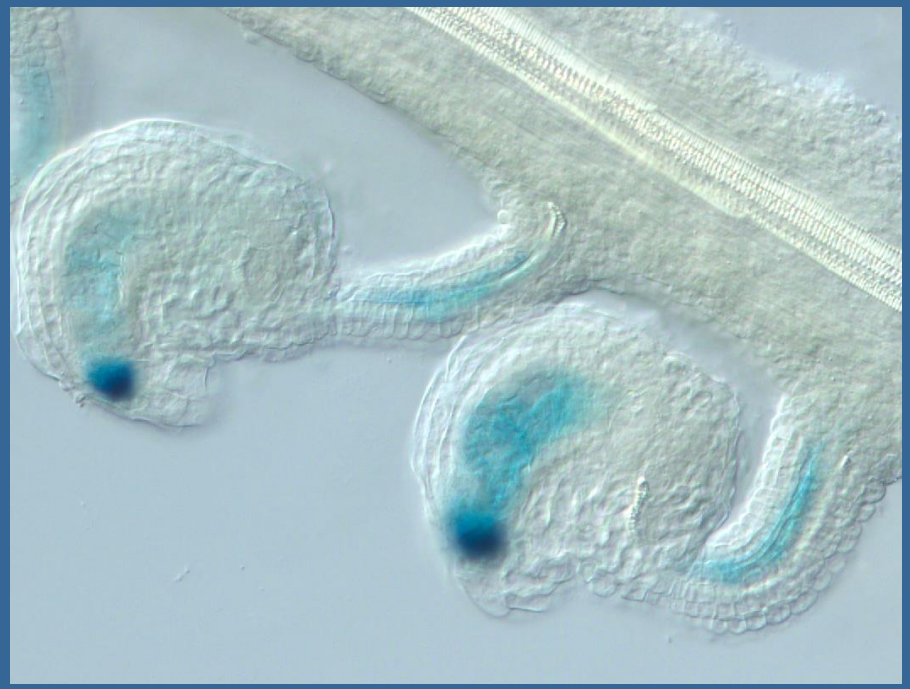

BioISI

Biosystems & Integrative Sciences Institute

Report 2016

Biosystems and Integrative Sciences Institute

Ciências ULisboa

Front Page Figure - The GUS activity in*ckx7:gus* single mutant Arabidopsis plants. Expression domains of the *CKX7* gene were examined by histochemical localization of ß-glucuronidase activity in trangenic plants expressing the GUS reporter gene under the control of the *CKX7* promoter gene. *AtCKX7:GUS* was expressed in the mature embryo sac with the highest activity associated with the synergids.
Provided by Ana Lopes, PFG Group - UPorto

Contents

BioISI Identification

Name of the Research Unit: Biosystems & Integrative Sciences Institute

Unit Acronym: BioISI

Scientific Director: Margarida D. Amaral

Scientific Areas:

Multidisciplinary/Interdisciplinary Research

Life and Health Sciences	Biomedicine
Exact Sciences & Engineering	Physics
Natural Science & Environment	Bio-based Product Technology or Food Sciences

Profile of the Research Unit

- Basic Research: 75%
- Applied research: 25%

Keywords

Molecular Systems Biology	Integrative Sciences
Agent and Systems Modelling	Biological Physics

Total Funding: 3 499 766 € (583 294 €/yr)

FCT Evaluation (2014): 24/25 - Excellent

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Introduction

BioISI[1] was officially created as a new institute in January 2015 with the vision of pursuing cutting-edge research on biosystems and integrative sciences so as to become the leading centre at the forefront of research in this area not just in Portugal but also internationally. By gathering scientists from bio-, physics and computational sciences, **BioISI** benefits from a unique environment for multidisciplinary research. The main focus of **BioISI** research is thus to understand biological systems using integrative approaches to address emergent complex problems in Biology and Medicine and thus contribute to solve societal challenges related to human health and biotechnology.

The Institute's missions however, extend beyond research across its five sites (BioISI is also located at INSA[2], as well as Universities of Porto, Minho, and Trás-os Montes, besides at the managing institution - FCUL[3]). Indeed, **BioISI** provides **research infrastructures** to its members through its facilities for bioimaging, physics, computing, mammalian cell culture, plant house, etc. **BioISI** also contributes to **advanced training**, as it hosts the multidisciplinary **BioSys PhD programme**[4] on *Biological Systems, Functional & Integrative Genomics* which already counts with 44 enrolled PhD students, it participates in three more PhD programmes (DAEPHYS - on Applied & Engineering Physics, EnviHealth&Co - on Environmental Health and AEM - on Applied and Environmental Microbiology) and it launched in 2016 a **BioISI post-doc programme**, besides its continuous mentoring of young PIs to establish themselves independently. **BioISI** offers advanced training to external visitors in the scope of collaborations or to use its facilities and through the organization of international workshops. **Technology development** is another key mission of **BioISI** through the joint research of physicists and computational scientists working together with biologists to develop new instruments and technologies (e.g., innovative atomic force microscopy for bio-applications, biodevices to monitor biozards or to assess biomedical biomarkers or software generation for the life sciences). Finally, **BioISI** drives innovation through **technology transfer (KTT)** – as a significant proportion (25%) of **BioISI** activities are on applied research on a tight interaction with the socio-economic environment, at the level of both established companies and start-ups.

The 108 fully integrated members of **BioISI** come from different scientific backgrounds: Molecular and Cell Biology, Genetics, Biomedicine, Biochemistry, Microbiology, Plant Biology, Biophysics, Soft Matter Physics, Computational Sciences and Bioinformatics. The synergy and integration of researchers with complementary expertise from different disciplines at **BioISI** fosters creative thinking to solve problems through integrative approaches and creates a truly interdisciplinary and collaborative environment – a distinctive feature of **BioISI** – that provides an exciting environment for young creative scientists: MSc and PhD students from BioSys, post-docs – namely from the new post-doc-programme

[1] http://bioisi.ciencias.ulisboa.pt/
[2] Portuguese National Institute of Health, a State Laboratory of the Ministry of Health (www.insa.pt/sites/INSA/English)
[3] FCUL – Faculty of Sciences, the University of Lisboa (http://ciencias.ulisboa.pt/en)
[4] [4] http://biosys.campus.ciencias.ulisboa.pt/

and also young PIs who, together with the BioISI interdisciplinary projects programme (launched in 2016) constitute a valuable "cement" that strongly contributes to consubstantiate common interests. These multidisciplinary research results in significant scientific outputs and contribute to improve human health, solve biotechnological questions as well as to create novel instruments, so as to keep the country at the forefront of innovation, while generating new economic opportunities.

In order to keep up with the rapid technological progresses and breakthroughs so as to achieve its ambitious goals, **BioISI** maintains key collaborations – throught networking and partnerships – with top international institutions, namely through: promotion of collaborative projects; co-supervision of PhD students and post-docs; updating in technology advances by organizing hands-on courses; and by accessing their cutting-edge facilities. This is an excellent way of internationalizing Portuguese science and of setting very high standards for a national research institution.

The dissemination of **BioISI** activities are carried out by the **BioISI Communications & Outreach Office** (BioISI-Com) which organizes BioISI seminars and BioISI dissemination events (European Researcher's night, Science & Technology week, interactions with schools, etc). It also works tightly with FCUL press office to disseminate BioISI's activities, major achievements and prizes of its researchers, etc.

For its interactions with industry and KTT activities, **BioISI Company Liaison Office** (BioISI-Tech) collaborates with TecLabs[5], FCUL's organization for the creation and economic valorising of scientific knowledge.

FFCUL[6] has acted as the legal front institution of **BioISI** (as of most FCUL's research centres) by supporting R&D activities with financial and administrative management of projects. In 2017 this will change its legal status from being a public to a private institution (FCiencias.ID) so as to lessen the administrative burden of its operational procedures. Despite its substantial long-term benefit, this change will impose significant challenges ahead in the short-term (namely in 2017) for theirs research centres.

The present report provides a concise overview of the research which **BioISI**'s 8 large research groups, supported by **BioISI**'s facilities, have conducted in 2016 along its 4 major Thematic Lines – **Biomedicine, Biotechnology, Biophysics and Bioinformatics** – to comprehensively understand the underlying principles and mechanisms of living systems from single molecules, through cells and tissues, to entire organisms. We believe that the integrative research already conducted during its 2 years of operation have set the stage to route **BioISI** science into the next level and leave us to be optimistic about its future.

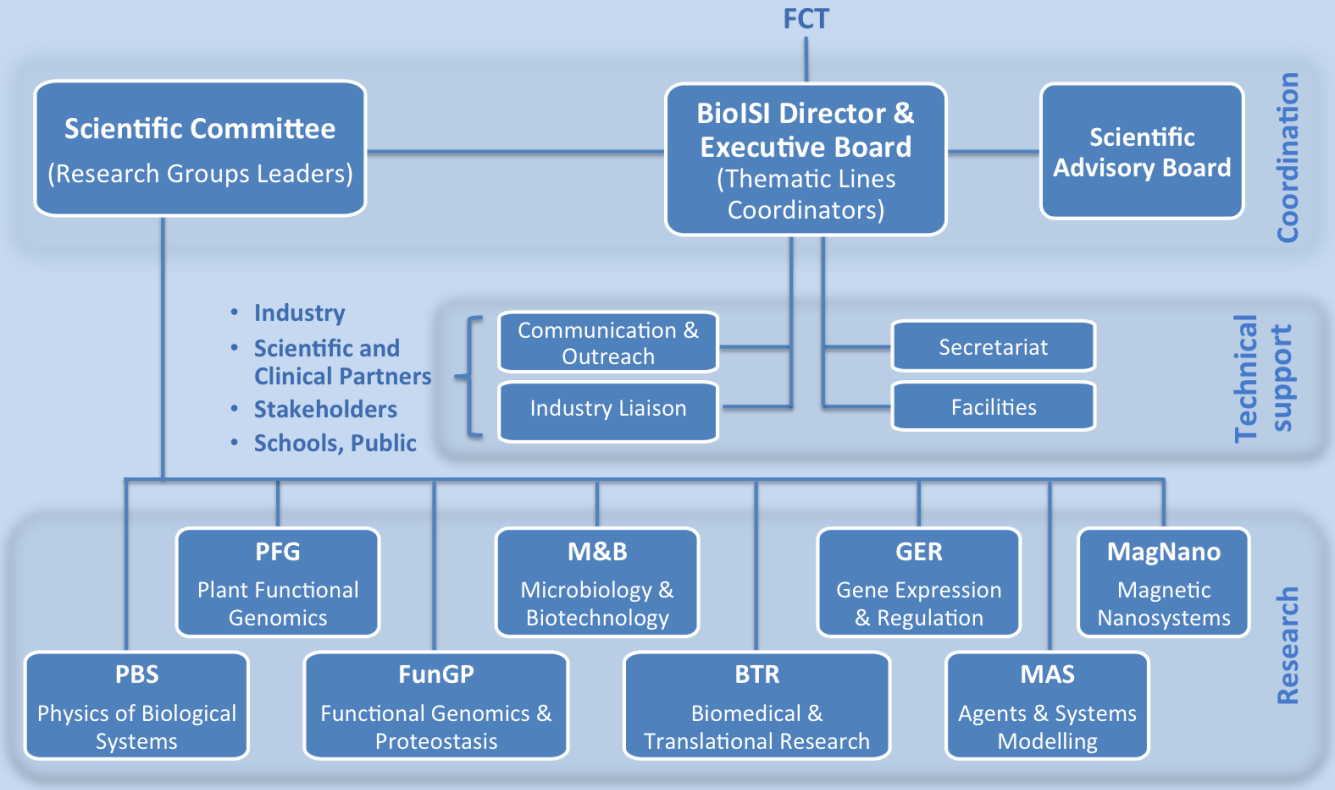
At a time of balance we also want to thank **BioISI's** Scientific Advisory Board (SAB) for critically evaluating our research, and for helping us guiding our progress.

Margarida Amaral
BioISI Director

[5] http://www.teclabs.pt
[6] Foundation of FCUL (http://ciencias.ulisboa.pt/pt/fundação-da-fcul)




BioISI Organization



Scientific Advisory Board:

Rainer Pepperkok (Molecular & Cell Biology). EMBL- European Molecular Biology Laboratory, Heidelberg (Germany)

Lothar Willmitzer (Plant Molecular and Cell Biology). Max-Planck Institute for Molecular Plant Physiology, Potsdam (Germany)

Juan Valcarcel Juarez (Genomics and Systems). CRG-Centre de Regulacio Genomica & ICREA, Barcelona (Spain)

Michael Gill (Systems Medicine). Institute of Molecular Medicine, Trinity College Health Sciences Centre,Dublin (Ireland)

Eugene Shakhnovich (Physics). Biophysics Laboratory, Harvard University, Cambridge (MA, USA)

Dario Floreano (Informatics). EPFL- Laboratory of Intelligent Systems, Lausanne (Switzerland)

Institutions:

FCT Fundação para a Ciência e a Tecnologia
Ciências ULisboa Faculdade de Ciências da Universidade de Lisboa
Instituto Nacional de Saúde Doutor Ricardo Jorge
Universidade do Minho Escola de Ciências
Universidade de Trás-os-Montes e Alto Douro utad

Biomedicine

In the Biomedicine thematic line (TL) of BioISI, biologists work closely together with researchers from other areas (bioinformaticians, physicists, mathematicians) to elucidate the basic mechanisms underlying human diseases at the molecular and cellular levels but also by uncovering genetic and epigenetic determinants of disease.

By using human disease as a starting point, BioISI researchers characterize individual molecular cellular processes – such as protein membrane trafficking, RNA metabolism, signalling, cell differentiation, gene expression or disease-causing gene variants – under physiological and pathological situations.

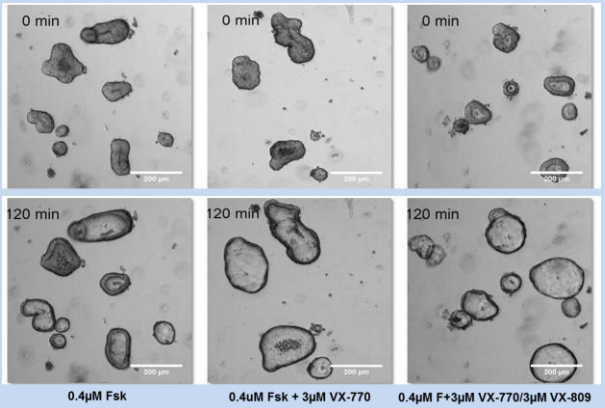


Figure: Forskolin Swelling Assay (FIS) for intestinal organoids from a patient with Cystic Fibrosis

These processes need to be studied as integrated events in the cells, thus requiring innovative and global experimental approaches that enable defining such 'network biology'. Thus, the study of molecular and cellular processes using 'omics', takes a leading place. In parallel, the use of quantitative and modelling methods is essential for the analysis of such large datasets and to generate novel mechanistic hypotheses.

Continuous development of methodologies to answer key questions using omics approaches – such as biological assays and cellular systems for high-throughput microscopy, development of new methods for deep RNAseq data analysis or genomic data mining and computer simulations – are a particular strength of this TL.

Intersection with other TLs. Biomedicine intersects deeply with the mainstream topics of the other BioISI TLs. It shares interests and approaches with Bioinformatics to unravel biological meaning from large datasets. It deeply cooperates with Biophysics for the construction of equipment with new features to solve biological questions but also to develop devices that address biomedical unmet needs. It strongly interacts with Biotechnology namely in sharing methodologies and in finding candidate therapies from unique bioresources.

Institutional cooperation. To keep at the forefront of Biomedical research, BioISI Biomedicine TL keeps key collaborations – through networking and partnerships – with key international institutions (such as EMBL or Karolinska Institute). BioISI researchers also maintain key collaborations with National hospitals and academic clinical centres (namely from the University of Lisboa) which will likely develop into closer partnerships where BioISI will become a member of National Reference Centres for specific diseases (e.g., Cystic Fibrosis).

Facilities. Biomedicine benefits from the facility of high-throughput microscopy – which is currently being reinforced by the acquisition of a confocal high-through put microscope. The establishment of a genomics facility (NGS) is being considered for the next operation period

Future plans:

- To uncover the basic mechanisms underlying human disease.
- To accomplish translational science by providing new diagnosis and prognosis tools as well as innovative therapeutic approaches for the clinic.
- To understand the molecular mechanisms and regulatory networks underlying traffic of membrane proteins related to disease – namely, those regulating physiological ion transport across epithelia – and to use this knowledge to propose novel therapeutic approaches.
- To help elucidate the role of RNA metabolism in disease, and to develop novel diagnostic and therapeutic strategies based on this knowledge.
- To unravel cell signalling mechanisms related to cancer.
- To explain mechanisms of Alzheimer's disease (AD) by in vitro studies of self-assembly and amyloid formation of proteins involved in AD.
- To develop innovative therapeutic strategies, based on tests in patients own cells/tissues towards personalized medicine.

"Flagship" projects: Cystic Fibrosis, Autism

Biotechnology

The research performed in the Biotech-TL is framed by the H2020 key enabling technologies and societal challenges: Health and Wellbeing [Functional foods for disease prevention, environmental rehabilitation, new drugs from marine organisms], food security and sustainable agriculture.

Research was conducted to acquire knowledge and develop modular tool kits that will enable rapid responses to unforeseen challenges, such as the emergence of new plant or diet-related diseases, changes in the distributions of plant pathogens and vectors, the emergence of new environmental conditions or the impact assessment of new bio-based products.

Plant health and crop improvement

Functional characterization of plants with relevant traits, namely those with increased tolerance to biotic (e.g., pest) or abiotic (e.g., temperature, drought, salinity) stress, ripening control and better nutritional characteristics.

Grapevine and cork oak studies are flagship projects for BioISI translational research and benefit from fundamental cutting-edge studies in the model plant *Arabidopsis*.

This key action involved networking activities of M&B (symbiotic and pathogen interaction), MagNano (phenotypic analysis – membrane and cell wall AFM imaging), GER and MAS (for protogenomics and systems networks).

(internal funded projects – "OPTICAL TECHNIQUES FOR THE AUTOMATIC IDENTIFICATION OF FUNGAL INFECTION-RESISTANT GRAPEVINE CULTIVARS" & "Grapevine shotgun proteomics as a tool for the characterization of downy mildew associated resistance traits and improvement of grapevine genome annotation").

Phytoremediation

Functional characterization of plants which are able to concentrate pollutants (e.g. Ni stress). *This involved mapping of signaling pathways and identification of genes expressed in adaptation and survival.*

Marine microbial biotechnology

Omics-based characterization of marine microbes for bioactivity profiles and biochemical extract composition; development of novel bioactives for personal care, therapeutics, and greener industrial processes.

This key action involved High Throughput Microscopy Screening of natural compounds extracts regarding F508del-CFTR traffic rescue with networking activities of M&B and FunGP groups (internal post-doc and funded project – "Natural compounds as a source of novel drug leads for Cystic Fibrosis"). (Fig.1)

Microbial pharmacogenomics

Identification of molecular targets for development of therapeutic compounds and next generation of diagnostics to treat infectious diseases. Determination of mechanisms of action (MoA) based on Biolog phenoarrays; use of yeast genetic systems and their stress-specific transcriptional networks to dissect the effects of stress agents (anti-cancer drugs, irradiation and fungicides) so as to understand their MoAs and potential effects in mammalian systems.

This key action involved networking activities of M&B with MagNano groups concerning evaluation of the effects of antimicrobial compounds at a nanoscale by AFM) (internal funded project – "Magnetic nanoparticles for hyperthermia") (Fig.2)

Wine microbial biotechnology

Development and integrative characterization of adaptive evolved wine yeasts with higher performance and increased stress tolerance, to cope both with new tendencies of reducing wine preservatives and technological processment.

This key action involved networking between M&B, MAS (development of computational pipelines, complex metabolic traits) and MagNano groups - AFM-based characterization of yeast cell physiology and morphology changes in response to stress. (Fig.3)

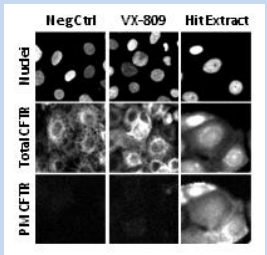


Fig 1.

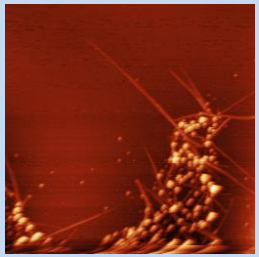
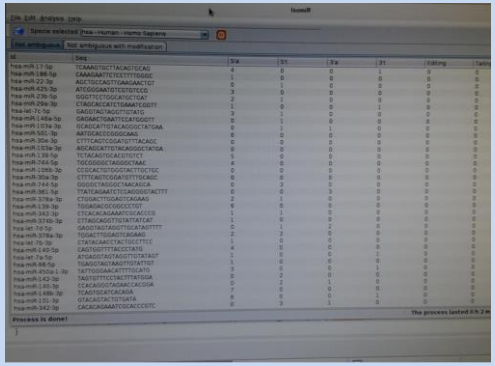


Fig 2

Fig 3.

Bioinformatics

The main scientific goal of BioInformatics thematic line BioInf TL is twofold: to research fundamental properties of bio inspired models and to gather BioISI research around the common goal of cellular processes modelling. BioInf TL aggregates research of BioISI concerning computational models and tools for molecular, biological, biomedical and social systems. The scope of modelling in BioISI is vertical in terms of systems, from the physical basis of biological systems to social organisation of such systems. Agent based modelling and simulation are basic techniques widely used in the BioInf TL. Seven research groups of BioISI have activities that converge into BioInf TL. In common all use numerical and algorithmic models of living systems for which computational implementations are fundamental. In particular, we can identify computer processing activities typical of BioInf TL.



Key Actions:

- Computing & storage common infrastructure set up
- Preprocessing pipelines for data analysis
- Data mining tools and data analysers
- Development of new computational tools to manage, integrate and interpret data

Actions in 2016

A post-doc grant is running (Hugo Martiniano), hopefully for two years, in a joint project of BTR and MAS groups, focusing on Autism Spectrum Disorder Genomic Data Analysis – started: April. Hugo has also been very active in setting up common computing facilities, taking advantage of good quality national (INCD) and european (EGI) infrastructures to which BioISI has access. The usage of common computational infrastructures (national and European) is being exploited as one way of overcoming funding limitations.

Major achievements in flagship projects

Four of the internally launched one year research projects are concerned with BioInf TL: Optigrape, CFTR-Proteins, IsomiR, and Proteograpе. stressing in promoting interdisciplinary research in promising areas. Results obtained are encouraging and the new internal call for projects will try to combine extension of the most relevant ones with funding new ideas.

Biophysics

The Thematic Line Condensed Matter and Biological Physics (CM & BioPHYS) merges the expertise of experimental condensed matter and atomic physicists (MagNano) and theoretical biological physicists (PBS) and takes advantage of the unique research opportunities offered by the multidisciplinary environment of BioISI. The overall goal of this TL is to boost in BioISI and FCUL an interdisciplinary research activity rooted in Physics, based on well-established synergies between Physics, Chemistry, Biology and Engineering.

During 2016, the BioPHYS-TL, focused on the study of selected bio and nanosystems, biomolecules and magnetic nanoparticles, and on nanoscale studies of cells and plants with relevant traits, namely the model plant Arabidopsis, aiming at the detection of morphology changes in response to stress. The research performed within this TL has a potential social and economical impact and is aligned with the H2020 EU Program.

Development and refinement of Atomic Force Microscopy (AFM)/Force Feedback Microscopy (FFM) techniques

Relying on the implementation of AFM/FFM techniques and on the input of the interdisciplinary team the creation of a platform for interdisciplinary research specialized on single molecule experiments is aimed. The research work, in 2016, involved different collaboration activities between MagNano and:
PFG - membrane and cell wall AFM imaging and mechanical properties (Fig 1), M&B - AFM based characterization of yeast cell changes in response to stress (FCT project 2106 – 2019), and FunGP (internal funded project and post-doc) –"Atomic Force Microscopy approaches to study protein self-assemblies & interactions" (see project progress report).

The development of novel simulation approaches to study protein aggregation to unravel the aggregation mechanism of selected proteins with biomedical interest, complemented by FFM measurements

This research line involved: simulation results on CFTR showing that the protein populates a misfolded intermediate state highly enhanced by deletion of residue 508; study of the steric confinement provided by the GroEL chaperonin predicting that environment assists the folding by enhancing the knotting frequency; exploration of the aggregation early stage of the HB2m using an integrative approach framed on molecular simulations (see PBS publications).

The optimization of selected nanostructured magnetic systems aiming at the development of methodologies for magnetic hyperthermia and biosensors for nanodiagnostic

The research work performed on the growth and characterization of magnetotactic bacteria aiming at magnetic hyperthermia applications (internal funded project "Magnetic nanoparticles for hyperthermia") has shown M. magnetotacticum strain DSMZ 3856T bacteria more efficient in producing magnetosomes than M. gryphiswaldense strain DSMZ 6361T, and the existence of very thin crystalline magnetic structures (see project report) (Fig.2)

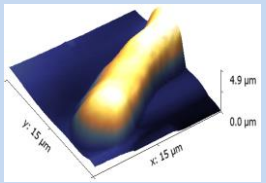


Fig.1 Arabidopsis thaliana pollen tube imaged by AFM

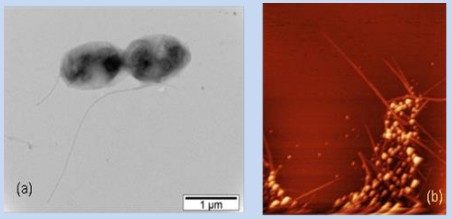


Figure 2: (a) TEM image of two bacteria from strain DSMZ 3856T (b) AFM image of magnetic structures associated with the flagella.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BioISI Projects

BioISI opened a call for projects of 1 year duration. These projects aimed to develop activities strongly related to BioISI Thematic Lines and the Strategic Project 2015-2020. This call required the involvement of PIs from two different BioISI groups from different areas, and were evaluated by their scientific excellence, originality and impact and relation to BioISI strategic programme by the BioISI SAB by the end of 2015.

In 2016 these included 7 projects:

1. Natural compounds as a source of novel drug leads for Cystic Fibrosis
PIs: Hugo M. Botelho | Helena M. Vieira
Thematic Lines involved: Biomedicine | Biotechnology

2. Magnetic nanoparticles for hyperthermia
PIs: Maria Margarida Cruz | Lélia Chambel
Thematic Lines involved: Biophysics | Biotechnology

3. Protein networks stabilizing CFTR at the plasma membrane – an integrated interactomics approach to find novel therapeutic targets in CF
PIs: Peter Jordan, Paulo Matos, Carlos Farinha
Thematic Lines involved: Biomedicine | Bioinformatics

4. Grapevine shotgun proteomics as a tool for the characterization of downy mildew associated resistance traits and improvement of grapevine genome annotation (ProteoGrape)
PIs: Andreia Figueiredo, Andreia J. Amaral
Thematic Lines involved: Biotechnology | Bioinformatics

5. The IsomiR Window: bringing the analysis of sequence complexity of miRNAs and their functional impact to the biomedical community
PIs: Margarida Gama-Carvalho | Beatriz Carmo
Thematic Lines involved: Bioinformatics | Biomedicine

6. Optical techniques for the automatic identification of fungal infection-resistant grapevine cultivars (OPTIGRAPE)
PIs: Jorge Marques da Silva & Pedro Mariano
Thematic Lines involved: Biotechnology | Bioinformatics | Biophysics

7. Atomic Force Microscopy approaches to study protein self-assemblies and interactions
PIs: Cláudio M. Gomes | Mário S Rodrigues
Thematic Lines involved: Biomedicine | Biophysics

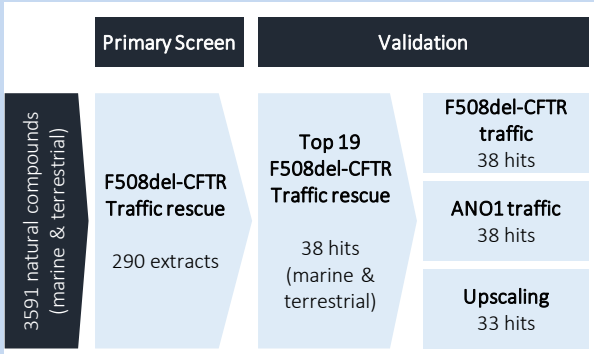
1. Natural compounds as a source of novel drug leads for Cystic Fibrosis

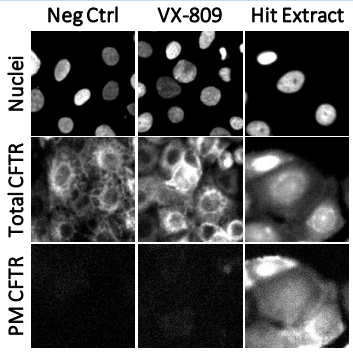
PIs - Hugo M. Botelho | Helena M. Vieira

Biomedicine | Biotechnology

Cystic Fibrosis (CF) is the most common life-shortening rare disease affecting ~85,000 individuals worldwide. CF is caused by mutations in the CFTR gene, encoding an epithelial chloride/bicarbonate channel. Most patients succumb to a progressive lung disease with airway mucus obstruction, bacterial infection and inflammation. About 85% of CF cases are due to F508del, a mutation preventing CFTR traffic to the plasma membrane. Currently, only two drugs are approved for clinical use in CF but most eligible patients only enjoy modest lung function improvement. In this projected we aimed at screening a diverse natural products library (marine & terrestrial origin) to discover improved CFTR modulator leads as well as modulators of the alternative chloride channel ANO1 to improve CF pharmacotherapy.

Results:





Project workflow and sample results

3591 natural compounds were screened with High Throughput Microscopy for F508del-CFTR traffic rescue. 290 extracts significantly increased traffic and were superior to the well established positive control VX-809. The top 19 extracts of each marine and terrestrial organisms were selected for dose response, specificity and toxicity screenings and also for ANO1 traffic screening. Upscalling and re-validation is in process for 33 hit extracts. Shown is total and plasma membrane (PM) CFTR fluorescent labeling in the cell model used in this project.

Conclusion:

33 extracts rescuing F508del-CFTR traffic were selected. Purification of the active compound(s) and testing of their effects over ANO1 is ongoing.

Outputs

Botelho HM (2016) Innovating the search for novel cystic fibrosis therapies using high content microscopy screening. BioISI Post Grad Seminar. October 13

Baptista C (2016) Identification of new natural compounds of high therapeutic potential for Cystic Fibrosis by high-throughput microscopy screens. FunGP/Amaral lab seminar. July 1

2. Magnetic nanoparticles for hyperthermia

PIs - Maria Margarida Cruz | Lélia Chambel

Biophysics | Biotechnology

The project goal is the study of magnetosomes, chains of magnetic nanoparticles surrounded by a biological membrane, produced by magnetotactic bacteria in different conditions. The magnetosomes are anisotropic organized magnetic nanostructures that have high heating efficiencies for hyperthermia. In this project, two bacteria strains were selected for production, 3856 and 6361, the first one being determined to produce a higher fraction of magnetosome containing bacteria. The influence of the environment magnetic field during 3856 bacteria growth on the magnetosomes was explored and their hyperthermia efficiency was determined. Magnetic force microscopy results indicate that flagella can also be magnetic.

Results:

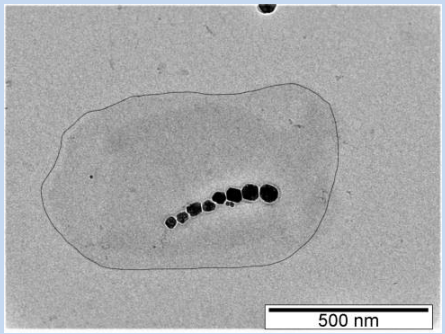


Fig1: TEM image of magnetosomes in DMS 3856.

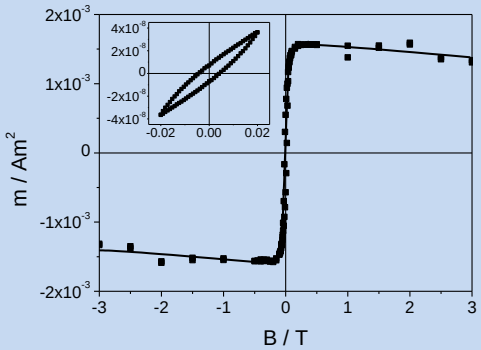


Fig2: Magnetic hysteresis evidencing the magnetosomes ferrimagnetic behaviour

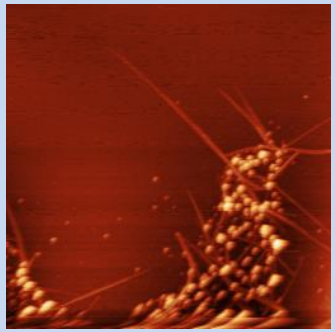


Fig3: Atomic force image of magnetic structures in DMS 3856.

Conclusions:

- **Flagella can be magnetic**
- **Magnetosomes have high hyperthermia efficiency**

Outputs

"Magnetic flagella in magnetotatic bacteria" *paper in preparation*

"Study of magnetic nanoparticles produced by magnetotactic bacteria", scientific internship 2016, Simon Vernay from Polytech Grenoble.

3. Protein networks stabilizing CFTR at the plasma membrane – an integrated interactomics approach to find novel therapeutic targets in CF

PIs - Peter Jordan | Paulo Matos | Carlos Farinha

Biomedicine | Bioinformatics

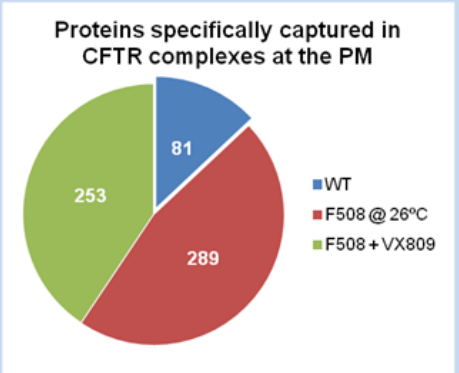
Previously, the proposing teams had revealed novel mechanisms regulating the stability of the CFTR protein at the plasma membrane: phosphorylation of CFTR by spleen tyrosine kinase, EPAC1 activation through the increase of cellular cAMP levels and Rac1-dependent NHERF1 and Ezrin-mediated anchoring of F508del-CFTR to the cytoskeleton. This project proposed to identify proteins underlying these mechanisms and involved in macromolecular complexes with CFTR, thus representing novel therapeutic targets. Following the set-up of co-immunoprecipitation or peptide-pull down strategies, lists of candidate proteins were obtained by sequencing the complex protein mixtures. These candidates are currently being analyzed by gene ontology and interactome databases to select lead hits for experimental validation.

Results:

1) One SH2-domain adaptor protein recognizes tyrosine phosphorylated CFTR;

2) The number of proteins identified to interact specifically with CFTR at the cell surface were: 81 for wtCFTR, 253 for F508del-CFTR when rescued by low temperature, and 289 when rescued by treatment with VX809;

3) The mechanisms of CFTR stabilization at the PM through EPAC1 activation was characterized in detail and published in Journal of Cell Science.



<u>Conclusion</u>:

Lists of candidate CFTR-interacting proteins were identified and represent a major breakthrough for further functional validation

Outputs:

3 ongoing PhD theses

Lobo et al (2016) J Cell Sci129, 2599-2612.

4. ProteoGrape - Grapevine shotgun proteomics

PIs - Andreia Figueiredo | Andreia J. Amaral

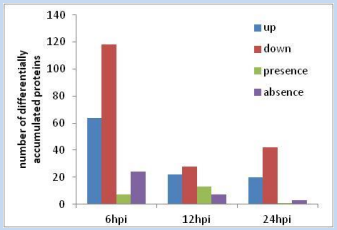
Biotechnology | Bioinformatics

Grapevine downy mildew is caused by the obligate biotrophic oomycete P. viticola, and it was introduced into European vineyards in the 1870s and quickly spread to all major grape-producing regions of the world. Nowadays is one of viticulture major concerns and knowledge on this pathosystem is crucial for the establishment of new disease control measures. With this project we aimed at a large scale proteome characterization of grapevine resistance towards P. viticola by comparing inoculated versus non-inoculated leaves of the resistant Vitis vinifera cultivar, 'Regent' at 6, 12 and 24 hpi, with a shotgun proteomics approach using Maxis Impact Q-TOF MS system. We also aimed at using proteogenomic searching, which is a useful method for identifying novel proteins, annotating genes and identifying peptides unique to an individual genome. This would allow producing an important contribution to the improvement of grapevine genome using the generated MS dataset as well as publicly available grapevine MS datasets.

Results:

A

B



C

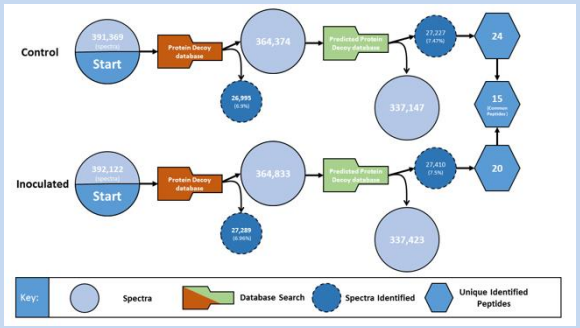


Figure 1 A- Grapevine inoculation with *Plasmopara viticola* (sampling at 6, 12 and 24hpi); B- preliminary results on the comparative analysis (inoculated and non-inoculated leaves); C- The proteogenomics workflow: all spectra produced (18) were compared to a protein decoy database generated from all known gravevine protein sequencences. Remaining spectra were further compared with a protein decoy database generated from predictions based in the grapevine genome. Only peptides with IDR <0.01 were further selected.

Conclusion:

Preliminary results on the comparative analysis between inoculated and non-inoculated grapevine leaves allowed the identification of 349 differentially accumulated proteins mainly involved in photosynthesis, signalling and defense mechanisms. Almost 50% of the identified proteins were unnnamed, uncharacterized or hypothetical *Vitis vinifera* proteins. Thus we have used a proteogenomics approach to improve database annotation. Preliminary results indicate that the analysis of our MS dataset allowed the identification of 29 novel peptides, which 15 are present in both conditions (non-inoculated and inoculated).

Outputs:

Figueiredo A (2016) Estudo de um caso: Resistência da videira ao míldio (Plasmopara viticola). Workshop Oleavalor "A proteómica em ciência vegetal

Figueiredo J, et al (2016) Signaling pathways in grapevine resistance against downy mildew. PathProt 9 - The international forum on Pathway Analysis in Proteomics, Oeiras – Portugal

5. The IsomiR Window: bringing the analysis of sequence complexity of miRNAs and their functional impact to the biomedical community

PIs - Margarida Gama-Carvalho | Beatriz Carmo

Bioinformatics | Biomedicine

IsomiRs derive from altered biogenesis or editing of precursor microRNA hairpins or SNPs and have the potential to significantly impact system function. Current tools for analysis of small RNA-Seq data do not systematically report IsomiRs. This project aims to improve the computational efficiency of a PERL based pipeline developed by the GER group for the identification of all types of IsomiRs and implement it into a user-friendly interface, including enhanced visualization tools to promote the understanding of global changes in microRNA processing and their biological impact. We further aim to explore the analytic power of this tool through the analysis of available sRNA-seq datasets, generating new biological insights into the relevance of isomiRs, supported by experimental validation.

Results:

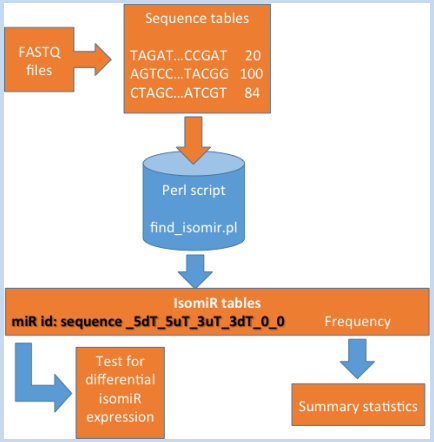


Figure 1

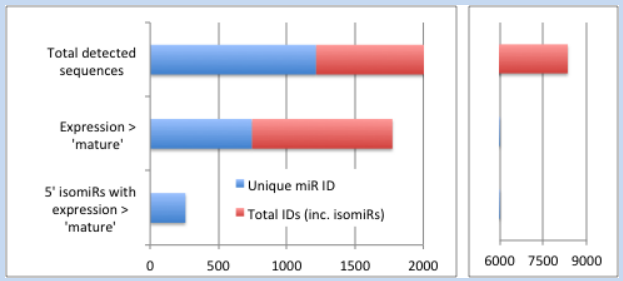


Figure 2

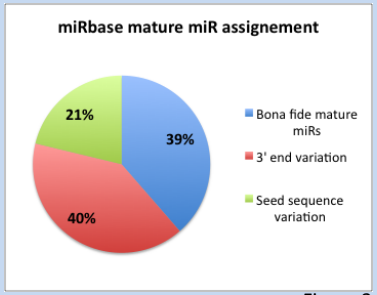


Figure 3

Figure 1: Overview of the basic pipeline for analysis of 5' and 3' end variations in isomiR sequences and structure of the isomiR code.

Figure 2: Absolute numbers of mature and isomiR sequences in a dataset of small RNA-seq from human naïve CD4 T cells reveal the existence of a significant number of 'isomiRs', including seed sequence variants, with expression levels above the assigned mature miR canonical sequence.

Figure 3: Estimated correct and dubious assignment of mature miRs in the miRBase repository based on our T cell expression data.

Conclusion:

We have generated a novel and useful tool for analysis of microRNA variation from RNA-seq data with powerful visualization of global expression profiles. The application of this tool to available datasets suggests there are major issues to be addressed in the field regarding proper identification of reference miR sequences.

6. Optical techniques for the automatic identification of fungal infection-resistant grapevine cultivars (OPTIGRAPE)

PIs - Jorge Marques da Silva | Pedro Mariano

Biotechnology | Bioinformatics | Biophysics

Enhancing the resistance of cultivated grapevine to fungal pathogens constitutes a major goal for breeders. Diagnostic assays based on optical techniques have the advantage of being noninvasive and time- and cost-effective, being therefore effective in high-throughput plant phenotyping. In this project we aimed to develop an optical diagnosis system that may automatically distinguish between Vitis genotypes resistant and sensitive to fungal pathogens. We compared the efficacy of different optical and spectroscopic systems. Collected data was used to construct classifiers based on different Machine Learning methods. The expected outputs have the potential for widespread application on the emerging field of plant phenomics.

Results:

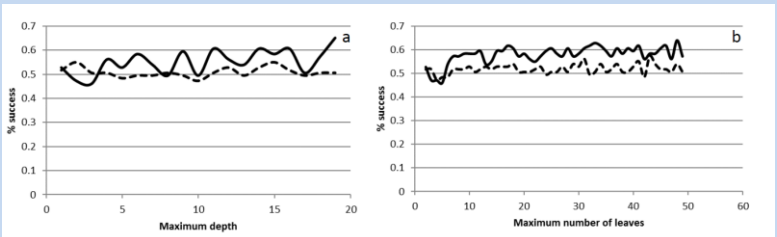


Fig. 1: Percentage of success of the classification of *Vitis riparia* leaves in four RWC classes as a function of the maximum depth of the trees (a) and the maximum number of leaves on the trees (b); solid line represents the gini criterion; dashed lines represent the entropy criterion.

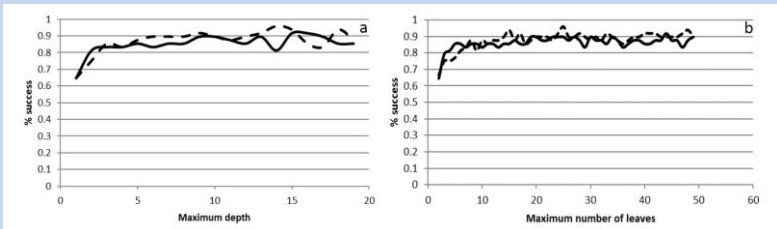


Fig. 2: Percentage of success of the classification of assayed leaves into three horticultural species (*B. oleracea*, *S. muricatum* and *P. tenax*) as a function of the maximum depth of the trees (a) and the maximum number of leaves on the trees (b); solid line represents the gini criterion; dashed lines represent the entropy criterion.

Conclusion:

Preliminary results show a moderate success in the automatic identification of the closely related species V. riparia and V. vinifera. Automatic identification of water stressed Vitis plants was also only partly achieved. On the contrary, a high success was obtained in the automatic identification of less phylogenetically related horticultural species. We are now improving the plants growth conditions, optimizing the spectroscopic protocols and exploring new classification algorithms.

Outputs:

Gameiro et al. 2016. Preliminary results on the use of chlorophyll fluorescence and artificial intelligence techniques to automatically characterize plant water status. Actas del XIII Simposio Hispano-Portugués de Relaciones Hídricas en las Plantas. Pamplona, Espanha, 18 - 20 octubre, pp 15 – 18

Matos et al. 2016. Analysis of fatty acids and photosynthetic pigments profiles highlight differences between Vitis species differing in their tolerance to fungal pathogens. XIX National Congresso of Biochemistry, december 8 – 10, Guimarães (oral presentation)

7. Atomic Force Microscopy approaches to study protein self-assemblies and interactions

PIs - Cláudio M. Gomes | Mário S Rodrigues

Biomedicine | Biophysics

Protein self-assembly is a highly complex reaction that involves changes in protein structure and dynamics that result in a variety of transient and polymorphic oligomers, protein fibrils or complex quaternary arrangements. Therefore, many of the underlying morphologies and mechanistic details of this process remain to be fully clarified at the nanoscale level. Our overarching goal is to undertake interdisciplinary work combining molecular biology, structural biochemistry, biophysics and physics, to study protein supramolecular protein assemblies, amyloid aggregates and protein interactions.

AFM is a high-resolution imaging and force mapping technique with vast potential to characterize both protein topographies and dynamic protein-protein and protein-membrane interactions. It is particularly useful to investigate protein self-assemblies, functional high order oligomers as well as pathologic aggregates and amyloids.

Results:

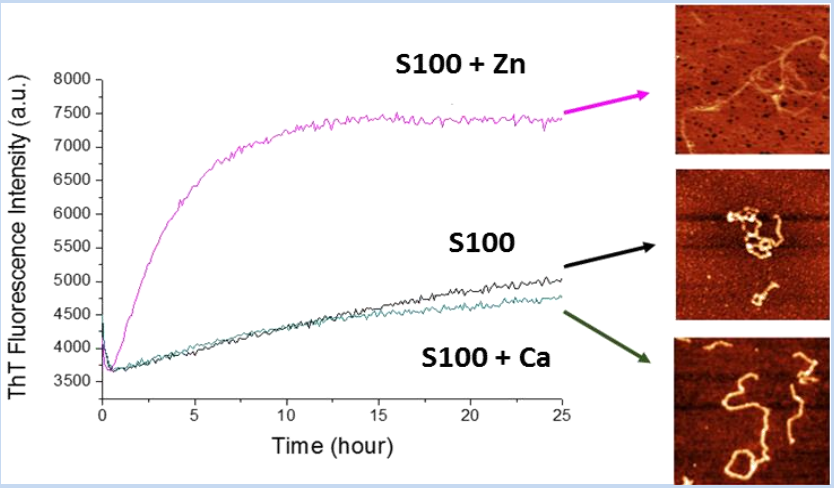


Fig. 1: Tht fluorescence intensity and AFM topography images of S100 in presence of different ions.

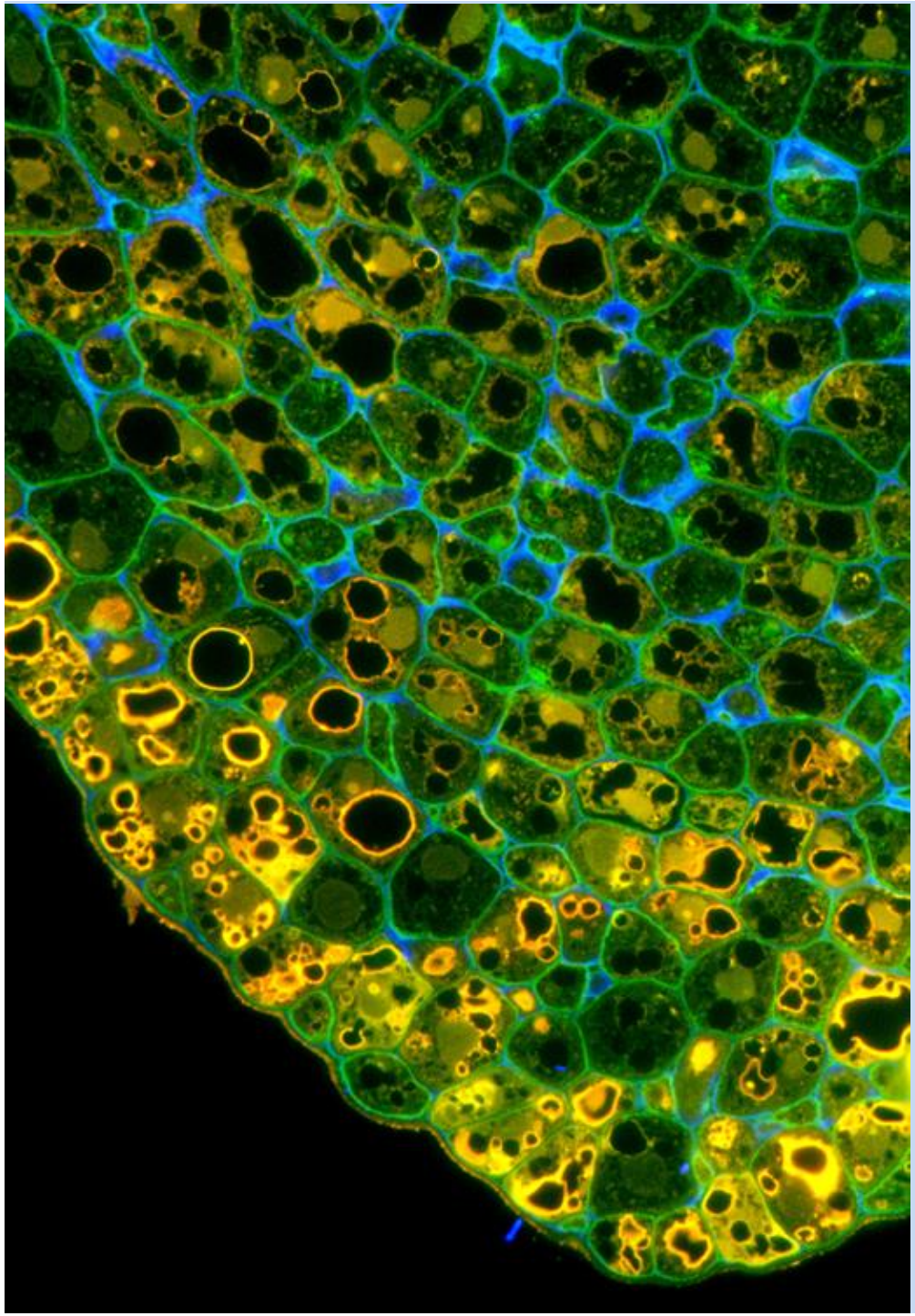
Conclusion:

Work developed in 2016 has allowed the characterization by AFM of different supramolecular S100 and Aβ amyloid assemblies. We have investigated time course protein assembly combining data from AFM topography and amyloid fluorophores, in different environmental conditions, including in the presence of S100-binding metal ions, which results in different assemblies.

Future work will allow further protein-protein interaction studies using functionalized AFM probes and to investigate interactions with biomembranes by using lipid-coated micas.

Outputs:

Master Thesis, Master in Biochemistry/FCUL, Gonçalo Nogueira, 2016



BioISI Research Units (Groups)

PFG Group

Plant Functional Genomics

http://bioisi.ciencias.ulisboa.pt/node/15

Research topic - Study of multiple aspects of plant growth and development with emphasis on functional aspects aiming biotechnological applications:

- Characterization of signalling and secretory pathways regulating growth and morphogenesis -omics analysis of plant (and fruit) development and responses to biotic interaction (parasitic and symbiotic) and abiotic stresses
- Plant responses to pollutants and their use as remediation tools
- Genetic variability and plant cytogenomics

Major Achievements:

- Transcriptome and metabolome analysis in *Vitis. vinifera* upon biotic infection revealed putative new proteins involved in plant resistance and stress responses.
- Functional characterization of oak roots symbiotic association with ectomycorrhizal fungus.
- Characterization of genetic tools for analysis of ploidy levels and crop diversity.
- Analysis of signaling pathways and physiological indicators upon abiotic metal toxicity stress.
- Characterization of novel proteins involved in angiosperms (Arabidopsis and Quercus) sexual reproduction.
- 2 research projects initiated with members of MagNano, MAS and GER groups

Selected Publications:

Pereira AM., et al. "Love Is Strong, and You're so Sweet": JAGGER Is Essential for Persistent Synergid Degeneration and Polytubey Block in *Arabidopsis thaliana*. Mol Plant 9: 601-614.

Grimplet J., Agudelo-Romero P., Teixeira R.T., Martinez-Zapater J. M., Fortes A. M. Structural and functional analysis of the GRAS gene family in grapevine indicates a role of GRAS proteins in the control of development and stress responses. Frontiers Plant Sci. 7: 353.

Sebastiana M, Martins J, Figueiredo A, Monteiro F, Sardans J, Pernlas J, Silva A, Roepstorff P, Pais MS, Coelho AV.
Oak protein profile alterations upon root colonization by an ectomycorrhizal fungus. Mycorrhiza Figueiredo J, Costa GJ, Maia M, Paulo OS, Malhó R, Sousa Silva M, Figueiredo A. Revisiting *Vitis vinifera* subtilase gene family: A Possible role in grapevine resistance against *Plasmopara viticola*. Frontiers Plant Sci., 7: 1783.

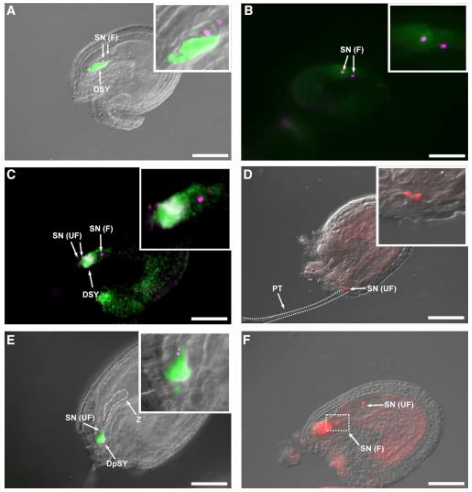


Figure 1

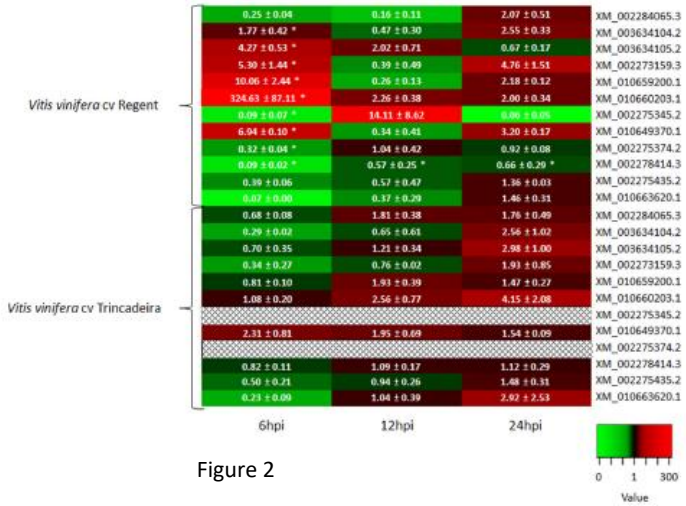


Figure 2

Key Funded Projects:

PTDC/AGR-FOR/3356/2014- FCT - Characterisation of cork formation and reproductive biology in a cork hybrid population, 1 January 2016- 31 December 2018, 57.115,00 €, Partners.

Characterizing and monitoring cashew economically important diseases in West Africa as a prospective measure for sustainable production: a case study on GuineaBissau. FCT. 140.000€, PI. Jan2017-Dez2018.

Sexual Plant Reproduction – Seed formation. Project 690946 – SexSeed. H2020 MSCA-RISE-2015. 01 March 2016, ends 28 February 2020. Total amount 720000.00€, BioISI 193500.00€. Coordination INTERACT - Integrated Research in Environment, Agro-Chain and Technology, NORTE-01-0145-FEDER-000017.

Group Leader

Rui Malhó

Integrated PhDs from:

Ciências ULisboa

U.PORTO

Universidade do Minho
Escola de Ciências

UNIVERSIDADE DE TRÁS-OS-MONTES E ALTO DOURO
utad

Investigadores FCT: Ana Margarida Fortes, Andreia Figueiredo

Pós-docs: Mónica Sebastiana, Filipa Monteiro, Susana Serrazina, Fernando Vaz Dias, Ana Isabel Carvalho, Sónia Gomes, Maria Manuel Romeiras

Academia (ULisboa): Anabela Silva, Ana Rita Matos, Jorge Silva, Rui Malhó

Academia (UMinho): Rui Tavares, Teresa Lino-Neto, Maria Manuela Costa

Academia (UPorto): José Pissarra, Sílvia Coimbra, Jorge Teixeira, Fernanda Fidalgo, Luis Gustavo Pereira, Susana Pereira, Isabel Amorim, Paula Melo

Academia (UTAD): José Eduardo Lima-Brito, Paula Martins Lopes, Maria João Gaspar, Manuela Matos, Isaura Castro, Fernanda Leal

PhD Students: 14

Figure 1: Localization of *jagger* in the ovaries of Arabidopsis plants.
Figure 2: Heatmap of the 14 grapevine subtilase expression in V.vinifera

FunGP Group
Functional Genomics & Proteostasis

http://bioisi.ciencias.ulisboa.pt/node/16

Biomedicine: translating genes and genomics into personalized & systems medicine; elucidating mechanisms of disease; development of innovative therapeutic strategies & drug discovery; performing pharmaco-genetics & pharmaco-resistance tests.

1. Translational science and personalized medicine in Cystic Fibrosis.
2. Molecular and cellular mechanisms of secretory traffic of CF-related ion channels: CFTR, anoctamins.
3. Signalling/ signal transduction pathways in human disease.
4. Systems approaches to tackle mechanisms of disease: Cystic Fibrosis, cancer and neurodegeneration.
5. Drug development for CF, cancer and neurodegeneration.

Major Achievements:

- **Translational science and personalized medicine in Cystic Fibrosis (CF):** Novel RNA-based genetic diagnosis methodology [Felício et al, *Clin Genet* 2016]; HE4 as a novel serum inflammatory biomarker in CF [Nagy et al, *Chest* 2016]; correction of a CF splicing mutation by antisense oligonucleotides [Igreja S *et al*, *Hum Mutat* 2016]
- **Mechanisms of CF Disease:** mechanism of CFTR stabilization at the plasma membrane by the cAMP sensor EPAC1 [Lobo *et al*, J Cell Sci 2016]
- **Mechanisms of disease in Cancer:** Role of Rac1b in thyroid carcinogenesis [Faria *et al, PlosOne 2016,* 2nd revision]
- **Mechanisms of Alzheimer's disease (AD):** *In vitro* self-assembly and amyloid formation mechanisms for proteins involved in AD and regulation by neuronal proteins and metal ions [Adam *et al*, *J Alzheim Dis* 2016].

Selected Publications:

Lobo MJ, Amaral MD, Zaccolo M, Farinha CM (2016) "EPAC1 activation by cAMP stabilizes CFTR at the membrane by promoting its interaction with NHERF1". J Cell Sci 129, 2599-2612.

Matos P, Gonçalves V, Jordan P (2016) Targeting the serrated pathway of colorectal cancer with mutation in BRAF. *Biochim Biophys Acta* **1866**: 51-63.

De Boeck K, Amaral MD (2016) Highlights of progress in therapies for cystic fibrosis. *Lancet Respir Med* 4, 662-74

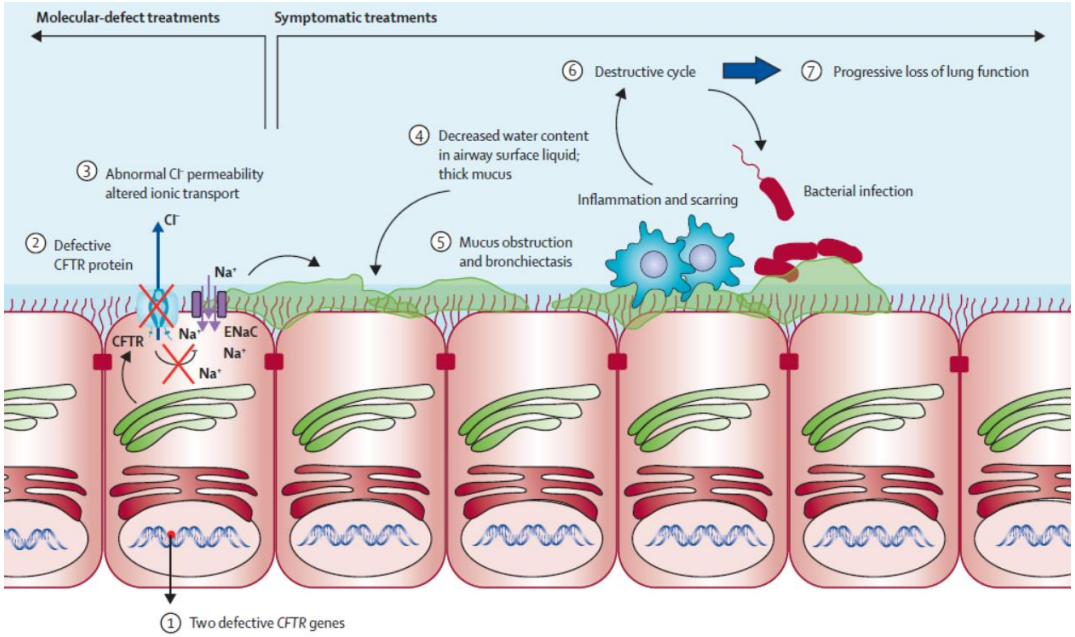


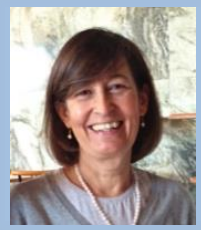
Figure 1: Pathogenetic cascade that causes cystic fibrosis lung disease

Key Funded Projects:

CFF Cystic Fibrosis Foundation, USA (Ref. AMARAL16I0) "*Characterization of Orphan CFTR mutations*". Budget: 108K$; 2 yrs. PI: MD Amaral.

CFF Cystic Fibrosis Foundation, USA (Ref. AMARAL15XX1) "*RNA LIFE – Novel RNA Regulators as Potential Drug Targets for Cystic Fibrosis*". Budget: 324K$; 2 yrs. PI: MD Amaral.

FCT/POCTI (PTDC/BIM-MEC/2131/2014) "*DIFFTARGET-Novel Factors of CFTR Traffic Related to Epithelial Cell Differentiation: Potential Therapeutic Targets for Cystic Fibrosis*". Budget: 200K€; 3 yrs. PI: MD Amaral.



Group Leader

Margarida Amaral

PI's


Luka Clarke


Carlos Farinha


José Pedro Gil


Cláudio Gomes


Paulo Matos

Post Docs: Bárbara Henriques | Catarina Batista (BioISI) | Hugo Botelho| Ines Pankonien | Iris Silva | Javier Fernandéz | Miqueias Lopes-Pacheco | Patrícia Barros | Susana Igreja

PhD Students: Ana Matos (BioSys) | Daniel Cruz (BioSys) | João Santos (BioSys) | Joana Cristovão | Joana Lérias (BioSys) | Luís Sousa (BioSys) | Madalena Pinto (BioSys) | Márcia Faria (BioSys) | Margarida Quaresma (BioSys) | Mariana Romão (BioSys) | Nikhil Awatade (BioSys) | Sara Canato (BioSys) | Tânia Lucas | Verónica Felício

MSc Students: Ana Fonseca | Anna Pedrola Gómez | Filipa Simões | Iris Lameiro | Sofia Ramalho Rafaela | Furtado Pereira

Technician: José Múrias

M&B Group

Microbiology & Biotechnology

http://bioisi.ciencias.ulisboa.pt/node/17

Research M&B-BioISI focused on innovative integrated approaches in several areas of M&B and linking group know-how and expertise with SMEs and industry.

R&D translation to society was further achieved through participation of PhD members in networks of key value chains (Bluebio Alliance, Rede Agro, Rede Mar).

Major Achievements:

Yellow and White M&B

- Genome sequence of the non-conventional wine yeast *Hanseniaspora guilliermondii UTAD222*
- Selection and integrative analysis of saccharomyces and non-saccharomyces yeasts as novel starters for wine industry
- Unveiling of the molecular basis of chitosan toxicity in yeast to pave the way for its use as a new preservative in wine and food industries to replace sulfite
- Development and validation of a multiplex-PCR method for detection of acetic acid bacteria

Grey and Green M&B

- Reappraisal of genera and species in the Botryosphaeriaceae, a fungal family with relevance in eucalyptus canker and dieback diseases
- Taxonomic novelties in fungi: one new family, three new genera and eleven new species
- Selection and validation of genomic markers for detection of *Xanthomonas arboricola pv. juglandis*, the agent of walnut blight
- Evaluation of the differential efficiency of conventional and organic crop management systems on microbial rizhosphere features

Blue M&B

- Whole-genome sequence of an hydrothermal vent strain with biotechnological potential
- Integrated step-forward approach using whole genome sequencing for identification of industrial relevant enzymes from deep sea vent prokaryotes

Gold and Red M&B

- Innovative modular information system, intelligent and adaptable to support clinical decision making in the field of antimicrobial resistance, infection control, epidemiological surveillance and hospital management
- Comparative genomic analysis in *Brucella* and disclosure of genomic and structural differences between Iberian and Central-European clones of *B. suis biovar 2*
- Evaluation of MoA from selective investigational drugs able to modify the etiology of cystic fibrosis using yeast-based genetic tools to screen oxidative drugs
- Isolation and NGS-based characterization of Arrabida Virus, a novel phlebovirus from sandflies in South Portugal
- Production of bacterial magnetosomes under distinct magnetic fields to be assayed as more efficient anisotropic magnetic nanoparticles for hyperthermia cancer therapy

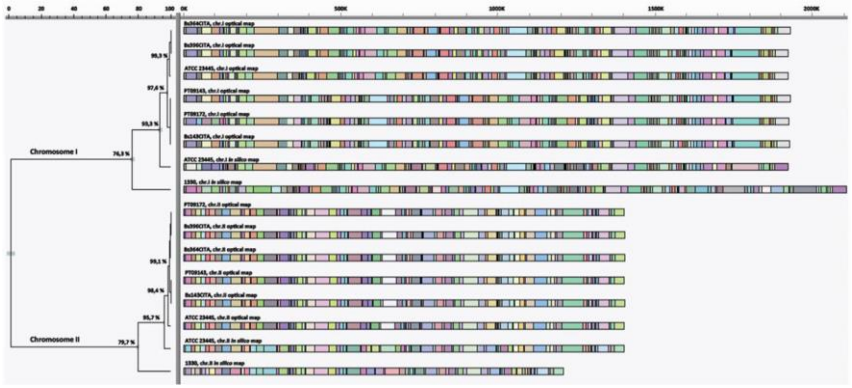


Figure 1

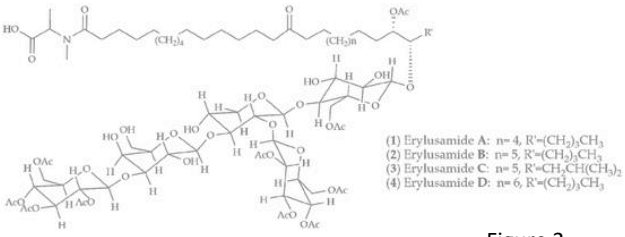


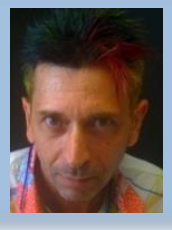
Figure 3

Figure 2

Figure 1: Map similarity cluster of chromosomes I and II of *B. suis* strains …

Figure 2: Range of ascus and ascospore morphology in the Botryosphaeriales

Figure 3: Structures of erylusamides A–D.



Group Leader

Rogério Tenreiro

Post Docs: Catarina Baptista| Patrícia Anacleto

PhD Students: Ana Cristina Inácio| Anabela Esteves | Inês Alemida | Joana Cruz | João Pais | Patrícia Lage | Pedro Teixeira | Susana Marques | Tiago Silva

MSc Students: Alexandra Lança | Ana Catarina Rocha | Ana Isabel Lemos | Ana Marta Lourenço | Ana Sofia Oliveira | Fabiana Quintas | Filipa Rosa | Inês Santos | Isabel Seixas | João Melo | Mariana Nascimento | Tatiana Cordeiro

Lab Staff: Cláudia Luís| Filipa Silva

Key Funded Projects:

RESISTIR - Intelligent information system to control infection and personalized antibiotherapy. POCI and POR Lisboa. P2020 project nº 3379. Proponent Company: MAXDATA Software SA. Partner: FCUL. 2016-2018. Total funding: 1.02 M€. M&B-BioISI funding: 531 k€. FCUL PI: R. Dias (FCUL/BioISI). [Gold/Red M&B]

SMARTWINE - Smarter wine fermentations: integrating Omics-tools for development of novel mixed-starter cultures for tailor-made wine production. FCT, COMPETE, FEEI. PTDC/AGR-TEC/3315/2014, 2015-2019. Total funding: 196 k€. No BioISI amount. PI: A. Mendes-Faia (UTAD/BioISI). [Yellow/White M&B]

BIOCLUB - Designing biofertilizers by mimicking plants' recruitment of rhizospheric partners. FCT. PTDC/AGR-PRO/1852/2014. 2016-2019. Proponent: FFCUL (CE3C). Total funding: 199 k€. No BioISI amount. BioISI partner: R. Tenreiro (FCUL/BioISI). [Grey/Green M&B]

Selected Publications:

Dissanayake AJ, Phillips AJL, Li XH, Hyde KD (2016). Botryosphaeriaceae: Current status of genera and species. Mycosphere 7.

Ferreira AC, Dias R, de Sá MI, Tenreiro R (2016). Whole-genome mapping reveals a large chromosomal inversion on Iberian *Brucella suis* biovar 2 strains .Vet Microbiol 192: 220-5.

Seixas I, Barbosa C, Salazar SB, Mendes-Faia A, Wang Y, Güldener U, Mendes-Ferreira A, Mira NP (2016). Genome sequence of the non-conventional wine yeast *Hanseniaspora guilliermondii* UTAD222. Genome Announcements . Accepted.

BTR Group

Biomedical and Translational Research

http://bioisi.ciencias.ulisboa.pt/node/18

Understanding how genetic, epigenetic, clinical, lifestyle and environmental determinants and modulators interact to influence health, disease and treatment efficacy; integrating large human datasets and translating findings into personalized medicine tools for improved diagnosis and intervention using Systems Medicine frameworks.

Major Achievements:

- Gene variants involved in oxidative stress, folate metabolism, DNA repair or DNA methylation were shown to influence survival of myelodysplastic syndrome and acute myeloid leukemia patients and may improve diagnostic and prognostic molecular accuracy or constitute potential therapeutic targets for these disorders;
- The ASDEU autism population study was launched, examining demographic, clinical, genetic and environmental factors, while a new integrative project, MEDPERSYST, provides a window to brain physiology in autism;
- Excess detoxification and barrier gene variants suggest environmental sensitivity mediated by genetic factors increases autism risk;
- The etiology of dyslipidaemia in patients with clinical familial hypercholesterolaemia (FH) was further unraveled by the identification of patients with a lysosomal acid lipase deficiency, changing prognosis and treatment. Other FH patients negative for known mutations are under study to discover novel FH genes;
- A comprehensive FH mutation database was compiled with relevant information to improve genetic diagnosis of FH;
- The first study on genetic aetiology of deafness in patients from S. Tomé and Príncipe Islands suggested that GJB2 coding mutations are of little significance in the islands;
- The Deafness Research Group became member of the European Network of Reference Centers for Genetic Deafness.

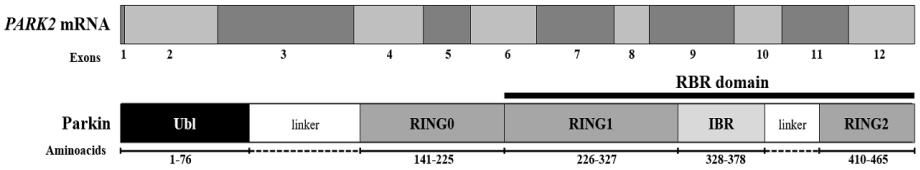


Figure 1: Schematic representation of the structure of the *PARK2* mRNA and the Parkin protein with its functional domains:. The mRNA codes for the corresponding protein domain below.

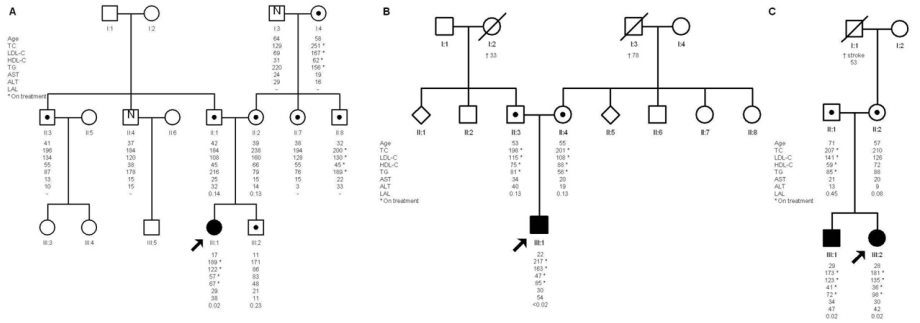


Figure 2: Pedigree with dyslipidemia caused by a lysossomal acid lipase deficiency.

Group Leader
Astrid Vicente

Post Docs: Ana Catarina Alves|Celia Rasga|Claudia Branco|Ines Conceicao|Tiago Matos |Renato Pires | Hugo Martiniano

PhD Students: Ana Margarida Medeiros|Ana Rita Marques(BioSys)| Cibelle Mariano(BioSys)|Cristina Caroca|Haula Haider|JoanaChora| João Pedro Santos (BioSys)| Muhammad Asif (BioSys)|Niccolo Rosi (BioSys)| Ana Cristina Goncalves

Technicians: Joana Canilho| Joana Duarte| Lisa M Esteves

Selected Publications:

Gonçalves AC, (...) and Mota-Vieira L (2016). Genetic variants involved in oxidative stress, base excision repair, DNA methylation, and folate metabolism pathways influence myeloid neoplasias susceptibility and prognosis. Mol Carcinog, doi: 10.1002/mc.22478.

Conceição IC, Rama MM, Oliveira B, Café C, Almeida J, Mouga S, Duque F, Oliveira G, Vicente AM.Definition of a putative pathological region in PARK2 associated with autism spectrum disorder through insilico analysis of its functional structure. Psychiatr Genet. 2016 Nov. 7

Chora JR, Alves AC, Medeiros AM, Mariano C, Lobarinhas G, Guerra A, Mansilha H, Cortez-Pinto H; Bourbon M. Lysosomal Acid Lipase Deficiency: A hidden disease among cohorts of familial hypercholesterolaemia? (Accepted for publication in J Clin Lipid).

Key Funded Projects:

Autism Spectrum Disorders in Europe (ASDEU). 2015-2018. Funded by the Health Programme of the European Union DG-SANCO, Portugal budget 144 000€. Astrid Vicente Partner

Synaptic networks and Personalized Medicine Approaches to Understand Neurobehavioural Diseases Across the Lifespan (MEDPERSYST). 2016-2019. Funded by PROGRAMAS DE ATIVIDADES CONJUNTAS (PAC), Portugal 2020 Total budget: 2.487.042,85€. FFCUL – BioISI funding 469.678,33€. Astrid Vicente Task leader, Collaborating partner.

LALD.pt 2015-2017 Funded by Alexion Pharmaceuticals, Total Budget 104000€. PI Mafalda Bourbon

GER Group

Gene Expression and Regulation

http://bioisi.ciencias.ulisboa.pt/node/20

Our research aims to explore the organization and regulation of eukaryotic genomes and gene expression programs at the transcriptional and post-transcriptional levels and their connection to signalling pathways, with a preferential focus on the study of processes relevant for human health and disease. Our approach ranges from dissecting molecular mechanisms to understanding their impact on systems level regulation, using a combination of molecular, cell biology and computational approaches.

Major Achievements:

- **sncRNAs:** miR-34c-5p is a novel regulator of TCR-stimulation in human naïve CD4 T cells, linking cell activation and HIV-1/HIV-2 replication and being down-regulated by an anti-viral cell response, potentially to limit HIV infection.
- **Genomes and repetitive DNA:** evolutionary insights into the role of genome rearrangements and repetitive sequences across mammals and disclosure of cellular pathways involving the corresponding non-coding RNAs.
- **Translation mechanisms:** demonstration of cap-independent translation for AGO1 and mTOR mRNAs and dissection of biochemical interactions of eIF3 subunits that allow mRNA circularization during initiation.
- **Signaling and splicing:** novel cellular models to study signal exchange between epithelial colon and surrounding stroma-derived cells and identification of kinases that regulate a splicing event through modulation of the nuclear abundance of a key splicing factor.
- **RNA in neurodegeneration:** novel algorithm to identify cross-disease genes and identification of conserved SMA pathways.

Selected Publications:

Amaral AJ, et al (2016). miRNA profiling of human naive CD4 T cells links miR-34c-5p to cell activation and HIV replication. EMBO J. In Press. DOI 10.15252/embj.201694335

Pereira et al (2016). The third dimension: new developments in cell culture models for colorectal research. Cell Mol Life Sci. 73, 3971-3989.

Vieira-da-Silva A, Adega F, Guedes-Pinto H, Chaves R (2016) LINE-1 distribution in six rodent genomes follow a species-specific pattern. J Genet 95(1):21-33.

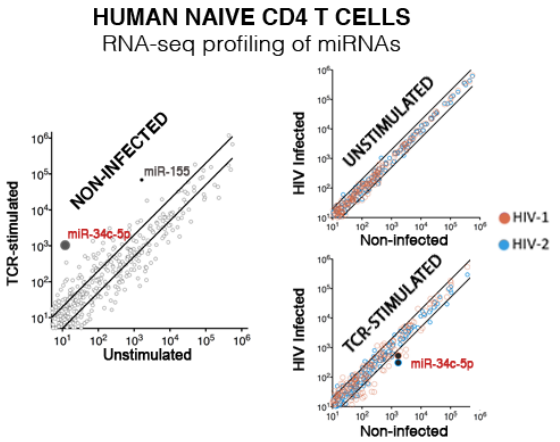


Figure 1

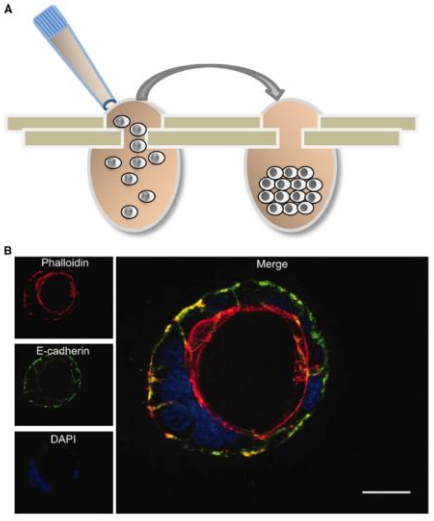


Figure 2

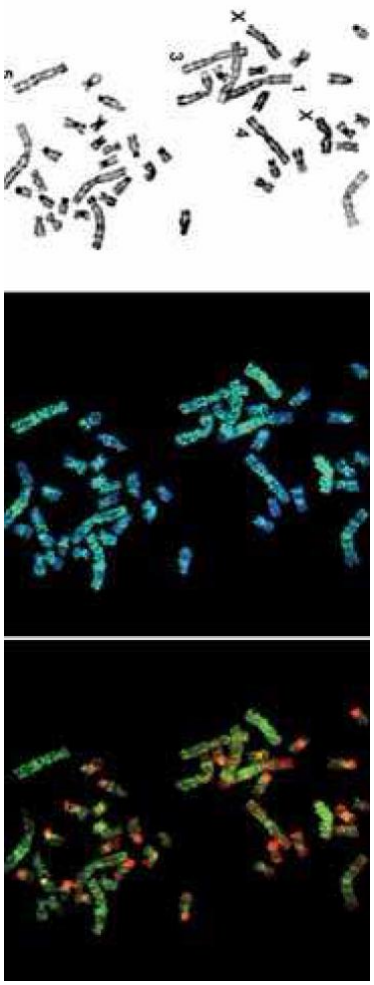


Figure 3

Key Funded Projects:

Nonsense-mediated mRNA decay in genetic diseases and cancer: key players, mechanisms, and a novel approach for suppression therapy, PTDC/BIM-MEC/3749/2014, March 2016-Feb 2019 Budget: 200K€

LungCARD. EU project 734790 Call H2020-MSCA-RISE-2016. Proponent: STAB VIDA. Jan 2017-Dec 2020 Budget: 1M€ global/144K€ local

FlySMALS: Common RNA-dependent pathways for motorneuron degeneration in SMA and ALS. EU Joint Program in Neurodegenerative Disorders (JPND-CD/0002/2013) May 2015-April 2018 Budget: 796K€ global/139K€ local

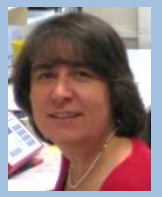
Group Leader
Margarida Gama-Carvalho

PI's


Raquel Chaves


Francisco Pinto


Peter Jordan


Luísa Romão

Post Docs: Andreia Amaral | Maria Filomena Adega | Vânia Gonçalves | Juliane Menezes | Christian Ramos

PhD Students: Ana Borges | Paulo Costa | Nuno Domingues | Ana Escudeiro | Rafael Fernandes | Daniela Ferreira | Marina Garcia-Vaquero | Andreia Henriques | Cláudia Loureiro | Daniel Olivença |Joana Pereira | Hugo Santos | Rafaela Santos | Ana Cristina Silva | Joana Silva

Other researchers: Tânia Monteiro Marques | João Paulo Silva | Inês Martins | Andreia Duarte | Liliana Costa | Sara Felício | Bárbara Martins | Patrícia Dias

Figure 1: Human naïve T–cell miR expression profile response to TCR stimulation and HIV-1/HIV-2 infection
Figure 2: 3D cell culture models for colorectal research
Figure 3: Line-1 distribution in rodent genomes

PBS Group

Physics of Biological Systems

http://bioisi.campus.ciencias.ulisboa.pt/node/21

The PBS group develops research in complex adaptive networks (CAN), disease spread (DS), and physics of protein folding (PPF).

Major Achievements:

- **DS** - Simulation results highlight the importance of heterogeneity in the human immune response for understanding influenza A phenomenology (1).
- **PPF** - Simulation results predict that steric confinement as that provided by the GroEL chaperonin environment assists the folding of proteins embedding physical entaglements in their native structure by ehnacing the knotting frequency (2).
- **PPF** – Simulation results predict that protein CFTR adopts a misfolded intermediate whose population is highly enhanced by deletion of residue 508. The intermediate's stabilization results from the increased non-native coupling between various key regions of the α-helical subdomain and ATP-binding subdomain. The formation of this intermediate is not blocked by second-site suppressor mutations (3).

Selected Publications:

T. Aquino and A. Nunes, Host immunity and pathogen diversity: A computational study, Virulence 7, 122:128 (2016) IF: 5.418

M. A. Soler, A. Rey and P.F.N. Faísca, Steric confinement and enhanced local flexibility assist knotting in simple models of protein, Phys. Chem. Chem. Phys. 18, 26391-26403 (2016) IF: 4.449

S. G. Estácio, H. Martiniano, P.F.N. Faísca, Thermal unfolding simulations of NBD1 domain variants reveal structural motifs associated with the impaired folding of 5F08del-CFTR, Mol. BioSys. 12, 2834-2848 (2016) IF: 2.289

Group Leader
Patrícia Faísca

PI

Ana Nunes

PhD Students: Rui João Loureiro (BioSYS), João Pedro Santos (BioSYS – with BTR)

Figure 1

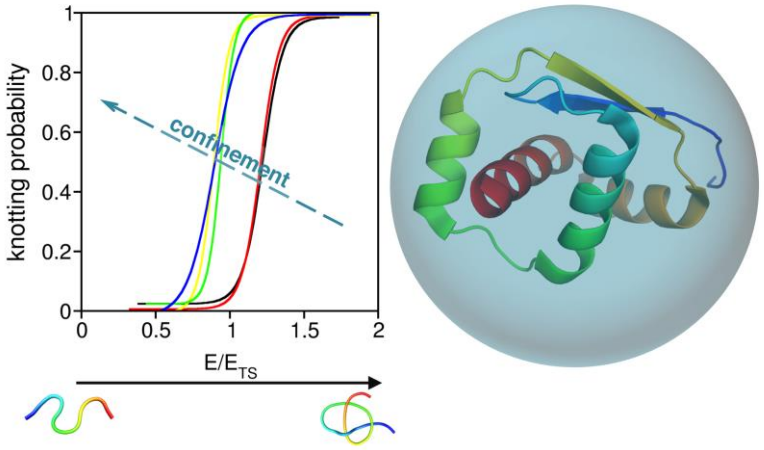


Figure 2

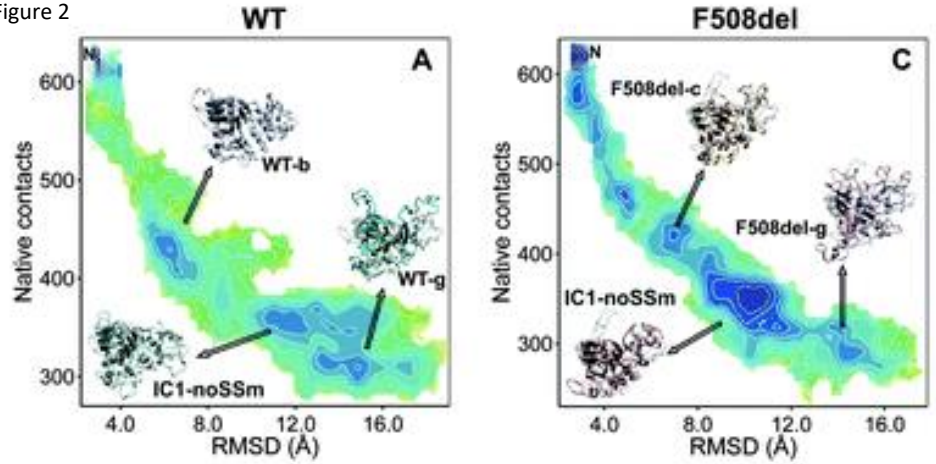


Figure 1: Enhancement of knotting probability under steric confinement

Figure 2: Conformational space of CFTR highlihhting the population of a conserved intermediate IC1

MagNano Group

Magnetic Nanosystems

http://bioisi.ciencias.ulisboa.pt/node/22

MagNano is a group of physicists with a strong expertise on magnetic/atomic systems, nanophysics and nanotechnology methods/techniques. Research activities are focused on, i) the development/refinement of Atomic Force Microscopy related techniques (AFMRT) aimed at the study of physical/biological systems, ii) the investigation of nanostructured magnetic systems for diverse applications (spintronics, biomedicine), iii) the specific use of high resolution techniques for magnetic properties assessment of different systems with potential applications in nanomedicine, catalysis and sensors technology.

Within BioISI strategic project MagNano's contribution is convened in the Cond Mat & BioPHYS thematic line (TL) though interactions with other TLs have already been explored.

Magnetic nanoparticles for biological/biomedical applications

- Improvement of the inducition heating experimental set-up to determined the participation of the group in the ring tests organized within COST Action TD1402 – RADIOMAG to standardize/optimize experimental conditions and analysis of magnetic hyperthermia measurements.
- Magnetic hyperthermia results obtained for ferrite nanoparticles prepared using natural templates have shown an increased hyperthermia performance after the high magnetic anisotropy induced.

MagNano expertise/facilities

- Information obtained by SQUID magnetometry and Mössbauer measurements have become central in the identification of the spin state and local geometry of transition metal complexes with interest for catalytic reactions and magnetic sensors.

Force Feedback Microscope (FFM) development

- New locally built FFM equipment became fully operational
- Development of a software prototype enabling the complete control of an FFM/AFM head, important milestone for AFMs development at reduced budget
- Development of a model allowing to extract the sliding friction coefficient from harmonic oscillator data; work expected to have a major impact in nanotechnology.
- Systematic AFM study of Ca and Zn effect on the aggregation of S100 proteins, which play a role in Alzheimer's disease.

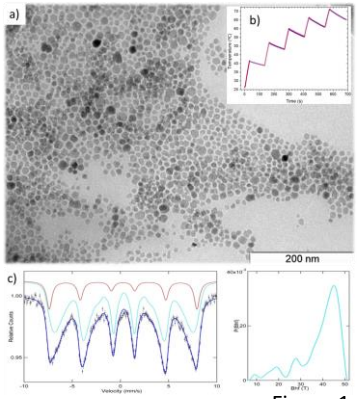


Figure 1

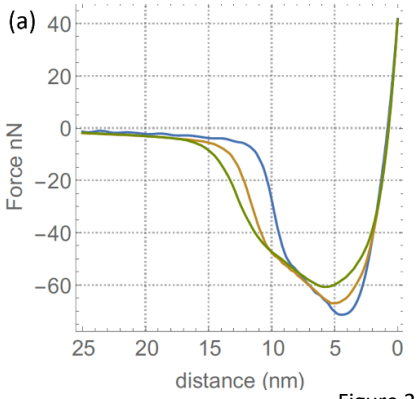


Figure 2

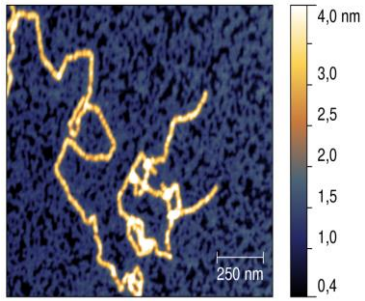


Figure 3

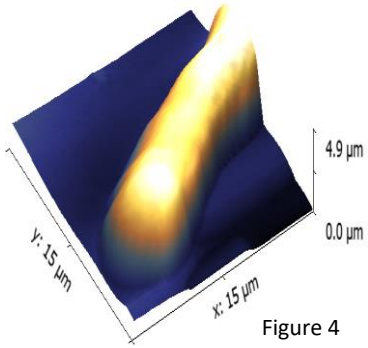
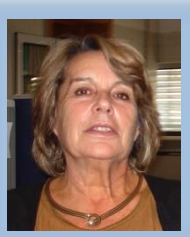


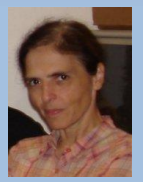
Figure 4



Group Leader

Maria Margarida Godinho

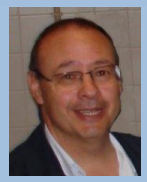
PI's



Margarida Cruz

Liliana Ferreira

Mário Rodrigues



José Pires Marques

Post Docs: Mário S. Rodrigues | Andrii Vovk

Other Integrated members: Guiomar Evans | Thomas Peter Gasche | António Casaca | Teresa Madeira Amorim | Jorge M. Sampaio | Pedro Amorim

PhD Students: Miguel Vargas Vitorino | Cátia Silva | Bruno Ribeiro | Rodrigo Antunes

MSc Students: Ricardo Antunes | Rafael Vieira | Pedro Matos | Arthur Vieira | Catia Rato

Key Funded Projects

Molecular and Mechanical Forces in Biology measured with Force Feed-back Microscopy", FCT project grant ; Start Date: 01/04/2016 – 3 years ; BioISI total amount - 145.5600,0€; Total amount of the project – 199.979,0€, PI: Mário Silveira Rodrigues (project involving MagNano, PFG and M&B BioISI groups)

Multifunctional Luminescent Spin Labile Hybrid Materials, FCT Project grant; Start Date: 01/03/2016 – 3 years ; BioISI total amount 27.500,0€ ; Total amount of the project – 191.879,0€ ; BioISI Partner: Liliana Ferreira

Figure 1. TEM image (a), temperature versus time variation under magnetic field (b) and Mossbauer results (c) for magnetite Fe_3O_4 size distributed NPs (≅ 15 nm).

Figure 2. FFM measurements: force versus distance at different approach speeds (the jump - in force - indicates the formation of a water capillary bridge; plot of distance vs speed allows to deduce the water bridge nucleation time)

Figure 3. AFM image of S100 proteins showing a long fiber like structure composed of small building blocks.

Figure 4. Arabidopsis thaliana pollen tube imaged by AFM

MAS Group

Agent and Systems Modelling

http://bioisi.ciencias.ulisboa.pt/node/19

MAS research focuses three main themes:

- Artificial intelligence approaches of agent and multi-agents systems, mobile robotics, artificial life, and natural language
- Complex multi-agent systems, including agent visualisation and animation, and social simulation
- Data mining and knowledge discovery

Major Achievements:

- Supervised learning classifier, M3GP, uses an evolutionary algorithm, effectively creating *n* hyper-features from the original ones, where the optimal *n* is also automatically found. It provides classifications as accurate as the best state-of-the-art, while additionally providing highly readable information (Silva S et al, 2016).

Keynote talks:

H Coelho, Univ. Fed. Bahia, Salvador, Brazil; 3rd Int'l Conf. Philosophy of Science, Lisbon, Portugal

L Correia at Workpedia 2016, Niterói, Brazil

Best student papers awards:

Aubakirov S, Trigo P, Ahmed-Zaki D. Comparison of Distributed Computing Approaches to Complexity of n-gram Extraction, in DATA 2017, Madrid, Spain

Silva F, Correia L, Christensen AL. Online Hyper-Evolution of Controllers in Multirobot Systems, in SASO 2016, Augsburg, Germany

Best paper award:

Silva S, Correia L, An experiment about the impact of social influence on the wisdom of the crowd effect, in Workpedia 2016, Niterói, RJ, Brazil

Figure 1: Virtual agents for human interaction

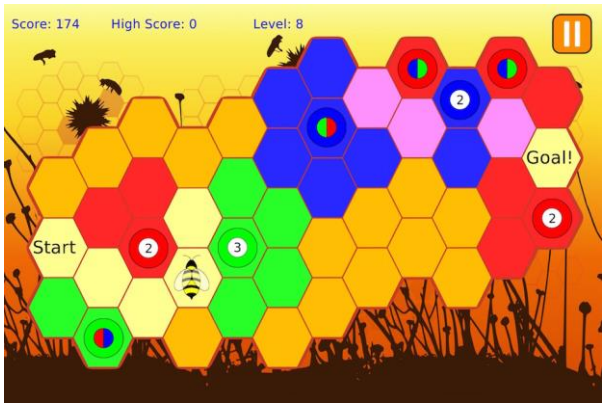
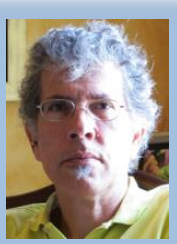


Figure 2: BeeFish game for dissemination of ASSISIbf project



Group Leader
Luís Correia

PI's


Helder Coelho


Luís Antunes


Paulo Urbano


Sara Silva


Beatriz Carmo

Post Docs: R. Mills| R. Antunes

Other members: A.P. Claúdio | I. Nunes | J. Balsa | J. Neto | P. Mariano | P. Trigo |L. Morgado

PhD Students: F. Silva| J. Gomes | D. Nunes | C. Lemos | N. Magessi | C. Reginaldo | P. Pombinho

Key Funded Projects:

EU-FP7 Animal and robot Societies Self-organise and Integrate by Social Interaction (ASSISIbf)", 1/Feb/13 - 31/Jan/18 (BioISI funding 515.776 EUR). Main contractor Univ. Graz (Austria) / local coordinator L. Correia

FCT VIRTUAL TUTORING. Funding FFCUL / BioISI: 60.967€, of total 199.706€. Main contractor Univ. Aberta / Local coordinator AP Cláudio.

FCT EXPL/EEI-SII/1861/2013 - "A Novidade guia a Evolução através de Gramáticas", PI P Urbano. April 2014 to March 2015, BioISI fund. 22,594 €

Selected Publications:

Silva S, Munoz L, Trujillo L, Ingalalli V, Castelli M, Vanneschi L (2016). Multiclass Classification Through Multidimensional Clustering. In Kordon A, et al, Genetic Programming Theory and Practice XIII, Springer

Silva F, Duarte M, Correia L, Oliveira SM, Christensen AL (2016). Open Issues in Evolutionary Robotics. Evolutionary Computation, 24(2):205–236

Trujillo L, Muñoz L, Galván-López E, Silva S (2016). neat Genetic Programming: Controlling bloat naturally. Information Sciences, Volume 333, 10 March, pp 21-43

Technology & Instrumentation

Gathering physicists and computational scientists together with biologists in one institute, puts BioISI in a privileged, unique multidisciplinary position in Portugal to develop new instruments. In 2016 BioISi filed 2 patents and 6 computational applications:

Patents:

- Bruno Loureiro, Fernanda Leal (2016) Meio protector para meios de cultura de base gelificante (Submitted)
- Gonçalo Costa, Patrick de Oliveira Freire, Romana Santos, Inês Gabriel e Silva Batista e Guinote, Ana Cristina Ferreira (2016) US Provisional Patent, Antifouling composition & process for production

Computational Applications:

- Sara Silva, GPLAB - A Genetic Programming Toolbox for MATLAB version 4 (Figure1)
- Hugo Botelho, ShinyHTM (Figure2)
- Hugo Botelho, Organoid Explorer (Figure3)
- Hugo Botelho, Leica Transfer Tool (Figure4)
- Hugo Botelho, Zeiss Transfer Tool (Figure5)
- Arthur Vieira and Mário Rodrigues, Vegrandis

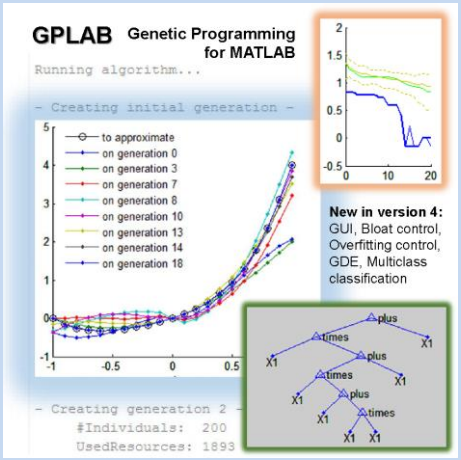


Figure 1

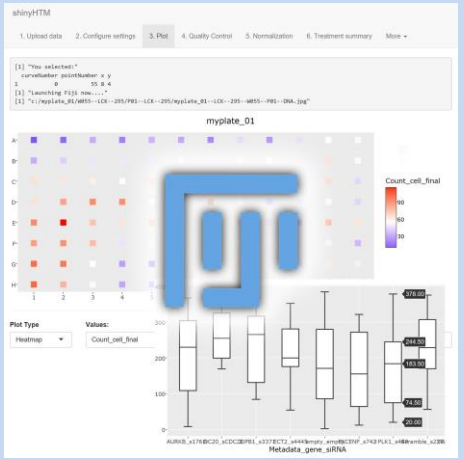


Figure 2

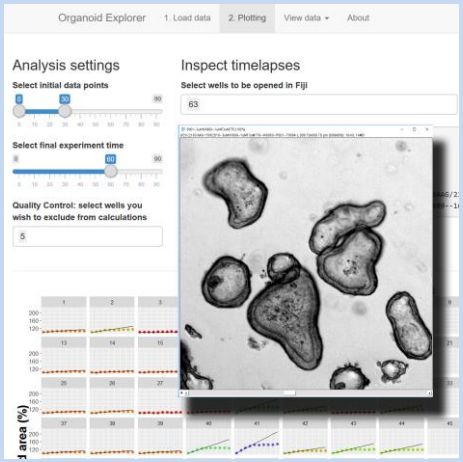


Figure 3

Figure 4

Figure 5

BioISI Facilities & Services

Coordinator: Rui Malhó

At BioISI facilities constitute an important instrument to recruit the most talented young scientists and significantly contribute to advanced training: PhD, MSc students, workshops. In 2015-2020, resources will be applied to maintain, update, and support BioISI facilities with expert staff, so that their usage can be applied to maximize expertise and technologies to solve specific biological problems.

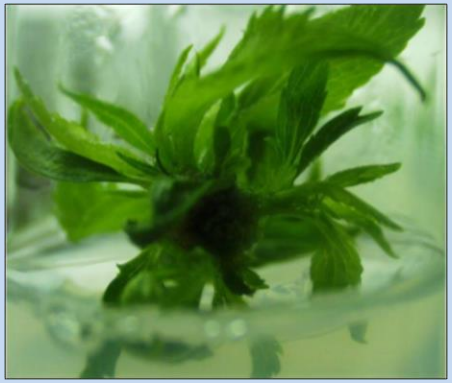
The goals of BioISI facilities are:

1) Providing excellent services with state-of-the-art equipment, user support and appropriate computational infrastructure;
2) Turning BioISI into a key player in the creation and operation of the next generation of biological research infrastructures within ULisboa;
3) Making lab available to society initiative goals (FabLabs as proposed by the PRP-National Reform Plan for Portugal) by which citizens, companies, researchers and public institutions work together (in co-creation) to innovate faster and more effectively.

Science Support Facilities

Mammalian Cell Culture: This facility provides expertise and advice in advanced methodologies for mammalian cell culture. Mammalian cell culture facility services include: expert consultation for researchers regarding primary cultures of human cells and organoids; general cell culture (media and experimental design); large-scale production of cells; cryopreservation of cell lines; mycoplasma screening; training in usage of environmental and safety of laminar flow hoods, incubators, cell seeder and microporator.

Plant House: The Plant House Facility has specialized plant growth chambers and provides support to research groups. Several chambers are capable of providing exceptional environmental conditions i.e. low temperature (chilling), high temperature, different light intensities and different relative humidity, allowing precise environmental simulation across different climate zones and the simulation of various environmental stress conditions.



NGS (INSA): The goal of the Next Generation Sequencing Facility is to provide cutting edge next generation sequencing technology to its users. NGS has become a key analysis method for biological research. The capacity to expand analysis from defined genomic regions to genome wide studies has boosted the pace of research discovery and enabled researchers to obtain a global view on biological processes.

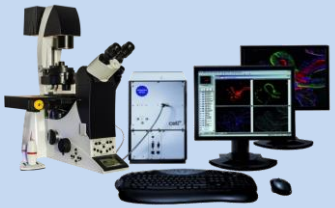
BioImaging

BioISI BioImaging facility is part of FCUL Microscopy Facility, a research and academic infrastructure that functions as a service provider and technical support hub for Research Units and teaching staff, as well as the rest of the scientific and student communities.

Its main areas of operation are:
1) Research: microscopy services for in-house, as well as external, Research Units
2) Academia: bioimaging tutoring and facilities for FCUL undergraduate classes
3) Outreach: guided tours and science communication events for high school visits
4) Mentoring: advanced courses and workshops on bioimaging for students and researchers

Technology: confocal microscope | widefield & fluorescence microscopes | fluorescence stereoscope | scanning and transmission electron microscope | high-throughput imaging system.

Technicians: Telmo Nunes (FCUL) | Luís Marques



Physics

The Atomic Force Microscopy and Related Techniques Laboratory (AFM-RT Laboratory) serves both scientists and students. There are 3 microscopes: one commercial AFM, one commercial AFM converted into an FFM and one home developed Force Feedback Microscope (FFM). The main activities of this laboratory are:
1) Research
   - Imaging: protein structures, cells, DNA, surfaces in general
   - Mechanical properties of cells
   - Instrumentation: development of new instruments, software and experimental strategies that support our research activity
   - study of nanotribology and nanofluidics by AFM and similar techniques
2) Education: AFM training classes for graduate students
3) Outreach: Visits from high school students and displays for the general public.

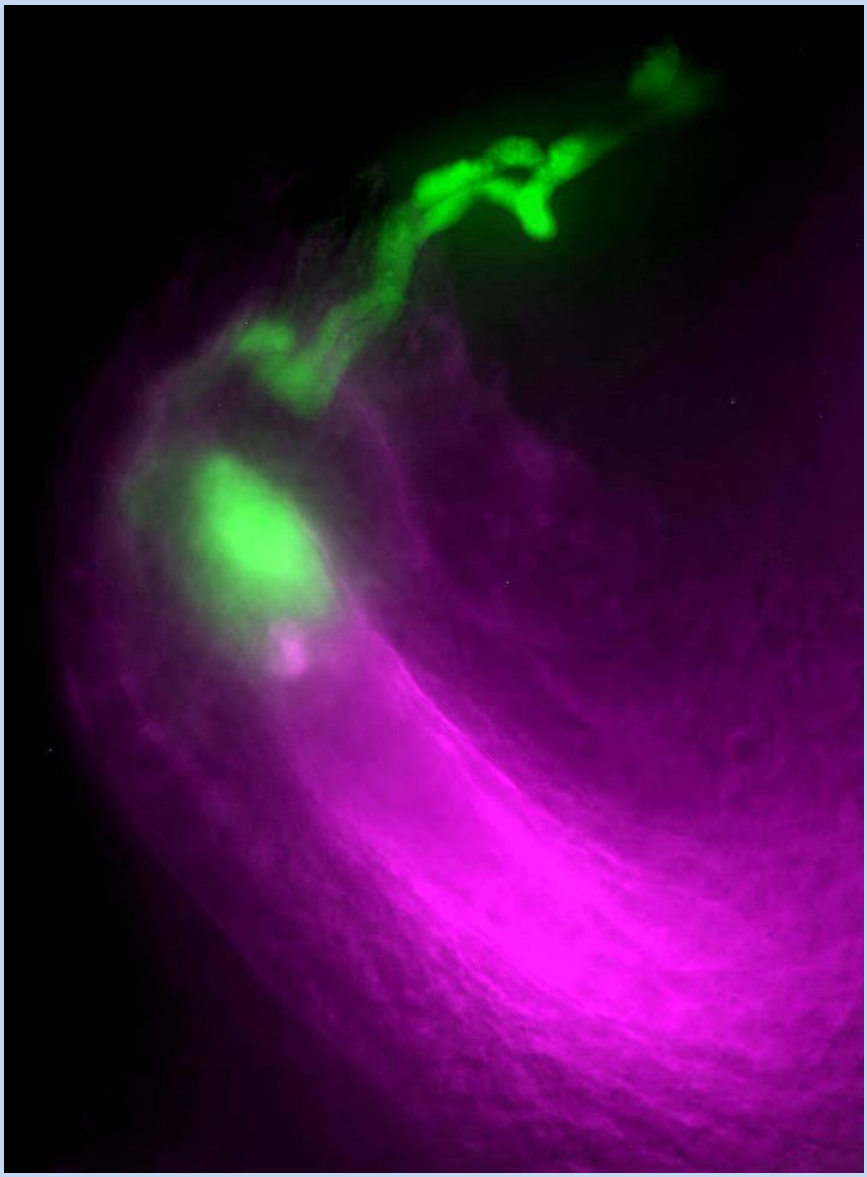
Computing

In terms of computing and data storage facilities, BioISI has currently installed 408 cores, 1144 GB RAM, and 88 TB storage in equipment concentrated essentially in 4 groups: GER, PBS, M&B, and FunGP.

We have been following an approach of exploiting common facilities available nationwide and at european level, INCD and EGI, respectively. The former is currently operational with an availability for BioISI of 200 virtual CPUs, 870 GB RAM and 5 TB storage.

Infraestrutura Nacional de **Computação Distribuída**

BioISi Facilities WebSite: http://bioisi.ciencias.ulisboa.pt/node/24



Teaching &Training

BioISI contributes to advanced training, as it hosts the multidisciplinary BioSys PhD programme and participates in two more PhD programmes. In 2016 BioISI launched a post-doc programme, besides its continuous mentoring of young PIs to establish themselves independently. BioISI offers also advanced training to external visitors in the scope of collaborations or to use its facilities and through the organization of international workshops.

BioSYS PhD Programe

BioSys - PhD Program in Biological Systems, Functional & Integrative Genomics, is a multidisciplinary PhD Programme in the framework of the FCT PhD Programmes Call.

BioSys was awarded with 11 PhD scholarships for each edition of the Programme for a total of 4 editions. BioSys has already enrolled 33 highly promising young scientists and will enroll another 11 students in 2017. BioSYS received more than 250 applications from all around the world and select 44 students from 6 different countries.

Our International PhD Programme offers a post-graduate training during the first semester involving manely international experts in different fields that bring their own experience to the discussion. This will allow each student to contact with internationaly recognized researchers and make contacts and collaborations with them. The following 3 ½ years are devoted to research in either national or international laboratories.

BioSys-PhD

BioISI Post-Doc Programe

BioISI has the ideal training environment for post-docs to further develop as scientists. BioISI post-docs find a supportive and mentoring faculty, have access to facilities, and are part of a lively scientific community. BioISI Post-Doc programme includes four 2yr fellowships to enrol into activities related with BioISI Thematic Lines:

Hugo Martiniano - Develop of computational pipelines combining machine learning/data mining and systems biology methods for multilevel data analysis, Supervisors: Luís Correia, Astrid Vicente

Catarina Baptista - The identification of new natural compounds of high therapeutic potential for Cystic Fibrosis by high-throughput microscopy screens, Supervisors: Hugo Botelho, Helena Vieira

Carlos Marcuello - Exploring protein-protein interactions with Atomic Force Microscopy, Supervisors: Margarida Godinho, Mario S. Rodrigues, Cláudio Gomes, Carlos Farinha

BioISI Post-DOC

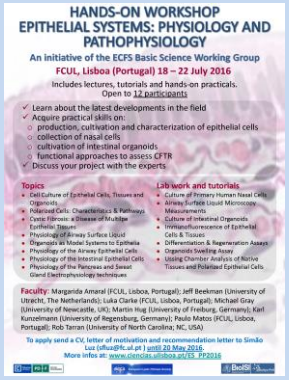
BioISI Workshops

One of the BioISI missions is to share knoledge with the scientific community and society. To accheve this goal BioISI invites to our intituition many international experts on theis working areas to teach in several workshops such as:

- HTM2016 | Hands-On Workshop On Fluorescence And High-Throughput Microscopy, 11-15 July 2016, Lisboa

- Epithelial Systems: Physiology and Pathophysiology Workshop, 18-22 July 2016, Lisboa

- Steering Living and Life-like Complex Systems, Cancún, Mexico, 4 July 2016



BioSYS 1- Enrolled Students

- **Ana Margarida Matos** - siRNA screen for modulators of CFTR surface retention, Supervisor - Paulo Matos (FCUL), Co-supervisor - Rainer Pepperkok (EMBL) *
- **Cibelle Costa** - System Biology Approach for Cardiovascular Medicine, Supervisor - Mafalda Bourbon (FCUL), Co-supervisor - Marília Antunes (FCUL)
- **Cláudia Loureiro** - Regulation of epithelial chloride transport by phospho-tyrosine-initiated protein networks, Supervisor - Peter Jordan (FCUL), Co-supervisor - Luka Clarke (FCUL)
- **Daniel Olivença** - A mathematical model of the phosphoinositide pathway in human pulmonary epithelial cells., Supervisor - Francisco Pinto (FCUL), Co-supervisor - Eberhard Voit (Georgia Institute of Technology) *
- **Hugo Santos** - Gene networks for motor neuron degeneration: from disease model transcriptomes to cellular systems, Supervisor - Margarida Gama-Carvalho (FCUL), Co-supervisor - David Van Vactor (Harvard Medical School) *
- **Joana Lérias** - Anoctamin 1 - A Member of A Novel Family of Ion Channels with Extended Functions and Significance in Disease, Supervisor - Rainer Schreiber (Univ Regensburg), Co-supervisor - Margarida Amaral (FCUL) *
- **Muhammad Asif** - System medicine approach to improve diagnosis and prognosis in Autism Spectrum Disorders (ASD), based on extensive genomic, biochemical and clinical data, Supervisor - Astride Vicente (FCUL), Co-supervisor - Francisco Couto (FCUL)
- **Nikhil Awatade** - CFTR2Drugs - Using a Systems Approach to Identify the Mechanism of Action of Correctors, Supervisor - Margarida Amaral (FCUL), Co-supervisor - Rainer Pepperkok (EMBL) *
- **Paulo Costa** - Functional networks in which the DIS3 and DIS3L1 exosome subunits participate and their relevance in colorectal cancer, Supervisor - Luísa Romão (FCUL), Co-supervisor - Margarida Gama-Carvalho (FCUL)
- **Rita Catarino** - Functional studies of members of the matrix-plasma membrane-actin cytoskeleton continuum and responses to abiotic stress, Supervisor - Rui Malhó (FCUL), Co-supervisor - Patrick Hussey (Univ Durham) *
- **Sara Canato** - The ER quality control: Dissecting protein networks to identify drug targets for Cystic Fibrosis, Supervisor - Carlos Farinha (FCUL), Co-supervisor - André Falcão (FCUL)

*International / mixed scholarships

BioSYS 2- Enrolled Students

- **Ana Marques** - Neuropsychiatric disease clustering in families with Autism Spectrum Disorder (ASD): genetic, epigenetic and environmental issues., Supervisor - Astride Vicente (FCUL), Co-supervisor - Luísa Romão (FCUL)
- **André Lamúrias** - Development of a Text Mining Approach to Disease Network Discovery, Supervisor - Francisco Couto (FCUL), Co-supervisor - Luka Clarke (FCUL)
- **Andreia Henriques** - Regulation of glucose uptake in mammalian cells by protein phosphorylation networks, Supervisor - Peter Jordan, Co-supr - Luka Clarke (FCUL)
- **Joana Silva** - Analysis of the translatome by ribosome profiling in colorectal cancer, Supervisor - Luísa Romão (FCUL), Co-supervisor - Augusto Luchessi (Univ. de Campinas) *
- **João Santos** - Nucleotide signalling in the regulation of CFTR trafficking and function, Supervisor - Carlos Farinha (FCUL), Co-supervisor - Manuela Zaccolo (Univ. de Oxford) *
- **Luís Sousa** - Role of CFTR in epithelial differentiation by functional genomics, Supervisor - Margarida Amaral (FCUL), Co-supervisor - Marc Chanson (Univ Geneva) *
- **Niccolò Rossi** - Identiflcation and characterization of the cause of lipid metabolism disruption in patients with severe and unexplained familial dyslipidaemia, Supervisor - Mafalda Bourbon (FCUL), Co-supervisor - Cesar Martin (Univ País Vasco) *
- **Nuno Domingues** - sncRNA regulatory networks in T cell activation and viral response, Supervisor - Margarida Gama-Carvalho (FCUL), Co-supervisor - Francisco Pinto (FCUL)
- **Rui João Loureiro** - The aggregation mechanism of β2-microglobulin in amyloid disease investigated through molecular simulations, Supervisor - Patrícia Faísca (FCUL), Co-supervisor - Eugene Shakhnovich (Univ Harvard) *
- **Rute Teixeira** - The role of sorting nexins and binding phosphoinositides in metabolite (ex)changes in tip growing cells., Supervisor - Rui Malhó (FCUL), Co-supervisor - Patrick Moreau (Univ Bordeaux) *
- **Samina Kausar** - An integrated systems approach to identify receptor and ion-channel binding networks in the Human brain, Supervisor - André Falcão (FCUL), Co-supervisor - Rita Mendes (Fac Farmácia - ULisboa)

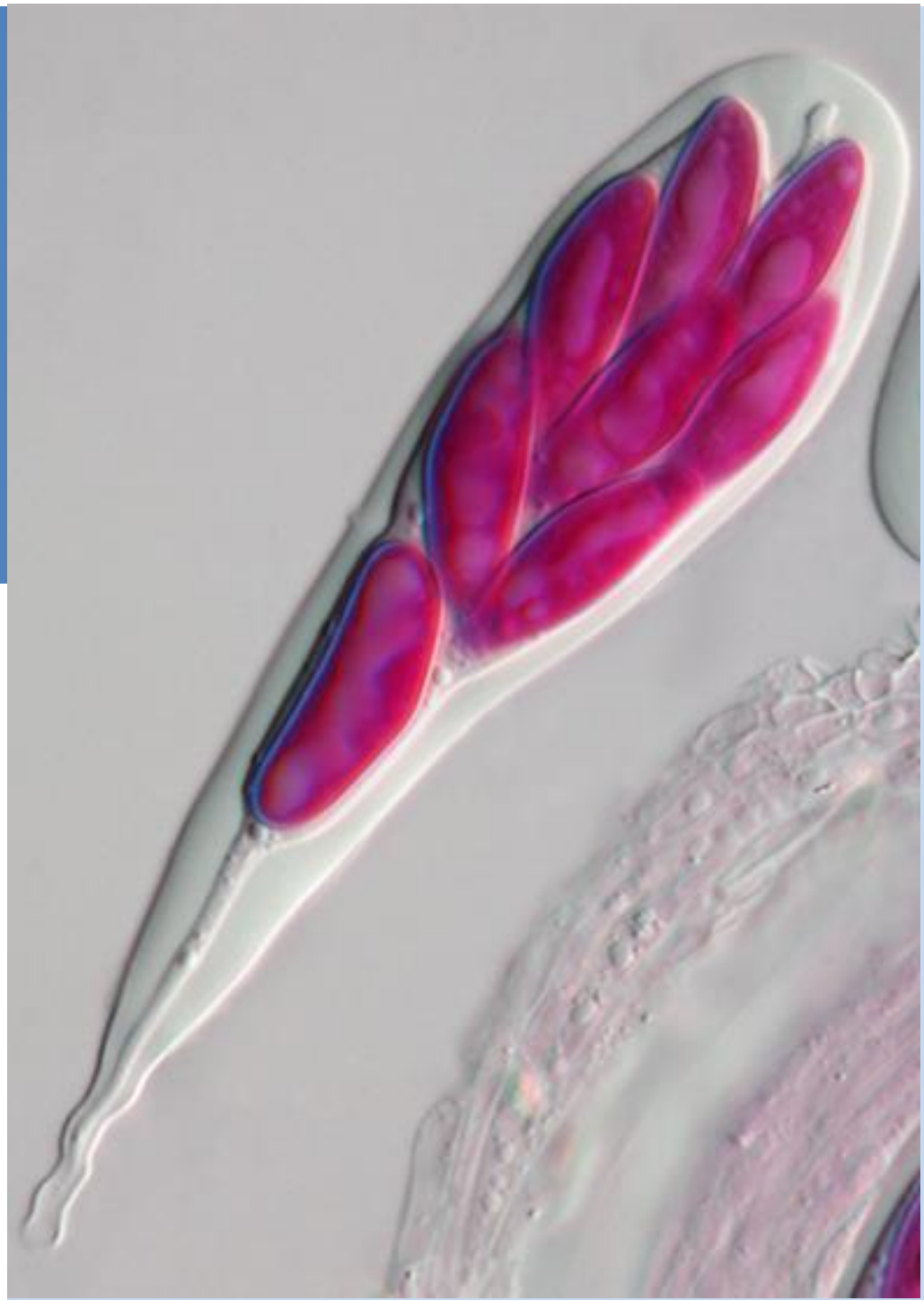
BioSYS 3- Enrolled Students

- **Daniel Cruz** - LMTK2 signalling in cystic fibrosis: an interactomics approach, Supervisor - Carlos Farinha (FCUL), Co-supervisor - Agnieszka Swiatecka-Urban (UPitt) *
- **Diana Pimentel** - Functional Genomics applied to the study of resistance against powdery mildew in grapevine, Supervisor - Ana Margarida Fortes (FCUL), Co-supervisor - Antonio Granell *
- **João Pedro Santos** - Gene-Environment interactions in Autism Spectrum Disorders (ASD), Supervisor - Astride Vicente (FCUL), Co-supervisor - Ana Nunes
- **Madalena Pinto** - Anoctamin 6 - A novel ion channel regulator with extended functions and significance in disease, Supervisor - Karl Kunzelmann (UReg/FCUL), Co-supervisor - Margarida Amaral (FCUL) *
- **Márcia Faria** - Targeting Rac1-signaling to enhance iodide-related therapy in breast cancer, Supervisor - Paulo Matos (FCUL), Co-supervisor - Rune Matthiesen (INSA)
- **Margarida Quaresma** - Role of CFTR in epithelial mesenchymal transition (EMT) by functional genomics, Supervisor - Margarida Amaral (FCUL), Co-supervisor - Jonas Fuxe (I Karolinska) *
- **Maria Teresa Braga** - Functional studies of plant cytoskeleton and membrane trafficking in responses to abiotic stress, Supervisor - Rui Malhó (FCUL), Co-supervisor - Patrick Hussey (Univ Durham) *
- **Mariana Romão** - S100 Proteins as novel modifiers of proteostasis in cancer and neurodegeneration, Supervisor - Cláudio Gomes (FCUL), Co-supervisor - Frederic Rousseau
- **Marina Luque** - A systems approach to the mechanisms of neurodegeneration, Supervisor - Margarida Gama-Carvalho (FCUL), Co-supervisor - Javier De Las Rivas (USalamanca) *
- **Marta Correia** - LiPID - Lipid profile ID - Identification of novel biomarkers to distinguish polygenic and monogenic dyslipidemia by a system biology approach, Supervisor - Mafalda Bourbon , Co-supervisor - Margarida Gama-Carvalho (FCUL)
- **Rafael Fernandes** - Regulation of nonsense-mediated mRNA decay (NMD) and the transcriptome: implications for physiology and myocardial infarction, Supervisor - Luísa Romão (FCUL), Co-supervisor - Mafalda Bourbon (FCUL)

BioSYS 4- Enrolled Students

- **Ana Rita Mendes Cavaco** - Lipid signaling in grapevine resistance against fungal pathogens, Supervisor - Andreia Figueiredo (FCUL), Co-supervisor - Ana Rita Matos (FCUL)
- **Filipa Simões** - Functional characterization of complexes regulating chloride and mucus transport and their significance in disease, Supervisor - Karl Kunzelmann, Co-supervisor - Margarida Amaral (FCUL) *
- **Flávio Soares** - Functional analysis of VviPAT6 and orthologous SlGRAS10: role in non-climacteric and climacteric fruit ripening, Supervisor - Ana Margarida Fortes (FCUL), Co-supervisor - Serge Delrot *
- **Gonçalo Nogueira** - The interplay between the mechanisms of PTC definition, mRNA translation, and NMD, Supervisor - Luísa Romão (FCUL), Co-supervisor - Francisco Pinto (FCUL)
- Identification of biotechnological potential on genomic nonfunctionalized orthologs elements, Supervisor - Ricardo Dias (FCUL), Co-supervisor - Christopher Henry *
- **Joana Vilela** - Regulatory RNAs in Autism Spectrum Disorder – modulation of genomic variant effects on clinical phenotype and brain structure and function, Supervisor - Astrid Moura Vicente (FCUL), Co-supervisor - Guiomar Oliveira (U Coimbra)
- **Lúcia Santos** - CFTR orphan mutations in Cystic Fibrosis – towards a detailed understanding of disease mechanisms, Supervisor - Carlos M Farinha (FCUL), Co-supervisor - Patrick T Harrison *
- **Mariana Pinhão** - What are the determinants of human genetic individuality?, Supervisor - Francisco Couto (FCUL), Co-supervisor - Margarida Gama-Carvalho (FCUL)
- **Pedro Correia** - Feeding 10 Billion: building upon plant systems biology to understand grain productivity in a warming climate, Supervisor - Jorge Marques da Silva (FCUL), Co-supervisor - Elizabete Carmo-Silva
- **Rafael Graça** - Functional genomics in familial dyslipidaemia, Supervisor - Mafalda Bourbon (FCUL), Co-supervisor - Rainer Pepperkok (EMBL) *
- Systems-wide Identification of Cystic Fibrosis Disease Map, Supervisor - André Falcão (FCUL), Co-supervisor - Margarida Amaral (FCUL) and Alexander Mazein *

* International / mixed scholarships



BioISI Post-Doc programme

Hugo Martiniano

Sup: Luís Correia | Astrid Vicente

Bioinformatics | Biomedicine

Development and application of combined data mining/machine learning and systems biology approaches to multilevel data (demographic, life style, clinical, physiological, genetic) from cohorts of Autism Spectrum Disorder (ASD) patients, with the objective of understanding the biological processes underlying this pathology, predicting the effects of molecular perturbations and ultimately developing improved diagnostic tools and more efficient and personalized therapeutic targets.

Major Achievements

Development of an analysis pipeline for exome sequencing data
Development of a machine learning model for ASD diagnosis.

BioISI Projects involved: MedPersyst

Carlos Marcuello Anglés

Sup: Cláudio Gomes | Carlos Farinha | Mário Rodrigues | Margarida Godinho
Biomedicine | Biophysics

Work performed can be divided in 2 sections: I) Analysis of S100A9 in presence of different metals and II) Get the mechanostability parameters of avidin:biotin complex.

- S100A is a large protein family related to Alzheimer's disease. Due to its polymorphism is not an easy task to find evidences of factors which boost the different assembly's formation and their role. Here, we try to elucidate them.
- Avidin: biotin is used as a test to measure the mechanostability parameters of this complex. Next step will be the use of the present setup to get the mechanical parameters of complexes related to cystic fibrosis and Alzheimer diseases.

In both sections, Atomic Force Microscopy (AFM) is the technique used due to the high accuracy to gather information at single molecule level.

Major Achievements

- Study the role of calcium and zinc metals in S100A9 morphology. Different reaction times, protein concentrations and incubation times were assayed.
- AFM tip bioconjugation. Biotin molecule is attached at the extremity of AFM tip apex. A succession of different organic chemical steps was followed.
- Obtain mechanostability parameters of avidin:biotin complex. k_{off} (dissociation rate at zero force) and x_β (barrier distance along energy landscape coordinate) parameters were acquired examining the most probable unbinding force monoevent at different loading rates.

BioISIProjects Involved: Atomic Force Microscopy approaches to study protein self-assemblies and interactions

Catarina Baptista

Sup: Hugo M. Botelho | Helena M. Vieira
Biomedicine | Biotechnology

Cystic Fibrosis (CF) is the most common life-shortening rare disease, often characterized by severe respiratory impairment. For almost 30 years it is known that CF is caused by mutations in a single gene – CFTR – that codes for an epithelial anion channel. 85% of CF cases are caused by F508del, a mutation preventing CFTR traffic to the plasma membrane. Two CFTR-targeting drugs are in clinical use but afford modest lung function improvement for most eligible patients. In this project we aim at improving CF pharmacotherapy by generating novel drug leads. We screened a diverse natural products library of marine and terrestrial origin which pinpointed extracts correcting F508del-CFTR traffic. Assessment of anion homeostasis restoration via activation of the alternative Cl- channel ANO1 is ongoing.

Major Achievements

- High Throughput Microscopy Screening of ~4000 natural compounds extracts regarding F508del-CFTR traffic rescue
- Selection of 290 extracts for secondary dose response screening
- Selection and ranking of 38 hits (19 marine origin and 19 terrestrial origin) for dose response, specificity and toxicity screening
- Preliminary testing in primary cell cultures

BioISI Projects involved: "Natural compounds as a source of novel drug leads for Cystic Fibrosis"

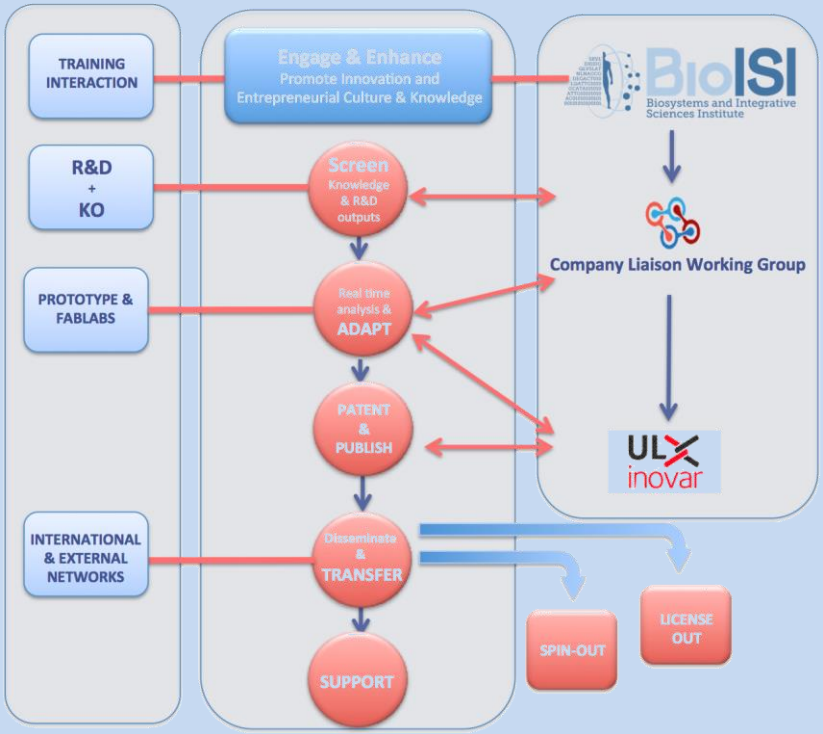
BioISI - KTT
Knowledge & Technology Transfer

BIOISI's team believes deeply in the concept of science contributing back to society. That is the principle behind the KTT concept of BIOISI – Knowledge & Technology Transfer. BioISI is actively engaged in developing its scientific and technological discoveries to benefit society, as indeed 25% of BioISI activities are on applied research. Thus, interacting with the socio-economic environment is an important BioISI aim.

To achieve such goal the centre has created the BioISI Company Liaison Working Group (CL-WG) which will help PIs to screen, develop and promote R&D knowledge outputs and support their market valorisation and industry interaction, given its privileged links to industry. A strategic KTT activities within the centre comprise, amongst other:

- internal and external awareness activities for the current KTT thematic realities, opportunities and challenges
- promote, via UL-INOVAR, the KTT office of ULisboa (www.inovar.ul.pt), other activities, like service providing, contract R&D, project collaborations, Fablabs, etc, that can lead to economic valorisation of the knowledge outputs generated by the centre
- promote intergroup extended collaborations and strengthen international and external reach activities and outputs

The management of KTT within BioISI will be under the responsibility of each PI who will communicate on commercially valuable results to the UL-INOVAR, after which they will work closely with CL-WG and external IP experts to identify and develop all necessary steps for IP protection and commercial exploitation deals.



Communication and Outreach Workgroup

Workgroup Coordinator: Margarida Gama Carvalho

The main aim of the Communication and Outreach Workgroup is the promotion of scientific knowledge and its impact on society, making the public aware of the value of research for society and human well-being through the promotion of the public dissemination of BioISI's science

Major Achievements:

- **BioISI Website:** development of the new BioISI website.
- **Social Media:** investiment in social media comunication (Facebook and linkedin) to promote BioISI's visibility.
- **European Researcher's Night 2016:** continued participation.
- **Science and Technology Week:** continued participation with focus on the Biotechnology Thematic line, with the active participation of industry and community leaders.
- **Outreach publications:** leaflets, press-releases and support for BioISI researchers actively engaged in sicence writing.

Figure 1

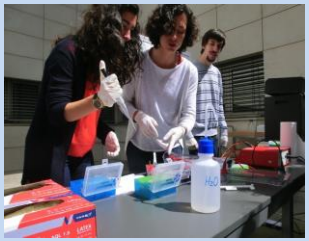


Figure 2

Figure 3

Figure 4

Figure 5

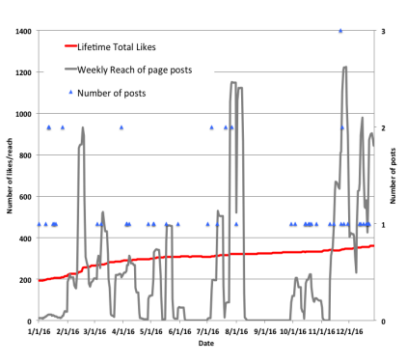


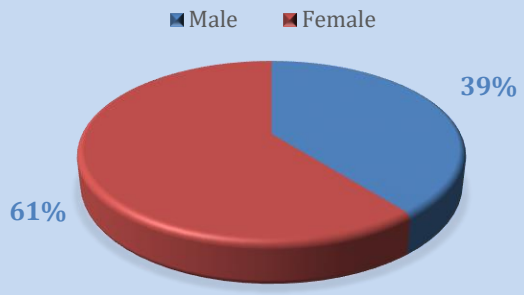
Figure 6

Figure 1: FCUL Open Day - April'16 "Observing nucleic acids"
Figure 2: September 30th European Researcher's Night – "The patient in the Lab: personalized solutions for Cystic Fibrosis"
Figure 3: The new BioISI Webpage
Figure 4: Leaflet Biotechnology at BioISI: 'Grape culture and Wine Science"
Figure 5: Key metrics for BioISI social media – Facebook page – (posts, reach and evolution of total likes for 2016
Figure 6: "Wines with Science" - Wine Tasting Event - Science and Technology Week

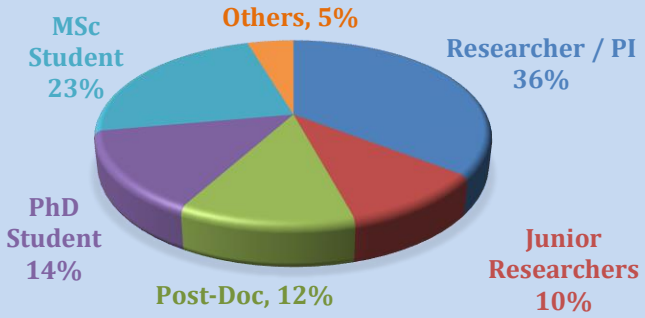
BioISI in Numbers

Members:

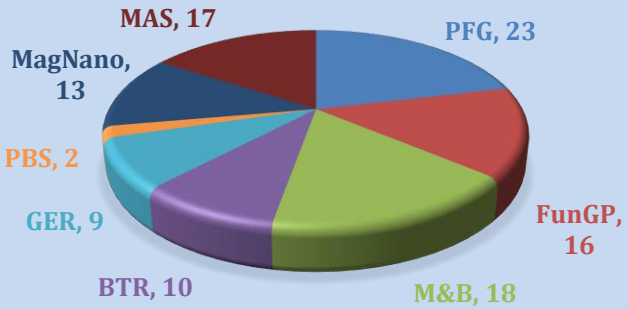
BioISI Gender Distribution

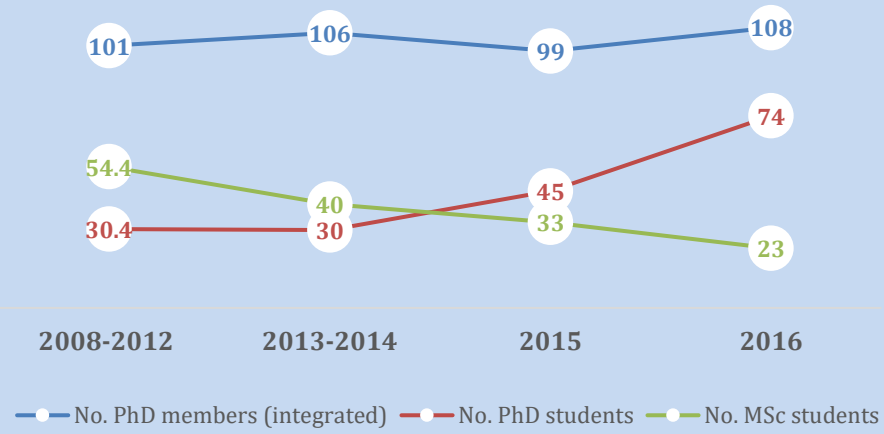


BioISI Members per Positions

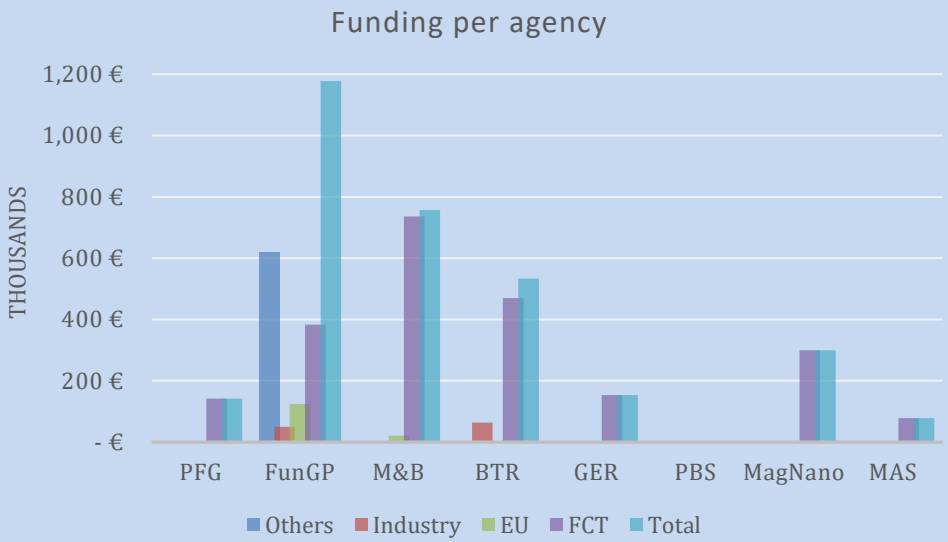


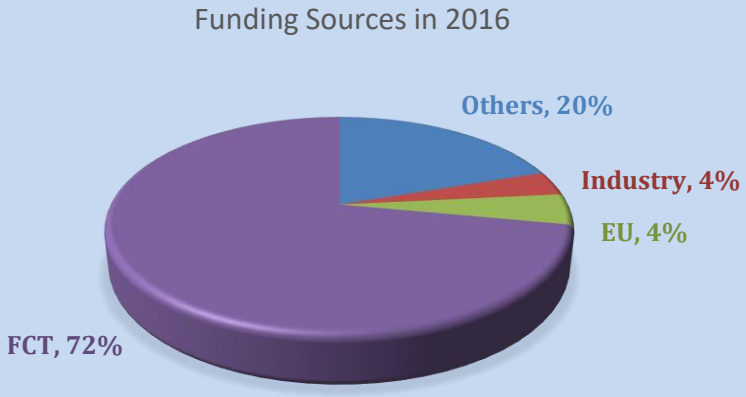
Integrated Members per Group
Total 108



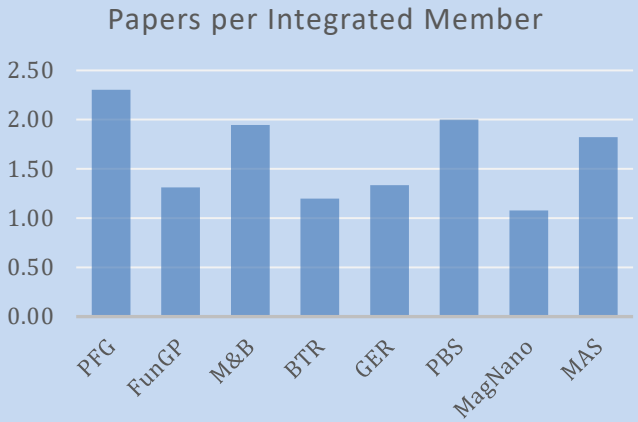


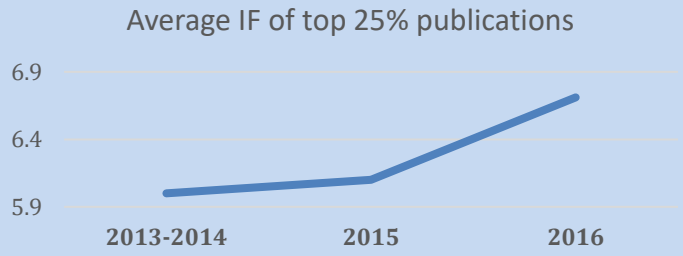
New Funding in 2016

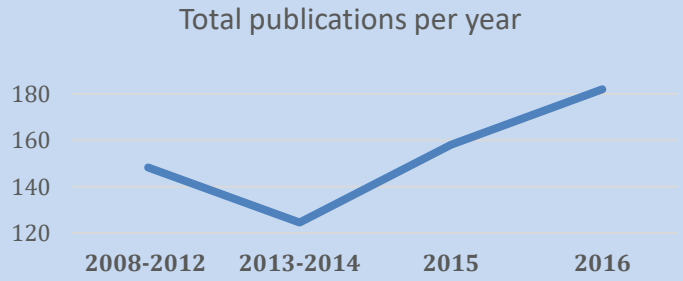




Bibliometrics







BioISI Publications

PFG Group

Amélia M. Silva, Sandra C. Silva, Jorge P. Soares, Carlos Martins-Gomes, João Paulo Teixeira, Fernanda Leal, Isabel Gaivão (2016) Exposure of HepG2 cells to Ginkgo biloba L. leaves aqueous extract: evaluation of cytotoxicity, genotoxicity and DNA protection against paraquat-induced oxidative damage. Journal of Ethnopharmacology, 23 pp

B. Duarte, M. T. Cabrita, C. Gameiro, A. R. Matos, R. Godinho, J. C. Marques, I. Caçador (2016) Disentangling the photochemical salinity tolerance in Aster tripolium L.: connecting biophysical traits with changes in fatty acid composition. Plant Biology, DOI: 10.1111/plb.12517

Barroca, M., Rodrigues, P., Sobral, R., Costa, M.M.R., Chaves, S., Machado, R., Casal, M., Collins (2016) Antibiotic free selection for the high level biosynthesis of a silk-elastin-like protein. Scientific Reports

Besson C., Lousada J. L., Gaspar M.J., Correia I. E., Soares David, T. M., Soares P., Cardoso R., Russo A. C., Varino F., Mériaux C.,Trigo R. M., Gouveia C. M (2016) The effects of the recent minimum temperature and water deficit increases on Pinus pinaster wood radial growth and density in southern Portugal. Functional Plant Ecology. 1, 10416666666667, DOI: 10.3389/fpls.2016.01170

Castro, PH; Couto, D; Freitas, S ; Verde, N ; Macho, A ; Huguet, S ; Botella, MA; Ruiz-Albert, J ; Tavares, RM ; Bejarano, ER (2016) SUMO proteases ULP1c and ULP1d are required for development and osmotic stress responses in Arabidopsis thaliana . Plant Molecular Biology 92, Issue 1-2, 143-159. DOI: 10.1007/s11103-016-0500-9

Coito, J.L., Ramos, M.J.N., Cunha, J., Silva, H.G., Amâncio, S., Costa, M.M.R., Rocheta, M. (2016) VviAPRT3 and VviFSEX: two genes involved in sex specification able to distinguish different flower types in Vitis. Frontiers in Plant Science

Costa ML, Solís M-T, Testillano PS, and Coimbra, S. (2016) In situ/Subcellular localization of arabinogalactan protein expression by fluorescent in situ hybridization, FISH. In The plant cell wall: Methods and protocols. Ed. Zoe Popper. 2nd edition.

Cotrim H., MONTEIRO F., Sousa E., Pinto M.J., Fay M.F. (2016) Marked hybridization and introgression in Ophrys sect. Pseudophrys in the western Iberian Peninsula. American Journal of Botany 103, 677-691 DOI: 10.3732/ajb.1500252

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Pedro Cardoso, Dulce Domingos, Ana Paula Cláudio (2016) Indoor navigation systems for reduced mobility users: The w4all case study. International Conference on ENTERprise Information Systems/International Conference on Project MANagement/International Conference on Health and Social Care Information Systems and Technologies, CENTERIS/ProjMAN / HCist 2016, 1200-1207.DOI: 10.1016/j.procs.2016.09.143

Nuno Magessi, Luis Antunes (2016) So Dark is the Con of Men. Social Simulation Conference Proceedings of SSC, Rome, September 2016

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Diana Galvío, Joel Lehman, Paulo Urbano (2016) Novelty-driven Particle Swarm Optimization. 12th Conf. on Artificial Evolution Volume 9554 of the Lecture Notes in Comp. Sci., 177-190 DOI: 10.1007/978-3-319-31471-6_14

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Books

PFG Group

Book Chapter

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FunGP Group

Book Chapter

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M&B Group

Book Chapter

Alves MJ, ZéZé L, Amaro F, Osório HC (2016) REVIVE 2011-2015 Culicídeos. In REVIVE 2011-2015 - Culicídeos e Ixodídeos: Rede de vigilÃ¢ncia de vetores. Centro de Estudos de Vectores e Doenças Infecciosas Doutor Francisco Cambournac. Instituto Nacional de Saúde Doutor Ricardo Jorge(INSA,IP) (Eds) , 11567. ISBN (ebook): 978-989-8794-21-5

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Ana Mendes-Ferreira, M. Olmo, José García-Martínez, and José E. Pérez-Ortín (23016) Functional genomics in wine yeast: DNA Arrays and Next Generation Sequencing. In Biology of Microorganisms on Grapes, in Must and in Wine. König, Helmut, Unden, Gottfried, Fröhlich, Jürgen (Eds.)

C. São-José, M. A. Santos and M.J. Schmitt (2016) Viruses of yeast and bacteria. In Biology of Microorganisms on Grapes, in Must and in Wine. König, Helmut, Unden, Gottfried, Fröhlich, Jürgen (Eds.)

BTR Group

Book Chapter

João Lavinha (2016) Widening medical support to infertility: ARTful birthrate increase? In Cunha V, Vilar D, Wall K, Lavinha J, Trigo Pereira P (organizadores) A(s) Problemática(s) da Natalidade em Portugal - Uma Questão Social, Económica e Política. Lisboa: Imprensa de Ciências Sociais.

GER Group

Book Chapter

Mendes-da-Silva A, Adega F, Chaves R (2016) Importance of Fluorescent In Situ Hybridization in Rodent Tumor. Technical Aspects and Applications of Toxicological Immunohistochemistry. 21-49 DOI: 10.1007/978-1-4939-1516-3_3

MAS Group

J Kolodziej, L Correia, JM Molina (Eds.) (2016) Intelligent Agents in Data-intensive Computing. DOI: 10.1007/978-3-319-23742-8

Book Chapters:

Sara Silva, Luis Muñoz, Leonardo Trujillo, Vijay Ingalalli, Mauro Castelli, Leonardo Vanneschi (2016) Multiclass Classification Through Multidimensional Clustering. Genetic Programming Theory and Practice XIII, DOI: 10.1007/978-3-319-34223-8

Mateus Calado, Luis Antunes, Ana Matos (2016) Managing the Access to Medical Emergencies Services. Distributed Computing and Artificial Intelligence, 13th International Conference Volume 474 of the series Advances in Intelligent Systems and Computing, Springer, pp359-365 DOI: 10.1007/978-3-319-40162-1_39

Nuno Magessi, Luis Antunes (2016) Risk Perception: Why Different Theories? Theodore Spencer (ed.), Risk Perception: Theories and Approaches, Nova Science Publishers, Series "Psychology Research Progress", chapter 1

BioISI Theses

MSc theses:

PFG Group

Raquel Vanessa dos Santos Frazão. Mestrado em Ecologia e Gestão Ambiental. Supervisors: Maria Romeiras (BioISI & CE3C/ FCUL); Maria Filomena Magalhães (CE3C/FCUL)

Ana Rita Leal Pena. Mestrado em Bioinformática e Biologia Computacional. Supervisors: Maria Romeiras (BioISI & CE3C/ FCUL), Octávio Paulo (FCUL).

Joana Mendes Casimiro. Mestrado em Biologia da Conservação. Supervisors: Maria Romeiras (BioISI & CE3C/ FCUL); Maria Filomena Magalhães (CE3C/FCUL)

FunGP Group

Ana Fonseca (2016) Importance of Anoctamins for Calcium Signalling in Different Cellular Localizations. Supervisors: K Kunzelmann (U Regensburg, Germany) & MD Amaral. MSc Thesis in Biochemistry.

Gonçalo Raimundo Nogueira (2016) Study of the self-assembly of the pro-inflammatory S100A9 protein driven by metal ion binding. Supervisor: Claúdio GOmes

Ana Águeda Pinto (2016) 2,4-dichlorophenoxy acetic acid-mediated stress in tomato plants: a biochemical and molecular approach.

Filipa Simões (2016) "Role of CFTR and TMEM16 for Regulated Cell Death". Supervisors: K Kunzelmann (U Regensburg, Germany) & MD Amaral. MSc Thesis in Biochemistry.

M&B Group

Soares, A.F.S. (2016) The relevance of mycorrhizosphere on the antimicrobial activity mediated by Streptomyces spp. Interactions. Supervisors: Ana Reis. Applied Microbiology Master.

Kryshen, A. (2016) Evaluation of the antimicrobial potential of essential oils and nisin. Supervisors: Ana Reis. Applied Microbiology Master

Catarina Isabel Nunes Alexandre (2016) Biodegradation treatment of petrochemical wastewaters. Supervisors: Lélia Mariana Marcão Chambel. Applied Microbiology Master

Tiago Manuel Marques Touret (2016) Isolation and characterization of microorganisms with probiotic potential. Supervisors: Lélia Mariana Marcão Chambel. Applied Microbiology Master

Catarina Isabel Ventura Pereira (2016) Análise Genotípica de Isolados Clínicos de Mycobacterium tuberculosis de Imigrantes provenientes da Comunidade de Países de Língua Portuguesa. Supervisors: Lélia Mariana Marcão Chambel. Applied Microbiology Master

Isabel Seixas (2016) Molecular basis of Saccharomyces cerevisiae adaptation to nitrogen-limiting fermentation conditions: impact on yeast growth and hydrogen sulfide formation. Supervisors: Alexandra Mendes Ferreira, Catarina Barbosa.

Ana Lemos (2016) Genome-wide phenotypic analysis of Saccharomyces cerevisiae in response to chitosan. Supervisors: Alexandra Mendes Ferreira, Patrícia Lage.

Inê Maria Pinto Mateus Valbom (2016) Caracterização de amostras de mel por Next Generation Sequencing. Supervisors: Sandra Mourinha Chaves.

Marcin Makowski (2016) Mechanism of action and membrane selectivity of a novel antimicrobial peptide. Supervisors: Ana Tenreiro.

Filipa Faria Rosa (2016) Towards improvement of Haematococcus pluvialis cultures by cell sorting and UV mutagenesis. Supervisors: Ana Tenreiro.

Catarina Rocha (2016) Adaptive Evolution of Non-Saccharomyces Yeasts to Produce Wines with Low Ethanol Content. Supervisors: Rogério Tenreiro, Ana Tenreiro. Master in Microbiology UL

Tatiana Cordeiro (2016) Lactic acid fermentation of peppers: isolation, characterization and evaluation of starter cultures. Supervisors: Rogério Tenreiro, Lélia Chambel. Master in Microbiology UL

João Melo (2016) Microbiology of Vinegar: from Isolation, Phenetic Characterization and Detection of Acetic Acid Bacteria to Microbial Profiling of an Industrial Production. Supervisors: Rogério Tenreiro, Ana Tenreiro. Master in Microbiology UL

GER Group

Marina Garcia Luque-Vaquero (2016) Exploring the interactions between neuron degeneration and RNA homeostasis through biological network analysis

André Gabriel (2016) Suppression therapy of Î²-thalassemia using Kanamycin and Gentamicin

Ana Raquel Guedes (2016) The role of SMG6 and PM/SCL100 ribonucleases in mRNA degradation mechanisms

Cláudia Estima (2016) The effect of G418 and PTC124 as suppression therapy for beta thalassemia

Gerson Asper (2016) mRNA Metabolism: Nonsense Mediated mRNA Decay as a Tool for Gene Therapy and the Role of Human DIS3L2 in Transcript Degradation

MagNano Group

Ricardo José Antunes (2016) Susceptibilidade magnética de nanopartículas para utilização em hipertermia magnética. Supervisor: Margarida Cruz. Mestrado Integrado em Engenharia Física

Laila Chahrazad Witzgall (2016) Nonparametric Segmentation of Nonstationary Time Series. Supervisor: J. P. Marques. Physics Master Thesis, Lisbon University, September 2016

MAS Group

Gonçalo Silva (2016) Simbologia em Realidade Aumentada Móvel. Supervisors: Maria Beatriz Carmo e co-orientadora Ana Paula Afonso

Alexandre Antonio de Carvalho (2016) Reconstrução Digital de Espaços Históricos: o caso de estudo de Mértola Virtual. Supervisors:Ana Paula Cláudio e co-supervisor Maria Beatriz Carmo

Ana Jacinta Pessoa da Pinha (2016) Humanos Virtuais no Treino de Competências de Comunicação em Ciências Farmacêuticas. Supervisors Ana Paula Cláudio e co-supervisor Maria Beatriz Carmo

Nuno Narciso Carreiro (2016) Técnicas de Visualização para Melhorar o Desempenho de Jogos Online. Supervisors: Ana Paula Afonso, co-supervisor Maria Beatriz Carmo

Daniel Onofre Nunes Soares (2016) Serviços Web para uma aplicação de Realidade Aumentada. Supervisors: António Ferreira, co-supervisor Maria Beatriz Carmo

PhD theses:

PFG Group

Irene Gouvinhas (2016) Olive fruit behavior during Colletotrichum acutatum colonization and maturation. Supervisors: Paula Martins-Lopes and Sónia Gomes. PhD in Chemical and Biological Sciences.

Teresa Maria Martins Deuchande (2016) Internal browning disorders of 'Rocha' pear during long-term storage. Supervisor: Fernanda Fidalgo

Andreia Vanessa Afonso Delgado (2016) Detection of genomic rearrangements in allopolyploids of the Triticeae tribe. Supervisor: José Lima-Brito, co-supervisor: Ana Carvalho.

Irene Pereira Gouvinhas, 2016. Olive fruit behavior during Colletotrichum acutatum colonization and maturation. Doutoramento em Ciências Químicas e Biológicas, com bolsa FCT ref. SFRH/BD/78013/2011, Universidade de Trás-os-Montes e Alto Douro, Vila Real (Orientadoras: Ana Barros, Paula Martins Lopes e Sónia Maria Alves Gomes).

GER Group

Rafaela Lacerda Santos (2016) Non-canonical translation initiation of proteins with potential relevance in colorectal cancer

MagNANO Group

Catia Patrícia Santos Silva (2016) Magnetic thin films and multilayers for applications in Spintronics. Supervisor: Margarida Cruz. PHd Thesis - submitted to FC/UL - October 2016 - waiting for defence

MAS Group

Paulo Miguel Ciríaco Pinheiro Pombinho de Matos (Provas em 21 de dezembro de 2015) Visualização de Informação em ambientes móveis. Supervisor: Ana Paula Afonso, co-supervisor Maria Beatriz Carmo. ULisboa

BioISI Funded Projects in 2016

PFG Group

2016 Conservation of plant biodiversity in the Macaronesian Hotspot: Integrating phylogenetic, taxonomic, and ecological approaches to study the Cape Verde endemic flora, FCT. PI Maria Manuel Romeiras

2016 Identificação de espécies pelo seu código de barras genético, Programa Ciência Viva no Laboratório - Ocupação Científica de Jovens nas Férias (OCJF). Project coordination: Maria M. Romeiras & Dora Batista.

2016 Characterisation of cork formation and reproductive biology in a cork oak hybrids population /Caracterização da formação da cortiça e da biologia reprodutiva numa população de híbridos de sobreiro, FCT. Budget: 10 002€ (total amount of the project: 199987) 2016-2019. BioISI PI: Partner in this project

2016 PLATAFORMA DE INOVAÇÃO DA VINHA E DO VINHO - INNOVINE&WINE, FEDER through NORTE 2020. No budget for BioISI (total amount of the project: 5.293.984,76€) 2016-2018. BioISI PI: Paula Martins-Lopes, Ana Carvalho, Manuela Matos, Fernanda Leal, Sónia Gomes, José Lima-Brito

2016 INTERACT project - Integrated Research in Environment, Agro-Chain and Technology•, European Regional Development Fund (ERDF) through NORTE 2020 (North Regional Operational Program 2014/2020. No budget for BioISI (total amount of the project: 3.508.607,47€) 2016-2018. BioISI PI: Paula Martins-Lopes, Manuela Matos, Ana Carvalho, Sónia Gomes, Fernanda Leal, José Lima-Brito

2014 RESIMPROVE - Desenvolvimento de processos de produção e extracão de resina de pinheiro para a melhoria da eficiência, racionalização e expansão da atividade", PRODER. No budget for BioISI (total amount of the project: 108.550, 67€) 2014-2017. BioISI PI: Maria João Gaspar, Ana Carvalho, José Lima-Brito

2017 Characterizing and monitoring cashew economically important diseases in West Africa as a prospective measure for sustainable production: a case study on GuineaBissau, FCT. Budget: 21 780€ (total amount of the project: 140 375€); 2017-2016. BioISI PI: Filipa Monteiro

2017 Hg-PLANKTARCTIC - Unravelling interactions between phyto- and zooplankton and mercury cycling in Deception Island waters impacted by volcanic-mercury, Propolar. No budget for BioISI (total amount of the project: 1700); 2017. BioISI PI: Ana Rita Matos

FP7-KBBE-2013-7-613781 - "EUROLEGUME - Enhancing of legumes growing in Europe through sustainable cropping for protein supply for food and feed" (2014-2017) No budget

FunGP Group

2016 RNA LIFE - Novel RNA Regulators as Potential Drug Targets for Cystic Fibrosis, CFF Cystic Fibrosis Foundation, USA. Budget: 305 000€; 2016-2017. BioISI PI: MD Amaral

2016 CFTR mRNA Stability Studies for PTC Mutations, CFF Cystic Fibrosis Foundation, USA. Budget: 209 000€; 2016-2018. BioISI PI: MD Amaral

2016 DIFFTARGET-Novel Factors of CFTR Traffic Related to Epithelial Cell Differentiation: Potential Therapeutic Targets for Cystic Fibrosis, FCT/POCTI. Budget: 200 000€; 2016-2018. BioISI PI: MD Amaral

2016 Predicting Clinical Drug Efficacy of CFTR Protein Modulators Using Intestinal Organoids and Nasal Cells from Patients with Cystic Fibrosis, Gilead GENESE Programme. Budget: 30 000€; 2016-2018. BioISI PI: MD Amaral

2016 Mechanisms NIS expression at the plasma membrane of thyroid cells. SPEDM/Genzyme. Budget BioISI: 5 000€ (total amount of the project: 10 000€); 2016-2018. BioISI PI: Matos P

2016 Regulação da beta oxidação mitocondrial por modificações pós-traducionais não-enzimáticas na saúde e em estados patológicos, FCT. Budget: 182 810€; 2016-2019. BioISI PI: Bárbara J. Henriques and Cláudio M. Gomes

2016 INSTINCT - Induced Pluripotent Stem Cells for Identification of Novel Drug Combinations Targeting Cystic Fibrosis Lung and Liver Diseasefunded by ERARE15-pp-010/JTC 2015. Budget: 124000€; 2016-2018. BioISI PI: MD Amaral

2016 Characterization of Orphan CFTR mutations, CFF Cystic Fibrosis Foundation, USA. Budget: 101 500€; 2016-2017. BioISI PI: MD Amaral

2016 Complete CFTR gene mutation analysis in Portuguese patients with Cystic Fibrosis, Vertex Pharmaceuticals. Budget: 20K€, 2017. BioISI PI: MD Amaral.

M&B Group

2016 RESISTIR, Portugal 2020 and Private equity. Budget: 449 000€ (total amount of the project: 1 059 675, 85€); 2016-2019. BioISI PI: R Dias, R Tenreiro, A Tenreiro

2016 SMARTWINE - Smarter wine fermentations: integrating OMICS tools for the development of novel mixed-starter cultures for tailor-made wine production, FCT and co-financed by FEDER through

COMPETE 2020 - Programa Operacional Competitividade e Internacionalização (POCI) and Programa Operacional Regional de Lisboa. Budget: 0 (total amount of the project: 196 180€) years. BioISI PI: Arlete Mendes Faia, Alexandra Mendes Ferreira, Catarina Barbosa

2016 INTERACT project - - œIntegrated Research in Environment, Agro-Chain and Technology - •, no. NORTE-01-0145-FEDER-000017, in its line of research entitled VitalityWINEfunded by European Regional Development Fund (ERDF) through NORTE 2020 (North Regional Operational Program 2014/2020).Budget: 123903(total amount of the project: 4122773) years. BioISI PI: Arlete Mendes-Faia, Alexandra Mendes-Ferreira, Catarina Barbosa

2016 I&D INNOVINE&WINE - Vineyard and Wine Innovation Platform, operação NORTE-01-0145-FEDER-000038. Activity 3.2 - Managing fermentation practices towards the production of targeted high quality wines with regional character, Fundo Europeu de Desenvolvimento Regional (FEDER) through NORTE 2020 (Programa Operacional Regional do Norte 2014/2020). Budget: 123 340 € (total amount of the project: 5 293 987€) years. BioISI PI: Alexandra Mendes-Ferreira

2017 Cost Action 16107 - Integrating science on Xanthomonadaceae for integrated plant disease management in Europe (Acronym: EuroXanth), EU framework programme H2020. Budget: 0(total amount of the project: 68000000) 2017-2022. BioISI PI: Leonor Cruz

2017 Projet Euphresco 2016-A-180 - Development, validation and verification of a diagnostic tool for detection and identification of Ralstonia solanacearum and Clavibacter michiganensis subsp. sepedonicus directly on plant tissue, Euphresco network/ INIAV. Budget: 20 589€ (total amount of the project: 79 929€; 2017-2020. BioISI PI: Leonor Cruz

2016 Unveiling host specificity and host pathogen interactions of Streptococcusfunded by FCT.Budget: 20 000€ (total amount of the project: 199 782€); 2016-2018. BioISI PI: Lélia Chambel, Rogerio Tenreiro

2016 BioClub: Designing biofertilizers by mimicking plants' recruitment of rhizospheric partnersfunded by FCT.Budget: 20 000€ (total amount of the project: 199 143€); 2016-2019. BioISI PI: Ana Reis, Ana Tenreiro, Sandra Chaves, Rogerio Tenreiro

BTR Group

2016 LALD Portugal - molecular testing of LIPA gene. Funded by Alexion Pharmaceutical. Budget: 50 000€; 2016-2017. BioISI PI: Mafalda Bourbon

2016 FH genetic diagnosis: development and validation of support documentation for the molecular diagnosis of Familial Hypercholesterolaemiafunded by Gendiag EXE, S.L. Budget: 13 880 €; 7 months. BioISI PI: Mafalda Bourbon

2017 Synaptic networks and Personalized Medicine Approaches to Understand Neurobehavioural Diseases Across the Lifespan (MEDPERSYST), PROGRAMAS DE ATIVIDADES CONJUNTAS (PAC), Portugal 2020. Budget BioISI: 469 678,33€ (total amount of the project: 2 487 042,85€); 2017-2020. BioISI PI: Astrid M Vicente, Margarida Gama Carvalho, Luis Correia, Patricia Faísca, Hugo Martiniano

GER Group

2016 Molecular evaluation of HER2 and Topoisomerases in feline mammary carcinoma - Developing rational stratagies for effective diagnosis and cancer chemoimmunotherapy, FCT.Budget: N/A. BioISI PI: Adega F, Chaves R

2017 LungCARD - Blood test for clinical therapy guidance of non-small cell lung cancer patients, 20-MSCA-RISE-2016/H2020-MSCA-RISE-2016. Budget: 1530 00€ (total amount of the project: 976 500€); 2017-2021. BioISI PI: Margarida Gama-Carvalho. BioISI Team: Raquel Chaves, Filomena Adega, Francisco Pinto, Ana Escudeiro, Daniel Olivença, Hugo Santos, Nuno Domingues, Marina Luque e Marta Correia

NMD in genetic diseases and cancer: key players, mechanisms, and a novel approach for suppression therapy (FCT/PTDC/BIM-MEC/3749/2014); PI: Luísa Romão.

Protein networks stabilizing CFTR at the plasma membrane – an integrated interactomics approach to find novel therapeutic targets in CF, PI: Peter Jordan, BioISI internal funding for interdisciplinary projects, 10 000€, Janeiro 2016 – Dezembro 2016

MagNano Group

2016 Interações Moleculares e Mecânicas em Biologia estudadas por Microscopia de Força Atómica com Retroação em Força, FCT. Budget: 149 568€ (total amount of the project: 197 568€); 2016-2019. BioISI PI: Mario S Rodrigues

2016 Molecular and Mechanical Forces in Biology measured with Force Feed-Back Microscopy, funded by FCT. Budget: 150 000€ (total amount of the project: 198 000€) years. BioISI PI: Mario Rodrigues (Project PI); M. Godinho; Rui Malhó

MAS Group

2016 PERSEIDS - Personalizing cancer therapy through integrated modeling and decisionfunded by FCT. Budget: 17 591 (total amount of the project: 199 997€) 2016-2019. BioISI PI: Sara Silva

2016 Geometria Intuitiva e Interativa, Fundação Calouste Gulbenkian. No budget for BioISI (total amount of the project: 45500); 2016-2017 BioISI PI: Ana Paula Cláudio; Maria Beatriz Carmo

2016 VIRTUAL TUTORING - the virtual tutor as learning mediating artifact in online university education, FCT. Budget: 60 967€ (total amount of the project: 199 706€) 2016-2018. BioISI PI: Ana Paula Cláudio, João Balsa