



RESEARCH REPORT

(2013-2015)



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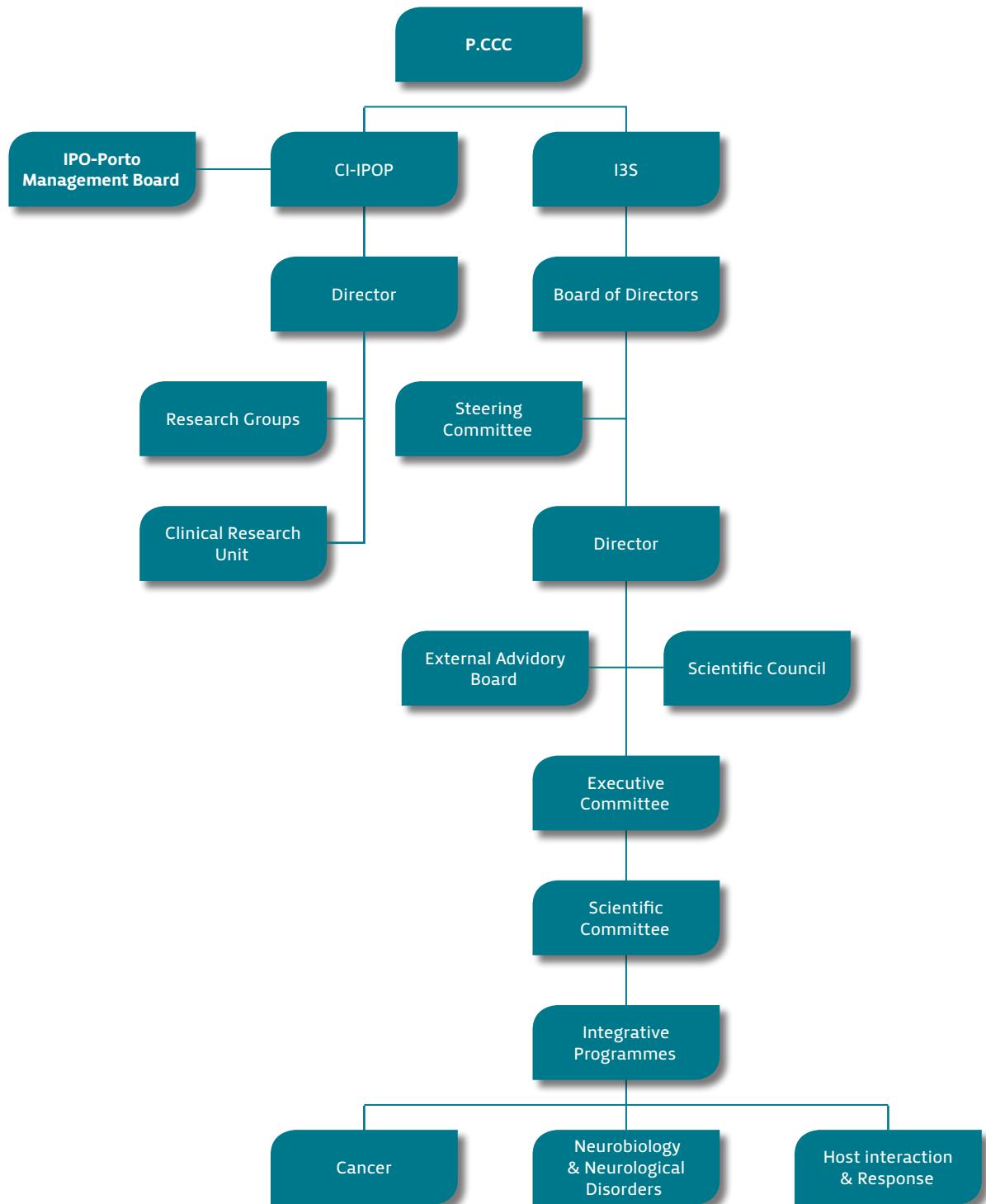


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STRUCTURE & ORGANIZATION: RESEARCH UNITS



1 | STRUCTURE & ORGANIZATION: RESEARCH UNITS





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P.CCC
SCIENTIFIC EXTERNAL
ADVISORY BOARD



From their start CI-IPOP and all the Institutes incorporated in I3S had Scientific Advisory Boards (composition below) with a similar way of action, according to recommendations from the Portuguese Science Foundation (FCT).

Recently a joint Board was appointed for I3S. This board is partly composed by members of individual institutes but also by new Board Members (composition below). In CI-IPOP and all Institutes there was an annual site visit and a report was issued with recommendations for the Institutes and for the groups. The reports from the CI-IPOP and I3S, available to Board Members before de site visit, guided the priorities for the local activities that included review of support facilities, interviews with group leaders, post-docs and PhD and Master students.

- ¬ **Andrés J. García**, Woodruff School of Mechanical Engineering, Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, USA
- ¬ **Angel Carracedo**, University of Santiago de Compostela, Spain
- ¬ **Carlos Caldas**, Cancer Research UK Cambridge Research Institute, University of Cambridge, UK;
- ¬ **Christopher Leaver**, University of Oxford, Oxford, UK (chair)
- ¬ **David Huntsman**, Pathology and Laboratory Medicine and Obstetrics and Gynaecology at the University of British Columbia, Canada
- ¬ **Erich Nigg**, University of Basel, Switzerland
- ¬ **Felix Mitelman**, Clinical Genetics Department, Lund University, Sweden.,
- ¬ **Fernando Lopes da Silva**, Vrije Universiteit, Amsterdam, The Netherlands
- ¬ **Fred Bosman**, Université de Lausanne, Switzerland
- ¬ **Ivan Damjanov**, University of Kansas, USA
- ¬ **Jacques Neefjes**, The Netherlands Cancer Institute, Amsterdam, The Netherlands
- ¬ **James Fawcett**, Cambridge Centre for Brain Repair, Cambridge, UK
- ¬ **James Kirkpatrick**, Institute of Pathology, Johannes Gutenberg University, Mainz, Germany
- ¬ **Jean Marc Egly**, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Strasbourg, France
- ¬ **Jean-Pierre Gorvel**, Centre d'Immunologie de Marseille-Luminy, France
- ¬ **Josep Planell**, Centro de Investigación en Ingeniería Biomédica (CREB), ETSEIB, Barcelona, Spain
- ¬ **Manel Esteller**, the Bellvitge Institute for Biomedical Research (IDIBELL), Spain;
- ¬ **Marc Mareel**, Universiteit Gent, Belgium
- ¬ **Nuria Verdaguera**, Instituto de Biología Molecular de Barcelona, Barcelona, Spain
- ¬ **Peter Heutink**, Vrije Universiteit, Amsterdam, The Netherlands
- ¬ **Reinhard Faessler**, Max Planck Institute of Biochemistry, Germany



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ONCOLOGY RESEARCH STRATEGY PLAN

CI-IPOP was officially established in September 15, 2003, and is hosted by the Instituto Português de Oncologia do Porto Francisco Gentil (hereafter IPO-Porto), the largest specialized Portuguese cancer institution with a staff number of about 1.800 and more than 10.000 new patients per year that has a triple role: (1) patient care, (2) research, and (3) education in Oncology. IPO-Porto is a leading institution in treating patients with cancer and precancerous lesions, and this excellence in patient's care is rooted in a strong enforcement in research. CI-IPOP includes currently five research groups working on translational cancer research, all having a high intensity laboratory level. Furthermore, CI-IPOP included a Clinical Research Unit and a number of clinical staff that publishes regularly.

CI-IPOP has the mission to promote translational scientific activity in Oncology and its main objective is the understanding of the pathobiologic mechanisms underlying the development of cancer, enabling prevention, early diagnosis, accurate prognostic evaluation, and development of more effective therapies.

CI-IPOP was formally recognized by the Science and Technology Foundation, the governmental agency that manages scientific and technological activities in Portugal, as an R&D Unit in 2004 and it was classified as "Very Good" in its last external evaluation (2015).

IPATIMUP was created in 1989 under the auspices of the University of Porto as a Non-Profit Private Association of Public Utility, mainly devoted to cancer research. Since 2000, IPATIMUP is also an Associated Laboratory in Health Sciences of the Ministry of Science and Technology of Portugal. IPATIMUP aims are: (1)To be a leading health science research institution through internationally competitive science on molecular pathology and molecular and population genetics. (2)To serve society through science by directing discoveries to the improvement of cancer prevention and management of cancer patients, and through communicating the significance of the Institution's findings to the public.(3)To enjoy a reputation for doing good translational research and for providing appropriate training conditions, i.e., for successfully translating good science into good clinical practice and for ensuring good advanced training. (4) As an Associated Laboratory, the IPATIMUP collaborates with the Government in health and wealth creation, quality of life and public awareness of Science.

In 2014 a Consortium - I3S – resulted from the joined forces of IPATIMUP and two other research Institutes from Porto: INEB, founded in 1989, devoted to promoting research, advanced training and technology transfer in Biomedical Engineering, and IBMC, founded in 1997 and devoted to research in Life Sciences. Both Institutes are leading scientific organizations, internationally acknowledged in their areas of expertise. The I3S was evaluated in 2015 and rated as "Exceptional", obtaining the highest score and the highest financing among all research institutions in Portugal.

Together with IPO-Porto, a renovated **Porto Comprehensive Cancer Centre – P.CCC** – was established in a recent agreement signed in 2016, under the auspices of the Ministry of Health and the Ministry of Science and Technology. At this stage, the aggregation of INEB and IBMC to the **P.CCC** will add relevant research on biomaterials and basic research, most importantly a strong group in the biology of cell division. This further step boosts the critical mass both at the translational and the basic research level. P.CCC is from the very first day the major player in cancer research in Portugal and also, in some of its areas of expertise, a major player at the European level. The P.CCC joins together two institutions coming from the Ministry of Health (IPO-Porto) and the Ministry of Science and Technology (I3S) integrating basic, pre-clinical and clinical research, creating a regional platform that, in the long run, will reinforce the role that these institutions already play at the national level. As a start, IPO-Porto and IPATIMUP were instrumental in the creation, in 2013, of the Portuguese Association for Cancer Research (ASPIC) that connects cancer researchers from all scientific areas and is affiliated to EACR. This initiative showed the ability of **P.CCC** to launch a nationwide cancer program.

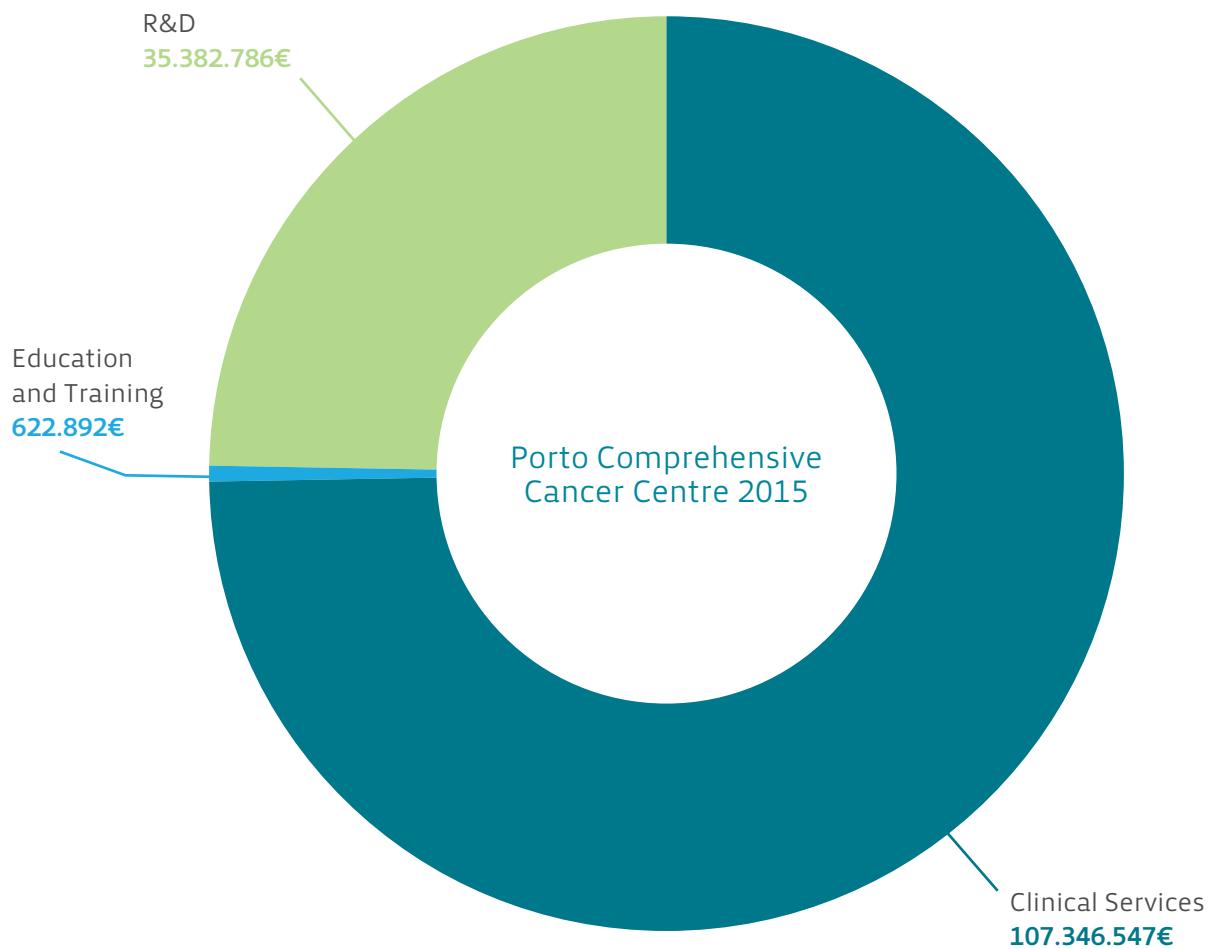
P.CCC will help to create an environment where differences in the activities of clinical and basic researchers will be harmonized, facilitating the entry of MDs in the scientific environment and providing the tools for clinicians to access research facilities and expertise usually segregated in institutions that live apart. Access to funding at national and international levels will be boosted and education and training of young researchers, both clinical and basic, will benefit from an environment where the biology underlying patient's treatment can be understood and where basic research will be challenged to translate discoveries into the clinic. The culture on the move is to have all participating in the international endeavor to increase preventive attitudes, to improve early diagnosis, to better stratify patients for treatment options of today and tomorrow, in brief, to meet the grand challenge of dealing with cancer every day in a better way for patient's benefit.



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GLOBAL BUDGET (2013-2015)

Porto Comprehensive Cancer Centre	2013	2014	2015
Clinical Services	108.856.936€	114.507.219€	107.346.547€
Education and Training	478.027€	1.136.319€	622.892€
R&D	30.772.126€	31.708.465€	35.382.786€
Global Budget	140.107.089€	147.352.002€	143.352.225€



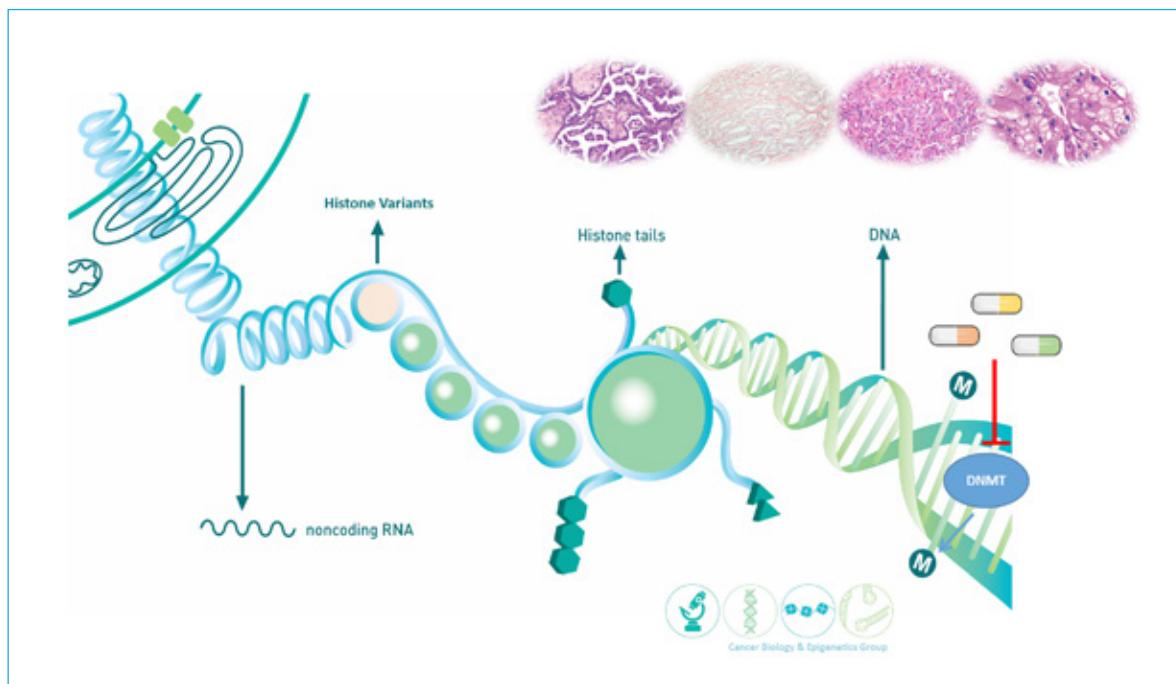


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RESEARCH GROUPS

CANCER BIOLOGY & EPIGENETICS

GROUP LEADER: Carmen Jerónimo



ABOUT

The long term core goal of the Cancer Biology and Epigenetics Group (CBE) has been to portray the epigenetic mechanisms involved in the genesis of cancer, with a particular emphasis in urological cancers.

Thus, we focus our research on the characterization of histone modifications and respective modifying enzymes involved, together with promoter methylation, in deregulation of urological cancer-related genes. Simultaneously, we are investigating the contribution of microRNAs deregulated expression and its interaction with other epigenetic mechanisms. For this purpose, several tumor models are used to ascertain the pattern of epigenetic alterations that may induce/promote malignant transformation.

In the context of Precision Medicine, we investigate the use of epigenetic modulators (eg: DNA methyltransferase and histone deacetylases inhibitors) for cancer therapy, through the manipulation of cell lines, characterizing their biological effects and antineoplastic potential.

Owing to the relevance that Immunoncology has acquired in recent years, we will investigate the epigenetic modulation of expression of biomolecules involved in immune checkpoint regulation, aiming at the improvement of immunotherapeutic strategies by combination with epidrugs.

The scientific, academical and professional background of the members of the Cancer Biology and Epigenetics Group has solid foundations in Cancer Biology and Pathology, so that the study of mechanisms of carcinogenesis is also an integral part of the group's interests, through the collaboration with other research teams.

PAST RESEARCH

The CBE Group has been established in January 2008. Since then, our major findings were the identification and validation of novel cancer biomarkers, derived from the epigenetic signature of cancer cells, enabling early detection by means of non- or minimally-invasive methods, as well as conveying clinically relevant prognostic and predictive information. Indeed, the group members held a 40% share of a patent (Methods and biomarkers for detection of bladder cancer US 20130210011/ EP 2630261 A1/ WO 2012052844 A1) for detecting Bladder cancer in urine sediments, based in a study performed in collaboration with the Norwegian Radium Hospital. Moreover, we were able to confirm the usefulness of that same panel of methylated genes in upper urinary tract.

Similarly, we demonstrated that microRNA's expression might be clinically valuable for accurate discrimination of the 4 major subtypes of renal cell tumors in biopsy specimens, enabling a more accurate pre-therapeutic characterization of suspicious renal masses.

Recently, we discovered that a novel Histone methyltransferase, SMYD3 (SET And MYND Domain Containing 3) plays an oncogenic role in Prostate cancer.

Regarding the line of research in epidrugs, our data demonstrated that hydralazine (a methyltransferase inhibitor) and enoxacin (miRNA biogenesis' inducer) attenuated the malignant phenotype of PCa cells, and might constitute useful therapeutic tools for prostate cancer patients.

PUBLICATIONS

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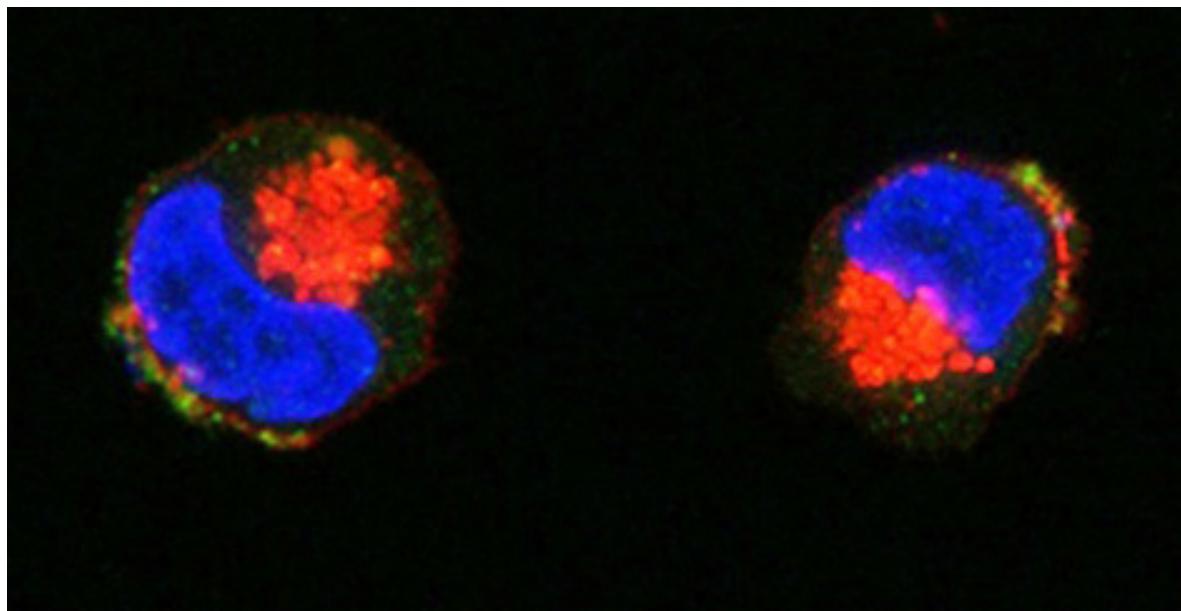
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TEAM MEMBERS

Senior scientists	1
Post-docs	2
Clinicians with laboratory sessions	9
PhDs students	6
Research assistants	3
MSc students	6
Graduate students	2
Technicians	5

CANCER DRUG RESISTANCE

GROUP LEADER: **Maria Helena Vasconcelos**



ABOUT

Our overall objective is to better understand the molecular mechanisms and identify novel inhibitors of cancer drug resistance.

Cancer drug resistance may be highly associated with overexpression of drug-efflux or anti-apoptotic proteins. Recent evidence indicates that P-glycoprotein (P-gp) is not only a drug-efflux pump but also an inhibitor of apoptosis. Our first aim is to understand the association between P-gp and apoptosis. As experimental models, various isogenic tumor cell lines and the filamentous fungus *Neurospora crassa* will be used. Through gene silencing (in cell lines) and mutational (in fungi) approaches we expect to gain knowledge into the interaction between P-gp and apoptosis and identify novel therapeutic molecular targets.

Extracellular vesicles (EVs) are mediators of intercellular communication and may transfer cancer drug resistance phenotype from resistant to sensitive cells. Our second aim is to study the mechanisms involved in EVs-mediated transfer of P-gp and of miRs that regulate or are regulated by P-gp, from drug resistant to drug sensitive cells. Additionally, we expect to get *in vivo* data on this network of interactions in *Neurospora crassa*, in human tumor xenografts in mice and in human samples. This work will combine technical approaches such as EVs isolation, RNAi, proteomics, miRs silencing and quantification. We expect to improve the basic understanding and the translational potential of EVs to overcome drug resistance.

Finally, our third aim is to study the effects of novel anti-P-gp small molecules on P-gp levels/activity and their impact on EVs-mediated transfer of drug resistance. The approach will consist in studying molecules that are inhibitors of P-gp synthesis in isogenic tumor cell lines and in tumor xenograft models in mice. We expect to identify a novel inhibitor of P-gp mediated transfer of drug resistance.

PAST RESEARCH

This research Group results from the merging of two previously existing groups, the “Cancer Drug Resistance Group” from IPATIMUP headed by M. Helena Vasconcelos and the “Mitochondria Group” from IBMC headed by Arnaldo Videira.

The Cancer Drug Resistance Group at IPATIMUP has focused on translating basic science findings into validation of new molecular targets for cancer therapy. In addition, in an attempt to counteract cancer drug resistance, the group has been involved in testing newly synthesized compounds ("small molecules"), to target proteins such as P-gp, p53 and antiapoptotic proteins. The work was carried out using several human tumor cell lines, human tumor xenografts in nude mice and human tumor samples.

The Mitochondria Group at IBMC has focused on the characterization of proteins and molecular pathways involved in drug-induced programmed cell death and on the devise of strategies to modulate the process. In addition, the group has worked on the characterization of mitochondrial proteins/complexes involved in mitochondrial biogenesis and function and their involvement in programmed cell death and mitochondrial disease. Moreover, the group has carried out structural and functional characterization of a drug efflux pump involved in drug response. This group has worked mainly on *Neurospora crassa* as a model organism and some of the work has been extended to cancer cell lines.

PUBLICATIONS

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5 | RESEARCH GROUPS

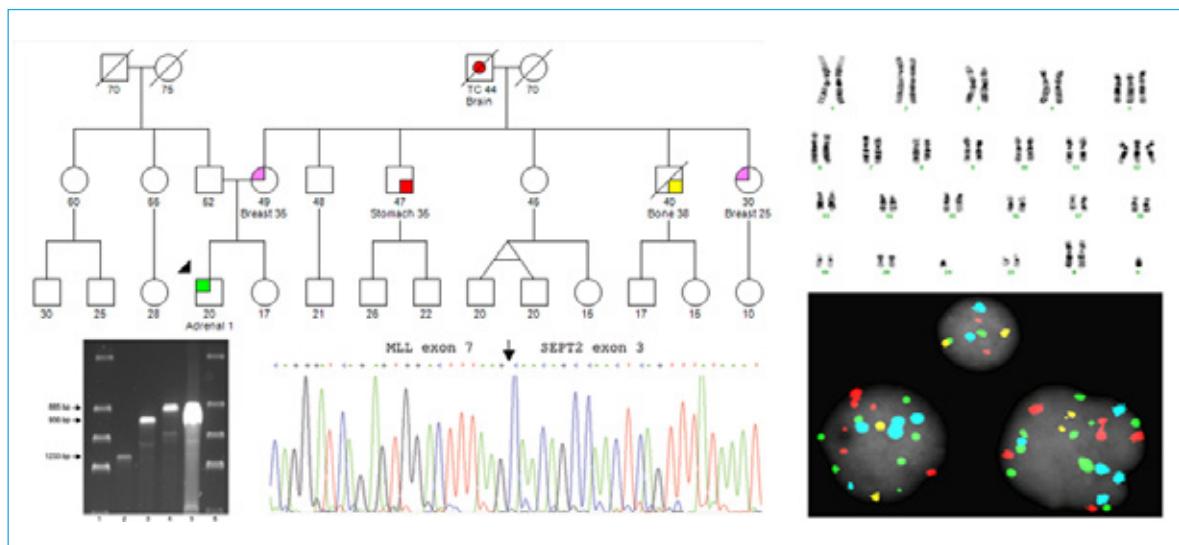
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TEAM MEMBERS

Affiliated	Non Affiliated
Senior scientists	2
Post-docs	1
PhDs students	4
MSc students	1
Technicians	4
Collaborators:	1
Visiting Researchers	4
Research Trainees	1

CANCER GENETICS

GROUP LEADER: Manuel R. Teixeira



ABOUT

The general objectives of the Cancer Genetics Group are to characterize the pattern of acquired genetic alterations that presumably give rise to cancer, as well as to understand the mechanisms of tumor progression and therapy response. In addition, we want to characterize the inherited mutations associated with cancer predisposition, as well as the pattern of somatic genetic changes that occur in hereditary cancer syndromes. Several biologically and clinically relevant tumor models are studied, as they can provide transversal input. To make possible tailor-made therapy specifically directed towards the altered metabolism of tumor cells, exact knowledge about the inherited and acquired genomic abnormalities of individual patients, not just about diagnostic categories, is becoming a decisive factor in the selection of the optimal therapy.

One major line of research for the next years aims to identify and characterize genetic causes predisposing to inherited prostate cancer (PCa). We have completed the recruitment of a series of 462 families with early-onset or familial PCa and performed whole exome sequence for 96 PCa patients from 45 of these families (discovery series). This project is likely to result in the identification of at least part of the missing heritability associated with highly penetrant mutations that is expected to exist in up to 10% of the PCa cases, especially those with early onset and heavy family history of the disease. Besides providing the possibility for a molecular diagnosis of inherited predisposition for these families, finding the genes will allow pre-symptomatic testing of relatives at risk. This will enable offering targeted screening to high-risk carriers, since it is likely that this will result in increased positive predictive value for biopsy as compared to population-based studies. Pre-symptomatic testing for high-risk genes will also avoid unspecific PCa screening in non-carriers of a known high-risk family mutation, thereby avoiding the risk of overdiagnosis and overtreatment in men that have the population risk in spite of belonging to a high-risk family.

The second major line of research for the next years involves using circulating cell-free tumor DNA (ctDNA) to perform molecular diagnosis, predictive testing for targeted therapy, and cancer screening. In theory, somatic

genetic changes present in cancer cells can be used as markers for early cancer detection, as well as during follow up to evaluate therapy response. The detection of mutations in ctDNA has emerged as a noninvasive strategy to assess primary tumors as well as eventual secondary lesions. This strategy has already been implemented in our group for monitoring the response and the mechanisms of resistance to targeted therapy and will be tested also in high-risk carriers in the context of families with hereditary breast/ovarian cancer and Lynch syndrome.

PAST RESEARCH

Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array

Twenty-three new prostate cancer susceptibility loci were identified at genome-wide significance. The top 1% of the risk distribution has a 4.7-fold higher risk than the average of the population being profiled, thus facilitating population risk stratification for clinical studies (Nat Genet. 2013;45(4):385-91).

Novel 5' fusion partners of ETV1 and ETV4 in prostate cancer

We identified two novel chimeric genes OR51E2-ETV1 and UBTF-ETV4, as well as two novel gene fusion combinations of previously described genes, namely, SLC45A3-ETV4 and HERVK17-ETV4. Our findings contributed significantly to characterize the heterogeneous group of ETS gene fusions (Neoplasia. 2013;15(7):720-6).

The MSH2 c.388_389del mutation shows a founder effect in Portuguese Lynch syndrome families

We found a shared haplotype in carriers from 16 different families sharing the MSH2 c.388_389del mutation, indicating that screening for this alteration as a first step may be cost-effective in the genetic testing of Lynch syndrome suspects originating from the north of Portugal (Clin Genet. 2013;84(3):244-50).

Constitutional and somatic rearrangement of chromosome 21 in acute lymphoblastic leukemia

This work showed that individuals born with the rare constitutional Robertsonian translocation between chromosomes 15 and 21, rob(15;21)(q10;q10)c, have approximately 2,700-fold increased risk of developing iAMP21 ALL compared to the general population (Nature. 2014;508(7494):98-102).

Pathogenicity evaluation of BRCA1 and BRCA2 unclassified variants identified in Portuguese breast/ovarian cancer families

This work highlights the contribution of DNA, RNA, and in silico data to assess the pathogenicity of BRCA1/2 variants of uncertain significance, which, in turn, allows more accurate genetic counseling and clinical management of the families carrying them (J Mol Diagn. 2014;16(3):324-34).

The role of targeted BRCA1/BRCA2 mutation analysis in hereditary breast/ovarian cancer families of Portuguese ancestry

This work characterized the germline mutation pattern of hereditary breast/ovarian cancer (HBOC) families. We recommend that all suspected HBOC families from Portugal or with Portuguese ancestry, even those fulfilling moderately stringent clinical-criteria for genetic testing, should be specifically analyzed for the two most common BRCA1/BRCA2 founder mutations (Clin Genet. 2015;88(1):41-8).

Identification of previously unrecognized FAP in children with Gardner fibroma

This work represents the first comprehensive characterization of the pathogenetic mechanisms of Gardner fibroma, which may be a sentinel lesion of previously unrecognized Familial Adenomatous Polyposis families (EJHG. 2015;23(5):715-8).

Target gene mutational pattern in Lynch syndrome colorectal carcinomas according to tumor location and germline mutation

This study compared the target gene mutational pattern in microsatellite instability (MSI) colorectal carcinomas (CRC) from Lynch syndrome patients stratified by tumor location and germline mutation and the results indicate that the pattern of genetic changes differs in CRC depending on tumor location and between Lynch syndrome and sporadic MSI CRC (Br J Cancer. 2015;113(4):686-92).

Specific and redundant activities of ETV1 and ETV4 in prostate cancer aggressiveness revealed by co-overexpression cellular contexts

By combining the phenotypic impact data and the gene expression profiles of in vitro models with clinico-pathological features and gene expression profiles of ETS-subtyped tumors, we identified a set of genes associated with advanced stage and another associated with higher Gleason score, supporting an oncogenic role of ETV1 and ETV4 overexpression (Oncotarget. 2015;6(7):5217-36).

Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer

This work showed that breast and ovarian cancer risks and age at diagnosis varies by type and location of germline BRCA1/BRCA2 mutations. These data may have implications for risk assessment and cancer prevention decision making for carriers of BRCA1 and BRCA2 mutations (JAMA. 2015;313(13):1347-61).

PUBLICATIONS

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5 | RESEARCH GROUPS

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TEAM MEMBERS

Affiliated

Post-docs	5
PhDs students	3
Assistant researcher	4
Other researchers	10
MSc students	5
Graduate Students	1

CANCER SIGNALLING & METABOLISM

GROUP LEADER: Paula Soares

ABOUT

The group aims to identify molecular mechanisms involved in human cancer development with potential applications in the diagnosis, prognosis and targeted therapy, using as models thyroid and other neuroendocrine tumors. Besides the component of translational research, the group has basic research interests such as oncogenic signaling, survival mechanisms and mechanisms/molecules involved in mobility and invasion. Within this frame, a particular attention is paid to: a) signalling induced by genetic alterations in tyrosine kinase receptors and signal transducing molecules involved in the MAPK and the PI3K/mTOR pathway; b) survival mechanisms of cancer cells, including telomerase reactivation and apoptosis dysregulation; c) molecular mechanisms of metabolic alterations secondary to mitochondrial DNA mutations/deletions or to mutations in nuclear genes encoding metabolic enzymes.

PAST RESEARCH

In 2003, we identified BRAFV600E mutation as a major oncogenic event in papillary thyroid carcinoma. Since then the group has been focusing on the genetic alterations underlying genotypic-phenotypic correlations and in the signaling of oncogenic activation in thyroid tumors. This line of research is still being pursued through the study of thyroid tumors as well as other tumor types characterized by a high prevalence of BRAF mutations (nevi and melanoma), using *in vitro* and *in vivo* models to progress in the understanding of the BRAF-induced cellular effects. We also addressed the etiopathogenesis of familial forms of thyroid cancer, namely medullary thyroid carcinoma. In close collaboration with clinicians we have been collecting families with thyroid cancer aggregation. Regarding the effect of environmental factors in thyroid carcinogenesis we have been following-up a cohort of individuals that suffered, 50 to 60 years ago, epilation by scalp X-ray irradiation for Tinea capitis treatment. We verified that mtDNA large deletions are a hallmark of Hurthle cell tumours. The results obtained in the field of mitochondrion-rich tumors were the starting point for the study of mitochondrial and metabolic dysfunction in cancer, a sub-area in which our group is using several models other than thyroid tumors.

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5 | RESEARCH GROUPS

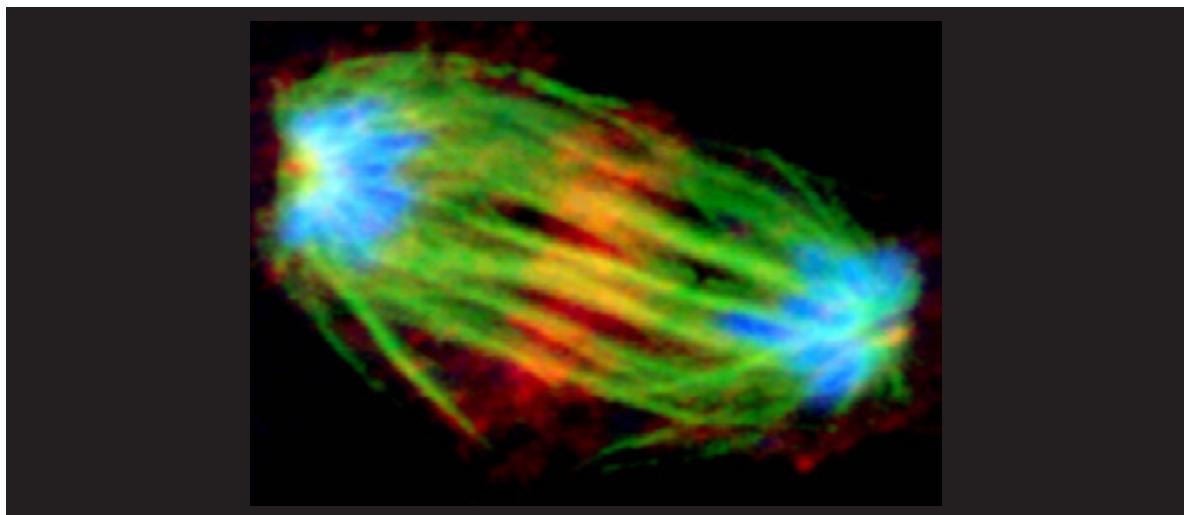
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TEAM MEMBERS

Affiliated	Non Affiliated
Senior scientists	3
Post-docs	5
PhDs students	14
MSc students	7
Technicians	4
Visiting Researchers	1
Collaborators	3

CELL DIVISION & GENOMIC STABILITY

GROUP LEADER: Claudio Sunkel



ABOUT

Our group was formed almost 30 years ago by Claudio Sunkel who carried out an extensive gene discovery program aimed to understand the fundamental mechanisms that ensure the fidelity of chromosome segregation during cell division. Using Drosophila, we identified, a number of conserved and essential genes required for the regulation of mitotic progression including the first POLO-like kinase. Subsequently, the group was involved in the genetic characterization of proteins involved in chromosome structure and of components of the Spindle Assembly Checkpoint that monitors Kinetochore-Microtubule interactions. In recent years the group has expanded its interests to understand how a monolayered epithelium coordinates cell polarity with cell division to control overall tissue architecture during growth and development. We are currently organized into three lines of research, each headed by independently funded PIs:

Claudio Sunkel (Co-PI Pedro Resende and António Pombinho) - Aneuploidy and tumorigenesis/drug screening.

We are developing tumor models in Drosophila caused by deregulation of chromosome segregation. We want to understand the molecular events that take place in tumor formation and relate those to conserved pathways in human cancer cells. This project aims to study the impact of aneuploidy in adult stem cell behavior and determine its relationship with tumorigenesis. Furthermore, this research line aims to carry out a drug discovery program that is using human tissue culture cells to identify compounds that interfere with the Spindle Assembly Checkpoint (SAC). The objective is to develop compounds that could target SAC-competent tumor cells.

Carlos Conde – Uncovering the molecular mechanisms that control and monitor the interaction of chromosomes with spindle microtubules

The fidelity of chromosome segregation relies on the attachment of sister kinetochores to microtubules of opposite spindle poles and on the Spindle Assembly Checkpoint (SAC), a biochemical pathway that prevents anaphase onset until the former state is achieved. Mitotic kinases are key regulators of both processes, which

are frequently deregulated in malignant cells. Our team combines *Drosophila* genetics, human cultured cells, high-resolution imaging and biochemical approaches to provide a detailed understanding of the mechanisms orchestrating kinetochore-microtubules interactions and SAC signaling. We aim to unveil the molecular and mechanical switches that fine-tune the action of key mitotic kinases at kinetochores and how these are relayed to microtubule attachment regulation and translated into biochemical signals that control SAC activity. Our findings generate critical knowledge to understand how dividing cells prevent aneuploidy.

Eurico Morais-de-Sá - Spatiotemporal control of epithelial polarity during cell division

The epithelial tissue forms a critical barrier between the organs of multicellular organisms, whose disruption has enormous impact on human disease. We combine the power of *Drosophila* genetics with quantitative imaging of intact tissues, and *in vitro* biochemical approaches to understand how epithelial architecture is controlled to ensure the homeostasis of proliferating tissues. Our work is focused on how dramatic changes in the cytoskeleton and cell shape are synchronized with the re-organization of distinct epithelial cortical domains during division.

PAST RESEARCH

Claudio Sunkel

Our main objective has been to identify and characterize the molecular mechanisms involved in faithful chromosome segregation during mitosis. Our major contribution to the field was the cloning and characterization of the Polo-like kinase family of mitotic regulators. We demonstrated that Polo is required for centrosome organization and function, for regulation of the spindle and in kinetochore assembly. Later we identified and characterized the CLASP family of microtubule regulators and demonstrated their role in mitosis. More recently, we have devoted our attention to the Spindle Assembly Checkpoint that monitors microtubule-kinetochore attachment and chromosome segregation. We characterized the role of Mad2, BubR1, Bub3 and Mps1 in this process and integrated our results into a molecular pathway that also involves Aurora B and Polo. We have studied the molecules involved in mitotic chromosome structure and analyzed the role of condensins showing for the first time their essential role in sister chromatid resolution prior to anaphase onset. We also localized for the first time the cohesion subunit DRAD21 to the centromere of mitotic chromosomes.

Carlos Conde

Our research in the field of mitosis has been focused on SAC signalling and its regulation by mitotic kinases. My team undertook a comprehensive dissection of the hierarchical framework controlling SAC function in *Drosophila* and found that Polo kinase lies upstream of the pathway promoting Mps1 activation at unattached kinetochores. Our findings also showed that active Mps1 promotes BubR1 phosphorylation to generate the 3F3/2 phosphoepitope at tensionless kinetochores. Furthermore, we were able to uncouple for the first time, 3F3/2 levels from inter-kinetochore tension, which helped us to show that the molecular outcome of 3F3/2 formation is to promote the association of Cdc20 with BubR1 to allow proper kinetochore recruitment of Cdc20 and MCC assembly required for a sustained SAC response.

Eurico Morais-de-Sá

Past research has been focused on epithelial cell polarity and *Drosophila* anterior-posterior axis formation. Since his move to IBMC, he found that the localization of Adherens junctions controls the asymmetry of epithelial cytokinesis, showing also that this process is essential to maintain epithelial architecture during proliferation. Recently, his team revealed that the subcellular organization of basolateral tumour suppressors is coordinated with the cell cycle to control the orientation of cell division and the consequent positioning of the daughter cells within the epithelial tissue.

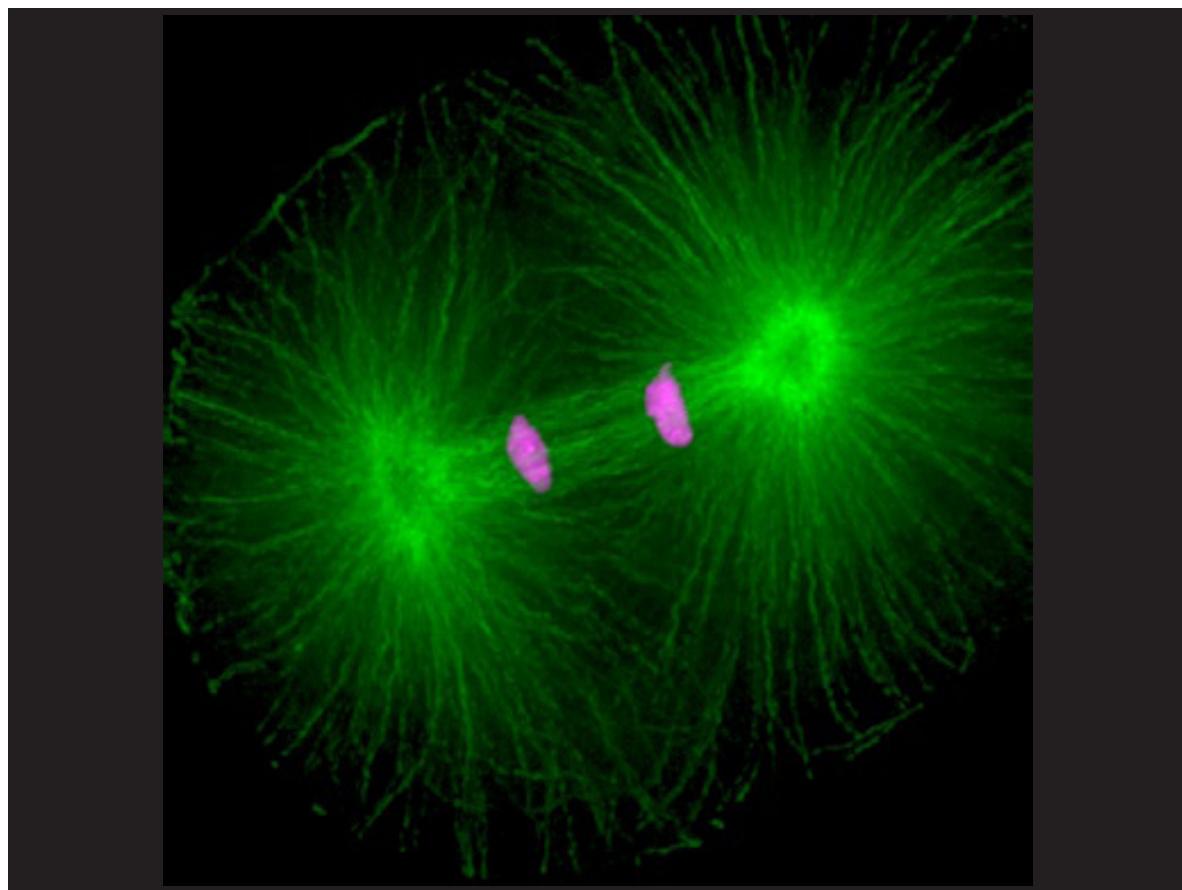
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Affiliated		Non Affiliated	
Senior scientists	2	Research Trainees	3
Post-docs	2	Collaborators	3
PhDs students	3		
MSc students	4		
Technicians	5		

CELL DIVISION MECHANISMS

GROUP LEADER: **Reto Gassmann**



ABOUT

Cytoplasmic dynein 1 (dynein), a multi-protein complex of 1.4 megadaltons, is the predominant microtubule minus-end-directed motor in animals. Dynein participates in a wide range of essential cellular activities, ranging from the transport of proteins, mRNA, and vesicles to nuclear migration and cell division. Our group is interested in the regulatory mechanisms that give rise to dynein's functional diversity. We use live-cell fluorescence microscopy, genetics, and biochemical approaches in the roundworm *Caenorhabditis elegans* and mammalian cultured cells to study the roles and molecular mechanisms of co-factors that associate with dynein to modulate localization, interaction with cargo, and motor activity. We currently focus on the functional dissection of two essential dynein co-factors: dynactin, a complex made up of 12 different sub-units that is required for most dynein functions in dividing and non-dividing cells, and the 3-subunit Rod/Zwilch complex, which together with the protein Spindly recruits dynein to kinetochores, the sites of microtubule attachment on mitotic chromosomes. Another main goal is the discovery of additional proteins that contribute to dynein pathway regulation: we have performed a genome-wide RNAi-based synthetic lethal screen with a null mutant of *nud-2*, the *C. elegans* homolog of the ubiquitous dynein co-factors NudE and Nudel, and we are using proteomics to identify proteins that associate with dynein and its major co-factors.

PUBLICATIONS

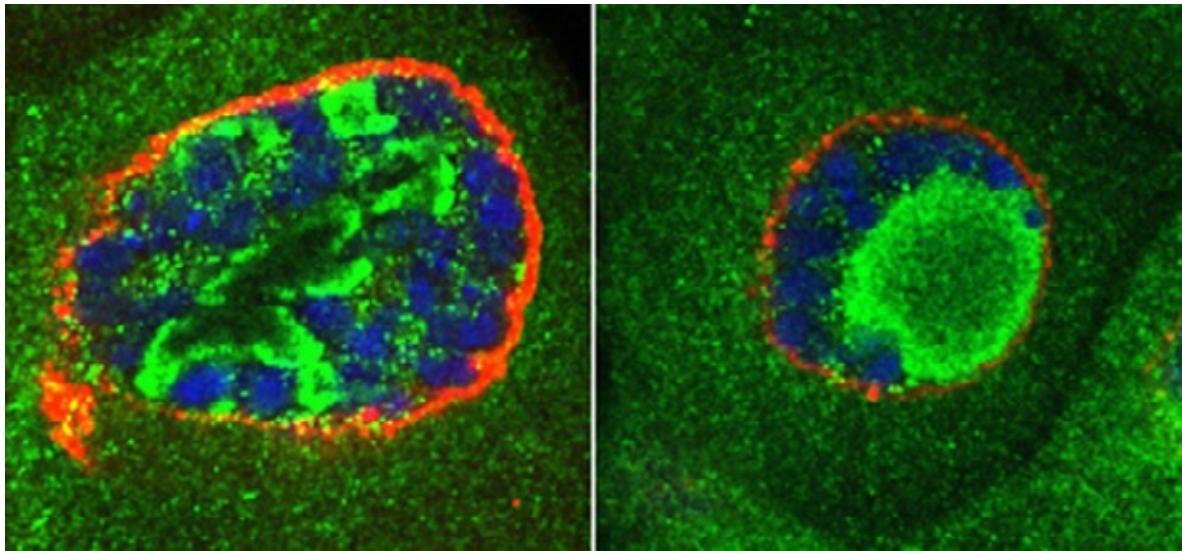
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TEAM MEMBERS

Affiliated	Non Affiliated
Post-docs	5
PhDs students	2
MSc students	1
Technicians	2
Collaborators	1

CELL GROWTH & DIFFERENTIATION

GROUP LEADER: **Paulo Pereira**



ABOUT

Our group studies the regulation of cellular properties by transcriptional and signaling networks during organogenesis. The complex coordination of these processes makes mandatory the use of *in vivo* contexts for the characterization of key genes and genetic networks. For that aim, we use two genetically tractable model organisms: the fruit fly and zebrafish.

Line 1: Functional genomics approaches to study cell growth and differentiation in *Drosophila* (Paulo Pereira) Myc and TGF β signaling pathways are required for tissue growth, patterning and differentiation. At the cellular and molecular level we are looking at the nucleolar-based mechanisms mediating the tissue-specific control of cell growth and differentiation by Myc and TGF β pathways. In parallel, we are exploring *in vivo* tissue-targeted screens to identify genes that interact with these pathways. Subsequent functional analyses of validated targets will focus on genes potentially relevant for the generation of models for human disease. We also explore the *Drosophila* eye as a model to gain a better understanding of the control of photoreceptor neurons and retinal glia development and interplay.

Line 2: Genome-wide genetic screens in a vertebrate organism.

The setup of the zebrafish model in our group results from the recruitment of J. Bessa and R. Freitas, both awarded with "Investigator FCT Starting grants" (2013), who have developed extensive work using this model. The main research aim of J. Bessa and R. Freitas is the study of how key transcription factors control genomic cis-regulatory regions to establish dynamic gene expression states in the context of the pancreas and limb development.

We propose to integrate the *Drosophila* and zebrafish models in a functional genomics platform to study biological processes as well as disease phenotypes. The use of *Drosophila* and zebrafish models will be complementary because *Drosophila* allows fast and low-cost identification of candidate genes, and zebrafish is used for further validation of these candidate genes in a vertebrate animal.

PAST RESEARCH

In 2011, we reported the characterisation of Viriato/Nol12 as a novel Myc-target gene and an important mediator of dMyc function in the stimulation of nucleolar biogenesis and cell growth (1). Recently, we developed a tissue-targeted double-RNAi screen that identified a further role for Viriato in TGFbeta signalling (2). Our participation in a collaborative effort led by F Casares and J Gómez-Skarmeta at the CABD (Seville, Spain) demonstrated that evolutionarily conserved CTCF binding sites can serve as a guide in assigning noncoding mutations to target genes, including those associated with human diseases (3).

Our recent effort in establishing the drosophila eye as a model to study neuron-glia cross-talk led to the report of the distinct functions of PS2 and PS3 integrins in retinal glia migration from the brain and in axonal projections (Tavares et al. 2015; in collaboration with João Relvas, I3S).

José Bessa studies transcriptional cis regulation in embryonic development and disease using the zebrafish as a vertebrate model organism. As main past achievements Jose Bessa has contributed with the development of new tools to explore the non-coding genome, performing a large genetic screen to isolate regulatory mutations in zebrafish (5) and has used the retina (6) and pancreas (7) as systems to understand the basic principles of Developmental Biology. Currently Jose Bessa is addressing how regulatory mutations impact in pancreatic diseases such as Diabetes and Pancreatic Cancer.

R. Freitas studies HoxD gene function, exploring the involvement of these genes in vertebrate limb evolution. As past achievements, she characterized their ancient expression profiles in lamprey and shark appendages (8,9). She then explored how their transcriptional modulation may have potentiated the evolution of limb morphology using transgenic and functional assays in zebrafish (10).

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5 | RESEARCH GROUPS

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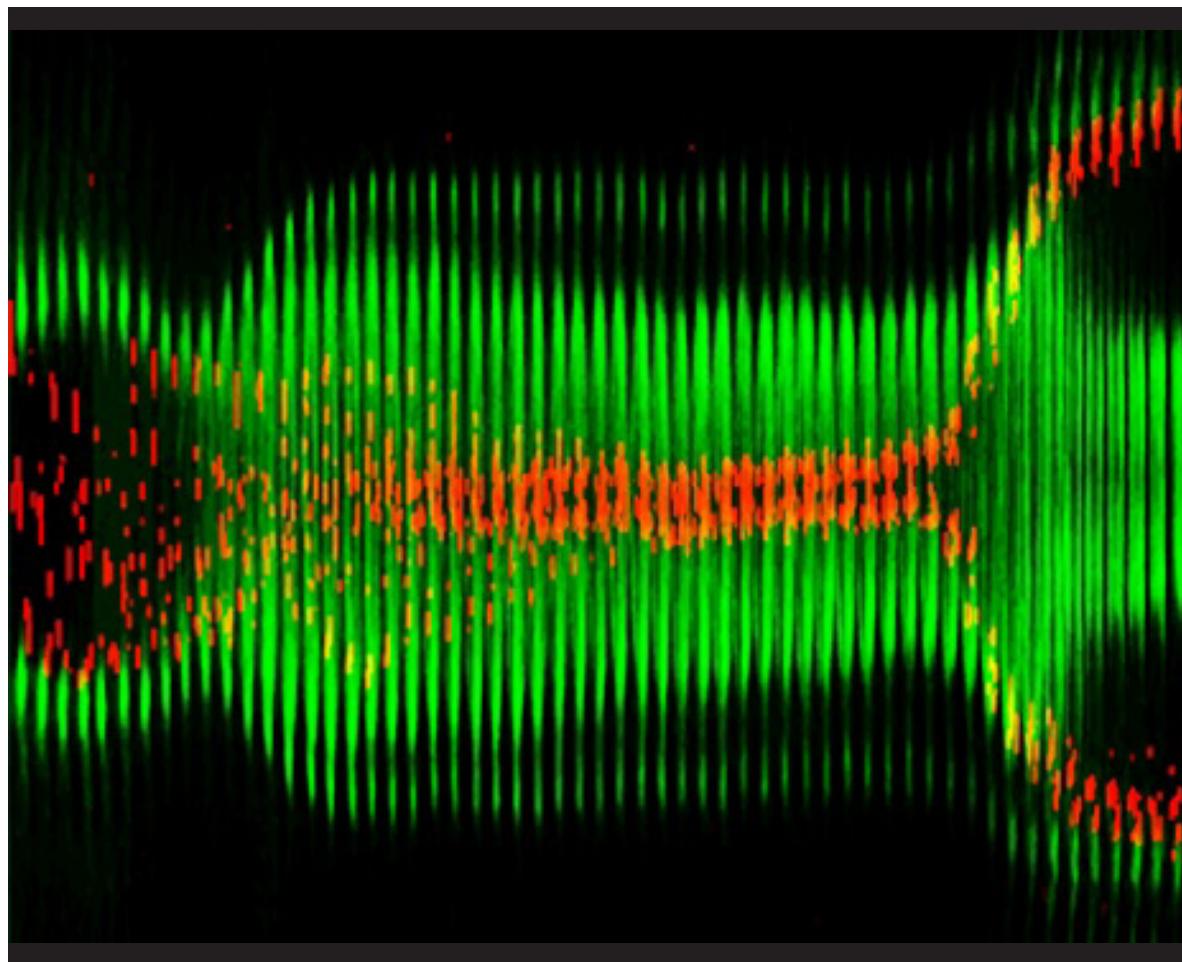
TEAM MEMBERS

Affiliated	
Senior scientists	2
Post-docs	2
PhDs students	2
MSc students	2
Technicians	3

Affiliated	
Research Trainees	3
Collaborators	1

CHROMOSOME INSTABILITY & DYNAMICS

GROUP LEADER: Helder Maiato



ABOUT

The group of Chromosome Instability & Dynamics is headed by Helder Maiato and is focused on two research programs, one related with the cell biology of chromosome segregation and another related with the development of technology for live-cell microscopy studies. A third research line investigated by an independently funded sub-group is directed by Elsa Logarinho and is focused on the study of chronological ageing and human aneuploidy and their implications for mitotic fidelity. Traditionally, the cell biology program is the research core of the Group and attracts the vast majority of human resources. The technology development program was born out of a necessity from the cell biology program and concentrates highly specialized human and infrastructural resources. The management of these three research programs is facilitated by one lab. manager that also provides laboratory technical support. Within the context of the thematic strand, the Chromosome Instability & Dynamics group will participate in the Interface Program on Cancer due to the well-established links between cancer and chromosomal instability and ageing, and a growing need for interaction between clinical oncologists/pathologists with fundamental cell biologists to understand and control the problem of cancer.

PAST RESEARCH

We have established the constitutive nature of a centrosome-independent spindle assembly program and how this program is adjusted to the presence/absence of centrosomes in animal somatic cells.

We demonstrated that mammalian CLASPs contribute to mitotic fidelity not only by regulating kinetochore-microtubule attachments, but also by preventing irreversible spindle multipolarity through distinct molecular partnerships at kinetochores and centrosomes. We have also shown that tension uniformity at metaphase kinetochores and subsequent anaphase synchrony is promoted by relaxation of the kinetochore-microtubule interface associated with spindle microtubule flux. We further obtained evidence for the existence of a conserved and functional spindle matrix in live animal cells and showed it to be required for proper chromosome segregation and spindle checkpoint function. Finally, we have uncovered a potential chromosome separation checkpoint that regulates the anaphase-telophase transition.

We have recently started a new research line that uses long-term phase-contrast microscopy and high-resolution spinning-disk confocal microscopy to record live human primary dermal fibroblasts of young, middle and old age individuals, to investigate the effects of ageing on chromosomal instability.

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TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists	2	Research Trainees	3
Post-docs	7		
PhDs students	6		
MSc students	6		
Technicians	3		

CLINICAL RESEARCH UNIT

GROUP LEADER: José Dinis Silva

ABOUT

IPO-Porto's Clinical Research Unit was created in 2006; its activities are supported by a professionalized team of over 50 MDs, 50 Nurses, 15 pharmacists and multiple technicians of a wide variety of areas of expertise. IPO-Porto is considered as a reference centre for Clinical Trials conducted in Portugal, in the large majority of pathologies treated in the institution. Being present at the highest level of Clinical Trials demands great discipline and dedication from all professionals.

IPO-Porto's Clinical Research Unit has a full-time dedicated team of 14 people, whose daily activity includes supporting Clinical Trials recruitment and conduct, assist in protocols compliance and support all related procedures involving the multidisciplinary professionals of the institution.

PAST RESEARCH

As a consequence of the work developed, a progressive and sustained growth on the number of Clinical Trials conducted and patients recruited has been achieved, in parallel with faster implementation timelines, with the consequent gain in competitiveness.

In 2015, more than 110 Clinical trials were ongoing, which corresponded to almost 390 patients being treated under the context of a clinical trial, of which more than 240 were recruited in the given year.

PUBLICATIONS

2015

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2014

2. Vassiliki Saloura, Ezra E.W. Cohen, Lisa Licitra, Salem Billan, Jose Dinis, Steen Lisby, Thomas Christoph Gauer. An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck. *Cancer Chemother Pharmacol.* 2014 Jun; 73(6):1227-39.
3. Eric Pujade-Lauraine, Felix Hilpert, Beatrice Weber, Alexander Reuss, Andres Poveda, Gunnar Kristensen, Roberto Sorio, Ignace Vergote, Petronella Witteveen, Aristotelis Bamias, Deolinda Pereira, Pauline Wimberger, Ana Oaknin, Mansoor Raza Mirza, Philippe Follana, David Bollag, and Isabelle Ray-Coquard. Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial. *J Clin Oncol.* 2014 May 1;32(13):1302-8.

4. William P.Tew, Nicoletta Colombo, Isabelle Ray-Coquard, Josep M. del Campo, Amit Oza, Deolinda Pereira, Serafina Mammoliti, Daniela Matei, Giovanni Scambia, Katia Tonkin, Zhenming Shun, Lars Sternas, David R. Spriggs. Intravenous Aflibercept in Patients With Platinum-Resistant, Advanced Ovarian Cancer. Results of a Randomized, Double-Blind, Phase 2, Parallel-Arm Study. *Cancer* 2014 Feb 1: 335-343.

2013

5. Vassiliki Saloura, Ezra E.W. Cohen, Lisa F. Licitra, Salem Billan, Jose Dinis, Steen Lisby, Thomas Christoph Gauler. An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck. *J Clin Oncol* 31, 2013 (suppl; abstr 6065)
6. Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O, Hajek R, Dmoszynska A, Paiva B, Vidriales MB, Esteves G, Stoppa AM, Robinson D Jr, Ricci D, Cakana A, Enny C, Feng H, van de Velde H, Harousseau JL. Randomized Phase II Study of Bortezomib, Thalidomide, and Dexamethasone With or Without Cyclophosphamide As Induction Therapy in Previously Untreated Multiple Myeloma. *J Clin Oncol*. 2013 Jan 10;31(2):247-55.

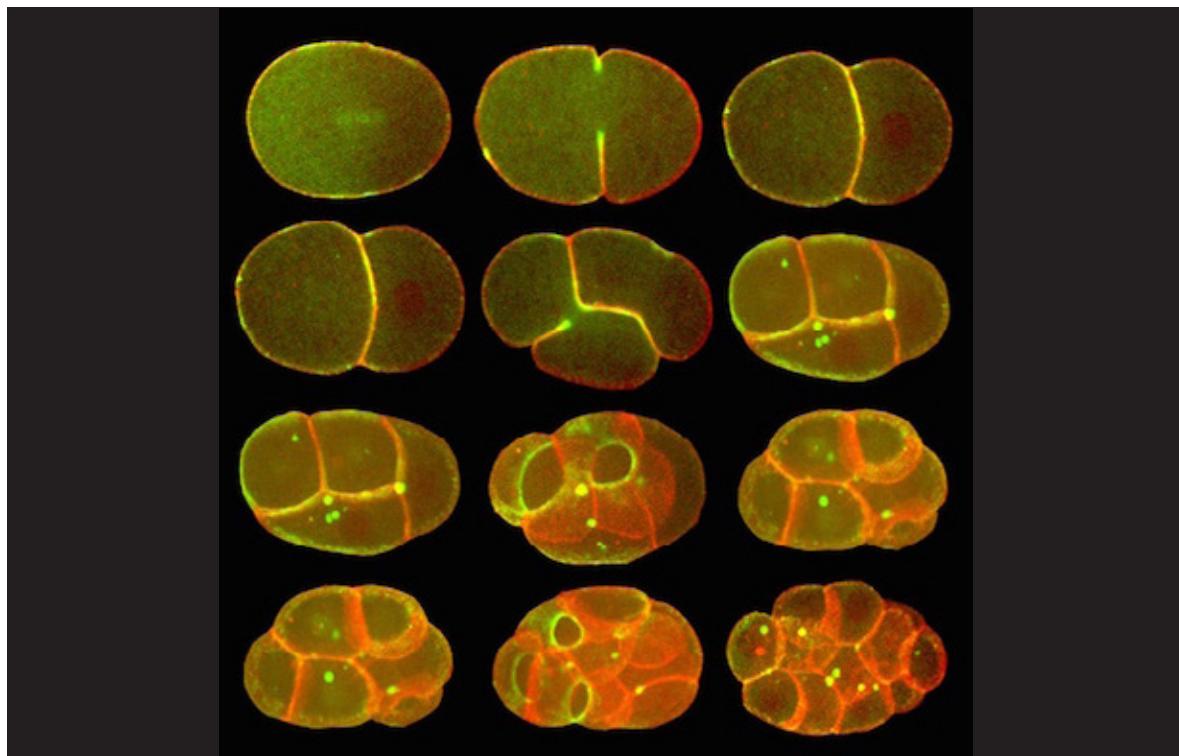
TEAM MEMBERS

Affiliated

Clinicians	50
Pharmacists	15
Nurses	50
Data Managers	7
Clinical Trial Assistant	4

CYTOSKELETAL DYNAMICS

GROUP LEADER: Ana Xavier Carvalho



ABOUT

The interest of our team lies in understanding the regulation, organization and dynamics of acto-myosin contractile networks. We are particularly interested in the contractile ring, which functions during cytokinesis to partition the contents of the mother cell to the two daughter cells. The contractile ring assembles around the cell equator beneath the plasma membrane after the replicated chromosomes have segregated. Constriction of the ring draws the plasma membrane inwards, closing the gap between the two daughter cells. Our goal is to dissect its mechanisms of assembly and constriction. Gaining mechanistic insight into cytokinesis is of significance for the understanding of tumorigenesis as failure of cytokinesis gives rise to polyploid cells, which have been postulated to be critical intermediates in the development of cancer. In addition, lessons learned about the contractile ring will help us understand other essential cellular processes that utilize acto-myosin contractile networks, namely tissue morphogenesis, wound healing, cell migration, and cell invasion.

We use the nematode *C. elegans* as animal system and a combination of cell biological and biochemical approaches. Actin, non-muscle myosin II and most of their regulators are well conserved in *C. elegans* and a variety of cellular contexts that involve actomyosin contractility are experimentally accessible in this system. These include cytokinesis, polarity establishment, tissue morphogenesis, muscle contraction, and neuronal development. Our favorite experimental approaches include live cell microscopy and the development of image-based quantitative assays, molecular replacement technology for generation of transgenic worms and structure-function studies, and genetics.

PUBLICATIONS

1. Xavier de Carvalho A, Maiato H, Maia AF, Ribeiro SA, Pontes P, Bickmore W, Earnshaw WC, Sambade C (2015) Reed-Sternberg Cells Form by Abscission Failure in the Presence of Functional Aurora B Kinase. *PLoS ONE* 10(5): e0124629.
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3. Davies T, Jordan SN, Chand V, Sees JA, Laband K, Carvalho AX, Shirasu-Hiza M, Kovar DR, Dumont J, Canman JC. High-resolution temporal analysis reveals a functional timeline for the molecular regulation of cytokinesis. *Developmental Cell*. 2014. 30(2):209-23.
4. Chan, Fung-Yi; Sun, Ning; A. C. Neves, Marco; Lam, Chun-Hung; Chung, Wai-Hong; Wong, Lai-King; Chow, Ho-Yin; Leung, Ma, Dik-Lung; Leung, Yun-Chung; Chan, Tak-Hang; Abagyan, Ruben; Wong, Kwok-Yin (2013) Identification of a new class of FtsZ inhibitors by structure-based virtual and in vitro screening. *Journal of Chemical Information and Modeling*, 53, 2131-2140.
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6. Carvalho A., Olson S.K., Gutierrez E., Zhang K., Noble L.B., Zanin E., Desai A., Groisman A., Oegema K. (2011) Acute drug treatment in the early *C. elegans* embryo. *PLoS One* 6: e24656
7. Carvalho A., Desai A., Oegema K. (2009) Structural memory of the contractile ring makes the duration of cytokinesis independent of cell size. *Cell* 137: 926-37.
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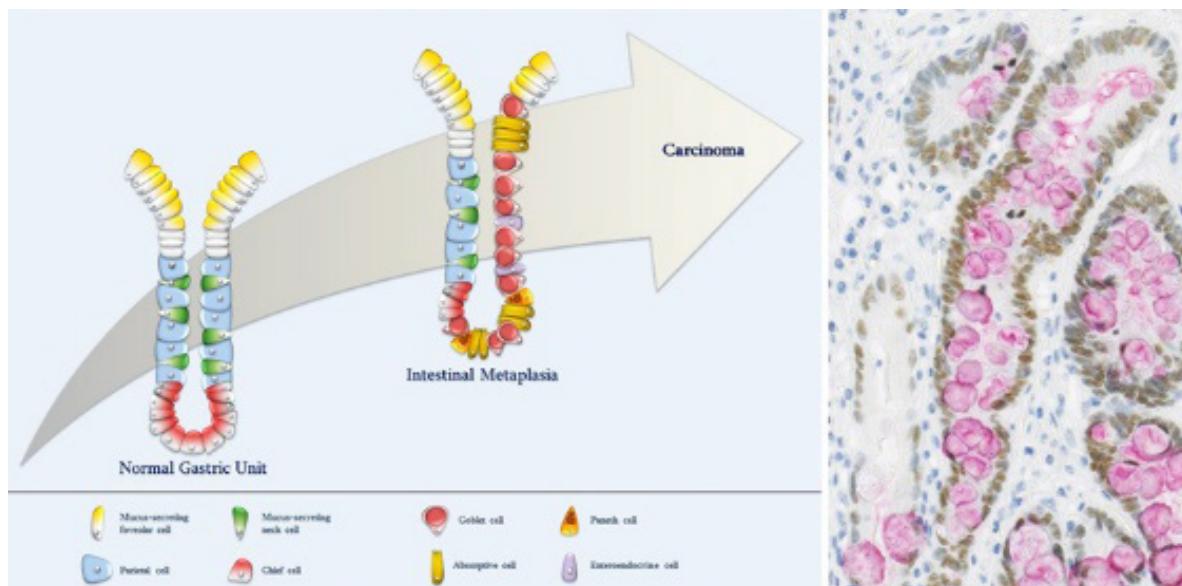
TEAM MEMBERS

Affiliated

Post-docs	5
Fellow	2
PhDs students	1

DIFFERENTIATION & CANCER

GROUP LEADER: Raquel Almeida



ABOUT

Our aim is to understand and manipulate the mechanisms that drive differentiation switches, which constitute the starting point of a significant number of carcinogenic processes, namely in the GI tract. Our ambition is to perform at the highest standard by adopting an integrative approach, using clinical specimens, cellular systems and animal models and in this way progress in the understanding of the biology of cancer. Two main research lines will be trailed.

1. Pathophysiology of differentiation switches in cancer. Here, our objectives are to:

- Characterize the interaction of CDX2 with SOX2 in the onset and progression of gastroesophageal preneoplastic lesions and cancers.
- Characterize the cellular phenotype associated with MEX3A expression and post-transcriptional regulation of key differentiation transcription factors, namely CDX2, in normal and pathological conditions. We will use a transcriptomic approach a knock-out MEX3A mouse model (financed by the Infrafrontier-I3 Programme).
- Progress in the study of molecular mechanisms involved in gastric preneoplastic and neoplastic lesions, namely the BMP pathway.

2. Glycoproteome remodeling and biomarker identification. Here, our objectives are to:

- Generate CDX2 knock-out cell lines, using the zinc finger nuclease strategy, to study the CDX2-dependent glycoproteome and phenotypic alterations and its contribution for carcinogenic processes.
- Identify cancer-associated MUC16 glycoforms using a recently developed MUC16 antibody and also assess MUC16 role in interaction of tumor cells with mesothelin.
- Evaluate the impact of MUC1 splice variants in pancreatic tumors by identifying associated oncogenic signaling pathways.

PAST RESEARCH

We have identified CDX2 as the key player in the transdifferentiation of the gastric mucosa to an intestinal phenotype, in that way predisposing to cancer. We have made great strides in understanding the mechanisms involved in CDX2 regulation – the BMP pathway, autoregulation, post transcriptional regulation through MEX3A. We have shown a direct link between Helicobacter pylori infection and some of these regulatory mechanisms, namely the BMP pathway. We have tackled the relevance of other transcription factors, in particular SOX2, for gastric carcinogenesis as well as its interaction with CDX2.

We have contributed to the understanding of the glycoproteome remodeling that occurs during gastric carcinogenesis, leading to specific biomarkers of disease, namely adapting the protocol “Proximity Ligation Assay” to glycoprotein detection (collaboration with the company Olink). We have shown that CDX2 is involved in the glycoproteome remodeling of intestinal metaplasia regulating MUC2 and the enzyme ST6GalNAc-I, leading to the biosynthesis of the glycoprotein MUC2/Sialyl-Tn specific of these lesions. Finally, mucin and glycosyltransferase polymorphisms were shown to be relevant risk factors both for the establishment of *H. pylori* infection and subsequent carcinogenic cascade.

PUBLICATIONS

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2. Pereira B., Sousa S., Barros R., Carreto L., Oliveira P., Oliveira C., Chartier N.T., Plateroti M., Rouault J.P., Freund J.N., Billaud M., Almeida R. (2013) CDX2 regulation by the RNA-binding protein MEX3A: impact on intestinal differentiation and stemness. *Nucleic Acids Res.* 41: 3986-99.
3. Barros R., Freund J.N., David L., Almeida R. (2012) Intestinal metaplasia revisited: function and regulation of CDX2. *Trends Mol. Med.* 18: 555-63.
4. Camilo V., Barros R., Sousa S., Magalhães A.M., Teresa Lopes, Santos A.M., Pereira T., Figueiredo C., David L., Almeida R. (2012) Helicobacter pylori and the BMP pathway regulates CDX2 and SOX2 expression in gastric cells. *Carcinogenesis.* 33: 1985-92.
5. Pinto R., Carvalho A.S., Conze T., Magalhães A., Picco G., Burchell J.M., Taylor-Papadimitriou J., Reis C.A., Almeida R., Mandel U., Clausen H., Söderberg O., David L. (2012) Identification of new cancer biomarkers based on aberrant mucin glycoforms by *in situ* Proximity Ligation. *J. Cell. Mol. Med.* 16: 1474-84.
6. Barros R., Costa L.T., Pinto-de-Sousa J., Duluc I., Freund J.N., David L., Almeida R. (2011) CDX2 autoregulation in human intestinal metaplasia of the stomach: impact on the stability of the phenotype. *Gut*, 60: 290-8.
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8. Barros R., Pereira B., Duluc I., Azevedo M., Mendes N., Camilo V., Jacobs R.J., Paulo P., Santos-Silva F., van

5 | RESEARCH GROUPS

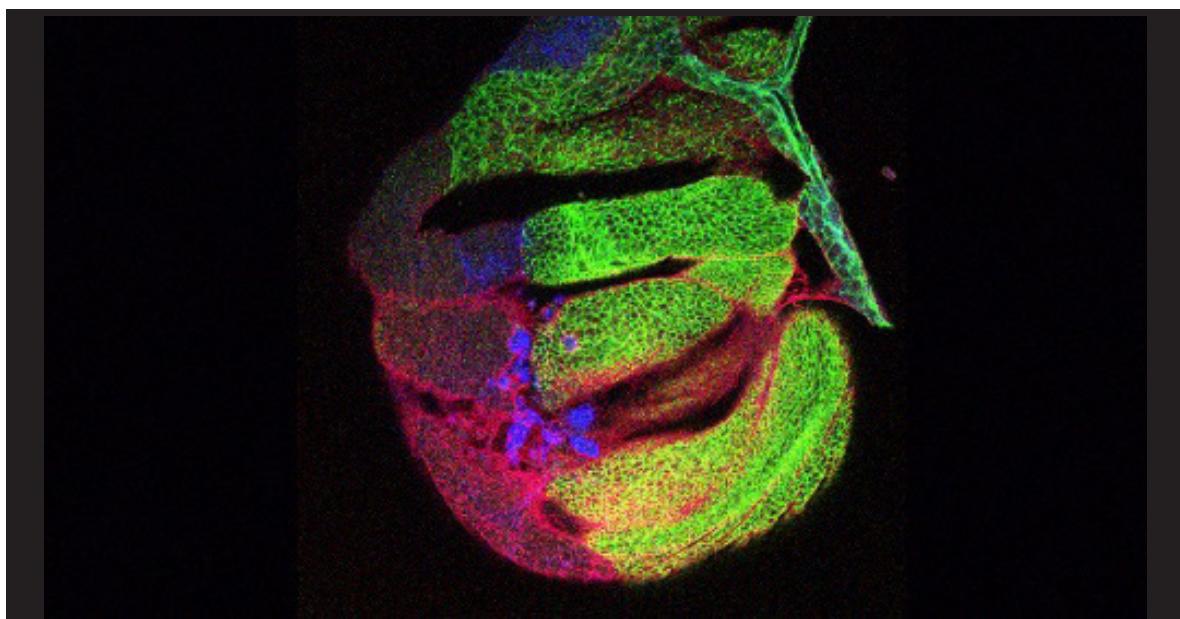
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10. Marcos N.T., Magalhães A., Ferreira B., Oliveira M.J., Carvalho A.S., Mendes N., Gilmartin T., Head S.R., Figueiredo C., David L., Santos-Silva F., Reis CA. (2008) Helicobacter pylori induces beta3GnT5 in human gastric cell lines, modulating expression of the SabA ligand sialyl-Lewis x. *J. Clin. Invest.* 118: 2325-36.

TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists: 2	2	Collaborators: 1	1
Post-docs: 4	4		
PhDs students: 2	2		
MSc students: 2	2		
Technicians: 1	1		

EPITHELIAL INTERACTIONS IN CANCER

GROUP LEADER: Raquel Seruca



ABOUT

The long term goal of the EPIC (EPithelial Interactions in Cancer) group is to uncover how epithelial cell-cell and cell-matrix junctions, as well as the surrounding microenvironment, can influence cancer progression. Specifically, and based on three common epithelial-derived cancers (gastric, breast, and colorectal), the group will establish the contribution of adhesion molecules (E- and P-cadherins), infections (*Helicobacter pylori* and the microbiota), and non-neoplastic components of the tumor tissue (fibroblast-like cells, the cancer cell secreted peptides and the elements of the extracellular matrix), to alter epithelial homeostasis and influence cancer development.

EPIC researchers have expertise in adhesion cancer-associated molecules and in host-*H. pylori* interactions, and complementary skills on genetics, molecular and cell biology, microbiology, pathology, and oncology. The group has available biological reagents that include stable cell lines expressing wt and mutants of the E- and P-cadherin, series of primary tumors, and several in vitro and in vivo experimental models (CAM, *Drosophila*, and nude mice).

The group is structured in three working teams headed by the 3 core CVs. SERUCA's team (group coordinator) aims at identifying the key molecules and signaling networks mediated by E-cadherin mutants in cancer, namely gastric cancer. PAREDES's working team will concentrate on the relevant role of the adhesion molecule P-cadherin in cancer. FIGUEIREDO's working team will dissect the molecular mechanisms and functional consequences underlying *H. pylori*-mediated gastric cancer.

The accomplishment of these research goals will contribute to the development of new tools for cancer screening, prevention, and patient surveillance, as well as therapeutic strategies based on the modulation of cancer cell interactions.

PAST RESEARCH

SERUCA's team is the worldwide expert of functional assays of germline mutations of E-cadherin associated to hereditary diffuse gastric cancer. Using stable cell lines carrying CDH1 germline missense mutations we identified the underlying signaling pathways associated to cancer cell motility and survival (EGFR and Notch1). Moreover, we verified that E-cadherin is regulated by mechanisms of Endoplasmic Reticulum Quality Control. Using Drosophila we identified genes interacting with mutant human E-cadherin.

PAREDES's team found that the adhesion molecule P-cadherin is overexpressed in 30% of breast carcinomas, being associated to cancer invasion and poor patient prognosis. Further, it was demonstrated that P-cadherin confers cancer stem cell properties to breast cancer cells, surviving in anchorage independent conditions and resisting to standard cancer therapies.

FIGUEIREDO'S team has shown that particular *H. pylori* genotypes increase the levels of gastric inflammation and epithelial damage, and the risk for gastric atrophy and cancer. Regarding interactions between *H. pylori* and the host gastric epithelial cells, the team has shown that *H. pylori* targets E-cadherin and accentuates loss of cell-cell adhesion and increases cell invasion via c-Met activation and increased matrix metalloproteases activity.

PUBLICATIONS

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3. Ferreira AC, Suriano G, Mendes N, Gomes B, Wen X, Carneiro F, Seruca R, Machado JC. E-cadherin impairment increases cell survival through Notch-dependent upregulation of Bcl-2. Human Molecular Genetics 21:334-43, 2012.
4. Caldeira J, Simões-Correia J, Paredes J, Pinto MT, Sousa S, Corso G, Marrelli D, Roviello F, Pereira PS, Weil D, Oliveira C, Casares F, Seruca R. CPEB1, a novel gene silenced in gastric cancer: a Drosophila approach. Gut 61:1115-23, 2012.
5. Paredes J, Figueiredo J, Albergaria A, Oliveira P, Carvalho J, Ribeiro AS, Caldeira J, Costa AM, Simões-Correia J, Oliveira MJ, Pinheiro H, Pinho SS, Mateus R, Reis CA, Leite M, Fernandes MS, Schmitt F, Carneiro F, Figueiredo C, Oliveira C, Seruca R. Epithelial E- and P-cadherins: role and clinical significance in cancer. Biochimica Biophysica Acta - Reviews on Cancer 1826:297-311, 2012.
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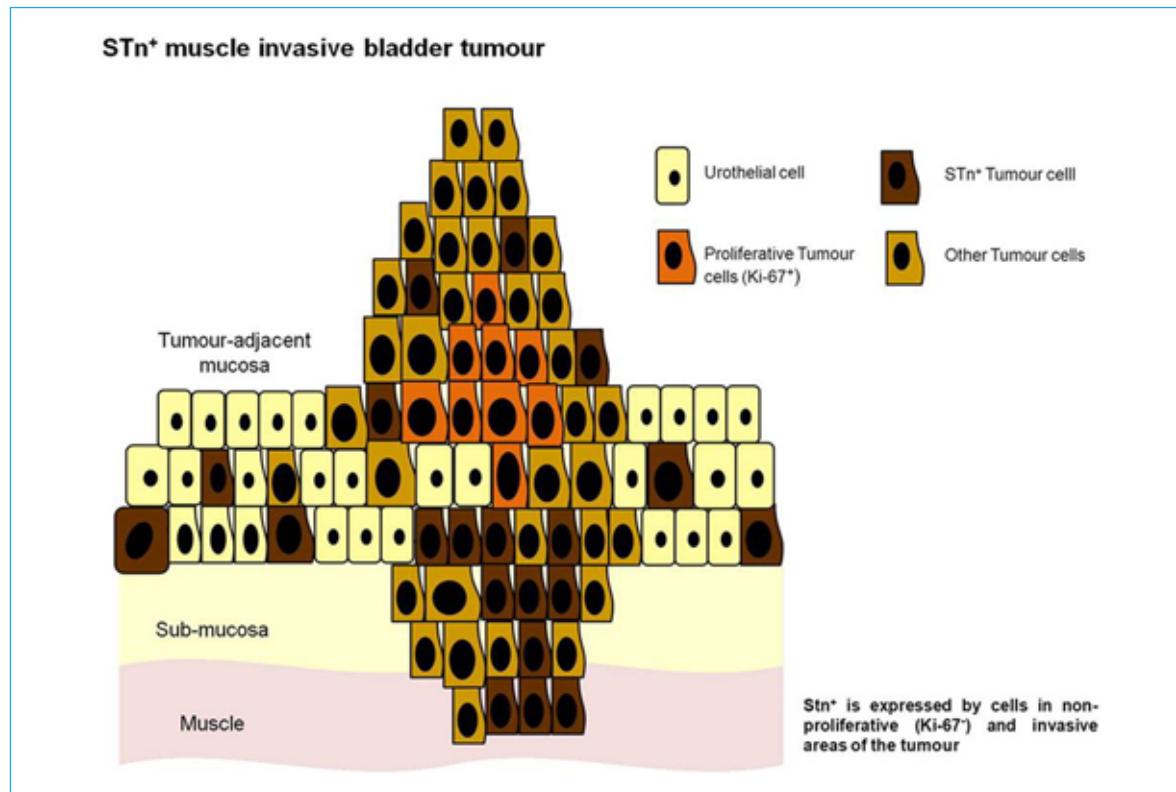
7. Gonzalez CA, Figueiredo C, Bonet C, Ferreira RM, Pardo ML, Ruiz Liso JM, Alonso P, Sala N, Capella G, Sanz-Anquela JM. Helicobacter pylori cagA and vacA genotypes as predictors of progression of gastric preneoplastic lesions: a long term follow up in a high-risk area in Spain. American Journal of Gastroenterology 106: 867-74, 2011.
8. Ribeiro AS, Albergaria A, Sousa B, Correia AL, Bracke M, Seruca R, Schmitt FC, Paredes J. Extracellular cleavage and shedding of P-cadherin: a mechanism underlying the invasive behaviour of breast cancer cells. Oncogene 29:392-402, 2010.
9. Oliveira MJ, Costa AM, Costa AC, Ferreira RM, Sampaio P, Machado JC, Seruca R, Mareel M, Figueiredo C. CagA associates with c-Met, E-Cadherin, and p120-aatenin in a multiproteic complex that suppresses Helicobacter pylori-induced cell-invasive phenotype. Journal of Infectious Diseases 200: 745-55, 2009.
10. Oliveira MJ, Costa AC, Costa AM, Henriques L, Suriano G, Atherton JC, Machado JC, Carneiro F, Seruca R, Mareel M, Leroy A, Figueiredo C. Helicobacter pylori induces gastric epithelial cell invasion in a c-Met and type IV secretion system dependent manner. Journal of Biological Chemistry 281:34888-96, 2006.

TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists	4	Visiting Researchers	1
Post-docs	9	Collaborators	1
PhDs students	8		
MSc students	1		
Technicians	4		

EXPERIMENTAL PATHOLOGY AND THERAPEUTICS

GROUP LEADER: Lúcio Lara Santos



ABOUT

The Experimental Pathology and Therapeutics group has been studying the pathobiologic mechanisms behind cancer to improve prevention and/or treatment. The group is devoted to translational cancer research, using *in vivo* and *in vitro* models and comparative pathology to address the process of neoplastic transformation, with the main focus being bladder cancer. The current aims are:

- a) Identify biomarkers that allow a refinement of the prognosis and better allocation of treatment resources;
- b) Identify therapeutic targets;
- c) Develop new drugs and personalized treatments;
- d) Study the mechanisms of resistance to anti-cancer therapies;
- e) Develop experimental models that allow to study anti-cancer therapeutics;
- f) Study malignancies associated with infection.

PAST RESEARCH

In the past years, it has been evaluating the response of bladder tumors to available drugs to define prognostic groups (molecular) and seeking novel agent combinations. The group has also established non-human models for drug testing (*cell cultures*; *xenografts*, chemically induced bladder tumors in animal models). More recently it has also focused on determining the molecular mechanisms associated with Infection with *Schistosoma*

haematobium, an endemic parasite of Angola and other parts of Africa and Asia, in an attempt to determine its role in the development of chronic infections and ultimately bladder cancer.

In the field of bladder cancer biomarkers, the group has studied cell-surface protein glycosylation associated with malignant transformations. This allowed the identification of a cell-surface cancer-associated protein glycosylation termed sialyl-Tn (sTn) associated with bladder cancer invasion and metastasis. This has been one of the top research highlights of the group published in 2013. The sTn antigen offers potential to target aggressive cancer cells and control disease progression; the group is now devoted to develop therapeutics based on this glycan. Other biomarker research topics included the establishment of a panel of biomarkers (histologic, genetic, and molecular) of response to Bacillus Calmette-Guerin immunotherapy, the gold standard therapeutics for bladder cancer patients at a high-risk of recurrence/progression. This score may be a helpful tool to identify patients with poor prognosis and to improve clinical decision. The group further described lymphovascular invasion, and RKIP, CD147 and MCT1 expressions, as relevant prognostic and/or predictive biomarkers of bladder cancer, and as promising areas of therapeutic intervention.

The group has also been devoted to improving the therapeutics for invasive bladder tumors. It was observed that combination of temsirolimus or everolimus, two mammalian targets of rapamycin (mTOR) inhibitors, with cisplatin and gemcitabine enhanced cytotoxicity efficacy, namely in the muscle-invasive urinary bladder-cancer cell lines. Although further studies are necessary to complement this data, the results open new perspectives in muscle invasive urinary bladder cancer treatment.

In the field of animal models of cancer, the group has developed realistic models for developing innovative diagnostic and therapeutic strategies. The group has collaborated with UTAD in the establishment and characterization of two animal (mouse and rat) bladder cancer models, induced by oral nitrosamine administration. These models represent a muscle-invasive and papillary bladder urothelial carcinoma. The group has now also established direct bladder cancer xenografts in nude mice. All these models showed remarkable similarities with human lesions and are in use for testing innovative bladder cancer treatments. Recently, other chemically induced models have been developed, namely a rat mammary cancer and a mouse liver cancer model. These models are currently being characterized morphologically and molecularly, so they can be made available for testing diagnostic and therapeutic strategies.

PUBLICATIONS

1. Ferreira JA, Videira PA, Lima L, Pereira S, Silva M, Carrascal M, Severino PF, Fernandes E, Almeida A, Costa C, Vitorino R, Amaro T, Oliveira MJ, Reis CA, Dall'olio F, Amado F, Santos LL. Overexpression of tumour-associated carbohydrate antigen sialyl-Tn in advanced bladder tumours. Mol Oncol. 2013 Jun;7(3):719-31. www.ncbi.nlm.nih.gov/pubmed/23567325 IF: 5.935
2. Lima L, Severino PF, Silva M, Miranda A, Tavares A, Pereira S, Fernandes E, Cruz R, Amaro T, Reis CA, Dall'Olio F, Amado F, Videira PA, Santos L, Ferreira JA. Response of high-risk of recurrence/progression bladder tumours expressing sialyl-Tn and sialyl-6-T to BCG immunotherapy. Br J Cancer. 2013 Oct 15;109(8):2106-14. www.ncbi.nlm.nih.gov/pubmed/24064971 IF: 4.817
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5 | RESEARCH GROUPS

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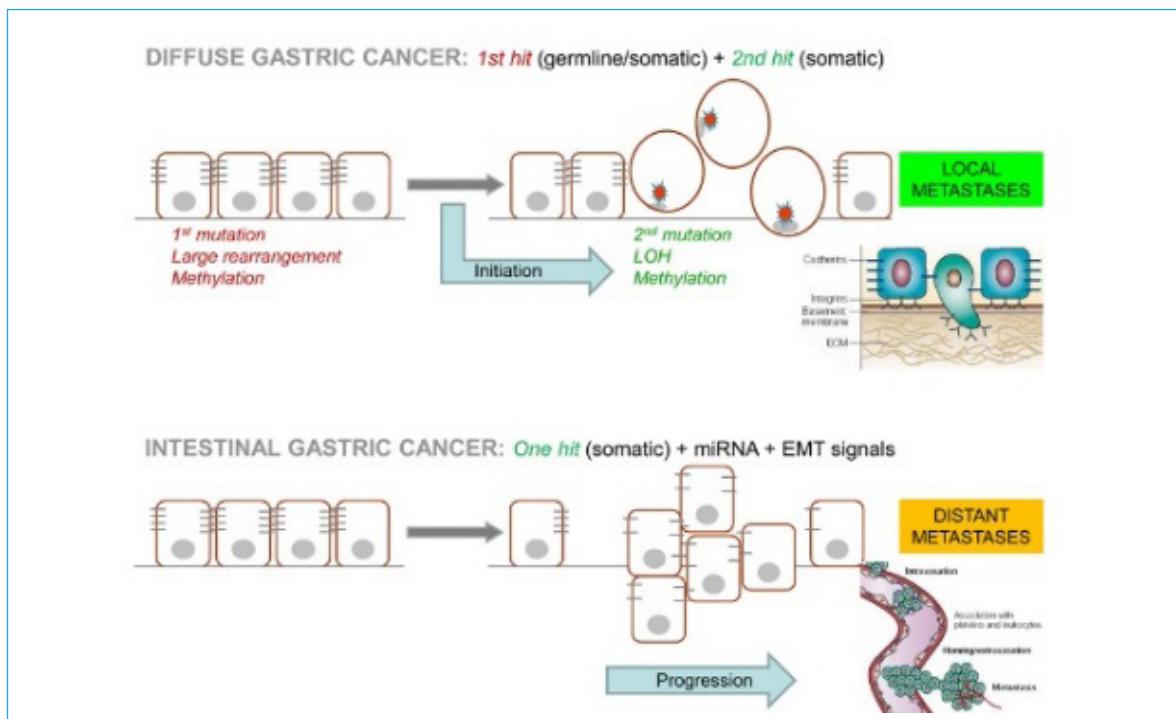
TEAM MEMBERS

Affiliated

Senior scientists	3
Post-docs	2
Clinicians with laboratory sessions	1
PhDs students	7
Technicians	2

EXPRESSION REGULATION IN CANCER

GROUP LEADER: Carla Oliveira



ABOUT

The general goal of the Expression Regulation in Cancer Group is to disclose germline and somatic regulatory mechanisms and molecular circuitries, acting to increase gastric cancer susceptibility, and to confer advantageous features to tumour cells. This research contribution is expected to improve gastric cancer diagnosis and patients' management as well as molecular stratification, prognosis and targeted therapy of gastric cancer.

In particular, our research objectives are:

1. Identification of germline and somatic defects underlying familial aggregation of gastric cancer, using NGS, transgenic zebra fish and funding from the American Association “No Stomach for Cancer”;
2. Identification of intra-tumor molecular landscapes and mediators of cellular crosstalk (exosomes and microvesicles) during gastric initiation and progression, through cell line models of Epithelial-Mesenchymal-Epithelial transition, patients' cohorts and FCT funding;
3. Identification of gastric cancer-specific molecular signatures with impact in patient survival and therapy, using NGS and patients' cohorts, and funding from Coimbra Genomics and BGI.

The team is multidisciplinary with strong background in oncobiology and genetics, and supported by technical expertise in molecular and cellular biology, NGS, bioinformatics and therapy response assessment. The group developed dynamic cancer cell line models, orthotopic xenograft mouse models, and has access to large gastric cancer cohorts (familial and sporadic), through long lasting collaborations with research groups, Consortia, Hospitals, and companies.

PAST RESEARCH

The expression Regulation in Cancer Group focuses on molecular mechanisms and clinical implications related to familial and sporadic forms of gastric cancer, namely hereditary diffuse gastric cancer (HDGC). Carla Oliveira, the head of the group belongs to the International Gastric Cancer Linkage Consortium from its creation in 1999, and her team disclosed molecular and clinical aspects of worldwide series of families and sporadic gastric cancer cases, found novel germline CDH1 genetic defects, defined somatic events with impact for patient management and therapy, and reported an association between germline CDH1 mutations and developmental malformations. The group has also deeply characterized primary gastric cancers and metastases to disclose molecular causes of E-cadherin impairment and their impact of patient's prognosis and therapy. Major collaborators are: D Huntsman, CA; The International Gastric Cancer Linkage Consortium (IGCLC); F Roviello, Univ Sienna, IT; F Carneiro, Centro Hospitalar S. João Porto, PT; N Bonito from the Port. Ins. Oncol, IPO-Coimbra, PT; K Bedard from Univ. Halifax, CA; M Santos, Univ. Aveiro, PT; P Granja, INEB-Porto, PT; José Bessa, IBMC-Porto, PT.

PUBLICATIONS

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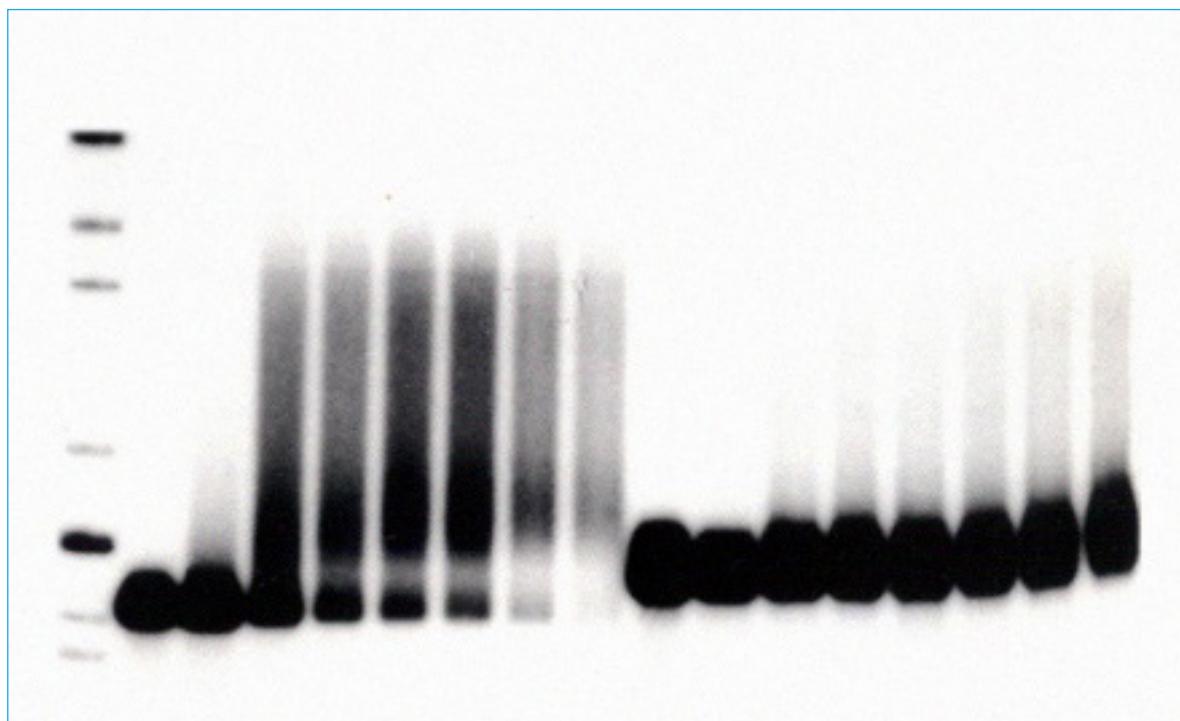
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TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists	3	Research Trainees	2
Post-docs	3		
PhDs students	4		
MSc students	3		
Technicians	1		

GENE REGULATION

GROUP LEADER: Alexandra Moreira



ABOUT

The main objective of our group is to understand and elucidate the molecular mechanisms involved in regulating gene expression at the pre-mRNA processing level, in particular in polyadenylation and alternative splicing, with a specific interest in inflammatory and cancer cells. We mainly use molecular biology methodologies and take advantage of different model systems, in particular *Drosophila melanogaster* and human cells.

Many genes go through alternative pre-mRNA processing – splicing and polyadenylation - in different physiological conditions, with important implications in health and disease. Some of the fundamental question that remain unanswered and that we address in our group is how the cell chooses one polyA signal or a splicing signal instead of another in biologically relevant genes, how is this selection regulated and integrated with RNAPII transcription.

Polo/Plk1 is a key cell cycle kinase conserved in humans and *Drosophila*, overexpressed in a wide spectrum of cancers and a promising target in oncology. We are exploring new functions for Polo, specifically in transcriptional events.

The development of some human diseases (eg autoimmune diseases and cancer) is controlled by epigenetic mechanisms. We are identifying APA and AS "signatures" as new biomarkers in human diseases and we will apply our knowledge into the development of new diagnostic/therapeutic tools, in collaboration with more clinically oriented researchers.

PAST RESEARCH

We demonstrated that the physiological consequences of proper polyadenylation site selection in the 3' untranslated region are remarkable, as deletion of the distal polyadenylation signal of the polo gene in Drosophila is lethal, in a collaboration work with CE Sunkel and NJ Proudfoot. We have also established the molecular mechanisms underneath this observation: the longer mRNA isoform produced by distal polyadenylation signal choice is more efficiently translated into Polo protein than the shorter isoform, and this increase in Polo levels is necessary for rapid cell division. We further demonstrated that alternative polyadenylation is regulated by Polo and the RNA polymerase II elongation rate *in vivo*, and proposed a new model integrating transcription kinetics and alternative polyadenylation (Pinto et al, EMBO J 2011).

In human T lymphocytes we focused on CD6, which has been associated with multiple sclerosis. We have identified a new CD6 alternatively spliced isoform with a distinct function in the immunological synapse, in collaboration with A Carmo (Castro et al, JI 2007). More recently, we have dissected the molecular mechanisms behind the generation of the CD6 alternative isoform that is induced upon T cell activation. We showed that a complex combination of chromatin acetylation marks, increases in RNA polymerase II occupancy and CD6 transcription, and a decrease in the levels of the splicing factor SRSF1, all contribute to up-regulate this CD6 isoform following T cell activation (Da Glória et al, JI 2014).

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5 | RESEARCH GROUPS

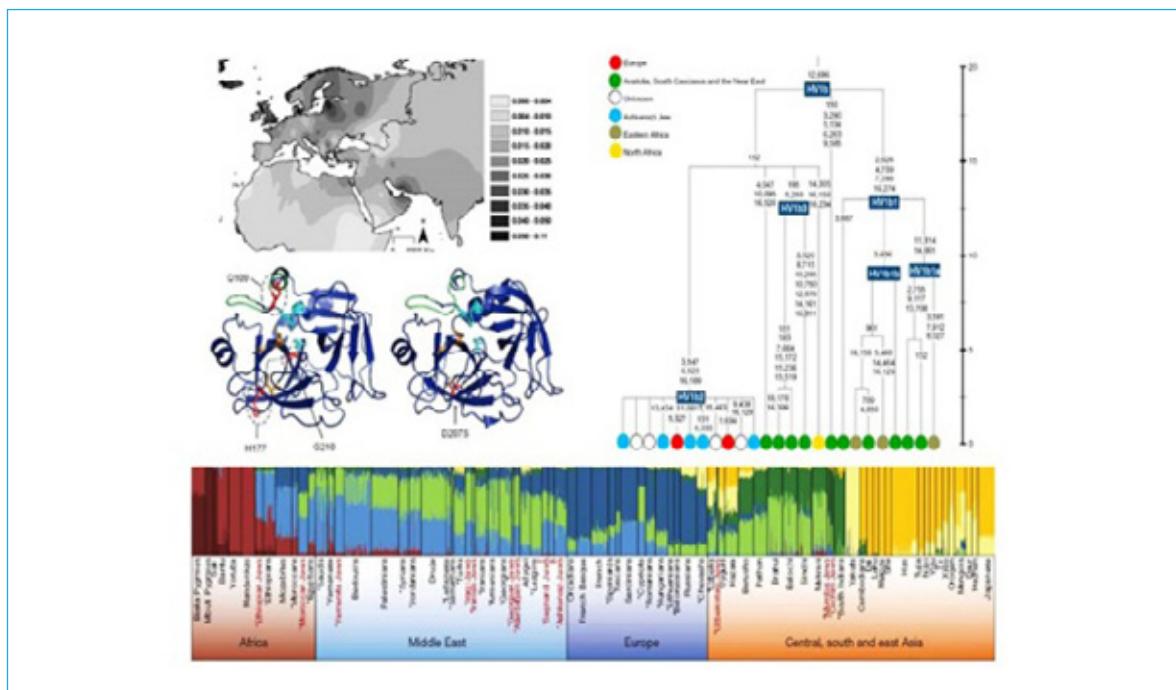
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TEAM MEMBERS

Affiliated	
Post-docs	2
PhDs students	1
Technicians	1

GENETIC DIVERSITY

GROUP LEADER: **Luísa Pereira**



ABOUT

The group aims to establish a bridge between human population and clinical genetics. We study evolution, drift, migration, expansion, bottleneck and selection, which are the major forces designing the worldwide genetic diversity. Then we apply the evolutionary based studies to identify candidate genes/variants which model human adaptation and health. Our work is largely multidisciplinary, involving collaborations with anthropologists, statisticians, bioinformaticians, molecular and clinical geneticists.

We are internationally recognised to perform top-research in the phylogenetic characterisation of world-wide mitochondrial DNA diversity. As mitochondria play major roles in many life-sustaining functions, they have been implicated in many complex phenotypes, including cancer. We have shown that the phylogenetic knowledge is essential to disentangle between neutral and pathologic variants, and we are investigating the cross-talk between the mitochondrial and nuclear genomes.

Another line of research consists in the study of proteolysis genes (SERPINS, WFDC and KLKs). These genes underlie a common European Mendelian disease (alpha1-antitrypsin deficiency) and are involved in reproduction biology and response against pathogens. We are identifying advantageous variants with impact on human health and detecting adaptive events in primate evolution.

Accompanying the advances of the genomics era, we are surveying genome-wide chips and whole genome sequences. These allow unbiased overall evaluations of candidate genes and population structure, which we are pursuing in the contexts of global human evolution and susceptibility to dengue infection.

PAST RESEARCH

Since July 2006, 5 FCT funded projects were coordinated by members of the group and we were co-applicants of 2 EU funded projects, a Marie Curie Initial Training Network (EUROTAST) and a FP7-HEALTH-2011-single-stage (DENFREE). Four members of the team obtained their PhD (3 in Univ. Leeds, UK; and 1 in FCUP), co-supervised by colleagues from international institutions. We published 58 papers (26% in journals with IF>10; 40% with IF>5). We maintain active collaborations with: statisticians David C. Samuels (Univ. Vanderbilt, USA) and Vincent Macaulay (Univ. Glasgow, UK); anthropologist Viktor Cerny (Academy of Sciences, Czech Republic); geneticists Martin Richards (Univ. Huddersfield, UK), Doron Behar (Rambam Health Care Campus, Israel), Belen Hurle (NIH, USA), Victor Quesada (Univ. Oviedo, Spain) and Anavaj Sakuntabhai (Institut Pasteur, France).

Headlines of our work: Out-of-Africa migration dated to 70 ka and confirmation of its first steps in the Gulf Oasis; autosomal Jewish background from the Near East, but 80% of maternal Ashkenazi lineages have European ancestry; mtDNA purifying selection eliminates pathogenic variants from population, although cancer samples escape their effect; selective signatures are detected in proteolysis genes, linked to response against infection (WFDC8, SPINT4 and SERPINB11) and shaped by reproduction (KLK2/3).

PUBLICATIONS

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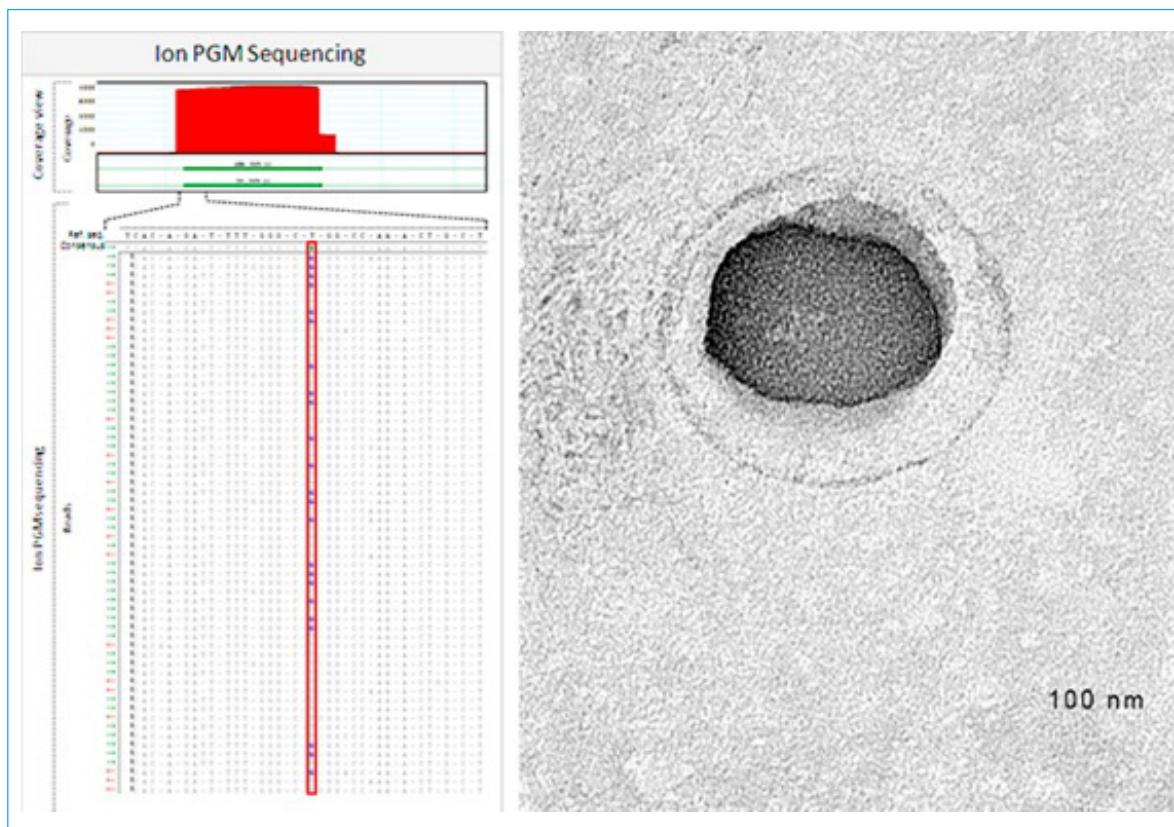
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TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists	2	Collaborators	1
Post-docs	3		
PhDs students	1		
MSc students	1		
Technicians	3		

GENETIC DYNAMICS OF CANCER CELLS

GROUP LEADER: José Carlos Machado



ABOUT

The scientific question that drives our research group is how genetic information is transferred between cancer cells, and how does that transference impact on the heterogeneity, diversity and plasticity of cancer cells. We want to understand how genetic mutations arise in tumor cells and how they spread in tumor cell subpopulations. We want to understand why these tumor cell subpopulations fluctuate over time, and how does this influence, and is influenced, by clinical events such as therapy and disease progression. We address these questions in two research lines:

- 1** The study of canonical “vertical transmission” cell division-based models where genetic information is transmitted between cancer cells and their progeny.
- 2** The study of extracellular vesicles called exosomes that are released by all cell types and that can transfer their cargo to various recipient cells, as an example of “horizontal transmission” of genetic information.

We believe that our group deals with a fundamental and innovative question in the field of cancer biology, that may allow for a better understanding of the dynamics of tumor progression as either the commonly accepted evolutionary competition between differentially adapted tumor cells, or alternatively, as an exosomes-mediated cooperative process to form a unit of malignancy that is able to invade, metastasize and relapse after treatment.

PAST RESEARCH

Jose C. Machado and Fatima Carneiro played a central role in gastric cancer-related research, including investigating the role of E-cadherin mutations in diffuse gastric cancer, genetic susceptibility to sporadic gastric cancer and the role of Helicobacter pylori infection in gastric cancer. JCM has a solid scientific background in human and cancer genetics with large experience in the study of both constitutional and somatic genetic changes in cancer, and in molecular genetic diagnosis. FC is an international reference in gastrointestinal pathology and a leading researcher in the ethiopathogenesis of gastrointestinal diseases. Sonia Melo joined our group recently, after spending the last three years at Harvard Medical School in Boston, USA, and at the MD Anderson Cancer Center in Houston, USA. SM has been playing a major role in investigating the role of exosomes in cancer and co-authored some of the key publications in this research area. Altogether, the three nuclear researchers of our group co-author more than 350 scientific publications, including publications in high-impact journals (IF>10) such as *Cancer Cell*, *Gastroenterology*, *Gut*, *Journal of the National Cancer Institute*, *Molecular Cell*, *Nature Genetics*, *Nature Cell Biology* and *New England Journal of Medicine*.

PUBLICATIONS

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5 | RESEARCH GROUPS

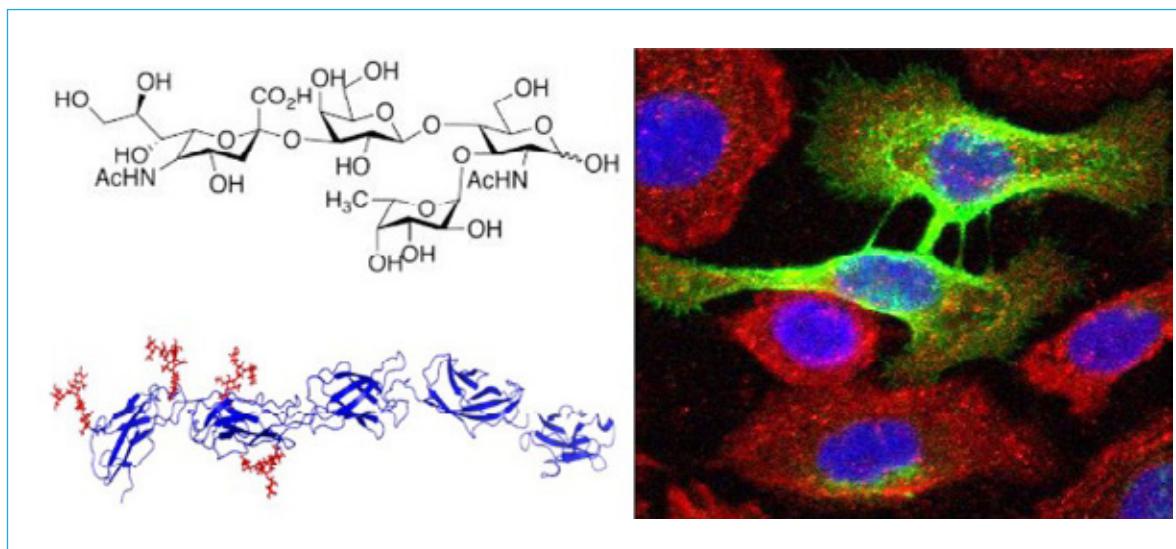
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TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists	6	Collaborators	2
Post-docs	4	Research Trainees	1
PhDs students	2		
Technicians	4		

GLYCOBIOLOGY IN CANCER

GROUP LEADER: Celso Reis



ABOUT

The group “Glycobiology in Cancer” focus on the role that glycosylation plays in human cancer aiming at the understanding of the molecular mechanisms controlling alterations of glycosylation that are important in the process of carcinogenesis and cancer progression.

The main research projects are:

- 1) Characterization of the molecular mechanisms underlying the glycan-mediated adhesion of *Helicobacter pylori* and the understanding of the importance of the host-pathogen crosstalk for the chronic infection and gastric carcinogenesis.
- 2) Evaluation of the role of glycans and glycan-binding proteins in cancer and pre-cancerous conditions addressing the molecular mechanisms controlling glycosylation of key molecules involved in cancer development and progression, and identification of novel glycan-based biomarkers for clinical application.

The group applies multidisciplinary approaches combining molecular and cell biology, biochemistry, genomics, (glyco)proteomics and animal models for understanding and addressing key mechanisms and functions played by glycosylation in cancer.

PAST RESEARCH

The group member's main achievements include:

- The understanding of how *H. pylori* modulates the host gastric mucosa glycophenotype and the evaluation of the impact of these glycosylation modifications on bacterial adhesion.
- The biological implications of glycosylation in *H. pylori* adhesion and infection using human clinical samples and genetically modified animal models.
- The design of novel glycan-based therapeutic strategies for *H pylori* infection.

5 | RESEARCH GROUPS

- The characterization of the role of glycans and the glycosyltransferases controlling their biosynthesis in key cancer related molecules, such as E-cadherin, TKR and CEACAMs, providing novel biomarkers with clinical applications.
- The characterization of glycosylation impact in the pathogenesis of pre-malignant conditions, such as inflammatory bowel disease.
- The elucidation of the sialylated glycans biosynthesis and the role of glycan-binding proteins in cancer progression.

PUBLICATIONS

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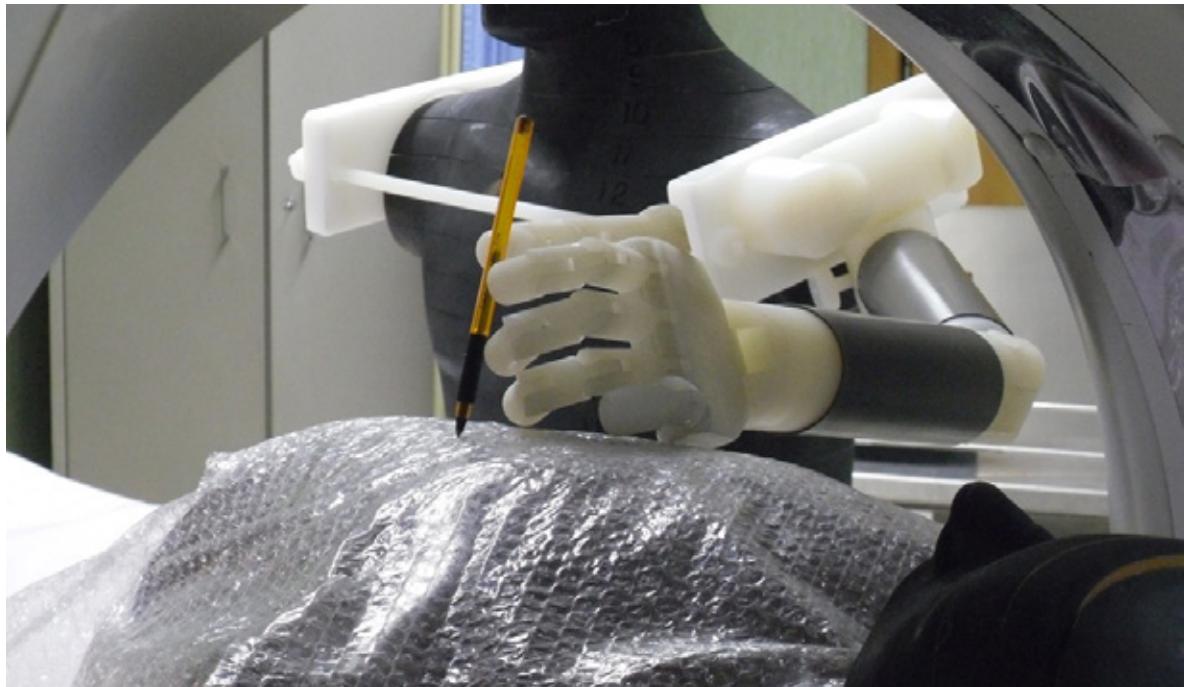
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TEAM MEMBERS

Affiliated	Non Affiliated
Senior scientists	3
Post-docs	1
PhDs students	5
Technicians	4
Visiting Researchers	1

MEDICAL PHYSICS, RADIobiology AND RADIATION PROTECTION

GROUP LEADER: João A. M. Santos



ABOUT

The Medical Physics and Radiation Protection Group was established in the beginning of 2008. The work of the group focuses on the application of the methodology of physics and radiobiology to solve specific problems related to health care, both from the perspective of the patient or in the perspective of the protection in the event of exposure to ionizing radiation. One of the areas in which the group is involved is the study of the radiobiological effects of radiotherapy with labelled peptides with somatostatin analogues that are currently being used as an effective treatment modality for somatostatin receptor positive, unresectable neuroendocrine tumors. Another area where the group works intensively is the survey of doses to the extremities of professionals during the procedure of CT fluoroscopy in interventional radiology.

PAST RESEARCH

During the FIBDOSE project, the following objectives were achieved: research in radioluminescent materials with emission in the infrared spectrum, optimizing final cost of dosimetric prototype, development of luminescent dosimeter point in optical fiber to measure dose brachytherapy place, with the endoscopic monitoring potential, dose in real time, development of dosimetric prototype to measure distributed volume, provision of various points of measurement distributed in 3D space of the field ionizing radiation, and examined by optical multiplexing to characterize and assistance in planning for Intensity Modulated Radiation Therapy (IMRT). Under the development of the Fluoro-CT project, several objectives have been accomplished: (i) comparative analysis of the results with and without the gripper; (ii) metrological characterization of dosimeters i2 RaySafe; (iii) bioethical issues associated with this new technology, the inherent imponderables risks, medical

physics role in its management, as described in the last milestone of the project, and (iv) characterizing the dose profile. The development of this project has led to several measures not initially foreseen. A Monte Carlo description and simulation of the used CT was accomplished.

An implementation of a Monte Carlo simulation of External Radiotherapy IMRT using PRIMO (Penelope code based software) was achieved and further work on this topic is under development.

Under the intraoperative electron radiation therapy (IOERT) project, the objective was to characterize in vivo dose distributions during pelvic IOERT for rectal cancer and to assess the alterations introduced by irregular irradiation surfaces in the presence of bevelled applicators. In vivo measurements were performed with Gafchromic films during 32 IOERT procedures. 1 film per procedure was used for the first 20 procedures. The methodology was then optimized for the remaining 12 procedures by using a set of 3 films. Both the average dose and two-dimensional dose distributions for each film were determined. Phantom measurements were performed for comparison. For flat and concave surfaces, the doses measured in vivo agree with expected values. For concave surfaces with step-like irregularities, measured doses tend to be higher than expected doses. Results obtained with three films per procedure show a large variability along the irradiated surface, with important differences from expected profiles. These results are consistent with the presence of surface hotspots, such as those observed in phantoms in the presence of step-like irregularities, as well as fluid build-up. Clinical dose distributions in the IOERT of rectal cancer are often different from the references used for prescription. Further studies are necessary to assess the impact of these differences on treatment outcomes. In vivo measurements are important, but need to be accompanied by accurate imaging of positioning and irradiated surfaces. These results confirm that surface irregularities occur frequently in rectal cancer IOERT and have a measurable effect on the dose distribution.

PUBLICATIONS

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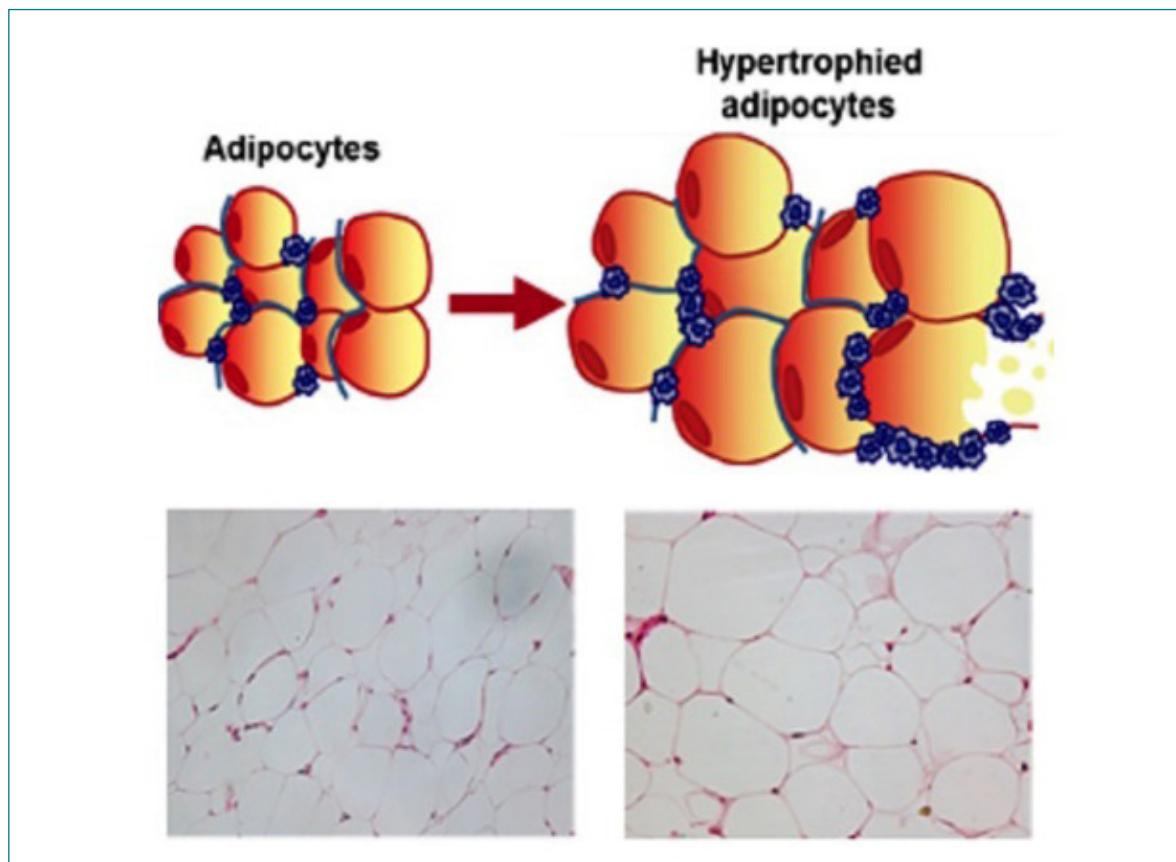
TEAM MEMBERS

Affiliated

Senior scientists	16
Post-docs	1
PhDs students	1
MSc students	11

METABOLISM, NUTRITION & ENDOCRINOLOGY

GROUP LEADER: Raquel Soares



ABOUT

The present group addresses the study of metabolic disorders that stand behind cancer, by investigating metabolic pathways, hormonal and nutritional cues, and preventive/ therapeutic novel approaches. Metabolic diseases incidence is increasing worldwide, being attributed to lifestyle features of XXI century, such as environmental factors (food components, stress, organic pollutants). These conditions, including obesity, diabetes, lipodystrophies and heart failure, result in increased morbidity and mortality rates, and contribute to high medical costs. Insulin resistance, glucose intolerance, hypertension and dyslipidemia are often seen as major contributors to chronic metabolic disturbances. Nevertheless, the ethiopathogenesis of these conditions is highly complex, partly due to the multiple and varied partakers.

The major outcome of our study is to identify putative disease causes, disease progression mechanisms and preventive/therapeutic strategies against these endocrine-related disorders. We currently live in a toxic food environment that may induce overeating, generating obesity and metabolic diseases. Nutrition research helps improve quality of life, creating knowledge not only to treat, but also prevent illness. Our expertise in both pedagogical and research nutrition domains, enables us to fulfill this crucial point, by developing and validating food and nutritional strategies that control the wide variety of metabolic syndrome-associated conditions.

PAST RESEARCH

The present team has a large research tradition in different R&D units located at FMUP, on basic and clinical research regarding metabolic disease. Interesting data has been obtained regarding:

- diet-induced metabolic syndrome (fructose ingestion or high fat diet) in animal models;
- the role of transmembrane transporters as vehicles for external-internal environment interaction (e.g. glucose, butyrate, diet polyphenols, bile acids, drugs, folic acid) in carcinoma cells and in gestational diabetes conditions
- organochlorine pesticide (POPs) detection in morbid obese patients adipose tissue; their effect during the periconceptional period on offsprings metabolic phenotype; epigenetic basis; offspring susceptibility for obesity and comorbidities
- Angiogenic paradox in diabetes in animal models; their modulation by diet polyphenols; Effect of Hyperbaric oxygen therapy in patient diabetic foot ulcers
- Lipodystrophies characterization as adipose metabolism dysfunction; results corroboration using adipocyte cultures and animal models
- new treatment approaches in patients with obstructive sleep apnea refractory to continuous positive airway pressure
- cohort of aortic stenosis patients stratified by diagnostic imaging and therapeutic strategies.

PUBLICATIONS

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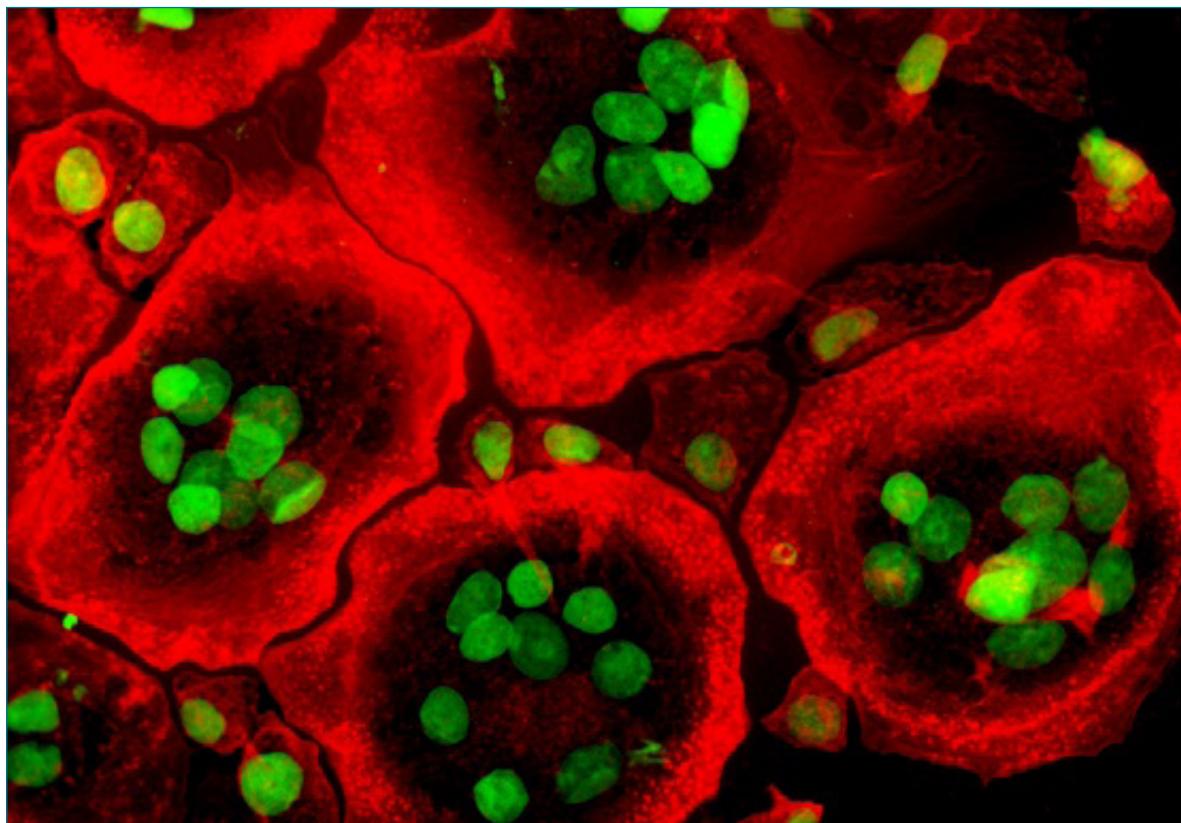
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TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists	25	Research Trainees	1
Post-docs	6		
PhDs students	10		
MSc students	4		
Technicians	1		

MICROENVIRONMENTS FOR NEW THERAPIES

GROUP LEADER: Mário Barbosa



ABOUT

The Microenvironments for NewTherapies group is constituted by complementary teams led by independent PIs, structured around the concept that microenvironments play a key role in cell behavior.

Our research activities have been designed to systematically dissect the cellular and non-cellular (extracellular matrix/ECM) microenvironment elements that contribute to reestablish homeostasis upon disease and/or injury. Envisaging clinical applications, our Group aims to bioengineer microenvironments in an effort to modulate host response, leading to tissue regeneration/functional restoration. The Group is focusing on different disease model-systems, i.e., osteoarticular conditions, intervertebral disc (IVD) degeneration, hematocardiovascular pathologies and the contribution of immune cells to cancer cell invasion and metastasis.

Research teams

1. Bioengineered microenvironments for repair/regeneration (PI: MA Barbosa)
2. Stem-cell microenvironments in repair/regeneration (PI: P Pinto-do-Ó)
3. Microenvironments in cancer cell invasion and metastasis (PI: MJ Oliveira)

Key words: Repair/regeneration and cancer microenvironments; Cell-biomaterial, cell-ECM, cell-cell Interactions; Stem/progenitor cells; Inflammation in repair/regeneration.

PAST RESEARCH

Bioengineered microenvironments for repair/regeneration

Biomaterials incorporating inflammatory signals were evaluated showing that: Chitosan(Ch) led to M2c macrophage polarization in vitro; the degree of acetylation of Ch affected macrophage phenotype in vivo; Fibrinogen(Fg)-modified Ch increased NK adhesion, modulated MSC invasion and lead to increased resorption by osteoclasts. In a rat critical size bone defect model higher bone formation correlated with higher proportion of B and myeloid cells in draining lymph nodes for Ch-Fg materials.

Stem-cell microenvironments in regeneration/repair

Pre-clinical testing of human Warton's jelly-derived MSC (ECBio) and of adult cardiac progenitors (CPC) revealed a paracrine beneficial effect upon MI. A central role of YAP/TAZ on adult CPC mechano-sensing and fate decision has been further demonstrated. Microenvironments in cancer invasion and metastasis

Human macrophages (MF) stimulate gastric and colorectal cancer cell invasion, motility/migration and proteolysis. MF-mediated invasion requires the activation of EGF receptor. M1- MF were less efficient in stimulating cancer cell invasion, migration, proteolysis and angiogenesis than M2- MF.

PUBLICATIONS

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TEAM MEMBERS

Affiliated	Non Affiliated
Senior scientists	7
Post-docs	7
Fellow	2
PhDs students	19
MSc students	4
Technicians	4
Visiting Researchers	1

MOLECULAR ONCOLOGY AND VIRAL PATHOLOGY

GROUP LEADER: Rui M. Medeiros

ABOUT

The Molecular Oncology & Viral Pathology Group was established in 2002.

The group research aims are especially focused on Pharmacogenomics and Molecular Epidemiology, including the role of tumor viruses on cancer development and treatment. The fundamental objective of the group is the molecular characterization of the mechanisms associated with the onset of cancer and its response to cancer therapy, particularly through the identification of biomarkers for cancer development and therapeutic outcome.

The research on Pharmacogenomics and Comparative Personalized Medicine is incorporated in individualized medicine that focuses on how biomolecular factors may influence individual responses to different medications affecting drug efficacy, drug side effects, and adverse events related to drug therapy. The long-term goal is the identification of responder patients and non responders to medications and thus avoid adverse events and optimize drug dose. Our research activities are aimed to define clinically useful tools to improve clinical outcomes as a result of the right medicine tailored specifically for that patient. The ultimate outcome of our research will be the development of rational drug treatment algorithms based on a patient's genotype linking to other predictive biomarkers, demographics, disease state, as well as other coadministered drugs. The group also develops projects in the field of tumor virology, studying the association of viral pathogenesis (especially Human Papillomavirus and Epstein-Barr Virus) with carcinogenesis. Furthermore, the influence of virus on tumor behavior is under evaluation for Comparative Personalized Medicine.

PAST RESEARCH

Since the beginning, the Molecular Oncology and Viral Pathology Group contributed to the training of young researchers in the several steps of academic activity (Bachelor, Master, Doctoral and Postdoctoral). During its running period the group Doctorate 14 PhD students (4 MD/clinicians and 10 Biomedical researchers) and contribute to the academic training of MSc (>50) and BSc students (>50). The scientific output of Molecular Oncology and Viral Pathology Group in the period 2002-2015 includes a total of 240 international peer reviewed publications. During 2014, we published 35 manuscripts and the sum of the impact factors of the journals where it published was 93.2. During 2015, we published 25 manuscripts and the sum of the impact factors of the journals where it published was 55. Specifically, during the period 2013-2015 a total of 84 manuscripts were published in Scopus indexed international peer reviewed publications leading to an average score of 28 per year. Researchers from the group have been invited to participate as reviewers/referees for leading journals in their working field as follows: Archives of Virology, Jornal of Medical Virology, Annals of Human Genetics, BMC Cancer, BMC Medical Genetics, Brazilian Journal Biological Research, Carcinogenesis, Cancer Detection and Prevention, Cancer Genetics and Cytogenetics, Cancer Letters, Cancer Drugs, Cancer Research, Disease Biomarkers, European Journal of Cancer, Gynecologic Oncology, Human Mutation, Human Reproduction, International Journal of Obesity, Indian Journal of Cancer, International Journal of Cancer, International Journal of Gynecologic Cancer, Journal of Clinical Pathology, Molecular Human Reproduction, Oncotarget, Pharmacogenomics, Pharmacogenomics Journal, PLOS One, Tumour Biology and Virology. Furthermore, researchers from the group were invited to Lecture/Talk in International meetings as invited speaker.1-Medeiros R, Pharmacogenomics of Castration-resistant Prostate Cancer. Second Congress

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of European Society of Pharmacogenomics and Theranostics Congress, Lisbon, September 2013;2-Medeiros R, Cervical Cancer: From Virology to Pharmacogenomics. 25th European Congress of Pathology, Lisbon, September, 2013;3- Medeiros R, Depression/Cancer interaction and Relevant Genes. Systems Medicine, Personalized Health and Therapy, 7th Santorini Conference Biologie Prospective, September 2014, Greece;4-Medeiros R, Ancestry, Pharmacogenomics and Leukemia. EORTC- Children Leukemia Meeting Group, October 2014 , Portugal;5-Medeiros R, Presenting the Scientific Programme of the 30th International Papillomavirus Conference & Clinical and Public health Workshops (HPV 2015).HPV2014- 29 th Int. Pap. Conf. & Clin. and Public health Workshops, August 2014, Seattle, USA;6-Medeiros R, Circulating HPV DNA and Hematogenous Spread. 30th International Papillomavirus Conference & Clinical and Public health Workshops (HPV 2015), September 2015, Portugal;7-Medeiros R, The Natural History of An HPV Conference. 30th International Papillomavirus Conference & Clinical and Public health Workshops (HPV 2015), September 2015, Lisboa, Portugal;8-Medeiros R, Reducing Cervical Cancer Risk and HPV Research. ECL-Annual Conference, November 2015, Belfast, Northern Ireland;

Moreover, researchers from the group were directly involved in the organization of International scientific events namely: 30th International Papillomavirus Conference & Clinical and Public health Workshops (HPV 2015), September 2015, Lisbon, Portugal and the Second Congress of European Society of Pharmacogenomics and Theranostics Congress, Lisbon, September 2013.

PUBLICATIONS

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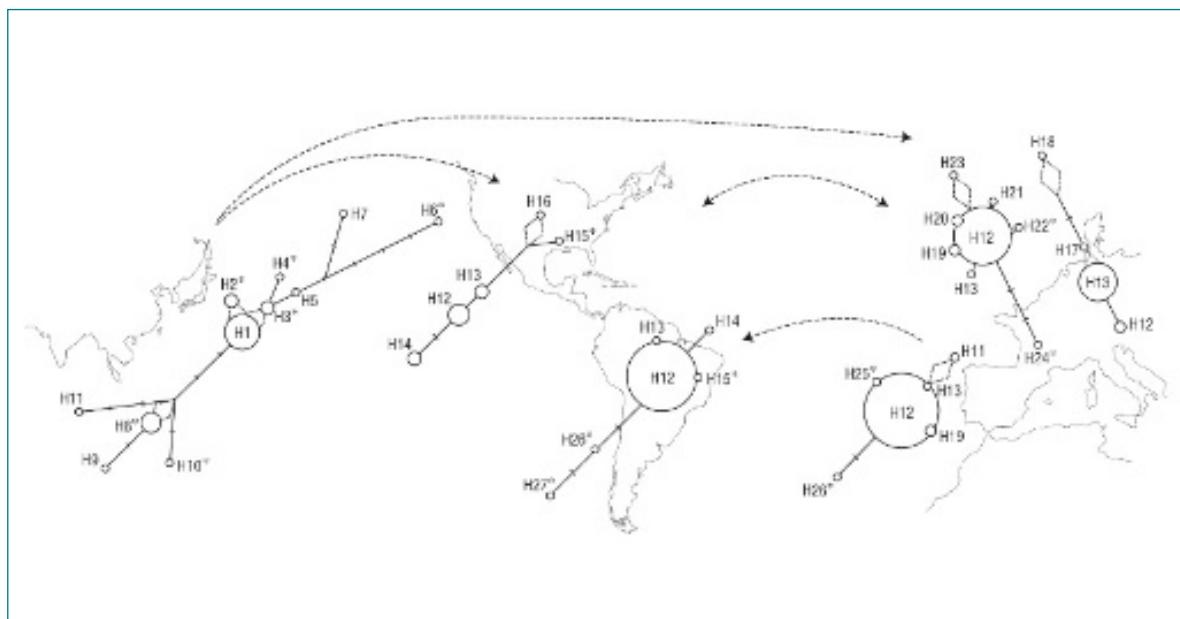
TEAM MEMBERS

Affiliated

Senior scientists	3
Post-docs	5
Clinicians with laboratory Sessions	2
PhDs students	9
MSc students	12
Graduate students	6

POPULATION GENETICS & EVOLUTION

GROUP LEADER: António Amorim



ABOUT

We aim at understanding the origin, evolution and consequences of genetic diversity, using a variety of model systems and approaches under the perspective of population genetics theory.

The development of tools for the identification of variants and their interactions contributing to the aetiology of, or the susceptibility to, genetic or infectious diseases is a main theme of research, in order to develop efficient screenings and diagnostics, and to identify individuals at high risk of developing a disease, improving genetic counselling and treatment, including the study of the genetic variation in the response to xenobiotics and pharmacogenetics.

The role of coding and non-coding sequences in gene expression regulation and the impact of structural genomic variation on fertility and disease susceptibility, is investigated by two strategic approaches: an evo-devo line based on the evolutionary comparison of specific genomic regions and their expression patterns in ontogeny, and genome wide methods.

Besides health an applied line of research is related to forensics and quality control issues through the development of methods, techniques, and the design of exercises, recommendations and guidelines.

The research strategy described for humans is also applied to the history, conservation and management of domesticates and laboratory animals, identification and diagnostic tools and food quality.

The Group is also devoted to the mathematical modelling of generalized kinship relations, automated DNA sequence analyses and to the history, migration and substructure of metapopulations.

PAST RESEARCH

CAG instability in Machado-Joseph disease
SCA2 repeats and ALS risk
Erythrocyte enzymes and malaria resistance
Hospital dispersion of *A. fumigatus*; mutations in antifungals resistance
Individual cancer risks and drug dosage
Epigenetic and genetic 2nd hits in gastric cancer
Pathogenic mutations origins and mechanisms
Epistasis in respiratory and Golgi complexes
Selection at mtDNA secondary structure and deletions associated with non-B conformations
Evolution and diversification of gene families
Overlapping genes: evolution of splicing and polyA signals
Software for analysis and classification of mtDNAs
Assessment of ancestry and interethnic admixture
Human fertility increases with marital radius
Y chr. genes essential for spermiogenesis
Transcriptional changes in a Turner mouse model; clustering of inactivation escapees
Derivation of the sets of pedigrees with same IBD and generalization to X-chr.
PCR method and software for species and breed identification in food or degraded samples
Neandertal X-chr. haplotype in all non-African populations
History of the Roma and pathogenic mutational spectrum

PUBLICATIONS

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2. PEREIRA F, SOARES P, CARNEIRO J, PEREIRA L, RICHARDS MB, SAMUELS DC, AMORIM A (2008) Evidence for variable selective pressures at a large secondary structure of the human mitochondrial DNA control region. *Mol Biol Evol.* 25(12): 2759-70. ; IF= 14.3 n°C= 15
3. SUAREZ-KURTZ G, AMORIM A, DAMASCENO A, HUTZ MH, MORAES MO, OJOPPI EB, PENA SDJ, PERINI JA, PRATA MJ, RIBEIRO-DOS-SANTOS A, ROMANO-SILVA MA, TEIXEIRA D, STRUCHINER CJ (2010) VKORC1 polymorphisms in Brazilians: comparison with the Portuguese and Portuguese-speaking Africans and pharmacogenetic implications. *Pharmacogenomics.* 11(9):1257-67; IF=3.4; n°C=10
4. LOPES AM, BURGOYNE PS, OJARIKRE A, BAUER J, SARGENT CA, AMORIM A, AFFARA NA (2010) Transcriptional changes in response to X chromosome dosage in the mouse: implications for X inactivation and the molecular basis of Turner Syndrome. *BMC Genomics.* 11(1): 82. IF= 4.0 n°C= 19
5. PEREIRA F, CARNEIRO J, MATTHIESSEN R, VAN ASCH B, PINTO N, GUSMÃO L, AMORIM A (2010) Identification of species by multiplex analysis of variable-length sequences. *Nucleic Acids Res.* 38(22):e203 if=8.8 n°C= 3

5 | RESEARCH GROUPS

6. SANTOS NP, RIBEIRO-RODRIGUES EM, RIBEIRO-DOS-SANTOS AK, PEREIRA R, GUSMÃO L, AMORIM A, GUERREIRO JF, ZAGO MA, MATTE C, HUTZ MH, SANTOS SE (2010) Assessing individual interethnic admixture and population substructure using a 48 insertion-deletion ancestry-informative marker panel. *Hum Mutat.* 31(2): 184-90; IF= 5.05 n°C= 70
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8. GOMES V, SÁNCHEZ-DIZ P, AMORIM A, CARRACEDO A, GUSMÃO L (2010) Digging deeper into East African human Y chromosome lineages. *Hum Genet.* 127(5):603-13, IF=4.5 n°C= 15
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10. MARTINS S, SOONG BW, WONG VC, GIUNTI P, STEVANIN G, RANUM LP, SASAKI H, RIESS O, TSUJI S, COUTIN-HO P, AMORIM A, SEQUEIROS J, NICHOLSON GA (2012) Mutational origin of Machado-Joseph disease in the Australian Aboriginal communities of Groote Eylandt and Yirrkala. *Arch Neurol* 69:746-51, IF=7.0 n°C=1

TEAM MEMBERS

Affiliated		Non Affiliated	
Senior scientists	5	Collaborators	3
Post-docs	5	Visiting Researchers	9
PhDs students	5		
MSc students	12		
Technicians	4		



6

CORE FACILITIES SCIENTIFIC PLATFORMS



ADVANCED LIGHT MICROSCOPY UNIT

ANIMAL FACILITY

BIOIMAGING CENTER

BIOCHEMICAL AND BIOPHYSICAL TECHNOLOGIES

BIOSCIENCES SCREENING UNIT

BIOINTERFACES AND NANOTECHNOLOGY

CELL CULTURE AND GENOTYPING SERVICE

GENOMICS CORE FACILITY

HISTOLOGY AND ELECTRON MICROSCOPY SERVICE

IN VIVO CAM ASSAYS UNIT

PROTEOMICS CORE FACILITY

TRANSLATIONAL CYTOMETRY

TUMOR BANK

X-RAY CRYSTALLOGRAPHY PLATFORM

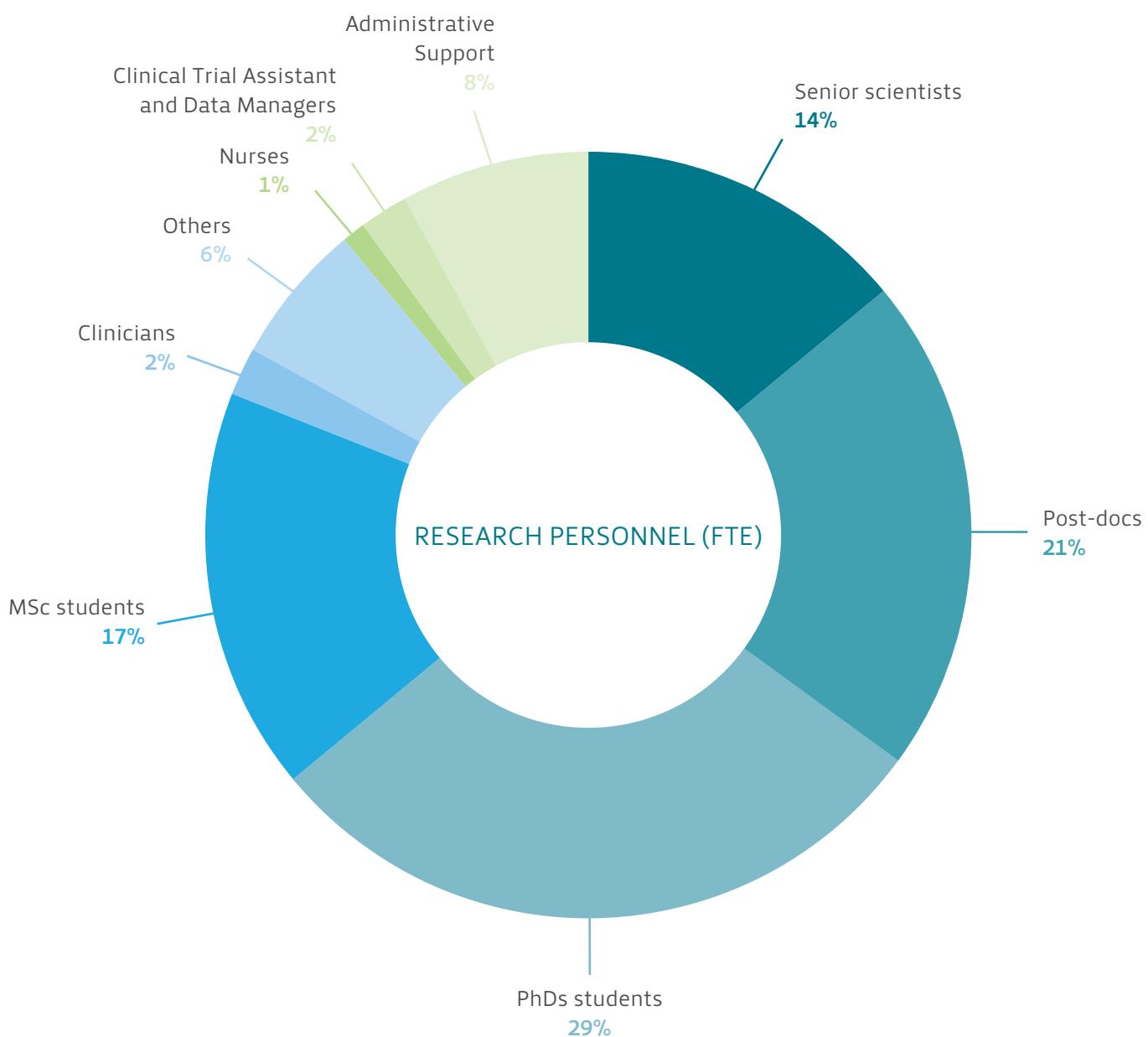


7

RESEARCH PERSONNEL (FTE)

7 | RESEARCH PERSONNEL (FTE)

Overall, more than 600 persons are directly involved in cancer research at P.CCC.



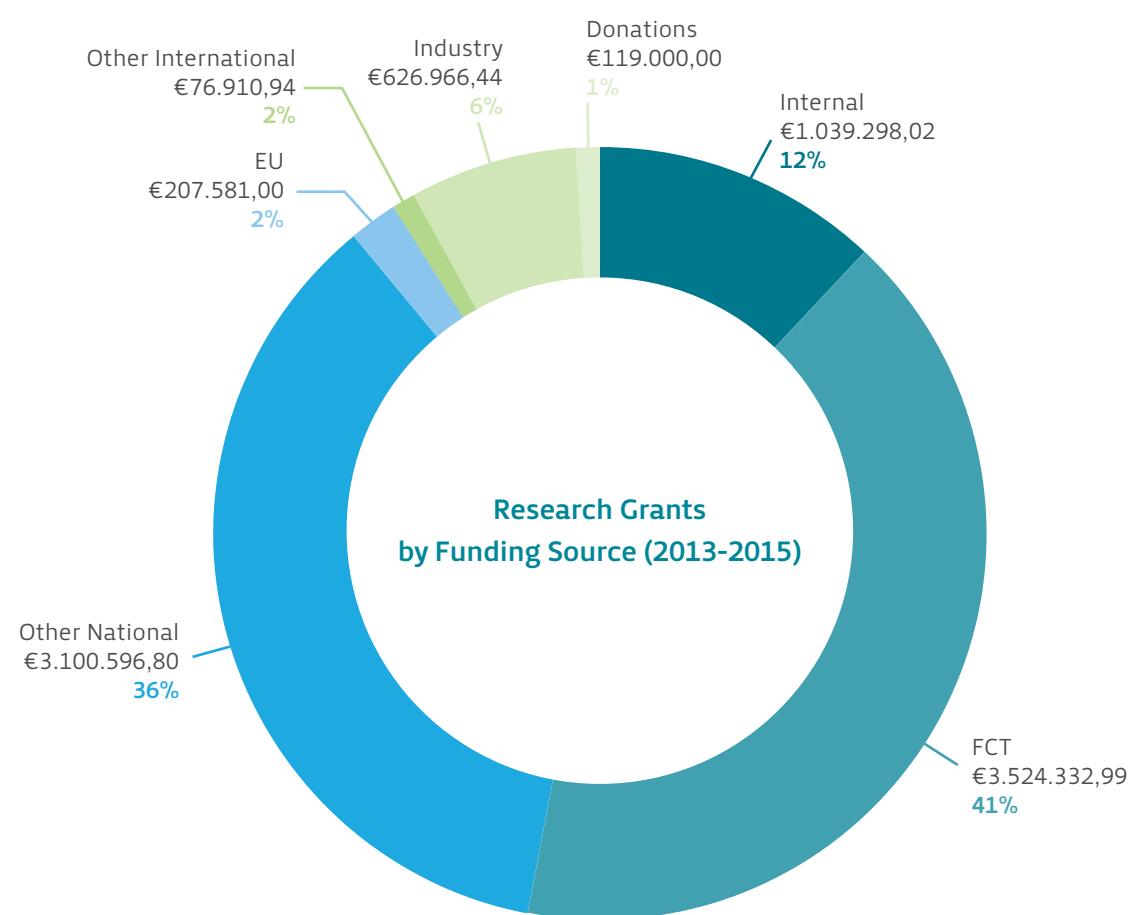
8

NUMBER FINANCED
ONCOLOGY RESEARCH
PROJECTS

CANCER RESEARCH GRANTS (2013-2015)

Funding Agency	Number
Internal	23
FCT	32
Other National	11
EU	1
Other international	2
Industry	9
Donations	2
Total	80

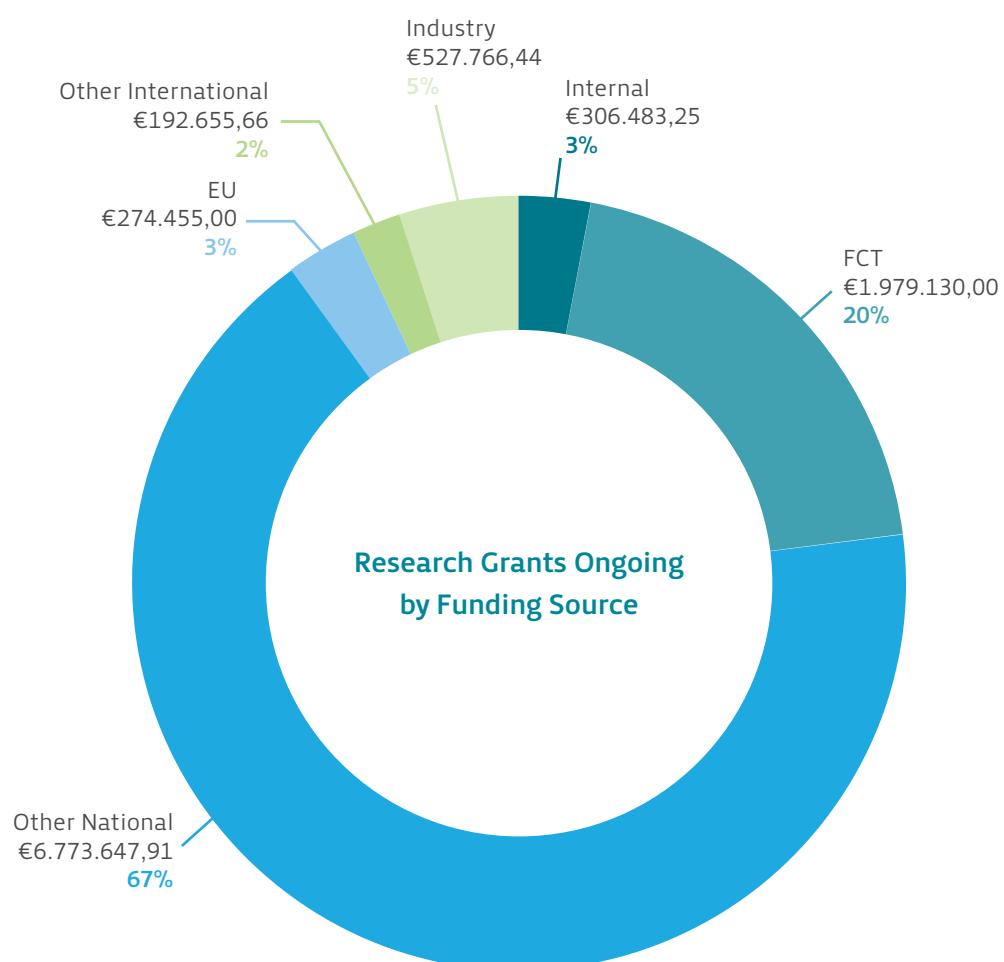
More than 8 Million Euros were obtained for research projects development.

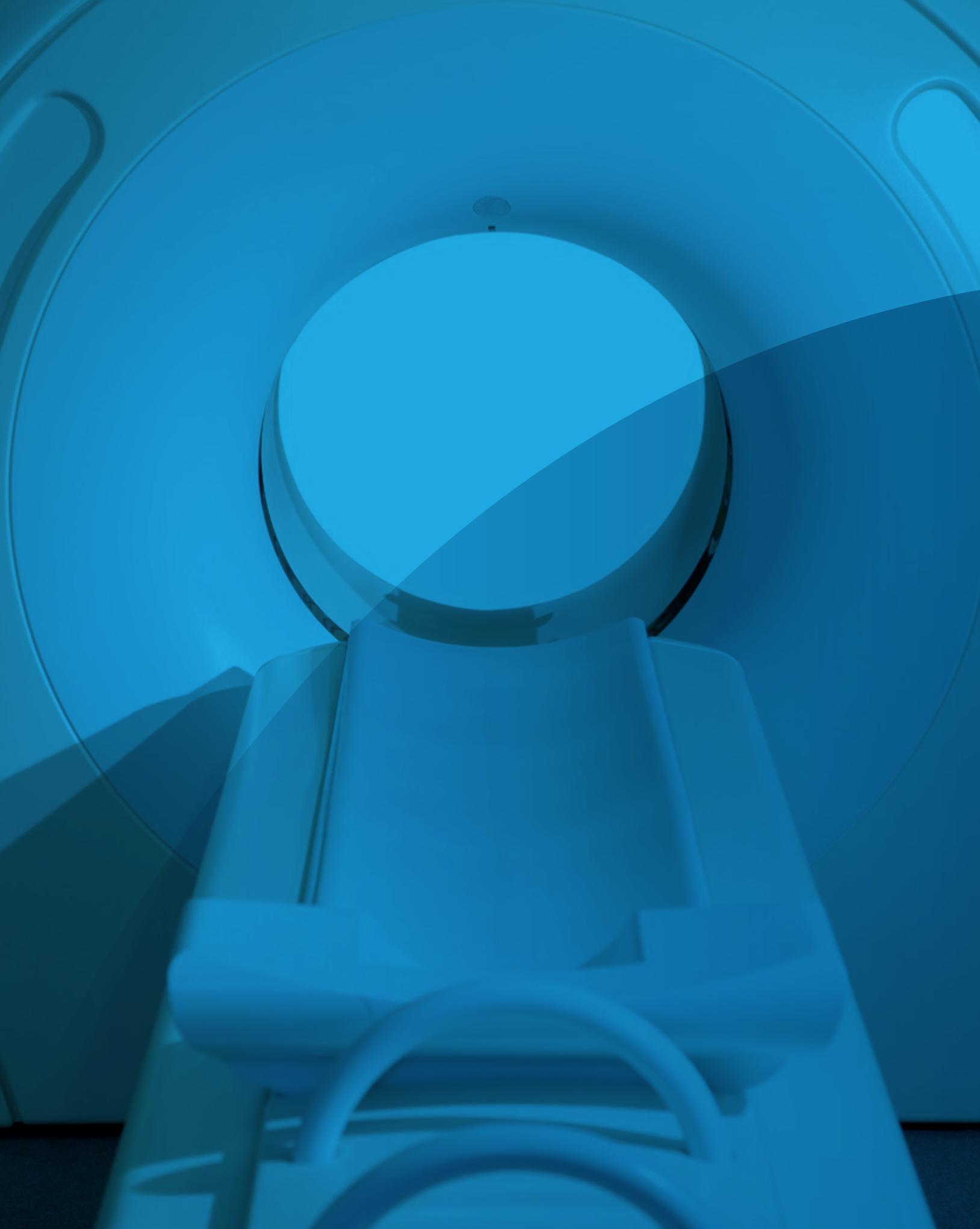


CANCER RESEARCH GRANTS ONGOING (IN ONCOLOGY)

Funding Agency	Number
Internal	12
FCT	19
Other National	15
EU	2
Other international	2
Industry	6
Total	56

The ongoing projects are directly supported by more than 10 Million Euros





9

LIST OF ONGOING PROJECTS

LIST OF PROJECTS ONGOING IN CANCER

Start Date	End Date	Title	Company Sponsor	Budget (€)
2010-06-01	2016-06-01	"FIBROSIS: dosimeters IN FIBER FOR DOSIMETRY IN VITRO, IN VIVO, IN RADIATION THERAPY FOREIGN AND BRACHYTHERAPY"	FCT	16.400,00
2011-05-12	2016-11-30	"Conhecer a doença: Os doentes em primeiro lugar"	FCG	80.000,00
2012-06-29	2016-06-20	CIMBA	MAYO Clinic Rochester	36.910,94
2013-05-01	2017-04-30	"Initial Training Network - Systems Glycobiology of Gastric Cancer."	FP7	207.581,00
2013-09-01	2016-11-30	"Using NGS to uncover structural and regulatory variation in Gastric Cancer"	Coimbra Genomics S.A	84.858,00
2013-11-01	2016-12-31	"Glycosylation of cellular receptors in Cancer."	Industry	269.808,44
2014-01-01	2018-12-31	"Epithelial stromal crosstalk as a major driver of colorectal cancer development and progression: an approach to identify its master regulations."	FCT	50.000,00
2014-01-01	2018-12-31	"Improving gastric cancer patient stratification towards personalised therapy"	FCT	198.168,00
2014-02-20	2017-02-19	"Estudo Acertive"	GEDII	15.000,00
2014-02-20	2017-02-19	"Estudo CISAE"	GEDII	10.000,00
2014-07-01	2016-10-01	"Identification of a potential new prognostic biomarker to select IBD patients that fail standard therapy"	Abbvie Lda (pharma)	120.500,00
2014-07-01	2019-06-30	"The functional role of exosomes in tumor heterogeneity and cancer all plasticity."	FCT	50.000,00
2014-09-01	2017-08-31	"HYPE - Healthy Youth through Prevention Education"	FCG	185.280,00
2014-09-01	2017-08-31	"Cytological training at European Standard through telepathology."	EU	66.874,00
2014-12-10	2016-12-31	"Atenção integrada ao doente oncológico no Hospital Central de Maputo - Reforço da capacidade institucional"	FCG	9.044,60
2015-01-01	2016-12-31	"Renal cell carcinoma-derived exosome: the microRNA content as a new disease predictive biomarker and an opportunity to invasive/metastatic disease management under the genetic background"	IPO-Porto	22.500,00
2015-01-01	2016-12-31	"Pharmacogenomic determinants of therapeutic response of urogynecological cancer: The European Pharmacogenetics Consortium Project (Eu-PIC)"	IPO-Porto	27.500,00
2015-01-01	2016-12-31	"Characterization of cytomegalovirus resistant strains in hematopoietic stem cell transplanted patients"	IPO-Porto	6.000,00
2015-01-01	2016-12-31	"Geometric uncertainties in external radiotherapy"	IPO-Porto	27.812,88
2015-02-01	2017-01-31	"Assess Somatic Alterations in Plasma of Lung Cancer Patients."	FPEM	10.500,00
2015-02-05	2017-02-05	"MK8259-022: An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under golimumab (Evolution)"	Merck	11.100,00
2015-03-01	2016-09-01	"Chemotherapy effect on Kinetics of regulatory T cells in Acute Myeloid Leukemia and high risk Myelodysplastic Syndromes"	Celgene	27.000,00
2015-03-01	2016-11-30	"microRNAs as biomarkers of drug response/resistance in multiple myeloma"	SPH	15.697,00
2015-04-01	2018-04-01	"MGAT5 as a potential new gene determining severity in inflammatory Bowel Disease"	GEDII	15.000,00
2015-04-21	2017-04-21	"Maratonas da Saúde 2015"	Maratonas da Saúde	25.000,00
2015-05-01	2020-04-30	"Understanding the impact of acquired and germline genetic variants in the complexity of gastric cancer."	FCT	50.000,00
2015-05-11	2017-05-10	"Núcleo nacional de Excelência para Formação avançada em áreas específicas da Patologia e Patologia Molecular"	FCG	12.000,00
2015-06-01	2017-06-01	UID/DTP/00776/2013 - UNIDADES DE I&D	FCT	150.000,00
2015-06-01	2017-06-01	"Stop Infecção"	FCG	20.000,00 €

9 | LIST OF ONGOING PROJECTS

Start Date	End Date	Title	Company Sponsor	Budget (€)
2015-06-15	2020-06-14	"Population genetics and molecular evolution of HIV and cancer tumor cells"	FCT	171.168,00
2015-07-01	2017-03-31	"Mesenchymal stem cells in inflammatory bowel disease: Therapeutic strategy or cancer promoters"	GEDII	9.000,00
2015-08-03	2017-08-02	"StaTreat - Estaminas como tratamento do cancro gástrico"	SPG	5.000,00
2015-10-15	2016-10-14	"Dog research antibody - cancer testis antigens"	KIROMIC	14.500,00
2015-11-01	2016-11-01	" O momento de prevenir - desenvolvimento de um modelo de comunicação audiovisual"	FCG	29.767,50
2016-01-01	2016-12-31	"Inherited predisposition to prostate cancer"	IPO-Porto	40.356,93
2016-01-01	2016-12-31	"Identification of somatic and germline mutations in circulating tumor DNA in ovarian cancer patients and in germline BRCA1/BRCA2 mutation carriers undergoing cancer screening"	IPO-Porto	20.000,00
2016-01-01	2016-12-31	"Detection of cancer specific genetic alterations in circulating free tumor DNA as a tool for early cancer diagnosis and follow up in Lynch syndrome patients"	IPO-Porto	20.000,00
2016-01-01	2016-12-31	"Assessment and validation of a panel of methylation-based Biomarkers in cell free DNA for Detection of recurrent first primary cancer (RFPC) and second primary cancers (SPC)"	IPO-Porto	27.473,67
2016-01-01	2016-12-31	CBEG-Funding	IPO-Porto	24.006,77
2016-01-01	2016-12-31	"Circulating Viral Genomes in the blood of cervical cancer patients"	IPO-Porto	15.000,00
2016-01-01	2016-12-31	"Development of monoclonal antibodies based in glicobiomarkers as therapeutics for chemoresistant bladder cancer"	IPO-Porto	25.833,00
2016-01-01	2016-12-31	PDT and immunoncology	EPTC_IPO	50.000,00
2016-02-01	2019-01-31	"The role of Exosomes in Tumor Heterogeneity: More than Just Bubbling"	FCT	199.086,00
2016-02-01	2019-01-31	"O yin e o yang das mutações somáticas na imunovigilância do cancro."	FCT	49.008,00
2016-03-01	2019-02-28	"Transferência horizontal de resistência à terapia: mudança de paradigma na monitorização de pacientes com cancro."	FCT	67.062,00
2016-05-01	2019-04-30	"Advancing cancer research: from basic knowledgment to application"	NORTE2020	6.332.358,81
2016-06-01	2019-05-31	"Gastric Microbiota & Cancer: More than Helicobacter Pylori"	AICR	155.744,72
2016-06-01	2019-06-01	"A 3D microarray platform for the high-throughput analysis of the role of the extracellular matrix in cancer-associated epithelial-to-mesenchymal transitions."	FCT	50.000,00
2016-06-01	2019-06-01	"PYLORIBINIDERS- Tratamento/diagnóstico da infecção gástrica utilizando biomaterias específicos para a Helicobacter pylori sem recurso a antibióticos"	FCT	50.000,00
2016-06-01	2019-06-01	"Tracing gastric cancer using quantitative bioimaging analysis."	FCT	13.200,00
2016-07-01	2019-07-01	Cellular glycoengineering for evaluation of post-translational modifications of receptors in cancer: theragnostic applocations	FCT	199.368,00
2016-07-01	2019-07-01	"Glycans as novel immunomodulators in Inflammatory Bowel Disease: na opportunity for new therapeutic strategies."	FCT	199.080,00
2016-07-01	2019-07-01	"Length matters: Causes and consequences of centriole length deregulation in cancer"	FCT	195.960,00
2016-07-01	2019-07-01	"Sensing dysfunctional E-cadherin cells in gastric epithelia (SENSE)"	FCT	51.600,00
2016-07-01	2019-07-01	"Inherited predisposition to prostate cancer: finding the missing heritability by combining exome sequencing and haplotype analyses in a population with strong founder effects"	FCT	196.030,00
2016-07-01	2019-07-01	Towards a single therapy with a synergistic drug combination against triple negative breast cancer and neuroblastoma by nucleoli-mediated multicellular targeting	FCT	23.000,00



10

PRIZES, HONOURS AND AWARDS

10 | PRIZES, HONOURS AND AWARDS

EACR Travel grant to Pedro Costa-Pinheiro, 23rd Biennial Congresso EACR, Pedro Costa-Pinheiro, Filipa Quintela Vieira, João Ramalho-Carvalho, Jorge Torres-Ferreira, Jorge Oliveira, Rui Henrique, Carmen Jeronimo. "The role of miR-375 in prostate carcinogenesis". Munich, Germany, 2014.

OECI-EurocanPlatform Fellowship to João Ramalho-Carvalho: EurocanPlatform's Summer course in Translational Cancer Research. Albufeira, Portugal, 2014.

OECI Meeting Bursary Award to João Ramalho-Carvalho: 5th EACR-OECI Joint Training course "Molecular Pathology Approach to Cancer". Amsterdam, The Netherlands, 2015.

EACR travel bursary to Inês Graça - 'Cancer Genomics' Inês Graça, Diogo Almeida-Rios, Filipa Quintela Vieira, João Ramalho-Carvalho, Jorge Oliveira, Rui Henrique, Carmen Jerónimo "The Oncogenic Role of PRMT6 in Prostate Cancer". Cambridge, UK, 2015.

Travel Award to João Ramalho-Carvalho: 11th World Congress on Urological Research. João Ramalho-Carvalho, João Barbosa-Martins, Lina Cekaitė, Jorge Torres-Ferreira, Inês Graça, Pedro Costa-Pinheiro, Ina Andrassy Eilertsen, Luís Antunes, António Morais, Jorge Oliveira, Ragnhild A. Lothe, Rui Henrique, Carmen Jerónimo. "Epigenetic disruption of miR-130a promotes prostate cancer by targeting SEC23B and DEPDC1". Nijmegen, The Netherlands, 2015.

Travel grant to Inês Graça CMST COST Action CM1406-EPIGEN MEETING. Inês Graça, Carmen Jerónimo. "Impact of Epigenetic modulators on malignant phenotype of Prostate Cancer Cells". Budapest, Hungary, 2015.

2015 prize by Grupo de Investigação de Cancro Digestivo (GICD)/Bayer Portugal. Diana Pinto, Carla Pinto, Joana Guerra, Manuela Pinheiro, Rui Santos, Ana Peixoto, Catarina Santos, Pedro Pinto, Paula Lopes, Rui Henrique, and Manuel R. Teixeira Contribution of MLH1 constitutional methylation for Lynch syndrome diagnosis in patients with tumor MLH1 downregulation.

Bolsa de Investigação APU/PFIZER 2013 Identification of bladder cancer stem cell glycoproteins based on chemotherapy sorting approach. Dr. Ricardo Cruz, Jorge Oliveira, Lúcio Santos, Alexandre Ferreira, Rui Vitorino, Francisco Amado, Carlos Palmeira, Luís Lima, Teresina Amaro, Elisabete Fernandes, Beatriz Parreira: GlycoStem-Cell: Identification of bladder cancer stem cell glycoproteins based on chemotherapy sorting approach.

Bluepharma innovation award 2013 DeCellMab. Angelina Sá Palma, Maria João Romão, Ana Luísa Carvalho, José Alexandre Ferreira, Luís Lima, Paula Videira. Trifunctional antibodies and dendritic cell-based technologies: a combined approach to cancer immunotherapy.

The Enrico Anglesio Prize was awarded to Clara Castro by Fondo Anglesio Moroni, in Ottawa (Canada) on 28 June 2014, for her presentation of the study "Predicting cancer incidence in the north of Portugal for the years 2013, 2015 and 2020".

1st Prize in Clinical Investigation (ex-Aequo), Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo, XIV Congresso Português de Endocrinologia, 2013. Miguel Melo, Gracinda Costa, Cristina Ribeiro, Francisco Carrilho, Maria João Martins, Adriana Gaspar da Rocha, Manuel Sobrinho-Simões, Manuela Carvalheiro, Paula Soares. Valor preditivo da tiroglobulina no momento da terapêutica ablativa com 131I utilizando TSH humana recombinante.

Prémio Prof. Manuel Pinheiro Hargreaves, Best Poster on “endocrinologia, Diabetes e Metabolismo” no XIX Curso Pós Graduado de Endocrinologia, Diabetes e Metabolismo, 2013. Pereira S.S., Morais T., Costa, M., Monteiro, M.P., Pignatelli, D. Immunohistochemistry markers in the differential diagnosis of adrenocortical tumors.

2º Poster Prize, Reunião Anual da Sociedade Portuguesa de Hematologia 2013. Hugo Seca, Raquel T. Lima, Gabriela M. Almeida, Manuel Sobrinho-Simões, Rui Bergantim, José E. Guimarães, M. Helena Vasconcelos “miR-128 induces DNA damage and sensitizes AML cells to etoposide and doxorubicin”.

Travel grant to Rui Ferreira - United European Gastroenterology Week (UEGW 2013). Berlim, Germany. Rui Ferreira, Jose L. Costa, Ceu Figueiredo, Jose C. Machado. Characterization of the gastric microbiota in patients with chronic gastritis and gastric carcinoma.

TEMTIA Best Poster Award, VI International Epithelial-Mesenchymal Transition Meeting. Alicante, Spain. Ana Sofia Ribeiro, Ana Rita Nobre, André Vieira, André Albergaria, Bárbara Sousa, Rene Gerhard, Raquel Seruca, Fernando Schmitt, Joana Paredes. P-cadherin activates Src-kinase: A new signaling pathway with implications in breast cancer progression.

Prémio do “melhor trabalho apresentado” na XXVI Reunião da Sociedade Portuguesa de Gasterenterologia e Nutrição Pediátrica (2013). Vilamoura, Portugal. Fátima Carneiro. O papel dos anticorpos IgA anti-endomisio no diagnóstico de doença celíaca numa amostra pediátrica.

GOLDBLATT AWARD 2013. International Academy of Cytology. Paris, France, 2013. Fernando Schmitt.

Best work presented in the Meeting “10th International Medical Postgraduate Conference”, Hradec Králové, Republica Checa. Bruno Pereira. Regulation of CDX2 and intestinal differentiation in homeostasis and carcinogenesis: unveiling the role of the RNAbinding protein MEX3A.

2º Prize for oral Communications. 13º Congresso da Sociedade Portuguesa de Oncologia, 2014, Porto. Nathalia Cristina Campanella, Ricardo Celestino, Ana Pestana, Cristovam Scapulatempo-Neto, Maria José Brito; António Gouveia; José Manuel Lopes, Denise Peixoto Guimarães, Paula Soares, Rui M. Reis. TERT increased transcriptional activity and oncogenic TERT promoter mutations in GIST.

Prize SPGH Best presentation. 18.^a Reunião da SPGH, 2014, Lisboa. Vinagre J, Almeida A, Pópolo H, Batista R, Lyra J, Pinto V, Coelho R, Celestino R, Prazeres H, Lima L, Melo M, da Rocha AG, Preto A, Castro P, Castro L, Pardal F, Lopes JM, Santos LL, Reis RM, Cameselle-Teixeiro J, Sobrinho-Simões M, Lima J, Máximo V, Soares P. Frequency of TERT promoter mutations in human cancers (Nat Commun. 2013;4:2185.).

1º Prize Investigação Clínica XV Congresso Português de Endocrinologia/65^a Reunião Anual da Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo, 2014. Melo M et al; As mutações do promotor da TERT são um indicador major de mau prognóstico em carcinomas diferenciados da tireoide.

Best Oral presentation. 3^a Reunião Ibérica de Cirurgia Endócrina, 2014, Porto. Boaventura P., Mendes A., Teixeira-Gomes J., Soares P. Hipertireoidismo Primário numa Coorte de Indivíduos Irradiados na Infância para o Tratamento da Tinea Capitis.

Grant Laço 2014. Joana Paredes “Dasatinib as an option to treat P-cadherin-overexpressing poor prognosis breast cancer”.

ASPIC Best Poster Award. 1st ASPIC Meeting, Lisbon, Portugal 2014.Ribeiro AS, Nobre AR, Monteiro J, Carvalho F, Vieira AF, Sousa B, Albergaria A, Seruca R, Santos NC, Paredes J. Targeting P-cadherin/Src induced mechanotransduction signaling: dasatinib as a promising therapeutic approach for invasive breast cancer.

Meeting Bursary to attend the EACR conference Goodbye Flat Biology: 3D models and the tumour microenvironment. Bruno Pereira, 2014.

The NSFCF - No Stomach for Cancer Foundation Award 2014. Carla Oliveira: “Defining the Contribution of Mutations in CDH1 Non- Coding Regions and Other Known Susceptibility Genes to Hereditary Gastric Cancer”; Collaboration and Partnership with David Huntsman from the BCCA, Vancouver Canada and the International Gastric Cancer Linkage Consortium (IGCLC).

The L'Oréal Portugal Medals of Honor for Women in Science 2014, Sónia Melo.

Best oral communication in Semana Digestiva 2014. Fátima Carneiro: Remissão endoscópica e histológica induzida pelo infliximab na colite ulcerosa moderada a grave – estudo hérnico”. Magro F., Lopes S, Lopes J, Rodrigues-Pinto E, Portela F, Silva M, Cotter J, João Moreira M, Lago P, Lopes C, Caetano C, Peixe P, Chagas C, Carvalho L, Lopes S, Rosa B, Albuquerque A, Camila C, Afonso J, Geboes K, Carneiro F.

Best oral communication in the XXVII International Workshop on Helicobacter and Microbiota in Inflammation and Cancer. Carlos ResendeL1B signaling leads to increased cell survival of gastric carcinoma cells”. Resende C, Regalo G, Durães C, Xiaogang W, Figueiredo C, Machado JC.

Young Scientist Award - Best Oral Communication, 11th Workshop on Pathogenesis and Host Responses in Helicobacter Infections, Helsingør, Denmark. Irina Amorim.



11

INTERNATIONAL COLLABORATION

RESEARCH CONSORTIA

CIMBA: The Consortium of Investigators of Modifiers of BRCA1/2 - a collaborative group of researchers working on genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers (coordinated by Georgia Chenevix-Trench, PhD, Queensland, Australia). IMPACT: Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls (coordinated by Ros Eeles, MD, PhD, London, UK).

PRACTICAL: Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome - a collaborative group of researchers interested in inherited risk of prostate cancer (coordinated by Ros Eeles, MD, PhD, London, UK).

BCAC: The Breast Cancer Association Consortium – a forum of investigators interested in the inherited risk of breast cancer (coordinated by Doug Easton, PhD, Cambridge, UK).

COGENT: COlorectal cancer GENeTics – a collaborative group of researchers working on inherited predisposition of colorectal cancer. EU funding by COST Action BM1206: Cooperation Studies on Inherited Susceptibility to Colorectal Cancer (coordinated by Sergi Castellví-Bel, PhD, Barcelona, Spain).

EPICHEM: Epigenetic Chemical Biology – a collaborative group of researchers working on epigenetic drugs. EU funding by COST Action CM1406 (coordinated by A Ganesan, PharmD, PhD, Norwich, UK).

IGO: International Glycoconjugate Organization (President, Prof. Jianxin Gu, China). The aims of the International Glycoconjugate Organization (IGO) are: 1. to further international collaboration for the study of glycoconjugates; 2. to ensure the proper arrangement of the biennial International Glycoconjugate Symposia; 3. to select recipients of the IGO Award and the IGO Young Glycoscientist Award as well as administer the Award Fund.

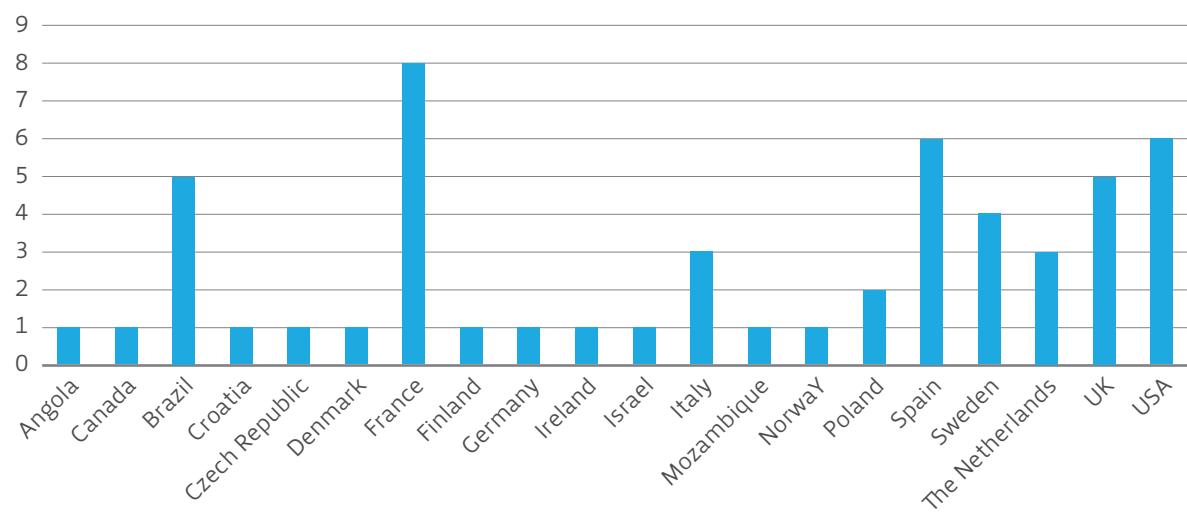
ME-HAD: European Network on Microvesicles and Exosomes in Health and Disease. A collaborative group of researchers fostering a multidisciplinary approach to enhance basic understanding and translational potential of Microvesicles and exosomes. EU funding by COST Action BM1202 (coordinated by Lorraine O'Driscoll, PhD, Dublin, Ireland).

StemChem: Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells. a collaborative group of researchers working on drug design and the medicinal chemistry of synthetic and natural compounds and investigators dedicated to the understanding the mechanisms governing drug resistance in cancer stem cells. EU funding by COST Action CM1106 (coordinated by Daniele Passarella, PhD, Milano, Italy).

Genturis ERN: European Reference Network (ERN) for GENetic TUMour RIsk Syndromes (GENTURIS) on CDH1-related Hereditary Diffuse Gastric Cancer. This consortium aims to improve the identification, diagnosis and surveillance of a wide range of rare inherited syndromes, predisposing to tumour development at any stage during life.

Individual groups have collaborative networks that are reflected in the intense co-authorship in publications. Some collaboration has been intense and stable, and those are the ones listed below:

International Collaborations Ongoing



ANGOLA

Clinica Sagrada Esperança, Luanda

CANADA

British Columbia Cancer Agency, Vancouver

BRAZIL

Barretos Cancer Hospital, S. Paulo

Centro de Pesquisa Experimental, Hospital de Clínicas de Porto Alegre, Porto Alegre

National Cancer Institute Instituto Nacional do Cancer (INCA), Rio de Janeiro

Universidade Federal de Minas Gerais, Belo Horizonte

Universidade Federal do Rio Grande do Sul, Porto Alegre

CROATIA

Bošković Institute, Zagreb

CZECH REPUBLIC

Nuclear Physics Institute, Prague

DENMARK

Faculty of Health Sciences of the University of Copenhagen

FRANCE

Centre National de la Recherche Scientifique (CNRS); Laboratory Epigenetic Targeting of Cancer (ETaC), Toulouse
INSERM, Grenoble
INSERM, Hôpital Saint-Antoine, Paris
INSERM, Nantes
INSERM, Strasbourg
Institut Pasteur, Paris
Institut de Radioprotection et de Surete Nucléaire (IRSN), Paris
University of Lille

FINLAND

University of Helsinki, Helsinki

GERMANY

University Hospital, Heidelberg

IRELAND

Dublin City University & National Institute for Cellular Biotechnology, Dublin

ISRAEL

Weismann Institute, Rehovot, Israel

ITALY

Cluster in Biomedicine, Trieste

University of Bologna

University of Siena

MOZAMBIQUE

Hospital Central Maputo

NORWAY

Institute for Cancer Research of the Norwegian Radium Hospital of Oslo University Hospital

POLAND

Instytut Fizyki Jadrowej, Krakow

National Centre for Nuclear Research, Swierk

SPAIN

Catalan Institute of Oncology, Barcelona

Complexo Hospitalar Universitario, Vigo

Universitat de Lleida, IRBLleida, Lleida

Universitat Autònoma de Barcelona

University of Navarra

University of Santiago de Compostela, Santiago de Compostela

Universitat Politècnica de Catalunya, Barcelona

SWEDEN

Karolinska Institute, Stockholm, Sweden
Umea University
University of Gothenburg
University of Uppsala, Uppsala

THE NETHERLANDS

The Netherlands Cancer Institute, Amsterdam
University Nijmegen Medical Centre, Nijmegen,
University of Groningen, Groningen

UK

Cancer Research UK Beatson Institute, Glasgow, Scotland
Paterson University of Manchester
University College London
University of Cambridge
University of Leicester & Leicester University Hospitals
University of Newcastle upon Tyne & formerly Newcastle Freeman Hospital

USA

Cancer Center & Louisiana State University
Center for Cancer Research, National Cancer Institute, Bethesda
Department of Cell Biology, Harvard Medical School, Boston
Massachusetts General Hospital, Boston
Memorial Sloan-Kettering Cancer Center, New York
University of Michigan
University of Nebraska Medical Center



12

INNOVATION

START-UP/TRANSFER OF KNOWLEDGE

I3S has a dedicated technology transfer Unit with the mission to create value from the commercial exploitation of intellectual property (I.P.) and to stimulate the creation and growth of spin-off companies based at IPATIMUP/I3S. Through consulting and coaching, the Innovation Unit helped researchers achieve the different steps in the innovation cycle of services and products derived from their core research activities. The Innovation Unit undertakes four main lines of action: 1) Registration of I.P. and Licensing to established companies; 2) Application to Innovation funding programs/awards; 3) Launching of new spin-off companies; 4) Direct presentation of projects to Venture Capitals and investors.

The Unit provides support to all steps of registration and exploitation of IP, through experts in IP with strong scientific background and previous experience in licencing IP to established companies. In the cancer research field we have licensed 3 proprietary products/methods/technologies.

We have partnerships with companies in the framework of innovation-oriented research:

Targetalent, co-promotion project to develop Digital cytology-based diagnostic platform for oral cancer;

U-monitor, research for development and clinical validation of urine-based method for bladder cancer surveillance.

The technology transfer unit supports all steps of business development, from idea to market. In the last 3 years we provided relevant business development support to at least 7 cancer-related projects, including preparation of business plans, applications to innovation awards, meetings with potential clients and investor presentations. Five of these have launched start-ups: Expertus (<http://www.expertus.pt/>); Bioinf2bio (<http://www.frombioinformatics2biology.com/>); Glyco4Clinics (<http://www.glyco4clinics.pt/>); Targetalent (<http://portugalstartups.com/2014/11/targetalent-winner-young-entrepreneurship-award/>); U-Monitor (<https://www.fundacioneveris.com/node/177>)

PATENTS 2013-2015

Description	Date	File number
BIMARCADORES SÉRICOS PARA DIAGNÓSTICO DO CANCRO DO ESTÔMAGO	10-01-2013	PT 106727
UTILIZAÇÃO DO RECEPTOR LRP1B OU SEUS DERIVADOS PARA MODULAR MÚLTIPLOS FACTORES NO AMBIENTE EXTRACELULAR	14-01-2013	PT 105286
N-GLICOSILAÇÃO DO RECETOR DAS CÉLULAS T: UM NOVO BIOMARCADOR NA DOENÇA INFLAMATÓRIA INTESTINAL	30-05-2013	PT 106981
LEITURA DIGITAL DA EXPRESSÃO PROTEICA NAS INTERFACES INTER- E INTRACELULARES.	30-05-2013	PT 106982
CO-EXPRESSÃO DE CEA E GLICANOS SLEX COMO BIOMARCADOR NO CANCRO GÁSTRICO	27-06-2013	PT 107028
BIOMARCADORES PREDITIVOS DA SOBREVIDA AO CANCRO GÁSTRICO	23-04-2014	PT 107603
TAMANHO E PERFIL PROTEICO DE VESICULAS EXTRACELULARES COMO MARCADORES DE MULTIRESISTÊNCIA ÀS TERAPÉUTICAS ANTI-NEOPLÁSICAS	08-08-2014	PT 107841
ENHANCED EFFECT OF TOPICAL ADMINISTRATION OF AN IMMUNOMODULATORY AGENT IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE	27-01-2015	PT 108173
MICROSFERES FOR TREATING HELICOBACTER PYLORI INFECTIONS	11-03-2015	EP 2844301
MÉTODOS UKTRASENSÍVEIS PARA DETECÇÃO DAS MUTAÇÕES C.-124 C>T E C.-146 C>T NOPROMOTOR DO GENE HTERT	30-04-2015	PT 108419
VOLTAGE-GATED POTASSIUM CHANNELS IN THE DIAGNOSIS AND TREATMENT OF FAMILIAL AND SPORADIC THYROID CANCER	30-04-2015	PT 108420
BLOCKING MUC16 GLYCOPROTEIN WITH ANTIBODIES AS A STRATEGY TO INHIBIT PERITONEAL CARCINOMATOSIS	23-07-2015	PT 108720
MICROBIOME MARKERS FOR GASTRIC CANCER	04-11-2015	PT 109319



13

EDUCATION AND ADVANCED TRAINING

PHD PROGRAMMES

GABBA (ICBAS, FMUP, FCUP, IBMC, INEB, IPATIMUP)

Biotech Health (ICBAS, FFUP, INEB, IBMC, IPATIMUP, Requimte, CHP)

Biomedicine (FMUP)

Pathology and Molecular Genetics (ICBAS, FMUP)

Molecular Oncology and Medicine (FMUP/ICBAS)

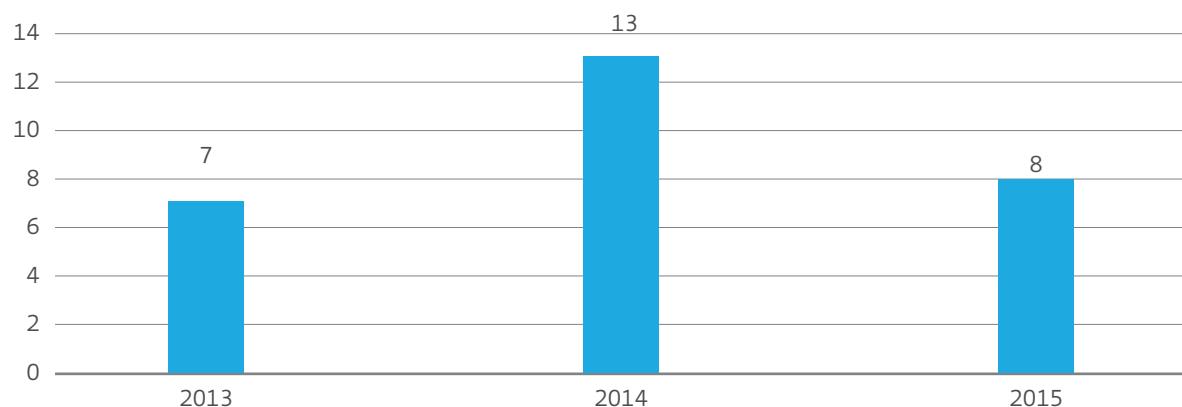
ADVANCED COURSES

Workshop on Cancer Research (IPATIMUP/ICBAS) (Yearly 2013, 2014, 2015)

PHD THESES (2013-2015)

Overall, 28 PhD theses in cancer research were completed at P.CCC.

Number of PhD theses completed per year



2013

- ▶ Renata Bordeira Carriço, FMUP, Suppressor-tRNAs as therapeutic tools for cancer associated syndromes: HDGC as a model system; Supervisor: Carla Oliveira
- ▶ Ricardo Jorge Pinto, ICBAS- UPorto, Characterization of a population with increased risk of gstric cancer: first degree relatives of early onset gastric carcinoma patients; Supervisor: Fátima Carneiro
- ▶ Luís Pedro Resende, ICBAS- UPorto, The role of the headcase gene in the Drosophila melanogaster testis and intestinal stem cells niches; Supervisor: Leonor David
- ▶ Bruno Miguel Correia Pereira, FMUP, Regulation of CDX2 and intestinal differentiation in homeostasis and carcinogenesis: emphasis on the role of MEX3A; Supervisor: Raquel Almeida
- ▶ Diana Raquel Fernandes Martins, ICBAS- UPorto, Transition from In Situ to Invasive Breast carcinoma; Supervisor: Fernando Schmitt
- ▶ Catarina de Sena Bastos Gomes, FMUP, Discovery of novel biomarkers in gastric cancer based on post-translational modifications of glycoproteins; Supervisor: Celso Reis
- ▶ Hugo Seca Teixeira, FFUP, Increasing sensitivity to drugs in leukemias by modulation of microRNA expression; Supervisor: Helena Vasconcelos

2014

- ▶ Ana Filipa Quintela Vieira, ICBAS- UPorto, The role of Histone methyltransferases & desmethylases in prostate carcinogenesis; Supervisor: Rui Henrique
- ▶ Maria Inês Pinho dos Santos Graça, ICBAS- UPorto, Impact of Epigenetic Modulators on the Malignant Phenotype of Prostate Cancer Cells; Supervisor: Carmen Jerónimo
- ▶ Ana Luisa Pereira Teixeira, ICBAS- UPorto, Signalling Pathways of EGF/EGFR-HER2 and TGF β 1/TGF β RII and the development of urologic cancer: Molecular Epidemiology and Pharmacogenomics, Supervisor: Rui Medeiros
- ▶ Ana Elisabete Pereira Correia de Oliveira, FFUP, Methotrexate Study of Genetic Factors Involved in Pain Perception and Morphine Analgesia in Cancer-Related Pain, Supervisor: Rui Medeiros
- ▶ Ana Carina Martins Pereira, ICBAS- UPorto, Role of Polymorphisms in Prostaglandin E2 (PGE2) pathway genes in Colorectal Carcinogenesis, Supervisores: Rui Medeiros
- ▶ Ana Barbosa de Sousa Nogal, ICBAS-UPorto, Proteomic Characterization of Lung Cancer and Chronic Obstructive Pulmonary Disease, Supervisores: Rui Medeiros
- ▶ Luís Carlos Oliveira Lima, ICBAS-UPorto, Predictive factors of response to therapy Intravesical BCG. Supervisor: Lúcio Lara Santos
- ▶ Cristiana Tavares Branco da Cunha, FMUP, Deconstruction CD44 - Engineering 3 D matrices to elucidate CD44 modulation in gastric malignancy; Supervisor: Raquel Seruca
- ▶ Lara Patrícia Marcos da Silva, FMUP, Mucin MUC16- CA125 cancer biomarker: biological functions and development of new biomarker assays; Supervisor: Leonor David
- ▶ Vânia Raquel Gomes Camilo, FMUP, Sox2 modulation in the establishment of CDX2-dependent intestinal metaplasia; Supervisor: Raquel Almeida
- ▶ Bárbara Beatriz Pinheiro Ribeiro de Sousa, ICBAS, Underlying the role of P-cadherin in cancer metabolism; Supervisor: Joana Paredes
- ▶ Irina Ferraz Amorim, ICBAS- UPorto, Canine gastric pathology. Helicobacter spp. Infection in dogs - an epidemiological and molecular study; Supervisor: Fátima Gartner
- ▶ Cristiana Branco da Cunha, FMUP, Deconstructing CD44 - Engineering 3D matrices to elucidate CD44 modulation in gastric malignancy, Supervisor: Pedro Granja

2015

- ▶ Maria de Lurdes Pontes Rebelo, FMUP, Autosomic SNPs and Forensics Biology; Supervisor: Rui Medeiros
- ▶ José Miguel Lourenço Aviz Miranda de Melo, Univ. Coimbra, Biomarcadores moleculares de prognóstico e seleção terapêutica em carcinomas da tireoide de diferenciação folicular; Supervisor: Paula Soares
- ▶ Rita Isabel Morais Pinto, FMUP, CDX2 Homeobox Gene in Cancer Glycoproteome Regulation, Supervisor: Leonor David
- ▶ Carlos Alberto Trindade Resende, ICBAS- UPorto, The Role of CREB and C/EBP transcription factors in gastric carcinogenesis; Supervisor: José Carlos Machado
- ▶ André Emanuel Ferreira da Silva, FMUP, Role of the mitochondrial Dynamics proteins in the mitochondrion-rich tumours; Supervisor: Valdemar Máximo
- ▶ Diana Alexandra Vieira Campos, FMUP, A glycoproteomics discovery strategy for gastric cancer biomarkers; Supervisor: Celso Reis
- ▶ Sandra dos Santos Carvalho, ICBAS- UPorto, Decoding E-cadherin glycans functions in cancer: from functional glycomics to clinical applications; Supervisor: Salomé Pinho
- ▶ Ana Patrícia Pereira Cardoso, FEUP, Novel therapeutic targets against cancer invasion: dissecting molecular mechanisms between macrophages and gastric cancer cells, Supervisor: Maria José Oliveira



14

SCIENTIFIC DIFFUSION

ORGANIZATION OF INTERNATIONAL CONFERENCES

XXII Porto Cancer Meeting 2013 "Translational Research in Cancer" Porto, April 2013
The third TASTE Workshop, Porto, October 2013
Glyco-T 2014 "9th International Symposium on Glycosyltransferases", Porto, June 2014
XXIII Porto Cancer Meeting 2015 "Stem Cells and Cancer", Porto, May 2015
OECI ONCOLOGY DAYS, Porto, June, 2015.

MEMBERS AT EDITORIAL BOARDS OF SCIENTIFIC JOURNALS

Advances in Anatomic Pathology
American Journal of Cancer Therapy and Pharmacology
Annales de Génétique
Annals of Human Genetics
BMC Cancer
BMC Clinical Pathology
Clinical Epigenetics
Computational Biology and Bioinformatics
Current Diagnostic Pathology
Dataset Papers in Biology
Dataset Papers in Oncology
Endocrine Pathology
Endocrine Related Cancer
European Journal of Cancer Prevention
European Journal of Human Genetics
Forensic Science International. Genetics
Frontiers in Genetics
Frontiers in Genomic Assay Technology
Helicobacter
Histopathology
International Journal of Medical Students
International Journal of Surgical Pathology
ISRN Genomics
Journal of Clinical Pathology
Journal of Integrated OMICS
Journal of Pathology
Open Pathology Journal
Pathology, Research and Practice
Patologia

PloS one
Research in Cancer and Tumor
Seminars in Diagnostic Pathology
The Open Forensic Science Journal
The Scientific World Journal
Ultrastructural Pathology
Virchows Archiv: an International Journal of Pathology
World Journal of Biological Chemistry
World Journal of Clinical Infectious Diseases
World Journal of Gastroenterology



15

SCIENTIFIC PRODUCTION
AT A GLANCE
(2013-2015)



130

15 | SCIENTIFIC PRODUCTION AT A GLANCE (2013-2015)

	Total
Number of international patents over the last 5 years	2
Number of peer-reviewed publications per year (in the year specified) international	611
Impact factor cumulative	3093
Number of publications with impact factor > 10	36
Number of publications with impact factor > 10 with first or last author from the centre	12
Number of publications with impact factor > 10 co-authored by the centre	25
Prizes and awards	30
PhD Theses	28

OECI EVALUATION CIRTERIA

Criteria OECI for CCC	PCCC
Number of peer-review scientific publications : > 125	611
Number of scientific publications with IF over 10: > 17	36
Number of scientific publications with IF 5-10: > 50	139
Active Clinical Trials : > 75	114



CAUTION
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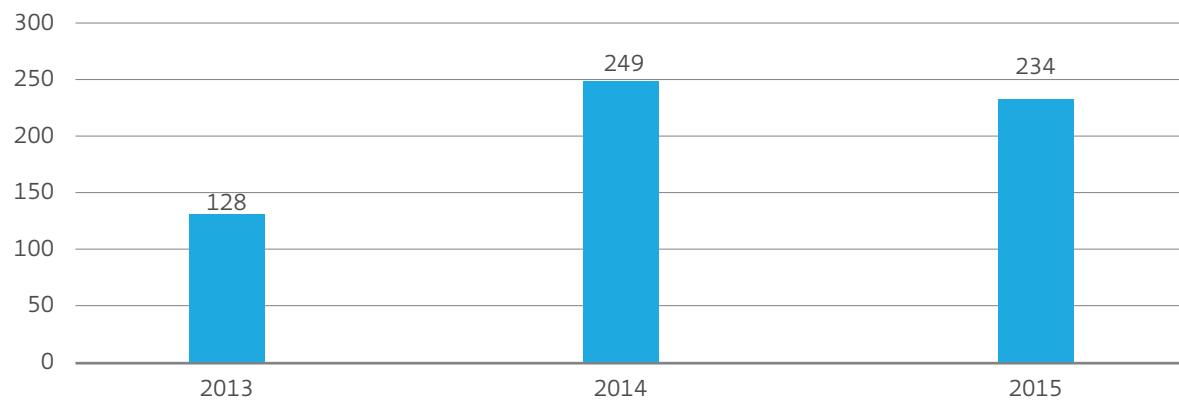
16

NUMBER OF PUBLICATIONS
PER YEAR (2013-2015)



16 | NUMBER OF PUBLICATIONS PER YEAR (2013-2015)

Number of publications per year



135



17

LIST OF PUBLICATIONS (2013-2015)



138

1. Abrantes D, Pimentel-Nunes P, Dinis-Ribeiro M, Coimbra M: Identifying technology interaction opportunities within a gastroenterology exam room. *Studies in health technology and informatics* 2015, 210:652-656. Impact factor: NA.
2. Abreu MH, Gomes M, Menezes F, Afonso N, Abreu PH, Medeiros R, Pereira D, Lopes C: CYP2D6*4 polymorphism: A new marker of response to hormonotherapy in male breast cancer? *Breast (Edinburgh, Scotland)* 2015, 24(4):481-486. Impact factor: 2.381.
3. Afonso J, Longatto-Filho A, Da Silva VM, Amaro T, Santos LL (2014) Phospho-mTOR in non-tumour and tumour bladder urothelium: Pattern of expression and impact on urothelial bladder cancer patients. *Oncol Lett* 8(4): 1447-1454.
4. Afonso J, Santos LL, Miranda-Goncalves V, Morais A, Amaro T, Longatto-Filho A, Baltazar F: CD147 and MCT1-potential partners in bladder cancer aggressiveness and cisplatin resistance. *Molecular carcinogenesis* 2015, 54(11):1451-1466. Impact factor: 4.808.
5. Aguiar A, Gomes Pereira H, Azevedo I, Gomes L: Evaluation of axillary dose coverage following whole breast radiotherapy: variation with the breast volume and shape. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2015, 114(1):22-27. Impact factor: 4.363.
6. Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, Benlloch S, Hazelett DJ, Wang Z, Saunders E, Leongamornlert D, Lindstrom S, Jugurnauth-Little S, Dadaev T, Tymrakiewicz M, Stram DO, Rand K, Wan P, Stram A, Sheng X, Pooler LC, Park K, Xia L, Tyrer J, Kolonel LN, Le Marchand L, Hoover RN, Machiela MJ, Yeager M, Burdette L, Chung CC, Hutchinson A, Yu K, Goh C, Ahmed M, Govindasami K, Guy M, Tammela TL, Auvinen A, Wahlfors T, Schleutker J, Visakorpi T, Leinonen KA, Xu J, Aly M, Donovan J, Travis RC, Key TJ, Siddiq A, Canzian F, Khaw KT, Takahashi A, Kubo M, Pharoah P, Pashayan N, Weischer M, Nordestgaard BG, Nielsen SF, Klarskov P, Roder MA, Iversen P, Thibodeau SN, McDonnell SK, Schaid DJ, Stanford JL, Kolb S, Holt S, Knudsen B, Coll AH, Gapstur SM, Diver WR, Stevens VL, Maier C, Luedke M, Herkommer K, Rinckleb AE, Strom SS, Pettaway C, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chokkalingam AP, Cannon-Albright L, Cybulski C, Wokolorczyk D, Kluzniak W, Park J, Sellers T, Lin HY, Isaacs WB, Partin AW, Brenner H, Dieffenbach AK, Stegmaier C, Chen C, Giovannucci EL, Ma J, Stampfer M, Penney KL, Mucci L, John EM, Ingles SA, Kittles RA, Murphy AB, Pandha H, Michael A, Kierzek AM, Blot W, Signorello LB, Zheng W, Albanes D, Virtamo J, Weinstein S, Nemesure B, Carpten J, Leske C, Wu SY, Hennis A, Kibel AS, Rybicki BA, Neslund-Dudas C, Hsing AW, Chu L, Goodman PJ, Klein EA, Zheng SL, Batra J, Clements J, Spurdle A, Teixeira MR, Paulo P, Maia S, Slavov C, Kaneva R, Mitev V, Witte JS, Casey G, Gillanders EM, Seminara D, Riboli E, Hamdy FC, Coetzee GA, Li Q, Freedman ML, Hunter DJ, Muir K, Gronberg H, Neal DE, Southey M, Giles GG, Severi G, Cook MB, Nakagawa H, Wiklund F, Kraft P, Chanock SJ, Henderson BE, Easton DF, Eeles RA, Haiman CA (2014) A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. *Nature genetics* 46: 1103-1109.
7. Albergaria A, Resende C, Nobre AR, Ribeiro AS, Sousa B, Machado JC, Seruca R, Paredes J, Schmitt F: CCAAT/enhancer binding protein β (C/EBP β) isoforms as transcriptional regulators of the pro-invasive CDH3/P-cadherin gene in human breast cancer cells. *PloS one*, 2013; 8: e55749. Article] DOI: 10.1371/journal.pone.0055749 PMID: 23405208.

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- 140
8. Albuquerque A, Cardoso H, Lopes J, Cipriano A, Carneiro F, Macedo G. Familial occurrence of nodular regenerative hyperplasia of the liver. *The American journal of gastroenterology*; 2013; 108: 150-1. [Letter] DOI: 10.1038/ajg.2012.370
<http://www.ncbi.nlm.nih.gov/pubmed/23287953>
 9. Albuquerque A, Rios E, Carneiro F, Macedo G. Evaluation of clinico-pathological features and Helicobacter pylori infection in gastric inflammatory fibroid polyps. *Virchows Archiv : an international journal of pathology*, 2014; 465: 643-7. [Article] DOI: 10.1007/s00428-014-1659-6 PMID: 25257403.
<http://www.ncbi.nlm.nih.gov/pubmed/25257403>
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 12. Almeida IF, Pinto AS, Monteiro C, et al. (2015) " Protective effect of *C. sativa* leaf extract against UV mediated-DNA damage in a human keratinocyte cell line." *J Photochem Photobiol B*. 2015 Mar; 144:28-34.
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 14. Almeida MT, Mesquita FS, Cruz R, Osório H, Custódio R, Brito C, Vingadassalom D, Martins M, Leong JM, Holden DW, Cabanes D, Sousa S. Src-dependent Tyrosine Phosphorylation of Non-muscle Myosin Heavy Chain-IIA Restricts *Listeria monocytogenes* Cellular Infection. *The Journal of biological chemistry*, 2015; 290: 8383-95. [Article] DOI: 10.1074/jbc.M114.591313 PMID: 25635050.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=25635050>
 15. Alvarez R, Esteves S, Chacim S, Carda J, Mota A, Guerreiro M, Barbosa I, Moita F, Teixeira A, Coutinho J, Principe F, Mariz JM, Silva MG (2014) What determines therapeutic choices for elderly patients with DLBCL? Clinical findings of amulticenter study in Portugal. *Clinical lymphoma, myeloma & leukemia* 14: 370-379.
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19. Amaral, C., Varela, C., Azevedo, M., Da Silva, E.T., Roleira, F.M.F., Chen, S., Correia-Da-Silva, G., Teixeira, N. Effects of steroid aromatase inhibitors on sensitive and resistant breast cancer cells: Aromatase inhibition and autophagy. *Journal of Steroid Biochemistry and Molecular Biology*, 2013, 135 (1), pp. 51-59.
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APPENDIX

IPATIMUP	2013	2014	2015
Services	1.453.589€	1.718.065€	1.820.041€
Contracted research service contract with industry)	119.869€	230.683€	159.501€
Projects - FCT	1.019.397€	1.440.816€	1.381.283€
Projects - other non-pharmaceutical entities	1.405.655€	2.008.831€	1.244.336€
Projects - Pharmaceutical industry	49.480€	34.000€	44.074€
Program Science/ Investigator FCT/ Incentive FCT	333.533€	345.022€	320.331€
Strategic project - CT	920.938€	920.938€	1.734.125€
Other incomings	418.003€	184.772€	172.132€
Financial incoming	185.682€	134.650€	97.102€
Grants and donations	163.453€	258.546€	62.677€
Total	6.069.598€	7.276.322€	7.035.601€

INEB	2013	2014	2015
Services	153.923€	352.625€	106.025€
Contracted research service contract with industry)	6.500€	13.963€	9.750€
Projects - FCT	639.576€	731.457€	724.863€
Projects - other non-pharmaceutical entities	607.285€	526.127€	479.627€
Projects - Pharmaceutical industry	0€	0€	0€
Program Science/ Investigator FCT/ Incentive FCT	116.936€	268.745€	126.229€
Strategic project - CT	751.400€	751.400€	1.316.871€
Other incomings	3.591€	29.928€	4.788€
Financial incoming	12.492€	1.381€	121€
Grants and donations	0€	0€	0€
Total	2.291.703€	2.675.626€	2.768.275€

IBMC	2013	2014	2015
Services	1.542.225€	1.194.364€	1.293.194€
Contracted research service contract with industry)	46.104€	70.341€	119.905€
Projects - FCT	3.307.371€	2.690.192€	1.780.146€
Projects - other non-pharmaceutical entities	1.086.516€	1.675.818€	1.304.457€
Projects - Pharmaceutical industry	48.000€	168.264€	271.237€
Program Science/ Investigator FCT/ Incentive FCT	765.024€	1.054.695€	1.012.656€
Strategic project - CT	2.254.186€	2.254.186€	3.105.900€
Other incomings	1.172.274€	1.345.820€	1.345.101€
Financial incoming	336€	1.356€	158€
Grants and donations	63.470€	51.720€	27.010€
Total	10.285.504€	10.506.755 €	10.259.764€

I3S	2013	2014	2015
Services	3.149.737€	3.265.054€	3.219.260€
Contracted research service contract with industry)	172.473€	314.987€	289.156€
Projects - FCT	4.966.344€	4.862.465€	3.886.291€
Projects - other non-pharmaceutical entities	3.099.456€	4.210.776€	3.028.421€
Projects - Pharmaceutical industry	97.480€	202.264€	315.311€
Program Science/ Investigator FCT/ Incentive FCT	1.215.492€	1.668.462€	1.459.217€
Strategic project - CT	3.926.524€	3.926.524€	6.156.896€
Other incomings	1.593.868€	1.560.519€	1.522.021€
Financial incoming	198.509€	137.387€	97.380€
Grants and donations	226.923€	310.266€	89.687€
Total	18.646.805€	20.458.704€	20.063.640€

IPO-PORTO	2013	2014	2015
Clinical Services	108.856.936€	114.507.219€	107.346.547€
Education and Training	478.027€	1.136.319€	622.892€
R&D	12.125.321€	11.249.760€	15.319.146€
Cross-cutting platforms for research support	7.134.903€	7.355.571€	7.927.000€
Funded Projects - own resources	3.949.178€	2.236.919€	5.851.249€
Funded Projects - public entities	250.199€	206.548€	252.080€
Funded Projects - private entities	791.041€	1.450.723€	1.288.817€
Donations	542.761€	485.286€	594.837€
Global Budget	122.003.045€	127.378.584€	123.883.422€

