Book of Abstracts

7th Meeting of the MSc in Biochemistry and Biomedicine

February 11th, 2025

Faculdade de Ciências da Universidade de Lisboa

Ciências ULisboa

Sociedade Portuguesa de Bioquímica SPB

Outline

Organizing Committee

Margarida Gama-Carvalho, Faculdade de Ciências, Universidade de Lisboa.

Ana Jorge, Faculdade de Ciências, Universidade de Lisboa.

Alice Abrantes, Faculdade de Ciências, Universidade de Lisboa.

Miguel Trigo, Faculdade de Ciências, Universidade de Lisboa; Instituto de Tecnologia Química e Biológica.

Ruy Domingos, Faculdade de Ciências, Universidade de Lisboa.

Note – The number of abstracts presented here does not correspond to the total number of oral and poster presentations, as abstract submission was not mandatory. Thank you for your understanding. O – Oral presentation; P – Poster presentation.

Program

Tuesday, February 11th, 2025

09:00 – 09:30 Registration and Opening

09:30 – 10:30 Session I: Mechanism of Disease and Cellular Pathways

- The Role of Insulin and Insulin-Like Growth Factor 1 on Neuronal Glycogen Metabolism: Insulin-Sensitivity vs. Insulin-Resistance – **Duarte Dias**.

- Exploring TDP-43 Modulation in Neurodegenerative Proteinopathies: The Impact of Chaperones and RNA on Phase Separation, Aggregation, and Cellular Localization – **Carolina Silva**.

- Molecular Profiling of Amyotrophic Lateral Sclerosis using Fourier Transform Mass Spectrometry – **Ana Jorge**

- Dissecting the Role of BIN1 in Alzheimer's Disease – **Ana Fernandes**

- Understanding the Role of Acylations on Mitochondria Beta Oxidation Proteins – **Ruy Domingos**

- Dissecting the Mechanisms Underlying the Reduction of Lipofuscin Like Autofluorescent Granules Load in Cellular Models of Age-Related Macular Degeneration – **Leonor Devesa**

- Alternative Translation Initiation of Argonaute 1 and Its Potential Function in Cancer – **Verónica Silva**

- The Mechanism of Nonsense-Mediated Decay in Human Cells – **Miguel Carvalho**

10:30 – 11:00 Coffee Break

09:30 – 10:30 Hot Topics in Biochemistry and Biomedicine

- From Personalized Therapies to One-Size-Fits-All Treatments: Rising to Meet the Challenges of the 21st Century – **Rita Fior** (Champalimaud Foundation) and **Miguel Castanho** (GIMM).

12:30 – 14:30 Lunch Break

14:30 – 15:30 Session II: Therapeutic Strategies and Disease Models

- Understanding Gut-Brain Signalling in Autism Using Stem Cell-Derived 3D Organ-On-A-Chip Models – **Carolina Manaças**

- Enhancing Iodide Uptake in Refractory Thyroid Cancer: Investigating Modulators of Cell Matrix Adhesion Signaling Affecting NIS Abundance and Retention at The Plasma Membrane – **Carolina Freitas**

- Targeting Melanosome and Lysosome Exocytosis to Impair Cutaneous Melanoma Progression – **Mariana Feliciano**

- Radiation as a Therapeutic Tool Against Neurodegeneration: Pilot Studies in New Cellular Models of Huntington's Disease – **Sílvia Landeau**

- New Psychoactive Substances: Mechanisms Of Toxicity and Cellular Effects – **Beatriz Alves**

- Exploring hiPSC-derived 3D Models to Tackle the Brain's Innate Immune Response to Gene Therapy rAAVs – **Marta Gomes**

- Nonsense Mutations in Cystic Fibrosis – Molecular Mechanisms and Rescue Strategies – **Alice Abrantes**

- Characterization of RNA Regulatory Elements Able to Control Protein Expression in Distinct Human Cell Types – **Lara Mouga**

15:30 – 16:00 Coffee-Break

16:00 – 17:00 Session III: Molecular Interactions, Membranes and Structural Biology

- Understanding The Interaction Between Rhodopsin-1 And Xport-A in *Drosophila Melanogaster* – **Miguel Trigo**

- Design and Application of Nanodiscs for Structural Studies of Membrane Proteins – **José Quintal**

- Molecular Mechanisms of Cystic Fibrosis – CFTR Interactions at The Membrane – **João Oliveira**
- Sphingolipids Play a Leading Role in Plasma Membrane Organization - Implications in Antifungal Action – **Eva Santos**

- The Interplay Between Phages and Integrative-Conjugative Elements in Helicobacter Pylori – **Mafalda Guimarães**

- Exploring Malate: Quinone Reductases from Pathogenic Bacterium Pseudomonas Aeruginosa – **Margarida Silva**

- Computational Model of Phosphatidylinositol Protonation: Insights into Membrane and Protein Interactions – **Ana Figueiredo**

- Optimising The Biological Activity of Natural Product Extracts Using Nanotechnology – **Ana Miranda**

Abstracts

Session 1

TDP-43 self-assembly in Neurodegenerative Proteinopathies: Regulation of Phase Separation, Aggregation and Cellular Localization by a Molecular Chaperone (O|P)

Carolina M. Silva [1,2], Margarida Gama-Carvalho [1,2], Cláudio M. Gomes [1,2]

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Transactive response DNA-binding protein 43 (TDP-43) proteinopathy is a hallmark of amyotrophic lateral sclerosis (ALS) and tau-negative frontotemporal dementia, with growing evidence implicating it in Alzheimer's disease. TDP-43 is a 414-residue nucleic acid-binding protein primarily localized in the nucleus, where it regulates RNA metabolism and drives the formation of membraneless organelles. In pathology, TDP-43 undergoes proteolysis, leading to cytoplasmic accumulation of fragments containing the intrinsically disordered low-complexity domain (TDP-43 LCD, residues 274–414). The biochemical determinants governing TDP-43 self-assembly—whether LLPS or aggregation—remain poorly understood, and even less is known about its biological regulation through molecular chaperones.

This project investigates whether S100B, a small dimeric Ca^{2+}-binding protein abundant in the brain and present in both nucleus and cytoplasm, functions as a regulator of TDP-43 self-assembly, given its neuroprotective role in inhibiting tau and amyloid-β self-assembly in a Ca^{2+}-dependent manner.

To explore this, we first used AlphaFold3 to generate a predictive structural model of the Ca^{2+}-bound S100B dimer in complex with TDP-43 LCD. The model revealed interactions between self-assembly-promoting stretches within the LCD and the known regulatory cleft in S100B, which also binds other amyloidogenic clients.

Experimentally, we next successfully expressed and purified recombinant human TDP-43 LCD at high purity (>95%) and yield (2.65 mg/L). To validate the computational predictions, we employed biolayer interferometry to characterize the interaction between S100B and TDP-43 LCD, determining that it occurs with high affinity (KD = 55.6 nM) exclusively in the Ca^{2+}-bound state.

Motivated by this finding, we next assessed in preliminary experiments whether S100B could disrupt TDP-43 LCD aggregation and/or LLPS. Using bis-ANS to induce LLPS, we observed that equimolar Ca^{2+}-bound S100B reduced TDP-43 LCD phase separation by twofold. Thioflavin-T kinetic assays further demonstrated that equimolar Ca^{2+}-S100B completely abolished TDP-43 LCD aggregation, while sub-stoichiometric levels significantly delayed aggregation, increasing the half-time by threefold.

Molecular Profiling of Amyotrophic Lateral Sclerosis using Fourier Transform Mass Spectrometry (O|P)

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Genomics has advanced our understanding of neurodegenerative diseases. However, by exploring proteins and, specially, metabolites, we can get a much closer look at the phenotype and the molecular mechanisms at play. Proteins are the product of genes, but they are also the effectors of most biochemical actions and respond to alterations imposed by the environment. As the proteome changes, so does the metabolome. In this work, we aim to analyze the proteome and metabolome of serum samples from Amyotrophic Lateral Sclerosis (ALS) patients. The proteomic analysis will be performed using an Astral Orbitrap mass spectrometer, through a collaboration with the Karolinska Institutet, in Sweden. The metabolomic profiling will be performed in a Fourier-Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer, available at the Faculty of Science of Lisbon University (FCUL). For the first time, proteomic and metabolomic analyses using FT mass spectrometry (FTMS) will be integrated to characterize ALS samples. We used NIST Standard Reference Material for Human Plasma for the calibration of sample analyses on the FT-ICR mass spectrometer. This ensures the reliability and accuracy of the subsequent analysis of ALS patients' serum. Beyond enhancing biomarker discovery, this study seeks to deliver an unprecedented molecular characterization of ALS, leveraging the exceptional mass accuracy and high-throughput capabilities of FTMS.

Understanding the role of Acylations on Mitochondrial Beta Oxidation Proteins - Sirtuin 5 regulates Succinylation of Medium Chain Acyl-CoA Dehydrogenase (MCAD) (O|P)

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Metabolic regulation encompasses a complex interplay of genomic, proteomic and metabolic adjustments, several of which become compromised in disease states. Some of these adjustments occur in the form of post translational modifications (PTMs). Recently, a class of non-enzymatic PTMs known as acylations has emerged as an important regulator of mitochondrial enzymes. This is due to the reactivity of acyl-CoA compounds, such as succinyl-CoA and glutaryl-CoA, present in the organelle and its basic pH. Recently, these types of PTMs have been proposed to function as a nutrient-sensing regulators by controlling the metabolic flux between different pathways, which coupled with regulatory Sirtuin 5 mediated removal of modifications from target proteins, has created a complex and largely unexplored field of research. Taking this into account, how these modifications regulate protein function and how these modifications are regulated in both healthy and disease states are still major questions that remain to be answered. Previous work showed that GCDH activity is impaired by glutarylation and succinylated ETF presents compromised function (unpublished results). To date, our work has shown that MCAD is heavily succinylated and glutarylated in various conditions, in vitro. Interestingly, despite being similar, and despite not heavily affecting MCAD's structure, these modifications have different functional effects. Whilst succinylation increases MCAD's activity for several substrates, glutarylation only increases MCAD's activity for long chained substrate. In addition to this we have shown that succinylation of MCAD is reversed by Sirtuin 5 leading to a decrease in activity to unmodified MCAD levels. Overall, our results shed light on the importance of non-enzymatic PTMs, in particular negative charge acylations, as fine regulators of mitochondrial energy metabolism, by uncovering the first example of a β-oxidation enzyme presenting increased activity upon modification.

Alternative translation initiation of Argonaute 1 and its potential function in cancer (O)

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Translation is one of the most regulated and energy-consuming cellular processes crucial for proper cell function. Translation is initiated by the canonical cap-dependent mechanism. However, under stress conditions, the initiation of canonical translation is inhibited, which allows the translation of specific proteins via alternative mechanisms, such as that mediated by internal ribosome entry sites (IRES). The IRES-mediated alternative translation is involved in regulating many oncogenes and growth factors, contributing to cell adaption and survival. In addition, IRES trans-acting factors (ITAFs) regulate this non-canonical translation and play an important role in the stress response, which can promote cancer progression. This project aims to understand the biological relevance of alternative protein synthesis mechanisms in AGO1 (Argonaute 1) expression. The AGO1 (Argonaute 1) protein is involved in microRNA regulation, gene expression modulation and inhibition. AGO1 is also involved in the regulation of gene expression by RNA interference (RNAi), and its deregulation can lead to the activation of oncogenes or the suppression of tumor suppressor genes, contributing to the development and progression of cancer. Our lab showed that AGO1 can be synthesized by a cap-independent translation initiation mechanism. In addition, an upstream open reading frame (uORF) was identified in the 5' UTR (Untranslated Region) of AGO1. According to the zipper model of translation control, the interaction between uORF and IRES could modulate mRNA structure, thereby influencing AGO1 alternative translation initiation, particularly under stress conditions. This project aims to understand how these alternative mechanisms of mRNA translation initiation can influence AGO1 expression and help explain their potential roles in certain pathologies and cancer progression, such as colorectal cancer.

Session 2

Exploring hiPSC-derived 3D models to tackle the brain's innate immune response to gene therapy rAAVs (O|P)

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Mucopolysaccharidosis type VII (MPS VII) is a severe lysosomal storage disorder caused by mutations in the GUSB gene, leading to β-glucuronidase (GUSB) deficiency and the accumulation of glycosaminoglycans (GAGs) in lysosomes, extracellular compartments, and tissues. This accumulation disrupts cell-to-cell and cell-to-extracellular matrix (ECM) adhesion, triggering neuroinflammation—a hallmark of neuronopathic MPS. Activated microglia and astrocytes release neurotoxic molecules, exacerbating central nervous system (CNS) dysfunction and cell death. While recombinant adeno-associated viral vector (rAAV)-based gene therapy has shown promise for MPS VII, its efficacy remains limited, potentially due to the poor survival of transgene-expressing cells in a neuroinflammatory microenvironment.

To better model MPS VII neuropathology and evaluate gene therapy strategies, a three-dimensional (3D) neural platform based on human-induced pluripotent stem cells (hiPSCs) has been developed. This system utilizes perfusion bioreactors to generate neurospheroids composed of neurons, astrocytes, and oligodendrocytes, recapitulating key disease features, including GAG accumulation, lysosomal dysfunction, and impaired neural connectivity. Given the prominent role of neuroinflammation in MPS VII, this project aims to further optimize the model by incorporating microglia, enabling the study of astrocyte-microglia crosstalk and its impact on rAAV-mediated gene therapy. Specifically, the study will focus on three main objectives: (1) implementing a 3D neurospheroid model of MPS VII and its isogenic corrected controls, (2) integrating microglia into the MPS VII neurospheroids, and (3) investigating the innate immune response to rAAVs, with an emphasis on microglia activation and its effects on gene therapy efficacy.

Nonsense Mutations in Cystic Fibrosis – Molecular Mechanisms and Rescue Strategies (O|P)

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Cystic Fibrosis is a life-threatening autosomal recessive disease caused by mutations in the CFTR gene. The over 2,100 CFTR genetic variants that have been reported can be organized into seven classes (Classes I-VII) according to their effect on the CFTR protein. Modulator therapy is available for many people with CF (pwCF) that retain partial expression of full-length CFTR. However, for approximately 10% of pwCF, no specific treatment is available, including those carrying nonsense mutations (Class I). These affect protein production through the introduction of premature stop codons (PTCs), causing degradation of mRNA by nonsense-mediated decay (NMD). G542X (c.1624G>T) is the most common Class I and the second most common CF-causing mutation. We have identified several differentially expressed transcripts and proteins in cells bearing the G542X mutation that might contribute to NMD of CFTR transcript and the absence of protein in these cells. The main goal of this work is to identify G542X (and class I)-related specific signatures, that can be modulated to inhibit mRNA degradation and promote PTC readthrough in cells with nonsense mutations to rescue CFTR expression and function. We have validated 7 upregulated and 4 downregulated genes unique to G542X. Ongoing work identified that the knockdown of the RNA binding proteins TUT1 and HNRNPUL2 has a considerable effect in the levels of CFTR mRNA in G542X cells. A similar effect was found upon overexpression of ZNF793. We are currently evaluating the effect on protein expression and performing combination experiments with other strategies to identify synergistic and additive effects.

We have identified novel RNA binding proteins as regulators of the abundance of G542X CFTR mRNA. This will allow us to test various strategies to correct nonsense variants and uncover a combined approach where our identified targets lead to NMD inhibition and PTC readthrough to rescue CFTR in these individuals.

Session 3

Understanding the interaction between Rhodopsin-1 and Xport-A in *Drosophila Melanogaster* (O|P)

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The Drosophila melanogaster eye serves as a powerful model for studying retinal cellular and molecular processes, with Rhodopsin-1 (Rh1) being a key focus due to its structural similarity to human rhodopsin. Rh1 maturation requires glycosylation at N20, a crucial modification for proper folding and transport. Misfolded or persistently glycosylated Rh1 is retained in the endoplasmic reticulum (ER), triggering Unfolded Protein Response (UPR) pathways and degradation via the ER-associated degradation (ERAD) system. ERAD prevents misfolded Rh1 from reaching the rhabdomeres—the specialized photoreceptor organelles responsible for phototransduction—by targeting it for ubiquitin-proteasome degradation. While the roles of chaperones such as NinaA and calnexin are well-characterized, the specific function of Xport-A in Rh1 biogenesis remains unclear.

Recent studies using AlphaFold 3 predict that Xport-A interacts with Rh1 TMD1-5 but not with full-length Rh1. However, the precise mechanism of interaction remains unknown. To validate these predictions, we performed co-immunoprecipitation assays in both Drosophila S2 cells and fly eyes. Contrary to AlphaFold 3 predictions, our results indicate that both full-length Rh1 and Rh1 TMD1-5 interact with Xport-A in S2 cells. Furthermore, when four transmembrane amino acid residues of Xport-A were mutated to leucine, Rh1 no longer interacted with Xport-A, suggesting that their interaction occurs within the transmembrane domains of both proteins.

Additionally, we performed an assay using GFP-NinaC, a marker for photoreceptor integrity, as NinaC is essential for the cytoskeletal structure of rhabdomeres. This assay allowed us to assess photoreceptor degeneration by evaluating the presence or absence of GFP-NinaC. We observed no degeneration in Xport-A null heterozygous mutants, however, in Xport-A null homozygous mutants, photoreceptor degeneration was evident.

Design and Application of Nanodiscs for Structural Studies of Membrane Proteins (O|P)

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Membrane proteins (MPs) are fundamental to cellular processes, including infection by pathogens, and represent ~30% of an organism's open reading frames. However, only about 2% of the structures in the Protein Data Bank (PDB) are MPs, illustrating the challenges in expressing, purifying and maintaining these proteins in a stable form suitable for structural studies. The objective of this work is to express, purify and reconstitute MPs (e.g. Translocated Intimin Receptor (Tir)) into nanodiscs (NDs), evaluating their biochemical and structural behavior. This approach aims to deepen our understanding of the pathogenic mechanisms associated with the global burden of foodborne illness. NDs are nanoscale disc-like structures that mimic the native phospholipid bilayer of cell membranes, enabling subsequent analysis by techniques such as Small-Angle X-ray Scattering (SAXS), Nuclear Magnetic Resonance (NMR), Circular Dichroism (CD) and Dynamic Light Scattering (DLS). Thus far, we have successfully expressed and purified membrane scaffold proteins (spNW15, spNW25) as well as membrane proteins (FL-Tir pHTP9), performing preliminary structural and biophysical analyses confirming their proper folding and stability. In future work, these MPs will be incorporated into NDs and studied using advanced techniques – such as NMR, SAXS, CD, and DLS – to gain deeper insights into their structural and functional properties.

Exploring malate:quinone reductases from pathogenic bacterium Pseudomonas aeruginosa (O|P)

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1. BioISI - Biosystems and Integrative Sciences Institute, Faculdade de Ciências, Universidade de Lisboa, Lisbon, Portugal

Pseudomonas aeruginosa is an opportunistic bacterium, linked to a wide range of infections, mainly affecting the airways and urinary tract. P. aeruginosa is one of the most common causes for healthcare-associated infections, especially in individuals in the intensive care units (ICU) and already immunocompromised. The World Health Organization (WHO) considers P. aeruginosa a major global health issue since resistance to available antibiotics is increasing. Despite the threat, the versatile metabolism, particularly the respiratory enzymes, is not fully understood. Energy is fundamental to all organisms, so studying the proteins involved in key processes could aid in the development of novel antibiotics. The project aims to expand the knowledge into P. aeruginosa metabolism exploring two putative malate:quinone oxidoreductases (MqoA and MqoB) and elucidate the different metabolic pathways connected to the respiratory chain. The characterization of these monotopic flavoproteins will be performed by biochemical, biophysical and cellular methodologies. For protein production, the two genes encoding Mqos have been cloned and inserted into the plasmid pET28(+) with a His-tag and transformed into E. coli. MqoA production is still in progress, while MqoB production was successfully achieved in E. coli Rosetta. MqoB was purified by chromatographic procedures using an AKTA His-trap column. The protein purification protocol is still undergoing optimization. Activity assays were performed by UV-Visible spectroscopy following the reduction of a ubiquinone analogue, DDB, at 278nm. MqoB showed malate:quinone activity, but further optimization is needed. For cellular characterization, the knockout mutants of the genes encoding the proteins of interest are in progress using CRISPR-Cas9 technology. The next steps include cell growth in different controlled conditions monitoring OD600 nm and the medium pH values, as well as study the metabolomic profiles. Understanding the role of Mqo in P. aeruginosa flexible metabolism and antibiotic resistance could ease the infections impact in public health.

Computational Model of Phosphatidylinositol Protonation: Insights into Membrane and Protein Interactions (O|P)

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Phosphatidylinositols (PIPs) are ubiquitous signalling molecules, whose functions range from membrane trafficking to cellular growth. Most PIPs, if not all, have distinct biological roles, being implicated in an array of medical conditions, including several types of cancer. Their structural properties are mainly determined by the characteristics of the polar group, consisting of an inositol ring that can be phosphorylated in positions 3, 4, and 5, separately or in combinations, such as PI(4,5)P2. At physiological pH, the polar group is very negatively charged and with the possibility of establishing strong electrostatic interactions. The global protonation state of PIPs strongly influences their binding affinities and specificity for certain protein domains, their interaction with other lipids (including PIPs themselves), and with divalent cations. These interactions are highly specific and also depend on the position of the phosphate of the inositol ring. Although their structural properties rely on the characteristics of the polar group, PIPs have been studied at the molecular level using computational methodologies that introduce large approximations regarding their preferred protonation states. In light of that, this project aims to use constant-pH molecular dynamics (CpHMD) simulations to investigate the acid-base equilibrium of PIPs in solution, lipid bilayers, and their specific interaction with certain proteins. To achieve our goals, we simulated PIPs free in solution and embedded in a lipid bilayer at pH values ranging from 0 to 9. We used our in-house CpHMD code with the CHARMM force field. In this communication, we will present the titration curves and respective pKa values obtained from the simulations, together with their validation with experimental NMR data.

Optimising the Biological Activity of Extracts Natural Product using Nanotechnology (O|P)

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Seaweeds are sustainable sources of macro and micronutrients, as well as bioactive compounds with potential health benefits, including antioxidant and antimicrobial properties. Based on their coloration and taxonomic classification they can be classified into three main groups: green (Chlorophyta), red (Rhodophyta) and brown (Phaeophyceae). Nanotechnology has emerged as a promising approach to enhance the stability and efficacy of bioactive compounds from natural sources in health applications. Nanoparticles (10-1000 nm) can improve the effectiveness of these compounds in various applications. This study explores how silver nanoparticles (AgNPs) can improve the biological properties of bioactive compounds derived from seaweed. By combining the extracts with AgNPs, the aim is to enhance antimicrobial and regenerative effects. The research focuses on improving the release and stability of the compounds, with potential applications in healthcare, particularly in skin regeneration. Three species of seaweed, Ulva sp. (green), Gracilaria sp. (red) and Fucus vesiculosus (brown) were used to obtain the extracts, which were analysed for their total phenolic content (TPC), antioxidant activity and chromatographic profile by HPLC-DAD. The preliminary results indicated that the Gracilaria sp extract, containing 0.76 mg of TPC/mg of dry extract, performed best in all the parameters analysed, namely antioxidant activity (27.4%) and bioactive compound profile in the HPLC-DAD analysis, and was therefore selected for the preparation of AgNPs using different formulations. In the next steps, the AgNPs will be further characterized using advanced techniques such as FTIR and AFM. In addition, studies will be carried out to assess the stability and safety of both the extracts and the nanoformulations. The antimicrobial activity will also be evaluated, as well as the ability of the AgNPs to be retained in the skin, using a model of human cell lines.