

FUNDAÇÃO CALOUSTE GULBENKIAN

**INSTITUTO GULBENKIAN de CIÊNCIA**

**ANNUAL REPORT**

**1999**

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*This Report can be consulted at the IGC website: <http://www.igc.gulbenkian.pt>*

## **TABLE OF CONTENTS**

THE FUNDAÇÃO CALOUSTE GULBENKIAN

BOARD OF ADMINISTRATION

INSTITUTO GULBENKIAN DE CIÊNCIA

BOARD OF DIRECTORS

SCIENTIFIC ADVISORY BOARD

STAFF

UNITS AND SERVICES

INTERNATIONAL RESEARCH STRUCTURES

NATIONAL RESEARCH STRUCTURES

INSTITUTIONAL AGREEMENTS

ACTIVITIES

SUMMARY

INTRODUCTION

RESEARCH

PROJECT REPORTS

PUBLICATIONS (1998-1999)

PUBLICATIONS FROM LAST YEAR'S REPORT

PARTICIPATION OF IGC IN SCIENTIFIC MEETINGS

TEACHING

THE GULBENKIAN PhD PROGRAMME (PGDBM)

SCIENCE TEACHING AND SCIENCE & SOCIETY

THESES

PARTICIPATION IN ACADEMIC COMMITTEES

HONOURS AND AWARDS

ORGANIZATION OF SYMPOSIA AND CONFERENCES

## SEMINARS AT THE IGC

**BOARD OF ADMINISTRATION  
OF THE  
FUNDAÇÃO CALOUSTE GULBENKIAN**

The Fundação Calouste Gulbenkian, established by Calouste Sarkis Gulbenkian by his Will dated June 18, 1953, is a private Institution of general public utility, endowed with legal personality. The aims of the Foundation are charity, art, education and science. The members of the Board of Administration in 1999 were:

Doutor Victor de Sá Machado (Chairman)

Dr. José Blanco

Dr. Pedro Tamen

Dr. Mikhael Essayan

Dr. Emílio Rui Vilar

Prof. Doutor Diogo de Lucena

Dra. Isabel Mota

## **BOARD OF DIRECTORS**

The Board of Directors for the Instituto Gulbenkian de Ciência (IGC) ensures that the activities at the Institute follow the guidelines and objectives defined by the Board of Administration of the Calouste Gulbenkian Foundation. The members of the Board of Directors for 1999 were:

Dr. Emílio Rui Vilar (Chairman)  
Prof. Doutor António Coutinho  
Prof. Doutor João Caraça  
Prof. Doutor Manuel Rodrigues Gomes  
Dr. Horácio Menano  
Dr. Manuel Carmelo Rosa

The Board of Directors met at the IGC on March 25, 1999.

## **SCIENTIFIC ADVISORY BOARD**

The Scientific Advisory Board of the IGC scrutinises the scientific progress and teaching programmes, as well as the recruitment and activity of personnel and research groups. The Scientific Advisory Board also advises the Board of Administration of the Fundação Calouste Gulbenkian on all matters relevant to the mission of the Institute. The members of the Scientific Advisory Board for 1999 were:

Prof. Sydney Brenner (Chairman)  
Prof. Nicole Le Douarin  
Prof. Martin Raff  
Prof. Susumu Tonegawa  
Prof. Hans Wigzell  
Prof. Lewis Wolpert  
Prof. Kai Simons

The Scientific Advisory Board met at the IGC on May 27-28, 1999. Prof. Kai Simons joined the Board in 1999, after the meeting.

## **STAFF**

### **DIRECTOR**

António Coutinho

### **DEPUTY-DIRECTORS**

Sérgio Gulbenkian

Maria José Marinho (to her retirement in December 1999)

José Mário Leite (from January 2000)

### **RESEARCH MEMBERS**

The IGC is not divided into departments, and its scientific activities are not organised in rigid hierarchical structures; research is autonomously conducted by individual scientists who are free to associate in projects and groups; there are no designations other than “member” of the scientific personnel. It should be noted that nearly all the scientists at the IGC are affiliated at other institutions or supported by national or international organisations; these are indicated in parenthesis. Some of those listed below were present at the IGC for only part of the year.

José António Belo (FCG)

Sergiy Bobrovnyk (Palladin Inst. Biochemistry, Kiev/OTAN)

Jorge Carneiro (FCT)

António Gil Pereira de Castro (FCT)

Pierre-André Cazenave (Univ. de Paris VI/Inst. Pasteur/CNRS /FCT)

Sukalyan Chattergee (FCT)

Mário Arala Chaves (ICBAS)

Melvin Cohn (Salk Inst./FCT)

Suzanne Bourgeois Cohn (Salk Inst.)

António Coutinho (CNRS/FCG)

Luísa Cyrne (FCUL)

Jocelyne Demengeot (FCT)

José Faro (Univ. Salamanca/FCT)

José Feijó (FCUL)

Lisete Fernandes (FCUL)

Carlos Alberto Ferreira (HUSM)

Constantin Fesel (Weizmann Institute/FCG)

Carlos Penha Gonçalves (Umea Univ./Min. Defesa/FCG)

Alf Grandien (Stockholm Univ.)

Zvi Grossman (Tel Aviv Univ./FCT)  
Paulo Guerreiro (Esc. Sup. Tec. Saúde Lisboa)  
Sérgio Gulbenkian (FCG)  
Matthias Haury (FCG)  
Veronique Havelange (Univ. Tech. Compiègne)  
Dan Holmberg (Umea Univ./FCT)  
Shohei Hori (Tokyo Univ./FCG)  
Rodney Langman (Salk Inst./FCT)  
Isabel Solange Oliveira (Univ. Évora)  
Joaquim Sainhas de Oliveira (Fac. Motricidade Humana)  
Isabel Palmeirim (FCG)  
Sylviane Pied (INSERM/FCT)  
Claudina Rodrigues-Pousada (FCG/ICBAS)  
Tomaz Mota Santos (Univ. Fed. Minas Gerais/CAPES)  
Helena Soares (Esc. Sup. Tec. Saúde Lisboa)  
João Pedro Simas (ICBAS)  
Charles Steinberg (Basel Inst. Immunology/UCSF/FCT)  
John Stewart (Univ. Tech. Compiègne/CNRS/FCT)  
Alvaro Augusto Tavares (IST)  
Solveig Thorsteinsdottir (FCUL)  
Tatiana Vassilevskaia (Associação de Protecção do Diabético de Portugal)  
Nelson Vaz (Univ. Fed. Minas Gerais)  
Astrid Moura Vicente (FCT/Instituto Piaget/FCG)  
Luisa Mota Vieira (Hospital Ponta Delgada)  
Paulo Vieira (FCG)  
Gillian Wu (Univ. Toronto)

## **STUDENTS**

The following students worked at the IGC for all or part of the year.

### **Ph.D. Students**

Fernando Afonso (FMVUTL)  
Dulce Azevedo (ICBAS/FCT)  
Vasco Barreto (Univ. Paris VI/PGDBM)  
Carla P. Barroso (FCUL/FCT)  
Catja Behrschmidt (Univ. Cologne)  
Evguenia Bekman (ICBAS/FCT)  
Marie-Louise Bergman (Univ. Umea)  
Déborah Braun (Univ. Paris VI/École Normale Supérieure)  
Caroline Brissac (Univ. Paris VII/ Inst. Pasteur)  
Alexandre Michelato Bubel (Univ. São Paulo)  
Ana Sofia Cachaço (FCUL/FCT)

Susana Gomes Campino (FCUL/FCT)  
Iris Caramalho (ICBAS)  
Thiago Lopes Carvalho (Univ. Estadual Campinas/FCG/FCT)  
Cristina Casalou (FCUL/FCT)  
Ana Catarina Certal (FCUL/FCT)  
Manuel Cunha e Sá (FCMUNL)  
Margarida Duarte (LNIV)  
Constantin Fesel (Weizmann Institute)  
Mário Rui Filipe (FCUL)  
Orfeu Flores (FCTUNL)  
Ana Cristina Gaspar (FCUL/FCT)  
Susana Godinho (FCUL)  
Kalet León Monzón (Univ. Havana)  
Leonor Orge (LNIV)  
João Pedro Pereira (ICBAS/FCT)  
M<sup>a</sup> Gabriela Rodrigues (FCUL)  
Nélson Saibo (ICBAS/FCT)  
Gabriela Silva (FCUL/FCT)  
Rui M. Silva (FFUL)  
João Sousa (FCUL/Inst. Rocha Cabral/FCT)  
Victor Hugo Sousa (FCUL/EMBL))  
Ing-Marie Sundqvist (Univ. Umea)

### **M.Sc. Students**

Sónia Marlene Martins (Univ. DeMontfort, Leicester)

### **B.Sc. Students**

Nuno Duarte Afonso (FCUL)  
Ricardo Bandarrinha (FCUL)  
Ana Cristina Borges (FCUL)  
Sofia Cordeiro (FCUL/FCT)  
Sílvia Pereira Costa (FCUL)  
Nádia Silva Duarte (FCUL)  
Mariana Faria (FCUL)  
Luís Figueiredo (FCUL)  
Sara Cristina Pinto Garcia (FCTUNL)  
Pedro Geraldès (FCUL)  
Maria João Grade Godinho (Univ. Évora)  
Brigitte de Lima (FCUL)  
Vanessa Zuzarte Luís (FCUL)  
Ana Margarida Prado (FCUL)  
João Pedro Preto (FCUL)  
Mónica Cruz Rosa (FCUL)

Rui Soares (FCUL)  
Ana Maria Vieira (FCUL)  
Cláudia Vieira (FCTUNL)

### **OTHERS**

The IGC benefits from a large number of visitors/students each year. Most come to follow up collaborations with colleagues at the IGC. Visitors listed here did laboratory or theoretical work at the IGC during 1999.

Marta Agostinho (FCUP/FCT)  
Sebastien Bagot (Inst. Pasteur Paris, Hosp. Pitié-Salpêtrière)  
Fernanda Maria Bajanca (FCUL/FCT)  
António Bandeira (CNRS/Inst. Pasteur)  
Marta Ribeiro Barreto (FCT)  
Leonor Boavida (FCUL/FCT)  
Manuela Broco (FCUL/FCT)  
Magda Carlos (FCT)  
Dina Carrilho (ITQB)  
Claudia Rocha Carvalho (Univ. Fed. Minas Gerais)  
Luciana Maria G. da Costa (FCTUNL)  
Ana Margarida Coutinho (FCT)  
Rodrigo Cunha (FCUL)  
Ana Isabel Pereira Duarte (FMUL)  
Maria do Carmo Fonseca (FMUL)  
Catarina Elias de Freitas (FCUL/IGC)  
Caren Furlonger (Ontario Cancer Institute)  
Alexandre Delaunay Gomes (EAN)  
Tracy Nevitt Gonçalves (UEG/IGC)  
Domingos Henriques (FMUL)  
Patrícia Madureira (FCT)  
Sara Lopes Marques (FLAD)  
Sofia Bizarro Nolasco (FCT)  
Vanessa Oliveira (FCT)  
Stacy Olson-Hirano (Ontario Cancer Institute)  
Ana Pinto (ISA)  
Sofia de Albuquerque Rodrigues (FCUL/IGC)  
Daniel Mota Santos (Univ. Fed. Minas Gerais)  
Valerie Soulard (Inst. Pasteur Paris, Hosp. Pitié-Salpêtrière)  
Bruno Verdolim (Univ. Fed. Minas Gerais)

## **Abbreviations**

CNRS	Centre National Recherche Scientifique (France)
DGV	Direcção Geral de Veterinária
EAN	Estação Agronómica Nacional
FCUL	Faculdade de Ciências da Universidade de Lisboa
FCUP	Faculdade de Ciências da Universidade do Porto
FMUL	Faculdade de Medicina da Universidade de Lisboa
FCMUNL	Faculdade de Ciências Médicas da Universidade Nova de Lisboa
FCT	Fundação para a Ciência e Tecnologia
FCTUNL	Faculdade de Ciência e Tecnologia da Universidade Nova de Lisboa
FMVUTL	Faculdade de Medicina Veterinária da Universidade Técnica de Lisboa
FFUL	Faculdade de Farmácia da Universidade de Lisboa
IBMC	Instituto de Biologia Molecular e Celular da Universidade do Porto
ICBAS	Instituto de Ciências Biomédicas Abel Salazar
INSA	Instituto Nacional de Saúde Dr. Ricardo Jorge
ISA	Instituto Superior de Agronomia da Universidade Técnica de Lisboa
INSERM	Institut National de la Santé et de la Recherche Médicale
ISCE	Instituto Superior de Ciências Educativas
ITQB	Instituto de Tecnologia Química e Biológica
LNIVL	Laboratório Nacional de Investigação Veterinária de Lisboa

## **ADMINISTRATIVE, SECRETARIAL AND TECHNICAL STAFF**

The administrative, secretarial, and technical staff of the IGC provides support to the research and teaching activities. Everyone here worked at the IGC for all or part of 1999.

### **Administrative and Secretarial Staff**

Ana Paiva Brandão  
Manuel Carvalho  
Manuela Cordeiro  
Jorge Costa  
António Croca (retired December 1999)  
Alcino Gonçalves  
Fátima Mateus  
Helena Matias (left September 1999)  
Maria Matoso  
Greta Martins  
João Nunes  
João Pinheiro (retired July 1999)  
Ana Lícia Pires  
Manuela Ramalho  
Ana Maria Santos  
M<sup>a</sup> Eduarda Santos  
Abílio Simões  
Teresa M<sup>a</sup> Sousa  
Lurdes Torres  
Maria Vasconcelos

### **Laboratory Technical Staff**

M<sup>a</sup> Ressurreição Alpiarça  
Dolores Constantino  
Ana C. Homem  
Bruce Lenhart  
Júlia Lobato  
Isabel Marques  
Rute Marques  
João Romão (retired May 1999)  
Rosa M<sup>a</sup> Santos  
Urbino Santos (retired December 1999)  
Maria Dolores Venâncio (retired December 1999)

### **Technical Support Staff**

Luís Arroja (left December 1999)

José A. Correia

Jaime Telmo Costa (retired December 1999)

Joaquim F. D. Gafaniz (left December 1999)

António Gomes

Fernando Lapa (left July 1999)

António C. Ligeiro

João Carlos Lopes

Paulo J. L. Martinho

Carlos Nunes

Carlos Pires (left December 1999)

João António B. Pires

António Sousa

Vítor Varão

## **UNITS AND SERVICES**

The IGC has set up and runs a series of differentiated Services and research-supporting Units that are manned, operated and financed under institutional responsibility. These Services and Units provide regular scientific and technological expertise and advice, as well as personnel support, to the researchers at the IGC and elsewhere in the campus, while open to others in Portugal and abroad.

### **Cell Imaging**

Sérgio Gulbenkian/Matthias Haury

### **Genetic Manipulation of Mice and Rats**

Paulo Vieira

### **DNA Sequencing and Genotyping**

Claudina Rodrigues-Pousada (to her retirement in December 1999)

Carlos Penha Gonçalves (from January 2000)

### **Bioinformatics**

Pedro Fernandes

### **Library and Scientific Information**

Pedro Fernandes

### **Animal Facility**

João Romão (**to his retirement in May 1999**)

Bruce Lenhart/Carlos Penha Gonçalves (from June 1999)

## **INTERNATIONAL RESEARCH STRUCTURES AT THE IGC**

### **European Mouse Mutant Archive (EMMA)**

The Unit for Genetic Manipulation of Mice and Rats has joined the European Mouse Mutant Archive (EMMA) in 1997, as one of its 5 “nodes”: CNR, Montorotondo, Italy; CNRS, Orleans, France; MRC, Harwell, UK; IGC, Oeiras, Portugal; Karolinska Institute, Huddinge, Sweden. The specific mission of the IGC Unit within EMMA is the transfer to germ-free conditions of targeted mouse lines with immunological defects. 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 special transportation at the risk of losing the “germ-free” condition, the IGC decided to open its laboratories and facilities to external scientists engaged in these studies.

### **Laboratoire Européen Associé CNRS “Génétique et développement de la tolérance naturelle “**

The LEA CNRS (Centre National de Recherche Scientifique) was created at the IGC by an agreement between several French and Portuguese organisations, aiming at synergising human competencies and resources in research on the genetic and developmental aspects of immunological tolerance. The LEA was created for a 4-years period, and its scientific activity will be submitted to evaluation after 2 years. António Coutinho was appointed Director of the LEA and several international experts accepted to join the respective Board. The agreement was signed at the IGC on September 21, in the presence of the Minister of Science and Technology of the Portuguese Government, and the French Ambassador in Lisbon, by the Directeur-General de l’Institut Pasteur, the Directeur du Département des Sciences de la Vie du CNRS, the Vice-President de l’Université Pierre et Marie Curie, the Presidente da Fundação para a Ciência e Tecnologia, the Presidente do Instituto para a Cooperação Científica e Tecnológica Internacional, and the Administrador para a Ciencia do Conselho de Administracao da Fundação Calouste Gulbenkian. Several of the scientists from the participating French laboratories were also present and, together with colleagues at the IGC, presented the scientific programme of the laboratory.



## **NATIONAL RESEARCH STRUCTURES AT THE IGC**

### **Unidade de Investigação da Fundação para a Ciência e Tecnologia “Tolerância natural”**

This Unit was created in 1999 to begin operation in 2000, after the positive report of the international committee appointed by the FCT for a site visit at the IGC. The research programme of the Unit, involving some 15 scientists at the IGC and several collaborations in other institutions, concerns immunology, virology, and genetics of autoimmune diseases in mouse and man. The Unit has launched collaboration programmes with several Portuguese institutions (Associação de Protecção do Diabético de Portugal, Associação dos Doentes de Lupus, Hospital Pediátrico de Coimbra and Núcleo de Investigação at the Hospital do Divino Espírito Santo, Ponta Delgada, Azores).

## **INSTITUTIONAL AGREEMENTS**

### **Faculdade de Medicina da Universidade de Lisboa and FCG/IGC**

A cooperation agreement between the Faculdade de Medicina da Universidade de Lisboa and the IGC was signed on 2 March 1999, by the Chairman of the Board of Directors of the Faculdade de Medicina and the Director of the IGC. The protocol aims at improving the utilisation of resources at each of the institutions in various scientific and pedagogic projects.

## **SUMMARY**

Along 1999, the reform of the IGC continued as planned. The Board of Administration of the Fundação Gulbenkian having approved a significant investment in the reconstruction of laboratories and in the acquisition of equipments, nevertheless maintaining the Institute's operation budget, has allowed for a sustained recovery of activity. The re-structure that was conducted in 1997 had prepared the Institute for a profound renewal. Early in 1998, the IGC was essentially empty of scientists, research groups, and laboratory equipments; its staff and services were to be adjusted, and adapted to a novel organisation and to other types of research and teaching activities; all its spaces were in urgent need of reconstruction, dated by over 30 years of design and utilisation with less than optimal maintenance. The strategic decision was taken to proceed stepwise with the reconstruction and re-equipment, and to launch new research activities as soon as laboratory spaces would become available. This decision has proved appropriate, already in 1999: it avoided a long period of complete institutional inactivity, it fostered the renewed motivation of the staff, and it allowed for reaching minimal levels of operation in a very short time. Thus, in 1999, while working at only some 25% of its capacity, the "new" IGC has already become an attractive scientific institution, as judged by several objective criteria: the interest of Portuguese and foreign research groups in joining the Institute, the results of several formal evaluations on our plans and activity that were conducted by national and international research organisations, the critical opinion of the Institute's Scientific Advisory Board, but also by the vitality of the intellectual environment and daily scientific activity, by our competitiveness in the search of external grant support, even by the emergent scientific production reflected in publications and in the participation of IGC's scientists in national and international meetings and conferences. We are well aware, however, that bringing the Institute to a relevant position in the international community, characterised by a profile of "thoughtful science" and better qualitative and quantitative levels of activity, will take much longer. Recent examples in Portugal indicate that more than 6 years are required for establishing similar research institutions, even if based on groups previously formed at the Universities. Every one at the IGC is motivated to try to shorten this period.

As to infrastructures, a new wing of laboratories was open and equipped, while another one was brought close to completion, new systems for safety and security were installed, and a complete face-lifting of the main laboratory buildings was carried out. The plans for the renewal of the animal facilities, of the cafeteria/lecture rooms building, and of two other wings were completed. The installation of the Units for Cell Imaging and for DNA Sequencing and Genotyping was completed, with the multiphoton confocal microscope and the high-speed cell sorter entering regular operation, and with the acquisition of

another automatic DNA sequencer.

A total of 13 functionaries in several services at the Institute retired during the year, and 2 were recruited. Several new research groups were installed in the respective laboratories and initiated their research activities. By the end of the year, there were 11 research groups working at the IGC, and a total of 75 scientists and students worked here on a regular basis. The policy of receiving short and long-term visitors was actively pursued with the support of the Fundacao para a Ciencia e Tecnologia, such that the total number of scientists and students who worked at the Institute in 1999 actually reached 128. Two new research structures were open at the IGC, after evaluation of the research proposals by the respective committees: in September, a Laboratoire Européen Associé was created by the Centre National de la Recherche Scientifique in co-operation with the Institut Pasteur, the Université de Pierre et Marie Curie, the Fundação para a Ciência e Tecnologia, the Instituto para a Cooperação Científica e Tecnológica Internacional, and the Fundação Calouste Gulbenkian; in November, a Unidade Plurianual de Investigação of the Fundação para a Ciência e Tecnologia was approved to start operating in 2000.

The research at the Institute was consolidated around the topics that were previously defined: genetics of complex human autoimmune diseases, molecular and cellular analysis of immunological tolerance and autoimmunity, genetic basis of susceptibility/resistance to infections in mouse models, molecular basis of virus/host interactions, molecular and cellular biology of the cytoskeleton, developmental biology in animals and plants. The first publications describing the work done here have appeared in the respective specialised international journals, and the scientific life at the IGC entered its normal rhythm, with two or more institutional seminars/week, and multiple group seminars and journal clubs.

Teaching activities at the Institute were centred on the Gulbenkian PhD Programme in Biology and Medicine, of which the 6th class completed the year of graduate teaching, and the 7th was initiated. The Programme continued to count on a large faculty of teachers and instructors, for a total of 162 along the year. As in previous years, number of thematic “modules” of the Programme were open to application and attendance by external scientists and students. Several sessions for biology teachers on “Biology in modern times” were held, and visits of a large number of secondary school students were organised. The Institute organised, alone or together with the Science Sector of the Fundacao Gulbenkian, several international symposia and workshops bringing to Portugal a considerable number of highly respected scientists in neurosciences, immunology, developmental biology and evolutionary genetics.

The continued support of the Fundação Gulbenkian, the encouragement and guidance we receive from its Board, as well as the generous collaboration and expertise provided by the various Sections and Services at the Fundação, are deeply acknowledged by all of us at the Institute.

## **INTRODUCTION**

The Gulbenkian Science Institute (IGC, for Instituto Gulbenkian de Ciência) represents the direct intervention of the Calouste Gulbenkian Foundation in science, one of its four statutory areas. The Institute is primarily dedicated to research and post-graduate education in biology and biomedicine, while attending to the education of biology teachers and of laboratory technicians, as well as to the public understanding of science. Keeping its specificity, the IGC collaborates closely with other Sectors in the Foundation (Science, Health and Social Protection, Education) and with the public authorities, in order to promote those goals.

### “Pour l’honneur de l’esprit humain”

Scientific research strives for knowledge, for the understanding of this universe where life appeared, of the world around us, and of ourselves. The very first goal of scientific research is, therefore, a grand project of mankind: to gain ground to ignorance and to further advance the frontiers of knowledge, to define the fundamental questions at each moment in History, to understand where we come from, and what we are. In contrast with other “forms of knowledge” and explanations of the world that do not progress – Nostradamus’ astrology is as “advanced” as that of contemporary future-tellers - scientists “stand on the shoulders of giants”: scientific research departs from an ever wider and stronger body of knowledge, and it addresses questions that are progressively more complex and fundamental, such that scientific knowledge produces answers that are progressively more exact and general. This is only possible through a universal process of validation of the explanations of the world - the scientific method - that promotes hypotheses or individual “opinions” to “verifiable evidence” and is thus accepted by everyone who wants to use reason (that is, be rational and reasonable). In principle, however, all accepted scientific

explanations are destined to be corrected, improved, included in the frame of wider “truths”, or even to be falsified and excluded. Hence, scientific knowledge grows in the domain of doubt, and the quality of scientists is largely dependent on their ability to “manage” plausibility versus unlikelihood, as well as the risk of novelty versus the security of accepted concepts.

The understanding of nature, its composition and organisation, to know ourselves and the world, are also the object of philosophy, and Ionian philosophers were the first scientists in History, for they launched the search for natural explanations of the phenomena around us, abandoning previous approaches based on supra-natural causes, derived from beliefs and dogmas. The progress of natural science in modern times, however, has progressively conquered that objective from philosophy and occupied that cultural space, often with the full agreement of the philosophers themselves, some going as far as to suggest that science alone has legitimacy to speak of reality, while philosophy would have no other role but to clarify, unify and organise language. Although this position is not universally accepted, it is unquestionable that natural science serves in modern societies at least part of the role that philosophy played for some 2,500 years. The process of scientific inquiry shares with philosophical thinking the requirement for internal coherence, but it additionally relies upon experimental observation that reveals “the book of nature” and serves as a method for universal validation. This specific process of validation of knowledge also demarcates scientific research - as a human manifestation of explanatory creativity - from “the arts” that wish to explain the world by “recreating” it in a most individual manner. Thus, short of that process of universal validation, the value of each contribution in the arts remains a matter of equally individual opinions, that can not be “validated” but by “l’air du temps” and public success. The knowledge and understanding of the world that are produced by science are transferred outside the scientific community, notably to the younger generations, thus integrating and progressively enriching our common “culture”. This greater understanding of the world and of ourselves is one of the absolute values of knowledge, a sign of maturity of human kind.

Knowledge of the universal laws of life and of the universe, produced by biology and physics, also provides the bases for all technological advances that, in turn, are the motor of individual and social progress and welfare, and of economic development as well. Today, all technological “inventions” require a very solid basis of scientific competence and, therefore, scientific research is the ultimate basis for economic development and social progress. While modern science and technology are thus “co-constituted” and inseparable, the two are distinct, however, and it will always be fundamental to promote the understanding of the respective differences. Science generates knowledge, irrespective of whatever we can do with it; in the words of Jacobi to Legendre

more than 150 years ago, “le seul but de la science est l’honneur de l’esprit humain”. In contrast, technology aims at using the regularities and laws of nature to the profit of the user, irrespective of any knowledge or understanding of those regularities and laws. Among the many reasons why science and technology have to be distinguished, two are particularly relevant today. First, while it will always be absolutely crucial to ensure the progress of knowledge and thus fight all attempts to restrict scientific research, it will be also necessary that society decides upon, and often limits, the use of that knowledge (technology). Second, science and technology must be distinguished by the different domains of their practice, namely, doubt and certainty, respectively. Thus, scientists, in their exploration of the unknown, claim the right to be wrong, while this is excluded for those in charge of technology: the “string theory” of matter or the current hypothesis on the origin of life may well be wrong, and this does not detract of their value; in contrast, error is not allowed to a pilot of a jumbo jet, a bridge engineer, or a brain surgeon, and society may punish them for malpractice. An extreme attention of all citizens to these questions is ever more important, in view of the rapid technological progress and of the enormous economic interests involved, since technology generates profit, as opposed to science that generates understanding. It seems fundamental that society’s decisions are based on an ever better and greater information on scientific and technological issues; this goal requires that science and the body of scientists play their social roles and invest their time and competence in promoting public information and comprehension. All the more so because the media often deal with this type of information in manners that are light, biased, sensationalist, or even entirely false.

### Science, management of doubt and democracy

Science generates tolerance not only by its product - knowledge and “sense” - but as much by its very practice. Because science is constructed in the domain of doubt, scientists know that they may well have to change their current explanations of nature. Scientific practice thus brings respect for the doubt and love for the diversity of opinions, promoting a profound understanding of the value of individuals, of each individual, be that the most “distant of the mode and mean”, in the tails of the “gaussian”. In short, doing science breeds tolerance, and produces knowledge that provides a full justification for being tolerant. As pointed out by others, it is not by chance that science and democracy were born simultaneously, for both require tolerance for other’s opinions and are based upon the “management of doubt” that opens the possibility for incremental improvements. Freedom of expression, the right to disagree, and the value of dissent and diversity, the Socratic certainty that, collectively or individually, we do not hold the truth but possess a method that ensures “progress”, are all values of science that are essential to democracy. If we add to

these the intrinsic value of a greater understanding of nature and of ourselves by natural explanations, it becomes clear that science (and scientific practice) is indeed a strong pillar of democracy, and that the scientific method - universal validation of incremental knowledge in the domain of doubt - contributes values that could well inform other aspects of human activity. History has repeatedly shown the danger of “final solutions”, and these were the doing of ignorants operating in the conviction of certainty. As Erwin Schrodinger said, "Socially and morally dangerous misgivings may spring, and occasionally have sprung - not, of course, from people knowing too much - but from people believing that they know a good deal more than they do."

### Science support

This long, but not disquisitional, defence of science-support for reasons other than technological and economic interests but, instead, fundamental for culture and democracy, seemed appropriate to open the first report of a scientific institution supported by a non-for-profit Foundation. Thus, if the unique goal of science is the honour of human spirit, if science is the stuff of culture in modern societies and a pillar of their democratic organisation, is there a better agenda for a Foundation entirely devoted to Man and Society, than to promote science for science, independently of individual interests, of national or international impositions, of fashions or trends, and of eventual profits?

Never before in the history of mankind, has so much been invested in science. This is particularly true in biomedicine, today described, by economists and politicians alike, as “the key to economic success in the next millennium”. While among the lowest of the developed countries, public investment in science and technology in Portugal has grown at high rates over the last years. The share of the Fundação Gulbenkian in the total spending in science and technology in Portugal is little more than a drop in the ocean, and it is infinitesimal at the world level. For these reasons, the investment of the Fundação in the IGC has to be justified, both in its existence and in its content. Clearly, it is not in the interest of the Foundation to engage in activities that substitute for, let alone compete with, the intervention of the public authorities. Any strategy for defining the organisational model and types of activities at the IGC should thus consider both the national and the international scene.

Public investments must consider all citizens and respect the will of majorities, being therefore, essentially “reactive” and aimed at solving existing problems; private investments, on the other hand, are strictly justified by the profit they generate; in contrast with both, however, the investments of a Foundation can be “pro-active” and “ahead of time”, bettering society by predicting the evolution of its needs, preparing it for new challenges, creating

new dynamics. Foundations can take the risks of innovation, and thus base their strategic decisions on somewhat “subjective” choices of their leaders, while public powers must use objective criteria, whatever these might be. If innovative, non-for-profit private investments can be experimental, because the society and the public deciders can always profit from such experiences. Moreover, the investments of a Foundation can be directed at particular sectors of society, if these are the motor of wider developments. Foundations can thus promote the “culture of excellence” even if that would principally exclude most individuals, for it is unquestionable that true excellence includes its own proselitism.

### Biomedical research

What an extraordinary time is ours, therefore, for a Foundation to invest in research in biomedical sciences. First of all, because it is essential for the survival of the “spirit” of science that truly uninterested vision comes to rescue the seeds of the search of knowledge for the mere value of knowledge, “pour l’honneur de l’esprit humain”. This is particularly relevant today, as biomedical sciences are currently paying the price of their extraordinary success over the last 25 years. On the one hand, progress in basic knowledge of biological systems has brought about the possibility, often remote but nevertheless real, of using that knowledge for profit making. Biology is today at the verge of a technological revolution that will certainly supersede that of the chemistry- and physics-based technologies which have so drastically changed our lives in the last Century or two. Vaccines and antibiotics, insulin and the birth-control pill are poor forerunners of this evolution. Obviously, there are tremendous economic interests involved: for example, multinational pharmaceutical drug companies are said to not invest in research of new products unless they ensure sales for a 1 billion dollars/year.

There is of course nothing wrong with the fact that for-profit enterprises only invest in profitable projects. It makes less sense, however, and for several types of reasons, if public and academic investments in science are submitted to the same principle of profit-making, as is the tendency today almost every where. First, for reasons of rentability and coherence: thus, it has been repeatedly reported that every dollar invested in basic biomedical science in the USA has resulted in public health savings that are 10, often 100, times higher; furthermore, the recent years of the American “success story” with a flourishing economy driven by (bio)technologies demonstrate, if necessary it was, that the highest socio-economical returns are obtained by investing in basic science and science education, with no short-term profit perspectives. By contrast, the economic protectionism that the European Union and national governments have been practising, by deviating science funding to finance for-profit “start-ups” and “biotechs” is contradictory to the free market agenda, and it selects for less

capable individual initiatives. Worse, this is short-sighted, as it fails to understand that “applied science”, technological development, industrial transfer and economical returns can only appear as consequences of a strong “basic science”. Nobody expects to harvest fruits after cutting the roots of a tree. Bad basic science should obviously not be supported, but top-down measures that encourage bad scientists to turn into industrial managers will not solve the problem of the economy, and threaten scientific research. Moreover, while public institutions should be asked for accountability, it is obviously dangerous that economic pressures on Universities and non-for-profit institutions turn them into “corporations” searching for economic sustainability and growth. If the mirages of quick economical returns in public institutions substitute for scientific judgements, there is no future: far from fostering diversity, innovation and excellence, this will at best satisfy the demands of the industry of the day.

Biomedical sciences are thus becoming ever more “money minded and product driven”. In addition to growing concerns with the limitations of the free flow of scientific information imposed by economic reasons, it is dangerous if the interest of the questions for our common understanding no longer determines which questions to address; rather, research will concentrate on what may sell well. This is perhaps the major reason why the most devastating diseases of the world are given comparatively so little attention: for example, research investments in malaria and tuberculosis, the greatest killers world-wide, are ashamingly small - because they concern populations and countries that are not rich enough to pay for the eventual new products where the investors want to collect their returns. As many institutions fall for the new economic mermaids, “selling well” has also become important for the careers of individual scientists, strengthening the limitations in the “peer-review” system, on which all modern science is based. It has long been apparent that peer-review, even if appropriately conducted, may discourage originality and innovation; adding “economic criteria” to scientific evaluations can only make it worse, open the door to opportunisms and narrow the scope of fundamental research. Thus, the attention given to particular areas and questions is self-amplified for reasons other than true scientific interest (e.g., publication, financing), such that the frontiers of progress are concentrated in too few specifics, leaving unattended many an important question. Biomedical sciences also suffer today from the predominance of “component analysis” that has been the extremely successful agenda of modern biology. Clearly, we need more “organism-centred” or “systems biology”, because a full understanding of physiopathology is required for eventual medical transfers. Again, however, “organism-centred biology” is long-term research, often not patentable, and is thus outside of the scope of most current investments.

True non-for-profit investment in science is thus necessary, today more

than ever, and it could contribute qualitative shifts out of the “more of the same” that massively contaminates efforts in biomedicine. Thus, the level of current investments and the number of institutions and people involved are so enormous that very large amounts of data are continuously produced. The doubling time of knowledge in biology is calculated by be around 2 years, and in some preferred disciplines, such as immunology, one new article is published every 20 minutes! The extraordinary progress in storing and communicating information, however, did not solve the problem of the fragmentation of knowledge that necessarily results from this activity. Hence, we need, more than ever, a class of scientists who, rather than producing more observations, try to “make sense” of all information, defining the relative importance of the questions, “organising” the relevance of the data in ways that should be independent of the mechanisms determining the current “importance” of each topic. In short, we do need more “thoughtful science”, developing above all compromises, out of fixed frames into unpredictable grounds, creative, critical, and interdisciplinary.

### Biomedical science at the IGC

For the research strategies at the IGC, today’s situation has clear implications. First of all, it would seem an obvious mistake to try to do “a little bit more of the same” that is done elsewhere. Thus, there is no possible comparison between the research potential of the IGC and of many other institutions in Europe, the US, and Japan. Biomedical research today requires heavy investments in infrastructures and equipment, and the best scientists are disputed by those institutions much in the same manner as television stars or football players, and are offered such laboratory conditions and levels of financial support for very large groups, that place them entirely outside the scope of our possibilities. Moreover, internationally competitive research requires a set-up of surrounding competencies, an efficacy of support services, and a whole network of interactions that are all absent in a country devoid of scientific tradition for many years. In other words, the IGC can not be competitive with the best, if we were to try to run as fast and produce as much. This also applies at the domestic level. Thus, several Institutes dedicated to biomedical research have been set up in the last 10 years in Portugal, which are much larger than the IGC, can count on higher support and on privileged relationships with Universities that ensure them “free” research personnel. In other words, it would not be appropriate for the IGC to “do the same” as these Institutes, both in the form and in the content. On the other hand, there is only “one kind” of science, and it would make no sense to withdraw from the most interesting areas of research, precisely where competition is fierce.

It would seem advisable, therefore, particularly as a non-for-profit institute, to aim at medium- or long-term research programmes, driven by

intellectual quality and intrinsic relevance, rather than immediacy or public impact. While submitted to “market rules” when competing for public financing, the IGC could be provided, through the investments of the Fundação Gulbenkian, with a solid and stable basis of research policies aimed at innovative, risky projects of “thoughtful science” in “organism-centred biomedicine”. The by-laws of the IGC, therefore, define its scientific goal as “research in the genetic basis of development and evolution of complex systems”, and request the additional mission of a strong role in post-graduate education. Our mission must also be one of bringing into the country the internationalisation that is required for qualitative improvements in scientific research. Moreover, rather than attending exclusively, or in priority, to its own scientific agenda, the IGC must orient its strategies according to wider needs in Portugal, by initiating new areas of research, and helping to solve current limitations in other structures and institutions. Accordingly, we have introduced genetics of complex traits and genome-wide approaches in human diseases as well as the supportive fundamental research in mouse models, and we are seriously investing in developmental biology. Furthermore, much of our efforts are dedicated, in collaboration with the Sectors for Science, Health and Social Protection, and Education of the Fundação Gulbenkian, to promote post-graduate education in clinical research, science education in secondary schools and the public understanding of science.

### The institutional model

As a private institution cultivating excellence, the Fundação Gulbenkian has systematically launched innovative, experimental programmes, notably in its scientific sector. From the 1960’s, the IGC introduced in Portugal the practice of full-time, “professional” scientific research, as well as post-graduate education. More recently, the Gulbenkian PhD Programme in Biology and Medicine was the first in the country, and is now taken as an example for several other programmes in different areas. In its new model of a host institution, the IGC continues experimenting with innovative schemes, now in respect to the fluidity of structure, the mobility of scientific personnel, and the fostering of new, young leaderships. Thus, several of the “group leaders” at the Institute are at the “post-doc” stage in their careers, but are nevertheless encouraged to assume complete autonomy, to ensure the financing of their own research projects, to supervise PhD students, and to establish their own position in the international scientific community. In most other institutions, even abroad, “post-docs” are allowed none of these hallmarks of independence. Our young investigators know, however, that their ability to find the next “position” at another institution in a few years will be significantly enhanced if they have already given proof of independence. They also understand that the space at the IGC and the resources of the Fundação Gulbenkian must be invested in supporting many such “new

leaders” rather than be reserved and frozen for the first arrivals.

The IGC has no departments or hierarchies, all pieces of equipment are common property, new approaches and technologies are introduced through extensive collaborations that start to result in common scientific concerns and projects, as well. Such a “horizontal” structure at the Institute encourages scientific exchange and collaborations, and it certainly generates the emerging intellectual atmosphere. The “fluidity” obtained by a determined effort in maintaining a good number of short- or medium-term visitors, and also by installing research groups lead by experienced scientists who are only here part of their time, also contributes to the excitement. The policy of investing in the organisation of symposia and workshops that regularly bring to Portugal world-wide known personalities as well as young post-docs, together with the large “visiting faculty” of the PhD Programme, are other ingredients in the strategy of building an institution whose collective spirit and style count more than any one of its individual members. Just as we learn in biology, to keep alive, institutions must turn-over their components (individuals, approaches and projects), and their most interesting properties can not be reduced to those of the components but emerge from the dynamics of their interactions. Moreover, biology also tells us that variation and diversity are the solution to the unknown, and institutions must be built keeping in mind the value of individuals in their diversity.

Having to reconstruct laboratories, office spaces, facilities and infrastructures, while wishing to launch new activities, the decision was taken to initiate the reconstruction in a step-wise fashion and proceed to occupy new spaces as they became available. This decision generates some inconvenience, but this is largely compensated by the presence of a growing number of scientists and students. Of the 8 wings in our main building, 3 were made available in 1999, for housing administrative services, meeting rooms, guest offices and the first research groups. Simultaneously, the acquisition of new equipment and the installation of the support Units was continued, corresponding to an effort of investment by the Fundação Gulbenkian that must be emphasised.

In 1999, 5 new groups were established, and those already operating were consolidated, bringing the total number of scientists and students at the IGC to 138 distributed in 11 research groups. Many of these were here for only a part of the year, but this is precisely the objective: to use the capacities of the Institute for as many people as possible, to make it a “meeting place” for students and scientists, medical doctors and biologists, pursuing its general goals. For 2000, we plan to open one new wing, complete the renovation of the animal quarters, and initiate the reconstruction of two more wings. This is a sizeable task, for we must also see to the renewal of support infrastructures - library and informatics, teaching labs, lecture rooms, canteen and faculty residence, as well as to the

project of a “science garden” in the campus.

With the support of the “invited scientists programme” of the Fundação para a Ciência e Tecnologia, and of the “Gulbenkian Professorships” of the Science Sector of the Fundação Gulbenkian, the IGC pursued the policy of hosting distinguished guests for periods varying from a few weeks to one year or two. In 1999, five long-term, and ten short-term visiting scientists worked at the IGC, generously bringing their experience to the use of the younger colleagues, and contributing to the atmosphere of intellectual excitement that characterises life at the Institute. This effort, as well as the quality of our scientific projects, were recognised by the opening, last September, of a CNRS European Associated Laboratory, that involves research groups at the IGC together with CNRS labs at the Institut Pasteur, and the Université Pierre et Marie Curie in Paris.

These plans and strategies involve serious risks, and it is far too early to aim at drawing indications of eventual results. The continuing support of the Fundação Gulbenkian is all the more necessary. It is a pleasure to acknowledge, in name of all of us at the IGC, the vision of the Board of Administration of the Fundação and the encouragement that we have systematically been given.

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Charles Steinberg died on September 17 1999 in Basel, after several years of fighting a terrible disease. In the short life of the new IGC, Charley had been an emblematic figure for all of us; enormously respected for his intellect and scientific insight, deeply loved for his gentleness, his memory will remain with the Institute through the example of his life. Charley Steinberg had attended the Annual Meeting of the Gulbenkian PhD Programme in September 1998, and was preparing to come back in 1999. He spent 3 months in Oeiras in the Spring of 1999, when he was kind enough to give us a beautiful seminar on mutation, that will remain as his last and actually one of the few he gave in his life. The manuscript that he wrote from that seminar is an extraordinarily elegant and profound piece of science, and it gives the IGC as Charley’s affiliation. This is an example up to which we will look.

Someone who was Delbrück’s student and taught Feinman all he knew about biology (both were in his PhD Thesis Committee) cannot be a common scientist. Charley, in addition, lived his life as he did his science, with consilience and entirety, in that tremendously generous and yet critical manner that will guide us for long. Science needs more of his calibre.

António Coutinho

Oeiras, February 10, 2000

## RESEARCH

The IGC's scientific interests are focused on the genetic basis of development and evolution of complex systems, privileging organism-centred approaches and using experimental models that include plants, yeast, flies and mice, while working on the genetics of complex human diseases as well. A strong theoretical sector is also one of the IGC's specificities.

## PROJECT REPORTS

### **Cellular responses to oxidative challenges: Transcription regulation mediated by Yap proteins**

Members: Lisete Fernandes, Sukalyan Chatterjee

Eukaryotic cells respond to both intrinsic (originating within the cytoplasm) and extrinsic (extracellular) stimuli, e.g. oxidative stress, by activating cascades which are diverse but with discrete specificity. Cells undergoing oxidative stress modulate their gene expression, and it has been suggested that transcriptional regulation is as a key regulatory step in this event. In *S. cerevisiae* transcriptional factors belonging to the bZIP family of proteins, globally designated by YAP (Yeast *AP*-1), have been shown to perform a determining role in transcription regulation under oxidative stress.

Despite similarities of sequence among different members of this family, each Yap apparently plays distinct biological functions. For example, Yap1 is a regulator of the yeast antioxidant response while Yap4 is required for chromosome and/or cytoskeleton stability. Yap2-mediated transcription is minimally affected by oxidants and it was found not to be required in yeast cells undergoing oxidative stress. The most consistent data on the function of this protein is the reproducible observation that cells lacking yap2 frequently lose their normal mitochondrial activity. Previous identification of genetic interactions between Yap1 and Yap4, in cold-sensitive phenotypes, as well as between Yap2 and Yap4, under oxidative stress conditions, led us to address the possibility that Yap2 is specifically involved in oxidative stress response, when mitochondria are compromised. The role of Yap1-Yap2-Yap4 in both transcription regulation and cytoskeleton dynamics under oxidative stress, are still under investigation. Nevertheless, new insights in regulation of YAP2 gene expression were reported as an alternative start of translation, which may be the major control of Yap2 transcriptional activity. A putative post-translational modification on Yap1 under different oxidative challenges was also identified.

Complementary studies to elucidate the function of Yap2 were also pursued in collaboration with Dr V. Iyer (P. Brown laboratory, Beckman Medical Center, Stanford Univ, CA), which involved in the identification of target genes for Yap2 by exploiting the DNA-*microarrays* methodology.

**Study of the *Tetrahymena* tubulin complexes: an attempt to establish a functional relationship with microtubule assembly and dynamics.**

Member: Maria Helena Antunes Soares  
Students: Cristina Casalou, Sofia Nolasco

In exponentially growing *Tetrahymena* cells, tubulin seems to exist in different protein complexes with molecular masses ranging from 120 kDa to 540 kDa, that appear to not contain (chaperonin-containing TCP1) CCT subunits. Remarkably, the amount of the 120 kDa complex increases in cells submitted to a hyperthermic stress, an event that probably requires cytoskeleton re-arrangements. These observations suggest that such complexes may play an important role in (microtubule) Mt dynamics.

The present project aims at understanding the role of these tubulin-containing complexes in Mt biogenesis and dynamics and their relationship with the function of the CCT. Furthermore, we want to investigate whether one or more of the complexes are involved in the transport of tubulin to the growing end of an intracellular microtubule or to the tip of a growing cilia.

**Possible role of the *Tetrahymena* cytosolic-chaperonin CCT in the biogenesis and dynamics of microtubules: an attempt to correlate with the effects of antimitotic agents.**

Member: Maria Helena Antunes Soares  
Students: Cristina Casalou, Sofia Nolasco

The discovery that tubulin is one of the major substrates of the CCT raises the possibility that the chaperonin is involved in the biogenesis of functional, specific Mt arrays. On the other hand, it is well known that tubulin is a target for Mt polymerizing and depolymerizing compounds, for example, Taxol, Colchicine and Nocadazole. These compounds affect essentially the Mts involved in cell cycle, *e.g.*, Taxol blocks the cell cycle by stabilizing the Mt cytoskeleton against depolymerization, making it an important new drug for treatment of certain cancers. However, little is known about the mechanisms of stabilization/destabilization of Mts by the action of these drugs. Preliminary results obtained with *Tetrahymena* cells show that the expression of CCT-subunit

genes, as well as tubulin genes, is modified in response to the treatment of the cells with Taxol, Colchicine and Nocodazole. These observations suggest that the CCT complex might be also involved in the dynamic of Mt polymerization/depolymerization that occur in the cell. It is our aim to establish a functional relationship between the CCT and the biosynthesis and dynamic instability of distinct functional classes of Mts.

## **Mitosis**

Member: Álvaro Tavares

Students: Brigitte de Lima, Mariana Faria, Suzana Godinho

The accurate segregation of chromosomes at mitosis is essential for the provision of genetic material to ensure cell viability. Defects in any stage of this process can lead to cell death or, in higher organisms, the development of cancer. Multipolar spindles have often been observed in human cancers in situ as well as an abnormal number of centrosomes. Identification of the molecular targets of centrosome kinases and elucidation of the pathways that regulate centrosome duplication, separation and function provide novel opportunities for therapeutic intervention.

We previously showed that the protein kinase polo is a centrosomal kinase, and that is required for the formation of a bipolar spindle and for the proper execution of cytokinesis. We wish to understand how the activity of the polo protein kinase is regulated and how it functions at the level of the centrosomes. We previously found that polo proteins, either from *Drosophila* embryo extracts or from *Xenopus* egg extracts, bind to several proteins forming different stable complexes. We are now on the process of identifying the complexes' components in total embryo extracts and in centrosome preparations. We want to characterize these proteins, sorting which are polo substrates and which are activators. *Drosophila* and *Xenopus* are used as working models due to their amiability to genetics and biochemical studies respectively.

Taking advantage of *Drosophila* genetics we have also searched and isolated new genes required for spindle assembly and centrosome function, some of which coding for proteins with high degree of homology with the *Saccharomyces cerevisiae* proteins. We are now on the process of characterising these genes.

We are also starting a new line of research, using the chicken cell line DT40 to identify the function of the vertebrate homologues of the centrosomal kinases polo and aurora, and of other centrosomal components. We hope to create null lines and specific mutation lines to analyze the role of the conserved aminoacids in the non-catalytic conserved regions of the kinases. We will take advantage of the cell line ability to be synchronized to look for substrates at specific phases of the cell cycle.

## **Mechanisms of plant cell growth and morphogenesis**

Member: José Feijó

Students: Ana Catarina Certal, Sofia Cordeiro, Ricardo Bandarrinha Almeida, Ana Margarida Prado, Ana Maria Vieira, Sílvia Costa, Leonor Boavida

We are developing a systematic approach to the basic phenomena underlying cell growth and morphogenesis. We intend to tackle some of these issues by means of state-of-the-art biophysical approaches aimed at understanding some of the fundamental physiological regulatory loops in growing pollen tubes grown in vitro, a paradigmatic model for studying apical growth. Data gathered with electrophysiology and imaging techniques is to be integrated on a coherent theoretical background by established collaborations with physicists and theoretical biologists. On the other hand a systematic molecular approach will now be started to establish the molecular counterparts of the physiological models.

### **Pollen stigma interaction and sexual plant reproduction.**

Member: José Feijó

Students: Ana Catarina Certal, Sofia Cordeiro, Ricardo Bandarrinha Almeida, Ana Margarida Prado, Ana Maria Vieira, Sílvia Costa, Leonor Boavida

Sexual Plant Reproduction represents the evolutionary context in which pollen tubes evolved and fit in. We aim to apply the knowledge on the mechanisms that control growth to a better understanding of the complex communication and guidance behaviour of pollen tubes within the female tissue. This objective will imply development of a number of fluorescent tags for pollen tubes and advanced imaging inside living pistils using multi-photon microscopy. On the other end mutants of *Petunia* and *Arabidopsis* defective on reproductive steps will be screened, and characterized in terms of the inherent physiological deficiencies.

A lateral effort is being made on the establishment of sexual cycles in a number of non-studied species, especially with forestry or fructiculture interest. Besides the immediate applied interest of the results, this effort has continuously pumped out biological specificities that we aim to explore on a fundamental perspective.

### **Molecular and biochemical analysis of the mouse gene *cerberus*-like.**

Member: José António Belo

Students: Mário Rui Filipe, Ana Cristina Borges

Technician: Sara Lopes Marques

We reported the isolation of mouse cerberus-like (*cer-1*), a gene encoding a novel secreted protein that is specifically expressed in the anterior visceral endoderm during early gastrulation. Mouse *cer-1* shares some sequence similarity with *Xenopus* head inducing factor cerberus (*Xcer*). *Mcer-1*, like *Xcer*, is a multifunctional growth-factor inhibitor in the extracellular space: it inhibits the activity of Nodal and BMP proteins.

We have genetically inactivated by homologous recombination in ES Cells the *cer-1* gene. Currently, we are studying possible genetic interactions of *cer-1* with these other genes involved in head formation, aiming at finding compensatory pathways involved in this process, and at deriving a model of how head and trunk development might be regulated.

### **Molecular and biochemical analysis of the mouse gene *cerl-2*.**

Member: José António Belo

Students: Mário Rui Filipe, Ana Cristina Borges

Technician: Sara Lopes Marques

By degenerated PCR, cDNA sequences related to *cer-1* were identified. One, designated *cerl-2* has been selected for further analysis, in view of its pattern of expression and putative role(s) on the *cer-1* and/or nodal pathway(s). We are in the process of generating a targeting vector to inactivate this gene in ES Cells, in order to create a loss of function mutant. We also plan to study the activity of this gene by over expression experiments, involving injection of the respective mRNA into *Xenopus* embryos. Biochemical analysis will also be performed in order to access the possible interactions of the protein product of this gene.

### **Molecular screening for neural inducing genes.**

Member: José António Belo

Students: Mário Rui Filipe, Ana Cristina Borges

Technician: Sara Lopes Marques

Using a differential screening approach, we are on the way to try to isolate novel genes expressed at the gastrula stages and with neural inducing properties. Using our unique collection of genetically modified mouse strains, we are generating cDNA pools that can be subtracted from wild-type ones. This already successfully used method, will enable us to isolate these differentially expressed messages.

## **Vertebrate Segmentation.**

Member: Isabel Palmeirim

Students: Catarina Freitas, Cláudia Vieira, Nuno Afonso, Vanessa Luís

Technician: Sofia Rodrigues

In the vertebrate embryo, somites constitute the basis of the segmental pattern of the body and they give rise to the axial skeleton, the dermis of the back and all striated muscles of the adult except those of the head. In the chick embryo, a pair of somites buds off every 90 minutes, in a highly coordinated fashion, from the cranial end of the presomitic mesoderm (PSM). Very little is known about the spatial and temporal coordination of this segmentation process in vertebrates, in contrast to insects. Recently, an avian homologue of the hairy *Drosophila* gene, *c-hairy1*, was cloned, and the study of its expression pattern showed that this gene is dynamically and cyclically expressed in the PSM with a periodicity corresponding to the formation time of one somite. The dynamic expression pattern of this gene provided the first molecular evidence for the existence of a developmental clock linked to somitogenesis. We intended to study this subject further.

In the vertebrate embryo a pair of somites buds off from the cranial end of the unsegmented paraxial mesoderm. Concomitantly, new mesenchymal cells enter the caudal part of this tissue, coming from the anterior part of primitive streak, as a consequence of gastrulation. We are interested in studying how presomitic cells are generated at the Hensen's node level.

## **Analysis of epithelium to mesenchyme transitions in integrin b1D knock-in embryos.**

Member: Solveig Thorsteinsdóttir

The b1 integrin subunit undergoes alternative splicing in its cytoplasmic domain giving rise to four different splice variants. One of these is the b1D splice variant which is present in both adult cardiac and skeletal muscle and starts being expressed very late in embryogenesis in both skeletal and cardiac muscle (van der Flier et al. *Dev. Dyn.* 210:472-486, 1997). Exon-specific b1D knock-in mouse embryos were recently generated via homologous recombination in embryonic stem cells in which b1A was replaced by b1D; this was lethal at midgestation (Baudoin et al. *Genes Dev.* 12:1202-1216, 1998). In this project, we perform a detailed analysis of the defects observed in b1D knock-in embryos, concentrating on defects in epithelium to mesenchyme transitions and in the migratory potential of various cell populations (in collaboration with Dr. Arnoud

Sonnenberg, Netherlands Cancer Institute, Amsterdam and Dr. Christine L. Mummery, Hubrecht Laboratory, Utrecht, The Netherlands).

### **Rag-1 and Rag-2 overexpression leads to a severe defect in early lymphopoiesis.**

Members: Jocelyne Demengeot  
Student: Vasco Barreto  
Technician: Rute Marques

The role of Rag proteins in late events of lymphocyte development has been reported (from VH region reshuffling to light chain editing). To investigate further the function of the rag genes, we generated double transgenic mice for Rag1 and Rag2, such that expression of the genes will be sustained at all stages of lymphocytes development. Analysis of those transgenic mice reveal that (1) ectopic expression of Rag1 and/or Rag2 during development or at early stages of post-natal life is lethal, (2) overexpression of those genes in the lymphoid lineage is associated with severe lymphopenia; (3) overexpression of Rag genes in the lymphocyte lineage induces a developmental block at the stage where the first event of VDJ recombination occurs.

### **IFN-1 and threshold of BCR triggering.**

Members: Jocelyne Demengeot, Sergiy Bobrovnyk  
Students: Déborah Braun, P. Geraldes

We have demonstrated that IFN 1 regulates B cell responses to BCR ligation and acts as an amplifier of BCR signal. Consequences of this effect on the fate of B cells during development and activation are now under evaluation. These experiments lead us to assess the regulation of terminal differentiation in natural immunity and in the responses to infection, as well as the role of IFN1 in the of susceptibility to autoimmune disease.

### **Quantitative evaluation of V-region repertoires.**

Members: Jocelyne Demengeot, Shohei Hori, Jorge Carneiro, John Stewart

CD4<sup>+</sup>CD25<sup>+</sup> cells have been reported as the effectors in the control of natural tolerance. In order to assess whether defects in this population are at the origin of common autoimmune diseases, we initiated a global analyses of TCR repertoire

distributions in various spontaneous autoimmune mouse models. This required the establishment of a method allowing for the rapid and precise quantitation of global TCR diversity and repertoire distribution. We used the RT-PCR-based “Immunoscope” technique, to which we introduced serial dilution analyses, and applied statistical calculations based on the Poisson distribution. Such method allows for the accurate quantitation of the number of cells that utilize a given Vbeta-Jbeta combination with a given CDR3 length in any cell population, including very small samples (16 cells).

### **Modelling the process of somatic hypermutation in immunoglobulin genes during the germinal centre reaction.**

Members: Jorge Carneiro, José Faro

The complex set of processes constituting the germinal centre reaction (GCR) is currently an open problem in immunology. The GCR has already been approached theoretically and some dynamic mathematical models have been presented. We proposed, however, to analyse the GCR by means of a model that takes into consideration primarily the mutational process, because some of the essential corresponding variables can be monitored experimentally.

We have derived a minimal conceptual model of the GCR incorporating explicitly mutational parameters (mutation rates along antibody variable-region genes) and the selective pressures acting on the distinct mutations in those variable regions. This model, was designed to allow the direct comparison with experimental data on antibody (Ab) hypermutation during the humoral immunoresponse to oxalozone (Ox). In this well studied system there are two main point mutations that increase, each of them, the affinity of anti-Ox Abs. Those two particular mutations, when simultaneously present rise even more the affinity of the mutated Abs. Since the distribution of B cells with different mutations and its change with time is known, we can use now this model to test different hypothesis in respect to the probability distribution of the mutational process along a variable region-encoding nucleotide sequence. In order to do this, we have been implement a genetic algorithm for that model.

It is widely held that GCs are oligoclonal. The particular mechanism responsible for the oligoclonality of GCs can have an important impact on the behaviour of our model of GCR with mutations. However, this oligoclonality remains presently unexplained. Because of this, we have started to analyse different potential mechanisms aimed at explaining it. Preliminary calculations indicate that oligoclonality of GCs can be simply explained by a rate of entrance of B cells into follicles similar to the proliferation rate of follicular Ag-specific B cells. For

instance, for a proliferation rate of B cells and a rate of entrance into a follicle equal to  $0.08 \text{ h}^{-1}$ , the clone of cells derived from the first founding cell already accounts for more than 60 % of the total GC B cell population. Moreover, the descendants of the first five founding cells account for more than 99 % of the total GC B cell population. We are elaborating on two experimentally testable alternative mechanisms that can account for a relatively low rate of entrance of Ag-specific B cells into follicles.

### **Specificities of regulatory cells.**

Members: Jocelyne Demengeot, Shohei Hori, Matthias Haury  
Student: Thiago Carvalho

Elucidation of the mechanisms of tolerance will require identification of the specificities (reactivities) of regulatory T cells. As demonstrated by Lafaille et al. (Cell 78:399; 1994) mice carrying a transgene encoding an MBP-specific TCR develop spontaneous EAE if monoclonal (Rag-1-deficient), while the transfer of a small number of peripheral T cells from normal animal prevents emergence of disease. Our preliminary data indicate that this beneficial control is mediated by CD4 CD25+ cells. In addition, in normal TCR anti-MBP transgenic mice, few T cells bearing endogenous encoded TCR can be produced preventing emergence of EAE. In such system, manipulation of subsets of CD25+ T cells purified at different stages of development, according to the nature of their TCR, will provide understanding of the specificity requirements for regulatory cell function.

## **Control of immune pathology by regulatory T cells.**

Members: Jocelyne Demengeot, Shohei Hori, Matthias Haury  
Student: Thiago Carvalho

A subpopulation of T cells (CD4<sup>+</sup> CD25<sup>+</sup>) has been reported to suppress CD4<sup>+</sup> T cell proliferation induced by commensal bacteria in the intestine. The same population seems to orchestrate dominant tolerance to self components. In order to elucidate the paradox of effective immune responses versus active tolerance, the boundaries of this suppressive effect will be followed in mouse models presenting local inflammation. The nature of the cellular targets (CD4, CD8 and B cells) submitted to suppression will be investigated. As a first set of results, we have shown that lung inflammation by *Pneumocystis Carinii*, targets a massive and fatal local T cell expansion that can be controlled by CD4<sup>+</sup>CD25<sup>+</sup>. Extension of this work will assess requirements for foreign antigens in uncontrolled lymphoproliferation, chronic inflammation as an organ targeting event in autoimmune disorder, and the regulation of chronic versus acute infection.

## **Mechanisms of lymphocyte co-operation involved in immune regulation: an experimental and biomathematical approach.**

Members: Jorge Carneiro, Jocelyne Demengeot, Shohei Hori  
Students: João Sousa, Kalet Léon Monzon, Vanessa Carvalho

The mechanisms by which the immune response is regulated are very important both for their fundamental interest and for their clinical applications in the modulation of immune responses (either to increase them in case of vaccination; or to decrease them in case of transplantation and autoimmunity). Despite the fact that many different experiments indicate that immune responses can be inhibited by regulatory lymphocytes, the precise mechanisms by which this regulation occurs are still poorly understood. The difficulties are twofold: on the one hand, specific regulatory cells have not been isolated and cloned thus far; on the other hand, the experimental settings are so diverse that overall conclusions can not be easily drawn.

The aim of the present project is to overcome these difficulties by following an alternative approach. We will try to confirm or infirm hypotheses on the mechanisms of interaction and co-operation between regulatory and effector cells, by identifying their quantitative implications and testing whether or not those are fulfilled empirically. Mathematical modelling is instrumental here for the design and analysis of quantitative experiments. This is a means of: a)

making predictions across levels of organisation; b) systematically and adequately comparing different mechanisms; and c) narrowing down the number of alternative explanations for regulatory phenomena.

We propose the following procedure. We identify all classes of alternative mechanisms of interaction and co-operation between regulatory and effector lymphocytes. We build those generic classes of mechanisms into mathematical models of cell population dynamics, such that we can predict their quantitative implications. We calibrate these models by adequate *in vitro* experiments. These experiments are co-cultures of regulatory and effector cell populations, in variable amounts, in which we quantify the immune response of the effectors as a function of the initial composition. Calibrating the model means to estimate parameters, to define whether predicted dynamic attractors exist, and, ultimately, to be able to predict the outcome of such cultures. Once these models are fully calibrated *in vitro*, we try to fit them to data obtained by measuring immune responses in recipient animals co-transferred with variable amounts of regulatory and effectors cell populations. The capacity or incapacity of these models to fit and predict the magnitude of immune responses in the recipient animals, will allow us to conclude whether the built in mechanisms are or are not operative.

### **Cytokines involved in rejection or acceptance of allografts.**

Members: Paulo Vieira, António Gil Castro

We are using a murine system of thyroid lobe transplantation under the kidney capsule to study the mechanisms of allograft rejection. This system allows us to recover the cellular infiltrate that destroys the organ and characterise the cellular and molecular components involved in allograft rejection. So far, our data show that CD4<sup>+</sup> T cells producing IFN $\gamma$ , but not IL-4, play a major role in rejection. Further, blocking IFN $\gamma$  activity in recipient mice significantly delays rejection. In order to determine whether the inhibition of a Th 1 response prevents allograft rejection we have generated new lines of transgenic mice, producing either IL-4 or IL-10 under the control of an inducible promoter. These mice are under characterisation at the moment, and we will use them to set up a system for inducible, organ specific, cytokine expression, thus minimizing the systemic effects associated with cytokine therapy.

### **Modelling the activation and differentiation of lymphocytes.**

Members: Jorge Carneiro, José Faro, Zvi Grossman

Student: João Sousa

The aim of this project is to understand the activation and differentiation of mature lymphocytes as the co-ordinated operation, the *co-operation*, of receptor signalling and receptor expression pathways, using mathematical modelling and computer simulation as main tool.

A model of the signal transduction via the T-cell antigen receptor (TCR) has been developed by J. Sousa and J. Carneiro (submitted to *Eur. J. Immunol.*). This model describes the mechanism of serial triggering of the TCR by its ligand the MHC-peptide complexes (Valitutti, et al. 1995). According to the serial triggering hypothesis a single MHC-peptide complex can trigger many different TCRs, such that a few of these complexes can lead to large enough pool of triggered TCRs that can lead to full T cell activation (Valitutti, et al. 1995). We used the kinetic data of TCR-downregulation, caused by TCR triggering, to try to identify which are the early events that take place during TCR signal transduction. We identified kinetic properties from which we formulated a quantitative model of ligand-dependent TCR triggering and signal transduction. The model is robust from the phenomenologic point of view and explains a large variety of experimental data available in the literature.

One of us has previously developed, with colleagues at the National Institutes of Health (USA) (Grossman & Paul, 1992, Proc Natl Acad Sci U S A 89, 10365; Grossman, 1993, Immunol Rev. 133, 45), a conceptual theory of the way the T cell discriminates antigens by the affinity of binding and the kinetics of presentation and of how the cell adapts its responsiveness to environmental conditions based on its own experience. These ideas have been published and are presently subject to experimental testing. We are using this theoretical framework together with the model developed by Sousa and Carneiro, to try to understand in general terms what are the functional requirements of a signal transduction pathway.

The signal transduction pathway initiated by cytokine receptors is fundamental for the understanding of the modes of activation, differentiation and commitment of T lymphocytes. Signal transduction triggered by cytokine involves the Jak-STAT pathway. We elaborated a preliminary model that includes the activation of cytoplasmatic STATs and their translocation to the nucleus. Although this model is very simple it is already able to describe the experimental data on the nuclear translocation of STAT1 dimmers in cells cultivated in the presence of IL-6 (Haspel, et al. ,1996, Embo J 15(22): 6262-8).

Finally, a general computational tool that will allow us to simulate large-scale signal transduction networks in terms of boolean networks is under development. In order to calibrate and validate these boolean networks we are

recasting the different ODE models of the TCR signaling and Jak-STAT pathways and comparing the general qualitative results. The goal is to be able to have an efficient tool to address interactions between different pathways of signaling and hopefully to be able to model.

### **Characterization of the biological activities of two novel Toll-like receptors.**

Members: Paulo Vieira, Jocelyne Demengeot, Matthias Haury  
Student: João Pedro Pereira

Toll-like Receptors (TLRs) comprise an expanding family of molecules structurally related to *Drosophila* Toll which signals innate immune recognition of many pathogens. In mammals, several TLRs have been reported and in this project we are concerned with the molecular characterization and biological activities of two new TLRs, provisionally designated TLRKB6 and TLRKB7. The human homologues of TLRKB6 and TLRKB7 are located in chromosome Xp22 in a region where several human genetic diseases, associated to developmental problems (e.g. ocular albinism-Oa 1), have been mapped. Syntheny studies map both mouse compartments also to chromosome X, in a region near Oa1. Expression analysis by quantitative PCR showed similar patterns of expression for these genes, only in macrophage lines. Such restricted expression suggests that these two novel receptors may, also in mice, be involved in the recognition by the innate system of invading microorganisms. Mouse embryonic stem cells were transfected with a targeting vector in an attempt to knock-out mTLRKB6. Screening of ES clones deficient for TLRKB6 is currently ongoing. Because they may have overlapping activities we will generate double knockout mice deficient for both mTLRKB6 and TLRKB7. Understanding the role of TLRs in the immune recognition of pathogens may be useful to develop strategies to stimulate these receptors in order to activate specific antimicrobial defense mechanisms. This is a collaborative project with R. Kastelein and F. Bazan (DNAX Research Institute, USA).

### **TLRs and newly derived wild mice strains.**

Members: Jocelyne Demengeot, Pierre-André Cazenave, Paulo Vieira  
Student: Déborah Braun

B cells from newly derived inbred mouse strains were assessed for their ability to respond to various mitogens. A significant diversity of responses between strains was observed suggesting heterogeneous genetic components. Analysis of TLRs distribution in those mice at the RNA and DNA level will provide tools to

investigate mechanism of B cell activation, and assess a putative diversity of this receptor family.

### **T cell response in immune regulation of malaria infection.**

Members: Sylviane Pied, Sérgio Gulbenkian

Students: Sébastien Bagot, Valérie Soulard

Technician: Maria Ressurreição Alpiarça

This work is concentrated on different aspects of T cell responses in immunoregulation occurring during infection, particularly in mechanisms involving the balance between protection and pathology. Our initial approach to investigate general T-cell responses in severe and uncomplicated malaria with respect to a potential role in pathogenesis is (1) to study the nature and specificity of T-cells in the induction of disease, (2) to analyze to which extent TCR gene usage influences susceptibility to Cerebral Malaria (CM) and (3) to analyze whether there is an inherited polymorphism or an operational selection of particular V-region families and MHC haplotypes.

### **Genetics of malaria in wild mouse models.**

Members: Dan Holmberg, Carlos Penha Gonçalves, Sylviane Pied, Pierre André Cazenave

Students: Susana Campino, Catja Berschmidt

The identification of genetic factors controlling resistance to clinical forms of malaria will provide an important contribution to the understanding of malaria pathogenesis and will suggest therapeutic and vaccinal strategies to improve resistance to disease. This project aims to identify genetic factors that control resistance to clinical forms of malaria in mouse models. The work plan comprises (1) genetic mapping of malaria resistance loci using genetic crosses of mouse strains that are resistant to malaria and (2) isolation of the genetic factors involved, combining “candidate gene” and “positional cloning” approaches. Inbred mouse strains that were recently derived from wild stocks were first genotyped for a number of markers in all chromosomes. Next, these strains were screened, in parallel with conventional laboratory strains, for susceptibility/resistance to death by either “cerebral malaria” or by hyperparasitemia, upon infection with sporozoites from *Plasmodium berghei*. Polar, informative strains were thereafter crossed and reciprocal F1, F2 and “backcross” progenies phenotyped and genotyped. Available results indicate

that susceptibility/resistance to “cerebral malaria” segregates as a single locus, while the ability to resist hyperparasitemia is a more complex trait.

### **Gammaherpesvirus latency and immunevasion.**

Members: João Pedro Simas, Alexandra Teixeira  
Students: Leonor Orge, Patrícia Madureira, Sofia Marques

Our research interests are centered on the utilization of a gammaherpesvirus, designated murine herpesvirus 68 (MHV-68), whose pathogenesis can be readily investigated in the laboratory mouse. MHV-68 is genetically related to Epstein-Barr virus (EBV) and Human herpesvirus 8 (HHV-8; also known as Kaposi's sarcoma associated herpesvirus). The major biological characteristics of these viruses are (1) their ability to establish latent infections within lymphocytes, (2) their ability to induce lymphoproliferative disease and (3) their close association with a variety of both lymphoid and non-lymphoid cell tumors. MHV-68 is a natural pathogen of wild murid rodents and experimental infection of inbred strains of mice results in acute productive infection of the lung followed by latent infection of B-lymphocytes. Chronic infection has been associated with important pathologies, including tumors, vasculitis of the great arteries and splenic fibrosis. A general feature of gammaherpesvirus genomes is the presence of cellular gene homologues that have been captured from host DNA relatively recently in evolutionary time. In MHV-68 these genes include: a homologue of a serpin; a complement control protein; a D-type; an Il-8 receptor homologue and, an ORF with similarity to bcl-2 family. In addition to these genes, MHV-68 encodes a series of unique genes that encode ORFs with no homology to any known protein sequences in the data base. Our research interests are focused in trying to understand how these cellular homologues and unique ORFs coordinated their functions with those of a B-lymphocyte that will result in immune evasion and persistent infection. To this end we have adopted a basic strategy of constructing recombinant viruses with specific genes deleted and study their phenotype upon infection of mice.

### **Pathogenesis of transmissible spongiform encephalopathies.**

Members: João Pedro Simas, Alexandra Teixeira  
Students: Leonor Orge, Patrícia Madureira, Sofia Marques

We are currently strain-typing the BSE agent in Portugal and studying if tissue-specific PrPc glycosylation determines PrPsc infectivity in peripheral tissues. We are also determining Prnp gene polymorphisms in selected Portuguese sheep

populations to assess the genetic susceptibility of Portuguese sheep to scrapie and BSE.

### **Genetics of murine IDDM.**

Members: Dan Holmberg, Carlos Penha Gonçalves

Students: Marie Luise Bergman, Ctaja Behrscmidt, Suzana Campino

This project aims at identifying and genetically map subphenotypes associated with disease development in the Non-Obese Diabetic (NOD) mouse model for type 1 diabetes. Previous quantitative trait locus analysis has identified the chromosomal location of a locus contributing to the apoptosis resistance of immature CD4<sup>+</sup>8<sup>+</sup> thymocytes. More recently, we found that immature thymocytes of female NOD mice proliferate with a relatively low rate compared to non-autoimmune C57Bl/6 mice and mapped this trait to the same region on chromosome 6. We will now continue our search of genes that mediate these effects by fine mapping using congenic mouse strains established over the distal region of mouse chromosome 6.

### **Genetics of human autoimmune diabetes.**

Members: Dan Holmberg, Luisa Mota Vieira, Carlos Penha Gonçalves, Tatiana Vassilevskaia, Astrid Vicente

Student: Catja Berschmidt

Technician: Marta Barreto

The overall goal of this project is to localise, molecularly clone, and investigate the functions of genes predisposing to human autoimmune diseases, focusing first on insulin dependent diabetes mellitus (IDDM). To overcome the genetic heterogeneity problem of these complex traits, the approach used is the genetic mapping of disease associated phenotypes that are likely to contribute to the pathogenesis of the disease. These are under a more simple genetic control and, thus, more easily subjected to positional cloning strategies for identifying contributing genes. Immunologically related traits associated with the disease are identified, and chromosomal regions with candidate susceptibility genes for these "subphenotypes" are sought for, aiming at the genetic mapping and positional cloning of individual risk genes. Our preliminary results have identified a disease subphenotype in the Portuguese population related to the deregulation of the CTLA-4 gene, which is known to be involved in lymphocyte homeostasis. Furthermore, we have found that the CTLA-4 gene is associated

with IDDM in a sample of 87 Portuguese patients. The project is developed in intimate collaboration with the Associação do Diabético de Portugal.

### **Genetics of SLE.**

Members: Carlos Ferreira, Dan Holmberg, Luisa Mota Vieira, Carlos Penha Gonçalves, Astrid Vicente

Student: Catja Berschmidt

Technician: Marta Barreto

The project (1) aims at a central question in immunology - the physiopathology of natural tolerance to body tissues, (2) approaching it genetically with modern technologies for identifying loci contributing to complex traits, (3) and combining the values of human population genetics and disease diversity with well-defined mouse disease models and basic research on molecular, cellular and systemic mechanisms. The programme also attempts to contribute into clinical research the benefits of the rapidly increasing knowledge in basic immunology and of the human genome project advances. The project is developed in intimate collaboration with the Associação de Doentes com Lupus, and it involves several clinical centres in mainland Portugal and the Azores.

### **Genetics of autism**

Member: Astrid Moura Vicente

Technician: Ana Coutinho

This research project that is developed with the support of the Serviço de Saúde e Protecção Social (FCG) concerns the genetics of autism spectrum disorders, and aims at the genetic mapping of susceptibility loci predisposing to autism. In collaboration with clinical centres throughout mainland Portugal and the Azorian islands, we are establishing a database for autism spectrum disorders that includes extensive clinical information, biochemical measurements and DNA genotypes from patients and their families. A corresponding DNA/cell/serum bank is being set up including nuclear and multiplex families. Candidate genes and genomic regions are being evaluated in this population. Patients are also screened for disease-associated phenotypes, biological and behavioural, in an effort to identify less genetically complex traits more amenable to genetic mapping. The genetic control of the patients response to specific medication is also under study. Concomitantly, we are conducting a genetic epidemiology study of autism spectrum disorders in the Portuguese population.

## **Genetics of lymphoid homeostasis.**

Member: Carlos Penha Gonçalves

Student: Nadia Duarte

The goal of this project is to characterize the genetic control of the number of lymphocytes along the development of the lymphoid organs in mouse. The work plan includes (1) to study the establishment of lymphocyte homeostasis during the ontogenesis of the lymphoid organs in different laboratory mouse strains and (2) to genetically map and to identify the genetic factors involved in the homeostatic mechanisms that control the number of lymphocytes in the lymphoid organs of the mouse.

The total number of cells in the tissues and organs of multicellular organisms is under strict control but little is known on the homeostatic mechanisms that control the number of lymphocytes. On the other hand, it is known that a number of immune dysfunctions, such as immunodeficiencies and certain autoimmune diseases, occur with lymphopenia. The notion that certain lymphocyte populations can regulate the size of other lymphocyte populations raises the interesting possibility that maintenance of lymphocyte cellularity is a function of the immune system that is important for the responsiveness towards foreign antigens and to the maintenance of self tolerance.

We investigate the genetic variation of the number of cells within several lymphocyte populations both in the thymus and in the spleen. Different mouse strains (including BALB/c and C57Bl/6) are analysed, covering serial time points during the ontogeny of the mouse immune system. Characterization of phenotypic differences in cellularity will be followed by genetic mapping studies aiming to identify genetic factors controlling genetic variation in lymphocyte numbers.

## **Genetics, disease and biology.**

Member: John Stewart

The general thesis being explored is that when a genetic disease is controlled by a large number of loci, it is likely that disease results from an epistatic interaction and that the "susceptibility" alleles at each locus separately are frequent in the population. Exploring this hypothesis requires integrating theoretical population genetics with specific pathophysiological identification of phenotypes and subphenotypes.

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*The following publications were, or should have been, included in previous Annual reports. They are repeated here in order to correct and complete the bibliographic data:*

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## **PARTICIPATION OF IGC PERSONNEL IN CONFERENCES, SEMINARS, COURSES AND SCIENTIFIC MEETINGS**

### **January**

Coutinho A.

*Une conclusion au cours d'Immunologie Approfondie.*

Cours d'Immunologie Approfondie de l'Institut Pasteur, Centre d'Enseignement de l'Institut Pasteur, Paris, France.

### **February**

Coutinho A.

*Academic and Science Policy in Small Countries: The Case of Portugal.* Harvard University, Minda de Gunzburg Center for European Studies, Boston, USA.

Demengeot J.

*Type 1 IFN and B cells: a new function for an old cytokine.*

ICBAS, Porto, Portugal.

Demengeot J.

*Type 1 IFN and B cells: a new function for an old cytokine.*

Centre d'Immunologie de Marseille Luminy, Marseille, France.

### **March**

Fernandes P.

*Data resources for biomedical research available at the IGC. Facts, figures and literature.*

ITQB, Oeiras, Portugal.

### **April**

Ministrini G., Mathe E., Adams R., Tavares A., Salzberg A., Bellen H., Carmena M., Riparbelli M., Callaini G., and Glover D.

*Pavarotti is a kinesin-like protein related to mammalian MKLP-1 with a role in cytokinesis.*

BSCB/BSDB Joint Spring Meeting, Manchester.

## **May**

Carneiro, J.  
*On the phylogeny of dominant tolerance.*  
Centro de Imunologia Molecular, Havana, Cuba.

Carneiro J.  
*Towards a taxonomy of the mechanisms of dominant tolerance.*  
Centro de Imunologia Molecular, Havana, Cuba.

Coutinho A. Chairman of the conference *Patogenia da Auto-Imunidade XIII Jornadas da Sociedade Médica dos Hospitais da Zona Sul*, Hotel do Mar, Sesimbra, Portugal.

Coutinho A.  
*Que utopia para o Século XXI ? “ Ciência e Sociedade ”.*  
II Bienal de Cascais – Utopia 99, Teatro Gil Vicente, Cascais, Portugal.

Cohn M.  
*Why should we care about Science?*  
Opening Conference for the Prémio Gulbenkian de Ciência 1998, Fundação Calouste Gulbenkian, Lisboa, Portugal.

Stewart J. *From autopoiesis to semantic closure.*  
International Workshop on Closure, University of Gent, Belgium.

## **June**

Belo J.A., Agius E., Bachiller D., Piccolo S. and De Robertis E.M.  
*Molecular mechanisms of action of the mouse cerberus-like gene: biochemical and KO approaches.*  
“From Life’s Design to Molecular Medicine” The 1999 Conference in Developmental Biology. Oslo, Norway.

Bourgeois-Cohn.  
*What everyone should know about cancer – and a little bit more.*  
Faculdade de Medicina de Lisboa, Hospital de Santa Maria, Lisboa, Portugal.

Carneiro J., van der Pol L. and de Boer R.J.  
*IVIg and the Brambell Fc-Receptor: Can IVIg act in autoimmune disorders by accelerating the clearance of antibodies?*  
SMB Annual Meeting/41th ESMTB Meeting. Theory and Mathematics in Biology and Medicine. Amsterdam, Holland.

Coutinho A.

*Discurso de Aceitação como Académico Titular da Academia Portuguesa de Medicina.*  
Fundação Eng. António de Almeida, Porto, Portugal.

Sousa, J. and Carneiro J.

*Serial triggering of the T cell receptor: Requirement for a cooperative rate-limited step.*  
SMB Annual Meeting/41th ESMTB Meeting. Theory and Mathematics in Biology and Medicine. Amsterdam, Holland.

Stewart J.

*La modélisation en Biologie.*

Seminar Co-organized by the Calouste Gulbenkian Foundation and the Association Diderot. Lisbon, Portugal.

### **July**

Coutinho A.

*T Lymphocytes - Structure and Function.*

35-years of the MRC Cellular Immunology Unit, Medical Research Council, University of Oxford, Oxford, England.

Coutinho A.

*My scientific biography and science.*

EMBO Fellows Meeting, Heidelberg, Germany.

### **August**

Demengeot J.

Symposium "*Immunology and cancer*".

Harvard Medical School, Boston, USA.

Demengeot J.

*Type 1 IFN and B cells: a new function for an old cytokine.*

Ontario Cancer Institute, Toronto, Canada

Tavares A., Avides M.C., and Glover D.

*Polo protein kinase and Asp are required for centrosome microtubule nucleation.*

14<sup>th</sup> Meeting of the European Cytoskeleton Forum. Oeiras.

### **September**

Paulo Vieira

*Cytokines involved in rejection of allografts*  
Catholic University of Louvain, Belgium.

### **October**

Carneiro J.

*Immune system modelling.*

Second short course of the Portuguese Biophysical Society: Simulation of Biological Processes. Practical Approaches. ISLA Auditorium, Santarem, Portugal.

Carneiro J.

*History and context in the immune system: lessons from mathematical modelling and evolutionary reconstitution.*

Advanced Course on Immunotherapy of Cancer. Instituto de Embriologia e Histologia. Hospital de Sta. Maria, Lisbon, Portugal.

Coutinho A.

*Presentation of Prof. Sydney Brenner.*

VI Encontro da FML – II Encontro da FML/HSM, Hospital de Santa Maria, Lisbon, Portugal.

Fernandes P.

*Acesso nacional aos recursos bioinformáticos disponíveis no IGC.*

Instituto de Genética Médica Jacinto de Magalhães, Porto, Portugal.

Stewart J.

*L'intentionnalité en biologie.*

Colloque “Perception du monde, perception du langage”, University of Strasbourg, France.

### **November**

Bergman M-L, Penha-Gonçalves C, Campino S and Holmberg D.

*Low rate of proliferation of non-obese diabetic mouse thymocytes maps to diabetes susceptibility region Idd6.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

Braun D.

*Type 1 Interferon sets the threshold of BCR triggering.*

French Society of Immunology, Lille, France.

Coutinho A.

*Evolution of development in the immune system.*

Patterning and differentiation during development of the nervous system, Fondation Treilles, Nice, France.

Coutinho A.

*Chairman of "Natural Sciences and Mathematics Panel".*

Portugal: Strategic options in a European context, Minda de Gundzburg center for European Studies, Harvard University, USA.

Campino S, Behrschmidt C, Bagot S, Penha-Gonçalves C, Holmberg D, Pied S and Cazenave P-A.

*Hyperparasitemia in wild mice resistant to malaria is controlled by a locus on chromosome 9.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

Carvalho T, Mota-Santos T., Demengeot J. and Vieira P.

*Severe lymphopenia associated with hyperglobulinemia in IL7 deficient mice.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

Fernandes P.

*Global Biodiversity information Facility (GBIF).*

II Encontro de Biodiversidade, Porto, Portugal.

Hori S., Stewart J. and Demengeot J.

*A new method for quantitative repertoire analysis.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

Leon K, Perez R., Lage A., Carneiro J.

*Modelling T cell mediated immunosuppression.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

Pereira J.P., Martins S., Demengeot J., and Vieira P.

*Towards the characterization of the biological activities of the mouse Toll-like receptors KB6 and KB7.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

Sousa J. and Carneiro J.

*A mathematical model of TCR triggering.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

Vicente AM, Barreto M, Vasilevskaya T, Gardette-Correia L, Penha Gonçalves C and Holmberg D.

*Genetic analysis of the CTLA-4/CD28 gene region and type 1.*

XXV Reunião Anual da Sociedade Portuguesa de Imunologia. Lisbon, Portugal.

**December**

Carmo Avides M, Tavares A and Glover D.

*The abnormal spindle protein, Asp, and Polo kinase are required for the integrity of mitotic centrosomal microtubule organising centers.*

Thirty-Ninth Annual Meeting of the American Society for Cell Biology, Washington, USA.

Coutinho A.

*Evolution of the immune system.*

Cátedra Gulbenkian em Biologia. Universidade Federal do Rio de Janeiro, Brazil.

Coutinho A.

*The Evolution of Complexity and Biodiversity. The immune system.*

Cátedra Gulbenkian em Biologia. Universidade Federal de Minas Gerais, Brazil.

Paulo Vieira.

*Characterization of the biological activities of 2 novel Toll-like receptors*

University of Umea, Sweden.

Paulo Vieira

*Spontaneous B cell activation in IL-7 targeted mice.*

University of Stockholm, Sweden.

## TEACHING

Post-graduate education has always been a strong valence of the IGC, and this tradition has been maintained through the establishment of the Gulbenkian Programme in Biology and Medicine.

### **Gulbenkian PhD Programme in Biology and Medicine**

The Gulbenkian PhD Programme in Biology and Medicine was launched and is conducted by the Fundação Calouste Gulbenkian together with the Secretaria de Estado do Ensino Superior, the Fundação para a Ciência e Tecnologia e a Fundação Luso-Americana para o Desenvolvimento. The Programme is developed in collaboration with a large number of Universities and Institutes in Portugal and abroad, under the responsibility of the IGC.

The PGDBM recruits students from very diverse university curricula (from Medicine to Physics, Agronomy and Economy) on a fully egalitarian basis. The Programme provides one full year of graduate courses, followed by three years of supervised research work, leading to a doctoral thesis. The graduate courses aim at providing the students with the “common language” of modern biology, and at exposing them to some of the most active research areas and respective leaders. They are organised in 4 “blocks” of 6 weeks each (structural biology, cell biology, genes & development, evolution), followed by a number of one- or two-weeks thematic “modules”, the subject of which may vary (e.g., hematopoiesis, visual system, apoptosis, signalling, genetics of complex diseases). Students are required to take all 4 blocks and 12 thematic modules that they may choose amongst the 20 or so proposed. Teaching takes place at the IGC, at the Instituto de Biologia Molecular e Celular (Universidade do Porto) and at several other University Institutes in Lisbon, Coimbra and Porto, according to the respective course-leaders. A Faculty of over 120 includes a majority of foreign scientists and is also considerably renewed every year (see listings). A limited number of places are available for students outside the Programme for every thematic module. Students who successfully complete the first year of graduate courses proceed to prepare and submit a 3-year research project in a topic of their preference, to be conducted at an institution of their choice, under the supervision of one or two scientists credited by the Programme. The resulting Thesis can be presented at a Portuguese or a foreign University.

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Adriano Henriques (ITQB-UNL, Portugal)  
Jules Hoffmann (IBMC-Strasbourg, France)  
Dan Holmberg (IGC, Portugal and Umea Univ., Sweden)  
Mónica Holmberg (Umea Univ., Sweden)  
Jonathan Howard (Inst. Genetics, Germany)  
Juan Carlos Ispizua-Belmonte (The Salk Institute for Biological Studies, USA)  
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Paola Minoprio (Institut Pasteur Paris, France)  
Serge Morand (CNRS Perpignan, France)  
Alvaro Moreno (Universidad del País Vasco, Spain)  
Jaime Mota (ITQB-UNL, Portugal)  
Luísa Mota-Vieira (Hosp. Ponta Delgada, Portugal)  
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Erin Murphy (DNAX, USA)  
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Maureen O'Connor (Biotechnology Research Inst., Canada)  
Anne O'Garra (DNAX, USA)  
Margarida Oliveira (DBV-FCUL, Portugal)  
Solange Oliveira (ITQB-UNL, Portugal)  
Isabel Palmeirim (IGC, Portugal and IECM-CNRS, France)  
Louis du Pasquier (Basel Institute for Immunology, Suisse)  
Inês C. Pereira (ITQB-UNL, Portugal)  
Manuela Pereira (ITQB-UNL, Portugal)  
Pablo Pereira (Institut Pasteur, France)  
Stefano Piccolo (UCLA, USA)  
Sylviane Pied (INSERM Paris, France; IGC, Portugal)  
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Manuel Prieto (IST-UTL, Portugal)

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Thierry Vernet (Inst. Biologie Structurale J-P. Ebel, France)  
Astrid Moura Vicente (IGC, Portugal)  
Concepcion Martinez Vidal (Univ. de Santiago Compostela, Spain)  
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Wolfgang Wurst (Max-Plank Institute, Germany)  
António V. Xavier (ITQB-UNL, Portugal)

**Students of the Gulbenkian PhD Programme in Biology and Medicine for 1999/2000**

Filipa Carreira de Avelar Barbosa  
Ana Margarida Gonçalves Campilho  
Tiago Daniel Basto Linhares Carneiro  
Nuno Miguel Maçarico Amorim da Costa  
Ricardo Manuel Benites Costa  
Ana Isabel Dias Neto Domingos  
Rosalina Maria Regada Carvalho Fonseca  
Andrea Costa Veludo Gouveia  
Mário Martins Rodrigues Grãos  
Maria João de Lemos Pinto Estrela Leão  
Susana Sá Couto Quelhas Lima  
Mariana Ferreira de Carvalho Metello Nápoles  
Manuel da Silva Rebelo  
Sheila Dias dos Santos  
Rui Pedro Domingos Tavares de Sousa  
Andrea Lages Lino Vala

**Students of the Gulbenkian PhD Programme in Biology and Medicine for 1998/1999 (Class Aurélio Quintanilha)**

Irene Marta de Almeida  
Mara Solange Silva Almeida  
Joana Raquel de Castro Barros  
Tânia Reis de Almeida Bastos  
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Sheila Dilai Martins Vidal

## **Programme for 1998/1999 conducted at the IGC in 1999**

### **Block III – Developmental Biology**

Head: José António Belo/Isabel Palmeirim (IGC, Portugal)

6-29 January	Development
1-5 February	Plant development – The molecular and cellular basis
8-12 February	Cognition, Biology, Technology – The science and philosophy of embodied meaning

### **Block IV – Evolution**

Head: Pedro João Silva (FCUL, Portugal)

15 February-5 March	Evolution/ Evo-Devo
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### **Coercive Modules**

These courses are held mainly for the PGDBM students but also accept external students

22 March - 3 April	Neurobiology of the visual system
5-9 April	Apoptosis, causes and mechanisms of cell death
12-16 April	Nucleocytoplasmic transport
19-21 April	Hematopoiesis
21-23 April	Immunology I
26-30 April	Immunology II
3-7 May	Immunology Topics

### **Optional Modules**

14-21 June	Genetics of complex diseases
21-25 June	MHC Evolution
28 June-2 July	Human diseases
5-9 July	Cytokines
12-16 July	Immunity and parasitism
19-23 July	Viral pathogeneses
2-6 August.	Signalling

## **Programme for 1999/2000 conducted at the IGC in 1999**

### **Block I – Structural biology**

29-30 September	Network computing resources for biological research
8 October	Protein folding
9-11 October	Mechanisms of gene expression: an eukaryotic perspective
14-18 and 22 October	Molecular and cell biology
20 October	Bioinformatics
25 October-12 November	Structure and function of proteins

## **Block II - Cell biology (IHEFML, Lisboa)**

Head: M<sup>a</sup> do Carmo Fonseca (IHEFML, Portugal)

29 Nov.-17 December      Cell biology

### **Annual Meeting in Curia (19-25 September 1999)**

As in the past years, the Annual PGDBM Meeting of Curia took place from 19 to 25 September, thereby completing the sixth working year of the Gulbenkian PhD Programme in Biology and Medicine. The scientific sessions counted on the participation of around 100 students, as well as Portuguese University Professors who are involved in the teaching of the graduate courses or in the supervision of theses work. The last day of the Meeting was dedicated to the distribution of diplomas to students who completed their “graduate courses year” in 1999 with merit, and to pay homage to Prof. Aurélio Quintanilha, patron of the 6<sup>th</sup> Class of the PGDBM. The respective commendations were made by Prof. Miguel Mota and Prof. Francisco Carvalho Guerra.

In this session, conferences were given by Prof. Hans Wigzell (Rector of the Karolinska Institute) entitled “Biomedical research and society”, and Prof. Luca Cavalli-Sforza (University of Stanford, USA) who talked about “Discoveries about ourselves taken from the “Recent” evolution of the human species”

This Meeting counted on the presence of the Senhor Presidente da República, Dr. Jorge Sampaio, the President of the Fundação para a Ciência e Tecnologia, Prof. Dr. Luís Magalhães, the Trustee for Science of the Board of Administration of the Fundação Calouste Gulbenkian, Dr. Emílio Rui Vilar, as well as the Trustees and members of the Scientific and Pedagogic Council of the Programme, and other University personalities.

## **Public understanding of science**

The teaching of science as well as the public understanding of science are also concerns of our “teaching” activities. The IGC, while studying the possibility of launching new science teaching programmes, regularly organizes “open sessions” on interesting biological and biomedical questions with our scientific personnel, primarily directed at biology teachers in secondary schools.

The IGC is open to visits of students and teachers from secondary schools, and regularly participates in the “Semana da Ciência e Tecnologia” – an initiative of the “Programa Ciência Viva” of the Ministério da Ciência e Tecnologia.

### **Open sessions for secondary school biology teachers: “Biologia dos tempos modernos”**

*Morphogenesis and computational simulation*

Joaquim Sáinhas (IGC/Faculdade de Motricidade Humana/UTL, Portugal)

*Viruses and prions*

Pedro Simas, (IGC/Instituto de Ciências Abel Salazar, Portugal)

*Control of cellular division and cancer*

Álvaro Tavares (IGC/IST/UTL, Portugal)

*Resistance to antibiotics*

Mário Ramirez (IGC/ ITQB, Portugal)

*All that you ever wanted to know about sex in plants but never had the courage to ask!*

José Feijó (IGC /FCUL, Portugal)

*Development of the embryo*

Isabel Palmeirim (IGC, Portugal)

*Genetic Diseases: New Perspectives*

Astrid Moura Vicente (IGC/Inst. Piaget, Portugal)

### **Secondary school visits at the IGC**

Escola EB 2,3 – Caxias (20 students)

Colégio Valsassina – Lisboa (34 students)

Escola Secundária Patrício Prazeres – Lisboa (17 students)

Escola Secundária D. Pedro V – Lisboa (72 students)

Escola Secundária Quinta do Marquês – Oeiras (44 students)

## THESIS

The following PhD Theses were prepared in part at the IGC and were presented in 1999.

**Caroline Brissac** presented her thesis entitled “Caractérisation des IgM sériques naturelles de la souris: diversité fonctionnelle et variabilité du répertoire individuel d’immunoréactivité” at the University of Paris XII. January 22, 1999.

**Carlos Penha Gonçalves** presented his thesis entitled “Genetic analysis of lymphocyte traits in the non-obese diabetic mouse” at the University of Umea. May 21, 1999.

## PARTICIPATION IN ACADEMIC COMMITTEES

### **Jorge Carneiro**

- ?? “Examineur” in the Jury of the Ph.D thesis of Caroline Brissac. University of Paris XII, Paris, France.
- ?? Member of the Jury of the Ph.D. thesis of Manuel Vilanova. University of Porto, Porto, Portugal.

## HONOURS AND AWARDS

### **António Coutinho**

- ?? Elected Ordinary Member of the Portuguese Academy of Medicine (Chair XLII)
- ?? Elected Member of the Advisory Board of the Associação dos Antigos Alunos da Faculdade de Medicina de Lisboa
- ?? Elected Member of the Council of the European Molecular Biology Organization (EMBO)
- ?? Member of the Advisory Board of the National Institute of Administration (INA)
- ?? Honorary Member of the Portuguese Society of Immunology
- ?? Member of the Ibero-American Molecular Biology Organization (IMBO)

?? Member of the Review Committee “Molecular Approaches” of the Human Frontier Science Programme (HFSP)

**Paulo Vieira**

?? President of the Portuguese Society of Immunology

**Jorge Carneiro**

?? Secretary of the Portuguese Society of Immunology

## **SYMPOSIA, CONFERENCES AND MEETINGS ORGANISED BY THE IGC**

### **May**

#### **Clinical Parameters in Research on the Genetics of Autism**

IGC, Oeiras – 9 May

Participants: Astrid Moura Vicente (FCG/IGC), Guiomar Oliveira (Clínica do Autismo, Hospital Pediátrico de Coimbra), Karin Dias (Neuropediatria, Hospital D. Estafânia), Pedro Caldeira (Unidade de Primeira Infância, Hospital D. Estafânia), Ana Moreira (Neuropediatria, Hospital de Faro), Lurdes Ventosa (Pediatria do Desenvolvimento, Hospital Garcia d’Orta)

#### **Genetics of Autoimmune Diseases**

IGC, Oeiras – 10 May

Participants: Carlos Alberto Ferreira (Hospital Sta Maria/Assoc. de Lupus), António Silva Graça (Assoc. Portuguesa de Diabetes), Filipe João Raposo (Assoc. Portuguesa de Diabetes), Tatiana Vassileskia (Assoc. Portuguesa de Diabetes /IGC), Luisa Mota Vieira (Hospital de Ponta Delgada, Açores), Ana Quental/IGC), Guiomar Oliveira (Hospital Pediatrica, Coimbra), Dan Holmberg (Univ. Umea /IGC), Monica Holmberg (Univ. Umea, Sweden) Astride Moura Vicente (IGC)

#### **Conferences of the IGC Scientific Advisory Board**

Fundação Calouste Gulbenkian and IGC – 27 May

A series of public Conferences, integrated in the cycle “Science and the contemporary world”, organized jointly with the Serviço de Ciência of the Fundação Calouste Gulbenkian.

*The human genome sequence – implications for medicine.*

Sydney Brenner (The Molecular Science Institute, Inc, California, USA)

*The ins and outs of cell death.*

Martin Raff ((MRC, LMBC, University College, London, UK)

*Pattern formation in development.*

Lewis Wolpert ((University College, London, UK)

*Patterning of the neural primordium in Amniote vertebrates.*

Nicole Le Douarin (Institut d'Embriologie Moléculaire et Cellulaire, France)

## **August**

### **14th Annual Meeting of the European Cytoskeleton Forum**

Hotel Praia-Mar, Carcavelos, 28 August-2 September

The European Cytoskeletal Forum started at the end of the 1970s when a small group of researchers based in European laboratories and interested in several aspects of cytoskeletal biology decided to organise periodic meetings in order to discuss the several aspects of cytoskeletal biology. The 14<sup>th</sup> meeting of the European Cytoskeleton Forum was organised by Claudina Rodrigues-Pousada, Helena Soares and Luisa Cyrne and held in Oeiras. 150 participants attended this meeting.

## **September**

### **II Gulbenkian Symposium on Cognitive Neuroscience: Consciousness**

Convento da Arrábida, 5-7 September

In 1998, the IGC together with the Science Sector at the Fundação Calouste Gulbenkian and the Fundação Oriente, launched a regular Symposium series aimed at convening every year some of the world's specialists in various aspects of Cognitive Neurosciences/Consciousness. Retreated for a few days into a pleasant and quiet setting, the group informally discusses current problems, approaches and progresses, recent developments and difficulties, eventually drawing a chart of essential steps to accomplish in the field. The Symposium is to be held every year for 10 years, fostering the emergence of a collective impact in the development of the theme.

The First Gulbenkian Symposium on Consciousness was held last year, and the Second Symposium was held from September 5 to September 7 1999.

João Caraça (FCG, Portugal); Miguel Castelo Branco (Max-Planck Institute for Brain Research, Germany); Jean-Pierre Changeux (Institut Pasteur, France); Jonathan Cole (Poole Hospital and University of Southampton, UK); António Coutinho (IGC, Portugal); António Damásio (University of Iowa, USA); Jean Decety (INSERM, France); Stanislaus Dehaene (INSERM, France); Daniel Dennett (Tufts University, USA); Jeffrey Gray (Institute of Psychiatry, UK); Giacomo

Rizzolatti (University of Parma, Italy); Wolf Singer (Max-Planck Institute for Brain Research, Germany); Francisco Varela (Hôpital de la Salpêtrière, France)

## **II Gulbenkian Seminar on Science and Consciousness**

Fundação Calouste Gulbenkian, Lisbon, 8 September

A series of public Conferences organized jointly with the Serviço de Ciência of the Fundação Calouste Gulbenkian.

*Brain's Consciousness, Consciousness of Brain.*

Francisco Varela (CNRS, Hôpital de la Salpêtrière, Paris, France)

*Consciousness: real problems and mythical problems.*

Daniel Dennett (Tufts University, Medford, USA)

*Drugs use and abuse.*

Jean-Pierre Changeux (Collège de France/Institut Pasteur, Paris, France)

*Once more with feeling.*

António Damásio (University of Iowa, Iowa, USA)

## **II Gulbenkian Autumn Meetings: Adaptation by transfer of genetic information**

IGC, Oeiras, 26-28 September

As in 1998, the IGC organised a workshop primarily aimed at the active participation of recent PhD graduates who are developing promising scientific activities in various European and American laboratories. Another objective of these meetings is to establish or strengthen contacts between these young researchers and the PhD students and post-doctoral fellows at the IGC and in the PGDBM. The theme of this years' meeting that was organized by Mário Ramirez a PGDBM graduate, now a scientist at the ITQB in Oeiras, was "Adaptation by transfer of genetic information", related to diverse areas in biomedical science, such as, resistance of bacteria to antibiotics, or evolution of pathogenic viruses. This meeting was distinguished by the participation of Bruce R. Levin, of Emory University, Atlanta, USA, who gave a conference at the open session entitled "Conditions for existence, the evolutive role and the consequences of accessory genetic elements in bacterial populations".

Lin Chao (University of California, San Diego, USA); Isabel Couto (ITQB, CREM, Universidade Nova de Lisboa, Portugal); Colin Dale (CTVM, University of Edinburgh, UK); Francisco Dionísio (PGDBM, Institut Jacques Monod, France);

Michelle L. DuBois (Fred Hutchinson Cancer Research Center, USA); Caroline Laemmlli (EAWAG, ETH, Switzerland); Bruce Levin (Emory University, USA); Eric M. Ostertag (University of Pennsylvania, USA) ; Sally R. Partridge (CSIRO Molecular Science, Macquarie University, Australia), Mário Ramirez (PGDBM, ITQB, Portugal); Roald Ravatn (EAWAG, ETH, Switzerland); Eduardo P. C. Rocha (Universoté Paris VI, Institut Pasteur, France); Paul E. Turner (Instituto Cavanilles de Biodiversidade y Biología Evolutiva, Spain); Roeland C. H. J. Van Ham (Instituto Cavanilles de Biodiversidade y Biología Evolutiva, Spain).

## ***October***

### **I Gulbenkian Symposium on Dominant Tolerance**

Convento da Arrábida, 18-21 October

For several years, a small number of research groups have been calling the attention to immunological phenomena in which tolerance can be transferred by T cells from tolerant donors. This form of tolerance is thus designated by “dominant”, and it obviously pertains to the whole animal, rather than individual lymphocytes. The experimental systems showing this behaviour are quite heterogeneous, ranging from protection of autoimmune diseases that spontaneously develop in monoclonal TCR transgenic mice, to induction of tolerance to allogenic skin grafts by thymic epithelium in embryos or by anti-CD4 antibodies in the adult, to prevention of inflammatory disease caused by lymphopenic states. The biomedical importance of this topic derives from its potential value in strategies for intervention in a number of increasingly frequent autoimmune diseases and in cancer immunotherapy. The novelty of this area called for a meeting gathering essentially all specialists, aiming at drawing the limits of current theory, approaches and results. Together with the Science Sector of the Fundação Calouste Gulbenkian and the Fundação Oriente, the IGC organised the first Symposium in this new series that will deal with a research topic actively pursued by IGC scientists.

Participants: Antonio Bandeira (Institut Pasteur, Paris, France); António Coutinho (IGC, Oeiras, Portugal); Irun Cohen (The Weizmann Institute of Science, Rehovot, Israel); Philippe Druet (Hopital Purpan, Toulouse, France); Werner Haas (Shionogi BioResearch Corp, Boston, USA); Juan Lafaille (NYU Medical Center, New York, USA); Fiona Powrie (John Radcliffe Hospital, Oxford, UK); Shimon Sakaguchi (Kyoto University, Japan); Eli Sercarz (La Jolla Institute for Allergy & Immunology, San Diego, USA); Howard Weiner (Brigham and Women’s Hospital, Boston, USA)

## **Autoimmune diseases: mechanisms and novel therapies**

Faculdade de Medicina de Lisboa, Lisbon, 21 October

A series of public Conferences organised jointly with the Faculdade de Medicina de Lisboa.

### *Introduction.*

António Coutinho (IGC, Oeiras, Portugal)

### *Treatment of autoimmune diabetes by specific peptide vaccination.*

Irun Cohen (Weizmann Institute, Rehovot, Israel)

### *Mechanisms of autoimmunity.*

Philippe Druet (INSERM U28, Hopital Purpan, Toulouse, France)

### *New approaches to the treatment of autoimmune diseases.*

Werner Haas, SBR, Boston, USA

## **November**

### **Meeting on “Clinical Features of Systemic Lupus Erythematus”**

IGC, Oeiras, 20 November

Participants: Carlos Ferreira (Hospital Sta Maria/Assoc. Lupus), Rita Andreia (Assoc. Lupus), John Stewart (Costech, France/IGC), Dan Holmberg (Univ. Umea, Sweden/IGC), Luisa Mota Vieira (Hospital Ponta Delgada, Açores), Astride Vicente (IGC), Carlos Penha Gonçalves (IGC), Tatiana Vassilevskia (Assoc. Diabetes Portugal)

## **December**

### **Gulbenkian Chair at the Universidade Federal do Rio de Janeiro**

Rio de Janeiro, Brazil, 22 November – 3 December

This Chair functions in close collaboration with the UNESCO Chair at the Federal University of Rio de Janeiro. The 1999 programme included a two-week course ministered by a large faculty from France, USA and Portugal:

Nicole Le Douarin (Head of the UNESCO Chair of Developmental Biology, College de France & Institut d'Embryologie, CNRS, France), António Coutinho (IGC), Anne Eichmann (Institut d'Embryologie, CNRS, France), Anne-Maria Duprat (Université Paul Sabatier, France), Charles Babinet (Institut Pasteur de Paris, France), Dominique Morello (Université Paul Sabatier, France), Françoise Dieterlen (Institut d'Embryologie, CNRS, France), Jean Antoine Lepesant (Institut Jacques Monod – CNRS, France), Marc Moreau (Université Paul Sabatier, France), Marie-Aimée Teillet (Institut d'Embryologie, CNRS, France), Marnie Halpern (John Hopkins University, USA), Nipam H. Patel (Howard Hughes Medical Institute, USA), Roberto Mayor (Universidad de Santiago de Chile, Chile), Vivaldo Moura Neto (Departamento de Anatomia, UFRJ, Brazil), Jorge Guimarães (CAPES and UFRGS, Brazil), Moyses Nussenzweig (COPEA and Instituto de Física, UFRJ, Brazil), Roberto Lent (Departamento de Anatomia, UFRJ, Brazil), Simone Engelender (Departamento de Anatomia, UFRJ, Brazil).

Other than the enrolled students who participated in the theory and practical lessons, the course was also regularly attended by a population of around 70 “free” listeners, from various departments of the UFRJ and other research institutions of Rio de Janeiro (Fundação Oswaldo Cruz, Instituto Nacional do Cancro, Universidade Federal Fluminense). The Gulbenkian Professors for 1999 were Prof. Jean David, CNRS, France and Prof. António Coutinho, I.G.C., Portugal.

The Gulbenkian Chair also organised, with Prof. Jean David as president, a **Symposium on Evolution and Development in Drosophila** which counted on the participation of a considerable number of South American faculty and a numerous audience.

## **Gulbenkian Chair at the Universidade Federal de Minas Gerais**

Belo Horizonte, Brazil, 6-10 December

With the local co-ordination of the Institute of Biological Sciences of the UFMG and the organisation of Thiago Carvalho from the IGC, a 5-day Symposium on the Evolution of Complexity and Biodiversity took place, that also counted on the local support of the UFMG and of the firm Yakult Brazil which has, for many years, invested in Biology in Brazil. This Symposium was able to unite both the two Gulbenkian Professors of the Rio de Janeiro Cathedra (Profs. Jean David and António Coutinho) who traveled to Belo Horizonte and the two Gulbenkian Professors of the UFMG Chair – Profs. J. Tyler Bonner and K. S. Bawa.

## SEMINARS AT THE IGC

### **January**

Ernesto Moreno (Center for Molecular Immunology, Havana, Cuba). *Structural studies on antibody carbohydrate interactions: development of a docking programme.*

Jocelyne Demengeot (IGC).

*Type 1 Interferon and B lymphocytes: An old cytokine with a new function.*

Carlos Penha Gonçalves (IGC).

*Genetic analysis of thymocyte defects in murine autoimmune diabetes.*

Constantin Fesel (Institut Pasteur/IGC).

*IgM repertoire reactions to immunization and their association with aninducible autoimmune disease.*

Adriano Henriques (ITQB, Portugal).

*Gene expression and morphogenesis during development in bacillus Subtilis.*

### **February**

Jorge Carneiro (IGC).

*Is the therapeutic effect of intravenous immunoglobulin (IVIg) in autoimmune disorders due to a perturbation of the catabolism of antibodies?*

Helena Soares (IGC).

*The Chaperonin CCT complex in Tetrahymena: studies during cilia recovery and in cells treated with polymerizing/depolymerizing agents.*

Martin Raff (University College of London, UK).

*Cell number control in animal development.*

Gillian Wu (Ontario Cancer Institute, Canada).

*Generation of Ig diversity.*

Astrid Moura Vicente & Tatiana Vassilevskaia (IGC).

*Diabetis and CTLA - 4: studies in a Portuguese population.*

Carlos Faro (Universidade de Coimbra, Portugal).

*Structural and functional aspects of cardosins, the milk-clotting enzymes from the flowers of cardoon.*

### **March**

Sylviane Pied (INSERM/IGC).  
*T Cell response in the pathogenesis of cerebral malaria.*

Charles Steinberg (Basel Institute for Immunology, Switzerland).  
*An experimental solution for the Luria-Delbrück fluctuation problem in measuring hypermutations rates.*

Pedro Fernandes (IGC).  
*Data Resources for Biomedical Research available at the IGC.*

Mário Arala Chaves (ICBAS, Portugal).  
*First evidence for induced immunoprotection against fungi in primates.*

António Gil de Castro (IGC).  
*Cellular and molecular mechanisms in Allograft rejection.*

Miguel Angelo Garcia (Universidad Autónoma de Madrid, Spain).  
*Transcriptional regulation of the APOE gene, one of the genes involved in Alzheimer's disease.*

Álvaro Tavares (IGC).  
*Isolation of cell-cycle regulatory proteins: how useful flies can be.*

## **April**

Michael Reth (Max Planck Institute of Freiburg, Germany).  
*Signalling.*

Alf Grandien (University of Stockholm, Sweden).  
*Viral FLIP: a tumor progression factor ?*

Maria João Marcelo Curto (INETI, Portugal).  
*Industrial property rights: The R&D Inventor and the Patent World.*

Iron Cohen (Weizmann Institute of Science, Israel).  
*The Immunological Homunculus and auto-immune diseases.*

Dan Holmberg (IGC/ Umea University, Sweden).  
*A genetic approach to study auto-immune diseases.*

Melvin Cohn (The Salk Institute, USA).  
*Understanding the immune system.*

Tai Nang-Huang (Shionogi BioResearch Corp., USA).  
*Modern drug development.*

Guy Cox (University of Sydney, Australia).  
*Plants that swim - three dimensional architecture of the Chlamydomonas Cytoskeleton.*

Maria do Carmo Avides (University of Dundee, Scotland).  
*Controlling division: centrosomes and the focusing of the spindle.*

Simon Kollnberger (Pinbright Laboratory, UK).  
*Defining potentially protective epitopes of African swine fever virus.*

Armelle Regnault (Institut Curie, France).  
*Antitumor Immunotherapy by exosomes.*

Mildred Foster-Cuevas (Pirbright Laboratory, UK).  
*The immune response to foot-and-mouth disease virus in the natural host.*

Graham Brown (Bio - Rad, UK).  
*Principles and Applications of Multi-Photon Microscopy.*

Leonor Cancela (Centro de Ciências do Mar, Universidade do Algarve, Portugal).  
*Molecular cloning and expression of Bone Gla and Matrix Proteins in lower vertebrates.*

## **May**

Pedro Fernandes (IGC).  
*Searching for Scientific Literature.*

Rob Kastelein (DNAX Research Institute, USA).  
*Sequences, structures and cytokine signalling mechanisms.*

Vasco Barreto (IGC/Institut Pasteur, France).  
*Ig Heavy Chain Allelic Exclusion: short stories and ragtime.*

Sukalyan Chatterjee (IGC/University of Connecticut, USA).  
*Promoter Specificity & Transactivation in Eukaryotes.*

Rui Appelberg (IBMC, Portugal).  
*To kill, be killed or die to kill.*

Suzanne Bourgeois-Cohn (The Salk Institute, USA).  
*What everyone should know about cancer - and a little bit more.*

Shohei Hori (IGC).

*A novel scavenger receptor from Sarcophaga (flesh fly) hemocytes: its implications in tissue reorganization during metamorphosis.*

## **June**

Tomaz da Mota Santos (IGC/Universidade Federal de Minas Gerais, Brasil). *"We precious few": T and B cells in the IL-7 knock out mouse.*

Ezequiel di Paolo (Institute for autonomous intelligent systems, GMD, Sankt Augustin, Germany).

*The emergence of rhythm and coordination in a model of embodied interaction: an operational approach to animal communication.*

Suzanne Bourgeois-Cohn (The Salk Institute, USA). *What everyone should know about cancer - and a little bit more.*

Carl Smythe (University of Dundee, Scotland).

*Probing the mechanism of nuclear reassembly and cell cycle progression using a xenopus cell-free system.*

José Feijó (IGC/Faculdade de Ciências da Universidade de Lisboa, Portugal).

*Sex, Video and some true facts about pollen tubes.*

João Pedro Simas (IGC/ICBAS, Portugal).

*Gammaherpesvirus latency in germinal centers.*

Nelson Vaz (IGC/ Universidade Federal de Minas Gerais, Brasil).

*Biology of cognition and an explanation of immunological phenomena.*

Jean-Emmanuel Faure (École Normale Supérieure, Lyon, France). *Fertilization: of maize and mice.*

## **July**

Manuel Santos (Universidade de Aveiro, Portugal).

*The molecular mechanism of a genetic code alteration in the pathogenic yeast Candida albican.*

Anne O'Garra (DNAX Research Institute, USA).

*Factors determining commitment of T helper cell phenotype.*

Serge Morand (CBETM, CNRS Perpignan, France).

*Parasites and the evolution of host life history traits.*

Genevieve Milon (Institut Pasteur, Paris, France).

*Leishmania major within the mouse dermis: a relevant model?*

Paola Minoprio (Institut Pasteur, Paris, France).

*Pre-existing B-cell repertoire in resistant and susceptible mice to Trypanosoma cruzi infection.*

Antonio Alcami (University of Cambridge, UK).

*Blockade of chemokines by soluble receptors: lessons from poxviruses.*

Dominique Rueff-Juy (Institut Pasteur, France).

*T cell tolerance to maternal Immunoglobulins.*

Hermann Froehlich and Monika Beutelspacher (Boehringer Ingelheim Fonds, Stuttgart, Germany).

*Boehringer Ingelheim Fonds - A Foundation in Progress.*

José António Belo (IGC).

*Molecular mechanisms of action of the mouse cerberus-like gene: biochemical and KO approaches.*

Pierre-André Cazenave (IGC/ Institut Pasteur, France).

*The Mus genus model in Immunology: from cousins (laboratory strains) to panmictic populations (wild derived mice).*

### **September**

Damian Brunner (Imperial Cancer Research Fund, London, UK).

*Linking Microtubules to Cell Polarity in Fission Yeast.*

João Sousa (IGC).

*T cell activation: I. Kinetics of TCR triggering and down-regulation.*

Jean-Luc Jestin (Institut Pasteur, France).

*New in vitro selection of proteins for catalytic activity using phage-display*

Atanasio Pandiella (CSIC/Microbiologia - Universidade de Salamanca, Spain).

*Regulation of cell-cell communication by proteolytic cleavage of membrane proteins.*

### **October**

Margarida Lima (Hospital de Santo António, Porto).

*Lymphoproliferative disorders of large granular lymphocytes (cytotoxic T-cells and NK-cells): definitions, biological significance and clinical implications.*

Rui Gonçalo Martinho (MRC-CMU, University of Sussex, UK).

*Analysis of DNA dependent Checkpoint responses in fission yeast.*

Deborah Braun (IGC).

*IFN type I modulates B lymphocytes sensitivity to BcR ligation.*

### **November**

Marie-Louise Bergman (IGC).

*Genetic analysis of thymocyte defects in the Non-Obese Diabetic mouse.*

Anneliese Schimpl (Institute for Virology and Immunobiology, University of Wurzburg, Germany).

*Blimp-1 in B cell differentiation and apoptosis.*

Ana Catarina Certal (IGC).

*Apples and Almonds: a tasteful reason for studying sex in fruit trees.*

Alexandra Manaia (Instituto de Histologia e Embriologia, Faculdade de Medicina de Lisboa, Portugal).

*Early Hematopoietic development in the mouse embryo: combined analysis of the expression of different factors involved in hematopoiesis.*

Pedro L. Vieira (University of Amsterdam, The Netherlands).

*Environmental induction of Th1- and Th2-promoting capacity in dendritic cells.*

Philippe Alard (Université Libre de Bruxelles, Belgique).

*WWW2GCG, Web access to GCG programmes.*

Gennadii Bocharov (Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow).

*Mathematical models applied to the analysis of the murine LCMV system: CD8+ T cell responses, systemic virus spread and immunopathology.*

### **December**

Armand Leroi (Imperial College, UK).

*Giants and Dwarves among the Worms.*

Alexandre Carmo (IBMC, Portugal).

*Interplay between CD2 and CD5 in T cell activation.*

Elisa Marti Gorostiza (Inst. Cajal de Neurobiologia, Spain).

*Dorso-Ventral patterning of the vertebrate neural tube: interaction between Sonic hedgehog and extracellular matrix.*

Kenneth R. Robinson (Purdue University, USA).

*Dynamics of calcium and pollen tube growth.*

Ken Smith (The Cambridge Institute for Medical Research and the Department of Medicine, University of Cambridge, UK).

*Regulation and death in the normal and autoimmune B cell response.*