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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

<table>
<thead>
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## PUBLICATIONS

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## THESIS CONCLUDED

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<td>MSc thesis</td>
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</tr>
</tbody>
</table>
Organization of CNC.IBILI

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

SCIENTIFIC AREAS AND RESEARCH GROUPS

At present, research programmes and projects are organized in 3 research scientific areas, each coordinated by a senior scientist. The programme for each area is implemented by small research groups each headed by a research leader in his field of study. In 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 Griffith Jones)
ImmonoMetabolic 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: Armando Salvador)
Medical Microbiology Group (Head: Teresa Gonçalves)
Molecular Mycobacteriology Group (Head: Nuno Empadinhas)
Medicinal Chemistry & Drug Discovery Group (Head: Maria Luisa Sá e Melo)
Pharmacometrics Group (Head: Amilcar Falcão)

Biotechnology

Microbiology of Extreme Environments Group (Head: Milton Costa)
Molecular Biotechnology Group (Head: Carlos Faro)
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 performed 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 dysfunction 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 IR techniques (spectroscopy, morphometry and function), molecular imaging (PET with 11C and 18F Chemistry), Transcranial 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
Emília Conceição Duarte PhD
Irina Moreira PhD
João Miguel Peça-Silvestre PhD
Paulo Cesar Pinheiro PhD
Ramiro Daniel de Almeida PhD
Angela 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
Marilíne Silva PhD Student
Jeannette Schmidt PhD Student
Glady's Caldeira PhD Student
Lara Franco PhD Student
Mohamed Hussien PhD Student
Blanka Kellermayer PhD Student
Mário Carvalho PhD Student
Pasqualino de Luca MSc Student
Beatrix Rodrigues MSc Student
Dêbora Serrenho MSc Student
Joana Freire Costa MSc Student
Marina Rodrigues MSc Student
Renato Sousa MSc Student
João Calmeiro Pereira Grant Technician

**REDFOX 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 Leda 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 Oliveira 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
João Pereira Figueira PhD
João Santos Relvas PhD
Joaquim Carlos Neto Murta PhD
Jorge de Andrade Saravia PhD
José Paulo Domingues PhD
José Vitor Oliveira Sereno PhD
Luís Filipe Caseiro Alves PhD
Mª Conceição da Fonseca PhD
Mª Cristina Januário Santos PhD
Mª João Vidigal PhD
Miguel Patricio 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 Itáli 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
Andrei 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 Abupaiba  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
Andrea Sofia Pereira  Grant Technician
Angéla 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
Lídia Pereira Jorge  Grant Technician
Márcia Sofia Andrade  Grant Technician
Margarida Maria Marques  Invited Assistant
Nadia Isabel Canário  Grant Technician
Ricardo José Martins  Grant Technician
Sônia 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 Kőfalvi  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
Nélia 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
Patricia Sofia Alçada Morais  PhD Student
Sofia Ferreira  PhD Student
Xinli Xu  PhD Student
Tiago Alfaro  PhD Student

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

António Francisco Ambrósio  PhD (Head of Group)

**MITOCHONDRIAL DYSFUNCTION AND SIGNALING IN NEURODEGENERATION GROUP**

Ana Cristina Carvalho Rego  PhD (Head of Group)
Carla Lopes  PhD
Elisabete Baptista Ferreira  PhD
Ildefe Luisa Araújo Ferreira  PhD
Mário Laço  PhD
Sandra Mota  PhD Student
António Silva  PhD Student
Luana Naia  PhD Student
Catarina Carmo  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
António Macedo e Santos  PhD
Bruno Oliveira Manadas  PhD
Inês Esteves Baldeiras  PhD
Joaquim Cerejeira  PhD
Manuela Grazina  PhD
Mª Isabel Santana  PhD
Mª Joana Barbosa de Melo  PhD
Sandra Freitas  Post Doctoral Fellow
Ana Rita Gaspar  PhD Student
Cátia Santa  PhD Student
Mafalda Bacalhau  PhD Student
Sandra Anjo  PhD Student
Carlo Rabaça  Collaborator
Célia Gomes  Collaborator
Helena Beatriz Santiago  Collaborator
José Alves  Collaborator
Mª Olinda Rebelo  Collaborator
Mariana Freitas  Collaborator
Mário Simões  Collaborator

**URINES IN BRAIN DISEASES GROUP**

Elisa Regina Campos  PhD

Diogo Canhoto  MSc Student
Filipa Almeida  MSc Student
Lígia Fão  MSc Student

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

António Francisco Ambrósio  PhD (Head of Group)

**MITOCHONDRIAL DYSFUNCTION AND SIGNALING IN NEURODEGENERATION GROUP**

Ana Cristina Carvalho Rego  PhD (Head of Group)
Carla Lopes  PhD
Elisabete Baptista Ferreira  PhD
Ildefe Luisa Araújo Ferreira  PhD
Mário Laço  PhD
Sandra Mota  PhD Student
António Silva  PhD Student
Luana Naia  PhD Student
Catarina Carmo  MSc Student

**AGING AND BRAIN DISEASES: ADVANCED DIAGNOSIS AND BIOMARKERS GROUP**

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Bruno Oliveira Manadas  PhD
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Joaquim Cerejeira  PhD
Manuela Grazina  PhD
Mª Isabel Santana  PhD
Mª Joana Barbosa de Melo  PhD
Sandra Freitas  Post Doctoral Fellow
Ana Rita Gaspar  PhD Student
Cátia Santa  PhD Student
Mafalda Bacalhau  PhD Student
Sandra Anjo  PhD Student
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Mª Olinda Rebelo  Collaborator
Mariana Freitas  Collaborator
Mário Simões  Collaborator

**URINES IN BRAIN DISEASES GROUP**

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Filipa Almeida  MSc Student
Lígia Fão  MSc Student
Filipa Isabel Baptista  Post Doctoral Fellow
Filipa Solange Cardoso  Post Doctoral Fellow
Mafalda Sofia Cândido  Post Doctoral Fellow
Ana Margarida Teixeira  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 Alexandre 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
Patricia Pereira  Grant Technician
Ricardo Jorge Teixo  Grant Technician
Victor Hugo Teixeira Pinheiro MD
Vitor César Arantes Pinheiro MD
Ana Catarina Neves  Collaborator
Inês Sofia Dinis Aires  Collaborator
Joana Margarida Martins  Collaborator
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 controlling the assembly of new presynapses.

(ii & iii) Glutamatergic synapses and neuropsychiatric disorders (PIs: Ana Luisa 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 synapses 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 Achievements
(i) Local proteasome regulation in neuronal development (PI: Ramiro Almeida)
To understand the axonal intrinsic processes underlying formation of presynaptic clusters, we relied on microfluidic devices for the isolation of axons. We used this platform to specifically inhibit the proteasome in axons. We observed that axonal proteome inhibition increases the number of presynaptic sites. Importantly these new presynaptic boutons are functional since they are able to recycle FM dyes. We also show a localized decrease in proteasome activity at the presynapse during the formation of axodendritic 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.

(ii) Structural characterization of protein-based interactions in D2R activity (PI: Irina Moreira)
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(iii) Structural characterization of protein-based interactions in D2R activity (PI: Irina Moreira)
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(iv) GABAergic synapse dysfunction and neuronal death in brain ischemia (PI: Carlos Duarte)
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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).

(ii & iii) Glutamatergic synapses and neuropsychiatric disorders (PIs: Ana Luisa 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)

3. 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).

(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 'NO  
concentration dynamics is decreased in the hippocampus,  
striatum and cerebral cortex during age and that these  
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 yielding ethyl nitrite the human  
stomach following consumption of alcoholic beverages and  
lettuce (source of nitrate). In turn, ethyl nitrite 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 polyphenols, 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 insulin 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 Y1 and Y5 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 Iet-7 microRNA modulation prevents central and peripheral alterations induced by high-fat diet in mice (Sousa-Ferreira et al., in preparation)

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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 Networks, 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 thorough background for translational research approaches. These allowed to separate low vs. high level impairment in visual cognition neurodevelopmental models of impaired perception and decision making such as autism, and neurogenetic conditions such as Autism, 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 of 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 informatics 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, such 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 FP7 and H2020 projects, such as BRAINTRAIN. We finally also achieved a worldwide patent together with IBA, the world leader in cyclotron production.

Our basic research goal: testing the GABA inhibition hypothesis in autism

Our conceptual approach: to test gene-brain physiology - behaviour relationships with a focus on inhibition

We believe that our project will have important implications for understanding the disease mechanism by studying the impact of impaired inhibition in the neurobiological manifestations of autism
**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 as 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 Patricia Simões, Samira Ferreira, Nélvio Gonçalves).

**Main Achievements**


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).


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).


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 Ca²⁺; and ΔΨm.
Aβ+NMDA enhance mitochondrial Ca²⁺ retention and organelle depolarization through the ER.

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 flavonoids 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 analyzed 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 parenthetically 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+ (Ca2+) and mitochondrial membrane potential (Δψm) in primary cortical neurons. Exposure to Aβ+NMDA largely increased Ca2+ and induced mitochondrial depolarization. Aβ-induced Ca2+ and mitCa2+ rise were inhibited by ifenprodil and in GluN2B(-/-) neurons, implicating the involvement of GluN2B subunit. Moreover, Aβ+NMDA-induced mitCa2+ rise involved ER Ca2+ release through IP3R and mitochondrial entry through mitCa2+ uniporter. Data highlight mitCa2+ 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 analyzed oxidative stress 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 Ca2+ 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 increased 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)

Objectives
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 Achievements**

1) **Biomarkers of Neurodegenerative Diseases**

According to our data the estimated number of Portuguese people with dementia aged 260 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 43MC/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 implementation 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 14-3-3 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 SQT7M1 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 vivo 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 genotypype-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 22q11 may 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/PDSPPT), 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.1448T>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 heterozygosity 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 on 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/degneration, 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 Bisphosphonates 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.

Activation of adenosine A3 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.


Diabetes reduces Ca2+ permeability of extrasynaptic AMPA receptors in All 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”.

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**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/mm².
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Barbosa JS,
Sanchez

Neurosci.
Lett
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Vieira MM, Schmidt J, Ferreira JS, She K, Oku S, Mele M, Santos AE, Duarte CB, Craig AM, Carvalho AL. Multiple domains in the C-terminus of NMDA receptor GluN2B subunit contribute to neuronal death following in vitro ischemia. Neurobiol Dis. (In Press)
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, osteoarthritis, 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.
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<td>Helena Carvalheiro</td>
<td>Post Doctoral Fellow</td>
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<tr>
<td>Ludgero Tavares</td>
<td>Post Doctoral Fellow</td>
</tr>
<tr>
<td>Tiago Sousa</td>
<td>PhD Student</td>
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<tr>
<td>Laisa Sá</td>
<td>Grant Technician</td>
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<td>Pauline Santos</td>
<td>Grant Technician</td>
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<td>Rusbene Carvalho</td>
<td>Grant Technician</td>
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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 nitrrosative 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 photoexcitation.

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 HAPTNIZATION 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 transdifferentiate 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 (osteocorticoid) or anticatabolic (antiresorptive, 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.

Genetic and Environment

![Diagram of heart and skin with molecular mechanisms]

INSULIN RESISTANCE / DIABETES / COMPLICATIONS
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. miRNA 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 (1H-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+ 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+ cells are mostly ignored. However, they do not embody the whole complexity of the disease process. Even though, CD8+ 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-13C]lactate, derived from the [U-13C]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-13C]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.

![Graphical representation of metabolic shifts in CD8+ T cells in RA](image-url)
PUBLICATIONS


Pantazi, Palmeira, Paiva, Amaral, Rodriguez, Canyellas, Correig, Ballescà, Camel, Nunes, Alves, Tomás, Conde, Cristóvão, Moreira, Oliveira, Silva.


**In Press**


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 SMEscompanies (e.g., Criostaminal, QJAGEN) 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 iP5-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/tailed. 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.

Coordinator: Luis Pereira de Almeida

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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
Elíana Maria Barbosa Souto PhD
Henrique Santos Faneca PhD
João Nuno Moreira PhD
Luís 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
Raghú 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
Lígia de Sousa Ferreira Post Doctoral Fellow
Líliana Simões Mendonça Post Doctoral Fellow
Rita Perfeito Post Doctoral Fellow
Rui Jorge Gonçalves Nobre Post Doctoral Fellow
Rui Manuel Lopes Post Doctoral Fellow
Slavorima Dormorovova Post Doctoral Fellow
Sônia Patrícia Dias Duarte Post Doctoral Fellow
Ana Cristina Ferreira PhD Students
Ana Cristina Gonçalves PhD Students
Ana Cristina Romano PhD Students
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Sandra Jesus PhD Students
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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 CRUNHA MSc Student
Rute Araújo MSc Student

STEM CELL BIOTECHNOLOGY GROUP

Lino da Silva Ferreira PhD (Head of Group)
Akhiilesh 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 Santana PhD Student
Emanuel Quarimr 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 Pitre Pereira Grant Technician
Tânia Barata Grant Technician
Fábio Rosa MSc Student

SYSTEMS AND COMPUTATIONAL BIOLOGY GROUP

Armindo Salvador PhD (Head of Group)
Alessandro Boli 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 Pedroso 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

Pedro Cunha MSc Student
Rute Araújo MSc 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

**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 Veríssimo Pires  PhD
André Soares  PhD Student
Ana Sofia Lourenço  PhD Student
Pedro Curto  PhD Student
Euclides Pires  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
Lígia 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

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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 transverse membranes and efficiently deliver their cargo into the cell.

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

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.

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**Main Achievements**

Hydrogen peroxide (H$_2$O$_2$) 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$_2$O$_2$ concentrations? How are H$_2$O$_2$ signals transduced? Why does the PTTRS show distinct responses to H$_2$O$_2$ 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$_2$O$_2$ 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$_2$O$_2$ 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$_2$O$_2$ 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$_2$O$_2$ 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$_2$O$_2$ supply rates Prx is abruptly hyperoxidized to the peroxidatically inactive but holdase-active form. H$_2$O$_2$ 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 Mycobacteriology:

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


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:


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 submitted** - Lisa Rodrigues, Isabel Miranda, Geanne Andrade, Marta Mota, Luisa 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 of 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<sub>A</sub> receptor and mimicking the key endogenous allopregnanolone, 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. Additionally we also focused on the anti-Leishmania activity of semisynthetic lupane triterpenoids derivatives of betulin and betulinic acid. Effects on the cell cycle, apoptosis/necrosis events, morphology and DNA integrity were also planned.

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 transformation) 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 Asatic Acid (AA) derivatives were successfully synthesized, tested for their anti proliferative 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: Amilcar 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.

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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 the side chains annotated.

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, sheep, and cow milk (3L), pasteurize d or raw as indicated, were used for cheese production using VRen as milk clotting agent. The cheeses were ripened for about 3 weeks. For comparison, a parallel experiment using synthetic chymosin (MaxiRen®) as the coagulant agent (commercial rennet). (Almeida et al., 2015, Appl Microbiol Biotechnol, doi:10.1007/s00253-014-5902-5)](insert image here)
Macrophage Mitochondrial and Stress Response to Ingestion of Candida, Cryptococcus, Aspergillus and dermatophyte species.


**IN PRESS**


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.

**Publications**


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

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**


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

Projects in collaboration

NEUROSCIENCE, VISION AND BRAIN DISEASES

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-supervised 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:


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 Microelectrode 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.


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 Otín - 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)

Licío 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


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)
Participation 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. Amsterdam, 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 (JPN, 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 Christine Métin (CNRS, Institut Fer à Moulin, Paris) and Christophe Bernard (INSERM, Univ. Méditerranée, Marseille).

Graduate training:
Co-supervision of a post-doctoral student (Samira Ferreira) with Nuno Sousa (Univ. Minho)
Co-supervision of a PhD student (Silvia Sousa) with Christophe Mulle (Univ. Bordeaux, France)
Co-supervision of a PhD student (Marta Carmo) with Geanne Matos (Univ. Federal Ceará, Brazil)
Co-supervision 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 entitled ‘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).

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)

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.
Aging and Brain diseases: advanced diagnosis and biomarkers


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:


979


**METABOLISM, AGING AND DISEASE RESEARCH LINE**

**Cell Metabolism and Quality Control**


Carmen García-Rodríguez 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 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
Lilian 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 Rossoelo, 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:


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, 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)


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; Küglert, 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


Research:


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


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 Važáo (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).
Participation in Working Group 4: "Novel Technologies and Future Developments"

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), Patricia 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 Abecassiss (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), Sezun 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), Andrea 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$_2$O$_2$ sensor with memory

University of Heidelberg (Germany) and Technical University of Kaiserslautern (Germany):
Researchers: Tobias Dick (UH) and Bruce Morgan (TUUK)
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:


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


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:


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), Forschungszentrum Jülich, 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

29ª 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: Armando 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: Octobre 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 Committee 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
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 neuropathy 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 ARTDIS – 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  

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

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

Bioorganic piezoelectric materials: structure, 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  
Pediatric Hospital, CHUC  
Faculty, of Medicine, University of Coimbra  

The impact of psychostimulants on blood-brain barrier 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 nigro-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 Oliveira  
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
Proteassas de polen de Acacia caven y su importancia en alergias
2015

Daniela Luís
Regulação genética do receptor SHT2A 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
February 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 triple transgenic 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 na 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 ²H NMR analysis of glycerol²H 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$_2$A 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 Fragozo
Avaliação in vivo de receptores de estrogénios no cancro da mama
June 2015

Joana de Matos Rodrigues
Dos Genes à radiorrresistência 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 Goncalves 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-synthetictriterpenoids
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 role 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 antimicrobianos 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. aureus resistente à meticilina numa superfície alimentar da Guarda*  
July 2015  
Supervisor: Ligia Salgueiro Couto

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

Ricardo Vieira  
*Alteration in GABA,R 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 Transcranial 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 óleos essenciais de plantas aromáticas na preservação de produtos cárneos*  
July 2015  
Supervisor: Ligia 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 A2A 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 Petroniño
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 baumannii
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
Translational research and technology transfer have been progressively developed in CNC leading to a promising interaction with Industry and local authorities.

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

**BIOCANT**

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

**Companies operating in Biocant Park**

At the present 20 companies operate in Biocant Park: AP-Bio, Biocant Ventures, Biotrend, Converde/CEV, 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.
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).

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.

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.cnc.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).
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”.

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).

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

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

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

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

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 offers 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.
The Microscopy Imaging Center of Coimbra, at the Center for Neuroscience and Cell Biology (MICC-CNC), is an 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 BiImaging (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.

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.
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/LC Packings). 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)
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, isocitrate 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 highthroughput 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 intergenic 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:

<table>
<thead>
<tr>
<th></th>
<th>Blood (Serum/Plasma)</th>
<th>CSF</th>
<th>Urine</th>
<th>Brain extracts</th>
<th>Other extracts</th>
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<tbody>
<tr>
<td>Cytochemistry and electrophoresis</td>
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<td>IgG Oligoclonal bands</td>
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<tr>
<td>Vitamin A/E</td>
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<td>Purines &amp; Pyrimidines</td>
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<tr>
<td>Anti-neuronal antibodies</td>
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<td>CSF levels of 5-MTHF</td>
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<td>CSF Tau, p-Tau and Aβ42</td>
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<td>CSF 14-3-3 protein</td>
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<tr>
<td>Prion protein isoforms</td>
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<tr>
<td>Oxidative Stress</td>
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<td></td>
<td>25</td>
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</tbody>
</table>
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 widen 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.
Paolo 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 Luisa 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


Team: Patricia 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 Engineering, SIEMENS, Téxtil 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, financed 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:


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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**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 environment and human systems.

Our Background

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

Technology

Seahorse XF96 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 criogênica 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 eletrões 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 microprocessor 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 diferença 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

<table>
<thead>
<tr>
<th>Serviço</th>
<th>1</th>
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<th>3</th>
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<td>Processamento da amostra (total)</td>
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<td>17,00</td>
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<td>30,00</td>
<td>35,00</td>
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</table>

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 accessories**

High-density array caps of electrodes, that come in different sizes (children to adult) and render possible faster subject preparation for simultaneous recordings with many electrodes. This is an absolute requirement for high-density recordings. Accessories include rechloridng 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 Ade

Contact Information

Contact Person: Cláudia Caridade Ade
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 opthalmology 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.
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€ distributed as follows:

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<tr>
<th>Description</th>
<th>Amount</th>
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<tr>
<td>Strategical Project_ UID/NEU/04539/2013</td>
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<td>Incentivo/SAU/LA0001/2014</td>
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<td>Projects</td>
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<tr>
<td>Science Program:</td>
<td>337.170,36€</td>
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</tbody>
</table>

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
<table>
<thead>
<tr>
<th>Title</th>
<th>Financing Agency</th>
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<td><strong>NATIONAL PROJECTS:</strong></td>
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<td>“Rede Nacional de Espectrometria de Massa” Coordinator: Euclides Pires</td>
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<td>“Caracterização dos princípios de design de circuitos metabólicos prevalentes.” Coordinator: Armindo Salvador Participants: Universidade de Coimbra; Universidade do Minho</td>
<td>FCT Ref#: REDE/1506/REM/2005</td>
<td>01/04/2012 to 30/09/2015</td>
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<td>25.281,26€</td>
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<td>“Terapia gênica Não invasiva e Não viral da doença de Machado-Joseph” Coordinator: Luis Almeida</td>
<td>FCT Ref#: PTDC/QUI-BIQ/119657/2010</td>
<td>01/04/2012 to 31/08/2015</td>
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<td>“Estudo do mecanismo patogênico da Doença de Machado-Joseph num novo modelo de células estaminais pluripotentes induzidas.” Coordinator: Luis Almeida</td>
<td>FCT Ref#: PTDC/SAU-NMC/116512/2010</td>
<td>24/01/2012 to 30/07/2015</td>
<td>145.360,00</td>
<td>25.121,72€</td>
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<td>“Avaliação Neuropsicológica e Investigação Bigenómica nas Demência Frontotemporal.” Coordinator: Maria Manuela Grazina</td>
<td>FCT Ref#: PTDC/SAU-EP1/121811/2010</td>
<td>01/01/2012 to 30/06/2015</td>
<td>199.699,00</td>
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<td>“TranstirRetina é uma metaloprotease: possíveis implicações em doenças do sistema nervoso.” Coordinator: Sukalian Chaterjee Proponent: Instituto de Biologia Molecular e Celular (IBMC)</td>
<td>FCT Ref#: PTDC/SAU-ORG/118863/2010</td>
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<td>“Alterações na transmissão sináptica GABAérgica na isquemia cerebral - mecanismos moleculares responsáveis pela internalização dos receptores GABAA.” Coordinator: Carlos Duarte</td>
<td>FCT Ref#: PTDC/SAU-NMC/0198/2012</td>
<td>01/07/2013 to 30/06/2015</td>
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<td>44.080,00€</td>
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<td>“DEMTEST: Diagnóstico de demências rapidamente progressivas baseado em biomarcadores - otimização de protocolos de diagnóstico.” Coordinator: Catarina Resende de Oliveira</td>
<td>FCT Ref#: JPND/0001/2011</td>
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<td>“Regulação do metabolismo energético no cérebro pelo óxido nítrico: solução para a glicólise aeróbia” Coordinator: João Laranjinha</td>
<td>FCT Ref#: PTDC/BBB-BQB/3217/2012</td>
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<td>“Previsão da diabetes e feridas em familiares em primeiro grau de diabéticos tipo 2” Coordinator: John Jones Proponent: Associação Protetora dos Diabéticos de Portugal (APDP)</td>
<td>FCT Ref#: EXCL/DTP-PIC/0069/2012</td>
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<tr>
<td>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</td>
<td>Ana Luisa Colaço Cardoso</td>
<td>PTDC/BIM-MEC/0651/2012</td>
<td>01/03/2013</td>
<td>31/08/2015</td>
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<tr>
<td>Do controlo da neuroinflamação à neuroproteção: bloqueio dos receptores A2A para o tratamento do glaucoma</td>
<td>Ana Raquel Sarabando Santiago</td>
<td>PTDC/BIM-MEC/0913/2012</td>
<td>01/06/2013</td>
<td>30/09/2015</td>
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<tr>
<td>Efeitos do peptídeo orexigénico grelina na transmissão sináptica glutamatérgica</td>
<td>Sandra Manuela Domingues dos Santos</td>
<td>PTDC/NEU-NMC/1098/2012</td>
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<tr>
<td>A Sabedoria do faminto: modulação por ghrelina da neurogénese e da sua relação com a memória</td>
<td>Jorge Gómez</td>
<td>EXPL/NEU-SCC/1193/2012</td>
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<tr>
<td>A natureza das ligações de carbono e azoto como fator discriminante da origem da matéria orgânica solúvel em água de aerossóis atmosféricos</td>
<td>Luisa Ramos</td>
<td>PTDC/AAG-MAA/2584/2012</td>
<td>01/07/2013</td>
<td>30/09/2015</td>
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<tr>
<td>CARDIOSTEM: Tecidos cardiacos e terapias baseadas em células estaminais para aplicações cardiovasculares</td>
<td>Lino Ferreira</td>
<td>MITP-TB/ECE/0013/2013</td>
<td>01/12/2014</td>
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<tr>
<td>Regulação do sistema ubiquitina-proteassoma pelo BDNF nas sinapses do hipocampo: importância na plasticidade sináptica.</td>
<td>Carlos Duarte</td>
<td>PTDC/SAU-NMC/120144/2010</td>
<td>10/02/2012</td>
<td>31/08/2015</td>
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<td>Fibrilas Interrompidas: Inibição de interacções aberrantes proteína-proteína em Amilóides.</td>
<td>Rui Brito</td>
<td>PTDC/QUI-QUI/122900/2010</td>
<td>01/03/2012</td>
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<td>Nova Abordagem na Luta Contra a Tuberculose.</td>
<td>Maria Otília Vieira</td>
<td>HMSP-ICT/0024/2010</td>
<td>01/01/2012</td>
<td>30/06/2015</td>
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<td>Contribuição para a erradicação da malária. Uma nova abordagem para atingir multi-alvos no ciclo de vida do parasita.</td>
<td>Luísa Melo</td>
<td>PTDC/SAU-FAR/118459/2010</td>
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<tr>
<td>O Óxido Nitrico na Doença de Alzheimer - Molécula Sinalizadora e Mediador de Patogénese.“</td>
<td>Ana Ledo</td>
<td>Universidade do Minho</td>
<td>PTDC/BIA-BCM/116576/2010</td>
<td>01/04/2012 to 31/03/2015</td>
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<td>Desenvolvimento de nanopartículas multifuncionais inovadoras para o tratamento do cancro de mama.”</td>
<td>João Nuno Moreira</td>
<td>Universidade do Minho</td>
<td>PTDC/SAU-DMA/121028/2010</td>
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<td>O sistema neuropeptídeo Y: potencial novo alvo terapêutico na retinopatia diabética</td>
<td>Francisco Ambrósio</td>
<td>Universidade de Coimbra</td>
<td>PTDC/NEU-OSD/1113/2012</td>
<td>01/05/2013 to 31/08/2015</td>
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<td>Estratégia terapêutica combinada baseada na modulação de miRNAs direcionada para glioblastoma multiforme: um novo nanosistema de base lipídica para entrega sistémica.”</td>
<td>Maria Conceição Pedroso Lima</td>
<td>IBMC/UP</td>
<td>PTDC/DTP-FTO/0265/2012</td>
<td>02/03/2013 to 01/06/2015</td>
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<td>Um Novo Modelo para a Esquizofrenia: Defeitos na Plasticidade Homeostática Mediada por Stargazina.”</td>
<td>Ana Luísa Carvalho</td>
<td>IBMC/UP</td>
<td>PTDC/NEU-NMC/0750/2012</td>
<td>01/07/2013 to 30/09/2015</td>
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<td>Ambiguidade e virulência em patogénios humanos.”</td>
<td>Nuno Empadinhas</td>
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<td>PTDC/BBB-BEP/0695/2012</td>
<td>01/07/2013 to 30/09/2015</td>
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<td>Tratamento da doença de Alzheimer com um novo peptídeo inibidor da BACE1.”</td>
<td>Armanda Santos</td>
<td>IBMC/UP</td>
<td>PTDC/SAU-SCC/1351/2012</td>
<td>15/06/2013 to 30/09/2015</td>
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<td>Plataformas combinatoriais para promover a sobrevivência celular- PROSURVIVAL.”</td>
<td>Hugo Fernandes</td>
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<td>PTDC/BIM-MED/1118/2012</td>
<td>01/07/2013 to 30/09/2015</td>
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<td>Papel da sirtuina 3 na função mitochondrial e desacetilação de alvos mitocondriais: relevância para a doença de Huntington”</td>
<td>Tatiana Rosado Rosentstock</td>
<td>IBMC/UP</td>
<td>EXPL/BIM-MEC/2220/2013</td>
<td>01/04/2014 to 30/09/2015</td>
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<td>Anestesia no peixe-zebra (Danio rerio)e potenciais implicações na investigação - substituição, redução e refinamento de técnicas e procedimentos”</td>
<td>Anália do Carmo</td>
<td>IBMC/UP</td>
<td>PTDC/CVT-WEL/4672/2012</td>
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<th>Desvendar a vulnerabilidade das células do musculo liso de pacientes com Progeria - Smooth_Progeria</th>
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<td>Ref#: EXPL/BIM-MED/2267/2013</td>
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<td>Coordinator: Catarina Oliveira, Lino Ferreira</td>
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<td>Ref#: MIT-Portugal 2015</td>
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<th>Novas estratégias para a recuperação da fertilidade e potencial genético de felídeos selvagens: desenvolvimento do xenotransplante e da transplantação de células espermatozigônicas estaminais em gato doméstico como modelo para felídeos selvagens.</th>
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<th>Modulação da actividade de células estaminais hematoipoéticas por acção de nanopartículas capazes de libertar factores de transcrição – STEMCELLMODULATORS.</th>
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<th>Modulação da piruvato desidrogenase cinase e pluripotência: Implicações para cancro e biologia de células estaminais.</th>
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<th>Produção e propagação de linhas de células estaminais pluripotentes usando modulação metabólica.</th>
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<th>BIOMARKAPD: Biomarcadores para Doença de Alzheimer e Doença de Parkinson.</th>
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<th>Bioprospecção de enzimas com capacidade de degradar biomassa vegetal no metagenoma do sistema digestivo de Porcellio dilatatus (Crustacea,Isopoda).</th>
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<th>Patofisiologia da Toxicidade Cardíaca Persistente da Doxorubicina: Uma ligação entre Mitocondria e Epigenética</th>
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<td>implicações na doença de Parkinson”</td>
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<td>Biology of polissacarídios raros de metilmanose em micobactérias não</td>
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<td>&quot;Investigação bigenómica translacional na Neuropatia Ótica Hereditária de</td>
<td>Manuela Grazina</td>
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<td>&quot;Celulas e progressão tumoral: dos mecanismos moleculares às consequências</td>
<td>Maria Carmen Alpoim</td>
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<td>Miguel Mano</td>
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<td>espermatogénese e microscopia confocal Raman para análise da função</td>
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<td>&quot;Papel e mecanismos da propagação da sinucleina e da ataxina-3 nas doenças</td>
<td>Luís Almeida</td>
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<td>&quot;Combinación de high-throughput screening and analysis single-cell for the</td>
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<td>study of RNA regulators involved in the initial stages of Campylobacter&quot;</td>
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<td>Carlos José Fialho da Costa Faro</td>
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<td>&quot;Ibercivis.pt - Uma plataforma de computação voluntária para a Península Ibérica.&quot;</td>
<td>Rui Manuel Pontes M. F. Brito</td>
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<td>&quot;Aging, Stress and Chronic Diseases: From mechanisms to therapeutics&quot;</td>
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<td>&quot;New Strategies do manage Brain Diseases.&quot;</td>
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<td>&quot;Engenharia Epigenética para reverter o Fonótipo Celular da Doença de Parkinson&quot;</td>
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<td>André Valente</td>
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<td>&quot;Plataformas de Bioimagem, Comportamento e Electrofisiologia@CNC&quot;</td>
<td>Catarina Isabel Neno Resende de Oliveira</td>
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<td>&quot;Evaluation of oxidative stress and mitochondrial dysfunction in animal models and patients of Huntington’s disease using Cu(II)-ATSM PET&quot;</td>
<td>Ana Cristina Carvalho Rego</td>
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<td>&quot;The up-regulation of hippocampal adenosine A2A receptors is necessary and sufficient to trigger memory dysfunction in Alzheimer’s disease“</td>
<td>Rodrigo Pinto S. A. da Cunha</td>
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<td>“Cellular and Synaptic Dissection of the Neuronal Circuits of Social and Autistic Behavior” Coordinator: João Peça Silvestre</td>
<td>Brain &amp; Behavior Research Foundation: “2013 Narsad Young Investigator Grant”</td>
<td>15/01/2014 to 14/07/2016</td>
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<td>“Silencing Machado-Joseph Disease/Spinocerebellar ataxia type 3 through the systemic route” Coordinator: Rui Nobre Jorge</td>
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<td>10.823,71€</td>
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<td>“Promoting endothelial progenitor cell function in diabetes would healing” Coordinator: Ermelindo Carreira Leal</td>
<td>European Foundation for the Study of Diabetes/IDRF/Novo Nordisk European Programme in Type 1 Diabetes Research</td>
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<td>Unveiling Carbon fixation in three deep serpentinization-driven hyeralkaline springs. Coordinator: Igor Clemente Tiago</td>
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<td>Novel nanoparticles for drug delivery to the skin Coordinator: Lino Ferreira</td>
<td>Queen Mary - 289454 Ref.ª: FP7-PEOPLE-2011-ITN</td>
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<td>“The effect of TCF7L2 on Glucose Metabolism” Coordinator: John Jones</td>
<td>Mayo Clinic SRo1DK078646-08</td>
<td>01/08/2014 To 31/07/2015</td>
<td>17.395,53€</td>
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<td>“Activating autophagy to block Machado-Joseph disease progression” Coordinator: Luís Pereira de Almeida</td>
<td>Association Française contre les Myopathies Ref.: 180151</td>
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<td>“New Treatments for Stress-induced Dysregulation of Circuits Regulating Reward, Fear, and Habit Learning”. Coordinator: Rodrigo Cunha</td>
<td>Massachusetts Institute of Technology Ref.: DARPA-BAA-009-68</td>
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<td>“CAFFEIN-Cancer Associated Fibroblasts (CAF) Function in Tumor Expansion and Invasion”. Coordinator: João Nuno Moreira</td>
<td>Marie Curie grant 316610 Ref# FP7-People-2012-ITN</td>
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<td>&quot;Transplantation of neural stem cells (NSC) as a new therapeutic strategy for Machado-Joseph disease (MJD)&quot;</td>
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<td>&quot;Mitochondrial Trafficking In Alzheimer Disease: Revealing the Role of Hummr.&quot;</td>
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<td>&quot;In chemico, in silico and in vitro modelling to predict human respiratory allergens&quot;</td>
<td>John Hopkins Bloomberg</td>
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<td>&quot;Ghrelin: a novel therapeutic intervention to rescue the phenotype of Hutchinson-Gilford progeria syndrome&quot;</td>
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<td>&quot;Peripheral NPY reverts HGPS phenotype: a study in human fibroblasts and mouse model&quot;</td>
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<td>72.249,25</td>
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<td>&quot;The role of ataxin-2 in in Machado-joseph disease:a molecular therapy approach with viral vectors&quot;</td>
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<td>&quot;159302-1-2009-1-NL-ERA MUNDUS-EMJD – Blanka Kellermay&quot;</td>
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<td>&quot;Role of Adenosine A2A Receptors in the Accumbens and mygdala in the control of Chronic Stress Neuropathology&quot;</td>
<td>Brain &amp; Behavior Research Foundation: &quot;2014 Narsad Independent Investigator Grant&quot;</td>
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<td>&quot;Cellular and synaptic dissection of the neuronal circuits of social and autistic behavior&quot;</td>
<td>João Peça</td>
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<td>&quot;AFM: Ataxin-2 as a new molecular target in Machado-Joseph disease: from translation regulation to disease alleviation&quot;</td>
<td>Clévio Nobrega</td>
<td>01/03/2015</td>
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<td>&quot;Schizophrenia as a Disruption of Developmental Homeostatic Plasticity: A Role for Stargazin&quot;</td>
<td>Ana Luisa M. Carvalho</td>
<td>15/09/2015</td>
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<td>&quot;P2Y1 receptor-CRMP2 control synaptic loss and memory impairment in early AD&quot;</td>
<td>Ricardo Rodrigues</td>
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<td>&quot;Mechanisms underlying hemogenic induction in human fibroblasts&quot;</td>
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<td>“From neuroinflammation control to neuroprotection: blocking adenosine A2A receptor for the treatment of glaucoma”</td>
<td>FCT PTDC/BIM-MEC/0913/2012</td>
<td>01-06-2013 to 31-05-2015</td>
<td>124.431,00 €</td>
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<td>Coordinator: Raquel Santiago</td>
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<td>“Neuropeptide Y system: a new potential therapeutic target in diabetic retinopathy”</td>
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<td>01-03-2013 to 28-02-2015</td>
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<td>“Methylphenidate and blood-brain barrier changes in health and attention deficit hyperactivity disorder”</td>
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<td>01-05-2013 to 30-04-2015</td>
<td>74.040,00 €</td>
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<td>“A breath to overcome lung cancer: EGFR targeted nanoparticles to carry photodynamic therapy”</td>
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<td>01-03-2013 to 28-02-2015</td>
<td>161.200,00 €</td>
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<td>“Unveiling preclinical idiopathic macular hole formation: structural changes by high-definition optical coherence tomography and machine learning”</td>
<td>FCT PTDC/BBB-BMD/2739/2012</td>
<td>01-05-2013 to 30-04-2015</td>
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<td>Frederico Pereira</td>
<td>FCT EXPL/DTP-DES/0104/2013</td>
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<td><strong>HOMETECH</strong></td>
<td>Miguel Castelo-Branco</td>
<td>QREN Nº23218</td>
<td>01-09-2012</td>
<td>30-06-2015</td>
<td>311.234,86, 130.634,77 €</td>
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<td><strong>“Age-related macular degeneration - can metabolomic profile distinguish progressors?”</strong></td>
<td>Inês Laíns</td>
<td>FCT HMSP - ICI/0006/2013</td>
<td>01-07-2014</td>
<td>30-06-2016</td>
<td>46.525,00, 19.137,94 €</td>
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<td><strong>Protocolo Delta – FMUC</strong></td>
<td>Ana Raquel Santiago</td>
<td>DELTA</td>
<td>29-01-2014</td>
<td>28-01-2016</td>
<td>4.900,00, 2.683,02 €</td>
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<td><strong>From molecules to man</strong></td>
<td>Miguel Castelo-Branco</td>
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<td>1.745.400,66, 425.592,20 €</td>
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<td>**CNC.IBLI</td>
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<td>Miguel Castelo-Branco, Francisco Ambrósio</td>
<td>FCT UID/04538/2015</td>
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<td><strong>“Physical, biochemical and histological analysis of human amniotic membrane: contribution to preterm premature rupture of fetal membranes study”</strong></td>
<td>Margarida Abrantes</td>
<td>FMUC A Abrantes.GAI2015</td>
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<td><strong>“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”</strong></td>
<td>Raquel Santiago</td>
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<td>02-01-2015</td>
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<td><strong>“Pinning down TRVP1: acupuncture analgesia”</strong></td>
<td>Frederico Pereira</td>
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<td><strong>“A novel function for gap junction protein Connexin 43: targeting tumor therapy via exosomes”</strong></td>
<td>Maria João Pinho</td>
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<td><strong>“A non-canonical mechanism for selective macroautophagy”</strong></td>
<td>Steve Catarino</td>
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### INTERNATIONAL

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<td>&quot;NK cell-based adoptive therapy targeting human bladder cancer stem cells: impact on tumor progression using a humanized orthotopic animal model&quot;</td>
<td>Célia Gomes Astellas Foundation - Uro Oncology 2014</td>
<td>12-03-2014 to 11-03-2016 €108,070,00 €33,336,60</td>
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<td>&quot;Stimulating Innovation Management of Polypharmacy and Adherence in The Elderly (SYMPATHY)&quot;</td>
<td>Joao Malva European Union HP-PJ-2014</td>
<td>€99,124,00 €18,473,58</td>
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<td>&quot;Multidisciplinary Institute of Ageing (MIA)&quot;</td>
<td>João Malva European Union H2020-WIDESPREAD-2014-1</td>
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<td>&quot;Enhancing Research in Ageing at the University of Coimbra (ERA@UC)&quot;</td>
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<td>&quot;European young Investigators network for Usher Syndrome&quot;</td>
<td>Joao Malva EU-FCT E-RARE4/SAU/0001/2008</td>
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<td>&quot;Taking imaging into the therapeutic domain: self-regulation of brain systems for mental disorders&quot;</td>
<td>Miguel Castelo-Branco BRAINTRAIN</td>
<td>01-11-2015 to 30-10-2018 €638,000,00 €137,218</td>
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<td>Managing inflammation in diabetic retinopathy</td>
<td>Ana Raquel Santiago Bayer Healthcare</td>
<td>1-12-2015 to 31-12-2016 €44,341,00 €980</td>
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### STAFF LIST

#### SERVICE STAFF

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<tr>
<th>Name</th>
<th>Position</th>
<th>Time % at CNC.IBILI</th>
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<tbody>
<tr>
<td>Ana Carina Dias</td>
<td>Graduate Technician, CNC</td>
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<td>Ana Cristina Franco dos Santos</td>
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<td>Ana Margarida Ferreira</td>
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<td>António José Azevedo Teles Grilo</td>
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<td>Catarina João Marques Simões</td>
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#### TECHNICAL STAFF

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<td>Adalberto Fernandes</td>
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<td>Alda Rodrigues</td>
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<td>Anabela Marisa Azul</td>
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<td>Cândida Elsa Frias Mendes</td>
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#### ADMINISTRATIVE STAFF

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<td>Alda Gonçalves</td>
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## RESEARCH STAFF AND STUDENTS / SCIENTIFIC RESEARCH LINE

**NEUROSCIENCE, VISION AND BRAIN DISEASES | MIGUEL CASTELO-BRANCO**

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<th>Members holding PhD</th>
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<td>Alda Maria Abreu Cardoso</td>
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Sergio José Do Carmo (Investigator) 30
Sônia 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**

Ana Patrícia Simões 100
Ana Raquel Santiago 100
Ángela 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 Ferreira 100
Filipa Isabel Baptista 100
Filipa Solange Cardoso 100
Gabriel Ferreira da Costa 100
Graciano Leal 100
Ildete Luisa 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**

Amber Kerkhofs 100
Ana Isabel Rodrigues 100
Ana Margarida Teixeira 100

**TIME % AT CNC.IBILI**
Ana Maria Batista 100
Ana Patrícia Marques 100
Ana Salomé Pires 100
Ana Rita Gaspar 100
Andreia Martins Rosa 100
Anna Plisssova 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
Marilene Silva 100
Mário Carvalho 100
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Mohamed Hussien 100
Otilia d’Almeida 100
Patrícia Sofia Alçada Morais 100
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**Technicians / Others**

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**Collaborators**
João Calmeiro Pereira  (Grant Technician, CNC)  100
João Filipe Lima  (Grant Technician)  100
João Paulo Andrade  (Grant Technician)  100
José Alves  (Technician, CHUC)  Collaborator
Lilia Pereira Jorge  Grant Technician  100
Márcia Sofia Andrade  (Grant Technician)  100
Margarida Maria Marques  (Invited Assistant)  30
Mª Olinda Rebelo  (Technician, CHUC)  Collaborator
Nâdia 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**

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| 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                  |

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**POST-DOC MEMBERS**

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