IMM
2011
REPORT
INSTITUTO DE MEDICINA MOLECULAR
FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA
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The Instituto de Medicina Molecular (IMM, www.imm.fm.ul.pt) is a non-profit private research institute affiliated with the University of Lisbon Medical School and located in the campus of the Santa Maria Hospital. The mission of IMM is to foster basic, clinical and translational biomedical research with the aim to contributing a better understanding of disease mechanisms, developing novel predictive tests, and diagnostic and therapeutic approaches.

IMM was created in December 2001 through the merging of five centers that carried out research activities in the areas of Cell and Molecular Biology, Developmental Biology, Biochemistry, Immunology, Nutrition and Neurosciences at the University of Lisbon Medical School. IMM was awarded the special status of Laboratório Associado by the Portuguese Ministry of Science, Technology and Higher Education. Three years later, in 2004, pre-existing groups moved their laboratories to Edifício Egas Moniz, a newly built facility. A long-term recruitment policy was then launched to attract Group Leaders among junior scientists most of whom had been trained abroad. Between 2004 and 2011, thirteen new Group Leaders were recruited, and the total number of researchers increased from 150 to 435.

We are pleased to highlight some of IMM’s accomplishments in 2010/2011. We would like to emphasize the increasing number of scientific papers published in high impact journals and internationally registered patents. IMM researchers succeeded in attracting more competitive funds to the Institute, which was reflected by an increase in total annual expenditure and a wider international recognition. Namely, Luisa Figueiredo who had won an EMBO Installation Grant in 2010 to establish her research group at IMM, was appointed in 2011 a “promising scientific leader of the future” by the Howard Hughes Medical Institute (HHMI), and João Gonçalves was awarded a Bill & Melinda Gates Foundation Grant. IMM was invited to the European Parliament, and João Barata’s research on leukemia was officially praised at the Portuguese Parliament. IMM scientists were also double winners in the 2011 edition of Pfizer Awards, with João Barata receiving the Clinical Research Award and Sérgio de Almeida getting the Basic Research Award.

The success of IMM relies on the hard work and creativity of dedicated researchers, students, administrators and support teams. We are fully aware that we can still improve the effectiveness of our efforts and we look forward to an even stronger collective participation in this exciting endeavor.
SCIENTIFIC ADVISORY BOARDS:

**CELL AND DEVELOPMENTAL BIOLOGY PROGRAMME**
- Ira Mellman, Genentech, San Francisco, USA
- Fiona Watt, Cancer Research UK, London, UK
- John G Gribben, Barts Cancer Institute, Queen Mary University of London, UK

**IMMUNOLOGY AND INFECTIOUS DISEASES PROGRAMME**
- Anne O’Garra, National Institute for Medical Research, UK
- Alain Fischer, Hôpital Necker Enfants Malade, Paris, France
- William Paul, National Institute of Allergy and Infectious Diseases, NIH, USA
- Philippe Sansonetti, Institut Pasteur, France
- António Freitas, Institut Pasteur, France

**NEUROSCIENCES PROGRAMME**
- Michael Spyer, University College London, UK
- Christine Gall, University of California, USA
- Charles Warlow, Western General Hospital, Edinburgh, UK
- Reinhard Dengler, Medizinische Hochschule, Hannover, Germany
IMM AT A GLANCE

TOTAL RESEARCHERS
435
with PhD
210
PhD or MD/PhD students
111

RESEARCH UNITS
28
START UPS
3

CELL AND DEVELOPMENTAL BIOLOGY PROGRAMME
RNA Biology & Therapeutics
Cancer Biology
Tissue Regeneration
Stem Cell Biology & Therapeutics

IMMUNOLOGY AND INFECTIOUS DISEASES PROGRAMME
HIV/AIDS
Malaria
Allergy
Inflammation
Tumor Immunology
Arthritis & Bone Disorders

NEUROSCIENCES PROGRAMME
Stroke
Parkinson’s disease
Alzheimer’s disease
Amyotrophic Lateral Sclerosis
Neurophysiology
TOTAL EXPENDITURE

11,414,588 €

EXPENDITURE / PAPERS JIF≥5
140,920 €

EXPENDITURE / CITATION
3,705 €

COMPETITIVE EXTERNAL FUNDING

4,917,622 €

National FCT: 2,956,764 €
Other national: 19,414 €
International EU: 1,472,584 €
Other International: 294,124 €
**RESEARCH HIGHLIGHTS**

**PAPERS 2011**

- 287 papers published in peer reviewed journals
- 23 publications in journals with an impact factor higher than 10
- 58 publications in journals with an impact factor between 5-10

**CITATIONS PER YEAR**

- 3081 citations in 2011

**IMPACT FACTOR OF PUBLICATIONS PER YEAR**

- Publications JIF > 10
- Publications JIF 5-10


Howard Hughes Medical Institute International Early Career Scientist (HHMI) 2011  
Luísa Figueiredo  
-  
Early Career Bayer Hemophilia Award 2011  
Vanessa Oliveira  
Boosting dendritic cell function to facilitate tolerance induction to recombinant clotting factor  
-  
Bill & Melinda Gates Foundation, Grand Challenges Explorations Programme 2011  
João Gonçalves  
Nanotechnology against viral latency: Sensor strategies to eliminate HIV-1 infected cells  
-  
ERC Starting Grant 2010  
Bruno Silva-Santos  
Differentiation of pro-inflammatory T cell subsets in vivo  
-  
Bill & Melinda Gates Foundation, Grand Challenges Explorations Programme 2010  
Miguel Prudêncio  
A new whole-organism vaccine against malaria  
-  
EMBO Young Investigator 2010  
Bruno Silva-Santos  
-  
EMBO Installation Grant 2010  
Luísa Figueiredo  
-  
Michael J. Fox Rapid Response Innovation Award 2010  
Tiago F. Outeiro  
Deciphering the molecular effects of alpha-synuclein in the nucleus: DNA binding and transcription regulation  
-  
ERC Starting Grant 2008  
Henrique Veiga-Fernandes  
Role of the proto-oncogene Ret during lymphocyte development and function  
-  
ERC Starting Grant 2008  
António Jacinto  
RESEAL – Epithelial Resealing  
-  
EMBO Installation Grant 2008  
Henrique Veiga-Fernandes  
-  
EMBO Installation Grant 2008  
Tiago F. Outeiro  
-  
US61/114362:  
“Foxp3+ natural killer t-cells and the treatment of immune related diseases”  
Owner IMM/UL/Acellera Therapeutics  
-  
PT20111000041319 (Provisional):  
“Means and methods for the inhibition of the flavivirus replication”  
Owner IMM/UL/UFRJ  
-  
PT20111000069101 (Provisional):  
“The anthracycline epirubicin triggers an atm-dependent protective response to the mouse model of sepsis”  
Owner IMM  
-  
PT20111000039048 (Provisional):  
“Generation of peripheral blood gamma-delta t-cells expressing natural cytotoxicity receptors for cancer immunotherapy”  
Owner IMM/UL  
-
1 YEAR IN THE LIFE OF IMM

2011

22-23 FEBRUARY
Visit of the Scientific Advisory Committee to evaluate the IMM research programme in Neurosciences.

18 MARCH
IMM open day on Brain awareness week. Neuroscientists and health professionals share with secondary school students and adults brain science, behavior and drugs. Facebook challenges, a theatre-debate and hands-on activities organized by researchers and students.

21 MARCH
Rob Pinnock, Licensing Officer from Merck Sharp & Dome visits IMM to meet with IMM group leaders.

18-25 MARCH
The artist Maria Manuela Lopes installs her working studio at the lobby to show researchers and health professionals her work in progress in the artistic residency she is developing at IMM and Hospital de Santa Maria.

29 MARCH
The Duchess of Cornwall Camilla visits IMM in a joint event organized with APOROS, the Portuguese Association against Osteoporosis.
18 APRIL
IMM Executive Director Carmo Fonseca receives 2010 Prémio Pessoa from Portuguese President Professor Aníbal Cavaco Silva in a ceremony held at Caixa Geral de Depósitos, Lisbon.

28 APRIL
IMM external group leader João Gonçalves wins a Bill & Melinda Gates Foundation Grand Challenges Explorations Award.

19 APRIL
IMM hosts the session “Clinical Trials: from molecule to drug” for patients associations, promoted by Apifarma, Bayer and Merck Sharp & Dome.

MARCH-MAY
Pedaling against Cancer - Fundraising campaign led by 2 IMM group leaders in collaboration with the Portuguese League Against Cancer. The researchers proposed to pedal through Portugal from North to South while raising funds via Facebook to support the league’s social action.

30 APRIL
IMM President Professor João Lobo Antunes and Executive Director Carmo Fonseca among the 100 most influential people in Portugal elected by the newspaper Expresso.

6-7 MAY
Lisbon Medical School closes its 100 years commemorations with a scientific meeting on “Science and Medical Education”.

13 MAY
Clive Wood, Senior Vice president and Head, Global Biologics at Bayer HealthCare AG visits IMM to meet with IMM group leaders.
15 JUNE
IMM at the European Parliament hosted by MEP Maria da Graça Carvalho, who organized “Research of Excellence at the European Parliament – a day with IMM”.

5 JULY
IMM researcher Vanessa Oliveira wins an Early Career Bayer Hemophilia Award. Vanessa was the only European researcher to win this funding scheme in the 2011 round, in a total of 5 researchers funded worldwide.

17 JUNE
1st IMM challenger: IMM PhD students organize outdoor activities to bring IMMers, friends and families together.

4-10 SEPTEMBER
IMM-INSERM workshop in “Emerging Tools in Quantitative Fluorescence Microscopy for Systems Biology”.

9 SEPTEMBER
Portuguese Science is officially praised at the Portuguese Parliament due to IMM group leader João Barata’s research work in acute leukemia.
25-27 SEPTEMBER
IMM PhD students retreat.

17-18 OCTOBER
V IMM PhD students' scientific meeting.

12-14 OCTOBER
Herwig Turk’s installation in the lobby as part of his artistic residency at IMM.

17 NOVEMBER
Double victory for IMM research teams at Pfizer Awards: João Barata (Clinical Research Award) and Sérgio Almeida (Basic Research Award) win 2011 edition.
Adelaide Passos, grandmother of an 8-year-old patient treated from a brain tumor launches a fundraising campaign based on the Royalties from her book “O Céu pode esperar” and aimed at attracting private donations for IMM brain tumor research.

IMM group leader Luísa Figueiredo becomes a Howard Hughes Medical Institute (HHMI) International Early Career Scientist. Luísa was considered by HHMI “a future scientific leader” and her work will be funded for 5 years with 715,000 USD.

Upon HHMI Awards, Portuguese science is praised in the New York Times and Science.

Science magazine publishes “Portugal’s Age of Enlightenment”, a letter from IMM group leader Nuno Santos about Portuguese science.
A TYPICAL WEEK AT IMM

The IMM offers an extensive series of public scientific seminars, aimed at providing researchers access to a wide diversity of scientific topics and cutting edge science, technology or clinical practice.

**MONDAY**

12H30 Renowned chemist Jon Clardy from the Harvard Medical School, USA is the invited speaker at the IMM Monday Lecture, to talk about Bacterial symbiosis and the discovery of new drugs. IMM Monday Lectures series bring top quality researchers to IMM every week.

14H Launching of the CAML Advanced Course Scientific integrity, one of the circa 10 Advanced courses the Lisbon Academic Medical Center PhD programme organizes every year.

**TUESDAY**

10H Robert J. Motzer from the Memorial Sloan-Kettering Cancer Center, USA, talks about Targeted Therapy for Advanced Renal Cell Carcinoma at the Oncology Series, a seminar series dedicated to clinical investigation in cancer.

12H IMM PhD student Telma Lança presents her project about Understanding the dual role of murine gammadelta T-cells in tumour immune surveillance at the Pizza Seminar, a forum for PhD students and postdocs to have feedback about their research projects.

**WEDNESDAY**

13H Chalk Talks, IMM PIs join brainstorming meetings to discuss future and ongoing scientific projects

13H Luísa Moita, group leader at IMM speaks at the Wednesday Lecture about Sepsis: new uses for old drugs. These lectures occur every other Wednesday, alternating with chalk talks.

17H Maria Luísa Vasconcelos from Champalimaud Foundation talks about In search of the circuits of female fly courtship behavior speaks at the Lisbon Area Neurosciences Meetings, a series organized by the neurosciences community.

**THURSDAY**

13H Andreia Amaral from IMM debates her project Small Non-Coding RNAs in CD4 T cell activation and in HIV defence at the Immunology Club, organized by the Lisbon area immunology community.

**FRIDAY**

12H Renowned immunologist Tom Huizinga, Leiden Academic Medical Centre, is the invited speaker to talk about The burden of IL6 in RA physiopathology: therapeutic implications at the IMM Rheumatology Series, a series that brings to IMM top researchers.

15H Invited speaker Steve Russell, University of Cambridge, visits IMM and talks about Transcription and Chromatin Architecture: a View from the Fly Genome.
The Cell and Developmental Biology programme at IMM covers basic and translational research themes with a high degree of interdisciplinarity, from the study of single molecules, to their functions in cellular activity and role in the development of organisms and in disease.

The molecular mechanisms and principles that underlie the sophisticated organisation and behaviour of cells, the units of life, are at the core of our research interests. The nucleus occupies a central role in processing cell information and the study of mechanisms that regulate gene expression, such as chromatin remodelling and gene splicing, are an important focus of several groups. We are also very interested in studying several types of interactions that cells establish with their environment, which range from the physical properties of biomembranes to active processes such as phagocytosis and cell migration.

In order to understand how cells work together to make functional tissues and organisms we are studying how signalling pathways control embryonic axis specification, cell fate determination, neural and blood stem cell differentiation, vascular biology and tissue homeostasis.

We use a variety of animal models and cell culture assays to investigate these processes.

We also have a strong interest in understanding how cellular malfunction can lead to disease, thus there are groups studying the molecular mechanisms of cancer with the ultimate aim of identifying novel molecular markers for diagnosis and targets for therapeutic intervention.
Our research focuses on the role that both cell-intrinsic aberrations and microenvironmental factors might play during tumorigenesis. We have shown that IL-7 accelerates human T-cell leukemia development (Cancer Res 2011). Notably, we further found that around 9% of T-cell acute lymphoblastic leukemia (T-ALL) patients display oncogenic gain-of-function mutations in the alpha subunit of IL-7 receptor (Figure A; Nat Genet 2011).

While cancerigenesis is traditionally viewed as relying on a series of genetic and epigenetic alterations, it is evident that the intracellular landscape that is altered in the context of cancer progression and functionally involved in many of its steps includes different non-genetic lesions. For instance, we have shown that in most primary T-ALL patient samples, in contrast to cell lines and to many solid tumors, PTEN is not genetically deleted but rather functionally inactivated by posttranslational modifications mediated by the oncogenic kinase CK2 and by reactive oxygen species (Figure B; J Clin Invest 2008).
The vision of the Unit headed by Carmo-Fonseca is to discover pathways of gene regulation controlled by RNA molecules. Our long-term goal is to contribute for the development of novel RNA-targeted therapeutic strategies. Projects in our Unit make use of a multidisciplinary approach that combines live-cell microscopy, computational modelling, molecular biology, biochemistry and bioinformatics. Carmo-Fonseca has authored 99 original research articles, 24 review articles and 6 book chapters with a total of over 5 thousand citations.

Several lines of recent evidence support a role for chromatin in splicing regulation. Our work shows that splicing can also contribute to histone modification, which implies a bidirectional communication between epigenetics and RNA processing (de Almeida et al. NSMB 2011).

In the nucleus of higher eukaryotes, maturation of mRNA precursors involves an orderly sequence of transcription-coupled interdependent steps. Our data suggest that recruitment of splicing factors and correct assembly of the spliceosome are coupled to transcription termination and this might ensure a proofreading mechanism that slows down release of unprocessed transcripts from the transcription site (Martins, Rino, et al. NSMB 2011).

**SELECTED PUBLICATIONS**


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**Group Leader**

**MARIA CARMO-FONSECA**

MD (1983) and PhD (1988) in Cell Biology at Faculdade de Medicina da Universidade de Lisboa (FMUL)

Post-doctoral research at EMBL in Heidelberg, Germany

Professor at FMUL

Executive Director of the IMM since 2002

**Other Principal Investigators**

Francisco Enguita, Sérgio de Almeida
Our research unit studies peptide-lipid interactions. In 2011 we have:

- Proved that a covalent conjugation of an anti-inflammatory hydrophobic molecule (ibuprofen) with a previously designed kyotorphin derivative (analgesic dipeptide) has improved, synergistic, efficacy. (Ribeiro M.M., et al., 2011, Molecular Pharmaceutics, Oct 3;8(5):1929-40);
- Demonstrated a correlation between the efficacy of both HIV fusion inhibitors and anti-HIV antibodies with their membrane-interaction properties (Franquelim H.G., et al., 2011, AIDS, Feb 20;25; Franquelim H.G., et al., 2011, Soft Matter, Oct; 7:11089-11092);
- Optimized the imaging of bacteria with lesions resulting from the local action of antimicrobial peptides (AMP’s) using Atomic Force Microscopy, which brought significant advancements both to imaging of bacteria itself and the mechanism of action of AMP’s.

**SELECTED PUBLICATIONS**


**SIGNAL TRANSDUCTION PATHWAYS**

The role of the cell membrane in signal transduction is not limited to the passive anchoring of receptor proteins; it can also act as a reservoir for precursors of secondary messengers. This is the case of the phosphoinositides, which can be cleaved into the messenger molecules inositol-trisphosphate and diacylglycerols. The juxtaposition of hydrophilic and hydrophobic environments in the bilayer, coupled to the anisotropy of the phospholipid acyl chains, constrains the localization and orientation of both membrane proteins and their ligands. This aspect is central to the enzymatic processes that take place in the cell membrane.
Vascular Endothelial Growth Factor Receptor-2 (VEGFR2) is the major mediator of the angiogenic effects of VEGF. In addition to its well known role as a membrane receptor that activates multiple signaling pathways, VEGFR2 also has a nuclear localization. We found that VEGFR-2 activates its own promoter and by this mechanism could be involved in amplifying the angiogenic response.

Radiotherapy is a widely used treatment option in cancer. However, recent evidence suggests that doses of ionizing radiation delivered inside the tumor target volume, during fractionated radiotherapy, can promote tumor invasion and metastasis. Furthermore, the tissues that surround the tumor area are also exposed to low doses of ionizing radiation that are lower than those delivered inside the tumor mass. We found that low doses of ionizing radiation induce angiogenesis (A) and promote metastasis in a VEGF receptor dependent manner (B).

**SELECTED PUBLICATIONS**

Domingues I, Rino J, Demmers JAA, de Lanerolle P, Santos SCR (2011) VEGFR2 Translocates to the Nucleus to Regulate Its Own Transcription. PLoS ONE 6, e25668


SELECTED PUBLICATIONS

The Clinical and Translational Oncology Research Unit is focused in developing patient-driven research. Our main research lines center in the process of cancer metastization, either in the identification of new prognostic factors through the analysis of molecular signatures specific of cancer cells, or in the unraveling new therapeutic opportunities through the study of cancer cells molecular pathways. New molecular markers in colorectal cancer can be used for prognostic and stratification of patients according to their risk of relapse into specific organs, contributing for an improved follow-up and adjuvant therapy efficacy. To achieve this goal a large collection of paired samples comprising both primary tumors and metastasis from the same patients will be screened at gene expression level using cDNA microarrays. In bone metastatic disease, we aim to identify which specific subgroups of patients could benefit from bone-targeted therapies. New therapeutic possibilities based in the molecular triad RANK-RANKL-MMP1, specially aiming for an anti-tumoral effect, may improve patients overall survival and quality of life by decreasing skeletal-related effects.
The research work being developed at the Developmental Biology Unit aims to elucidate the molecular mechanisms that regulate the genesis of neurons in vertebrate embryos. Our goal is to understand how the establishment of neural precursors is regulated in vertebrate embryos, how these cells are maintained throughout development, and how they give rise to the multitude of neurons that compose the adult CNS. A better knowledge about these fundamental mechanisms is a pre-requisite for the future development of cellular therapies to treat neurodegenerative diseases.

An additional area of research at the Developmental Biology Unit is aimed at investigating the molecular mechanisms underlying the establishment of pluripotency in embryonic stem cells, focusing on the central role of Nanog in these molecular networks.

**SELECTED PUBLICATIONS**


Ramos C, Rocha S, Gaspar C, Henrique, D (2010) Two Notch ligands, Dll1 and Jag1, are differently restricted in their range of action to control neurogenesis in the mammalian spinal cord. PLoS One 24;5(11):e15515. (4 Citations and 1.014


Rocha SF, Lopes SS, Gossler A and Henrique D (2009) Dll1 and Dll4 function sequentially in the retina and pV2 domain of the spinal cord to regulate neurogenesis and create cell diversity; Dev. Biology 328:54-65

Henrique D, Bally-Cuif I (2010) A cross-disciplinary approach to understanding neural stem cell in development and disease, Development 137(12): 1933-8
Sepsis remains a poorly understood systemic inflammatory condition with high mortality rates and limited therapeutic options in addition to organ support measures. Most often, sepsis is triggered by a bacterial infection that causes excessive production of pro-inflammatory mediators, including the initial critical tumor necrosis factor (TNF) and interleukin 1β (IL-1β), leading to the activation of spiraling signaling cascades ultimately causing multi-organ failure and death. We have used a drug screen to identify the clinically approved group of anthracyclines as potent in vitro inhibitors of two key initiators of sepsis, TNF and IL-1β. In vivo, anthracyclines confer strong protection against severe sepsis induced by cecal ligation and puncture (CLP) in mice. This protective effect relies on the induction of autophagy and on an anti-inflammatory program that increase the tolerance to infection without reducing bacterial burden. Using an shRNA-based screen we identified the Ataxia Telangiectasia Mutated (ATM) as a mediator of the protective effect of anthracyclines. ATM deficient (Atm-/-) mice are refractory to this protective effect succumbing to severe sepsis with similar kinetics to the non-treated wild-type mice. Our results have identified the group of anthracyclines as effective therapeutic options in sepsis, and ATM as a potential molecular target in inflammation-driven conditions.
Inflammation aims to eliminate noxious agents to regain body homeostasis. At the microcirculation level, it involves the action of inflammatory mediators and vascular and blood cells that conduct the process either onto resolution or to a chronic stage. In this respect, we aim to dissect the cellular and molecular mechanisms that control leukocyte recruitment and erythrocyte function by studying: (1) the CD47/fibrinogen binding mechanisms and its repercussions on NO metabolism in blood and microvascular cells in acute and chronic inflammation; (2) the role of systemic hemorheological and inflammatory biomarkers in disease progress and as prognostic markers and (3) how distinct inflammatory cues, as chemokines and hydrogen peroxide, concert their action in driving leukocyte migration.

**SELECTED PUBLICATIONS**


**Group Leader**

CARLOTA SALDANHA

PhD (1986) in Biochemistry at Universidade Nova de Lisboa
Master (2000) in Medical Education joint degree at University of Wales and Faculdade de Medicina da Universidade de Lisboa (FMUL)
Associate Professor with Habilitation at FMUL

**Other Principal Investigator**

Ângelo Calado

Fluorescence microscopy images of the recruitment of eGFP-labelled neutrophils in tail transected 3dpf mpx:GFP larvae, pre-injected with the indicated morpholinos (MO), at 6 hours post wounding (hpw). Scale bar = 200µm. by Sofia de Oliveira

Fluorescent images of EGFP neutrophil infiltration 2h after induction of an intraperitoneal inflammatory stimulus. by Ana Silva-Herdade, Vanda Vitorino de Almeida and Cláudia Ferreira.
Biochemical and biophysical processes occurring at the level of the membranes of human cells, as well as of their viral and bacterial pathogens. Study of the two steps of the life cycle of enveloped viruses (mainly HIV-1 and dengue virus) that involve biomembranes – the entrance of the virus or its content into the target cell and the assembly of new virions. Study of the binding of fibrinogen to the erythrocyte membrane and its relevance as cardiovascular risk factor. Pre-clinical evaluation of the membrane activity and mechanism of action at the molecular level of antimicrobial peptides (AMP) and cell-penetrating peptides (CPP). On the Nanotechnology / Nanomedicine area, the structural characterization of metal nanoparticles conjugated with proteins or nucleic acids, for biomedical application.

**SELECTED PUBLICATIONS**

Carvalho FA, Carneiro FA, Martins IC, Assunção-Miranda I, Faustino AF, Pereira RM, Bozza PT, Castanho MARB, Mohana-Borges R, Da Poian AT, Santos NC (2012) Dengue virus capsid protein binding to hepatic lipid droplets (LD) is potassium ion dependent and is mediated by LD surface proteins. J. Virol., 86, 2096-2108


Matos PM, Castanho MARB, Santos NC (2010) HIV-1 fusion inhibitor peptides enfuvirtide and T-1249 interact with erythrocyte and lymphocyte membranes. PLoS ONE 5, e9830

The axial skeleton and skeletal muscles formation from the embryonic somites is a fascinating developmental process. As somites split off from the anterior end of the presomatic mesoderm, mesoderm progenitors in the tailbud continually generate new mesoderm cells and feed them into the posterior presomatic mesoderm. Using zebrafish as a model organism we were able to show that in the conversion of progenitors into presomatic mesoderm, differentiation is coupled with cell movement through Msgn1. In addition, we were able to complete the description of the Mesp proteins in zebrafish, a family that plays a crucial role in somite formation. We started to make a bridge between the fundamental developmental processes that we have been studying with the mechanisms that have to be activated during regeneration upon severe injury. In our first publication in the regeneration field we demonstrated that the regenerative capacity of zebrafish caudal fin is not affected by repeated amputations or ageing.

SELECTED PUBLICATIONS
Azevedo AS, Grotek B, Jacinto A, Weidinger G and Saúde L (2011) The regenerative capacity of the zebrafish caudal fin is not affected by repeated amputations. PLoS ONE Vol. 6(7); e22820
Lourenço R, Lopes S S and Saúde L (2010) Left-right function of dmrt2 genes is not conserved between zebrafish and mouse. PLoS ONE 5(12); e14438

How different cell types arise during vertebrate embryonic development and how do they organize into specific tissues and functional organs are fascinating questions in Biology that we wish to answer. From left-up to right-down: ciliated laterality organ in zebrafish; somite progenitors and notochord cells in zebrafish; musculature in zebrafish pectoral fin; heart tube bending to the right in chicken; vacuolated notochord in zebrafish; charon expression in the zebrafish laterality organ; expression of a segmentation clock gene in zebrafish; skeletal muscle fibers in zebrafish; cell proliferation upon amputation in a zebrafish caudal fin; somites in zebrafish; bony rays in the zebrafish caudal fin; crystalline lens of the eye fluorescently labeled in zebrafish; the gastrula organizer in chicken; one bony ray in a zebrafish caudal fin; labeled cells in the gastrula organizer in chicken; heart tube bending to the left in zebrafish; fluorescent zebrafish embryos; laterality organ in zebrafish.
The study of the immune response has had major contributions to human health, especially in what concerns the rational design of vaccination strategies against multiple infectious agents. The ultimate success case has been the eradication of smallpox in 1979. However, immunologists and microbiologists still face major challenges, such as the prevalence of Malaria, Tuberculosis and AIDS, and the emergence of novel strains of antibiotic-resistant bacteria. Moreover, the incidence of diseases like cancer, allergy and autoimmune disorders has risen very dramatically in the last half century, posing growing challenges to immunologists. The Programme of Immunology and Infectious Diseases at IMM aims at elucidating the basic biological mechanisms that underlie the dynamic interaction between the host and distinct pathogens, such as retroviruses (HIV), gamma herpes viruses, Streptococcus, and parasites – Trypanosome and Plasmodium (Malaria causing agent). We are also concerned with other aspects of the immune system, particularly its overactivation in autoimmune diseases (such as rheumatoid arthritis) and allergy. We aim at testing new protocols that tune down undesirable immune responses. Finally, we investigate the potent anti-tumor activity of some cells of the immune system (such as T lymphocytes), aiming at improving the prospects of treating cancer through immunotherapy. Altogether, our research is directed at understanding how humans interact with and defend themselves from pathogens, while maintaining a controlled and healthy immune system. Only a comprehensive knowledge of these processes will allow the development of novel and sustainable strategies to combat these major threats to human health.
The only Research Nutrition and Metabolism Unit in Portugal, its high quality of advanced Education and Research are widely recognized. Both achievements are highlighted by Publications in Journals with high impact factors, e.g. Hepatology/Journal of Hepatology/The Oncologist/Journal of Clinical Oncology/The Lancet Oncologist, and in the internationalization with major roles in international bodies, lectures in major national and international Congresses and advanced teaching. A small multidisciplinary team has reached international recognition via cutting edge research of excellence in two main areas: Liver Fat Metabolism, from clinical to translational research; Nutrition and Cancer. The Unit is increasingly involved in advanced teaching: chosen for the integrated Master Degree in Medicine, Nutrition Master and PhD Programs.

**SELECTED PUBLICATIONS**


**Group Leader**

**MARIA ERMELINDA CAMILO**

MD, PhD – retired since June 2008 from Auxiliary Professor Faculdade de Medicina da Universidade de Lisboa

**Other Principal Investigators**

Helena Cortez-Pinto, Isabel Monteiro Grillo, Paula Ravasco
**SELECTED PUBLICATIONS**


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**Antigenic Variation**

*Trypanosoma brucei* escapes the host immune system by periodically switching its surface coat made of Variant Surface Glycoproteins.

**Parasite with a mosaic VSG coat**

If antigenic variation is not properly regulated, parasites may lose the capacity to express only one VSG coat at a time.
Ongoing research projects at the Rheumatology Research Unit are devoted to the study of the early burden of inflammatory rheumatic diseases on bone and vessel, seeking prognostic markers, predictors of treatment response and new treatment targets.

The Unit has characterized the cytokine network, the behavior of B cells, the role of neutrophils and the contribution of the inflammasome during the early phase of rheumatoid arthritis. Additionally, we have described the mechanisms of the degradation of bone biomechanical properties in patients and animal models of arthritis, as well as the changes in bone gene expression that occur in rheumatoid arthritis and also in fragility fracture patients.

We have also identified clinical and biological risk factors for atherogenesis and proposed pharmacogenetic and prognostic genetic markers relevant in the context of rheumatic diseases.

The Unit has coordinated, on behalf of the Portuguese Society of Rheumatology, the national registry of rheumatic patients, Reuma.pt, the Portuguese Rheumatology Biobank, integrated in IMM Biobank and is involved in the national epidemiologic study of rheumatic diseases, EpiReumaPt.

SELECTED PUBLICATIONS


Authors Rita Casção, Rita Moura and Joana Lopes
The Cellular Immunology Unit studies the mechanisms underlying the induction and maintenance of immune tolerance. We found that CD4-blockade can induce long-term tolerance in a mouse model of multiple sclerosis and rheumatoid arthritis. Tolerance is associated with alteration of Th17/Treg ratio, as well as elimination of pre-committed effector cells. We have also shown that long-term tolerance to allergens can be induced with anti-CD4 antibodies, including in an animal model of peanut-induced anaphylaxis. In 2011 we were among the first groups to report a novel subset of follicular helper T cells (Tfh) that express Foxp3 and regulate the germinal centre reaction. We named these cells as follicular regulatory T cells (Tfr).

**SELECTED PUBLICATIONS**


Agua-Doce A, Graça L (2011) Prevention of house dust mite-induced allergic airways disease in mice through immune tolerance. PLoS ONE 6(7):e22320


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Group Leader

**LUÍS GRAÇA**

MD (1995) at Faculdade de Medicina da Universidade de Lisboa (FMUL)

PhD (2002) in Immunology at the University of Oxford, UK

Post-doctoral research at University of Oxford, UK, and at University of Western Australia, Perth

Assistant Professor at FMUL
A universal feature of sexual development is the storage of mRNA to provide coding potential for proteins during early post-fertilisation development. Stabilisation of quiescent mRNA pools in Plasmodium gametocytes depends on an evolutionarily conserved protein core. Gene deletion mutants of key components of the mRNP (DOZI, CITH) are fertilization-competent, but zygotes fail to develop further. Through RNA pull down and immunoprecipitation, and global expression profiling of mutants we highlighted crucial repressors of maternally supplied mRNAs. Our data define P bodies as critical components for development in the initial stages of Plasmodium mosquito infection. During transmission from mosquito vector to mammalian host we have identified the RNA binding protein Pumilio as a regulator of development; in its absence sporozoites develop prematurely into liver stage forms with accompanying changes in gene expression profiles that are typical of liver stage development.

**SELECTED PUBLICATIONS**


Aiming to uncover Plasmodium requirements to establish in its host, we have performed the first large-scale studies that identified key host factors involved in hepatocyte infection by Plasmodium. Additionally, we have revealed that during the liver stage of infection Plasmodium co-opts a host enzyme, HO-1, to be protected from the host inflammatory response. Interestingly, we also show that this same host enzyme and its end-product carbon monoxide promote host survival during blood stage of infection. As such, we then became extremely interested on how liver and the blood stages of infection influence each other. We showed that blood-stage parasitaemia impairs the establishment of a subsequent liver infection, explaining why Plasmodium superinfection is rarely found in young non-immune children.

**SELECTED PUBLICATIONS**


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Identification of lineages of *S. pneumoniae* with different invasive disease potential within groups sharing the same serotype. Description of a stable population of *S. agalactiae* causing invasive neonatal disease in a period of 10 years. Evaluation of different sampling methodologies to determine confidence intervals of congruence agreement measures and identification of the best approach. Proposal of a new directional agreement metric.

Development of a novel and rapid flow cytometry based assay for antimalarial drug sensitivity testing, using detection of haemozoin without any further reagents. Synthesis and purification of synthetic haemozoin and from *P. falciparum* culture, and evaluation of its immunomodulatory properties in human and mouse leukocytes. In-vivo effect of haemozoin in a mouse model on re-infection with *Plasmodium* spp. Interactions of haemozoin with *M. tuberculosis* in an in-vitro model using mouse monocytes. Effect of haemozoin on phagocytosis using a *Salmonella* model.

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**SELECTED PUBLICATIONS**


We study the biology of T lymphocytes and their key roles in immunity to infection and cancer. Our projects concentrate on the development of these cells in the vertebrate thymus, and on their functions upon export to the periphery. We have recently identified new molecular players in the differentiation and activation of murine γδ T cells (see below) and Foxp3+ regulatory αβ T cells. We also investigate human γδ T cells, and we have made important original contributions on the molecular mechanisms of tumor cell recognition and elimination, thus aiming at the design of novel cancer immunotherapy strategies.

Model for the differentiation and activation of functional γδ T cell subsets.

From TCRγδ + CD27+ CD25− thymocyte progenitors, two mature CD25− subsets are derived: γδ 27+ and γδ 27− cells. CD27 signaling promotes the development of γδ 27+ thymocytes which commit to IFN-γ expression. By contrast, γδ 27− thymocytes acquire the exclusive capacity to express IL-17. Mature γδ T cell subsets maintain their distinct functional properties in peripheral lymphoid organs, where γδ 27+ cells expand upon TCR plus CD27 stimulation, whereas γδ 27− cells proliferate in response to innate signals downstream of TLR2 and TLR4, namely IL-1β and IL-23 produced by macrophages (Mac) and dendritic cells (DC). (Based on Ribot et al. Nature Immunol 2009 and Ribot et al. J Immunol 2010)

The Natural Cytotoxicity Receptor Nkp30 is specifically expressed on activated human Vδ1+ T lymphocytes. Our data showed that, within human γδ T cells, Nkp30 can be selectively induced in the Vδ1+ subset, thus endowing these lymphocytes with enhanced cytotoxicity against leukemia and other tumor cells (D.V. Correia et al. Blood 2011).

SELECTED PUBLICATIONS


Group Leader
BRUNO SILVA-SANTOS
PhD (2002) in Immunology at University College London, UK
Post-doctoral research at King’s College London, UK
Auxiliary Professor at Faculdade de Medicina da Universidade de Lisboa

Other Principal Investigators
Ana Pamplona
The overall aim of the Viral Pathogenesis Unit is to gain an understanding of the basic molecular mechanisms involved in the modulation of cellular function by herpesviruses. Herpesviruses are a major cause of disease worldwide and are amongst the most successful human pathogens, with specific viruses infecting more than 90% of the world’s population. The main biological feature of these viruses is their ability to persist and reactivate in a primed immunocompetent host. The control of herpesviruses infections thus represents an important clinical goal. To achieve this we must first understand the basic mechanisms of viral pathogenesis. We use a laboratory animal model of infection with murine gamma-herpesvirus-68 (MHV-68), which establishes latent infection in B-lymphocytes. The ability to genetically manipulate both the virus and the host allows the dissection of the molecular mechanisms involved in the virus/host interaction.

### SELECTED PUBLICATIONS


The Clinical Immunology Unit (UIC) prioritizes the “bedside to the bench” approach and, given the transversal nature of Clinical Immunology, brings together physician/clinical researchers from different medical areas, and basic researchers. Our research on HIV-2 infection, an attenuated naturally occurring model of HIV disease, has provided important contributions to the understanding of HIV/AIDS Immunopathogenesis.

UIC’s research on immune reconstitution, a critical translational area in human immunology, aims to uncover regulatory T cell development in the human thymus, and the role of IL-7 as a major cytokine in T cell homeostasis.

UIC is part of a reference Centre for Primary Immunodeficiency involving the Hospital Santa Maria and the FMUL, and has made significant contributions to the study of these rare diseases, which, as unique natural models allow an improved understanding of the immune system.

SELECTED PUBLICATIONS


Differential mechanisms for enteric organogenesis: We have found that LTin cells are critical players in the earliest phases of enteric lymphoid organ development. Thus, adhesion mediated motility arrest of Lymphoid Tissue initiator (LTin) cells determine early maturation of enteric mesenchymal cells in a RET dependent, chemokine independent manner.

Role of neurotrophic factors during haematopoiesis: Neurotrophic factors of the GDNF family ligands (GFLs) signal through the RET tyrosine kinase receptor and are critical molecules for nervous system function. Our work showed that RET is a novel and critical molecule for HSCs survival, opening new horizons for the usage of RET/GFL signalling axes as therapeutic targets in HSC transplantation protocols.

Role of RET in enteric homeostasis: Using a RET reporter mouse line we found that this kinase is highly expressed in mucosal lymphocytes. Using loss and gain of RET function models we have found a critical role of RET in mucosal homeostasis.

Generation of transgenic models for de-regulated Ret expression in lymphocytes: In the laboratory we have generated different genetically modified mouse models: Ret conditional KO mice; Ret KI in the Rosa26 locus; hCD2-Ret; hCD2-RetMEN2A and hCD2-RetMEN2B transgenic mice. We have obtained several founders and part of them had germ-line transmission. These transgenic lines are currently being characterised.

Role of Retinoic Acid (RA) in enteric lymphoid organogenesis: Genetic analysis revealed that RA signalling is critically involved in haematopoietic cell differentiation.

SELECTED PUBLICATIONS


Neurological diseases represent important medical and socioeconomic problems and raise fascinating neuroscience questions. At the IMM we use basic scientific approaches to study major disorders of the nervous system, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, Amyotrophic Lateral Sclerosis, epilepsy or stroke. It is likely that the molecular profiles of diseased brains and nerve cells at the central and peripheral nervous system, established by genomic, proteomic and other approaches, coupled to detailed functional studies, will identify the mechanisms of relevant neurological dysfunctions. Importantly, we couple novel molecular approaches with extensive expertise in pharmacology and functional neuroscience. A close proximity of basically oriented and clinically oriented research groups also enables the IMM Neurosciences Programme to position as leader in translational research. Overall, the Neurosciences Program establishes a bridge from molecular and cell investigation to clinical application, according to a translational model of research. We aim to better understand the functioning of the nervous system in order to establish new strategies to improve diagnosis, treatment and prevention of the neurological conditions. Throughout the history of neuroscience, the investigation of neurological conditions has driven scientific progress in Neurosciences. We intend to be part of this dynamic process, covering from the molecule to the brain and cognition.
We have developed scientific research on Amyotrophic Lateral Sclerosis (wireless control of home-ventilation, trial on respiratory exercise in ALS, genetic abnormalities, biomarkers of disease progression) and in Familial Amyloid Polyneuropathy (early markers of disease progression). We also reached major achievements on the clarification of the inner mechanisms regulating choroidal circulation; on the elucidation of the autonomic interference in the genesis and maintenance of atrial fibrillation and its relationship to molecular expression of ion channels, connexins and cardiac purinergic system; on demonstrating the role central sympathetic areas hyperexcitability on neurogenic hypertension; on showing that autonomic remodeling is on the basis of life quality improvement in patients with neurocardiogenic syncope; on the mathematical development and software validation applied to autonomic evaluation (mod HHT, coherence, forecasting, FISIOSINAL); development of a prototype to evaluate urinary bladder volume non-invasively and a LED sensor to detect non invasively blood gases. Our research team members have driven significant advances on dysfunctional emotional processing, behavioural changes, the neural circuits that generate tics in Tourette’s syndrome and conflict adaptation. The main target of our group in the future is to join all these different approaches in a common strategy.

SELECTED PUBLICATIONS


In cerebral venous thrombosis, the description was made of the risk factors for venous thrombotic events, and identification of the patients who benefit most from prolonged anticoagulation and from decompressive surgery. Regarding vascular white matter changes, the risk of specific subtypes of dementia and identification of its clinical, imagiological and neuropsychological predictors was accomplished. Advances were made on the understanding of memory complaints in healthy young and elderly adults, and the determination of the prognosis of elderly people with cognitive complaints who do not fulfill criteria for Mild Cognitive Impairment. New data were published on the relationship of genetic risk factors and mitochondrial genome polymorphisms with susceptibility to Behçet’s Disease. Significant progresses were done on the study of language recovery after early brain lesions and the development of new assessment tools and normative data for language and cognitive evaluation. Concerning the study of dreams, preliminary but promising novel data were presented. The analysis of the impact of illiteracy on neuropsychological test performance, as an approach to understand human cognition and its brain organization under normal and abnormal conditions, was also accomplished.

SELECTED PUBLICATIONS


The Basic Neurosciences Unit at IMM has been devoted to the knowledge on how to protect the brain and to understand dysfunctions in the perspective of synaptic and cognitive changes that occur during the pathological processes. Our main focus is on availability of neurotransmitters to operate synapses in its tripartite compartments: nerve endings, postsynaptic neuron and glia. During the last years our main achievements were:

1. The discovery that adenosine A2A receptors enhance or even trigger synaptic actions of neurotrophic factors either in young or aged animals. With these data it might be possible to develop pharmacological approaches for neurodegenerative diseases, since A2A receptor activation by substances that easily reach the brain after systemic administration may overcome the difficulties with direct administration of neurotrophic factors, which hardly cross the blood brain barrier.

2. The discovery that chronic blockade of adenosine A2A receptors reverts chronic stress-induced synaptic disfunctions, with impact upon learning and memory performance even long after the stress insult. These data allow envisaging a relevant role of A2A receptor blocker in stress-related diseases.

3. The discovery that chronic caffeine consumption, through an upregulation of adenosine A1 receptors, exacerbates memory dysfunction caused by THC, an active substance of the cannabis plant, highlighting the possibility of functional interactions between caffeine and cannabinoid consumption, with implications for memory performance.

4. By discovering that adenosine A2A receptors control transporters, namely adenosine transporters and GABA transporters, either on nerve endings or astrocytes, and that they do so as a function of neuronal activity, therefore playing an active role in astrocyte to neuron communication at the tripartite synapse.

5. Adenosine A1/A2A receptor heteromers have been identified for the first time in non-immortalized cells; the heteromer stoichiometry was discovered and the nature of G-protein coupling identified.

SELECTED PUBLICATIONS


Within the scope of the three IMM research programmes, a number of partnerships have been established with research teams based at other national institutions, termed External Units. IMM hosts also double appointments of group leaders affiliated to both IMM and other international institutions, which are termed Associate Units. These partnerships promote ideas and technology sharing, aiming at creating and developing synergies between the partners.
The ability of Koch’s bacilli (Mtb) to create tuberculosis or a latent infection relay, in part, on the powerful mechanisms it has evolved to parasitize host macrophages and dendritic cells. Our major aim is to better understand the molecular mechanisms by which 1) Mtb controls the acquisition of cathepsins and their inhibitors cystatins within phagosomes, an important phenomenon for antigen presentation and inflammasome activation 2) Mtb PAMPs activates distinct inflammasomes 3) trafficking host factors are involved in Mtb uptake by macrophages, phagosome maturation and exosome secretion and finally 4) micro RNAs controls actin dynamics during early steps of Mtb phagocytosis.

We found that Mtb activates the over-expression and down-regulation of a set of miRNAs during macrophage phagocytosis and that some are involved in controlling actin dynamics. We studied the distribution of key cathepsins (catB, cat L and cat S) inside human macrophages and dendritic cells infected with M.tuberculosis complex. It was found that the enzymatic containment and function is distinct in both cells.

We evaluated the antimycobacterial effect of extracts from medicinal plants from Mozambique. Indeed chemical compounds prodrugs derived with activity against PZA resistance mycobacteria strains and species were characterized (patent application submitted). A Systematic Identification of NLR and CARD-domain containing proteins involved in IL-1β response to Mtb was performed and CARD9 was common to several conditions.

**SELECTED PUBLICATIONS**


*joined first authors


We are interested in identifying cellular proteins and pathways involved in the process of HIV-1 latency and restriction to infection that may result in the discovery of strategies to eradicate the virus. By manipulating the transcription of genes controlling the HIV-1 life-cycle, specifically using zinc-finger library screening we aim to answer questions related to the mechanism of APOBEC3G expression/regulation and discovery of HIV restriction factors. To eradicate HIV-1 or inhibit viral infectivity we are developing strategies based on the platform of small antibody scaffolds and design of zinc-fingers that recognize specific regions of HIV-1 sequence. We identified novel restriction pathways deleterious for HIV-1 replication in T lymphocytes. This study brings new insights for the complex interplay of HIV-1/host cell and opens new possibilities for antiviral strategies. We designed new synthetic small domain antibodies that are able to target gp41 and gp120 that are capable to inhibit HIV-1 and HIV-2 infection. We have submitted a patent that addresses HIV-1 fusion inhibition using bacterial derived peptides. In addition, to address the issue of increasing the half-life of small antibody domains we submitted a patent application concerning the invention of an albumin-binding domain to improve the pharmacokinetic of therapeutic proteins. We demonstrated the applicability of protein complementation assay to quantitatively study the interaction between HIV-1 Vif and APOBEC proteins.

SELECTED PUBLICATIONS
In biology several important processes occur at spatial dimensions currently beyond the reaches of light microscopy. Our lab focuses on biological questions at this scale as they are related to gene expression. We study RNA transcription, metabolism and transport, as well as the development and innovation of technology to study these problems. Dynamic multi-molecular complexes in the eukaryotic cell nucleus remain well outside the resolution of light microscopy. Intrinsic to RNA transcription are modifications to nuclear architecture and the repositioning of chromosomal loci, and the interplay of ribonucleic proteins. These events remain opaque at the single molecule level, and are intensively researched by our research group. The laboratory published two publications in the last months and also developed new releases of its QuickPALM software for super resolution microscopy. In addition a European patent was awarded to the PI of the laboratory in late 2011.

SELECTED PUBLICATIONS


Protein misfolding disorders. The overall aim of our laboratory is to understand the cellular and molecular basis of neurodegenerative disorders such as Parkinson’s, Alzheimer’s or Huntington’s diseases. These disorders are characterized by the presence of protein aggregates in the brain, which are thought to play a key role in neurodegeneration. By means of innovative methods, we are now able to reproduce the production of protein aggregates in cells in culture and thus find genetic and pharmacological modifiers of these disorders. In the upper picture, a mutant form of the huntingtin protein, the causative agent of Huntington’s disease, forms oligomers (diffuse fluorescence) and large aggregates (fluorescent dots) in the cytoplasm of human cells. A blue fluorescent staining (DAPI) shows the cell nuclei. Our laboratory has similar cellular models for the study of Parkinson’s disease.

SELECTED PUBLICATIONS


Alongside with research, IMM has a core of resource facilities, which complement and maintain the high quality service environment. In the spirit of shared resources, IMM offers recently equipped state-of-the-art Facilities: Biobank, Flow Cytometry, Bioimaging, Animal House and Zebra Fish, Biosafety Level 3 Laboratory (P3) and a Histology Service. All resource units have dedicated staff that provides support to IMM community and develops initiatives to promote research.
The Biobank has the mission of fostering translational and clinical research in the Lisbon Academic Medical Centre. It will promote the study of the pathogenesis of diseases with impact on human health, contributing to the identification of new prognostic and diagnostic tests and novel therapeutic targets. The Biobank will act as a catalytic factor for the cooperation between national and international academic researchers and between the academia and the pharmaceutical industry. It includes biological samples (from surgery, biopsies, blood samples and other biological products) that are donated voluntarily, after written informed consent, for preservation and future use in biomedical research. All samples are accompanied by clinical information, a crucial factor for subsequent investigation, and a dedicated information system manages the biological and clinical depository. The Biobank is approved by the Institutional Ethics Committee and by the National Commission for Data Protection. It is integrated in an European Network of Biobanks. All the deposited collections have a written agreement between the project’s principal investigator and IMM. To apply for the use of Biobank samples a contact with the collection’s principal investigator has to be done and a research project has to be previously approved by an Ethics Commission and by the Scientific Committee of the Biobank.

The Bioimaging Unit constitutes the core microscopy facility of the IMM, serving as a support structure to carry out and nurture research done with Light Microscopy inside the institute. We aim at providing IMM scientists and visitors with excellence in scientific know-how and expertise in using advanced light microscopy methods for their research. We assist in project planning, experiment design, provide advice and support on sample preparation, image analysis and processing and in writing research papers with microscopy data. Together with continuous training of new users, we organize regular courses and workshops on basic and advanced microscopy techniques. We research novel microscopy techniques for detecting protein-protein interactions and measuring protein dynamics in collaboration with research units with challenging biological problems.
The IMM houses a 70 m2 BSL3 Facility meeting the highest safety standards as defined by European and International guidelines. Work to be carried out in this Facility includes all experimental procedures biosafety level 3 pathogens. The Facility is available to IMM internal and affiliated researchers, as well as to external researchers from academia, pharma and biotech. The Facility provides education, training, and guidance for researchers and is constantly monitored by a fully dedicated technical supervisor. Applications to use the IMM’s BSL3 laboratories are reviewed and must be approved by the Facility’s supervisor and Scientific Commission before access is granted.

**BIOSAFETY LEVEL 3 LABORATORY**

**Head of Unit**

**Miguel Prudêncio**  
PhD (2000) from University of East Anglia (UK)  
Post-doctoral research Fellow at University of Leiden (The Netherlands) and at the IMM  
Staff scientist at the IMM since 2008  
Head of Facility since 2009

**Staff**  
Inês Matos (Technician)

**FLOW CYTOMETRY**

**Head of facility**

**Maria Soares**  
PhD (2002) in Immunology at University College London  
Post-doctoral research fellow at University College London, UK and at IMM  
Staff scientist at the IMM since 2008  
Head of Facility since July 2009

**Staff**  
Ana Isabel Pinto (Technician),  
Ana Isabel Vieira (Technician)

The Flow Cytometry Unit provides support and training in flow cytometry to IMM and external users. This training takes place on an individual basis or through workshops. We provide support in experiment planning, instrument operation, data analysis and interpretation. A substantial part of our work is taken by the cell sorting service. The two High Speed Cell Sorters available are operated by our staff only and are equipped with distinct lasers allowing a significant degree of flexibility in fluorochrome choice for our users. In 2011 UCF users comprised a total of 31 Units, representing a total of 152 researchers. Our staff also ensures adequate quality control and maintenance on all instruments. The involvement of UCF staff in research projects enables us to be up-to-date with advances in the technology and provides a stimulating working environment.

**HISTOLOGY SERVICE**

**Head of Unit**

**Sandra Casimiro**  
PhD (2007) in Molecular Biology, at FCUL-UL, Lisbon, Portugal  
Post-doctoral Fellow at IMM since 2007

**Staff**  
Afonso Fernandes (Scientific Consultant),  
Andreia Pinto (Technician),  
Ana Farinho (Technician)

Starting on September 2009, the Histology Service (HS) was implemented in IMM, resulting from collaboration with the Histology Institute of Faculdade de Medicina da Universidade de Lisboa (FML). The Histology Service has a permanent technician, and is located in the Histology facilities of the Histology Institute of FML.

The main objectives of the Histology Service are: processing tissue samples for routine histochemical procedures; processing and visualization of samples for Transmission Electron Microscopy (in collaboration with the Instituto Gulbenkian de Ciência); processing of samples for Laser Capture Microdissection; training new users in sample preparation and analysis with the available equipment in the laboratory; and provide tutorship in the design and implementation of immunostaining and other procedures not performed in the Service.

Since the Histology Service implementation a total of 22 IMM research Units have used the available services in a regular basis. The HS also provides services for five external users, including biotech companies and hospitals. In 2011 we upgraded our services in Transmission Electron Microscopy (TEM), by establishing a new collaboration with Prof. Dr. Fernando Fonseca, EPE (Amadora-Sintra) for visualization of samples, offering now two different equipments to our users. In the last year we also implemented processing of samples and tutorship on Laser Pressure Microdissection.
The IMM Rodent Facility has two main units: one conventional and one SPF. The conventional unit started in 2003 as a small set of 4 rooms with the total capacity to house 1200 animals. During the autumn of 2011 this unit has been remodeled and now has the capacity to house 7500 mice and rats. The SPF unit hosts about 10000 mice and rats, in either the Production or the Experimental area. In the experimental area, there are three rooms for experimental work with animals: two procedure rooms and one surgical suite. All husbandry and manipulation procedures are performed according to high standards of biocontainment and bioexclusion, in order to ensure the best possible conditions in terms of health and safety. This unit is highly committed to follow the 3Rs – Replacement, Reduction, Refinement – and provides education, training, and guidance for researchers, according to the Portuguese and international laws/recommendations for good practices and animal welfare.

The zebrafish (Danio rerio) is a representative of the vertebrate species and is used for the study of human genetic diseases such as cancer, cardiovascular disorders, neurological diseases, inflammation, angiogenesis, muscle-associated diseases and osteoporosis. Unlike humans, the zebrafish is one of the few vertebrate species that can fully restore the shape, structure and function of body parts lost after severe injury or amputation. Therefore, it has become a powerful model for regenerative medicine. The IMM zebrafish facility hosts over 5000 fish in a state-of-the-art housing system. Besides wild type lines there are 33 transgenic lines and 17 mutant lines available to the IMM scientific staff for research purposes. As a service we can provide technical help to manage line stocks, identify transgenic and mutant lines, electroporate DNA and morpholino oligos into adult fish, microinject DNA, RNA and morpholino oligos into embryos, cell/tissue transplantation in embryos. The IMM zebrafish facility is committed to follow the 3Rs principles – Replace, Reduce and Refine – for responsible use of laboratory animals.

Since September 2011 the Zebra Fish Facility is hosting a new business unit from Technophage, called TechnoZeb.
ONGOING PARTNERSHIPS:

Lisbon Academic Medical Centre: IMM is associated with the Faculdade de Medicina da Universidade de Lisboa and with the Santa Maria teaching hospital through the Lisbon Academic Medical Centre of Lisbon (CAML). CAML is a newly formed consortium that aims at promoting the academic dimension in clinical practice, renewing the teaching hospital concept.

- IMM is also a partner of the Harvard Medical School – Portugal programme, sponsored by the Portuguese Fundação para a Ciência e a Tecnologia. This programme aims at promoting translational and clinical research and the dissemination of medical and health information.

- IMM and Inserm, aware of the need to develop international cooperation in the fields of life sciences and health research and of health, assigned an agreement in 2010 to establish a partnership which builds on sound research expertise of both institutions to deliver scientific international workshops, short-term staff exchanges and research mentoring for MD students.

- IMM fosters scientific ideas to turn into products and technologies that make difference in health care. Presently, there are three companies incubated at IMM: Genomed, Technophage and Thelial.

- IMM is one of the leading founders of the Health Cluster Portugal, a consortium that promotes initiatives to increase the national competitiveness, innovation and technology in health care in Portugal.
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