

I B I L I
FACULTY OF MEDICINE
UNIVERSITY OF COIMBRA

A N N U A L R E P O R T [2 0 0 6]

0 | INDEX

1 INTRODUCTION	5
RP1 PHENOTYPING AND TREATING RETINAL AND BRAIN DEGENERATIONS, UNDERSTANDING RETINO-CORTICAL PROCESSING IN HEALTH AND DISEASE	9
RP1.1 BRAIN MAPPING OF VISUAL CORTICAL FUNCTION: PARALLEL PROCESSING WITHIN RETINOCORTICAL AND CORTICAL DORSAL/VENTRAL STREAM PATHWAYS	11
RP1.2 BRAIN MAPPING OF VISUAL OBJECT RECOGNITION PATHWAYS	12
RP1.3 PERCEPTUAL LEARNING IN THE HUMAN VISUAL SYSTEM: RELATION WITH OTHER MEMORY SYSTEMS IN HEALTH AND IN MILD COGNITIVE IMPAIRMENT	13
RP1.4 NEUROCOGNITIVE STUDIES OF IMPLICIT LEARNING AND MEMORY	14
RP1.5 NEW METHODOLOGICAL APPROACHES TO STUDY BRAIN FUNCTION THROUGH MAGNETIC RESONANCE	15
RP1.6 EVALUATION OF VISUAL PLASTICITY AND FUNCTIONAL REORGANIZATION UPON DAMAGE OF OPTIC AND/OR NEURAL PATHWAYS	16
RP1.7 BASIC MECHANISMS OF RETINOCORTICAL PROCESSING AND MECHANISMS OF DISEASE IN OPTIC NEURITIS AND MULTIPLE SCLEROSIS	17
RP1.8 MOLECULAR IMAGING OF THE BRAIN IN AGEING AND DEMENTIA. DISEASE MECHANISMS IN MOVEMENT DISORDERS	18
RP2 A TRANSLATIONAL APPROACH TO DEVELOP NEW METHODS OF DIAGNOSIS AND INNOVATIVE THERAPIES FOR AGE-RELATED DEGENERATIVE DISEASES	19
RP2A PHENOTYPING, IDENTIFICATION OF RISK MARKERS AND TESTING EMERGING THERAPIES	20
RP2.A1 HUMAN HEREDITARY DISEASES	20
RP2.A2 AGE-RELATED MACULAR DEGENERATION	21
RP2.A3 DIABETIC RETINOPATHY	22
RP2.A4 GLAUCOMA	23
RP2.A5 BRAIN DEGENERATIVE DISEASES	24
RP.2B GENOTYPES TO PHENOTYPES: MOLECULAR MECHANISM OF DEGENERATION AND DESIGN OF NEW THERAPIES	25
RP2.B1 MODELS OF AGE-RELATED DEGENERATIONS	26
RP2.B2 RETINAL DYSFUNCTION AND REPAIR	27
RP2.B3 SUBCELLULAR TRAFFICKING IN RPE	28
RP2.B4 MOLECULAR AND CELL IMAGING	29
RP2.B5 FUNCTIONAL STUDIES OF DRUG ACTION AT SYSTEMS LEVEL, INCLUDING THE RETINA AND THE BRAIN. MECHANISMS OF DRUGS ABUSE	30
RP2.B6 AGEING AND CELL MECHANISMS OF HEART DYSFUNCTION	31
RP.2C UNDERSTANDING AND TREATING DIABETES AND DIABETIC ENDOTHELIAL DYSFUNCTION	32
RP.3 TOOLS FOR CLINICAL IMAGING AND NEW METHODS FOR DRUG DELIVERY	33
RP.3.A NEW TOOLS FOR CLINICAL IMAGING OF THE RETINA, OPTIC NERVE AND BRAIN	34
RP3.A1 CLINICAL IMAGING OF THE RETINA AND OPTIC NERVE	35
RP3.A2 INCREASING OPTICAL COHERENCE TOMOGRAPH (OCT) MAPPING RESOLUTION	36
RP3.A3 FLUORESCENCE LIFETIME IMAGING OF RETINA	37
RP3.A4 IMAGE AND SIGNAL PROCESSING	38
RP.3B DRUG DELIVERY	39
RP3.B1 OVERCOMING DRUG RESISTANCE	39
RP3.B2 NANOTECHNOLOGIES - TARGETED CONTRAST AGENTS AND DRUG TRANSPORTERS	40
RP3.B3 NANOMEDICINES. DEVELOPMENT OF SUPRAMOLECULAR STRUCTURES FOR DRUG DELIVERY	41
2 SCIENCE COMMUNICATION AND PUBLIC RELATIONS DEPARTMENT. URL MANAGEMENT.	43

3 INTERNATIONALIZATION PROGRAM	45
4 GRADUATE STUDIES PROGRAM	49
4.1 DOCTORAL PROGRAM IN AGEIND AND DEGENERATION OF COMPLEX SYSTEMS	50
4.2 DOCTORAL PROGRAM IN NEUROPSYCHOLOGY	55
4.3 DOCTORAL PROGRAM IN BIOMEDICINE OF CNC	57
4.4 INTERDISCIPLINARY DOCTORAL PROGRAM IN VISUAL SCIENCES WITH UNIVERSITY OF VALLADOLID AND MURCIA	58
4.5 MASTER'S DEGREE IN MEDICAL RETINA AND PEDIATRIC OPHTHALMOLOGY	59
4.6 MASTER'S DEGREE IN VISION SCIENCES	60
5 THESIS CONCLUDED IN 2004-2006	61
6 EXTERNAL FUNDED RESEARCH PROJECTS	64
7 PUBLICATIONS 2004-2006	67

IBILI is a research Institution of the Faculty of Medicine – University of Coimbra and relies on excellent clinical and laboratory facilities as well as on a highly skilled and multidisciplinary scientific staff. IBILI is an internationally recognised centre of excellence for research in health sciences. Particular strengths include research in Vision Sciences. IBILI is evaluated regularly by an independent panel from “Fundação para a Ciência e Tecnologia” (FCT) and has been judged as “Excellent” both in 1999 and 2004 evaluations.

IBILI fosters an environment for research, education and training that promotes a multi-disciplinary approach to health sciences, crossing traditional boundaries between Medicine, Biology and Engineering. Integration between basic and clinical research is essential for the advance of modern health sciences and IBILI commits a major effort to support such integrated research programmes. As a research unit of the Faculty of Medicine, IBILI is also strongly committed to continuously promote and foster the highest possible standards in post-graduate teaching. IBILI coordinates 2 Doctoral Programmes 1 in Ageing and Degeneration of Complex Biological Systems and Master Courses in Vision Sciences and Biomedical Engineering and collaborates in two international PhD programmes: PhD Program in Vision Sciences (together with Universities of Valladolid, Murcia and Madrid, Spain) and PhD Program in Experimental Biology and Biomedicine (together with CNC).

IBILI has recently received funds for acquisition of new equipment as part of the “FCT - Programa Nacional de Re-equipamento Científico”, particularly for Electron Microscopy and Functional Imaging of Brain and Retina. These new infrastructures will further expand the scientific and technological competences of IBILI and may constitute additional opportunities to consolidate existing expertise as well as for development of innovative research programs.

In a highly competitive and fast moving scientific environment, alliances and broad collaborations are vital to insure scientific excellence. IBILI is committed to pursue a model of translational research at international level to facilitate the achievement of excellence in areas such as ageing and age-related eye and brain diseases. This strategy creates a rich scientific environment that may further help to attract gifted scientists to Portugal. IBILI actively participates and leads a number of International Research programmes including “The European Vision Institute” (EVI) and the Evi-Genoret EU-funded consortium, which aims to build on our understanding of the fundamental molecular and cell biology of the retina, of its development and the way it is perturbed by genetic mutation, environmental factors and ageing. The project integrates population genetics, clinical and experimental phenotyping, molecular genetic approaches, genomic high throughput methods of transcriptional and proteomic pattern recognition, as well as in depth analytical approaches to analyse protein function and its integration into complex protein functional networks. A continued effort will be made to attract to Portugal highly competent scientists and research teams as to improve the critical mass of the institute.

The research activity at IBILI is carried out under the umbrella of three major research programmes each having dedicated staff and budget:

RP1: Phenotyping and treating retinal and brain degenerations, understanding retino-cortical processing in health and disease

Coordinator: Miguel Castelo-Branco

RP2: A logical translational approach to develop new methods of diagnosis and innovative therapies for degenerative diseases of the retina, optic nerve and brain

Coordinator: Paulo Pereira

RP3: Tools for clinical imaging and new methods for drug delivery

Coordinator: Filomena Botelho

Coordinator: Miguel Castelo-Branco

In our recent work, we aimed to understand visual function from the photoreceptor to visual cortical level, using multiple level conceptual and methodological perspectives, ranging from functional imaging, electrophysiological and psychophysical approaches, to characterize genetic photoreceptor degenerations and neural aging. We have established new structure-function and genotype phenotype correlations in human genetic models of photoreceptor degenerations. Furthermore, we could isolate specific magnocellular/visual motion dysfunction in a genetic neurodevelopmental model, Williams Syndrome. We have further studied parallel pathways to quantitatively analyse visual aging in neurodegenerative disorders of the retina and the brain (Glaucoma and Parkinson Disease). We now aim to go a step further, and dissect spatial/temporal mechanisms in human retinocortical processing.

Furthermore we aim to explore higher level neural correlates of object recognition by means of the establishment of structure-function correlations within the visual ventral stream, striatal and limbic circuits in health and disease.

RP1.1 | BRAIN MAPPING OF VISUAL CORTICAL FUNCTION: PARALLEL PROCESSING WITHIN RETINOCORTICAL AND CORTICAL DORSAL/VENTRAL STREAM PATHWAYS

Head: Miguel Castelo-Branco

Main goals: Retinocortical visual processing in normal and pathological aging and neurodevelopment, Functional mapping of the cross-talk between retinal magno and parvocellular pathways and between dorsal and ventral stream visual cortical pathways.

Concerning basic questions, we aim to now pursue in humans a result that we have obtained in the animal model. In a well cited paper published in the *J. of Neuroscience*, we had performed neuronal simultaneous recordings at three levels of visual processing of the cat's visual system: the retina, the LGN and the cortex. We found that the encoding of stimulus properties could be correlate with temporal patterns of activity across these 3 distinct levels. In particular we found neuronal oscillations whose frequency and pattern of synchronization across areas were stimulus dependent. These temporal patterns were identified in neuronal and local field potential recordings. We now aim to perform simultaneous non-invasive electrophysiological recordings from the human retina (multifocal electrophysiology) and brain (high-density ERP recordings) in order to generalize our findings to human visual perception. The advantage of the human model is that we can obtain direct online measurements of perceptual performance (by means of button presses and eye movement recordings) and directly correlate these events to neuronal patterns of activity, which in the animal can only be obtained indirectly. The relevance of this approach stems from an outstanding question in current cognitive neuroscience: into which extent does information processing depend on temporal neural codes?

We aim to link this question to the understanding the functions of distinct colour and motion visual pathways and how they relate to genetic and circuit level mechanisms. We manipulate stimulus coherence in the colour and motion domains and ask the question whether such manipulations of coherence can be revealed in retinocortical temporal codes. Motion coherence is believed to be encoded in retino-cortical dorsal pathways whereas coherence in the colour space domain is signalled in retinocortical ventral pathways. Stimulus coherence manipulations can also be correlated with thresholds and amplitude and phase of specific colour and motion evoked neural signals. Given the recent evidence for early visual impairment in PD we will now perform visuomotor studies in familial forms PD (using eyetracking and sensory electrophysiological measures) and compare their phenotype with more classical forms of the disease. We do believe that these multiple integrated approaches, ranging from genetics to visual behavior will help shed light on normal and impaired cognitive function.

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RP1.2 | BRAIN MAPPING OF VISUAL OBJECT RECOGNITION PATHWAYS

Head: José Rebola and Miguel Castelo-Branco

The neural circuits involved in object recognition are relatively well localized, but the relevance of effective functional networks to distinct cognitive operations in this domain is still largely unknown. In particular, the circuits involved in visual face processing have been intensely debated concerning the degree of functional specialization of the cortical modules that respond to faces and their effective connectivity to structures that are pivotal in the recognition and expression of facial emotions. It is likely that face processing involves a dedicated type of expertise as is also revealed by its central role in social cognition. Studies of event-related brain potentials (ERPs) have been useful in the investigation of the neural correlates of neutral face stimuli and emotional expression processing in human subjects and we aim to use them in our approach. Neuroimaging studies have further shown that the perceptual analysis of neutral facial attributes is based in the occipito-temporal cortices and that perception of fearful faces primarily involves the amygdala. An interesting dissociation is however related to the processing of disgust, which has been linked to the insula and basal ganglia. The posterior part of the STS, has also been previously related to the perception of changeable face aspects including facial expression.

We plan to study responses to neutral and standard emotional faces that that have been morphed between distinct levels of relative emotions (following Perret et al.). The morphing procedure will allow for the implementation of a parametric neuroimaging design

that will enable to isolate how specific are the neural networks processing facial expressions of fear and disgust and how prone they are to hysteresis. As identification of sigmoidal BOLD neuroimaging response profiles will help define a clearcut separation between such networks we do believe that our experimental paradigm will help solve the current debate on the separability of such circuits.

We will apply these paradigms both in normal subjects and in clinical models of striatal and amygdala dysfunction (Parkinson&Huntington disease and Williams Syndrome (WS), respectively). Symptomatic Huntington's disease patients are impaired in interpreting facial and vocal expressions of disgust (Hennenlotter et al., 2004) although recognition of other emotions is also affected. To ensure that the role of the caudate nucleus is specifically addressed, we will study pre-symptomatic HD carriers, as well as patients in early disease stages. Behavioral measures (eye movements, reaction times, recognition scores) will be correlated with neuroimaging (structural/functional) measures concerning striatal structures.

Concerning WS, the recent findings of Meyer-Lindenberg et al. (2005) have been taken to suggest a genetically controlled circuitry regulating social behavior. This claim is based on reduced amygdala responses to threatening face stimuli in individuals with WS, as opposed to threatening scenes. We aim to understand the role of the massive visual input to the amygdala in WS. This becomes even more important when one takes into account the previous findings of significant visual-amygdala covariations of activity in normal subjects (Sabatinelli et al., 2005). We will analyse abnormal patterns of anatomical reorganization in the sensory and orbitofrontal input circuitry of the amygdala, and will assess alternative models of abnormal functional connectivity. To achieve this goal we will perform functional imaging, face processing ERP tasks and volumetry tasks in normal subjects and WS.

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**RP1.3 | PERCEPTUAL LEARNING IN THE HUMAN VISUAL SYSTEM: RELATION WITH OTHER MEMORY SYSTEMS
IN HEALTH AND IN MILD COGNITIVE IMPAIRMENT**

Head: Patrícia Figueiredo

Multiple memory systems have been identified which are characterized by distinct behavioral as well as neural correlates. Perceptual learning involves one type of implicit memory whereby performance improvement is achieved through practice.

Although its behavioral aspects are well documented, the underlying neural mechanisms remain largely unknown. We are interested in understanding the neural correlates of perceptual memory in the human brain and their relation with explicit forms of memory.

The visual system provides an ideal model to study perceptual learning because feature maps can be identified with fine resolution in individual subjects, from primary visual cortex up to higher order parieto-occipital areas. Learning effects may then be unambiguously localized in the brain and assessed as a function of those features. In this project, we aim to use functional magnetic resonance imaging (fMRI) in order to investigate the role of different visual areas in various aspects of perceptual learning, and to compare this with their involvement in explicit forms of memory, both in healthy subjects and in patients with Mild Cognitive Impairment (MCI). In a first stage, robust protocols for mapping retinotopic, object-related and motion visual cortical areas will be implemented based on well documented fMRI methodology. In parallel, a set of previously studied quantitative psychophysics tasks will be developed to investigate learning mechanisms as a function of training. In particular, structure from motion perception, object recognition and visual search tasks will be used to probe different stages of the visual processing pathway. Learning curves will be fully characterized through the application of psychophysics methodology and learning paradigms that are suitable for application of neuroimaging techniques will then be identified. Finally, fMRI will be performed on selected groups of subjects, before and after training, in order to determine changes in activity as well as in functional connectivity between specific brain regions as a function of learning. Specific hypothesis concerning regions of interest defined a priori will also be tested. Results will be compared with those obtained from matched explicit memory tasks. In a second stage, we propose to investigate the performance of a group of MCI patients and respective controls in both explicit and implicit learning tasks, by employing a classical neuropsychological evaluation followed by a comprehensive psychophysics assessment of visual function and perceptual memory. Patients in this prelude to dementia are characterized by explicit memory impairments and by some visual dysfunction. We therefore wish to investigate whether visual perceptual learning may also be disrupted. In summary, the proposed work will elucidate on the specific neural correlates of perceptual learning mechanisms across the brain, through neuroimaging investigations of healthy subjects, as well as through the neuropsychological and psychophysical evaluation of MCI patients.

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RP1.4 | NEUROCOGNITIVE STUDIES OF IMPLICIT LEARNING AND MEMORY

Head: Marieke van Asselen

Learning and memory are critical parts of human cognition, enabling us to encode and recall a wide variety of information. An important aspect of learning and memory is the fact that we can process information without being aware of it. This is particularly relevant, since our attentional resources are very limited. This process is called implicit memory and can be contrasted with explicit learning, which is a conscious process. Although explicit memory and its neural correlates have been studied extensively over the past decades, less is known about implicit learning and memory. Therefore, a combined approach is used, in which cognitive-experimental research is corroborated by neuropsychological and neuroimaging studies to find converging evidence of the mechanisms underlying implicit context memory and its neural correlates. Paradigms will be developed to study complex, higher-order forms of implicit memory, including contextual information (i.e. space) and emotional expressions. Additionally, complementary research methods will be used to define the neural correlates of specific implicit memory processes. First, patients will be studied with damage to specific brain areas, including patients with Parkinson's and Huntington's disease. This will give us important information about the involvement of brain areas such as the basal ganglia and medial temporal lobes. Additionally, neuroimaging techniques will be used to further study the role of the different brain areas and their functional connectivity. Finally, eye movements will be recorded in healthy participants and patients with brain damage, in order to study attention mechanisms and search behavior in implicit context learning.

Research Strategies:

- Development of paradigms aimed to differentiate between implicit and explicit memory processes (i.e. contextual information, emotional expressions), using behavioral measures and eye movement data.
- Defining the neural correlates of specific learning and memory processes by assessing patients with damage to specific brain areas such as the basal ganglia and medial temporal lobes.
- Neuroimaging techniques will be used to study activation during different phases of learning. This part of the research will be specifically aimed at defining functional connectivity between the MTL and CN.
- Studying phenomenology of specific neuropsychological syndromes in patients with neurological diseases such as Huntington and Parkinson's disease and Williams Syndrome.
- Using neuroimaging techniques to improve the methods that can be used to study the relation between brain damage and cognitive functions (lesion-overlap techniques).

Neurocognitive studies of implicit learning and memory.

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RP1.5 | NEW METHODOLOGICAL APPROACHES TO STUDY BRAIN FUNCTION THROUGH MAGNETIC RESONANCE

Head: José Pedro Marques

Although conventional fMRI techniques using blood oxygenation level dependent (BOLD) contrast have been around for over a decade, a complete understanding and quantification of the physiological mechanisms responsible for the contrast has not yet been achieved. Arterial spin labelling (ASL) perfusion imaging methods provides a more stable and quantitative measure of brain activity that constitutes an interesting complement to BOLD contrast. Moreover, a recently developed diffusion-weighted imaging (DWI) technique seems to provide an independent, quantitative measure of activation, therefore offering additional information. Protocols for the combined acquisition of BOLD, ASL and DWI fMRI will be implemented and validated using robust and quantifiable visual stimulation paradigms.

BOLD contrast - Functional magnetic resonance imaging (fMRI) rapidly became the method of choice in neuroimaging studies of brain function after its appearance in the 1990's and the blood oxygen level dependent (BOLD) contrast is by far the most commonly used method today. It is known to result from a complex combination of multiple physiological parameters including cerebral blood flow (CBF), cerebral blood volume (CBV) and the cerebral metabolic rate of oxygen consumption (CMRO₂) [Ogawa S et al. Functional brain mapping by blood oxygenation level dependent contrast magnetic resonance imaging: A comparison of signal characteristics with a biophysical model. *Biophys. J.* 64(3): 803-812 (1993)]. It therefore includes, not only the effects of the haemodynamic response associated with the neural activity of interest, but also any other potentially confounding vascular effects that are expected to result from various normally occurring within- and between-subject factors.

Perfusion imaging - A quantitative measure of CBF can be obtained using ASL [Williams DS et al., Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc. Natl. Acad. Sci. USA.* 89(1):212-6 (1992)]. Although this method presents a number of practical limitations that have hindered its extensive applicability to functional imaging studies, the fact that it provides a potentially quantitative measure of CBF make it particularly suitable for longitudinal studies such as learning and aging [Aguirre GK, Detre JA, Wang J. Perfusion fMRI for functional neuroimaging. *Int Rev Neurobiol.*66:213-36. Review. (2005)].

Diffusion fMRI - A more recent technique has recently been reported to yield an independent measure of brain activity through the use of diffusion weighting imaging (DWI). Although correlated spatially, this measure is not directly related to the haemodynamic response but it has rather been proposed to be linked to the swelling of capillaries [Le Bihan D et al., Direct and fast detection of neuronal activation in the human brain with diffusion MRI. *Proc Natl. Acad. Sci. USA.* 103(21):8263-8268 (2006)].

Integration of different functional modalities will improve our understanding of the physiological mechanisms associated with normal brain function. The ability to accurately quantify such mechanisms can shed new light on more complex mechanisms such as learning and aging.

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RP1.6 | EVALUATION OF VISUAL PLASTICITY AND FUNCTIONAL REORGANIZATION UPON DAMAGE OF OPTIC AND/OR NEURAL PATHWAYS

Heads: J. Murta and Miguel Castelo-Branco

The functional plasticity of the human visual system during postnatal development and adulthood is a fascinating topic that only now is receiving its deserved attention.

We will focus both on mechanisms of functional recovery upon damage to the neural structures of the eye and optic nerve and damage to the optical pathways of the eye. Combined studies within this framework will enable us to dissect low and high level neural mechanisms of compensation upon visual impairment, and to understand what are the mechanisms underlying visual plasticity upon distinct types of injury. The key goal will be to achieve understanding of pathophysiological mechanisms leading to visual disturbances.

Concerning the optical pathways of the eye, refractive surgery is still one of the most innovative and evolving fields in ophthalmology. The primary goal of refractive surgery is not only to eliminate spectacles or contact lenses but to improve or at least prevent deterioration of the optical performance of the eye. The ideal refractive surgery would allow patients to detect and recognize large and small objects of high and low contrast, at all distances and under all lighting conditions. However glare disability, image degradation and loss of contrast sensitivity under scotopic or mesopic lighting conditions – “night vision disturbances”- are problems that may occur in patients who have otherwise excellent vision during the day. Contrast sensitivity appears to be most affected by corneal surface asphericity and quality of the ablated surface, as corneal surface quality degradation causes light scatter. Wavefront-guided refractive surgery has a new goal: to correct or at least minimize all optical aberrations of the eye, improving the visual performance especially under scotopic conditions. However aberrations are a moving target because of variability ranging from seconds to years.

Methodologies that obtain objective measurements of quality vision, namely night vision are mandatory in order to create future strategies which decrease post-refractive vision disturbances. We will focus in the evaluation of the quality of vision in patients submitted to refractive surgery under mesopic conditions with the use of Mesopic Peripheral High Resolution Test - a new psychophysical methodology less prone to artifacts – which analyse visual performance within multiple visual channels both in the fovea and in the periphery, using tests which tackle the function of different pathways in an independent manner; and the Optical Quality Analysis System which provides an objective measurement of the optical quality eye (compares pre and post refractive surgery measurements, shows the effect of ocular aberrations in VA and the effect of accommodation through the quality of the retinal image).

Concerning impairment of the neural pathways of the eye, we will focus on mechanisms of recovery upon damage at distinct levels of the retinocortical pathway, from the photoreceptor to ganglion cell, optic nerve and cortical level. We will perform psychophysical, eyetracking, electrophysiological and imaging studies to evaluate the neural constraints of visual compensation upon neural damage. We believe that comparison of visual plasticity upon damage to either optical or distinct neural structures will give strong insight into the fundamental mechanisms that can play a role in visual rehabilitation.

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RP1.7 | BASIC MECHANISMS OF RETINOCORTICAL PROCESSING AND MECHANISMS OF DISEASE IN OPTIC NEURITIS AND MULTIPLE SCLEROSIS

Head: Miguel Castelo-Branco

This quest embeds both fundamental and applied research questions in which we aim to understand disease mechanisms in disorders of retinocortical processing such as multiple sclerosis and hereditary and acquired optic neuritis.

The fact that relatively specific signals and temporal patterns can be isolated from the magno, konio and parvocellular retinocortical pathways will be important to study their relative vulnerability in optic neuropathies and in particular multiple sclerosis (MS)/optic neuritis.

We will use new tools for in vivo histology of the retina, in particular the axonal layer from retinal ganglion cells, and methods to isolate ganglion cell function, namely spectral electrophysiology, psychophysics, and scanning laser imaging coupled with direct retinal stimulation in humans. The understanding how motion/color information are routed into parallel pathways will help us better establish genotype-phenotype relationships and design new rehabilitation strategies. To better achieve these goals we have started a collaboration aiming to identify secondary mutations in the same genes whose primary mutations lead to Hereditary Leber Optic Neuropathy, in order to address the question whether particular genetic profiles contribute to particular tropism of the optic nerve, in terms of disease susceptibility in MS. Concerning rehabilitation strategies we have developed new psychophysical, electrophysiological, and neuroimaging tools to study cortical retinotopic plasticity after damage to particular pathways in central and peripheral vision. These tools are being studied in the context of retinal/optic nerve degenerations and also in diseases with neuromodulation of sensory processing (Parkinson Disease).

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RP1.8 | MOLECULAR IMAGING OF THE BRAIN IN AGEING AND DEMENTIA. DISEASE MECHANISMS IN MOVEMENT DISORDERS

Head: Durval Campos Costa

Molecular Imaging using PET, PET-CT and SPECT will enhance our multimodal studies of normal and pathological ageing. We will focus on Mild Cognitive Impairment and Dementia, and also on Neurodegenerative diseases with strong visuomotor impairment, such as Parkinson Disease, Lewis Body Dementia and Huntington Disease.

Activities within this long term project with international links will establish range from development of new radioligands from bench to clinical application.

The key references below demonstrate this range of activities. We have been dedicating our time to the basic pharmacokinetic properties research of newly designed radiotracers, followed by clinical application and investigation of their potential to improve patient management and clinical outcome. Finally we managed to propose and develop the use of newly investigated radioligands into the clinical scenario. This has culminated into the acceptance of their use as an important part of criteria for clinical diagnosis and also inclusion for clinical research.

Our main objectives for the future are a continuum of previous description.

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**RP2 | A TRANSLATIONAL APPROACH TO DEVELOP NEW METHODS OF DIAGNOSIS AND
INNOVATIVE THERAPIES FOR AGE-RELATED DEGENERATIVE DISEASES**

Coordinator: Paulo Pereira

Ageing is associated with cell and tissue degeneration that, in many cases, leads to debilitating diseases. A large number of organs and systems are affected during ageing including the eye, heart, brain, vascular system, kidney and the immunoinflammatory system. In some instances cell and tissue degenerations are intimately associated with the pathophysiology of the disease whereas in other cases ageing makes tissues more prone to damage. Most tissue degeneration and organ dysfunction comprise both a genetic predisposition and environmental risk factors. The relationship between genotypes or specific mutations and phenotypes such as retinal degeneration, heart disease, vascular disease, kidney disease, cancer, allergic diseases, autoimmunity and immunosenescence related diseases, is still unclear. Genes operate in a complex cellular environment and the interaction between proteins and other cell components or structures is often complex in determining a phenotype.

This project aims at an integrated multidisciplinary approach covering various aspects from early genetic mechanisms of age-related diseases and intermediate mechanisms of age-related cell damage, ending up in development of improved means to characterize and validate complex phenotypes such as of age-related retinal degeneration. The major research areas under this programme include chronic diabetic complications, endothelial cell dysfunction upon ageing and diabetes, mechanisms of tissue repair by endothelial progenitor cells in the heart, mitochondrial dysfunction in heart diseases, molecular mechanisms of age-related retinal degeneration, neuroinflammation in brain injury and studies of age-related changes in immune system response. This approach will involve studies of gene expression, mechanisms of cell damage and cell response to stress, development of animal models of disease and pharmacological studies in human patients. Finally a major effort is directed at development of methods to characterize phenotypes both in animal models of age-related eye diseases and in human patients. The outcomes of this program will be to elucidate molecular mechanisms underlying cell lesion associated with age-related diseases in order to generate new tools to validate innovative therapies.

RP2A | PHENOTYPING, IDENTIFICATION OF RISK MARKERS AND TESTING EMERGING THERAPIES

Coordinator: José Cunha-Vaz

RP2.A1 | HUMAN HEREDITARY DISEASES

Head: Eduardo Silva

Examination, in Portugal, of the prevalence and incidence of childhood disorders, through a national network of collaborating clinical units, in order to facilitate the planning of screening and treatment programs, and establish a database of patients within the framework of a large European Union Project – EVI-Genoret.

- This research group is exploring disease mechanisms – phenotypic studies of children with known genetic mutations. These studies will be performed using innovative and detailed electrophysiological and psychophysical testing and novel methods of imaging.
- Investigate the changes in the brain which underlie amblyopia and situations of major visual deficiency in hereditary diseases using clinical, electrophysiological, psychophysical and functional imaging methods.

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RP2.A2 | AGE-RELATED MACULAR DEGENERATION

Head: Rufino Silva

AMD is the major cause of blindness in the developed countries in patients over 55 years of age.

We aim to continue with the characterization of different phenotypes of AMD, using a variety of methods: fundus photography, fluorescein angiography and autofluorescence imaging and optical coherence tomography. We have developed new methods for clinical identification and mapping retinal pigment epithelium damage using the Retinal Leakage Analyzer.

Our research group is particularly interested in identifying markers for conversion from “dry” AMD to “wet” AMD. An alteration of the outer Blood-Retinal Barrier appears to play a fundamental role in this process.

Quantification of fluorescence changes occurring in Fluorescein Angiography in AMD progression and response to therapy has been achieved recently by our group (ARVO 2007). This capability opens new perspectives when following the progression of the disease and its response to therapy.

Another important area of interest is to assess the predictive value of blood-retinal barrier changes for progression of vision loss in Geographic Atrophy (GA). Mapping of blood-retinal barrier changes using the Retinal Leakage Analyzer and Topography (RLA+T) will allow the identification of functional changes in the retinal pigment epithelium and to correlate these changes over a 2-year period with known indicators of visual acuity (VA) loss: best corrected VA (BCVA) and retinal sensitivity using microperimetry.

The outcomes of this study are expected to examine the role of BRB alterations (RPE functional alteration) as a predictive factor for GA progression. Confirmation of this hypothesis will open entirely new perspectives for the management of patients with GA.

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Head: Conceição Lobo

Our group will focus its research on diabetic macular edema in diabetes type 2. Our research group has contributed with original work in this research area for many years and is a world leader in this research area (Refs.)

Diabetic macular edema, even with timely laser treatment, often leads to a poor visual outcome. This is an important area because of its impact in healthcare with the progressive increase in the incidence of diabetes.

Our research is focused on early diagnosis and early intervention. We have developed new methods of imaging the retina capable of quantifying and mapping macular edema, using measurements of leakage (alteration of BRB), retinal thickness (edema) and of rate of formation of new microaneurysms.

The development of these biomarkers are expected to contribute to the definition of different risk profiles in diabetes type 2 patients. Preliminary work has shown that there are three different phenotypes of diabetic retinopathy which may be identified at the early mild nonproliferative diabetic retinopathy stage.

The ongoing research aims to validate a predictive model of diabetic retinopathy progression to clinically significant macular edema (CSME) needing photocoagulation and/or vision loss. The Coimbra Predictive Model (CPM), based on retinal thickness, microaneurysms number, HbA_{1c} and LDL levels, established on a set of 52 diabetic patients, will be tested on a population of 400 patients/eyes to be enrolled into the study. These patients will perform 2 visits at 6-month interval (V0 and V6) to classify each patient into one of the 3 previously established phenotypes. Two-hundred patients are expected to be classified into phenotype I (50%), 120 (30%) and 80 (20%) in phenotypes II and III, respectively. Two years after (V24) all patients from phenotypes II and III will be reexamined, while only 50% of the patients of phenotype I will be reexamined since no progression to the end-points (CSME needing photocoagulation and/or vision loss) is expected to be found.. The work proposed here aims to validate our predictive model of diabetic retinopathy progression to CSME needing photocoagulation and/or vision loss (CPM - Coimbra Predictive Model).

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Head: Pedro Faria and Miguel Castelo-Branco)

Glaucoma covers a heterogeneous group of conditions that show progressive optic neuropathy and is associated with aging.

Our group is focusing its research in improving diagnostic techniques to achieve earlier diagnosis of glaucoma and reliable detection of progression. Our efforts have shown that psychophysical methods may dissect and identify the earliest cellular alterations occurring in glaucoma. We are also seeking to link genotyping with phenotyping and relate these to the natural history of glaucoma and its response to therapy.

Our group has also special interest in relating structural and functional changes occurring in the retina and optic nerve in glaucoma looking for appropriate methods to test neuroprotective therapies.

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Head: António Freire, Isabel Santana and Cristina Januário)

The human visual system: relation with other brain systems in health and in mild cognitive impairment

Cognitive impairment in older people has recently been classified in a number of different ways (e.g., age-associated memory impairment, age associated cognitive decline, mild cognitive impairment, cognitive impairment no dementia). Of these classifications, mild cognitive impairment (MCI) has shown the greatest clinical utility, carrying with it a heightened risk of conversion to dementia, particularly Alzheimer's disease (AD). It is thought to represent a transitional stage within a cognitive continuum that spans from normal aging to early dementia (Petersen et al., *Arch Neurol* 2001, 58:1985-92). The potentially predictive value of this condition has motivated a great amount of research aiming at identifying individuals who may be in the earliest stages of decline. But how normally aging individuals are distinguished from mildly impaired individuals continues to pose a problem for researchers and clinicians alike.

The cortical degeneration characteristics of Alzheimer's Disease (AD), including neurofibrillary tangles and neuritic plaques, are also present in the visual cortical areas, especially in the visual association areas, leading to the hypothesis that visual function may be affected in this condition. Visual impairments have in fact been reported in AD, ranging from contrast sensitivity and colour perception deficits to deficits in higher-order visual functions, including structure from motion perception, object and face perception and visual attention, as well as visual memory and learning (Rizzo et al., *Neuropsychologia*. 2000;38(8):1157-69). Documented visual sensory impairments are believed more reflective of cortical disturbances than of AD-associated optic neuropathy.

It is therefore expected that such deficits may already be present at the stage of MCI, with a potential conversion predicting value. The purpose of this study is therefore to investigate visual function impairments in MCI, at various levels, in comparison to AD and control subjects.

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RP.2B | GENOTYPES TO PHENOTYPES: MOLECULAR MECHANISM OF DEGENERATION AND DESIGN OF NEW THERAPIES

Coordinator: Paulo Pereira

Ageing is associated with cell and tissue degeneration that, in many cases, leads to debilitating diseases. A large number of organs and systems are affected during ageing including the eye and brain. In some instances cell and tissue degenerations are intimately associated with the pathophysiology of the disease whereas in other cases ageing makes tissues more prone to damage.

Retinal degenerations are intimately related to ageing processes and are the main feature of age-related macular degeneration, diabetic retinopathy and glaucoma. These age-related eye diseases are the leading causes of blindness in Western countries with high socio-economic costs. Most likely retinal degeneration comprises both a genetic predisposition and environmental risk factors. Genes operate in a complex cellular environment and the interaction between proteins and other cell components or structures is often complex in determining a phenotype. The relationship between genotypes or specific mutations and phenotypes such as retinal and brain degeneration is still unclear.

This research program aims at an integrated multidisciplinary approach covering various aspects from early genetic mechanisms of retinal degeneration and intermediate mechanisms of age-related cell damage, to improved characterization of retinal phenotypes. This approach will involve gene expression, molecular mechanisms of cell damage, animal models of retinal disease, new methods of phenotypic classification of retinal degenerations. Moreover the program aims at developing new strategies for prevention and therapy of age-related eye diseases. Particular emphasis is given to development of viral-vectors for gene and drug delivery as well as the development of nanoparticles and hydrogels for drug delivery in diseases such as age-related macular degeneration and glaucoma. The outcomes of this project will be to elucidate molecular mechanisms underlying retinal cell lesion, to generate improved characterization of phenotypes of human retinal degeneration and to develop innovative approaches for phenotype rescuing in animal models of diseases that may lead to new strategies for prevention and treatment of retinal degeneration and other age-related eye diseases in humans.

Head: Paulo Pereira

The vast majority of eye diseases are age-related. Cataract, age-related macular degeneration and retinopathies, including diabetic retinopathy, account for most cases of blindness in Western countries. The molecular mechanisms underlying many of the pathophysiological changes associated with such diseases remain to be elucidated. These however, are likely to comprise both a genetic predisposition and environmental risk factors. Increased productions of damaging agents and/or loss of ability of cells to respond to stress are causally related to various age-related eye diseases.

During ageing there is a progressive accumulation of damaged biomolecules in tissues, including DNA, lipids and proteins. This line of research aims at studying a number of such age-related mechanisms and we have shown, for example, that accumulation of products of lipid oxidation such as cholesterol oxides interferes with intercellular communication and differentiation of lens epithelial cells into fibers, as well as disrupt organisation of cytoskeleton proteins.

Obsolete or otherwise damaged proteins, no longer perform useful roles in the cells and, in many instances, are cytotoxic. The ability to efficiently dispose of these proteins from lens or retina by proteolytic systems such as the ubiquitin-proteasome pathway (UPP) constitutes an important repair mechanism and is a major research interest at our unit. Aging and disease-related changes on the activity of UPP may further compromise a number of critical cell mechanisms. For example, we have shown that, on diabetes, UPP assists on regulation of intercellular communication throughout gap junctions as well as glucose transport into retinal endothelial cells by controlling degradation of connexin 43 and GLUT1 respectively.

Over the last two years the objectives of this research unit has focused on the study of the molecular mechanisms associated with regulation of protein degradation in conditions such as Diabetic Retinopathy and Age Related Macular Degeneration. For example, it has been shown that a balance between degradation of ubiquitinated proteins and molecular "chaperons" is critical to maintain biological activity of many proteins.

Both diabetic retinopathy and age-related macular degenerations are associated with increased neovascularization of the retina which often leads to blindness. Proliferation of endothelial cells and formation of new vessels is, in part, regulated by the transcription factor Hypoxia Inducible Factor (HIF). A major objective of his research unit is to understand the molecular mechanisms and signalling events that may interfere with proteasome-dependent degradation of HIF-1. The accumulation of HIF-1 leads to transcription of its target genes such VEGF, which results in retinal neovascularization.

This new approach to neovascularization on diabetes is likely to create new opportunity for prevention and therapy of retinal degenerations.

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Head: Francisco Ambrósio

Age-related retinal diseases, such as diabetic retinopathy, age-related macular degeneration and glaucoma, and inherited retinal degenerations still do not have an effective treatment, which has been hampered, at least in part, because the pathogenic processes at molecular level are not clearly elucidated yet.

Some of these diseases are characterized by the existence of an inflammatory component and by the breakdown of blood-retinal barrier. Considering that retina is composed by several cell types, our main goal is to give insight on the molecular and cellular mechanisms underlying neuronal, glial, endothelial and retinal pigment epithelial cell dysfunction, mainly in diabetic retinopathy and age-related macular degeneration. The cross-talk between some of these cell types will be also addressed. We are mainly interested in the role played by glutamate, ATP, neuropeptide Y (NPY), oxidative/nitrosative stress, and by some inflammatory mediators. We intend to identify new molecular targets that might allow the development of new therapeutic strategies, and we also intend to develop new therapeutic strategies to treat both age-related retinal diseases and inherited retinal degenerations. Therefore, our specific aims are:

1. To investigate the impact of hyperglycemia in the physiology of AMPA receptors, which have a major role in retinal physiology.
2. To investigate the impact hyperglycemia has on neurotransmission in the retina, and in the hippocampus.
3. To investigate the role of inflammatory mediators, particularly IL-1 beta, TNF-alpha and nitric oxide, in the breakdown of blood-retinal barrier, and to test the potential use of anti-inflammatory drugs to treat age-related retinal diseases.
4. To investigate the role of ATP in the inflammatory process underlying age-related retinal diseases, and its possible involvement in retinal degeneration and in blood-retinal barrier breakdown.
5. To investigate the role of NPY in retinal physiology, and in retinal cell neurogenesis and differentiation. The elucidation of its role might be useful to develop cell therapies to treat retinal disorders.
6. To develop new therapeutic strategies to treat age-related retinal diseases, based on the development of nanostructures, using viral and non-viral vectors, and RNA interference. VEGF and VEGF receptors, which are responsible for retinal vascular permeability and neovascularization, will be the main targets.
7. To develop stem cell-based therapies to treat inherited retinal degenerations. We will study the potential use of embryonic and umbilical cord blood stem cells in an animal model of retinitis pigmentosa.
8. Finally, we will evaluate the toxic effect of drugs of abuse in the retina, namely ecstasy, but also other amphetamines.

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Head: José Ramalho

Age-related macular degeneration (AMD) is a leading cause of severe visual loss and legal blindness in elderly population. AMD is untreatable and there is a need for improved management of this condition. Its pathogenesis is likely to be multifactorial. However, there is evidence that impairment of ROS phagocytosis or retinal pigmented epithelium – mediators (RPE-mediators) secretion may contribute to the onset of AMD. In addition, proteins such as MyoVIIa have been implicated on phagocytic pathway and reported to interact directly or indirectly with Rab27a, a small GTPase and its effectors. The molecular study of the function of Rab27a effectors such as Myrip will lead to a detailed understanding of some RPE pathways, including the phagocytic pathway, may serve as models for understanding human degenerative diseases and provide the tools for developing new therapeutic approaches. Recently we have shown that the distribution of melanosomes, a lysosome-related vesicle, within the mouse RPE is likely to be regulated by Rab27a/Myrip/MyoVIIa. We are currently investigating the possibility that some of these proteins are involved on lysosome/phagosome motility and also on identification of the proteins domains involved in formation of this complex. Our recent results have shown that the function of this Rab27a effector protein in RPE is not restricted to melanosome transport but is also implicated on other vesicle transport. However, the lack of functional studies does not permit evaluation of the importance of the role of these proteins in retina physiology. Our main goal is to study the function of Rab27a effectors in the retina, in particular in the RPE and to evaluate the role in disease. The RNAi technology has been applied to the RPE cells in culture or to the retina *in vivo* using adenovirus, lentivirus or adeno-associated (AAV) vectors in order to down-regulate the selected gene and investigate their involvement in retinal pathways. Thus, RPE cells or mice retinas will be transduced with viral vectors-expressing shRNA targeting Rab27a effectors. Although, we have focused our efforts on Myrip, we intend to extend the work to other members of the same family functionally poorly characterised (such as Sytl2, Sytl3, Sytl4, Sytl5, Mlph and Slac2-b) that are expressed in the retina as well as in RPE. The phenotype of such transduced cells or animal models have been characterised by histological and biochemical assays, and functionally assayed for phagocytosis and secretion of important RPE factors, such as VEGF, PEDF, PDGF, FGF, IGF-I, TGF- β , TIMP and interleukins. This approach for generating knock-down mice by injection of viral vectors expressing shRNA might give crucial clues about the cellular function of Rab27a effectors in the retina and may also be used as a potential tool to understand the function of a variety of unknown genes. On the other hand, this approach can be used as a powerful tool to the treatment of complex disorders such as those involving degeneration, inflammation and angiogenesis by targeting sustained intraocular delivery of therapeutic agents.

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Head: Miguel Morgado

There is great variety of new optical reporter technologies for *in vivo* tagging of cellular and subcellular processes. Optical imaging is the most versatile visualization modality in clinical research. One of the reasons to use optical imaging is the range of contrast mechanisms that can be used (i.e., polarization, interference, fluorescence lifetime, etc.) and light-tissue interactions involved at the molecular level (i.e., multiphoton absorption, second-harmonic generation, fluorescence, etc.).

We intend to do research on new instrumentation and methodologies for molecular and cell fluorescence imaging, with a focus on direct fluorescence imaging with active and activable probes. Our aim is to develop instruments and techniques for microscopic and macroscopic molecular imaging of small animals for phenotyping retinal degenerations and evaluating new strategies for therapy.

Multi-pixel and single pixel illumination and detection methods will be developed. Multi-pixel methods combine development and operation simplicity with great throughput, although at high cost. However, the recorded fluorescence intensity has a strong nonlinear dependence on lesion depth and tissue optical properties. Sampling systems can be designed to limit the multiple scattering of signal photons. Sampling small regions provides optimal linearity with fluorophore concentration.

New fluorescence imaging modalities such as fluorescence lifetime imaging and fluorescence anisotropy imaging will be evaluated. Fluorescence lifetime imaging allows to discriminate amongst different fluorophores and to get information on the molecules micro-environment, leading to information on local pH, viscosity, oxygen concentration in cells, etc. So, measurements of fluorescence lifetimes can be used as indicators of these parameters. Fluorescence lifetimes are not affected by the transmission properties of the ocular media. Fluorescence anisotropy imaging is a mobility sensing technique. It may be used to discriminate between free and bonded fluorophores.

The design of new fluorescent probes is fundamental for *in vivo* fluorescence imaging. The use of fluorescent nanodiamonds (ND) as the basis of specific active probes is a new exciting field that yields great promise. Diamond is characterized by having a unique set of physical and chemical properties making it the ideal material to be used as interface between molecules and biological systems. It has an extraordinary resistance to most chemicals and is biologically compatible with extremely low toxicity. Its surface can be functionalized with bioactive molecules. When bounded to biomolecules, ND can function as probes for *in vivo* tissue and cells analysis and observation of biological and structural processes at nanometric scale. Studies proved that ND exhibit low cytotoxicity.

Collaboration was established with CICECO - Centre for Research in Ceramics and Composite Materials, from the University of Aveiro, for the development of nanodiamond-based fluorescent probes.

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Heads: Tice Macedo and Carlos Fontes Ribeiro

Methamphetamine addiction is now an epidemic of global proportions, and its medical consequences have emerged as a major international public health problem. There has been a resurgence of interest in the role of striatum, the major division of the basal ganglia, in addiction. Along with dopamine, glutamate (Glu) has also been implicated in the striatal neurotoxicity produced by METH. Although the inhibitory GABA plays a critical role in the neuronal networks of the basal ganglia, its role in METH-induced striatal toxicity is still unknown. Moreover the impact of METH on the balance of these excitatory and inhibitory circuits within striatum calls for clarification.

The mechanisms by which methamphetamine (METH) causes neurotoxicity are not well understood but recent studies have suggested that METH-induced neuropathology may result from a multicellular response in which glial cells play a prominent role. Indeed, evidence is emerging that microglia can contribute to the neuronal damage associated with disease, injury, or inflammation, but their role in methamphetamine-induced neurotoxicity has received little attention. The key problem remains whether the inflammatory process is the cause of brain toxicity or is simply a consequence of the tissue degeneration. Besides the possible involvement of pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha), another target has been raised as neuroprotector against METH-induced cell death: the neuropeptide Y (NPY). Moreover, striatum has been the most explored brain region but recently a study involving human subjects (METH abusers) clearly showed deficits in deep temporal lobe structures that support learning and recall, including the hippocampus.

Moreover, the apparent region-selective effects associated with activated microglia suggest that pro-inflammatory cytokines may play a dual role in the brain: cytotoxic to some brain regions and neurotrophic/neuroprotective in others. These studies will be further complemented functional imaging studies of brain in drug addiction using blood (SPET), metabolic (FDG) and receptor tracer (DATscan).

The integrative research proposed "from the molecular level to the live animal" will help in understanding the interplay between pro-inflammatory cytokines, NPY and METH-induced toxicity and reinforcing effect, which is probably a major key issue in the research of new pharmacological strategies to deal with drug abuse as well to improve an understanding on the mechanisms of cell damage associated with such drugs.

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Head: Lino Gonçalves

A number of research units at IBILI have committed a major effort in establishing new structure-function and genotype-phenotype correlations in humans as well as in animal models of various age-related diseases and disabilities. These, range from heart dysfunction, to visual and neuronal dysfunction associated with ageing and other degenerative processes.

Specific aspects of structure-function correlation will be studied in the heart, particularly in conditions of heart failure, ischemic heart disease and related pathologies, such as diabetes and obesity. A special attention will be given to the identification of cell signalling pathways involved in these diseases and their impact on inflammatory and oxidative stress markers, using both animal models and human cardiac tissue.

The basic research activities in Cardiology have focused on diabetes and ischemic cardiopathy. We used an animal model of type 2 diabetes, the Goto-Kakizaki rat to pursue some of our goals. This model was used in two different experimental settings: an acute one, where ischemia-reperfusion was induced in the whole heart, which was then submitted to differential centrifugations to isolate the mitochondrial and cytosolic fractions. We have been interested in the study of various parameters, including mitochondrial swelling, calcium buffering capacity, oxidative stress and caspase cascade activation. The effect of hischemia in hearts was further assessed in the presence or absence of several drugs, including insulin, metformin and atorvastatin.

As part of an alternative approach, animals were treated with several drugs during four weeks (insulin, metformin, atorvastatin and gliclazide) and then submitted to global ischemia-reperfusion or preconditioning. After this protocol, the same parameters as in the previous setting were evaluated. Before being treated with a drug and again before being sacrificed, blood and urine were taken to measure inflammatory and oxidative stress markers, in order to assess their modification by the drugs studied.

We have also started the preliminary phase of another study protocol, designed to study the cell and molecular biology of the cardiac tissue from hearts explanted from subjects with advanced heart failure and treated with cardiac transplantation.

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Head: Raquel Seica

IBILI has over the past years committed a great effort to bring together clinicians and basic scientists to elucidate critical molecular mechanisms that may contribute to cell injury and tissue damage on diabetes. A better understanding of the mechanisms of disease may further help to develop innovative strategies to delay or prevent diabetic complication. This research line involves an integrated multidisciplinary approach to diabetic disease and brings together areas such as ophthalmology, physiology, cardiology and neurosciences. Vascular dysfunction is a common thread to a number of diabetic complications including retinopathy, nephropathy and heart disease. Diabetes exerts its greatest impact throughout the vascular system. The effect includes the well described consequence of small vessel diseases leading to serious complications, but also a substantial predisposition to premature and accelerated disorder of large blood vessel, macrovascular disease. Indeed, leakage of blood from damaged small blood vessels in the eye can lead to macular oedema, while retinal ischemia can lead to neovascularization of the retina associated with progression of diabetic retinopathy. Diabetic nephropathy is also caused by angiopathy of the capillaries supplying the kidney, leading to kidney failure, while neuropathic disorders associated with diabetes are thought to be the result of damage to the blood vessels supplying nerves. The effect of diabetes on large vessels can be seen among others in coronary arteries. The heart in diabetes is affected in different ways, with variable contribution from myocardial dysfunction, autonomic neuropathy and ischaemic heart disease. The latter, as a consequence of the coronary occlusive process, contributes to substantial morbidity and mortality that arises from large vessel disease in diabetes.

The mechanisms that lead to endothelial dysfunction are still unclear but are likely to be multifactorial. We have recently made some progress in identifying new mechanism whereby glycolytic intermediates may account for the loss of tissue response to hypoxia resulting in cell death and tissue damage. For example we have shown that methylglyoxal, which is increased in diabetes, may disrupt cell response to hypoxia, leading to apoptotic cell death. By understanding the molecular mechanisms and the different players involved in such de-regulation it is possible to design new pharmacological or gene-based therapies to prevent or treat endothelial dysfunction associated with diabetes. Moreover this group has an extensive expertise in animal models of diabetes as well as on the characterization of diabetes-associated phenotypes in retina, kidney, heart and brain. Therefore, any putative therapeutic approach can be easily tested and its efficiency assessed in animal models such as GK mice.

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RP3 | TOOLS FOR CLINICAL IMAGING AND NEW METHODS FOR DRUG DELIVERY

Coordinator: Filomena Botelho

Early diagnosis, identification of biomarkers of disease progression and development of methods of improved drug delivery are fundamental factors in the management of retina and brain degenerative diseases.

Improved methods of clinical imaging and new methods of drug delivery have immediate application and their need is felt in everyday clinical practice.

This research programme will focus into the technology transfer of findings obtained in the laboratory and ongoing clinical trials to the development of practical tools that may be applicable to immediate use in human disease.

Results obtained by the research groups at AIBILI and IBILI have shown that our researchers have the necessary expertise to achieve this task with success.

Head: Rui Bernardes

The most frequent eye diseases causing blindness in the European Union and Western World are age-related macular degeneration, diabetic retinopathy and glaucoma. Early diagnosis is entirely based on imaging of the eye fundus, retina and optic nerve. Furthermore, recent epidemiological studies have shown that imaging of the retina and retinal vessels is the best indicator for development of stroke and is also a marker for coronary heart disease.

Our group has contributed with original work on this area. Specially by identifying microaneurysm location in the retina and their rate of accumulation overtime (Ref.), rate of progression of macular edema in relation to the foveola (Ref.) and his measurement of fluorescence changes occurring in the fundus after intravenous injection of fluorescein for the routine test of fluorescein angiography.

Multimodal mapping of the macula is a new concept introduced by our group that is expected to give much information on early diagnosis, characterization of specific phenotypes and appropriate time for treatment or retreatment of retinal degenerative disease.

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Head: Rui Bernardes

Our research group has been focused on the clinical imaging of the human retina, *in vivo*, in the last decade, and has developed and/or improved some image-based methodologies with applications in different pathologies, e.g., diabetic retinopathy and AMD.

We have been working on clinical applications for diabetic retinopathy and we were able to develop a blood retina-barrier (BRB) function map by measuring, *in vivo*, its permeability index. Thereafter it was possible to correlate diabetic patient maps with permeability maps from a healthy control population and precise the location, extent and degree of change of the BRB permeability.

Following the previous development, BRB permeability maps were cross-correlated with retina thickness maps, which led to the development of the multimodal macula mapping concept, further developed by bringing new imaging modalities into co-registration, hence establishing correlations between complementary imaging sources into the same retina location.

The application of this multimodal macula mapping approach led to some clinical publications, where for the first time correlations were established between BRB changes and retinal edema and the pattern of progression of diabetic retinopathy was proposed by following a group of diabetic patients over a three-year period.

Our research group has been involved in developing and bringing into the clinical practice the multimodal macula mapping (MMM) concept. In fact, important steps have been given in developing tools, as image registration tools suited for retinal images, which consist on the basic units for the MMM approach. Additionally, we have been able to prove the usefulness of the MMM when applied to clinical research and the added value of integrating information usually available in separate pieces.

Currently available techniques, already in application on the research field in our research/clinical environment, should be spread into the daily clinical practice, therefore needing to be made more robust in the processing sense, as to user interaction, image quality, etc.

In this project, this robustness will be sought for and integrated into the existing processes, allowing to apply these techniques out of our center and control.

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RP3.A2 | INCREASING OPTICAL COHERENCE TOMOGRAPH (OCT) MAPPING RESOLUTION

Heads: Torcato Santos and Rui Bernardes

Although ultra-fast high resolution optical coherence tomographs now exist available in the market, they are still very expensive and therefore available mostly at relatively large and well equipped sites. On the other hand, comparatively low-cost devices will be still available for the next decade, mostly at ophthalmology offices and/or small clinics.

As opposed to the new generation devices, capable of mapping the human macula thickness to 20 microns lateral resolution, OCT devices up to the Stratus version perform the macula thickness mapping based on six-radial line scans only, therefore performing a large interpolation in between the 30 degrees between consecutive radial line scans.

Our research group was recently able to develop a mapping strategy to improve the final macula mapping resolution, using currently available options from the regular, and therefore widely available, instrumentation.

This project aims to improve the aforementioned increased mapping resolution strategy and spread it into the daily clinical practice.

In this project, the spread of a new mapping methodology able to increase the macula mapping resolution of low-resolution OCT devices, will be sought for. For this, the retinal thickness atlas (RT-Atlas) of the human macula needs to be further improved, by increasing the number of sampled healthy individuals and by increasing the area covered by the atlas. So far, and due to the small number of healthy volunteers scanned, only the common area to all maps was considered for the RT-Atlas. In this way, registration of OCT scans can only be made using a fraction of their length, thus not allowing to guarantee the global minimum for the error function under minimization. A larger area needs to be considered by increasing the number of samples from periphery areas, either by just increasing the sample or by modifying the acquisition protocol for that specific purpose.

By doing so, a considerable large number of A-scans, for each OCT B-scan, will be taken into account for the registration by the optimization process, thus allowing to achieve an increased global registration accuracy.

Furthermore, the optimization approaches and techniques currently in use need to be deployed in order to achieve a better final solution out of the optimization process. This is to say the convergence into the global minimum needs to be guaranteed, right from the initial steps, and the integration of new scans and scan types (radial and circular scans) should lead to the same solution.

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Head: Miguel Morgado

Fluorescence lifetime imaging (FLI) is a new and effective method that can be used to study complex biological samples, either at microscopic or macroscopic levels. The map of fluorescence lifetime allows to discriminate amongst different fluorophores and to achieve valuable insights into the behaviour of emitting molecules, leading to information on local pH, viscosity, oxygen concentration in cells, etc. Therefore, measurements of lifetimes can be used as indicators of these parameters. Furthermore, these measurements are generally absolute, being independent of the concentration of the fluorophore or excitation light power. Fluorescence lifetimes are not affected by the transmission properties of the ocular media, which make rather difficult the discrimination of different retinal fluorophores based on their spectral features. We believe that FLI can enhance greatly the current range of ocular fluorometry techniques, expanding the information provided by *in vivo* ocular fluorescence studies.

Metabolic imaging of the retina can be possible by measuring changes in the fluorescence of NAD and FAD. These changes indicate the oxygen requirements for the mitochondria. The reduced form NADH is fluorescent whereas the oxidized form exhibits only weak fluorescence. In contrast, the oxidized form of FAD is fluorescent whereas the reduced form (FADH₂) has almost no fluorescence. This approach is being tested by our group in corneal tissue. *In vivo* functional imaging of corneal cells can be accomplished through redox imaging. This technique monitors cellular respiratory function by measuring fluorescence emission from redox pairs (NAD-NADH; FAD-FADH₂) involved in substrate oxidation.

It is not possible to excite retinal NADH fluorescence since its excitation spectra lies below 400nm. However, retinal metabolic changes might be detectable by fluorescence of FAD. When excited at 450 nm FAD emits fluorescence in the region of 550 nm. These signals are covered by several other retinal fluorophores, like lipofuscin (the dominant fluorophore, which accounts for the large majority of fundus fluorescence), melanin, macular pigments (lutein, zeaxanthin) and also collagen and elastin present in connective tissue. Fluorescence lifetimes can be used as fingerprint of fluorophores on living tissue. Using this technique, a very weak fluorophore can be discriminated from an intensive emitting fluorophore if their lifetimes are sufficiently different.

Our labs are equipped with picosecond pulsed diode lasers and high speed gated intensified CCD cameras. A fluorescence lifetime microscope was also acquired. With this equipment we intend to develop a fluorescence lifetime imaging ophthalmoscope for imaging retinal autofluorescence and to use it to produce metabolic maps of the retina. In this project we will develop an instrument capable of assessing corneal cells function and mapping corneal endogenous fluorescence. The instrument will be non-invasive and suitable for operation in clinical environment. This instrument will fulfil a long-held objective in ophthalmology giving the clinician the advantage of diagnosing cells dysfunction prior to its pathologic expression. This represents a clear advance in the current state of ocular diagnosis.

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Head: Filomena Botelho

We have further developed our research in image formation processes for biomedical applications, focusing in particular in image acquisition, reconstruction and co-registration. The main topics that were covered include:

- Software development for data acquisition and control of a Positron Emission Mammography (PEM) scanner, which is being currently assembled in the framework of the ClearPEM consortium project.
- A new algorithm for camera pose estimation has been developed and is being applied in a co-registration system involving nuclear medicine and video images. Several applications including patient movement correction and optical/functional image fusion are being implemented.
- A new quantitative image method for the diagnosis and progression of Parkinson disease was developed based on the determination of parametric images for patient classification relative to a database of co-registered normal patients. A MSc thesis was achieved.
- A new iterative algorithm was proposed for reconstruction of tomographic images, based on an alternative definition of projection data subsets.
- Two projects with patients (cocaine addicts and allergic) are running. In the first project, a statistical evaluation, which involves brain co-registration into the Tailarach space, is being performed. This work received a prize for the best paper in a Psychiatry Meeting. The second project, involves several groups of allergic patients that are under immunotherapy treatment. Nuclear images show fast response of the immunological system after vaccination. This work received a prize by the SPAIC.

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RP.3B | DRUG DELIVERY

RP3.B1 | OVERCOMING DRUG RESISTANCE

Head: Filomena Botelho

In the last two years we have extended our research interests in the area of drug resistance mechanisms in tumours, such as those mediated by the overexpression of ATP-binding cassette transporters, with particular emphasis on the application of ^{99m}Tc-labelled cationic lipophilic radiotracers; oxidative stress and cell death pathways, from chemical to visualization/treatment of specific agents. Another field of interest is the cytotoxicity tests for new drugs/transporters systems and imaging compounds, as well as several cellular culture models, a flourishing and promising field to provide insight into the effects of multifactor pathophysiological mechanisms, injury and repair, apoptosis/necrosis, and other processes that may be involved in several diseases and cancer (e.g. internalization/externalization studies, binding assays, resistance to drugs) and animal experiments to culminate the process (e.g. surgical techniques, biodistribution studies).

Our research is also focused on the development of animal models of human tumours (bone, lung, colo-rectal and skin) to study the multidrug resistance mechanisms mediated by the overexpression of ATP-binding cassette transporters, using ^{99m}Tc-labelled cationic lipophilic radiotracers (e.g. Sestamibi, Tetrofosmin, etc.). Recent results have demonstrated that ^{99m}Tc-Sestamibi can be used to monitor *in vivo* the functional activity of MDR-related transporters and to evaluate the efficacy of MDR inhibitors. These applications might be of extreme benefit both as a prognostic factor as well to plan alternative therapeutical strategies in the clinical management of poor responders to chemotherapy.

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Head: Filomena Botelho

Diseased tissues overexpressing these receptors will internalise and accumulate them, allowing location by Nuclear Medicine techniques or by conventional MR imaging. Furthermore, these agents will open the way, through the choice of the targeting group, to characterisation of tumours, earlier detection of diseases and tailored molecular therapies. Three main types of metal based radioligands are currently being investigated: 1) M(III) chelates with sugar-based targeting ligands; 2) radiolabeled peptides for tumour diagnostic and therapy; 3) amphiphilic metal complexes with improved efficiency to be used as MRI contrast agents.

Another important area of interest is the targeted drug delivery of several drugs/imaging and/or therapy agents, one of the most actively pursued goals of nowadays research. Drug transporters provide important information to allow improvements in drug delivery or drug design. The use of transporter function offers the possibility of delivering a drug to the target organ, avoiding distribution to other organs (thereby reducing the chance of toxic side effects), controlling the elimination process, and/or improving bioavailability. In order to make the drug targeting system more effective, simple and technological, we have developed some delivery systems both for imaging and therapeutic approaches (liposomes for lung, cardiac and lymphatic imaging studies, and nanocapsules/nanospheres for lymphatic and tumour visualization and therapy).

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Head: Francisco Ambrósio

Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness in the elderly in developed countries. It is estimated that AMD affects around 30 million people worldwide. At present, this disease has no cure, but some novel therapies directed against vascular endothelial growth factor (VEGF), which is considered the main player in the pathogenesis of AMD, have been developed. However, these therapies are based on repetitive intravitreal injections, which may cause intraocular inflammation, cataract formation, increased intraocular pressure and retinal detachment. Therefore, the development of new strategies, that could surpass repetitive intravitreal injections, and that can be selectively directed onto the choroid and retinal pigment epithelium have been considered. Taking this into account, we intend to develop new therapies against AMD, that can be also used to treat cancer, based on the design of intelligent drugs. These drugs are supramolecular structures – nanostructures – (using virus, liposomes and polymeric particles), that will be used to silence the genes of interest, namely VEGF and VEGF receptor 2. We also intend to develop structures that allow a selective target and delivery of the genetic material to the choroid and retinal pigment epithelium.

Communication of science to the general public and society in general is an important mission of all scientific institutions, and our program emphasizes this important component.

Three main types of action were undertaken:

1. Direct involvement in the “Ciência Viva” Program. Several of the members of our research team have been directly involved in many of the actions of this yearly program promoted by the Ministry for Science and Superior Education.
2. Participation in the Dana Alliance Brain Awareness actions.
3. Direct communication with the main interface with the general public: the media. We aim to improve the communication with media professionals specialized in science communication in order to help improve a better public awareness of the diseases related to visual impairment and their alleviation/remediation.
4. Communication with Patient Associations, by providing Scientific Counseling and promoting Actions that help promoting the quality of life of patients with visual impairment.
5. Improved management of our website, in order to make it accessible not only to other scientists, but also patients with visual impairment, the media, and the general public.

SCIENCE AND SOCIETY

In a time of global communication and strategic alliances, it is vital that science can find new audiences and explore innovative forms of communications to reach a broader audience and to disseminate its proceedings in new social contexts.

For example IBILI has participated within the program “Ciência Viva” in a number of activities to disseminate science particularly with young students as well as on other open activities, including numerous visits from students from different parts of the country. The scientists working at IBILI advise public authorities and private organizations on their areas of expertise and there are frequent reports on the national and local media pertaining innovative scientific developments of IBLI.

Over the last 6 years IBILI is strongly committed in finding alternative ways to interface with society. Scientists at IBILI have been developing a large-scale interdisciplinary research programme with various national and international artists, called BLINDSPOT (www.theblindspot.org). This project has been supported by IA – The institute of Arts, FCT- Fundação para a Ciência e Tecnologia and the Austrian Ministry of Culture.

Indeed, biomedicine and aesthetics is a rapidly growing field of artistic practice and academic reflection, dealing with an array of issues, from the public engagement with current biomedicine to methodological overlaps between the practices of artists and laboratory researchers. A characteristic part of science and art projects is the fact that the knowledge created is produced close to sites of public dissemination and that there is a strong commitment to disseminate the results to an heterogeneous audience.

The project BLINSPOT has already been shown in various international museums and art galleries. Moreover, a number of lectures about this interdisciplinary project have been presented in various universities and other public venues.

There is a commitment for a continuing support for a stronger and closer interaction between biomedical science and art pursuing the highest possible standards of international excellence and creating new and innovative forms to disseminate the results of this joint programme in abroad social context.

- Strengthening the cooperation within the framework of the Evi-Genoret European Network

EVI-GENORET

AIBILI is one of the partners involved in the Integrated Project Functional Genomics of the Retina in Health and Disease - EVI-GENORET (6th EU Framework Programme LSHG-CT-512036). The aim of this project is to build on our understanding of the fundamental molecular and cellular biology of the retina, of its development and the way it is perturbed by genetic mutation, environmental factors and age.

1. Setting-up new research agreements within the scope of this European Network (aside from the already existing concerning Monogenic Retinal Dystrophies and Age-Related Macular Degenerations).
2. Developing translational research collaborations that extend our expertise in genotype-phenotype correlations in humans also to animal models.

EVI.CT.SE - European Vision Institute. Clinical Trials. Sites of Excellence

European Vision Institute. Clinical Trials. Sites of Excellence (EVI.CT.SE) is a network of European Ophthalmologic Clinical Research Sites, dedicated to perform clinical research in ophthalmology with the highest standards of quality. The EVI.CT.SE Network is a Special Committee of the EVI and its Coordinating Office is located at AIBILI, in Coimbra, Portugal.

This Network aims to perform clinical trials efficiently and professionally, striving for excellence in clinical research following the European and International Directives for clinical trial research (Declaration of Helsinki, ICH GCP Guidelines, Clinical Directive EU and local legislations). This is accomplished by certification of the Candidate Clinical Sites that fulfil Basic Requirements. All Clinical Sites are subject to an independent Evaluation Visit in order to confirm that they comply with ICH GCP Guidelines and they need to implement EVI.CT.SE organizational Standard Operating Procedures (SOPs) in order to perform clinical trials according to ICH GCP Guidelines.

This Network aims to be a professional and attractive resource to the Pharmaceutical Industry when planning to perform a multicentric Clinical Trial in ophthalmology, in Europe.

It is an efficient way to identify experienced qualified professional Clinical Sites with expertise and well equipped to perform Clinical Trials in Ophthalmology according to ICH GCP Guidelines.

During AAO 2006 (Las Vegas, USA) a meeting was held with representatives from the major Companies Alcon, Allergan, Novartis, Pfizer and Théa, to sign with EVI.CT.SE an Agreement in order to sponsor the EVI.CT.SE Network with an unrestricted grant for a period of 2 years.

EVI.CT.SE Network was also presented to EMEA - European Medicines Agency that considered the Network an essential component in their policy to guarantee uniformity and quality of data collection. EMEA would very much support the development of EVI.CT.SE harmonized procedures and techniques in the area of Ophthalmology.

EVI.CT.SE is expected to create the appropriate environment for efficient and high quality clinical trial performance in Europe.

At the moment the Network has 36 members (from 14 European countries) in the process of certification and another 7 candidate centres.

For more information about EVI.CT.SE please visit: www.europeanvisioninstitute.org

Collaborations with Brain Imaging Center in Maastricht

In this collaboration, we will focus on two main areas: 1. mechanisms of short and long term visual plasticity in health and disease 2. mechanisms of motion perception and multimodal auditory and visual integration.

1. Mechanisms of short and long term visual plasticity in health and disease

A. Short term plasticity

This Research collaboration will focus on neuronal mechanisms of vision from receptor cell level to cortical visual centres. Physiological as well as pathophysiological neuronal mechanisms should be addressed in multiple visual pathways. As a final goal we aim to set a firm scientific ground for improvement of visual perception by low vision aids and training.

As a model of short term plasticity, we will study visual filling-in. This refers to the phenomenon that occurs when, after a few seconds, a figure steadily presented in peripheral vision becomes perceptually filled-in by its background, as if it “disappeared”.

This visual illusion referred to as perceptual filling-in, occurs because the visual system interpolates information across regions of the visual field where physical evidence of that information is lacking,

Perceptual filling-in occurs quasi-instantaneously across the blind spot, as has been described in physiological studies (e.g., Komatsu, Kinoshita, & Murakami, 2000, 2002; Fiorani, Rosa, Gattass, & Rocha-Miranda, 1992). This is also the case also for pathological scotomas (Sergent, 1988; Bender & Teuber, 1946) as well as across entopic images of vasculature (Coppola & Purves, 1996). Slower filling-in within the range of a few seconds has been reported under conditions of artificial retinal stabilization (Yarbus, 1967; Gerrits, de Haan, & Vendrik, 1966; Ratliff, 1958), and during stabilization of peripheral images under natural fixation (Riggs, Ratliff, Cornsweet, & Cornsweet, 1953; Troxler, 1804).

It is an open question whether similar neural interpolation mechanisms that underlie perceptual filling-in also play a role during normal surface perception (Paradiso & Nakayama, 1991; Gerrits & Vendrik, 1970; Walls, 1954). The time required before perceptual filling-in depends on level of retinal stabilization and ensuing adaptation of boundary representations, figure size and the length of its boundaries projected on the retinotopic cortex, the relative sizes of figure and background (Sakaguchi, 2001; De Weerd, Desimone, & Ungerleider, 1998), and salience of the figure (Stuerzel & Spillmann, 2001; Welchman & Harris, 2001).

Fast (on a time scale of milliseconds) filling-in of brightness during normal surface perception has been demonstrated with a masking procedure by Paradiso and Nakayama (1991). The basic finding has been replicated in other experimental (Paradiso & Hahn, 1996; Rossi & Paradiso, 1996; Todorovic, 1987) and theoretical ((Neumann et al., 2001; Arrington, 1994; Grossberg & Todorovic, 1988) studies. It is believed that neural interpolation is a consequence of activity increases resulting from an adaptation of inhibitory inputs to the neurons with classical RFs overlapping with the figure, such that ordinarily ineffective excitatory inputs from the background in the RF surround became effective in driving these neurons (for review, Tremere, Pinaud, & De Weerd, 2003).

It is likely that mechanisms of figure-ground segregation and interpolation are in part carried out by distinct feature dependent mechanisms in different cortical areas (Gattass, Pessoa, De Weerd, & Fiorani, 1998; Ramachandran & Gregory, 1991). Interpolation mechanisms are likely to involve horizontal connections (Gilbert & Wiesel, 1989) as well as feedback connections. Indeed, long-range horizontal connections have a tendency to connect orientation columns with similar preferred orientations (Gilbert & Wiesel, 1989) may contribute to the perceived similarity of filled-in line texture across the figure and background.

B. Mechanisms of long term plasticity upon visual impairment

We will focus on two main disease models

Retinitis pigmentosa and annular impairment of peripheral vision.

Glaucoma and piecemeal impairment of peripheral vision.

Genetic and acquired macular degeneration as models to study impairment of central vision, and remediation strategies (eg. Training of novel preferred fixation loci).

In order to understand mechanisms of cortical reorganization we will study the dynamics of filling-in processes in long term scotomas and study their remapping in cortical retinotopic maps.

2. Mechanisms of motion perception and multimodal auditory and visual integration.

We will continue our ongoing collaboration to study the neural correlates of local/global visual motion perception.

We will further extend this collaboration on ongoing work that attempts to understand how visual and auditory motion signals are integrated by the human brain.

- **Projects within the 7th Framework Program with an emphasis on Ageing and Medical Imaging**

- MIRROR: Multi-modal non-invasive in vivo imaging of the ocular fundus as a predictor for morbidity in older adults (7FP - Collaborative Project)
- EuroVisionNet: Visual Impairment and Degeneration: A Road-map for Vision Research within Europe (7FP – Coordination Action)

ANNUAL EDUCATIONAL PROGRAMME ON TRANSLATIONAL RESEARCH

2006-2007

Fridays 13:00 – 15:00

Themes	Coordinators
Molecular Aging of the Eye and AMD	Paulo Pereira and Rufino Silva
Clinical Research in Ophthalmology	Luísa Ribeiro - AIBILI
Psychophysical Testing and Glaucoma Phenotyping	Miguel Castelo-Branco e Pedro Faria
Update for users radioactive materials	Maria Filomena Botelho
Imaging in Ophthalmology	Rui Bernardes - AIBILI
Multimodal Macula Mapping in Macular Edema	Rui Bernardes and João Figueira
Cell Trafficking in RPE and Monogenic Dystrophies	José Ramalho and Eduardo Silva
Psychophysics and Evaluation of Quality of Vision after Surgery	Aldina Reis and Joaquim Murta
Macula Mapping in Cataract Surgery	Pedro Baptista and Conceição Lobo
Blood Retinal Barrier, Glutamate and Diabetic Retinopathy	Francisco Ambrósio and José Cunha-Vaz
Confocal Microscopy, Fluorescence and Corneal Disease	Miguel Morgado and M. João Quadrado
Day of Centre of Ophthalmology and Coimbra International Meeting of Ophthalmology	
Pharmacotherapy Studies in Primary Care	Tice Macedo - AIBILI

4.1 | DOCTORAL PROGRAM IN AGEING AND DEGENERATION OF COMPLEX SYSTEMS

COORDINATORS: Paulo Pereira and José Cunha-Vaz

4.1.1 | INTRODUCTION

Ageing is associated with cellular dysfunction and degeneration of multiple tissues and organs which frequently lead to debilitating diseases. Most of the human diseases associated with ageing probably comprise a combination of genetic predisposition and environmental factors. Genes operate in a complex cellular environment and the interaction between proteins and other cell components and structures determine phenotypes in a complex, non-linear and difficult to anticipate manner.

The integrated program that we are proposing promotes the acquisition of highly specialized knowledge in the field of cellular lesion associated to ageing and degenerative diseases. This approach includes the pathway from the initial genetic mechanisms to the cellular phenotypes originating the disease. Main research areas, in the framework of this program, include degenerative diseases, such as age-related retinal degeneration, neurodegeneration, neuroinflammation, cerebral lesions, pathological complications of diabetes, mitochondrial dysfunction in cardiac diseases and age-related alterations of the immunological system. This program aims to deliver the most recent scientific developments which may result in innovative therapies for prevention and treatment of age-related diseases. And it consequently aims to train highly skilled scientists, capable of validating hypotheses and designing experiments which may contribute to the scientific progress in Biomedicine and Health Sciences.

4.1.2 | STRUCTURE OF THE DOCTORAL PROGRAM

The model for the Doctoral Program in Ageing and Degeneration of Complex Systems (PDESC), keeping high exigencies of scientific and pedagogic quality, aims to encourage lighter and more flexible forms of teaching in specific areas of Biomedicine. The program is addressed to graduate students in Medicine, Biology, Biochemistry, Pharmaceutical Sciences or other adequate areas. The organization of advanced teaching courses is the structured block of this specialized area of Biomedical Sciences. In the framework of this PhD program proposal, students are chosen on the basis of attending Theoretical Advanced Courses (TAC) and Advanced Practical Courses (APC) which promote a more informal and participating interaction between students and professors as well as the production of work and presentations by student groups. TAC courses will take 1 week and the APC courses 3 weeks. TAC and APC courses typically correspond to advanced courses lectured by highly recognized national and international scientists, on one of the themes in the area of the Doctoral Program, as shown in annex 1. Courses include themes in the clinical area as well as in basic research, stimulating interdisciplinarity in teaching and the acquisition of complementary competences.

Aiming the flexibility of the teaching system and to provide the students with a choice spectrum as large as possible, part of the TAC courses may be chosen among the yearly available courses at the Faculty of Medicine, University of Coimbra, or at any other institution or university, with which specific protocols are to be established for this purpose. The credits obtained by attending TAC and APC courses may be exported in the form of transposable units (TU) to other doctoral programs.

4.1.3 | ORGANIZATION OF THE PHD COURSE

To obtain a PhD in Ageing and Degeneration in Complex Systems the student must perform at least five TAC and two APC courses, chosen among those indicated in annex III. The list of advanced TAC and APC courses will be yearly imparted by the Doctoral Program Coordinator. Proposed is also the creation of a web site where the available courses will be yearly registered

and where the students may perform their pre-application in the courses they think are best suitable for their training. The final group of courses in the framework of the Doctoral Program must be approved by the student's scientific preceptor and the coordinator of the Doctoral course.

TAC and APC modules are grouped under the generic designation of "Transposable Units" – TUs. This designation aims to reflect the flexibility of these training modules and the possibility of being chosen among a broader spectrum of courses in the framework of other Doctoral programs. Finally we propose that these Transposable Units may be such in their form and structure that they may allow any student, at any stage of his training, to credit these TUS in other training programs without losing their academic validity and the time invested in their execution.

At the end of the first year, the student must present his research project proposal (15 ECTS), for the elaboration of his Doctoral studies. This project must include a review of the state of the art of the knowledge in the scientific area of the research project, a clear presentation of the study purposes, results to obtain and methodology to be used. This seminar intends to verify and establish the quality and exequibility of the proposed work for the PhD project, as well as simultaneously evaluate the student's competences for the design and execution of a research project in Health Sciences.

4.1.4 | NON-CREDIT ACTIVITIES

During its whole lasting period, the Doctoral Course in Ageing and Degeneration in Complex Systems includes also non-credit mandatory activities (NCA). This module may include seminars, lectures or other forms of scientific disclosure and discussion, by invited Portuguese or international scientists, whose seminars or lectures, even in the framework of other University activities, may be included in the annual program of the PhD course.

SUMMARY OF THE STRUCTURE OF THE PHD COURSE IN AGEING AND DEGENERATION OF COMPLEX SYSTEMS

1 | DEFINITION

The Doctoral Program in Ageing and Degeneration of Complex Systems allows the student to obtain the degree of Doctor or the accumulation of credits (ECTS) which may be transferred to other doctoral programs, according to the legislation of the Doctoral Program in Health Sciences -Law 1377/2006 (2nd series) of January 19, and completed, in what may be relevant, by what was presented in this proposal. Students with MD degree, at the end of the course, obtain the Doctor degree in Medicine, speciality PDESC – PhD Course in Ageing and Degeneration of complex Systems. Students with other degrees in the area of Biomedicine, at the end of the course, obtain the Doctor degree in Biomedical Sciences, speciality PDESC PhD Course in Ageing and Degeneration of complex Systems.

2 | COMPOSITION AND DURATION

The PDESC- PhD Course in Ageing and Degeneration of complex Systems has 8 lective semesters. The first two semesters correspond to a training period and include credit and non-credit training activities. The last 6 semesters are intended to develop a research project and to perform non-credit activities.

3 | ACCESS

The candidates must have a degree in Biology, Biochemistry, Pharmaceutical Sciences, Medicine or other adequate areas of Biomedicine. The selection of candidates must include curriculum analysis and an interview.

4 | STRUCTURE

To obtain the degree of Doctor in Medicine or Biomedical Sciences, specialization Ageing and Degeneration of Complex Systems, one must :

- a) perform 4 Curricular Units (CU) of the common frame (20 ECTS), as described in Law 1377/2006 (2nd series);
- b) perform 2 Advanced Courses with Practical Training (APC) and 5 Theoretical Advanced Courses (TAC) in the area of Ageing and Degeneration in Complex Systems (45 ECTS);
- c) participate in a seminar for the presentation of a critical review work on one of the themes included in the seminar list (20ECTS);
- c) present a Research Project (RP) to the scientific committee of the Doctoral Program, undergoing an evaluation, with the classification of able or not able to continue the Doctoral Program (15 ECTS);
- d) participate in the non-credit activities (NCA) divulged every 6 months;
- e) perform a research Project (135 ECTS) and make a public presentation on the project subject;

5 | ACCUMULATION OF TRANSPOSABLE UNITS

At any stage of the course, the student can move to other post-graduate courses, including doctoral programs, where the ECTS obtained in any transposable unit accomplished in the framework of the Doctoral Program may be credited, with the authorization of the coordinators or follow-up commission of the programs where the TUs are to be credited.

6 | IMPORT OF TRANSPOSABLE UNITS

Students may import, to the PDESC - PhD Course in Ageing and Degeneration of complex Systems, ECTS from other courses or Doctoral Programs, once the requested authorization from the program coordinators is obtained.

7 | NUMBER OF VACANCIES

The Doctoral Program will have, annually, a maximum of 12 students.

8 | TEACHING STAFF

Coordinators: Paulo Pereira and José Cunha-Vaz

TAC and APC courses will be coordinated by 1 investigator/docent of the Faculty of Medicine, with the collaboration of national and international experts in the area of each course.

9 | FINANCING

Financing of the Doctoral Program, without prejudice of other alternative forms of financing, will be the result of the main following sources: student fees, items from the Faculty of Medicine, Fundação para a Ciência e Tecnologia.

**PROPOSAL OF CONTENTS FOR THEORETICAL ADVANCED COURSES AND ADVANCED COURSES WITH
PRATICAL TRAINING**

BASIC BIOLOGY AND BIOMEDICINE

MOLECULAR ISSUES IN AGE-RELATED DISEASES
BIOLOGY OF AGEING
CELLULAR DAMAGE AND REPAIR
ANIMAL MODELS OF AGE-RELATED DISEASES
INTRACELLULAR TRANSPORT DURING DISEASE DEVELOPMENT
MOLECULAR MECHANISMS OF SIGNAL TRANSDUCTION

CLINICAL AREA

OCULAR COMPLICATIONS ASSOCIATED WITH DIABETES
DEGENERATION OF VISUAL SYSTEMS
NEURODEGENERATIVE DISEASES
FROM GENES TO PERCEPTION

BIOTECHNOLOGIES

BIOINFORMATICS
BIOMATERIALS AND NEW THERAPIES
MOLECULAR BIOTECHNOLOGY
GENE THERAPY

4.2 | DOCTORAL PROGRAM IN NEUROPSYCHOLOGY

Coordinator: Mário Simões

In collaboration between the Faculty of Psychology and Education Sciences and the Faculty of Medicine; Biomedical Research Institute on Light and Image.

Number of credits according to the European Credit Transfer System (ECTS), necessary to obtain the degree: 180.

Normal course duration: 6 SEMESTERS

Scientific areas and credits which must be summed up to obtain the degree:

SCIENTIFIC AREA	ACRONYM	CREDITS	
		MANDATORY	OPTIONAL
STATISTICS	ST	5	
PSYCHOLOGY	PSY	35	
MEDICINE	MED	10	
PSYCHOLOGY OR MEDICINE	PSY/MED		10
DISSERTATION	PSY	120	
TOTAL		170	10 (1)

Study Planning:

1st Year / 1st and 2nd Semesters

CURRICULUM UNITS	SCIENTIFIC AREA	TYPE	WORKING TIME (HOURS)		CREDITS	OBSERVATIONS
			TOTAL	CONTACT		
Seminar I	ST	Semester	135	30 TP (2x15)	5	Mandatory
Seminar II	MED	Semester	135	30 TP (2x15)	5	Mandatory
Seminar III	PSY	Semester	135	30 TP (2x15)	5	Mandatory
Seminar IV	PSY	Semester	135	30 TP (2x15)	5	Mandatory
Seminar V	PSY or MED	Semester	135	30 T (2x15)	5	Optional
Seminar VI	PSY or MED	Semester	135	30 T (2x15)	5	Optional
Total (1st semester)			810	180	30	
Seminar of thesis follow-up (2nd semestre)	PSIC	Semester	810	30 OT (2x15)	30	Mandatory
Total (1.º ano; 1.º e 2.º semestrers)			1620	210	60	

2nd year / 1st and 2nd semester

CURRICULUM UNIT	SCIENTIFIC AREA	TYPE	WORKING TIME (HOURS)		CREDITS	OBSERVATIONS
			TOTAL	CONTACTO		
(1)	(2)	(3)	(4)	(5)	(6)	(7)
Seminar of thesis follow-up	PSY	Annual	1620	30 OT (1x30)	60	Mandatory

3rd.^o year / 1st and 2.^o semester

CURRICULUM UNITS	SCIENTIFIC AREA	TYPE	WORKING TIME(HOURS)		CREDITS	OBSERVATIONS
			TOTAL	CONTACTO		
(1)	(2)	(3)	(4)	(5)	(6)	(7)
Seminar of thesis follow-up	PSY	Annual	1620	30 OT (1x30)	60	Mandatory

CURRICULUM UNITS						
(1)						
Seminário I: Advanced methods of data analysis (Mandatory) [ST]						
Seminário II: Basic Neurobiology (Mandatory) [MED]						
Seminário III: Neuropsychological evaluation (Mandatory) [PSY]						
Seminário IV: Techniques of neuropsychology research (Mandatory) [PSY]						
Seminário V (Optional) e Seminário VI (Optional): To choose among the following: Cognitive neuropsychology [PSY]; Developmental neuropsychology [PSY]; Psychopathology [PSY]; Compared Neuropsychology [MED]; Ageing neurobiology [MED]; Psychometrics [PSY]; Neuropsychological rehabilitation [PSY].						

4.3 | DOCTORAL PROGRAM IN BIOMEDICINE OF CNC

The programme provides advanced, research-oriented training in emerging areas of contemporary Biology and Biomedicine:

- Molecular Cell Biology
- Neuroscience and Disease
- Molecular Biotechnology
- Medical and Environmental Toxicology
- Biophysics and NMR
- Microbiology
- Development and Human Fertility
- Visual Sciences

The programme comprises:

- Advanced Courses
- Seminars
- Laboratory Rotation
- Research leading to the doctoral thesis.

The courses are taught by leading portuguese and foreign scientists. The curriculum is designed to expose students to top research areas and to instigate the development of analytical, technical and communicative skills required of today's biologists.

Thesis: Research projects leading to the doctoral thesis are carried out in portuguese laboratories and abroad, by following the international research networks organized by CNC "Laboratório Associado" (<http://www.uc.pt/cnc>).

Key features

- Intensive training in cutting-edge research
- Flexibility in completing course program
- Admission of students with degrees from non-biological areas

Students may choose to do their thesis within international research networks organized by CNC "Laboratório Associado"

The programme at a glance

- **Advanced Courses** (October through March). The courses, usually one week-long, are taught by international leading scientists in collaboration with local investigators. The course work of the programme aims at providing the graduate students with the concepts, experimental approaches, and current problems of modern cellular and molecular biology.
- **Seminars** Attendance to the weekly seminars of CNC.
- **Research** work leading to the doctoral thesis. A written research proposal describing the intended thesis project must be defined during the first year. The final doctoral thesis will be evaluated before a faculty committee, upon an oral defense. The examination evaluates the student's ability to master a body of background material, to organize a plan of research, and to understand the context, aims, methods and limitations of the proposed research.

The students who choose to do their doctorate at the Faculty of Science and Technology of the University of Coimbra may have the advanced courses credited as disciplines G200 through G300, seminars as G400, and research as G500.

4.4 | INTERDISCIPLINARY DOCTORAL PROGRAM IN VISUAL SCIENCES WITH UNIVERSITY OF VALLADOLID AND MURCIA

Coordinator: Yollanda Diebold, IOBA, Valladolid, Spain

Coimbra representative: Paulo Pereira

Ph.D. equivalent programs possess two parts: a theoretical/practical initiation to get knowledge and abilities to do research in Visual Sciences and an original research project, the Doctoral Thesis (*Thesis Doctoral*) which has to be publicly defended by the trainee at the end of the training period.

The first part of the program is organized in courses (theoretical and practical) and seminars. Students of the doctoral training program have to complete 32 credits (1 credit should be equivalent to 10 hours of attendance) in no less than 2 academic years (from September to July). Trainees are devoted to get 20 credits by attendance to courses of their election during the first year. During the second year of training, students must prepare and develop a research project to get the remaining 12 credits. Trainees will count on the guidance of a preceptor designed by the Doctorate Program Committee along their training period. Eventually, trainees are awarded with a certificate which enables them to initiate the Doctoral Thesis.

The second part of the program will take at least two years. Trainees will be devoted to develop his/her Doctoral Thesis research project and to attend to scientific activities organized by the Institute. They will count on the guidance of a thesis director, who may or may not be his/her previous preceptor. During this period, trainees are encouraged to present his/her results in national and international meetings according to his/her thesis director guidance. The Doctoral Thesis Defense Seminar will take place when the research project is complete. 'Defense Seminar' of the Doctoral Thesis means an academic act open to the public that has two parts: a dissertation in front of a five expert panel and a session to answer the questions proposed by the experts.

The aim of the Inter University Ph.D. –equivalent Program in Vision Sciences from IOBA and the Applied Optics and Physics Department (University of Valladolid), the Institute of Optics "Daza de Valdés" (CSIC) and the Ophthalmology, Otolaryngology and Pathological Anatomy Departments (Area of Ophthalmology), the Physics Department (Area of Optics) (University of Murcia) as well as the Instituto Biomédico de Investigação da Luz e Imagem (IBILI, University of Coimbra) is to train investigators both in the biomedical and in the physical (optical) aspects of the Vision Sciences from a multidisciplinary, applied perspective of quality.

Two training blocks have been proposed, with diverse specific courses and the common one, the course called "Foundations of Vision", which will establish the minimal level of general knowledge that all the students who are trained in Vision Sciences should have on the anatomical, pathological, genetic, optical, physiological and ophthalmologic (clinical) aspects of the vision process. Of these two blocks, one has a physical - optical approach and is orientated fundamentally to training in the optical aspects of vision. The other block consisting of has a biomedical approach and contributes to sight threatening vision diseases of knowledge in general aspects of the biomedical research.

Five courses of methodological nature (this means courses designed to get the knowledge and the skills in research techniques) are also offered including the course named "Basic Elements of Scientific Investigation", which trains the students in the basic skills that he/she will use in the development of any investigation project (ethical procedures, good laboratory practices, bibliographical searches, statistics and preparation of scientific articles).

4.5 | MASTER'S DEGREE IN MEDICAL RETINA AND PEDIATRIC OPHTHALMOLOGY

Coordinators: José Cunha-Vaz and Joaquim Murta

The Master's degree course in Medical Retina and Pediatric Ophthalmology was approved by ruling no. 12190/2002 in 25/05. It answers to the need for Academic clinical training in this specialised area of ophthalmology. These proposals under the new conditions constituted by the recent restructuring of the Master's and post-graduate degree courses, fundamentally aims to answer the contemporary needs of academic training in a clinical area of medicine that is of great importance and which has great social impact, as in cases of diabetic retinopathy and age-related macular degeneration.

Licentiatees in Medicine with appropriate professional scientific curriculum vitae are accepted as candidates for registration in the course.

The course has a maximum duration of 2 academic years, consisting of the attendance of 3 of the 4 seminars in the first year, as stipulated. The second year will be dedicated to writing and defending the thesis. This will be prepared in one of the seminars attended in the first year of the Course, in accordance with the Regulation of the Master's Degree of the Faculty of Medicine of the University of Coimbra. In the second year, a thesis must be prepared that once defended and approved in public, is equal to 60 ECTS.

Medical Retina Curriculum Units

SEMINARS	DURATION	CREDITS	ECTS
Age-Related Macular Degeneration	Annual	6	20
Diabetic Retinopathy	Annual	6	20
Retinal Arterial Obstructions	Annual	6	20
Retinal Vascularization	Annual	6	20

Pediatric Ophthalmology Curriculum Units

SEMINARS	DURATION	CREDITS	ECTS
Pediatric Cataracts	Annual	6	20
Congenital Ocular Malformations	Annual	6	20
Pediatric Oncology	Annual	6	20
Retinal Heretodegeneration	Annual	6	20

4.6 | MASTER'S DEGREE IN VISION SCIENCES

Coordinators: José Cunha-Vaz and Paulo Pereira

The Centre of Ophthalmology is committed to promote post-graduate education in life sciences and particularly in vision sciences. It aims to define and foster the highest standards in post-graduate training and research, favouring interdisciplinary areas. The main teaching areas are Biochemistry, Molecular and Cell Biology, Instrumentation, Psychophysiology of Vision and Imaging.

The Master Course aims at a multidisciplinary approach to Vision Sciences and accepts candidates holding a degree in Biology, Medicine, Biochemistry, Physics and Engineering or other graduates areas.

The Master Course in Vision Sciences has a strong research component that relies on specially tailored seminars. These seminars depend on the active participation of various lecturers from the University of Coimbra and from abroad. The Master Course is designed to stimulate students' hands-on research by introducing them to a research environment and by promoting their active participation in ongoing research programmes.

Students are encouraged to attend the seminars at the Centre of Ophthalmology and to engage to in specific research projects.

After completion of the second year, students are asked to submit their Thesis to the Faculty of Medicine.

Most of the staff at the Centre of Ophthalmology holds a Doctorate Degree and is available to supervise the Master Thesis. Supervision can also involve scientists from other Departments or Universities.

Ph.D. Thesis

- Fernandes R.: Regulação dos transportadores da glucose na retina normal e diabética. Tese de Doutoramento, Faculdade de Medicina, Universidade de Coimbra, 2005.
- Girão, H.: Alvos em movimento: contribuição para o estudo da degradação proteica em sistema visuais. Faculdade de Medicina, Universidade de Coimbra, 2006.
- Remondes, M.: Funções da Via Temporoamónica no Hipocampo do Rato; Fisiologia e Comportamento. Faculdade de Medicina, Universidade de Coimbra, 2006.

Master Thesis

- Antunes, J.: Desenvolvimento de Liposomas com Afinidade para Áreas Miocárdicas Isquémicas. Tese de Mestrado em Engenharia Biomédica apresentada à Faculdade de Medicina da Universidade de Coimbra, 2004.
- Costa, P.: Desenvolvimento de um Conversor e Visualizador de imagens (GE-DICOM) com suporte em rede. Tese de Mestrado em Engenharia Biomédica apresentada à Faculdade de Medicina da Universidade de Coimbra, 2004.
- Reis, A.: Avaliação da espessura retiniana por tomografia de coerência óptica. Estudo comparativo dos valores obtidos pré e pós cirurgia da catarata. Tese de Mestrado em Ciências da Visão apresentada à Faculdade de Medicina da Universidade de Coimbra, 2004.
- Campos, S.: Estudo da função cromática na doença de Best e correlação com a clínica. Tese de dissertação de Mestrado em Ciências da Visão apresentado à Faculdade de Medicina da Universidade de Coimbra, 2004.
- Forjaz, V.: Avaliação da Função Cromática em Modelos de Disfunção dos Fotoreceptores e Células Ganglionares: Perspectiva Psicofísica, 2004.
- Nunes, S.: Contribuição da análise de clusters para a Identificação de diferentes Fenótipos na retinopatia Diabética Faculdade de Medicina, Universidade de Coimbra, 2006.

5 | RESEARCH STAFF

Members holding a PhD Degree

R.P.1

Miguel Castelo-Branco
Alda Ambrósio
António Freire
Durval Costa
Isabel Santana
Joaquim Murta
Jorge Saraiva
José Pedro Marques
Marieke Van Asselen
Mário Simões
Nuno Ferreira
Patrícia Figueiredo
Salomé Pinho
Maria Ribeiro

R.P.2

Paulo Pereira
Américo Figueiredo
Ana Paula Silva
Carlos Fontes Ribeiro
Conceição Lobo
Cristina Sena
Dulce Cotrim
Eduardo Silva
Francisco Ambrósio
Henrique Girão
José Cunha-Vaz
José Faria de Abreu
José Paulo Domingues
José Ramalho
Lino Gonçalves
Óscar Tellechea
Pedro Fonseca
Raquel Seíça
Rosa Fernandes
Rui Proença
Sérgio Lemos
Teresa Morgadinho
Tice Macedo

R.P.3.

Maria Filomena Botelho
Cristina Santos
Emanuel Ponciano
Isabel Prata
Miguel Morgado
Nuno Ferreira

PhD students

Aldina Reis
Alexandre Fernandes
Ana Rita Carvalho
Carla Bento
Carla Marques
Célia Aveleira
Célia Gomes
Eduardo Ferreira
Ermelindo Carreira Leal
Fátima Silva
Gabriel Pires
João Filipe Ferreira
João Vasco Ferreira
José Rebola
Mafalda Mendes
Maria João Quadrado
Paula Moreira
Paula Raquel Gomes
Pedro Faria
Raquel Santiago
Ricardo Marques
Rufino Silva
Rui Bernardes
Sofia Fertuzinhos
Steve Catarino
Susana Lopes

MsC Students

Ana Cristina Andrade
Ana Rita Santos
Áurea Castilho
Elsa Nunes
Fausto Carvalheira
João Figueira
João Duarte
Joaquim Carvalho
Lillianne Duarte
Luis Duarte
Margarida Abrantes
Maria Isilda Sousa
Paulo Matafome
Sónia Roque
Susana Bicho
Teresa Louro

Technical Staff

Cristina Ramos
Graciete Abreu

Administrative Staff

Alda Gonçalves
Cláudia Caridade
Pedro Maria

6 | EXTERNAL FUNDED RESEARCH PROJECTS

"Mechanisms of cell degeneration in diabetic retinopathy"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/CBO/38545/2001

Principal Investigator: Francisco Ambrósio

"Characterization of the mechanisms of resolution of diabetic macular edema after photocoagulation treatment with laser"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/CBO/43061/2001

Principal Investigator: J. R. Faria de Abreu

"Degradation of GLUT1 by ubiquitin proteasome pathway as a novel regulatory mechanism for glucose transport on diabetic retinopathy"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/MGI/39142/2001

Principal Investigator: Paulo Pereira

"Identification and fisiological role of deubiquitining enzymes in the lens: A novel function for ubiquitin"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/MGI/39142/2001

Principal Investigator: Paulo Pereira

"Role of the tight junctions proteins in the pathophysiology of the Blood-Retinal Barrier Breakdown"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/CBO/42969/2001

Principal Investigator: Rui Proença

"Functional brain mapping in epilepsy – relevance for basic and clinical research"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/NSE/46438/2002

Principal Investigator: Miguel Castelo-Branco

"Psychophysiological bases of visual consciousness phenomenons"

Financing Institution: BIAL

Principal Investigator: Miguel Castelo-Branco

"Gated acquisition of Xenon 133 gammagraphy to obtain regional data of the breathing tree in impulse oscillometry"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/CBO/39284/2002

Principal Investigator: João José Pedroso Lima

"Development of a fluorescence lifetime imaging ophthalmoscope"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/CBO/39298/2001

Principal Investigator: J.P. Domingues

"Perceptual learning in the human visual system: relation with other memory systems in health and mild cognitive"

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/PSI/56325/2004

Principal Investigator: Patrícia Figueiredo

"ClearPEM – Development of a Positron Emission Mammography"

Financing Institution: Agência de Inovação

Principal Investigator: Nuno Ferreira

"Free Radicals and neurotransmission modulation during morphine plus cocaine and amphetamine abuse"

Financing Institution: National Institute for Drug Addiction

Principal Investigator: Tice Macedo

“Degradação e distribuição subcelular do Glut1 em células endoteliais em resposta ao stress oxidativo. Implicações na retinopatia diabética”

Financing Institution: CRUP

Principal Investigator: Paulo Pereira

“Estímulo à Excelência”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal

Principal Investigator: José Cunha-Vaz

“Structure-function imaging for quantitative phenotyping of retinal degenerations”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POSI/EEA-SRI/60716/2004

Principal Investigator: Jorge Dias

“Biology of human photoreceptors and ganglion cells in health and disease: Phenotyping retinal degenerations”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/SAU-OBS/57070/2004

Principal Investigator: Miguel Castelo-Branco

“Functional Mapping of higher order visual and polymodal cortical brain areas”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/SAU-NEU/60281/2004

Principal Investigator: Miguel Castelo-Branco

“Aerobic exercise, methamphetamine, striatal dopamine overflow and apoptosis in the rat”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/DES/60227/2004

Principal Investigator: Carlos Fontes Ribeiro

“Filling in the GAP: the missing link between intercellular communication and diabetic retinopathy”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/SAU-MMO/57216/2004

Principal Investigator: Paulo Pereira

“What HIF? Degradation is better than growth in preventing angiogenesis in diabetic retinopathy”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal - POCTI/SAU-OBS/57772/2004

Principal Investigator: Paulo Pereira

“Psicofísica e Imagem multimodal do cérebro e da retina: aplicação a estudos da neurobiologia do envelhecimento”

Financing Institution: Fundação Calouste Gulbekian

Principal Investigator: Miguel Castelo-Branco

“The role of the cortico-basal ganglia circuit in learning and memory”

Financing Institution: Fundação Calouste Gulbekian

Principal Investigator: Marieke Van Esselen

“In vivo corneal metabolic imaging”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal – PDTC/SAU-BEB/73425/2006

Principal Investigator: Miguel Morgado

“Regulation of AMPA receptors by hyperglycemia in the retina”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal – PDTC/SAU-NEU/71228/2006

Principal Investigator: Francisco Ambrósio

“Validation of a predictive model to estimate the risk of conversion to clinically significant macular edema and/or vision loss in mild nonproliferative retinopathy in diabetes type 2”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal – PDTC/SAU-OSM/72635/2006

Principal Investigator: José Cunha-Vaz

“A new route for endothelial dysfunction of diabetes to molecules

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal – PDTC/SAU-OSM/67498/2006

Principal Investigator: Paulo Pereira

“Microglial and neuroglial changes in the hippocampus induced by methamphetamine: Role of inflammatory”

Financing Institution: Fundação para a Ciência e Tecnologia, Portugal – PDTC/SAU-FCF/67503/2006

Principal Investigator: Ana Paula Silva

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