10TH ANNIVERSARY EDITION

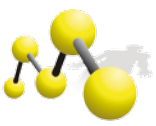


IMM REPORT 2012

INSTITUTO DE MEDICINA MOLECULAR

FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

INSTITUTO DE MEDICINA MOLECULAR
FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA



INSTITUTO DE
MEDICINA MOLECULAR

FACULDADE DE MEDICINA DA
UNIVERSIDADE DE LISBOA

INSTITUTO DE MEDICINA MOLECULAR (IMM)
FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA
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PROJECT CONCEPT AND MANAGEMENT
IMM Communication and Public Affairs Unit | immcomunicacao@fm.ul.pt

DESIGN
Formas do Possível | www.formasdopossivel.com

EDITION
1.000 copies

PHOTOS
IMM
Prof. Luis Costa's photo on page 27: Jorge Correia Luís, JasFarma 2011

March, 2013

UNIÃO EUROPEIA
Fundo Europeu de Desenvolvimento Regional

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

QREN QUADRO DE REFERÊNCIA ESTRATÉGICO NACIONAL

IMM REPORT 2012

INSTITUTO DE MEDICINA MOLECULAR

FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

CONTENTS

EDITORIAL 06

IMM AT A GLANCE 08

RESEARCH HIGHLIGHTS 09

1 YEAR IN THE LIFE OF IMM 14

A TYPICAL WEEK AT IMM 18

RESEARCH UNITS 19

Anes, Elsa
TUBERCULOSIS AND INNATE IMMUNITY 20

Barata, João Taborda
SIGNALING IN CANCER 21

Camilo, Maria E.
NUTRITION AND METABOLISM 22

Carmo-Fonseca, Maria
RNA AND GENE REGULATION 23

Carvalho, Mamede
BRAIN, COGNITION, AND MOTOR CONTROL. AUTONOMIC REGULATION AND PERIPHERAL NERVE 24

Castanho, Miguel
PHYSICAL BIOCHEMISTRY OF DRUGS AND TARGETS 25

Constantino, Susana
ANGIOGENESIS REGULATION AND THERAPEUTIC IMPLICATIONS 26

Costa, Luís
TRANSLATIONAL ONCOBIOLOGY 27

Ferro, José
CLINICAL RESEARCH IN NON-COMMUNICABLE NEUROLOGICAL DISEASES 28

Figueiredo, Luísa
BIOLOGY OF PARASITISM 29

Fonseca, João Eurico
ARTHRITIS AND BONE 30

Gonçalves, João
MOLECULAR VIROLOGY AND APPLIED BIOTECHNOLOGY 31

Graça, Luís
LYMPHOCYTE REGULATION 32

Henrique, Domingos
STEM CELLS AND NEUROGENESIS 33

Mair, Gunnar
GENE REGULATION IN THE MALARIA PARASITE 34

Mhlanga, Musa
GENE EXPRESSION AND BIOPHYSICS 35

Moita, Luís Ferreira
INNATE IMMUNITY AND INFLAMMATION 36

Mota, Maria M.
BIOLOGY AND PHYSIOLOGY OF MALARIA AND OTHER INFECTIONS 37

Outeiro, Tiago Fleming
PROTEIN MISFOLDING AND NEURODEGENERATION 38

Ramirez, Mário
MOLECULAR MICROBIOLOGY AND INFECTION 39

Saldanha, Carlota
ERYTHROCYTE, LEUKOCYTE RECRUITMENT AND INFLAMMATION 40

Santos, Nuno C.
BIOMEMBRANES AND NANOMEDICINE 41

Saúde, Leonor
EMBRYONIC DEVELOPMENT AND REGENERATION 42

Sebastião, Ana
NEURONAL COMMUNICATION AND SYNAPTOPATHIES 43

Silva-Santos, Bruno
T-CELL DIFFERENTIATION AND TUMOR TARGETING 44

Simas, Pedro
HERPES VIRUS PATHOGENESIS 45

Sousa, Ana E.
HUMAN IMMUNODEFICIENCY AND IMMUNE RECONSTITUTION 46

Veiga-Fernandes, Henrique
LYMPHOCYTE FUNCTION AND DEVELOPMENT 47

FACILITIES AND SERVICES 49

Biobank 50

Bioimaging 50

Biosafety level 3 Laboratory 51

Flow Cytometry Unit 51

Histology Service 52

Small Rodents 52

Zebra Fish Facility 53

ONGOING PARTNERSHIPS 54

CONTRACTS WITH INDUSTRY 55

EDITORIAL

by J. Lobo Antunes and Maria Carmo-Fonseca

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

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 University of Lisbon Medical School. 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 among junior scientists trained abroad. Up to present, sixteen new Group Leaders were recruited, and the total number of researchers increased from 150 to 480.

IMM is centered on 29 cutting-edge laboratories working in a broad range of fields that encompass multidisciplinary approaches ranging from basic to clinical and translational research. Presently it has 480 researchers with expertise on Cell and Developmental Biology, Immunology, Infection, Neurosciences and Oncobiology. Its research is also clinically oriented and addressing 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 30 talented scientists from 15 nations and four different continents, as well as Portuguese nationals returning from abroad.

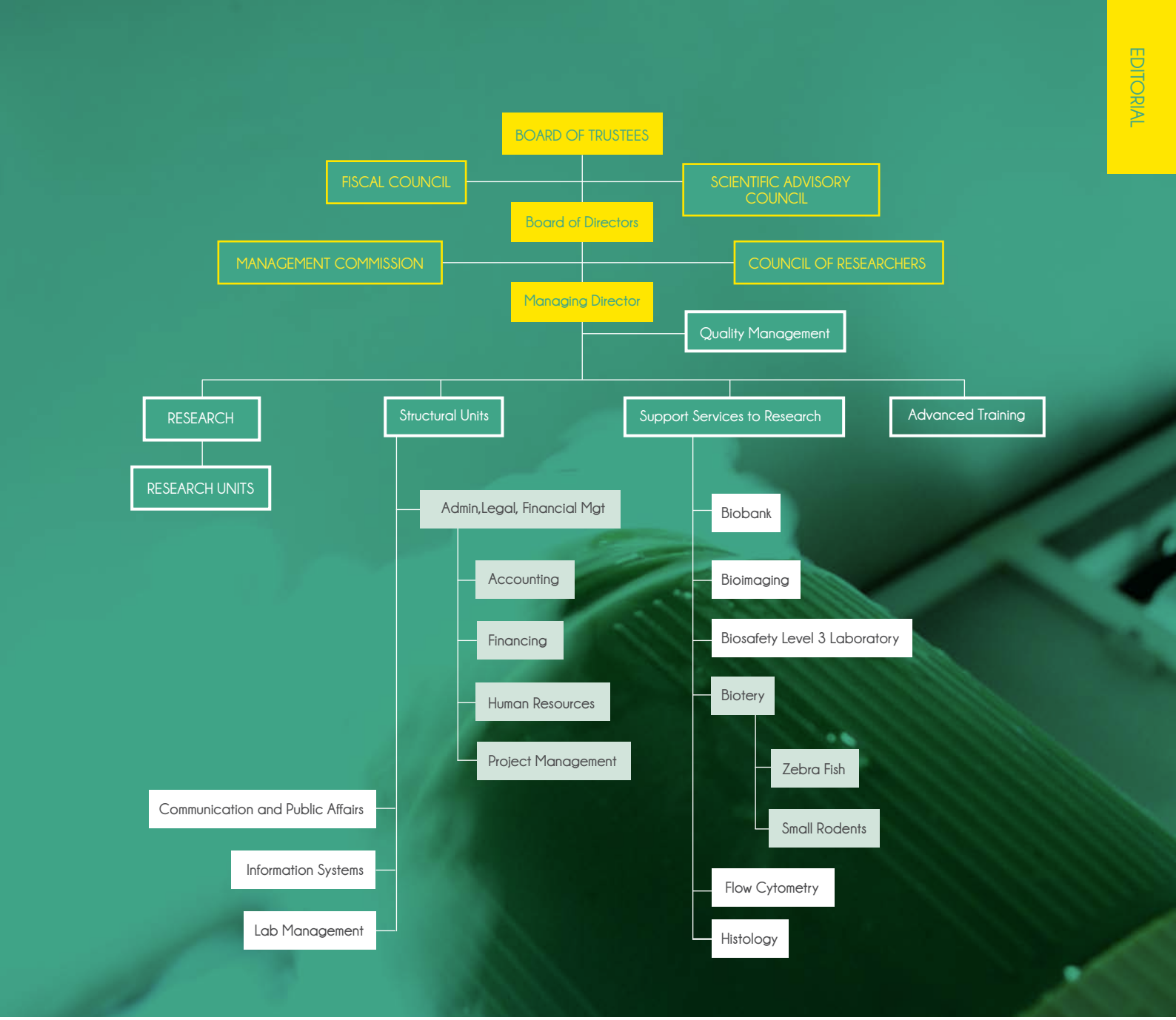
IMM currently hosts 89 PhD students, 30% of which have a medical background. Since 2008 we have been receiving an average of 18 new PhD students each year. The vast majority of students that graduated at IMM are currently employed in academia (82%), hospitals (5%) and industry (4%).

We are pleased to highlight some of IMM's accomplishments in 2012. 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, Maria Mota was awarded a European Research Council Starting Grant.

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.

J Lobo Antunes
President

Maria Carmo-Fonseca
Executive Director



SCIENTIFIC ADVISORY BOARDS:

CELL AND DEVELOPMENTAL BIOLOGY

- Ira Mellman, Genentech, San Francisco, USA
- Fiona Watt, Cancer Research UK, London, UK
- John G Gribben, Barts Cancer Institute, Queen Mary University of London, UK
- Petra Schwille, Max Plankt Institute of Biochemistry, Munich

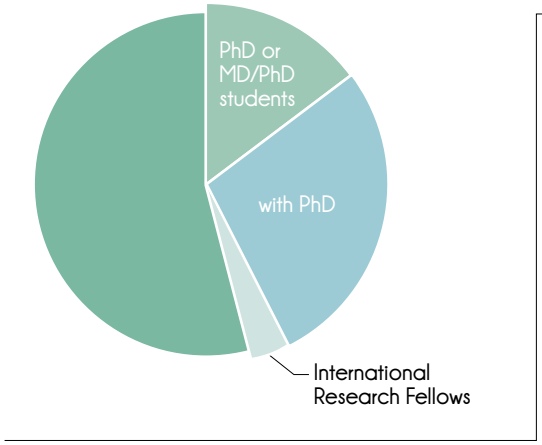
IMMUNOLOGY AND INFECTION

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

NEUROSCIENCES

- Michael Spyer, University College London, UK
- Christine Gall, University of California, USA
- Charles Warlow, Western General Hospital, Edinburgh, UK
- Reinhard Dengler, Medizinische Hochschule, Hannover, Germany

IMM AT A GLANCE



TOTAL RESEARCHERS
480

with PhD
206

PhD or MD/PhD students
108

International Research Fellows
30

RESEARCH UNITS
29

START-UPS
3

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

IMM HIGHLIGHTS 2012

TOTAL EXPENDITURE

in euros

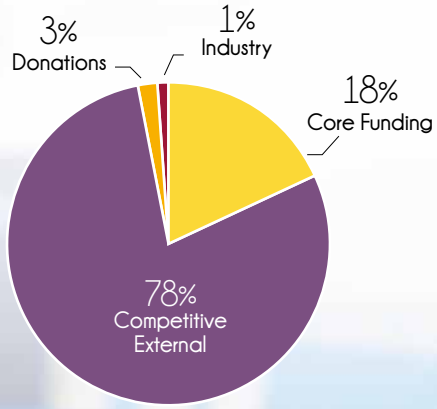
TOTAL
14.799,606 €

CORE FUNDING
2.699,412 €

COMPETITIVE EXTERNAL
11.582,941 €

DONATIONS
364,359 €

INDUSTRY
152,895 €



COMPETITIVE EXTERNAL FUNDING

in euros

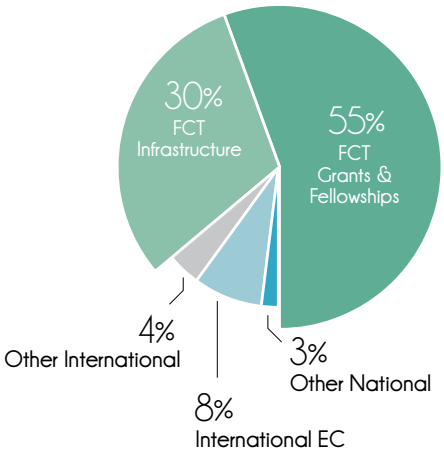
TOTAL
11.582,941 €

NATIONAL FCT
FCT
INFRASTRUCTURE
3.478,893 €
FCT
GRANTS & FELLOWSHIPS
6.411,432 €

OTHER NATIONAL
278,087 €

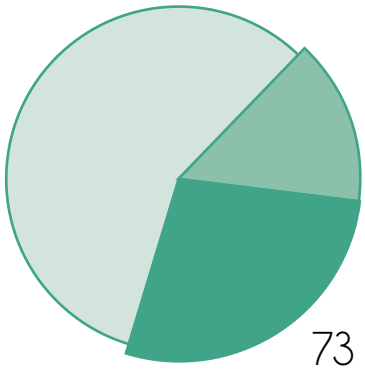
INTERNATIONAL EC
937,652 €

OTHER INTERNATIONAL
476,877 €



RESEARCH HIGHLIGHTS

PAPERS 2012



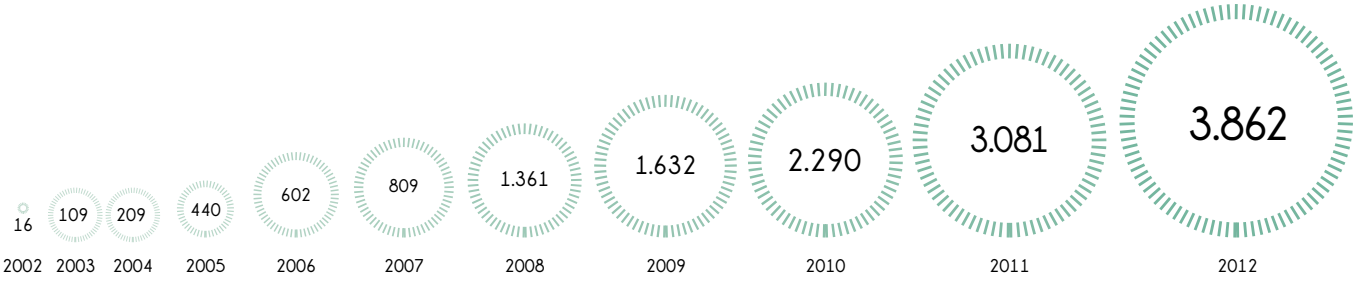
355
papers published in peer reviewed journals

12
publications in journals with an impact factor higher than 10

73
publications in journals with an impact factor between 5-10

SUM OF THE TIMES CITED: 14.411

CITATIONS PER YEAR



Source: Web of Knowledge

MOST RELEVANT PAPERS

Grosso, AR, de Almeida, SF, Braga, J, Carmo-Fonseca, M. (2012) Dynamic transitions in RNA polymerase II density profiles during transcription termination. Genome Research 22 (8): 1447-1456. Journal impact factor: 13.6

Dávalos A, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, Serena J, Segura T, Cruz VT, Masjuan J, Cobo E, Secades JJ; International Citicoline Trial on acute Stroke (ICTUS) trial investigators. (2012) Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). Lancet 380: 349-357. Journal impact factor: 38.278

Traylor M, Farrall M, Holliday EG, et al. (2012) Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. Lancet Neurology 11: 951-962. Journal impact factor: 23.462

Santos T, Ferreira R, Maia J, Agasse F, Xapelli S, Cortes L, Bragança J, Malva JO, Ferreira L, Bernardino L. (2012) Polymeric nanoparticles to control the differentiation of neural stem cells in the subventricular zone of the brain. ACS Nano 6: 10463-10474. Journal impact factor: 11.421

Sergi Padilla-Parra, Pedro M. Matos, Naoyuki Kondo, Mariana Marin, Nuno C. Santos, Gregory B. Melikyan. (2012) Quantitative imaging of endosome acidification and single retrovirus fusion with distinct pools of early endosomes. Proc Natl Acad Sci U S A. 109: 17627-17632. Journal impact factor: 10.472

Sinthuvanich C.*, Veiga A.S.*, Gupta K., Gaspar D., Blumenthal R., Schneider J.P. (2012) Anticancer b-hairpin peptides: membrane-induced folding triggers activity. Journal of the American Chemical Society 134: 6210-6217. (*Equal contributions) Journal impact factor: 9.907

Hudspeth K, Fogli M, Correia D, Mikulak J, Roberto A, Della Bella S, Silva-Santos B* and Mavilio D*. (2012) Engagement of NKp30 on Vdelta1+ T-cells induces the production of CCL3, CCL4 and CCL5 and suppresses HIV-1 replication. Blood 119(17): 4013-4016. (*Equal contributions) Journal impact factor: 9.898

Lionel Franz Poulin, Yasmin Reyal, Heli Uronen-Hansson, Barbara Schraml, David Sancho, Kenneth M. Murphy, Ulf K. Håkansson, Luis Ferreira Moita, William W Agace, Dominique Bonnet, and Caetano Reis e Sousa. 2012. DNGR-1 is a specific and universal marker of mouse and human Batf3-dependentdendritic cells in lymphoid and non-lymphoid tissues. Blood 119(25): 6052-6062. Journal impact factor: 9.898

Derbyshire ER, Prudêncio M, Mota MM, Clardy J. (2012) Liver-stage malaria parasites vulnerable to diverse chemical scaffolds. Proc Natl Acad Sci U S A. 109(22): 8511-8516. Journal impact factor: 9.681

Galindo-Villegas J, García-Moreno D, de Oliveira S, Meseguer J, Mulero V. (2012) Regulation of immunity and disease resistance by commensal microbes and chromatin modifications during zebrafish development. Proc Natl Acad Sci U S A. 109(39): E2605-14. Journal impact factor: 9.681

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 impact factor: 8.435

Lee JM, Ramos EM, Lee JH, et al. (2012) CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. Neurology 78: 690-695. Journal impact factor: 8.312

Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, Suhr O, Campistol J M, Conceição I, Schmidt HJ, Trigo P, Kelly J, Labaudinière R, Chan J, Packman J, Wilson A, Grogan DR. (2012) Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology 21: 785-792. Journal impact factor: 8.312

Jokinen H, Lipsanen J, Schmidt R, Fazekas F, Gouw AA, van der Flier WM, Barkhof F, Madureira S, Verdelho A, Ferro JM, Wallin A, Pantoni L, Inzitari D, Erkinjuntti T; LADIS Study Group. (2012) Brain atrophy accelerates cognitive decline in cerebral small vessel disease: the LADIS study. Neurology 78: 1785-1792. Journal impact factor: 8.312

Bobrie A, Krumeich S, Reyal F, Recchi C, Moita LF, Seabra MC, Ostrowski M, Théry C. (2012) Rab27a supports exosome-dependent and -independent mechanisms that modify the tumor microenvironment and can promote tumor progression. Cancer Research 72(19): 4920-4930. Journal impact factor: 7.856

Bernardino L, Eiriz MF, Santos T, Xapelli S, Grade S, Rosa A, Cortes L, Bragança J, Agasse F, Ferreira L, Malva JO. (2012) Histamine stimulates neurogenesis in the rodent subventricular zone. Stem Cells 30: 773-784. Journal impact factor: 7.781

Sancenon V, Lee SA, Patrick C, Griffith J, Paulino A, Outeiro TF, Reggiori F, Masliah E, Muchowski PJ. (2012) Suppression of Ð-synuclein toxicity and vesicle trafficking defects by phosphorylation at S129 in yeast depends on genetic context. Human Molecular Genetics 21(11): 2432-2449. Journal impact factor: 7.636

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 5(235): ra55. Journal impact factor: 7.5

Sampaio-Marques B, Felgueiras C, Silva A, Rodrigues M, Tenreiro S, Franssens V, Reichert AS, Outeiro TF, Winderickx J and Ludovico P. (2012) SNCA (alpha-Synuclein)-induced toxicity in yeast cells is dependent on sirtuin 2 (Sir2)-mediated mitophagy. Autophagy 8(10): 1494-509. Journal impact factor: 7.453

Veiga A.S., Sintuvanich C., Gaspar D., Franquelim H.G., Castanho M., Schneider J.P. (2012) Arginine-rich self-assembling peptides as potent antibacterial gels. Biomaterials 33: 8907-8916. Journal impact gactor: 7.404

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): 11750-11762. (* Equal Contributions) Journal impact factor: 7.12


BioRad

INTERNATIONAL AWARDS 2008-2012

European Research Council Starting Grant attributed to Maria M. Mota
Total amount of 1.500,000 EUR for the period of 2012-2017. Nutrient sensing by parasites.

AXA Research Fund attributed to Maria Carmo-Fonseca
Total amount: 173.500 EUR for the period of 2012-2015. Identification and manipulation of molecular pathways relevant for age-dependent tissue regeneration

EFSD - European Foundation for the Study of Diabetes attributed to Luís Graça
Total amount: 100.000 EUR for the period of 2012-2014. Cellular therapy to induce local immune suppression in islet transplantation

National Blood Foundation (USA) attributed to Henrique Veiga Fernandes
Total ammount:75.000 USD for the period of 2012-2014 . Modulation of RET signaling in hematopoetic stem cell transplantation

Howard Hughes Medical Institute International Early
Career Scientist (HHMI) 2011
Luísa Figueiredo

Bill & Melinda Gates Foundation, Grand Challenges Explorations Programme 2011
João Gonçalves
Nanotechnology against viral latency: Sensor strategies to eliminate HIV-1 infected cells

ERC Starting Grant 2010
Bruno Silva-Santos
Differentiation of pro-inflammatory T cell subsets in vivo

Bill & Melinda Gates Foundation, Grand Challenges Explorations Programme 2010
Miguel Prudêncio
A new whole-organism vaccine against malaria

EMBO Young Investigator 2010
Bruno Silva-Santos

EMBO Installation Grant 2010
Luísa Figueiredo

ERC Starting Grant 2008
Henrique Veiga-Fernandes
Role of the proto-oncogene Ret during lymphocyte development and function

ERC Starting Grant 2008
António Jacinto
RESEAL – Epithelial Resealing

EMBO Installation Grant 2008
Henrique Veiga-Fernandes

EMBO Installation Grant 2008
Tiago F. Outeiro

PATENTS

BR20120047785 *(Definitive) PT; PCT*
"Means and methods for the inhibition of the flavivirus replication"
Nuno Santos

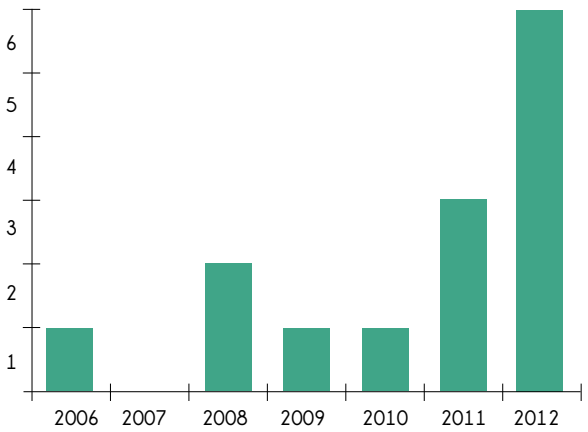
PT106262 *(Provisional) PT*
"Genetically modified rodent plasmodium parasites as platforms for a whole-organism malaria vaccine"
Maria Mota, Miguel prudêncio

PT106359 *(Provisional) PT*
"Dengue virus capsid protein-lipoproteins interactions"
Nuno Santos

PT106393 *(Provisional) PT*
"Green fluorescent protein labeling of dopaminergic neurons in zebrafish for the study of the molecular basis of parkinson's disease"
Tiago Outeiro

PT106413 *(Provisional) PT*
"Ret agonist molecules are critical to haematopoietic stem cell (hsc) expansion protocols and hsc transplantation therapy"
Henrique Veiga Fernandes

PT106523 *(Provisional) PT*
"The per2 gene is a biomarker of obstructive sleep apnea syndrome"
Luís Ferreira Moita



NEW PROVISIONAL PATENTS PER YEAR

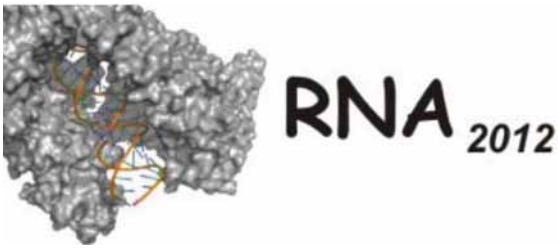
1 YEAR IN THE LIFE OF IMM

JAN 26/27 FEV MAR 23 31 APR 13/14

2012

JANUARY 26/27
Portuguese RNA meeting 2012

The program included plenary talks from international and national experts in addition to short oral communications selected from the submitted abstracts.



MARCH 23
Best Practices Workshop

The Best Practices training course organized by "Laboratório de Farmacologia Clínica e Terapêutica" is aimed at all professionals with interest in clinic research studies design and management.

MARCH 31
Hemorrheology, Hemostasis and Inflamation in Vascular Pathology

These scientific gatherings are a privileged opportunity for knowledge sharing and clinic issues discussion. They also allow for a knowledge update on the specific domains of vascular pathologies.

APRIL 13/14

IMM group leader Ana Espada de Sousa was distinguished with the NEDAI Award for Basic Research in Autoimmunity with the project Differentiation of human thymic regulatory T cells at the double positive stage.
Under the same call IMM Principal Investigator Sofia Oliveira was awarded the NEDAI Award for Clinical Research in Autoimmunity.

NEDAI
núcleo de estudos de doenças auto-imunes

APR MAY 18/19/20 JUN 21 JUL AUG SEP 21 28

MAY 18/19/20
IMM PhD Students retreat

JUNE 21
Workshop qTower - qPCR in 60 minutes – From Sampling Preparation to Real-Time PCR

IMM organizes different workshops with national and international renown companies in order to provide high potential technologies to its researchers.

SEPTEMBER 21
Bike to Work Day

On september 21th, IMM participate in the "Bike to Work Day" event.

SEPTEMBER 28
Europarliamentarian Maria da Graça Carvalho Highlights IMM´s Performance

Under the subject "Active Aging and Generation Solidarity Year", European Parliamentarian Maria de Graça Carvalho chose IMM to make her promotional video. The selected participating projects were Rheumatology (Prof. Helena Canhão) and Basic Research (Henrique Veiga Fernandes).
The video also featured a testimonial by IMM Chairman João Lobo Antunes.

IMM Bye Bye Summer Party

IMM PhD Students organized an outdoor party to bring IMMers, friends and families together

1 YEAR IN THE LIFE OF IMM

OCT 3 23

OCTOBER 3
Public Launching of Biobanco-IMM

On October 3rd, the School of Medicine of the University of Lisbon hosted the public presentation of Biobanco-IMM. Among 400 participants who attended this session were numerous personalities from the Science and Health sector: José Manuel Silva, President of the Bar of Doctors, General Health Director Francisco George, President of the Champalimaud Foundation Leonor Beleza; and former journalist Maria Elisa.
The event arose very high interest among the participants, who considered using Biobanco-IMM as part of ongoing and future research projects.

OCTOBER 23

Professor José Ferro and Sofia Oliveira identified new stroke genes, paving the way for therapeutic innovation.

NOV 29 DEC 14 19

NOVEMBER 29
VI PhD Students Meeting

Opened by IMM Chairman Prof.Lobo Antunes, the meeting featured honorable speakers, such as Prof. Carlos Caldas and Bioalvo CEO Helena Vieira

DECEMBER 19

IMM Researchers Sofia Oliveira, Luísa Lopes, Maria Mota, Leonor Saúde, Gonçalo Bernardes, Sérgio Almeida, Miguel Prudêncio and Cláudio Areias Franco won the newly launched FCT Investigator positions.

DECEMBER 14
Open Day

Biobanco-IMM's Open Day aimed to raise awareness among the general population, but also amidst scientific, medical and academic communities regarding the importance of biobanks for scientific research and development of new therapeutic approaches.

A TYPICAL WEEK AT IMM

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

MONDAY

11:00 - Neurosciences Seminar
This weekly series included in IMM's Neuroscience Program and in the IMM/FMUL Neurosciences Masters/Doctoral Program consists of informal meetings, where members of different IMM lab groups and external invited speakers give 50-minute talks on their current research and receive feedback from the audience.

12:30 - Monday Lecture
The Monday Lecture series brings top-notch researchers to IMM every week. Visiting from Rockefeller University of New York, renowned chemist George Cross was the invited speaker at IMM Monday Lecture to talk about *Antigenic variation in trypanosomes: it's all about persistence.*

TUESDAY

12:00 - Pizza Seminar
IMM Post-Doc Ana Magalhães presents her project *Does high systemic cholesterol influence the endothelia of target organs to facilitate metastasis?* at the Pizza Seminar, a forum for PhD students and Post-Docs to have peer feedback about their research projects.

WEDNESDAY

10:00 - Computational Biology and Bioinformatics Seminars
The Computational Biology and Bioinformatics Seminar (CBBS) is a monthly series of seminars that aim to create a platform for dialogue and discussion among researchers interested in developing and applying computational and mathematical approaches to solve significant problems in biology and biomedicine.

13:00 - Chalk Talk
Chalk talks, IMM PIs join brainstorming meetings to discuss future and ongoing scientific projects.

13:00 - IMM Internal Seminars
These occur every other Wednesday, alternating with chalk talk.

17:00 - Lisbon Area Neurosciences Meetings
Lisbon Area Neurosciences meetings are regularly organized by the neurosciences community.

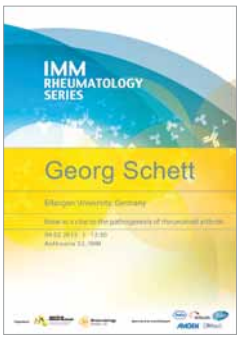
THURSDAY

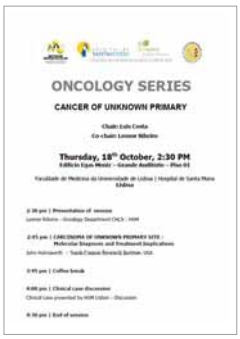
13:00 - Immunology Club
Diana Fontinha from IMM debates her project *Herpes virus modulation of immune synapses defense* at the Immunology Club, organized organized by IMM's Immunology community.

14:30 - Oncology Series
John Hainsworth from Sarah Cannon Research Institute, USA, talks about *Carcinoma of Unknown Primary Site: Molecular Diagnosis and Treatment Implications* at the Oncology Series, a seminar series dedicated to clinical investigator in cancer.

FRIDAY

12:00 - Rheumatology Series
IMM's Rheumatology Research Unit introduced in 2012 a monthly conference cycle called "IMM Rheumatology Series", featuring many speakers.
The main goal of this conference cycle is to bring to our academic center expertise from the rheumatology area, to share experience, as well as to foster debate.
These conferences allow for great interaction between doctors and basic/clinical researchers in a dynamic environment.
The conferences are open to general public, yet rheumatologists and researchers remain the main target.





RESEARCH UNITS

IMM is centered on 29 cutting-edge laboratories working in a broad range of fields that encompass multidisciplinary approaches ranging from basic to clinical and translational research. Our expertise is focused on Cell and Developmental Biology, Immunology, Infection, Neurosciences and Oncobiology.

Scientists at IMM work toward a more complete understanding of the sophisticated functions of cells, the units of life. They study mechanisms that regulate gene expression, as well as signaling pathways that control embryonic axis specification, cell fate determination, stem cell differentiation, angiogenesis and tissue homeostasis. There is also a strong focus on cancer research with the ultimate aim of identifying novel molecular markers for diagnosis and targets for therapeutic intervention. Our laboratories employ the full range of modern cell and molecular tools, including live-imaging, flow cytometry, atomic force microscopy, bioinformatics, computer modeling and simulation, and high-throughput sequencing.

The immune system lies at the heart of many critical recent advances in biomedicine, especially in what concerns the rational design of vaccination strategies against infectious agents, resistance to tumors and autoimmune disease. IMM scientists apply cell and molecular biology approaches to study the processes underlying undesirable immune responses that cause autoimmune diseases such as rheumatoid arthritis and allergy.

Currently, immunologists and microbiologists around the world face major challenges, such as the prevalence of malaria, tuberculosis, AIDS, and the emergence of novel strains of antibiotic-resistant bacteria. At IMM we aim at elucidating the basic biological mechanisms that underlie the dynamic interaction between the host and distinct pathogens, such as retroviruses (HIV), gamma herpes viruses, Streptococcus, and parasites – *Trypanosome and Plasmodium*.

Neurological diseases represent important medical and socioeconomic problems and raise fascinating scientific questions about how the brain works. At IMM we combine basic cell and molecular biology approaches with pharmacology, functional neuroscience and clinical research tools to study major disorders of the nervous system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy and stroke.

Group Leader

ELSA ANES

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

TUBERCULOSIS AND INNATE IMMUNITY

Our work focuses on the findings that 90% of *Mycobacterium tuberculosis* (*Mtb*) infected individuals control tuberculosis and also on the fact that, after phagocytosis, *Mtb* can be killed by activated macrophages. The *Mtb* containing phagosome maturation is blocked protecting the bacteria from degradation. Several signalling lipids, were shown to be involved in reversion of *Mtb* phagosome maturation blockade and in mycobacteria intracellular killing. Some lipids control NF-KB and we linked NF-KB with the regulation of many lysosomal enzymes and membrane-trafficking regulators. Recently, we have unveiled a distinct containment of key Cathepsins (Cts) inside *Mtb* infected macrophages and dendritic cells. We intend to explore phagosome trafficking pathways namely those involved in intracellular distribution of Cts and their inhibitors (cystatins), an important phenomena for proteolytic cleavage required for bacteria killing or antigen presentation. We propose to decipher how the manipulation of lysosomal proteases can affect the survival of Mtb, in particular during the co-infection with HIV. The discovery of new regulatory elements in tuberculosis alone or during co-infection with HIV will represent a critical advancement that will allow the rationale development of new therapies against infectious diseases.

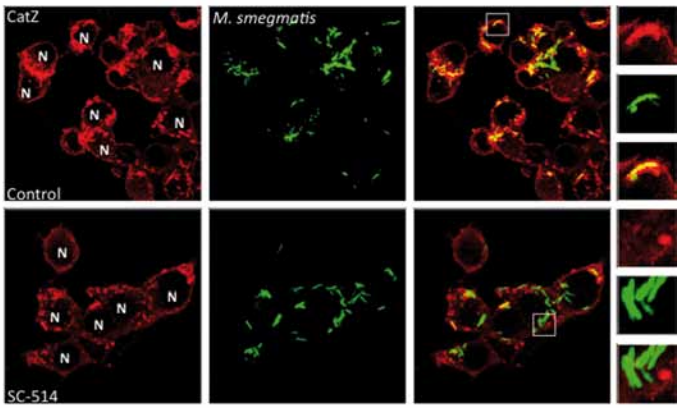


Fig. NF-KB activation controls late endosome/lysosome fusion-mediated killing of mycobacteria by macrophages. Lysosomal enzymes found under NF-KB activation includes cathepsins B, C, H and Z. The NF-KB inhibitor SC-514 prevents cathepsin acquisition into mycobacteria containing phagosomes.

RECENT MOST RELEVANT PUBLICATIONS

Mishra, BB, Moura- Alves, P, Sonawane, A, Hacohen, N, Griffiths, G, Moita, LF, Anes, E. 2010 *Mycobacterium tuberculosis* protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. Cell Microbiol. 12(8):1046-63. Times cited: 39. Journal impact Factor: 5.8

Kuehnel, M, Rybin, V, Anand, P, Anes, E, 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. Times cited: 15. Journal impact Factor: 6.4

Gutierrez, MG*, Mishra, BB*, Jordao, ML, Elliot, E, Anes, E, Griffiths, G 2008 NF-kappa B activation controls phago-lysosome fusion-mediated killing of mycobacteria by macrophages. J. Immunology 18(4): 2651-63 *joined first authors. Times cited: 25. Journal impact Factor: 6.1

Jordao, L, Bleck, CKE, Mayorga, L, Griffiths, G, Anes, E 2008 On the killing of mycobacteria by macrophages. Cell Microbiol 10(2): 529-48. Times cited: 31. Journal impact Factor: 5.6

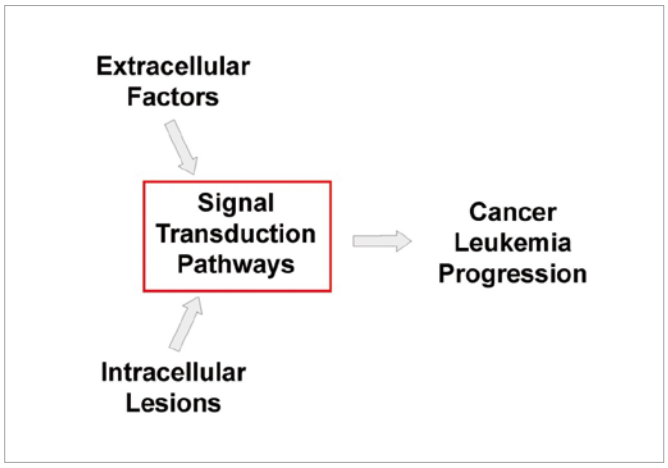
Anes, E, Kuhnel, MP, Bos, E, Moniz-Pereira, J, Habermann, A, Griffiths, G 2003 Selected lipids activate phagosome actin assembly and maturation resulting in killing of pathogenic mycobacteria. Nat Cell Biol 5(9): 793-802. Times cited: 118. Journal impact Factor: 20.8

Group Leader
JOÃO TABORDA BARATA

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

SIGNALING IN CANCER

Cancer, the uncontrolled growth of abnormal cells in the body, is one of the leading causes of death worldwide. A deeper understanding of cancer biology is required to allow the development of novel, more efficient and selective treatments. We showed that interleukin-7 (IL-7) accelerates the progression of human T-cell acute lymphoblastic leukemia (T-ALL), an aggressive form of childhood cancer, and that around 9% of T-ALL patients display gain-of-function mutations in the IL-7 receptor, leading to constitutive signaling and oncogenesis. Interestingly, we also found that PTEN, a tumor suppressor that negatively regulates the major IL-7-activated pathway PI3K/Akt/mTOR, is not genetically deleted in most T-ALL patient samples, contrary to what happens in solid tumors. Instead, PTEN is functionally inactivated by posttranslational modifications mediated by reactive oxygen species and the kinase CK2. By looking not only at genetic lesions but also beyond, into the posttranslational aberrations and microenvironmental cues that converge on the activation of specific pro-tumoral signaling pathways, we aim to continue identifying players and mechanisms involved in cancer development.



We study not only genetic lesions but also, as illustrated in the cartoon, the posttranslational aberrations and extracellular cues converging on the activation of signaling pathways that contribute to cancer progression, with emphasis on leukemia. In doing so, we aim to have a better understanding of cancer biology and identify key players and mechanisms involved in cancer development that may constitute targets for therapeutic intervention.

RECENT MOST RELEVANT PUBLICATIONS

Zenatti, PP, Ribeiro, D, Li, W, Zuurbier, L, Silva, MC, Paganin, M, Tritapoe, J, Hixon, JA, Silveira, AB, Cardoso, BA, Sarmento, LM, Correia, N, Toribio, ML, Kobarg, J, Horstmann, M, R. Pieters, R, Brandalise, SR, Ferrando, AA, Meijerink, JP, Durum, SK, Yunes, JA, Barata, JT 2011 Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nature Genetics 43 932. Times cited: 25. Journal impact factor: 35.5

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. Times cited: 93. Journal impact factor: 13.069

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. Times cited: 96. Journal impact factor: 13.853

J.T. Barata, A.A. Cardoso, L.M. Nadler, V.A. Boussiotis 2004 Interleukin-7 promotes survival and cell cycle progression of T-cell acute lymphoblastic leukemia cells by down-regulating the cyclin-dependent kinase inhibitor p27kip1. Blood 98 1524. Times cited: 89. Journal impact factor: 9.898

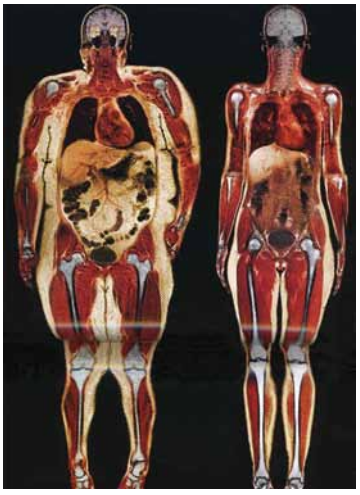
Group Leader

MARIA ERMELINDA CAMILO

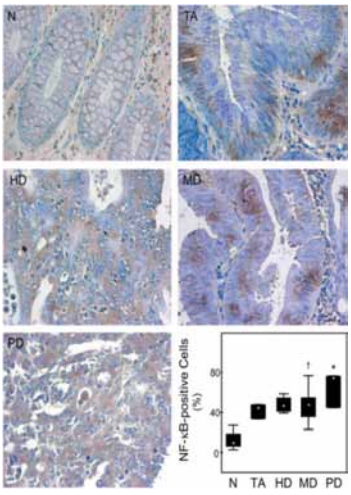
MD, PhD – retired since June 2008 from Auxiliary Professor Faculdade de Medicina da Universidade de Lisboa
Other Principal Investigators: Helena Cortez-Pinto, Isabel Monteiro Grillo, Paula Ravasco

NUTRITION AND METABOLISM

UNM focuses on clinical/translational research in nutrition/metabolism; publications reveal the major influence of nutritional factors on cancer course/survival as well as on obesity and liver disease. A small multidisciplinary team reached international excellence in 2 main areas: H. Cortez-Pinto in liver fat metabolism, P. Ravasco in Nutrition and Cancer. Both are prized speakers with major roles in international bodies, lectures/advanced teaching in national/international Congresses. Developments: 1. in Steatohepatitis, a large study on the prevalence of fatty liver in Portugal investigate potential/complex interactions with alcohol, obesity, insulin resistance, in order to understand underlying biological and metabolic mechanisms; using fibroscan/coefficient attenuation techniques allowing to measure fibrosis and steatosis degrees and investigate correlations with ultrasound; other area: obesity and its relationship with liver inflammation and the importance of microbiota. Nutrition and cancer explores nutritional therapy on weight maintenance, body composition, functional capacity and symptoms; a screening/intervention protocol fostering routine implementation of timely referrals to individualized care is being tested; in cancer cachexia various cytokine polymorphisms may detect early nutrition deterioration. Results may improve patients' prognosis by dramatically changing patients' disease course and management. UNM is increasingly involved in Medicine and Nutrition Master/PhD Programs.



Body composition with DEXA & CT scans in cancer: associations with Quality of Life and tolerance to treatments



Nutrients and gene/cell expression

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Machado MV, Cortez-Pinto H. 2011 Osteopontin: A Missing Link between Hedgehog Signaling and Fibrosis in Nonalcoholic Steatohepatitis. Editorial. Hepatology 53 382-384. Times cited: 2. Journal impact factor: 11.665

Machado MV, Oliveira AG, Cortez-Pinto H 2010 Hepatic steatosis in patients coinfectd with human immunodeficiency virus/hepatitis C virus: A meta-analysis of the risk factors. Hepatology 52 71-78. Times cited: 9. Journal impact factor: 11.665

Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G 2010 A position statement on NAFLD/NASH based on the EASL 2009 special conference. Journal of Hepatology 53 372-384. Times cited: 84. Journal impact factor: 9.264

Guerreiro, CS., Ferreira, P., Tavares, L., Moura Santos, P., Neves, M., Brito, M., Cravo, M. 2009 Fatty acids, IL-6 and TNF-? polymorphisms: An example of nutrigenetics in Crohn's disease. American Journal Gastroenterology 104 2241-2249. Times cited: 16. Journal impact factor: 7.282

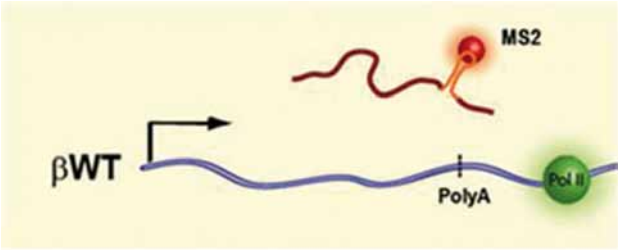
Ravasco, P., Monteiro Grillo. I., Camilo. M. 2012 Dietary individualized counseling benefits in colorectal cancer: the long term follow-up of a randomized controled trial of nutritional therapy. American Journal of Clinical Nutrition 96 1346-1353. Times cited: 15. Journal impact factor: 6.971

Group Leader
MARIA CARMO-FONSECA

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

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. Early molecular biologists thought and taught for many years that RNA molecules served mainly as carriers of genetic information from DNA, and adaptors for protein synthesis. Today we are aware of a wealth of new functions carried out by RNA in cells and organisms. The great challenge ahead will be to understand how RNAs affect the function of cells in the human organism and how this knowledge can be translated into novel disease biomarkers and therapies. Work from our group argues that reciprocal interconnectivity between the different steps required for gene activation plays a critical role ensuring efficiency and fidelity of gene expression. We currently study co-transcriptional pre-mRNA processing and surveillance, and the role of RNA splicing in cancer. Our projects make use of a multidisciplinary approach that combines live-cell microscopy, computational modelling, molecular biology, biochemistry and bioinformatics.



Our live-cell imaging observations argue that in actively transcribed genes, RNA polymerase II (Pol II) persists associated with the DNA template downstream of the polyA site, after the mRNA (visualized with the MS2 system) has already been released.

RECENT MOST RELEVANT PUBLICATIONS

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. Times cited: 20. Journal impact factor: 12.7

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. Times cited: 10. Journal impact factor: 12.7

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. Times cited: 12. Journal impact factor: 8.0

Grosso, A.R., Gomes, A.Q., Barbosa-Morais, N.L., Caldeira, S., Thorne, N.P., Grech, G., von Lindern, M., and Carmo-Fonseca, M 2008 Tissue-specific splicing factor gene expression signatures. Nucleic Acids Research 36 4823-32. Times cited: 36. Journal impact factor: 8.0

Braga J, Desterro JM, Carmo-Fonseca M 2004 Intracellular macromolecular mobility measured by fluorescence recovery after photobleaching with confocal laser scanning microscopes. Mol. Biol. Cell 15 4749-4760. Times cited: 100. Journal impact factor: 4.9

Group Leader

MAMEDE DE CARVALHO

MD (1985) at Faculdade de Ciências Médicas, Universidade Nova de Lisboa
PhD (2000) at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Associate Professor at FMUL
Other Principal Investigators: Isabel Rocha

BRAIN, COGNITION, AND MOTOR CONTROL. AUTONOMIC REGULATION AND PERIPHERAL NERVE

The Translational Clinical Physiology Unit investigates the motor neuron function and degeneration autonomic nervous system and cardiovascular regulation, peripheral nerve function, behaviour and imaging-neurocomputational models of brain dysfunction. This Unit has contributed to a more complete comprehension of the electrophysiological signs in motor neuron degeneration, the role of the autonomic nervous system in heart regulation and about the activity of brain structures in behaviour disturbances. In the future we aim to approach brain function and autonomic dysfunction, computational models of frontal degeneration in motor neuron disease, new techniques to evaluate small nerve fibre evaluation, and the interaction between brain and nerve excitability. We address to develop a broader understanding of central-peripheral nerve function interface; this can open different horizons to novel rehabilitation techniques. Our activity encompasses laboratory and clinical research following a translational strategy, for this purpose we include basic scientists, engineers, healthy technicians and medical doctors. We anticipate a relevant impact of our activities on heart arrhythmia, amyloid polyneuropathy, amyotrophic lateral sclerosis and attention deficit hyperactive disorder.

RECENT MOST RELEVANT PUBLICATIONS

Costa J, Swash M, de Carvalho M 2012 The Awaji criteria for the diagnosis of ALS: a systematic review. Arch Neurol 69:1410-1416. Journal impact factor: 7.584

Maia, TV, Frank M J 2011 From reinforcement learning models to psychiatric and neurological disorders. Nat Neuroscience 14: 154-162. Journal impact factor: 14.191

Horga G, Maia TV, Wang P, Wang Z, Marsh R, Peterson, BS 2011 Adaptation to conflict via context-driven anticipatory signals in the dorsomedial prefrontal cortex. J Neuroscience 31:16208-16216. Journal impact factor: 7.270

Oliveira M, da Silva N, Cunha P, Ramos R, Marques F, Santos S, Rocha I, Silva-Carvalho L, Ferreira R 2011 Effects of acute autonomic modulation on atrial conduction delay and local electrograms duration in paroxysmal atrial fibrillation. Int Journal Cardiol 149: 290-295. Journal impact factor: 6.802

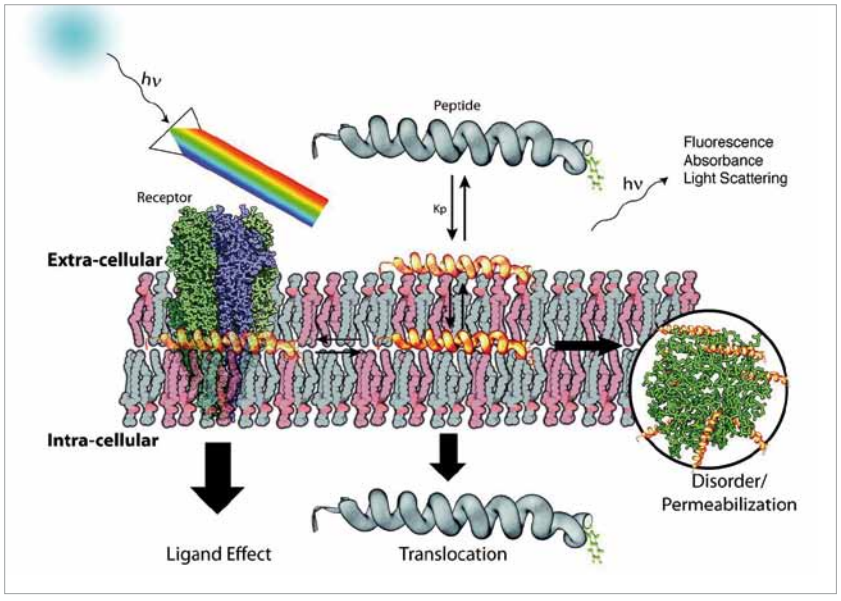
Turner MR, Benatar, M Brooks, BR Chio, A, de Carvalho M, Hardiman O, Ince PG ,Lin C, Miller RG, Mitsumoto H, Nicholson G, Ravits J, Shaw PJ, Swash M, Talbot K, Traynor BJ, Van den Berg LH, Veldink JH, Vucic S, Kiernan MC, Kiernan M (in press). Controversies and priorities in ALS research: the Fort Denison paper. Lancet Neurology. Journal impact factor: 23.460

Group Leader
MIGUEL CASTANHO

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

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 epithelia or innate immune defence. Some of these may be inspiring to develop 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 and antimicrobials. T20 (Enfuvirtide), T1249 and sifuvirtide are among anti-HIV drugs in clinical use or undergoing clinical trials that we have studied recently. Likewise, Omiganan is an antimicrobial peptide drug that went through clinical trials and was studied by our group. Amidated kyotorphin and the tandem drug ibuprofen-amidated kyotorphin are powerful analgesic molecules developed by us for their cationicity and ability to interact with lipids, therefore prone to cross the blood-brain barrier. Our work combines optical spectroscopies, atomic force microscopy, Flow Cytometry, and Isothermal Calorimetry, which we use in unique tailored methodologies, with timely medical issues and cutting edge scientific problems.



Lipid bilayers concentrate membrane-active peptides, which may facilitate interaction with receptor or severely perturb the membrane structure. Some peptides translocate lipid bilayers without perturbation. All these events may be studied using optical spectroscopies.

RECENT MOST RELEVANT PUBLICATIONS

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 14 6210. Times cited: 4. Journal impact factor: 9.907

Ribeiro MM, Pinto AR, Domingues MM, Serrano I, Heras M, Bardaji ER, Tavares I, Castanho MA 2011 Chemical conjugation of the neuropeptide kyotorphin and ibuprofen enhances brain targeting and analgesia. Mol Pharm 8 1929-40. Journal impact factor: 5.4

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 25 419-428. Journal impact factor: 6.2

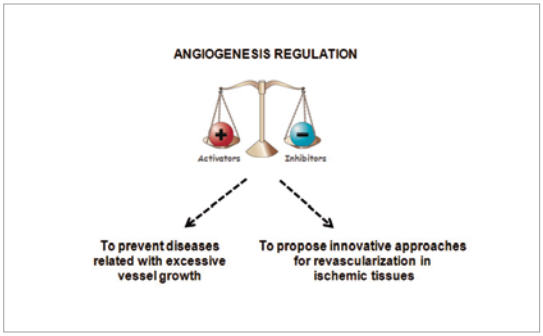
Ribeiro, MMB ; Melo, MN ; Serrano, ID ; Santos, NC ; Castanho, MARB 2011 Drug-lipid interaction evaluation: why a 19th century solution? Trends in Pharm Sciences 31 9. Journal impact factor: 10.927

Group Leader
SUSANA CONSTANTINO

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

ANGIOGENESIS REGULATION AND THERAPEUTIC IMPLICATIONS

Angiogenesis is the formation of new blood vessels from pre-existing ones and is orchestrated by a variety of pro- and anti-angiogenic signals. Their imbalance, promoting either excessive or insufficient angiogenesis, can lead to disease. Therefore, it is recognized that therapeutic interference with vasculature formation offers a tool for clinical applications. Whereas inhibition of angiogenesis can prevent diseases with excessive vessel growth such as cancer, stimulation of angiogenesis would be beneficial in the treatment of diseases such as peripheral arterial disease. Recently, we demonstrated that angiogenesis is induced by low doses of ionizing radiation (IR) in tumor surrounding areas and consequently these new vessels could promote tumor spreading and metastasis formation during or following radiotherapy. We are now evaluating the pro-angiogenic effects of low doses of IR in a human model. Our findings will be of utmost importance to improve current oncology protocols.
Regarding the putative beneficial effects of angiogenesis, we also decided to investigate if these low doses can promote therapeutic angiogenesis in ischemic diseases.



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.

RECENT MOST RELEVANT PUBLICATIONS

Domingues I, Rino J, Demmers JAA, de Lanerolle P, Santos SCR 2011 VEGFR2 Translocates to the Nucleus to Regulate Its Own Transcription PLoS ONE 6 e25668. Journal impact factor: 4.4

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. Journal impact factor: 4.4

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. Journal impact factor: 5.4

Constantino Rosa Santos S, Miguel C, Domingues I, Calado A, Zhu Z, Wu Y and Dias S 2007 VEGF and VEGFR-2 (KDR) internalization is required for endothelial recovery during wound healing. Exp Cell Res 313 1561-1574. Journal impact factor: 3.7

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. Times cited: 99. Journal impact factor: 10.6

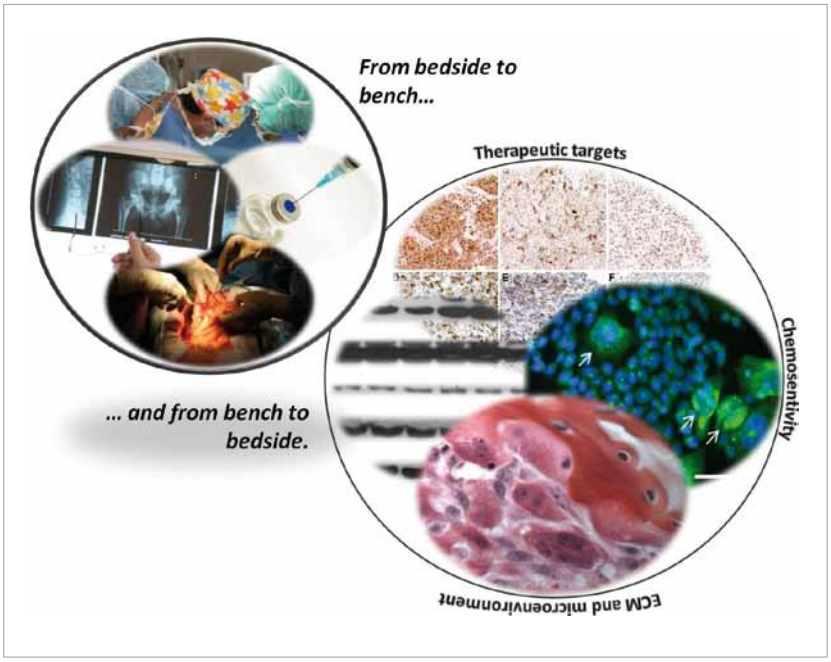
Group Leader

LUÍS COSTA

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

TRANSLATIONAL ONCOBIOLOGY

Solid tumors are the most frequent type of cancer and cause of cancer mortality. Cancer progression is characterized by heterogeneity and clonal evolution, major challenges to cancer treatment. Besides the intrinsic cancer cell genetic alterations, interactions between cancer cells and cells in target organs of metastases drive a new metastatic microenvironment. Bone metastases represent the best example in oncology where specific therapies targeting cross-talks between cancer and the target organ are successful. Nevertheless, it remains unclear, do metastases genetically and phenotypically recapitulate the primary tumors?, and how are reflected the tumor-target organ/host interactions? We have previously identified new ECM factors, with clinical relevance as biomarkers of bone metastases progression, and demonstrated that combination of anti-resorptive agents may overwhelm the effect of single agents in blocking the vicious cycle of bone metastases. Currently, we are performing comparative genomic analysis of intra-tumor and inter-tumor metastization patterns. We aim to discover new therapeutic strategies by studying the role of tumor-associated ECM components in cancer progression and new therapeutic combinations. Our research is directed to address at the preclinical level the mechanistic effects that explain our major clinical questions and findings in the human setting.



RECENT MOST RELEVANT PUBLICATIONS

Eswaran J, Gupta S, Dutt A, Toi M, Pillai MR, Costa L, Knapp S, Badwe RA, and Kumar R. 2012 The Global Cancer Genomics Consortium: Interfacing Genomics and Cancer Medicine. Cancer Research 5 3720. Times cited: 0. Journal impact factor: 7.856

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. Times cited: 2. Journal impact factor: 3.524

Fernandes I, Pacheco TR, Costa A, Santos AC, Fernandes AR, Santos M, Oliveira AG, Casimiro S, Quintela A, Fernandes A, Ramos M, and Costa L 2012 Prognostic significance of AKT/mTOR signaling in advanced neuroendocrine tumors treated with somatostatin analogues. OncoTargets and Therapy 5 409. Times cited: 4. Journal impact factor: 1.261

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. Times cited: 0. Journal impact factor: 6.425

Henry D, Costa L et al. 2011 A Randomized, Double-blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. J Clin Oncol 29(9) 1125. Times cited: 29. Journal impact factor: 18.372

Group Leader
JOSÉ FERRO

MD (1975) and PhD (1987) at Faculdade de Medicina da Universidade de Lisboa (FMUL)
Full Professor and Chairman at FMUL and the Santa Maria Hospital
Other Principal Investigators: Alexandre Castro Caldas, Alexandre de Mendonça, Cristina Sampaio, Isabel Pavão Martins, Joaquim Ferreira, José Pimentel, Patrícia Canhão, Sofia A. Oliveira, Teresa Paiva

CLINICAL RESEARCH IN NON-COMMUNICABLE NEUROLOGICAL DISEASES

Brain disorders such as stroke, dementia and Parkinson's disease assumed a major importance in public health. The identification of environmental and the genetic determinants, as well as risk factors and protective factors, for these major prevalent and disabling brain disorders has become a health priority.

We described the risk factors for an important and often neglected cause of stroke, cerebral venous thrombosis, and identified the patients who benefit most from prolonged anticoagulation and decompressive surgery. We also pinpointed the clinical, imagiological and neuropsychological predictors of vascular white matter changes and risk for dementia. New data were published on the relationship of genetic risk factors and stroke. Advances were made on the development of new assessment tools and normative data for language and cognitive evaluation, and determination of the long-term prognosis of non-demented elderly people with cognitive complaints.

We will take advantage of the multidisciplinary characteristics of the research unit, involving specialists with different clinical and basic research backgrounds, to further develop and assess interventions able to delay or prevent transition from a healthy, independent state to disability and death, and to participate in clinical trials to find new drugs for the treatment of these prevalent and disabling brain disorders.

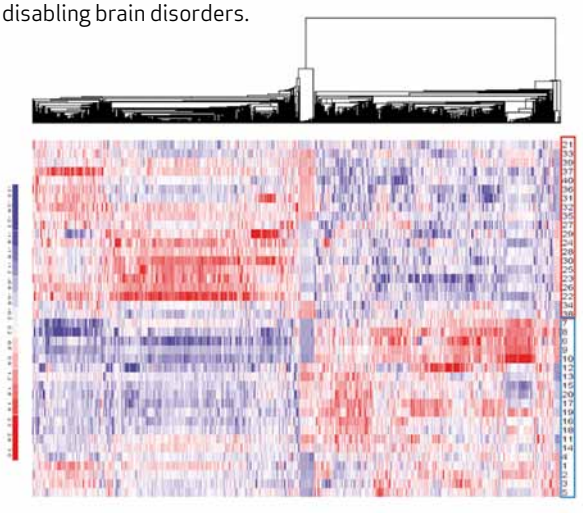


Figure Illustration of the expression pattern differences among ischemic stroke cases and controls.

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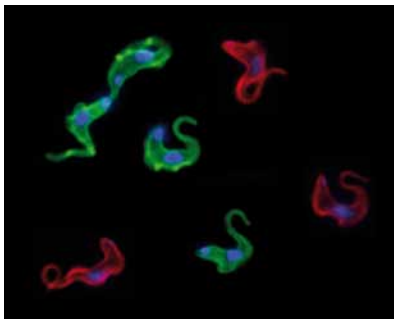
Group Leader
LUÍSA FIGUEIREDO

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

BIOLOGY OF PARASITISM

African Sleeping sickness is a neglected disease that affects around 300.000 people in sub-Saharan Africa. There is no vaccine and drug treatments are very limited. This disease is caused by *Trypanosoma brucei*, a unicellular parasite that lives in the bloodstream of its mammalian host. In this hostile environment, the parasites escape the host immune system by a process known as antigenic variation, which consists in periodically shedding its surface coat of variant surface glycoproteins (VSG). This process relies on the expression of a single VSG gene at a time, while maintaining all other members of the VSG gene family silent. The molecular mechanism that governs antigenic variation is still poorly understood. In our unit, we study the role of chromatin in VSG gene regulation. We use biochemical and genetic approaches to identify novel chromatin constituents and regulators of both the active and silent VSGs. Because VSG expression is at the basis of virulence of this parasite, it is possible our studies uncover potential drug targets against Sleeping sickness.



Trypanosomes wear different coats to avoid the immune system. Each coat consists of 10 million copies of variant surface glycoproteins.

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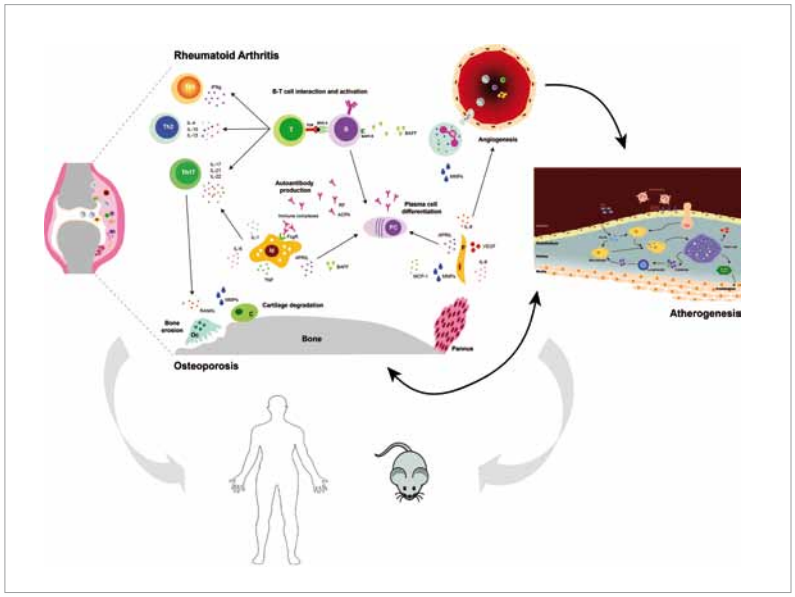
Group Leader

JOÃO EURICO FONSECA

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

ARTHRITIS AND BONE

The Rheumatology Research Unit (RRU) has its activities and researchers integrated in the 3 pillars of the Lisbon Academic Medical Centre (IMM, Faculdade de Medicina da Universidade de Lisboa and Santa Maria Hospital). At the RRU basic scientists and clinicians work closely together to promote translational research and clinical excellence in the field of Rheumatology. The existence of a network of biologists, biomedical engineers and physicians, sharing a common mission, goals and values promotes highly interactive work that allow us to be leaders at a national level in translational research in the field of Rheumatology and to be internationally highly competitive partners.
The mechanisms underlying loss of bone quality in early arthritis; the relationship between vessel and systemic inflammation and poor bone quality; as well as clinical, laboratorial, imaging and genetic predictors of progression are the focus of our research. Experimental methodologies at the RRU are based on a dual approach, which includes human samples and animal models of rheumatic and bone diseases. Our research projects aim at the discovery of new diagnostic and prognostic markers and therapeutic targets to ultimately improve treatment and quality of life of patients with inflammatory and bone diseases.



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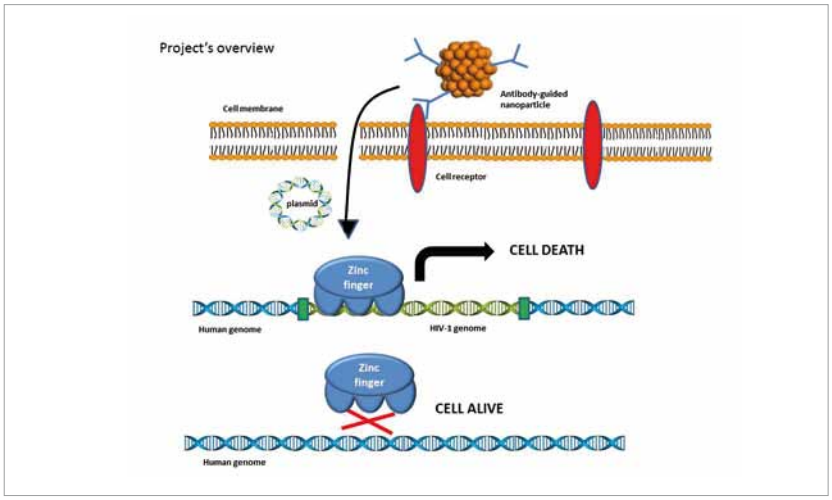
Group Leader
JOÃO GONÇALVES

PhD (1996) at EMBL, Heidelberg, Germany
Research Assistant at Harvard Medical School, USA
Post-doctoral researcher at Scripps Research Institute, USA
Associate Professor at Faculdade de Farmácia da Universidade de Lisboa
Awardee of Bill & Melinda Gates Foundation Grand Challenges Programme
Other Principal Investigator: Mariana Santa-Marta, Paula Brito
External Group Leader at IMM

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.



Combine antibody engineering, genetic delivery systems and synthetic biology are being developed in our lab to eliminate cells containing viral genomes.

RECENT MOST RELEVANT PUBLICATIONS

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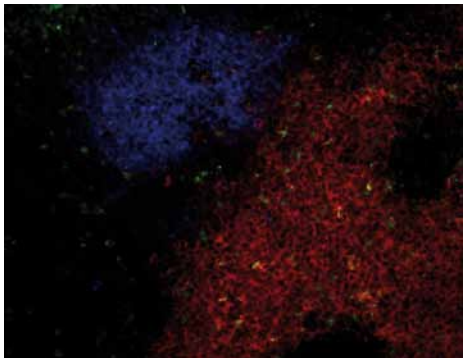
Group Leader

LUÍS GRAÇA

MD (1995) at Faculdade de Medicina da Universidade de Lisboa (FMUL)
PhD (2002) in Immunology at the University of Oxford, UK
Post-doctoral research at University of Oxford, UK, and at University of Western Australia, Perth
Assistant Professor at FMUL

LYMPHOCYTE REGULATION

Among the most frequent human diseases are pathologies directly caused by immune disregulation. It is the case of allergy and asthma, and autoimmune diseases such as rheumatoid arthritis or multiple sclerosis. In addition, the efficacy of several medical interventions can be limited by immune responses targeting the therapeutic product, or in the case of transplantation, targeting the foreign tissue.
Our previous work have shown it is possible to use monoclonal antibodies targeting molecules on the T cell, to reprogram the immune system in a way that allows long term survival of a transplant, or protection from allergic asthma or autoimmunity in mice. In these conditions tolerance is maintained by a population of T cells with the ability to regulate disease-inducing T cell responses – and for that reason known as regulatory T cells. We found that several types of regulatory cells can be needed for protection from immune-mediated diseases with distinct characteristics. We are currently studying the molecular requirements of different populations of regulatory cells for the induction and maintenance of immune tolerance in distinct anatomic contexts.



Micrograph of a lymph node, where the germinal centre is labelled in blue, the T cell area in red, and regulatory T cells are labelled in green.

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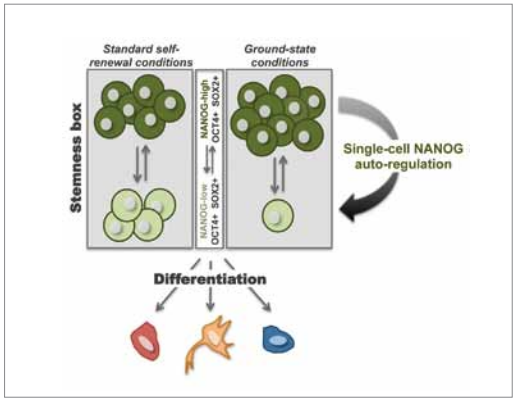
Graca L, Cobbold SP, Waldmann H 2002 Identification of regulatory T cells in tolerated allografts. J Exp Med 195 1641. Times cited: 321. Journal impact factor: 15.837

Group Leader
DOMINGOS MANUEL PINTO HENRIQUE

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

STEM CELLS AND NEUROGENESIS

Generation of tissues and organs during embryonic development relies on complex cell fate decision processes that establish the multitude of cellular types present in the body. Our work aims to provide a deeper understanding of how cell fate decisions are controlled at the single-cell level, while at the same time 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.



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 appplications of stem cells.

RECENT MOST RELEVANT PUBLICATIONS

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Fior, R., Henrique, D 2005 A novel hes5/hes6 circuitry of negative regulation controls Notch activity during neurogenesis. Developmental Biology 53. Journal impact factor: 4.407

Group Leader

GUNNAR MAIR

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

GENE REGULATION IN THE MALARIA PARASITE

Malaria parasites adapt to varying intra- and extracellular host environments with the generation of specific life cycle stages and defined transcription profiles. The mechanisms underlying these often rapid changes in gene expression are unknown. Our lab has demonstrated that during transmission developmental progression of Plasmodium gametocytes relies on translational activation of large translationally quiescent mRNA pools and the activation of specific transcriptional programs; sporozoites undergo similar changes when infecting a new host. We focus on the identification of key proteins that are instrumental in shaping these transcriptional and post-transcriptional programs and define the gene expression switches. Our work will highlight evolutionarily ancient programs involved in gene expression regulation and advance the development of transmission blocking strategies that are an essential component in the fight for malaria eradication. Interfering with protein translation and transcription during malaria transmission stages is a novel approach that can impact related diseases like Toxoplasmosis, Theilerosis and Babesiosis that affect humans but also domestic animals.

RECENT MOST RELEVANT PUBLICATIONS

Mwai L, Diriye A, Masseno V, Muriithi S, Feltwell T, Musyoki J, Lemieux J, Feller A, Mair GR, Marsh K, Newbold C, Nzila A, Carret CK 2012 Genome wide adaptations of Plasmodium falciparum in response to lumefantrine selective drug pressure. PLoS ONE 7(2) e31623. Times cited: 0. Journal impact factor: 4.092

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Group Leader
MUSA MHLANGA

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

GENE EXPRESSION AND BIOPHYSICS

In biology several important processes occur at spatial dimensions beyond the reaches of light microscopy. The molecular players implicated in gene expression and its regulation exist at this scale. These include those involved in RNA transcription, nuclear architecture, chromosomal and chromatin dynamics within the eukaryotic cell nucleus.
Highly reduced our most ambitious questions are: Determining whether co-regulated genes assemble in multi-gene complexes as a cause of transcription; if gene looping nucleates the formation of these complexes. The role of the non-coding genome in this process? How pathogens influence the assembly of these complexes?
Our research has focused on harnessing the power of nucleic acids to understand the most fundamental questions in cell biology. In recent years we have focused our advances in the areas of single molecule detection, tracking and nanoscopy. We have developed molecular tools, built microscopy platforms and developed computational approaches and software that enables us to confront many of the ambitious questions we have posed. We have developed an optical imaging setup and quantitative analytical tools that allow the imaging of gene expression with super-resolution.

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LG Kostrikis, S Tyagi, MM Mhlanga, DD Ho, FR Kramer 1998 Spectral genotyping of human alleles. Science 279 1228. Times cited: 309. Journal impact factor: 32.45

Group Leader

LUÍS FERREIRA MOITA

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

INNATE IMMUNITY AND INFLAMMATION

Inflammation is a response to harmful stimuli that limits tissue damage and aims at restoring homeostasis. In the susceptible host, overproduction of inflammatory mediators or an exaggerated response to their presence can lead to severe disease. Sepsis remains a poorly understood systemic inflammatory condition with high mortality rates and limited therapeutic options in addition to organ support measures. We have recently shown that the clinically approved group of anthracyclines can be used therapeutically at low regimen to confer robust protection against severe sepsis in mice. This salutary effect is strictly dependent on the activation of DNA damage responses and the autophagy pathways specifically in the lung. The protective effect of anthracyclines acts irrespectively of pathogen burden, conferring disease tolerance to severe sepsis. We have now initiated a research program to dissect the molecular mechanisms at the basis of the regulation of inflammation and tissue protection by components of the DNA damage response machinery. Our research will provide new insights to the field of inflammation by elucidating the molecular mechanisms that connect DNA damage response to the regulation of the immune response.

RECENT MOST RELEVANT PUBLICATIONS

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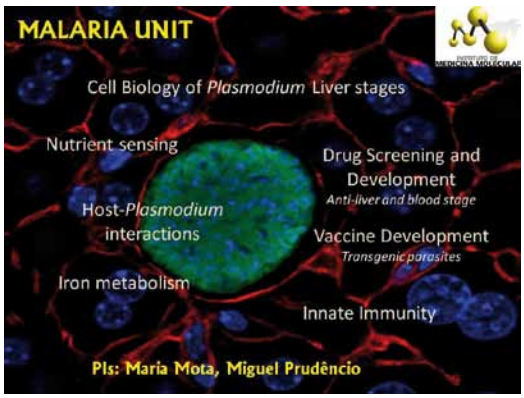
Group Leader

MARIA M. MOTA

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

BIOLOGY AND PHYSIOLOGY OF MALARIA AND OTHER INFECTIONS

Malaria is one of the most serious parasitic infectious diseases, with a toll of up to 1 million deaths every year. While this unacceptable health burden and its economic and social impact have made it a focal point of the international development agenda, it became consensual that malaria control or elimination will never be feasible until we gain a better understanding of the complex interactions occurring between its main players: Plasmodium, the causative agent of disease, and its hosts. As any other obligate parasite, Plasmodium depends on its host and on the resources it provides to survive and complete its life cycle. Yet, important gaps subsist in our knowledge on the processes that occur at the parasite-host interface. Thus, the overall goal of our laboratory is to identify key host factors and host-parasite interactions that contribute to: (i) the establishment of a malaria infection during the initial steps of Plasmodium replication inside liver hepatocytes and (ii) the onset of malaria pathology while Plasmodium infects red blood cells. Through addressing fundamental aspects of the intricate host-pathogen interactions we aspire to contribute decisively to the combat against some of the deadliest diseases of our time.



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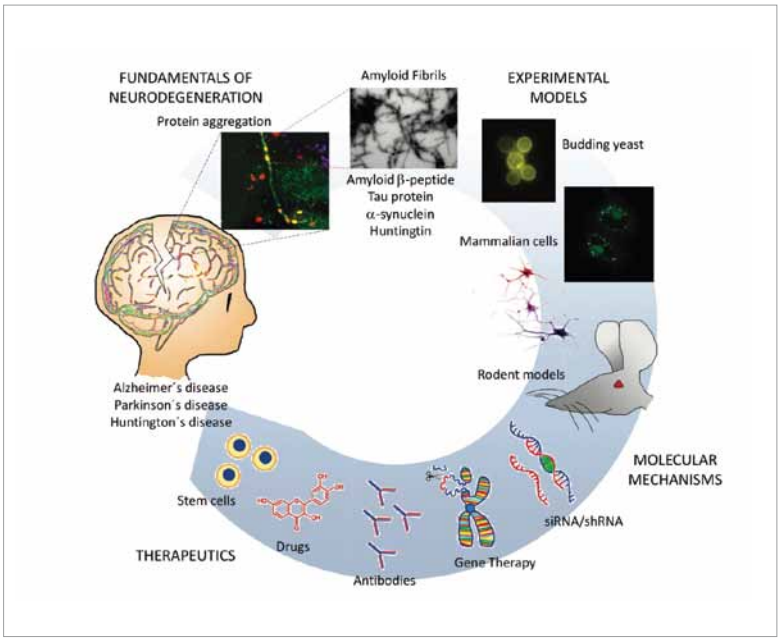
Group Leader

TIAGO FLEMING OUTEIRO

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

PROTEIN MISFOLDING AND NEURODEGENERATION

The brain is one of the most fascinating and intriguing organs due to its multiple roles in controlling basic as well as superior functions, such as emotions and consciousness. Thus, brain malfunction is associated with a large number of conditions with devastating consequences for the organism. Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's disease are age-associated disorders, all of which are associated with the misfolding and deposition of specific proteins. While these disorders have been known for over 100 years, our understanding of the cellular and molecular mechanisms underpinning neurodegeneration is still limited. We are employing molecular genetics, imaging, and translational approaches to investigate how protein misfolding and aggregation leads to neuronal cell dysfunction and death. Ultimately, our research will not only contribute to our understanding of the molecular basis of disease but also to our understanding of the nervous system as a whole. The tools, knowledge, and collaborations developed through our research have broad applicability to other areas of biomedical research, and enable us to tackle numerous problems in biology.



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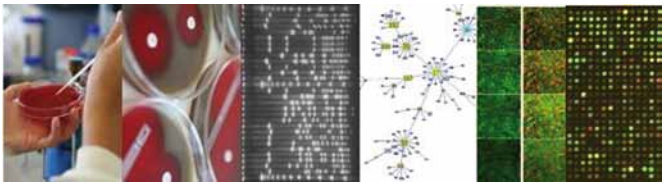
Group Leader
MÁRIO RAMIREZ

PhD (1998) in Molecular Biology at Universidade Nova de Lisboa
and at The Rockefeller University, USA
Post-doctoral research at Instituto de Tecnologia Química e Biológica, Oeiras
Associate Professor at the Faculdade de Medicina da Universidade de Lisboa
Other Principal Investigators: José Melo Cristino, Thomas Hänscheid, João Carriço

MOLECULAR MICROBIOLOGY AND INFECTION

We have documented the bacterial population structure of several pathogens of the genus Streptococcus and found differences between bacteria that are asymptomatically carried and those causing distinct infections in the various age groups. We identified genes that are unevenly distributed in the bacterial population, potentially explaining the propensity of certain clones for particular hosts or infections. We have also studied the flow of genetic information between bacteria and the factors enhancing or limiting these exchanges. We are refining existing approaches to handle next generation sequence data and are developing tools for storing and mining this data in a unified platform, integrating information from existing databases. We are also studying streptococci causing infections in humans and animals to identify key events allowing the adaptation to a different host species and to evaluate the current potential for zoonotic acquisition. Understanding the dynamics and responses of a bacterial population to the multiple selective pressures imposed on it and the key genetic events allowing the differentiation of specific clones will allow us to better predict bacterial pathogen evolution.



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Hänscheid, T., Egan, T.J., Grobusch, M.P 2007 Haemozoin: from melatonin pigment to drug target, diagnostic tool, and immune modulator. Lancet Infect. Dis. 7 675-685. Journal impact factor: 17.391

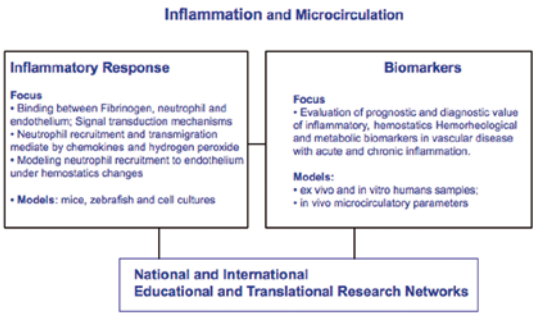
Group Leader

CARLOTA SALDANHA

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

ERYTHROCYTE, LEUKOCYTE RECRUITMENT AND INFLAMMATION

Inflammation aims to eliminate invading agents and recover tissue homeostasis. It comprises cellular and microvascular events mediated by important players like fibrinogen and neutrophils. Currently, it is not fully understood how fibrinogen regulates neutrophil recruitment and how distinct chemoattractants concert their action in this process. We have shown that soluble fibrinogen under physiological concentrations modulates neutrophil functions. Our studies also showed that fibrinogen targets CD47 in erythrocytes in dependence of nitric oxide signaling. In zebrafish, we have demonstrated that CXCL8 chemokines are crucial for neutrophil recruitment in inflammation. Future works will aim to decipher how fibrinogen mediates neutrophil action and how chemokines and hydrogen peroxide cooperate for recruiting neutrophils. In our scope will also be the validation of inflammatory biomarkers in vascular diseases and the development of theoretical simulations of phenomena occurring at the leukocyte-endothelium interface. Overall, our research will provide a detailed inspection onto the function of relevant mediators in neutrophil recruitment. We expect to disclose potential approaches for developing novel therapeutics for worldwide major public health concerns, like sepsis and cardiovascular diseases.



Basic and clinical inflammation research interrelationship with educational networks

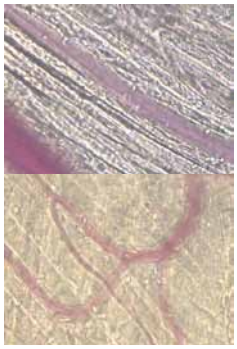


Image 1 Post-capillary venule in mouse cremaster muscle superfused with bicarbonate-bufered saline and observed by intravital microscopy (200x). by Ana Silva-Herdade and Vanda Vitorino de Almeida

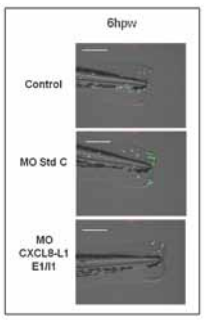


Image 2 Fluorescence microscopy images of the recruitment of eGFP-labelled neutrophils in tail transected 3dpf mpx:GFP larvae, pre-injected with the indicated morpholinos (MO), at 6 hours post wounding (hpw). Scale bar = 200µm. *by* Sofia de Oliveira

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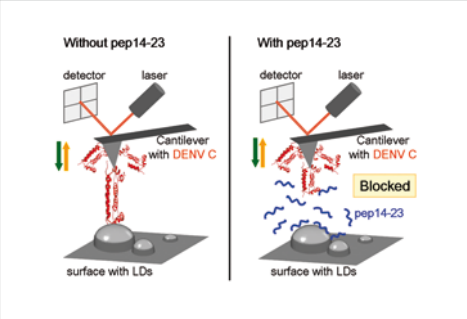
de Almeida VV, Calado A, Rosário HS, Saldanha C 2012 Differential effect of soluble fibrinogen as a neutrophil activator. Microvasc Res. 83(3) 332-6. Times cited: 0. Journal impact factor: 2.828

Group Leader
NUNO C. SANTOS

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

BIOMEMBRANES AND NANOMEDICINE

The Biomembranes Unit is mainly focused on biochemical and biophysical processes occurring at membrane level on human cells, as well as on their viral and bacterial pathogens.
We have been studying the two steps of the life cycle of enveloped viruses (mainly HIV-1 and dengue virus) that involve biomembranes: the entrance of the virus or its content into the target cell and the assembly of new virions.
We have also been studying the fibrinogen-erythrocyte membrane binding and its relevance as cardiovascular risk factor. At this level, we identified a previously unknown erythrocyte receptor, which is altered in some human pathologies.
Our Unit is also involved on the pre-clinical evaluation of the activity and mechanism of action of antimicrobial peptides (AMP) and cell-penetrating peptides (CPP).
On the Nanomedicine area, we are also working on the development of innovative biosensor systems, with improved selectivity and sensitivity (nanoparticles and amyloid-based biosensors).
Based on the results obtained so far, our work may contribute for the identification of new drug targets, therapeutic strategies and/or diagnostic methods for important human pathologies, such as cardiovascvular diseases, HIV/AIDS and dengue.



Dengue virus capsid protein (DENV C) binds to proteins on the surface of intracellular lipid droplets (LDs), majorly perilipin 3. We have found that this interaction, essential for viral replication, depends on the high intracellular potassium concentration, and may regulate the availability of the C protein, allowing its proper participation on the virus replication cycle. Using atomic force microscopy (AFM) based force spectroscopy measurements, we have also showed that a peptide designed based on a conserved segment within the disordered N-terminal region of DENV C region is able to inhibit DENV C – LDs binding.

RECENT MOST RELEVANT PUBLICATIONS

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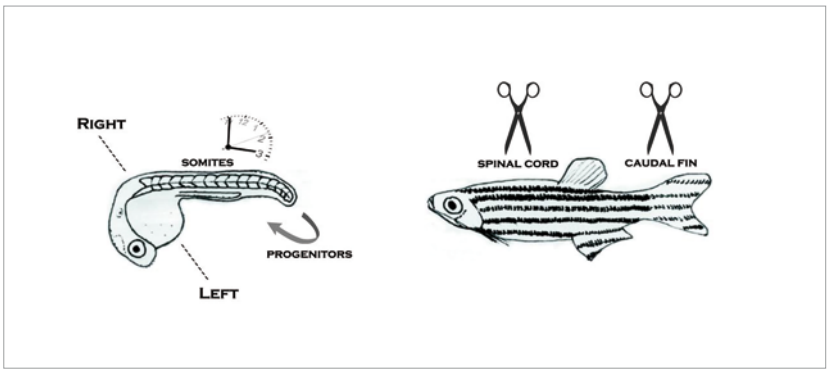
Group Leader
LEONOR SAÚDE

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

EMBRYONIC DEVELOPMENT AND REGENERATION

We are interested in basic principles that generate the body plan during embryonic development. We have shown that the transcription factor Mesogenin 1 controls the rate of differentiation and movement of presomitic mesoderm progenitors ensuring that a progenitor population is maintained until the correct number of somites, and therefore of vertebrae/muscles, are formed. We also contributed to the unexpected finding that symmetry is not a default embryonic state by showing that somites can only proceed in a bilaterally synchronized fashion because they are actively protected from the left-right information through a new mechanism triggered by the transcription factor Dmrt2a.
More recently, we become interested in the potential link between the developmental processes in the embryo with the developmental processes that need to be activated in order to regenerate adult organs upon severe damage. We demonstrated that the adult zebrafish caudal fin has an almost unlimited capacity to regenerate upon consecutive repeated amputations, reinforcing its extraordinary quality as a model to study regenerative processes.



How are progenitors maintained until development ends such that the body axis does not truncate? How is left-right asymmetry established so that visceral organs form in stereotypic positions? How is the formation of somites protected from these asymmetric signals so that a bilateral symmetric skeleton and musculature is produced? How is the adult zebrafish able to regenerate various tissues and organs like the spinal cord and appendages in contrast to adult mammals that are unable to do so? These are the questions that we are exploring in our laboratory.

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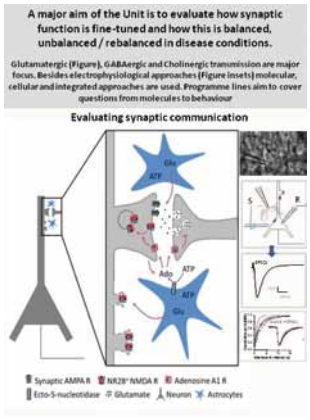
Group Leader
ANA SEBASTIÃO

PhD (1987) in Cell Physiology, New University of Lisbon
Post doctoral researcher at Instituto Gulbenkian de Ciência, Oeiras
Associate Professor with Habilitation, Faculdade de Medicina da Universidade de Lisboa
Other Principal Investigators: Joaquim Alexandre Ribeiro, Alexandre Valério Mendonça, Luísa V. Lopes, Maria José Diógenes, Cláudia A.V. de Castro

NEURONAL COMMUNICATION AND SYNAPTOPATHIES

The nervous system is the core of sensory, motor and emotional processing, and gives rise to movement, thought, creativity and curiosity. Neurological and neuropsychiatric diseases constitute an overwhelming social and economic load, with predicted exponential increase in the near future due to ageing, drug abuse, stressful life styles. Breakthrough advances are urgently needed to modify this evolution. The innovation of the approach used by the Unit comes from the growing awareness that though cells and circuits may differ for each disease, common principles of synaptic, cellular and network dysfunctions are highly comparable. This provides new possibilities to apply knowledge related to one disease to another, forming a major impetus to explore common aspects rather than differences between disorders. A common feature is abnormal synaptic function leading to dysfunction of neural plasticity and synchronization, as it happens in diseases as epilepsy, schizophrenia, autism, Alzheimer's and Parkinson's disease. Synaptic transmission is a high regulated process to properly convey information transfer within the circuit, and as we showed, synaptic functioning is markedly affected by adenosine G-protein coupled receptors (GPCRs). As very recently shown by the Unit, manipulation of the activation state of adenosine receptors at synapses may allow correcting pathologic dysfunctions as aberrant plasticity after stroke or memory dysfunction induced by cannabinoids. Being aware of the peculiarities of different receptors, synapses and specific circuits they operate, we will concentrate on common ways to modify synaptic function and plasticity throughout ageing, drug abuse or in selected disease models. Manipulations aimed to correct aberrant synaptic function are quite feasible ex vivo, and new insights will be transferred to a higher level of organization in animal models in vivo. Thus, knowledge on the ways synapses are regulated and how specific synapses control well defined networks, allows reciprocal translation of basic/clinical findings, and will most probably lead to the emergence of rational therapies to socially burning diseases. The originality of our projects and the solid background of the Unit members ensure excellence and competitivity at the international level.



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; lowe: spontaneous) recordings

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Sousa VC, Assaife-Lopes N, Ribeiro, JA, Pratt JA, Brett RR, Sebastião AM 2011 Regulation of hippocampal cannabinoid CB1 receptor actions by adenosine A1 receptors and chronic caffeine administration: implications for the effects of Δ9-tetrahydrocannabinol on spatial memory. *Neuropsychopharmacology* 36 472-487. Times cited: 9. Journal impact factor: 7.991

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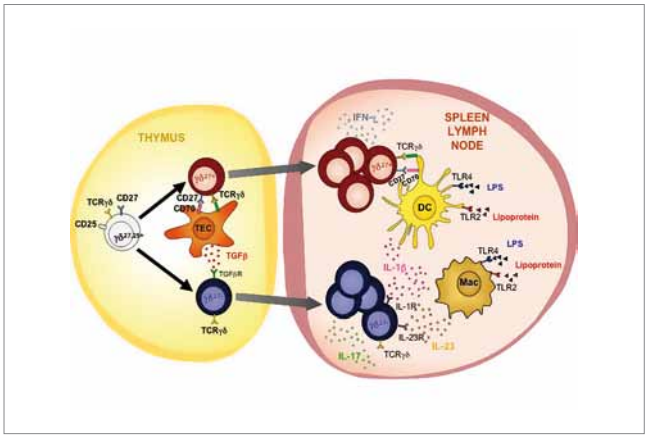
Sebastião AM, Ribeiro JA 2000 Fine tuning neuromodulation by adenosine. Trends in Pharmacoogical Sciences (TIPS) 21 341-346. Times cited: 157. Journal impact factor: 10.927

Group Leader
BRUNO SILVA-SANTOS

PhD (2002) in Immunology at University College London, UK
Post-doctoral research at King's College London, UK
Auxiliary Professor at Faculdade de Medicina da Universidade de Lisboa
Other Principal Investigators: Ana Pamplona

T-CELL DIFFERENTIATION AND TUMOR TARGETING

T lymphocytes are white blood cells that evolved to protect vertebrate hosts from infectious microorganisms. Furthermore, the killing properties of T lymphocytes can be exploited for cancer treatment. However, as their "dark side", T lymphocytes are a major cause of allergy, autoimmunity and transplant rejection. These paradoxical roles of T lymphocytes depend on their cellular and molecular activities, namely the production of cytotoxic molecules and pro- versus anti-inflammatory cytokines. These can further segregate with particular subpopulations of T lymphocytes that play strikingly different roles within an inflamed tissue or tumor. In our Unit we employ in vitro and in vivo models to study the differentiation, activation and expansion (in response to infections or tumors) of murine and human T lymphocytes.
We have previously demonstrated that the development of important T lymphocyte subsets, namely gamma-delta T cells and regulatory T cells, is orchestrated by interactions between the receptor CD27 (on T cell progenitors) and its ligand CD70 (on thymic epithelial and dendritic cells). We have also identified key molecular determinants of tumor cell recognition by human gamma-delta T cells, based on natural killer (NK) receptors such as NKG2D or NKp30. We are currently applying this knowledge to the pre-clinical targeting of acute and chronic leukemias, aiming at future therapeutic benefit for cancer patients.



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

RECENT MOST RELEVANT PUBLICATIONS

Hudspeth K, Fogli M, Correia D, Mikulak J, Roberto A, Della Bella S, Silva-Santos B* and Mavilio D*. (2012) Engagement of NKp30 on Vdelta1+ T-cells induces the production of CCL3, CCL4 and CCL5 and suppresses HIV-1 replication. Blood 119(17): 4013-4016. (*Equal contributions) Journal impact factor: 9.898

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. Times cited: 7. Journal impact factor: 10.555

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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 γδ T-cell cytotoxicity. Blood 115 2407-11. Times cited: 21. Journal impact factor: 10.555

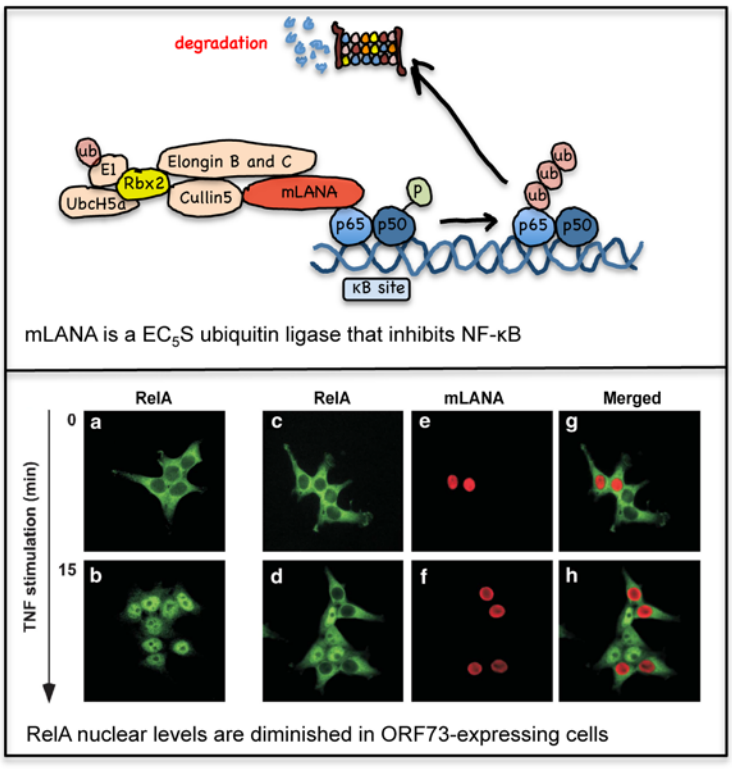
Ribot JC, deBarros A, Pang DJ, Neves JF, Peperzak V, Girardi M, Borst J, Hayday AC, Pennington DJ and Silva-Santos B 2009 CD27 is a thymic determinant of the balance between IFN-?- and IL-17-producing γδ T cell subsets. Nature Immunology 10 427-36. Times cited: 90. Journal impact factor: 26.218

Group Leader
PEDRO SIMAS

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

HERPES VIRUS PATHOGENESIS

Viruses hijack cellular mechanisms to promote their own life cycle. Thus, viruses can be used as model systems to understand biology that range from structural aspects, to cells, to systems. Our research has focused on the utilization of a γ-herpesvirus infection of laboratory mouse to relate molecular mechanisms of virus and host interaction. For example, we have uncovered that during infection of B-lymphocytes, the virus expresses a protein that functions as the substract recognition partner of a heteromolecular complex with E3 ubiquitin ligase activity. This viral protein, during virus-induced lymphoproliferation, targets the cellular transcription factor NF-κB for degradation. This inhibition of NF-κB is essential for virus infection. We are now taking further these studies and devising experiments to correlate the crystal structure of this viral protein. This knowledge will enable the rational design of molecules that will interfere with viral replication in an in vivo context of infection using laboratory mouse.



RECENT MOST RELEVANT PUBLICATIONS

Pires de Miranda M, Lopes FB, McVey CE, Bustelo XR, Simas JP 2013 Role of Src-homology domain binding in signaling complexes assembled by the murid gammaherpesvirus M2 protein. Journal of Biological Chemistry 288(6):3858-70. 2012 Dec 20. [Epub ahead of print]. Journal impact factor: 4.773

Habison AC, Beauchemin C, Simas JP, Usherwood EJ, Kaye KM 2012 Murine Gammaherpesvirus 68 LANA acts on terminal repeat DNA to mediate episome persistence. Journal of Virology 86:11863-76. Journal impact factor: 5.402

Sehrawat S, Kirak O, Koenig PA, Isaacson MK, Marques S, Bozkurt G, Simas JP, Jaenisch R, Ploegh HL 2012 CD8(+) T Cells from Mice Transnuclear for a TCR that Recognizes a Single H-2K(b)-Restricted MHV68 Epitope Derived from gB-ORF8 Help Control Infection. Cell Reports. May 31;1(5):461-71. Epub 2012 Apr 26. Journal impact factor: N/A

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 EC_5S ubiquitin-ligase. The EMBO Journal 6;28(9):1283-95. Epub 2009 Mar 26. Journal impact factor: 9.205

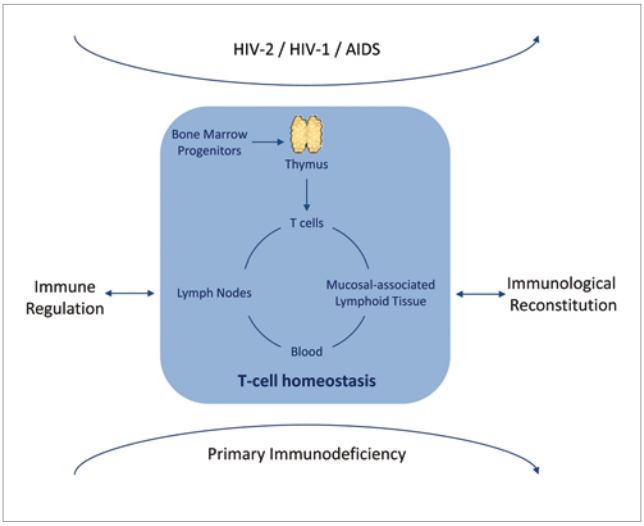
Marques S, Alenquer M, Stevenson PG, and Simas JP 2008 A single $CD8^+$ T cell epitope sets the long-term latent load of a murid herpesvirus. PLoS Pathogens 4(10): e1000177. Journal impact factor: 9.127

Group Leader
ANA E. SOUSA

MD (1986) and PhD (2000) in Clinical Immunology at Faculdade de Medicina da Universidade de Lisboa (FMUL) Investigator and Auxiliary Professor at FMUL
Other Principal Investigators: Rui M.M. Victorino, Íris Caramalho, João F. Lacerda

HUMAN IMMUNODEFICIENCY AND IMMUNE RECONSTITUTION

Health relies on a competent immune system. Our aim is to understand the pathogenesis of immunodeficiency and find new strategies for immune reconstitution. We revealed mechanisms involved in human T cell homeostasis and immune regulation through the study of unique clinical settings, such as HIV-2 infection. HIV-2 establishes a better equilibrium with the host than HIV-1, leading to a much slower rate of disease progression and lower levels of circulating virus. The comparative study of these two infections allowed us to clarify central issues in AIDS immunopathogenesis, taking advantage of the fact that Portugal is the only non-African country with a significant HIV-2 prevalence. Additionally, our unit integrates a reference centre that performs diagnosis, specialized follow-up and research in primary immunodeficiencies, rare diseases considered natural experiments from which we can learn a great deal about the human immune system. The ultimate goal is that our research on T-cell development in the human thymus and on lymphoid tissue preservation, particularly in the context of persistent immune activation, translates into innovative immune-based therapies.



RECENT MOST RELEVANT PUBLICATIONS

Rita Cavaleiro, António P. Baptista, Rui S. Soares, Rita Tendeiro, Russell B. Foxall, Perpétua Gomes, Rui M. M. Victorino, Ana E. Sousa 2009 Major Depletion of Plasmacytoid Dendritic Cells in HIV-2 Infection, an Attenuated Form of HIV Disease. PLoS Pathogens 5 e1000667. Times cited: 13. Journal impact factor: 9.127

Rita I. Azevedo, Maria V. D. Soares, João T. Barata, Rita Tendeiro, Ana Serra-Caetano, Rui M. M. Victorino, Ana E. Sousa 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. Times cited: 18. Journal impact factor: 9.898

Maria C. Pereira-Santos, António P. Baptista, Alcinda Melo, Rodrigo R. Alves, Rui S. Soares, Elisa Pedro, Manuel Pereira-Barbosa, Rui M. M. Victorino, Ana E. Sousa 2008 Expansion of circulating Foxp3+ CD25bright CD4+ T cells during specific venom immunotherapy. Clinical & Experimental Allergy 38 291. Times cited: 27. Journal impact factor: 5.032

Ana E. Sousa, Jorge Carneiro, Martin Meier-Schellersheim, Zvi Grossman, Rui M. M. Victorino 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. Times cited: 243. Journal impact factor: 5.788

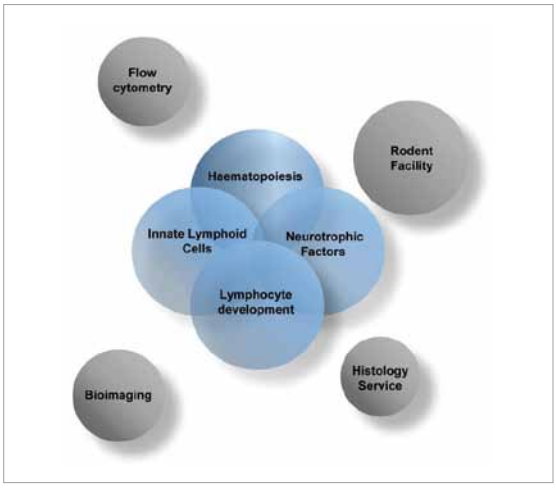
Zvi Grossman, Martin Meier-Schellersheim, Ana E. Sousa, Rui M. M. Victorino, William E. Paul 2002 CD4+ T-cell depletion in HIV infection: are we closer to understanding the cause?. Nature Medicine 8 319. Times cited: 283. Journal impact factor: 22.462

Group Leader
HENRIQUE VEIGA-FERNANDES

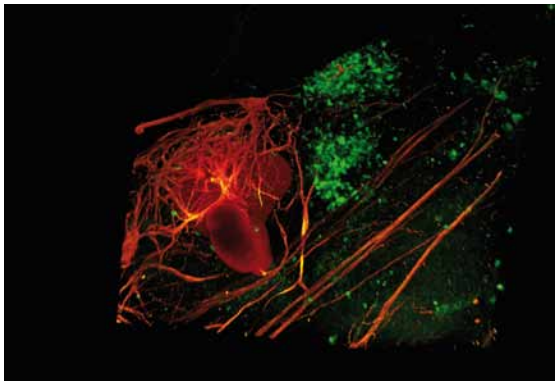
PhD (2002) in Molecular and Cellular Biology at Université René Descartes Paris V, France
Post-doctoral research at NIMR, UK and at the Institut Necker, France
Senior investigator scientist at NIMR, UK (2006-08)
Awardee of an European Research Council Starting Grant in 2008

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. In our laboratory we explore novel communication pathways that determine immune cell fate and disease progression. Understanding these general rules will shed light on the intricate co-evolution among tissues and the environmental pressure, thus providing import information for innovative therapeutic approaches.



Our expertise



Cross-talk of neurons and lymphocytes in the intestine

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. Times cited: 0. Journal impact factor: 7.5

Veiga-Fernandes H, Kioussis D, Coles M 2010 Natural killer receptors: the burden of a name. J Exp Med 207 269-72. Times cited: 7. Journal impact factor: 13.9

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. Times cited: 63. Journal impact factor: 36.2

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. Times cited: 38. Journal impact factor: 13.9

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. Times cited: 56. Journal impact factor: 26

FACILITIES AND SERVICES

BIOBANK

Head of Unit

João Eurico Cabral da Fonseca

MD, PhD - Assistant Professor at Faculdade de Medicina da Universidade de Lisboa and Rheumatologist at Centro Hospitalar Lisboa Norte EPE, Hospital de Santa Maria. Group Leader at IMM.

Staff

Joana Lopes, PhD (Post Doc Fellowship, FCT)
Rita Cascão, PhD (Biobank Staff)
Ana Sofia Zhao, MSc (Biobank Staff)
Ângela Afonso, BSc (Biobank Staff)
Joaquim Pereira, MD (Biobank Staff)
Ricardo Pires, BSc (Biobank Staff)
Vanessa Oliveira, BSc (Master Student)

The vision of 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. Our aim is 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. Currently having thousands of samples - including blood, serum, saliva, urine, DNA and tumor tissue- and the respective clinical information, Biobanco-IMM is a unique platform for the support of research on the etiology of diseases with high impact on public health, such as cancer or osteoporosis. Biobanco-IMM currently has over 34.600 samples across 14 collections stemming from 4.333 donors.

BIOIMAGING

Head of Unit

José Rino

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

Staff

António Temudo, MSc (Technician)
Ana Nascimento (Technician)

The BioImaging Unit constitutes IMM's core microscopy facility, serving as 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. Aside from continuous training for 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 in collaboration with research units with challenging biological problems.

BIOSAFETY LEVEL 3 LABORATORY

Head of Unit

Miguel Prudêncio

PhD (2000) from University of East Anglia (UK).
Post-doctoral research Fellow at University of Leiden (NL) (2000-2004) and at IMM (2004-2008).
Principal Investigator at IMM since 2008.
Head of Facility since 2009.

Staff

Inês Matos (Technical supervisor)

IMM hosts a 70 m2 BSL3 Facility, which meets the highest safety standards as defined by European and International guidelines. Our portfolio includes all experimental procedures involving biosafety level 3 pathogens. The lab is available to IMM internal and affiliated researchers, as well as to external researchers from academia, pharma and biotech. Applications to use IMM's BSL3 laboratories are reviewed and must be approved by the BSL3 Facility's Scientific Commission. 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. IMM's BSL3 laboratories follow strict admission rules. Accordingly, we will provide education, training, and guidance for researchers and will be constantly monitored by fully dedicated staff.

IMM's BSL3 facility comprises two fully equipped tissue culture rooms and one animal experimentation room for rodents. All rooms meet the highest safety standards as defined by European and International guidelines. Available equipment includes incubators, benchtop centrifuges, refrigerators and freezers, microscopes, a -80 freezer, and an ultracentrifuge.

FLOW CYTOMETRY UNIT

Head of Unit

Maria Godinho A.V. Duarte Soares

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

Staff

Ana Isabel Pinto, MSc (Technician)
Ana Isabel Vieira, BSc (Technician)
Sofia Marques, PhD (Technician)

The Flow Cytometry Unit (UCF) provides a cell sorting and support service to users wishing to take advantage of the instruments available. The Unit is equipped with 2 High Speed Cell Sorters (FACSAria I and FACSAria III) and 3 analysers (2 BD LSR Fortessa and one FACSCalibur). The Cell Sorters are operated by facility staff and have distinct optical layouts that allow flexibility in flurochorme detection. In addition to providing a cell sorting service, a substantial part of our work is to provide training in flow cytometry concepts, experiment planning, experimental controls, instrument operation and data analysis. This is achieved through workshops and one-on-one tuition. An additional component of our work is to ensure adequate quality control and maintenance of all instruments.

UCF users comprise a very diverse and challenging set of researchers, creating a very stimulating work environment that calls for constant knowledge of new developments in the field on the part of our staff.

HISTOLOGY SERVICE

Head of Unit
Sandra Casimiro
PhD (2007) in Molecular Biology,
at FCUL-UL, Lisbon, Portugal
Postdoctoral research at IMM since 2007

Staff
Andreia Pinto (Technician)
Ana Margarida Santos (Technician)

MAJOR INTERESTS

On September 1st, 2009 a new Histology Service was implemented at IMM resulting from collaboration with the Histology Institute of Medical School of the University of Lisbon. Our team includes two permanent technicians with a degree in Technical Pathology, Anatomy and Histology.
The main objectives of the Histology Service are to provide technical work, expertise and know-how in Histology and histopathology techniques to all IMM researchers, academia, and other institutions.

Our main tasks include processing tissue samples for routine histochemical procedures, TEM (transmission electron microscopy), LCM (Laser capture microscopy), and IHC (immunohistochemistry); human and veterinary pathology assistance; training new users in sample preparation with the available equipment in the laboratory; and providing tutorship in the design and implementation of different techniques.

SMALL RODENTS

Head of Unit
Joana Marques
PhD

Staff
Joana Marques, PhD (Facility Director)
Dolores Bonaparte (Veterinarian)
Iolanda Moreira (Technician / colony manager)
Carlos Barata Silva (Technician / colony manager)
Cecília Simão (Animal caretaker)
Felícia Ramos (Animal caretaker)
José Vila Chã (Animal caretaker)
Nuno Inácio (Animal caretaker)
Olena Pinho (Animal caretaker)
Wilma Zovo (Animal caretaker)
Ana Rafaela Dinis Coelho (Animal caretaker)

IMM's Rodent Facility has two main units: one conventional and one SPF. The conventional unit started in 2003 as a small set of 4 rooms with the total capacity to house 1.200 animals. During the autumn of 2011 this unit has been remodeled and now has the capacity to house 7.500 mice and rats. The SPF unit hosts about 10.000 mice and rats, in either the Production or the Experimental area. In the experimental area, there are three rooms for experimental work with animals: two procedure rooms and one surgical suite. All husbandry and manipulation procedures are performed according to the highest standards of biocontainment and bioexclusion, in order to ensure the best possible conditions in terms of health and safety. This unit is highly committed to follow the 3Rs – Replacement, Reduction, Refinement – and provides education, training, and guidance for researchers, according to the Portuguese and international laws/recommendations for best practices and animal welfare.

ZEBRA FISH FACILITY

Head of Unit
Leonor Saúde
PhD and Group Leader at IMM – Invited Auxiliary Professor, FML

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

The zebrafish *(Danio rerio)* is a representative of the vertebrate species and is used for the study of human genetic diseases such as cancer, cardiovascular disorders, neurological diseases, inflammation, angiogenesis, muscle-associated diseases and osteoporosis. Unlike humans, the zebrafish is one of the few vertebrate species that can fully restore the shape, structure and function of body parts lost after severe injury or amputation. Therefore, it has become a powerful model for regenerative medicine. IMM's zebrafish facility currently has 6.000 fish in a state-of-the-art housing system. Of these lines, 26 are transgenic and 13 mutant, all of which available to IMM's scientific staff for research purposes. As a service we can provide technical help to manage line stocks, identify transgenic and mutant lines, electroporate DNA and morpholino oligos into adult fish, microinject DNA, RNA and morpholino oligos into embryos, cell/tissue transplantation in embryos.

The IMM zebrafish facility is committed to follow the 3Rs principles – Replace, Reduce and Refine – for responsible use of laboratory animals.

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

ONGOING PARTNERSHIPS

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

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

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

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

CONTRACTS WITH INDUSTRY

Abbott Laboratorios, Lda	
Abbvie	
Alfagene	
Amgen	
Angelini Farmacêutica, Lda	
Astrazenca	
Axa SA	
BES	
Bial	
Biogen Idec	
ECBio, S.A. Exergia-Projectos de Engenharia, S.A.	
Gilead Sciences, Lda	
Glaxo SK	
Grunenthal S.A.	
Grupo Taper	
Institut de Recherches Servier	
Janssen-Cilag Farmacêutica, Lda	
Laboratórios Pfizer, Lda	
Linde Sogás, Lda	
Medtronic Portugal, Lda	
Merck Chemicals Ltd	
Merck Sharp & Dohme	
Merck, S.A.	
Novartis Farma, S.A.	
Roche	
Sanofi - Aventis	
Servier Portugal	
TcLand Expression	
Teva Pharma, Lda.	
UCB Pharma	