IMM 2011 REPORT

INSTITUTO DE MEDICINA MOLECULAR
FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

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FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA
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-
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Communication Unit of IMM

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IMM
Luis Costa Photo in page 25: Jorge Correia Luís, JasFarma 2011

May, 2012

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FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

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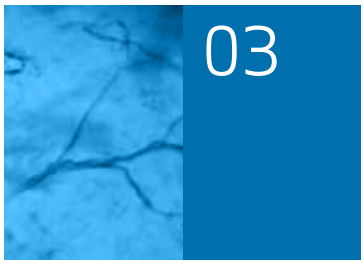
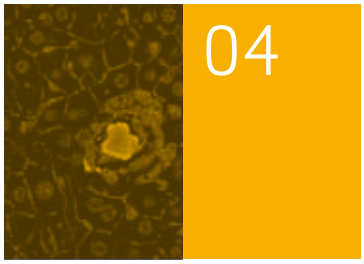




EDITORIAL

by J. Lobo Antunes and Maria Carmo-Fonseca

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.

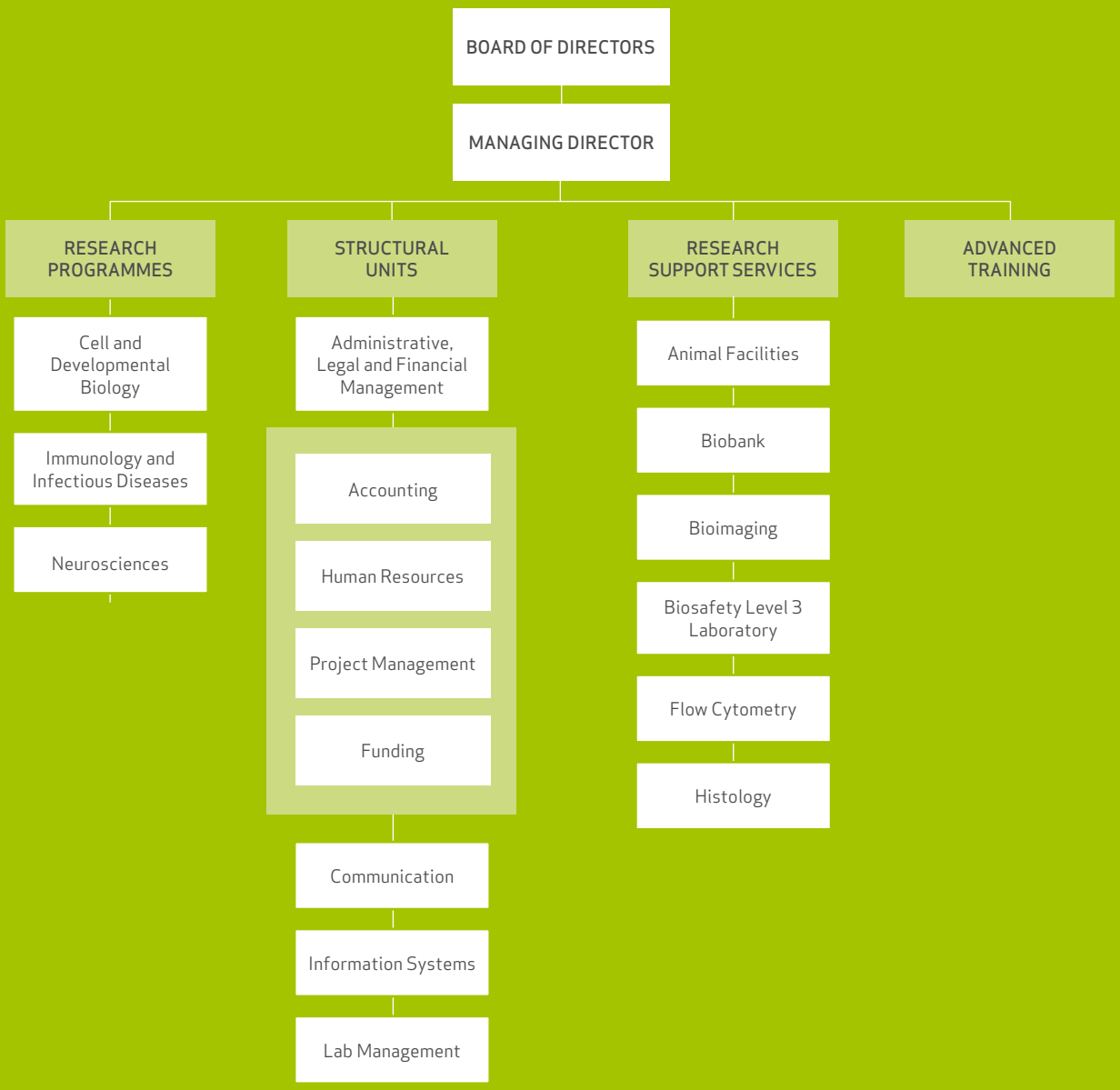
IMM was created in December 2001 through the merging of five centers that carried out research activities in the areas of Cell and Molecular Biology, Developmental Biology, Biochemistry, Immunology, Nutrition and Neurosciences at the University of Lisbon Medical School. IMM was awarded the special status 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.

J Lobo Antunes
President

Maria Carmo-Fonseca
Executive Director



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

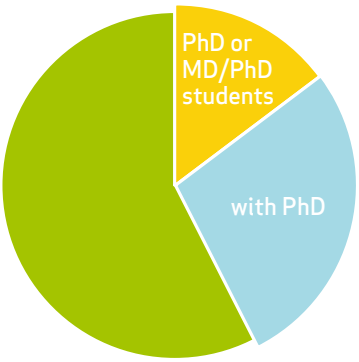
IMMUNOLOGY AND INFECTIOUS DISEASES PROGRAMME

- 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

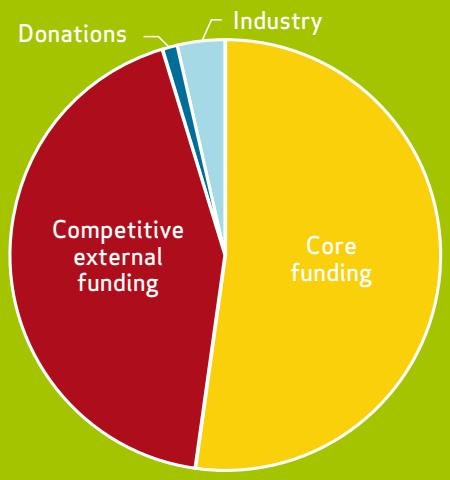
- Stroke
- Parkinson 's disease
- Alzheimer 's disease
- Amyotrophic Lateral Sclerosis
- Neurophysiology

TOTAL EXPENDITURE

TOTAL EXPENDITURE
11.414.588 €

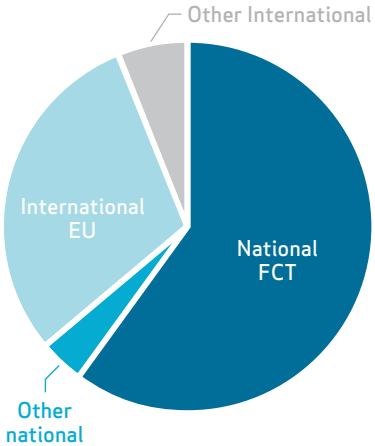
EXPENDITURE / PAPERS JIF≥5
140.920 €

EXPENDITURE / CITATION
3.705 €



COMPETITIVE EXTERNAL FUNDING

in euros



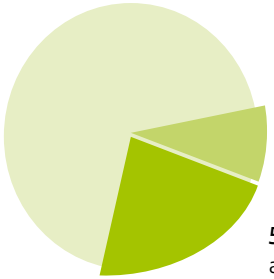
TOTAL
4917622 €

National FCT:	International EU:
2956764 €	**1472584 €**
Other national:	Other International:
194149 €	**294124 €**

RESEARCH HIGHLIGHTS

PAPERS 2011 :

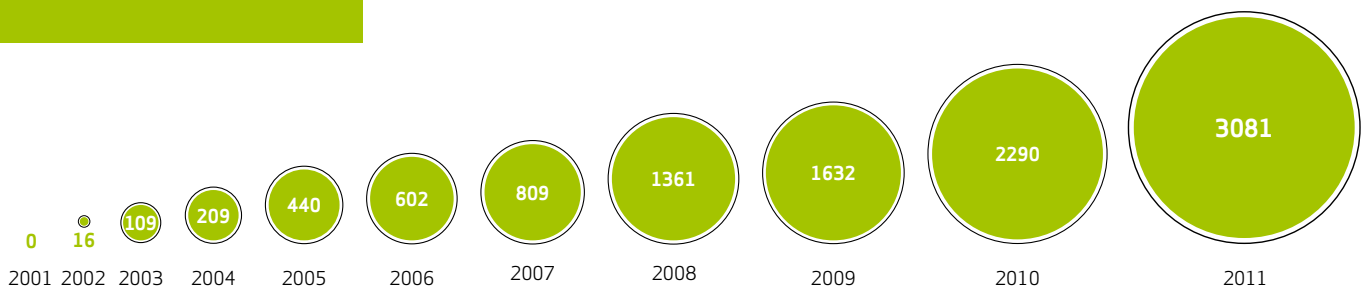
287 papers published in peer reviewed journals



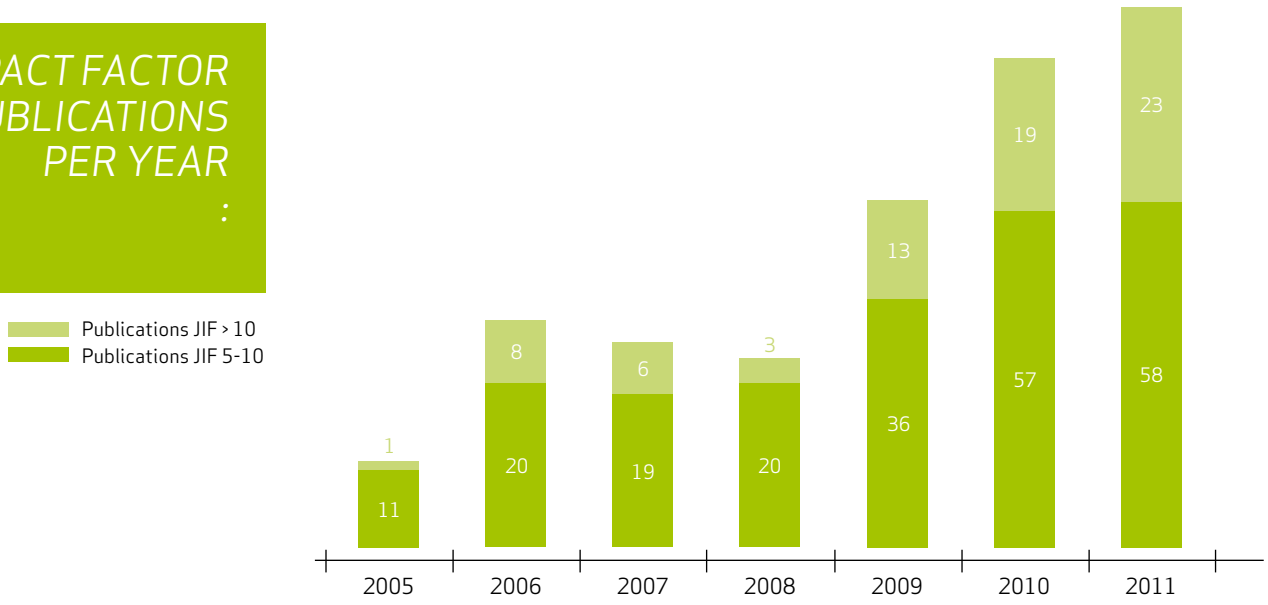
23 publications in journals with an impact factor higher than 10

58 publications in journals with an impact factor between 5-10

CITATIONS PER YEAR :



IMPACT FACTOR OF PUBLICATIONS PER YEAR :



RECENT MOST RELEVANT PAPERS :

Zenatti PP, Ribeiro D, Li W,Zuurbier L, Silva MC, Paganin M, Tritapoe J, Hixon JA, Silveira AB, Cardoso BA, Sarmento LM, Correia N, Toribio ML, Kobarg J, Horstmann M, Pieters R, Brandalise SR, Ferrando AA, Meijerink, JP, Durum SK, Yunes JA, Barata JT (2011) Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. *Nature Genetics* 43 (10): 932-939. (Journal IF: 36.377)

Portugal S, Carret C, Recker M, Armitage A, Sullivan D, Roy Cindy, Newbold CJ, Drakesmith H, Mota MM (2011) Host-mediated control of Malaria Superinfection. *Nature Medicine*. 17(6):732. (Journal IF: 25.430)

Ostrowski M, Carmo NB, Krumeich S, Fanget I, Raposo G, Savina A, Moita CF, Schauer K, Hume AN, Freitas RP, Goud B, Benaroch P, Hacohen N, Fukuda M, Desnos C, Seabra MC, Darchen F, Amigorena S, Moita LF* Thery C*. (2010) Rab27a and Rab27b control different steps of the exosome secretion pathway. *Nature Cell Biology* 12 (1), 19-30. *Corresponding authors. (Journal IF: 19.527)

Henriques R, Lelek M, Fornasiero EF, Valtorta F, Zimmer C, Mhlanga MM (2010) QuickPALM: 3D real-time photoactivation nanoscopy image processing in Image. *Nature Methods* 7 (5), 339-340. (Journal IF: 16.874)

Batalha VL, Pego J M, Fontinha B M, Costenla A R, Valadas J S, Baqi Y, Radjainia H, Müller C E, Sebastião A M and Lopes L V (2012) Adenosine A_{2A} receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation. Molecular Psychiatry , (28 February 2012) | doi:10.1038/mp.2012.8 (Journal IF: 15.470)

de Almeida SF, Grosso AR, Koch F, Fenouil R, Carvalho S, Andrade J, Levezinho H, Gut M, Eick D, Gut I, Andrau JC, Ferrier P, Carmo-Fonseca M (2011) Splicing enhances recruitment of methyltransferase HYPB/Setd2 and methylation of histone H3 Lys36. *Nature Structural & Molecular Biology* 18 (9): 977-983. (Journal IF: 13.69)

Martins SB, Rino J., Carvalho T, Carvalho C, Yoshida M, Klose JM, de Almeida SF, Carmo-Fonseca M (2011) Spliceosome assembly is coupled to RNA polymerase II dynamics at the 3' end of human genes. *Nature Structural & Molecular Biology* 18 (10): 1115-1123. (Journal IF: 13.69)

Foreid H, Bentes C, Pimentel J (2010) The use of placebo as a provocative test in the diagnosis of psychogenic non epileptic seizures. *Neuroethics* 3, 95-98. (Journal IF: 12.79)

Correia DV, Fogli M, Hudspeth K, da Silva MG, Mavilio D, Silva-Santos B (2011) Differentiation of human peripheral blood Vσγ1+ T cells expressing the natural cytotoxicity receptor NKp30 for recognition of lymphoid leukemia cells. *Blood:* Epub 1 Jun 2011. (Journal IF: 10.555)

Markert ML, Marques JG, Neven B, Devlin BH, McCarthy EA, Chinn IK, Albuquerque AS, Silva SL, Pignata C, de Saint Basile G, Victorino RM, Picard C, Debre M, Mahlaoui N, Fischer A, Sousa AE (2011) First use of thymus transplantation therapy for FOXN1 deficiency (nude/SCID): a report of two cases. *Blood* 117, 688-96. (Journal IF: 10.555)

Henriques CM, Rino J, Nibbs RJ, Graham GG, Barata JT (2010) IL-7 induces rapid clathrin-mediated internalization and JAK3-dependent degradation of IL-7Rα in T cells. *Blood* 115 (16): 3269-3277. (Journal IF: 10.555)

Lança T, Correia DV, Moita CF, Raquel H, Ferreira C, Ramalho JS, Barata JT, Moita LF, Gomes AQ and Silva--Santos B (2010) The MHC class Ib protein ULBP1 is a non-redundant determinant of leukemia/ lymphoma susceptibility to γσ T-cell cytotoxicity. *Blood*. 115 (12), 2407-2411. (Journal IF: 10.555)

Martins LR, Lúcio P, Silva MC, Gameiro P, Silva MG, Barata JT (2010) Targeting CK2 overexpression and hyperactivation as a novel therapeutic tool in Chronic Lymphocytic Leukemia. *Blood* 116 (15), 2724-2731. (Journal IF: 10.555)

AWARDS 2008-2012 :

PATENTS :

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
-

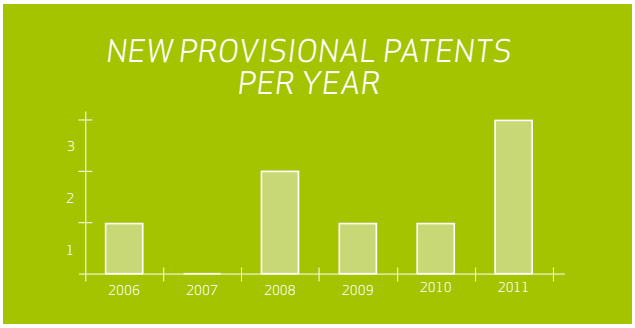
EMBO Installation Grant 2008
Henrique Veiga-Fernandes
-

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 Therapeuticals
-

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

JAN | FEB 22-23 | MAR 18 | 21 | 18-25 | 29

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.

19 APRIL

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

28 APRIL

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

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.

Pedalar Contra o Cancro

30 APRIL

IMM President Professor João Lobo Antunes and Executive Director Carmo Fonseca among the 100 most influent 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.

JUN | 15 | 17 JUL | 05 SEP | 4-10 | 9

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".

17 JUNE

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

5 JULY

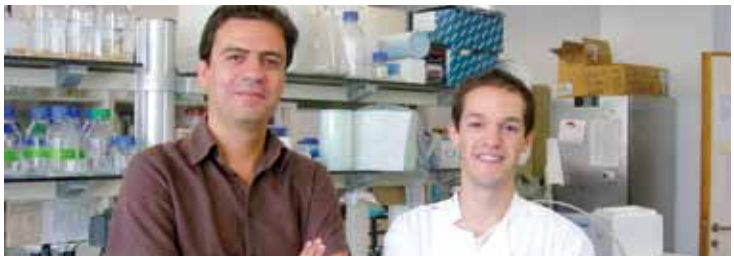
IMM researcher Vanessa Oliveira wins an Early Career Bayer Hemophilia Award. Vanessa was the only European researcher to win this funding scheme in the 2011 round, in a total of 5 researchers funded worldwide.

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.

12-14 OCTOBER

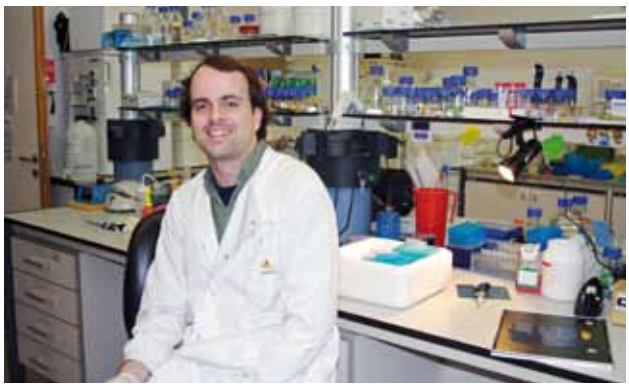
Herwig Turk's installation in the lobby as part of his artistic residency at IMM.

17-18 OCTOBER

V IMM PhD students' scientific meeting.

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.



2012

DEC 05 | 17 **JAN** 24 | 27

5 DECEMBER

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.

17 DECEMBER

IMM Group Leaders retreat.

24 JANUARY

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.

24 JANUARY

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

27 JANUARY

Science magazine publishes "Portugal´s Age of Enlightment", 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

Oncology Series

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 Luís 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.

Lisbon Area Neuroscience Meeting

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*.

01

CELL AND DEVELOPMENTAL BIOLOGY PROGRAMME

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.

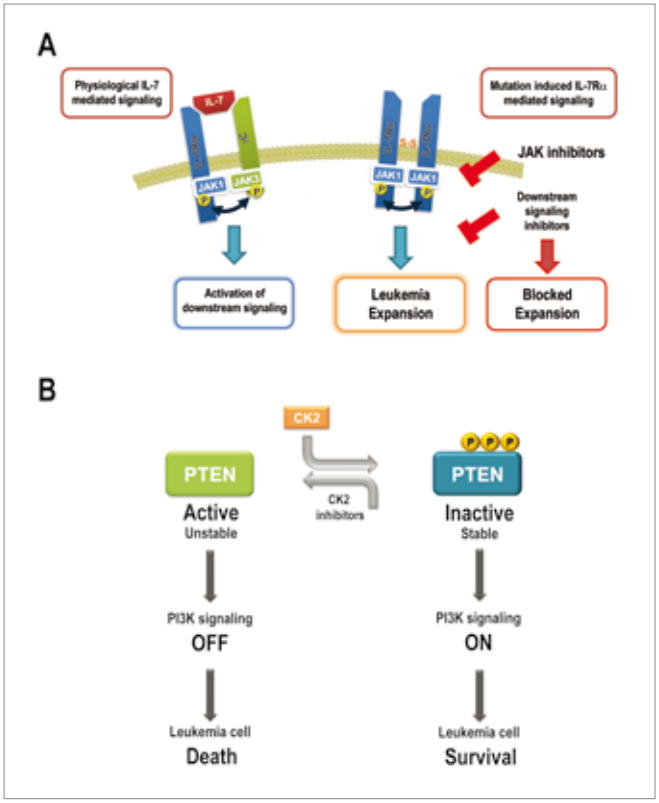
Group Leader

JOÃO TABORDA BARATA

PhD (2003) in Biomedical Sciences at Harvard Medical School, USA, and University of Porto
Post-doctoral research at IMM, Institut Pasteur, France, and Utrecht University, The Netherlands

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).



SELECTED PUBLICATIONS

Zenatti PP, Ribeiro D, Li W,Zuurbier L, Silva MC, Paganin M, Tritapoe J, Hixon JA, Silveira AB, Cardoso BA, Sarmento LM, Correia N, Toribio ML, Kobarg J, Horstmann M, Pieters R, Brandalise SR, Ferrando AA, Meijerink, JP, Durum SK, Yunes JA, Barata JT (2011) Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nature Genetics 43 (10): 932-939

Silva A, Laranjeira ABA, Martins LR, Cardoso BA, Demengeot J, Yunes JA, Seddon B, Barata JT (2011) IL-7 contributes to the progression of human T-cell acute lymphoblastic leukemias. Cancer Research 71 (14): 4780-4789

Martins LR, Lúcio P, Silva MC, Gameiro P, Silva MG, Barata JT (2010) Targeting CK2 Overexpression and Hyperactivation as a Novel Therapeutic Tool in Chronic Lymphocytic Leukemia. Blood 116 (15): 2724-2731

Silva A, Yunes JA, Cardoso BA, Martins LR, Jotta PY, Abecasis M, Nowill AE, Leslie NR, Cardoso AA, Barata JT (2008) PTEN Posttranslational Inactivation and Hyperactivation of the PI3K/Akt Pathway Sustain Primary T Cell Leukemia Viability. Journal of Clinical Investigation 118: 3762-3774

Barata JT, Silva A, Brandão JG, Nadler LM, Cardoso AA, Boussiotis VA (2004) Activation of PI3K is Indispensable for Interleukin 7-Mediated Viability, Proliferation, Glucose Use, and Growth of T Cell Acute Lymphoblastic Leukemia Cells. J. Exp. Med. 200: 659-669

-

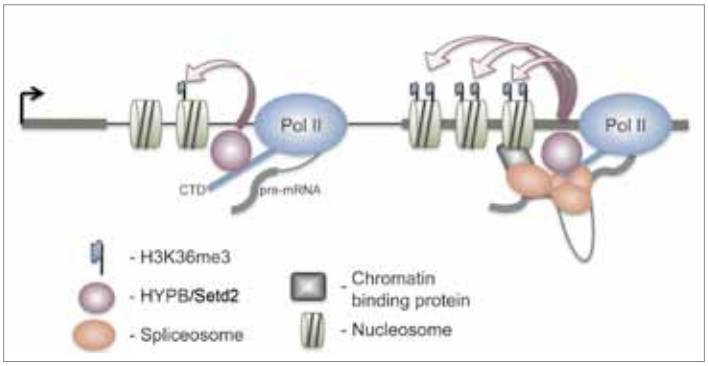
Group Leader

MARIA CARMO-FONSECA

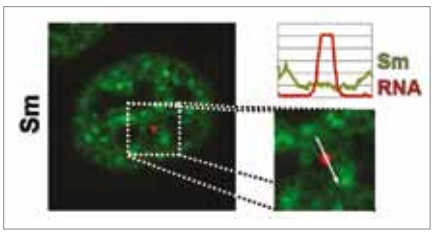
MD (1983) and PhD (1988) in Cell Biology at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Post-doctoral research at EMBL in Heidelberg, Germany
Professor at FMUL
Executive Director of the IMM since 2002

Other Principal Investigators
Francisco Enguita, Sérgio de Almeida

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 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

Martins SB, Rino J, Carvalho T, Carvalho C, Yoshida M, Klose JM, de Almeida SF, Carmo-Fonseca M (2011) Spliceosome assembly is coupled to RNA polymerase II dynamics at the 3' end of human genes. Nat. Struct. Mol. Biol. 18 (10): 1115-1123

de Almeida SF, Grosso AR, Koch F, Fenouil R, Carvalho S, Andrade J, Levezinho H, Gut M, Eick D, Gut I, Andrau JC, Ferrier P, Carmo-Fonseca M (2011) Splicing enhances recruitment of methyltransferase HYPB/Setd2 and methylation of histone H3 Lys36. Nat. Struct. Mol. Biol. 18 (9): 977-983

Grosso AR, Gomes AQ, Barbosa-Morais, NL, Caldeira S, Thorne NP, Grech G, von Lindern M, and Carmo-Fonseca, M (2008) Tissue-specific splicing factor gene expression signatures. Nucleic Acids Research 36: 4823-32

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Group Leader

MIGUEL CASTANHO

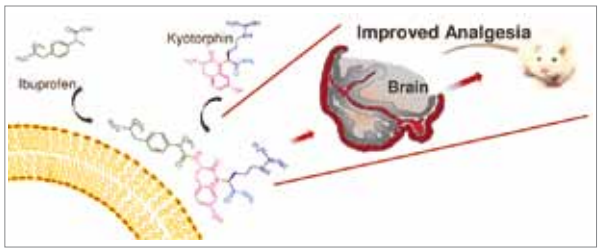
PhD (1993) in Molecular Biophysics at Universidade Técnica de Lisboa
Post-doctoral research at University of Hawaii, USA, and at Rocasolano Institute, Madrid, Spain
Full Professor at Faculdade de Medicina da Universidade de Lisboa

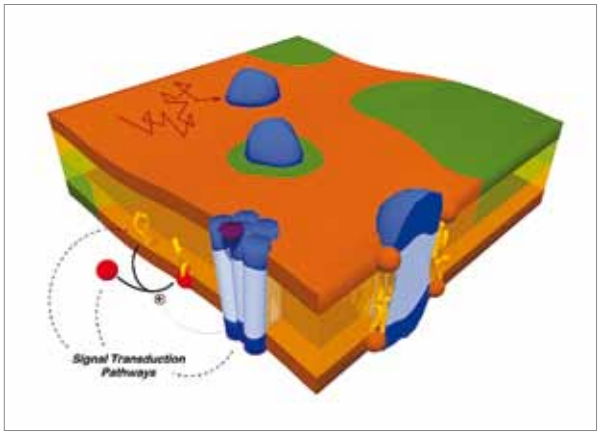
Our research unit studies peptide-lipid interactions.
In 2011 we have:

• Proved that a covalent conjugation of an anti-inflammatory hydrophobic molecule (ibuprophen) 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.





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.

SELECTED PUBLICATIONS

Ribeiro MM, Pinto AR, Domingues MM, Serrano I, Heras M, Bardaji ER, Tavares I, Castanho MA (2011) Chemical conjugation of the neuropeptide kyotorphin and ibuprofen enhances brain targeting and analgesia, Molecular Pharmaceutics, Oct 3;8(5):1929-40

Franquelim HG, Chiantia S, Veiga AS, Santos NC, Schwille P, Castanho MARB (2011) Anti-HIV-1 antibodies 2F5 and 4E10 interact differently with lipids to bind their epitopes. AIDS Feb 20;25(4):419-28

Ribeiro MMB, Melo MN, Serrano ID, Santos NC and Castanho MARB (2010) Drug-lipid interaction evaluation: why a 19th century solution? Trends Pharmacol Sci. 31, 449-454

Melo MN, Ferre R and Castanho MARB (2009) Antimicrobial peptides: linking partition, activity and high membrane-bound concentrations. Nat Rev Microbiol 7, 245-250

Franquelim HG, Loura LMS, Santos NC and Castanho MARB (2008) Sifuvirtide screens rigid membrane surfaces. Establishment of a correlation between efficacy and membrane domain selectivity among HIV fusion inhibitor peptides. J Am Chem Soc 130, 6215-6223

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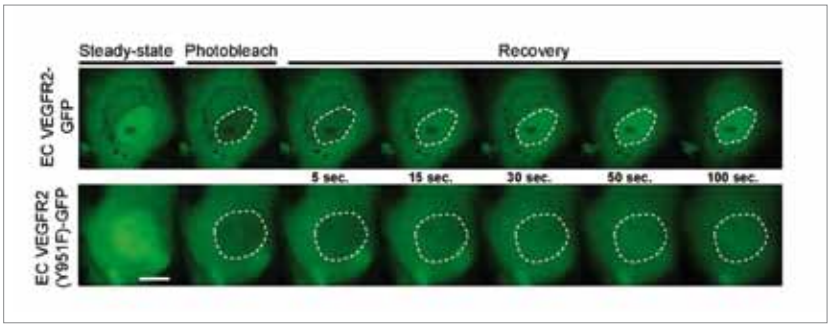
Group Leader

SUSANA CONSTANTINO

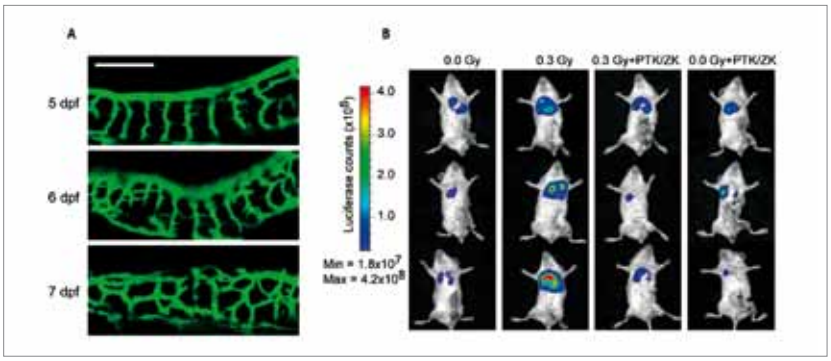
PhD (2001) in Bases Fondamentales de l'Oncogénèse at Université de Paris 7, France
Post-doctoral research at Instituto Português de Oncologia, Lisbon
Assistant Professor at the Faculdade de Medicina da Universidade de Lisboa
Group leader at IMM since 2008

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.



Domingues et al.2011. PLoS ONE 6, e25668

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).



Vala et al.2010. PLoS ONE 5, e11222

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

Vala I, Martins L, Imaizumi N, Nunes R, Rino J, Kuonen F, Carvalho LM, Rüegg C, Grillo IM, Barata JT, Mareel M and Constantino Rosa Santos S (2010) Low doses of ionizing radiation promote tumor growth and metastasis by enhancing angiogenesis. PLoS ONE 5, e11222

Constantino Rosa Santos S, Vala I, Miguel C, Barata J, Garção P, Agostinho P, Mendes M, Coelho A, Oliveira C, Martins e Silva J and Saldanha C (2007) Expression and subcellular localization of a novel nuclear Acetylcholinesterase protein. J Biol Chem 282, 25597-603

Constantino Rosa Santos S, Miguel C, Domingues I, Calado A, Zhu Z, Wu Y and Dias S (2007) VEGF and VEGFR-2 (KDR) internalization is required for endothelial recovery during wound healing. Exp Cell Res 313, 1561-1574

Constantino Rosa Santos S and Dias S (2004) Internal and external autocrine VEGF/KDR loops regulate survival of subsets of acute leukemia through distinct signaling pathways. Blood 103, 3883-3889

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Group Leader

LUÍS COSTA

MD (1985) at Faculdade de Medicina da Universidade de Lisboa (FMUL)
PhD (2002) in Medical Oncology at FMUL
Post-doctoral research at Santa Maria Hospital and IMM, Lisbon
Director of the Oncology Division, HSM; Auxiliary Professor, Faculdade de Medicina da Universidade de Lisboa

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.

SELECTED PUBLICATIONS

Casimiro S, Luis I, Fernandes A, Pires R, Pinto A, Gouveia AG, Francisco AF, Portela J, Correia L, and Costa L (2012) Analysis of a bone metastasis gene expression signature in patients with bone metastasis from solid tumors. Clin Exp Metastasis 29, 155-164, published online in 2 December 2011

Henry D, Costa L, et all (2011) A Randomized, Double-blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. J Clin Oncol 29 (9), 1125-1132

Ha N et al. (2011) Lactoferrin- Endothelin-1 Axis Contributes to the Development and Invasiveness of Triple Negative Breast Cancer Phenotypes. Cancer Res 71(23), 7259-7269

Luis I, Casimiro S, Ribeiro J and Costa L (2010) Zoledronic Acid: Its Use in the Treatment of Breast Cancer. Clinical Medicine Insights: Therapeutics 2, 903-926

Casimiro S, Guise TA, Chirgwin J (2009) The critical role of the bone microenvironment in cancer metastases. Mol. Cel. Endoc., 310, 71-81

Costa L, Major PP (2009) Effect of bisphosphonates on pain and quality of life in patients with bone metastases. Nat. Clin. Prac. Oncol., 6(3), 163-174

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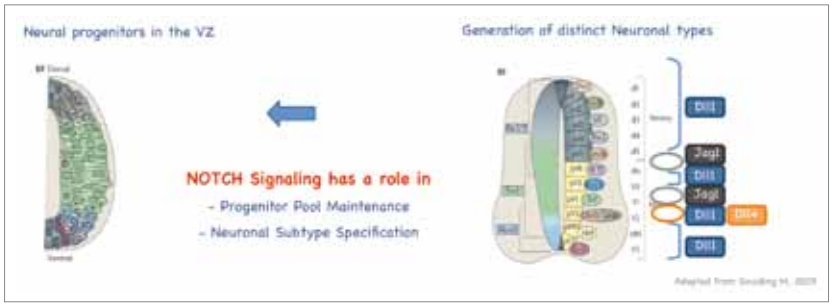
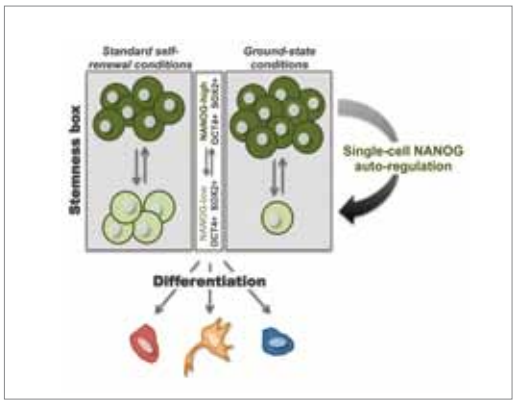
Group Leader

DOMINGOS HENRIQUE

PhD (1991) at Universidade de Lisboa
Post-doctoral research at NIMR and ICRF, UK and Institut d'Embryologie Cellulaire et Moleculaire, France
Investigator at Faculdade de Medicina da Universidade de Lisboa

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

Vilas-Boas F, Fior R, Swedlow JD, Storey KG, Henrique D (2011) A novel Reporter of Notch Signalling indicates regulated and random Notch Activation during Vertebrate Neurogenesis. BMC Biology, 9:58

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)

Abranches E, Silva M, Pradier L, Schulz H, Hummel O, Henrique D, Bekman E (2009) Neural Differentiation of Embryonic Stem Cells in vitro: a Road Map to Neurogenesis in the Embryo, PLos ONE 4(7):e6286

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 L (2010) A cross-disciplinary approach to understanding neural stem cell in development and disease, Development 137(12): 1933-8

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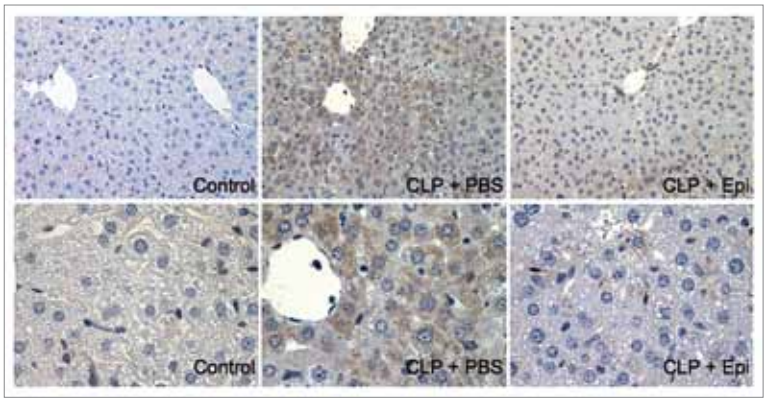
Group Leader

LUÍS FERREIRA MOITA

MD (1997) at Universidade de Lisboa
PhD (2003) in Cell and Molecular Biology at EMBL in Heidelberg, Germany
Post-doctoral research at Harvard Medical School and MIT, USA
Assistant Professor at Faculdade de Medicina da Universidade de Lisboa
Awardee of the Human Frontier Science Program

Other Principal Investigator
Angelo Chora

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 1ß (IL-1ß), 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-1ß. *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.



Epirubicin limits CLP-initiated target organ injury. HMGB-1 staining (brown) in liver sections of control mice (Control), non-treated sepsis (CLP+PBS) and epirubicin-treated sepsis (CLP+Epi). Top row 40x. Lower row 100x.

SELECTED PUBLICATIONS

Cebrian I, Visentin G, Blanchard N, Jouve M, Bobard A, Moita C, Enninga J, Moita LF (2011) Amigorena S, Savina A. Sec22b regulates phagosomal maturation and antigen crosspresentation by dendritic cells. Cell 147(6):1355-68

Colvin AR, Means TK, Diefenbach TJ, Moita LF, Friday RP, Sever S, Campanella GSV, Abrazinski T, Manice LA, Moita C, Andrews NW, Wu D, Hacohen N, Luster AD (2010) Synaptotagmin mediated vesicle fusion regulates cell migration. Nature Immunology 11(6):495-502

Ostrowski M, Carmo NB, Krumeich S, Fanget I, Raposo G, Savina A, Moita, CF, Schauer K, Hume AN, Freitas RP, Goud B, Benaroch P, Hacohen N, Fukuda M, Desnos C, Seabra MC, Darchen F, Amigorena S, Moita LF*, Thery C* (2010) Rab27 controls constitutive exosome secretion. Nat Cell Biol 12(1):19-30
*Corresponding authors.

Savina A, Peres A, Cebrian I, Carmo N, Moita C, Hacohen N, Moita LF, Amigorena S (2009) Rac2 controls phagosomal alkalinization and crosspresentation selectively in CD8+ dendritic cells. Immunity 30(4):544-55

Oberdoerffer S, Moita LF, Neems D, Freitas RP, Hacohen N, Rao A (2008) Regulation of CD45 alternative splicing by heterogeneous ribonucleoprotein, hnRNPLL. Science 321(5889):686-91

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Group Leader
CARLOTA SALDANHA

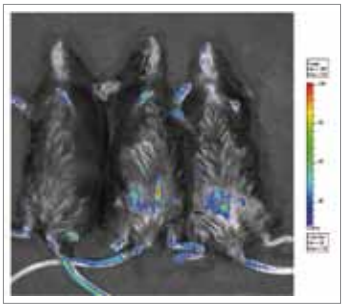
PhD (1986) in Biochemistry at Universidade Nova de Lisboa
Master (2000) in Medical Education joint degree at University of Wales and Faculdade de Medicina da Universidade de Lisboa (FMUL)
Associate Professor with Habilitation at FMUL

Other Principal Investigator
Ângelo Calado

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.

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

Post-capillary venule in mouse cremaster muscle superfused with bicarbonate-bufered saline and observed by intravital microscopy (200x). by Ana Silva-Herdade and Vanda Vitorino de Almeida



Fluorescent images of EGFP neutrophil infiltration 2h after induction of an intraperitoneal inflammatory stimulus. by Ana Silva-Herdade, Vanda Vitorino de Almeida and Claúdia Ferreira.

SELECTED PUBLICATIONS

de Oliveira S, de Almeida VV, Calado A, Rosario HS, Saldanha C (2011) Integrin-associated protein (CD47) is a putative mediator for soluble fibrinogen interaction with human red blood cells membrane. Biochim Biophys Acta 1818 (3), 481-490

Artoli AM, Sequeira A, Silva-Herdade AS, Saldanha C (2007) Leukocytes rolling and recruitment by endothelial cells: hemorheological experiments and numerical simulations. J Biomech 40 (15), 3493-502

Santos NC, Martins-Silva J, Saldanha C (2005) PTEN "meets" DMSO. Leuk Res 29 (4), 361-362

Lund E, Guttinger S, Calado A, Dahlberg JE, Kutay U (2004) Nuclear export of microRNA precursors. Science 303, 95-98

Rosário HS, Waldo SW, Becker SA, Schmid-Schönbein GW (2004) Pancreatic trypsin increases matrix metalloproteinase-9 accumulation and activation during acute intestinal ischemia-reperfusion in the rat. Am J Pathol. 164, 1707-16

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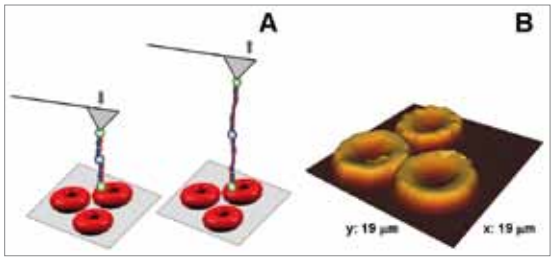
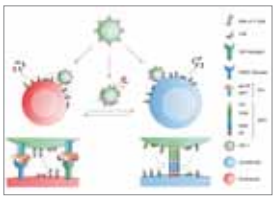
Group Leader

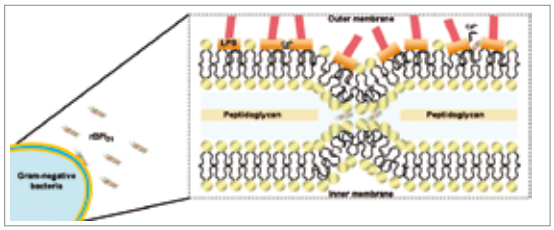
NUNO C. SANTOS

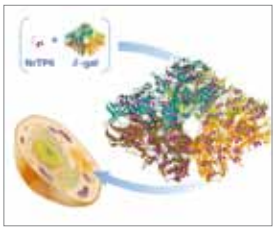
PhD (1999) at Universidade de Lisboa
Former researcher at Universidade Técnica de Lisboa and at University of California,Santa Barbara, USA
Assistant Professor with Habilitation at Faculdade de Medicina da Universidade de Lisboa

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

Rodrigues M, de la Torre BG, Rádis-Baptista G, Santos NC, Andreu D (2011) Efficient cellular delivery of ß-galactosidase mediated by NrTPs, a new family of cell-penetrating peptides. Bioconjugate Chem. 22, 2339-2344

Carvalho FA, Connell S, Miltenberger-Miltenyi G, Pereira SV, Tavares A, Ariëns RAS, Santos NC (2010) Atomic force microscopy-based molecular recognition of a fibrinogen receptor on human erythrocytes. ACS Nano 4, 4609-4620

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

Ribeiro MM, Melo MN, Serrano I, Santos NC, Castanho MARB (2010) Drug-lipid interaction evaluation: Why a 19th century solution? Trends Pharmacol. Sci. 31, 449-454

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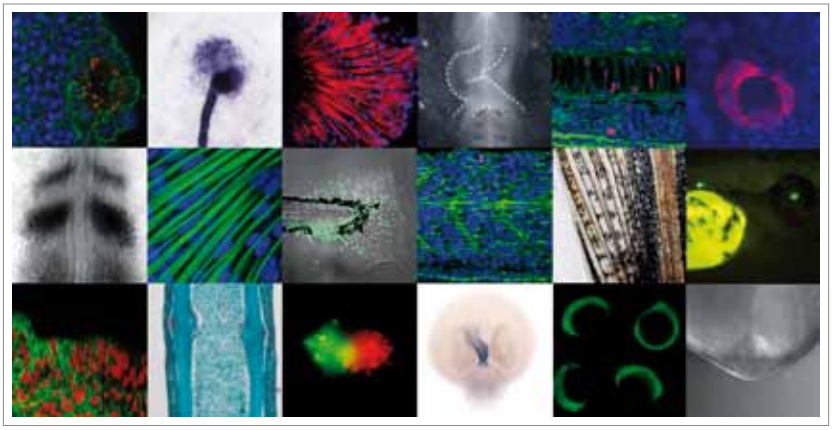
Group Leader

LEONOR SAÚDE

PhD (2001) in Developmental Biology at University College London, UK
Post-doctoral research at Instituto Gulbenkian de Ciencia (IGC)
Group Leader at IGC (2005-07) and at IMM since 2008
Invited Auxiliary Professor at Faculdade de Medicina da Universidade de Lisboa

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 presomitic mesoderm, mesoderm progenitors in the tailbud continually generate new mesoderm cells and feed them into the posterior presomitic mesoderm. Using zebrafish as a model organism we were able to show that in the conversion of progenitors into presomitic 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.



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

SELECTED PUBLICATIONS

Cutty SJ, Fior F, Henriques PM, Saúde L and Wardle FC (2012) Identification and expression analysis of two novel members of the Mesp family in zebrafish. The International Journal of Developmental Biology (in press)

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. PlosONE 5(12); e14438

Lopes S S, Lourenço R, Pacheco L, Moreno N, Kreiling J and Saúde L (2010) Notch signalling regulates left-right asymmetry through ciliary length control. Development 137(21); 3625-32

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IMMUNOLOGY AND INFECTIOUS DISEASES PROGRAMME

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.

Group Leader

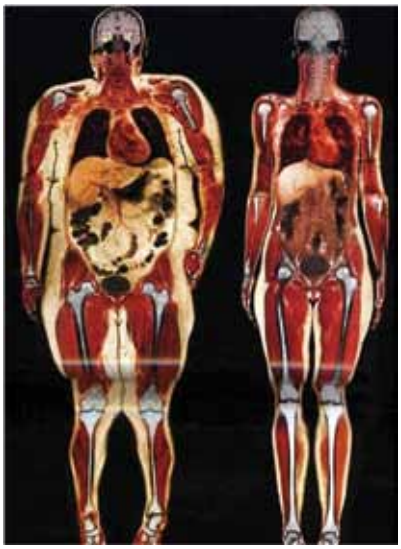
MARIA ERMELINDA CAMILO

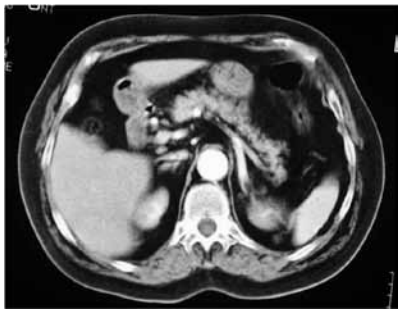
MD, PhD – retired since June 2008 from Auxiliary Professor Faculdade de Medicina da Universidade de Lisboa

Other Principal Investigators

Helena Cortez-Pinto, Isabel Monteiro Grillo, Paula Ravasco

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.





Whole body imaging with DEXA and CT scans to evaluate body composition and its association with Quality of Life and tolerance to cancer treatments

SELECTED PUBLICATIONS

Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G (2010) A position statement on NAFLD/NASH based on the EASL 2009 special conference Journal of Hepatology 53: 372-384

Guerreiro CS, Cravo ML, Brito M, Vidal PM, Fidalgo PO, Leitão CN (2007) The D1822V APC polymorphism interacts with fat, calcium, and fiber intakes in modulating the risk of colorectal cancer in Portuguese persons. American Journal of Clinical Nutrition 85: 1592-1597

Marques-Vidal P, Ravasco P, Camilo ME (2006) Foodstuffs and colorectal cancer risk: A review. Clinical Nutrition 25: 14-36

Machado M, Cortez-Pinto H (2006) Non--alcoholic steatohepatitis and metabolic syndrome. Current Opinion in Clinical Nutrition and Metabolic Care 9: 637-642

Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, Ferenci P, Holm E, von Dahl S, Müller MJ, Nolte W (2006) ESPEN Guidelines on Enteral Nutrition: Liver disease. Clinical Nutrition 25: 285-294

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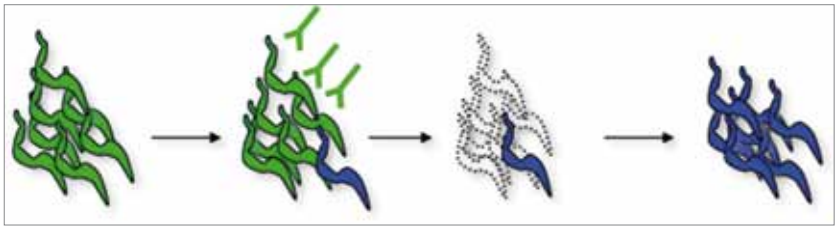
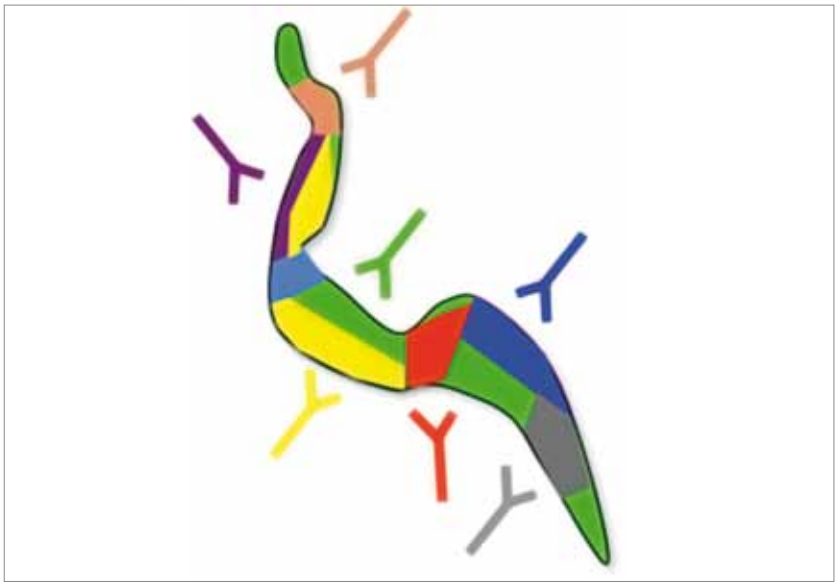
Group Leader

LUÍSA FIGUEIREDO

PhD (2002) from University of Porto and Institut Pasteur, France
Post-doctoral research at The Rockefeller University, New York, USA
Research Associate at The Rockefeller University, New York, USA (2008-2009)
Group Leader at IMM since 2009



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 loose the capacity to express only one VSG coat at a time.

SELECTED PUBLICATIONS

Figueiredo LM, Cross GAM (2010) Nucleosomes are depleted at the VSG expression site transcribed by RNA polymerase I in African trypanosomes. Eukaryot Cell, 9: 148-154

Yang X, Figueiredo LM, Espinal A, Okubo, E, Li B (2009) RAP1 is essential for silencing telomeric Variant Surface Glycoprotein genes in Trypanosoma brucei. Cell, 137: 99-109

Siegel TN, Hekstra DR, Kemp LE, Figueiredo LM, Lowell JE, Fenyo D, Wang X, Dewell S, Cross GAM (2009) Four histone variants mark the boundaries of polycistronic transcription units in Trypanosoma brucei. Genes Dev, 23: 1063-1076

Figueiredo LM, Cross GAM, Janzen CJ (2009) Epigenetic regulation in African trypanosomes: a new kid on the block. Nat Rev Microbiol, 7: 504-513

Figueiredo LM, Janzen CJ, Cross GAM (2008) A histone methyltransferase modulates antigenic variation in African trypanosomes. PLoS Biol, 6: e161

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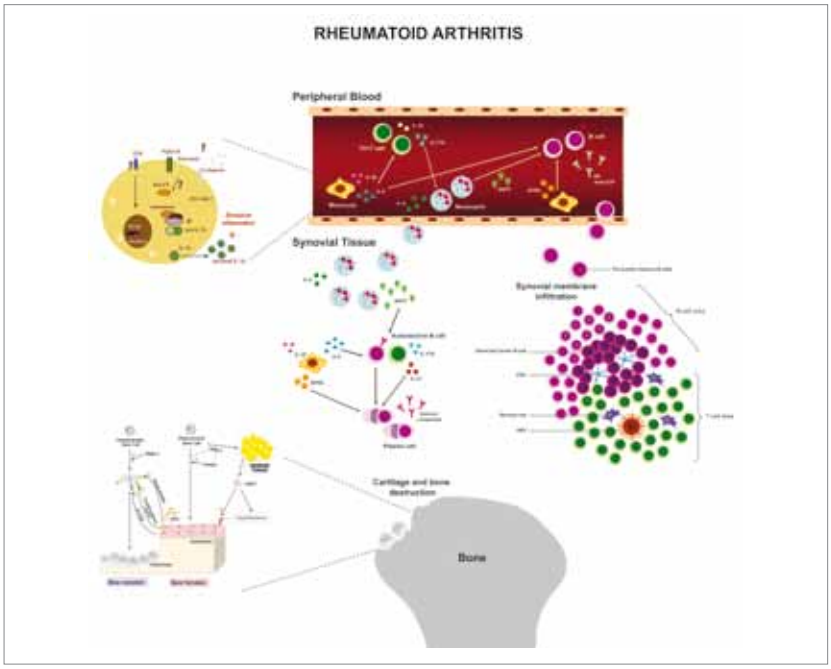
Group Leader

JOÃO EURICO FONSECA

MD (1992) and PhD (2004) in Rheumatology at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Assistant Professor with Habilitation FMUL
Rheumatologist, Rheumatology Department, Santa Maria Hospital (HSM)

Other Principal Investigators
Helena Canhão

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.



Authors Rita Cascão, Rita Moura and Joana Lopes

SELECTED PUBLICATIONS

Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, Bombardier C, Carmona L, van der Heijde D, Bijlsma JW, Boumpas DT, Canhao H, Edwards CJ, Hamuryudan V, Kvien TK, Leeb BF, Martín-Mola EM, Mielants H, Müller-Ladner U, Murphy G, Østergaard M, Pereira IA, Ramos-Remus C, Valentini G, Zochling J, Dougados M (2009) Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 68: 1086-93

Fonseca JE, Santos MJ, Canhão H, Choy E (2009) Interleukin-6 as a key player in systemic inflammation and joint destruction. Autoimmun Rev; 8: 538-42

Fonseca JE, Carvalho T, Cruz M, Nero P, Sobral M, Mourão AF, Cavaleiro J, Abreu I, Carmo Fonseca M, Branco JC (2005) Polymorphism at position –308 of the tumor necrosis factor alpha gene and rheumatoid arthritis pharmacogenetics. Ann Rheum Dis 64: 793-4

Fonseca JE, Cortez-Dias N, Francisco A, Sobral M, Canhão H, Resende C, Castelão W, Macieira C, Sequeira G, Saraiva F, da Silva JA, Carmo-Fonseca M, Viana Queiroz M (2005) Inflammatory cell infiltrate and RANKL/OPG expression in rheumatoid synovium: Comparison with other inflammatory arthropathies and correlation with outcome. Clin Exp Rheumatol 23(2):185-92

Fonseca JE, Edwards JC, Blades S, Goulding NJ (2002) Macrophage subpopulations in rheumatoid synovium: reduced CD163 expression in CD4+ T lymphocyte-rich microenvironments. Arthritis Rheum; 46: 1210-6

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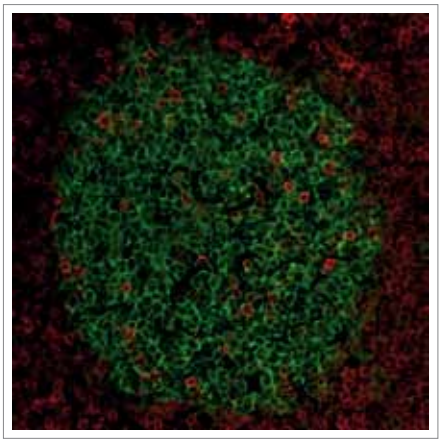
Group Leader

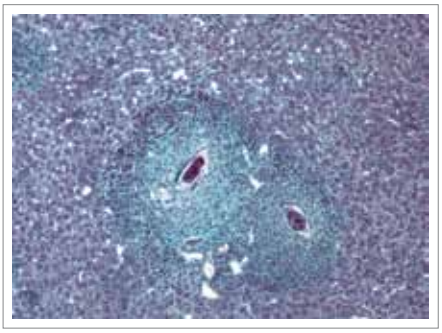
LUÍS GRAÇA

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

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).



Germinal centre, the anatomical structure where antibody-producing B cells (green) are selected, showing the presence of follicular helper T cells (red).
(Author: Ivonne Wollenberg)



Masson's trichrome staining in liver section of a mouse infected with *Schistosoma mansoni*.
(Author: Alexandre Varela)

SELECTED PUBLICATIONS

Wollenberg I, Agua-Doce A, Hernández A, Almeida C, Oliveira V, Faro J, Graça L (2011) Regulation of germinal centre reaction by Foxp3+ follicular regulatory T cells. J Immunol. 187(9):4553-60

Oliveira VG, Caridade M, Paiva RS, Demengeot J, Graca L (2011) Sub-optimal CD4 T cell activation triggers autonomous TGF-βdependent conversion to Foxp3+ regulatory T cells. Eur J Immunol. 41: 1249-1255

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

Monteiro M, Almeida CF, Caridade M, Ribot JC, Duarte J, Agua-Doce A, Wollenberg I, Silva-Santos B, Graca L (2010) Identification of Regulatory Foxp3+ Invariant NKT Cells Induced by TGF-ß. J Immunol. 185: 2157-2163

Curotto de Lafaille MA, Lafaille JJ, Graca L (2010) Mechanisms of tolerance and allergic sensitization in the airways and the lungs. Curr Opin Immunol. 22: 616-622

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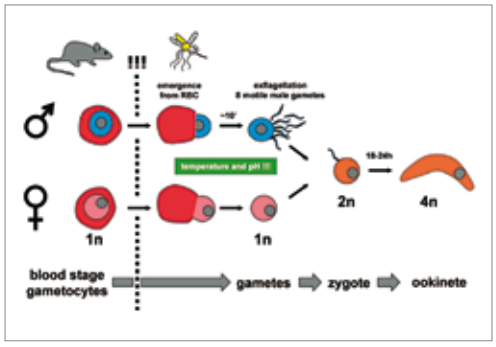
Group Leader

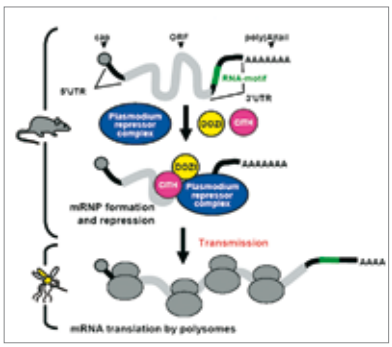
GUNNAR MAIR

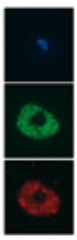
PhD (1998) in Molecular Parasitology at Queen's University Belfast, UK
Post-doctoral research at Queen's University Belfast, UK, the Leiden University Medical Center, The Netherlands, and Yale Medical School, USA
Group leader at IMM since 2008

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.



Plasmodium sexual development





Gametocyte P-bodies

SELECTED PUBLICATIONS

Laurentino EC, Taylor S, Mair GR, Lasonder E, Bartfai R, Stunnenberg HG, Kroeze H, Ramesar J, Franke-Fayard B, Khan SM, Janse CJ, Waters AP (2011) Experimentally controlled down regulation of the histone chaperone FACT in Plasmodium berghei reveals that it is critical to male gamete fertility. Cell Microbiol 13(12):1956-74

Gomes-Santos CSS, Braks JAM, Prudêncio M, Carret CK, Gomes ARB, Pain A, Feltwell T, Khan SM, Waters AP, Janse CJ, Mair GR, Mota MM (2011) Transition of Plasmodium Sporozoites into Liver-Stage Forms is Regulated by the RNA Binding Protein Pumilio. PLoS Pathogens 7(5):e1002046

Mair GR, Lasonder E, Garver LS, Franke-Fayard B, Carret CK, Wiegant J, Dirks R, Dimopoulos G, Janse CJ, Waters AP (2010) An evolutionarily ancient P body controls sexual development in the protozoan Plasmodium. PLoS Pathog 6(2):e1000767

Mwai L, Diriye A, Masseno V, Muriithi S,

Feltwell T, Musyoki J, Lemieux J, Feller A, Mair GR, Marsh K, Newbold C, Nzila A, Carret CK (2012) Genome Wide Adaptations of Plasmodium falciparum in Response to Lumefantrine Selective Drug Pressure. PLoS One 7(2):e31623

Baum J, Papenfuss AT, Mair GR, Janse CJ, Waters AP, Cowman AF, Crabb BS, de Konig-Ward T (2009) Molecular genetics and comparative genomics suggests RNAi is not functional in malaria parasites. Nucleic Acid Research 37(11):3788-3798

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Group Leader

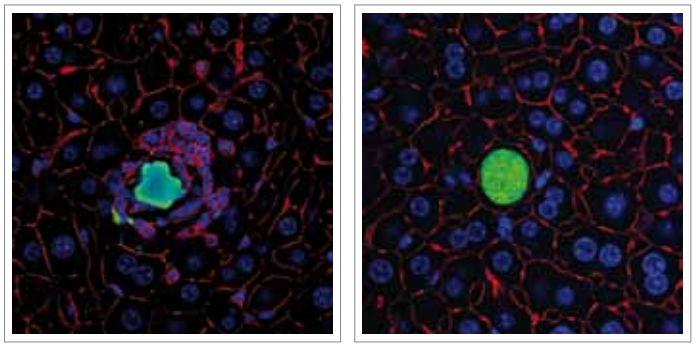
MARIA M. MOTA

PhD (1998) in Molecular Parasitology at University College London, UK
Post-doctoral research at New York University Medical Center, USA
Principal Investigator at Instituto Gulbenkian de Ciência, Oeiras (until 2005)
Associate Professor at the Faculdade de Medicina da Universidade de Lisboa
European Science Foundation Young Investigator (2004-2009)
International Research Scholar, Howard Hughes Medical Institute, USA (since 2005)

Other Principal Investigators

Miguel Prudêncio

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.



P. berghei-GFP EEFs in murine liver, 44 hours post-infection; phalloidin in red, DAPI in blue, P. berghei-GFP in green. In the left image, the parasite has been detected by the immune system, and the infected hepatocyte along with the parasite are being cleared, while the parasite in the right image grows, undetected.

SELECTED PUBLICATIONS

Gomes-Santos CS, Braks J, Prudêncio M, Carret C, Gomes AR, Pain A, Feltwell T, Khan S, Waters A, Janse C, Mair GR, Mota MM (2011) Transition of Plasmodium sporozoites into liver stage-like forms is regulated by the RNA binding protein pumilio. PLoS Pathog. 7(5):e1002046

Portugal S, Carret C, Recker M, Armitage A, Sullivan D, Roy Cindy, Newbold CJ, Drakesmith H, Mota MM (2011) Host-mediated control of Malaria Superinfection. Nature Medicine. 17(6):732

Epiphanio S, Campos MG, Pamplona A, Carapau D, Pena AC, Ataíde R, Monteiro CA, Félix N, Costa-Silva A, Marinho CR, Dias S, Mota MM (2010) VEGF promotes malaria-associated acute lung injury in mice. PLoS Pathog. 6(5):e1000916

Prudêncio M, Rodrigues CD, Hannus M, Martin C, Real E, Gonçalves LA, Carret C, Dorkin R, Röhl I, Jahn-Hoffmann K, Luty AJ, Sauerwein R, Echeverri CJ, Mota MM (2008) Kinome--wide RNAi screen implicates at least 5 host hepatocyte kinases in Plasmodium sporozoite infection. PLoS Pathog. 4(11):e1000201

Rodrigues CD, Hannus M, Prudêncio M, Martin C, Gonçalves LA, Portugal S, Epiphanio S, Akinc A, Hadwiger P, Jahn--Hofmann K, Röhl I, van Gemert GJ, Franetich JF, Luty AJF, Sauerwein R, Mazier D, Koteliansky V, Vornlocher HP,5 Echeverri CJ and Mota MM (2008) Host scavenger receptor SR-BI plays a dual role in the establishment of malaria parasite liver infection. Cell Host & Microbe. 4(3):271-82

Epiphanio S, Mikolajczak SA, Gonçalves LA, Pamplona A, Portugal S, Albuquerque S, Goldberg M, Rebelo S, Anderson DG, Akinc A, Vornlocher HP, Kappe SH, Soares MP, Mota MM (2008) Heme oxygenase-1 is an anti-inflammatory host factor that promotes murine plasmodium liver infection. Cell Host & Microbe. 3(5):331-8

Pamplona A, Ferreira A, Balla J, Jeney V, Balla G, Epiphanio S, Chora A, Rodrigues CD, Gregoire IP, Cunha-Rodrigues M, Portugal S, Soares MP, Mota MM (2007) Heme oxygenase-1 and carbon monoxide suppress the pathogenesis of experimental cerebral malaria. Nature Medicine. 13:703

Prudêncio M, Rodriguez A, Mota MM (2006) The silent path to thousands of merozoites: the Plasmodium liver stage. Nat Rev Microbiol. Nov;4(11):849-56

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Group Leader

MÁRIO RAMIREZ

PhD (1998) in Molecular Biology at Universidade Nova de Lisboa
and at The Rockefeller University, USA
Post-doctoral research at Instituto de Tecnologia Química e Biológica, Oeiras
Associate Professor at the Faculdade de Medicina da Universidade de Lisboa

Other Principal Investigators
José Melo Cristino, Thomas Hänscheid, João Carriço

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.

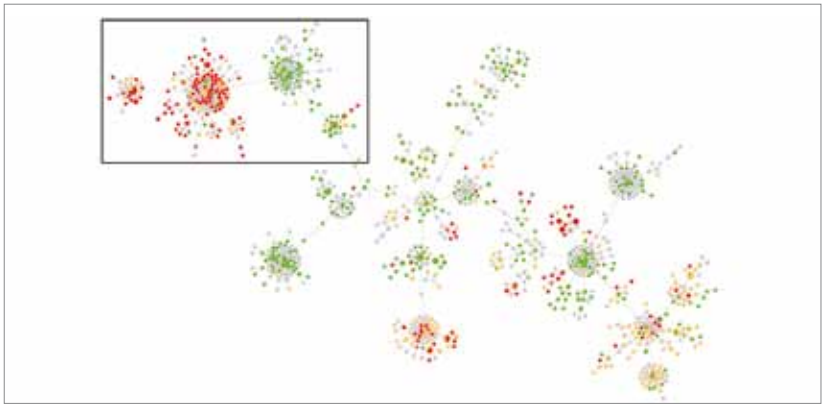

Figure created with PHYLOViZ (www.phyloviz.net). Representation of the major clonal complex of *Streptococcus pneumoniae* indicating susceptibility to penicillin. The inset shows the sequence type that acquired the resistant PBP and subsequently expanded

SELECTED PUBLICATIONS

Ramirez M, and Melo-Cristino J (2010) Expanding the diagnosis of pediatric bacteremic pneumococcal pneumonia from blood cultures to molecular methods: advantages and caveats. Clin. Infect. Dis 51:1050-1052

Aguiar S I, Pinto FR, Nunes S, Serrano I, Melo-Cristino J, Sá-Leão R, Ramirez M, and de Lencastre H (2010) Increase of Denmark14-230 clone as a cause of pneumococcal infection in Portugal within a background of diverse serotype 19A lineages. J. Clin. Microbiol. 48:101–108

Francisco A P, Bugalho M, Ramirez M, and Carriço JA (2009) Global optimal eBURST analysis of multilocus typing data using a graphic matroid approach. BMC Bioinformatics 10:152

Silva-Costa C, Pinto FR, Ramirez M, Melo-Cristino J, and the Portuguese Surveillance Group for the Study of Respiratory Pathogens (2008) Decrease in macrolide resistance and clonal instability among Streptococcus pyogenes in Portugal. Clin. Microbiol. Infect. 14:1152-1159

Hänscheid T, Egan TJ, Grobusch MP (2007) Haemozoin: from melatonin pigment to drug target, diagnostic tool, and immune modulator. Lancet Infect. Dis. 7:675-685

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Group Leader

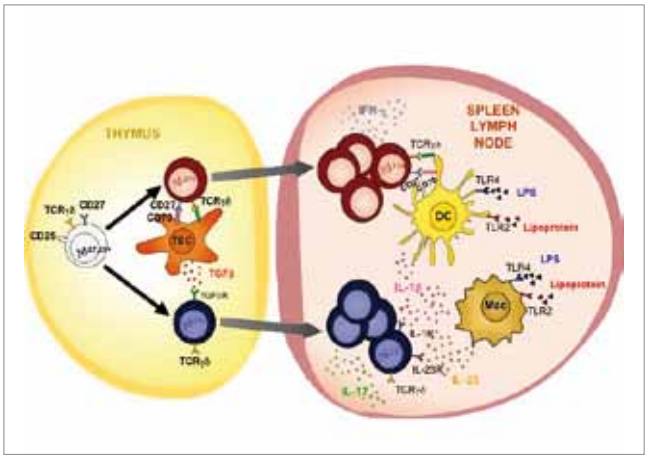
BRUNO SILVA-SANTOS

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

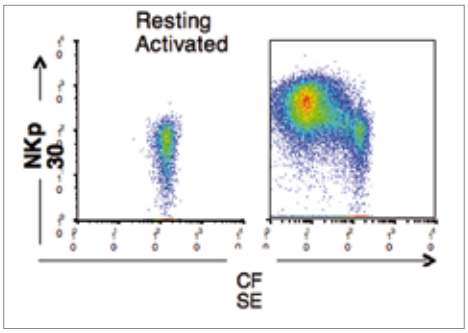
Ana Pamplona

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 gd 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-g 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-1b 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 Vd1+ T lymphocytes. Our data showed that, within human γδ T cells, NKp30 can be selectively induced in the Vd1+ subset, thus endowing these lymphocytes with enhanced cytotoxicity against leukemia and other tumor cells (D. V. Correia et al. *Blood* 2011).

SELECTED PUBLICATIONS

Correia DV, Fogli M, Hudspeth K, da Silva MG, Mavilio D and Silva-Santos B (2011) "Differentiation of human peripheral blood Vδ1+ T cells expressing the natural cytotoxicity receptor NKp30 for recognition of lymphoid leukemia cells", ***Blood***: Epub 1 Jun 2011

Lança T, Correia D V, Moita C F, Raquel H, Ferreira C, Ramalho J S, Barata J T, Moita L F, Gomes A Q and Silva-Santos B (2010) The MHC class Ib protein ULBP1 is a non-redundant determinant of leukemia/ lymphoma susceptibility to γδ T-cell cytotoxicity. *Blood:* 115(12):2407-11

Ribot J C, Chaves-Ferreira M, d'Orey F, Wencker M, Gonçalves-Sousa N, Decalf J, Simas J P, Hayday AC and Silva-Santos B (2010) Cutting Edge: Adaptive versus innate signals selectively control the pool sizes of IFN-γ- or IL-17-producing γδ T cells upon infection. *J Immunol:* 185(11):6421-5

Gomes A Q, Correia D V, Grosso A R, Lança T, Ferreira C, Lacerda J F, Barata JT, Gomes da Silva M and Silva-Santos B (2010) Identification of a panel of ten cell surface protein antigens associated with immunotargeting of leukemias and lymphomas by peripheral blood γδ T cells. *Haematologica:* 95(8):1397-404

Ribot J C, deBarros A, Pang D J, Neves J F, Peperzak V, Girardi M, Borst J, Hayday AC, Pennington DJ and Silva-Santos B (2009) CD27 is a thymic determinant of the balance between IFN-γ- and IL-17-producing γδ T cell subsets. *Nature Immunology* 10: 427-436

Pennington DJ, Silva-Santos B, Silberzahn T, Escorcio-Correia M, Dyson PJ, and Hayday AC (2006) Early events in the thymus affect the balance of effector and regulatory T cells. Nature 444, 7122: 1073-7

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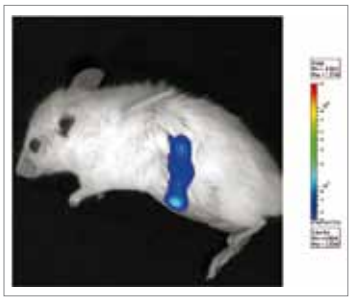
Group Leader

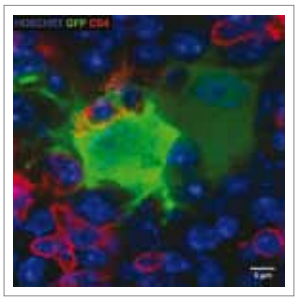
PEDRO SIMAS

PhD (1994) in Viral Pathogenesis at the University of Cambridge, UK
Post-doctoral research at the University of Cambridge, UK
Principal Investigator at Instituto Gulbenkian de Ciência (until 1999)
Associate Professor at Faculdade de Medicina da Universidade de Lisboa

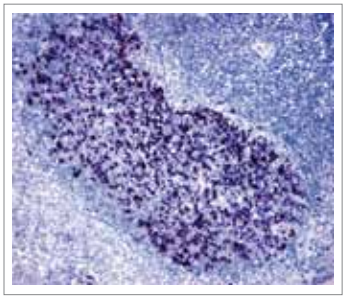
The overall aim of the Viral Pathogenesis Unit is to gain an understanding of the basic molecular mechanisms involved in the modulation of cellular function by herpesviruses. Herpesviruses are a major cause of disease worldwide and are amongst the most successful human pathogens, with specific viruses 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.



Intranasal infection of mice with a luciferase expressing MuHV-4. Splenic infection can be observed.



In situ visualization of fluorescently tagged MuHV-4 infected cells.



In situ hybridisation for viral RNAs evidences infected germinal centre cells in splenic sections of MuHV-4 infected mice.

SELECTED PUBLICATIONS

Stevenson PG, Simas JP, Efstathiou S (2009) Immune control of mammalian gamma-herpesviruses: lessons from murid herpesvirus-4. *J Gen Virol.*90 (Pt 10), 2317-30

Rodrigues L, Filipe J, Seldon MP, Fonseca L, Anrather J, Soares MP, Simas JP (2009) Termination of NF-kappaB activity through a gammaherpesvirus protein that assembles an EC5S ubiquitin-ligase. *EMBO J.* 28 (9), 1283-95

Milho R, Smith CM, Marques S, Alenquer M, May JS, Gillet L, Gaspar M, Efstathiou S, Simas JP, Stevenson PG (2009) In vivo imaging of murid herpesvirus-4 infection. *J Gen Virol* 90 (Pt 1), 21-32

Marques S, Alenquer M, Stevenson PG, Simas JP (2008) A single CD8+ T cell epitope sets the long-term latent load of a murid herpesvirus. *PLoS Pathog* 4 (10), e1000177

Pires de Miranda M, Alenquer M, Marques S, Rodrigues L, Lopes F, Bustelo XR, Simas JP (2008) The Gammaherpesvirus m2 protein manipulates the Fyn/Vav pathway through a multidocking mechanism of assembly. *PLoS One.* 3 (2):e1654

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Group Leader

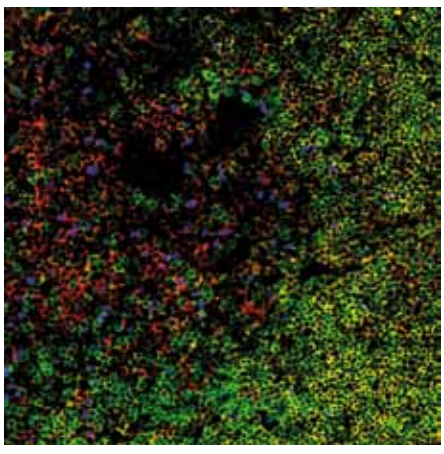
ANA E. SOUSA

MD (1986) and PhD (2000) in Clinical Immunology at Faculdade de Medicina da Universidade de Lisboa (FMUL) Investigator and Auxiliary Professor at FMUL

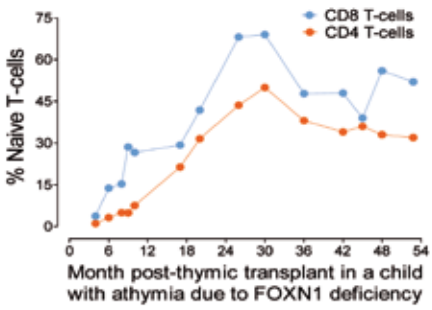
Other Principal Investigators

Rui M.M. Victorino, Maria Conceição Pereira-Santos, Íris Caramalho, João F. Lacerda

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.



FOXP3 expression in the human thymus



SELECTED PUBLICATIONS

Markert ML, Marques JG, Neven B, Devlin BH, McCarthy EA, Chinn IK, Albuquerque AS, Silva SL, Pignata C, de Saint Basile G, Victorino RM, Picard C, Debre M, Mahlaoui N, Fischer A, and Sousa AE (2011) First use of thymus transplantation therapy for FOXN1 deficiency (nude/SCID): a report of two cases. *Blood* **117**, 688-96

Nunes-Cabaço H, Caramalho I, Sepúlveda N and Sousa AE (2011) Differentiation of human thymic regulatory T cells at the double positive stage. *Eur J Immunol* l **41**, 3604-3614

Cavaleiro R, Baptista AP, Soares RS, Tendeiro R, Foxall RB, Gomes P, Victorino M, and Sousa AE (2009) Major Depletion of Plasmacytoid Dendritic Cells in HIV-2 Infection, an Attenuated Form of HIV Disease. *PLoS Pathog* **5**(**11**): e1000667. doi:10.1371/journal.ppat.1000667

Azevedo RI, Soares MV, Barata JT, Tendeiro R, Serra-Caetano A, Victorino RM, Sousa AE (2009) IL-7 sustains CD31 expression in human naive CD4+ T cells and preferentially expands the CD31+ subset in a PI3K-dependent manner. *Blood* **113**:2999-3007

Sousa AE, Carneiro J, Meier-Schellersheim M, Grossman Z, and Victorino RM (2002) CD4 T cell depletion is linked directly to immune activation in the pathogenesis of HIV-1 and HIV-2 but only indirectly to the viral load. *J Immunol* **169**:3400-3406

Grossman Z, Meier-Schellersheim M, Sousa AE, Victorino RM, and Paul WE (2002) CD4+ T-cell depletion in HIV infection: are we closer to understanding the cause? *Nature Medicine* **8**:319-321

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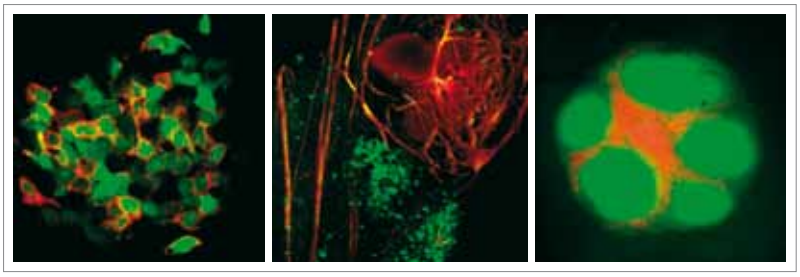
Group Leader

HENRIQUE VEIGA-FERNANDES

PhD (2002) in Molecular and Cellular Biology at Université René Descartes Paris V, France
Post-doctoral research at NIMR, UK and at the Institut Necker, France
Senior investigator scientist at NIMR, UK (2006-08)
Group leader at IMM since 2008
Awardee of an European Research Council Starting Grant in 2008

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.



Immune cells from mice expressing fluorescence proteins in specific cell lineages.
Left: developing lymph node; haematopoietic cells (green-GFP), CD4 (red).
Middle: developing lymphoid structure in the intestine; haematopoietic cells (green-GFP), neuronal axons (red).
Right: Peyer's patch; B cell areas (Green-GFP), T cell areas (Red-DsRed).

SELECTED PUBLICATIONS

Veiga-Fernandes H, Kioussis D, Coles M (2010) Natural killer receptors: the burden of a name. J Exp Med. 207(2):269-72

Gascoyne DM, Long E, Veiga-Fernandes H, de Boer J, Williams O, Seddon B, Coles M, Kioussis D, Brady HJ (2009) The basic leucine zipper transcription factor E4BP4 is essential for natural killer cell development. Nat Immunol. 10:1118-24

Veiga-Fernandes, H, Coles, MC, Foster, KE, Patel, A, Williams, A, Natarajan, D, Barlow, A, Pachnis, V and Kioussis, D (2007) Tyrosine kinase receptor Ret is a key regulator in Peyer's Patch organogenesis. Nature 446, 547-51

Peixoto A, Evaristo C, Munitic I, Monteiro M, Charbit A, Rocha B and Veiga-Fernandes H (2007) CD8 single-cell co-expression reveals three different effector types present at distinct phases of the immune response. J. Exp. Med. 204:1193-205

Veiga-Fernandes H and Rocha B (2004) High expression of active CDK6 in the cytoplasm of CD8 memory cells favors rapid division. Nature Immunol. 5, 31-37

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03

NEUROSCIENCES PROGRAMME

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.

Group Leader

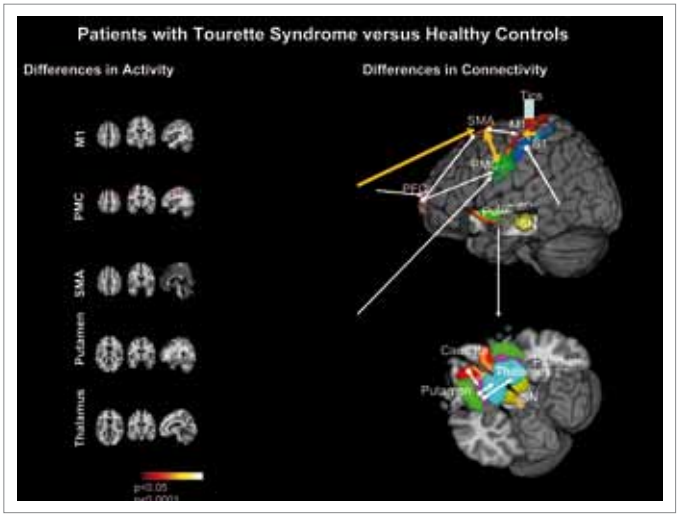
MAMEDE DE CARVALHO

MD (1985) at Faculdade de Ciências Médicas, Universidade Nova de Lisboa
PhD (2000) at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Associate Professor at FMUL

Other Principal Investigators

Isabel Rocha

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, conexins and cardiac purinergic system; on demonstrating the role central sympathetic areas hiperexcitability on neurogenic hypertension; on showing that autonomic remodelling 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.



Abnormalities in brain activity (left) and connectivity (right) in patients with Tourette's syndrome (TS) as compared to healthy controls (revealed with functional magnetic resonance imaging). Patients were scanned while they spontaneously had tics; healthy controls were scanned while they mimicked the tics of patients with TS in such a way that the mimicked tics were indistinguishable from real tics. Patients with TS had hyperactive motor circuits (left), encompassing all regions involved in the motor cortico-striatal-thalamo-cortical loop. M1: primary motor cortex; PMC: premotor cortex; PFC: prefrontal cortex; S1: primary somatosensory cortex; SMA: supplementary motor area; SN: substantia nigra.

SELECTED PUBLICATIONS

Maia, TV, Frank M J (2011) From reinforcement learning models to psychiatric and neurological disorders. Nat Neuroscience 14: 154-162

Lee T, Li YR, Ingre C, Weber M, Grehl T, Gredal O, de Carvalho M, Meyer T, Tysnes OB, Auburger G, Gispert S, Bonini NM, Andersen PM, Gitler AD (2011) Ataxin-2 intermediate--length polyglutamine expansions in European ALS patients. Hum Mol Genet; 20, 1697-1700

Oliveira M, da Silva N, Cunha P, Ramos R, Marques F, Santos S, Rocha I, Silva-Carvalho L, Ferreira R (2011) Effects of acute autonomic modulation on atrial conduction delay and local electrograms duration in paroxysmal atrial fibrillation. Int Journal Cardiol 149: 290-295

Oliveira M, Silva N, Matos L, Xavier R, Geraldes V, Ferreira R, Silva-Carvalho L, Rocha I (2011) Effect of vagal stimulation on atrial refractoriness and vulnerability to induce atrial fibrillation in the anaesthetized rabbit. Exp Physiol. 96: 125-33

Pinto S, de Carvalho M, Swash M (in press) Respiratory exercise in amyotrophic lateral sclerosis. Amyotr Lat Scler 13, 33-43

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Group Leader

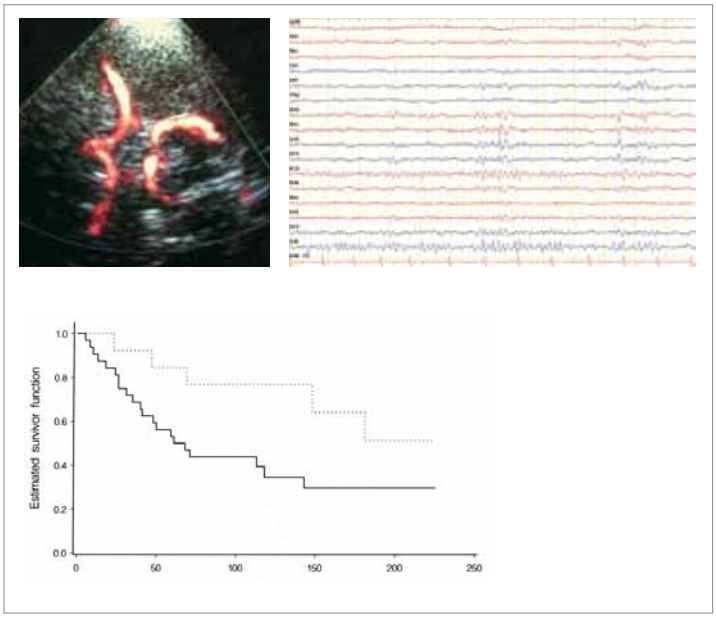
JOSÉ FERRO

MD (1975) and PhD (1987) at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Full Professor and Chairman at FMUL and the Santa Maria Hospital

Other Principal Investigators

Alexandre Castro Caldas, Alexandre de Mendonça, Cristina Sampaio, Isabel Pavão Martins, Joaquim Ferreira, José Pimentel, Patrícia Canhão, Sofia A. Oliveira, Teresa Paiva

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

Vellas B, Andrieu S, Sampaio C, Coley N, Wilcock G (2008) European Task Force Group. Endpoints for trials in Alzheimer's disease: a European task force consensus *Lancet Neurol*

Xavier JM, Shafiee NM, Ghaderi F, Rosa A, Abdollahi BS, Nadji A, Shahram F, Davatchi F, Oliveira SA (2011) Association of mitochondrial polymorphism m.709G>A with Behçet's disease (BD). *Ann Rheum Dis* 70, 1514-16

Aisen PS, Andrieu S, Sampaio C, Carrillo M, Khachaturian ZS, Dubois B, Feldman HH, Petersen RC, Siemers E, Doody RS, Hendrix SB, Grundman M, Schneider LS, Schindler RJ, Salmon E, Potter WZ, Thomas RG, Salmon D, Donohue M, Bednar MM, Touchon J, Vellas B. Report of the task force on designing clinical trials in early (predementia) AD: (2011) *Neurology*: 18;76(3):280-6. Epub 2010 Dec 22

Jokinen H, Gouw AA, Madureira S, Ylikoski R, van Straaten EC, van der Flier WM, Barkhof F, Scheltens P, Fazekas F, Schmidt R, Verdelho A, Ferro JM, Pantoni L, Inzitari D and Erkinjuntti T; LADIS Study Group (2011) Incident lacunes influence cognitive decline: the LADIS study. *Neurology* 76, 1872-1878

Moreno-López C, Santamaría J, Salamero M, Del Sorbo F, Albanese A, Pellecchia MT, Barone P, Overeem S, Bloem B, Aarden W, Canesi M, Antonini A, Duerr S, Wenning GK, Poewe W, Rubino A, Meco G, Schneider SA, Bhatia KP, Djaldetti R, Coelho M, Sampaio C, Cochen V, Hellriegel H, Deuschl G, Colosimo C, Marsili L, Gasser T, Tolosa E. (2011) Excessive Daytime Sleepiness in Multiple System Atrophy (SLEEMSA Study) *Arch Neurol* 68(2):223-30

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Group Leader

ANA SEBASTIÃO

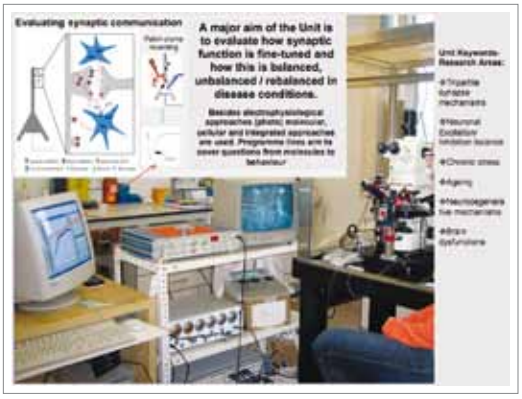
PhD (1987) in Cell Physiology, New University of Lisbon
Post doctoral researcher at Instituto Gulbenkian de Ciência, Oeiras
Associate Professor with Habilitation, Faculdade de Medicina da Universidade de Lisboa

Other Principal Investigators

Joaquim Alexandre Ribeiro, Alexandre Valério Mendonça, Luísa V. Lopes, Maria José Diógenes, Cláudia A.V. de Castro

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 caffeiane 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 comsumption, 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-imortalized cells; the heteomer stoicheometry was discovered and the nature of G-protein coupling identified.



SELECTED PUBLICATIONS

Batalha VL, Pego JM, Fontinha B, Costenla AR, Valadas J, Baqi Y, Radjainia H, Müller CE, Sebastião AM, Lopes LV (2012) Adenosine A2A receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation. Molecular Psychiatry, Epub Feb 28

Dias RB, Ribeiro JA, Sebastião AM (2012) Enhancement of AMPA currents and GluR1 membrane expression through PKA- coupled adenosine A2A receptors. Hippocampus, 22, 276-291

Pousinha PA, Correia AM, Sebastião AM, Ribeiro JA (2012) Neuromuscular transmission modulation by adenosine upon aging. Neurobiol Aging, Epub Feb 22.

Cristóvão-Ferreira S, Navarro G, Brugarolas M, Pérez-Capote K, Vaz SH, Fattorini G, Conti F, Lluis C, Ribeiro JA, Mccormick PJ, Casadó V, Franco R, Sebastião AM (2011) Modulation of GABA transport by adenosine A1R-A2AR heteromers, which are coupled to both Gs and Gi/0 proteins. J Neurosci., 31,15629-15639.

Vaz SH, Jorgensen TN, Cristovão-Ferreira S, Duflot S, Ribeiro JA, Gether U, Sebastião AM (2011) Brain-derived neurotrophic factor (BDNF) enhances GABA transport by modulating the trafficking of GABA transporter-1 (GAT-1) from the plasma membrane of rat cortical astrocytes. J Biol Chem., 286, 40464-40476.

Diógenes MJ, Costenla AR, Lopes LV, Jerónimo-Santos A, Sousa VC, Fontinha, BM, Ribeiro JA, Sebastião AM (2011) Enhancement of LTP in aged rats is dependent on endogenous BDNF. Neuropsychopharmacology, 36,1823-1836.

Aroeira RI, Ribeiro JA, Sebastião AM, Valente CA (2011) Age-related changes of glycine receptor at the rat hippocampus: from the embryo to the adult. J Neurochem., 118,339-353.

Sousa VC, Assaife-Lopes N, Ribeiro, JA, Pratt JA, Brett RR, Sebastião AM (2011) Regulation of hippocampal cannabinoid CB1 receptor actions by adenosine A1 receptors and chronic caffeine administration: implications for the effects of Δ9-tetrahydrocannabinol on spatial memory. Neuropsychopharmacology, 36, 472-487.

Assaife-Lopes N, Sousa VC, Pereira DB, Ribeiro JA, Chao MV, Sebastião AM (2010) Activation of adenosine A2A receptors induces TrkB translocation and increases BDNF-mediated phospho-TrkB localization in lipid rafts: implications for neuromodulation. J Neurosci, 23, 8468-8480.

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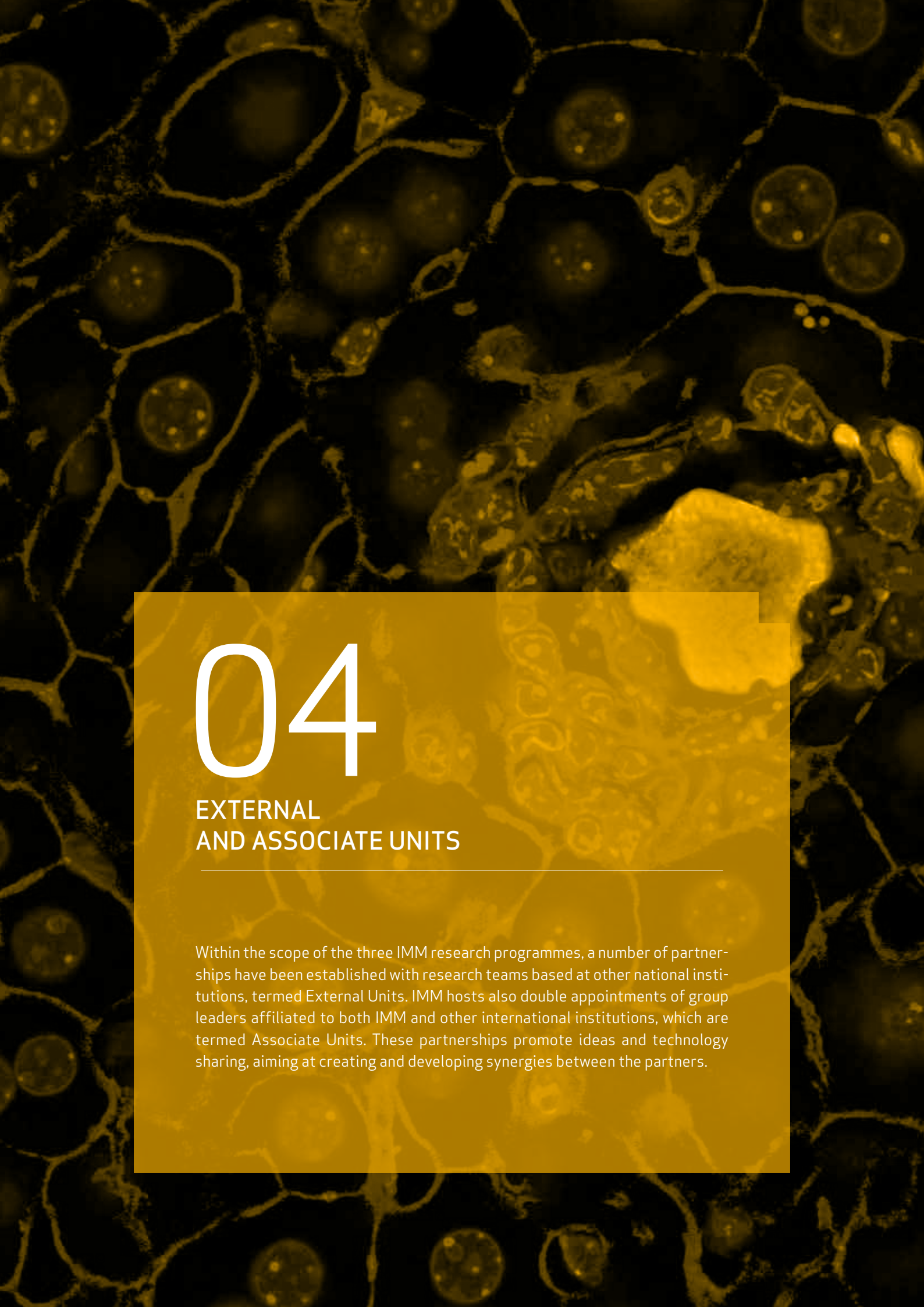


04

EXTERNAL AND ASSOCIATE UNITS

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.

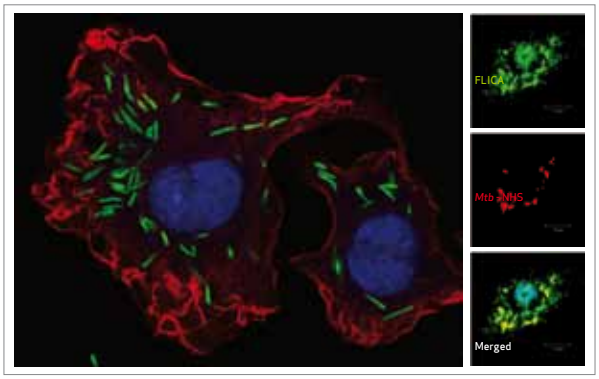
EXTERNAL UNIT

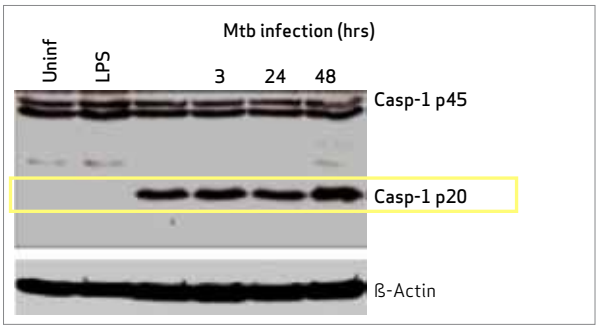
Group Leader

ELSA ANES

PharmD (1988) and PhD (1998) from Faculdade de Farmácia da Universidade de Lisboa (FFUL)
Visiting Post-doc at EMBL (2000-2005)
Associate Professor at FFUL
External Group Leader at IMM since 2008

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--1ß response to Mtb was performed and CARD9 was common to several conditions.





M. tuberculosis (green on top, red midlle bottom) infected macrophages activates caspase 1 (FLICA bottom left) to produce the pro-inflammatory cytokine IL1-betta, via distinct inflammasomes.

SELECTED PUBLICATIONS

Mishra BB, Moura- Alves P, Sonawane A, Hacohen N, Griffiths G, Moita LF and Anes E (2010) Mycobacterium tuberculosis protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. Cell Microbiol. 12(8):1046-63

Kuehnel M, Rybin V, Anand P, Anes E and Gareth Griffiths (2009) Lipids regulate P2X7 receptor-dependent actin assembly by phagosomes via ADP translocation and ATP synthesis in the phagosome lumen. J Cell Science 122(Pt 4):499-504

Gutierrez MG*, Mishra BB*, Jordao ML, Elliot E, Anes, E and Griffiths G 2008. NF-kappa B activation controls phago-lysosome fusion-mediated killing of mycobacteria by macrophages. J. Immunology 18(4): 2651-63
*joined first authors

Jordao L, Bleck CKE, Mayorga L, Griffiths G, and Anes E (2008) On the killing of mycobacteria by macrophages. Cell Microbiol 10(2): 529-48

Anes E, Kuhnel MP, Bos, E, Moniz-Pereira J, Habermann A and Griffiths, G (2003) Selected lipids activate phagosome actin assembly and maturation resulting in killing of pathogenic mycobacteria. Nat Cell Biol; 5(9): 793-802

Group Leader

JOÃO GONÇALVES

PhD (1996) at EMBL, Heidelberg, Germany
Research Assistant at Harvard Medical School, USA
Post-doctoral researcher at Scripps Research Institute, USA
Associate Professor at Faculdade de Farmácia da Universidade de Lisboa
Awardee of Bill & Melinda Gates Foundation Grand Challenges Programme

Other Principal Investigator

Mariana Santa-Marta, Paula Brito

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

Cadima-Couto I, Saraiva N, Santos AC, Goncalves J (2011) HIV-1 Vif interaction with APOBEC3 deaminases and its characterization by a new sensitive assay. J Neuroimmune Pharmacol 6(2):296-307

Esteves AIS, Nicolai M, Humanes M and Goncalves J. Sulfated Polysaccharides in Marine Sponges: Extraction Methods and Anti-HIV Activity. Mar. Drugs 2011, 9(1), 139-153; doi:10.3390/md9010139 (published online 24 January 2011)

Oliveira SS, Aires da Silva F, Lourenco S, Freitas-Vieira A, Santos AC, Goncalves J (2012) Assessing combinatorial strategies to multimerize libraries of single-domain antibodies. Biotechnology and Applied Biochemistry

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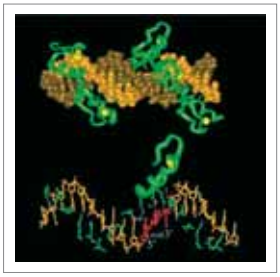
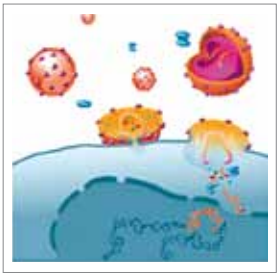


Synthetic zinc-finger binding to DNA.



HIV infectivity and neutralization by antibodies.

Model of VH-derived small domain antibody.

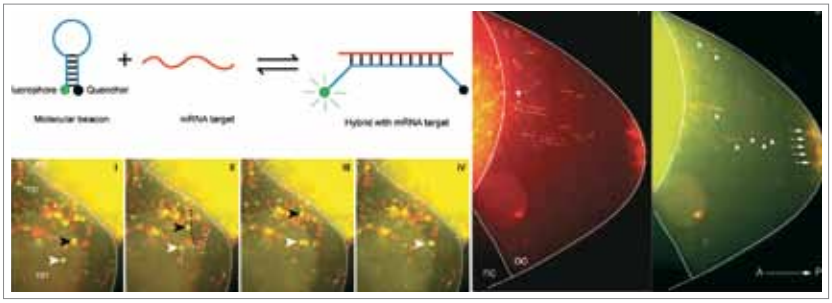
ASSOCIATE UNIT

Group Leader

MUSA MHLANGA

PhD (2003) in Cell Biology at the New York University School of Medicine, USA
Postdoctoral research at Institut Pasteur, France
Group Leader at IMM since 2008
Research Group Leader, New York University School of Medicine

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

Henriques R, Lelek M, Fornasiero EF, Valtorta F, Zimmer C and Mhlanga, MM (2010) QuickPALM: 3D real-time photoactivation nanoscopy image processing in ImageJ. Nature Methods 7 (5), 339-340

Henriques R, Mhlanga, MM (2009) PALM and STORM: What hides beyond the Rayleigh limit? Biotechnology journal 4 (6), 846-857

Mhlanga, MM, Vargas DY, Fung CW, Kramer FR, Tyagi S (2005) tRNA-linked molecular beacons for imaging mRNAs in the cytoplasm of living cells Nucleic acids research 33 (6), 1902-1912

Bratu DP, Cha BJ, Mhlanga, MM, Kramer FR, Tyagi S (2004) Visualizing the distribution and transport of mRNAs in living cells Proceedings of the National Academy of Sciences of the United States of America

Kostrikis LG, Tyagi S, Mhlanga, MM, Ho DD, Kramer FR (1998) Spectral genotyping of human alleles Science 279 (5354), 1228

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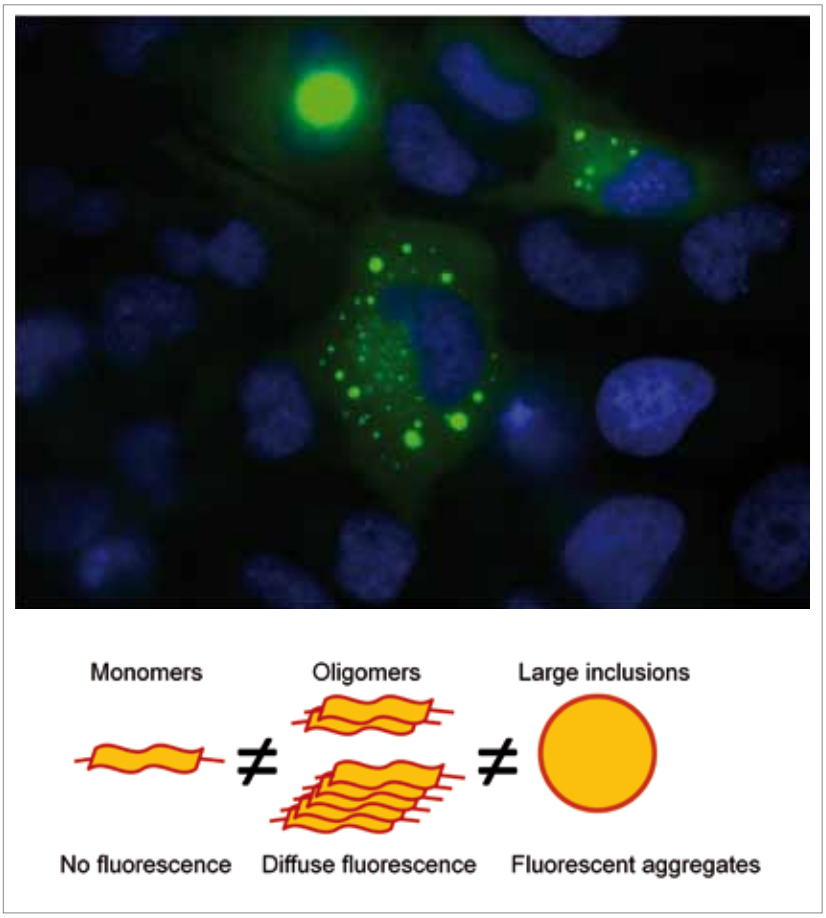
Group Leader

TIAGO FLEMING OUTEIRO

PhD (2004) at the Whitehead Institute for Biomedical Research, MIT, EUA
Post-doctoral research at Harvard Medical School and at FoldRx Pharmaceuticals, USA
Co-founder of BioEPI Clinical and Translational Research Center, Portugal
Auxiliary Professor Faculdade de Medicina da Universidade de Lisboa
Full Professor University Medizin Gottingen, Germany

Other Principal Investigator

Teresa Pais, Ana Dulce Correia



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 cytosol 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

Herrera F, Outeiro TF βSynuclein modifies huntingtin aggregation in living cells. FEBS Lett. (2012) Jan 2;586(1):7-12

Näsström T, Gonçalves S, Sahlin C, Nordström E, Screpanti Sundquist V, Lannfelt L, Bergström J, Outeiro TF, Ingelsson M (2011) Antibodies against alpha-synuclein reduce oligomerization in living cells. PLoS One 6(10):e27230

Outeiro TF, Putcha P, Tetzlaff JE, Spoelgen R,

Koker M, Carvalho F, Hyman BT, McLean PJ (2008) Formation of toxic oligomeric alpha--synuclein species in living cells. PLoS One 3(4):e1867. Erratum in: PLoS One. 2008;3(5)

Outeiro TF, Kontopoulos E, Altmann SM, Kufareva I, Strathearn KE, Amore AM, Volk CB, Maxwell MM, Rochet JC, McLean PJ, Young AB, Abagyan R, Feany MB, Hyman BT, Kazantsev AG (2007) Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. Science 317(5837):516-9

Outeiro TF, Lindquist S (2003) Yeast cells provide insight into alpha-synuclein biology and pathobiology. Science 302(5651):1772-5

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FACILITIES AND SERVICES

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.

BIOBANK

Head of Unit

João Eurico Fonseca
MD (1992) and PhD (2004) in Rheumatology at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Assistant Professor with Habilitation FMUL
Group Leader at IMM
Rheumatologist, Rheumatology Department, Santa Maria Hospital (HSM)

Staff

Ângela Afonso (Technician)

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.

BIOIMAGING

Head of Unit

José Rino
PhD (2007) in Biophysics at Faculdade de Ciências da Universidade de Lisboa
Post-doctoral research fellow at the IMM
Staff scientist at the IMM since 2009
Head of Facility since 2008

Staff

António Temudo (Technician)

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.

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)

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.

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.

RODENT FACILITY

Head of Unit

Joana Marques

PhD (2007) in Laboratory Animal Science at Swedish University of Agricultural Sciences, Uppsala, Sweden
Post-doctoral research fellow at Institute for Molecular and Cell Biology, Porto, Portugal
Head of Facility since September 2010

Staff

Dolores Bonaparte (Veterinarian), Iolanda Moreira (Technician), Carlos Barata Silva (Technician), Cecília Simão (Animal Caretaker), Felícia Ramos (Animal Caretaker), José Vila Chã (Animal Caretaker), Nuno Inácio (Animal Caretaker), Olena Pinho (Animal Caretaker), Wilma Zovo (Animal Caretaker)

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.

ZEBRA FISH FACILITY

Head of Unit

Leonor Saúde

PhD (2001) in Developmental Biology at University College London, UK
Post-doctoral fellow at Instituto Gulbenkian de Ciência (IGC)
Group Leader at IGC (2005-07) and at IMM since 2008
Assistant Professor at Faculdade de Medicina da Universidade de Lisboa
Head of Facility since 2008

Staff

Lara Carvalho (Unit Manager),
Aida Barros (Technician)

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.

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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.

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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.

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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**.

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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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CONTRACTS WITH INDUSTRY :

Abbott	Abbott A Promise for Life
Alfagene	alfagene
Amgen	AMGEN
Angelini	ANGELINI
Astella Pharma	astellas
Astrazenca	AstraZeneca
Axa	AXA
Bayer	BAYER
Biosurfit	biosurfit
Bristol-Myers Squibb	Bristol-Myers Squibb
Crioestaminal	crioestaminal
ECBIO	ecbio
FSG	FSG
Glaxo SK	gsk GlaxoSmithKline
Grunenthal	GRUNENTHAL
Grupo Taper / Zeiss	GRUPO TAPER ZEISS
Lab Pfizer	Pfizer
Leica	Leica
Merck	MERCK
Mundinter	mundinter
Nestec	Nestlé
Novartis	NOVARTIS
Roche Farmaceutica	Roche
Schering Plough	Schering-Plough
Tecnifar	GRUPO tecnifar
Wyeth	Wyeth Pharmaceuticals