Lisboa

Instituto
de Medicina
Molecular

Report

2014

Instituto De Medicina Molecular — iMM Lisboa
Faculdade De Medicina Da Universidade De Lisboa
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Project concept and management
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GBNT — Shaping Communication
www.gbnt.pt

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October, 2015

chasing questions :

contents

Director´s message

Maria M. Mota – Executive Director

“

(...) we envisage an atmosphere where everyone (...) feels that she or he contributes to the institution; and that the institution sets a common goal of creating new knowledge that will impact human health.”

The Instituto de Medicina Molecular is now over a decade old. From the beginning and under the direction of Carmo Fonseca, iMM has established itself as a biomedical research institute of excellence, conducting basic and clinical research with the mission of improving human life. A constant slope towards excellence-driven, high-impact research, with a clear emphasis on quality over quantity, marks that same decade. Last year the executive lead was passed to me, with Carmo becoming *President*; and a *Board of Directors* was swiftly set.

I am a scientist because I fell madly in love when I saw an electron micrograph of a *Leishmania* parasite inside a host macrophage. Since then I have “changed subject” a few times but questioning how microbes survive inside the host and how these 2 entities cross-talk powers my life. While I do not know the details of when and how my fellow scientists of the board of directors – Bruno Silva-Santos and Henrique Veiga-Fernandes - fell in love with science, I have no doubt that our common denominator is the constant excitement about the questions that keep sprouting in our minds. And for Margarida Pinto-Gago, our Finance Director, discoveries made at iMM are surely a big and important part of her life.

Together we are determined to make iMM a place where world-class ingenious scientists with an ambitious research portfolio are supported by state-of-the-art technology and flexible resources that maximize creativity towards discoveries without boundaries.

We are convinced that groundbreaking science should be supported by encouraging individual freedom to pursue creative approaches, which are often different from mainstream ideas. In an environment, devoid of conventional departments, that fosters freedom to explore different areas of science, all parts, including students, post-doctoral fellows and group leaders, can and should play important roles in designing their own paths. Ultimately it enables collaboration and interdisciplinary research, always with the goal to pursue the most fundamental questions. For students and post-docs, it provides flexibility to work with more than one group leader and to develop a project that moves into the frontier of different disciplines. In that context iMM wants to attract highly motivated and curious individuals from anywhere in the world with a true passion for science and discovery from different academic backgrounds as it will provide tools and mental diversity to address different scientific problems enlarging the “tool kit” available to our community. For group leaders, it allows them to pioneer distinct and alternative ideas. Precisely with this in mind, we have launched in 2014 the first internal call for “Breakthrough Ideas” - where group leaders request funds to develop their team’s best idea – something risky but of possibly high gain.

We are also strong supporters of the idea that investing on outstanding science will create the knowledge that will hopefully lead to a significant number of applications. We are working on different possible solutions to ensure that ideas and discoveries with potential for translation can be readily identified and supported.

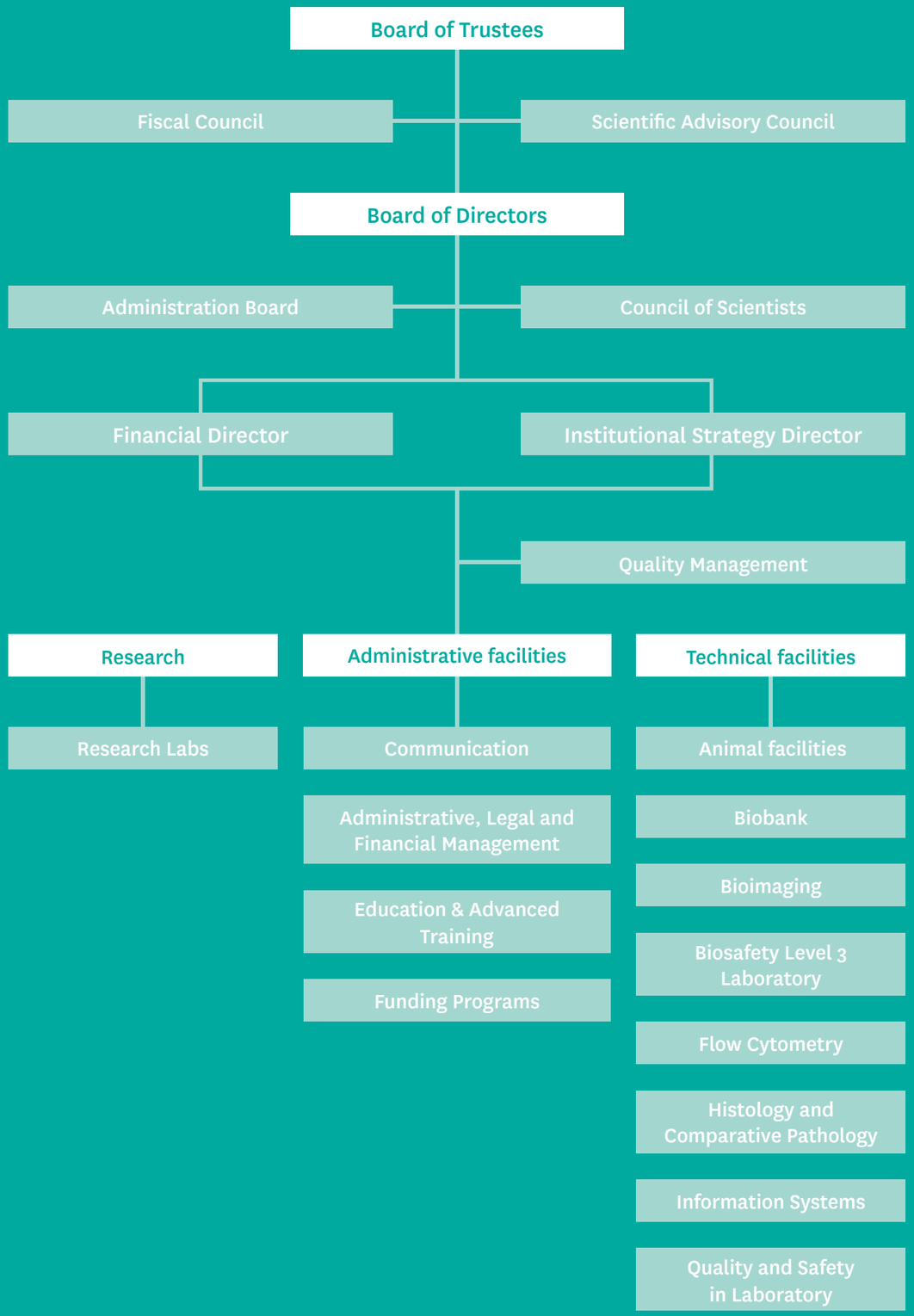
2014 was a memorable year for many reasons. In the last days of the year we had the result of the evaluation process led by FCT, in which iMM was evaluated as “Excellent”. Most importantly, iMM was awarded almost the full budget requested for the strategic plan over the next 3 years. Additionally, the result of the *FCT Investigator* call was outstanding. Eight of our researchers, including 4 group leaders, were awarded these 5-year positions. But most notably, researchers at iMM have published several breakthrough discoveries during 2014. Out of all the papers that we published, one sticks out particularly: the discovery that exposure to vitamin A-derived retinoids in the womb determines proper development of secondary lymphoid organs and life-long immunity. The work was published in Nature and basically implies that immune health in adulthood can be preset by nutritional status during fetal life – or, as Nature Reviews immunology wrote in a comment, “we are what mum eats!”. This is a truly seminal result from the laboratory of Henrique Veiga-Fernandes and his team, who had an amazing year and published a second Nature paper revealing that haematopoietic stem cells and neurons are regulated by a set of similar signals. But many other papers also helped to embellish this awesome year. Our very young group leader Sérgio Almeida and his team published in *Elife* work showing that a protein called SETD2 modifies histones so that they can recruit the enzymes that repair the DNA via a relatively error-free mechanism, thus illustrating how histone modifications and DNA damage checkpoints work in concert to suppress cancer. My own laboratory published in *Nature Medicine* data revealing an innate immune response mounted against *Plasmodium* liver stage, which refuted a dogma that persisted in the field for decades: that during natural infections *Plasmodium* was undetectable while developing and replicating in the hepatocyte. And Leonor Saúde´s laboratory published in *Developmental Cell* that N-cadherin is critical for the establishment of stereotypic left-right asymmetric distribution of internal organs by stopping key leftward cell movements. These papers, among many others, illustrate the wide range of themes that characterize biomedical research at iMM.

To finish I would like to dedicate this report to every iMMer and stress that, while promoting individual freedom and ambition, our vision is not of a culture of individuality. Instead, we envisage an atmosphere where everyone – either a researcher, a member of the technical or administrative staff – feels that she or he contributes to the institution; and that the institution sets a common goal of creating new knowledge that will impact human health.

And that, as they say, will make my day!

Structure and Organisation

Board of Directors (left-to-right) — Margarida Pinto Gago, Henrique Veiga-Fernandes, M. Carmo-Fonseca, Bruno Silva-Santos and Maria M. Mota



Board of Directors

The Board of Directors is responsible for the management of the Institute according to the plans approved by the Trustees. The Board of Directors is elected by the Trustees.

João Lobo Antunes
MD, PhD — President Emeritus

M. Carmo-Fonseca
MD, PhD — President

Maria M. Mota
PhD — Executive Director

Bruno Silva-Santos
PhD — Vice President

Scientific Advisory Council

Undertake periodic evaluations to the iMM Lisboa specific programmes and include international experts of scientific fields analysed:

Carlos Caldas
MD, PhD — Cambridge Cancer Centre, UK

Gustave Moonen
MD, PhD — Université de Liége, Belgium

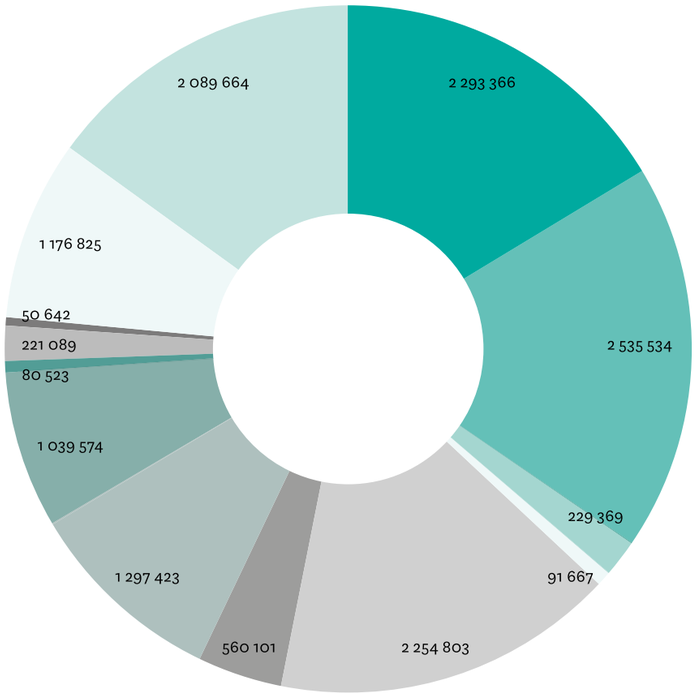
Paul Peter Tak
MD, PhD — University of Amsterdam, Netherlands

Philippe Sansonetti
MD, PhD — Pasteur Institute, France

Maria da Graça Carvalho
European Parliament

iMM Lisboa
Highlights 2014

Total Expenditure
13.920.579 €



Institutional
5 149 935 €

- Core
- Competitive
- Donations
- Services

Research Labs
8 770 644 €

- FCT Grants
- Other National Grants
- EU Grants
- Other International Grants
- Awards
- Donations
- Services
- Work contracts FCT
- Fellowship FCT

Patents

New patent applications or provisional patent applications in 2014

PT107692 "Compositions for the treatment of malaria"
GL Maria Mota
Provisional Patent Application

PT107693 "Compositions for the treatment of malaria"
GL Maria Mota
Provisional Patent Application

PT108040 "Understanding dengue virus capsid protein disordered n-terminus and pep14-23-based inhibition"
GL Nuno Santos
Provisional Patent Application

Ongoing patent applications at 31·12·2014

PCT/PT2012/000034
"The anthracycline for the treatment of sepsis"
GL Luis Ferreira Moita
Patent Application - PCT

PCT/IB2012/052545
"Generation of peripheral blood gamma-delta t-cells expressing natural cytotoxicity receptors for cancer immunotherapy"
GL Bruno Silva-Santos
Patent Application - PCT

PCT/BR2012/000162
"Denv derived peptides for the inhibition of the flavivirus replication"
GL Nuno Santos
Patent Application - PCT

PCT/IB2013/053050
"Genetically modified rodent plasmodium parasites as platforms for a whole-organism malaria vaccine"
GL Maria Mota
GL Miguel Prudêncio
Patent Application - PCT

PCT/IB2013/055261
“The use of ret agonist molecules for haematopoietic stem cell expansion protocols and transplantation therapy and a ret agonist kit”
GL Henrique Veiga-Fernandes
Patent Application -PCT

PT107692 “Compositions for the treatment of malaria”
GL Maria Mota
Provisional Patent Application

PT107693 “Compositions for the treatment of malaria”
GL Maria Mota
Provisional Patent Application

PT108040 "Understanding dengue virus capsid protein disordered N-terminus and pep14-23-based inhibition"
GL Nuno Santos
Provisional Patent Application

iMM Lisboa at a glance

193
Publications
International Journals

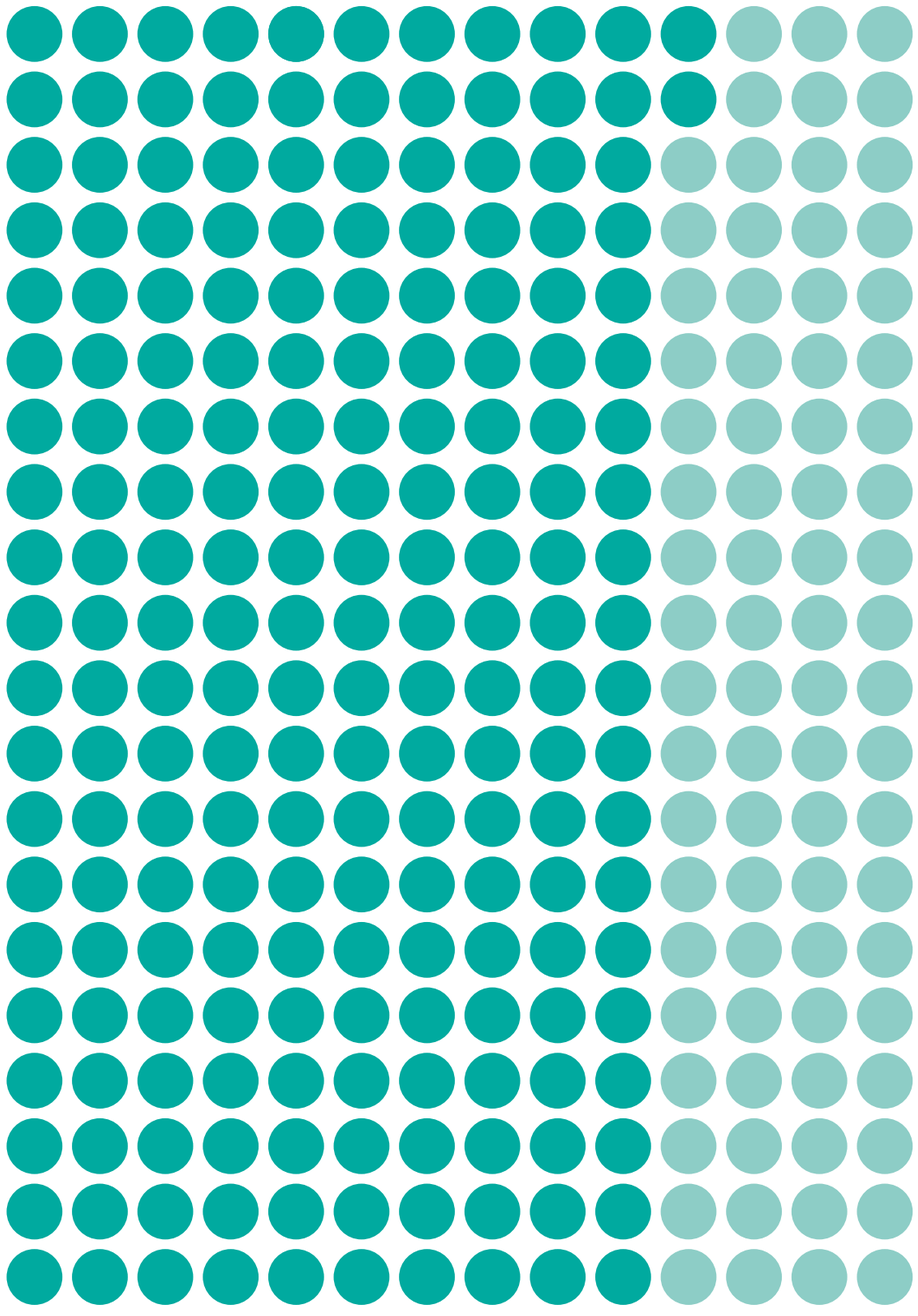
72
...in journals with an impact factor between 5 – 10

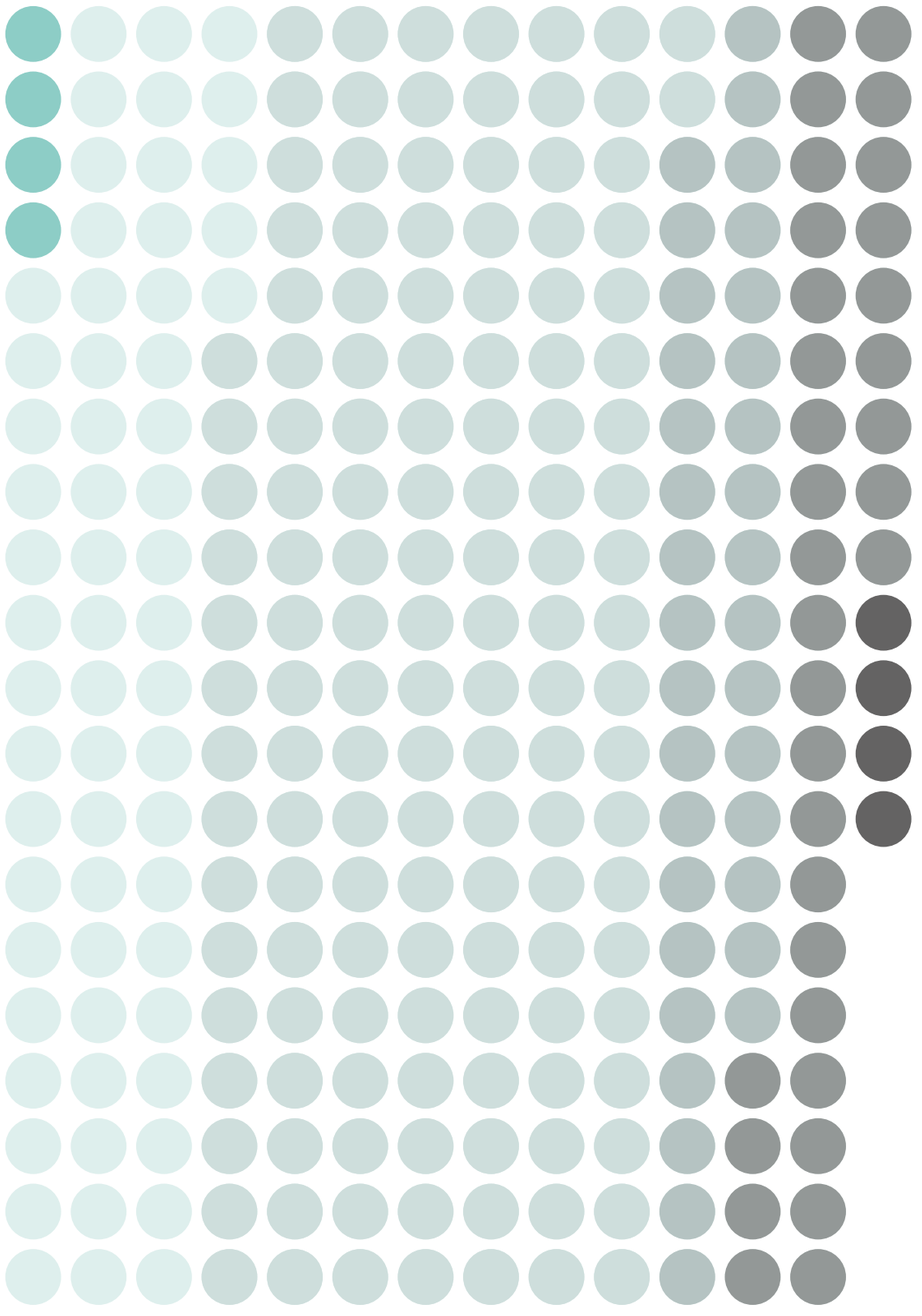
29
...in journals with an impact factor higher than 10

Research Highlights

21.699
Sum of the times cited papers

4775
Citations per year



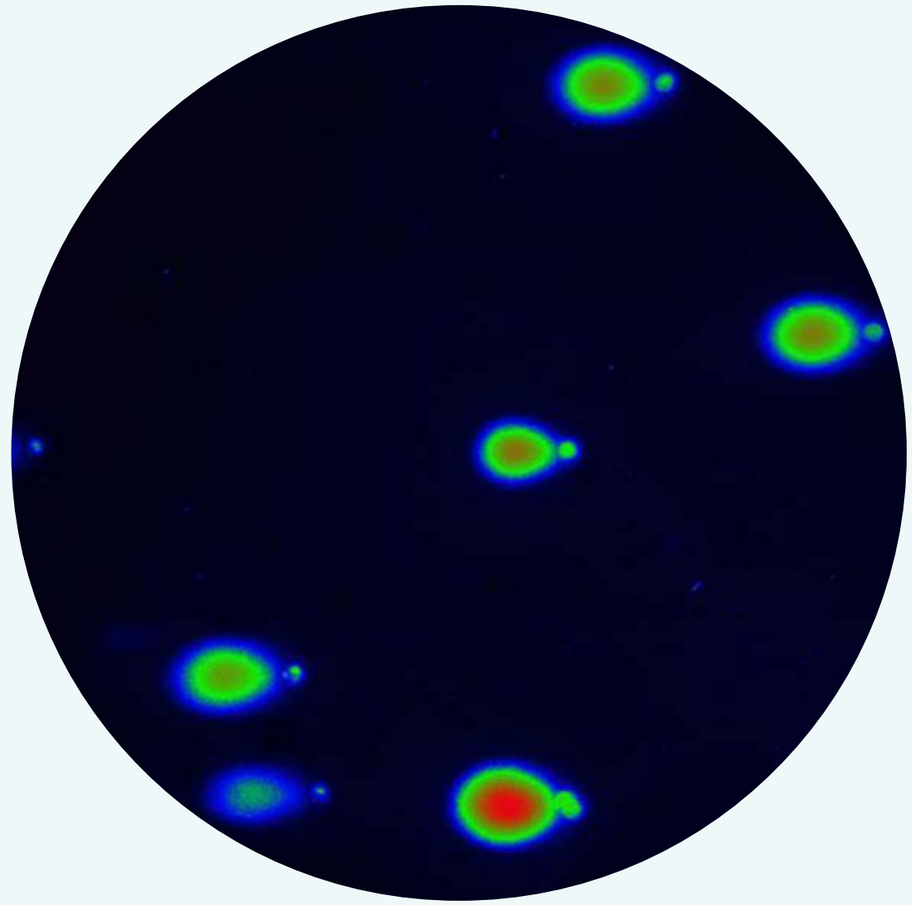


- **202** PhD researchers
- **82** PhD Students
- **61** M.Sc researchers
- **137** Bachelor researchers
- **34** International Research Fellows
- **33** Research Laboratories
- **4** Start-ups

496 Researchers

Biomedical diversity at iMM Lisboa

Published in 2014



A comet assay showing damaged DNA (comet’s tail) migrating away from the cell nucleus (comet’s head) in response to an electrical field. Photo by Sérgio de Almeida Lab

Modification of histones, the DNA packaging proteins, guides DNA damage repair to suppress kidney cancer

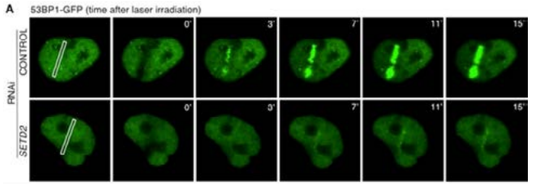
Normal wear and tear, exposure to chemicals, and ultraviolet light can all damage DNA, so cells relyon a range of sensors and mechanisms to detect and repair damaged DNA. Cells also package DNA molecules inside structures called histones to protect them against damage.

Double-strand breaks—one of the most serious forms of DNA damage—are detected by an enzyme called ATM, and can be repaired in two ways. Bringing the broken strands back together is an obvious method, but it is also error prone. Using templates to generate new DNA to repair the damage is less prone to error, but it can only happen at certain times of the cell cycle.

Some cancers are linked to the faulty repair of double-strand breaks. Moreover, a type of kidney cancer called clear cell renal carcinoma is linked to a lack of activity by a protein called p53, even in individuals who don't have mutations in the gene for this protein. However, many people with this type of cancer have mutations in the gene for a protein called SETD2.

To investigate the links between SETD2 and DNA repair, Carvalho et al. compared cells with and without mutations in the gene for SETD2. It emerged that SETD2 must be present for DNA repair to take place: the SETD2 modifies the histones so that they can recruit the enzymes that repair the DNA via the template approach (which is relatively error free). SETD2 may be particularly important for repairing damage to genes without introducing errors.

Carvalho et al. also show that mutations in SETD2 are sufficient to inactivate p53. The gene for this protein, which impedes the proliferation of cells with genomic aberrations, such as double-strand breaks, is mutated in most cancers. Overall the results help to illustrate how histone modifications and the DNA damage repair mechanisms and checkpoints work in concert to suppress cancer.



Source

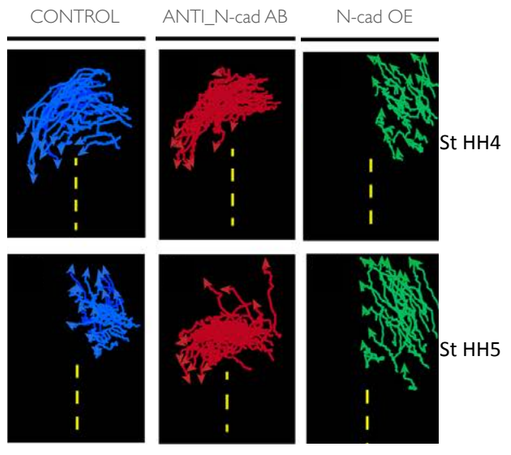
Carvalho S, Vitor A, Sridhara SC, Martins FB, Raposo AC, Desterro JM, Ferreira J, de Almeida SF (2014) SETD2 is required for DNA double-strand break repair and activation of the p53-mediated checkpoint. eLife 3, e02482.

N-cadherin stops leftward movements of node cells

Much attention has been given to the processes/signals that initiate left-right asymmetry in the vertebrate embryo, which is a crucial event to place the asymmetric organs inside the body cavities. In the chicken embryo it is clear that a leftward movement of node cells initiates a cascade of asymmetric signaling. However, we did not know how this leftward movement of cells terminates once the asymmetric signals are established in the node. Moreover, we did not know would be the developmental outcome if this process would go on for an extended period of time.

In this study, the team of Leonor Saúde from iMM Lisboa wasable to show that a cell-cell adhesion mechanism mediated by N-cadherin terminates the leftward movements of node cells, thus locking the left-right asymmetries established earlier. Furthermore, they provide evidence that this locking of left-right asymmetries in the node is essential to transfer the correct molecular information to the lateral plate mesoderm, allowing the proper asymmetric looping of the heart at later stages.

"We believe that the mechanism stopping cell movement that we have uncovered in this study will be of interest to a diverse range of audiences since it has implications on several developmental/disease events such as morphogenesis and tumor invasion" explains Leonor Saúde developmental biologist from iMM Lisboa.



Source

Mendes RV, Martins GG, Martins AM and Saúde L. (2014)
N-cadherin locks left-right asymmetry by ending the leftward movement of Hensen's node cells.
Developmental Cell 30(3), 353-60

The malaria parasite does not hide under an invisibility cloak

Plasmodium parasites, prior to infect red blood cells and cause malaria, must infect liver hepatocytes. During this obligatory step, each parasite divides into thousands of new parasites without causing any symptoms. This led to the assumption that this stage progressed invisible to the host defenses. This paper that this is not true and that the host is able to detect and actively tries to combat the very few parasites that reach the liver. Unexpectedly, the host uses a sensor mechanism that until now was only known to detect certain type of viruses that are radically different from parasites. This novel discovery has strong implications on how certain viral infections may affect the spread of malaria but most importantly on how intervention strategies should be designed to efficiently kill the parasite.

Source

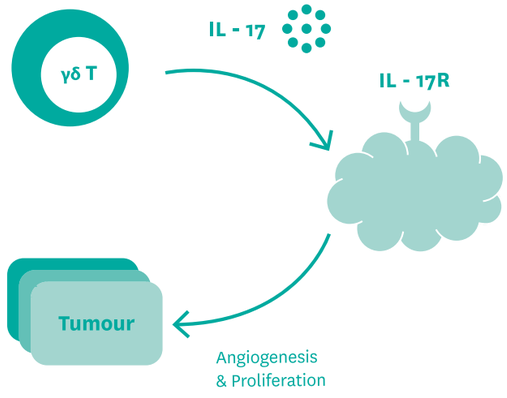
Liehl P, Zuzarte-Luís V, Chan J, Zillinger T, Baptista F, Carapau D, Konert M, Hanson KK, Carret C, Lassnig C, Müller M, Kalinke U, Saeed M, Chora AF, Golenbock DT, Strobl B, Prudêncio M, Coelho LP, Kappe SH, Superti-Furga G, Pichlmair A, Vigário AM, Rice CM, Fitzgerald KA, Barchet W, Mota MM. (2014)"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

A new immune mechanism that supports cancer growth

A team led by Bruno Silva-Santos discovered an immune cell crosstalk that promotes ovarian cancer growth. The work characterized a novel axis involving γδ T lymphocytes, the cytokine interleukin-17 (IL-17) and small peritoneal acrophages (SPM), which promotes tumour development *in vivo*.

It is known that the development of solid cancers is influenced by multiple white blood cell subsets that can inhibit or, paradoxically, promote tumour cell growth. In this study, the iMM team, in collaboration with colleagues from Queen Mary University of London (UK), described a cellular cross-talk between γδ T lymphocytes and small peritoneal macrophages (SPM), which is mediated by the pro--inflammatory cytokine interleukin-17 (IL-17), and stimulates ovarian cancer growth in the peritoneal cavity.

The key molecule, IL-17, is preferentially produced by a particular population of γδ T lymphocytes, and this associates with the recruitment of SPM macrophages, which in turn produce molecules that help the tumour to grow. These findings were p ublished in PNAS (*Proceedings of the Natural Academy of Sciences of the USA*) and identify new potential targets for immuno-oncology strategies.



Source

Rei M, Gonçalves-Sousa N, Lança T, Thompson RG, Mensurado S, Balkwill FR, Kulbe H, Pennington DJ and Silva-Santos B (2014).
Murine CD27(-) V γ6(+)γδ T cells producing IL-17A promote ovarian cancer growth via mobilization of protumor small peritoneal macrophages.
Proc Natl Acad Sci U S A 111, (34), E3562-70.

We are what mum eats!

Maternal vitamin A impacts the development of the fetal immune system and health in adulthood.

Veiga-Fernandes' laboratory has shown that the offspring of pregnant mice raised on a low-vitamin A diet developed small lymph nodes. Similarly embryos genetically engineered to have defective receptors for the vitamin A have defective lymphoid organs. Most strikingly, a normal diet after birth did not reverse the effects of the in-utero deficiency, which hindered mice in fighting infections as adults.

"There is a tight link between the maternal diet during pregnancy and the immune fitness of the offspring. In other words, whatever the mother eats during pregnancy will have an irreversible impact on the later health of the progeny." - Referred Henrique Veiga-Fernandes.

During immune system development, group 3 innate lymphoid cells (ILC3) are important for the formation of lymph nodes and other secondary lymphoid organs. ILC3 have been considered to be developmentally regulated, but the researchers now found that ILC3 and lymphoid organ development can be regulated by maternal behaviour and micronutrients.

An estimated 250 million preschool children are vitamin A deficient and it is likely that in vitamin A deficient areas a substantial proportion of pregnant women is vitamin A deficient.

Source

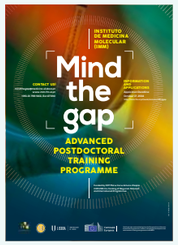
van de Pavert SA, Ferreira M, Domingues RG, Ribeiro H, Molenaar R, Moreira-Santos L, Almeida FF, Ibiza S, Barbosa I, Goverse G, Labão-Almeida C, Godinho-Silva C, Konijn T, Schooneman D, O'Toole T, Mizee MR, Habani Y, Haak E, Santori FR, Littman DR, Schulte-Merker S, Dzierzak E, Simas JP, E. Mebius R, Veiga-Fernandes, H (2014).
Maternal retinoids control type 3 innate lymphoid cells and set the offspring immunity.
Nature 508, 123-127

1 year in the life of iMM Lisboa

2014 1 year in the life of iMM Lisboa

January

Edgar Gomes and Miguel Remondes become new Group Leaders at iMM



Launch of Mindthegap, the iMM Advanced Postdoctoral Training Program

February

Professor João Lobo Antunes receives the *Universidade de Lisboa Award*

March

2nd edition of the LisbonBioMed PhD Program

April

New iMM Board of Directors

iMM receives Marie Geoghehan-Quinn - European Commissioner for Research, Innovation and Science, Maria da Graça Carvalho - member of the European Comission and Leonor Parreira - Secretary of State for Science

May

Diana Gaspar is awarded the Associação Laço Research Grant

VIII Annual PhD Students Meeting

June

II iMM PostDoc Day

August

Mamede de Carvalho is distinguished by The American Clinical Neurophysiology Society (ACNS) with the *Robert S Schwab Award*

iMM Lisboa Facilities are certified in ISO 9001:2008

September

Open Day Biobanco-IMM

Gonçalo Bernardes is awarded the Silver Medal of the European Young Chemists Award (EYCA)

October

Haakan Norell receives the *APCL Research Grant*

November

New Biobanco-IMM Board of Directors

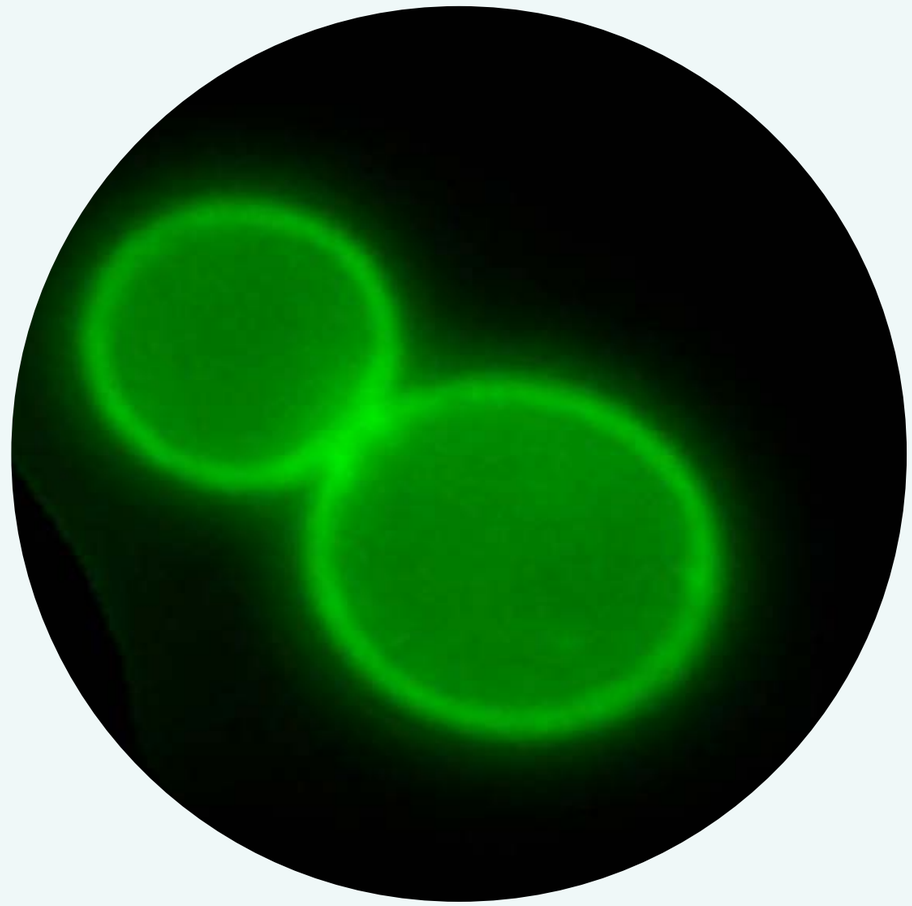
João Lacerda wins coordination of H2020 European project

December

João Barata and Henrique Veiga-Fernandes are awarded the *Clinical and Basic* Prémios *Pfizer 2014*, respectively

iMM Christmas Party

Laboratories



Yeast cells expressing the human protein alpha-synuclein in fusion with GFP, a cellular model used to study Parkinson’s disease basic molecular mechanisms. Photo by Sandra Tenreiro

Almeida, Sérgio F.

Sérgio de Almeida :
Group Leader at iMM Lisboa since 2013

PhD (2007) in Biomedical Sciences at Universidade do Porto

Post-doctoral research (2007-2013) at iMM Lisboa

—

sergioalmeida@medicina.ulisboa.pt

Keywords

Epigenetics · Chromatin Biology · Cancer Biology · Gene expression · DNA repair

The regulation of gene expression and the maintenance of genomic integrity involve complex processes that are altered in several pathological conditions.

Our research focuses on the mechanisms that regulate chromatin dynamics during transcription and DNA damage response and how they coordinate with the processes that safeguard the genome integrity. Our group aims to: i) investigate molecular aspects of the different stages of the transcription cycle, focusing on chromatin modification events; ii) study the molecular mechanisms that sense, signal and repair DNA damage; and iii) understand how changes in transcription, chromatin modification and DNA repair are linked to the development of human diseases such as cancer.

Our research has the potential to uncover surprising and thus far unknown facets of genome regulation and oncogenic transformation including novel molecular targets for cancer treatment.

— Carvalho S, Vitor A, Sridhara SC, Martins FB, Raposo AC, Desterro JM, Ferreira J, de Almeida SF (2014), **SETD2 is required for DNA double-strand break repair and activation of the p53-mediated checkpoint,** *eLife* **3**, e02482.

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

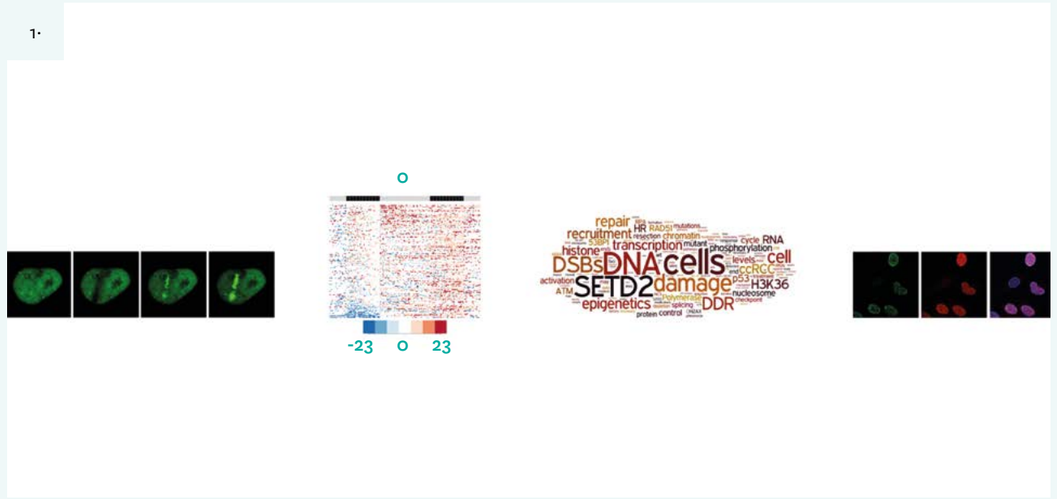
— Grosso AR, de Almeida SF, Braga J and Carmo-Fonseca M. (2012), **Dynamic transitions in RNA polymerase II density profiles during transcription termination,** *Genome Research*, **22**(8):1447-56.

— de Almeida SF and Carmo-Fonseca M. (2012) **Design principles of interconnections between chromatin and pre-mRNA splicing,** *Trends in Biochemical Sciences* **37**(6):248-53

— 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 Struct. Mol. Biol* **18,** 977-983.

1· Schematic representation of our main research interests.

1·



Barata, João T.

João Taborda Barata :
Group Leader at iMM Lisboa since 2006

PhD (2003) in Biomedical Sciences at Harvard Medical School, USA, and Universidade do Porto

Post-doctoral researcher at iMM Lisboa, Institut Pasteur, France, and Utrecht University, The Netherlands

—

joao_barata@medicina.ulisboa.pt

Keywords

Oncobiology · Leukemia · Signal transduction · Cellular and molecular biology

Despite enormous research efforts, a deeper understanding of cancer biology is still required to allow the rational development of more effective and selective treatment strategies that eventually eliminate the tumour without impacting normal cells.

We aim to understand the role of cell-autonomous alterations and microenvironmental cues in the development of cancer, focusing mainly on the dissection of signalling pathways essential for tumour maintenance. To do so, we make use of patient material, as a key source of insights into the disease, and integrate different biochemical, cellular and molecular biology techniques with appropriate in vitro and in vivo models - enabling an overall appreciation of the molecular, cellular and systemic nuances associated with cancer.

Ultimately, our research will lead to the identification and characterization of crucial molecular targets for the development of novel, more selective therapies against cancer.

1· Our research focuses on the role that both cell-intrinsic aberrations (at the gene and protein levels) and microenvironmental factors (particularly cytokines) might play during tumor development.

— Sarmento LM, Póvoa V, Nascimento R, Real G, Antunes I, Martins LR, Moita C, Alves PM, Abecasis M, Moita LF, Parkhouse RME, Meijerink JPP, Barata JT (2014), **CHK1 overexpression in T-cell acute lymphoblastic leukemia is essential for proliferation and survival by preventing excessive replication stress,** *Oncogene* **18;**0. doi: 10.1038/onc.2014.248.

— Mendes RD*, Sarmento LM*, Canté-Barrett K, Zuurbier L, Buijs-Gladdines J, Póvoa V, Smits WK, Abecassis M, Yunes JA, Sonneveld E, Horstmann MA, Pieters R, Barata JT**, Meijerink JPP** (2014), **PTEN micro-deletions in T-cell acute lymphoblastic leukemia are caused by illegitimate RAG-mediated recombination events.** *Blood* **124** (4): 567-578.

— Lonetti A*, Antunes IL*, Chiarini F, Orsini E, Buontempo F, Ricci F, Tazzari PL, Pagliaro P, Melchionda F, Pession A, Bertaina A, Locatelli F, McCubrey JA, Barata JT**, Martelli AM** (2014), **Activity of the pan-class I phosphoinositide 3-kinase inhibitor NVP-BKM120 in T-cell acute lymphoblastic leukemia,** *Leukemia 28*, **6,** 1196–1206.

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

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

*co-first authors; **co-senior authors

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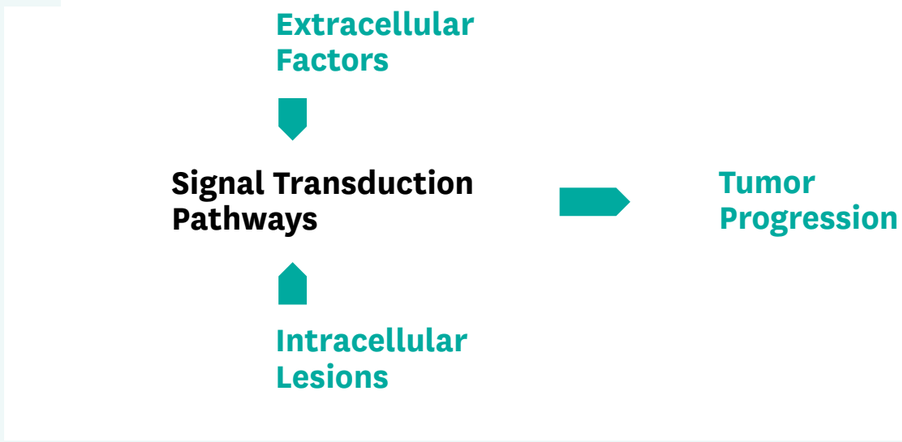

Bernardes, Gonçalo J.L.

Gonçalo Bernardes :
Group Leader at iMM Lisboa since 2013

DPhil (2008) in Chemical Biology at the University of Oxford, UK

Post-doctoral studies at the Max-Planck Institute (Berlin, Germany) and ETH Zürich (Switzerland)

Group Leader – Royal Society University Research Fellow at the Department of Chemistry, University of Cambridge, UK since 2013

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Keywords

Chemical Biology · Site-selective protein modification · Synthetic biologics · Targeted cancer therapeutics · Carbohydrate-based vaccines

The Chemistry-Biology interface is an exciting and innovative research area with great potential for synthetic and mechanistic advances in Biomedicine.

Research in the Bernardes lab falls under the broader field of Chemical Biology, focusing on the development and use of novel site-selective protein modification reactions in aqueous media to understand key biological processes and to generate chemically-defined protein conjugates for targeted therapeutics and vaccines. Our research is motivated by the potential development of novel chemical methods for imaging key biological processes at the molecular level. A precise understanding of the molecular basis of diseases hold great potential for the development of more potent, more specific and less toxic therapeutic solutions for a multitude of human diseases.

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— Bernardes GJL, Steiner M, Hartmann I, Neri D, Casi G (2013) **Site-specific Chemical Modification of Antibody Fragments with Traceless Cleavable Linkers.** *Nature Protocols*,**8**, 2079-2089.

— Steiner M, Hartmann I, Perrino E, Casi G, Brighton S, Jelesarov I, Bernardes GJL*, Neri D (2013), **Spacer length shapes drug release and therapeutic efficacy of traceless disulfide-linked ADCs targeting the tumor neovasculature,** *Chemical Science*, **4**, 297-302.

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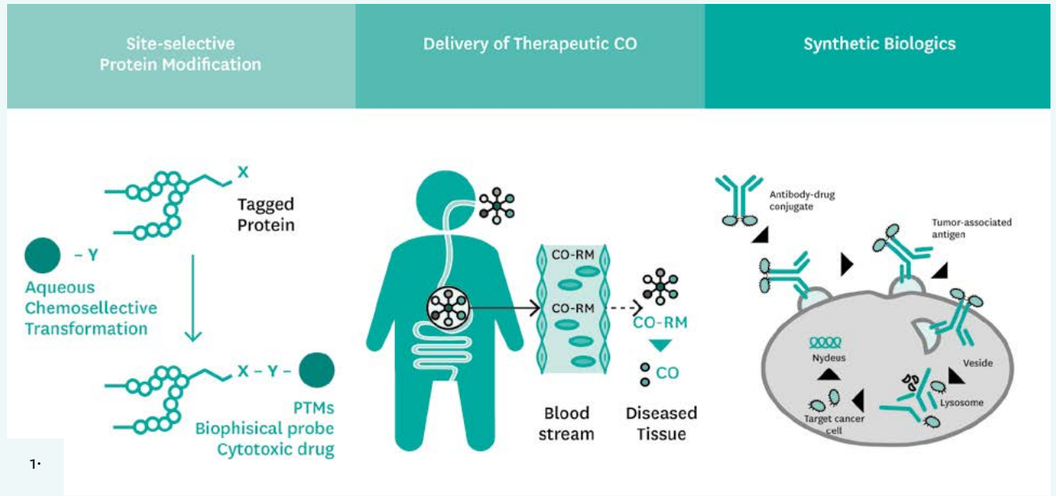
— García-Gallego S, Bernardes GJL (2014), **Carbon-monoxide releasing molecules for the delivery of therapeutic CO in vivo,** *Angew. Chem. Int. Ed.* **53,** 9712.

*Corresponding authors

1· We work at the interface of Chemistry and Biology with a focus on new methods for protein modification and their use to provide new biological insight and towards the development of protein-based therapeutics



1·

Carmo-Fonseca, Maria

Maria Carmo-Fonseca **:**
President of the iMM Lisboa since 2014

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

Post-doctoral researcher at EMBL in Heidelberg, Germany

Full Professor at Faculdade de Medicina da Universidade de Lisboa

Executive Director of iMM Lisboa between 2002-2014

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Keywords

Cell and Molecular Biology · RNA biology · RNA in disease

Gene regulation is central to all biology. RNA molecules, with their ability to both encode information and exert catalytic activities, play a key role in the regulation of gene expression.

Our group aims to discover molecular pathways and mechanisms implicating RNA in human health and disease. More specifically, we study co-transcriptional mRNA quality control and the role of RNA in the regulation of gene expression in cancer and human aging. We are also exploring new medical applications for RNA.Understanding how RNAs affect the function of cells in the human organism and translating this knowledge into novel disease biomarkers and therapies holds an immense potential in Biomedicine.

— Rino J, Martin RM, Carvalho T, Carmo-Fonseca M (2014) **Imaging dynamic interactions between spliceosomal proteins and pre-mRNA in living cells.** *Methods* **65**, 359-366.

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

— 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**, 1447-1456.

— 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 Struct. Mol. Biol* **18,** 977-983.

— 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 Struct. Mol. Biol.* **18**, 1115-1123.

1· Time-lapse imaging of gene expression.

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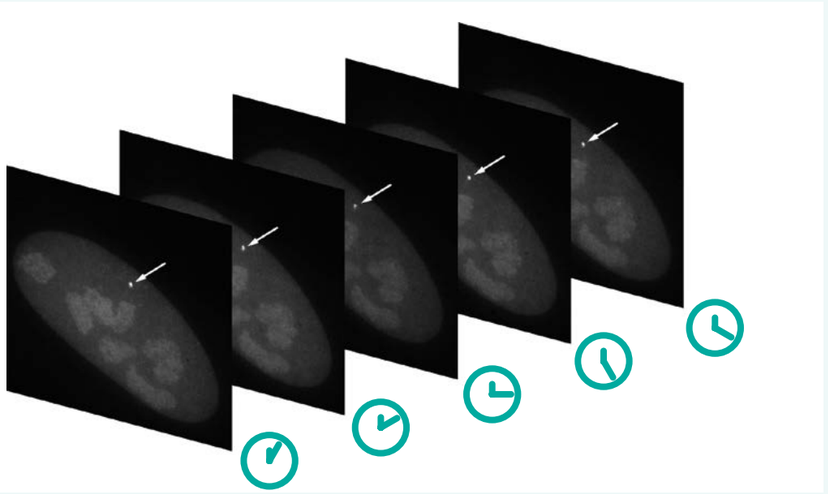

Castanho, Miguel

Miguel Castanho :
Group Leader at iMM Lisboa since 2008

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

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Keywords

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

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 new innovative therapeutical tools.

The aim of our laboratory 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.

We are interest not only in drug targets and drug discovery itself, but also in the molecular-level mechanism of action of drugs that are known for their therapeutic efficacy and safety. We are particularly interested on the central nervous system and translocation of the blood-brain barrier.

We expect our results to impact the state-of-the-art in different areas namely, i) tailored methodologies; ii) peptide-membrane biological events; and iii) delivery of new drug leads for subsequent industrial development.

— Freire JM, Veiga AS, Rego de Figueiredo I, de la Torre BG, Santos NC, Andreu D, Da Poian AT, Castanho MA. (2014)
Nucleic acid delivery by cell penetrating peptides derived from dengue virus capsid protein: design and mechanism of action.
FEBS J. **281**, 191-215. (Journal IF: 3.986, Citations: 4)

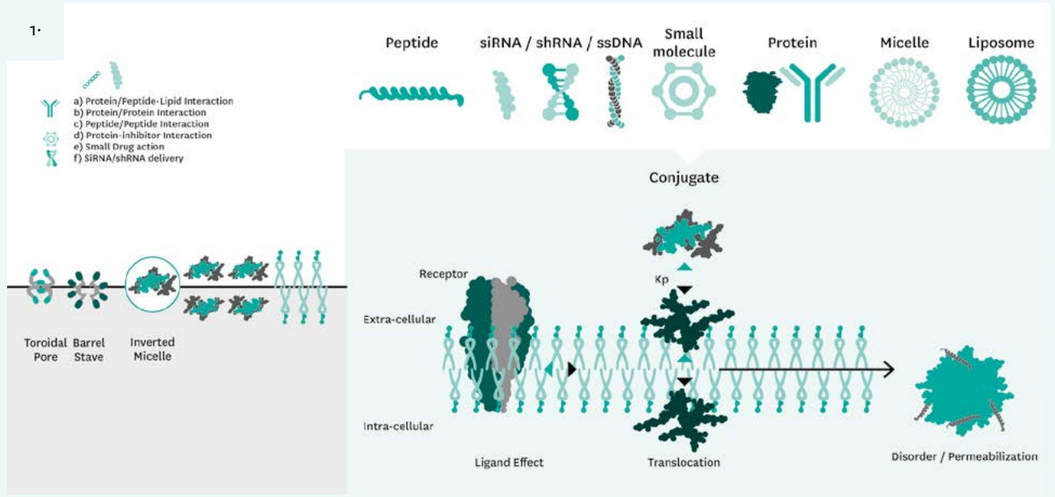
— Sinthuvanich C, Veiga AS, Gupta K, Gaspar D, Blumenthal R, Schneider JP. (2012)
Anticancer β-hairpin peptides: membrane-induced folding triggers activity.
JACS.**134**(14):6210-7.

— 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** (5):1929-40.

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

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

1· Biochemistry and biophysics of Peptide-lipid interactions



Costa, Luís

Luís Costa :
Group Leader at iMM Lisboa since 2007

MD (1985) and PhD (2002) in Bone metastases at Faculdade de Medicina da Universidade de Lisboa (FMUL)

Associate Professor at Faculdade de Medicina da Universidade de Lisboa

Director of Oncology Division at Hospital de Santa Maria–CHLN–Lisboa

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Keywords

Metastasis · Bone "vicious cycle" · Tumour microenvironment · Extracellular matrix · Tumour heterogeneity · Tumoural pathway-targeted therapies

Solid tumours are the most frequent type of cancer and cause of cancer mortality. Cancer progression is characterized by heterogeneity and clonal evolution and these are major challenges to the available cancer treatment strategies.

Focusing on metastasis, our research aims to understand if metastases genetically and phenotypically recapitulate the primary tumours, and how important are the tumour-target organ/host interactions. Our major interests are: i) to identify prognostic and/or predictive markers, and new therapeutic targets in bone metastases; ii) to identify a molecular signature of colorectal cancer metastization, and to determine if chemotherapy-induced cell senescence may be related with relapse; iii) to understand the role of phospholipase C epsilon in tumour progression ; and iv) to identify new therapeutic strategies by studying the role of tumour-associated ECM in cancer progression.

Importantly, we intend to direct our research to address at the pre-clinical level the mechanistic effects that explain our major clinical questions and findings in the human setting. Our approaches represent a new area of great potential for cancer therapeutic opportunities.

— Costa L. (2014), **Which bisphosphonate to treat bone metastases?,** *Lancet Oncol.* **15,** (1), 16-16.

— Casimiro S, Fernandes A, Oliveira AG, Franco M, Pires R, Peres M, Matias M, Tato-Costa J, Guerra N, Ramos M, Cruz J, Costa L (2014)
Metadherin expression and lung relapse in patients with colorectal carcinoma.
Clin Exp Metastasis **31**, 689.

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

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Analysis of a bone metastasis gene expression signature in patients with bone metastasis from solid tumors.
Clin Exp Metastasis **29,** 155.

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1· Translational research relies on a strict interplay between clinicians and researchers. A multidisciplinary approach is fundamental to successfully translate important clinical questions into relevant research projects with impact in the course of diseases. In our projects, whereas clinical co-investigators at HSM collaborate in the collection and analysis of clinical samples and data, researchers at our laboratory use techniques that integrate basic science (using in vitro approaches, animal models and human samples) into clinical outcomes.

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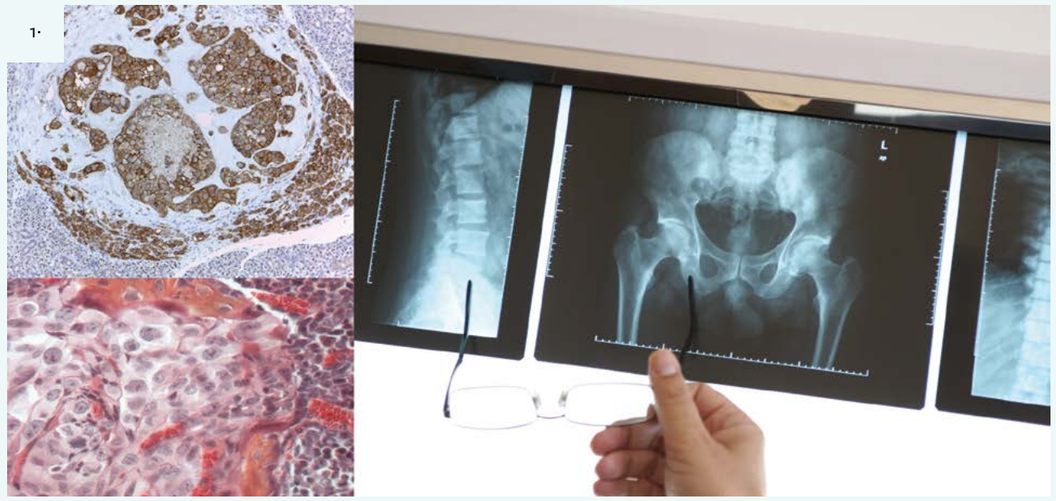

De Carvalho, Mamede

Mamede de Carvalho :
Group Leader at iMM Lisboa since 2005

1985 MD at Faculdade de Ciências Médicas, Universidade Nova de Lisboa

2000 PhD at Faculdade de Medicina da Universidade de Lisboa

Professor at Faculdade de Medicina da Universidade de Lisboa

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Keywords

Amyotrophic Lateral Sclerosis · Neurophysiology and respiratory involvement · Atrial fibrillation and autonomic nervous system · Neurocomputational modelling of brain disorders · Familial Amyloid Polyneuropathy and early markers of disease · Attention deficit hyperactivity disorder

Physiology covers the normal function of the living body, its organs and their dynamic interplay. Many complex structures and systems are involved and any disease results from its dysfunction.

Our research focuses on the motor neuron function and its degeneration, the autonomic nervous system and cardiovascular regulation, peripheral nerve function, behaviour and imaging, and neurocomputational models of brain dysfunction. We aim to approach: i) function of motor system and autonomic nervous system; ii) computational models of frontal degeneration; iii) new techniques to evaluate small nerve fibre; and iv) the interaction between brain and nerve excitability.

Our activity encompasses laboratory and clinical research following a translational strategy and the impact of our activities will be major in diseases such as heart arrhythmia, amyloid polyneuropathy, amyotrophic lateral sclerosis and attention deficit hyperactive disorder.

— Geraldes V, Gonçalves-Rosa N, Liu B, Paton J, F & Rocha, I. (2014), **Chronic depression of hypothalamic paraventricular neuronal activity produces sustained hypotension in hypertensive rats,** *Experimental physiology,* **99**(1), 89-100

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

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1· Activation of the striatum during reinforcement learning in humans (left). Activation of the putamen distinguishes subjects who learn from those who do not (right). From Horga*, Maia*, et al. in Human Brain Mapping, Vol. 36, No. 2, pp. 793-803. *Authors contributed equally.

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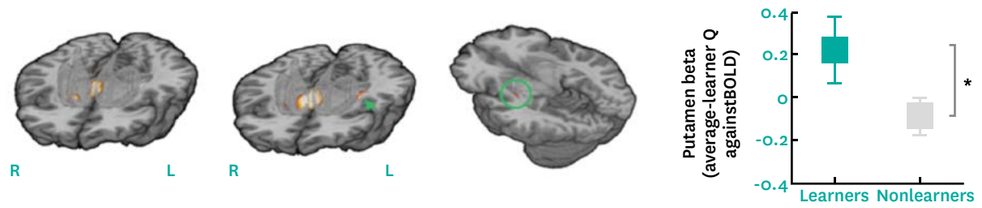

Dias, Sérgio

Sérgio Dias :
Group Leader at iMM Lisboa since 2012

PhD (1998) in Tumor Immunology, University College London, UK

Post-doctoral (1999-2001) at the Department of Hematology, Cornell University, New York

Principal Investigator (2002-2012) and coordinator (2003-2012) of the Molecular Pathobiology Department at Instituto Português de Oncologia Francisco Gentil (IPO Lisboa)

Associate Professor (2012) at Faculdade de Medicina da Universidade de Lisboa

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sergiodias@medicina.ulisboa.pt

Keywords

Angiogenesis · Tumor spread · Metabolism

Neovascularization, i.e., the formation of functional microvascular networks with red blood cell perfusion, occurs in both healthy tissues and where circulation has been impaired by trauma or disease.

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

Advances on the interplay of blood vessels and cellular components of the bone marrow in cancer onset and progression will provide useful knowledge for the development of new and effective preventive and therapeutic strategies to fight cancer.

— Dos Santos CR, Domingues G, Matias I, Matos J, Fonseca I, de Almeida JM, Dias S. (2014), **LDL-cholesterol signaling induces breast cancer proliferation and invasion.** *Lipids Health Disease.* **13**(1):16

— Costa A, Afonso J, Osório C, Gomes AL, Caiado F, Valente J, Aguiar SI, Pinto F, Ramirez M, Dias S (2013), **miR-363-5p regulates endothelial cell properties and their communication with hematopoietic precursor cells.** *J Hematol Oncol.* **21**;6(1):87.

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1· Tumor cell : blood vessel interactions. Confocal image of an In vitro co-culture of breast tumor cells (arrows) and blood vessel endothelial cells. Endothelial VE-cadherin molecules are stained in red to show cell to cell contacts. Nucleus are depicted in blue. This system is used to study transmigration of cancer cells through endothelial monolayers during metastasis.

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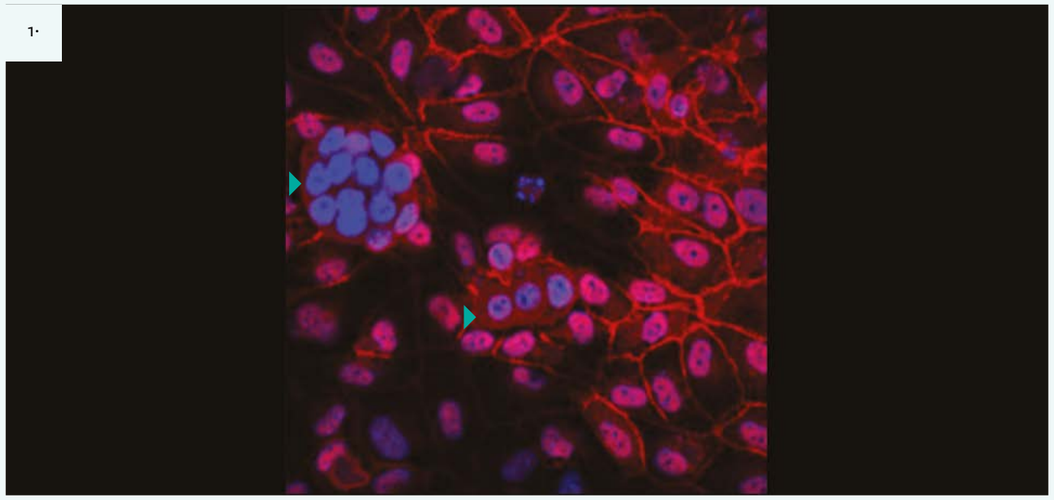

Ferreira, Joaquim J.

Joaquim Ferreira :
Group Leader at iMM Lisboa since 2013

MD (1992) and PhD (2009) in Neurology at Faculdade de Medicina da Universidade de Lisboa

Associate Professor at Faculdade de Medicina da Universidade de Lisboa since 2012

Director of Laboratory of Clinical Pharmacology and Therapeutics, FMUL (2011)

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Keywords

Parkinson's disease · Huntington Disease · Movement disorders · Neuropharmacology · Clinical trials · Systematic reviews

The advances in neurobiology have provided increasing insights into the pathophysiology of neurodegenerative diseases, and opened doors to the development of the so much needed targeted therapies.

Our research aims to contribute to the development of effective and safe therapeutic interventions through the establishment of optimized methodologies for the design, conduction, analysis and report of clinical trials.

Our emphasis is mainly on novel, early phase proof-of-principle clinical studies and new methodological and trial designs but the scope extends throughout the clinical development spectrum. Our results will have a great impact on clinical advances, in particular in neurodegenerative diseases (mainly Parkinson's Disease and Huntington's Disease), neglected patient populations (e.g. paediatric, rare diseases, late stage populations) and "orphan" interventions (e.g. rehabilitation, non-pharmacological and non-surgical interventions).

— Caldeira D, Costa J, Pinto FJ, Ferreira JJ (2014) **The risk of infection with new oral anticoagulants: a meta-analysis,** *International journal of Cardiology,* **72**, (1):267-8.

— Caldeira D, David C, Santos AT, Costa J, Pinto FJ, Ferreira JJ (2014), **Efficacy and safety of low molecular weight heparin in patients with mechanical heart valves: systematic review and meta-analysis.** *Journal of Thrombosis Haemost*, **12**, (5):650-9.

— Ferreira JJ, Katzenschlager R, Bloem BR, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampaio C, Schüpbach M, Tolosa E, Trenkwalder C, Schapira A, Berardelli A, Oertel WH (2013), **Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease,** *Eur J Neurol*, **20**(1):5-15

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— Ferreira JJ, Rascol O, Poewe W, Sampaio C, Rocha JF, Nunes T, Almeida L, Soares da Silva P (2010), **A Double-Blind, Randomized, Placebo and Active-Controlled Study of Nebicapone for the Treatment of Motor Fluctuations in Parkinson's Disease,** *CNS Neuroscience & Therapeutics*, **16**(6):337-347

1· Clinical Pharmacology Laboratory Functional Subunits

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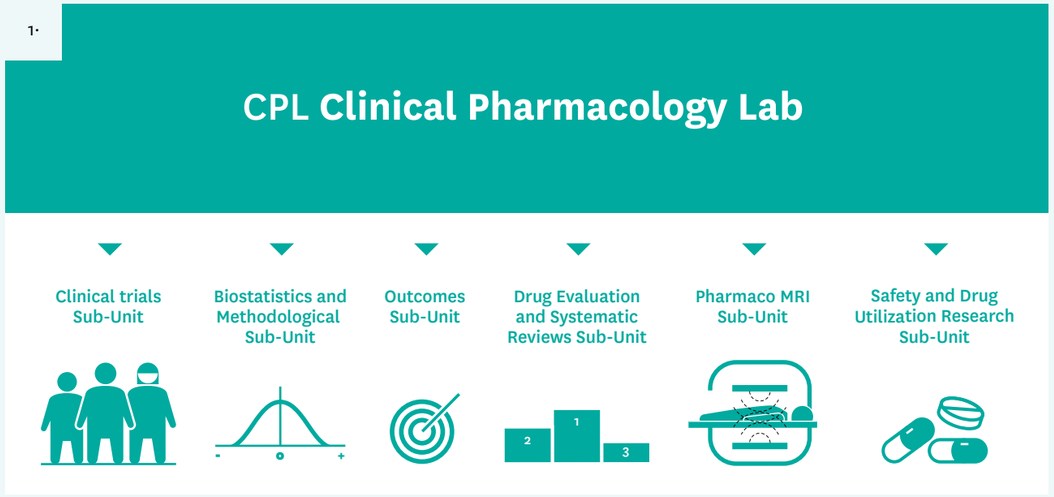

Ferro, José

José Ferro :
Group Leader at iMM Lisboa since 2003

MD (1975) and PhD (1987) at Faculdade de Medicina da Universidade de Lisboa (FMUL)

Full Professor and Chairman at FMUL and Hospital de Santa Maria

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Keywords

Stroke · Cognitive decline · Complex diseases · Genetics · Clinical trials · Cerebral venous thrombosis

With the ageing of the population, brain disorders have assumed a major importance in public health.

The identification of environmental and genetic determinants of these complex diseases, with establishment of risk and protective factors is thus a growing necessity.

Our research aims to increase the knowledge and foster the prevention and treatment of these major prevalent and disabling disorders, placing a particular focus on the quality of life dimensions, and also on the detection and detailed characterization of the initial phases of neurological diseases like stroke and dementia. For this, we take advantage of the ultidisciplinary characteristics of our research group, 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.

These approaches together with a strong participation in clinical trials to find new drugs for efficacious treatments are crucial to achieve an effective impact on these prevalent and disabling brain disorders that have become an health priority.

— Fonseca AC, Brito D, Pinho e Melo T, Geraldes R, Canhão P, Caplan LR, Ferro JM (2014), **N-terminal pro-brain natriuretic peptide shows diagnostic accuracy for detecting atrial fibrillation in cryptogenic stroke patients.** *Int J Stroke* **9**, 419-425.

— Crespo ÂC, Silva B, Marques L, Marcelino E, Maruta C, Costa S, Timóteo A, Vilares A, Couto FS, Faustino P, Correia AP, Verdelho A, Porto G, Guerreiro M, Herrero A, Costa C, de Mendonça A, Costa L, Martins M (2014), **Genetic and biochemical markers in patients with Alzheimer's disease support a concerted systemic iron homeostasis dysregulation,** *Neurobiol Aging* **35**, 777-785.

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— 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**:349-57.

— Xavier JM, Shafiee NM, Ghaderi F, Rosa A, Abdollahi BS, Nadji A, Shahram F, Davatchi F, Oliveira SA (2011), **Association of mitochondrial polymorphism m.709G>A with Behçet's disease (BD),** *Ann Rheum Dis* **70,** 1514-1516.

1· PET-PIB in Alzheimer disease patient 2· PET-FDG in Alzheimer disease

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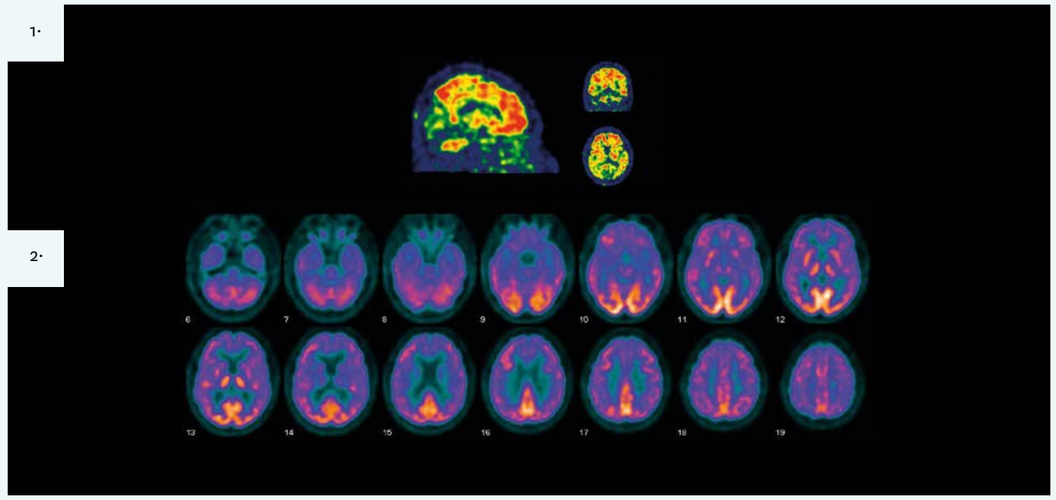
2·



Figueiredo, Luísa

Luísa M Figueiredo :
Group Leader at iMM Lisboa since 2009

PhD (2002) from Universidade do Porto and Institut Pasteur, France

Post-doctoral research at The Rockefeller University, New York, USA

Research Associate at The Rockefeller University, New York, USA (2008-2009)

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Keywords

Antigenic variation · Gene expression · Parasitology · Host-parasite interaction · Glycobiology · Circadian rhythm · Fat

Parasitism is the ability of an organism to exploit its host, which may increase reproductive success of the parasite, usually by enhancing its transmission efficiency. Sleeping sickness is a fatal neglected disease caused by *Trypanosoma brucei* a unicellular parasite responsible for 10,000 deaths every year in Africa. *T. brucei* relies on sophisticated mechanisms such as antigenic variation and cell differentiation to overcome the host immune system and to ensure its transmission to a new host, respectively. *T. brucei* interferes with the host sleep pattern and other circadian rhythms. Efficient parasitism relies therefore on a cross-talk between parasite, host and environment.

Our aim is to study the aforementioned interactions using genetic, biochemical and molecular approaches. This line of research, supported by the multidisciplinary expertise and knowledge of our group, will result in important contributions and advances on both areas of molecular parasitology, particularly in Sleeping sickness, and on the chromatin field, namely on the dynamics of chromatin remodelling, epigenetic inheritance and monoallelic expression.

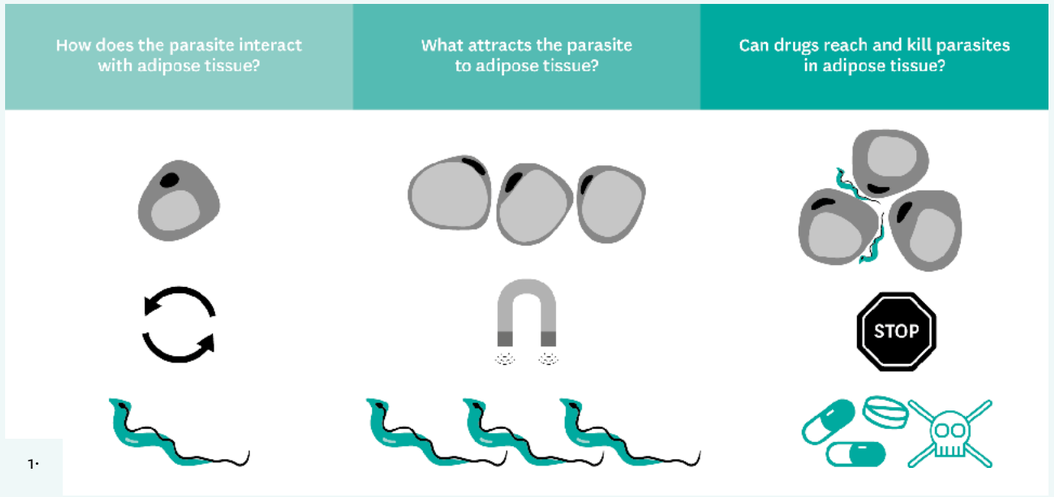
— Pena AC, Pimentel MR, Manso H, Vaz-Drago R, Pinto-Neves D, Aresta-Branco F, Rijo-Ferreira F, Guegan F, Pedro Coelho L, Carmo-Fonseca M, Barbosa-Morais NL, Figueiredo LM (2014) **Trypanosoma brucei histone H1 inhibits RNA polymerase I transcription and is important for parasite fitness in vivo.** *Molecular Microbiology*, **93**(4):645- 63

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

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

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

1· In the bloodstream, Trypanosoma brucei parasites are covered by an electronic dense coat of Variant Surface Glycoproteins, which is shed periodically to avoid elimination by the cells of the immune system.



1·

Filipe, Paulo

Paulo Filipe :
Group Leader at iMM Lisboa since 2014

PhD in Medicine (2005) at Faculdade de Medicina da Universidade de Lisboa

MD (1988) at Faculdade de Medicina de Lisboa da Universidade de Lisboa

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pfilipe@medicina.ulisboa.pt

Keywords

Human Th9 and Tc9 cells · Human Th17 and Tc17 cells · Keratinocyte · Neutrophil · Psoriasis · Pityriasis versicolor

Psoriasis is a common (~2% in western populations), chronic immune-mediated inflammatory disease associated with lowered quality of life and relevant co-morbidities, namely an increased risk of cardiovascular disease and mortality.

Our research aims at elucidating the earliest molecular signatures in the skin of psoriatic patients for a better selection of biologic therapeutic agents and prevention of relapse. We are particularly interested in elucidating the role of cells such as keratinocytes, neutrophils, cross-talk between Th9 and Th17 cells in the initiation and maintenance of the inflammatory process associated with psoriasis.

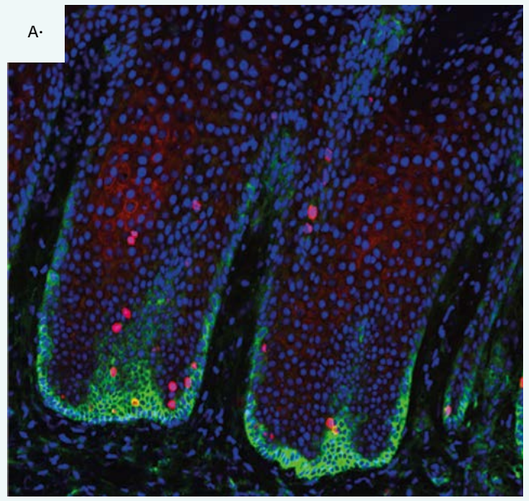
Our results will lead to advances on the search for clinically useful markers and drug targets in common skin diseases afflicting humans such as psoriasis and superficial mycosis.

— de Vasconcelos P, Goyri-O'Neill J, Soares-Almeida L, Ferreira J, Filipe P.(2014), **Subungual ectopic hair studied by scanning electron microscopy,** *J Eur Acad Dermatol Venereol.* **20**. DOI: 10.1111/jdv.12855

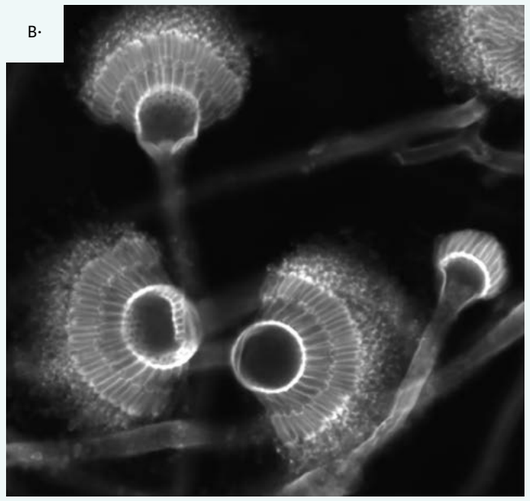
A. **Psoriasis** — Skin lesion from a psoriatic patient is shown. Proliferating epidermal cells (red signal), basal epidermal cells (green signal), nuclei (blue signal).

B. ***Aspergillus terreus*** — cultivated from a skin ulcer on the leg.

A·



B·



Fonseca, João E.

João Eurico-Fonseca :
Group Leader at iMM Lisboa since 2004

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

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Keywords

Joint inflammatory diseases - pathogenesis · early diagnosis · prognosis and pharmacogenetics · Rheumatoid arthritis · Psoriatic arthritis · Ankylosing spondylitis and juvenile idiopathic arthritis · Systemic effects of inflammation and effects of inflammation on bone- osteoporosis · osteoarthritis and rheumatoid arthritis · Atherosclerosis and bone · Epidemiology of rheumatic diseases.

The mechanisms underlying loss of bone quality in early arthritis; the relationship between vessel and systemic inflammation and poor bone quality; clinical, laboratorial, imaging and genetic predictors of progression and treatment response in distinct types of arthritis.

Our specific research objectives are the study of i) the impact of inflammatory joint diseases (such as rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthritis and systemic lupus erythematosus) on bone and vessel and ii) the relevance of genetic polymorphisms and other clinical and laboratorial variables in the prognosis and pharmacogenetics of rheumatic diseases. Our research will allow the characterization of potential tools for early diagnosis and prognosis, as well as potential targets for novel and effective therapies.

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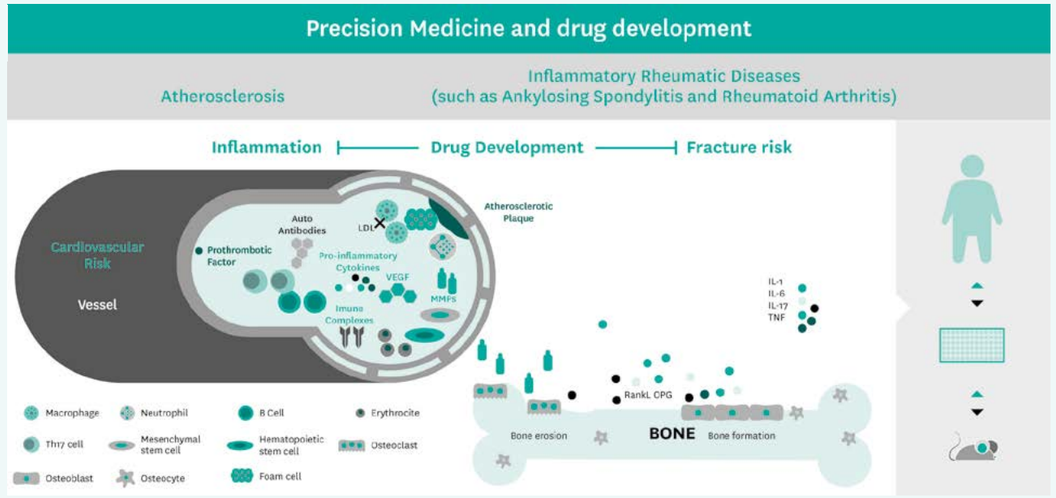
— Caetano-Lopes J, Canhão H, Fonseca JE (2009) **Osteoimmunology-the hidden immune regulation of bone.** *Autoimmun Rev* 8,250-5.

1· Our Unit is devoted to the translational study of the early burden of inflammatory rheumatic diseases on bone and vessel, seeking prognostic markers, predictors of treatment response and new treatment targets

1·



Franco, Cláudio A.

Cláudio Franco :
Group Leader at iMM Lisboa since 2013

PhD (2004-2008) at Pierre and Marie Curie University, France

Post-Doctoral (2009-2013) research at London Research Institute – CRUK, UK

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Keywords

Angiogenesis · cell migration · tumour angiogenesis · endothelial cells · vascular patterning

The formation of a functional vascular network is essential for embryonic development, growth and wound healing.

Importantly, many human disorders arise from mis-patterning of blood vessels, such as in diabetic retinopathy, ischemia, stroke, or tumour angiogenesis.
Our research aims to understand the molecular mechanisms regulating coordinated endothelial cell behaviour during sprouting and remodelling phases
of the angiogenic process. Namely, we focus on: i) novel regulators of endothelial cell migration in sprouting angiogenesis; ii) molecular regulation of endothelial cell axial polarity; iii) the effects of haemodynamic forces in vascular patterning; and iv) novel anti-angiogenic therapies blocking tumour angiogenesis.
We are confident that improving the knowledge on the molecular regulation of vascular morphogenesis will certainly create new possibilities for medical prevention and treatment of various human conditions.

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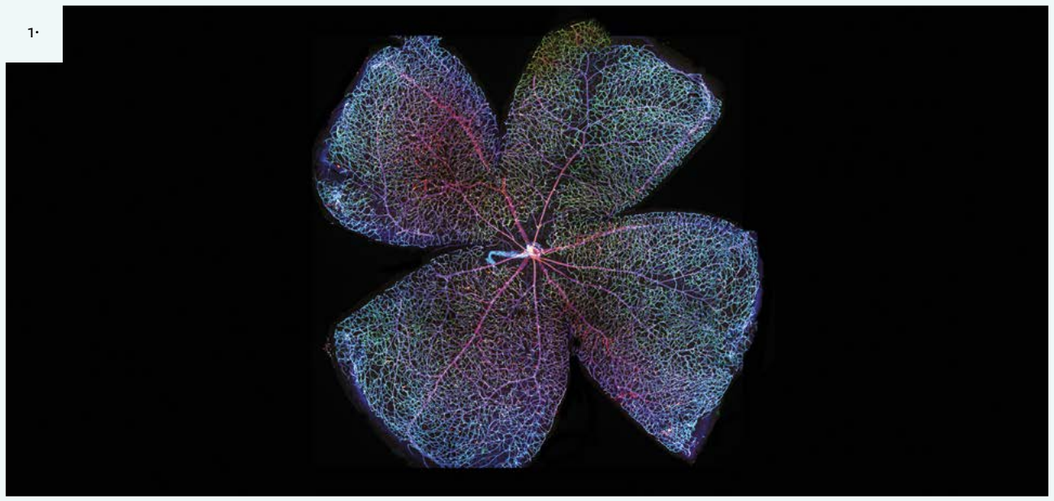
— Jakobsson L, Franco CA, Bentley K, Collins RT, Ponsioen B, Aspalter IM, Rosewell I, Busse M, Thurston G, Medvinsky A, Schulte-Merker S, Gerhardt H.(2010), **Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting,** *Nat Cell Biol*. 10:943-53.

*co-last; **co-second

1· Blood vessels in a mouse retina: Overview of the complexity and hierarchical structure of the vascular network using IsolectinB4 (blue), Icam2 (green) and collagenIV (red).

1·



Gomes, Edgar R.

Edgar Gomes **:**
Group Leader at iMM Lisboa since 2013

PhD in Cell Biology (2002) at Center for Neuroscience, Universidade de Coimbra, Portugal

Pos-Doctoral research (2002-2007), Department of Anatomy and Cell Biology, Columbia University, New York, USA

Team leader (since 2007) UMR S 787 - Group Myologie, Paris France

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Keywords

Cell Biology · Cytoskeleton · Cell Migration · Skeletal Muscle

Cell architecture is critical for cellular, development and organism activity. In particular, defects on nuclear positioning are associated with multiple diseases, such as muscle disorders and neuronal pathologies. Given that nuclear positioning within the cell cytoplasm requires the connection between the nucleus and the cytoskeleton, this connection becomes relevant for multiple cellular processes and disruption of these connections result in multiple pathologies.

Our research aims at understanding the processes involved in these connections and the role for nuclear positioning in cell function. Our studies focus cell migration and skeletal myofiber formation which involves the connection between the nucleus and the cytoskeleton and precise nuclear positioning.

By identifying mechanisms and understanding the role of nuclear positioning in myofiber function, we will lay the foundations for future studies to ameliorate or treat muscle disorders as well as other conditions where nucleus positioning may prove to play a role such as cancer.

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N-WASP is required for Amphiphysin-2/BIN1 dependent nuclear positioning and triad organization in skeletal muscle and is involved in the pathophysiology of centronuclear myopathy.
EMBO Mol Med, **6**, 1455.

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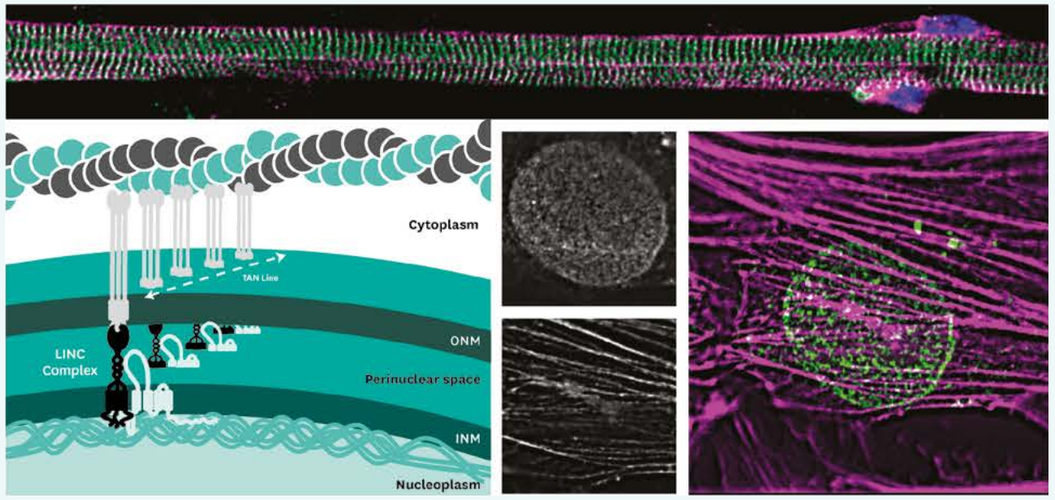
Fast, Multi-Dimensional and Simultaneous Kymograph-Like Particle Dynamics (SkyPad) Analysis.
PLoS ONE **9**(2): e89073

1· **Connecting the nucleus to the cytoskeleton.**
Top - skeletal muscle fiber differentiated in vitro with highly differentiated transversal triads and nuclei at the periphery. Bottom left - how the nuclear envelope connects to the actin cytoskeleton using the linc complex. Bottom right - the actin cytoskeleton surrounds the nucleus of migrating cells.



Graça, Luís

Luís Graça :
Group Leader at iMM Lisboa since 2005

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

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

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Associate Professor at Faculdade de Medicina da Universidade de Lisboa

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Keywords

Immune tolerance · Regulatory T cell subsets · T follicular helper (Tfh) cells · Allergy · Autoimmunity · Transplantation

Among the most frequent human diseases are pathologies directly caused by immune dysregulation.

The development of strategies aiming to reprogram the immune system towards a state of unresponsiveness but without amputating its overall protective function, something known as immune tolerance, has been a major goal in immunology and a clear unmet medical need.

Our research focuses on the study of the mechanisms underlying induction and maintenance of immune tolerance. In addition, we are interested in defining the functional properties of lymphocytes that can promote immune tolerance by suppressing pathogenic immune responses. For this, we have been studying how different types of lymphocytes with regulatory function can be induced in the periphery.

We believe that in the foreseeable future antibody therapy, as well as other strategies to modulate the immune system, will have an important repercussion in the quality of life of people suffering from immune mediated pathological conditions such as allergy, autoimmunity and transplant rejection.

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— Duarte J, Carrié N, Oliveira VG, Almeida C, Agua-Doce A, Rodrigues L, Simas P, Mars LT, Graca L. (2012), **T cell apoptosis and induction of Foxp3+ regulatory T cells underlie the therapeutic efficacy of CD4-blockade in experimental autoimmune encephalomyelitis,** *J Immunol.* **189**. 1680.

— Wollenberg I, Agua-Doce A, Hernández A, Almeida C, Oliveira VG, Faro J, Graca L. (2011), **Regulation of the germinal center reaction by Foxp3+ follicular regulatory T cells.** *J Immunol.* **187**, 4553.

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

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

1· Our research interests are focused on the acquisition of specialized functional characteristics by T cell subsets, and the functional impact of those T cells in immune pathology. We are particularly interested in studying different Foxp3+ lymphocyte subsets, and their role in the regulation of germinal centre responses (micrograph in the bottom) and allergic diseases (images on top).

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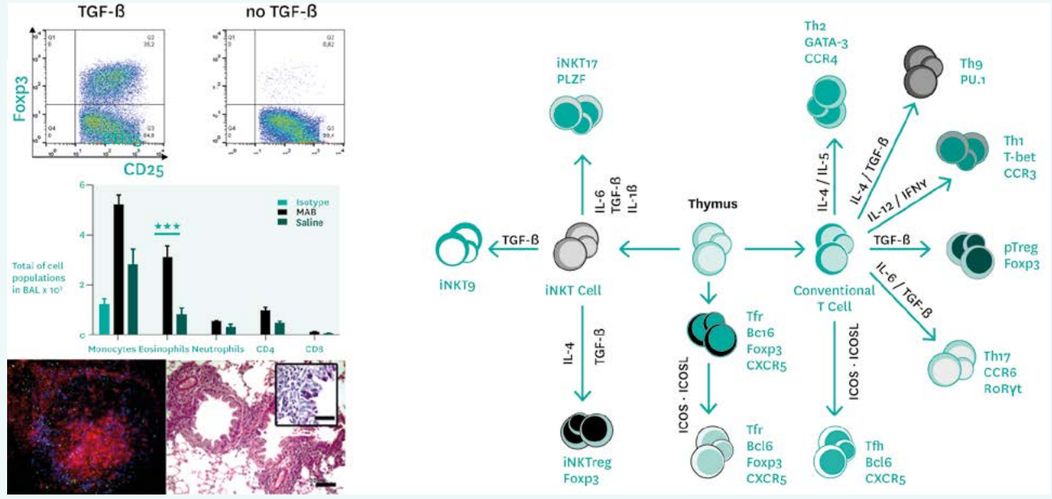

Henrique, Domingos

Domingos Henrique :
Group Leader at iMM Lisboa since 2005

PhD (1991) at Universidade de Lisboa

Pos-Doctoral research at NIMR and ICRF, UK and Institut d' Embryologie Cellulaire et Moleculaire, France

Investigator at Faculdade de Medicina da Universidade de Lisboa

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Keywords

Stem cells · Notch signalling · Pluripotency · Neurogenesis · Gene regulatory Networks · Systems Biology

A central question in developmental biology is how cells decide which differentiation paths they follow to generate tissues and organs during embryonic development.

Our research aims to elucidate the gene regulatory networks that control cell-fate decision processes in the embryo, using 2 experimental models: i) embryonic stem cells to study the mechanisms underlying their pluripotent state, and ii) neural retina to investigate how progenitors acquire their multipotent character and generate the variety of neurons that compose the mature retina.

These studies shall contribute to a deeper understanding of the mechanisms governing the decision processes that stem/progenitor cells employ to exit the pluri/multipotent state and differentiate along various paths, thereby generating correctly patterned tissues and organs.

Our research shall contribute to design more rational strategies to direct the in vitro and in vivo production of specific cell types, which might then be used to develop cell-replacement therapies in humans, aimed at regenerating damaged tissues and organs.

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— Vilas-Boas F, Fior R, SwedlowJ D, Storey K G, Henrique D (2011), **A novel Reporter of Notch Signalling indicates regulated and random Notch Activation during Vertebrate Neurogenesis,** *BMC Biology* **9**, 58.

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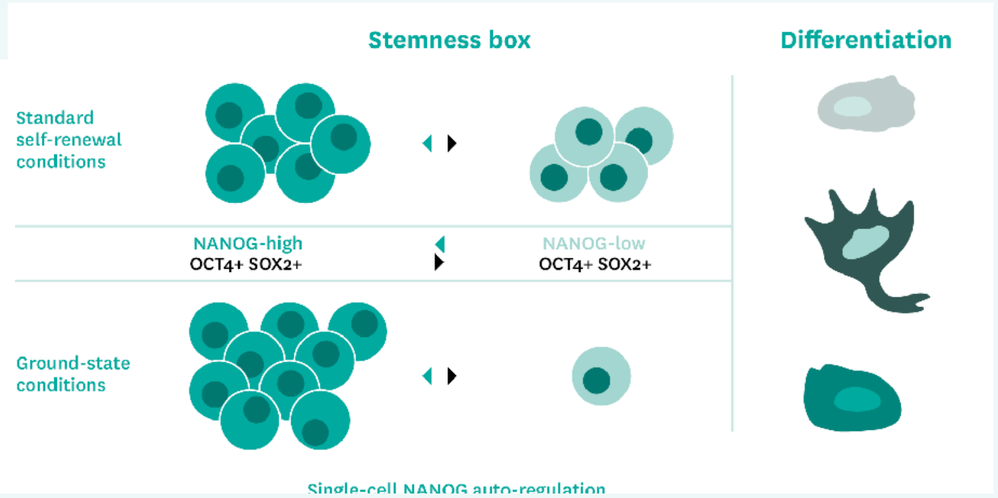
1· Embryonic stem cells fluctuate between different states of competence to differentiation, in a process controlled by the Nanog gene. Understanding how pluripotency is maintained, and how exit to differentiation is controlled, is fundamental to progress into clinical applications of stem cells.

1·



Lacerda, João F.

João Forjaz de Lacerda **:**
Group Leader at iMM Lisboa since 2013

MD (1988), PhD (1998), Universidade de Lisboa

Hematology and Bone Marrow Transplant Fellowship, Hospital de Santa Maria, Lisboa, and Memorial Sloan-Kettering Cancer Center, New York (1991-1995)

Senior Attending Physician at the Hematology and Marrow Transplantation Service, Hospital de Santa Maria, Lisboa (since 2005).

Associate Professor with Habilitation, Faculdade de Medicina da Universidade de Lisboa (since 2010)

Senior Staff Scientist (2008-2013) at iMM Lisboa

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Keywords

Immune reconstitution · Hematopoietic stem cell transplantation · Regulatory T cells · Immunotherapy · Graft versus host disease · Pathogen-specific immunity · Genetic susceptibility for fungal and viral infections · Hematology

Hematopoietic stem cell transplantation (HSCT) is an important medical procedure most often performed in patients with severe haematological malignancies, such as acute leukaemia. Donor-derived immune cells play a pivotal role not only in the emergence of graft-versus-host disease (GVHD) and graft-versus-leukaemia effect (GVL) after HSCT, but also in the protection against pathogens after HSCT, such as *Aspergillus*, CMV and EBV.

Our research focuses in the study of immune reconstitution and in strategies to modulate immune responses after HSCT. In particular, we aim to: i) identify immunological risk factors and the mechanisms by which both GVHD and GVL emerge post-transplant; ii) develop immunological strategies that may be translated into the clinical setting, such as the use of pathogen-specific T cells, donor regulatory T cells for GVHD and disease-specific T cells after HSCT.

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N Engl J Med. 30; 370(5):421-32

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Haematologica.99(6):1062-8

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Long-term immune reconstitution of naive and memory t cell pools after haploidentical hematopoietic stem cell transplantation.
Biol Blood Marrow Transplant. 19(5):703-12.

*Joint final authors

1· Our work at JLacerda's Lab has been mainly focused on the prospective monitoring of immune reconstitution in patients undergoing allogeneic Hematopoietic Stem Cell Transplantation (HSCT) (upper panel). As a translational research unit, we further aim to develop adoptive T cell therapy strategies to treat severe complications post-HSCT, such as infusing donor regulatory T cells (Treg) to treat graft-versus-host disease (GVHD) or donor pathogen-specific T cells to treat viral infections post-transplant (lower panel).

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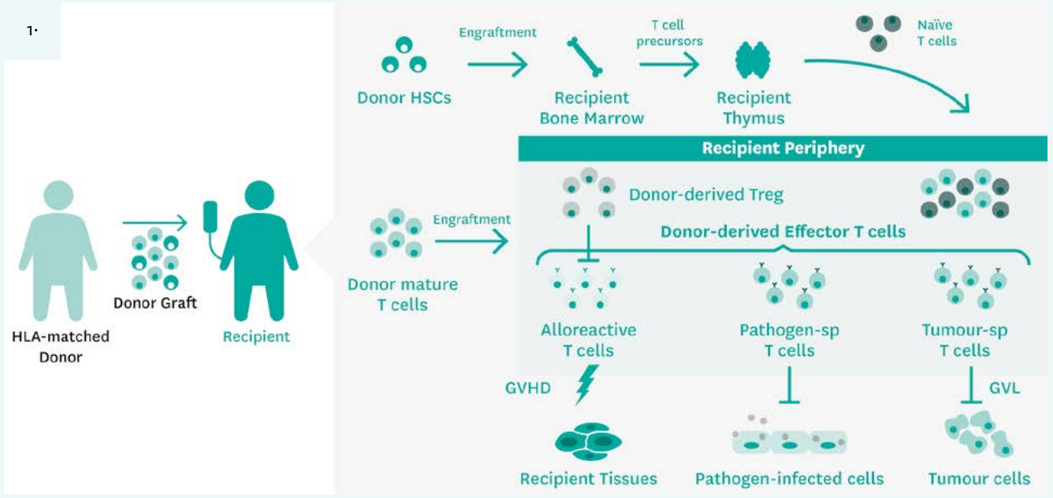

Lopes, Luísa V.

Luísa V. Lopes :
Group Leader at iMM Lisboa since 2013

2003 - PhD in Neurosciences, FMUL, University Lisbon; Dept Pharmacology, University of Cambridge and Karolinska Institute, Sweden

2003-2006 - Postdoctoral research fellow at Nestlé Research Center, Lausanne, Switzerland

Staff Scientist (Ciência 2007-2008-2012) and Postdoctoral research fellow (2006-2008) at iMM Lisboa-FMUL

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Keywords

Aging · Neurosciences · Cognition · Hippocampus · Stress

Aging, stress and neurodegenerative diseases are among the conditions that most contribute to the accelerated loss of cognitive function.

Our research is focused on understanding the mechanisms inducing this “early-ageing”, which render the hippocampus - the brain area related to learning and memory – particularly susceptible; namely in stress, neurodegeneration and aging. In particular, we focus on characterizing the molecular mechanisms associated to hippocampal loss of function and its outcome in behaviour performance and synaptic function, using rodent models. We ensure the translation to the human brain, by testing these molecular imprints in healthy and diseased human brain tissue. Detailed characterization and increased knowledge of these mechanisms is of paramount relevance to advance on novel prevention and therapeutic strategies with clinical impact.

— Sousa VC, Vital J, Costenla AR, Batalha VL, Sebastião AM, Ribeiro JA, Lopes LV (2014), **Maternal separation impairs long term-potentiation in CA1-CA3 synapses and hippocampal-dependent memory in old rats,** *Neurobiol Aging*. **35**, 1680-5.

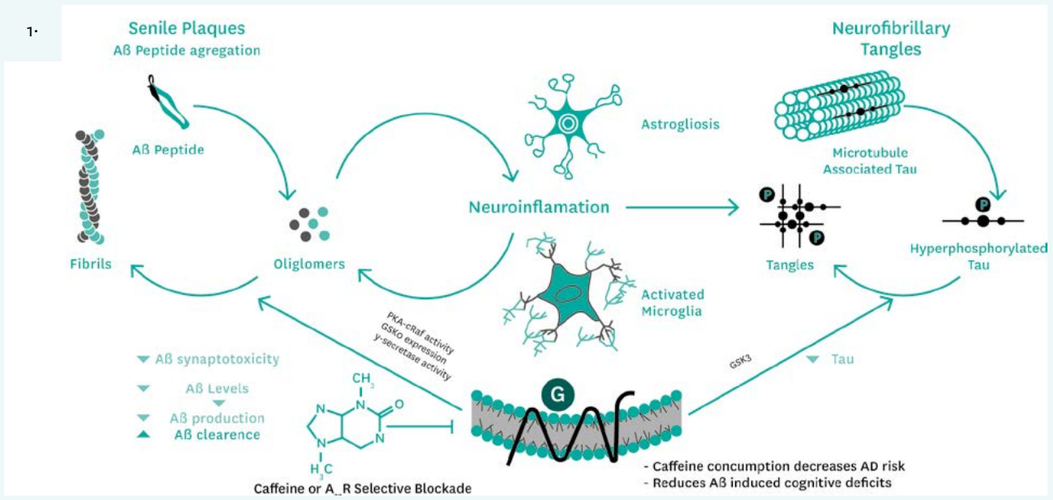
— Coelho JE, Alves P, Canas PM, Valadas JS, Shmidt T, Batalha VL, Ferreira DG, Ribeiro JA, Bader M, Cunha RA, do Couto FS, Lopes LV (2014), **Overexpression of Adenosine A2A Receptors in Rats: Effects on Depression, Locomotion, and Anxiety.** *Front Psychiatry*. **5**, 67

— Batalha VL, Pego JM, Fontinha BM, Costenla AR, Valadas JS, Baqi Y, Radjainia H, Müller CE, Sebastião AM, Lopes LV. (2013) **Adenosine A(2A) receptor blockade reverts hippocampal stress-induced deficits and restores corticosterone circadian oscillation,** *Molecular Psychiatry* **18**, 320.

1· Potential pathways involved in protective effects provided by caffeine and adenosine A2A receptor blockade in Alzheimer’s disease, characterized by accumulation of senile plaques (composed of aggregated Aß peptide) and neurofibrillary tangles (composed by hyperphosphorylated Tau) in the brain.

Source: *Laurent C, Burnouf S, Ferry B,* ***Batalha VL****, Coelho JE, Baqi Y, Malik E, Marciniak E, Parrot S, Van der Jeugd A, Faivre E, Flaten V, Ledent C, d’Hooge R, Sergeant N, Hamdane M, Humez S, Müller CE,* ***Lopes LV****, Buée L, Blum D. A2A adenosine receptor deletion is protective in a mouse model of Tauopathy.* Molecular Psychiatry (in press, 2015).

1·



Mota, Maria M.

Maria Manuel Mota :
Executive Director at iMM Lisboa since 2014

PhD (1998) in Molecular Parasitology
at University College London, UK

Post-doctoral research at New York University
Medical Center, USA (1999-2001)

Principal Investigator at Instituto Gulbenkian
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Professor at the Faculdade de Medicina
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European Science Foundation Young Investigator (2004-2009)
International Research Scholar Howard Hughes Medical
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Keywords

Host-Plasmodium interactions · Nutrient acquisition · Innate immune response against Plasmodium infection · Iron metabolism during Plasmodium infection · parasites as malaria vaccines

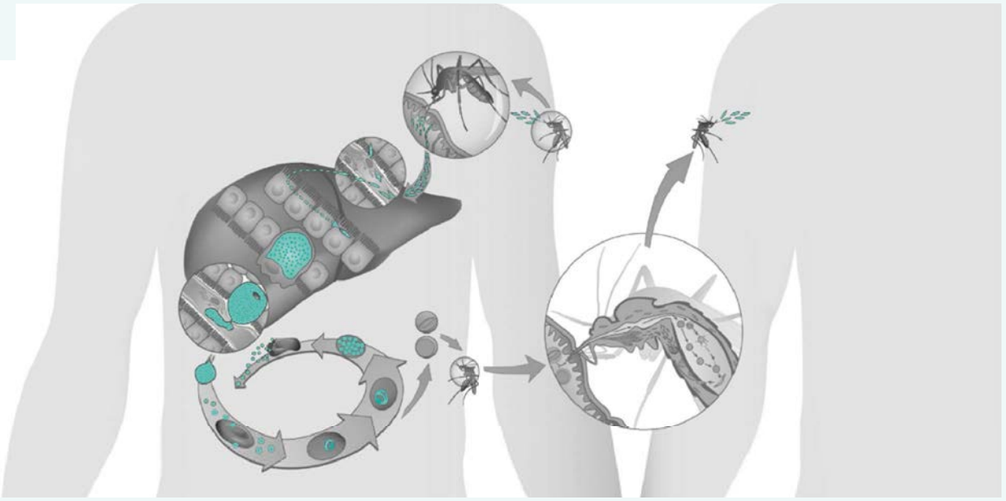
Despite renewed eradication efforts from the international community, malaria still exerts an enormous disease burden, with nearly half the planet's population at risk of infection. Within the human host, the disease-causing *Plasmodium* parasites pass through two distinct lifecycle stages, each in a different cellular environment.

During the liver stage, a single *Plasmodium* sporozoite will invade a hepatocyte, and while sheltered there gives rise to thousands of new parasites, which will go on to initiate the subsequent blood stage of infection. While only 10-20 new parasites will be generated inside an erythrocyte, consecutive cycles of cell lysis and reinfection causing a potent host response, as well as the symptoms of malaria. It is becoming 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.

Our ongoing work indicates that the web of host-*Plasmodium* interactions is densely woven, with liver stage-mediated innate immune system activation (Liehl et al., 2014. *Nature Medicine*), host nutritional status (*unpublished*), and an antagonistic relationship between the two parasite stages themselves (Portugal et al., 2011. *Nature Medicine*) all working to modulate the balance between parasite replication and human health. Altering this balance will be required if we aim to efficiently control this deadly parasite.

1· Life cycle of the Plasmodium parasite species which infect mammalian hosts. The life cycle of the parasites responsible for Malaria disease comprises 3 main obligatory stages: the liver-stages, the blood-stages and the Anopheles mosquito vector stages.

1·



— Itoe MA, Sampaio JL, Cabal GG, Real E, Zuzarte-Luis V, March S, Bhatia SN, Frischknecht F, Thiele C, Shevchenko A, Mota MM. (2014), **Host cell phosphatidylcholine is a key mediator of malaria parasite survival during liver stage infection.** *Cell Host Microbe*. **16**(6):778-86.

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

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

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Keywords

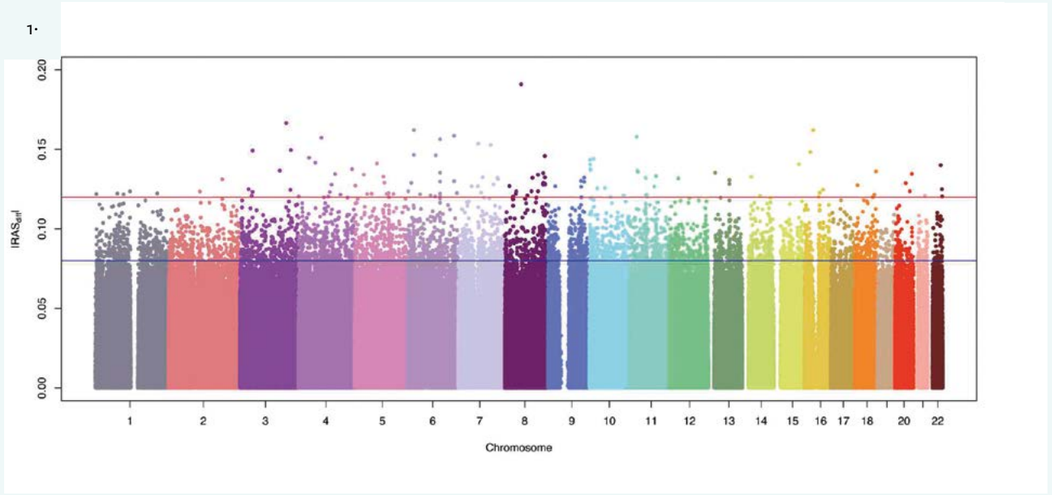
Genetics · Genomics · Complex traits

Common diseases result from the interaction of environmental and genetic factors, and an in-depth evaluation of their genetic underpinnings will not only unravel complex inheritance patterns but will also enable a better understanding of the environmental risks.

Our research focuses on understanding the genetic architecture of complex diseases such as Stroke, Behçet's Disease, Primary Spontaneous Pneumothorax, and Intracranial Aneurysms, using both traditional and novel approaches to more efficiently identify susceptibility genes.

We believe that our multidisciplinary framework will have the greatest success in dissecting the complex etiology of common disorders and will ultimately lead to the development of novel prevention strategies and targeted therapies.

1· Modified Manhattan plot for the primary spontaneous pneumothorax genome-wide association study. The absolute value of the relative allele score difference between cases and controls (|RASdiff|) is shown for 868,260 autosomal SNPs, ordered by chromosomal position. The red and blue lines represent the 12% and 8% |RASdiff| thresholds, respectively.



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Prudêncio, Miguel

Miguel Prudêncio :
Group Leader at iMM Lisboa since 2013

PhD (2000) in Biochemistry at University of East Anglia, Norwich, UK

Post-doctoral researcher (2000-2004) at University of Leiden, Leiden, The Netherlands

Post-doctoral researcher (2004) at Instituto Gulbenkian de Ciência, Oeiras, Portugal

Post-doctoral researcher (2005-2008) at iMM Lisboa

Senior Staff Scientist at iMM Lisboa (2008-2013)

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Keywords

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

Malaria is a devastating disease, its eradication being a necessary but still unmet clinical achievement. *Plasmodium* infection has a clinically silent, obligatory developmental phase in the liver. While this pre-erythrocytic stage of infection holds immense immunologic and prophylactic potential, it is also one about which important gaps in our knowledge subsist.

Our interests span a wide range of topics within the malaria field, with particular emphasis on the hepatic stage of infection. In particular, our research focuses on i) elucidating novel aspects of the biology of *Plasmodium* infection; ii) unveiling novel host-parasite interactions; iii) understanding co-infections between *Plasmodium* and other parasites; and iv) developing new drug- and vaccine-based anti-malarial strategies. Efforts to combat this disease must be multi-faceted, requiring both targeted approaches and an increased understanding of the biology of *Plasmodium*. We expect our findings will contribute to the elimination of malaria by developing targeted anti-malarial approaches, namely vaccines, and unveiling novel and crucial aspects of the biology of infection.

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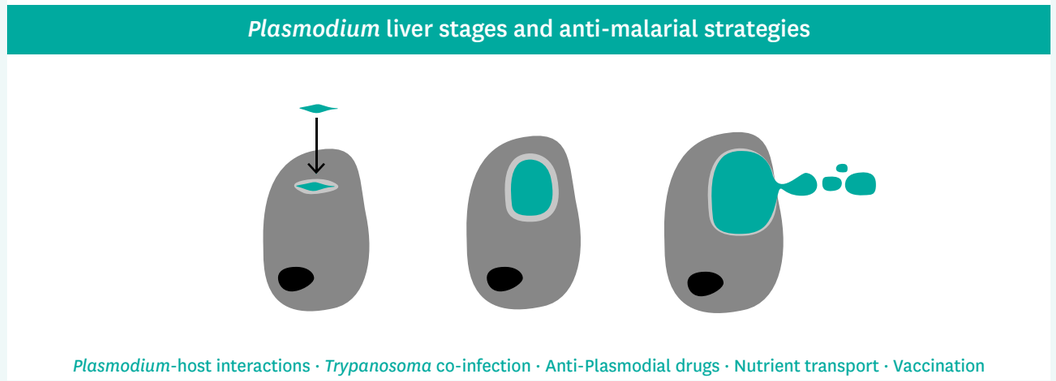
*Corresponding author; **Equally contributing authors

1· Plasmodium liver stages and anti-malarial strategies

1·



Ramirez, Mário

Mário Ramirez :
Group Leader at iMM Lisboa since 2004

PhD (1998) in Molecular Biology at Universidade Nova de Lisboa and at The Rockefeller University, USA

Post-doctoral research at Instituto de Tecnologia Quimica e Biologica, Oeiras

Associate Professor at Faculdade de Medicina da Universidade de Lisboa

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Keywords

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

In spite of the successful use of antibiotics and vaccination, bacterial infections are still a major cause of morbidity and mortality worldwide.

Our laboratory aims to understand the dynamics of populations of bacterial pathogens and how they respond to selective forces focusing on the effect of antimicrobial use, human vaccination and host diversity on bacterial populations.

Exploring the relationships between commensal and disease causing populations of the same bacterial pathogen is helping to identify particularly successful clones at causing disease as well as successful colonizers. Our research includes a strong bioinformatics approach in the area of bacterial population simulation, microbial typing data sharing, data analysis and visualization. Our laboratory is also active in developing novel diagnostic and antimicrobial susceptibility testing tools, particularly for plasmodium.Our findings will not only translate into a better prediction of bacterial pathogen evolution but will also allow anticipating the potential benefits of vaccination, help guide the optimal empirical and specific chemotherapy and improve time and yield of etiological diagnosis.

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1· Integrating metadata with MLST using PHYLOViZ: the example of the ST156 and ST162 subgroups on the largest CC in Streptococcus pneumoniae. The colors represent penicillin susceptibility: Susceptible (Green) MIC ≤ 0.064 mg/L; Intermediate (Orange) 0.09mg/L ≤ MIC ≤ 1 mg/L; Resistant (Red) MIC > 1 mg/L.

1·

Remondes, Miguel

Miguel Remondes :
Group Leader at iMM Lisboa since 2014

PhD (1998) Candidate in the VI Gulbenkian Ph.D. Program in Biology and Medicine

PhD(1999) in Biomedical Sciences – Neuroscience, California Institute of Technology and University of Coimbra (Medical School).

Postdoctoral Scholar(2004) at the Picower Institute – Massachusetts Institute of Technology

Research Scientist (2009) at the Picower Institute – Massachusetts Institute of Technology

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Keywords

Neurophysiology · Behavior · Optogenetics and Chemogenetics

Explaining how billions of neurons connected trillions of times generate mental functions remains one of the greatest tasks science faces today. One such function, declarative memory, involves the association and storage of information from distinct brain regions, orchestrated by a medial temporal structure called the hippocampus, through a mechanism called activity-dependent neural plasticity. Research on the mechanisms of memory has focused primarily on the physiology of memory circuits, and less so on the way sensory information is integrated in memory, or on how is memory used for other brain functions.

Our research aims to understand the way memory circuits integrate incoming sensory information, and how the brain governs the use of memory for other brain functions. We will make use of recently developed technologies, chemo- -and optogenetics, to address causal relations between physiology and behaviour, while recording activity from multiple single-neurons, during active behaviour and sleep.

By investigating how is primary sensory information integrated in memory networks, and how are memories “read” to inform decisions, our research will shed light on diverse, socially pervasive, mental diseases arising from the disruption of such mechanisms.

— Remondes M and Wilson M (2013), **Cingulate-Hippocampus Coherence and Trajectory Coding in a Sequential Choice Task** *Neuron,* **80**(5), 1277-1289.

1· The MRemondes Lab develops joint neural recordings, chemo- and optogenetics, neural manipulation achieved by ligand- or light-activation of membrane proteins, to investigate mechanistically the neural processing of sensory information, and the way this information is transferred within the brain, in the awake-behaving rodent. This knowledge will eventually be applied to explain the bases of neurological and psychiatric disease.

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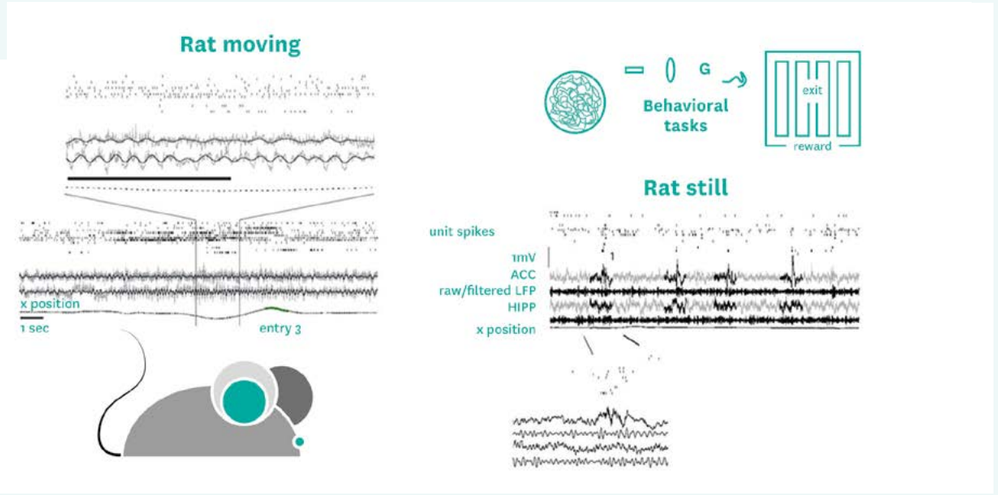

Saldanha, Carlota

Carlota Saldanha :
Group leader at iMM Lisboa since 2008

PhD (1986) in Biochemistry (Cellular Physiology) at Universidade Nova de Lisboa

Master(2000) in Medical Education joint degree at University of Wales and University of Lisbon Associate

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Keywords

Inflammation · Microcirculation · Neutrophil · Erythrocyte · Leukocyte recruitment · Inflammation · Hemorheology · Microcirculation

Inflammation is part of the immune response elicited towards an injury or infection to eliminate the inflammatory agent and recover the normal tissue function. Pivotal for the comprehension of the mechanisms underlying inflammation is the understanding of how leukocyte recruitment is governed and regulated.

Our main research interests focuses on i) the molecular partners targeted by fibrinogen in neutrophil action and how chemokines and hydrogen peroxide cooperate in neutrophil recruitment; ii) simulation models of the leukocyte-vascular wall interface; and iii) the study of fibrinogen-mediated signal transduction on erythrocytes bioavailability of nitric oxide and the validation of inflammatory biomarkers in vascular diseases. We expect to translate our findings towards a better understanding and management of inflammatory pathologies, like sepsis and cardiovascular diseases.

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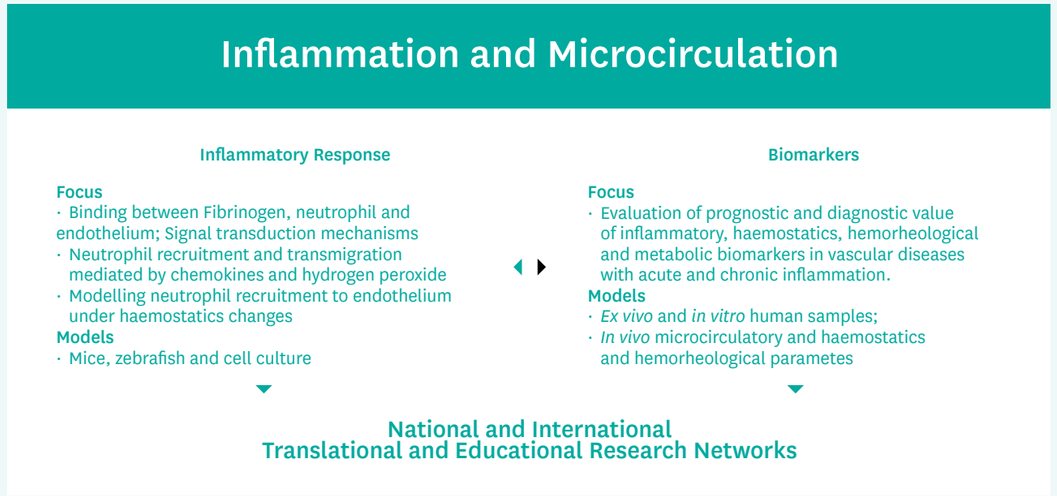
1· Representation of the current research lines in inflammation of our lab

1·



Santos, Nuno C.

Nuno C. Santos :
Group Leader at iMM Lisboa since 2008

PhD (1999) at Universidade de Lisboa

Research at the Universidade Técnica de Lisboa and at the University of California, Santa Barbara (USA)

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Keywords

Membranes · HIV and Dengue Virus · Peptide-based therapies (antiviral peptides · AMPs · CPPs) · Atomic Force Microscopy (AFM) · Fibrinogen · Nanomedicine

The biochemical and biophysical processes occurring in membranes of human cells, as well as of their viral and bacterial pathogens are key factors involved in a variety of pathological conditions.

Our research is focused on i) the study of two steps of the enveloped viruses life cycle (mainly HIV-1 and dengue virus) that involve biomembranes – the entrance of the virus or its content into the target cell and the assembly of new virions; ii) study of the binding of fibrinogen to the erythrocyte membrane and its relevance as cardiovascular risk factor; and iii) pre-clinical evaluation of the membrane activity and mechanism of action of antimicrobial peptides (AMP) and cell-penetrating peptides (CPP). Additionally,on the Nanomedicine area, we work on the development of innovative protein-ligand interactions biosensor systems, with improved selectivity and sensitivity (nanoparticles and amyloid-based biosensors). Our findings will contribute for the identification of new drug targets, therapeutic strategies and/or diagnostic methods for important human pathologies, such as cardiovascular diseases, HIV/AIDS and dengue.

— Augusto MT, Hollmann A, Castanho MARB, Porotto M, Pessi A, Santos NC (2014), **Improvement of the HIV fusion inhibitor C34 efficacy by membrane anchoring and enhanced exposure.** *J.* Antimicrob. *Chemother.* **69**, 1286-1297.

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1· Major research projects ongoing at Nsantos lab.
A – Studying fibrinogen-erythrocyte interactions in cardiovascular diseases;
B - Dengue virus capsid protein: towards a novel drug target;
C - Understanding the mechanism of action of HIV-fusion inhibitors;
D – The potential therapeutic use of new antimicrobial agents.

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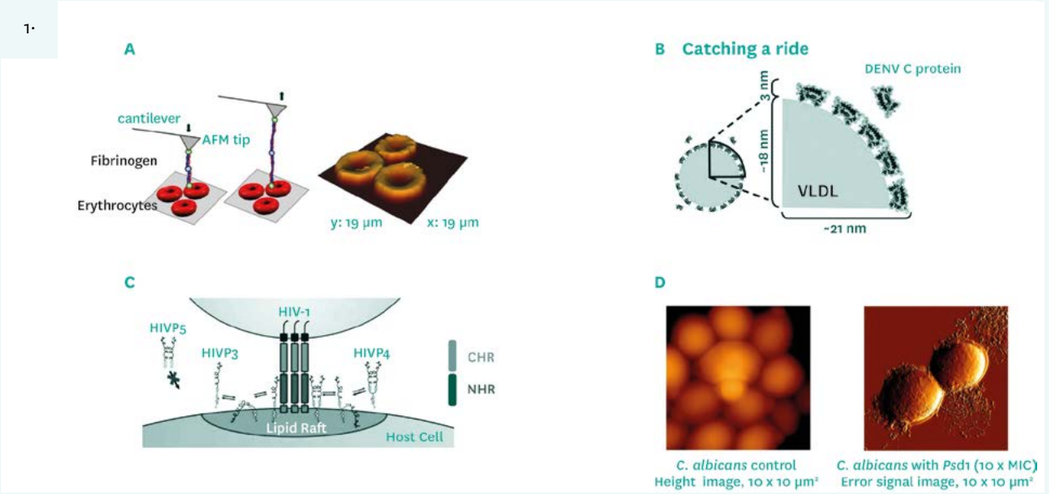

Saúde, Leonor

Leonor Saúde :
Group Leader at iMM Lisboa since 2007

PhD (2001) in Developmental Biology at University College London, UK

Post-doctoral research at Instituto Gulbenkian de Ciência (IGC)

Group Leader at IGC (2005-07)

Invited Auxiliary Professor at Faculdade de Medicina da Universidade de Lisboa

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Keywords

Left-right asymmetry · Somite formation · Tissue/organ regeneration

A fascinating question in biomedicine is how a single cell, the fertilized egg, differentiates into a variety of cell types in their correct positions allowing the formation of impeccably allocated organs, that constitute a perfect body.

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

We expect our research to help uncover the etiology of human disorders such as congenital heart and vertebrae malformation as well as contribute to new therapeutic strategies for human neuronal diseases based on the ability to generate long-term persisting neurons and glial cells after lesion.

— Mendes RV, Martins GG, Martins AM and Saúde L. (2014) **N-cadherin locks left-right asymmetry by ending the leftward movement of Hensen's node cells,** *Developmental Cell* **30**(3), 353-60.

— Fior R, Maxwell AA, Ma TP, Vezzaro A, Moens CB, Amacher SL, Lewis J. and Saúde L. (2012), **Differentiation and movement of presomitic mesoderm progenitor cells are both controlled by Mesogenin1,** *Development* **139**(24), 4656-65.

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1· The zebrafish is an important vertebrate model to dissect mechanisms of development and regeneration.

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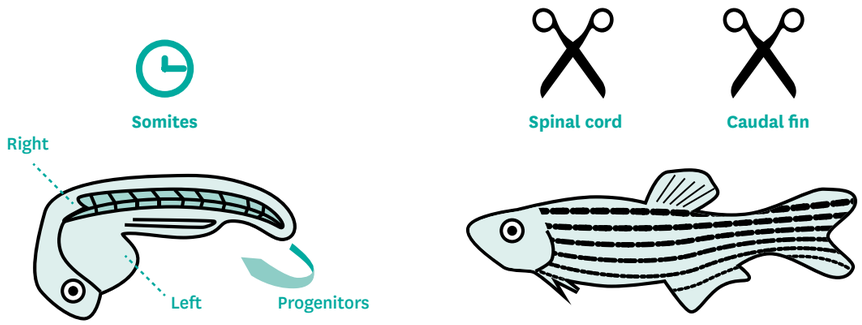

Sebastião, Ana

Ana Sebastião :
Group Leader at iMM Lisboa since 2003

PhD (1987) in Cell Physiology, Universidade Nova de Lisboa

Pos-Doctoral research at Instituto Gulbenkian de Ciências, Oeiras

Full Professor at Faculdade de Medicina da Universidade de Lisboa

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Keywords

Tripartite synapse mechanisms · Neuronal excitation/ inhibition balance · Neurodegenerative Mechanisms · Ageing · Epilepsy · Drug Abuse

Neurological and neuropsychiatric diseases constitute a main challenge to Neurosciences representing an overwhelming social and economic load. The growing awareness that although cells and circuits may differ for each disease, common principles of synaptic, cellular and network dysfunctions are highly comparable providing new possibilities to apply knowledge related to one disease to another.

We aim to elucidate how the neuronal and glial components of the tripartite synapse are fine-tuned under normal and dysfunctional situations. How endogenous modulators affect the pre-post and glial components of the tripartite synapse, neuronal excitability, neuronal and glial cell renewal, neuronal and glial maturation and degeneration, under normal and pathological conditions.

Understanding these processes will most probably lead to the emergence of rational therapies to socially burning diseases including the ones we use as model diseases namely, Alzheimer's and Parkinson's disease, epilepsy, amyotrophic lateral sclerosis and multiple sclerosis.

— Rombo DM, Dias RB, Duarte ST, Ribeiro JA, Lamsa KP, Sebastião AM (2014), **Adenosine A1 receptor suppresses Tonic GABAA receptor currents in hippocampal pyramidal cells and in a defined subpopulation of interneurons,** *Cereb Cortex*.

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1· Glutamatergic (figure), GABAergic and Cholinergic transmission are major focus. Besides electrophysiological approaches (Figure Insets) molecular, cellular and integrated approaches are used. Programme lines aim to cover questions from molecules to behaviour.

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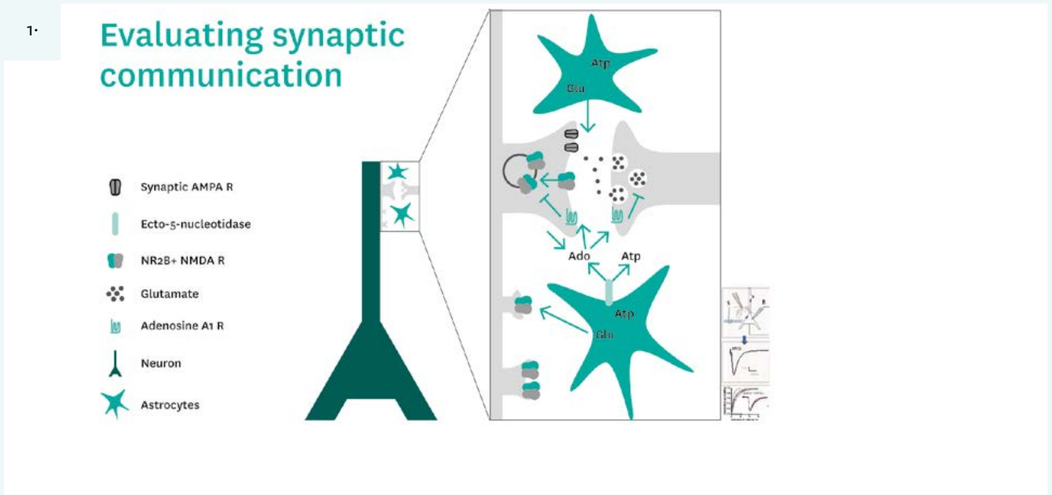

Silva-Santos, Bruno

Bruno Silva-Santos :
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PhD (2002) in Immunology at University College London, UK

Post-Doctoral (2002-2005) research at King's College London, UK

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Keywords

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

T lymphocytes are white blood cells that evolved to protect vertebrate hosts from infectious microorganisms. However, as their "dark side", T lymphocytes are a major cause of allergy, autoimmunity and transplant rejection.

Our research focuses on the biology of T lymphocytes and their key roles in immunity to infection and cancer. We investigate differentiation and activation signals for T cells in the mouse system, which provides crucial in vivo models for infectious (such as malaria) and autoimmune diseases. We also study human peripheral blood T cells and, in particular, their recognition and elimination of lymphomas and leukemias.

Overall, we envisage the identification of molecular mechanisms involved in the differentiation, activation and function of T cells, aiming towards the design of new treatments for cancer, on the one hand, and (auto)immune disorders, on the other.

1· Our work has shown that gamma-delta T cells differentiate into two distinct subsets in the murine thymus, which segregate with CD27 expression and produce either interferon-gamma or interleukin-17. These subsets can play strikingly opposing roles in tumor progression: whereas CD27+ gamma-delta T cells promote tumor eradication, their CD27- IL-17+ counterparts promote inflammation, angiogenesis and ultimately tumor growth.

— Rei M, Gonçalves-Sousa N, Lança T, Thompson RG, Mensurado S, Balkwill FR, Kulbe H, Pennington DJ and Silva-Santos B (2014), **Murine CD27(-) V γ6(+)γδ T cells producing IL-17A promote ovarian cancer growth via mobilization of protumor small peritoneal macrophages.** *Proc Natl Acad Sci U S A* **111,** (34), E3562-70.

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

— 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.

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

*Co-first Authors; **Co-senior Authors

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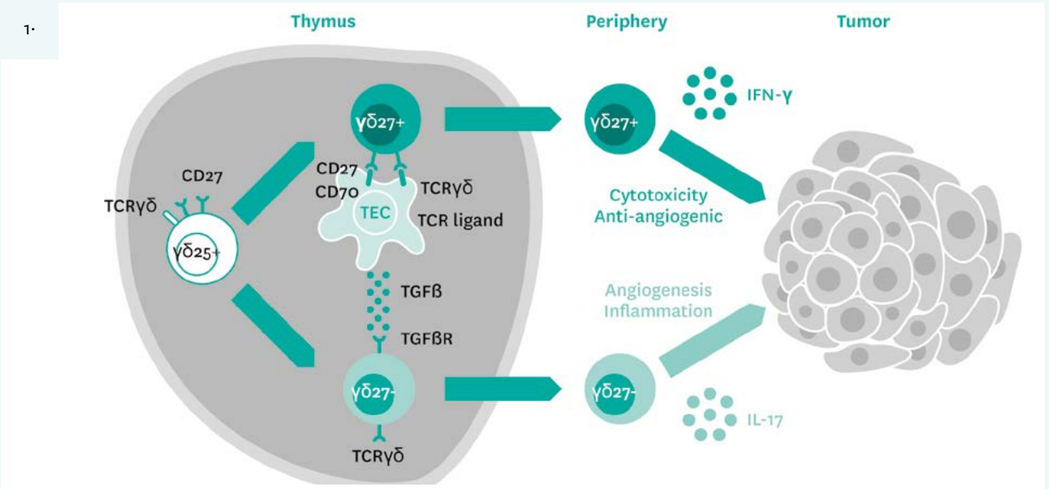

Simas, Pedro

Pedro Simas :
Group Leader at iMM Lisboa since 2004

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)

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Keywords

Herpes virus · B lymphocytes · E3 ubiquitin ligase · Kaposi sarcoma herpesvirus (KSHV) · B cell and Lymphomas · MuHV-4 and animal model of infection

Viruses are obligatory intracellular parasites that cause important diseases in humans.

Our laboratory is currently focused on a single protein, kLANA, of a major human tumorigenic virus, Kaposi´s sarcoma associated herpesvirus (KSHV). KSHV is the etiologic agent of Kaposi's Sarcoma (KS) and primary effusion lymphoma. kLANA mediates KSHV episome persistence in latently infected tumour cells. kLANA is central to latent infection and tumor cell viability.

Our strategy lies on the development of an innovative model system to disrupt kLANA function in vivo and eradicate virus latent infection hence associated tumours. We are using murid herpesvirus 4 (MuHV-4), which is genetically related to KSHV and infects laboratory mice, to create a chimera virus encoding kLANA in place of the endogenous MuHV-4 mLANA.

The rational design of molecules that will interfere with viral replication in the unique setting of a mouse model of infection has great potential for therapeutic strategies in the treatment of γ-herpesviruses associated diseases such as lymphomas.

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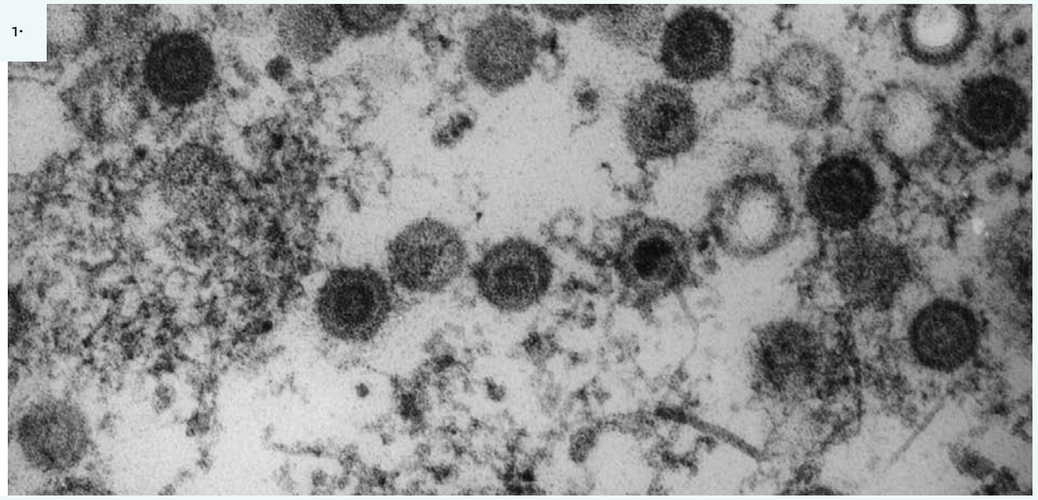
*corresponding authors

1· Herpes Virus (MuHV-4) in infected cells visualized by electron microscopy.

1·



Sousa, Ana E.

Ana E. Sousa :
Group Leader at iMM Lisboa since 2003

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

Investigator and Associate Professor at FMUL

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Keywords

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

The maintenance of a competent immune system is essential for health. Thus, understanding the mechanisms underlying immunodeficiency and the identification of new strategies for immunological reconstitution are essential for clinical practice.

Our research focuses on human T cell homeostasis and immune regulation, with an important part of our efforts centered on primary immunodeficiency and on HIV/AIDS immunopathogenesis, mainly through the study of HIV-2 infection, a naturally attenuated form of acquired immunodeficiency.

We expect that our research will translate into innovative immune-based therapeutic strategies particularly relevant in the areas of chronic infection, autoimmunity, and transplantation.

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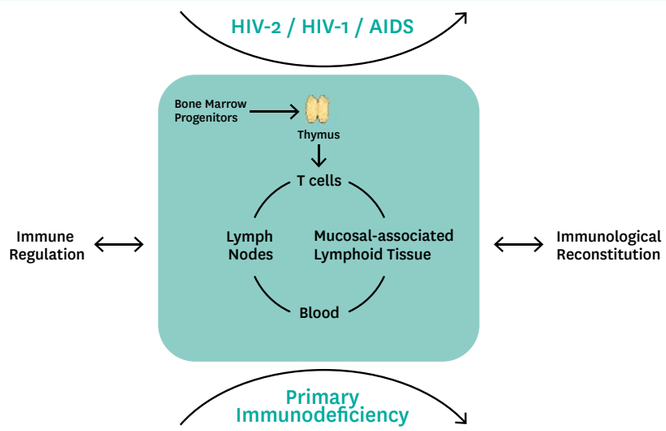
1· T cell homeostasis, human immunodeficiency, and immune reconstitution

1·



Veiga-Fernandes, Henrique

Henrique Veiga-Fernandes :
Group Leader at iMM Lisboa since 2008

PhD (2002) in Molecular and Cell Biology at Université Rene Descartes Paris V, France

Post-doctoral research at Institut Necker, France and NIMR, UK

Senior investigator scientist at NIMR, UK (2006-08)

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Keywords

Lymphoid organogenesis · Haematopoiesis · Innate Lymphoid Cells · Lymphocyte function

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 unexplored.

Our research is centered on novel communication pathways that determine immune cell fate and disease progression in the context of lymphoid organogenesis and lymphoid cell development and function.

Increased knowledge on these regulatory mechanisms is likely to pave the way for new therapeutic strategies in immune mediated diseases that are major Public Health concerns.

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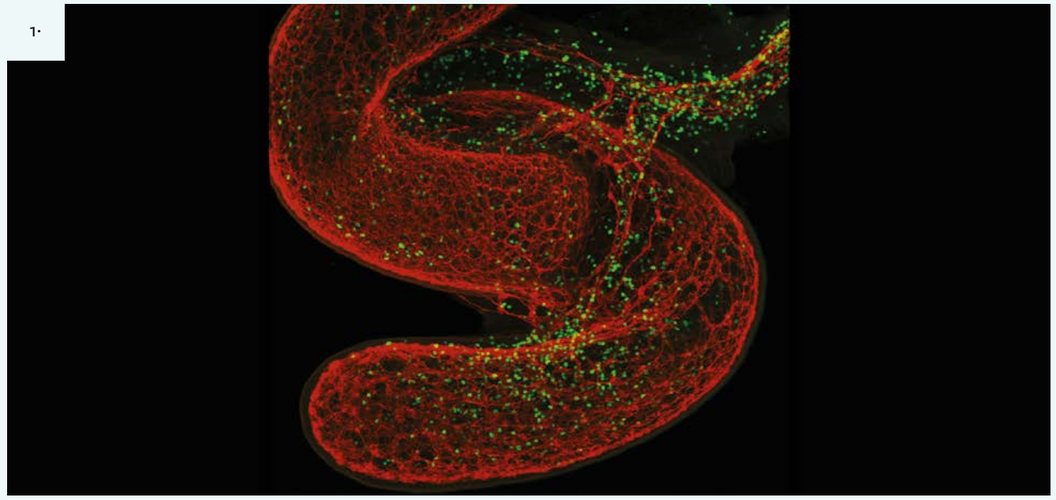
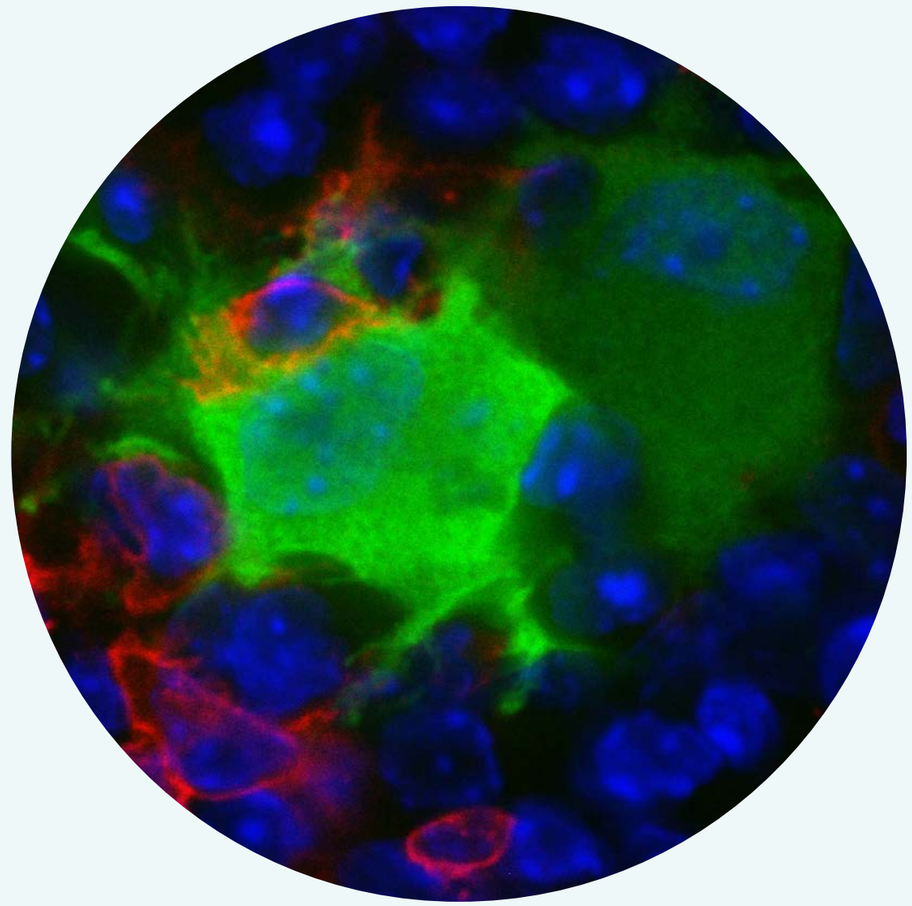
1· Fetal intestine. Red: neurons; Green: innate lymphoid cells

1·



Technical Facilities



Infection of germinal centre B cells by a murid gammaherpesvirus-4 (MuHV-4) expressing green fluorescent protein.
This experiment demonstrated that infection by MuHV-4 in B cells is not a stochastic event as neighbouring GC B cells of hen egg lysozyme (red cells) are not infected. Photo by Pedro Simas Lab.

Animal Facility

Joana Marques PhD | Head of facility
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The rodent facility of the iMM Lisboa aims to support state-of-the-art animal research. For that purpose we provide the best housing and care of laboratory rodents and support training and education in Laboratory Animal Science.

Zebra Fish Facility

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Provide a fully functional facility to be used by the iMM Lisboa research Labs. Provide technical assistance to facilitate the use of zebrafish in a wide range of experimentation sets.

Biobank

Sérgio Dias, PhD and
Joaquim Polido Pereira, MD, PhD |
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In the early years of Biobanco-IMM CAML several priorities were established, such as communication (through the society and scientific partners), expanding collections, promoting collaborations and standardizing procedures. One of our major goals is promote the collections with added value. Our control collection represents 70% of the samples requested in the last year. Biobanco-IMM Lisboa CAML aims to achieve sustainable growth, focused on improving quality, not only in samples but also in data management. We are working on several aspects of serum and DNA quality control parameters. Other strategic goals are to promote national biobanking networking with standardized procedures and established synergies as well as international integration of biobanking networks.

Bioimaging

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

Biosafety Level 3 Laboratory

Miguel Prudêncio PhD | Head of facility
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The iMM Lisboa houses a 70 m2 BSL3 Facility meeting the highest safety standards as defined by European and International guidelines. The purpose of this facility is to enable researchers to carry out work with infectious agents that require BSL3 containment conditions, including research that involves rodent models. The Facility is available to iMM Lisboa internal and affiliated researchers, as well as to external researchers from academia, pharma and biotech. All work to be carried out in the BSL3 Lab must follow the established SOPs, as defined in the Facility's Rules and Guidelines Manual. The iMM Lisboa's BSL3 Facility comprises two fully equipped tissue culture rooms and one animal experimentation room for rodents. Available equipment includes incubators, benchtop centrifuges, refrigerators and freezers, microscopes, a -80 freezer, and an ultracentrifuge.

Flow Cytometry

Ana Vieira | Facility Manager
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The Flow Cytometry is a core facility that provides support and training to iMM Lisboa and external researchers who require this technology in their research projects. The Unit is currently equipped with 3 cell analysers (1 FACSCalibur and 2 BD LSR Fortessa) and 2 cell sorters (FACSAria I and FACSAria III). One LSR Fortessa is equipped with High Throughput Sampler (HTS), which allows the automated acquisition of samples from 96 and 384 well plates.
A substantial part of our work is to provide training in flow cytometry concepts, experiment planning, experimental controls, instrument operation and data analysis. UCF staff further ensures quality control and maintenance procedures on all instruments and the implementation of the Quality Management System, according to ISO 9000.

Histology and Comparative Pathology Laboratory

Tânia Gilot Mendes de Carvalho Barão PhD | Head of facility
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The Histology and Comparative Pathology Laboratory aims at providing histology and comparative pathology support to iMM Lisboa scientists investigating animal models of human disease, and scientists/physicians investigating human disease. Services are also available for extramural investigators. Services include Histology (tissue processing for paraffin-embedding; gelatin/OCT-embedding and cryosectioning; histochemistry), iMM Lisboaunohistochemistry, Transmission Electron Microscopy and Veterinary Pathology . We also provide assistance in study design and procedural training for researchers (necropsy, tissue harvesting).

Information Systems

José Braga PhD | Head of facility
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The Information Systems mission is to help researchers reach their maximum productivity by using adequate

Information Technology resources. Our aims are:
1. Provide state-of-the-art information technology infrastructure and support services.
2. Contribute significantly to improve productivity of researchers and research outcomes.
3. Facilitate and optimize management business processes.

The Information Systems intervenes mainly in the following areas:
1. Information Technology (IT) support to iMM Lisboa users.
2. Planning, implementation and maintenance of the infrastructure to store, process and protect research data.
3. Design, implement and integrate information systems to facilitate scientific and management processes.

Quality and Safety in Laboratory

Alexandra Maralhas | Head of facility
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Quality and Safety in Laboratory is divided in three different areas, each one dedicated to improve the quality of research of the Institute and comply with National and International guidelines and best practices. The Washing Room is responsible for the cleaning and sterilization of lab material, both common and specific of all research units. The Purchasing Office centralizes all the Institute acquisitions, namely products, services and equipments and provides important information related to prices and ongoing promotions to all research units. The Lab Management is responsible for the adequate selection and installation of new equipment, the preventive and corrective maintenance of common equipment; design/renewal of laboratory infrastructures; advisory and authority regarding safety with products, equipment and infrastructure.

Administrative Facilities

Communication

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

Management

Margarida Pinto Gago | Head of facility
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iMM legal, Human Resources and general administrative and financial matters: - Accounts –iMM statutory accounts and tax returns; cost accounting; - Projects management - from contractual start until final report submission; related support to researchers; - Human Resources - contracts and salaries; performance assessment - Legal – Institutional and researchers support: namely on intellectual property and consortium agreements; - Quality Management System - General Administrative and financial support The Management also gives support to the Executive Director and the other Statutory Boards in relation to organizational issues, inter-institutional collaborations, financial and budget management strategy.

Education & Advanced Training

Sónia Arroz | Training Officer
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General Aim: Provide training opportunities for success in science to researchers at different stages in their careers. Ongoing Activities: · Ensure full running of ongoing PhD (CAML, LisbonBioMed) and Postdoctoral Programs: Launch Calls; Administrative execution; Managerial Support to PhD and Postdoctoral fellows activities; Support PhD and Postdoctoral Fellows throughout their training. Update UEFA Webpages within new iMM site. · Run Advanced Courses, scheduled upon CAML & LisbonBioMed Scientific Boards approval; cover all organizational aspects. New Programs: · Launch & implementation of Mindthegap- Postdoctoral Training Program approved for funding under Marie Curie Actions; · Join EMBL- lead international consortium for Horizon 2020 application: outreach as post-graduate training.

Funding Programs

Ana Filipa Nunes PhD | Head of facility
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Initially created in 2008 the Funding Programs Office was restructured in February 2013. It facilitates and streamlines every step of the pre-award process, including grant preparation, submission, and contract negotiation, in compliance with institutional, government and sponsor policies and regulations. In addition, the Office acts as liaison with academia, enterprises and other organizations for the development of strategic collaborations. Our specific goals include:

i) promote a service of funding opportunities tailor-made for iMM researchers;
ii) prepare institutional grant applications;
iii) promote academic/entrepreneurial scientific collaborations underpinning the establishment of national/ international grant applications;
iv) promote partnerships with companies and explore relevant financial opportunities;
v) assist obtaining funding for entrepreneurial projects.

Ongoing Partnership

Centro Académico de Medicina de Lisboa

Centro Académico de Medicina de Lisboa (CAML): iMM Lisboa is associated with the Faculdade de Medicina da Universidade de Lisboa and with the Santa Maria teaching hospital through the Medical Academic Centre of Lisbon (CAML). CAML is consortium that represents an infrastructure aiming to promote the academic dimension in clinical practice, renewing the teaching hospital concept.

Genomed · Technophage · Lymphact · TcLab

iMM Lisboa fosters scientific ideas to turn into products and technologies that make difference in health care. To achieve this goal IMM develops ties and strategic plans with companies, namely companies incubated at iMM Lisboa: Genomed, Technophage, Lymphact and TcLab.

Harvard Medical School – Portugal

iMM Lisboa is also a partner of the **Harvard Medical School – Portugal** programme, sponsored by Fundação para a Ciência e Tecnologia. This programme, directed by M. Carmo-Fonseca (iMM Lisboa/FMUL), results from a Memorandum of Understanding between Portuguese Ministry of Science, Technology and Higher Education and Harvard Medical School to encourage internationalization and cooperation between Portuguese schools of medicine and major national research centers working in biomedical and health sciences.

iMM Lisboa is associated with the Doctoral Programme for Physicians, PFMA, supported by the Gulbenkian and Champalimaud Foundations, the Ministry of Health and the Foundation for Science and Technology.

Health Cluster Portugal

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

Institutional Partnership

www.bayer.com

www.smd.qmul.ac.uk

www.biogen.com

www.bms.com

www.celgene.com

www.embo.org

www.janssen.pt

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