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Funded by FEDER funds through the Operational Programme Factors Competitiveness - COMPETE 2020 and by National Funds through FCT - Foundation for Science and Technology under the Strategic Project: COMPETE: POCI-01-0145-FEDER-007440
CNC.IBILI is a multidisciplinary research consortium created at the University of Coimbra in 2015 that results from the fusion of two biomedical research institutes of excellence, CNC, recognized by FCT as a “Laboratório Associado” in 1990, and IBILI a research institute of Biomedical Sciences at the Faculty of Medicine, University of Coimbra. CNC.IBILI incorporates the largest critical mass of biomedical investigators in the Center region of Portugal.

As stated in the project proposal, research at CNC.IBILI is organized in three Thematic Strands: The Neuroscience, Vision and Brain Diseases Strand, focused on understanding brain and visual function at the molecular and cellular levels focusing particularly in defects on synaptic processes, brain metabolism and biomarkers of brain diseases, in order to increase diagnosis accuracy and to design patient-tailored therapies; the Metabolism, Aging and Disease Strand, centered on unraveling the links between cellular dysfunction (namely mitochondrial activity, oxidative stress, endoplasmic reticulum dysfunction and protein folding), with metabolism-based changes in diabetes, neurodegenerative and aging-related disorders, aiming to identify possible molecular and cellular therapeutic targets, and provide novel non-invasive diagnostic strategies using metabolite tracers; the Stem-cellbased and Molecular Therapies Strand that aims at investigating translational advanced therapies for neurodegenerative, cardiovascular and infectious diseases, as well as cancer, taking advantage of stem cells and of molecular therapy strategies. The close connection to the Coimbra University Hospital Center (CHUC), one of the largest in Portugal, provides access to clinical know-how, patient samples, and patients themselves, fostering translational and clinical research 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 2019, CNC.IBILI pursued its main goal, the understanding of brain and vision function and disease mechanisms leading to the development of target-oriented therapies, supported by novel molecular biology approaches and by a tight interaction with Coimbra University Medical Center (CHUC).

CNC.IBILI was also strongly committed to postgraduate education and training, being involved in the coordination of master and PhD Programs at the University of Coimbra and also in international training networks (Marie-Curie and ITN).

Through the outreach program, innovative actions aiming to improve society scientific education have been developed in schools and in collaboration with “Ciência Viva” and “Instituto de Educação e Cidadania”.

The specific objectives of each strand and of the respective research groups are described in detail in the respective reports of activity.
FACTS & FIGURES

From Year 2019

RESEARCH STAFF

| Members holding Ph.D. | 204 |
| Members holding MSc  | 197 |
| Other members         | 77  |

PUBLICATIONS

| Scientific papers published | 354 |

THESIS CONCLUDED

| Ph.D. thesis | 14 |
| MSc thesis   | 86 |
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 2019, the research groups for Thematic Strand can be identified, according to the following organization:

**NEUROSCIENCE, VISION AND BRAIN DISEASES STRAND**

Ana Luísa Carvalho

Synapse Biology Group (Head: Carlos B. Duarte)

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

Neuroendocrinology and Aging Group (Head: Claudia Cavadas)

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

Purines in brain diseases (Head: Rodrigo Cunha)

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

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

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

**METABOLISM AGING, AND DISEASE STRAND**

João Ramalho Santos

Cell Metabolism and Quality Control Group (Head: Paula Moreira)

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

Metabolic Control Group (Head: John Griffith Jones)

**STEM CELL-BASED AND MOLECULAR THERAPIES STRAND**

Luís 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: Arminho Salvador)

Medical Microbiology Group (Head: Teresa Gonçalves)

Molecular Mycobacteriology Group (Head: Nuno Empadinhas)

Medicinal Chemistry & Drug Discovery Group (Head: Jorge Salvador)

**BIOTECHNOLOGY**

Microbiology of Extreme Environments Group (Head: Milton Costa)

Molecular Biotechnology Group (Head: Isaura Simões)

**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)
RESEARCH ACTIVITY

NEUROSCIENCE, VISION AND BRAIN DISEASES
COORDINATOR: ANA LUIZA CARVALHO

GENERAL OBJECTIVES
Research at the Neuroscience, Vision and Brain Diseases (NVBD) research area investigates brain function and the causes of diseases of the nervous system, and develops novel strategies for disease prevention and treatment. This research line comprises 8 research groups in the areas of molecular, cellular, circuits and behavioral neuroscience, along with brain imaging, to understand the brain at different scales, from the level of single cells to brain circuits and behavior.

In collaboration with the Coimbra University Hospital (CHUC), NVBD groups explore different potential candidates, such as altered synaptic neuromodulation, mitochondrial dysfunction, neurovascular coupling and neuroinflammation, in order to develop novel interventions and identify biomarkers for brain and vision disorders.

MAIN ACHIEVEMENTS
In 2019, researchers in the NVBD research line identified a post-transcriptional mechanism of regulation of synaptic transmission (Silva et al., 2019), and how the neurotrophin BDNF impacts NMDA receptors, by enhancing local translation (Afonso et al., 2019). They have also characterized an additional role for the cell adhesion molecule Caspr2 in regulating AMPA receptor-mediated transmission, which is disrupted by antibodies from patients with autoimmune synaptic encephalitis (Fernandes et al., 2019). A study led by the most recent group in the NVBD research line (coordinated by João Peça) revealed abnormal mGluR-mediated synaptic plasticity and autism-like behaviours in Gprasp2 mutant mice (Edfawy et al., 2019).

Studies on the neuromodulation by purines have continued in 2019. One group found that synaptic and memory dysfunction in Alzheimer’s disease depends on increased formation of ATP-derived extracellular adenosine (Gonçalves et al., 2019), and that enhanced AT release and adenosine formation sustain adenosine A2A receptor activation in a model of Parkinson’s disease (Aires et al., 2019). The role of adenosine receptor in the microglia has been explored. One study showed region-specific control of microglia by adenosine A2A receptors, and uncoupled its role in mediating anxiety and cognitive deficits in female animals (Duarte et al., 2019). A second study revealed that blockade of microglial adenosine A2A receptor suppresses elevated pressure-induced inflammation and cell death in retina cells (Aires et al., 2019).

One focus of the NVBD area is on neurodegeneration and aging. Age-related differences in event-related potentials and pupillary responses were found in cued reaction time tasks (Ribeiro et al., 2019). In young and older adults, neural correlates of anticipatory cardiac deceleration were described, and found to be associated with the speed of perceptual decision-making (Ribeiro et al., 2019). Longitudinal multimodal in vivo molecular imaging studies showed progressive early hippocampal volume decrease and taurine loss in a model of Alzheimer’s disease (Chiquita et al., 2019), and that retinal thinning of inner sub-layers is associated with cortical atrophy (Chiquita et al., 2019). This last study supports the concept of the retina as a window to look into the brain or a mirror of the brain, and proposes that retinal alterations could constitute new reliable biomarkers to detect Alzheimer’s disease at an early stage.

Our clinical studies have generated important data, in particular for identifying biomarkers of disease. A cross-sectional study showed an association between adipokines and biomarkers of Alzheimer’s disease (Leitão et al., 2019), the lumipulse G cerebrospinal fluid assays have been clinically validated for routine diagnosis of Alzheimer’s disease (Vieira et al., 2019), and lower CSF Amyloid-Beta 1-42 has been found to predict a higher mortality rate in Frontotemporal Dementia (Vieira et al., 2019).

Technical achievements include the characterization of oxSWATH, an integrative method for a comprehensive redox-centered analysis combined with a generic differential proteomics screening (Anjo et al., 2019), the validation of an LC-MS/MS method for the quantification of caffeine and theobromine (Mendes et al., 2019), and the characterization of a platiniized carbon fiber-based glucose microbiosensor designed for metabolic studies in brain slices (Lourenço et al., 2019).

This summary of the main achievements in the NVBD line highlights some of the important contributions from research groups in this area. Please refer to the individual NVBD group reports for other important studies during 2019.
### Synapse Biology Group

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<tr>
<td>António Gomes</td>
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<td>Mónica Santos</td>
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<tr>
<td>João Laranjinha</td>
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### Neuroendocrinology and Aging Group

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### Vision, Brain Imaging and Cognitive Neuroscience Group

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### Grant Technician

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### Post Doctoral Fellow

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Neuromodulation Group

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- Anna Piassova  PhD Student
- Astília Kofalvi  PhD
- Paula Canas  PhD
- Paula Agostinho  PhD
- Ângelo Tomé  PhD
- Cátia Lopes  Student
- Ricardo Rodrigues  PhD
- Joana Marques  PhD
- Nélvio Gonçalves  PhD
- Xini Xu  PhD Student
- João Rocha  Student
- Ana Sá  Student
- João P. Lopes  PhD
- Ana P. Simões  PhD
- Francisco Gonçalves  PhD
- Liliana Dias  Student
- Henrique Silva  PhD
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Inês Caramelo  PhS Student
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Mª Margarida Coelho  PhD Student
Rémy Cardoso  PhD Student
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Anabela Matos  MD
Gustavo Santo  MD
Luís Negrão  MD
Diana Duro  Superior Technic.
Inês Correia  MD
Mª Carina Macario  MD
Anuschka Spinola  Student
Miguel Rosado  Student
Diana Carvalho  Student
Sara Pêgo  Student
Vanessa Costa  Volunteer

New Targets and Therapeutics for Chronic Diseases Group

- António F. Ambrósio  PhD (Head of Group)
- Catarina Gomes  PhD
- Ana Abrantes  PhD
- Filipa Baptista  PhD
- Célia Cabral  PhD
- Flávio Reis  PhD
- Eunice Carrihalho  PhD
- Elisa Campos  PhD
- Bárbara Gomes  PhD
- Célio Gomes  PhD
- Belmário Parada  MD
- Ana Santiago  PhD
- Fernando Mendes  PhD
- Carlos Ribeiro  PhD
- Ana Pires  PhD
- Ana Brito  PhD
- Ana P. Martins  PhD
- João Malva  PhD
- José Tralhão  PhD
- Mafalda Cândido  PhD
- Manuel Veríssimo  PhD
- Manuel Ferreira  PhD
- Marcos Barbosa  PhD
- Mª Filomena Botelho  PhD
- Mª João Carvalho  PhD
- Natália António  PhD
- Paulo Santos  PhD
- Rosa Fernandes  PhD
- Ricardo Leitão  Student
- Sofia Viana  PhD
- Sónia Santos  PhD
- Ana Costa  MD
- Ana Gaspar  Student
- Ana Pais  Student
- António Figueiredo  MD
- Carlos Marto  MD
- David Castelo  MD
- Diogo Fonseca  MD
- Edgar T Silva  MD
- Euroico Ribeiro  MD
- João Lopes  MD
- José Ives  MD
- Ana Santos  MD
- Leonor Barroso  MD
- Filipe Palavra  MD
- Raquel Boia  MD
- Rui Martins  MD
- Rui Oliveira  MD
- Sara Nunes  MD
- Beatriz Martins  MD
- Inês Aires  MD
- Inês Pita  MD
- Joana Martins  MD
- Luciana Fernandes  MD
- Miguel Pinheiro  MD
- André Alves  MD
- Inês Preguiça  MD
- Alda Gonçalves  MD
- Joana Cipriano  MD
- Ana Santiago  MD
- Inês Ventura  MD
- Sofia Galvão  MD
- Ana Ferreira  MD
- Maria Cotrim  MD
- Isabel Pereira  MD
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Mitochondrial Dysfunction and Signaling in Neurodegeneration Group

- Ana C. Rego  PhD Head of Group
- Bruno Moraes  Research Assis.
- Bruno Santos  Student
- Carla Lopes  PhD
- Daniela Lopes  Student
- Ildeber Ferreira  PhD
- Laura Neves  Student
- Lígia Fá  Student
- Margarida Beatrix  Student
- Patrícia Coelho  Student
- Rita Vilaça  PhD
- Sandra Mota  PhD

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- Patrícia Coelho  Student
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Aging and Brain diseases: advanced diagnosis and biomarkers Group

- Catarina R. Oliveira  PhD Head of Group
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- Mª Rosario Almeida  Student
- Mª Isabel Santana  PhD
- Mª Manuela Grazina  PhD
- Sandra Anjo  PhD
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- Mª Rosario Almeida  Student
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- Miguel Pereira  MD
- Ricardo Morais  MD
OBJECTIVES

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

Opioid receptors are present in the central nervous system and can induce several cellular responses such as analgesia, euphoria, or reduced inflammation, being important receptors in pain relief studies. One additional goal of the group is to understand how these receptors couple with their partners to induce downstream cellular responses.

SYNAPSE FUNCTION AND DYSFUNCTION IN BRAIN DISORDERS

The ability of synapses to change their strength is thought to be the cellular correlate of learning and memory. Synaptic dysfunction is a hallmark of neuropsychiatric disorders, and it is an early event in neurodegenerative disorders. We use a combination of techniques such as primary cultures of dissociated neurons and brain slices, biochemistry, molecular and cellular biology, mouse molecular genetics, electrophysiology and behavior analysis to address the role of molecular players that regulate synaptic function. Furthermore, we investigate disease-related alterations in synaptic function, either genetic or triggered by antibodies produced by autoimmune synaptic encephalitis patients, to understand how synaptic dysfunction underlies disease pathogenesis. This fundamental research has strong implications to cognitive disorders, since genetic variants in multiple synaptic proteins are linked to intellectual disability, schizophrenia, bipolar disorder and autism spectrum disorders. An additional aim of the group is to identify how specific genetic and environmental factors alter circuit level properties, ultimately leading to anxiety disorders, affecting social interactions or causing autism and other neurodevelopmental defects. 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.

UNDERSTANDING THE CONTRIBUTION OF THE NEUROIMMUNE SYSTEM TO THE ESTABLISHMENT OF NEURONAL CIRCUITS AND THE DEVELOPMENT OF NEUROPATHOLOGIES

In this line of research, we hope to unravel how microglia cells, responsible for innate immune responses in the brain, contribute to neuronal homeostasis and circuit establishment during neuronal development and throughout life and how they respond to environmental insults during the early life period. In addition, we are also interested in studying the biochemical processes through which microglia and other innate immune cells, such as macrophages and monocytes, potentiate neuronal damage in dementia-associated disorders, such as Alzheimer’s disease and Frontotemporal Lobar Degeneration, and in neurodevelopmental diseases, such as Autism spectrum disorder and Attention Deficit and Hyperactivity Disorder (ADHD).

TARGETING THE K+-Cl– COTRANSPORTER (KCC2) TO MAINTAIN GABAERGIC NEUROTRANSMISSION: A NOVEL THERAPEUTIC STRATEGY FOR EPILEPSY

Inhibitory neurotransmission in the CNS is largely mediated by GABA which plays an essential role in maintaining the excitatory/inhibitory balance required for correct brain function. Deficits in functional expression of GABAARs have been implicated in the pathogenesis of several neurological and psychiatric diseases, including epilepsy. In many patients with epilepsy, seizures are controlled with anti-epileptic drugs (AEDs) but 30% of epileptic patients do not respond to the treatment because of a progressive internalization of postsynaptic GABAARs and to a shift of the GABAAR reversal potential due to an alteration in chloride homeostasis (Mele et al., 2014). Previous unpublished results from our laboratory have shown an enhanced internalization of GABAAR during Status Epilepticus (SE). Furthermore, SE is correlated with an impaired GABAAR recycling, indicating that GABAAR synaptic stability is compromised in this condition. The downregulation of GABA inhibitory activity may arise from a positive shift in GABAAR reversal potential, due to an alteration in chloride homeostasis. However, the contribution of alterations in the Cl– gradient in this phenomenon is not yet established. In this project we investigated the role of chloride homeostasis mechanisms in the alterations of inhibitory synapses induced by status epilepticus, focusing on the KCC2 K+-Cl– cotransporter as a potential target for SE treatment.

DECODING PARTNER SPECIFICITY IN G-PROTEIN COUPLED RECEPTORS

Opioid receptors are present in the central nervous system and can induce several cellular responses such as analgesia, euphoria, or reduced inflammation, being important receptors in pain relief studies. Under constant opioid stimulation the receptors can be less internalized leading to the opioid tolerance, in other words, there is a never-ending increase of opioid doses to produce the same cellular response. This problem is described as the opioid crisis and is directly related to drug abuse. There are currently 13 structures deposited on online databases, 5 from mouse (Mus musculus) and 8 from human (Homo sapiens); 10 structures were solved by X-ray crystallography and the other 2 by cryo-electron microscopy; 4 structures are in an active state, the other 9 are inactive. The active structures are: 3 µ receptors from mouse and a k receptor from human. Although the number of structures had steadily increased in recent years, we are still far from understanding how these receptors couple with their partners and how the differences in the established interface influence their structure and function.
MAIN ACHIEVEMENTS

i) Synaptic function and dysfunction in brain disorders

PI: Ana Luísa Carvalhalho

1. We have identified a role for miRNA-186-5p in the regulation of AMPA receptor subunit composition, by targeting the GluA2 subunit of AMPA receptors (Siva et al., 2019). We also found that miRNA-186-5p mediates synaptic scaling in the hippocampus. We are presently studying abnormal upregulation of miRNA-186-5p levels in the brain during chronic stress, and whether it is implicated in chronic stress-related alterations in synaptic transmission.

2. We have described a new role for the cell adhesion molecule Caspr2 in regulating excitatory synaptic transmission (Fernandes et al., 2019). CASPR2 is also an auto-antigen in synaptic autoimmune encephalitis, and we found that anti-CASPR2 auto antibodies from patients disrupt the role of Caspr2 in regulating AMPA receptor function and synaptic transmission in the visual cortex. We are interested in understanding differential effects produced by anti-CASPR2 antibodies from patients targeting different epitopes, and with different antibody users, and how those effects correlate with the clinical symptoms found in patients.

3. We have produced knock-in mice which express a human mutation in the CACNG2 gene (coding for stargazin) associated with intellectual disability. These mice reproduce alterations in cognitive and social behavior reminiscent of the clinical symptoms found in patients. Morphological and electrophysiological analyses revealed that stargazin knock-in mice present abnormalities in neuronal morphology and synaptic function in the hippocampus, which constitute a potential disease mechanism (Caldeira, Inácio et al., in preparation).

PI: João Peça

1. In collaboration with the group of Guoping Feng at MIT we have found that specific deletion of GPRASP2 in hypothalamic neurons is sufficient to induce obesity. We have also found that genetic ablation of GPRASP2 in paraventricular (PV) positive interneurons is sufficient to recapitulate severe memory deficits in mice.

2. Using behavioral studies, electrophysiology and imaging, we have characterized the changes that emerge in juvenile, adolescent and adult rodents upon exposure to an early life stress paradigm that mimics maternal stress and neglect. Maternal separation induced long-term changes in social behavior and social hierarchy (Franco et al., 2020).

3. We concluded a study on the potential utility of miRNA-31 in Alzheimer’s Disease progression by targeting APP and BACE1. This microRNA, previously found to be decreased in AD patients, simultaneously reduced the levels of APP and BACE1 mRNA in the hippocampus of 17-month-old AD triple-transgenic (3xTg-AD) female mice, leading to a significant improvement of memory deficits and a reduction in anxiety and cognitive inflexibility. In addition, lentivirus-mediated miR-31 expression significantly ameliorated AD neuropathology in this model, drastically reducing Aβ deposition in both the hippocampus and subiculum (Vegas et al., 2020).

4. In collaboration with MIT, we participated in a study on the regulation of thalamic information processing. The goal of this work was to gain a thorough understanding of the genetic, electrophysiological and network properties of the thalamic reticular nucleus, a key region involved in attention, sleep and sensory processing, with clear links to autism and ADHD (Li et al., Nature 2020).

PI: Monica Santos

NT3/TRkC signaling in the regulation of fear. C57Bl6j animals were trained in the contextual fear conditioning and extinction paradigms, as described previously (D’Amico et al., 2017), and sacrificed at timepoints that represent different phases of fear processing: fear conditioning, fear memory, fear extinction acquisition, fear extinction memory. For each test group, appropriate control groups were also included. All animals were previously tested in the elevated plus maze and open field paradigms to monitor anxiety and exploratory locomotor activity. We found that only a subset of conditioned WT animals showed a reduction of 30% in their freezing levels, as compared to freezing levels at the fear retrieval phase, showing effective fear extinction. In a retrospective analysis of the data, animals in this “extinction-success” group also performed better in the extinction training phase, as compared to the “extinction-failure” animals, but no differences were observed between the two groups in fear retrieval or fear conditioning phases. We hypothesized that putative NT3 and TrkC levels in brain regions of the fear circuit could influence performance in CFC and CFExt and aimed at quantifying NT3 protein levels by ELISA, and pTrkC and TrkC by Western blot. Our first results with ELISA showed no differences among groups in the levels of NT3 in the PFC or in the amygdala, at the fear extinction retrieval phase.

PI: Carlos B. Duarte

1. Regulation of glutamatergic synapses by BDNF. We reported that BDNF induces synaptic delivery of GluN2B-containing NMDA receptors (NMDAR) by a mechanism mediated by activation of Pyk2 and dependent of protein synthesis (Monséo et al., 2019). Furthermore, BDNF upregulated dendritic Pyk2 protein levels by a mechanism dependent of hnRNP K, a ribonucleoprotein that binds the kinase mRNA. The results show a key role for Pyk2 synthesis at the synapse as a mediator of the effects of BDNF on the synaptic distribution of NMDAR, which may have an impact on LTP.

2. Targeting the K+-Cl- cotransporter (KCC2) to maintain GABAergic neurotransmission: a novel therapeutic strategy for epilepsy

The results obtained so far showed that exposure of hippocampal neurons to conditions that model Status Epilepticus (SE) in vitro downregulates KCC2 surface expression, by a mechanism sensitive to the inhibitor of astrin dependent endocytosis dynasore, and this effect was correlated with an increase in the (Glu; CLP257, a compound that enhances KCC2 activity drastically reduced the SE effects on the distribution of KCC2, maintaining its surface expression much more stable when compared with the SE condition in absence of the KCC2 activator. These results suggest that activation of KCC2 may be considered a possible strategy to maintain the surface levels of the transporter in epileptic conditions, and indicate that KCC2 may be a new target for the treatment of epilepsy.

ii) Decoding Partner Specificity in G-Protein Coupled receptors

PI: Irina Moreira

An extensive characterization of opioid receptor (OR) family was carried out to create new knowledge about the physiological and pharmacological properties of these important drug targets. Homology modeling was used to generate reliable structures of complexes of OR bound to either G-protein or ARR. A wide range of computational methods was applied to assess and provide a detailed description of the interaction interfaces of all members of the OR family (µ (MOR), δ (DOR), k (KOR), noceoptin (NOP), (ZOR)) with their corresponding binding partners (ARRs). G-proteins: G1i, G2i, G3i, Gs, Gob, Gz, Gs G1i, G14, G15, Ga1a, G alpha(i, j). Moreover, dynamic analysis under the scope of Normal Mode Analysis (NMA) was also performed. The construction and analysis of these models involving OR represents a novel and exciting big data analysis of OR-Partners interface determinants, and it constitutes a further step into the understanding of OR family functional specificity.
OBJECTIVES

The group’s research programs address:

(a) The molecular mechanisms inherent in neuromodulation and aging under an umbrella that characterizes the bidirectional communication between neurons and microvasculature by addressing quantitatively, in vivo, and in real-time the role of nitric oxide as a diffusional intercellular messenger, coordinating the neurovascular and neurometabolic coupling axis. The study of the neurovascular-neurometabolic coupling axis, encompasses mechanistic as well nutritional approaches with potential to restore the functionality of neurovascular coupling and cognition.

(b) Technological innovation in terms of the project, design and implementation of microarray technology consisting of micro(bio)sensors for the real-time monitoring of neuromodulators, neurotransmitters and metabolic intermediates in the brain of anesthetized and conscious, freely behaving animals. This program is developed in collaboration with the Center for Microelectrode Technology, University of Kentucky (Lexington, USA).

(c) The mechanisms of action of plant-derived dietary phenolic compounds in terms of protection against vascular endothelial dysfunction, anti-inflammatory properties, as well as their impact on nitrite-driven regulatory processes along the nitrate:nitrite:nitric oxide pathway, encompassing the non-enzymatic production of nitric oxide from dietary nitrite in the gastric compartment and the brain.

Funding sources:
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The main achievements incorporate both, technological and scientific components.

**Technological developments:** We developed a glucose microbiosensor suitable for glucose measurement in vivo and validated their suitability by measuring evoked changes in extracellular glucose in brain slices. This is a valuable tool to investigate the complex nature of glucose utilization in brain tissue linked to neuronal activation both in physiological and pathological conditions, particularly during neurovascular coupling.

**Scientific achievements:** Elaborating on ongoing research that is taking place in the lab for the last decades on the healthy benefits of dietary polyphenols, mitigating cardiovascular, metabolic and neurological diseases, during the current period:

1. We have identified molecular mechanisms by which polyphenols from red wine exhibit intestinal anti-inflammatory actions, supporting the notion that red wine polyphenolic extract might represent a readily available therapeutic intervention against intestinal inflammation and inflammatory bowel disease (IBD), promoted by cytokines and bacteria. In particular, the beneficial effects encompass:
   a) prevention of the altered expression and subcellular distribution of tight junction proteins during cytokine-induced inflammation, thus averting dysfunction of intestinal barrier;
   b) cyanidin-3-glucoside in particular was very effective in counteracting intestinal LPS-induced inflammation via, among others, inhibition of NF-kB and activator protein-1 (AP-1) pathways;
   c) providing evidences that the E. coli strain triggered the death of the intestinal epithelial cells through the production and release of a toxin and that the wine polyphenols through both, a direct interaction with bacterial exotoxin and the epithelial cells, prevented the action of the toxin on the cells, significantly reducing cell death.

   In view of the increasing antibiotic resistance, this study might open new therapeutic avenues for development of polyphenols from red wine as natural antimicrobial agents.

3. Given the paramount importance of gut microbiota for the establishment of communication between the gut and the brain, the microbiota-gut-brain axis has been increasingly explored within the scope of neurosciences. We have reviewed key cellular signaling pathways underlying chronic intestinal inflammation and the influence of chronic intestinal inflammation and dysbiosis on brain disorders and have further developed the notion that polyphenols reach high local concentration in the intestine setting the conditions for modulating the “gut-brain axis” with impact in neurological disorders, notably autism spectrum disorders.
NEUROENDOCRINOLOGY AND AGING

Head: Cláudia Cavadas

OBJECTIVES

Our group has been contributing for the hypothesis that aging and age-related disorders are controlled by the hypothalamus or its related functions. This brain region regulates body homeostasis through specialized neurons that sense and integrate central and peripheral signals to properly coordinate several survival functions, including sleep, food intake, metabolism and neuroendocrine axis. The research developed by the group aims to answer to the following questions:

- How can we delay premature aging or natural aging by targeting the hypothalamus or by using hypothalamic related mechanisms?
- Do hypothalamic neuropeptides, as caloric restriction mimetic approaches, prevent peripheral aging and related dysfunctions? What are the underlying mechanisms?
- Does circadian rhythm dysfunction prevention protect against peripheral aging and age-related disorders?

More specifically the group has been investigating strategies and mechanisms aiming to delay ageing and age-related disorders: 1) Neuroendocrine strategies; 2) Circadian rhythm and biological clocks 3) molecular hallmarks of aging (senescence, inflammation, and dysfunction of intracellular communication, autophagy, sirtuins).

To address these questions the group has been using gene delivery approaches to modulate critical mechanisms or pathways in the hypothalamus (NPY, microRNAs, sirtuin-2, ataxin-2), and intranasal and peripheral administration of small molecules or neuropeptides (as NPY, ghrelin). The projects developed by the group have been contributing to emphasize the crucial role of hypothalamus in aging and potentially open new strategies to delay aging and aging related diseases.
a) We investigated the role of NPY and ghrelin in rescuing the aging phenotype in experimental models of ageing, using Hutchinson-Gilford Progeria Syndrome (HGPS) experimental models. The results obtained show that NPY and also ghrelin decrease cellular hallmarks of premature aging of progeria fibroblasts, such as enhanced progerin clearance, autophagy stimulation, rescued nuclear abnormalities, increased cell proliferative capacity and delayed cellular senescence of HGPS cells. In in vivo experiments, we observed that ghrelin was able to ameliorate aging phenotype of HGPS mouse model. These results support that these peptides can be considered a promising strategy to delay or block the premature aging of HGPS.

b) Modulation of ataxin-2 in mice hypothalamus regulates energy balance and metabolism: including changes in body weight and response to insulin, through reestablishment of clock gene levels.

c) SIRTUIN 2 is abundantly expressed in major mouse hypothalamic nuclei and hypothalamic SIRT2 expression changes upon high fat diet (HFD), which triggers insulin resistance, suggesting that hypothalamic SIRT2 levels are modulated by nutrient availability.

d) NPY and NPY receptors are present in chondrocytes of articular cartilage. New studies are needed to further investigate the role of NPY and its receptors in development and progression of cartilage aging related disease, the osteoarthritis.

e) The preliminary data show that peripheral cells (PBMCs) from obstructive sleep apnea (OSA) patients present some hallmarks of aging.
VISION, BRAIN
AND COGNITIVE
NEUROSCIENCE

Head: Miguel Castelo-Branco

OBJECTIVES

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

Our group has continued participation in Eurobioimaging and coordination of the core Infrastructure of National Brain Imaging Network, a consortium of 5 Universities with the leadership of the U. of Coimbra, where the main central equipment is located and which obtained funding within the scope of the National Program for Scientific Reequipment, after international evaluation.

We have continued work on Vision, Perception and Decision-making research streams. Our Clinical Neurosciences Pillar has continued to generate scientific production along the following Themes: 1. Normal Ageing: Cognitive Models and Neuroimaging 2. Neurodegenerative Disorders with a focus of mechanisms of disease, impaired neurotransmission and neurophysiology 3. Neurodevelopmental Disorders with a similar focus on multimodal explanatory approaches 4. Cortical plasticity in the maturing and adult brain: implications for neurorehabilitation 5. Neuropsychiatric disorders, with a focus on decision making and cognitive control. Our hierarchical approach in fundamental visual neuroscience ranges from sensory biophysics to visual attention and high level processes in human neurophysiology. Our recent work in high level vision has addressed temporal dynamics of perceptual decision mechanisms and the role of context. This provides a thorough background for translational research approaches. These allowed to separate low vs. high level impairment in visual cognition neurodevelopmental models of impaired perception and decision making such as autism, and neurogenetic conditions such as Autism and Neurofibromatosis Type I. We are studying parallel pathways to quantitatively analyze visual cognition, decision making and action control and motor aging in neurodegenerative disorders, in particular Parkinson Disease, and Huntington disease. Our expertise in Visual and Cognitive Impairment questions, and characterization of several disease models of genetic vs. acquired visual impairments, is allowing us to further refine novel models of visual neuroplasticity.

Our success in generating interdisciplinary work with scientists working in the field of cognitive neuroscience, neurology, medical imaging 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 a broad set of international partners.
MAIN ACHIEVEMENTS

We continued to published a consistent flow of papers in prestigious journals in the fields of Ageing and Neurodegenerative Disorders, Neurodevelopmental Disorders and Vision Research. This group has therefore continued to publish in the fields of visual science, systems neurobiology, clinical neuroscience and biomedical Engineering with a focus on imaging. Basic science achievements and Translational Research Achievements: Clinical Neuroscience and Translational Research Achievements are highlighted by publications in the above mentioned fields.

Our translational work on integrating human and animal neurodevelopmental phenotypes has also progressed. Our work in the new IMI-2 H2020 initiative is in good progress. We also contributed publications in top journals in neuroimaging. Methodological Achievements can also be underlined by the successful publication of methodological papers.

In sum we were able to publish in leading journals in the following areas: Cognitive Neuroscience, Human Neuropsychology, Visual Neuroscience, Human Psychophysics, Functional Brain Imaging and translational research in Neurology. We are participating in European Projects and after achieving a worldwide patent together with IBA, our technology transfer approaches are also evolving steadily within the newly created clinical trial unit.
NEUROMODULATION

Head: Rodrigo Cunha

OBJECTIVES

The general objective of the group is to identify modulation systems that can be targeted to interfere with the evolution of neurodegenerative diseases, with a central focus on purines (adenosine and ATP). We concentrate on the initial stages of neurodegenerative disorders, under the working hypothesis that one of the key early features transversal to different such diseases is the dysfunction of synapses. This involves both neuronal and glial (astrocytes and microglia) maladaptive changes, with alterations of receptors, metabolic support and neuroinflammatory status, leading to abnormal synaptic plasticity and synaptic pruning that recapitulates features of neurodevelopment.

Our efforts over the years have identified a key role of adenosine A2A receptors (A2AR) in the control of neurodegenerative disorders. We have shown that their blockade prophylactically prevents alterations in animal models of Alzheimer’s disease, epilepsy or diabetic encephalopathy; this is in remarkable agreement with the prophylactic benefit afforded by the regular consumption of caffeine (an adenosine receptor antagonist) against diseases such Alzheimer’s or Parkinson’s.

We post that A2AR up-regulation may actually be a causative factor of aberrant synaptic plasticity underlying abnormal phenotypic changes, through a combination of direct neuronal control of synaptic plasticity (Angelo R. Tomé and Henrique Silva), and glial control of synaptic function involving altered astrocyte-to-neuron communication (Paula Agostinho). In parallel, we are developing a new research line exploring the impact of purines in brain development and synaptic wiring under the assumption that features of brain development are aberrantly recruited to attempt restoring the diseased brain (Ricardo J. Rodrigues and Joana M. Marques). In parallel, four emergent lines within the group are exploring the role of purines and of cannabinoids in the control of brain metabolism (Attila Kofalvi), the role of extracellular ATP as a danger signal in brain diseases (Ricardo J. Rodrigues), the exploration of human brain samples collected during autopsy for translational efforts (Paula Canas) and the impact of A2AR in neurodegenerative (João Pedro Lopes) and neuropsychiatric disorders (Ana Patrícia Simões, Samira Ferreira).
MAIN ACHIEVEMENTS

1- The adenosine modulation system mainly controls allostatics rather than homeostasis.

2- Adenosine A2A receptor (A2AR) overfunction increases the susceptibility to brain damage.

3- The overfunction of A2AR depends both of an up-regulation of A2AR and increased formation of ATP-derived extracellular adenosine.

4- Non-toxic concentrations of caffeine only affect information flow in brain circuits through the antagonism of A1R and A2AR.

5- Prefrontocortical A2AR control decision-making.
OBJECTIVES

The research group “Mitochondria and Neurodegenerative Disorders” aims to understand fundamental cell and molecular mechanism in early stages of brain neurodegenerative disorders, namely in Huntington’s (HD), Parkinson’s (PD) and Alzheimer’s (AD) diseases. These are chronic, debilitating, and age-related brain disorders, characterized by selective brain neurodegeneration and cognitive decline. Misfolded proteins due to posttranslational or oxidation modifications (among other processes) or pre-identified mutations acquired beta-sheet structures and tend to aggregate, progressively forming insoluble/fibrillary aggregates. In the form of oligomers, modified proteins interfere with neuronal function, potentially causing deregulated mitochondrial function and bioenergetics, and altered intracellular redox signaling, namely after activation of glutamatergic synapses, or lead to defective neurogenesis, which may impact on brain cognitive reserve. Although there are several mechanisms by which neurons degenerate, the initial pathways of neuronal dysfunction, occurring before the main disease-related symptoms, are not completely understood.

In 2019 we focused our research in intracellular signaling pathways governing redox changes, in chronic stress conditions that may precipitate AD and the effect of amyloid-beta peptide (Aß) on neural stem cells (NSC) fate, and alpha-synuclein (a-Syn) role in the nucleus and the impact of protein phosphorylation.

Thus, we studied:

1. The activation of cell survival-related signaling proteins, c-Src and Nrf2, and the influence of c-Src kinase on Nrf2 regulation after exposure to hydrogen peroxide (H2O2), demonstrating a novel c-Src/PKCδ/Nrf2 interplay following oxidant stimulus;
2. The impact of chronic stress on dendritic development and structural maturation of newborn neurons in the dentate gyrus (DG) of the adult hippocampus (collaborative study);
3. Influence of Aß on neurogenesis. NSC fate and mitochondrial parameters, including biogenesis, dynamics, and oxidative stress (collaborative study);
4. The mechanisms underlying aSyn-mediated transcription deregulation by assessing its effects in the nucleus and the impact of aSyn phosphorylation (collaborative study).

In this perspective, by using molecular, cellular, ex-vivo and in vivo/animal approaches, we aim to investigate early disease-related modifications affecting mitochondrial function and signaling processes linked to redox deregulation, glutamate postsynaptic dysfunction and/or modified neurogenesis in different models of neurodegenerative disorders and in peripheral human cells derived from patients and non-affected individuals.

The last envisages a closer interaction with neurologist at the local hospital, particularly in HD and AD. Identification of early disease mechanisms are envisaged to uncover relevant molecular targets for therapeutic interventions. Therefore, the group aligns basic and potential translational research with a main interest in early disease stages, as well as investigation on neuroprotective therapies based on modifiers of mitochondrial function and dynamics or glutamatergic synapses using pharmacological compounds, modulation of protein expression and/or gene correction strategies.
In the context of redox deregulation occurring in many neurodegenerative disorders, we demonstrated that the c-Src/PKCδ/Nrf2 pathway constitutes a novel signaling pathway stimulated by H2O2 (Fão et al., Biochim Biophys Acta Mol Cell Res, 2019). Cytosolic activation of Nrf2 (a transcription factor involved in expression of cell antioxidants) was modulated through phosphorylation by PKCδ, an enzyme controlled by Src Tyr kinases. Acute exposure of HT22 mouse hippocampal neural cells to H2O2 increased c-Src and Nrf2 phosphorylation/activation at Tyr416 and Ser40, respectively. Nrf2 P-Ser40, its nuclear accumulation and transcriptional activity involving heme oxygenase-1 (HO-1) expression were dependent on c-Src activation. Moreover, modulation of Nrf2 activity by c-Src occurred through PKCδ phosphorylation at Tyr311. The work supported that c-Src regulates Nrf2 activity through PKCδ after an oxidant stimulus, constituting a potential target for diseases involving redox deregulation.

In collaboration with Dr. Ioannis Sotiropoulos (ICVS, University of Minho, Portugal), we showed that chronic stress, a precipitant factor of several brain pathologies, such as depression and AD, triggers divergent dendritic alterations in immature neurons of the adult hippocampus (Dioli et al., Transl Psychiatry, 2019). Specifically, the density of the DCX-positive immature neurons whose dendritic tree reaches the inner molecular layer (IML) of DG was reduced in stressed animals, whereas the dendritic complexity was increased. DCX+ cells displayed complex and longer dendritic compartments located in the granular cell layer of the DG under stress conditions; on the contrary, their dendritic segments localized into the M/OML were shorter and less complex. Data highlight the complex and dynamic stress-driven neuroplasticity of immature neurons in the adult hippocampus.

In collaboration with Dr. Cecília Rodrigues (Faculty of Pharmacy, University of Lisbon, Portugal), we showed that Aβ compromises NSC by irreversibly disturbing mitochondrial oxidative state and blocking mitochondrial biogenesis and dynamics, bringing new perspectives for endogenous NSC-based strategies in AD (Ribeiro et al., Mol. Neurobiol., 2019). Aβ impaired NSC viability and proliferation and blocked neurogenic differentiation, by disrupting mitochondrial signaling of self-renewing NSCs. Aβ decreased ATP levels, generated oxidative stress, affecting radical scavenger system through SOD2 and SIRT3. Aβ also reduced mtDNA and mitochondrial biogenesis. Aβ compromised NSC commitment and survival by irreversibly impairing mitochondria and thwarting any neurogenic rescue through mitochondrial biogenesis, dynamics or radical scavenger system.

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In the context of PD, and both as co-supervisor of Raquel Pinho (PhD student – defended in 2017) and in collaboration with Dr. Tiago Outeiro (University Medical Center Göttingen, Germany), we studied how nuclear localization and phosphorylation of aSyn modulated its pathological effects (Pinho et al., Hum. Mol. Genet., 2019). aSyn induced severe transcriptional deregulation, including the downregulation of important cell cycle-related genes. Transcriptional deregulation was concomitant with reduced binding of aSyn to DNA. In the presence of aSyn in the nucleus (aSyn-NLS), we found the accumulation of high molecular weight aSyn species, altered gene expression and reduced cytotoxicity, which were modulated by aSyn phosphorylation on Ser129. We hypothesize that the role of aSyn on gene expression and/or toxicity may be modulated by phosphorylation status and nuclear presence of different aSyn species. Data may open novel avenues for the design of future strategies for therapeutic intervention in PD and other synucleinopathies.
OBJECTIVES

The main objective of this Group is the identification of new biomarkers of aging and brain disorders, promoting the translation of knowledge generated in basic research to the clinic.

A close interaction with clinicians at Coimbra University Hospital (CHUC) has been shown to be relevant, allowing the access to human biological samples and clinical data, related with neurodegenerative and neuropsychiatric diseases, neurodevelopmental and bigenomic disorders and cancer.

Biomarker-based diagnosis and prognosis of neurodegenerative dementias is an important area of interest of this group. In 2019 we have: i) evaluated the analytical performance of a novel fully automated chemiluminescence enzyme immunoassays (Lumipulse) for the quantification of Alzheimer’s Disease (AD) biomarkers in Cerebrospinal fluid (CSF); ii) participated in a modelling study, including people with mild cognitive impairment (MCI) from single-centre and multicentre cohorts in Europe and North America, aimed to establish robust prediction models of disease progression; iii) been actively involved in Genetic Frontotemporal Dementia Initiative (GENFI), which is a multicentre cohort study of families with genetic frontotemporal dementia across Europe and Canada, with the objective of studying longitudinal biomarker trajectories in people with presymptomatic and symptomatic genetic frontotemporal dementia (FTD); and iv) performed the genetic analysis of several patients with neurological diseases including early onset dementias.

“OMICS” methodologies have been applied, in a translational perspective, to the study of brain disorders, generating tools for diagnosis, prognosis and progression markers.

Bigenomic investigation of disorders aiming to find molecular and genetic risk factors in mitochondrial DNA (mtDNA) and nuclear genes associated with mitochondrial biology was also addressed. The group was updated in the latest developments in molecular genetics, including the analysis of exome by Next Generation Sequencing (NGS) technique, and other methodological assays that were developed to support functional genomics. These advances have made possible the functional studies for pathogenicity investigation of novel mutations identified in patients, which became more frequent with the application of NGS analysis.

Regarding the pharmacogenomics studies the main focus was the identification of genetic alterations and copy number variations that will determine the metabolic profile or targeting depending on genetics, to provide tools for more accurate diagnosis and more rationale treatments, managing risks and preventing drug adverse reactions, in the scope of theranostics.
Regarding biomarker-based diagnosis and prognosis of neurodegenerative diseases, the Lumipulse assays showed a very good analytical performance and an excellent diagnostic accuracy, therefore making them well-suited for CSF clinical routine measurements. In the multicenter modelling study, we were able to generate risk models that were robust across cohorts, which adds to their potential clinical applicability. Such models could aid clinicians in the interpretation of CSF biomarker and hippocampal volume results in individuals with MCI, and help research and clinical settings to prepare for a future of precision medicine in Alzheimer’s disease.

Regarding the GENFI, our findings showed the value of blood NfL as a disease progression biomarker in genetic frontotemporal dementia and suggested that longitudinal NfL measurements could identify mutation carriers approaching symptom onset and capture rates of brain atrophy.

The genetic analysis unveiled the pathogenic variants underlying different neurological conditions, providing the molecular diagnosis of several symptomatic individuals as well as offering predictive tests to other family members, still asymptomatic, in the context of genetic counseling. New proteomic methodologies were developed, to validate diagnostic categories and improve its boundaries and discrimination among neuropsychiatric disorders.

The contribution of nuclear gene variants in subunits and proteins involved in the mitochondrial protein import and processing of imported precursor proteins, as genetic modifiers in Leber’s Hereditary Optic Neuropathy (LHON), was provided by a screening using whole-exome sequencing data. The variants c.280C>T and c.170delA/c.172_176delGGCAC, in MIPEP and TOMM20L, respectively, were identified in a LHON individual with m.14484T>C mutation. Regarding the identified variants, although promising for the outcome of mitochondrial assembly, they do not seem to be conditioning this level of impairment.

In a prospective observational study analyzing CYP2D6 pharmacogenetics in 55 Portuguese adult women undergoing elective cesarean, the association with pain score, was studied. A positive association between alleles *4, *10 and pain was found and also between predicted reduced or null activity of CYP2D6 and increased pain. So, CYP2D6 genotyping was suggested useful for adjusting the needs for analgesia and opioid dose, in order to maximize clinical efficacy and avoiding adverse reactions.

Under the scope of the “CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics and Pharmacogenomics (RIBEF)”, a collaborative study of a broad spectrum of Native American populations from different ethno-linguistic groups showed how autochthonous diversity shaped the distribution of pharmaco-alleles and gave insights on the prevalence of clinically relevant phenotypes associated with drugs, such as paroxetine, tamoxifen, warfarin, and clopidogrel.

By using genomic tools, the assessment of new biomarkers in different pathologies, namely in cancer, was performed. Furthermore, we contributed to detect a metabolomic signature in Urine of patients with Age-Related Macular Degeneration.

Under the scope of an international collaboration we also participated in the discussion regarding the rights and duties of Clinical Laboratory Geneticists in genetic healthcare systems.

MAIN ACHIEVEMENTS
NEW TARGETS AND THERAPEUTICS FOR CHRONIC DISEASES

Head: António Francisco Ambrósio

OBJECTIVES

The Group has been mainly focused in chronic disorders that affect the retina and brain, but also other organs such as the heart, kidney, nose and lungs, as well as on applied ageing research. In general, our goals are:

- to elucidate the molecular and cellular mechanisms underlying the pathophysiology of chronic disorders affecting the retina, brain and other organs;
- to identify new potential drug targets and develop more efficient therapeutic strategies for the treatment of chronic disorders affecting those organs as well as evaluate the response to therapy.
- research on ageing with significant social impact in the elderly. Particular objectives have been defined in different sub-areas, as follows:

Vision Sciences

We have a major focus on retinal degenerative diseases, namely diabetic retinopathy, glaucoma and age-related macular degeneration (AMD). We are particularly interested in clarifying the contribution of microglia-mediated neuroinflammation and the crosstalk between different cell types to retinal neural, vascular and epithelial dysfunction and degeneration. We have been exploring strategies that modulate adenosine receptors and dissecting the role of exosomes, PINK1/PARKIN and mitochondrial DNA. We also aim to clarify the protective mechanisms of incretin-based therapies and evaluate the role of α-adducin in the structure and function of the retina. In a translational perspective, we are trying to identify new biomarkers in the tear fluids for the diagnosis of retinal degenerative diseases and to develop biodegradable intraocular implants for drug delivery systems.

The concept of “the retina as a window to the brain” has emerged with possible implications in various pathologies, such as Alzheimer’s disease (AD). We aim to understand when changes start appearing in the retina and brain, how changes progress, and if they are correlated, and also to investigate whether the retina can be used as a reliable tool to facilitate an early diagnosis of Alzheimer’s disease.

Neuroscience

We intend to pinpoint the role of lifestyle, including diet, food supplementation, physical exercise, and drugs of abuse and CNS modifiers consumption, such as methamphetamine and methylphenidate, on brain health and cognitive dysfunction, giving a particular attention to neuroinflammation and blood-brain barrier dysfunction. We also intend to unravel the neurobiology behind Attention Deficit Hyperactivity Disorder (ADHD), the role of peripheral immunity in Parkinson’s disease and the impact of glioblastoma multiforme on blood-brain barrier.

We are also investigating the impact of prenatal stress mediators, including diabetes during pregnancy and exposure to dexamethasone, on early neurodevelopment and mental health throughout life, namely the risk for anxiety and depression, giving a particular attention to microglial cells. Moreover, we aim to understand if sex differences in these cells underlie the differential clinical presentation of psychiatric disorders between men and women.

Experimental Therapeutics

We are evaluating the impact of therapeutic and nutraceutical options in cardiometabolic and cardiorenal disorders, such as atherosclerosis, obesity, type 2 diabetes and its vascular complications, namely nephropathy and chronic renal failure.

Ageing Research

- To develop applied ageing research with significant societal impact focusing on: a) health literacy to support the adoption of healthy lifestyles by citizens; b) to develop and implement distance learning courses to capacitate formal and informal providers to better manage care for older people.
- To implement a successful ERA Chair project on ageing at the University of Coimbra and to launch a successful second stage application for the Teaming project of the Multidisciplinary Institute of Ageing (MIA-Portugal).
Vision Sciences

- The intravitreal injection of the A2AR antagonist controls neuroinflammation, affords protection against retinal cell loss and reduces vascular leakage associated with diabetes. Therefore, antagonists of A2AR could be envisaged as a therapeutic approach for the early complications of diabetes in the retina.

- Microglia are main contributors for retinal cell death during elevated pressure. A2AR expressed in microglia can be targeted to control retinal neuroinflammation and prevent neural apoptosis elicited by elevated pressure.

- Porous poly (ε-caprolactone) (PCL)-based intraocular implants are well tolerated by rats and can be envisaged for prolonged drug delivery applications.

- Quantification of TNFα at the picogram level in human tears using a rapid and sensitive biosensor technology based on electrochemical impedance spectroscopy (EIS).

- Similar neural changes can be found in the retina, hippocampus and visual cortex, i.e., retinal and brain thinning, in a triple transgenic mouse model of Alzheimer’s disease (3×Tg-AD). The retinal physiology is also altered. These observations support the possibility of using the eye as an additional tool (noninvasively) for early AD diagnosis and therapeutic monitoring.

- Retinal texture biomarkers may help to discriminate between Alzheimer’s and Parkinson’s disease patients and healthy controls.

Neuroscience

- A lower dose of MPH in normal rats improves memory performance, being associated with the modulation of astrocytic morphology and synaptic machinery. However, a higher dose of MPH leads to BBB dysfunction and memory impairment.

- The cross-talk between microglia and glioblastoma multiforme cells trigger the release of IL-6 and the downstream JAK/STAT3 pathway activation, leading to endothelial barrier dysfunction and hyperpermeability.

- A dietary imbalance, related with hypoproteic or high-fat content impairs BBB properties potentially favoring the transmigration of peripheral immune cells and induces both a peripheral and central neuroinflammatory status.

- We identified differences in microglia cellular (and subcellular) morphology, portraying microglia as a unique cell type with a sex identity, which is locally determined according to the brain region. Moreover, there is a correlation between this morphologic plasticity and behavior with anxiety and depression.

Experimental Therapeutics

- The dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin inhibits oxidative stress and ameliorates glomerular lesions in a rat model of type 1 diabetes.

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

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

Ageing

The team successfully implemented the project HeaLiq4Cities, funded by EIT Health. This project has implemented a vehicle equipped with an innovative concept and tools for lifestyle assessment of citizens in rural areas. Moreover, the team has been active in the implementation of three editions of the distance learning course on Active and Healthy Ageing for Care Providers, a project implemented by the University of Coimbra. Our team is the leader of the EIT Health consortium EpIDEMPrev that implemented the preparatory year of the EIT Health Ageing PhD School, a network and educational portfolio awarded with the EIT Label Certificate, seal of excellence.

Giving continuity to the successful implementation of the ERA Chair (ERA@UC) project and the phase I of the Teaming project to launch the Multidisciplinary Institute of Ageing (MIA-Portugal), the team was successful in securing funding for the second stage and implementation of the new center of excellence in ageing research.
RESEARCH ACTIVITY

MATLABISM, AGING AND DISEASE
COORDINATOR: JOÃO RAMALHO-SANTOS

GENERAL OBJECTIVES

The general goal of the strand is to carry out excellent basic and translational research linking metabolic issues, notably mitochondrial function and intermediate metabolism-based pathways and biomarkers, with aging and disease, including neurodegenerative and neurobehavioral disorders, diabetes, infertility, immune-based disorders, cardio-vascular disorders, and fatty liver disease, and cancer. The goal was to create critical mass, and bring basic research closer to more interventional activities, as well as better diagnostics tools. It should be reminded that the ImmunoMetabolic Pharmacology Group is no longer part of the CNC.IBILI Consortium, and was removed from the current report.

MAIN ACHIEVEMENTS

One of the main achievements was the beginning of the successful European applications linked to three ETN training grants (FOIE_GRAS, TREATMENT, Rep-EAT) and a RISE action (mtFOIE_GRAS), that link metabolism research with liver disease, infertility and schizophrenia. Both FOIE_GRAS and mtFOIE_GRAS are coordinated by CNC. The groups continued their work on targeting mitochondria for both diagnostic and therapeutic purposes with novel chemical entities based on dietary polyphenols and other molecules that may decrease cardiotoxicity of known drugs and alleviate menopause symptoms. In terms of neurodegenerative disorders our data suggests that new BACE1 inhibitors have the potential to be a disease-modifying therapy in AD.

Furthermore, the stand has done innovative research in terms of both mitochondrial function and the microbiome of AD and PD patients, and continued to focus on sex-specific differences and the effects of diabetes. Some of these effects seem to be modulated by diet and the adipose tissue, and have consequences in terms of vascular and cardiac function, and influence wound healing, which could be potentiated using microRNAs and antimicrobial peptides. In terms of novel methodologies, the strand also developed stable-isotope methodologies for quantifying liver and adipose tissue fatty acid and glycerol biosynthesis from specific precursors using a combination of deuterated water and 13C-enriched substrates. We were also able to certify a lab using the Good Laboratory Practices methodology, officially approved by INFARMED, Portugal using the international OECD guidelines, and have one of the few labs in Portugal in this field to have such a certification. This will be used to fulfil industry contracts.

FUTURE PLANS

The strand will continue to focus on the goals of linking basic with translational research, trying to move the field forward at different levels. In terms of targeting mitochondria this will continue to be another key aspect of future research plans, in terms of aging, cancer and brain and improving liver mitochondrial bioenergetics during estrogen withdrawal in menopause or mitochondrial function affected by other toxic therapeutic interventions. In terms of the nutritional aspects noted, this work will be carried out in close association with the CNC Spinoff MitoDiets. Similarly the continued research on following metabolic pathways in vivo via non-invasive quantification of key metabolites will be carried out in close association with the SpinOff LifeTag. One of the goals of the Strand is to try to create opportunities for researchers beyond research. Future plans also involve submissions for competitive funding taking into account the successful ETN/RISE partnerships in the four funded actions, in order to expand the themes beyond the human resources funding that was made available. The new BACE1 inhibitors we were developing last year will continue to be extended to preclinical models. The strand will also focus of characterizing and manipulating the microbiome in neurodegenerative disorders. Data from the strand also reinforced the need to establish sex/gender-specific preventive and/or therapeutic approaches and an appropriate time window for the efficient treatment against metabolic and neurodegenerative conditions and this will be followed up, also focusing on vascular and cardiac changes in metabolic-based disorders, in collaboration with the University Hospitals. We will also continue to follow our heart failure (HF) data in patients with and without diabetes given that epicardial adipocytes may be a possible therapeutic target for HF treatment. Finally we will make full use of our novel NMR-based methodology to animal models of non-alcoholic fatty liver disease in order to determine the contributions of glucose and fructose to lipid biosynthesis.
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**Note:** The positions are indicated as follows: PhD (PhD Head of Group), PhD (PhD), PhD (MD), PhD (Superior Techn.), PhD (Health Sup. Techn.), Student, Trainee, Volunteer.
CELL SIGNALING
AND METABOLISM
IN DISEASES

Head: Paula Moreira

OBJECTIVES

Our research Group aims:

To investigate a) how cardiovascular risk factors contribute to Alzheimer disease (AD) (like) pathology, putting the focus on brain energy metabolism; b) how sex/gender modulates the risk for AD and c) the preventive and therapeutic potential of antidiabetic agents and mitochondrial modulators. To determine a) how mitochondrial damage-associated molecular patterns (DAMPs), which trigger sterile pro-inflammatory immune responses, drive AD and Parkinson disease (PD) neurodegeneration; b) how gut microbiota of AD and PD patients could trigger neuronal innate immunity activation through mitochondrial dysfunction; c) new therapeutic strategies to avoid mild chronic inflammation, thus preventing AD and PD relevant protein oligomers formation and mitochondrial damage.

To investigate the disturbance of the Endoplasmic Reticulum (ER) stress response and of ER-mitochondria contacts in neurodegenerative disorders such as AD and in psychiatric illnesses, namely bipolar disorder and schizophrenia. The therapeutic potential of compounds obtained from Portuguese natural resources is another goal of our research.

To evaluate the molecular mechanisms involved in peripheral and neuroinflammation and changes in the cells of the immune system associated with the inflammatory response; and to develop methodologies to evaluate the ability of natural and industrial chemicals to modulate innate immunity, with a special focus on macrophages and dendritic cells. It is intended that the scientifically relevant data generated by the first aim may contribute to the development of efficient laboratory tests in screening for possible new drugs or potentially immunotoxic chemicals.
Using post-mortem human brain tissue, in vivo and in vitro models of AD, we observed that O-GlcNAcylation, the post-translational modification of intracellular proteins by O-GlcNAc, contributes to "mitochondrial pathology". A reduction in global O-GlcNAcylation levels was shown to be strongly correlated with hampered mitochondrial bioenergetic function, disruption of the mitochondrial network and loss of cell viability. Conversely, the pharmacological modulation of O-GlcNAcylation levels with Thiamet-G restored O-GlcNAcylation levels and cell viability (Pinho et al., 2019). Overall, these results suggest that O-GlcNAcylation is involved in AD pathology functioning as a potential link between mitochondrial energetic crisis and synaptic and neuronal degeneration. Findings from our laboratory also demonstrate that the antidiabetic drug liraglutide, a glucagon-like peptide 1 (GLP-1) mimic, can be efficient against AD neuropathology.

We demonstrated that acetylation of Beclin-1 modulates autophagy in Alzheimer’s disease cellular models (Esteves et al., 2019). Additionally, we proved that acetylation is a major determinant to microtubule-dependent autophagy in AD and PD. Since mitochondria are evolutionary descendants of endosymbiotic alphaproteobacteria, we speculate that human gut microbiota may produce neuroactive toxins to target bacteria and, "collaterally", their endosymbiotic successors, the mitochondria. Indeed, our results show that bacterial pathogen-associated molecular patterns (PAMPs) alter mitochondrial function in mesencephalic and cortical neurons, namely decrease mitochondrial membrane potential and increases mitochondrial reactive oxygen species (ROS) production. Additionally, bacterial PAMPs activate the inflammasome and induce the production of AD and PD histopathologic hallmarks both perceived as an “arm” of neuronal innate immune response.

We obtained evidences demonstrating that ER-mitochondria communication is involved in NLRP3 inflammasome activation under ER stress conditions in human innate immune cells, and found a correlation between perturbations in the ER stress response and sterile inflammation in monocytes from patients with bipolar disorder (Pereira et al, in preparation). Our findings also support the bioactivity of Portuguese thermal waters from the Center region (Oliveira et al. 2019; Silva et al, under revision). We demonstrated that thiol reactive skin allergens activate NLRP3 inflammasome through lysosomal destabilization and subsequent cathepsin leakage. Inhibition of cathepsin activity impaired NLRP3 activation and also allergen-induced maturation of dendritic-like cells, thus disclosing an innate immune mechanism crucial for the development of allergic contact sensitization.
 MITOCHONDRIA, METABOLISM AND DISEASE

Head: Paulo Oliveira

OBJECTIVES

Mitochondria are critical organelles for cell physiology. Mitochondria are the cell energy powerplants, producing most of the chemical energy for cell metabolism, and playing a key role in cell death and quality control processes.

Since mitochondria are also active players in cellular redox and calcium homeostasis, as well as in intermediate metabolism, the overarching objective of our group is to provide insights into the role of mitochondria in cellular metabolism, redox signaling and stress responses associated with chemical toxicology, as well as on the pathophysiology of aging and lifestyle diseases.

The role of mitochondria in stem cell biology as well as the development of mitochondria-directed therapeutic agents are other of the group objectives. Specifically, the group is focused in various research lines:

1. Mitochondrial role in aging and lifestyle-diseases: a) molecular pathways behind CDCA’s anti-obesogenic effects b) role of sestrin and sirtuin modulation as inducers of mitohormesis: preservation of mitochondrial function under pathologic stress, c) molecular mechanisms responsible for miRNA regulation in several biological and disease processes, particularly the miRNAs acting in mitochondria or in mitochondria-related mechanisms, d) mechanisms of mitochondrial disruption in non-alcoholic fatty liver disease and diabetes, e) mitochondrial metabolism and dynamics in non-neuronal cell samples from amyotrophic lateral sclerosis and Parkinson’s disease patients, f) mitochondrial profiling in non-invasively obtained stem cells from young and old donors, g) mitochondrial remodeling and autophagy during cancer stem cell differentiation and carcinogenesis, h) interactions between the extracellular matrix (ECM), stromal and tumor cells and the various cytokines embedded in the ECM, and how that contributes to the neoplastic phenotype, i) involvement of exosomes on cytokines’ release and inter-cellular communication, and role of human bronchial fibroblasts and their ECM in dedifferentiation, j) new strategies to block cancer stem cells formation and to modulate stromal cells phenotype to improve therapy’s efficacy, k) mitochondrial metabolic profile in bone cells differentiation and function, in absence and presence of estradiol (E2) or selected phytoestrogens, evaluating their potential in bone anabolic (osteoanabolic) or anticyclobolic (antiresorptives, with action on osteoclasts) treatment of postmenopausal osteoporosis and l) in utero programming of fetal energy deficit states in liver and heart, with impact in the development of adult diseases.

2. Mitochondrial Toxicology: a) mechanisms of drug-induced mitochondrial dysfunction caused by different xenobiotics, including drug-induced injury (e.g. anthracyclines) and nanoparticles, b) development of high-throughput methods to investigate mitochondrial function in the context of drug development and toxicology, c) identification of active compounds from different algae species with potential anti-tumor action.

3. Mitochondria-targeted therapeutics: a) intrinsic, pharmacological, or non-pharmacological (exercise or diet) regulation of mitochondrial biogenesis/metabolism and quality control to reduce organ injury during disease or chemical toxicity, b) novel mitochondrial-directed antioxidants based on dietary components in models for human diseases (cardiovascular/hepatic), c) new pharmacological conditioning strategies, resulting in the reduction of morbidity and mortality of liver resection surgery.
1. Mitochondrial role in aging and lifestyle-diseases: Related with cancer, and in a multi-institutional project we demonstrated recovery of respiration and tumor formation by mtDNA-depleted cells. We show that pyrimidine biosynthesis dependent on respiration-linked dihydroorotate dehydrogenase (DHODH) is required to overcome cell-cycle arrest, while mitochondrial ATP generation is dispensable for tumorigenesis. Still related with cancer, strategies to overcome chemotherapy resistance were developed based on the findings that resistance was due to the dedifferentiation of malignant cells to cancer stem cells as result of chemotherapy. Those strategies were based on the findings that inflammation sustained the cancer stem cell state, in a mechanism involving Toll-Like receptor 9. In the context of liver diseases and transplantation, our research has been looking into the development of new ways to preserve organs. We observed that mild hypothermia during reperfusion reduced the effect of ischemia-reperfusion injury on mitochondrial activity in liver tissue and promoted an increase in bioenergetic availability compared with normothermic reperfusion.

2. Mitochondrial Toxicology: Continuing our studies on the mechanisms of doxorubicin (DOX) cardiotoxicity, we showed that nanomolar DOX pretreatment of cardiomyoblasts induced a beneficial and possibly epigenetic-based mitochondrial adaptation, raising the possibility that an early sub-therapeutic DOX treatment can be used as a preconditioning and protective approach during anticancer therapies. By using an in vivo acute DOX cardiotoxicity study, by using an exploratory data analysis, we observed cardiac-specific alterations after DOX treatment for mitochondrial complexes III, IV, and preferentially for complex I. Interestingly, H2O2 production by the mitochondrial respiratory chain as well as loss of calcium-loading capacity, markers of subchronic toxicity, were not reliable indicators of acute DOX cardiotoxicity in this animal model. By using sequential principal component analysis and feature correlation analysis, we demonstrated for the first time alterations in sets of transcripts and proteins, but not functional measurements, that might serve as potential early acute markers of cardiac-specific mitochondrial toxicity, contributing to explain the trajectory of DOX cardiotoxicity and to develop novel interventions to minimize DOX cardiac liabilities.

3. Mitochondria-targeted therapeutics: Following previous work, and in collaboration with the University of Porto, we have developed novel multi-target agents designed to prevent progressive mitochondrial dysfunction, which act as mitochondria-targeted antioxidants with iron-chelating properties. Some of those molecules include derivatives from hydroxybenzoic and hydroxycinnamic acids and benzoic-acid-derived nitrones. Some of the new compounds were able to permeate a layer of hCMEC/D3 cells in a time-dependent manner, suggesting proper blood-brain barrier permeability activity, as well as serve as potential acetylcholinesterase inhibitors. The results validate the use of some of the new molecules in in vivo models of neurodegenerative diseases.
OBJECTIVES

a) Evaluating the effects of refined sugar intake on hepatic and visceral tissue intermediary metabolism: The increased consumption of sugar is implicated in the surge of nonalcoholic fatty liver disease (NAFLD) in Western societies. High sugar intake can modify intermediary metabolism of intestinal microbiota and visceral adipose tissues in addition to that of liver. Our group has developed stable-isotope tracer methodologies for quantifying glucose and fructose metabolism by liver and visceral fat using 13C-enriched fructose and glucose. These methods were applied to animal models of diet-induced NAFLD with the aim of improving our understanding of the role of extrahepatic sugar metabolism in the pathogenesis of NAFLD.

The effect of high fat intake on the metabolic disposition of these sugars is of particular interest since under normal conditions, lipid metabolites inhibit the main pathways of sugar metabolism including glycolysis, de novo lipogenesis and glycogen synthesis.

b) Mitochondrial dysfunction in early disease pathogenesis: My preliminary work suggests that overlapping mechanisms of metabolic dysregulation, including mitochondrial dysfunction, can impact cell and organ damage very early in life, much before symptoms can be measured, leading to several common diseases, including diabetes. Building on this work, I have begun to investigate whether mitochondrial function could be used to identify metabolic dysregulation locally in tissues and whether local tissue dysregulation can be picked up by measuring mitochondrial function in circulating cells and in specific tissues.
a) Obtained fundamental insights on the coupling of hepatic de novo lipogenesis with pentose phosphate pathway activity with glucose-6-phosphate as the provider of carbons for fatty acid synthesis as well as hydrogens for NADPH formation (Belew et al., 2019). This has important implications for the control of de novo lipogenesis in physiological and pathophysiological states such as non-alcoholic fatty liver disease and hepatocellular carcinoma.

b) We demonstrated that dietary fructose carbons were incorporated into the glycerol and fatty acid components of mesenteric adipose tissue triglyceride but not into the triglyceride of subcutaneous adipose tissue (Silva et al., 2019). This indicates that the mesenteric adipose tissue has privileged access to dietary carbohydrate and is able to use fructose as a lipogenic substrate. This has important implications for visceral adipose tissue function and expansion in obesity and related complications such as non-alcoholic fatty liver disease and Type-2-diabetes.

c) Mitochondrial function in tissues has been measured by high resolution respirometry using the Oroboros and circulating cells using the Seahorse technologies. Part of this work was funded by the Center for Childhood Obesity Prevention, an NIGMS COBRE (P20GM109096; JL Weber, PI) project where I was a primary research project leader. Preliminary data and findings being prepared for publication undergird my hypothesis that atypical mitochondrial respiration might be a protective and unresolved adaptation in response to stress. In addition, I believe that environmental factors, such as lifestyle and drugs, strongly influence this metabolic imbalance giving rise to insulin resistance early on that can easily be detected by important circulating mediators, including factors secreted by adipocytes, cytokines and microRNAs. Assessing circulating factors, including the microRNA profile of obese subjects, early, before any symptoms of disease arise, will be imperative for early diagnosis. So far 2 publications have results of these studies and several others are in preparation.
RESEARCH ACTIVITY

STEM CELL-BASED AND MOLECULAR THERAPIES
COORDINATOR: LUÍS PEREIRA DE ALMEIDA

GENERAL OBJECTIVES
The Stem Cell-Based and Molecular Therapies thematic strand brings together nine core research groups committed to the investigation and development of innovative tools and applications for prevention and treatment of target disorders, namely neurodegenerative, ischemic and infectious diseases, as well as cancer.

Being biotechnological in nature, the strand also accommodates a cluster of research groups devoted to structural biotechnology, computational modeling and protein engineering, as well as targeted biotechnological approaches.

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

MAIN ACHIEVEMENTS
Overall, research efforts originated nearly 140 publications in peer-reviewed international journals and book series (not counting meeting abstracts), 52% of them including fruitful collaborations with institutions (academic and otherwise) from 34 different foreign countries. 20 of the publications involved hospital and healthcare units/entities (notably the Coimbra University Hospitals (CHUC)) and around 36% counted with the participation of other Portuguese institutions (including several companies) not affiliated with the University of Coimbra.

As for the international collaborations, the USA features the largest co-authorships (12%), followed by Italy and Germany. More than half the publications are Open Access.

The majority of the publications (80%) are Q1, and 45% are in Top 10% journals, including ACS Nano, Acta Neuropathologica, Biomaterials, Angewandte Chemie, Nature Communications, Seminars in Cancer Biology, PNAS, and Redox Biology, which puts in evidence not only the quality but also the diversity of addressed subjects and multidisciplinary nature of the ongoing research. They account for research achievements such as the development of a light-triggerable nanoparticle library for the controlled release of non-coding RNAs (Angewandte Chemie), the discovery of a novel mechanism for replication and recycling of a mycobacterial intracellular polysaccharide that modulates fatty acid metabolism (PNAS) or how restoring brain cholesterol turnover improves autophagy and has therapeutic potential for treatment of spinocerebellar ataxia (Acta Neuropathologica).

Indeed the areas of research of the publications range from Pharmacology & Toxicology, to Genetics & Heredity, from Neurosciences & Neurology to Haematology. In terms of Category Normalized Citation Impact (InCites), it is worth mentioning the publications in the areas of Pharmacology & Toxicology (1.50) and Neuroscience & Behaviour (1.43).

The members of this thematic strand are also actively involved in advanced training, featuring several PhD students in doctoral programmes coordinated by CNC/IBILI researchers, notably the PhD Programme in Experimental Biology and Biomedicine (PDWEB) where advanced courses on Computational Biology, Drug Development or Advanced Therapies are the responsibility of this strand.

The implementation efforts of the new core facility ViraVector, for on-demand viral vector engineering and production, led CNC to be accepted in the National Hub of the EATRIS ERIC, the European Advanced Translational Research Infrastructure in Medicine, for the ATMP and Biological Biomarkers platforms of this network.

FUTURE PLANS
For the next 5-years, the Stem Cell-based and Molecular Therapies Thematic strand will be restructured to accommodate 11 groups and rebranding itself to Innovative Therapies.

It will focus on promoting interdisciplinary research translatable into the development of innovative tools and approaches for the prevention and treatment of disorders that are exacerbated in the aged population, such as neurodegenerative, ischemic, infectious and cancer diseases.

Capitalizing on the recently generated results and intellectual property, the groups in this thematic strand will use recent advances in high-throughput screening, deep sequencing, delivery formulations, medicinal chemistry, bioimaging and animal models to develop innovative therapies.

They will work in close collaboration with the other two strands of CIBB in the development of tools such as therapeutic biomolecules (mRNAs, protein, antibodies), in vitro models (e.g. in vitro blood brain barrier models) and bioinformatics models to explore large datasets (e.g. microbiome and metagenomes, etc).

The microbiology-driven groups will be paying particular attention to antimicrobial resistance and expand their interests to the intersection of molecular microbiology with neurodegenerative and chronic diseases so as to identify biomarkers associated to these pathologies that might be used for early detection.

The thematic strand will also continue to create translational and economical value for the Center Region of Portugal in the area of biotechnology/health sciences, benefiting from the long-standing links and collaborations with the BIOCANT biotechnology park (host of 40% of the biotech companies in Portugal) and the Coimbra University Hospitals (CHUC).
Vectors and Gene Therapy Group

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Pedro Curto PhD
Andrea Barro PhD
Bárbara Teixeira PhD

Inês Céu Sousa PhD
VECTORS AND GENE THERAPY

Head: M. Conceição Pedroso de Lima

OBJECTIVES

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

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

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

We are also studying the role of Claspin in cancer. Due to its functions in monitoring DNA replication, activation of CHK1-mediated checkpoint responses and triggering of DNA repair, we believe Claspin may act as a (and may be an important) tumour suppressor. We have found several genetic changes in CLSPN in cancer patients and we are now investigating if these changes may contribute to tumour development.
Regarding non-viral-mediated gene delivery, an extensive screening of a variety of cell penetrating peptides and cationic polymers for their capacity to generate efficient nucleic acid delivery systems has been carried out and structure-activity relationships have been established.

A miRNA-based therapy addressing GBM cancer stem-like cells to tackle human GBM is currently being developed. In this regard, we have observed that overexpression of miR-128 and miR-302a rendered human GBM stem cells susceptible to new generation chemotherapeutic drugs, such as axitinib, as revealed by a significant decrease of cell viability as compared to non-transfected cells. Mechanistically, this effect cannot be attributed to cell cycle arrest, apoptosis or mitotic catastrophe. However, miR-128 and miR-302a upregulation led to a strong increase in the expression of astrogial differentiation markers, similarly to that resulting from stem cell exposure to BMP4 (a recognized differentiation agent), a reduction of cell proliferation capacity being observed in both conditions. Combination of axitinib or sunitinib (another MTKI) with modulation of membrane lipid composition of GBM cells, through the silencing of key enzymes of lipid metabolism, such as glucosylceramide synthase (GCS), also showed to be a highly promising therapeutic approach towards GBM. Thus, GCS downregulation in combination with axitinib synergistically promoted the apoptosis of GBM cells, the efficiency of this strategy being likely correlated with an excessive generation of reactive oxygen species (ROS).

Delivery of miR-144 and miR-200c, downregulated in GBM cells and involved in bioenergetic metabolism pathways, resulted in loss of migratory ability. Combination of the miRNA modulation and treatment with the mitochondria-targeting drug dichloroacetate resulted in tumor cell death.

Furthermore, we found that oxidative stress and apoptosis may be involved in chemoresistance in acute leukemia and that influx/efflux transporters (decreased OCT1 and OCNT2 and increased GL-P and BCRP, respectively) were involved in Chronic Myeloid Leukemia (CML) resistance to imatinib. Simultaneous administration of imatinib and everolimus re-sensitized resistant cells.

Long non-protein coding RNAs (lncRNAs) are currently being studied regarding their potential as therapeutic targets for GBM. In particular, downregulation of IncRNA MVIH, overexpressed in a primary GBM cell line, as well as in human GBM tumor samples, reduced the tumor cell migratory and invasive ability in vitro. Furthermore, the combined treatment consisting of IncRNA MVIH silencing followed by GBM cell incubation with the MTKI cediranib led to tumor cell death.

Regarding neurodegenerative diseases, we have generated lentiviral and adeno-associated viral vectors to study their pathogenesis focusing on Machado-Joseph disease/spinocerebellar ataxia type 3 (MJD). Development of lentiviral-based in vivo models of MJD, in which we are experts, allowed fruitful investigation of disease-modifying strategies involving gene silencing, interaction of ataxia-related proteins, autophagy activation, proteolysis inhibition and neural stem cell transplantation.

Regarding glucan-based NPs for hepatitis B vaccination, the results of immunization revealed that NPs constitute an excellent HBsAg adjuvant. Immunotoxicological studies showed that the size of the NPs has an important influence on the results.

With regard to Claspin, we have found CLSPN genetic changes that were associated with cancer development and caused partial exon skipping, decreased Claspin expression and reduced Chk1 activation. We are also interested on new targeted therapeutic drugs in several hematological neoplasias as well as in the mechanisms involved in resistance to conventional chemotherapy and to targeted therapies in order to identify new therapeutic approaches and markers of drug response. This line of research highlighted the therapeutic potential of cellular signaling inhibitors, namely mTOR and farnesyltransferase inhibitors in lymphoid neoplasias. Moreover, we found that influx/efflux transporters were involved on imatinib resistance, and administration of imatinib and Reversine 205 or with Everolimus re-sensitize resistant cells. In addition, in CML patients, we create a predictive model of optimal response after one year of treatment using a combined profile of miRs.
STEM CELL BIOTECHNOLOGY

Head: Lino Ferreira

OBJECTIVES

The main scientific objectives of the group are: (i) to use stem cell-based therapies for the treatment of ischemic diseases, (ii) to develop innovative strategies for cell reprogramming, (iii) to implement stem cell-based assays and in silico approaches for drug screening and (iv) to deliver novel therapeutic compounds identified in the previous high-throughput approaches using nanotechnology-based non-viral vectors.

1- Stem cell-based therapies for the treatment of ischemic diseases. To evaluate the therapeutic effect of stem cells in the treatment of ischemic diseases (e.g. stroke, myocardial infarction and chronic wounds). The ongoing clinical trial (phase I/II clinical trial) with the Hospital Rovisco Pais and Centro Hospitalar e Universitário de Coimbra, with the participation of a stem cell banking company, Crioestaminal, will evaluate the therapeutic effect of CD34+ cells isolated from bone marrow of stroke patients in acute or sub-acute phases and transplanted by catheter to the brain.

2- To develop innovative strategies for cell reprogramming. The objective is to understand the molecular determinants underlying cellular reprogramming and hematopoietic specification. Cellular reprogramming can be achieved experimentally in different ways, including nuclear transfer, cell fusion or expression of transcription factors. The emergent ability to reprogram any human cell into desired hematopoietic cell-types is opening avenues to the discovery of new therapies for immune and blood diseases. The goals were a) to understand at the molecular level how hematopoietic cellular identities are specified employing cellular reprogramming and b) to use this knowledge to manipulate genes and pathways that ultimately may allow the generation of patient-specific hematopoietic cells for regenerative medicine and immunotherapy.

3- To implement stem cell-based assays and in silico approaches for drug screening. Develop several tissue models from stem cells as platforms for drug discovery programs related to ischemic diseases. Develop biomaterials and bioengineering platforms for the efficient maturation/specification of stem cells and their progenies and the high-throughput identification of non-coding RNAs to modulate (stem) cell activity, by the design of new biomaterials with relevant biological information, molecular and cell biology, microfluidic systems, high content analysis, and animal experimentation.

4- Development of novel therapeutic compounds identified from high-throughput approaches using nanotechnology-based non-viral vectors.

The main training/outreach activities objectives of the group were: (i) to participate in post-graduate programs, specifically in the PhD program of CNC “Biomedicine and Experimental Biology” and the PhD program of MIT-Portugal in “Bioengineering” and (ii) to participate in outreach activities organized by CNC/IBILI or associated institutions (IEC).
In 2019 the group continued to achieve progresses to address the scientific questions that drives the research of the group: (i) can we use stem cells to generate in vitro models of ageing and for drug screening? (ii) can we modulate stem cell niche by nanomaterials? (iii) what are the miRNAs involved in (stem) cell survival after transplantation to ischemic sites? (iv) what transcription factors are necessary for cell reprogramming into hematopoietic or T cells?

We have shown that fully functional arterial- and venous-like endothelial cells can be derived from induced pluripotent stem (iPSC) cells (Rosa et al, Scientific Reports 2019) and these cells can be used to generate in vitro vascular models for nanotoxicology screenings (Estronca et al, manuscript in preparation). We have generated a human in vitro model of ageing based on iPSC cells derived from patients with Progeria and we have studied the reasons of Progeria-smooth muscle cells vulnerability using iPSCs obtained from Progeria fibroblast patients (Pitrez et al, Nature Communications 2020). We also have derived brain-like endothelial cells from human iPSC derived endothelial progenitor cells and successfully developed a BBB in vitro model (Praça et al, 2019) that can be used for drug screenings.

We have shown how cellular stemness is intimately related with mechanical properties of the cell by inducing low cellular contractility and stiffness we are able to increase the reprogramming efficiency of mesenchymal stem/stromal cells into induced pluripotent stem cells (Gerardo et al, Scientific Reports 2019).

We have successfully synthesized a light-activatable nanoparticle (NP) library and that some NPs can be used for controlled release of non-coding RNAs with higher efficiency (up to 500%) than commercially available lipofectamine in gene-knockdown activity (Blersch et al, Angew Chem Int Ed 2020), and the NPs showed to be very effective in the release of siRNA and miRNA. Light-activatable NPs offer a new strategy to topically deliver non-coding RNAs.

Our research in small extracellular vesicles (SEVs) have confirmed that SEVs are promising strategies for tissue regeneration and we have revealed that the kinetics of SEVs delivery has a significant impact in tissue regeneration at tissue, cellular, and molecular levels (Antunes et al, ACS Nano 2019). We also have developed a positron-emission tomography (PET)/magnetic resonance imaging (MRI) platform that are able to track SEVs in vivo (Banerjee et al, Nanoscale 2019).

We have shown that SEVs can be efficiently modulated with miRNAs of interest (we showed proof-of-concept using pro survival miRNAs, identified by the group using high-throughput screening strategies). Moreover, we showed that the miRNA-modulated SEVs were efficient delivery systems both in vitro as well as in vivo (using a mouse model of diabetic wound healing). We are currently exploring new strategies to modulate the SEVs cargo/surface with the final goal of developing a translational drug-delivery platform capable of playing a key role in Regenerative Medicine at large.

We have shown that cooperative transcription factor binding mediates hemogenic induction and pioneered cell fate reprogramming approaches in immunology with induced dendritic cells. This conceptual shift opens exciting opportunities to merge cellular reprogramming and cancer immunotherapy. 5 papers were published in 2019 exploring these reprogramming approaches as well as a collaborative study in cancer stem cells.
OBJECTIVES

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

1. Organization principles of biochemical systems. The main goal of this research line is to discover, understand and exploit generic rules (organization principles) that (a) relate the design (i.e. naturally evolved molecular mechanisms) of biochemical systems to their function, and (b) hold across processes, cell types and organisms. We envisage that these network-structure / function relationships will play in biomedicine and bioengineering a role analogous to that of QSAR in pharmacology. Objects of interest in our current research are metabolic networks, antioxidant defense and redox signaling. Our group has identified recurrent structural and functional motifs in all these biomolecular networks and derived design principles (relationships among kinetic parameters and component concentrations) that these motifs must fulfill so that they perform their function adequately. These predictions are thoroughly supported by experimental observations in a variety of organisms and permitted rationalizing the phenotypes of mutations and stress responses. We are working towards exploring translational implications of these design/function relationships in degenerative diseases. In parallel, we are developing novel experimental (fluxomics and synthetic biology) methodologies to determine critical parameters in these applications.

2. Modeling the permeation through physiological barriers. The long-term goal of this research line is to develop quantitative structure-activity relationships (QSAR) for the permeation of physiological barriers by drugs, namely tight endothelia such as the blood-brain barrier (BBB). Failure to cross the BBB is the main factor of attrition in the development of psycho-active drugs, and is causing some of the main pharmaceutical corporations to abandon the development of such drugs altogether. The bioavailability of xenobiotics at the brain is strongly affected by their interaction with lipid bilayers and blood components (albumin, lipoproteins, erythrocytes and membranes of endothelial cells). Our work shows that the partition of drugs among the compartments strongly affects the timing and effectiveness of their permeation across the BBB. We are working towards modeling how molecular features of the xenobiotics impact on the kinetics of these critical steps and to achieve better predictions of overall permeability.

3. Computational tools for biomolecular systems. The main goal of this research line is to develop effective computational tools to simulate and analyze complex biomolecular systems and reaction networks. Namely, in support of the activities of the research lines described above. Developments range from fundamental computer-science methods that speed-up numerical computation in a broad range of computational biology applications, to tools for characterizing the relationship between design and performance of biomolecular reaction networks.
Bile salts (BS) are biosurfactants crucial for emulsification and intestinal absorption of cholesterol and other hydrophobic compounds such as vitamins and fatty acids. The interaction of BS with lipid bilayers is relevant for passive diffusion of acids. The interaction of BS with lipid compounds such as vitamins and fatty acids like cholesterol and other hydrophobic emulsification and intestinal absorption of BS, as well as their specific interactions with water and host lipid, such as hydrogen bonding and ion-pair formation, were studied in detail. Membrane properties were also investigated to obtain information on the degree of perturbation induced by the different BS. Differences in macroscopic membrane partition thermodynamics and translocation kinetics were rationalized in terms of the distinct structures and atomic-scale behavior of the bile salt species. In particular, the faster translocation of cholate is explained by its higher degree of local membrane perturbation. On the other hand, the relatively high partition of the polar glycine conjugates is related to the longer and more flexible side chain, which allows simultaneous efficient solvation of the ionized carboxylate and deep insertion of the ring system. [Front. Physiol. 10, 393. DOI:10.3389/fphys.2019.00393]

In higher organisms, the 2-Cys peroxiredoxin II (Prx2) is involved in the H2O2-mediated regulation of cell proliferation, apoptosis, cell migration, neuroprotection, angiogenesis and tumorigenesis. Understanding the mechanisms of those regulatory processes, Prx2 is a pentamer of dimers in antiparallel juxtaposition. Each monomer carries a very H2O2-reactive Cys (peroxidatic Cys, CP), proximal to a less reactive (resolving, CR) Cys in the other monomer. In the catalytic cycle, CP reduces H2O2, being oxidized to a sulfenic acid (CP-SOH), which in turn undergoes a condensation with the proximal CR, forming a disulfide. Through an iterative theoretic-experimental approach in collaboration with the labs of Dr. Christine Winterbourn (U. of Otago, NZ) and Dr. Flávia Meotti (U. of São Paulo, Brazil) we have previously demonstrated the occurrence of positive cooperativity between the two sites in a dimer in the H2O2 reduction step and negative cooperativity in the condensation step. Over 2019 we extended these studies to examine the interactions of Prx2 with glutathione (GSH) and towards clarifying the molecular underpinnings of cooperativity. We showed that GSH is able to reduce the Prx2 disulfide through a thiol-disulfide exchange reaction showing mild positive cooperativity. Furthermore, through an analysis of the pH dependence of the rate of the homocondensation reaction we showed that the redox state of one site in a dimer does not significantly influence the pKa’s of the CP-SOH and of the CR-SH at the other site. Therefore, the observed cooperativity is not mediated by the modulation of these site’s acidity. Instead, the redox state of one site substantially influences the rate constants for the condensation reactions between the CP-SOH (H) and the CR-Si(H) in the various protonation states. Together with other evidence, this observation suggests that cooperativity in condensation results from the modulation of the collisional frequency among the CP-SOH and the CR-SH groups at one site by the redox state of the other site [DOI: 10.1101/2020.05.11.087908]. Molecular dynamics studies in collaboration with the Data Driven Molecular Design group at CNC to further clarify the molecular underpinnings of this phenomenon are ongoing.
OBJECTIVES

The main interests of the group are centered in microbial agents of human disease, its biological traits relevant to infection and seeking for innovative therapies. Elderly, more susceptible to infection, is one of our major focus, including modulation of gut inflammation and chronic respiratory diseases.

During the period of this report (2019) our specific objectives were to seek for novel therapies to eradicate fungal infections with a focus on oral and filamentous fungi affecting the respiratory system. We continue to pursue how the purinergic metabolism and adenosine A2A receptors can be modulated to ameliorate pathological conditions of the elderly such as chronic inflammation of the gut.
MAIN ACHIEVEMENTS

-Mycobiome of the upper respiratory system of allergic patients and, IgEs against fungal cell wall extracts and EVs from the fungi isolated from those patients.

-Antifungal activity of plant extracts

-Response of macrophages to Alternaria infectoria spores (11046_2019_339_MOESM2_ESM.mp4)
MOLECULAR MYCOBACTERIOLOGY AND MICROBIOME

Head: Nuno Empadinhas

OBJECTIVES

Research activities in center around 3 research lines (Microbial Pathways, Microbiome in Chronic Diseases, Public Health Microbiology):

Mycobacterial Pathways and biosynthesis of antimicrobials - Mycobacteria cause serious infections beyond tuberculosis (TB), mostly in the chronically ill and in the elderly. They are “a global priority for which innovative new treatments are urgently needed” (WHO, 2017).

We aim at deciphering pathways for mycobacterial polymethylated polysaccharides, regulators of their cell wall assembly and potential targets for rational drug design.

An emerging line of research aims at genetic, enzymatic and structural characterization of a novel secondary metabolite from a soil actinobacterium, known for being source of great chemical diversity and biological activities (antibacterial, antifungal, antiparasitic, antiviral, anticancer, anti-inflammatory) with potential biomedical and industrial applicability.

Public Health - We have comprehensively screened domestic water distribution systems to assess the prevalence of some dangerous opportunistic nontuberculous mycobacteria increasingly reported to cause pulmonary infections in susceptible individuals. Ongoing genomic fingerprinting will allow understanding of the epidemiology and antimicrobial resistance determinants associated to this rapidly growing health threat.

Microbiome and Chronic Diseases – We are interested in understanding the contribution of neurotoxin-producing microbes found in dysbiotic gut microbiomes of Parkinson’s patients to neurodegeneration. Another objective in this line of research is to detect unique microbial signatures in diabetic skin microbiomes aiming at bacteriotherapeutic intervention. The unique and extensive DFU microbial biobank created recently in our group will be essential for research in this huge health problem.
Molecular Mycobacteriology & biosynthesis of antimicrobials – A novel mechanism for replication and recycling of a mycobacterial intracellular polysaccharide that modulates fatty acid metabolism and assembly of the cell envelope was identified and characterized (Ripoll-Rozada et al, 2019, PNAS). These findings build on previous achievements from our group that identified the genes of two essential mycobacterial pathways and new promising enzyme targets that were the founding members of new enzyme families at the IUMB database (Cereja et al, 2019, IUCrJ). The group has also identified an Actinobacterial orphan biosynthetic cluster that hints at a completely novel class of secondary metabolites. A family of kinases was revealed (Manso et al, 2019, mBio), which is likely to represent the missing link for incorporation of environmental glucosamine into an antibiotic biosynthesis pathway.

Parkinson’s Gut Microbiome - The gut microbiomes of Parkinson’s Disease (PD) patients was comprehensively characterized and their profiles revealed unique microbial signatures. In vitro and in vivo results confirmed how a specific microbial neurotoxin imparts chronic neuronal mitochondrial damage and probably the onset of PD features.

Diabetic Wounds Microbiome - Sampling of over 200 diabetic patients skin and wounds and isolation of relevant microbiota allowed the creation of a DFU biobank with over 2000 strains of over 50 species. Antimicrobial susceptibility trials and interspecific competition assays revealed bacterial communication phenomena in the DFU ecosystem. Genomes of relevant DFU microbiota were sequenced. We could successfully modulate mice DFU microbiomes toward healthier profiles with topical administration of certain neuropeptides.

Public Health - We isolated multidrug resistant strains nontuberculous mycobacteria (NTM) from hospital wards (Pereira et al 2019, BMC Microbiol). NTM patients’ houses and water distribution systems were sampled and numerous mycobacterial species could be isolated and identified by WGS (Tiago et al, 2019, Microbiol Resour Announc), including opportunistic pathogens members of M. abscessus-chelonae clade.
OBJECTIVES

Pentacyclic triterpenoids are a class of pharmacologically active and structurally rich natural products with privileged motifs for further modifications and SAR analyses. We focused on the anticancer activity of the semisynthetic oleanane and ursane triterpenoids derivatives of glycirrethynic and madecassic acid. We synthetized a series of novel glycirrethynic and madecassic acid (MEA) derivatives and screened them for antitumor activity against the NCI-60 cancer cell line panel. Alzheimer’s disease is a severe neurodegenerative disorder and so far there is no prevention or treatment of this disorder.

Our main goal is the identification of novel anti-Alzheimer’s agents, namely molecules targeting BACE1, ang glutaminyl cyclase by combining distinct but complementary approaches.

The work plan regarding computational studies includes pharmacophore-based virtual screening and molecular docking studies with the purposed in identifying hits acting with high affinity on BACE1 and glutaminyl active sites (allowing a reduction in the number of compounds to evaluate), and prediction of in silico pharmacokinetic (e.g., blood-brain barrier (BBB) permeation) and toxicity properties to assure only the compounds with the suitable profile will be experimentally tested. The biological evaluation aims to assess the hits BACE1 and glutaminyl cyclase inhibition potency, cellular toxicity and in vivo efficacy of the best candidate using animal models of the disease.

Antimicrobial resistance (AMR) is considered one of the major Public Health threats nowadays, with very few therapeutic options for the treatment of multidrug resistant Gram-negative bacteria infections. It is crucial to characterize resistance mechanisms and to understand the epidemiology of drug resistance at molecular level, and to investigate new strategies/molecules to fight AMR. Our objectives were focused on resistance dissemination by conjugation and natural transformation in clinically relevant Gram-negative bacteria, the role of heavy metals in AMR spread that supplement animal food and to ascertain the activity of polyphenols in gut bacterial infection.
A series of novel madecassic acid (I) derivatives was synthesized, and their cytotoxicity was evaluated against the NCI-60 panel of cancer cell lines. Several analogues exhibited broad-spectrum cytotoxic activities over all nine tumor types represented in the panel, with more potent antiproliferative activities observed against selected cancer cell lines, including multidrug-resistant phenotypes. Among them, the best compound showed GI50 (50% growth inhibition) values ranging from 0.3 to 0.9 µM against 26 different tumor cell lines and selectivity for one colon (COLO 205) and two melanoma (SK-MEL-5 and UACC-257) cell lines at the TGI (total growth inhibition) level. The mode of action of this compound was predicted by CellMiner bioinformatic analysis and confirmed by biochemical and cell-based experiments to involve inhibition of the DNA replication process, particularly the initiation of replication, and disruption of mitochondrial membrane potential. The present findings suggest this novel madecassic acid derivative may have potential as an anticancer therapeutic lead for both solid and hematological tumors. DOI: 10.1021/acs.jnatprod.8b00864

The treatment options for a patient diagnosed with Alzheimer’s disease (AD) are currently limited. The cerebral accumulation of amyloid-β is a critical molecular event in the pathogenesis of AD. When the amyloidogenic β-secretase (BACE1) is inhibited, the production of Aβ peptide is reduced. Henceforth, the main goal of our study is the discovery of new small bioactive molecules that potentially reach the brain and inhibit BACE1. The work was conducted by a customized molecular modelling protocol, including pharmacophore-based and molecular docking-based virtual screening (VS). Structure-based (SB) and ligand-based (LB) pharmacophore models were designed to accurately screen several drug-like compound databases. The retrieved hits were subjected to molecular docking and in silico filtered to predict their ability to cross the blood–brain barrier (BBB). Additionally, 34 high-scoring compounds structurally distinct from known BACE1 inhibitors were selected for in vitro screening assay, which resulted in 13 novel hit-compounds for this relevant therapeutic target. This study disclosed new BACE1 inhibitors, proving the utility of combining computational and in vitro approaches for effectively predicting anti-BACE1 agents in the early drug discovery process. https://doi.org/10.3390/biom10040535

We demonstrated the ability of AMR determinants to undergo natural transformation in different clinical Acinetobacter spp. isolates, which may facilitate AMR dissemination in the hospital environment, and we showed by genetic studies that heavy metals can select for AMR genes and contribute for its emergence and spread. Moreover, Portuguese red wine polyphenols prevent the pathogenicity of Escherichia coli at gut level, which deserves to be further explored as an antimicrobial strategy to fight infection.
BIOTECHNOLOGY:

MICROBIOLOGY OF EXTREME ENVIRONMENTS

Head: Milton Costa

OBJECTIVES

1. Continued studies on the mechanisms involved in stress adaptation of thermophilic, halophilic and desiccation-resistant bacteria.

2. To identify new compatible solutes and elucidate their biosynthetic pathways and their role in stress tolerance.

3. To isolate and characterize novel organisms from extreme environments for basic studies and for their biotechnological potential.

4. Metagenomics of extreme environments in Portugal, namely hot springs, salt mines and solar exposed rock surfaces to look for enzymes involved in the degradation of plastics and wood products such as cellulose, lignin and xylan.
MAIN ACHIEVEMENTS

1. Recent research led to the description of new bacteria and archaea from extreme environments with the purpose of finding new organisms that have biotechnological potential. These organisms have different origins that also contribute to our knowledge of microbial diversity and their metabolic and biosynthetic processes. The genomes sequence analysis of over 20 genomes has been the source of genes that have biotechnological potential.

2. We embarked on an extensive study on the biodiversity of several geothermal areas in Portugal using in situ examination of 16S rRNA gene sequences as a modern assessment of biodiversity. It is well known that this methodology produces an extremely good picture of the biodiversity since the vast majority of organisms cannot be isolated in culture.

3. We also continued our studies of the identification and function of compatible solutes isolated from extremophilic organisms, namely slightly halophilic thermophiles, as well as extremely radiation resistant organisms. Several candidate genes were identified in the metagenomes of the hot springs.
OBJECTIVES

The long-term goal of our group is to contribute to a better understanding of the molecular mechanisms of microbial pathogenicity and facilitate the identification of new factors/molecular pathways that may constitute pathogen- or host-directed targets for therapeutic intervention. Our current research interests can be summarized in the following strands:

i) Study of proteolysis and proteostasis in the context of infection, both on the relevance of these mechanisms for bacterial pathogenesis and for modulating host-pathogen interactions. Our main working model is Spotted Fever Group (SFG) Rickettsia.

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

iii) Identification of bacterial virulence proteins (e.g. surface-exposed membrane proteins) susceptible of antibody-based targeting strategies, for both structural and functional characterization and/or ultimate therapeutic intervention.

In a parallel strand we also aim to:

iv) Continue exploring the functional and biotechnological aspects of plant proteases, namely their role and potential targetability in allergic disorders.

These research programs combine diverse methodologies from cell biology, structural and molecular biology, recombinant DNA technology and heterologous protein production, biochemical and biophysical protein characterization, protein chemistry, complemented with various system-wide quantitative approaches.
MAIN ACHIEVEMENTS

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

- We pursued with studies to understand in detail the role of macrophages in rickettsial pathogenesis. We evaluated early host transcriptional responses by RNAseq (at 1 hpi) (ref. a) and proteome signatures by SWATH-MS (at 24 hpi) (ref. b) of THP-1 macrophages infected with R. conorii and R. montanensis. Our results revealed that infection with pathogenic R. conorii interfered with a myriad of cellular processes (e.g., inflammatory responses, metabolic responses, survival, proteostasis network, and transcription). These results provide evidence for a substantial reprogramming and mechanistic differences between Rickettsia-macrophage-tropic vs. non-tropic phenotypes, providing multiple testable hypotheses that we are now validating.


2) Development of a core platform specialized on antibody-based products and services

- We have continued the implementation and promotion of a unique technological platform for production of antibodies in avian models (e.g. chicken, quails); the platform supports antibody discovery campaigns against multiple targets of interest (from microbial to human ones) and will ultimately enable the development of novel immunotherapies and immunoresearch tools. The core of the antibody technological platform is the CNC Avian Technological Unit, a unique animal research unit also implemented by the group and fully dedicated to exploit birds as bioreactors (http://www2.biocant.pt/structuralbiotechnology/index.php/resources/). This is the only unit of its kind in Portugal, holding IP on avian experimentation systems that enable core R&D activities (PCT/IB2017/054766).

   - We have contributed to a review in the field of Parasitology, that presents the most relevant applications of avian IgY antibodies in the fight and control of parasitic infections (ref. a).


3) Biochemistry, biology and biotechnology potential of plant proteases

- We characterized a novel atypical aspartic protease (AP) expressed in Arabidopsis roots (ASPR1). Recombinant ASPR1 produced by transient expression in Nicotiana benthamiana displayed atypical biochemical properties and unique specificity preferences resembling those of fungal APs. ASPR1 overexpression suppressed primary root growth and lateral root development, implying a previously unknown biological role for an AP (ref. a).


- Acacia caven (Mol.) Molina pollen causes pollinosis in South America. The aim of this work was to characterize the proteolytic enzymes of A. caven pollen, and study their influence on allergy. A 75-kDa peptidase (Acacian peptidase) was purified and classified as a serine peptidase. We showed that Acacian peptidase can alter the integrity of the epithelium barrier, causing cell permeability, increasing the allergic sensitization and exacerbating the overall bronchoconstrictive effect detected in asthmatic lungs. This novel serine peptidase constitutes a relevant therapeutic target in the treatment of allergic disorders (ref a).


- In this invited review, we give an overview of the current knowledge on the distinctive features and functions of both atypical and nucellin-like APs, and discuss this emerging pattern of functional complexity and specialization among plant pepsin-like proteases.

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

Projects in Collaboration

NEUROSCIENCE, VISION AND BRAIN DISEASES STRAND

Synapse Biology


- Supervision of Orsolya Antal, PhD student in Syn2Psy – Synaptic Dysfunction in Neuropsychiatric Disorders, an ITN funded by the Marie Skłodowska Curie Actions (2019-2023) (Supervisors: Ana Luisa Carvalho, Thomas Knöpfel)

- Collaboration with Andrea Barberis from the Italian Institute of Technology (ii) in the project entitled “The K+-Cl− cotransporter (KCC2) to maintain GABAergic neurotransmission: a novel therapeutic strategy for epilepsy”.

- Collaboration with Maurizio Taglialetela (University Federico II, Naples), for the study of mechanisms that regulate Kv7 channels

- Collaboration with Angela Vincent and Sarosh Irani (University of Oxford), in a project focused on anti-CASPR2 autoimmune encephalitis

- Collaboration with Inbal Israely (Columbia University, NY) in studying how metabolic hormones regulate spine dynamics in the hippocampus


**Redox Biology and Brain Sensing**

Ongoing research collaboration and student mentoring is maintained active (although no collaborative paper was published during 2019) with Enrique Cadenas from University of Southern California, LA, USA on redox regulation in aging brain and neurodegeneration and with Greg Gerhardt from Center for Microelectrode Technology, University of Kentucky, USA on technological development of microbiosensors for stereotaxic insertion into the brain.

**Neuroendocrinology and Aging**


Angela Relógio - Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt - Universität zu Berlin, and Berlin Institute of Health, Institute for Theoretical Biology, Germany (circadian rhythm, co-supervisor)

Carlos Lopez Otin - Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain (Collaborative Research, Graduate training; Premature aging and progeria models; hallmarks of aging; scientific advisor).

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

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

João Pedro Magalhães – Liverpool University – projecto collaborator;

**Vision, Brain Imaging and Cognitive Neuroscience**

Papers (international collaboration)
See European Projects and publications of the group

Book Chapter (international collaboration)
3Rui Bernardes, Lila Jorge, Ana Nunes, and Miguel Castelo-Branco Machine Learning Approaches in OCT: Application to Neurodegenerative Disorders Book Chapter in OCT in Central Nervous System Diseases The Eye as a Window to the Brain Editors: Grzybowski, Andrzej, Barboni, Piero (Eds.) Springer 2020

Scientific collaborations
Reza Farivar, McGill University, Canada
Rainer Goebel, University of Maastricht
Agnetta Nordberg, Karolinska Institute
Alcino Silva, University of California at Los Angeles
Richard Edden, John Hopkins University

Post-graduation and post-docs interchange
Bruno Direito (Carnegie Mellon University)

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 (H2020): STIPED, IMI-2

**Neuromodulation**

- Networks:
  International Alliance for Healthy Ageing (with Univ. Newcastle, Groningen Medical School, Univ.Copenhagen, Mayo Clinics) Association for Science and Information on Coffee

- Research grants:
  CAPES-FCT program with Rui Prediger (Univ. Federal Santa Catarina, Brazil)
  Joint project of the Association Nationale de Recherche ‘ROle of Adenosine Receptors on synapse stabilization (ROAR)’ with Sabine Levy (CNRS, Institut Fer à Moulin, Paris) and Christophe Bernard (INSERM, Univ.Méditerrannée, Marseille).

- Graduate training:
  Co-supervision of a PhD student (Mara Yone Fernandes) with Geanne Matos (Univ. Federal Ceará, Brazil)
  Co-supervision of a PhD student (Angela Patricia França) with Rui Prediger (Univ. Federal Santa Catarina, Brazil)
  Co-supervision of a PhD student (Lisiane Souza) with Pablo Pandolfo (Univ. Federal Fluminense, Brazil)
  Co-supervision of a PhD student (Xinli Xu) with Nelson Rebola (Univ.Bordeaux, France)

**Mitochondrial Dysfunction and Signaling in Neurodegeneration**

Graduate Training:
- “Neuroscience and Mental Health: a Clinical and Molecular Perspective in Neuropsychiatric and Neurodegenerative Disorders”, The Doctoral Programme in Health Sciences, organized by the Faculty of Medicine, University of Coimbra. Coordinators: Ana Cristina Rego and João O. Malva Date:April 1-5, 2019

- “Molecular and cellular mechanisms of ageing and neurodegeneration” EIT Health_EpiDEMPrev advanced course Coordinators: Ana Cristina Rego and João O. Malva Date:April 2-5, 2019

International collaborative publications:
- Pinho R, Paiva I, Jericic KG, Fonseca-Ornelas L, Gerhardt E, Fahibusch C, Garcia-Esparcia

Invited speaker in international meetings:
Rego A. C. (2019) Mitochondrial and Ca2+ deregulation in neurons in early stages of Alzheimer’s disease pathogenesis and brain aging following immediate exposure to amyloid-beta oligomers. “Ageing: models, mechanisms and therapies” conference _ Session III: Ageing mechanisms (under the project ERAChair@UC), 28-29th June, University of Coimbra, Coimbra, Portugal.

Research collaboration with the following researchers:
- Flaviano Giorgini (PhD), Department of Genetics and Genome Biology, University of Leicester, U.K.
- George Daley (MD, PhD), Harvard Medical School and Boston Children’s Hospital, Boston, USA
- Thorsten Schlaeger (PhD) Boston Children’s Hospital, Boston, MA, USA
- Michael Hayden (MD, PhD), University of British Columbia, Vancouver, Canada
- Tiago Fleming Outeiro (PhD), University Medizin Goettingen, Goettingen, Germany

Aging and Brain Diseases: Advanced Diagnosis and Biomarkers


Chincarini, A., Peira, E., Morbelli, S., Pardini, M., Bauckneht, M., Arbizu, J., et al. Semi-quantification and grading of amyloid PET:


New Targets and Therapeutics for Chronic Diseases

Collaborative publications


Member of the editorial board
Raquel Santiago: Guest Editor of the Special Issue ”Retinal Ganglion Cells” in International Journal of Molecular Sciences together with Dr. Marta Agudo-Barriuso (Experimental Ophthalmology Group, Instituto Murciano de Investigación Biosanitaria-Virgen de la Arrixaca & Universidad de Murcia, Murcia, Spain) and Dr. Eloisa Herrera (Instituto de Neurociencias CSIC-UMH, Alicante, Spain).

CAMPUS Training
CRISH 2 – Co-creating Innovative Solutions for Health 2.0
EIT Health – CAMPUS Training for Executives and Professionals
Coordination: Joan Escarrabíl - Hospital Clinic Barcelona and Barcelona Institute for Global Health (ISGlobal)
Graduate Training
José Maria Cabrera Maqueda
Doctoral Programme in Vision Sciences (University of Murcia, Spain)
January – April 2019
Rosalba Vitagliano
ERASMUS training - Student from the “Università degli Studi del Sannio di Benevento”, Benevento, Italy
May – July 2019
Shelly Fegleyman
Research Exchange Programme
Medical student - Faculty of Medicine of Rappaport, Israel
**Cell Signaling and Metabolism in Diseases**

Neurodegenerative diseases, course PhD Program “Experimental Biology and Biomedicine” (PDBEB), CNC, Univ. Coimbra, Coimbra, Portugal, 08-12 April, 2019. Invited speakers: Michael Heneka (Univ. Hospital of Bonn, Bonn, Germany), Pascal Derkinderen (Univ. Nantes & Centre Hospitalier Universitaire de Nantes, France), Tiago F. Outeiro (Univ. Medical Center Goettingen, Germany)


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

Maurício Sforcin, Departamento de Microbiologia e Imunologia, Instituto de Biociências, UNESP, Botucatu, SP, Brasil. Collaborative Projects (Própolis: Modulação da apresentação antigênica e ativação diferencial de linfócitos T; Entidade Financiadora: FAPESP, Brasil, Referência: 2015/03493-3.

Cosmetics Europe (https://www.cosmetics-europe.eu), which represents about 40 of the world’s largest cosmetics companies, including L’Oreal, Unilever, Procter & Gamble, Henkel, GSK, Beiersdorf, Colgate-Palmolive SA, Shiseido, among others. Collaborative Project.

Other national publications (6000.)


**Mitochondria Metabolism and Disease**

Collaborations:

Albert Rizvanov, Kazan Federal University, Russia

Alessandro Valli, Centro Cardiologico Monzino, Italy

Anatoly Zhitzkovich, Brown University, USA

Anika Hartz, Bjorn Bauer, University of Kentucky, USA

Bart Ghesquiere, VIB, Leuven, Belgium

Clemens Steegborn, University of Bayreuth, Germany

Daniel Dorta, University of São Paulo, Brazil

David Sinclair, Harvard Medical School, USA

Elmar Heinzle, Universität des Saarlandes, Germany

Erich Gnaiger, Oroboros, Austria

Faustino Mollinedo, CSIC, Spain

Ignacio Vega-Naredo, University of Oviedo, Spain

Jan Kopecky, Academy of Sciences, Czech Republic

Jeffrey Stuart, Brock University, Canada

Jiiri Neuzil, Griffith University, Australia

Joan Rosello, CSIC, Spain

John Wise, University of Louisville, Louisville, USA

Laura Vergani, University of Genoa, Italy

Louise Torp Dalgaard, Department of Science, Systems and Models, Denmark

Maria Almeida, University of Arkansas, USA

Maria Felice Brizzi, Università degli Studi di Torino, Italy

Mariusz Wieckowski, Nenski Institute, Poland

Mark Nijland, Laura Cox, University of Texas Health Science Center, USA

Nika Danial, Dana-Farber Cancer Institute, USA

Patricia Scott, Jon Holy, Kendall Wallace, University of Minnesota, USA

Peter Nathanielsz, University of Wyoming, USA

Piero Portincasa, University of Bari, Italy

Pinchas Cohen, University of Southern California, USA

Saber Hussain, Wright State University, USA
Werner Koopman, Radboud University Medical Centre, The Netherlands

Coordination of networks:
“FOIE GRAS”, H2020-MSCA-ITN-2016, Ref. 722619, 2017-2020
“mtFOIE GRAS”, MSCA-RISE-2016, Ref. 734719, 2017-2020

**Metabolic Control**


Collaborations with:
Elisabet Borsheim and Shannon Rose at the Arkansas Children Research Institute, US
Project Title: Assessment of oxidative capacity in obese children.

Louise Daalgard and Havard Jenssen at Roskilde University, Denmark
Project Title: Combination therapy synergistically accelerates diabetic wound closure

Mirela Delibegovic at the University of Aberdeen, UK
Project Title: Effects of PTP1b modulation on Wound Healing

Jan Eriksson and Maria Joao Pereira at Uppsala University, Sweden
Project Title: Antipsychotic drug induced metabolic dysfunction

Morten Bjerregaard-Andersen at the University of Southern Denmark, Denmark
Project Title: COVID-19 and Type 1 Diabetes – a multicentre study
INTERNATIONALIZATION

STEM CELL-BASED AND MOLECULAR THERAPIES STRAND

V E C T O R S A N D G E N E T H E R A P Y G R O U P

Projects under international Consortiums/Networks:
- New diagnostic and therapeutic tools against multidrug resistant tumors - COST action CA17104 (2018/2022).

Collaborative Publications:

S T E M C E L B I O T E C H N O L O G Y

Nanomaterials for modulation of the Bone Marrow niche. Cristina Lo Celso (Imperial College of London, UK), Emanuel Quartin (CNC, Portugal), Delfim Duarte (IPS, Portugal), Lino Ferreira (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).

S Y S T E M S A N D C O M P U T A T I O N A L B I O L O G Y

University of Otago (New Zealand):
Researchers: Christine Winterbourn, Alexander Peskin Projects:
- Characterizing the operation of the Prx2/Trx1/TrxR system in human erythrocytes.
- Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins.
- Understanding the redox responses of erythrocytes of G6PD-deficient children.

University of São Paulo (Brasil):
Researcher: Flávia Meotti
Project: Characterizing the kinetics and molecular mechanisms of human 2-Cys peroxiredoxins.

University Sains Islam Malaysia (Malaysia):
Researchers: Fook-Choe Cheah

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.

MOLECULAR MYCOBACTERIOLOGY AND MICROBIOME GROUP

Graduate Training


REWIRE (Reinforcing Women In Research) Programme, University of Vienna (https://rewire.univie.ac.at/), Vienna, Austria (Nuno Empadinhas).

Editorial Board Member (Nuno Empadinhas)

Scientific Reports

Frontiers in Immunology (Guest Associate Editor in Nutritional Immunology)

Collaborations

Gunilla Kallenius and Christopher Sundling, Karolinska Institutet, Stockholm, Sweden.

Tom Blundell and Vitor Mendes, University of Cambridge, United Kingdom.

Reinaldo B. Oriá, Federal University of Ceará, Fortaleza, Brazil.


Training


Microbiology of Extreme Environments
Collaborative publications in Publications

Collaborative project led by Ramon Roselló-Moré and some twenty other worldwide investigators to investigate high salt sites by metagenomic analysis and culture dependent isolation of hyperhalophilic organisms. Ongoing.

Collaboration with two Polish colleagues from the University of Lodz to isolate and to perform metagenomic analysis and culture dependent isolation of hyperhalophilic organisms. Ongoing.


Graduate Training Networks


Microbiology of Extreme Environments
Collaborative publications in Publications

Collaborative project led by Ramon Roselló-Moré and some twenty other worldwide investigators to investigate high salt sites by metagenomic analysis and culture dependent isolation of hyperhalophilic organisms. Ongoing.

Collaboration with two Polish colleagues from the University of Lodz to isolate and to perform metagenomic analysis of hyperhalophiles in Polish salt Mines. Ongoing.


Molecular Biotechnology
Collaborative publications:


Barcia C., Coelho AS, Barberis S, Veríssimo P . Collaborative publications: Dr. Alexander Wlodawer, Macromolecular Crystallography Laboratory, NCI-Frederick, USA; Dr. Alice Y. Cheung, University of Massachusetts at Amherst, Amherst, USA; Dr. Juan J. Martinez, Department of Pathobiological Sciences, LSU School of Veterinary Medicine, Baton Rouge, USA; Dr. Pitter Huesgen, Central Institute for Engineering, Electronics and Analytics (ZEA-3), Forschungszentrum Jülich, Germany; Dr. Dirawijam Thirumalai, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Medicinal Chemistry & Drug Discovery
PARTICIPATION IN THE ORGANIZATION OF SCIENTIFIC MEETINGS

FEBRUARY 2019

Organizing of the meeting: "XIII Congress of the Portuguese Neuropediatrics Society", Coimbra
Date: February 7-8, 2019
CNC.IBILI members involved in the organization: Catarina R. Oliveira

MARCH 2019

Organizing of the meeting: "Sessão de Encerramento (Oficial) da Semana Internacional do Cérebro 2019 - Quando o Cérebro fica Dependente", FNAC – Fórum Coimbra, Portugal
Date: March 17, 2019
CNC.IBILI members involved in the organization: Ana Cristina Rego

MAY 2019

Organizing of the meeting: "Symposium at the 53rd Annual Scientific Meeting of the European Society for Clinical Investigation, Coimbra, Portugal,
Date: May 2019
CNC.IBILI members involved in the organization: Armando Salvador

Organizing of the meeting: "EASD-NAFLD Study group Annual Meeting", Lisbon
Date: May 8-9 2019
CNC.IBILI members involved in the organization: John Jones

JUNE 2019

Co-organizer of the Symposium: Prieto LXX XXL Lx Fest - a one-day symposium on the occasion of the academic jubilee of Manuel J. E. Prieto”, Lisbon, Portugal
Date: June 2019
CNC.IBILI members involved in the organization: Luis Loura

Organizing of the Meeting: "Conference on Ageing: Models, Mechanisms and Therapies", Faculty of Medicine, University of Coimbra, Polo III,
Date: June 28- 29, 2019
CNC.IBILI members involved in the organization: Lino Ferreira, Cristina Rego, Claudia Cavadas

JULY 2019

Organizing of the Meeting: "MiP/MitoEAGLE Training School 2019. Mitochondrial respiratory physiology: Challenges on data sharing, reproducibility, and interpretation., Coimbra, Portugal
Date: July 08-12, 2019
CNC.IBILI members involved in the organization: Paulo Oliveira

Organizing of the meeting: "XIV European Meeting on Glial Cells in Health and Disease - Contribution of glial extracellular vesicles to neurodegenerative diseases", Porto,
Date: July 10-13, 2019
CNC.IBILI members involved in the organization: Francisco Ambrósio

SEPTEMBER 2019

Organizing of the meeting: "Synuclein Meeting 2019: "Where we are and where we need to go", Axis Hotel Ofir, Porto, Portugal
Date: September 1-4, 2019
CNC.IBILI members involved in the organization: Ana Cristina Rego

Organizing of the Meeting: "2nd FEBS Advanced Lecture Course on Oncometabolism," Luso, Portugal.
Date: September 1-6, 2019
CNC.IBILI members involved in the organization: Paulo Oliveira
Organizing of the meeting: "2019 Summer School on Computational Biology, Coimbra (Portugal)"
Date: September 2-12, 2019
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the meeting: "4th course of Basics in Human Genetic Diagnostics – A Course for CLGs in education (in collaboration with the ESHG European Medical Board), Figueira da Foz,
Date: September 9 - 13, 2019
CNC.IBILI members involved in the organization: Aging And Brain Diseases:Advanced Diagnosis and Biomarkers group members

Organizing of the meeting: "8th European Calcium Society (ECS) Workshop "Calcium Signaling in Aging and Neurodegenerative Diseases", Hotel Tryp, Coimbra, Portugal
Data: September 18-20, 2019
CNC.IBILI members involved in the organization: Ana Cristina Rego, Claudia Pereira

OCTOBER 2019

Organizing of the conference: "16th International Conference in Molecular Systems Biology, Manila, Philippines"
Date: October 2019
CNC.IBILI members involved in the organization: Armindo Salvador

Organizing of the meeting: "CRISH Course – Co-creation of innovative solutions for health", Coimbra
Date: October 3-4, 2019
CNC.IBILI members involved in the organization: Francisco Ambrósio

Organizing of the meeting: "33th Meeting of the "Grupo de Estudos de Envelhecimento Cerebral e Demência”", Curia,
Date: 11-12 October 2019
CNC.IBILI members involved in the organization: Catarina R. Oliveira

Date: 11-13 October 2019,
CNC.IBILI members involved in the organization: Mª João Moreno

Organizing of the Meeting: "European Vision Research Association Meeting 2019", Nice, France
Date: October 17-19, 2019
CNC.IBILI members involved in the organization: Miguel Castelo-Branco

NOVEMBER 2019

Organizing of the Meeting: “23th Annual Meeting of “Sociedade Portuguesa de Genética Humana (SPGH)”, Coimbra
Date: November 14-16 2019
CNC.IBILI members involved in the organization: Aging And Brain Diseases:Advanced Diagnosis and Biomarkers group members

DECEMBER 2019

Organizing of the meeting: "Encontro de Jovens Investigadores em Biologia Estrutural e Computacional (EJIBCE), Lisbon, Portugal"
Date: December, 2019
CNC.IBILI members involved in the organization: Irina Moreira

Organizing of the Meeting: "Congress of Microbiology and Biotechnology (MicroBiotec 2019)", Coimbra, University of Coimbra, Portugal.
Date: 5-7 December,2019
CNC.IBILI members involved in the organization: Gabriela Silva, Teresa Gonçalves

Organizing of the meeting: "CIBB Meeting 2019", Coimbra
Date: December 19-20, 2019
CNC.IBILI members involved in the organization: Francisco Ambrósio
During 2019 CNC.IBILI organized 12 Advanced Courses (inserted at the Doctoral Programme in Experimental Biology and Biomedicine - PDBEB at CNC) and hosted XX 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 14 Ph.D. and 86 M.Sc. theses were concluded.

**ADVANCED COURSES 2019**

**Core Technologies @ CNC**
January 21 - February 1, 2019
Coordinator: Luisa Cortes

**Connecting the Researchers with the society**
February 18 - 22, 2019
Coordinator: Sara Amaral

**Computational biology**
February 25 - March 1, 2019
Coordinators: Irina S. Moreira & Alexandra P. Carvalho & Armindo Salvador

**Oncometabolism: Principles and Applications**
March 11 - 15, 2019
Coordinator: Paulo Oliveira & João Ramalho

**Fighting infection**
March 18 - 22, 2019
Coordinator: Nuno Empadinhas & Isaura Simões

**Neuronal circuits & behavior**
April 1 - 5, 2019
Coordinator: João Peça

**Neurodegenerative disorders**
April 8 - 12, 2019
Coordinators: Paula I. Moreira, Cláudia Pereira, Armanda Santos, Teresa Cruz, Sandra M Cardoso

**Advanced Therapies**
April 22 - 26, 2019
Coordinator: Luís Almeida & Lino Ferreira

**Synapse structure and function**
April 29 - May 3, 2019
Coordinator: Ana Luisa Carvalho & Carlos Duarte

**Proteomics Approaches in Life Sciences**
May 6 - 10, 2019
Coordinator: Bruno Manadas, Isaura Simões & Sandra Anjo

**Drug development**
May 13 - 24, 2019
Coordinator: João Nuno Moreira & Luís Almeida

**Animal experimentation**
May 28 - 30, 2019
Coordinator: Paula Mota
CNC.IBILI SEMINARS

JANUARY

9.1.2019 | The mechanism of wound healing through the fibroblast switching between two states
Rui Dilão (Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal)
Host: Hugo Fernandes

10.1.2019 | Arc/Arg3.1 as a major coordinator of cognition
Sonia A. L. Correa (School of Pharmacy and Medical Sciences, Faculty of Life Sciences, University of Bradford, UK)
Host: Luis P Almeida

10.1.2019 | Funding Opportunities EIT Health
Jorge Figueira (DITS), Marta Passadouro (DITS), Jorge Pimenta (IPN)
Host: Sara Amaral

11.1.2019 | Action at a distance on object–related ventral temporal representations
Jorge Almeida (Center for Research in Neuropsychology and Cognitive and behavioral intervention (CINEICC), University of Coimbra)
Host: Claudia Cavadas

23.1.2019 | Mechanisms of nuclear positioning during cell migration and muscle development
Edgar Gomes (Institute of Molecular Medicine, University of Lisbon)
Host: Mário Grãos

30.1.2019 | Amyotrophic Lateral Sclerosis in the Lab and in the Society
Filomena Silva (CNC, University of Coimbra), Pedro Souto (President APELA), Maria Eulália Ribeiro (Vice-President APELA)
Host: Sara Amaral

FEBRUARY

1.2.2019 | Microbial signatures in diabetic skin: opportunities for therapeutic intervention
Ana Maranha (CNC, University of Coimbra)
Host: Sónia Pereira

6.2.2019 | Rational Protein Engineering
Alexandra Carvalho (CNC, UC-Biotech)
Host: Lino Ferreira

15.2.2019 | Deregulation of BDNF signalling in Alzheimer’s Disease: new opportunities for treatment
Maria José Diógenes (IMM, University of Lisbon)
Host: Ana Cristina Rego

19.2.2019 | Journalists and scientists: how to communicate?
Teresa Firmino (Jornal Público)
Host: Sara Amaral
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Speaker</th>
<th>Institution</th>
<th>Host</th>
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<tbody>
<tr>
<td>20.2.2019</td>
<td>Blockchain: What is it? Good for?</td>
<td>Paulo Rupino (CISUC, Department of Informatics Engineering, University of Coimbra)</td>
<td>Host: Ricardo Pires</td>
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<td>22.2.2019</td>
<td>Fine Timescale Coordination of Thalamic Activity with mPFC and CA1 non-REM Oscilations</td>
<td>Carmen Varela (Psychology Department Florida Atlantic University)</td>
<td>Host: Ana Luisa Carvalho</td>
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<td>22.2.2019</td>
<td>Science Communication in Portugal - how far are we?</td>
<td>Joana Lobo Antunes (ITQB-UNL and Rede SciComPT)</td>
<td>Host: Sara Amaral</td>
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<tr>
<td>15.3.2019</td>
<td>The ATPase Inhibitory Factor 1: A double-edge sword?</td>
<td>Jose M. Cuezva (Universidad Autónoma de Madrid, Spain)</td>
<td>Host: Paulo Oliveira</td>
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<td>20.3.2019</td>
<td>The CRISPR revolution</td>
<td>Chase Beisel (Helmholtz Center for Infection Research, University of Würzburg, Germany)</td>
<td>Host: Isaura Simões</td>
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<tr>
<td>27.3.2019</td>
<td>Quantum GX2 MicroCT System for in vivo Imaging - from bone to heart</td>
<td>Sasha (Alexandre) Belenkov (Applications Scientist, PerkinElmer, Inc.)</td>
<td>Host: Vilma Sardão</td>
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<tr>
<td>29.3.2019</td>
<td>Regulation of neuronal connectivity and synaptic plasticity by endo- and fitocannabinoids</td>
<td>Ana M. Sebastião (IMM and Faculty of Medicine, University of Lisbon)</td>
<td>Host: Carlos Duarte</td>
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<tr>
<td>1.4.2019</td>
<td>Imaging the brain and cerebrospinal fluid at the nanoscale</td>
<td>Juan Varela (School of Biology, University of St. Andrews, UK)</td>
<td>Host: Mariana Bexiga</td>
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<td>3.4.2019</td>
<td>Using biomarkers to define disease risk in pre-clinical Alzheimer’s disease</td>
<td>Lefkos Middleton (Imperial College London, UK)</td>
<td>Host: João Malva &amp; Ana Cristina Rego</td>
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<tr>
<td>3.4.2019</td>
<td>A medicinal chemistry approach for the development of novel anti-tumor agents by targeting p53-MDM2/X interactions</td>
<td>Maria M.M. Santos (Med.ULisboa, University of Lisbon)</td>
<td>Host: Irina Moreira</td>
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<td>5.4.2019</td>
<td>Store-operated calcium entry in stroke models</td>
<td>Agnese Secondo (Università degli Studi di Napoli Federico II, Napoli, Italy)</td>
<td>Host: Ana Cristina Rego &amp; João Malva</td>
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<td>5.4.2019</td>
<td>Microglia-mediated synapse loss in the pathogenesis of neurodegeneration</td>
<td>Rosa Paolicelli (University of Lausanne, Switzerland)</td>
<td>Host: João Peça</td>
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<td>10.4.2019</td>
<td>Neuroinflammation in Alzheimer’s disease</td>
<td>Michael Heneka (University Hospital Bonn, Germany)</td>
<td>Host: Organizers on the BEB advanced course</td>
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<td>12.4.2019</td>
<td>Targeting Proteases for the Treatment of Distinct Neuropathologies: Inhibiting a Protease (Calpain) vs. Enhancing a Protease (Cathepsins)</td>
<td>Ben Bahr (William C. Friday Laboratory, University of North Carolina – Pembroke, USA)</td>
<td>Host: Carlos Duarte</td>
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<td>12.4.2019</td>
<td>Is PD a Low-grade Inflammatory Bowel Disease?</td>
<td>Pascal Derkinderen (Nantes University, France)</td>
<td>Host: Organizers on the BEB advanced course</td>
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<td>17.4.2019</td>
<td>The peculiarities of prostate cancer metabolism</td>
<td>Silvia Socorro (CICS-UBI-Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior)</td>
<td>Host: Vilma Sardão</td>
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May

3.5.2019 | The role of the hippocampal CA2 area in social memory (dys)function
Torcato Meira (Life and Health Sciences Research Institute (ICVS), University of Minho, Portugal and Department of Neuroscience, Zuckerman and Kavli Institutes, Columbia University, USA.)
Host: Angela Inácio

8.5.2019 | Deciphering signal transduction using PTMScan: An affinity proteomics method for quantitative profiling of post-translational modifications
Sriram Aravamudhan (Cell Signaling Technology, Inc)
Host: Bruno Manadas

9.5.2019 | Evolution and functional relevance of protein phosphorylation
Pedro Beltrão (European Bioinformatics Institute (EMBL-EBI))
Host: Bruno Manadas

10.5.2019 | Protease networks in skin inflammation and repair
Ulrich auf dem Keller (Technical University of Denmark (DTU))
Host: Isaura Simões

16.5.2019 | Early Life Exposure to Cadmium, Diet-Induced Liver Disease and the Role of Zinc
Jamie Young (Department of Pharmacology and Toxicology, School of Medicine, University of Louisville, USA)
Host: Carmen Alpoim

17.5.2019 | Design and optimization of potent, CNS-penetrant transthyretin stabilizers with a little help from Machine Learning
Carlos Simões (Chief Technology Officer, BSIM Therapeutics)
Host: João Nuno Moreira

22.5.2019 | CRB1-inherited retinal dystrophies Milestones towards a gene therapy treatment for Retinitis Pigmentosa
Henrique Alves (ICBR)
Host: Hugo Fernandes

24.5.2019 | Olfaction and social behavior in a MeCP2-null mouse model of Rett syndrome
Mónica Santos (CNC-Center for Neuroscience and Cell Biology)
Host: Carlos Duarte

June

5.6.2019 | Coffee, Caffeine and Health
Rodrigo Cunha (CNC-Center for Neuroscience and Cell Biology)
Host: Lino Ferreira

7.6.2019 | Evolving Brains, Health and Lifestyle
Nuno Lourenço (CISUC, Department of Informatics Engineering, University of Coimbra)
Host: Teresa Oliveira & Paulo Oliveira

14.6.2019 | Phenotypic Plasticity: a non-genetic way of tumor cells to evade therapy
Célia Gomes (iCBR - Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine of University of Coimbra)
Host: Francisco Ambrósio

19.6.2019 | Metabotropic receptors as a common dysfunction in neurodevelopmental disorders
João Peça (CNC-Center for Neuroscience and Cell Biology)
Host: Lino Ferreira

21.6.2019 | Neuronal KCNQ channelopathies: a paradigm for rare developmental disorders highlighting therapeutic targets for more common diseases
Maurizio Taglialatela (Department of Neuroscience, University of Naples Federico II, Naples, ITALY)
Host: Ana Luisa Carvalho

July

3.7.2019 | Modeling and optimizing metabolism: applications in metabolic engineering and human health
Miguel Rocha (University Minho)
Host: Irina Moreira

5.7.2019 | Multidrug resistant tumours: searching for novel biomarkers, molecular targets and therapeutic tools
M. Helena Vasconcelos (i3S/IPATIMUP, FFUP)
Host: Amália Jurado

12.7.2019 | ATP-derived adenosine controls synaptic and memory dysfunction in β-amyloid models of Alzheimer's disease
João Pedro Lopes (CNC-Center for Neuroscience and Cell Biology)
Host: Ricardo Rodrigues
16.7.2019 | The lysosomal iron throne takes control of mitochondria
Nuno Raimundo (Independent Group Leader Universitätsmedizin Göttingen Institute of Cellular Biochemistry)
Host: Paulo Oliveira

16.7.2019 | Regulation of vesicle acidification at the neuronal synapse
Ira Milosevic (Ph.D. - Principal Investigator European Neuroscience Institute (ENI) University Medical Center Göttingen (UMG))
Host: Ana Cristina Carvalho

17.7.2019 | Glycosylation in cancer biology and cellular communication: molecular mechanisms and clinical implications
Celso Reis (I3S - Instituto de Investigação e Inovação em Saúde IPATIMUP - Institute of Molecular Pathology and Immunology)
Host: Hugo Fernandes

19.7.2019 | Política de Inovação na Universidade de Coimbra
Luís Simões da Silva (Vice-Reitor para a Inovação e Empreendedorismo Departamento de Engenharia Civil da Universidade de Coimbra Diretor do ISISE – Institute for Sustainability and Innovation in Structural Engineering)
Host: Lino Ferreira

22.7.2019 | Your Fast and Flexible Slide Scanner
Soren Prag (PhD, Application Specialist, Carl Zeiss Microscopy, GmbH)
Host: Luísa Cortes

24.7.2019 | Development of phage-based medicines-the Portuguese reality
Clara Leandro (TechnoPhage, SA)
Host: Isaura Simões

26.7.2019 | An RNA modification on the polyA tail promotes mRNA stability
Luísa Miranda Figueiredo (Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa)
Host: Paulo Oliveira

SEPTEMBER

11.9.2019 | FluidFM: nanotechnology for single cell experiments
Maria Milla & Paul Monnier (Life Science Application Specialist)
Host: Paulo Oliveira

12.9.2019 | O (en)canto de investigar
Ricardo Neves (CNC)
Host: Sara Amaral

13.9.2019 | The Comics of Science
André Caetano (Illustrator)
Host: Sara Amaral

18.9.2019 | Modeling and optimizing metabolism: applications in metabolica engineering and human health
Miguel Rocha (University of Minho)
Host: Irina Moreira

24.9.2019 | Principles of Quantitative Westerns in 15 mins
Jan Wolfram (Azure Byosystems, CA, USA)
Host: Vilma Sardão

25.9.2019 | Mechanical and functional plasticity of cells
Inês Pinto (INL - International Iberian Nanotechnology Laboratory)
Host: Armando Salvador

27.9.2019 | Investigação em Síndrome de Angelman - Apresentação do ANGEL e da ASA
Manuel Costa Duarte & Catarina Costa Duarte (ANGEL President & Vice President)
Host: João Ramalho Santos

27.9.2019 | On stress, vulnerability to psychopathology and neuroscience communities
Carmen Sandi (BMI-EPFL Switzerland & Fens - Federation of European Neuroscience Societies)
Host: Ana Luísa Carvalho

OCTOBER

2.10.2019 | Measuring forces at the nanoscale for cardiovascular risk evaluation
Nuno Santos (Faculty of Medicine of Lisbon University & IMM-Lisbon)
Host: Akhilesh Rai
CNC.IBILI SEMINARS

4.10.2019 | Receptor dynamics and nano-organization: new facets of NMDAR functions
Joana Ferreira (IIINS, University of Bordeaux)
Host: Ana Luísa Carvalho

11.10.2019 | Basic research fueling clinical studies for new therapeutic approaches for age-related macular degeneration
Sandra Tenreiro (CEDOC, Nova Lisbon University)
Host: Francisco Ambrósio

16.10.2019 | Acetyl-CoA: a signaling metabolite at the intersection of metabolism, epigenetic and cell plasticity
Alessandro Carrer (Veneto Institute of Molecular Medicine (VIMM), Padova, Italy)
Host: Miguel Mano

25.10.2019 | Os cientistas e os outros
Ana Sanchez (ITQB, Nova Lisbon University)
Host: João Ramalho-Santos

28.10.2019 | Fifty years of neuroscience research: where are we standing right now?
Wil Smeets (VU University Medical Center, Faculty of Medicine, Amsterdam, Netherlands)
Host: Carlos Duarte

30.10.2019 | Deep learning potential to fill the gene-disease gap
Joel Arrais (Informatic Engineering Department, University of Coimbra)
Host: Isaura Simões

NOVEMBER

6.11.2019 | Sensitive and automated assessment of DNA strand break by AUREA gTOXXs
Paula Braun & Frank Gehring (3T Analytic, Tuttingen, Germany)
Host: Paulo Oliveira

8.11.2019 | Synaptogenesis stimulates a proteasome-mediated ribosome reduction in axons
Rui Costa (CNC)
Host: Ramiro Almeida

11.11.2019 | Basic research fueling clinical studies for new therapeutic approaches for age-related macular degeneration
Sandra Tenreiro (CEDOC, Nova Lisbon University)
Host: Francisco Ambrósio

15.11.2019 | Microglia: responders or inducers of neurodegenerative disorders
Adelaide Fernandes (iMED.ULisbon & Faculty of Pharmacy, University of Lisbon)
Host: Ana Luísa Cardoso

22.11.2019 | Fatty liver: The experience of an internal medicine service
Armando Carvalho & Jorge Leitão (Faculty of Medicine, UC & Coimbra University Hospital Center)
Host: Paulo Oliveira

27.11.2019 | Improvement of aging hallmarks by mitotic competence rewire
Elsa Logarinho (IBMC-i3S, University of Porto)
Host: Lino Ferreira

29.11.2019 | Mitochondrial dynamics in synapse development
Cátia Silva (Netherlands Institute for Neuroscience)
Host: Ricardo Rodrigues

DECEMBER

Delfim Duarte (i3S, IPO Porto & Faculty of Medicine, University of Porto)
Host: Lino Ferreira

13.12.2019 | Science and Theatre
Mário Montenegro (Marionet & CEIS20, FLUC)
Host: Sara Amaral

18.12.2019 | Integrative modelling of bimolecular complexes
Alexandre Bonvin (Faculty of Science, Utrecht University)
Host: Irina Moreira
Ana Rita de Carvalho Acúrcio
Discovery and development of novel small-molecule immune system modulators
December 17, 2019
Co-Supervisor: Jorge António Ribeiro Salvador

Ana Oliveira
The role of HOXA9 as a modulator of the tumor microenvironment in glioblastoma
2019
Supervisor:

Catarina Araujo Gomes Rebelo
Nanomedicine to modulate brain activity
2019
Supervisor: Lino Ferreira

Celso Alves
Sphaerococcus coronopifolius bromoterpenes: Antitumor activity and intracellular signal pathways characterization on in vitro human cellular cancer models
November 8, 2019
Supervisor: Carmen Alpoim

Dina Pereira
The role of ageing in polyglutamine-induced neurodegeneration. A study in Machado-Joseph disease models
2019
Supervisor: Luis Almeida

João Filipe Alves Amorim
Understanding the underlying mechanisms regulating aging and longevity
December 11, 2019
Supervisor: Carlos Palmeira

Lara Franco
Long-term impact of early life stress on adult social behavior and prefrontal cortical circuits
2019
Supervisor: João Peça

Luciana Ferreira
Pathophysiology of Persistent Doxorubicin Cardiotoxicity: a Mitochondrial-epigenetics Link
June 26, 2019
Supervisor: Paulo Oliveira

Mafalda Santos Costa
Mycobacterial methylmannose polysaccharides’ biosynthesis
July 22, 2019
Supervisor: Nuno Empadinhas

Michelle Vang
Peptides and their effects on wound healing
2019
Co-Supervisor: Eugenia Carvalho

Romina Paula de Aguiar Guedes
Targeting the proteasome in anticancer therapy by a computational based drug discovery approach
December 16, 2019
Co-Supervisor: Jorge António Ribeiro Salvador

Samuel Filipe Duarte Chiquita
The changing brain in Alzheimer’s disease: is the retina a mirror of disease onset and progression?
September 27th, 2019
Supervisor: Francisco Ambrósio, Miguel Castelo- Branco

Sofia Alexandra Ramos Ferreira
The role of P2 receptors in the migration of medial ganglionic eminence-derived interneurons
January 29, 2019
Supervisor: Ricardo Rodrigues

Sofia Ferreira Anastácio
Coxiella burnetii and Q Fever: an emergent zoonosis in Portugal?
2019
Supervisor: Gabriela Jorge da Silva
MSC THESIS CONCLUDED
IN 2019

Alexander Michael Ribeiro Santos
Transitirretina e Apnéia Obstrutiva do Sono
2019
Supervisors: Cláudia Cavadas, Ana Rita Álvaro

Ana Carolina Silva Caetano
Identification of blood brain barrier modulators
2019
Supervisor: Lino Ferreira

Ana Carolina Silva
Allele-specific silencing of Machado-Joseph Disease
September 2019
Supervisor: Ana Luisa Carvalho, Rui Nobre

Ana Catarina da Silva Franco
Neuroendocrine peptides as therapeutic strategy to delay skin aging
2019
Supervisors: Cláudia Cavadas, Célia Aveleira

Ana Lousã Rodrigues Mendes Santos
Utilização do MLPA na identificação do perfil genético do carcinoma da cavidade oral, no follow up e na conduta médica
2019
Supervisor: Joana Barbosa Melo

Ana Luisa Bernardo
Impact of traumatic brain injury on Astrocytes: role of neuropeptide Y
September 2019
Supervisor: Francisco Ambrosio

Ana Rita Moura Fernandes
Resetting the clock on metabolic dysfunction: a new role for ataxin-2
2019
Supervisors: Cláudia Cavadas, Sara Carmo Silva

Ana Sofia Ferreira
Gender-specificities of exercise effects in a model of chronic anxiety: focus on the peripheral metabolism and glucose homeostasis
September 13, 2019
Supervisor: Francisco Ambrosio

Ana Teresa Capitão Moreira de Sá
Targeting adenosine A2A receptors to manage Angelman syndrome symptoms
July 15, 2019
Supervisor: Paula Canas, Angelo Tomé

André Filipe Conceição
CRISPR/Cas9 as a tool for gene therapy in Machado-Joseph disease: silencing ATXN3 and CAG expansion correction
September 2019
Supervisor: Ana Luisa Carvalho, Carlos Matos

André Santos Paula
Usher syndrome: dysfunctional olfactory brain regions and statistical classification of disease status using fMRI
June 2019
Supervisor: Miguel Castelo- Branco

Andrea Cristina Rodrigues dos Santos
Pesquisa dos protozoários Giardia e Cryptosporidium em moluscos bivalves através de técnicas moleculares
2019
Supervisor: Maria do Céu Rodrigues de Sousa

Andrea Marques
Alpha-synuclein in Extracellular Vesicles - the spreading mechanism behind Parkinson’s disease?
October 2019
Supervisor: Luis Almeida, Rita Perfeito

Anianna Piscosquito
rhBMP-7 effects on wound healing in diabetic mice - a pilot study
2019
Supervisor: Eugenia Carvalho, Carlos Duarte

Bárbara Vicente dos Santos
Biomarkers of aging in Obstructive Sleep Apnea
2019
Supervisors: Cláudia Cavadas, Ana Rita Álvaro

Beatriz Lapa
Metabolism as a therapeutic target in acute myeloid leukemia – glycolysis or oxidative phosphorylation
2019
Supervisor: Ana Cristina Gonçalves

Caren Jane Rodrigues
The role of neuropeptide Y in articular chondrocyte functions
2019
Supervisor: Alexandrina Mendes, Claudia Pereira
MSC THESIS CONCLUDED IN 2019

Carolina Freitas  
Impacto socioeconómico nos cuidadores informais de doentes de Alzheimer  
February 2019  
Co-supervisor: Isabel Santana

Caroline Veloso  
Role of Mitochondria-Targeted Novel Antioxidants based in Dietary Polyphenols  
October 11, 2019  
Supervisor: Paulo Oliveira

Catarina Coval  
Pesquisa de Fatores de Patogenicidade de Escherichia coli Isoladas de Géneros Alimentícios e de Ambientes de Produção Alimentar  
2019  
Supervisor: Jorge Salvador

Catarina Milheiro Soares da Silva  
Elucidating GATA2 Transcription Factor Role during DNA Replication and Epigenetic Inheritance.  
2019  
Supervisors: Filipe Pereira, Paula Veríssimo

Cinzia Miarelli  
Alterations of Neural K+Cl- Cotransporter KCC2 During Status Epilepticus: Possible Impact on GABAergic Neurotransmission.  
September 2019  
Supervision: Miranda Mele  
Co-supervision: Carlos B. Duarte

Clarissa Becher  
High-Throughput screening for extracellular vesicle content modulation for cardiovascular application  
2019  
Supervisor: Hugo Fernandes

Cristiana Bento  
Esteronização supercrítica de aerogéis de polímeros naturais para aplicações biomédicas  
2019  
Co-Supervisor: Nuno Empadinhas

Daniel Agostinho  
Diagnóstico diferencial de doenças neurodegenerativas com base em dados multimodais de imagem (PET e Ressonância Magnética)  
September 2019  
Supervisor: Miguel Castelo- Branco

Daniela Catarina Gaspar Santos  
Histological and morphological analysis of developing neuronal precursors derived from human iPSC cells  
Supervisor: Claudia Pereira

Daniela Filipa Correia de Almeida  
Deteção dos protoszoários Giardia lamblia e Cryptosporidium sp. em saladas embaladas prontas a consumir  
July 2019  
Supervisor: Maria do Céu Rodrigues de Sousa

Débora Tatiana de Sousa Mena  
Effect of dual therapy with liraglutide and ghrelin on brain metabolism and intracellular stress in the Huntington’s disease R6/2 mouse model  
Supervisor: Ana Duarte, António Moreno

Diana Andrade  
Effects of DNMT1, DNMT3 and DNMT3b gene expression on chronic lymphocytic leukemia  
Supervisor: Ana Bela Sarmento Ribeiro

Diogo Rafael Mendes Pessoa  
Classificação automática de vocalizações ultrassônicas de roedores: estudo do neurodesenvolvimento  
November 2019  
Supervisor: Miguel Castelo- Branco

Duarte Silva  
Aldehyde dehydrogenase polymorphisms: its role in myelodysplastic syndromes and acute myeloid leukemia  
2019.  
Supervisor: Ana Cristina Gonçalves

Filipa Alexandra Silva  
Skin sensitizers: moving forward new approaches for toxicity prevision and sensitization management  
Supervisor: Mª Teresa Cruz Rosete

Flávia Rodrigues  
Combined therapeutic strategies for hepatocellular carcinoma mediated by nanosystems  
September 2019  
Supervisor: Henrique Faneca, Paula Veríssimo

Gabriela Oliveira  
Role of the Adenine Nucleotide Translocator 2 in P19 Embryonal Carcinoma Stem Cells Mitochondrial Profile  
September 18, 2019  
Supervisor: António Moreno

Hugo Rafael Santos Ferreira  
Characterization of the emotional fingerprint of METH intoxicated animals  
2019  
Supervisor: Francisco Ambrosio
Inês João Dinis Ferreira
Investigating Appetite Regulation System in an Animal Model of Progeria
Supervisors: Cláudia Cavadas, Célia Aveleira
2019

Inês Morais
Urine extracellular vesicles: a promising tool for Regenerative Medicine?
Supervisor: Hugo Fernandes
2019

Ivo Manuel Ferreira Machado
Modulation of complex I and oxidative capacity in cells under metabolic stress: the crosstalk between miR-378 and metformin
July 23, 2019
Supervisor: Anabela Pinto Rolo

Jessica De Pascale
Mitochondria-associated membranes: a platform for transferring endoplasmic reticulum stress signals to mitochondria in innate immune cells. does lithium promote an adaptive cellular response and survival?
Supervisor:

Jéssica Gonçalves Da Silva
Avaliação das propriedades imunotoxicológicas de nanopartículas de PLA
Supervisor: Olga Borges, Sandra Jesus
2019

Joana Cláudia Ferreira da Silva
Assessing the safety profile of biodegradable poly(κ-caprolactone) implants – effect on microglia-mediated neuroinflammation
March 7, 2019
Supervisor: Francisco Ambrósio

Joana Sampaio
Reorganização do cérebro e plasticidade neurosensorial
July 2019
Supervisor: Miguel Castelo- Branco

João Braz
Establishment and Characterization of Human Pluripotent Stem Cells derived Brain Organoids
October 2019
Supervisor: Luis Almeida, Liliana Mendonça

João Lima
The effect of gambogic acid and silybinin in Acute Myeloblastic Leukemia
Supervisor: Ana Bela Sarmento Ribeiro
2019

João Pedro Ferreira da Costa Novo
Effect of methylphenidate on microglia: tracking direct and brain endothelial cells-mediated changes
September 9, 2019
Supervisor: Francisco Ambrosio

João Pedro Estêvê Campos Silva
Controller Implementation For A SSVEP-Based BCI With Resource To Non-Valitional Neurofeedback
September 2019
Supervisor: Miguel Castelo- Branco

João Vieira
Utilization of a Silica Nanoparticle for transport and delivery of a recombinant protein for cancer treatment
September 2019
Supervisor: Henrique Faneca, Paula Verissimo

Laura Carvalho
Impact of nucleolin downregulation on cellular features of triple negative breast cancer cells
Supervisor: João Nuno Moreira
2019

Luís Filipe Henriques Oliveira
Understanding the Genetic Program of Conventional Dendritic Cells Type 2 (cDC2) with Direct Cell Reprogramming
Supervisores: Filipe Pereira, Ana Luísa Carvalho
2019

Luís Grilo
Obesity-induced hepatic changes during pregnancy
Supervisor: António Moreno, Susana Pereira
September 12, 2019

Luís Perpetuo Silva
NMR analysis of urinary acetaminophen-glucuronide enrichments from 2H and 13C metabolic tracers in mouse models
February 2019
Supervisor: John Jones

Manuel Moura Ramos
Exploring success network in real time functional magnetic resonance imaging (rffMRI) neurofeedback
Supervisor: Miguel Castelo- Branco
2019

Margarida Fernandes Beatriz
Mitochondrial characterization in Huntington’s disease fibroblasts and iPSC-derived cells
September 2019
Supervisor: Ana Cristina Rego, Carla Lopes

Margarida Silva
P-Cadherin Role on the Mitochondrial Biology of Breast Cancer Cells
September 12, 2019
Supervisor: António Moreno

Maria da Paz Olímpio Lardosa Paz
Analysis of eyetracking data applied to autism spectrum disorder during virtual reality experiments
September 2019
Supervisor: Miguel Castelo- Branco
MSC THESIS CONCLUDED IN 2019

Maria Inês Barros
Assessing the putative role of mesenchymal stromal cells’ effectors in Machado-Joseph disease
March 2019
Supervisor: Luis Almeida, Catarina Miranda

Maria Inês Alves
Effect of Sex on Brain Metabolism and Intracellular Stress in Type 2 Diabetes
2019
Supervisor: Ana Duarte, António Moreno

Mariana Biscaia
Targeted delivery of doxorubicin and C6-ceramide combinations to non-small cell lung cancer cells: key factors for C6-ceramide’s cytotoxicity 2019
Supervisor:

Mariana Terra
Development of gene and drug delivery nanosystems for hepatocellular carcinoma cells
September 2019
Supervisor: Henrique Faneca, Rosemary Cordeiro

Marlene Santos Domingues
Impact of astrocytes on memory: role of astrocytic adenosine A2A receptors
January 19, 2019
Supervisor: Paula Agostinho, Ângelo Tomé

Marta Barão
Uncover the mechanism behind miRNA function on cell survival 2019
Supervisor: Hugo Fernandes

Marta Silva Lapo Pais
Diagnóstico diferencial de doenças neurodegenerativas com base em dados de PET em correção com outras modalidades de imagem 2019
Supervisor: Miguel Castelo- Branco

Marta Sofia Pereira
Skin allergens: molecules with an improbable therapeutic application for Alzheimer’s disease
Supervisor: Claudia Pereira, Mª Teresa C. Rosete

Martins IG
Cerebral small vessel disease and its neuropsychological correlates: unraveling socio-emotional impairment in a sample with sporadic CSVD 2019
Co-supervisor: Isabel Santana.

Miguel Rosado
A different perspective of circulatory biomarker in neurodegenerative diseases: focus on blood peptidome and complexome 2019
Co-supervision: Bruno Manadas

Natalia Sozza Bernardi
Avaliação das propriedades imunotoxicológicas das nanopartículas de PCL e PCL/Glucano 2019
Supervisor: Olga Borges, Sandra Jesus

Nuno Rocha de Jesus
Sirtimus and metformin on acute lymphoblastic leukemia in childhood 2019
Supervisor: Ana Bela Sarmento Ribeiro

Olga Fokt
Mitochondrial respiratory chain complexes and antioxidant enzymes analysis in diabetes and chronic periodontitis-derived human blood mononuclear cells
July 2019
Supervisor: Ana Cristina Rego

Pedro Matos
A Computational Method to Predict the Combinatory Effect of Drugs in Cancer 2019
Supervisor: Irina Moreira
Co-Supervisor: Luis Pereira de Almeida

Rafaela Ferrão
Mitochondria-based screening of drug neurotoxicity in differentiated SH-SYSY cells
September 16, 2019
Supervisor: Teresa Oliveira, António Moreno

Rodrig Carreira
Evaluation of antioxidant effects of mitochondria-targeted polyphenolic agents in Human Skin Fibroblasts
January 15, 2019
Supervisor: António Moreno
Rosa Mafalda Amorim Figueiredo
GABA levels relate to BOLD signal in Neurofibromatosis Type 1
June 2019
Supervisor: Miguel Castelo-Branco

Rui Gomes
IREB2 gene polymorphisms in colorectal cancer and its relation with the disease
2019
Co-Supervisor: Ana Bela Sarmento Ribeiro

Rute Pino
Finding Hidden Patterns on Cardiovascular Toxicology Problem: The case of Doxorubicin
July 18, 2019
Supervisor: Nuno Lourenço

Sara Martins Pego
Developing Real-time PCR genetics tests for fast diagnosis of LHON and Hearing Loss
2019
Co-supervision: Manuela Grazina

Sara Pereira
Application of innovative and minimally invasive methods for cancer detection in a population context
2019
Supervisor: Sara Valente

Sara Valente
Mitochondrial performance during osteoblast differentiation: searching new targets to counteract osteoporosis
September 10, 2019
Supervisor: Vilma Oliveira, António Moreno

Silvia Magro
Toward the identification of novel antileishmanial compounds. In vitro profile of semisynthetic compounds from Eremurus persicus and arylalkenilamines
February 20, 2019
Supervisor: Maria do Céu Sousa

Silva-Spínola A
Unraveling the pathophysiological mechanisms behind white matter lesions: a study on cerebrospinal fluid and blood markers in patients with cerebral small vessel disease
2019
Supervisor: Inês Baldeiras

Sofia dos Reis Galvão
Gender-specificities of exercise benefits in a model of chronic anxiety: focus on the neuroimmune axis
September 13, 2019
Supervisor: Francisco Ambrosio

Sofia Santiago
Development of silica nanoparticles to mediate antitumor strategies
2019
Supervisor: Susana Vieira Pinto da Cunha

Susana Vieira Pinto da Cunha
Characterization of the interaction and permeation of drug-like molecules through membrane models including P-glycoprotein
September 2019
Supervisor: Ana Luisa Carvalho

Vanessa Fernandes
Patient-specific iPSC-derived NESC for Machado-Joseph disease treatment
September 2019
Supervisor: Carlos Duarte, Liliana Mendonça

Vanessa Simões Lourenço
Adenosinergic control of fear extinction: the role of adenosine A2A receptors in the basolateral amygdala
July 24, 2019
Supervisor: Ana P. Simões, Ângelo Tomé

Vera Cristina Martinho Pais
Effect of class I histone deacetylase inhibitors in 3xTg-AD mice
July 2019
Supervisor: Ana Cristina Rego
The biomedical and biotechnological nature of the research performed at CNC brings an additional responsibility towards society. As such, our institute has been committed in allocating the knowledge and technologies here developed to local industries and organizations through technology transfer.

Technology transfer is the process of sharing knowledge, skills, facilities, and technologies among institutions for further development and exploitation. In the context of CNC, the main goal of technology transfer is to valorise the intellectual assets of our institute through a transaction that is beneficial to all parties involved. As long-term goals, technology transfer assures the practical use of the scientific and technological advances by the general public and research community, creates qualified jobs, promotes the recognition and reputation of our institute, generates revenue for further research funding, and stimulates the local and regional socioeconomic development.

During 2019, CNC gave the first steps towards the construction of a technology transfer office through the execution of a project—“LifeSciences ByCENTRO: Valorização do Conhecimento em Ciências da Vida”—and the hiring of a technician in this area. Our institute dynamized and performed the following tasks and events in technology transfer:

- scouted the intellectual assets of our institute and created a portfolio—named “Technological Portfolio CNC”—to be soon disseminated in the new institutional website (Figure 1);
- developed and implemented a “Scorecard” system to evaluate technology maturation according to the international recognized Technology Readiness Levels scale (evaluated 20 technologies);
- financed five proof-of-concept and prototypes of innovative technologies and products;
- organized the event “Innovation Day@CNC” to promote technology transfer, innovation, and entrepreneurship among researchers;
- participated in several events (forums, summits, conferences, meetings, and networking/information sessions) to advertise the technologies, patents and scientific platforms of CNC;
- submitted five provisional patent applications;
- established contacts with industry and investors towards commercial valorisation of the intellectual CNC assets.
One of the major challenges of the contemporary research is to develop new and innovative ways to engage society in science and scientific topics. This is the main role of Science Communication Office - disseminating scientific advances to the benefit of society and to the research process itself, liaising between the different areas of the research institute, the media, and the publics.

Science Communication Office goals are:

• To foster dialogue between scientists and different groups of society - students, elderly, teachers, etc;
• To provide public accountability, ethically justified by the public nature of scientific funding;
• To engage society in research process;
• To spread our scientific findings through media (newspaper, radio, TV) and social networks;
• To create scientific culture through public engagement projects in order to construct a truly scientific citizenship and a more knowledgeable society;
• To consolidate CNC institutional image for the national and international scientific system, national and regional political decision-makers, public and private funders, and different types of publics;
• To inspire and engage scientist in science communication initiatives, give them tools that improve the public engagement;
• To evaluate our science communication strategies in order to improve and understand the best practices to engage community in science and scientific themes;
• To establish strategies that contributes to a better communication and team spirit inside the research center.

Our partnerships – Ciência Viva, Science Museum of the University of Coimbra, University of Coimbra, Maratona da Saúde, Instituto de Educação e Cidadania, Jornal Público, Dana Foundation, between others – are crucial to strategically target different publics. Our activities have been supported by several associations and scientific societies as Biochemical Society, Federation of European Neuroscience Societies, Sociedade Portuguesa de Neurociências, Sociedade Portuguesa de Imunologia, Associação Portuguesa do Sono, Alzheimer Portugal, Associação Portuguesa de Doentes de Huntington, Associação Portuguesa de Diabéticos de Portugal, Associação Portuguesa de Ataxias Hereditárias and Sociedade Portuguesa de Biologia da Reprodução.

Therefore, CNC.IBILI has been strongly committed to promoting and disseminating scientific knowledge to society through the enthusiastic involvement of its researchers in science communication projects using different strategies.
Social 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 2019 CNC.IBILI was in the news 629 times with an advertising value of 2,820,216 euros, reaching a total number of 33,197.77 audiences.

Social Networks

To reach a wider population we improve our presence in social networks. At the end of 2019 we have more than 12,000 followers at different social networks: Facebook, Twitter, Linkedin, Instagram and Youtube.
**Public Engagement in Science**

CNC.IBILI is strongly involved in Public Engagement in Science projects that engage society. We participated in several national and international initiatives that involves different stakeholders / audiences all over the year.

**Brain Awareness Week (BAW)**
March 2019

The Brain Awareness Week (BAW) 2019 organized by CNC.IBILI consortium of University of Coimbra happened in Coimbra during March (1st - 31st March 2019). The project “Brain O’Clock – time to make it right!” was supported by FENS, DANA Foundation and SPN. In 2019, CIBB neuroscientists invite the citizens for several challenges during BAW. Our proposal aimed to promote a healthy lifestyle and an active aging by engaging society in neuroscience and increasing the scientific culture. This project also aimed to involve a bigger number of researchers in Science Communication compared to the previous years. In this regard, we took advantage of our “know-how” in the following fields: Neuroscience, Metabolism and Biotechnology. The project promoted several initiatives for different publics.

**Food time**
We distributed a flyer to several places with illustrations promoting a healthy diet and an active lifestyle and explaining its relevance in our metabolism.

**Debate time**
“When the brain becomes dependent” - 17th March, FNAC Coimbra Session for general audience about dependencies at a public café in a shopping center. The initiative counted with the participation of a psychologist, three medical doctors and neuroscientist.

**Selfie time**
In order to create meeting places between science and society, we produced audio-visual contents about neuroscience research and brain facts. We produced four small videos, “Selfie Science”, where different neuroscientists explained in an informal way their research projects. The videos were shared at CNC youtube channel and social networks (Facebook and Twitter).

**Travel time**
During one week, we promoted speed datings between scientists and the public, while they traveled together the city by bus. The researchers had the opportunity to share their researcher in an informal way and citizens received scientific information in an unexpected way.

**Radio time**
The neuroscientists approached brain-related topics and explain their research in the podcast “Ciência aos Domingos” at RUC - Rádio Universidade de Coimbra.

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

**Lab time**
During BAW researchers from CNC.IBILI opened the doors of their laboratories and received visits from different publics that can explore different themes in neuroscience as: Can we enhance our brain?; How does the sleep affects our metabolism?; Study of human behavior; How do we have energy to the brain?; How neurons die in Alzheimer’s disease?; Neurons, obesity and aging; Brain development; How can you address neurodegenerative disorders?
**Game time**

Neuroscientists played a board-game with the public during a session promoted at the bar “Casa das Artes” in Coimbra. The game is called “Braindemic” and players are researchers whose mission is to treat neurodegenerative disorders. This event was frequented by adults and young adults.

**Quiz time**

We organized a public quiz at “Aqui Base Tango”, a local coffee shop. The neuroscientists developed the questions and the public was challenged to explore brain-related themes. This type of activity is very popular in Coimbra and often frequented by young adults.

**Pub time**

Researchers participated in the 16th edition of PubhD Coimbra. This event challenge PhD students from different research areas to talk about their PhD projects. March edition was centered in the brain.

**Movie time**

During the 19th edition of our internal “Beer for Thought” event, the researchers saw the movie “Inside Out”, in order to inspire them to address emotions and brain-related topics in a funny and simplified way.

**Sleep time**

In the context of the World Sleep Day on March 15th, CNC.IBILI researchers collaborated with the Portuguese Sleep Association (APS) to promote healthy sleep habits as part of a healthy lifestyle and an active aging. We organized the following initiatives: a) development of new hands-on activities for different publics; b) an animation about the brain and sleep to share online (website and social media); c) public event “Sleep Well, Aging Well”, that gathered scientists, medical doctors, and the society, with a theatre performance about Sleep Apnea disorder.

Our activities involved 100 researchers and reached directly more than 2400 people from different publics in the following activities: school time and lab time (37 schools have participated), food time, debate time, travel time, game time, quiz time, pub time, and sleep time.

In digital media — Facebook, Twitter and Instagram - we made 76 posts about BAW. The radio time initiative reached 3589 people in our social media and the videos “Selfie Science” reached to 13461. Moreover, the awareness spot for the World Sleep Day reached 100.000 people on social media and 1.265.780 people on television audience.

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**Science in the Lab**

September 2019

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Table 1 – Internships for high-school students from “Science in the Lab” programme.
During 20 days, Science Communication Office, with Rómulo Science Center and Science Museum, developed activities to society in streets of the Coimbra’s downtown (Café Santa Cruz) in order to bring scientific knowledge close to community. 10 researchers actively participated in this initiative.

**European Researchers’ Night (ERN)**
September 2019

European Researchers’ Night is an initiative promoted by the European Union that aims to join education and entertainment creating meeting places between scientists and different public, promoting a real interaction through science communication strategies as hands-on activities, one-on-one conversations, exhibitions and artistic performances. In Coimbra ERN was organized by University of Coimbra CNC has been a partner of this event in Coimbra since 2009. In 2019 CNC.IBILI were at Coimbra Botanical Garden and at Science Museum. We developed a set of hands-on activities (in different fields as neuroscience, cell biology, microscopy) and CNC.IBILI researchers participated in one-to-one conversations with publics. More than 100 researchers from CNC.IBILI participated in this initiative with 24 hands-on activities and speed-dating initiatives. More than 700 people visited Botanical Garden and Science Museum during ERN 2019.

**Educational initiatives with IEC**

Instituto de Educação e Cidadania (IEC) is a science center in Mamarrosa that promotes the science education among the local community. CNC actively collaborate with IEC initiatives: overall 183 people participated in the activities that involved 20 CNC researchers. In 2019, CNC researchers participate in 2 conferences for a broad audience and 17 advanced courses for high-school students. This activities engaged more than 400 people.

**Theatre & Science**

Since 2009 CNC has participated in several activities that use the artistic language to explore scientific subjects in one attempt to create new ways of communicating with the public. Several theatre plays were staged in close collaboration with CNC.IBILI researchers, either as actors, authors or sources of inspiration. In 2019 our researchers collaborate with three different projects with Marionet theatre company:

- **Sistemas corporais**
CNC was an active partner in “Sistemas Corporais” project. In 2019 (January @ Convento de São Francisco, Coimbra), CNC organized an art&science workshop targeting children about the brain and neurons, integrated in the “The Secret gland play”. About 50 children participated at the workshop.

- **Unknownness Lab**
The ‘Unknownness Lab’ is a research and creation initiative to tackle scientific challenges with an interdisciplinary team of scientists and artists. The aim is to address unresolved scientific problems using artistic perspectives, tools and techniques, trying to achieve, eventually, some progress or enlightenment regarding those problems, and to evaluate the process and possible advantages of addressing scientific questions in an interdisciplinary way. In 2019, the ‘Un_n__nn___Lab’ promoted an event – A Máquina dos Sonhos - during N&D CIBB Retreat (May @ Casa das Artes, Miranda do Corvo). 6 CNC researchers were involved in the meetings, discussion and preparation of the theatre performance. More than 100 CIBB members were at the retreat.

- **Holy CIBB**
Theatre play presented in CIBB annual meeting (December @ UC) with the participation of 20 CNC.IBILI researchers.
MICRODay

This event, promoted by the Portuguese Platform of Bioimage (PPBI), had the main goal of allowing students to explore microscopy. The participants had the opportunity of exploring microscopy in diseases such as schizophrenia and autism, and in other themes. More than 25 high-school students participated in MICRODay 2019 at CNC.IBILI.

Unistem Day

Outreach day dedicated to Stem Cells research. This international event engaged about 30 high-school students that visited CNC.IBILI labs.

Immunology Day

We commemorated the Day of Immunology, in our UC-Biotech building, Cantanhede. 60 participants from high school had the opportunity to explore several themes in immunology field with the participation of 6 CNC.IBILI Researchers.

Science & Technology Week

November 2019

During Science & Technology Week CNC.IBILI researchers promoted several science communication initiatives in different venues. This initiative involved 40 CNC.IBILI researchers and more than 780 persons. 14 schools participated (students from kindergarten to high-school).

PubhD Coimbra

PubhD is an informal science communication initiative where PhD students share their projects, avoiding a formal presentation. The event happens monthly in a very popular pub in Coimbra. During 2019, 8 researchers from CNC.IBILI participated in PubhD during 2019. Each edition has an average audience of 40 people then about 480 people interacted with this event.

Comics

In order to explore different languages to communicate scientific topics and to target wide audiences we developed a partnership with Jornal Público, one of the most prestigious daily newspaper in Portugal (daily circulation number: 33 000). In this context we produced one comics, involving different researchers and an illustrator; about tuberculosis, launched in World Tuberculosis Day.

Semana da Ciência & da Tecnologia 2019

24 – 30 novembro

> 780 estudantes envolvidos

14 escolas participantes

> 40 investigadores envolvidos
**Audiovisual Materials**

In 2019, CNC.IBILI have been developing science communication videos focusing on different research topics: the video lines Selfie Science and ASK (Always Seeking Knowledge) Researchers. Selfie Science episodes aim to schematically explain scientific research projects to a non-academic public. ASK Researchers series promotes the online interaction with society - everyone can submit their questions to the featured researcher to be answered in an interview format. We launched the projects in March of 2019 and since then we explored several scientific topics, by releasing an episode of each video line on a monthly basis. In 2019 we launched 8 ASK Researchers and 9 Selfie Science. All the videos are available at Youtube channel.

Additionally, we produced an animation about Machado-Joseph Disease, with a close collaboration of the researchers from Gene and Stem Cell Therapies for the Brain group, available at http://www.cnbc.pt/outreach/DMJ-infografia_leg_versaofinal.mp4.

### Table 2 – 2019 ASK Researchers videos

<table>
<thead>
<tr>
<th>Name</th>
<th>Researcher</th>
<th>Research Field</th>
<th>Views</th>
</tr>
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<tbody>
<tr>
<td>Autism: from the lab to the society</td>
<td>Catarina Seabra</td>
<td>Neuroscience</td>
<td>2125</td>
</tr>
<tr>
<td>Progeria: Benjamin Button backwards?</td>
<td>Célia Aveleira</td>
<td>Neuroscience</td>
<td>769</td>
</tr>
<tr>
<td>Male infertility: and when we don’t know why?</td>
<td>Sandra Amaral</td>
<td>Metabolism</td>
<td>991</td>
</tr>
<tr>
<td>Quail eggs to produce new drugs?</td>
<td>Ricardo Pires</td>
<td>Biotechnology</td>
<td>769</td>
</tr>
<tr>
<td>Mycobacteria: naturally resistant to antibiotics!</td>
<td>Susana Alarico</td>
<td>Microbiology</td>
<td>445</td>
</tr>
<tr>
<td>Alzheimer’s disease: why do we fall into oblivion?</td>
<td>Francisco Queiroz</td>
<td>Neuroscience</td>
<td>758</td>
</tr>
<tr>
<td>Nutrition and physical activity during pregnancy: a way to potentiate children’s health?</td>
<td>Susana Pereira</td>
<td>Metabolism</td>
<td>882</td>
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<tr>
<td>Alzheimer’s disease: An impossible cure!</td>
<td>Sandra Mota</td>
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### Table 3 – 2019 Selfie Science videos

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<td>Stress and microglia in brain development</td>
<td>Ana Luisa Cardoso</td>
<td>Neuroscience</td>
<td>2120</td>
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<tr>
<td>Depression and A2A receptors</td>
<td>Anna Plássova</td>
<td>Neuroscience</td>
<td>2184</td>
</tr>
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<td>mTOR and paused pluripotency</td>
<td>Bibiana Silva</td>
<td>Metabolism</td>
<td>4793</td>
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<tr>
<td>Messengers in our brain and Alzheimer’s disease</td>
<td>Fábio Sousa</td>
<td>Neuroscience</td>
<td>1796</td>
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<tr>
<td>Reprogramming cells to combat tumors?</td>
<td>Luís Oliveira</td>
<td>Biotechnology</td>
<td>4057</td>
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<td>Machado-Joseph’s disease and the brain mail</td>
<td>Catarina Miranda</td>
<td>Biotechnology</td>
<td>3897</td>
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<td>Obstructive sleep apnea: should we sleep on it?</td>
<td>Laetitia Gaspar</td>
<td>Neuroscience</td>
<td>2581</td>
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<td>Stargazin and its involvement in cognitive defects</td>
<td>Gladys Caldeira</td>
<td>Neuroscience</td>
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<td>Green leaves and brain-vascular communication</td>
<td>João Gonçalves</td>
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### Advanced Course

**Connecting Researchers with the Society**

February 2019

Give tools and inspire scientists to communicate is crucial and requires knowledge not only of science, but of about ethics, information technologies, journalism, visual communication and public engagement. Science Communication Office organized an advanced course, integrated in PhD Programme in Experimental Biology and Biomedicine (PDBEB), in order to help scientists to engage the public in different environments. 22 students, from PDBEB and from other PhD programs, participated in this intensive course (5-days) with the participation of 18 speakers from different fields as public engagement in science, visual communication, media, technology transfer, career development and art & science.

![Fig 7 – Summary of Science Communication Activities numbers in 2019](image)
CORE FACILITIES AT CNC

ANIMAL HOUSE
Head: João Laranjinha, PhD.

Staff:
Paula Mota (Designated Veterinarian and Animal Facilities Coordinator)
Carmen Semião (FMUC/CNC Animal Facility coordinator, Animal Welfare responsible and caretaker)
Fátima Graça (FMUC/CNC caretaker)
Mónica Serrano (FMUC/CNC assistant technician and caretaker)
Maria Eugénia Campos (FMUC/CNC assistant technician and caretaker)
Sandra Freire (FMUC/CNC Animal Welfare responsible and caretaker)
Tânia Ribeiro (UC-BIOTECH Animal Facility Coordinator and Animal Welfare responsible)
Fátima Moreira (UC-BIOTECH Animal Welfare responsible and caretaker)

Trainees:
Cristina Teixeira (caretaker)
Milene Ribeiro (caretaker)

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

At the present CNC runs two animal facilities, UC-BIOTECH Animal Facility located at UC-BIOTECH building in Cantanhede and FMUC/CNC Animal Facility located at Faculdade de Medicina, Polo I, Coimbra.
The FMUC/CNC Animal Facility is a conventional type facility with the capacity to house about 4000 animals, mice and rats (Mus musculus and Rattus norvegicus). It has a “clean” area for animal production and an experimental area that includes animal rooms, procedures room and quarantine room.

The CNC UC-BIOTECH Animal Facility has the capacity to house 1500 specific pathogen free (SPF) animals. It has a barrier area for animal production, a quarantine area and an experimental area. In the experimental area there is a level 2 biosafety area (ABSL2) for performing animal experiments associated with agents with moderate potential risk to humans and/or the environment, including agents that cause mild diseases in humans and are not transmitted by aerosols.

The animal facilities house rodents with wildtype phenotype, but also genetically altered strains, either due to spontaneous mutations or due to human manipulations. At this time the genetically altered strains are related to changes in the neurological system, immune system and in metabolic control and expression of reporter genes.

The animal facilities provide specialized animal services, namely breeding and housing of transgenic/knockout strains, production of rats/mice embryos and litters and support to animal experimentation procedures. And technological advances by the general public and research community, creates qualified jobs, promotes the recognition and reputation of our institute, generates revenue for further research funding, and stimulates the local and regional socioeconomic development.
The Flow Cytometry Unit, at the Center for Neuroscience and Cell Biology, provides scientific and technical support to all CNC researchers, external academic units and companies. The Unit is divided between Polo I in Coimbra and in UC-Biotech in Cantanhede, that are currently equipped with a Becton Dickinson FACSCalibur cell analyser (4 colours) and a Partec CyFlow Space cell sorter (7 colours), and with a Becton Dickinson Accuri™ C6 cell analyser (4 colours) with auto-sampler and a Beckton Dickinson FACSaria III cell sorter (12 colours), respectively.

Since 2007, when the unit was created, flow cytometry has emerged as an important and central technique for the fulfilment of many CNC research projects, and there has been an important investment in acquiring state of the art technology so that new research areas can be implemented.

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

MICROSCOPY IMAGING CENTER OF COIMBRA
Head: Luisa Cortes, PhD.

The Microscopy Imaging Center of Coimbra at the Center for Neuroscience and Cell Biology (MICC-CNC) is an open infrastructure that provides researchers with equipment and expertise required for multi-dimensional imaging of cells and tissues at high resolution and to perform quantitative image analysis. Resources include widefield, confocal and laser capture microdissection microscopy, as well as equipment for live cell imaging and image analysis. In fact, the MICC has a highly skilled and multidisciplinary scientific staff committed to training users to operate the microscopes and helping on the implementation of advanced imaging techniques, as well as on the design of robust image analysis protocols. Training is mandatory before users can access the equipment and this has two main outputs: minimizing improper handling, extending the lifetime of each equipment, and decreasing repair costs. Additionally, MICC-CNC offers technical support from project planning to data presentation, through the choice of reagents and equipment, analysis of experimental results and image processing. Technical support is extended to external academic units interested in using the Laser Capture Microdissection (LCM) technology present in our unit (MICC). This technology consists of a PALM Laser-Catapulting Microdissecting Microscope that employs laser microdissection and pressure catapulting to extract biological material of interest out of a tissue specimen, and is one of the few systems present in Portugal.

In 2019, MICC-CNC has been actively involved in the organization of advanced fluorescence microscopy courses such as the ‘Basic Concepts on Imaging Tools and Data Analysis’ integrated in the Syn2Psy Network School I, that provided PhD and Master students with the fundamentals of light microscopy, fluorescence microscopy, live cell imaging, and specific light microscopy imaging methodologies applied to Biomedicine. Furthermore, the team participated in the organization and coordination of the Core Technology Course of the BEB PhD program (2019/2020) that aimed to provide an overview of the technological platforms available at CNC.

Moreover, MICC-CNC, in collaboration with Carl Zeiss, organized the workshop ‘Tissue Clearing Workshop’ (20th – 22nd March 2019), a 3 days intensive workshop that covered various topics in tissue clearing by hands-on experience, from optimization and application of various clearing techniques, to light-sheet microscopy imaging, 3D visualization and quantification. This was the first course fully dedicated to Tissue Clearing organized in Portugal.

The MICC team, especially Luisa Cortes as president of the organizing committee (main organizer), was involved in the organization of SPAOM 2019 - Spanish and Portuguese Advanced Optical Microscopy, from 6th to 8th of November 2019. SPAOM is a joint effort from the Red Española de Microscopía Óptica Avanzada (REMOA) and the Portuguese Platform of Biomedical Imaging (PPBI), that aims to promote new insights in microscopy applications, developments and technologies, fostering interactions and collaborations between scientific community and industry. SPAOM 2019 offered a great opportunity for attendees to learn the most recent developments in the field of light microscopy, and their impact in the advance of life science research, from an impressive group of invited speakers.

MICC-CNC is part of the PPBI - Portuguese Platform of Bioimaging, a national research infrastructure of the National Roadmap of Research Infrastructure, and belongs to the Zeiss labs@location community providing in depth knowledge and dedicated services.
CORE FACILITIES AT CNC

MASS SPECTOMETRY UNIT
Head: Bruno Manadas, PhD.

During 2019 the Life Sciences Mass Spectrometry lab developed several research projects coordinated by CNC, but also national and international collaborations. The research performed over the last years resulted in a significant number of publications, along with the continuation of an FCT project headed by the lab and several co-headed by the lab, all with a strong proteomics and metabolomics component. The certified services under the ISO 9001 compliance have been extended and new plans to cover the remaining laboratory research methods under this compliance have been implemented (being the only ISO 9001 certified research-based mass spectrometry lab in Portugal).

MAIN ACHIEVEMENTS:
The impact of our research in the community has raised quite significantly as the number of publications, projects, and services provided clearly show. However, we also believe that the invitations to: i) perform collaborative projects, ii) write book chapters and tutorials, and iii) disseminate our research through invitations to: i) perform collaborative projects, ii) write book chapters and tutorials, and iii) disseminate our research through presentations in national and international congresses, demonstrates the influence of the research being performed in the group. Our strong technological capabilities, developed over the last years, are now resulting in higher biological impact research papers and demonstrating their potential to be transposed to biomarker research mainly in association with translational approaches. These indicators have contributed to increase the clinician’s perception regarding the potential of the technology existent in the lab which resulted in the establishment of integrative screening projects for the search of new biomarkers for several diseases.

PUBLICATIONS (Accumulated impact factor of 82, 11 publications in Q1 (1 in top 5%; 4 in top 10%), 5 in Q2 and 3 non indexed):


FASTKD2 protein was significantly reduced to half of controls’ average, which should explain the moderate reductions, both in detected enzymatic activity and in the assembly status. Considering the reporting that the effects of a FASTKD2 alteration appeared to be cell or tissue specific, the results were evaluated as regards the consequences on mitochondrial gene expression and possible association with heterogeneous clinical phenotypes.

**GENETIC ANALYSIS**

Genetic screening is the only available tool for attainment of a definitive diagnosis in many diseases. Concerning OXPHOS disorders and given its dual genetic origin, complexity and heterogeneity, the study of nuclear genome, mitochondrial DNA (mtDNA) and bigenomic crosstalk factors, using a genetic integrative approach is mandatory, although very complex.

Thiry-eight samples (blood – 34 and muscle – 4) were received for DNA extraction. Seven DNA samples were also received for genetic analysis.

**mtDNA GENOMES STUDIES**

Molecular differential analyses of mitochondrial cytopathies have been performed by total mtDNA sequencing analysis using Next Generation Sequencing (NGS), covering all mtDNA sequence variations, including confirmed pathogenic mutations associated to MRC diseases. During 2019, 42 samples of 40 patients were analysed using this strategy and the findings included several polymorphisms in all samples and two point mutations (m.3460G>A and m.11778G>A) in three patients (6.3%). These pathogenic mutations were further confirmed by PCR-RFLP and automated sequencing.

The 24h testing of the Top 3 LHON primary mutations was implemented in order to give a faster response to the cases and some patients suspected of LHON were screened.

Copy number (mtDNA) assays are part of the genetic mitochondrial genome screening for diagnostics of Mitochondrial DNA depletion syndromes (MDS), which is caused by defects in intergenomic communication and comprising a heterogeneous group of diseases, namely due to nuclear genes mutations leading to severe reduction of mtDNA content, with energy failure. Concerning mtDNA copy number assays for depletion screening, we investigated 4 samples of 4 patients, comprising a total of 111 real time PCR reactions.

Concerning the screening of nuclear genome (nDNA) defects causative of MRC diseases, 10 samples were screened by next generation sequencing (NGS).

Additionally, POLG2 and POLG1 genes were analysed in 1 and 9 samples, respectively, allowing the detection of sequence variations, but none was considered pathogenic.

Screening of OPA1 gene (5 samples) and OPA3 gene (2 samples) also revealed sequence variations without pathogenicity.

**RNA integrity analysis, using capillary electrophoresis, was also performed as part of our Molecular Biology and Genetics Services. During the last year we have analysed 192 samples, divided in 16 RNA nano chips.**

**BIOINFORMATICS’ ANALYSES**

Regarding the bioinformatics analysis and following the genetic screening of both genomes, including mtDNA content, the application of in silico tools is a highly laborious task that allows the identification of sequence variants in the patients, but also the prediction of its pathogenicity.

According to the procedure followed at the LBioMiT, around 1280 sequence variations were assigned in the mtDNA, including several polymorphisms, some reported alterations and two point mutations (m.3460G>A and m.11778G>A), both associated with LHON, in three patients.

Regarding the Exome analysis, the bioinformatics approach is highly complex and laborious. The workflow for the bioinformatics’ analysis at the LBioMiT was fulfilled, allowing detection of thousands of genetic variations, which were submitted to several bioinformatics’ filtering algorithms for identification of the most probable cause of the disease. Among the samples in study, the full examination and application of the decision diagrams was completed in thirteen cases.
During 2019, the Neurogenetics Laboratory continued to pursue the genetic analysis of patients with Neurological diseases, providing molecular diagnostic tests to the affected individuals as well as offering predictive tests to other family members, still asymptomatic, in the context of genetic counseling. The methodologies involved were mainly, Next Generation Sequencing technology (NGS) with subsequently Sanger sequencing to confirm all the pathogenic variants identified. However, other techniques have been also used, in particular RP-PCR and ELISA assays, to detect the C9orf72 expansion and the serum GRN level, respectively, to study the patients with Frontotemporal lobar degeneration (FTLD) and/or Amyotrophic lateral sclerosis (ALS).

The majority of the patients were followed at the different units of the Neurology Department of Centro Hospitalar e Universitário de Coimbra (CHUC), although a significant number of patients have been referred from other hospitals in the country. Variant interpretation was performed using a multistep process workflow developed in the previous year, to individually assess variants pathogenicity, based on the use of population databases and in silico prediction tools. Population databases included 1000 Genomes (1000G), exome aggregation consortium database (ExAC) and genome aggregation database (GnomAD). The in silico prediction tools included SIFT, PolyPhen, Mutation Taster, MUTPred and CADD.

To investigate the effect of the different variants found, other databases and tools have been employed such as: dbSNP, HGMD, ClinVar, ENSEMBL, VarSome and UMD-Predictor. Thus, with this procedure, several pathogenic variants underlying different conditions, have been identified, some of which were novel, expanding the disease spectrum mutations. In addition, genetic dissection has been successful disclose the molecular profile of some complex clinical cases, and thereby explain patients clinical phenotype.

In 2019, the Neurogenetics laboratory has been focused in studying patients with the clinical diagnosis of Parkinson disease, Alzheimer disease, FTLD and ALS as in previously years. Also during this year; an increase number of patients with cerebral small vessel disease (SVD) have been also studied, in which CADASIL constituted the most representative group (>20 families).

Of note, glioblastoma and cavernous malformations patients followed at the Neurosurgery unit of CHUC, continued to be referred to the laboratory to be genetic analyzed in order to improve their diagnosis and clinical management.
SERVICES AT CNC

CELLULAR MECHANOBIOLGY
Head of Unit: Mário Grãos

Our laboratory is composed by the Laboratory of Cellular Mechanobiology, which is dedicated to R&D, and the Laboratory of Cell Biology focused on service providing.

In 2019, we continued the 2 main services. One service allows the simultaneous determination of several bio-molecules using the multiplex xMAP technology. The other is related to testing the viability and differentiation capacity of Mesenchymal Stem/Stromal Cells (MSCs) obtained from cryopreserved tissue samples (ISO 9001-2015 certification for Cell and tissue culture), which resulted in the processing of 4687 samples.

The research activities were mostly focused on the field of Cellular Mechanobiology, namely in the context of oligodendrocytes and MSCs. During 2019, the laboratory was focused on the project (FCT grant) ‘BrEin-MS — Brain Elasticity in Multiple Sclerosis and implications in mechanomodulation of oligodendrocytes: a cellular and clinical approach’. We also developed projects focused on the mechanobiology of MSCs, resulting in one published article in 2019 (https://doi.org/10.1038/s41598-019-45352-3) and one in preparation (to be published in 2020). During this year, we integrated the MScellProduction project (a P2020/POCI/ERDF funded project led by Crioestaminal, SA) aiming to demonstrate the ability to manufacture GMP cell therapy products from different tissues. We also participated in collaboration R&D projects, namely with the laboratory of Bruno Manadas. The laboratory’s scientific output was as follows: 3 peer-reviewed research articles (two Q1 and one top 5% in Scimago Multidisciplinary Sciences), 2 invited oral presentations (international), 2 conference abstracts (international) and 3 poster presentations (1 international and 2 national).

The laboratory continued to provide advanced training, hosting 1 post-doctoral researcher and 2 PhD students, 2 undergraduate students and several lab rotation students from MSc programs from the University of Coimbra. The PI served as examiner of 1 MSc thesis and lab members were examiners of 2 undergraduate theses.

The PI taught courses in the fields of Mechanobiology, Stem Cells and Apoptosis, in several MSc and PhD programmes (MBCM, MIB, PD-BEB), and academic & career development in biomedical research for students of the degree in Biology, all at the University of Coimbra.

Several outreach activities were carried out. The PI presented a lecture for high school students and teachers (about stem cells) and taught 2 courses (‘Cell cycle and apoptosis’, within the Cell Signalling course) organized by IEC (Instituto de Educação e Cidadania). The PI and lab members participated in several outreach activities organized by the CNC under the scope of the Brain Awareness Week.
SERVICES AT CNC

LABORATORY OF GENOME SEQUENCING

Head of Unit: Conceição Egas
Staff:
Graduate Technician | Cristina Barroso
Principal Technician | Maria José Simões
Bioinformatician | Hugo Froufe

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

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

Services available at Genoinseq (sequencing and bioinformatics):
• Small genome sequencing and annotation
• Exome sequencing and variant annotation
• Whole transcriptome and RNA-Seq
• Biodiversity studies on environmental communities
• Metagenome sequencing and annotation

The Laboratory is part of GenomePT - National Facility for Genome Sequencing and Analysis (RNIE) (ref.01/SAICT/2016) and is certified under NP EN ISO 9001:2015 for next generation sequencing of nucleic acids and bioinformatics tools for DNA and RNA analysis.

In 2019 the Laboratory sequenced 1183 samples for external clients, in a total of 177 Gb. Biodiversity samples were the most requested application, with 32.5 Gb. Sequencing services and bioinformatics were additionally provided for CNC users, with 185 samples sequenced in a total of 112 Gb.


Graduate students
Diogo Pinho, Ph.D. student
Raquel Varandas, Ph.D. student
Daniel Martins, Ph.D. Student

OUTREACH
Genoinseq presented the core facility, sequencing applications and research results in 9 external events.

RESEARCH PAPERS:


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RESEARCH PAPERS:


Background: During drug development, the road towards successful market entry also depends on whether toxicity to tissues is properly predicted in pre-clinical stages. At this critical time for the development of novel drugs, it is critical to assess whether a drug candidate presents cellular and mitochondrial liabilities which may cause off-target toxicity. Since mitochondria are the cell powerhouses and responsible for many critical tasks in cell metabolism, chemical entities which cause mitochondrial liabilities lead to a bioenergetic disruption of the cell, followed by organ failure. One example is drug-induced liver injury, which is the mechanism behind several cases of drug withdrawal from the market. Prediction of mitochondrial toxicity in early pre-clinical stages is thus essential to pharma companies for a more successful road to market.

Our mission: The main objective of MitoXT service platform is to support companies or academic research groups in predicting the mitochondrial toxicity of single molecules or mixtures with applications in pharmaceutical industry, environmental sciences, nanoparticles and polymer development, food industry, as well as other applications, with the ultimate objective of introducing safer chemicals in the environment and human systems. Our team has know-how in cell and mitochondrial metabolism and toxicology, standard and verified protocols that can be adapted to high-throughput screening as well as in data analyses.

Technology available: Seahorse XF96 Extracellular flux Analyzer; Cytation 3 Multiplate Reader; gTOXXs analyzer; MBIO AquaSpec mid-infrared spectroscopy analyzer; Hansatech Oxygraph, CFX-96 qRT-PCR machines.

R&D: Developing new screening methods and identifying biomarkers of disease and drug-induced mitochondrial toxicity; developing in-silico predictors of mitochondrial toxicity.

CLIENTS: Clients for our service have included Universities in Portugal and abroad (USA, Czech Republic), and private research centers (Spain).
In 2019 funding of “Laboratório Associado – Centro de Neurociências e Biologia Celular” ascended the amount of 9,562,069.56€.

The main financing contribution was made by “Fundação para a Ciência e Tecnologia (FCT)”, concerning global institution programs and national projects, namely amount of 7,915,290.36€ distributed as follows:

- Strategical Project_ UID/NEU/04539/2019: 2,012,209.39€
- Science Program: 1,801,519.15€
- FCT Projects: 4,101,561.82€

The related items supported the main part of Center for Neuroscience and Cell Biology expenses during 2019.

Besides Center for Neuroscience is financed by other national and international agencies. In 2019 Center for Neuroscience received the amount of 1,462,937.64€, whereas other services had expenditure of amount 183,841.56€.

Main Services, not listed, is another important vector of our institution which ascends 650,236.45€ in 2019.

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

Note: Financing values apart from main services are based on expenditure values 2019.
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Melhoria cognitiva no cérebro idoso e demência vascular em humanos através da funcionalização do acoplamento neurovascular: uma estratégia mecanística - COORDINATOR: João António Nave Laranjinha - PROPONENTE: Centro de Neurociencias e Biologia Celular - PARTICIPANTS: CHUC, UC

Influência das antocianinas extraídas de mirtilos cultivados em Portugal na conexão entre o intestino e o cérebro nas perturbações do espetro do autismo: utilização de modelos in vitro e in vivo - COORDINATOR: Leonor Martins de Almeida

Monitorização in vivo de marcosadores neurometabólicos com biossensores baseados em microeléctrodos - COORDINATOR: Rui Manuel Silva G. Barbosa - PROPONENTE: Universidade de Coimbra - PARTICIPANTS: CNBC

Bloqueio da neurodegenerescência por dispersão de silenciadores gênicos. - COORDINATOR: Luís Pereira de Almeida

O papel dos grânulos de stress nas doenças de poliglutaminas: da patogénese à terapia molecular - COORDINATOR: Luís Pereira de Almeida - PROPONENTE: Universidade do Algarve

Papel da desregulação dos microRNAs na doença de Machado - Joseph: Desenvolvimento de uma estratégia terapêutica baseada em microRNAs - COORDINATOR: Sonia Patricia Dias Duarte

O impacto do transplante de células estaminais neuroepiteliais derivadas de células estaminais pluripotentes induzidas na doença de Machado-Joseph - COORDINATOR: Liliana Mendonça
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<td>Joana Medeiros Vieira Marques</td>
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<td>Rui Jorge Gonçalves P. Nobre</td>
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<td>Adenosine A2A receptors as a new opportunity to manage and detail the neurobiology of emotional distress.</td>
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<td>Ana Teresa Antunes Simões</td>
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<td>Nuno Miguel Silva Empadinhas</td>
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<td>Inhibition of macrophage protein tyrosine phosphatase 1B (PTP1B) as a novel therapy for improved wound healing in diabetes</td>
<td>Eugénia Maria L. Carvalho</td>
<td>17/09/2018</td>
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<td>Silencing the SCA3-causing gene ATXN3 through CRISPR interference</td>
<td>Carlos Adriano A. Andrade Matos</td>
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<td>A system approach to find a blood-based biomarker for Machado-Joseph Disease</td>
<td>Magda Santana</td>
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<td>Novas terapias para Doença de Chagas: reposicionamento de drogas com efeito sinergístico com Benzonidazol para combater infecção por Trypanosoma cruzi</td>
<td>Miguel L. C. Mano</td>
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<td>Milton Simões da Costa</td>
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<td>Agencia Estatal CSIC - REF. TREATMENT-721236</td>
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<td>Queen Mary University (QMUL) - REF. NANOSTEM - 764958</td>
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<td>Improving drug delivery to the brain and glioblastoma treatment using temperature Nano Brain</td>
<td>European Commission - REF.Nano_Brain 842405</td>
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<td>147 816,04</td>
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<td>Production and Testing of humAn-derived Neurons and brain organoids: advanced model probing in neurodevelopment disorders</td>
<td>European Commission - REF.ProTeAN-799164</td>
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<td>Fundação para Ciência e a Tecnologia - REF. Nó da RNEM - Dr. Bruno Manadas</td>
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<td>From Protein Structure to biological function through interactomics - an integrated view (2nd edition) - COORDINATOR: Bruno José F. O. Manadas</td>
<td>- REF. Cursos Bruno Manadas</td>
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<td>8º Workshop da Sociedade Europeia de Cálcio - COORDINATOR: Cláudia Pereira</td>
<td>- REF. 8º Workshop da Sociedade Europeia de Cálcio</td>
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<td>Summer School - COORDINATOR: Armando José Alves S. Salvador</td>
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<td>Brain without borders - COORDINATOR: Luis Pereira de Almeida</td>
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<td>Formações do Gab. Comunicação - COORDINATOR: Sara Varela Amaral</td>
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The table above lists various events and their associated costs and time frames. Each event is coordinated by an individual or an institution, and the ref. code is likely a unique identifier for each event. The costs are listed in Euros, and the hours are in total. The dates range from 2016 to 2019, indicating the duration of the events.
<table>
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<tr>
<th>Project Description</th>
<th>Coordinator/PropONENT</th>
<th>Start Date</th>
<th>End Date</th>
<th>Budget</th>
<th>Co-Investigator</th>
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<td>Stress, Resilience and Epigenetic alterations: Frontal cortex and Social dominance.</td>
<td>Ana Cristina Carvalho Rego</td>
<td>01/01/2018</td>
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<td>AAV-miATXN3w, AAV-GFP reporter, and new to develop transgene-containing AAVs</td>
<td>Luis Pereira de Almeida</td>
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<td>31/12/2025</td>
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<td>Evaluation of MJD/SCA3 preclinical drug discovery model systems</td>
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<td>European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative</td>
<td>Luis Pereira de Almeida</td>
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<td>Targeting mutant ATXN3 for the treatment of Spinocerebellar Ataxia 3 (SCA3)</td>
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<td>Pharmatex In vitro Studies Program - INNOTECH 2015</td>
<td>João Ramalho de Sousa Santos</td>
<td>31/12/2014</td>
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<td>218 086,76</td>
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<td>Revascularização e angiogénese</td>
<td>João Ramalho de Sousa Santos</td>
<td>20/12/2016</td>
<td>31/12/2020</td>
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<td>TimeUp - INESPO III</td>
<td>Susana Isabel Elias Alarico</td>
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<td>Exploring the role of pridopidine on mitochondrial function and dynamics in Huntington’s disease models</td>
<td>TEVA Pharmaceutical Indust. - REF Exploring the role of pridopidine_TEVA</td>
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<td>Supplementation of Coriolus versicolor (biomass) - a nutritional presymptomatic approach against cognitive deficits</td>
<td>Ana Cristina Carvalho Rego - TEVA Micology Research Laboratories</td>
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<td>NIH - 75N95020P00076 - COORDINATOR: Attila Köfalvi</td>
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<td>DDZ_FLAME_L_study - COORDINATOR: John Griffith Jones</td>
<td>German Diabetes Center - REF DDZ_FLAME_L_study</td>
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<td>- REF. Comparison the acute effects..</td>
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<td>Faturação Dr. Lino Ferreira - COORDINATOR: Lino Ferreira</td>
<td>Universidade de Coimbra - REF Faturação Universidade de Coimbra</td>
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<td>MSCellProduction: Produção de Células Estaminais Mesenquimais em Conformidade com os requisitos de Boas Práticas de Fabrico - COORDINATOR: Mário Grãos</td>
<td>- REF. MSCellProduction</td>
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## IBILI FINANCIAL REPORT 2019

**2019 Annual Accounts**

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<th>Title</th>
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<th>Principal Investigator</th>
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<th>Ending Date</th>
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<td>ExoSwitch - Understanding the switch between dry and wet AMD: role of exosomes</td>
<td>BAYER -GOAP</td>
<td>Rosa Fernandes</td>
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<td>PET com sistema inovador de leitura dupla para correção de DOI</td>
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<td>NECSUS - Neuroadaptation After Cataract and Refractive Surgery Study</td>
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<td>Regulação farmacológica das proteínas da família p53: a caminho de novas terapias anticancerígenas</td>
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<td>PPBI – Plataforma Portuguesa de Bioimagem</td>
<td>Agência Desenvolvimento e Coesão</td>
<td>Henrique Girão</td>
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<td>A novel mechanism to repair HFpEF and endothelial damage</td>
<td>FCT RE-PAIR - 032179</td>
<td>Henrique Girão</td>
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<td>Tailored microenCAPsulation technology for Extreme Oxygen-Sensitive BACteria with beneficial effects on gut microbiota: Production, stability and functionality enhancements in various carriers</td>
<td>FCT CAPEOSBAC - 031400</td>
<td>Flávio Reis</td>
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<td>Use of blueberry juice as a nutraceutical strategy targeting gut dysbiosis to prevent the progression from prediabetes to diabetes</td>
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<td>Flávio Nelson Reis</td>
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<td>Speed, crash and run: exersomes boost neuroenergetics and mood in mice on speed</td>
<td>FCT MOOD EXERSOMES - 030786</td>
<td>Frederico G.S.C. Pereira</td>
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<td>Modeling Angiogenesis in Type 2 Diabetes Mellitus - integrating experimental and theoretical approaches</td>
<td>FCT ANGIODIA -031743</td>
<td>Raquel Seiça</td>
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<td>On the right side: unveiling the mechanisms of pulmonary hypertension reversibility and the heart failure progression</td>
<td>FCT RIGHT-2H -032414</td>
<td>Rui Baptista</td>
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<td>Environmental enrichment protects adult hippocampal neurogenesis and memory decline induced by systemic inflammation</td>
<td>FCT MercuMemory - 031699</td>
<td>Carlos Fontes Ribeiro</td>
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<td>Dialysis membranes by design: targeting neutrophil elastase to reduce inflammation/oxidative stress in end-stage renal disease</td>
<td>FCT DIAL4LIFE - 031322</td>
<td>Flávio Reis</td>
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<td>Ana Paula Martins</td>
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<td>Nova Terapêutica de RNA de Interferência para o Glaucoma</td>
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<td>António Francisco Ambrósio</td>
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<td>Francisco Caramelo</td>
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<td>iPET - Sistema PET inteligente para imagiologia pré-clínica</td>
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<td>Ana Cristina Santos</td>
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**SYNAPSE BIOLOGY GROUP**


**REDOX BIOLOGY AND BRAIN SENSING GROUP**


Serra D, Almeida LM, Dinis TCP (2019) Polyphenols as food bioactive compounds in the con-


NEUROENDOCRINOLOGY AND AGING GROUP


VISION, BRAIN IMAGING AND COGNITIVE NEUROSCIENCE


MITOCHONDRIAL DYSFUNCTION AND SIGNALING IN NEURODEGENERATIVE GROUP


AGING AND BRAIN DISEASES: ADVANCED DIAGNOSIS AND BIOMARKERS


Lucena S, Coelho AV, Anjo SI, Manadas B, Mrlijak V, Capela ESF, et al. Comparative proteom-


NEW TARGETS AND THERAPEUTICS FOR CHRONIC DISEASES


MITOCHONDRIA, METABOLISM AND DISEASE GROUP


METABOLIC CONTROL GROUP


Vectors and Gene Therapy Group


Biocompatible and high-magnetically responsive iron oxide nanoparticlese for protein loading.; Andre Gaspar; Paulo Santos; Olga Borges; Benilde Costa; Luísa Duraes; submitted to Journal of Physics and Chemistry of solids Volume 34, November 2019, Pages 273-285; doi.org/10.1016/j.jpcs.2019.06.016.


Chitosan plus compound 48/80:formulation and preliminary testing as a Hepatitis B vaccine adjuvant.; Dulce Bento, Sandra Jesus; Filipa Lebre; Teresa Gonçalves; Olga Borges (2019)


Jonas Walter, Silvia Bolognin, Paul M.A. Antony, Sarah L. Nickels, Suresh K. Poovathingal, Luis Salamanca, Stefano Magni, Rita Perfeito, Fredrik Hoel, Xiaobing Qing, Javier Jarazo, Jonathan Arias-Fuenzalida, Tomasz
STEM cell BIOTECHNOLOGY GROUP


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Molecular Mycobacteriology Group


Medicinal Chemistry & Drug Discovery Group


 Structural insights and binding analysis for determining the molecular bases for programmed cell death protein ligand-1 inhibition, RC Acín, C. Leonardo-Sousa, AT García-Sosa, JA Salvador; MedChemComm, 2019, 10 (10), 1810-1818.

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Synthesis and antiproliferative activity of novel heterocyclic Glycurrythric acid derivatives, DPS Alho, JAR Salvador, M Cassante, S Marin, 2029, Molecules 24 (4), 766.


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Molecular Biotechnology Group


## STAFF LIST

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Ana Manuela Veloso da Silva 100%
Ana Maria da Graça Fernandes Vasconcelos 100%
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Ana Reis Costa 100%
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Giorgio Belperio 100%
Isadora Pombeiro 100%
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