'08

ANNUAL REPORT

INSTITUTO GULBENKIAN DE CIÊNCIA | IGC

FUNDAÇÃO CALOUSTE GULBENKIAN
Instituto Gulbenkian de Ciência

The **INSTITUTO GULBENKIAN DE CIÊNCIA** (IGC) is an international biomedical research and graduate training institute, founded and supported by the Calouste Gulbenkian Foundation, in Portugal. The IGC operates as a host institution, where research groups develop their research in complete financial and intellectual autonomy, underpinned by world-class services and facilities.

This Annual Report covers the Instituto Gulbenkian de Ciência's financial year, from 1st January to 31st December 2008.

Instituto Gulbenkian de Ciência

ADD Rua da Quinta Grande, 6
2780-156 Oeiras, Portugal

TEL +351 21 440 7900 FAX +351 21 440 7970

EMAIL info@igc.gulbenkian.pt

WEB www.igc.gulbenkian.pt

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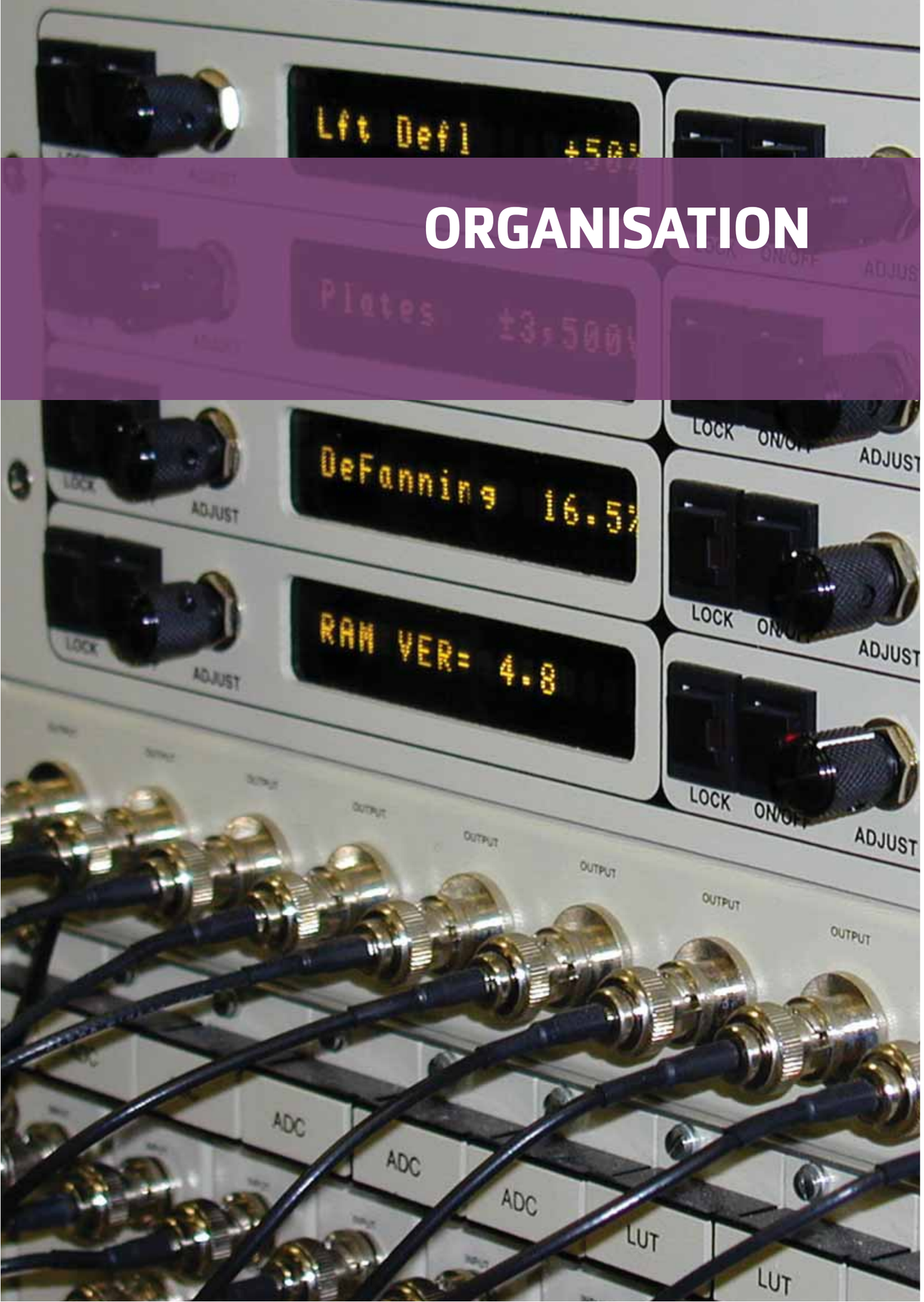

ORGANISATION

CALOUSTE GULBENKIAN FOUNDATION BOARD
The Calouste Gulbenkian Foundation is a Portuguese private institution of general public utility established by Calouste Sarkis Gulbenkian through his will, in 1953. The purposes of the Foundation are charitable, artistic, educational and scientific.

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SCIENTIFIC ADVISORY BOARD
The Scientific Advisory Board of the IGC oversees the scientific progress, graduate programmes, recruitment and overall performance of staff and research groups. The Scientific Advisory Board also advises the Board of the Calouste Gulbenkian Foundation on all matters of relevance to the mission of the Institute.

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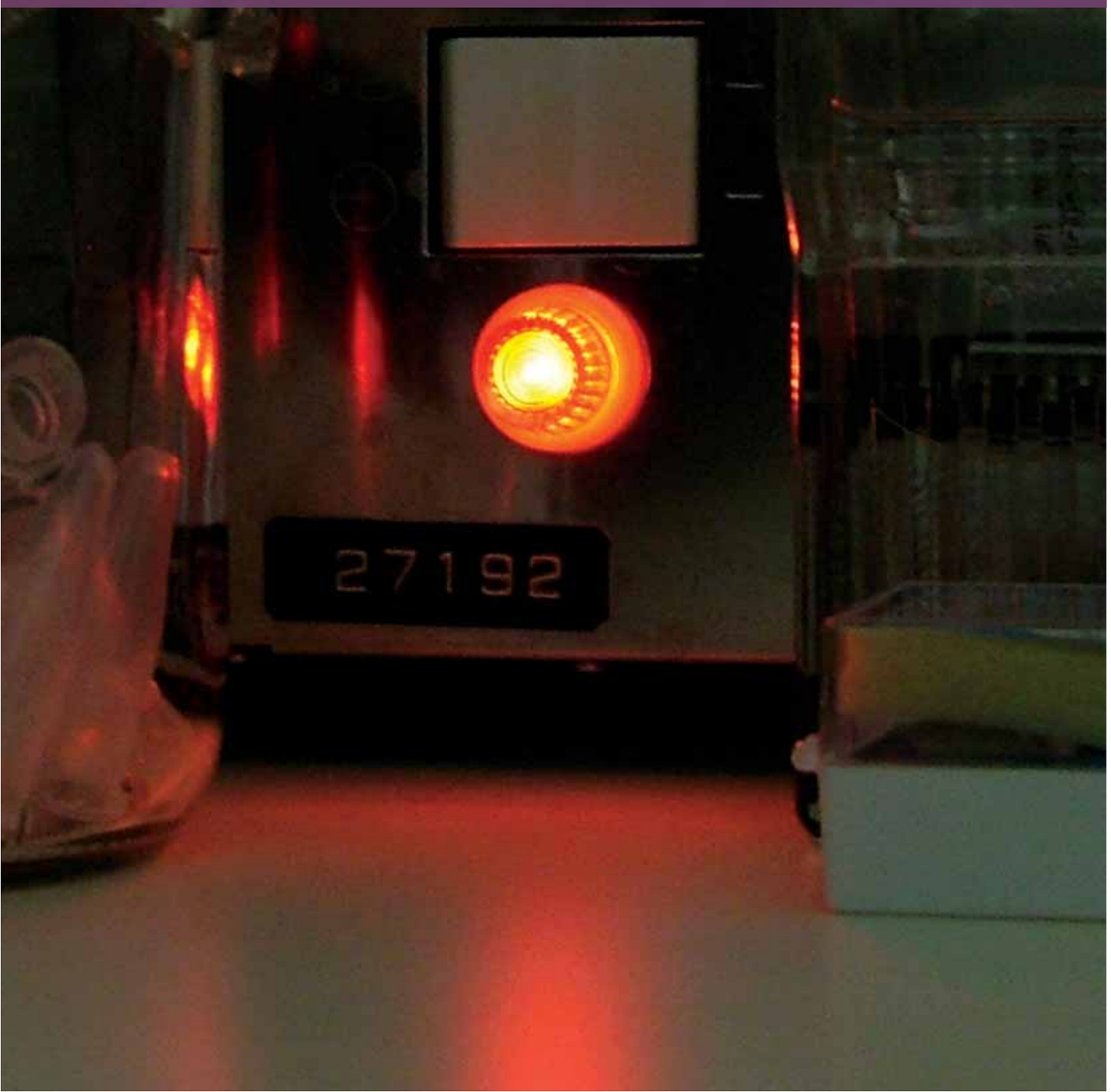
FOREWORD BY THE DIRECTOR



2008 was a special year for the IGC in a number of ways. To start with, it has been a decade since the first couple of new research groups were installed, following the decision of the Board of Administration of the Calouste Gulbenkian Foundation to shift the mode of IGC's operation to that of a host institution. Niels K. Jerne, who invented perhaps the most successful research institute of this type, used to say that, to be alive, institutions should follow "the usual rules" (of Biology, he obviously meant): to be born, grow to maturation and die, hopefully after having reproduced. Adding that 10 years might be the appropriate life cycle. Chronologically at least, the IGC has thus reached maturity, and should now be prepared to give way to new alternatives. All the more so as the IGC has already "reproduced": through the 460 PhD students who first met the wonders of science here, in the well over a 1,000 students, scientists and technicians who have worked here for the last 10 years. The hope is that they all took with them the values that serve as the basis for our activity, as well as the principles that have guided both small and important decisions through the years.
I would wish to know how to express our collective gratitude to those in charge of the governance of the Institute: the Board of Administration of the Foundation for its vision and for the autonomy awarded to the Institute, allowing us to operate with full responsibility and many degrees of freedom, yet with the constant guidance and support from the Board Member in charge of Science; and the Scientific Advisory Board that has helped so much to settle, from the start, those very values and principles.

I am fully aware that, when speaking about the life cycle of institutions, Jerne did not mean the name, the location, the buildings, labs and offices, perhaps not even the people or the scientific questions addressed. He was referring to the particular operational model, to the particular combination of individuals and their way of being in science that define the profile of an institution, the unique strategy on how best to use the available resources to reach a wider range of objectives and to further the values of science. Science progresses and so does the world. Hence, institutions must change. If, as Sydney Brenner says, "scientists solve problems", it is worth noting that the most relevant problems, be they local, regional or global, change with time, just as the best approaches to solve them change, as well as the conditions that must be met on the way to obtaining solutions. Only values and principles remain constant. It follows that the death of an institution may well be the birth of another, as good as or even better than the first, but different, in its mode of operation and in its objectives. Private Foundations are in a privileged position to experiment and innovate, taking risks in the drawing up of institutional models. In its direct intervention in science, the Gulbenkian Foundation has not shied away from doing precisely this. The IGC has thus far lived through three cycles: as the first lasted for 24 years, and the second for only 13, it is perhaps time to move on, after a decade in the third. There has been a tremendous evolution in the conditions for doing science in this country, and the IGC has contributed in significant manners to that evolution. Clearly, the missions that were given to the IGC in 1998 are less, if at all, appropriate to the current situation. Perhaps the best strategy to serve science and Portugal at the present time is no longer to "incubate new leaderships" or "serve as an entrance hall to the country", for we now have a scientific community with many excellent scientists who are open to the world. Perhaps what the country does need is an institution of true world excellence, capable of competing with the best in Europe and in the US, pulling along others to the same level of quality. Equally clear is the fact that such new objectives are not compatible with less than optimal conditions to compete in the global market for the best people and for the best working conditions: a lot was done with little money and small resources in the last 10 years, but were those objectives to be adopted, these are certainly no longer sufficient. The IGC has proven capable of the initial missions, and many of us here feel we are now ready to aim at other goals. Also because of scientists' attachment to the excitement of novelty; to continue doing the same after proving the point, however fundamental and enriching this may be, will inescapably bring with it "public-service routines" that command little imagination and dampen enthusiasm. And even the greatest dedication to a mission will not resist long if there is no fun. Perhaps time and conditions are ripe for the Institute to attempt now what was obviously impossible 10 years ago. The Institute has also shown that it delivers the best possible outputs for the resources it uses, offering some degree of confidence that it may be capable

of new challenges, risky as they may be. Peter Medawar wrote that science is the "art of the possible": great ideas are rather useless if they are so much ahead of time that they cannot be experimentally addressed and leave little or no impact in the collective thinking. Perhaps the same is true for the missions of scientific institutions.

Unquestionably, the Champalimaud Neuroscience Program at the IGC was of great help in the recent shaping of the Institute: it has attracted a number of excellent scientists and students, enriched the breath of the science done here, increased the density of productive interactions into new ground, and provided all of us with the rewarding feeling of actively participating in the building up of a new project. I must thank both the Champalimaud and the Gulbenkian Foundations for their wisdom and generosity in reaching this agreement that has already proven most valuable in the pursuit of stronger and better science. I also believe that everyone wins, as is usually the case with cooperation.

The second milestone that marked 2008 was the completion of the renewal of laboratory spaces, such that the IGC reached full capacity. Year after year, wing after wing, all labs were renovated, while the next labs were already in full research activity. Here is an example where the limitation in resources turned out to be favorable. Thus, would the resources have been available, we would probably had delayed launching all research and teaching activities for a year or two, renew all the buildings and start working only then. This would have avoided many a hassle with noise and dust for everyone, feelings of "pedestrian isolation" for the starting groups, and it would have resulted in a more homogeneous style of benches and offices, indeed, most likely in a more coherent planning of all spaces at the Institute. The wish to start working, however, was stronger, and brought at least two more unexpected advantages. On the one hand, the institution grew in size steadily and progressively, such that its shape could be effectively adapted to functional requirements, many of which could not have been anticipated, as they resulted from its very activity. The IGC's profile is certainly not derived from its physical characteristics in the first place; yet, as these progressively emerged from the growing institutional profile, they are now integral part of whatever defines the IGC as a "special" place, as a new member recently put it – a "science summer camp the whole year". There are, perhaps, no two identical offices or labs at the IGC; rather than causing inequities and potential conflicts, these conditions actually turned out to help establish the essential notion that there are no two equal researchers or research groups, rather each has its own identity and local profile, yet all contribute in equivalent, if very different, manners to the profile of the organism. On the other hand, the conditions of this period of growth that is now completed provided the extraordinary advantage that the IGC has never had free, empty spaces, not even when it hosted only a few groups. Empty labs are always sad to see, fostering two reactions that are both quite negative. The smaller problem is the unwanted, if justifiable, expansion of groups into space that remained unused, with the consequent loss of efficiency in space occupation and in the operation of the groups, let alone the desertification of human contacts (crowding is always positive, if we all share common goals); in turn, this establishes expectations and standards that will never be fully reversed in the future. The major problem, however, concerns the inescapable temptation of directions to rush to occupy the empty space at all costs, including lowering the stringent selection of newcomers. The IGC was protected from this: every time new spaces became available, there were groups –that had already been rigorously selected – waiting to move in and occupy them. With hindsight, I am now happy for the financial limitations that so often were a matter of serious concern.

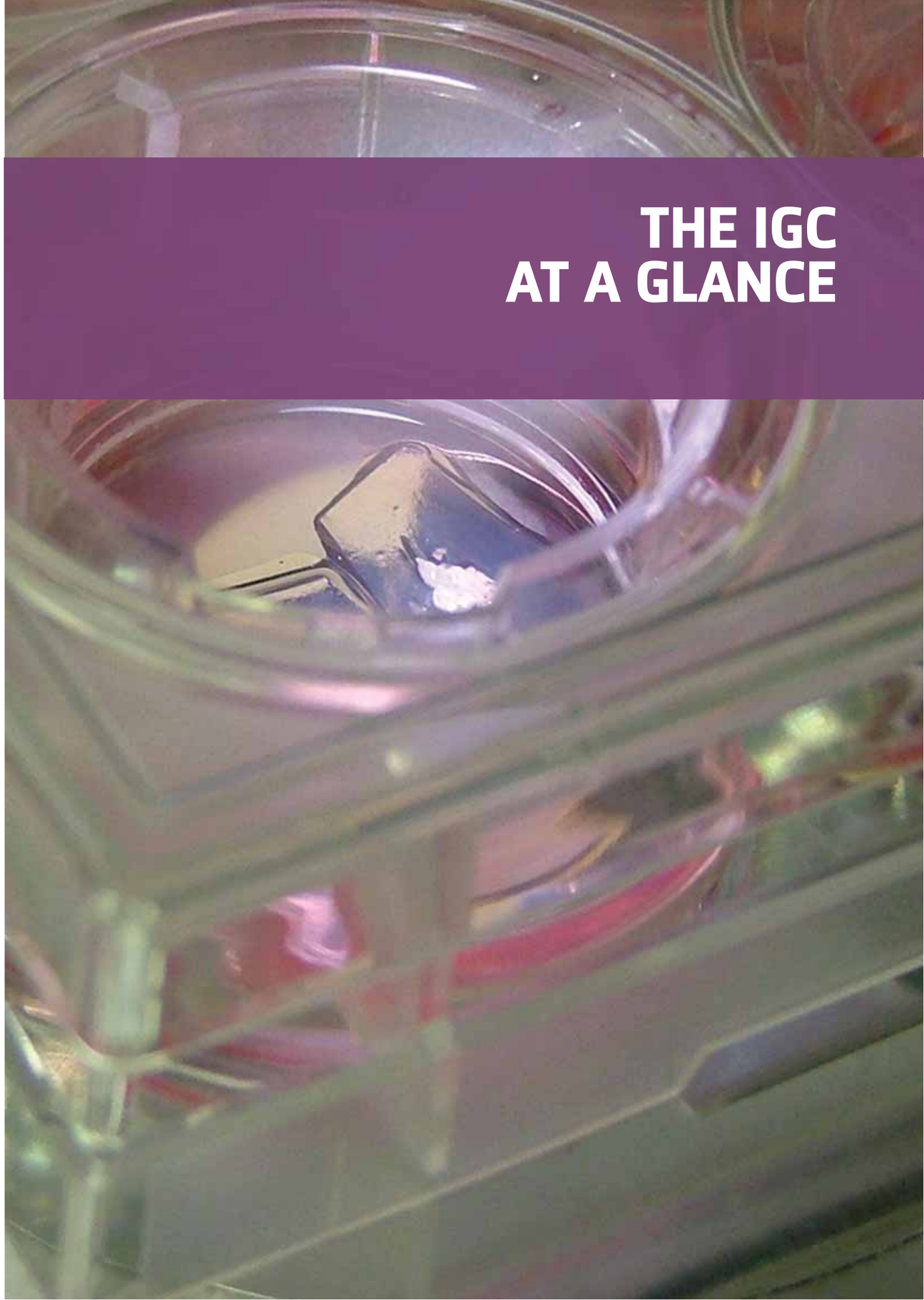
With the renovation now complete and the Institute having reached full capacity, the question of the ideal institutional size is again on the table, but it may now be approached with the wisdom gained from experience. The answer could not be clearer: considering the institutional profile that was intended, and the missions the IGC had to pursue, any further growth will necessarily result in loss of efficiency and quality, maybe even of the institutional "spirit". Thus, much of the Institute's strength, perhaps its greatest strategic asset and certainly much of the pleasure to work here, derive from the high density of human contacts, from the basic condition that everyone knows what everyone else is doing, allowing for novel productive interactions, for spontaneous, often unexpected, exchanges, sometimes for collaborations. In short, such network conditions embody the institutional life, in its scientific and human aspects, fostering creativity at all levels. Further growth, by decreasing the K/N value, will result in that everyone is a stranger to most of the others, in that each will be sitting in her/his lab or office corner, the institution becoming just a place where we all happen to work. If the basic strategy is to think the institution as a living organism, if this necessarily implies a network structure and the ensuing dynamics, it must become a necessary guideline on all decisions, also those concerning scientific matters, choices of research areas and groups. A network structure requires complementarities, that is, differences, to start with in the scientific interests that are primarily pursued by each group or individual. If we would all be doing, say, membrane protein traffic, or lymphocyte signaling pathways, or bacterial mutation rates, or genetics of human diseases, the institution would be a much narrower and hierarchical network, perhaps losing its dynamics to a few "dominant nodes" at the cost of all others. Differentiation of cellular components is the key to the evolution of multi-cellular organisms. Most importantly, if we would all be doing the same thing, we would certainly keep doing it for as long as the institution would survive, because innovation could only come from rare mutational events, rather than from the wealth of novelty generated by cooperativity, brought about by very diverse interactions and interests. And, for those who remain passionate for the extraordinary beauty of the wonders of nature, it would certainly be much duller to be here. The IGC currently hosts 43 research groups, nearly all with the standard size of a PI and five others (post-docs, students or technicians), a few twice this size, some with a Fellow and a couple of others. All these can only work because there are another 100 or so people who care to ensure that working conditions are the best possible, from helping to get funding and managing purchases and accounts, to setting up technical facilities and running them, to promoting what we do and science in general to society, to keeping it all tidy and pleasant, to convincing authorities that the IGC uses resources in a reasonable manner, to ensuring that students have the best education, to see to it that we do not spend too much money on electricity or CO_2. It is now my conviction that the ideal institutional size is an equilibrated mix of around 100 scientists (PIs, Fellows and post-docs), with 100 PhD students, and another 100 support personnel for technical and administrative responsibilities. With over 300 people, the IGC is slightly too big. Those who enjoy gardening know only too well that it is most useful, after periods of intensive growth such as the one we have undergone for 10 years, to trim, cut and clean up, for this will bring renewed strength and abundant flowering, let alone re-equilibrating the ecosystem, getting rid of the parasitic seeds, and helping each tree or bush to get the best shape and size in the arrangement of the most appealing garden. Short of pushing it to the levels of bonzai culture, this will have to be done now.

2008 was also a special year for a third reason: thanks to the notion of an "open institution" and to the "biology-based" policy of keeping high-turnovers in order to ensure survival, aiming at best serving other institutions in the country and promoting individual careers and mobility, well over a 1,000 persons have worked at the IGC since the reform. Having started in late 1998 with a few dozen, progressively adding more groups as conditions allowed, this is a most rewarding result. It would be enough that a fraction of those 1,000 who passed here would have taken with them the same commitment to science, the same joy of doing it with others, the same urgency of sharing its values, for a full reward of all the efforts and worries of all those who built the new IGC. For we all share the conviction that science is the solution to the world problems and the best investment in our collective future. The younger these new messengers, the longer their influence in society will be, the higher the probability that they will contribute solutions to some of our problems. Hence, the reward is greatest for all the students that first met the pleasures of serious science at the IGC. In September last year, with the arrival of the new students for the three PhD programs run here, the IGC had helped 450 doctoral students to start science, and each to find her/his own unique way. In October, the Institute was most pleased to incorporate the 10 students of the new Program for advanced scientific training of Medical Doctors – an initiative of the sector for Health and Human Development of the Gulbenkian Foundation, also supported by the Champalimaud Foundation

and by the National Research Council (FCT). The Program aims at educating a number of MDs currently working either as residents or specialists in public hospitals in Portugal, in experimental life sciences. It has been most satisfying for all of us at the IGC to discover how avid of modern scientific knowledge, how dedicated to fundamental values and devoid of "small" career plans, how excellent in sorting out relevant information, these student-MDs turned out to be. They are of course, older than science students and have had a longer university education; in addition, they have had some years of professional experience embodied in critical decision-making. As a result of their intrinsic quality and their excellent performance, the IGC has now altered the previous policy of recruiting PhD students as early as possible: for the first time in the 2009 admissions, there will be no age limit for applicants, and previous professional experience will be valued. No doubt, these MD-PhD students have been the single most important novel event in graduate education at the IGC over the last years. We do hope that the Program will continue, at least for as long as it will serve those who are truly committed to science-based medicine, that is, before its success will attract all sorts of career-minded opportunists. As we all feel that the new MD-PhD students became full IGC members, the number of PhD students who started at the Institute was brought to 460. From all of them, we expect two things: first, that they will for ever consider the IGC as their home, and will care to keep to the fundamental values they practiced here; second, that they will do great things in science for "l'honneur de l'esprit humain", as Karl Jaccobi put it, but also for the well being of individuals and society.

Lamarkian as it is, education is perhaps the noblest of all human activities, even for the Darwinians that we are. It represents the only path to escape the fantastic inexorability of biological evolution and laws that seem so "merciless" to the human point of view; it embodies the rise of "free will", would it only exist, above the randomness of mutations, the workings of human invention to speed up, to within a life time, the extremely slow biology towards a better society. In Biology, education is particularly rewarding, for it uses a most solid anchor, provided by understanding evolutionary principles. Looking at the world in that light, knowing that humans are of the same nature and have the same origin as all other living beings, comprehending that the tremendous success of human societies owes only to the size of the brain and higher levels of neuronal cooperativity, provides for a full understanding of education: the contrast between the uselessness of individuals and the unique value of each human being. The Institute is most proud for two prizes it has been awarded in 2008. The University of Lisbon distinguished the IGC for achievements in graduate education, a Prize that acquires a very high significance coming from the Institution that is officially entitled with that mission. The IGC was also awarded the "Ciência Hoje - Seeds of Science Prize" for Science Communication, reminding us all here that our collective mission may well be summarized to doing and promoting science for a better world.

ANTÓNIO COUTINHO
Director



THE IGC AT A GLANCE

'When I came to the IGC to interview for a Group Leader position, I felt like I was at a science Summer camp', says Lars Jansen, a Dutch molecular geneticist, who joined the IGC in 2008, straight from a post-doc in San Diego, California. Indeed, visitors to the IGC (some 200 invited speakers and even more students each year) are struck by the dynamic, thriving nature of the IGC, by the commitment and enthusiasm, drive and leadership skills of IGC researchers, right through from undergraduate students to group leaders.

As a leading life science research and graduate training centre, the IGC is unique in many ways. Its horizontal structure, with no Departments (and, consequently, no department heads), ensures total financial and intellectual autonomy to foreign and Portuguese scientists wishing to carry out their research programmes and develop their careers.

IGC research is organism centred, focused on understanding the genetic bases of development and evolution of complex systems. Research spans a diversity of areas including evolution, genetics, cell biology, immunology, systems biology and neuroscience. This broad 'portfolio' of research programmes is matched by a multidisciplinary approach: from molecular to population level, with recourse to a variety of model organisms (bacteria, yeast, worms, fruit fly, zebrafish, chick, and rodents) and both empirical and theoretical approaches to hypothesis-driven research questions.

This range of research interests ensures a varied seminar series, and lays the ground for fruitful and transdisciplinary collaborations between research groups in (apparently) different research fields. With some 150 seminars each year, by IGC researchers and world-leading scientists from across the globe, there is no lack of intellectual stimulation for students and researchers. The Friday Seminars, by external speakers, are always followed by lunch with the speaker, which students and post-docs are encouraged to attend. The IGC has also become a much sought after centre for international researchers to spend their Sabbatical leave. Their stay at the IGC allows for fruitful discussions and mentoring of the many young scientists at the institute.

The IGC is located in Oeiras, outside Lisbon, in what has become known as the Oeiras Campus, home to several other basic and applied research centres in biology, biotechnology and chemistry. In particular, the Instituto de Tecnologia Química e Biológica (ITQB) and the Instituto de Biologia Experimental e Tecnológica (IBET) have complementary research interests and capacities to those of the IGC, and strong interactions are fostered, within the Oeiras Associated Laboratory, made up by the three institutes.

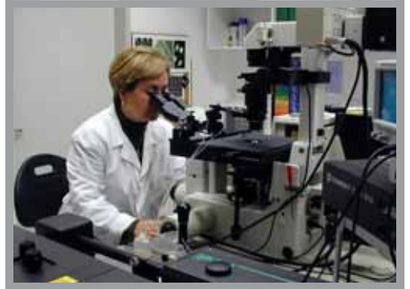
Thanks largely to the support of the Calouste Gulbenkian Foundation, IGC scientists have at their disposal state-of-the-art equipment, services and facilities, with highly qualified and experienced support staff. All common equipment and facilities are freely accessible to all researchers (another break with traditional research institutes), thus freeing group leaders' time and dedication for their own research groups and projects. Besides technical support, the IGC also provides support in other aspects of research life: the grant application and administration teams are invaluable in optimising researchers' funding success, the science communication and outreach team ensures media interest and public engagement in IGC research, and the library provides up-to-date online subscriptions to over 16000 journals.

Graduate training has always been core to the IGC mission. Indeed, since its foundation in 1961, the IGC has spearheaded the professionalisation of scientists in Portugal, also through regular graduate training programmes. In the 1990s, the IGC pioneered structured 4-year PhD programmes in Europe; there are now over 400 Gulbenkain Alumni, all over the world. Today, students who join the IGC PhD programmes receive six months to a year of intensive graduate training, led by distinguished local and international researchers, participating in hands-on projects, symposia and workshops. After this training, students are encouraged to develop their own research projects, either at the IGC or in a research laboratory abroad or in Portugal.

Our research community is made up of 250 undergraduates, graduate students, post-docs and group leaders, hailing from 24 different countries, in Europe, America, Asia and Africa. English is the official language at the IGC.

The spirit of 'horizontality' and 'cooperativity', nurtured in IGC research, extends into this community. PhD students and Post-docs hold annual retreats, in picturesque settings outside the IGC, where they present their work to all IGC researchers. These retreats are not only intellectually stimulating, but also make for relaxing and exciting social occasions. Numerous other social events - from the PhD students' Beer Hours, to themed parties - create a friendly, supportive environment and contribute to a strong 'esprit de corps'.

The town of Oeiras, where the IGC is located, is just 20km from Lisbon, on the coast. The IGC is at walking distance from the beach, and there is easy public transport access to Lisbon. The IGC's parent organisation, the Calouste Gulbenkian Foundation in Lisbon has both a fine arts and a contemporary art center where IGC members have free access. The Foundation also has a world class concert season, and the IGC's adjacent gardens has its own summer concerts, organised by the City Council - Chick Corea and Diane Krall have performed within view of the labs.



RESEARCH

PLANT STRESS SIGNALLING

Elena Baena González

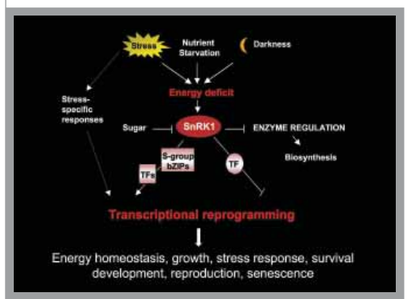
PhD in Plant Physiology and Molecular Biology
University of Turku, Finland
E-mail: ebaena@igc.gulbenkian.pt

THIS GROUP WAS ESTABLISHED AT THE IGC IN OCTOBER 2008.

In contrast to animals, plant growth and development are largely conditioned by environmental inputs. Stress can have a great impact on the decision to grow, to initiate organogenesis as well as on the characteristics of the newly formed organs. Often associated with stress is a reduction in photosynthesis and/or respiration, which in turn results in an energy deficit in the cell and a subsequent growth arrest. We use *Arabidopsis thaliana* as a model and a combination of cell-based assays, functional genomics, bioinformatics, mutant screens and genetics to understand how this stress-triggered energy deprivation is sensed, translated into an initial growth arrest and ultimately into plant adaptation, development and survival.

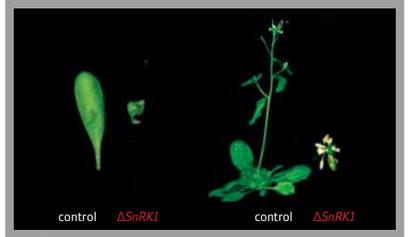
ENERGY SIGNALING IN THE STRESS RESPONSE

Despite their distinct origin and mode of perception, different stresses trigger largely similar downstream responses that include overlapping patterns of gene expression. Our work has shown that this general stress transcriptome is partly regulated by the evolutionarily conserved energy sensor protein kinases, SNF1 (sucrose non-fermenting1) in yeast, SnRK1 (Snf1-related kinase1) in plants, and AMPK (AMP-activated protein kinase) in mammals. Upon sensing the energy deficit associated with stress, SnRK1 triggers extensive transcriptional changes that contribute to restoring metabolic and energy homeostasis, promoting cell survival and allowing the elaboration of longer-term responses for adaptation. Most importantly, long-term defective SnRK1 signaling results in developmental alterations, suggesting that these protein kinases serve as integration points of metabolic, hormonal and environmental signals. The goal is to gain insight on how growth and developmental decisions are made based on environmental inputs and to understand the role of SnRK1 as a mediator of these processes, using Arabidopsis thaliana as a model and a combination of cell-based assays, functional genomics, bioinformatics, mutant screens and genetics. Since arriving at the IGC, in October 2008, I have been setting up the laboratory and recruiting group members.



Stress interferes with photosynthesis and/or respiration, resulting in a decrease in the cellular energy pool. This energy deficiency is sensed by the SnRK1 protein kinases that initiate an energy-saving program at several levels, including massive transcriptional reprogramming. Besides contributing to the maintenance of cellular energy homeostasis and tolerance to stress, SnRK1 has profound effects at the whole organism level influencing growth, viability, reproduction and senescence (Figs 2 and 3), and is thus proposed to be central in the integration of metabolic, stress and developmental signals.

SnRK1 overexpression delays growth and senescence.



SnRK1 silencing causes growth arrest and premature ageing.

THIS GROUP COLLABORATES WITH:
Jen Sheen (Massachusetts General Hospital, Harvard Medical School, Boston, USA)

FUNDING
European Commission Framework Programme 7 (FP7)
- Marie Curie International Reintegration Grant

EPIGENETICS AND SOMA

Vasco M. Barreto

PhD in Immunology
Université Paris VI, France
E-mail: vbarreto@igc.gulbenkian.pt

THIS GROUP WAS ESTABLISHED AT THE IGC IN JANUARY 2008.

We are interested in expanding studies which have been classically associated with the antigen receptor genes of B lymphocytes: random mono-allelic expression (RMAE) and DNA modification reactions, namely, somatic hypermutation (SHM) and class switch recombination (CSR).
RMAE is the most striking example of an epigenetic phenomenon, because at the level of each cell only one of two identical molecules (the alleles) is expressed. We are studying the immunoglobulin genes as a model to dissect early epigenetic mechanisms that determine which allele is going to be expressed and are designing screens to identify additional regions in the genome undergoing RMAE.
Activation-Induced Deaminase (AID) plays a pivotal role in adaptive immunity because it is essential for SHM and CSR. AID has also been implicated in B lymphomas and other neoplasias. We are trying to further understanding of the biology of AID.

STUDIES ON RANDOM MONOALLELIC EXCLUSION

We plan to use classical molecular approaches and genetically engineered mice to discover AID co-factors for CSR, to address the rules governing AID targeting to the immunoglobulin loci and to establish murine models to evaluate the impact of ectopic expression of AID. In addition, we plan to adapt a functional assay we developed previously to characterize orthologous AID forms which can be adapted to clone molecules from distant species that are able to introduce lesions in DNA, with the goal of better elucidating the evolution of somatic DNA modification.
Towards these goals we have carried out rederivation of AID knockout mice and optimized the transfection and transduction techniques. Furthermore we have identified and functionally characterised a new AID null mutant from patients with HIgM (type 2).

STUDIES ON RANDOM MONO-ALLELIC EXPRESSION

We will perform a experiment to test whether there is a stable epigenetic mark that during B cell differentiation dictates which Ig heavy chain allele and which Ig kappa chain allele rearrange first. The idea is to differentiate B cell clonal progenitors *in vitro* and track the fate of IgH and Igk distinguishable alleles. If these loci are under epigenetic (i.e. clonal) constraints, the collection of clones should have a characteristic pattern of Ig surface expression and Ig gene rearrangements, distinct from what will be observed in the absence of an epigenetic constraint.
We propose to generate transgenic lines in zebrafish that will have artificial alleles for different fluorescent encoding genes, so that the contribution of each allele will be easily followed in vivo.
Taking advantage of the Tlr4 polymorphisms that we have detected in healthy donors, we will address whether in humans, similarly to what happens in mice, Tlr4 undergoes monoallelic expression.
Finally, we will conduct a new global screen for regions under monoallelic expression based on the observation that the alleles of genes under monoallelic expression replicate asynchronously.
We have gathered preliminary data on the B cell clones, identified TLR4 human polymorphisms and concluded cloning of the vector to produce transgenic fish.

GROUP MEMBERS
Catarina Cortesão (Post-doc)
Clara Pereira (PhD Student)
Daniel Espadinha (MSc Student)
Nadine Caratão (Laboratory Technician)

FUNDING
Fundação Calouste Gulbenkian - IGC start up fund
European Commission Framework Programme 7 (FP7)
- Marie Curie International Reintegration Grant
Fundação para a Ciência e a Tecnologia (FCT), Portugal

VARIATION: DEVELOPMENT AND SELECTION

Patrícia Beldade

PhD in Evolution and Development
University of Leiden, The Netherlands
E-mail: pbeldade@igc.gulbenkian.pt

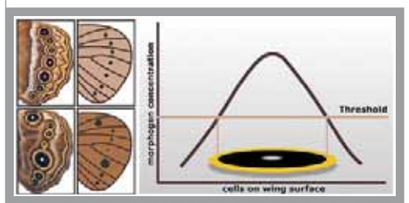
THIS GROUP WAS ESTABLISHED AT THE IGC IN MARCH 2008.

Our research in the area of evolutionary developmental biology is focused on trying to dissect the genetic and developmental bases of phenotypic variation and adaptation. Heritable phenotypic variation is the raw material of evolution by natural selection, and a universal property of biological systems – including traits of medical and economic importance. Understanding the mechanisms that generate phenotypic variation is, thus, a key challenge in contemporary biological research. What are the gene types (e.g. transcription factors versus enzymes), specific genes, and gene regions (e.g. regulatory versus coding sequence) that contribute to evolutionarily relevant variation? How do these genes lead to change developmental programmes and translate into variant adult phenotypes and finally into phenotypic diversification? To address these and other questions Patrícia Beldade's research has so far concentrated on a diverse and ecologically-relevant phenotype that represents a laboratory-tractable system for the dissection of variation in complex traits: wing color patterns on butterfly wings.

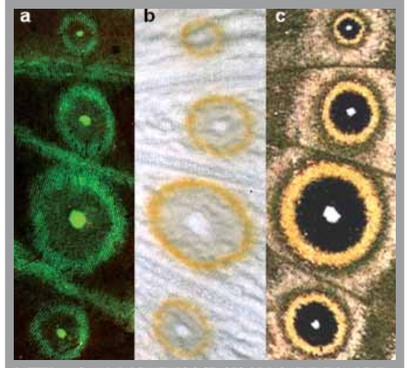
EVOLUTIONARY DIVERSIFICATION: GENETIC BASIS AND ADAPTIVE SIGNIFICANCE OF VARIATION IN BUTTERFLY WING PATTERNS

The aim of this project is to study the genetic basis of variation in eyespot size (an example of a complex morphological trait that is ecologically-relevant and very diverse) using gene mapping and expression-profiling approaches. In 2008, a laboratory technician was hired and trained to work on this project. We have produced a linkage map for the target butterfly species with markers in expressed genes and including color pattern loci. This map is the densest gene-based map ever published for a butterfly and allowed an extensive analysis of synteny (i.e. conservation of gene location and order along chromosomes) with the model lepidopteran species (the silkworm *Bombyx mori*). Furthermore, we have validated a number of microsatellite markers in genes expressed during wing development to be used in genetic mapping experiments (work now accepted for publication in *Molecular Ecology Resources*) and pursued the cloning of candidate genes which previous work has suggested might contribute to wing pattern variation. We now have sequence information for the genes *Antennapedia* (Hox gene expressed in the eyespot organizing centers) and *shaggy* (part of the Wg-signaling pathway redeployed in eyespot formation). We still have not been able to clone *axin* (another Wg signaling gene).

GROUP MEMBERS
Maria Adelina Jerónimo (Laboratory Technician)
Ana Rita Mateus (joint IGC-University of Leiden PhD Student)



DEVELOPMENTAL BASIS OF THE EVOLUTIONARY DIVERSIFICATION OF SERIAL REPEATS.
Eyespots diversify not only between species (compare top and bottom pictures) but also between individual repeats (compare size and position of different eyespots on bottom picture). Work in a "butterfly lab-rat", Bicyclus anynana, enables the dissection of the developmental components (e.g. morphogen titers and epidermal thresholds cf. right diagram) responsible for changes in morphology of individual repeats. While morphogen titers can vary locally (represented by the diameter of the black circles in the middle diagrams), epidermal thresholds are a property of the whole wing surface (represented by the brown shading in the middle diagrams). After Allen et al. BMC Evol Biol (2008) and Beldade et al. J Exp Zool (2008).



PATTERNING AND BIOSYNTHESIS STAGES OF PIGMENTATION DEVELOPMENT.
During wing pattern formation in Bicyclus anynana butterflies, Engrailed protein (green) is found in early pupal scale-forming cells (a) which will later synthesise the yellow pigment (b) that makes up the golden ring of adult eyespots (c).

THIS GROUP COLLABORATES WITH:
Tony Long (University of California at Irvine, USA)
Paul Brakefield (University of Leiden, The Netherlands)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

CELL CYCLE REGULATION

Mónica Bettencourt Dias

PhD in Molecular Cell biology
University College London
E-mail: mdias@igc.gulbenkian.pt

Centrioles are essential for the formation of several microtubule (MT) – organising structures including centrosomes, cilia and flagella. In the centrosome, two centrioles associate with the pericentriolar matrix (PCM), constituting the primary microtubule organising centre in animal cells. In interphase or quiescent ciliated cells, at least one centriole, called the basal-body, is tethered to the membrane, where it grows the axoneme, the MT-based structure of cilia and flagella.
Our research questions are: How are centrioles formed? How did centrioles evolve? How is centriole biogenesis coordinated with cell cycle progression so that only one centrosome is formed in each cycle? What is the physiological function of centrioles?

REGULATION OF SAK/PLK4

We have shown in the past that SAK/PLK4 triggers centriole biogenesis. How SAK/PLK4 activity is regulated throughout the cell cycle and the identity of its substrates are crucial questions to this field and to the understanding of the role of centrosomes in human disease. We have shown that SAK/PLK4 is ubiquitinated, and that ubiquitination arises as a consequence of phosphorylation of SAK/PLK4 followed by interaction with the SCF/slimb complex. In parallel we follow a non-biased route to find new regulators and substrates of SAK/PLK4. We have isolated complexes bearing this protein by affinity purification and sequenced novel proteins using Mass Spectrometry. The role of these proteins in centriole/centrosome duplication is being screened using RNAi assays that we have developed.

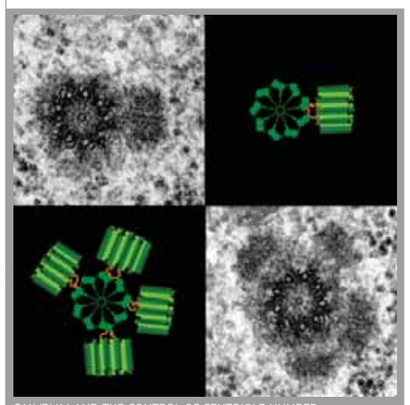
FUNCTION OF CENTRIOLES IN THE ORGANISM

Somatic cell divisions proceed normally in a fly without centrioles. We showed that mitotic abnormalities arise in syncytial PLK4-derived mutant embryos resulting in lethality. Moreover male meiosis fails in both PLK4 and DSAS-4 mutant spermatids that have no centrioles. These results show diversity in the need for centrioles in cell division. This suggests that tissue specific constraints selected for different contributions of centrosome-independent and dependent mechanisms in spindle function (Rodrigues-Martins et al. 2008 Cell Cycle).

REGULATION OF CENTRIOLE BIOGENESIS AND FUNCTION: AN INTEGRATIVE APPROACH

We asked whether there is a universal centriole/basal body assembly mechanism in eukaryotes, by creating sequence footprints and studying the phylogenetic distribution of the six families of proteins known to play an important role in centriole/basal body assembly in collaboration with the computational genomics laboratory at IGC. To our surprise, only the founders of the SAS6, SAS4/CPAP, BLD10/CEP135 and polo-kinase families are ancestral, SPD2/CEP192 and CP110 were created in specific branches. Amongst the ancestral molecules BLD10/CEP135 is not present in all centriole-containing species, suggesting it is not part of a core assembly pathway. We showed that unlike DmSAS6, SAS4/CPAP and SAK/PLK4, DmBLD10 is not essential for centriole biogenesis in Drosophila. Surprisingly, DmBLD10 is necessary for elongation of the sperm basal body and motile axoneme biogenesis. Our data strongly suggests there is a universal set of molecules involved in centriole/basal body biogenesis in eukaryotes, which is involved in triggering and defining the nine fold symmetrical structure. The regulation of centriole biogenesis is likely to have evolved through the addition of new molecules that couple the formation of the structure to other cellular functions of modern eukaryotic life.

GROUP MEMBERS
Ana Rodrigues Martins (External PhD Student)
Zita Carvalho Santos (PhD Student)
Ines Bento (Research Fellowship/PhD Student)
Francisco Freixo (MSc Student)
Inês Cunha Ferreira (PhD Student)
Pedro Machado (Research Fellowship)
Pedro Branco (Part-time Electron Microscope Technician)
Filipe Leal (PhD Student)



SAK/PLK4 AND THE CONTROL OF CENTRIOLE NUMBER.
Top – Normal centrosome with two centrioles, a mother and a daughter (scheme on the right). **Bottom** – When SAK/PLK4 is not degraded each mother centriole has more than one daughter.

THIS GROUP COLLABORATES WITH:
José Pereira Leal (IGC)
David Glover (University of Cambridge, UK)
Ryoko Kuriyama (University of Minnesota, USA)
Eric Karsenti (CRMB Montpellier, France)
Carsten Janke (EMBL Heidelberg, Germany)

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Crioestaminal – Saúde e Tecnologia, SA, Portugal
– Crioestaminal Award 2007

QUANTITATIVE ORGANISM BIOLOGY

Jorge Carneiro
PhD in Biomedicine
University of Porto, Portugal
E-mail: jcarneir@igc.gulbenkian.pt

Cells of multicellular organisms cooperate to ensure body development and maintenance. They do this in a collectively distributed manner, without a plan or global perspective. The Quantitative Organism Biology group studies the multilevel mechanisms that give rise to whole organism properties, in search for general principles of biological organisation and, eventually, the design of artificial systems. One of our main research interests is the immune system, where cells collectively ensure body housekeeping and homeostasis, prevent autoimmune diseases, and fight cancer and infections. We also investigate cell and tissue morphodynamic processes taking place during embryonic development to generate metazoan body shapes.

GENETIC AND BIOCHEMICAL CONTROL OF CERL-2 ACTIVITY DURING EARLY DEVELOPMENT

Correct establishment of the left/right (L/R) body asymmetry in the mouse embryo requires asymmetric activation of the evolutionarily conserved Nodal signaling cascade in the left lateral plate mesoderm. Nodal antagonist, Cerl-2 plays a key role in restricting the Nodal signaling pathway toward the left side of the mouse embryo by preventing its activity in the opposite side. The general objective of this project is to study the regulation of Cerl2 gene expression, exploring several mutations. To gain quantitative insights into Cerl2 regulation of Nodal we develop mathematical models that take into account and try to reproduce the behaviour of the key players acting during the breaking of symmetry in the node and its propagation to the LPM.
An integrated simulation framework was developed that incorporates the basic knowledge on Nodal, Cerl2, and Lefty expression in the node and lateral plate mesoderm. In this framework we explicitly describe: 1) each epithelial cell, its identity, and the genetic network it contains; 2) the spatial arrangement of epithelia in relation to the node, lateral plate mesoderm, and midline; 3) the paracrine activity of molecules in the medium bathing the cells, as well as in the interstitial space; 4) the juxtacrine signals propagated by cell-to-cell contact; 5) the vesicle parcels and their transport in the node. Using this framework we simulated the spatial patterning of these genes in the node and lateral plate mesoderm in wild type embryos and in mutants for cerl2, lefty, and nodal flow. The simulations reproduce the patterns of gene expression observed in wild type embryos, but the model must be refined, since it cannot explain all mutant patterns.

GROUP MEMBERS
Nuno Sepúlveda (PhD Student)
Tom Weber (Visiting PhD Student
Gonçalo Picado (Trainee)
Claudine Chaouiya (Visiting Scientist)

THIS GROUP COLLABORATES WITH:
José António Belo (University of the Algarve, Portugal)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

POPULATION AND CONSERVATION GENETICS

Lounès Chikhi
PhD in Population Genetics
Université Pierre et Marie Curie, France
E-mail: chikhi@igc.gulbenkian.pt

LOUNES CHIKHI IS CHARGÉ DE RECHERCHE 1ÈRE CLASSE (CR 1) OF THE CNRS (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE), FRANCE, WITHIN THE 'EVOLUTION ET DIVERSITÉ BIOLOGIQUE' UNIT OF THE UNIVERSITÉ PAUL SABATIER, TOULOUSE, FRANCE.

We are interested in the use of genetic data to address issues related to the recent evolution of populations and closely related species. This includes the detection, quantification, and dating of population collapses, expansions, or admixture events, using neutral markers and the identification of markers under selection. We use/test existing methods and develop new ones to uncover such events. The aim is to determine to which extent genetic data can actually be used as inferential tools and separate conflicting scenarios.
Applications go from human evolution (e.g. the Neolithic transition in Europe) to conservation genetics of wild (e.g. orang-utans, lemurs) and domesticated species (e.g. cattle, sheep).
While most of the work currently done involves data analysis and simulation, we have set up a laboratory and a number of ongoing projects also involve field work, some of which in collaboration with groups in Portugal, the U.K., France, Madagascar, or Malaysia.

DEMOGRAPHIC AND GENETIC RESPONSES TO HABITAT FRAGMENTATION AND HABITAT LOSS IN TWO LARGE FOREST MAMMALS

The aim of this project is to increase our understanding of the genetic processes in fragmented or structured populations. It focuses on two species of large mammals, namely the Sabah elephant (*Elephas maximus*) and the orang-utan (*Pongo pygmaeus*), both from Borneo. Fecal material is collected in the field and DNA is extracted. Different genetic markers will be developed and/or typed to determine whether different populations (i) have similar levels of genetic diversity, (ii) are genetically different from each other. We shall also determine (iii) whether habitat fragmentation can be correlated to genetic diversity and differentiation, and (iv) whether the demographic history of the populations can be reconstructed (for instance we shall ask whether they were submitted to population bottlenecks).
More than 400 elephant samples have been obtained in the field and 224 were extracted, amplified and genotyped at 18 microsatellites. The first statistical analyses suggest that genetic diversity is low in all elephant populations, and that there are very large deficits in heterozygotes (Fis values > 0.2). We are currently trying to determine whether this is caused by technical problems such as null alleles, by sampling biases (a Wahlund effect) or the social structure of elephants. We shall determine whether new primers have to be designed (i.e. eliminate the null alleles if any). Two papers related to the project were submitted and accepted in 2008, *Molecular Ecology Resources* and *Genetics*.

CONSERVATION, PHYLOGEOGRAPHY AND GENETICS OF LEMURS IN THE FRAGMETNED HABITATS OF MADAGASCAR AND THE COMOROS ARCHIPAELAGO

The aim of the project is to study the patterns of genetic differentiation in two groups of lemur species: sifakas (genus *Propithecus*) and true lemurs (genus *Eulemur*). Lounès Chikhi is responsible for the work related to the *Propithecus* whereas the work on *Eulemurs* is the responsibility of Prof. B. Crouau-Roy.
For sifakas, we aim to understand the effect of habitat fragmentation (the fact that the species habitat is not continuous) and of potential barriers (rivers, roads) on patterns of genetic diversity. We also aim to understand the history of three sifaka species (*P. tattersalli*, *P. perrieri*, and *P. coquereli*) whose distributions are non-overlapping.
Altogether, 404 *P. tattersalli* samples were collected during two field missions, in 2006 and 2008, in the Daraina region, in northern Madagascar. The field work carried out in 2008 allowed us to also estimate the density of *P. tattersalli* in several forest fragments and combine these data with those

GROUP MEMBERS
Vitor Sousa (PhD Student)
Rita Rasteiro (PhD Student)
Bárbara Parreira (PhD student)
Erwan Quéméré (External PhD Student)
Tim Bray (External PhD Student, examined November 2008)
Aurélien Delay (MSc Student, July-September 2008)
João Alves (Optimus Alive Fellow)

GOLDEN CROWNED SIFAKA *(PROPITHECUS TATTERSALLI)*.
This is a rare and endangered lemur species only found in a small region in the North of Madagascar.

obtained in 2006, to provide new estimates for the size of the whole species. We also gathered data on the plant species on which *P. tattersalli* was observed to feed. Samples from these plants were collected and have been given to the Tzimbazaza Zoological and Botanical Garden in Antananarivo for identification. Two hundred and ninety two (292) individuals had their DNA extracted, amplified and genotyped at 13 microsatellite loci, out of which 250 provided reliable extracts and 230 corresponded to different individuals. Two manuscripts were submitted in 2008; one was accepted for publication in *Conservation Genetics*; the second manuscript has been submited to the *American Journal of Primatology* and is under revision.

THIS GROUP COLLABORATES WITH:
Mike Bruford, Benoit Goossens (Cardiff University, UK)
Brigitte Crouau-Roy (CNRS, France)
Benoit Goossens, Mohd Fairus Jalil (Universiti Malaysia Sabah, Malaysia)
Brigitte Crouau-Roy, Christophe Thébaud
(Paul Sabatier University, Toulouse, France)
Clément Rabarivola (Université de Mahajanga, Madagascar)
Fanamby (Non-Governmental Organisation)
Pedro Fernandes, Isabel Gordo (IGC)
Manuela Coelho (University of Lisbon, Portugal)
Mark Beaumont (Reading University, UK)
Ute Radespiel (University of Veterinary Medicine, Hannover, Germany)
Guido Barbujani (Ferrara University, Italy)

FUNDING
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OptimusAlive!08 Oeiras-IGC Partnership

LYMPHOCYTE PHYSIOLOGY

Jocelyne Demengeot
PhD in Cellular and Molecular Biology
Université d'Aix-Marseille II, France
PI's E-mail: jocelyne@igc.gulbenkian.pt

A healthy immune system discriminates self from non-self components, and amongst the latter, innocuous commensals and food antigens from infectious agents. It also relies on robust regulatory mechanisms that ensure return to equilibrium (homeostasis) after an immune challenge or other stresses.
Autoimmune and immuno-inflammatory diseases, are both caused by "not enough regulation" while chronic infections result from impaired immune responses associated with "too much regulation". Likewise, immune surveillance of tumor requires overriding tolerance to self components, while long-term heterologous graft acceptance requires tolerance induction to genetically different organs and tissues.

Inflammatory components in the biology of regulatory T cells and the prevention of auto-immune disease
Using well-characterised mouse models we aim to directly test the hypothesis according to which inflammatory compounds that trigger regulatory T cells are not only beneficial but also necessary to maintain a healthy, regulated immune system.
This year, we concluded the demonstration that Foxp3 expression in natural Treg is labile during homeostatic expansion such that Treg may also induce inflammation upon severe IL-2 deprivation (accepted in European Journal of Immunology). We obtained evidence that *de novo* generation of protective and healing regulatory T cells can be induced through specific pro-inflammatory immunisation and also revealed that the pro-inflammatory cytokine IL-6 prevents differentiation of mature naïve cells but not of immature thymocytes into Treg, upon TGF-beta exposure (submitted). We concluded a study evidencing that, contrary to other immunosuppressors, and to high dose hydrocortisone, a low dose hydrocortisone regimen does not significantly alter Treg number and activity (accepted in Journal of Auto-immunity). Moreover, we reported that LPS administration induces protection from autoimmune diabetes in NOD mice through the enhancement of regulatory T cell functions (submitted). Finally our analysis of mice raised in various levels of biocontainment, Germ free, SOPF and SPF, support the notion that specific intestinal flora positively regulate Treg differentiation and numbers.

QUANTITATIVE AND QUALITATIVE T CELL RECEPTOR REPERTOIRE REQUIREMENTS FOR IMMUNE TOLERANCE ESTABLISHMENT AND MAINTENANCE

In this project we aimed to formally establish the essential feature of the Treg TCR repertoire and evaluate the contribution of T-B cell repertoire interaction to te establishment of immune tolerance.
Investigating the process of Treg differentiation we revealed that 1) the maturation stage determines T cells susceptibility to acquire a Treg phenotype both in the thymus and in the periphery; 2) peripheral antigens reach the thymus and locally drive Treg differentiation; 3) antigens provided by haematopoietic cells can be presented by thymic epithelium to drive Treg differentiation (two manuscripts are in preparation). Analysis of B cell-deficient mice and of recipient mice of various adoptive transfers provided definitive evidence that B cells positively affect peripheral but not thymic Treg numbers. Ongoing experiments address whether the role of B cells in the physiology of Treg relies on their capacity to present antigens and/or their secretion of Ig and whether Ig diversity is required.

IVIG THERAPY IN SLE: REGULATING THE REGULATORS

We proposed to establish whether the beneficial effect of ivIg in Systemic Lupus Erythematosus is at least in part due to restoration of the Treg pool, in term of number, production and effector function.

GROUP MEMBERS
Santiago Zelenay (Post-doc, left October 2008)
Marie-Louise Bergman (Post-doc)
Leonor Sarmento (Post-doc)
Andreia Lino (Post-doc)
Maria Catarina Martins (Laboratory Manager)
Maria Francisca Moraes-Fontes (PhD Student)
João Henrique Duarte (PhD Student)
Ricardo Paiva (PhD student)
Ana Mónica Gabriel (MSc Student, left August 2008)
Inês Trancoso (MSc Student)
Melissa Pinheiro (Trainee, left October 2008)

Following a group of patients before, during and after ivIg therapy indicates that activation and re-sensitisation of T-cell subsets and particularly regulatory T-cells is likely to be part of the therapeutic effects of ivIg treatment. The mechanistic basis of these observations is being tested in mouse models.

Effects of the Recombination Activating Genes 1 and 2 on the Vertebrate Genome Stability: Consequences at the Cellular and at the Organism level.
RAGs are site-specific recombinases that mediate the somatic rearrangements of DNA gene segments encoding the T and B cell receptors. Their activity is essential for lymphocytes differentiation and for the generation of the very large diversity of antigen-receptors. We are investigating three issues related to RAG activities: 1) the mechanism at the basis of lymphopaenia-induced autoimmunity seen in Rag hypomorphic mutants, as in the human Omen syndrome. 2) to which extend aberrant Rag activity promotes tumor formation and tumor progression in lymphoid and non-lymphoid tissues, and 3) the consequence at the genomic level of the emergence of Rag activity in jawed vertebrates.
We generated mice and fly transgenic for the Rag genes, constructed new molecular reporters for Rag activity, established tools to test specific DNA sequences for their capacity to target Rag mediated DNA recombination and are tentatively developing novel algorithms to identify cryptic Recombination Signal sequences in various genomes.

THIS GROUP COLLABORATES WITH:
Carlos Penha Gonçalves, Jorge Carneiro, Miguel Soares, José Pereira Leal, Constantin Fesel (IGC)
António Jacinto (IMM, Lisbon)
Marc Dionne (King's College, London)

FUNDING
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Fundação para a Ciência e a Tecnologia (FCT), Portugal
L'Oréal, Portugal – L'Oréal Portugal Women in Science 2008 Prize (awarded to Leonor Sarmento)

PLANT MOLECULAR BIOLOGY

Paula Duque
PhD in Biology (Physiology and Biochemistry)
University of Lisbon, Portugal
E-mail: duquep@igc.gulbenkian.pt

We use *Arabidopsis thaliana* as a model system to investigate how plants perceive and respond to environmental signals and endogenous developmental cues at the molecular level. In particular, we are focusing on the role of pre-mRNA splicing in the regulation of gene expression. The versatility of this mode of regulation suggests that it is likely to play an important contribution in ensuring the developmental plasticity and stress tolerance that are essential for plant survival.

ALTERNATIVE SPLICING IN PLANT DEVELOPMENT AND STRESS RESPONSE

Alternative splicing recently emerged as a crucial mechanism for generating proteome diversity and regulating gene expression. Very few examples of alternatively-spliced transcripts have been reported in plants and still fewer are known to generate functionally distinct proteins. The unique developmental plasticity and stress tolerance developed by plants as a result of their sessile growth habit suggests that they offer exceptional opportunities to reveal alternative splicing mechanisms, which are likely to play a key role in the adaptation of plants to changes in their environment. We are investigating functional significance of different splice variants of specific development- and stress-associated genes, using reverse genetic approaches in *Arabidopsis thaliana*. Moreover, we are analysing the function of individual serine/arginine-rich (SR) proteins, established key players in mammalian alternative splicing.
During the first 12 months of this project, we have initiated the arduous task of uncovering the precise function of each *Arabidopsis* SR protein. Results from ongoing work have validated our general working hypothesis that SR proteins are central players in plant responses to the environment. A genetic null mutant for the *Arabidopsis SCL30a* gene displays hypersensitivity to the exogenous application of the stress phytohormone ABA, and a knockout mutant for the *SR45* gene is impaired in the sugar signalling pathway.

HERBICIDE RESISTANCE IN ARABIDOPSIS THALIANA: ROLE OF PLANT MULTIDRUG RESISTANCE TRANSPORTERS

The widespread use of herbicides has led to an increasing number of resistant weed species and classes of herbicides to which resistance has evolved. A group at Instituto Superior Técnico (IST) has recently shown that three *Saccharomyces cerevisiae* genes encoding plasma membrane multiple drug resistance (MDR) transporters determine yeast resistance to 2,4-dichlorophenoxyacetic acid (2,4-D), one of the herbicides most successfully used worldwide. Based on these findings, we have been analysing *Arabidopsis thaliana* MDR transporter genes showing high sequence similarity to the yeast resistance determinants. In the first 18 months of this project, our group has identified seven *Arabidopsis thaliana* MDR transporter-encoding genes whose expression is affected by treatment with the herbicide 2,4-dichlorophenoxiacetic acid (2,4-D). The yeast TPO1 gene encodes an MDR plasma membrane transporter of the Major Facilitator Superfamily (MFS) previously found by the IST team to confer resistance to 2,4-D in yeast and to be transcriptionally activated in response to the herbicide. The IST group has now demonstrated that Tpo1p expression is required to reduce the intracellular concentration of 2,4-D. Functional heterologous expression of one of the *A. thaliana* MFS genes we chose for further analysis was found to confer increased resistance to the herbicide in both mutant tpo1 and wild-type cells, through the reduction of the intracellular concentration of 2,4-D. The heterologous expression of this gene in yeast also leads to increased resistance to Al^{3+} and Tl^{3+}. Thus, the gene encodes the first plant putative MFS transporter to be suggested as involved in MDR. These results have been submitted for publication.

GROUP MEMBERS
Estelle Remy (Post-doc)
Sofia Carvalho (PhD Student)
Raquel Carvalho (PhD Student)
Pedro Miranda (Trainee, left September 2008)
Rita Saraiva (Trainee)
Rafaela Santos (Trainee)

An *Arabidopsis thaliana* SR45 knockout shows dwarf stature.

An *Arabidopsis thaliana* SR45 knockout displays reduced root elongation.

ALTERNATIVE SPLICING OF AN ARABIDOPSIS RING E3 UBIQUITIN LIGASE INVOLVED IN PLANT STRESS AND DEVELOPMENT

As sessile organisms, plants developed adaptive physiological strategies to cope with environmental stress, and the basis of this adaptation capacity lies ultimately at the level of the genome. Alternative splicing is an important mechanism for generating proteome diversity and regulating gene expression, while the protein degradation ubiquitin/26S proteasome pathway contributes significantly to plant stress tolerance by affecting a wide range of processes. We have identified an Arabidopsis thaliana gene encoding a RING E3 ligase involved in protein ubiquitination that undergoes alternative splicing. The alternatively-spliced transcripts are differentially upregulated during senescence and upon application of the stress-response hormone abscisic acid, strongly suggesting a role for alternative splicing of this gene in plant stress responses. Stress-specific expression and splicing patterns will be investigated and reverse genetics approaches in *Arabidopsis* used to examine the functional significance of both splice forms of this RING E3 ligase. In the first six months of this project, RT-PCR analysis of the expression pattern of the RING gene revealed constant transcript levels at different developmental stages and in different tissues, and upregulation under a high concentration of glucose. A T-DNA knockout line was initially found to be glucose-insensitive, but further analyses did not confirm these results. A new search of the Arabidopsis genome retrieved a gene recently annotated as a duplicated form of our first subject. Both predicted proteins share a high degree of homology, and the two genes show similar expression patterns during development and under all stress conditions tested. We have set out to obtain a double mutant by isolation and crossing of single knockout lines for each RING gene and/or simultaneous silencing of both genes using RNA interference (RNAi). Once obtained, the double mutant will be used for phenotypical analysis and compared to the two single knockout mutants in order to analyse the function of both RING genes.

THIS GROUP COLLABORATES WITH:
Nam-Hai Chua (The Rockefeller University, USA)
Isabel Sá-Correia (Instituto Superior Técnico, Portugal)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

PLANT DEVELOPMENT

José Feijó
PhD in Cell Biology
University of Lisbon
E-mail: jfeijo@fc.ul.pt

Our research is concerned with developing integrated models of cellular growth and morphogenesis using the pollen tube as a biological model, ion dynamics as an experimental paradigm and theoretical modeling as an integrative tool. We have characterised novel ion channels involved in pollen tube growth and morphogenesis, by means of imaging, electrophysiology, genetics and molecular biology, and, furthermore, unravelled some of the genetic and cellular mechanisms behind pollen tube guidance and fertilisation in plants. Our group has provided novel insight into the transcriptional status of plant male gametes and its consequences for plant reproduction and improvement. The members of the group have been pivotal in the strengthening of the imaging, transcriptomics and vibrating probe electrophysiology services of the IGC.

GENETIC AND FUNCTIONAL CHARACTERISATION OF GLUTAMATE RECEPTORS IN POLLEN TUBE GROWTH

Calcium is one of the most ubiquitous second messengers in all eukaryotic cells, participating in a number of fundamental processes, from coordination of development to neural impulse transmission. In plant cells, in general, and growing pollen tubes in particular, the way calcium is taken up by cells is still a mystery, and no channel has been formally identified as such from a genetic and physiological point of view, despite an impressive amount of information on cytosolic calcium modulation of various processes. In 2008 we have taken significant steps towards the identification of glutamate receptors equivalent to those in the animal nervous system, as one of the components that regulate calcium influx and control pollen tube growth.

MOLECULAR PARTNERS AND EVOLUTION OF SYMBIONTS DURING MYCHORRIZA ESTABLISHMENT

Symbiotic associations in Nature are amongst the most intriguing and fascinating biological phenomena. Mychorriza are widespread plant root with fungus associations. These associations play fundamental ecological and physiological roles. We have established the patterns and profiles of various free soil ions, namely protons, as key partners in the establishment of the symbiotic reaction, and characterised the early events of fungal priming towards the root.

INTEGRATED THEORETICAL MODELLING OF ION PHYSIOLOGY AND POLLEN TUBE GROWTH

Over several years we have been developing a toolbox of molecular and physiological features that characterise pollen tube growth. We have reached a state where theoretical modelling is not only possible, but very likely to help in defining an integrative view of the mechanisms and minimal sets of conditions needed to understand how complex biological phenomena self-arise from the interactions of the underlying components. This year we have definitely advanced in the proposition of both mechanical and ionic models of growth that account for most of what is know about ion dynamics in pollen, but also allow further advance in testing specific hypotheses regarding the mechanistic organisation of these cells.

CHLORIDE CHANNEL SCREENING AND CHARACTERISATION IN POLLEN TUBES

Despite the prevalent and ubiquitous importance of anions on plant cell growth, the molecular description of the underlying channels is still lagging, and so far no specific channel has been described as being strictly specific to chloride. Yet in pollen tubes we have evidence showing a pivotal role of chloride on water conductance and, consequently, on volume increase (Zonia et al, 2002). In 2008 we have for the first time established, using patch-clamp, that such channels exist and are active in pollen in collaboration, with the group of Ana Bicho at the FCT-UNL. Furthermore we are screening for a number of phenotypes in *Arabidopsis thaliana* that may lead us to the molecular and genetic characterisation of one such channel.

GROUP MEMBERS
Jorg Becker (Post-doc, left January 2008)
Erwan Michard (Post-doc)
Filipa Alves (Post-doc)
Alessandro Ramos (Post-doc, left October 2008)
Kai Konrad (Post-doc)
Ana Catarina Silva (Lab Manager)
Pedro Lima (MSc Student)
Bárbara Santos (joint PhD Student with Universidade Nova de Lisboa)
Filipe Borges (Graduate Research Student, left January 2008)

THIS GROUP COLLABORATES WITH:
Jorg Becker (IGC)
Ana Bicho (Univerisdade Nova de Lisboa, Portugal)

YEAST STRESS

Lisete Fernandes
PhD in Biochemistry
University of Lisbon, Portugal
E-mail: lisete@igc.gulbenkian.pt

Adaptation and survival to intracellular and extracellular environmental challenges (stresses) are fundamental processes in all organisms. Pathogens and all micro-organisms in general are widely exposed to oxidative environments imposed by phagocytosis and chemical/physical stress agents, respectively. In fact, exposure to many fungicides and anti-cancer drugs generates oxidative stress; similarly, exposure to temperatures below the optimal value has effects on the intracellular oxidative environment. In the first instance, adaptation/survival to environmental stresses depends on the accuracy and specificity of intracellular signal/stimuli propagation and efficient counter-acting/compensatory response(s). Despite the remodelling of gene expression at different steps, transcription by RNA polymerase II (pol II) is a crucial process under stress stimuli. In this respect, understanding how the 'oxidative stimuli' propagate in the cytoplasm to reach transcription factors and modulate nuclear events, is far from being a clear subject. In this context, in *Saccharomyces cerevisiae* we studied: pol II machinery components as targets/signalling molecules of oxidative stimuli; cytoskeleton and related factors as vehicles for oxidative signaling. We are also interested in understanding adaptation from the population point of view (in collaboration with Isabel Gordo at the IGC).

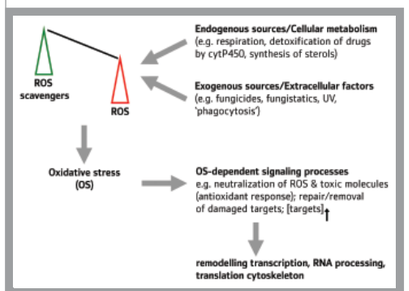
TRANSACTIVATOR YAP1 – CROSSROAD OF COLD AND OXIDATIVE STRESS SIGNALING PATHWAYS IN *SACCHAROMYCES CEREVISIAE*

The Yap family of bZIP transcription factors in *Saccharomyces cerevisiae* contains members that are central players in cellular responses to stress challenges, namely Yap1, in oxidative stimuli. The activator Yap1 is mainly regulated at the level of cyto-nuclear localisation upon inducing stimuli. Both in yeast and mammalian cells, integrity of the cytoskeleton has been shown to be essential for the intracellular regulated mobility of some activators, for example Gln3 and p53, respectively. In addition to its involvement in nuclear-cytoplasmic trafficking of transcription factors, the cytoskeleton network is a well-known target of oxidative stimuli. In this context, we studied if Yap1 activity induced by oxidative stress agents is specifically dependent on the cytoskeleton.
In 2008 we showed expression of a selection of specific target gene/activator(s), including Msn2/4, induced by oxidative stress agents; effects of the different stress agents on the cytoskeleton as determined by fluorescence microscopy and evaluated the transcriptional activity in cells with affected cytoskeleton.

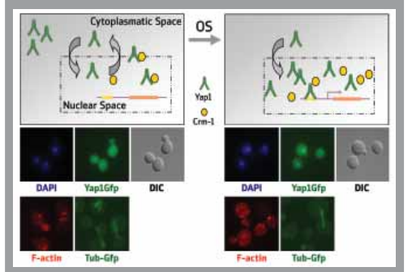
MOLECULAR MECHANISMS BRIDGING PROTEIN FOLDING AND TRANSCRIPTION ACTIVATION.

GimC, also known as prefoldin, is a cytoplasmatic complex composed of 6 distinct subunits (Gim1-Gim6 and Pfd1-Pfd6 in *Saccharomyces cerevisiae* and mammals, respectively) that promotes the formation of functional actin and tubulin, essential components of the cytoskeleton. GimC binds to nascent chains of these substracts, delivering them, after completion, to the chaperonine TRiC/CCT for efficient folding. However, the Gim proteins are not essential and data in the literature suggest alternative functions for several of the GimC subunits. Our results obtained with *gim*-mutants pinpoint different activities of each Gim subunit within the cell, in particular, under environmental stresses, and differential contribution for stress-gene(s) expression. Considering that activation of transcription is the common regulated event in the cellular response(s) to the stress(es) that requires the identified stress-gene(s), we are interested in understanding if folding is required for transcription by RNA pol II, and the role of Gim(s) in regulated transcription. Our findings in the past year suggest that impairment of transcriptional activation and/or basal transcription is not due to defects at the level of DNA-binding regulators.

GROUP MEMBERS
João Coelho (Research Fellow)
Susana Broa (Trainee, left September 2008)
Mafalda Cavaleiro (MSc student)



Oxidative stress signaling.



Yap1 intracellular localization, F-actin and microtubule cytoskeleton of *Saccharomyces cerevisiae* prior and upon exposure to oxidative environments by fluorescence microscopy.

THIS GROUP COLLABORATES WITH:
Isabel Gordo (IGC)
Martine Collart (University of Geneve, Switzerland)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

TELOMERES AND GENOME STABILITY

Miguel Godinho Ferreira
PhD in Cell Biology
University College London, United Kingdom
E-mail: mgferreira@igc.gulbenkian.pt

Telomeres protect the ends of linear eukaryotic chromosomes from being recognised as deleterious DNA double strand breaks (DSBs). Just a single DSB is able to stop cell cycle progression and activate repair processes. In contrast, all telomeres prohibit DNA repair, as it may lead to chromosome-end fusions - a source of genomic instability and a step in tumourigenesis. This fundamental function fades as telomeres get progressively shorter in cells of older people, thus limiting the capacity of tissue renewal and increasing the probability of cancer.
Our aim is to understand how telomeres block DNA repair and, when this function fails, how cells respond to unprotected chromosomes. Using fission yeast as a model system, we plan to identify key players and the mechanisms underlying these events. In this way we hope to provide important insights into the initial stages of cancer formation as well as specific candidate targets for future therapeutic interventions.

END-PROTECTION AND DNA REPAIR AT S. POMBE TELOMERES

The aims of this project are twofold: to find new players and further characterise the known components responsible for chromosome-end protection, and to understand the principles governing dysfunctional telomeres as substrates for DSB repair.
Taking a broader approach to the issue of telomeric protection, we developed an assay that would allow screening for genes involved in telomere capping. For that end, a linear plasmid containing 40bp of telomeric sequences at each end was developed, in such a way that, when joined together, a marker gene (his3+, responsible for the production of histidine) would be expressed. This strategy was meant for direct selection of mutants that cause telomere fusions through uncapping.
Screening of candidate genes is currently being undertaken by overexpression of potential candidates, using a cDNA library. This initial straightforward screen should produce novel telomere protectors.

INHIBITON OF GENOMIC INSTABILITY BY TELOMERE PROTECTION

We plan to identify and characterise new components responsible for chromosome-end protection in a screen based on a novel assay. Previous attempts to discover proteins involved in telomere protection have been based on telomere functions unrelated to end-protection (such as sub-telomere gene silencing). In contrast, the strategy proposed in this study is designed to directly capture telomere-telomere fusions.
We initiated work in screening for candidate genes, first by overexpression of potential candidates, using a cDNA library, which bore no significant results, and then by performing mass random mutagenesis in a wild-type background. From these, temperature-sensitive (ts) mutants were selected, that were able to grow in the absence of histidine at 36°C, but not at 25°C. Initial candidates were then subjected to an independent screening through Pulsed Field Gel Electrophoresis (PFGE) to confirm chromosome fusions. Analysis of these mutants is still ongoing.

IDENTIFICATION OF ANTI-CHECKPOINT PROTEINS AT FISSION YEAST TELOMERES

We propose to identify and characterize the mechanism that protects telomeres from being recognized as damaged DNA. We have generated two novel assays that will allow us to directly test whether a protein or a process is required for telomere protection. The first will allow us to screen for components that are involved in preventing chromosome-end fusions or DNA damage recognition. The second assay will test whether these components are sufficient to confer telomere-like protection to a newly formed DSB.

GROUP MEMBERS
Clara Reis (Post-doc)
Tiago Carneiro (Post-doc)
Hugo Almeida (PhD Student)
Ana Teresa Avelar (PhD Student)
Vanessa Borges (MSc Student, left September 2008)
Miguel Teixeira (Trainee, left October 2008)
Maria Gallo (Trainee)

We have shown thus far that removal of Taz1 from fission yeast telomeres, while having no effect in the cell cycle progression, renders taz1- telomeres vulnerable to DNA repair. This, in turn initiates a DNA damage response that does not lead to a cell cycle arrest due to failure of accumulating Crb2 at these dysfunctional telomeres. However, removal of Pot1 in this setup results in a full checkpoint activation leading to a cell cycle arrest demonstrating that Pot1 is the true anti-checkpoint protein.

THIS GROUP COLLABORATES WITH:
Stephane Marcand, (CEA/Saclay, France)
Aidan Doherty (Sussex Centre for Genome Damage and Stability, UK)
Tim Humphrey (University of Oxford, UK)

FUNDING
Association for International Cancer Research, UK
Fundação para a Ciência e a Tecnologia (FCT), Portugal

THEORETICAL EPIDEMIOLOGY

Gabriela Gomes
PhD in Mathematics
University of Warwick, United Kingdom
E-mail: ggomes@igc.gulbenkian.pt

Infectious agents that do not induce sterilising immunity pose major challenges to vaccine development and evaluation. A duality between individual-level phenomena (such as modes of immune response) and population-level measurements (such as patterns of disease incidence) is established through mathematical models. Research in the Theoretical Epidemiology group is primarily developed around the dual concepts of "partial immunity" and "reinfection thresholds", linking biological bases with epidemiological consequences.
More generally, we develop conceptual models that combine the ecology and evolution of infectious agents in order to detect selection in sequence data and guide the design of medical interventions.
In addition to scientific research, we are actively involved in fostering and implementing public databases and raising public awareness for the diversity of scientific research associated with infectious diseases.

REINFECTION THRESHOLDS AND THE MANAGEMENT OF RECURRENT INFECTIONS

The aim of this project is to refine the reinfection threshold concept as to become a standard measure in public health practice. The project focuses on tuberculosis, influenza, malaria, pertussis and dengue.
We have formulated the frailty hypothesis in tuberculosis, to reconcile partial immunity with the conflicting observations of reinfection rates that are higher that rates of new tuberculosis. We have identified an eradication threshold for malaria in regions of mesoendemic transmission and proposed specific strategies to eliminate the disease from those communities. We have developed models to estimate biological parameters for influenza from incidence data collected by Gripenet - an internet-based system to monitor influenza epidemics with the participation of the community. We have developed models for multiple serotype transmission in dengue and established a role for temporary cross-immunity in sustaining chaotic dynamics.

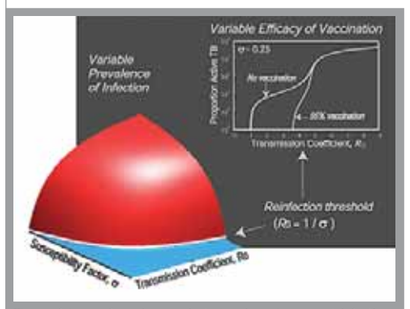
STRAIN DYNAMICS: THEORETICAL FRAMEWORK FOR ANTIGENIC DIVERSITY

The am of this project is to categorise existing models for antigenically diverse pathogens, identify any gaps and build any hybrid models that are needed to be able to fully describe relationships.
Focusing on influenza, we have investigated associations between antigenic diversity and other phenomena, such as pathogen evolution and host heterogeneity.

GRIPENET

The aim of this project is to develop an internet-based monitoring system for influenza-like illness (ILI) where automated functions are prioritised. A platform has been implemented to satisfy criteria of transportability to other countries and other diseases, such as gastroenteritis and dengue.
For the influenza season 2007/08, we collected around 35,000 questionnaires on ILI incidence. The database is freely available online, for research purposes. During 2008, the Gripenet database and computational infrastructure were moved to the server network of the National Foundation for Scientific Computation/FCCN. A partnership with Portugal Telecom was set-up and the partnership with the University of Porto, established in 2007, was maintained. Furthermore, several information sessions were carried out at Senior Universities (for mature students) of the Lisbon metropolitan area, resulting in an increased participation of older age groups, thus improving the sample representation. Also, we developed tools for real-time visualisation of the results, and extended the system to monitor gastrointestinal symptoms Gastronet (active since October 2008).

GROUP MEMBERS
Jaime Combadão (Post-doc)
Flávio Codeço Coelho (Post-doc)
Philip Gerrish (Post-doc)
Marta Nunes (Post-doc)
Andrea Parisi (Post-doc)
Ana Cristina Paulo (Post-doc, left May 2008)
Nico Stollenwerk (Post-doc, left September 2008)
Gareth Weedall (Post-doc, left October 2008)
Paula Rodrigues (PhD Student)
Ricardo Águas (PhD Student)
Sander van Noort (PhD Student)
Nuno Oliveira (MSc Student, left October 2008)
Susana Pinheiro (Trainee)
Maíra Aguiar (External PhD Student)
Stefan Wieland (External PhD Student)
José Miguel Lima Lourenço (Informatics Technician left September 2008)
Joseph Ssentongo (Research Technician)
Vitor Faustino (Gripenet Executive Coordinator)
Inês Crisóstomo (Programme Manager)



The usefulness of vaccines against chronic and recurrent infectious diseases is debatable. Measured protection spreads over wide ranges and low impact appears associated with high pre-vaccination levels of disease. The figure illustrates a new concept where vaccine protection is a curve whose essence cannot be collapsed into a number.

MOLECULAR EPIDEMIOLOGY OF *MYCOBACTERIUM TUBERCULOSIS* IN PORTUGAL

The importance of reinfection in *M. tuberculosis* transmission is well recognised. Direct identification of reinfection cases in a community requires the widespread use of genotyping techniques and these data are essential to parameterise mathematical models of transmission. The primary objectives of this project are: (i) to define the distribution and origin of genotypes that circulate in Portugal; (ii) to infer patterns of transmission and pathogenesis; (iii) to setup a database of *M. tuberculosis* genotypes circulating in Portugal.
We have selected the SNPs markers that will be correlated with geographic distribution, phylogeny and antibiotic resistance of the strains. We have conducted a pilot study with 57 bacterial isolates, using 64 SNPs.

THIS GROUP COLLABORATES WITH:
José Pereira-Leal, Carlos Penha Gonçalves (IGC)
António Fonseca-Antunes (Direcção-Geral da Saúde, Portugal)
Anabela Miranda, Susana David
(Instituto Nacional de Saúde Dr Ricardo Jorge, Portual)
Julia Gog (Cambridge University , UK)

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Fundação para a Ciência e a Tecnologia (FCT), Portugal
Royal Society, UK
POSC - Programa Operacional Sociedade do conhecimento, Portugal

EVOLUTIONARY BIOLOGY

Isabel Gordo
PhD in Biology
University of Edinburgh, United Kingdom
E-mail: igordo@igc.gulbenkian.pt

Our group combines both theoretical and empirical work aiming at a better understanding of the major forces that shape variation in populations.
The model organisms we use are *Escherichia coli* and *Tetrahymena thermophila* (and related ciliate species). We test predictions of evolutionary genetics theory about the evolution of mutation rates, recombination rates and the genetics of adaptation. Current work involves mainly: measuring genetic interactions in bacterial genomes (with applications to the evolution of antibiotic resistance), assessing the role of biotic interactions in the emergence and maintenance of species diversity, and understanding the molecular signatures of adaptive variation in pathogen populations.

GROUP MEMBERS
Lilia Perfeito (PhD student, graduated September 2008)
Sara Magalhães (Post-doc, left September 2008)
Ana Margarida Sousa (Post-doc)
Patricia Brito (Post-doc)
Sandra Trindade (PhD Student)
Inês Conceição (External PhD Student)
Migla Miskinyte (PhD Student)

RATES AND EFFECTS OF MUTATIONS IN *TETRAHYMENA THERMOPHILA*

The aims of this project are: to estimate genomic mutation rate to fitness altering mutations in the ciliate *Tetrahymena thermophila,* to assess the role of copy number variation in the macronucleous in mutational meltdown occurring during evolution under intensified genetic drift and to evaluate the role of sexual reproduction.
We have performed a classical mutation accumulation experiment in *Tetrahymena thermophila*. Much to our surprise we have found that all the 20 lines of *Tetrahymena thermophila* that were propagated go extinct within 20 bottlenecks. This was not at all expected in our initial planning of this project and has led us to formulate a new hypothesis, whereby we postulated that for *Tetrahymena thermophila* populations to survive they would have to conjugate frequently.
This initial result and hypothesis generate new questions amenable to experimental testing:
a) how does the closely related species *Tetrahymena pyriformis*, which lacks micronucleous and is asexual, evolve when subject to bottlenecks? b) Can we show that natural populations of *Tetrahymena thermophila* frequently engage in sex?
Our preliminary data obtained with *Tetrahymena pyriformis* suggest that this species is more resistant to extinction. Our results indicate that asexual species of protozoa are more resistant to mutational meltdown than sexual species. We postulate that copy number variation is the key for understanding these results. If this is a correct hypothesis then it can be tested by showing that *Tetrahymena pyriformis* has a higher mean copy number. More generally, we hypothesise that asexual ciliates derive from sexual ones through loss of micronuclei and increments of ploidy of the macronuclei.
In the context of our data, recent literature on the role of sex (Keightley and Otto, Nature 2006) and the need of a quantitative interpretation of the experimental data, we began mathematical modelling. Our studies have led to the publication of a paper in *Genetics*, on the evolutionary advantage of sex and recombination.

DIVERSITY AND MOLECULAR EVOLUTION OF PATHOGEN POPULATIONS

Genetic diversity of pathogen populations contains important information about their epidemiology and evolution. Understanding this diversity is an important subject in evolutionary biology, ecology, epidemiology, population genetics and biomedical sciences.
In this project, we aim to develop and apply a mathematical framework integrating ecological/epidemiological and population genetics concepts towards a better understanding of pathogen molecular variation, understand the role of compensatory mutations during microbial evolution and study the importance of biotic interactions in microbial evolution.
We have been developing a mathematical framework that aims integrate models in epidemiology and models in population genetics and that should

contribute to a better understanding of pathogen molecular variation. In 2008 we published a paper in *Biol. Letters* and submitted another to *PLoS One*.
We have studied the levels and patterns of neutral genetic variation in classical epidemiological models such as the Susceptible-Infected-Susceptible (SIS) and Susceptible-Infected-Recovered SIR) models. We have shown that the level of pathogen variation is well predicted by analytical expressions, such that pathogen neutral molecular variation is bounded by the level of infection and increases with the duration of infection. We then introduced selection into the model, identified the molecular signatures during the replacement of new selected strain and compared these with those observed in sequences of influenza A.
We have studied a model of adaptation with application for a wide range of microbes. Ongoing work involves quantification of epistasis amongst antibiotic resistance mutations in bacterial populations, an issue of significant importance both at the fundamental research level but also leading towards increased understanding of the epidemiological patterns of multi-resistant pathogens, such as M. tuberculosis.

THIS GROUP COLLABORATES WITH:
Lisete Fernandes, Gabriela Gomes, Helena Soares (IGC)
Francisco Dionisio (University of Lisbon, Portugal)
Paulo Campos (Universidade Federal Rural de Pernambuco, Brazil)
Doris Bachtrog (University of California at Berkeley, USA)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

ACTIN DYNAMICS

Florence Janody
PhD in Developmental Biology
Université de la Mediterranée, Marseille, France
E-mail: fjanody@igc.gulbenkian.pt

Actin is one of the most abundant and highly conserved proteins in Eukaryotes. Actin monomers can polymerise into filaments, forming the actin cytoskeleton, which controls numerous processes, including the generation and maintenance of cell morphology and polarity, endocytosis, intracellular trafficking, contractility and cell division. Polymerisation, depolymerisation and organisation of actin filaments into functional higher-order networks are controlled by a plethora of actin-binding proteins (ABP), that are highly conserved between species. Several lines of evidence strongly suggest that, in epithelia, distinct dynamical actin filament populations exist with specialised functions depending on cell identity.
Using *Drosophila* as a model system, which allows for relatively easily manipulation of gene expression *in vivo*, we aim to understand how cytoskeletal organisation is regulated in distinct epithelia. Research in our group addresses a fundamental aspect of cell biology, but may also contribute to broaden our understanding of diseases associated with actin dynamics, such as cancer.

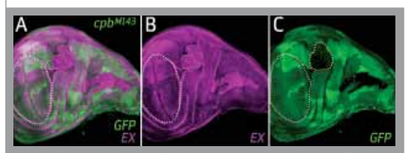
USING *DROSOPHILA* TO UNDERSTAND THE MOLECULAR CONTROL OF ACTIN DYNAMICS IN ABERRANT ACTIVE CELL MIGRATION

The goal of this project is to gain some insight on how the dynamics of the actin cycle is regulated to prevent tumour formation.
In the last year we have shown that *CP* prevents neoplastic tumor formation of restricted epithelia. In the wing blade epithelium, mutant cells for *CP* show neoplastic tumour characteristics: discrete patches of *CP* mutant cells loose polarity, extrude and die, while cells can survive if the whole tissue is affected. Moreover, expressing the Ras^{V12} oncogene results in neoplastic overgrowths of *CP* mutant clones. Furthermore, apoptotic *CP* depleted cells kept alive by overexpressing *p35*, induce excessive mitotic signals, such as Wingless and promote extra growth and proliferation of surviving *CP* depleted cells. The tumour suppressor function of CP might be to promote the formation of a subopulation of actin filaments required for remodeling of E-Cadherin, since CP interact genetically with aPKC and both stimulate endocytosis.
We have also sown that CP restricts growth by controlling the Hippo (Hpo) pathway. Loss of *CP* induces tissue overgrowth of the polarised distal hinge epithelium monolayer associated to upregulation of Hpo target genes. *CP* interacts genetically with *hpo* and may act upstream of *hpo*, since depleting *CP* does not restore growth of cells overexpressing *hpo*. Taken together our findings suggest that CP regulates a pool of actin filaments that respond to changes in cortical tension exerted through contact with neighboring cells to promote Hpo activation.

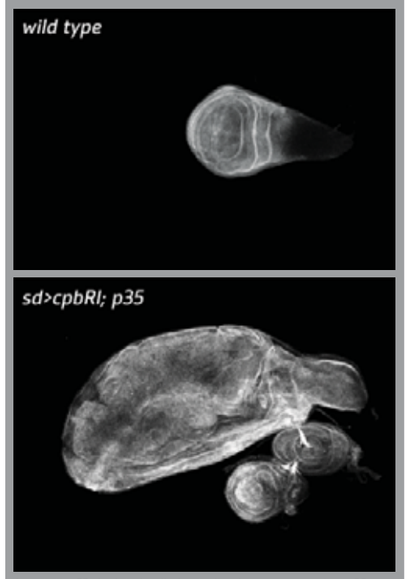
MOLECULAR CONTROL OF ACTIN DYNAMICS AND CHANGE IN CELL SHAPE IN THE MORPHOGENETIC FURROW DURING *DROSOPHILA* EYE DEVELOPMENT

The goal of this research project is to understand how the dynamics of the actin cycle is regulated to promote the change in cell shape in the morphogenetic furrow.
During the last year we have shown that actin genes are differentially regulated in the eye disc epithelium. All actin genes are differentially expressed in the eye disc epithelium. Moreover, each actin incorporates into specific filament structures. Interestingly, actin 42A is upregulated in a stripe, which might correspond to the MF and incorporates strongly in apical actin filament structures, suggesting that this actin forms a distinct apical population, able to respond to myosin II and induce change in cell shape in the MF.
We have also demonstrated that Actin-Capping Protein (CP) is required for the transient change in cell shape in the MF and for photoreceptor differentiation to occur normally. Interestingly, CP maintains apical localisation of the

GROUP MEMBERS
Sofia Rebelo (Laboratory Technician, left March 2008)
Maurícia Vinhas (Laboratory Technician, left September 2008)
Pedro Miguel Gaspar (External MSc Student)
Barbara Jezowska (PGD PhD Student)
Beatriz Garcia Fernández (Post-doc)
Catarina Bras-Pereira (Post-doc)



Group of cells mutant for *CP*, marked by the absence of GFP (green in A and C) are not recovered in the wing blade epithelium (dashed white line) but seem to overgrowth in the remainder of the disc (yellow dashed line) and accumulate Expanded (Magenta in A and B).

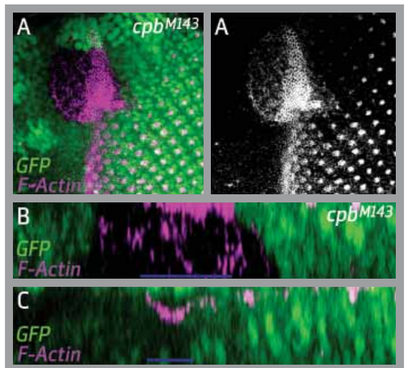


Apoptotic *CP* depleted cells kept alive by overexpressing *p35* promote extra growth and proliferation of surviving *CP* depleted cells. Compare wild type (upper panel) to *sd>cpbRI; p35*- expressing discs (lower panel)

b-Catenin homolog Armadillo and E-Cadherin. The role of CP in the MF might be to maintain the integrity of the apical actin belt, which provides the motile force necessary for apical constriction through Myosin II.
Our recent findings suggest that dachshous (dac), the most downstream element among the known components of the RDGN, is required for the propagation of retinal differentiation and maintains the shape of differentiating photoreceptor cells.

UNDERSTAND HOW CYTOSKELETON ORGANISATION IS REGULATED IN GENETICALLY DISTINCT EPITHELIA

The goal of this project is to determine how patterning genes regulate cytoskeleton organisation to achieve distinct morphological outcomes. Until very recently, it was assumed that all epithelia are equivalent in terms of cytoskeleton and/or junctional properties. However, we found that epithelial cells do not have the same requirement for Capping Proteins (CP), suggesting that cytoskeleton organisation is tightly regulated in genetically distinct epithelia. Extrusion of *cpa* mutant cells is dependant of the Vestigial (Vg) transcription factor, which specifies the wing blade epithelium and enhances transcription of *cpa* in this region. Thus, one function of Vg is to specify the cytoskeletal changes that lead to morphogenesis of the adult wing. To get some insights on how patterning genes, such as *vg*, regulate cytoskeleton organisation to achieve distinct morphological outcomes, we are investigating which domains of CP mediate CP functions in divers epithelia by performing a structure function analysis of the CP heterodimer in transgenic flies. Moreover, we are performing a candidate screen to identify molecules that suppress or enhance the CP depletion phenotype.



CP prevents ectopic actin filament accumulation anterior to the MF (A) and promote the change in cell shape in the MF (B). **Upper panel** - Standard confocal sections. **Lower panel** - Optical cross sections through the eye imaginal disc. *cpb* mutant cells are marked by the absence of GFP (in green) and stained for Phalloidin, which marks F-actin (in Magenta). The blue lines indicate the MF in *cpb* mutant cells (B) or *wild type* cells (C).ing.

THIS GROUP COLLABORATES WITH:
Helen Richardson (Peter MacCallum Cancer Institute, Australia)
Nicolas Tapon (Cancer Research UK, UK)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

EPIGENETIC MECHANISMS

Lars Jansen
PhD in Molecular Genetics
Leiden University, The Netherlands
E-mail: ljansen@igc.gulbenkian.pt

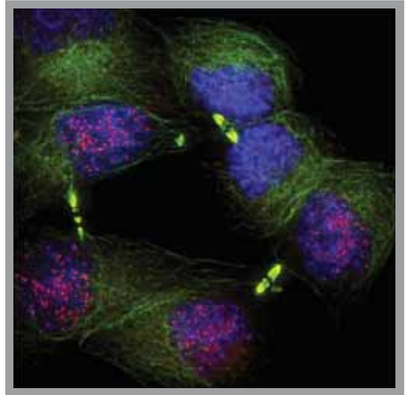
THIS GROUP WAS ESTABLISHED AT THE IGC IN APRIL 2008.

During human development a single zygote differentiates into approximately 200 different cell types that, despite being genetically identical, maintain their cellular identity through mitotic divisions. Therefore, in addition to the genomic information embedded in the primary DNA sequence, epigenetic information is propagated as well, that "memorizes" gene activity states and specific chromatin structures across somatic division and sometimes even across generations. Several molecular components such as histone proteins and modifications thereof have been implicated in this process but in most cases we don't understand the logic of how something other than DNA can be faithfully duplicated when a cell divides. We have a broad interest in how this works. We are using molecular genetic and cell biological tools with a focus on novel fluorescent labeling techniques, high-end microscopy and the latest tricks in genetic engineering of human cells to tackle a wide range of problems in this emerging and fascinating area of biology.

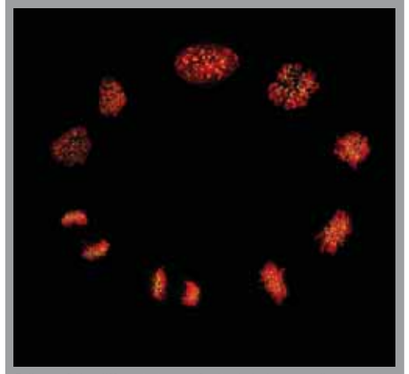
THE MECHANISM OF EPIGENETIC CENTROMERE ASSEMBLY

This project aims at elucidating aspects of centromere inheritance by focusing on the centromere specific histone H3 variant CENP-A. We have previously established, using a novel fluorescent pulse labeling technique that CENP-A is assembled into centromeric chromatin during a unique cell cycle window in early G1. We proposed here to determine the mechanism of CENP-A assembly and its cell cycle control. This will be achieved by using fluorescence techniques that include SNAP-tagging. Using a multifaceted approach we aim at understanding the molecular details of how CENP-A as an epigenetic mark is itself inherited. Such insight will uncover general principles of epigenetic inheritance which so far are lacking.
Thus far, in the initial 10 months this project is running we have determined how the cell cycle dependent timing of CENP-A assembly is controlled and how it is linked to mitotic exit. Furthermore, we have identified constitutive centromere components that facilitate the assembly of CENP-A chromatin. Lastly, we have established a large panel of cell lines expressing SNAP-tagged centromere components that we are currently analyzing for turnover and assembly to identify the stable core of the centromere complex.

GROUP MEMBERS
Mariana Silva (PhD Student)
João Mata (Research Technician)
Nuno Martins (Trainee)



Formation of nascent centromeric chromatin (red foci) in human G1 phase cells visualized by fluorescent pulse labelling. Microtubules and DNA are shown in green and blue respectively to indicate cell cycle position.



Collage of the different stages of mitosis in human cells expressing a YFP-tagged centromeric histone that is engineered at the endogenous genomic locus (yellow foci). DNA is shown in red.

FUNDING
Calouste Gulbenkian Foundation, Portugal - IGC start up fund
European Commission Framework Programme 7 (FP7)
- Marie Curie International Reintegration Grant

TISSUE MORPHOGENESIS

Mathias Koeppen
PhD in Cellular and Molecular Biology
University of Wisconsin-Madison, USA
E-mail: koeppen@igc.gulbenkian.pt

THIS GROUP WAS ESTABLISHED AT THE IGC IN MAY 2008.

Our focus is the analysis of fundamental mechanisms of tissue morphogenesis in the zebrafish embryo, using high-resolution live microscopy in combination with genetic and embryological techniques. Specifically, we are interested in the morphogenetic behaviour of the embryonic surface epithelium, the enveloping layer. During the first few hours of zebrafish development, this tissue enwraps and seals the embryo in a process called epiboly. This process is of general interest, since it occurs in many developmental contexts and during the healing of wounded tissue. Interestingly, we recently found that the enveloping layer plays a central role during the formation of the first zebrafish organ, Kupffer's vesicle. The laboratory will therefore pursue two main lines of investigation; (1) Analysis of the cellular and molecular mechanisms that control the spreading and sealing of the enveloping layer; (2) Study of the origin and morphogenesis of Kupffer's vesicle.

GENETIC AND MECHANICAL BASIS OF ENVELOPING LAYER MORPHOGENESIS

We are genetically testing the mechanisms driving enveloping layer epiboly, with a specific focus on tight junctions. These junctions link the tissue to the underlying yolk surface, which likely plays a critical role in the movement process. Furthermore, we are investigating the forces driving the epiboly process using laser microsurgery, and developing methods to systematically analyze the pattern of cell shape changes during epiboly.
We have recently shown that inhibiting the tight junction protein ZO-3 impairs EVL movement, highlighting the role of tight junctions during the process. Phenotypic analysis will continue using the new multi-photon microscope at IGC to reveal specific defects in dynamic cell behaviour. Using the same microscope, we have established the methodology to generate local lesions in the enveloping layer, allowing us to identify forces within the tissue. Also, we are now able to perform semi-automated cell shape analysis using a software developed at the MPI in Dresden. This allows systematic analysis of effects on cell morphology given various manipulations.

GROUP MEMBERS
Susana Lopes (Post-doc)
Inês Cristo (Research Technician)
Paulo Raimundo (Trainee)
Pedro Almada (Visiting Undergraduate Student)

A 10-somite zebrafish embryo.

FUNDING
Calouste Gulbenkian Foundation, Portugal - IGC start up fund

ORGANOGENESIS

Joaquin Rodriguez Léon
PhD in Biology
University of Extremadura, Spain
E-mail: jrodleon@igc.gulbenkian.pt

Our scientific research is focused in developmental biology. The main interest of the lab is to elucidate the genetic and molecular cascades controlling cell differentiation and how they contribute to organogenesis and morphogenesis of different structures during development and regeneration. The main organs we use as a model are limb buds and fins. In the team we are using the chick embryo and zebrafish as animal models.

ROLE OF FLRT3 DURING LIMB BUD DEVELOPMENT

The aim of this study is to unravel the role of flrt3 during limb bud development. For this purpose we have described the expression pattern of flrt3 during limb development, studied its relationship with different signaling molecules and performed functional studies involving silencing of flrt3 expression.
Our results show that flrt3 expression in limb buds is restricted to the AER and a small portion of the surrounding ectoderm, co-localising its expression with fgf8 and pERK activity. Moreover, we have observed that flrt3 expression is not regulated by FGF activity, although ectopic Wnt3a is able to induce flrt3 expression. Loss-of-function studies have shown that silencing flrt3 affects the integrity of AER and, subsequently, its proper activity during limb bud outgrowth.

THE ROLE OF ERG1 (KV11.1) POTASSIUM CHANNEL IN VERTEBRATE LIMB INDUCTION AND OUTGROWTH

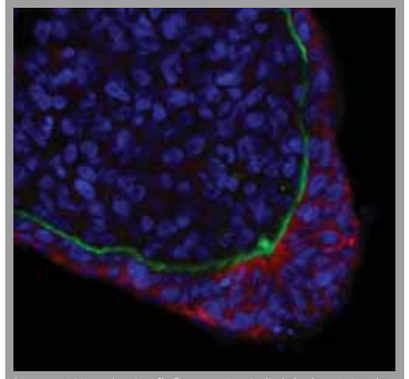
During limb bud initiation, a cross-talk between the mesoderm and the ectoderm in the lateral side of the embryo has been described as critical. This genetic cascade has been shown to be conserved among all vertebrates studied. One suggested epigenetic mechanism for limb bud initiation involves endogenous electric current loops in the limb field. Our group has found that the potassium channel ERG1 (the homolog of human hERG, also known as Kv11.1) is expressed in the prospective limb field and, in later stages, its expression is restricted to the progress zone, a highly proliferative region of the limb bud. Experiments of down-regulation of erg1 by RNAi result in limb truncation suggesting that this channel does indeed play an important role in limb induction and outgrowth. ERG channels are well-known voltage-dependent potassium channels involved in cardiac repolarisation. Recently, new roles have been assigned to these channels such as in hormone secretion, cell proliferation and cell migration. Our results also point to a control of cell proliferation by Erg1 in the limb and we will test the molecular model proposed for cancer cells in limb induction.

PITX2 REGULATES GONAD MORPHOGENESIS

Organ shape and size, and ultimately, organ function, relates in part to the cell and tissue spatial arrangement that takes place during embryonic development. How specific gene functions are linked to specific morphogenetic processes during the establishment of organ size and shape is still not clearly understood. Focusing on chick gonad embryogenesis, we have described findings that represent a first step towards understanding, at a cellular level, how the transcriptional activity of Pitx2 might regulate morphogenesis and organ function.
In 2008, we provided evidence that, in vertebrates, a key determinant of left-right asymmetry, the transcription factor Pitx2, is capable of influencing organ shape and size and consequently, organ function and morphogenesis, by altering somatic cell morphology, extracellular matrix composition, spindle orientation and cell proliferation. Furthermore, our results suggest that Pitx2c, in concert with CyclinD1, might be part of a mechanism that allows the somatic cell compartment to control PGC survival and proliferation and consequently, provide sufficient numbers of PGCs to fill the stem cell niches formed during avian gonad embryogenesis.

GROUP MEMBERS
Ana Catarina Certal (Post-doc)
Ana Tavares (Post-doc)
Ana Raquel Tomás (PhD Student)
Joana Monteiro (Research Technician)
Frederico Matos (External MSc Student)
Ana Rita Aires (External MSc Student)

Expression of the potassium channel Erg1 in stage 20 chick embryo, visualised by in sity hybridisation.



Immunostaining showing flrt3 expression in limb buds restricted to the AER in the developing chick limb bud.

FUNDING
Fundação para a Ciência e a tecnologia (FCT), Portugal
European Commission Framework Programme 6 (FP6)
- Cells into Organs Network of Excellence
Instituto de Salud Carlos III, Spanish Ministry of health, Spain
TV3 La Marató Foundation, Spain

SYSTEMS NEUROSCIENCE

Zachary Mainen
PhD in Neurosciences
University of California, San Diego, USA
E-mail: zmainen@igc.gulbenkian.pt

THIS GROUP IS A MEMBER OF THE CHAMPALIMAUD NEUROSCIENCE PROGRAMME AT THE IGC.

We are interested in understanding the principles underlying the complex adaptive behaviour of organisms. Starting with quantitative observations of animal behaviour, we aim to integrate quantitative cellular and systems level experimental analysis of underlying neural mechanisms with theoretical, ecological and evolutionary contexts. Rats and mice provide flexible animal models that allow us monitor and manipulate neural circuits using electrophysiological, optical and molecular techniques. We have made progress using highly-controlled studies of a simple learned odor-cued decision task and are extending our focus toward more complex behaviours. Projects in the lab are wide-ranging and continually evolving. Current topics include: olfactory sensory decision-making, the function of the serotonin system and the role of uncertainty in brain function and behaviour.

GROUP MEMBERS
Masayoshi Murakami (Post-doc)
Guillaume Dugué (Post-doc)
Gil Costa (External PhD Student)
Niccolò Bonacchi (External MSc Student)
Maurícia Vinhas (Research Technician)
Raquel Gonçalves (Research Technician)
Jörg Löhken (Informatics Technician)
Pedro Garcia Da Silva (Trainee)
Alexandra Piedade (Trainee)
Paula Santos (Programmer)
Maria Inês Vicente (PhD Student)

NEURAL MECHANISMS OF UNCERTAINTY

Humans and other animals must often make decisions on the basis of imperfect evidence. What is the neural basis for such judgments? How does the brain compute confidence estimates about stimuli and decisions? Previously, we found that a population of neurons in the orbitofrontal cortex (OFC) can track the difficulty of a decision. We seek to extend these initial observations by trying to establish that confidence-related neural activity in the OFC is causally related to confidence judgments. We hypothesize that confidence-related neural activity in OFC can predict the willingness to wait for a reward, on a trial-by-trial basis. Moreover, we also intend to address how the uncertainty about a stimulus in the course of decision-making is computed in a sensory cortex. These experiments will give us further insights into the nature of the neural processes underlying confidence estimation.
Our preliminary results show that if a rat is surer about the circumstances that lead to his decision, it is willing to wait more for the reward, and vice-versa. Also, rats reported their confidence differently when they were making a correct decision or a wrong one. Furthermore, pharmacological inactivation of OFC seems to impair rats' ability to report confidence without affecting olfactory discrimination performance. These results suggest that a dynamic representation of and access to an internal measure of decision confidence is fundamental to adaptive behaviour.

OPTICAL-GENETIC IDENTIFICATION AND CONTROL OF SEROTONIN NEURONS IN BEHAVING ANIMAL

Serotonin is an important neurotransmitter implicated in a wide variety of physiological functions and pathophysiologies but whose function is not well understood. Critically, very little is known about the activity of serotonin-releasing neurons in the brain. This problem is greatly exacerbated by the difficulty in identifying serotonin-containing neurons. To address these problems we will use a combination of behavioural analysis, electrophysiological recording and optical-genetic probes targeted through specific promoters to this class of cells. By selectively activating serotonin neurons with light delivered through implanted fiber optics, we will be able to positively identify them during recordings and to specifically activate them, allowing us to test specific hypotheses concerning the role of serotonin in brain function and behaviour.
To be able to selectively activate serotonin neurons in vivo, we need to selectively express the photosensitive protein Channelrhodopsin-2 (ChR2) in serotonin neurons. In 2008, we tested a viral expression strategy to deliver ChR2 to serotonin neurons in rats. This strategy is based on adeno-associated viruses carrying a custom-made transgene. This transgene contains a regulatory element that drives expression specifically in serotonin neurons. Using standard histological techniques, we were able to show that this strategy results in a strong, stable and specific expression of ChR2 in serotonin neurons. In parallel, we developed a system for fiberoptic light delivery in behaving animals.

FRONTAL CONTROL OF IMPULSIVE ACTION

Inhibition of behaviour is as important as its generation, and impulsivity is a common central feature of pathologies including attention deficit hyperactivity disorder, drug addiction and obsessive compulsive disorder. The aim of the project is to understand how the frontal cortex is involved in inhibiting impulsive actions. The specific aims are 1) to reveal the activity of frontal cortical neurons while rats are engaged in impulse control task and 2) to examine the effect of inactivating subregions of frontal cortex on impulse control behaviour.
We recorded from neurons in the medial prefrontal cortex (mPFC) and the secondary motor cortex (M2), while rats were performing the impulse control task. We found that the activity of subpopulations of mPFC and M2 neurons predict the impulse control performance of rats in the task, which suggests the role of those frontal areas in withholding impulsive action.
In order to examine the causal role of the frontal cortex in withholding impulsive action, we examined the effect of reversible inactivation of the mPFC on impulse control behaviour. Inactivation of the mPFC impairs the ability of rats to inhibit impulsive action.
These results suggest a role of frontal cortex in withholding impulsive actions.

THIS GROUP COLLABORATES WITH:
Susana Lima (IGC)

FUNDING
Champalimaud Foundation, Portugal
- Champalimaud Neuroscience Programme start up fund

PATTERNING AND MORPHOGENESIS

Moises Mallo
PhD in Biochemistry and Molecular Biology
Universidad de Santiago de Compostela, Spain
E-mail: mallo@igc.gulbenkian.pt

Our group is interested in several aspects of vertebrate embryonic development. The ultimate goal of our research is to understand the molecular mechanisms that translate patterning information into morphogenetic processes during formation of the vertebrate embryo. For a number of years, we have explored different developmental processes, including the ear formation, the neural crest induction/migration and differentiation of branchial arches. Specific emphasis was put on the role genes like Hoxa2, Ptx1, Bmp2 or Tbx1 played in those processes. Most recently our focus moved a bit and we are now exploring other biological processes, but still mostly linked to vertebrate embryonic development.

THE ROLE OF HOX GENES IN THE DEVELOPMENT OF THE VERTEBRATE AXIAL SKELETON

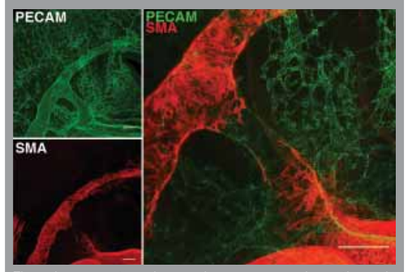
Hox genes are essential players in the proper formation of the axial skeleton of vertebrates. With this project we want to understand the mechanisms that mediate Hox gene activity in this process.
We have shown that Hox genes of the paralog group 6 are able to induce rib development, indicating that these genes are involved in the specification of the thoracic area. Analysis of these transgenics containing ribs in every vertebrae, together with those that have no ribs as a consequence of the activity of Hox group 10 genes led to the identification of some of the genes and mechanisms mediating their activity. In particular, we have shown that the Hox group 6 and group 10 genes control expression of the myogenic factors Myf5 and Myf6 in a specific embyonic domain: the hypaxial myotome. Expression of these genes in the myogenic precursors then induce skeletogenesis in adjacent myotomal cells, eventually inducing rib formation. Hox group 6 genes promote Myf5/6 expression in this domain and Hox group 10 genes block it, thus defining rib-containing and rib-less regions in the vertebral column. We also showed that the effect of these Hox genes is direct, as they interact in vivo with a Myf5 distal enhancer responsible for its expression in the relevant domain.

REMODELATION OF THE AORTIC TREE

Proper formation of the arteries that canalize the distribution of the blood that exit from the heart into the body requires a complex remodelation of an embryonic aortic system known as the aortic arches. We are interested in understanding the mechanisms responsible for this remodelation.
The remodelation of the embryonic aortic tree includes the regression of the first and second branchial arches. We found that early in development these arches form a vessel that does not contain smooth muscle cells. The third and fourth aortic arches, which do not regress, become associated to smooth muscle cells after they form a vessel, suggesting that this association is relevant for the stability of the vessels. To test this we looked at the aortic arches of two different mutants, with specific phenotypes in this area. The Pbx1 mutants only keep one aortic arch and analysis of the smooth muscle cells in this area showed that this is the only arch that becomes associated to smooth muscle cells. Conversely, the Endothelin1 mutants, in which have persistent second aortic arches, contain smooth muscle cells associated to these arteries. Finally, we forced smooth muscle cell differentiation in the area of the first and second arches through expression of myocardin using a transgenic approach and we found persistence of the second arches in these transgenics together with their association with smooth muscle cells. We conclude that the ability or not of the aortic arches to recruit smooth muscle cells is instrumental to the persistenence or regression of the embryonic aortic arteries.

GROUP MEMBERS
Natalia Moncaut (Pots-doc, left November 2008)
Jennifer Rowland (Post-doc)
Filipa Moraes (PhD Student)
Tânia Vinagre (PhD Student)
Ana Nóvoa (Research Technician)
Vanessa Urbano (Technical Assistant)
Isabel Guerreiro (Trainee)

The figure shows the skeletons of a wild type and of a transgenic embryo expressing the Hoxb6 gene in the presomitic mesoderm. The transgenic embryo has ribs associated to all vertebrae. This experiment shows that Hoxb6 is able to specify the thoracic character in the axial skeleton.



The embryonic aortic arches are shown in green and smooth muscle cells in red, after they were stained by immunofluorescence with antibodies against PECAM (endothelium) and smooth muscle actin (SMA, smooth muscle cells). Images were aquired with a confocal microscope. This figure illustrates the finding that only those aortic arteries that get associated with smooth muscle cells avoid regression.

THE ROLE OF GNE IN THE PATHOGENESIS OF THE HETEROLOGOUS INCLUSION BODY MYOPATHY

The Gne gene encodes for a key enzyme of sialic acid biosynthesis. Its mutation originates the human neuromuscular disorder Heterologous inclusion body myopathy (HIBM). While the patients suffer from muscular problems, Gne seems not to be expressed in the muscle but in liver cells. We want to understand the tissue specific requirements of Gne using a conditional mutagenesis approach to inactivate this gene either in the liver or in the muscle.
During the first phase of this project we have amplified by PCR different genomic regions of the GNE gene, which were confirmed by sequencing. With these pieces, a targetting construct was built, which included LoxP sites at introns 3 and 4. The neo selection cassette that was used for this construct was flanked by FRT sites to allow removal by Flp recombinase. This construct was used to electroporate ES cells and positive clones were obtained that will be used to generate mouse chimeras by injection into blastocysts.

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal
Advancement of Research for Myopathies (ARM), USA
(Jennifer Rowland and Moises Mallo)

EARLY FLY DEVELOPMENT

Rui Martinho
PhD in Biology
University of Sussex, United Kingdom
E-mail: rmartinho@igc.gulbenkian.pt

Our main research goal is to understand cell polarization, specifically, in the context of tissue morphogenesis and asymmetric mitotic division. We are also interested in germ line development as a model system to study cell totipotency and polarisation.

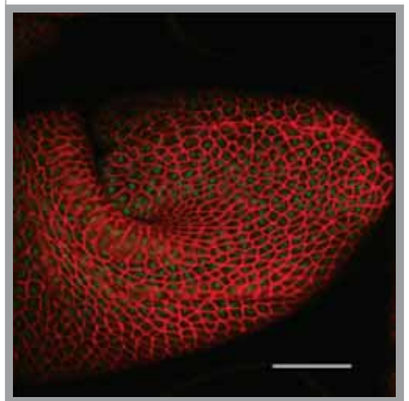
CHARACTERISATION OF THE TRANSCRIPTIONAL ACTIVATION OF THE QUIESCENT ZYGOTIC GENOME AFTER OOCYTE FERTILISATION

The aim of this project is to define the molecular process required for transcriptional activation of the zygotic genome.
Previously we isolated close to 300 independent *Drosophila* mutants lines that are defective for formation and morphogenesis of epithelial cells during blastoderm cellularisation and germ-band extension. We expect our mutants to belong to one of the following classes: 1) Cell cycle and nuclei migration mutants, 2) Transcription mutants, 3) RNA stability mutants, 4) Cell polarity or membrane invagination mutants. Through a candidate gene approach, we concluded that three of the isolated 2R complementation groups are allelic to genes known to be important for the formation and morphogenesis of epithelial cells. Additionally through the use of the 2R deficiency kit and a candidate gene approach, we also concluded that another 2R complementation group was allelic to the gene *separation* anxiety (*san*). *san* encodes an acetyltransferase and was previously identified as being important for sister-chromatid cohesion in Drosophila larvae brains.
One of the initial premises of this project is that we would isolate mutants defective for maternal to zygotic transition (MZT). Unfortunately until now we have failed to isolate any mutant that clearly belongs to this class. A possible exception is a recently characterised and mapped complementation group (G7) whose affected gene appears to be a transcription factor. This mutant shows a normal blastoderm cellularisation, yet fails early germ-band extension. We hypothesize that MZT is induced abnormally in this mutant. Further work is needed to fully characterize the function of this gene during Drosophila early embryonic development.
Given that since the submission of this grant in 2006 several important manuscripts describing MZT in Drosophila have been published in high profile papers, and since he have failed (until now) to isolate mutants clearly involved in MZT we decided to analyse further some of the isolated mutants not directly related with MZT. This work has allowed us to report a manuscript in an international peer-reviewed journal describing a gene required for chromosome segregation during syncytial blastoderm.

DEFINING THE MOLECULAR PROCESS REQUIRED FOR GERMLINE SEGREGATION DURING *DROSOPHILA MELANOGASTER* DEVELOPMENT

Segregation of the germline is a fundamental event during early development. In Drosophila, germ cells are specified at the posterior embryonic pole by the presence of polar granules and their associated factors. In particular, one factor called polar granule component (pgc) represses transcription in germ cells. Conversely, somatic cells become transcriptionally active in early development, even those that lie in close vicinity to germ cells. The fate of the somatic cells next to the germ cells is specified by the Torso (Tor) RTK and in tor mutants these somatic cells fail to properly cellularise.
Our work showed that extra copies of pgc lead to a similar phenotype to torso mutants and that both the excessive pgc and lack of tor phenotypes are associated with an impairment of transcription in somatic cells. Moreover, lack of pgc ameliorates the cellularisation defect of tor mutants. This suggests the existence of a functional antagonism between pgc and tor in the specification of germ-line and somatic properties.
As transcriptional quiescence is a general feature of germ cells, similar mechanisms might operate in many organisms to "protect" somatic cells that abut germ cells from inappropriately succumbing to transcriptional quiescence.

GROUP MEMBERS
Leonardo Guilgur (Post-doc)
Ema Alves (Post-doc)
Ana Rita Marques (PhD Student)
Tânia Ferreira (PhD Student)
Pedro Prudêncio (Lab Manager)
André Rosa (MSc Student, left December 2008)



Wild-type *Drosophila* embryo during germ band extension (GBE). GBE is a dramatic example of epithelial morpogenesis that results form the intercalation of the embryonic ventral-lateral epithelial cells. DNA (green) and membrane marker (red).

THIS GROUP COLLABORATES WITH:
António Jacinto (Institute for Molecular Medicine, Lisbon)
Cláudio Gomes (Instituto de tecnologia Química e Biológica, Portugal)
Carlos Cordeiro (University of Lisbon, Portugal)
Jordi Casanova (CSIC/IRB Barcelona, Spain)
Ruth Lehmann (HHMI/Skirball Institute, New York, USA)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal
Scientific Cooperation Agreement FCT - Spain (CSIC)

BEHAVIOURAL NEUROSCIENCE

Marta Moita
PhD in Neuroscience
University of Porto, Portugal
E-mail: moita@igc.gulbenkian.pt

THIS GROUP IS A MEMBER OF THE CHAMPALIMAUD NEUROSCIENCE PROGRAMME AT THE IGC.

We are interested in understanding the neural mechanisms underlying behavioural plasticity using a combination of behavioural, pharmacological, molecular and electrophysiological tools. We are particularly interested in studying the neural basis of memory formation. We chose to focus on fear learning, where animals learn to fear cues that are predictive of aversive events or threats. Studying fear learning presents several advantages: it is conserved across species; it entails fast robust learning and very long lasting memories; its neural circuitry is well described; it may bring insights into the neural mechanisms underlying anxiety disorders. More recently, we started studying learning and decision making in the context of social interactions. Our goal is to bridge the studies on fear learning and social behaviour in an attempt to look at the fear system in all its complexities.

NEURAL MECHANISMS OF TRACE AUDITORY FEAR CONDITIONING

This project focuses on the role of the hippocampus and the amygdala in trace auditory fear conditioning (tAFC). We study what kind of information the hippocampus is processing during this form of learning, and how it conveys this information to the amygdala using a combination behavioural and pharmacological. We aimed at clarifying the role of the spatial context in the ability to learn the association of two stimuli separate in time. We tested whether rats can learn this association using episodic memory which links events that occur in the same spatio-temporal context, i.e. does tAFC depend on contextual learning?
Using a modified version of tAFC, which blocks the association between the context and shock, we found that rats did not fear of the training environment and their fear of the tone was decreased, when long trace intervals were used. When short trace intervals were used, rats learned to fear the tone despite the absence of fear of the training context. This suggests that the strategy used by the rats depends on the length of the trace interval used. In accordance with these results we found that temporary inactivation of the hippocampus affects tAFC only when long trace intervals are used.

NEURAL MECHANISMS OF DISCRIMINATIVE AUDITORY FEAR CONDITIONING

This project aims at elucidating the role of the different auditory input pathways to the amygdala a crucial structure for the acquisition of auditory fear conditioning. Information about the tone reaches the amygdala, either directly from the auditory thalamus, or indirectly via the auditory cortex. We would like to test the hypothesis that the direct pathway, 'the low route', allows for a rapid response to a threat but provides little accuracy, whereas indirect pathway, the 'high route´, enables animals to discriminate between sounds that are predictive of a threat from sounds that are not. The auditory thalamus, MG, is subdivided into two main nuclei - MGv, part of the indirect more specific pathway and the MGm, part of the direct, less specific but faster, pathway. Thus, to test the role of each pathway we specifically lesioned MGv or MGm.
We found that both input pathways are necessary for intact auditory discrimination, in the context of fear learning. Thus, although either one alone is sufficient for the acquisition of fear of a sound, neither one can establish normal discrimination between a tone that is followed by shock and one that is not.

COOPERATION IN SOCIAL DILEMMAS IN RATS

Game theory and the Prisoner´s Dilemma (PD) game in particular, have constituted a powerful tool in the study of the mechanisms of reciprocity. However, in non-human animals most tests of reciprocity in PD games have resulted in sustained defection strategies. As a consequence, it has been suggested that humans alone have evolved the necessary cognitive abilities to engage in

GROUP MEMBERS
Rosalina Fonseca (Post-doc)
Mark Seldon (Post-doc, left October 2008)
Susana Santos (Post-doc)
Marta Guimarães (PhD Student)
Raquel Antunes (PhD Student)
Andreia Cruz (MSc Student)
Ana Gregório (Research Technician)

reciprocity under such stringent conditions as the PD game, namely, numerical discrimination, memory and control of temporal discounting. We decided to revisit rats' ability to perform all necessary computations for cooperation to emerge in the PD game.
We use an iterated PD game to test rats (Rattus norvegicus) for the presence of such cognitive abilities by manipulating the strategy of the opponent, Tit-for-Tat and Pseudo-Random, or the relative size of the temptation to defect, 2R>T and T>2R. We found that rats shape their behaviour according to the opponent's strategy and the relative size of the payoff resulting from cooperative or defective moves. Finally, our results show that the rat's behaviour is contingent upon their motivational state. The validation of the rat as a model to study reciprocity during the PD game opens the possibility of studying the neural mechanism of decision making in the context of social dilemmas.

CELLULAR MECHANISMS OF SYNAPTIC PLASTICITY

This project aims at investigating the molecular mechanisms underlying aspects of synaptic plasticity, such as input specificity, synaptic tagging and competition between synapses. We will test on hand the role of the actin cytoskeleton and protein turnover in hippocampal synaptic plasticity. On the other hand we will test whether synaptic plasticity in the amygdala has similar properties as the ones described in hippocampus, with particular emphasis on synaptic tagging.
We have performed intracellular in the hippocampus acute slices, and found that synaptic tagging exists at the single cell level (previous reports of this phenomenon could not distinguish tagging at the single cell or at the population level). Furthermore, with extra cellular recording experiments we found that actin plays a fundamental role in the induction and maintenance of synaptic plasticity, probably by regulating accessibility of the synapse for protein turnover. Finally we have established intracellular recordings in amygdala, we will study in the future.

THIS GROUP COLLABORATES WITH:
Élio Sucena (IGC)
Hugh Blair (UCLA, USA)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal
Fundação BIAL, Portugal
L'Oréal, Portugal - L'Oréal Portugal Women in Science 2007 Prize
(Awarded to Rosalina Fonseca)

INFECTION AND IMMUNITY

Michael Parkhouse
PhD in Biochemistry
University of London, United Kingdom
E-mail: parkhous@igc.gulbenkian.pt

Pathogens, as a consequence of many years of co-evolution with their host, have 1) Provided the driving force for the evolution of a multicompetent, multifunctional immune system and 2) Evolved genes/strategies to manipulate and/or evade host cell biology and immune responses. Thus the study of pathogen strategies for host cell manipulation may not only provide new tools for the control of infectious and non-infectious diseases, but may also give new insights into host cell biology and immune responses. Our group focuses on virus host evasion genes targeting cell division, apoptosis and interferon responses. These may be considered as valuable ready-made tools to extend, explore and exploit the regulation of the basic cellular processes that they manipulate.

EVALUATING AND CONTROLLING THE RISK OF AFRICAN SWINE FEVER IN THE EU

The aim os this project is to provide new tools and strategies for the control of African Swine Fever (ASF) in Africa and reduce the risk of importation and/or spread of the disease in EU member states.
Our previous work has identified the 12 principle serological determinants of ASFV and in this project recombinant forms of these proteins have been produced as potential serological diagnostic probes. Their utility has now been assessed using sera from infected pigs and two antigens gave high levels of sensitivity as diagnostic antigens. One of these has potential for the diagnosis of recent infections through detection of IgM antibodies.

MECHANISM AND APPLICATION OF A NEW APOPTOSIS INDUCING HERPES VIRUS GENE

The principal aims of the project will be to 1) Confirm that UL76 is responsible for growth arrest after HCMV infection. (2) Characterise the mechanism of action of UL76 and (3) Explore how UL76 favours the virus. This project may provide a rational basis for the construction of attenuated herpes virus vaccines and novel approaches for manipulation of host cell biology in health and disease.
We have obtained confirmation that the UL76 gene of HCMV induces cell cycle arrest in both human and mouse cells, as do the α, β and γ human homologues in all herpesviruses, a finding which is directly relevant to this as yet unexplained feature of HCMV biology. To inhibit UL76 expression during wild type HCMV infection we constructed a UL76 deletion mutant HCMV virus. In order to exclude the possibility of unpredicted sequence changes occurring during construction of the deletion mutant viruses, the approach also included the necessity of restoring the UL76 gene to the deletion mutant. Both mutant and revertant viruses were characterised to confirm that their pathogenesis is identical to that of the wild type virus.

THE POTENTIAL AND APPLICATION OF VIRUS HOST EVASION GENES THAT MODIFY APOPTOSIS AND CYTOKINE RESPONSES

In this project, we aim to identify and exploit viral modifiers of cell biology and immunity as a potential source of novel healthcare pharmaceuticals for manipulation of immune responses and treatment of certain diseases. Such virus genes are being identified by nucleotide sequence and functional analysis of cloned viral ORFs of two large DNA viruses (African swine fever (ASFV) and Mouse herpes virus (MHV 68)). As a direct approach towards identifying novel virus evasion genes, which do not have homologies in the database, the genes of these two viruses are being systematically screened in functional assays for their impact on cellular and immune responses.
To date, we have identified novel viral genes inhibiting interferon responses, inducing cell cycle arrest and up-regulating synthesis of IL-8. The mechanisms

GROUP MEMBERS
Rute Nascimento (Post-doc)
Sílvia Almeida (Post-doc, left December 2008)
Sílvia Correia (Post-doc)
Helena Costa (PhD Student)
Sónia Ventura (PhD Student)
Vivian Oliveira (PhD Student)
Hugo Soares (MSc Student, left July 2008)
João Dias (Laboratory Technician)

and downstream cellular targets of these "evasion" genes are being identified, and the role of these genes in pathogenesis is being studied through the construction of deletion mutants. The deletion mutants provide a rational approach for the construction of attenuated, live virus vaccines.

CONTROL OF HUMAN, BOVINE AND PORCINE CYSTICERCOSIS THROUGH VACCINATION AND IMPROVED DIAGNOSIS

The zoonotic tapeworm *Taenia solium*, causal agent of life threatening human neurocysticercosis, constitutes an increasingly major health risk. This project focuses on the shorter-term, more cost-effective strategies of improving pig and cow management, including village pig vaccination (transmission control) and the development of sensitive and specific diagnostic assays to detect parasites and anti-parasite antibodies; the latter based on synthetic peptides, recombinant reagents and PCR, not parasite material. New diagnostic assays will improve hospital patient monitoring/treatment and man/pig screening and hence epidemiological knowledge.
To date, we have succeeded in developing the following diagnostic tests: 1) PCR tests for the differential diagnosis of cestode parasites (*Taenia solium, Taenia saginata* and *E chinococcus*); 2) Synthetic peptide based assays to detect antibodies to Taenia parasites 3) An ELISA assay which detects secreted metacestode antigens and thus viable metacestode parasites in pigs, cattle and man and 4) An ELISA assay, detecting adult parasite "coproantigen" in human faeces in order to detect human carriers of the adult worm and thus, by treatment, interrupt the cycle of transmission to man and pig (with our Venezuelan collaborator). These diagnosis tools are all now being applied in endemic areas, principally Mexico, Peru, Bolivía and Venezuela, and, on occasions, clinical material in Spain.

THIS GROUP COLLABORATES WITH:
H. Garcia (Universidad Peruana Cayetano Heredia, Peru)
T. Garate (Centro Nacional de Microbiologia, Spain)
L. Harrison (University of Edinburgh, UK)
M. Cortez (Universidad de Carabobo, Venezuela)
E. Sciutto (Universidad Nacional Autonoma de Mexico, Mexico)
Alexandre Leitão (Universidade Técnica de Lisboa, Portugal)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal
The Wellcome Trust, UK

DISEASE GENETICS

Carlos Penha Gonçalves
PhD in Immunology
Umea University, Sweden
E-mail: cpenha@igc.gulbenkian.pt

Our scientific interests are concerned with the understanding of the genetic basis of resistance/susceptibility to disease. The vast majority of common diseases studied to date have been shown to depend on multiple genetic factors. This is the case of several autoimmune and infectious diseases where the main challenge is now to reveal the contribution of individual genetic factors to the disease process. We are developing a research programme based on the systematic analysis of individual genetic factors involved in disease resistance or disease susceptibility both in humans and in murine models. The diseases under study are primarily type 1 diabetes and malaria. The research programme is based in 4 distinct but convergent perspectives: (1) mouse genetics, (2) human genetics, (3) statistical genetics and (4) bioinformatics.

GENETIC DETERMINANTS OF RESISTANCE TO HEPATIC INFECTION IN MURINE MALARIA MODELS

The workplan entails the genetic mapping of liver resistance to malaria infection, proceeds through the fine genetic mapping by construction of congenic and subcongenic mouse strains, towards the identification of the positional candidate genes of malaria resistance.
Data of congenic and subcongenic mouse strains have dissected two loci (*belr1* and the H2 locus) displaying a phenotype of reduced parasite liver burden. The *belr1* locus is now mapped within a region of 4 Mb that contains 49 genes, 13 of which are known to be expressed in the liver.

GENETIC ANALYSIS OF RESPONSE TO TOLL LIGANDS IN THE NON-OBESE DIABETIC MOUSE

This project proposes a genetic approach to study the involvement of the innate immune system activities in the pathogenesis of the autoimmune process evolving in the NOD mouse. We will focus on the response linked to the toll-like receptors (TLR) in the cells of the innate system.
We found that the level of serum IgM was controlled by a QTL on chromosome 13 that was named IgMSC1. We proposee that the Irf4 gene is a positional and functional candidate for the IgMSC1 locus that controls IgM homeostatic levels at the level of B-cell terminal differentiation.

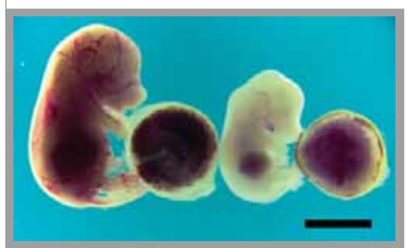
TYPE 1 DIABETES: ASSOCIATED IMMUNOPATHOLOGY AND GENETIC SUSCEPTIBILITY

We are adopting a multidisciplinary effort to study the genetic basis of the immunopathology associated to T1D in the Portuguese population with the aim to collect data to test the hypothesis that organ-specific autoimmunity entails susceptibility genetic factors conferring general predisposition to autoimmunity
We have obtained the cellular phenotypes and genotyping information for a collection of 98 T1D nuclear families.

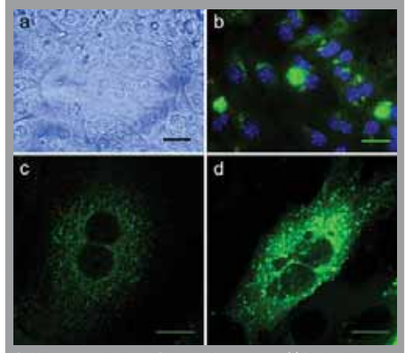
IMMUNOLOGICAL AND PATHOLOGICAL COMPONENTS OF PREGANANCY ASSOCIATED MALARIA (PAM) IN MOUSE MODELS

We are establishing mouse models for PAM that reproduce the main characteristics observed in human malaria pregnancy, namely increased disease susceptibility and parasite recrudescence. PAM mouse models will be useful in the dissecting the molecular mechanisms involved in the placental pathology and the cellular components of the PAM acquired resistance.
In 2008 we developed a PAM experimental model that captures many pathology features analogous to severe malaria manifestations in pregnant women and may provide opportunities to investigate the pathogenesis mechanisms of malaria in pregnancy.

GROUP MEMBERS
Cláudio Marinho (Post-Doc, left August 2008)
Maria de Jesus Trovoada (Post-Doc)
Luciana Moraes (Post-Doc)
Lígia Gonçalves (PhD Student)
Rita Neres (PhD Student)
Rosário Sambo (PhD Student)
Joana Rodo (PhD Student)
Joana Corte-Real (PhD Student)



Plasmodium Bergei-GFP infection impairs pregnancy outcome and fetus development. Feuses from uninfected (left) and infected (right) mothers.



Cell biology applications of cultured hepatocytes. (a) Light microscopy image of a hepatocyte monolayer at 24 h culture. (b) Immunofluorescence image of hepatocytes 36 h after infection with GFP-expressing *Plasmodium bergei* and DAPI staining. (c) Confocal image of hepatocyte stained with monoclonal antibodies to Transferrin receptor labelled with Alexa488 (Invitrogen). (d) Confocal image of hepatocyte transfected with an EGFP construct using Lipofectamine reagent (Invitrogen). Bars, 20 μm.

THIS GROUP COLLABORATES WITH:
Dan Holmberg (Umea University, Sweden)
Rosário Sancho, Dário Ligeiro
(Centro Histocompatibilidade do Sul, Portugal)
Guilhermina Fonseca, Rosa Pina (Hospital D. Estefânia, Portugal)
Maria Manuela Madeira, Lurdes Sampaio (Hospital de Santa Maria, Portugal)
José Manuel Boavida, Rui Duarte
(Associação Protectora dos Diabéticos de Portugal, Portugal)
Manuela Catarino (University of Lisbon, Portugal)
Maria Mota (IMM, Portugal)
Chris Janse (Leiden University, The Netherlands)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal
Bilateral Tunisia (MESICT Tunísia) - Portugal (FCT) Cooperation

COMPUTATIONAL GENOMICS

José Pereira Leal
PhD in Biomedical Sciencies
University of Porto, Portugal
E-mail: jleal@igc.gulbenkian.pt

We are interested in the evolutionary mechanisms underlying the origins and evolution of cellular life and the complex structures within the cell, the transitions to multi-cellularity, and the medical applications of evolutionary genomics. Our research encompasses themes that are broadly classified as evolutionary cell biology, systems biology, pathogenomics, and translational or medical bioinformatics.

EVOLUTIONARY CELL BIOLOGY

In this project, we aim to understand the origins on intracellular structures and compartments. In the last year, we established an algorithm for the automatic identification and classification of Rab GTPases from complete genomes sequences - these proteins are markers for organelle diversity and their correct classification allows us to conclude which particular pathways are present in an organism. We are now establishing a public resource to make this algorithm available to the community and running it on all completely sequenced eukaryotic genomes

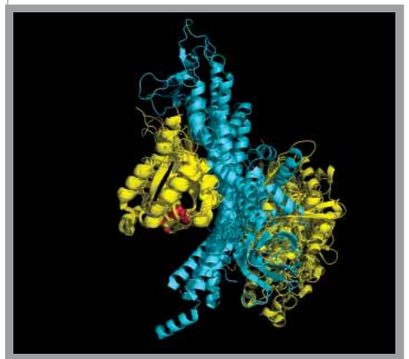
We also conducted a study on the evolution of centriolar components that predicted a minimal core for centriole assembly and duplication, and which particular components could be dispensable. These predictions are now being tested in the lab.

GENOME EVOLUTION AND PATHOGENOMICS

This project aims to understand the evolution of genomes and in particular how the evolution of the genomes of pathogenic organisms can inform us on the mechanism of pathogenesis, identification of drug targets and new therapies.

We studied the dynamics of protein family evolution in genome compaction that is seen in intracellular pathogens and endosymbiontes. We discovered that these pathogenic organisms selectively lose genetic redundancy in their adaptation to the host. We found the first empirical link between environmental predictability and robustness, a link that had been predicted by theoretical studies but not yet substantiated.

GROUP MEMBERS
Renato Alves (Trainee)
Filipe Cadete (MSc Student)
André Mendonça (MSc Student, left September 2008)



The evolution of transient interactions: an overlay of human Rabs (yellow) complexed with its effectors (blue), showing diversity of effector orientations

THIS GROUP COLLABORATES WITH:
Miguel Seabra, Mónica Bettencourt-Dias (IGC)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

MEMBRANE TRAFFIC IN DISEASE AND NOVEL THERAPIES

Miguel Seabra
PhD in Biochemistry and Molecular Biology
University of Texas Southwestern Medical Center, USA
E-mail: mseabra@igc.gulbenkian.pt

One of the most important challenges for the Biomedical Sciences this century is to develop a comprehensive knowledge of the fundamental unit of life, the cell. One main question in molecular cell biology is focused on understanding how cells achieve their highly sophisticated internal compartmentalisation. Each organelle is individualised by membranes, which contain specific proteins and lipids to execute specific functions. How are proteins and lipids sorted and retained to different locations, or, in other words, how are organelles made, maintained (identified) and how do they communicate with each other? Our work in the last 15 years has dealt with this problem and our approach has been to study both normal cells and disease processes. We are currently working on a variety of diseases with different phenotypes whose common feature is dysfunction of intracellular membrane trafficking pathways. We also wish to apply the fundamental knowledge to develop new therapeutic approaches to these diseases.

MOLECULAR MECHANISMS OF PARASITOPHOROUS VACUOLE FORMATION

Plasmodium species, the causative agents of malaria, upon entry into the mammalian host, are able to migrate and invade host liver cells, forming a parasitophorous vacuole membrane (PVM) around it, a process which occurs partially by an invagination of the host's plasma membrane. Very little is known about the formation and composition of this membrane. The aim of this project is to characterise the formation of the Parasitophorous vacuole membrane (PVM) and the involvement of the host cell endocytic and phagocytic pathways during *Plasmodium* invasion of liver cells. The ultimate goal is to elucidate the molecular mechanism involved in *Plasmodium* invasion, as has been partially done with many other intracellular pathogens. This will provide a better understanding of the mechanisms used by this pathogen to invade host cells and possibly provide clues for its control and/or subversion.

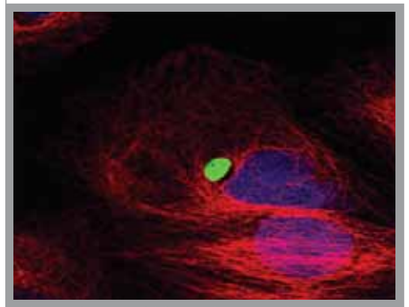
We were able to define the kinetics of *Plasmodium* sporozoite invasion in liver cells and observe that host late endocytic organelles aggregate around the developing sporozoite vacuole.

MOLECULAR MECHANISMS OF ORGANELLE MOTILITY

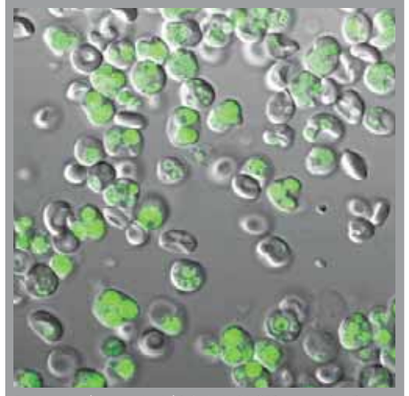
The aim of this project is to understand molecular mechanisms by which Rab GTPases control membrane traffic, in particular organelle motility. We have been interested in studies of organelle dynamics and membrane trafficking pathways in skin melanocytes and retinal cells, particularly retinal pigment epithelium (RPE). We use the pigment granule or melanosome as a model organelle system, and one focus of our research is the study of Rab27a, a Ras-like GTPase. A long-term objective is to understand the mechanisms that regulate assembly and disassembly of the Rab27a: myosin complexes to enable switching of melanosomes from microtubule to actin-based transport. We also wish to address a downstream problem of melanosome transport: the melanocyte-keratinocyte transfer of melanosomes required for skin pigmentation. Our aim is to determine whether melanosome transfer occurs by secretion or phagocytosis.

Myrip is a Rab27a and MyosinVIIa (MyoVIIa) linking protein that may regulate melanosome transport in the retinal pigment epithelium (RPE). Myrip also binds MyosinVa (MyoVa) *in vitro* however it is unclear whether this interaction is of sufficient affinity to be physiologically relevant. Here we addressed the questions of whether Myrip interacts with MyoVa in cells and the molecular basis of cellular activation of MyoVa and MyoVIIa by Myrip. To answer these questions we used melanosome transport in skin melanocytes and RPE cells as read-outs of MyoVa and MyoVIIa activity. We found that Myrip recruits and activates MyoVa on skin melanosomes with similar

GROUP MEMBERS
Elsa Seixas (Post-doc)
Stephanie Unterreitmeier (Post-doc)
Laura Santos (Post-doc)
Mafalda Silva (PhD Student)
Carolina Matos (External PhD Student)
Maria Margarida Silva (Trainee)
Maria Inês Patrício (External PhD Student)



A liver cell (hepatocyte) infected with the malaria parasite *Plasmodium Bergei*, 24 hours after infection. The parasite is in green, the cell's microtubules in red and the nucleus in blue.



Eryhtrocytes (red blood cells) infected with GFP -expressing *Plasmodium bergei* (in green).

efficiency to the established MyoVa activator Melanophilin (Mlph). Mutagenesis showed that a Myrip-Mlph conserved amphipathic helix (MMAH) is essential for MyoVa interaction while other Myrip regions, including the MyoVa exon F binding domain (EFBD) equivalent, play non-essential roles in this interaction. This suggests that, in contrast to Mlph, Myrip interacts with MyoVa lacking melanocyte specific exon F. Parallel studies of RPE melanosome transport reveal that Myrip-specific inserts, but not the MMAH, are essential for MyoVIIa activation. We conclude that Myrip is a versatile Rab27a associated Myosin activating protein that mediates cellular activation of MyoVa and MyoVIIa via non-overlapping domains.

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

INFLAMMATION

Miguel Soares
PhD in Science
University of Louvain, Belgium
E-mail: mpsoares@igc.gulbenkian.pt

Inflammation is a beneficial host response to foreign challenge or tissue injury, leading to restoration of tissue structure and function. It is characterised by local and transient extravasation of soluble molecules and leukocytes from blood into non-lymphoid tissues. Inflammatory reactions are controlled via the coordinated expression of pro- and anti-inflammatory genes. Expression of pro-inflammatory genes promotes the "onset" of inflammatory reactions while expression of anti-inflammatory genes promotes their "resolution". Failure to express adequate levels of pro- or anti-inflammatory genes can lead to increased susceptibility to infectious diseases or to the development of "inflammatory diseases", respectively. Our research effort is aimed at understanding the cellular and molecular mechanisms underlying the resolution of inflammatory reactions.

GROUP MEMBERS
Rasmus Larsen (Post-doc)
Raffaella Gozzelino (Post-doc)
Ana Ferreira (Post-doc)
Viktória Jeney (Post-doc)
Gabriela Silva (Post-doc, left December 2008)
Andreia Cunha (PhD Student)
Nadja Pejanovic (PhD Student, left December 2008)
Ivo Marguti (PhD Student)
Nuno Palha (MSc Student, left December 2008)
Matteo Villa (External MSc Student, left December 2008)
Maria Linares (External PhD Student, left December 2008)
Sílvia Cardoso (Research Assistant)
Sofia Rebelo (Laboratory Manager)

OXIDIZED HAEMOGLOBIN IS AN ENDOGENOUS PROINFLAMMATORY AGONIST THAT TARGETS VASCULAR ENDOTHELIAL CELLS

This project aims to assess whether oxidised haemoglobin exerts proinflammatory effects in vascular endothelial cells.
There are a variety of inflammatory conditions which are associated with the occurrence of hemolysis and therefore with the production of cell-free haemoglobin. Upon exposure to free radicals, haemoglobin can be oxidised into methaemoglobin or in the case of more extensive oxidation into Ferryl haemoglobin (FerrylHb). This unstable oxidised form of Hb is characterised by the production of tyrosyl radicals that can form covalent dityrosine bonds leading to inter- and intra-molecular cross-linking and subsequently to polymerisation of FerrylHb. We found that FerrylHb acts as potent proinflammatory agonist that induces vascular endothelial cells to rearrange their actin cytoskeleton and to form intercellular gaps that disrupt the integrity of the endothelial cell monolayer. In addition FerrylHb induces the expression of adhesion molecules in endothelial cells, through activation of the nuclear factor kappa B (NF-kB) family of transcription factors, the c-Jun N-terminal kinase (JNK) and the p38 mitogen activated protein kinase (MAPK) signal transduction pathways. FerrylHb can exert proinflammatory effects *in vivo*, such as when administered into naïve mice. In conclusion, we demonstrate that FerrylHb acts as a *bona fide* proinflammatory agonist that targets vascular endothelial cells, in a manner that contributes to explain the pathogenesis of a variety of inflammatory conditions associated with the occurrence of hemolysis.

IN VIVO DELIVERY OF ANTI-INFLAMMATORY CHIMERIC PROTEINS: ASSESSMENT OF THERAPEUTIC APPLICATION

We aim to deliver anti-inflammatory therapeutic proteins *in vivo*, using a 'food-grade' delivery system. We are assessing the feasibility of delivering a recombinant transduction domain (PTD) protein via the food-grade bacterium *Lactococcus lactis*. We will then deliver the anti-inflammatory chimeric protein TAT-*Hmox1 in vivo*, aiming at the treatment of inflammatory diseases.
In order to assess and optimise PTD-protein delivery *in vivo*, we are employing a reporter mouse strain, called ROSA26R in which intra-cellular Cre activity induces the expression of beta-galactosidase (beta-gal). Recently, we have generated a number of different PTD-fused cre-recombinase protein (TAT-Cre), to be used in the setup of *in vivo* delivery of PTD proteins. Additionally, we are generating a bacterial *Lactococcus lactis* strain that expresses and secretes TAT-Cre. Once delivery of TAT-Cre has been optimised, we will proceed to test the effect of *Lactococcus lactis* delivered TAT-HO-1 in inflammatory diseases, such as atherosclerosis in mice. Additionally, we will ask whether 'food-grade' delivery of TAT-HO-1 can prevent the development

of acute inflammatory diseases driven from infection, such as severe cerebral malaria (caused by *Plasmodium* infection) endotoxin-induced septic shock and sepsis (caused by polymicrobial infection). TAT-HO-1 was shown to afford protection against these diseases when administered before challenge.

MOLECULAR MECHANISM UNDERLYING HAEM SENSITISATION TO PROGRAMMED CELL DEATH IN MALARIA

We aim to assess the mechanisms through which free haem sensitises non-hematopoietic cells to undergo tumor necrosis factor (TNF)-mediated programmed cell death, an effect associated with the pathologic outcome of *Plasmodium chabaudi chabaudi* infection in mice.

During homeostasis, Fe protoporphyrin IX (haem) acts as a prosthetic group in haemoproteins that, under inflammatory conditions, release non-covalently bound haem and generate cytotoxic free haem. Our laboratory found that survival of a *Plasmodium*-infected host is strictly dependent on its ability to up-regulate the expression of haem oxygenase-1 (HO-1), a stress-responsive enzyme that catabolyzes free haem into biliverdin, free iron (Fe) and carbon monoxide. The deleterious effect of free haem is presumably due to its hydrophobic nature, which allows the Fe contained within its protoporphyrin IX ring to cross cell membranes and other lipid structures. We have shown over this year that free haem displays a unique pathologic feature: it sensitises non-hematopoietic cells to TNF-mediated programmed cell death, thus leading to the onset of severe malaria. We observed that although under homeostasis, the pro-apoptotic effects of TNF are repressed via a series of immediate early TNF-responsive cytoprotective genes, free haem primes hepatocytes to undergo programmed cell death through a mechanism independent of transcription and/or translation. We found that free haem can override this protective effect, acting as a potent pro-oxidant catalyst and leading to unfettered generation of free radicals in response to TNF, an effect that that triggers hepatocytes to undergo apoptosis. This effect was shown to promote the lethal outcome of *Plasmodium* infection in mice.

CROSSTALK BETWEEN NITRIC OXIDE (NO) AND CARBON MONOXIDE (CO) IN SUPPRESSING THE PATHOGENESIS OF CEREBRAL MALARIA

Both NO and CO prevent the development of experimental cerebral malaria in *Plasmodium* berghei ANKA infected C57BL/6 mice. The aim of this work is to test whether there is a crosstalk between the two gasotransmitters in preventing the pathogenesis of experimental cerebral malaria.

NO is generated by NO synthases *Nos1*, *Nos2* and *Nos3*. We tested whether CO inhalation (250 ppm) can prevent the onset of experimental cerebral malaria induced by *Plasmodium* berghei ANKA infection in mice deficient for *Nos1* or *Nos2*. Both *Nos1* and *Nos2* deficient mice were rescued by CO suggesting that the effect of CO is independent of NO generated by these two isoforms. Also, pharmacological inhibition of NOS with a non-selective NOS inhibitor failed to abrogate the protective effect of CO, again suggesting an independent role of CO in preventing experimental cerebral malaria. We started to generate *Nos1*$^{-/-}$/*Nos2*$^{-/-}$, *Nos1*$^{-/-}$/*Nos3*$^{-/-}$, *Nos2*$^{-/-}$/*Nos3*$^{-/-}$ double deficient mice in order to test the effect of CO on the onset of experimental cerebral malaria.

HAEM OXYGENASE-1 UNDERLIES THE "PROTECTIVE TRAIT" AFFORDED BY SICKLE CELL DISEASE AGAINST SEVERE ACUTE MALARIA

We wish to assess whether sickle cell disease protects against the development of severe acute malaria via the induction of haem-oxygenase-1 expression.

Sickle cell disease is caused by a single amino acid substitution in the b-chain of haemoglobin occurring in either the homozygous or compound heterozygous form. While asymptomatic *per se*, the heterozygous sickle cell trait confers survival advantage against malaria. Despite widespread recognition of this protective effect, understanding of its mechanism of action has remained elusive. The prevailing view is that sickle cell trait reduces parasite load, so that severe forms of malaria do not develop as frequently. However, this does not explain protection against cerebral malaria, a prevailing and often lethal form of severe malaria occurring under relatively low parasite load. Our data supports the existence of a novel mechanism that relies on increased expression of haem oxygenase-1 (HO-1; encoded by *Hmox1*), the rate-limiting enzyme in the catabolism of haem. When infected by *Plasmodium Hb*^{SAD} mice, a transgenic mouse strain that develops a mild form of sickle cell disease, express increased levels of HO-1 and are protected against experimental cerebral malaria (ECM). HO-1 expression and activity are strictly required to suppress ECM in *Hb*^{SAD} mice, as demonstrated by functional deletion of the *Hmox1 locus* or pharmacologic inhibition of its enzymatic activity without interfering with parasite load.

REGULATORY EFFECT OF CYTOPROTECTIVE GENES IN THE PATHOGENESIS AND REMISSION OF MULTIPLE SCLEROSIS

This project aims to test whether expression of NF-E2-related factor-2 (Nrf2)-dependent cytoprotective genes in oligodendrocytes can modulate the progression of murine experimental autoimmune encephalomyelitis (EAE). The experimental approach consists in assessing whether EAE severity is exacerbated in transgenic mice in which Nrf-dependent gene expression is blocked specifically in oligodendrocytes by the expression of a dominant negative mutant form of Nrf2 (Nrf2^{DNM}).

We have cloned Nrf2^{DNM} under the myelin oligodendrocyte glycoprotein (MOG) and the proteolipid protein (PLP) promoters, which afford low and high expression levels, respectively. We have generated three independent mouse transgenic lines expressing MOGNrf2^{DNM} or PLPNrf2^{DNM}. We followed up the studies on the Nrf-dependent gene, heme oxygenase-1 (*Hmox1*/HO-1) that we have shown to control EAE severity EAE. For this purpose, we have assessed the expression HO-1 in specific cells of the central nervous system at the peak of EAE and observed that its expression coincides, but is not restricted to, areas of lesion and can be expressed by several central nervous system cell types.

IDENTIFICATION OF KINASES AND PHOSPHATASES CONTROLING THE TRANSCRIPTIONAL ACTIVITY OF NUCLEAR FACTOR KAPPA B (NF-KB) P65/RELA IN ENDOTHELIAL CELLS

We aim to use a functional RNA interference (RNAi) based gene screen in *Drosophila* S2 cells to identify kinases controlling Drosophila p65/RelA homologues, i.e. Dorsal and Dif.

Activation of the transcription factor nuclear factor kappa B (NF-kB) is a central event in the regulation of inflammation and immunity. Given that the NF-kB signal transduction pathway is highly conserved throughout evolution we have developed an assay allowing to monitor Toll/Dorsal/Dif activity based on the expression of Drosomycin-luciferase (*Drs-luc*) reporter. We found that targeting specific kinases by specific dsRNAs modulated Toll/Dorsal/Dif activity. Besides identifying a new mechanism targeting NF-kB activity this observation served as a "proof of concept" that our approach can be used to screen for other kinases modulating NF-kB activity. We have done so by using a full Drosophila dsRNA kinome and identified about 40 putative kinases targeting this pathway that are presently being validated in terms of their involvement in the regulation of Dorsal and/or Dif activity.

A ROLE FOR THE HAEM/HO-1 SYSTEM IN DENDRITIC CELL BIOLOGY

In this project we aim to test whether the expression of HO-1 in dendritic cells (DC) modulates its ability to activate T cells, thus controlling the pathological outcome of immune-mediated inflammatory diseases.

Haem oxygenase-1 (HO-1, encoded by the *Hmox1* gene) critically regulates the pathologic outcome of a broad range of immune-mediated inflammatory diseases in which adaptive immunity, i.e. T cells, is involved. Dendritic cells (DC) play an essential role in the initiation of adaptive immunity, mainly by promoting T cell activation and acquisition of effector function. Our results show that DC from animals that express (*Hmox1*$^{+/+}$) or not HO-1 (*Hmox1*$^{-/-}$) have similar expression levels of molecules involved in T cell activation, both *in vivo* and *in vitro*. However, we have shown that the production of pro-inflammatory cytokines involved in the acquisition of effector function by T cells is significantly increased in DC from *Hmox1*$^{-/-}$ mice. The relevance of these findings for T cell activation and, presumably, the pathological outcome of immune-mediated inflammatory diseases are being investigated.

FUNDING
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European Commision Framework Programme 7 (FP7)
– Marie Curie Actions
GEMI Fund Linde Healthcare

STRESS AND CYTOSKELETON

Helena Soares
PhD in Biomedical Sciences
University of Porto, Portugal
E-mail: msoares@igc.gulbenkian.pt

Microtubules (Mts) are polarised polymers of α/β-tubulin heterodimers participating in a wide range of cell functions. How Mts accomplish this variety of functions is far from being completely understood. One of the most attractive issues in the field of Mt biogenesis is still how the native tubulin 3D-structure is related with Mt biogenesis and dynamics. The maturation of tubulin heterodimers is a complex process involving the interaction of tubulins with molecular chaperones (CCT) and the tubulin cofactors (TBCA-TBCE).
Our main goal is to understand how the components of the tubulin folding pathway control tubulin synthesis, flux, transport, recycling and are targets for regulation of the Mt assembly and dynamics. Specifically is our aim to study: (1) how cilia assemble and are involved in signal transduction, (2) how TBCA-TBCE are involved in Mt dynamics, (3) the biophysical properties of Mts using AFM and (4) the role of the Mt cytoskeleton of Apicomplexa parasites in host cell invasion.

RATE AND EFFECTS OF MUTATIONS IN THE PROTOZOA *TETRAHYMENA THERMOPHILA*

This project is a collaboration with the Evolutionary Biology group of the IGC, headed by Isabel Gordo. The aim os this proejct is to measure several mutational properties of the ciliate protozoan Tetrahymena. Therefore, we will: 1) estimate the genomic mutation rate; 2) quantify fitness decline due to strong population bottleneck; 3) estimate the deleterious mutation rate and average effect of mutations that decrease fitness 4) quantify the rate of fitness recovery and the rate at which compensatory mutations arise.
We have performed a classical mutation accumulation experiment in *Tetrahymena thermophila*. We have evolved 20 lines of *Tetrahymena* (mating type II) under strong period bottlenecks of a single individual, from a founding clonal population. Surprisingly all the 20 lines propagated go extinct within 20 bottlenecks. This was not at all expected and has led to formulate new hypothesis. It is known that *Tetrahymena* population size (N) fluctuates drastically in natural habitats. Given our results, we postulated that for Tetrahymena populations to survive strong reductions in N they would have to conjugate frequently. This initial result and hypothesis generates new questions amenable to experimental test: a) the role of sexual reproduction in avoiding mutational meltdowns, in particular: how the closely related species *Tetrahymena pyriformis*, which is asexual, evolves when subject to bottlenecks, b) can we show that natural populations of Tetrahymena frequently engage in sex?
We think that the mechanism responsible for the results we obtained is not standard accumulation of mutations (the extinction is just too fast), but variation in copy number of genes in the macronucleus. We have planned experiments to test this. Furthermore we started a similar experiment in *Tetrahymena pyriformis* that showed that this specie is more resistant to extinction.

MTUBE - STUDY OF PHYSICAL PROPERTIES OF MICROTUBULES BY AFM TECHNIQUES

The objectives of this project are: to establish the possibility of effectively promoting oriented adhesion of microtubules (MTs) to surfaces; to understand the behaviour of MTs under electromagnetic fields, and, to provide tools for understanding the extent to which it is possible to control motor protein movement using electromagnetic fields. We demonstrated previously that MTs have an electrical moment as predicted theoretically since they could be aligned under an electrical field. This property could have strong implications, both biological - to which extent external electromagnetic field can influence MT-based processes? - and technological, as controlled alignment could be useful for establishing a MT framework for microfluidic chips.

GROUP MEMBERS
Sofia Nolasco (Post-doc)
Ruben Ramalho (PhD Student)
João Gonçalves (PhD Student)
Rita Cardoso, (PhD Student)
Alexandra Tavares (Trainee)

Based on our previous results we designed a microengineered surface (chip) to apply localised electric fields while adsorbing MT, as a basis for patterning MT for bionanotechnological applications, e.g. hybrid biomolecular-mic roelectromechanical systems. MT alignment assays showed locally controlled alignment to be possible. MTs adsorbed in areas between electrodes. We determined the frequency of distribution of MT angles and the density curve estimation for these data, showing that MT alignment is biased by the electric field. In control samples, MTs may also present a small unimodal alignment bias, roughly parallel to the electrodes. The complex distribution of Mts adsorbed in electric field would then result from the combination of both effects.

ROLE OF *BESNOITIA BESNOITI* CYTOSOLIC CHAPERONIN IN HOST CELL INVASION

Besnoitia besnoiti is an Apicomplexa parasite, related to *Toxoplasma gondii*, affecting bovine and causing significant economic losses. During the last two decades, an increasing number of cases of bovine besnoitiosis have been reported in Portugal, Spain, France and recently in Germany. Our main goal is to contribute to better understanding of the mechanisms underlying *Besnoitia besnoti* host cell invasion/infection. Based on our results we hypothesise that tubulin folding machinery, namely the cytosolic Chaperonin (CCT) and TBCA-E, play a crucial role in Mt arrays rearrangements and dynamics, and is essential for invasion.
Based on literature and our data we have chosen CCTα-subunit and TBCB and TBCE to clone the genes, and used them as tools to study their pattern of expression and their role during host cell invasion. We already cloned *cctα* gene, and studies are being undertaken to understand its importance in *Besnoitia* invasion of the host cell. Little is known about *Besnoitia* molecular biology, therefore to characterise the *cctα* gene we designed primers that could amplify its coding sequence taking advantage of the available sequences for *cctα* of *T.gondii* and *Neospora Caninum*. A comparison between the *Besnoitia* predicted partial aminoacid sequence and those of *Toxoplasma*, *Plasmodium* and *Theileria* reveals that the *Besnoitia* protein has 95% identity with the *Toxoplasma* protein, while values ranging from 69% to 62% were obtained with those of *Plasmodium* and *Theileria, respectively*. An alignment of the predicted amino acid sequence of *Besnoitia* also shows that this protein contains the conserved characteristic motives of CCT-subunits, namely TNDGATIL and GDGTTSV, present in the first 1/3 of the protein.

THE ROLE OF TUBULIN COFACTORS IN VERTEBRATES

Tubulin cofactors were first described more than a decade ago, as participating in the tubulin folding pathway mainly by *in vitro* folding assays supported by genetic studies in yeast. However when they recently started to be to be studied using mammalian models it became clear that they play crucial roles, not always directly related to their expected role in the tubulin folding pathway.
Is our aim to contribute to the clarification of the role of tubulin cofactors *in vivo*.
We showed that TBCA is mainly involved in mature heterodimers tubulin recycling and that the irreversible effect of colchicine in comparison to other depolymerising drugs is due to the inability of TBCE and TBCB to dissociate the colchicine tubulin dimer. Mice contain two TBCA encoding genes (in chromosomes 16 and 13 respectively). Although both genes show different patterns of expression during spermatogenesis, which suggest a developmental regulation, we were unable to demonstrate that TBCA16 product exists, even using MALDI analysis. Interestingly, we found that *Tbca*16 is transcribed as a noncoding antisense RNA. This indicates the possible involvement of anti-TBCA16 RNA in the regulation of TBCA13 during the spermatogenesis, which is supported by the RNAi experiments. We recently observed that the uncharacterised protein TBCCD1, a related protein to TBCC and RP2 (retinitis pigmentosa-2-protein), was present in human cells, at the centrosome, spindle midzone, midbody and basal body/axoneme of primary cilia. Interestingly, the *tbccd1* gene is preferentially expressed in tissues of mouse and zebrafish where cilia/flagella are known to assemble. In zebrafish, in situ hybridization analysis showed that in 24h embryos the gene is more abundantly expressed in the eye and brain ventricles.

THIS GROUP COLLABORATES WITH:
Alexandre Leitão
(Instituto de Investigação Científica Tropical (CIISA), Portugal)
Luís Melo (Instituto Superior Técnico, Portugal)
Helder Cortes (Universidade de Évora, Portugal)
Juan Zabala (Universidad de Cantabria, Spain)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

EVOLUTION AND DEVELOPMENT

Élio Sucena

PhD in Genetics, Evolution and Development
University of Cambridge, United Kingdom
E-mail: esucena@igc.gulbenkian.pt

Our lab's main research topic concerns the evolution of developmental mechanisms, with special emphasis on the generation of novelty. We use the genetic model *Drosophila melanogaster* and other related dipterans to approach the developmental basis for alternative morphologies, by means of the comparative method.
Our case studies focus on the evolution of oogenesis and the immune system. We recently started to approach the process of evolution by gene duplication. In collaboration with Marta Moita and Isabel Gordo, both at the IGC, we have developed new experimental paradigms for the study of game theory using the rat as a model organism.

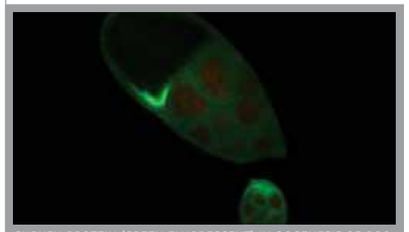
VERTICAL TRANSMISSION OF WOLBACHIA BACTERIA IN DROSOPHILA

The mains aim of this project is to establish a mechanistic link between horizontal and vertical transmission of *Wolbachia* between *Drosophila* species. There is accumulated evidence for the occurrence of both phenomena in Nature. Maternal vertical transmission has been widely studied and we are just beginning to understand some of its underlying mechanisms. Regarding horizontal transfer, its existence is inferred from the incoherence between the *Wolbachia* and the host´s phylogenies. Using different *Wolbachia* strains and environmental challenges we are trying to force horizontal transfer events and subsequently monitor likeliness of bacterium stable vertical transmission.
We have established a novel protocol for infection that is currently being tested. Also, we have been able to reproduce published methodologies for the purification of viable *Wolbachia* bacteria outside the cell environment and for the stable horizontal transfer (through injection) of adult *Drosophila*. Combining these different methods is the current basis of our approach, which should soon shed light onto ecologically relevant connections between horizontal and vertical transmission.

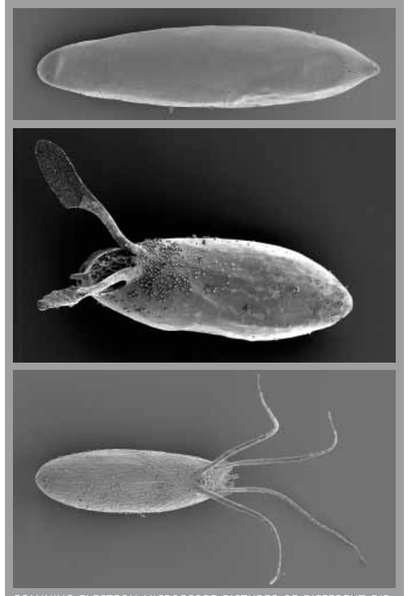
DISSECTING THE DEVELOPMENTAL GENETIC BASIS OF EVOLUTIONARY NOVELTY

This project aims to study the evolution of novelty by comparing oogenesis across different fly species. The eggs appendages are set during oogenesis of Drosophilidae but are absent in other dipterans outside this family. Taking advantage of the detailed knowledge of the developmental genetics setting this structures in *D. melanogaster*, we intend to infer the evolutionary processes that have led to the evolution of this feature in this particular lineage. We have set a culture of *Ceratitis capitata* in the lab. Also, we have cloned most of the *C. capitata* orthologous genes for the pathway and are currently performing an exhaustive description of the corresponding expression patterns in this dipteran.

GROUP MEMBERS
Barbara Vreede (PhD Student)
Alexandre Leitão (MSc Student)
Vítor Faria (MSc Student)
Emília Santos (Research Assistant, left June 2008)



GURKEN PROTEIN (GREEN FLUORESCENT) IN OOGENESIS OF *DROSOPHILA MELANOGASTER*.
Gurken is the first signal of the pathways leading to dorsal-ventral axis determination and the differentiation of follicle cells to form dorsal eggshell structures.



SCANNING ELECTRON MICROSCOPE PICTURES OF DIFFERENT DIPTERAN EGGS.
Top - *Ceratitis capitata* has no dorsal appendages, or other structures on the dorsal-anterior side of the eggshell. **Middle** - *Drosophila erecta* has two appendages, with flat ends. **Bottom** - *Zaprionus indianus* has four appendages, all of which are slim and have pointed ends.

THIS GROUP COLLABORATES WITH:
Marta Moita, Isabel Gordo (IGC)
Louis du Pasquier (University of Basel, Switzerland)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

MITOSIS

Álvaro Tavares

PhD in Molecular Biology
University of Porto, Portugal
E-mail: tavares@igc.gulbenkian.pt

We are interested in understanding the mechanisms governing proper cell division and chromosome seggregation. An increasing number of cell cycle regulatory molecules are found at the centrosomes and on the kinetochores. The inactivation or amplification of their activity has been associated with genomic instability and oncogenesis. We believe that knowledge of the basic processes of centrosome cycle and mitotic spindle dynamics will lead to greater understanding of the biology of cancer cells and will point the way towards novel therapeutic approaches. With a view to reaching this goal we have developed a method of identifying new kinetochore and spindle checkpoint proteins and are elucidating their function in the regulation of chromosome seggregation, by a combined approach of genetics and biochemistry. We are equally interested in determining the role of centrosomes in the regulation of cytokinesis, and have been analysing the function of human and Drosophila Mob-like proteins.

SPINDLE DYNAMICS

The aims of the European Union Research and Training Network, within which this project is being carried out, have to do with identification and characterisation of genes involved in proper chromosome congression and segregation during mitosis.
We found that lack of Sgt1, in a null Sgt1 Drosophila mutant, results not only in the degradation of Polo, but also of other centrosomal components, namely α-tubulin, Sas4, Cnn and pericentrin. Mutant cells are therefore incapable of forming a proper mitotic spindle and arrest in a pro-metaphase-like state. We have also concentrated our efforts on the characterisation of Cenp-Ana mutant stocks. This proved to be more difficult than anticipated because of the number of second site mutations present in the stocks. To clean the stocks of these second sites, we used meiotic recombination. We finally succeded in producing a final clean stock of Cenp-Ana, that proved to be a null for the gene. Preliminary results indicate that it is embryonic lethal.

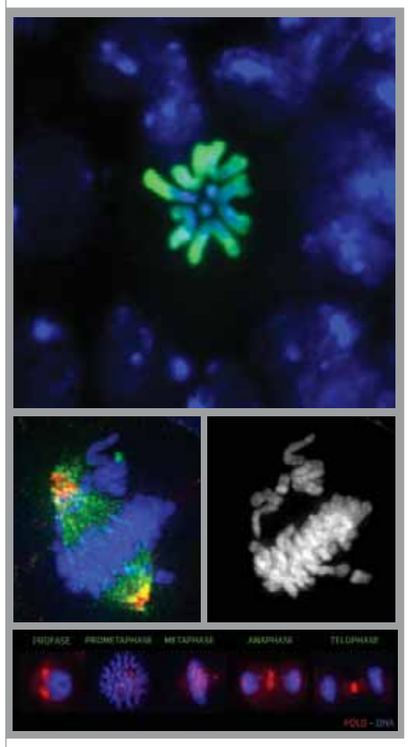
CHARACTERISATION OF THE MITOTIC CHECKPOINT IN DROSOPHILA: FUNCTION OF THE PROTEINS MPS1 AND CENP-ANA

This project aims at characterising the function of the proteins Mps1 and CENP-ana in the mitotic checkpoint in Drosophila.
One major task that was achieed in 2008 was the identification of Mps1 protein interactors, using the TAP-DMps1 transgenic flies. We have succefully purified the protein from embryo extracts. The purified protein was analysed on poliacrylamide gels (1D and 2D) and co-purifying proteins were identified by MALDI. We have thus identified three different Mps1 binding proteins: the kinesin-like protein Cenp-meta and two proteins encoded by uncharacterised Drosophila genes. The characterisation of these new genes is under way. We have also created transgenic flies expressing TAP-Cenp-Ana, and used them to isolate and identify Cenp-ana molecular partners, much in the way of what was done for MPS1. Two potential candidates were identifyed, both kinetochore proteins (see bellow) and the role of the interaction with Cenp-ana is now being studied. One such interactor is the protein Sgt1, previously uncharacterised in Drosophila. The gene Sgt1 was described in S.cerevisiae as essencial for kinetochore assembly. We demonstrated the interaction between Sgt1 with cenp-ana not only by affinity purification but also by co-immunoprecipitation assays. The intriguing interaction between Cenp-ana and Sgt1 is now being studied in detail.

STUDY OF THE ROLE OF VERTEBRATE ADTK1, A NOVEL DUAL-SPECIFICITY SER/THR/TYR KINASE GENE FAMILY

The aim of this project is to determine the role of the gene ADTK1 in heart development.

GROUP MEMBERS
Claudia Florindo (Post-doc)
Lucia Mentelova (Post-Doc, left September 2008)
Olga Makarova (PhD Student, left May 2008)
Ramakrishna Prabhu (PhD Student, left May 2008)
Sara Esteves (MSc Student)
Nuno Baltazar (MSc Student)
Ana Severiano (Trainee)



In order to determine the function of ADTK1 it is important to identify its molecular partners, all the more so since ADTK1 seems to be a dead kinase. In order to do so, we cloned the gene in fusion with GST and expressed the fusion protein in Xenopus embryos, after injection. The expressed protein was purified by affinity chromatography and interactors were identifyed by mass spectrometry after SDS-PAGE.

MOLECULAR DETERMINANTS OF BRAIN SIZE

In this project we aim to determine the genes that are determinant for brain size in higher eukaryotes (namely humans). In particular we will address the function of the gene Asp and why mutations on this cell cycle gene cause microcephaly.

Drosophila melanogaster abnormal spindle *(asp),* is localised in the mitotic centrosome and is known to be essential for both the organisation of the microtubules at the spindle poles and the formation of the central mitotic spindle during mitosis and meiosis. Mutations in *asp* cause dividing neuroblasts to arrest in metaphase, resulting in reduced central nervous system development. Asp has proved to be a highly conserved protein and Asp-like proteins have recently been described in many species including humans.

We have now sucessefully created a Drosophila stock for RNAi in Asp and two null mutants (the first such mutants) in Drosophila Asp gene. Their phenotype is now being characterised.

THIS GROUP COLLABORATES WITH:
David Glover (University of Cambridge, UK)

FUNDING
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European Commission Framework Programme 6 (FP6)
– Marie Curie Training Network

EVOLUTIONARY GENETICS

Henrique Teotónio
PhD in Evolutionary Biology
University of Lisbon, Portugal
E-mail: teotonio@igc.gulbenkian.pt

The main objective of our group is to study the genetics of adaptation using experimental evolution, by testing current evolutionary theory. Adaptation and the study of natural selection and its consequences are central to any understanding of biology because they provide a comprehensive framework for the origin, divergence and maintenance of diversity. We use experimental evolution to integrate the study of variation at the phenotype level with the study of variation at the genotype level.

EXPERIMENTAL REVERSE EVOLUTION IN DROSOPHILA

The main aim of this project is to describe patterns of gene diversity evolution during experimental reverse evolution in D. melanogaster

In 2008, aproximately 100 single nucleotide polymorphisms were genotyped in over 40 experimental populations. Computational and statistical analysis was performed. Linkage disequilibrium does not appear to have evolved, and natural selection is detected at several loci. Evolution results from standing genetic variation and implicates interactions among large-scale genomic modules causing phenotyping evolution and adaptation.

EXPERIMENTAL EVOLUTION IN C. ELEGANS

This project aims to determine the role that varying levels of outcrossing and standing genetic variation have on rates of adaptation to novel environments. After experimental evolution during 100 generations, phenotypic characterisation of evolved populations was performed for male and female function. Inbred lines from evolved populations were derived so to describe genotypic effect distributions. Approximately 100 SNPs were genotyped in all derived populations.

GROUP MEMBERS
Ivo Chelo (Postdoc)
Sara Carvalho (PhD Student)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

LYMPHOCYTE ACTIVATION

Salvatore Valitutti

MD, residency in Pathology
University of Rome, Italy
E-mail: svalitutti@igc.gulbenkian.pt

Our research team employs a combination of morphological, biochemical and functional approaches to investigate the activation of effector T lymphocytes and their communication with Antigen Presentig Cells (APC). Our specific aim is to study the molecular dynamics occurring at the interface between effector T cells and APC and the functional consequences of this interaction.

DELAYED KILLING OF MELANOMA CELLS BY CTL: MULTIPLE HITS MUST BE PROVIDED FOR TUMOR CELL ANNIHILATION

It is well established that Cytotoxic T cells (CTL) are triggered to kill target cells offering a very small number of specific peptide/MHC (pMHC) complexes. It is also known that lethal hit delivery is a very rapid response that occurs within a few minutes after cell-cell contact. Whether cytotoxicity is efficient and rapid in the context of CTL interaction with tumor target cells is still elusive and it is the subject of our investigation.
We addressed this question by visualising the dynamics of human CTL interaction with melanoma cells and their efficiency in eliciting cytotoxicity. Our results show that in spite of CTL activation to lethal hit delivery, killing of melanoma cells was inefficient (Caramalho et al., 2008). Time-lapse microscopy showed that individual CTL rapidly polarised their lytic machinery towards target cells, yet the apoptotic process in melanoma cells was delayed as compared to conventional target cells, since it required a prolonged time after receiving lytic granules. These results indicate that while CTL activation to lethal hit delivery can be viewed as a "digital" phenomenon rapidly triggered by a few ligands, melanoma cell annihilation is an "analogue" response requiring multiple hits and prolonged contact time. Our next aim is to explore novel strategies to enhance CTL activity against tumour cells that may be relevant for tumour vaccine implementation.

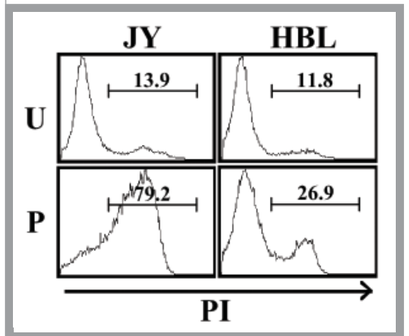
ADJUVANTICITY OF MICROBIAL-DERIVED PARTICLES AND SYNTHETIC ANALOGS *IN VITRO*

This project is described in its full extent under Elisabeta Padovan's page, in the Research Fellows section of this report.

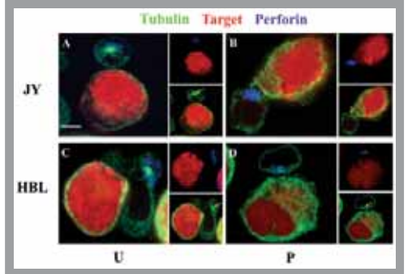
HOW PATTERN RECOGNITION RECEPTORS SIGNALLING CONTROLS T LYMPHOCYTES ACTIVATION

This project is described in its full extent under Elisabeta Padovan's page, in the Research Fellows section of this report.

GROUP MEMBERS
Íris Caramalho (Post-doc)
Lurdes Duarte (Laboratory Technician, left August 2008)
Cláudia Oliveira (Trainee, left September 2008)
Elisabetta Padovan (Group Coordinator, until November 2008)
Inês Ramos (Trainee, left November 2008)



MELANOMA CELLS EXHIBIT A REMARKABLE RESISTANCE TO CTL-MEDIATED KILLING.
Frequency of JY and HBL cells either unpulsed (U) or pulsed (P) with 10μM pp65 peptide that incorporated PI after 4 hours conjugation with pp65-specific CTL. A representative result out of at least 8 independent experiments performed in duplicates is shown. Numbers indicate the frequency of PI positive cells.



CTL EFFICIENTLY POLARIZE THEIR LYTIC GRANULES TOWARDS MELANOMA CELLS.
CTL were conjugated with either JY or HBL cells previously loaded with CMTMR (red), as indicated. After 15 min conjugation, cells were stained with anti-tubulin (green) and anti-perforin (blue) mAbs. Target cells were either unpulsed (U), (panels A and C) or pulsed (P), (panels B and D) with 10μM pp65. Small inserts correspond to the original image where either the green (top insert) or the blue (lower insert) color was removed. Yellow arrows indicate the MTOC of CTL. Data are representative of 3 independent experiments (bar=5μm).

THIS GROUP COLLABORATES WITH:
Jocelyne Demengeot (IGC)

INNATE BEHAVIOUR

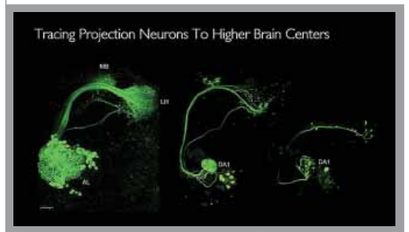
Maria Luísa Vasconcelos

PhD in Neuroscience
Universidade Nova de Lisboa, Portugal
E-mail: vasconcelos@igc.gulbenkian.pt

THIS GROUP WAS ESTABLISHED AT THE IGC IN JUNE 2008 AND IS A MEMBER OF THE CHAMPALIMAUD NEUROSCIENCE PROGRAMME AT THE IGC.

Animals exhibit behavioural repertoires that are often innate and result in stereotyped sexual and social responses to their environment. Innate behaviours do not require learning or experience and are likely to reflect the activation of developmentally programmed neural circuits. We are interested in the nature of defined neural circuits: how activation of circuits elicits specific behaviours. In complex organisms it has been extremely difficult to study a circuit beyond the early stages of sensory processing. *Drosophila melanogaster* is an attractive model system to understand a circuit because flies exhibit complex behaviours that are controlled by a nervous system that is numerically five orders of magnitude simpler than that of vertebrates. We use a combined behavioural, genetic, imaging and electrophysiological approach to determine how defined neural circuits and their activation elicit specific behaviours.
In 2008 we established a fully functional multiphoton imaging set-up, established behavioural protocols for courtship and CO2 avoidance in the newly designed behavioural room and trained the laboratory technician in fly husbandry, histology and molecular biology techniques. The laboratory is set for the 2009 projects.

GROUP MEMBERS
Sophie Dias (Laboratory technician)



Tracing projections to higher brain centres in *Drosophila* melanogaster.

FUNDING
Oeiras City Council, Portugal – Professor Doutor António Xavier Scientific – Young Scientists' Installation Award

BACTERIAL SIGNALLING

Karina Xavier
PhD in Biochemistry
Universidade Nova de Lisboa, Portugal
E-mail: kxavier@igc.gulbenkian.pt

Bacteria use small chemical molecules called autoinducers to communicate with one another by a process called quorum sensing. This process enables a population of bacteria to regulate behaviours which are only productive when many bacteria act in concert as a group, similarly to what happens with multi-cellular organisms. Behaviours regulated by quorum sensing are often crucial for successful bacterial-host relationships whether symbiotic or pathogenic. In our laboratory, we use biochemical and genetic approaches to study the molecular mechanisms underlying quorum sensing, with an emphasis on systems promoting bacterial inter-species communication. This research includes an integrated study involving elucidation of the chemical molecules that are used as signals, the network components involved in detecting the signals and processing information inside individual cells, and finally characterisation of the behaviour of the bacterial community in multi-species bacterial consortia. Our ultimate goal is to understand how bacteria use inter-species cell-cell communication to coordinate population-wide behaviours in consortia and in microbial-host interactions.

IDENTIFICATION AND CHARACTERISATION OF QUORUM SENSING SYSTEMS INVOLVED IN BACTERIAL INTER-SPECIES COMMUNICATION

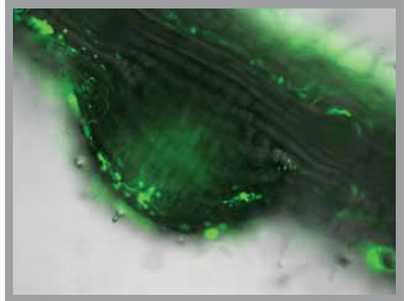
The broad use of the bacterial molecule AI-2 as a quorum sensing signal makes it an especially interesting system to study bacterial inter-species communication. In this project a newly identified AI-2 internalisation system in the plant symbiont *Sinorhizobium meliloti* will be characterised in order to evaluate the function of this system during the symbiosis this organism establishes with its host, the alfalfa plant, and its interaction with soil bacteria. The AI-2 detection systems from additional soil bacteria species will be identified and characterised. Mutants impaired in these AI-2 signalling pathways will be constructed, and used to study bacteria-bacteria, and bacteria-host interactions in multi-species consortia.
In 2008 we demonstrated that *Sinorhizobium meliloti*, a plant symbiont well known for its ability to form nodules on the roots of several legumes where it fixates nitrogen, has an AI-2-inducible operon. This operon encodes a functional AI-2 interference mechanism capable of clearing the AI-2 signal produced by soil bacteria like the *Erwinia carotovora* **(C)**, a plant pathogen that can co-exist with *S. meliloti* in the rhizosphere. We hypothesise that the ability of *S. meliloti* to interfere with the quorum sensing of plant pathogens like *Erwinia carotovora* that use AI-2 to regulate virulence could be beneficial to the plant and we have developed a laboratory system to study these type of interactions during the infection of potato tubers by mono- or multi-species bacteria cultures.

QUORUM SENSING IN *ESCHERICHIA COLI*

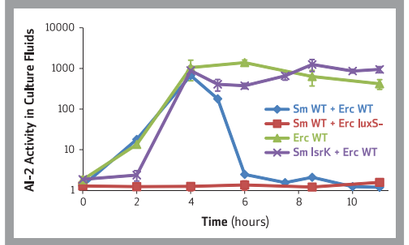
We have shown that in the enteric bacterium *Escherichia coli*, AI-2 regulates a system that has the consequence of interfering with other species' ability to use AI-2 to regulate their group behaviours by quorum sensing. We predict that this mechanism of interference with AI-2 signalling has important consequences in natural niches colonised by *E. coli*, such as the human gut, where many different species of bacterial species co-exist and depend on quorum sensing for efficient colonisation. The aim of this project is to characterise the molecular mechanisms in *E. coli* involved in accumulation and perception of the AI-2 signal at the species level and identify the bacterial behaviours regulated by this system during in mono- and multi-species interactions.
We are characterising the series of biochemical events involved in regulating the accumulation and perception of the AI-2 signal in *E. coli*. We have characterised the first enzyme involved in turning off this signal thus terminating the positive feed-back loop involved in the AI-2 signalling cycle. One product of this reaction is mutagenic and preliminary results indicate that mutants impaired in this process have lower mutation rates. We are addressing the possible benefit of this system to *E. coli*'s adaptation to stressing environments.

GROUP MEMBERS
Michal Bejerano-Sagie (Post-doc)
Catarina S. Pereira (PhD Student)
João Carlos Marques (Trainee, left September 2008)
António Santos (Trainee, left December 2008)
Andreia Correia (Trainee)

A *Sinorhizobium meliloti* colony.



An alfala root nodule inoculated with S.melilolti marked gfp.



Extracellular AI-2 activity in co-cultures of *S. meliloti* with *E. carotovora*.

THIS GROUP COLLABORATES WITH:
Bonnie L. Bassler (Princeton University, USA)
Stephen T. Miller (Swarthmore College, USA)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Poritugal
Fundação Luso-Americana,Portugal
- Portugal-US: Networks and partnerships for research 2005

RESEARCH FELLOWS

These small teams are headed by experienced researchers who have established independent lines of research, within an institutional framework under direct responsibility of the Director, approved by the Scientific Advisory Board.

EDITING PROCESSES IN MOLECULAR EVOLUTION AND IMMUNITY

Alekos Athanasiadis

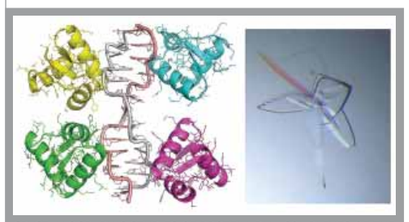
PhD in Structural Biology
University of Crete/IMBB, Greece
E-mail: alekos@igc.gulbenkian.pt

THIS GROUP WAS ESTABLISHED AT THE IGC IN DECEMBER 2008.

RNA and DNA editing are enzymatic modifications which alter the information content of nucleic acids. Organisms have found in such mechanisms the means for creating sequence diversity, as is gloriously illustrated in the diversification of the immunoglobulin genes. The recent realisation that multi-cellular organisms achieve phenotypic complexity without a parallel increase in number of genes has highlighted the importance of post-transcriptional RNA modifications, like RNA editing, in creating and fine-tuning a much larger repertoire of proteins originating from a small number of genes. While editing plays a creative role in the generation of much needed sequence diversity it also plays important roles in immunity by scrambling the genetic material of pathogens.

We are interested in the study of the molecular mechanisms involved in such diversification of RNA and DNA sequences, as well as in understanding the consequences of such processes for molecular evolution dynamics.

GROUP MEMBERS
Matteo de Rosa (Post-doc)
Délio Figueiredo (Trainee)



CRYSTALLOGRAPHIC STUDIES OF PROTEIN-DNA COMPLEXES OF THE EDITASE ADAR1.
Left - Four Zalpha domains bound to extended CpG repeats forming a Z-Z DNA junction at 2.6Å resolution. **Right** - Crystals of the ADAR1_Zalpha/DNA complex under polarized light.

THIS GROUP COLLABORATES WITH:
Rich Alex (Massachusetts Institute of Technology, USA)
Maria Armenia Carrondo (ITQB, Oeiras)
Maas Stefan (Lehigh University)

FUNDING
European Commission Framework Programme 7 (FP7)
- Marie Curie International Reintegration Grant

PLANT GENOMICS

Jörg Becker

PhD in Biology
University of Bielefeld, Germany
E-mail: jbecker@igc.gulbenkian.pt

Our group is primarily interested in the mechanisms underlying sexual reproduction and early embryogenesis, with a particular focus on the role of the male gametes. Contrary to previous assumptions, recent studies have shown that male gametes both in the plant and animal kingdom carry complex sets of RNA molecules, including not only mRNAs but also small RNAs. We are particularly interested in the role of these two RNA classes before, during and after double fertilisation as it occurs in higher plants.

Using *Arabidopsis thaliana* as our experimental model we are addressing specific questions like: (1) What are the functions of small RNA and DNA methylation pathways in sperm cells? (2) Do sperm cell derived RNAs play a role after fertilisation? (3) How are cell cycle transitions controlled in the sperm cells?

In a second research line we are analysing the symbiotic transcriptome of the model legume *Medicago truncatula*, both for nodule and mycorrhizal symbiosis, leading to the creation of a gene expression database that will allow the in-depth analysis of the symbiotic genetic programme of leguminous plants.

A COMPARATIVE ANALYSIS OF THE ARABIDOPSIS SPERM CELL TRANSCRIPTOME TO DECIPHER THE ROLE OF THE MALE GAMETES IN DOUBLE FERTILISATION

In flowering plants, the two sperm cells are embedded within the cytoplasm of the growing pollen tube and as such are passively transported to the embryo sac, wherein double fertilisation occurs upon their release. Understanding the mechanisms and conditions by which male gametes mature and take part in fertilisation are crucial goals in the study of plant reproduction. This study aimed at developing a fluorescence-activated cell sorting method to isolate sperm cells from Arabidopsis, allowing GeneChip analysis of their transcriptome at a genome-wide level in this model plant. The functional analysis of the data is expected to create new hypotheses for sperm cell biology and double fertilisation.

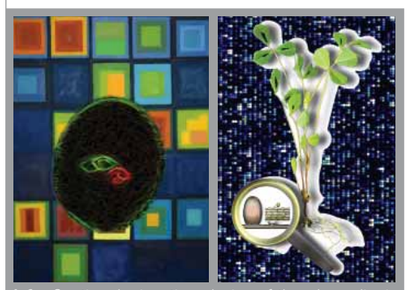
We obtained and analysed the sperm cell transcriptome after optimising a FACS protocol (published in Plant Physiology 148: 1168-1181 (2008)). In addition we used our protocol for the isolation of small RNAs and genomic DNA from sperm cells in a collaboration with Rob Martienssen (Cold Spring Harbor Laboratory).

EXPRESSION PROFILING STUDIES TO SPECIFY THE SYMBIOTIC GENETIC PROGRAMME OF THE MODEL LEGUME *MEDICAGO TRUNCATULA*

This project aims to provide the first true large-scale analysis of the symbiotic transcriptome of the model legume *Medicago truncatula*, a key component of the use of legumes in sustainable agricultural systems. Selected stages of nodule and mycorrhizal symbioses will be analyzed on Affymetrix *Medicago truncatula* GeneChip arrays and data will be made freely accessible in the Truncatulix database.

More than 30 of the 50 sample types within this project have been obtained and processed by array analysis. The available datasets include a nodulation time-course and distinct mycorrhizal colonisation processes under varying inorganic phosphate fertilisation levels, among others. The Truncatulix database has been prepared to accept and process GeneChip expression data.

GROUP MEMBERS
Filipe Borges (Trainee)
Patrícia Pereira (Trainee)



Left - Genetic and epigenetic mechanisms of the male germline in Arabidopsis highlighted by genome-wide transcriptomics. An artist's impression showing a mature pollen grain of Arabidopsis enclosing the two gametes (sperm cells) and the companion vegetative nucleus, overlaid on an oil painting representing a DNA microarray. **Right** - A gene expression map of *Medicago truncatula* root symbioses. Schematic representation of root nodule and mycorrhizal symbiosis formed by the model legume plant Medicago, superimposed on unprocessed expression data as obtained by DNA microarray analysis.

THIS GROUP COLLABORATES WITH:
Rui Martinho (IGC)
Rob Martienssen (Cold Spring Harbour Laboratory, USA)
Arp Schnittger (CNRS, Strasbourg, France)
Thomas Dresselhaus (University of Regensburg, Germany)
Liam Dolan (John Innes Centre, UK)
Ji He (The Samuel Roberts Noble Foundation, USA)
Helge Küster (University of Bielefeld, Germany)
Leonilde Moreira (Instituto Superior Técnico, Portugal)
Cristina Silva Perreira (ITQB, Portugal)
Sofia Perreira (Instituto Superior de Agronomia, Portugal)
Helena Carvalho (IBMC, Portugal)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

LUPUS AND AUTOREACTIVE IMMUNE REPERTOIRE

Constantin Fesel

PhD in Immunology
Université Paris VI / Institut Pasteur, France
E-mail: cfesel@igc.gulbenkian.pt

While the detection of molecular mechanisms and of genetic disease risk factors rapidly evolves, the systemic diversification of specificity repertoires, which is of obvious relevance for the pathogenesis of human autoimmune diseases, is still poorly understood. In this situation, it is increasingly relevant to combine different types of knowledge in order to model the pathogenetic processes that lead to autoimmune diseases as a whole, since they are known to depend on complex interactions of a variety of molecular and cellular mechanisms acting on different levels.
Systemic Lupus Erythematosus (SLE) is a human autoimmune disorder where altered physiologies and self-reactive repertoires of both B- and T-cells are intimately connected. Autoreactive IgG antibodies are the diagnostic hallmark of SLE and diversify over long time periods before disease becomes manifest; however, this depends also on nonspecific factors, such as type I interferons. Our current approach is to model, in a stepwise fashion, the ways in which different genetic factors and molecular mechanisms are interconnected in SLE pathogenesis, by analysing their relatedness in reference to standardised and quantitative broad-spectrum immunoblot autoantibody profiles. In this context, we are particularly interested in the role of T-cell regulation. Since we found particular relations between antibody reactivity and regulatory T-cells in unaffected relatives of SLE patients, who often share elevated titres of SLE-associated auto-antibodies, we follow the hypothesis that these auto-antibody-positive unaffected relatives bear a particular capacity to regulate autoreactive immune repertoires that breaks down in clinically manifest disease. Consequently, our principal approach to model SLE pathogenesis is actually focused on genetic factors and molecular mechanisms relevant for T-cell regulation, in combination with a systematic study of first-degree relatives of SLE patients. In parallel, we study T-cell regulation in mouse models and the effect of therapy with intravenous immunoglobulin (ivIg).

AUTOANTIBODY REPERTOIRES AND REGULATORY T-CELLS IN HUMAN AND MURINE LUPUS

We aim to study the relation of autoantibody patterns, in terms of a multiparametric quantitative immunoblot assay, with T-cell regulation, and to test different mouse models for whether they reflect T-cell regulatory effects
Analysis revealed a positive correlation of autoantibody reactivity with peripheral blood CD25bright regulatory T-cell frequencies within unaffected relatives (who frequently show SLE-associated autoantibody reactivity) but not in the group of SLE patients themselves, or in unrelated control subjects. This strongly suggests a compensation mechanism which is active in non-affected relatives which present SLE-type autoantibodies depending on CD25bright regulatory T-cells.
Using the Sequenom platform of the IGC, we have furthermore genotyped 180 SNPs, focusing on genetic variation in loci relevant for T-cell regulation and particularly the IL-2 signalling system. Genotyping included tag SNP coverage of the loci encoding IL2, CD25, CD3Z, CD28, JAK1 and STAT4, but also known SLE-associated polymorphisms and some other loci such as IGH. In terms of genetic association, we found some yet unpublished significant associations with SLE and with CD25bright peripheral T-cell frequencies, which, however, differed within the unaffected relatives group and within SLE patients. These results support our hypothesis of a particular state of T-cell regulation in the unaffected relatives.

GROUP MEMBERS
Nuno Costa (Trainee)

THIS GROUP COLLABORATES WITH:
Jocelyne Demengeot, Carlos Penha-Goncalves (IGC)
Joao Faro Viana, Francisca Moraes-Fontes
(Centro Hospitalar de Lisboa Ocidental, Lisbon)
Cristina João (Insituto Português de Oncologia, Lisbon)
Carlos Ferreira (Hospital Santa Maria Lisbon)
Jorge Martins (Hospital dos Marmeleiros, Madeira)
Berta Martins (Instituto de Ciências Biomédicas Abel Salazar, Porto)
Carlos Vasconcelos, Margarida Lima (Hospital Geral Santo Antonio, Porto)

FUNDING
Fundação para a Ciência e a Tecnologia (FCT), Portugal

NEUROETHOLOGY

Susana Lima

PhD in Neuroscience
University of Lisbon, Portugal
E-mail: slima@igc.gulbenkian.pt

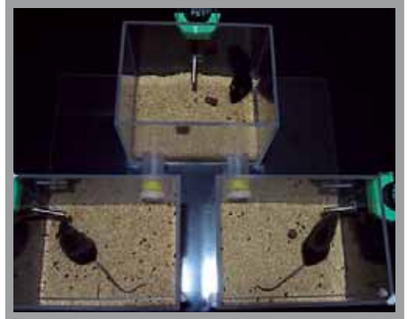
THIS GROUP IS A MEMBER OF THE CHAMPALIMAUD NEUROSCIENCE PROGRAMME AT THE IGC.

Mate choice is a critical driving force in evolution yet the mechanisms underlying it remain poorly understood. Mate selection requires the perception of specific cues, that indicate the characteristics of prospective mates, and a decision based on those cues. While a variety of studies have investigated the nature of sensory signals emitted by animals, very little is known about the downstream processes that underlie mate assessment.
By combining behavioural and neuroanatomical approaches and using the mouse as a model system, we are investigating which brain structures are specifically involved in mate assessment and choice. For that purpose, we are making use of various behavioural tests (involving either direct interactions between choosers and test animals or presentation of urine from the test animals) to assess mate preference by female towards different prospective mates. Second, to identify candidate brain regions involved in mate choice, we are assessing neuronal activity in the female brain elicited by this decision process using immediate early genes as a read-out.

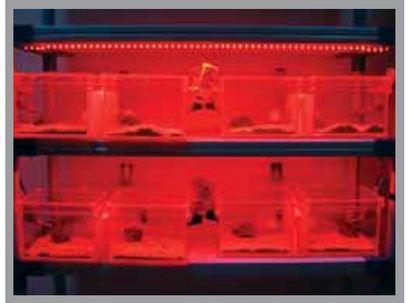
NEURAL MECHANISMS UNDERLYING INBREEDING AVOIDANCE IN MICE

It has been shown in several studies that female mice, when given the opportunity of choosing amongst several different partners, will prefer to mate with males whose genotype is more dissimilar from their own (dissortative mating). The goal of this project is to understand how information about genetic quality is transformed into neuronal activity that can guide this decision process.
In 2008, we developed the behavioural apparatus, video capturing and analysis software to perform preference tests in mice.

GROUP MEMBERS
Léa Zinck (Post-doc)



Top view of the behavioral apparatus of the test-preference assay: Female mice are given the option of choosing amongst two different males (which vary in social status, familiarity or genetic background). The males are confined to their cage because they are tethered with a leash and collar; the female is free to move through the 3 boxes and choose her preferred partner.



A side view of the same apparatus. Experiments are performed during the night, since mice are nocturnal animals. In order to visualise the experiments, the room is illuminated with red and infra-red light emitting diodes which are invisible to the mice.

FUNDING
Calouste Gulbenkian Foundation - IGC start-up fund
Champalimaud Foundation
- Champalimaud Neuroscience Programme Start-up Fund
Fundação para a Clência e a Tecnologia (FCT), Portugal

ANTIGEN PRESENTATION AND T CELL ACTIVATION

Elisabetta Padovan
PhD in Immunology
University of Padova, Italy
E-mail: epadovan@igc.gulbenkian.pt

T cells are central actors in antigen-specific immune responses and their function is strongly influenced by signalling through Pattern Recognition Receptors (PRR). While the instructive role of PRR in the cell fate decisions of naïve T lymphocytes has been largely investigated, a careful analysis of how PRR agonists modulate effector T cell function is still missing and is the topic of our investigation.
Our specific goals are to: i) study adjuvant activity and pyrogenicity of PRR agonists using human lymphocyte cultures; ii) dissect how cooperation among different APC and PRR agonists influences the expansion of functionally different effector T cells; iii) study the biological outcome of the interaction between effector T cells with different types of APC; iv) characterize the molecular dynamics occurring at the interface of APC/T cell conjugates.

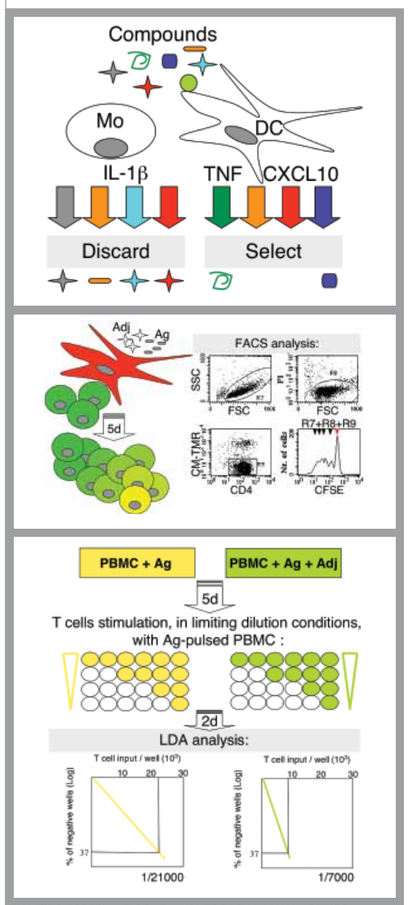
ADJUVANTICITY OF MICROBIAL-DERIVED PARTICLES AND SYNTHETIC ANALOGUES *IN VITRO*

Methods currently used in toxicology for mandatory safety tests rely heavily on the dosing of animals. In the context of vaccinology, compounds of unknown functions are tested *in vivo* for adjuvancy without any clue of their toxicity. These procedures often cause animal pain, distress and even death before any indication of immune protection.
As new compounds become available, there is ethical, political and commercial pressure to reduce animal tests and ensure that tested animals undergo minimum pain and distress. In this context, new tests based on human lymphocyte cultures *in vitro* are particularly needed, also considering the important differences between human and animals that render animal models poorly suited for identifying new safe immune enhancers for human vaccines.
The aim of this project is to develop an applicable system to identify human-compatible adjuvants *in vitro*.
Based on molecular profiles of human lymphocyte cultures and functional assays of T cell activation in the presence or absence of putative standard adjuvants, we have defined TNF/CXCL10 and IL-1β as molecular signatures of adjuvanticity and pyrogenicity, respectively. We propose a new method of adjuvant screening, whereby potentially safe adjuvants are first identified *in vitro* for the capacity of inducing TNF and/or CXCL10 release by DC, and absence of IL-1β release by monocytes (step 1). Selected compounds are then assessed for the capacity to enhance antigen-specific T cell activation in bulk cultures (step 2) and limiting dilution assays (step 3). Only compounds with high immune enhancer activity *in vitro* will, finally, be assessed in animal models before admission to clinical application.

HOW PATTERN RECOGNITION RECEPTORS SIGNALLING CONTROLS T LYMPHOCYTES ACTIVATION

Classically, CD4+ T cell responses result from the triggering of their T cell receptor (TCR) by MHC-II/peptide complexes expressed on APC, and the outcome of this process is influenced by the engagement of PRR. Cooperation between functionally different APC and PRR agonists is likely to influence CD4+ T cell activation with both positive and detrimental consequences.
We employ human T cell clones producing IFN-γ (Th1) or IL-17 (Th17) to assess the capacity of these cytokine-polarised effector T cells to communicate with APC and participate in immuneregulation.
We have generated polyclonal T cell lines by culturing CD4+ T lymphocytes with autologous monocytes in the presence of Superantigens (SAg) that expand specific TCR-Vβ T cell subsets. Assessment of cytokine-production revealed that the large majority of SAg-specific T cells produced IFN-γ. A minority of the cells also expressed IL-17 in combination with IFN-g. These dual expressor T cells, were instable and were no longer detectable after two weeks of culture. Addition of Peptidoglycan (PGN) from *S. aureus* or LpOspA lipoprotein from *B. burgdorferi* at the time of priming stabilised Th1/Th17 dual expressors and even expanded single IL-17 producing T cells.
A collection of Th1 and Th17 clones has been isolated and is currently being employed to dissect the crosstalk established with different types of APC.

GROUP MEMBERS
Inês Ramos (Laboratory Technician)



IN VITRO SCREENING OF ADJUVANTS FOR HUMAN VACCINES.
Top - *Step 1: Pre-screening*. Safe potential adjuvants are identified in vitro for the capacity of inducing TNF and/or CXCL10 release by human dendritic cells (DC), and absence of IL-1β release by monocytes. **Middle** - *Step 2: Adjuvanticity Test I*. Human DC are labeled with the red fluorescent dye CM-TMR and co-cultured with autologous purified CD4+ T lymphocytes, labeled with the green fluorescent dye CFSE, in the presence or absence of antigen (Ag) and adjuvant (Adj). T cell proliferation after 5 days of culture is measured by the loss of green fluorescence in live CD4+ T lymphocytes (in R7 and R8) excluding red-labeled DC from the analysis (R9). In the CFSE staining histogram plot red arrow specifies the non-dividing parent generation. **Bottom** - *Step 3: Adjuvanticity Test II*. Human Peripheral Blood Mononuclear Cells (PBMC) are primed *in vitro* with Ag in the presence or absence of Adj, without exogenous cytokines. After 5 days, cells are restimulated in limiting dilutions and the frequency of Ag-specific T cells determined by Limiting Dilution Analysis (LDA).

THIS GROUP COLLABORATES WITH:
Jocelyne Demengeot, Jorge Carneiro (IGC)
Iris Caramalho (IGC)
Markus Simon, Marina Freudenberg
(Max Planck Institute for Immunebiology, Freiburg)
Gennaro de Libero, Regine Landmann
(Department of Research, University Hospital, Basel)

FUNDING
3R Research Foundation Switzerland 92/04
Fundação para a Ciência e a Tecnologia (FCT), Portugal

DOPAMINE IN ACTION LEARNING

Joseph Paton

PhD in Neurobiology and behaviour
Columbia University, USA
E-mail: jpaton@igc.gulbenkian.pt

THIS GROUP IS A MEMBER OF THE CHAMPALIMAUD NEUROSCIENCE PROGRAMME AT THE IGC.

Learning to adaptively respond to cues in the environment that predict behaviourally relevant events is critical for survival. However, in a noisy environment, where animals are exposed to myriad sensory stimuli, inferring the predictive value of cues for things that the animal cares about is non-trivial. At its core, it is a problem of statistical inference in the time domain... ie, when things occur relative to meaningful events is what determines their information content, their usefulness, and thus, whether they warrant learning about. However, we still do not understand how the brain keeps track of the times of events. Thus, if we are ever to understand learning of this type, we must first understand brain mechanisms for time. We approach this problem by examining neurophysiology in behaving rodents performing tasks in which they must estimate time intervals.

NEURAL ENCODING OF TIMING IN MOTOR CORTICAL AND BASAL GANGLIA LOOPS

By parametrically varying a time interval that a rat must estimate, while simultaneously recording action potentials from single neurons at two locations within a sensory motor loop, we will identify neurons whose activity is correlated with a change in estimated interval. We will use the whisker system as a platform to study this process, as its circuitry is relatively well-defined, motor signals in our task are relatively simple, and a large amount of neural tissue is devoted to this system in the rat brain. The particular profile of action potential firing that we find will constrain the number of possible neural models that we can propose to explain the phenomenon of time estimation. We will begin by recording from phasically active neurons in the striatum. We will test the hypothesis that phasically active neurons will shift their latency of response as we shift the time interval that rats must estimate.
We have succeeded in training rats to use their whiskers to contact targets in order to gain rewards at defined intervals. Rats' rate of responding begins to increase at roughly two-thirds of reinforcement interval, peaking around the time of reinforcement. We then shift the interval of reinforcement in blocks of trials to a different interval and animals shift the time at which they begin to respond, thus giving us a behavioural readout of when the animal perceives an interval to have elapsed. We are currently developing quantitative measures of this interval timing behaviour that we will ultimately relate to neural activity that we record. In addition we have built a neurophysiology setup and are preparing to begin the recording studies.

GROUP MEMBERS
Gustavo Mello (MSc Student)

THIS GROUP COLLABORATES WITH:
Joshua T. Dudman (HHMI Janelia Farm Research Campus, USA)
Rui M. Costa (Champalimaud Neuroscience Programme at IGC)

FUNDING
Calouste Gulbenkian Foundation - IGC start-up fund
Champalimaud Foundation
- Champalimaud Neuroscience Programme Start-up Fund

CARDIAC REGENERATION

Luis Rosário

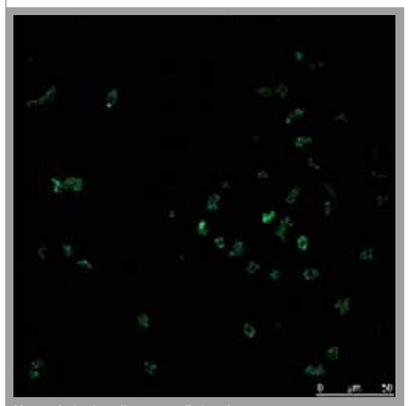
PhD in Medicine and Physiology
University of Lisbon, Portugal
E-mail: lrosario@igc.gulbenkian.pt

Until recently, the heart was considered a post-mitotic organ. The discovery, in 2001, that cardiac myocytes can divide and of a resident population of cardiac stem cells has the potential to overturn our understanding of cardiac biology and physiology, as well as of the pathology and therapeutic approaches to cardiovascular diseases.
Research in our group is dedicated to understanding the physiology of cardiac stem cells from two main perspectives: the physiologic control of proliferation versus differentiation and the physiologic integration of transplanted cardiac stem cells. For the first perspective the approach has been the development of *in vitro* models of cardiac stem cell differentiation or proliferation and identification of the mechanisms involved in determining cell fate. Regarding the latter perspective, we have developed an infarct model which we will use to verify whether cardiac stem cells integrate into the recipient myocardium.

MODULATION OF CARDIOVASCULAR ADAPTATION TO DISEASE: IMPACT OF STEM CELL TRANSPLANTATION ON POST MYOCARDIAL INFARCT REMODELLING AND ARRHYTHMIAS

The main aim of this project is to evaluate potential arrhythmias that may be associated to stem cell transplantation.
In 2008 we isolated c-kit$^+$ and sca-1$^+$ cardiac stem cells from the mouse, and showed that under appropriate cell culture conditions these cell lines proliferated and differentiated into spontaneously beating cardiomyocytes.

GROUP MEMBERS
Marta Martins (Post-doc, left Octber 2008)
Laura Rodrigues (Msc Student)
Isa Matos (Trainee, left July 2008)
Alex Matsuda (Trainee)

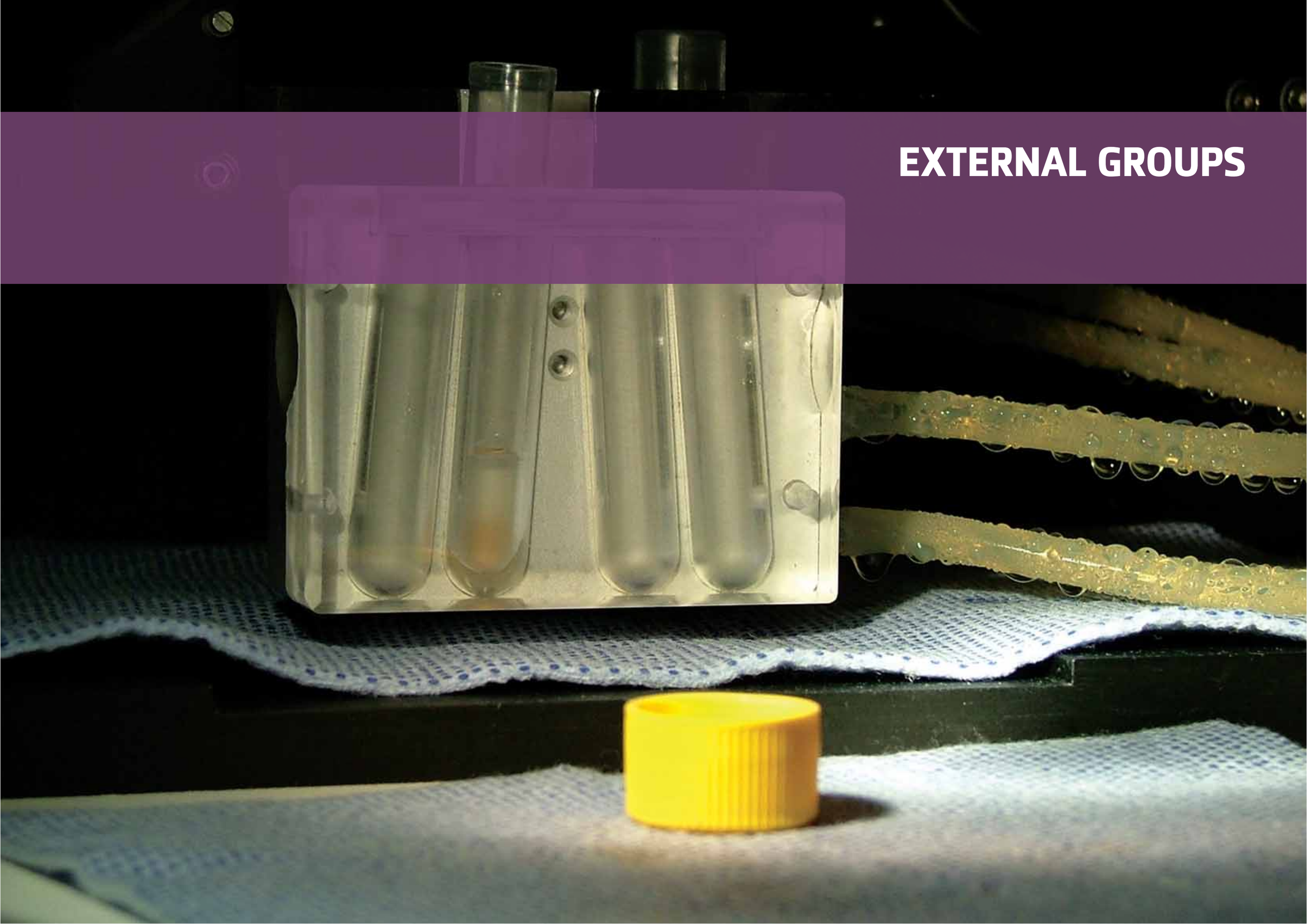


Mouse-derived cardiac stem cells in culture.

THIS GROUP COLLABORATES WITH:
Carlos Cordeiro Margarida Carvalho (University of Lisbon)
Miguel Dias (Instituto Superior de Ciências do Trabalho e da Empresa)
Miguel Soares (IGC)

FUNDING
Calouste Gulbenkian Foundation, Portugal

EXTERNAL GROUPS



THE FOLLOWING GROUPS DEVELOP THEIR RESEARCH AT EXTERNAL ASSOCIATED LABORATORIES:

GASTRULATION – José Belo
(University of Algarve, Portugal)

NEOANGIOGENESIS – Sérgio Dias
(Instituto Português de Oncologia, Lisbon, Portugal)

POPULATION GENETICS – Francisco Dionísio
(University of Lisbon, Portugal)

ANTÓNIO DUARTE – Vascular Development
(Technical University of Lisbon, Portugal)

SYSTEMS IMMUNOLOGY – José Faro
(University of Vigo, Spain)

CELLULAR IMMUNOLOGY – Luis Graça
(Institute for Molecular Medicine, Lisbon, Portugal)

NEURAL DEVELOPMENT – Domingos Henrique
(Institute for Molecular Medicine, Lisbon, Portugal)

MORPHOGENESIS – António Jacinto
(Institute for Molecular Medicine, Lisbon, Portugal)

MALARIA CELL BIOLOGY – Maria Mota
(Institute for Molecular Medicine, Lisbon, Portugal)

AZORES GENETICS – Luísa Mota Vieira
(Divino Espírito Santo Hospital, Azores, Portugal)

ANIMAL BEHAVIOUR – Rui Oliveira
(Instituto Superior de Psicologia Aplicada, ISPA, Lisbon, Portugal)

HUMAN GENETICS – Sofia Oliveira
(Institute for Molecular Medicine, Lisbon, Portugal)

HAEMATOPOIESIS – Leonor Parreira
(Institute for Molecular Medicine, Lisbon, Portugal)

SYMMETRY AND DEVELOPMENT – Leonor Saúde
(Institute for Molecular Medicine, Lisbon, Portugal)

MOLECULAR IMMUNOLOGY – Bruno Silva Santos
(Institute for Molecular Medicine, Lisbon, Portugal)

VIRAL PATHOGENESIS – João Pedro Simas
(Institute for Molecular Medicine, Lisbon, Portugal)

EXTRACELLULAR MATRIX – Solveig Thorsteinsdóttir
(University of Lisbon, Portugal)

GENETIC EPIDEMIOLOGY – Astrid Vicente
(Instituto Nacional de Saúde Dr. Ricardo Jorge, Lisbon, Portugal)

FACILITIES AND SERVICES

ANIMAL HOUSE

Head: Jocelyne Demengeot
Group Leader
E-mail: jocelyne@igc.gulbenkian.pt

THE IGC ANIMAL FACILITY CONSISTS OF FIVE INDEPENDENT UNITS:

- Production facility (barrier);
- Experimental facility (barrier);
- Experimental facility (conventional);
- Quarantine (barrier);
- Germ-free facility.*

* The germ-free facility is open to the international community, through the EMMA consortium (www.emmanet.org).

The whole Animal Facility hosts over 130 mouse strains and 2 rat strains. This corresponds to a total of 4500 cages and about 12000 animals (mice 95%, rats 5%). During 2008, the Production Unit ensured the breeding and housing of more than 40 different mouse strains that are available to the scientific staff for research purposes. Twelve new strains were introduced and are now ready to be used. Compared to 2007, this number corresponds to an increase of 26% of available mice strains from the Production Unit.

AS SERVICES, THE IGC ANIMAL FACILITY MAY PROVIDE:

- Research opportunities for external researchers/institutions;
- Rederivation of mouse lines into Specific Pathogen Free (SPF) conditions;*
- *In vitro* fertilisation;
- Cryopreservation of mouse germplasm.

* According to the FELASA recommendations

LIST OF EQUIPMENT (Major equipment):

- 7 autoclaves;
- 15 IVCs (Isolated Ventilated Cages) rack system;
- 6 Germ-Free Isolators;
- 1 osmosis reverse system;
- 1 vapor-phase hydrogen peroxide decontamination system;
- 1 transfer and decontamination chamber;
- 1 animal transfer chamber.

The Germ-free service hosted by the animal facility is part of the European Mouse Mutant Archive (EMMA) consortium.
The specific mission of the IGC Unit within EMMA is the transfer to germ-free conditions of genetically modified mouse lines. These lines are then made available, upon request from interested scientists in Europe. In order to facilitate the analysis of such animals, notably avoiding costly specialised transportation at the risk of losing the "germ-free" condition, the IGC opens its laboratories and facilities to external scientists engaged in these studies.
In 2008, seven requests from the international community were satisfied. In addition, two projects by IGC scientists were started.

The Animal Facility is a repository for the collection and archiving *via* cryopreservation of in house mouse strains. The generation of genetically engineered mice is costly and time-consuming. Because of this investment, it is wise to bank embryos of an important mouse strain to safeguard against the possibility of losing the line in case of an infection or any kind of adversity. In addition, at the end of a project, it is often desirable to maintain a line in case it will be required in the future. Consequently, it can be costly to maintain the line as it entails the use of expensive animal space. To accommodate researchers of the IGC in either of these instances, the Animal Facility offers mouse cryopreservation services in the form of frozen embryos and spermatozoa. In 2008, the archiving of 50 new strains were initiated, 17 of them were completed.

FACILITY STAFF:
Manuel Rebelo (Manager of the Facility)
Tatiana Vassilevskaia (Technician)
Joana Bom (Technician)
Rubina Caldeira (Technician)
Carina Brilha (Administrative Assistant)
Carlos Pires (Caretaker responsible for the experimental Unit E0)
João Lopes (Caretaker responsible for the Production Unit)
Joaquim Gafaniz (Caretaker responsible for the experimental Unit E1, left Decmeber 2008)
Graça Ramalho (Caretaker responsible for the Quarantine Unit)
Samira Varela (Caretaker)
Sandra Costa (Caretaker)
Luís Arroja (Caretaker)
Cláudia Gafaniz (Caretaker)
Olinda Queirós (Caretaker)
Rogério Silva (Caretaker)

An important activity of the Animal Facility is the importation of rodents for researchers. In 2008, we concluded 55 different importation processes of live animals (an increase of 57% compared to 2007). These 55 importation processes corresponded to 25 new strains of mice. From those, 13 strains required cleansing: 7 rederivations were concluded and 6 are ongoing. The two strategies routinely used in our Facility for rederivation are in vitro fertilisation (IVF) and embryo or foetus transfer. IVF techniques have been also applied to specific projects run by IGC scientists to improve mice production due to poor breeder performance.

TRANSGENICS FACILITY

Head: Moises Mallo
Group Leader
E-mail: jocelyne@igc.gulbenkian.pt

The Transgenics Unit is the gene manipulation unit. The unit provides transgenic services to the research staff. Both classic transgenics, by pronuclear microinjection, and gene targetting, by blastocyst injection of embryonic stem (ES) cells, are offered as a service. The unit also offers the cryopreservation of embryos for long term storage

THE UNIT IS EQUIPPED WITH:

- Two microinjection set-ups, one with a Nikon inverted microscope and Narishige micromanipulators, and the other with a Leica inverted microscope and Narishige micromanipulators;
- a Zeiss SV 6 Stereomicroscope with training head;
- Two additional Zeiss SV 6 Stereomicroscopes;
- a Sutter P-87 Flaming/Brown micropipette puller;
- a CO_2 incubator.

The Unit regularly performs both pronuclear DNA injections and blastocyst injections of ES cells. A total of 104 DNA injections were performed in 2008, which produced 181 transgenic embryos or founders. Most transgenics were produced by microinjection into the FVB/N background. In addition, injections were also performed into the C57BL/6 background mostly to produce founders directly in this background, to better fit the experimental requirements of the requesting groups, which prefer this genetic strain for immunology-related projects.
In most of the FVB/N injections, the phenotypes were not dependent on the strain and most of the times led to embryonic lethality, which implied that the studies had to be performed using a transient transgenic approach. Therefore, the use of this strain for the experiments increased the production of transgenic embryos.
The overall transgenic efficiency was 31% and 26% for injections in the FVB/N and C57BL/6 backgrounds, respectively. In the case of blastocyst microinjections, three chimeras were produced using ES cells from the 129sv background.

FACILITY STAFF:
Ana Nóvoa (Research Technician)

ZEBRAFISH FACILITY

Head: Mathias Koeppen
Group Leader
E-mail: koeppen@igc.gulbenkian.pt

Zebrafish has become one of the preeminent vertebrate model organisms for biological research in recent years. Among other advantages, it combines the possibility of genetic investigation and high-power microscopy with relative ease of maintenance. The IGC is in the process of accommodating a growing zebrafish research community, which focuses on a wide range of topics including tissue morphogenesis and regeneration. Our current facility hosts several wild-type and transgenic lines and is maintained by a dedicated technician. However, to accommodate the increasing needs of the users, a new, larger facility is in the final stages of construction. It will house several hundred tanks and provide space and state-of-the-art equipment for key procedures, such as phenotypic inspection and microinjection. The existing facility will serve as a quarantine room to protect the main facility from infections.

The existing zebrafish facility is equipped with an Aquatic Habitats Z-mod Z72 system and a Microinjection setup. The new facility will include a Tecniplast Zebtec system, 6 racks for up to 300 tanks total and three injection setups.

The zebrafish facility supports the research projects of several IGC laboratories. The group of Mathias Koeppen investigates mechanisms of tissue morphogenesis in the zebrafish embryo. For this, the facility provides several fish lines that are used to obtain embryos and provides the equipment to carry out microinjections. The group of Joaquin Leon investigates mechanisms of fin regeneration in the zebrafish, using several fish lines of the facility. In addition, zebrafish projects are being initiated in the IGC laboratories of Vasco Barreto and Miguel Godinho.

FACILITY STAFF:
Paulo Raimundo (Short Term Apprentice)

DROSOPHILA FACILITY

Head: Rui Martinho
Group Leader
E-mail: rmartinho@igc.gulbenkian.pt

Drosophila melanogaster is a small invertebrate that over the past 100 years has established itself as powerful model system to investigate most questions in biology. The IGC Fly Facility hosts thousands of mutant lines that are available for research purposes. Several groups at the IGC use the facility, working in cell cycle, early development, actin dynamics, evolution and neuroscience.

As a service, the fly facility provides technical help to microinject DNA, in the production of different types of fly food, and "fly-pushing".

PLANT FACILITY

Users: Paula Duque, Elena Baena-González and José Feijó
E-mail: duque@igc.gulbenkian.pt

The Plant Facility at the IGC ensures the growth and maintenance of *Arabidopsis thaliana* plants, the model organism used by the plant research groups hosted by the Institute. The facility consists of a custom-built greenhouse with lighting control and temperature regulation and three custom-made fully controlled growth chambers with short day, long day and continuous light settings.

Four research groups make use of the IGC Plant Facility, as all use *Arabidopsis thaliana* as a model system in their research work. The Plant Development group develops integrated models of cellular growth and morphogenesis using the pollen tube as a biological model, ion dynamics as an experimental paradigm and theoretical modeling as an integrative tool. The Plant Molecular Biology group investigates how plants perceive and respond to environmental signals and endogenous developmental cues at the molecular level, focusing on the role of pre-mRNA splicing in the regulation of gene expression. The Plant Stress Signaling group is interested in the mechanisms underlying tolerance to multiple types of stress and on how these signaling cascades interact with other physiological and hormonal cues to orchestrate growth and development. Finally, the Plant Genomics group focuses on the role of male gametes during double fertilisation.

CELL IMAGING UNIT

Head: José Feijó
Group Leader
E-mail: jfeijo@fc.ul.pt

The cell imaging unit's main goal is to provide access to high-end technology and cutting-edge technical support for the biosciences research. We provide a unique facility that allows ready access to a wide range of technologies and expertise in an integrated manner that can help drive forward the research efficiently. Researchers are trained through regular workshops on basic and advanced light microscopy techniques as well as in flow cytometry, and image acquisition software themselves, with technical assistance when necessary to ensure collection of high quality images and analysis of their data. All users receive basic training in the systems and troubleshooting, and advice for experimental designs. We have developed a strong and broad base of users and continue to train new users. Because microscopy is currently in high demand and new systems and techniques are developed continuously to meet increasing scientific need, we try to expand the facilities to keep accessibility problems low and to introduce the latest innovations (in microscopy and flow cytometry) to the research community. The unit currently stands as an international reference laboratory for confocal and multi-photon microscopy, as well as for high-throughput cell sorting. We currently run two cell sorters, two confocal microscopes, DeltaVision deconvolution microscope system and two multi-photon microscopes.

THE UNIT HAS AT ITS DISPOSAL THE FOLLOWING EQUIPMENT:

- Light Microscopes: Olympus BH2, Olympus IMT-2, Leica DMLB2;
- Widefield Microscopes: Leica inverted DMIRE2, Leica upright DMRA2, Zeiss AxioImager M1;
- Confocal microscopes: Leica SP5, Zeiss LSM 510 Meta;
- Multiphoton: Bio-Rad MRC 1024 with Coherent Mira-Verdi laser system, Prairie TPE microscope with Coherent Chameleon laser system;
- DeltaVision - Deconvolution microscope system from Applied Precision, Inc.
- Cell Sorters: MoFlo, FACSAria;
- Analyzers: FACSCan, FACSCalibur.

THE FACILITY CARRIES OUT SEVERAL TECHNOLOGY DEVELOPMENT PROJECTS:

- Development of a method for adaptive autofocus and exposure times for long time lapse microscopy;
- Integrate a CCD camera with hardware shutter for better performance for live cell imaging assays synchronized with an illumination;
- Assembling of an imaging system for luminescence using 1/4 of the price of a turn key system;
- Development of equipment monitoring systems - the quality and accuracy of the data acquired in a Flow Cytometer is highly dependent on factors such as time delay between lasers, which can be affected by differences in pressure. For this purpose, we are developing inexpensive but highly accurate sensors do monitor the equipment's physical properties that can influence data acquisition. These monitors can be adapted to any machine, and may be used for maintenance purposes, since they can be connected to a computer log system;
- Sex Sorting Mouse Sperm - regulating the sex of mouse offspring is of interest to a few groups at the IGC, and is of great interest for an animal facility. We are currently adapting a known flow cytometric technique to sort mammalian sperm based on their X or Y chromosome content.

THE FACILITY CONTRIBUTED TO SEVERAL RESEARCH PROJECTS IN 2008, NAMELY:

- Arabidopsis sperm cell sorting - Accessing pure samples of pollen and its contents, sperm cells and vegetative nucleous are of great importance for genomics, transcriptomics, and other types of studies with these cells. Adapting from a previous flow cytometry technique to sort pollen grains from Arabidopsis, we have developed a flow protocol to sort sperm cells contained in the pollen grain;

- Developing Flow Cytometry techniques for sperm FISH analysis - Sperm aneuploidy assessment is of clinical relevance in severe male factor infertility and in men with abnormal karyotype. Flow cytometry-based approaches to aneuploidy scoring have been proposed as an alternative to the burdensome manual counting of fluorescent *in situ* hybridization (FISH) signals. Collaborating with a group from the Instituto de Medicina Molecular (IMM) we have developed a simple flow cytometry-based S-FISH technique specifically for chromosome enumeration in cell suspensions of human spermatozoa.

FACILITY STAFF:
Nuno Moreno (Technician)
Rui Gardner (Manager, Flow Cytometry Laboratory)
Carlos Tadokoro (Researcher)
Bárbara Fekete Beltrame (Technician)
Telma Lopes (Technician)
Gabriel Martins (Technician, left January 2008)

RELATED PUBLICATIONS:

- Filipe Borges, Gabriela Gomes, Rui Gardner, Nuno Moreno, Sheila McCormick, José A. Feijó, and Jörg D. Becker (2008) "Comparative Transcriptomics of Arabidopsis Sperm Cells" *Plant Physiol.* 148: 1168-1181.
- Isa Matos, Paulo Navarro-Costa, Rui Gardner, Bárbara Marques, Marta Carvalho, Fernanda Leal, Isabel Cordeiro, Joaquim Nunes, Ana Paula Soares, Carlos Calhaz-Jorge, Carlos E. Plancha "Suspension fluorescence in situ hybridization (S-FISH) protocol for flow cytometric analysis of human spermatozoa" *Cytometry Part A*, Accepted in 2008.

GENOTYPING AND SEQUENCING UNIT

Head: Carlos Penha-Goncalves

Group Leader
E-mail: cpenha@igc.gulbenkian.pt

THE GENOTYPING AND SEQUENCING FACILITY PROVIDES TECHNOLOGICAL SUPPORT AND EXPERTISE FOR RESEARCH AT THE GENOME SCALE AND IS COMPOSED BY THE TWO FOLLOWING SERVICES:

- The Sequencing Service offers DNA sequencing and fragment analysis using both multicapillary and slab-gel electrophoresis with the ABI 3130XL automatic sequencer. Taqman® Technology in a 384-well format is also available to users both for SNP genotyping and Real-Time PCR gene expression with 7900 HT Fast Real-Time PCR System;
- The Genotyping Service offers the Sequenom iPLEX technology, allowing rapid SNP genotyping assays with up to 40 SNPs assayed simultaneously. The facility collaborates with researchers on: SNP choice and SNP Assay Design, Sequenom Procedure and Data Management for Genetic Studies, using BC/GENE. The equipment is composed of two robotic pipetting devices (Matrix); five thermocycling machines, ABI 9700, a chip spotting device (MassARRAY Nanodispenser) and a MassARRAY Compact Analyser (MALDI-TOF).

SEQUENCING SERVICE

In 2008, 21 internal and two external IGC groups used the Sequencing Service, amounting to a total of 10 500 samples being sequenced. The following internal groups used the Sequencing Service: Epigenetics and Soma; Development and Selection; Cell Cycle Regulation; Lymphocyte; Plant Molecular Biology; Plant Development; Telomeres and Genome Stability; Evolutionary Biology; Actin Dynamics; Epigenetic Mechanisms; Patterning and Morphogenesis; Early Fly Development; Infections & Immunity; Membrane Traffic in Disease and Novel Therapies; Inflammation; Stress & Cytoskeleton; Evolution and Development; Mitose; Evolutionary Genetics and Bacterial signaling; Human Genetics. Externally to the IGC, the Symmetry & Development and Viral Pathogenesis groups, both at the Insitute for Molecular Medicine, in Lisbon, used the service.
Furthermore, 8 groups have used the Fast Real-Time PCR System on a regular base, to detect gene expression of several genes.

GENOTYPING SERVICE:

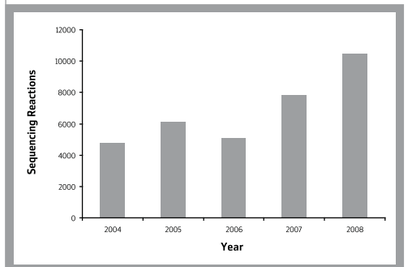
Six internal and two external IGC groups used the Genotyping Service on the following projects:

INTERNAL GROUPS

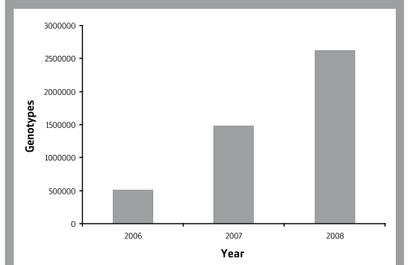
- Human Genetics - Project: *Genetic epidemiology of stroke in the post-genomic era*;
- Evolutionary Genetics - Projects: a) *Experimental reverse evolution in Drosophila Melanogaster*; b) *Evolution of outcrossing in Caenorhabditis Elegans*;
- Lupus and autoreactive immune repertoires - Project: *Autoantibody repertoires and regulatory T-cells in human and murine lupus*;
- Disease Genetics - Projects: a) *Type 1 Diabetes: Associated immunopathology and genetic susceptibility*; b) *Genetics of Malaria in the Príncipe Population*; c) *Genetic Susceptibility to Cerebral Malaria in Angolan Children*;
- Disease Genetics & Faculté de Médecine de Sfax - Laboratoire d'Immunologie, Tunisia - Collaborative Project: *Genetic predisposition to chronic inflammatory bowel disease and polyendocrinophaties in Tunisia*;
- Service Unit: Animal House - Project: *Mouse genetic quality control*.

EXTERNAL GROUPS

FACILITY STAFF:
Maria Isabel Marques (Senior Laboratory Manager)
João Costa (Research Assistant)
Jaqueline Garcia (Research Assistant)



Number of sequencing reactions per year.



Number of genotypes per year.

- Genetic Epidemiology (INSA, Lisboa) - Projects: a) *Genetic Epidemiology of Autism*; b) Genetic *factors involved in susceptibility to stroke and in outcome after 3 and 12 months*; c) *Alzheimer*;
- Center of Metabolism and Endocrinology (F.M.Lisboa) - Project: *Genetic Screening of Cardiomyopathies*.

A total number of 2 470 000 SNP genotypes have been produced, corresponding to approximately twice that of the previous year. The Genotyping Service has contributed to research by IGC internal and external groups and their results were published in eleven scientific posters, nine oral presentations and eight research publications (either published or submitted in 2008).

PUBLICATIONS TO WHICH THE GENOTYPING SERVICE CONTRIBUTED IN 2008 (INLCUDES PAPERS PUBLISHED AND/OR SUBMITTED IN 2008):

- Henrique Teotónio, Ivo M Chelo, Martina Bradi, Michael R Rose and Anthony D Long. "Experimental evolution reveals natural selection on standing genetic variation". Nature Genetics 41, 251 - 257.
- Alexandra Rosa, Benedita V Fonseca, Tiago Krug, Helena Manso, Liliana Gouveia, Isabel Albergaria, Gisela Gaspar, Manuel Correia, Miguel Viana-Baptista, Rita Moiron Simões, Amélia Nogueira Pinto, Ricardo Taipa, Carla Ferreira, João Ramalho Fontes, Mário Rui Silva, João Paulo Gabriel, Ilda Matos, Gabriela Lopes, José M Ferro,Astrid M Vicente and Sofia A Oliveira. "Mitochondrial haplogroup H1 is protective for ischemic stroke in Portuguese patients". BMC Med Genet. Jul 1; 9:57. IF 2.420 NC 0.
- Manso H, Krug T, Sobral J, Albergaria I, Gaspar G, Gouveia L, Correia M, Viana-Baptista M, Simões RM, Pinto AN, Taipa R, Ferreira C, Fontes JR, Silva MR, Gabriel JP, Matos I, Lopes G, Ferro JM, Vicente AM, Oliveira SA, Vicente AM. "The neuronal nitric oxide synthase gene (NOS1) contributes to increased risk of stroke". American Journal of Human Genetics (submitted).
- Correia C, Coutinho AM, Almeida J, Lontro R, Lobo C, Miguel T, Gallagher L, Conroy J, Gill M, Oliveira G, Vicente AM. "Association of the α4 integrin subunit gene (ITGA4) with autism". American Journal Medical Genetics Neuropsychiatric Genetics. (submitted).
- Correia C, Coutinho AM, Silva S, Sousa I, Lourenço L, Almeida J, Lontro R, Lobo C, Miguel T, Duque F, Galllagher L, Gill M, Ennis S, Oliveira G, Vicente AM. "Disruption of the BDNF/TrkB signalling pathway in autism: increased BDNF levels and association with the NTRK2 gene" Biological Psychiatry. (submitted).
- Manso H, Krug T, Sobral J, Fonseca BV, Albergaria I, Gaspar G, Ferro JM, Vicente AM, Oliveira SA, Vicente AM.."Variants of the Metalloproteinase-2 (MMP-2) but not the Metalloproteinase-9 (MMP-9) genes influence functional outcome after stroke". Stroke.(submitted)
- M. Rosário Sambo, M. Jesus Trovoada, Carla Benchimol, Lígia A. Gonçalves, Vatúsia Quinhento, Paulo Almeida, Rute Vieira, Isabel Marques, António Coutinho, Carlos Penha-Gonçalves. "Transforming growth factor Beta2 and haem oxydase1 genes are risk factors for the Cerebral Malaria Syndrome in Angolan Children". PLOS Genetics. (submitted).

GENE EXPRESSION UNIT

Head: Jorg Becker
Research Fellow

The Affymetrix Core Facility (ACF) provides GeneChip services for academic institutions in Portugal at net cost prices since the installation of its Affymetrix GeneChip System in April 2002. The ACF was granted the status of a Core Lab by Affymetrix, thus making it the reference lab for Affymetrix technology in Portugal. As such we offer services for the full range of applications using GeneChip arrays, from gene expression analysis over large-scale genotyping including cytogenetics applications to re-sequencing. In addition we have experience in the design of Affymetrix custom arrays for eukaryotic and prokaryotic species. From experimental design over processing of samples to expert advice on data analysis the ACF is committed to providing high quality services to its users, clearly reflected in the 19 publications to date including expression data produced by the facility.

THE FACILITY IS WELL/EQUIPPED WITH

- a Hybridization Oven 640;
- a Fluidics Station 450;
- a Scanner 3000 7G with Autoloader;
- a Bioanalyzer 2100;
- Two MJ Research PTC-100 Thermocyclers;
- Partek Genomics Solution software.

AT THE IGC, THE GENE EXPRESSION FACILITY HAS BEEN USED BY THE FOLLOWING GROUPS IN 2008:

- Plant Genomics - *Medicago truncatula* symbioses; cross-kingdom comparative analysis of sperm cells;
- Organogenesis - development of the chicken hemangioblast, organogenesis - zebrafish fin regeneration;
- Infections and Immunity - transgenic expression of A238L in mouse cells.

External users, in 2008, include the Instituto de Tecnologia Química e Biológica (ITQB), Oeiras, the Instituto Superior Tecnico, the Institute for Molecular Medicine and Instituto Português de Oncologia, in Lisbon, the Instituto de Biologia Molecular e Celular, Porto, the University of Minho, Braga and the University of Freiburg, Germany.

FACILITY STAFF:
Julia Lobato (Technician)

THE GENE EXPRESSION FACILITY CONTRIBUTED TO THE FOLLOWING PUBLICATIONS, IN 2008:

- Igreja C, Fragoso R, Caiado F, Clode N, Henriques A, Camargo L, Reis EM, Dias S: Detailed molecular characterisation of cord blood-derived endothelial progenitors. Experimental Hematology 2008, 36(2):193-203.
- Batista R, Saibo N, Lourenço T, Oliveira MM: Microarray analyses reveal that plant mutagenesis may induce more transcriptomic changes than transgene insertion. Proceedings of the National Academy of Sciences of the United States of America 2008, 105(9):3640-3645.
- Trindade A, Kumar SR, Scehnet JS, Lopes-da-Costa L, Becker J, Jiang W, Liu R, Gill PS, Duarte A: Overexpression of Delta-Like 4 induces arterialization and attenuates vessel formation in developing mouse embryos. Blood 2008, 112:1720-1729.
- Borges F, Gomes G, Gardner R, Moreno N, McCormick S, Feijó JA, Becker JD: Comparative transcriptomics of Arabidopsis thaliana sperm cells. Plant Physiology 2008, 148: 1168-1181.

HISTOLOGY UNIT

Head: Susana Lima / Cristina Afonso
Research Fellow / Post-doc
E-mail: slima@igc.gulbenkian.pt

The Histology Unit provides assistance in processing tissue samples for routine histochemical and immunostaining procedures. The unit provides training to new users in sample preparation and sectioning using the equipment available in the unit.

SERVICES PROVIDED INCLUDE:

- Paraffin embedding and sectioning;
- Cryostat sectioning;
- Vibratome sectioning;
- Immunohistochemistry;
- Transmission Electron Microscopy (TEM).

FACILITY STAFF:
Ana Santos (Technician)

BIOINFORMATICS AND COMPUTATIONAL BIOLOGY UNIT

Head: José Pereira-Leal
Group Leader

THE UNIT'S GOALS ARE:

- To promote the use of computational methods in biological research, through training and development of resources and materials;
- To support the graduate programmes of the Associated Laboratory of Oeiras (LAO);
- To provide direct user support in biological data analysis using computational methods;
- To conduct research and development in bioinformatics, in particular in data-flow, data warehousing and data analysis, supporting the LAO;
- To provide a computing infrastructure suited for biocomputing.

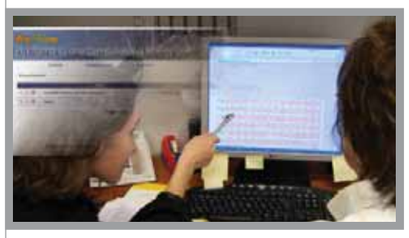
THE UNT IS EQUIPPED WITH:

- two dual-dual core disk servers used for data ware housing for the IGC;
- a web server;
- a mini laptop;
- four workstations, of which one is for user access.

THE UNIT'S CURRENT PROJECTS ARE:

- data warehousing for the IGC – we developed a database for flow cytometry data that is now in test phase, and are experimenting with open source database systems for microarray data and for microscopy data;
- bioinformatics clinic, providing direct user support for the IGC, the LAO and groups in others institutions – in 2008 we provided support to 13 IGC groups and 4 external groups, and it resulted in several publications;
- "Bioinformática na Escola" – development of resources for secondary school-level education, developed in partnership with three schools;
- National bioinformatics network – the unit is involved in setting up a national network aimed at increasing synergies in equipment, education and research in the area of Bioinformatics.

SERVICE STAFF:
Isabel Marques (Senior Specialist)
Paulo Almeida (Technician)



HIGH PERFORMANCE COMPUTING RESOURCE FOR BIOINFORMATICS

Head: Pedro Fernandes
E-mail: pfern@igc.gulbenkian.pt

The HPCC is a 60 node computer cluster based on high density IBM Power PC JS20 dual processor, single core Blades. The aggregate computing power of these 120 CPUs, served by a high availability storage system of 4.2 TeraByte, is a giant step in delivering high speed Bioinformatics applications to the portuguese users community. We use the iNquiry suite in which there is a mixture of open access, licensed ones and locally added programmes. Some of them use the cluster's high availability feature (many "free" processors), others do take a great deal of advantage of the parallel architecture by breaking complex tasks into subtasks that can execute simultaneously. We also hold a fairly large collection of Molecular Biology databases with regular updates. Hermes' hardware was built on IBM's e-server Blade Center technology that provides high compactness and added reliability/maintainability, and runs the Novell Suse Linux SLES9 operating system on all the nodes.
We can presently provide more than 150 bio-molecular databases and more than 400 operational programmes, accesssible through a uniform user interface with webservices behind. More than 250 users benefit from this service.

The facility provided support for the BioGrid Project, run in cooperation with INESC-ID that aimed at deploying research grade software for Motif Finding and Bi-Clustering for microarray data. The MSc Thesis of Sérgio Mendes Costa (IST, November 14th 2008) has emerged from this project http://kdbio.inesc-id.pt/projects/biogrid/.

The facility has supported the computational needs of several IGC groups namely those headed by Gabriela Gomes, Lounès Chikhi and Isabel Gordo.

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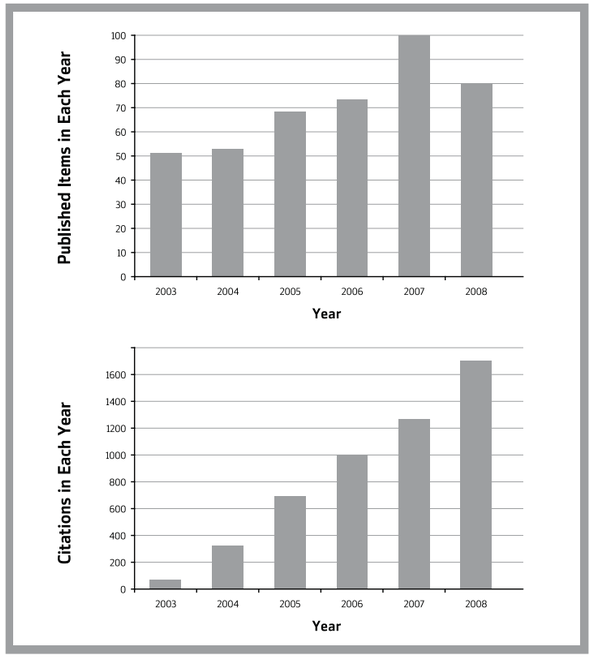
PROCEEDINGS

Aguiar M, Stollenwerk N, Kooi BW Torus bifurcations, isolas and chaotic attractors in a simple dengue model with ADE and temporary cross immunity. *Proceedings of 8th Conference on Computational and Mathematical. Methods in Science and Engineering, CMMSE 2008*, ISBN 978-84-612-1982-7. (2008).

Van Noort S, Stollenwerk N From dynamical processes to likelihood functions: an epidemiological application to influenza. *Proceedings of 8th Conference on Computational and Mathematical. Methods in Science and Engineering, CMMSE 2008*, ISBN 978-84-612-1982-7. (2008)

SUMMARY OF IGC PUBLICATIONS AND CITATION REPORT IN THE LAST FIVE YEARS (2003/08)



AWARDS

JOÃO MIGUEL FERNANDES ALVES (Population and Conservation Genetics)
OptimusAlive!08 Oeiras-IGC Research Fellowships in Biodiversity, Genetics and Evolution
Everything is New, Portugal
December 2008

ÂNGELO CHORA AND MIGUEL SOARES
NEDAI Research Prize in Auto-Immunity
Portuguese Society of Internal Medicine (SPMI)
(sponsored by Schering-Plough Laboratories)
September 2008

MELVIN COHN
Professor Doutor António Xavier Scientific Excellence Award
Oeiras City Council, Portugal
December 2008

ANTÓNIO COUTINHO
2008 University of Lisbon Award, Portugal
June 2008

ANTHONY DEAN
Professor Doutor António Xavier Scientific Excellence Award
Oeiras City Council, Portugal
December 2008

GUILLAUME DUGUÉ (Systems Neuroscience)
Marie Curie Intra-European Fellowship for Career Development
European Commission Framework Programme 7
October 2008

MIGUEL GODINHO FERREIRA
Career Development Award
Fundação para a Ciência e a Tecnologia (FCT), Portugal
January 2008

ALEXANDRE CASTANHO BARATA LEITÃO (Evolution and Development)
Optimus Alive!08 Oeiras-IGC Research Fellowships in Biodiversity, Genetics and Evolution
Everything is New, Portugal
December 2008

SUSANA LIMA
Bial Science Research Grant
Fundação Bial, Portugal
November 2008

ANA MARTINS (Cell Cycle Regulation)
The American Society for Cell Biology
December 2008

MASAYOSHI MURAKAMI (Systems Neuroscience)
Bial Science Research Grant
Fundação Bial, Portugal
November 2008

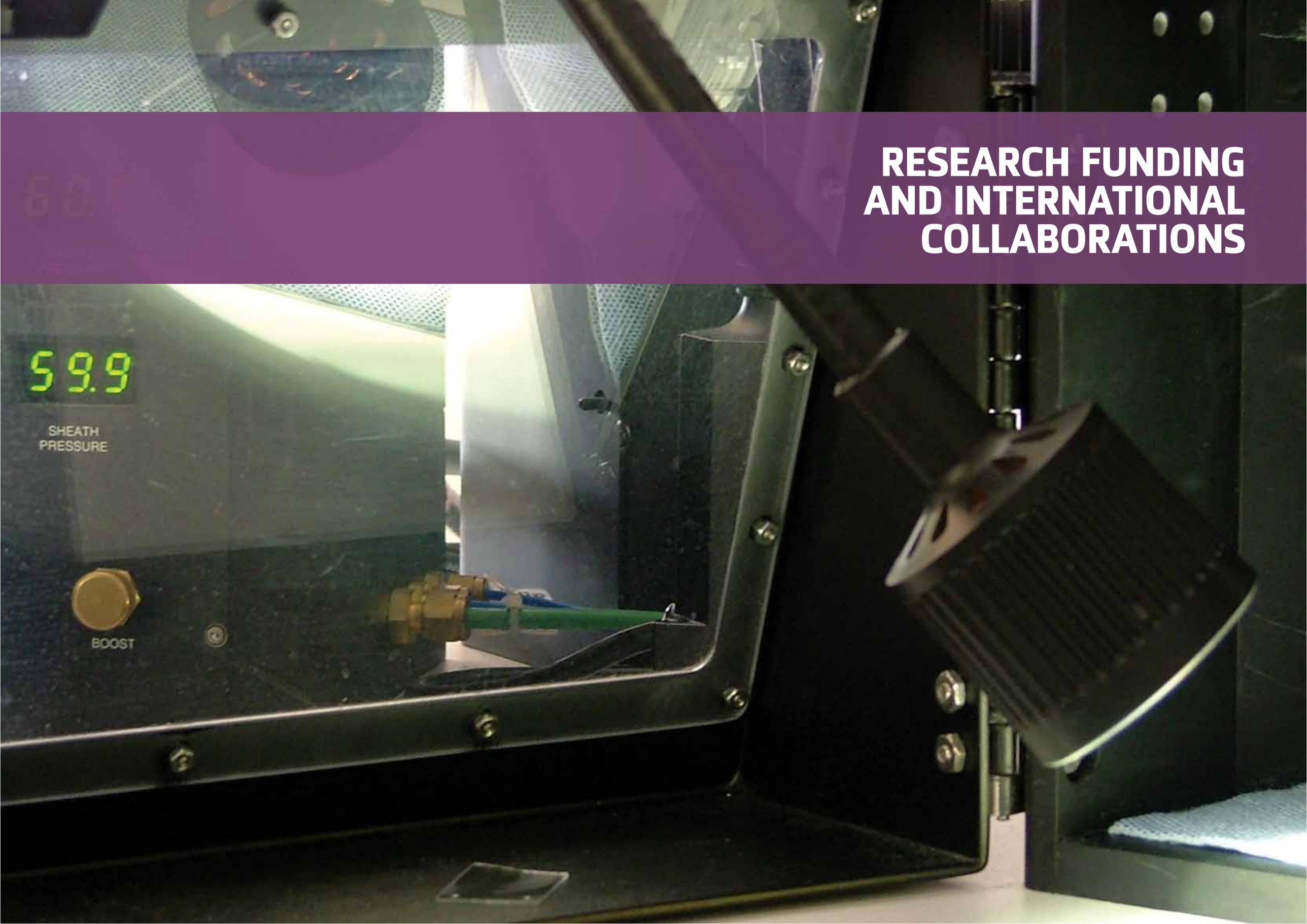
LEONOR SARMENTO (Lymphocyte Physiology)
Bolsas NRS/LPCC - Terry Fox - Investigação Clínica em Oncologia,
Liga Portuguesa Contra o Cancro, Portugal
April 2008

NUNO SEPÚLVEDA (Quantitative Organism Biology)
Prémio SPE 2008
Sociedade Portuguesa de Estatística (Portuguese Society for Statistics), Portugal
August 2008

LUISA VASCONCELOS
Professor Doutor António Xavier - Young Scientists' Installation Award
Oeiras City Council, Portugal
December 2008

IGC SCIENCE COMMUNICATION AND OUTREACH
Seeds of Science Award for Science Communication 2008
Ciência Hoje
October 2008

RESEARCH FUNDING AND INTERNATIONAL COLLABORATIONS



THE IGC AS A WHOLE, OR INDIVIDUAL RESEARCH GROUPS, ARE MEMBERS OF SEVERAL NATIONAL AND INTERNATIONAL RESEARCH STRUCTURES, INCLUDING:

- European Mouse Mutant Archive (EMMA);
- European Molecular Biology Network (EMBnet);
- FCT Unit of Genetics and Development of Natural Tolerance (*Unidade de Genética e Desenvolvimento da Tolerância Natural*);
- FCT Unit of Developmental Biology (*Centro de Biologia do Desenvolvimento*);
- Ministry of Science Associated Laboratory of Oeiras (with the Instituto de Tecnologia Química e Biológica);
- Computational Biology Collaboratorium;
- Champalimaud Neuroscience Programme at the IGC;
- Lisbon Epidemiology Consortium (CEL).

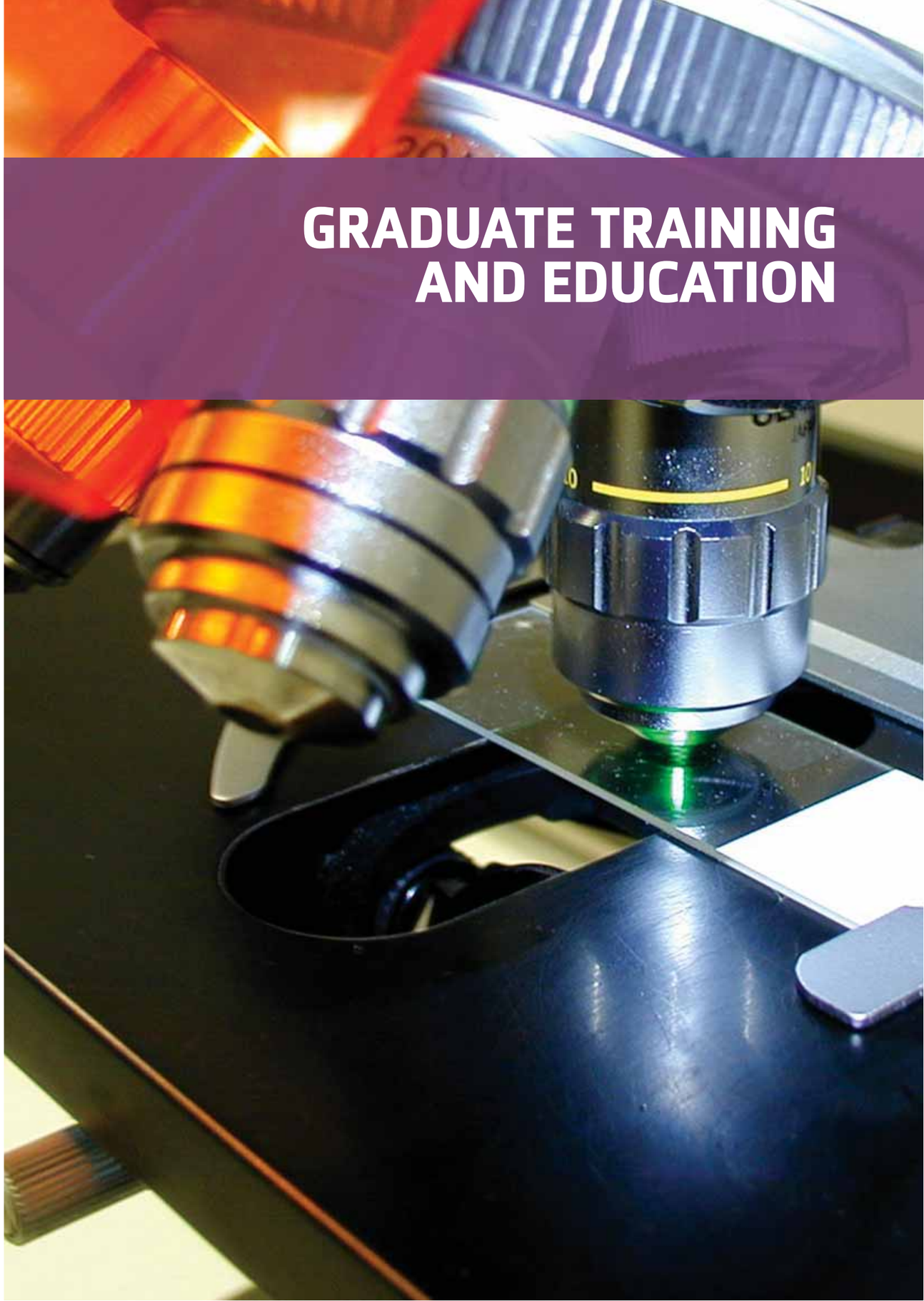
IN 2008, RESEARCH AT THE IGC WAS FUNDED BY THE FOLLOWING AGENCIES AND ORGANISATIONS:

RESEARCH FUNDING BODY	NUMBER OF GRANTS
Fundação para a Ciência e a Tecnologia (FCT), Portugal	58
European Commission Framework Programmes 7 (FP7), Europe	6
European Commission Framework Programmes 6 (FP6), Europe	4
L'Oréal Portugal	2
European Molecular Biology Organisation (EMBO), Europe	1
Wellcome Trust, UK	1
Association for International Cancer Research, UK	1
3R Research Foundation Switzerland, Switzeland	1
GEMI Fund – Linde Healthcare, Sweden	1
National Multiple Sclerosis Society, USA	1
Advancement of Research for Myopathies, USA	1
Phillip Morris, USA	1
Octapharma, Portugal	1
Fundação Bial, Portugal	1
Luso-American Foundation, Portugal	1
Crioestaminal – Saúde e Tecnologia, SA, Portugal	1
Calouste Gulbenkian Foundation, Portugal	1
POSC – Programa Operacional Sociedade do Conhecimento, Portugal	1
Scientific Cooperation Protocol – Portugal (FCT) – Spain(CSIC)	1
Bilateral cooperation Protocol – Tunisia (MESICT Tunísia) – Portugal (FCT)	1
Champalimaud Foundation, Portugal	Seed money

BREAKDOWN OF THE AGENCIES AND ORGANISATIONS THAT PROVIDED SUPPORT FOR RESEARCH CAREERS AT THE IGC

The table refers only to positions within the IGC research groups, and does not include career support for facilities, units and services staff.

CAREER FUNDING	NUMBER OF AWARDS
Fundação para a Ciência e a Tecnologia (FCT), Portugal	102
European Commission – Marie Curie Actions, Europe	22
Fundação Champalimaud, Portugal	18
Instituto Gulbenkian de Ciência (IGC), Portugal	13
Instituto de Emprego e Formação Profissional (IEFP), Portugal	13
Oeiras Associated Laboratory – Ciência 2007 Programme	10
University Faculty	9
Oeiras Associated Laboratory – Principal Investigator Positions	7
European Union Framework Programme 6 (FP6), Europe	4
Fundação Calouste Gulbenkian (FCG), Portugal	3
3Rs Research Foundation Switzerland	2
Association of International Cancer Research, UK	2
CNRS, France	2
Octapharma Ltd, Portugal	2
EMBO, Europe	2
Oeiras Associated Laboratory – MIT–Portugal Programme	2
Oeiras–OptimusAlive!	2
Advancement of Research for Myopathies (ARM), USA	1
Volkswagen Foundation, Germany	1
Angolan Funding Agency, Angola	1
INSERM, France	1
Ramn Y Cajal Porgramme, Spain	1
Crioestaminal – Saúde e Tecnologia SA, Portugal	1
Oeiras City Council, Portugal	1



GRADUATE TRAINING AND EDUCATION

PHD PROGRAMME IN MULTIDISCIPLINARY LIFE SCIENCES (PGD)

Programme Director: Henrique Teotónio
Group Leader
E-mail: teotonio@igc.gulbenkian.pt

This is the in/house PhD programme of the IGC, sponsored by the Fundação para a Ciência e a Tecnologia, Portugal and the Calouste Gulbenkian Foundation. The Programme aims to attract the best students in Biology to work at the IGC. We seek independent and creative thinkers. The programme includes a teaching module, with lectures and workshops by leading scientists from around the world. The teaching modules cover most areas of biology, with special emphasis on the conceptual basis of biological research. At the end of this module, students are given time to develop and propose their own research projects, and the opportunity to do their thesis work at the institute. Students are strongly encouraged to design projects that encompass two or more of the areas of the IGC, from immunology to cell cycle, from pollen tube morphogenesis to evolutionary genetics, and take full advantage of model systems available. Candidates with a strong interest in modeling, bioinformatics and theoretical biology are strongl encouraged to apply.
This PhD programme welcomes candidates from all nationalities, including those outside of European Union member states. We also encourage interested candidates at all stages of their career to apply. Doctors, engineers, dentists and other professionals are eligible regardless of when they concluded their university degree.

2008/09 STUDENTS

Claudia Martinho	Biology
Rui Jorge Cunha Azevedo	Biomedical Sciences
Nuno Oliveira	Biology
Thiago S. Guzella	Electrical Engineering
Raquel Maria Marques Ambrósio	Biological Engineering
Elizabeth Ann Ball	Biomedical Sciences
Inês Fernandes Bento	Biology
Arnon Dias Jurberg	Biology
Rita Susana da Silva Valente	Microbiology
Mariluz Gomez	Genetics
Lurdes da Glória Rodrigues Duarte	Biology

2008 MODULES

Introduction to the PhD programmes; what is biology, exercises in group building
22 – 26 September, 2008
Zachary Mainen (Champlalimaud Foundation, Organiser), Jorge Carneiro (IGC, Organiser), Henrique Teotónio (IGC, Organiser), Rita Venturini (USA), Paul Bush (USA)

Hypothesis-driven research; how to observe biology diversity and research design
29 September – 3 October,2008
Rui Martinho (Organiser, IGC), Bruno Lemaître (Switzerland), William Theurkauf (USA), Holger Knaut (USA), Barry Dickson (Austria)

Statistics; experimental design and statistical inference
13 – 24 October, 2008
Jorge Carneiro (IGC)

Genetics; phenotype-genotype mapping
27 – 31 October, 2008
Élio Sucena (IGC, Orgnaiser), Fernando Roch (France), Matthew Rockman (USA), Luis Teixeira (UK)

SUPPORT STAFF:
Manuela Cordeiro (Administrative Assistant)

Evolutionary Biology; Population and quantitative evolutionary genetics
3 – 14 November, 2008
Henrique Teotónio (IGC, Organiser), Christian Braendle (France), Charlie Baer (USA)

Within and Between-Cell Biology; transcription/translation; cell division; developmental biology; population cell biology/Immunology
17 November – 5 December, 2008
Miguel Godinho (IGC, Organiser), Leonor Saúde (IMM, Orgnaiser), Frank Uhlmann (UK), Madalena Tarsounas (UK), Ana P. Costa-Pereira (UK), Gennaro De Libero (Switzerland), Gilbert Weidinger (Germany), Elisabeta Padovan (IGC), Jocelyne Demengeot (IGC), Carlos Penha-Gonçalves (IGC), Alekos Athanasiadis (IGC), Constantin Fesel (IGC), Vasco Barreto (IGC)

Integrative Biology; genomics; phenomics; gene-networks; ecology
8 – 19 December, 2008
Zachary Mainen (Champlalimaud Foundation, Organiser), Jorge Carneiro (IGC, Organiser), Henrique Teotónio (IGC, Organiser), Frederic Geissmann (UK), Glenn Turner (USA), Vivek Jayaraman (USA)

PHD PROGRAMME IN COMPUTATIONAL BIOLOGY (PDBC)

Direction: Jorge Carneiro (Programme Director)
E-mail: jcarneir@igc.gulbenkian.pt
Cláudio Soares (Deputy Director)
Luis Rocha (Collaboratorium Director)
Claudine Chaouiya (local coordinator)

The PhD Programme in Computational Biology is a pilot graduate programme that aims to create a critical mass of researchers in computational biology, who will act as the future leaders in the field. To this end it operates in close association with its twin initiative, the Collaboratorium in Computational Biology, and is promoted by the Portuguese Ministry for Science and Technology, the Calouste Gulbenkian Foundation, and Siemens SA, and co-sponsored by several institutions including PT Foundation, FCCN and FLAD.
The PDBC has a definitive lifespan and was planned to educate 4 generations of 12 students each year, starting in 2005. Education is organised as four-year programme divided into one year of full-time courses, workshops and projects, beginning in September. These courses cover the main aspects of computational biology from the biological, computational, mathematical, chemical and physical points of view, and three years of research training in a recognised laboratory anywhere in the world, including Portugal. Non-national citizens are accepted if they do their research training in a Portuguese research lab. The choice of laboratory is left to the student but must meet the standards set by the Programme Direction.
In 2008, the programme reached full maturity having until then coached 45 students who are doing their research training in labs in Europe and beyond, and recruited the last generation of students.
URL: http://bc.igc.gulbenkian.pt/pdbc/

SUPPORT STAFF:
Manuela Cordeiro (Administrative Assistant)
João Sousa (IT Systems Administrator)

2008/09 STUDENTS

António Luis Alves Miranda	Biology
António Manuel Mendes Rodrigues	Computer Engineering
António Miguel Guarita Pires Rosa Prôa	Biology
Bruno Acácio de Castro Moreira dos Santos	Biology
Carlos Manuel Marques Afonso	Physics Engineering
Daniel Santa Cruz Damineli	Biology
José Miguel Lima Lourenço	Software Engineering
Sylvie de Jesus Estrela	Biochemistry
Tiago da Rocha Macedo	Biomedical Engineering
Tiana Gonçalves	Biology
Yoan Diekmann	Bioinformatics

2008 COURSES

Molecular Sequences and structures-Structures (DNA, RNA and proteins)
Biomolecular simulation and Structural Bioinformatics
7 January - 20 January, 2008
Cláudio Soares, Isabel Bento, Pedro Lamosa, António M. Baptista, Diana Lousa, Sara Campos, Miguel Machuqueiro, João Damas, Bruno Victor, A. Sofia F. Oliveira (ITQB/UNL, Oeiras, Portugal)

Nucleic acid structure and function
21 January - 1 February, 2008
RNA Structure and Function
Eric Westhof, Pascale Romby (IBMC/CNRS, Starsbourg, France)

Drug Design
Nuno Palma (BIAL, Portugal)

Evolutionary and functional genomics
4 February - 8 February, 2008
Algorithms on trees and graphs
Gabriel Valiente (Technical Univ. of Catalonia, Spain)

Organisation and dynamics of prokaryotic genomes
11 February - 15 February, 2008
Eduardo Rocha (Inst. Pasteur Paris, France)

Finding regulatory elements and regulatory motifs/Molecular Evolution and Comparative Genomics
18 - 22 February, 2008
Molecular evolution and Comparative Genomics
Jotun Hein (Univ. of Oxford, UK)

Finding regulatory elements and regulatory motifs
Eric van Nimwegen (Univ. Basel, Switzerland)

Chromosome Organisation/Evolution of non-coding DNA
25 - 29 February, 2008
Chromosome organisation
Benjamin Audit (CNRS, Lyon, France)

Evolution of non-coding DNA
Gerton Lunter (Univ. of Oxford, UK)

Analysis of DNA expression microarrays/MicroRNA genomics
3 - 7 March, 2008
MicroRNA genomics
Anton Enright (Sanger Institute, Cambridge, UK)

DNA expression microarrays technology
Jorg Becker (IGC, Oeiras, Portugal)

Proteomics/Machine learning and artificial neural networks
10 - 14 March, 2008
Computational approaches to Proteomics
Nuno Bandeira (UC San Diego, USA), Marc Sturm (Univ. Tuebingen, Germany)

Principles of Bayesian inference and statistics
17 - 21, 2008
José-Miguel Bernardo (Univ. Valencia, Spain)

Introduction to Dynamic Systems
Tiago Paixão (Univ. Houston, USA)

Machine learning and artificial neural networks
Hugues Bersini (Univ. Libre de Bruxelles, Belgium)

Open Day Computational Biology at Oeiras
31 March, 2008

Generic aspects of networks/Protein interaction networks
2 - 4 April, 2008
Protein interaction networks; Evolutionary origins of modularity; Prediction of protein interactions; Algorithms to detect modularity
Jose Pereira-Leal (IGC, Oeiras, Portugal)

Structural evolution of protein interactions; Evolutionary classification of quaternary structure
Emmanuel Levy (MCR-LMB, Cambridge, UK)

Experimental approaches to protein interaction networks
Adriano Henriques (ITQB-UNL, Oeiras, Portugal)

Bifurcation Theory/Transcriptional Networks
7- 11 April, 2008
Bifurcation theory
Frank Hilker (Univ. Alberta, Canada)

Transcriptional networks
Ernest Fraenkel (MIT, Cambridge, USA)

Metabolic network modeling/Computational biology of cellular rhythms
14 - 18 April, 2008
Albert Goldbeter (Univ. Libre de Bruxelles, Belgium), Rui Alves (Univ. de Lleida, Spain), Pedro Mendes (Univ. Manchester, UK), Armindo Salvador (FCT-Univ. Coimbra, Portugal)

Petri nets and logical networks in metabolic and genetic network modeling
21 - 24 April, 2008
Ina Koch (Technical University of Applied Sciences Berlin, Berlin, Germany), Claudine Chaouiya (Univ. Marseille, France)

Computational approaches to cell cycle/Gene network modelling
28 April - 2 May, 2008
Gene network modelling
Rene Thomas (Univ. Libre de Bruxelles, Belgium)

Computational approaches to cell cycle
Attila Csikasz-Nagy (Univ. of Trento, Italy), Lars Juhl Jensen (EMBL, Heidelberg, Germany)

Metabolic and genetic network modelling
5 - 7 May, 2008
Hidde de Jong (INRIA Rhône-Alpes, France)

Workshop - Evolutionary Cell Biology 2008
9 - 10 May, 2008
Speakers: Julliete Azimzadeh, Patricia Beldade, Martijn Huynen, Joel Dacks, Andrew Murray, Eugene Koonin, Mark Field, Adriano Henriques, Tatiana Koonin

Dynamic Systems-Cellular Automata/Stochastic dynamics of biomolecular networks/Pi-calculus
Stochastic dynamics of biomolecular networks; Cellular Automata
12 - 15 May, 2008
Andrzej Kierzek (Univ. of Surrey, UK). Andreas Deutch (Univ. of Dresden, Germany)

Population biology, epidemiology and immune systems
19 - 23 May, 2008
Paula Rodrigues, Ricardo Águas, Isabel Gordo (IGC, Oeiras, Portugal), Ruy Ribeiro (Los Alamos National Laboratory, USA)

Drosophila segmentation/Modelling development
26 - 30 May, 2008
Hans Meinhardt (UNiv. Tuebingen, Germany), John Reinitz (Stony Brook Univ., NY; USA), Denis Thieffry (Univ. de Marseille, France), Filipa Alves (IGC, Oeiras, Portugal), Ana Paula Leite (MIT, Cambridge, USA)

Cell-based models of development
5 - 6 June, 2008
Stan Marée, Veronica Grieneisen. (Utrech Univ. the Netherlands)

Cytoskeleton and cell morphogenesis, motion and chemotaxis modeling
16 - 20 June, 2008
Francois Nedelec, Jonathan Ward (EMBL, Heidelberg, Germany)

Control theory/Computational Neurosciences
24 -27 June, 2008
Pedro Lima (IST, Lisboa, Portugal), Zach Meinen (IGC, Oeiras, Portugal), Christian Machens (ENS, Paris, France), Luis Rocha (Univ. of Indiana, USA)

Science Communication Workshop
3 - 4 July, 2008
Ana Godinho (IGC, Oeiras, Portugal), Malcolm Love (Bristol, UK)

Career Development Workshop
7 July, 2008
Dave Jensen (CareerTrax, Arizona, USA)

First Portuguese Forum on Computational Biology (FPBC2008)
10 - 12 July, 2008
Keynote speakers: Denis Noble, David Baker, Marta Cascante

Speakers: Jonas de Almeida, Filipa Alves, Rui Alves, Fernando Antunes, António Baptista, Andreas Bohn, Rui Brito, João Carriço, Claudine Chaouiya, Lounès Chihki, Francisco Couto, Francisco Dionísio, Patrícia Faísca, Ana Teresa Freitas, Gabriela Gomes, Isabel Gordo, José Pereira-Leal, Paulo Martel, Ana Nunes, Arlindo Oliveira, José Luis Oliveira, Jorge Pacheco, Francisco Pinto, Maria João Ramos, Luis Rocha, Miguel Rocha, Armindo Salvador, João Aires de Sousa, André Valente e Susana Vinga

Introductory Module
17 September - 11 October, 2008
Dinis Pestana (FC-UL, Lisboa, Portugal)

Introduction to the PhD programmes; what is biology, exercises in group building
22 - 26 September, 2008
Henrique Teotonio, Zach Mainen, Jorge Carneiro, Leonor Parreira (IGC, Oeiras, Portugal), Hugues Bersini(Univ. Libre de Bruxelles, Belgium), Rita Venturini & Paul Bush (Berkeley, USA)

Hypothesis driven research
William Theurkauf (Univ. of Masachussetts, USA) Holger Knaut (New York Univ., USA), Barry Dickson Univ. of Vienna, Austria), Bruno Lemaître (Global Health Institute, Lausanne, Switzerland), Rui Martinho, Monica Dias, Lars Jansen, Alvaro Tavares, Moises Mallo, José Pereira-Leal, Luisa Vasconcelos, Vasco Barreto, Rui Martinho (IGC, Oeiras, Portugal)

A primer in algorithms and data structures/Statistics with R/Probability and Statistics/Python
13 - 25 October, 2008
Dinis Pestana (FC-UL, Lisboa, Portugal), Claudine Chaouiya,Nuno Sepúlveda (IGC, Oeiras, Portugal), Aurelien Naldi (Univ. de Marseille, France), Andreas Bohn (ITQB/UNL, Oeiras, Portugal)

Logics/ Genetics
27 - 31 October, 2008
Logics
Manfred Kerber (Univ. of Birmingham, UK)

Genetics
Matthew Rockman (New York Univ., USA), Fernando Roch (Univ. de Toulouse, France), Anna Tramontano (Univ. of Rome, Italy), Elio Sucena, Rui Martinho, Miguel Godinho Ferreira, Moises Mallo, Matthias Koppen, Luis Teixeira, Jocelyne Demengeot, Vasco Barreto, Henrique Teotónio (IGC, Oeiras, Portugal)

Evolutionary Biology/ Theory of evolution and population genetics
3 - 15 November, 2008
Karl Thomaseth (Univ, of Padova, Italy), Henrique Teotónio, Isabel Gordo, Lounès Chikhi, José Pereira-Leal (IGC, Oeiras, Portugal)

Theory of evolution and population genetics
Brian Charlesworth (Univ. of Edinburgh, UK)

Evolutionary Biology: Mutation; Evolution of sex; Evolution of development; Canalization
Charlie Baer (Florida State Univ., USA), Christian Braendle (Univ. of Marseille, France), Henrique Teotonio (IGC, Oeiras, Portugal)

Cell Biology - Within and between cell biology/ PCA and Linear discriminant analysis
17 - 21 November, 2008
Madalena Tarsounas (Univ. of Oxford, UK), Frank Uhlmann (CancerResearch UK, London, UK), Ana Costa-Pereira (Imperial College, London, UK), Lars Jansen, Monica Dias, Rui Martinho (IGC, Oeiras, Portugal)

PCA and Linear discriminant analysis
Jorge Cadima (ISA, Lisboa, Portugal)
Cell Biology - Within and between cell biology/Stochastic processes and Markov chains
24 - 28 November, 2008

Cell Biology
Soren Prag, Solveig Thorstendottir, Gabriel Martins, Rita Fior. Leonor Saude, Margarida Ramos, Catarina Certal, Karina Xavier, Elisabetha Padovan, Matthias Koeppen.

Stochastic processes and Markov chains
Grant Lythe (Univ. of Leeds, UK)

Cell Biology/Biomolecular simulation and Structural Bioinformatics/Within and between cell biology
2 – 4 December, 2008
Biomolecular simulation and Structural Bioinformatics
Claudio M Soares, Isabel Bento (ITQB/UNL, Oeiras, Portugal)

Cell Biology/Within and between cell biology – Inflammation; Cancer; Regeneration
Miguel Soares (IGC, Oeiras, Portugal), Raquel Seruca (FM-UL, Lisboa, Portugal), Gilbert Weidinger (Univ. of Dresden, Germany)

Biomolecular simulation and Structural Bioinformatics
9 – 19 December, 2008
António M. Baptista, Pedro Lamosa, Carla Baltazar, Pedro Magalhães, Sara Campos, Miguel Machuqueiro, Cláudio Soares, Luis Pereira, Luis Filipe, Bruno Victor, Diana Lousa, João Damas, A. Sofia F. Oliveira (ITQB/UNL, Oiras, Portugal)

GULBENKIAN/CHAMPALIMAUD PHD PROGRAMME IN NEUROSCIENCE (PG/CN)

Programme Director: Zachary Mainen
Group Leader of the Champalimaud Neuroscience Programme at the IGC
E-mail: zmainen@igc.gulbenkian.pt

The second edition of the PhD Programme Gulbenkian-Champalimaud Neuroscience, aims to train students to perform innovative and integrative research into the biological bases of behaviour, and is sponsored by the FCT, Champalimaud Foundation (CF) and Gulbenkian Foundation (FCG) in close collaboration with the Champalimaud Neuroscience Programme (CNP) at IGC.
During the first year, students attend courses organized and taught by a combination of internal faculty and invited international researchers. This initial training phase aims at providing students with a broad background and common language in biology. The curriculum is varied in format and emphasises active participation, discussion and practical exercises, as well as advanced workshops and symposia. The goal is to develop critical and creative thought and to gain exposure to a variety of perspectives on the biology of the nervous system.
Spring courses start with a general introduction and include physiology, development, sensory and motor systems, learning and cognition. Autumn courses focus on core concepts in biological systems including genetics, evolution, within and between cell biology, and ecology. These courses are co-organized with the two other PhD programmes at IGC. Each course aims to span from basic introduction to current research topics. Perspectives and approaches are designed toward maximizing diversity and include engineering, biomedicine, ethology, evolutionary biology and computational neuroscience. There is a strong quantitative component to the curriculum, and students are instructed in Matlab and data analysis, models and other projects.
The first year takes place at IGC. During the spring semester of the first year, students choose a laboratory to conduct their thesis research project, guided by the programme director and neuroscience core faculty. Portuguese students are eligible to work any laboratory in the world. Foreign students can choose laboratories at the IGC or elsewhere in Portugal. A yearly retreat is planned in conjunction with CNP laboratories.

STAFF:
Coordinator: Joe Paton (from September 2008)
Administrative Assistant: Manuela Cordeiro (until June 2008), Alexandra Piedade (form September 2008)

STUDENTS IN 2008

André Mendonça	Technological Physics Engineering
Ana Rita Fonseca	Physics Engineering
Clara Ferreira	Biology
Fernando Santos	Pharmaceutical Sciences (MSc)
João Marques	Pharmaceutical Sciences
Ana Pereira	Pharmaceutical Sciences
Ana Amaral	Physics
Scott Rennie	Psychology and Evolutionary Psychology (MSc)
Ana Mafalda Vicente	Biological Engineering
Dennis Herrmann	Biochemistry

2008 INDIVIDUAL MODULES/COURSES

Introduction to Neuroscience
7 – 18 January, 2008
Zach Mainen (IGC), Rui Costa (CNP & NIH), Marta Moita (IGC)

Tinkering with Brain Function
21 – 25 January, 2008
Elly Nedivi (MIT), Luisa Vasconcelos (IGC)
Neurophilosophy, Neuroethology and the Senses
28 January – 2 February, 2008
Brian Keeley (Pitzer College)

Normative Theories of Brain Function
4 – 9 February, 2008
Konrad Kording (Northwestern U, Chicago)

Constructing Neural Circuits
11 – 23 February, 2008
Domingos Henrique (IMM, Lisbon)

Single Neuron Information Processing
5 – 11 March, 2008
Josh Dudman (JFRC)

Learning: Evolving Behavioural Plasticity
12 – 22 March, 2008
Sara Magalhães, Marta Moita, Rosalina Fonseca (IGC)

Movement Into Action
24 – 29 March, 2008
Rui Costa (NIH & IGC)

Hippocampus and Navigation
31 March – 5 April, 2008
Miguel Remondes (MIT), Máté Lengyel (Cambridge)

The Psychology of the Single Cell
14 – 19 April, 2008
Ken Harris (Rutgers)

The Neuroscience of Social Interactions
21 April – 3 May, 2008
Zach Mainen (IGC), Gowan Tervo (JFRC), Susana Lima (IGC)

Predator and Prey
5 – 10 May, 2008
Marta Moita (IGC)

From Vision to Decision
19 – 24 May, 2008
Joe Paton (Columbia/CF/IGC),Greg Corrado (Stanford), Brian Lau (Columbia)

Reinforcement Learning
26 – 31 May, 2008
Quentin Huys (Columbia)

Introductory Week
22 – 26 September, 2008
Jorge Carneiro, Zach Mainen and Henrique Teotónio (IGC)

Hypothesis Driven Research
29 September – 11 October, 2008
Rui Martinho (IGC)

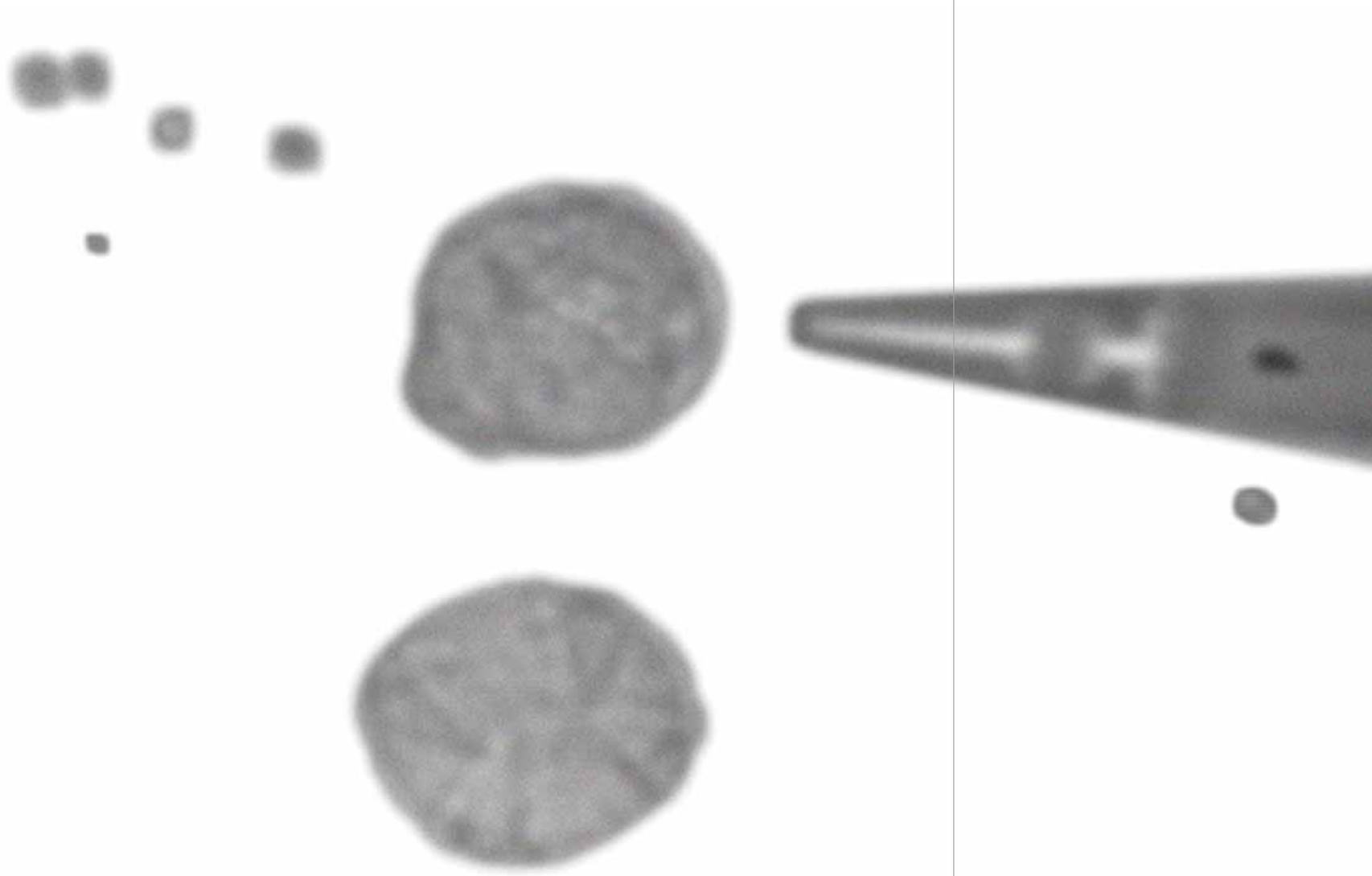
Statistics and Quantitative Biology
13 – 25 October, 2008
Jorge Carneiro (IGC)

Genetics
27 October – 1 November, 2008
Elio Sucena (IGC)

Evolution
3 – 15 November, 2008
Henrique Teotónio (IGC)

Within & Between Cell Biology
17 November – 6 December, 2008
Miguel Godinho (IGC) and Leonor Saúde (IMM)

Systems and Integrative Biology
8 – 19 December, 2008
Jorge Carneiro, Zach Mainen and Henrique Teotonio



PROGRAMME FOR ADVANCED MEDICAL RESEARCH – DOCTORAL PROGRAMME FOR PHYSICIANS

Programme Director: Leonor Parreira

Professor of Histology and Developmental Biology, Faculdade de Medicina de Lisboa and Associate Investigator of Instituto Gulbenkian de Ciência
E-mail: lparreira@igc.gulbenkian.pt

The Programme aims at fostering and supporting the practice of high-quality medical research by physicians. It is specifically targeted at practicing clinicians who whish to pursue research activities as a long-term professional project, providing a broad education in biomedical and clinical sciences in a strong interdisciplinary perspective. Ten physicians, interns or specialists are selected every year, five in a full-time regime and other five in part-time. The students accepted for the programme are highly motivated towards clinical and translational research activities. They believe that a solid scientific background is the basis for excellent medical research, as well as better clinical practice and wish, in the future, to develop multidisciplinary and cooperative projects as a complement to their clinical activity.
The first six months are dedicated to the educational component, followed by 2.5 years of research in Health Units or at Research Institutes in Portugal or abroad. The aim of the educational component is to offer a broad education in modern biomedical sciences to practicing physicians rather than produce professional scientists. All educational modules are strongly science-based, classes are in tutorial style and the faculty mostly international, from leading research laboratories across the world. Non-medical scientists, mostly young PhD-students of the host Institutions, also attend the majority of the modules. Being deeply commited to biomedical research, they not only appreciate the contact with clinicians but are very much open to "medically-informed" ways of thinking to better develop their own projects.
The Programme is supported by the Gulbenkian and Champalimaud Foundations, the Ministry of Health and the Fundação para a Ciência e a Tecnologia, Portugal.

STUDENTS IN 2008

FULL-TIME:

Ana Sofia Cerdeira	Intern in Gynecology	Hospital Geral de Santo António
Filipe Martins	Intern in Gynecology	Hospitais da Universidade de Coimbra
Maria Rita Dionísio Abreu	Specialist in Oncology	Instituto Português de Oncologia de Lisboa
Sandra Garcês Gama	Intern in Rheumathology	Hospital Garcia de Orta
Sofia Santos Braga	Specialist in Oncology	Instituto Português de Oncologia de Lisboa

PART-TIME:

Ana Bastos Carvalho	Intern in Ophtalmology	Hospital de Santa Maria
Joana Azevedo	Intern in Hematology	Centro Hospitalar de Coimbra
Nuno Leitão Figueiredo	Intern in Surgery	Hospital de Santa Maria
Ricardo Fernandes	Intern in Pediatrics	Hospital de Santa Maria
Teresa Lima Braga	Intern in Surgery	Hospital de Santa Maria

2008 MODULES HELD AT IGC

Cell Cycle, Cytoskleton & Disease
3 – 7 November, 2008
Introduction to Neuroscience
Mónica Bettencourt-Dias (Organiser, IGC, Oeiras, Portugal*), Phong Tran (University of Philadelphia, Philadelphia, USA), Karim Labib Paterson (Institute for Cancer Research, London, United Kingdom), Helder Maiato (IBMC, Porto, Portugal), Erich Nigg (Max Planck Institute, Martinsried, Germany), Tim Mitchison (Harvard Medical School, Boston, USA), Martin Eilers (Philipps Universität, Marburg, Germany), Florence Janody, Miguel Godinho, Alvaro Tavares and Lars Jensen (IGC, Oeiras,* Portugal)

Genetics
10 –1 5 November, 2008
Dan Holmberg (Organiser, University of Umea, Umea, Sweden), Carlos Penha-Gonçalves (Local organiser, IGC, Oeiras, Portugal), Richard Rosenqvist (University Upssala, Sweden), Arn van den Maagdenberg (University Leiden, Leiden, The Netherlands), Simon Tuck (University of Umea, Umea, Sweden), Sofia Oliveira and Constantin Fesel (IGC, Oeiras, Portugal) Susana Campino (Cambridge University, Cambridge, United Kingdom)

PROGRAMME MANAGEMENT
Maria Hermínia Cabral (FUndação Calouste Gulbenkian)

ADMINISTRATIVE AND TECHNICAL SUPPORT
Maria Matoso
José Ricardo

Computacional Biology
20 – 25 November, 2008
José Leal (Organizer, IGC, Oeiras, Portugal), Nuria Lopez Bigas (University Pompeu Fabra, Barcelona, Spain), Fiona Brinkman (University Simon Fraser, California, USA), Dietrich Rebholz Schumann (EMBL European Bioinformatics Institute, Cambrigde, United Kingdom), James Brenton (Cancer Research UK, Cambridge, United Kingdom), David Balding (Imperial College, London, United Kingdom), Karen Nelson (The J. Craig Venter Institute, Maryland, USA)

Biostatistics & Epidemiology (Introduction to Biostatistics and Epidemiology course)
26 November – 12 December, 2008
Gabriela Gomes (Organiser, IGC, Oeiras, Portugal), Armando Teixeira-Pinto (Organiser, Faculdade de Medicina da Universidade do Porto, Porto, Portugal), Erich Tchetgen (Harvard University. School of Public Health, Boston, USA), Laura Rodrigues (London School Hygiene &Tropical Medicine, London, United Kingdom), John Edmunds (London School Hygiene &Tropical Medicine, London, United Kingdom), Eduardo Massad (University of São Paulo, São Paulo, Brasil), Claudio Struchiner (Fundação Oswaldo Cruz, Rio de Janeiro, Brasil), António Silva (University of Maranhão, Maranhão, Brasil)

GTPB – THE GULBENKIAN TRAINING PROGRAMME IN BIOINFORMATICS

Head: Pedro Fernandes
E-mail: pfern@igc.gulbenkian.pt

The GTPB provides practical, hands-on, intensive bioinformatics user training. The attendees acquire skills in the use of Biological data resources and analytical tools, in the scope of a well-defined conceptual framework for each individual course. The learning rate has been maximised by an improved set of techniques that have resulted from running these courses regularly at the IGC since 1999. GTPB runs courses at the "introductory", "regular" user and "power user" levels. The programme is paired withparallel initiatives in Hinxton (EBI), Cambridge (University of Cambridge, Dep Genetics) and Valencia (CIPF).

In 2008, a total of 147 sudents attended the GTPB training programme: 106 Portuguese students and 41 from several countries in Europe, America and Japan.

INDIVIDUAL MODULES/COURSES

IB08 Introductory Bioinformatics
7 – 11 April, 2008
David Judge, University of Cambridge, Cambridge, UK
Pedro Fernandes – Instituto Gulbenkian de Ciência, Oeiras, PT

Molecular Evolution, Phylogenetics and Adaptation
14 – 18 April, 2008
Hernan Dopazo – Centro Invest Principe Felipe, Valencia, ES
Leonardo Arbiza – Centro Invest Principe Felipe, Valencia, ES

Microarray Data Analysis using GEPAS nad BABELOMICS
21 – 23 May, 2008
Joaquin Dopazo – Centro Invest Principe Felipe, Valencia, ES
Ignacio Medina – Centro Invest Principe Felipe, Valencia, ES
David Montaner – Centro Invest Principe Felipe, Valencia, ES

ENSEMBL: Browsing Genes and Genomes
27 – 28 May, 2008
Giulietta Spudich – European Bioinformatics Institute, Hinxton, UK

ENSEMBL: API access, Programmeming workshop
29 – 30 May, 2008
Daniel Rios – European Bioinformatics Institute, Hinxton, UK

Molecular Markers and Population Genetics
23 – 27 June, 2008
Mark Beaumont- University of Reading, Reading, UK
Vitor Sousa – Instituto Gulbenkian de Ciência, Oeiras, PT
Lounès Chikhi – Instituto Gulbenkian de Ciência, Oeiras, PT

Powerful Search and Mining in Biological Databases
15 – 19 September, 2008

Proteomics Data Analysis
24 – 26 September, 2008
Ola Forsstrom-Olsson – Ludesi Corp, Malmö, Sweden and Boston, MA (USA)
Roman Zubarev – BMC, Uppsala University, Sweden
Lennart Martens – European Bioinformatics Institute, Hinxton, UK
Phillip Jones – European Bioinformatics Institute, Hinxton, UK

Microarray Data Analysis using R and Bioconductor
24 – 26 September, 2008

Nuno Barbosa-Morais – University of Cambridge, Cambridge, UK
Christina Curtis – University of Cambridge, Cambridge, UK
Mark Dunning – University of Cambridge, Cambridge, UK

Pharmacogenomics: New opportunities for drug discovery
3 – 7 November, 2008
Marc A. Marti-Renom – Centro Invest Principe Felipe, Valencia, ES
Antonio Pineda-Lucena – Centro Invest Principe Felipe, Valencia, ES

THESES

PhD THESES

Inês Ribeiro Alves. The role of the transcription factors Tbx3 and Tbx2 in heart development inzebrafish (Danio rerio) and mouse (Mus musculus) embryos. University of Lisbon, Portugal. May 2008.

Angelo Chora. ***Role of the protective gene Heme Oxygenase-1 in the control of T cell-mediated immune responses***. Faculty of Medicine, University of Lisbon, Portugal. July 2008.

Sílvia Correia. Viral modulation of interferon responses. Universidade Nova de Lisboa, Portugal. October 2008.

Luciana Itida Ferrari (former visiting Ph.D. student). Uma metodologia para extração de informação sobre o sistema imunológico. Universidade Federal do Rio de Janeiro, Brazil. December 2008.

Lilia Perfeito. Adaptation in *Escherichia coli.* Universidade Nova de Lisboa, Portugal. September 2008.

Ana Luisa Reis. Cloning, Immunogenicity and functional analysis of African Swine Fever Virus serological immunodeterminants. Faculdade de Medicina Veterinária, Universidade Técnica de Lisboa, Portugal. July 2008.

Ana Cecília Seixas. Study of cilia assembly in Tetrahymena and the role of cytosolic chaperonin CCT. Faculdade de Ciências, Universidade de Lisboa, Portugal. May 2008.

MSc THESES

Vanessa de Sousa Ferreira Borges. Identificação da actividade anti-checkpoint nos telómeros. Faculdade de Ciências da Universidade de Lisboa, Portugal. January 2008.

Catarina Baeta da Luz Bourgard. Caracterização de mutantes em genes que codificam proteínas do cinetocoro em drosophila melanogaster. Faculdade de Ciências da Universidade de Lisboa, Portugal. October 2008.

Ana Catarina Correia. Evaluation of the I329L as a candidate to delete for production of a viral attenuated vaccine against ASFV. Faculdade de Medicina de Lisboa, Universidade de Lisboa, Portugal. September 2008.

Eliane Cortez. *Regulation of T cell responses by heme oxygenase-1.* Faculdade de Ciências da Universidade de Lisboa, Portugal. June 2008.

Ana Mónica Carvalho de Sousa Gabriel. Regulation of T cells in SLW patients treated with IVIG. Faculdade de Ciências da Universidade de Lisboa, Portugal. April 2008.

Pedro Miguel Gaspar. Understanding the role of the actin cytoskeleton in vesicle trafficking to restrict growth of *Drosophila* epithelia. Faculdade de Ciências da Universidade de Lisboa, Portugal. November 2008.

André Mendonça. Simulations of Random and Selective Gene Loss for the Study of Reduced Bacteria. Instituto Superior Técnico - Dept. Physics, Portugal. November 2008.

Nuno Oliveira. Modelling virus induced control of pest species: Regulation of cat populations in island ecosystems by FIV. Faculdade de Ciências da Universidade de Lisboa, Portugal. January 2008.

Nuno Palha. ***Heme oxygenase-1 underlies the "protective trait" afforded by Sickle Cell Disease against Severe Acute Malaria.*** Faculdade de Ciências da Universidade de Lisboa, Portugal. December 2008.

Sofia Raquel Paula Rebelo. Understand how capping of actin filaments prevents epithelium to mesenchymal-like transition in genetically defined epithelial tissues. Faculdade de Ciências da Universidade de Lisboa, Portugal. February 2008.

André Rosa. Two novel players involved in morphogenesis. Universidade Nova de Lisboa, Portugal. December 2008.

Hugo Soares. Utility of virus host evasion genes: the African Swine Fever Virus non-assigned gene I329L inhibits TLR-3 signal transduction. Faculdade de Ciências e Tecnologia, Universidade de Coimbra, Portugal. September 2008.

Íris Vilares. Instituto Superior de Agronomia, Portugal. December 2008.

BSc THESES

Miguel Henriques dos Santos Caracol Teixeira. Knock-out reversível de telómerase em leveduras de fissão. Universidade Lusófona, Portugal. August 2008.

SEMINARS, WORKSHOPS, AND MEETINGS

SEMINARS AT THE IGC

JANUARY 2008

7/1/08
Xoana Troncoso
Barrow Neurological Institute, Arizona, USA
The role of corner angle in human visual physiology and brightness perception

8/1/08
Luis Graça
IGC
Reprogramming the immune system towards tolerance: regulation without regulatory cells

9/1/08
Ricardo Brentani
Cancer Hospital, S.Paulo, Brazil
Genomics in Clinical Oncology

9/1/08
Tony Bell
Redwood Center for Theoretical Neuroscience
Towards a cross-level theory of neural learning

11/1/08
Santiago Elena
Inst. de Biología Molecular y Celular de Plantas, CSIC, Spain
Mechanisms of Mutational Robustness in RNA Viruses

15/1/08
Luísa Mota-Vieira / Paula Pacheco
IGC
Epidemiology of recessive mutations in São Miguel population and insights into breast cancer

21/1/08
Robert Gould
MIT, Cambridge, MA, USA
Discovery of a Novel Pain Medication

22/1/08
Miguel Soares
IGC
Heme oxygenase-1: A protective gene that limits the deleterious effects of inflammation and immunity

24/1/08
Peter So
MIT, Cambridge, MA, USA
3D Tissue Cytometry: The next step in bioinformatics?

25/1/08
Claudine Chaouiya
TAGC InsermERM 206, Université de la Méditerranée
Qualitative modelling and analysis of regulatory networks: application to the Drosophila segment-polarity module

28/1/08
Brian Keeley
Pitzer College, Claremont, CA
Making Sense of the Senses: Neuroethology and the attribution and individuation of sensor stimuli

29/1/08
Iris Caramalho
IGC
"Killing me softly": the dynamics of CTL-mediated tumour cell death

29/1/08
Constantin Fesel
IGC
Systemic Lupus Erythematosus, autoantibodies, T-cell regulation and a new approach to functional genetics

30/1/08
Chris Braun
Hunter College, NY, USA
Creating the aquatic Umwelt: The acoustic, hydrodynmaic and electrosensory systems of fish

31/1/08
Jan Schmoranzer
Columbia University, New York, USA
Visualising polarity in migrating cells – membrane trafficking and centrosome positioning

31/1/08
Fátima Cairrão
Centre de Biologie du Développement, Univ. Paul Sabatier, France
The role of AU-rich elements in Drosophila mRNA decay

FEBRUARY 2008

1/2/08
Almudena Ramiro
Centro Nac.de Investigaciones Oncológicas, Madrid, Spain
AID beyond antibody diversification

5/2/08
Konrad Kording
Northwestern University, Chicago
Causal inference in movement

6/2/08
Robert Jacobs
University of Rochester, NY, USA
Ideal Observers

7/2/08
Wei Ji Ma
University of Rochester, NY, USA
Bayesian decision making with neural populations

7/2/08
Malcolm MacIver
Northwestern University, IL, USA
The evolution of planning

8/2/08
Elly Tanaka
Max Planck Institute of Molecular Cell Biology and...
Regeneration in vertebrates

8/2/08
Guilgur Gastón
Lab. de Ictiofisiología y Acuicultura, Inst. Inves. Biotecnológicas, Inst. Tec. Chasco, Buenos Aires
Characterisation of the GnRH System in Pejerrey fish

8/2/08
Charles Kemp
Carnegie Mellon University
Bayesian models of cognitive development

12/2/08
Sílvia Correia
IGC
Anti-Immunity: Evasion of Interferon response

13/2/08
James Briscoe
NIMR, Mill Hill, London, UK
Graded Shh signaling and the control of neural cell fate

14/2/08
Susan Dymecki
Genetics Dep., Harvard University, USA
From Cell Fate to Cell Function in the Brain Stem

15/2/08
Martyn Goulding
Molecular Neurobiology Lab., Salk Institute, San Diego, USA
Dissecting the spinal cord circuits that control movement

18/2/08
Jean-François Brunet
ENS, Paris, France
Breathing with Phox2b, from the Cambrian to the Bedside

18/2/08
Ricardo Brentani
Cancer Hospital, S.Paulo, Brazil
Neurophysiology of prions

19/2/08
Philip Gerrish
IGC
A cheating limit for structured communities

20/2/08
Alain Ghysen
Université Montpellier II, France
Control of cell migration: the case of the fish lateral line

21/2/08
Richard Mann
Dep. of Biochemistry and Molecular Biophysics, Columbia University,
New York, USA
Deciphering mechanisms controlling animal development at high resolution

21/2/08
Eve Marder
Brandeis University, MA, USA
Variability, Compensation and Homeostasis in a Rhythmic motor network

22/2/08
Leonard Zon
Stem Cell Program and Div. of Hematology/Oncology,
Howard Hughes Medical Institute, Boston, USA
Pathways regulating self renewal in blood stem cells

26/2/08
Francisco Dionísio
IGC
Biological Warfare – selective conditions of their evolution

29/2/08
Juergen Knoblich
IMBA-Inst. of Molecular Biotechnology, Vienna, Austria
Asymmetric cell division and proliferation control in stem cell lineages

MARCH 2008
4/3/08
Alexander Athanasiadis
IGC/ITQB
RNA Editing in Molecular Evolution and Innate Immunity

7/3/08
Raquel Seruca
IPATIMUP, Universidade do Porto
Hereditary diffuse gastric cancer a genetic disease and a cancer model to unerstand cell invasion

José Pereira-Leal
IGC
Evolution of space-traveling terrorists and midget genomes

12/3/08
Paschalis Sideras
Foundation for Biomedical Research of the Academy of Athens, Greece
Role of Activins in Respiratory inflammation and tissue remodelling

14/3/08
Ingo Bechmann
Dr. Senckenbergische AnatomiInst. for Clinical Neuroscience,
Goethe Institut, Frankfurt am Maim
Immune privilege and blood-brain barrier: concepts and misunderstandings

18/3/08
Moisés Mallo
IGC
A guided tour to Hox-land

20/3/08
Luc-Alain Giraldeau
Université du Québec à Montréal, Canada
Evolutionary Game Theory In the Lab

24/3/08
Joseph McIntyre
Université Paris 5
Moving the arm: control schemes, reference frames and internal models

25/3/08
Elizabeth Torres
California Institute of Technology
Space and time decoupling for voluntary action planning

25/3/08
Álvaro Tavares
IGC
One Ring to find them, One Ring to bind them and One ring to binf them all: kinetochores and chromosome segregation

26/3/08
Daniel Mucida
La Jolla Institute for Allergy and Immunology, La Jolla, California, USA
The role of retinoids in mucosal immune regulation

26/3/08
Javier Medina
University of Pennsylvania
Searching the neural orchestra for sources of movement imprecision: is it the conductor's fault?

27/3/08
Henry Yin
Duke University
The role of cortico-basal ganglia networks in action and habits

28/3/08
Jacek Gaertig
Warsaw University, Poland
Deciphering the Microtubule Code in Tetrahymena and zebrafish

28/3/08
Jose M. Carmena
University of California, Berkeley
Brain-machine interfaces: implications for motor learning and cortical plasticity

31/3/08
Stephen Doxsey
The University of Massachusetts Worcester Campus, Massachusetts, USA
Unexpected roles of midbodies and primary cilia proteins

APRIL 2008

1/4/08
Ana Ferreira
IGC
Heme oxygenase-1 underlies the "protective trait" afforded by sickle cell disease for acute malaria

1/4/08
Margarida Carneiro
IGC
Treating experimental arthritis with anti-CD8 antibodies

4/4/08
Michael Bruford
Cardiff School of Biosciences, UK
The Orlog model and process-based conservation in great apes

11/4/08
Alex Webb
Dep. of Plant Sciences, Univ. of Cambridge, Cambridge, UK
The Circadian Regulation of Signalling in Plants

14/4/08
C. Lowe
University of Chicago
Evolution of Animal Nervous Systems, from Sponges to Humans

17/4/08
K. Harris
Rutgers University
The stability of the fittest: a theory for learning through neural competition

18/4/08
Marc Dionne
Depts of Craniofacial Development and Microbiology,
Kings College London, UK
Infections and metabolic disruption in Drosophila

22/4/08
Salvatore Valitutti
IGC
Inter-cellular information transfer at the immunological synapse: role in inflammation and surveillance against cancer

24/4/08
Laurent Keller
University of Lausanne
Ant behavior is modulated by complex interactions between genes and social environment

25/4/08
Catherine Dulac
Harvard University
Sex and Smell: molecular biology of pheromone perception in animals

28/4/08
Rui Oliveira
IGC/ISPA
From hormones to behavior and back: neuroendocrine mechanisms underlying behavioural plasticity

29/4/08
Leonor Saúde
IGC/IMM
Left-right patterning in vertebrates: a non-conserved perspective

30/4/08
Nuno Ferrand
CIBIO, Universidade do Porto
The European Rabbit Genome Initiative: Prospects for comparative genomics of domestication and the analysis of the early stages od speciation

MAY 2008

2/5/08
Christian Dahmann
Max Planck Inst. of Molecular Cell Biology and Genetics,
Dresden, Germany
Developmental control of epithelial cell shape

6/5/08
Miguel Seabra
IGC
Membrane traffic in hematopoietic cells and implications to disease

9/5/08
Eugene Koonin
National Center for Biotechnology Information, USA
Origins of the eukaryotic cell

9/5/08
Nicolas Malmanche
IBMC - Instituto de Biologia Molecular e Celular, Porto
Cross talk between bubR1 and mei41-ATR through centromeric pairing: linking meiotic cycle progression to embryonic patterning in Drosophila oogenesis

13/5/08
Cristina João
IGC
Improvement of immune reconstitution with lvlg or its fragments

13/5/08
Ana Tavares
IGC
Origin and fate of hemangioblasts in the early embryo

15/5/08
Jakob Winther
Protein biology group, Dep. of Biology - Univ. of Copenhagen
Global analysis of cellular thiol-disulfide redox pools

16/5/08
Sigal Ben-Yehuda
Dep. of Molecular Biology, The Hebrew Univ. of Jerusalem, Israe
Spatial organization of a replicating bacterial chromosome

20/5/08
Aniruddha Das
Columbia University
Entraining to Task Expectation in Primary Visual Cortex?

20/5/08
Patrícia Beldade
IGC/Univ. of Leiden
Genetic and developmental basis of phenotypic variation: Beyond classical model organisms

22/5/08
Michael Goldberg
Columbia University
On the agnosticism of spikes: saccades, salience, and attention in the lateral intraparietal area

23/5/08
Mark Field
Dep. of Pathology, Univ. of Cambridge, UK
Intracellular transport in trypanosomes; understanding mechanism, control, virulence and evolution

27/5/08
Helena Soares
IGC
The tubulin folding pathway revisited

27/5/08
Roger Karess
Dynamique de la division cellulaire, Institut Jacques Monod, Paris
Mad2 and BubR1: A few surprises from the spindle checkpoint in Drosophila

29/5/08
Chandra Kilburn
University of Bolder, Colorado, USA
Identification and characterization of Tetrahymena basal body components

29/5/08
Herrmann-Josef Thierse
Dep. of Dermatology and Univ. Medical Center Mannheim,
Ruprecht Karls Univ. of Heidelberg
Proteomic interaction analysis reveals a new function for heat shock protein 70 in human allergy

30/5/08
Graham Bell
McGill Univ., Montreal, Quebec, Canada
Adaptation or extinction after environmental change

JUNE 2008

2/6/08
Jens Hauser
Paris, France
Approaches to Art involving Biotechnology

2/6/08
George Gessert
Oregon, USA
Struggle for Survival Paradise Garden

3/6/08
Karina Xavier
IGC
Inter-species Bacterial Quorum Sensing

5/6/08
Noni Franklin Tong
School of Biosciences, Univ. of Birmingham, U.K.
Recognition of "self" can be deadly: self-incompatibility signalling networks trigger programmed cell death in pollen

6/6/08
Buzz Baum
Dep. of Biochemistry and Molecular Biology, Univ. College London, UK
Cell shape through the cell cycle

11/6/08
José Mário Leite
IGC
Registo de tempos nos Projectos com financiamento Externo

17/6/08
Susana Lopes
IGC
Multiple roles for Notch signalling pathway during Left-Right development

17/6/08
Madalena Martins
IGC
Genomics in Neurodegenerative Diseases

19/6/08
Emanuel Hanski
Hhmi Int. Research Scholar, Hebrew Univ.-Hadassah Medical School,
Jerusalem, Israel
Regulation of streptococcal virulence by the autoinducer peptide-SilCR

20/6/08
Mohammed Daha
Dep. of Nephrology, Leiden Univ. Medical Center, The Netherlands
Role of complement in innate host defense and autoimmunity

24/6/08
João Pedro Simas
IGC
A single CD8+ T cell epitope sets the long-term latent load of a murid herpesvirus

27/6/08
Michel Bornens
UMR 144 CNRS/Institut Curie, Paris, France
Shape, Polarity and Individuation of Animal Cells during Division

JULY 2008

1/7/08
Marta Moita
IGC
Fear learning and social dilemmas in rats

3/7/08
Julie Cooper
Telomere Biology Lab., London Research Inst., Cancer Research, UK
Telomeres and the challenges to chromosome integrity

4/7/08
Titia de Lange
The Rockefeller University, New York, USA
How telomeres protect chromosome ends

8/7/08
Carla Shatz
Bio-X, Stanford University, USA
Tuning up the brain: unexpected role for immune genes in synaptic plasticity

9/7/08
Hannele Ruohola-Baker
Institute for Stem Cell and Regenerative Medicine,
University of Washington, Seatle, USA
microRNAs regulate human embryonic stem cell division

9/7/08
Duarte Barral
Division of Rheumatology, Immunology and Allergy
The intracellular pathway of CD1a antigen presentation

11/7/08
Paula Duque
IGC
SR45, a plant-specific splicing factor, negatively regulates sugar signaling in Arabidopsis

15/7/08
Ana Catarina Certal
IGC
The role of the potassium channel ERG1 during vertebrate limb development

15/7/08
Nuno Afonso
IGC
FLRT3 modulates FGF signalling during regeneration of the adult zebrafish caudal fin

18/7/08
Nuno Ferrand
CIBIO, Porto
The European rabbit (Oryctolagus cuniculus) as a model species in evolutionary biology: new insights in the analysis of colonizing populations

22/7/08
Rui Martinho
IGC
From stem cells to epithelial morphogenesis: the devil is in the detail

25/7/08
Alexander Schier
Harvard University, Cambridge MA, USA
MicroRNAs in embryogenesis and signaling

29/7/08
Monica Dias / Zita Santos/ Inês Ferreira
IGC
Centrosome Architecture, Number and Evolution: a summer tale in three acts

SEPTEMBER 2008

2/9/08
Anna Zaidman
IGC
Drosophila: From the regulation of innate immunity to wound inflammation

5/9/08
John Sinclair
Department of Medicine, University of Cambridge, UK
Latency and reactivation of human cytomegalovirus - regulation by chromatin structure

9/9/08
Catarina Correia
Instituto Nacional de Saúde Dr. Ricardo Jorge, Lisbon, Portugal
Autism: endophenotypes and susceptibility genes

10/9/08
Tim Stearns
Stanford University, CA, USA
Centrosomes, cilia, and the cell cycle

16/9/08
Sander van Noort
IGC
Variant surface antigen repertoire of Plasmodium falciparum shaped by two-level selection

16/9/08
Rute Nascimento
IGC
Viral subversion of host cell cycle

19/9/08
Susana Godinho
Dep. of Pediatric Oncology, Dana-Farber Cancer Institute,
Harvard Medical School, Boston, USA
Mechanisms to suppress multipolar divisions in cancer cells with extra centrosomes

22/9/08
Björn Hegemann
Research Institute of Molecular Pathology, Vienna, Austria
Systematic analysis of mitotic protein complex organisation and phospho-regulation

23/9/08
Lisete Fernandes
IGC
Cytoskeleton and prefoldin/GimC: from stress signalling to transcription

25/9/08
Michiko Taga
Massachusetts Institute of Technology, Dep. of Biology, USA
A Symbiotic Nitrogen-Fixing Bacterium Reveals the Last Missing Step in Vitamin B12 Biosynthesis

26/9/08
Lawrence Loeb
Dept. Pathology, Univ. of Washington, USA
Mutations Drive the Evolution of Human Cancers

30/9/08
Gabriel G. Martins
IGC
Dynamic cell re-organizations mediated by fibronectin are essential for somitogenesis

OCTOBER 2008

1/10/08
Zvi Grossman
Laboratory of Immunology, National Institute of Allergy
and Infectious Diseases, NIH, Bethesda MD, USA
Mathematical analysis of in vivo BrdU labeling in SIV infection: New insights into T cell dynamics in health and disease

2/10/08
Yumi Kim
University of California, San Diego
Mechanism of mitotic kinesin CENP-E in tethering kinetochore to spindle microtubules

3/10/08
Holger Knaut
Skirball Institute for Biomolecular Medicine, NYU-Medical Center, NYC, USA
Assemblying a nerve cluster - Ganglion Development

7/10/08
Zachary Mainen
IGC
Neural mechanisms of decision making

10/10/08
Barry Dickson
Institute of Molecular Pathology, Vienna, Austria
Wired for sex: the genetics and neurobiology of Drosophila reproductive behaviour

13/10/08
Jordi Casanova
IBMB-CSIC, Barcelona, Spain
From genes to shape: notions from the study of the Drosophila tracheal system

14/10/08
Isabel Gordo
IGC
Microbial evolution: the triple helix

17/10/08
Dinis Pestana
Faculdade de Ciências da Universidade de Lisboa
Statistical Tools for Knowledge Building

21/10/08
Joaquín León
IGC
Oct4 controls Apical Ectodermal Ridge integrity and function during limb bud development

24/10/08
José C. Principe
University of Florida
Co-Adaptive Brain Machine Interfaces

27/10/08
Fernando Roch
CBD, CNRS, Toulouse, France
Ly6/CD59/uPAR proteins in Drosophila, a new family of cell adhesion molecules

28/10/08
Maria Luísa Vasconcelos
IGC
The sexually dimorphic brain

29/10/08
Anna Tramontano
University of Rome La Sapienza, Italy
From genomes to proteins and back

30/10/08
Kevin Brick
Istituto Superiore di Sanitá , Roma
Computational analysis of promoter regions in the genome of the human malaria parasite Plasmodium falciparum
31/10/08
Matthew Rockman
New York University, USA
Linked selection shapes phenotypic variation in C. elegans

NOVEMBER 2008

3/11/08
Karl Thomaseth
National Research Council, Institute of Biomedical Engineering ISIB-CNR, Padova, Italy
Identification of Mathematical Models of Complex Biological Systems: Theoretical and Statistical Tools for Heuristic Approaches

4/11/08
Karim Labib
Paterson Institute for Cancer Research, Manchester, UK
The beginning and the end of the Cell Cycle

4/11/08
Lounès Chikhi
IGC
Can population structure explain genetic bottlenecks detected in orang-utans and other endangered species?

5/11/08
Martin Eilers
Inst. of Molecular Biology and Tumor Research (IMT), Marburg, Germany
Transcriptional Repression: The Dark Side of Myc

6/11/08
Tim Mitchison
Dept. Systems Biology, Harvard Medical School, USA
Pharmacology of the mitotic spindle

7/11/08
Debate On: *Where to go in research in cell cycle and cancer?*

7/11/08
Erich Nigg
Max Planck Inst. of Biochemistry, Martinsried, Germany
Cell Cycle Control of Genome Integrity: Focus on Mitosis and the Centrosome Cycle

11/11/08
Lars Jansen
IGC
The centromere: a showcase for epigenetic inheritance

14/11/08
Jeff Friedman
The Rockefeller University, New York, USA
Leptin and the Homeostatic Control of Food Intake and Body Weight

17/11/08
Frank Uhlmann
Chromosome Segregation Lab., London Research Inst., Lincoln's Inn Fields Lab., London, UK
Establishment of sister chromatid cohesion during DNA replication

18/11/08
Joe Paton
IGC
Teaching the brain about value and how to act on it: amygdala, dopamine, and basal ganglia mechanisms.

24/11/08
Edgar R. Gomes
UMR-S 787 Inserm, France
Mechanisms of nuclear positioning during cell polarization

25/11/08
Vasco Barreto
IGC
Ig loci hallmarks

25/11/08
John Martin
University College London, UK
Stem cell therapy or gene therapy: which is the future for repairing the heart?

28/11/08
Gennaro de Libero
Basel University Hospital, Switzerland
Rules of lipid antigen recognition by T Cells

DECEMBER 2008

2/12/08
Carlos Penha Gonçalves
IGC
Malaria genetics in mouse and man

3/12/08
Margarida Prado
IGC
Getting your hands on intellectual property

4/12/08
Benjamin Kottler
Université d'Orsay
Discovery and analyses of new long-term memory mutant

9/12/08
Mathias Koeppen
IGC
How to Move Cells and Build Organs in Zebrafish

11/12/08
Rolf Bredemeier
Goethe-University, Frankfurt, Germany
With a little help of my friends: Polypeptide-transporting proteins of the Omp85 family

12/12/08
Frederic Geissmann
King's College, London, UK
Studies on the functions of blood monocytes

16/12/08
Susana Lima
IGC
Neural Mechanisms Underlying Mate Choice

19/12/08
Teresa Teixeira
Lab. de Biologie Moléculaire de la Cellule (LBMC),
CNRS / ENS-Lyon / Université Lyon1, France
The telomere, the eukaryotic cell, its proliferation & its control

22/12/08
Miguel Coelho
Tolic-Norrelykke Lab., MPI-CBG, Dresden, Germany
Fission yeast is immortal!

22/12/08
Florian Engert
Molecular and Cellular Biology Harvard University
Seeing through the brain: neural processing in the larval zebrafish

PRESENTATIONS BY IGC RESEARCHERS AT INTERNATIONAL MEETINGS

RICARDO ÁGUAS
Prospects for Malaria Eradication in sub-Saharan Africa.
First IGC & MRC Students meeting
Ericeira, Portugal
April, 2008

Prospects for Malaria Eradication in sub-Saharan Africa.
MORU (Mahidol-Oxford Tropical Medicine Research Unit) Scientific Seminars
Bangkok, Thailand
23 June, 2008

Modelos com heterogeneidade na susceptibilidade à infecção
– o caso da Tuberculose.
Regular seminars of CMA- Center of Mathematics and Applications
of Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa
Monte da Caparica, Portugal
15 October, 2008

MAÍRA AGUIAR
Rich dynamics in multi-strain models: non-linear dynamics and deterministic chaos in dengue fever epidemiology.
European Conference on Mathematical and Theoretical Biology (ECMTB)
Edinburgh, Scotland
13 – 16 June, 2008

Torus bifurcations, isolas and chaotic attractors in a simple dengue model with ADE and temporary cross immunity.
8th International Conference on Computational and Mathematical Methods in Science and Engineering (CMMSE)
Murcia, Spain
29 June – 4 July, 2008

ELENA BAENA-GONZALEZ
Arabidopsis KIN10 and KIN11 are central mediators of convergent transcriptional responses in energy and stress signaling
ASPB (American Society of Plant Biology) meeting,
Mérida, Mexico
27 July – 1 August, 2008

Convergent energy and stress signaling
FESPB (Federation of European Societies of Plant Biology) meeting
Tampere, Finland
17-22 August 2008

VASCO BARRETO
Percursos
Faculdade de Ciência da universidade de Lisboa, Lisbon, Portugal
March, 2008

The antibody Problem and beyond
Somatic Hypermutation
The immune system and the brain
Faculdade de Ciência da universidade de Lisboa, Lisbon, Portugal
April, 2008

AID: generation of somatic diversity
Instituto Português de Oncologia (IPO), Lisbon, Portugal
October 30, 2008

*A New Activation-Induced Cytidine Deaminase (AID) mutation in a Brazilian family**
*Pedro H Reis, Nadine Caratão, Cristina M. Jacob, António C. Pastorino, Magda Carneiro-Sampaio, Vasco Barreto
Portuguese Society for Immunology Annual Meeting
Porto, Portugal
26 – 28 October, 2008

JORG BECKER
Microarrays and their Applications in Research and Diagnostics
Plenary Lecture at 3rd Jornadas de Engenharia Biológica, Instituto Superior Técnico, Lisbon, Portugal
21 March, 2008

Genetic basis of sexual reproduction in higher plants: a focus on the male gametes
Plenary Lecture at 1st Jornadas de PCR em Tempo Real, Universidade de Trás-os-Montes e Alto Douro, Portugal
2 October, 2008

Comparative transcriptomics of Arabidopsis thaliana *sperm cell**
*Borges F, Gomes G, Gardner R, Moreno M, McCormick S, Feijó JA, Becker JD
Frontiers of Sexual Plant Reproduction III
Tucson, USA
19 October, 2008

Services of the Affymetrix Core Facility
Integrated Genomics Seminar Series
Institute for Molecular Medicine (IMM), Lisbon, Portugal
28 November, 2008

A Whole-Genome Transcriptomics Approach to Sexual Reproduction in Arabidopsis thaliana
Universidade do Minho, Departamento de Biologia, Portugal
2 December, 2008

A Whole-Genome Transcriptomics Approach to Sexual Reproduction in Arabidopsis thaliana
Biocant- Biotechnology Innovation Centre
Cantanhede, Portugal
3 December, 2008

PATRICIA BELDADE
Evolutionary Diversification of Form: Serial repeats and evolutionary novelties
Department of Ecology & Evolutionary Biology of Princeton University
Princeton, New Jersey, USA
6 March, 2008

Evo-Devo & the Diversification of Animal Form: Examples from butterfly wings
Workshop on Evolutionary Cell Biology
Instituto Gulbenkian de Ciência, Oeiras, Portugal
9 - 10 May, 2008

Co-option of shared pathways and the evolution of morphological novelties
*due to last minute problems this talk was delivered by P. Beldade's Ph.D. student in Leiden, S.V. Saenko
Euro Evo Devo 2008 Conference*
Ghent, Belgium
29 July - 1 August, 2008

Genetic and developmental basis of evolutionary diversification
III Encontro Nacional de Pós-Graduação em Ciências Biológicas, Centro de Ciências do Mar da Universidade do Algarve, Faro, Portugal
5 September, 2008

Genes, development, and morphological evolution
Max Planck Institute for Plant Breeding Research.
Köln, Germany
17 September, 2008

Evolução e Desenvolvimento: Variações a dois tempos e muitas cores
"Darwin: No caminho da evolução" seminar series
Fundação Calouste Gulbenkian, Lisbon, Portugal
5 November, 2008

MARIE LOUISE BERGMAN
In vivo *induction of Treg differentiation upon chronic* Helicobacter hepaticus (H.hepaticus) *infection*
XXXIV Annual Meeting of The Portuguese Society of Immunology.
Porto, Portugal
October, 2008

MONICA BETTENCOURT-DIAS
The New Kid On The Block: SAK/PLK4
David Glover 60th Birthday Symposium
Cambridge, United Kingdom
11 April, 2008

Right Time, Right Place and Only Once: the Control of Centrosome Number
The Cell Cycle and Genomic Stability Meeting
Roscoff, France
26 - 30 April, 2008

Right Time, Right Place and Only Once: the Control of Centrosome Number
School of Life Sciences, Dundee University
Dundee, United Kingdom
20 May, 2008

Controlling centriole architecture and number
Department of Biochemistry, Oxford University
Oxford, United Kingdom
19 June, 2008

Mitos e Factos do Regresso a Portugal
Luso2008 Meeting
Oxford, United Kingdom
20 June, 2008

Experimenting with Evo-Cell, what can evolution tell us about cellular structures
VIII Workshop on Cell and Developmental Biology of Drosophila
Balneari Prats, Spain
15 July, 2008

Keeping Centrosome Number Under Control
EPFL Life Science Symposium 2008: Cancer and the Cell Cycle
21-23 August, 2008

The Control of Centrosome Number
Chair of session at ELSO (European Life Science Organization) 2008
Nice, France
28 August - 2 September, 2009

The Control of Centrosome Number
1st EMBO Conference on Centrosomes and Spindle Pole Bodies at EMBL
Heidelberg, Germany
12 - 16 September, 2008

SAK/PLK4 And The Control Of Centriole Biogenesis
Chair of session at EMBO workshop: Polo like kinases: from the fly to the clinic 20 years onwards
Porto, Portugal,
24 - 29 September, 2008

Centrosome Biogenesis
VII CRG Annual Symposium: Mechanims Regulating Cell Growth and Division
Barcelona, Spain
16 - 17 October, 2008

Control of Centrosome Biogenesis
Stanford University
Stanford, USA
11 December, 2008

JORGE CARNEIRO
Why is regulation of autoimmunity so robust?
Biotechnology Institute, Universidade Nacional Autónoma de México
Cuernavaca, Mexico
18 February, 2008

Handshare entre a ciência de computadores e a Biologia
Departamento de Ciência de Computadores, Universidade do Porto
Porto, Portugal
26 February, 2008

Catching them in the act: cell morphodynamic imaging and modeling
Magma Seminar Series,
Marseille, France
May, 2008

Como as células constroem um corpo sem terem um plano
"Das Sociedades Humanas às Sociedades Artificiais,
Instituto de Sistemas e Robótica" - Instituto Superior Técnico
Lisboa, Portugal
28 May, 2008

Regulação e expressão estocástica: a dupla vida de um gene
"A matemática nas Ciências Biológicas", Instituto Superior de Agronomia
Lisboa, Portugal
14 July, 2008

From cell cooperation mechanisms to peripheral T cell repertoire selection
Challenges For Experimental And Theoretical Immunology,
ESF (European Science Foundation) Exploratory Workshop
Leeds, United Kingdom
2 September, 2008

Dynamics of T cells Before Amplification
Physics of Biological Systems
Braga, Portugal
11 September, 2008

Morphogenesis and positional information in immune repertoires
"Physics of Biological Systems: From genes to societies",
Complexo Interdisciplinar
Lisboa, Portugal
3 October, 2008

La double vie d'un gene
Discrete models of biological network: from structure to dynamics
Marseille, France
3 - 7 November, 2008

Morphogenesis and patterning of CD4 T cell repertoires
British Society for Immunology Meeting
Glasgow, UK
20 November, 2008

Noise in the molecular machinery of the cell: lessons from stochastic monallelic gene expression
Centro de Matemática e Aplicações Fundamentais
Lisbon, Portugal
9 December, 2008

LOUNES CHIKHI
Conservation genetics of orangutans: can we separate demography from population structure?
Portuguese Forum on Computational Biology, Instituto Gulbenkian de Ciência
Oeiras, Portugal
10 - 12 July, 2008

Approximate Bayesian computation (ABC) without summary statistics: The case of an admixture model
14th European Meeting of PhD Students in Evolutionary Biology
Einsiedeln, Switzerland
8 - 13 September, 2008

L'ADN fait de la résistance
Palais de la Découverte, La Recherche
Paris, France.
30 September, 2008

Approximate Bayesian computation (ABC) without summary statistics: The case of an admixture model
GDR CNRS 1928- Génomique des Populations et Génomique Évolutive
Sète, France,
15 - 17 October, 2008

Estimation of admixture proportions using Approximate Bayesian Computation (ABC) with applications to study human populations
PopGroup Meeting 2008
Cardiff, United Kingdom
16 - 19 December, 2008

Can population structure explain genetic bottlenecks detected in orang-utans and other endangered species?
Department of Anthropology
Zurich, Switzerland
17 - 21 December, 2008

CLAUDINE CHOUIYA
New means for the qualitative analysis of large regulatory networks
First Portuguese Forum on Computational Biology
Intituto Gulbenkian de Ciência, Oeiras, Portugal
July, 2008

PAULA DUQUE
SR45, a plant-specific splicing factor, negatively regulates sugar signaling in Arabidopsis
XVIth National Congress of Biochemistry
Ponta Delgada, Portugal
22 October, 2008

Percursos
Faculdade de Ciências da Universidade de Lisboa: Percursos em Biologia
Lisbon, Portugal
15 May, 2008

Pedro Fernandes
O valor da infra-estrutura de armazenamento e de análise dos dados de biodiversidade
Conservação e Biodiversidade: o Papel dos Jardins Botânicos (workshop)
11 November, 2008

JOSÉ FEIJÓ
Plant Imaging
EMBO workshop: Developmental Imaging
Instituto Gulbenkian de Ciência
June, 2008

Excitement in sexual plant reproduction: the remarkable biophysics of pollen tubes
Biophysics Society
Lisbon, Portugal
July, 2008

Excitement in sexual plant reproduction: the remarkable biology of pollen tubes and their urges for models
MBI (Mathematical Bioscience Institute)
Ohio, USA
September, 2008

Two-photon fluorescence in plant sciences
FEBS Microspectroscopy Course
Wagenigen, The Netherlands
September, 2008

Excitação Durante a Reprodução Sexuada de Plantas: A Notável Biologia dos Tubos Polínicos
Jornadas de Genética e Biotecnologia, Universidade de Vila Real
Vila Real, Portugal
November, 2008

MIGUEL GODINHO FERREIRA
MRN complex is required for NHEJ-dependent telomere fusions in fission yeast
Maintenance of Genome Stability, meeting
Puerto Vallarta, Mexico.
March, 2008

Telomeres prevent checkpoints in spite of ongoing DNA repair
Telomeres and the DNA damage response (EMBO´s meeting)
Villars, Switzerland.
September, 2008

MARIA FRANCISCA MORAES FONTES
A regulação do Sistema Imunitário
14º Congresso Nacional de Medicina Interna
Vilamoura, Portugal
March, 2008

A regulação do Sistema Imunitário
Jornadas de Hematologia do Centro Hospitalar de Lisboa Ocidental
Lisbon, Portugal
May, 2008

PC61 Administration Induces Sudden Death In Colitic Mice
XXXIV Annual Meeting of The Portuguese Society of Immunology.
Porto, Portugal
October, 2008

ANA GODINHO
*How can dialogue and debate feature in science communication training?**
*S. Miller, A. Godinho, E. Poupardin, A. Visnjevac, B. Trench and D. Fahy
Public Communication in Science and Technology (PCST)-10 Conference
Malmö, Sweden
23 – 27 June, 2008

GABRIELA GOMES
Epidemiologia da Gripe: monitorização, modelação e previsão
Faculdade de Medicina, Universidade do Porto
Porto, Portugal
8 February, 2008

The Reinfection Threshold: theory and applications in epidemiology and pathogen population biology.
London School of Hygiene and Tropical Medicine
London, United Kingdom
25 February, 2008

Prospects for malaria eradication.
Wister Institute Philadelphia
Philadelphia, USA
25 March, 2008

Qual o possível impacto das doenças tropicais na Europa?
Tertulia Científica
Viana do Castelo, Portugal
11 April, 2008

The Reinfection Threshold: theory and applications in epidemiology and pathogen population biology.
Instituto de Física, Universidade Federal da Bahia
Salvador, Brazil
22 April, 2008

Erradicação da malária: modelos e perspectivas.
Plenary Talk, Encontro Nacional da Sociedade Portuguesa de Matemática
Coimbra, Portugal
28 June, 2008

Prospects for malaria eradication.
First Portuguese Fórum on Computaitonal Biology
IGC, Oeiras, Portugal
10-12 July 2008
Prospects for malaria eradication.
Third Workshop on Statistics, Mathematics and Computation, Universidade Aberta, Portugal
21 – 22 July, 2008

Variant surface antigen repertoires of Plasmodium falciparium *shaped by within-host competition and between-host transmission.*
Workshop on Modeling the Impact of Policy Options during Public Health Crises, BIRS
Canada
27 July – 1 August, 2008

Variant surface antigen repertoire of Plasmodium falciparium *shaped by two-level selection.*
Conference on Dynamics and Application (Dyna2008), Universidade do Minho
Portugal
8 – 12 September, 2008

Population heterogeneities and disease incidence.
International Workshop Facing the Challenge of Infectious Diseases – Integrating mathematical modeling, computational thinking and ICT applications, ISI Foundation
Turin, Italy
13 – 17 October, 2008

Population heterogeneities, disease incidence and intervention impact.
International Symposium on Operational Research (ISOR'08)
Alger, Algeria
2 – 5 November, 2008

Pathogen diversity and disease evolution: Models and realities.
ESF Workshop on Mathematical Modelling to Link Contact Network Analysis and Molecular Typing of Pathogens, Utrecht University, *Utrecht*,
The Netherlands
6 – 7 November, 2008

PHILIP GERRISH
Mutation rate evolution and the stability of networked mutualisms.
Instituto de Ecologia
Xalapa, México
6 August, 2008

Mutation rate and the evolution of cooperation in structured populations.
Workshop on Physics of Biological Systems: From Genes to Societies, Universidade de Lisboa
Lisbon, Portugal
2 – 3 October, 2008

Evolution of the Genomic Mutation Rate: Implications for Asexual Populations
Kavli Institute for Theoretical Physics Programme: Population Genetics and Genomics
Kavli Institute, University of California Santa Barbara, USA
14 November, 2008

ISABEL GORDO
On sex, stress and mutation interactions
Institute for Genetics, University of Cologne
Cologne, Germany
April, 2008

Rate and effects of mutations in Escherichia coli
Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa
Lisbon, Portugal
June, 2008

Genetic diversity In the SIR model of pathogen evolution
Workshop on Evolution of Cancer and Infectious diseases
IGC, Oeiras, Portugal
September, 2008

Clonal Interference in microbial populations
CMAF, Faculdade de Ciências Universidade de Lisboa
Lisbon, Portugal
October, 2008

Mutation, selection and epistasis in Escherichia coli
Institut für Population genetics, University of Vienna
Vienna, Austria
December, 2008

Integrating epidemiology with population genetics
Encontro Nacional Biologia Evolutiva, Instituto Biologia Molecular e Celular
Porto, Portugal
December, 2008

FLORENCE JANODY
Proper regulation of cytoskeletal genes is essential to restrain growth of epithelia
Carry-le-Rouet - France
24 November, 2008

LARS JANSEN
Assembly and Maintenance of Centromeric Chromatin
Chromosome Segregation: Centromeres & Kinetochores
Arcachon, Bordeaux
September - 2 October, 2008

Pulse chase study of centromeric proteins in live cells using SNAP-tag technology.
American Society for Cell Biology meeting
San Francisco, USA
14 December, 2008

SUSANA LIMA
In vivo electrophysiological identification of Channelrhodopsin2-tagged neuronal subpopulations
Integrative Approaches to Brain Complexity, Wellcome Trust Conferece
Cambridge, UK
October, 2008

In vivo electrophysiological identification of Channelrhodopsin2-tagged neuronal subpopulations
Genetic Manipulation of Neuronal Activity Meeting Janelia Farm Research Campus
Virginia, USA
5 November, 2008

ZACHARY MAINEN
Neural circuits and decision making in rodents
Janelia Farm
Ashburn, VA, USA
April, 2008

How the brain computes and uses decision confidence
Instituto Superior de Psicologia Aplicada
Lisbon, Portugal
May, 2008

How the brain computes and uses decision confidence
École Normal Superieur
Paris, France
May, 2008

How the brain computes and uses decision confidence
IMP (Institute Molecular Pathology)
Vienna, Austria
October, 2008

How the brain computes and uses decision confidence
Stanford University
San Francisco, USA
12 December, 2008

How the brain computes and uses decision confidence
Fórum Internacional de Investigadores Portugueses, IMM(Instituto de Medicina Molecular)
Lisbon, Portugal
19 December, 2008

MOISES MALLO
Overexpression of HoxC13 in the presomitic mesoderm causes truncation of axial elongation associated with reduced Wnt3a expression.
Joint Meeting for the British and Spanish Developmental Biology Societies
Seville, Spain
May, 2008

Making the vertebrate skeleton: Hox genes at work
1st CABD International Course on Developmental Biology and Functional Genomics
Carmona, Spain
June, 2008

Hox genes at work in the mouse embryo
EMBO Practical course
Zagreb, Croatia
September, 2008

MARTA MOITA
Fear learning and social dilemmas in rats
University of Groeningen
Groeningen, Netherlands
July, 2008

The role of multiple memory systems in the associative learning
VI Encontro do FIIP (Fórum Internacional de Investigadores Portugueses) Lisbon, Portugal.
17 December, 2008

MARTA NUNES
Modelling infection dynamics with realistic recovery profiles.
Workshop "Facing the Challenge of Infectious Disease", ISI Foundation
Turin, Italy
13 - 17 October, 2008

ANDREA PARISI
Modelling infection dynamics with realistic recovery profiles
5th European Conference on Complex Systems
Jerusalem, Israel
14 - 19 September, 2008

Mike Parkhouse
Control of cysticercosis
Meeting of the cysticercosis working group in Europe
11 - 12 March, 2008

Host-pathogen interaction
Talk at Veterinary Laboratory Agencies
Weybridge, United Kingdom
4 April, 2008

Cysticercosis a Neglected Tropical Disease
International Conference in the framework of a European Foundations Initiative
Bamako, Mali
24 - 28 September, 2008

El papel del Diagnostic en le Control de Neurocysticercosis
Latin American Congress of Neurology and Neuroinfection
Maracay, Venezuela
20 - 25 October, 2008

Cysticercosis: una Infección Tropical Desatendida
6th Congress of Investigation of the University of Carabobo
Maracay, Venezuela
October, 2008

CARLOS PENHA-GONCALVES
Pregnancy Associated malaria in the mouse
Annual meeting of the Portuguese Society of Immunology
Porto, Portugal
October, 2008

CATARINA S. PEREIRA
Sinorhizobium meliloti, *A Species Lacking the Autoinducer-2 Synthase, Responds to Exogenously Supplied Signal.*
2nd ASM Conference on Beneficial Microbes: Beneficial Host-Microbial Interactions.
San Diego, USA
12 - 16 October, 2008

JOSÉ PEREIRA-LEAL
What are functional modules in biological networks
INESC-ID (Instituto de Engenharia de Sistemas e Computadores- Investigação e Desenvolvimento)
Portugal
February, 2008

Gene loss in intracellular endosymbiontes and parasites
University of Dundee
Dundee, United Kingdom
May, 2008

Bioinformatics, Biotechnology and Medicine
National Meeting of the "Laboratórios Associados"
Fundação Calouste Gulbenkian, Lisbon, Portugal
July, 2008

Intracellular life styles and the nature of the minimal genome
1st Portuguese Forum of Computational Biology
IGC, Oeiras,Portugal
July, 2008

Gene loss in intracellular endosymbiontes and parasites
Coimbra, Portugal
September, 2008

Modular Cell Biology
IST (Instituto Superior Técnico)
Lisbon, Portugal
October, 2008

Modularity, Gene Gain and gene loss
San Francisco, *USA*
December, 2008

Modular Cell Biology
Instituto Superior Técnico (IST), Portugal
October, 2008

LÍLIA PERFEITO
The effect of spatial structure in the adaptation of asexual populations
SMBE (Society for Molecular Biology and Evolution) meeting
Barcelona, Spain
June, 2008

PAULA RODRIGUES
Modelos com heterogeneidade na susceptibilidade à infecção - o caso da Tuberculose.
Regular seminars of CMA- Center of Mathematics and Applications of Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa,
Monte da Caparica, Portugal
15 October, 2008

MIGUEL SEABRA
ELSO Annual Meeting
Nice, France

Choroideremia Research Foundation USA Annual Meeting
Baltimore, USA

FASEB Summer Conference on Ras-like GTPases
Saxtons River, VT, USA

Institute of Molecular Pathology and University of Vienna
Austria
JOCEM (Portuguese Medical Students Conf)
Lisbon, Portugal

SINAL 2008
Porto, Portugal

British Society for Cell Biology
Warwick, UK

NUNO SEPÚLVEDA
*Diversity and shape of peripheral effector and regulatory T cell repertoires: validating the crossregulation model with experimental data**
*(co-author with Jorge Carneiro)
Society for Mathematical Biology Conference
Centre for Mathematical Medicine, Fields Institute, Toronto, Canada
July - 2 August, 2008

HELENA SOARES
Behind Microtubule dynamics: the puzzling players of the tubulin folding pathway.
Faculdade de Farmácia, University of Lisbon
10 October, 2008

NICO STOLLENWERK
Reinfection models, theory and applications: A colorful talk about SIRI.
European Conference on Mathematical and Theoretical Biology (ECMTB)
Edinburgh, Scotland
13 – 16 June, 2008

From dynamical processes to likelihood functions: an epidemiological application to influenza.
8th International Conference on Computational and Mathematical Methods in Science and Engineering (CMMSE)
Murcia, Spain
29 June – 4 July, 2008

ÉLIO SUCENA
O dilema do rato prisioneiro: Cooperar ou denunciar
Centro Ciência Viva
Bragança, Portugal
October, 2008

Drosophila dorsal appendages as a case-study of evolutionary novelty
Molecular basis of evolutionary innovations
Koln, Germany
November, 2008

ÁLVARO TAVARES
Studying mitosis in flies
David Glover 60th Birthday Symposium
Cambridge, United Kingdom
10 – 12 April, 2008

Molecular characterisation of Drosophila kinetochore
4th Spindle Dynamics Workshop
Kolympari, Greece
1 – 3 July, 2008

Human Mob1 genes regulate the transition from mitosis to interphase
EMBL PhD Students 2008 Retreat
Costa da Caparica, Portugal
5 – 7 September, 2008

Centrosomal human Mob1 is essencial for cytokinesis by destabilizing microtubules at the midbody
EMBO/EMBL Conference in Centrosomes and Spindle pole bodies, EMBL
Heidelberg, Germany
12 – 16 September, 2008

Identification and characterization of new kinetochore components
EMBO Workshop Chromosome Segregation : Centromeres and kinetochores
Arcachon, France
27 September, 2008

Identification and characterisation of new kinetochore components
IRB (Institute for Research in Biomedicine)
Barcelona, Spain
3 December, 2008

Drosophila Sgt1 is essencial for centrosome stability
University of Massachusetts Medical School
Worcester, USA
12 December, 2008

HENRIQUE TEOTÓNIO
Experimental reverse evolution in D. melanogaster
Annual Meeting of the Society for the Study of Evolution
Minneapolis, USA
June, 2008

Experimental evolution in C. elegans
C. elegans Topic Meetings: Development & Evolution
Madison USA
June, 2008

Experimental reverse evolution in D. melanogaster
ESF Workshop on Thermal Adaptation in Ectotherms
Wageningen, The Netherlands
October, 2008

SALVATORE VALITUTTI
Regulatory T cells maintain effector cells at check in NOD mice protected from Diabetes by LPS treatment
Universidade de Coimbra
Coimbra, Portugal
13 February, 2008

Visualising the dynamics of human Cytotoxic T Lymphocyte/melanoma cell interaction: multiple hits must be delivered for tumor cell annihilation
Universidade de Coimbra
Coimbra, Portugal
13 March, 2008

Regulatory T cells maintain effector cells at check in NOD mice protected from Diabetes by LPS treatment
XII National Meeting of Biology Students
Braga, Portugal.
18 March, 2008

Visualising CTL/melanoma cell interaction dynamics: need of multiple hits for tumor annihilation
XXXIV Meeting of the Portuguese Society for Immunology
Porto, Portugal
27 October, 2008

Visualising CTL/melanoma cell interaction dynamics: need of multiple hits for tumor annihilation
Faculdade de Medicina da Universidade de Lisboa
Lisbon, Portugal
12 December, 2008

STEFAN WIELAND
Disease Dynamics Through Coupling of Strain Mutation and Immune Response
4th PhD European Complexity School, Hebrew University
Jerusalem, Israel
September, 2008

Interplay of Disease Dynamics and Contact Network Structure.
Workshop "Facing the Challenge of Infectious Disease", ISI Foundation
Turin, Italy
October, 2008

KARINA XAVIER
Small non-coding RNAs controlling pathogenesis.
18th European Congress of Clinical Microbiology and Infectious Diseases.
Barcelona, Spain
19 – 22 April, 2008

Processing the inter-species quorum sensing signal AI-2.
Gordon Research Conference– Microbial Stress Response
Mount Holyoke College South Hadley, USA.
6 – 11 July, 2008

SANTIAGO ZELENAY
Thymocytes differentiate into protective Foxp3+ regulatory T cells upon peripheral pro-inflammatory immunization.
Immunity and Cancer Unit, Curie Institute
Paris, France
23 January, 2008

Thymocytes differentiate into protective Foxp3+ regulatory T cells upon peripheral pro-inflammatory immunization.
The Skirball Institute, New York University
New York, USA
9 April, 2008.

Thymocytes differentiate into protective Foxp3+ regulatory T cells upon peripheral pro-inflammatory immunization.
Pathology Department of the Massachusetts General Hospital, Harvard Medical School
Boston, USA.
12 April, 2008

Thymocytes differentiate into protective Foxp3+ regulatory T cells upon peripheral pro-inflammatory immunization.
Immune Disease Institute, Harvard Medical School
Boston, USA
13 April, 2008

Thymocytes differentiate into protective Foxp3+ regulatory T cells upon peripheral pro-inflammatory immunization.
Cancer Research UK
London, United Kingdom
25 July, 2008

Thymocytes differentiate into protective Foxp3+ regulatory T cells upon peripheral pro-inflammatory immunization.
ETH (Eidgenössische Technische Hochschule), Institute of Microbiology
Zurich, Switzerland
29 October, 2008

WORKSHOPS, COURSES AND MEETINGS

Towards a Unifying Theory of Cooperation and Mutualism
8 - 11 January, 2008
Organiser: Francisco Dionísio

Quantitative image processing
26 - 2 7 February, 2008
Organisers: Cell Imaging Unit
Imaging analysis, though very powerful, is also subject to several artifacts which have to be taken into account when considering experimental design and acquisition. Notwithstanding, it is the desirable method for acquiring information in microscopy. This course focused on the need of this approach, acquisition details and results obtained within this scope.

Influenzanet Meeting
29 February - 1 March, 2008
Organisers: Gabriela Gomes
This meeting brought together the Gripenet team and its European partners: De Grote Griep Meting (Netherlands and Belgium) and Influweb (Italy), as well as colleagues from the United Kingdom and Israel. A multidisciplinary atmosphere was created with science communicators, mathematicians, epidemiologists, biologists, physicists and informatics engineers. As a result a European platform was launched – Influenzanet. This platform aims not only to expand the self-reporting influenza monitoring programme throughout Europe, but also to be a vehicle for science communication and public engagement.

Meeting of Cysticercosis working group in Europe
11 - 12 March, 2008
Organisers: Michael Parkshous, with organisational support from the World Health Organization (WHO)/Food and Agricultural Organization of the United Nations (FAO) Collaborating Centre for Parasitic Zoonoses in Denmark and the University of Edinburgh, Scotland.
This meeting brought together representatives from various European-based institutes and organisations involved in cysticercosis research and control efforts, to exchange information about their various activities. The meeting was well attended by scientists actively involved with cysticercosis investigations in Europe, particularly in Spain and Portugal. The information provided served as a basis for discussion sessions aimed at finding ways to achieve a more effective, concerted approach to combating cysticercosis in Europe as well as in the main cysticercosis-endemic areas of Africa, Asia, and Latin America.

Computational and Theoretical Biology Open Day
13 March, 2008
Organisers: José Pereira Leal (IGC), Cláudio Soares (ITQB)
This Open Day was targeted at prospective MSc and PhD students, with the aim of raising awareness of the theoretical and computational biology research carried out at the Associated Laboratory of Oeiras (LAO).

Hippocampus workshop
31 March - 4 April, 2008
Organisers: Zachary Mainen (IGC/Champalimaud Foundation)
The main theme for this week-long course was spatial navigation, memory, and the hippocampus. The course ranged from the microcircuit to the behavioural level and embraced experimental as well as theoretical approaches. Besides standard lectures, the course included journal clubs, focus lectures (theoretical and experimental pairs of talks on the same subject), debate sessions (in which students will debate opposing views on a controversial topic) and evening lectures (off-the-mainstream lectures on exciting / emerging themes).

Cytometric Bead Array (CBA) Workshop
April, 2008
Organiser: Cell Imaging Unit
The CBA workshop was organised jointly with Enzifarma (Becton-Dickinson) mostly for people at the IGC to promote a technique which has become essential for detecting multi-cytokine panels directly from serum or culture. It is a flow-cytometry-based technique which reduces significantly time and cost compared with the standard Elisa procedures.

Evocell 2008
9 - 10 May, 2008
Organisers: José Pereira Leal
A workshop organised in the context of the PhD Programme in Computational Biology, open to the scientific community, and aimed at discussing the need for an evolutionary perspective in the understanding of cell biology.

IGC Scientific Advisory Board Meetings
19 - 20 May, 2008
Organiser: Antonio Coutinho

MRC-Gulbenkian PhD Student Conference
23 - 26 May, 2008
Organisers: IGC and MRC PhD students

Mini-symposium: Computational Psychiatry
26 - 30 May, 2008
Organisers: Quentin Huys and Zach Mainen
This one-week course aimed at the application of reinforcement learning (RL) to normal animal behaviour; to the main neuromodulatory systems of the brain; and, combining the two, finally to psychiatry. The course had a two-day overview over the fundamentals of classical animal learning theory and RL. Day three brought these together and introduced students to modelling of animal behaviour with RL tools, while day four made for discussion on the close relationship between RL and neuromodulation. The last day was devoted to a mini-symposium on "computational psychiatry", bringing together researchers working at the intersection of psychiatry, RL and animal behaviour.

Workshop "Bioinformática na escola – um ano de actividade"
4 June, 2008
Organisers: José Pereira Leal (IGC), Isabel Marques (IGC), Paulo Almeida (IGC)
This workshop aimed to evaluating one year of activity of the project *Bioinformática na Escola*, with the presence of teachers, students, the Municipality of Oeiras, and members of an Education Department section, CRIA-FCUL.

Practical Course on 3D Developmental Imaging - EMBO
23 June - 1 July, 2008
Organiser: Cell Imaging Unit
This practical course was focused on addressing several aspects of 3D imaging, with special emphasis on their application to the study of Developmental Biology. The course was aimed at young researchers in the Developmental Biology research field, interested in answering specific questions that require observation of cell movement and tissue morphogenesis in whole embryos, which are particularly difficult using conventional optical microscopy techniques. Participants had the opportunity to learn and test state-of-the-art techniques/protocols for imaging whole embryos (both fixed and live), and were expected to apply the techniques to their experimental model of choice, obtain high quality 3D images, learn to manage, process and analyse multi-dimensional data-sets, and learn strategies for publishing 3D images/movies.

1st meeting of the "Rede Nacional de Bioinformática"
9 July, 2008
Organisers: José Pereira Leal
The inaugural meeting of the national bioinformatics network, involving staff scientists and lab heads of the majority of Portuguese research groups working in the area of Bioinformatics.

First Portuguese Forum on Computational Biology
10 - 18 July 2008
Organisers: PhD Programme in Computational Biology
The forum aimed to launch and be the first edition of a regular annual gathering of Portuguese and international researchers to communicate and discuss recent progress and key issues in Computational Biology. It was an initiative of the students of the PhD Programme in Computational Biology, and jointly promoted by the FLAD Computational Biology Collaboratorium.
David Baker (Seatle), Marta Cascante (Barcelona) and Denis Noble (Oxford) gave keynote lectures and overviewed the latest developments on the topics of protein structure prediction, metabolomics, and integrative systems biology, respectively. About 34 invited researchers from Portuguese academic institutions "from north to south" gave short talks. The poster sessions, open to the community, included up to 56 posters on different topics. The 150 participants in the forum created a lively scientific environment during the three days of the conference.
http://bc.igc.gulbenkian.pt/fpbc2008/

Denguenet
18 July, 2008
Organisers: Gabriela Gomes (IGC)
Workshop with the Gripenet team and a Brazilian team of epidemiologists, physicists, and public health professionals, to develop an internet-based monitoring system for dengue in Brazil. The new system is motivated by Gripenet, successfully running in Portugal since 2005. The workshop was sponsored by the Brazilian Ministry of Health.

Evolution in Health and Disease
22 - 26 September, 2008
Organisers: Gabriela Gomes
A workshop combining two traditionally separate paradigms - infectious disease and cancer - in order to explore the increasingly appreciated overlap between them. The workshop brought together around 50 participants: experimentalists, mathematical modelers and epidemiologists from both paradigms. The workshop was sponsored by the European Commission - Marie Curie Actions.

Toll 2008 Meeting: Recent Advances in Pattern Recognition
24 - 27 September, 2008
Local Organiser: Miguel Soares

IGC Post-doc Retreat
3-5 October
Organiser: Rute Nascimento

Introduction to GIMP
15 October, 2008
Organiser: Cell Imaging Unit
GIMP is a freely distributed Image Manipulation Program. This course was aimed primarily at first-time GIMP users, those who have used other image editing tools but aren't sure how that knowledge translates to GIMP. The course covered the basics, namely creating graphics and logos, resizing and cropping photos, changing colors, combining images using a layer paradigm, removing unwanted image features, converting between different image formats, and more advanced topics, such as combining several images, adding text or lines, handling layers, adjusting brightness, contrast, and colors and simple fixes for problem photos.

Workshop on Cell Cycle, Cytoskeleton and Human disease
3 - 7 November, 2008
Organisers: Mónica Bettencourt-Dias (IGC)
This workshop was held within the context of the Gulbenkian/Champalimaud PhD Programme for Clinicians. Several IGC group leaders - Florence Janody, Lars Jensen, Rui Martinho, Miguel Godinho, Mónica Bettencourt-Dias - and leading international researchers - Tim Mitchison (Harvard), Erich Nigg (Martinsried), Karim Labib (Manchester), Martin Eilers (Marburg), Phong Tran (Philadelphia), Helder Maiato (Porto) - made up the faculty.

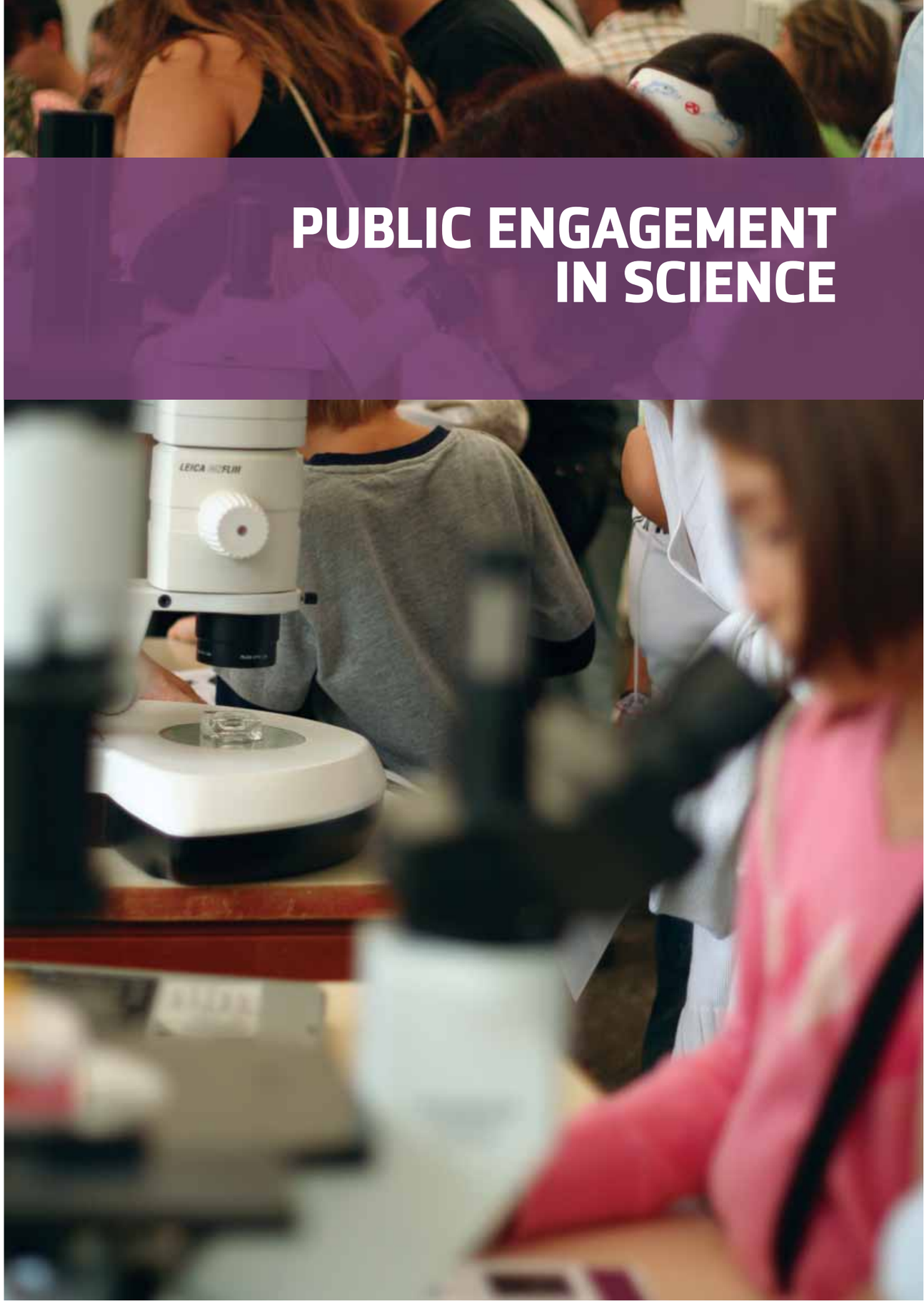
FP7 – Informative Session: The European Research Council Starting grants (call 2008)
5 November, 2008
Organisers: Sheila Vidal (IGC), Margarida Trindade (IMM)
The ERC Starting Grants are highly competitive grants which can provide young independent researchers (3 to 8 years after PhD) with up to 2 million euro funding for a maximum of 5 years. The aim of this work session was to inform and guide potential applicants (especially in the Life Sciences field) into the insights of the application procedure, with the aim of providing

rounding for successful applicaitons. The session was repeated at the Institute for Molecular Medicine, Lisbon, on the same day, in collaboration with the Communication and Training Unit.

PathProt-I
8 - 10 November, 2008
Organisers: Pedro Fernandes
The meeting, with 85 partcipants, was organised around the theme of Pathway Analysis, its intrinsic value, its current status and its future as we see it, in the direction of Systems Biology, with the aim to establish a common basis of understanding.
For two and a half days, more than 15 hours of scientific presentations and ample periods of discussion allowed participants to collect opinions for a white paper that summarised the progress that the meeting generated, centered on the identification of difficulties, priorities and needs.
Pathway Analysis of quantitative Proteomics data is making its way up in providing insight into the biochemical cascades, into establishing the state of the organism under study, as well as predicting the outcome of ongoing processes.

BioImaging Nano Courses
12, 19, 26 and 28 November, 2008
Organiser: Cell Imaging Unit
This course covered both the theoretical background and the practical hands on skills for a wide range of microscopy and imaging applications. Participants worked in small groups providing a well balanced mix of lectures and practical hands-on training always with a concentration towards the hands on. As a microscopy user, the participants had an excellent opportunity to learn about advanced techniques as well as use high-end systems such as confocal, live imaging, FRET, FRAP and advanced image processing and programming.

Gulbenkian Alumni Meeting (GAMeets – 4th edition)
27 December, 2008
Organisers: Vasco Barreto (IGC), Ana Godinho (IGC), Helena Soares (Pasteur Insitute, France), Sílvia Costa (ISPA, Lisbon)
GAMeets is an annual meeting of Gulbenkian Alumni, with the main aim of discussing key issues in research and science policy. It is also a forum for the Gulbenkian Alumni to meet each other regularly and network amongst themselves and with current IGC graduate students and researchers. The 2008 meeting was dedicated to Alternative Careers in Science. Several PhD holders were invited to give presentations on their experience in moving from active research to careers in publishing, consultancy, pharma, NGOs and science communication.



PUBLIC ENGAGEMENT IN SCIENCE

SCIENCE COMMUNICATION AND OUTREACH

Head: Ana Godinho
PhD in Developmental Neurobiology
University of London, UK
E-mail: agodinho@igc.gulbenkian.pt

Engaging the public in biomedical research and its funding is important to inform decision making both at the individual level, and around issues of public interest. The IGC implements a dedicated science communication and outreach programme, thus acknowledging that scientists are increasingly accountable in the public arena and indeed have become central actors in promoting informed discussion and debate with non-scientific audiences. The emphasis of the programme is on raising the profile of IGC research and promoting public participation in science and its funding, through two-way, dialogue-based interactions between researchers and students, and a range of audiences: the media, students, teachers, the general public and policy makers.

MEDIA RELATIONS
In 2008, we established a database of 32 national and international media outlets, including print, broadcast, online media and the national Portuguese news agency, Lusa. The IGC registered with the two major science news agencies - Eurekalert in the USA and Alphagalileo in Europe - thus reaching a population of over 6,600 and 7,000 reporters, respectively, in over 60 countries. We put out 13 media releases, covering scientific publications, awards and prizes, funding partnerships and outreach at the IGC. From these releases, a total of 123 news items, in print, broadcast and online outlets were monitored, the vast majority of which in Portuguese media. Coverage in Portuguese media included the major broadsheets, national television and radio. On two occasions coverage on the European Commission website, Cordis, was achieved.

	PORTUGUESE	INTERNATIONAL	TOTAL
Print	40	0	40
Broadcast	14	0	14
Online	60	9	69
TOTAL	**114**	**9**	**123**

In 2008 the IGC received eight spontaneous (i.e. not prompted by IGC media releases) media enquiries, from print and broadcast reporters. The enquiries included requests for interviews or expert opinions, for scientific props for a photo-shoot by a national broadsheet newspaper, and for a feature article by a student reporter for a teenage-targeted supplement of a major weekly Portuguese news magazine.

SCHOOL VISITS TO THE IGC
The IGC runs a programme of structured school visits, for students in the last four years of school, and undergraduates. Visits are structured around a general introduction to the IGC, by a science communication and outreach team member, followed by guided visits to research laboratories or facilities. The aims of these visits are to engage students and teachers with cutting edge research questions and approaches, through direct, two-way interactions with researchers.
In 2008, a total of 805 students visited the IGC, on 25 separate visits, throughout the year, with an average of two school visits per month. The largest number of visits (14 visits) was by students in their final year of high school (12º ano). These students (32%) and the 14-15 year old students (33%) together made up for 65% of the total student number visiting the IGC. In all, 25 different IGC research groups and/or facilities were visited; on average, each group/facility hosted two visits during the year.
Feedback from teachers (structured questionnaires) and students (informal feedback in post-it notes) has been positive: the vast majority of teachers

TEAM MEMBERS:
Maria João Leão (Post-doc, Fundraising Project Manager)
Sílvia Castro (Post-doc, Media Liaison Officer)
Filipa Barbosa (Post-doc, Schools Outreach Officer)
Sandra Moreira (Trainee, Designer)
Sara Catita (MSc Student)

(>90%) feel that the aims of the visits were achieved, would return to the IGC for another visit and would recommend the IGC to their colleagues. Students' feedback has also been overwhelmingly positive. Both teachers and students would like to have more hands-on experience during the visits.

SCHOOLS OUTREACH
During 2008, IGC researchers and the Science Communication and Outreach team developed several hands-on activities for schools, upon invitation form teachers and students:

'Fin regeneration in zebrafish', for 15 year olds
June, 2008
Escola Secundária Camões, Lisbon
Hands-on experiment into regeneration of zebrafish fins
Organisers: Paulo Raimundo (Zebrafish Facility), José Feijó (Plant Development)

'In touch with science' project developed by final year students (16-17 year old)
November, 2008
Escola Secundária do Marquês, Oeiras
A series of hands-on experiments: Gene Game; Immunology game; DNA extraction
Organiser: Filipa Barbosa (Science Communication and Outreach team)

SUMMER STUDENTS
In 2008, the IGC hosted three secondary school Summer students (in the Telomere and Genome Stability and Plant Development groups), and two undergraduate Summer students (in the Theoretical Epidemiology and Cell Cycle Regulation groups).

BIOINFORMATICS AT SCHOOL PROJECT
This project is being developed by the Bioinformatics and Computational Biology Unit. Its main aims are to provide bioinformatics resources for secondary-school, based on current research projects, with an aim to encourage and support enquiry-based learning of science in the classroom. In 2008, the pilot study, with three schools in and around Oeiras was completed, and a bioinformatics package completed for rollout to all schools, pending further funding.

RESEARCHERS' NIGHT 2008: SCIENTISTS ACROSS PORTUGAL
26 September, 2008 - Cultural Centre of Belém
Funding: European Commission Framework Programme 7, People programme (FP7-People) (http://ec.europa.eu/research/researchersineurope/)
Researchers' Night is an annual initiative aimed at bringing scientists and the public together, simultaneously across several European countries. In Portugal, the 2008 edition was organised and carried out by a consortium of three institutions: the IGC, the University of Oporto (www.up.pt) and Inova+ (www.inovamais.pt). In Lisbon, all events and activities were organised by the IGC, and included: the 'Real time scenctists blog', a fundraising Walk for Science, speed-dating with scientists, sci-art installations, hands-on experiments, a 'Scientists' Bands' stage and interactive science in the Champimóvel, provided by the Champalimaud Foundation.
This public engagement and fundraising event had 2000 visitors, of all ages, and over 100 researchers, across several fields of research and from a range of institutions, took part.

2008 IGC OPEN DAY
11 October, 2008
Funding: Oeiras Vive a Ciência Project (Oeiras City Council)
This was the 3rd edition of the annual IGC public open day, aimed at providing the public a glimpse of life at a research institute, and engaging them in research practices and issues. In all, 1140 visitors, of all ages, explored the research programmes at the IGC, through discussion and dialogue with IGC researchers, students and staff, hands-on activities modelled on actual experimental protocols, guided tours of selected IGC laboratories. Feedback from visitors, obtained through short questionnaires, reveals that 94% of respondents were either very satisfied or satisfied with the visit.

INSTITUTIONAL VISITS

In 2008, we organised, with the Director, two institutional visits, in which several Group Leaders took part. Both visits were structured around a general introduction to the IGC, by the Director and group leaders, followed by a guided tour to selected laboratories and/or facilities. The aim of both visits was to provide an overview of research carried out at the IGC and also of the ethos of the institute.

Hague Club
5 September, 2008
Speakers: António Coutinho, Miguel Soares, Mónica Bettencourt-Dias, Isabel Gordo, Jorge Carneiro, Lar Jansen, Zachary Mainen, Ana Godinho
Laboratory tours: Imaging Facility, Fly facility, Computational Biology, Neuroscience.

Calouste Gulbenkian Directors and Deputy-Directors
29 September, 2008
Speakers: António Coutinho, Miguel Soares, Mónica Bettencourt-Dias, Isabel Gordo, Jorge Carneiro, Florence Janody, Mathias Koeppen, Zachary Mainen, Ana Godinho
Laboratory tours: Imaging Facility, Fly facility, Plant facility, Computational Biology, Neuroscience

INSTITUTIONAL COMMUNICATION

The IGC Newsletter, Quinta Grande
In 2008 we launched the IGC Newsletter, 'Quinta Grande' ('Big Farm', in English - a play on the name of the street where the IGC is located, and the use of several animal models at the IGC). The newsletter aims to be a means of both internal and external communication: a forum to raise awareness of the activities of the IGC and, furthermore, provide insight into the day-to-day lives of IGC researchers and staff. The newsletter, published trimestrally, is available in English and Portuguese, in print (copy of 400) and online at http://www.igc.gulbenkian.pt/node/view/119.

PRESENCE AT 1ST SCIENCE JOB FAIR

Calouste Gulbenkian Foundation, Lisbon
17 December, 2008
Organised within the *Annual Meeting of the Associação de Bolseiros de Investigação Científica (ABIC)* this Job Fair was attended by final year undergraduates and recent graduates. The Science Communication and Outreach Team of the IGC was provided information on research programmes and PhD programmes available at the IGC.

COMMUNICATION OF CALLS FOR 2008/09 PHD PROGRAMMES:

The Science Communication and Outreach team was directly involved in:

- coordinating the design of posters for the three programmes: International PhD Programme in Multidisciplinary Life Science, PhD Programme in Computational Biology and Gulbenkian/Champalimaud PhD Programme in Neuroscience;
- liaising with Calouste Gulbenkian communications department to palce advertisements of calls in two national newspapers (Público and Diário de Notícias);
- placing of advertisements for calls in Nature;
- E-mailing the call to research institutes, universities and individual researchers, in Portugal and abroad.

FUNDRAISING

In 2008 we continued the public fundraising activiites begun in 2007 aimed at involving the scientific community, the private sector and the general public in funding for science.

Lisbon Mini- and Half-Marathon
15 March, 2008
A group of IGC scientists, staff, their friends and families, took part in the Lisbon half and mini Marathons. This was the first time that scientists from different leading research centres in Portugal came together to engage both scientists and the public in promoting biomedical research, in a relaxed atmosphere. Adidas, one of the major supporters of the Lisbon marathons, sponsored the IGC providing participants with specially designed T-shirts for the occasion.

Breaking down stereotypes of scientists: IGC scientists and festival goers 'speed-date' at the OptimusAlive!08 Oeiras music and arts festival.

Cycling for leukaemia research at Researchers' Night 2008.

The IGC - "Everything is New" Partnership and Optimus Alive! 08 Oeiras
8 - 10 July, 2008
We established a novel partnership between IGC and "Everything is New", promoter of Optimus Alive! 08 Oeiras, an international music and art event in Oeiras. This partnership ensured two one-year fellowships in Biodiversity, for recent graduates, and the presence of the IGC at the *OptimusAlive!08 Oeiras* music and arts event. The partnership was announced at a well-attended press conference, on 15 May.

The call for the fellowships had 74 applications from young graduates around the country. The fellowships were awarded to young graduates for research to be carried out in the Population and Conservation Genetics and Evolution and Development groups of the IGC, in collaboration with international institutions.

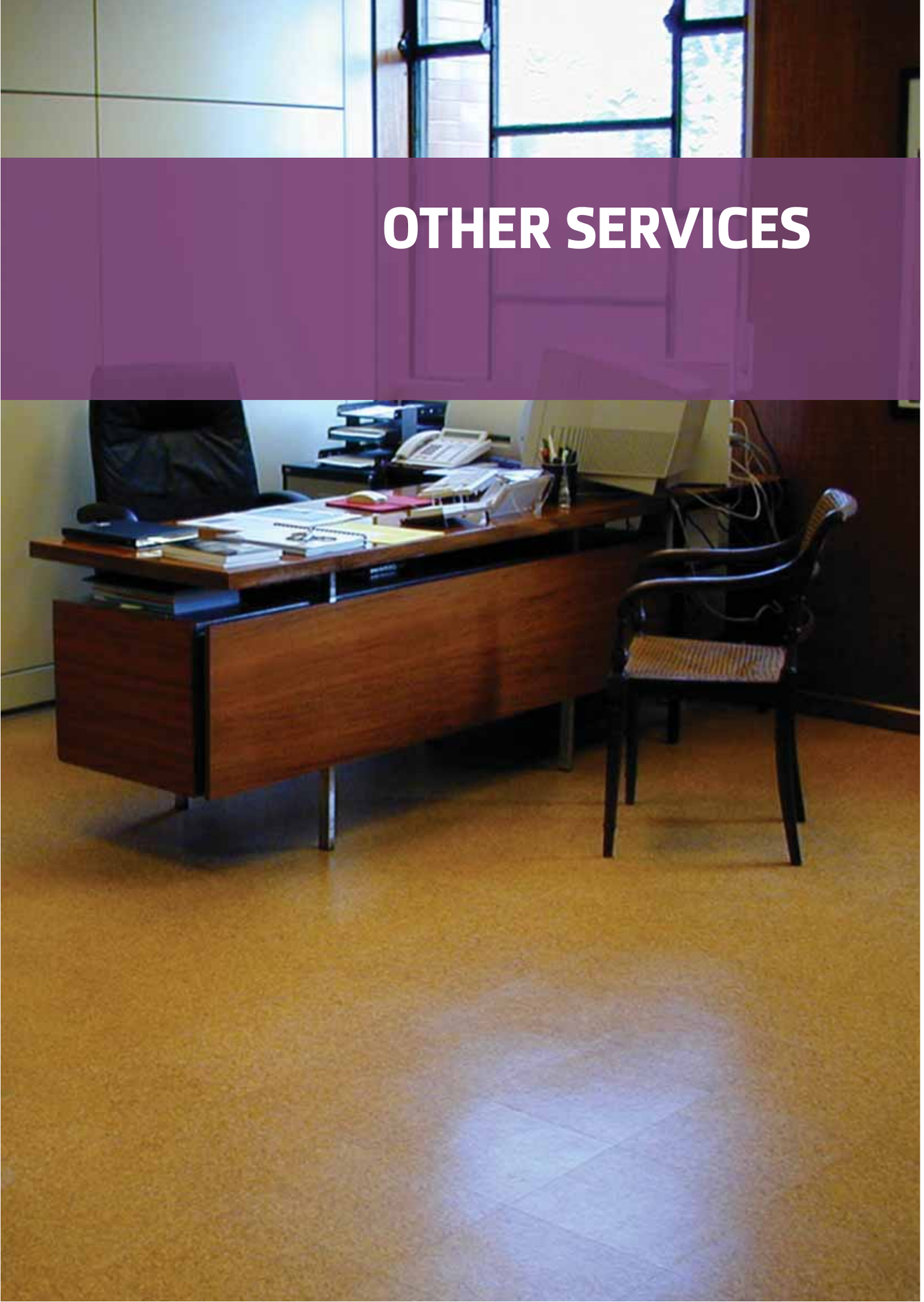
Over 700 visitors came through the IGC pavillion at *OptimusAlive!08 Oeiras* , taking part in the several activities that were available: speed-dating, scientific cooking, interactive games and sci-art installations. Around 80 scientists volunteered for this event. Two episodes of a weekly science magazine programme, on national TV, were recorded at the IGC pavillion. Feedback showed that the majority of visitors that returned the questionnaires were between 20 and 29 years old (51%/average age 24) and between 10 and 19 years old (30%/average age 17.04).

'Walk for Science' at Researchers` Night 2008
26 September, 2008
The 'Walk for Science' was a fundraising event created and held as part of Researchers' Night 2008, specifically to support leukaemia research. The money raised, €4000 in total, was delivered to the Associação Portuguesa Contra a Leucemia, a Portuguese leukaemia research charity. Visitors to Researchers' Night were invited to cycle and walk on treadmills to raise funds for leukaemia research. In return for a small donation, participants were given a T-shirts and automatic entry into a prize draw for a Researchers' Night 2008 bicycle. Both scientists and members of the public took part in the 'walk', so that the walk provided a unique opportunity not only to bring life scientists and the public together, in an informal and fun setting, but also to encourage the public to contribute to research funding.

Science Winter Fundraising Party at Majong Bar in Lisbon
5 December, 2008
This fundraising party was organised together with the IGC PhD students to raise funds for the 2nd PhD AMeeGuS meeting, via donations from attendees at the party. IGC research staff and general public were present at this event that also included projections of scientific images and movies.

IGC Calendar for 2009
December, 2008
A fundraising partnership between IGC and the Portuguese newspaper Público was established to advertise and distribute the IGC Science Calendar for 2009 across several cities in Portugal.

Partners and sponsors
Several partnerships and sponsorships have been established to support scientific research, education and science communication and outreach activities at IGC, either financially or in kind: Adidas, Associação Portuguesa contra a Leucemia (APCL), Associação Viver a Ciência (VaC), Bar Majong, Bio-Rad, Champalimaud Foundation, Évora City Council, Clarkemodet, Cooking Lab, Diário de Notícias, DELTA Cafés, Everything is New, Fundação Luso-Americana, Fundação PT, Lisbon City Council, Natura Algarve, NzyTech, Oeiras City Council, Portugal Telecom (PT), Público, Roche, SAPO, SATA, Siemens, Sportis, Unicer.



OTHER SERVICES

GRANT ADMINISTRATION
HEAD: SHEILA VIDAL
PhD in Drosophila Immunity
University Paris SUD XI , Paris, France
E-mail: svidal@igc.gulbenkian.pt

The Grant Administration office is responsible for identifying the best suited research funding opportunities in order to maximise the available public and private funding from various national and international grant programmes to IGC researchers. The office provides strategic support in all steps of grant applications (including filling administrative application forms and supporting grant writing and submission) and performing any necessary negotiations with the funding agency officials.

INFORMATICS
HEAD: JOÃO SOUSA
PhD in Theoretical Biochemistry
University of Lisbon, Portugal
E-mail: jsousa@igc.gulbenkian.pt

STAFF:
MANUEL CARVALHO (Informatics technician)
ANA MAYA (Informatics technician)
JOÃO GARCIA (Systems and database administrator)

The Informatics Technical Infrastructure (ITI) manages the computer and network infrastructure of the IGC, maintaining almost all of the central and administrative IT of the institute.

ADMINISTRATION AND ACCOUNTS
JOÃO NUNES
VITOR SANTOS
ANA LÍCIA PIRES
ANA MARIA SANTOS
FÁTIMA MATEUS
JORGE COSTA
INÊS CARVALHO

DIRECTION SECRETARIES
GRETA MARTINS
MARIA MATOSO (left March 2008)
ANA PAULA PIRES

LIBRARY
MARGARIDA MEIRA (Librarian)

LABORATORY TECHNICAL STAFF
ANA HOMEM
JÚLIA LOBATO
NUNO MORENO
ROSA MARIA SANTOS
CARLA RODRIGUES
FRANCICO HENRIQUES
NUNO MORENO
PEDRO ANACLETO
TATIANA ROCHA
PAULO DUARTE
TERESA GOMES

SUPPORT STAFF
ANTÓNIO SOUSA (Maintenance)
CARLOS NUNES (Driver)
TERESA SOUSA (Reception)
ABÍLIO SIMÕES (Stores)

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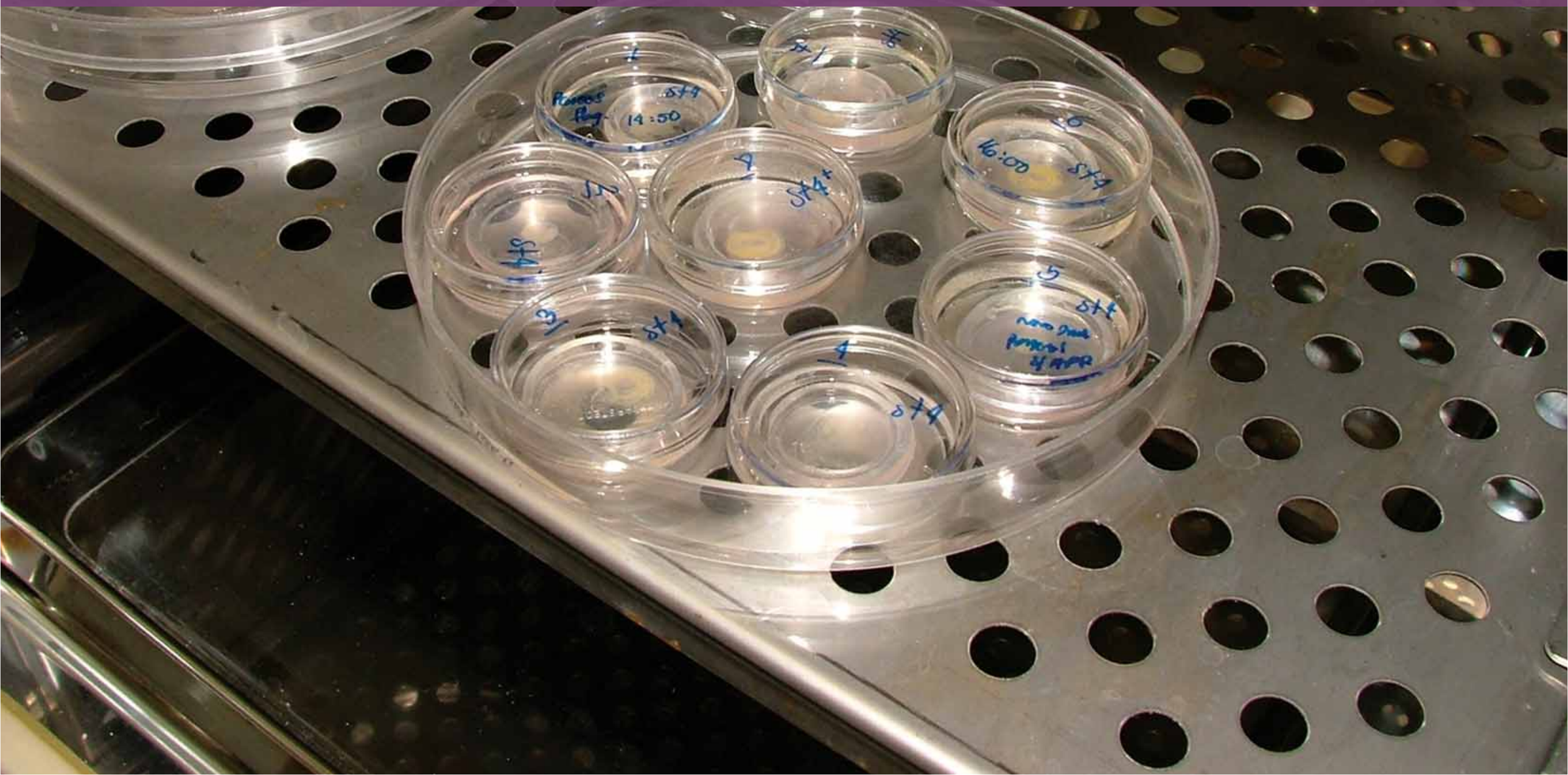

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PROJECT MANAGER
ANA GODINHO, Instituto Gulbenkian de Ciência

EDITING
ANA GODINHO
SÍLVIA CASTRO

LAYOUT AND DESIGN
DESIGNWAYS

PRINTING
TEXTYPE

The Instituto Gulbenkian de Ciência Annual (IGC) Report is also available to download from the IGC website at www.igc.gulbenkian.pt.

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Instituto Gulbenkian de Ciência
Rua da Quinta Grande, 6
2781-156 Oeiras
Portugal
Tel.: +351 21 440 7900
Fax.: +351 21 440 7970
E-mail: info@igc.gulbenkian.pt
www.igc.gulbenkian.pt

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Instituto Gulbenkian de Ciência

ADD Rua da Quinta Grande, 6
2780-156 Oeiras, Portugal

TEL +351 21 440 7900 FAX +351 21 440 7970

EMAIL info@igc.gulbenkian.pt

WEB www.igc.gulbenkian.pt