IMM 2009.2010 REPORT

INSTITUTO DE MEDICINA MOLECULAR
FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

INSTITUTO DE MEDICINA MOLECULAR

INSTITUTO DE MEDICINA MOLECULAR (IMM)
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1000

Photos
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May, 2010

IMM 2009.2010 REPORT

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FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

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THE DIRECTOR'S REPORT

by J. Lobo Antunes and Maria Carmo-Fonseca

"(...) we expect that everybody gives their best, knowing that the road is sometimes hard and demanding. But there is no other way to achieve excellence in science."

The IMM was founded in 2001, but its activity as an independent institution ("Laboratório Associado") of the Ministry of Science began in 2004. This coincided with the installation in the new Egas Moniz Building.

The initial purpose was to assemble all Laboratories of the Faculty of Medicine of the University of Lisbon that had been ranked as centers of excellence by international panels in a single institution. The advantages seemed to us quite obvious: to create a critical mass of independent researchers, that could lead to a fruitful interdisciplinary collaboration, to develop common educational and doctoral programs, and share technical expertise and facilities.

We were able to achieve these goals but, of course, we were aiming to expand them further, and we soon realized that we had to follow two main rules: the periodic critical evaluation by outside experts, and a stringent policy of hiring only the most promising young scientists, thus following the recommendation of specialized panels from outside of IMM. This policy has been, by our estimation, remarkably successful. We have presently working in our Institute about 160 PhD holders and 290 non PhD holders, and 94 PhD students. The progress in the quality of our research projects has been outstanding, judging by the output of papers published in highly ranking journals and the increase in funding from international sources.

We also appreciate that much was to be gained by fostering our ties with the medical school and the university hospital, and we are now full partners of the new Academic Medical Center. We hope this will create the opportunity to collaborate in training programs, both pre-graduate and post-graduate and, furthermore, develop translational medicine projects and give stronger support to the ones already existing, in areas such as clinical neurosciences, rheumatologic disorders, oncology and clinical immunology.

IMM is also a founding member of the Health Cluster Portugal, which was created to strengthen alliances between biomedical research institutes, major health care programs and hospitals and pharmaceutical and medical device industries in Portugal.

We are also involved in the new Harvard Medical School-Portugal programme, and we have started a partnership with Inserm-France.

IMM also aims to be the perfect environment for scientific ideas to grow and turn into products and technologies that make difference in health care. To achieve this goal IMM develops ties and strategic plans with companies committed to innovation and new solutions for the sake of patients. Partnerships are established to strengthen positions in the competitive markets of drug discovery and diagnostics. These partnerships involve both companies incubated by IMM and external companies. The high quality of work developed by all research units of the IMM, either alone or in collaboration, is generating an increasing level of intellectual property rights, namely a few patents of invention with an acknowledged biomedical and/or pharmaceutical use. At the same time, IMM researchers are becoming more aware of questions related to IP rights or technology transfer.

In 2005 we started GenoMed, a molecular diagnosis laboratory, in partnership with Espírito Santo Saúde, Espírito Santo Capital, Farmindústria and Fundo de Sindicação de Capital de Risco (IAPMEI). The volume and sophistication of the tests available has expanded, and the scientists working in this laboratory have developed independent research projects.

We are indeed very proud of the achievements of our scientists, but we are keenly aware of the challenges and difficulties we face, particularly in what regards the sustainability of biomedical research in Portugal. We are fully aware that for a scientist to be productive we need to create the proper ecology, where new ideas and projects may flourish, and we have been, we believe, successful in achieving this. But we will always aim for more in this ever unended quest.

"It is said that Albert Einstein had written on the wall of his office at Princeton that "not everything that can be counted counts, and not everything that counts can be counted".

J Lobo Antunes
President

Maria Carmo-Fonseca
Executive Director

IMM AT A GLANCE

3 RESEARCH PROGRAMMES
Cell and Developmental Biology
Immunology and Infectious Diseases
Neurosciences

29 RESEARCH UNITS

2 EXTERNAL UNITS

2 COMPANIES

5 TECHNOLOGICAL FACILITIES

375 RESEARCHERS IN 2009
158 PhD holders

1 INTERNATIONAL PHD PROGRAMME
17 new PhD students in 2009

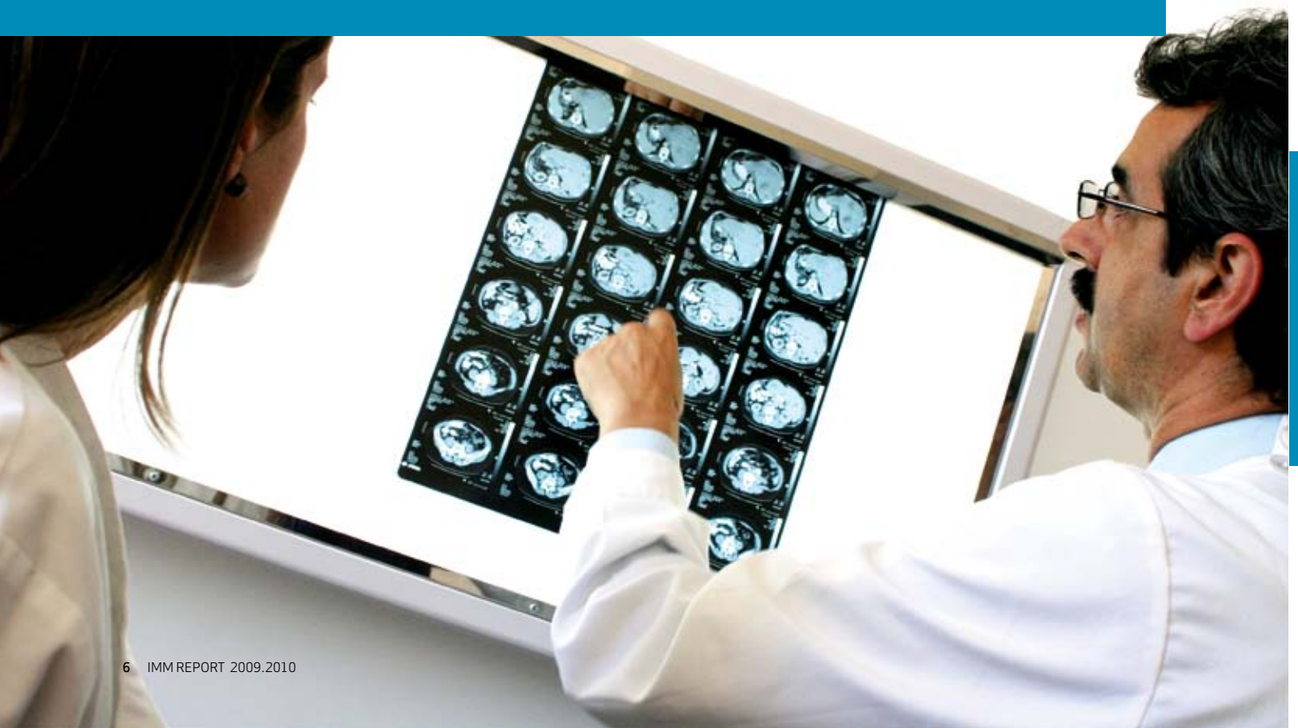
36 RESEARCH GRANTS STARTING IN 2009
19 Public National - FCT
10 EC-FP7
1 Embo
6 Private

187 PEER-REVIEWED SCIENTIFIC PUBLICATIONS IN 2009
13 in journals with > 10 impact factor

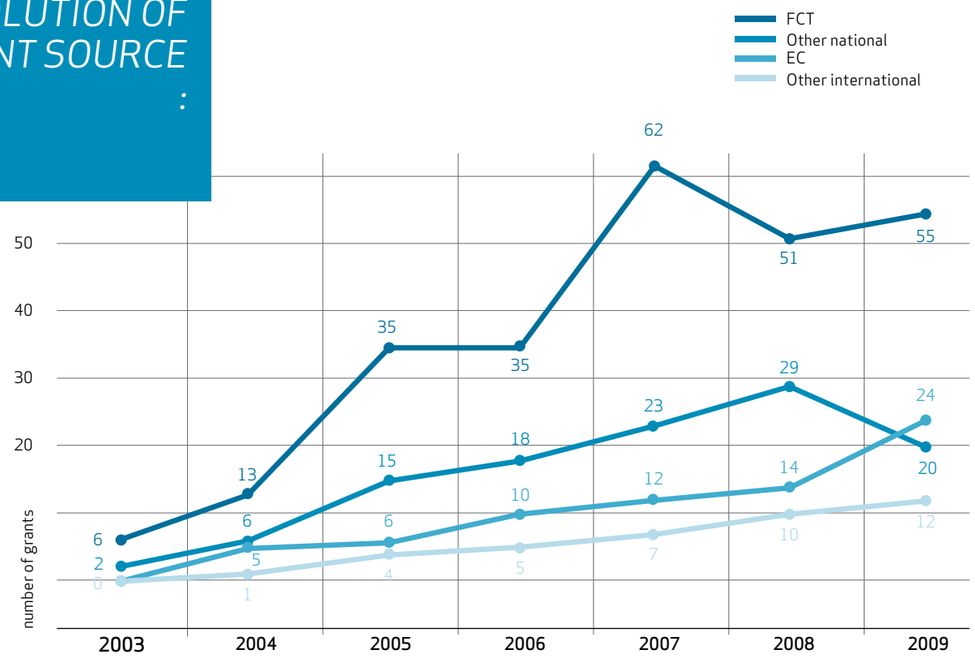
2 ERC LAUREATES

1 EURYI LAUREATE

1 HOWARD HUGHES SCHOLAR



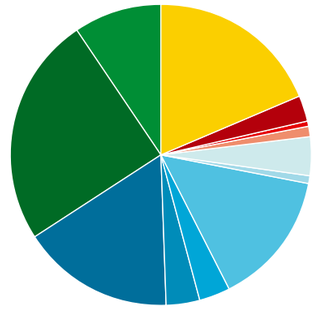
EVOLUTION OF GRANT SOURCE :



IMM FUNDING 2009 :

Expenditure in 2009 by Funding Source

Total expenditure: 9,450,192 €



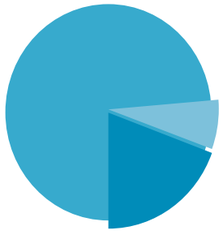
- 24,97%. Core Funds FCT
- 9,32%. Ciência Programme Funds
- 18,97%. Faculdade de Medicina da Universidade de Lisboa
- 2,63%. Protocols and donations
- 0,74%. Awards
- 1,03%. Other

Research Grants:

- 4,12%. International/ Private
- 0,29%. International/Public/Other
- 14,52%. International/Public/EC
- 3,23%. National/Private
- 3,83%. National/Public/Other
- 16,34% . National/ Public/FCT

RESEARCH HIGHLIGHTS

PAPERS 2009 :

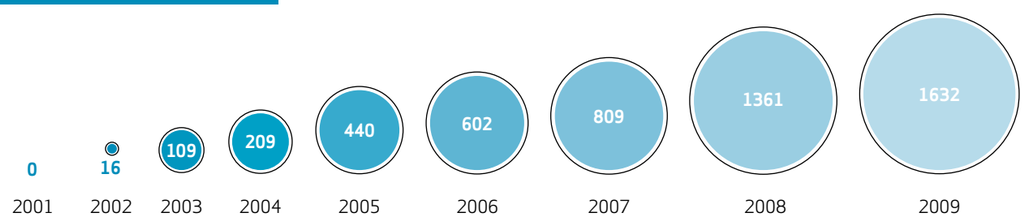


187
papers published in peer-reviewed journals:

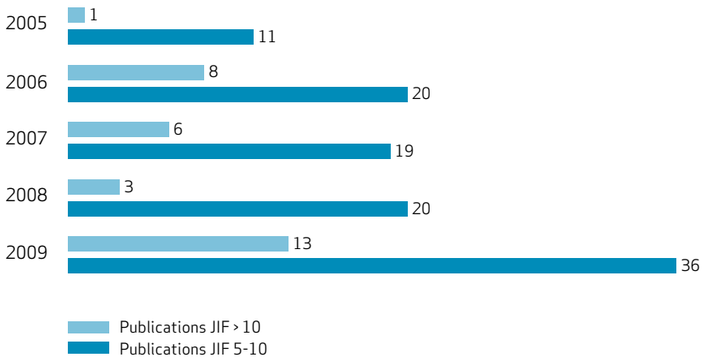
13 publications in journals with an impact factor higher than 10

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

CITATIONS PER YEAR :



IMPACT FACTOR OF PUBLICATIONS PER YEAR :



10 MOST CITED ARTICLES 2001 -2009 :

Grossman, Z., Meier-Schellersheim, M., Sousa, A.E., Victorino, R.M. and Paul W.E. (2002) CD4+ T-cell depletion in HIV infection: are we closer to understanding the cause? Nat. Med. 8: 319-321 **(Times cited: 230)**(Journal IF: 27.553)

Di Fonzo, A., Rohe, C.F., Ferreira, R.J., Chien, H.F., Vacca, L., Stocchi, F., Guedes, L., Fabrizio, E., Manfredi, M., Vanacore, N., Goldwurm, S., Breedveld, G., Sampaio, C., Meco, G., Barbosa, E., Oostra, B.A. and Bonifati, V. (2005) A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson's disease. Lancet 365: 412-415 **(Times cited: 190)** (Journal IF: 28.409)

Sousa, A.E., Carneiro, J., Meier-Schellersheim, M., Grossman, Z., and Victorino, R.M. (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 **(Times cited: 182)**(Journal IF: 6.000)

Ribeiro, J.A., Sebastião, A.M. and De Mendonça, A. (2002) Adenosine receptors in the nervous system: pathophysiological implications. Prog. Neurobiol. 68, 377-392 **(Times cited: 162)**(Journal IF: 9.130)

Duarte, A., Hirashima, M., Benedito, R., Trindade, A., Diniz, P., Bekman, E., Costa, L., Henrique, D. and Rossant, J. (2004) Dosage-sensitive requirement for mouse D114 in artery development. Gene Dev. 18: 2474-2478 **(Times cited: 140)**(Journal IF: 13.623)

Carmo-Fonseca, M. (2002) The contribution of nuclear compartmentalization to gene regulation. Cell 108:1-20 **(Times cited: 118)**(Journal IF: 31.253)

Emre, M., Aarsland, D., Brown, R., Bum, D.J., Duyckaerts, C., Mizuno, Y., Broe, G.A., Cummings, J., Dickson, D.W., Gauthier, S., Goldman, J., Goetz, C., Korczyn, A., Lees, A., Levy, R., Litvan, I., McKeith, I., Olanow, W., Poewe, W., Quinn, N., Sampaio, C., Tolosa, E. and Dubois, B. (2007) Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement. Dis. 22: 1689-1707 **(Times cited: 101)** (Journal IF: 3.898)

Stamm, S., Riethoven, J.J., Le Texier, V., Gopalakrishnan, C., Kumanduri, V., Tang, Y.S., Barbosa-Morais, N.L. and Thanaraj, T.A. (2006) ASD: a bioinformatics resource on alternative splicing Nucleic Acids Res. 34 (Special Issue): D46-D55 **(Times cited: 91)**(Journal IF: 6.878)

Santos, N.C., Figueira-Coelho, J., Martins-Silva, J. and Saldanha, C. (2003) Multidisciplinary utilization of dimethyl sulfoxide: pharmacological, cellular, and molecular aspect. Biochem. Pharmacol. 65: 1035-1041 **(Times cited: 89)**(Journal IF: 4.838)

Bonifati, V., Rohe, C.F., Breedveld, G.J., Fabrizio, E., De Mari, M., Tassorelli, C., Tavella, A., Marconi, R., Nicholl, D.J., Chien, H.F., Fincati, E., Abbruzzese, G., Marini, P., De Gaetano, A., Horstink, M.W., Maat-Kievit, J.A., Sampaio, C., Antonini, A., Stocchi, F., Montagna, P., Toni, V., Guidi, M., Dalla Libera, A., Tinazzi, M., De Pandis, F., Fabbrini, G., Goldwurm, S., de Klein, A., Barbosa, E., Lopiano, L., Martignoni, E., Lamberti, P., Vanacore, N., Meco, G. and Oostra, B.A. (2005) Early-onset parkinsonism associated with PINK1 mutations - Frequency, genotypes, and phenotypes. Neurology 65: 87-95 **(Times cited: 79)**(Journal IF: 7.043)

2009 AWARDS :

Bial Award in Clinical Medicine (edition 2008)

Fonseca, J.E., Canhão, H., Santos, M.J., Mourão, A.F., Sousa, E., Caetano-Lopes, J., Moura, R., Weinmann, P., Pereira da Silva, J.A., Cunha-Branco, J., Viana-Queiroz, M.

A new vision of inflammatory rheumatic diseases: an example of interaction of cell and molecular biology to the clinic.

-

Grunenthal Award in Pain Research (edition 2008)

Tavares, I., Ribeiro, M. and Castanho M.A.R.B.

Leading kytorphin derivatives to the central nervous system: experimental validation of a novel analgesic molecule.

-

Competition Idea To Product®, Austin, Texas, USA - 2nd place

Graça, L., Monteiro, M., Cristina, D.

Innovative cellular therapy to prevent complications after liver transplantation.

-

Calouste Gulbenkian Foundation Programme to Stimulate Creativity and Quality on Scientific Research

Domingues, M.

Area: *Molecular Recognition.*

-

Pfizer Award in Clinical Research

Silva-Santos, B.

Lymphocyte activation and molecular recognition of malignant cells: implications for cancer immunotherapy.

-

PAPERS WITH RELEVANT MEDIA COVERAGE :

IMM research is regularly highlighted in the media. Scientific articles, relevant funding and awards are amongst the most popular references.

01.

T Lymphocytes: defenders against infection or promoters of autoimmune diseases?

IMM researchers from the Molecular Immunology Unit, IMM, showed how to identify and control cells populations from the immune system that are responsible for antagonic consequences: defend the organism against infection or develop immune auto-immune disease. The study describes a process of cellular re-education, which may open novel perspectives in cancer immunotherapy and in the combat against autoimmune diseases. Research was developed at IMM, in collaboration with scientist from The Neederlands, USA and UK.

-

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

-

02.

How stem cells differentiate into neurons in vitro: IMM researchers publish study with roadmap

Researchers at the Developmental Biology Unit of IMM developed and published a study in PLoS One that identifies the molecular mechanisms involved in the differentiation of embryonic stem cells into neurons. The study, which helps to understand how the embryonic stem cells differentiate to generate neurons, is an important step for the development of new therapies against lesions on the nervous system resulting from trauma or neurodegenerative diseases. The researchers improved the efficiency of a previously known method for in vitro neuron production and identified the molecules that control the various stages of the process of neuronal differentiation.

-

Elsa Abranches, first author of the article, in TV interview.

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.

-

03.

IMM Researchers identify novel viral mechanism associated to the development of lymphomas

Researchers from the Viral Pathogenesis Unit at IMM identified a viral-mediated molecular mechanism that manipulates the host immune system, leading to persistence of herpes virus in the host organism and related to the development of lymphomas. The study involved the collaboration of Portuguese and American researchers.

-

Rodrigues L, Filipe J, Seldon MP, Anrather J, Soares MP and Simas JP (2009). Termination of NF-κB activity via a gherpesvirus protein that assembles an EC5S ubiquitin-ligase. The EMBO Journal 6;28(9):1283-95. Epub 2009 Mar 26.

-

STRUCTURE & ORGANIZATION

The Academic Medical Centre of Lisbon has been created as a consortium of the Santa Maria Hospital, the Lisbon Faculty of Medicine and **Instituto de Medicina Molecular** with the aim to develop an integrated perspective of Medicine, fostering translational biomedical research from bench to clinic and back to the bench. IMM is a private, non-profit organization which has acquired the status of Laboratory Associated to the National Ministry of Science, Technology and Higher Education. IMM is mainly supported by national public funds and European Union funds. The research expenditure is also supported by funds obtained from peer reviewed competitive grants, private donations and industrial partnerships.

IMM ID

Type private, non-profit research association

Created December 2001

Associate Members Universidade de Lisboa, Faculdade de Medicina da Universidade de Lisboa, Santa Maria Hospital, Fundação Universidade de Lisboa, Associacão para a Investigação e Desenvolvimento da Faculdade de Medicina, Fundação Oriente

History the IMM results from the fusion of 5 former research centres from the Faculdade de Medicina da Universidade de Lisboa.

The IMM is managed by a **Board of Directors** responsible for the accomplishment of its mission and the annual approval of the plan of activities and budget. The **Administration Board**, composed by the Board of Directors, the Research Programme Coordinators, and the Directors of the *Faculdade de Medicina and Santa Maria* Hospital, defines scientific strategies and actions, administrative organization plans and budgetary priorities. The **Council of Scientists**, composed by all IMM Principal Investigators, meets at least once per year to discuss the scientific strategies and plan of actions proposed by the Board of Directors. The scientific development of the Institute is monitored by **Scientific Advisory Committees** of international experts who are periodically involved in evaluations of the Institute and its units.
The executive arm of the Institute is the **Management Unit**, responsible for providing overall administrative support to IMM, including Human Resources, Accounts, Finance, Legal Affairs and Project Management. As funding for research projects comes from several national and international sources, IMM management requires the skills of experienced administrative staff.

PREVIOUS SCIENTIFIC ADVISORY COMMITTEES :

IMMUNOLOGY AND INFECTIOUS DISEASES
2010

António Freitas (Chair), Institut Pasteur, Paris
Alain Fisher, Necker Hospital Enfants-Malades, Paris
Anne O'Garra, National Institute for Medical Research, London
Philippe Sansonetti, Institut Pasteur, Paris
William Paul, National Institute of Allergy and Infectious Diseases, NIH, Bethesda

CELL AND DEVELOPMENTAL BIOLOGY
2006

Philip Ingham (Chair), University of Shefield/Institute of Molecular and Cell Biology, Singapore
Frank Grosveld, Centre for Biomedical Genetics, Erasmus University, Rotterdam
Outi Hovatta, Karolinska Institut, Stockholm
Iain Mattaj, European Molecular Biology Laboratory, Heidelberg
Axel Pries, Department of Physiology, Charité-Berlin, Berlin

NEUROSCIENCES
2005

Hanna Damasio (Chair), University of Southern California
Charles Warlow, Western General Hospital, Edinburgh
Michael Swash, Royal London Hospital
S. Grillner, Karolinska Institute, Stockholm
K.M. Spyer, University College of London

IMMUNOLOGY AND INFECTIOUS DISEASES
2005

António Freitas (Chair), Institut Pasteur, Paris
John Skehel, National Institute for Medical Research, London
George Griffin, St. George's Medical School, London
Waleria Hryniewicz, National Institute of Public Health, Warsaw
Steffen Gay, University Hospital Zurich
Jeff Platt, Mayo Clinic, USA

ORGANIGRAM

BOARD OF DIRECTORS

President João Lobo Antunes
Vice-President Joaquim Alexandre Ribeiro
Executive Director Maria Carmo Fonseca

EXECUTIVE DIRECTOR

Maria Carmo Fonseca

MANAGING DIRECTOR

Margarida Pinto Gago

RESEARCH

Cell and Developmental Biology Programme

António Jacinto
Luís Moita

15 Research Units

Immunology and Infectious Diseases Programm

José Moniz Pereira
Mário Ramirez
Rui Victorino

11 Research Units

Neurosciences Programme

Ana Sebastião
Mamede de Carvalho

5 Research Units

ADVANCED TRAINING

PhD Programme

FACILITIES

Bioimaging
Flow Cytometry
Rodents
Zebrafish
Histology
Microarrays
Biosafety Level 3 Laboratory (P3)

SUPPORT UNITS

Management
Lab Management
Information Systems
Communication and Funding

"The Administration Board, composed by the Board of Directors, the Research Programme Coordinators, and the Directors of the *Faculdade de Medicina* and *Santa Maria Hospital*, defines scientific strategies and actions, administrative organization plans and budgetary priorities."

RHEUMATOLOGY
RESEARCH UNIT

Normal female mice vertebra, with an amplification of 2000 by scanning electron microscopy. The trabecular structure of bone can be clearly observed.

RESEARCH

DEVELOPMENTAL BIOLOGY UNIT
-
A section of the neural tube of a mouse embryo at E12.5, where the activity of the Notch target gene NRARP is visualized in red. This gene is active in neuroepithelial progenitors located close to the lumen of the neural epithelium.

01

CELL AND DEVELOPMENTAL BIOLOGY PROGRAMME

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 studing 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

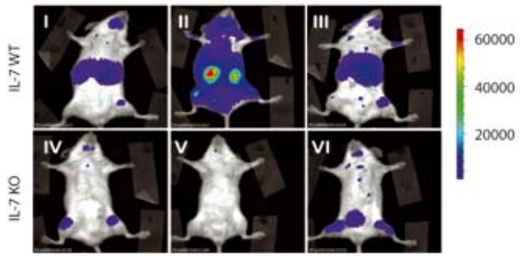
Research Team

2 Post-doctoral fellows, 5 PhD students, 1 Technician and 1 Trainee

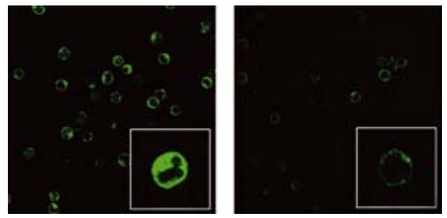
CANCER BIOLOGY UNIT

MAJOR INTERESTS

Cell-autonomous alterations and microenvironmental cues cooperate in the development of cancer. Our work on lymphoid leukemia aims to dissect the cell-intrinsic and extra-cellular factor-dependent signal transduction mechanisms by which tumor cells acquire a selective advantage over their normal counterparts. To do so, we integrate different biochemical, cellular and molecular biology techniques and *in vitro* and *in vivo* models of leukemia. The basic and pre-clinical research performed in the lab is translation-oriented and complemented by active ongoing collaborations with clinicians. Our ultimate goal is to identify and characterize molecular targets for the development of novel, more selective therapeutic tools against cancer.



T-ALL cells versus normal control. Constitutive activation of PI3KAkt pathway in tumor cells: Levels of PIP3 in malignant (left) versus normal T cells (right).



IL-7 accelerates leukemia progression in vivo. Mice with (IL-7 WT) or without (IL-7 KO) IL-7 xenotransplanted with T-ALL cells: Tumor burden imaged in live animals.

SELECTED PUBLICATIONS

Cardoso, B.A., Martins, L.R., Santos, C.I., Nadler, L.M., Boussiotis, V.A., Cardoso, A.A. and Barata, J.T. (2009) Interleukin-4 stimulates proliferation and growth of T-cell acute lymphoblastic leukemia cells by activating mTOR signaling. Leukemia 23: 206-208 (Journal IF: 8.634)

Silva, A. , Yunes, J.A., Cardoso, B.A. , Martins, L.R., Jotta, P.Y., Abecasis, M., Nowill, A.E., Leslie, N.R., Cardoso, A.A. and Barata, J.T. (2008) PTEN posttranslational inactivation and hyperactivation of the PI3K/Akt pathway sustain primary T cell leukemia viability. J. Clin. Invest. 118: 3762-3774 (Journal IF: 16.559)

Barata, J.T., Silva, A., Brandão, J.G., Nadler, L.M., Cardoso, A.A. and Boussiotis, V.A. (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 (Journal IF: 15.463)

Barata, J.T., Boussiotis, V.A., Yunes, J.A., Ferrando, A.A., Moreau, L.A., Veiga, J.P., Sallan, S.E., Look, A.T., Nadler, L.M. and Cardoso, A.A. (2004) IL-7-dependent human leukemia T-cell line as a valuable tool for drug discovery in T-ALL. Blood 103: 1891-1900 (Journal IF: 10.432)

Barata, J.T., Cardoso, A.A., Nadler, L.M. and Boussiotis, V.A. (2001) Interleukin-7 promotes survival and cell cycle progression of T-cell acute lymphoblastic leukemia cells by down-regulating the cyclin-dependent kinase inhibitor p27kip1. Blood 98: 1524-1531 (Journal IF: 10.432)

Group Leader
MARIA CARMO-FONSECA

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

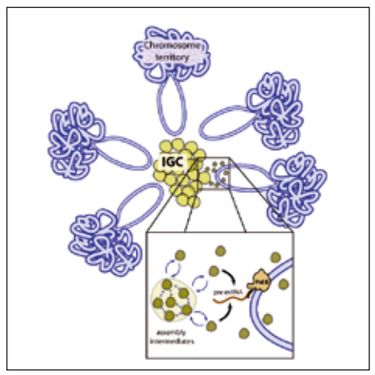
Other Principal Investigators
Francisco Enguita

Research Team
5 Lecturers, 3 Post-doctoral fellows, 2 PhD students and 2 Technicians

CELL BIOLOGY UNIT

MAJOR INTERESTS

Recent progress in microarray and high-throughput sequencing data analysis has revealed an unimagined complexity of the human transcriptome. We know now that alternative splicing generates a huge diversity of transcript variants and disruption of splicing regulatory networks is emerging as a major contributor to various diseases. There is increasing evidence that a better understanding of splicing mechanisms and their physiological regulation is needed for the development of novel intervention strategies for diagnosis, prognosis and treatment of human disease. Making use of a multidisciplinary approach that combines live-cell microscopy, computational modeling, molecular biology, biochemistry and bioinformatics, our group developed expertise to study how the dynamic properties of RNA-protein complexes contribute to post-transcriptional gene regulation. We have discovered and are further dissecting a surveillance mechanism that blocks release of abnormal RNAs from the gene template. We have also developed life-cell microscopy tools to visualize the dynamics of transcription, spliceosome assembly and splicing, and we are using these methodologies to determine how transcription and splicing are functionally coupled.



Spliceosome recruitment to nascent transcripts in the nucleus. Transcriptionally active genes loop out of more condensed territories and occupy the periphery of interchromatin granule clusters (IGCs or nuclear speckles), where transient interactions occur between spliceosomal proteins. Formation of short-lived assembly intermediates likely contributes to increase the local concentration of spliceosomal components, thus enhancing spliceosome assembly on nascent pre-mRNA. (adapted from *Rino and Carmo-Fonseca, The spliceosome: a self-organized macromolecular machine in the nucleus? Trends Cell Biol. 19: 357-384, 2009*).

SELECTED PUBLICATIONS

Calapez, A., Pereira, H.M., Calado, A., Braga, J., Rino, J., Carvalho, C., Tavanez, J.P., Wahle, E., Rosa, A.C. and Carmo-Fonseca, M. (2002) The intranuclear mobility of messenger RNA binding proteins is ATP-dependent and temperature-sensitive. J. Cell Biol. 159: 795-805 (Journal IF: 9.120)

Braga, J., Desterro, J.M. and Carmo-Fonseca M. (2004) Intracellular macromolecular mobility measured by fluorescence recovery after photobleaching with confocal laser scanning microscopes. Mol. Biol. Cell 15: 4749-4760 (Journal IF: 5.558)

Rino, J., Carvalho, T., Braga, J., Desterro, J.M., Lührmann, R. and Carmo-Fonseca, M. (2007) A stochastic view of spliceosome assembly and recycling in the nucleus. PLoS Comput. Biol. 10: 2019-2031 (Journal IF: 5.895)

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Grosso, A.R., Gomes, A.Q., Barbosa-Morais, N.L., Caldeira, S., Thorne, N.P., Grech, G., von Lindern, M. and Carmo-Fonseca, M. (2008) Tissue-specific splicing factor gene expression signatures. Nucleic Acids Res. 36: 4823-4832 (Journal IF: 6.878)

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Group Leader
MIGUEL CASTANHO

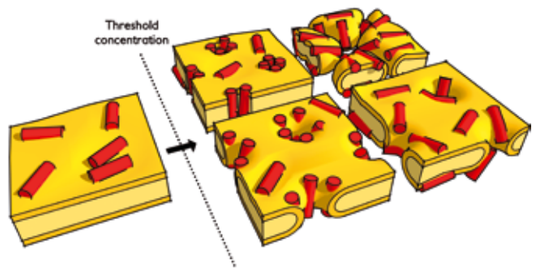
PhD (1993) in Molecular Biophysics at Universidade Técnica de Lisboa
Post-doctoral research at University of Hawaii, USA, and at Rocasolano Institute, Madrid, Spain
Full Professor at Faculdade de Medicina da Universidade de Lisboa

Research Team
1 Lecturer, 1 MD-PhD researcher, 4 Post-doctoral fellows, 3 PhD students, 2 MD research students, 4 Undergraduate research students and 1 Technician

PHYSICAL BIOCHEMISTRY UNIT

MAJOR INTERESTS

Have you ever noticed that all cells in every living being have the same kind of frontier to separate them from the other cells? Have you ever realized that if we find the right molecules to control or take advantage from this fact, the impact can be tremendous? In the Physical Biochemistry Unit we study molecules of great potential to interact with cell membranes: peptides. Some are analgesic, some are antimicrobial (they selectively kill bacteria), some are anti-viral (they block HIV at the entrance of cells), and some are carriers of other molecules but they all share a common characteristic: they have refined ways to interact with lipids. We study those ways and then use our findings to conceive innovative drugs, improve drugs or help on innovative therapeutical approaches, such as gene therapy, for instance. Our ultimate goal is to take our knowledge into the industrial world so that it can be transformed into products that help people live longer and have healthier lives.



Antimicrobial peptides (in red) may permeabilize bacterial lipid membranes in different ways. The most common are depicted in this picture

SELECTED PUBLICATIONS

Melo, M.N., Ferre, R. and Castanho, M.A.R.B. (2009) Antimicrobial peptides: linking partition, activity and high membrane-bound concentrations. Nat. Rev. Microbiol. 7: 245-250 (Journal IF: 14.31)

Franquelim, H.G., Loura, L.M.S., Santos, N.C. and Castanho, M.A.R.B. (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 (Journal IF: 8.091)

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Santos, N.C., Prieto, M. and Castanho, M.A.R.B. (2003) Quantifying molecular partition into model systems of biomembranes: an emphasis on optical spectroscopic methods, Biochim. Biophys. Acta 1565: 29-35 (Journal IF: 4.180)

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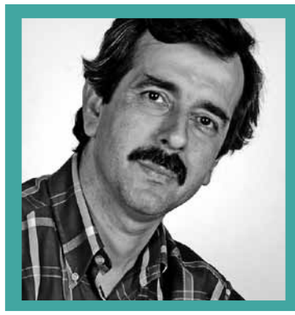


Group Leader

LUIS 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 at the Santa Maria Hospital

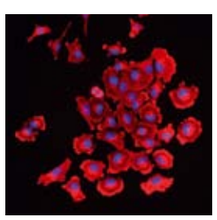
Research Team

2 Lectures, 1 Post-doctoral fellow, 3 MD researchers, 2 PhD students and 1 Technician

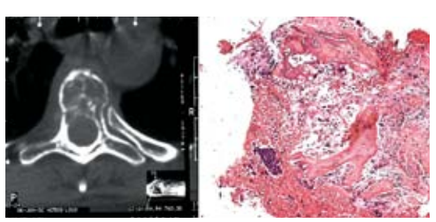
CLINICAL AND TRANSLATIONAL ONCOLOGY RESEARCH UNIT

MAJOR INTERESTS

The Clinical and Translational Oncology Research Unit studies mechanisms of invasion and progression in solid tumors, particularly in organs such as bone and liver. Tumor invasion and metastasis (tumor spreading to distant organs) are the hallmarks of malignancy, the major causes of death in cancer patients and the main challenge to medicine to improve cure rates in cancer. Our research is performed mostly in human tumor tissues and results are correlated with clinical information. It is our goal to contribute for the identification of tumor cells molecular markers that can correspond to an increased risk factor for metastases occurrence and to identify possible therapeutic targets. New advances in these fields have been achieved and are a good example of productive interaction between basic and clinical research. Our research is conducted in collaboration with a well-built network of international researchers, clinicians and laboratories.
The research projects ongoing in our Unit have the collaboration of some of the best scientific personalities in the field and generated, already, the interests of drug development department and biomarkers department of some drug companies that have leadership in the oncology field. We also work in close relation with the Oncology fellows from Hospital de Santa Maria, supporting PhD projects of Medical Doctors in training, and encouraging also the participation of other specialists or fellows (surgery, pathology, among others) into the research areas in development at our Unit.
We strong believe that collaboration between research clinicians and basic research scientists is a key to develop successful projects driven to answer important clinical questions.



Breast cancer cell line MDA-MB-231. Immunofluorescence staining with anti-actin antibody (red) and DAPI (nucleus, blue).



Breast cancer metastasis to the spine. Left panel: CT scan shows partial destruction of a vertebral body by cancer; Right panel: the microscopic observation of this lesion obtained by biopsy shows bone destruction by a small group of breast cancer cells (arrow). This case is on study for molecular markers of bone metastases.

SELECTED PUBLICATIONS

Costa, L. and Major, P.P. (2009) Effect of bisphosphonates on pain and quality of life in patients with bone metastases. Nat. Clin. Prac. Oncol. 6: 163-174 (Journal IF: 9.113)

Lipton, A., Campbell-Baird, C., Harvey, H., Kim, C., Demers, L. and Costa, L. (2010) Phase I trial of Zoledronic acid + Imatinib mesylate (Gleevec) in patients with bone metastases. Am. J. Clin. Oncol. 33: 75-78 (Journal IF: 1.792)

Casimiro,S., Guise, T.A. and Chirgwin, J. (2009) The critical role of the bone microenvironment in cancer metastases. Mol. Cel. Endoc. 310: 71-81 (Journal IF: 3.611)

Vitor, R.F., Esteves, T., Marques, F., Raposinho, P., Paulo, A., Rodrigues, S., Rueff, J., Casimiro, S., Costa L. and Santos, I. (2009) (99mTc)-Tricarbonyl complexes functionalized with anthracenyl fragments: synthesis, characterization and evaluation of their radiotoxic effects in murine melanoma cells. Cancer Biother. Radiopharm. 24: 1-13 (Journal IF: 1.318)

Aapro, M., Abrahamsson, P. A., Body, J. J., Coleman, R. E., Colomer, R., Costa, L., Crino, L., Dirix, L., Gnant, M., Gralow, J., Hadji, P., Hortobagyi, G. N., Jonat, W., Lipton, A., Monnier, A., Paterson, A. H. G., Rizzoli, R., Saad, F. and Thurlimann, B. (2008) Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann. Oncol. 19: 420-422 (Journal IF: 4.935)

Group Leader

SUSANA CONSTANTINO SANTOS

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

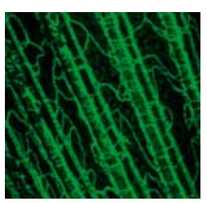
Research Team

1 Post-doctoral fellow, 2 PhD students and 1 Technician

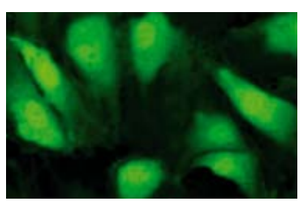
ANGIOGENESIS UNIT

MAJOR INTERESTS

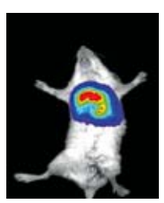
Angiogenesis is the formation of new blood vessels from pre-existing ones and is an essential process during development. Nonetheless, it also occurs in adulthood, during wound healing and restoration of blood flow to injured tissues. Angiogenesis is orchestrated by a variety of pro and anti-angiogenic signals. Their imbalance, promoting either excessive or insufficient angiogenesis, can lead to disease. In cancer, diabetic eye disease and rheumatoid arthritis, excessive angiogenesis feeds diseased tissue and destroys normal tissue. Conversely, insufficient angiogenesis underlies conditions such as coronary heart disease, stroke and delayed wound healing, where inadequate blood-vessel growth leads to poor circulation and tissue death.
The overall goal of the Angiogenesis Unit is to study the molecular and cellular mechanisms that regulate the angiogenic process. In endothelial cells, we described that one of the most important pro-angiogenic factors, the VEGF, and its receptor, KDR, are internalized and have a nuclear localization that is required for endothelial recovery during wound healing. We are now interested in the role of nuclear KDR. Does it function to silence KDR membrane signalling or does it have another specific role? We aim to answer this last question in order to identify new mechanisms that may be targeted in situations of wound healing failure or tumor angiogenesis.
Another focus of our unit is to understand the effects of ionizing radiation in the vasculature. Radiotherapy, alone or combined with surgery and chemotherapy, is used as a treatment of choice for tumors. However, several studies showed that ionizing radiation induces the production of pro-angiogenic molecules by the tumors that may activate pro-angiogenic responses in other cells. These observations have led us to study the differential response of the vasculature to low doses of ionizing radiation in order to develop novel radio- and chemotherapeutic strategies to better control of tumor re-growth and metastasis.



Live imaging: Zebrafish caudal fin vaculature (by Inês Vala)



Live cell imaging: Human endothelial cells overexpressing the GFP-KDR fusion protein (by Inês Domingues)



Bioimaging: Lung metastases were quantified by bioimaging (By Inês Vala)

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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 (Journal IF: 3.948)

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Constantino Rosa Santos, S., Lacronique, V., Bouchaert, I., Monni, R., Bernard, O., Gisselbrecht, S. and Gouilleux, F. (2001) Constitutively active STAT5 variants induce growth and survival of hematopoietic cells through a PI 3-Kinase/AKT dependent pathway. Oncogene 20: 2080-2090 (Journal IF: 7.216)

Monni, R., Constantino Rosa Santos, S., Mauchauffe, M., Berger, R., Ghysdael, J., Gouilleux, F., Gisselbrecht, S., Bernard, O. and Pernard-Lacronique, V. (2001) The TEL-Jak2 oncoprotein induces Socs1 expression and altered cytokine response in BaF3 cells. Oncogene 20: 849-858 (Journal IF: 7.216)

Constantino Rosa Santos, S., Dumon, S., Mayeux, P., Gisselbrecht, S. and Gouilleux, F. (2000) Cooperation between STAT5 and phosphatidylinositol 3-kinase in the IL-3 dependent survival of the bone marrow derived cell line. Oncogene 19: 1164-1172 (Journal IF: 7.216)

Group Leader

JOÃO FERREIRA

MD (1983) and PhD (1999) in Cell Biology at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Medical Residency in Dermatology, Curry Cabral Hospital, Lisbon (1987-90)
Associate Professor at FMUL

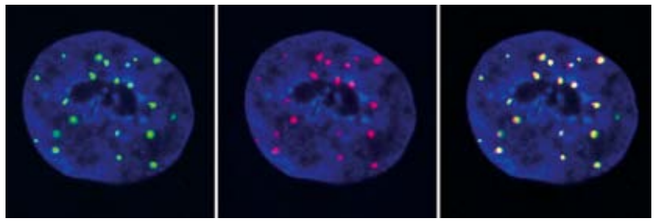
Research Team

1 Post-doctoral fellow, 1 PhD student and 1 Trainee

CHROMATIN BIOLOGY UNIT

MAJOR INTERESTS

The main objective is to investigate the role of chromatin structure and topology in genome function and propagation. We are particularly interested in disclosing how topoisomerases, the molecules that control the topology of DNA/chromatin inside the cell nucleus, are targeted to their sites of activity and influence nuclear phenomena namely the repair of DNA lesions and the biogenesis of specific types of chromatin. We also wish to investigate to what extent post-translational modifications of topoisomerase II influence chromosome segregation during mitosis. Finally, we wish to contribute to the understanding of how cytotoxic drugs that target topoisomerases exert their effects in cancer cells and which cellular factors affect chemoresistance. In this context, we shall address how chromatin and splicing regulators affect the accelerated cellular senescence programme that is triggered in cancer cells by inhibitors of topoisomerases.



Nucleus (blue signal) of a cell exposed to a topoisomerase-specific drug. Sites of damaged DNA (green signal) concentrate DNA repair proteins (red signal), as best seen in the merged (right) image.

SELECTED PUBLICATIONS

Agostinho, M., Santos, V., Ferreira, F., Costa, R., Cardoso, J., Pinheiro, I., Rino, J., Jaffray, E., Hay, R.T. and Ferreira, J. (2008) Conjugation of human topoisomerase 2 with SUMO-2/-3 in response to topoisomerase inhibitors: cell cycle stage and chromosome domain specificity. Cancer Res. 68: 2409-2418 (Journal IF: 7.514)

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Poot, R., Bozhenok, L., van den Berg, D.L.C., Steffensen, S., Ferreira, F., Grimaldi, M., Ferreira, J. and Varga-Weisz, P. (2004) The Williams Syndrome transcription factor interacts with PCNA to target chromatin remodeling by ISWI to replication foci. Nat. Cell Biol. 6: 1236- 1244 (Journal IF: 17.774)

Group Leader

DOMINGOS HENRIQUE

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

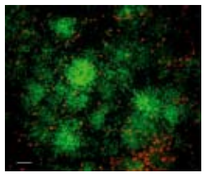
Research Team

4 Post-doctoral fellows, 2 PhD students, 1 Lab Manager and 1 Technician

DEVELOPMENTAL BIOLOGY UNIT

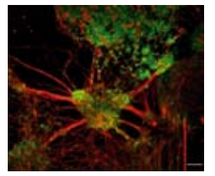
MAJOR INTERESTS

In vertebrates, neurogenesis starts very early during embryonic life and the majority of neurons is produced before birth. A conserved genetic circuitry, comprising the action of both proneural and neurogenic genes, is known to control the production of neurons during embryonic development. Our work aims to address how this circuitry functions to regulate the establishment of neural precursors in vertebrate embryos and how they give rise to the multitude of neurons that compose the adult CNS. We are particularly interested in dissecting the function of the Delta/Notch signaling pathway during neurogenesis in the developing spinal cord and neural retina, using transgenic approaches in mice embryos. We have also developed methods to use Embryonic Stem cells for *ex vivo* production of neurons and are interested in dissecting the mechanisms responsible for the emergence and maintenance of stem cells in the embryo. We believe that a better knowledge about these fundamental mechanisms is a pre-requisite for the development of cellular replacement therapies to treat neurodegenerative diseases, with a significant impact on human health.

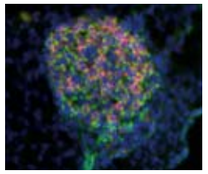


Neural Rosettes in culture containing ES-derived neuroepithelial progenitors (labelled in green) engaged on neuronal production (neurons are labelled red).

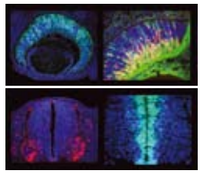
A section of the neural tube of a mouse embryo at E12.5, where the activity of the Notch target gene NRARP is visualized in red. This gene is active in neuroepithelial progenitors located close to the lumen of the neural epithelium.



Differentiated neurons (green) generated in vitro from ES cells, showing extended neuronal processes (labelled in red).



A section of a region of the embryonic CNS of a chicken embryo, containing the developing dorsal root ganglia where neurons (labelled in green) of the PNS are generated.



Pictures of the mouse embryonic retina (a,b) and spinal cord (c,d), showing undifferentiated progenitors and maturing neurons.

SELECTED PUBLICATIONS

Rocha, S.F., Lopes, S.S., 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. Biol. 328: 54-65 (Journal IF: 4.416)

Abranches, E., Silva, M., Pradier, L., Schulz, H., Hummel, O., Henrique, D. and Bekman, E. (2009) Neural differentiation of embryonic stem cells *in vitro*: a road map to neurogenesis in the embryo. PLoS ONE 4: e6286 (Journal IF: NA)

Diogo, M.M., Henrique, D. and Cabral, J.M.S. (2007) Optimization and integration of expansion and neural commitment of mouse embryonic stem cells. Biotechnol. Appl. Biochem. 49: 105-112 (Journal IF: 1.288)

Afonso, C. and Henrique, D. (2006) PAR3 acts as a molecular organizer to define the apical domain of chick neuroepithelial cells. J. Cell Science 119: 4293-4304 (Journal IF: 6.247)

Fior, R. and Henrique, D. (2005) A novel hes5/hes6 circuitry of negative regulation controls Notch activity during neurogenesis. Dev. Biol. 281: 318-333 (Journal IF: 4.416)

Fior, R. and Henrique, D. (2009) "Notch-Off": a perspective on the termination of Notch signalling. Int. J. Dev. Biol. 53: 1379-1384 (Journal IF: 2.359)

Group Leader

ANTÓNIO JACINTO

PhD (1999) in Developmental Biology at the Imperial College of Science and Technology and Medicine, University of London, UK
Post-doctoral research at University College London, UK
Group Leader at Instituto Gulbenkian Ciência (2001-04) and at IMM since 2004
Assistant Professor at Faculdade de Medicina da Universidade de Lisboa
Awarded a European Research Council Starting Grant
Awarded a Human Frontier Science Program Grant

Other Principal Investigator
Soren Prag

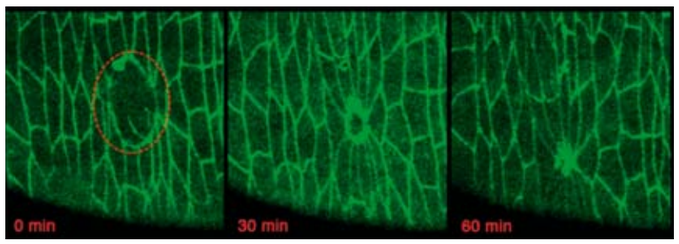
Research Team
9 Post-doctoral fellows, 6 PhD students, 2 researchers, 1 Master student and 2 Technicians

TISSUE MORPHOGENESIS AND REPAIR UNIT

-

MAJOR INTERESTS

Epithelia have the essential role of acting as a barrier that protects living organisms and its organs from the surrounding environment. It is crucial for epithelial tissues to have robust ways of maintaining their integrity despite the frequent damage caused by injury, inflammation and normal cell turnover. Our objective is to understand molecular and cellular processes that regulate epithelial resealing, a conserved fundamental repair mechanism that acts in several types of simple epithelia, both in embryos and in adults, and across species. The organism of choice has been the fruit fly *(Drosophila melanogaster)* due to the amenability of this model system to genetic manipulation and live imaging analysis. We are also using flies to investigate the mechanisms that control the recruitment of macrophage-like blood cells to wound sites to clear damaged cells and to study a natural occurring morphogenetic movement, dorsal closure, that has striking similarities to wound repair. Recently we have started using Zebrafish to translate our *Drosophila* findings to a vertebrate model and to explore more complex tissue repair mechanisms, such as epimorphic regeneration.



This sequence of images shows a region of a *Drosophila* embryonic epithelium where the outlines of the cells are marked with GFP. A wound of about 20 micrometers (dashed line) induced with a laser closes in about 1 hour. The molecular mechanisms that regulate this process are largely unknown and are under intense study in our laboratory.

SELECTED PUBLICATIONS

Campos, I., Geiger, J.A., Santos, A.C., Carlos, V. and Jacinto, A. (2010) Genetic screen in *Drosophila melanogaster* uncovers a novel set of genes required for embryonic epithelial repair. Genetics 184: 129-140 (Journal IF: 4.002)

Wood, W. and Jacinto, A. (2007) *Drosophila melanogaster* embryonic haemocytes: masters of multitasking. Nat. Rev. Mol. Cell Biol. 8: 542-551 (Journal IF: 35.423)

Simões, S., Denholm, B., Azevedo, D., Sotillos, S., Martin, P., Skaer, H., Castelli-Gair Hombria, J. and Jacinto, A. (2006). Compartmentalization of Rho regulators directs cell invagination during tissue morphogenesis. Development 133: 4257-4267 (Journal IF: 6.812)

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Wood, W., Jacinto, A., Grose, R., Gale, J., Wilson, C. and Martin, P. (2002) Wound healing recapitulates morphogenesis , co-ordinated regulation of actin cytoskeletal elements by small GTPases during repair of epithelial wounds in Drosophila embryos. Nat. Cell Biol. 4: 907-912 (Journal IF: 17.774) 4: 907-912.

-

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

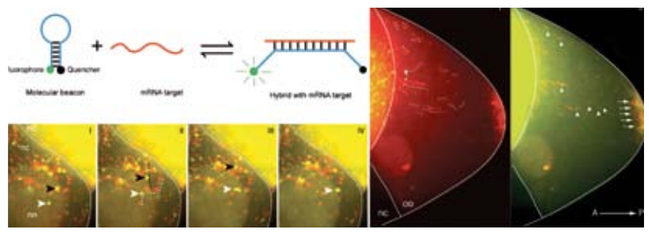
Research Team
1 PhD student and 1 Trainee

GENE EXPRESSION AND BIOPHYSICS UNIT

-

MAJOR INTERESTS

In biology several important processes occur at spatial dimensions currently beyond the reaches of conventional light microscopy. Our laboratory is concerned with those biological questions related to gene expression. As such the study of RNA transcription, metabolism and transport as well as its relation with dynamic compartmentalized multi-molecular complexes in the eukaryotic cell nucleus remain well outside the resolution of most optical microscopy techniques. The direct observation of these events at the single molecule level, is currently the subject of intense research. Intrinsic to RNA transcription are modifications to the nuclear architecture and the dynamic repositioning of chromosomal loci, as well as the interplay of several ribonucleic proteins (RNPs). These events remain opaque at the single RNA transcript level, and questions such as the timing and spatial position of interactions of these RNPs with RNA, the number of genes targeted in the transcriptional process at a single spatial location, the splicing and the export of RNA, remain unresolved. Understanding and visualizing these processes has implications not only for our understanding of basic biology, but extends to mechanisms in development and disease. Through the use of novel nucleic acid based probes (molecular beacons) for the detection of mRNA in living cells, we have recently extended these approaches to the imaging of gene expression and RNA transport in living cells. We are currently extending our ability to do single molecule biology through the development of super-resolution imaging techniques.



SELECTED PUBLICATIONS

Henriques, R., Mhlanga, M.M. (2009) PALM and STORM: What hides beyond the Rayleigh limit? Biotechnol. J. 4: 846 – 857 (Journal IF: NA)

Mhlanga, M.M., Bratu, D.P., Genovesio, A., Rybarska, A., Chenouard, N., Nehrbass,U. and Olivo-Marin, J.C. (2009) "In vivo" colocalisation of oskar mRNA and trans-acting proteins revealed by quantitative imaging of the Drosophila oocyte. PLoS One 4: e6241 (Journal IF: NA)

Mhlanga, M.M. and Tyagi, S. (2006) Using tRNA-linked molecular beacons to image cytoplasmic mRNAs in live cells. Nat. Protoc. 1: 1392-1398 (Journal IF: 4.170)

Mhlanga, M.M., Vargas, D.Y., Fung, C.W., Kramer, F.R. and Tyagi, S. (2005) tRNA-linked molecular beacons for imaging mRNAs in the cytoplasm of living cells. Nucleic Acids Res. 33: 1902-1912 (Journal IF: 6.878)

Bratu, D.P., Cha, B.J., Mhlanga, M.M., Kramer, F.R. and Tyagi, S. (2003) Visualizing the distribution and transport of mRNAs in living cells. Proc. Natl. Acad. Sci. USA 100: 13308-13313 (Journal IF: 9.380)

Mhlanga, M.M. and Malmberg, L. (2001) Using molecular beacons to detect single nucleotide polymorphisms with real-time PCR. Methods 25: 463-471 (Journal IF: 3.291)

Kostrikis, L.G., Tyagi, S., Mhlanga, M.M., Ho, D.D. and Kramer, F.R. (1998) Spectral genotyping of human alleles. Science 279: 1228- 1229 (Journal IF: 28.103)

-

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
Nina Matova

Research Team
4 Post-doctoral fellows, 1 PhD student, 1 MD-PhD Student, 2 MD researchers and 1 Technician

CELL BIOLOGY OF THE IMMUNE SYSTEM UNIT

-

MAJOR INTERESTS

The study of host-pathogen interactions is critical for the understanding of the outcome of immune responses (tolerance vs. immunity) and has the potential to lead the way for the design of novel effective therapeutic strategies. As a novel approach to understand how the physical and biochemical nature of particulate antigens influences their uptake and fate in Antigen Presenting Cells (APCs), we are studying the internalization, traffic and processing of 'synthetic pathogens' - model particles with distinct, well-defined physical and biochemical properties. We are comparing how signals from host opsonins or pathogen structure/composition itself modulate phagocytosis and subsequent immunity in the context of a single well-defined particle platform- to allow individual parameters of pathogen structure/composition to be varied and their effects compared in a single model system. We hope to better understand how pathogen structure and chemistry dictates signaling, intracellular traffic, antigen processing, immune responses and pathogen survival or elimination.
In addition to the studies on pathogen structure and composition (Fig. 1), our Unit uses RNA interference (RNAi) to identify genes with a previous uncharacterized role in several processes (Fig.2, for example) that are relevant for immune responses. We are currently focusing on two main questions: (1) what is the role of alternative splicing in the regulation of the immune response? And, (2) what are the molecular mechanisms of antigen cross-presentation?
Since RNA interference (RNAi) was discovered to work in mammalian cells, this genetic manipulation technique has been hailed as a revolutionary new approach to basic biological research and drug development and discovery. RNAi is expected to provide critical insights into the mechanisms underlying human disease and accelerating development of treatments for cancer, AIDS and a host of other disorders.

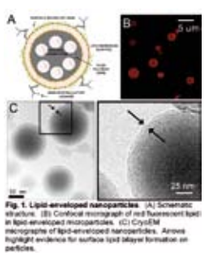
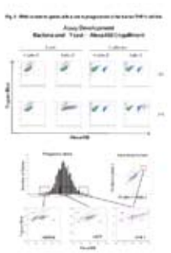


Fig. 1. Lipid-enveloped nanoparticles. (A) Schematic structure. (B) Confocal micrograph of red fluorescent lipid in lipid-enveloped microparticles. (C) Cryo-EM micrographs of lipid-enveloped nanoparticles. Arrows highlight evidence for surface lipid bilayer formation on particles.



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Robinson, M., Osorio, F., Rosas, R., Freitas, R., Schweighoffer, E., Groß, O., Verbeek, J.S., Ruland, J., Tybulewicz, V., Brown, G.D., Moita, L.F., Taylor, P.R. and Sousa, C.R (2009) Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. J. Exp. Med. 206: 2037-2051 (Journal IF: 15.463)

Savina, A., Peres, A., Cebrian, I., Carmo, N., Moita, C., Hacohen, N., Moita, L.F., and Amigorena, S. (2009) Rac2 controls phagosomal alkalinization and crosspresentation selectively in CD8+ dendritic cells. Immunity 30: 544-555 (Journal IF: 20.579)

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Moita, L.F.*, Wang-Sattler, R., Michel, K., Zimmermann, T., Blandin, S., Levashina, E.A. and Kafatos, F.C. (2005) *In vivo* phagocytic screen in *A. gambiae*: new players and conserved pathways of engulfment. Immunity 23: 65-73 *Corresponding author (Journal IF: 20.579)

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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)
Associated Professor with Habilitation at FMUL

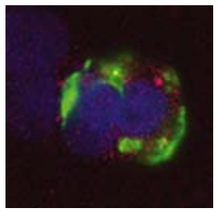
Research Team
2 Lecturers, 1 Teaching assistant, 2 PhD students, 1 Trainee and 1 Technician

MICROVASCULAR BIOLOGY AND INFLAMMATION UNIT

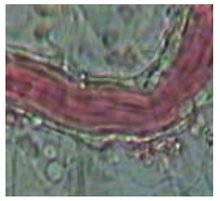
-

MAJOR INTERESTS

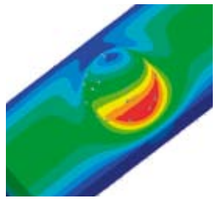
The vascular wall stays at the cornerstone of inflammation controlling the participation and recruitment of circulating blood cells. Our research is focused on the molecular and cellular processes occurring at blood-vessel wall interface in the context of inflammation. To address this, we conjugate molecular and cellular biology approaches with microcirculation studies, such as high-speed intravital microscopy imaging of in vivo animal models.
By using rat, mice and zebrafish models, our research aims at understanding the mechanisms that govern leukocyte recruitment and cell-cell interaction in inflammation. We are currently addressing the role of specific inflammatory mediators, in modulating blood-vessel wall interaction in inflammation and the mechanisms that regulate neutrophil-induced monocyte recruitment during the inflammatory response. We research on the role of erythrocyte as a pro-active blood component on inflammation.
Based on these studies, we collaborate at developing theoretical simulation models of phenomena occurring at the level of leukocyte-vascular wall interface, particularly related to inflammatory processes.
We are also collaborating with a start-up biotech company in the development of new methodologies for the determination of hemorheologic parameters.



Neutrophils labeled with DAPI (blue), fibrinogen (green) and integrin Mac-1 (red).



Mesenteric venule in animal model (rat) for observation of leukocyte-vascular wall interaction.



Mathematical simulation of a leukocyte approaching the endothelial wall.

Neutrophils (green) in a 3 day post-fertilization transgenic mpx::egfp zebrafish.

SELECTED PUBLICATIONS

Carvalho, F.A., Martins-Silva, J. and Saldanha, C. (2004) Amperometric measurement of nitric oxide in erythrocytes. Biosens. Bioelectron. 20: 505-508 (Journal IF: 5.143)

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Santos, S.C.R., Vala, I., Miguel, C., Barata, J.P., Garção, P., Agostinho, P., Mendes, M., Coelho, A.V., Calado, A., Oliveira, C.R., Martins e Silva, J. and Saldanha, C. (2007) Expression and subcellular localization of a novel nuclear acetylcholinesterase protein. J. Biol. Chem. 282: 25597-25603 (Journal IF: 5.520)

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Rosário, H.S., Waldo, S.W., Becker, S.A., Schmid-Schönbein, G.W. (2004) Pancreatic trypsin increases matrix metalloproteinase-9 accumulation and activation during acute intestinal ischemia-reperfusion in the rat. Am. J. Pathol. 164: 1707-1716 (Journal IF: 5.697)

-

Group Leader

NUNO C. SANTOS

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

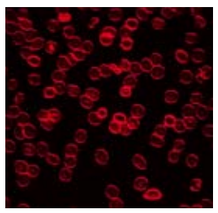
Research Team

1 MD researcher, 4 Post-doctoral fellows, 4 PhD students and 1 Technician

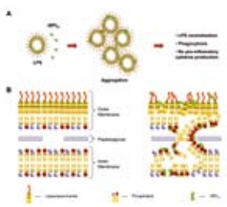
BIOMEMBRANES UNIT

MAJOR INTERESTS

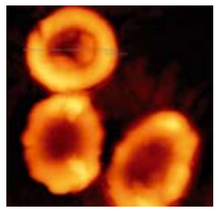
Biological membranes serve not only as biological boundaries but also as dynamic structures essential for several cellular events, both on health and disease. The scope of the Unit is the study of biochemical and biophysical processes occurring at the level of the membranes of human cells and of their viral and bacterial pathogens, even without the involvement of membrane receptors. The Unit is mainly focused on the two steps of the life cycle of enveloped viruses (mainly HIV and dengue virus) that involve biomembranes: the entry of the virus in a target cell and the release of new virus. The questions that we try to answer are related to specific lipid recruitment during viral assembly, virus-target cell interactions conditioning by viral lipid composition and, the role of lipid rafts (heterogeneous membrane areas enriched in specific components) on the virus life cycle and on the action of some anti-HIV drugs. The answering of some of these questions may reveal specific interactions, show how they can be modulated and, hopefully, identify new targets for antiretroviral therapy. Adding to this main focus, we are also involved in collaborative projects on: i) the evaluation of the activity of microbicides that bind to a specific component of the membranes of some bacteria; ii) the study of the binding of a plasma protein to red blood cells and its relevance as cardiovascular risk factor; iii) the evaluation of a potential marker in Alzheimer disease; and, iv) on the Nanomedicine / Nanotechnology area, the structural characterization of metal nanoparticles conjugated with proteins for biomedical applications (e.g., biosensors).



Red blood cells labeled with the membrane potential probe Di-8-ANEPPS.



rBPI21 Mechanism of action



Red blood cells imaging by atomic force microscopy (AFM).

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Santiago, P.S., Moura, F., Moreira, L.M., Domingues, M.M., Santos, N.C. and Tabak, M. (2008) Dynamic light scattering and optical absorption spectroscopy study of pH and temperature stabilities of the extracellular hemoglobin of Glossoscolex paulistus. Biophys. J. 94: 2228-2240 (Journal IF: 4.683)

Veiga, A.S., Santos, N.C., Loura, L.M.S., Fedorov, A. and Castanho, M.A.R.B. (2004) HIV fusion inhibitor peptide T-1249 is able to insert or adsorb to lipidic bilayers. Putative correlation with improved efficiency. J. Am. Chem. Soc. 126:14758-14763 (Journal IF: 8.091)

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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 Ciência (IGC)
Group Leader at IGC (2005-07) and at IMM since 2008
Assistant Professor at Faculdade de Medicina da Universidade de Lisboa

Research Team

3 Post-Doctoral fellows, 3 PhD students, 1 Master student, 1 Technician

EMBRYONIC DEVELOPMENT OF VERTEBRATES UNIT

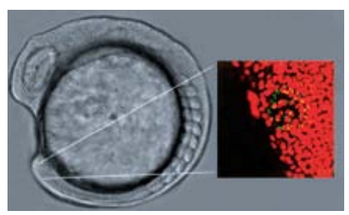
MAJOR INTERESTS

How does a single cell, the fertilized egg, divides into millions of cells that will organize themselves into the tissues and organs that compose the human body is a fascinating question in Biology. Our long-term research goal is to understand the genes, the molecules and the mechanisms that orchestrate the assignment of different cell types into the correct positions within the developing embryo. Once we uncover these developmental pathways, we will be able to fully understand inherited human defects and find ways of repairing and replacing tissues.

Our Unit addresses several questions. How is the left-right asymmetric localization, structure and function of vital organs like the heart, the liver and the brain achieved? How is this coordinated? The different vertebrae that constitute the vertebral column and the muscles that move the skeleton are not formed all at the same time, but rather in a periodic and sequential manner under the control of a molecular clock. When and how is this molecular clock started in the embryo? Is this molecular clock used to control the progressive laid down of skeletal elements that will form a fully functional fin? Is the molecular clock reused to control the timing of repair after organ injury or amputation?

We use zebrafish, chick and mouse embryos as animal models. They offer complementary embryological, molecular and genetic approaches, allowing a more comprehensive understanding of the mechanisms of development. The large and flat chick embryo allows position specific surgical manipulations. The genetics of mouse and zebrafish is a powerful tool to analyse the effects of loss of gene function and interactions among genes. In addition, the transparency of the zebrafish embryo allows the visualization of developmental processes in the living embryo using high-resolution microscopes.

A mouse embryo with 9 days of development expresses a gene named terra in the somites.



A zebrafish embryo with 12 hours of development. In the tail region, cilia can be spotted with a green labelling inside an organ called Kupffer's vesicle. These cilia control the positioning of the internal organs inside the body cavities.

SELECTED PUBLICATIONS

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Coutinho, P., Parsons, M.J., Thomas, K.A., Hirst, E.M., Saúde, L., Campos, I., Williams, P.H. and Stemple D.L. (2004) Differential requirements for COPI transport during vertebrate early development. Dev. Cell 7: 547-558 (Journal IF: 12.882)

Feldman, B., Concha, M.L., Saúde, L., Parsons, M.J., Adams, R.J., Wilson, S.W. and Stemple D.L. (2002) Lefty antagonism of Squint is essential for normal gastrulation. Curr. Biol. 12: 2129-2135 (Journal IF: 10.777)

Saúde, L., Woolley, K., Martin, P., Driever, W. and Stemple D.L. (2000) Axis-inducing activities and cell fates of the zebrafish organizer. Development 127: 3407-3417 (Journal IF: 6.812)

Heisenberg, C-P., Tada, M., Rauch, G-J., Saúde, L., Concha, M.L., Geisler, R., Stemple, D.L., Smith, J.C. and Wilson S.W. (2000) Silberblick/Wnt11 mediates convergent extension movements during zebrafish gastrulation. Nature 405: 76-81 (Journal IF: 31.434)

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02

IMMUNOLOGY AND INFECTIOUS DISEASES PROGRAMME

RHEUMATOLOGY RESEARCH UNIT

TRAP positive monocyte-derived osteoclasts a TNF-antagonist treated patient (400x magnification).

02

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 erradication 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 CAMILO

MD, PhD, retired

Other Principal Investigators
Isabel Monteiro Grillo; Helena Cortez-Pinto; Paula Ravasco

Research Team
1 PhD student, 1 MD, 3 Nutritionists and 1 PharmD researcher

NUTRITION AND METABOLISM UNIT

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MAJOR INTERESTS

The Unit has two main goals Research in Clinical Nutrition and Metabolism and Education (Undergraduate and post-graduate). Namely the unit promotes an undergraduate degree in Dietetics and Nutrition and another on Nutrition and Clinical Research education for national and international Medical students, moreover, we sponsor two undergoing Master Programs: Dietetics and Nutrition (in the phase of Projects to attain the Degree) and another in Nutrition, which started in January 2010 in accordance with the implementation of the Bologna process. The Unit also collaborates in International Programs of Advanced Studies: 1) DIETS Network = *Dieticians Improving Education Training Standards across Europe*, an Erasmus EU financed network Program, in which a close interaction with the UK leading Group is maintained; 2) *"RED MEI-CYTED - NETWORK TO EVALUATE DISEASE-ASSOCIATED MALNUTRITION"* - Network to evaluate disease-associated malnutrition; 3) "COSPI"= *Combating Obesity: Strategies for Prevention and Intervention*; 4) "DELPHI" (EPCRC-project - international scientific EU-funded consortium of Palliative Cancer Care investigators): panel of 17 European, Canadian and US experts on cachexia, aiming to guide treatment, define inclusion criteria for clinical trials and implement results from research into evidence based practice.

With regard to Research, the Unit aims to foster clinical, basic and translational Biomedical research, at both national and international level in collaboration with multicentre networks (South and Central America, Spain, Europe).

Disease management, nutrition/life-style related risk factors prevail in all lines of investigation. At present, main research areas are focused on: nutrition and cancer, nutrition and Quality of Life, metabolic dysfunction(s), nutrients and disease modulation, nutritional therapy and disease prognosis, obesity, fatty liver and insulin resistance. To develop translational research is also a most important goal, hence the progressive focus on: a) genetic polymorphisms of inflammatory mediators or b) humoral regulators, signalling and their receptors, either as pathogenic mechanisms of lesion and/or nutritional deterioration or to investigate their implications in metabolism. We also aim to explore changes of cellular nuclei and DNA degradation, pathogenic gene mutations in cancer and inflammatory diseases and their interaction with nutrients.

Furthermore, investigators deliver services to the Hospital and/or to the Community.

SELECTED PUBLICATIONS

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Machado, M., Marques-Vidal, P. and Cortez-Pinto, H. (2006) Hepatic histology in obese patients undergoing bariatric surgery. J. Hepatol. 45: 600-606 (Journal IF: 7.056)

Ravasco, P., Monteiro-Grillo, I., Marques-Vidal, P. and Camilo, M.E. (2005) Dietary counselling improves patient' outcomes: a prospective randomized controlled trial in colorectal cancer patients undergoing radiotherapy. J. Clin. Oncol. 23: 1431-1438 (Journal IF: 17.157)

Ravasco, P., Monteiro-Grillo, I., Marques-Vidal, P. and Camilo, M.E. (2005) Impact of nutrition on outcome: A prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. Head & Neck 27: 659-668 (Journal IF: 2.603)

Ribeiro, P., Cortez-Pinto, H., Solá, S., Castro, R., Ramalho, R., Baptista, A., Moura, M., Camilo, M.E. and Rodrigues, C. (2004) Hepatocyte apoptosis, expression of death receptors and activation of NF-κB in the liver of non-alcoholic and alcoholic steatohepatitis patients. Am. J. Gastroenterol. 99: 1708-17017 (Journal IF: 6.444)

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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

Research Team
to be established

PARASITE MOLECULAR GENETICS UNIT

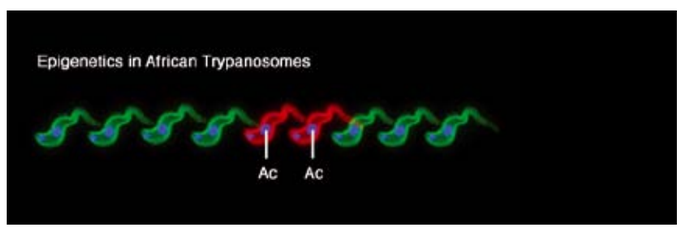
-

MAJOR INTERESTS

To escape the grip of the human immune system, *Trypanosoma brucei*, the parasite that causes African sleeping sickness, performs an infamous disappearing act. Every time the host's immune system gets close to eliminating the infection, a small number of trypanosomes avoids detection by shedding their surface 'coat' and putting on a new one, distinct from those the immune system already recognizes. The coat covers the entire surface of the parasite and consists of a dense layer of a Variant Surface Glycoprotein (VSG). This process of changing coats is known as antigenic variation.

There are hundreds of *VSG* genes throughout the trypanosome's genome, but, at any given time, only one is actively transcribed from a specialized subtelomeric locus known as the expression site. During antigenic variation, some parasites switch transcription to a new expression site, causing the surface coats to change their molecular identity. Such transcriptional changes do not involve alterations in the DNA sequence but are inherited nevertheless, which indicates that VSG transcription is under epigenetic control. Recently, it was shown that enzymes that remodel or modify the structure of chromatin at expression sites are important for antigenic variation. Moreover we now know that the active expression site is organized in a more open chromatin structure than of silent sites.

Our goal is to understand the role chromatin plays in antigenic variation in *T. brucei*. Specifically, we intend to identify the mechanisms and molecules that define open and closed chromatin structures at expression sites. To that end, we will use modern molecular and genetic strategies including RNA interference, chromatin immunoprecipitation, high-throughput deep sequencing and bioinformatics. Understanding how antigenic variation works should allow us to develop drugs that will disrupt VSG regulation, which in turn, would make parasites, at long last, more vulnerable to the host immune defences.



SELECTED PUBLICATIONS

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Figueiredo, L.M., Cross, G.A.M. and Janzen, C.J. (2009) Epigenetics in African trypanosomes. Nat. Rev. Microbiol. 7: 504-513 (Journal IF:14.31)

Yang, X., Figueiredo, L.M., Espinal, A., Okubo, E. and Li, B. (2009) RAP1 Is essential for silencing telomeric variant surface glycoprotein genes in *Trypanosoma brucei*. Cell 137: 99-109 (Journal IF: 31.253)

Figueiredo, L.M., Janzen, C.J. and Cross, G.A. (2008) A Histone methyltransferase modulates antigenic variation in African Trypanosomes. PLoS Biology 6: e161 (Journal IF: 12.683)

Figueiredo, L.M., Freitas-Junior, L.H. and Scherf, A. (2002) A central role for *Plasmodium falciparum* subtelomeric regions in spatial positioning and telomere length regulation. EMBO J. 21: 815-824 (Journal IF: 8.295)

-

Group Leader
JOÃO EURICO FONSECA

MD (1992) and PhD (2004) in Rheumatology at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Auxiliary Professor at FMUL

Other Principal Investigators
Helena Canhão, MD, PhD

Research Team
2 Post-doctoral fellows, 3 MD-PhD students, 5 PhD students, 3 Master students and 2 Trainees

RHEUMATOLOGY RESEARCH UNIT

-

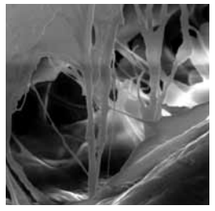
MAJOR INTERESTS

The Rheumatology Research Unit is a partnership between IMM and the Rheumatology and Bone Metabolic Diseases Department of the Hospital de Santa Maria. Basic scientists and clinicians work side by side with the vision of foster translational research and clinical excellence in the field of Rheumatology.

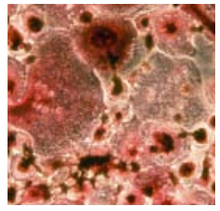
Our specific research aims are the study of the pathogenesis of inflammatory joint diseases (Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis, Spondyloarthropaties and Systemic Lupus Erythematosus (SLE)) and bone disorders (such as osteoporosis) in order to characterize potential tools for early diagnosis and prognosis and potential targets for novel therapies.

Ongoing research projects are devoted to the study of neutrophils, monocytes and B cells in very early arthritis, to the analysis of the effects of inflammation on atherogenesis in RA and SLE and to the relevance of TNF polymorphisms in the prognosis and pharmacogenetics of several joint diseases. We are also involved in research of bone quality in cooperation with Instituto Superior Técnico.

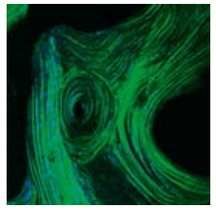
All these research efforts are based on a dual approach, which includes both human samples and animal models of rheumatic diseases. Finally, we are involved in clinical trials, development of registries (in collaboration with the Portuguese Society of Rheumatology) and epidemiological studies, in providing services to the community, including expertise advisory to governmental institutions, and in postgraduate teaching.



Normal female mice vertebra, with an amplification of 2000 by scanning electron microscopy. The trabecular structure of bone can be clearly observed.



TRAP positive monocyte-derived osteoclasts a TNF-antagonist treated patient (400x magnification).



Transversal paraffin sections from the femoral head of a human patient subjected to hip replacement surgery due to hip osteoporotic fracture by multiphoton microscopy. Collagen detected by the backward-SHG channel (green) is mainly immature collagen fibril segments, indicative of ongoing fibrillogenesis, while collagen detected by the forward-SHG channel (blue) is essentially mature polymerized collagen.

SELECTED PUBLICATIONS

Ligeiro, D., Fonseca, J.E., Abade, O., Abreu, I., Cruz, M., Nero, P., Cavaleiro, J., Teles, J., Trindade, H., Caetano, J.M. and Branco, J. (2007) Influence of human leucocyte antigen-DRB1 on the susceptibility to rheumatoid arthritis and on the production of anti-cyclic citrullinated peptide antibodies in a Portuguese population. Ann. Rheum. Dis. 66: 246-248 (Journal IF: 7.188)

Fonseca, J.E., Cavaleiro, J., Teles, J., Sousa, E., Andreozzi, V.L., Antunes, M., Amaral-Turkman, M.A., Canhão, H., Mourão, A.F., Lopes, J., Caetano-Lopes, J., Weinmann, P., Sobral, M., Nero, P., Saavedra, M.J., Malcata, A., Cruz, M., Melo, R., Braña, A., Miranda, L., Patto, J.V., Barcelos, A., da Silva, J.C., Santos, L.M., Figueiredo, G., Rodrigues, M., Jesus, H., Quintal, A., Carvalho, T., da Silva, J.A., Branco, J. and Queiroz, M.V. (2007) Contribution for new genetic markers of rheumatoid arthritis activity and severity: sequencing of the tumor necrosis factor-alpha gene promoter. Arthritis Res. Ther. 9: R37 (Journal IF: 4.485)

Fonseca, J.E., Cortez-Dias, N., Francisco, A., Sobral, M., Canhão, H., Resende, C., Castelão, W., Macieira, C., Sequeira, G., Saraiva, F., Pereira da Silva, J.A., Carmo-Fonseca, M. and Viana Queiroz, M. (2005) Inflammatory cell infiltrate and RANKL/OPG expression in rheumatoid synovium– comparison with other inflammatory arthropaties and correlation with outcome. Clin. Exp. Rheumatol. 23: 185-192 (Journal IF: 2.364)

Fonseca, J.E., Carvalho, T., Cruz, M., Nero, P., Sobral, M., Mourão, A.F., Cavaleiro, J., Abreu, I., Carmo-Fonseca, M. and Branco, J.C. (2005) Polymorphism at position –308 of the tumor necrosis factor alpha gene and rheumatoid arthritis pharmacogenetics. Ann. Rheum. Dis. 64: 793-794 (Journal IF: 7.188)

Fonseca , J.E., Edwards, J.C., Blades, S. and Goulding, N.J. (2002) Macrophage subpopulations in rheumatoid synovium: reduced CD163 expression in CD4+ T lymphocyte-rich microenvironments. Arthritis Rheum. 46: 1210-1216 (Journal IF: NA)

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Group Leader
LUIS 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

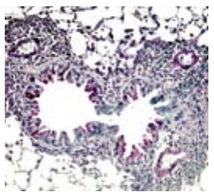
Research Team
2 Post-doctoral fellows, 4 PhD students and 1 Master student

CELLULAR IMMUNOLOGY UNIT

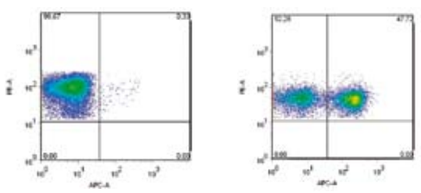
-

MAJOR INTERESTS

The Cellular Immunology Unit studies the mechanisms underlying induction and maintenance of immune tolerance. In other words: we attempt to reprogramme the immune system when it is causing disease, as it happens in allergy, autoimmunity and transplant rejection.
In the last 50 years, it has been observed a marked increase in the frequency of diseases with immune system disregulation as a direct cause. For instance allergic diseases, which have increased over 200% in the last two decades, or autoimmune diseases, where the immune system attacks normal constituents of the body. In addition, organ transplantation is increasingly more frequent, while rejection mediated by the immune system remains the most serious problem for patients. Hence, the control of pathologic immune responses in such situations has been one of the major goals of immunology.
Recently, it has become apparent the therapeutic potential of antibodies - molecules produced by the immune system capable of identifying with great precision and binding to target components of cells and tissues. One can exploit the antibody specificity in order to block key molecules on the surface of T cells (critical cells in the control of immune responses), thereby using a component of the immune system to alter immune system function. We research new methods to induce tolerance in allergic asthma, food allergy, and an animal model of rheumatoid arthritis using antibodies or cells from the immune system able to regulate excessive immune responses. Due to differences between animal and human physiology, we collaborate with clinical scientists to validate our experimental data with human samples. We believe that in the foreseeable future antibody therapy, as well as other strategies to modulate the immune system, will be important for improving the quality of life of people suffering from allergy, autoimmunity and transplant rejection.



Histological section of an asthmatic lung. (image: A. Agua-Doce)



Flow cytometry data: in vitro expansion of T cells that suppress excessive inflammatory responses (upper right quadrants). (image: V. Oliveira)

SELECTED PUBLICATIONS

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Graça, L., Le Moine, A., Cobbold, S.P. and Waldmann, H. (2003) Dominant Transplantation Tolerance. Curr. Opin. Immunol. 15: 499-506 (Journal IF: 10.455)

Graça, L.*, Lin, C-Y.*, Cobbold, S.P. and Waldmann, H. (2002) Dominant transplantation tolerance impairs CD8+ T cell function but not expansion. Nat. Immunol. 3: 1208-1213 * Joint first authors (Journal IF: 25.113)

Graça, L., Thompson, S., Lin, C-Y., Adams, E., Cobbold, S.P. and Waldmann H. (2002) Both CD4+CD25+ and CD4+CD25- regulatory cells mediate dominant transplantation tolerance. J. Immunol. 168: 5558-5565 (Journal IF: 6.000)

Graça, L., Cobbold, S.P. and Waldmann, H. (2002) Identification of regulatory T cells in tolerated allografts. J. Exp. Med. 195: 1641-1646 (Journal IF: 15.504)

-

Group Leader
GUNNAR RUDOLF 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

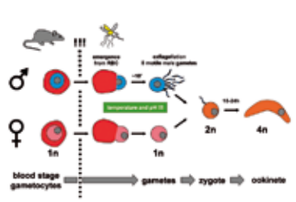
Research Team
1 Post-doctoral fellow, 1 Master student, 1 Research student and 1 Technician

MOLECULAR PARASITOLOGY UNIT

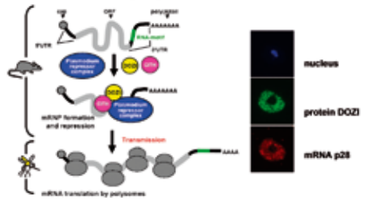
-

MAJOR INTERESTS

Malaria parasites (Plasmodium) cause severe disease in humans. The parasites develop and multiply asexually as haploid forms in red blood cells in the human host and move through a mosquito vector in order to infect new individuals. Transmission from the human host (or a mammalian model such as the mouse) to the mosquito, and vice versa, represent not only a severe bottleneck in the parasites' life cycle but depends on the development of specialized cell types with defined proteome profiles. Male and female forms differentiate in the blood and once they arrive in the mosquito midgut - having been taken up during a blood meal of a female mosquito - participate in fertilization. The resulting diploid zygote develops into a motile ookinete that leaves the midgut pushing through the epithelium to continue its life cycle as an oocyst; sporozoites finally reside in mosquito salivary glands ready to infect a new individual. We have recently shown that post-transcriptional gene silencing is essential for the development of the zygote; 100s of mRNAs are stockpiled in female gametocytes only to be translated after fertilisation. Similarly, related mechanisms play a role in the sporozoite. Our aim is to understand the protein factors that are involved in the storage of mRNA and how transcription, RNA steady state levels and protein synthesis are controlled at these crucial moments. Strategies that interfere with sexual development and thus the Plasmodium life cycle may help reduce the spread of malaria.



Plasmodium sexual development



Gametocyte P-bodies

SELECTED PUBLICATIONS

Mair, G.R., Lasonder, E., Garver, L.S., Franke-Fayard, B., Carret, C.K., Wiegant, C.A.G., Dirks, R.W., Dimopoulos, G., Janse, C.J. and Waters, A.P (2010) Universal features of post-transcriptional gene regulation are critical for *Plasmodium* zygote development. PLoS Pathog. 6: e1000767 (Journal IF: 9.125)

Baum, J., Papenfuss, A.T., Mair, G.R., Janse, C.J., Waters, A.P., Cowman, A.F., Crabb, B.S. and de Konig-Ward, T. (2009) Molecular genetics and comparative genomics suggests RNAi is not functional in malaria parasites. Nucleic Acid Res. 37: 3788-3798 (Journal IF: 6.968)

Yuda, M., Iwanaga, S., Shigenobu, S., Mair, G.R., Janse, C.J., Waters, A.P., Kato, T. and Kaneko, I. (2009) Identification of a transcription factor in the mosquito-invasive stage of malaria parasites. Mol. Microbiol. 71: 1402-1414 (Journal IF: 5.462)

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Khan, S.M., Franke-Fayard, B., Mair, G.R., Lasonder, E., Janse, C.J., Mann, M. and Waters, A.P. (2005) Proteome analysis of separated male and female gametocytes reveals novel sex-specific Plasmodium biology. Cell 121: 675-687 (Journal IF 29.887)

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Group Leader

MARIA MANUEL 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 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

Research Team

6 Post-doctoral fellows, 4 PhD students, 1 Lab manager and 1 Technician

MALARIA UNIT

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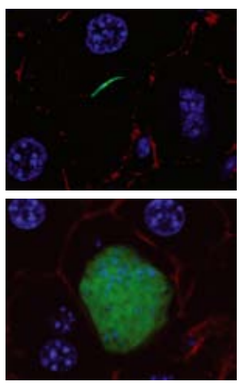
MAJOR INTERESTS

Malaria, caused by *Plasmodium* species transmitted between *Anopheles* mosquitoes and humans, continues to be a major devastating disease and global public health problem. Annually, more than 300-400 million people worldwide develop malaria and nearly 1 million children die. There is no highly effective, deployable malaria vaccine, and the prevalence of drug-resistant malaria is increasing throughout Africa, Asia and South America which has been associated with increasing morbidity and mortality.
Today's efforts towards the control of malaria are limited by our current understanding of the biology of *Plasmodium* and of the complex relationships between the three components of the malaria triad—the human, the mosquito, and the parasite. Despite work in each of these systems advancing rapidly in the last decade, the malaria science community is now at a turning point where many believe the success of current and future control efforts will depend on making significant advances in our understanding of the biology of malaria. A potential approach to malaria control is to target mechanisms crucial for the development of *Plasmodium* and/or the pathology caused by its infection. This requires detailed knowledge of the complex host cell-*Plasmodium* interaction. The Malaria Unit is focusing its efforts on the study of mechanisms used by *Plasmodium*-induced host factors important for the establishment and control of a malaria infection and the pathology associated with it. Determining the host proteins that either promote infections or help ward them off would not only shed light on the basic mechanisms of malaria infection but also provide potential new targets for therapy.



These two images depict hepatocytes in a liver section
Parasites are shown in green, hepatocyte nuclei in blue and > hepatocyte membranes in red.
(top panel) This image was performed after one hour of injection Plasmodium sporozoites from the salivary glands of infected mosquitoes and shows one parasite establishing inside one of the hepatocytes.
(bottom panel) This image was performed 40 h later and shows a replicating Plasmodium parasite leading to thousands new parasites.

SELECTED PUBLICATIONS

Albuquerque, S.S., Carret, C., Grosso, A.R., Tarun, A.S., Peng, X., Kappe, S.H., Prudêncio, M. and Mota, M.M. (2009) Host cell transcriptional profiling during malaria liver stage infection reveals a coordinated and sequential set of biological events. BMC Genomics 10: 270 (Journal IF: 3.926)

Rodrigues, C.D., Hannus, M., Prudêncio, M., Martin, C., Gonçalves, L.A., Portugal, S., Epiphanio, S., Akinc, A., Hadwiger, P., Jahn-Hofmann, K., Röhl, I., van Gemert, G.J., Franetich, J.F., Luty, A.J.F., Sauerwein, R., Mazier, D., Koteliansky, V., Vornlocher, H.P., Echeverri, C.J. and Mota, M.M. (2008) Host scavenger receptor SR-BI plays a dual role in the establishment of malaria parasite liver infection. Cell Host Microbe 4: 271-282 (Journal IF: 7.436)

Epiphanio, S., Mikolajczak, S.A., Gonçalves, L.A., Pamplona, A., Portugal, S., Albuquerque, S., Goldberg, M., Rebelo, S., Anderson, D.G., Akinc, A., Vornlocher, H.P., Kappe, S.H., Soares, M.P. and Mota, M.M. (2008) Heme oxygenase-1 is an anti-inflammatory host factor that promotes murine Plasmodium liver infection. Cell Host Microbe 3: 331-338 (Journal IF: 7.436)

Pamplona, A., Ferreira, A., Balla, J., Jeney, V., Balla, G., Epiphanio, S., Chora, A., Rodrigues, C.D., Gregoire, I.P., Cunha-Rodrigues, M., Portugal, S., Soares, M.P. and Mota, M.M. (2007) Heme oxygenase-1 and carbon monoxide suppress the pathogenesis of experimental cerebral malaria. Nat. Med. 13: 703-710 (Journal IF: 27.553)

Prudêncio, M., Rodriguez, A. and Mota, M.M. (2006) The silent path to thousands of merozoites: the Plasmodium liver stage. Nat. Rev. Microbiol. 4: 849-856 (Journal IF: 14.310)

Mota, M.M., Pradel, G., Vanderberg, J., Frevert, U., Hafalla, J.C.R., Nussenzweig, R., Nussenzweig, V. and Rodriguez, A. (2001) Migration of Plasmodium sporozoites through cells before infection. Science. 291: 141-144 (Journal IF: 28.103)

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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

Research Team

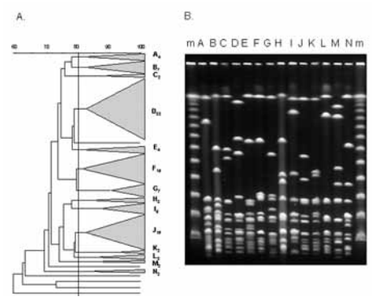
5 PhD students

MOLECULAR MICROBIOLOGY AND INFECTION UNIT

-

MAJOR INTERESTS

Our main objective is to understand the dynamics of populations of bacterial pathogens and how they respond to selective forces. Current work focuses on characterizing the effect of antimicrobial use and human vaccination on the bacterial population. We also investigate the relationships between commensal and disease causing populations of the same bacterial pathogen with the aim of identifying particularly successful clones at causing disease as well as successful colonizers. Current work if focusing on genomic approaches to characterize the differences between these two populations that may explain the associations bacteria establish with the human host.
A strong emphasis on quantitative biology has led to development of research in the area of computational biology. We are developing new methods for the quantitative analysis of partition congruence, comparative genomic analysis and for inferring the phylogenetic relationships between isolates in a bacterial population. These methodologies have been implemented in online tools or freely distributed software.
The development of novel laboratory methodologies for the diagnosis of infectious diseases is also an active area of research. Investigations followed the recent realization that flow cytometric principles allow the detection of malaria pigment. This finding was explored with the development of this application to the diagnosis of malaria and it may eventually also be adapted to novel sensitivity tests and evaluated for its usefulness as marker of disease severity.



Pulsed-field gel macrorestriction profile analysis of group C and G streptococci.
A) Dendrogram showing UPGMA cluster analysis of the PFGE profiles.
B) PFGE profiles of representatives of each clone.

SELECTED PUBLICATIONS

Hänscheid, T., Egan, T.J. and Grobusch, M.P. (2007) Haemozoin: from melatonin pigment to drug target, diagnostic tool, and immune modulator. Lancet Infect. Dis. 7: 675-685 (Journal IF: 13.165)

Martins, E.R., Pessanha, M.A., Ramirez, M., Melo-Cristino, J. and the Portuguese Group for the Study of Streptococcal Infections (2007) Analysis of Group B streptococcal isolates from infants and pregnant women in Portugal revealing two lineages with enhanced invasiveness. J. Clin. Microbiol. 45: 3224-3229 (Journal IF: 3.945)

Carriço, J.A., Silva-Costa, C., Melo-Cristino, J., Pinto, F.R., de Lencastre, H., Almeida, J.S. and Ramirez, M. (2006) Illustration of a common framework for relating multiple typing methods by application to macrolide- resistant *Streptococcus pyogenes*. J. Clin. Microbiol. 44: 2524-2532 (Journal IF: 3.945)

Silva-Costa, C., Ramirez, M. and J. Melo-Cristino (2005) Rapid inversion of the prevalences of macrolide resistance phenotypes paralleled by a diversification of T and emm types among *Streptococcus pyogenes* in Portugal. Antimicrob. Agents Chemother. 49: 2109-2111 (Journal IF: 4.716)

Serrano, I., Melo-Cristino, J., Carriço, J.A. and M. Ramirez (2005) Characterization of the genetic lineages responsible for pneumococcal invasive disease in Portugal. J. Clin. Microbiol. 43: 1706-1715 (Journal IF: 3.945)

-

Group Leader
BRUNO SILVA-SANTOS

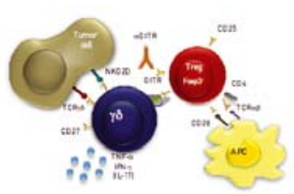
PhD (2002) in Immunology at University College London, UK
Post-doctoral research at King's College London, UK
Assistant Professor at Faculdade de Medicina da Universidade de Lisboa
Awarded an EMBO Installation Grant in 2007

Research Team
1 Post-doctoral researcher, 1 Post-doctoral fellow, 3 PhD students and 1 Technician

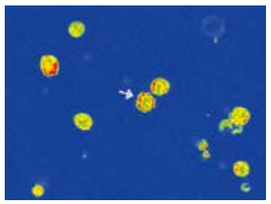
MOLECULAR IMMUNOLOGY UNIT

MAJOR INTERESTS

Our research is dedicated to T lymphocytes, key players of the immune system, capable of destroying cancer and viral-infected cells, on one hand, but also necessary to prevent the establishment of inflammatory and autoimmune diseases, on the other. These diversified functions derive from the existence of specialized populations of T cells, usually identified by the presence of specific proteins on their cell surface, allowing us to target a particular subset for immunotherapy.
In our laboratory we are interested in the processes of generation, activation and regulation of T lymphocytes. Using state-of-the-art research tools (cDNA microarrays, RNA interference, bioinformatics), we envisage the identification of molecules involved in those processes and their integration in cellular mechanisms.
One of our main areas of study is T cell development in the thymus, using the mouse as a model system. Our goal is to elucidate how cells that protect from infections, on one hand, and from autoimmunity, on the other, are generated, and how the critical balance between these two subsets is set up in the thymus.
Our other major focus is the anti-tumor activity of human T cells. We try to dissect the signals that T cells need to receive from tumor cells in order to efficiently eliminate them, while also trying to understand how tumors may evade immune surveillance through the production of T cell inhibitory factors. We aim at providing fundamental knowledge that can be used for the rational design of novel immunotherapy strategies against cancer.



Molecular interactions between γδ T cells and tumor cells, on one hand, and regulatory (Treg) cells, on the other. Key molecular players are indicated. (APC, antigen presenting cell).
(See *Eur J Immunol* 2009, issue 40 (1): pages 6 and 61-70).



γδ T cells purified from human peripheral blood were analyzed by confocal microscopy. Antibody labeling for the CD27 receptor, with levels of expression increasing from green to red. *(Ana de Barros)*

SELECTED PUBLICATIONS

Ribot, J.C., deBarros, A., Pang, D.J., Neves, J.F., Peperzak, V., Girardi, M., Borst, J., Hayday, A.C., Pennington, D.J. 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 Immunol. 10: 427-436 (Journal IF: 26.218)

Correia, D.V., d´Orey, F., Cardoso, B.A., Lança, T., Grosso, A.R., deBarros, A., Martins, L.R., Barata, J.T. and Silva-Santos B. (2009) Highly active microbial phosphoantigen induces rapid yet sustained MEK/ Erk- and PI-3K/ Akt-mediated signal transduction in anti-tumor human γδ T cells. PloS One: e5657 (Journal IF: NA)

Gomes, A.Q., Correia, D.V. and Silva-Santos, B. (2007) Non-classical MHC proteins as determinants of tumor immunosurveillance. EMBO Rep. 8: 1024-1030 (Journal IF: 7.099)

Pennington, D.J., Silva-Santos, B., Escorcio-Correia, M., Silberzahn, T. and Hayday, A.C. (2006) Early events in the thymus affect the balance of effector and regulatory T cells. Nature 444: 1073-1077 (Journal IF: 31.434)

Silva-Santos, B., Pennington, D.J. and Hayday, A.C. (2005) Lymphotoxin-mediated regulation of γδ T cell differentiation by αβ T cell progenitors. Science 307: 925-928 (Journal IF: 28.103)

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Group Leader
PEDRO SIMAS

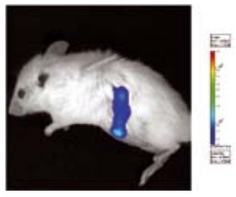
PhD (1994) in Viral Pathogenesis at the University of Cambridge, UK
Post-doctoral research at the University of Cambridge, UK
Principal Investigator at Instituto Gulbenkian Ciência (until 1999)
Associate Professor at Faculdade de Medicina da Universidade de Lisboa

Research Team
5 Post-Doctoral fellows, 2 PhD students, 1 Technician

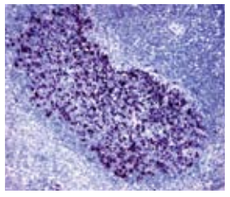
VIRAL PATHOGENESIS UNIT

MAJOR INTERESTS

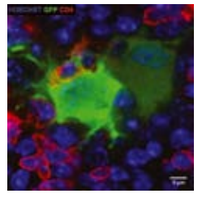
We seek to define molecular functions of viral proteins and define their contribution to pathogenesis. There are very few laboratory mouse models of virus infection that enable linking defined viral functions to pathogenesis. Murid herpesvirus 4 (MuHV-4) is one such model and serves as the only mouse model system to study the pathogenesis of Kaposi´s sarcoma herpesvirus (KSHV). KSHV has an etiological role in Kaposi´s sarcoma, the leading AIDS malignancy, and in certain lymphomas. The availability of an in vivo model provides a system to test the ability of small-molecule inhibitors of specific viral functions to control infection and thus associated tumorigenesis.
We use MuHV-4 to study virus-host interactions. MuHV-4 is inoculated intra-nasally, causes a transient pneumonia followed by persistence of latent infection in memory B cells. Access to memory B cells is preceded by expansion of infection in germinal centre B cells. Our focus is to identify and characterize molecular functions that are crucial for induction of proliferation and differentiation of GC B cells. We then generate recombinant viruses with site-specific mutations that we analyze upon infection of wild type or genetically altered mice. Using this strategy we aim to understand how a defined molecular function of a viral protein contributes to pathogenesis.
Thus far, we have defined molecular functions and associated viral phenotypes but we still do not understand the physiology of such phenotypes. For example, the MuHV-4 encoded mORF73 protein is selectively expressed in GC B cells during the expansion of latent infection and it is a strong inhibitor of NF-κB. Viruses lacking this inhibitory function do not expand in GC B cells and do not persist. The question is why does NF-κB, as a key transcription factor, need to be switched off in proliferating GC B cells? To address these questions we propose a two fold strategy. To further define the molecular function of key viral proteins to include structural studies, and to develop tools to refine our pathogenesis studies such as tagged viruses that enable in vivo tracking.



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



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



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

SELECTED PUBLICATIONS

Orge, L., Oliveira, A., Machado, C., Lima, C., Ochoa, C., Silva, J., Carvalho, R., Tavares, P., Almeida, P., Ramos, M., Pinto, M.J. and Simas, J.P. (2010) Putative emergence of classical scrapie in a background of enzootic atypical scrapie. J. Gen. Virol. *In press* (Journal IF: 3.092)

Stevenson, P.G., Simas, J.P. and Efstathiou, S. (2009) Immune control of mammalian gammaherpesviruses: lessons from murid herpesvirus-4. J. Gen. Virol. 90: 2317-2330 (Journal IF: 3.092)

Rodrigues, L., Filipe, J., Seldon, M.P., Fonseca, L., Anrather, J., Soares, M.P. and Simas, J.P. (2009) Termination of NF-kappaB activity through a gammaherpesvirus protein that assembles an EC5S ubiquitin-ligase. EMBO J. 28: 1283-1295 (Journal IF: 8.295)

Marques, S., Alenquer, M., Stevenson, P.G. and Simas, J.P. (2008) A single CD8+ T cell epitope sets the long-term latent load of a murid herpesvirus. PLoS Pathog. 4: e1000177 (Journal IF: 9.125)

Pires de Miranda, M., Alenquer, M., Marques, S., Rodrigues, L., Lopes, F., Bustelo, X.R. and Simas, J.P. (2008) The Gammaherpesvirus m2 protein manipulates the Fyn/Vav pathway through a multidocking mechanism of assembly. PLoS One 3: e1654 (Journal IF: NA)

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Group Leader

ANA ESPADA DE SOUSA

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

Other Principal Investigators

Rui MM Victorino, Maria Conceição Santos, Íris Caramalho, João F Lacerda

Research Team

2 Post-doctoral fellows, 5 Lecturers, 8 PhD students and 2 Research fellows

CLINICAL IMMUNOLOGY UNIT

MAJOR INTERESTS

The Clinical Immunology Unit (UIC)'s research focuses on human T cell homeostasis and immune regulation with the ultimate goal of identifying new strategies for immunological reconstitution and targets for immune-based therapies.
An important part of UIC's research effort is centred on HIV/AIDS immunopathogenesis mainly through the study of HIV-2, a naturally attenuated form of HIV infection. We have shown that in HIV-2, as in HIV-1 infection, CD4 depletion is directly linked to immune activation. HIV-2 is closely related to HIV-1, and has been shown to be equally cytopathic *in vitro*. Moreover, despite plasma viremia remaining low or undetectable throughout HIV-2 infection, we and others have shown that proviral DNA levels do not significantly differ from those found in HIV-1 infected individuals, suggesting a similar ability to disseminate and establish a pool of infected cells. Nevertheless, HIV-2 establishes a better equilibrium with the host than HIV-1, leading to a much slower rate of disease progression, lower levels of circulating virus and a limited impact in the mortality rate of the majority of HIV-2 infected adults. The UIC has been intensively involved in the investigation of possible contributing factors to this distinct viral-host equilibrium, taking advantage of the high prevalence of HIV-2 in Portugal due to connections to West Africa where HIV-2 infection is endemic.
Other major foci of UIC's research are: the role of IL-7, a major homeostatic cytokine, in human naïve T cell homeostasis; and human T cell development in the thymus with particular interest in the development of regulatory T cells, a subset known to have a key role in protecting from autoimmunity and from the immune-mediated pathology associated to persistent infections.
The UIC recently became involved in the diagnosis of primary immunodeficiencies (PID) in response to the National Health Service's request for a facility in advanced immunologic diagnosis and follow-up which runs in parallel with research in this field.
The UIC is also involved in advanced diagnosis in Allergology with some applied research in this area, and receives MDs for 5 month periods, in accordance with the requirements for the allergologist laboratory training in Portugal.

SELECTED PUBLICATIONS

Cavaleiro, R., Baptista, A.P., Soares, R.S., Tendeiro, R., Foxall, R.B., Gomes, P., Victorino, R.M. and Sousa, A.E. (2009) Major depletion of plasmacytoid dendritic cells in HIV-2 infection, an attenuated form of HIV disease. PLoS Pathog. 5: e1000667 (Journal IF: 9.125)

Azevedo, R.I., Soares, M.V., Barata, J.T., Tendeiro, R., Serra-Caetano, A., Victorino, R.M. and Sousa, A.E. (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 (Journal IF: 10.432)

Albuquerque, A.S., Cortesão, C.S., Foxall, R.B., Soares, R.S., Victorino, R.M. and Sousa, A.E. (2007) Rate of increase in circulating IL-7 and loss of IL-7Rα expression differ in HIV-1 and HIV-2 infections: two lymphopenic diseases with similar hyper immune-activation but distinct outcomes. J. Immunol. 178: 3252-3259 (Journal IF: 6.000)

Sousa, A.E., Carneiro, J., Meier-Schellersheim, M., Grossman, Z., and Victorino, R.M. (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 (Journal IF: 6.000)

Grossman, Z., Meier-Schellersheim, M., Sousa, A.E., Victorino, R.M. and Paul W.E. (2002) CD4+ T-cell depletion in HIV infection: are we closer to understanding the cause? Nat. Med. 8: 319-321 (Journal IF: 27.553)

-

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
Awarded a European Research Council Starting Grant in 2008
Awarded a EMBO Installation Grant in 2008

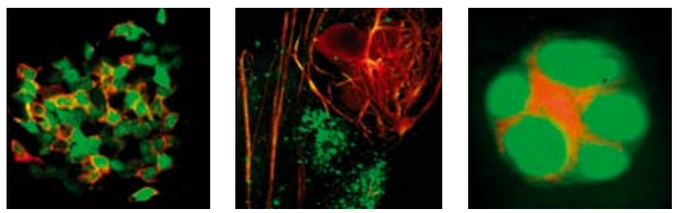
Research Team

1 Post-doctoral fellow, 1 PhD student, 2 Master students, 2 Technicians and 1 Trainee

IMMUNOBIOLOGY UNIT

MAJOR INTERESTS

Immunological studies are crucial for public health providing knowledge for vaccine development and for the treatment of immune disorders, transplantation rejection, infectious diseases and cancer. Understanding the mechanisms underlying differentiation of immune cells and the control of immune responses involves analyses ranging from lymphoid organogenesis to lymphocyte differentiation and function.
The adaptive immune system has evolved to control and protect the host from infection. Immune protection involves the generation of immunological memory, through which an individual acquires the capacity to respond better to the initial antigen on re-exposure. Immune and neuronal memory are characterized by obvious differences, but also striking parallels. Indeed, mounting evidence indicates that some of the most potent neurotrophic factors may act on or are produced by immune cells. The neuronal growth factor family includes the glial cell-line derived neurotrophic factor (GDNF) ligands, which signal through the RET tyrosine kinase receptor.
Our research projects are centred on the cellular and molecular mechanisms governing haematopoiesis in general and on the role of the proto-oncogene *Ret* in lymphocyte function in particular. By using state of the art research tools, translated on combined genetic, cellular, and molecular approaches, we plan to observe, quantify and manipulate the functions of the proto-oncogene *Ret* in the immune system, and to shed light into the mechanisms underlying the development of lymphoid structures.



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

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Peixoto, A., Monteiro, M., Rocha, B. and Veiga-Fernandes, H. (2004) Quantification of multiple gene expression in individual cells. Genome Res. 14: 1938-1947 (Journal IF: 10.176)

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Veiga-Fernandes, H., Walter, U., Bourgeois, C., McLean, A. and Rocha, B. (2000) Response of naive and memory CD8+ T cells to antigen stimulation in vivo. Nat. Immunol. 1: 47-53 (Journal IF: 25.113)

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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

Research Team

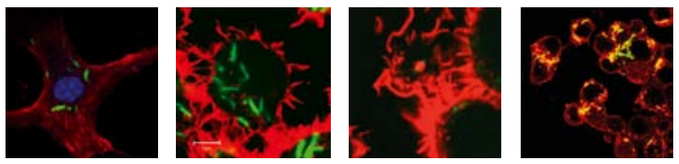
1 Post-doctoral fellow, 3 PhD students and 3 Master students

MYCOBACTERIA-HOST INTERACTIONS UNIT

-

MAJOR INTERESTS

The hallmark of pathogenic mycobacteria is their ability to survive within the macrophage phagosome. Our unit aims to explain this trait by addressing two central questions: First, how do mycobacteria survive within the phagosome hostile enviroment? And second, how are macrophages able to, under some conditions, kill mycobacteria? For example 90 percent of infected people show no signs of disease. Killing of mycobacteria by macrophages is known to improve by treatment of cells with gamma-interferon, with pro-inflammatory lipids or with extra-cellular ATP - although the mechanism is unknown, all three treatments enhance the maturation of pathogenic mycobacterial phagosomes. Our goal is to provide a molecular evidence that proteins in the lumen of the phagosomes directly kill mycobacteria and give the first global map of the proteins in a mycobacterial phagosome, both under normal conditions and under conditions in which killing is enhanced. Finally, we would like to understand the role of pH and redox of the intra-phagosomal environment and how it contributes to killing.



J774 macrophages infected with M. tuberculosis. Killing effectors by phagolysosome fusion: Nitric oxide mediated by iNos, Arachidonic acid mediated actin nucleation, Cathepsin Z acquision and NF-KB translocation to the nucleus.

SELECTED PUBLICATIONS

Kuehnel, M., Rybin, V., Anand, P., Anes, E. and Griffiths, G. (2009) Lipids regulate P2X7 receptor-dependent actin assembly by phagosomes via ADP translocation and ATP synthesis in the phagosome lumen. J. Cell Sci. 122: 499-504 (Journal IF: 6.4247)

Gutierrez, M.G.*, Mishra, B.B.*, Jordão, M.L., Elliot, E., Anes, E. and Griffiths, G. (2008) NF-kappa B activation controls phago-lysosome fusion-mediated killing of mycobacteria by macrophages. J. Immunol. 18: 2651-2663 *Joint first authors (Journal IF: 6.000)

Jordao, L., Bleck, C.K.E., Mayorga, L., Griffiths, G. and Anes, E. (2008) On the killing of mycobacteria by macrophages. Cell Microbiol. 10: 529-548 (Journal IF: 5.598)

Anes, E., Peyron, P., Staali, L., Jordão, L., Gutierrez, M.G., Kress, H., Hagedorn, M., Maridonneau-Parini, I., Skinner, M.A., Wildeman, A.G., Kalamidas, S.A., Kuehnel, M. and Griffiths, G. (2006) Dynamic life and death interactions between *Mycobacterium smegmatis* and J774 macrophages. Cell Microbiol. 8: 939-960 (Journal IF: 5.598)

Anes, E., Kuhnel, M.P., 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: 793-802 (Journal IF: 17.774)

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Group Leader

JOÃO GONÇALVES

PhD (1996) at EMBL, Heidelberg, Germany
Research Assistant at Harvard Medical School, USA
Post-doctoral research at Scripps Research Institute, USA
Associate Professor at Faculdade de Farmácia da Universidade de Lisboa
Awardee of the Human Frontier Science Program

Other Principal Investigator

Inês Soeiro

Research Team

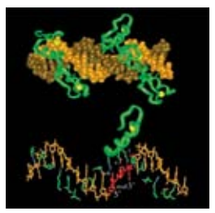
1 Lecturer, 3 Post-doctoral fellows, 6 PhD students and 3 Research assistants

RETROVIRUSES AND ANTIVIRAL RESEARCH UNIT

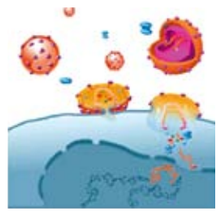
-

MAJOR INTERESTS

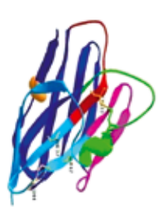
We study retroviruses molecular interactions with the host cell and their replication strategies, aiming to apply these knowledge for biotechnological applications. We try to understand the mechanisms underlying the function of cellular restriction factors and co-factors in HIV-1 and HIV-2 infection. Specifically, we focus on the viral protein Vif and investigate how it can protect viral infectivity of HIV by neutralizing APOBEC family proteins. We are interested in answering questions related to the mechanism of APOBEC3G inhibition and regulation and how Vif can overcome the antiviral restriction of this family of deaminases. This goal is integrated in a broader study to comprehend the host-virus interaction at the cellular and molecular level. Here, the importance of cellular proteins and miRNA to help or restrict HIV-1 infection is crucial to develop concepts of viral infectivity or latency. By using shRNA libraries and zinc-finger libraries we look into elucidate the major pathways of virus interaction with the cell.
In a different angle of research and using our understanding of HIV biology we aim to identify biochemical targets for viral neutralization and develop molecular strategies to block HIV-1 infection. We are interested in impede viral entry into cells and intervene in viral latency. The strategies we explore are based on the platform of synthetic zinc-fingers and engineering antibody-derived protein scaffolds that use unique variable regions. Our goal is to develop more effective and adapted strategies that can explore the weaknesses of the virus.
Ultimately our unit wants to explore HIV-1 replication strategies for biotechnology purposes, generate novel therapeutic proteins and better gene therapy strategies by programming cell targeting of engineered lentiviral particles.



Synthetic zinc-finger binding to DNA.



HIV infectivity and neutralization by antibodies.



Model of VH-derived small domain antibody.

SELECTED PUBLICATIONS

Aires da Silva, F., Corte-Real, S. and Goncalves, J. (2008) Recombinant antibodies as therapeutic agents: pathways for modeling new biodrugs. BioDrugs 22: 301-314 (Journal IF: 2.253)

Corte-Real, S., Fonseca, L. , Barbas, C.F. 3rd, Chang, Y., Moore, P. and Goncalves, J. (2008) Intrabody-based mapping of Latency-Associated Nuclear Antigen from Kaposi's Sarcoma-Associated Herpesvirus show conserved epitopes for viral latency inhibition. Virology: Res. Treatment 1: 43-48 (Journal IF: NA)

Ferreira, G.N., Encarnação, .J.M., Rosa, L., Rodrigues, R., Breyner, R., Barrento, S., Pedro, L., Aires da Silva, F. and Goncalves J. (2007) Recombinant single-chain variable fragment and single domain antibody piezoimmunosensors for detection of HIV1 virion infectivity factor. Biosens Bioelectron. 23: 384-392 (Journal IF: 5.243)

Santa-Marta, M., Aires da Silva, F., Fonseca, A.M., Rato, S. and Gonçalves J. (2007) HIV-1 Vif protein blocks the cytidine deaminase activity of B-cell specific AID in *E. coli* by a similar mechanism of action. Mol. Immunol. 44: 583-590 (Journal IF: 3.555)

Corte-Real, S., Collins, C., Aires da Silva, F., Simas, .J.P., Barbas, C.F. 3rd, Chang, Y., Moore, P. and Goncalves, J. (2005) Intrabodies targeting the Kaposi sarcoma-associated herpesvirus latency antigen inhibit viral persistence in lymphoma cells. Blood 106: 3797-3802 (Journal IF: 10.432)

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03

NEUROSCIENCES PROGRAMME

NEUROMUSCULAR UNIT

Intraepidermal nerve fibers density is a sensitive measure of small fiber injury. In this illustration a sample from a healthy control is shown with the tissue stained with PGP9.5, the small nerve fibers are represented as red filaments.

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, or stroke. It is likely that the molecular profiles of diseased brains and nerve cells, established by genomic, proteomic and other approaches, will identify a myriad of alterations that may be causal to the diseases or physiological processes under study. Importantly, we couple novel molecular approaches with extensive expertise in pharmacology and functional neuroscience. The close proximity to clinical groups also enables us to position ourselves as leaders in translational research. Our research is directed at advancing the understanding of the nervous system to the point where rational strategies can be developed to better treat and prevent these devastating conditions. Throughout the history of neuroscience, the investigation of neurological conditions has catalyzed, often driven, neuroscientific discovery. Therefore, in many of our studies we also explore what neurological impairments can teach us about normal neural functions.

Group Leader

JOSÉ M. 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, Isabel Pavão Martins, José Pimentel, Cristina Sampaio, Teresa Paiva, Sofia Oliveira

Research Team

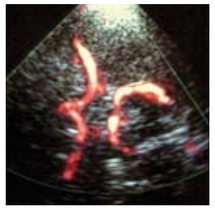
7 Post-doctoral clinical investigators, 2 Post-doctoral fellows, 29 MD researchers, 2 PhD students, 12 Technicians and 3 Trainees

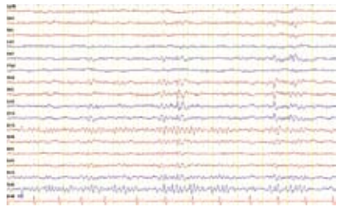
NEUROLOGICAL CLINICAL RESEARCH UNIT

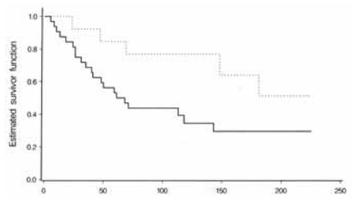
MAJOR INTERESTS

The general aim of this Unit is to study the clinical epidemiology of diseases involving the nervous system. The research at the NCRU focuses on large samples and on prevalent, disabling, chronic CNS conditions such as dementia, stroke and Parkinson's disease. Our aim is to identify risk factors, including ecological and genetic ones, and prognostic factors leading from an independent life to dependency or death, and on the development and assessment of therapeutical interventions that could be able to delay or prevent transition from a healthy, independent state to disability and death. Measures of disability will include neurophysiological and quality of life dimensions. The large samples of patients afflicted with such chronic conditions offer a unique opportunity for detailed neuropsychological and neuroimaging studies and the development and testing of cognitive neuropsychological models.

NCRU has an additional aim of training young medical and non-medical clinical researchers and to disseminate an evidence-based and patient-oriented view of the research and practice in Clinical Neurosciences.







SELECTED PUBLICATIONS

Canhão, P., Ferro, J.M., Lindgren, A.G., Bousser, M.G., Stam, J., Barinagarrementeria, F.; ISCVT Investigators (2005) Causes and predictors of death in cerebral venous thrombosis. Stroke 36: 1720-1725 (Journal IF: 6.499)

Costa, J., Borges, M., David, C. and Vaz-Carneiro, A. (2006) Efficacy of lipid-lowering drug therapy for diabetic and non-diabetic patients: a meta-analysis of randomized, controlled trials. BMJ 13: 1115-1124 (Journal IF: 12.827)

DeRouen, T.A., Martin, M.D., Leroux, B.G., Townes, B.D., Woods, J.S., Leitão, J., Castro-Caldas, A., Luis, H., Bernardo, M., Rosenbaum, G. and Martins, I.P. (2006) Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. JAMA 295: 1784-1792 (Journal IF:)

Emre, M., Aarsland, D., Alberto, A., Byrne, E.J., Deuschl, G., De Deyn, P.P., Durif, F., Kulisevsky, J., van Laar, T., Lees, A., Poewe, W., Robillard, A., Rosa, M.M., Wolters, E., Quarg, P., Tekin, S. and Lane, R. (2004) Rivastigmine for dementia associated with Parkinson's disease. N. Engl. J. Med. 351: 2509-2509 (Journal IF: 50.017)

Ferro, J.M., Canhão, P., Stam, J., Bousser, M.G., Barinagarrementeria, F.; ISCVT Investigators. (2004) Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 35: 664-670 (Journal IF: 6.499)

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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

Research Team

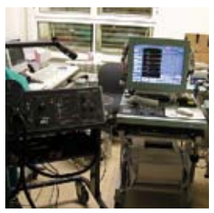
4 Lecturers, 4 MD researchers, 3 PhD students, 1 Master student and 1 Speech therapist

NEUROMUSCULAR UNIT

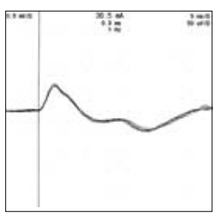
-

MAJOR INTERESTS

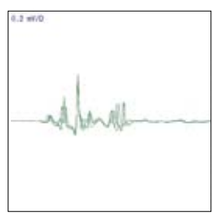
The Neuromuscular Unit is aimed to perform clinical, neurophysiological, neuropathological and molecular research in neuromuscular disorders. Our scientific activity covers many areas, including neuropathies, myopathies, myasthenia gravis, motor neuron disease, respiratory function and neuro-rehabilitation. Over the last years we have target our main endeavor in two main diseases: familial amyloid polyneuropathy (FAP) and amyotrophic lateral sclerosis/motor neuron disease (ALS/MND). In FAP we investigated markers of early disease involvement, using neurophysiology and skin biopsy to study epidermal nerve fibers. That approach in essential in testing new compounds to treat these patients. In ALS/MND we are interested in: sensitive respiratory function tests, including neurophysiology; respiratory rehabilitation; exercise; wireless control of respiratory management; neurophysiological studies; measurement disease progression and molecular biomarkers. Moreover, we investigate brain plasticity, caffeine effect on motor cortex, motor unit recruitment, muscle abnormalities in obesity, mitochondrial changes in myopathies and specific phenotypes of motor neuron disease. We collaborate in several international projects.



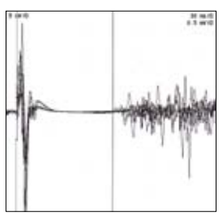
Laboratory room: magnetic stimulation apparatus, on the left, and electromyograph



Stable motor responses recorded from the diaphragm by phrenic nerve stimulation



Unstable complex motor unit of the diaphragm in a patient with ALS



Cortical silent period represented by a period of inhibited muscle activation after brain magnetic stimulation during muscle contraction

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Conceição, I., Castro, J.F., Scotto, M. and de Carvalho, M. (2008) Neurophysiological markers in familial amyloid polyneuropathy: early changes. Clin. Neurophysiol. 119: 1082-1087 (Journal IF: 2.972)

de Carvalho, M., Dengler, R., Eisen, A., England, J.D., Kaji, R., Kimura, R., Mills, K., Mitsumoto, H., Nodera, H., Shefner, J. and Swash, M. (2008) Electrodiagnostic criteria for diagnosis of ALS: consensus of an International Symposium sponsored by IFCN. Clin. Neurophysiol. 119: 497-503 (Journal IF: 2.972)

Pinto, S., Turkman, A., Pinto, A., Swash, M. and de Carvalho, M. (2009) Predictive value of respiratory tests for respiratory insufficiency in amyotrophic lateral slerosis. Clin. Neurophysiol. 120: 941-946 (Journal IF: 2.972)

Pugdahl, K., Fuglsang-Frederiksen, A., Johnsen, B., Tankisi, H., de Carvalho, M., Fawcett, P., Labarre-Vila, A., Liguori, R., Nix, W. and Schofield, I. (2010) Variation in the neurophysiological examination of Amyotrophic Lateral Sclerosis in Europe. Amyotr. Lat. Scler. *In press* (Journal IF: 1.815)

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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
Group leader at IMM since 2007

Other Principal Investigator

Teresa Pais

Research Team

7 Post-doctoral fellows, 5 PhD students, 1 Master student, and 3 Technicians

CELL AND MOLECULAR NEUROSCIENCE UNIT

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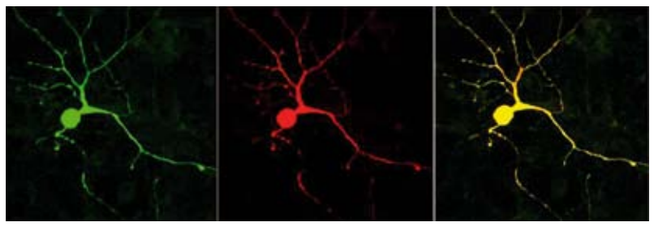
MAJOR INTERESTS

In a time when the world population is rapidly aging, our existence faces ever growing challenges. The brain, the amazing machine which controls the essence of our existence, is not 'immune' to the aging process. Unfortunately, for reasons we do not yet fully understand, many of us end up suffering of the so called 'neurodegenerative diseases', such as Alzheimer's, Parkinson's, multiple sclerosis, or the Prion diseases. Alzheimer's disease, the most common neurodegenerative disorder, affects about 3% of people over 65 years old, but the number rises to a scary 50% in people over 85. It is estimated that by 2040, about 80 million people around the world will be affected by Alzheimer's disease. Likewise, it is estimated that over 6 million people are currently affected by Parkinson's disease.

We use molecular biology to dissect the molecular mechanisms which lead to neurodegeneration in diseases such as Parkinson's, Huntington's, or Alzheimer's disease, which are all intimately associated with protein misfolding and aggregation in specific regions of the brain.

Because the molecular pathways involved in protein homeostasis are highly conserved, we employ a wide variety of model organisms, from the simple but powerful budding yeast to mammalian cell culture and mice. We also employ sophisticated microscopy techniques, such as confocal and multi-photon microscopy, to unveil the mechanisms underpinning neurodegeneration.

Our ultimate goals are to develop novel therapeutic approaches for these and other related disorders. We are working closely together with clinicians in order to accelerate drug discovery efforts, translating basic research into clinical applications that will improve the lives of patients.



Primary cortical neurons expressing alpha-synuclein. The N-terminus of the protein is labeled in green and the C-terminal is labeled in red. The merged image is shown in yellow.

SELECTED PUBLICATIONS

Outeiro, T.F. and Ferreira, J. (2009) Current and future therapeutic strategies for Parkinson's disease. Curr. Pharm. Des. 15: 3968-3976 (Journal IF: 4.399)

Outeiro, T.F., Klucken, J., Bercury, K., Tetzlaff, J., Putcha, P., Oliveira, L.M., Quintas, A., McLean, P.J. and Hyman, B.T. (2009) Dopamine-induced conformational changes in alpha-synuclein. PLoS One 4: e6906 (Journal IF: NA)

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Bodner, R.A., Outeiro, T.F., Altmann, S., Maxwell, M.M., Cho, S.H., Hyman, B.T., McLean, P.J., Young, A.B., Housman, D.E. and Kazantsev, A.G. (2006) Pharmacological promotion of inclusion formation: a therapeutic approach for Huntington's and Parkinson's diseases. Proc. Natl. Acad. Sci. USA 103: 4246-4251 (Journal IF: 9.380)

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Willingham, S., Outeiro, T.F., DeVit, M.J., Lindquist, S.L. and Muchowski, P.J. (2003) Yeast genes that enhance the toxicity of a mutant huntingtin fragment or alpha-synuclein. Science 302: 1769-1772 (Journal IF: 28.103)

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Group Leader

JOAQUIM ALEXANDRE RIBEIRO

MD (1965) at Faculdade de Medicina Universidade de Lisboa (FMUL)
PhD (1982) at the University of Edinburgh, UK
Post-doctoral Research at the Faculty of Medicine, University of Edinburgh
Head of the Laboratory of Pharmacology of Instituto Gulbenkian de Ciência until 1997.
Full Professor at FMUL

Other Principal Investigators
Ana Maria Sebastião, Luísa Vaqueiro Lopes, Maria José Diógenes

Research Team
2 Post-doctoral fellows, 4 Lectures, 14 PhD students, 8 Master students, 4 Trainees and 5 Technicians

NEUROSCIENCES UNIT

MAJOR INTERESTS

The brain can adjust neuronal activity to its specific needs, by means of substances that either enhance or depress communication between neurones. Our unit focuses on how these substances interplay and are involved in diseases of the nervous system , using the following approaches: 1) electrophysiology; 2) neurochemistry, 3) imaging and 4) behaviour.
Our unit consists of four research groups each headed by a principal investigator. The Neuromodulation and Plasticity Group (Joaquim Alexandre Ribeiro) is devoted to understand the way neurotransmitter release and action is controlled at the synaptic level and its implications in neuronal plasticity and in brain dysfunctions. The Neuroprotection Group (Ana M. Sebastião) investigates mechanisms involved in neuronal protection against common pathological insults such as low oxygen, low glucose, seizures, or in situations that occur in neurodegenerative diseases, such as Alzheimer's or Parkinson's disease (lack of neurotrophic factors or peptide deposition). The Receptor biology and cognition group (Luisa V. Lopes) is studies how brain structures involved in memory are affected in situations of cognitive decline and their impact on several pathological conditions, namely depression and anxiety, epilepsy, neurodegenerative diseases. The Regulation of Neuronal Death group (Maria José Diógenes) works on neuronal cell death mechanisms induced by toxic conditions and the potential role of neurotrophins as neuroprotectors. Of interest is the loss of endogenous neuronal trophic support that occurs in Alzheimer's disease patients and the group aims to evaluate the potential direct involvement of AÐ aggregates in this loss. Age-related changes of neurotrophins-mediated control of synaptic transmission and plasticity are also a focus of the group.

Patch-clamp setup to record bioelectrical signals at synapses to measure 'on line' communication between brain neurons

Fluorescence setup to measure intracellular calcium signals in living cells of the brain. Calcium is a mediator of cell communication and also of cell death.

Facility for rodent behavior analysis

SELECTED PUBLICATIONS

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Fernandes, C.C., Pinto-Duarte, A., Ribeiro, J.A. and Sebastião, A.M. (2008) Postsynaptic action of brain-derived neurotrophic factor attenuates alpha7 nicotinic acetylcholine receptor-mediated responses in hippocampal interneurons. J. Neurosci. 28: 5611-5618 (Journal IF: 7.452)

Chen, J.F., Sonsalla, P.K., Pedata, F., Melani, A., Domenici, M.R., Popoli, P., Geiger, J., Lopes, L.V., de Mendonca A. (2007) Adenosine A2A receptors and brain injury: broad spectrum of neuroprotection, multifaceted actions and "fine tuning" modulation. Prog. Neurobiol. 83: 310-331 (Journal IF: 9.130)

Queiroz, C., Gomes, C., Pak, A.C., Ribeiro, J.A., Goldberg, S.R., Hope, B.T. and Ferre, S. (2006) Blockade of adenosine A2A receptors prevents protein phosphorylation in the striatum induced by cortical stimulation. J. Neurosci. 18: 10808-10812 (Journal IF: 7.452)

Diógenes, M.J., Fernandes, C.C., Sebastião, A.M. and Ribeiro, J.A. (2004) Activation of adenosine A2A receptor facilitates BDNF modulation of synaptic transmission in hippocampal slices. J. Neurosci. 24: 2905-2913 (Journal IF: 7.452)

Group Leader

ISABEL ROCHA

PharmD (1991) at Faculdade de Farmácia da Universidade de Lisboa
PhD (2000) and Agregação (2009) in Physiology at the Faculdade de Medicina da Universidade de Lisboa (FMUL)
Associate Professor at FMUL
Board member at European Federation of Autonomic Societies (EFAS)
Chairman of the EFAS education committee

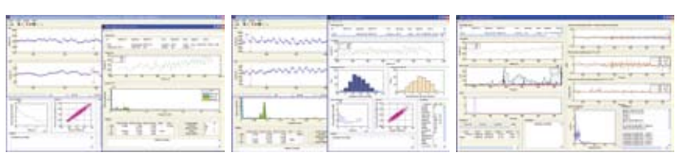
Other Principal Investigator
Pedro Freire Costa, JL Ducla Soares

Research Team
3 Lecturers, 1 Post-doctoral fellow, 2 MD-PhD students, 2 PhD students and 5 research students

AUTONOMIC NERVOUS SYSTEM UNIT

MAJOR INTERESTS

Body functions are regulated at least, in part, by reflex mechanisms which are included in the autonomic nervous system which activity despite essentially autonomous depends in certain conditions from the voluntary control. Obeying in a broader definition to the concept of reflex arc, the main efferent pathways of this system are the sympathetic and the parasympathetic nervous systems. Being a system that struggles to maintain a dynamic equilibrium of visceral functions, the autonomic nervous system is able to mask its own dysfunction. However, when this becomes impossible due to functional disease, physical damage of the neuronal network or during the ageing process, an autonomic failure or dysautonomy is declared. An autonomic failure can be primary or secondary in its origin. In the first case, is due to a failure in the system itself and in the second case is concomitant to other pathologies like parkinsonisms, diabetes, neurocardiovascular syndromes (eg, syncope, hypertension, atrial fibrillation), sleep disturbances, diseases of urinary bladder, sexual organs and gastrointestinal system among others. In clinical medicine, the evaluation of the autonomic nervous system involves a set of standardized procedures which purpose is to define whether autonomic function is normal or not, and in the last case to establish a diagnosis, a therapeutic and to follow-up patients. In physiology, human subjects and animal models are used to deeply understand the mechanisms that are underlying the normal autonomic function and its alterations as well as to develop new ways of autonomic evaluation that can be more targeted, more accurate and more predictive. In our unit, we are particular devoted to the study of cardio-respiratory regulation by central nervous system areas and to the control of ocular circulation both in normal conditions or in particular disease status such as atrial fibrillation, neurogenic hypertension and glaucoma both in human subjects and animal models. Complementing the functional studies the application of methodologies of signal processing to detect an autonomic signature in the recorded physiological signals (eg, blood pressure, ECG, respiratory rate) that could be a precocious marker of disease or have a prognostic value is also one of the goals of our multidisciplinary group.



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Ribeiro, M.A., Cabral, H.O. and Costa, P.F. (2007) Modulatory effect of NO on sodium currents in a neuroblastoma cel line: aspects of cell specificity. Neurosci. Res. 58: 361-370 (Journal IF: 2.473)

Rocha, I., Gonçalves, V., Bettencourt, M.J. and Silva-Carvalho, L. (2008) Effect of stimulation of sublobule IX-b of the cerebellar vermis over cardiac function. Physiol. Res. 57: 701-707 (Journal IF: 1.653)

Lima, P.A., Vicente, M.I., Alves, F.M., Dionísio, J.C. and Costa, P.F. (2008) Insulin increases excitability via a dose-dependent dual inhibition of voltage-activated K+ currents in differentiated N1E-115 neuroblastoma cells. Eur. J. Neurosci. 27: 2019–2032 (Journal IF: 3.385)

Delgado, E., Marques-Neves, C., Rocha, I., Sales-Luis, J. and Silva-Carvalho, L. (2009) Intrinsic vasomotricity and adrenergic effects in a model of isolated rabbit eye. Acta Ophthalmol. Scand. 87: 443-449 (Journal IF: 2.138)

Oliveira, M., Nogueira-da-Silva, M., Timoteo, A., Feliciano, J., Sousa, L., Santos, S., Silva-Carvalho, L. and Ferreira, R. (2009) Inducibility of atrial fibrillation during electrophysiologic evaluation is associated with increased dispersion of atrial refractoriness. Int. J. Cardiol. 136: 130-135 (Journal IF: 3.121)

FACILITIES AND SERVICES

Alongside with research, IMM has a core of resource units, which complement and maintain the high quality scientific environment. Among these are the Management, the Information Systems, Communication & Training and Lab Management. In addition to these transversal units, and in the spirit of shared resources, IMM offers recently equipped state-of-the-art Facilities: Flow Cytometry, Bioimaging, Animal House and Zebra Fish, as well as a 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.

MANAGEMENT

Head of Unit

Margarida Pinto Gago

Degree in Management (1978) at Instituto Superior de Economia e Gestão da Universidade Técnica de Lisboa

Staff

André Fialho (Legal); Claúdia Soeiro (Front desk); Sandra Duarte, Isabel Roque, Inês Bernardes, Vera Rego and Ana Marcelino (Accounts); Andreia Vaz, Maria José Antunes and Filipa Aperta (Project management)

MISSION

The Management Unit is responsible for the overall IMM legal, administrative and financial support. At IMM, funding for research projects comes from many different sources – national and international, public and private – requiring the skills of experienced administrative staff. The unit is responsible for accounts and budget management – performing all the required activities to assure proper IMM legal accounts, updated cost accounting per project/activity and budget control – and for Project Management, which deals with all administrative and financial aspects of research projects, from the moment of funding approval to the date of final report.
We also manage Human Resources, undertaking all tasks necessary to hire new staff and terminate contracts (advertising, selection, contracts preparation, all legally required registrations).
Moreover the Management Unit is responsible for tax reporting, a considerable task, given the specifications of the legal status of IMM combined with the number and variety of activities and collaboration protocols contracted. In addition, within our unit we have a Lawyer who provides legal support to researchers, namely intellectual property issues and consortium agreements.

INFORMATION SYSTEMS

Leading Consultant

Tito Santos Silva

PhD (2003) in Computer Science at Universidade Técnica de Lisboa
Associate Professor at Universidade Católica Portuguesa, Lisbon

Staff

Daniel Silva (PhD student),
Pedro Eleutério (Helpdesk)
Ruben Alves (Systems analyst)

MISSION

The Information Systems Unit provides, manages and develops Information Technology Resources in order to facilitate the work of IMM researchers and increase their productivity. Moreover, it enforces process compliance with international and internal norms and procedures. The Information Systems Unit designs and implements several projects in the areas of 1) Information System Design; 2) Integration of Existing and New Information Systems; 3) Web Site (in collaboration with the Communication and Training Unit); 4) Documentation and Information Workflow; 5) Physical Support (Backups, Storage, Network Reliability, Network Performance, Security); 6) Knowledge Management. Support to IMM researchers includes the provision of a help-desk support service, assured by a help-desk team that is scheduled in order to respond all working days of the year. This help-desk team receives all help requests from the users, acts as their only contact and, if necessary, works in cooperation with the Information Technology Unit of the *Faculdade de Medicina da Universidade de Lisboa*.

COMMUNICATION & TRAINING

Head of Unit

Marta Agostinho

PhD (2007) in Biomedical Sciences at Faculdade de Medicina da Universidade de Lisboa
Post Graduate Diploma (2009) in Science and Society at The Open University, UK.
Staff scientist at the IMM since 2009
Head of unit since 2008

Staff

Margarida Trindade (Science funding coordinator), Inês Crisóstomo (Advanced training coordinator), Joana Costa (Post-doctoral fellow) Cheila Almeida (Communications assistant), Catarina Rebelo (Trainee)

MISSION

The Communication & Training Unit was created in 2008 to develop a coordinated framework for Science Communication, Advanced Training and Science Funding.
The Unit has dedicated staff to address Science in Society activities, in collaboration with national and international partners. A science communication programme has been developed, which builds on researchers' initiatives as well as projects aiming at developing two-way interaction between scientists and a wide range of audiences. Activities include workshops, hands-on activities for younger generations, meetings involving scientists and different publics, the development of educational resources and communication training activities for scientists. Schools and the media are among privileged partners/audiences.
At UCOM we are responsible for the overview and coordination of Advanced Training initiatives. Moreover, we provide the link with the "Centro Académico de Medicina de Lisboa" and foster collaborations amongst national and international education and/or research institutions. The core of our educational programmes is the IMM PhD Programme, for which we oversee and guarantee the progress of all its activities, namely: course organization; students' events; promotion of the programme; and record management.
We provide assistance and advice on funding and grant management issues. IMM researchers can find support in applying for national and international funding, from provision of funding information to application and contract conclusion.
In addition to these three core areas, the Unit also serves a range of transversal areas including External Relations, Internal Communication, IMM Events, and Support to the Direction.

LAB MANAGEMENT

Lab Manager

Alexandra Maralhas

Scientific Advisor

Luís Moita

Staff

Rita Soares and Alexandre Jesus (Lab manager assistants); Sandra Lopes and Ana Rita Vicente (Purchasing office); Edna Gomes, Paula Correia and Fernanda Vila-Chã (Washing room technicians)

MISSION

The Lab Management Unit is responsible for the maintenance and safety of the laboratories infrastructures and equipments, ensuring high standards of usability and quality for all research units. Moreover, the unit manages chemical products (namely it supplies carbon dioxide, dry ice, liquid nitrogen); develops standard operating procedures and implements good health and safety practices, according to National Legislation.
Within the Lab Management Unit are the Purchasing Office (Supply Center and Internal Storehouse) and the Washing Room. The Purchasing Office deals with all acquisitions (products, services and equipments), including import / export services and provides information on prices, ongoing promotions, new products and delivery conditions. In addition, a stock of consumables is maintained in the Storehouse, for the IMM community. The Washing Room provides researchers with clean and sterilized material, being equipped for all types of materials and solutions, required by IMM researchers.

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 (Support)

MISSION

The BioImaging Unit acts as a support structure to help and nurture research done with Light Microscopy inside the institute. Besides managing resources, the unit provides IMM scientists and visitors with excellence in scientific know-how and expertise in using light microscopy methods for their research. We assist in planning microscopy-oriented projects, choosing materials and equipment, analyzing experimental results, processing acquired images and presenting data. Together with continuous training of new users, we organize regular courses to introduce users to the most recent microscopy techniques and foster interactions and collaborations between microscopy users at the IMM.
The BioImaging Unit presently manages 3 laser scanning confocal microscopes, 2 widefield systems and other imaging resources such as brightfield microscopes and a bioluminescent imaging system. The systems are prepared for advanced applications which include live cell imaging, automated long-term time-lapse and intra-vital imaging, enabling researchers to image dynamic events and molecular interactions inside living cells and tissues with state-of-the-art techniques such as FRET, FRAP and Photoactivation.
Access to top-of-the-line microscopy systems is becoming a widespread necessity for groups with challenging research programs. Such high-cost systems represent a significant investment which may exceed the financial capabilities of a single group. For this reason, we also provide advice and act as a communication and decision making platform for groups interested in the joint acquisition of novel imaging systems.

FLOW CYTOMETRY

Head of Unit
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 Luísa Caetano (Technician)
Alexandre Varela (Technician)

MISSION

The Flow Cytometry Unit provides a state of the art flow cytometry service to the IMM and external researchers. It is currently equipped with a Becton Dickinson FACSAria high speed cell sorter, a FACSCanto and two FACSCaliburs cell analysers. It also has separate computers and software to enable researchers to analyse their data. The cell analysers are available 7 days a week-24 hours a day by trained researchers. The FACSAria is operated by dedicated UCF staff at normal Monday to Friday working hours. Our unit also provides education, training, and advice to researchers wishing to use flow cytometry in their studies. It runs regular flow cytometry courses targeted at new users that combines lectures on flow cytometry principles and research applications with practical hands-on tutorials. Occasional seminars are also presented by Unit members or invited speakers on new techniques and instrumentation. Our Unit is used by nearly all the research units of the IMM, with an average of 300 hours of flow cytometer usage per month in 2009. UCF staff is also actively involved in research projects in collaboration with other IMM Units.

HISTOLOGY SERVICE

Coordinator
Sandra Casimiro
PhD (2007) in Molecular Biology, at FCUL, Lisbon, Portugal
Post-doctoral research fellow at IMM since 2007

Staff
Andreia Pinto (Technician)

MISSION

The IMM Histology Service results from collaboration between IMM and the Histology Institute of *Faculdade de Medicina da Universidade de Lisboa* (FMUL), and aims to provide technical work, expertise and know-how in Histology techniques to IMM researchers. The Histology Service is located in the Histology facilities of the FMUL Histology Institute, and is open during normal Monday to Friday working hours. The Service staff includes a permanent technician, with a degree in Technical Pathology, Anatomy and Histology.
The Histology Service main tasks are: processing tissue samples for routine histochemical procedures; training new users in sample preparation; and providing tutorship in the design and implementation of different histology techniques.

ANIMAL FACILITY

Head of Unit
Domingos Henrique
PhD (1991) at Universidade de Lisboa
Post-doctoral research at NIMR and ICRF, UK and at the Institut d'Embryologie Cellulaire et Moléculaire, France
Investigator at Faculdade de Medicina da Universidade de Lisboa
Head of Facility since 2008

Staff
Lara Alina Costa (Manager), Dolores Bonaparte (Veterinarian), Yuri Leite (Technician), Joel Filipe (Technician), Olena Pinho (Animal caretaker), Nuno Inacio (Animal caretaker), Jose Vila-Cha (Animal caretaker)

MISSION

The IMM has currently one conventional animal facility, and is starting a new, larger barrier Facility. The conventional facility is currently used at 100% of its capacity by IMM researchers. 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. The new barrier facility, with an area of 800m^2, will host mice and rats in microisolators and individually ventilated cages, and will be available for both IMM and external researchers. The new animal quarters include one Production facility, one Experimental Facility, one Quarantine room, two Transitional Animal Rooms, one Surgical Suite, two Procedure Rooms and one gamma irradiation suite. The new quarters include a biosafety level 3 room and one procedure room. The Animal Facility provides both internal and external services for academia, pharma, biotech and other fields of research. These services will range from animal hosting to procedure performance such as: experimental procedures, surgical procedures, *in vivo* imaging and assisted reproduction techniques such as timed pregnancies, *in vitro* fertilization, embryo & cesarean derivation, and cryopreservation.
This unit is highly committed to follow the 3Rs principles – *Replace, Reduce and Refine* – for a conscious and responsible use of laboratory animals, while supporting high quality science. For this reason, it provides education, training and guidance for researchers, according to Portuguese and international law and recommendations for good practices and animal welfare.

ZEBRAFISH 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 (Manager), Fábio Valério (Technician), Patrícia Matos (Part-time technician)

MISSION

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 approximately 3000 fish in a state-of-the-art housing system. Besides wild type lines there are 16 transgenic lines and 22 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.

P3 FACILITY

Coordinator
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)

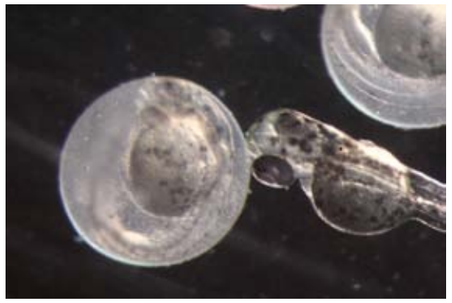
MISSION

The IMM is building a P3 Facility that will be ready in the first trimester of 2010. The 70 m^2 facility includes two tissue culture rooms and one animal room. All rooms will be fully equipped and will meet the highest safety standards as defined by European and International guidelines. Work to be carried out in this Facility includes all experimental procedures involving *Mycobacterium tuberculosis*, HIV and other Biosafety level 3 pathogens. The IMM's P3 Facility will follow strict admission rules. Accordingly, the Facility will provide education, training, and guidance for researchers and will be constantly monitored by dedicated staff. The Facility will be available to IMM internal and affiliated researchers, as well as external researchers from academia, pharma and biotech.

ABOUT IMM

TECHNOLOGY TRANSFER

"(...) IMM develops ties and strategic plans with companies committed to innovation and new solutions for the sake of patients."



Legend

Innovative approaches to drug discovery include using zebrafish as an in vivo model system in regeneration

IMM aims to be the perfect environment for scientific ideas to grow and turn into products and technologies that make difference in health care. To achieve this goal IMM develops ties and strategic plans with companies committed to innovation and new solutions for the sake of patients. Partnerships are established to strengthen positions in the competitive markets of drug discovery and diagnostics. These partnerships involve both companies incubated by IMM and external companies. IMM is one of the leading founders of the Health Cluster Portugal consortium, a group of major players for the development of health sciences and technologies.

The high quality of work developed by all research units of the IMM, either alone or in collaboration, is generating an increasing level of intellectual property rights (IP rights), namely a few patents of invention with an acknowledged biomedical and/or pharmaceutical use. At the same time, IMM researchers are becoming more aware of questions related to IP rights or technology transfer.

Therefore, IMM takes on the responsibility and the commitment to support the costs involved in the process of patent application and protection, and shares incoming royalties with the inventors, whether as part of any IP rights licensing process or as the core of any emerging biotechnological start-up.

IMM policy is to encourage researchers to become inventors and help their discoveries to thrive and develop beyond the limits of academy, so that they can contribute for a better quality of life of patients and their families.

"IMM policy is to encourage researchers to become inventors and help their discoveries to thrive and develop beyond the limits of academy, so that they can contribute for a better quality of life of patients and their families."

TechnoPhage, SA is a Biotech company with labs located at the IMM, under a collaboration protocol signed by these two entities. TechnoPhage, SA is engaged in two main R&D programs:

1) Bacteriophages

R&D of novel products, based on the unique properties of bacteriophages, for the treatment, diagnosis and prevention of bacterial infections. Current work is focused on the R&D of new products targeting nosocomial, community and food industry infections. Different products are being developed with two main purposes:

a) Specific elimination of antibiotic-resistant bacteria (therapy and sanitation)

b) Detection and quantification of live microorganisms (diagnostic devices)

2) Recombinant antibodies

R&D on recombinant antibodies with therapeutic and diagnostic applications

TechnoPhage, SA continuously strives to increase the number of proprietary products, through an active R&D program and collaboration agreements. TechnoPhage, SA also delivers R&D services for diverse pharmaceutical companies.

Miguel Garcia
Director and Chief Executive Officer

www.technophage.pt

GenoMed is a spin-off company of IMM created in 2004. The mission of GenoMed is to provide cutting-edge technology transfer services relevant for medical applications. Currently, GenoMed offers over 100 different tests that are used in diagnosis, prognosis and therapeutic follow up. GenoMed acts in 3 main medical areas:

Oncology: Molecular and Cytogenetics tests for Hemato-Oncology, including follow up of bone marrow transplantation. Molecular diagnosis (FISH) for Oligodendroglio mas and urinary tract cancer. Hereditary breast cancer.

Infectious Diseases: Sequencing the HIV genome to detect resistance to anti-viral therapy. Genotyping Hepatitis B and C genomes and detecting resistance to anti-viral therapy. Genotyping Human Papillomavirus. Infection by Aspergillus in immuno suppressed patients: detection of Galactomannan Antigen.

Genetic Diseases: Alzheimer and Parkinson diseases; Fronto-Temporal Dementia. Wilson Disease, Hemochromatosis, Porphyria. Hyperthropic cardiomyopathy; Familial Hypercholesterolemia; Brugada and Long QT Syndromes. Bone Dysplasias. Pharmacogenetics: Genetic testing to reduce bleeding associated with Warfarin in take. Genetic testing for management of antidepressive drug therapy. Additionally, GenoMed provides parental and ancestry DNA testing.

Teresa Porta Nova
Director

www.genomed.pt

IMM fosters clinical and translational research - our mission is to go from bench to bedside, and back to the bench, i.e., not only to take new discoveries and technologies for the clinical practice but also to bring the patient care know-how to the laboratory. The close relationship with hospitals, particularly with Hospital of Santa Maria (HSM), a founding partner of IMM, places the institute in a privileged position to bridge the gap between bench research and clinical practice.

FROM ***BENCH TO CLINIC***

" IMM is involved in several research networks from the 7th Framework Programme of the European Commission that aim to search, improve and/or develop therapies for neurodegeneration, rheumatoid arthritis and Malaria."

Recently funded Clinical and Translational Research Grants from competitive calls:

- 15 ongoing clinical research grants, from the Fundação para a Ciência e Tecnologia. These grants were awarded under the 2007 call for clinical research, where IMM had a 48% success rate (National success rate was 19%).

- Maria Mota, a group leader at IMM, won one of the three collaborative research grants under the 2009 call of the Harvard Medical School - Portugal Programme.

IMM is involved in several research networks from the 7th Framework Programme of the European Commission that aim to search, improve and/or develop therapies for neurodegeneration, rheumatoid arthritis and Malaria.

Ongoing research projects spam a multiplicity of topics: cancer research, regenerative medicine, cardiovascular diseases, inflammation, neurosciences, infectious diseases and drug discovery. Among these are strictly clinical projects but also projects that arose from the collaboration of basic research and clinical research units.

- IMM Angiogenesis Unit actively collaborates with the radiotherapy department of Hospital de Santa Maria to unveil the biological effects of ionizing radiation in the vasculature and cancer development.

- The Cellular Immunology and **Rheumatology Research Units** are actively collaborating, resulting in the recent publication of three papers in international peer-reviewed journals.

- The Cell Biology of the Immune System and **Clinical Neurological Research Units** have a grant to decipher the contribution of the immune response for sleep and cardiovascular disorders.

- The Cell and Molecular Neuroscience and Clinical Neurological Research Units work closely together to accelerate drug discovery efforts and develop novel therapeutic approaches for Parkinson's disease.

- The Clinical Neurological Research and the **Tissue Morphogenesis and Repair Units** are searching for novel risk factors for Genetic diseases, such as Non-syndromic cleft lip, and in parallel developing functional studies on an animal model, the Zebrafish.

The **IMM clinical research units –** namely, the Neuromuscular, the Clinical Neurology Research and the Clinical Oncology Research Units are involved in different international multicenter studies such as clinical trials and registries. From these collaborations resulted important publications

Costa, L. and Major, P.P. (2009) Effect of bisphosphonates on pain and quality of life in patients with bone metastases. Nat. Clin. Prac. Oncol. 6: 163-174. (Journal IF: 9.113)

CLOTS Trials Collaboration, Dennis, M., Sandercock, P.A., Reid, J., Graham, C., Murray, G., Venables, G., Rudd, A. and Bowler, G. (2009) Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet 373: 1958-1965 (Journal IF: 28.409)

Connolly, S.J., Ezekowitz, M.D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P.A., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B.S., Darius, H., Diener, H.C., Joyner, C.D., Wallentin, L.; RE-LY Steering Committee and Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N. Engl. J. Med. 361: 1139-1151 (Journal IF: 50.017)

Olanow, C.W., Rascol, O., Hauser, R., Feigin, P.D., Jankovic, J., Lang, A., Langston, W., Melamed, E., Poewe, W., Stocchi, F., Tolosa, E.; ADAGIO Study Investigators (2009) A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N. Engl. J. Med. 361: 1268-1278 (Journal IF: 50.017)

Sampaio, C. (2009) Can focusing on UPDRS Part II make assessments of Parkinson disease progression more efficient? Nat. Clin. Pract. Neurol. 5: 130-131 (Journal IF: 6.979)

AWARDS FOR ACCOMPLISHMENTS THAT BRIDGE BASIC AND CLINICAL RESEARCH :

- **Miguel Castanho** and his team at the Physical Biochemistry Unit succeeded in devising an analgesic dipeptide that was able to cross the Blood-Brain Barrier and remain effective. This work was awarded the 2008 Grunenthal Award on Pain and originated the registry of a patent.

- **Luís Graça** and **Marta Monteiro** of the Cellular Immunology Unit won an international entrepreneurship contest to develop a business plan for a new cellular therapy that reduces the risk of rejection after a liver transplant.

- The 2009 Senior Clinical Research and Career Development of the Harvard Medical School – Portugal Program was awarded to **Helena Canhão**, an IMM researcher and Rheumatologist at Hospital Santa Maria.

- 2008 Bial Award in Clinical Medicine to **João Eurico da Fonseca and team** (Rheumatology Research unit)

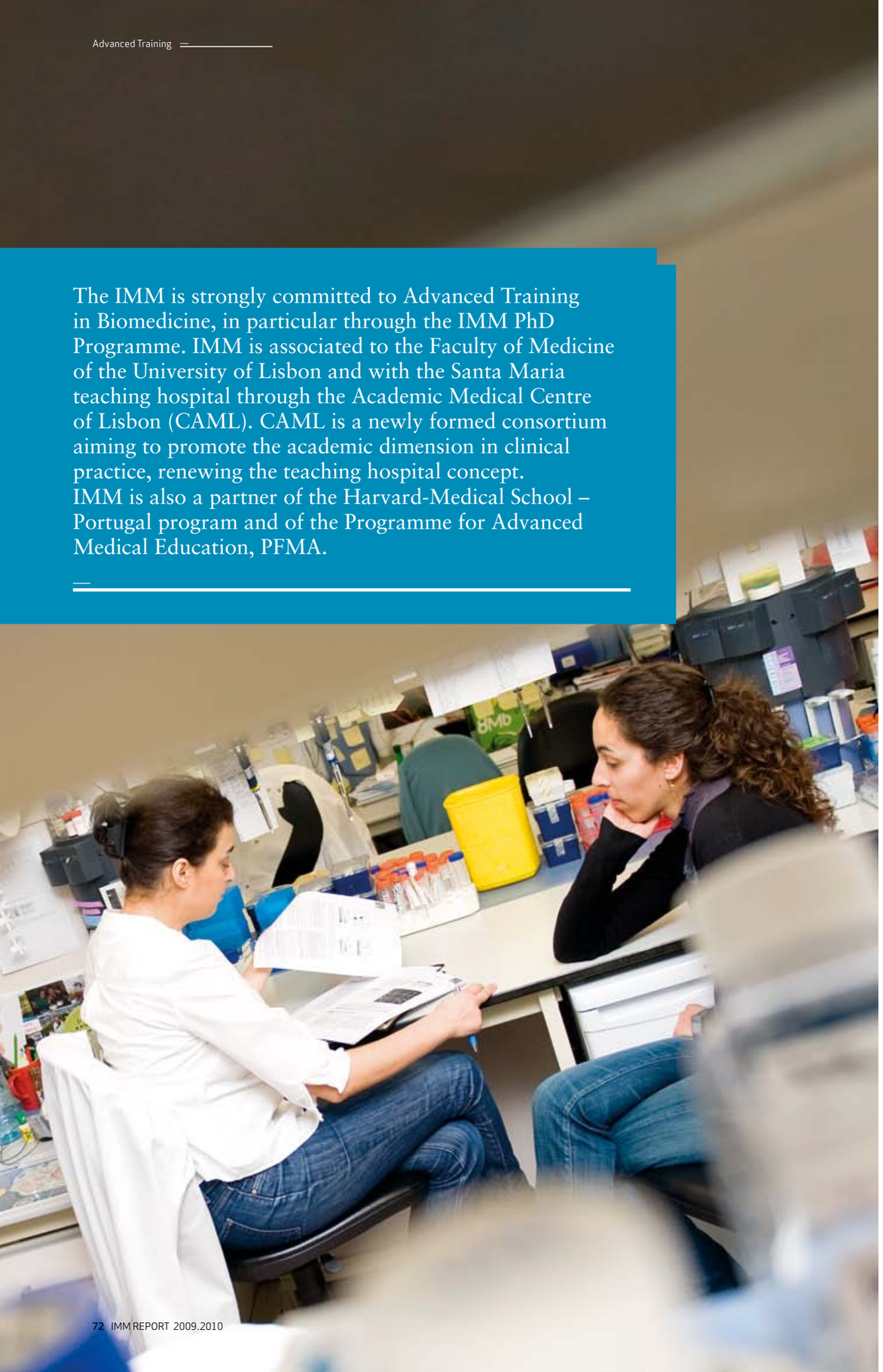
- 2009 Pfizer Award in Clinical Research to **Bruno Silva Santos** (Molecular Immunology Unit)

Another area is diagnosis, where the Clinical Immunology Unit (Group leader Ana E. Sousa) provides services in the area of Primary Immunodeficiencies in response to the medical community's needs. Furthermore, IMM hosts a spin-off company, GenoMed, which offers over 150 different tests that are used in diagnosis, prognosis and therapeutic follow up.

Besides research and technology transfer to the clinical practice, IMM organizes scientific meetings and courses, namely the "HIV/AIDS: Closing the Gap between Basic Research and Clinical Practice" (IMM, January 2010). IMM researchers also set-up meetings aimed at patients and caregivers such as the "Parkinson's Disease course for caregivers and family members" (IMM, May 2010).

To further develop and support clinical biomedical research in Portugal, IMM created a Biobank. This infrastructure reinforces the connections between basic and clinical research, promoting the prevention, diagnosis and therapeutics of several diseases.

The IMM is strongly committed to Advanced Training in Biomedicine, in particular through the IMM PhD Programme. IMM is associated to the Faculty of Medicine of the University of Lisbon and with the Santa Maria teaching hospital through the Academic Medical Centre of Lisbon (CAML). CAML is a newly formed consortium aiming to promote the academic dimension in clinical practice, renewing the teaching hospital concept.
IMM is also a partner of the Harvard-Medical School – Portugal program and of the Programme for Advanced Medical Education, PFMA.



ADVANCED TRAINING

IMM PhD PROGRAMME

The IMM International PhD Programme in Biomedical Sciences recruits every year highly motivated students to join one of the three IMM research programmes: Cell & Developmental Biology, Immunology & Infectious Diseases and Neurosciences.
IMM's mission is to enable these students to be able to carry out independent, original and scientifically significant research, and become critical thinkers. The core of the IMM PhD Programme is the research project, which is complemented by a "student-oriented" training component. IMM PhD students are accompanied by a supervisor and by a Thesis Committee that includes the student´s Tutor. Moreover, students are challenged to organize one or more activities.

The PhD training component has a flexible modular structure that includes:

- **Nanocourses**, IMM offers a wide selection of courses, aimed to provide:
  fundamental scientific knowledge in specific topics among the IMM research programmes transferable skills training
- **Workshops,** organized by IMM or by other national or international research institutions
- **Seminars and Scientific meetings.**

PROGRAMME TEAM

Director
Miguel Carneiro de Moura

Executive Coordinator
Inês Crisóstomo

Programme Manager
Joana Costa

Scientific Advisory Board
António Jacinto
Ana Espada de Sousa
Isabel Pavão Martins

Legend
2009 Students Retreat
in Quinta dos Amarelos; Alentejo

COURSES OFFERED AT IMM 2009/2010 :

Advanced Course on Protein Expression and Purification: Tips and Tricks

BioImaging Nanocourse on Microscopy

Bioinformatics: What? When? How?

Biology of Cancer

Biostatistics

Cell Adhesion and Migration in Health and Disease

Flow Cytometry Workshop - From Basic Concepts to multicolor analysis

Get the best from your sequences

Interacting with different publics

Nanomedicine

New frontiers, new careers: science outside academia

Presenting your research: from bench to peers

Technology Transfer and Intellectual Property in Biomedicine

PhD PROGRAMME IN NUMBERS :

94 Students (December 2009)

85 Students with fellowships from Fundação para a Ciência e Tecnologia (FCT)

Other PhD fellowships:

1 Axa Research Fund

1 Marie Curie Initial Training Network

2 MD Resident (PFMA-FCT)

1 IMM

10 PhD Thesis Defenses in 2009

Legend

Students, faculty and guests socializing during the 2009 Students Annual Meeting

SCIENCE & SOCIETY

1.

2.

3.

Legend

1. School visit to IMM "Exploring the human body", 4-6 year old children, December 2009

2. "IMM Restaurant: choose your menu on human cells". Workshop delivered in a variety of venues (this photo: Fundação Gulbenkian, Lisbon, September 2009)

3. Setting the Stage in Portugal: researchers and the public come together through theatre. Forum theatre and movement theatre performances in Lisbon, September, 2009.

Promoting an informed discussion on health and biomedical research issues is a priority for the IMM. This has been achieved through the engagement of researchers and non-scientific partners in the IMM's Outreach programme. The programme includes training for younger generations, an Annual School Visits scheme (which in 2009 benefited more than 600 students from all levels of schooling), and specific outreach projects, such as the EU Researcher's Night. In 2009, IMM co-organized the project *Setting the Stage in Portugal: researchers and the public come together through theatre*, which engaged over 13.000 people.

REGULAR COLLABORATION WITH THE MEDIA :

4-5/week
Participations in the media

10-15 / year
Press releases

> 40 /year
Media visits to IMM

1 / year
Training course for researchers

A major effort is also placed in regular collaboration with the media, in particular in the promotion of dialogue and opinion making in health and biomedicine (e.g. public debate in H1N1 pandemic flu), as well as in highlighting the research developed by IMM teams.
A proactive attitude towards the media includes regular production of press releases and articles, support to press conferences and media visits at IMM, contact management and media training for researchers.

IMM PARTICIPATION IN THE MEDIA (2009)

MEDIA TYPE

Specialized	69
General	237

CHANNEL

Press	153
Internet	87
Radio	27
T.V.	39

ARTICLE

Debate	4
Interview	13
News	288
News story	7
Film/Photo	1

TOPIC

Public Eng.	8
Event	16
Funding	7
Research	81
Award	57
Personnal	58
Health	64
Science	15

IMM ***LIFE***

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. Attendance to seminars is greatly encouraged as it is believed to foster scientific discussion of on-going projects through exchange of ideas, experiences and problem-solving tips.

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. Attendance to seminars is greatly encouraged as it is believed to foster scientific discussion of ongoing projects through exchange of ideas, experiences and problem-solving tips.
In adition, IMM host initiatives developed by researchers and support staff that aim at creating a team spirit and pleasant environment to work.

Legend

1. After IMM Christmas Party, PhD students deliver the presents offered by IMM collaborators to the children of Pediatrics service, Hospital de Santa Maria, December 2009

2. Stand up commedy scientist and his audience at IMM, July, 2009

3. Eric Wieschaus' Seminar, January, 2010.

1.

2.

THE IMM SEMINAR SERIES INCLUDES:

IMM SEMINARS
These seminars are open to the general scientific community. They happen weekly and the speakers list include group leaders from IMM and external experts working in different areas of biomedical research.

CHALK TALKS
These seminars are exclusive to PIs and happen every fortnight. The aim is to discuss current research and internal administration of IMM.

ePI – SEMINARS
Invited external senior researchers give a talk and discuss scientific issues with whom interested. All IMM community is invited to attend.

PIZZA SEMINARS
Informal seminars held biweekly. They are an opportunity for PhD students and postdoctoral fellows to present on-going research projects.

THEMATIC SERIES
Seminars in specific biomedical topics, organized by research teams from IMM and other research centers from the great Lisbon area. Examples include the Tissue Regeneration forum, Lisbon Area Neurosciences Meetings, Neurosciences Seminars, Oncology Series and the Immunology Club.

ANNUAL RETREATS
IMM's Group Leaders and several invited researchers gather every year over a weekend to interact and discuss present and future research at the institute. Similarly, IMM PhD students and post docs organize an annual retreat to discuss science, careers, and life at IMM.

SCIENTIFIC MEETINGS AND WORKSHOPS
The IMM researchers organize regularly national and international scientific meetings held at IMM, with the support of resource units. In addition, the Edifício Egas Moniz hosts other similar range of activities, such as workshops, courses, public seminars, special events, to which the IMM staff has free and easy access.

NUMBERS (2009)

124
Scientific Seminars

7
IMM scientific meetings and workshops

3.

1 YEAR IN THE LIFE OF IMM

2009

05 FEBRUARY *(AND SEP 10)*

Collaboration *in prep.*
VIP visit of a committee lead by Professor André Syrotard, General Director of INSERM, to establish a scientific collaboration between IMM and Inserm, France.

12 MARCH

FMUL candidate day
IMM joins Lisbon Faculty of Medicine's open day and reveals its biomedical research.

16 MARCH

Renown oncologist **Klaus Pantel** (University of Hamburg, Germany) opens the 2009 edition of the Oncology Series, a seminar series dedicated to clinical investigation in cancer.

20 MARCH

IMM Open day
on Brain Awareness week
neuroscientists share with secondary school students brain science under the motto The brain and arts.

27 APRIL

H1N1 in the public agenda
IMM virologist Pedro Simas takes on a long lasting commitment to engage the public in informed discussion on H1N1 pandemic flu, participating in over 80 interventions in the Portuguese media.

6 MAY

João Eurico Fonseca and team (Rheumatology Unit) receive 2008 BIAL Prize in Clinical Medicine from Portuguese President Professor Aníbal Cavaco Silva in a ceremony hosted by the Faculty of Medicine of Lisbon.

16-17 MAY

Debating science, careers and IMM
2nd PhD students retreat in Alentejo, Portugal.

29 MAY

IMM's **new website** is launched

MAY-SEP

On Monday and Wednesdays' evenings, the seminar room was converted in theatre rehearsal room for scientists/actors to develop research-related plays.

25 SEPTEMBER

EU initiative *Setting the Stage* - Researchers and public come together through theatre.

29 SEPTEMBER

External Evaluators from the Institutional Evaluation Programme of the University of Lisbon visit the IMM.

8 OCTOBER

Following the protocol signed in December 8, 2008, the official creation of Medical Academic Centre of Lisbon - a consortium of IMM, Lisbon Medical School and Hospital de Santa Maria - is published *in Diário da Republica.*

12-13 OCTOBER

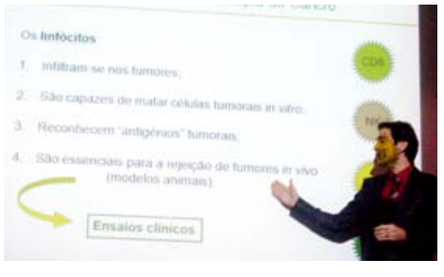
3rd PhD Students Meeting
Under the students initiative, IMM receives Nobel Prize winning Tim Hunt and discusses biomedical science.

30 OCTOBER

Innovative cellular therapy developed at IMM by researchers Luis Graça, Marta Monteiro and David Cristina win 2nd prize at the international competition Idea To product®, in Texas, USA. The innovative therapy prevents complications after liver transplantation.

24 NOVEMBER

Award Ceremony where Bruno Silva Santos and team (Molecular Immunology Unit) received Pfizer Prize in Clinical Medicine.



2010

Several areas of medicine will be discussed at the campus of the Academic Medical Centre of Lisbon.
The Meeting "HIV/AIDS: Closing the gap between basic research and clinical practice" (IMM, January) was the first of such clinical research events.
The course on Parkinsons' Disease for caregivers and family members (IMM, April) brought together researchers, clinicians and caregivers.
Young IMM researchers have already won a national contest of entrepreneurship and may represent Portuguese universities later on in the international competition.
Novel ways of engagement with partners and citizens are being developed, by initiating IMM presence at social and professional networks.
The visit from the International Scientific Advisory Committee of the IMM Neurosciences Programme is scheduled to occur late in 2010.