

António Coutinho

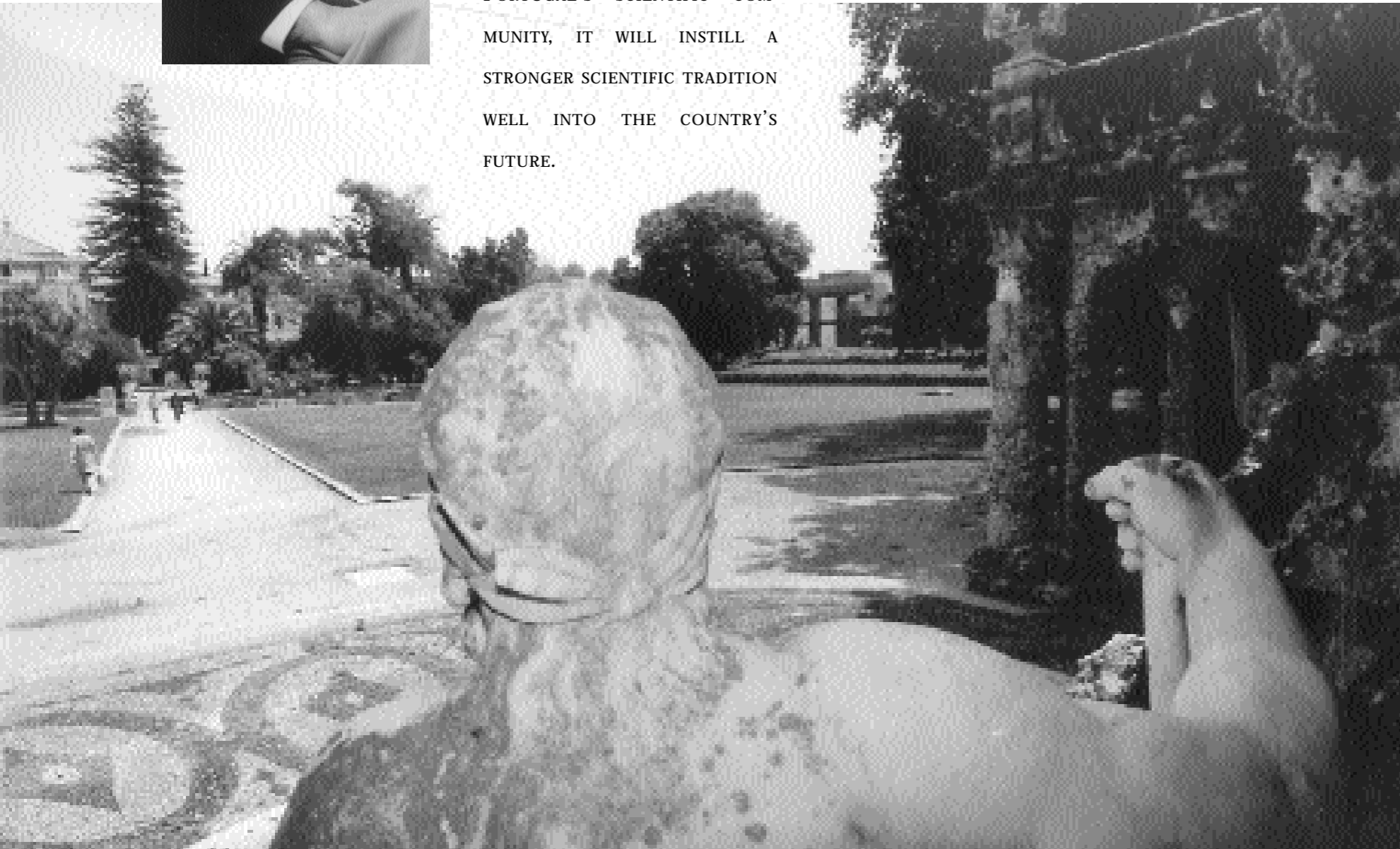
CULTIVATION OF A MODERN LANDSCAPE

THE GULBENKIAN INSTITUTE OF SCIENCE

▶ THE GULBENKIAN INSTITUTE OF SCIENCE – OEIRAS CAMPUS IS A CATALYST FOR CHANGE. THE TRANSFORMATIONS TAKING PLACE WILL NOT ONLY MODERNIZE PORTUGAL’S SCIENTIFIC COMMUNITY, IT WILL INSTILL A STRONGER SCIENTIFIC TRADITION WELL INTO THE COUNTRY’S FUTURE.

WHEN CALOUSTE GULBENKIAN BEQUEATHED financial support for the creation of a foundation that would bear his name in 1953, he endowed it with the four-pronged mission of cultivating charity, art, education and science. Today the institute is home to an extensive collection of works by Lalique, a world famous dance troupe, an equally famous symphonic ensemble and a burgeoning community that promises to robustly boost the standard of biomedical research performed in Portugal. One division helping to fulfill this philanthropist’s commitment to science is the Gulbenkian Institute of Science or IGC’s (*Institute Gulbenkian Ciencias*) Oeiras Campus.

Since basic research and medicine were not a priority during the fascist regime that reigned in Portugal between 1929 to 1974, resources for conducting research or practicing medicine tended to be limited. Long after his death, Gulbenkian’s philanthropic commitment is helping the nation move on from this time. Although fascist rule ended more than thirty years ago, raising the standard of excellence in science has proved to be a long-term and incremental task. One way the IGC at Oeiras has been working to achieve this goal is through the implementation of a postgraduate studies programme. The Oeiras campus has assumed the strategic mission of attracting to Portugal promising young scientists and providing conditions that would allow them to prove their competence in a fully autonomous manner. The programme is designed to foster new leadership and as these students go on to work in Portuguese universities or industry, they improve the state of science in the country. ▶



“EVERYTHING HAD TO BE CHANGED SO WE BEGAN WING BY WING”

In 1991, the institute sought the advice of António Coutinho regarding implementation of the postgraduate courses. Coutinho is a native of Portugal who left his homeland in 1969 for political reasons and went on to conduct research at leading institutes in Sweden (Karolinska, Stockholm) and France (Pasteur, Paris). Coutinho explained that when the Gulbenkian approached him, Portugal gravely needed a PhD programme outside its university system. “Students are entirely in the hands of professors. A good deal of nepotism and personal conditions may often be tied to advancement.” IGC’s system chooses students based on quality even without a research project. The programme currently includes mathematicians and an economist.

Eventually, Coutinho accepted a position, as Head of the IGC’s Oeiras campus but courting this world-renowned researcher back to his native soil was not easy. The Gulbenkian Institute had to make three major concessions. Since science received only seven per cent of the funding available to the Gulbenkian – a distortion of the original charter that divided the pie equally between art, charity, science and education – Coutinho required an administrative commitment to correcting the balance. He also requested the Institute submit to the advice of a scientific advisory board instead of the general Board of Directors. Their newly instituted scientific advisory board includes Nobel laureates Susumu Tonegawa and Sydney Brenner. By far the greatest demand was Coutinho wanted to return home to a clean house. In other words, he required that the institute’s research facility in Oeiras

be cleared of the people in its employ, their equipment and “nearly anything else that was not nailed down,” as he described.

In mid-1998, Coutinho arrived to reside over an institute with no scientists and no equipment. “Even the air conditioning was not functioning. Everything had to be changed, so we began wing by wing.” Today the renovations are nearly 60 percent complete and about 50 researchers and nearly 40 PhD students inhabit the campus along with some short-term visitors and undergraduate students.

Not unlike a great architect, Coutinho is carefully compiling the perfect combination of unique elements in order to create an optimal atmosphere except in his case it is for conducting biomedical research and promoting learning. The advantage of having started with a blank slate is “I was never under pressure to hire a scientist because I had to occupy the laboratory,” he explains. Interesting when asked about the qualities he looks for in the researchers he chooses to bring into the institute, his first response was “generosity.” “People able to think outside the box,” was also on what turned out to be an extensive list. Along with a passion for science, these two qualities are easily observed in the people and the research that is ongoing at IGC.

SEGMENTATION AND SYSTEMS

ISABEL PALMEIRIM STUDIES DEVELOPMENT using chicken embryos. Palmeirim picked up her microsurgical technique while completing a PhD in Nicole Le Douarin’s laboratory at the CNRS in Paris. She returned to Portugal because the Gulbenkian provided her with “the



Left to Right: Matthias Haury, Isabel Palmeirim and José Feijó

opportunity to create something in Portugal,” she explains.

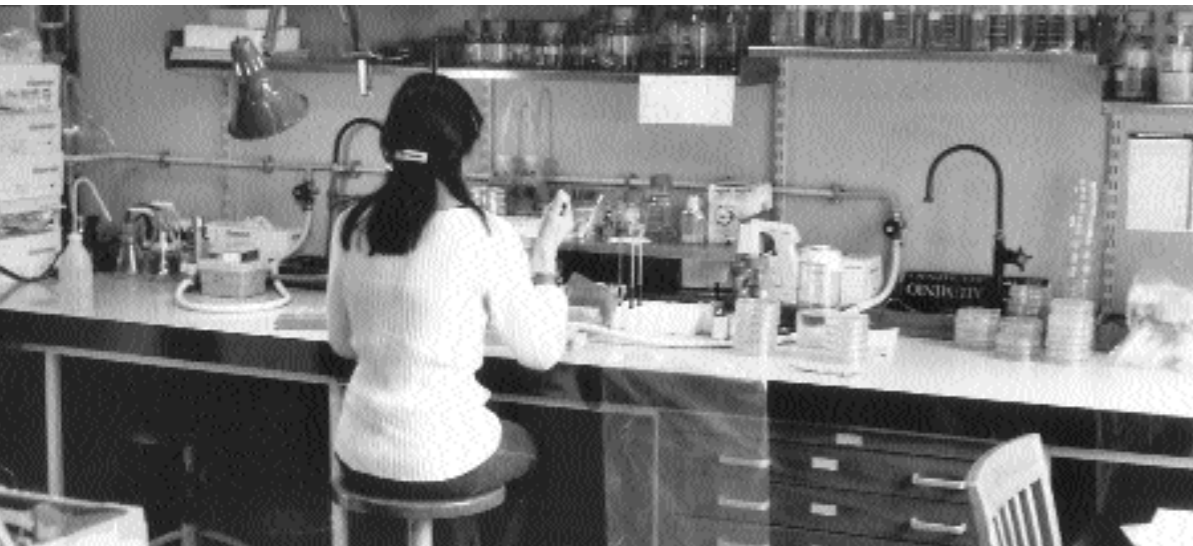
In the chick embryo a pair of somites bud off in a highly coordinated fashion every 90 minutes from the cranial end to the presomitic mesoderm (PSM). Palmeirim goes on to detail that the establishment of segmentation in vertebrates is under molecular control and she describes her model as “big and seeable molecular biology.” Using the chick embryo Palmeirim investigates the existence of the molecular clock. *Drosophila* hairy genes (*c-hairy-1* and *c-hairy-2*) expressed in a repetitive wave in the PSM provided the first evidence of the existence of this clock. Palmeirim evaluates the expression of these two genes in chick embryos autonomous of each portion of the PSM to detect any controlling signals coming from either the anterior, lateral or medial portion.

According to José Feijó, “microtubules are 100 times more dynamic in plants than animals.” Not surprisingly, Feijó explores the ionic dynamics of cells using pollen tubes “one of the fastest growing cells in nature.” Feijó characterizes ion dynamics as the message carriers and cellular signals of plants. He

works with the well-established premise that cells should display spatial and temporal ion dynamics. Pollen tubes do not divide therefore they constitute a highly malleable single cell system for studying these dynamics during development.

After fertilization the pollen tube lengthens and sperms move through the tube. The tube becomes a highly polarized cell and ion currents around the growing tube organize. Feijó has engineered a state-of-the-art system that couples an ion-vibrating probe with a highly-sensitive imaging system and with it he can detect faint variations in the cell’s internal concentrations and make correlations to external fluctuations in current. He has constructed a description map of the four major ions Ca , Cl , K and pH surrounding the development of these tubes. For example, Ca is found entering the growing tip in high concentrations.

Using fluorescent protein markers, Feijó can also observe ion-carrier distribution along the cell wall. Though exploring the ion dynamics of pollen tube development seems a far cry from biomedicine, the two topics are not as distant as one might think. For ➤



PALMEIRIM DESCRIBES HER MODEL AS “BIG AND SEEABLE MOLECULAR BIOLOGY”

example perturbations in the pollen tube's channels or pumping mechanisms can lend insight into developmental disorders such as cystic fibrosis. Feijó is taking a systemic molecular approach to establish the molecular counterparts of this physiological model in addition to collaborating with theoretical biologists and physicists.

Matthias Haury confesses his work at the institute is more management than science. Since he claims to be part computer programmer as well as part mechanic, the opportunity to set up the systems laboratory at the Gulbenkian was very appealing. Over the last two years Haury has helped to make functional the institutes flow cytometer and cell sorter and cell imaging systems including a multiforme confocal microscope. In collaboration with the laboratory of António Andeira (Pasteur Institute) Haury is in the process of characterizing in more detail the immuno subphenotype of regulatory T-cells and their localization using multicolor flow cytometry and and multiphoton confocal microscopy.

IMMUNOLOGY AND INFECTIOUS DISEASE

COUTINHO IS A PROPONENT OF THE THEORY that autoimmune disease (AID) results from deficits of autoreactive T-cell generation. Jocelyne Demengeot, a principal investigator at the Gulbenkian, is also a proponent of the theory. She is conducting eloquent mouse studies that have linked the absence of a highly specialized T-cell population with the onset of AID. Since Demengeot was unavailable for an interview, Shohei Hori, a post-doc from Japan working in her laboratory, discussed

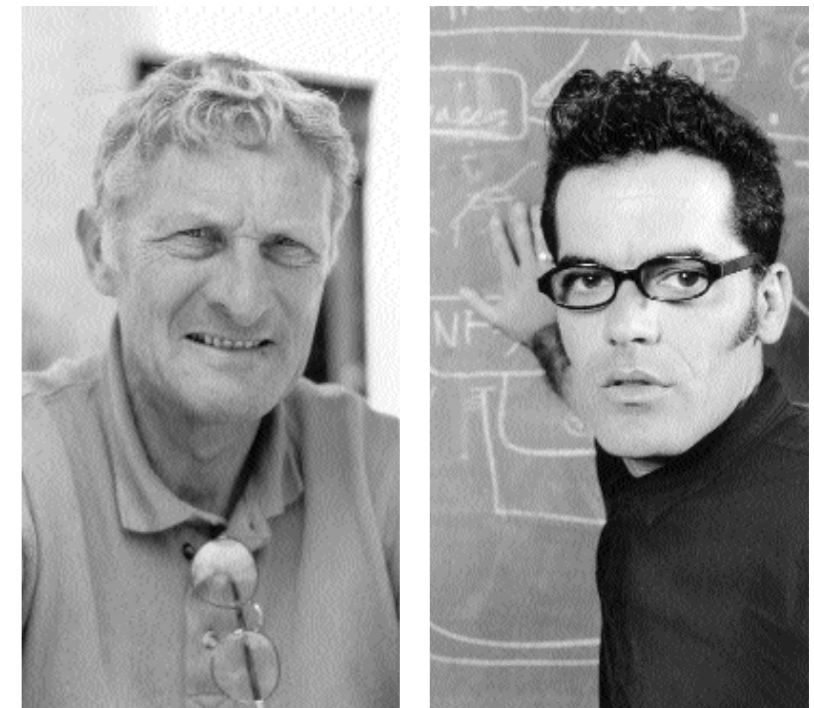
their ongoing research. Hori mentioned that a Japanese group identified two reactive subsets of CD 4+ cells [CD25+ (10 %) and CD25- (90%)]. Introduction of CD25- cells into a nude mouse caused various organ-specific AIDS (*e.g.*, gastritis, oophoritis) while the CD25+ cells alone caused no disease onset. The chimeric model also showed no disease.

Hori and his colleagues hypothesize that the CD25+ cells exerted a protective effect over the pathogenic CD25- cells, not only during AID but also during inflammation caused by infectious agents. Studies of the two cell populations in Rag 2 -/- mice infected with *Pneumocystis carinii* attributed a suppressor effect to CD25+ cells. Rag 2 -/- mice cannot produce mature T or B cells and CD25- cells introduced into the infected Rag 2 mice proliferated exponentially (10^{6-7}) in the lung and caused fatal pneumonia. When introduced with CD25+ cells, the number of CD25- cells remained low (10^{4-5}) and the animals healthy. Demengeot is also obtaining some corollary results using a model of experimental autoimmune encephalomyelitis otherwise known as a mouse model of multiple sclerosis in humans.

As an “immunologist with an interest in infectious disease,” David Parkhouse designs his investigations based on the principle that viruses have been studying the human immune system for much longer than the research community. He feels the mechanisms viruses developed to evade capture can reveal a great deal about the immune system. “If the process has not been interfered with by a virus how important can it be?” he commented.

More specifically, Parkhouse and other re-

Michael Parkhouse (left)
and Miguel Soares
(right)



searchers at the institute investigate large DNA viruses and ways in which they manipulate host responses. Control over apoptosis is one characteristic of interest to Parkhouse and his colleague Pedro Simas. They study relevant genes encoded by three large DNA viruses [*i.e.*, mouse herpes, mousepox and African Swine Fever Virus (ASFV)]. Although seemingly unrelated, all three DNA viruses modify apoptosis to promote their own survival. In search of some structural homology, Parkhouse and colleagues are comparing the genes regulating apoptosis in each of these organisms.

ASFV is asymptomatic in its host (*e.g.*, the bush pig and warthog) but causes severe hemorrhagic disease in domestic pigs. The sequence of ASFV's genome has revealed that products of the *ikB* sequence inhibit transcription via cellular NFkB. When NFkB is inhibited, cells are signaled to undergo apoptosis. Pathogenesis of ASFV in the domestic pig involves extensive lymphoid apoptosis.

Miguel P. Soares is also investigating apoptosis. His newly established laboratory at the IGC is interested in the study of protective genes that are expressed in vascular endothelial cells and that suppress inflammation as well as apoptosis. Among them is the stress

response gene Heme oxygenase-1. It generates the signalling molecule carbon monoxide (CO) and CO suppresses the expression of pro-inflammatory genes and prevents endothelial cells from undergoing apoptosis (*see Helix* Vol X, Issue 2). At IGC, he is setting up *in vitro* assays to take a closer look at the mechanism by which CO acts to suppress inflammatory reactions and curtail cell death.

Coutinho's interest in immunology was sparked in the 1960s as a practising physician in Portugal. While treating a young girl with AML, he observed that the platelets transfused from the father persisted in her for a week but those taken from the child's mother were cleared in a day. The incident coupled with a disagreeable fascist war prompted him to pursue an immunology research career in a foreign land. When he received the offer to head the Gulbenkian he knew it meant more than returning home. It also meant “abandoning the bench to be an administrator for several years.” Though he feels “science is something you do until you die,” At the time, Coutinho also felt, “maybe I should do something for other people.” With the institute operating at 60 per cent, his return to the bench is a not so distant prospect. ◀

BY BARBARA NASTO
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