30
Teresa Gonçalves	(Assistant Prof., FMUC)	40
Teresa Maria C. Martins	(Assistant Inv., IPO)	80
Vanessa Mendes		100
Vera Lúcia Dantas Moura	(Manager Science & Tech., UC)	35

POST-DOC MEMBERS	**TIME % AT CNC.IBILI**
Akhilesh Rai	100
Alessandra Zonari	100
Ana Cristina Gonçalves	50
Ana Luisa Cardoso	100
Ana Rita Polónia	100
Ana Teresa Simões	100
Angela Fernandes	100
Carlos Matos	100
Catarina Miranda	100
Célia Cabral	30
Chantal Fernandes	100
Clévio Nóbrega	100
Cristiana Pires	100
Henrique Almeida	100
Hugo Fernandes	100
Isabel Onofre	100
Liliana Mendonça	100
Lisa Rodrigues	100
Luís Estronca	100
Nuno Mendonça	100
Patrícia Pitrez	100
Rita Perfeito	100
Rui Nobre	100
Sandra Pinto	100
Sezin Aday	100
Sónia Luzia Pinho	100
Sónia Patricia Duarte	100
Susana Alarico	100
Susana Rosa	100
Susana Simões	100
Vítor Francisco	100

PHD STUDENTS	TIME % AT CNC.IBILI
Adriana Marcelo	100
Ana Alexandra Miranda	100
Ana Cristina Ferreira	100
Ana Filipa Cruz	100
Ana Francisca Lima	100
Ana Rita Acúrcio	10
Ana Rita Cruz	100
Ana Sofia C. Valdeira	100
Andreia Marques Gomes	100
António Rufino Ramos	100
Catarina Mendes Morais	100
Catarina Praça Almeida	100
Catarina Rebelo	100
Daniela Costa	100
Dina Farinha	100
Emanuel Quartim Costa	100
Edna Filipa Soares	100
Fábio Rosa	100
Inês Vasconcelos Miranda Santos	75
Ivana Kostic	100
João Ribas	100
Joana Balça Pinheiro	100
Joana Jorge	100
Joana Saraiva	100
João Laranjeira	100
Mª Helena Antunes	100
Mª Inês Martins	100
Mª Mafalda Costa	100
Mª de la Salete J. Baptista	100
Mª Manuel Mendes	100
Mariangela Natale	100
Marta Mota	40
Michela Comune	100
Miguel Angelo Costa	20
Miguel Maria Lino	100
Patrícia Rosado Albuquerque	100
Pedro Cunha	100
Pedro Curto	100
Pedro José Gouveia	100
Raquel Alves	50
Ricardo Silva	100
Rita Severino	100
Romina Guedes	10
Rui Soares	40
Sandra Figueiredo	100
Sara Lopes	100

Sofia Anastácio		80
Sofia Pereira Romano		100
Tânia Barata		100
Udaya Geetha Vijayakumar		100
Vitor Carmona		100

MSc Students		**Time % at CNC.IBILI**
Alexandra Ferreira		100
Catarina Pechincha		50
Daniela Antunes		100
Daniela Santo		100
Marguerita Rosa		50
Miguel Lopes		100
João Barata		100
Rita Alves		100

Technicians / Others		**Time % at CNC.IBILI**
Ana Maranha Tiago		50
Dulce Bento		Collaborator
Fátima Nunes		25
Filipe Lebre	(Grant Technician)	Collaborator
Mariana Conceição		Collaborator
Sandra Jesus		Collaborator
Sílvia Neves		Collaborator
Steve Edwing		100