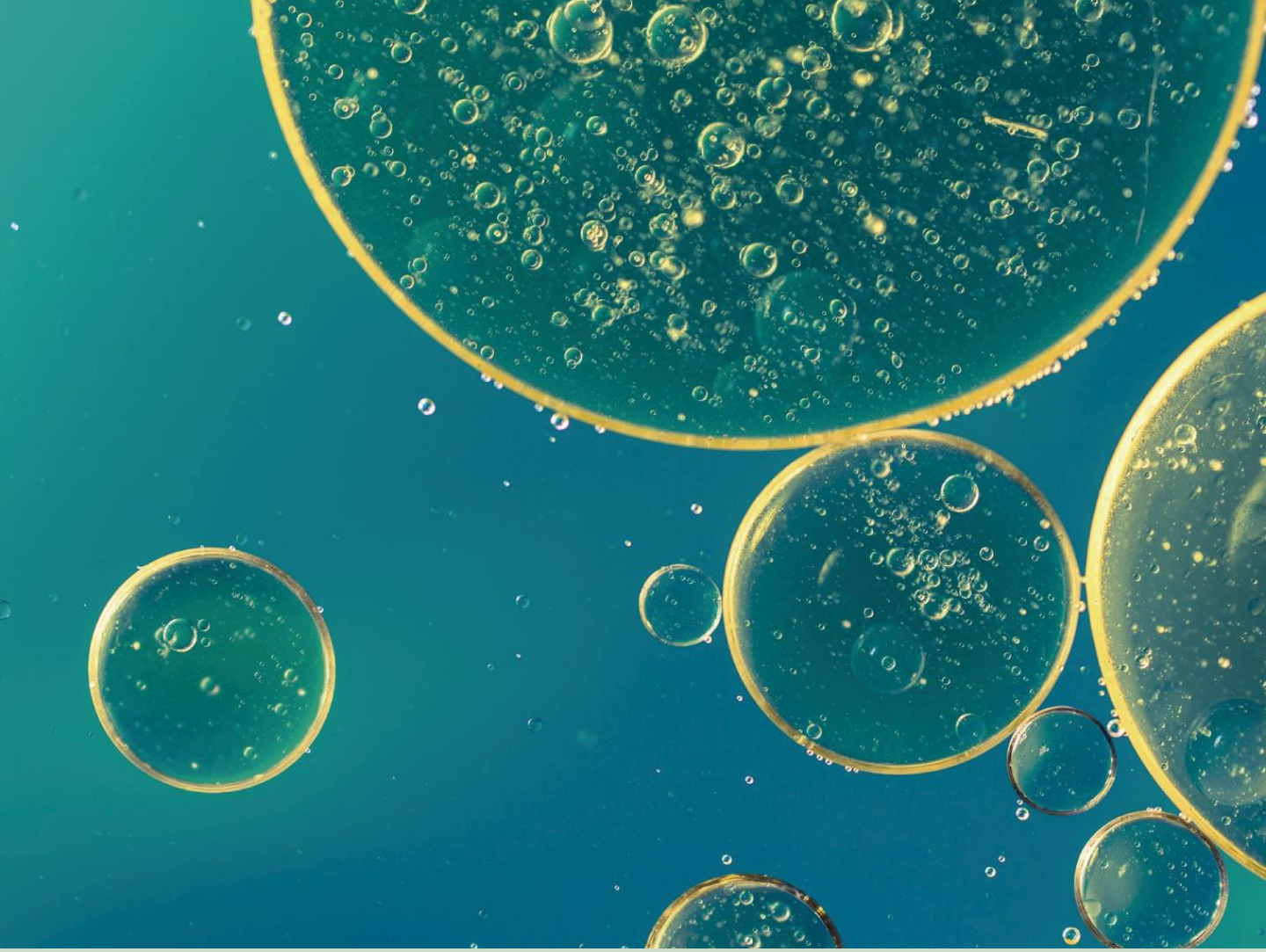

Biosystems & Integrative Sciences Institute
Strategic Programme 2019-2022

BioISI
Biosystems and Integrative Sciences Institute

BioISI Programme

2018-2022

Application form for Evaluation of FCT R&D Units

BioISI
Biosystems and Integrative Sciences Institute

February 2018

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Part 1: Identification of the R&D Unit, the Management Institutions and the Participant Institutions

01 IDENTIFICATION OF THE R&D UNIT

1.1 ID Number
4046

1.2 Name of the R&D Unit
BioSystems and Integrative Sciences Institute

1.3 Acronym
BioISI

1.4 Coordinator
Margarida Sofia Pereira Duarte Amaral

1.5 Scientific areas
Exact and Natural Sciences – Physics
Exact and Natural Sciences - Biological sciences
Exact and Natural Sciences - Chemistry
Exact and Natural Sciences – Health Sciences

1.6 Keywords

- Molecular Systems Biology
- Integrative Sciences
- Quantitative Biology
- Bioinformatics & Computational Modelling

1.7 R&D Unit Contacts and Address
Postal Address: Faculdade de Ciências da ULisboa, Edifício C8, 8.2.42, Campo Grande 1749-016 Lisboa
Telephone number: 217500857
Email: BioISIdirector@fc.ul.pt

1.8 R&D Unit Home Page URL
www.BioISI.pt

02 EVALUATION PANEL TO WHOM THE R&D UNIT SUBMITS THE CURRENT APPLICATION

HEALTH SCIENCES – Biomedicine and Molecular Biology

03 INVOLVED INSTITUTIONS

3.1 Main Management Institution
FCiências.ID – Associação para a Investigação e Desenvolvimento em Ciências

3.2 Other Management Institutions
Instituto Nacional de Saúde Dr. Ricardo Jorge (INSARJ)
Universidade do Minho (UM)
Universidade de Trás-os-Montes e Alto Douro (UTAD)

3.3 Participating Institutions
Instituto Nacional de Saúde Dr. Ricardo Jorge (INSARJ)
Instituto Politécnico de Lisboa (IPL)
Instituto Superior de Engenharia de Lisboa (ISEL/IPL)
Instituto Politécnico de Setúbal (IPSetúbal)
Universidade Aberta (UAberta)
Universidade do Minho (UM)
Faculdade de Ciências da Universidade de Lisboa (FC/ULisboa)
Universidade de Trás-os-Montes e Alto Douro (UTAD)
Universidade dos Açores (UAçores)
Hospital do Divino Espírito Santo de Ponta Delgada, EPE (HDESPD, EPE)
Instituto Nacional de Investigação Agrária e Veterinária, I.P. (INIAV)

04 RESEARCH UNIT DESCRIPTION AND MAIN CONTRIBUTIONS OF THE TEAM OF INTEGRATED RESEARCHERS

4.1 General description of the R&D Unit

Vision: BioISI, a new institute created in 2015, aims to pursue cutting-edge research on biosystems and integrative sciences to become the leading center at the forefront of research in this area in Portugal and internationally.

Goal & Missions: BioISI´s goal is to understand and address biological questions using integrative - Systems-approaches at the vanguard of life sciences research. It gathers scientists from bio-, physics and computational sciences, thus offering a unique multidisciplinary environment to its researchers/ students and fostering creative thinking to solve biological problems through integrative approaches.

BioISI pursues 5 major missions:

1) Research in BioSystems & Integrative Sciences

Biosystems display complex properties that cannot be predicted from studying isolated parts. BioISI aims to solve emergent complex problems in biology and biomedicine, from molecules to cells, organisms to populations using Systems approaches. Its research focuses on 4 Thematic Lines (TLs) (see also 12): Biomedicine (BioMed); Biotechnology (BioTech); Biophysics (BioPhys); Bioinformatics (Bioinf).

2) Technology & Instrumentation (T&I)

Addressing the complexity of living systems requires integrative, innovative analyses. T&I development is thus a key BioISI mission. Gathering physicists, computational scientists and biologists, puts BioISI in a privileged, unique multidisciplinary position in Portugal to achieve this goal. One key example are new developments in atomic force microscopy (AFM) for bio-applications.

3) Facilities & Services

BioISI facilities offer its scientists (also external & companies) cutting-edge methodologies/ services to address scientific questions. They include: 1) bioimaging; 2) screening; 3) physics; 4) computing/bioinformatics; 5) animal house (shared). Several are part of National/European Infrastructures Networks. In 2018 2 new facilities (Genomics, Proteomics/Metabolomics) were created.

4) Teaching & Training

BioISI hosts BioSys PhD programme on Systems Biology (http://biosys.campus.ciencias.ulisboa.pt/) enrolling 55 highly promising young scientists (half internationally co-supervised) and evaluated ´Exceptionally strong PhD program with essentially no weaknesses´. BioISI participates in 2 other PhD programs (DAEPHYS, EnviHealth&Co) and hosts a PostDoc programme. Other training: a) mentoring young PIs for independence; b) early career researchers; c) international workshops/seminars; d) external visitors; and e) outreach (at schools, science dissemination).

5) Knowledge/ Technology Transfer (KTT)

BioISI is actively engaged in putting its discoveries to benefit society, as 25% of BioISI funds come from private sources. Interacting with the socio-economic environment is thus an important BioISI activity achieved with Tec-Labs (www.teclabs.pt) FCUL´s innovation center. BioISI has used UL-INOVAR (former KTT office of ULisboa) to identify, protect, exploit its intellectual property (IP) facilitating KTT from basic research to industry.

Organization: Most BioISI research is conducted at FCUL campus but given its national poles (see 03) and international links (Visiting Professors, BioSys PhD students, collaborations with top institutions, large joint projects) it has national impact and worldwide relevance. BioISI has 8 Research Groups (RG), each with various PIs and one Group Leader (GL). To promote interdisciplinarity and integrative research, RGs contribute to >1 of the 5 Thematic Lines (TLs), each also headed by a Coordinator (TLC). A Scientific Committee (TLCs&RGLs chaired by BioISI Director and advised by the SAB) is responsible for strategic plan implementation. Communication & Outreach activities are carried out by BioISI jointly with FCUL press office and an external communication company for media dissemination. BioISI management is supported by 2 Post-Doc scientific managers, 1 secretary, plus FCID/FCUL admin staff.

4.2 Identification and brief description of contributions obtained by BioISI researchers

The main contributions obtained by the researchers integrated into BioISI were as follows (more details on achievements under 9 – Proposed Research Groups):

Crop & grapevine and wine product improvement.
BioISI plant research has provided significant contributions to grapevine plant/wine yeasts directly or from basic mechanisms revealed on model organisms then translated into strategies to improve quality of plants and products.

1) Identification of genes involved in resistance/susceptibility of grapevine genotypes upon pathogen infection by Omics analysis. Outputs: Agudelo-Romero et al (2015) J Exptl Bot 66:1769-1785; Figueiredo et al (2017) J Proteomics 152:48-57

2) Characterization of plant phosphatidylinositol proteins involved in seed production, plant development and ageing. Outputs: Serrazina et al (2014) New Phytol 203:784-793; Saavedra et al (2015) Plant Physiol 169:2572-8

3) Identification of oxidative and osmotic stress responsive genes using yeast transcriptional networks. Outputs: Amorim et al (2017) Biochim Biophys Acta 1860: 773-781

4) Whole-genome sequencing by 4th NGS of a cellulose producing strain of acetic acid bacteria and integration of omics-tools in the development of novel mixed-starter yeast cultures for fermentation practices and tailor-made wine production. Outputs: Large industry-academia partnership projects: COMPETE, FEEI and FEDER.

Systems approaches to rare diseases and neurodegeneration.

BioISI´s distinctive approach to Systems Biomedicine results from its capacity to generate biomedical big data from both established and innovative approaches (eg, original microscopy assays for functional genomics, 4th gen sequencing) together with its in-house ability to create computational tools to analyse these datasets in full context for clinical translation.

1) Discovery of global regulators ion channel function in Cystic Fibrosis and of the proteostasis network in folding diseases by functional genomics; novel pipelines for drug discovery in protein traffic disorders. Outputs: Almaça et al (2013) Cell 154: 1390-1400; Patent for DGKi as a drug target for CF;Silva et al (2013) PLoS Genet 9: e1003711;Lérias et al (2017) BBA- Mol Cell Res, in Press;Botelho et al (2015) Sci Rep 5: 9038.

2) Identification and functional assessment of variants found in patients with severe dyslipidaemias and development of algorithms for variant classification. Outputs: Alves et al (2014) Hum Mol Genet 23:1817-28; Alves et al (2015) J Am Coll Cardiol 66:2152-4; Fernández-Higuero et al (2015) Sci Rep 5:18184.

3) Identification of genetic mechanisms in ASD and documentation of a genetic overlap among major neuropsychiatric diseases through the Autism Genome Project and Psychiatric Genomics Consortium. Outputs: Pinto et al (2014) Am J Hum Genet 94:1-18; Hadley et al (2014) Nat Commun 5:4074; Buxbaum et al (2014) Mol Autism 5:34; Maier et al (2015) Am J Hum Genet 96:283-94; Weiner et al (2017) Nat Genet 49:978-985.

Contributions to Bioeconomy.

A remarkable differentiating strength of BioISI is its success in achieving long-standing industry-academia partnerships (~25% of its funding). The M&B group has led the way by exploiting links with SMEs and industrial networks to develop innovative approaches, services and products in several BioISI key areas of high potential to solve industrial challenges (albeit not always publishable).

1) Bioeconomy from the sea: evaluation of sea host-associated microbiomes and characterization of bioactivity profiles of marine microbes and other bioresources for several purposes in health, food, cosmetics, industrial applications, etc. Outputs: Calado et al (2017) on Grand Challenges in Marine Biotechnology. Chapter in Elsevier book Series; Gaspar et al (2016) Mar Drugs 14: 179; Martins et al (2014) Mar Drugs 12:1066-1101.

2) Development of bio-products, services and circular economy-based solutions: through industrial partnerships BioISI researchers have fostered new solutions in innovation, testing and certification. Outputs: support to new start-ups (Biomimetix, Lumisense, Biotask, etc); partnerships with Biotech/Agro-Food (Proenol, Sogrape, Cork Supply, etc) or BioPharma companies (AstraZeneca, AtralCipan, Proteostasis, etc); association with FabLab (Lisboa Municipality); entrepreneurship events (eg Young Creators, European Maker Week, etc); involvement in EU Bioeconomy networks (BBI-JU, ERA-NET Marine Biotech).

Enabling technologies: AFM related approaches.

BioISI is in a privileged position to develop new instruments by gathering physicists, computational scientists and biologists. Novel atomic force microscopy (AFM)/force feedback microscopy (FFM) approaches were developed to determine unique characteristics of biological systems.

1) FFM development as an original approach to circumvent a big AFM limitation, the "jump-to contact", leading to increased force sensitivity. Output: Rodrigues et al (2013) "Device for measuring an atomic force commonly referred to as Force Feedback Microscope (FFM)". Patent WO 2013057426 A1.

2) Illustration of a major FFM advantage ie, the tip excitation frequency can be arbitrarily chosen thus leading to new spectroscopic techniques. Output: Costa et al (2014) PLoS One 9: e101687.

3) The role of DGK4 enzyme in Arabidopsis pollen tube growth was demonstrated from mechanical and adhesion properties assessed by AFM. Output: Vaz Dias et al (2017) New Phytologist, submitted.

Innovative computational tools: applications for biosystems and bio-inspired approaches.

1) Pipelines for analysis human and HIV sncRNAs in deep sequencing data leading to identify novel regulators of cell activation and viral replication pathways. Outputs: Amaral et al (2017) EMBO J 36:346-360.

2) Structurally resolved picture of the aggregation mechanism of protein b2-microglobilin leading to dialysis related amyloidosis. Outputs: Estácio et al (2014) PLoS Comput Biol 10:e1003606;Loureiro et al (2017) Proteins 85:2045.

3) Novel evolutionary approaches that first allowed to develop online robot controllers for robotic swarms with real robots and with heterogeneous agents and robots. Outputs: Silva et al (2017) R Soc Open Sci 4:160938; Gomes et al (2017) IEEE Trans Evol Comput. In press.

4) A model of structured agent societies with context permeability across multiple coexisting social networks, and a model of selforganised demonstrations. Outputs: Nunes & Antunes (2015) Artif Intell 229:175-199; Lemos et al (2016) Int J Intell Syst 31:106-127

5) Development of protein interaction network-based methods to discover novel autism genes from within GWAS Statistical Noise. Outputs: Correia et al (2014) Int J Mol Sci 15:17601-17621; Correia et al (2014) PLOS One 9: e112399.

4.3 Main publications in 2013-2017 authored by Integrated Researchers registered in the current application

- Almaça, J., Faria, D., Sousa, M., Uliyakina, I., Conrad, C., Sirianant, L., Clarke, L.A., Martins, J.P., Santos, M., Heriché, J.-K., Huber, W., Schreiber, R., Pepperkok, R., Kunzelmann, K., Amaral, M.D., 2013. High-content siRNA screen reveals global ENaC regulators and potential cystic fibrosis therapy targets. Cell 154, 1390-400
- Alves, A.C., Etxebarria, A., Medeiros, A.M., Benito Vicente, A., Thedrez, A., Passard, M., Croyal, M., Martin, C., Lambert, G., Bourbon, M., 2015. Characterization of the First PCSK9 Gain of Function Homozygote. J. Am. Coll. Cardiol. 66, 2152-2154
- Duarte, F.J.S., Poli, G., Calhorda, M.J., 2016. Mechanistic Study of the Direct Intramolecular Allylic Amination Reaction Catalyzed by Palladium (II). ACS Catal. 6, 1772-1784
- Gomes, J., Mariano, P., Christensen, A.L., 2017. Dynamic Team Heterogeneity in Cooperative Coevolutionary Algorithms. IEEE Trans. Evol. Comput. X, 1-1.
- Amaral, A.J., Andrade, J., Foxall, R.B., Matoso, P., Matos, A.M., Soares, R.S., Rocha, C., Ramos, C.G., Tendeiro, R., Serra-Caetano, A., Guerra-Assunção, J.A., Santa-Marta, M., Gonçalves, J., Gama-Carvalho, M., Sousa, A.E., 2017. miRNA profiling of human naive CD4 T cells links miR-34c-5p to cell activation and HIV replication. EMBO J. 36, 346-360
- Pereira, F.J.C., Teixeira, A., Kong, J., Barbosa, C., Silva, A.L., Marques-Ramos, A., Liebhaber, S.A., Romão, L., 2015. Resistance of mRNAs with AUG-proximal nonsense mutations to nonsense-mediated decay reflects variables of mRNA structure and translational activity. Nucleic Acids Res. 43, 6528-44
- Vicente, A.I., Joseph, A., Ferreira, L.P., de Deus Carvalho, M., Rodrigues, V.H.N., Duttine, M., Diogo, H.P., Minas da Piedade, M.E., Calhorda, M.J., Martinho, P.N., 2016. Dynamic spin interchange in a tridentate Fe(iii) Schiffbase compound. Chem. Sci. 7, 4251-4258
- Serrazina, S., Dias, F.V., Malhó, R., 2014. Characterization of FAB1 phosphatidylinositol kinases in Arabidopsis pollen tube growth and fertilization. New Phytol. 203, 784-793
- Loureiro, C.A., Matos, A.M., Dias-Alves, Â., Pereira, J.F., Uliyakina, I., Barros, P., Amaral, M.D., Matos, P., 2015. A molecular switch in the scaffold NHERF1 enables misfolded CFTR to evade the peripheral quality control checkpoint. Sci. Signal. 8, ra48-ra48
- Saavedra, L., Catarino, R., Heinz, T., Heilmann, I., Bezanilla, M., Malho, R.M., 2015. Phosphatase and tensin homolog (PTEN) is a growth repressor of both rhizoid and gametophore development in the moss Physcomitrella patens. Plant Physiol. 169, pp.01197.2015
- Silva, F., Duarte, M., Correia, L., Oliveira, S.M., Christensen, A.L., 2016. Open Issues in Evolutionary Robotics. Evol. Comput. 24, 205-236
- Agudelo-Romero, P., Erban, A., Rego, C., Carbonell-Bejerano, P., Nascimento, T., Sousa, L., Martínez-Zapater, J.M., Kopka, J., Fortes, A.M., 2015. Transcriptome and metabolome reprogramming in Vitis vinifera cv. Trincadeira berries upon infection with Botrytis cinerea. J. Exp. Bot. 66, 1769-1785
- Nunes, D., Antunes, L., 2015. Modelling structured societies: A multi-relational approach to context permeability. Artif. Intell. 229, 175-199

- Marreiros, B.C., Sena, F. V., Sousa, F.M., Batista, A.P., Pereira, M.M., 2016. Type II NADH:quinone oxidoreductase family: phylogenetic distribution, structural diversity and evolutionary divergences. Environ. Microbiol. 18, 4697-4709
- Lobo, M.J., Amaral, M.D., Zaccolo, M., Farinha, C.M., 2016. EPAC1 activation by cAMP stabilizes CFTR at the membrane by promoting its interaction with NHERF1. J. Cell Sci. 129, 2599-612
- Teixeira, V.H., Vila-Viçosa, D., Reis, P.B.P.S., Machuqueiro, M., 2016. p K a Values of Titrable Amino Acids at the Water/Membrane Interface. J. Chem. Theory Comput. 12, 930-934
- Amorim, A.F., Pinto, D., Kuras, L., Fernandes, L., 2017. Absence of Gim proteins, but not GimC complex, alters stress-induced transcription. Biochim. Biophys. Acta 1860, 773-781
- Estácio, S.G., Krobath, H., Vila-Viçosa, D., Machuqueiro, M., Shakhnovich, E.I., Faísca, P.F.N., 2014. A simulated intermediate state for folding and aggregation provides insights into deltaN6 ß2-microglobulin amyloidogenic behavior. PLoS Comput. Biol. 10, e1003606
- Aquino, T., Nunes, A., 2016. Host immunity and pathogen diversity: A computational study. Virulence 7, 121-128
- Realista, S., Fitzpatrick, A.J., Santos, G., Ferreira, L.P., Barroso, S., Pereira, L.C.J., Bandeira, N.A.G., Neugebauer, P., Hrubý, J., Morgan, G.G., van Slageren, J., Calhorda, M.J., Martinho, P.N., 2016. A Mn(III) single ion magnet with tridentate Schiff-base ligands. Dalt. Trans. 45, 12301-12307

4.4 Description of other relevant contributions resulting from the activities in 2013-2017 of Integrated Researchers registered in the current application

BioISI vision and goals for 2018-22 are substantiated in several achievements and track record in 2013-17 by its ~130 integrated researchers from different disciplines (biology, chemistry, physics, computer science), which evidence how BioISI contributes with significant added value of to the development of national scientific and technological system, namely:

a) Science of Excellence: BioISI significantly contributes to the scientific knowledge as evidenced by its outputs of excellence, expressed in an impressive scientific track record in 2013-17 of 872 original publications in peer reviewed journals (~174/yr) with an average impact factor of 8.9 for the top 25% papers, and an H-index of 93;

b) Competitive funding: BioISI group leaders have had major success in in securing competitive funding being able to attract on average ~3.6 M€/yr;

c) Internationalization: BioISI researchers interact and collaborate with top institutions in several scientific areas, shown by its joint publications (55%); 20 ongoing large collaborative projects, eg H2020 (25% of all); 16 networks (eg Cost actions and unique Portuguese-speaking countries networks); co-supervision of PhD students (54%). BioISI researchers also participate in several European Infrastructures (EuroBioimaging, INSTRUCT, ESRF, EU-OpenScreen under application);

d) Advanced training: BioISI has a strong commitment to international education and career development programmes, through the coordination of a highly competitive international FCT-funded PhD programme focussed on Systems Biology (BioSys), and the participation in three other multi-

institutional FCT-funded PhD programmes. It has in place an Interdisciplinary Post-doctoral Programme (IPP) and young PIs are continuously mentored to become independently established. BioISI counted in 2013-17 with an impressive number of 45 completed PhD theses (9 theses/yr) and 129 MSc theses (~26/yr); BioISI has currently 69 PhD students;

e) Initiation of students into science: BioISI is at FCUL campus (being most of its researchers FCUL faculty members) which hosts >1,000 BSc and >300 MSc students in the biological areas, several starting as junior researchers at BioISI labs;

f) Organization of conferences, workshops and seminars: 12 meetings/workshops organized by BioISI in 2013-17, including several international workshops;

g) Patents, prototypes and products: In 2013-17 BioISI members registered 4 patents and 12 computational models, thus evidencing its KTT activities;

h) Knowledge & technology transfer, spin-offs: BioISI has solid collaborations with industry and a perfect balance of academic environment and proximity to industry, as 25% of BioISI activities are funded by the private sector, having significantly contributed to the creation of several its 17 start-ups and spin-offs at TecLabs (FCUL´s Innovation Centre: http://teclabs.pt/en);

i) Maintenance and curation of databases (at INSA): Database of the Portuguese Familial Hypercholesterolamia (FH) LDLR, APOB and PCSK9 variant database [recently published in Chora et al, Genet Med 2017]; involvement in ClinGen - the Clinical Genome Resource (https://www.clinicalgenome.org); e_COR database on the prevalence of cardiovascular risk factors of Portuguese population; IOCHEM-BD (www.iochem-bd.org) database, an open access free platform for parsing computational chemistry data [Álvarez-Moreno et al, J Chem Inf Model 2015];

j) Promotion of scientific & technological culture (Outreach): BioISI promotes awareness of its research societal impact through organization of science outreach events; dissemination via a newsletter, presence in social networks and, online, printed and TV coverage media news;

k) Actions of special relevance for society: BioISI strongly contributes to interactions with industry which works side-by-side with 28 companies at TecLabs; BioISI helped creating a FabLab (citizens, companies, researchers, public institutions working together for innovation);

Part 2: Description of the R&D Unit, main contributions of the team of integrated researchers in the application and funding in 2013-2017

05 REPORTS AND MEMBERSHIP OF EXTERNAL ADVISORY BOARD

5.1 External Advisory Board reports in 2013-2017

BioISI Scientific Advisory Board report for 2016

10th January 2016

The panel would like to thank the director, staff and students associated with BioISI for putting together an interesting and helpful programme of written reports and presentations. Scientific activities during the last year were described, along with plans for the next period, new project funding applications and descriptions of the developing BioISI structures and collaborations.

It was abundantly clear to the SAB that BioISI has come together as an entity and that it is more than the simple sum of its parts. Compared to the previous SAB review there is a much stronger synergy between component parts. BioISI shows strong interdisciplinary activity and this was evident particularly at the level of the junior staff who were strongly positive and excited about BioISI and the opportunities it provided.

Impressive progress has been made in several flagship programmes. These activities, despite having the capacity to thrive without BioISI, have been strengthened by the interdisciplinary efforts and technologies and expertise provided by BioISI. This was a significant, even if not entirely expected outcome given the diversity of topics and approaches across BioISI.

Bioinformatics is now better integrated and has an emerging leadership within BioISI, but should continue to develop into a more unified resource of benefit to all BioISI research groups. Many distributed servers remain and should, over time, be combined to provide a high performance computer service with a single set of cores and storage available centrally. Future BioISI funding proposals might take this into account. The data management and analysis expertise of this group has the capacity to grow and be a significant resource for BioISI and the wider academic community.

The BioISI leadership should continue to monitor the balance between quality and quantity. BioISI should aim to achieve an international reputation, but it cannot and should not try to do so across all areas. The concept of flagship projects is strongly supported by the SAB, but the bar must be set high to achieve and retain that status. BioISI must be dynamic and foster organic growth, but should also be able to discontinue activity and support in areas not making sufficient progress.

It was clear to the SAB that the future success of BioISI will be affected by its position and added value within its governing and host bodies. It will be scientifically beneficial for BioISI to develop towards a recognizable physical entity with the individual groups better co-located. The SAB urge the BioISI leadership, and the BioISI governing and host bodies to work together to develop

a strategy to achieve better co-localization over time. Space constraints appear to have the capacity to restrict the future growth and development of BioISI and should be addressed as a matter of urgency.

The SAB believes that BioISI would greatly benefit from being a fluid structure and should encourage other strong groups and individuals with research strengths aligned with BioISI to join and benefit from the interdisciplinary structures and dynamism of BioISI. The proposed 2017 FCT review may present opportunities to encourage other strong groups to join the network.

Additionally BioISI would greatly benefit from stronger outreach activities both internally and nationally. It is important that the colleagues who are not BioISI members are aware of additional research capabilities provided by BioISI and and availability of collaborations enabling expansion of current research at the University into modern directions including advanced imaging, bioinformatics genomics and proteomics, which are core strengths of BioISI. Such outreach would make BioISI an integral part of the research community at University of Lisboa and beyond and might facilitate the efforts to consolidate its facilities in close proximity to each other.

Sustainability of BioISI beyond what has been a strong beginning will require all parties, BioISI, Schools and Faculty to be aware of and to acknowledge the added value of the existence of BioISI and to reflect this in their respective strategic plans. A successful BioISI will be of value to all parties, reflected in increased scientific reputation and output, attraction of the best academic staff, increased exchequer and non-exchequer funding, and improved teaching at both undergraduate and postgraduate levels.

BioISI director and senior staff should seek to identify similar multidisciplinary systems research centres internationally, against which to benchmark BioISI performance and to establish academic links with potential for cooperation and exchange of knowledge and research staff and students.

The planned creation of a BioISI outstation including the development of a genomics core facility close to Lisbon area is considered of highest value. This will increase further the potential of BioISI to start collaborations with industry, as a number of interested companies exist in this area. It will not only allow raising funds for BioISI research that is currently not accessible, but extent the portfolio of expertise and services available to BioISI.

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

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

Eugene Shakhnovich (Chemistry and Chemical Biology). Biophysics Laboratory, Department of Chemistry and Chemical Biology, Harvard University, Cambridge (MA, USA)

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

1st Annual BioISI Annual Meeting, 10-11th December 2015

Scientific Advisory Board Report

1 - The Advisory Board members would like to congratulate the BioISI group leaders and researchers for the initiative to establish a Center of Excellence in Systems Biology and for the high-quality work carried out during the first year, as demonstrated by the good level of publications in their respective fields.

2- Although the current structure and strategic plan of BioISI should be sufficient to ensure continuous progress and collaborative work, the AB felt that BioISI should aim higher and strategically plan to become a center of excellence in Systems Biology not only in Portugal, but also competitive on the world stage.

3- In order to achieve that higher level of ambition, obtain a deserved funding increment at the intermediate site visit, and go beyond the first 6 years of FCT funding, the AB recommends to focus the strategic plan and strengthen the leadership structure with the overarching goal of maximizing the added value of the existing human, technical and scientific resources available in the consortium.

4- In particular, the AB suggests that BioISI should articulate the strategic directions into the four thematic lines. BioISI should seek to strengthen them by supporting with the newly available FCT funding in BioISI preferentially those projects, which represent a clear added value to the thematic lines rather than to support individual PI's research themes alone. However, in this regard projects of individual groups/teams, which make contributions of added value to the thematic lines or a core facility associated with them, should be considered for strategic funding. The important message is that a thematic line should be more than a collection of projects in a give theme. Rather, a thematic line should aim to become a competence area that catalyses new projects and attracts new collaborations either because there is human capital with specific expertise or because there are unique technical facilities. The AB suggested renaming the thematic lines with easier to understand names:- for example, Biomedicine, Biotechnology, Biophysics, and Bioinformatics.

5- The budget allocated to the strategic plan should aim at reinforcing the four thematic lines so that they become nationally and internationally competitive and become a catalyst of new collaborations and funding. The budget might in the future include programs, such as post-doctoral funding aimed at reinforcing competences in specific areas of the four thematic lines. Collaborative strategic projects should be rewarded as in the present post-doctoral proposals, but in the future, individual projects should also be granted on the basis of their contributions to strengthening a thematic line. Because of the extensive links between groups, the AB recommends that the selection of collaborative grant and postdoc awards is made, as far as possible, on the basis of external evaluations. Intensive brainstorming between

groups and among thematic lines should help to strengthen the proposals, improve their collaborative value and their potential for generating results and technological advances of greater added value for BioISI and the Portuguese scientific community.

6- The AB suggest that the proportion of BioISI funding that is strategic should increase over time, and that direct support for the participating research teams should correspondingly decrease, while keeping a performance-based criterion which should be based not only on bibliometric parameters but also on the status of the groups assessed through international peer review. The funding will still support research teams but now in their strategy alignment with the thematic lines.

7- The existing leadership structure should be reinforced by giving the BioISI director executive powers and responsibilities for the success of the center, and empower the thematic lines by allocating one strong leader to each of them. The BioISI Director could be helped by the thematic line leaders to define strategic plans, budget allocation, and performance criteria. The key decision making group is the executive – the Director and the four thematic leaders. The AB suggest that the research team PIs might form a committee, and elect a representative who might sit on, or be in attendance at the Executive group meetings. The involvement of young faculty in establishing and moving forward transversal actions across thematic lines is strongly encouraged

8- Existing groups should consider if they would like to merge or cooperate with other groups. This should be considered where group size is small, heavily dependent on BioISI core funding and where it makes scientific sense. This should come about by agreement with the relevant group leaders and the executive and should be seen as a way to enhance the scientific profile of all parts involved.

9- Each group should formally align to one thematic line but with additional thematic contributions where relevant. Each group should be free to contribute to one or more BioISI thematic lines, and receive funding, as long as they fulfill the overarching strategic plan of the corresponding platform(s).

10- The faculties that host BioISI should work towards the physical localization of the components of BioISI in a way that best allows BioISI to achieve its strategic aims and to strengthen its identity. This is especially important for the thematic lines where they are providing a shared resource or expertise.

11- Proposed acquisition of new computing infrastructure should be carefully compared technically and financially with the use of cloud computing services, such as those offered by Amazon. Ethical and data protection concerns will need to be addressed.

12- The AB also congratulates BioISI by the excellent implementation of their strong PhD Program. The newly obtained resources from FCT should help to further

improve interdisciplinary training and a culture of scientific dialogue among the excellent community of PhD students. The possibility to establish a Graduate Committee as an official forum for student's participation in the discussion of matters relevant to their training and life at BioISI should be considered.

22nd December 2015

Prof. Michael Gill, Professor of Psychiatry, Trinity College Dublin and Clinical Director, Wellcome Trust/HRB CRF at St. James' Hospital

Prof. Juan Valcarcel Juarez
ICREA and Center for Genomic Regulation (CRG) Dr. Aiguader 88
08003 Barcelona, Spain

Prof. Dr. Dario Floreano Swiss Federal Institute of Technology
Laboratory of Intelligent Systems, Director
Swiss National Center of Robotics, Director

Prof. Eugene Shakhnovich, Professor of Chemistry and Chemical Biology, Harvard University

Dr. Rainer Pepperkok, Head of core facilities, Head of advanced light microscopy core facility, team leader and senior scientist, EMBL, Heidelberg

BioISI Scientific Advisory Board report for BioISI 2017 activities and 2018-2022 strategic plan

30th January 2018

The BioISI scientific advisory board met on the occasion of the third BioISI annual meeting taking place from 9-10 January 2018 at the University of Lisbon. Prior to the meeting the board members received the BioISI annual report for the year 2017. In the morning of the first meeting day thematic line leaders presented the work and achievements during 2017 and future plans for the coming five years. This was followed by a strategic discussion of the board members and thematic lines leaders on the BioISI plans for the period 2018-2022. Progress of current BioISI projects and new projects applying for funding in 2018 were presented during day two of the meeting. The board members would like to thank the director, staff and students of BioISI for putting together a very exciting programme of written reports and presentations.

During the three years of its existence BioISI has developed an impressive environment of complementary multidisciplinary research competences, as they are required for cutting edge systems biology. The scientific output of BioISI is excellent in terms of publications and patents, but also in the number of excellent PhD and MSc theses. Compared to earlier years the collaborative and interdisciplinary nature of BioISI has grown further, and it has become evident that the synergy between the different thematic lines has become more than the sum of the pieces. The BioISI leadership needs to be commended in particular for this achievement, as the compartmental discipline-specific nature of the traditional University environment of BioISI needs to be softened before such synergies can be achieved. Junior staff from the different thematic lines has in a number of interdisciplinary projects demonstrated this exceptional strength of BioISI's approach to conduct cutting edge life science at the international level. This has resulted in several interdisciplinary joint publications with high impact and potential to be eligible for further competitive funding outside the BioISI funding structure. A number of outreach activities have increased the visibility and the public awareness of the unique research capabilities of BioISI.

In order to bundle BioISI's compartmentally distributed expertise and make it available to its entire faculty and even beyond to the Lisbon life science community BioISI has begun to establish core facilities providing service and expertise in tissue culture, imaging and imaging based screening. For the latter one plans exist to join the ESFRI infrastructure EU Open Screen, which will allow BioISI to have access to an internationally coordinated resource of

compounds, reagents, and technical know-how in this important field. Two further core facilities for next generation sequencing and proteomics are planned to be set up in the near future. This will strengthen BioISI's possibilities considerably and the SAB members strongly encourage to continue to set-up core facilities based on the existing expertise in individual laboratories of BioISI members and when well-defined demands by its faculty exist. It will be a unique opportunity to develop these types of expertise in BioISI into a core facilities infrastructure with well-defined services openly offered to a community even larger than BioISI itself.

BioISI has also started to develop fruitful collaborations with industry, in particular the wine producing industry. These collaborations do provide additional funding and expertise for BioISI's research activities and have generated already intellectual property. The SAB members consider this activity as highly valuable for BioISI's future. It has however also become clear that currently an adequately experienced office for technology transfer is lacking in BioISI and neither is one available through the University of Lisbon. Therefore, BioISI's future plans to invest in the set-up of a well functioning office for technology transfer, which interacts with the scientists to identify and develop innovations in collaboration with industrial partners need to be valued highly.

In summary, BioISI has developed into an internationally oriented interdisciplinary institution with exciting opportunities for the coming years. The different thematic lines and the contributing faculties of the Lisbon area as well as integrated scientists from other Portuguese institutions (at BioISI poles) have generated synergies that go well beyond the sum of the pieces, and it can be expected, should central basic funding continue, that it will develop into an internationally competitive institute contributing to a high visibility for Portugal's life sciences offering also excellent opportunities for collaborations for emerging companies in the field in the Lisbon area.

Specific comments

The SAB members see the addition of the thematic line biological chemistry very positive. It nicely complements the existing thematic lines and provides access to important expertise in chemistry hat has been lacking so far in BioISI. It can be expected to strengthen in particular BioISI's efforts to identify and develop lead compounds for therapy of rare diseases such as Cystic Fibrosis.

The SAB is of the opinion that focus on only few (max. two to three) flagship projects to which most BioISI thematic lines contribute synergistically is of

high importance in order to achieve its ambitious goal to become an institution of high international visibility. The fields of particular strength currently represented in BioISI, which could be the basis for such flagship projects, are crop development and rare diseases along with enabling technologies (e.g., atomic force microscopy (AFM) related methodologies or novel bioinformatics tools). It is recommended to focus the future plans and visions of BioISI along these topics. Definitions of such vision and focus will be also important for future recruitments of BioISI's junior faculty.

The development of a technology transfer office, which interacts closely with BioISI's scientists and develops interactions with national and international industrial partners, should be an important aim for BioISI's future plans. One route to achieve this ambitious goal may be to identify already established national or international offices, which are interested to consult BioISI's leadership in the set-up of its own office and the formulation of a patent strategy.

The development of bottom up core facilities is considered as very important for the long-term future of BioISI. Currently a vast number of techniques and expertise exist in the various thematic lines and their contributing laboratories. These techniques are offered currently on a collaborative basis to collaborating laboratories. It will be a unique opportunity to develop those, which are considered as important or essential for the success of BioISI's major goals and visions, into properly structured facilities, which provide well defined access to cutting edge techniques with a funding scheme that guarantees sustainability for the years to come.

Bioinformatics has become essential for almost any branch in life sciences and in particular the ones represented in BioISI. Although bioinformatics at BioISI has become successfully integrated in several exciting BioISI projects, the SAB members expect it to grow even further in its importance. It is thus recommended to strengthen this thematic line and provide funding, if available, to develop it into a unified resource of BioISI research groups. In addition to the funding for these activities, it will be equally if not more important to be able to recruit high calibre junior staff into this thematic line. Approaching the respective faculties of the Lisbon University and provide information on the exciting possibilities in BioISI may be one way in succeeding in this mission.

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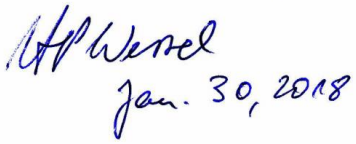
BioISI Scientific Advisory Board Report 2017 – Signature Sheet

Dr. Rainer Pepperkok
Head of Scientific Core Facilities
Teamleader and Senior Scientist in
Cell Biology/Biophysics Unit
European Molecular Biology Laboratory
(EMBL), Heidelberg

Dr. Klaus Palme
Distiguished Professor, Ph.D., Board of Directors
Institute of Biology II / Molecular Plant Physiology
Center for Biological Systems Analysis - ZBSA
Center for Biological Signalling Studies - BIOSS
Albert-Ludwigs-Universität Freiburg
Schänzlestr. 1
79104 Freiburg

Dr. Hans Peter Wessel
Invited Full Professor
University of Aveiro, Portugal
Past Vice Director of
F.Hoffmann-La Roche Ltd., Basel, Switzerland



Centre of Chemistry and Biochemistry
Faculty of Sciences
University of Lisbon

A report by
An International Scientific Advisory Board

1. Introduction

According to its Mission Statement the Centre of Chemistry and Biochemistry at the University of Lisbon has three main aims, to investigate challenging problems in Chemistry and Biochemistry; to train the next generation of highly trained chemists and biochemists and to create social, economic and cultural value from scientific knowledge.

We are an international group established by the Centre to provide advice and critical support to the staff and students largely at a strategic level but with due regard to its operations. In order to discharge our remit we review high-level materials submitted to us by the Centre on a regular basis and make an approximately annual visit to the Centre. On the latter occasions we are able to interact with a large number of the personnel within the Centre and, in particular, to listen to presentations and view posters describing the scientific work within the Centre. It is the view of the International Group that these arrangements allowed them to form an overall view of the Centre, of the quality of its work and its strategic direction as well as the aspirations and expectations of the staff at various levels. The most recent visit of the International Group was in the summer of 2017. The Group is grateful to the staff of the Centre and to the students for the open and positive way in which they have engaged with the discourse that has enabled full coverage of the issues in a short time.

2. Structure

In our previous reports we have noted that the twelve scientific groupings within the Centre cover an extremely wide range of Chemistry and Biochemistry and we have observed, as a consequence, very disparate activities and what we considered a lack of focus. We are now pleased to see in the documents of the Centre greater attention paid to this structural issue. Thus, whereas the number of scientific groups remains unchanged, the extent and variety of interactions between them has significantly increased and special attention is paid to it in both their 2017 report and the discussions. Naturally, the intensity of the interactions and their success are not uniform but it is a significant development.

3. Scientific Quality

We find that Science developed at the Chemistry and Biochemistry Centre (CQB) remains of extremely high quality and have no reason to differ from previous assessments of the activity of the Centre reported to FCT. There were no obvious

areas weaker than others. These conclusions were based on the international journals used for publication (impact factor), the volume of publication and the citations received. It recognizes that for some of the areas in which CQB engages the impact factors for the entire subject are much lower than for others. It is very encouraging that the numbers of papers in international journals has been increased in 2017 at over one hundred and has reached record levels. It is also noteworthy that the numbers of papers that occur in high impact factor journals has increased with the papers falling into the top categories of highly-cited papers increasing significantly. At the same time we note again as in previous reports that while some publications had occurred in high impact journals, there were few reported papers in journals with the absolute highest impact factors among the scientific literature in the world such as Nature or Science. This is indicative of a Centre that is making good progress towards its goals and the staff and students are to be congratulated.

The Board repeats its observation from earlier studies that the science conducted is of an exceptional breadth. Indeed, the Group continues to be concerned with the conclusion that the breadth of topics covered in research may preclude the advancement of the science to the very highest international level. This is indicated by the relative absence of papers in the most prestigious journals in some fields. It is very important to stress that this is not a result of any weakness in the staff but almost certainly stems from a lack of specific focus.

Among other measures of performance there are some exceptional high spots among the staff and students including significant international recognition through awards and lectures. However, it remains true that these achievements are concentrated among a rather few of the staff. It could be argued correctly that this is connected to the age distribution among the bulk of the staff however, one might expect more experienced staff to more often feature in this way. For example, it should be possible for more staff to be acting as editors of journals or at least on editorial boards giving them greater international exposure.

4. PhD Students

The Group has been told repeatedly by a great majority of Ph.D. students that Portuguese industry is not interested in giving them jobs. In view of the fact that the number of Ph.D. graduates has increased very considerably and that Universities cannot possibly offer everyone tenured teaching positions, industry should be encouraged to open its doors to Ph.D. graduates. From its side, the Center could pay more attention to adjusting the focus of research to the needs of the Portuguese industry, following the practice of other advanced countries. We have previously made recommendations on the measures that might be taken to ameliorate this problem. Now we add one more based upon the observations that the number of contracts with industry both within and without Portugal is rather small. Further attempts should be made to seek joint funding of projects and students with industry. The relationships built through this mechanism always have beneficial effects upon student employment.

5. Research Funding

The Group find that whereas the grant acquisition by CQB has been maintained, the base of funding for research remains rather narrow and dependent on FCT itself to a large extent. The average size of grant from FCT is rather small nationally and is not likely to increase in the short term. On the one hand this situation encourages the fragmentation and lack of focus apparent in some of the research activity and, on the other hand, it makes CQB vulnerable to fluctuations in FCT funding. In addition, many grants were too small to invest in modern instrumentation. It is often true that the instrumentation available is far from international standard.

6. Future Development

Early in 2018 the panel were informed of changes in the structure of Research Centres in the general area of Chemistry and Biochemistry that are planned in the Lisbon Area. They are unaware at the time of writing of the exact details of what is proposed but would wish to comment that whatever changes are planned should preserve the best of what CQB has been able to develop over its 16 year lifetime. It has delivered excellent science in this period over a wide range of areas and that must be recognized. If the changes planned allow a greater focus for parts of CQB in some new configuration then that is to be welcomed as being in line with our own arguments. However, it is important still to retain scale in all remaining components of CQB so that they are cost-effective in terms of resources as well as scientifically coherent.

Professor Sir William Wakeham FREng

Professor Roman Zubarev

Professor Hans Peter Wessel

January 26, 2018

5.2 Current External Advisory Board membership

1- Rainer Pepperkok | EMBL- European Molecular Biology Laboratory, Heidelberg (Germany)
2- Klaus Palme | Institute of Biology II Molecular Plant Physiology, Freiburg (Germany)
3- Juan Valcarcel Juarez | CRG-Centre de Regulacio Genomica & ICREA, Barcelona (Spain)
4- Michael Gill | Institute of Molecular Medicine, Trinity College Health Sciences Centre, Dublin (Ireland)
5- Eugene Shakhnovich | Dept Chemistry & Chemical Biology Harvard University, Cambridge (MA, USA)
6- Dario Floreano |EPFL - Laboratory of Intelligent Systems, Lausanne (Switzerland)
7- Hans Peter Wessel| University of Aveiro (Portugal)

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1- Rainer Pepperkok | EMBL- European Molecular Biology Laboratory, Heidelberg (Germany)
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4- Michael Gill | Institute of Molecular Medicine, Trinity College Health Sciences Centre, Dublin (Ireland)
5- Klaus Palme | Institute of Biology II Molecular Plant Physiology, Freiburg (Germany)
6- Eugene Shakhnovich | Dept Chemistry & Chemical Biology Harvard University, Cambridge (MA, USA)

06 FUNDING IN 2013-2017

6.1 Annual funding in 2013-2017

FUNDING SOURCES (TOTAL FUNDING)	2013	2014	2015	2016	2017	TOTAL (K€)
Fundação para a Ciência e a Tecnologia, I.P. - FCT	2,412	1,995	2,133	2,616	2,803	11,959
R&D Unit Pluriannual funding	325	40	635	653	650	2,303
Project funding	1,326	894	296	613	615	3,744
Funding for contracts of researchers with PhD (1)	200	288	233	125	236	1,082
Funding for PhD, PostDoc or other fellowships (2)	557	773	969	1,225	1,302	4,826
Other funding	4	-	-	-	-	4
Other national sources	441	780	583	301	366	2,471
Funding received from Participant or Management Institutions	59	39	40	23	15	176
Public sources (3)	297	667	485	243	337	2,029
Companies, industry and other private sources based in Portugal (3)	84	74	58	35	14	265
Any other funding source (3)	1	-	-	-	-	1
International sources	589	647	815	788	741	3,58
European Commission (3)	371	295	362	361	330	1,719
Companies, industry and other private sources not based in Portugal (3)	166	252	359	427	406	1,61
Other funding sources (3)	52	100	94	-	5	251
TOTAL (K€)	3,442	3,422	3,531	3,703	3,91	18,01

(1) Payed through an institution or directly to researchers with PhD integrated in the R&D Unit

(2) Payed directly to fellows, researchers or students integrated in the R&D Unit

(3) Grants, projects, fellowships, prizes received, etc

07 INTEGRATED RESEARCHERS, PhD students and research contracts in 2013-2017

7.1 Total numbers of Integrated Researchers, PhD students and research contracts in 2013-2017

Researchers and students	2013	2014	2015	2016	2017
No. of integrated researchers	113	119	210	229	200
No. of Integrated researchers with PhD	113	119	110	120	130
No. of PhD students advised by integrated members of the R&D Unit	56	61	49	79	70
No. of research contracts with national public or private entities	74	44	30	30	33
No. of research contracts with international bodies	19	20	23	20	18

Part 3: Research team with links to CVs and ORCID record

08 LISTS OF RESEARCHERS IN THE CURRENT APPLICATION

8.1 List of the Integrated Researchers of the R&D Unit who hold a PhD degree

Name	Nuclear CV	ORCID iD
Margarida Sofia Pereira Duarte Amaral	Yes	0000-0002-0828-8630
Alan John Lander Phillips	Yes	0000-0001-6367-9784
Ana Alexandra Mendes Ferreira	No	0000-0002-2624-0761
Ana Catarina dos Santos Alves	No	0000-0003-3157-7542
Ana Cristina Ribeiro Alves Ferreira Inácio	No	0000-0002-9607-7576
Ana Elisa Ferreira Santos Melo	No	0000-0001-8851-0598
Ana Isabel Ferreira de Carvalho	No	0000-0002-6049-9291
Ana Isabel Ferreira Franco Vicente	No	0000-0002-1253-8161
Ana Margarida Costa Macedo Fortes	No	0000-0001-7552-0164
Ana Maria de Fátima da Silva Martins Gonçalves Reis	No	0000-0003-3363-5953
Ana Maria Gomes Moura Pires de Andrade Tenreiro	No	0000-0002-0178-958X
Ana Maria Ribeiro Ferreira Nunes	Yes	0000-0003-2760-3277
Ana Patrícia Matos Carapeto	No	0000-0003-2654-6848
Ana Paula Boler Claudio	No	0000-0002-4594-8087
Ana Rita Barreiro Alves de Matos	No	0000-0002-3495-2195
Anabela Rosa Bernardes dos Santos da Silva	No	0000-0002-4904-7470
Andreia Cristina Silva Viegas Mata Figueiredo	No	0000-0001-8156-7700
António Joaquim Pereira Pagarete	No	0000-0003-1347-0282
António Manuel Carreiras Casaca	No	0000-0002-5774-6618
Arlete Mendes Faia	No	0000-0002-3033-3418
Astride Moura Vicente	Yes	0000-0001-7134-8037
Bárbara Joana de Almeida Henriques	No	0000-0002-1724-9545
Benedito Jose Costa Cabral	No	0000-0003-4824-3530
Carlos Miguel Ribeiro da Silva Farinha	No	0000-0002-5467-1710
Catarina da Costa Rodrigues Barbosa	No	0000-0003-2383-2101
Catarina Duarte Galhardo Baptista	No	0000-0002-1263-7880
Célia Maria Batalha Silva Rasga	No	0000-0002-9969-6241
Célia Maria Romba Rodrigues Miguel	No	0000-0002-1427-952X
Cláudia Margarida Aguiar Castelo Branco	No	0000-0002-7028-4657
Claudio Emanuel Moreira Gomes	Yes	0000-0003-4662-6933
Diana Lina Jerónimo da Cunha Reis	No	0000-0002-0900-9306
Diogo Ruivo dos Santos Vila Viçosa	No	0000-0001-6620-0484
Elisabete Ribeiro Silva	No	0000-0001-6679-4374
Fernanda Maria Madaleno Rei Tomás Leal Santos	No	0000-0002-1332-8342
Fernando Manuel Vaz Dias	No	0000-0001-8109-2063
Filipa dos Santos Tomé	No	0000-0001-8559-5274

Filomena Cristina Coelho da Luz Duarte	No	0000-0002-3738-1412
Francisco Rodrigues Pinto	No	0000-0002-4217-0054
Hélder Manuel Ferreira Coelho	No	0000-0001-7622-8624
Helena Margarida Guerreiro Galla Gaspar	No	0000-0002-1613-7023
Helena Margarida Moreira de Oliveira Vieira	No	0000-0002-3663-289X
Hugo Filipe de Mesquita Costa Martiniano	No	0000-0003-2490-8913
Hugo Miguel Raposo Correia Botelho	No	0000-0002-4208-1086
Ines Pankonien	No	0000-0002-4622-7521
Iris Alexandra Lopes da Silva	No	0000-0002-8062-5558
Joana Margarida Cordeiro Henriques	No	0000-0002-2045-8954
João Carlos Balsa da Silva	No	0000-0001-8896-8152
João Lavinha	Yes	0000-0002-7474-6871
João Luís de Carvalho Baptista Ferreira	No	0000-0003-4216-396X
João Pedro Guerreiro Neto	No	0000-0002-3974-0685
Jorge Miguel Carvalho Gomes	No	0000-0002-4684-209X
Jorge Miguel Luz Marques da Silva	No	0000-0002-5583-2715
José Eduardo Lima-Brito	No	0000-0001-6204-009X
José Manuel Pires Marques	No	0000-0002-3797-3880
José Manuel Veiga Ribeiro Cascalho	No	0000-0002-5176-4882
Juliane Menezes	No	0000-0003-3727-2096
Lélia Mariana Marcão Chambel	No	0000-0002-1672-1473
Líbia Maria Marques Zé-Zé	No	0000-0001-7258-1439
Liliana Maria Pires Ferreira	No	0000-0001-9006-4443
Lisete Celestina Perpétua Fernandes	No	0000-0002-3384-2031
Luciana Maria Gonçalves da Costa	No	0000-0003-4897-7104
Luis Alberto dos Santos Antunes	No	0000-0002-8237-6524
Luis Filipe Graça Morgado	No	0000-0002-3107-9044
Luis Manuel Ferreira Fernandes Moniz	No	0000-0002-9948-9453
Luís Manuel Pereira Sales Cavique Santos	No	0000-0002-5590-1493
Luis Miguel Parreira e Correia	Yes	0000-0003-2439-1168
Luisa Maria Ferreira Romão Loison	No	0000-0002-5061-5287
Luisa Maria Quental Mota Vieira	No	0000-0003-1451-6705
Luka Alexander Clarke	No	0000-0003-3254-9121
Mafalda Vieira da Rocha Peixoto e Bourbon de Sampaio Pimentel	No	0000-0001-8843-3799
Manuela Alexandra de Abreu Serra Marques Pereira	Yes	0000-0003-2033-4553
Marcelo Luís Monteiro Pereira	No	0000-0002-1424-9275
Margarida Henriques da Gama Carvalho	No	0000-0002-0365-6916
Margarida Maria Moreira Calejo Pires	No	0000-0001-9210-3880
Maria Beatriz Duarte Pereira do Carmo	No	0000-0002-4768-9517
Maria da Graça de Figueiredo Rodrigues Gaspar	No	0000-0002-3106-0423
Maria Estrela Borges Melo Jorge	No	0000-0003-2348-432X
Maria Filomena Lopes Adega	No	0000-0001-5646-5534
Maria Graça Monteiro Azevedo Fialho	No	0000-0001-9696-6448
Maria Helena de Figueiredo Ramos Caria	No	0000-0002-2175-2303

Maria Isabel Batalha Reis Gama Nunes	No	0000-0003-3966-4966
Maria João Magalhães Gaspar	No	0000-0002-2082-4205
Maria José Diogo da Silva Calhorda	Yes	0000-0002-6872-3569
Maria Leonor Pato da Cruz	No	0000-0002-0053-5422
Maria Luís Moral Westerman Cardoso	No	0000-0002-8139-216X
Maria Luisa Mourato de Oliveira Marques Serralheiro	No	0000-0001-7541-9613
Maria Manuela Outeiro Correia de Matos	No	0000-0002-9584-6636
Maria Manuela Ribeiro Costa	No	0000-0001-9032-5690
Maria Margarida Baleiras dos Santos Couto	No	0000-0003-4267-7506
Maria Margarida Colen Martins da Cruz	No	0000-0001-8152-3054
Maria Margarida da Fonseca Beja Godinho	Yes	0000-0002-5373-2753
Maria Salome Soares Pais	No	0000-0002-3068-5851
Maria Teresa Correia Guedes Lino Neto	No	0000-0002-1385-4799
Mário Manuel do Carmo de Almeida Santos	No	0000-0002-9447-1553
Mário Manuel Silveira Rodrigues	No	0000-0002-0468-1910
Marta Susana Pontes Saraiva	No	0000-0002-8631-7011
Miguel Ângelo Dos Santos Machuqueiro	No	0000-0001-6923-8744
Miquéias Lopes Pacheco	No	0000-0002-7444-9359
Monica Guita Sebastiana	No	0000-0001-8735-7632
Morand Jules	No	0000-0002-6149-8901
Nuno Alexandre Guerreiro Bandeira	No	0000-0002-5754-7328
Nuno Jorge Rosa Lopes Galamba	No	0000-0003-1704-2242
Patrícia Alexandra Sousa Barros	No	0000-0001-5063-5766
Patrícia Ferreira Neves Faísca	No	0000-0002-2493-2748
Paula Filomena Martins Lopes	No	0000-0001-8229-0117
Paulo Henrique Carrasquinho de Matos	Yes	0000-0002-9379-9696
Paulo Jorge Cunha Vaz Dias Urbano	No	0000-0003-1038-2949
Paulo Jorge Ferreira de Matos Costa	No	0000-0002-0492-6666
Paulo Manuel Trigo Cândido da Silva	No	0000-0001-5850-615X
Paulo Nuno Barradas Pereira Martinho	No	0000-0003-2552-6263
Pedro Lopes da Silva Mariano	No	0000-0003-3813-1009
Pedro Luis Vieira Falé	No	0000-0002-4644-7655
Peter Jordan	Yes	0000-0002-1425-9211
Rafaela Lacerda Santos	No	0000-0002-5582-9823
Raquel Maria Garcia Santos Chaves	No	0000-0002-5970-7428
Ricardo Pedro Moreira Dias	No	0000-0002-9214-2166
Rita Isabel Dias Pacheco	No	0000-0001-5192-3006
Rob Mills	No	0000-0002-3614-6963
Rogério Paulo Andrade Tenreiro	Yes	0000-0003-3097-3236
Rómulo Sacramento Sobral	No	0000-0003-3798-3154
Rui Filipe Nicolau Lima Antunes	No	0000-0003-3268-3005
Rui Manuel Peixoto Tavares	No	0000-0002-1702-256X
Rui Manuel Santos Malhó	Yes	0000-0001-5287-869X
Sara Catarina Costa Laranjeira	No	0000-0002-4354-2219
Sara Guilherme Oliveira da Silva	Yes	0000-0001-8223-4799

Simão Filipe Cunha da Luz	No	0000-0001-5649-583X
Sónia Maria Alves Gomes	No	0000-0002-3536-0300
Susana Cristina Moura da Igreja	No	0000-0003-2811-4766
Susana Maria Traquete Serrazina	No	0000-0002-8864-0277
Tiago Daniel Lopes Morim Pereira de Matos	No	0000-0001-7643-927X
Vânia Marina Cristovão Goncalves	No	0000-0003-1934-4279

8.2 List of the Integrated Researchers of the R&D Unit who do not hold a PhD degree

Name	**is PhD Student?**	**ORCID iD**
Ana Catarina Sobral da Rocha	No	0000-0002-4379-3149
Ana Cláudia Brandão Gomes Paulo Escudeiro	Yes	0000-0002-6139-7131
Ana Cristina da Silva Alves	Yes	0000-0001-7919-4896
Ana Margarida Cabeleira Medeiros	Yes	0000-0003-2972-0872
Ana Margarida Fernandes Pereira de Matos	Yes	0000-0002-0160-256X
Ana Rita Fernandes Marques	Yes	0000-0003-4144-7020
Ana Rita Sebastião Mendes Cavaco	Yes	0000-0001-8364-655X
Ana Teresa Talhinhas Barata Alhinho	No	0000-0001-8590-6183
André Francisco Martins Lamúrias	Yes	0000-0001-7965-6536
Andreia Filipa Almeida Henriques	Yes	0000-0002-1631-7454
Andreia Filipa Martins Cristóvão Reis	No	0000-0001-7397-6360
Arthur Freitas Vieira	No	0000-0002-2541-8337
Catarina Isabel Ventura Pereira	Yes	0000-0002-8437-7432
Cibelle Neiva Cavalcanti Mariano	Yes	0000-0002-7841-5674
Cláudia Almeida Loureiro	Yes	0000-0002-6969-3285
Cláudia Manuela Oliveira Castro	Yes	0000-0003-4178-5265
Cláudia Sofia Rodrigues Fernandes	Yes	0000-0002-5908-2958
Daniel Filipe Soares Pereira da Cruz	Yes	0000-0001-7559-4876
Daniel Vigário Olivença	Yes	0000-0001-5474-2657
Daniela Filipa Fernandes Costa	Yes	0000-0001-8398-3580
Daniela Perneta Ferreira	Yes	0000-0002-7094-4969
Diana Margarida Alpoim de Andrade Pimentel	Yes	0000-0002-8191-0916
Elisabete Cristina Jesus dos Santos	Yes	0000-0003-2603-691X
Eugénio Luís Fraga Diogo	Yes	0000-0002-4127-9525
Filipa Bica Simões	Yes	0000-0003-2010-1282
Filipa Maria Rodrigues Pardal Dias Antunes Marçal da Silva	No	0000-0003-0442-6618
Flávio João Magalhães Soares	Yes	0000-0001-6246-9398
Francisca Rodrigues dos Reis	Yes	0000-0002-0873-061X
Gonçalo Raimundo Nogueira	Yes	0000-0002-7420-6576
Hamilton Diniz Chiango	Yes	0000-0002-5826-9964
Helena Sofia Gomes Da Silva	Yes	0000-0002-9183-6561
Hugo Alexandre Feiteira dos Santos	Yes	0000-0002-4018-0312

Isabel Maria Machado Seixas	Yes	0000-0002-7051-6040
Joana Filipa de Sousa Pereira	Yes	0000-0001-7463-1137
Joana Filipa Pereira Ferreira	No	0000-0002-5455-7053
Joana Filipa Pires Silva	Yes	0000-0003-1014-7981
Joana Margarida Lopes da Silva Cristóvão	Yes	0000-0003-3833-0016
Joana Maria de Almeida Pereira Vilela	Yes	0000-0002-2465-5795
Joana Ramos Rapaz Lérias	Yes	0000-0002-9874-5259
Joana Rita Gaspar de Barros Martinho Chora	Yes	0000-0003-4942-1730
João Filipe Delgado dos Santos	Yes	0000-0001-5809-0203
João Pedro Xavier dos Santos	Yes	0000-0003-2797-5513
Lúcia Alexandra Rosa dos Santos	Yes	0000-0002-3748-3697
Luís Fernando Rosa Portela Marques	Yes	0000-0003-4853-4792
Luís Miguel dos Santos Sousa	Yes	0000-0002-2982-3233
Madalena do Carmo Fragoso Pinto	Yes	0000-0001-9045-269X
Márcia Carina da Silva Faria	Yes	0000-0002-6601-1138
Margarida Cuco Quaresma	Yes	0000-0001-7978-4685
Maria Teresa da Costa Braga	Yes	0000-0001-5682-4867
Mariana Amoroso das Neves Romão	Yes	0000-0002-5915-3074
Mariana Salvado Pinhão	Yes	0000-0002-8774-7435
Marina Luque García-Vaquero	Yes	0000-0001-5994-9462
Marta Sofia da Silva Correia	Yes	0000-0001-9312-4114
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Muhammad Asif	Yes	0000-0001-9144-7630
Niccolò Rossi	Yes	0000-0002-8285-7627
Nikhil Tanaji Awatade	Yes	0000-0003-1560-7991
Nuno Manuel Cardoso Domingues	Yes	0000-0002-0692-9270
Olga Regina Vieira Ferreira	Yes	0000-0002-4406-7544
Patricia Pinheiro Lage	Yes	0000-0001-5857-5083
Paulo Jorge Gomes Pereira da Costa	Yes	0000-0002-9749-9965
Pedro Miguel Agostinho Escudeiro	Yes	0000-0001-7754-6077
Pedro Miguel Pereira Correia	Yes	0000-0003-2692-7691
Rafael de Santana Nunes	Yes	0000-0002-9014-0570
Rafael José Ferreira Nunes Graça	Yes	0000-0003-3725-0268
Rafael Queirós Fernandes	Yes	0000-0003-4847-9869
Rodrigo Gonçalves David	No	0000-0002-5985-863X
Rui João de Sousa Loureiro	Yes	0000-0002-3458-8741
Rute Monteiro Teixeira	Yes	0000-0002-5772-040X
Samina Kausar	Yes	0000-0002-5207-7136
Sara Inês de Ascensão Tavares Canato	Yes	0000-0002-1102-0192
Sofia Alexandra Gonçalves Correia	No	0000-0001-5544-2701
Sweta Singh	Yes	0000-0003-4126-4822
Tânia Gomes Lucas	Yes	0000-0002-3967-6476
Tânia Renata Monteiro Marques	No	0000-0002-2738-2876
Tiago João Pereira da Silva	Yes	0000-0003-0120-557X
Verónica Manuela Roxo Felício	Yes	0000-0001-6753-323X

8.3 List of the Collaborator Researchers of the R&D Unit

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Ana Rita Rodrigues Neves	
Anabela Barreiro Gomes Vilares Bendada Esteves	
André Osório e Cruz Azeredo Falcão	0000-0002-3588-8746
Andreia Bento de Oliveira	0000-0003-1885-3469
Bruna Filipa Francisco Pereira	
Bruno Miguel Freire Boa de Jesus	
Claudio Reginaldo Alexandre	
Cristina Maria de Paiva Chaves Lopes Caroça Tomé de Jesus	0000-0001-8096-8895
Cristina Maria Nobre Sobral de Vilhena da Cruz Houghton	0000-0003-3100-463X
Diogo Miguel Cristo Reis	0000-0003-0174-9593
Fernando António de Freitas Costa Parente	0000-0003-4703-0066
Fernando Goulart da Silva	0000-0003-2702-9295
Filipa Isabel de Almeida Monteiro	0000-0002-1505-2140
Filipe Miguel Monteiro Centeno da Costa	
Gabriela Alexandra Rodrigues Simões	
Ganna Rozhnova	0000-0002-6725-7359
Gonçalo Miguel Mendes Pais Costa Laureano	
Haúla Faruk Haider	0000-0002-3860-5895
Hélder Filipe de Oliveira Bastos	0000-0002-1629-6382
Inês Alexandra de Jesus Martins	
Inês D. S. Pires	
Inês Filipa Fernandes Ramos	
Inês Graça Gonçalves dos Santos	
Joana Frazão Figueiredo	0000-0002-7795-2531
Joao Paulo de Sá e Silva	
João Tiago Roque Alves	0000-0003-3423-3913
José Pedro Planco Panadés Gil	0000-0002-6107-9379
Karl Kunzelmann	0000-0002-4583-7037
Leonardo Trujillo Reyes	0000-0003-1812-5736
Leonardo Vanneschi	0000-0003-4732-3328
Lisa Susana Marques Esteves	0000-0002-0799-0567
Lúcia de Mendonça Heitor	0000-0002-9396-4401
Manuel Nuno Condinho Rodrigues Reis de Carvalho	0000-0003-4079-3378

Margarida Maria Lucas de Almeida Souto Themudo Barata	0000-0002-2851-608X
Maria Helena Pires Bragança	0000-0002-7957-5493
Maria Leonor Gonçalves Pereira	
Mariana Mara Nascimento	
Mário Jorge Barbosa de Almeida	
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Marisa Raquel Gomes Maia	0000-0003-3202-0797
Mauro Castelli	0000-0002-8793-1451
Miguel Ângelo da Silva Guerreiro	
Miguel Tavares Paiva Santos Pereira	0000-0003-0529-0214
Monica Sofia Vieira Cunha	0000-0003-0401-0276
Nuno Andrade da Cruz Henriques	0000-0002-7328-4900
Nuno Filipe Baltazar Maia Costa de Oliveira	
Nuno Gonçalo Trindade Magessi	0000-0002-1348-6957
Pablo Carril Vaglini	0000-0001-5612-1053
Patrícia Sofia Martins Dias	0000-0001-5405-4811
Patrick de Oliveira Freire	0000-0003-0676-3618
Paulo Jorge Mestre Vieira	
Pedro Jorge Dias Teixeira	0000-0001-8557-8968
Pedro Reis	
Rui Francisco Costa Marcos do Nascimento	0000-0002-0478-336X
Sandra Isabel Mourinha Lopes Chaves	0000-0002-2792-7303
Sara Isabel Mourão Barrias	0000-0003-2536-2107
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Tomás de Campos Aquino	
Tomás Fernandes da Silva	0000-0003-4608-2673

09 PROPOSED RESEARCHED GROUPS

Reference	Name	Principal Investigator
RG-4046-376656	PFG - Plant Functional Genomics	Rui Manuel Santos Malhó
RG-4046-400174	FunGP - Functional Genomics & Proteostasis	Margarida Sofia Pereira Duarte Amaral
RG-4046-400175	M&B - Microbiology & Biotechnology	Rogério Paulo Andrade Tenreiro
RG-4046-400176	BTR - Biomedical & Translational Research	Astride Moura Vicente
RG-4046-400178	GER - Gene Expression & Regulation	Margarida Henriques da Gama Carvalho
RG-4046-400179	CBS - Chemistry for Biological Systems	Maria José Diogo da Silva Calhorda
RG-4046-400181	BioPhysNano - Bio-Physics & Nanosystems	Maria Margarida da Fonseca Beja Godinho
RG-4046-400182	MAS - Modelling of Agents & Systems	Luís Miguel Parreira e Correia

9.1 Research Group: Plant Functional Genomics (PFG)

9.1.1 Description of the Research Group

9.1.1.1 Reference of the Research Group

RG-4046-376656

9.1.1.2 Name of the Research Group in Portuguese

PFG – Genómica Funcional de Plantas

9.1.1.3 Name of the Research Group in English

PFG - Plant Functional Genomics

9.1.1.4 Keywords

- Functional Genomics of Crops
- Cell Signalling in Model Plants
- Plant Biotechnology
- Sustainable Agriculture

9.1.1.5 Existed in 2008-2012

Yes

9.1.2 Researchers of the Research Group

9.1.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Rui Manuel Santos Malhó – Principal Investigator
Ana Isabel Ferreira de Carvalho
Ana Margarida Costa Macedo Fortes
Ana Rita Barreiro Alves de Matos
Anabela Rosa Bernardes dos Santos da Silva
Andreia Cristina Silva Viegas Mata Figueiredo
Célia Maria Romba Rodrigues Miguel
Fernanda Maria Madaleno Rei Tomás Leal Santos
Fernando Manuel Vaz Dias
Jorge Miguel Luz Marques da Silva
José Eduardo Lima-Brito
Maria João Magalhães Gaspar
Maria Manuela Outeiro Correia de Matos
Maria Manuela Ribeiro Costa
Maria Salomé Soares Pais
Maria Teresa Correia Guedes Lino Neto
Monica Guita Sebastiana
Paula Filomena Martins Lopes
Rómulo Sacramento Sobral
Rui Manuel Peixoto Tavares
Sara Catarina Costa Laranjeira
Sónia Maria Alves Gomes
Susana Maria Traquete Serrazina

9.1.1.2 List of Integrated Researchers of the R&D Unit who do not hold a PhD degree and belong to the Research Group

Ana Cristina da Silva Alves
Ana Rita Sebastião Mendes Cavaco
Ana Teresa Talhinhas Barata Alhinho
Cláudia Manuela Oliveira Castro
Cláudia Sofia Rodrigues Fernandes
Daniela Filipa Fernandes Costa
Diana Margarida Alpoim de Andrade Pimentel
Elisabete Cristina Jesus dos Santos
Flávio João Magalhães Soares
Francisca Rodrigues dos Reis
Hamilton Diniz Chiango
Helena Sofia Gomes Da Silva
Maria Teresa da Costa Braga
Pedro Miguel Pereira Correia
Rute Monteiro Teixeira
Sweta Singh

9.1.3 Description of the main contributions of the Research Group in 2013-2017

9.1.3.1 General description of the Research Group

Scope

PFG is devoted to the study of plant growth and development with emphasis on functional aspects. It includes members from three institutions (FCUL, UM, UTAD) forming a national network to promote plant research. Despite its pivotal role in science and society, the area is facing a global decrease in interest from decision makers and young biologists. PFG aims to attenuate such trend by joining experts in fields as diverse as functional genomics, physiology, cell biology, and biochemistry with a successful collaborative track record. PFG has a project-oriented organization with PIs reporting to the GL ensuring flow of information and maximizing resources.

Main objectives

FunGP aims to contribute to the exploration of plant resources and sustainable agriculture in crops of high national economic relevance. We will pursue innovative approaches and internationalization while maintaining a strong commitment to post-graduation and knowledge transfer.

Contributions to I&D

1) Plant Systems and Signalling:
    a. Characterization of signalling pathways regulating growth and morphogenesis;
    b. OMICS studies of plant development and responses to biotic (parasitic and symbiotic) and abiotic (drought, temperature) stresses;
    c. Transcriptional control of flower asymmetry and embryo development
2) Systems approaches for crop improvement and plant health:
    a. Genome editing of relevant crops/ cultivars for better traits and increased resistance;

b. Functional analysis of physiological parameters (e.g. photosynthetic efficiency, water loss) in resting and stress conditions to be used in phenotyping platforms;
c. Development of molecular markers (SNPs) for disease resistance

3) Food authenticity and traceability
   a. Assessment of genetic variability in economically relevant cultivars;
   b. Development of DNA-based technologies for wine and olive oil varietal identification;
   c. Cytogenomic analysis of crops for breeding purposes

9.1.3.2 Identification and summary description of Research Group Contributions

1) Plant systems and signalling in model plants

PFG performed genetic, molecular and cellular characterization of phosphatidylinositol protein kinases and phosphatase involved in pollen tube growth, fertilization, seed production, plant development and ageing. Through analysis of single to quadruple mutants we assigned functional roles for these proteins linking the secretory pathway to vacuolar acidification through ROS signaling and differential expression of cell cycle genes (New Phytol 203, 784-793 [PMID: 24807078]; Plant Physiol 169, 2572-8 [PMID: 26463087]). Using similar approaches we also identified three MYB-like proteins that underlie a molecular antagonism in flower asymmetry and are essential for the establishment of meristematic domains (Plant J 75, 527-538 [PMID: 23638688]) and assigned a role of floral organ identity genes in the development of unisexual flowers, a major step towards the characterization of the mechanisms involved in reproductive organ identity in a monoecious tree (Scientific Reports 7, 10368 [PMC5583232]).

2) Systems approaches for crop improvement and plant health

We studied transcriptome and metabolome reprogramming in *Vitis vinifera* cv. Trincadeira berries upon infection with *Botrytis cinerea* and specific adjustments in grapevine leaf proteome discriminating resistant/ susceptible grapevine genotypes to *Plasmopara viticola*. This represents the first combined analysis of the transcriptome and metabolome associated with fungal infection (J Exptl Bot 66, 1769-1785 [PMC4669548]) and the data identified ROS and lipid associated signalling as crucial for resistance (J Proteomics 152, 48-57 [PMID: 27989945]). As part of this topic and in a consortium work (involving members of all BioISI PFG poles), we also performed a comprehensive assessment of the transcriptome of cork oak (*Quercus suber*) through EST sequencing (BMC Genomics 15:371 [PMID:24885229]) and made a global overview of the transcriptome of an ectomycorrhizal host root through RNA-Seq Derived Transcript Identification and Expression Profiling (PLos One 9(5):e98376 [PMID:24859293])

3) Food authenticity and traceability

PFG, using DNA-based technologies (e.g. high-resolution melting) made a characterization of genetic tools for analysis of ploidy levels and crop diversity in parallel to wine and olive oil varietal identification (Genet Resour Crop Evol 63: 945-951; Food Chemistry 216: 80-86). These technologies represent a fast and efficient method for tracing food authenticity and analysis of genomic diversity which can be complemented to conventional cytogenomic analysis.

9.2 Research Group: Functional Genomics & Proteostasis (FunGP)

9.2.1 Description of the Research Group

9.2.1.1 Reference of the Research Group

RG-4046-400174

9.2.1.2 Name of the Research Group in Portuguese

FunGP - Genómica Funcional e Proteostase

9.2.1.3 Name of the Research Group in English

FunGP - Functional Genomics & Proteostasis

9.2.1.4 Keywords

- Rare & neurodegenerative disorders
- Molecular & cellular mechanisms of disease
- Omics & disease maps
- Personalized biomedicine & therapeutics

9.2.1.5 Existed in 2008-2012

Yes

9.2.2 Researchers of the Research Group

9.2.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Margarida Sofia Pereira Duarte Amaral – Principal Investigator
Bárbara Joana de Almeida Henriques
Carlos Miguel Ribeiro da Silva Farinha
Catarina Duarte Galhardo Baptista
Cláudio Emanuel Moreira Gomes
Filipa dos Santos Tome
Hugo Miguel Raposo Correia Botelho
Ana Patrícia Matos Carapeto
Ines Pankonien
Iris Alexandra Lopes da Silva
Luka Alexander Clarke
Miquéias Lopes Pacheco
Patrícia Alexandra Sousa Barros
Paulo Henrique Carrasquinho de Matos
Simão Filipe Cunha da Luz
Susana Cristina Moura da Igreja

9.2.2.2 List of Integrated Researchers of the R&D Unit who do not hold a PhD degree and belong to the Research Group

Ana Margarida Fernandes Pereira de Matos
André Francisco Martins Lamúrias

Andreia Filipa Martins Cristóvão Reis
Catarina Isabel Ventura Pereira
Joana Margarida Lopes da Silva Cristóvão
Joana Ramos Rapaz Lérias
João Filipe Delgado dos Santos
Lúcia Alexandra Rosa dos Santos
Luís Fernando Rosa Portela Marques
Luís Miguel dos Santos Sousa
Madalena do Carmo Fragoso Pinto
Márcia Carina da Silva Faria
Margarida Cuco Quaresma
Mariana Amoroso das Neves Romão
Rodrigo Gonçalves David
Sara Inês de Ascensão Tavares Canato
Sofia Alexandra Gonçalves Correia
Tânia Gomes Lucas
Verónica Manuela Roxo Felício
Daniel Filipe Soares Pereira da Cruz
Filipa Bica Simões
Joana Filipa Pereira Ferreira
Nikhil Tanaji Awatade
Samina Kausar

9.2.3 Description of the main contributions of the Research Group in 2013-2017

9.2.3.1 General description of the Research Group

Scope

FunGP unravels disease mechanisms by combining molecular and cell biology with omics and systems-level approaches. The workgroup consists of 4 independent research labs, whose scientific focus coalesce into goals of the Biomedicine TL, albeit contributing to all BioISI activities. Two of the research labs have an international reputation in the competitive field of monogenic disease Cystic Fibrosis (CF), while the other 2 are leaders in signal transduction in cancer and in molecular mechanisms of protein misfolding in neurodegeneration, respectively.

Main objectives

FunGP aims to contribute to personalized biomedical approaches and improved health by:
1) understanding molecular and cellular mechanisms in rare diseases and neurodegeneration;
2) translating high-throughput biology into disease risk, diagnosis, and prognosis;
3) developing innovative therapies & drug discovery.

Expected Outcomes

1) Elucidation of molecular/cellular mechanisms of rare diseases and neurodegeneration:
    a. Defining mechanisms of secretory traffic of membrane proteins (ion channels) focusing on the characterization of ER-quality control and membrane stability
    b. Establish molecular and cellular mechanisms of protein misfolding and amyloid formation
    c. Characterize signalling pathways in human disease, namely cancer and CF
2) Systems approaches to disease: Cystic Fibrosis, cancer and neurodegeneration:

a. Defining complex networks by large loss-of-function (RNAi) screens and interactomics
b. Creation of disease maps combining different 'omics' data

3) Drug development, translational and personalized medicine
   a. Developing drug candidates using innovative cell-based assays and HT microscopy screens
   b. Identification of novel molecular biomarkers and targets for ameliorating disease
   c. Repurposing existing drugs using patient-derived test platforms, eg organoids
   d. Development and characterization of biologics for neuroinflammation (nanobodies).

9.2.3.2 Identification and summary description of Research Group Contributions

1) Mechanisms of disease: Cystic Fibrosis (CF), cancer and neurodegeneration:

- Demonstration that the epithelial chloride transport by CFTR protein (mutated in CF) requires the calcium chloride channel TMEM16A/ANO1 [Benedetto *et al*, *Sci Rep* 2017]
- Plasma membrane (PM) stability of CFTR: i) role of Rac1A signalling and NHERF1-mediated cytoskeleton anchoring in CFTR PM stability; ii) proposal of new therapeutic strategies through HGF and ezrin [Moniz *et al*, *ACS Chem Biol* 2013; and patent; Loureiro *et al*, *Sci Signal* 2015]; iii) regulation of CFTR PM stability by phosphorylation [Luz *et al*, *J Biol Chem* 2014] and cAMP signalling [Lobo *et al*, *J Cell Sci* 2016]
- Alzheimer's Disease (AD): elucidation of the mechanism underlying the aggregation of S100 proteins and role of metals and neuronal metal binding proteins in [Carvalho *et al*, *PLoS One* 2013; Cristóvão *et al*, *Oxid Med Cell Longev* 2016]

2) Systems approaches to Cystic Fibrosis (CF) and neurodegeneration:

- Identification of a novel drug target for CF (DGK-iota) by functional genomics (siRNA screens) aimed at to identifying global regulators of the sodium channel ENaC [Almaça *et al*, *Cell* 2013; and patent]
- Identification of novel regulators of the proteostasis network in folding diseases by genetic screens and novel pipelines for drug discovery in protein traffic disorders [Silva *et al*, *PLoS Genet* 2013; Lérias *et al*, *BBA- Mol Cell Res* 2017; Botelho *et al*, *Sci Rep* 2015]
- Common differential and global gene expression profiles in CF and other respiratory disorders identified by transcriptome meta-analysis [Clarke *et al*, *Genomics* 2015; Clarke *et al*, *Resp Res* 2013]

3) Drug development, translational and personalized biomedicine

- Unveiling of the mechanism of action for the novel drug (VX-809) treating the most common basic defect (F508del) in CF [Farinha *et al*, *Chem & Biol* 2013; Farinha *et al*, *Pharm Res Perspect* 2015]
- Proposal of novel therapeutic strategies and repurposing of approved drugs for rare mutations in CF [Awatade *et al*, *E-Biomedicine* 2015; Igreja *et al*, *Hum Mutat* 2016; Tian *et al*, *Br J Pharmacol* 2013]
- Characterization of the disease liability of the top frequent 160 CFTR mutations and validation of novel robust biomarkers for CF [Sosnay *et al*, *Nature Genet* 2013; Servidoni *et al*, *BMC Gastroenterology* 2013; Nagy *et al*, *Chest* 2016]
- Defining therapeutic approaches using riboflavin as a pharmacological chaperone in mitochondrial energy metabolism disorders [Henriques *et al Curr Drug Targets* 2016]

9.3 Research Group: Microbiology & Biotechnology (M&B)

9.3.1 Description of the Research Group

9.3.1.1 Reference of the Research Group

RG-4046-400175

9.3.1.2 Name of the Research Group in Portuguese

M&B – Microbiologia e Biotecnologia

9.3.1.3 Name of the Research Group in English

M&B - Microbiology & Biotechnology

9.3.1.4 Keywords

- Microbial diversity
- Omics & microbiomes
- Integrative microbiology
- Applied microbiology: 'Rainbow biotechs'

9.3.1.5 Existed in 2008-2012

Yes

9.3.2 Researchers of the Research Group

9.3.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Rogério Paulo Andrade Tenreiro – Principal Investigator
Alan John Lander Phillips
Ana Alexandra Mendes Ferreira
Ana Cristina Ribeiro Alves Ferreira Inacio
Ana Maria Gomes Moura Pires de Andrade Tenreiro
Ana Maria de Fátima da Silva Martins Gonçalves Reis
António Joaquim Pereira Pagarete
Catarina da Costa Rodrigues Barbosa
Catarina Duarte Galhardo Baptista
Filomena Cristina Coelho da Luz Duarte
Helena Margarida Moreira de Oliveira Vieira
Joana Margarida Cordeiro Henriques
João Luís de Carvalho Baptista Ferreira
Lélia Mariana Marcão Chambel
Líbia Maria Marques Zé-Zé
Lisete Celestina Perpétua Fernandes
Arlete Mendes Faia
Maria Leonor Pato da Cruz
Maria Margarida Baleiras dos Santos Couto
Mário Manuel do Carmo de Almeida Santos
Ricardo Pedro Moreira Dias

9.3.2.2 List of Integrated Researchers of the R&D Unit who do not hold a PhD degree and belong to the Research Group

Ana Catarina Sobral da Rocha
Eugénio Luís Fraga Diogo
Filipa Maria Rodrigues Pardal Dias Antunes Marçal da Silva
Isabel Maria Machado Seixas
Patricia Pinheiro Lage
Pedro Miguel Agostinho Escudeiro
Tiago João Pereira da Silva

9.3.3 Description of the main contributions of the Research Group in 2013-2017

9.3.3.1 General description of the Research Group

Scope

M&B focuses on innovative approaches in several areas of M&B and on the establishment of successful and fruitful links with SMEs and industry.

M&B-BioISI know-how and expertise represent an integrated knowledge, covering microbial biodiversity and genomics, molecular microbial physiology and ecology, mycology, applied microbiology and biotech applications.

The group adopted the 'rainbow biotech' colours (CHEMIK 2012,66,8,811) to organize the fields of research and adopted a project-oriented organization. Each project is ruled by a PI who reports to GL. This flexible structure copes with both changes in team members and societal challenges and industry-academia partnerships, ensuring efficient management, competitiveness and a continuous challenge to excel in research.

Main objectives and future contributions to R&D

In line with EU directives and BioISI vision, M&B will further exploit links with SMEs and industrial networks to develop horizontal integrated approaches of several key areas of M&B. A major effort will be towards innovation and internationalization aiming solutions to societal challenges and needs. Main examples are:

- Omics-analysis of Douro Wine Region microbiome adaptation to climate changes and innovative strategies to select yeast starters (Yellow M&B)
- Novel bioactive compounds from marine microbes for therapeutics, cosmetics and agrosciences (Blue M&B)
- Intelligent Decision Support Systems for personalized prevention and management of infectious diseases (Red/Gold M&B)
- Integrative taxonomy and novel detection approaches of phytopathogenic fungi and bacteria and environmental microbiomes (Green/Grey M&B)
- Robotized phenotyping of M&B microbial collections and 4th NGS based-identification of industrial enzymes (White/Gold M&B).

M&B will keep on its long-standing role in post-grad teaching and KTT, and the open-status of the 'Bugworkers Lab' that also supports SMEs incubated at TecLabs Innovation Center of FCUL.

9.3.3.2 Identification and summary description of Research Group Contributions

1) Systems approaches to rainbow biotechs

- Unveiling yeast genomic expression programs in mixed-culture wine fermentations, adaptive yeast response to stress and links of yeast nitrogen metabolism with wine aroma and quality.
- New yeast genetic tools developed for screening of drugs targeting Stress Transcriptional Networks and with broad relevance for pharmaceutics and environmental impact.
- Novel microbial strains with increased potential for biodegradation of fat/oil/grease and hydrocarbon contaminated wastewaters obtained from *in vitro* adaptive evolution.
- Establishment of integrated step-forward approach using 3G whole-genome sequencing for identification of industrial relevant enzymes from deep sea vent prokaryotes.
- Identification of genomic markers for detection of *Xanthomonas arboricola* pv. *juglandis*, the agent of walnut blight.
- Enlargement of the M&B-BioISI microbial collection that currently holds more than 5000 microbes (bacteria, yeasts and molds), collected from habitats so diverse as humans, plants (trees and herbaceous), insects, saltmarshes, acid mines, hydrothermal vents, soil, food products and wine/must.

2) Integrative approaches in microbial diversity and function

- Unveiling the evolutionary history of fungal families and genera through dating divergence time in relation to major evolution events of angiosperms on a geological timescale.
- Reappraisal of genera and species in the *Botryosphaeriaceae*, a fungal family with relevance in eucalyptus canker and dieback diseases.
- Disclosure of the role of prophages in the cross-talk of the zoonotic *Streptococcus dysgalactiae* subsp. *dysgalactiae* agent with streptococci pathogenic to humans by 3G whole-genome sequencing.
- Identification by RNAseq of 154 genes differentially expressed in *Xanthomonas campestris* pv. *campestris / Brassica oleracea* pathogen/host interactome.
- Integrated view of cytoskeleton dynamics in environmental Stress Transcriptional Networks.

3) R&D translation to society

This activity was achieved by fostering and promoting new start-ups (e.g. Biomimetix), participation in national networks of key value chains (*e.g.* Bluebio Alliance, Rede Agro, Rede Mar), partnerships established with SMEs and companies (eg Proenol, Sogrape, AtralCipan, Biopremier, Biotask, BioRah, Vasverde, Cork Supply, Mendes Gonçalves, Dois Corvos, COTHN, SGS, MaxData), training in applied microbiology for societal challenges in PALOPs, association with FabLab Lisboa (Lisbon Municipality) and co-involvement in outreach events like Young Creators, DIY Biohacking Meet-up in European Maker Week, Science Days and International Microorganism Day.

The inclusion of a group member as an international expert at BioBased and Bioeconomy networks in EU (BBI-JU and ERA-NET MARINE BIOTECH) and EU Commission expert for marine biotech simultaneously recognized our outputs at international level, having a major impact in driving research to other fields of societal and economical relevance.

9.4 Research Group: Biomedical & Translational Research (BTR)

9.4.1 Description of the Research Group

9.4.1.1 Reference of the Research Group

RG-4046-400176

9.4.1.2 Name of the Research Group in Portuguese

BTR – Investigação Biomédica e Translacional

9.4.1.3 Name of the Research Group in English

BTR – Biomedical & Translational Research

9.4.1.4 Keywords

- Systems medicine of complex disorders
- (Epi)genomics in human disease
- Human genes, traits and environment in disease
- Personalized medicine and pharmacogenomics

9.4.1.5 Existed in 2008-2012

Yes

9.4.2 Researchers of the Research Group

9.4.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Astride Moura Vicente – Principal Investigator
Ana Catarina dos Santos Alves
Célia Maria Batalha Silva Rasga
Cláudia Margarida Aguiar Castelo Branco
João Lavinha
Luciana Maria Gonçalves da Costa
Luisa Maria Quental Mota Vieira
Mafalda Vieira da Rocha Peixoto e Bourbon de Sampaio Pimentel
Maria Graça Monteiro Azevedo Fialho
Maria Helena De Figueiredo Ramos Caria
Maria Luís Moral Westerman Cardoso
Tiago Daniel Lopes Morim Pereira de Matos
Hugo Filipe DE Mesquita Costa Martiniano

9.4.2.2 List of Integrated Researchers of the R&D Unit who do not hold a PhD degree and belong to the Research Group

Ana Margarida Cabeleira Medeiros
Ana Rita Fernandes Marques
Cibelle Neiva Cavalcanti Mariano
Joana Maria de Almeida Pereira Vilela

Joana Rita Gaspar de Barros Martinho Chora
João Pedro Xavier dos Santos
Marta Sofia da Silva Correia
Muhammad Asif
Niccolò Rossi
Rafael José Ferreira Nunes Graça

9.4.3 Description of the main contributions of the Research Group in 2013-2017

9.4.3.1 General description of the Research Group

Scope

BTR's main question is how biological factors, lifestyle and the environment interact to influence health, disease and treatment. BTR consists in several research teams that employ common approaches (large population datasets, genomics, integrative data analysis) to investigate human traits or diseases, including autism spectrum disorders, cardiovascular and metabolic diseases, hearing loss, sickle cell disease, therapeutic response.

Main objectives

BTR aims to understand the interaction between multilevel determinants for disease and treatment, including (epi)genetic factors, clinical and lifestyle determinants and environmental modulators, using systems medicine frameworks, and translate findings into tools for personalized diagnosis and treatment.

Future main contributions to R&D:

1) Systems medicine for complex disorders: autism spectrum disorders, dyslipidemias, heart conditions, metabolic diseases, stroke, hearing loss, sickle cell anemia
    a. Genomic variant discovery and phenotype-genotype correlations to improve disease categorization
    b. Understand epigenetic mechanisms and defining networks and pathways underlying pathology
    c. Identify data patterns contributing to prediction of disease risk and prognosis using data mining and machine learning algorithms in large patient datasets with genetic, epigenetic, demographic, environmental, lifestyle and clinical data
    d. Understand the impact of gene-environment interactions in phenotypic heterogeneity
2) Molecular mechanisms of disease
    a. Functional analysis of novel disease variants
    b. Understand the role of regulatory RNAs in disease
3) Personalized diagnosis and treatment
    a. Develop gene variant databases; genomic-based guidelines; gene panels for diagnosis, prognosis, treatment
    b. Understand the pharmacogenetics of drug response in dyslipidemias and treatment-resistant neuropsychiatric patients
    c. Develop and test pharmacogene panels for adverse drug reactions

9.4.3.2 Identification and summary description of Research Group Contributions

1) Population studies:

- Uncovering genetic factors underlying hereditary hearing impairment in Portuguese patients (Matos et al *Int. J. of Audiology* 2013) and nonsyndromic sensorineural hearing loss was investigated in the Sub-Saharan African Island Population of São Tomé and Príncipe (Caroça et al *OMICS* 2016, *BMC Public Health* 2017, *Int J Med Res Health Sci* 2017)
- Cardiovascular risk assessment of disease in general populations (Medeiros et al *J Lipid Res.* 2014 & *Genet Med* 2015)
- Participation in international stroke studies, with results showing that the contribution of common variants to complex disorders can be clarified through cooperative efforts analyzing very large datasets (Holmes et al *Brit Med J* 2014; Malik et al Neurol 2016; Rannikmäe et al Neurol 2017)

2) Determinants and mechanisms of disease

- Participation in large research consortia, namely the Autism Genome Project and the Psychiatric Genomics Consortium (PGC), contributed to the understanding of genetic mechanisms in ASD and documented the genetic overlap with other major neuropsychiatric diseases (Pinto et al *AJHG* 2014; Hadley et al *Nat Commun* 2014; Buxbaum et al *Mol Autism* 2014; Maier et al *AJHG* 2015; ASD Work Gp of PGC *Mol Autism* 2017; Weiner et al *Nat Genet* 2017)
- Identification of novel genes and genotype-phenotype correlations for ASD (Correia et al, *Mol Autism* 2014; Conceição et al *Psych Gen* 2017)
- Identification of genetic mutation spectrum, biomarkers, social and environmental factors determining age-related hearing loss (Haider et al Aging Neurosci 2017)
- Molecular pathology studies of congenital heart diseases (CHD) and hereditary hemochromatosis (HH) (Cabral et al *Ann Hum Biol* 2016; Branco et al. PLoS One, 2015)
- Identification and functional assessment of variants found in severe dyslipidaemias (Alves et al *Hum Mol Genet* 2014 & *J Am Coll Cardiol* 2015; Fernández-Higuero et al *Sci Rep* 2015)
- Dissecting the polygenic control of rare monogenic diseases: sickle cell anaemia as a model (Coelho et al, *Eur J Haematol* 2014; Silva et al *Clin Hemorheol Microcirc* 2016; David et al *Immunogen* 2018)

3) Systems approaches and personalized medicine

- Establishment of a variant database with >2000 variants from Familial Hypercholesterolaemia (FH) patients and adaptation of the ACMGG algorithms guideline for variant classification. (Bourbon et al Curr Opin Lipidol 2017; Chora et al Genet Med 2017; Bourbon et al Atheroscler 2017; Benito-Vicente et al *Genet Med* 2015)
- New clinical insights of the 22q11.2 microduplication syndrome (Pires et al *BMC Genetics* 2014; Vaz et al 2015 *BMC Pediat*)

- Determining genotype-phenotype correlations regarding the occurrence of tinnitus in older adults (Haider et al *Front Neurosci* 2017)
- Development of a protein network-based method for discovery of novel genes/pathways for ASD (Correia et al *Int J Mol Sci* 2014 & *PLOS ONE* 2014; Network & Pathway Gp of PGC *Nat Neurosci* 2015)

9.5 Research Group: Gene Expression & Regulation (GER)

9.5.1 Description of the Research Group

9.5.1.1 Reference of the Research Group

RG-4046-400178

9.5.1.2 Name of the Research Group in Portuguese

GER – Expressão Génica e Regulação

9.5.1.3 Name of the Research Group in English

GER – Gene Expression & Regulation

9.5.1.4 Keywords

- Mechanisms & principles of gene expression
- Genomic regulation by non-coding elements
- Regulatory network analysis & modelling
- RNA processing, translation & decay

9.5.1.5 Existed in 2008-2012

Yes

9.5.2 Researchers of the Research Group

9.5.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Margarida Henriques da Gama Carvalho – Principal Investigator
Francisco Rodrigues Pinto
Juliane Menezes
Luisa Maria Ferreira Romão Loison
Marcelo Luís Monteiro Pereira
Maria Filomena Lopes Adega
Peter Jordan
Rafaela Lacerda Santos
Raquel Maria Garcia Santos Chaves
Vania Marina Cristovão Goncalves

9.5.2.2 List of Integrated Researchers of the R&D Uit who do not hold a PhD degree and belong to the Research Group

Andreia Filipa Almeida Henriques
Cláudia Almeida Loureiro
Daniel Vigário Olivença
Gonçalo Raimundo Nogueira
Hugo Alexandre Feiteira dos Santos
Joana Filipa de Sousa Pereira
Joana Filipa Pires Silva
Mariana Salvado Pinhão

Marina Luque García-Vaquero
Nuno Manuel Cardoso Domingues
Paulo Jorge Gomes Pereira da Costa
Rafael Queirós Fernandes
Tânia Renata Monteiro Marques
Ana Cláudia Brandão Gomes Paulo Escudeiro
Daniela Perneta Ferreira

9.5.3 Description of the main contributions of the Research Group in 2013-2017

9.5.3.1 General description of the Research Group

Scope

GER comprises 5 labs exploring molecular mechanisms and global regulation of eukaryotic genomes and gene expression programs, with a focus on human health and disease. Three labs take a predominantly experimental approach to mechanisms and regulation, while 2 teams rely more on 'omics' and bioinformatics to address systems level events. GER research thus primarily integrates within BioMed and BioInf TLs. All teams actively engage in collaborative work, synergizing their complementary expertise.

Main objectives

GER aims to generate a mechanistic and quantitative understanding of gene expression processes at the molecular, cellular and systems level that can be harnessed to predict and manipulate the behaviour of biological systems for useful applications, namely in human health and disease.

Future main contributions to R&D:

1) Mechanisms and models of gene expression
    a. Biochemical exploration of mRNA metabolism processes in model gene systems for potential therapeutic applications
    b. Novel metrics to query biological networks and genomic data, addressing disease mechanisms and drug discovery
    c. Uncovering new regulatory principles: establish mechanistic hypotheses through analysis of genome-wide datasets and mathematical models
2) Global misregulation of gene expression: cancer and neurodegeneration
    a. Connections between signal transduction, transcription and splicing in cancer, with a focus on *in vitro* 3D culture models
    b. Unravelling the global disruption of translational control and mRNA surveillance in cancer
    c. Dissection of gene expression pathways underlying neurodegeneration, focusing on cross-disease pathways
3) The non-coding genome in health and disease
    a. Dissecting the role of repeat elements and their transcripts in genomic stability and cell function supported by new 4th Gen Sequencing methods
    b. Exploring the role of small ncRNAs in the immune system and as modulators of host-virus interactions

9.5.3.2 Identification and summary description of Research Group Contributions

1) Mechanisms of translational control and mRNA surveillance in health and disease:

- Novel mechanistic model for the NMD pathway explaining the 'AUG-proximity effect', whereby some mRNAs harbouring premature termination codons are resistant to decay, with potential therapeutic impact for the targeting of truncated proteins in hereditary diseases and cancer [Pereira NAR 2015].
- Demonstration of cap independent translation initiation and uORFs as key players in the dynamic regulation of gene expression in stress and disease [Barbosa PLoSGen 2013; Barbosa RNA 2014; Onofre MCB 2015; Lacerda CMLS 2017], including a novel regulatory mechanism for mTOR expression required for cell cycle progression under translational inhibitory conditions [Marques-Ramos RNA 2017].

2) Signalling pathways and post-transcriptional regulatory networks in cancer:

- First mechanistic evidence for a tumour-suppressing role of WNK2 that is related to Rac1 signalling and tumour cell invasion and proliferation [Moniz Hum Mol Gen 2013]
- Identification of signalling pathways that regulate the expression of oncogenic Rac1b splicing variant in colorectal cancer, involving altered subcellular localization of a key splicing factor [Gonçalves RNA 2014; Genes 2017]; demonstration that the increased expression of the Rac1b splice variant is linked to the escape of colorectal tumor cells from B-Raf-induced senescence [Henriques Cancer Lett 2015].
- Demonstration that stromal cues can trigger changes in Rac1b expression in the colon and that ibuprofen is a highly specific and efficient inhibitor of Rac1b overexpression in colorectal tumours, suggesting its use may be beneficial in the treatment of patients with serrated colorectal tumours or with inflammatory colon syndromes [Matos Neoplasia 2013; Matos BBA 2016].

3) Non-coding elements in cell function and genome regulation

- Characterization of a mouse adult cardiac stem cell miRNA signature distinct from heart embryonic or mesenchymal stem cells, identifying post-transcriptional control networks for fate mapping with implications for cardiac regeneration [Bras-Rosario PLoS One 2013].
- Deep sequencing of sncRNAs in primary human naïve CD4 T cells, leading to identification of miR-34c-5p as a novel regulator of T cell activation and HIV replication, and identification of novel classes of host/HIV-derived sRNAs with the potential to regulate infection [Amaral EMBOJ 2017].
- Novel evolutionary insights into the role of repetitive sequences in genome rearrangements across mammalian species, including detailed characterization of the cat archetypal satDNA FA-SAT, and disclosure of cellular pathways involving the corresponding non-coding RNAs in cancer [Louzada Mol Phyl & Evol 2015; Chaves Genome Biol & Evol 2017].

9.6 Research Group: Chemistry for Biological Systems (CBS)

9.6.1 Description of the Research Group

9.6.1.1 Reference of the Research Group

RG-4046-400179

9.6.1.2 Name of the Research Group in Portuguese

CBS – Química para Sistemas Biológicos

9.6.1.3 Name of the Research Group in English

CBS – Chemistry for Biological Systems

9.6.1.4 Keywords

- New molecules and functional materials (41)
- Computational (bio)chemistry (28)
- Cell proteomes and metabolomes (26)
- Molecular & cellular bioenergetics (32)

9.6.1.5 Existed in 2008-2012

No

9.6.2 Researchers of the Research Group

9.6.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Maria José Diogo da Silva Calhorda – Principal Investigator
Ana Elisa Ferreira Santos Melo
Ana Isabel Ferreira Franco Vicente
Diana Lina Jerónimo da Cunha Reis
Diogo Ruivo dos Santos Vila Viçosa
Elisabete Ribeiro Silva
Helena Margarida Guerreiro Galla Gaspar
Manuela Alexandra de Abreu Serra Marques Pereira
Maria Luisa Mourato de Oliveira Marques Serralheiro
Marta Susana Pontes Saraiva
Miguel Ângelo Dos Santos Machuqueiro
Nuno Alexandre Guerreiro Bandeira
Nuno Jorge Rosa Lopes Galamba
Paulo Jorge Ferreira de Matos Costa
Paulo Nuno Barradas Pereira Martinho
Pedro Luis Vieira Falé
Rita Isabel Dias Pacheco

9.6.2.2 List of Integrated Researchers of the R&D Unit who do not hold a PhD degree and belong to the Research Group

Olga Regina Vieira Ferreira
Rafael de Santana Nunes

9.6.3 Description of the main contributions of the Research Group in 2013-2017

9.6.3.1 General description of the Research Group

Scope

CBS aims at developing new molecules and materials, studying how they interact with each other, the environment, and biological systems. We also seek to understand the bioenergetic metabolism of prokaryotes, with emphasis on pathogens, by combining molecular and cellular experimental methodologies with computational approaches. CBS is organized in 4 independent labs contributing mainly to BChem TL and sharing research interests with several groups and TLs.
We are internationally recognized as experts in different fields.

Main objectives

To contribute to understanding (bio)chemical systems by: 1) designing, synthesizing, detecting, and isolating new bioactive molecules and materials; 2) studying molecular interactions in small molecules, proteins or membranes, and determining reaction mechanisms; 3) investigating the molecular mechanisms of energy conservation and the impact of energetic metabolism in other fundamental cellular processes.

Future main contributions to R&D

1) New bioactive molecules and materials:
    a. New molecules towards future applications in biological systems (eg storing information at the molecular level)
    b. Chiral structures as luminescent sensors
    c. New drug leads and bioactivity from natural products and infusions
    d. Environment-friendly antifouling and self-cleaning technologies
    e. Selective sustainable catalysts and activation of small molecules.
2) Computational strategies:
    a. pH effects in simulations of proteins and membranes and molecular recognition of small molecules
    b. Mechanisms of protein aggregation
    c. Mechanisms of reactions catalyzed by transition metals.
3) Molecular and cellular bioenergetics:
    a. To integrate molecular and cellular approaches on the role of the different respiratory enzymes
    b. To provide mechanistic insights in respiratory proteins and define their role in the cell context
    c. To investigate the temporal and spatial cellular organization of respiratory enzymes.

9.6.3.2 Identification and summary description of Research Group Contributions

1) How to get new molecules and materials and understand their reactivity

- New bioactive molecules from Portuguese marine organisms (algae and sponge) were isolated and identified; new psychoactive substances were discovered in seized products; infusions of natural products displayed bioactivity. [Gaspar et al (2016) Marine Drugs 14: 1[PMID: 27727161]; Ressaissi et al (2017) Arch Pherm Res 40: 1278 [PMID: 28936788]]
- The first Fe(III) functional material exhibiting simultaneously spin crossover and thermosalient effect during several cycles was developed. [Vicente et al (2016) Chem. Sci. 7, 4251 [DOI: 10.1039/C5SC04577K]]
- Selective (chiral) catalysts were developed and the mechanisms of transition metal catalyzed reactions with interest for organic synthesis were unravelled [Saraiva et al (2015) Appl. Catal., A 180: 130 [10.1016/j.apcata.2015.01.040]; Duarte et al (2016) ACS Catal. 6: 1772 [DOI: 10.1021/acscatal.5b02091]; Cachatra et at (2015) Org Lett. 17: 5622 [PMID: 2655105]; Bandeira et al (2017) ChemistrySelect 2: 11071 [DOI: 10.1002/slct.201701801]]
- A new strategy of immobilizing biocides in suitable polymeric matrices, such as marine coatings, to avoid their release into the aquatic environment, was developed. The novel technology was validated on field trial ship hulls tests [Patent WO2016/093719].

2) Computational tools and new simulation methods towards understanding (bio)chemical phenomena at the molecular level

- The new CpHMD methodology adds pH effects in simulations of biomolecules, including membrane proteins, at the water/membrane interface [Santos et al (2015) J. Chem. Theory Comput. 11: 5973 [PMID: 26588046]; Teixeira et al (2016) 12: 930 [PMID: 26863409]]
- Enhanced sampling techniques coupled with CpHMD simulations are now used to include pH effects in molecular recognition and binding [Reis et al (2017) MOL2NET 3 [DOI: 10.3390/mol2net-03-05080]; Vila-Viçosa et al (2017) MOL2NET 3 [10.3390/mol2net-03-05081]]
- New applications of halogen bonds and comprehension of solvation effects on the nature and strength of charge-assisted halogen bonds capable of recognizing chloride [Nunes et al (2017) Chem. Asian J. 12: 586 [PMID: 28052536]; Nunes et al (2017) MOL2NET 3 [DOI: 10.3390/mol2net-03-05075]]

3) Unraveling enzyme molecular mechanisms

- Exploring the diversity of membrane respiratory chains [Marreiros et al (2016) Biochim Biophys Acta 1857: 1039 [PMID: 27044012]]
- Investigation of NDH-2, a protein involved in the energetic metabolism of S. aureus, a worldwide problem in clinical medicine and recognized as potential target for novel antimicrobial therapies [Sena et al (2015) Mol. Micro. 98: 272-288 [PMID: 26172206], Marreiros et al (2016)*Environ Microbiol.* 18, 4697-4709 [PMID: 27105286]and Marreiros (2017) et al Sci Rep. 7: 42303 [PMID: 28181562]
- Study of energy coupling in respiratory complexes [Castro etal (2016) Biochim Biophys Acta 1857, 928 [PMID: 26711319].

9.7 Research Group: BioPhysics & Nanosystems (BioPhysNano)

9.7.1 Description of the Research Group

9.7.1.1 Reference of the Research Group

RG-4046-400181

9.7.1.2 Name of the Research Group in Portuguese

BioPhysNano - Bio-Física e Nanosistemas

9.7.1.3 Name of the Research Group in English

BioPhysNano – Bio-Physics & Nanosystems

9.7.1.4 Keywords

- Condensed Matter & Nanotechnology
- Protein Physics
- Magnetic Nanostructures
- Complex Quantum and Classical Systems

9.7.1.5 Existed in 2008-2012

Yes

9.7.2 Researchers of the Research Group

9.7.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Maria Margarida da Fonseca Beja Godinho – Principal Investigator
Ana Maria Ribeiro Ferreira Nunes
Ana Patrícia Matos Carapeto
António Manuel Carreiras Casaca
Benedito José Costa Cabral
José Manuel Pires Marques
Morand Jules
Liliana Maria Pires Ferreira
Margarida Maria Moreira Calejo Pires
Maria Estrela Borges Melo Jorge
Maria Margarida Colen Martins da Cruz
Mário Manuel Silveira Rodrigues
Patrícia Ferreira Neves Faísca

9.7.2.2 List of Integrated Researchers of the R&D Unit who do not hold a PhD degree and belong to the Research Group

Arthur Freitas Vieira
Miguel Vargas Vitorino
Rui João de Sousa Loureiro

9.7.3 Description of the main contributions of the Research Group in 2013-2017

9.7.3.1 General description of the Research Group

Scope

Bio-PhysNano is the core group of the Bio-Phys TL although its researchers are involved in all the other TLs either through joint projects or sharing of facilities. It is organized in 2 sub-groups

- MagNano (Magnetism & Nanosystems) a team with a large experience in magnetism and atomic physics studies and in developing nanotechnology methods and techniques, recently focused on biological systems and applications (PI: MMCruz)
- PBS (Physics of Biological Systems) created in 2008 with protein physics as one of its major topics, pioneered in Portugal the physical study of biological systems, an area that it still leads nationally (PI: A Nunes)

Main objectives

Biol-PhysNano uses physical approaches and tools to contribute to solving biological problems.
MagNano develops experimental/theoretical research centred in the study of nanostructured systems electronic properties and nanoscale experiments using atomic force microscopy (AFM) and force feedback microscopy (FFM) techniques.
PBS develops innovative methods for theoretical, physics-based approaches providing a unique contribution to the understanding of biological systems (see below).

Future main contributions to R&D

1) Nanostructured systems
    a. Organized magnetic nanoparticles systems for hyperthermia therapy applications;
    b. Magnetic study of molecular complexes;
2) AFM/FFM development
    a. FFM measurement strategies consolidation to probe interactions on biosystems;
    b. Conjugation of AFM and fluorescence microscopy;
3) Protein physics
    a. Folding and knotting mechanisms of knotted proteins inside the GroEL-GroES chaperonin;
    b. Physical mechanism of in vivo aggregation of proteins of biomedical interest
4) Dynamics and electronic structure of complex supramolecular systems
    a. Modified cromophores for increased performance in dye sensitized solar cells;
    b. Molecular design of new photoactive molecules for solar energy storage.

9.7.3.2 Identification and summary description of Research Group Contributions

1) Nanostructured systems, molecular and atomic studies

a. Identification of the relationship composition-size for iron oxide chemically synthesized nanoparticles (a significant issue in biomedical science) using complementary information from high resolution magnetic techniques [MD Carvalho *et al, J. Solid State Chem.* 2013]
b. Natural templates were used to induce organization of magnetic nanoparticles resulting in an increased heating efficiency of the system determinant within magnetic hyperthermia cancer therapy applications [MM Cruz *et al*, *RSC Adv* 2016]

c. Magnetic study (Squid magnet & Mossbauer spect) of transition metal complexes– 1st example of a dynamic spin interchange observation [AI Vicente *et al, Chem Sci* 2016]
d. Study of Auger decay of a hollow atom created after the impact of a highly charged ion onto a solid - collaboration work with CRC 1242 (Univ Duisburg-Essen) on the highly-charged ion neutralization and de-excitation driven by multiple interatomic coulombic decay [RA Wilhelm *et al*, *Phys Rev Lett* 2017]

2) Atomic Force Microscopy related techniques

a. Patent: Device for measuring an atomic force, Mário S Rodrigues et al, WO 2013057426 A1 (2013), commonly referred to as Force Feedback Microscope (FFM). It allows to circumvent one of the greatest limitations in Atomic Force Microscopy, the "jump-to-contact".
b. In contrast to conventional dynamic AFM techniques, by using the novel FFM approach the tip excitation frequency can be arbitrarily chosen, leading to new spectroscopic techniques. In this way the PC12 cell membrane mechanical response was found to be frequency dependent in 1-10kHz range with a damping coefficient consistently decreasing with increased excitation frequency. This work illustrates one important advantage of the FFM technique [Luca Costa *et al*, PLoS ONE 9(7): e101687, 2014]
c. Using AFM techniques to assess mechanical and adhesion properties of Diacylglycerol Kinase 4 (DGK4) Arabidopsis pollen tubes it was possible to demonstrate its role in tube growth [Fernando Vaz Dias, *et al*, submitted to New Phytologist, 2017]

3) Physics of complex systems

a. By integrating results from folding and protein-protein docking simulations we provided a microscopic rationale for the *in vitro* amyloidogenic behaviour of the wild-type form, the DN6 variant and the D76N mutant of beta-2-microglobulin a tumour marker for some blood cell cancers [Estácio *et al*, *PLoS Comput Biol* 2014]
b. A minimal model of a mutating pathogen in a host population with a weak immune response was shown to reproduce the main qualitative features of influenza A evolution, highlighting the importance of heterogeneity in immune response to understand influenza phenomenology [T Aquino, A Nunes, *Virulence* 2016]
c. Establishement of a new correlation between magnetic shielding constants and electron binding energies [BJC Cabral, *J Chem Phys* 2017]

9.8 Research Group: Modelling of Agents & Systems (MAS)

9.8.1 Description of the Research Group

9.8.1.1 Reference of the Research Group

RG-4046-400182

9.8.1.2 Name of the Research Group in Portuguese

MAS – Modelação de Agentes e Sistemas

9.8.1.3 Name of the Research Group in English

MAS – Modelling of Agents & Systems

9.8.1.4 Keywords

- Artificial intelligence
- Data mining and knowledge discovery
- Autonomous agents and multi-agent systems
- Visualisation and animation

9.8.1.5 Existed in 2008-2012

Yes

9.8.2 Researchers of the Research Group

9.8.2.1 List of Integrated Researchers of the R&D Unit who hold a PhD degree and belong to the Research Group

Luis Miguel Parreira e Correia – Principal Investigator
Ana Paula Boler Cláudio
Helder Manuel Ferreira Coelho
Hugo Filipe DE Mesquita Costa Martiniano
João Carlos Balsa da Silva
João Pedro Guerreiro Neto
Jorge Miguel Carvalho Gomes
José Manuel Veiga Ribeiro Cascalho
Luis Alberto dos Santos Antunes
Luis Filipe Graça Morgado
Luis Manuel Ferreira Fernandes Moniz
Luís Manuel Pereira Sales Cavique Santos
Maria Beatriz Duarte Pereira do Carmo
Maria da Graça de Figueiredo Rodrigues Gaspar
Maria Isabel Batalha Reis Gama Nunes
Paulo Jorge Cunha Vaz Dias Urbano
Paulo Manuel Trigo Cândido da Silva
Pedro Lopes da Silva Mariano
Rob Mills
Rui Filipe Nicolau Lima Antunes
Sara Guilherme Oliveira da Silva

9.8.3 Description of the main contributions of the Research Group in 2013-2017

9.8.3.1 General description of the Research Group

Scope

MAS carries out research in Artificial Intelligence (AI) in general, including machine learning and visualization. A strong focus is on agent-based approaches and exploring links between biology and physics with AI, self-organized systems and bio-inspired computation. Two specific research areas (sub-groups) are: social simulation (GUESS), and computational artificial life (GruVA).

Main objectives

- To improve data mining, knowledge discovery and data visualisation tools for big data
- To develop general multi-agent models of complex systems and in particular, the crossing of morality with power, leadership and culture is being studied within agent models to better simulate aspects of human societies;
- To research bio-inspired computational models of living and engineered systems.

Future main contributions to R&D:

1) Application of an evolutionary game-theoretical approach to model extremist behaviour in a social context, and conversion of dynamics across different complex social systems
1) Genetic Programming developed as a general machine learning approach, expecting to integrate symbolic regression with agent-based models in a productive way to guide discovery of complex (bio)system models
2) Interaction models of heterogeneous swarms of animals and robots resulting from bio-hybrid swarms research as the main conclusion of EU project ASSISIbf
3) Further exploitation of evolutionary algorithms with a multi-set representation of populations and specific operators, and a symbiogenetic approach as a form of co-evolution, to improve performance
4) Adaptation and deployment of augmented reality visualisation models to mobile devices and extension of interactive applications to create virtual exhibitions
5) Research in integration of visualisation and human crowd simulation of behaviour design/configuration to produce ever more realistic scenes, to be designed by a non-expert; instantiations of ancient villages will be generalised to other contexts.

9.8.3.2 Identification and summary description of Research Group Contributions

1) Multi-agent models of power and leadership were developed for human societies and their organisations. This produced an approach to model structured agent societies with context permeability across multiple coexisting social networks [Nunes D, Antunes L (2015) Modelling structured societies: A multi-relational approach to context permeability. *Artificial Intelligence*, 229:175-199] and a model of self-organised demonstrations and their behaviour [Lemos C, Lopes RJ, Coelho H (2016), On Legitimacy Feedback Mechanisms in Agent-Based Modeling of Civil Violence. *Int J Intell Syst*, 31: 106-127]

2) An evolutionary approach was developed to build online robot controllers based on artificial neural networks, for robotic swarms. This work was applied in simulation and in real robots and it was an

original achievement since no previous solution existed for online development of robotic swarm controllers [Silva *et al, Royal Society open science* 2017]

3) Development of new cooperative coevolutionary algorithms for the synthesis of controllers for heterogeneous multiagent systems. The proposed algorithms were evaluated in simulated agents and real robots and were shown to overcome fundamental limitations in this class of evolutionary algorithms. This work established cooperative coevolution as a promising approach for evolving cooperative multiagent systems [Gomes *et al*, *IEEE Trans Evol Comput* 2017].

4) A review and discussion of open issues in evolutionary robotics with analysis of promising research approaches was published with the goal of contributing to the establishment of evolutionary robotics as a canonical approach for the engineering of autonomous robots. This article received the Best of Computing 2016 award, by ACM Computing Reviews [Silva F, Duarte M, Correia L, Oliveira SM, Christensen AL (2016) Open Issues in Evolutionary Robotics. Evolutionary Computation. 24(2):205-236. doi: 10.1162/EVCO_a_00172]

Part 4: Plan of Activities for 2018-2022

10 SUMMARIES OF THE PLAN OF ACTIVITIES 2018-2022

10.1 Summary in Portuguese for general dissemination purposes

Os sistemas biológicos apresentam propriedades complexas que não se preveem a partir do estudo isolado dos seus componentes. Para abordar tal complexidade são necessárias análises integrativas que combinem metodologias de alto rendimento e ferramentas computacionais que descrevem e preveem comportamentos dinâmicos.

A visão do BioISI, um novo instituto criado em 2015 (http://www.bioisi.pt) é explorar a investigação de ponta em biossistemas e ciências integrativas para se tornar o centro líder desta área nacional e internacionalmente.

O objetivo do BioISI é compreender e resolver problemas complexos emergentes em biologia e biomedicina na vanguarda da investigação das ciências da vida. Os seus investigadores beneficiam dum ambiente multidisciplinar único que fomenta o pensamento criativo para resolver problemas de forma integrativa.

O BioISI tem 5 principais missões:

1) Investigação em Biossistemas e Ciências Integrativas
2) Tecnologia e Instrumentação
3) *Facilities* e Serviços
4) Ensino e Formação
5) Transferência de Conhecimento e Tecnologia

Outputs que Apoiam a Visão e Objetivos Estratégicos

A visão do BioISI 2018-22 é fundamentada nos vários outputs e realizações em 2013-17 atingidos pelos seus ~130 investigadores doutorados de diferentes áreas (biologia, química, física, informática) que demonstram como o BioISI contribui com significativo valor acrescentado para o desenvolvimento do sistema de I&D nacional.

Objetivos estratégicos para 2018-2022

1. Liderar a investigação em Biossistemas e Ciências Integrativas
2. Conduzir a investigação para desenvolvimentos tecnológicos e inovação
3. Treinar a próxima geração de cientistas líder em biossistemas e ciências integrativas
4. Proporcionar *core-facilities* e serviços de investigação interna e externamente
5. Assumir um papel relevante de interação com a indústria e na transferência de conhecimento e tecnologia nas ciências da vida

Estes objetivos estratégicos serão implementados nas 5 linhas temáticas do BioISI: Biomedicina; Biotecnologia, Química Biológica; Bioinformática; Biofísica com o objetivo de contribuir para 3 principais projetos:

1) Melhoramento de colheitas/produtos & contribuições para a bioeconomia: vinha e vinho
2) Abordagens de sistemas a doenças raras: Fibrose Quística e neurodegeneração

3) Tecnologias capacitadoras: para impulsionar pesquisa inovadora em biossistemas

Para atingir os seus fins estratégicos 2018-22 propõe-se:

1) Fortalecer a investigação, tecnologia e inovação pela contratação de novos investigadores
2) Reforçar a formação de estudantes júnior/ de doutoramento, e de jovens pós-docs
3) Investir nas core-facilities para servir investigadores internos/externos e empresas
4) Estimular a disseminação científica pela organização de conferências, seminários, cursos
5) Fomentar a cultura científica e tecnológica na sociedade promovendo múltiplos eventos
6) Transpor resultados de investigação para a sociedade através dum Programa de Parceria BioISI-Indústria.

10.2 Summary in English for general dissemination purposes

Biological systems display complex properties that cannot be predicted from studying isolated parts. Addressing such complexity calls for integrative analyses combining high-throughput Omics with quantitative science and computational tools to describe and predict dynamical behaviours. The vision of BioISI, a new institute created in 2015 (http://www.bioisi.pt) is to pursue cutting-edge research on biosystems and integrative sciences to become the leading centre at the forefront of research in this area in Portugal and internationally. BioISI's goal is to understand and address biological questions using integrative -Systems- approaches at the vanguard of life sciences research. Is researchers benefit from a unique multidisciplinary environment that fosters creative thinking to solve problems through integrative approaches.

To achieve its vision BioISI pursues 5 major missions:

1) Research in BioSystems & Integrative Sciences
2) Technology & Instrumentation
3) Facilities & Services
4) Teaching & Training
5) Knowledge/Technology Transfer

Outputs Supporting the vision and strategic objectives

BioISI vision and goals for 2018-22 are substantiated in several achievements and track record in 2013-17 by its critical mass of ~130 researchers (with PhD) from different disciplines (biology, chemistry, physics, computer science), evidencing how BioISI contributes with significant added value of to the development of national R&D system.

Strategic objectives for 2018-2022

1. Taking a lead role in Biosystems/Integrative Sciences research nationally and internationally
2. Driving research and progress through technology development and innovation
3. Training next generation of scientific leaders on Biosystems/Integrative Sciences
4. Providing research facilities and services to BioISI researchers and externally
5. Become a major player in industry partnerships and technology transfer for life sciences

These strategic objectives will be implemented along BioISI's 5 main Thematic Lines: Biomedicine; Biotechnology; Biological Chemistry; Bioinformatics; Biological Physics with the goal of contributing to 3 main projects:

1) Crop/product improvement & contributions to bioeconomy: grapevine & wine
2) Systems approaches to rare diseases: Cystic Fibrosis and neurodegeneration
3) Enabling technologies: to boost innovative research in biological systems

To achieve its strategic 2018-22 goals BioISI proposes:

1) **Strengthen BioISI research, technology & innovation** by hiring new researchers
2) **Reinforce training** of junior and PhD students and young postdoc researchers
3) **Invest in core-facilities** to serve internal, external researchers or companies
4) **Stimulate scientific dissemination** by organizing conferences, seminars, workshops, courses
5) **Foster scientific/technological culture on society** by promoting multiple outreach events
6) **Encourage translation of research results to society**, establishing BioISI-Industry Partnership.

10.3 Summary in English for evaluation

Biological systems display complex properties that cannot be predicted from studying isolated parts. Addressing such complexity calls for integrative analyses combining high-throughput Omics with quantitative science and computational tools to describe and predict dynamical behaviours.

Vision in Systems Biology

The vision of BioISI, a new institute created in 2015 (http://www.bioisi.pt) is to pursue cutting-edge research on biosystems and integrative sciences to become the leading centre at the forefront of research in this area in Portugal and internationally.

Goal & Missions

BioISI's goal is to understand and address biological questions using integrative -Systems- approaches at the vanguard of life sciences research. Is researchers benefit from a unique multidisciplinary environment that fosters creative thinking to solve problems through integrative approaches.

To achieve its vision BioISI pursues 5 major missions:

1) Research in BioSystems & Integrative Sciences
2) Technology & Instrumentation
3) Facilities and Services
4) Teaching and Training
5) Knowledge/ Technology Transfer

Outputs Supporting the vision and strategic objectives

BioISI vision and goals for 2019-22 are substantiated in several achievements and track record in 2013-2017 by its critical mass of ~130 researchers from different disciplines (biology, chemistry, physics, computer science), evidencing how BioISI contributes with significant added value of to the development of national R&D system. Highlights of the 2013-17 were:

- **Science of Excellence**: **872 original publications** in peer reviewed journals (~174/yr) with an average impact factor of **8.9 for the top 25% papers**, and an **H-index of 93**;
- **Competitive funding:** an average of ~**3.6 M€/yr** of competitive funding were attracted (25% of which from private sector);
- **Internationalization**: 55% of BioISI publications and 54% of its PhD students had international collaborators/co-supervisors; it has 36 ongoing large collaborative projects/networks; it participates in several EU Infrastructures;
- **Advanced training**: 45 completed PhD and 129 MSc theses (currently; 69PhD students) namely from BioSys a highly competitive FCT-funded PhD programme on Systems Biology (BioISI participates in 3 other); BioISI has in place an Interdisciplinary Post-doctoral Programme (IPP) and mentor young PIs for independence;
- **Promotion of scientific & technological culture and Actions of special relevance for society** BioISI promotes awareness of its research societal impact through organization of science outreach events and strongly contributes to interactions with industry;
- **Other**: 12 meetings/workshops organized; 4 patents and 12 computational models registered, having contributed to the creation 17 start-ups/ spin-offs; maintains and curates several databases,

Strategic objectives for 2018-2022

6. Taking a lead role in Biosystems/Integrative Sciences research nationally and internationally
7. Driving research and progress through technology development and innovation
8. Training next generation of scientific leaders on Biosystems/Integrative Sciences
9. Providing research facilities and services to BioISI researchers and externally
10. Become a major player in industry partnerships and technology transfer for life sciences

These strategic objectives will be implemented along BioISI's 5 main Thematic Lines (TLs):
1) **Biomedicine**: to understand molecular/cellular mechanisms of disease and translate findings into improved diagnoses/prognoses and better personalized therapies.
2) **Biotechnology**: to characterizing at systems-level economically relevant plants and microbes to sustainably meet the challenges of global climate changes while safeguarding the environment.
3) Biological Chemistry: to develop bioactive molecules (by synthesis or from natural sources) and understand molecular mechanisms of (bio)chemical systems (eg, molecular/cellular bioenergetics).
4) **Bioinformatics**: to promote digital biology at large, fostering the generation of systems-level knowledge and models to describe and predict the behaviour of complex biological systems.
5) **Biological Physics**: to boost interdisciplinarit rooted in Physics, eg, atomic force microscopy (AFM) related techniques for bio-systems or simulation approaches to protein (mis)folding.

BioISI strategy is to cluster its competences in 3 main societal challenges as ´Flagship projects´:

1) Crop/product improvement & contributions to bioeconomy: grapevine and wine
2) Systems approaches to rare diseases: Cystic Fibrosis and neurodegeneration
3) Enabling technologies: AFM/FFM tools and innovative computational approaches

To achieve its strategic 2018-22 goals BioISI proposes:

1) **Strengthen BioISI research, technology development & innovation** by: hiring of 10 new PIs in key BioISI areas; expanding current BioISI internal multidisciplinary projects
2) **Reinforce training**: create a Junior Studentships Programme dedicated to early career researchers; expand both PhD (BioSys2) and Interdisciplinary Postdoctoral Programme (IPP) programmes;
3) **Invest in core-facilities**: hire dedicated human resources; upgrading equipment;
4) **Stimulate scientific dissemination**: organize conferences, seminars, workshops, courses;
5) **Foster scientific & technological culture on society**: promote multiple outreach events;
6) **Encourage collaborations with industry and boost knowledge & technology transfer (KTT)**: Establish a BioISI-Industry Partnership Programme and hire a dedicated KTT officer.

Organisation

BioISI has 1 main +3 other institutions, 8 research groups (headed by a group leader), each RG contributing to the 5 TLs which are headed by a TL Coordinator. This structure promotes cooperative interactions to foster integrative research. The BioISI Director, assisted by the TLCs and RGLs (Scientific Committee) and advised by the external Scientific Advisory Board (SAB) is responsible for the implementation of the strategic plan.

11 DESCRIPTION OF THE PLAN OF ACTIVITIES FOR 2018-2022

11.1 Objectives and strategy of the R&D Unit for 2018-2022

1.Objectives

For its vision of developing research of excellence on biosystems and integrative sciences, BioISI 2018-22 strategy will strengthen its 5 key missions:

1. Taking a lead role in Biosystems/Integrative Sciences research nationally and internationally
2. Driving research and progress through technology development and innovation
3. Training next generation of scientific leaders on Biosystems/Integrative Sciences
4. Providing research facilities and services to BioISI researchers and externally
5. Become a major player in industry partnerships and technology transfer for life sciences

This unique mix of activities functions synergistically and is key to BioISI success in integrative approaches to Biosystems with high societal impact.

These goals stem from BioISI impressive scientific achievements and track record in 2013-17, evidencing significant added value to the development of national R&D system.

A set of strategic objectives were defined to achieve the above ambitious goals. We briefly present the highlights of this integrated, cohesive strategy for 2018-22.

2. Strategy

Systems Biology is a recent research field anchored on quantitative, interdisciplinary and integrative approaches to biology that holds promise to deliver high impact solutions for world-wide societal challenges. Due to its multidisciplinary environment, BioISI is uniquely positioned in Portugal to contribute to this field. But a real interdisciplinary mindset is not always easy to implement, being required for Systems Biology to achieve its potential impact on medicine, industry and society.

In 2018-22, by rooting an interdisciplinary collaborative mindset, BioISI will focus its research in solving key 21st century questions in Biomedicine/Biotechnology: its flagship projects.

BioISI short-term strategy resulted from the combined analysis of: 1) the defined long-term strategy; 2) a thorough evaluation of the strengths and installed capacity at BioISI; 3) the social and economic needs of the Lisboa region, Portugal and Europe. This has led to the identification of the domains that need to be strategically nourished in the next 5 yrs.

Globally, this strategy will place BioISI among the leading European interdisciplinary research institutes in Systems Biology, as it will focus and support the most promising research which will be strengthened to leverage research excellence of the entire scientific community of the institute.

3.AIM 1: Carrying out Forefront Research in BioSystems & Integrative Sciences

BioISI has outputs of excellence contributing to outstanding basic and translational research, as expressed by its scientific track record in areas that are key to Systems Biology: Molecular & Cell Biology, Omics, Biophysics, Bioinformatics, Computational Biology and recently Biological Chemistry.

It also embraces a collaborative research environment across its 5 scientific thematic lines (TLs). Interdisciplinarity has been promoted by calls for internal 'cross-area' projects bridging the gaps across all TLs [see BioISI reports].

One of BioISI's key priorities in its proposed strategy for 2018-22 is to strengthen a culture of interdisciplinarity among its researchers.

3.1 Flagship projects

BioISI research strategy will focus on the clustering of the available key competences at BioISI in 3 main societal challenges as ´Flagship projects':

1) Crop/product improvement & contributions to bioeconomy: grapevine and wine
2) Systems approaches to rare diseases: Cystic Fibrosis and neurodegeneration
3) Enabling technologies: AFM/FFM tools and innovative computational approaches

Strategy:

-To recruit 6 new PIs to reinforce the above ´flagship´ areas and to bridge gaps among areas for increased interdisciplinarity

-To expand current BioISI internal projects programme.

3.2 Internationalization

BioISI has a high level of internationalization. It submitted (2017) a joint Twinning proposal to H2020-Widening (Oct 2017) with EMBL + Karolinska Institute. Such key partnership will facilitate scientific collaborations, access to infrastructures (eg, databases, facilities, instrumentation, services and training activities) provided by the international partners.

Strategy:

-Increasing participation in EU projects/networks, Widening (Twinning, ERA Chairs). A new science manager (post-doc) was hired in 2018 to support these applications.

-Explore the possibility expressed by EMBL Director of establishing a partnership with EMBL, excellent for BioISI internationalization but also for Portuguese science.

3.2 National partnerships & networks

Besides its poles and partner institutions. BioISI has strong interactions with national institutions, by integrating 7 national networks (National Infrastructures Networks; Agro-Food; Marine Resources, etc). BioISI researchers are members of 9 national societies.

Strategy:

-Strengthen strategic national collaborations for scientific exchanges of know-how, namely through BioISI facilities and services.

-Actively participate in the large thematic networks within ULisboa.

4. AIM 2: Driving research and progress through technology development and innovation

BioISI flagship project ´Enabling Technologies for Cutting-edge Research' is driven by scientific/ society needs. For 2018-22 these will be:

a) Develop AFM/FFM tools for biological applications
b) Create innovative computational approaches
c) Optimizing nano-methods for bio-measurements and biodevices
d) Discovering new drugs to correct the basic defect underlying human diseases

Strategy:
-To recruit 4 new PIs to reinforce the above technology development areas.

5.AIM 3: Providing research facilities and services to BioISI researchers and externally
As a strong asset to facilitate research enabling scientists to achieve ambitious research goals in a cost-effective way, BCore-Facilities up-dating is a priority to maximise available resources, leverage BioISI research excellence, catapult research outputs, attract the most talented new PIs, and make a difference in advanced training.
Strategy:
In 2018-22 BioISI aims to become a key player in the operation of cutting-edge biological research infrastructures/services in the Lisboa region by:
-Providing excellent services with state-of-the-art equipment and creating 2 new facitilies: flow cytometry and protein core
-Offering user support by highly specialized dedicated staff by hiring: 5 Post-docs, 3 technicians
-Promoting international training to facilities staff in new technologies
-Hosting heads/staff from other facilities to help in organization

6.AIM 4: Training next generation of scientific leaders on Biosystems/Integrative Sciences
BioISI aims to train the next generation of scientific leaders on Biosystems/Integrative Sciences with a strong commitment to advanced training and career development through mentoring. Thus, in 2018-22 we will reinforce this at various levels (1 scientific manager will be hired to support training activities):

6.1 Junior Studentships Programme (JSP)
Being at FCUL campus (hosting >1,000 BSc, >300 MSc bio-students) BioISI maintains a strong tradition of initiating young students to science research (129 MSc theses in 2013-17).
Strategy:
Create a programme dedicated to initiate early career researchers in science

6.2 BioSys2 PhD programme
BioISI has a successful BioSys PhD programme on Systems Biology and participates in 3 other (45 PhD theses in 2013-17)
Strategy:
Expand PhD programme to BioSys2

6.3 Interdisciplinary Postdoctoral Programme (IPP)
BioISI interdisciplinary research was greatly reinforced by its pilot Interdisciplinary Postdoctoral Programme (IPP) with 4 post-docs over 2-3 yrs.
Strategy:
Expand IPP to offer more positions into 3 tracks

6.4 New independent PIs
BioISI 1st priority is to foster challenging and long-term research projects at the highest level in its key areas which can only be accomplished by continuously recruiting new PIs.

Strategy:
Recruit 10 new PIs on key areas [see above] who will receive scientific and professional mentoring from senior colleagues for their independent establishment

6.5 Organization of conferences, seminars, workshops and courses

BioISI conferences, seminars, workshops and courses will be essential to disseminate its research internally and externally [see TLs in 12].

Strategy:
BioISI will keep 3 cycles of internal seminars (PhD students & Post-docs; PIs; visitors), multiple international workshops (also for BioSys2) and will launch a conferences cycle [see TLs in 12]

7.AIM 5: Become a major player in industry partnerships and technology transfer for life sciences

Based on its solid collaborations with industry (with 25% private funding; contributed to 17 start-ups/spin-offs) BioISI is strategically positioned to contribute to knowledge translation by solving societal problems in a perfect balance of academia/industry partnerships.
In 2018-22 BioISI will foster *Knowledge & technology transfer (KTT)* to ensure translation of promising outputs to societal uses. Since former KTT office of ULisboa (UL-INOVAR) closed, BioISI will reinforce its Company Liaison Office (BioISI-Tech) operating at TecLabs.

Strategy:
-Hire a KTT post-doc officer to actively identify, protect, and exploit BioISI exciting results into real life-applications facilitating intellectual property protection (IPP) and KTT from basic research to society
-Establish a BioISI-Industry Partnership Programme (BIPP) to promote formal/informal academia-industry activities and make BioISI expertise/services available to industry.

8.Other relevant aspects

Including Outreach and Preservation/Dissemination of Data/Results *(Open Research Data Pilot*).

11.2 Organization of the R&D Unit for 2018-2022

Research at BioISI focuses on integrative approaches to biological problems at the forefront of life-sciences. In order to benefit from a unique multidisciplinary environment which gathers scientists from diverse areas, BioISI research is organized into 5 Thematic Lines (TLs) each functioning as a collaborative project led by a Coordinator (TLC) and Vice-Coordinator (TLVC), namely:

1) Biomedicine (BioMed): MD Amaral/C Gomes
2) Biotechnology (BioTech): R Malhó/R Tenreiro
3) Biological Physics (BioPhys): MM Godinho/A Nunes
4) Bioinformatics (BioInfo): L Correia/ MG-Carvalho
5) Biological Chemistry (BioChem): MJ Calhorda/P Costa

Each TLC is a former centre coordinator with past experience managing internationally funded research, being also a research group leader (RGL). TLCs/VCs promote specific activities and exchange of information to exploit collaborations enhancing multidisciplinary research.

Research groups

BioISI has 8 research groups (RGs) each headed by a RG leader (RGL) and containing multiple teams (headed by PIs).

1. Plant Functional Genomics Group (PFG): R Malhó
2. Functional Genomics and Proteostasis Group (FunGP): MD Amaral
3. Microbiology & Biotechnology Research Group (M&B): R Tenreiro
4. Biomedical & Translational Research (BTR): A Vicente
5. Gene Expression and Regulation (GER): M G-Carvalho
6. Bio-Physics & Nanosystems (BioPhysNano): MM Godinho
7. Agents and Systems Modelling (MAS): L Correia
8. Chemistry for Biological Systems (CBS): MJ Calhorda

Each RGL will coordinate research by the involved teams contributing to different TLs. Each RGL reports progress to the EB (see below). The teams are grouped based on common scientific areas, methodologies and shared technologies.

Technical Support

BioISI **Management Team** comprises 2 post-doc scientific managers and 1 secretary (1 more to be hired) who, together with FCID provide all support to BioISI Director, EB and SAB on BioISI management and reporting activities, also ensuring communication flow among BioISI researchers.

BioISI's **Communication & Outreach Office** is headed by M Gama-Carvalho and outsourced services with a media agency (Beeineditus).

BioISI is establishing an **Industry Liaison & KTT Office** headed by R Tenreiro and H Vieira (with large expertise in Innovation and Entrepreneurship) and will hire an Officer to foster interactions with the productive sector and ensure the exploitation of results and dissemination of foreground knowledge.

BioISI core-facilities are headed by a Director (R Malhó) who by directing the respective technical staff ensures their proper functioning for its researchers and externally by providing services, reporting to the EB.

Advanced Training

BioISI hosts a PhD programme **BioSys2** headed by a Director (CM Farinha) and organizes an Interdisciplinary Post-doc programme (**IPP**) for junior post-docs, also headed by a Director (MJ Calhorda), being both assisted in all tasks by the secretariat and reporting to the EB. A new programme for 20 early career young scientists (**BioJunior**) will start in 2019.

Multidisciplinary research is potentiated by jointly supervised students/post-docs from these programmes, as a major driving force to collaborative work among BioISI teams.

Governance

BioISI governance is ensured at research, advanced training, technical and coordination levels.

BioISI Director General (DG): All BioISI activities are led by BioISI General Director who also chairs the Executive Board (see below). The current BioISI Director (MD Amaral) has significant expertise in leading large international projects. As EMBL alumna, she has a strong vision to promote science of excellence and a high international standing. Activities at EMBL and other top institutions are intensely disseminated, and usage of facilities strongly promoted among BioISI researchers. A Vice-Director (R Malhó) assists and replaces the DG, when needed.

Executive Board (EB): BioISI Director, assisted by the TLCs/VCs, form an E**xecutive Board (EB)** who implements BioISI strategic plan and **Scientific Advisory Board** (SAB) recommendations and proposes strategic guidelines to the **Steering Scientific Committee** (SSC) The SSC is formed by all RGLs, TLCs/VCs and a representative of each pole) being responsible for:

- Keeping track of scientific and integrative research carried out by RGs;
- Promoting interactions and build RGs synergies based on their complementary resources and expertise;
- Discussing strategies, scientific and integration issues, adjust work plans and other relevant issues proposed by the EB;
- Fostering effective external collaborations (e.g., participation in EU projects and industrial interactions);
- Carrying out overall management, including risk management, resolution of conflicts;

A **Scientific Council** comprising all integrated BioISI PhD researchers is the basis for BioISI decisions. at the scientific, technical and strategic levels and also for electing BioISI Director.

Management Institutions

FCiencias.ID (FCID) is BioISI's main managing institution of, whereas the participating institution FCUL provides the infrastructures accommodating most of BioISI labs and facilities.

Other BioISI managing institutions (poles) include:

1) **INSARJ:** is the reference national institute of health in Portugal, and its involvement is of high strategic relevance for the impact of BioMed-TL research results. Being within FCUL walking distance, interactions among BioISI researchers at INSARJ and FCUL occur as if they were at FCUL campus.
2) **UTAD & UM**: both in Northern Portugal, involv teams in BioMed & BioTech TLs. Despite being far FCUL, their involvement in BioISI is of strategic for the establishment of an inter-regional

network on specific societal topics. Regular webconferences ensures discussion of progresses among teams involved and joint supervision of internal projects and students strengthens collaborative work.

All managing institutions are responsible for local administrative and financial procedures in coordination with FCID to optimize research and avoid hurdles.
Each pole has a local project manager and a scientific coordinator ensuring optimal flow of information to and from BioISI director.

Ensuring collaborative research
BioISI's structure ensures constant dissemination of results from its training and research activities. Updates take place at BioISI seminars. Group collaborations are fostered through BioISI projects (see below). Additionally, BioISI international seminars bring experts in cutting-edge topics fostering network activities and exploring applications to international calls (eg H2020, COST actions, Twinning). A member of the managing team supports these large applications.

BioISI internal projects: BioISI already had 3 competitive internal calls funding in total 21 research projects led by different PIs in the scope of the TLs. These trigger applications to national and international collaborative projects, thus functioning as 'seed funding'.

12 THEMATIC LINES

Reference	Name	Principal Investigator
TL-4046-3131	BioMed - Biomedicine	Margarida Sofia Pereira Duarte Amaral
TL-4046-3145	Biotech - Biotechnology	Rui Manuel Santos Malho
TL-4046-3192	BChem - Biological Chemistry	Maria José Diogo da Silva Calhorda
TL-4046-3193	BioInf - Bioinformatics	Luis Miguel Parreira e Correia
TL-4046-3194	BioPhys - Biophysics	Maria Margarida da Fonseca Beja Godinho

12.1 Thematic Line Biomedicine (BioMed)

12.1.1 ID number of Thematic Line
TL-4046-3131

12.1.2 Thematic Line name in Portuguese
Biomedicina

12.1.3 Thematic Line name in English
Biomedicine

12.1.4 Thematic Line Coordinator
Margarida Sofia Pereira Duarte Amaral

12.1.5 Description of the Thematic Line

Goals
BioMed-TL aims at:
1) understanding molecular/ cellular mechanisms of disease;
2) translating high-throughput biology into disease risk, diagnosis, and prognosis;
3) developing innovative therapies & drug discovery, all contributing to personalized approaches and improved health.

Introduction
Conventional approaches relying in exploration of a single gene or a single process/target are no longer valid. We thus seek to implement new approaches to solve health problems based on a systems-level analysis of causative pathways including genes, biomolecules, environment, lifestyle.

Proposed Research
BioISI is ideally positioned to pursue ambitious research on systems biomedicine for personalised diagnosis, molecular/ cellular disease mechanisms & therapies. Its disruptive research blends classical (molecular/cell biology) with emerging disciplines (omics, computational, systems biology) and taking the most of BioISI facilities. We have the required expertise, resources and track record to leverage significant advances in biomedicine of complex systems.

Research highlights for 2018-22:
i)Mechanisms and networks of rare diseases and neurodegeneration
To understand rare diseases eg, cystic fibrosis (CF) or complex ones eg. Alzheimer's Disease (AD) we will apply classical methodologies and quantitative, computational, biophysical approaches towards functional genomics and pathway analysis using cutting-edge approaches (e.g., HT bioimaging).

ii) Genomic and environmental factors of multifactorial disorders

To establish genetic, clinical, lifestyle and environmental determinants in complex diseases eg autism or familial hypercholesterolemia, by handling large biomedical datasets and creating tools to translate them into clinical meaning.

iii) Signalling processes in health and disease
To characterise processes in CF, cancer or AD and develop potential therapeutic modulators, we will create disease maps, interactomes, of specific pathways and apply them to clinical use.

iv) Personalised therapies: molecular biomarkers, biologics and small molecule drugs
To translate omics into personalised therapies for CF, AD or β-thalassemia we will propose innovative therapeutic strategies from tests in new cell/organoid models, and do drug discovery by screening for proteostasis or RNA modulators (small molecules/ biologics).

Key Actions
BioMed will continue organizing 2 international workshops/yr on "*HT Microscopy*" and "*Epithelial Systems*" also offered to BioSYS PhD students. BioMed will organize 1 Summer school "*Data-driven Biology*" and a 2-day Conference on "*Systems Biology in Biomedicine*".

Integrated Research
BioMed contributes to BioISI mission of implementing system-level approaches to solve biomedical problems. Collaborative integration with other TLs will be actively executed, eg development of new enabling technologies/biomedical devices (Bio-Phys), Omics/ big-data analyses (BioInf), drug development (BChem), drug discovery from bioresources (Biotech).

12.1.6 Research Groups that contribute to the Thematic Line
FunGP - Functional Genomics & Proteostasis (RG-4046-400174)
BTR - Biomedical & Translational Research (RG-4046-400176)
GER - Gene Expression & Regulation (RG-4046-400178)

12.2 Thematic Line Biotechnology (BioTech)

12.2.1 ID number of Thematic Line
TL-4046-3145

12.2.2 Thematic Line name in Portuguese
Biotech - Biotecnologia

12.2.3 Thematic Line name in English
Biotech - Biotechnology

12.2.4 Thematic Line Coordinator
Rui Manuel Santos Malho

12.2.5 Description of the Thematic Line

Goals
Biotech-TL aims at:
1) characterizing at systems-level economically relevant plants and microbes to sustainably meet the challenges of global climate changes while safeguarding the environment;
2) identifying natural compounds so as to become drugs or added-value nutraceuticals;
3) ensure food traceability and authenticity.

Introduction
Knowledge derived from integrative studies can bring about a non-negligible positive impact. Thus, characterization of plants and microbes at the genetic, molecular and physiological level can significantly increase their biotech potential.

Proposed Research
Biotech-TL is framed by societal challenges: functional foods for disease prevention, new drugs from marine organisms, safe and sustainable agriculture.
Systems-level research will generate new knowledge and develop modular tools to enable rapid responses to new challenges, eg the emergence of new plant or diet-related diseases, changes in pathogens/ vectors distribution or impact assessment of new bio-based products.

i)Plant health
Characterization of plants with increased tolerance to biotic (eg pest) or abiotic (eg temperature, drought) stress, ripening control and better nutritional, growth characteristics. Cutting-edge studies in the model plant *Arabidopsis* and translational research in grapevine and cork oak given their exceptional value for Portuguese economy.

ii)Crop improvement and security
Assessment of plant cells/ organs for pro-drugs/ nutraceuticals production (eg anti-inflammatory, anti-cancer, anti-oxidants). Global gene expression profiling in adaptation and survival for genome

editing and breeding programs. Development of accurate, cost-effective methods for food traceability and authenticity.

iii)Microbial biotechnology

Omics-based characterization of microbes for bioactivity profiles, screening, extraction and identification of novel compounds for therapeutics, agrosciences and greener industrial processes. Integrative characterization of wine yeasts of higher stress tolerance/performance, to cope with impact of global climatic changes in grape maturation and to reduce wine preservatives.

iv)Microbial pharmacogenomics

Identification of molecular targets to develop pro-drugs and diagnostic tools for infectious diseases. Use of yeast transcriptional networks to dissect stress responses (to anti-cancer drugs, radiation, fungicides).

Key Actions

BioTech will organize 2 industry-oriented workshops (e.g. 4th GenSequencing, Genome editing) and industry networking events/yr. Annual post-grad courses (e.g. Applied microbiology/Mycology) will promote Biotech among young researchers and dissemination events will raise public awareness.

Integrated Research

BioTech contributes to BioISI mission of implementing system-level approaches to address biological questions.It integrates with other TLs by developing new enabling technologies/field devices (Bio-Phys), analysing Omics/big-data (BioInf), drug discovery from bioresources (BChem/BioMed).

12.2.6 Research Groups that contribute to the Thematic Line

PFG - Plant Functional Genomics (RG-4046-376656)
M&B - Microbiology & Biotechnology (RG-4046-400175)
CBS - Chemistry for Biological Systems (RG-4046-400179)

12.3 Thematic Line Biological Chemistry (BChem)

12.3.1 ID number of Thematic Line
TL-4046-3192

12.3.2 Thematic Line name in Portuguese
BChem – Química Biológica

12.3.3 Thematic Line name in English
BChem – Biological Chemistry

12.3.4 Thematic Line Coordinator
Maria José Diogo da Silva Calhorda

12.3.5 Description of the Thematic Line

Goals
BChem-TL aims at:
1) developing bioactive molecules either by synthesis or extraction from natural sources;
2) understanding molecular mechanisms of (bio)chemical systems, from small molecules, to proteins, membranes, and cells;
3) widening the knowledge of molecular and cellular bioenergetics.

Introduction
Chemical knowledge at the molecular level is a key factor to design better drugs, understand structural changes triggered by the environment (eg pH or binding of a substrate), or study mechanisms related to enzyme function. We thus wish to solve health problems using integrative (bio)chemical approaches.

Proposed Research
We have the expertise to advance BioISI objectives significantly in rare disease diagnoses and therapy at both molecular & cellular levels. We combine computational and experimental approaches ranging from (in)organic to biochemical and cellular levels. We plan to address health and environmental safety problems, either directly (eg new leads) or indirectly (solving mechanisms or designing eco-friendly molecules and processes, or by unravelling pathogens bioenergetics).

i)Bioactive molecules
Isolation of compounds from natural confirmed sources of new drug leads with bioactivity, eg marine organisms, infusions or extracts. Synthesis of new molecules with special properties (discreet molecular magnets, cytotoxicity) or probes for biological racemic mixtures. Development of eco-friendly agents and non-toxic antifouling polymers with tethered agents.

ii)Molecular mechanisms of (bio)chemical systems

To understand mechanisms at the molecular level, computational methods ranging from quantum-chemical to molecular modeling calculations will address: the recognition of small molecules and/or peptides by proteins and membranes, taking advantage of unusual bonds or including pH effects, to enhance current computer-aided drug-design methods; the thermodynamic and molecular origin of protein aggregation; the mechanisms of transition metal catalyzed reactions.

iii)Molecular and cellular bioenergetics

To integrate a molecular approach with a cellular perspective on the role of different respiratory enzymes, providing mechanistic insights in respiratory proteins and defining their cellular role. To investigate temporal/ spatial organization of enzymes under different energetic provisions and explore the relation of energetic metabolism with other cellular processes, eg cell division, cell shape.

Key actions

BChem will organize 2 international workshops/yr on Biological Chemistry,1 (biannually) on "Multifunctional Magnetic Materials" (SPINON), and participate in organization of 2 H2020-MSCA-ITN-2018 topics and 9th EuCheMS Chemistry Congress 2020 in Lisboa.

Integrated research

BChem contributes to the drug development (BioMed), development of sensors/ new technologies (Bio-Phys, BioTech). Most of the computational approaches involve close collaboration with experimental BioISI groups and from abroad.

12.3.6 Research Groups that contribute to the Thematic Line

M&B - Microbiology & Biotechnology (RG-4046-400175)
CBS - Chemistry for Biological Systems (RG-4046-400179)

12.4 Thematic Line Bioinformatics (BioInf)

12.4.1 ID number of Thematic Line
TL-4046-3193

12.4.2 Thematic Line name in Portuguese
BioInf - Bioinformática

12.4.3 Thematic Line name in English
BioInf - Bioinformatics

12.4.4 Thematic Line Coordinator
Luís Miguel Parreira e Correia

12.4.5 Thematic Line Coordinator

Goals
BioInformatics thematic line (BioInf) promotes the development of digital biology at large, fostering the generation of systems-level knowledge and models to describe and predict the behaviour of complex biological systems.

Introduction
Computational means have become an essential tool to advance the study of living systems globally. At BioISI we follow this systems-level approach through research and development of tools for: 1) quantitative biology and multilevel, real-time, large-scale integration of biological data; 2) digital representation, modelling and simulation of biological systems; 3) knowledge production, sharing and innovation.

Proposed Research
The highlights of BioInf research for the next 5 years are:

i)Novel computational tools for multilevel data integration and modelling
from: i) clinical and epidemiological data for public health decision-making; ii) association studies, variant prioritization and mutation discovery of complex and rare diseases; and iii) omics data of diseased cells/ tissues or non-model organisms (namely crop plants, associated pathogens and microbiomes).

ii)Innovative algorithms for knowledge discovery from Nanopore-based devices
Real-time requirements are crucial for point-of-care discovery, biodigitization and bioeconomy based on data collected by 4th Generation Sequencing platforms, with a focus on (epi)genomics.

iii)Models of gene regulatory networks in signalling and protein-protein interactions

Computational implementation of mathematical models of pathways perturbed in diseased vs healthy cellular states, namely in rare diseases and neurodegeneration, both to elucidate disease mechanisms and to support innovative drug discovery.

iv)Multi-agent models and simulations of living and artificial life systems
To produce algorithms for the modelling of complex collective systems, and bio-inspired algorithms to solve complex problems.

Key Actions
BioInf will take initiatives to position BioISI in relevant European and national bioinformatics and systems biology networks.
We will organise focused yearly one day sessions for brainstorming on 'computation for life sciences' themes with invited experts, and (2-3 days) Workshops on BioInf topics/yr (upcoming in 2018: Integrative Approaches in Neurodegeneration; next: Bioinformatics and computational modelling for Systems Biology).

Integrated research
BioInformatics is above all an integrative research domain naturally overlapping computational and living systems. At BioISI we have been pursuing an interdisciplinary approach that is highlighted in bioinformatics. We plan to invest on computational means, hardware and common processing pipelines for standard biodata analysis to allow coping with the new composition of BioISI and to allow deeper work in this line. The continuous production of publicly available open-source software tools will contribute to significantly increase the international visibility and reputation of BioISI.

12.4.6 Research Groups that contribute to the Thematic Line
GER - Gene Expression & Regulation (RG-4046-400178)
MAS - Modelling of Agents & Systems (RG-4046-400182)

12.5 Thematic Line Biophysics (BioPhys)

12.5.1 ID number of Thematic Line
TL-4046-3194

12.5.2 Thematic Line name in Portuguese
BioPhys – Biofísica

12.5.3 Thematic Line name in English
BioPhys - Biophysics

12.5.4 Thematic Line Coordinator
Maria Margarida da Fonseca Beja Godinho

12.5.5 Description of the Thematic Line

Goals
Bio-Phys aims to boost interdisciplinary research rooted in Physics, in particular by developing:
1) nanostructured systems to act as bio/ biomimetic-devices;
2) atomic force microscopy (AFM)/force feedback microscopy (FFM) to probe mechanical and intermolecular interactions in bio-systems;
3) novel simulation approaches to study protein (mis)folding & aggregation;
4) theoretical studies of dynamics and electronic structure in molecular systems.

Introduction
A systems-level analysis unravels the interplay of processes at different scales. The expertise of the physics team in AFM and magnetic studies is crucial to probe and manipulate biosystems at the smallest scales. Theoretical understanding at these scales involves physical models and computational approaches that are also part of our expertise.

Proposed Research
Modelling, computational and high-resolution approaches will be applied to help solving biological problems, namely: i) protein folding, a long-standing interest in the core group; ii)biomedical applications of the core group's expertise in magnetism (eg magnetic nanoparticles for hyperthermia); iii)physical studies of biological systems at nanoscale (using AFM/FFM or *ab initio* methods applied to molecular mechanisms in photosynthesis).

i)Protein folding physics
Establishment of testable theoretical predictions on the *in vivo* folding mechanism of proteins with knots, namely model systems with the 3_1 and the 5_2 knots.

ii)Nanostructured magnetic systems

Study of magnetic nanostructures/ atomic systems to develop magnetic hyperthermia methodologies and assessment of potential applications as biomedical devices/biosensors, using theoretical and high-resolution experimental approaches.

iii)Development of AFM/FFM methodologies
The enabling technology of AFM/FFM and related ones will undergo further refinement and engineering to assess nanomechanical properties and biological interactions at the molecular level.

iv)Biomimetic photosynthesis and molecular solar energy storage
Design of modified cromophores for increased energy absorption and charge transfer in dye sensitized solar cells. Molecular design of new photoactive molecules for solar energy storage. Molecular analysis of photoprotection mechanisms for models of eumelanin pigments.

Key Actions
BioPhys will promote per 2 workshops or international Summer Schools to disseminate BioISI exciting research to young researchers; and one conference (1-2 days) "*The Physics of Living Systems*" on innovative physical approaches to tackle biological issues with BioISI and external experts.

Integrative Research
Bio-Phys develops new enabling technologies and devices for biosystems research (BioTech, BioMed) eg use of optical techniques for crop control (BioTech), the expertise in magnetism and high-resolution magnetic measurements (BioChem), innovative modelling/ computational approaches (BioChem, BioInf).

12.5.6 Research Groups that contribute to the Thematic Line
CBS - Chemistry for Biological Systems (RG-4046-400179)
BioPhysNano - Bio-Physics & Nanosystems (RG-4046-400181)

13 ETHICAL ISSUES

BioISI researchers follow the values and principles of ethical scientific research, namely truth, freedom, responsibility, integrity, collaboration and professionalism.
All research activities in current practice at BioISI already comply with existing legislation on Ethics and when appropriate eg., research on human subjects [see below] has **already received ethical approval by the Ethics Committees of the institutions involved**. All Ethical aspects related to the development of the current project **adopt the Charter of Fundamental Rights of the EU (2000/C 364/01)**.

BioISI researchers **will not be involved** in research activities which might have controversial ethical implications such as cloning, stem cells research or modifications of the human genome. Research involving human embryos/foetus animals is not planned, and all outcomes will have exclusive focus on civil applications and will not generate any results of potential misuse or military applications. There will be no research activities with third countries which do not adopt equivalent Ethical principles.
In all activities proposed, the basic principles, existing directives and drafted or approved legislation from national, European (EU) or International organizations (WHO, UNESCO, etc) on human health and on IPR, will be taken into consideration and widely disseminated and discussed among its partners.

Besides the Charter of Fundamental Rights of the EU, research conducted at BioISI will conform to current legislation and regulations in Portugal, namely regarding:

1) **Confidentiality and personal data**: Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
2) **Usage of genetically modified micro-organisms** (GMOs): EU Parliament Directive 2001/18/EC and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.
3) **Protection** of **biotechnological inventions**: Directive 98/44/EC of European Parliament and Council of 6 July 1998 on the legal protection of biotechnological inventions.
4) **Medicinal products for human use**: Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation laid down by law, regulation or administrative action relating to proprietary medicinal products.
5) **New technologies**: opinions of the European group of advisers on the Ethical Implications of Biotechnology (1991 –1997); European Group on Ethics in Science and New Technologies (1998).
6) **Research involving human subjects** [see also below] will follow international conventions and declarations: Helsinki Declaration in its latest version; Universal Declaration of Human Rights of 1948; The Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) International Declaration on Human Genetic Data (UNESCO, 2003); CIOMS/WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993, reviewed in 2001); EU directive 20/2000 addressing the reference level for ethic committee approval; Convention of Human Rights and Biomedicine (Oviedo Convention – 1997) the Additional Protocol on the Prohibition of Cloning Human Beings signed in Paris on 12 January 1998 and its Additional Protocol on Biomedical research (2002); The Commission Directive 2005/28/EC, Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and

75/319/EEC on GCP relating to investigational medicinal products for human use and authorisation the manufacturing or importation of such products

Research on human subjects

This will receive special attention and BioISI researchers at host institution (FCUL) or at the pole National Institute of Health (INSA) possess wide experience in complying with Ethical procedures and in getting authorization from the national data protection authorities and/or for the acquisition of human native tissues.

Analysis of human native tissues ex vivo

All ethical, social and legal aspects of the research activities carried out by BioISI researchers which involve the usage of human tissues are well taken into consideration.

Collection of human native tissues has already obtained approval by the researchers involved, through their respective Ethics Committees. These collections always involve **informed consent** by patients (>18 yrs) or their legal representatives (<18yrs). Such informed consent contains a thorough explanation of the reasons and interest to perform the analyses, a complete explanation of the procedure, and information participation or not in the study will have no influence whatsoever on the patient's treatment.

Analysis clinical (or other) data from patients

Moreover, **all patients' data will be protected**, by complying with the norms of confidentiality, i.e., by not sharing patient data with third parties, although the overall results of the study will be disseminated.

The original patients data set will be considered as an identified data set and treated accordingly, namely such data set will be stored in a secure data-encrypted form kept in a secure location. The following principles will be adopted:

a) the identity data collected will be kept to the minimum needed (name, birth date) and a research number will be associated to describe the individual in the research protocol (the identity key data set will then be split from subsequent research de-identified data sets):
b) the data will be de-identified as soon as possible after collection and separated from identifiable elements.
c) the identity key data set will be stored in a secured location (computer with password);
d) the access to identity key data set will be limited to individuals with legitimate need;
e) it will be ensured that this computer can be professionally administered and managed.

14 ASPECTS OF THE PLAN OF ACTIVITIES INVOLVING REQUESTS OF PROGRAMMATIC FUNDING

14.1 Pluriannual plan for PhD fellowships to be awarded in 2019-2022

Name of the PhD program	*BioSys2 – Biological Systems: An Integrative Approach*
Institution	Faculty of Sciences, University of Lisboa
Year of accreditation (actual/expected)	2014
Presently functioning	Yes
R&D Unit involvement/Contribution of PhD researchers/Scope of the work	This PhD program follows up on *BioSys: Biological Systems: Functional and Integrative Genomics*, funded in 2014-18 by FCT. BioSys2 aims to train a new generation of young researchers to address biological questions at systems level, bridging the gap between biology and computational sciences, physics and chemistry, while allowing creative insights into truly interdisciplinary research. BioSys2 will provide: 1) interdisciplinary research offering exciting projects in a unique environment for biologists, chemists, physicists, computer scientists or mathematicians wishing to pursue a PhD in molecular life sciences; 2) internationality, with faculty members from top international institutions and stays abroad at these institutions through mixed PhD fellowships (~1/2 of all); 3) dedicated mentoring by outstanding expertise in advanced training by BioISI researchers (**35** PhD and **129** MSc theses completed in 2013/17); 4) demonstrated capacity to conduct a successful international PhD programme (BioSys) and many advanced training initiatives (10 conferences/ meetings in 2014-17); 5) outputs of excellence in 2014-17 in (**872** publications, for top 25%: **IF 8.9** in 2017); KTT (4 patents); and competitive funding (3.6 M€/yr) 6) high-quality facilities to support advanced training and research activities. **Project selection**: Each year, BioISI Executive Board will select the best 16 PhD projects with 2 supervisors from different BioISI groups and research topics covering research in the scope of 2 BioISI TLs fostering interdisciplinary. A balance of different research topics and of more experienced vs younger PIs will be sought. **Governance**: candidate selection (by Selection Committee), admission, and progress monitoring (annually by Thesis Advisory Committees) will be as in BioSys. **Curriculum**: BioSys2 will include formal training in systems biology in the 1st semester consisting of workshops and seminars by international faculty plus transferrable skills courses.
2019	16
2020	16
2021	16
2022	16
No. of expected fellowships	**64**

14.2 Pluriannual plan for hiring new researchers holding a PhD in 2019-2022

NEW RESEARCHERS TO HIRE	2019	2020	2021	2022	Total
No. researchers	19	0	0	19	38

Short description of the type of researchers to hire, their expected added-value to the R&D Unit activities, expect contract duration, conditions of co-responsability of higher education or research institutions through which the contracts will be awarded, and of the finantial and material conditions that still need to be fulfilled.

1. Independent Researchers

BioISI's vision for recruiting 10 new PIs is to attract the best scientific minds to contribute to its strategic areas and/or flagship projects and work in an interactive environment that encourages communication and supports collaborations among research groups starting from 2019. BioISI will also offer 25k to support each new PI for operational setting-up their labs, making also its core-facilities fully available.

Six PIs will reinforce BioISI research activities in the following strategic areas [AIM 1]:

- **Molecular & Cellular Neurosciences** (IA): 1 early/mid-career investigator in the field of molecular mechanisms of neurodegenerative diseases (protein aggregation/RNA granules/mitochondria/inflammation) with skills on in vitro and cell/animal models, pathway analysis to develop integrated research (omics, molecular, cellular) towards new biomarkers and targets
- **Molecular & Cellular Epithelial Physiology** (2IA): 2 early/mid-career investigators in the fields of: 1) global approaches to lung/ intestinal physiology, epithelial chloride channels and electrophysiology skills; and 2) omics of epithelial physiology of lung/ intestinal cellular models, pathways and drug target identification, and pharmacology
- **Plant geneticist** (IA): 1 early/mid-career investigator in the field of plant genetics and gene editing for plant breeding approaches
- **Human geneticist & gene editing (IA)**: 1 early/mid-career investigator in the field of human genomics, gene editing and vector development for gene therapy approaches
- **Mycology** (IJ): 1 early-career investigator in the fields of fungal systematics & phylogeny, and fungal population genetics, to work in close association with M&B benefiting from the unique know-how and expertise in mycology.

2. Technical (Post-doctoral) staff

Another 4 PIs will be hired to drive research and progress through technology development and innovation [AIM 2], namely in:

- **Computational Biology** (IA): 1 early/mid-career researcher in the field of Computational Biology/ Bioinformatics with skills in programming, algorithm development, machine learning, artificial intelligence to handle large-scale data analysis and perform integrative research, and to develop computational tools for systems medicine and biology

- **Computational Chemistry & Simulation** (IP): 1 mid-career investigator with background in computational methods (quantum calculations and/or molecular dynamics simulations) applied to the study of reaction mechanisms and/or the study of (bio)chemical systems
- **Biosensors & Biodevices** (IA): 1 early/mid-career investigator in the area Condensed Matter Physics & Nanotechnology with skills in heterostructures/devices preparation
- **Novel Bioactive Molecules** (IA): 1 mid-career investigator with experience in synthesis of molecules or in identification and separation of extracts of bioactive natural products

Nine additional (post-doc) contracts will be open to:
-**5 specialized dedicated facilities positions (4IJ; 1IA)**: AFM/FFM; BioImaging/Screening; Genomics; Proteomics; Flow Cytometry
-**3 scientific managers** (1 IA, 2IJ) to support: 1) general management (BioISI accounting, reports); 2) large collaborative proposals, industry interactions, post-doc programme; 3) advanced training (BioSys2); workshops, seminars
-1 KTT/IPP officer

3. Interdisciplinary Postdoctoral Programme (IPP)
BioISI wishes to reinforce this programme given the success of a pilot IPP-Interdisciplinary Postdoctoral Programme (4 post-docs over 2-3 yrs, 2015-2017) in fostering BioISI interdisciplinary research. IPP will be expanded in 2019-22 to offer 2 editions of 9 PosDocs/2 yrs.
All applicants should apply with their own interdisciplinary research projects from one of the three available tracks (see below) already at the application stage and will be encouraged to contact their potential BioISI supervisor(s) of choice while developing the project proposal prior to submission.
Applicants should choose among 3 different tracks, namely:

i. Interdisciplinary IPP: Interdisciplinary research projects
Projects involve 2 PIs: one supervisor and one co-supervisor from two different BioISI groups to carry out research in BioISI strategic areas and/or contribute to flagship projects.
Aimed at an academic career path.

ii. International/inter-institutional IPP: Interdisciplinary international research projects
Projects involve one (or two) BioISI supervisor(s) and one external academic partner from an international institution. Potential external partners are expected to come from BioISI strategic areas and/or contribute to flagship projects.

iii. Intersectorial IPP: Academia/Industry partnership research projects
Designed to foster exposure to the applied/commercial side of science, they involve (or two) BioISI supervisor(s) and either one industry partner or an active involvement of IP generation, out-licensing and, if applicable, in the first steps towards a spin-off activity.
Industry partners are expected to come from, but not be limited to, members of BIPP, the BioISI-Industry Partnership Programme. Additional industry partners who show interest will be invited to join the BIPP.

Training & career development
Fellows who take part in the BIPP programme will be supported by a career development program and complete a series of training activities.

Recruitment
The recruitment for all the positions will be internationally announced. The applicants will submit a project meeting BioISI strategy, which will depend on the specific type of position (1.Independent Researchers, 2.Technical (Post-doctoral) staff, 3.Interdisciplinary Postdoctoral Programme). The applications will be analysed by external evaluators. They will be complemented by a lecture on a research topic and by an interview conducted by a panel.

14.3 Support for participation in infrastructures or international networks in 2019-2022

BioISI has several of its facilities linked to the European Infrastructures, namely:

EuroBioimaging (EuBI)
BioISI is a key promoter of FCUL participation in EuroBioImaging (EuBI), a consortium that provides open physical user access to a broad range of state-of-the-art technologies in biological and biomedical imaging for life scientists; BioISI is responsible for the High throughput and high screening node. EuBI is of crucial relevance for Biomedicine, Biotechnology and BioInformatics TLs of BioISI concerning instrumentation, data repositories and analysis tools. Considering the number of participating institutions, the participation of FCUL within EuBI will require from BioISI an annual fee of up to 3K€ per institute per year.

EUOpenScreen
BioISI is committed to support PT-OPENSCREEN, a network created to promote collaboration in the area of High Throughput and High Content Screening with the goal of initiating contacts so that Portugal can participate in the ESFRI program EU-OPENSCREEN. 17 institutions joined the Kick-off meeting of PT-OPENSCREEN (Dec 2017) and committed to constructing a national compound library whether by providing infrastructure and assays for screening or with providing compounds. Considering the number of participating institutions, it is expected that the participation of Portugal within EU-OPENSCREEN will require an annual fee of up to 5K€ per institute per year.

Instruct
Similarly to EuBI, BioISI is also involved in Instruct, a network related to structural biology and to the development of cutting edge tool for integrating individual macromolecules and complexes into higher-order structures. BioISI participation is of high relevance for Biomedicine, Biophysics and Chemical Biology TLs. An annual fee of up to 5K€ per institute per year is estimated.

European Synchrotron Radiation Facility (ESRF)
Members of BioISI are involved with ESRF, a joint facility focused on the use of X-ray radiation for chemistry and physics studies (e.g. protein crystallography). Continued participation in ESRF will benefit Biophysics, Chemical Biology and Biomedicine TLs. An annual fee of up to 5K€ per institute per year is estimated.

Infrastructure for Systems Biology Europe (ISBE)
Considering our objective and mission, BioISI aims to become a partner of ISBE. Presently, no Portuguese institution is part of this consortium through which researchers will be able to gain easy access to the best systems biology expertise, resources and services including state-of-the-art facilities, data, models, tools and training. An annual fee of up to 5K€ per institute per year is estimated.

14.4 Other types of support for which the R&D Unit requests Programmatic Funding in 2019-2022
BioISI ambitious objectives and strategy set the pace to a number of strategic activities for the 2018-22 period. Activities requiring financial support are detailed in the current section.

1) Reinforce BioISI research, technology development & innovation

-Hiring of 10 new PIs in key BioIS areas

-To expand current BioISI internal projects programme to 4 editions of 10 x 1-yr projects (renewable) 25K€ each to be assessed externally (usually by SAB members).
Total amount: 250K€/yr (2019-22)

2) Training

-Junior Studentships Programme (JSP) dedicated to early career researchers offering each year (2019-22) 24x 1-yr fellowships for MSc holders (13.5K€ each/yr).
Total amount: 324K€/yr (2019-22)

-BioSys2 PhD programme
-BioSys retreats: 1/yr (3K€)
Total amount: 3**K€/yr (2019-22)**

-Interdisciplinary Postdoctoral Programme (IPP): will be offered as 2 editions in (2019/20 and 20121/22) for 9 Pos-Doctoral fellowships/2 yrs into 3 tracks: 6 national (20K€ each/yr) 3 international (30K€ each/yr)
-PPI+postdocs retreat: 1/yr (5K€)
Total amount: 120K€+90K€+5K€/yr (2019-22)

3) Facilities

-Hire 4 Facilities technicians for:1) Cell Core; 2) Proteomics; 3) Bioinformatics Core; 4) Protein Core, with MSc degree: 4x 1-yr fellowships for MSc holders (13.5K€ each/yr).
Total amount: 54K€/yr (2019-22)

-Acquire key equipment to upgrade facilities equipment, namely (more detail at:):

- AFM upgrade (50K€)
- LC liquid chromatography (85K€)

- Flow cytometer (450K€)
- Bioinformatics & computational core (250K€)
- Protein core ITC (isothermal titration calorimetry) + DLS (dynamic light scattering) + protein chromatography (200K€)

  Total amount: 1.05M€ (2019)

- Adaptation of facilities and buildings (200K€ in 2019)
- Equipment maintenance (25K€/yr)

  Total amount: 200K€ (2019) + 25K€/yr (2019-22)

4) Organization of conferences, seminars, workshops and courses

-One (post-doc) manager will be hired to be in charge of this activity
-Organization of 10 Workshops/yr (7.5K€/WS): 75K€/yr
-International seminars: 12/yr (~0.4K€/Sem): 5K€/yr
-Conferences: 1/yr (10K): 10K€/yr
Total amount: 90K€/yr (2019-22)

5) Outreach: promote scientific & technological culture and its impact on society

Outreach activities will be developed to target young people, school teachers and general public, so as to raise awareness, understanding and involvement in the systems approach to biology and BioISI research in particular.
BioISI also put into practice the new concept of 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.
BioISi keeps an external contract with a communication company (Beeineditus) and has a secretariat member supporting these activities.
Total: 20K€/yr (2019-22)

6) Other activities

- BioISI secretariat: hire 2 managers for BioISI secretariat for:1) General secretariat and training (BioSys2, workshops, IPP); 2) Support to BioISI Director, Executive Board and Steering Committee: 2 BGCT fellowships for MSc holders (13.5K€ each/yr)
- BioISI mtgs to involve all PIs, Post-docs, PhD students into an annual conference: 1/yr (3K€)
- SAB mtgs: Annual meetings of BioISI Steering Committee with Scientific Advisory Board: 1/yr (5K€/yr)
- Industry partnerships actions: 1/yr (7K€/yr)
- BioISI Missions to represent the institute at national European infrastructures; strategic partnership meetings (eg, EU proposals); training of facilities staff abroad: 8€K/yr

Total: 50K€/yr (2019-22)

7) Other relevant aspects

Including Preservation, curation and dissemination of data and results (*as defined in the Open Research Data Pilot*)

BioISI is eager to participate in the Open Research Data Pilot (ORD Pilot), as an extremely effective method of disseminating the achieved scientific results with maximal impact. Thus, a Data Management Plan (DMP) will be developed and updated regularly. The DMP will clearly specify which data will be shared openly, without jeopardizing IP rights and exploitation of researchers and involved industrial partners. According to DMP, the Executive Board will ensure that data generated by BioISI research will be timely deposited on a repository, certified as Trustworthy Digital Repository (eg http://zenodo.org). The information on tools and instruments used for validation of results will also be provided there. Unrestricted and royalty-free access to this depository will allow 3rd parties mining, exploit, reproduce and disseminate BioISI-generated data. All open-access publications will be deposited on RCAAP (http://projecto.rcaap.pt) as in Open Access policy, and linked to respective original data, to simplify access to and use of data externally.
Strategy: One of the BioISI managers will support this activity.

15 EXPECTED FUNDING AND BUDGET FOR 2018-2022 FOR EVALUATION PURPOSES

15.1 Expected funding of the R&D Unit for 2018-2022

FUNDING SOURCES (TOTAL FUNDING)	2018	2019	2020	2021	2022	TOTAL (K€)
Fundação para a Ciência e a Tecnologia, I.P. - FCT	2.520	1.010	541	223	41	4.335
R&D Unit Pluriannual funding awarded for 2018	641	-	-	-	-	641
Project funding expected to be received	661	143	28	18	15	865
Expected funding for contracts of researchers with PhD (1)	252	232	188	138	-	810
Expected funding for PhD, PostDoc or other fellowships (2)	966	635	325	67	26	2.019
Other funding	-	-	-	-	-	-
Other national sources	355	306	142	-	-	803
Funding expected to be received from Participant or Management Institutions	20	-	-	-	-	20
Public sources (3)	335	306	142	-	-	783
Companies, industry and other private sources based in Portugal (3)	-	-	-	-	-	-
Any other funding source (3)	-	-	-	-	-	-
International sources	280	119	90	82	51	622
European Commission (3)	211	82	82	82	51	508
Companies, industry and other private sources not based in Portugal (3)	64	32	3	-	-	99
Other funding sources (3)	5	5	5	-	-	15
Total (K€)	3.155	1.435	773	305	92	5.760

(1) Payed through an institution or directly to researchers with PhD integrated in the R&D Unit

(2) Payed directly to fellows, researchers or students integrated in the R&D Unit

(3) Grants, projects, fellowships, prizes received, etc.

15.2 Expense budget of the R&D Research Unit in the Main Management Institution for 2018-2022
FCiências.ID - Associação para a Investigação e Desenvolvimento de Ciências (Fciências.ID)

Expense Budget items	2018	2019	2020	2021	2022	TOTAL (K€)
Human Resources	491	189	36	26	26	768
Contracts of researchers with PhD	40	40	-	-	-	80
PhD, PostDoc or other fellowships	451	149	36	26	26	688
Contracts of technical or secretarial staff	-	-	-	-	-	-
Researchers external missions	115	44	32	9	9	209
Temporary visiting researchers or consultants	11	-	-	-	-	11
Patents registration and maintenance	3	5	2	-	-	10
Service or product procurement and acquisition	500	85	19	-	-	604
Equipment	138	-	-	-	-	138
Adaptation of facilities and buildings		-	-	-	-	
Other expenses	271	60	19	9	9	368
Total (K€)	1.529	383	108	44	44	2.108

15.3 Expense budget of the R&D Research Unit in the other Management Institutions for 2018-2022

Instituto Nacional de Saúde Dr. Ricardo Jorge (INSARJ)						
Expense Budget items	**2018**	**2019**	**2020**	**2021**	**2022**	**TOTAL (K€)**
Human Resources	10	-	-	-	-	10
Contracts of researchers with PhD	-	-	-	-	-	-
PhD, PostDoc or other fellowships	10	-	-	-	-	10
Contracts of technical or secretarial staff	-	-	-	-	-	-
Researchers external missions	22	-	-	-	-	22
Temporary visiting researchers or consultants	-	-	-	-	-	-
Patents registration and maintenance	6	-	-	-	-	6
Service or product procurement and acquisition	77	-	-	-	-	77
Equipment	7	-	-	-	-	7
Adaptation of facilities and buildings	-	-	-	-	-	-
Other expenses	5	-	-	-	-	5
Total (K€)	127	-	-	-	-	127

Universidade do Minho (UM)						
Expense Budget items	**2018**	**2019**	**2020**	**2021**	**2022**	**TOTAL (K€)**
Human Resources	9	-	-	-	-	9
Contracts of researchers with PhD	-	-	-	-	-	-
PhD, PostDoc or other fellowships	9	-	-	-	-	9
Contracts of technical or secretarial staff	-	-	-	-	-	-
Researchers external missions	10	-	-	-	-	10
Temporary visiting researchers or consultants	-	-	-	-	-	-
Patents registration and maintenance	10	-	-	-	-	10
Service or product procurement and acquisition	43	-	-	-	-	43
Equipment	-	-	-	-	-	-
Adaptation of facilities and buildings	-	-	-	-	-	-
Other expenses	7	-	-	-	-	7
Total (K€)	79	-	-	-	-	79

Universidade de Trás-os-Montes e Alto Douro (UTAD)						
Expense Budget items	**2018**	**2019**	**2020**	**2021**	**2022**	**TOTAL (K€)**
Human Resources	43	43	20	-	-	106
Contracts of researchers with PhD	-	-	-	-	-	-
PhD, PostDoc or other fellowships	43	43	20	-	-	106
Contracts of technical or secretarial staff	-	-	-	-	-	-
Researchers external missions	4	4	-	-	-	8
Temporary visiting researchers or consultants	-	-	-	-	-	-
Patents registration and maintenance	-	-	-	-	-	-
Service or product procurement and acquisition	23	23	4	-	-	50
Equipment	-	-	-	-	-	-
Adaptation of facilities and buildings	-	-	-	-	-	-
Other expenses	6	6	1	-	-	13
Total (K€)	127	76	25	-	-	177

15.4 Estimated percentages of application by general expense budget items of Base Funding in case it will be awarded by FCT, I.P. for 2018-2022 following the evaluation

Expense Budget items	**%**
Human Resources	15
Contracts of researchers with PhD	6
PhD, PostDoc or other fellowships	4
Contracts of technical or secretarial staff	9
Researchers external missions	9
Temporary visiting researchers or consultants	2
Patents registration and maintenance	2
Service or product procurement and acquisition	40
Equipment	10
Adaptation of facilities and buildings	2
Other expenses	20
Total	100

16 JUSTIFICATION OF THE BUDGET FOR 2018-2022

16.1 Justification of the total proposed budget

For the 2018-22 period, BioISI secured already a total of 5.8 M€ - with ~600K€ from the pluriannual funding awarded by FCT for 2018 and a total of ~5.2 M€, already granted from a diversity of projects and grants from different sources

This total of ~5.2 M€ is the sum of funded projects and human resources. The 41 funded projects that run through the next five years sum up a total of 2.4 M€ for 2018-2022 - with 30% coming from international and 70% from national sources (37% funded by FCT and 33% funded by other national sources).

The remaining 2.8 M€ are allocated to human resources and are paid directly to the researchers (20% for contracts with PhD Researchers and 80% for pre- and post-doctoral fellowships).

The 13 international projects already secured span across the different thematic lines such as Biomedicine, Biotechnology and Biological Chemistry, and include:

- Assisted Living Technologies for the health tourism sector (ALHTOUR, 2014-18) - 323K€
- Autism Spectrum Disorders in Europe (ASDEU, 2015-18) - 144K€
- Blood test for clinical therapy guidance of non-small cell lung cancer patients (LungCARD, 2017-21) - 153K€
- Personalised Treatment for Cystic Fibrosis Patients with Ultra-rare CFTR Mutations (Hit-CF, 2018-22) - 257K€
- 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 2016-A-180, 2017-20) – 20K€
- Cost Actions in Molecular Machines and Biochemistry (CM1305, CA15128, CM1306) – Summing up 14 K€

BioISI has secured funding from national sources with the most relevant projects including:

- Nonsense-mediated mRNA decay in genetic diseases and cancer: key players, mechanisms, and a novel approach for suppression therapy (2016-18) – 200 K€
- Novel Factors of CFTR Traffic Related to Epithelial Cell Differentiation: Potential Therapeutic Targets for Cystic Fibrosis (DIFFTARGET, 2016-18) – 192 K€
- Multifunctional Luminescent Spin Labile Hybrid Materials (2016-19) – 192 K€;
- Molecular and Mechanical Forces in Biology measured with Force Feedback Microscopy (2016-19) – 197 K€
- Intelligent information system to control infection and personalized antibiotherapy (RESISTIR, 2016-19) – 449 K€
- Synaptic networks and Personalized Medicine Approaches to Understand Neurobehavioural Diseases Across the Lifespan (MEDPERSYST, 2017-20) – 470 K€.

Additionally to these already funded projects, BioISI has a significant amount of submitted projects. In the 2017 national call for projects, BioISI submitted 33 proposals with a total of ~7M€ requested budget. Moreover, BioISI researchers have also submitted projects to the European commission such as a Twinning proposal (2SysBio) as well as to other international sources (companies, patient foundations, research societies).

The 2SysBio proposal aims to reinforce BioISI capacity for outstanding basic and translational research, by creating a dynamic cluster of excellence within the Lisboa region in the field of Systems Biology research with nation-wide impact. 2SysBio consortium joints BioISI to two leading research institutes: EMBL-European Molecular Biology Laboratory and the Karolinska Institute.

It should be noted that the successful accomplishment of the above projects and proposals is strongly dependent on the overall ability of BioISI and, ultimately, on the funding resulting from this evaluation process. This will allow the development of BioISI infrastructures - reinforcing current facilities and establishing new ones - which is crucial for BioISI´s research activities.

16.2 Justification of the Human Resources component in total proposed budget

BioISI already secured a total of ~ 3.7 M€ to human resources for the period of 2018-22 – 25% in contracts for researchers and 75% in fellowships.

Most of the contracts for researchers are funded by FCT through the past calls for "Researcher FCT" and one of the researchers is paid through a project supported by national funds.

70% of the 2018-22 fellowships awarded to BioISI Researchers are funded directly by FCT (20% postdoc, 80% PhD). 30% of the 2018-22 fellowships are awarded by the host institutions or through the projects in which the PI is a BioISI member.

The Human Resources already secured for the period 2018-22 are allocated to the different thematic lines according to the following distribution:

- Biomedicine – 26 PhD fellowships, 9 Post-Doc fellowships, 1 Contracted researcher
- Biotechnology – 20 PhD Fellowships, 7 Post-Doc fellowships, 4 Contracted researchers
- Bioinformatics – 8 PhD Fellowships, 5 Post-Doc fellowships, 1 Contracted researcher
- BioPhysics – 2 PhD Fellowships, 3 Post-Doc fellowships, 1 Contracted researcher
- Biological Chemistry – 9 PhD Fellowships, 6 Post-Doc fellowships, 2 Contracted researchers

33 of the secured PhD fellowships (2018-22) come from the PhD program run by BioISI – the BioSYS started in 2014 within BioISI and is a multidisciplinary program focused in Life & Health Sciences. The teaching and research topics have a major focus on Systems Biology; Omics approaches; Bioinformatics; Computational modelling; and Quantitative Biology. The first students are delivering their thesis in Feb/Mar 2018 and will soon be granted their PhD. We are proposing a renewal of the program under the name "BioSys2" in the current evaluation process.

According to national regulations (Law 57/2017), BioISI anticipates that till August 2018, 18 new researchers will be contracted reinforcing the thematic lines as described below:

- Biomedicine – 5 Contracted researchers
- Biotechnology – 4 Contracted researchers
- Bioinformatics - 2 Contracted researcher
- BioPhysics - 1 Contracted researcher
- Biological Chemistry – 6 Contracted researchers

Although the high quality of the human resources already working at BioISI, it should be noted there is a lack of personal in specific BioISI strategic areas as pointed before (section 14.2) which can compromise the full accomplishment of BioISI Strategy.

16.3 Justification of the Equipment component in total proposed budget

From the funds already secured for 2018-22, the total budget for equipment is only ~150K€. During the period 2013-2017, BioISI invested in essential equipment for its activities, mainly to establish and reinforce BioISI Facilities:

- Microscopy facility: Leica Confocal microscope and Incubation Box for high throughput microscopy;
- Bioinformatics Facility: Computational equipment;
- Physics facility: AFM components;

The equipment expenses already allocated for 2018 is mostly related with the depreciation of the equipment bought in the previous period (~120K from the total of ~150K€).
The remaining amount will be used for the maintenance of the equipment available at each institution. However, it should be noted that the full accomplishment of BioISI Research activities depends strongly on the development of its infrastructures/facilities that includes both the maintenance of the already existing ones and the establishment of new ones, with the aim of supporting the activity of the unit and its researchers, as mentioned in the previous section 14.4. This will allow BioISI to proceed with its research in a sustained/sustainable way and is therefore strongly dependent on the funding resulting from the current evaluation process.

17 REVIEWERS PROPOSED BY THE R&D UNIT

17.1 Proposed experts for consideration of FCT, I.P. for eventual request of opinion about applications submitted by R&D Units for evaluation

Name: Charles Auffray, MD
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Name: Marcelo Bento Soares, PhD
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Name: George Perry, PhD
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Name: Dirk Inzé, PhD
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