CNCIBILI

2015 Annual Report

INDEX

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INTRODUCTION

The 2015 Annual Report is the first report of activities of the CNC.IBILI Research Consortium recently created at the University of Coimbra, whose scientific skills in most of the sub-themes 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.

CNC.IBILI results from the fusion of two biomedical research institutes of excellence, CNC and IBILI, and 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.

Building upon an outstanding tradition of past research achievement , the synergies created by the fusion of CNC and IBILI will generate the opportunity for developing its research strategic plan in neurosciences, vision, aging, brain diseases and advanced therapies.

The consortium integrates 21 research groups organized in three Thematic Strands: Neuroscience, Vision and Brain Diseases; Metabolism, Aging and Disease and Stem-cell-based and Molecular Therapies.

The close connection to the Coimbra University Hospitals Health System (CHUC) provides access to clinical know-how, patient samples, and patients themselves, ensuring the possibility of both CNC.IBILI pioneered initiatives, and the participation in international consortia. On the other hand, collaboration with industry, namely in the biotechnology entrepreneurship campus created in Biocant Park, ensures that novel scientific ideas and methodologies will contribute to a more competitive knowledge-based economy in the region.

In-house masters and PhD Programs and international training networks coordinated by CNC.IBILI ensure the high-level and multidisciplinary mentoring of PhD students, clinicians and postdoctoral fellows in an environment that fosters creative critical thinking in both basic and applied science.

The Annual Report 2015 highlights some of the main scientific achievements within the various research themes of the CNC.IBILI Consortium.

Facts & Figures (2015)

RESEARCH STAFF

Integrated Members holding Ph.D.	276 (93 Post Doctoral Fellows)
Ph.D.Students	170
MSc Students	32
Technicians / Others	87

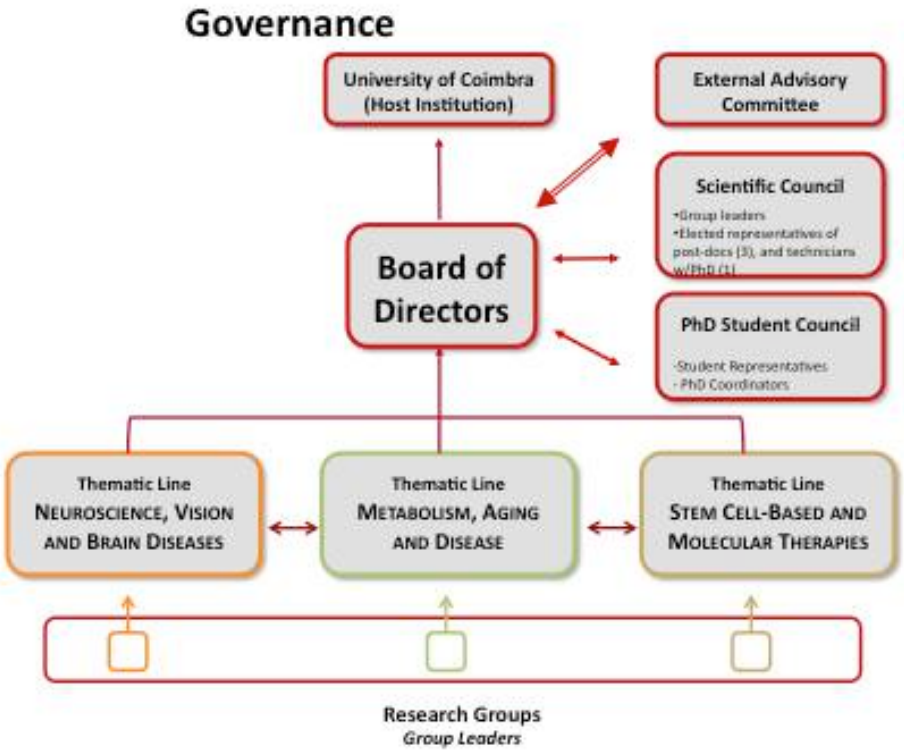
PUBLICATIONS

Scientific papers published	315
Scientific papers *In Press*	72

THESIS CONCLUDED

Ph.D. thesis	35
MSc thesis	89

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 2015, the research groups for Thematic Strand can be identified, according to the following organization:

Neuroscience, Vision and Brain Diseases | *Miguel Castelo-Branco*

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)*

ImmunoMetabolic Pharmacology *(Head: Margarida Carneiro)*

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: Miguel Castelo-Branco

The main aim of the Neuroscience, Vision and Brain Diseases Thematic Strand is to provide a fully translational research approach, from molecule to man, by bringing together research groups with different areas of expertise, from cellular and molecular neuroscience of brain and vision disorders to systems approaches, focused on the understanding of normal brain function and disease mechanisms.

This Thematic Strand is composed of 8 research groups, with extensive know-how in molecular and cellular neuroscience, in analyzing mechanisms of disease using animal models and a combination of biochemistry, electrophysiology and behavior analysis, as well as in human studies using cutting-edge brain imaging approaches. Additionally, successful genetic therapeutic approaches to neurodegeneration have been introduced. The groups are organized around central scientific questions, and bring together approaches at different levels. All groups have a solid track-record, are engaged in strong international collaborations with leader labs in their field, and have international visibility. There is a long-tradition of collaboration between the groups, and of cross fertilization between ideas and experimental approaches.

The research groups address both fundamental questions about brain function and tackle the mechanisms of brain disease and strategies to resolve them, using animal models and human patients. The research perfomed focuses the following aspects:

1. Synaptic Processes

Established know-how in molecular and cellular neuroscience, and in evaluating synaptic function/dysfunction is instrumental in addressing one of the overarching hypotheses of central nervous system diseases, which proposes an early role for synapse malfunction in disease etiology, both in neuropsychiatric and in neurodegenerative disorders. This flagship brings together groups working on synapse development and function, and on synaptic neuromodulation, as well as groups using animal disease models to detect or interfere with synaptic dysfunction, and groups testing hypotheses related to deficient neurotransmission involving the retina (a window to the brain), developmental and neuropsychiatric disorders. Key long-standing goals are 1) to understand the cellular mechanisms that govern synapse formation, function and plasticity; 2) to develop synaptic markers to evaluate synaptic function and dysfuntion in living animals and patients to confirm the validity of this hypothesis in an *in vivo* setting.

2. Brain Metabolism

The central nervous system is the major responsible for body energy consumption. There is increasing recognition that limitations of energy supply to neuronal networks in terms of allocation of energy resources, as well as flexibly among regions according to neural demand, is tightly associated with retina and brain dysfunction. The flagship fosters several inter-twinned goals, namely: 1) to probe if, how and where dysfunction of mitochondria (the main cell power plant) affects neuronal function and viability; 2) to grasp the determinants of neuronal and neurovascular coupling, the basis of imaging techniques in human patients; 3) to address the role of astrocytic and microglial metabolism in connection with neuronal activity, with the hope to understand neuronal metabolic dysfunction, as well as to develop imaging markers for astrocytes to be used in human patients, given that humans have a 10 times greater astrocytic density than rodents.

3. Vision and Brain Imaging

Understanding visual and brain function and their impairment requires integrating the evaluation of molecular and phenotypic changes with state-of-the-art assessment of structure-function correlations in the central nervous system. This is carried out by combining the evaluation of behavior in animal models and in patients with *in vivo* physiological recordings and imaging of the brain. Decision-making is an important feature of brain function and comprises several levels, from simple perceptual decisions to goal-oriented behaviour under complex emotional and social contexts. We aim to elucidate the functional connectivity of core and extended neural architectures underlying choice behaviour, by combining unique multimodal approaches including MR techniques (spectroscopy, morphometry and function), molecular imaging (PET with 11C and 18F Chemistry), Transcraneal Magnetic Stimulation and large scale data integration. A translational research focus will be placed on the retina and visual pathways as neurophysiological biomarkers of brain function and dysfunction. A major goal is the elucidation of the pathogenesis and the identification of potential therapeutic targets in diseases that affect vision and brain function. Altogether these approaches provide the appropriate translation from *in vitro* and *in vivo* studies towards therapeutic targets of diseases of the retina and the brain.

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
Ângela Inácio	PhD
Graciano Leal	PhD
Joana Fernandes	PhD
Miranda Mele	PhD
Rui Miguel Oliveira da Costa	PhD
Susana Louros	PhD
Tatiana Andreia Catarino	PhD
Ivan Salazar	PhD Student
Sara Oliveira	PhD Student
Joana Pedro	PhD Student
Mª Joana Pinto	PhD Student
Pedro Afonso	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
Mohamed Hussien	PhD Student
Blanka Kellermayer	PhD Student
Mário Carvalho	PhD Student
Pasqualino de Luca	MSc Student
Beatriz Rodrigues	MSc Student
Débora Serrenho	MSc Student
Joana Freire Costa	MSc Student
Marina Rodrigues	MSc Student
Renato Sousa	MSc Student
João Calmeiro Pereira	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
Barbara da Silva Rocha	Post Doctoral Fellow
Cátia Filipa Marques	Post Doctoral Fellow
Diana Serra	PhD Student
Sónia Rosa Pereira	PhD Student
Cassilda Pereira	PhD Student
Nuno Ricardo Ferreira	Collaborator

NEUROENDOCRINOLOGY AND AGING GROUP

Claudia Margarida Cavadas	PhD *(Head of Group)*
Ana Rita Álvaro	PhD
António Pedro Gomes	PhD
Armando Jorge Cristóvão	PhD
Célia Alexandra Aveleira	PhD
Joana Rosmaninho Salgado	PhD
Ligia de Sousa Ferreira	PhD
Magda Santana	PhD
Ana Patrícia Marques	PhD Student
Janete Santos	PhD Student
Mariana Botelho Rocha	PhD Student
Sara Silva	PhD Student
Ana dos Santos Carvalho	Collaborator
Caetana Carvalho	Collaborator
João Pedro Magalhães	Collaborator

VISION, BRAIN IMAGING AND COGNITIVE NEUROSCIENCE

Miguel Castelo-Branco	PhD *(Head of Group)*
Aldina Conceição Pires Reis	PhD
Alda Maria Abreu Cardoso	PhD
Antero Afonso de Abrunhosa	PhD
António Gonçalves Freire	PhD
Bárbara dos Santos Oliveiros	PhD
Eduardo José Silva	PhD
Francisco Cerqueira Alves	PhD
Francisco Caramelo	PhD
Francisco Oliveira	PhD
Gina Maria Costa Caetano	PhD
Guiomar Gonçalves Oliveira	PhD
Inês Bernardino	PhD
Inês Ribeiro Violante	PhD
João Miguel Santos Pereira	PhD
João Miguel Castelhano	PhD
Joao Pereira Figueira	PhD
João Santos Relvas	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
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
Sónia Isabel Gonçalves	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
José Eduardo Lima Rebola	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 Isabel Rodrigues	PhD Student
Ana Maria Batista	PhD Student
Andreia Martins Rosa	PhD Student
Carlos Manuel Amaral	PhD Student
Filipa Lima Júlio	PhD Student
João Valente Duarte	PhD Student
Marco António Simões	PhD Student
Maria Luísa Ferreira Ribeiro	PhD Student
Marta Cristina Teixeira	PhD Student
Otília d'Almeida	PhD Student

Pedro Luís s Fonseca	PhD Student
Raquel Maria Oliveira	PhD Student
Sulaiman I S Abuhaiba	PhD Student
Susana Figueiredo e Silva	PhD Student
Susana Isabel Simão Mouga	PhD Student
Teresa Maria da Silva Sousa	PhD Student
Ana Mafalda Teixeira	Grant Technician
Andreia Sofia Pereira	Grant Technician
Ângela Sofia Miranda	Grant Technician
Carlos Daniel Ferreira	Technician
Carlos Manuel Pereira	Grant Technician
Carolina César Alves	Grant Technician
César Alejandro Nunes	MD
Diliana Rebelo Santos	Grant Technician
Hélio Jorge Gonçalves	Grant Technician
Hugo AlexandreQuental	Grant Technician
Isabel Catarina Duarte	Technician
João Filipe Lima	Grant Technician
João Paulo Andrade	Grant Technician
Lília Pereira Jorge	Grant Technician
Márcia Sofia Andrade	Grant Technician
Margarida Maria Marques	Invited Assistant
Nádia Isabel Canário	Grant Technician
Ricardo José Martins	Grant Technician
Sónia Maria Ferreira	Grant Technician
Tânia Maria Marques	Grant Technician
Vítor Hugo Alves	Grant Technician

PURINES IN BRAIN DISEASES GROUP

Rodrigo A. Cunha	PhD *(Head of Group)*
Attila Köfalvi	PhD
Angelo Ribeiro Tomé	PhD
Paula Maria Agostinho	PhD
Ricardo Rodrigues	PhD
Ana Patrícia Simões	Post Doctoral Fellow
Joana Marques	Post Doctoral Fellow
João Pedro Lopes	Post Doctoral Fellow
Nélio Gonçalves	Post Doctoral Fellow
Paula Canas	Post Doctoral Fellow
Samira Ferreira	Post Doctoral Fellow
Amber Kerkhofs	PhD Student
Francisco Queiroz Gonçalves	PhD Student
Anna Pliássova	PhD Student
Patrícia Sofia Alçada Morais	PhD Student
Sofia Ferreira	PhD Student
Xinli Xu	PhD Student
Tiago Alfaro	PhD Student

MITOCHONDRIAL DYSFUNCTION AND SIGNALING IN NEURODEGENERATION GROUP

Ana Cristina Carvalho Rego	PhD *(Head of Group)*
Carla Lopes	PhD
Elisabete Baptista Ferreiro	PhD
Ildete Luisa Araujo Ferreira	PhD
Mário Laço	PhD
Sandra Mota	PhD
António Silva	PhD Student
Luana Naia	PhD Student
Catarina Carmo	MSc Student
Carina Maranga	MSc Student
Diogo Canhoto	MSc Student
Filipa Almeida	MSc Student
Lígia Fão	MSc Student

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
Sandra de Carvalho Bos	PhD
Sandra Freitas	Post Doctoral Fellow
Ana Rita Gaspar	PhD Student
Cátia Santa	PhD Student
Mafalda Bacalhau	PhD Student
Sandra Anjo	PhD Student
Carlos Rabaça	Collaborator
Célia Gomes	Collaborator
Helena Beatriz Santiago	Collaborator
José Alves	Collaborator
Mª Olinda Rebelo	Collaborator
Mariana Freitas	Collaborator
Mário Simões	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
Flávio Nelson Reis	PhD
Frederico G. Pereira	PhD
Isabel Santos Pereira	PhD
João Filipe da Costa Martins	PhD
João José Oliveira Malva	PhD
José Guilherme Tralhão	PhD
Manuel Marques Ferreira	PhD
Mª Dulce Ferreira Cotrim	PhD
Mª Filomena Botelho	PhD
Mª Margarida Caramona	PhD
Mª Margarida Caetano	PhD
Paulo Fernando Santos	PhD
Paula Cristina Vaz Tavares	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
Mafalda Sofia Cândido	Post Doctoral Fellow
Ana MargaridaTeixeira	PhD Student
Ana Salomé Pires	PhD Student
António Campos Figueiredo	PhD Student
Diogo André Fonseca	PhD Student
Eurico Miguel Fial Ribeiro	PhD Student
Fernando José Mendes	PhD Student
Filipe Manuel Farto Palavra	PhD Student
Maria Helena Bica Madeira	PhD Student
Maria João Carvalho	PhD Student
Raquel Sofia Freitas Bóia	PhD Student
Ricardo Alexande Leitão	PhD Student
Samuel Filipe Chiquita	PhD Student
Sara Raquel Martins Neves	PhD Student
Sara Raquel Nunes	PhD Student
Sofia Andreia Viana	PhD Student
Vanessa Filipa Santos	PhD Student

Helena A. Ribeiro Pinheiro	MSC Student
Iolanda John Mora de Cruz	MSc Student
Joana Filipa Mendes Duarte	MSc Student
José Carlos Ribeiro Pereira	MSc Student
Nuno Filipe Henriques Silva	MSc Student
Daniela Isabel Oliveira	Grant Technician
Inês Roque Antunes Pita	Grant Technician
Patrícia Pereira	Grant Technician
Ricardo Jorge Teixo	Grant Technician
Victor Hugo Teixeira Pinheiro	MD
Vítor César Arantes Pinheiro	MD
Ana Catarina Neves	Collaborator
Inês Sofia Dinis Aires	Colaborator
Joana Margarida Martins	Colaborator

Synapse Biology Group *(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 controling the assembly of new presynapses.

(ii & iii) Glutamatergic synapses and neuropsychiatric 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, and synaptic dysfunction is present in neuropsychiatric 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, optogenetics and behavior analysis. 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. The main goal of our work is focused on understanding neuropsychiatric disorders while dissecting the neuronal circuits controlling behaviors. We study synaptic and postsynaptic density proteins implicated in autism and schizophrenia across specific cell-types and neuronal circuits. We want to understand how synaptic computations give rise to social behavioral programs and to uncover the genetic elements that regulate sociability. 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 D2R 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. Our new approaches will be applied to a relevant biological system: the dopamine receptor type 2 (D2R), a typical member of Class A GPCRs involved in many cognitive, emotional and motor functions. For this particular target we aim to understand both the dynamics of the D2R and its interactions with the binding partners (Arrestins and G-protein).

Main Achievments

(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.

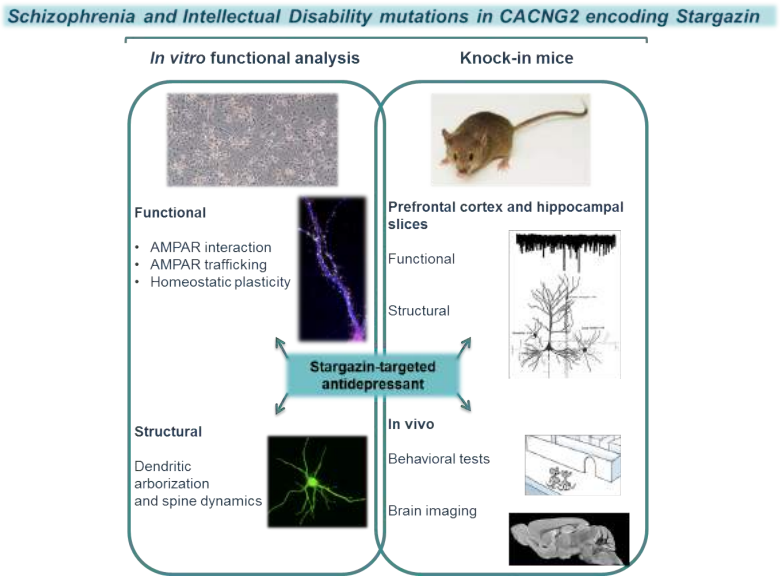


***Fig. 1**: Schizophrenia- and Intellectual Disability-associated mutations in the CACNG2 gene encoding the AMPA receptor auxiliary protein stargazin are being studied. In vitro characterization of the functional consequences of these mutations revealed alterations in the protein function. Knock-in mice expressing disease-associated mutations in CACNG2 are currently being generated. Behavioral, electrophysiological and brain imaging analyses of these mice will reveal a disease signature associated to mutations in CACNG2.*

(ii & iii) Glutamatergic synapses and neuropsychiatric disorders (PIs: Ana Luísa Carvalho and João Peça)

1. We generated novel ChR2 variants using Time-dependent density functional theory (TDDFT), producing blue-shifted and red-shifted mutations. (Calmeiro, João MSc Thesis)

2. We identified a role for GluN2B-containing NMDA receptors in the maintenance of the synaptic scaffold and in the basal regulation of synaptic AMPA receptors through synaptic anchorage of the proteasome (Ferreira et al., 2015)

2. We characterized molecular domains in GluN2B 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.

3. We identified a schizophrenia-associated mutation in the CACNG2 gene encoding the AMPA receptor auxiliary protein stargazin, and found that this mutation alters 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 disease (schizophrenia and intellectual disability)-associated mutations in CACNG2 are currently being generated (Caldeira et al., in preparation).

4. We identified GPRASP2, a susceptibility gene for autism, as a regulator of mGluR5 trafficking and characterized its role in the modulation of neuronal morphology and spine maturation (Edfawi et al, in preparation)

5. We generated a GPRASP2 conditional knockout mouse line as a model for autism spectrum disorders (Edfawi et al, in preparation).

6. We identified early life stress as trigger for subordinate behavior in adulthood. Using RNA-seq we determined that 120 genes are up- or down-regulated as a consequence of this form of stress (Franco et al, in preparation).

(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 GABAA receptors. The consequent decrease in inhibitory activity was shown to play 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. 2016).

(v) Structural characterization of protein-based interactions in D2R activity (PI: Irina Moreira)

We have established new algorithms for the determination of HS at protein-based interactions, which were also applied to membrane proteins such as GPCRs. These systems are particularly difficult due to the lipidic environment that surrounds them. We have also used unbiased Molecular Dynamics simulations of various types of arrestins mutants, and established their activation mechanism and identified the functionally critical regions on arrestin structure that can be targeted with drugs or chemical tools for functional modulation. The revelation of the mechanism of activation that prepares arrestin for selective interaction with GPCRs will be crucial for the clarification of their coupling to D2R.

Redox Biology and Brain Sensing Group *(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

1. The impairment in the glutamate-NMDAr-nNOS pathway represents a functional critical event in the cognitive decline during aging. This was supported by experiments in vivo in rodents showing that the glutamate-induced $^{\bullet}NO$ concentration dynamics is decreased in the hippocampus, striatum and cerebral cortex during age and that theese changes are accompanied by decreased performance in behavior testing of short-term and spatial memory.

2. Dietary nitrite induces post-translational modification of functional proteins in the stomach via S- and N-nitrosation that may be translated into biological effects in the inner epithelium. In this regard mucus proteins act as chemical barrier for potential deleterious effects of nitrite-derived species an inner mucosa layers.

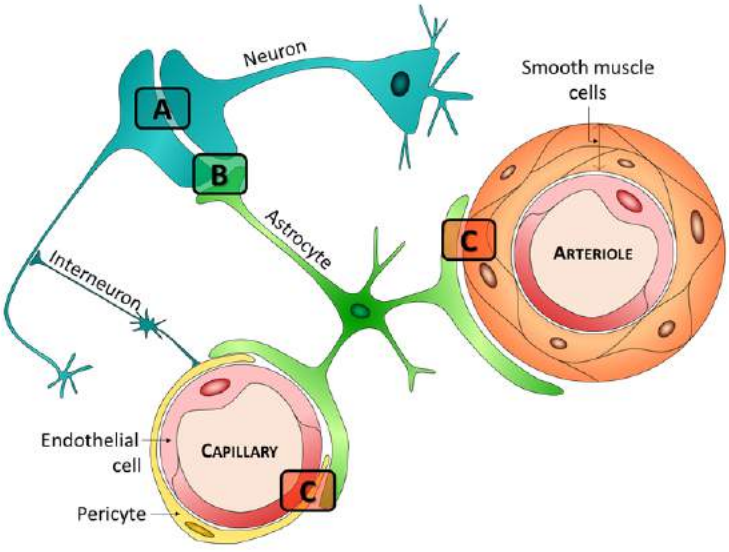
In humans, ethanol from wine can be nitrosated under acidic conditions by nitrite yiedling ethyl nitrite the human stomach following consumption of alcoholic beverages and lettuce (source of nitrate). In turn, ethylnitrite act as a nitric oxide (NO) donor at physiological pH, modulating gastric smooth muscle relaxation. So, ethanolic beverages and dietary nitrate, via NO-triggered ethanol nitrosation, may modulate gastric functions and possibly more systemic functions via NO release.

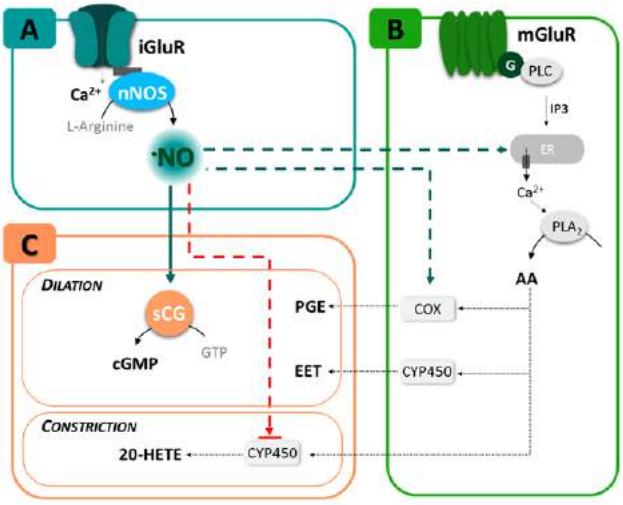
3. The imbalance in the regulation of the neurovascular and neurometabolic coupling, resulting from cerebrovascular dysfunction, are precocious events in neurodegeneration and brain aging. This shift in paradigm and the role of vascular redox status of brain microcirculation may be crucial for development of adequate therapeutically strategies that hamper cognition defects and neurodegeneration.

4. The anti-inflammatory action of red wine is exerted at complementary levels by its content in polypenols, via suppression of the JAK/STAT inflammatory pathway and positive modulation the activity of the Nrf2. These results point to the potential use of the red wine polyphenols as an efficient, readily available and inexpensive therapeutic strategy in the context of the gastrointestinal inflammation.

5. we have developed a biosensor optimized for the joint measurement of neuronal network dynamics and spontaneous choline fluctuations in the brain *in vivo* with an effective limit of detection in the nanomolar range. The biosensor will permit in the future to measure from multiple brain regions in behaving animals and optogenetic investigation of the neuronal circuits underlying cholinergic signals will help understanding the wide range of choline dynamics we have reported.

6. Ascorbate and neuronal-derived nitric oxide (NO) play regulatory roles in the brain that are dependent on their compartmentalization and diffusion. The coupling between NO and ascorbate upon glutamatergic activation points to a functional impact on the activities of both compounds and lays the foundations for new regulatory mechanisms in the brain.





Neuroendocrinology and Aging Group

(Head: Claudia Cavadas)

Objectives

In our group we investigate the hypothalamus and hypothalamic related systems/mechanisms as underlying mediatora and targets for interventional strategies in counteracting aging and 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 insuline resistance?

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

Main Achievements

a) We demonstrate that CR induces autophagy in hypothalamic neurons, and this effect is mediated, in part, by NPY receptors activation. In addition, evidence from both hypothalamic neuronal *in vitro* models and mice overexpressing NPY in the hypothalamus, show that NPY *per se*, stimulates autophagy in the hypothalamus (Figure 1). Mechanistically, the activation of NPY Y_1 and Y_5 receptors increases autophagy in hypothalamic neurons and this effect is tightly associated with the concerted activation of PI3K, MEK/ERK and PKA signaling pathways. Since both hypothalamic autophagy and NPY levels decrease with age, the rescue of hypothalamic NPY levels provides a new putative strategy to delay aging (Aveleira and Botelho et al., PNAS 2015).

b) Caloric restriction (CR) mimetic medium induces autophagy in rat cortical neurons in culture and blocking NPY or Ghrelin receptors inhibits this effect. Moreover, NPY and ghrelin, *per se*, stimulate autophagy and NPY mediates, in part, ghrelin-induced autophagy in rat cortical neurons. Since autophagy impairment occurs in aging and age-related neurodegenerative diseases, this NPY and ghrelin synergistic effect on autophagy stimulation may suggest a new strategy to delay aging process (Marques and Aveleira et al, in revision).

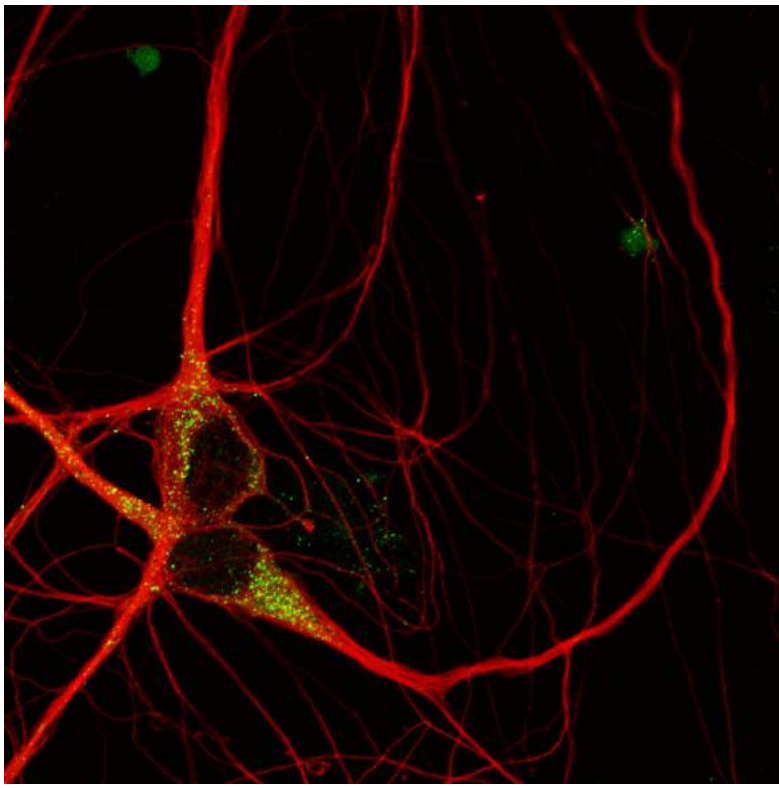
c) The microRNA pathway is impaired in the hypothalamus of obese rodents as shown by alterations in the expression levels of miRISC genes and specific microRNAs. Moreover, hypothalamic let-7 microRNA modulation prevents central and peripheral alterations induced by high-fat diet in mice (Sousa-Ferreira et al., in preparation)

d) 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.

e) SIRT2 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 (Santos et al., in preparation)

f) NPY changes circadian clock genes in hypothalamic neurons

g) 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, associated to neurodegeneration of specific brain regions including cerebellum and striatum. We observed that NPY levels are decreased in two MJD patients' *cerebella* and in *striata* and *cerebella* of MJD mouse models. Furthermore, CR or overexpression of NPY in specific brain areas alleviate the motor coordination impairments and attenuated the related MJD neuropathological parameters (Duarte-Neves et al., 2015; Cunha-Santos et al., in revision).



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

Objectives

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

Our group has continued to coordinate 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. Our Cognitive Neurosciences Pillar has further developed Vision, Perception and Decision-making research streams. The Clinical Neurosciences Pillar has generated 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, Williams Syndrome 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, which has an impact on understanding og cognitive control, attention and decision. 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. Our contribution to studies of plasticity based on multimodal structure-function and genotype-phenotype correlations has helped to provide an explanatory framework for plasticity is helping to define novel rehabilitation strategies.

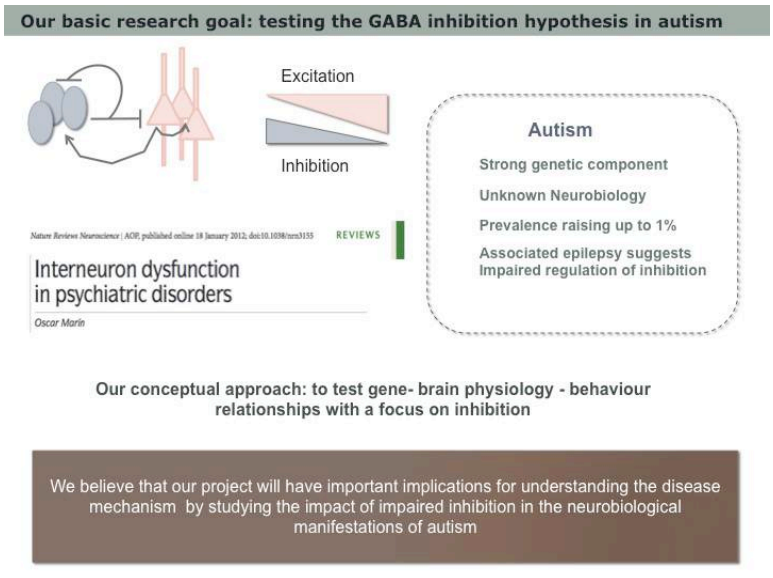
Our success in generating interdisciplinary work with scientists working in the field of cognitive neuroscience, neurology, medical imaging neuroinformatics and neuroengineering, is anchored on our national and international collaborations which also enabled proof of concept publications showing the 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, the Universities of Maastricht, Cardiff, Tuebingen, University College London, John Hopkins University, US as well as the Department for Neurophysiology of the Max-Planck Institute for Brain Research.

Main Achievements

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. This led to publication in Neurology one of the top Journals in the field of Neurology. We also had a recent paper accepted in 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 to publications in top journals in neuroimaging, sucha as Human Brain Mapping. Methodological Achievements can also be underlined by the successful use of statistical classification methods to separate disease states (publication in Human Brain Mapping) 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. We finally also achieved a worldwide patent together with IBA, the world leader in cyclotron production.



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, and glial control of synaptic function involving altered astrocyte-to-neuron communication and modified microglia-dependent neuro-inflammatory context. 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 neuropsychiatric disorders (Ana Patrícia Simões, Samira Ferreira, Nélio Gonçalves).

Main Achievements

1-We defined a prophylactic and therapeutic ability of A2AR antagonists to prevent emotional and memory disturbances upon chronic stress (*Kaster MP, et al (2015) Proc Natl Acad Sci USA 112, 7833-7838*).

2-We established that A2AR activation, either pharmacological (*Pagnussat N, et al (2015) Br J Pharmacol 172, 3831-3845*) or optogenetic (*Li P, et al (2015) Mol Psychiatry 20, 1339-1349*) is sufficient to impair memory performance.

3-We found that A2AR display a biased transducing system in different brain areas (*Li P, et al (2015) Mol Psychiatry 20, 1339-1349*).

4-We extended that A2AR shift presynaptic modulation from inhibitory to excitatory since A2AR activation down-regulates presynaptic CB1 receptors (*Ferreira SG, et al (2015) Br J Pharmacol 172, 1074-1086*).

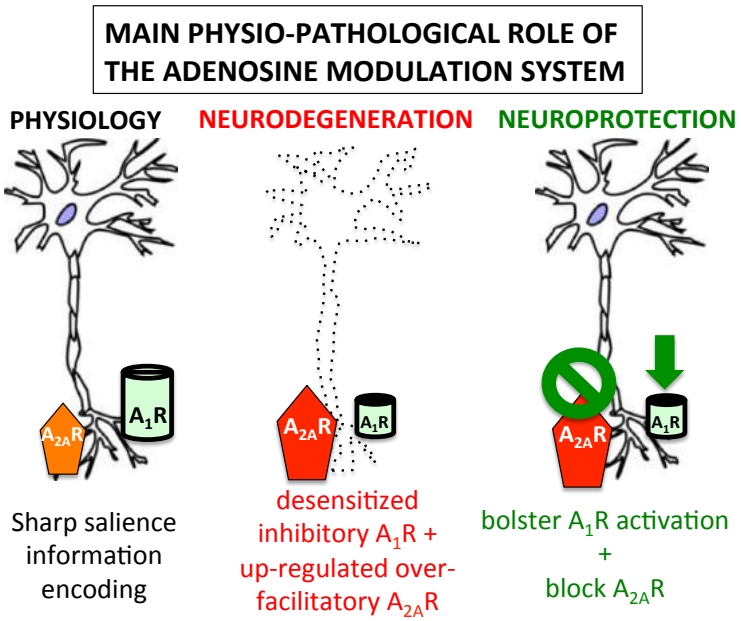
5-A2AR are upregulated in synapses early in the course of neurodegenerative disorders and their over-activation dampens memory performance, as found in an animal model of Huntington's disease (*Tyebji S, et al (2015) Neurobiol Dis 74, 41-57.* and *Li W, et al (2015) Neurobiol Dis 79, 70-80*).

6-By exploring the role of A2AR in astrocytes, we unraveled an astrocyte-to neuron wave of communication, so that the selective elimination of astrocytic A2AR causes a synaptic imbalance and a schizophrenia-like phenotype (*Matos M, et al (2015) Biol Psychiatry 78, 763-774*).

7-We described the synaptic and subsynaptic localization of APP (*Agostinho P, et al (2015) J Alzheimers Dis 45, 329-347* and *Pliássova A, et al (2015*) Mol Neurobiol (in press)) and found that the CSF levels of theobromine correlate inversely with deterioration of AD patients (*Travassos M, et al (2015) J Alzheimers Dis 47, 1069-1078*).

8-We found that A2AR critically control the toxicity of α-synuclein (a PD-associated protein) (*Ferreira DG, et al (2015) Cer Cortex (in press)*) and optimized an animal model of Parkinson's disease allowing to study memory (*Matheus FC, et al (2016) Beh Brain Res 301, 43-54*) and emotional dysfunction (*Matheus FC, et al (2015) Mol Neurobiol (in press*)) independently of motor impairment.

9-We consolidated the concept of ATP as a danger signal in the brain (*Rodrigues RJ, et al (2015) Front Neurosci 9, 148*) by showing that ATP is released from microglia to control its proliferation (*George J, et al (2015) Glia 63, 1636-1645*).

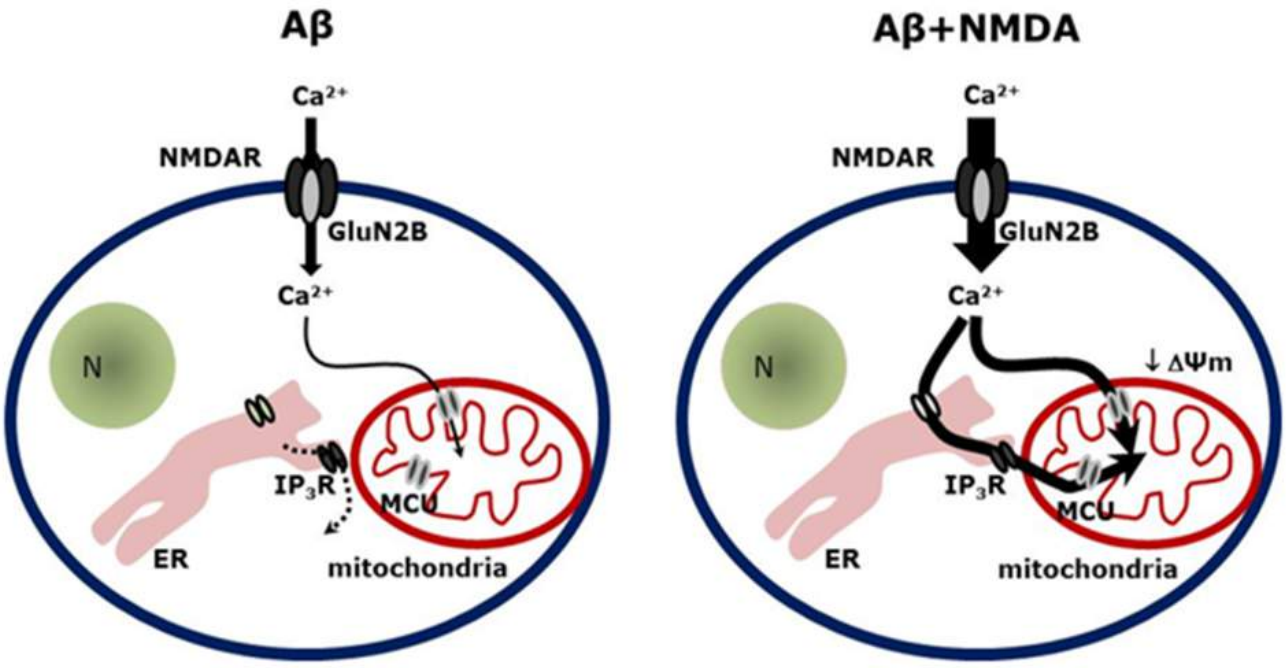


Mitochondrial Dysfunction and Signaling in Neurodegeneration Group *(Head: A. Cristina Rego)*

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 also aims to characterize molecular targets for therapeutic intervention.

Early cognitive deficits in AD seem to be correlated to dysregulation of glutamate receptors evoked by amyloid-beta (Aβ) peptide. Indeed, Aβ interference with the activity of N-methyl-D-aspartate receptors (NMDARs), as shown previously by us, may be a relevant factor for Aβ-induced mitochondrial toxicity and neuronal dysfunction. This led us to evaluate the role of mitochondria (and endoplasmic reticulum, ER) in NMDARs activation and intracellular calcium dyshomeostasis mediated by Aβ in rat primary cortical neurons (*Ferreira and Ferreiro et al., 2015, Neurobiol. Aging*). Considering that oxidative stress and ER stress have been associated with AD progression, we further analyzed whether oxidative stress involving changes in nuclear factor (erythroid-derived 2)-like 2 (Nrf2, a transcription factor that regulates the expression of antioxidant proteins) and ER stress might constitute early events in AD pathogenesis by using human peripheral blood mononuclear cells (PBMCs) and an AD transgenic mouse model at different disease stages (*Mota et al., 2015, Biochim Biophys Acta - Molecular Basis of Disease*).



Aβ alone or Aβ plus NMDA differentially modulate Ca^{2+}_i and ΔΨm.
Aβ+NMDA enhance mitochondrial Ca^{2+} retention and organelle depolarization through the ER.

Legend: NMDAR- NMDA receptor; ER- endoplasmic reticulum; IP_3R- inositol-1,4,5-triphosphate receptors; MCU- mitCa^{2+}uniporter, $\Delta\Psi_m$- mitochondrial membrane potential. In: Ferreira I. L. and Ferreiro E. et al. (2015) Neurobiol. Aging 36, 680-692.

HD is an autosomal dominant disease caused by an expansion of CAG repeats in the *HTT* gene, encoding for the huntingtin protein, and the most prevalent polyglutamine expansion disorder. Mitochondrial dysfunction associated with energy failure and oxidative stress play an important role in this untreated pathology. Unfortunately, there is no cure or neuroprotective treatment for HD. Because flavones are compounds with a protective and potential antioxidant role in several neurodegenerative processes, we also analyzed the effect of luteolin and luteolin derivatives in HD mouse striatal cells (**Oliveira et al., 2015, *Neurochem. Int.***). By continuing our previous line of research, we analysed the role of insulin-like growth factor-1 (IGF-1)/Akt pathway in HD; for this purpose we used lymphoblasts obtained from HD patients or unaffected parentally related individuals to study the protective role of IGF-1 *versus* insulin (at low nM) on signaling and metabolic and mitochondrial functions (*Naia and Ferreira et al., 2015, Mol. Neurobiol)*. In addition, since the lack of brain-derived neurotrophic factor (BDNF) in the striatum has been proposed to explain HD pathogenesis, we studied the influence of BDNF and TrkB receptors in intracellular signaling pathways and caspase-3 activation in HD striatal cells (*Silva et al., 2015, Neurodegener. Dis.)*

Main Achievements

To evaluate the role of mitochondria in NMDARs activation mediated by Aβ, we followed *in situ* single-cell simultaneous measurement of cytosolic free Ca2+ ($Ca_i(2+)$) and mitochondrial membrane potential (Δψm) in primary cortical neurons. Exposure to Aβ+NMDA largely increased $Ca_i(2+)$ and induced mitochondrial depolarization. Aβ-induced $Ca_i(2+)$ and mitCa(2+) rise were inhibited by ifenprodil and in GluN2B(-/-) neurons, implicating the involvement of GluN2B subunit. Moreover, Aβ+NMDA-induced mitCa(2+) rise involved ER Ca(2+) release through IP3R and mitochondrial entry through mitCa(2+) uniporter. Data highlight mitCa(2+) dyshomeostasis and subsequent dysfunction as mechanisms relevant for early neuronal dysfunction in AD linked to Aβ-mediated GluN2B-composed NMDARs activation (*Ferreira and Ferreiro et al., 2015, Neurobiol. Aging*).

By using human peripheral blood cells and an AD transgenic mouse model at different disease stages we analysed oxidative stress involving changes in Nrf2 and ER stress in early stages of AD. Enhanced oxidative stress and increased phosphorylated Nrf2 (p(Ser40)Nrf2) were observed in human PBMCs isolated from individuals with mild cognitive impairment (MCI). We observed impaired ER Ca(2+) homeostasis and increased ER stress markers in PBMCs from MCI individuals and mild AD patients. Evidence of early oxidative stress in AD was substantiated by increased p(Ser40)Nrf2 in 3 month-old 3xTg-AD male mice PBMCs, and increased nuclear Nrf2 levels in brain cortex. However, SOD1 protein levels were decreased in human MCI PBMCs and in 3xTg-AD mice brain cortex; the latter further correlated with reduced superoxide dismutase 1 (SOD1) mRNA levels. Results suggest markers of prodromal AD linked to oxidative stress associated with Nrf2 activation and ER stress that may be followed in human PBMCs (*Mota et al., 2015, Biochim Biophys Acta – Mol.Basis Dis.*).

In the context of HD, we studied the protective effects of luteolin (Lut, 3',4',5,7-tetrahydroxyflavone) and four luteolin derivatives bearing 3-alkyl chains of 1, 4, 6 and 10 carbons (Lut-C1, Lut-C4, Lut-C6, Lut-C10) in striatal cells derived from HD knock-in mice expressing mutant Htt. HD cells treated with Lut-C4 and Lut-C6 showed decreased caspase-3 activation and intracellular reactive oxygen species, and enhanced nuclear levels of phospho(Ser40)Nrf2 and Nrf2/ARE transcriptional activity. Lut-C6 also enhanced SOD1 mRNA and SOD activity and glutamate-cysteine ligase catalytic subunit (GCLc) mRNA and protein levels, suggesting that Lut-C6 might be relevant as antioxidant strategy in HD (*Oliveira et al., 2015, Neurochem. Int.*).

By using HD human lymphoblasts we showed that IGF-1 (and partially insulin) stimulated IR/IGF-1R, AKT and ERK. IGF-1 and insulin also augmented huntingtin phosphorylation at Ser421 and rescued energy levels in HD cells. Moreover, IGF-1 ameliorated O2 consumption and Δψm in HD lymphoblasts, and increased cytochrome c levels. Constitutive phosphorylation of huntingtin restored Δψm in lymphoblasts expressing an abnormal expansion of polyglutamines. Data support an important role for IR/IGF-1R mediated activation of signaling pathways on improved mitochondrial and metabolic function in HD human lymphoblasts (*Naia and Ferreira et al., 2015, Mol. Neurobiol.*).

To study the influence of BDNF and TrkB receptors we used HD mutant and wild-type mouse striatal cells transduced with preproBDNF or full-length TrkB receptors to analyze BDNF processing, AKT and ERK activation and the activity of caspase-3. BDNF-mCh overexpression rescued decreased AKT phosphorylation and reduced caspase-3 activation in HD cells. Overexpression of TrkB-eGFP and exposure of TrkB-eGFP-transduced mutant cells to recombinant human BDNF decreased caspase-3 activation in HD cells. Results highlight the importance of BDNF-induced TrkB receptor signaling in rescuing HD-mediated apoptotic features in striatal cells (*Silva et al., 2015, Neurodegener. Dis.).*

Aging and Brain diseases: advanced diagnosis and biomarkers

(*Head: Catarina Resende Oliveira*)

Objetives

Research in the "Aging and Brain diseases: advanced diagnosis and biomarkers" aims at identifying new biomarkers of aging and brain disorders leading to the design of patient-tailored preventive and therapeutic interventions, under a translational research perspective. For this purpose, molecular, genetic and biochemical and "-OMICS" approaches have been used, associated with clinical and neuropsychological evaluation. According to the specific aims of the group, the following domains have been addressed: biomarkers of neurodegenerative disorders, namely dementia, aiming to perform an early diagnosis and improve differential diagnosis accuracy (i), and characterization of diagnosis strategies of early life cognitive dysfunction (ii) and neuropsychiatric disorders, particularly schizophrenia and bipolar disease (iii).

One additional goal of this group is focused on Bigenomic Disorders and Personalized Medicine (iv).

1) Biomarkers of Neurodegenerative Diseases

Epidemiological-data about dementia in our country is scarce although being crucial for the organization of care and the delineation of national dementia strategies. Our specific goals of investigation were to obtain indirect up-to-date information about the prevalence of dementia/AD in Portugal, to estimate the number of cases effectively diagnosed and to determine illness-costs with specific treatment. We have been involved in the validation of several neuropsychological instruments that allow the screening and characterization of cognitive decline related to ageing and dementia. Furthermore we are developing translation studies incorporating cognitive measures, CSF-biomarkers and susceptibility genes in order to investigate its potentials in the early diagnosis of Alzheimer´s disease and in the prediction of disease-evolution.

As a partnership of the EADC consortium, our memory clinic collaborated in multi-cohort studies intended to investigate the potential and accuracy of the new diagnostic criteria for Alzheimer´s disease and we also contributed to a meta-analysis evaluating the added value of Cerebrospinal fluid biomarkers in clinical trials for Alzheimer and Parkinson diseases.

Through the involvement in two European projects aimed at a standardized assessment of established and new fluid biomarkers for AD and PD (BIOMARKAPD) and the optimization of protocols for biomarker based diagnosis of rapid progressive dementias (DEMTEST), we had the opportunity to create and validate detailed standardised operating procedures for sample collection, storage, analytical procedures and clinical use of biomarkers; to be included in a network of harmonised laboratories in Europe; to participate in european biobanks for validating new biomarkers.

We have performed the mutation analysis of more than 200 hundred patients with the clinical diagnosis of Alzheimer's disease, Frontotemporal Lobar Degeneration, Parkinson's disease and Amyotrophic Lateral Sclerosis. This procedure contributed and/or improved the molecular diagnosis, the differential diagnosis accuracy as well as the identification of high-risk relatives still asymptomatic. The genetic characterization of these patients cohort increased also the knowledge of the genetic background of our population with the identification of novel mutations, not previously reported, and was crucial for planning patient's management and follow-up.

In Parkinson's Disease (PD),the major objectives of the project "DJ-1 neuronal rescue under oxidative stress: implications for Parkinson's disease" were to: i) identify the dynamic interactome of endogenous DJ-1 under oxidative stress conditions, ii) study the role of point mutations on this dynamic interactome and iii) evaluate the neuroprotective effect of exogenously added DJ-1 to neuronal cells.

2) Diagnosis of Early Life Cognitive Dysfunction

This line of research focused is the characterization of new biomarkers of different neurodevelopmental disorders associated with cognitive impairment, with the ultimate goal of improving patients' diagnosis and therapeutic interventions. The impact of fetal chromosome disorders on maternal blood metabolome was also analysed, exploring new putative biomarkers.

3) Diagnosis Strategies in Neuropsychiatric Disorders

The main goal of this line of research was the study of the phenotypic dimension of psychosis, namely schizophrenia and bipolar disorder and by combining proteomics, metabolomics and targeted gene analysis to create a single predictive model, which based on a reduced panel of biomarkers will provide enough information to be used as diagnosis or prognosis for schizophrenia, alone or in combination with the clinical interview. The patients' molecular signature can indicate them as responder or non-responders of the current therapy prescribed, along with potential disease progression.

In parallel with the genomic and phenotypic studies of schizophrenia and bipolar disorder, we have developed a range of clinical investigations in areas in which a more clear understanding of the phenotypic definitions and boundaries were needed. These studies have focused in the area of **personality** (subclinical traits), namely studying **perfectionism** and its relationship with psychopathology.

Another important area of interest is the study of **affective disorders in the perinatal period**, a topic which have been relatively neglected. Apart from the perinatal depressive symptoms evaluation we also intend to evaluate the previously identified risk-factors (lifetime history of depression, high negative affect, antenatal insomnia, high PDSS scores) with instruments developed and validated by our team.

4) Biomedical Research in Bigenomic Disorders and Personalized Medicine

Bigenomic investigation of neurodegenerative disorders, particularly dementias aims to find genetic risk factors, from bigenomic origin, which will contribute to identify new tools for early diagnosis and to a better knowledge of the underlying causes.

Furthermore, pharmacogenomic studies have been implemented, with the main goal of identifying genetic alterations and copy number variation that will determine the metabolic profile or targeting depending on genetics, providing tools for more rational treatments, managing risks and preventing drug adverse reactions. These studies are

integrated in the CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics and Pharmacogenomics (RIBEF).

The group pursued with the study of the pathogenic mechanisms underlying mitochondrial respiratory chain (MRC), in which it has a long tradition and robust knowledge.

Main Achievments

1) Biomarkers of Neurodegenerative Diseases

According to our data the estimated number of Portuguese people with dementia aged ≥60 years, is 156.546 (5.84% of this population-stratum). Alzheimer's Disease (AD) is responsible for 50-70% of all cases, which means that there are between 78.273 and 109.582 AD-patients, but only 68.396 receive effective treatment, indicating that dementia is under-diagnosed with a cost of specific medication of 43M€/year.

Normative and validation studies of neuropsychological tests developed by our group have been published in international journals and a comprehensive manual of scales to be used by Portuguese investigators and neuropsychologists was published. The correlation between cognitive tests and biomarkers and the added value of using these measures in the framework of the new diagnostic criteria for AD was confirmed. The value of a novel CSF α-synuclein (α-Syn) assay as an attractive tool for comparing α-Syn measurements in diverse settings and the implemention of CSF α-Syn measurements as an additional marker to differentiate Lewy-Body Dementia and AD was confirmed. A wide range of possible confounders that could have an impact on CSF –AD biomarkers was tested, including pre-analytical conditions, genetic variants, brain volume and caffeine consumption.

CSF Aβ40 was shown to increase the discrimination between subjects with dementia from controls.

We participated in the creation of an european central and a virtual biobank for body fluids and associated data, from subjects with neurodegenerative diseases.

We contributed to the estimation of the increase in prevalence of brain amyloid pathology with age (from 50 to 90 years) and with the ApoE-ε4 carrier status in non-demented groups (normal cognition, subjective cognitive impairment, or mild cognitive impairment).

A novel 14-3-3γ ELISA assay was validated as the best single predictive assay for sporadic CJD (sCJD) diagnosis. The added value of t-Tau protein in clarifying 14-3-3 borderline results in sCJD probable cases has also been established.

The mutation analysis of more than 200 hundred patients with the clinical diagnosis of AD, FTLD, PD and ALS was performed. Two families with double mutations, one family with a pathogenic *C9orf72* expansion and a mutation in *SQSTM1* gene, developed FTLD and Paget bone disease, whereas the family carrying 2 mutations in *PGRN* gene developed FTLD and neuronal ceroid lipofuscinosis.

In PD, over 1100 DJ-1 binding partners were identified, with over 800 being quantified and presenting a dynamic interactome under oxidative stress conditions. Five binding partners were validated in vitro using confocal microscopy showing that DJ-1 binds to cytoplasmic, mitochondrial and nuclear proteins. These targets are associated with apoptotic mechanisms (mitochondrial and cytoplasmic proteins) and modulation of gene expression (nuclear proteins). Altogether the results point to potential short term (mitochondrial and cytoplasmic) and long term (nuclear) effects of DJ-1 under oxidative stress stimuli. The point mutations show a differential interactome in relation to wild-type revealing a potential loss of function, and the exogenously added DJ-1 led to an increase in neuronal survival while its depletion results in increased cell death under oxidative stress.

Overall the results show an endogenous and exogenous neuroprotective effect of DJ-1 with potential short and long term modulation of neuroprotection mechanisms.

2) Diagnosis of Early Life Cognitive Dysfunction

According to our aims, we showed that a deletion in chromosome 19q13.11q13.12, in a region encompassing four zinc finger genes, is likely to be responsible for a syndrome recognizable by pre and postnatal growth retardation, microcephaly, developmental delay/intellectual disabilities, speech disturbance, hypospadias (in males) and signs of ectodermal dysplasia and cutis aplasia over the posterior occiput. We found that an interstitial deletion of chromosome 12q21.1q22 is responsible for a phenotype that includes failure to thrive and development delay. A genotype-phenotype correlation for this chromosomal abnormality was done taking into account other reported patients.The clinical phenotypes of 51 patients with Oculo-auriculo-vertebral spectrum (OAVS), a craniofacial developmental disorder, was analyzed, discussing that recurrent dosage anomalies on 22q11may contribute to, or increase the risk of OAVS. The clinical evaluation and follow-up of two patients affected by 22q11.2 rearrangements, was reported, emphasizing new phenotypic features associated with duplication and triplication of this genomic region). A classification that contributes to the genotype/phenotype correlation, with the delineation of laboratory criteria, which help to classify the different CNVs detected, led to the clustering of our findings in 1000 patients with developmental delay into five classes.

The impact of fetal chromosomal disorders on maternal blood metabolome, was also evaluated.Previously reported data on first-trimester Trissomy 21 were confirmed and additional information on time-course metabolic changes was provided, in particular regarding plasma lipid composition, demonstrating the potential of plasma metabolomics in the identification of new biomarkers of this pathology.

Additionally, we used several genomic tools for the assessment of new biomarkers in different pathologies, namely in cancer, leading to international collaborations and reported in several publications.

3) Diagnosis Strategies in Neuropsychiatric Disorders

In collaboration with the Center for Genomic Psychiatry at USC and integrated in the Genomic Psychiatry Cohort (GPC), a convergent genetic-genomic approach has led to the identification of several areas in the human genome that may harbour susceptibility genes for SCZ or BP. In SCZ, a region on 5q31–5q35 with a NPL score of 3.28 which was replicated in the BP was identified. Further study of this region showed positive SNP associations with several GABA receptor subunit genes in patients with SCZ. In BP, another region on 6q22 (NPL-Z=4.2), was identified. In case-control studies a number of significant associations were reported for several genes: syntaxin 1A; NRG1, GABA receptor subunit genes; Neurogranin; CHRNA7, and DRD2. More recently, our studies with copy number variants (CNVs) led to the identification of 22q11.2, 15q13.2 and 1q21.1 as regions with high number CNVs in SCZ. An exploratory WGA study in the Portuguese SCZ probands was carried out identifying a total of 55 SNPs that showed significant associations with schizophrenia at a

threshold of $P < 1 \times 10^{-4}$. Two of these SNPs survived FDR correction (rs6638512 on chromosome X, and rs4907606 on chromosome 13). However, when considering the region of maximal linkage on chromosome 5q31-35, only one of the 22 candidate genes, glutamate receptor, ionotropic, AMPA 1 (GRIA1) was found to have multiple SNPS showing significant association at $p<10^{-4}$.

More recently, we are contributing to a genome-wide analysis of rare and common SNPs, common haplotypes, and CNVs using the Illumina 2.5 million SNP Platform. This is a unique opportunity to study populations that trace ancestry to continents other than Europe, with the potential to lead to novel risk factors and to alleles for which discovery power is different in different populations.

In parallel, we have developed clinical investigations focused in the area of **personality** (subclinical traits), namely studying **perfectionism** and its relationship with psychopathology. An association between the maladaptive aspects of perfectionism and a broad range of psychopathological conditions and health problems (e.g. sleep problems) was established. Using a multilevel cognitive model we confirmed *the hypothesis that Repetitive Negative Thinking (RNT) is a significant mediator of the relationship between perfectionism and psychological distress, as well* as, with disordered eating behaviours and OC symptoms.

Preliminary data analysis from a sample of 250 families shows that young adults' negative perfectionism, RNT, emotional regulation strategies and psychological distress correlates more with their perception of their parents' perfectionism than with their parents' actual perfectionism.

Another important area of interest is the study of **affective disorders in the perinatal period**.

In 2015 we have been analysing the predictive ability of the new instrument (Perinatal Depression Screening and Prevention Tool/PDSPT), developed by our group, to screen for perinatal depression. Its acceptability and predictive ability at five weeks post-partum have been proved.

Due to the lack of a diagnostic interview according to DSM-5, we developed a brief diagnostic interview to assess depression and a selection of the most prevalent anxiety disorders and other disorders in the postpartum - Diagnostic Interview for Psychological Distress.

By exploring the association between mindfulness, self-compassion and depressive symptoms in pregnant women, we have found that *Nonjudging of experience* and *Self-kindness* are protective for antenatal depressive symptoms and psychological distress.

4) Biomedical Research in Bigenomic Disorders and Personalized Medicine

The involvement of mitochondrial DNA (mtDNA) in the pathogenesis of Frontotemporal Lobar Degeneration (FTLD), the second most common early-onset dementia, was analyzed. The sequencing of total mtDNA genome was performed in 100 FTLD patients. A total of 558 different alterations were found in different genes: 352 in protein-encoding genes, 45 in rRNAs, 29 in tRNAs and 132 in control region. The majority of the alterations identified have been described as polymorphisms, some are also mutations that have been already associated to other diseases and other are unpublished variants. Although the majority of these alterations are not pathogenic, an interaction with other mutations may occur, leading to the disease, worsening its expression or influencing age of onset. The high number of mtDNA variations in the FTLD, suggests the involvement of mtDNA in the disease.

A pharmacogenomic and functional genomics study is ongoing, focused on drug addicts undergoing drug withdrawal with methadone therapy, aiming to understand the genetic factors underlying heterogeneity in detoxification fulfillment. The genes HTR2A, COMT and OPRM and the predicted CYP2D6 metabolic profile have been studied in 95 subjects for further analysis and correlation with clinical data. Furthermore, analysis of MRC activity in 24 subjects showed a significant reduction of energy production capacity.

In collaboration with RIBEF, the frequency of the most relevant pharmacogenetic biomarkers and metabolic phenotypes in Central American healthy volunteers was studied, and its interethnic variability was determined. The frequency differences showed the interethnic variability within Central American and with other Latin American populations.

In Leber´s hereditary optic neuropathy (LHON), the "mitochondriome" (interaction of the mitochondrial and nuclear genomes, transcripts and proteins related to OXPHOS function), was investigated, aiming to clarify the disease etiopathogenesis.

The MRC activity analysis was concluded in 30 samples of lymphocytes (22), skeletal muscle (5) and skin derived fibroblasts (3) of LHON cases. The results showed a deficiency isolated or combined, in 43% of the patients' samples when compared with healthy age-matched control sample. The higher percentage of deficiency in muscle biopsies affects complex I activity, whereas in lymphocytes, in 21% of cases, complex III or complex IV deficiencies were found. Fibroblasts showed complexes I, III and IV deficiencies.

Plasma ATP levels were not altered, suggesting a compensatory stimulation of glycolysis. A significant decrease of Coenzyme Q10 plasma levels was found in 7 patients, which could contribute to OXPHOS impairment and decline of antioxidant defenses.

The entire human mitochondrial genome was sequenced in 30 LHON cases, in order to investigate sequence variations and its involvement in the disease. All the cases have multiple alterations in mtDNA: 344 in total, being 136 different. However, 5 patients have one of the top 3 mutations: 3 with the m.11778G>A (60%), one with the m.3460G>A and one with the m.14484T>C, all homoplasmic, except the m.3460G>A (90.23% of the mutant allele). In the remaining samples, 5 present haplogroup markers previously considered as secondary mutations and 3 presented multiple deletions.

In an unusual LHON case of a family where all individuals of the maternal lineage are carriers of the m.11778G>A mutation, but only the proband expresses clinical manifestations of LHON-plus, a complete functional study identified a putative novel mechanism to explain the bigenomic communication failure in LHON cases with genetic mutations in both mtDNA and nDNA, with further importance due to the presence of a combined heterozygozity affecting a nuclear genome encoded gene, responsible for complex I functional assembly, in this patient. The pathogenicity of relevant nuclear alterations found in NDUFAF5 gene, suggest the involvement of nDNA in this disease.

These results contribute to understand the role of m.11778G>A mutation in the context of LHON, also providing evidence that this genetic alteration may not be sufficient *per se* to cause the expression of clinical manifestations associated to this disease.

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, bone and mouth. 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 shared also by glaucoma. We aimed 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.

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.

We have also been developing animal models of ocular melanoma and retinoblastoma, which will be useful to develop new therapeutic approaches.

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, as well as MPTP, a basal ganglia neurotoxin, on CNS, given a particular attention to blood-brain barrier (BBB) dysfunction, brain edema, 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.

We are also trying to understand how microglia respond to immune challenges, namely during brain development, the modulatory role of ATP and adenosine in this response, and the way this response impact on brain circuits and mental health.

Stem Cells

We have been exploring the role of cancer stem cells (CSCs) in tumor progression and response to therapy in osteosarcoma and bladder cancer, with the ultimate goal to identify new CSC-targeted therapeutic approaches and treatment modalities.

We also intend to establish a cell dedifferentiation protocol that allows obtaining mesenchymal stem cells for use in Dental Regenerative Medicine.

Experimental Therapeutics

Regarding chronic diseases that affect the heart, kidney and the peripheral vascular system, there is a marked interest on inflammatory processes. We have been exploring experimental and clinical therapeutic strategies to improve prevention/treatment of disease or ameliorate drug-induced toxicity.

We also aimed evaluating the bioactivity of a new dentin regeneration material, Biodentine™ and the possibility of its effective and safe use in direct pulp protection in humans, as well as characterizing whole saliva and biofilm of type 1 diabetic adults treated with continuous subcutaneous insulin infusion, and to evaluate the impact of the treatment with Biotène® and Parodontax® mouthwashes on oral microbial levels and on saliva and biofilm composition. Moreover, we intend to analyse the effect of bone regeneration with calcium phosphates (CaP), bioglasses and glass-ceramics, the effect of Biphosphonates on development of osteonecrosis of the jaw, and to investigate the effect of materials on teeth replantation and revascularization of teeth transplantation.

Main Achievements

c-Src function is necessary and sufficient for triggering microglial cell activation. *Socodato et al., Glia 2015.*

Microglial responses to immune challenges are oppositely regulated by purines, namely ATP and adenosine, and depend on the nature of the immune stimulus. *George et al., Glia 2015.*

Blockade of adenosine A2AR prevents retinal ganglion cells death triggered by elevated pressure and mediated by microglial cells activation and neuroinflammation. *Madeira et al., J. Neuroinflammation 2015; Madeira et al., Transl. Res. 2016.*

Activation of adenosine A_3 receptor is neuroprotective against retinal neurodegeneration. *Galvão et al., Exp. Eye Res. 2015.*

Activation of Neuropeptide Y receptors modulates retinal ganglion cell physiology and exerts neuroprotective actions. *Martins et al. ASN Neuro 2015.*

Sildenafil acutely decreases visual responses in ON and OFF retinal ganglion cells. *Martins et al., Invest. Ophthalmol. Vis. Sci. 2015.*

Diabetes disrupts a neural microcircuit in the rod pathway of the mammalian retina. *Castilho et al., J. Neurosci. 2015.*

Diabetes reduces Ca2+ permeability of extrasynaptic AMPA receptors in AII amacrine cells. *Castilho et al., J. Neurophysiol. 2015.*

Development of potential new therapeutic approaches, such as photodynamic therapy, for the treatment of retinoblastoma.*Teixo et al., Cancer Metast Rev 2015; Santos et al., Eur J. Med. Chemistry 2015.*

High sucrose consumption induces memory impairment in rats associated with electrophysiological modifications, but not with metabolic changes in the hippocampus. *Lemos et al., Neuroscience 2016.*

Methamphetamine interferes directly with brain endothelial cells properties or indirectly via astrocytes through the release of TNF-α and subsequent activation of NF-κB pathway culminating in barrier dysfunction. *Coelho-Santos et al., J. Cereb. Blood Flow Metab. 2015.*

Muscle-invasive bladder cancer harbors distinct cell subsets reflecting molecular features of stem-like cells, together with an aggressive phenotype characterized by enhanced chemoresistance and tumor initiating ability. *Ferreira-Teixeira et al., Oncotarget 2015.*

Exposure to conventional chemotherapy induces a phenotypic cell transition towards a stem-like phenotype through activation of the Wnt/β-catenin pathway in osteosarcoma. *Martins-Neves et al., Cancer Lett. 2016.*

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. *Ribeiro et al., Biofactors 2016.*

Neuro 8 Group assumed CNC.IBILI leadership in the efforts of joining the University of Coimbra, Instituto Pedro Nunes, the University Hospital of Coimbra and BIAL Pharma in EIT Health consortium. The consortium InnoLIFE KIC (now named as EIT Health) accepted the four partners of Centro/Norte Portugal as a node in InnoSTARS. InnoSTARS are regions with lower performance, but with high innovation and grow potential. João Malva was elected (2015) Deputy Director of InnoSTARS and conducted the negotiations to build the management structure and formal constitution of a legal entity “EIT Health - InnoSTARS”.

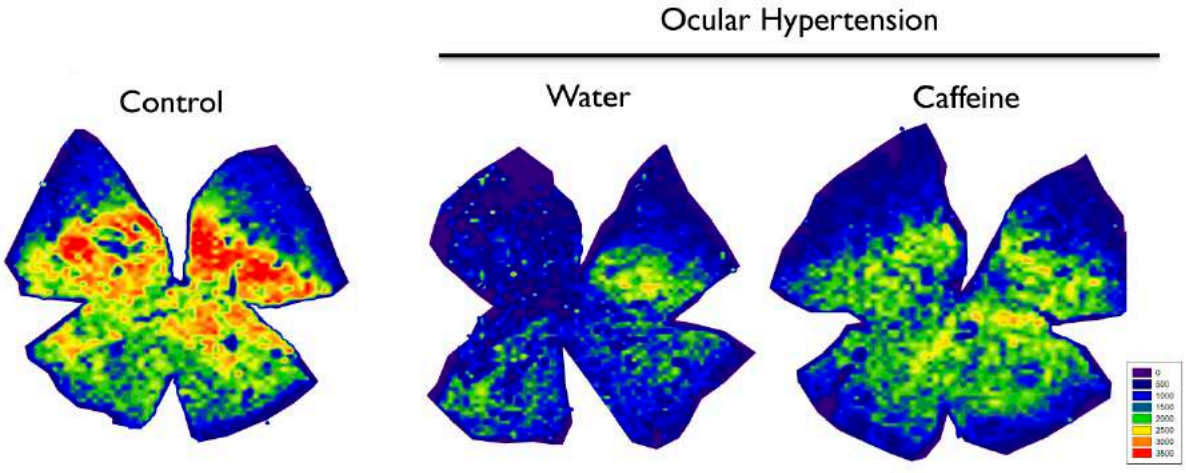


Fig.1: Representative isodensity maps from retina whole-mounts demonstrating the topological distribution of Brn3a-labelled retinal ganglion cells, in a normal rat retina and in retinas after 7 days of ocular hypertension, from animals drinking water or caffeine (1g/L). Color scale range from 0 (dark blue) to 2500 or higher RGCs/mm^2.

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METABOLISM, AGING AND DISEASE

Coordinator: João Ramalho Santos

The Metabolism, Aging and Disease (MAD) strand includes Research Groups or varying size and structure, from relatively small groups with only one PI and few research lines (ImmunoMetabolic Pharmacology), to larger groups with several PIs and research lines that are clustered along common goals (Mitochondria, Metabolism and Disease; Cell Metabolism and Quality Control, Metabolic Control). The Metabolic Control Group comprises 3 independent, but related, lines: Biology of Reproduction and Stem Cells, Intermediary Metabolism, Obesity Diabetes and complications

The main goal of all groups is to carry out research on the metabolic aspects of human disorders, and notably on those disorders that have clear metabolic origins, and how they may be interlinked. Researchers in this Strand carry out basic research on metabolic pathways and mitochondrial function, but also aim to perform translational research with relevant models (cell cultures, animal models, human samples) in order to address distinct issues, from novel diagnostic tools to possible therapeutic interventions.

One crucial main achievement is that the Groups have retained a reasonable amount of funding in the past years, and have been active in tapping wide variety of funding sources, both National and International, Public and Private, Academic and Enterprises (including several service contracts).

In terms of research there are three main focuses that are worthy of attention: 1- Using mitochondrial activity to characterize and possibly treat several disorders; 2- Developing novel metabolic-based diagnostic tools; 3- Studying the role of metabolism in defining immunological and inflammation responses in several conditions.

1- Researchers in this strand have provided clear links between several aspects of mitochondrial (dys)function and the possibility of predicting/controlling cancer and stem cell fate, or in terms the development and progression of several Neurodegenerative disorders (Alzheimers, Parkinsons), as well as diabetes, cardiovascular disorders, cancer and infertility.

2- The development of several diagnostic tools that can allow for the characterization of metabolic fluxes and metabolic status in several types of disorders (Diabetes, fatty liver disease, male and female infertility immunology-based disorders) has also been a staple of this Strand. In some cases using non-invasive NMR-based methodologies, which are currently being moved into more extensive patient studies.

3- The metabolic basis of the immune response and inflammation and how it can contribute to the management of rheumatoid arthritis, ostheoarthritis, allergies, diabetic wound healing, cardiovascular disorders or transplantation have also been studied, in all cases with close clinical collaborations that we hope will accelerate translational impact.

CELL METABOLISM AND QUALITY CONTROL GROUP

Paula Isabel Moreira	PhD (*Head of Group*)
Alexandrina Ferreira Mendes	PhD
Américo Figueiredo	PhD
Ana Teresa Rufino	PhD
António Manuel Pires	PhD
Armanda Santos	PhD
Carla Isabel dos Marques	PhD
Cláudia M. Fragão Pereira	PhD
Cristina Maria Sena	PhD
Hans Christian Eickhoff	PhD
Henrique Manuel Girão	PhD
João Vasco Ferreira	PhD
Lino Manuel Gonçalves	PhD
Maria João Jorge Pinho	PhD
Maria Teresa Cruz	PhD
Mariana Pinto	PhD
Monika Zuzarte	PhD
Raquel Maria Fino Seiça	PhD
Sandra Morais Cardoso	PhD
Ana Duarte	Post Doctoral Fellow
Ana Raquel Esteves	Post Doctoral Fellow
Ana Silva	Post Doctoral Fellow
Cristina Carvalho	Post Doctoral Fellow
Diana Silva	Post Doctoral Fellow
Elisa Aida da Silva Ferrada	Post Doctoral Fellow
Paulo Nuno Matafome	Post Doctoral Fellow
Rosa Cristina Fernandes	Post Doctoral Fellow
Rosa Maria Resende	Post Doctoral Fellow
Sonia Correia	Post Doctoral Fellow
Steve Mendes Catarino	Post Doctoral Fellow
Susana Cardoso	Post Doctoral Fellow
Ana Plácido Fernandes	PhD Student
Andreia Gonçalves	PhD Student
Bruno Alexandre Almeida	PhD Student
Cátia Sousa	PhD Student
Daniel Santos	PhD Student
Emanuel Candeias	PhD Student
Fernanda Carrilho	PhD Student
Filipa Carvalhal Marques	PhD Student
Joana Crisóstomo da Silva	PhD Student
Joana Liberal	PhD Student
João Demétrio Martins	PhD Student
João Pedro Oliveira	PhD Student
Liliana Rita Velindo Letra	PhD Student
Mª Madalena Ribeiro	PhD Student
Paula Cristina Martins	PhD Student
Rui Batista	PhD Student
Rui Miguel Baptista	PhD Student
Ricardo Jorge Pereira	PhD Student
Sara Ramos	PhD Student
Tânia Sofia Marques	PhD Student
Teresa Rodrigues	PhD Student
Tiago Daniel Rodrigues	PhD Student
Isabel Ferreira	Grant Technician
João Ferreira	Grant Technician
Marisa Marques	Grant Technician
Fernando Judas	Collaborator
Maria Gonçalves Fernandes	Collaborator
Paulo Pereira	Collaborator
Rui Travasso	Collaborator
Rita Carvalho	Collaborator
Christian Neves	MSc Student

MITOCHONDRIA, METABOLISM AND DISEASE GROUP

Paulo Oliveira	PhD (*Head of Group*)
Anabela Pinto Rolo	PhD
António Moreno	PhD
Carlos Palmeira	PhD
Cármen Alpoim	PhD
Ignacio Vega Naredo	PhD
Maria Sancha Santos	PhD
Filipe Valente Duarte	Post Doctoral Fellow
João Paulo Teodoro	Post Doctoral Fellow
Mª Teresa Oliveira	Post Doctoral Fellow
Vilma Sardão	Post Doctoral Fellow
Ana Maria Silva	PhD Student
Ana Raquel Coelho	PhD Student
Cláudia Deus	PhD Student
Katia Mesquita	PhD Student
Luciana Ferreira	PhD Student
Nuno Gabriel Machado	PhD Student
Carlos Rodrigues	Grant Technician
Susana Pereira	Grant Technician
Eurico Serrano	MSc Student
Marco Cunha	MSc Student
Rui Simões	Collaborator

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

John Griffith Jones	PhD (*Head of Group*)
Ana Paula Sousa	PhD
Ana Teresa Almeida Santos	PhD
Eugenia Carvalho	PhD
João Alves	PhD
João Ramalho Sousa Santos	PhD
Maria Alexandra Amaral	PhD
Ana Catarina Fonseca	Post Doctoral Fellow
Ana Caldeira Burgeiro	Post Doctoral Fellow
Ermelindo Carreira Leal	Post Doctoral Fellow
Ivan Martins Viegas	Post Doctoral Fellow
Mª Cristina Barosa Oliveira	Post Doctoral Fellow
Patrícia Seraphim	Post Doctoral Fellow
Paula Cristina Mota	Post Doctoral Fellow
Sandra Catarina Amaral	Post Doctoral Fellow
Sandro Pereira	Post Doctoral Fellow
João Rito	PhD Student
João Silva	PhD Student
Mª Inês Sousa	PhD Student
Marcelo Correia	Collaborator
Renata Tavares	Collaborator
Ana Sofia Rodrigues	Collaborator
Tânia Perestrelo	Collaborator

IMMUNOMETABOLIC PHARMACOLOGY GROUP

Mª Margarida S. Carneiro	PhD (*Head of Group*)
Ana Rita Figueiras	PhD
Elisario Tavares	PhD
Fernanda Roleira	PhD
Francisco Veiga	PhD
Helena Carvalheiro	Post Doctoral Fellow
Ludgero Tavares	Post Doctoral Fellow
Tiago Sousa	PhD Student
Laisa Sá	Grant Technician
Pauline Santos	Grant Technician
Rusbene Carvalho	Grant Technician

Cell Metabolism and Quality Control Group

(*Head: Paula Moreira*)

Objectives

We aimed to clarify the involvement of mitochondria, inflammation and quality control mechanisms 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 are also studied. We intend 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, are another focus of our research. We are also interested in the identification and validation of biomarkers. Ultimately, our goal is to identify novel therapeutic targets and to develop effective treatment strategies for the abovementioned diseases.

Specific objectives:

To study and compare brain mitochondrial function, biogenesis and autophagy in rodent models of AD and type 2 diabetes (T2D);

To elucidate the role of gender in the susceptibility of the diabetic brain to develop AD-like features;

To test the efficacy of glucagon-like peptide 1 (GLP-1) receptor agonists in AD and diabetic brains;

To investigate the role of ER stress response in neuronal and endothelial dysfunction in aging and AD;

To develop a disease-modifying treatment for AD based on peptidomimetic inhibitors of BACE1;

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

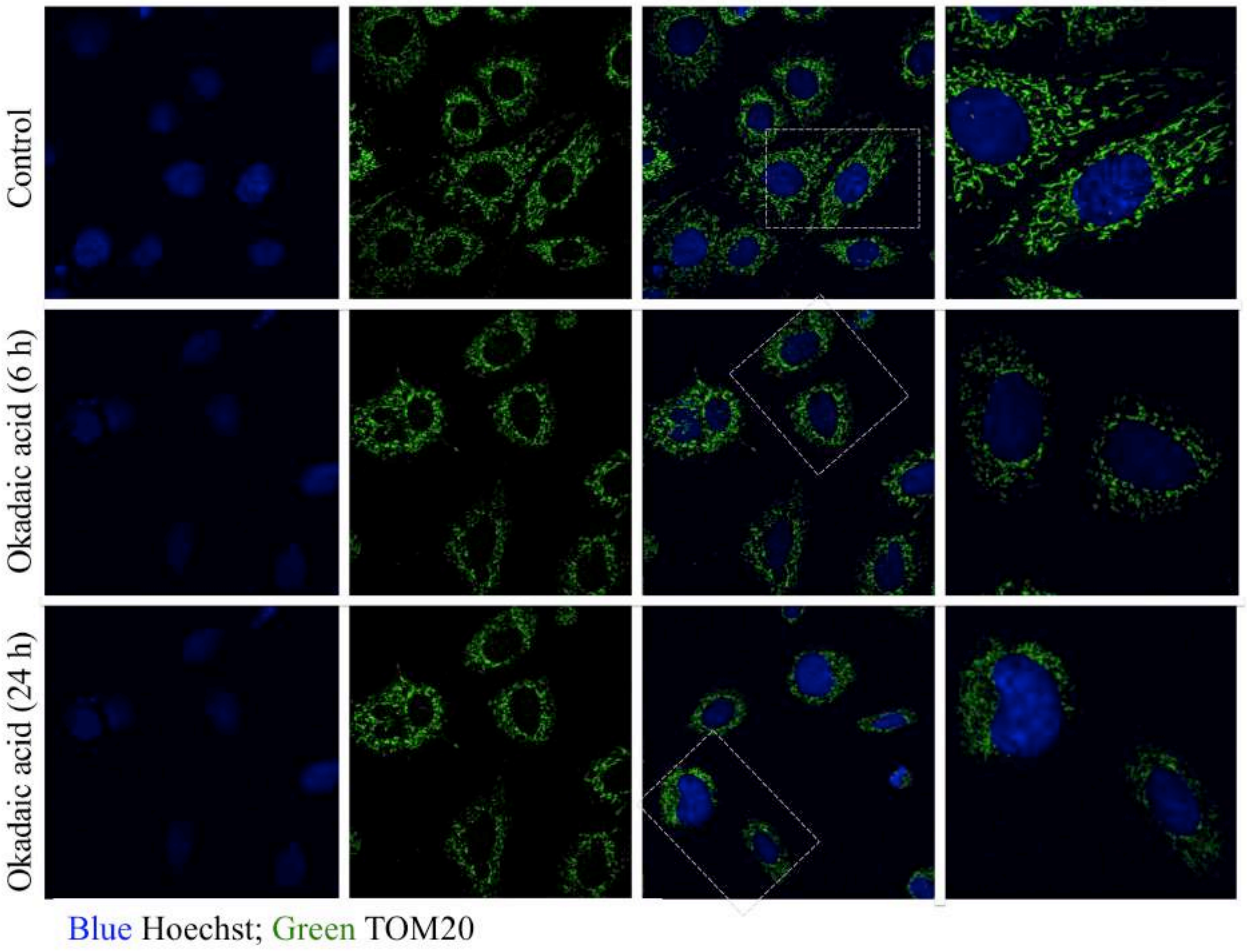


Fig. 1. *Effect of phosphatase 2A inhibition on spatial and structural mitochondrial network organization in brain endothelial cells. After treatment of cells with okadaic acid (10 nM) for 6 or 24 h, changes in the mitochondria network were evaluated by fluorescence microscopy using an anti-TOM20 antibody to label mitochondria and Hoechst 33342 to stain nuclei (Plácido et al., Mol Neurobiol in press)*

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

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

To identify new compounds of natural origin with potential anti-osteoarthritic activity, as well as with potential activity against other diseases with a chronic inflammatory component;

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

To search for molecules with anti-inflammatory and antitumor properties obtained from medicinal plants;

To explore the potential of exosomes as biomarkers for respiratory and cutaneous allergens hazard;

To evaluate the efficacy of novel photosensitizers for the treatment of cancer.

Main Achievements

AD and T2D impair mitochondrial function and biogenesis and autophagy in brain cortex and hippocampus contributing to the loss of synaptic integrity. These results support the idea that T2D increases the risk of developing AD.

AD and T2D promote similar vascular dysfunction of the aorta, this effect being associated with elevated oxidative and nitrosative stress and inflammation. Also, AD-associated vascular alterations are potentiated by T2D. These findings support the idea that metabolic alterations predispose to the onset and progression of dementia.

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 loss of protein quality control mechanisms, namely the ER stress-induced Unfolded Protein Response (UPR), the ubiquitin-proteasome system (UPS) and macroautophagy, is implicated in the vascular alterations occurring in the AD brain.

ER stress plays a central role in the amyloidogenic processing of APP and Aβ generation in brain endothelial cells. Also, our findings support that ER stress plays a key role in early AD stages as observed in primary neuronal cultures as well as in patient-derived peripheral blood cells.

We developed new peptidomimetic compounds that inhibit BACE1 in a dose dependent manner, as assessed by a cell-free assay. Also, these compounds inhibit Aβ production both in vitro and in vivo and do not interfere with the APP cleavage by α-secretase suggesting a selective inhibition of BACE1-mediated APP processing. These findings suggest that these compounds have the potential to be a disease-modifying therapy.

Pharmacological activation of autophagy inhibits chondrocyte and cartilage damage caused by diabetic conditions both *in vitro* and *in vivo*.

We established the molecular mechanisms whereby autophagy contributes to degradation of the gap junction protein (GJ) connexin43 (Cx43) during ischemia in cardiac cells.

The Cx43 interactome in the heart, and the impact of ischemia and ischemia-reperfusion (I/R) upon the modulation of such interactions were uncovered.

We demonstrated that, besides direct intercellular communication through GJ, Cx43 also mediates long-distance communication via exosomes.

A new mathematical model for angiogenesis was developed.

We established that cholinergic stimulation with pyridostigmine protects myocardial infarcted rats against ischemic-induced arrhythmias preserving gap junction mediated intercellular communication.

The new complexes tetra-platinum(II)-thiopyridylporphyrin and tetra-platinum(II)-thiopyridylporphyrinato Zn(II) and Pt(II)-corrole were shown to interact with DNA and HSA.

Both tetra-platinum(II)-thiopyridylporphyrin and tetra-platinum(II)-thiopyridylporphyrinato Zn(II) are photostable and able to generate singlet oxygen (1 O2) after light irradiation. The tetra-platinum(II)-thiopyridylporphyrinato Zn(II) demonstrates a particular intercalation binding mode with DNA and an ability to cleave DNA after photo-excitation

Phthalocyanines bearing phosphonic acid groups at the periphery exhibit high phototoxicity to bladder cancer cells, by inhibiting the activity of urokinase plasminogen activator and matrix metalloproteinase-9.

AN IN SILICO AND IN VITRO INTEGRATIVE APPROACH TO ASSESS THE POTENCY OF CONTACT ALLERGENS. Provisional Patent Application (nº 20151000098221)

FUNCTIONALIZED MATRICES TO DETECT THE HAPTENIZATION CAPACITY OF XENOBIOTICS. Provisional Patent Application (nº 20161000025206)

Mitochondria, Metabolism and Disease Group

(Head: Paulo Oliveira)

Objectives

Mitochondria are critical organelles for cell physiology. Mitochondria are the cell energy powerplants, producing the majority of 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 angle approach to the main scientific question, focusing in various specific aims:

1) 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.

2) Evaluate the impact of sestrin and sirtuin modulation as inducers of mitohormesis: preservation of mitochondrial function under pathologic stress.

3) 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.

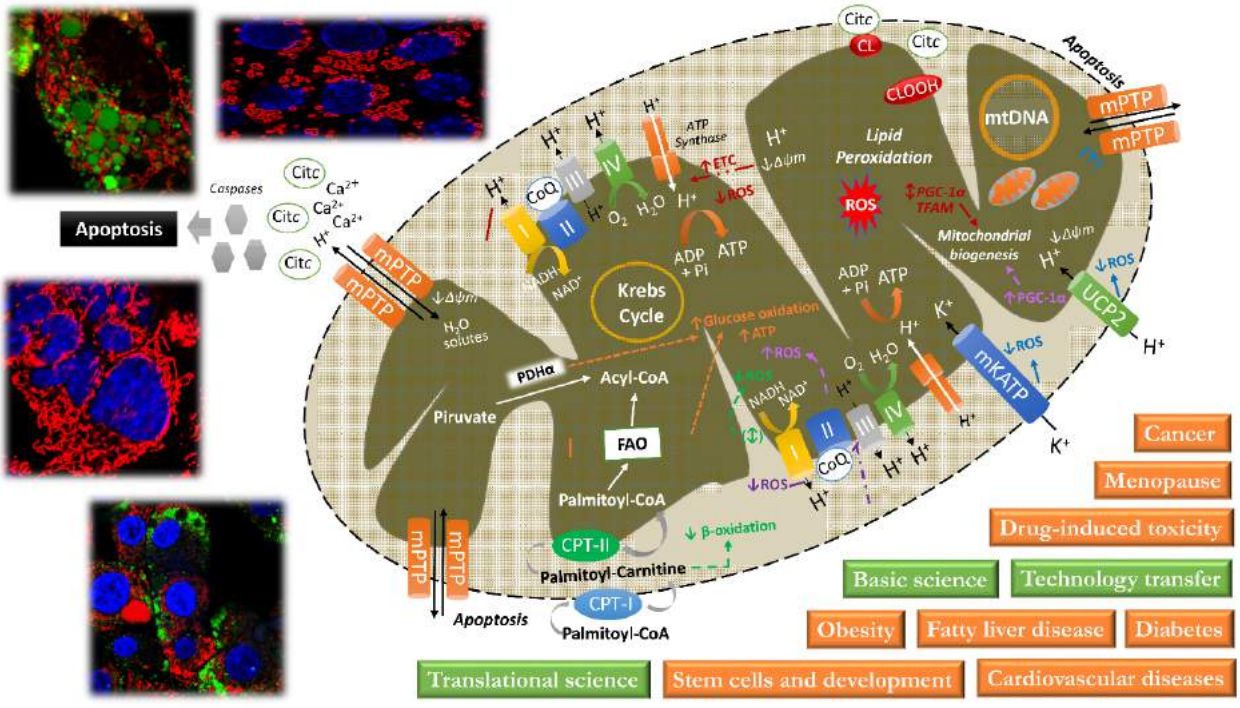
4) Investigate the interactions between the extracellular matrix (ECM), stromal and tumor cells and the various cytokines embedded in the ECM and how that contributes to the neoplastic phenotype and create a desmoplastic stroma through which malignant epithelial cells trans-differentiate and acquire 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.

5) Unravel mechanism of mitochondrial dysfunction caused by different xenobiotics, including drug-induced injury (e.g. anthracyclines)

6) 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.

7) 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.

8) Develop high-throughput methods to investigate mitochondrial function in the context of drug discovery or safety assessment of molecules of human interest.



9) Identify molecular mechanisms responsible for miRNA regulation in several biological processes, particularly the miRNAs acting in mitochondria or in mitochondria-related mechanisms.

Main Achievements

Our group has provided a series of seminal contributions in the context of the role of mitochondria in pathophysiology:

1) By continuing research on the mechanisms of anthracycline-induced cardiotoxicity, namely doxorubicin (DOX), we observed that DOX treatment induces p66Shc protein up-regulation specifically in nuclear fractions of H9c2 cardiomyoblasts. Treatment with the antioxidant and protein kinase C (PKC-β) inhibitor hispidin decreased DOX-induced activation of caspase 9 and p66Shc alterations. Also, mitochondrial remodeling caused by stimulating basal rates of oxidative phosphorylation decreased DOX-induced apoptotic signaling and increased DOX-induced autophagy in H9c2 cardiomyoblasts.

2) In the context of *in utero* programming of mitochondrial alterations in the offspring, and by using a non-human primate model for maternal nutrient restriction (MNR), we concluded that transcripts encoding fetal renal mitochondrial energy metabolism proteins are nutrition sensitive in a sex-dependent manner. We demonstrated fetal sex-specific differential mRNA expression encoding mitochondrial metabolite transport and dynamics proteins.

3) Regarding regulation of mitohormesis, we obtained evidence that mild stress induced by menadione induces Sesn2 and activates autophagy/mitophagy as a cell survival strategy. Absence of Sesn2 results in accumulation of mitochondrial damage induced by ROS decrease in cell viability.

4) Evidence suggests that mitochondrial function is of paramount importance for liver regeneration. We observed a relationship between mitochondrial function, duration of hepatic pedicle clamping and clinical outcome after hepatectomy. Mitochondrial bioenergetics can potentially assist in earlier diagnosis of postoperative liver dysfunction, and as a target for future pharmacological therapies.

5) We studied undifferentiated and differentiated P19 embryonic stem cells in order to investigate whether differences in resistance to chemotherapeutics between both groups of cells could be due to not only differential mechanisms of DNA damage sensing and repair, but also activation of alternative cell death/survival pathways. In fact, we found an overactivation of autophagy in P19 stem cells promoting their resistance to therapy. Also, melatonin cytotoxicity was only observed in differentiated cells with an active mitochondrial function.

6) A careful characterization was carried out to find biomarkers of lung cancer stem cells (CSC) in tumors induced in nude mice. These cell lines were positive for OCT3/4 and ALDH activity, and unexpectedly negative for CD133. Chemoresistance studies were performed using gemcitabine, methotrexate and cisplatin. As expected the non-malignant systems succumbed soon after treatment, while malignant systems showed a progressively higher resistance particularly the CSCs which, surprisingly, displayed the ability not only to survive chemotherapy, but to keep dividing in the presence of the drug.

7) We demonstrated that acute estradiol (E2) administration in ovariectomized (OVX) animals induced osteocytes to increase aerobic glycolysis in an attempt to compensate for the metabolic deficit associated with ovaries removal. Regarding in vitro phytoestrogens (PE) toxicity, by using two murine osteoblast-(MLO-Y4) and osteocyte-like (MLO-A5) cell lines, we observed that coumestrol (CM) and resveratrol (RV) had no toxicity in both cell types, and did not alter the cell cycle. MLO-A5 presented a notorious glycolytic profile, and in increasing order, E2, CM and RV increased the ECAR parameter after the addition of glucose. The oxygen consumption analysis during mitochondrial stress tests in MLO-Y4 showed a slight increase after FCCP addition. MLO-A5 cell line showed a clear glycolytic profile, slightly increased in the presence of those PEs.

Metabolic Control Group

(Head: John Grifith Jones)

Objectives

The main objectives for 2015 were as follows:

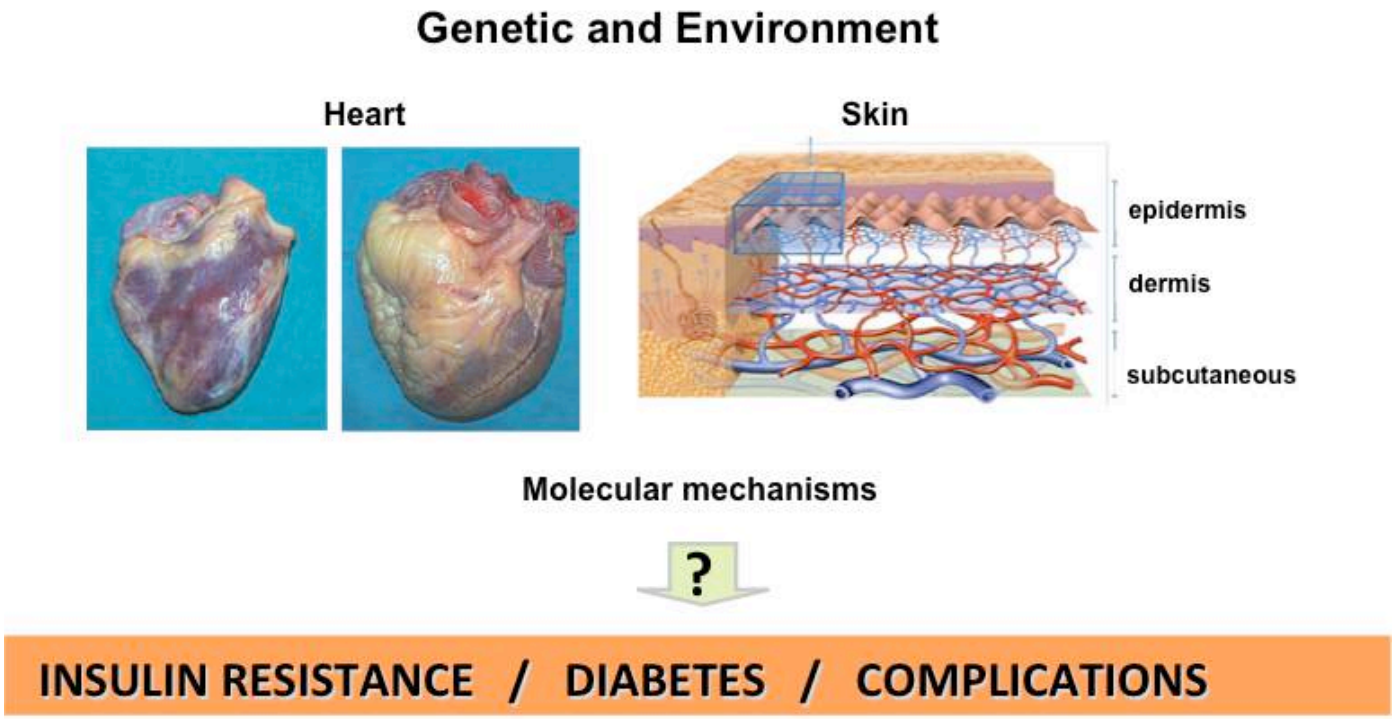
a) Develop a novel intestinal permeability probe to evaluate intestinal barrier integrity in diet-induced metabolic diseases such as Type 2 Diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD). The rationale for this is the recent evidence for intestinal dysbiosis between enterocytes and gut microflora as a possible factor in promoting the development of hepatic inflammation and insulin resistance through compromising the intestinal barrier and allowing leakage of endotoxin and other proinflammatory factors into portal vein blood. Although there are many studies focusing on gut microflora species and population dynamics during diet-induced T2D and/or NAFLD, surprisingly little research has been carried out on intestinal barrier function – whose failure is a necessary condition for leakage of proinflammatory agents from the gut into the circulation. This is at least in part due to the lack of simple practical tests for measuring intestinal permeability. Our goal was therefore to develop such a test that could be used in both animal models and humans.

b) Phenotyping of epicardial adipose tissue (EAT): EAT is a very special type of fat depot surrounding the heart, having a major impact in cardiovascular (CV) health due to its direct cross-talk with cardiomyocytes. One of our main objectives was to phenotype this cell in terms of autophagy and endoplasmic reticulum (ER) stress.

c) Screening and identifying miRNAs from skin tissue that are dysfunctional in diabetes, and that might be contributing to impaired wound healing. Impaired wound healing is a serious late-diabetic complication with significant associated morbidity. Locally generated microRNAs (miRNAs) may be involved in the regulation or misregulation of the wound healing process since they can alter gene regulation at a post-transcriptional level and are themselves dynamically regulated by hormonal and by environmental factors.

d) Using in vitro models to study the effects of diabetes on gametogenesis and gamete function. Diabetes is known to affect reproductive function, but the mechanisms involved in terms of gonad homeostasis and gamete metabolism remain unknown due to the multifactorial nature of the disease. The goal was therefore to tackle distinct aspects of this process using simplified *in vitro* models.

e) Using metabolic cues to influences pluripotent stem cell fate. Pluripotent stem cells are known for having specific metabolic profiles (shared with other proliferating cells) that change as they differentiate into specific cellular fates. The goal was to use these features in order to predict/direct stem cell differentiation.



Main Achievements

a) Development of a commercial intestinal permeability probe: In collaboration with a Lab at CEDOC, UNL, we developed an inexpensive and sensitive high-throughput method for measuring intestinal permeability. The measurement was tested in rodent models of diet-induced fatty liver disease and was shown to be more sensitive to the onset of hepatic insulin resistance compared to conventional measurements. The transfer of this idea into a commercial product was pursued through enrollment into the 2015 COHITEC program of one Ph.D. student from our group (Joao Silva) and one Postdoctoral Fellow from CEDOC (Fatima Martins). The idea was selected for seed funding to further develop its commercialization and a startup company (LifeTag) has been created.

b) Characterizing endoplasmatic reticulum stress in human epicardial adipose tissue (EAT): We were able to successfully evaluate and report that insulin-stimulated glucose uptake and lipolysis are impaired in isolated EAT cells from nearly 100 subjects with heart failure with and without diabetes. In addition, both autophagy and ER stress pathways are significantly different when comparing between EAT and subcutaneous fat from the same subjects.

c) Comparison of skin tissue microRNA (miRNA) profiles between diabetic subjects with and without diabetic wounding: miRNA profile was determined for up to 561 unique miRNAs using Taqman MicroRNA array cards. 288 different miRNAs were identified with a Ct level<32, and the majority (189) was decreased more than 1.5 fold by wounding, and 63 were more than 1.5 fold decreased in diabetic skin, whereas 41 miRNAs were increased more than 1.5 fold by wounding and 94 were increased by diabetes. Technical replication of findings for 14 different miRNAs confirmed these were significantly altered by either wounding or chronic hyperglycemia. mRNA array data from wounded skin were filtered for predicted miRNA targets (TargetScan database) and pathway analysis was done using Gene-Ontology (GO) Biological Process terms. Predicted mRNAs collectively targeted by miRNAs up-regulated in diabetes (miR-21, miR-29a, miR-126, miR-146a, miR-155 and miR-210) were significantly enriched in categories related to cellular biosynthetic processes and transcription ($p<0.05$ and $p<0.004$).

d) Using in vitro models to study the effects of diabetes on gametogenesis and gamete function. We were able to successfully show the establishment of *in vitro* mouse spermatogenesis models that allowed us to conclude that high glucose concentrations *per se* do not play a role in decreased testicular function in diabetic animals. Furthermore, we characterized for the first time the metabolome of mature sperm using both proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy and gas chromatography-mass spectrometry (GC-MS), showing that the techniques are complementary and suggest the presence of several distinct pathways. The identification of these pathways, and how they may be affected in diabetic males, is currently under investigation.

e) Using metabolic cues to influences pluripotent stem cell fate. We successfully used pharmacological inhibitors of the glycolytic pathway to steer pluripotent stem cells away from pluripotency and towards a differentiated cellular state, notably by acting on the Pyruvate Dehydrogenase switch, controlled by Pyruvate Dehydrogenase kinase. This led to the uncovering of other metabolism-related control points of stem cell fate that are currently being explored. In parallel we carried out and published an evaluation of an outreach project involving communicating the science of stem cells towards a general audience, in step with Outreach and Science & Society initiatives.

ImmunoMetabolic Pharmacology

(Head: Margarida Carneiro)

Objectives

$CD8^+$T cells are classically viewed as human leukocyte antigen (HLA) class I-restricted cytotoxic effector cells involved in the cellular immune response against viruses, intracellular bacteria and tumor cells. The involvement of $CD8^+$T cells in autoimmune disorders has remained rather elusive, even though they have been implicated in the pathogenesis of multiple sclerosis, encephalomyelitis, diabetes mellitus, systemic lupus erythematosus, Crohn's disease and vitiligo.

The current paradigm for the role of T cell in rheumatoid arthritis (RA) pathogenesis is centered on the concept that $CD4^+$T cells are the orchestrators of the disease process, while $CD8^+$T cells are mostly ignored. However, they do not embody the whole complexity of the disease process. Even though, $CD8^+$T cells comprise about 40% of the T cells infiltrating the rheumatoid synovial compartment, and they are detected in the preclinical stages of disease development, their role in disease pathogenesis is poorly defined. Moreover, it is still unclear, how current therapeutic strategies used in RA treatment influence the function and subtypes of $CD8^+$ T cells in RA patients. Another core question that needs to be addressed when studying the role of $CD8^+$T cells in RA is how they meet their energetic demands to maintain their immunologic functions in an hypoxic environment as the RA synovial membrane. In particular, which are the molecular mechanisms coordinating $CD8^+$T cell effector functions and metabolic shifts in RA, and how do $CD8^+$T cell effector functions and metabolic demands change with RA disease activity.

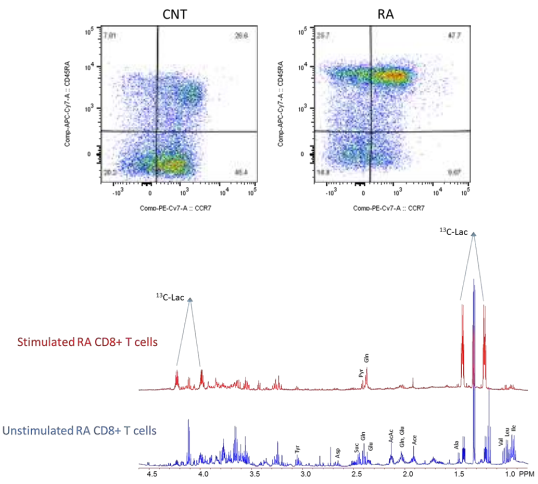
By addressing these issues, we aim at defining the potential of $CD8^+$ T cells as disease progression and drug-response biomarkers. By gaining a deeper understanding of $CD8^+$T cell metabolism in RA we may be able to manipulate it thus opening new paths for future therapeutic strategies.

Main Achievements

Blood and synovial fluid samples were collected from RA patients, psoriatic arthritis (PsA) and ankylosing spondylitis (SpA) attending the outpatient clinics of the Rheumatology Departments of the University Hospitals of Coimbra and Heidelberg. After preparation of the peripheral blood mononuclear cells we assess $CD8^+$ T cell phenotypes, production of cytokines, and production of cytotoxic molecules in the peripheral blood (PB) and synovial fluid (SF) of patients with RA at different disease stages, and compared them to healthy donors. Additionally, purified PB $CD8^+$ T cells from healthy donors and RA patients under anti-TNF therapy or only disease modifying anti-rheumatic drugs (DMARD) were stimulated in vitro, to assess changes in functional phenotype and cytokine production. We demonstrated that there was an increased production of proinflammatory cytokines by $CD8^+$T cells in active RA patients as opposed to remission patients. $CD8^+$T cells found in the synovial fluid were mainly effector memory cells with an activated phenotype. The production of proinflammatory cytokines and proteolytic enzymes by synovial fluid $CD8^+$T cells correlated to that observed in paired peripheral blood samples, showing that $CD8^+$T cells from the peripheral blood mirror those found in the synovial fluid. Moreover, phenotypes and cytokine production levels of peripheral blood $CD8^+$T cells correlated with disease activity. Additionally, we observed that after in vitro stimulation RA patients had significantly fewer naïve $CD45RA^+CCR7^+$ $CD8^+$T cells but comparable levels of central memory $CD45RA^-CCR7^+$ $CD8^+$T cells, indicating that the former subset might be the major contributor to the lower CCR7-expressing pool in RA patients. Additionally, we observed a significant decrease in naïve $CD45RA^+CCR7^+$ $CD8^+$T cells in the patients receiving anti-TNF drugs, but no changes in the central memory $CD45RA^-CCR7^+$ subset, nor did we find any differences in the levels of secreted IFNγ, IL-6, and IL-10.

Our preliminary studies on NMR isotopomer analysis of peripheral blood $CD8^+$T cell metabolism have revealed some interesting metabolic shifts upon *in vitro* activation. When comparing the lactate content of $CD8^+$ T cell culture media from healthy controls and patients with different forms of chronic arthritis, we observed that RA cells had a distinct metabolic footprint. At rest, particularly in healthy control individuals, and SpA and PsA patients, levels of [U-^{13}C]lactate, derived from the [U-^{13}C]glucose in culture media, were quite low, denoting a basal metabolism not particularly dominated by aerobic glycolysis and consistent with low biosynthetic activity. In contrast, in RA patient's $CD8^+$T cells the [U-^{13}C]lactate levels are consistently higher and compatible with a stronger energetic and biosynthetic/proliferative demands from $CD8^+$T cells even at rest. These differences were exacerbated upon in vitro stimulation. This characteristic metabolic profile combined with the production of cytotoxic molecules allowed us to calculate receiver-operator curves which could clearly distinguish between seronegative RA patients and PsA patients, and between seronegative and seropositive RA patients. These results prove the potential of using $CD8^+$T cell metabolism and immune-function as biomarkers for clinically elusive cases of RA and other chronic arthritis.

Finally, when quantifying the expression of several key glycolytic and TCA enzymes in $CD8^+$T cells, we observed that RA patients had an enzymatic expression profile reminiscent of an exacerbated Warburg effect. Based on these findings we are currently investigating how different inhibitors of the glycolytic and TCA pathways are capable of modifying the RA $CD8^+$T cell response, changing it from a pro-inflammatory into an anti-inflammatory type.



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STEM CELL-BASED AND MOLECULAR THERAPIES

Coordinator: Luis Pereira de Almeida

The Stem Cell-Based and Molecular Therapies thematic strand brings together seven core research groups committed 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.

During 2015, the groups in this strand were particularly successful in attracting competitive funding from several framework/ operational programmes, namely Horizon2020 and Portugal2020-POCI, as well as from international sources such as the French Muscular Dystrophy Association (AFM, France), the National Ataxia Foundation (NAF, USA) and the BioBlast Pharma (Israel). Several funded projects include partnerships with SMEs/companies (e.g., Crioestaminal, QIAGEN) and other non-academic entities.

Overall, research efforts originated more than 100 publications in peer-reviewed international journals (2015 issues), the majority resulting from fruitful collaborations with nearly a hundred different institutions (academic and otherwise) from 19 different countries. Of those, many involved the University Hospitals (CHUC) and ca. 42% 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 (10% and 9% respectively), followed by the USA (7%), UK, Italy, Germany and Canada (roughly 5% each). The majority of the publications (58%) are Q1, of which 23 papers in high-impact journals (IF>5), including *Circulation Research*, *Brain*, *PNAS*, *Biomaterials*, *Antioxidants & Redox Signaling*, *Analytical Chemistry*, *Scientific Reports*, *Trends in Food Science & Technology*, *Biochimica et Biophysica Acta* and *Oncotarget*, 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: three patent applications on biomaterials for regenerative therapeutics, another on the preparation/ formulation of a cork extract, a provisional patent application on production processes of mycobacterial intermediates and one granted US Patent on anti-proliferative agents. From the Stem-cell Biotechnology group, a new company − the Exogenus Therapeutics (Exo-T) – was spun off that is developing a new product for the treatment of chronic wounds.

The members of this thematic strand are also actively involved in advanced training, notably in the MIT-Portugal PhD programme in Bioengineering, being responsible for one mandatory and one elective module of the 2015 edition of this programme. Also worth mentioning are the three FP7 Marie-Curie Training Networks (ITN) *TreatPolyQ*, *NanoDrug* and *CAFFEIN*, still running in 2015 and featuring three strand groups as participants with several PhD-trainees hosted by their laboratories.

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 planned.

As for stem cell-based investigation, it will keep its focus on tissue regeneration, aimed at treating ischemia and non-healing wounds in chronic patients. 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.

VECTORS AND GENE THERAPY GROUP

Mª Conceição Pedroso Lima	PhD (*Head of Group*)
Ana Bela Sarmento Ribeiro	PhD
Ana Luísa Cardoso	PhD
Anália Vital do Carmo	PhD
Eliana Maria Barbosa Souto	PhD
Henrique Santos Faneca	PhD
João Nuno Moreira	PhD
Luis F. Pereira Almeida	PhD
Manuel Joaquim Garrido	PhD
Maria Amália Jurado	PhD
Maria Celeste Lopes	PhD
Nuno Fonseca	PhD
Olga M. F. Borges Ribeiro	PhD
Raghu Kalluri	PhD
Sergio Paulo M. Simões	PhD
Teresa Maria Martins	PhD
Vera Caldeira de Moura	PhD
Ana Maria Cardoso	Post Doctoral Fellow
Ana Teresa Simões	Post Doctoral Fellow
Catarina Sofia Miranda	Post Doctoral Fellow
Clevio David Nóbrega	Post Doctoral Fellow
Ligia de Sousa Ferreira	Post Doctoral Fellow
Liliana Simões Mendonça	Post Doctoral Fellow
Rita Perfeito	Post Doctoral Fellow
Rui Jorge Gonçalves Nobre	Post Doctoral Fellow
Rui Manuel Lopes	Post Doctoral Fellow
Slavomira Doktorovova	Post Doctoral Fellow
Sónia Patrícia Dias Duarte	Post Doctoral Fellow
Ana Cristina Ferreira	PhD Students
Ana Cristina Gonçalves	PhD Students
Ana Cristina Romano	PhD Students
Ana Filipa Cruz	PhD Students
Ana Viegas	PhD Students
Ângela Fernandes	PhD Students
Catarina Morais	PhD Students
Diana Azenha	PhD Students
Dina Farinha	PhD Students
Dina Pereira	PhD Students
Dulce Bento	PhD Students
Edna Soares	PhD Students
Filipa Lebre	PhD Students
Isabel Onofre	PhD Students
Joana Balça Silva	PhD Students
Joana Fangueiro	PhD Students
Joana Guedes	PhD Students
Joana Neves	PhD Students
Mariana Conceição	PhD Students
Mariangela Natale	PhD Students
Marta Pereira	PhD Students
Nuno Mendonça Silva	PhD Students
Patrícia Albuquerque	PhD Students
Raquel Alves	PhD Students
Sandra Jesus	PhD Students
Sara Lopes	PhD Students
Sofia Pereira Romano	PhD Students
Udaya Geetha	PhD Students
Vítor Carmona	PhD Students
Carlos Matos	Grant Technician
Vanessa Monteiro	Grant Technician
Ana Catarina Sousa	MSc Student
Daniela Santo	MSc Student
David Coelho	MSC Student
José Codesso	MSc Student
Pedro Cunha	MSc Student
Rute Araújo	MSc Student

STEM CELL BIOTECHNOLOGY GROUP

Lino da Silva Ferreira	PhD (*Head of Group*)
Akhilesh Rai	PhD
Alessandra Zonari	PhD
Carlos Filipe Pereira	PhD
Hugo Agostinho Fernandes	PhD
Ricardo Pires Das Neves	PhD
Adrián Jiménez Balsa	Post Doctoral Fellow
Ana Barradas	Post Doctoral Fellow
Luís Estronca	Post Doctoral Fellow
Renato Cardoso	Post Doctoral Fellow
Sezin Aday	Post Doctoral Fellow
Sonia Luzia Claro de Pinho	Post Doctoral Fellow
Susana Rosa	Post Doctoral Fellow
Susana Simões	Post Doctoral Fellow
Vítor Francisco	Post Doctoral Fellow
Ana Francisca Lima	PhD Student
Andreia Marques Gomes	PhD Student
Catarina Praça Almeida	PhD Student
Catarina Rebelo	PhD Student
Deolinda Santinha	PhD Student
Emanuel Quartim Costa	PhD Student
Ivana Kostic	PhD Student
João Sargento Freitas	PhD Student
Josephine Blerch	PhD Student
Mª Helena Antunes	PhD Student
Michela Comune	PhD Student
Miguel Lino	PhD Student
Pedro Gouveia	PhD Student
Sandra Pinto	PhD Student
Patrícia Pitrez Pereira	Grant Technician
Tânia Barata	Grat Technician
Fábio Rosa	MSc Student

SYSTEMS AND COMPUTATIONAL BIOLOGY GROUP

Armindo Salvador	PhD (*Head of Group*)
Alessandro Bolli	Post Doctoral Fellow
Gianluca Selvaggio	PhD Student
Inês Vasconcelas Santos	PhD Student
Pedro Branco	PhD Student
Rui Benfeitas Vicente	PhD Student
David Bowman	Collaborator
Luís Loura	Collaborator
Mª João Pedrosa Silvestre	Collaborator

MEDICAL MICROBIOLOGY GROUP

Teresa Oliveira Gonçalves	PhD (*Head of Group*)
Nuno Miguel Empadinhas	PhD
Vítor Gonçalo Mendes	PhD
Carolina Isabel Paiva Coelho	Post Doctoral Fellow
Chantal Fernandes	Post Doctoral Fellow
Susana Isabel Elias Alarico	Post Doctoral Fellow
Ana Maranha Tiago	PhD Student
Lisa Rodrigues	PhD Student
Patrícia Nunes	PhD Student
Rui Soares	PhD Student

Mª Mafalda Costa	PhD Student
Ana Monteiro	MSc Student
Cristina Martins	MSc Student
Célia Nogueira	Collaborator
Daniela Costa	Collaborator
Sónia Pereira	Collaborator

MEDICINAL CHEMISTRY & DRUG DISCOVERY GROUP

Mª Luisa Vaz Sá Melo	PhD (*Head of Group*)
Alcino Leitão	PhD
Gabriela Jorge da Silva	PhD
Jorge Ribeiro Salvador	PhD
Mª Céu Sousa	PhD
Mª Manuel Cruz Silva	PhD
Sara Margarida Domingues	PhD
Ana Sofia Valdeira	PhD Student
Bruno Gonçalves	PhD Student
Maria La Salete Batista	PhD Student
Rui Figueiredo	PhD Student
Sandra Figueiredo	PhD Student
Sofia Anastácio	PhD Student
Vanessa Mendes	PhD Student
Fátima Nunes	Grant Technician
Ana Maria Alves	Collaborator
João Carvalho	Collaborator
Miguel Ângelo Costa	Collaborator
Mónica Serra	Collaborator
Patrícia Ferreira	Collaborator
Samuel Silvestre	Collaborator

PHARMACOMETRICS GROUP

Amílcar Falcão Ferreira	PhD (*Head of Group*)
Ana Cristina Fortuna	PhD
Artur Figueirinha	PhD
Bruno Neves	PhD
Carla Vitorino	PhD
Carlos Manuel Cavaleiro	PhD
Fernando Jorge dos Ramos	PhD
João José de Sousa	PhD
Ligia Salgueiro Couto	PhD
Maria José Gonçalves	PhD
Maria Teresa Batista	PhD
Nuno Ricardo Mendonça	PhD
Célia Cabral	Post Doctoral Fellow
Ana Serralheiro	PhD Student
Daniela Gonçalves	PhD Student
Gustavo Costa	PhD Student
Joana Almeida e Sousa	PhD Student
Joana Bicker Aparício	PhD Student
Marisa Gaspar	PhD Student
Paulo Magalhães	PhD Student
Renato Pires	Collaborator
Vera Calhau	Collaborator

BIOTECHNOLOGY

MICROBIOLOGY OF EXTREME ENVIRONMENTS GROUP

Milton Simões da Costa	PhD (*Head of Group*)
Ana Catarina M. Ferreira	PhD Student
Luís França	PhD Student
Tânia Leandro	PhD Student
António Veríssimo	Collaborator
Joana Costa	Collaborator

MOLECULAR BIOTECHNOLOGY GROUP

Carlos José Costa Faro	PhD (*Head of Group*)
Isaura Simões	PhD
Paula Verissimo Pires	PhD
André Soares	PhD Student
Ana Sofia Lourenço	PhD Student
Pedro Curto	PhD Student
Euclides Pires	Collaborator

Vectors and Gene Therapy Group

(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. These lines of research have included a component of translational research, following the collaboration with the Portuguese Institute of Oncology from Coimbra and the Faculty of Medicine and the Hospital of the University of Coimbra.

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 mucosal vaccination (oral and nasal) using antigens (protein or DNA) encapsulated in polymeric nanovectors, to target the lymphoid structures of the mucosal immune system. In this regard, new chitosan-based delivery systems able to simultaneously encapsulate antigens and an immunopotentiator (mast cell activator c48/80, aluminum compounds and exosomes) have been developed and tested (*in vitro* and *in vivo*) with the purpose of modulating immune response.

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. Several characteristics susceptible of modulation emerged as critical to improve vector performance, e.g. hydrocarbon chain length and spacer chemical nature in gemini surfactants; combinatory proportions of copolymer components and the corresponding cloud point; amino-acid sequence, presence of specific amino acid residues (e.g. histidine) and acylation in cell penetrating peptides.

Regarding targeted cancer gene therapy, we have generated novel lipid-based systems exhibiting the ability to specifically and efficiently deliver DNA into hepatocellular carcinoma cells through its specific binding to the asialoglycoprotein receptor. A new multimodal miRNA-based therapeutic strategy, employing the previously developed tumor-targeted stabilized nucleic acid lipid particles (SNALPs), was successfully applied in a GBM orthotopic mouse model. We have shown that systemic delivery of the generated targeted SNALPs carrying anti-miR-21, followed by oral administration of sunitinib, resulted in a significant decrease in tumor size and tumor cell proliferation, as well as in enhanced apoptosis, decrease in angiogenesis and improvement of animal

survival. Our findings set up an approach for efficient GBM treatment with potential of clinical translation. An enhancement of GBM cell susceptibility to chemotherapeutics was also obtained by modulating membrane lipid composition through the delivery of siRNAs addressing the activity of key-enzymes of lipid metabolism. 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.

Liposomes functionalized with the nucleolin-binding F3 peptide, targeted simultaneously, nucleolin-overexpressing putative breast CSC and non-SCC, which was paralleled by OCT4 and NANOG mRNA levels in cells from triple negative breast cancer (TNBC) origin. In murine embryonic stem cells, both nucleolin mRNA levels and F3 peptide-targeted liposomes cellular association were dependent on the stemness status. This proposed link between nucleolin expression and the stem-like phenotype in TNBC enabled 100% cell death mediated by F3 peptide-targeted synergistic drug combination, suggesting the potential to abrogate the plasticity and adaptability associated with CSC and non-SCC.

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 polymeric NP-based vaccination, we elucidate better the adjuvant mechanisms of chitosan and chit/PCL nanoparticles. For instance both NPs have in common their capacity to promote mast cell activation and a Th17 immune response. The *in vivo* immunogenicity of HBsAg was considerably increased.

Stem Cell Biotechnology Group

(Head: Lino Ferreira)

Objectives

The research group has several 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 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 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 several miRNAs that are capable of enhancing stem cell survival. The mechanism of action of the top two miRNAs is being investigated using bioinformatics (collaboration with Matthias Futsick group, University Algarve) and the selected targets validated in our lab. In vivo studies are ongoing in order to validate the effect of the selected miRNAs in vivo (collaboration with the group of Seppo Herttuala, Finland).

Systems and Computational Biology Group

(*Head: Armindo Salvador)*

Objectives

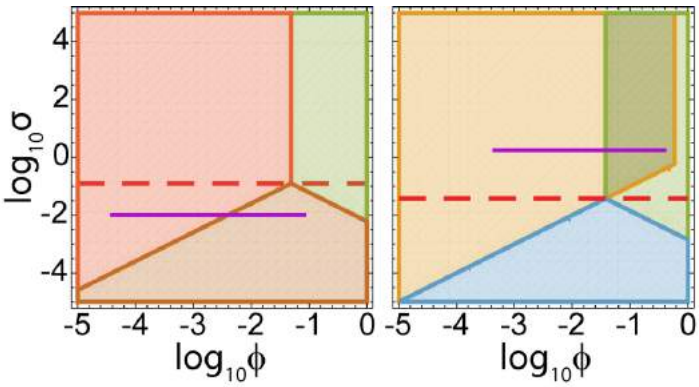
Research at the Computational & Systems Biology Group is distributed by the following three research lines:

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.

Objects of interest in this research line are metabolic networks, 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.



Predicted behavior of the PTTRS as function of the scaled H_2O_2 supply (ϕ) and TrxR activity (σ) for human erythrocytes (left) and Jurkat T cells (right). Green regions correspond to extensive Prx sulfinylation, and brown (left) / blue (right) ones to accumulation of Prx and Trx in disulfide form. Reddish/cream regions at low ϕ show optimal signaling and antioxidant properties. This region overlaps the green one in the case of Jurkat T cells, indicating multistability and hysteresis under stress. The purple lines represent the estimated physiological range of ϕ and σ for each cell, and the dashed red line separates the region where high ϕ cause accumulation of Prx in sulfinic (top) or disulfide (bottom) form. The design space analysis correctly predicts the experimentally observed responses of Prx redox state to H_2O_2 challenges in both cases.

Main Achievements

Hydrogen peroxide (H_2O_2) signaling through the peroxiredoxin (Prx) / thioredoxin (Trx) / Trx reductase (TrxR) system (PTTRS) is important in cell proliferation, neuroprotection, angiogenesis and tumorigenesis. However, the following fundamental questions remain unclear. What are the physiologically relevant H_2O_2 concentrations? How are H_2O_2 signals transduced? Why does the PTTRS show distinct responses to H_2O_2 challenges in distinct human cell types? To address the first question we devised an artificial gene circuit that retains memory of the maximal extracellular H_2O_2 concentration to which an *E. coli* lineage was exposed and reports it as a fluorescence color code. The circuit was implemented in Dr. Timothy Lu's lab (MIT). In collaboration with Dr. Miguel Godinho Ferreira's lab (IGC) we are using it to determine, for the first time, the extracellular H_2O_2 levels attained in a living animal under inflammation/infection. In collaboration with Dr. Tobias Dick (University of Heidelberg) and Dr. Bruce Morgan (Technical University of Kaiserslautern) we are also

developing methods to determine absolute intracellular H_2O_2 concentrations. We addressed the other questions, with the collaboration of Dr. Rui Travasso's lab (University of Coimbra), through mathematical modeling based on the kinetic properties and abundances of the PTTRS proteins. Our results favor a signaling mode through spatially localized redox relays, whereby peroxiredoxins at once act as the H_2O_2 sensors, maintain strong gradients, and relay the redox signal to effector proteins. Further, our studies indicate that in many cell lines and tumor cells the PTTRS shows bi-stability and hysteresis, such that at high H_2O_2 supply rates Prx is abruptly hyperoxidized to the peroxidatically inactive but holdase-active form. H_2O_2 then penetrates deeply into the cell and can eventually trigger the Antioxidant Response Element (ARE)-mediated response. We established the conditions (relationships between protein concentrations and kinetic parameters) under which this or an alternative response where both Prx and Trx accumulate in disulfide form ensue. Finally, we derived the design principles for optimal operation of this circuit. We are establishing new collaborations with experimental groups to test these hypotheses and explore their translational implications.

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. Probes based on the fluorophore 7-nitrobenz-2-oxa-1,3-diazol-4-yl (NBD) are widely used in experimental studies of membrane properties related to permeability, but the interpretation of results is complicated by uncertainties about the location and orientation of the probes when inserted in lipid bilayers. We clarified these issues in a molecular dynamics study of a complete homologous series of NBD-labeled fatty amines inserted in lipid bilayers of compositions designed to mimic the physical properties of cellular membranes [Filipe et al. (2015) Phys. Chem. Chem. Phys. 17:20066; ibid. 27534]. Priority for 2016 will be the development of improved methods to estimate permeation rate constants from molecular dynamics simulations, building on the computational breakthroughs reported in 2014.

Design space analysis [Coelho et al. (2009) PLoS Comp. Biol. 5, e1000319; Savageau et al. (2009) PNAS 106, 6435-6440] is instrumental in connecting design to function of molecular circuits. In support of the studies reported in the first paragraph we developed an effective matrix method to expedite the analysis and overcome previous limitations in applications to systems containing coupled reversible cycles. The method was implemented in the form of a parallel algorithm in the Mathematica platform and new features to facilitate visualization and analysis of the results were also added.

Medical Microbiology Group

(*Head: Teresa Gonçalves*)

Objectives

Medical Microbiology:

A. Antifungal effect of algal extracts

B. Synergy between melanin synthesis inhibitors and antifungals

C. Purines and purinergic receptors impact in fungal infection and colonization.

Molecular Mycobacterology:

Our research is focused on mycobacterial pathogens such as the agent of tuberculosis (TB) and nontuberculous mycobacteria (NTM), which include multidrug-resistant emerging pathogens causing life-threatening infections in the chronically ill, in those with immune fragilities, and in the elderly.

We have recently expanded our interests to the intersection of molecular microbiology and neurodegenerative disorders (Parkinson's disease), and chronic diseases (diabetes), aiming to decipher microbial biomarkers associated to each of these pathologies that might lead the way to new preventive and therapeutic approaches.

1) New mycobacterial targets

Genetic and biochemical resources of mycobacteria remain largely enigmatic, which protract the path toward new therapies. We have identified the functions of genes involved in the biosynthesis of methylglucose lipopolysaccharide (MGLP), a vital intracellular polymer regulating fatty acids metabolism and cell envelope assembly. This role of MGLP renders its function and of the key enzymes attractive targets for therapeutic intervention. Our goal is to comprehensively decipher this pathway at the genetic, biochemical and structural levels and its regulation and contribution to cell envelope dynamics, for therapeutic intervention.

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

We have performed a preliminary survey of 6 Parkinson's disease (PD) patients' gut microbiomes with focus on a neurotoxin-producing microbial group, which may chronically colonize patients' intestines leading to sub-clinical progressive neurodegeneration. We have assembled a multidisciplinary team and obtained stool, plasma and brain (post-mortem) samples from PD patients (Portugal, Finland and Spain) and will try to experimentally validate our biomarker hypothesis using NGS and mass spectrometry approaches.

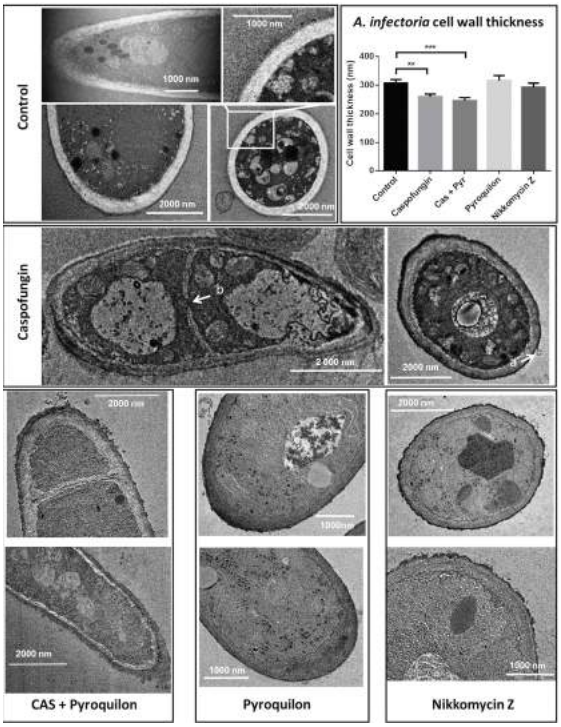
3) Diabetic wound healing - ulcer microbiome dynamics

We started characterizing the microbiome of skin and wounds of diabetic animal models in collaboration with the "Obesity, Diabetes and complications" Group at CNC, with funding from EFSD/Novartis Programme 2015 (PI: Eugénia Carvalho). We will test the effects of new formulations of selected peptides with combined antimicrobial and cell proliferating activities.

Our funding perspectives for these different areas naturally include applications to national and international agencies and partnerships with the pharmaceutical and chemical industries.

Main Achievements

Medical Microbiology:



A. Extracts of two different species of red algae proved to inhibit filamentous growth and not unicellular fungi. The still unknown bioactive molecules target the cell wall synthesis machinery leading to fragile cell walls.

Achievements:

Two MSc thesis

MS accepted - Soares F, Fernandes C, Silva P, Pereira L and Gonçalves T (2016). Antifungal activity of carrageenan extracts from the red alga Chondracanthus teedei var. lusitanicus. J Appl Phycol (in press) DOI 10.1007/s10811-016-0849-9

B. We proved that the production of melanin is a salvage mechanism against antifungals. Inhibition of DHN-melanin synthesis by pyroquilon resulted in a lower minimum effective concentration (MEC) of caspofungin and enhanced morphological changes, characterized by thinner and less organized cell walls.

Achievements:

MS accepted - Fernandes C, Prados-Rosales R, Silva B, Nakouzi-Naranjo A, Zuzarte M, Chatterjee S, Stark RE, Casadevall A, Gonçalves T . Activation of melanin synthesis in Alternaria infectoria by antifungal drugs. Antimicrob Agents Chemother (in press)

C. In what respects ectonucleotidase and ectophosphatase We found that *Candida albicans* does not have a classical ecto-5'-nucleotidase enzyme and 5'AMP is cleaved by a phosphatase instead of exclusively by a nucleotidase that also can use 3'AMP as a substrate. Moreover, these enzymatic activities are not dependent on secreted soluble enzymes and change when the yeast cells are under infection conditions, including low pH, and higher

temperature and CO2 content.

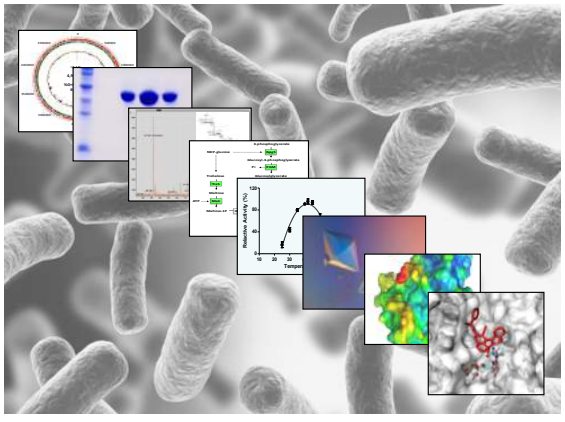
Using an in vivo murine model of gut infection we also find a relation between host age and susceptibility to over-colonization or infection by *C. albicans*, and its impact on the inflammation of the gut, and explored the localization and density of adenosine A2A receptors.

Achievements:

MS accepted - Rodrigues L, Russo-Abrahão T, Cunha RA, Gonçalves T and Meyer-Fernandes JR (2015) Characterisation of extracellular nucleotide metabolism in Candida albicans. FEMS Microbiol Lett DOI: http://dx.doi.org/10.1093/femsle/fnv212

MS submitted - Lisa Rodrigues, Isabel Miranda, Geanne Andrade, Marta Mota, Luísa Cortes, Acácio Rodrigues, Rodrigo Cunha, and Teresa Gonçalves. Blunted dynamics of adenosine A2A receptors is associated with increased susceptibility to Candida albicans infection in the elderly.

Molecular Mycobacterology:



We have identified several the functions of essential genes of a mycobacterial pathway for a vital intracellular polysaccharide that modulates fatty acids metabolism. The collaboration of crystallographers allowed determination of the 3D structures of some of the essential enzymes, experimental scaffolds for drug screening/ design (see publications). We have anticipated critical links between MGLP biosynthesis and folate metabolism, a previously unrecognized intersection that will grant new targets to fight mycobacterial infections.

We have been recently invited to collaborate with a EU-US consortium funded by the Cystic Fibrosis Foundation, which were very interested on a gene that was found to be consistently mutated in virulent strains of M. abscessus by WGS approaches, and whose function we identified (unpublished). This emerging pathogen is resistant to multiple antibiotics and a serious health threat, especially in patients with chronic lung diseases and in the elderly.

We have patented a method for the synthesis and purification of acylated intermediates of the mycobacterial MGLP, which were previously unknown to science and are now available to the market for research. We have developed an efficient method for production of two rare phosphorylated intermediates from a vital mycobacterial pathway. The strategic program (InovC-UC, Oct 2014 - Jan 2015), funded this work. The compounds were made available to the market under a contract agreement between CNC, UC and Extremochem (subsidiary of 73100, Lda.) for production and distribution of rare phosphorylated sugars from mycobacteria.

Medicinal Chemistry & Drug Discovery Group

(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 oxysterols, modulation of their anticancer activity has been a subject revisited. To enlarge the structural diversity of cytotoxic ring-B oxysterols, stereoselective pathways of synthesis and in depth studies on cell cycle and cell death, including high density and heterogenous cell toxicity, were planned. Moreover, 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. Additionaly we also focused on the 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.

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. Antimicrobial resistance is becoming increasingly frequent and is causing a global health crisis that cannot be ignored. The genetic characterization of resistance determinants and the comprehension of its molecular epidemiology will light our understanding of how resistance evolves and will help in fighting resistant infections and the search for new antibacterial compounds by re-purposing or alteration of compound structures.

The research activities of the group are supported by the following expertise:

a) Computational approaches in drug discovery: 4D (pocket ensemble) molecular docking; pharmacophore- and structure-based drug design; virtual screening; focused library design based on hit and target.

b) Synthesis in drug discovery: asymmetric synthesis for chiral drugs; biocatalysis; chemo-enzymatic methods; clean processes.

c) Biological evaluation *in vitro*.

d) Analysis of structure-activity relationships (SAR) to predict potency and improve “hits” to “lead candidates” by optimizing their selectivity against the target and pharmacokinetics.

e) To test in vitro antimicrobial activity

f) Molecular biology: molecular characterization of resistance genes and genetic support; evaluation of horizontal gene transfer (conjugation and natural tansformation) and molecular bacterial epidemiology

g) Biologic evaluation of new compounds

Main Achievements

1. Concerning the cytotoxic studies on the oxysterols prepared, it has been proved they are cell type dependent and, correlations of their structures with cytotoxicity, selectivity and type of cell death, have been achieved. Cell cycle and cell death studies were also performed at high cellular densities. These updated studies revealed different outcomes on the structure-activity correlations of the oxysterols under evaluation and predicting a potential improvement on their anticancer activities in vivo (unpublished results). 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 with importance to anti-convulsant activity (Steroids, 2015, accepted).

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, 2015, in press).The anti-Leishmania activity of new semisynthetic lupane triterpenoids derivatives of betulin and betulinic acid were evaluated. Drug interactions between the active compounds and one current antileishmanial drug, miltefosine, were assessed using the fixed ratio isobologram method. In addition, effects on the cell cycle, apoptosis/necrosis events, morphology and DNA integrity were studied (unpublished results).

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.

4. We found: **1**, that important clinical bacteria carrying resistance genes are spreading into environment through hospital effluents, leading to the urgent need of wastewater treatment (WWT) of hospital discharges before getting into municipal WWT plants; 2, resistance is disseminated in food chain (*Salmonella enterica*) and, despite the ban of antibiotics in growth promotion in Europe, we found that metals (used as additives or biocides) can select for antimicrobial resistance genes; **3**, antibiotics can select for more virulent strains of S. enterica non-Typhi, carrying the active toxin CDT, usually produced by the highly pathogenic S. Typhi; **4**, the carbapenemase KPC-3 with the ability of inactivating all beta-lactam antibiotics has emerged and disseminated in Coimbra University hospital in multidrug resistant nosocomial bacteria such as *Klebsiella pneumoniae*; **5**, a few semi-synthetic triterpenoids derived from ursolic acid showed good antimicrobial activity against Gram-positive bacteria.

Pharmacometrics Group

(*Head: Amílcar Falcão*)

Objectives

The principal aim of the Pharmacometrics Group is to early predict kinetic and dynamic behaviors of drug candidates employing a wide methodological approach including *in silico*, *in vitro* and *in vivo* 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 of P-glycoprotein and characterize the bioavailability and biodisposition of new therapeutic drugs, evaluating their concentrations in plasma and tissues (including liver, kidney, brain, etc).

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.

Main Achievements

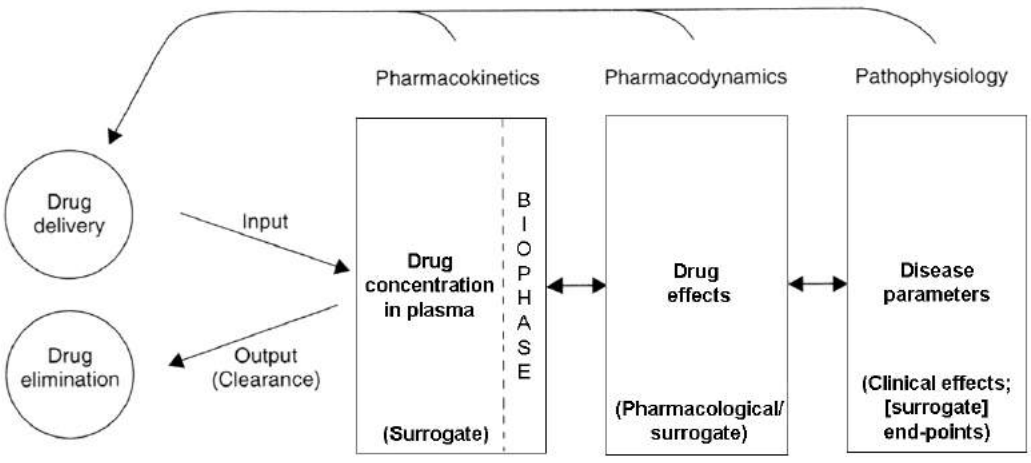
Optimization and validation of PAMPA model to foresee the ability of new therapeutic compounds to reach the brain and its application on new drug candidates.

Similarly to the results achieved in 2014, for intranasal delivery of carbamazepine, in vivo intranasal administration of lamotrigine also afforded a high plasma absolute bioavailability (≈ 100%), however a slower passage into the brain, where relevant drug concentration levels were sustained for up to 24 h. This novel approach seemed to be a more promising strategy on chronic pharmacotherapy and on the management of the refractory epilepsy than on emergence situations as carbamazepine showed before.

Regarding our the natural drug discovery approach, it was demonstrated that some plant extracts and compounds, particularly essential oil´s terpenoids and phenolic compounds, inhibited nitric oxide 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.

Moreover, significant antioxidant and antifungal properties were verified for different extracts and fractions, suggesting their potential application for pharmaceutical, cosmetic or alimentary industries.

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.



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) 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.

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BIOTECHNOLOGY

Molecular Biotechnology Group

(*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. Furthermore, we have 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. Our research activities are subdivided into 4 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. However, our understanding of this full protease web is still in its infancy for plant proteases. Identification of native substrates (degradomes), correlation of processing events with biological processes and a better understanding of structure-function relationships are, therefore, crucial tasks to understand the role of proteases in plant biology. 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. The presence of APs of both pepsin and retropepsin-type in prokaryotes has always been a matter of debate and our work has provided the first unequivocal documentation of these types of activities 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, a hereditary form of epilepsy; as well as on the detailed structural/interactomics' characterization of SAPAP3, a postsynaptic scaffolding protein, suggested to be involved in obsessive-compulsive disorder.

The role of pollen proteases in allergic respiratory disorders.

Pollens are important triggers for allergic disorders. In the past 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 evaluated their contribution on immunologic and inflammatory response.

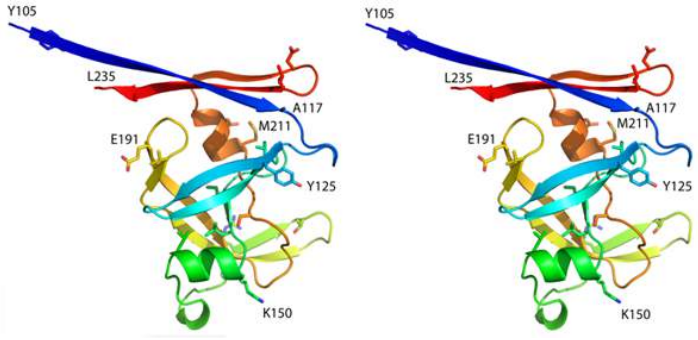

Fig1. A cartoon-style stereoview showing the monomer of APRc from Rickettsia conorii in rainbow colors (changing smoothly from blue at the N-terminus to red at the C-terminus). Secondary-structure elements are indicated by ribbons and selected amino-acid side chains are shown in stick representation, with some of them labelled. (Lima et al, 2015, Acta Cryst D, doi:10.1107/s1399004715013905.

Main Achievements

1) Biochemistry, biology and biotechnology potential of plant APs

A new cardosin B-derived rennet produced in the GRAS yeast *K. lactis* (named VRen) was demonstrated to be effective for manufacturing sheep, goat, and cow cheeses (Almeida *et al*, AMB, 2015;Q1 Biotechnology & Applied Microbiology). The structure of this cardosin B-derived form was obtained and comparative specificity profiling performed (using PICS). The results anticipate more restricted specificity preferences for this form of the protease, further reinforcing its potential as an alternative rennet (manuscript in preparation).

We pursued with the functional characterization of 2 atypical APs from Arabidopsis. Phenotypic analysis of KO mutants for each gene revealed significant reductions in primary root length and in lateral root number. Moreover, our results suggest that these genes may be involved in two

different regulatory mechanisms of lateral root formation. Therefore, these genes were designated RLR1 and RLR2 (Regulator of Lateral Root).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 degradomics studies are ongoing to identify RLR1 and RLR2 natural substrates. (This work is part of the PhD Dissertation project of André Soares).

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

We published the first ever documented structure of a retropepsin-like protease from prokaryotes. The results clearly show that the fold of APRc monomer resembles that of viral retropepsin. Overall, our results support the concepts that APRc may indeed represent a putative common ancestor of monomeric and dimeric aspartic proteases, as well as possible existence of a different evolutionary pathway for these enzymes. (Li et al, Acta Cryst. D, 2015; (Q1 in category Crystallography; Biochemistry & Molecular Biology; Biophysics)

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. Moreover, we provide first evidence of expression of active shewasin D in *S. denitrificans* cells. (manuscript in preparation).

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

We reported the biophysical characterization of laforin-carbohydrate interaction using soluble glycans. (Faria *et al*, Phys Chem Chem Phys., 2015; Q1 Chemistry & Physical).

Regarding SAPAP3, ESPRIT technology resulted in the identification of one domain with higher yields of accumulation of soluble protein – C-terminal domain 19 – which was produced in larger scale and protein purification methods optimized. 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, one mutant associated with OCD (K910R) and another associated with schizophrenia (R770L). Results from these analysis revealed an association between SAPAP3 and mitochondria related components. To our knowledge, 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 entitled: "Biochemical and interactomic characterization of SAPAP3 - a scaffolding protein involved in obsessive-compulsive disorder", submitted for defense by Ana Sofia Lourenço).

4) The 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.

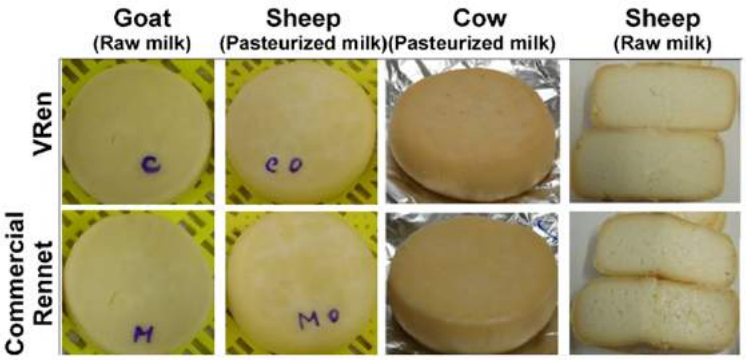

Fig2. Cheeses produced with VRen. Goat, shep, and cow milk (3L), pasteurize dor raw as indicated, were used for cheese production using VRen as milk clotting agent. The cheeses were ripened for about 3 weeks. For comparision, a parallel experiment using synthetic chymosin (MaxiRen®) as the coagulant agent (commercial rennet). (Almeida e tal, 2015, Appl Microbiol Biotechnol, doi:10.1007/s00253-014-5902-5)

PUBLICATIONS

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Rodrigues V, Cabral C, Évora L, Ferreira I, Cavaleiro C, Cruz MT, Salgueiro L. Chemical composition, anti-inflammatory activity and cytotoxicity of *Thymus zygis* L. subsp. *sylvestris* (Hoffmanns. & Link) Cout. essential oil and its main compounds. *Arabian Journal of Chemistry. (In Press)*

BIOMEDICAL INTER-INSTITUTIONAL RESEARCH PROGRAMME

RESEARCH IN BRAIN TUMORS

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

On the first part of this project, 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 being detected, which were associated with both the histopathological subtype and the grade of the tumor.

The 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.

Regarding the cell signalling transduction pathways, the results performed in glioma cell lines indicate that the activation of PI3K/Akt and MAP kinase signaling pathways contribute to the chemoresistance that characterizes glioma cells. We screened for different types of cell death induced by some chemicals in glioblastoma cell lines and explored the possible ways to increase cell death execution and/or abolish survival signalling, aiming to identify commonly altered pathways where to interfere in order to maximize cell and avoid drug resistance.

Next, the high-density single-nucleotide polymorphism array (SNP-array) was performed to investigate genome-wide copy number (CN) alterations in glioblastoma multiforme (GBM) samples. We have shown 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.

In the last part of this project, the studies of multiparametric flow cytometry were performed to identify and characterize the different cell population coexisting in meningiomas, and their patterns of protein expression. The results suggest the involvement of different signalling pathways in the distinct cytogenetic subgroups of meningiomas, at the same time they would contribute to explain the close association between tumor cytogenetic and patient outcome.

PUBLICATION

Balça-Silva J, Matias D, Carmo A, Girão H, Moura-Neto V, Sarmento-Ribeiro A, Lopes MC (2015). Tamoxifen in combination with Temozolomide induce a synergistic inhibition of PKC-pan in GBM cell lines. *Bioch. Biophys. Acta*, 1850: 722-732.

Melo-Lima S, Lopes MC and Mollinedo F (2015). ERK1/2 acts as a switch between necrotic and apoptotic cell death in ether phospholipid edelfosine-treated glioblastoma cells. *Pharmacol. Research*: 95, 2-11.

Crespo I, Vital AL, Gonzalez T M, Patino MC, Otero A, Lopes MC, Domingues PH, Orfao A, Tabernero MD (2015). Molecular and genomic alterations in GBM. *Am. J. Path.,* 185 (7):1820-33.

Domingues P, Tablas MG, Otero A, Pascual D, Ruiz L, Miranda D, Sousa P, Gonçalves JM, Lopes MC, Orfao A and Tabernero MD (2015). Tumor infiltrating immune cells in gliomas and meningiomas. *Brain Behavior and Immunity,* pii: S0889-1591(15)00414-6.

Domingues P, Tablas MG, Otero A, Pascual D, Ruiz L, Miranda D, Sousa P, Gonçalves JM, Lopes MC, Orfao A and Tabernero MD (2015). Genetic/molecular alterations of meningiomas and the signalling pathways targeted. *Oncotarget,* 6 (13),10671-88.

Coelho-Aguiar J, Andreiuolo F, Gebhardt H *et al.* (2015). The Role of the Cytoskeleton in Cell Migration: its influence on stem cells and the role of GFAP in glial functions. *In book*: The Cytoskeleton in Health and Disease, Chapter: 4, Publisher: springer, Editors: Heide Schatten, pp.87-119.
Domingues PH, Teodósio C, Otero A, Sousa P, Gonçalves JM, Nieto AB, Lopes MC, de Oliveira C, Orfao A, Tabernero MD (2015). The protein expression profile of meningioma cells is associated with distinct cytogenetic tumour subgroups. *Neuropathol. Appl . Neurobiol*. 41(3):319-32.

NOVEL TECHNIQUES FOR THE DIAGNOSIS AND TREATMENT OF HUMAN INFERTILITY

Teresa Almeida Santos (CHUC, FMUC, CNC), Ana Paula Sousa (CHUC, CNC), Alexandra Amaral (CNC), Renata Tavares (CNC), Alexandra Carvalho (CNC), Francisca Mora (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.

The most recent aspect is 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.

PUBLICATIONS

Cordeiro MH, Kim SY, Ebbert K, Duncan FE, Ramalho-Santos J, Woodruff TK. (2015) Geography of follicle formation in the embryonic mouse ovary impacts activation pattern during the first wave of folliculogenesis. *Biol Reprod.* 93(4):88. doi: 10.1095/biolreprod.115.131227.

Paiva C, Amaral A, Rodriguez M, Canyellas N, Correig X, Ballescà JL, Ramalho-Santos J, Oliva R. (2015) Identification of endogenous metabolites in human sperm cells using proton nuclear magnetic resonance ((1) H-NMR) spectroscopy and gas chromatography-mass spectrometry (GC-MS). *Andrology*. 3(3):496-505. doi: 10.1111/andr.12027

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

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).

Invited Seminars by Ana Luisa Carvalho at IDIBELL, Barcelona (April 2015) and Departamento di Neuroscienze, School of Medicine, Universidade de Nápoles "Federico II", Naples, Italy (October 2015).

Invited Seminar by Carlos Duarte at the Departamento di Neuroscienze, School of Medicine, Universidade de Nápoles "Federico II", Naples, Italy

A master student from Martin-Luther Universitat Halle-Wittenberg joined the group of Irina Moreira for an internship under the theme: “Structural characterization of dopamine receptors in complex with dopamine and the binding partner G-protein”.

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* 89, 223-234.

B. Mollereau, NM Rzechorzek, BD Roussel, M Sedru, D Van denBrink, B Bailly-Maitre, F Palladino, DB Medinas, PM Domingos, S Hunot, S Chandran, S Birman, T Baron, D Vivien, CB Duarte, HD Ryoo, H Steller, F Urano, E Chevet, G Kroemer, A Ciechanover, EJ Calabrese, RJ Kaufman, C Hetz C (2016) Adaptive Preconditioning in Neurological Diseases Therapeutic Insights from Proteostatic Perturbations. Brain Research. In press. (doi: 10.1016/j.brainres.2016.02.033)

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. (doi: 10.1007/s12035-015-9283-2) (in press)

Ferreira JS, Schmidt J, Rio P, Aguas R, Rooyakkers A, Li KW, Smit AB, Craig AM, Carvalho AL (2015) GluN2B-Containing NMDA Receptors Regulate AMPA Receptor Traffic through Anchoring of the Synaptic Proteasome. *J Neurosci* 35, 8462-8479.

Almeida B, Abreu IA, Matos CA, Fraga JS, Fernandes S, Macedo MG, Gutierrez-Gallego R, Pereira PJ, Carvalho AL, Macedo-Ribeiro S (2015) SUMOylation of the brain-predominant Ataxin-3 isoform modulates its interaction with p97. *Biochim Biophys Acta* 1852, 1950-1959.

M Curcio, IL Salazar, AR Inácio, EP Duarte, LM Canzoniero, CB Duarte (2015) Brain ischemia downregulates the neuroprotective GDNF-Ret signaling by a calpain-dependent mechanism in cultured hippocampal neurons. Cell Death Dis 6, e1645.

M Curcio, IL Salazar, AR Inácio, EP Duarte, LMT Canzoniero, CB Duarte (2015) Brain ischemia downregulates the neuroprotective GDNF-Ret signaling by a calpain-dependent mechanism in cultured hippocampal neurons. Cell Death Dis 6, e1645.

Munteanu CR, Pimenta AC, Fernandez-Lozano C, Melo A, Cordeiro MNDS, Moreira IS (2015) SASA-Based Hot-Spot Detection 2 (SBHD) method for protein-protein and protein-nucleic acid interfaces. J Chem Info Model 55, 1077-1086.

Redox Biology and Brain Sensing

Enrique Cadenas - Dept. Pharmaceutical Sciences, University of Southern California, USA. Nitric oxide in neurodegeneration and aging.

Greg Gerhardt - Dept. Anatomy and Neurobiology, and Center for Microlelectrode Technology (CenMet) University of Kentucky, Lexington, Kentucky, USA. Development of microsensors for nitric oxide measurement in tissues.

Rafael Radi - Facultad de Medicina, Universidad de la República, Montevideo, Uruguay. New biological functions for wine polyphenols: Cellular regulation and anti-inflammatory actions via nitric oxide production from nitrite.

Homero Rubbo - Facultad de Medicina, Universidad de la República, Montevideo, Uruguay. New biological functions for wine polyphenols: Cellular regulation and anti-inflammatory actions via nitric oxide production from nitrite.

Jon O. Lundberg - Department of Physiology and Pharmacology, Karolinska Institutet, Sweden. New biological functions for wine polyphenols: Cellular regulation and anti-inflammatory actions via nitric oxide production from nitrite.

Neuroendocrinology and Aging

Research training for fourteen days at LabSinCel in University of Campinas, Brazil, under the project funded by FCT-CAPES arrangement.

On going collaborators:
Carlos Lopez Otin - Departamento de Bioquímica y Biología Molecular Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain. (Project collaborator).

Leonard Guarente - Glenn Laboratory for the Science of Aging at MIT; USA - (Co-supervisor of PhD student)

Licio Velloso - University of Campinas, Brasil (FCT-Capes Project)

Tamas Horvath - Section of Comparative Medicine; Yale School of Medicine PO Box 208016, New Haven, USA (Co-supervisor of PhD student)

Vision, Brain Imaging and Cognitive Neuroscience

Papers

Leuzy et al. Pittsburgh Compound-B imaging and cerebrospinal fluid amyloid-β in a multicentre European memory clinic study Brain, IN PRESS 2016

Violante et al., GABA deficiency in NF1: a multimodal [11C]-Flumazenil and spectroscopy study Neurology, IN PRESS 2016

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 Jun 10. doi: 10.1111/gbb.12305. [Epub ahead of print] 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.

Martins J, Elvas F, Brudzewsky D, Martins T, Kolomiets B, Tralhão P, Gøtzsche CR, Cavadas C, Castelo-Branco M, Woldbye DP, Picaud S, Santiago AR, Ambrósio AF. Activation of Neuropeptide Y Receptors Modulates Retinal Ganglion Cell Physiology and Exerts Neuroprotective Actions In Vitro. ASN Neuro. 2015 Aug 26;7(4). pii: 1759091415598292. Doi 0.1177/1759091415598292. Print 2015 Jul-Aug.

Pinho AL, Ullén F, Castelo-Branco M, Fransson P, de Manzano Ö. Addressing a Paradox: Dual Strategies for Creative Performance in Introspective and Extrospective Networks. Cereb Cortex. 2015 Jun 17. pii: bhv130. [Epub ahead of print] PubMed PMID: 26088973.

Martins J, Kolomiets B, Caplette R, Sahel JA, Castelo-Branco M, Ambrósio AF,Picaud SA. Sildenafil acutely decreases visual responses in ON and OFF retinal ganglion cells. Invest Ophthalmol Vis Sci. 2015 Mar 26. pii: IOVS-14-15964. doi: 10.1167/iovs.14-15964. [Epub ahead of print] PubMed PMID: 25814000

Banca P, Voon V, Vestergaard MD, Philipiak G, Almeida I, Pocinho F, Relvas J, Castelo-Branco M. Imbalance in habitual versus goal directed neural systems during symptom provocation in obsessive-compulsive disorder. Brain. 2015 Mar;138(Pt 3):798-811. doi: 10.1093/brain/awu379. Epub 2015 Jan 6.

Ribeiro MJ, Violante IR, Bernardino I, Edden RA, Castelo-Branco M. Abnormal relationship between GABA, neurophysiology and impulsive behavior in neurofibromatosis type 1. Cortex. 2015 Mar;64:194-208. doi: 10.1016/j.cortex.2014.10.019. Epub 2014 Nov 11. PubMed PMID: 25437375.

Banca P, Vestergaard MD, Rankov V, Baek K, Mitchell S, Lapa T, Castelo-Branco. M, Voon V. Evidence Accumulation in Obsessive-Compulsive Disorder: the Role of Uncertainty and Monetary Reward on Perceptual Decision-Making Thresholds. Neuropsychopharmacology. Neuropsychopharmacology. 2015 Mar 13;40:1192-202. doi: 10.1038/npp.2014.303. epub 2014 Nov 26. doi: 10.1038/npp.2014.303. PMID: 25425323.

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

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)

EU Joint Programme – Neurodegenerative Disease Research (JPND, BIOMARKAPD) with Alexandre de Mendonça (Inst. Molecular Medicine, Univ. Lisbon), Magda Tsolaki (Univ. Thessaloniki, Greece), Sermin Genc (Univ. Izmir, Turkey), Anja Simonsen (Univ.Copenhagen, Denmark), Elisabeth Kapaki (Univ. Athens, Greece)

Member of the Coffee and Health Forum managed by the Institute for Scientific Information of Coffee

Research grants:

Joint research project sponsored by DARPA with Ki Ann Goosens and Ann Graybiel (McGovern Institute, MIT, USA)

Ciência sem Fronteiras program with Lisiane Porciúncula (Univ. Federal Rio Grande do Sul, Brazil)

Joint project of the *Association Nationale de Recherche* 'ROle of Adenosine Receptors on synapse stabilization (ROAR)' with Cristine Métin (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 (Silvia Sousa) with Christophe Mulle (Univ. Bordeaux, France)

Co-supervision of a PhD student (Marta Carmo) with Geanne Matos (Univ. Federal Ceará, Brazil)

Co-supervison of a PhD student (Filipe Matheus) with Rui Prediger (Univ. Federal Santa Catarina, Brazil)

Co-supervision of a PhD student (Jimmy George) with Thierry Amédée (Univ. Bordeaux, France)

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)

Graduate teaching:

Course entitled 'Fronteiras da Ciência', Univ. Federal Santa Maria, Brazil

Course entitle 'G-protein coupled receptors', Univ. Federal Ceará, Brazil

Mitochondrial Dysfunction and Signaling in Neurodegeneration Group

Organization of 2 international PhD courses:

"Neuroscience and Mental Health" course, *The Doctoral Programme in Health Sciences* (PhDHS) and *The Doctoral Programme in Aging and Chronic Disease* (PhDOC) (http://www.phdhs.org/), Faculty of Medicine, University of Coimbra (11-15th May, 2015).

"Neurodegenerative disorders" course, *The Doctoral Programme in Experimental Biology and Biomedicine* (PDBEB, http://beb.cnbc.pt/), Center for Neuroscience and Cell Biology and Institute for Interdisciplinary Research, University of Coimbra (27-30 April, 2015).

Participation in international meetings:

9th International Meeting of the Portuguese Society for Stem Cells and Cell Therapies (SPCE-TC), 15-16 de outubro, ITQB/iBET, Oeiras, Portugal (1 abstract)

ISSCR (International Society for Stem Cell Research) 2015 Annual Meeting, June 24-27, Stockholmsmassan Convention Centre, Stockholm, Sweden (2 abstracts)

The 2015 Abcam conference on "Adult Neurogenesis: Evolution, Regulation and Function". 6-8th May 2015, Dresden, Alemanha (3 abstracts)

Invited speaker in international meeting, foreign institute/university:

AC Rego: Invited Seminar at Department of Neurochemistry, University of Stockholm, Sweden (15th October, 2015)

AC Rego: Invited communication at Life Science Mission to Portugal – Led by Nobel Laureate Dr. Craig Mello, FLAD-Fundação Luso Americana para o Desenvolvimento, Lisboa, Portugal (1st June, 2015)

Research collaboration with:

George Daley (MD, PhD), Harvard Medical School, Boston, USA _ study of HD_iPS cells (partial doctoral work of Carla Lopes).

Sandrine Humbert (PhD), Institut Curie, Orsay, France _ partial doctoral work of Carla Lopes.

Michael Hayden (MD, PhD), The University of British Columbia, Vancouver, Canada _ studies in the YAC128 mice.

Tiago Fleming Outeiro (PhD), University Medizin Goettingen, Goettingen, Germany _ study of phosphorylated alpha-synuclein (undergoing); doctoral work of Raquel Pinho.

António Cuadrado (PhD), Instituto de Investigaciones Biomédicas "Alberto Sols", UAM-CSIC, Madrid, Spain_study of Nrf2 and wnt3a signalling in adult hippocampal neurogenesis in the context of AD

Collaborative publications:

Silva A., Naia L., Dominguez A., Ribeiro M., Rodrigues J., Vieira O. V., Lessmann V., Rego A. C. (2015) Overexpression of BDNF and full-lengthTrkB receptor ameliorate striatal neural survival in Huntington's disease. *Neurodegener. Dis.* 15, 207-218.

Naia L., Ferreira I. L., Cunha-Oliveira T., Duarte A. I., Ribeiro M., Rosenstock T. R., Laço M. N., Ribeiro M. J., Oliveira C. R., Saudou F., Humbert S., Rego A. C. (2015) Activation of IGF-1 and insulin signaling pathways ameliorate mitochondrial function and energy metabolism in Huntington's disease human lymphoblasts. *Mol. Neurobiol.* 51, 331-348.

Esteves S., Duarte-Silva S., Naia L., Neves-Carvalho A., Teixeira-Castro A., Rego A. C., Silva-Fernandes A., Maciel P. (2015) Limited effect of chronic valproic acid treatment in a mouse model of Machado-Joseph disease. *PLoS One* 10, e0141610.

Nunes J. B., Peixoto J., Soares P., Maximo V., Carvalho S., Pinho S., Vieira A., Paredes J., Rego A. C., Ferreira I. L., Gomez-Lazaro M., Sobrinho-Simoes M., Singh K. K., Lima J. (2015) OXPHOS dysfunction regulates integrin-β1 modifications and enhances cell motility and migration. *Hum. Molec. Genet.* 24, 1977-1990.

Aging and Brain diseases: advanced diagnosis and biomarkers

The use of biomarkers for the etiologic diagnosis of MCI in Europe: an EADC survey. Bocchetta M, Galluzzi S, Kehoe PG, Aguera E, Bernabei R, Bullock R, Ceccaldi M, Dartigues JF, de Mendonca A, Didic M, Eriksdotter M, Felician O, Frolich L, Gertz HJ, Hallikainen M, Hasselbalch SG, Hausner L, Heuser I, Jessen F, Jones RW, Kurz A, Lawlor B, Lleo A, Martinez-Lage P, Mecocci P, Mehrabian S, Monsch A, Nobili F, Nordberg A, Rikkert MO, Orgogozo JM, Pasquier F, Peters O, Salmon E, Sanchez-Castellano C, Santana I, Sarazin M, Traykov L, Tsolaki M, Visser PJ, Wallin AK, Wilcock G, Wilkinson D, Wolf H, Yener G, Zekry D and Frisoni GB. Alzheimers Dement. 2015. 11(2): 195-206 e1. Web of Science® Citações: 6 Scopus citações: 6. Factor de impacto (2014/2015): 12,407 (Q1 Clinial Neurology)

Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. Vos SJ, Verhey F, Frolich L, Kornhuber J, Wiltfang J, Maier W, Peters O, Ruther E, Nobili F, Morbelli S, Frisoni GB, Drzezga A, Didic M, van Berckel BN, Simmons A, Soininen H, Kloszewska I, Mecocci P, Tsolaki M, Vellas B, Lovestone S, Muscio C, Herukka SK, Salmon E, Bastin C, Wallin A, Nordlund A, de Mendonca A, Silva D, Santana I, Lemos R, Engelborghs S, Van der Mussele S, Alzheimer's Disease Neuroimaging I, Freund-Levi Y, Wallin AK, Hampel H, van der Flier W, Scheltens P and Visser PJ. Brain. 2015. 138(Pt 5): 1327-38. Web of Science® Citações: 8 Scopus citações: 10. Factor de impacto (2014/2015): 9,196 (Q1 Clinical Neurology)

Cerebrospinal fluid biomarkers in trials for Alzheimer and Parkinson diseases. Lleo A, Cavedo E, Parnetti L, Vanderstichele H, Herukka SK, Andreasen N, Ghidoni R, Lewczuk P, Jeromin A, Winblad B, Tsolaki M, Mroczko B, Visser PJ, Santana I, Svenningsson P, Blennow K, Aarsland D, Molinuevo JL, Zetterberg H and Mollenhauer B. Nat Rev Neurol. 2015. 11(1): 41-55. Web of Science® Citações: 11 Scopus citações: 12. Factor de impacto (2014/2015): 15,358 (Q1 Clinical Neurology)

Prevalence of Cerebral Amyloid Pathology in Persons without Dementia: A Meta-Analysis. Willemijn J. Jansen, Rik Ossenkoppele, Dirk L. Knol, Betty M. Tijms, Philip Scheltens, Frans R. J. Verhey, Pieter Jelle Visser and the Amyloid Biomarker Study Group. JAMA 2015; 313(19):1924-1938. doi:10.1001/jama.2015.4668

Validation of a quantitative cerebrospinal fluid alpha-synuclein assay in a European-wide interlaboratory study. Kruse N, Persson S, Alcolea S, Bahl JMC, Baldeiras I, Capello E, Bocchio Chiavetto L, Emersic A, Engelborghs S, Eren E, Frisoni G, García-Ayllón MS, Genc S, Gkatzima O, Heegaard NHH, Janeiro AM, Kováčech B, Kuiperij HB, Leitão MJ, Lleó A, Martins M, Matos M, Mollergard HM, Nobili F, Öhrfelt A, Parnetti L, Oliveira CR, Rot U, Sáez-Valero J, Struyfs H, Tanassi JT, Taylor P, Tsolaki M, Vanmechelen E, Verbeek MM, Zilka N, Blennow K, Zetterberg H, Mollenhauer B. Neurobiology of Aging 2015; 36(9):2587-2596. DOI: 10.1016/j.neurobiolaging.2015.05.003

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 2015 May 7. DOI 10.1007/s12035-015-9167-5

Does caffeine consumption modify CSF amyloid beta levels in patients with Alzheimer's disease? Maria Travassos, Isabel Santana, Inês Baldeiras, Magda Tsolaki, Olymbia Gkatzima, Sermin Genc, Görsev G. Yener, Anja Simonsen, Steen G.

Hasselbalch, Elisabeth Kapaki, Mara Bourbouli, Rodrigo Cunha, Paula Agostinho, Kaj Blennow, Henrik Zetterberg, Vera M. Mendes, Bruno Manadas, Alexandre de Mendonça. J Alzheimer's Dis 2015; 47:1069-1078. doi: 10.3233/JAD-150374.

Chasing the effects of Pre-analytical Confounders - a Multicentric Study on CSF biomarkers. Maria João Leitão, Inês Baldeiras, Sanna-Kaisa Herukka, Maria Pikkarainen, Ville Leinonen, Anja Hviid Simonsen, Armand Perret-Liaudet, Anthony Fourier, Isabelle Quadrio, Pedro Mota Veiga, Catarina Resende de Oliveira. Fontiers in Neurology 2015; 6:153. doi:10.3389/fneur.2015.0015.

The central biobank and virtual biobank of BIOMARKAPD: a resource for studies on neurodegenerative diseases. Babette Reijs, Charlotte Elisabeth Teunissen, Nikolai Goncharenko, Fay Betsou, Kaj Blennow, Inês Baldeiras, Frederic Brosseron, Enrica Cavedo, Tormod Fladby, Lutz Froelich, Tomasz Gabryelewicz, Hakan Gurvit, Elisabeth Kapaki, Peter Koson, Luka Kulic, Sylvain Lehmann, Piotr Lewczuk, Alberto Lleó, Walter Maetzler, Alexandre de_Mendonça, Anne-Marie Miller, José Luis Molinuevo, Brit Mollenhauer, Lucilla Parnetti, Uros Rot, Anja Schneider, Anja Hviid Simonsen, Fabrizio Tagliavini, Magda Tsolaki, Marcel M Verbeek, Marzena Zboch, Frans R Verhey, Bengt Winblad, Philip Scheltens, Henrik Zetterberg and Pieter Jelle Visser. Front Neurol. 2015 Oct 15; 6:216. doi: 10.3389/fneur.2015.00216.

Rare Variants in PLD3 Do Not Affect Risk for Early-Onset Alzheimer Disease in a European Consortium Cohort. Cacace R, Van den Bossche T, Engelborghs S, Geerts N, Laureys A, Dillen L, Graff C, Thonberg H, Chiang HH, Pastor P, Ortega-Cubero S, Pastor MA, Diehl-Schmid J, Alexopoulos P, Benussi L, Ghidoni R, Binetti G, Nacmias B, Sorbi S, Sanchez-Valle R, Lladó A, Gelpi E, Almeida MR, Santana I, Tsolaki M,Koutroumani M, Clarimon J, Lleó A, Fortea J, de Mendonça A, Martins M, Borroni B,Padovani A, Matej R, Rohan Z, Vandenbulcke M, Vandenberghe R, De Deyn PP, Cras P,van der Zee J, Sleegers K, Van Broeckhoven C; Belgium Neurology (BELNEU) Consortium and the European Early-Onset Dementia (EU EOD) Consortium. Hum Mutat. 2015 Dec;36(12):1226-35. doi:10.1002/humu.22908.

Genetic variability in SQSTM1 and risk of early-onset Alzheimer dementia: a European early-onset dementia consortium study. Cuyvers E, van der Zee J, Bettens K, Engelborghs S, Vandenbulcke M, Robberecht C, Dillen L, Merlin C, Geerts N, Graff C, Thonberg H, Chiang HH, Pastor P,Ortega-Cubero S, Pastor MA, Diehl-Schmid J, Alexopoulos P, Benussi L, Ghidoni R, Binetti G, Nacmias B, Sorbi S, Sanchez-Valle R, Lladó A, Gelpi E, Almeida MR,Santana I, Clarimon J, Lleó A, Fortea J, de Mendonça A, Martins M, Borroni B, Padovani A, Matěj R, Rohan Z, Ruiz A, Frisoni GB, Fabrizi GM, Vandenberghe R, De Deyn PP, Van Broeckhoven C, Sleegers K; BELNEU Consortium and of the EU EOD Consortium. Neurobiol Aging. 2015 May;36(5):2005.e15-22. doi: 10.1016/j.neurobiolaging.2015.02.014.

Céspedes-Garro C, Naranjo ME, Ramírez R, Serrano V, Fariñas H, Barrantes R, LLerena A; CEIBA Consortium of the Ibero-American Network of Pharmacogenetics and Pharmacogenomics RIBEF. Pharmacogenetics in Central American healthy volunteers: interethnic variability. Drug Metabolism and Personalized Therapy. 2015. 30(1):19-31. DOI: 10.1515/dmdi-2014-0025.

Apellániz-Ruiz M, Inglada-Pérez L, Naranjo ME, Sánchez L, Mancikova V, Currás-Freixes M, de Cubas AA, Comino-Méndez I, Triki S, Rebai A, Rasool M, Moya G, Grazina M, Opocher G, Cascón A, Taboada-Echalar P, Ingelman-Sundberg M, Carracedo A, Robledo M, Llerena A, Rodríguez-Antona C. High frequency and founder effect of the CYP3A4*20 loss-of-function allele in the Spanish population classifies CYP3A4 as a polymorphic enzyme. Pharmacogenomics J. 2015 Jun;15(3):288-92. doi: 10.1038/tpj.2014.67.

METABOLISM, AGING AND DISEASE RESEARCH LINE

Cell Metabolism and Quality Control

Ali Mobasheri from School of Veterinary Science and Medicine, University of Nottingham, England. Collaborative projects: a) Metabolic activity and viability of chondrocytes in cryopreserved human osteochondral allografts and b) Mechanisms of chondrocyte resistance to hyperglycemia: modulation of ATP-dependent K^+ channels and causes of failure in osteoarthritis. Co-supervision of one PhD student.

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

David Busija from Tulane University School of Medicine, USA. Co-supervision of one postdoc fellow.

Francisco Blanco from CIBER-BBN, Centro de Investigación Biomédica, Centro Hospitalario Universitario A Coruña, Spain. Modulation of the chondrogenic potential of adipose tissue derived mesenchymal stem cells. Co-supervision of one PhD student.

Frederick Bellinger from John A. Burns School of Medicine, University of Hawaii, USA. Collaborative research and publication.

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

Marcia Haigis from Harvard Medical School, USA. Co-supervisor of one PhD student.

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

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

Russel H. Swerdlow from Kansas University, USA. Collaborative research and publications.

Short Term Scientific Mission given by COST Action BM 1307 (Student: Teresa Rodrigues Ref: COST-STSM-BM1307-25206), Host: Michael Clague, Institute of Translational Medicine, University of Liverpool (UK)

Member of the Management Committee (Henrique Girao- Portuguese representative) - European Research Concerted Action COST BM1307 - PROTEOSTASIS

Group Leader of the Working group 2 (Henrique Girao) of European Research Concerted Action COST BM1307 – PROTEOSTASIS

Portuguese representative (Henrique Girao) on the application - European Research Concerted Action COST OC-2015-2-20032: European connexin and pannexin research network

Mitochondria Metabolism and Disease Group

Visting researchers

Alberto Rossetti (University of Turin, Italy)

Bruno Mokette Mokette, University of Yaounde I, Cameroon

Irina Starostina, Kazan Federal University, Russia

Krzysztof Kochel, University of Lodz, Poland

Lílian Pereira (University of São Paulo, Brazil)

Murilo Panzini (University of São Paulo, Brazil)

Vilena Ivanova, Kazan Federal University, Russia

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 Maine, Portland (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

Collaborative publications:

Schneeberger, M., Gómez-Valadés, A.G., Altirriba, J., Sebastián, D., Ramírez, S., Garcia, A., Esteban, Y., Drougard, A., Ferrés-Coy, A., Bortolozzi, A., Garcia-Roves, P.M., Jones, J.G., Manadas, B., Zorzano, A., Gomis, R. and Claret, M. Reduced a-MSH underlies hypothalamic endoplasmic reticulum stress-induced hepatic gluconeogenesis. *Cell Reports,* 2015**, 12***,* 361-370.

Jones, J.G., Kahl, S., Carvalho F., Barosa, C., and Roden, M. Simplified analysis of acetaminophen glucuronide for quantifying gluconeogenesis and glycogenolysis using deuterated water. *Anal. Biochem*., 2015**,** 479*,* 37-39*.*

Viegas, I., Rito, J., Jarak, I., Leston, S., Caballero-Solares, A., Metón, I., Pardal, M.A., Baanante, I.V. and Jones, J.G. Contribution of dietary starch to hepatic and systemic carbohydrate fluxes in European seabass (*Dicentrarchus labrax L.*) quantified using deuterated water. *British J. Nutrition*, 2015**,** 113*,* 1345-1354*.*

Burgess, S.C., Merritt, M.E., Jones, J.G., Browning, J.D., Sherry, A.D., Malloy, C.R. A new model of intermediary metabolism in the liver. *Nature Medicine,* 2015**,** 21*,* 109-110.

Leal E, Carvalho E, Tellechea A, Dinh T, Pradhan L, Kafanas A, V, Lyons T, Veves A Substance P promotes wound healing in diabetes by modulating inflammation and macrophage phenotype. Am J Pathol. 2015, 185:1638-48.

Paiva C, Amaral A, Rodriguez M, Canyellas N, Correig X, Ballescà JL, Ramalho-Santos J, Oliva R. Identification of endogenous metabolites in human sperm cells using proton nuclear magnetic resonance ((1) H-NMR) spectroscopy and gas chromatography-mass spectrometry (GC-MS). *Andrology.* 2015, 3, 496-505. doi: 10.1111/andr.12027.

Cordeiro MH, Kim SY, Ebbert K, Duncan FE, Ramalho-Santos J, Woodruff TK. Geography of follicle formation in the embryonic mouse ovary impacts activation pattern during the first wave of folliculogenesis. *Biol Reprod.* 2015 **9**:88-96. doi: 10.1095/biolreprod.115.131227.

BIOTECHNOLOGY RESEARCH LINE

Vectors and Gene Therapy Group

Collaborative research with publications:

Herman F. Staats; Duke University School of medicine, USA

Edvani C. Muniz, University of Maringá, Brasil

Adley F. Rubira, Universidade de Maringá, Brasil

Gerrit Borchard, University of Geneve, Suisse

Hirokazu Hirai, Gunma University, Japan

Brian Kaspar, University of Columbus, USA

Sebastian Kuegler, University of Goettingen, Germany

Wilfred F.A. den Dunnen, University of Groeningen, Netherlands

Collaborative publication:

Bento D, Staats HF, Gonçalves T, Borges O.; Development of a novel adjuvanted nasal vaccine: C48/80 associated with chitosan nanoparticles as a path to enhance mucosal immunity.; Eur J Pharm Biopharm. 2015 Jun;93:149-64. doi: 10.1016/j.ejpb.2015.03.024. (Impact factor: 3.853; Q1 in pharmaceutical science).

Bento D, Staats HF, Borges O.; Effect of particulate adjuvant on the anthrax protective antigen dose required for effective nasal vaccination.; Vaccine. 2015 Jul 17;33(31):3609-13. doi: 10.1016/j.vaccine.2015.06.037. (Impact factor: 3.624; Q1 in category Immunology and microbiology area)

Adriana P. Gerola, Danielle C. Silva, Sandra Jesus, Rui A. Carvalho, Adley F. Rubira, Edvani C. Muniz, Olga Borges and Artur J. M. Valente; Synthesis and controlled curcumin supramolecular complex release from pH-sensitive modified gum-arabic-based hydrogels; RSC Adv.**,** 2015, 5**,** 94519-94533 (Impact factor: 3.84; Q1 chemistry)

Clévio Nóbrega, Sara Carmo-Silva, David Albuquerque, Ana Vasconcelos-Ferreira, Udaya-Geetha Vijayakumar, Liliana Mendonça, **Hirokazu Hirai**, Luís Pereira de Almeida. Reestablishing Ataxin-2 downregulates translation of mutant ataxin-3 and alleviates Machado-Joseph disease. **Brain**. 2015 Dec;138(Pt 12):3537-54. doi: 10.1093/brain/awv298. [IF:9.196], Q1

Joana Duarte-Neves, Nélio Gonçalves, Janete Cunha-Santos, Ana T. Simões, **Wilfred F.A. den Dunnen, Hirokazu Hirai, Sebastian Kügler**, Cláudia Cavadas and Luís Pereira de Almeida. Neuropeptide Y mitigates neuropathology and motor deficits in mouse models of Machado-Joseph Disease. **Human Molecular Genetics.** 2015 Oct 1;24(19):5451-63. doi: 10.1093/hmg/ddv271 *2015 Jul 27.* [IF:6.393], Q1

Aveleira, CA; Botelho, M; Carmo-Silva, S; Pascoal, JF; Ferreira-Marques, M; Nóbrega, C; Cortes, L; Valero, J; Sousa-Ferreira, L; Álvaro, AR; Santana, M; **Kügler, S**; de Almeida, LP; Cavadas, C (2015). Neuropeptide Y stimulates autophagy in hypothalamic neurons: a caloric restriction mimetic mechanism. **Proc Natl Acad Sci USA**. pii: 201416609R. [IF:9.809] Q1

Liliana S. Mendonça, Clévio Nóbrega, **Hirokazu Hirai, Brian Kaspar**, Luís Pereira de Almeida. Transplantation of cerebellar neural stem cells improves motor coordination and neuropathology of Machado-Joseph disease mice. **Brain.** 2015 Feb;138(Pt 2):320-35. doi: 10.1093/brain/awu352. Selected for presentation to the Press at SFN2014. [IF:9.196] Q1

Research:

SynSpread: 2013 JPND Joint Programme on Neurodegenerative Diseases- Transnational call: €150.000; Mar 2015-Mar 2018. European network with groups from Luxembourg, and France.

Eranet E-Rare4/0003/2012, €141581; Mar 2013 – Dec 2016. European network with german, dutch and israeli groups.

FP7-PEOPLE2012-ITN, €209781, 2013 – 2016. (CAFFEIN - Cancer associated fibroblasts function in tumor expansion and invasion).

FP7-PEOPLE2012-ITN, 264508 SEVENTH FRAMEWORK PROGRAMME; €211441; Mar 2011 - Mar 2015. Treat PolyQ

Graduate Training:

Advanced course on Neuroepigenetics - CNC PhD program on Biomedicine and Experimental Biology - Ana Luísa Cardoso; CNC, February.

Advanced course on Principles and Practice in Drug Development - MIT-Portugal PhD program - João Nuno Moreira, Luís Pereira de Almeida and Sérgio Simões.

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).

Ricardo Neves has participated in the graduate training course “Curso Teórico-Práctico sobre Células Troncales y Embriología Clínica Humana” - "Estrategias de Ingeniería y Biología Celular para el estudio de células troncales y su aplicación a la terapia celular" 2015 University of Alicante, Spain

During 2015, 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 cardiac cells. Thomas Braun (Max Planck 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 (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).

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:

Nunes-Costa D, Alarico S, Dalcolmo MP, Correia-Neves M, Empadinhas N. The looming tide of nontuberculous mycobacterial infections in Portugal and Brazil. Tuberculosis doi: 10.1016/j.tube.2015.09.006. (with Fiocruz-Fundação Oswaldo Cruz, Brazil)

Mendes V, Blaszczyk M, Maranha A, Empadinhas N, Blundell TL (2015) Structure of Mycobacterium thermoresisitibile GlgE defines novel conformational states that contribute to the catalytic mechanism. Scientific Reports 5:17144. (with the University of Cambridge, UK)

Maranha A, Moynihan PJ, Miranda V, Correia EL, Nunes-Costa D, Fraga JS, Pereira PJB, Macedo-Ribeiro S, Ventura MR, Clarke AJ, Empadinhas N (2015) Octanoylation of early intermediates of mycobacterial methylglucose lipopolysaccharides. Scientific Reports 5:13610. (with the University of Guelph, Canada)

Bento C, Empadinhas N, Mendes V (2015) Autophagy in the fight against tuberculosis. DNA and Cell Biology 34(4):228-42. (with the University of Cambridge, UK)

Medicinal Chemistry & Drug Discovery

Collaborative Publications

Blackler RW, De Palma G, Manko A, Da Silva GJ, Flannigan KL, Bercik P, Surette MG, Buret AG, Wallace JL. Deciphering the Pathogenesis of NSAID-Enteropathy Using Proton Pump Inhibitors and a Hydrogen Sulfide-Releasing NSAID. Am J Physiol Gastrointest Liver Physiol. 2015, 308: G994-1003

Domingues S, Da Silva GJ, Nielsen KM. Global dissemination patterns of common gene cassette arrays in class 1 integrons. Microbiol-SGM, 2015, 161:1313–1337.

Figueiredo R, Card R, Nunes C, AbuOun M, Bagnall MC, Nunez J, Mendonça N, Anjum MF, da Silva GJ. Virulence Characterization of *Salmonella enterica* by a New Microarray: Detection and Evaluation of the Cytolethal Distending Toxin Gene Activity in the Unusual Host *S.* Typhimurium. PLoS One, 2015, 10: e0135010.

Gonçalves BMF, Salvador JAR, Marín S, Cascante M Synthesis and anticancer activity of novel fluorinated asiatic acid derivatives. Eur J Med Chem, in press. doi.org/10.1016/j.ejmech.2016.02.057

Kasal A, Budešínsky M, Pavel M, Krištofíková Z, Leitão A J, Sá e Melo M L, Cruz Silva M M. Neurosteroids: Can a 2alpha,3alpha-epoxy ring make up for the 3alphahydroxyl group? Steroids, Accepted November 19, 2015 http://dx.doi.org/10.1016/j.steroids.2015.11.007

Motta JP, Flannigan KL, Agbor TA, Beatty JK, Blackler RW, Workentine ML, Da Silva GJ, Wang R, Buret AG, Wallace JL Hydrogen sulfide protects from colitis and restores intestinal microbiota biofilm and mucus production. Inflamm Bowel Dis. 2015, 21: 1006-1017.

Pimenta L, Alegria N, Anastácio S, Sidi-Boumedine K, da Silva G, Rabiço Â, Simões J. Prevalence of *Coxiella burnetii* antibodies in Portuguese dairy cattle herds. Tropical Animal Health and Production. 2015, 47: 227-30.

Wallace JL, Blackler RW, Chan MV, Da Silva GJ, Elsheikh W, Flannigan KL, Gamaniek I, Manko A, Wang L, Motta JP, Buret AG. Anti-inflammatory and cytoprotective actions of hydrogen sulfide: translation to therapeutics. Antioxid Redox Signal, 2015, 22: 398-410.

Woegerbauer M, Kuffner M, Domingues S, Nielsen KM. Involvement of *aph(3')-IIa* in the formation of mosaic aminoglycoside resistance genes in natural environments. Front. Microbiol, 2015, 6: 442.

Research, Graduate Training Networks

FCT: SFRH/BD/77823/2011, *Coxiella burnetii* and Q Fever: an emergent zoonosis in Portugal

Co-supervisor: Dr. Karim Sidi-Boumedine, DVM, PhD, Co-Head of the National Reference Laboratory on Q fever, French Agency for Food, Environmental and Occupational Health Safety (ANSES), Sophia-Antipolis, France

FCT: SFRH/BD/78833/2011, Microarray-based detection of antibiotic resistance and virulence factors genes of *Salmonella* spp. isolated from food-producing animals and processed food

Co-supervisor: Dr. Muna Anjum, Honorary Associate Professor, Molecular Lead: Antimicrobial resistance and enteric pathogens, Dept. of Bacteriology, Animal and Plant Health Agency, Woodham Lane, London, United Kingdom.

Pharmacometrics

School of Biological, Biomedical and Environmental Sciences da Universidade de Hull, UK.

Faculty of Pharmacy of University of Salamanca, Spain.

Molecular Biotechnology Group

Collaborative publication:

Li M., Gustchina A., Cruz R., Simões M., Curto P., Martinez J., Faro C., Simões I.** & Wlodawer A.** (2015). Structure of RC1339/APRc from Rickettsia conorii, a retropepsin-like aspartic protease. Acta Cryst. D71, 2109-2118 doi:10.1107/S1399004715013905 (Impact factor 2014: 2.674; Quartile in category Crystallography; Biochemistry & Molecular Biology; Biophysics: Q1)

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. Biophysical characterization of laforin-carbohydrate interaction. Biochemical J. (accepted for publication) (Impact factor 2014: 4.396; Quartile in category Biochemistry & Molecular Biology: Q1)

Collaborative research:

Dr. Alexander Wlodawer, Macromolecular Crystallography Laboratory, NCI-Frederick, USA,

Dr. Alice Y. Cheung, University of Massachusetts at Amherst, Amherst, USA.

Dr. Juan J. Martinez, Department of Pathobiological Sciences, LSU School of Veterinary Medicine, Baton Rouge, USA

Dr. Pitter Huesgen, Central Institute for Engineering, Electronics and Analytics (ZEA-3), ForschungszentrumJülich, Germany

Graduate training:

PhD Thesis: Cristina Susana Barcia: "Proteasas de polen de Acacia caven y su importancia en alergias"**;** Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis, Argentina

PARTICIPATION IN THE ORGANIZATION OF SCIENTIFIC MEETINGS

January 2015

Organizing Committee, BIOINFORMATICS 2015. 6th International Conference on Bioinformatics Models, Methods and Algorithms
Date: January 12-15, 2015
CNC.IBILI members involved in the organization: Armindo Salvador

29 ªS Actualizações em Oncologia/ 4º Congresso do CIMAGO
Date: January 29-30, 2015
CNC.IBILI members involved in the organization: Isabel Carreira

February 2015

Meeting Cancer Epigenetics and Metabolism: Connecting the Dots, Biocant, Portugal
Date: February 2-3, 2015
CNC.IBILI members involved in the organization: Paulo Oliveira

Multiscale molecular modeling and simulation: an increasingly indispensable tool in materials R&D
Date: February 5, 2015
CNC.IBILI members involved in the organization: Paulo Oliveira

March 2014

Seminar "Antioxidant Therapy: Lights and Shadows"
Date: March 13, 2015
CNC.IBILI members involved in the organization: Paulo Oliveira

FRAME Training School in Experimental Design and Statistical Analysis of Biomedical Experiments
March 30 - April 1, 2015
CNC.IBILI members involved in the organization: CNC.IBILI Post-Docs Forum

April 2015

Organization of the Annual Meeting of the European Neuroscience Campus in Coimbra
Date: April 26-28 April 201
CNC.IBILI members involved in the organization: Rodrigo Cunha

Organization of the Seminar Mouse and worm models of Machado-Joseph disease: tools for therapy development
Date:April 30, 2015
CNC.IBILI members involved in the organization: Ana Cristina Rego

May 2015

Seminar "Biology of Cell Death in Disease: from Associations to Interactions"
Date: May 1, 2015
CNC.IBILI members involved in the organization: Paulo Oliveira

Organization of the Seminar Language in the brain
Date: May 11, 2015
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organization of the Seminar Translational research in Alzheimer's and Parkinson's diseases
Date: May 14, 2015
CNC.IBILI members involved in the organization: Ana Cristina Rego

Workshop "Mitochondria: from Organelle to Patient", part of the Annual Meeting of the European Society of Clinical Investigation, Cluj, Romania
May 27-May 30, 2015
CNC.IBILI members involved in the organization: Paulo Oliveira

June 2015

Doctoral programme Course "Metabolic Basis of Human Diseases"
Date: June 1- 5, 2015
CNC.IBILI members involved in the organization: Paulo Oliveira, Anabela Rolo, Carlos Palmeira

Seminar "Mechanisms of age-related osteoporosis: the role of ROS and FoxOs"
Date: June 6, 2015
CNC.IBILI members involved in the organization: Vilma Sardão

Oxygen Club of California World Congress (OCC 2015). Oxidants and Antioxidants in Biology
Date: June 24-26, 2015.
CNC.IBILI members involved in the organization: João Laranjinha

July 2015

Organization of the Symposium 'Coffee Break – re-wiring and re-balancing the brain with caffeine at the 9th World Congress of IBRO
Date: 7-11 July 2015
CNC.IBILI members involved in the organization: Rodrigo Cunha

Workshop Cardiostem Project: Engineered cardiac tissues and stem cell-based therapies for cardiovascular applications at the 8th Lisbon Summer Meeting
Date: 2-4 July 2015
CNC.IBILI members involved in the organization: Lino Ferreira

September 2015

Coordination, Summer School on Computational Biology, Coimbra
Date: 2-11 September, 2015
CNC.IBILI members involved in the organization: Armindo Salvador

From protein structure to biological function through interactomics, an integrated view
Date: 7-11 September 2015
CNC.IBILI members involved in the organization: Isaura Simões, Bruno Manadas

October 2015

Organization of the Seminar Is Huntington disease a developmental disorder?
Date: 2nd October, 2015
CNC.IBILI members involved in the organization: Ana Cristina Rego

Annual Meeting Coração ao Centro 2015
Date: 9-10 October, 2015
CNC.IBILI members involved in the organization: Henrique Girão

Corse Hands On de Imagem Multimodal da Sociedade Portuguesa de Neuroradiologia
Date: Outober de 2015
CNC.IBILI members involved in the organization: Miguel Castelo-Branco

November 2015

Biostatistic Course
Date: November 2-5, 2015
CNC members involved in the organization: Miguel Castelo-Branco

Course Brain structure and function: a multimodal overview, Hands-on laboratory Sessions
Date: November 4, 2015
CNC members involved in the organization: Miguel Castelo-Branco

BIOIMAGING 2015, 4th Symposium in Applied Bioimaging
Date: November 5-6, 2015
CNC members involved in the organization: Miguel Castelo-Branco

December 2015

Member of the Scientific Comittee of the the Congresso de Química Orgânica e Química Terapêutica on "Thinking Organic and Medicinal Chemistry in an inspiring atmosphere SPQ, Porto, Portugal
Date: December 1-3, 2015
CNC.IBILI members involved in the organization: Maria Luisa Sá e Melo

Annual Meeting OF Brain Imaging Network : Methodological Challenges in Systems Neuroscience
Brain Imaging Network of Portugal & CNC.IBILI
Date: December 2, 2015
CNC members involved in the organization: Miguel Castelo-Branco

VII Annual Meeting of IBILI
Date: December 3-4, 2015
CNC.IBILI members involved in the organization: Miguel Castelo-Branco

3º EJIBCE – "Encontro de Jovens Investigadores de Biologia Computacional e Estrutural", Coimbra, Portugal
Date: December 18th, 2015
CNC.IBILI members involved in the organization: Irina Moreira

GRADUATED STUDIES PROGRAMME

During 2015 CNC.IBILI organized 11 Advanced Courses (inserted at the Doctoral Programme in Experimental Biology and Biomedicine - PDBEB at CNC) and hosted 84 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 35 Ph.D. and 89 M.Sc. theses were concluded.

Advanced Courses 2015

Core courses
19-30 January 2015
CNC Technological Platforms

Cancer Epigenetics and Metabolism: Connecting the Dots
2-4 February 2015
Paulo Oliveira

Neuroepigenetics
5-6 February 2015
Ana Luísa Cardoso

Molecular and Cellular Neuroscience
16-27 February 2015
Ana Luísa Carvalho

Cell and Tissue Engineering
9-13 March 2015
Lino Ferreira

Neurodevelopment and Neurodevelopmental disorders
16-20 March 2015
Carlos B Duarte & João Peça

Drug development
6-17 April 2015
Luís P Almeida & João Nuno Moreira

Neurodegenerative disorders
27-30 April 2015
Ana Cristina Rego & Claudia M. F. Pereira

Neuronal circuits and behavior
18-29 May 2015
João Peça

Mitochondria, Metabolism & Disease
1-5 June 2015
João Ramalho-Santos

Core Courses
November 23-26, 2015
CNC Technological Platforms

Seminars

JANUARY

Stem cells and regenerative medicine: are we doing it right?
2015.1.7
Hugo Fernandes
UC-Biotech
Cantanhede, Portugal

How to grow an axon: from cytoskeleton dynamics to axonal transport
2015.1.9
Mónica Sousa
IBMC, University of Porto
Porto, Portugal

The impact of psychostimulants on blood-brain barrier function
2015.1.16
Ana Paula Silva
Institute of Pharmacology and Therapeutics
Institute for Biomedical Imaging and Life Sciences (IBILI)
Faculty of Medicine, University of Coimbra
Coimbra, Portugal

Recent advances and novel clinical applications of extracorporeal life support
2015.1.21
Roberto Roncon
University of Porto
Porto, Portugal

Neurobiology of diabetic neuropathyc pain: from peripheral to central nervous system
2015.1.23
Isaura Tavares
Faculty of Medicine, University of Porto
Porto, Portugal

Biomarkers of osteoarthritis: can imaging and biochemical markers be combined to develop new combination markers for improved patient stratification?
2015.1.23
Ali Mobasheri
Professor of Musculoskeletal Physiology & Head of Department of Pre-Clinical Animal Science &Veterinary Pre-Clinical Studies, University of Surrey, U.K

Hypothalamic dysfunction in obesity: from mice to men
2015.1.27
Licio A. Velloso
Department of Internal Medicine
and Laboratory of Cell Signaling
University of Campinas, Brazil

Cell, Run!!…Energy, Speed, Obstacles and the Finish Line
2015.1.30
Ricardo Pires das Neves
Center for Neuroscience and Cell Biology (CNC), UC-Biotech
University of Coimbra

FEBRUARY

The role of the Lipocalin Apolipoprotein D in the glial response to injury
2015.2.5
Diego Sanchez
Instituto de Biología y Genética Molecular
Faculty of Medicine
University of Valladolid
Valladolid, Spain

Multiscale molecular modeling and simulation: an increasingly indispensable tool in materials R&D
2015.2.5
Pedro Simões
CIEPQPF/DEQ, FCTUC
Coimbra, Portugal

Roles of cytoskeleton in hippocampal synaptic plasticity
2015.2.6
Yasunori Hayashi
Brain Science Institute, RIKEN
Saitama, Japan

Role of 3D chromatin organization in neuronal gene expression and plasticity
2015.2.6
Angel Barco
Neurosciences Institute (UMH-CSIC)
Alicante, Spain

Long-term Plasticity of Neocortical GABAergic Synapses
2015.2.11
Alberto Bacci
Brain and Spine Institute, Paris, France

AKT signaling in cancer: from human to mouse
2015.2.13
Donatella Malanga
Department of Experimental and Clinical Medicine Magna Græcia,
University of Catanzaro
Catanzaro, Italy

Adhesives for tissue repair: from the bench to the bedside
2015.2.13
Maria Pereira
Gecko Biomedical,
Paris, France

Ser or Leu? Establishing the missing links between genetic code alterations and virulence in a human pathogen
2015.2.20
Sandra M. Ribeiro
IBMC, University of Porto
Porto, Portugal

Running exercise boosts the depressive-like mood from methamphetamine-injected mice
2015.2.27
Frederico Pereira
Institute of Pharmacology and Therapeutics
Institute for Biomedical Imaging and Life Sciences (IBILI)
Faculty of Medicine, University of Coimbra
Coimbra, Portugal

MARCH

Biomedical applications of AFM-based force spectroscopy: from cardiovascular risk to dengue virus replication
2015.3.4
Nuno Santos
IMM, University of Lisbon
Lisbon, Portugal

NMR metabolomics in cancer research
2015.3.6
Ana Gil
CICECO, Department of Chemistry
University of Aveiro.
Aveiro, Portugal

Mechanisms of cell fate decisions in the developing nervous system: lessons from the retina
2015.3.13
Michel Cayouette
Institut de Recherches Cliniques de Montréal
Montreal, Canada

Antioxidant Therapy: Lights and Shadows
2015.3.18
Fernanda Borges
University of Porto
Porto, Portugal

APRIL

Epigenetic regulation of pluripotent and oligodendrocyte progenitor cell states
2015.4.7
Gonçalo Castelo Branco
Karolinska University
Stockholm, Sweden

Harnessing the potential of miRNAs in Alzheimers disease
2015.4.10
Ana Luisa Cardoso
Center for Neuroscience and Cell Biology (CNC)
University of Coimbra
Coimbra, Portugal

The molecular mechanisms of memory persistence: imaging how single synapses learn in real time
2015.4.15
Miguel Bosch
The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, MIT, Cambridge, US
Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain

Investigating the contribution of endocytic trafficking defects to Alzheimer s disease development
2015.4.17
Cláudia G. Almeida
CEDOC, NOVA Medical School
New University of Lisbon
Lisbon, Portugal

Sirtuin 2 as a novel regulator of insulin sensitivity
2015.4.24
Pedro Gomes
Center for Neuroscience and Cell Biology (CNC)
University of Coimbra
Coimbra, Portugal

Molecules, cells and stiffness of tissues
2015.4.29
Paula Oliveira
Department of Mathematics
University of Coimbra
Coimbra, Portugal

Mouse and worm models of Machado-Joseph disease: tools for therapy development
2015.4.30
Patrícia Maciel
ICVS, U. Minho
Braga, Portugal

MAY

FluidFM and ARTIDIS – Next-Level Nanotechnology Tools
2015.5.5
Marco Portalupi
Nanosurf AG

Endoplasmic reticulum stress in the Drosophila eye
2015.5.8
Pedro Domingos
ITQB, UNL
Lisbon, Portugal

Structure-based approaches for biotechnology
2015.5.13
Ricardo Pires
CNC, Portugal

Oxytocin, excitatory-inhibitory balance, and social behavior
2015.5.15
Robert Froemke
Skirball Institute of Biomolecular Medicine, New York University School of Medicine

Transplantation of cerebellar neural stem cells improves motor coordination and neuropathology in Machado-Joseph disease mice
2015.5.15
Liliana Mendonça
CNC, Portugal

Genetic and epigenetic factors that modulate neuro- and glia-plasticity: relevance for depression
2015.5.19
Luisa Pinto
ICVS, School of Health Sciences, University of Minho

Dopaminergic modulation of cognitive processing in pain
2015.5.20
Vasco Galhardo
I3S, Faculty of Medicine, University of Porto

In vivo optogenetic manipulation of cerebral vascular responses: decoding communication between neuronal and vascular networks
2015.5.22
Tyler C. Brown
Brown University, Providence, Rhode Island

Brain maps for choice behaviors
2015.5.26
Miguel Remondes
Instituto de Medicina Molecular (IMM), Faculty of Medicine, University of Lisbon

Materials for Medicinal Chemistry: Some Case Studies
2015.5.27
João Rocha
Institute of Materials (CICECO), University of Aveiro

An amygdala-nucleus accumbens circuit regulates the persistence of fear extinction
2015.5.28
Susana Correia
Massachusetts Institute of Technology (MIT), Cambridge, MA, US

JUNE

Eat me! Mitochondria morphology and mitophagy in health and disease
2015.6.1
Elena Ziviani
Univ. Padova, Italy

Mitochondria: from structure to function
2015.6.1
Elena Ziviani
Univ. Padova, Italy

Biology of Cell Death in Disease: from Associations to Interactions
2015.6.1
Cecília Rodrigues
Faculty of Pharmacy, University of Lisbon

Efficient communication between cardiac cells is vital to maintain heart homeostasis
2015.6.2
Henrique Girão
IBILI

Targeting dysfunctional HDL metabolism to reduce residual cardiovascular risk
2015.6.2
Flávio Reis
IBILI

Structure-based approaches for biotechnology
2015.6.5
Ricardo Pires
Center for Neuroscience and Cell Biology

Investigating Merkel cells specification during Embryonic Development
2015.6.8
Carolina Perdigoto
Icahn School of Medicine at Mount Sinai, New York, USA

Mechanisms of age-related osteoporosis: the role of ROS and FoxOs
2015.6.9
Maria Schuller Almeida
Division of Endocrinology and Metabolism - Center for Osteoporosis and Metabolic Bone Diseases
Department of internal Medicine
University of Arkansas for Medical Sciences - Little Rock, Arkansas, USA

Programming Definitive Hematopoiesis
2015.6.11
Filipe Pereira
Center for Neuroscience and Cell Biology (CNC)
UC- Biotech

Neuroprotective potential of phenolic sulfates, abundant bioavailable polyphenol metabolites
2015.6.12
Claudia Santos
IBET/ITQB, New University of Lisbon

A new job for an old acquaintance. Gap junction protein Connexin43 mediates intercellular communication via exosomes
2015.6.19
Henrique Girão
Institute for Biomedical Imaging and Life Sciences (IBILI)

Unraveling the role of mesenchymal stem cells secretome in CNS regenerative medicine
2015.6.26
António Salgado
Life and Health Sciences Research Institute (ICVS)
School of Health Sciences, University of Minho

The Quest for the Thymus. Thymic Epithelial Cell differentiation and Function: The foundation of Immunity and Tolerance Induction
2015.6.26
Nuno Lages Alves
Institute for Molecular and Cell Biology (IBMC)
University of Porto

JULY

Seminários Talk@Biotech "Do Ampliseq ao Open Array Digital"
2015.7.1
João Caldeira
Life Sciences Solutions, Thermo Fisher Scientific

Exploring high-throughput screening as a functional genomics tool in biomedicine
2015.7.17
Miguel Mano
Center for Neuroscience and Cell Biology
University of Coimbra

β-adrenoceptors signaling in the heart under stress
2015.7.15
Regina Celia Spadari
Federal University of Sao Paulo, Brasil

Involvement of mitochondria in the neurotoxicity of ecstasy
2015.7.10
Felix Carvalho
UCIBIO/REQUIMTE
Faculty of Pharmacy, University of Porto

Biology of cell death in liver disease: an evolving interaction
2015.7.8
Cecília Rodrigues
Research Institute and Pharmaceutical Sciences, iMed.Ulisboa
Faculty of Pharmacy, University of Lisbon

Structural analysis of Protein-based interactions
2015.7.3
Irina Moreira
Center for Neuroscience and Cell Biology, University of Coimbra

Rhocking glia and other tunes
2015.7.24
João Relvas
Institute for Molecular and Cell Biology
University of Porto

SEPTEMBER

AMPA Receptor intracellular transport and synaptic physiology
2015.9.9
Francoise Coussen
CNRS, Interdisciplinary Institute for Neuroscience
University of Bordeaux, Bordeaux France

Consequenses of Inflamation on functional recovery after stroke
2015.9.11
Karsten Ruscher
Laboratory for Experimental Brain Research
University of Lund, Sweden

Moving IP from Portuguese Universities to real businesses: a smooth or a bumpy road? - The case of PROBLAD@CEV/CONVERDE
2015.9.16
Sara Monteiro
Converde, Cantanhede

Bio-engeneering strategies to modulate adult stem cell fate
2015.9.18
Hugo Fernandes
Center for Neuroscience and Cell Biology
University of Coimbra

Bio-engeneering strategies to modulate adult stem cell fate
2015.9.25
Rogério Ribeiro
APDP - Portuguese Diabetes Association, Lisbon

Bioorganic piezoelectric materials: stucture, properties, applications
2015.9.30
Andrei Kholkin
Centre for Research in Ceramics & Composite Materials (CICECO)
University of Aveiro

OCTOBER

Is Huntington disease a developmental disorder?
2015.10.2
Sandrine Humbert
Grenoble Institute of Neurosciences, GIN - INSERM U836 -
University Joseph Fourier, La Tronche, France

Lipidomics, towards understanding the role of glycolipids in central nervous system related diseases
2015.10.9
Maria do Rosário Domingues
Department of Chemistry, University of Aveiro

Why asymptomatic bacterial colonization matters
2015.10.14
Fernanda Rodrigues
Pedriatric Hospital, CHUC
Faculty, of Medicine, University of Coimbra

The impact of psychostimulants on blood-brainbarrier function
2015.10.16
Ana Paula Silva
IBILI, Faculty od Medicine
University of Coimbra

Critical time windows of CGG permutation expression in Fragile X-associated tremor/ataxia syndrome
2015.10.16
Mónica Santos
Department of Genetics and Molecular Neurobiology, Institute of Biology
Otto-von-Guericke-University, Magdeburg, Germany

Synthetic nucleic acids technologies and therapeutic applications
2015.10.23
Pedro Moreno
INEB, Faculty of Porto

Deregulation of Circadian time and its Correlation with Tumour Progression & Anion Transport in Lysosomal Function and Cell Volume Regulation: From Biophysics Physiology
2015.10.28
Angela Relógio
Institute for Theoretical Biology Charité Medical University of Berlin, Germany
&
Tobias Stauber
Institute of Chemistry and Biochemistry Freie Universitaet Berlin , Germany

Nutrition-modulated metabolic stress response in aquatic organisms
2015.10.28
Leonardo Magnoni
CIIMAR
University of Porto

Making a hematopoietic stem cell
2015.10.30
Filipe Pereira
Center for Neuroscience and Cell Biology
UC-Biotech

NOVEMBER

Molecular Mechanisms of Diastolic Dysfunction
2015.11.10
Adelino Leite-Moreira
Medical School, University of Porto
& S. João Hospital

Modulation of Cell steaminess and differentiation by biochemical and mechanical factors
2015.11.13
Mário Grãos
CNC/ UC-Biotech
University of Coimbra

Methamphetamine at the cytoskeletal level: morphologic, molecular and behavioural effects
2015.11.6
Teresa Summavielle
IBMC, University of Porto

Leishmania peroxiredoxins
2015.11.18
Ana Tomás
IBMC, University of Porto

Maternal nutrition: beyond the genome, beyond the womb
2015.11.20
Elisa Keating
CINTESIS - Center for Health Technology
and Services Research, Faculty of Medicine, University of Porto

Melatonin antiproliferative effects require active mitochondrial function in embryonal carcinoma cells
2015.11.27
Ignacio Vega-Naredo
CNC-UC/Biotech
University of Coimbra

DECEMBER

Vaccine against multi-resistant bacteria
2015.12.2
Pedro Madureira
Immunethep, Biocant Park

Loss of mitotic fitness during human ageing
2015.12.4
Elsa Logarinho
IBMC, University of Porto

Biology of Tumor Exosomes
2015.12.11
Sónia Melo
Faculty of Medicine, University of Porto, Institute for Research and Innovation in Health (I3S)

StemCell2MAX - Neurotrophic factors control HSC survival and transplantation
2015.12.15
CEO: Maria Brandão de Vasconcelos & CSO: Henrique Veiga-Fernandes
Stem2Max, Biocant Park

PHD THESIS CONCLUDED IN 2015

Ana Carla Lima Nunes
Estudo do efeito neuroprotetor da berberina sobre o dano neuronal, comportamento motor e memória de ratos com degeneração nidro-estriatal por 6-OHDA
2015
Supervisors: Rodrigo Cunha

Ana Patrícia Domingues
Parto Prematuro – estudo epidemiológico e genético. O envolvimento do gene HBD1
April 29, 2015
Supervisors: Mª Manuela Grazina

Ana Pinho
Bases neurais dos processos criativos na música
2015

Ana Teresa de Oliveira Rufino
Glucose sensing and modulation of human chondrocyte functions by hyperglycemia: relevance as pharmacological targets for diabetes–associated osteoarthritis
January 23, 2015
Supervisors: Alexandrina Mendes, Carlos Cavaleiro

Andreia Adrião
MEF2: Expression, regulation and interaction with target genes in health and diseases
December 10, 2015
Co-Supervisor: Mª Manuela Grazina

Andreia Alexandra Ribeiro Freitas
Development and Validation of Analytical Methodologies for the Determination of Antibiotics in Food of Animal Origin for Human Consumption
July 28, 2015
Supervisors: Fernando Ramos

Bárbara Oliveiros
Técnicas de Classificação, Diagnóstico e Avaliação de Risco em Doenças com Compromisso da Visão
June 19, 2015
Supervisors: Miguel Castelo-Branco, Joaquim Murta

Bruno Graça
Cardiovascular magnetic resonance and computed tomography imaging for the assessment of cardiovascular complications of type 2 diabetes mellitus
April 6, 2015
Supervisors: Filipe Caseiro Alves, Miguel Castelo-Branco, Maria João Ferreira

Carla Maria Nunes Lopes
Characterization of human stem cells and therapeutic strategies involving IGF-1 and shRNA in Huntington's disease
October 2 , 2015
Supervisors: Ana Cristina Rego

Carla Paiva
Human sperm motility: Proteins and metabolites towards the same journey's end
July 30, 2015
Supervisors: João Ramalho-Santos

Carlos A Matos
Regulation of ataxin-3 by phosphorylation: relevance for Machado-Joseph Disease
February 2015
Supervisors: Ana Luisa Carvalho

Catarina Mateus
Novos biomarcadores no glaucoma e neuropatias ópticas hereditárias: implicações para o diagnóstico precoce e monitorização da evolução clínica
June 23, 2015
Supervisors: Miguel Castelo-Branco

Cristina Susana Barcia
Proteasas de polen de Acacia caven y su importancia en alergias
2015

Daniela Luís
Regulação genética do receptor 5HT2A na Demência Frontotemporal.
February 19, 2015
Supervisors: Mª Manuela Grazina

Diana Margarida Martins Carvalho
Identification of the intragenic copy number alterations and fusion genes in pediatric high grade glioma
February 20, 2015
Supervisors: Maria Celeste Lopes, Rui Reis

Diogo Silva
Desenvolvimento de um método analítico para quantificação de catecolaminas por LC-MS/MS
2015
Supervisor: Bruno Manadas

Eunice Maria Campos Ruas Matoso
Desequilíbrios genómicos nas patologias do desenvolvimento e do comportamento
2015
Supervisors: Isabel Carreira

Filipa Carvalho
Clarification of the Mitochondrial Role in the Cardiotoxicity of Doxorubicin Using a Whole Heart Perfusion System - Impact of Different Doxorubicin Treatment Regimen
Febraury 26, 2015
Supervisors: Paulo Oliveira, Rui Carvalho

Filipe Carvalho Matheus
Dissociando anedonia de outros sintomas da depressão na doença de Parkinson em um modelo experimental em ratos: papel do estriado dorsolateral e do córtex pré-frontal
2015
Supervisors: Rodrigo Cunha

Isabel Maria Aguilar Carvalho Andrade Ramalho
Contributo dos marcadores de síntese e de absorção do colesterol na terapêutica hipocolesteolemiante
July 27 2015
Supervisors: Fernando Ramos

Joana Ribeiro Guedes
Inflammation in Alzheimer's disease: miRNA deregulation and modulation in the mononuclear phagocyte system
December 22, 2015
Supervisors: Mª Conceição P. Lima, Ana Luisa Cardoso

João Castelhano
Neural substrates of 2D/3D object perception: a combined EEG/fMRI approach
January 6, 2015
Supervisors: Miguel Castelo-Branco

João Filipe da Costa Martins
Modulation of Ganglion Cell Function and Implications for Neuroprotection
May 29, 2015
Supervisors: Francisco Ambrósio, Miguel Castelo-Branco

Ludgero Tavares
Unraveling cancer metabolism through flux analysis and metabolic engineering
July 29 July, 2015
Supervisors: Paulo Oliveira, Rui Carvalho

Maria Joana Guimarães Pinto
Presynaptic formation an function under the control of the ubiquitin and the proteasome
December 17, 2015
Supervisors: Ramiro Almeida, Ana Luisa Carvalho

Marília Cordeiro
Generation of a VASA/GDF-9/ZP3-promoter driven trple transgenetic reporter mouse line as a tool to study ovarian dynamics
March 23, 2015
Supervisors: João Ramalho-Santos

Marta Isabel Heitor Cerejo
Contribution to drug discovery and development for tauopathies using yeast as a model
December 16, 2015
Supervisors: Ana Cristina Rego

Marta Regina Santos do Carmo
Efeito neuroprotetor do antagonismo dos receptores P2X7 no parkinsonismo experimental induzido por 6-OHDA
2015
Supervisors: Rodrigo Cunha

Natália Sofia Cláudia António
Endothelial progenitor stem cells of diabetic patients with acute coronary syndromes: effects of antidiabetic and lipid lowering drugs
January 28, 2015
Supervisors: Carlos Fontes Ribeiro, Lino Gonçalves, Rosa Fernandes

Nuno André Carvalho Fonseca
Targeted intracellular delivery of synergistic drug combinations: tackling drug resistance in human breast
July 17, 2015
Supervisors: João Nuno Moreira, Sergio Simões

Patrícia Henriques Domingues
Patterns of protein expression and cytogenetic alterations in meningiomas: relationship with clinical and biological features of the disease
January 9, 2015
Supervisors: Alberto Órfão, Maria Celeste Lopes

Paula Banca
Bases Neurais da Neurose Obsessivo Compulsiva
February 12,2015
Supervisors: Miguel Castelo-Branco, Valerie Voon

Rita Margarida de Almeida Santos Videira
Pesquisa de Inibidores Enzimáticos em Óleos Essenciais: Estudo da Actividade em BACE-1, uma Protease Aspártica Envolvida na Doença de Alzheimer
December 14, 2015
Supervisors: Carlos Cavaleiro, Carlos Faro

Sara Varela Amaral
Desafios na inovação da comunicação em ciência em Portugal
December 22, 2015
Supervisors: Teresa Girão, João Ramalho-Santos

Vera Mónica Vinha Tavares Calhau
Virulence factors associated with antimicrobial resistance determinants among Escherichia coli and Klebsiella spp. isolated from clinical samples and environment
April 23, 2015
Supervisors: Gabriela Silva, Nuno Mendonça

MASTER THESIS

Adriana Leal
Neuroengineering contributions in Parkinson tremor characterization using accelerometry and surface electromyography
February 2015
Supervisor: Miguel Castelo-Branco

Ana Carolina Martins
Coagulação Intravascular Disseminada – Estado da arte
2015
Supervisors: Ana Bela Sarmento Ribeiro

Ana Catarina Martins Cardoso
Hidrolases de Agrocybe aegerita e Macrolepiota procera: Purificação parcial e caracterização
2015

Ana Claudia Pica-Milho
Desenvolvimento de uma vacina oral contra Giardia Lamblia
2015
Supervisors: Olga Borges

Ana Filipa Sousa
Anemia Megaloblástica – Da fisiopatologia à terapêutica
2015

Ana Isabel Ramos Martins
Aplastic Anemia - From pathophysiology to diagnosis, management and treatment
2015
Supervisors: Ana Bela Sarmento Ribeiro

Ana Marta Silva
Role of mitochondrial p66Shc in nefazodone-induced mitochondrial toxicity on HepG2 cells
2015
Supervisor: Paulo Oliveira

Ana Rita Cruz
Gene Therapy-Based Strategies for Glioblastoma Towards Chemosensitization: Use of Gemini Surfactants as Drug Delivery Systems
2015
Supervisors: Luís Pereira de Almeida

Ana Rita Rocha
The role of BMP7 in wound healing in diabetes
2015

Ana Sousa
Efficient and synergistic gene delivery mediated by a combined polymeric-based nanosystem
2015

André Duarte Morais Guerreiro de Almeida Borralho
Contribuição para desenvolvimento de suplemento alimentar proteico e antioxidante produzido a partir de subprodutos da indústria alimentar
September 2015
Supervisor: Fernando Ramos

André Ferreira
Pathophysiology of Persistent Doxorubicin Cardiotoxicity: a Mitochondrial-Epigenetics Link
2015
Supervisor: Paulo Oliveira

André Ferreira Santos
Desenvolvimento de uma base de dados relacional para registo e pesquisa de dados de array CGH
2015
Supervisor: Joana Barbosa Melo

Andreia Filipa Simões Batista
Desenvolvimento de metodologias de biologia molecular para a deteção de Cynara scolymus e Silybum marianum em suplementos alimentares à base de plantas
July 2015
Supervisor: Fernando Ramos

Annalisa Manganielo
Role of purinergic receptors in the establishment of synaptic connectivity
2015
Supervisor: Rodrigo Cunha

Ayrlana da Silva Fonseca
Avaliação de compostos bioativos em farinhas de trigo melhoradas geneticamente: Fibra e arabinoxilanos
July, 2015
Supervisor: Fernando Ramos

Carolina Martins de Oliveira Alves
White Matter Perfusion Quantification with Single Voxel Arterial Spin Labeling
February 2015
Supervisor: Miguel Castelo-Branco

Carolina Rodrigues
Modulation of mitochondrial stress response by Sestrin 2
2015
Supervisor: Anabela Pinto Rolo

Carolina Silva
Proteomic characterization of peripheral blood mononuclear cells
2015
Supervisor: Bruno Manadas

Catarina Sofia Rodrigues Carmo
Role of sirtuin 3 on mitochondrial dynamics in Huntington's disease striatal cells
December 14, 2015
Supervisors: Ana Cristina Rego

Cátia Filipa Mota Nunes
Sequence optimization in pseudo-continuous arterial spin labeling
February 2015
Supervisor: Miguel Castelo-Branco

Catia Marques
Quantifying triglyceride futile cycling with deuterated water and ^{2}H NMR analysis of glycerol ^{2}H enrichment
September 24, 2015
Supervisor: John Jones

Clara Matos
Sleep Patterns In Neurofibromatosis Type 1: A Questionnaire Based Approach
June 2015
Supervisor: Miguel Castelo-Branco

Daniela Almeida
Metabolic Changes underlying caloric restriction and diabetes impact upon intercellular communication activity in the heart
September 14, 2015
Supervisor: Henrique Girão, Mª João Pinho

Daniela Costa
Molecular and biochemical characterization of a rare glucokinase with a cryptic function in environmental mycobacteria
June 17, 2015
Supervisor: Nuno Empadinhas

Delfino Vubil
Molecular characterization of Klebsiella pneumoniae beta-lactamases from patients admitted to the University Hospital of Coimbra
July 17, 2015
Supervisor: Gabriela Jorge da Silva

Diana Alcaide
Behavioral And Neuroimaging Approaches As Tools To Dissect Non-Motor Manifestations In Parkinson´S Disease: A Focus On The Visual System
June 2015

Diana Gonçalves
O Cérebro e a Magia: Mecanismos Neuroquímicos
May 26, 2015
Supervisor: Mª Manuela Grazina

Edmilson António Borges Semedo
Semi-síntese de novos derivados flavonóides bioactivos. Estudo de reacções de acilação regiosselectiva da rutina sob catálise enzimática
March 27, 2015
Supervisors: Jorge António Ribeiro Salvador and Maria Manuel Cruz Silva

Edson Vladimiro Alves Cabral dos Santos
Qualidade Microbiológica e Físico – Química de Queijo Fresco de Leite de Cabra produzido em Cabo Verde
July 2015
Supervisor: Fernando Ramos

Fabiana Soares
Antifungal, antibacterial and antiviral activity of Chodracanthus teedei var. lusitanicus (Gigartinaceae, Rhodophyta)
2015
Supervisor: Teresa Gonçalves

Filipa Ferreira de Brito
Pharmacological modulation of mutant ataxin-3 translation and it potential therapeutic effect in Machado-Joseph disease
September 11, 2015
Supervisors: Clévio Nóbrega, Henrique Girão

Guilherme Alvarinhas de Assis Loureiro
Effects of vitamin D deficiency in the diabetic brain: focus on insulin signaling
2015
Supervisor: Paula Moreira, António Moreno

Helena Leal
Impact of obesity on hypothalamic microRNAS: from pathophysiology to gene therapy approach
September 2015
Supervisors: Ligia Ferreira

Inês Margarida Dias Cabaço Amaral
Adenosine A_{2A} receptors and stress-induced alterations in the rat ventral striatum
September 15, 2015
Supervisors: Paula Canas

Inês Saragoça Dias
The role of GHSR1 in dentate gyrus adult neurogenesis*
September 11, 2015
Supervisors: Ana Cristina Rego

Iolanda Coutinho
Trombocitopenia Imune Primária – Uma revisão
2015
Supervisors: Ana Bela Sarmento Ribeiro

Joana Maria Teixeira Fragoso
Avaliação in vivo de receptores de estrogénios no cancro da mama
June 2015

Joana de Matos Rodrigues
Dos Genes à radiorresistência no cancro da cabeça e do pescoço
December, 2015
Supervisor: Isabel Carreira

João Calmeiro
Optogenetics and Biotechnology: Production and in vitro characterization of Ab-Initio designed Channelrhodopsin-2 mutants
November 2015
Supervisors: João Peça-Silvestre

João Génio Ramos
Morphometric analyses of brain atrophy in diabetes type 2: evidence from both T1 and T2 MRI
June 2015

Jorge Miguel Alves Silva
Bioactive properties of Daucuscarotasubsp. carota phenolic-enriched extracts and essential oils
July 2015
Supervisor: Ligia Salgueiro, Susana Cardoso

Kátia Silva
Mitochondria-directed Antioxidant as Anticancer Agents
2015
Supervisor: Paulo Oliveira

Laura Nunes Soares Sequeira Salavessa
Endocytic trafficking mechanisms in Alzheimer's disease: role of the actin regulators Bin1 and CD2AP
June 25, 2015
Supervisor: Claudia Pereira

Leisa Nélida Pinto Évora
Bioactivity of essential oils obtained from Rosmarinus officinalis L
July 2015
Supervisor: Mª Teresa Cruz Rosete, Ligia Salgueiro Couto

Liliana Gonçalves Grazina
Deteção e quantificação de soja geneticamente modificada em alimentos por técnicas baseadas na reação em cadeia da polimerase
July 2015
Supervisor: Fernando Ramos

Liliana Santos
Sirtuin 2 in hypothalamus: an emerging target in insulin resistance?
July 2015
Supervisors: António Pedro Gomes

Luís Oliveira
O papel das adipocitocinas nas Gamapatias Monoclonais
2015

Mafalda Alves Fernandes Bispo
Galactodendritic silicon phthalocyanines for bladder cancer treatment
2015

Manuela Cerqueira
Mechanisms underlying peripheral insulin resistance in a rat model of pre-diabetes
September 23, 2015
Supervisor: Eugenia Carvalho

Manuela Santos Pereira
Synthesis and evaluation of antimicrobial activity of semi-shyntetictriterpenoids
March 27, 2015
Supervisors: Jorge António Ribeiro Salvador and Gabriela Jorge da Silva

Marcelo Dias Catarino
Phenolic characterization and evaluation of the antioxidant and anti-inflammatory properties of Eriocephalus africanus and Geranium robertianum extracts
2015
Supervisor: Susana Cardoso, Mª Teresa Cruz Rosete

Marcelo Ribeiro
Metabolism and possible tole of sirtuin 3 in mESC
September 9, 2015
Supervisor: João Ramalho-Santos

Mariagrazia Lanzillo
Impact of hyperglycemia on neurogenesis in Alzheimer's disease
2015
Supervisors: Ana Cristina Rego

Mariana Lucas
Processamento executivo na Perturbação do Espetro do Autismo: Análise de uma tarefa de controlo inibitório e relação com frequência e tipo de comportamento repetitivo e restrito
January 2015

Mariana Ribeiro
The interplay between genetic and epigenetic in myelodysplasic syndromes
2015
Supervisors: Ana Bela Sarmento Ribeiro, João Nuno Moreira

Mário Luís Nôro Laço
Increased brain levels of hydrogen peroxide in a transgenic mouse model of Huntington's disease
May 26, 2015
Supervisors: Ana Cristina Rego

Maura de Rosa
Evaluation of protein levels in mitochondrial and cytosolic fractions of YAC128 mice brain cortex: relevance for oxidative stress in Huntington´s disease
2015
Supervisors: Ana Cristina Rego

Milena da Motta Xavier
Perfil de Segurança das Prescrições de antibióticos de uso restrito numa unidade de terapia intensiva pediátrica
July 2015
Supervisor: Ana Fortuna, Marília Rocha

Nancy Ferreira
Optimization of a Viral Culture System to Evaluate Antiviral Activity
2015
Supervisor: Teresa Gonçalves

Nelson Monteiro
A novel MYO7A compound Heterozygous Mutation in a USH1 Portuguese Patient: a Translational Multidisciplinary Study
2015
Supervisor: João Nuno Moreira

Nuno Filipe Gomes Silva
Estudo da Capacidade Antioxidante de Cogumelos Comestíveis
September 2015
Supervisor: Fernando Ramos

Nuno Jordão
Study of the cell surface proteome for the analysis of Parkinson's disease associated DJ-1 mutations
2015
Supervisor: Bruno Manadas

Patrícia Costa
Hemofilias – Uma abordagem actualizada
2015
Supervisors: Ana Bela Sarmento Ribeiro

Paula da Silva
Ketone bodies as brain substrates
January 26, 2015

Paula Susana Lopes Ribeiro da Costa
Steroidal endoperoxides in the synthesis of novel antimalarial hybrids
September 29, 2015
Supervisors*:* Maria Luisa Sá e Melo and Maria Manuel Cruz Silva

Pedro Cunha
On the development of a novel targeted miRNA-based therapy towards glioblastoma
2015

Rafael Azevedo Dias
Role of reactive oxygen species in inflammasome activation in microglia under stress conditions
2015

Rafael de Almeida Paiva
Cardiac ischemia brings communication noise into the conversation between cardiomyocytes and macrophages
September 14, 2015
Supervisor: Henrique Girão, Teresa Cruz

Raquel Costa
The role of miR-29b in the regulation of progranulin and DNA methyltransferases 3A and 3B: Therapeutic potential in Glioblastoma
2015

Raquel Alexandra Fernandes Teixeira
Prevalência de S. aurus resistente à meticilina numa superfície alimentar da Guarda
July 2015
Supervisor: Ligia Salgueiro Couto

Raquel Inês Tavares
Análise do genoma mitocondrial na DLFT: contribuição dos rRNRs e correlação com o fenótipo bioquímico
September 16, 2015
Supervisor: Mª Manuela Grazina

Ricardo Vieira
Alteration in $GABA_AR$ trafficking in epilepsy
September 2015
Supervisors: Carlos Duarte

Rita Carvalho
Exosomes release by cardiomyocytes modulate angiogenic response in heart ischemia
2015

Rita Gouveia
The Role Of EEG As A Biomarker Tool In Assessing Plastic Changes Induced By Transcraneal Magnetic Stimulation In Stroke Patients
June 2015
Supervisor: Miguel Castelo-Branco

Rita Sá Ferreira
Interaction between Cx43 and LC3 directs Gap Junctions to ubiquitin-independent autophagy degradation
September 14, 2015
Supervisor: Henrique Girão, Steve Catarino

Rui Felix Batista Fernandes
Avaliação do potencial de revestimentos de origem proteica incorporados com extractos e/ou óleo essencial de plantas aromáticas na preservação de produtos cárneos
July 2015
Supervisor: Lígia Salgueiro Couto

Rute Araújo
Impacto de uma Nova Estratégia Nanoterapêutica em Células Estaminais Tumorais de Cancro do Pulmão
2015
Supervisors: João Nuno Moreira

Sabine Cardoso Almeida
Leucemia promielocítica Aguda - Abordagem clínica, diagnóstica e terapêutica
2015

Sara Beatriz Gomes Fernandes
Adenosine A_{2A} receptors role in stress-induced neurobiological modifications
September 14, 2015
Supervisors: Ricardo Rodrigues

Sara Patrícia Castelo Branco Moreira Dias
Síntese de fármacos híbridos antimaláricos. Uma nova estratégia terapêutica envolvendo esteróides
February 27, 2015
Supervisor: Maria Luisa Sá e Melo

Sara Petronilo
The effect of spliceosome inhibitors in hematological malignancies - A study in cell lines
2015

Sara Sousa Fernandes
Influência do perfil genético de transportadores ABC no desenvolvimento de neoplasias mieloides
2015

Sara Veiga
Avaliação da expressão de microRNAs na Síndrome Mielodisplásica – implicações no diagnóstico e terapêutica
2015
Supervisors: Ana Bela Sarmento Ribeiro, João Nuno Moreira

Sofia Matos Lisboa
Characterization of the Genetic and Epigenetic of Tongue Squamous Cell Carcinoma
July, 2015.
Supervisor: Isabel Carreira

Sónia Raquel Nunes Henriques
Microglia as cellular targets for immunomodulation during neurodevelopment
2015
Rodrigo Cunha

Susana Cristina Xavier Lages de Oliveira
Estudo de Monitorização farmacocinética de amicacina no tratamento de infeções nosocomiais por Acinetobacter baumanni
January 2015
Supervisor: Ana Fortuna, Amilcar Falcão

Vanessa Alexandra Freire Marques
Genetic Epigenetic Characterization of laryngeal carcinoma
July, 2015.
Supervisor: Isabel Carreira

Vanessa Ventura
Identification of biomarkers for Schizophrenia disease
2015
Supervisor: Bruno Manadas

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.

OUTREACH PROGRAMME

Outreach / Science and Society

Science Communication Office
Coordinator: Cláudia Cavadas, PhD.

The Science Communication Office is responsible for the cultural, textual, and visual mediation of CNC scientific work, fostering a social appropriation of the scientific world, contextualized in the different perspectives of our extra/intra/interdisciplinary publics. The mediation is conducted in a macro-level through: i) a process of public relations with regional, national and international media, in coordination with the University of Coimbra Press Office; ii) the internet (social media, CNC website, e-mail) schools, associations, science centers, university institutions and local science communication events inserted in national strategies (of Ciência Viva - National Agency for Scientific and Technological Culture, and Portuguese Society of Neurosciences) or international strategies (Dana Foundation and Federation of European Neuroscience Societies); and the mediation is conducted also in a micro-level within CNC research community

CNC Science Communication Office objectives are;

- to provide public accountability, ethically justified by the public nature of CNC funding;

- to anticipate and resolve (media and institutional) communication crises that compromise the fundamental relationship between science and 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 mediate contextualized scientific knowledge as an investment in a society with a critical thinking about new scientific challenges;

- to create bridges and institutional belonging in CNC members

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 2015, CNC was in the news 1230 times with an advertising value of **2,870,528** Euros. Some examples are available in CNC website (*http://www.cnbc.pt/outreach/outreach00.asp#divNews*).
The online media contributed to 73% for the total number of news about CNC in the media (Figure 1A). The Regional press contributed to 84% of the news about CNC in the press (Figure 1B).

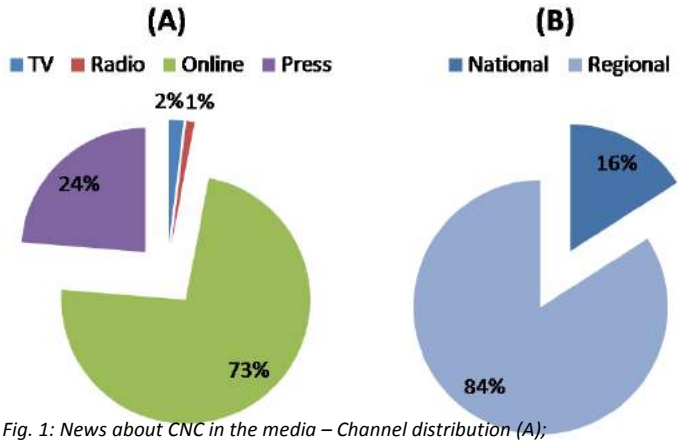


Fig. 1: News about CNC in the media – Channel distribution (A); Press Geography (B)

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 3704 page 'likes' in 2015 (Figure 2), an increase compared to 2014 (in 2014 CNC Facebook page had 2462 "likes"). Moreover, 297 posts were added and it had 471.632 visits in 2015.

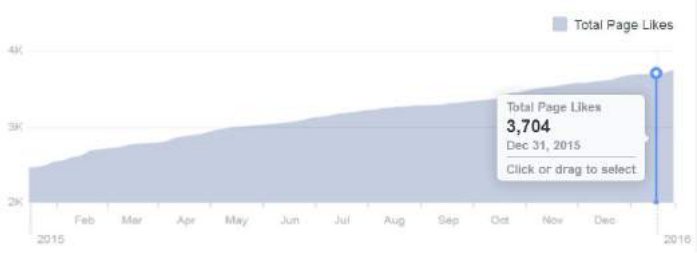


Fig.2: CNC Facebook page "Likes" during 2015

The Science Communication Office promotes an optimization of this networking tool (along with CNC Youtube Channel) for the mediation of CNC research, News, seminars, Science Communication activities, awards and science culture.

Brain Awareness Week 2015, March 14 – 26

The CNC actively participated in the international Brain Awareness Week 2015, supported by Dana Foundation, Federation of European Neuroscience Societies (FENS) and Sociedade Portuguesa de Neurociências, included several events under the title "The Brains Go Around the Town": a) "Brain Buskers" weekend (for families) – Hands-on activities at the biggest shopping center of the Portugal center region (Forum Coimbra): painting brain models; microscopic observations; construction of a neuron model, photos at a "scientific photo boot"; and electrophoresis; b) "Science for all" (for disabled students and elderly people) – Lectures at the *Portuguese Association of Parents and Friends of the Disabled Citizen*, and in two "Senior Universities"; c) "Neuroquiz" (for quiz players & occasional publics) – a public quiz that challenge the participants to explore brain-related issues through appealing themes like art and pop culture; d) "Neuroscientists go to Schools"; (for elementary, middle and high school students) 20 neuroscientists visited 8 schools and 2 science centers giving lectures on brain related subjects; e) "Open Laboratories" (for students and elderly people): CNC's research groups organized visits to their laboratories. Overall, 48 researchers were involved, 1000 estimated audiences reached, and the students were the biggest audience (76%).

Fig. 3: Example of activities organized and performed by CNC researchers during Brain Awareness Week 2015

World Biotech Tour, April 10-11

The World Biotech Tour (WBT) is a multi-year initiative that will bring biotechnology to science centers and museums worldwide. The program, supported by the Association of Science-Technology Centers (ASTC) and Biogen Foundation, is scheduled to run from 2015-2017, with the 2015 cohort in Belgium, Japan, and Portugal. The WBT will increase the impact and visibility of biotechnology among youth and the general public through hands-on and discussion-led learning opportunities. Seven CNC researchers participated in the event held in Pavilhão do Conhecimento in Lisbon, with the following hands-on activities: a) "How to transport DNA to the Cells?"; b) "Substitution of Animal Testing"; c) "Proteins: from Weight to Identity"; d) "Shine of the Proteins and Lottery of the Egg". The initiative reached 2000 people.

Fig. 4: Example of activities organized and performed by CNC researchers during World Biotech Tour, at Pavilhão do Conhecimento (Lisbon)

"Science in the Holidays" Programme 2015 at CNC, July 22-26

Ten Portuguese high school students participated in a one-week internship programme during Summer Holidays, promoted by Ciência Viva Agency. Students were tutored by CNC researchers and included in 5 research groups (Researchers: Anabela Rolo; Cláudia Cavadas; Paulo Oliveira; Ramiro Almeida; Rosa Resende). The students had the opportunity to run several molecular/cell biology techniques as part of short projects, experiencing the daily life of a researcher in CNC facilities and laboratories.

Fig. 5: "Science in the Holidays" Programme for high school students at CNC

Participation of CNC in the European Researchers' Night 2015, September 25

The Science Communication Office of CNC, together with the Science Museum of the University of Coimbra, took part for the 8th time in the organization of the activities of the European Researchers' Night (Figure 6). This initiative is promoted by the European Commission in order to bring the different publics closer to the researchers in an appealing and informal environment. Forty two CNC researchers organized and performed activities for general public, were involved in a "speed-dating" event, and participated in a theatre play, "Luz de Perdição", co-created with the theater company Marionet that focused the theme of 'light' and has been written by the participant researchers. The hands-on activities organized and performed by CNC researchers included: "The Craziest Mitochondrial Races of the World"; "The Shinning Force that Move us"; "Colorful Brain"; "The Paper of Science"; "Where the Sperm Swims?" "Super Stem & Mega Mat: Fighting for a Cure".

Fig. 6: Participation of CNC at the "European Researchers' Night"

Participation of CNC in the Science and Technology Week 2015, November 23-29

CNC, during this week and celebrating the National Day for Scientific Culture, organized lectures and hands-on activities in schools of the Centro Region (Coimbra, Cantanhede, Penacova, Viseu) and visits to the laboratories. The initiative engaged a total of 324 students (from Elementary School, High School and University) and 12 CNC researchers (Figure 7).

Fig. 7: Participation of CNC in the "Science and Technology Week" 2015, November 23-29

Atos de Laboratório, December 18

The Science Communication Office engaged in the organization with Marionet of the theater play "Atos de Laboratório", in the 2015 CNC Annual Meeting, as an internal communication action, that can be viewed online: *https://www.youtube.com/watch?v=kRc8vgHt1rU&feature=youtu.be*. More information about the play: *http://www.cnbc.pt/outreach/outreach00_ac.asp.*

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 husbrandry, for all CNC and FMUC scientists using animals in their research.

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

Animal room – IVC cages (type I)

The Animal House contains a barrier maintained facility, with 8 positive pressurised rooms, which are kept at 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)

Laminar flow chamber

FLOW CYTOMETRY UNIT

Head of Unit: Isabel Nunes Correia

The flow cytometry unit provides scientific and technical support both to CNC and external researchers. Currently, it is equipped with a Becton Dickinson FACSCalibur cell analyser and a Partec CyFlow® Space cell sorter. For researchers wishing to use flow cytometry, the unit offer assistance in planning projects, choosing fluorochromes, analyzing experimental results and presenting data.

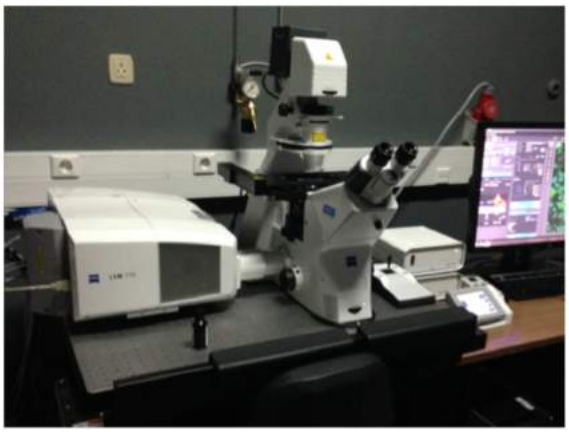
The unit organizes annual flow cytometry seminars with the purpose to initiate new users and make this powerful technology known to all researchers, endeavouring to deepen CNC research.

Since 2007, when the unit was created, the number of users is increasing every year, and presently flow cytometry is an important and central technique for the fulfilment of many CNC investigation projects.

FACSCalibur cell analyzer

MICROSCOPY IMAGING CENTER OF COIMBRA - CNC

Head of Unit: Luísa Cortes



Confocal LSM 710 (34 channels)

The Microscopy Imaging Center of Coimbra, at the Center for Neuroscience and Cell Biology (MICC-CNC), is a open infrastructure where users receive the support needed to carry out conventional and advanced imaging techniques, based on Light Microscopy. MICC-CNC is a reference partner of Carl Zeiss initiative Microscopy Labs@location. Moreover, MICC-CNC is part of the Portuguese Platform for BioImaging (PPBI), and it is the coordinating node of this platform for the Center pole of Portugal. MICC-CNC participates in the EuroBioImaging network, which is an ESFRI initiative.

The MICC has highly skilled and multidisciplinary scientific staff, which is involved in several activities present on the imaging platform, namely:

• Training users to operate confocal microscopes, and fluorescence microscope and implement advanced techniques. First time users receive training by the technician in charge for the equipment.

• Designing robust image analysis and data presentation regimes.

• Organizing advanced courses that provide the PhD and Master students with the fundamentals of light microscopy, fluorescence microscopy, live cell imaging applied to Biomedicine, in the scope of Masters and PhD training courses.

• Testing and specifying new equipment and software.

• Maintaining strong relationships with the microscope manufacturers and service teams.

• Troubleshooting, repairing and overseeing maintenance of the microscopes.

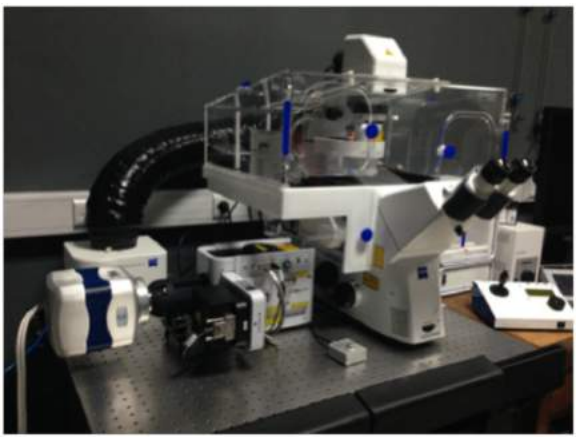
• Responsibility for the safety issues pertaining to microscopes.

• Keeping the information about MICC-CNC updated on the CNC webpage.

• Disseminate the available resources and services on other national technologic platforms, such as SciPort and PPBI webpages.

Confocal Cell Observer Spinning-Disk

Presently, the unit manages two laser scanning confocal microscopes, a spinning disk confocal microscope, a live cell imaging station, a epifluorescence microscope with structure illumination (Apotome2) and stereology analysis (StereoInvestigator), a P.A.L.M. laser microdissection microscope, a single cell calcium imaging system, and other brightfield microscopes. The systems are prepared for advanced applications, including live cell imaging and single cell calcium measurements, enabling the researchers to image dynamic events and molecular interactions. The P.A.L.M. laser microdissection microscope is a perfect tool for the isolation of different cell populations within a sample, allowing it full characterization. The MICC-CNC has dedicated workstations for imaging analysis, with the following software: Neurolucida, Huygens, Matlab, Metafluor, FIJI/ImageJ, and CellProfiler.



Widefield AxioImager Z2 with ApoTome2

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.

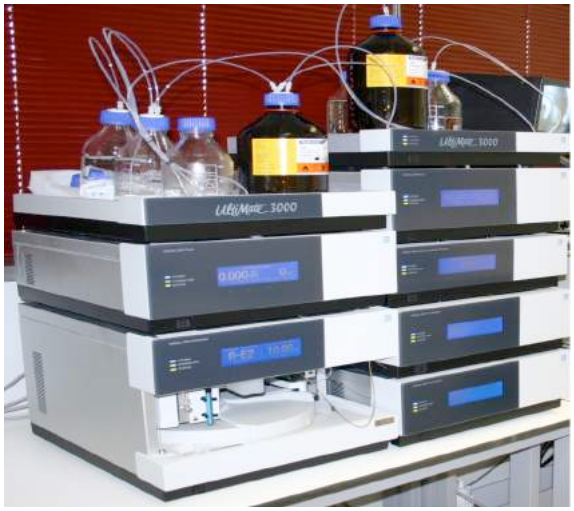
Presently, the Mass Spectrometry Unit is equipped with state of the art technology, namely: a 4000 QTRAP mass spectrometer (Applied Biosystems/MDS Sciex), hybrid triple quadrupole/ion-trap mass spectrometer with capacity of MS3, and a two-dimensional liquid chromatography system Ultimate 3000 (Dionex/LCPackings).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

Coordinator: Manuela Grazina

Certification NP EN ISO 9001:2008

The coordinator of 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 (Clinical Biochemistry Department, Hospital Sant Joan de Déu - Barcelona, Spain).

Biochemical analysis

Mitochondrial Respiratory Chain (MRC) and Krebs cycle enzymes

Biochemical assays related to MRC biogenesis, functioning and maintenance are essential for achieving the probable diagnosis of MRC and Krebs Cycle Diseases.

Thirty-one subjects suspected of Mitochondrial Cytopathy were studied, corresponding to the analysis of 31 samples, in 310 assays, including lymphocytes isolated of peripheral blood (19), muscular (10) and liver (2) biopsies. A MRC deficiency was detected in 20 patients (19%).

Krebs cycle enzymes (fumarase, alfa-ketoglutarate dehydrogenase, malate dehydrogenase, aconitase, isocytrate dehydrogenase) analysis was performed in 3 patients, corresponding to 21 assays. A deficiency of fumarase was found in one of these patients, as previously suspected, according to the clinical manifestations. These tests represent an important set up for improving diagnostic of mitochondrial bioenergetic defects. Control values have been set up to offer these analyses as a service available at LBG.

Analysis of Coenzyme Q10

The equipment available is out of order and the samples were analysed in collaboration with Dr. Rafael Artuch, at Clinical Biochemistry Department, Hospital Sant Joan de Déu - Barcelona, Spain.

Five samples (plasma and muscles) were studied, in 35 assays. A deficiency of CoQ10 content was found in one patient sample.

Detection of Coenzyme Q10 deficiency represents a key tool in diagnosis of MRC diseases (MRCD), since this is the only treatable deficiency in this group of inherited errors of metabolism.

Amino Acid Analysis

The patients investigated were categorized in three clinical conditions: (1) selective screening of metabolic disorder, characterized by either primary or secondary abnormalities in the amino acid profile (2) amino acid profile changes secondary to proximal renal tubular or hepatic dysfunction of any origin; (3) nutritional evaluation of patients with protein restrictive diets.

Until the end of March, we have received 33 samples (26 plasmas and 7 urines) of physiological fluids for amino acid analysis, corresponding to 99 assays. The majority of samples are from children, although less frequently, adults and adolescents are also monitored.

Amino acids analysis is a very important approach in early metabolic disorder diagnosis, and frequently helps to prevent mental retardation or even death.

This service was discontinued in April.

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*: 42** samples (blood - 34, muscle -6 and liver – 2) were received for DNA extraction.

Molecular differential analysis of mitochondrial cytopathies, as a highthrouput 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. Total mtDNA sequencing or gene panel analysis was also performed in selected samples, according to clinic manifestations and results from previous biochemical and/or genetic screening.

Forty-five patients suspected of Mitochondrial Cytopathy were studied, in 2,435 assays, allowing detection of 253 mtDNA alterations. A pathogenic mutation was found in 27 patients.

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 now part of the genetic mitochondrial genome screening. Nuclear genes screening includes 9 genes related to MRC function and or mtDNA biogenesis.

Concerning **mtDNA copy** number assays for depletion screening, we investigated 11 samples of 10 patients, comprising a total of 308 real time PCR assays.

Implementation of analysis for other genes, such as ANT, TK, MPV17 and twinkle has continued, in the attempt of finding the cause for mtDNA depletion or multiple deletions, but limitations in personnel available did not allow the completion of this objective.

Concerning the **screening of *nDNA defects causative of MRCD***, we have screened 20 samples, comprising a total of 2,150 assays.

POLG1 gene was screening in 16 samples of 16 patients. We have identified 128 sequence variations and 3 pathogenic mutations in 3 patients, comprising a total of 2,080 assays.

Screening of **DGUOK gene** (1 sample of 1 patient, 55 assays) did not show any alteration, but it was relevant for genetic diagnosis and genetic counselling.

Three cases (family relatives) were also analysed to confirm mutations detected in index cases.

Staff: Marta Simões, Maria João Santos. Carolina Ribeiro has participated as voluntary. (Cândida Mendes and João Pratas until the end of April, Carla Veríssimo until the end of October)

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 - New assay

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 - New assay

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 the year of 2015, the Neurochemistry Unit has received around 750 blood and 500 CSF samples and has performed the following analysis:

	Blood (Serum/Plasma)	CSF	Urine	Brain extracts	Other extracts
Cytochemistry and electrophoresis	398	398			
IgG Oligoclonal bands	216	216			
Vitamin A/E	198				
Redox Satus	22	4			
Purines & Pyrimidines			1		
Anti-neuronal antibodies	49				
Antiepileptic drugs	6				
ADA2 activity in serum/plasma	78				
CSF levels of 5-MTHF		8			
CSF Tau, p-Tau and Aβ42		246			
CSF 14-3-3 protein		114			
Prion protein isoforms				8	
Oxidative Stress	163				25

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 and an increasing number of referrals per month have been observed as compared to year 2014, in respect to Frontotemporal Lobar degeneration (FTLD), Familial Alzheimer Disease (AD) and Parkinson´s Disease (PD). As with the previous years, a continuous effort has been made to ensure that the methodologies and diagnostic strategies used in the laboratory are in accordance with the current scientific knowledge in the field. The recent discovery of additional causative-genes along with costs associated with their genetic screening, have made the clinicians to contact often the laboratory for help concerning the selection of the best genetic approach to study their patients. Therefore, during 2015, the laboratory tried to wide its activity not only in the bench but also near the clinicians, discussing, interpreting and clarifying the published scientific genetic evidence on this topic. Thus, for familial forms of AD and/or early onset AD cases, the mutations analysis available in the laboratory involved *PSEN1*, *PSEN2* and *APP* genes. For FTLD and/or ALS cases, the mutations analysis encompassed several genes such as: *C9orf72*, *PGRN*, *MAPT*, *SQSTM1*, and *FUS* gene. Ultimately, for PD cases the most common screened genes were *PARKIN* and *LRRK2*, responsible for the recessive and dominant forms of the disease, respectively. Also, the susceptibility factor, *GBA* gene has been tested for PD patients with cognitive impairment and/or ocular movement. In addition, with the use of next generation sequencing technology by external laboratories, with which the clinicians frequently worked with, our team made efforts to show how informative this technique could be to test patients who presented large symptoms overlap.

Finally, the Neurogenetics Laboratory which was certified according to NP EN ISO 9001 : 2008 by APCER , Record No. PT- 2011 / CEP.3971, was audited on 29th October and obtained a renewal of the certificate ensuring the required quality in all the procedures.

***Team**: Mª Rosário Almeida and Ana Cristina Santos*

LABORATORY OF CELL BIOLOGY

Coordinator: Mário Grãos

The Laboratory of Cell Biology develops its activity between research projects and service providing.

In terms of research, the year of 2015 resulted in the ongoing participation in 4 FCT-funded projects, mostly in the area of stem cells, neural differentiation and neurodegenerative disorders (2 as PI, 1 as co-PI and 1 as team member). Two international peer-reviewed publications were produced (1 research article and 1 book chapter) as well as several reports for FCT. Moreover, 2 MSc theses were produced by 2 students supervised by the PI.

The laboratory has continued efforts to provide advanced training. The PI was co-supervisor of 1 PhD student and supervisor of 2 MSc students, 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.

In terms of advanced courses, the PI taught in 2 courses of MBCM, 1 course of PDBEB PhD Programme, was invited teacher at the 'Human Cell Culture' course organized by the Instituto Politécnico de Braçança and speaker at the CNC seminar series. Two elements of the lab taught 2 classes about cell culture techniques for students of the Biotechnology degree at ESAC (Escola Superior Agrária de Coimbra).

Several outreaching 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 has continued its 2 services. One service supplies the determination of bio-molecules using the multiplex xMAP technology (Bio-Plex), and during 2015, 54 analytes were determined. Since each kit uses a 96-well plate format, this represents a multitude of data points obtained (approximately 4000 sample data points were determined). Another service is related to testing the viability of cryopreserved tissues samples. During the year of 2015, a total of approximately 3500 samples were tested (47% increase compared with the year 2014).

In 2015 the lab has also implemented the ISO 9001-2008 certification for *Cell and tissue culture*.

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 checkpoint inhibitors therapy. 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

Phosphoepitope flow cytometry (PhosFlow), Flow cytometry

Next-Generation Sequencing (NGS)

Proliferation assays

Monitoring of cellular immune responses, Enzyme-Linked ImmunoSpot (**ELISPOT**) assay

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 five years a robust and sustainable service, increasing its capacity to provide specialized tests to the community.

Development and Innovation

During 2015, our laboratory developed new tests for characterisation of cancer stem cells and immune monitoring of cancer and infection diseases.

Collaborations

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.

Frederico Costa Pereira, 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.

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 Sofia Vale Pereira, Institute of General Pathology, Faculty of Medicine University of Coimbra, Portugal.

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

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.

Publications

Fonseca NA, Rodrigues AS, Rodrigues-Santos P, Alves V, Gregório AC, Valério-Fernandes Â, Gomes-da-Silva LC, Rosa MS, Moura V, Ramalho-Santos J, Simões S, Moreira JN. Nucleolin overexpression in breast cancer cell sub-populations with different stem-like phenotype enables targeted intracellular delivery of synergistic drug combination. Biomaterials. 2015 Nov;69:76-88. doi: 10.1016/j.biomaterials.2015.08.007. Impact Factor 8.56.

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Team: *Patrícia Couceiro, Jani Sofia Almeida*

Genome Sequencing Biology

Coordinator: Conceição Egas

The genome sequencing unit - Genoinseq – Genoinseq, the Next Gen Sequencing Unit, is specialized in the field of omics. The Unit grants access to the full potential of state-of-the-art of next generation sequencing equipment and bioinformatics data analysis. The Unit has a multidisciplinary team of experts in sequencing, genotyping and bioinformatics, delivering personalized solutions, from consultancy in experimental design to large scale data analysis with user-friendly outputs.

Genoinseq provides services to companies and research groups in the field of Life Sciences, collaborates in R&D projects with other companies or institutes.

Services available at Genoinseq:

Small genome sequencing and re-sequencing (includes sequencing, assembly and annotation).

Exome sequencing, variant discovery and annotation (includes variant calling and annotation in our ExomeLoupe pipeline).

Whole transcriptome and RNA-Seq (includes sequencing, de novo assembly or mapping, transcript annotation and differential gene expression analysis).

Amplicon sequencing, including biodiversity analysis in ecosystems or variant discovery in genes.

Genoinseq provided a total of 56 services in human exome sequencing (13 samples), bacterial genome sequencing (1 sample), bacterial RNA-Seq (5 samples) and amplicon sequencing (1014).

The Unit participated in the research Project DoIT - Development and Operation of Translational Research" in the ""Diamarker: Genetic susceptibility of multisystemic complications of diabetes type 2: novel biomarkers for diagnosis and monitoring of therapy" activity. The project involved the sequencing and analysis of 100 exomes of diabetic patients, the organization of the variants found in a database and the development of variant annotation and prioritization tools for data analysis, ExomeLoupe. Main project results were the identification of candidate genes with rare variants for T2D complications (diabetic retinopathy, diabetic nephropathy).

The unit also collaborated in projects from research groups that resulted in the publication of 5 papers in peer-reviewed journals. On the other hand, the results of sequencing and/or bioinformatics analysis to the clients resulted in 25 publications in peer-reviewed journals.

This year the unit was granted the ISO 9001:2008 certification by APCER in next generation sequencing of nucleic acids and bioinformatics tools for DNA and RNA analysis.

Detailed information

Sequencing and Bioinformatics services:

Type of clients: R&D groups and companies

Type of services:

Small genome sequencing and annotation

Exome sequencing

Whole transcriptome and RNA-Seq

Amplicon sequencing

Services in 2015: 54 sequencing services in human exome sequencing (11 samples), bacterial genome sequencing (1 sample), bacterial RNA-Seq (5 samples) and amplicon sequencing (1014).

Implementation of the NP EN ISO 9001:2005

The Unit was granted the ISO 9001:2008 certification in next generation sequencing of nucleic acids and bioinformatics tools for DNA and RNA analysis.

Projects:

Project DoIT - Development and Operation of Translational Research. This Project involved a consortium of Portuguese R&D institutions and companies: AIBILI, BIAL, BIOCANT, Center for Neuroscience and Cell Biology, CRITICAL HEALTH, S.A., EUROTRIALS - FRULACT, GENETEST, Hospitals of the University of Coimbra, S. João Hospital- Porto, IMM – Institute for Molecular Medicine, Portuguese Institute of Oncology, IPATIMUP, PLUX – Biosensor Engeneering, SIEMENS, Têxtil Manuel Gonçalves, University of Aveiro, University of Coimbra, University of Minho. Financed by QREN, 2012-2015. Our group was involved in the task "Diamarker: Genetic susceptibility of multisystemic complications of diabetes type 2: novel biomarkers for diagnosis and monitoring of therapy".

Project duration: 2012-2015, finnanced by the Portuguese Innovation Agency and QREN - the Portuguese Strategic Reference Framework (Projecto Mobilizador n.º 13853)

The project involves the sequencing and analysis of 100 exomes of diabetic patients, the organization of the variants found in a database and the development of variant annotation and prioritization tools for data analysis.

Main results are the identification of candidate genes with rare variants for T2D complications (diabetic retinopathy, diabetic nephropathy).

Group Publications:

Members of Genoinseq authored five scientific papers in the fields of biodiversity, gene functional analysis and exome sequencing.

Papers:

Landi M, Araújo A, Lobo J, et al. Ancient DNA in Archaeological Garum Remains from the South of Portugal. In: Oliveira C, Morais R, Cerdán ÁM, eds. Chromatography and DNA analysis in archaeology. Esposende: Municipio de Esposende; 2015.

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Clients' publications and/or citations

The sequencing and/or data analysis results produced at Genoinseq resulted in the publication of 25 scientific papers in peer-reviewed journals.

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Martins MJF, Lago-Leston A, Anjos A, et al. A transcriptome resource for Antarctic krill (*Euphausia superba* Dana) exposed to short-term stress. Mar Genomics. 2015;23:45-7. doi:10.1016/j.margen.2015.04.008.

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Pereira R, Oliveira J, Ferraz L, Barros A, Santos R, Sousa M. Mutation analysis in patients with total sperm immotility. J Assist Reprod Genet. 2015;32(6):893-902. doi:10.1007/s10815-015-0474-6.

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Riquelme C, Câmara S, Dapkevicius M de LNE, et al. Characterization of the bacterial biodiversity in Pico cheese (an artisanal Azorean food). Int J Food Microbiol. 2015;192:86-94. doi:10.1016/j.ijfoodmicro.2014.09.031.

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Laboratory of Brettanomyces by FCM

Coordinator: Margarida Carneiro

The main activity of the Laboratory of Brettanomyces by FCM is to provide accurate and rapid determination of the presence of contaminating Brettanomyces/ Dekkera yeast in wines during the different stages of wine maturation. This service is offered to wine producers in Portugal. The bulk of these analyses has been done under contracts celebrated with wine producers, and also sporadic analysis were done on fee-for-service basis. In the future we plan on expanding both the number of long-term contracts as well as the pallet of analytic services offered to the wine producers.

MitoXT Services Laboratory

Coordinator: Paulo Oliveira

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: Paulo Oliveira (coordenador), Vilma Sardão, Teresa Oliveira, Tatiana Martins

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*)

- **BIO-IMAGING AND ELECTRON MICROSCOPY**

O Laboratório de Bio-imagem Celular de Alta Resolução é uma plataforma tecnológica gerida pela Faculdade de Medicina da Universidade de Coimbra (FMUC) e inclui equipamentos financiados pela Fundação para a Ciência e Tecnologia na sequência da criação do Pólo da Universidade de Coimbra da Rede Nacional de Microscopia Electrónica (RNME).

O Pólo de Coimbra da RNME constitui a única infra-estrutura tecnológica de microscopia electrónica de transmissão (TEM) especialmente dedicada a aplicações em Ciências da Saúde, na região centro do país. Com a criação deste pólo são disponibilizadas técnicas de imagem ultraestrutural de elevada resolução como uma ferramenta diferenciada para aplicações em Biomedicina.

O Laboratório de Bio-imagem Celular de Alta Resolução dispõe ainda de equipamentos altamente diferenciados incluindo um Microscópio Confocal, Microscópio de fluorescência, com possibilidade de aquisição de imagens de células vivas em tempo real (live cell imaging) e uma unidade de preparação de amostras constituída por um ultramicrótomo, com unidade criogénica que permite o seccionamento de amostras biológicas ultracongeladas para observação em TEM.

Equipamento

O Laboratório de Bio-imagem Celular de Alta Resolução dispõe dos seguintes equipamentos para observação e preparação de amostras:

- Microscópio electrónico de transmissão TEM FEI-Tecnai G2 Spirit Biotwin equipado com uma unidade com canhão de electrões de filamentos de tungsténio, operando até 120 kV, uma câmara CCD lateral acoplada (MegaView III– SIS), unidade de refrigeração e compressor de ar, o que permite a aquisição de imagens de amostras biológicas com elevada resolução.

- Unidade de preparação de amostras constituída por um ultramicrótomo, com unidade Cryo (Leica EM UC6 + EM FC6), com controlo de microprocessador para as funções de controlo da velocidade e espessura do corte, e controlo da iluminação da amostra, o que permite o seccionamento de amostras biológicas ultracongeladas para observação em TEM.

- Microscópio de fluorescência Leica DM IRE2, com câmara com sistema de controlo de CO2 e temperatura, permitindo aquisição de imagens de células vivas, em tempo real (live cell imaging).

- Microscópio Confocal LSM 710 Carl Zeiss, inclui 3 canais espectrais R7FL, 5 linhas de laser: 458, 488, 514, 561 e 633; software Zen 2009; permite acoplar sistema de controlo de CO2 e temperatura para “live cell imaging”.

Reservas e Contactos

MICROSCOPIA ELECTRÓNICA

PREÇOS

O custo dos serviços prestados pelo Laboratório de Bio imagem Celular de Alta Resolução da Faculdade de Medicina da Universidade de Coimbra, tem por referência uma Tabela de Preços de Serviços que deve considerar a diferenciação de quatro classes de utilizadores:

1 - Organismos da FMUC e CNC.IBILI
2 - Restantes organismos da UC (incluindo CHUC)
3 - Organismos académicos (outras Universidades e Instituições Superiores)
4 – Empresas

Serviço	**1**	**2**	**3**	**4**
Processamento da amostra (total)	15,00	17,00	20,00	30,00
Processamento da amostra (parcial)	6,00	8,00	12,00	20,00
Ultramicrótomo (por amostra)	5,00	6,00	10,00	20,00
Tecnai G2 Spirit Biotwin (por hora)	30,00	35,00	50,00	100,00

Tabela de preços em euros e IVA não incluído

RESERVAS E CONTACTOS

Para aceder ao Sistema de Reserva de Equipamentos do Laboratório de Bio-imagem Celular de Alta Resolução da Universidade de Coimbra deverá preencher o seguinte formulário:

Requisicao_TEM_Polo_Coimbra

Para mais informações contactar:

Dr. Henrique Girão (*hmgirao@fmed.uc.pt*)

Tel. 239 480 221

CONFOCAL MICROSCOPE

General overview

The laboratory provides technical support on various microscope techniques and live cell imaging.

The unit currently stands with a Confocal Microscope LSM 710 Zeiss, as well as other fluorescence microscopes (Leica DMIRE2 and Olympus CKX41) and a cell live imaging station from Leica (with temperature and CO2 controllers: temp control 37-2 digital and CO2-IR sensor CTI Controller 3700).

The system is available to all FMUC researchers, as well as for users external to FMUC. All users will need to contact the lab before planning any work or before any sample observation.

The services provided are:

- Discussion of the protocols

- Guidance and help in the preparation of samples

- Guidance in the manipulation of the confocal/fluorescence systems and acquisition of images

- Help in the interpretation of data

Booking and admission conditions

Until the online booking system is available, booking will be done by the technician responsible for the unit, using the contacts provided in this page.

First time users will receive training by the technician in charge for the equipment. The duration of the training will be adjusted according to the previous knowledge and progress of each individual user.

All users need to be registered before using the confocal system. In order to perform the registration, it is mandatory to fill the registration form available on the website.

All new users should contact the facility to discuss the needs and payment methods prior to the first appointment.

Confocal facility rates

The service fees consider the differentiation of four classes of users:

1 – FMUC and IBILI.CNC users

2 – Users external to FMUC and IBILI.CNC but that belong to the University of Coimbra

3 – Users from other public universities/institutes

4 – Users from private institutions; users from university/industry interfaces

- ***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.

Courses in 2015:

FRAME training school - March 30 to April 1

Staff

Scientific Coordinator:

Miguel Castelo-Branco, MD. Ph.D

Teaching and Research Staff and collaborators:

Bárbara Oliveiros, Ph.D.

Francisco Caramelo, Ph.D.

Francisco Oliveira, Ph.D.

Margarida Marques, B.Sc.

Marisa Loureiro, M.Sc.

Miguel Patrício, Ph.D.

Administrative Staff:

Cláudia Caridade

Contact Information

Contact Person: Cláudia Caridade

Address: Azinhaga Santa Comba, Celas

3000-548 Coimbra

Phone: +351 239480028

Fax: +351 239480217

Email: *bioestatistica@fmed.uc.pt*

- **Library**

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

- **Bar**

- **Auditorium**

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

FUNDING AT CNC

In 2015 funding of "Laboratório Associado – Centro de Neurociências e Biologia Celular" ascended the amount of 10.734.928,19€.

The main financing contribution was made by "Fundação para a Ciência e Tecnologia (FCT)", concerning global institution programs and national projects, namely amount of 3.625.683,39 € distribuited as follows:

Strategical Project_ UID/NEU/04539/2013	1.552.772,60€
Incentivo/SAU/LA0001/2014	80.463,68€
Projects:	1.655.276,75€
Science Program:	337.170,36€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2015.

Besides Center for Neuroscience is financed by other national and international agencies. In 2015 Center for Neuroscience received the amount of 5.077.695,29€ concerning other national projects and 943.929,43€ concerning international projects.

Services is another important vector of our institution which ascends 985.619,32€

The amount of other resting funds, which are not listed, attains an amount of 102.000,76€.

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

Note: Financing values are based on expenditure values 2015

ONGOING PROJECTS

Title	Financing Agency	Duration	Budget (CNC)	Expenditure 2015
NATIONAL PROJECTS:				
"Rede Nacional de Espectrometria de Massa" Coordinator: Euclides Pires	FCT Refª: REDE/1506/REM/2005	01/01/2009 to 30/12/2015	25.405,96	25.405,96€
"Caracterização dos princípios de design de circuitos metabólicos prevalentes." Coordinator: Armindo Salvador Participants: Universidade de Coimbra; Universidade do Minho	FCT Refª: PTDC/QUI-BIQ/119657/2010	01/04/2012 to 30/09/2015	117.226,00	25.281,26€
"Terapia génica Não invasiva e Não viral da doença de Machado-Joseph" Coordinator: Luis Almeida	FCT Refª: PTDC/SAU-FAR/116535/2010	01/04/2012 to 31/08/2015	108.280,00	41.839,89€
"Estudo do mecanismo patogénico da Doença de Machado-Joseph num novo modelo de células estaminais pluripotentes induzidas." Coordinator: Luis Almeida	FCT Refª: PTDC/SAU-NMC/116512/2010	24/01/2012 to 30/07/2015	145.360,00	25.121,72€
"Avaliação Neuropsicológica e Investigação Bigenómica nas Demência Frontotemporal." Coordinator: Maria Manuela Grazina	FCT Refª: PTDC/SAU-EPI/121811/2010	01/01/2012 to 30/06/2015	199.699,00	80.927,28€
"TranstirRetina é uma metaloprotease: possíveis implicações em doenças do sistem nervoso." Coordinator: Sukalian Chaterjee Proponent: Instituto de Biologia Molecular e Celular (IBMC)	FCT Refª: PTDC/SAU-ORG/118863/2010	01/05/2012 to 30/09/2015	56.152,00	12.669,21€
"Alterações na transmissão sináptica GABAérgica na isquemia cerebral - mecanismos moleculares responsáveis pela internalização dos receptores GABAA." Coordinator: Carlos Duarte	FCT Refª: PTDC/SAU-NMC/0198/2012	01/07/2013 to 30/06/2015	141.136,00	44.080,00€
"DEMTEST: Diagnóstico de demencias rapidamente progressivas baseado em biomarcadores - optimização de protocolos de diagnóstico." Coordinator: Catarina Resende de Oliveira	FCT Refª: JPND/0001/2011	01/06/2012 to 31/05/2015	35.000,00	162,78€
"Regulação do metabolismo energético no cérebro pelo óxido nítrico: solução para a glicólise aeróbia" Coordinator: João Laranjinha	FCT Refª: PTDC/BBB-BQB/3217/2012	03/07/2013 to 30/09/2015	134.938,00	83.433,06€
"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 31/05/2016	173.264,00	49.797,20€

“Estudo da contribuição dos miRNAs para o metabolismo do peptídeo b-amilóide: desenvolvimento de uma plataforma lentiviral para expressão de múltiplos miRNAs no contexto da doença de Alzheimer” Coordinator: Ana Luísa Colaço Cardoso	FCT Refª: PTDC/BIM-MEC/0651/2012	01/03/2013 to 31/08/2015	100.800,00	9.558,99€
“Do controlo da neuroinflamação à neuroproteção: bloqueio dos reptores A2A para o tratamento do glaucoma” Coordinator: Ana Raquel Sarabando Santiago	FCT Refª: PTDC/BIM-MEC/0913/2012	01/06/2013 to 30/09/2015	32.401,00	10.277,06€
“Efeitos do peptídeo orexigénico grelina na transmissão sináptica glutamatérgica” Coordinator: Sandra Manuela Domingues dos Santos	FCT Refª: PTDC/NEU-NMC/1098/2012	01/07/2013 To 30/11/2015	199.975,00	92.901,78€
A Sabedoria do faminto: modulação por ghrelina da neurogénese e da sua relação com a memória Coordinator: Jorge Gómez	FCT Refª: EXPL/NEU-SCC/1193/2012	01/04/2014 to 30/09/2015	49.980,00	19.977,32€
A natureza das ligações de carbono e azoto como fator discriminante da origem da matéria orgânica solúvel em água de aerossóis atmosféricos Coordinator: Luisa Ramos	FCT Refª: PTDC/AAG-MAA/2584/2012	01/07/2013 to 30/09/2015	3.720,00	2.665,54€
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	56.105,83€
“Regulação do sistema ubiquitina-proteassoma pelo BDNF nas sinapses do hipocampo: importância na plasticidade sináptica.” Coordinator: Carlos Duarte	FCT Refª: PTDC/SAU-NMC/120144/2010	10/02/2012 to 31/08/2015	154.678,00€	29.674,14€
“Fibrilas Interrompidas: Inibição de interacções aberrantes proteína-proteína em Amilóides.” Coordinator: Rui Brito	FCT Refª: PTDC/QUI-QUI/122900/2010	01/03/2012 to 31/08/2015	113.768,00€	26.369,34€
“Nova Abordagem na Luta Contra a Tuberculose.” Coordinator: Maria Otília Vieira	FCT Refª: HMSP-ICT/0024/2010	01/01/2012 to 30/06/2015	206.610,00€	26.966,59€
“Contribuição para a erradicação da malária. Uma nova abordagem para atingir multi-alvos no ciclo de vida do parasita.” Coordinator: Luísa Melo Proponent: Faculade de Farmácia da Universidade de Coimbra; Participants: Instituto de Medicina Molecular (IMM/FM/UL)	FCT Refª: PTDC/SAU-FAR/118459/2010	01/03/2013 to 31/08/2015	5.500,00€	2.456,26€

“O Óxido Nítrico na Doença de Alzheimer - Molécula Sinalizadora e Mediador de Patogénese.” Coordinator: Ana Ledo	FCT Refª: PTDC/BIA-BCM/116576/2010	01/04/2012 to 31/03/2015	81.698,00€	6.693,44€
“Desenvolvimento de nanoparticulas multifuncionais inovadoras para o tratamento do cancro de mama.” Coordinator: João Nuno Moreira Proponent: Universidade do Minho	FCT Refª: PTDC/SAU-DMA/121028/2010	20/04/2012 to 30/09/2015	76.857,00€	48.641,28€
“O sistema neuropeptídeo Y: potencial novo alvo terapêutico na retinopatia diabética” Coordinator: Francisco Ambrósio Proponent: Universidade de Coimbra	FCT Refª: PTDC/NEU-OSD/1113/2012	01/05/2013 to 31/08/2015	36.000,00€	15.871,75€
“Estratégia terapêutica combinada baseada na modulação de miRNAs direcionada para glioblastoma multiforme: um novo nanosistema de base lipídica para entrega sistémica.” Coordinator: Maria Conceição Pedroso Lima	FCT Refª: PTDC/DTP-FTO/0265/2012	02/03/2013 to 01/06/2015	99.768,00€	19.415,75€
“Um Novo Modelo para a Esquizofrenia: Defeitos na Plasticidade Homeostática Mediada por Stargazina.” Coordinator: Ana Luísa Carvalho	FCT Refª: PTDC/NEU-NMC/0750/2012	01/07/2013 to 30/09/2015	117.262,00€	58.533,19€
“Doença de Machado-Joseph, agregação e degradação proteicas, biologia de células estaminais, proteostase, neurodegeneração.” Coordinator: Luís Almeida	E-RARE4/0003/2012	01/03/2013 to 31/12/2016	141.581,00€	31.788,92€
“Ambiguidade e virulência em patogénios humanos.” Coordinator: Nuno Empadinhas Proponent: IBMC Instituto de Biologia Molecular e Celular - IBMC/UP	FCT Refª: PTDC/BBB-BEP/0695/2012	01/07/2013 to 30/09/2015	69.840,00€	18.745,96€
“Tratamento da doença de Alzheimer com um novo peptídeo inibidor da BACE1.” Coordinator: Armanda Santos	FCT Refª: PTDC/SAU-SCC/1351/2012	15/06/2013 to 30/09/2015	177.611,00€	119.327,36€
“Plataformas combinatoriais para promover a sobrevivência celular- PROSURVIVAL.” Coordinator: Hugo Fernandes	FCT Refª: PTDC/BIM-MED/1118/2012	01/07/2013 to 30/09/2015	130.000,00€	58.910,25€
“Papel da sirtuina 3 na função mitochondrial e desacetilação de alvos mitocondriais: relevância para a doença de Huntington” Coordinator: Tatiana Rosado Rosentstock	FCT Refª EXPL/BIM-MEC/2220/2013	01/04/2014 to 30/09/2015	37750,89€	28.509,27€
“Anestesia no peixe-zebra (Danio rerio)e potenciais implicações na investigação - substituição, redução e refinamento de técnicas e procedimentos” Coordinator: Anália do Carmo Proponent: : IBMC Instituto de Biologia Molecular e Celular - IBMC/UP	FCT Refª PTDC/CVT-WEL/4672/2012	01/07/2013 to 30/09/2015	7200,00€	3886,98€

‘‘Projeto de investigação Exploratória’’ Coordinator: João Peça	FCT Refª IF/00812/2012/CPO151/CT0001	19/06/2014 To 18/06/2018	50.000,00€	37.607,27€
‘‘Projeto de investigação Exploratória” Coordinator: Ricardo Pires	FCT Refª IF/00123/2013	01/08/2014 to 31/07/2018	50.000,00€	17.815,76€
‘‘Desvendar a vulnerabilidade das células do musculo liso de pacientes com Progeria - Smooth_Progeria’’ Coordinador: Lino Ferreira	FCT Refª: EXPL/BIM-MED/2267/2013	01-03-2014 to 31-05-2015	49.800,00	27.548,82
Programa MIT Coordinator: Catarina Oliveira, Lino Ferreira	FCT Refª: MIT-Portugal 2015	01/01/2015 to 31/12/2015	7635,00€	7.014,56€
“Novas estratégias para a recuperação da fertilidade e potencial genético de felídeos selvagens: desenvolvimento do xenotransplante e da transplantação de células espermatogoniais estaminais em gato doméstico como modelo para felídeos selvagens.” Coordinator: Paula Mota	FCT Refª: PTDC/CVT/119477/2010	01/05/2012 to 30/09/2015	62.813,00	18.611,72€
“Modulação da actividade de células estaminais hematopoiéticas por acção de nanopartículas capazes de libertar factores de transcrição – STEMCELLMODULATORS.” Coordinator: Ricardo Pires das Neves	FCT Refª: PTDC/CTM-NAN/120552/2010	01/05/2012 to 30/09/2015	115.884,00	18.951,06€
“Modulação da piruvato desidrogenase cinase e pluripotência: Implicações para cancro e biologia de células estaminais.” Coordinator: João Ramalho	FCT Refª: PTDC/QUI-BIQ/120652/2010	06/05/2012 to 31/08/2015	130.000,00	28.730,12€
“Produção e propagação de linhas de células estaminais pluripotentes usando modulação metabólica.” Coordinator: João Ramalho	FCT Refª: PTDC/EBB-EBI/120634/2010	06/05/2012 to 05/09/2015	94.000,00	16.441,77€
“BIOMARKAPD: Biomarcadores para Doença de Alzheimer e Doença de Parkinson.” Coordinator: Catarina Oliveira	FCT Refª: JPND/0005/2011	01/06/2012 to 31/05/2015	48.500,00	14.746,25€
“Bioprospecção de enzimas com capacidade de degradar biomassa vegetal no metagenoma do sistema digestivo de Porcellio dilatatus (Crustacea,Isopoda).” Coordinator: António Veríssimo	FCT Refª: PTDC/AGR-TEC/3789/2012	01/05/2013 to 30/09/2015	90.000,00	29.958,38€
“Patofisiologia da Toxicidade Cardíaca Persistente da Doxorubicina: Uma ligação entre Mitocôndria e Epigenetica” Coordinator: Paulo Oliveira	FCT Refª: PTDC/DTP-FTO/1180/2012	01/05/2013 to 31/08/2015	175.000,00	13.442,15€
“O metilfenidato e as alterações na barreira hemato-encefálica numa situação fisiológica e na perturbação de hiperatividade com défice de atenção” Coordinator: Ana Paula Silva Proponent: Universidade de Coimbra	FCT Refª: PTDC/NEU-OSD/0312/2012	01/06/2013 to 30/09/2015	60.336,00	42.563,62€

“Mecanismos de protecção neuronal contra stress oxidativo mediados pela DJ-1: implicações na doença de Parkinson” Coordinator:Bruno Manadas Participant:Biocant, Univ.Minho, U.Beira Interior	FCT Refª: PTDC/NEU-NMC/0205/2012	01/05/2013 to 30/09/2015	113.870,00	32.963,28€
“Biossíntese de polissacáridos raros de metilmanose em micobactérias não tuberculosas” Coordinator:Nuno Empadinhas Participant:IBMC,ITQB	FCT Refª PTDC/BIA-MIC/2779/2012	01/07/2013 to 30/09/2015	100.360,00	37.658,71€
“Investigação bigenómica translacional na Neuropatia Ótica Hereditária de Leber: Correlação Genótipo-Fenótipo” Coordinator:Manuela Grazina Participant:CCMAR-Alg	FCT Refª: PTDC/DTP-EPI/0929/2012	01/04/2013 to 31/08/2015	192.780,00	101.191,93€
"Células estaminais tumorais e progressão tumoral: dos mecanismos moleculares às consequencias clínicas" Coordinator:Maria Carmen Alpoim	FCT Refª: PTDC/BBB-BQB/2450/2012	01/05/2013 to 30/09/2015	132.248,00	63.264,48€
‘‘Projeto de investigação Exploratória’’ Coordinator: Miguel Mano	FCT Refª: IF/00694/2013	10/07/2014 to 30/06/2018	50.000,00	30.223,14€
‘‘Projeto de investigação Exploratória’’ Coordinator: Paulo Pinheiro	FCT Refª: IF/01302/2012	01-01-2014 to 30-09-2018	50.000,00	6.699,33€
“Nova abordagem da disfunção reprodutora na diabetes: análise 3D da espermatogénese e microscopia confocal Raman para análise da função mitocondrial” Coordinator:Sandra Amaral	FCT Refª: PTDC/BEX-BCM/0224/2012	03/07/2013 to 02/01/2015	48132,00	0,0€
‘‘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	4.838,98€
‘‘Projeto de investigação Exploratória’’ Coordinator: Irina Moreira	FCT Refª: IF/00578/2014/CP1258/CT0002	15/01/2015 to 14/01/2020	50.000,00	0,0€
'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	200,20€
'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	28.809,86€
Sub – Total FCT				**1.655.276,75€**

OTHER NATIONAL PROJECTS				
"CNC Biotech – Investigação em Biotecnologia e capacitação do sector empresarial Coordinator: Carlos José Fialho da Costa Faro	Mais Centro-Programa Operacional Regional do Centro Refª: ICT_2009_02_041_1769	18/06/2009 to 30/09/2015	10.834.801,05	3.976.904,35
"Ibercivis.pt - Uma plataforma de computação voluntária para a Península Ibérica." Coordinator: Rui Manuel Pontes M. F. Brito	UMIC - Agência para a Sociedade do Conhecimento	16/06/2010 to 30/06/2015	87.380,00	8.812,55€
''DoIT – projeto nº 013853'' Coordinator: Catarina Oliveira	Agência da Inovação, S.A.	01/07/2010 to 28/02/2015	378.154,38	55.305,16€
"Aging,Stress and Chronic Diseases:From mecanisms to therapeutics" Coordinator:Luis Almeida Proponent:Universidade de Coimbra	Mais Centro-Programa Operacional Regional do Centro Refª: SCT_2011_02_006_4819	01/06/2013 to 30/06/2015	128.093,92	49.828,12€
'Prémio FLAD Life SCience 2020' Coordinator:Ana Cristina Rego	Fundação Luso-Americana	01/01/2015 to 31/12/2017	300.000,00	22.183,89€
"New Strategies do manage Brain Diseases." Coordinator: Luís Almeida Proponent: Universidade de Coimbra	Mais Centro-Programa Operacional Regional do Centro Refª:SCT_2011_02_002_4756	01/06/2013 To 30/06/2015	305.220,15€	118.250,33€
QREN-Amilotera: 021622 Coordinator: Rui Brito	Agência da Inovação, S.A	01/09/2011 to 31/08/2014	85.804.45€	24.889,98€
"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€	40.140,20€
"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€	3.255,69€
"Stemcell based platforms for Regenerative and Therapeutic Medicine" Coordinator: Carlos José Fialho da Costa Faro Proponent: Universidade de Coimbra	Mais Centro-Programa Operacional Regional do Centro Refª: SCT_2011_02_008_4832	01/02/2013 To 30/09/2015	682.875,01	345.823,92€
"Plataformas de Bioimagem, Comportamento e Electrofisiologia@CNC Coordinator: Catarina Isabel Neno Resende de Oliveira	Mais Centro-Programa Operacional Regional do Centro Refª: ICT-2013-05-030-5377	01/01/2014 to 30/09/2015	987.923,50€	319.701,48€
"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€	42.102,56€
"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€	70.497,07€

Sub – Total Other				**5.077.695,30€**
Total National Projects				**6.732.972,05€**
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€	20.763,39€
"Silencing Machado-Joseph Disease/Spinocerebellar ataxia type 3 through the systemic route" Coordinator: Rui Nobre Jorge	National Ataxia Foundation	01/01/2014 to 31/12/2015	10.823,71€	3.629,11€
"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 31/12/2016	50.000,00€	21.222,52€
"Industrial Academic Initial Network towards treatment of Polyglutamine diseases" Coordinator: Luís Almeida	Marie-Curie-264508 Ref.ª FP7-PEOPLE-ITN-2010	01/03/2011 to 28/02/2015	202.332,86€	39.073,78€
Unveiling Carbon fixation in three deep serpentinization-driven hyeralkaline springs. Coordinator: Igor Clemente Tiago	Marine Biological Laboratory	01/05/2014 To 31/05/2015	10.000,00€	506,76€
Novel nanoparticles for drug delivery to the skin Coordinator: Lino Ferreira	Queen Mary - 289454 Ref.ª: FP7-PEOPLE-2011-ITN	01/11/2011 to 31/10/2015	471.627,60€	118.795,13€
"The effect of TCF7L2 on Glucose Metabolism" Coordinator: John Jones	Mayo Clinic 5Ro1DK078646-08	01/08/2014 To 31/07/2015	17.395,53€	6.041,90€
"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€	69.946.06€
"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 30/11/2015	944.680,00€	76.267,87€
"DFRH/WIIA/51/2011 - Welcome II" Coordinator: Catarina Oliveira/Otília Vieira	Marie Curie Actions DFRH/WIIA/51/2011 - Welcome II	01/02/2012 to 31/01/2015	119.740,50€	12.462,59€
"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 30/09/2014	209.781,00€	48.143,52€

"Trigerralde 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€	127.903,57€
"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 31/12/2014	10.823,71€	5205,94€
"Mitochondrial Trafficking In Alzheimer Disease: Revealing the Role of Hummr." Coordinator: Paula Moreira	Alzheimer Association NIRG-13-282387	01/11/2013 to 30/06/2014	71.495,56€	14.641,89€
"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 31/01/2015	11547,12€	17.625,02€
"Ghrelin: a novel therapeutic intervention to rescue the phenotype of Hutchinson-Gilford progeria syndrome" Coordinator: Célia Aveleira	Progeria Research Foundation	01/04/2015 To 31/03/2016	61.718,64€	34.565,81€
"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	121.412,96€	18.973,02€
"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€	300,00€
''Pharmacological activation of autophagy to alleviate Machado-Joseph disease'' Coordinator: Luís Almeida	National Ataxia Foundation	01-01-2014 to 31-12-2015	72.249,25	788,17
''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	2.648,03
''ENC Network Cycle 4-2013 - PT - 04 -Amber Kerkhofs'' Coordinator: Rodrigo Cunha	European Neuroscience Campus Network Cycle	01/10/2013 to 30/09/2015	121.900,00	38.564,94€
''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	37.825,31€
''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	78.206,20	42.812,34€
''ENC Network Cycle 4-2013 - PT - 07 - Xin-Li Xu'' Coordinator: Rodrigo Cunha	European Neuroscience Campus Network	01/10/2013 to 30/09/2015	126.400,00	46.939,49€

"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	14.483,49€
"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 31/08/2017	37.000,00€	14.044,17€
"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	83.477,54€	10.974,81€
"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€	12.619,01€
"Mechanisms underlying hemogenic induction in human fibrobalsts" Coordinator: Carlos Filipe Ribeiro Lemos Pereira	Marie Curie FP7-People-2013-IIF PIIF-GA-2013-628761	18/02/2015 to 17/02/2017	202.630,00€	86.161,79€
Total International Projects				**943.929,43€**
TOTAL				**7.676.901,47€**

FUNDING AT IBILI

ONGOING PROJECTS

TITLE	FINANCING AGENCY	DURATION	BUDGET (IBILI)	EXPENDITURE 2015
NATIONAL				
"From neuroinflammation control to neuroprotection: blocking adenosine A2A receptor for the treatment of glaucoma" Coordinator: Raquel Santiago	FCT PTDC/BIM-MEC/0913/2012	01-06-2013 to 31-05-2015	124.431,00	67.029,02 €
"Neuropeptide Y system: a new potential therapeutic target in diabetic retinopathy" Coordinator: Francisco Ambrósio	FCT PTDC/NEU-OSD/1113/2012	01-03-2013 to 28-02-2015	95.715,00 €	34.370,50 €
"Methylphenidate and blood-brain barrier changes in health and attention deficit hyperactivity disorder" Coordinator: Ana Paula Silva	FCT PTDC/NEU-OSD/0312/2012	01-05-2013 to 30-04-2015	74.040,00 €	43.594,69 €
"A breath to overcome lung cancer: EGFR targeted nanoparticles to carry photodynamic therapy" Coordinator: Filomena Botelho	FCT PTDC/BIM-ONC/0979/2012	01-03-2013 to 28-02-2015	161.200,00 €	36.762,79 €
"Unveiling preclinical idiopathic macular hole formation: structural changes by high-definition optical coherence tomography and machine learning" Coordinator: Conceição Lobo	FCT PTDC/BBB-BMD/2739/2012	01-05-2013 to 30-04-2015	32.424,00 €	7.616,08 €
"Sistemas Moleculares e Nano para Teranóstica de Cancro" Coordinators: Antero Abrunhosa and Filomena Botelho	FCT EXCL/QEQ-MED/0233/2012	01-06-2013 to 31-05-2016	70.000,00 €	-
"Insuficiência Cardíaca e diastólica: Novos mecanismos Fisiopatológicos e Seu Potencial Como Alvos Terapêuticos "Coordinator: Raquel Seiça	FCT EXCL/BIM-MEC/0055/2012	01-01-2014 to 31-12-2015	20.400,00 €	3.506,43 €
"Mathematical an Computational Modeling of Human Physiology" "Mathematical an Computational Modeling of Human Physiology" Coordinator: Ricardo Jorge Pereira	EXCL/MAT-MAN/0114/2012	15-05-2013 to14-05-2016	9.000,00 €	5.996,25 €
"Exercício físico na Doença de Parkinson: mo dulação da função dos recetores dos produtos de glicação avançada"	FC	0		

"Exercício físico na Doença de Parkinson: modulação da função dos recetores dos produtos de glicação avançada" Coordinator: Frederico Pereira	FCT EXPL/DTP-DES/0104/2013	01-03-2014 to30-06-2015	46.519,00 €	11.941,30 €
HOMETECH Coordinator: Miguel Castelo-Branco	QREN Nº23218	01-09-2012 to 30-06-2015	311.234,86 €	130.634,77 €
"Age-related macular degeneration - can metabolomic profile distinguish progressors?" Coordinator: Inês Laíns	FCT HMSP - ICJ/0006/2013	01-07-2014 to 30-06-2016	46.525,00 €	19.137,94 €
Protocolo Delta – FMUC Coordinator: Ana Raquel Santiago	DELTA Proj. Cafeína e Glaucoma	29-01-2014 to 28-01-2016	4.900,00 €	2.683,02 €
"From molecules to man" Coordinator: Miguel Castelo-Branco	QREN N.º 13853	01-06-2013 to 30-06-2015	1.745.400,66 €	-
CNC.IBILI | Participants: Universidade de Coimbra and CNC Coordinators: Miguel Castelo-Branco, Francisco Ambrósio	FCT UID/04538/2015	01-01-2015 to 31-12-2017	1.833.000,00 €	425.592,20 €
Novartis Coordinator: Francisco Ambrósio	Novartis	-	30.000,00 €	-
"Physical, biochemical and histological analysis of human amniotic membrane: contribuition to preterm premature rupture of fetal membranes study" Coordinator: Margarida Abrantes	FMUC AAbrantes.GAI2015	01-01-2015 to 31-12-2015	5.000,00 €	4.923,27 €
"Biodegradable intravitreal porous implants for extended release of A3 adenosine receptor agonist for the protection of retinal ganglion cells – a potential therapeutic strategy for the treatment of glaucoma" Coordinator: Raquel Santiago	FMUC ASantiago.GAI2015	02-01-2015 to 01-01-2016	5.000,00 €	5.075,92 €
"Pinning down TRVP1: acupuncture analgesia" Coordinator: Frederico Pereira	FMUC FPereira.GAI2015	03-01-2015 to 02-01-2016	5.000,00 €	4.875,45 €
"A novel function for gap junction protein Connexin 43: targeting tumor therapy via exosomes" Coordinator: Maria João Pinho	FMUC MPinho.GAI2015	04-01-2015 to 03-01-2016	5.000,00 €	4.546,64 €
"A non-canonical mechanism for selective macroautophagy" Coordinator: Steve Catarino	FMUC SCatarino.GAI2015	05-01-2015 to 04-01-2016	5.000,00 €	4.995,28 €

INTERNATIONAL				
"NK cell-based adoptive therapy targeting human bladder cancer stem cells: impact on tumor progression using a humanized orthotopic animal model" Coordinator: Célia Gomes	Astellas Foundation - Uro Oncology 2014	12-03-2014 to 11-03-2016	108.070,00 €	33.336,60€
"Stimulating Innovation Management of Polypharmacy and Adherence in The Elderly (SYMPATHY)" Coordinator: Joao Malva	European Union HP-PJ-2014		99.124,00 €	18.473,58€
"Multidisciplinary Institute of Ageing (MIA)" Coordinator: João Malva	European Union H2020-WIDESPREAD-2014-1		197.529,00 €	22.825,16€
"Enhancing Research in Ageing at the University of Coimbra (ERA@UC)" Coordinator: João Malva	European Union H2020-WIDESPREAD-2014-2		2.486.165,00 €	10.408,70€
"EIT Health" Coordinator João Malva	European Union SUGA-2015-EIT HEALTH1		129.807,29 €	8.281,33€
"European young Investigators network for Usher Syndrome"	EU-FCT E-RARE4/SAU/0001/2008		183.284,00 €	42.053,20€
"Taking imaging into the therapeutic domain: self-regulation of brain systems for mental disorders" Coordinator: Miguel Castelo-Branco	BRAINTRAIN	01-11-2015 to 30-10-2018	638.000,00 €	137.218€
Managing inflammation in diabetic retinopathy Coordinator: Ana Raquel Santiago	Bayer Healthcare	1-12-2015 to 31-12-2016	44.341,00 €	980€

STAFF LIST

SERVICE STAFF

		Time % at CNC.IBILI
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
Cristina Barroso	(Graduate 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
Paulo Rodrigues-Santos	(Graduate Technician)	20

TECHNICAL STAFF

		Time % at CNC.IBILI
Adalberto Fernandes	(Grad. Tech., Science Communic. CNC)	100
Alda Rodrigues	(Technician, CNC)	100
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 Adelaide Oliveira	(Technician, CNC)	100
Maria do Céu Mendes Gomes	(Technician, CNC)	100
Maria Eugénia A. Silva Lopes Campos	(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)	100
Sara da Costa Jordão A. Lopes	(Technician, CNC)	100
Sandra Freire	(Graduate Technician, CNC)	100
Vera Mónica M. Mendes	(Technician, CNC)	100
Vítor José Lopes Nunes	(Technician, CNC)	100

ADMINISTRATIVE STAFF

		Time % at CNC.IBILI
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 | *MIGUEL CASTELO-BRANCO*

MEMBERS HOLDING PHD		TIME % AT CNC.IBILI
Alda Maria Abreu Cardoso	(Associate Investigator)	50
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 Rita Costa Álvaro	(Assistant Inv., CNC)	100
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
Armando Cristóvão	(Assistant Prof., FCTUC)	30
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
Caetana Carvalho	(Full Prof., FCTUC)	Collaborator
Carlos Alberto F. Ribeiro	(Full Professor)	50
Catarina A. Reis Gomes	(Assistant Professor)	50
Carla Nunes	(Assistant Prof., FFUC)	50
Carlos B. Duarte	(Associate Prof., FCTUC)	80
Carlos Matias	(Investigator, UTAD)	60
Catarina R. Oliveira	(Full Prof., FMUC)	60
Célia Maria Freitas Gomes	(Assistant Prof., IPC-UC)	100
Cláudia Cavadas	(Assistant Prof., FFUC)	70
Eduardo José Silva	(Assistant Professor)	30
Emília P. Duarte	(Assistant Prof., FCTUC)	80
Eunice Virgínia Carrilho	(Assistant Professor)	30
Fernando Aidos	(Assistant Professor, FCTUC)	30
Flávio Nelson Reis	(Assistant Investigator)	60
Francisco Cerqueira Alves	(Assistant Investigator)	30
Francisco Caramelo	(Assistant Professor)	80
Francisco Oliveira	(Assistant Investigator)	80
Frederico G. Pereira	(Assistant Professor)	50
Gina Maria Costa Caetano	(Investigator)	100
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)	30
João Filipe da Costa Martins	(Investigator)	100
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 Pedro Magalhães	(Investigator, Univ. Liverpool)	Collaborator
João Pereira Figueira	(MD)	30
João Santos Relvas	(Emeritus Professor)	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	(Assistant Professor)	Collaborator
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
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 Vidigal	(Professor)	30
Mª Manuela Monteiro Grazina	(Assistant Prof., FMUC)	60
Mª Margarida Caetano	(Assistant Professor)	30
Mª Margarida Caramona	(Full Professor)	30
Mariana Freitas	(Investigator)	Collaborator
Mário Simões	(Full Prof., FPCE-UC)	Collaborator
Miguel Castelo-Branco	(Associate Professor)	90
Miguel Patrício	(Assistant Investigator)	100
Nuno David Ferreira	(Assistant Professor)	30
Paula G. Agostinho	(Investigator, FMUC)	60
Paulo Pinheiro	(Assistant Inv., CNC)	100
Paulo Fernando Santos	(Assistant Professor)	40
Paula Cristina Vaz Tavares	(Assistant Professor)	30
Pedro Miguel Serranho	(Assistant Professor)	40
Ramiro Almeida	(Assistant Prof., Inst. Pol. Porto)	75
Ricardo Rodrigues	(Assistant Inv., CNC)	100
Rodrigo A. Cunha	(Associate Prof., FMUC)	75
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

Sandra Maria R. Carvalho Bós	(Assistant Inv., FMUC)	30
Sergio José Do Carmo	(Investigator)	30
Sónia Isabel Gonçalves	(Assistant Investigator)	100
Sônia Alexandra Santos	(Assistant Professor)	50
Susana Louros	(Investigator)	Collaborator
Teresa Dinis Silva	(Associate Prof., FFUC)	60

POST-DOC MEMBERS	**TIME % AT CNC.IBILI**
Ana Patrícia Simões	100
Ana Raquel Santiago	100
Ângela Inácio	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
Graciano Leal	100
Ildete Luísa Ferreira	100
Inês Teixeira de Almeida	100
Joana Fernandes	100
Joana Marques	100
Joana Teresa Gonçalves	100
João Pedro Lopes	100
José Eduardo Lima Rebola	100
Ligia de Sousa Ferreira	100
Lorena Itatí Petrella	100
Mafalda Sofia Cândido	100
Magda Santana	100
Mª Fatima Loureiro da Silva	100
Mª José Braga Ribeiro	100
Mário Laço	50
Miranda Mele	100
Monika Intaite	100
Nélio Gonçalves	100
Paula Canas	100
Rui Miguel Oliveira da Costa	100
Samira Ferreira	100
Sandra Freitas	60
Sandra Mota	100
Tatiana Andreia Catarino	

PHD STUDENTS	**TIME % AT CNC.IBILI**
Amber Kerkhofs	100
Ana Isabel Rodrigues	100
Ana Margarida Teixeira	100

Ana Maria Batista	100
Ana Patrícia Marques	100
Ana Salomé Pires	100
Ana Rita Gaspar	100
Andreia Martins Rosa	100
Anna Pliássova	100
António Campos Figueiredo	25
António Silva	50
Blanka Kellermayer	100
Carlos Manuel Amaral	100
Cassilda Pereira	100
Cátia Santa	100
Diana Serra	50
Diogo André Fonseca	100
Dominique Fernandes	100
Eurico Miguel Fial Ribeiro	80
Fátima Bastos	60
Fernando José Mendes	60
Filipa Lima Júlio	100
Filipe Manuel Farto Palavra	50
Francisco Queiroz Gonçalves	100
Gladys Caldeira	100
Ivan Salazar	100
Janete Santos	100
Jeannette Schmidt	100
João Valente Duarte	100
Lara Franco	100
Joana Pedro	100
Luana Naia	100
Mafalda Bacalhau	100
Marco António Simões	100
Mª Helena Bica Madeira	100
Mª Joana Pinto	100
Maria João Carvalho	30
Mª Luísa Ferreira Ribeiro	30
Mariana Botelho Rocha	100
Mariline Silva	100
Mário Carvalho	100
Marta Cristina Teixeira	100
Mohamed Hussien	100
Otília d'Almeida	100
Patrícia Sofia Alçada Morais	100
Pedro Afonso	100
Pedro Luís Fonseca	30
Raquel Maria Oliveira	100
Raquel Sofia Freitas Bóia	100
Ricardo Alexande Leitão	100
Samuel Filipe Chiquita	100
Sara Amaral	100
Sara Raquel Martins Neves	100
Sara Raquel Nunes	100
Sara Silva	100

Sofia Andreia Viana	50
Sulaiman I S Abuhaiba	100
Susana Figueiredo e Silva	100
Susana Isabel Simão Mouga	100
Susana Sampaio	100
Sandra Anjo	100
Sara Oliveira	45
Sofia Ferreira	100
Sónia Rosa Pereira	100
Teresa Maria da Silva Sousa	100
Tiago Alfaro	50
Vanessa Filipa Santos	100
Xinli Xu	100

MSc Students	**Time % at CNC.IBILI**
Beatriz Rodrigues	100
Carina Maranga	100
Catarina Carmo	100
Débora Serrenho	100
Diogo Canhoto	30
Filipa Almeida	100
Helena A. Ribeiro Pinheiro	100
Iolanda John Mora de Cruz	40
Joana Filipa Mendes Duarte	100
Joana Freire Costa	100
José Carlos Ribeiro Pereira	100
Lígia Fão	100
Marina Rodrigues	100
Nuno Filipe Henriques Silva	100
Pasqualino de Luca	100
Renato Sousa	100

Technicians / Others		**Time % at CNC.IBILI**
Ana Catarina Neves		Collaborator
Ana Mafalda Teixeira	(Grant Technician)	100
Andreia Sofia Pereira	(Grant Technician)	100
Ângela Sofia Miranda	(Grant Technician)	100
Carlos Daniel Ferreira	(Technician)	100
Carlos Manuel Pereira	(Grant Technician)	100
Carlos Rabaça Cordeiro	(MD)	Collaborator
Carolina César Alves	(Grant Technician)	100
César Alejandro Nunes	(MD)	30
Daniela Isabel Oliveira	(Grant Technician)	100
Diliana Rebelo Santos	(Grant Technician)	100
Helena Beatriz Santiago	(MD)	Collaborator
Hélio Jorge Gonçalves	(Grant Technician)	100
Hugo Alexandre Quental	(Grant Technician)	100
Inês Roque Antunes Pita	(Grant Technician)	100
Inês Sofia Dinis Aires		Colaborator
Isabel Catarina Duarte	(Technician)	90
Joana Margarida Martins		Colaborator

João Calmeiro Pereira	(Grant Technician, CNC)	100
João Filipe Lima	(Grant Technician)	100
João Paulo Andrade	(Grant Technician)	100
José Alves	(Technician, CHUC)	Collaborator
Lília Pereira Jorge	Grant Technician)	100
Márcia Sofia Andrade	(Grant Technician)	100
Margarida Maria Marques	(Invited Assistant)	30
Mª Olinda Rebelo	(Technician, CHUC)	Collaborator
Nádia Isabel Canário	(Grant Technician)	100
Nuno Ricardo Ferreira		Collaborator
Patrícia Pereira	(Grant Technician)	50
Ricardo José Martins	(Grant Technician)	100
Ricardo Jorge Teixo	(Grant Technician)	100
Sónia Maria Ferreira	(Grant Technician)	100
Tânia Maria Marques	(Grant Technician)	100
Vítor César Arantes Pinheiro	(MD)	30
Vítor Hugo Alves	(Grant Technician)	100
Victor Hugo Teixeira Pinheiro	(MD)	40

METABOLISM AGING, AND DISEASE | *JOÃO RAMALHO SANTOS*

MEMBERS HOLDING PHD		**TIME % AT CNC.IBILI**
Alexandrina F. Mendes	(Assistant Prof., FFUC)	80
Américo Manuel Figueiredo	(Associate Professor)	30
Ana Paula Marques de Sousa	(Investigator, CHUC)	50
Ana Rita Figueiras	(Assistant Prof., FFUC)	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
Elisario Tavares Silva	(Assistant. Prof. FFUC)	60
Eugénia Carvalho	(Associate Inv., CNC)	100
Fernanda Roleira	(Assistant. Prof. FFUC)	60
Fernando Judas	(CHUC)	Collaborator
Francisco Veiga	(Full Professor, FFUC)	50
Hans Eickhoff	(Investigator)	30
Henrique Manuel Girão	(Assistant Investigator)	100
Ignacio Vega-Naredo	(Assistant Inv., CNC)	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
Lino Manuel Gonçalves	(Associate Professor)	40
Mª Carmen Alpoim	(Associate Prof., FCTUC)	60

Mª João Jorge Pinho	(Investigator)	100
Mª Margarida Souto-Carneiro	(Assistant Inv., CNC)	100
Maria S. Santos	(Principal Inv., FCTUC)	100
Maria Teresa Cruz	(Assistant Prof. FFUC)	80
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 Travasso	(Assistant Professor)	Collaborator
Sandra Isabel M. Cardoso	(Assistant Prof., FMUC)	60

POST-DOC MEMBERS	**TIME % AT CNC.IBILI**
Ana Burgeiro	100
Ana Catarina Fonseca	100
Ana Duarte	100
Ana Raquel Esteves	100
Ana Silva	100
Cristina Barosa	100
Cristina Carvalho	100
Diana Silva	100
Elisa Aida da Silva Ferrada	100
Ermelindo Leal	100
Filipe Valente Duarte	100
Helena Carvalheiro	100
Ivan Viegas	100
João Paulo Teodoro	100
Ludgero Tavares	100
Mª Alexandra B. Amaral	30
Mª Teresa Cunha-Oliveira	100
Mariana Pinto	20
Monika Zuzarte	100
Patrícia Seraphim	100
Paula Mota	100
Paulo Nuno Centeio Matafome	100
Rosa Cristina Simões Fernandes	100
Rosa Resende	100
Sandra Catarina G. Amaral	100
Sandro Pereira	100
Sonia Correia	100
Steve Mendes Catarino	100
Susana Cardoso	100
Vilma Sardão Oliveira	100

PHD STUDENTS	**TIME % AT CNC.IBILI**
Ana Mª Silva	100
Ana Plácido	100
Ana Raquel Coelho	100
Andreia Gonçalves	100
Bruno Alexandre Almeida	100
Cátia Sousa	100
Cláudia Deus	100

Daniel Santos		100
Emanuel Candeias		100
Fernanda Carrilho		30
Filipa Carvalhal Marques		100
Joana Crisóstomo da Silva		100
Joana Liberal		100
João Demétrio B. Martins		100
João Pedro Oliveira		50
João Rito		50
João Silva		100
Katia Mesquita		100
Liliana Rita Velindo Letra		30
Luciana Ferreira		100
Mª Inês Almeida Sousa		100
Mª Madalena Ribeiro		100
Nuno Gabriel Machado		100
Paula Cristina Martins		30
Ricardo Jorge Pereira		30
Rui Miguel Baptista		30
Sara Ramos		50
Tânia Sofia Marques		100
Teresa Rodrigues		100
Tiago Daniel Rodrigues		30
Tiago R. Santos		33

MSc Students		**Time % at CNC.IBILI**
Christian Neves		100
Eurico Serrano		100
Marco Cunha		100

Technicians /Others		**Time % at CNC.IBILI**
Ana Sofia Rodrigues		100
Carlos Rodrigues	(Grant Technician, CNC)	100
Isabel Ferreira	(Grant Technician, CNC)	100
João Ferreira	(Grant Technician, CNC)	100
Laisa Sá	(Grant Technician)	Collaborator
Marcelo Correia		100
Margarida Coelho		100
Mª Gonçalves Fernnades		Collaborator
Marisa Marques	(Grant Technician, CNC)	100
Pauline Santos	(Grant Technician)	Collaborator
Renata Tavares		100
Rita Carvalho		Collaborator
Rui Simões		Collaborator
Rusbene Carvalho	(Grant Technician)	Collaborator
Susana Pereira	(Grant Technician, CNC)	100
Tânia Perestrelo		100

STEM CELL-BASED AND MOLECULAR THERAPIES | *LUIS PEREIRA DE ALMEIDA*

MEMBERS HOLDING PHD		TIME % AT CNC.IBILI
Akhilesh Rai	(Assistant Inv., CNC)	100
Alcino Jorge Lopes Leitão	(Assistant Prof., FFUC)	60
Amílcar Falcão	(Full Prof., FFUC)	50
Ana Cristina Fortuna	(Assistant Prof., FFUC)	30
Ana Luísa Cardoso	(Assistant Inv., CNC)	100
Ana Bela Sarmento Ribeiro	(Assistant Prof., FMUC)	40
Anália do Carmo	(Assistant Prof., FFUC)	35
André Xavier C. Negrão Valente	(Assistant Inv., CNC)	100
António Manuel Veríssimo Pires	(Assistant Prof., FCTUC)	Collaborator
Armindo J. Alves S. Salvador	(Assistant Inv., CNC)	100
Artur Figuerinha	(Assistant Prof., FFUC)	30
Bruno Miguel Neves	(Assistant Prof. FFUC)	40
Carla Vitorino	(Assistant Prof, FFUC)	30
Carlos Cavaleiro	(Assistant Prof, FFUC)	50
Carlos Faro	(Associate Prof., FCTUC)	30
Carlos Filipe Pereira	(Investigator, CNC)	100
Célia Nogueira	(Assistant Prof, FMUC)	Collaborator
Eliana Souto	(Assistant Prof., FFUC)	60
Euclides Pires	(Associate Prof., FCTUC)	Collaborator
Fernando Ramos	(Associate Prof, FFUC)	40
Gabriela Silva	(Assistant Prof., FFUC)	60
Henrique Faneca	(Assistant Inv., CNC)	100
Hugo Fernandes	(Assistant Inv., CNC)	100
Isaura Simões	(Assistant Inv., CNC)	100
Joana Cardoso Costa	(Inv. Assistant Prof., FCTUC)	Collaborator
João José Sousa	(Associate Prof, FFUC)	30
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
Manuel Garrido	(Investigator, Genibet)	30
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	(Full 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)	60
Mª Manuel da Cruz Silva	(Assistant Prof., FFUC)	60
Mª Teresa Batista	(Emeritus Prof., FFUC)	30
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
Nuno Mendonça	(Investigator, III)	30
Olga Maria F. Borges Ribeiro	(Assistant Prof., FFUC)	60

Paula Veríssimo Pires	(Assistant Prof., FCTUC)	40
Raghu Kalluri	(Investigator, HMS)	35
Ricardo Neves	(Assistant Inv., CNC)	100
Ricardo Pires	(Assistant Inv., CNC)	100
Sara Domigues	(Assistant Prof., FFUC)	60
Sérgio Simões	(Associate Prof., FFUC)	80
Teresa Gonçalves	(Assistant Prof., FMUC)	40
Teresa Maria C. Martins	(Assistant Inv., IPO)	80
Vera Lúcia Dantas Moura	(Manager Science & Tech., UC)	50
Vítor Gonçalo Mendes	(Investigator)	30

POST-DOC MEMBERS	**TIME % AT CNC.IBILI**
Adrian Balsa	100
Alessandra Zonari	100
Alessandro Boli	100
Ana Barradas	100
Ana Maria Cardoso	100
Ana Teresa Simões	100
Carolina Isabel Paiva Coelho	100
Catarina Miranda	100
Célia Cabral	30
Chantal Fernandes	100
Clévio Nóbrega	100
Liliana Mendonça	100
Luís Estronca	100
Mariana Bexiga	100
Renato Cardoso	100
Rita Perfeito	100
Rui Lopes	100
Rui Nobre	100
Sezin Aday	100
Slavomira Doktorovova	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**
Ana Catarina Ferreira	100
Ana Cristina Gonçalves	100
Ana Cristina Gregório	100
Ana Cristina Ferreira	100
Ana Filipa Cruz	100
Ana Francisca Lima	100
Ana Isabel Serralheiro	100
Ana Maranha Tiago	100
Ana Sofia Lourenço	100
Ana Sofia C. Valdeira	100
Ana Teresa Viegas	100

André Filipe M. Soares	100
Andreia Marques Gomes	100
Ângela Valério-Fernandes	100
Bruno Miguel F. Gonçalves	100
Catarina Mendes Morais	100
Catarina Praça Almeida	100
Catarina Rebelo	100
Daniela Gonçalves	100
Deolinda Santinha	100
Dina Farinha	100
Dina Pereira	100
Dulce Marisa Bento	100
Emanuel Quartim Costa	100
Edna Filipa Soares	100
Filipa Lebre	100
Geetha Vijayakumar	100
Gianluca Selvaggio	100
Gustavo Costa	100
Helena Antunes	100
Inês Vasconcelos Miranda Santos	75
Isabel Maria Santos Onofre	100
Ivana Kostic	50
João Freitas	100
Joana Balça Pinheiro	100
Joana Bicker Aparicio	100
Joana Filipa Fangueiro	50
Joana Filipa Neves	100
Joana Ribeiro Guedes	100
Joana Sousa	100
Josephine Blersch	100
Lisa Rodrigues	100
Luís França	100
Mª Mafalda Costa	100
Mª de la Salete J. Baptista	100
Mariana Conceição	100
Mariangela Natale	100
Marisa Gaspar	100
Marta Pereira	30
Michela Comune	100
Miguel Maria Lino	100
Nuno Mendonça	25
Patrícia Nunes	20
Patrícia Rosado Albuquerque	100
Paulo Magalhães	100
Pedro Curto	100
Pedro José Gouveia	100
Pedro Manuel Batista Branco	100
Raquel Alves	50
Rui Figueiredo	100
Rui Benfeitas Vicente	100
Rui Soares	40
Sandra Cristina Jesus	100

Sandra Figueiredo	100
Sandra Pinto	100
Sara Lopes	100
Sofia Anastácio	100
Sofia Pereira Romano	100
Tânia Leandro	100
Vanessa Mendes	100
Vitor Carmona	100

MSc Students	**Time % at CNC.IBILI**
Ana Catarina Monteiro	100
Ana Rita Cruz	100
Ana Sousa	100
Ângela Geraldo	100
Cristina Martins	100
Daniela Ferreira	100
Daniela Santos	100
David Coelho	100
Fábio Rosa	100
José Miguel Codeso	100
Pedro Cunha	100
Ricardo Silva	100
Rute Araújo	100

Technicians / Others		**Time % at CNC.IBILI**
Ana Maria B. Alves		Collaborator
Carlos Matos	(Grant Technician, CNC)	100
Daniela Costa		Collaborator
David Bowman		Collaborator
Fátima Nunes	(Grant Technician, CNC)	25
Heloisa Gerardo	(Estagiária IEFP, CNC)	100
João Fernando Carvalho		Collaborator
Miguel Costa		Collaborator
Mónica Serra		Collaborator
Patrícia Ferreira		Collaborator
Patrícia Pitrez	(Grant Technician, CNC)	100
Renato Pires		Collaborator
Samuel Silvestre		Collaborator
Sónia Conçalves Pereira		Collaborator
Tânia Barata	(Grant Technician, CNC)	100
Tânia Lourenço	(Grant Technician, CNC)	100
Vanessa Monteiro		100
Vera Calhau		Collaborator

http://cnc-ibili.cnc.uc.pt| cncibili@uc.pt