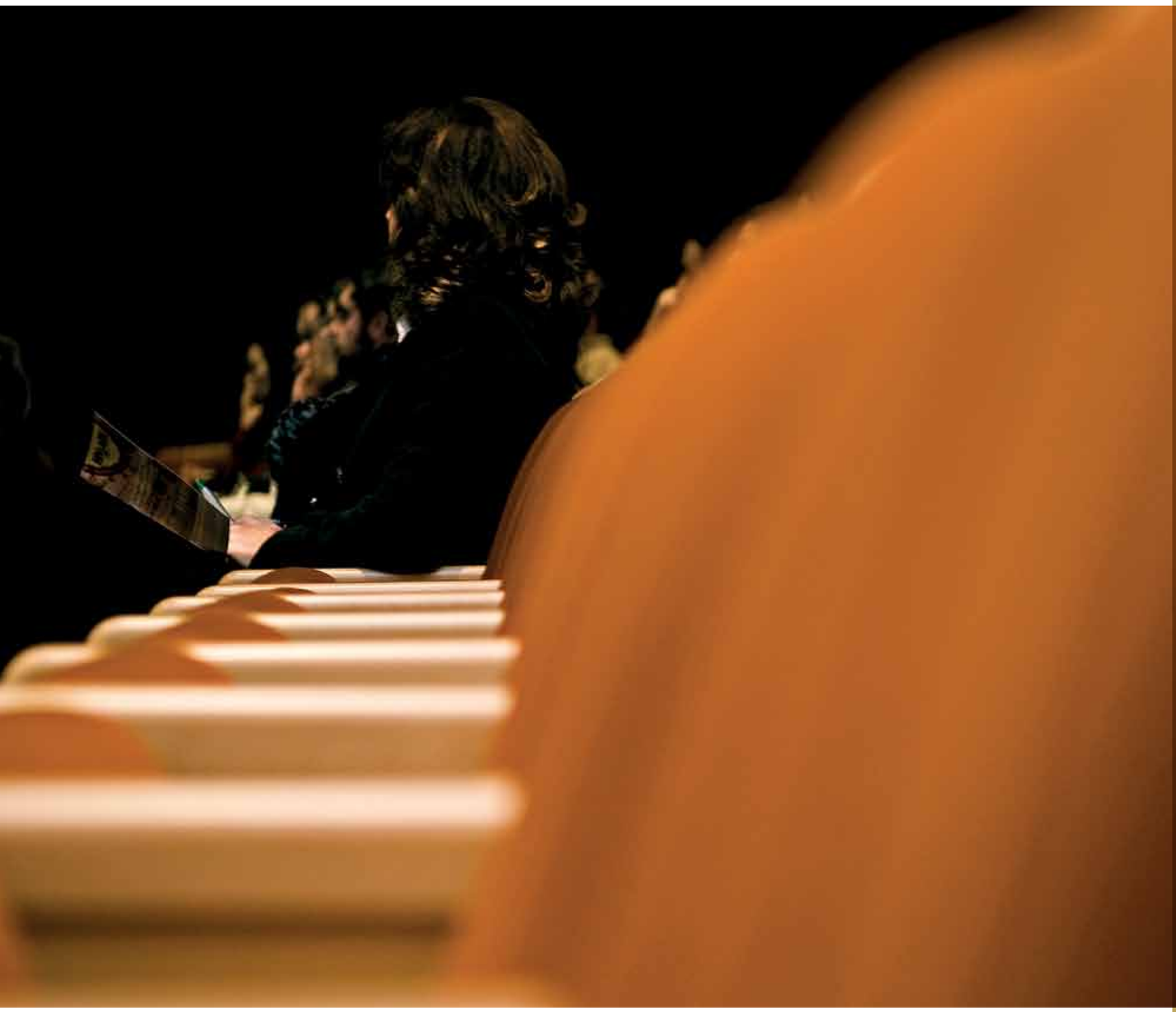
IMM REPORT 2013

INSTITUTO DE MEDICINA MOLECULAR

FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

WHERE SCIENCE MEETS MEDICINE

INSTITUTO DE MEDICINA MOLECULAR



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FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

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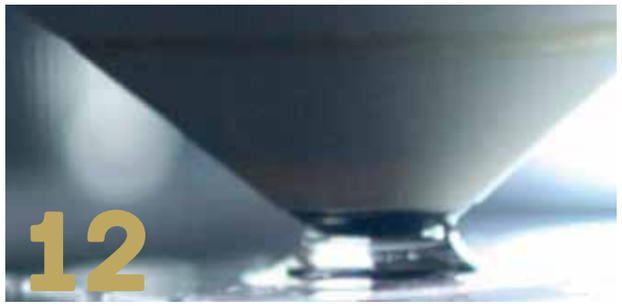
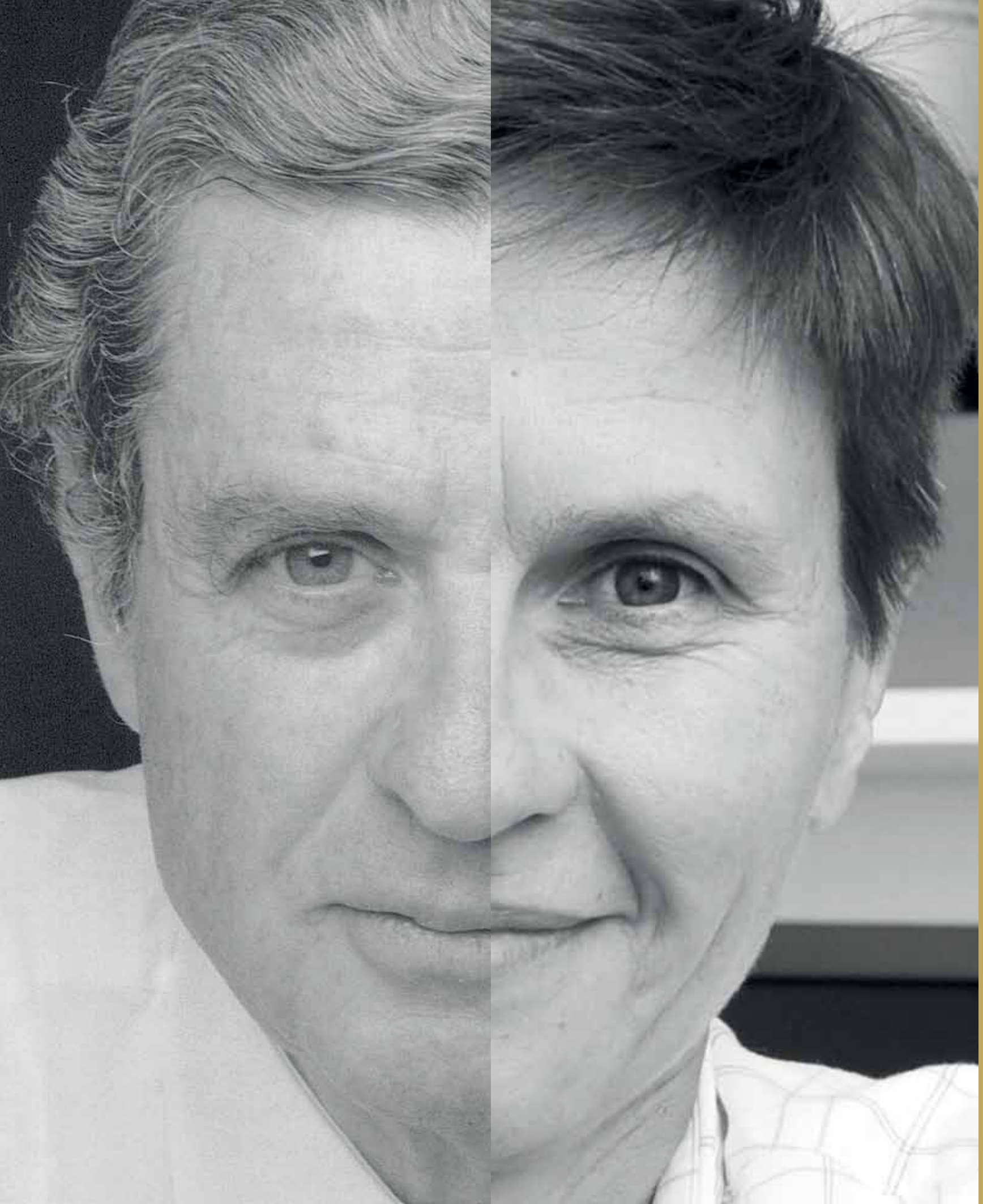
CONTENTS





EDITORIAL

The *Instituto de Medicina Molecular* (IMM) is one of the leading biomedical research institutions in Portugal. It is part of the *Centro Académico de Medicina de Lisboa*, which integrates the largest university hospital of the country and the School of Medicine of the University of Lisbon.

The IMM was created in 2002 following the merger of five centers dedicated to research in the areas of Cell and Molecular Biology, Developmental Biology, Biochemistry, Immunology, Nutrition and Neurosciences at the *Faculdade de Medicina da Universidade de Lisboa*. IMM was awarded the special status of *Laboratório Associado* by the Portuguese Ministry of Science, Technology and Higher Education. Our strategic priority has since been to attract Group Leaders amongst junior scientists trained abroad. Up to present, twenty six new Group Leaders were recruited, and the total number of people in the Institute increased from approximately 100 to over 450.

In 2013, IMM included 36 cutting-edge laboratories working in a broad range of fields that encompass multidisciplinary approaches ranging from basic to clinical and translational research. Altogether, 217 researchers holding a PhD degree and 83 PhD students work at IMM. Their expertise covers Cell and Developmental Biology, Immunology, Infection, Neurosciences and Oncobiology. Research at IMM is also clinically oriented and addresses the major disease areas of the XXIth century – from cancer to Alzheimer and stroke, arthritis, HIV/AIDS, or malaria.

We do not share the pessimistic view about the risk of "brain drain" in our country. In fact we are actually a case of "brain gain": the enthusiasm and vibrant atmosphere at our institute have managed to attract 37 talented scientists from 15 nations and four different continents, as well as Portuguese nationals returning from abroad.

We are pleased to highlight some of IMM's accomplishments in 2013. We would like to emphasize the increasing number of scientific papers published in high impact journals and internationally registered patents. IMM researchers continued to succeed in attracting international competitive funds to the Institute. Namely, Edgar Gomes was awarded a European Research Council Starting Grant, Henrique Veiga-Fernandes received an Innovator Award of the Kenneth Rainin Foundation, and Miguel Prudêncio was awarded a Phase II Bill & Melinda Gates Foundation Grant. IMM researchers were also highly appraised at national level: Prémio Pessoa was awarded to Maria Mota, Prémio Pfizer to Luís Moita, Prémio BES Inovação to Miguel Prudêncio, and Prémio Dona Antónia Ferreira to Carmo Fonseca.

The success of IMM relies on hard work and creativity of dedicated researchers, students, administrators and support teams. We do believe that we should aim to more and better science, so you can put the new knowledge to serve our main goals – the better understanding of disease and the development of new strategies of diagnosis and cure.

In September 21st we celebrated our X anniversary with a special meeting with our major stakeholders, in the presence of Paulo Macedo, the Minister of Health, and Leonor Parreira, Secretary of State for Science, dedicated to the topics: The convergence in life sciences; Basic and applied science: duel or duet; Teaching Medicine teaching Science: is there a difference. In December 13th we had a wonderful party for all the people that work at IMM and their families.

We are very fortunate that the IMM has been able to build an identity which combines excellence in research, cooperation between its scientists, openness in its management decisions, and an overall feeling of pride for what it has achieved to overcome the difficult challenges of our time and an immensurable joy in searching for answers to the problems that affect the patients we care, and unrevealing mysteries of the sciences of life.

BOARD OF TRUSTEES

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Quality and Safety in Laboratory

Research Support Services

Animal Facilities

Bioimaging

Biosafety Level 3 Laboratory

Flow Cytometry

Histology

IMM Biobank

Education & Advanced Training

SCIENTIFIC ADVISORY COMMITTEES

Undertake periodic evaluations to the IMM specific programmes and include international experts of scientific fields analysed.

CELL AND DEVELOPMENTAL BIOLOGY PROGRAMME (2013)

John G Gribben, Queen Mary's School of Medicine, University of London, UK

Petra Schwille, Max-Planck-Institute of Biochemistry, Germany

Phillippe Pierre, Centre d'Immunologie de Marseille-Luminy, France

Fiona Watt, King's College London, UK

NEUROSCIENCES PROGRAMME (2010)

Michael Spyer, University College London, UK

Christine Gall, University of California, USA

Charles Warlow, Western General Hospital, Edinburgh, UK

Reinhard Dengler, Medizinische Hochschule, Hannover, Germany

IMMUNOLOGY AND INFECTIOUS DISEASES PROGRAMME (2009)

Anne O'Garra, National Institute for Medical Research, UK

Alain Fischer, Hôpital Necker Enfants Malade, Paris, France

William Paul, National Institute of Allergy and Infectious Diseases, NIH, USA

Philippe Sansonetti, Institut Pasteur, France

Antonio Freitas, Institut Pasteur, France

IMM AT A GLANCE

TOPICS OF INTEREST

T cell Homeostasis
Immune tolerance
Innate Immunity
Inflammation
Malaria
HIV/AIDS
Host-pathogen interactions
Stroke
Parkinson's disease
Amyotrophic lateral sclerosis
Cognitive decline
RNA biology
Regulation of gene expression
Stem cells
Tissue and organ regeneration
Haematopoiesis
Angiogenesis
Metastasis
Osteoporosis and Arthritis
Drug discovery

TOTAL RESEARCHERS

457

with PhD
217

PhD Students
83

MSc Students
43

Bachelor Students
114

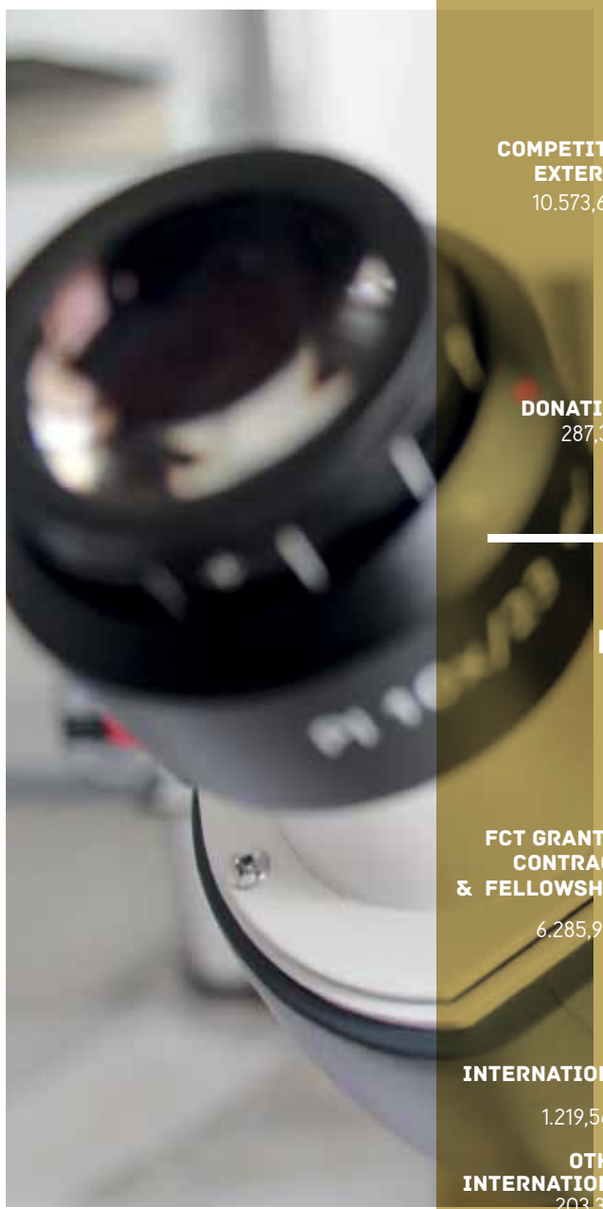
International Research Fellows
37

RESEARCH UNITS

36

START-UPS

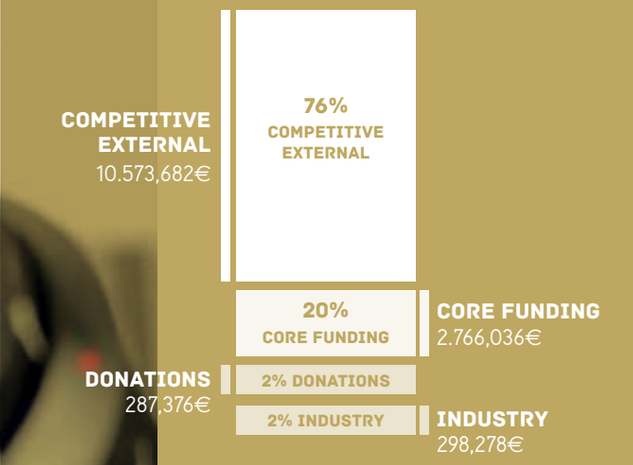
4



IMM HIGHLIGHTS 2013

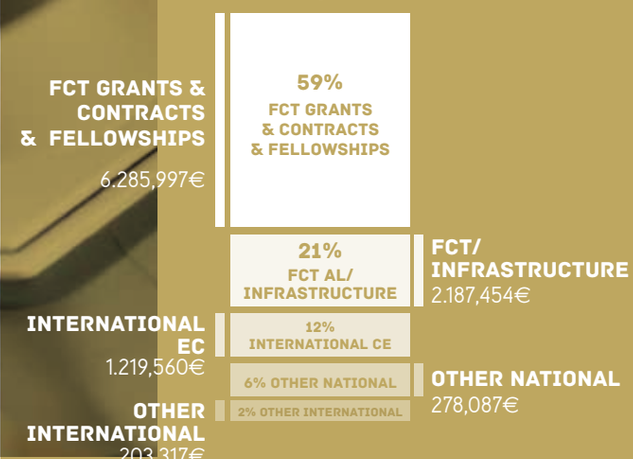
TOTAL EXPENDITURE
IN EUROS

13.925,388€



COMPETITIVE EXTERNAL FUNDING
IN EUROS

10.573,698€



RESEARCH HIGHLIGHTS

PAPERS 2013

23 publications in journals with an impact factor higher than 10

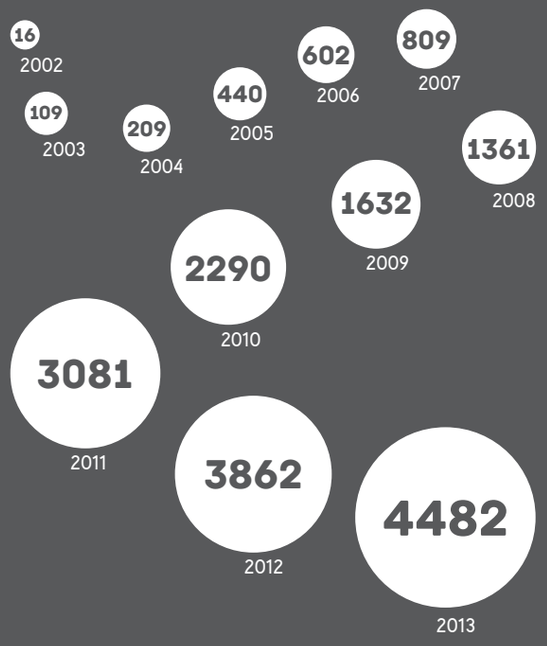
305 papers published in peer reviewed journals

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

20.233

SUM OF THE TIMES CITED PAPERS

CITATIONS PER YEAR



Note: This data is based on the information available on the Web of Science, hence it is not an exhaustive analysis of IMM publications

MOST RELEVANT PAPERS

Melo-Cristino J., C. Resina, V. Manuel, L. Lito, M. Ramirez. 2013. First case of infection with vancomycin-resistant Staphylococcus aureus in Europe. *The Lancet*. 382,205 (http://www.ncbi.nlm.nih.gov/pubmed/23791472)

Amaral M, Levy C, Heyes DJ, Lafite P, Outeiro TF, Giorgini F, Leys D, Scrutton NS (2013) Structural basis of kynurenine 3-monooxygenase inhibition. *Nature*. April 2013 496, (7445), 382-5. doi: 10.1038/nature12039.

Plenge RM, Greenberg JD, Mangravite LM, Derry JM, Stahl EA, Coenen MJ, Barton A, Padyukov L, Klareskog L, Gregersen PK, Mariette X,Moreland LW, Bridges SL Jr, de Vries N, Huizinga TW, Guchelaar HJ; International Rheumatoid Arthritis Consortium (INTERACT), Friend SH,Stolovitzky G. Collaborators: Cui J, Stahl EA, Saevarsdottir S, Miceli C, Diogo D, Mirkov, Canhao H, Ikari K, Terao C, Okada Y, Wedrï S, Askling J, Yamanaka H,Momohara S, Taniguchi A, Ohmura K, Matsuda F, Mimori T, Gupta N, Kuchroo M, Morgan AW, Isaacs JD, Wilson AG, Hyrich KL,Herenius M, Doorenspleet ME, Tak PP, Crusius JB, van der Horst-Bruinsma IE, Wolbink GJ, van Riel PL, van de Laar M, Guchelaar HJ,Shadick NA, Allaart CF, Huizinga TW, Toes RE, Kimberly RP, Bridges S Jr, Criswell LA, Moreland LW, Fonseca E, de Vries N,Raychaudhuri S, Weinblatt ME, Gregersen PK, Mariette X, Barton A, Alfredsson L, Klareskog L, Padyukov L, Coenen MJ, Karlson EW,Kremer J, Greenberg JD, Plenge RM. (2013) Crowdsourcing genetic prediction of clinical utility in the Rheumatoid Arthritis Responder Challenge. *Nat Genet*. 45, (5):468-9.

Stephanie Fanucchi, Youtaro Shibayama, Shaun Burd, Marc S Weinberg, Musa M Mhlanga (2013) Chromosomal Contact Permits Transcription between Coregulated Genes. *Cell* 155, 505 www.cell.com.

Schmolka N, Serre K, Grosso AR, Rei M, Pennington DJ, Gomes AQ, Silva-Santos B. 2013 Epigenetic and transcriptional signatures of stable versus plastic differentiation of proinflammatory gd T cell subsets. *Nat Immunol*. 14, (10):1093-100.

Liehl P, Zuzarte-Luís V, Chan J, Zillinger T, Baptista F, Carapau D, Konert M, Hanson KK, Carret C, Lassnig C, Müller M, Kalinke U, Saeed M, Chora AF, Golenbock DT, Strobl B, Prudêncio M, Coelho LP, Kappe SH, Superti-Furga G, Pichlmair A, Vigário AM, Rice CM, Fitzgerald KA, Barchet W, Mota MM. 2014. Host-cell sensors for Plasmodium activate innate immunity against liver-stage infection. *Nat Med* 20(1), 47-53

Ederle J, Davagnanam I, van der Worp HB, Venables GS, Lyrer PA, Featherstone RL, Brown MM, Jäger HR; ICSS investigators. Effect of white-matter lesions on the risk of periprocedural stroke after carotid artery stenting versus endarterectomy in the International Carotid Stenting Study (ICSS): a prespecified analysis of data from a randomised trial. *The Lancet Neurology* 2013; 866-872.

Nuno Figueiredo, Angelo Chora, Helena Raquel, Nadja Pejanovic, Pedro Pereira, Björn Hartleben, Ana Neves-Costa, Catarina Moita, Dora Pedroso, Andreia Pinto, Sofia Marques, Hafeez Faridi, Paulo Costa, Raffaella Gozzelino, Jimmy L. Zhao, Miguel P. Soares, Margarida Gama-Carvalho, Jennifer Martinez, Qingshuo Zhang, Gerd Döring, Markus Grompe, J. Pedro Simas, Tobias B. Huber, David Baltimore, Vineet Gupta, Douglas R. Green, João A. Ferreira and Luis F. Moita. Anthracyclines induce DNA damage response-mediated protection against severe sepsis, *Immunity* 39(5), 874-84

Dias RB, Rombo DM, Ribeiro JA, Henley JM, Sebastião AM (2013) Adenosine: setting the stage for plasticity. *Trends in Neuroscience* 36, 248-257.

Coquet J*, Ribot JC*, Babala N, Middendorp S, Xiao Y, Neves JF, Fonseca-Pereira D, Jacobs H, Pennington DJ, Silva-Santos B** and Borst J** (2013). Epithelial and dendritic cells in the thymic medulla promote CD4+ Foxp3+ regulatory T cell development via the CD27-CD70 pathway. *Journal of Experimental Medicine*. 210, (4):715-28. (*Co-first Authors; **Co-senior Authors)

Batalha VL, Pego JM, Fontinha B, Costenla AR, Valadas J, Baqi Y, Radjainia H, Müller CE, Sebastião AM, Lopes LV (2013). Adenosine A2A receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation. *Molecular Psychiatry* 18, 320-331.

Oliveira VG, Agua-Doce A, Curotto de Lafaille M, Lafaille JJ, Graca L. (2013) Adjuvant facilitates anti-CD4 mediated immune tolerance to recombinant factor VIII in hemophilia through a Foxp3-independent mechanism that relies on IL-10, *Blood* 121, 3938.

Correia NC, Durinck K, Leite AP, Ongenaert M, Rondou P, Speleman F, Enguita FJ, Barata JT (2013). Novel TAL1 targets beyond protein-coding genes: identification of TAL1-regulated microRNAs in T-cell acute lymphoblastic leukemia. *Leukemia* 27(7). 1603-6. doi: 10.1038/leu.2013.63.

A. Lonetti*, I.L. Antunes*, F. Chiarini, E. Orsini, F. Buontempo, F. Ricci, P.L. Tazzari, P. Pagliaro, F. Melchionda, A. Pession, A. Bertaina, F. Locatelli, J.A. McCubrey, J.T.Barata**, A.M. Martelli** (2013). Activity of the pan-class I phosphoinositide 3-kinase inhibitor NVP-BKM120 in T-cell acute lymphoblastic leukemia. 2013 Dec 6. doi: 10.1038/leu.2013.369. *co-first authors; ** co-corresponding authors

F. Buontempo, E. Orsini, L.R. Martins, I. Antunes, A. Lonetti, F. Chiarini, G. Tabellini, C. Evangelisti, C. Evangelisti, F. Melchionda, A. Pession, A. Bertaina, F. Locatelli, J.A. McCubrey, A. Cappellini, J.T. Barata, A.M. Martelli. (2013). Cytotoxic activity of the casein kinase 2 inhibitor CX-4945 against T-cell acute lymphoblastic leukemia: targeting the unfolded protein response signaling. *Leukemia*.

L.R. Martins, P. Lúcio, A. Melão, I. Antunes, B.A. Cardoso, R. Stansfield, M.T. Bertilaccio, P. Ghia, D. Drygin, M.G. Silva, J.T. Barata (2013). Activity of the clinical-stage CK2-specific inhibitor CX-4945 against chronic lymphocytic leukemia. *Leukemia* 2013

Castro RE, Ferreira DM, Afonso MB, Borralho PM, Machado MV, Cortez-Pinto H, Rodrigues CM. miR-34a/SIRT1/p53 is supressed by Ursodeoxycholic acid in rat liver and activated by disease severity in human non-alcoholic fatty liver disease. *J Hepatol*. 2013, 58(1), 119-25

Hanson KK, Ressurreição AS, Buchholz K, Prudêncio M, Herman-Ornelas JD, Rebelo M, Beatty WL, Wirth DF, Hänscheid T, Moreira R, Marti M, Mota MM. 2013. Torins are potent antimalarials that block replenishment of Plasmodium liver stage parasitophorous vacuole membrane proteins. *Proc Natl Acad Sci USA* 23;110(30):E2838-47; DOI:10.1073/pnas.1306097110. PMID: 23836641.

Klein Wolterink RG, Serafini N, van Nimwegen M, Vosshenrich CA, de Bruijn MJ, Fonseca Pereira D, Veiga Fernandes H, Hendriks RW, Di Santo JP (2013). Essential, dose-dependent role for the transcription factor Gata3 in the development of IL-5+ and IL-13+ type 2 innate lymphoid cells. *Proc Natl Acad Sci USA*. 110, (25):10240-5.

Machado MV, Cortez-Pinto H. Non-Invasive Diagnosis of Non-Alcoholic Fatty Liver Disease - A Critical Appraisal. *J Hepatol*. 2013, 58, 1007-19

Paiva RS, Lino AC, Caramalho I, Sousa AE, Zelenay S, Demengeot J (2013) Recent thymic emigrants are the preferential precursors of regulatory T cells differentiated in the periphery. *Proc Natl Acad Sci USA* 110, (16):6494-9.

1 YEAR IN THE LIFE OF IMM

JANUARY

L'ORÉAL PORTUGAL AWARD

Ana Catarina Ribeiro project for spinal medulla regeneration in zebra fishes received a 20.000,00 grant, a L'Oréal Portugal Award aimed at young researchers (under 35) who completed their doctoral studies and work in Portugal in the health and environmental areas.

Sérgio Almeida, Gonçalo Bernardes, Cláudio Franco, Luísa Lopes, Maria Mota, Sofia Oliveira, Miguel Prudêncio, Leonor Saúde won the FCT investigator positions.

01

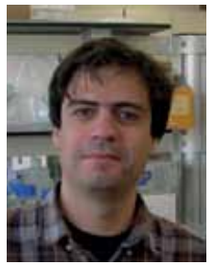
FEBRUARY

PEP2BRAIN:

Selected peptides as drug candidates directed to pain and neurodegeneration. IMM hosted the meeting that included plenary talks from international and national experts.

02

MARCH



SÉRGIO DIAS WON THE 1ST RESEARCH GRANT ON BREAST CANCER – ASSOCIAÇÃO LAÇO: Laço Associação de Solidariedade Social supports scientists working in Portugal to develop basic science research projects looking into the causes of breast cancer and metastatic breast cancer with an annual grant of 25.000€.

HEALTH CLUSTER PORTUGAL *O SECTOR DA SAÚDE: DA RACIONALIZAÇÃO À EXCELÊNCIA.*
IMM hosted and co-organised this meeting that was attended by major health and science stakeholders.

MIGUEL CASTANHO RECEIVED *CIÊNCIA SEM FRONTEIRAS GRANT:* The Ciência Sem Fronteiras (Science Without Borders) Program is a Brazilian program that seeks to promote the consolidation, expansion and internationalisation of science and technology, innovation and competitiveness through the exchange and international mobility.

"ADENOSINE A2A RECEPTOR BLOCKADE REVERTS HIPPOCAMPAL STRESS-INDUCED DEFICITS AND RESTORES CORTICOSTERONE CIRCADIAN OSCILLATION." Luísa Lopes and her team published in Molecular Psychiatry.

GONÇALO BERNARDES designated by an International Selection Committee as the winner of the EFMC Prize for a Young Medicinal Chemist in Academia. This Prize aims to acknowledge and recognize an outstanding young medicinal chemist (<35 years old) working in academia within Europe.

"NOVEL TAL1 TARGETS BEYOND PROTEIN-CODING GENES: IDENTIFICATION OF TAL1-REGULATED MICRORNAS IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA." João Barata and colleagues published in Leukemia.

"CYTOTOXIC ACTIVITY OF THE CASEIN KINASE 2 INHIBITOR CX-4945 AGAINST T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA: TARGETING THE UNFOLDED PROTEIN RESPONSE SIGNALLING" João Barata published another paper in Leukemia.

03

APRIL

The Association for Psychological Science elected Tiago Maia as a **RISING STAR** of the world scientific psychology.

"STRUCTURAL BASIS OF KYNURENINE 3-MONOOXYGENASE INHIBITION." Tiago Outeiro and his team published in Nature a paper about neurodegenerative diseases such as Huntington's, Alzheimer's and Parkinson's.

"ADJUVANT FACILITATES ANTI-CD4 MEDIATED IMMUNE TOLERANCE TO RECOMBINANT FACTOR VIII IN HEMOPHILIA THROUGH A FOXP3-INDEPENDENT MECHANISM THAT RELIES ON IL-10." Luís Graça and his team had their paper published in Blood journal.

"ADENOSINE: SETTING THE STAGE FOR PLASTICITY" Ana Sebastião and her team published an article at Trends in Neuroscience.

"EPITHELIAL AND DENDRITIC CELLS IN THE THYMIC MEDULLA PROMOTE CD4+ FOXP3+ REGULATORY T CELL DEVELOPMENT VIA THE CD27-CD70 PATHWAY." Julie Ribot and Bruno Silva-Santos study (as co-authors) on the role of the CD27 signaling in promoting thymic development of regulatory T cells was published in the Journal of Experimental Medicine.

04

MAY

Kirsten Hanson won the **GRAND CHALLENGES EXPLORATIONS BY BILL & MELINDA GATES FOUNDATION**

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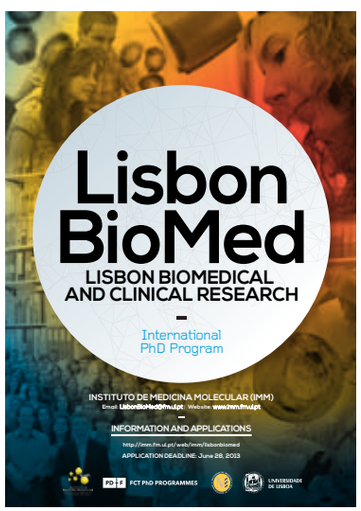
JUNE



LISBONBIOMED PHD PROGRAM
Launch of the new PhD program.

JULY

M. Carmo-Fonseca awardee with **D. ANTÓNIA ADELAIDE FERREIRA PRIZE:** Prize awarded for distinction of a personality by his entrepreneurial spirit, leadership, openness to innovation and creativity, sense of public service and social sensitivity.

Henrique Veiga-Fernandes received an **INNOVATOR AWARD OF THE KENNETH RAININ FOUNDATION:** The research project "Control of innate lymphoid cells and intestinal homeostasis by neurotrophic factors" was selected to receive the Innovator Award of the Kenneth Rainin Foundation (KRF) of $100.000 over one year period.

EMBO YOUNG SCIENTISTS FORUM 2013: The EMBO Young Scientists' Forum is aimed to bring together young European researchers in order to motivate and inspire students to pursue their career and education in life sciences. The meeting provided the opportunity to European and Portuguese Ph.D. students, post-docs and junior investigators to interact with Europe's most promising young scientists, members of the EMBO Young Investigator Programme.

Mário Ramirez and colleagues published the paper **"FIRST CASE OF INFECTION WITH VANCOMYCIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN EUROPE"** in The Lancet.

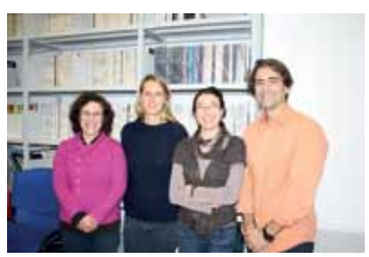
Claudio Areias Franco, Daniel Carapau, Filipa Cruz, Hakan Norell, Julie Ribot, Kirsten Hanson, Maria José Diógenes, Russell Foxall, Sandra Martins and Sales Ibiza received an **IC&DT FELLOWSHIP**.

Fabien Guegan received a **POST-DOCTORAL FELLOWSHIP OF THE AXA RESEARCH FUND.**

AXA Research Fund
Through Research, Protection

08

AUGUST



Bruno Silva-Santos, Nina Schmolka, Karine Serre, Anita Gomes, Ana Rita Grosso and Margarida Rei **UNVEILED THE MOLECULAR "RULES" THAT CONTROL THE GENERATION AND MAINTENANCE OF AN IMPORTANT POPULATION OF IMMUNE CELLS** and this work was published online in Nature Immunology.

João Barata and colleagues published in Leukemia the paper **"ACTIVITY OF THE CLINICAL-STAGE CK2-SPECIFIC INHIBITOR CX-4945 AGAINST CHRONIC LYMPHOCYTIC LEUKEMIA".**

SEPTEMBER

3RD GLOBAL CANCER GENOMICS CONSORTIUM SYMPOSIUM: FROM ONCOGENOMICS TO CANCER: Instituto de Medicina Molecular, affiliated with Faculdade de Medicina da Universidade de Lisboa, hosted the 3rd Global Cancer Genomics Consortium Symposium, a consortium of research institutions from the U.S., UK, India, Japan and Portugal.

IMM 10TH ANNIVERSARY CONFERENCE: In September 21st IMM celebrated the 10th anniversary with a special meeting with major stakeholders, in the presence of Paulo Macedo, the Minister of Health, and Leonor Parreira, Secretary of State for Science, dedicated to the topics: The convergence in life sciences; Basic and applied science: duel or duet; Teaching Medicine teaching Science: is there a difference.

Henrique Veiga-Fernandes won the **ERC PROOF OF CONCEPT** aimed to obtain funding for technological concept evidences.

The paper **"CHROMOSOMAL CONTACT PERMITS TRANSCRIPTION BETWEEN COREGULATED GENES"** by Musa Mlhanga et al was published in Cell.

IMM has participated on **"BIKE TO WORK DAY".**

Ivo Martins, Henrique Veiga-Fernandes, Ana Rita Fragoso, João Barata, Edgar Gomes and Luís Moita won **FCT INVESTIGATOR POSITIONS.**






09 10

OCTOBER

1ST POST-DOC DAY

Inês Rego Figueiredo received a **FUNDAÇÃO ASTRAZENECA INNOVATE COMPETITION FELLOWSHIP.**

Gonçalo Bernardes awarded a **ROYAL SOCIETY OF CHEMISTRY/BMOS YOUNG INVESTIGATOR AWARD.**

NOVEMBER

Miguel Prudêncio team received **PHASE II GRAND CHALLENGES EXPLORATIONS FUNDING**

Miguel Prudêncio won the **PRÉMIO NACIONAL DE INOVAÇÃO BES 2013:** National Innovation Prize to reward and divulge research, development and innovation projects in application areas linked to the endogenous resources of the country, viewing the improvement of products, processes or services.

BIOBANK MEETING: Report of two years of activity of the IMM Biobank and presentation of national and international success case studies of the undertaken partnerships.

"ANTHRACYCLINES INDUCE DNA DAMAGE RESPONSE-MEDIATED PROTECTION AGAINST SEVERE SEPSIS". Luís Moita and his colleagues published an article in Immunity that discovered that anthracyclines induce protection against sepsis.

João Barata was co-author of **"ACTIVITY OF THE PAN-CLASS I PHOSPHOINOSITIDE 3-KINASE INHIBITOR NVP-BKM120 IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA"**, a paper published in Leukemia.

11 12

DECEMBER

7TH IMM/CAML PHD MEETING

Maria Mota awardee of **PRÉMIO PESSOA 2013:** Prize that aims to highlight personalities of Culture, Arts or Science whose work has achieved featured on national scene.

IMM 10TH ANNIVERSARY PARTY: party for all the people that work at IMM and their families to celebrate the 10th anniversary.

"HOST-CELL SENSORS FOR PLASMODIUM ACTIVATE INNATE IMMUNITY AGAINST LIVER-STAGE INFECTION." Maria Mota and her team published in Nature Medicine a paper that unrevealed that host-cell sensors for Plasmodium activate innate immunity on malaria.

Luís Moita won **PRÉMIOS DE INVESTIGAÇÃO PFIZER 2013**, a prize that aims to stimulate research in Health Sciences in Portugal.

João Rodrigues received the **INITIAL TRAINING NETWORKS (ITN) - MARIE CURIE ACTIONS** to develop Glycopar project.

Edgar Gomes won the **ERC CONSOLIDATOR GRANT** and the **EMBO INSTALLATION GRANT.**

10TH ANNIVERSARY

10 YEARS OF SCIENCE MEETING MEDICINE

2013 was a year of celebration for IMM for its 10th anniversary.

In September 21st we celebrated a decade of our Science meeting Medicine with a special conference with our major stakeholders. In the presence of Paulo Macedo, the Minister of Health, and Leonor Parreira, Secretary of State for Science, and special guests, namely Douglas Lauffenburger, Head of Department of the Biological Engineering at MIT, USA, and Carlos Caldas, from the Cambridge Cancer Centre, UK, our researchers had the opportunity to debate the topics: The convergence in life sciences; Basic and applied science: duel or duet?; Teaching Medicine teaching Science: is there a difference?.

In December 13th we had a wonderful party for all the people that work at IMM and their families. It was a day of celebration as the success of IMM is due to the individual achievements of all past and present members of the IMM Family and everyone had an excellent evening, an historical moment for all at the IMM.

TUBERCULOSIS AND INNATE IMMUNITY | SIGNALING IN CANCER | NUTRITION AND METABOLISM | RNA AND GENE REGULATION | BRAIN, COGNITION, AND MOTOR CONTROL. AUTONOMIC REGULATION AND PERIPHERAL NERVE | PHYSICAL BIOCHEMISTRY OF DRUGS AND TARGETS | ANGIOGENESIS REGULATION AND THERAPEUTIC IMPLICATIONS | TRANSLATIONAL ONCOBIOLOGY | NEUROLOGICAL DISEASES | BIOLOGY OF PARASITISM | ARTHRITIS AND BONE | MOLECULAR VIROLOGY AND APPLIED BIOTECHNOLOGY | LYMPHOCYTE REGULATION | STEM CELLS AND NEUROGENESIS | GENE REGULATION IN THE MALARIA PARASITE | GENE EXPRESSION AND BIOPHYSICS | INNATE IMMUNITY AND INFLAMMATION | BIOLOGY AND PHYSIOLOGY OF MALARIA AND OTHER INFECTIONS | PROTEIN MISFOLDING AND NEURODEGENERATION | MOLECULAR MICROBIOLOGY AND INFECTION | ERYTHROCYTE, LEUKOCYTE RECRUITMENT AND INFLAMMATION | BIOMEMBRANES AND NANOMEDICINE | EMBRYONIC DEVELOPMENT AND REGENERATION | NEURONAL COMMUNICATION AND SYNAPTOPATHIES | T-CELL DIFFERENTIATION AND TUMOR TARGETING | HERPES VIRUS PATHOGENESIS | HUMAN IMMUNODEFICIENCY AND IMMUNE RECONSTITUTION | LYMPHOCYTE FUNCTION AND DEVELOPMENT

RESEARCH LABS

SÉRGIO ALMEIDA

LAB

PhD (2007) in Biomedical Sciences at University of Porto.
Post-doctoral research (2007-2013) at Instituto de Medicina Molecular.

Sérgio Fernandes de Almeida | Group Leader
sergioalmeida@medicina.ulisboa.pt

Alexandra Coitos Vítor Technician | **Ana Filipa Batalha Martins** Technician | **Ana Rita Fialho Grosso** Post-doctoral Investigator | **Ioana Posa** MSc Student | **Joana Patrícia Moreira Tavares** MSc Student | **S R Chaitanya Sridhara** PhD Student | **Silvia Filipa Camoeira Gonçalves de Carvalho** Technician

Chromatin dynamics and DNA damage response

Our research focuses on the mechanisms that control chromatin dynamics during transcription and DNA damage repair and how they coordinate with the processes that safeguard the genome integrity. Our general aims are twofold: first, we aim at investigating molecular aspects of the different stages of the transcription cycle, focusing on pre-mRNA processing and chromatin modification events; in addition, we study the molecular mechanisms that sense, signal and repair DNA damage. A major focus of our research is to understand how changes in transcription, pre-mRNA processing, chromatin modification and DNA damage response are linked to the development of human diseases such as cancer.

Research Areas

Chromatin dynamics, Epigenetics, Cancer Biology, DNA damage response.

Major scientific achievements

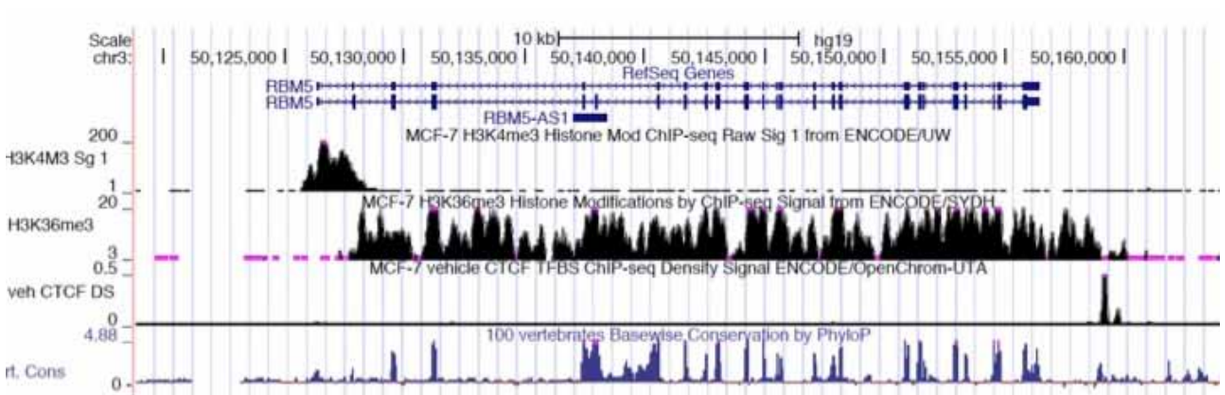
In 2013 the members of our Lab have:

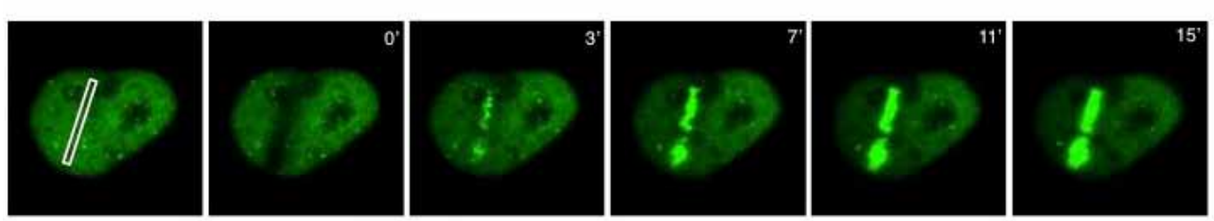
- Published an original manuscript in the international journal "Nucleic Acids Research" (Carvalho et al. 2013);
- Been elected Associate Members of the European network of excellence "EpiGeneSys";
- Started a new research project funded by FCT;
- Presented our research work in seven national and international conferences;
- Been awarded the "Best Poster Award" at the IMM PhD students meeting;
- Completed one MSc thesis.

Recent Most Relevant Publications

Carvalho S, Raposo AC, Martins FB, Grosso AR, Sridhara SC, Rino J, Carmo-Fonseca M, de Almeida SF (2013) Histone methyltransferase SETD2 coordinates FACT recruitment with nucleosome dynamics during transcription. *Nucleic Acids Research* **41**, 2881-93. (Journal IF: 8.3, Citations: 7)

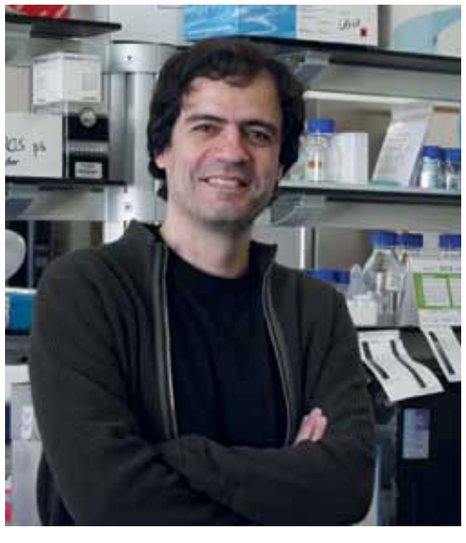
de Almeida SF, Carmo-Fonseca M (2012) Design principles of interconnections between chromatin and pre-mRNA splicing. *Trends in Biochemical Sciences* **37**, 248-53. (Journal IF: 13.1 (2012 IF), Citations: 14)





de Almeida SF, Grosso AR, Koch F, Fenouil R, Carvalho S, Andrade J, Levezinho H, Gut M, Eick D, Gut I, Andrau JC, Ferrier P, Carmo-Fonseca M (2011) Splicing enhances recruitment of methyltransferase HYPB/Setd2 and methylation of histone H3 lysine 36. *Nature Structural and Molecular Biology* **18**, 977-83. (Journal IF: 12.7 (2011 IF), Citations: 47)

de Almeida SF, Garcia-Sacristan S, Custodio N and Carmo-Fonseca M (2010) A link between nuclear RNA surveillance, the human exosome and RNA polymerase II transcriptional termination. *Nucleic Acids Research* **38**, 8015-26. (Journal IF: 7.8 (2010 IF), Citations: 19



JOÃO BARATA

LAB

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

João Taborda Barata | Group Leader
joao_barata@ medicina.ulisboa.pt

Understanding the development of cancer

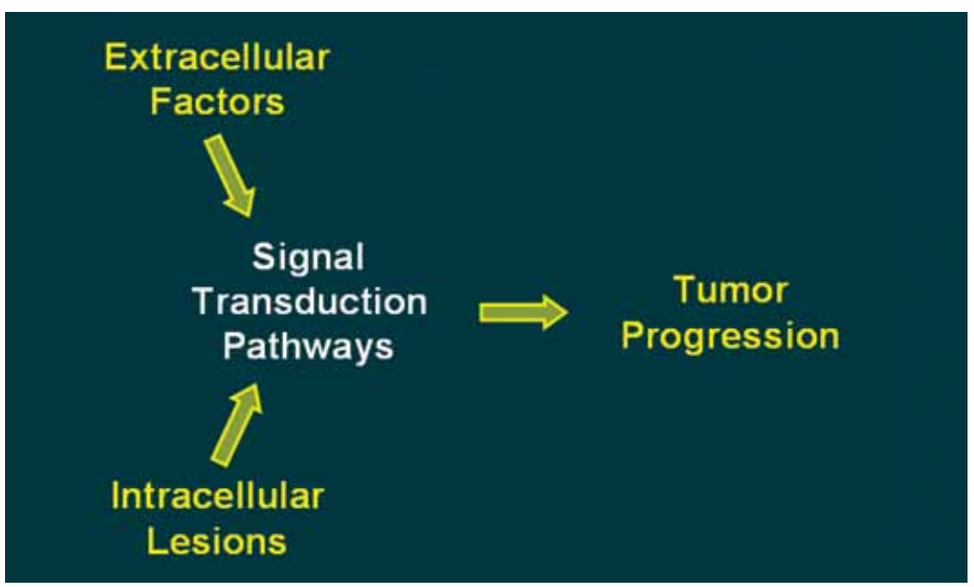
We aim to understand the role of cell-autonomous alterations and microenvironmental cues in the development of cancer, in particular lymphoid leukemias. We focus on the dissection of signaling pathways activated by cell-intrinsic events and extra-cellular factors to characterize the mechanisms implicated in the acquisition of a selective advantage by malignant cells. To do so, we integrate different biochemical, cellular and molecular biology techniques with appropriate in vitro and in vivo models. The basic and pre-clinical research performed in the lab is translation-oriented and complemented by ongoing collaborations with clinicians. Ultimately, our research aims to identify and characterize molecular targets for the development of novel, more selective therapies against cancer.

Research Areas

Oncobiology, Leukemia, Signal transduction, Cellular and molecular biology.

Major scientific achievements

Previously, we showed that PI3K/Akt signaling is hyperactivated in T-ALL and CLL due to CK2 overexpression. We now demonstrated that clinical-grade inhibitors of CK2 or PI3K delay tumor progression in vivo in pre-clinical models of T-ALL and CLL (Martins et al, *Oncotarget* 2013; Martins et al, *Leukemia* 2013; Lonetti, Antunes et al, *Leukemia* 2013; Buontempo et al, *Leukemia* 2013). These observations should contribute to the integration of CK2 and PI3K specific inhibitors in the therapeutic arsenal against these malignancies.



Alice Sofia dos Santos Melão PhD Student | **Ana Rita Freitas Martins de Matos Fragoso** Post-doctoral Investigator | **Ana Sofia Gírio Veloso** Post-doctoral Investigator | **Daniel Ribeiro** PhD Student | **Inês Lopes Antunes** Investigator | **Joana Filipa Pereira de Matos** MSc Student | **João Paulo Tavanez da Silva Fernandes** Post-doctoral Investigator | **Leila Raquel Galveias Casquinha Pires Martins** Post-doctoral Investigator | **Maria Leonor Saraiva de Carvalho Morais Sarmento** Post-doctoral Investigator | **Mariana Lobato de Oliveira** MSc Student | **Vanda Cristina Barroso Póvoa** Investigator

We identified several microRNA genes (e.g. miR-223, miR-146b-5p) that are regulated by SCL/TAL1, a transcription factor which is aberrantly expressed in T-ALL (Correia et al, *Leukemia* 2013). This is the first contribution to the understanding of the network of microRNA genes modulated by TAL1 that may contribute to its oncogenic potential.
In 2103 we also received a distinction from the Ministry of Health for our contributions to Biomedical research.

Recent Most Relevant Publications

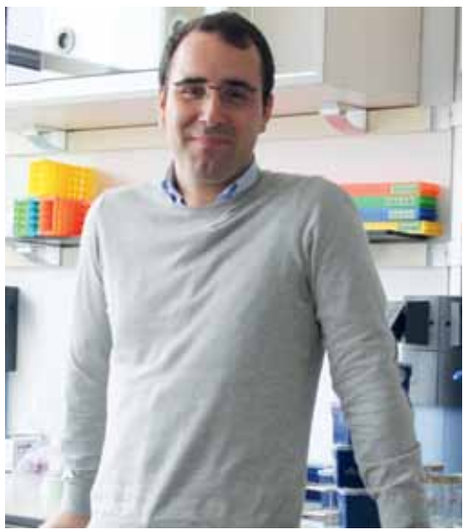
L.R. Martins, P. Lúcio, A. Melão, I. Antunes, B.A. Cardoso, R. Stansfield, M.T. Bertilaccio, P. Ghia, D. Drygin, M.G. Silva, J.T. Barata (2013). Activity of the clinical-stage CK2-specific inhibitor CX-4945 against chronic lymphocytic leukemia. *Leukemia* 2013 Aug 8. doi: 10.1038/leu.2013.232. [Epub ahead of print] (Journal IF: 10.164)

N. Correia, K. Durinck, A.P. Leite, M. Ongenaert, P. Rondou, F. Speleman, F.J. Enguita, J.T. Barata (2013). Novel TAL1 targets beyond protein-coding genes: identification of TAL1-regulated microRNAs in T-cell acute lymphoblastic leukemia. *Leukemia*. **27**, (7):1603-1606. (Journal IF: 10.164)

P.P. Zenatti, D. Ribeiro, W. Li, L.,.., S.K. Durum, J.A. Yunes, J.T. Barata (2011) Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. *Nature Genetics*. **43**, 932. (Journal IF: 35.209, Citations: 40)

A. Silva, J.A. Yunes, B.A. Cardoso, L.R. Martins, P.Y. Jotta, M. Abecasis, A.E. Nowill, N.R. Leslie, A.A. Cardoso, J.T. Barata (2008) PTEN Posttranslational Inactivation and Hyperactivation of the PI3K/Akt Pathway Sustain Primary T Cell Leukemia Viability. *Journal of Clinical Investigation*. **118**, 3762. (Journal IF: 12.812, Citations: 110)

J.T. Barata, A. Silva, J.G. Brandão, L.M. Nadler, A.A. Cardoso, V.A. Boussiotis (2004) Activation of PI3K is Indispensable for Interleukin 7-Mediated Viability, Proliferation, Glucose Use, and Growth of T Cell Acute Lymphoblastic Leukemia Cells. *Journal of Experimental Medicine* **200**, 659. (Journal IF: 13.214, Citations: 103)

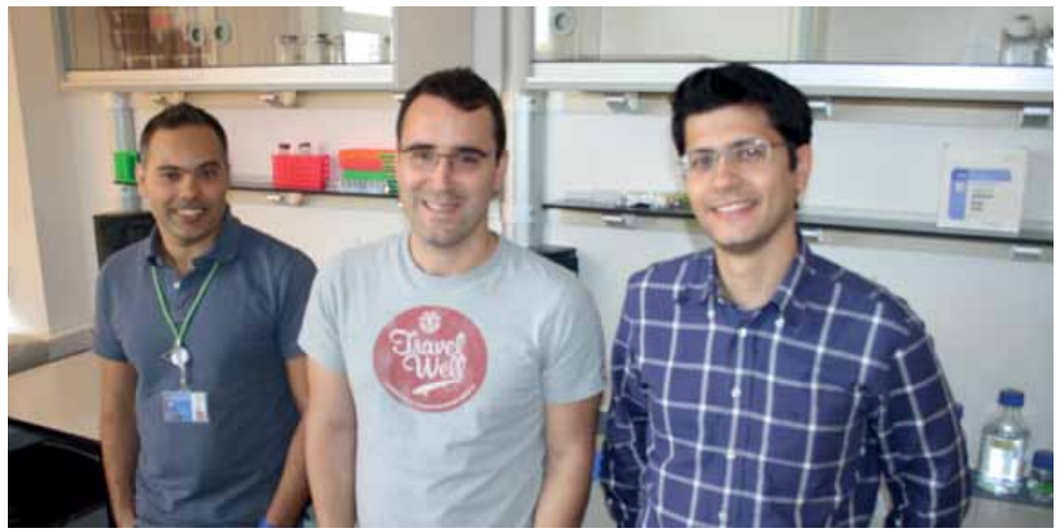


GONÇALO BERNARDES

LAB

DPhil (2008) in Chemical Biology at the University of Oxford, UK.
Post-doctoral studies at the Max-Planck Institute (Berlin, Germany) and ETH Zürich (Swizterland)
Group Leader – Royal Society University Research Fellow at the Department of Chemistry, University of Cambridge, UK since 2013.
Group Leader – Investigador FCT at the Instituto de Medicina Molecular (IMM) since 2013.

Gonçalo José Lopes Bernardes | Group Leader
gbernardes@medicina.ulisboa.pt



João Alexandre Guarita da Silva Rodrigues Principal Investigator | **Miguel Correia Botelho Chaves Ferreira** Technician

At the interfaces of Chemistry and Biology

Our research programme lies under the broader field of Chemical Biology. In particular, we are interested in the development of site-selective and rapid protein modification methods in aqueous systems as a means to understand key biological processes and to generate targeted therapeutics.

Research Areas

Site-selective protein modification, Protein therapeutics, Targeted cancer therapeutics, Carbohydrate-based vaccines, Small molecule drug discovery, Bioorthogonal labelling strategies.

Major scientific achievements

The Lab has made strong contributions in the fields of protein chemistry and protein therapeutics. Just recently, the antibody drug conjugate the PI developed while at the ETH Zürich has reached clinical development.

The PI has published four papers in 2013, published one patent and filled one patent application.

The Lab received funding from Marie Curie CIG, Marie Curie ITN, Investigador FCT 2012, Hovione PhD studentship (to start in 2014).

In 2013 the PI won the European Federation of Medicinal Chemistry – Young Investigator Award in Academia and the 2013 Royal Society of Chemistry/BMOS Young Investigator Award.

For his efforts in translational research, Gonçalo was distinguished by the Portuguese Ministry of Health (MH) of Portugal for relevant services to Public Health and Medicine

Recent Most Relevant Publications

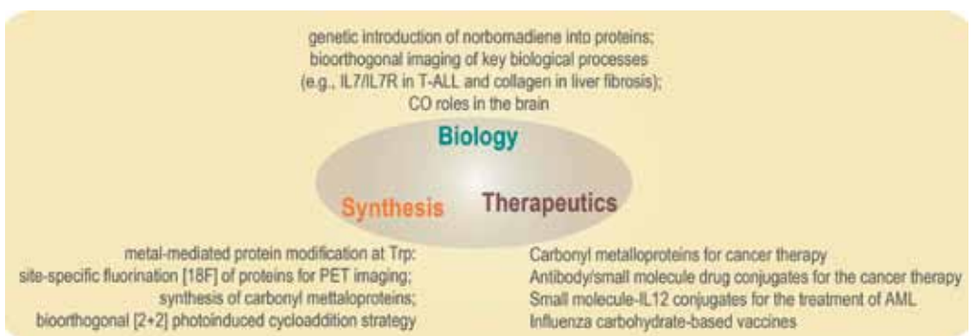
Bernardes, G.J.L.; Steiner, M.; Hartmann, I.; Neri, D.; Casi, G. (2013) Site-specific Chemical Modification of Antibody Fragments with Traceless Cleavable Linkers. *Nature Protocols* **8**, 2079 (Journal IF: 7.96, Citations: 1)

Bernardes, G.J.L.; Casi, G.; Trüssel, S.; Hartmann, I.; Schwager, K.; Scheuermann, J.; Neri, D. (2012) A Traceless Vascular Targeting Antibody-Drug Conjugate for Cancer Therapy. Angew. *Chem. Int. Ed.* **51**, 941 (Journal IF: 13.734, Citations: 23) Selected as a Very Important Paper (VIP).

Santos-Silva, T.; Mukhopadkyay, A.; Seixas, J.D.; Bernardes, G.J.L.*; Romão, C.R.; Romão, M.J. (2011) CORM-3 Reactivity Towards Proteins: The Crystal Structure of a Ru(II) Dicarbonyl-Lysosyme Complex. *J. Am. Chem. Soc.* **133**, 1192 (Journal IF: 10.677, Citations: 33)

Bernardes, G.J.L.; Chalker, J.M.; Errey, J.C.; Davis, B.G. (2008) Facile Conversion of Cysteine and AlkylCysteines to Dehydroalanine: Versatile and Switchable Access to Functionalized Proteins. *J. Am. Chem. Soc.* **130**, 5052. (Journal IF: 10.677, Citations: 104) Article highlighted in: *Nature Chemical Biology*. **4**, 527-528 and Chemical&Engineering News, March 31, 2008.

Bernardes, G.J.L.; Grayson, E.J.; Thompson, S.; Chalker, J.M.; Errey, J.C.; Oualid, F.E.; Claridge, T.D.W.; Davis, B.G. (2008) From Disulfide- to Thioether-linked Glycocoproteins. Angew. *Chem. Int. Ed.* **47**, 2244 (Journal IF: 13.734, Citations: 58)



MARIA ERMELINDA CAMILO

LAB

MD (1965) and PhD (1985) at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Assistant Professor at FMUL.
Retired from Auxiliary Professor FMUL and Consultant of Gastroenterology HSM since June 2008, remains voluntarily as Head of Unit.

Maria Ermelinda Camilo | Group Leader
maria@medicina.ulisboa.pt

Ana Isabel Paulos Ramos de Almeida PhD Student, Teaching Assistant | **Catarina Ferreira Murinello de Sousa Guerreiro** Investigator, Teaching Assistant | **Catarina João Monteiro Ferreira** Investigator | **Dina Raquel Fernandes João** PhD Student, Teaching Assistant | **Helena Maria Ramos Marques Coelho Cortez Pinto** MD/PhD Investigator, Clinical Specialist, Associate Professor | **Inês Vaz Bravo Carretero** MSc Student | **Maria Isabel de Freitas Ferreira Queimado Monteiro Grillo** Principal Investigator, Clinical Department Director | **Mariana Verdelho Machado** PhD Student, MD | **Paula Ravasco** Principal Investigator, Assistant Professor | **Sofia Catarina Carvalhana** Investigator

Nutrition and Metabolism

Clinical and translational biomedical/nutritional research in nutrition/metabolism in tune with investigators' interests. Disease management, nutrition/life-style related risk factors prevail, e.g. nutrition & cancer, nutrition & Quality of Life, metabolic dysfunction, body composition & genetic predisposition for cachexia, nutrients and disease modulation/therapy/prognosis, obesity, fatty liver & insulin resistance. Investigate interconnections with basic science, thus genetic polymorphisms studies of inflammatory/immuno-modulatory cytokines, as pathogenic mechanisms of lesion, nutritional deterioration or metabolic implications; the role of nutrigenetics in cancer and inflammatory diseases, as well as apoptosis in alcoholic/non-alcoholic liver disease.

Research Areas

Hepatology, steatohepatitis, obesity, insulin resistance, Oncology /radiotherapy, sarcopenia, cachexia.

Major scientific achievements

Still the only Research Nutrition and Metabolism Unit in Portugal, its high quality of Advanced Education and Research are widely recognized. Both achievements are highlighted by Publications in Journals with high impact factors and in the internationalization with relevant roles in international bodies, lectures in major international Congresses and advanced teaching. A small multidisciplinary team has reached international recognition via cutting edge research of excellence in two main areas:
Cortez-Pinto H focus on liver fat metabolism, from clinical to translational research, is an internationally recognized expert in steatohepatitis.

Ravasco P is a prized speaker in international meetings as expert in Nutrition and Cancer.

Recent Most Relevant Publications

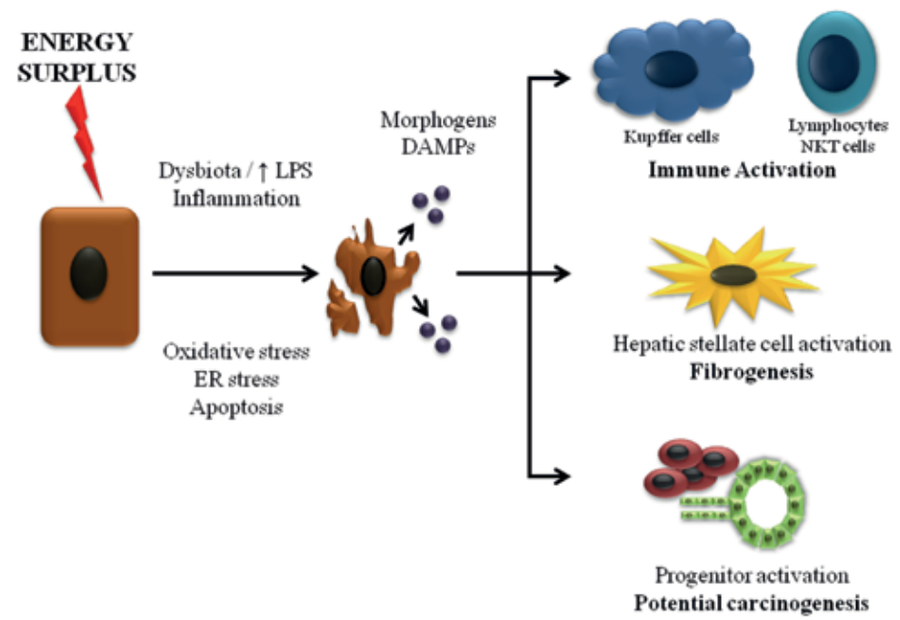
Machado MV, Cortez-Pinto H. Non-Invasive Diagnosis of Non-Alcoholic Fatty Liver Disease - A Critical Appraisal. *J Hepatol*. 2013, **58**, 1007-19 (Journal : 9.858)

Mathurin P, Hadengue A, Bataller R, Addolorato G, Burra P, Burt A, Caballeria J, Cortez-Pinto H, Day CP, Forrest EH, Gual A, Leon DA, Lligona A, Jepsen P, Mueller S, Pageaux GP, Roskams T, Seitz HK, Stickel F, Thursz, Naveau S, Morgan T, Nevens F. (2012) European Association for the Study of Liver. EASL Practical guidelines: management of alcoholic liver disease. *Journal of Hepatology* **57**, 399-420. (Journal IF: 9.858, Citations: 10)

Boléo-Tomé C, Chaves M, Monteiro Grillo I, Camilo ME, Ravasco P. (2011) Teaching nutrition integration: MUST screening in cancer. *The Oncologist* **16**, 239-245. (Journal IF: 4.095, Citations: 3)

Machado MV, Oliveira AG, Cortez-Pinto H. (2010) Hepatic Steatosis in Patients Coinfected with Human Immunodeficiency Virus/Hepatitis C Virus: A Meta-Analysis of the Risk Factors. *Hepatology* **52**, 71-78. (Journal IF: 12.003, Citations: 12)

Ravasco P. (2009) Cancer and nutrition: key determinants of Quality of Life. European *Journal of Cancer* **45**(supl1):409. (Journal IF: 5.061, Citations: 3)



Energy surplus leads to fat accumulation in the hepatocyte promoting oxidative stress, endoplasmic reticulum (ER) stress and apoptosis. The injury of hepatocytes is promoted by an inflammatory state, among other factors, favored by a deregulated gut microbiota and increase in lipopolysaccharide (LPS). Injured and dying hepatocytes release damage associated molecular patterns (DAMPs) and morphogens (e.g. hedgehog and Wnt), that act on the immune system increasing inflammation, in stellate cells and progenitors cells activating them and inducing fibrogenesis and pathways of hepatocarcinogenesis.

MARIA CARMO-FONSECA

LAB

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

Maria Carmo-Fonseca | Group Leader
carmo.fonseca@medicina.ulisboa.pt

RNA and Gene Regulation

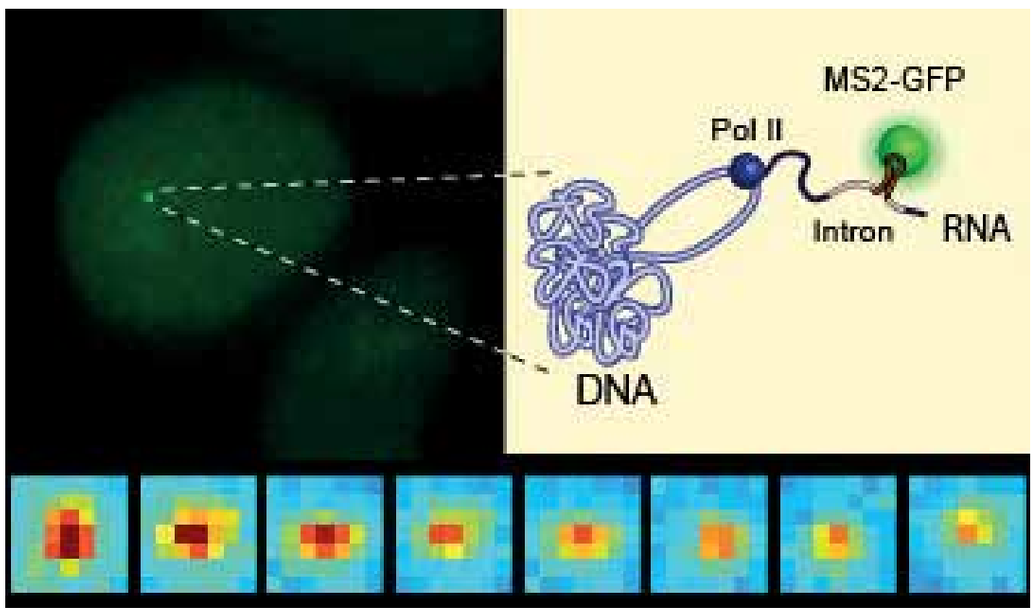
Gene regulation is central to all biology. RNA molecules, with their ability to both encode information and exert catalytic activities, play a key role in the regulation of gene expression. Our group aims to discover molecular pathways and mechanisms implicating RNA in human health and disease. More specifically, we study co-transcriptional mRNA quality control and the role of RNA in the regulation of gene expression in cancer and human aging, and we are exploring new medical applications for RNA.

Research Areas

Cell and Molecular Biology, RNA biology, Non coding RNA, RNA in disease, Cancer, Aging.

Major scientific achievements

How human cells control more than 100,000 alternative splicing decisions remains incompletely understood. To decipher how transcription and splicing occur in real time in the nucleus of living human cells, we combined genomic integration of a single reporter gene, intron labelling with the MS2 technique and spinning disk confocal microscopy. The results show that splicing of beta-globin transcripts is accomplished in 20-30 s. We further show that replacing the weak polypyrimidine tract in mouse IgM pre-mRNA by a U-rich Py decreases the intron lifetime, thus providing direct evidence that splice site strength influences splicing kinetics. We also found that RNA polymerase II transcribes at elongation rates ranging between 3 and 6 kb per minute, and that transcription is rate limiting for splicing. These results have important implications for mechanistic understanding of co-transcriptional splicing regulation in the live-cell context. (Martin, Rino, Carvalho et al. *Cell Rep*, 2013).



Alexandra Coitos Vítor MSc Student | **Ana Catarina de Jesus** Technician | **Ana Paula Santos Botelho Oliveira Leite** Post-doctoral Investigator | **André Daniel Faustino Mesquita** Undergraduate | **Bruno Miguel Bernardes de Jesus** Post-doctoral Investigator | **Catarina Alves do Vale** Undergraduate | **Catarina Pereira Santos** MSc Student | **Célia Carvalho** Investigator, Assistant Professor | **Dinora Levy** Administrative | **Francisco Javier Enguita** Principal Investigator, Assistant Professor | **Joana Desterro** Post-doctoral Investigator, Assistant Professor | **Jorge Gabriel Palma da Luz** MSc Student | **Marina Célia Nunes Ferreira C. H. Silva** Post-doctoral Investigator | **Marisa Cabrita** Lab manager, Assistant Professor | **Miguel Maria das Neves Sousa Pereira** MSc Student | **Noélia Maria Fernandes Custódio** Investigator, Assistant Professor | **Nuno Luís Barbosa Morais** Post-doctoral Investigator | **Paula Sofia Faria Oliveira** PhD Student | **Rita Catarina Vaz Drago** PhD Student | **Rita Mingot de Almeida Mendes de Almeida** PhD Student | **Robert M. Martin** Post-doctoral Investigator | **Sandra Martins** Post-doctoral Investigator, Assistant Professor | **Sérgio Alexandre Fernandes de Almeida** Principal Investigator, Assistant Professor | **Sérgio Manuel Pires Marinho** Technician | **Silvia Filipa Camoeira Gonçalves de Carvalho** Technician | **Teresa Carvalho** Investigator, Assistant Professor | **Tomás Pires de Carvalho Gomes** MSc Student

Recent Most Relevant Publications

Martin, RM, Rino, J, Carvalho, C, Kirchhausen, T, Carmo-Fonseca, M. (2013) Live-cell visualization of pre-mRNA splicing with single-molecule sensitivity. *Cell Reports* **4**(6), 1144-1155. (Journal IF: -, Citations: 0)

de Almeida SF, Grosso AR, Koch F, Fenouil R, Carvalho S, Andrade J, Levezinho H, Gut M, Eick D, Gut I, Andrau JC, Ferrier P, Carmo-Fonseca M (2011) Splicing enhances recruitment of methyltransferase HYPB/Setd2 and methylation of histone H3 Lys36. *Nature Structural & Molecular Biology* **18**, 977-983. (Journal IF: 12.7, Citations: 57)

Martins SB, Rino J, Carvalho T, Carvalho C, Yoshida M, Klose JM, de Almeida SF, Carmo-Fonseca M. (2011) Spliceosome assembly is coupled to RNA polymerase II dynamics at the 3' end of human genes. *Nature Structural & Molecular Biology* **18**, 1115-1123. (Journal IF: 12.7, Citations: 28)

de Almeida SF, García-Sacristan A, Custódio N, Carmo-Fonseca M. (2010) A link between nuclear RNA surveillance, the human exosome and RNA polymerase II transcriptional termination. *Nucleic Acids Research* **38**, 8015-26. (Journal IF: 8.0, Citations: 22)

Grosso AR, Gomes AQ, Barbosa-Morais NL, Caldeira S, Thorne NP, Grech G, von Lindern M, and Carmo-Fonseca M. (2008) Tissue-specific splicing factor gene expression signatures. *Nucleic Acids Research* **36**, 4823-32. (Journal IF: 8.0, Citations: 69)

MIGUEL CASTANHO

LAB

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.

Miguel Castanho | Group Leader
macastanho@medicina.ulisboa.pt

Ana Salomé Rocha do Nascimento Veiga Investigator | **Antónia Rosa Trindade Pinto** Technician | **Diana Maria Diez Gaspar** Post-doctoral Investigator | **Isa Domingues Serrano** Post-doctoral Investigator | **João Miguel Calado da Silva Freire** PhD Student | **Luís Rafael Pereira do Carmo Flores** MSc Student | **Rodrigo Lucarini** PhD Student | **Sandra Cristina Nunes Trigo Pinto** Technician | **Sónia Adelaide Queirós de Sá Santos Rocha** Post-doctoral Investigator | **Tiago Nascimento Figueira** MSc Student | **Vera Luisa Santos Neves** Post-doctoral Investigator

Physical biochemistry of drugs and targets

There are many biological processes that depend on the interaction between peptides/proteins and membrane lipids, such as viral fusion, translocation across epithelial or innate immune defence. Some of these may be inspiring to develop new innovative therapeutic tools. The goal of the Physical Biochemistry Unit is to unravel the physical principles that govern lipid-peptide interactions, with implications in viral fusion (HIV and Dengue virus are of particular interest), analgesia, antimicrobial, and anticancer agents. We are interested not only in drug targets and drug discovery itself, but also in the molecular-level mechanism of action of drugs that are known for their therapeutic efficacy and safety.

Research Areas

Drug discovery, Peptide, Antimicrobials, HIV, Dengue, Blood-brain barrier

Major scientific achievements

The main recent achievements were:

- Demonstration that T20, T1249 and sifuvirtide are anti-HIV molecules that make interactions with lipids as part of their mechanism of action;
- Amidated Kyotorphin and ibuprofen-amidated Kyotorphin exhibit powerful analgesic properties without the severe side effect of opioids;
- Kyotorphin was found in the cerebro spinal fluid (CSF) of humans and its level is decreased in Alzheimers' patients. kyotorphin may be the molecular link between pain and neurodegeneration. Moreover, Kyotorphin is a candidate biomarker for pain. In a parallel study it was demonstrated that Alzheimers' patients underreport the pain they feel, which leads to undertreatment;
- Discovering that viral proteins are sources of peptide-based drug delivery system;
- Elucidation of the role of electrostatics in Blood-brain Barrier translocation of small molecules.

Recent Most Relevant Publications

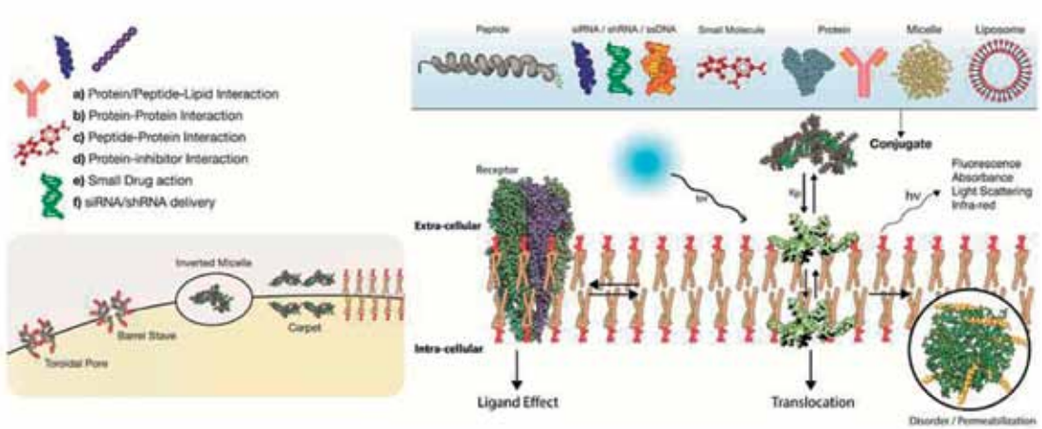
Santos MS, Garcia-Nimo L, Sá Santos S, Tavares I, Cocho JA, Castanho MA. (2013) Neuropeptide kyotorphin (tyrosyl-arginine) has decreased levels in the cerebrospinal fluid of Alzheimer's disease patients: potential diagnostic and pharmacological implications. *Frontiers in Ageing Neurosciences* **5**(68), 1-6. http://www.frontiersin.org/Journal/10.3389/fnagi.2013.00068/abstract. (Journal IF: 5.2, Citations: 0) doi: 10.3389/fnagi.2013.00068.

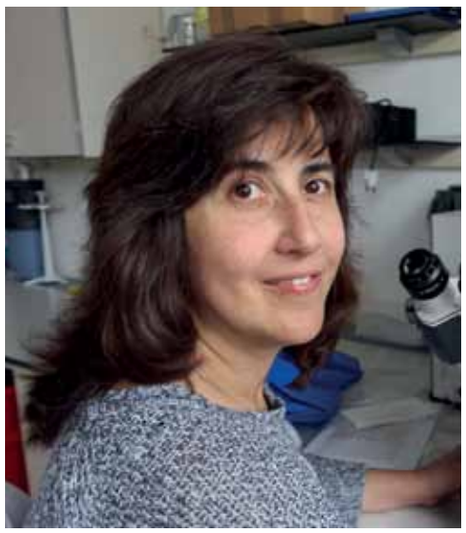
Sinthuvanich C, Veiga AS, Gupta K, Gaspar D, Blumenthal R, Schneider JP. (2012) Anticancer Beta-hairpin peptides: membrane-induced folding triggers activity. *J Am Chem* Soc DOI:10.1021/ja210569f. **14**, 6210. (Journal IF: 9.907, Citations: 16)

Franquelim, HG, Chiantia, S, Veiga, AS, Santos, NC, Schwille, P, Castanho, MARB. (2011) Anti-HIV-1 antibodies 2F5 and 4E10 interact differently with lipids to bind their epitopes. *AIDS* DOI:10.1097/QAD.0b013e328342ff11 **25**, 419. (Journal IF: 6.2, Citations: 13)

Ribeiro, MMB ; Melo, MN ; Serrano, ID ; Santos, NC ; Castanho, MARB (2011) Drug-lipid interaction evaluation: why a 19th century solution? *Trends in Pharm Sciences* DOI:10.1016/j.tips.2010.06.007, **31** (Journal IF: 10.927, Citations: 18)

M. N. Melo, R. ferre and M. Castanho. (2009) Antimicrobial peptides: linking partition, activity and high membrane bound concentrations. Nature Rev. *Microbiology* DOI:10.1038/nrmicro2095, **7**, 245. (Journal IF: 21.182, Citations: 141)





SUSANA CONSTANTINO

LAB

PhD (2001) in Bases Fondamentales de l'Oncogénèse at University of Paris 7, France.
Post-doctoral research at Instituto Português de Oncologia, Lisbon.
Assistant Professor at Faculdade de Medicina da Universidade de Lisboa.

Susana Constantino | Group Leader
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Angiogenesis regulation

Our group The Angiogenesis Group studies molecular and cellular mechanisms that regulate the angiogenic process. Our aim is to interfere with vasculature formation, preventing diseases related with excessive vessel growth or proposing innovative approaches for revascularization in ischemic tissues.

We are particular interested in:

a) Addressing a clinically relevant issue of radiotherapy and investigating the effects of low doses of ionizing radiation on the vasculature that surrounds the tumour area and their contribution to metastasis formation;

b) Evaluating the potential use of low doses of ionizing radiation as a novel approach to improve blood flow in vascular occlusive disease.

Research Areas

Angiogenesis, Ionizing radiation, Ischemia, Vasculature.

Major scientific achievements

In 2013 our Lab achieved:

1- Establishment of a clinical protocol to collect and analyse human irradiated and unirradiated samples from rectal cancer patients aiming the validation of the enhancement of angiogenesis by low doses of IR during radiotherapy;

2- In the setting of experimentally induced hindlimb ischemia, low doses of ionizing radiation could stimulate angiogenesis and collateral development and thereby improve blood perfusion in the ischemic limb. The outcome of these in vivo experiments performed in a mice model suggests that low doses of IR may have clinical use in the treatment of lower limb vascular insufficiency;

3- Transthyretin proteins regulate angiogenesis by conferring different molecular identities to endothelial cells.This work has critical implications in the prevention of early hepatic artery thrombosis in familial amyloidotic polyneuropathy patients after liver transplantation.

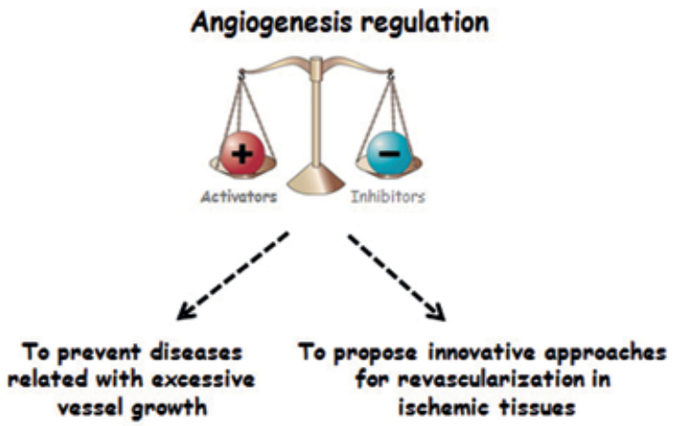
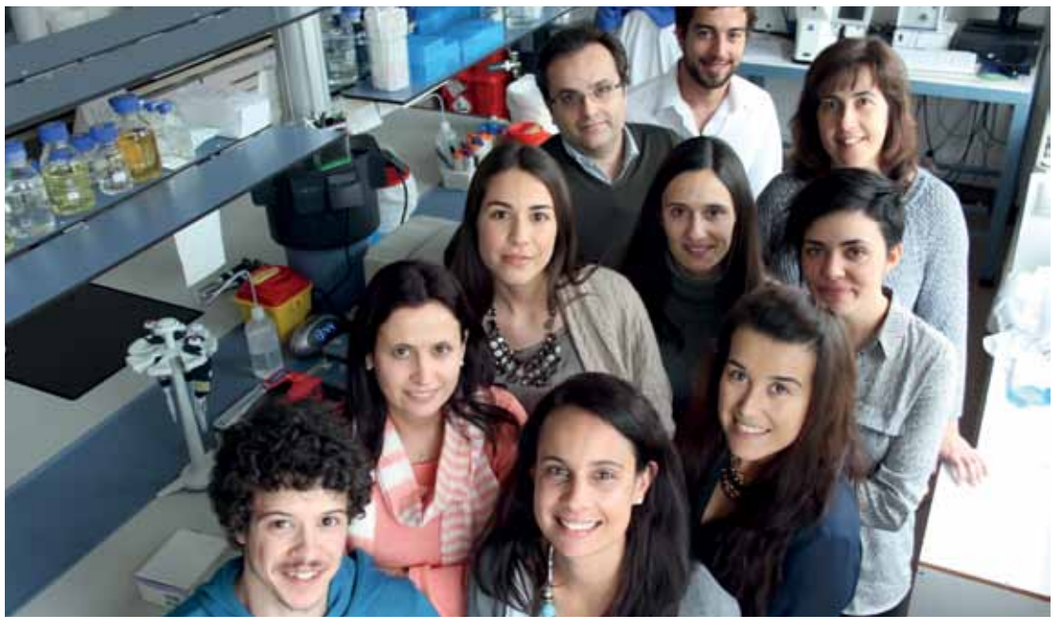


Figure 1: Our goal is to interfere with angiogenesis, regulated by a dynamic balance of activators and inhibitors, in order to prevent diseases related with excessive vessel growth such as cancer or to propose innovative approaches for revascularization in ischemic tissues.



Adriana de Fátima Dias Lisboa Correia MSc Student |**Ana Rita Duarte Simões Pereira** MSc Student | **Augusto Manuel Almeida Ministro** PhD Student | **Carolina Isabel Garcia Cardina** MSc Student |**Filipa Gil Marques** PhD Student | **Paula Alexandra Gomes de Oliveira** PhD Student | **Raquel João Santos Ferreira Nunes** Post-doctoral Investigator | **Tiago Filipe Ribeiro Ruas Maçarico** MSc Student

Recent Most Relevant Publications

Nunes RJ, de Oliveira P, Lages A, Becker JD, Marcelino P, Barroso E, Perdigoto R, Kelly JW, Quintas A. and Constantino Rosa Santos S. (2013) Transthyretin proteins regulate angiogenesis by conferring different molecular identities to endothelial cells. *J Biol Chem* **288**, 31752-60.http://www.jbc.org/content/early/2013/09/12/jbc.M113.469858.full.html#ref-list-1.(Journal IF: 5.023, Citations: 0)

Domingues I, Rino J, Demmers JAA, de Lanerolle P, Constantino Rosa Santos S. (2011) VEGFR2 Translocates to the Nucleus to Regulate Its Own Transcription. *PLoS ONE* **6**, e25668. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0025668. (Journal IF: 4.244, Citations: 11)

Vala I, Martins L, Imaizumi N, Nunes R, Rino J, Kuonen F, Carvalho LM, Rüegg C, Grillo IM, Barata JT, Mareel M and Constantino Rosa Santos S. (2010) Low doses of ionizing radiation promote tumor growth and metastasis by enhancing angiogenesis. *PLoS ONE* **5**, e11222. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0011222. (Journal IF: 4.244, Citations: 16)

Constantino Rosa Santos S, Vala I, Miguel C, Barata J, Garção P, Agostinho P, Mendes M, Coelho A, Oliveira C, Martins e Silva J and Saldanha C. (2007) Expression and subcellular localization of a novel nuclear Acetylcholinesterase protein. *J Biol Chem* **282**, 25597-603. http://www.jbc.org/content/282/35/25597.long. (Journal IF: 5.023, Citations: 25)

Constantino Rosa Santos S and Dias S (2004) Internal and external autocrine VEGF/KDR loops regulate survival of subsets of acute leukemia through distinct signaling pathways. *Blood* **103**, 3883-3889. http://bloodjournal.hematologylibrary.org/content/103/10/3883.long. (Journal IF: 9.338, Citations: 109)

LUÍS COSTA

LAB

MD (1985) and PhD (2002) in Bone metastases at Faculdade de Medicina da Universidade de Lisboa (FMUL).
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Director of Oncology Division at Hospital de Santa Maria – CHLN- Lisboa.

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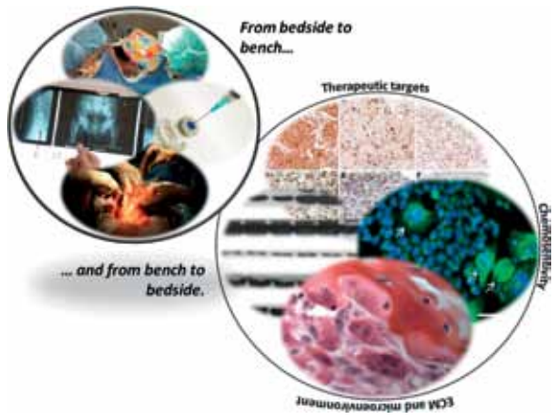
Translational Oncobiology

We direct our research to address at the pre-clinical level the mechanistic effects that explain our major clinical questions. Focusing in metastasis we aim to understand if metastases genetically and phenotypically recapitulate the primary tumors, and how are reflected the tumor-target organ/host interactions. Our major interests are: (I) to identify prognostic and/or predictive markers, and new therapeutic targets in bone metastases; (II) to identify a molecular signature of colorectal cancer metastization, and to determine if chemotherapy-induced cell senescence may be related with relapse; (III) to understand how tumors modulate the sensitivity to antineoplastic agents; and (IV) to identify new therapeutic strategies by studying the role of tumor-associated ECM in cancer progression.



Research Areas

Metastasis, bone vicious cycle, tumor microenvironment, extracellular matrix, tumor heterogeneity, tumoral pathway-targeted therapies.

Major scientific achievements

In 2013 we highlight our participation in the Global Cancer Genomics Consortium. In the scope of GCGC we hosted the The 3rd Global Cancer Genomics Consortium Symposium, at IMM. Our cooperative research originated two publications in 2013, and revealed an essential modifying role of the physiologic level of MTA1 in supporting pulmonary metastasis of breast cancer, and illustrated for the first time the power of RNA-sequencing in revealing the variation landscape of breast transcriptome, exemplifying the analytical strategies to search regulatory interactions among cancer relevant molecules.

We continued to dissect the importance of RANKL-RANK pathway in bone metastases and found that the use of the IAP antagonist AT-406 in the context of bone metastatic disease needs to be carefully monitored for the induction of increased bone resorption, but its combination with anti-RANKL directed therapies could have a beneficial effect, especially in RANK-positive tumors.

Recent Most Relevant Publications

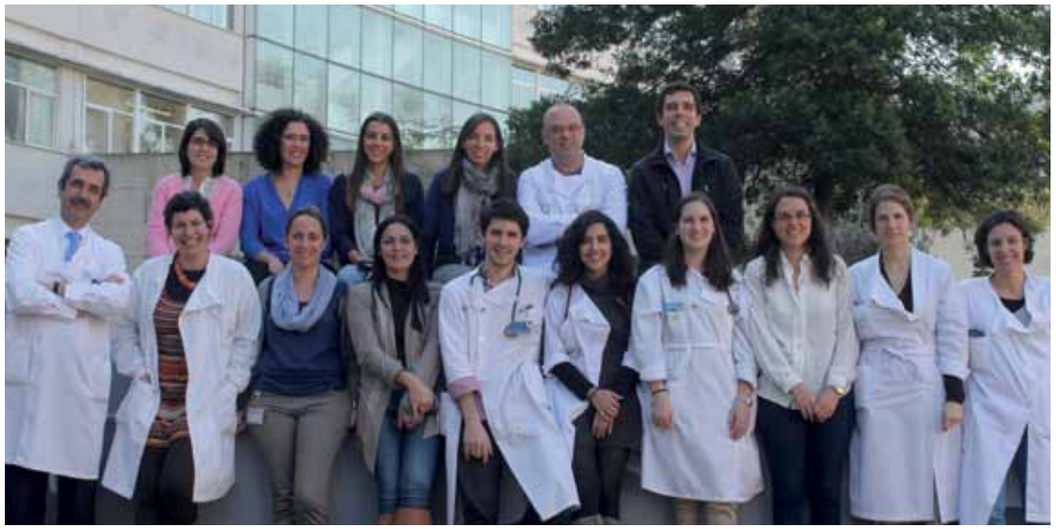
Casimiro S, Mohammad KS., Pires R, Tato-Costa J, Alho I, Teixeira R, Carvalho A, Ribeiro S, Lipton A, Guise TA, Costa L. (2013) RANKL/RANK/MMP-1 Molecular Triad Contributes to the Metastatic Phenotype of Breast and Prostate Cancer Cells In Vitro. *Plos One* **8**, e63153. (Journal IF: 3.730, Citations: 1)

Pakala SB, Rayala SK, Wang RA, Ohshiro K, Mudvari P, Reddy SDN, Zheng Y, Pires R, Casimiro S, Pillai MR, Costa L, Kumar R. (2013) MTA1 Promotes STAT3 Transcription and Pulmonary Metastasis in Breast Cancer. Cancer Research 73(12), 3761-3770 (Journal IF: 8.650; Citations: 0)

Horvath A, Pakala SB, Mudvari P, Reddy SDN, Ohshiro K, Casimiro S, Pires R, Fuqua SAW, Polyak K, Costa L, Toi M, Nair S, Sukumar S, Kumar R (2013) Novel Insights into Breast Cancer Genetic Variance through RNA Sequencing. *Scientific Reports* **3**, 2256. (Journal IF: 2.927, Citations: 0)

Casimiro S, Luis I, Fernandes A, Pires R, Pinto A, Gouveia AG, Francisco AF, Portela J, Correia L, and Costa L (2012) Analysis of a bone metastasis gene expression signature in patients with bone metastasis from solid tumors. *Clin Exp Metastasis* **29**, 155. (Journal IF: 3.524, Citations: 2)

Vaz-Luis I, Winer E, and Lin NU. (2012) Human epidermal growth factor receptor-2 positive Breast Cancer: Does Estrogen Receptor status define two distinct subtypes? *Annals of Oncology* **24**(2), 283. (Journal IF: 6.425, Citations: 0)



Afonso Camilo Rodrigues Fernandes Consultant | **Arlindo Júlio Rebelo da Silva Ferreira** Investigator, MD | **Carolina Coimbra Brandão Alves** Technician | **Diana Domingos de Matos** MSc Student | **Inês Maria Duarte Vaz Luis** Investigator, Teaching Assistant | **Irina Margarida Pereira Machado Alho Duarte** Technician | **Isabel Cristina Ferreira Fernandes Borges da Costa** Investigator, Clinical Specialist, Assistant Professor | **Joana Maria Tato Ribeiro Costa** Technician | **Margarida Caracol Castanho Lopes Matias Ghesquiere** Investigator, Clinical Specialist | **Maria José Palma Bettencourt** Undergraduate | **Mário Alberto Ferreira Maia Matos** MSc Student | **Ricardo Castanheira Pires** Technician | **Sandra Cristina Cana de Anjo Casimiro** Post-doctoral Investigator | **Sandra Sofia Chorão Lavajo Lucas** Administrative | **Sara Santos Henriques** MSc Student | **Teresa Raquel Duarte Pacheco** Post-doctoral Investigator

MAMEDE DE CARVALHO LAB

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.

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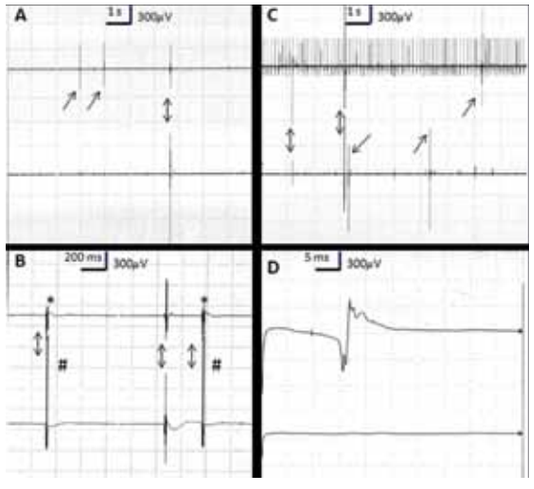
Brain, Cognition and motor control

Our unit focuses on basic, translational, and clinical research on the central, peripheral, and autonomic nervous systems.

We address multiple disorders that span these various levels of the nervous system: amyotrophic lateral sclerosis (ALS), familial amyloid neuropathy (FAP), disorders of autonomic regulation, Tourette syndrome, and neuropsychiatric disorders.

We use a variety of methodologies, including brain imaging, neurophysiological techniques including transcranial magnetic stimulation, clinical cardio-respiratory evaluation, animal models, histochemistry, molecular biomarkers and computational modeling.

We aim to explore the physiology and pathophysiology, but ultimately we are committed to improve the lives of patients.



Research Areas

Amyotrophic lateral sclerosis (ALS), Autonomic Nervous System, Neurophysiology, Neuroimaging computacional models, Tourette syndrome.

Major scientific achievements

Autonomic nervous system (ANS): we have detailed the mechanisms of paroxystic atrial fibrillation and its interplay with ANS dysfunction; novel methods for investigating heart rate variability were developed; the role of sweat tests, laser evoked potentials and sympathetic skin response to detect early changes in familial amyloid polyneuropathy were described. Neurophysiology: fasciculation potentials were set as a very early marker of motor neuron dysfunction in ALS. Neuroimaging computational models: Unknown alterations of frontosatriatal circuits and amygdalar activation in psychopathology, including in Tourette´s syndrome and in attention-deficit/hyperactivity disorder (ADHD) were reported.

Amyotrophic lateral sclerosis (ALS): the impact of non-invasive ventilation and exercise on survival and disease progression was studied, in addition advanced telemetry methods were implemented to control home-ventilation; the influence of ventilation-exercise on VEGF expression were explored.

Recent Most Relevant Publications

Turner MR, Hardiman O, Benatar M, Brooks BR, Chio A, de Carvalho M, Ince PG, Lin C, Miller RG, Mitsumoto H, Nicholson G, Ravits J, Shaw PJ, Swash M, Talbot K, Traynor BJ Van den Berg LH, Veldink JH, Vucic S, Kiernan MC (2013) Controversies and priorities in amyotrophic lateral sclerosis research. *Lancet Neurol* **12**, 310-322. (Journal IF: 23.917, Citations: 34).

Posner J, Marsh R, Maia TV, Peterson BS, Gruber A, Simpson HB (in press) (in press) Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder. Human Brain Mapping. *Human Brain Mapping* DOI: 10.1002/hbm.22371 (Journal IF: 6.878, Citations: 1).

Coelho T, Maia LF, da Silva AM, Cruz MW, Planté-Bordeneuve V, Suhr OB, Conceiçao I, Schmidt HH, Trigo P, Kelly JW, Labaudinière R, Chan J, Packman J,Grogan DR (2013) Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. *Neurology* **260**, 2802-14. (Journal IF: 8.250, Citations: 3).

de Carvalho M, Swash M (2013) Origin of fasciculations in ALS and benign fasciculation syndrome. *JAMA Neuro*, **70**(12), 1562-1565.I (Journal IF: 6.310., Citations: 1)

Couch Y, Anthony, DC, Dolgov O, Revischin A, Festoff B, Santos AI, Steinbusch HW, Strekalova T 2013 Microglial activation, increased TNF and SERT expression in the prefrontalcortex define stress-altered behavior in mice susceptible to anhedonia. *Brain Behav Immun* **29**, 136-46. (Journal IF: 5.612, Citations: 10)

Alberto Albino Granado Escalda Investigator, Assistant Professor | **Ana Rita Mendes Londral Gamboa** PhD Student | **Anabela Leuschner Fernandes Cardoso Pinto Noronha Sanches** Principal Investigator, Consultant, Associate Professor | **Andreia da Silva Borges Carapinha** Technician | **Andrés Díaz Campos** Investigator | **Ângela Raquel Amaro Leal** MSc Student | **Ângelo Rodrigo Neto Dias** MSc Student | **Anna Caroline Marques dos Anjos Braga** PhD Student | **Bruno Miguel Gil Rosa** PhD Student | **Cristiano Torres Tavares dos Santos** Investigator | **Diana Lina Jerónimo da Cunha Reis** Post-doctoral Investigator | **Fernando Manuel Pinto Ferreira Domingos** Investigator, Assistant Professor | **Gabriela Barbu Postolache** Investigator, Assistant Professor | **Inês Antunes de Santa Ana** MSc Student | **Isabel Casanova** MSc Student | **Isabel Conceição** Investigator | **Isabel Maria Teixeira Máxima Graça** Administrative | **João Nuno Marques Parracho Guerra da Costa** Investigator, Assistant Professor | **José Pedro Almeida** PhD Student | **José Castro** Investigator | **Leonel Almeida Luis** PhD Student | **Maria do Amparo Barros** Technician | **Maria Isabel de Sousa Rocha** Principal Investigator | **Mariana Santos Bento** Investigator | **Mário João Martins Oliveira Investigator,** Assistant Professor | **Marisa Brum** MSc Student | **Michael Swash** Investigator, Invited Full Professor | **Nataniel João Gonçalves Cleto Rosa** PhD Student | **Nuno Miguel Prata Gomes** MSc Student | **Pedro Jorge Filipe Pereira** PhD Student | **Pedro Miguel Tojais Rodrigues Alves** PhD Student | **Raquel de Sá da Silva Laires Rua** Technician | **Rita Alexandra Figueira Belo** MSc Student | **Sofia Batalha Reis de Almeida Santos** MSc Student | **Sofia Xavier** MSc Student | **Susana Cristina Da Costa Pinto** Investigator, Assistant Professor | **Tiago Maia Principal** Investigator | **Victor César Ferreira de Moura Gonçalves** Investigator, Assistant Professor

SÉRGIO DIAS

LAB

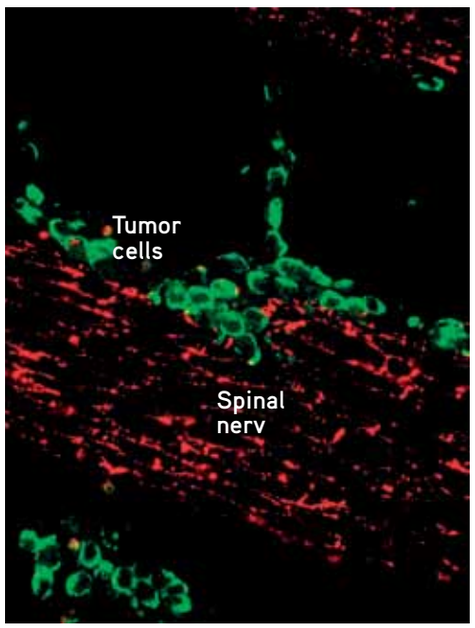
PhD (1998) in Tumor Immunology, University College London, United Kingdom.
Post-doctoral (1999-2001) at the Department of Hematology, Cornell University, New York.
Principal Investigator (2002-2012) and coordinator (2003-2012) of the Molecular Pathobiology Department at Instituto Português de Oncologia Francisco Gentil (IPO Lisboa).
Associate Professor (2012) at the Faculdade de Medicina da Universidade de Lisboa (FMUL).
Principal Investigator/Director (2012) of Neovascularization Unit at Hospital Santa Maria and Instituto de Medicina Molecular-FMUL.

Sérgio Dias | Group Leader
sergiodias@medicina.ulisboa.pt

Ana Cláudia Dourado Clemente MSc Student | **Ana Luísa Ferro Espadanal Torres Magalhães** Post-doctoral Investigator | **Ana Maria Matias de Barros** Post-doctoral Investigator | **Ana Raquel Machado Duarte** MSc Student | **Andreia Cristina Martins Silva Graduate** MSc Student | **Celina Maria dos Reis Parreira** MSc Student | **Germana Andreia Taipa Leandro Domingues** PhD Student | **Inês Mendes Matias** Lab Technician | **Inês Sofia Alvarez Martins** PhD Student | **Joana Cabrita Afonso** PhD Student | **Sandrina Nóbrega Pereira** Post-doctoral Investigator

Role of blood vessels in cancer

We study the role of blood vessels, and of endothelial cells, in regulating normal organ function and in disease. In detail, we study cancer (solid and hematologic) as a systemic disease that involves (and requires) blood vessels for its onset and progression. In addition to the role of blood vessels, we also study the involvement of bone marrow-derived cells and of metabolic systemic signals in cancer onset and progression.



We study cancer as a systemic disease. Here we show green (GFP) tumor cells adhering onto the spinal nerve (red), en route to forming CNS metastases.

Research Areas

Angiogenesis, Tumor spread, Metabolism.

Major scientific achievements

2013 was our first Year at IMM. As major achievements, we would like to highlight the "Laço" Award for Breast Cancer Research (the first Grant to be awarded by Laço) and the publication of the following papers:

- Costa A, Afonso J, Osório C, Gomes AL, Caiado F, Valente J, Aguiar SI, Pinto F, Ramirez M, Dias S. miR-363-5p regulates endothelial cell properties and their communication with hematopoietic precursor cells. J Hematol Oncol. 2013 Nov 21;6(1):87 (2013) This paper exploited the role of microRNAs in the regulation of bone marrow endothelial cell properties.

- Caiado F, et al and Dias S. Bone marrow-derived CD11b+Jagged2+ cells promote epitelial do mesenchymal transition and metastization in colorectal cancer. Cancer Research, 73(14):4233-46 (2013) This paper identified a population of bone marrow derived cells (CD11b+jagged2+) that induces EMT in colorectal cancer, starting the metastatic process.

The Team also started fruitful collaborations with several Units at IMM.

Recent Most Relevant Publications

Caiado F, Carvalho T, Rosa I, Remedio L, Costa A, Matos J, Heissig B, Yagita H, Hattori K, da Silva JP, Fidalgo P, Dias Pereira A and Dias S. (2013) Bone marrow-derived CD11b+Jagged2+ cells promote epitelial do mesenchymal transition and metastization in colorectal cancer. *Cancer Research* **73**(14), 4233-46. (Journal IF: 8.65, Citations: 3)

Real C, Remedio L, Caiado F, Igreja C, Borges C, Trindade A, Pinto-do-Ó P, Hyagita H, Duarte A, Dias S. (2011) Bone marrow-derived Endothelial Progenitors expressing Delta-like 4 (Dll4) regulate tumor angiogenesis. *PlosOne* **6**(4), e18323. (Journal IF: 4.1, Citations: 19)

Caiado F, Carvalho T, Silva F, Castro C, Clode N, Dye JF and Dias S. (2011) Fibrin E modulates endothelial progenitors adhesion, differentiation and angiogenic growth factor production and promotes wound healing. *Biomaterials* **32**(29), 7096-105. (Journal IF: 7.404, Citations: 14)

Gomes AL, Carvalho T, Torre C, Serpa J and Dias S. (2010) Hypercholesterolemia promotes bone marrow cell mobilization by perturbing the SDF1:CXCR4 axis. *Blood* **115**(19), 3886-94. (Journal IF: 9.9, Citations: 24)

Fragoso R, Pereira T, Wu Y, Zhu Z, Cabeçadas J and Dias S. (2006) VEGFR-1 (FLT-1) activation modulates acute lymphoblastic leukemia localization and survival within the bone marrow, determining the onset of extramedullary disease. *Blood* **107**(4), 1608-16. (Journal IF: 9.9, Citations: 76)

JOAQUIM FERREIRA LAB

MD (1992) and PhD (2009) in Neurology at Faculdade de Medicina da Universidade de Lisboa (FMUL).
Associate Professor at FMUL (2012).
Director of Laboratory of Clinical Pharmacology and Therapeutics, FMUL (2011) and Group Leader of Joaquim Ferreira Lab at Instituto de Medicina Molecular (2013).
Director of Clinical Research Centre, Lisbon Academic Medical Centre (2012).

Joaquim Ferreira | Group Leader
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Clinical Pharmacology Unit

The main mission of the CPU is to contribute to the development of effective and safe therapeutic interventions through the establishment of optimized methodologies for the design, conduction, analysis and report of clinical trials. The main clinical pharmacology domains of interest are clinical trials methodology, outcomes, systematic reviews, safety and drug utilization. The emphasis is mainly on novel, early phase proof-of-principle clinical studies and new methodological and trial designs but the scope extends throughout the clinical development spectrum. We also envision collaborations with the pharmaceutical industry, facilitating the conduction of clinical trials to a shared role in the early stages of drug and planning of clinical development.

Research Areas

Parkinson's disease, Huntington Disease, Movement Disorders, Neuropharmacology, Clinical trials, Syatematic reviews.

Major scientific achievements

The Clinical Pharmacology Unit (CPU) was formally created on the 1st of July 2013 based on the research team from the Neuropharmacology Unit of the Neurological Clinical Research Unit and the members of The Laboratory of Clinical Pharmacology (Faculty of Medicine). In these first months the research team was enlarged mainly with new MSc and PhD students. The Drug Evaluation and Systematic Reviews Sub-Unit (Movement Disorders Cochrane Collaboration Review Group) was consolidated and The Safety and Drug Utilization Research Unit (Pharmacovigilance Regional Unit) gained sustainability with a revised service contract with INFARMED. To CPU also supported the process for the creation of The Clinical Research Centre of the Lisbon Medical Academic Centre (CIC-CAML). A Biostatistics and Methodological Sub-Unit was developed. Funding for the next 3 years was guaranteed with the success in three international research grants.

Recent Most Relevant Publications

Vellas, B, Carrillo, MC,, Sampaio C, Brashear, HR,Siemers, E, Hampel, H, Schneider, LS, Weiner, M, Doody, R, Khachaturian, Z, Cedarbaum, J, Grundman, M, Broich, K, Giacobini, E, Dubois, B, Sperling, R, Wilcock, GK, Fox, N, Scheltens, P, Touchon, J, Hendrix, S, Andrieu, S, Aisen, P, EU US CTAD Task Force Members (2013) Designing drug trials for Alzheimer's disease: What we have learned from the release of the phase III antibody trials: A report from the EU/US/CTAD Task Force. *Alzheimers & Dementia* **4**, 438-444. (Journal IF: 14.483, Citations: 6)

Maetzler W, Domingos, J., Srulijes K, Ferreira JJ, Bloem BR (2013) Quantitative wearable sensors for objective assessment of Parkinson´s disease. *Movement Disorders* **12**, 1628-37. (Journal IF: 4.505, Citations: 0)

Ferreira JJ, Katzenschlager R, Bloem BR, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampai C, Schuepbach M, Tolosa E, Trenkwalder C, Schapira A, Berardelli A, Oertel W H, (2013) Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. *European Journal of Neurology* **1**, 5 (Journal IF: 3.692, Citations: 2)

Ana Cláudia Marques Salgueiro MSc Student | **Ana Margarida Faisca do Carmo Pires de Noronha** Administrative | **Ana Marta Teixeira Anes** Investigator | **Ana Patrícia Silva Pita Lobo** Investigator | **Ana Rita Simões Cardoso** MSc Student | **Ana Teresa Martins Sousa Santos** Manager | **Anabela Ferreira Valadas** Investigator, MD | **André Filipe da SIlva Lopes Cardoso** MSc Student | **Catarina Afonso Godinho** Investigator, Assistant Professor | **Cláudio Virgilio Antunes David** Investigator, MD | **Cristina Sampaio** Investigator | **Daisy Abreu** Investigator | **Daniel Gomes Caldeira** Investigator | **Ema Roque** Administrative | **Isabel Boaventura** Investigator | **João Costa** Investigator, Assistant Professor | **João Franco** Investigator | **Josefa Domingos** Investigator | **Leonor Correia Guedes** Investigator | **Márcio Correia Barra** MSc Student | **Margarida Borges** Investigator | **Margherita Fabbri** Investigator, DIBINEM Department of Biomedical and Neuromotor Science, University of Bologna, ALMA MATER STUDIORUM | **Maria Dulce dos Santos Neutel** Investigator | **Maria Finisterra** Administrative | **Mário Miguel Coelho da Silva Rosa** Investigator, MD, Associate Professor | **Miguel Coelho** Investigator | **Nádia Espada** Investigator | **Nilza Gonçalves** Investigator | **Ricardo Miguel Ribeiro Marques Cunha Fernandes** Investigator, MD |**Rita Cardoso** Investigator | **Sofia Cristina Pereira Coutinho Reimão** Investigator | **Tiago Mestre** Investigator | **Tiago Rodrigues Teodoro** Investigator | **Tiago Soares** Investigator | **Vanda Filipa Viseu Cândido Freitas Castro** Investigator

Caldeira D, Martins C, Alves LB, Pereira H, Ferreira JJ, Costa J (2013) Caffeine does not increase the risk of atrial fibrillation: a systematic review and meta-analysis of observational studies. *Heart* **9**, 1383-1389. (Journal IF: 5.014, Citations: 1)

Caldeira D, Fernandes R, David C, Costa J, Ferreira JJ (2013) Warfarin, acetylsalicylic acid ans risk of incident atrial fibrillation in patients with heart failure and sinus rhytm: A meta—analisys. International *Journal of Cardiology* **168**, 4842-4843. (Journal IF: 5.509, Citations: 0)

JOSÉ FERRO

LAB

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.

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Alcina Fraga Luz Investigator | **Alexandre Valério de Mendonça Principal** Investigator | **Ana Catarina Gaspar Fonseca** PhD Student | **Ana Isabel Figueira Verdelho** Investigator | **Bruno André e Silva Miranda** PhD Student | **Carolina Pires Maruta** PhD Student | **Catarina Carapeto da Silva Chester** MSc Student | **Dina Lúcia Gomes da Silva** PhD Student | **Elisabete Mendes Lopes** Investigator | **Fátima Soares** Investigator | **Frederico Simões do Couto** Investigator | **Helena Sofia Garrido Bárrios** Investigator, MD | **Isabel Pavão Martins** Investigator | **José Manuel Borges Fonseca** PhD Student | **Lara Isabel Pires Melo Caeiro** PhD Student | **Luisa Farrajota** Investigator | **Madalena Cristina Rocha Martins** Post-doctoral Investigator | **Mafalda Alexandra Ramos de Matos** Technician | **Maria Gabriela Mariano Leal** Investigator | **Maria Luisa Albuquerque** Investigator | **Maria Luisa Mendonça Correia Pires** Administrative | **Maria Manuela Gil Guerreiro** Investigator | **Marisa Marina Fatuda Costa** Administrative | **Mauricio de Jesus Dias Martins** PhD Student | **Patrícia Canhão** Investigator | **Paulo Maciel Mendes Batista** Investigator | **Raquel Santos Gil Gouveia** PhD Student | **Ruth Isabel de Gusmão Fernandes Geraldes Ramos Dias** Investigator | **Sofia Madureira** PhD Student | **Teresa Pinho e Melo** Investigator | **Vanda Filipa Viseu Cândido De Freitas** MSc Student | **Vitor Oliveira** Investigator

Knowledge of major prevalent disabling brain disorders

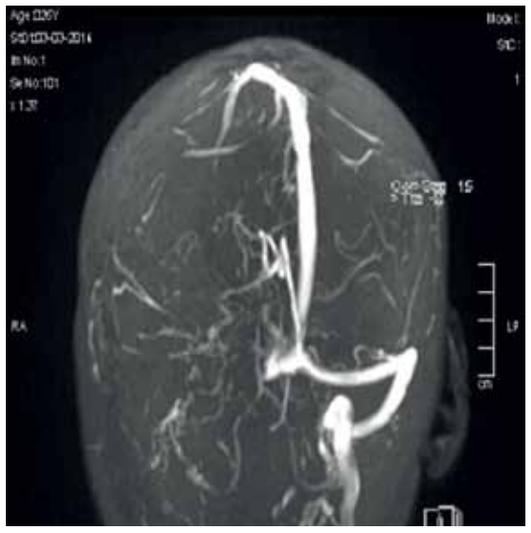
Increase the knowledge and foster the prevention and treatment of major prevalent and disabling disorders involving the brain, such as stroke and Alzheimer's disease. Main advantage of the lab: strong collaboration among the experienced Principal Investigators, and the development of multiple collaborations, both at IMM and at other national and international major research centers and networks, in the areas of basic neurosciences, clinical genetics, advanced statistical methods, biological engineering, and neuroimaging. We share common facilities and know-how that have allowed the conduction of many clinical trials as well as the assessment of the clinical impact of different interventions in a multinational effort to get new treatments for these prevalent and disabling brain disorders.

Research Areas

Stroke, Alzheimer's disease, Cognitive decline, Complex diseases, Genetics, Clinical trials.

Major scientific achievements

The researchers of José Ferro Lab made in 2013 significant scientific contributions expressed in full papers published in international peer-reviewed journals. Important results were obtained regarding treatment of cerebral venous thrombosis, age-related white matter changes, namely on the relationship between cerebral small vessel disease and brain atrophy, cognitive decline and depression in the elderly. Advances were made on the study of cognitive aging in primary care,



the understanding of subjective memory complaints, evaluation of quality of life and determination of the prognosis of elderly people with cognitive complaints. New data were published using traditional genetic approaches, like linkage and association, as well as new approaches, namely genome-wide association studies, exome sequencing and microRNA expression profiling, to identify susceptibility genes in neurological disorders. Novel genetic risk factors for ischaemic stroke and its subtypes were identified and new mutations.

Recent Most Relevant Publications

Caeiro L, Ferro JM, Pinho E Melo T, Canhão P, Figueira ML. (2013) Post-stroke apathy: an exploratory longitudinal study. *Cerebrovascular Diseases* **35**, 507-513. (Journal IF: 2.814, Citations: 0)

Canhão P, Abreu LF, Ferro JM, Stam J, Bousser MG, Barinagarrementeria F, Fukujima MM; for the ISCVT Investigators. (2013) Safety of lumbar puncture in patients with cerebral venous thrombosis. *European Journal of Neurology* **20**, 1075-1080 (Journal IF: 4.162, Citations: 0)

Martins IP, Leal G, Fonseca I, Farrajota L, Aguiar M, Fonseca J, Lauterbach M, Gonçalves L, Cary MC, Ferreira JJ, Ferro JM. (2013) A randomized, rater-blinded, parallel trial of intensive speech therapy in sub-acute post-stroke aphasia: the SP-I-R-IT study. *International Journal of Language & Communication Disorders* **48**, 421-431 (Journal IF: 1.441, Citations: 1)

Pires C, Coelho M, Valadas A, Barroso C, Pimentel J, Martins M, Duyckaerts C, de Mendonça A, Verdelho A, Miltenberger-Miltenyi G. (2013) Phenotypic variability of familial and sporadic Progranulin p.Gln257Profs*27 mutation. *Journal of Alzheimer's Disease* **37**, 335-342 (Journal IF: 4.174, Citations: 0)

Verdelho A, Madureira S, Moleiro C, Ferro JM, O'Brien JT, Poggesi A, Pantoni L, Fazekas F, Scheltens P, Waldemar G, Wallin A, Erkinjuntti T, Inzitari D; LADIS Study. (2013) Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes: the LADIS study. *Journal of neurology, neurosurgery, and psychiatry* **84**, 1250-1254 (Journal IF: 4.924, Citations: 3)

LUÍSA FIGUEIREDO

LAB

PhD (2002) from Universidade do 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).

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Biology of parasitism

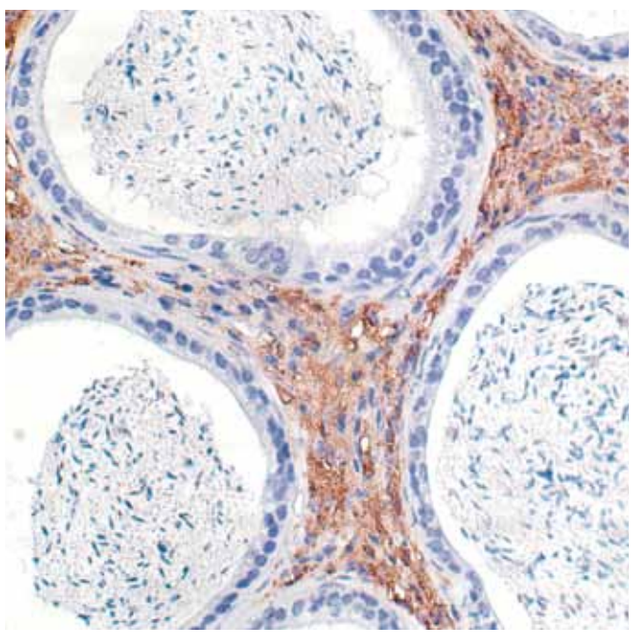
Trypanosoma brucei is a unicellular parasite that, in humans, causes a fatal disease called African sleeping sickness. While in the bloodstream, the parasite evades its host immune system through antigenic variation; specifically, it periodically switches from one dense, uniform coat of variant surface glycoprotein (VSG) to an antigenically distinct one. Although the *T. brucei* genome contains hundreds of VSG genes, all but one are transcriptionally silenced. Such transcriptional changes do not involve alterations in the DNA sequence but are inherited nevertheless, which indicates that VSG transcription is under epigenetic control. Our goal is to identify and characterize the factors involved in the epigenetic control of VSG gene expression.

Research Areas

Antigenic variation, chromatin, gene expression, parasitology, infection, chromatin.

Major scientific achievements

- Co-organizer of EMBO Young Scientists' Forum. IMM, Lisboa, Portugal;
- Session chairman at Kinetoplastid Molecular Cell Biology meeting, Woods Hole, MA, USA;
- AXA post-doctoral fellowship awarded to Fabien Guegan, a fellow in my group.



Ana Catarina Dias Pena PhD Student | **Ana Filipa de Almeida Rijo Ferreira** PhD Student | **Ana Margarida Roque Sanches Vaz** MSc Student | **Carla Andrea Sequeira Bejarano** Undergraduate | **Daniel Pinto de Oliveira Gonçalves Neves** MSc Student | **Diogo Maia e Silva** Undergraduate | **Fabien Marc Guegan** Post-doctoral Investigator | **Francisco Maria dos Santos e Silva Aresta Branco** PhD Student | **Helena Isabel Gomes Pires Manso** Post-doctoral Investigator | **Idálio de Jesus Contreiras Viegas** MSc Student | **Leonor Duarte Pinho** Lab manager | **Mafalda Ramos de Melo Pimentel** MSc Student | **Sandra Isabel Gonçalves Trindade** Post-doctoral Investigator

Recent Most Relevant Publications

Figueiredo LM, Cross GA (2010) Nucleosomes are depleted at the VSG expression site transcribed by RNA polymerase I in African trypanosomes. *Eukaryot Cel* **9**, 148-154. (Journal IF: 3.395, Citations: 15)

Yang X, Figueiredo LM, Espinal A, Okubo E, Li B (2009) RAP1 is essential for silencing telomeric Variant Surface Glycoprotein genes in *Trypanosoma brucei*. *Cell* **137**, 99-109 (Journal IF: 32.406, Citations: 30)

Siegel TN, Hekstra DR, Kemp LE, Figueiredo LM, Lowell JE, Fenyo D, Wang X, Dewell S, Cross GAM (2009) Four histone variants mark the boundaries of polycistronic transcription units in *Trypanosoma brucei*. *Genes Dev* **23**, 1063-1076. (Journal IF: 12.889, Citations: 88)

Figueiredo LM, Cross GAM, Janzen CJ (2009) Epigenetic regulation in African trypanosomes: a new kid on the block. *Nat Rev Microbiol* **7**, 504-513. (Journal IF: 20.686, Citations: 41)

Figueiredo LM, Janzen CJ, Cross GAM (2008) A histone methyltransferase modulates antigenic variation in African trypanosomes. *PLoS Biol* **6**, e161. (Journal IF: 12.472, Citations: 45)

JOÃO EURICO FONSECA

LAB

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

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Ana Catarina Coimbra do Vale PhD Student | **Ana Filipa Mourão** Investigator | **Ana Filipa Rodrigues Lopes** Lab manager | **Ana Henrique Baptista Daniel** MSc Student | **Ana Maria Ferreira Rodrigues** PhD Student | **Ana Rita Cascão Rodrigues** PhD Student | **Ana Rita Fernandes Vieira** MSc Student | **António José Nicolau Marques Fernandes** MSc Student | **Bruno Miguel Costa Vidal** PhD Student | **Cláudia Cristina Valente Quaresma** Investigator | **Diana de Almeida Carmona Fernandes** PhD Student | **Elsa Cristina Vieira de Sousa** Investigator | **Filipe Carlos Pereira dos Reis Cortes Figueiredo** MSc Student | **Helena Cristina de Matos Canhão** Principal Investigator | **Inês Pedro Perpétuo** PhD Student | **Joana Ribeiro Caetano Lopes** Post-doctoral Investigator | **Joaquim Miguel Polido Pereira** Investigator | **Luísa Sofia Campos Magalhães Garcia** MSc Student | **Marco Aurélio Carmelino Cardoso Sarmento** Investigator | **Maria Helena Regalo da Fonseca** Principal Investigator | **Maria João Gonçalves** Investigator, MD | **Maria José Parreira dos Santos** Investigator, Associate Professor | **Mónica Cristina Medina Lopes** MSc Student | **Rita Alexandra Pedra Aguiar de Moura** Post-doctoral Investigator | **Rita Maria Mendes Raposeiro** MSc Student | **Saba Abdulghani Oliveira da Silva** Post-doctoral Investigator | **Tânia da Cunha Branco dos Santos** Investigator | **Vanessa Sofia de Oliveira Artilheiro** MSc Student | **Vasco Madeira Crispim Romão** Investigator

Rheumathology research

The João Eurico Fonseca Lab results from a partnership between the IMM-FMUL and the Rheumatology Department of the Santa Maria Hospital. Is devoted to the translational study of the early burden of inflammatory rheumatic diseases on bone and vessel, seeking prognostic markers, predictors of treatment response and new treatment targets. We have created a network of biologists, biomedical engineers and physicians, sharing a common mission, goals and values, which allow the ongoing pattern of a highly interactive work that is leading the translational research in the field of Rheumatology in Portugal. The long-term objective of the Lab is to achieve recognition as an European League Against Rheumatism Centre of Excellence in Rheumatology.

Research Areas

- Joint inflammatory diseases - pathogenesis, early diagnosis, prognosis and pharmacogenetics - Rheumatoid Arthritis, Psoriatic Arthrits, Ankylosing spondylitis and Juvenile Idiopathic Arthritis;
- Systemic effects of inflammation and effects of inflammation on bone - Osteoporosis Osteoarthritis and Rheumatoid Arthritis;
- Bone biology, structure, biomechanics;
- Chronic Inflammation and cardiovascular risk - atherosclerosis and bone;
- Epidemiology of Rheumatic Diseases, Cohorts, Registries and Databases. Recommendations and Guidelines;
- Clinical Trials.

Major scientific achievements

1- Describe the gene expression pattern involved in bone fragility induced by rheumatoid arthritis;

2- Preclinical development of an arthritis treatment intervention with novel compounds inhibiting IL1 and TNF;

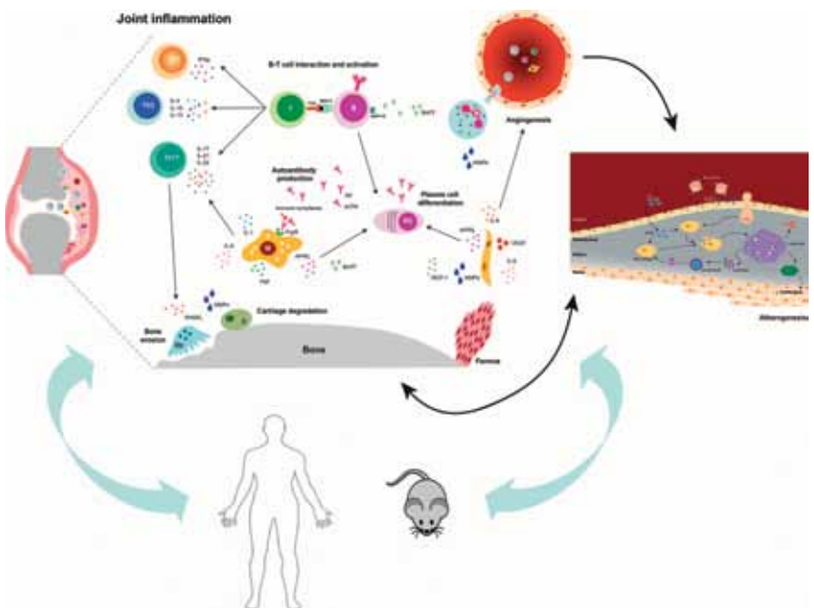
3- B cell gene expression in early arthritis;

4- Anti ribosomal P antibodies as potential diagnostic markers for Lupus;

5- Development of published protocols for mechanical and structural assessment of bone;

6- New genetic risk factors for rheumatoid arthritis and spondylarthritis;

7- Coordination of the Portuguese national registries of the Portuguese Society of Rheumatology and coordination of the Portuguese Rheumatology Biobank, a part of the IMM biobank;



8- Participation in multinational clinical trials as national coordinators allowing refractory patients to have access to the state of art in biotechnological therapies;

Recent Most Relevant Publications

Carmona-Fernandes D, Santos MJ, Canhão H, Fonseca JE.(2013) Anti-ribosomal P protein IgG autoantibodies in patients with systemic lupus erythematosus: diagnostic performance and clinical profile. *BMC Med*. **4**, (11):98. (Journal IF: 6.679, Citations: 1)

Cascão R, Vidal B, Raquel H, Neves-Costa A, Figueiredo N, Gupta V, Fonseca JE, Moita LF (2012) Effective treatment of rat adjuvant-induced arthritis by celastrol. *Autoimmun Rev*. 11, 856-62. (Journal IF: 7.975, Citations: 7)

Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, Bombardier C, Carmona L, van der Heijde D, Bijlsma JW, Boumpas DT, Canhao H, et al. (2009) Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis*. 68, 1086-1093. (Journal IF: 9.111, Citations: 128)

Fonseca JE, Santos MJ, Canhão H, Choy E. (2009) Interleukin-6 as a key player in systemic inflammation and joint destruction. *Autoimmun Rev*. 8, 538-542 (Journal IF: 7.975, Citations: 104)

Fonseca JE, Carvalho T, Cruz M, Nero P, Sobral M, Mourão AF, Cavaleiro J, Abreu I, Carmo Fonseca M, Branco JC. (2005) Polymorphism at position –308 of the tumor necrosis factor alpha gene and rheumatoid arthritis pharmacogenetics. *Ann Rheum Dis*. 64, 793-794. (Journal IF: 9.111, Citations: 38)

EDGAR GOMES

LAB

Degree in Biochemistry (1996), Universidade de Coimbra, Portugal.
PhD in Cell Biology (2002), Center for Neuroscience, Unversidade de Coimbra, Portugal.
Post-doctoral research (2002-2007), Department of Anatomy and Cell Biology, Columbia University, New York, USA.
Team leader (since 2007) UMR S 787 - Groupe Myologie, Paris, France and Group Leader (since 2013) at IMM.

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Cell migration and skeletal myofiber formation

Connecting the nucleus to the cytoskeleton is relevant for multiple cellular processes and disruption of these connections result in multiple pathologies. Nuclear positioning within cell cytoplasm requires the connection between the nucleus and the cytoskeleton. We are interested in understanding the processes involved in these connections and the role for nuclear positioning in cell function. We study cell migration and skeletal myofiber formation which required the connection between the nucleus and the cytoskeleton and precise nuclear positioning. We use different molecular and cellular approaches in combination with time-lapse imaging analysis to address these questions. signals in cancer onset and progression.

Research Areas

Cell Biology, Cytoskeleton, Cell Migration, Skeletal Muscle.

Major scientific achievements

Last year we established that the position of the nucleus in skeletal muscle cells is important for muscle physiology. This year we focused our efforts in understanding why nuclear positioning is important for cell migration. We developed new systems and engineer novel reagents able to address this question. Furthermore, we were awarded with the following grants:

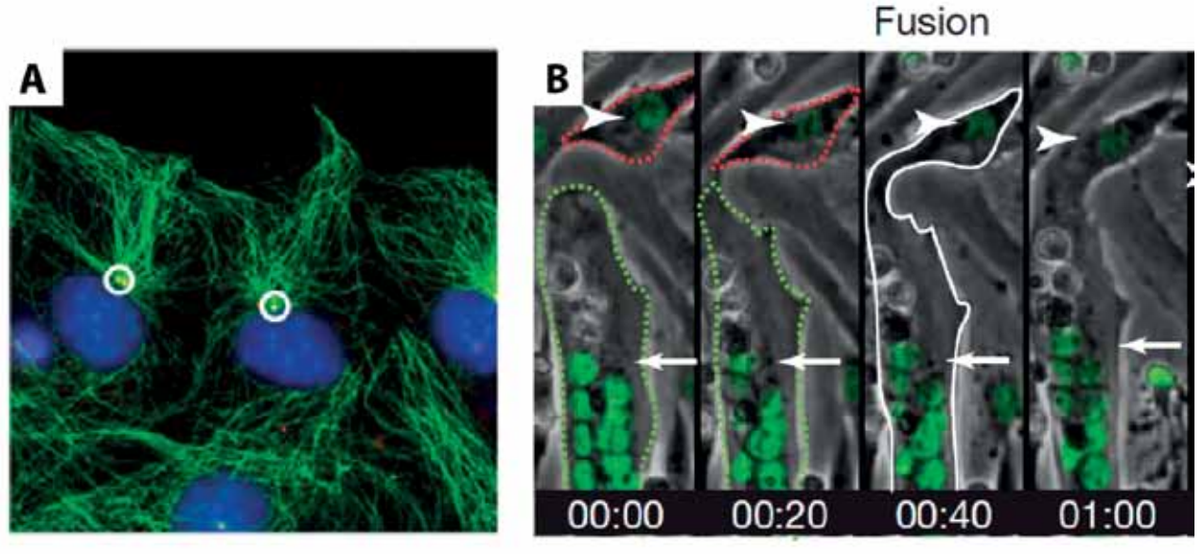
- ERC Consolidator Grant 2013 - "Positioning the nucleus for cell migration and muscle fiber function";
- EMBO Installation Grant 2014 - "Positioning the cell nucleus";
- Investigador FCT to Edgar Gomes.

Recent Most Relevant Publications

Metzger, T., Gache, V., Xu, M., Cadot, B., Folker, E., Richardson, B., Gomes, E.R., Baylies, M.K. (2012) MAP and Kinesin dependent nuclear positioning is required for skeletal muscle function. *Nature* **484**, 120 (Journal IF: 38.6, Citations: 23)

Luxton GW, Gomes ER, Folker ES, Vintinner E, Gundersen GG (2010) Linear arrays of nuclear envelope proteins harness retrograde actin flow for nuclear movement. *Science* **125**,1099. (Journal IF: 31.03, Citations: 83)

Telma Cristina Lourenço Carrilho Technician | Tiago Maria de Carvalho da Costa Amado Technician



A- Migrating fibroblasts position their nucleus away from the direction of migration. cricle denotes the centrosome that is positioned between the nucleus and the front of the cell.
B- time-lapse sequence of nuclear movement that occurs after cell fusion during muscle formation

LUÍS GRAÇA

LAB

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.

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Lymphocyte regulation

Our Lab studies mechanisms underlying induction and maintenance of immune tolerance. In other words, we research methods to reprogram the immune response in situations where the immune system is causing a disease, such as allergy, autoimmunity and transplant rejection.

In addition we are interested in defining the functional properties of lymphocytes that can promote immune tolerance by suppressing pathogenic immune responses. We have been studying how different types of lymphocytes with regulatory function can be induced in the periphery.

We believe that in the foreseeable future antibody therapy, as well as other strategies to modulate the immune system will have an important repercussion in the quality of life of people suffering from immune mediated diseases.

Research Areas

Immune tolerance, Regulatory T cells, Natural Killer T cells (NKT), Transplantation, Autoimmunity, Allergy.

Major scientific achievements

Our data on the induction of Foxp3 expression by peripheral iNKT cells challenges the idea that iNKT cells exit the thymus as functionally committed effectors. We found that iNKT cells respond to environmental cues acquiring different types of effector responses, namely IL-17 production. (*J. Immunol* 2013)

Our studies on tolerance induction with non-depleting anti-CD4 monoclonal antibodies led us to find evidence that an adjuvant may be necessary to allow efficient antigen presentation for tolerance induction to factor VIII in hemophilic mice. Surprisingly, tolerance, in this situation, appears to be Foxp3-independent (*Blood* 2013). Instead, we found that the molecular mechanism for tolerance induction that is Foxp3-independent relies on IL-10.

Recent Most Relevant Publications

Monteiro M, Almeida CF, Agua-Doce A, Graca L. (2013) Induced IL-17-producing invariant Natural Killer T cells require activation in presence of TGF-β, J Immunol 190, 805. (Journal IF: 5.745, Citations: 4)

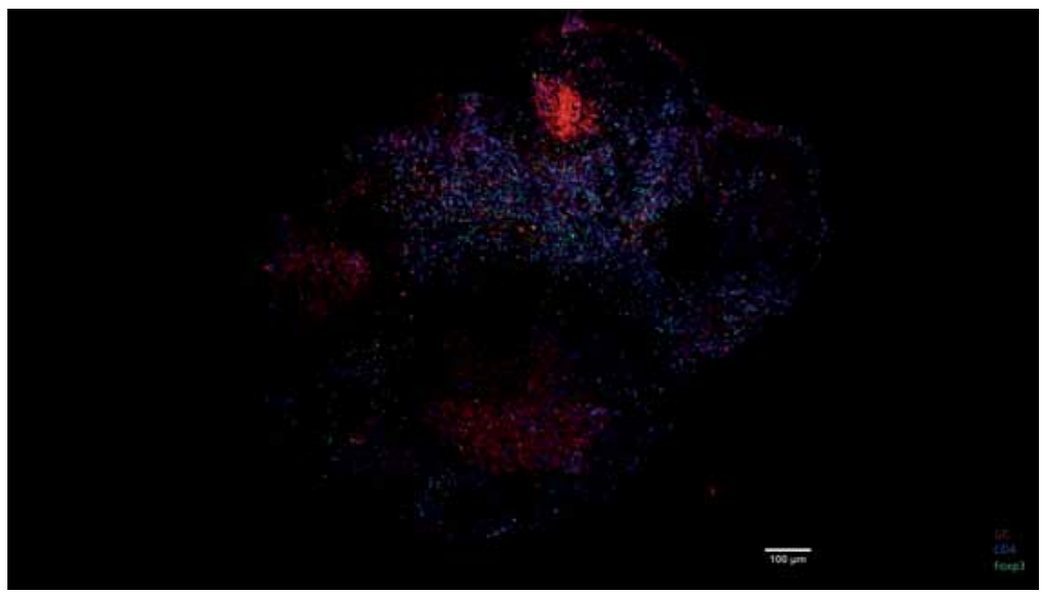
Wollenberg I, Agua-Doce A, Hernández A, Almeida C, Oliveira V, Faro J, Graca L (2011) Regulation of germinal centre reaction by Foxp3+ follicular regulatory T cells. *J. Immunol* **187**, 4553. (Journal IF: 5.745, Citations: 41)

Oliveira VG, Caridade M, Paiva RS, Demengeot J, Graca L (2011) Sub-optimal CD4 T cell activation triggers autonomous TGF-β-dependent conversion to Foxp3+ regulatory T cells. *Eur J Immunol* **41**, 1249-1255. (Journal IF: 5.179, Citations: 17)

Monteiro M, Almeida CF, Caridade M, Ribot JC, Duarte J, Agua-Doce A, Wollenberg I, Silva-Santos B, Graca L. (2010) J Immunol. 185: 2157-2163. (2010) Identification of Regulatory Foxp3+ Invariant NKT Cells Induced by TGF-β. *J Immunol* **185**, 2157.2163. (Journal IF: 5.646, Citations: 30)

Curotto de Lafaille MA, Lafaille JJ, Graca L (2010) Mechanisms of tolerance and allergic sensitization in the airways and the lungs. *Curr Opin Immunol* **22**, 616. (Journal IF: 10.881, Citations: 7)

Alexandre Varela Santos Costa Lab manager | **Ana Água-Doce** Post-doctoral Investigator | **Ana Raquel Maceiras Oliveira** PhD Student | **Joana Catarina Mendão Azeitão da Silva** PhD Student | **Jorge Ivan Ramirez Sepulveda** Investigator | **Marta Isabel de Carvalho Ferreira Gomes** MSc Student | **Marta Ribeiro Lopes Caridade** PhD Student | **Marta Sofia Ferreira Monteiro Coelho Antunes** Post-doctoral Investigator | **Raquel Filipa Reis de Freitas** Technician | **Ruy Miguel Sousa Soeiro de Figueiredo Ribeiro** Principal Investigator | **Sílvia Cristina de Paiva e Almeida** Post-doctoral Investigator | **Vanessa Alexandra Gonçalves de Oliveira Martins** Post-doctoral Investigator



DOMINGOS HENRIQUE

LAB

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

Domingos Manuel Pinto Henrique | Group Leader
henrique@medicina.ulisboa.pt

Aida Isabel Santos da Costa PhD Student | **Alexandra Isabel Freitas Rosa** Post-doctoral Investigator | **Ana Leonor Heitor Lopes** Trainee | **Ana Marisa Mendes Gonçalves Vinhais Guedes** PhD Student | **Ana Rita Ponce Álvares de Águeda Pedrosa** PhD Student | **Ana Sofia Temudo Duarte António** PhD Student | **Anna Pezzarossa** Post-doctoral Investigator |**Catarina Esteves Lopes Ramos** Post-doctoral Investigator | **Cláudia Sofia Cardoso Gaspar** Post-doctoral Investigator | **Dusan Djokovic** Post-doctoral Investigator, MD | **Elsa Margarida Cavaco Abranches** Post-doctoral Investigator | **Evguenia Pavlovna Bekman** Post-doctoral Investigator, Assistant Professor | **Pedro Miguel Branco Barbacena** MSc Student | **Sanja Ivkovic** Post-doctoral Investigator | **Sara Sofia Gasalho Ferreira** Technician | **Willianne Kaline Alves da Silva** MSc Student

Stem cells and neurogenesis

A central question in developmental biology is how cells decide which differentiation paths they follow to generate tissues and organs during embryonic development. Our aim is to elucidate the gene regulatory networks that control cell-fate decision processes in the embryo, using 2 experimental models: i) embryonic stem cells to study the mechanisms underlying their pluripotent state, and ii) neural retina to investigate how progenitors acquire their multipotent character and generate the variety of neurons that compose the mature retina. The main goal is to understand the mechanisms governing the decision processes that stem/progenitor cells employ to exit the pluri/multipotent state and differentiate along various paths, thereby generating correctly patterned tissues and organs.

Research Areas

Stem cells, Notch signalling, Pluripotency, Neurogenesis, Gene regulatory networks, Systems biology.

Major scientific achievements

Our work focused on how cell fate decisions are controlled at the single-cell level, revealing how cell-cell communication functions to coordinate the proper assembly of tissues and organs. In the developing nervous system, our research allowed us to unravel how neuronal differentiation is controlled by the timing of Notch activity. We have also investigated how the pluripotent state is regulated in embryonic stem (ES) cells. By monitoring the activity of the pluripotency gene Nanog, combined with mathematical modelling, our work uncovered the existence of significant stochastic gene expression noise in individual ES cells, which we propose allow these cells to explore the pluripotent decision space. This research shall contribute to design more rational strategies to direct the in vitro and in vivo production of specific cell types, required to develop cell-replacement therapies in humans, aimed at regenerating damaged tissues and organs.

Recent Most Relevant Publications

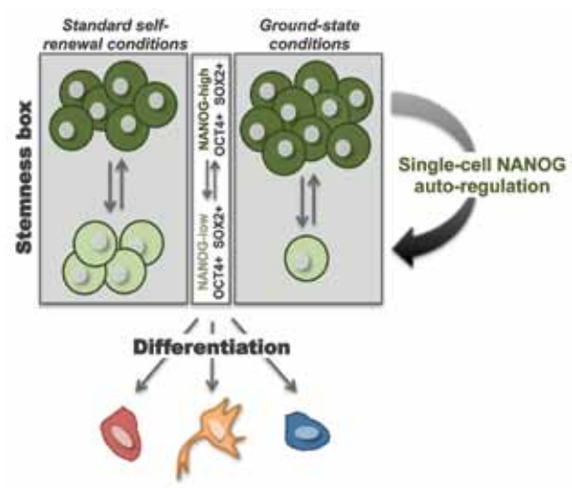
Vilas-Boas, F., Fior, R., Swedlow, J.D., Storey, K.G., Henrique, D. (2011) A novel Reporter of Notch Signalling indicates regulated and random Notch Activation during Vertebrate Neurogenesis. *BMC Biology*. **9**, 58. www.biomedcentral.com/1741-7007/9/58. (Journal IF: 5.841, Citations: 3)

Henrique, D. Bally-Cuif, L. (2010) A cross-disciplinary approach to understanding neural stem cell in development and disease. *Development*. **137**, (12):1933-8. http://dev.biologists.org/content/137/12/1933.short. (Journal IF: 7.,091, Citations: 2)

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. www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0006286. (Journal IF: 4.537, Citations: 39)

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. *Developmental Biology*. **328**, 54-65. www.sciencedirect.com/science/article/pii/S0012160609000293. (Journal IF: 4.407, Citations: 11)

Fior, R., Henrique, D. (2005) A novel hes5/hes6 circuitry of negative regulation controls Notch activity during neurogenesis. *Developmental Biology*. **281**, 318-333. (Journal IF: 4.407, Citations: 53)



Embryonic stem cells fluctuate between different states of competence to differentiation, in a process controlled by the Nanog gene. Understanding how pluripotency is maintained, and how exit to differentiation is controlled, is fundamental to progress into clinical applications of stem cells.

JOÃO LACERDA

LAB

MD (1988), PhD (1998) at Universidade de Lisboa. Fellow Hematology (1991-1995) at Hospital de Santa Maria, Lisbon and fellow BMT Service (1993-1995) at Memorial Sloan-Kettering Cancer Center, New York. Assistant Professor of Hematology and Immunology (1998-2003) and Assistant Professor of Medicine and Hematology (2003-2010) at Universidade de Lisboa. Principal Investigator (2008-2013) at Clinical Immunology Unit, Instituto de Medicina Molecular, Lisbon. Since 1996, attending Physician, Hematology and BMT Service, at Hospital de Santa Maria, Lisbon. Since 2007, Head of Hematology at Universidade de Lisboa. Aggregation Act (2008) at Universidade de Lisboa. Since 2010 Associate Professor of Medicine, at Universidade de Lisboa, and since 2013 Group Leader at Instituto de Medicina Molecular, Lisbon.

João Lacerda | Group Leader
jlacerda@medicina.ulisboa.pt

Immune responses in post-transplant

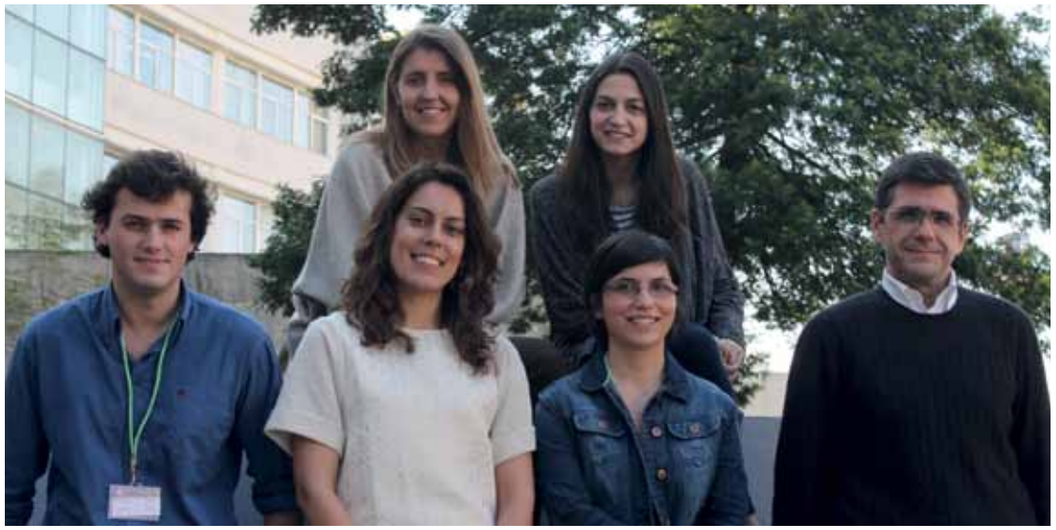
The main research focus of our laboratory is the study of immune reconstitution after hematopoietic stem cell transplantation (HSCT) in humans and the development of strategies that modulate immune responses and tolerance post-transplant. Donor immunity emerging post-transplant plays a pivotal role in the protection against pathogens, such as Aspergillus, CMV and EBV, as well as in the development of graft-versus-host disease (GVHD) and graft-versus-leukemia effect. Our laboratory aims to identify immunological risk factors and the mechanisms by which these complications emerge post-transplant. We are particularly interested in developing strategies that may be translated into the clinical setting, such as the use of pathogen-specific T cells, donor regulatory T cells for GVHD and disease-specific T cells, with the aim of improving patient survival. We also maintain research lines investigating the pathogenesis of hematologic malignancies.

Research Areas

Immune reconstitution after hematopoietic stem cell transplantation (HSCT), Homeostasis of regulatory T cells in patients submitted to HSCT, Cytomegalovirus-specific immunity after HSCT, Development of cellular adoptive immunotherapies under GMP conditions, Genetic susceptibility to invasive fungal and viral infections, Gene expression and signaling pathways of hematologic malignancies.

Major scientific achievements

Our Lab, officially created in July 2013, has established collaborations with national and international researchers working towards a multidisciplinary platform involving basic scientists, physicians and bioengineers with the aim of bringing into clinical practice adoptive cellular immunotherapy strategies for the prevention and treatment of invasive infections after hematopoietic stem cell transplantation (HSCT). We are also developing strategies to modulate immune tolerance after HSCT, such as the treatment of chronic graft versus host disease, by examining regulatory T cell homeostasis in this setting. Our lab is currently funded by a Collaborative Research Grant of the Harvard Medical School Portugal Program.



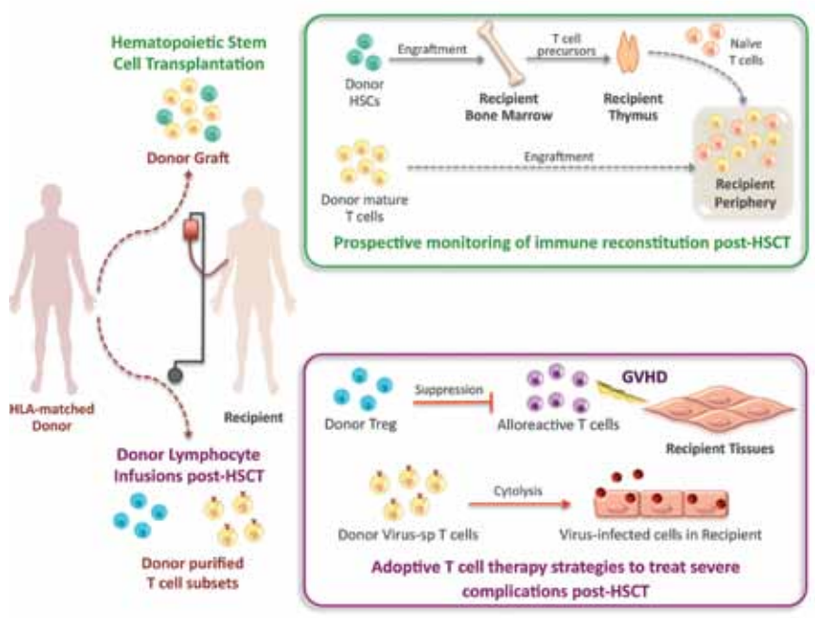
António Maria Moura Tavares de Sampaio Soares MScStudent | **António Maria Santa Marta de Soure** PhD Student | **Inês Raquel Antunes Ferreira** Technician | **Maria Godinho A.V. Duarte Soares** Principal Investigator | **Rita Isabel Silva de Azevedo** Post-doctoral Investigator | **Telma Raquel Martins da Palma** Post-doctoral Investigator

Recent Most Relevant Publications

Azevedo RI, Soares MV, Albuquerque AS, Tendeiro R, Soares RS, Martins M, Ligeiro D, Victorino RM, Lacerda JF, Sousa AE. (2013) Long-Term Immune Reconstitution of Naive and Memory T Cell Pools after Haploidentical Hematopoietic Stem Cell Transplantation. *Biology of Blood and Marrow Transplantation* **19**(5), 703-712. http://www.sciencedirect.com/science/article/pii/S1083879113000530 (Journal IF: 3.940, Citations: 0)

Gomes AQ, Correia DV, Grosso AR, Lança T, Ferreira C, Lacerda JF, Barata JT, Silva MG, Silva-Santos B (2010) Identification of a panel of ten cell surface protein antigens associated with immunotargeting of leukemias and lymphomas by peripheral blood gammadelta T cells. *Haematologica* **95**, 1397. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2913090 (Journal IF: 5.935, Citations: 19)

Ciceri F, Labopin M, Aversa F, Rowe JM, Bunjes D, Lewalle P, Nagler A, Di Bartolomeo P, Lacerda JF, Lupo Stanghellini MT, Polge E, Frassoni F, Martelli MF, Rocha V. (2008) A survey of fully haploidentical hematopoietic stem cell transplantation in adults with high-risk acute leukemia: a risk factor analysis of outcomes for patients in remission at transplantation. *Blood* **112**(9), 3574-3581.http://bloodjournal.hematologylibrary.org/content/112/9/3574.long. (Journal IF: 9.06, Citations: 81)



LUÍSA LOPES

LAB

Group leader (since March 2013) at Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa (IMM-FMUL), Portugal.
Staff Scientist (2008-2012) and Postdoctoral research fellow (2006-2008) at IMM-FMUL.
Postdoctoral research fellow (2003-2006) at Nestlé Research Center, Lausanne, Switzerland.
PhD student(2000-2003), FMUL; Dept Pharmacology, University of Cambridge, Karolinska Institute, Sweden.

Luísa V. Lopes | Group Leader
lvlopes@medicina.ulisboa.pt

Diana Gabriela Ribeiro Ferreira PhD Student | **Joana Fernandes Esteves Soares Coelho** Post-doctoral Investigator | **Rui Artur Paiva Loureiro Gomes** Investigator, Assistant Professor | **Sara Alexandra Fernandes Carvalho** MSc Student | **Vânia Luisa Neves Batalha** PhD Student

Neurodegenerative diseases

Ageing, stress and neurodegenerative diseases are among the conditions that contribute to the accelerated loss of cognitive function. Our Lab's work is focused on understanding the mechanisms inducing this "early-ageing", which render the hippocampus - the brain area related to learning and memory – particularly susceptible. We are now working on the hypothesis that brain adenosine A2A receptors drive age-related synaptic dysfunction.

Major research lines:

- Molecular switches from aging towards neurodegeneration in the hippocampus;
- Therapeutic actions of caffeine and caffeine analogs against memory deficits;
- Epigenetics and glucocorticoid actions in aging;
- Cognitive dysfunction in Alzheimer's mouse models;
- Molecular mechanisms of early cognitive deficits in Parkinson's disease.

Research Areas

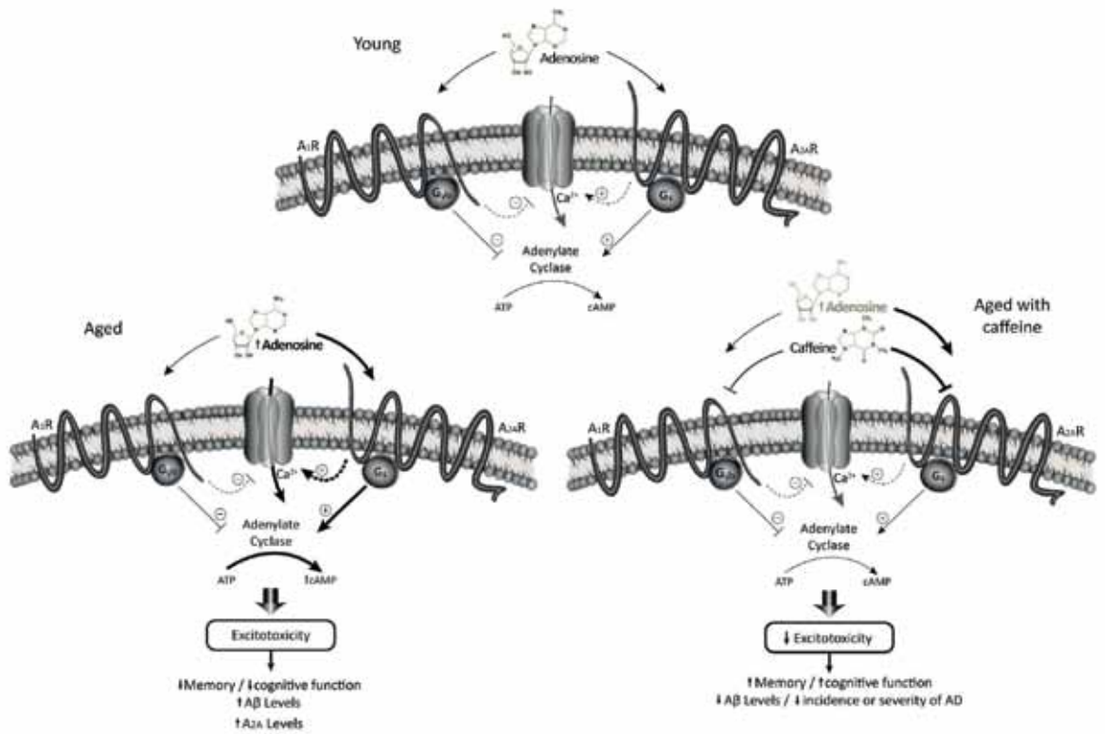
Aging, cognition, hippocampus, neurodegeneration, Alzheimer's Disease, Stress.

Major scientific achievements

Using animal models, we found that one common feature in stress and aging is the disruption of the hypothalamic-pituitary- axis (HPA) which in turn compromises hippocampal circuitry. We have established a link between adenosine A2A receptors (A2AR) upsurge and cognitive deficits. We described for the first time that the therapeutic administration of A2AR blockers reverts hippocampal-related impairments, including HPA imbalance.

Recent Most Relevant Publications

Batalha VL, Pego JM, Fontinha B, Costenla AR, Valadas J, Baqi Y, Radjainia H, Müller CE, Sebastião AM, Lopes LV. (2013) Adenosine A2A receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation. *Mol. Psychiatry* **18**, 320-31. (Journal IF: 15.4, Citations: n/a)



Diógenes MJ, Dias RB, Rombo DM, Miranda HV, Maiolino F, Guerreiro P, Nasstrom T, Franquelim HG, Oliveira LM, Castanho M, Lannfelt L, Bergstrom J, Ingelsson M, Quintas A, Sebastião AM, Lopes LV, Outeiro TF. (2012) Extracellular alpha-synuclein oligomers modulate synaptic transmission and impair LTP via NMDA-receptor activation. *Journal of Neuroscience* **32**, 11750. (Journal IF: 7.3, Citations: 7)

Valadas JS, Batalha VL, Ferreira DG, Gomes R, Coelho JE, Sebastião AM. Diógenes MJ, Lopes LV. (2012) Adenosine A2A receptors mediated neuroprotection is modulated by corticotrophin-releasing factor (CRF) in a model of glutamate induced cell death. *Journal of Neurochemistry* **123**, 1030. (Journal IF: 4.5, Citations: 2)

Diógenes MJ, Costenla AR, Lopes LV, Jerónimo AS, Sousa VC, Fontinha B, Ribeiro JA, Sebastião AM. (2011) Enhancement of LTP in aged rats is dependent on endogenous BDNF. *Neuropsychopharmacology* **36**, 1823. (Journal IF: 6.9, Citations: 19)

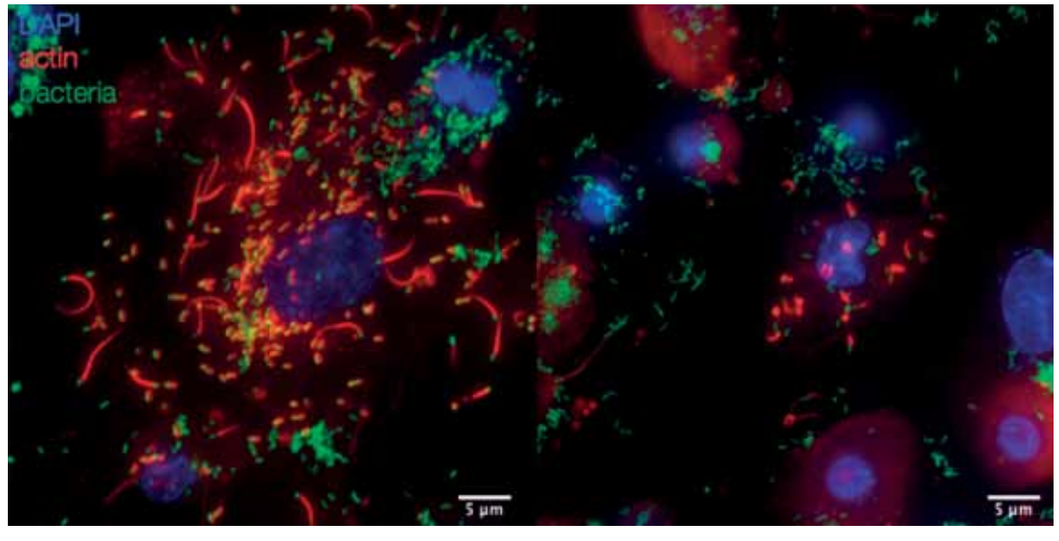
Chen JF, Sonsalla PK, Pedata F, Melani A, Domenici MR, Popoli P, Geiger J, Lopes LV, de Mendonça (2007) Adenosine A2A receptors and brain injury: broad spectrum of neuroprotection, multifaceted actions and "fine tuning" modulation. *Progress in Neurobiology* **83**, 310. (Journal IF: 11.8, Citations: 97)

MUSA MHLANGA

LAB

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

Musa Mhlanga / Group Leader
musa@medicina.ulisboa.pt



Ana Catarina Fidalgo Barata Investigator | **Jagdish Parihar** Technician | **Joana Rita Gonçalves da Cruz** MSc Student | **Luis Pedro Coelho** Post-doctoral Investigator | **Ricardo José dos Santos Duarte Vieira Henriques** Investigator | **Sílvia Almeida dos Santos Rosa** Investigator

Gene expression and biophysics

In biology several important processes occur at spatial dimensions currently beyond the reaches of light microscopy. Our lab focuses on biological questions at this scale as they are related to gene expression. We study RNA transcription, metabolism and transport, as well as the development and innovation of technology to study these problems. Dynamic multi-molecular complexes in the eukaryotic cell nucleus remain well outside the resolution of light microscopy. Intrinsic to RNA transcription are modifications to nuclear architecture and the repositioning of chromosomal loci, and the interplay of ribonucleic proteins. These events remain opaque at the single molecule level, and are intensively researched by our research group.

Research Areas

RNA biology, Super-resolution, Nuclear Architecture, Gene Expression, Host-Pathogen, Transcription.

Major scientific achievements

We published a few important papers this year. We were also a new EPO patent awarded and filed a number of other patents. We participated in a number of international conferences.

- **Publications:**
  Statin Therapy Reduces the Mycobacterium tuberculosis Burden in Human Macrophages and in Mice by Enhancing Autophagy and Phagosome Maturation, *Journal of Infectious Diseases*. Chromosomal Contact Permits Transcription between Coregulated Genes, Cell.

- **Patents:**
  Polynucleotide suitable for single cell based reporter assay to monitor gene expression patterns with high spatio-temporal resolution. EP Patent 2,036,989.

- **Major Conference Participation:**
  - Hong Kong University & Institut Pasteur Hong Kong - Molecular & Cell Biology Course - Speaker and organizer of practical.
  - EMBO conference: Nuclear Structure & Dynamics – Speaker.
  - EMBO Practical Course: Imaging Infection & Immunity - Speaker & Organizer.

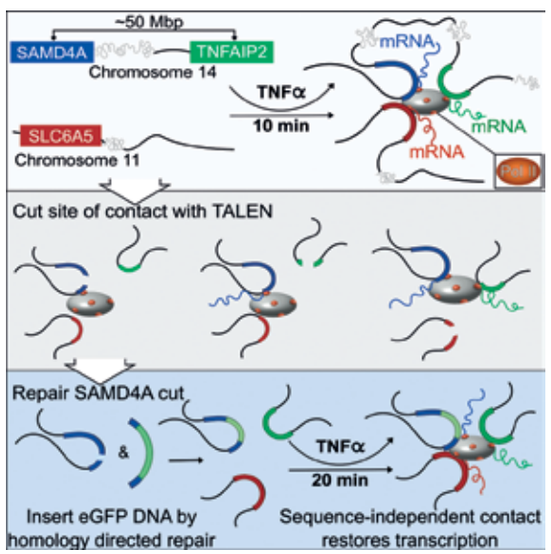
Recent Most Relevant Publications

Stephanie Fanucchi, Youtaro Shibayama, Shaun Burd, Marc S Weinberg, Musa M Mhlanga (2013) Chromosomal Contact Permits Transcription between Coregulated Genes. *Cell* **155**, 505 www.cell.com. (Journal IF: 34.366, Citations: 1)

R Henriques, M Lelek, EF Fornasiero, F Valtorta, C Zimmer, MM Mhlanga (2010) QuickPALM: 3D real-time photoactivation nanoscopy image processing in ImageJ. *Nature Methods* **7**, 339. (Journal IF: 23.565, Citations: 83)

MM Mhlanga, DY Vargas, CW Fung, FR Kramer, S Tyagi (2005) tRNA-linked molecular beacons for imaging mRNAs in the cytoplasm of living cells . *Nucleic acids research* **33**, 1902. (Journal IF: 8.026, Citations: 90)

DP Bratu, BJ Cha, MM Mhlanga, FR Kramer, S Tyagi (2004) Visualizing the distribution and transport of mRNAs in living cells. *Proceedings of the National Academy of Sciences* **100**, 13308. (Journal IF: 9.737, Citations: 304)



LUÍS MOITA LAB

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.

Luís Ferreira Moita | Group Leader
lmoita@medicina.ulisboa.pt

Innate immunity and inflammation

The general unifying goal of our research lab is to use unbiased functional genomic and genetic tools to identify and characterize human and mouse genes and signalling pathways that regulate central processes of an immune response, their targets and role in an in vivo immune response.

Research Areas

Innate Immunity, Dendritic Cells, Inflammation, Sepsis, RNAi.

Major scientific achievements

2013 Pfizer Award for Basic Research. "Anthracyclines induce DNA damage response-mediated protection against severe sepsis". Nuno Figueiredo, Angelo Chora, Helena Raquel and Luis Ferreira Moita.

Recent Most Relevant Publications

Nuno Figueiredo, Angelo Chora, Helena Raquel, Nadja Pejanovic, Pedro Pereira, Björn Hartleben, Ana Neves-Costa, Catarina Moita, Dora Pedroso, Andreia Pinto, Sofia Marques, Hafeez Faridi, Paulo Costa, Raffaella Gozzelino, Jimmy L. Zhao, Miguel P. Soares, Margarida Gama-Carvalho, Jennifer Martinez, Qingshuo Zhang, Gerd Döring, Markus Grompe, J. Pedro Simas, Tobias B. Huber, David Baltimore, Vineet Gupta, Douglas R. Green, João A. Ferreira and Luis F. Moita. Anthracyclines induce DNA damage, response-mediated protection against severe sepsis. *Immunity* **39**(5), 874-84, November 14, 2013.

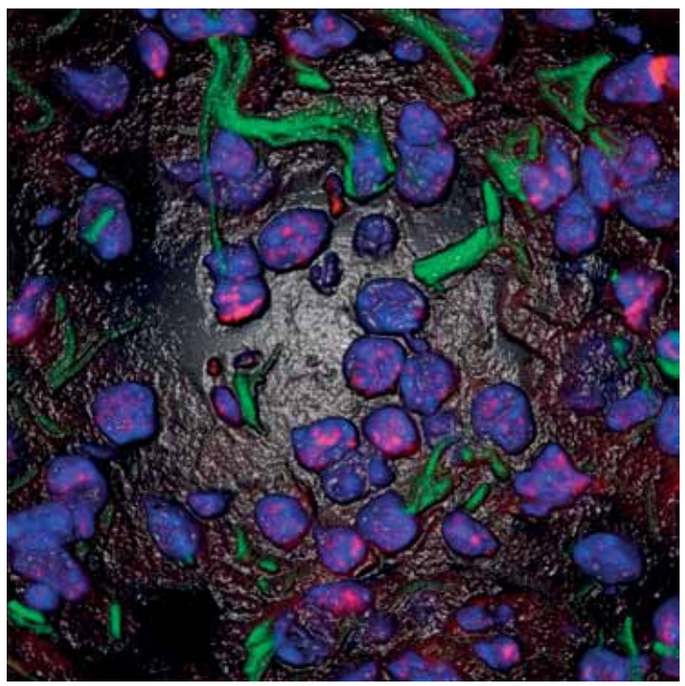
Cebrian I, Visentin G, Blanchard N, Jouve M, Bobard A, Moita C, Enninga J, Moita LF, Amigorena S, Savina A. (2011) Sec22b regulates phagosomal maturation and antigen crosspresentation by dendritic cells, *Cell* http://www.sciencedirect.com/science/article/pii/S0092867411013596. (Journal IF: 32.403, Citations: 26)

Robinson MJ, Osorio F, Rosas M, Freitas RP, Schweighoffer E, Gross O, Verbeek JS, Ruland J, Tybulewicz V, Brown GD, Moita LF, Taylor PR, Reis e Sousa C. (2009) Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. *Journal of Experimental Medicine* http://jem.rupress.org/content/206/9/2037.long. (Journal IF: 13.853, Citations: 148)

Ostrowski, M., Carmo, N.B., Krumeich, S., Fanget, I., Raposo, G., Savina, A., Moita, C.F., Schauer, K., Hume, A.N., Freitas, R.P., Goud, B., Benaroch, P., Hacohen, N., Fukuda, M., Desnos, C., Seabra, M.C., Darchen, F., Amigorena, S., Moita, L.F.*, Thery, C. (2010) Rab27 controls constitutive exosome secretion. *Nat Cell Biol* http://www.nature.com/ncb/journal/v12/n1/full/ncb2000.html. (Journal IF: 19.488, Citations: 139)

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* http://www.sciencedirect.com/science/article/pii/S107476130900137X. (Journal IF: 21.637, Citations: 61)

Ana Roxo Leão Neves Costa Post-doctoral Investigator | **Ângelo António Ferreira Chaves do Rosário Chora** Post-doctoral Investigator | **Catarina Susana Ferreira Moita** Post-doctoral Investigator | **Dora Cristina dos Santos Pedroso** Technician | **João António Augusto Ferreira** Principal Investigator | **Maria Helena Teixeira Raquel Gonçalves** Post-doctoral Investigator | **Nadja Pejanovic** Post-doctoral Investigator | **Pedro Martins Didelet Pereira** PhD Student | **Raquel Ferreira Rodrigues** Post-doctoral Investigator | **Richard Staats** PhD student | **Susana de Castro Luís Lopes Moreira** PhD Student | **Tiago Rodrigues Velho** MSc Student



This image is an artistic digital rendition of a confocal microscopy image of a lung section from a mouse after whole body irradiation (Dapi in blue, ĐH2AX (mAb) in red and autofluorescence in green). Original confocal image by João Ferreira. Image was stylized by Luis Ferreira Moita.

MARIA MOTA

LAB

PhD (1998) in Molecular Parasitology at University College London, UK.
Post-doctoral research at New York University Medical Center, USA.
Principal Investigator at Instituto Gulbenkian de Ciencia, 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).

Maria Manuel Mota | Group Leader
mmota@medicina.ulisboa.pt

Biology and physiology of malaria and other infections

Despite renewed eradication efforts from the international community, malaria still exerts an enormous disease burden, with nearly half the planet's population at risk of infection. Our overall goal has always been to understand how the disease-causing Plasmodium parasites establish and survive in their host as a way to design efficient and rational strategies to combat malaria.

Research Areas

Host-Plasmodium interactions, Nutrient sensing, Innate immune response against Plasmodium infection, Host metabolism and Plasmodium infection, Effects of dietary habits on malaria, Cell biology of Plasmodium liver stages.

Major scientific achievements

During 2013 the Mota Laboratory has:

- Shown that torins, developed as ATP-competitive mTOR kinase inhibitors, are fast-acting and highly potent antiplasmodial compounds (PNAS 110:E2838);
- Revealed, in collaboration with R. Moreira and F. Lopes (FFUL, PT), a number of new anti-malarial compounds (*J Med Chem*. **56**, 7679; *Eur J Med Chem*. **69**, 872);
- Established, in collaboration with S. Bhatia (MIT, USA), the liver stages for both human malaria parasites P. falciparum and P. vivax in a microscale human liver platform (*Cell Host Microbe* **14**, 104);
- Discovered that the host uses a sensor mechanism (until now only known to detect certain type of viruses) to detect Plasmodium parasites during liver stages of infection, ending the long disseminated dogma that this stage progressed invisible to the host defences (*Nat Med*. **20**, 47).

The Head of the Lab, Maria M. Mota, has received the "Prémio Pessoa", a highly prestigious Award given yearly to a Portuguese personality of Arts, Literature or Science.

Afonso Miguel Nunes Ferreira Trainee | **Ana Filipa Caetano Parreira** Technician | **Ana Filipa Pintéus da Cruz** Post-doctoral Investigator | **Ana Margarida Aires Alves Vigário** Investigator, Assistant Professor | **Ana Margarida Ferreira Góis** Technician | **Ana Margarida Roque Sanches Vaz** MSc Student | **António Manuel Barbeiro Mendes** Post-doctoral Investigator | **Carolina Martins Peralta Lopes da Silva** Technician | **Cláudia B. Rodrigues Sá e Cunha Mesquita Gabriel** Post-doctoral Investigator | **Daniel José Martins Carapau** Post-doctoral Investigator | **Eliana Real** Post-doctoral Investigator | **Fernanda Garcia Guedes Baptista** Lab manager | **Gabriela Stephanie Peres Cristo** MSc Student | **Ghislain Guillaume Nicolas Cabal** Post-doctoral Investigator | **Inês Isabel Fernandes Gomes** Post-doctoral Investigator | **Iset Medina Vera** Post-doctoral Investigator | **Joana Cristina da Silva Sales Dias** Investigator | **Kirsten Hanson** Post-doctoral Investigator | **Ksenija Slavic** Post-doctoral Investigator | **Lénia Marisa Pereira Rodrigues** Post-doctoral Investigator | **Liliana Mancio Silva** Post-doctoral Investigator | **Lisa Alves Azevedo** Technician | **Márcia Melo Medeiros** Post-doctoral Investigator | **Marco Andre Manso Domingues** Investigator | **Margarida Maria Teles Grilo Ruivo** Technician | **Maria Inês Sousa de Albuquerque** Technician | **Maurice Ayamba Itoe** Post-doctoral Investigator | **Miguel Dinis Monteiro dos Santos** Trainee | **Miguel Prudêncio** Principal Investigator | **Neide Marina Vieira Pereira** Post-doctoral Investigator | **Patrícia dos Santos Meireles** PhD Student | **Patrícia Irene da Silva Inácio** PhD Student | **Peter Liehl** Post-doctoral Investigator | **Sofia Pinto Guia Marques** Lab manager | **Vanessa Alexandra Zuzarte Luís** Post-doctoral Investigator

Recent Most Relevant Publications

Liehl P, Zuzarte-Luís V, Chan J, Zillinger T, Baptista F, Carapau D, Konert M, Hanson KK, Carret C, Lassnig C, Müller M, Kalinke U, Saeed M, Chora AF, Golenbock DT, Strobl B, Prudêncio M, Coelho LP, Kappe SH, Superti-Furga G, Pichlmair A, Vigário AM, Rice CM, Fitzgerald KA, Barchet W, Mota MM. 2014. Host-cell sensors for Plasmodium activate innate immunity against liver-stage infection. *Nat Med* **20**(1), 47-53. doi: 10.1038/nm.3424. Epub 2013 Dec 22. PMID: 24362933. (Journal IF: 27.14, Citations: 1)

Hänscheid T, Moreira R, Marti M, Mota MM. (2013) Torins are potent antimalarials that block replenishment of Plasmodium liver stage parasitophorous vacuole membrane proteins. *Proc Natl Acad Sci USA* **110**(30), E2838-47. (Journal IF: 9.74, Citations: 3)

Derbyshire ER, Prudêncio M, Mota MM, Clardy J. (2012) Liver-stage malaria parasites vulnerable to diverse chemical scaffolds. *Proc Natl Acad Sci* **109**, 8511-6. (Journal IF: 9.74, Citations: 14)

Hanson KK, Ressurreição AS, Buchholz K, Prudêncio M, Herman-Ornelas JD, Rebelo M, Beatty WL, Wirth DF,

Portugal S, Carret C, Recker M, Armitage AE, Gonçalves LA, Epiphanio S, Sullivan D, Roy C, Newbold CI, Drakesmith H, Mota MM. (2011) Host-mediated regulation of superinfection in malaria. *Nature Medicine* **17**(6), 732-7. (Journal IF: 27.14, Citations: 55)

Epiphanio S, Campos MG, Pamplona A, Carapau D, Pena AC, Ataíde R, Monteiro CA, Félix N, Costa-Silva A, Marinho CR, Dias S, Mota MM. (2010) VEGF promotes malaria-associated acute lung injury in mice.. *PLoS Pathogens* **6**(5), e1000916. (Journal IF: 9.13, Citations: 23)

SOFIA OLIVEIRA

LAB

Research fellow (1997-2001), Princeton University, USA.
PhD (2002) Faculdade de Medicina da Universidade de Lisboa (FMUL), Portugal.
Post-doctoral fellow (2001-2004), Center for Human Genetics, Duke University Medical Center, USA.
Principal Investigator (2004-2008), Instituto Gulbenkian Ciência, Oeiras, Portugal.
Principal Investigator (since 2008), Instituto de Medicina Molecular, Lisbon, Portugal.
Invited Assistant Professor (since 2008), FMUL, Portugal.

Sofia A. Oliveira | Group Leader
aaoliveira@medicina.ulisboa.pt

Identifying novel susceptibility genes for complex diseases

Our research focuses on understanding the genetic architecture of complex diseases such as stroke, Behçet's Disease, Primary Spontaneous Pneumothorax, and intracranial aneurysms. Common diseases result from the interaction of environmental and genetic factors, and an in-depth evaluation of their genetic underpinnings will not only unravel complex inheritance patterns but will also enable a better understanding of the environmental risks. We use both traditional and new approaches to identify novel susceptibility genes. We believe that studies with a multifaceted and multidisciplinary framework will have the greatest success in dissecting the complex etiology of common disorders and that they will ultimately lead to the development of novel prevention strategies and targeted therapies.

Research Areas

Genetics, Genomics, Complex diseases.

Major scientific achievements

In 2013, we published several papers describing for the first time:

1. The association of the neuroregulin signaling pathway with Behçet'disease (BD);

2. The FUT2 gene as a putative link between genes and environment in BD susceptibility. These novel findings were achieved through the convergence of several genome-wide approaches (e.g. microarray expression profiling, GWAS-genomewide assocation studies) and open new avenues for research into BD etiopathogenesis.

Furthermore, we were awarded the Prémio Robalo Cordeiro SPP/GSK 2013 from the Sociedade Portuguesa de Pneumologia in recognition of our pioneering work in the field of the genetic susceptibility to primary spontaneous pneumothorax (PSP).

Recent Most Relevant Publications

Xavier JM, Shahram F, Sousa I, Davatchi F, Matos M, Abdollahi BS, Sobral J, Nadji A, Oliveira M, Ghaderibarim F, Shafiee NM, Oliveira SA (2013). FUT2: filling the gap between genes and environment in Behçet's disease? *Annals of the Rheumatic Diseases* Dec 10, 2013. doi:10.1136/annrheumdis-2013-204475.(http://www.ncbi.nlm.nih.gov/pubmed/24326010) (Journal IF: 9.111, Citations: 0)

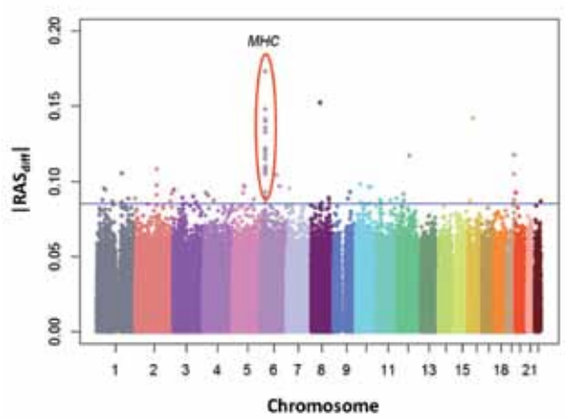
Krug T, Gabriel JP, Taipa R, Fonseca BV, Domingues-Montanari S, Fernandez-Cadenas I, Manso H, Gouveia L, Sobral J, Albergaria I, Gaspar G, Jiménez-Conde J, Rabionet R, Ferro JM, Montaner J, Vicente AM, Silva MR, Matos I, Lopes G, Oliveira SA. (2012) Tetratricopeptide repeat domain 7B emerges as a novel risk factor for ischemic stroke through the convergence of several genome-wide approaches.. *Journal of Cerebral Blood Flow and Metabolism* **32**, 1061-1072. (Journal IF: 5.398, Citations: 2)

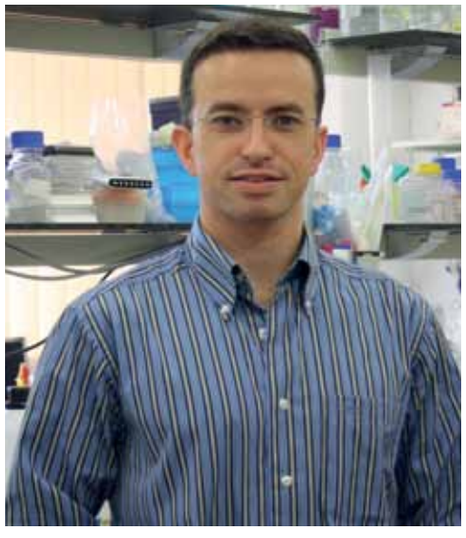
Xavier JM, Shahram F, Davatchi F, Rosa A, Crespo J, Abdollahi BS, Nadji A, Jesus G, Barcelos F, Patto JV, Shafiee NM, Ghaderibarim F, Oliveira SA. (2012) Association study of IL10 and IL23R-IL12RB2 in Iranian Behçet's disease patients. *Arthritis & Rheumatism* **64**, 2761-2772. (Journal IF: 7.477, Citations: 5)

Catarina Beatriz Silva Ferreira MSc Student | **Inês Girão Meireles de Sousa** Post-doctoral Investigator | **Joana Gonçalves de Gouveia Maia Xavier** PhD Student | **Madalena Cristina Rocha Martins** Post-doctoral Investigator | **Maria João Matos Rocha** MSc Student | **Patrícia Alexandra Silva Santos** MSc Student | **Patricia Carla Simões Abrantes** Post-doctoral Investigator | **Vânia Patrícia Ferreira Francisco** Technician

Xavier JM, Shafiee NM, Ghaderi F, Rosa A, Abdollahi BS, Nadji A, Shahram F, Davatchi F, Oliveira SA. (2011) Association of mitochondrial polymorphism m.709G>A with Behçet's disease (BD). *Annals of the Rheumatic Diseases* **70**, 1514-16. (Journal IF: 9.111, Citations: 1)

Martins M, Rosa A, Guedes LC, Fonseca BV, Violante S, Mestre T, Coelho M, Rosa MM, Martin ER, Vance JM, Outeiro TF, Wang L, Borovecki F, Ferreira JJ, Oliveira SA. (2011) Convergence of microRNA expression profiling, Ð-synuclein interacton and GWAS results support the role of the glycosphingolipid biosynthesis and the ubiquitin proteasome system in Parkinson's disease. *PLoS One* **6**, e25443. (Journal IF: 3.730, Citations: 13)





TIAGO OUTEIRO

LAB

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

Tiago Fleming Outeiro | Group Leader
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Protein misfolding and neurodegeneration

The Tiago Outeiro's Lab started in June 2007, with the goal of understanding the molecular basis of disorders intimately associated with protein misfolding and aggregation, mostly those which affect the brain, such as Parkinson's, Huntington's, or Alzheimer's disease.

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.

Our ultimate goal is 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.

Research Areas

Protein misfolding and aggregation, Yeast models of neurodegenerative disease, Neurodegeneration and Neuroinflammation, Genetic screens, In vivo imaging, Translational research.

Major scientific achievements

A major hurdle in the study of posttranslational modifications in alpha-synuclein, a central player in Parkinson's disease, is its purification from relevant biological materials. We developed a simple and effective method (*Journal of Neurochemistry*, 2013) that enabled us to conduct a series of studies demonstrating the contribution of different PTMs to its aggregation and toxicity (*Mol. Neurobiology*, 2013). In collaboration with colleagues in the UK, we determined the crystal structure of KMO, an important molecule in the context of several neurodegenerative disorders (*Nature*, 2013). In another study, we provided evidence, for the first time, that sirtuin 2 modulates the inflammatory responses of microglia, the resident immune cells in the brain (*The EMBO Journal*, 2013).

In 2013, Tiago Outeiro was awarded the Silver Medal of Merit from the Portuguese Ministry of Health for our contributions in the field of neurodegenerative disorders, a clear sign of recognition for our work.

Recent Most Relevant Publications

Sajjad MU, Green EW, Hands S, Miller-Fleming L, Herrera F, Kyriacou CP, Faull R, Morton AJ, Jones L, Outeiro TF, Giorgini F, Wyttenbach A (2013) DJ-1 modulates aggregation and pathogenesis in models of Huntington's disease. *Human Molecular Genetics* **23**, (3), 755-66 (Journal IF: 7.692, Citations: 0)

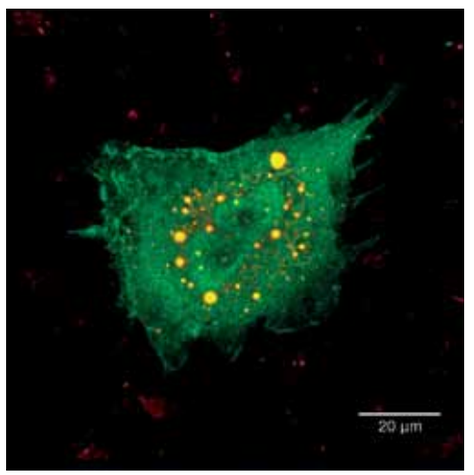
Pais TF, Szegö EM, Marques O, Miller-Fleming L, Antas P, Guerreiro P, de Oliveira RM, Kasapoglu B and Outeiro TF (2013). The NAD-dependent deacetylase sirtuin 2 is a suppressor of microglial activation and brain inflammation. *EMBO Journal* **32**, (19), 2603-16 (Journal IF: 9.822, Citations: 2)

Amaral M, Levy C, Heyes DJ, Lafite P, Outeiro TF, Giorgini F, Leys D, Scrutton NS (2013) Structural basis of kynurenine 3-monooxygenase inhibition. *Nature* **496**, (7445), 382-5 (Journal IF: 38.597, Citations: 2)

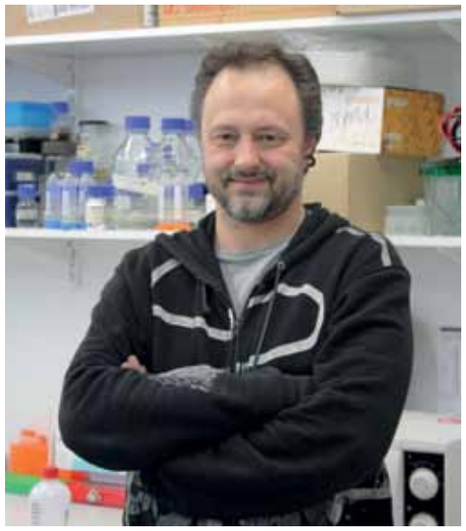
Diógenes, M.J.*, DiasR.B.*, Rombo, D.M.*, Vicente Miranda, H., Maiolino, F., Guerreiro, P., Nasstrom, T., Franquelim, H.G., Oliveira, L.M., Castanho, M.A.R.B., Lannfelt, L., Bergstrom, J., Ingelsson, M., Quintas, A., Sebastião, A.M., Lopes, L.V., Outeiro, T.F. (2012) Extracellular alpha-synuclein oligomers modulate synaptic transmission and impair LTP via NMDA-receptor activation. *Journal of Neuroscience* **32**, (34), 11750-62 (Journal IF: 6.908, Citations: 7)

Outeiro TF, Kontopoulos E, Altmann SM, Kufareva I, Strathearn KE, Amore AM, Volk CB, Maxwell MM, Rochet JC, McLean PJ, Young AB, Abagyan R, Feany MB, Hyman BT, Kazantsev AG (2007) Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. *Science* **317**, (5837), 516-9 (Journal IF: 31.027, Citations: 337)

Ana Dulce Correia Principal Investigator | **David Miguel de Jesus Pedras** MSc Student | **Diana Leonor Constantino Macedo** PhD Student | **Elisa Basso** PhD Student | **Federico Herrera García** Post-doctoral Investigator | **Filipa Magalhães da Silva** MSc Student | **Hugo Vicente Miranda** Post-doctoral Investigator | **Joana Margarida Marques Branco Santos** PhD Student | **João Tiago dos Santos Fernandes** PhD Student | **Madalena Reimao Pinto** Technician | **Márcia Santos Oliveira** Technician | **Marcos António dos Santos Rodrigues Gomes** Technician | **Maria Leonor Lemos Pereira Miller Fleming** PhD Student | **Maria Teresa A.S. Faria Pais** Principal Investigator | **Marta Sofia Pereira De Castro Vitorino** Technician | **Oldriska Marques** PhD Student | **Patricia Isabel da Silva Guerreiro** PhD Student | **Pedro Rafael da Costa Antas** Technician | **Rafaela Ferreira Cássio** MSc Student | **Renato Gomes da Silva Martinho** MSc Student | **Rita João de Oliveira** Investigator | **Rita João Rosado Serranito Ramos** Technician | **Rui Manuel da Silva Soares** Post-doctoral Investigator | **Sandra Clara Dias Jacinto Figueiredo** PhD Student, MD | **Sandra Isabel Nogueira Tenreiro** Principal Investigator | **Susana Alexandra de Barros Gonçalves** PhD Student | **Telma Elita Bertolin** Post-doctoral Investigator | **Tiago Nuno Calado Mendes** Technician | **Tomás Ribeiro da Silva Lopes da Fonseca** PhD Student



α-Synuclein aggregates colocalize with ubiquitin in H4 neuroglioma cell line. Cells were processed for immunocytochemistry with anti-Ð-synuclein (green) and anti-ubiquitin (red).



MIGUEL PRUDÊNCIO

LAB

Investigador FCT (since 2013) Group Leader - Instituto de Medicina Molecular-Faculdade de Medicina da Universidade de Lisboa (IMM-FMUL), Portugal.
Principal Investigator (2008-2013) and Post-doctoral researcher (2005-2008) at IMM-FMUL.
Post-doctoral researcher (2004) at Instituto Gulbenkian de Ciência, Oeiras, Portugal.
Post-doctoral researcher (2000-2004) at University of Leiden, Leiden, The Netherlands.
PhD (2000) in Biochemistry at University of East Anglia, Norwich, UK.
B.S. degree (10993) in Biochemistry at Universidade de Lisboa, Lisboa, Portugal.

Miguel Prudêncio | Group Leader
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Ana Margarida Roque Sanches Vaz MSc Student | **António Manuel Barbeiro Mendes** Post-doctoral Investigator | **Cláudia B. Rodrigues Sá e Cunha Mesquita Gabriel** Post-doctoral Investigator | **Inês Isabel Fernandes Gomes** Post-doctoral Investigator | **Maria Inês Sousa de Albuquerque** Technician | **Marta Monteiro Maia Machado** Technician | **Miguel Filipe Duarte** MSc Student | **Patrícia dos Santos Meireles** PhD Student

Hepatic stage of malaria infection

Our interests span a wide range of topics within the malaria field, with particular emphasis on the hepatic stage of infection. We are interested in elucidating hitherto obscure aspects of the biology of Plasmodium infection, unveiling novel host-parasite interactions, and developing new drug- and vaccine-based anti-malarial strategies. Our research areas are:

- Nutrient and ion transport and homeostasis during Plasmodium development inside hepatic cells;
- Novel host-Plasmodium molecular interactions;
- Bile acid metabolism and nuclear receptor-mediated signaling mechanisms in the context of Plasmodium liver infection;
- Novel compounds against Plasmodium liver stages;
- Malaria vaccines;
- The reciprocal influence of Plasmodium and Trypanosoma co-infections.

Research Areas

Malaria, Parasitology, Vaccines, Host-pathogen interactions, Liver-stage Plasmodium infection.

Major scientific achievements

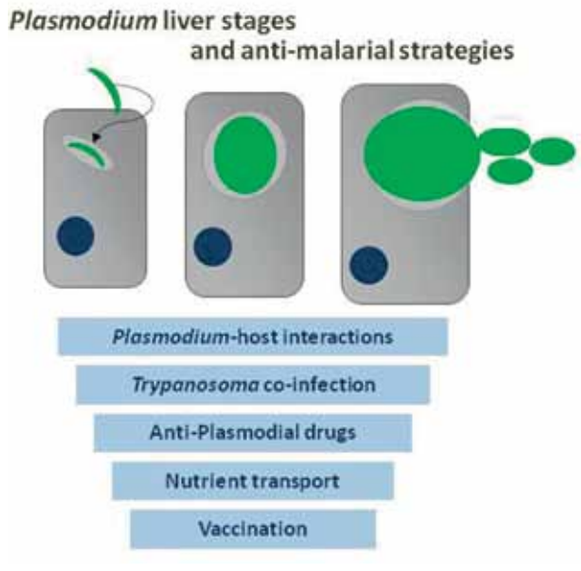
Since July 2013, when it was created, the Prudêncio Lab has:

- Published 5 collaborative papers in peer-reviewed, international journals;
- Been awarded a Phase II Grand Challenges Explorations award by the Bill & Melinda Gate Foundation;
- Filed one PCT international application (Genetically modified rodent Plasmodium parasites as platforms for a whole-organism malaria vaccine);
- Won the health track and the grand prize of the "BES inovação 2013" award;
- Won a honorary mention in the" Building Global Innovators 2013" contest;
- Participated in several International and National conferences and meetings;
- Organised a symposium on pre-erythrocytic malaria vaccines at the 6th MIM conference on malaria (South Africa);
- Had numerous media appearances in relation to its scientific activities.

In this period the lab has also expanded from its original 6 to the present 8 researchers, and established or furthered collaborations with several National and International research groups.

Recent Most Relevant Publications

Liehl P, Zuzarte-Luís V, Chan J, Zillinger T, Baptista F, Carapau D, Konert M, Hanson KK, Carret C, Lassnig C, Müller M, Kalinke U, Saeed M, Chora AF, Golenbock DT, Strobl B, Prudêncio M, Coelho LP, Kappe SH, Superti-Furga G, Pichlmair A, Vigário AM, Rice CM, Fitzgerald KA, Barchet W, Mota MM. 2014. Host-cell sensors for Plasmodium activate innate immunity against liver-stage infection. *Nat Med* **20**(1), 47-53. doi: 10.1038/nm.3424. Epub 2013 Dec 22. PMID: 24362933. (Impact Factor: 27.14; Citations: 0)



A.S. Ressurreição, D. Gonçalves, A.R. Sitoe, I.S. Albuquerque, J. Gut, A. Góis, L.M. Gonçalves, M.R. Bronze, T. Hanscheid, G.A. Biagini, P.J. Rosenthal, M. Prudêncio, P. O'Neill, M.M. Mota, F. Lopes, R. Moreira (2013) Structural optimization of quinolon-4(1H)-imines as dual-stage antimalarials: towards increased potency and metabolic stability. *J. Med. Chem* **56**, 7679-7960. (Journal IF: 5.8, Citations: 0)

T. Rodrigues, A.S. Ressurreição, F.P. da Cruz, I.S. Albuquerque, J. Gut, M. Carrasco, D. Gonçalves, M.M. Mota, P.J. Rosenthal, R. Moreira, M. Prudêncio, F. Lopes (2013). Flavones as isosteres of 4(1H)-quinolones: discovery of ligand efficient and dual stage antimalarial lead compounds. *Eur. J. Med. Chem.* **69**, 872-880. (Journal IF: 3.8, Citations: 0)

MÁRIO RAMIREZ

LAB

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

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Adriana Domingos Policarpo MSc Student | **Ana Catarina Martins Lameiras** Investigator | **Ana Isabel Aquino Friães** PhD Student | **Ana Paula da Silva Pereira** Administrative | **Ana Sílvia Soares Mendes Moreira** Investigator | **Andreia das Neves Horácio** PhD Student | **Andreia Sofia Agostinho Gravata** Trainee | **Bruno Filipe Ribeiro Gonçalves** MSc Student | **Carolina Isabel Glória Tempera** Technician | **Catarina Costa** PhD Student | **Catarina Teresa Condinho Pato** PhD Student | **Cláudia Patrícia Machado Lemos e Sousa** MSc Student | **Elisabete Martins** Post-doctoral Investigator | **Joana Alexandra Pimento Lopes** Technician | **Joana Gomes Martins Lopes** MSc Student | **João André Nogueira Custódio Carriço** Principal Investigator | **Jorge Miguel Diamantino Miranda** PhD Student | **José Melo Cristino** Principal Investigator | **Liliana Sofia Cardoso** Investigator | **Márcia Carlos Rocha Boura** MSc Student | **Marcos Pinho** Investigator | **Maria João Rua Frias** Post-doctoral Investigator | **Maria Sousa Rebelo** PhD Student | **Mickael Santos da Silva** MSc Student | **Nuno Miguel Santos Rodrigues** MSc Student | **Pedro Tiago Gonçalves Monteiro** Post-doctoral Investigator | **Raquel Baptista Arinto Garcia** MSc Student | **Rita Gaspar Cabrita** Undergraduate | **Rosangela Maria Rodrigues Carvalho Frita** PhD Student | **Rui Manuel São Martinho de Oliveira** Investigator | **Sandra Cristina Machado de Matos** Investigator | **Sandra Isabel Rodrigues de Aguiar** Post-doctoral Investigator | **Sérgio Miguel Cardoso Marcelino dos Santos** Investigator | **Thomas Hanscheid** Principal Investigator

Molecular microbiology and infection

We aim to understand the dynamics of populations of bacterial pathogens and how they respond to selective forces. We focus on the effect of antimicrobial use, human vaccination and host diversity on bacterial populations. Investigations are also exploring 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 for further characterization.

A strong bioinformatics effort in the area of bacterial population simulation, microbial typing data sharing, data analysis and visualization tools is ongoing. The development of novel laboratory methodologies for the diagnosis of infectious diseases is also an active area of research.

Research Areas

Population biology and epidemiology, Interactions of malaria and other infectious diseases, Bioinformatics, Molecular epidemiology, Diagnostic tools, Antibiotic resistance.

Major scientific achievements

Characterization of differences in virulence potential of S. pyogenes clones and changes in their major virulence factors. Identification of an unusual secretion mechanism of the lysins of pneumococcal phages.

Development of MLST for S. canis and characterization of its zoonotic origin. Documentation of continuing changes in S. pneumoniae causing invasive infections with vaccination and its consequences for future potential vaccines. Laying the foundations for the development of a typing and a NGS process ontology, with the aim of linking existing sequence based typing databases and novel NGS data. Development of a novel flow cytometry assay for antimalarial drug sensitivity testing, using detection of haemozoin without any further reagents.

Development of a novel and easy haemozoin inhibition assay to screen for haemozoin inhibiting antimalarial drugs. Interactions of haemozoin with a rodent model of tuberculosis and effects of hemozoin on phagocytosis and killing of Salmonella typhim.

Recent Most Relevant Publications

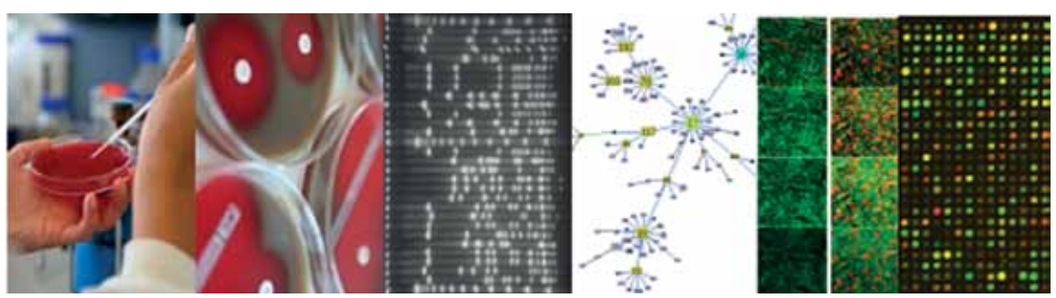
Melo-Cristino J., C. Resina, V. Manuel, L. Lito, M. Ramirez. (2013) First case of infection with vancomycin-resistant Staphylococcus aureus in Europe. *The Lancet*. **382**,205. http://www.ncbi.nlm.nih.gov/pubmed/23791472. (Journal IF: 39.060, Citations 1)

Rebelo, M., C. Sousa, H. M. Shapiro, M. M. Mota, M. P. Grobusch, and T. Hänscheid (2013) A novel flow cytometric hemozoin detection assay for real-time sensitivity testing of Plasmodium falciparum. *PLoS ONE***8**,e61606.http://www.ncbi.nlm.nih.gov/pubmed/23637865. (Journal IF: 3.730, Citations: 0)

Francisco, A. P., C. Vaz, P. T. Monteiro, J. Melo-Cristino, M. Ramirez, and J. A. Carriço. (2012) PHYLOViZ: Phylogenetic inference and data visualization for sequence based typing methods. *BMC bioinformatics* **13**,87. http://www.ncbi.nlm.nih.gov/pubmed/22568821. (Journal IF: 3.024, Citations: 21)

Martins E. R., A. Andreu, P. Correia, T. Juncosa, J. Bosch, M. Ramirez, and J. Melo-Cristino on behalf of the Microbiologist Group for the Study of Vertical Transmission Infections from the Catalan Society for Clinical Microbiology and Infectious Diseases. (2011) Group B streptococci causing neonatal infections in Barcelona are a stable clonal population: 18-year surveillance. *J Clin Microbiol* **49**,2911-2918. http://www.ncbi.nlm.nih.gov/pubmed/21697333. (Journal IF: 4.068, Citations: 9)

Aguiar, S. I., M. J. Brito, J. Gonçalo-Marques, J. Melo-Cristino, and M. Ramirez. (2010) Serotypes 1, 7F and 19A became the leading causes of pediatric invasive pneumococcal infections in Portugal after 7 years of heptavalent conjugate vaccine use. *Vaccine* **28**,5167–5173.http://www.ncbi.nlm.nih.gov/pubmed/20558247. (Journal IF: 3.492, Citations: 23)



CARLOTA SALDANHA

LAB

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

Carlota Saldanha | Group Leader
carlotasaldanha@medicina.ulisboa.pt

Ana Rosa Miranda dos Santos Silva Herdade PhD Student | **Angelo Calado** Principal Investigator | **Catarina Cabrita Ramos** Investigator | **Ekaterina Sergueevna Potapova** MSc Student | **Henrique Rosário** Investigator | **Mariana Mota Castro Dias** Investigator | **Marta Filipa Paulino Silvestre** PhD Student | **Nuno Alexandre Almeida Santos** MSc Student | **Patrícia Alexandra Veloso Napoleão** Post-doctoral Investigator | **Pedro Miguel Araújo Guerreiro Teixeira** MSc Student | **Rita Maria Santos Esteves** Investigator | **Sara Louro Moleirinho** Investigator | **Sara Maria de Almeida Beijinho** MSc Student | **Sofia Ludovina Novais de Oliveira** PhD Student | **Vanda Lúcia de Carvalho Vitorino de Almeida** PhD Student

Erythrocyte, leukocyte recruitment and inflammation

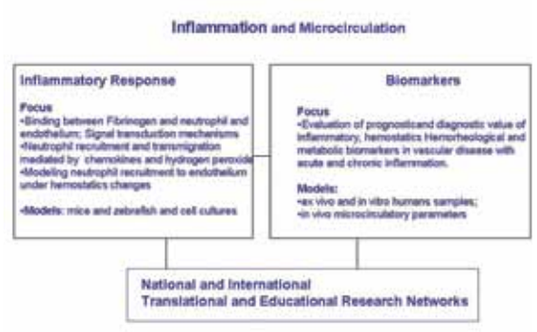
Understanding how leukocyte recruitment is governed and regulated is pivotal for the comprehension of the mechanisms underlying inflammation. We are focused on deciphering what molecular partners are targeted by fibrinogen as it modulates neutrophil action and how distinct chemoattractants, like chemokines and hydrogen peroxide, cooperate in neutrophil recruitment. We aim also to develop theoretical models to simulate phenomena occurring at the leukocyte-vascular wall interface. Under our scope are as well the study of fibrinogen-mediated signal transduction on erythrocytes and the validation of inflammatory biomarkers in vascular diseases. We expect to translate our findings towards a better understanding and management of inflammatory pathologies (ex: sepsis and cardiovascular diseases).

Research Areas

Inflammation, Microcirculation, Neutrophil, Erythrocyte, Hemorheology.

Major scientific achievements

Inflammation requires the interplay of distinct mediators, like erythrocytes and neutrophils as well as acetylcholine (ACh), fibrinogen, chemokines and hemodynamic forces. Importantly, it is associated with hemorheological abnormalities and a dysfunctional endothelium. In erythrocytes, we have demonstrated that soluble fibrinogen is able to target the membrane CD47 in an age-dependent way. We have also shown that the erythrocyte nitric oxide (NO) efflux increases under conditions simulating hyperfibrinogenemia in dependence of the induction of band 3 protein phosphorylation but remains unchanged in the presence of ACh. Moreover, erythrocyte NO efflux was shown to be negatively associated with carotid intima-media thickness in systemic lupus erythematosus and rheumatoid arthritis patients presenting a reduced whole blood viscosity and erythrocyte deformability and an increased erythrocyte aggregation tendency. We have also reported that soluble fibrinogen is able to increase neutrophil free radical production and to bind the neutrophil membrane independently of the integrin Mac-1.In fibrinogen-deficient mice, we have further documented compromised leukocyte recruitment in comparison to control animals, that showed a role for fibrinogen in this process.



We have further used the zebrafish model to study the function of the CXC chemokine, CXCL8, in inflammation. Both zebrafish homologs, cxcl8-l1 and cxcl8-l2, were shown to be up-regulated upon wounding. By combining their expression knockdown with the in vivo tracking of neutrophils, we have shown that both chemokines are crucial for neutrophil recruitment and inflammation resolution. Cxcl8-l2 was further shown to signal at least through the zebrafish CXC chemokine receptor 2 (Cxcr2) for inducing neutrophil recruitment. By analyzing neutrophil migration in vivo via the use of the tracking software, PhagoSight, we observed that in the absence of these chemokines, the speed of the neutrophils migrating to the wound was significantly increased in comparison to control ones, although the directionality of the movement was not affected. These results suggest that in the zebrafish, a neutrophil sub-population may be recruited to inflamed areas in Cxcl8-independent mode. The development of numerical simulations based on hemodynamic and hemorheological parameters obtained in vivo from animal models allowed us to discriminate the existence of regions with distinct shear stress properties on the surface of leukocytes approaching the endothelium. We have also shown that the hydrodynamic behaviour of a cluster of recruited leukocytes establishes a strong motive for additional leukocyte recruitment. In this situation, we have further observed an increased endothelial shear stress. Finally, we have disclosed a new association between CD3+ T lymphocytes, oxidized low-density lipoprotein, and C-reactive protein in patients with acute myocardial infarction (AMI), by using a multi-biomarker approach, thus confirming the specificity of the immune response in AMI towards myocardial inflammation and remodelling.

Recent Most Relevant Publications

de Oliveira, S., Reyes-Aldasoro, C.C., Candel, S., Renshaw, S.A., Mulero, V., Calado, A. (2013) Cxcl8 (Interleukin-8) mediates neutrophil recruitment and behavior in the zebrafish inflammatory response. *J.Immunol.* **190**, 4349-59. (Journal IF: 5.673, Citations: 4)

de Almeida VV, Silva-Herdade A, Calado A, Rosário HS, Saldanha C. (2012) Fibrinogen modulates leukocyte recruitment in vivo during the acute inflammatory response. Clin Hemorheol Microcirc. (Epub ahead of print) DOI: 10.3233/CH-121662 http://iospress.metapress.com/content/h7348151t0883757/?genre=article&id=doi%3a10.3233%2fCH-121662 (Journal IF: 3.398, Citations: 0)

de Almeida VV, Calado A, Silva-Herdade AS, Rosário HS, Saldanha C. (2012) An in vitro study on the modulation of the neutrophil adhesive behavior by soluble fibrinogen. Clin Hemorheol Microcirc. (Epub ahead of print) DOI: 10.3222/CH-121662;(http://iospress.metapress.com/content/h7348151t0883757/?genre=article&id=doi%3a10.3233%2fCH-121662) (Journal IF: 3.398, Citations: 0)

de Oliveira S, Vitorino de Almeida V, Calado A, Rosário HS, Saldanha C.(2012) Integrin-associated protein (CD47) is a putative mediator for soluble fibrinogen interaction with human red blood cells membrane. *Biochim Biophys Acta* **1818**, 481-490. (Journal IF: 5.000, Citations: 2)

de Almeida VV, Calado A, Rosário HS, Saldanha C. (2012) Differential effect of soluble fibrinogen as a neutrophil activator. *Microvasc Res* **83**, (3), 332-6. (Journal IF: 2.828, Citations: 1)

NUNO SANTOS LAB

PhD (1999) at Universidade de Lisboa.
Research at the Universidade Técnica de Lisboa and at the University of California, Santa Barbara (USA).
Awarded the Calouste Gulbenkian Foundation Prize (2001) and the José Luís Champalimaud Prize on HIV Research (2004 and 2005).
Associate Professor with Habilitation at the Faculdade de Medicina da Universidade de Lisboa.

Nuno C. Santos | Group Leader
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Ana Catarina Fidalgo Barata **Ana de Souto Martins** MSc Student | **Ana Filipa Guedes** PhD Student | **Ana Isabel Figueiredo Martins** Investigator | **André Faustino** PhD Student | **Axel Hollmann** Post-doctoral Investigator | **Filomena Carvalho** Investigator, Assistant Professor | **Gabriela Guerra** Investigator | **Ivo C. Martins** Post-doctoral Investigator | **Marcelo T. Augusto** Investigator | **Marco M. Domingues** PhD Student | **Margarida Rodrigues** PhD Student | **Maria Inês Malho** MSc Student | **Patrícia M. Silva** MSc Student | **Pedro M. Matos** PhD Student | **Saulo Vieira** PhD Student from Universidade Federal do Rio de Janeiro | **Sónia Gonçalves Abreu** Investigator | **Susana dos Reis Gregório** MSc Student | **Virgínia Amaral** PhD Student from Universidade Federal do Rio de Janeiro

Biomembranes and nanomedicine

Biochemical and biophysical processes occurring in membranes of human cells, as well as of their viral and bacterial pathogens. Study of two steps of the enveloped viruses life cycle (mainly HIV-1 and dengue virus) that involve biomembranes – the entrance of the virus or its content into the target cell and the assembly of new virions. Study of the binding of fibrinogen to the erythrocyte membrane and its relevance as cardiovascular risk factor. Pre-clinical evaluation of the membrane activity and mechanism of action of antimicrobial peptides (AMP) and cell-penetrating peptides (CPP). On the Nanomedicine area, work on the development of innovative protein-ligand interactions biosensor systems, with improved selectivity and sensitivity (nanoparticles and amyloid-based biosensors).

Research Areas

Membranes, Nanomedicine, HIV, Dengue Virus, Peptide-based therapies (CPPs, AMPs, pep14-23), Atomic Force Microscopy (AFM), Fibrinogen.

Major scientific achievements

Understanding dengue virus (DENV) replication mechanisms is required to identify new therapeutic targets. Using AFM-based force spectroscopy, DLS, NMR and computational studies, we showed that DENV capsid (C) protein binds specifically to very low-density lipoproteins (VLDL). DENV C-VLDL interaction is K+-dependent and is inhibited by a new drug lead that we recently developed. ApoE may be the DENV C ligand on VLDL. Thus, lipoviroparticles formation may potentially be targeted for DENV life cycle inhibition.

Singlet oxygen produced by the new broad-spectrum antiviral LJ001 and related compounds, as well as by dUY11, induces changes on the viral membrane resulting in the inhibition of the fusion pore necessary for cell infection by HIV and other enveloped viruses.
The enhanced interaction of C34 cholesterol-conjugates with membranes concomitant with an enhanced exposure of the pocked binding domain, due the addition of a PEG linker, result in a more efficient blocking of HIV entry.

Recent Most Relevant Publications

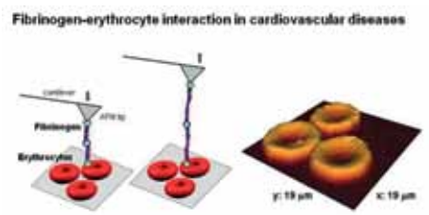
Domingues MM, Silva PM, Franquelim HG, Carvalho FA, Castanho MARB, Santos NC (2013) Antimicrobial protein rBPI21-induced surface changes on Gram-negative and Gram-positive bacteria. *Nanomedicine* (NBM), doi: 10.1016/j.nano.2013.11.002. (Journal IF: 6.930, Citations: 0)

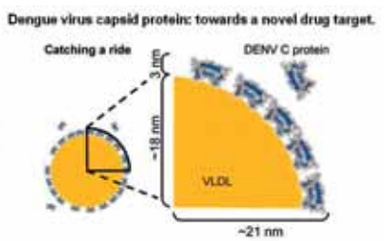
Padilla-Parra S, Matos PM, Kondo N, Marin M, Santos NC, Melikyan GB (2012) Quantitative imaging of endosome acidification and single retrovirus fusion with distinct pools of early endosomes. *Proc. Natl. Acad. Sci. USA* **109**, 17627-17632 (Journal IF: 9.737, Citations: 9)

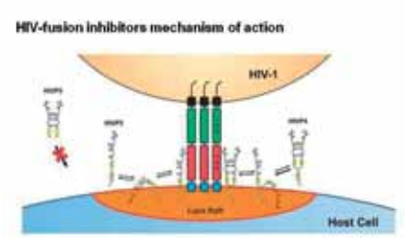
Carvalho FA, Carneiro FA, Martins IC, Assunção-Miranda I, Faustino AF, Pereira RM, Bozza PT, Castanho MARB, Mohana-Borges R, Da Poian AT, Santos NC (2012) Dengue virus capsid protein binding to hepatic lipid droplets (LD) is potassium ion dependent and is mediated by LD surface proteins. *J. Virol.* **86**, 2096-2108 (Journal IF: 5.076, Citations: 9)

Matos PM, Castanho MARB, Santos NC (2010) HIV-1 fusion inhibitor peptides enfuvirtide and T-1249 interact with erythrocyte and lymphocyte membranes. *PLoS ONE* **5**, e9830. (Journal IF: 3.730, Citations: 14)

Carvalho FA, Connell S, Miltenberger-Miltenyi G, Pereira SV, Tavares A, Ariëns RAS, Santos NC (2010) Atomic force microscopy-based molecular recognition of a fibrinogen receptor on human erythrocytes. *ACS Nano* **4**, 4609-4620 (Journal IF: 12.062, Citations: 24)







LEONOR SAÚDE

LAB

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

Leonor Saúde | Group Leader
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Ana Catarina Esteves Ribeiro Post-doctoral Investigator | **Ana Margarida da Silva Figueira** MSc Student | **Ana Margarida Pereira Cristovão Pinto** Technician | **Benedict Paul Both** MSc Student | **João Duarte Tavares da Silva Pereira** Post-doctoral Investigator | **José Guilherme Pereira de Almeida Santos** MSc Student | **Raquel Valente Mendes** PhD Student | **Rita Alexandra Rodrigues Pinto** PhD Student | **Rita Joana Soares Serrano** MSc Student | **Rita Leonor Alvares Cabral de Figueiredo Fior Sousa Soares** Post-doctoral Investigator | **Sara Maria Ferreira Fernandes** PhD Student | **Susana Alexandra Rodrigues Pascoal** Post-doctoral Investigator

Embryonic development and regeneration

We would like to understand the cellular and molecular mechanisms that control the left-right asymmetric placement of internal organs and the bilateral symmetric formation of musculoskeletal elements in vertebrates. In addition we are interested in make the bridge between the fundamental developmental processes that we have been studying with the mechanisms that have to be activated during regeneration upon severe injury.

Research Areas

Left-right asymmetry, Somite formation, Tissue/organ regeneration.

Major scientific achievements

We published one paper:
Pascoal P., de Lima J.E, Leslie J.D., Hughes S.M. and Saúde L. Notch signalling is required for the formation of structurally stable muscle fibres in zebrafish. *PloS ONE* **8**(6), e68021, 2013.

Raquel V. Mendes, a PhD student in the unit was awarded The Best Poster Award at the 2nd Meeting of the Portuguese Society of Developmental Biology (SPBD) and Benedict Both, a medical student working in our unit was awarded The Best GAPIC project.

Leonor Saúde was the co-organizer of the the 2nd Meeting of the Portuguese Society of Developmental Biology (SPBD) jointly with the Spanish Society for Developmental Biology (SEBD) in association with the Portuguese Society for Stem Cells and Cell Therapies (SPCE-TC).

Recent Most Relevant Publications

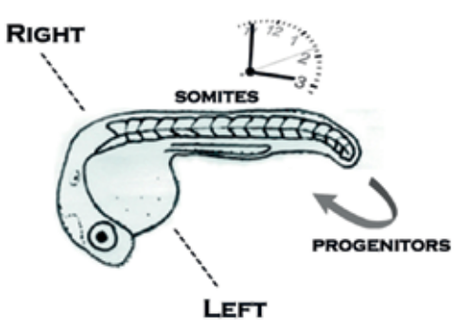
Fior R., Maxwell A.A., Ma T.P., Vezzaro A., Moens C.B., Amacher S.L., Lewis J. and Saúde L. (2012) Differentiation and movement of presomitic mesoderm progenitor cells are both controlled by Mesogenin1. *Development* **139**(24), 4656-65. (Journal IF: 7.09, Citations: 2)

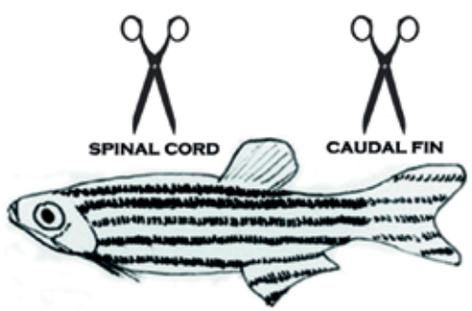
Azevedo A.S., Sousa S., Jacinto A. and Saúde L. (2012) An amputation resets positional information to a proximal identity in the regenerating zebrafish caudal fin. *BMC Developmental Biology* **12**(1), 24. (Journal IF: 2.79, Citations: 0)

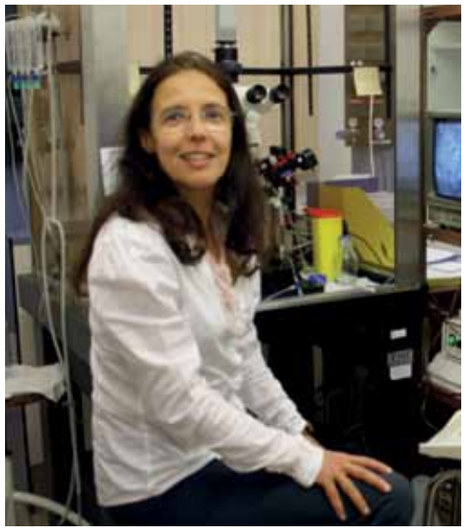
Azevedo A.S., Grotek B., Jacinto A., Weidinger G. and Saúde L. (2011) The regenerative capacity of the zebrafish caudal fin is not affected by repeated amputations. *PloS ONE* **6**(7), e22820. (Journal IF: 4.092, Citations: 5)

Lopes S.S., Lourenço R., Pacheco L., Moreno N., Kreiling J. and Saúde L. (2012) Notch signalling regulates left-right asymmetry through ciliary length control. *Development* **137**(21), 3625-32. (Journal IF: 7.09, Citations: 26)

Saúde L., Lourenço R., Gonçalves A. and Palmeirim I. (2005) terra is a left-right asymmetry gene required for left-right synchronization of the segmentation clock. *Nature Cell Biology* **7**(9), 918-920. (Journal IF: 19.488, Citations: 32)







ANA SEBASTIÃO

LAB

PhD (1987) in Cell Physiology, Universidade Nova de Lisboa.
Post-doctoral researcher at Instituto Gulbenkian de Ciência, Oeiras.
Associate Professor with Habilitation, Faculdade de Medicina da Universidade de Lisboa.

Ana Sebastião | Group Leader
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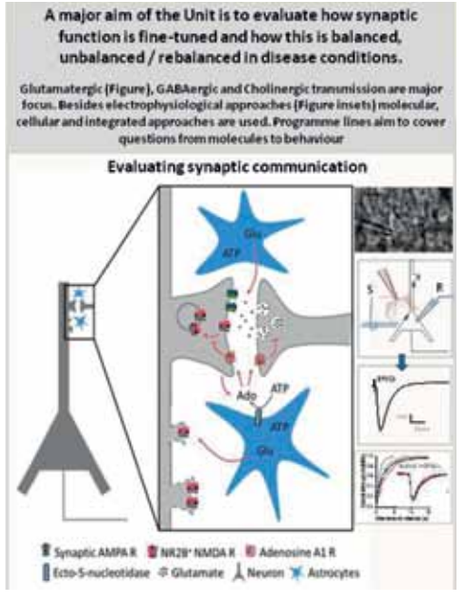
Neuronal communication and synaptopathies

A challenge in Neurosciences is to correct abnormal synaptic function, a commonality of most brain diseases. Interfering with endogenous processes that adjust synaptic function to the circuit needs has been proposed as a promising strategy to correct synaptic dysfunction. We aim to elucidate how the neuronal and glial components of the tripartite synapse are fine-tuned under normal and dysfunctional situations, and how it affects neuronal excitability. Tuning of neurogenesis, neuronal maturation and degeneration is also under Unit interests. We focus on endogenous modulators, namely on adenosine, endocanabinoids, neurotrophins and glycine. As disease models we have been focusing on Alzheimer's and Parkinson's disease, developmental epilepsy and amyotrophic lateral sclerosis.



Schematic drawing of a tripartite synapse, with the pre-synaptic, post-synaptic, as well as the astrocytic components, major player to shape neuronal communication. The scheme refers to a glutamatergic (excitatory) synapse, but GABAergic (inhibitory) synapses are also under Unit focus. On the left is show (from top to bottom) a microscopy image of a neuron under patch clamp recording (note electrode on the left), a scheme of the recording devices and synaptic currents (upper: evoked; lower: spontaneous) recordings

Research Areas

Tripartite synapse mechanisms, Neuronal excitation/inhibition balance, glia-to-neuron communication, Ageing, Neurodegenerative Mechanisms, Brain dysfunctions.

Major scientific achievements

1. Neuronal plasticity:

a) Adenosine affords endogenous regulation of ischemia-induced plasticity (Dias *et al* Neuropharmac) and may contribute to adjust the threshold for plasticity according to prior experience (Dias *et al* TINS)

b) A2ARs control the influence of BDNF TrkB receptors upon LTD (Rodrigues *et al*). A2A/TrkB interactions require lipid rafts (Assaife-Lopes *et al* 2013), which are perturbed in ageing (Sebastião *et al* 2013).

2. Astrocytes:

a) GlyT2 are expressed in astrocytes (Aroeira *et al* 2013).

b) Adenosine acts via a heterocomplex of adenosine receptors in astrocytes to control GABA transport (Cristóvão-Ferreira *et al* 2013)

3. Neurodegenerative diseases:

a) In ALS there are subtle dysfunctions on neuromuscular transmission that start well before appearance of overt motor symptoms (Rocha *et al* 2013).

Ana Filipa Ferreira da Cunha Ribeiro PhD Student | **Ana Sofia Cristovão Ferreira** Post-doctoral Investigator | **Ana Sofia Temudo Duarte António** PhD Student | **André Jerónimo Santos** PhD Student | **António Artur da Paz Ferreira Pinto Duarte** PhD Student | **Armando Dulcídio da Silva Cruz** PhD Student | **Bruno Miguel Ferreira Teixeira da Silva** Post-doctoral Investigator | **Catarina Reis Orcinha** Technician | **Cátia Alexandra Pêgas Palminha** MSc Student | **Clara Cunha Matos Patrício** MSc Student | **Cláudia Alexandra dos Santos Valente de Castro** Investigator | **Daniela Cristina Melo Magalhães** MSc Student | **Diana Gabriela Ribeiro Ferreira** PhD Student | **Diogo Miguel Rombo** PhD Student | **Fabio Marques Simoes de Souza** Principal Investigator | **Filipa Fiel do Carmo Glórias Ferreira** Investigator | **Filipe Jorge Nascimento Xavier Fernandes** MSc Student | **Francisco Melo Albuquerque Saraiva Mouro** PhD Student | **Gabriela Antunes** Post-doctoral Investigator | **Gonçalo Luis Monteiro Ramos** MSc Student | **Haíssa de Castro Abrantes** MSc Student | **Joana Fernandes Esteves Soares Coelho** Post-doctoral Investigator | **João Miguel Guerreiro Covita** MSc Student | **Joaquim Alexandre Ribeiro** Principal Investigator | **Luísa Maria Vaqueiro Lopes** Principal Investigator | **Maria Alexandra Pereira Botelho** Administrative | **Maria José Diógenes** Principal Investigator | **Mariana Colino Oliveira** PhD Student | **Noémia Marisa Félix Pereira** MSc Student | **Paula Alexandra Costa Marçal Correia** Investigator | **Pedro Dinis Avelar Agostinho** MSc Student | **Raquel Alice da Silva Baptista Dias** Post-doctoral Investigator | **Rita Cruz Coelho de Mira Ramalho** Post-doctoral Investigator | **Rita Isabel Pedro Aroeira** PhD Student | **Rui Artur Paiva Loureiro Gomes** Investigator, Assistant Professor | **Sandra Cristina Henriques Vaz** Post-doctoral Investigator | **Sara Alexandra Fernandes Carvalho** MSc Student | **Sara Alves Xapelli** Post-doctoral Investigator | **Vânia Luisa Neves Batalha** PhD Student

4. Cannabinoids:

a) CB1Rs induce neuronal differentiation (Xapelli *et al* 2013) and interact with caffeine to control neuronal signaling and behavior (Sousa *et al* 2013)

Recent Most Relevant Publications

Dias RB, Rombo DM, Ribeiro JA, Henley JM, Sebastião AM (2013) Adenosine: setting the stage for plasticity. *Trends in Neuroscience* **257**, 248. (Journal IF: 13.582, Citations: 0)

Aroeira RI, Sebastião AM, Valente CA (2013) GlyT1 and GlyT2 in brain astrocytes: expression, distribution and function. *Brain Struct Funct* (ePub Mar 2013). (Journal IF 7.837)

Sebastião AM, Ribeiro J A (2009) Adenosine Receptors in the Central Nervous System. Handbook of *Experimental Pharmacology*, **193**, 471-534. (Journal IF: 2.958, Citations: 66)

Diógenes MJ, Assaife-Lopes N, Pinto-Duarte A, Ribeiro JA, Sebastião AM (2007) Influence of age on BDNF modulation of hippocampal synaptic transmission: interplay with adenosine A2A receptors. *Hippocampus* **17**, 577-585. (Journal IF: 5.592, Citations: 40)

Diógenes, M.J., Fernandes, C.C., Sebastião, A.M., Ribeiro, J.A (2004) Activation of adenosine A2A receptor facilitates BDNF modulation of synaptic transmission in hippocampal slices. *Journal of Neuroscience* **24**, 2905-2913. (Journal IF: 6.908, Citations: 77)

BRUNO SILVA-SANTOS

LAB

PhD (2002) in Immunology at University College London, UK.
Post-doctoral research at King's College London, UK.
Associate Professor at Faculdade de Medicina da Universidade de Lisboa.

Bruno Silva-Santos | Group Leader
bssantos@medicina.ulisboa.pt

T-cell differentiation and tumor targeting

We study the biology of T lymphocytes and their key roles in immunity to infection and cancer. Our projects focus on the development of these cells in the vertebrate thymus, and on their functions upon export to the periphery. We investigate differentiation and activation signals for T cells in the mouse system, which provides crucial in vivo models for infectious (such as malaria) and autoimmune diseases. We also study human peripheral blood T cells and, in particular, their recognition and elimination of lymphomas and leukemias. Overall, we envisage the identification of molecular mechanisms involved in the differentiation, activation and function of T cells, aiming towards the design of new treatments for cancer, on the one hand, and (auto)immune disorders, on the other.

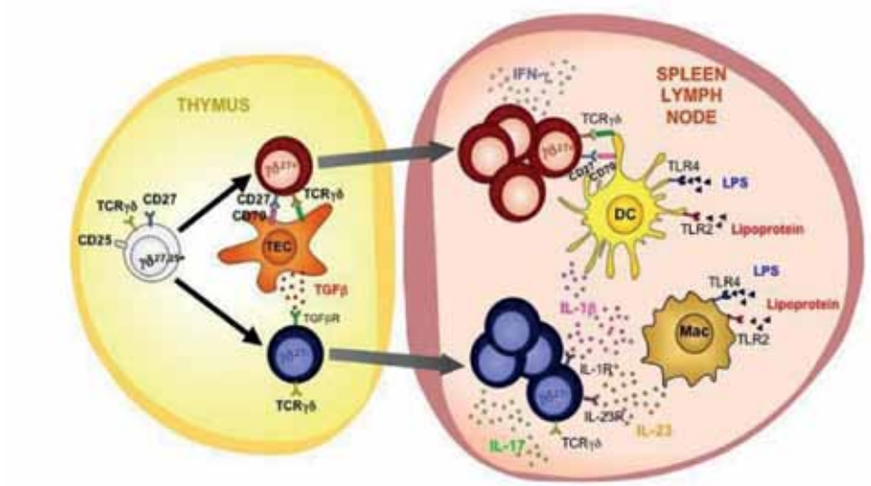
Research Areas

T cell development/ differentiation, T cell activation, Tumour immunology, Leukaemia clonal evolution, Immunopathogenesis of Severe Malaria

Major scientific achievements

Published 10 papers in peer-reviewed international journals, including in Nature Immunology (IF 26.2) and Journal of Experimental Medicine (IF 13.2).

Were awarded 2 Exploratory Project Grants from Fundação para a Ciência e Tecnologia (PIs: Haakan Norell e Julie C. Ribot).



We demonstrated that TCRγδ+ CD27+ CD25+ thymocyte progenitors originate two mature CD25- subsets: γδ27+ and γδ27- cells. CD27 signaling promotes the development of γδ27+ thymocytes which commit to IFN-γ expression. By contrast, γδ27- thymocytes acquire the exclusive capacity to express IL-17. Mature γδ T cell subsets maintain their distinct functional properties in peripheral lymphoid organs, where γδ27+ cells expand upon TCR plus CD27 stimulation, whereas γδ27- cells proliferate in response to innate signals downstream of TLR2 and TLR4, namely IL-1 and IL-23 produced by dendritic cells (DC). From Ribot *et al. Nature Immunol* 2009 and Ribot *et al. J. Immunol* 2010.

Ana de Oliveira Rodrigues Amorim MSc Student | **Ana Maria de Amarante Pamplona Dias dos Santos** Principal Investigator | **Anita Raquel Quintal Gomes** Investigator | **Daniel Vargas Correia** Post-doctoral Investigator | **Eva Sofia Alves Rolo** Investigator | **Francisco Landeck Moreira Franco Caiado** Post-doctoral Investigator | **Haakan Rolf Norell** Principal Investigator | **Ingrid Cecilia Brok** MSc Student | **Joana Luísa de Barros Martins** MSc Student | **Julie Cecile Caroline Ribot** Principal Investigator | **Karine Serre** Post-doctoral Investigator | **Maria Margarida Sousa Gonçalves Rei** PhD Student | **Michael Hamm** MSc Student | **Natacha Maria Gonçalves Silva Sousa** Lab manager | **Nina Alexandra Schmolka** PhD Student | **Rita Maria de Almeida Neres** Post-doctoral Investigator | **Sérgio Tiago de Freitas Ribeiro** PhD Student | **Sofia Mensurado Santos** Investigator | **Telma Sofia Martins Lança** PhD Student

Had a total of 21 communications in international conferences, of which four as invited speaker, including in the most prestigious International Congress of Immunology (B. Silva-Santos). Telma Lança successfully defended her PhD thesis with distinction and honours.

Recent Most Relevant Publications

Coquet J, Ribot JC, Babala N, Middendorp S, Xiao Y, Neves JF, Fonseca-Pereira D, Jacobs H, Pennington DJ, Silva-Santos B and Borst J (2013) Epithelial and dendritic cells in the thymic medulla promote CD4+ Foxp3+ regulatory T cell development via the CD27-CD70 pathway. *Journal of Experimental Medicine*. **210**, 715. (Journal IF: 13.216, Citations: 4)

Schmolka N, Serre K, Grosso AR, Rei M, Pennington DJ and Silva-Santos B (2013) Epigenetic and transcriptional signatures of stable versus plastic differentiation of pro-inflammatory gd T cell subsets. *Nature Immunology*. **14**, 1093. (Journal IF: 26.199, Citations: 0)

Correia DV, Fogli M, Hudspeth K, da Silva MG, Mavilio D and Silva-Santos B. (2011) Differentiation of human peripheral blood Vdelta1+ T cells expressing the natural cytotoxicity receptor NKp30 for recognition of lymphoid leukemia cells. *Blood*. **118**, 992-1001. (Journal IF: 10.555, Citations: 7)

Lança T, Correia DV, Moita CF, Raquel H, Ferreira C, Ramalho JS, Barata JT, Moita LF, Gomes AQ and Silva-Santos B. (2010) The MHC class Ib protein ULBP1 is a non-redundant determinant of leukemia/ lymphoma susceptibility to gd T-cell cytotoxicity. *Blood*. **115**, 2407-11. (Journal IF: 10.555, Citations: 24)

Ribot JC, deBarros A, Pang DJ, Neves JF, Peperzak V, Girardi M, Borst J, Hayday AC, Pennington DJ and Silva-Santos B. (2009) CD27 is a thymic determinant of the balance between IFN-g- and IL-17-producing gd T cell subsets. *Nature Immunology*. **10**, 427-36. (Journal IF: 26.218, Citations: 124)

PEDRO SIMAS

LAB

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

Pedro Simas | Group Leader
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Herpes virus pathogenesis

We utilize murid herpesvirus 4, which causes persistent infection in laboratory mice. We have identified two viral proteins critical for the virus life cycle. M2 that functions as an adaptor protein that assembles a signalosome with cellular proteins involved in the activation and differentiation of B-cells. The other, mLANA, secures viral episome persistence by tethering the viral genomes to mitotic chromosomes to segregate viral DNA to daughter nuclei. mLANA also regulates transcription and cell growth through E3 ubiquitin-ligase activity. The objective is that our work will enable future strategies to disrupt LANA function and control disease associated with persistent infection by herpes viruses.

Research Areas

Herpes virus, B lymphocytes, E3 ubiquitin ligase, SH2 and SH3, B cell signalosome, MuHV-4.

Major scientific achievements

During 2013 with our collaborators Maria Arménia Carrondo and Colin McVey at ITQB and Ken Kaye at Harvard Medical School, we have resolved 3D structure of the DNA binding domain of LANA, which includes the SOCS box E3 ligase motif. In addition we have defined that in addition to NF-kB, LANA also targets the cellular oncogene MYC for polyubiquitination. In contrast to NF-kB, where polyubiquitination mediated by LANA is degradative, MYC polyubiquitination is heterotypic and increases the stability of MYC. It turns out that MYC is essential for virus induced lymphoproliferation, offering a new target for blocking LANA, hence virus-induced lymphoproliferative disease.

Recent Most Relevant Publications

Rodrigues L, Popov N, Kaye K. M. and Simas J. P. (2013) Stabilization of Myc Through Heterotypic Poly-Ubiquitination by mLANA is Critical for gamma-Herpesvirus Lymphoproliferation. *PLoS Pathogens* **9**(8), e1003554. (Journal IF: 8.136, Citations: 0)

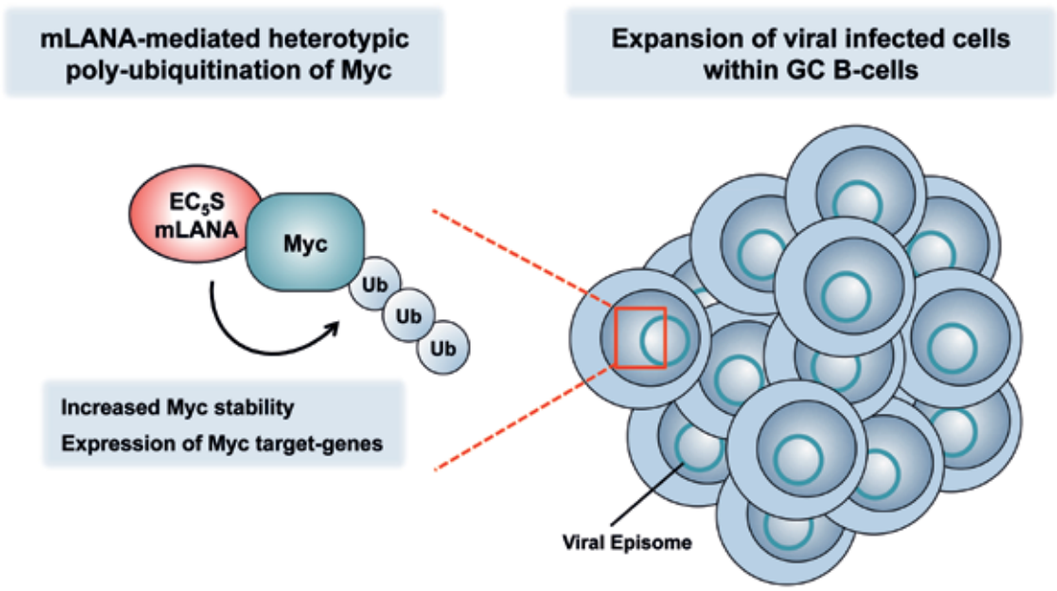
Correia, B., Cerqueira, S.A., Beauchemin, C., Pires de Miranda, M., Li S., and Ponnusamy, R., Rodrigues, L., Schneider, T.R., Carrondo, M.A., Kaye, K.M., Simas, J.P., McVey C.E. (2013) Crystal structure of the gamma-2 herpesvirus LANA DNA binding domain identifies charged surface residues which impact viral latency. *PLoS Pathogens* **9**(10), e1003673. (Journal IF: 8.136, Citations: 1)

Rodrigues L, Filipe J, Seldon MP, Anrather J, Soares MP and Simas JP (2009). Termination of NF-κB activity via a γherpesvirus protein that assembles an EC5S ubiquitin-ligase. The EMBO Journal 6;**28**(9):1283-95. Epub 2009 Mar 26 (Citations: 23)

Marques S, Efstathiou S, Smith KGC, Haury M, Simas JP (2003) Selective Gene Expression of Latent Murine Gammaherpesvirus 68 in B Lymphocytes. *Journal of Virology*. **77**,7308-7318 (Citations: 71)

Stevenson PG, May JS, Smith XG, Marques S, Adler H, Koszinowski HU, Simas JP, Efstathiou S (2002) CD8+ T cell evasion by K3 plays a critical role in the amplification of a latent γherpesvirus. *Nature Immunology* **3**,733-40. (Citations: 110)

Ana de Oliveira Rodrigues Amorim Cristina Sofia Godinho da Silva Investigator | **Diana Marisa Pinto Freire Fontinha** PhD Student | **Inês Marques Basto** MSc Student | **Lénia Marisa Pereira Rodrigues** Post-doctoral Investigator | **Marta Bebiano Alenquer** PhD Student | **Marta Pires de Miranda** Post-doctoral Investigator | **Sofia Isabel Arriaga Mimoso Cerqueira** PhD Student | **Sofia Pinto Guia Marques** Post-doctoral Investigator



ANA E. SOUSA

LAB

MD (1986) and PhD (2000) in Clinical Immunology at Faculdade de Medicina da Universidade de Lisboa (FMUL).
PhD Agregação, Associate Professor at FMUL.

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Adriana de Albuquerque Post-doctoral Investigator | **Alcinda Melo** Technician | **Ana Berta da Fonseca Vieira Álvares e Sousa Ferrand de Almeida** Investigator, Clinical Specialist, Assistant Professor | **Ana Isabel Lopes** Investigator, Clinical Specialist, Assistant Professor | **Ana Luisa Caetano** Technician | **Ana Margarida Matos** Lab Manager | **Ana Rita Pires** Lab Manager, Investigator | **Andreia de Jesus Fonseca** Post-doctoral Investigator | **Daniela Filipa Ferreira** Investigator | **Helena Nunes Cabaço** Post-doctoral Investigator | **Inês Filipa Martins** Consultant | **Íris Maria Caramalho** Principal Investigator | **Isabel Cristina e Castro de Menezes Esteves** Investigator, MD, Clinical Specialist, Teaching Assistant | **Jorge Andrade** Post-doctoral Investigator | **José Gonçalo Marques** Investigator, MD, Clinical Specialist, Teaching Assistant | **Maria Catarina Silva** PhD Student, MD | **Maria da Conceição dos Santos** Investigator | **Paula Cristina Matoso** Lab Manager, Investigator | **Rita Maria Rêgo** Post-doctoral Investigator | **Rui Manuel Victorino** Principal Investigator, Full Professor, Clinical Service Director | **Russell Bourne Foxall** Post-doctoral Investigator | **Sara Branco Silva** Investigator, MD, Clinical Specialist | **Susana Clara dos Anjos** PhD Student, MD, Clinical Specialist, Teaching Assistant | **Susana Mendes Fernandes** PhD Student, MD, Teaching Assistant

Human immunodeficiency and immune reconstitution

Our work is focused 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 our research effort is centered on HIV/AIDS immunopathogenesis, mainly through the study of HIV-2 infection, a naturally attenuated form of HIV disease.

We prioritize the "bedside to the bench" approach and, given the transversal nature of Clinical Immunology, bring together physician/clinical researchers, from different medical areas, and basic researchers.

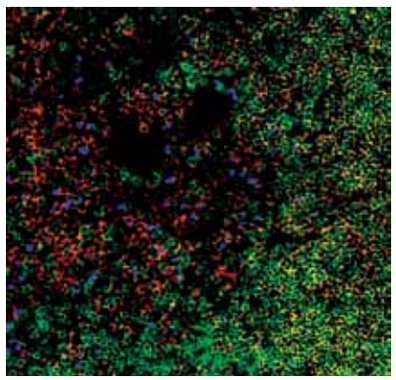
Research Areas

Human T cell Homeostasis, Immune Regulation, HIV/AIDS Immunopathogenesis, HIV-2 Infection, Primary Immunodeficiencies, Immunological Reconstitution.

Major scientific achievements

Our investigation of HIV/AIDS immunopathogenesis is focused on HIV-2 infection, which features a much slower course than HIV-1, often being asymptomatic for over 20 years without therapy. We showed preserved telomere length within naive and memory CD4 subsets, despite increased CD4 T-cell turnover. We also found a heightened state of monocyte and dendritic cell activation throughout HIV-2 infection with overexpression of the inhibitory molecule PD-L1, which may act by limiting inflammation, given the role of these cells as main orchestrators of immune responses. These data challenge current paradigms in HIV/AIDS and open new perspectives regarding potential strategies to modulate inflammatory states.

Our research related to the Primary Immunodeficiency Centre (a partnership with University Hospital de Santa Maria), was strengthened by the organization of 1st International Primary Immunodeficiency Congress/International Patient Organization for Primary Immunodeficiencies.



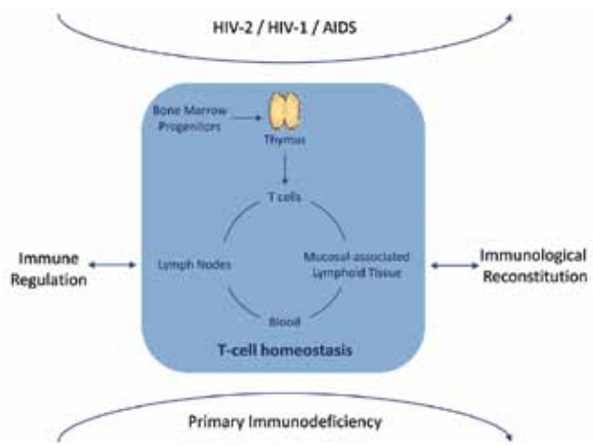
Recent Most Relevant Publications

Tendeiro R, Albuquerque AS, Foxall RB, Cavaleiro R, Soares RS, Baptista AP, Soares MV, Gomes P, Sousa AE (2013) Preserved CD4 T-cell telomere length during long-lasting HIV-2 infection. *AIDS*, Jan 14, **27**(2):289-92. (Journal IF: 6.348, Citations: 0)

Markert ML, Marques JG, Neven B, Devlin BH, McCarthy EA, Chinn IK, Albuquerque AS, Silva SL, Pignata C, de Saint Basile G, Victorino RM, Picard C, Debre M, Mahlaoui N, Fischer A, Sousa AE. (2011) First use of thymus transplantation therapy for FOXN1 deficiency (nude/SCID): a report of 2 cases. *Blood* **117**, 688. (Journal IF: 9.060, Citations: 10)

Azevedo RI, Soares M, Barata JT, Tendeiro R, Serra-Caetano A, Victorino R, Sousa AE. (2009) IL-7 sustains CD31 expression in human naive CD4+ T cells and preferentially expands the CD31+ subset in a PI3K-dependent manner. *Blood* **113**, 2999. (Journal IF: 9.060, Citations: 27)

Cavaleiro R, Baptista AP, Soares RS, Tendeiro R, Foxall RB, Gomes P, Victorino R, Sousa AE. (2009) Major Depletion of Plasmacytoid Dendritic Cells in HIV-2 Infection, an Attenuated Form of HIV Disease. *PLoS Pathogens* **5**, e1000667. (Journal IF: 8,136, Citations: 14)



Sousa AE, Carneiro J, Meier-Schellersheim M, Grossman Z, Victorino R. (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. *The Journal of Immunology*. **169**, 3400. (Journal IF: 5.520, Citations: 265)

HENRIQUE VEIGA-FERNANDES LAB

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

Henrique Veiga-Fernandes | Group Leader
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Lymphocyte function and development

The immune system is a key player in the resolution and prevention of severe pathologies, such as infectious and inflammatory diseases. To accomplish their function throughout life, immune cells interact with each other and with their external environment. Thus, all immune cell processes, ranging from haematopoiesis to immune cell response to pathogens, require the establishment of effective cellular and molecular interactions. However, the mechanisms that underpin immune cell function and communication with their environment remain largely elusive. Our research is cantered on novel communication pathways that determine immune cell fate and disease progression in the context of lymphoid organogenesis and lymphoid cell development and function.

Research Areas

Lymphoid organogenesis, Haematopoiesis, Innate Lymphoid Cells, Lymphocyte function.

Major scientific achievements

Publications:

- Klein Wolterink, R.G. et al. "Essential, dose-dependent role for the transcription factor Gata3 in the development of IL-5+ and IL-13+ type 2 innate lymphoid cells", Proceeding of National Academy of Science 110, 2013.
- Baptista AP et al. Colonic patch and colonic SILT development are independent and differentially regulated events, Mucosal Immunol, 2013 May,6 (3), 511-21.

Prize:

Innovator Award of the Kenneth Rainin Foundation (KRF) from Kenneth Rainin Foundation, USA, Aug 2013.

Patents:

The use of ret agonist molecules are critical to haematopoetic stem cells expansion protocols and transplantation therapy and a ret agonist kit. Submitted to WIPO as nr. 47679-13 (not published). Inventors: Henrique Veiga-Fernandes, Diogo Fonseca-Pereira, Silvia Madeira.

Organisation of international conference:

Young Scientist Forum EMBO. Lisbon, Portugal, 15-16 July 2013.

Recent Most Relevant Publications

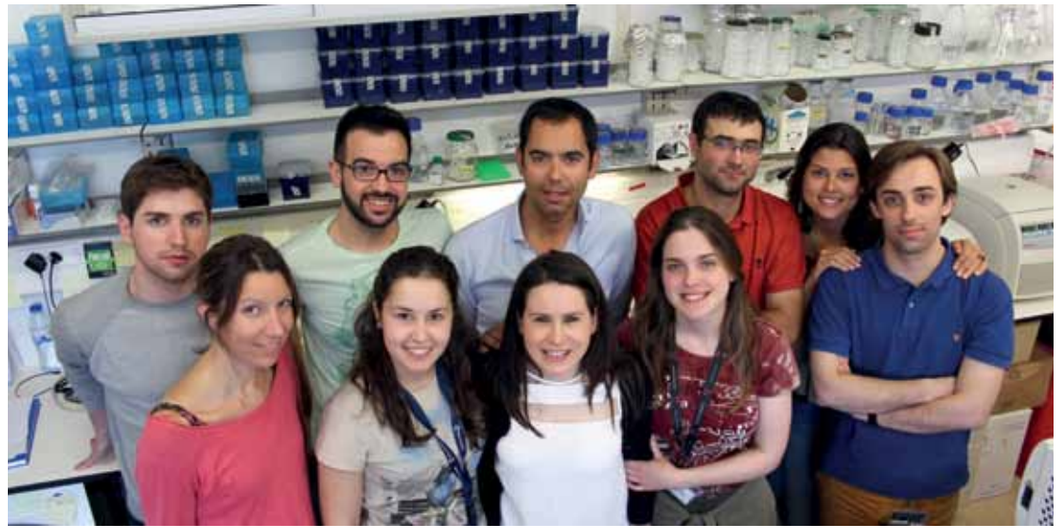
Patel, A, Harker, N, Moreira-Santos, L, Ferreira, M, Alden, K, Timmis, J, Foster, K, Garefalaki, A, Pachnis, P, Andrews, P, Enomoto, H, Milbrandt, J, Pachnis, V, Coles, M, Kioussis, D, Veiga-Fernandes, H. (2012) Differential RET Signaling Pathways Drive Development of the Enteric Lymphoid and Nervous Systems. *Science signaling* ra55. (Journal IF: 7.6, Citations: 2)

Veiga-Fernandes H, Kioussis D, Coles M. Natural killer receptors: the burden of a name (2010). Natural killer receptors: the burden of a name. *J Exp Med* **207**, 269-72. (Journal IF: 13.2, Citations: 9)

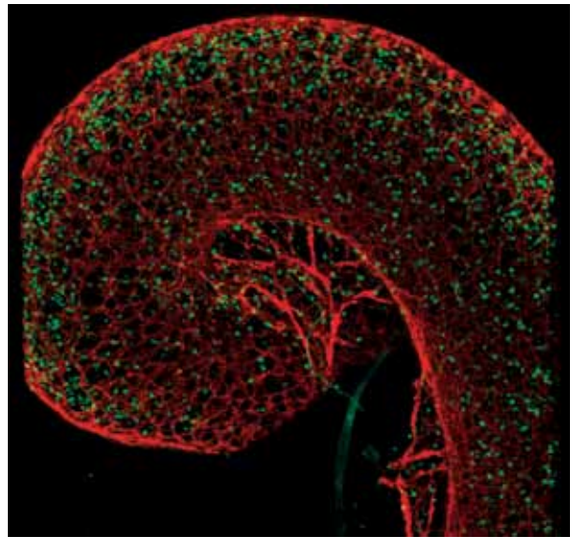
Veiga-Fernandes, H., Coles, M.C., Foster, K.E., Patel, A., Williams, A., Natarajan, D., Barlow, A., Pachnis, V. and Kioussis, D. (2007). Tyrosine kinase receptor Ret is a key regulator in Peyer's Patch organogenesis. *Nature* **446**, 547-51. (Journal IF: 38.6, Citations: 69)

Peixoto, A., Evaristo, C., Munitic, I., Monteiro, M., Charbit, A., Rocha, B. and Veiga-Fernandes, H. (2007). CD8 single-cell co-expression reveals three different effector types present at distinct phases of the immune response. *J. Exp. Med.* **204**, 1193-205. (Journal IF: 13.2, Citations: 43)

Veiga-Fernandes, H. and Rocha, B. (2004). High expression of active CDK6 in the cytoplasm of CD8 memory cells favors rapid division. *Nature Immunol*, **5**, 31-37. (Journal IF: 26, Citations: 63)



Afonso Rocha Martins de Almeida Post-doctoral Investigator | **Ana Teresa Veríssimo Alves Bento** MSc Student | **Bethania García Cassani** PhD Student | **Carlos Diogo Labão Alpiarça Sousa de Almeida** MSc Student | **Diogo da Fonseca Pereira** PhD Student | **Fátima Sofia dos Santos Cardoso** Investigator | **Hélder Manuel Piedade Ribeiro** Technician | **Manuela Cristina Fernandes Ferreira** Post-doctoral Investigator | **Rita Gomes Domingues** PhD Student | **Sales Ibiza** Post-doctoral Investigator | **Silvia Moura Arroz Nobre Madeira** PhD Student



Foetal intestine. Red: neurons; Green: innate lymphoid cells

ELSA ANES

LAB

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

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David Pires PhD Student | **Joana Bugalhão** MsC student | **Joana Marques MsC** student | **João Pombo** MsC student | **Nuno Baltazar Carmo** PhD Student | **Paulo Bettencourt** Post-Doc Investigator | **Pedro Timóteo** MsC student | **Vera Fernandes** MsC student

Tuberculosis and innate immunity

The ability of Koch's bacilli (Mtb) to create tuberculosis or a latent infection relay, in part, on the powerful mechanisms it has evolved to parasitize host macrophages and dendritic cells. Our major aim for the current period was to better understand the molecular mechanisms by which 1) Mtb controls the acquisition of cathepsins and their inhibitors cystatins within phagosomes, an important phenomenon for antigen presentation or bacteria intracellular killing; 2) trafficking host factors are involved in Mtb internalization by macrophages, phagosome maturation and exosome secretion; 3) micro RNAs controls actin dynamics during early steps of Mtb phagocytosis and finally 4) micro RNAs controls distinct phases of Mtb infection within macrophages.

Research Areas

Innate immunity, Intracellular trafficking, Host-pathogen interactions, Tuberculosis.

Major scientific achievements

We found that Mtb activates the over-expression of miRNA 142-3p during macrophage phagocytosis. We showed that miR142-3p is involved in controlling actin dynamics during infection (Bettencourt *et al.*, Front Cell Infect Microbiol, 2013, PhD thesis). Indeed the group found a microRNA over-expressed early during Mtb infection involved on the control of cathepsin S (Pires *et al.*, in prep) while others are controlling pro-inflammatory events.

By using RNA silencing we deciphered the role of cathepsins S, B and L during *M. tuberculosis* infection of macrophages and dendritic cells (DCs) (Pires *et al.*, in prep) relatively to pathogen intracellular survival or antigen presentation. Indeed an overall map of the gene expression of all cathepsins and their natural inhibitors cystatins during Mtb infection was clarified during the year in resting vs activated macrophages or in immature vs mature DCs.

In collaboration with Maria José Umbelino (iMed.ULisboa), we evaluated the antimycobacterial effect of extracts from medicinal plants from Mozambique and their effect *in vitro* and *ex vivo* (Luo, Pires *et al.*, J Ethnopharmacol, 2013).

Indeed chemical compounds prodrugs derived with activity against PZA resistance mycobacteria strains and species were characterized (World patent 2013/WO2013084214; Pires *et al.*, in prep).

We assessed the role of efflux pumps inhibitors and in combination with nanoparticles delivery systems containing antibiotics on the killing of intracellular Mtb (Machado, Pires et al., Microbiotec2013, manuscript in prep).

The group organized the "VI-Science-shop: TUBERCULOSE: development of new strategies to treat TB" FFUL, May, 21; Elsa Anes was part of the Scientific Committee of Microbiotec2013; David Pires was awarded with the prize Immunotools 2013; We organized the Course Cellular Microbiology as part of the Master/PhD program at FFUL.

Recent Most Relevant Publications

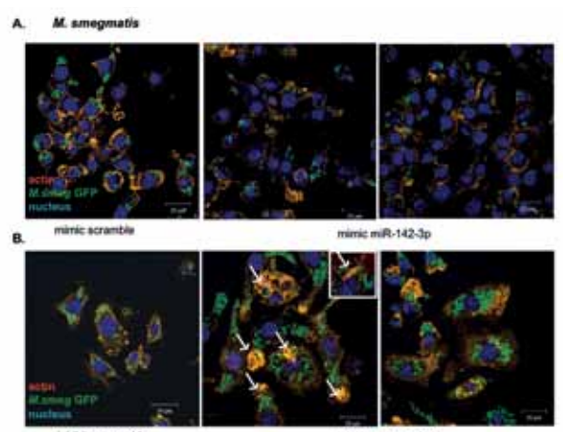
Mishra BB, Moura- Alves P, Sonawane A, Hacohen N, Griffiths G, Moita LF and Anes E. (2010). *Mycobacterium tuberculosis* protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. *Cell Microbiol.* **12**(8), 1046-63 (Journal IF: 5.8; Citations: 65)

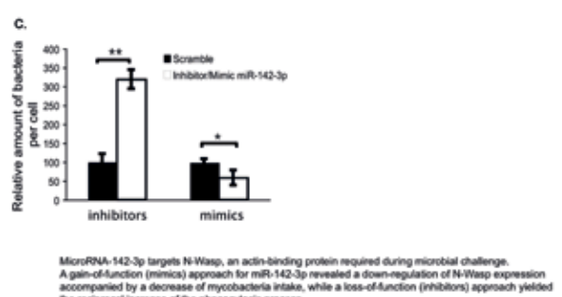
Kuehnel M, Rybin V, Anand P, Anes E and Gareth Griffiths. 2009. Lipids regulate P2X7 receptor-dependent actin assembly by phagosomes via ADP translocation and ATP synthesis in the phagosome lumen. *J Cell Science* **122**(Pt 4), 499-504. (Journal IF: 6.4; Citations: 20)

Gutierrez, MG*, Mishra, BB*, Jordao, ML, Elliot, E, Anes, E and Griffiths, G. 2008. NF-kappa B zactivation controls phago-lysosome fusion-mediated killing of mycobacteria by macrophages. *J. Immunology* **18**(4), 2651-63 *joined first authors (Journal IF: 6.1; Citations: 28)

Jordao, L., Bleck, CKE., Mayorga, L., Griffiths, G, and Anes, E. 2008. On the killing of mycobacteria by macrophages. *Cell Microbiol* **10**(2), 529-48. (Journal IF: 5.6; Citations: 39)

Anes, E., Kuhnel, M.P., Bos, E., Moniz-Pereira, J., Habermann, A. & Griffiths, G. 2003. Selected lipids activate phagosome actin assembly and maturation resulting in killing of pathogenic mycobacteria. *Nat Cell Biol*; **5**(9), 793-802. (Journal IF: 20.8; Citations: 126)





MicroRNA-142-3p targets N-Wasp, an actin-binding protein required during microbial challenge. A gain-of-function (mimics) approach for miR-142-3p revealed a down-regulation of N-Wasp expression accompanied by a decrease of mycobacteria intake, while a loss-of-function (inhibitors) approach yielded the reciprocal increase of the phagocytosis process.

JOÃO GONÇALVES

LAB

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

João Gonçalves | Group Leader
joao.goncalves@ff.ul.pt

Ana Catarina G. Santos PhD Student | **Ana Catarina Cunha Santos** PhD Student | **Cátia Cantante** PhD Student | **Luis Ferreira** PhD Student | **Mariana Santa-Marta** Principal Investigator | **Paula Brito** Post-Doc Student | **Pedro Perdigão** PhD Student

Molecular virology and applied biotechnology

Molecular virology has contributed greatly to the understanding of cellular responses to infection. Lentiviruses are valuable tools in applied biotechnology and gene therapy. We previously identified cellular proteins involved in the multistep processes of HIV-1 replication. We manipulated the transcription of genes that control HIV-1 to answer questions related to viral latency and antiviral restriction. We also developed small antibody scaffolds that inhibit HIV-1 infection and helped the specific targeting of lentiviral vectors. We now aim to explore reactivation of HIV-I latency and expression of restriction cellular factors to control and eradicate the virus. The use of validated pharmaceutical compound libraries will helps us in this endeavour of modulating viral expression and cellular antiviral defences. Alternative strategies that combine antibody engineering, genetic delivery systems and synthetic biology are being developed to eliminate cells containing viral genomes. Given the uniqueness and innovative strategies to approach these problems of HIV we believe to be well positioned at the international scientific level to contribute with original and groundbreaking research.

Research Areas

Antibody, HIV, drug screening, therapy.

Major scientific achievements

The Lab has a consolidated track record in several aspects of molecular microbiology and pathogenesis with strong emphasis in biotechnology. We foster the molecular understanding of microbial pathogenesis and the identification of essential steps in the infectious process that can constitute novel targets for therapeutic intervention. We aimed to manipulate the transcription of genes that control HIV-1 to answer questions related to viral latency and antiviral restriction. We also developed small antibody scaffolds that inhibit HIV-1 infection and helped the specific targeting of lentiviral vectors. The use of validated pharmaceutical compound libraries will helps us in this endeavor of modulating viral expression and cellular antiviral defenses. Alternative strategies that combine antibody engineering, genetic delivery systems and synthetic biology are being developed to eliminate cells containing viral genomes.

Recent Most Relevant Publications

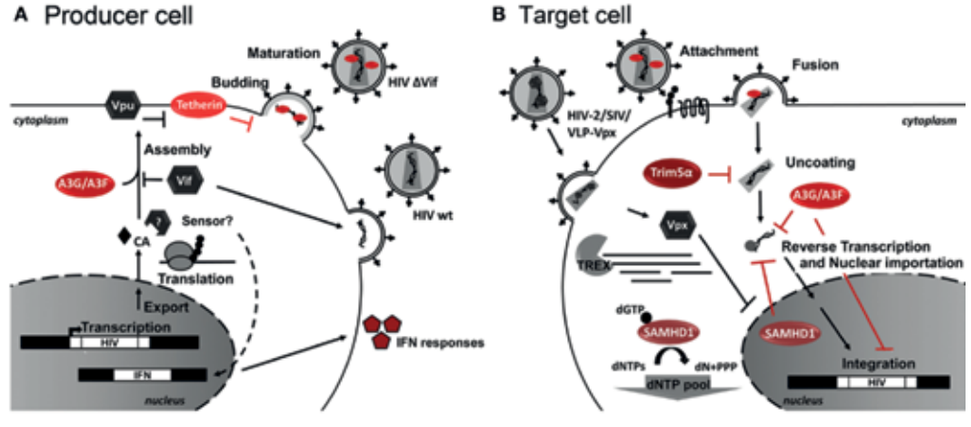
Santa-Marta M, de Brito PM, Godinho-Santos A, Goncalves J. (2013) Host Factors and HIV-1 Replication: Clinical Evidence and Potential Therapeutic Approaches. *Front Immunol*. 2013 Oct 24. **4**,343. eCollection 2013. Review. (Journal IF: , Citations: 2)

Morais M, Cantante C, Gano L, Santos I, Lourenço S, Santos C, Fontes C, Aires da Silva F, Gonçalves J, Correia JD. Biodistribution of a 67Ga-labeled anti-TNF VHH single-domain antibody containing a bacterial albumin-binding domain (Zag). *Nucl Med Biol*. pii: S0969-8051. (Journal IF: , Citations 0)

da Silva, F. A., Li, M., Rato, S., Maia, S., Malhó, R., Warren, K., Harrich, D., Craigie, R., Barbas, C. and Goncalves, J. (2012). Recombinant rabbit single-chain antibodies bind to the catalytic and C-terminal domains of HIV-1 integrase protein and strongly inhibit HIV-1 replication. *Biotechnology and Applied Biochemistry*, **59**, 353–366. doi: 10.1002/bab.1034. (Journal IF: 3.03, Citations: 4)

Cadima-Couto I, Saraiva N, Santos AC, Goncalves J. (2011) HIV-1 Vif Interaction with APOBEC3 Deaminases and its Characterization by a New Sensitive Assay. *J Neuroimmune Pharmacol*. (Journal IF: 4.5, Citations: 15)

Rato S, Maia S, Brito PM, Resende L, Pereira CF, et al. (2010) Novel HIV-1 Knockdown Targets Identified by an Enriched Kinases/Phosphatases shRNA Library Using a Long-Term Iterative Screen in Jurkat T-Cells. *PLoS ONE* **5**(2): e9276. doi:10.1371/journal.pone.0009276. (Journal IF: 5.3, Citations: 24)



Host restriction factors and their action during HIV-1 replication. Schematic representation of (A) HIV-1-infected producer cell, and (B) HIV-1 target cell. http://journal.frontiersin.org/Journal/10.3389/fimmu.2013.00343/full#sthash.0WLk59nj.dpuf

SERVICES AND RESOURCES

FACILITIES

ANIMAL FACILITY | BIOIMAGING | BIOSAFETY LEVEL 3 LABORATORY | FLOW CYTOMETRY UNIT | HISTOLOGY SERVICE | IMM BIOBANK | ZEBRAFISH FACILITY |

ANIMAL FACILITY

Joana Marques, PhD | Head of Facility
joanammarques@medicina.ulisboa.pt

Ana Catarina Jorge Mendes Technician | **Ana Rafaela Dinis Coelho** Technician | **Carlos Barata da Silva** Technician | **Cecília Gonçalves Simão** Technician | **Felícia Maria Augusto Ramos** Technician | **Iolanda Safira Sousa Moreira** Technician | **Janaina Gonçalves dos Santos de Barcelos** Technician | **Maria Dolores Paulos Bonaparte Figueira** Veterinarian | **Nuno Manuel Ribeiro Inácio** Technician | **Olena Pavlovska Borges de Pinho** Technician | **Pedro Manuel Nogueira dos Santos** Technician | **Wilma Eliandra de Lemos Zovo** Technician

The IMM's Rodent Facility aims to maintain the highest standards of animal welfare and to promote a responsible use of laboratory animals, hence providing the conditions for state-of-the-art animal-based research. The facility has capacity to host 15000 rodents and comprises one conventional unit and one SPF unit. The SPF unit includes one Production which hosts 70 genetically altered strains and one Experimental area, with four housing rooms and three rooms for experimental work with animals. All husbandry and manipulations are performed according to high standards of biocontainment and bioexclusion, in order to ensure the best possible conditions in terms of health and safety. This unit is highly committed to follow the 3Rs – Replacement, Reduction, Refinement - and provides education and guidance for researchers, according to the Portuguese and international laws/recommendations for good practices and animal welfare.

BIOIMAGING

José Miguel Rino Henriques, PhD | Head of Facility
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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

Ana Margarida Santos do Nascimento Technician
António Francisco Pinção Loução Homem Temudo Technician

The BioImaging Unit constitutes the core microscopy facility of the IMM, serving as a support structure to carry out and nurture research done with Light Microscopy inside the institute. We aim at providing IMM scientists and visitors with excellence in scientific know-how and expertise in using advanced light microscopy methods for their research. We assist in project planning, experiment design, provide advice and support on sample preparation, image analysis and processing and in writing research papers with microscopy data. Together with continuous training of new users, we organize regular courses and workshops on basic and advanced microscopy techniques. We research novel microscopy techniques and develop image processing software tools for quantitative microscopy applications.

BIOSAFETY LEVEL 3 LABORATORY

Miguel Prudêncio, PhD | Head of Facility
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Investigador FCT (since 2013) Group Leader - IMM-Faculdade de Medicina da Universidade de Lisboa (IMM-FMUL), Portugal.
Principal Investigator (2008-2013) and Post-doctoral researcher (2005-2008) at IMM-FMUL.
Post-doctoral researcher (2004) at Instituto Gulbenkian de Ciência, Oeiras, Portugal.
PhD (2000) in Biochemistry at Uni. of East Anglia, Norwich, UK.
Post-doctoral researcher fellow (2000-2004) at University of Leiden, Leiden, The Netherlands.
Head of Facility since 2009 and Group Leader at IMM since 2013.

Inês Antunes Cabral Queiroz de Matos Technician | **Maria Dolores Paulos Bonaparte Figueira** Veterinarian

The IMM houses a 70 m2 BSL3 Facility meeting the highest safety standards as defined by European and International guidelines. The purpose of this facility is to enable researchers to carry out work with infectious agents that require BSL3 containment conditions, including research that involves rodent models. The Facility is available to IMM internal and affiliated researchers, as well as to external researchers from academia, pharma and biotech. All work to be carried out in the BSL3 Lab must follow the established SOPs, as defined in the Facility's Rules and Guidelines Manual. The IMM's BSL3 Facility comprises two fully equipped tissue culture rooms and one animal experimentation room for rodents. Available equipment includes incubators, benchtop centrifuges, refrigerators and freezers.

FLOW CYTOMETRY UNIT

Maria Soares, PhD | Head of Facility
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PhD (2002) in Immunology at Uni. College London, and at IMM-FMUL.
Staff scientist at the IMM since 2008.
Head of Facility since 2009.

Ana Isabel da Silva Vieira Technician | **Sofia Pinto Guia Marques Lab** manager

The Flow Cytometry Unit (UCF) provides training and support to researchers performing flow cytometry studies. UCF users comprise a very diverse and challenging set of researchers, creating a very stimulating working environment that demands from our staff a constant knowledge of new developments in the field. Training in flow cytometry concepts, experimental controls and instrument operation is achieved through workshops and one-to-one tuition. UCF staff also provides support in experiment planning and data analysis. In addition, our trained staff operates the High Speed Cell Sorters providing a cell purification service. UCF staff further ensures quality control and maintenance procedures on all instruments and the implementation the Quality Management System, according to ISO 900.

HISTOLOGY SERVICE

Sandra Cristina Cana de Anjo Casimiro, PhD | Head of Facility
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PhD (2007) in Molecular Biology at FCUL, Lisbon, Portugal.
Post-doctoral research at IMM since 2007.

Ana Margarida dos Santos Technician | **Andreia Pinto** Technician | **Tânia Carvalho** Veterinarian Pathologist

Implemented in IMM on September 09, the Histology Service is devoted to provide technical and scientific support to all researchers from IMM, or other academical, medical or industry-related research teams, in the areas of histology and histopathology. We aim to continuously enlarge and optimize the services available at our Laboratory. We also provide tutorship in the design and implementation of any procedures not performed in the Service. Currently, the techniques available in the Histology Service include: processing of tissue samples and routine histochemical procedures; processing and visualization of samples for Transmission Electron Microscopy; processing of samples for Laser Capture Microdissection; automated immunohistochemistry.

IMM BIOBANK

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

The vision of the Biobanco-IMM, Lisbon Academic Medical Centre, is to position itself as a major member of the European Network of Biobanks within the next 5 years, offering excellent opportunities for translational and clinical research. Our mission is to promote and facilitate biomedical research that will lead to the identification of new diagnostic and prognostic tests, as well as to new therapeutic targets. We have set as our goals to collect a wide variety of high quality human biological samples associated with detailed relevant clinical information and to promote its use for research purposes based on scientific and ethical criteria.

Ana Filipa Rodrigues Lopes Lab manager | **Ana Filipa Soares Garcia** Technician | **Ana Rita Cascão Rodrigues** Technician | **Ana Sofia Zhao** Technician | **Ângela Maria Cerqueira Coelho Afonso** Technician | **Joana Ribeiro Caetano Lopes** Post-doctoral Investigator | **Joaquim Miguel Polido Pereira** Investigator | **Vanessa Gonçalves Silva** MSc Student

ZEBRA FISH FACILITY

Maria Leonor Tavares Saúde, PhD | Head of Unit
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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.
Invited Auxiliary Professor at Faculdade de Medicina da Universidade de Lisboa.

Aida Gonçalves Lino Barros Technician | **Lara Carvalho** Lab manager | **Sara Mulenas Sá de Matos** Technician

The Zebrafish Facility provides a fully functional facility to be used by the IMM research units. It provides technical assistance to facilitate the use of zebrafish in a wide range of experimentation sets.

UNITS

COMMUNICATION UNIT | EDUCATION & ADVANCED TRAINING UNIT | FUNDING PROGRAMS OFFICE | INFORMATION SYSTEMS UNIT | MANAGEMENT UNIT | QUALITY AND SAFETY IN LABORATORY UNIT |

COMMUNICATION UNIT

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Ana Cristina Borges Marques do Carmo Director | **Andreia Sofia Moita Machado** Administrative | **Maria Margarida Ferreira Trindade** Manager | **Silvana Daniela Fonseca Paules** Administrative

The Communication Unit is IMM's first line of interaction with society providing updated, reliable and relevant information on all of IMM's thematic areas, as well as promoting the very best scientific successes made by its research teams. Its mission is to support the internal and external communication of IMM's activities as well to advise IMM Direction on Public Affairs issues. With the firm belief that science should inform decisions because it impacts everyone's lives, the communication unit targets a wide range of audiences (policy makers, public opinion, patients associations, medical societies, schools, academia, industry, media, arts, amongst others). It serves as spokesman for the institute and it's responsible to manage IMM's image aligned with the institute values and mission.

EDUCATION & ADVANCED TRAINING UNIT

Maria Alexandra Gama Mendonça Simões Manaia | Head of Unit
mmanaia@medicina.ulisboa.pt

Sónia Silva Arroz Administrative

The general aim of the Education and Advanced Training Unit is to provide training opportunities for success in science to researchers at different stages in their careers. Ongoing Activities:

- Ensure full running of ongoing PhD (CAML, LisbonBioMed) and Postdoctoral Programs: Launch Calls; Administrative execution; Managerial Support to PhD and Postdoctoral fellows activities; Support PhD and Postdoctoral Fellows throughout their training. Update UEFA Webpages within new IMM site.
- Run Advanced Courses, scheduled upon CAML & LisbonBioMed Scientific Boards approval; cover all organizational aspects.

New Programs:

- Launch & implementation of Mindthegap- Postdoctoral Training Program approved for funding under Marie Curie Actions;
- Join EMBL-lead international consortium for Horizon 2020 application: outreach as post-graduate training.

FUNDING PROGRAMS OFFICE

Ana Filipa Duarte Nunes Almeida | Head of Unit
anafalmeida@medicina.ulisboa.pt

Joana Costa Manager | **Rudolfo Pais Mendes Ferreira Francisco** Administrative

Initially created in 2008 the Funding Programs Office was restructured in February 2013. It facilitates and streamlines every step of the pre-award process, including grant preparation, submission, and contract negotiation, in compliance with institutional, government and sponsor policies and regulations. In addition, the Office acts as liaison with academia, enterprises and research organizations for the development of scientific collaborations. Our specific goals include: i) promote a service of funding opportunities tailor-made for IMM researchers; ii) promote academic/entrepreneurial scientific collaborations underpinning the establishment of national/international applications; iii) promote partnerships with companies and explore relevant financial opportunities; iv) assist obtaining funding for entrepreneurial projects.

INFORMATION SYSTEMS UNIT

José Joaquim Carvalho da Costa Braga | Head of Unit
josebraga@medicina.ulisboa.pt

Daniel Alexandre Felício da Silva PhD Student | **Daniel José Vilhena Guerreiro** Technician | **Emanuela Simões** Technician | **Nuno Andrade da Cruz Henriques** Technician | **Pedro Miguel Bernardino Eleuterio** Technician | **Tito Lívio Santos Silva** Consultant

The primary goal of the Information Systems Unit (USI) is to help researchers reach their maximum productivity by using adequate Information Technology resources and following best practices. By accompanying the latest technological trends we also aim at providing researchers and managers at IMM with tools for enhancing data analysis and processing, communication and decision taking. To achieve this USI operates in several areas:

1. Planning, implementation and maintenance of the IT infrastructure to protect and secure research data. This involves constant monitoring of backups, storage and connectivity;
2. Designing and integrating Information Systems;
3. Maintenance of IMM website (with the Communication and Training Unit);
4. Documentation and Information Workflow;
5. IT Support.

MANAGEMENT UNIT

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The Management Unit is responsible for the overall IMM legal, human resources, administrative and financial issues. The main areas are accounts, budget management, projects management, human resources, legal, scientific protocols management, Quality Management System, and General Administrative support to all units and researchers.
The Management Unit also gives support to the Executive Director and the other Statutory Boards in relation to organizational issues, inter-institutional collaborations, financial and budget management strategy.

QUALITY AND SAFETY IN LABORATORY UNIT

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The Quality and Safety in laboratory (QSL) is divided in three main areas, each one dedicated to improve the quality of research of IMM and comply with National and International guidelines and best practices. The Lab Management works as an advisor and authority regarding safety with products and equipments. Training and development of standard operating procedures is the key to achieve high standards of safety and effectiveness in the use of equipment and infrastructures. It is also responsible for the design of (re) new laboratory infrastructures. The Purchasing Office is responsible for the Internal Storehouse and External Orders, centralizing all aquisitions. It also provides updated information on prices, ongoing promotions and new products. The Washing Room provides researchers cleaned and sterilized material, according to each specific requirement.

Alexandre Manuel Raposo de Jesus Technician | **André Paiva Antunes** Technician | **Cátia Vanessa Sanches Mesquita** Technician | **Rita Isabel Ganchas Soares Alves** Technician | **Ana Cristina dos Santos Anunciação Silva** Technician | **Carlos Filipe Ferreira Curado** Technician | **Edna Neias F. Gomes** Technician | **Susana Maria Andrade** Technician | **Ana Patrícia de Freitas Roque** Technician | **Ana Rita Fonseca Vicente** Administrative | **Sandra Isabel Francisco Lopes** Administrative | **Vânia Isabel Estevens Polido Marques Paula** Administrative

ONGOING PARTNERSHIPS

CENTRO ACADÉMICO DE MEDICINA DE LISBOA (CAML): IMM is associated with the Faculdade de Medicina da Universidade de Lisboa and with the Santa Maria teaching hospital through the Medical Academic Centre of Lisbon (CAML). CAML is consortium that represents an infrastructure 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 PROGRAMME,** sponsored by Fundação para a Ciência e Tecnologia. This programme, directed by M. Carmo-Fonseca (IMM/FMUL), results from a Memorandum of Understanding between Portuguese Ministry of Science, Technology and Higher Education and Harvard Medical School to encourage internationalization and cooperation between Portuguese schools of medicine and major national research centers working in biomedical and health sciences.

IMM is associated with the **DOCTORAL PROGRAMME FOR PHYSICIANS**, PFMA, supported by the Gulbenkian and Champalimaud Foundations, the Ministry of Health and the Foundation for Science and Technology.

IMM fosters scientific ideas to turn into products and technologies that make difference in health care. To achieve this goal IMM develops ties and strategic plans with companies, namely companies incubated at IMM: **GENOMED, TECHNOPHAGE, LYMPHACT AND TCLAB.**

IMM is one of the leading founders of the **HEALTH CLUSTER PORTUGAL,** a consortium that promotes initiatives and research projects to increase the national competitiveness, innovation and technology and encourages cooperation between companies, organizations, universities and public entities, seeking to expand economic areas related to health and to the improvement of health care.

INSTITUTIONAL PARTNERSHIPS

amc medical research
ANGELINI
AstraZeneca
AXA Research Fund
BAYER
BANCO ESPIRITO SANTO
Bial
BILL & MELINDA GATES foundation
Bristol-Myers Squibb
ARDLANE LIMITED
Celgene
Committed to improving the lives of patients worldwide
Ciência Viva
AGÊNCIA NACIONAL PARA A CULTURA CIENTÍFICA E TECNOLÓGICA
CONGREX SWITZERLAND
CONGREX TRAVEL
ecbio
Eisai
EMBO
FCT Fundação para a Ciência e a Tecnologia
GILEAD
gsk
GRUNENTHAL
FUNDAÇÃO CALOUSTE GULBENKIAN
Kenneth Rainin FOUNDATION
Linde
SANTA MARIA
FUNDAÇÃO LUSO-AMERICANA
Laço
L'ORÉAL PORTUGAL
MSD Viver bem
MERCK
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NOVARTIS
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Sociedade Portuguesa de Gastrenterologia
STERIS
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TEVA
THE UNIVERSITY OF ALABAMA
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