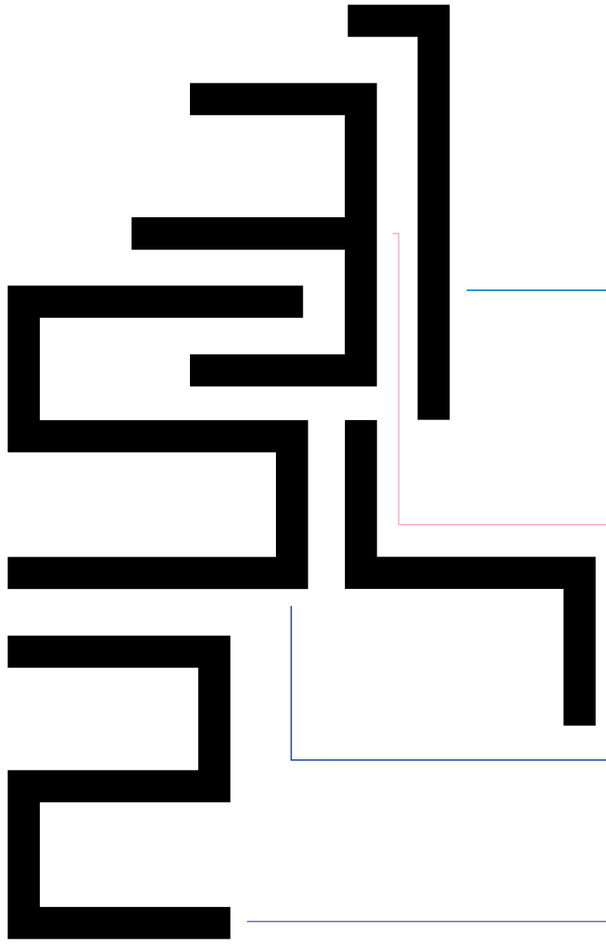
ANNUALREPORT2018

iMed. ULisboa



Foreword

message from the coordinator

CECÍLIA M. P. RODRIGUES
Coordinator, iMed.ULisboa

iMed.ULisboa fosters translational research, creates innovation in pharmaceutical and biomedical research and applies knowledge to the benefit of human health. Our approach spans scientific disciplines and takes a crosscutting, integrative view of biology, chemistry and pharmaceutical technology.

Many innovative ideas and powerful technologies are now fuelling breakthroughs in mechanistic biology and medicinal chemistry, which could potentially enable more effective searches of molecules and targets and accelerate success in drug discovery and development. However, such approaches also raise considerable conceptual, technical and organizational challenges. iMed.ULisboa aims to identify the approaches and technologies that could be implemented robustly, and critically analyse opportunities and challenges for their widespread application. We specifically build on enabling scientific platforms that enhance research inside and outside, providing opportunities to share our science, encouraging collaboration with academic and industry partners, and attracting emerging talents and young students. We want to continue valuing an environment that nurtures and rewards innovative research activities in translational science and technology dedicated to improving human health.

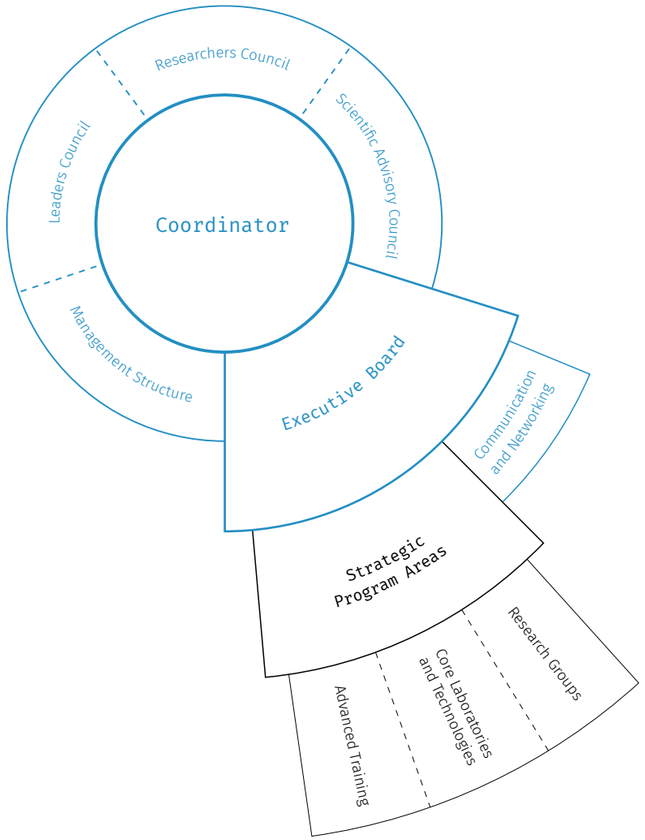
In 2019, we will assist to many other new developments such as the conclusion of the evaluation exercise of the research units, the consolidation of the individual and institutional support for scientific employment, the implementation of the collaborative laboratories, among others. iMed.ULisboa looks forward to contributing with coherence, planning and to the extent possible, stability to build an internationally competitive research community.

On behalf of iMed.ULisboa, I would like to thank everyone who has collaborated with us throughout this year. iMed.ULisboa has focused intensely on setting and refining research priorities, balancing our best science and unique ability to address unmet medical needs. Key ongoing mobilizing projects have been used as potential model approaches for shaping the research focus. iMed.ULisboa and its partners will maximize the efficiency with which research results and innovation are translated into applications, and provide tailored training and education, catalysing novel career paths and responding to challenges and promises of modern academic pharmaceutical sciences. We look forward to continuing joining forces together in 2019!

INTRODUCING IMED.ULISBOA

Organization and Structure .
Executive Board . Scientific Advisory
Board . Researchers and Students

Organization & Structure



Executive Board

This governing body is led by the coordinator and includes as members leaders of the four strategic program areas; ensures overall development and implementation of coordinated initiatives and activities from the strategic plan.

CECÍLIA M. P. RODRIGUES
Coordinator

JOÃO GONÇALVES
Drug Discovery Program Leader

RUI MOREIRA
Drug Design Program Leader

BEATRIZ SILVA LIMA
Drug Development Program Leader

FERNANDO FERNANDEZ-LLIMOS
Drug Usage Program Leader

Scientific Advisory Board

Independent eminent international scientists ensure that our strategic direction is in the best interest of science and society.

MARK MCALLISTER
Pfizer, UK

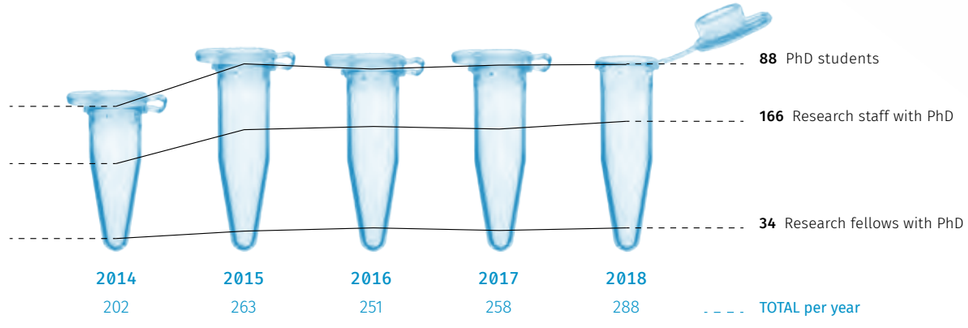
ANTONIO ZORZANO
University of Barcelona, Spain

STEPHEN CADDICK
University College London, UK

Researchers & Students

4 program groups

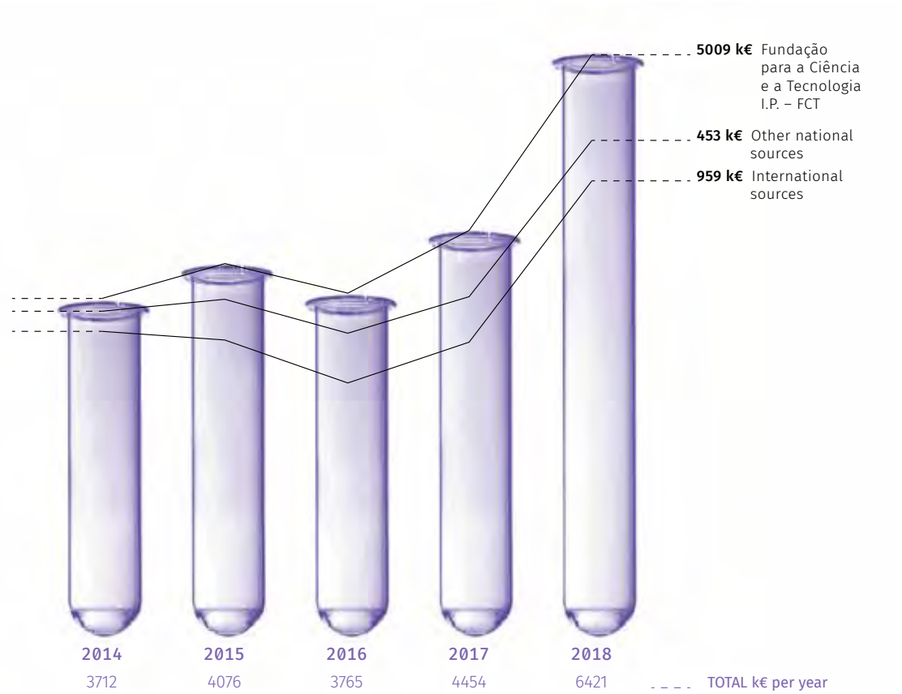
14 research groups



FACTS & NUMBERS

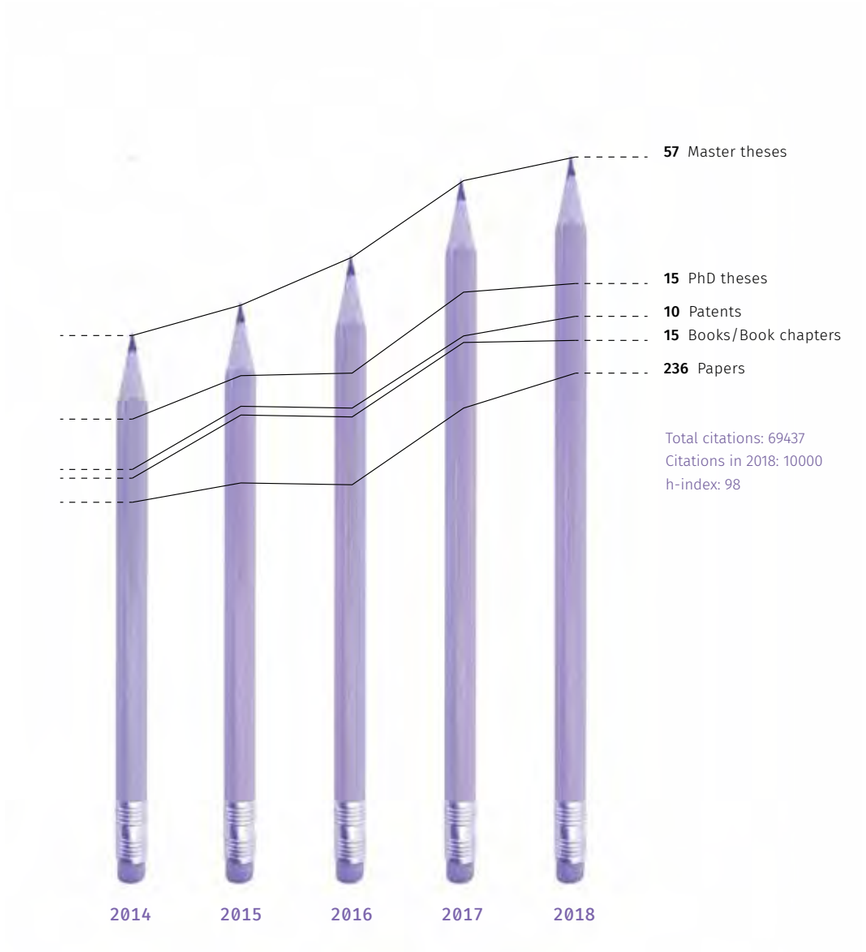
R&D Unit Funding . Scientific Communication .
Research Highlights . Patents .
Prizes and Recognitions . International
Projects . International Collaborations .
Organization of International Conferences

R&D Unit Funding



[Fundação para a Ciência e a Tecnologia – FCT] R&D Unit Pluriannual funding; projects; contracts of researchers with PhD; PhD, Post-doctoral or other fellowships.
[Other national sources] Funding received from participant or management institutions; public sources; companies, industry and other private sources.
[International sources] European Commission; companies, industry and other private sources.

Scientific Communication



Total citations: 69437
Citations in 2018: 10000
h-index: 98

Research Highlights

Unique type of aquaporin regulation controls body fat mass

Obesity is a major threat to global health and metabolically associated with glycerol homeostasis. Graça Soveral co-authors a study published in *Nature Communications* demonstrating that in human adipocytes, the decreased pH observed during lipolysis (fat burning) correlates with increased glycerol release and stimulation of aquaglyceroporin AQP10. The authors conclude that targeting the cytoplasmic gate to induce constitutive glycerol secretion may offer an attractive option for treating obesity and related complications.

Gotfryd K., **Mósca AF**, Missel JW, Truelsen S, Wang K, Spulber M, Krabbe S, Hélix-Nielsen C, Laforenza U, **Soveral G**, Pedersen PA, Gourdon P. Human adipose glycerol flux is regulated by a pH gate in AQP10. *Nature Commun* 2018; 9: 4749.

Combating tuberculosis

As tuberculosis (TB) remains one of the most deadliest diseases and currently ranks as the tenth leading cause of death worldwide, new approaches are urgently needed to combat this infectious disease and meet the World Health Organization target of ending TB in 2035. This first study published in *Nature Genetics* was aimed at addressing the gap between genotype and phenotypic drug resistance by using a Genome-Wide Association Study as well as state-of-the-art computational approaches. To date, this is the largest study of its kind including 6,465 clinical isolates from over 35 countries. This approach enabled the identification of a significant number of newly associated mutations which allows the inclusion of these mutations in established pipelines such as TB-Profiler, an online or locally deployable tool, also developed by this team for the rapid characterization of drug resistance from whole genome sequence data. New epistatic interactions likely related to mechanisms of drug resistance compensation were also identified and can now be evaluated as potentially new drug targets. The emergence of drug resistance is also approached under a different perspective in a second study published in *Science Advances*, which encompassed 1,669 M. tuberculosis isolates belonging to lineage 4. The latter has a wide distribution mostly driven by a therein demonstrated temporal relationship between European colonial expansion into Africa and the Americas. In this study associations between this lineage and drug resistance appear to be mostly restricted to local countries without significant cross-border transmission. Despite this, the iMed.ULisboa team has already detected cross-border drug resistant clusters across Portuguese-speaking countries through the CPLP-TB platform (http://cplp-tb.ff.ulisboa.pt), hosted and curated at iMed.ULisboa.

Coll F, Phelan J, Hill-Cawthorne GA, Nair M, Mallard K, Ali S, Abdallah A, Alghamdi S, Alsomali M, Ahmed A, Portelli S, Oppong Y, Alves A, Bessa T, Campino S, Caws M, Chatterjee A, Crampin A, Dheda K, Furnham N, Glynn J, Grandjean L, Há D, Hasan R, Hasan Z, Hibberd M, Joloba M, Jones-López, Matsumoto T, Miranda A, Moore D, Morcillo N, Panaiotov S, Parkhill J, **Portugal I**, Penha C, **Perdigão J**, Rchiad Z, Robledo J, Sheen P, Sesha N, Sirgel F, Sola C, Sousa E, Streicher E, Viveiros M, Warren R, McNerney R, Pain A, Clark T. Genome-wide analysis of multi- and extensively drug-resistant Mycobacterium tuberculosis. *Nat Genet* 2018; 50: 307-316.

Brynilsrud O, Pepperell C, Suffys P, Grandjean L, Monteserin J, Debech N, Bohlin J, Alfsnes K, Petterson J, Kirkleite I, Fandinho F, da Silva M, **Perdigão J**, **Portugal I**, Viveiros M, Clark T, Caws M, Dunstan S, Thai P, Lopez B, Ritacco V, Kitchen A, Brown T, van Soolingen D, O'neill M, Holt K, Feil E, Mathema B, Balloux F, Eldholm V. Global expansion of *Mycobacterium tuberculosis* Lineage 4 shaped by colonial migration and local adaptation. *Sci Adv* 2018 4(10):eaat5869

miR-21 regulation of necroptosis in cholestasis

Cholestasis is a pathological condition characterized by disruption of bile flow, resulting in liver damage, inflammation, progression to fibrosis and, ultimately, cirrhosis and premature death. Liver transplantation remains one of the few available options for these patients. This calls for novel therapeutic approaches, based in a better understanding of molecular, cellular and biochemical mechanisms underlying pathogenesis of cholestasis. Afonso and colleagues reported in *Cell Death and Differentiation* that miR-21 is overexpressed in the liver of patients with primary biliary cholangitis, associated with cholestasis and often end-stage liver disease. Further, the hepatic expression of miR-21 augmented in an animal model of cholestasis and biliary fibrosis, while miR-21 ablation ameliorated liver injury, necroptosis, oxidative stress and fibrosis. Deletion of miR-21 also provided an improved adaptive response to bile acids homeostasis. Finally, *in vitro* studies, further addressed a novel functional link between miR-21 and liver injury. Inhibition of miR-21 may arise as a promising approach to target multiple components of cholestatic liver disease. This study was conducted by an international multidisciplinary team led by iMed.ULisboa.

Afonso MB, **Rodrigues PM**, **Simão AL**, **Gaspar MM**, Carvalho T, Borralho P, Banales JM, **Castro RE**, **Rodrigues CMP**. miRNA-21 ablation protects against liver injury and necroptosis in cholestasis. *Cell Death Differ* 2018; 25: 857-872.

Global Burden of Disease study

Nuno Taveira, leader of the HIV Evolution, Epidemiology and Prevention Group at iMed.ULisboa collaborates in the Global Burden of Disease (GBD) study 2017 and co-authors several papers just published in *Lancet*. This year GBD, with results described in eight scientific papers, covers population and fertility, mortality and life expectancy, causes of death and years of healthy life lost, years lived with disability, overall burden of disease, risk factors, and the chances of each nation meeting 41 of the health-related indicators that are part of the United Nations Sustainable Development Goals (SDGs) for 2030. Some highlights from GBD 2017 show that non-communicable diseases accounted for 73% of all global deaths in 2017, with over half of all deaths (28,8 million) attributable to just four risk factors: high blood pressure, smoking, high blood glucose, and high body-mass index. Further, obesity prevalence has risen in almost every country in the world, leading to more than a million deaths from type 2 diabetes. Interestingly, estimates of health worker density show only half of all countries had the health-care workers required to deliver quality health care (estimated at 30 physicians, 100 nurses or midwives, and 5 pharmacists per 10,000 people). Perhaps related with this, GBD 2017 estimates that no country is on track to meet all of WHO's health-related Sustainable Development Goals by 2030.

GBD 2017 SDG Collaborators. Measuring progress from 1990 to 2017 and projecting attainment to 2030 of the health-related Sustainable Development Goals for 195 countries and territories: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 2091-2138.

Patents

Constantino L, Anes E, Simões M, Valente E (2018). **Pró-fármacos de ácidos orgânicos e composições farmacêuticas contendo os referidos pró-fármacos**. Patent Application No. PT 103495B.

Fanning S, Anes J, Rocha A, Afonso CAM, Lourenço NMT (2018). **Antimicrobial Compounds**. Patent Application No. UK 1804628.4.

Ferrara MA, Perales J, Rocha SLG, Girão LFC, Bom EPS, Corvo ML, Carvalheiro MC, Martins MBAF (2018). Patent Application No. BR 102018 069598 3.

Finch MD, Low W, Steer C, Munshi CB, Rodrigues CMP, Lucas de Oliveira SD (2018). **Deuterated Bile Acids**. Publication number US20180030084A1.

Finch M, Munshi CB, Rodrigues CMP, de Oliveira SDL (2018). **Fluorinated and Alkylated Bile Acids**. US Patent Application 15/556, 768, US20180044373A1.

Lourenço NT, Sobral L, Antunes R, Santos MMM, Espadinha M (2018). **Process for the preparation of umeclidinium bromide**. PCT/GB2017/053396, WO2018087561A1.

Melo T, Santos B, Pibnatelli R, Bartolo I, Taveira N (2018). **Novel spiro-lactam compounds, process and uses thereof.** PCT Application No. PCT/IB2018/053357.

Russo R, Padanha RI, Gois PMP (2018). **On the use of 3-Hydroxy Quinolinones as Boron Hot-Spot for the preparation of protein conjugates, their uses and methods for their preparation.** Patent Application No. PT 20181000078171 (INPI).

Satchi-Fainaro R, Florindo H, Conniot J, Scomparin A (2018). US Provisional Patent Application No. 62/785,715.

Vitorino CS, Pais AACC, Sousa JJ, Ferreira AC, Fortuna AC, Cova, TF, Nunes SC, Silva JF, Torres JD, Miranda AA, Almeida AJ, Mendes MM, Gonçalves LMD (2018). **Dual nanostructured lipid carrier as a multifunctional platform f or brain tumor therapy.** Patent Application No. PT 20181000070606.

Prizes and Recognitions

ANDRÉ SIMÃO. Best Abstract Presentation Prize at UEG Week 2018

MARTA B. AFONSO. EASL Mentorship Award 2018

MARIA JOÃO CATALÃO. ESCMID Research Grant

ALEXANDRA BRITO. ImmunoTools Special Award 2018

ELSA ANES, DAVID PIRES and **NUNO CARMO.** Janssen Prize for Innovation 2018

BRUNO SEPODES. Vice-President Committee for Medicinal Products for Human Use, EMA

BRUNO SEPODES. EURORDIS Black Pearl Award 2018

RICARDO FERREIRA. Best Doctoral Thesis in Medicinal Chemistry 2018

SUSANA SOLÁ. Honourable Mention at 10th Edition of Crioestaminal Award

RUI CASTRO. Biomedicine and Health Research Project Grant by Fundação La Caixa and FCT 2018

International Projects

Innovative Medicines Initiative (IMI)
LITMUS – Identification and validation of biomarkers for NASH and across the spectrum of NAFLD
Participant: Cecília M. P. Rodrigues

LIFE – Environment and Resource Efficiency
Improving current barriers for controlling pharmaceutical compounds in urban wastewater treatment plants
Participant: Cristina Almeida

Research Scholars Program in Liver Diseases – Gilead Sciences International
Role of mitofusin 2 in non-alcoholic fatty liver disease and targeting by miRNAs
Principal Investigator: Rui Castro

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Research Grant 2018
Decoding the peptidoglycan patterns associated with beta-lactams hypersusceptibility in drug-resistant Mycobacterium tuberculosis
Principal Investigator: Maria João Catalão

"La Caixa" Foundation – Health Research 2017
Exosomal fat liver axis in non-alcoholic fatty liver disease: function and targeting
Principal Investigator: Rui Castro

Cooperation Programme INTERREG V-A España-Portugal (POCTEP)
MicroRNAs as diagnostic biomarkers in liver damage evolution and their role in disease in elderly patients
Participant: Rui Castro

Water Joint Programing Initiative (WaterWorks)
Bioorganic novel approaches for food processing waste water treatment and valorization: Lupanine case study
Principal Investigator: Carlos Afonso

ERANet JPco-fuND EU Joint Programme – Neurodegenerative Disease Research
Generation of Improved cellular and animal models for identification of disease phenotype and new therapeutic targets of Alzheimer's Disease.
Participant: Dora Brites

ERANet-LAC Latin America Caribbean and European Union
Integrated valorization of lignocellulosic agroindustrial waste to furan based building blocks
Participant: Carlos Afonso

ERANet EuroNanoMed2 European Innovative Research & Technological Development Projects in Nanomedicine
(Nano) systems with active targeting to sensitize colorectal cancer stem cells to antitumoral treatment (Target4Cancers).
Participant: Mafalda Videira

ERANet EuroNanoMed2 European Innovative Research & Technological Development Projects in Nanomedicine
Modulation of melanoma-stroma interactions using a rationally designed nanomedicine combining BRAFi-, MEKi- and immunotherapies
Participant: Helena Florindo

ERANet EuroNanoMed2 European Innovative Research & Technological Development Projects in Nanomedicine
Nanotechnology based immunotherapy for glioblastoma
Participant: Mafalda Videira

Grant for Innovation – Merck KGaA
Targeting multiple sclerosis immune-and psycho-pathophysiology by modulation of neuroinflammation
Principal Investigator: Adelaide Fernandes

Aga Khan Development Network. Portugal Collaborative Research Network in Portuguese speaking countries in Africa
Epidemiology, drug resistance and pathogenesis of HIV in Cape Verde: the Cape Verde HIV Cohort
Principal Investigator: Nuno Taveira

European & Developing Countries Clinical Trials Partnership
Neonatal HIV early infant diagnosis (EID) versus standard of care EID – Impact on inFant hEalth (LIFE)
Participant: Nuno Taveira

Brainvectis
CYP46A1 as a new therapeutic target in Niemann-Pick type C disease
Principal Investigator: Elsa Rodrigues

Intercept Pharmaceuticals, Inc.
Targeting the NAFLD-HCC continuum with dual FXR/TGR5 agonists and miRNAs
Principal Investigator: Rui Castro

Academic Drug Discovery Consortium – AstraZeneca
High throughput screening with AstraZeneca's compound library
Principal Investigator: Cecília M. P. Rodrigues

Marie Sklodowska-Curie Innovative Training Networks
A training network for the chemical site-selective modification of proteins: Preparation of the next-generation of therapeutic chemically-defined protein conjugates
Participant: Pedro Góis

Marie Sklodowska-Curie Innovative Training Networks
Bioenergetic Remodeling in the Pathophysiology and Treatment of Non-Alcoholic Fatty Liver Disease
Participant: Cecília M. P. Rodrigues

Marie Sklodowska-Curie Research and Innovation Staff Exchange
Non-invasive Profiling of Mitochondrial Function in Non-Alcoholic Fatty Liver Disease
Participant: Cecília M. P. Rodrigues

International Collaborations

Research Institutes and Hospitals

- Albert Einstein College of Medicine, NY, USA
- Aga Khan Development Network (AKDN) – Portugal Collaborative Research Network in Portuguese speaking countries in Africa
- Center for Research in Sustainable Chemistry, Huelva, Spain
- Institute of Biology and Chemistry of Proteins, Lyon, France
- Institute of Chemistry for Life and Health Sciences, Paris, France
- Institute of Pharmacology and Structural Biology, Toulouse, France
- Institut Parisien de Chimie Moléculaire, Paris, France
- Karolinska Institutet, Sweden
- National Institute of Health, Mozambique
- Physiology and Pathology of the Neurovascular Unit, Biological Research Centre, Hungarian Academy of Sciences, Szeged, Hungary.
- Hospital Saint Louis, Université Paris Diderot, Paris, France
- The Francis Crick Institute, London, UK
- The Institute of Health Metrics and Evaluation, Washington, USA
- Weizmann Institute of Science, Rehovot, Israel

Pharmaceutical Industry

- AstraZeneca
- Hovione Farmaciência
- Intercept Pharmaceuticals
- Merck
- Laboratório Edol – Produtos Farmacêuticos, S.A., Portugal

Universities

- Cardiff University, Wales
- Charité-Universitätsmedizin Berlin, Germany
- College of Pharmacy, University of Michigan, USA
- Emory University School of Medicine, Atlanta, USA
- Faculty of Medicine, University of Szeged, Dóm, Hungary
- Faculty of Natural Sciences and Mathematics, Pedagogical University, Maputo, Mozambique

Organization of International Conferences

XII Spanish-Portuguese Conference on Controlled Drug Delivery, Tailoring drug delivery systems to the patients' needs
January 2018, Coimbra, Portugal
Manuela Gaspar, member of the Organizing Committee

245th American Chemical Society National Meeting I Symposium "Boron in Medicinal Chemistry and Chemical Biology"
March 2018, New Orleans, USA
Rui Moreira, member of the Organizing Committee

53rd International Liver Congress, European Association for the Study of the Liver I Basic Science Seminar "Targetable pathways in liver disease"
April 2018, Paris, France
Cecília Rodrigues, member of the Organizing Committee

9th Pan-European Process Analytical Technology Science Conference I EuPAT9
May 2018, Manchester, UK
João Lopes, member of the Organizing Committee

World Meeting of the International Society for Free Radical Research
June 2018, Lisbon, Portugal
Graça Soveral, member of the Organizing Committee

XIV European Meeting on Glial Cells in Health and Disease I Symposium "Role of microglia in neurodegeneration"
July 2018, Porto, Portugal
Dora Brites, member of the Organizing Committee

European School of Medicinal Chemistry I XXXVIII Advanced Course of Medicinal Chemistry
July 2018, Urbino, Italy
Rui Moreira, member of the Organizing Committee

46th Congress of the International Society for the History of Medicine
September 2018, Lisbon, Portugal
Helena Rebelo de Andrade, member of the Organizing Committee

RESEARCH AREAS

Drug Discovery . Cellular Function and Therapeutic Targeting . Host-Pathogen Interactions . Metabolism and Genetics . Molecular Microbiology and Biotechnology . Neuron-Glia Biology in Health and Disease . Drug Design . Bioorganic Chemistry . Medicinal Chemistry . Natural Products Chemistry . Drug Development . Chemical Biology and Toxicology . BioNanoSciences - Drug Delivery and Immunotherapy . Nanostructured Systems for Overcoming Biological Barriers . Pharmacological and Regulatory Sciences . Drug Usage . HIV Evolution, Epidemiology and Prevention . Pharmacoepidemiology and Social Pharmacy

Drug Discovery

JOÃO GONÇALVES
Programme Leader

CECÍLIA M. P. RODRIGUES

PhD (1996) in Pharmacy (Biochemistry), Universidade de Lisboa. Postdoctoral research at University of Minnesota, USA. Full Professor, Biochemistry and Human Biology, Faculdade de Farmácia, Universidade de Lisboa.

Cellular Function and Therapeutic Targeting

ELSA ANES

PhD (1998) in Pharmacy (Microbiology), Universidade de Lisboa. Post-Doctoral Fellow, EMBL, Heidelberg, Germany. Associate Professor, Microbiology and Immunology, Faculdade de Farmácia, Universidade de Lisboa.

Host-Pathogen Interactions

PAULA LEANDRO

PhD (2001) in Pharmacy (Biochemistry), Universidade de Lisboa. Assistant Professor, Biochemistry and Human Biology, Faculdade de Farmácia, Universidade de Lisboa.

Metabolism and Genetics

JOÃO GONÇALVES

PhD (1996) in Pharmacy (Microbiology), Universidade de Lisboa. Post-Doctoral Fellow, Harvard Medical School and Scripps Research Institute, USA. Associate Professor, Microbiology and Immunology, Faculdade de Farmácia, Universidade de Lisboa.

Molecular Microbiology and Biotechnology

DORA BRITES

PhD (1988) in Pharmacy (Biochemistry), Universidade de Lisboa. Investigator Coordinator, Biochemistry and Human Biology Faculdade de Farmácia, Universidade de Lisboa.

Neuron Glia Biology in Health and Disease

iMed.ULisboa encourages efforts to study the interaction of various diseases and conditions. The Drug Discovery Programme strives to forge new connections across research disciplines to advance understanding of molecular mechanisms and discovery of treatments for cancer, infectious diseases, neurodegenerative and inflammatory diseases.

To speed the movement of discoveries from the lab to the clinic, iMed.ULisboa will also accelerate and expand individualized ways of managing and preventing disease, such as pharmacogenomics and biomarkers. iMed.ULisboa will also support collaborations with "big data" specialists aimed at accessing, managing, analysing, integrating, and mining the huge amounts of data, being generated by iMed.ULisboa scientists.

To incorporate iMed.ULisboa vision into the Drug Discovery, our broad strategic lines are:

1. Genetic, molecular and cellular research to find new therapeutic interventions in cancer and metabolic diseases.
Genetic, cellular and metabolic approaches will identify key signalling and metabolic pathways that can be targeted with high-throughput drug screening and protein engineering and biochemistry, or that can give rise to better biomarkers of disease.

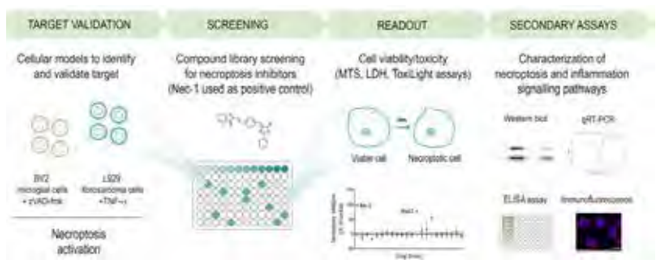
2. Neurobiology research to dissect new treatment strategies in neurodegenerative and age-related disorders.
The impact of neuron-glia-vascular interactions is of crucial value to provide new answers to neurodegenerative diseases. We aim to discover innovative strategies of understanding and ameliorating neurological disorders and aging.

3. Host-pathogen interaction to exploit infectious agents as a source of drug targets.
The molecular biology and epidemiology of mycobacteria, virus and phages aims to realise how these agents interact with host and how they explore their structural peculiarities to optimal replication. With this understanding we aim to develop novel anti-infective strategies and new biopharmaceutical drugs.

The Drug Discovery Programme drives a culture of technology transfer to hospitals, biotech and pharma industry. Funding for research is supported by competitive national and international sources both from public (H2020, IMI and FCT) and private institutions (Pharma and non-profit organizations) reaching more than 8 M€ in 2018 ongoing projects. As result, the track record during 2013-2018 shows also impactful publications and respectful international recognition of our science. Given the attractiveness of Drug Discovery areas to young scientists, ca. 50 PhD students finished their graduation during 2013-2018 and equivalent numbers are currently enrolled in the PhD Programme in Pharmacy, based in FCT and Marie Currie funded training in Medicines and Pharmaceutical Innovation, Medical Biochemistry and Biophysics, and Advanced Integrated Microsystems. Specific scientific platforms provide access to state-of-the-art facilities capable of performing protein, cellular and animal studies at single and high-throughput assessment.

Cellular Function and Therapeutic Targeting

CECÍLIA M. P. RODRIGUES
Group Leader



Workflow of the cell-based screening for new necroptosis inhibitors. A small library of compounds was screened for necroptosis inhibition using BV2 microglial and L929 fibrosarcoma cells, upon necroptosis activation by pan-caspase inhibitor zVAD-fmk or TNF-α, respectively. Secondary assays were performed to characterise the mechanisms of action of selected hits, namely necroptosis and inflammatory signalling pathways. From Oliveira *et al. Cell Death Disease* 2018; 9: 903.

KEYWORDS Molecular targets, biomarkers and therapeutics; Signalling pathways of cell proliferation, differentiation and death; Cell systems, murine models and human biological samples; Liver, gut and brain diseases.

ACHIEVEMENTS Hepatic fibrosis is the wound-healing response of the liver to many causes of chronic injury, of which non-alcoholic steatohepatitis (NASH) is the most common. Hepatocellular carcinoma (HCC) is rising in incidence worldwide and is a major cause of liver-related death in patients with cirrhosis. The transition from benign steatosis to NASH and HCC occurs through yet unclear mechanisms. A lack of tractable non-invasive biomarkers is hampering the diagnosis, risk stratification and monitoring of patients, with many remaining undiagnosed and presenting with advanced disease. We have recently profiled miRNAs and the microbiome in murine and human tissues and identified several changes with disease. As liver disease progresses and cell death and inflammation settle, miRNA profiles change, intestinal microbiota modifies, aggravating liver disease and, eventually, promoting tumour development. We are currently working on developing consensus on preclinical models of NAFLD/NASH and then back-translate biomarkers for validation.

The lack of biomarkers has also hampered drug development and conduct of clinical trials. We have shown that liver damage and RIPK3-dependent necroptosis are prevented in bile duct-ligated *miR-21* KO mice, via specific targets. More recently, we found that both miR-21 and RIPK3 ablation prevent long-term inflammation, fibrosis, proliferation and resistance to cell death, entailing therapeutic potential. Phenotypic high throughput screening is finding promising molecules that will soon be tested further in relevant preclinical models of disease. The development of microfluidic biochips to support the assessment of drug efficiency and toxicity will also be pursued in collaborative studies.

Consistent with the growing role that cell metabolism may play in neurodegeneration, we have used *in vitro* and *in vivo* experimental models and strategies to show that mitoprotective targeting attenuates neurodegeneration and influences lineage stem cell fate decision. The investigation of the gut-brain axis may bring some clarity to the crucial role of organ-to-organ communication in degenerative versus regenerative processes. We have also further dissected the molecular mechanisms involved in restoration of brain cholesterol homeostasis as a therapeutic strategy to treat neurodegenerative disorders.

SELECTED REFERENCES Afonso MB, Rodrigues PM, Simão A, Gaspar M, Carvalho T, Nunes P, Banales J, Castro RE, Rodrigues CM. miRNA-21 is overexpressed in primary biliary cholangitis and contributes to liver injury and necroptosis in bile duct-ligated mice. *Cell Death Differ*. 2018; 25: 857-872.

Soares R, Ribeiro FF, Xapelli S, Genebra T, Ribeiro MF, Sebastião AM, Rodrigues CMP, Solá. Tauroursodeoxycholic acid enhances mitochondrial biogenesis, neural stem cell pool, and early neurogenesis in adult rats. *Mol Neurobiol*. 2018; 55: 3725-3738.

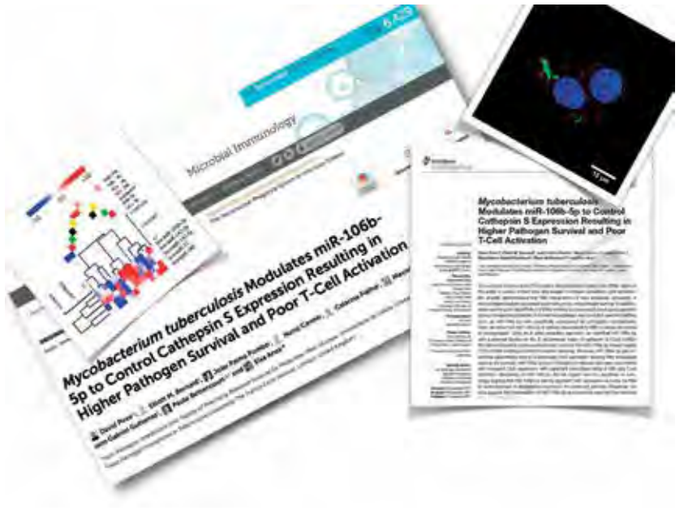
Rosa AI, Duarte-Silva S, Silva-Fernandes A, Nunes MJ, Neves Carvalho A, Rodrigues E, Gama MJ, Rodrigues CMP, Maciel P, Castro-Caldas M. Tauroursodeoxycholic acid improves motor symptoms in a mouse model of Parkinson's disease. *Mol Neurobiol*. 2018; 55: 9139-9155.

Mueller M, Castro RE, Thorell A, Marschall H-U, Auer N, Herac M, Rodrigues CM, Trauner M. Ursodeoxycholic acid: Effects on hepatic unfolded protein response, apoptosis and oxidative stress in morbidly obese patients. *Liver Int*. 2018; 38: 523-531.

Rodrigues PM, Afonso MB, Simão AL, Carvalho CC, Trindade A, Duarte A, Borralho PM, Machado MV, Cortez-Pinto H, Rodrigues CMP, Castro RE. miR-21 ablation and obeticholic acid ameliorate non-alcoholic steatohepatitis in mice. *Cell Death Dis*. 2017; 8: e2748.

Host-Pathogen Interactions

ELSA ANES
Group Leader



Pires et al. Front Immunol 2017; 8:1819.

KEYWORDS Tuberculosis; HIV; co-infection; *Helicobacter pylori*; Influenza virus; drug resistance.

ACHIEVEMENTS Our research group develops several lines of work for which funding has been obtained in 2018 through the funds of Portugal 2020 and FCT for a total of 6 projects and a ESCMID Research grant.

We started to explore *Mycobacterium tuberculosis* (Mtb), HIV mono-infections and the co-infection with the purpose of understanding the global transcriptome for cathepsins. Our goal is to identify new biomarkers for disease progression and pathogen clearance. In addition we found cathepsins manipulated by microRNAs during infection favouring pathogen survival. In the case of miR-106b, we were able to revert pathogen effect during infection and increase cathepsin S activity improving the macrophage killing ability and antigen presentation. This work was awarded with the Jansen Innovation Prize in infection 2018.

The group is investigating the association between HIV to neurodegenerative disorders. In HIV-neuronal cells interaction we demonstrated that, although microglia shows low levels of CD4 expression and astrocytes are CD4-negative, both cells were infected by HIV *in vitro*. We hypothesize that extracellular membrane vesicles mainly mediate the infection of microglia and particularly astrocytes.

Aiming to identify putative antiviral target regions within the NS1 influenza protein and to prioritize new compounds for the design of NS1 inhibitors for influenza A viruses the team members identified seventeen top-ranked hot spots for drug targeting. By studying the selective pressure acting on human influenza neuraminidase we were able to: ‹1› uncover a potential role of positive selection in the low-level and locally variable spread of A(H1N1)pdm09-H275Y drug-resistant viruses observed in the community; ‹2› detect a potential higher risk of spread of a synergistic AH1N1pdm09 drug-resistant or a AH1N1pdm09 or B/Victoria variant exhibiting reduced inhibition *in vitro*; and ‹3› identify 6 regions within the catalytic domain as potential new druggable hotspots.

For *Helicobacter pylori* in a time of continuous growing number of genomes available, we are searching for tools to explore genomes for prophage presence, or other mobile genetic elements and virulence factors, as well as to study their evolution and phylogeography.

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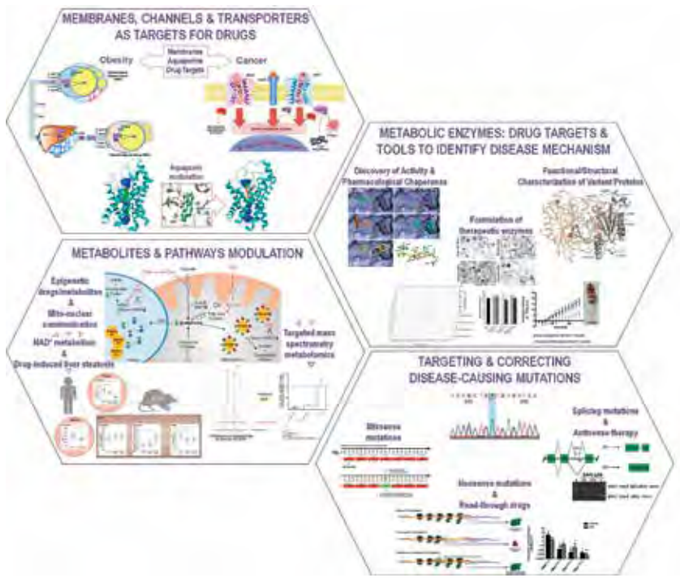
Metabolism and Genetics

PAULA LEANDRO
Group Leader



General representation of research activities.

KEYWORDS Genetic Orphan Diseases; Diabetes, Obesity & Cancer; Water & Energy Homeostasis; Gene Mutations & Personalized Therapies.

ACHIEVEMENTS The Metabolism and Genetics group has been carrying out research on the field of Genetic Rare Diseases, Diabetes, Obesity, Cardiovascular Disease (CVD) and Liver Disease, aiming to identify molecular mechanisms of pathogenesis ultimately leading to the discovery of disease biomarkers, identification of drug targets and development of new therapeutic approaches.

Major achievements: ‹1› Elucidation, at the structural level, of the allosteric response of human phenylalanine hydroxylase by SAXS thus opening new opportunities to develop allosteric drugs for the treatment of the Rare Genetic Disease Genetic Phenylketonuria; ‹2› Functional/structural characterization of the most common variant protein in MCAD deficiency using *in vitro* and *in silico* (molecular dynamic simulations) studies allowing the rational design of protein stabilizers aiming at the development of pharmacological strategies for this Rare Genetic Disease; ‹3› Development of an animal model to study the hypomethylation driven-atherosclerosis and its correspondent epigenetic signature – a microimaging technique by 14T-MR (Magnetic Resonance) was already used to allowing obtaining an accurate characterization of SAH-induced arteriosclerotic plaque extent; ‹4› Release of the crystal structure of human AQP10 determined at 2.3 Å resolution and identification of a unique type of aquaporin regulation important for controlling body fat mass. Disclosure of the mechanisms involved in the regulation of human AQP7 by acidification, which may help the design of selective modulators targeting obesity and aquaglyceroporin-related disorders. Characterization of aquaporin differential expression in white (WAT) and brown (BAT) adipose tissue and their modulation by dietary n-3 long-chain PUFA (EPA and DHA); ‹5› Identification of disease-causing mutations in patients carrying specific Genetic Rare Diseases thus allowing selection/development of the most effective therapeutic approach (mutation-based therapy; personalized medicines); ‹6› Novel insights on epigenetic modulation, metabolite signaling and the direct or indirect effects on prime targets of mitochondrial energy metabolism: CPT1A and PDH complex. The acetylation-mediated regulation of both enzymatic activities and their expression pattern were elucidated using liver tissues of Wistar rats treated *in vivo* with a lysine deacetylase inhibitor (KDACi). Drug-effects on modulation of acetyl-CoA availability and respective subcellular compartmentalization were explored, with impact on mitochondrial.

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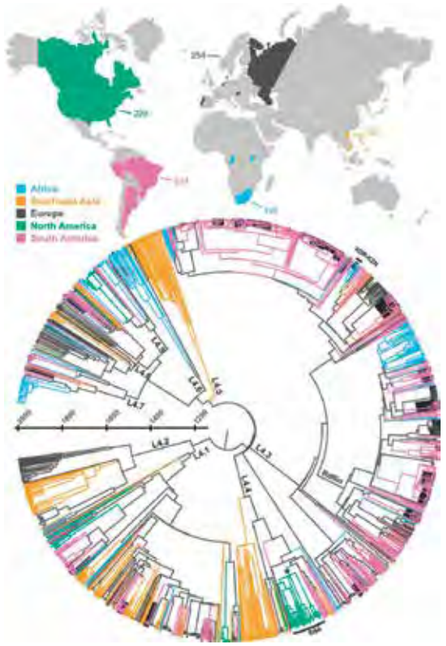
Molecular Microbiology and Biotechnology

JOÃO GONÇALVES
Group Leader



From Brynilsrud *et al. Sci Adv.* 2018.

KEYWORDS Antibiotic resistance; Enzybiotics; Endolysin Engineering; Antibody Engineering; HIV; Cancer.

ACHIEVEMENTS We aim to focus on molecular mechanisms underlying, promoting and maintaining infectious diseases, how pathogens evolve to other forms of virulence and drug resistance, in order to develop molecular strategies to control microbial infection.

To achieve the proposed goals, the research of our group was oriented: ‹1› To understand the mode of action and regulation of the lysis functions that bacteriophages employ to destroy the bacterial cell envelope; ‹2› To study mycobacteria-mycobacteriophage interactions, particularly the last step of a phage infection, which results in host lysis; ‹3› To study the genetic diversity of circulating *Mycobacterium tuberculosis* strains in Portugal and Portuguese-speaking countries; ‹4› To engineer chimeric antigen receptor T cells capable to detect and eliminate HIV latent cells; ‹5› Development of antibody derived biopharmaceuticals against cancer specific antigens to improve cell killing by toxin and cytotoxic drug delivery.

To understand the mode of action and regulation of the lysis functions that bacteriophages employ to destroy the bacterial cell envelope we have focused our attention in bacteriophage SPP1 and mycobacteriophages. We probed the function of the two holin-like proteins of bacteriophage SPP1. To step forward in studying mycobacteria-mycobacteriophage interactions, our group showed that bacteriophages that infect mycobacteria encode lysis protein that specifically target components of the mycobacteria cell wall.

The main contributions arrived in areas of activity also rely on the study of the molecular determinants of drug resistance and its association with specific phylohenetic clades; We helped to characterise the methylome across the 4 major lineages of M. tuberculosis and 2 lineages of M. africanum, the leading causes of tuberculosis disease in humans. Insights into lineage-specific methylomes will further elucidate underlying biological mechanisms and other important phenotypes of the epi-genome.

To develop molecular strategies to control viral infections we engineered new antibody derived proteins which are potent fusion inhibitor of HIV infection. These strategies were based on a rational strategy for synthetic antibody library construction. This molecular strategy provided new insights into engineering strategies for antibodies against new therapeutic targets in oncology (nucleolin) and the development of novel immunotoxins.

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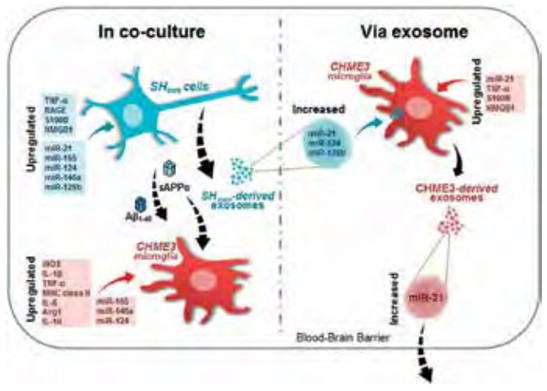
Neuron Glia Biology in Health and Disease

DORA BRITES
Group Leader



From Fernandes *et al. Biochimie* 2018.

KEYWORDS Advances in disease modelling; Blood-brain barrier across; Small extracellular vesicle; Glial cell activation; Inflammatory-associated miRNAs; Neurodegeneration and Neuroprotection.

ACHIEVEMENTS The group developed studies focused on their main topics to show that: ‹1› Cortical astrocytes isolated from 7-day old mice with mutated SOD1 (ALS model), replicate miRNA-146a deficit, as well as the upregulated HMGB1, S100B and Cx-43 and the decreased GLT-1 and GFAP, the aberrant glial markers found in the symptomatic stage. The study highlighted that upregulation of miRNA-146 in cortical astrocytes should be tested to recover their neuroprotective function (ongoing studies); ‹2› Depressed general inflammatory markers precede the disease onset in the ALS model with the upregulation of mediators of neuroinflammation and astrogliosis thereafter. Early (presymptomatic stage) and sustained markers (symptomatic stage) of glia deregulation in the spinal cord of the ALS model are the downregulation of MFG-E8, Arginase 1 and GFAP, together with the upregulation of miRNA-155. Current studies use antago-miRNA-155 in microglia to stop neuroinflammation; ‹3› APP695-Swedish mutant human neurons (AD model) show upregulated inflammatory mediators and increased secretion of Aβ1-40 that is cleared by human microglia with pro-/anti-inflammatory phenotypes and dysregulated miRNA-155/miRNA-146a/miRNA-124 when in coculture, and before acquiring senescent markers. These miRNAs, together with that of miRNA-21/miRNA-125b, were also found upregulated in the mutated neurons and transferred into small extracellular vesicles (sEVs). When collected by microglia these sEVs are degraded by lysosomes and lead to upregulation of S100B, HMGB1, TNF-α and miRNA-21, which is shuttled in microglia-derived EVs; ‹4› Increased levels of S100B in a perinatal model lead to a delay in oligodendrocyte differentiation, interfere in the myelinating process, promote astrogliosis, activate inflammatory signalling pathways and impair neuronal integrity, effects that were all prevented by RAGE antagonist. Findings highlight the harmful effects of S100B and that S100B-RAGE interaction may constitute a therapeutic strategy during neurodevelopment; ‹5› Polyphenols are able to be transported across the blood-brain barrier and have great promise as neuroprotective and anti-inflammatory compounds by attenuating oxidative stress and microglia activation, even when digested. Functional enrichment analysis indicate that they act on the cell cycle control of chromosomal replication, mTOR signaling, unfolded protein response pathway, in which the upregulated ATF4 seems to be the major regulatory pathway for neuroprotection.

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Drug Design

RUI MOREIRA
Programme Leader

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Medicinal Chemistry

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Natural Products Chemistry

The Drug Design Programme offers a chemistry-centred platform oriented to the discovery of biologically active chemical entities that target specific proteins or nucleic acid structures, with the ultimate goal of optimizing their therapeutic properties and value. Working in concert with other groups at iMed.ULisboa, Drug Design researchers develop solutions for cancer, infectious diseases and neurological disorders. The broad strategic lines that intersect all Drug Design groups are:

1. Innovative chemistry for innovative drugs

The development of bio-inspired and sustainable synthetic methodologies for the preparation of small molecule modulators of proteins identified as key therapeutic targets of important diseases is core to this programme, and one of the cornerstones of our technology transfer platform.

2. Tools for chemical biology, biotherapeutics & drug targeting

We provide unique chemistry-led solutions to manipulate molecules in order to interrogate and intervene in biological systems. This includes the development of probes to decipher the complex machinery of the proteome of diseases and to identify targets of therapeutic value. Cell-targeting is also addressed, e.g. by developing synthetic methods to modify a broad range of proteins and to construct therapeutically useful bioconjugates, or by using prodrug chemistry to develop site-specific drug delivery systems.

3. Medicinal chemistry solutions for lead generation

Our work focus on the druggability of protein and protein-protein interactions within multi-subunit protein complexes through innovative use of synergic computer aided drug design and synthetic approaches campaigns to identify new hits and optimize more effective leads that can modulate important cellular responses in cancer, infectious and neurodegenerative disorders, bringing hope to future cures.

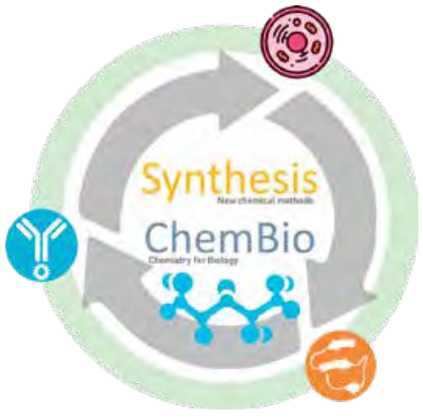
4. Natural products for drug discovery

Natural products remain an invaluable source of therapeutic agents. The Drug Design groups are committed in identifying novel chemotypes from natural sources and to develop new synthetic methods for the valorisation of natural resources.

Entrepreneurship is a hallmark of programme, with out-of-the-box solutions and methodologies contributing significantly to the patents portfolio of iMed.ULisboa. Training new generations of innovative scientists is also at the core of our mission. With stringent criteria of selection, we recruit the best students for the PhD Programme in Pharmacy, based in FCT and Marie Curie funded Medicinal Chemistry training. The required state-of-the-art facilities are in place to perform high-level computational studies, chemical synthesis, isolation and purification of compounds from natural sources, production of protein conjugates, and preclinical ADME studies.

Bioorganic Chemistry

PEDRO M. P. GÓIS
Group Leader



General representation of research activities.

KEYWORDS Synthesis; sustainable chemistry; chemical biology.

ACHIEVEMENTS In the past year, the Bioorganic group focused in the development of chemical methods to empower the discovery of new materials derived from renewable sources. Isolation and chemical valorization of oleuropein, a major secoiridoids found in the olive leaf, generated a carboxyclic structure that is a precursor of the natural product (-)-ajmalicine, approved as an antihypertensive drug. Glucose and fructose were used in the construction of 5-Hydroxymethylfurfural (HMF) and a new method was discovered to improve the thermal stability of HMF. This proved to be a fundamental discovery, because it underpins the potential use of HMF as a biorenewable platform. This was recognized by the journal ChemSusChem with the classification of this study as a VIP paper.

Recognizing the importance of heterocyclic structures in medicinal chemistry hit-to-lead programs, the group focused in the discovering of new scaffolds based on the cyclopent-2-enone. These studies culminated in the implementation of a versatile catalyzed method to synthesize trans-4,5-Diamino-cyclopent-2-enones which have demonstrated so far to be very promising antitumor agents.

Continuing a long standing interest in the discovery of new technologies to design functional linkers for the construction of bioconjugates for targeted delivery, the group disclosed N,O-iminoboronates as a pH sensitive linker for the selectively deliver to cancer cells.

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Medicinal Chemistry

RUI MOREIRA
Group Leader

General representation of research activities.

KEYWORDS Medicinal chemistry; *In silico* drug discovery; Drug targeting; Target identification.

ACHIEVEMENTS Our group combined synthetic and *in silico* medicinal chemistry approaches to target cancer and infectious diseases.

In oncology, we focused on ligands for immune checkpoint receptors, modulators of p53 protein, and organometallic anticancer agents. The major achievements were: ‹1› Identification of low-molecular-weight PD-L1 inhibitors through a virtual screening campaign, using different commercial available databases: These compounds can block PD-1/PD-L1 interaction and thus have the potential to overcome the disadvantages often associated to antibody therapy; ‹2› Development of a new selective p53-activator that revealed encouraging activity against colon cancer cells, either alone or in combination with conventional chemotherapeutics; ‹3› Discovery of a new spiropyrazoline oxindole that induced neural stem cell differentiation through reduced SOX2, while reducing stemness of glioma cancer cells by decreasing SOX2 protein levels, and promoting chemotherapy sensitization. These results highlight the potential of p53 modulators for brain cell differentiation; ‹3› Unravelling of an unprecedented family of potent organoruthenium(II) nucleoside conjugates. “Rock”-stable towards hydrolysis, these compounds revealed Nucleoside Transporters (NT) independent uptake, an advantage over current nucleoside analog chemotherapeutics, due to NT-down-regulation acquired resistance.

In the field of infectious diseases, we focused on our core area of drug discovery for malaria and tuberculosis, where the major achievements were: ‹1› Optimization of hybrid compounds active against different stages of malaria parasite life-cycle, by developing metabolically-stable tetraoxane-8-aminoquinoline conjugates capable of eliminating exo- and intraerythrocytic parasites, with the potential to be used in malaria eradication campaigns; ‹2› Discovery of novel chemotypes active against *Mycobacterium tuberculosis* and the development of prodrugs capable of selectively delivering antimycobacterial agents containing a carboxylic acid function inside the mycobacteria.

Finally, taking advantage of our Computer Assisted Drug Design (CADD) facility, we set up an artificial-intelligence (AI) platform to hunt for novel anticancer and anti-infectious therapies. We collaborated actively in developing data mining and machine learning models for predicting drug likeness and their disease or organ category.

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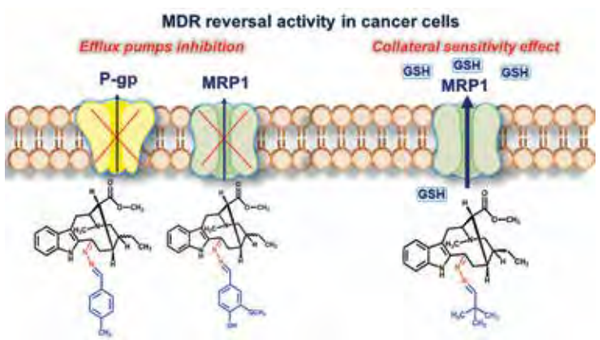
Natural Products Chemistry

MARIA J. U. FERREIRA
Group Leader



General representation of research activities.

KEYWORDS Bioactive plant-derived compounds; Anticancer agents; Multidrug Resistance (MDR); ABC-transporter modulators; Anti-infective agents – African medicinal plants.

ACHIEVEMENTS *Nitrogen-containing flavanone derivatives as new selective ABC transporter modulators* – Naringenin was derivatized yielding a set of imine and alkylated derivatives. While evaluating their effects as multidrug resistance (MDR) reversers in cancer cells, mediated by P-glycoprotein, multidrug resistance protein 1 (MRP1) and breast cancer resistance protein (BCRP), some hydrazones and azine derivatives showed an improvement in their MDR reversal activities against BCRP and carbohydrazides revealed an enhancement in MDR reversal activity towards MRP1. By pharmacophoric analysis and molecular docking, the spatial orientation of the substituents was identified as a key structural feature towards a possible mechanism underlying the experimentally observed MDR reversal activities.

Monoterpene indole alkaloid azine derivatives as MDR reversal agents – Aiming at generating a library of bioactive indole alkaloid derivatives as MDR reversers, two epimeric indole alkaloids were submitted to chemical transformations. The strongest and most selective P-gp inhibition was found for epimeric azines, bearing a *para*-methylbenzylidene moiety. Compounds with a di-substituted benzylidene portion, having methoxy and hydroxyl groups, selectively inhibited MRP1 drug-efflux. Moreover, compounds sharing an aliphatic substituent selectively killed MRP1-overexpressing cells. Addition of some of these compounds to these cells led to glutathione depletion, triggering cell death through apoptosis.

Terpenoids from Euphorbia pedroi as multidrug-resistance reversers – The phytochemical study of *Euphorbia pedroi* led to the isolation spiropedroxodiol, a new triterpene with an unusual *spiro* scaffold, along with several known terpenoids. Spiropedroxodiol was found to be a very strong MDR reversal agent. Derivatization of an *ent*-abietane diterpene, by introducing nitrogen-containing and aromatic moieties positively contributed to increase the MDR reversal activity. By molecular docking, the key residues and binding modes by which these compounds may interact with a murine P-gp model were identified, allowing additional insights on the efflux modulation mechanism of these compounds.

Triterpenoids from Momordica balsamina with collateral sensitivity effect for tackling multidrug resistance in cancer cells – Cucurbitanes exhibited MDR-selective antiproliferative effects together with high antiproliferative activity on three different human cancer entities: gastric, pancreatic and colon, each with two different multidrug resistant variants. Some compounds were found to be strong P-gp modulators, thus highlighting their potential as promising leads for overcoming MDR.

Bioactive compounds from the African medicinal plant Cleistochlamys kirkii as resistance modifiers in bacteria – C. kirkii constituents could be effective adjuvants in the antibiotic treatment of infections.

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Drug Development

BEATRIZ SILVA-LIMA

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BioNanoSciences – Drug Delivery and Immunotherapy

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Nanostructured Systems for Overcoming Biological Barriers

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Pharmacological and Regulatory Sciences

The Drug Development Programme is designed and implemented synergistically with other iMed.ULisboa programmes, validating newly identified products, targets, biomarkers or methods, with the goal of transforming drug leads into clinical candidates and ultimate facilitating patient access to innovation in health. Our research uses innovative technological platforms for formulation and targeted delivery of drugs and diagnostic agents, and addresses related safety concerns. Preclinical development further guarantees proof-of-concept efficacy and safety. Covering therapeutic areas, including cancer, genetic disorders and infection, strategic lines of our activity are:

1. Innovative targeting strategies

Innovation in polymer synthesis, formulation and targeting strategies are exploited for the delivery of synthetic- and natural-based candidate therapeutics to their specific site of action. At the frontiers between materials science and biology, these strategies aim to overcome biological barriers and modulate cellular checkpoints and gene regulators, including those crucial for cancer immune evasion.

2. Tools to test clinical candidates and diagnostic systems

Aiming at clinical translation of therapeutic and diagnostic agents with improved efficiency and reduced toxicity, we use in sillico modelling approaches, molecular biophysics, 3D-multicellular-based systems and mouse models of disease to predict and study pharmacology, biodistribution and pharmacokinetics, and toxicology. We also implement process analytical technology tools at early research stages to enable establishing critical process parameters and critical processes attributes for pharmaceutical products, reinforcing batch-to-batch reproducibility and cost-effectiveness, which are vital for progressing from bench-to-bedside translation.

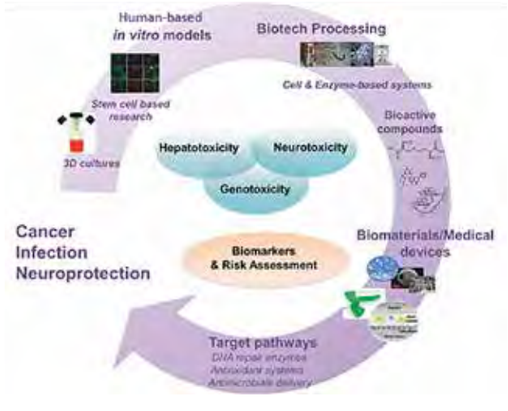
3. Regulatory science

Our research follows and promotes existing regulatory requirements to maximize the translational value of results from *in vitro* or *in vivo* tools into first-in-human research and beyond, including dedicated actions addressing specific regulatory questions.

Recognising the importance for scientific community and society to understand scientific and regulatory basis of medicines development, the Drug Development Programme is involved in international training initiatives for researchers, regulators and patients. Strategic collaborations with the European Medicines Agency, Portuguese regulator INFARMED, and the Innovative Medicines Initiative and specific support from Horizon 2020 ERA-NET and COST schemes strengthen the quality of our research and training outputs. Training initiatives for patients occur within the European Patients Academy for Technical Innovation and its Portuguese platform.

Chemical Biology and Toxicology

MARIA H. L. RIBEIRO
Group Leader



General representation of research activities.

KEYWORDS Human-based *in vitro* models; Cell and enzyme-based bioproducts; Biomaterials and medical devices; Genotoxicity, hepatotoxicity and neurotoxicity; Biomarkers & Risk Assessment.

ACHIEVEMENTS Towards the development of new drugs and innovative medical devices, exploring biotechnology processes and understanding the mechanisms of toxicity to prevent Disease and to promote Health, our main achievements include: ‹1› Covering therapeutic areas, such as inflammation and infection, innovative biotechnology and bioengineering complementary approaches were used in the manufacturing of new (bio)therapeutics or repurposing candidates and medical devices, with efficacy and bioavailability to and at the target site. Harnessing cellular factories and enzymes are the challenges addressed using miniaturized platform technologies and methodologies, targeting new glycocompounds. Innovation in polymer synthesis using hydrogels (e.g. PVA, chitosan), silicone, bone cements, cyclodextrins, magnetic and imprinted micro/nanobeads, were developed, characterized and used in bioproducts manufacturing (microbioreactors) and formulation. A high anti-inflammatory effect of encapsulated limonin (in solution and in functional foods) was revelead in *in vivo* chronic rheumatoid arthritis and acute inflammation models. Evaluation of the efficacy of local-drug-delivery systems for targeting Staphylococcus aureus associated bone infections was addressed. Insights on the interaction of antibiotics and polymers for catheter associated infections prevention; ‹2› Superoxide dismutase mimics (SODm) are catalytical polyfunctional antioxidants with the ability to modulate the cellular redox status. These compounds have shown to be beneficial in different contexts, including in cancer research. The SODm MnTnHex-2PyP, a manganese(III) porphyrin, revealed to decrease the migration and invasion of human renal cancer cells, as well as of doxorubicin-treated breast cancer cells, in *in vitro* models; ‹3› Mesenchymal stem cells (MSCs) have gained interest within the scientific community for they represent promising alternatives to the i) development of alternative *in vitro* systems and ii) repair and regeneration of damaged tissues and indeed, MSCs have shown the ability to differentiate in several cell types of different origins. Within this context and taking advantage of our expertise in 3D culturing, our focus was to develop improved MSC-derived hepatocyte cultures for *in vitro* toxicology applications. On the other hand, supported by strong plasticity data, the way MSCs exert their regenerative capacity is not so much by their ability for multipotent differentiation, but instead through the secretion of bioactive molecules which renders them potent inducers of pro-healing mechanism. Therefore, we aimed at demonstrating the viability of applying the 3D-primed MSC secretome for the wound healing; ‹4› Our focus on the role of antioxidant systems in health and disease proceed and we are now interested in use the cellular disturbance promoted by mercury compounds for repurposing in glioblastoma therapy. Moreover, the environmental risk of methylmercury formation by bacterial communities was studied and the effects of microplastics on mercury neurotoxicity, oxidative damage and energy-related changes were evaluated in the European seabass, Dicentrarchus labrax. Our studies on identification and development of biomarkers and human risk assessment to prevent Disease and promote Health are ongoing.

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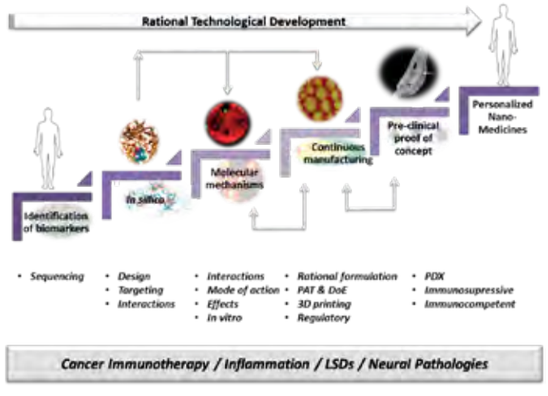
BioNanoSciences – Drug Delivery and Immunotherapy

HELENA F. FLORINDO
Group Leader



General representation of research activities.

KEYWORDS Translational Nanotechnology; Cell Membrane Interactions; Immune Modulation; Process Analytical Technologies (PAT); Imaging in Diagnostic & Therapeutic.

ACHIEVEMENTS A stepwise approach elucidated the effect of nano-vaccine composition and method of antigen association on the different steps involved on the development of the anti-cancer immune response: i) nanocarrier uptake by APC; ii) expression of activation/maturation markers at DC surface; iii) effect on T cell activation and expansion; iv) activation of T cell memory fundamental to protect patients against recurrence. Final proof of concept was evidenced regarding the immune therapeutic effect of our novel nano-vaccine on melanoma and Her2-specific breast carcinoma models. Those studies are of particular importance to evidence the potential of nano- vaccines to trigger a broad immune response against a breast carcinoma better resembling the human disease, namely the lower expression of cancer associated antigens. These mechanistic approaches provided further understanding of nanocarrier mechanisms of cellular dynamics of outmost importance to guide the design of optimized cancer vaccines.

Biological membranes are complex entities organized into compositionally and functionally distinct membrane domains that ensure physical separation of biological events and regulation of cell function. Current models support the concept of fluidity in biological membranes as original proposed by the fluid mosaic model. Our observations challenge this dogma, and demonstrate that sphingolipid-domains display biophysical features typical of the gel phase. This discovery defines a new paradigm for biological membranes, proposing the existence of biologically-relevant gel domains in cellular membranes. Understanding the biophysical and biological properties of these novel gel domains will open unprecedented opportunities to modulate membrane-associated cellular events and may lead to the identification of new therapeutic targets.

It was proved the feasibility of laminar extrudates to deliver small to large molecular weight active pharmaceutical ingredients (APIs) to patients either by oral or transdermal delivery routes of administration. Extrudates were manufactured by a green technology in the absence of heat or solvents. Furthermore extrudates were manufactured as single extrudates or coextrudates increasing the ability of the technoogy to individualize the therapy to patients.

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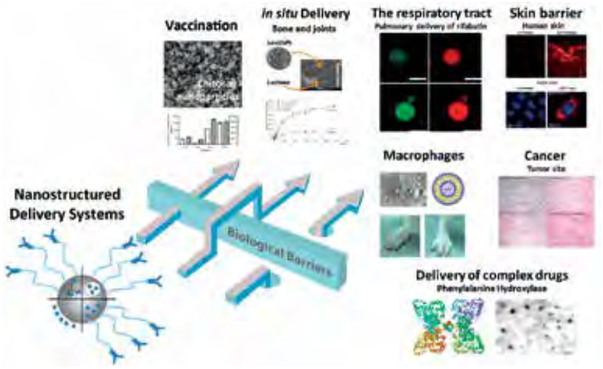
Nanostructured Systems for Overcoming Biological Barriers

ANTÓNIO J. ALMEIDA
Group Leader



General representation of research activities.

KEYWORDS Nanostructured carriers; Biological barriers; Drug delivery; Technology transfer; Preclinical evaluation; Alternative delivery routes.

ACHIEVEMENTS Through a process of capacity building over the years, the Group has addressed innovative strategies for effective modulation of drug transport across biological barriers, involving a remarkable variety of nanotechnology-based solutions that were successfully applied in the following 3 main achievements: ‹1› *Nanostructured platforms for pulmonary delivery of biopharmaceutical agents* – Novel delivery systems intended for deep-lung delivery have been developed based on hybrid nanostructured microparticles and liposomes. These allow direct pulmonary delivery of low molecular weight drugs, proteins or genetic material. The involved techniques are up-scalable, reproducible, while using pharmaceutically acceptable excipients, which afford stability and protection to the incorporated agents. The novel carriers showed a high *in vitro* performance, being biocompatible towards relevant pulmonary cell lines and easily taken up by macrophages. *In vivo* studies demonstrate the effectiveness of the strategy; ‹2› *Successful skin targeting using specifically designed DDS* – Advances were achieved in skin delivery from drug association to the DDS for transdermal and regio-specific dermal delivery. Using suitably developed animal models of skin inflammation and skin infection the group demonstrated the therapeutic potential and the superiority of the novel DDS. Transdermal drug delivery was obtained when small or large molecules were incorporated into deformable lipid carriers designed for non-invasive topical application; ‹3› *Establishment of cancer in vitro and in vivo models to evaluate the therapeutic potential novel synthesized and plant derived molecules* – Plant-derived molecules with potential anticancer activity showed selective cytotoxicity to pancreatic cell lines. Preclinical data demonstrated the therapeutic advantages of liposomes as a delivery system to target cytotoxic compounds to solid tumours.

In 2018, the group has produced 30 papers in international peer-reviewed journals with medium to high impact, 1 book chapter, 1 PhD thesis and 5 MSc theses.

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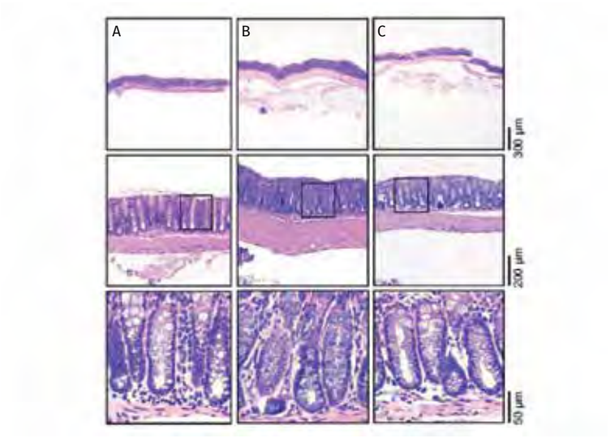
Pharmacological and Regulatory Sciences

BEATRIZ SILVA-LIMA
Group Leader



Effect of hemin treatment on histopathologic changes.
Notes: Each column corresponds with a different experimental group, namely (A) hemin10 group, (B) ethanol group, and (C) sham group.
From Mateus *et al. Clinical Exp Gastroenterol* 2018.

KEYWORDS Inflammatory Bowel disease; Inflammation; Pharmacology.

ACHIEVEMENTS *IBD Inflammatory Bowel Disease (results obtained in 2018)*
– Hemin treatment had a positive influence on the attenuation of inflammation associated with experimental colitis. This pharmaceutical approach promoted a reduction of fecal hemoglobin, ALP, MPO, and proinflammatory cytokines. Furthermore, hemin was also able to increase the anti-inflammatory cytokine, as well as abolish the renal and hepatic changes induced by rectal TNBS administration. In sum, hemin treatment decreases the severity of the disease, because it is able to reduce several inflammation markers, suggesting an anti-inflammatory effect of hemin by HO-1 induction. Hemin also decreases the extension of the intestinal lesions, which is corroborated by the histologic images. These findings suggest that hemin seems to significantly inhibit the acute inflammatory response in this experimental colitis.

This study allowed exploring the effect of hemin in the development of IBD, as well as its influence on response mechanisms to intestinal injury. Moreover, it represents a truly innovative contribution to the pharmacologic treatment of IBD, identifying the pro- and anti-inflammatory responses that can modulate the establishment and development of the disease, as well as a new therapeutic target that allows attenuating the IBD and contributing to the enrichment of the therapeutic opportunities of this disease.

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Drug Usage

FERNANDO FERNANDEZ-LLIMOS
Programme Leader

NUNO TAVEIRA

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HIV Evolution, Epidemiology and Prevention

FERNANDO FERNANDEZ-LLIMOS

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Pharmacoepidemiology and Social Pharmacy

The Drug Usage Programme aims at translating medicines research to real-world usage. We support the strategic lines of iMed.ULisboa by focusing on two main areas of research:

1. Evolution, epidemiology and prevention studies

We aim to characterize the *in vitro* and *in vivo* activity of new drugs against HIV-1 and HIV-2, as well as the epidemiology of drug resistance in Portugal and in Portuguese-speaking African countries (PALOP). Through the analysis of datasets describing the 2015-16 outbreak of yellow fever in central Africa, vector suitability, human demography, and mobility, we understand and predict the spread of yellow fever virus. With this understanding, we aim to show the contributions of ecological and demographic factors to the spread of the yellow fever outbreak and provide estimates of the areas that could be prioritized for vaccination. Based on our installed capacities, the Drug Usage Programme acts in the discovery of inter-individual and pathogen genetic variations that account for therapeutic failure and/or adverse drug reactions. We will expand actions to monitor drug activity and resistance in HIV infected individuals in the PALOP. Furthermore, we will continue to test the antimicrobial activity of new compounds with the final aim of identifying better drugs to treat and prevent infectious diseases. Finally, new tools and models are developed and applied to estimate the burden of virus diseases in Portugal and in the PALOP.

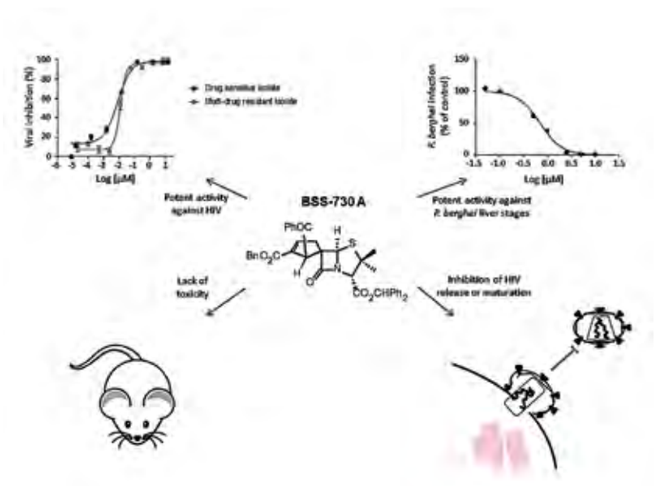
2. Quantitative and qualitative analyses of medicines use and outcomes

We use a variety of research methods such as epidemiological, evidence gathering, or mixed methods and qualitative analysis. We address determinants of inappropriate use of medicinal products, providing solutions that can be endorsed by Regulatory Agencies and healthcare professionals as a mean for maximizing the benefit-risk ratio of medication and ensuring a more efficient use of health care societal resources. Among these determinants, we mainly focus on communication between healthcare professionals and with the patient; quality of medicines information, addressed to both patients and healthcare professionals; gathering of comparative effectiveness and safety evidence; and intensive safety monitoring of new therapies and risk management.

The Drug Usage Programme comprises a multidisciplinary group of scientists who are committed to translational research in a collaborative environment with the other programmes at iMed.ULisboa, involving two participating groups, HIV Evolution, Epidemiology and Prevention and Pharmacoepidemiology and Social Pharmacy. We highlight here strategic collaborations with the Innovative Medicines Agency, European Medicines Agency, European Network in Pharmacovigilance, and regular contributions with impact on national and international public health policies and programmes. We also host pharmacovigilance regional units, supported by the Portuguese Regulatory Agency INFARMED.

HIV Evolution, Epidemiology and Prevention

NUNO TAVEIRA
Group Leader



General representation of research activities.

KEYWORDS Treatment and prevention of HIV infection; HIV drug resistance; Virus evolution; Phylogenetic analysis; phylogeography of viral diseases.

ACHIEVEMENTS TAF and OPB-601, two new RT inhibitors, were tested against HIV-2 isolates obtained from drug experienced patients failing therapy and were shown to have potent inhibitory activity. These results showed that TAF and OBP-601 should be considered for the treatment of HIV-2 infected patients failing therapy. Along the same lines we showed that a new compound named BSS-730A has potent *in vitro* activity against both HIV and Plasmodium (Figure). This compound could be useful for the treatment of both HIV infection and malaria.

We formulated the P3 peptide, a novel HIV fusion inhibitor, in a gel of hydroxyethyl cellulose (HEC) and evaluated its *in vitro* activity and stability, and its safety profile in Balb/c mice. HIV infection was fully blocked by the 1.5% gel formulation. The antiviral activity of the peptide did not change at 4°C and ay 65°C. P3 was stable and fully functional at different pHs and P3 maintained full antiviral activity under different concentrations of H2O2 and in the presence of seminal plasma and vaginal fluid. Finally, P3 peptide did not cause significant alterations in the vaginal epithelium or vaginal irritation in Balb/C mice. These findings indicate that P3 is an excellent candidate for the development of a microbicide for the prevention of HIV transmission in women.

We studied the effect of dense surface modification of EFV-loaded PLGA NPs with PEG on local PK using a murine model. PEG modification of EFV-loaded NPs provided prolonged drug residence at high levels at the lower colon, which could potentially translate into enhanced protection from HIV transmission. Our results support the usefulness of mucus-diffusive nanocarriers in engineering effective and safe rectal microbicides.

Finally, we performed the first characterization of the epidemic history of HCV genotypes and subtypes in Portugal. Five distinct epidemics were identified. The first significant HCV epidemic in Portugal occurred between 1930s and 1960s, was caused almost exclusively by GT1b and was likely associated with blood transfusions. Rapid expansion of GT3a occurred in the 1960s and GT1a in the 1980s, associated with intravenous drug use. The most recent epidemics were caused by GT4a and GT4d and seem to be associated with the resurgence of opioid use. The C316N substitution was found in 31% of GT1b-patients. Close surveillance of patients bearing this mutation will be important to determine its impact on treatment outcome.

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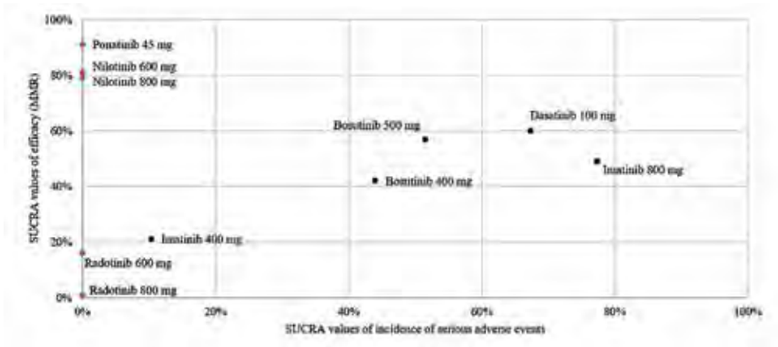
Pharmacoepidemiology and Social Pharmacy

FERNANDO FERNANDEZ-LLIMOS
Group Leader



General representation of research activities.

KEYWORDS Pharmaceutical Services; Pharmacovigillance; Evidence-Based Practice; Health Communication.

ACHIEVEMENTS PEPSocPh focuses its research on analysing and ensuring the determinants associated to an effective, safe and efficient use of medicines by patients and populations. By using cohort studies, adherence and quality of life achieved with the new glucose lowering drugs in Portugal. Patient safety is a major driver of PEPSocPh research. Adverse events associated to drug classes like hypoglycaemic cases in glucose-lowering drug users were investigated using real-world data. But also the role of the patient in reporting adverse drug reactions to pharmacovigilance systems, the influence of patients limited health literacy, and the preferences in the selection of brand names for medicines were topics covered under the patient safety research line.

PEPSocPh also focused the research on clinical pharmacy services aiming to increase medicines effectiveness and safety, like discharge medication counselling, or polypharmacy management programmes. But, medication adherence, the interventions to enhance it, and the clinical and economic consequences of non-adherence were a major focus in this research line.

Another significant research line of PEPSocPh is the generation of evidence about drug efficacy, effectiveness and safety, which included rare diseases like acromegaly, innovative biological treatments like disease-modifying therapies for relapsing-remitting multiple sclerosis, non-anti-TNF drugs for rheumatoid arthritis, or tyrosine kinase inhibitors for chronic myeloid leukaemia. Generating this evidence required the used of innovative techniques like network meta-analysis, which were also object of methodological research by PEPSocPh.

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FACILITIES & SERVICES

Animal Facility

Head: Maria Manuela Gaspar

The Animal Facility is a conventional facility for the housing of laboratory rodents licensed by the National Authorities "Direção Geral de Alimentação e Veterinária". Personnel and users are certified researchers according to European and Portuguese legislation. | Consists of several rooms for animal maintenance with housing capacity of around 500 small rodents (rats and mice), and rooms for experimental procedures (small surgeries and dissections). Metabolic cages are also available. Support rooms are used for cleaning, washing and sterilization of cages and other equipment, food and bedding. | Provides technical and scientific support to investigators on protocol development, refinement and advice in experimental procedures, simple surgical techniques, and services of husbandry and routine daily care (feeding, watering, and cage changing) by qualified animal care technicians. Pharmacology and toxicity studies are also provided to external entities upon request and contract.

Radioisotope Facility

Contact: M. Luísa Corvo

The Radioisotope Facility (gamma and beta emission) follows strict rules driven by requirements of improved safety for workers on radioactive sample handling. All new users must perform radiation safety training. | Consists of dedicated areas for labeling of proteins, other macromolecules and low molecular weight compounds by chemical modification. | Provides pharmacokinetics, biodistribution, and metabolite studies to investigators or external entities upon request and contract. The physical proximity to the Animal Facility enables *in vitro* and *in vivo* studies.

Cell Culture Facility

Head: Joana Amaral, Rui Silva

The Cell Culture Facility comprises dedicated cell culture rooms equipped with the required environment and equipment for a wide range of cell and tissue culture procedures, from maintenance and manipulation of cell lines and tissue samples, to cell observation and data analysis. In addition, the facility provides routine mycoplasma detection testing for mammalian cell lines. | Consists of laminar flow hoods (Esco, Class II Type A2), CO2 incubators (Hera Cell), inverted microscopes (Zeiss) coupled to an imaging system (Leica), and support equipment (centrifuges, water baths, refrigerators, freezers). Fluorescence and bright-field microscopes (Zeiss) with dedicated cameras (Leica) and imaging and acquisition systems are available. | Additional dedicated equipment provides cell analysis high-throughput capabilities with Multidrop Combi Reagent Dispenser (Thermo Scientific) for 6 to 1536-well plates; GloMax®-Multi+Microplate Multimode Reader (Promega), accepting 6 to 384-well plates, and accommodating luminometer, fluorescence, and visible/UV absorbance modules and dual injector system for 6 to 96-well plate formats; and xCELLigence RTCA SP (ACEA Biosciences) for real-time label free impedence-based cell analysis in 96-well format. | Provides biological evaluation of cell function, routinely determining the role of transgenes and the cytotoxic and cytoprotective activities of synthetic and natural compounds in multiple cell models, including immortalized cells (human, monkey, rat, mouse), primary cultures (rat and mouse liver, brain), and embryonic stem cells (rat and mouse). | A full service by experienced technical personnel is also provided to external entities upon request and contract.

Gene Expression Facility

Head: Rui Castro

The Gene Expression Facility is dedicated to sample quality monitoring and analysis of gene expression at DNA, RNA and protein levels, routinely performing a multitude of biochemical and molecular biology techniques. | Consists of equipment for sample quality monitoring and gene expression analysis, including a Qubit 2.0 fluorometer (Thermo Fisher Scientific) and a NanoDrop 2000c spectrophotometer (Thermo Scientific), standard gel electrophoresis (Bio-Rad), Trans-Blot Turbo System (Bio-Rad), absorbance plate readers (Bio-Rad), Chemidoc MP and Chemidoc XRS gel/membrane and X-ray film imaging (Bio-Rad), end-point

thermocyclers (Bio-Rad and Thermo Scientific), and real time PCR systems including the 7300 Real-Time PCR (Applied Biosystems) and sate-of-the-art QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems). The later enables high-throughput, quantitative gene expression, combining 384-well microfluidic gene expression, predesigned or customed card arrays, with multiplexing (21 filter combinations), and fast real-time capabilities. | Additional equipment includes a Guava easycyte 5HT benchtop flow cytometer (Merck Millipore) for high-throughput cell analysis in 96-well format, and stopped-flow (HiTech Scientific) and patch-clamp setups (Axon Instruments) used for kinetic analyses of ion channel activity. | Provides technical support ranging from advice in experimental design to data analysis.

Biosafety Level 3 Facility

Head: Quirina Santos Costa

The Biosafety Level 3 Facility is specifically dedicated to research involving biological pathogens of level 3 security. It was designed to minimize the risk of personnel and environmental exposure to potential hazardous agents according to European and Portuguese legislation. All users must undergo specific biosafety level 3 training, and must follow strict rules and guidelines while working in the facility. | Consists of an anteroom for material and personnel preparation, and a main procedure room equipped with tree vertical laminar flow chambers (type A2 and type B2), three CO2 incubators (Hera Cell), one regular incubator, two benchtop centrifuges (Eppendorff), a benchtop ultracentrifuge (Beckman), an aerosol-tight microfuge (Eppendorff), a Tecan infinite 200 multimode microplate reader, water baths, freezers, refrigerators, optical and inverted phase-contrast microscopes (Leica), and a dedicated double door pass-through autoclave (Matachana). | Available to external researchers.

Mass Spectrometry

Head: Maria do Rosário Bronze

The Mass Spectrometry Facility is part of the National Mass Spectrometry Network. | Consists of a Triple Quadruple mass spectrometer (Micromass Quattro Micro API, Waters) with electrospray ionization (ESI) atmospheric pressure chemical ionization (APCI) ion sources. This facility is also equipped with an Ion-Trap (LCQ-Fleet, Thermo) mass spectrometer dedicated to the characterization of proteins and biological conjugates. | Provides identification and quantification of small molecules in complex matrices, as biological fluids and extracts of natural products. Services are available for users on a "do-it-yourself" basis or self-service, for long-term studies, upon initial training requirements. A technician is also available for a full-service.

Molecular BioScreening

Head: Cecília Rodrigues, Vanda Marques

Molecular BioScreening is the newest infrastructure from iMed.ULisboa that offers an innovative and integrated approach of cell-based medium- to high-throughput assays for screening small molecules (natural or synthetic) and biologics, ultimately leading to discovery of new therapeutics. It combines the power of relevant cell models, phenotypic screens and live cell functional assays to both model disorders and search for drugs to treat disease.

BioImaging

Head: Liana Silva

At iMed.ULisboa there are several resources available for bioimage acquisition. | Both fluorescence and bright-field microscopes (Zeiss) with dedicated cameras (Leica) and imaging and acquisition systems are available within the Cell Culture facility. | The Leica TCS SP8 laser scanning confocal microscope is a new resource at iMed. ULisboa for fluorescence imaging. The inverted DMi8 fluorescence microscope is equipped with a fully motorized stage, fast z movement (Leica Super Z Galvo stage), 4 solid state lasers (405, 488, 552, 638 nm), four detectors (one HyD high-sensitivity, three PMT), a transmitted light detector with CCD camera, three dry objectives (5x, 10x and 20x) and two oil immersion objectives (40x and 63x), and allows several types of image acquisition (2D, z-stack and time-lapse). | Available for iMed.ULisboa researchers.

Computer Assisted Drug Design Facility

Head: Rita Guedes

The Computer Assisted Drug Design Facility consists of a Linux-based high performance computer cluster with 424 CPU cores, 4 to 8GB per CPU/GPU and 2 TB per node with a specific implementation of state-of-the-art software for molecular modeling, molecular dynamics, virtual screening, and *de novo* design. | Provides technical support ranging from advice in experimental design to data analysis.

Nuclear Magnetic Resonance

Head: Noélia Duarte

The Nuclear Magnetic Resonance (NMR) Facility is equipped with a Bruker Fourier 300 MHz Spectrometer. | Promotes the use of nuclear magnetic resonance spectroscopy in the areas of structure-based drug design, including structure characterization and fragment-based drug design. | Available to external researchers.

"Unidade de Farmacovigilância – Sul"

Head: Paula Barão de Sousa Ferreira

This facility provides competencies raging from reception, validation, analysis and evaluation of suspected adverse drug reactions, dissemination of pharmacovigilance in the Southern region of the country and training in pharmacovigilance field, to scientific activity and research related to drug use safety.

"Núcleo de Prestação de Serviços"

Head: Dora Brites, Isabel Tavares de Almeida, José Moniz Pereira

This facility provides services of clinical analyses for diagnosis and monitoring, open to general public, social services, healthcare units, state and private hospitals and non-profit organizations. | The Clinical Biochemistry laboratory offers unique means for the diagnosis of familial hyperbilirubinemias (Gilbert and Crigler Najjar syndromes), as well as for diagnosis and prognosis of various acute and chronic liver diseases, and their therapeutic monitoring. The diagnosis and therapy follow-up of inherited metabolic disorders is performed through the characterization of the metabolic profiling and biomarker identification. This laboratory is member of European Network ERNDIM and one of two laboratories in the country with the technological and scientific knowledge to perform these particular analyses. | The Clinical Microbiology laboratory is a reference in the diagnosis and monitoring of HIV infection/AIDS and other associated infections, such as tuberculosis and fungal infections. The Microbiological Control laboratory provides services for the control of pharmaceutical, biological and cosmetic products, antibiotics and others. | The Molecular Biotechnology laboratory performs immunogenicity assays against biotechnological drugs and quantification in the blood of therapeutic proteins.

ADVANCED TRAINING

PhD Programmes . iMed.ULisboa
Postgraduate Students Commission

PhD Programmes

The PhD in Pharmacy at the Faculty of Pharmacy, University of Lisbon has been accredited since 2008 by the evaluation agency in Portugal A3ES. This cycle of studies is based on five FCT-funded PhD Programmes, of which one, the PhD Programme in Medicines and Pharmaceutical Innovation – i3DU, is led by iMed.ULisboa and involves other national R&D Units, Universities and pharma/biotechs.

PhD Programme in Medicines and Pharmaceutical Innovation

The PhD Programme in Medicines and Pharmaceutical Innovation (i3DU) represents a strong commitment of academia and pharma in Medicines and Pharmaceutical Innovation training that meets well-defined standards for high quality international PhD training and is in line with the preconized research-innovation-education triangle in Europe. I i3DU is a joint initiative of two reference universities in Portugal, the University of Lisbon (ULisboa) and the University of Porto (UPorto), grouping competences and boosting quality in postgraduate training, in cooperation with the pharmaceutical industry. The consortium involves the Faculties of Pharmacy at ULisboa (FF/ULisboa) and UPorto (FF/U.Porto), and the Research Centers iMed.ULisboa at ULisboa, and REQUIMTE and IBMC. INEB at UPorto, in close and effective collaboration with Hovione and Novartis as major industry partners. The doctoral degree in Pharmacy and Pharmaceutical Sciences are awarded by ULisboa and UPorto.

Medicinal Chemistry PhD Programme

The Medicinal Chemistry PhD Programme (MedChemTrain) is designed to train the next generation of scientists to work at the interface between chemistry and biology at various stages of pre-clinical drug discovery. I It involves the Universities of Coimbra (UCoimbra) and Lisboa (ULisboa), in consortium with Bial, Bluepharma and Hovione. Both universities, which currently award the PhD degrees that will anchor the MedChemTrain program, are internationally recognized institutions hosting some of the largest and most reputed schools of science and technology in Portugal, such as the Faculty of Sciences and Technology and the Faculty of Pharmacy at UCoimbra, as well as the Faculty of Pharmacy and Instituto Superior Técnico at ULisboa. This joint initiative is supported by five research units, the Coimbra Chemistry Center and Center for Neuroscience and Cell Biology at UCoimbra, and the Research Institute for Medicines (iMed.ULisboa), Centro de Química Estrutural and Instituto de Medicina Molecular at ULisboa.

PhD Program in Integrative Neuroscience of the University of Lisbon

The ultimate goal of PhD Program in Integrative Neuroscience (NeurULisboa) is to train highly qualified professionals in neuroscience who will match the increasing demand in the field for multidisciplinary approaches and cutting edge technological developments. I NeurULisboa involves 6 leading Portuguese Institutions of basic and clinical research in neuroscience, as well as technically oriented groups ideally suited to provide them with sophisticated research tools. The supervisory board behind NeurULisboa is comprised of academic/research professionals working in biological, medical and pharmaceutical sciences or in engineering schools.

Medical Biochemistry and Biophysics Doctoral Programme

The aim of the Medical Biochemistry and Biophysics Doctoral Programme (M2B-PhD) is to train through research highly qualified professionals in the fields of Medical Biochemistry and Biophysics. I The Programme joins Portuguese academic centres of Medical Biochemistry and Biophysics, distributed by 3 universities in 3 different cities (University of Lisbon, University of Porto and University of Coimbra), to provide training through research in state-of-the-art environments. The team of educators/researchers involved in the M2B-PhD is composed of a core of biochemists and biophysicists complemented with researchers in closely related areas, mostly working in medical, pharmaceutical sciences or engineering schools. PhD students will be exposed to an interdisciplinary environment suitable for them to tailor their career plan. This may include future careers in academia, as clinicians, health technicians (advanced analytics, biomedical engineering) or biotech entrepreneurs.

Doctoral Programme Advanced Integrated Microsytems

The Doctoral Programme in Advanced Integrated Microsytems (AIM) has a focus on advanced integrated microsystems and its objective is to offer advanced training that includes: micro/nanofabrication of devices and systems; sensing and actuating; application to physical, biotechnological, pharmaceutical, and biomedical challenges. The team includes research groups from INESC Microsystems and Nanotechnologies, International Iberian Nanotechnology Laboratory INL, INESC ID, Instituto de Tecnologia Química e Biológica, Institute for Biotechnology and Bioengineering, and Research Institute for Medicines. The doctoral degrees are awarded by the Universidade de Lisboa and the Universidade Nova de Lisboa. The research will take place in the laboratories of the team institutions in Lisbon and Braga in Portugal, with stays in Portuguese and international associate partner laboratories in academia and in industry.

iMed.ULisboa
Postgraduate Students Commission

The main aims of iMed.ULisboa Postgraduate Students Commission (ipSC) are to promote complementary training of postgraduate students and stimulate interaction between different scientific areas, thus contributing to research excellence at iMed.ULisboa.

ipSC organises bimonthly monothematic workshops, the Annual Postgraduate Student Meeting and many social activities throughout the year.

2017-18 MEMBERS:

Ana Bárbara Carreira, Ana Ester Ventura, André Simão, David Cardoso, Inês Vieira da Silva, João António, Margarida Espadinha, Maria Ribeiro, Marta Barbosa, Rafael Gomes, Sofia Domingos.

RESEARCH INSTITUTE FOR MEDICINES
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