SCHOOL OF HEALTH SCIENCES

LIFE AND HEALTH SCIENCES RESEARCH INSTITUTE

(ICVS)

ANNUAL REPORT

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The present report, elaborated in the scope of the evaluation of the Life and Health Sciences Research Institute, on the 10th of December 2003, by the External Panel of the Foundation for Science and Technology (FCT), regards the year 2003 which was essentially a launching period for the research activities at the ICVS. A summary of the original objectives, evolution, goals and challenges of ICVS, specifically prepared to give the Panel an overview of the development of ICVS since its creation, is included as annex to the present report (Appendix I).

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1. INTRODUCTION

The Life and Health Sciences Research Institute (ICVS) is a fully incorporated research structure within the new School of Health Sciences (ECS) of the University of Minho (UM).

The ECS is being developed under a contract established with the Government in February 2000, with the aim to provide adequate infrastructural support for a new and innovative Medical Degree Programme, to be carried out in a research based environment. The contract explicitly included the financing of a new building (which includes an academic block of about 10 000 m^2 and a research block of around 6 000 m^2) and the equipments for the academic block. It was later agreed that a special contract for the research unit and the equipments for the research block would be signed later.

In this context and following the launching of the degree programme in October 2001, the years 2002-2003 were crucial for setting up the ICVS as a research unit integrated in the national system of science and technology. Two main proposals were formally submitted in early 2002 to the Foundation for Science and Technology for the financing the ICVS. Specifically:

- the financing of ICVS as a research unit integrated in the national system of science and technology;
- the financing of equipments for the research laboratories, aiming to establish an infrastructure of "Shared Instruments Facilities" in partnership with research units of the University of Minho in the areas of Biology, Physics Bioengineering and Biotechnology.

Unfortunately, there were significant delays in the responses to these proposals: both decisions have been postponed until now.

Even so, the School considered vital for its success the creation, from the very beginning, of adequate research conditions. To achieve such goal, the School and the University supported the development of appropriate laboratories in the provisional buildings. These laboratories have a dual function: teaching and researching. In this way, the academic staff could proceed with their research projects, overcoming in part the usual difficulties of the initial phase of a new School and attract young researchers to work with them. This approach meant a strong commitment of the School towards research, since it was necessary to save in every possible way in current expenses (including staff contracts), pushing the financial resources towards the preparation of the laboratories and the acquisition of equipments.

Particular attention was devoted to the creation of the Animal Experimental Facilities that are essential for all the priority research areas selected for the ICVS.

Given this strategy it was possible to finish the preparation of such facilities, albeit only in August 2002 (clean area), December 2002 (biosafety level 3) and November 2003 (biosafety level 3 accreditation).

In this way, when reading the present report it must be taken into consideration that the years 2002 and 2003 were essentially the set up period for the research activities at the ICVS. In spite of that, all members of the academic staff kept active in research and a meaningful number of research students and post-doctoral fellows were associated to the research projects. However, for the sake of coherency, it must also be emphasized that a significant part of the scientific activities developed by most of the ICVS staff members is yet associated with their research work outside the ICVS, both in their original institutions or in collaborating laboratories.

2. ORGANIZATION AND COORDINATION

? The Life and Health Sciences Research Institute should have its own governing bodies, according to the rules applied to the research units integrated in the national system of Science and Technology, namely:

- Scientific Council;
- Director, that liaises with the Scientific Council;
- External Advisory Committee.

? Meanwhile, and during the installation period, a Steering Committee (functionally equivalent to the Scientific Council) and a Coordinating Committee were nominated.

The Steering Committee was formally designated by the Rector of the UM in October 2002. The present composition is therefore the following:

- Maria Cecília Lemos Pinto Estrela Leão, Director
- All ICVS members with a doctoral degree:
    - Adhemar Longatto Filho
    - António Gil Pereira de Castro
    - Armando Alberto Pinto de Almeida
    - Fátima Baltazar
    - Fernando José dos Santos Rodrigues
    - Isabel Maria Mestre Palmeirim Esteves
    - Joana de Almeida Santos Pacheco Palha
    - João Pedro Antunes Pereira
    - Jorge Correia Pinto
    - Jorge Manuel Rolo Pedrosa
    - Nuno Jorge Carvalho de Sousa

- Patrícia Espinheira Sá Maciel
- Paula Cristina Ludovico
- Raquel Andrade
- Rui Manuel Vieira Reis

The Steering Committee meets on a monthly basis, concentrating its activities on the (i) planning of the ICVS development, (ii) evaluation of the activities, (iii) establishment of guidelines of the ICVS and (iv) reinforcement of the links within the ICVS research groups and with other research institutions.

The Coordinating Committee was internally nominated in January 2003. Its present composition is:

- Maria Cecília Lemos Pinto Estrela Leão (Coordinator)
- Jorge Pedrosa (Laboratory facilities, management and planning)
- Nuno Sousa (Research activities)
- Joana Palha (Post-graduation activities)

The Coordinating Committee meets on a weekly basis, concentrating its activities on (i) monitoring the on-going activities and (ii) establishing the operating rules for the shared equipment in order to guarantee its rational and optimal use and (iii) determining the sharing of running expenses.

? **At the operational level**, there are:

- Coordination Groups of each of the major research areas that are composed by the members of the area with doctoral degree;
- Principal Investigators of the projects;
- Coordinators for each laboratory.

? **The ICVS External Advisory Committee** will be created as soon as the research unit is formally created by the FCT. Meanwhile, the ICVS activities are being accompanied by the External Advisory Committee of the School.

3. ACTIVITIES IN 2003

3.1. PLANS AND STRATEGIES

From the very beginning it was defined that the main goal of ICVS should be to undertake competitive interdisciplinary biological and biomedical research with impact on health care.

At the same time, the ICVS, as a fully incorporated research structure within the ECS, should also assure that their staff develops a full academic career, including a strong involvement in research. The appropriate links between teaching and research were established in order to provide a research-based teaching and learning environment for undergraduate students.

The strategic research areas were defined taking into account prevalent health problems in the region and synergetic complementarities with other research units concerned with health sciences in the northern region of Portugal. In the initial proposal, the following areas were selected: Clinical Mycology; Immunology; Genetic Diseases; Neoplastic Diseases; Neurosciences; Developmental Diseases.

As the first research projects started to be developed under the coordination of the teaching staff hired since 2001, a more aggregated organization was envisaged, joining knowledge and expertise in wider areas. Therefore, at present the research activities of ICVS are focused on three main research areas:

- Infectious Diseases
- Neurosciences
- Development and Neoplasia

3.2. RESEARCH ACTIVITIES

3.2.1. ONGOING RESEARCH AREAS, TEAMS AND RESULTS

A brief description of the above mentioned research areas, the projects that are being developed in each of them and the corresponding teams are next presented. Some of the ongoing projects were started outside the ICVS, both in the original institutions of the ICVS members and in collaborating laboratories, but they are being transferred to the ICVS as the appropriate conditions are available. Presently most of them are already being developed at the ICVS laboratories.

A. INFECTIOUS DISEASES

The infectious diseases team is presently composed of 6 PhDs, 4 research assistants (4 B.Sc.'s), 3 Master student (3 B.Sc.'s), and 3 PhD students (3 B.Sc.'s).

Immunobiological studies of Virulence-Associated Immunomodulatory Proteins (VIP) secreted by mycobacteria

We tested 3 strains of *Mycobacterium avium* with different degrees of virulence for mice: *M. avium* 25291 > 2447 > 3509 and found that their *in vitro* growth rates inversely correlate with their capacity for infecting mice. We measured up-regulation of activation markers CD69 and CD25 in lymphocytes *in vitro* in response to culture filtrate proteins (CFP) of *M. avium* 25291. We also observed that mice treated with CFP from this strain produce higher levels of IL-10, as compared to mice treated with CFP from *M. avium* 3509. Preliminary results also indicate that macrophages from IL-10 KO mice have an enhanced capacity to control *M. avium* 25291 proliferation. We are currently analyzing the CFP of *M. avium* 25291 in order to identify and clone candidate VIP.

Biology of infection in mycobacteriosis of difficult treatment- Buruli Ulcer

Work by other groups has shown that mycolactone-enriched acetone-soluble lipids (ASLs) from several strains of *M. ulcerans* have different degrees of CPA, and the virulence of each strain was ranked according to the respective CPA value. However, animal models have not been explored to characterize the *in vivo* activity of such clinical isolates of *M. ulcerans*.

We carried out a comparative analysis of the virulence of 4 *M. ulcerans* strains of different origins and different CPAs, using the footpad mouse model. Our data showed that there is not a correlation between the CPAs described and virulence. Additionally, histopathological analysis showed that all strains of *M. ulcerans* induce an acute inflammatory response with a predominance of neutrophils. Later during the infection, the low virulent strains induce a histiocytic infiltrate with granuloma formation. On the other hand, virulent strains induce ulceration associated with apoptosis and massive tissue necrosis. Preliminary data obtained from infection of macrophages *in vitro* showed that *M. ulcerans* can have an intracellular growth phase. We also observed that low virulent strains, but not the high virulent ones, induce the production of high levels of TNF-α. At the present we are carrying out experiments to better elucidate the cellular and molecular mechanisms underlying resistance or susceptibility to *M. ulcerans*.

Expression and Activation of murine Toll-like receptors in B lymphocytes

We showed that activation of mature B lymphocytes by TLRs induces activation markers and co-stimulatory molecules, clonal expansion and differentiation. In addition, TLR expression in B lymphocytes is tightly controlled, even at the level of allele usage. However, the role played by TLR activation in B cells during infection is not yet fully understood and will be addressed.

The Immune Response to Allografts: Role of Anti-inflammatory Cytokines

We are characterizing two lines of transgenic mice, generated by Gil Castro, that

express either IL-10 or IL-4 under the control of a Zinc-inducible promoter. So far we measured up-regulation of IL-10 and IL-4 in the serum, brain and thyroid of mice fed with $ZnSO_4$ in the drinking water. Expression of these two cytokines in the thyroid is extremely relevant, since this organ will be used to perform allotransplantion. These transgenic mice will be used as donors and recipients of transgenic and wild type organs, respectively. The biological relevance of local cytokine production will thus be evaluated.

Development of drug delivery systems for the treatment of mycobaceriosis

Therapeutic systems for delivering anti-mycobacterial drugs to macrophages are being developed by collaborator laboratories. We will assess the effect of administration of different types of liposomes, different doses and treatment schedules in mouse models of mycobacteriosis.

Fungal infections

? Steroid hormones and paracoccidioidomycosis

Paracoccidioides brasiliensis, a dimorphic fungus, is the causative agent of the prevalent systemic mycoses in Latin America, paracoccidioidomycosis. To get expertise with biosafety level 3 practices, one of our PhD students has recently concluded a training period (4 months) in the Medical and Experimental Mycology Group of "Corporatión para Investigaciones Biológicas" in Colombia, with Professor Angela Restrepo. In the last month, a genomic library was constructed in an *Escherichia coli* plasmid to isolate autonomous replicating sequences. Additionally, and since clinical paracoccidioidomycosis is 13 times more common in men that in women, we are at present constructing a subtractive cDNA library from the inhibition of the transition of mycelia (saprophyte form) to yeast (parasitic form) due to 17 β-estradiol.

? Dermatophytosis

Epidemiology and therapy: We carried out a retrospective study of dermatophytosis infection, from January 1983 to December 2002, in Braga region (São Marcos Hospital) to achieve the etiology and frequency of dermatophyte infections. The results shown that *Trichophyton rubrum* was the highest prevalent agent (37.4%), followed by *Microsporum canis* (25.0%). As expected, from the overall economic, social and living conditions changes occurred in the District of Braga during the last twenty years an alteration of the dermatophyte prevalence patterns was observed in this study.

Research has also been focusing in the potential utilization of ethanol and acetic acid has antifungal agents. The results obtained with *Candida* species (*C. albicans*, *C. Krusei* and *C. glabrata*) have shown that the two agents studied induce a severe alteration in cell cycle progression and an impaired mitochondrial function. The work to be developed will clarify the relation of cell death process (active vs passive) induced by acetic acid and ethanol and the different profile of resistance/susceptibility observed

among the three species studied. Additionally, and in the scope of this project the yeast *Saccharomyces cerevisiae* has been used as a model to define the cellular/molecular targets of anti-fungal drugs such as ciclopirox olamine and undecylenic acid. The toxic effects of these two drugs were evaluated in the cell cycle progression, reactive oxygen species production, mitochondrial function/integrity and cell death process. Our results suggested that ciclopirox olamine induces a programmed cell death process while the death profile induced by undecylenic acid is compatible with a necrotic process. Moreover, the results obtained reinforce the utilization of *S. cerevisiae* as an excellent model system for the identification of drug targets and therefore further contributes to the elucidation of mechanisms of resistance observed in pathogenic fungi.

? Susceptibility of immunocompromised patients to systemic mycoses

Risk factors analysis: We aimed with this project to examine the epidemiology of systemic fungal infections in malignancy patients in Portugal, together with the identification of human genetic predisposition markers for these infections. In this last year, we contacted several hospital centres and their clinicians in order to collect samples to start this project.

Exploitation of yeast as a model to study mitochondrial and lisosomal associated diseases

? Cytochrome c oxidase deficiency and mitochondrial neuromyopathies

We are collecting and analysing samples from Hospital Geral de Santo António-Porto, Instituto de Genética Médica Dr. Jacinto de Magalhães-Porto and the Department of Neurology from John Macdonald Foundation-Center for Medical Genetics in the University of Miami. The molecular analysis of muscle biopsies from patients with specific cytocrome c oxidase deficiency revealed, among different patients, distinct patterns concerning the steady state levels of different cytochrome c oxidase subunits. At the same time *S. cerevisiae* has been used as a model for the study of cytochrome c oxidase assembly. Cytochrome c oxidase subunit II mutant was shown to be sensitive to death induced by different stimuli. We are at the moment deeply studying the role of cytochrome c oxidase complex and signalling of the downstream mitochondria programmed cell death pathway.

? Oxidative stress in the yeast model of Batten's disease

S. cerevisiae BTN1 gene is homologue and functionally equivalent to the human *CLN3* gene, associated with Batten's disease. Our results showed that yeast lacking Btn1p display a resistance phenotype to imposed oxidative stress when compared to the wild type strain, namely by the pro-oxidant agents hydrogen peroxide and menadione. The antioxidant enzymes, catalase, glucose 6-phosfate dehydrogenase, cytosolic and mitochondrial superoxide dismutases as well as glutathione seem not to be involved in the resistance phenotype of the mutant strain. Research is currently focusing on the possible involvement of down regulation of the expression of the gene YNL305c that

shows homology with the mice N-methyl-D-aspartate glutamate-binding receptor.

B. NEUROSCIENCES

The neuroscience team is presently composed of 3 PhDs, 1 MD PhD, 15 research assistants (10 MDs and 5 B.Sc.'s), 1 Master student (BSc.'s), 11 PhD students (2 MDs, 9 BSc.'s).

Neuroendocrinology: neurobiology of stress-behaviour and structural correlates; hypothyroidism and progeny psychomotor development

? Stress (*corticosteroid milieu*) and cognition.

We characterized the changes in behavioural profile following imbalances of the corticosteroid *milieu* and identified decreased locomotor and exploratory activity, signs of anxiety and depression-like traits, spatial and working memory deficits in dexamethasone-treated rats.

We performed *in vivo* ultrahigh-field magnetic resonance and stereological evaluation of the structure of the limbic brain and identified volumetric reductions and neuronal losses in the prefrontal cortex and amygdala in hypercortisolemic conditions, but no structural changes in the nucleus accumbens and retrosplenial cortex. The behaviour study of offsprings following *in utero* treatment with different ligands of corticosteroids revealed signs of increased anxiety following dexamethasone, but not corticosterone treatment. Our study of specific ligands of CRF receptors in anxiety-behavior demonstrated increased anxiety-traits in animals treated with urocortin – a CRF2 ligand.

Through topographic analysis of neurogenesis and neuronal apoptosis in the hippocampus in normal conditions and following mineralocorticoid receptor unoccupancy we have demonstrated increased granule cell turnover in adrenalectomized animals.

Analysis of the *in vivo* neurochemical profile of hippocampal metabolites in dexamethasone treated animals revealed increased glutamate in parallel with reduced glucose levels in the hippocampus.

In addition, we evaluated the role of stress as a predisposing factor for Alzheimer's disease and temporal lobe epilepsy. Alzheimer's disease: upon combined treatment of ß–amyloid and dexamethasone, the behavioural study revealed that cognitive deficits induced by stress were aggravated by ß–amyloid and dexamethasone treatment; the expression of different epitopes of tau phosphorylation was increased in these animals. Temporal lobe epilepsy: genetic, behavioural and function studies in association with febrile convulsions are currently being performed.

? Pharmacological interventions modulating corticosteroid-induced neurodegeneration and neurogenesis.

Results obtained during 2003 showed the role of different glutamatergic receptors

in the neurodegenerative process induced by glucocorticoid receptor activation: both iGluR and mGluR mediate the neurotoxic effects of glucocorticoids on hippocampal cells, whereas pre-treatment with low-doses of NMDA, by acting on synaptic and extrasynaptic receptors, promotes neuroprotection

We studied the role of lithium as a modulator of granule cell turnover, showing that treatment with lithium resulted in increased neurogenesis but did not affect neuronal apoptosis, either in normal conditions or following adrenalectomy.

? Transthyretin (TTR), thyroid hormone homeostasis, lipid metabolism and behaviour

We described that, in opposition to the most prevalent theories in this field, TTR (the major rodent serum and cerebrospinal fluid thyroxine carrier) is not necessary for thyroid hormone homeostasis in conditions of physiological and pathological increased hormone demand: exposure to cold and thyroidectomy, respectively.

Using TTR-null mice, we described, for the first time, that in the absence of this protein mice display increased locomotor activity and decreased depression-like behaviour, which might be related with the increased levels of norephinephrine present in the limbic forebrain. In addition, the amygdala of the TTR-null mice shows atrophy and neuronal loss in spite of signs of increased synaptic plasticity.

Preliminary studies suggest that mice lacking TTR have altered lipid metabolism and diabetic-like behaviour, as inferred from altered tolerance to glucose, insulin and fat administration, and by the altered levels of circulating lipids.

? Characterization of the iodine status of pregnant women in the Minho district

Minho is the district with highest birth rate in Europe; we have collected blood and urine from about 50 women (all trimesters of pregnancy) and 10 newborns; our preliminary data show thyroid hormone impairment in some of the pregnant women. Motor and intellectual performance of the newborns will be followed for a period of 2 years. The data is being compared and integrated in a European network.

Mechanisms of chronic and acute pain and endogenous pain control pathways

? Noxious stimulation of the larynx

Our study showed that peripheral fibers in the larynx mucosa, which are immunorreactive to neuronal markers of sensory nerves, reach the epithelium from the "lamina propria" of the mucosa and terminate between the cilia of the external epithelial cell layer. These data indicate that: (1) primary afferents in the larynx can be directly activated by noxious and inflammatory substances; (2) this organ can constitute a model for studying the peripheral inflammatory mechanisms involving the sensitization of nociceptors.

? Encephalic connections of brain centers implicated both in limbic (“emotional”) or stress physiology and pain modulation

The administration of retrograde tracers to the (1) central amygdaloid nucleus of

the amygdala (AMY) or (2) paraventricular hypothalamic nucleus (PVN) showed that a large spectrum of brain areas involved in sensitive, motor, autonomic and pain processing functions project to both the AMY (limbic system) and / or PVN (stress response).

? Analgesic action triggered by a chronic unpredictable stress model

The maintenance of high levels of corticosteroids during the time used by a model of chronic (1 month) unpredictable (one of several possibilities each day) resulted in a very strong increase in pain-like tolerance to a noxious stimulus applied to the rat tail 3 times in a row with a minute interval between them (tail-flick test). Data suggest that opioids (and not corticosteroids) may be responsible for these changes in pain tolerance induced by chronic stress.

Genetics and biochemistry of psychiatric and neurological disorders

? Schizophrenia

We described altered levels of circulating thyroid hormones in schizophrenic patients and no alteration of the thyroxine carrier, transthyretin (TTR), in the plasma or cerebrospinal fluid of schizophrenic patients. Searching for polymorphisms in candidate genes, we found a new polymorphism in TTR that does not seem to be associated with the disease. We did not find in our Portuguese and Brasilian shizophrenic populations any of the mutations described by other groups in the nuclear receptor Nurr1 in patients with schizophrenia and Parkinson's disease. In addition, we found two novel polymorphic markers in the prostaglandin D2 synthase gene, which are now being tested for association with schizophrenia.

? Hereditary movement disorders

We found no mutations in the genes *PRNP*, *Junctophilin-3*, *TBP*, *DRPLA*, *CBP* and identified eight individuals with sequence variants (pathogenicity to be confirmed) in the *N-OCT-3* gene, as well as one mutation in the *FTL* gene (see below) in a sample of 95 patients with a clinical presentation similar to Huntington disease but without an expansion of the CAG repeat on the *HD* gene (*Huntington-like*).

We identified a novel missense mutation inn the *FTL* gene (Ferritin Light polypetide) in a patient of the *Huntington-like* patient sample, demonstrated its absence from a control population and performed a detailed clinical, genetic, biochemical and neuroimaging study of the patient and his family.

We characterized the distribution of the $(CAG)_n$ repeat in the *HD* gene in a large sample of the Portuguese population.

We identified a new mutation on the *TITF1* gene (Thyroid Transcription Factor 1) in two patients presenting Benign Chorea (mother and son) and performed a detailed clinical, biochemical and neuroimaging study of the patient and his family.

? Machado-Joseph disease

We cloned the mouse homologue gene of the Machado-Joseph disease (*Mjd*) that encodes mouse ataxin-3. We performed the determination of its genomic structure and studied the expression pattern of mouse ataxin-3, during embryonic development and in the adult stage. We produced recombinant mouse ataxin-3 by expression in *E.coli* and produced a polyclonal antibody that recognizes it.

Using bioinformatics we characterized the mouse *Mjd* gene promoter region; and identified potential binding regions for certain transcription factors, namely, MyoD, Brn-2, E47 and SP1, which are conserved in human and mouse. We functionally characterized the promoter using plasmids carrying different lengths of the 5' region fused with the CAT reporter gene in both undifferentiated and differentiated P19 cells (neurons and myocytes).

We generated a new cDNA transgenic mouse model of the Machado-Joseph disease and established two founder lineages for this model, one that has a single copy of the transgene, another with multiple copies (8-12). We have confirmed expression of the mutant protein in the CNS of the animals. The biochemical and phenotypic studies in heterozygous animals with 6 months of age from the single-copy line revealed no abnormalities at this age.

? Rett syndrome

Mutation screening of the complete coding region of the *MECP2* gene in 120 Portuguese patients with clinical diagnosis of Rett syndrome revealed the presence of mutations in approximately half of the patients.

We cloned regions of the 3'UTR of the *MECP2* gene that are highly conserved among species in order to study their ability to (1) direct polyadenylation and/or (2) bind regulatory proteins in cellular extracts.

Mutation screening of the 3'UTR of the *MECP2* gene in 70 Portuguese patients with clinical diagnosis of Rett syndrome and 200 autism patients (collaboration with Dr Astrid Vicente, IGC, and Dr Steve Sommer, USA), showed the presence of sequence variants that are currently being further characterized.

C. DEVELOPMENT AND NEOPLASIA

The development team is presently composed of 2 PhDs, 4 MD PhD, 6 research assistants (4 MDs and 2 B.Sc.'s), 7 Master student (5MDs, 2 B.Sc.'s), 7 PhD students (2 MD, 5 B.Sc.'s).

Calcium regulatory proteins in an experimental model of pulmonary hypertension

These studies showed that in chronic pulmonary hypertension, impaired left ventricular (LV) function cannot be interpreted as a hemodynamic consequence of LV preload reduction and increase ventricular diastolic interaction. In fact, we demonstrated that in pulmonary hypertension there is a precocious decrease of LV diastolic tolerance to afterload, which is accompanied by expression of the fetal pattern

of myosin heavy chain (MHC) isoforms, whereas expression of SERCA2a and phospholamban (PLB) only presents changes at the transcriptional level. Load dependent myocardial relaxation and increased β-MHC preceded systolic dysfunction and SERCA2a and PLB down-regulation.

Fetal correlation between cardiac and lung growth in congenital diaphragmatic hernia

These studies demonstrated that the 'two hit hypothesis', recently suggested to explain antenatal lung hypoplasia in congenital diaphragmatic hernia are not valid to explain heart hypoplasia in this model. In fact, nonmechanical factors play a role in the pathogenesis of lung and heart hypoplasia manifested precociously in fetal life, whereas mechanical compression might influence only lung growth during late gestation. Thus, heart weight predicts lung weight only in early gestation. Consequently, we purpose that fetal echocardiography evaluation might have prognostic significance, whereas at end-gestation echocardiography evaluation has limited interest to estimate prognosis.

Ghrelin gene expression during fetal rat cardio-pulmonar development

In rat and human, we demonstrated that ghrelin gene/protein expression is evident in neuroendocrine cells since embryonic lung development stage reaching maximal expression in pseudoglandular stage. In humans, the number of cells producing ghrelin does not seem to be significantly reduced in lung of fetuses with congenital diaphragmatic hernia (CDH). Additionally, we had opportunity to show that there is also significant ghrelin gene expression during fetal cardiac development.

Fetal pharmacological treatment of lung hypoplasia in congenital diaphragmatic hernia

We tested the hypothesis that antenatal medical treatment either with vitamin A or ghrelin could be beneficial to reduce lung hypoplasia in experimental congenital diaphragmatic hernia. Vitamin A attenuates lung hypoplasia in CDH by interfering with early acting non-mechanical factors. In humans, prenatal diagnosis occurs late in gestation, but we could not demonstrate the benefit of late administration of vitamin A for lung development in CDH. In contrast, antenatal exogenous administration of ghrelin specifically increased lung parenchyma in experimental CDH.

Property of medial presomitic mesoderm (PSM) cells to segment autonomously

By performing series of *in ovo* quail-chick homotopic and heterotopic grafts, as well as *in ovo* insertion of barriers and *in ovo* tissue ablations, we determined: (1) that the lateral prospective somitic domain is located in the 100 - 150 μm most caudal part of *sinus rhomboidalis*; (2) that the removal of the prospective lateral PSM territory does not affect segmentation, but, in contrast, segmentation is arrested in embryos from which the prospective medial PSM territory has been removed; (3) that the prospective lateral PSM cells grafted into the medial prospective territory acquired the capacity to drive

segmentation, suggesting that the environment is determinant for medial prospective cells to acquire the autonomy for segmentation; (4) that the insertion of an impermeable *tantalum* barrier between the neural tube and the most caudal part of the PSM did not perturb segmentation. These results lead us to propose that medial prospective somitic cells under the influence of an unknown signal arising from the median pit acquire their intrinsic capacity for segmentation and then instruct more lateral ones in the process of somite formation.

Subtraction screening to identify medial presomitic mesoderm genes

In order to elucidate the molecular mechanism that confers segmentation autonomy to the Medial-PSM cells, we have performed a subtraction screening of cDNA libraries from Medial- versus Lateral-PSM. Several new genes were identified and their role in somitogenesis is being studied.

Characterisation of the molecular clock components by using the yeast Two-Hybrid technology

The yeast two-hybrid system is being employed to identify hairy1 interaction partners and elucidate its function and regulation, namely in the "Molecular Clock" linked to vertebrate segmentation and somitogenesis. During this year DNA-BD fusions have been created using the whole *hairy1* gene as well as multiple fragments encoding domains of the protein presenting different properties and specificities. RNA has been extracted from multiple parts of the chick embryo as well as from whole embryos in different developmental stages. This RNA has been analysed in search of multiple mRNAs, and characterisation of their UTRs has been performed. Moreover, the different RNA samples are being used to generate cDNA-AD fusion libraries for the two-hybrid screens underway.

The molecular clock is operating during limb bud development

We analyzed the expression pattern of the *hairy2* gene (known to be a part of the molecular clock controlling somitogenesis) during limb bud development. Our results suggest that *hairy2* could be involved in limb bud initiation, apical ectodermal ridge and zone of polarizing activity formation. Furthermore, we experimentally identified a temporal variation in the expression of *hairy2* in the progress zone (proximal-distal variation) and, surprisingly, also in the mesenchymal masses comprising muscle, tendon and connective tissue precursors (dorsal-ventral variation). Our results suggest that the molecular clock described for somitogenesis is also providing positional information to limb cells.

Analysis of myopithelial component role in breast cancer development

We analysed the distribution of p63, CK 5/6 and CK 14 immunohistochemical markers in 51 normal human tissue samples, 350 carcinomas, 25 malignant melanomas

(MMs), and 25 glioblastomas using three serial sections of tissue array research program (TARP)-4 multi-tumour tissue array. Also, we performed double immunostaining to characterize the differential distribution of p63/CK 5/6 and p63/CK 14 in normal breast, salivary gland and skin. p63, CK 5/6 and CK 14 were expressed in basal cells of the prostate and respiratory epithelia and in breast and bronchial myoepithelial cells. p63 was also expressed in cytotrophoblast cells of human placenta and in scattered cells of lymph node germinal centre. CK 5/6 and CK 14 also stained the cytoplasm of basal cells of esophageal-stratified squamous epithelium and transitional epithelial cells of the bladder. No mesenchymal, neural, endothelial, smooth muscle or adipose cells were stained by any of the markers. p63, CK 5/6, and CK 14 were respectively expressed in 92.6%, 75.0%, and 52.9% of the squamous cell carcinomas of the lung, 10.2%, 20.0%, and 7.4% of the ductal carcinomas of the breast, 12.9%, 34.4%, and 11.8% of the serous and 25.0%, 0%, and 0% of the endometrioid carcinomas of the ovary. Lungs, prostate and colonic adenocarcinomas, as well as MMs and glioblastomas, were only rarely decorated by one of the markers. Only matched samples of 16 squamous cell carcinomas and two ductal carcinomas of the breast co-expressed these three markers. In double immunostainings, p63-CK 5/6, as well as p63-CK 14 were co-expressed by basal/myoepithelial cells of the salivary glands and basal cells of the epidermis.

Analysis of DNA repair gene polymorphisms in a group of breast cancer patients from Portuguese origin

We analyzed DNA samples from 259 individuals: 84 Portuguese familiar breast cancer patients, 81 Portuguese control subjects, 64 Brazilian familiar breast cancer patients and 30 Brazilian control subjects, for *XRCC1-Arg399Gln, XPD-Lys751Gln, XRCC3-Thr241Met* and *RAD51-G135C* polymorphisms using PCR-RFLP. We observed that allelic and genotypic frequencies of all polymorphisms were similar to Portuguese and Brazilian controls. In the Portuguese group we found significant statistical differences in *XRCC3-241Met* allele frequencies between familiar breast cancer patients and control group (p=0,007; OR=2,04 95%CI 1,17-3,57), and also in the *XRCC3-Met241Met* genotype (p=0,005; OR=5,29 95% CI 1,47-19,1). In *XPD-751Lys* allele and *XPD-Lys751Lys* genotype frequencies there were significant statistical differences (p=0,043; OR=1,59 95%CI 0,99-2,57; and, p=0,015; OR= 0,45 95% CI 0,24-0,86, respectively). In the Brazilian group we observed significant statistical differences between familiar breast cancer patients and control group in *XRCC3-241Met* allele frequencies (p=0,048; OR=2,55 95%CI 0,92-7,40) and *XRCC3-Thr241Thr* genotype (p=0,034; OR=0,26 95% CI 0,07-0,96).

Study of lymphangiogenesis in breast cancer

A retrospective series of randomised cases was submitted to immunohistochemical assay with polyclonal VEGFR-3 antibody at 1:200. The reactions were classified as: negative (-), weak staining (+) (less than 10%), moderate staining (++) (10-50%) and

strong staining (+++) (more than 50%). From 38 cases, 11 (29,9%) were (+), 18 (47,3%) and 9 (23,68%) (+++).

Interestingly, the VEGFR-3 has marked lymphatic vessels (LV), but also blood vessels (BV) and myoepithelial cells. Our preliminary approach with lymphangiogenesis marker clearly demonstrated that VEGFR-3 lack LV specificity, or also is expressed in BV and myoepithelial cells under neoplastic conditions. Further assay is intended to clarify this puzzling point using other markers for lymphatic vessels such as Prox-1.

Analysis of receptor tyrosine kinases alterations in gliomas and breast tumors

In collaboration with the Hospital São João, Porto, we collected a glioma series. After tumour classification re-validation we have done DNA extraction from 137 paraffin embedded samples. We have also collected 89 invasive breast carcinomas. All cases were analysed for PDGFA and PDGFRα protein expression. Results of these immunohistochemistry works are being evaluated and scored. From 88 glioma cases we are also performing mutation analysis of *PDGFRa* gene (exons 12 and 18) by polymerase chain reaction-single-strand conformational polymorphism (PCR-SSCP). Seventeen cases showed mobility shift in the PCR-SSCP and are being DNA sequenced.

Study of molecular alterations predictive of therapy in malignant gliomas

We have performed mutation analysis of *BRAF* gene in 88 glioma cases. The screening of exon 15 showed the presence of a constitutive mutation, V599E in 4% of the cases. We are currently assessing the mutation status of exon 11. In addition we are setting-up the immunohistochemistry for EGFRT (III) antibody.

3.2.2. EXTERNAL FUNDING

1. **Cellular and molecular studies in the pathogenic fungi *Paracoccidioides brasiliensis*: Dimorphism and its regulation by steroid hormones**
   - **a.** Funding Agency: Fundação para a Ciência e Tecnologia (FCT)
   - **b.** Funding for the ICVS team: 61 980 Euros
   - **c.** Host Institution: ICVS / University of Minho
   - **d.** Duration: 2003-2006
   - **e.** ICVS team: Fernando Rodrigues (PI), Cecília Leão, Agostinho Almeida, Margarida Martins

2. **Molecules and mechanisms involved in the recognition of molecular patterns of pathogenic microorganims: Implications for the susceptibility to relevant public health infections**
   - **a.** Funding Agency: Fundação Calouste Gulbenkian (FCG)

b. Funding for the ICVS team: 170 000 Euros

c. Host Institution: ICVS / University of Minho

d. Duration: 2003-2006

e. ICVS team: Cecília Leão (PI), Fernando Rodrigues, Paula Ludovico, Jorge Pedrosa, Gil Castro, João Pedro Pereira, Agostinho Carvalho, Gustavo Valdigem

3. Cognitive modulation of pain: interaction between the limbic system and the supraspinal endogenous pain control system

a. Funding Agency: Fundação para a Ciência e Tecnologia (FCT)

b. Funding for the ICVS team: 90 000 Euros

c. Host Institution: ICVS/University of Minho

d. Duration: 2003-2006

e. ICVS team: Armando Almeida (PI), Nuno Sousa, Filipa Pinto-Ribeiro, Manuel Lima-Rodrigues, José Miguel Pêgo, João Cerqueira

4. Experimental evaluation of an antimycobacterial-drug delivery system to *M. tuberculosis* infected macrophages

a. Funding Agency: Fundação Calouste Gulbenkian

b. Funding for the ICVS team: 64 841 Euros

c. Host Institution: Instituto de Biologia Molecular e Celular, University of Oporto

d. Duration: 2003-2004

e. ICVS team: Jorge Pedrosa (PI), Manuel Teixeira da Silva, Martinha Oliveira

5. Mycobacteriosis of difficult treatment (multi-drug resistant tuberculosis and Buruli ulcer): Impact in public health

a. Funding Agency: Fundação Calouste Gulbenkian

b. Funding for the ICVS team: 100 000 Euros

c. Host Institution: Universidade do Minho

d. Duration: 2003-2005

e. ICVS team: Jorge Pedrosa (PI), Manuel Teixeira da Silva, Martinha Oliveira, António Gil Castro

6. The immune response to allografts: role of anti-inflammatory cytokines

a. Funding Agency: Fundação para a Ciência e Tecnologia (FCT)

b. Funding for the ICVS team: 60 000 Euros

c. Host Institution: Instituto de Biologia Molecular e Celular, Universidade do Porto

d. Duration: 2002-2004

e. ICVS team: António Gil Castro (PI), Sílvia Mota

7. New aspects on coordinating limb bud development

a. Funding Agency: Fundação para a Ciência e Tecnologia

b. Funding for the ICVS team: 85 000 Euros

c. Host Institution: ICVS / University of Minho

d. Duration: 2002-2005

e. ICVS team: Isabel Palmeirim (PI), Susana Pascoal

8. Genetics and hormones in schizophrenia: thyroid hormones, vitamin A and transthyretin. A pilot study

a. Funding Agency: Fundação para a Ciência e Tecnologia

b. Funding for the ICVS team: 64 840 Euros

c. Host Institution: Institute for Molecular and Cell Biology, University of Porto

d. Duration: 2001-2004

e. ICVS team: Joana Almeida Palha (PI) and Dina Ruano

9. Searching of an essential function for transthyretin in the central nervous system

a. Funding Agency: Fundação para a Ciência e Tecnologia

b. Funding for the ICVS team: 130 000 Euros

c. Host Institution: Institute for Molecular and Cell Biology, University of Porto

d. Duration: 2002-2005

e. ICVS team: Joana Almeida Palha (PI), Fernanda Marques, João Carlos Sousa

3.3. SCIENTIFIC PRODUCTION BY THE ICVS MEMBERS

As mentioned before, the activities of the ICVS started only in middle 2002. Therefore most of the scientific publications associated with the ICVS staff members listed below include results obtained outside the ICVS, both in the original institutions of the ICVS members or in collaborating laboratories.

3.3.1. INTERNATIONAL PUBLICATIONS

A. Articles

1. Alizadeh M, Babron MC, Birebent B, Matsuda F, Quelvennec E, Liblau R, Cournu-Rebeix I, Momigliano-Richiardi P, Sequeiros J, Yaouanq J, Genin E, Vasilescu A, Bougerie H, Trojano M, Martins Silva B, **Maciel P**, Clerget-Darpoux F, Clanet M, Edan G, Fontaine B, Semana G. Genetic interaction of CTLA-4 with HLA-DR15 in multiple sclerosis patients. *Ann. Neurol.*, **54**:119-22 (2003).
2. Araujo C, Sousa MJ, Ferreira MF, **Leao C.** Activity of essential oils from Mediterranean *Lamiaceae* species against food spoilage yeasts. *J. Food Prot.*,

66:625-632 (2003).

3. **Baptista MJ, Melo-Rocha G**, Pedrosa C, **Gonzaga S**, Areias JC, Flake AW, Leite-Moreira AF, **Correia-Pinto J**. Antenatal Vitamin A administration attenuates lung hypoplasia by interfering with early instead late determinants of lung underdevelopment in CDH. *J. Pediatr. Surg., in press*.
4. Barreirinho S, Ferro A, Santos M, Costa E, Pinto-Basto J, Sousa A, Sequeiros J, **Maciel P**, Barbot C, and Barbot J. Inherited and acquired risk factors and their combined effects in pediatric stroke. *Pediatr. Neurol.*, **28**:134-138 (2003).
5. Cano G, **Milanezi F**, Leitão D, Ricardo S, Brito MJ, **Schmitt FC**. Estimation of hormone receptor status in fine-needle aspirates and paraffin-embedded sections from breast cancer using the novel rabbit monoclonal antibodies SP1 and SP2. *Diag. Cytopath.*, **29**:207-211 (2003).
6. Cobos A, Lima D, **Almeida A**, Tavares I. Brain afferents to the lateral caudal ventrolateral medulla: a retrograde and anterograde tracing study in the rat. *Neuroscience*, **120**:485-498 (2003).
7. **Correia-Pinto J**, **Baptista MJ**, Pedrosa C, Estêvão-Costa J, Flake AW, Leite-Moreira AF. The Fetal heart development in the nitrofen-induced CDH rat model: the role of mechanical and non-mechanical factors. *J. Pediatric Surg.*, **38**:1444-1451 (2003).
8. **Correia-Pinto J**, Henriques-Coelho T, **Magalhães S**, Leite-Moreira AF. Pattern of right ventricular pressure fall and its modulation by afterload. *Physiol. Res., in press*.
9. **Correia-Pinto J**, Henriques-Coelho T, Oliveira S-M, Leite-Moreira AF. Distinct load dependence of relaxation rate and diastolic function in *Oryctolagus cuniculus* and *Ratus norvegicus*. *J. Comp. Physiol. B.*, **173**:401-407 (2003).
10. **Correia-Pinto J**, Leite-Moreira AF, Henriques-Coelho T, **Magalhães S**, Gillebert TC. Beat-to-beat modulation of right and left ventricular positive dP/dt by afterload. Implications for the evaluation of inotropy. *Acta Cardiologica*, **58**:327-334 (2003).
11. **Costa MC,** Guimarães L, Ferreirinha F, Sousa A, **Maciel P**, Sequeiros J. Molecular diagnosis of Huntington disease. *Eur. J. Hum. Genet.*, **11**:872-878 (2003).
12. Dugast C, **Almeida A**, Lima D. The medullary dorsal reticular nucleus (DRt) enhances the responsiveness of spinal nociceptive neurons to peripheral stimulation in the rat. *Eur. J. Neurosci.*, **18**:580-588 (2003).
13. Estêvão-Costa J, **Correia-Pinto J**, Soares-Oliveira M, Carvalho JL. Neonatal Splenic Necrosis Not Related to Wandering Spleen. *Eur. J. Pediatric Surg.*, **13**: 344-346 (2003).
14. Fragoso A, **Correia-Pinto J**, Carvalho JL, Dias JA, Troncoso MP, Estêvão-

Costa J. Ectopic pancreas and foveolar hyperplasia in a newborn: an unifying etiopathogeny for gastric outlet obstruction. *J. Pediatric Gastroent. Nutrition, in press.*

15. Freitas C, Rodrigues S, **Palmeirim I.** "Running after the clock". *Int. J. Devel. Biol., in press.*
16. **Lima-Rodrigues M**, Nunes R, **Almeida A.** Intraepithelial nerve fibers project into the lumen of the larynx. *Laryngoscope, in press*.
17. Lu J, Goula D, **Sousa N**, Almeida OFX. Glucocorticoid-induced apoptosis in hippocampal cells is mediated by ionotropic and metabotropic glutamate receptors but can be prevented by synaptic NMDA receptors. *Neuroscience*, **121**:123-131 (2003).
18. **Ludovico P, Sansonetty F,** Silva MT, Corte-Real M. Acetic acid induces a programmed cell death process in the food spoilage yeast *Zygosaccharomyces bailii*. *FEM Yeast Res.*, **3**:91-96 (2003).
19. **Maciel P**, Yan J, Feng J, Accurso F, and Sommer S. Single-tube method for determination of F508del genotype in the CFTR gene using bidirectional PCR amplification of specific alleles. *Biotechniques*, **34**:460-462 (2003).
20. **Maciel P**. Genetics of Rett syndrome: unanswered questions. *Rev Neurol, in press.*
21. Monteiro MC, Gonçalves MJ, **Sansonetty F**, Martínez M, O'Connor J.E. Aplicación de la citometría de flujo funcional a la monitorización del tratamiento antiplaquetario: Movilización de Ca2+ y expresión de P-selectina en sujetos tratados con ticlopidina. *Rev. Diag. Biol., in press*.
22. **Reis RM**, Lopes JM. Genetic Alterations of adult and paediatric astrocytic tumours. *Rev. Neurol., in press*.
23. **Reis-Filho JS**, Fulford LG, Lakhani SR, **Schmitt, FC**. A 62-year-old woman with a 4.5cm nodule in the right breast. *Arch. Pathol. Lab. Med.*, **127**:396-398 (2003).
24. **Reis-Filho JS**, **Milanezi F**, Amendoeira I, Albergaria A, **Schmitt FC**. Distribution of p63, a novel myoepithelial marker, in fine-needle aspiration biopsies of the breast. An analysis of 82 samples. *Cancer (Cancer Cytopahtol)*, **99**:172-179 (2003).
25. **Reis-Filho JS**, **Milanezi F**, Paredes J, Silva P, Pereira EM, Maeda S, Carvalho LV, **Schmitt FC**. Novel and classic myoepithelial/stem cell markers in metaplastic carcinoma of the breast. *Appl. Immunohistoch & Mol. Morpholol.*, **11**:1-8 (2003).
26. **Reis-Filho JS**, **Schmitt FC.** Lymphangiogenesis in tumors: what do we know? *Microsc. Res. Tech.*, **60**:171-180 (2003).
27. **Reis-Filho JS**, **Schmitt FC**. p63 expression in sarcomatoid/metaplastic

carcinomas of breast. *Histopathol.*, **42**:94-95 (2003).

28. **Reis-Filho JS**, Simpson PT, **Martins A,** Preto A, Gartner F, **Schmitt FC**. Distribution of p63, cytokeratins 5/6 and cytokeratin 14 in 51 normal and 400 neoplastic human tissue samples using TARP-4 multi-tumor tissue microarray. *Virchows Arch.*, **443**:122-132 (2003).
29. **Rodrigues F, Ludovico P,** Sousa MJ, Steensma HY, Corte-Real M, **Leão C.** The spoilage yeast *Zygosaccharomyces bailii* forms mitotic spores: A screening method for haploidization. *Appl. Environ. Microbiol.*, **69**:649-653 (2003).
30. **Rodrigues F,** Zeeman A-M, Cardoso H, Sousa MJ, Steensma HY, Corte-Real M, **Leão C.** Isolation of an acetyl-CoA synthetase gene (*ZbACS2*) from *Zygosaccharomyces bailii*. *Yeast*, in press.
31. **Ruano D,** Macedo A, Dourado A, Soares MJ, Valente J, Coelho I, Santos V, Azevedo, MH, Goodman A, Hutz M, Gama C, Lobato MI, Belmonte-de-Abreu P, **Palha JA**. NR4A2 and schizophrenia: lack of association in a Portuguese/Brazilian study. *Am. J. Med. Genet.*, in press.
32. **Santos M**, Pinto-Basto J, Rio ME, Sá MJ, Valença A, Sá A, Dinis J, Figueiredo J, Bigotte de Almeida L, Coelho I, Sawcer S, Setakis E, Compston A, Sequeiros J, **Maciel P**. A whole genome screen for association with multiple sclerosis in Portuguese patients. *J. Neuroimmunol.*, **143**:112-115 (2003).
33. **Santos MJ**, Rio ME, Costa MC, Rio ME, Sá MJ, Monteiro MC, Valença A, Sá A, Dinis J, Figueiredo J, Bigotte de Almeida L, Valongueiro A, Coelho I, Matamá MT, Pinto-Basto J, Sequeiros J, **Maciel P**. Genotypes at the APOE and SCA2 loci do not predict the course of multiple sclerosis in patients of Portuguese origin. *Multiple Sclerosis, in press*.
34. **Schmitt FC**, **Reis-Filho JS**. C-myc, not her2/neu, can predict the prognosis of breast cancer patients: how novel, how accurate, and how significant? *Breast Cancer Res.*, **5**:188-191 (2003).
35. **Sousa JC**, Grandela C, Fernández-Ruiz J, de Miguel R, Sousa L, Magalhães AI, Saraiva MJ, **Sousa N**, **Palha JA.** Transthyretin is involved in depression-like behavior and exploratory activity. *J. Neurochem.*, i*n press*.
36. Veiga A, Arrabaca JD, **Sansonetty F, Ludovico P,** Corte-Real M, Loureiro-Dias MC. 2003. Energy conversion coupled to cyanide-resistant respiration in the yeasts *Pichia membranifaciens* and *Debaryomyces hansenii. FEMS Yeast Res.*, **3**:141-148 (2003).

B. Book Chapters

1. **Lu J**, Némethy Zs, **Pêgo JM**, **Cerqueira JJ**, **Sousa N**, Almeida OFX. Cellular and molecular analysis of stress-induced neurodegeneration. In: Steckler T,

DeKloet ER. (eds), *"The Cellular Biology of the Stress Response*". Elsevier, *in press*.

2. Monteiro MC, Gonçalves M-J, **Sansonetty F**, O´Connor J-E. Flow Cytometric Analysis of Calcium Mobilization in Whole-Blood Platelets. Current Protocols in Cytometry 9.20.1-9.20.7 (2003).
3. **Rodrigues F**, Sousa MJ, Côrte-Real, **Leão C.** *Zygosaccharomyces bailii*: an yeast with a peculiar pattern for the regulation of acetic acid metabolism in the presence of glucose. In: Wolf K, Breunig K, Barth E. (eds), *"Lab Manual on Non-conventional Yeasts: Genetics, Biochemistry, Molecular Biology, and Biotechnology"*. Springer-Verlag, Germany, pgs. 409-416 (2003).

C. Abstracts in Congresses

1. **Almeida, A**, **Carvalho, A**, **Gonçalves, C**, **Valdigem, G**, **Ludovico, P**, **Rodrigues, F**, **Leão, C**. Saccharomyces cerevisiae ?btn1 as a model to study the neurodegenerative Batten's disease. *XXII ECCO Meeting*, Braga, Portugal (2003).
2. **Baptista MJ**, **Correia-Pinto J**, **Melo-Rocha G**, Pedrosa C, Estêvão-Costa J, Leite-Moreira AF. Effects of retinoids in early and late lung growth in experimental CDH. *Pediatric Res.*, **54**:118 (2003).
3. **Bastos P, Baptista MJ, Gonzaga S**, Henriques-Coelho T, **Melo-Rocha G**, Estevão-Costa J, **Palmeirim I**, Leite-Moreira AF, **Correia-Pinto J**. Ghrelin palys a role in pathogenesis of lung hypoplasia in CDH. *Pediatric Res.*, **54**:122 (2003).
4. Carvalho C, Rodriguez-Léon J, **Pascoal S**, Delphini MC, Vieira C, Duprez D, Izpisua Belmonte JC, **Palmeirim I**. The molecular clock is operating during limb bud development. *1st joint meeting of the British and French Societies for Developmental Biology*, Nice, France (2003).
5. Carvalho C, Rodriguez-Léon J, **Pascoal S**, Delphini MC, Vieira C, Duprez D, Izpisua Belmonte JC, **Palmeirim I**. The molecular clock is operating during limb bud development. *EMBO workshop: Boundaries in development: 30 years of progress*, Heidelberg, Germany (2003).
6. Carvalho S, Oliveira e Silva A, **Milanezi F**, Ricardo S, Leitão D, Amendoeira I, **Schmitt F**. Does breast phyllodes tumour harbour c-kit mutations ? *19th European Congress of Pathology, Ljubljana, Slovenia. Virchows Arch.*, **443**:309 (2003).
7. **Cerqueira JJ**, **Pêgo JM**, **Sousa N**. Dendritic alterations in the prefrontal cortex following corticosteroid treatment. *International Brain Research Organization Meeting*. Prague, Check Republic (2003).
8. **Correia-Pinto J**, Henriques-Coelho T, Roncon-Albuquerque R Jr, **Melo-**

Rocha G, Gillebert TC, Leite-Moreira AF. Left-ventricular dysfunction and molecular remodelling in pulmonary hypertension. Eur Heart J., 24 (Suppl.):170 (2003).

9. Côrte-Real M, **Sansonetty F**. Physiological Studies of Yeast Populations by Cytometry. *VIII Congresso da Sociedade Ibérica de Citometria* (2003).
10. Costa MC, Constante-Pereira M, Magalhães P, Matamá T, Ferreirinha F, Cerqueira J, Santos M, Sequeiros J, **Maciel P**. Genetic study of Portuguese patients with a Huntington disease-like phenotype. *Annual Meeting American Society Human Genetics. Am. J. Human Genet.,* **73**:P-2451, 586 (2003).
11. Dias N, Corte-Real M, **Sansonetty F**, Lima N. Flow cytometry as a tool to assess cytotoxic effects of the non-ionic surfactant triton x-100 in tetrahymena pyriformis. *5th Iberian Congress and 2nd Iberoamerican on Environmental Contamination and Toxicology*. Porto, Portugal (2003).
12. Ferro A, Castro MJ, Sousa A, Lemos C, Santos M, Silveira I, Pereira-Monteiro J, Sequeiros J, **Maciel P**: *The C677T MTHFR polymorphism is not a genetic risk factor for migraine in the Portuguese population. Abs. Genetics of Complex Diseases and Isolated Populations*, Genova, Itália, p.10 (2003).
13. Ferro A, Castro MJ, Sousa A, Lemos C, Santos M, Silveira I, Pereira-Monteiro J, Sequeiros J, **Maciel P**: *A case-control study reveals no association of C677T MTHFR polymorphism with migraine in the Portuguese population*. Abs. *Workshop on Comparative and Functional Genomics*, Cambridge, United Kingdom (2003).
14. Freitas C, Teillet M-A, **Palmeirim I**. When do medial PSM cells get the property to segment autonomously? *1st joint meeting of the British and French Societies for Developmental Biology*, Nice, France (2003).
15. Gillebert TC, Leite-Moreira AF, Pinho P, **Correia-Pinto J**, Bastos PT. Diastolic intolerance to increased afterload in CABG patients. *Acta Cardiologica International, Journal of Cardiology*, 58:69 (2003).
16. Gouvea AP, **Milanezi F**, Olson SJ, Leitão D, **Schmitt FC**, Gobbi H. Detecção do HER2 em carcinomas mamários invasivos: imunohistoquímica x FISH e relação com outros fatores prognósticos e sobrevida. *XXIV Congresso Brasileiro de Patologia, Florianópolis, SC, J. Bras. Patol. (Supl.),* **39**:37 (2003).
17. Henriques-Coelho T, **Correia-Pinto J**, Roncon-Albuquerque R Jr, Lourenço AP, Baptista MJ, Teles A, Leite-Moreira AF. Haemodinamic, morphological, and molecular effects of chronic administration of ghrelin in monocrotalin-induced pulmonary hypertension. Eur. Heart J., 24 (Abstr. Suppl.): 371.
18. Henriques-Coelho T, Roncon-Albuquerque R Jr, Gavina C, **Correia-Pinto J,** Leite-Moreira AF. Decreased diastolic tolerance to afterload and impaired systolic function after 6 hours of volume overload. *Eur. J. Heart Failure*, **5**

(Suppl.):372 (2003).

19. **Lu J**, Goula D, **Sousa N**, Almeida OFX. Ionotropic and metabotropic glutamate receptor mediation of glucocorticoid-induced apoptosis in hippocampal cells and the neuroprotective role of synaptic N-methyl-D-aspartate (NMDA) receptors. *International Brain Research Organization Meeting*. Prague, Check Republic (2003).
20. **Ludovico P**, **Rodrigues F**, **Leão C**. The key role of mitochondria in yeast cells degeneration. *1st Luso-Spanish Congress on Free Radicals*. Coimbra, Portugal (2003).
21. **Ludovico P**, Wissing S, Herker E, Decker T, Link A, Proksch A, Engelhardt S, **Rodrigues F**, Corte-Real M, Sigrist S, Madeo F. An AIF-related Protein Regulates Apoptosis in Yeast**.** *2nd International Meeting on Yeast Apoptosis*, Smolenice, Slovakia (2003).
22. **Palmeirim I**, Pinto-Machado J. Optional Studies for Medical Students. *WFME World Conference – Global Standards for Better Health Care*, Copenhagen, Dinamarca (2003).
23. **Pêgo JM**, **Cerqueira JJ**, **Palha J**, **Sousa N**. Morphological changes in the basolateral division of the amygdala of TTR-null mice. *International Brain Research Organization Meeting*. Prague, Check Republic (2003).
24. **Pinto-Ribeiro F**, **Almeida A**, **Pêgo JM**, **Cerqueira JJ** e **Sousa N**. Chronic stress modulates nociception in the rat: role of corticosteroid receptors. *Society for Neurosci. Abstr.*, New Orleans, USA **, 29**.
25. **Pinto-Ribeiro F**, **Almeida A**, **Pêgo, JM**, **Cerqueira JJ**, **Sousa N**. Chronic stress modulates nociception: the role of corticosteroid receptors. *4th EFIC Meeting*. Prague, Check Republic (2003).
26. **Reis RM**, van Elburg RM, Ylstra B, Schreuder MF, Fetter WPF, Meijer GA. Expression profile analysis of the small and large intestine of the Wistar rat. *International Conference on Applied Genomics, 9th ESACP / 16th ISDQP Meeting*, Amesterdam, The Netherlands (2003).
27. **Reis RM**, Weiss J, Ylstra B, Postma C, Eijk P, Snijders AM, Albertson D, Pinkel D, Kuipers E, Meijer GA. DNA copy number and expression profiles of gastric cancer correlate with clinical behavior. *Workshop - High Throughput Genomics*, Amesterdam, The Netherlands (2003).
28. **Reis-Filho JS**, **Martins A**, Preto A, Soares P, **Schmitt FC**. Distribution of p63, cytokeratins 5/6 and cytokeratin 14 in 51 normal and 450 neoplastic human tissue samples using TARP-4 multi-tumor tissue microarray. *Mod. Pathol.*, **16**:1493 (2003).
29. **Reis-Filho JS**, **Martins A**, Preto A, Soares P, **Schmitt FC**. Distribution of p63, cytokeratins 5/6 and cytokeratin 14 in 51 normal and 450 neoplastic

human tissue samples using TARP-4 multi-tumor tissue microarray. *Lab. Invest.*, **83**:1493 (2003).

30. **Reis-Filho JS**, Fulford LG, Simpson PT, **Martins A**, **Schmitt FC**. P63-driven nuclear accumulation of beta catenin is not a frequent event in human neoplasms. *19th European Congress of Pathology, Ljubljana, Slovenia. Virchows Arch.*, 443: 360 (2003).
31. **Reis-Filho JS**, **Martins A**, Preto A, Soares P and **Schmitt FC**. Distribution of p63, cytokeratins 5/6 and cytokeratin 14 in 51 normal and 450 neoplastic human tissue samples using TARP-4 multi-tumor tissue microarray. *92nd Annual Meeting of United States and Canadian Academy of Pathology*, Washington, EUA (2003).
32. Rodrigues S, Santos J, **Palmeirim I**. Somitogenesis runs differently in the first formed somites. *Workshop at Instituto Juan March*, Madrid, Spain (2003).
33. Saúde L, **Palmeirim I**. Subtraction Screen to Identify Medial Presomitic Mesoderm Genes, *ELSO 2003 Meeting*, Dresden, Germany (2003).
34. Saúde L, **Palmeirim I**. Subtraction Screen to Identify Medial Presomitic Mesoderm Genes. *ELSO 2003 Meeting*, Dresden, Germany (2003).
35. Sotoca R, Silva R, **Ludovico P**, **Sansonetty F**, Martinez-Peinado J, Corte-Real M. Hyperosmotic Stress Caused by Glucose Induces Programmed Cell Death in *Saccharomyces cerevisiae. 2nd International Meeting on Yeast Apoptosis*, Smolenice, Slovakia (2003).
36. Sotoca R, Silva R, **Ludovico P**, **Sansonetty F**, Martinez-Peinado J, Corte-Real M. 2003. Hyperosmotic Stress Caused by Glucose Induces Programmed Cell Death in *Saccharomyces cerevisiae. XXI International Conference on Yeast Genetics and Molecular Biology*, Göteborg, Sweden.
37. **Sousa JC**, Grandela C, Fernández-Ruiz J, de Miguel R, Sousa L, Magalhães AI, Saraiva MJ, **Sousa N**, **Palha JA**. Transthyretin is involved in behavior through the noradrenergic system. Society for Neurosciences. New Orleans, USA, 217.10.
38. Weiss J, Kuipers E, **Reis RM**, Eijk P, Snijders AM, Pinkel D, Albertson D, Ylstra B, Meijer GA. Both microarray-CGH and expression profiles predict survival in gastric cancer. *International Conference on Applied Genomics, 9th ESCAP / 16th ISDQP Meeting*, Amesterdam, The Netherlands (2003).
39. Weiss J, Ylstra B, **Reis RM**, Postma C, Eijk P, Snijders AM, Albertson D, Pinkel D, Kuipers E, Meijer GA. Both array-CGH and Expression profiles predict survival in gastric cancer. *AACR Oncogenomics*, Phoenix, EUA (2003).
40. Weiss J, Ylstra B, **Reis RM**, Postma C, Eijk P, Snijders AM, Albertson D, Pinkel D, Kuipers E, Meijer GA. Both array-CGH and Expression profiles predict survival in gastric cancer. *Dutch Pathological Society Meeting*, Ede, The

Netherlands (2003).

3.3.2. NATIONAL PUBLICATIONS

Articles: 1; Book Chapters: 1; Abstracts in Congresses: 23

3.3.3. UNDER-GRADUATE AND POST-GRADUATE THESIS

A. THESIS CONCLUDED IN 2003

? **Under-Graduate Thesis**

1. ***Agostinho Carvalho*** (Graduation in Applied Biology, University of Minho). *Supervisor:* **Fernando Rodrigues**, *Co-supervisor:* **Agostinho Almeida**
2. ***Alexandra Fraga*** (Graduation in Applied Biology, University of Minho). *Supervisor:* **Jorge Pedrosa**
3. ***Ana Goios*** (Graduation in Biology, University of Porto). *Supervisor:* **Paula Ludovico**
4. ***Ana Martins*** (Graduation in Applied Biology, University of Minho). *Supervisor:* **Isabel Palmeirim**
5. ***Carla Gonçalves*** Graduation in Applied Biology, University of Minho). *Supervisor:* **Fernando Rodrigues**, *Co-supervisor:* **Agostinho Almeida**.
6. ***Cátia Cruz*** (Graduation in Applied Biology, University of Minho). *Supervisor:* **Fernando Schmitt**, *Co-supervisor:* **Sandra Costa**
7. ***Joana Carvalho*** (Graduation in Biology, University of Porto). *Supervisor:* **Paula Ludovico**
8. ***Liliana Guerreiro*** (Graduation in Applied Biology, University of Minho). *Supervisor:* **Armando Almeida.**
9. ***Marta Lima*** (Graduation in Applied Biology, University of Minho). *Supervisor:* **Joana Palha**, *Co-supervisor:* **Dina Ruano**.
10. ***Tírcia Santos*** (Graduation in Applied Biology, University of Minho). *Supervisor:* **Gil Castro**

? **Master Thesis**

1. ***Egídio Torrado***. *"Study of the role of proteins secreted by Candida albicans and Mycobacterium avium in experimental infections, and their potential use as target antigens in immunoprotection". Master degree thesis in Biotecnology*. University of Minho.
   Supervisor: ***Jorge Pedrosa***.
2. ***Maria João Baptista***. *"Cardiopulmonar development in congenital diaphragmatic hernia"*. Master degree thesis in Molecular Medicine. Faculty of Medicine, University of Porto.
   Supervisors: ***Jorge Correia-Pinto*** and *Adelino Leite-Moreira*

B. THESIS UNDER DEVELOPMENT

The theses under development at ICVS are listed in Appendix II, together with their themes and supervisors.

3.4. RESEARCH PRIZES

1. Prize of the Young Researcher – *basic research* 2003 of the Sociedade Portuguesa de Cardiologia, to Jorge Correia-Pinto with the work "*Afterload-induced diastolic intolerance, myofilaments and SERCA2a in progression to heart failure*." by **Correia-Pinto J**, Henriques-Coelho T, Roncon-Albuquerque Jr, **Melo-Rocha G**, Leite-Moreira AF.

2. **Servier Prize in Heart Failure 2003** to the work *"Relevance of hemodynamics and molecular evaluation in progression to heart failure*." by **Correia-Pinto J**, Roncon-Albuquerque R, Henriques-Coelho T, Leite-Moreira AF.

3. **Honour Mention of the Pfizer Research Prize 2003** with the work *"Left ventricular molecular changes and functional consequences in progression to heart failure. Relative contribution of load and neuro-humoral activation*" by **Correia-Pinto J**, Lourenço A, Henriques-Coelho T, Roncon-Albuquerque, Leite-Moreira AF.

4. **Grünenthal Prize PAIN 2003** with the work "Chronic stress modulation of pain: the role of glucocorticoid receptors", by **Pinto-Ribeiro F**, **Almeida A**, **Pego JM**, **Cerqueira J**, **Sousa N.**

5. **Serono Prize** of the Neurological Portuguese Society for the work "Genetic study of multiple sclerosis" by **Maciel P**.

3.5. POST-GRADUATION COURSES

In 2003, and for the third consecutive year, high priority was given to the preparation and offer of post-graduation studies with a two-fold objective: i) to contribute to a highly specialized in-service training of medical doctors under conditions compatible with their normal duties and schedules; ii) to extend the opportunities for the acquisition of formal Master or Doctoral degrees in the field of life and health sciences.

These courses can be validated as credit units to use in post-graduation Master and PhD programmes in the field of biology and health sciences.

The post-graduation programme (PGP) in 2003 included seven international short intensive courses, targeting medical doctors as well as academic staff, researchers and health professionals, as follows.

"Microsurgical Anatomy in Neurosurgery"

Coordinators: Carlos Alegria and Nuno Sousa. May 20-21, 2003,http://ecs2002.ecsaude.uminho.pt/postgrad/2003/man.pdf

"Light Microscopy and Advanced Imaging"

Coordinators: Filipe Sansonetty and Armando Almeida. May 26-30, 2003http://ecs2002.ecsaude.uminho.pt/postgrad/2003/lmai.pdf

"Cell and Tissue Culture Techniques"

Coordinators: Filipe Sansonetty and Nuno Sousa. June 25-27, 2003. http://ecs2002.ecsaude.uminho.pt/postgrad/2003/ctct.pdf

"Cytometry: Applications in Cellular Biology and Medicine"

Coordinators: Filipe Sansonetty and Paula Ludovico. July 28-August 1, 2003. http://ecs2002.ecsaude.uminho.pt/postgrad/2003/cacbm.pdf

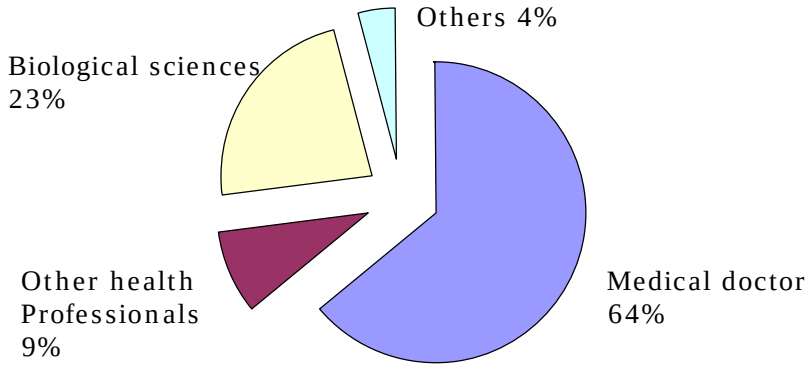
"Pediatric Cardiovascular and Pulmonary Physiology: From Research to Clinical Practice"

Coordinators: Jorge Correia-Pinto and Maria João Baptista. October 1-4 2003. http://ecs2002.ecsaude.uminho.pt/postgrad/2003/pcpp.pdf

"Lung Cancer: Advances in Molecular Diagnosis and Treatment"

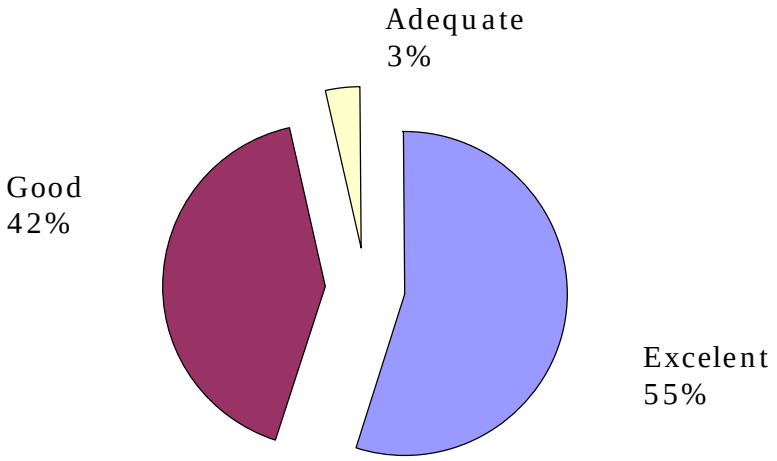
Coordinators: Filipe Sansonetty and Carlos Valério. December 5-6, 2003.

The post-graduation programme had 205 participants distributed in the following backgrounds:



A questionnaire was filled by most of the participants to evaluate the post graduation

activities. The overall evaluation provided the following results: excellent (55%), good (42%), adequate (3%), poor (0%), unsatisfactory (0%).



In all cases, participants considered that the courses should be repeated in years to come, which represents a great incentive to continue and consolidate our programme.

In addition, we offered an intensive short course on laboratory safety addressed to all professionals and students that use research, teaching and hospital laboratories (October 29-31. 2003.http://ecs2002.ecsaude.uminho.pt/postgrad/2003/lscr.pdf). The course, attended by 93 participants from various backgrounds, including high-school and university teachers, technicians from research and clinical laboratories, and graduate students; the overall evaluation was excellent (20%), good (55%), adequate (18%) and poor (7%).

3.6. COOPERATION WITH NATIONAL AND INTERNATIONAL INSTITUTIONS

A. PARTICIPATION IN BILATERAL ACTIONS

1. **Natural and pharmacological interventions for evaluation of hippocampal structure and function**. Exchange grant ICCTI/DAAD.

Principal Investigators: Nuno Sousa (ICVS, Portugal) and Osborne Almeida (Germany).
Duration: 2002-2004.

2. **Study of the molecular basis of schizophrenia in the Portuguese and Brasilian populations**. Exchange grant CAPES in Brasil and ICCTI in Portugal for exchange of expertise and training.

Principal Investigators: Joana Almeida Palha (ICVS, Portugal) and Paulo Belmonte de Abreu (Brazil).

Duration: 2001-2004

3. Vertebrate limb bud development. ICCTI/ (CRUP) and ICCTI/CSCI.

Principal Investigator: Isabel Palmeirim (ICVS, Portugal) and Delphine Duprez (CNRS, France).

Duration: 2003

4. Study of Axial/Paraxial Hindge function in vertebrate segmentation. ICCTI/Embassy of France.

Principal Investigators: Isabel Palmeirim (ICVS, Portugal) and Marie-Aimée Teillet (CNRS, College de France, France).

Duration: 2002-2003

B. PARTICIPATION IN INTERNATIONAL NETWORKS

Isabel Palmeirim

-Member of the "EU network of excellence on the development of mesodermal organ systems".

Jorge Pedrosa

- Member of the Steering Committee of the "European and Developing Countries Clinical Trial Programme for Poverty-related Diseases", as National Delegate (ICCTI).

Patrícia Maciel

- Member of the international consortium for the study of the genetic susceptibility to Multiple Sclerosis - GAMES (Genetic Analysis of Multiple Sclerosis in the EuropeanS).

3.7. "CIÊNCIA FALADA NO ICVS" - TALKING ABOUT SCIENCE AT THE ICVS

The ICVS institutionalized the so called "Ciência Falada no ICVS" consisting on regular seminars. In these meetings, internal and external scientists were invited to present their most recent results.

3.8. RESOURCES

3.8.1. HUMAN RESOURCES

The full composition of the regular research staff is summarised below and listed in Appendix III, together with their qualifications, rank and scientific area.

PhD Researchers

- **13** Lecturers
- **3** Post-docs
- **2** External Invited Researchers

Post-graduation students

- **2** External Invited Researchers
- **22** PhD students
- **7** Master students
- **29** Lic. Researchers (9 Assistants and 6 Monitor at ECS; 14 research scholarships)

Non Academic Staff, shared with the School

- **8** Administration
- **8** Laboratories
- **2** Medical Education Unit

3.8.2. INFRASTRUCTURES

ICVS is operating in provisional facilities. However, during the launching period of the institute the preparation of laboratories and scientific equipments was one of the main objectives. It has been possible to put into operation a set of research laboratories organized by function, in parallel with an intra network of Shared Facilities established to support, in a multidisciplinary way, the different research groups of the ICVS.

The use of internal funding for the acquisition of equipments and the training and recruitment of personnel was one of the most important achievements of the institute. Twenty laboratories (1500 m^2) are now fully operational and include facilities for the development of protocols in Animal models, Microbiology, Molecular Biology, Cell Culture, Microscopy, Flow Cytometry, Histology and Cytology. These laboratories are shared by the researchers and post-graduate students, even though they also represent 'home base' laboratories for the research groups. Since 2002, the following additions to facilities were made available:

BIOLOGICAL RESOURCES CENTER AND ANIMAL HOUSE - Biological Safety Laboratories of Level 3 including ultra-freezers, flow cytometry and cell culture equipments, up-grade of the animal facility for 1000 mice and 300 rats, external quarantine, 350 mice in Level 3 containment and systems for behavioural tests.

GENOMICS AND PROTEOMICS FACILITY – equipped with ultracentrifuge, additional PCR machines, real-time PCR, electrophoresis apparatus, spectrophotometer, 2D-PAGE, image acquisition and software for molecular biology.

Due to a significant delay in the construction of the new building of the ECS, the University approved an expansion to the upper floor. Administrative headquarters, offices for researchers and seminar rooms are presently located in this new area.

The new building for the School of Health Sciences, to be completed by the end of 2005, includes a specific area for the ICVS, with 6 000 m2. Further equipment ha been requested through several applications to FCT.

4. FINAL REMARKS

4.1. SELF-ASSESSMENT

We consider that, during the last two years, a great investment of the School has been done on:

- the preparation of research laboratories, acquisition of scientific equipments and support of projects within the ICVS;
- keeping all members of the academic staff active in research;
- attracting a meaningful number of graduate students into the research projects;
- offering master, doctoral and post-doctoral fellowships;
- developing interdisciplinary projects involving different research domains within and outside the ICVS.

As a consequence, presently, the **strongest points of ICVS** include:

- a highly qualified, motivated and dynamic research team;
- the availability of a number of fellowships in 2003 provided by a specific grant from FCT that gave an important boost to the ICVS activities;
- the availability of a set of research laboratories organized by function, in parallel with an intra-network of Shared Facilities established to support, in a multidisciplinary way, the different research groups of the ICVS;
- the capacity for implementing high standard international post-graduation programmes.

The **main weaknesses** are related with:

- the delay in the decision of Foundation for Science and Technology (FCT) regarding the proposals that were formally submitted in January 2002 for the financing of the ICVS, concerning:
  - (i) the regular financing of ICVS as a research unit integrated in the national system of science and technology (which, according to the FCT rules, involves basal and programmatical financing);
  - (ii) the financing of heavy scientific equipments for the research laboratories, aiming at the establishment of an infrastructure of "Shared Instruments Facilities" in partnership with related areas in the Biology, Physics and Biotechnology units of Minho University.
- the absence of calls for research projects grants (FCT) since May 2002;
- lack of funding for the:
  - (i) recruitment of graduated specialised technicians for all the prioritary scientific areas of ICVS;

(ii) implementation of a scientific library.

- the impossibility to fully develop the specialized health services and the launching of formal Master and Doctoral degrees associated with the post-graduation programme, due to constraints raised by the provisional facilities. However, the specialised advanced courses offered under this programme, besides their impact on life long learning for professionals in the local and regional health units, are credited as components of the formal post-graduation degree programmes to be started in the near future.

4.2. ESSENTIAL NEEDS

It is therefore crucial that FCT integrates the ICVS in its network of research units, providing financial support to the basal current functioning and also a special programmatic financing for equipment, in order to develop and be competitive.

The effort made by the ECS to start research activities without prior specific financing from the Government has no precedents in Portuguese Universities, but it has reached the limits of its possibilities. We have consequently insisted on our request for infrastructural funding, by presenting very recently a concrete proposal for a specific contract ("contrato programa"), in which we justify the demand for a grant of 3, 4 million Euros for laboratorial facilities in the areas of Biological Resources, Molecular and Cellular Biomedicine and Cell Imaging.

4.3. A FINAL COMMENT

In conclusion, it is our deep conviction that, albeit the above difficulties, all the main goals for these first years 2002-03 were achieved through the constant institutional support of the School together with the enthusiasm and commitment of all ICVS Members. We will continue our effort to establish the ICVS as an international research centre of excellence.

Cecília Leão

Director of ICVS
December, 2003

APPENDIXES

APPENDIX I
LIFE AND HEALTH SCIENCES RESEARCH INSTITUTE – Creation, Progression during 2002-2003, Goals and Challenges

APPENDIX II
Thesis under Development: Themes and Supervisors

APPENDIX III
Research Staff of ICVS |December 2003

APPENDIX I

LIFE AND HEALTH SCIENCES RESEARCH INSTITUTE

Creation, Progression during 2002-2003, Goals and Challenges

CREATION

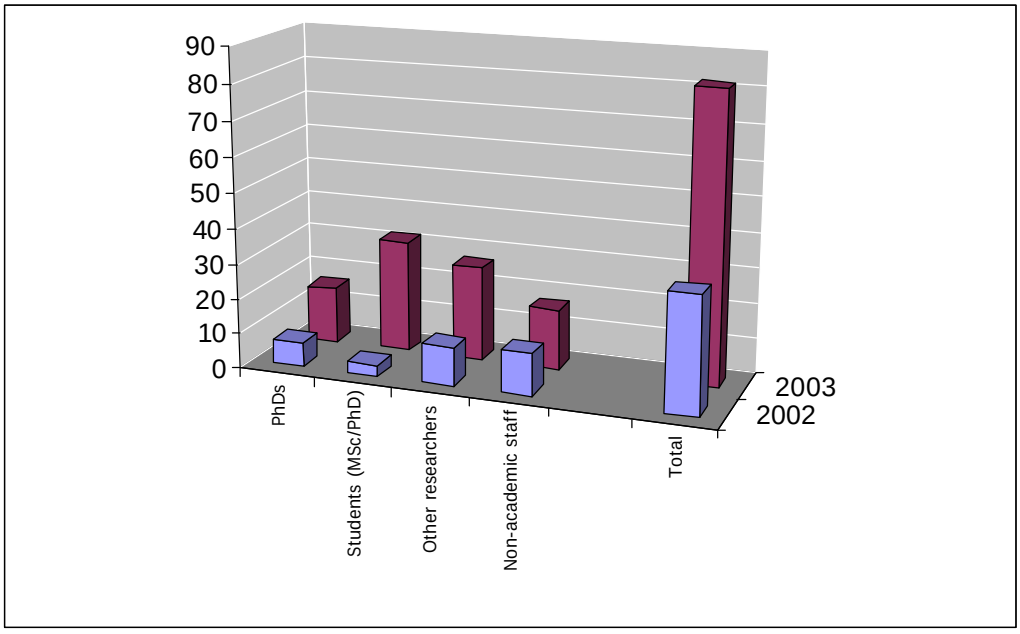
The Health Sciences School (ECS) is one of the newest additions of the University of Minho. The ECS was conceived to assure: i) training of medical students; ii) establishment of biomedical research groups and iii) delivery of specialised health services to the community.

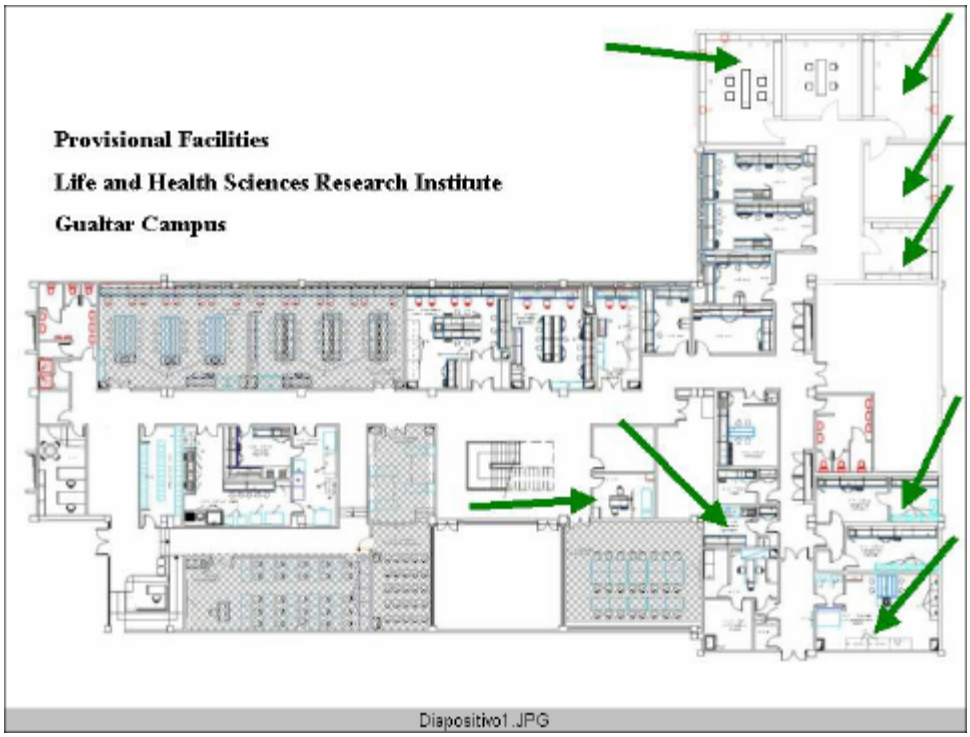
To achieve goals ii) and iii) the ECS created the Life and Health Sciences Research Institute (ICVS). Therefore, in recruiting academic staff, both teaching and research expertises were amongst the selecting criteria. This strategy strongly contributed to the success in training medical students, promoted the interaction between different fields of biomedical research and medical education, and it also resulted in the establishment of a wide range of research fields within the ICVS. In accordance, the initial proposal (April 2002) presented for the ICVS contained 6 research domains: neurosciences, neoplastic diseases, genetic diseases, infectious diseases (subdivided into mycosis and tuberculosis studies) and development diseases.

THE 2002-2003 PROGRESSION

Since its creation, two years ago, there was a significant expansion of both human resources and facilities (Fig.1 and 2), which allowed the consolidation of the research groups.

Fig. 1.





The ICVS is operating in provisional facilities. In 2002, twelve laboratories were available. During the last 20 months a great effort was concentrated in the preparation of additional laboratories and scientific equipments (indicated by arrows). A series of fully operational research laboratories organized by function was set up, in parallel with an internal network of shared facilities established to support, in a multidisciplinary way, the different research groups of the ICVS. At present, the research facilities consist of twenty laboratories (1500 m2). These include the following additions to the facilities available in 2002:

Biological Resources Center and Animal House. Biological Safety Laboratories of Level 3 including ultra-freezers, flow cytometry and cell culture equipments, up-grade of the animal facility for 1000 mice and 300 rats, external quarantine, 350 mice in Level 3 containment and systems for behavioural tests.

Genomics and Proteomics Facility. It is equipped with ultracentrifuge, additional PCR machines, real-time PCR, electrophoresis apparatus, espectophotometer, 2D-PAGE, image acquisition and software for molecular biology.

Due to a significant delay in the construction of the new building of the ECS, the University approved an expansion to the upper floor. Administrative headquarters, offices for researchers and seminar rooms are presently located in this new area.

STRATEGY FOR THE DEVELOPMENT OF ICVS

The strategy for development was based on consolidation and integration. The ICVS intends to be not just one more research unit, but rather, a NOVEL research unit. To achieve this goal the following procedures were (are being) implemented:

Integrated and shared management. One of the main and most common difficulties in setting up a new research unit is funding. The ICVS is not an exception. However, the ICVS counted with a crucial initial contribution from both the ECS and the University of Minho. This allowed the ICVS to build the current facilities. In addition, the ECS granted all groups a small basal funding, and covered the maintenance costs of equipment and general products. A rigorous application of the ECS contract plan, together with grants owned by the PIs, permitted therefore, to initiate the research activities at the ICVS.

Function-oriented laboratories. Integrated management avoids duplication of equipment and facilities and rationalizes human resources. The existence of specialized laboratories, in which in some cases individual groups are located, also promotes exchange of expertise and projects. The present function-oriented laboratories/facilities include: 1. Animal house, 2. Imaging facilities, 3. Tissue processing facilities, 4. Tissue and cell culture room; 5. Rodent behavioural laboratory; 6. Molecular biology laboratory, 7. Level 2 and Level 3 biosafety laboratories.

Multi- and inter-disciplinary research groups. The integrative policy implemented from the beginning has already given some results. It had an INTEGRATIVE effect, since all initial groups, being integrated in an environment favourable to the establishment of inter-group collaborations and complementary experimental approaches, merged, from the original six, into three wider research domains: infectious diseases, neurosciences, development and neoplasia. The critical mass of each has, therefore, been strengthened, which can certainly be considered a STRUCTURAL effect of the integrative policy.

Innovative post-graduation. In 2003, and for the third consecutive year, high priority was given to post-graduation studies with a dual objective: i) contribute to a highly specialized in-service training of medical doctors under conditions compatible with their normal duties and schedules; ii) extend the opportunities for the access to formal Master or Doctoral degrees in the field of life and health sciences. In accordance, we increased the number of MDs and professionals in health sciences enrolling in our courses/workshops and improved in their assessment of the Courses.

INSTITUTIONAL POLICY AND ASSESSMENT

The ICVS implemented a continuous assessment of this integrated management that allows to: i) encourage and examine the ability of the groups to develop collaborative projects ii) encourage and evaluate the efficient use of common facilities and laboratories and iii) redefine the existing common facilities/laboratories and research domains.

RESULTS

The main results achieved in 2003 are summarised in the next table.

International publications	
Papers	**36**
Book Chapters	**3**
Abstracts in Congresses	**40**
National publications	
Papers	**1**
Book Chapters	**1**
Abstracts in Congresses	**23**
Thesis concluded	
Master Thesis	**2**
Under-Graduate Thesis	**10**
Thesis under development	
PhD thesis	**18**
Master Thesis	**2**
Scientific research prizes	**5**
Post-graduation courses organized by the ICVS	**6**

PLANNING FOR 2004/2006

Consolidation of the research groups. 2004/2006 will represent a period of consolidation for each research group. We hope to increase scientific production by at least 25-50% in every group and to expand funded collaborative research projects. Attention will be more focused on optimising the scientific production of every researcher, rather than in a large expansion of human resources.

Expansion to the new ECS building. The new building for the School of Health Sciences, to be completed by the end of 2005, includes a specific area for the ICVS, with 6 000 m2. This will represent a significant improvement of the installations dedicated to research, although it also implies further equipment (several applications to FCT have been advanced).

Post-graduation. It is our aim that the involvement of health sciences professionals in the ICVS activities shifts in the near future to formal bounds in Masters and PhDs programmes. Taking advantage of being part of a Medical School, we wish to develop a MD/PhD program, for which we count with the enthusiastic collaboration of Thomas Jefferson Medical School, and Columbia University Medical School. Apart from these collaborative efforts, which must be formally established in the next two years, we will also present, during 2004, a programme to be developed indoors. This programme is intended to provide summer courses, and to develop most of the thesis projects as joint research between the ICVS and the health units in which the students develop their medical career.

Along these lines we also intend to present a programme of continuous medical education, to be implemented in the years 2005/6.

Translational research. The goal of the ICVS for 2004/2006 is to enhance the clinical research infrastructure through the expansion of the breadth of clinical research activities and by sustaining an increasing number of “active” physicians in its research faculty. This task is viewed as a critical tool to foster the productivity of physician-scientists who will strengthen translational research in academic health centers, both through their own studies as well as their mentoring of the next generation of physician-scientist trainees. Physician-scientists play a crucial role in the continuum of research that ensures a free flow of information and new treatments from the laboratory to the patient bedside and back again. Traditionally, clinical-oriented research centers have had an influent role in the development of medical advances, thereby setting standards for the practice of medicine and the quality of health care.

Specific Aims:

1. Increase the number of independent clinical research investigators utilizing the ICVS by at least 25% to competitively apply for general clinical research center funding.
2. Expand the research infrastructure to support at least 25% growth in clinical research studies.
3. Expand funded collaborative research projects.
4. Set specialised health services to the community.

IDENTIFICATION (AND SOLUTION) OF WEAKNESSES

Funding. The ICVS has managed to create very interesting conditions for its research groups. The quality of the facilities and the number of researchers is adequate, when considering national standards. The main constraint is presently financial support that would sustain and consolidate research activities in the ICVS. This assertion is valid both for **basal** (reagents and maintenance) as well as for **programmatic** (acquisition of equipment) funding. It is important to remember that existent equipment was integrally funded by the ECS. Without these conditions research will stagnate or, even, collapse.

We are aware of the crucial importance of diversification of funding sources. Despite the lack of tradition in private funding of research in Portugal, we are launching a *Funding Committee* aiming to find alternative sources of financial support.

Major equipment constraints are:

1. Electron microscopy
2. Confocal microscope
3. ? and ß-counter
4. DNA Sequencer
5. HPLC

Institutional collaborations. Due to its short existence, the ICVS has still a reduced number of institutional collaborations. It is our belief that the establishment of collaborations will increase scientific expertise and skills and, in addition, will facilitate proposals to international funding agencies.

Access to scientific information. Access to Scientific and Medical publications, preferably to the electronic versions of journals, is vital. Access to books is also limited. A national electronic library would be a valuable resource or, alternatively, regular funding for this purpose should be warranted.

APPENDIX II. THESIS UNDER DEVELOPMENT: THEMES AND SUPERVISORS

RESEARCH AREA	THESIS	STUDENT	SUPERVISOR(S)	SUBJECT
Infectious Deseases	PhD	Almeida, Agostinho	Cecília Leão Fernando Rodrigues (UM)	Cellular and molecular analysis of the dimorphic fungi *Paracoccidioides brasiliensis*
	PhD	Carvalho, Agostinho	Fernando Rodrigues Patrícia Maciel (UM)	Susceptibility to systemic mycosis in immunodeficient patients: analysis of molecular factors)
	MsC	Oliveira, Rodrigo	Paula Ludovico (UM)	Elucidation of the molecular basis of human mitochondrial neuromyopathies associated to citochrome oxidase deficiency: use of *Saccharomyces cerevisiae* as a model
	MsC	Martins, Margarida	Fernando Rodrigues (UM)	Studies in *Paracoccidioides brasiliensis*: Development of molecular tools
	PhD	Cruz, Andrea	Jorge Pedrosa (UM)	Understanding BCG vaccination: implications for the design of new preventive strategies against mycobacteriosis
	Post-Doc	Pereira, João Pedro	Jorge Pedrosa (UM)	Activation of toll-like receptors in B lymphocytes during mycobacterial infections
	PhD	Torrado, Egídio	Jorge Pedrosa (UM)	Immunobiological studies of secreted proteins from mycobacteria and *Candida albicans*: a role for vaccination
Neurosciences	PhD	Costa, Mª do Carmo	Patrícia Maciel (UM)	Studies in *Mus musculus* of the gene homologue for the Machado-Joseph disease
	MsC	Lessa, Lira	Patrícia Maciel (UM)	Studies in *Gallus gallus* of the gene homologue for the Machado-Joseph disease
	PhD	Marques, Fernanda	Joana Palha (UM)	Searching for the function of transthyretin in the energy metabolism and of the choroid plexus in inflammation
	PhD	Ruano, Dina	Joana Palha (UM)	Genetics of schizophrenia: the retinoid and thyroid hormone hypothesis
	PhD	Santos, Mónica	Patrícia Maciel (UM)	Pathogenesis study of Rett Syndrome. The role of the MeCP2 protein in neuronal function
	PhD	Sousa, João Carlos	Joana Palha (UM	Searching for an essential function for transthyretin in the central nervous system
	PhD	Almeida, Rui	Nuno Sousa (UM)	Application of telemetry to assessment of intracraneal parameters
	PhD	Cerqueira, João	Nuno Sousa (UM)	Structural reorganization of the prefrontal cortex by corticosteroids and CRH
	PhD	Lu, Jie	Nuno Sousa (UM)	Nuclear hormone receptor regulation of neurogenesis: combining gene transfection and genomic approaches

RESEARCH AREA	THESIS	STUDENT	SUPERVISOR(S)	SUBJECT
Neurosciences	PhD	Mesquita, Ana Raquel	Nuno Sousa (UM)	Assessing acute and long-term neurological sequelae of seizures on the "limbic" brain: the influence of early life stress and hyperthermia
	PhD	Pêgo, José Miguel	Nuno Sousa (UM)	Influence of stress upon the structure and function of the amygdale
	PhD	Silva, Rui	Nuno Sousa (UM)	Interventions modulating hippocampal postnatal neurogenesis: structural and functional implications
Development and Neoplasia	MsC	Basto, Diana	Rui M. Reis (UM)	Molecular alterations predictive of therapy in malignant gliomas
	MsC	Carvalho, Inês	Fernando Schimtt (UM)	PDGFR in breast cancer
	PhD	Costa, Sandra	Fernando Schmitt (UP/UM)	DNA repair gene polymorphisms in a group of breast cancer patients from portuguese origin
	PhD	Duarte, Fátima	Fernando Schimtt (UM)	Role of FGF in angiogenesis
	Post-Doc	Longatto, Adhemar	Fernando Schimtt (UM)	Lymphangiogenesis in breast cancer
	PhD	Milanezi, Fernanda	Fernando Schmitt (UP/UM)	Evaluation of therapeutical response in breast cancer
	PhD	Reis-Filho, Jorge	Fernando Schmitt (UP/UM)	Myoepithelial differentiation in breast carcinomas: pathological recognition and clinical implications
	Post-Doc	Andrade, Raquel	Isabel Palmeirim (UM)	Use of "two-hybrid" technology in the analysis of the molecular watch associated with the segmentation of vertebrate embryos
	MsC	Baptista, Maria João	Jorge Correia-Pinto (UM)	Retinoid modulation of fetal heart-lung growth in CDH
	MsC	Bastos, Rui Pedro	Jorge Correia-Pinto (UM)	Regulation of fetal lung growth/maturation through ghrelin-growth hormone secretagogue receptor pathway
	MsC	Magalhães, Sónia	Jorge Correia-Pinto (UM)	Hemodynamic study of Bi-ventricular Diastolic Function in Experimental Models of Pulmonary Hypertension
	MsC	Melo-Rocha, Gustavo	Jorge Correia-Pinto (UM)	Myocardial Gene Expression of Calcium Regulatory Proteins in Experimental Modeols of Myocardial Hypertrophy
	PhD	Pascoal, Susana	Isabel Palmeirim (UM)	New Aspects of the Coordination of Vertebrate Limb Bud Development
	PhD	Rodrigues, Sofia	Isabel Palmeirim (UM)	Molecular and Cellular Characterization of Somitogenesis in Early Chick Development
	MsC	Roriz, Mário	Jorge Correia-Pinto (UM)	Cardiovascular Physiology
	PhD	Santos, Marta	Jorge Correia-Pinto (UM)	Common genetic pathways in lung and limb development: *in vivo* and *in vitro* studies

MsC = Master thesis
UM= University of Minho; UP = University of Porto.

APPENDIX III

RESEARCH STAFF OF ICVS |December 2003

1- Phd Researchers

NAME (POSITION / DEGREE / RESEARCH AREA)	*FTE/Research*
1.1 Permanent Staff	
Isabel Mª M. M. Palmeirim A. Esteves (Assist. Prof./ MD/ PhD / **Development and Neoplasia)**	0.5
Jorge Manuel Correia Pinto (Assist. Prof./ MD /PhD / **Development and Neoplasia**)	0.25
Maria de Fátima M. Baltazar (Assist. Prof./ PhD / **Development and Neoplasia**)	0.5
Rui Manuel Vieira Reis (Assist. Prof./ PhD / **Development and Neoplasia**)	0.5
António Gil Pereira de Castro (Assist. Prof./ PhD / **Infectious Diseases**)	0.5
Maria Cecília Lemos Pinto Estrela Leão (Full Time Prof. / PhD / **Infectious Diseases**)	0.5
Fernando José dos Santos Rodrigues (Assist. Prof./ PhD / **Infectious Diseases**)	0.5
Jorge Manuel Rolo Pedrosa (Assist. Prof./ PhD / **Infectious Diseases**)	0.5
Paula Cristina C. A. Monteiro Ludovico (Assist. Prof./ PhD / **Infectious Diseases**)	0.5
Armando Alberto Nova Pinto de Almeida (Assist. Prof./ PhD / **Neurosciences**)	0.5
Joana Almeida Santos Pacheco Palha (Assist. Prof./ PhD / **Neurosciences**)	0.5
Nuno Jorge Carvalho de Sousa (Assist. Prof./ MD/ PhD / **Neurosciences**)	0.5
Patrícia Espinheira de Sá Maciel (Assist. Prof./ PhD / **Neurosciences**)	0.5
1.2 Non - Permanent Staff	
Adhemar Longatto Filho (Post-Doc / PhD / **Development and Neoplasia**)	1.0
Raquel Gláucia Varzielas Pêgo de Andrade (Post-Doc / PhD / **Development and Neoplasia)**	1.0
João Pedro Antunes Pereira (Post-Doc / PhD / **Infectious Diseases**	1.0
External Invited Researchers	
Fernando Carlos de Lánder Schmitt (MD/ PhD / **Development and Neoplasia** IPATIMUP-UP)	
Manuel Teixeira da Silva (MD/ PhD / **Infectious Diseases** / IBMC-UP)	

2. Post-graduation students

NAME (POSITION / DEGREE / RESEARCH AREA)	*FTE/Research*
2.1 PhD students	
Alberto Filipe Sansonetty Gonçalves (MD/ **Development and Neoplasia**)	0,6
Ana Raquel Marcelino Mesquita (**BD** / Lic / Biology / **Development and Neoplasia**)	1.0
Maria Fátima Pereira Duarte (Lic/ Biochemistry/ **Development and Neoplasia**)	1.0
Marta Alexandra R. dos Santos (Lic / Biochemistry / **Development and Neoplasia**)	1.0
Sandra Maria Araújo da Costa (**BD** / Lic / Biology / **Development and Neoplasia**)	1.0

Sérgio Reis Filho (**BD** /MD/ **Development and Neoplasia**) 1.0

Sofia Machado Cruz de A. R. M. Cristovão (**BD** / Lic / Biology / **Development and Neoplasia**) 1.0

Susana Alexandra Rodrigues Pascoal (**BD** / Lic / Biology/ **Development and Neoplasia**) 1.0

Agostinho João Ramalho de Almeida (**BD** / Lic / Biology / **Infectious Diseases**) 1.0

Agostinho Albérico Rodrigues de Carvalho (**BD** / Lic / Biology / **Infectious Diseases**) 1.0

Andreia Patrícia Ribeiro da Cruz (**BD** / Lic / Microbiology / **Infectious Diseases**) 1.0

Egídio Manuel Pires Torrado (**BD** / Lic / Biology/ **Infectious Deseases**) 1.0

Dina Ruano Neto (**BD** / Lic / Biology/ **Neurosciences**) 1.0

Fernanda Cristina Gomes Sousa Marques (**BD** / Lic / Biology/ **Neurosciences**) 1.0

Jie Lu (**BD** / MD/ **Neurosciences**) 1.0

João Carlos Cruz Sousa (Monitor – **BD**/Lic/ Biochemistry/**Neurosciences**) 0,2

João José Fernandes Cardoso de Araújo Cerqueira (Monitor / MD/ **Neurosciences**) 0,2

José Miguel Gomes Moreira Pêgo (Monitor / MD/ **Neurosciences**) 0,2

Maria do Carmo Pereira da Costa (**BD** / Lic / Biochemistry / **Neurosciences**) 1.0

Mónica Joana Pinto dos Santos (**BD** / Lic / Biology / **Neurosciences**) 1.0

Rui Jorge Marques Almeida (MD/ **Neurosciences**) 1.0

Rui Jorge de Freitas Silva (**BD**/ Lic / Biology/ **Neurosciences**) 1.0

2.2 Master students (Master thesis)

Diana Sofia de Sá C. G. Basto (Lic / Microbiology / **Development and Neoplasia**) 1.0

Gustavo Filipe Melo Alves da Rocha (Monitor / MD/ **Development and Neoplasia**) 0,2

Maria João Ribeiro Leite Baptista (Assistant/ MD/ **Development and Neoplasia**) 0.2

Rui Pedro da Rocha Bastos (Monitor / MD/ **Development and Neoplasia**) 0,2

Sónia Manuela Rodrigues Magalhães (Assistant/ MD / **Development and Neoplasia**) 0.2

Margarida Isabel de Barros C. Martins (Lic / Biochemistry / **Infectious Diseases**) 1.0

Lira de Carvalho Folgado Lessa (Lic / Microbiology/ **Neurosciences**) 1.0

2.3 Lic. Researchers

Carla Rolanda da Rocha Gonçalves (Assistant/ MD/ **Development and Neoplasia**) 0.2

Maria Fernanda Grillo Milanezi (Assistant/ MD / **Development and Neoplasia**) 0.2

Isabel Maria Simões Sousa Ribeiro Oliveira (Assistant/ MD/ **Development and Neoplasia**) 0.2

Luís Miguel Gonçalves Torrão (Assistant/ MD/ **Development and Neoplasia**) 0.2

André Filipe Couto Carvalho (Assistant / MD/ **Neurosciences)** 0.2

António Luís Ferreira dos Santos (Assistant / MD/ **Neurosciences**) 0.2

Filipa Santos Costa Pinto Ribeiro (Assistant/ Lic / Biology/ **Neurosciences**) 0.25

Manuel José Lima Costa Rodrigues (Assistant / MD / **Neurosciences**) 0.25

Vítor Manuel Varandas Moreira (Assistant / MD/ **Neurosciences**) 0.2

João Paulo Soares Fernandes (Monitor / MD / **Development and Neoplasia)** 0.2

Hugo Miguel Braga Almeida Tavares (Monitor / MD / **Neurosciences**) 0.2

João Miguel Seiça Bessa Peixoto (Monitor / MD / **Neurosciences**) 0.2

Maria Leonor Barbosa Gonçalves (Monitor / MD/ **Neurosciences** 0.2

Mário Jorge Alves Oliveira (Monitor / MD / **Neurosciences**) 0.2

Pedro Alexandre Leão A. G. Teixeira (Monitor / MD / **Neurosciences**)	0.2
Albino Manuel Pereira Martins (**BI**/ Lic / Biology/ **Development and Neoplasia**)	1.0
Ana Catarina Almeida Carrão (**BI** / Lic / Biochemistry / **Development and Neoplasia**)	1.0
Maria Susana González de Ribeiro Abreu (**BI** / Lic / Biochemistry / **Development and Neoplasia**)	1.0
Sandra Mónica Brandão de Almeida Ferreira (**BI** / Lic / Biology/ **Development and Neoplasia**)	1.0
Sara Isabel Rodrigues dos Santos (**BI** / Lic / Biochemistry / **Development and Neoplasia**)	1.0
Sílvia Gonzaga da Silva Santos (**BI** / Lic / Aquatic Sciences / **Development and Neoplasia**)	1.0
Alexandra Gabriel Fraga (**BI**/ Lic / Biology/ **Infectious Deseases**)	1.0
Gustavo Leão Valdigem (**BI**/ Lic / Biology/ **Infectious Deseases**)	1.0
Martinha Soares Oliveira (**BI** / Lic / Biology/ **Infectious Deseases**)	1.0
Rodrigo Emanuel Gomes Leite de Oliveira (**BI** / Lic / Pharmacology / **Infectious Deseases**)	1.0
Sílvia Alexandra Mota (**BI** / Lic / Pharmacology/ **Infectious Diseases**)	1.0
Anabela Silva Fernandes (**BI** / Lic / Biochemistry / **Neurosciences**)	1.0
Andreia Cristiana Teixeira de Castro (**BI** / Lic / Biochemistry / **Neurosciences**)	1.0
Hugo Miguel do Vale Leite Santos de Almeida (**BI** / Lic / Biochemistry / **Neurosciences**)	1.0

3. Non-Academic Staff shared with the School

NAME (CARGO / DEGREE / SERVICE)

Ana Cristina Martins Rodrigues Taboada (*Técnica Superior Estagiária / Lic.* / Laboratories)
Ana Paula Salgueira Rodrigues (*Técnica Superior Estagiária / Lic.* / UEM)
Catarina Nazaré Sousa de Freitas (*Assistente Administrativa* / Secondary Education / Secretariat)
Maria Celina Ferreira de Barros (*Auxiliar de Manutenção* / Basic Education / Laboratories)
Cláudia Manuel Borges Barreira (*Técnica Superior Estagiária* / Lic. / Post - Graduation)
Domingos Ferreira Dias (*Técnico de Informática Adjunto* / Secondary Education / Laboratories)
João Filipe Almeida Malheiro (*Auxiliar Técnico* / Secondary Education / Laboratories)
Helena Maria Alves Nascimento (*Assistente Administrativa* / Secondary Education / Secretariat)
Isabel Mª Vieites Barbosa (*Assistente Administrativa* / Secondary Education / Secretariat)
Jorge Manuel Afonso de Freitas *(Especialista de Informática Estagiário/* Bachelor / UEM)
Jorge Manuel Soares Gonçalves Paula (*Auxiliar Administrativo* / Basic Education / Laboratories)
José Carlos da Fonseca Henriques (*Assessor Principal /Lic.*/Head Office ECS)
Lucília Goreti Ribeiro Pinto (Téc. Diag. Terapêutica / Lic. / Laboratories)
Magda João Castelhano Carlos (*Técnica Superior de 2ª classe* / Lic. / Laboratories)
Maria Paulina D. Martins dos Santos (*Técnica Superior Estagiária* / Research)
Olga Maria de Sousa Miranda Abreu (*Assistente Administrativa Principal* / Secondary Education / Secretariat)
Paula Carla Ferreira Gomes Pereira (*Técnica Superior de 2ª classe* / Lic. / Human Resources)
Susana Isabel Vaz Santos (*Auxiliar Técnica* / Secondary Education / Laboratories)

Legend

FTE- Full Time Equivalent

Lic- "Licenciado"