



AIBILI

2012 REPORT

COORDINATING CENTRE OF EVICR.net

A European Disease-Oriented Clinical Research Network

COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH

Academic CRO for Translational and Clinical Research

CLINICAL TRIAL CENTRE – EVICR.net CS N.º 1

CENTRE OF NEW TECHNOLOGIES FOR MEDICINE

CENTRE FOR HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH

TRANSLATIONAL RESEARCH AND TECHNOLOGY TRANSFER

AIBILI TEAM

1st row: Miguel Castelo-Branco; Maria do Céu Fidalgo; Francisco Ambrósio; Carlos Fontes Ribeiro; Joaquim Murta; Tice Macedo; José Cunha-Vaz; Cecília Martinho; Sílvia Simão; Sandra Pardal; Aldina Reis; Luísa Ribeiro; Tatiana Gregório

2nd row: Ricardo Oliveira; Catarina Neves; Ana Pedroso; Teresa Morgadinho; Ana Rita Santos; Lílíana Carvalho; Isabel Simões; Cláudia Duarte; Gonçalo Bento; Pedro Melo; João Pedro Marques

3rd row: Maria da Luz Cachulo; Maria Viegas Nascimento; Sandrina Nunes; Conceição Lobo; Renata Castanheira; Catarina Eloy; João Figueira

4th row: Jorge Henriques; Andreia Rosa; Isabel Pires; Élia Gomes; Adozinda Simão; Ana Pascoal; Carla Duarte; Raquel Santiago; Joana Martins; José Monteiro; Telmo Miranda

5th row: Pedro Rodrigues; Sónia Simões; Rita Fernandes; João Silva; Filipe Martins; Carla Neta; Joana Ecsodi; Filipe Elvas; Rufino Silva; Pedro Correia; José Paulo Domingues

6th row: Daniel Fernandes; Miguel Morgado; Torcato Santos; Ricardo Simões; Paulo Barros; Diogo Mendes; Dan Brudzewsky; Carlos Alves; Francisco Batel Marques; Óscar Lourenço; Rui Bernardes; Marco Santos

AIBILI

association for
innovation and biomedical
research on light and image



AIBILI 2012 REPORT

1

Introduction
pg. 5

2

AIBILI at a Glance
pg. 7

3

AIBILI highlight numbers
pg. 8

A

Supporting Services – AIBILI as a Research Infrastructure
pg. 9

A1

EVICR.net Coordinating Centre
pg. 10

A2

4C-Coimbra Coordinating Centre for Clinical Research – an Academic CRO
pg. 14

A3

CORC – Coimbra Ophthalmology Reading Centre
pg. 17

A4

CHAD – Health Technology Assessment and Drug Research
pg. 19

B

Clinical Vision Research
pg. 21

B1

Biomarkers of Progression of Diabetic Retinopathy
pg. 22

B2

Phenotype/Genotype Correlations in Diabetic Retinopathy
pg. 23

B3

Novel Treatment Options for Complications of Diabetic Retinopathy
pg. 24

B4

Early Markers of wet Age-Related Macular Degeneration
pg. 25

B5

Retinal Neurodegeneration in Ageing and Diseases of Brain and Glaucoma
pg. 26

B6

Stem Cells in the treatment of Eye Diseases
pg. 27

B7

Industry-Sponsored Clinical Trials
pg. 28

C

Diagnostic Imaging through the Eye
pg. 31

C1

Functional Imaging with Optical Coherence Tomography
pg. 32

C2

Structural Imaging of the Retina with Optical Coherence Tomography
pg. 33

C3

Automated Analysis of Digital Fundus Photographs of the human macula
pg. 34

D

Pre-Clinical Research – Associate Unit
pg. 35

D1

Diabetic Retinopathy
pg. 36

D2

Glaucoma
pg. 37

4

Champalimaud Translational Centre for Eye Research – C-TRACER 2
pg. 38

5

Structural Units
pg. 39

5.1

Administrative Services
pg. 39

5.2

Quality Management
pg. 39

5.3

Translational Research and Technology Transfer
pg. 39

5.4

Information Technology
pg. 40

6

Education, Training, Meetings
pg. 41

7

Ethics Committee
pg. 42

8

Partnerships
pg. 43

9

AIBILI Building
pg. 44

BOARD OF DIRECTORS

President
José Cunha-Vaz

CEO

Cecília Martinho

Administrative Services

Cecília Martinho

Quality Management

Rita Fernandes

Translational Research and Technology Transfer

Daniel Fernandes

EVICR.net Coordinating Centre

Cecília Martinho

Coimbra Coordinating Centre for Clinical Research

Sandrina Nunes

Clinical Trial Centre

Luísa Ribeiro

Centre of New Technologies for Medicine

Rui Bernardes

Coimbra Ophthalmology Reading Centre

Conceição Lobo

Centre for Health Technology Assessment and Drug Research

Batel Marques

INTRODUCTION

1

AIBILI – Association for Innovation and Biomedical Research on Light and Image is a Research Technology Organisation in the health area dedicated to the development and testing of new products for diagnostic imaging and medical therapy.

It is a private non-profit organisation, founded in 1989, established to support translational research and technology transfer between academic institutions and the industry in the health area.

AIBILI is ISO 9001 certified since 2004 for the following activities:

- research and development in new technologies for medicine with particular emphasis in the areas of imaging, optics and light
- preclinical studies of new molecules of potential medical use
- performance of clinical trials
- performance of clinical pharmacology studies
- planning, coordination, execution and monitoring of clinical research activities
- health technology assessment.

Clinical trials are performed in accordance with ICH Guidelines for Good Clinical Practice (GCP) and the pharmacology studies are also developed in compliance with the OCDE Principles of Good Laboratory Practice (GLP).

AIBILI is located at the Health Campus of Coimbra University since 1994 and has its own building with 15,296 sq. feet and state-of-the-art equipment. Regarding human resources it has a permanent staff of 41 including medical doctors, researchers, engineers, pharmacologists, technicians, trial and project managers, regulatory affairs, trial coordinators and administrative personnel. Another 64 individuals collaborate regularly on a part-time basis involved mainly in research activities.

AIBILI is organized in Research Centres and Supporting Services.

The Research Centres are:

- EVICR.net – European Vision Institute Clinical Research Network
- Coimbra Coordinating Centre for Clinical Research (4C) – Academic CRO
- Clinical Trial Centre (CEC)
- Centre for New Technologies for Medicine (CNTM)
- Coimbra Ophthalmology Reading Centre (CORC)
- Centre for Health Technology Assessment and Drug Research (CHAD)

Structural Units are the Administrative Services, the Quality Management Unit, the Translational Research and Technology Transfer Unit and the Information Technology.

AIBILI has established crucial partnerships with national and international institutions:

- CF – Champalimaud Foundation
- FMUC – Faculty of Medicine of the University of Coimbra
- IBILI – Institute of Biomedical Research on Light and Image
- ICNAS – Institute of Nuclear Sciences Applied to Health
- CHUC – Coimbra University Hospital and its Centre of Responsibility in Ophthalmology
- ARSC – Health Administration of the Central Region of Portugal
- INFARMED – National Authority of Medicines and Health Products

In summary, the main goals of AIBILI are innovation and translational research that is to convert basic research knowledge into practical applications to enhance human health and wellbeing. It is important to realize that translational research has complementary domains:

- the “bench to bedside” - translating knowledge from the basic sciences into the development of new treatments (basic research to clinical research)
- translating the findings from clinical trials into everyday practice.

The main strategies of AIBILI are: innovation and internationalization, assuming a leading role in **translational research in vision and imaging** and bringing together academic institutions and industry.

Contacts

Phone: +351 239 480 100

E-mail: aibili@aibili.pt

Website: www.aibili.pt

**SUPPORTING
SERVICES**

**EVICR.net
Coordinating Centre**

**Academic CRO
4C**

**Ophthalmology
Reading Centre
CORC**

**Health Technology
Assessment and
Drug Research
CHAD**

**RESEARCH
PROGRAMMES
IN VISION
AND IMAGING**

**Clinical Vision
Research**

**Diagnostic
Imaging**

**Pre-Clinical
Research**

**STRUCTURAL
UNITS**

**Administrative
Services**

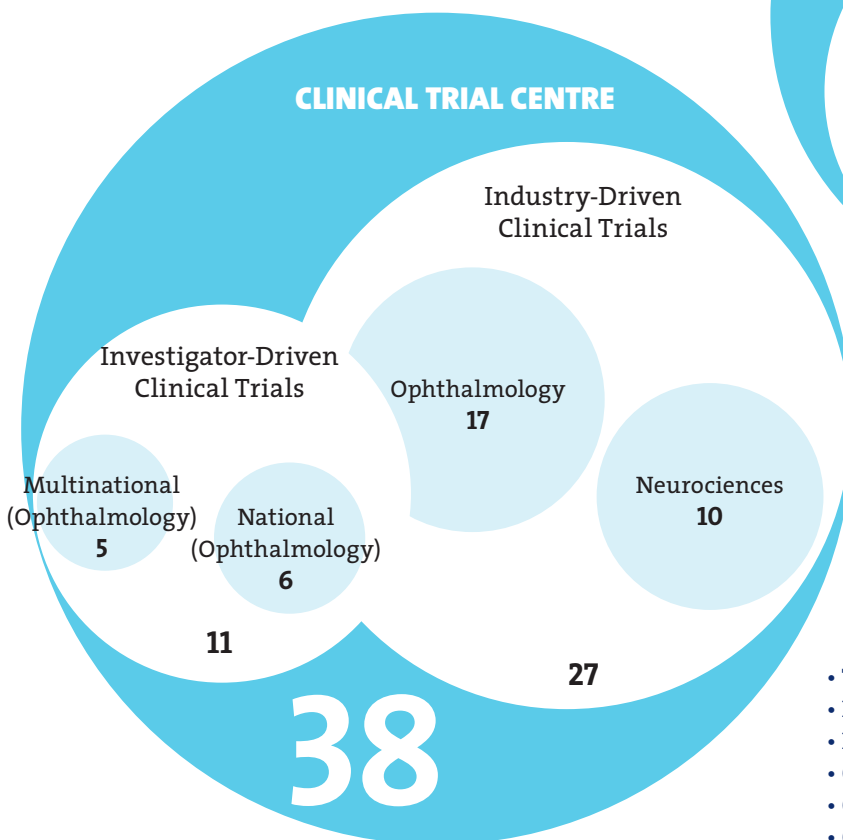
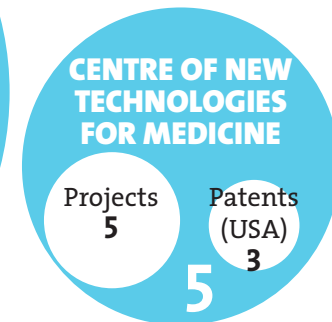
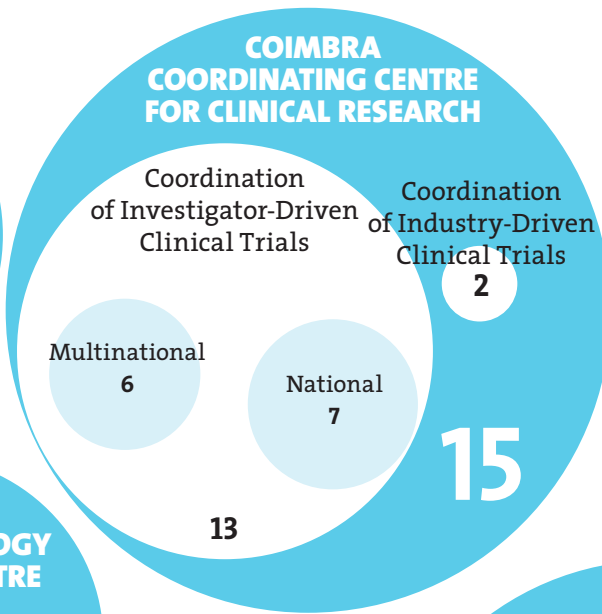
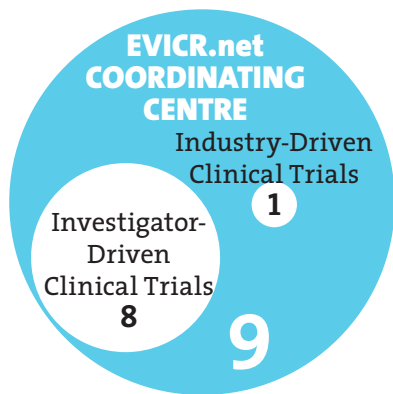
**Quality
Management**

**Translational
Research
and Technology
Transfer**

**Information
Technology**

AIBILI AT A GLANCE

2



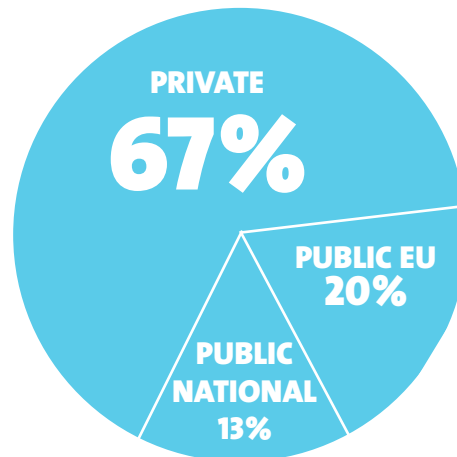
- Translational Research Organization
- Experienced Staff and Modern Facility
- Independent Ethics Committee
- C-TRACER 2 – Champalimaud Foundation
- Compliance with ICH-GCP Guidelines
- Compliance with OECD Principles of GLP
- ISO 9001 Certification
- Clinical Trial Centre – EVICR.net Certified Clinical Site of Excellence

3

AIBILI HIGHLIGHT NUMBERS

Area (sq. feet)	15.296 sq. feet
Fulltime Staff	41
N° of Consultants	23
N° of PhD	20
N° of PhD Students	16
N° of ongoing studies, services, projects, contracts	93
N° of patents	3 (USA)
N° of European Union funded projects ongoing	3
N° of publications (2011-2012)	106
N° of publications / PhD	5,3
Income (2012)	1.741.000 €

Funding (2012)



External Scientific Council

- Syed Ali, MD, PhD – National Center for Toxicological Research/FDA, Jefferson, USA
- Tos Berendschot, PhD – University Eye Clinic Maastricht, Maastricht, The Netherlands
- Neil Bressler, MD – Johns Hopkins Hospital, Baltimore, USA
- Anselm Kampik, MD, PhD – University Eye Hospital Munich, Munich, Germany
- José Carlos Pastor, MD, PhD – Instituto Universitario de Oftalmobiología Aplicada, Valladolid, Spain
- Jose Sahel, MD, PhD – Centre National d’Ophtalmologie des Quinze-Vingts, Paris, France
- Antonio Santamera, MD, PhD – Spanish Agency for Health Technology Assessment, Madrid, Spain
- Ran Zeimer, PhD – Johns Hopkins University School of Medicine, Baltimore, USA



Supporting Services – AIBILI as a Research Infrastructure

Translational research has proven to be a powerful process that drives the clinical research engine. A strong clinical research infrastructure is necessary to strengthen and accelerate this critical part of the clinical research enterprise. The major need to perform high-quality investigator-driven clinical research is access to an infrastructure that functions as an academic CRO offering centralized services and support in compliance with ICH-GCP Guidelines at affordable costs. This is particularly true when performing multinational clinical research bringing together clinical research sites of excellence from different countries where there are different requirements and a central coordination is crucial.

Centralized support in trial design, biostatistics and ethics is necessary to coordinate and support interactions between the individual Research Centres. Topics for research involving such a centralized facility including, for example, limiting risk to participants, preventing bias, improving recruitment and retention, developing innovative methods of enhancing the power of studies, capturing appropriate data, developing design and analysis plans for studies of unique or vulnerable populations or very small numbers of subjects, issues in diseases with limited treatment options and informed consent development. There is need for coordinating in order to implement and manage a multicentric clinical trial in the different countries. Other supporting activities that are essential for the execution of ophthalmological clinical trials are centralized Reading Centres and an infrastructure for Pharmacovigilance. Finally, for translational research it is essential to have expertise on development of business models that take into account the potential market value of the drug, biomarker or medical device from the beginning of the translational process until it reaches the patient and is implemented into every day clinical practice.

A1

EVICR.net COORDINATING CENTRE

Cecilia Martinho, BSc Econ

Staff: Daniel Fernandes, Maria do Céu Fidalgo, Maria Nascimento, Paulo Barros, Rita Fernandes



Contacts

Cecilia Martinho

BSc Econ

Phone: +351 239 480 101/15

E-mail: evicrnet@aibili.pt

Website: www.evicr.net

AIBILI is the headquarters and Coordinating Centre of the European Vision Institute Clinical Research Network – EVICR.net.

EVICR.net is a network of European Ophthalmological Clinical Research Sites, dedicated to perform clinical research in ophthalmology with the highest standards of quality, following the European, International Directives for Clinical Research and ICH-GCP Guidelines according to harmonized Standard Operating Procedures (SOPs).

The EVICR.net is an independent European Economic Interest Grouping (EEIG), established in 2010 in accordance with the Council Regulation (EEC) n.º 2137/85.

EVICR.net is a platform for clinical trial research in ophthalmology in Europe and a useful Industry resource in order to promote the development of new drugs and medical devices.

Any Clinical Research Site can apply for membership in EVICR.net if they fulfil basic requirements such as dedicated space to perform clinical trials, qualified and experienced personnel, experience of multicentric clinical trials and agree to implement organizational SOPs according to ICH GCP Guidelines, provided by EVICR.net.

Each Clinical Site will be submitted to an on-site evaluation visit by independent auditors and must agree to implement the recommended necessary actions in order to become a certified EVICR.net Clinical Site of Excellence.

This Network has an infrastructure for management of multicenter clinical trials located in the Coordinating Centre at AIBILI, Coimbra, Portugal. It has common and harmonized organizational and technical SOPs, quality control and staff training according to ICH GCP-Guidelines. EVICR.net serves as a fundamental resource for the development of translational research and particularly Pharmaceutical and Medical Devices Innovation in the European Union in the area of Ophthalmology and Vision Sciences. Scientifically it is organized by ophthalmology subspecialty Expert Committees namely: AMD and Retinal Dystrophies; Diabetic Retinopathy; Glaucoma; Cornea, Cataract and Refractive Surgery; Ocular Surface and Inflammation; and Reading Centres. It also has Transversal Sections on Rare Diseases, Epidemiology and Medical Devices. At present, EVICR.net has 79 Centres members from 16 European Countries. The Network has 9 clinical trials ongoing of which 3 are European Union funded projects.

EVICR.net MEMBERS (PER COUNTRY)

AUSTRIA (1)

CS n° 19: Medical University of Vienna, Department of Ophthalmology, Vienna

BELGIUM (3)

CS n° 8: Ghent University Hospital, Department of Ophthalmology, Ghent

CS n° 12: Antwerp University Hospital, Department of Ophthalmology, Antwerp

CS n° 18: University Hospital Leuven, Department of Ophthalmology, Leuven

DENMARK (2)

CS n° 30: Glostrup Hospital, Department of Ophthalmology, Copenhagen University, Glostrup

CS n° 73: Odense University Hospital, Department of Ophthalmology, Odense

FRANCE (8)

CS n° 3: Centre Hospitalier Creteil, University Eye Clinic, Paris

CS n° 6: Centre National d'Ophthalmologie des

Quinze-Vingts, Centre d'Investigation Clinique, Paris
CS n° 13: CHU Gabriel Montpied, Unité de Recherche Clinique, Service d'Ophthalmologie, Clermont-Ferrand
CS n° 14: Hôpital Lariboisière, Department of Ophthalmology, Paris

CS n° 42: University Hospital, CHU Dijon, Department of Ophthalmology, Dijon

CS n° 45: Hôpital Purpan, Service d'Ophthalmologie, Toulouse

CS n° 48: CLAIROP: Centre loco-régional d'Amiens pour l'Innovation et la Recherche en Ophthalmologie Pédiatrique, Amiens

CS n° 61: CHU Pellegrin, Service Ophthalmologie, Bordeaux

GERMANY (17)

CS n° 2: University Medical Center, Johannes Gutenberg University, Department of Ophthalmology, Mainz

CS n° 5: Faculty of Medicine Mannheim of the Ruprecht-Karls – University Heidelberg, Department of Ophthalmology, Mannheim

CS n° 9: University Hospital Tuebingen (UKT), STZ Biomed & STZ Eyetril at the Center for Ophthalmology, Tuebingen

CS n° 11: University Eye Hospital Munich, Munich
CS n° 15: University of Bonn, Department of Ophthalmology, Bonn
CS n° 21: University Medical Center Hamburg-Eppendorf, Department of Ophthalmology, Hamburg
CS n° 24: University of Freiburg, Department of Ophthalmology, Freiburg
CS n° 27: University Eye Hospital, Leipzig
CS n° 43: RWTH Aachen University, Department of Ophthalmology, Aachen
CS n° 44: University Eye Clinic, Center for Vision Science, Bochum
CS n° 47: Clinical Centre Karlsruhe, Department of Ophthalmology, Karlsruhe
CS n° 54: University of Düsseldorf, Department of Ophthalmology, Düsseldorf
CS n° 55: Eye Centre Spreebogen, Berlin
CS n° 56: University of Heidelberg, International Vision Correction Research Centre (IVCRC), Heidelberg
CS n° 59: Johann Wolfgang Goethe-University Frankfurt, Department of Ophthalmology, Frankfurt
CS n° 65: Justus-Liebig-University-Giessen, Department of Ophthalmology, Giessen
CS n° 77: Universität zu Köln, Zentrum für Augheilkunde, Köln

GREECE (2)

CS n° 57: University of Crete, Institute of Vision and Optics (IVO), Crete
CS n° 71: Laboratory of Research and Clinical Applications in Ophthalmology, Aristotle Univ. of Thessaloniki, Department of Ophthalmology, AHEPA Univ. Hospital, Thessaloniki

IRELAND (1)

CS n° 31: Mater Vision Institute (MVI), Dublin

ISRAEL (1)

CS n° 60: Tel Aviv Sourasky Medical Center, Department of Ophthalmology, Tel Aviv

ITALY (10)

CS n° 16: University of Milan, Centre for Clinical Trials at San Paolo Hospital, Milan
CS n° 20: G. B. Bietti Foundation - IRCCS, Rome
CS n° 34: Luigi Sacco Hospital, University of Milan, Department of Ophthalmology, Milan
CS n° 36: Catholic University, Institute of Ophthalmology, Rome
CS n° 37: Dipartimento di Scienze Biomediche, Biotecnologiche e Transazionali S.Bi.Bi.T., Parma

CS n° 39: University of Padova, Department of Ophthalmology, Center for Clinical Trials, Padova
CS n° 50: University of Udine, Department of Ophthalmology, Udine
CS n° 63: University G. d'Annunzio of Chieti-Pescara, Excellence Eye Research Centre, Chieti
CS n° 64: University of Bari, Department of Ophthalmology and Otolaryngology, Bari
CS n° 67: University Vita Salute – Scientific Institute of San Raffael, Department of Ophthalmology, Milan

POLAND (1)

CS n° 33: Poznan University of Medical Sciences, Department of Ophthalmology, Poznan

PORTUGAL (6)

CS n° 1: AIBILI - Association for Innov. and Biom. Research on Light and Image, Coimbra
CS n° 28: Instituto de Oftalmologia Dr. Gama Pinto, Lisbon
CS n° 32: Oporto Medical School – Hospital S. João, Department of Ophthalmology, Oporto
CS n° 62: Centro Hospitalar de Lisboa Central, Centro de Investigação, Serviço de Oftalmologia, Lisbon
CS n° 70: University Hospital of Coimbra, Ophthalmology Department, Coimbra
CS n° 80: Instituto de Retina e Diabetes Ocular de Lisboa (IRL), Lisbon

SLOVENIA (1)

CS n° 23: University Medical Centre of Ljubljana, University Eye Hospital, Ljubljana

SPAIN (10)

CS n° 4: IOBA – Instituto Universitario Oftalmobiología Aplicada, Valladolid
CS n° 7: Visum Corporación Oftalmológica Alicante, Alicante
CS n° 26: Centro de Oftalmología Barraquer, Barcelona
CS n° 38: Institut Català de Retina (ICR), Clinical Trial Unit, Barcelona
CS n° 41: Centro Médico Teknon, Institut de la Màcula i de la Retina, Barcelona
CS n° 51: Fundación Oftalmológica del Mediterráneo, Valencia
CS n° 52: University Hospital Josep Trueta of Girona, Department of Ophthalmology, Girona
CS n° 74: Hospital Vall d'Hebrón, Department of Ophthalmology, Barcelona
CS n° 75: Vallés Oftalmologia Research, Barcelona

CS n° 78: Instituto Oftalmologico Fernandez-Vega, Oviedo

Members: Prof. Rufino Silva, Prof. Bart Leroy, Dr. Adnan Tufail, Prof. Frank Holz, Prof. Jordi Monés, Prof. Ugo Introini, Prof. Carel Hoyng

SWITZERLAND (2)

CS n° 22: Inselspital, University of Bern, Department of Ophthalmology, Bern

DIABETIC RETINOPATHY

Coordinator: Prof. José Cunha-Vaz

CS n° 49: Jules Gonin Eye Hospital, Fondation Asile des Aveugles, Lausanne

Members: Dr. Catherine Egan, Prof. Pascale Massin, Prof. Reinier Otto Schlingemann, Prof. Edoardo Midena, Prof. Peter Scanlon, Prof. Anne Katrin Sjølie

THE NETHERLANDS (4)

CS n° 17: University Medical Centre St Radboud, Ophthalmic Trial Centre Nijmegen, Nijmegen

GLAUCOMA

Coordinator: Prof. Esther Hoffmann

CS n° 25: Academic Medical Center, Department of Ophthalmology, Amsterdam

Members: Dr. Luísa Ribeiro, Dr. Jonathan Clarke, Dr. Luca Rossetti, Prof. Thierry Zeyen, Prof. Alfonso Antón-López, Prof. Hans Geert Lemij

CS n° 40: Rotterdam Eye Hospital, Rotterdam

CS n° 76: University Eye Clinic, Maastricht

CORNEA, CATARACT AND REFRACTIVE SURGERY

Coordinator: Prof. Jorge Alió

UNITED KINGDOM (10)

CS n° 10: Moorfields Eye Hospital NHS Foundation Trust, Clinical Trial Unit, London

Members: Prof. Marie-José Tassignon, Prof. Luigi Mosca, Prof. H. Burkhard Dick, Prof. François Majo, Prof. George Kymionis, Prof. Conceição Lobo
Co-opted Member: Prof. Manfred Tetz

CS n° 35: The Queen's University and Royal Group of Hospitals Trust, Ophthalmology and Vision Science, Belfast

CS n° 53: Gloucestershire Hospitals NHS Foundation Trust, Clinical Trials Unit, Department of Ophthalmology, Gloucestershire

OCULAR SURFACE AND INFLAMMATION

Coordinator: Prof. Joaquim Murta

CS n° 58: Royal Liverpool University Hospital, Clinical Eye Research Centre, St. Paul's Eye Unit, Liverpool

Members: Dr. John Dart, Prof. Philippe Kestelyn, Prof. Frédéric Chiambaretta, Dr. Philipp Eberwein, Dr. Seerp Baarsma, Dr. Mario Nubile

CS n° 66: Frimley Park Hospital Foundation Trust, Ophthalmology Clinical Trials Unit, Surrey

READING CENTRES

Coordinator: Prof. Tunde Peto

CS n° 68: Heart of England NHS Trust, Ophthalmic Research Unit, Birmingham

Members: Dr. Maria Cachulo, D. Laurent Bataille, Dr. Ali Erginay, Dr. Steffen Schmitz-Valckenberg, Dr. Ute Wolf, Dr. Stela Vusojevic

CS n° 69: King's Health Partners, Laser and Retinal Research Unit, London

CS n° 72: Torbay Hospital Eye Department, Devon

CS n° 79: Clinical Trials Unit, Oxford Eye Hospital, Oxford

TRANSVERSAL SECTIONS

RARE DISEASES

Coordinator: Prof. Birgit Lorenz

CS n° 81: Royal Surrey County Hospital, NHS Foundation Trust, Ophthalmic Research Unit, Guildford

EPIDEMIOLOGY

Coordinator: Prof. J. F. Korobelnik

MEDICAL DEVICES

Coordinator: Prof. Marie-José Tassignon

SCIENTIFIC SECTIONS

EVICR.net is organized in Scientific Sections covering the following areas of research:

AMD AND RETINAL DYSTROPHIES

Coordinator: Prof. José-Alain Sahel

PROJECTS AND ACTIVITIES

Status	AMD and Retinal Dystrophies	Diabetic Retinopathy	Glaucoma	Anterior segment, Cataract and Ref. Surgery	Ocular Surface and Inflammation
Ongoing	USH – E-RARE ^(a) LHON ^(c)	RET-2010-02 ^(b) EUROCONDOR ^(a,b) POLARIS PROTEUS IRISS ^(c)	STRONG ^(a,b)	CCRS – 2010-01	
Total: 9	2	5	1	1	0

(a) EU Funded;
(b) Involving Reading Centers;
(c) Under Contractin

INVESTIGATOR-DRIVEN CLINICAL TRIALS

1. **ClinicalTrials.gov n° NCT01173614**

Project Gullstrand - European Project for the Determination of Average Biometric Values of Human Eyes
Protocol n° ECR-CCRS-2010-01

Coordinating Investigator: Jos Rozema

Participating Centres (13): Alicante, Antwerp, Barcelona, Chieti, Coimbra, Crete, Girona, Leipzig, Mainz, Milan, Rome, Tel Aviv, València.

Support: EVICR.net

2. **ClinicalTrials.gov n° NCT01145599**

Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures
Protocol n° ECR-RET-2010-02

Coordinating Investigator: José Cunha-Vaz

Participating Centres (19): Amsterdam, Antwerp, Barcelona, Bonn, Coimbra, Glostrup, Leipzig, Lisbon, London (2), Milan, Padova, Paris (3), València, Rome, Rotherdam, Surrey.

Support: EVICR.net

3. **EudraCT n° 2012-001200-38**

ClinicalTrials.gov n° NCT01726075

EUROCONDOR – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy

Project Coordinator: Rafael Simó

Clinical Trial Principal Investigator: José Cunha-Vaz
Participating Centres (11): Barcelona, Birmingham, Cheltenham, Coimbra, Liverpool, London, Milan, Odense, Padova, Paris, Ulm.

Financial Support: European Union 7th Framework Programme – Call Health 2011 – Project n° 278040-2

4. **STRONG – European Consortium for the Study of a Topical Treatment of Neovascular Glaucoma**

Project Coordinator: Norbert Pfeiffer

Participating Centres (4): Coimbra, Koln, London, Mainz. More Centres from EVICR.net will participate in the study.

Financial Support: European Union 7th Framework Programme – Call Health 2012 – Project n° 30532

5. **EUR-USH – E-RARE - European young investigators network for Usher syndrome**

Project Coordinator: Kerstin Nagel-Wolfrum

Participating Centres (5): Coimbra, Paris, Mainz, Montpellier, Nijmegen.

Financial Support: European Union 7th Framework Programme – Call E-RARE 2 – Project n° 12-058

6. **PROTEUS – Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP**

in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy

Project Coordinator: José Cunha-Vaz

Participating Centres (12): Alicante, Cheltenham, Coimbra, Dijon, Liverpool, London, Milan, Padova, Paris, Porto, Rome, Valencia.

Grant: Novartis

INDUSTRY SPONSORED CLINICAL TRIALS

POLARIS – A Prospective non-interventional study to assess the effectiveness of existing anti-vascular endothelial growth factor (Anti-VEGF) treatment regimens in patients with diabetic macular edema (DME) with central involvement

ClinicalTrials.gov n° NCT01771081

Sponsor: Bayer

Participating Centres (27): Alicante, Amiens, Barcelona (5), Berlin, Coimbra, Creteil, Dijon, Giessen, Girona, Hamburg, Leipzig, Lisbon, Milano (3), Mainz, Munich, Padova, Paris (2), Rome, Tuebingen, Udine.

CERTIFICATION OF TECHNICIANS

Best-Corrected Visual Acuity Technician's Certification for Allergan studies:

MACULAR EDEMA

1. **Protocol n.° MAF/AGN/OPH/RET-004**

8 technicians certified in France, Germany, Israel, Spain and UK.

2. **Protocol n.° 206207-024**

75 technicians certified in Austria, Belgium, Denmark, France, Germany, Israel, Italy, Spain, Sweden, The Netherlands and UK.

AGE-RELATED MACULAR DEGENERATION

3. **Protocol n.° 150998-001**

14 technicians certified in France, Germany, Israel, and Switzerland.

GLAUCOMA

4. **Protocol n.° 192024-041D**

2 technicians to be certified in Belgium.

ORGANIZATIONAL SOPS

There are 9 organizational SOPs that are provided for free to our members to implement in their centres with the help of the Coordinating Centre in order to become a certified Clinical Site of Excellence.

TECHNICAL SOPS

There are a total of 31 Technical Ophthalmological SOPs issued.

www.evicr.net.

A2

4C – COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH – AN ACADEMIC CRO

Sandrina Nunes, MSc

Staff: Ana Pedroso, Ana Rita Ribeiro, Cecília Martinho, Conceição Lobo, José Cunha-Vaz, Maria Nascimento, Miguel Ângelo Costa, Rita Fernandes, Sónia Simões



Contacts

Sandrina Nunes, MSc

Phone: +351 239 480 105

E-mail: sandrina@aibili.pt

The Coimbra Coordinating Centre for Clinical Research (4C) is a structure to support the development and coordination of Investigator-Driven and Industry-Sponsored Clinical Trials by providing the following services:

- Protocol design and Statistical planning
- Study documents elaboration
- Submission to the Regulatory Authorities
- Coordination and Study implementation
- Monitoring and Quality control
- Data management and Electronic Data Capture solutions

- Periodical reports to the Sponsor and/or Regulatory Authorities
 - Statistical analysis and Final Study Report
 - Medical writing and Publication support
 - Investigational Medical Product Management
- 4C is currently staffed by one Scientific Director and a Executive Director, four medical consultants, six project/clinical trial managers (CRA), two information technology project managers and one administrative assistant. The 4C has the support of Champalimaud Foundation as the core unit of AIBILI for C-TRACER activities.

PROJECTS – CLINICAL TRIAL SUPPORT

	Multinational	National
Investigator-Driven Clinical Trials	RET-2010-02 EUROCONDOR STRONG C-TRACER Project nº 1 PROTEUS VitaminD3-Omega3	Epidemiological study of AMD incidence Life style and food habits in population aged >55 Macugen vs PRP in Proliferative DR Lucentis vs PRP in Proliferative DR DIAMARKER Diabetic Retinopathy Phenotypes Genotypes/Phenotypes in Nonproliferative DR
Industry-Driven Clinical Trials	POLARIS	Pharmacokinetic assessment

MULTINATIONAL STUDIES

1. ClinicalTrials.gov nº NCT01145599

Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures
Protocol nº ECR-RET-2010-02

Coordinating Investigator: José Cunha-Vaz

Participating Centres (19): Amsterdam, Antwerp, Barcelona, Bonn, Coimbra, Glostrup, Leipzig, Lisbon, London (2), Milan, Padova, Paris (3), Valência, Rome, Rotherdam, Surrey.

4C Services: Protocol design, coordination, monitoring, data management and statistical analysis/final report.

2. EudraCT nº 2012-001200-38

ClinicalTrials.gov nº NCT01726075

EUROCONDOR – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy:

A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy
Protocol nº 4C-2011-02

Project Coordinator: Rafael Simó

Coordinating Investigator: José Cunha-Vaz

Participating Centres (11): Barcelona, Birmingham, Cheltenham, Coimbra, Liverpool, London, Milan, Odense, Padova, Paris, Ulm.

Financial Support: European Union 7th Framework Programme – Call Health 2011 – Project nº 278040-2

4C Services: Protocol design, coordination, data management and statistical analysis/final report.

3. STRONG - European Consortium for the Study of a Topical Treatment of Neovascular Glaucoma

Project Coordinator: Norbert Pfeiffer

Coordinating Investigator: Norbert Pfeiffer
Participating Centres (4): Coimbra, Koln, London, Mainz.
Financial Support: European Union 7th Framework Programme – Call Health 2012 – Project n° 305321
4C Services: Clinical Sites Coordination.

4. ClinicalTrials.gov n° NCT01607190

C-TRACER Project n° 1 – Biomarkers of Diabetic Retinopathy Progression
Protocol n° 4C-2011-02

Coordinating Investigator: José Cunha-Vaz
Participating Centres (2): Coimbra, Hyderabad (India)
Grant: Champalimaud Foundation
4C Services: Protocol design, coordination, monitoring, data management and publication.

5. ClinicalTrials.gov n° NCT01771081

POLARIS - A Prospective non-interventional study to assess the effectiveness of existing anti-vascular endothelial growth factor (Anti-VEGF) treatment regimens in patients with diabetic macular edema (DME) with central involvement
Project Coordinator: Cecília Martinho / Sandrina Nunes
Participating Centres (27): Alicante, Amiens, Barcelona (5), Berlin, Coimbra, Creteil, Dijon, Giessen, Girona, Hamburg, Leipzig, Lisbon, Milano (3), Mainz, Munich, Padova, Paris (2), Rome, Tuebingen, Udine.
Sponsor: Bayer
4C Services: Feasibility Assessment and Clinical Sites Coordination.

6. PROTEUS – Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy

Coordinating Investigator: José Cunha-Vaz
Participating Centres (12): Alicante, Cheltenham, Coimbra, Dijon, Liverpool, London, Milan, Padova, Paris, Porto, Rome, Valencia.
Grant: Novartis
4C Services: Protocol design, study development, coordination, data management, statistical analysis, final report.

7. ClinicalTrials.gov n° NCT01745263

VitaminD₃ – Omega₃ – Home Exercise HeALTHy Ageing and Longevity Trial (DO-HEALTH)
Principal Investigator: Heike A. Biscchoff-Ferrari
Financial Support: European Union 7th Framework Programme – Call Health 2011 – Project n° 278588-2
4C Services: IMP management.

NATIONAL STUDIES - IDCTS

1. ClinicalTrials.gov n° NCT01298674

Epidemiological study of the prevalence of Age-Related Macular Degeneration in Portugal
Protocol n° CC-01-2009
Coordinating Investigator: Rufino Silva
Participating Centres: Mira, Lousã
Grant: Novartis
4C Services: Protocol design, coordination, data management and statistical analysis/final report.

2. ClinicalTrials.gov n° NCT01715870

Life style and food habits questionnaire in the Portuguese population aged 55 or more
Protocol n° 4C-2012-04
Coordinating Investigator: Rufino Silva
Participating Centres: Mira, Lousã
Grant: Novartis
4C Services: Protocol design, coordination, data management and statistical analysis/final report.

3. ClinicalTrials.gov n° NCT01281098

EudraCT n° 2009-016760-36
Prospective, randomized, open label phase II study to assess efficacy and safety of Macugen® (pegaptanib 0.3 mg intravitreal injections) plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy
Protocol n° CC-02-2009
Principal Investigator: José Cunha-Vaz
Grant: Pfizer
4C Services: Protocol design, study submission, coordination and monitoring, data management and statistical analysis/final report.

4. ClinicalTrials.gov n° NCT01280929

Prospective, randomized, multicenter, open label

phase II study to access efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis® plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy

Protocol n° CRFB002DPT04T

Coordinating Investigator: José Cunha-Vaz

Grant: Novartis

4C Services: Protocol design, study submission, coordination and monitoring, data management and statistical analysis/final report.

5. ClinicalTrials.gov n° NCT01440660

Phenotypes of Nonproliferative Diabetic Retinopathy in Diabetes type 2 patients identified by Optical Coherence Tomography, Colour Fundus Photography, Fluorescein Leakage and Multifocal Electrophysiology (DIAMARKER Project: Genetic susceptibility for multi-systemic complications in diabetes type-2: New biomarkers for diagnostic and therapeutic monitoring)

Protocol n° 4C-2011-01

Principal Investigator: Luísa Ribeiro

Financial Support: QREN - Quadro de Referência

Estratégico Nacional - Sistema de Incentivos

à Investigação e Desenvolvimento Tecnológico

– Project n° 13853

4C Services: Protocol design, study submission, coordination and monitoring, data management and statistical analysis/final report.

6. EudraCT n° 2011-005089-39

Pharmacokinetic assessment of ceftriaxone

(Betasporina) or clavulanic acid or ceftriaxone plus clavulanic acid administered by the endovenous route

Protocol n° ATRAL/CFC/273/11

Principal Investigator: Carlos Fontes Ribeiro

Sponsor: Atral

4C Services: Monitoring.

7. ClinicalTrials.gov Identifier: NCT00840541

Observational Study of Type-2 diabetic subjects to

validate Diabetic Retinopathy Phenotypes

Protocol n° CNTMo18A

Principal Investigator: José Cunha-Vaz

4C Services: Statistical analysis and final report.

8. ClinicalTrials.gov Identifier: NCT01228981

Observational Study to Assess Genotypes/Pheno-

types Correlations in Type-2 Diabetic Retinopathy

Protocol n° PTDC/SAU-OSM/103226/2008

Principal Investigator: Conceição Lobo

4C Services: Statistical analysis and final report.

CORC – COIMBRA OPHTHALMOLOGY READING CENTRE

A3

Conceição Lobo, MD, PhD

Staff: Conceição Lobo, Isabel Pires, João Figueira, João Pedro Marques, José Cunha-Vaz, Maria Luísa Ribeiro, Maria da Luz Cachulo, Rufino Silva, Aldina Reis, Ana Paula Pascoal, Ana Rita Santos, António Pedro Melo, Catarina Neves, Christian Schwartz, Rui Alberto Pita, Sílvia Simão, Telmo Miranda

The Coimbra Ophthalmology Reading Center (CORC) focus its activities in grading color fundus photographs, OCT images of the retina and functional evaluations of the retina using mfERG.

It performs centralized reading for the Diabetic Retinopathy Screening Programme of the Central Region of Portugal and serves as centralized reading center for a series of IDCTs, some of them performed within the EVICR.net.

It uses novel software programmes developed in house – Retmarker® products – to reliably quan-

tify neovascularization of the retina, microaneurysm (MA) turnover in diabetic patients, to measure drusen size and disease activity in patients with AMD and also retina segmentation techniques based on OCT.

CORC has all the necessary equipment for grading retinal images and has, at the moment, 17 graders (8 ophthalmologist graders and 9 non-ophthalmologist graders), and one administrative secretary.

It has already certified technicians in other European countries for specific clinical trial studies.



Contacts

Conceição Lobo, MD, PhD

Phone: +351 239 480 135/6

E-mail: clobo@aibili.pt

Catarina Neves

Phone: +351 239 480 135/6

E-mail: corc@aibili.pt

MAIN ACTIVITIES

Area	Ongoing Projects	Type of exams	Type of grading
Diabetic Retinopathy	7	CFP	ETDRS Grading
			Automated MA assessment (RetmarkerDR®)
			Screening DR
		CFP/FA	High-risk PDR criteria and Quantification of neovascularization
		OCT	Retinal Thickness, Retinal Nerve Fiber Layer Thickness, Ganglion Cell layer Thickness
mfERG	Amplitude/Implicit time of P1 & Z-score analysis		
AMD	1	CFP	Classification/quantification of ARM lesions (RetmarkerAMD®)

DIABETIC RETINOPATHY

1. Prospective, randomized, multicenter, open label phase II study to access efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis® plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy.

ClinicalTrials.gov n° NCT01280929

Protocol n° CRFBoo2DPT04T

Coordinating Investigator: João Figueira

Grant: Novartis

Participating Centres (7): 7 nacional centres

N° of Patients (expected/included): 54/34

Duration of clinical phase: 1 year

CORC Services: Grading for High Risk-Proliferative Diabetic Retinopathy criteria on color fundus photography and fluorescein angiography and quantification of neovascularization.

2. Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures

ClinicalTrials.gov n° NCT01145599

Protocol n° ECR-RET-2010-02

Coordinating Investigator: José Cunha-Vaz

Support: EVICR.net

Participating Centres (19): Belgium (1), Denmark (1),

France (3), Germany (2); Italy (3), Netherlands (1),

Portugal (2), Spain (2), UK (4)

N° of Patients (included): 374

Duration of clinical phase: 1 year

CORC Services: ETDRS grading of color fundus photography and microaneurysm turnover assessment of color fundus photography using RetmarkerDR®.

3. Diabetic Retinopathy Screening – Central Region of Portugal

Coordination: Helder Ferreira (ARSC)

Financial Support: Health Administration of Central Region of Portugal (ARS Centro).
N° of Patients: 28849 screened diabetic patients between July 2011 and December 2012.
CORC Services: Grading of color fundus photography for Diabetic Retinopathy Screening purposes using an automated first-step analysis by Retmarker.

4. Phenotypes of Nonproliferative Diabetic Retinopathy in Diabetes type 2 patients identified by Optical Coherence Tomography, Colour Fundus Photography, Fluorescein Leakage and Multifocal Electrophysiology (DIAMARKER Project: Genetic susceptibility for multi-systemic complications in diabetes type-2: New biomarkers for diagnostic and therapeutic monitoring)

ClinicalTrials.gov n° NCT01440660
Protocol n° 4C-2011-01
Financial Support: QREN - Quadro de Referência Estratégico Nacional – Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico – Project n° 13853
Participating Centres (1): AIBILI-CEC, Coimbra, Portugal
N° of Patients (included): 20
Duration of clinical phase: 2 years
CORC Services: ETDRS grading of color fundus photography and microaneurysm turnover assessment of color fundus photography using RetmarkerDR®.

5. Retinal Disease Screening System (RDSS)

Project Coordinator: João Diogo Ramos
Financial Support: QREN – Quadro de Referência Estratégico Nacional – Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico – Project n° 22969
CORC Functions: co-partner of Critical Health for the development and validation of an informatics solution to support automated analysis for the grading of images in a DR screening programme.

6. Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, randomised controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy (EUROCONDOR)
EudraCT n° 2012-001200-38

ClinicalTrials.gov n° NCT01726075
Protocol n° 4C-2011-02
Project Coordinator: Rafael Simó
Financial Support: European Union 7th Framework Programme – Call Health 2011 - Project n° 278040-2
Participating Centres (11): Denmark (1), France (1), Germany (1), Italy (2), Portugal (1), Spain (1), UK (4).
N° of Patients (expected/included): 451/0
Duration of clinical phase: 2 years
CORC Services: ETDRS grading of color fundus photography and microaneurysm turnover assessment of color fundus photography using RetmarkerDR®; Grading of OCT (RNFL thickness, ganglion cell layer thickness and overall retinal thickness analysis); Grading of multifocal electroretinography (amplitude and implicit time of P1 wave and Z-score analysis).

7. 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

ClinicalTrials.gov n° NCT 00763802
Protocol n° PTDC/SAU-OSM/72635/2006
Participating Centres (1): AIBILI-CEC, Coimbra, Portugal
N° of Patients (included): 348
Duration of clinical phase: 2 years (ended)
Financial Support: Foundation for Science and Technology, Portugal - PTDC/SAU-OSM/72635/2006
CORC Services: ETDRS grading of color fundus photography of the first and last patients' visits.

AGE-RELATED MACULAR DEGENERATION

8. Epidemiological study of the prevalence of age-related macular degeneration in Portugal

ClinicalTrials.gov n° NCT01298674
Protocol n° CC-01-2009
Coordinating Investigator: Rufino Silva
Grant: Novartis
Participating ARSC Centres (2): Mira and Lousã, Portugal
N° of Patients (expected/included): Mira: 3000/2976; Lousã: 3000/1377 (ongoing)
CORC Services: Color fundus photography grading to determine presence of pathologies and Age-Related Macular Degeneration cases using RetmarkerAMD® research software.

CHAD – HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH

A4

Francisco Batel Marques, PhD

Staff: Ana Penedones, Carla Neta, Carlos Alves, Carlos Fontes Ribeiro, Daniel Fernandes, Diogo Mendes, Filipe Martins, João Silva, Óscar Lourenço, Tice Macedo

The Centre for Health Technology Assessment and Drug Research (CHAD) focus is on evaluation of medicines and other medicinal products for market access purposes, aiming at financing and reimbursement, pharmacovigilance and bioequivalence studies for generic drugs approval and drug safety monitoring.

The CHAD provides scientific information to support the decision making in healthcare policy and practice. Health Technology Assessment studies are necessary to ensure equity in the access to medicines and the most favourable benefit/risk and cost/effectiveness ratios in the drug use process.

HTA is, therefore, of capital importance in both drug reimbursement decisions at both ambulatory and hospital settings.

The CHAD is responsible for the Pharmacovigi-

lance Unit of the Centre Region of the National Pharmacovigilance System which is contracted with the National Authority of Medicines and Health Products (INFARMED, IP).

The CHAD is also a resource qualified to work closely with Pharmaceutical Industry in all the different phases of drug development.

It can perform bioavailability/bioequivalence and pharmacokinetic studies. For these it develops the protocols and other documents needed for these studies, the preparation of submission to regulatory authorities, development and validation of analytical methods, planning and performance of the clinical phase, dosage of samples, result analysis and final report.

All clinical pharmacology activities are performed according to Good Laboratory Practices (certification since 1999 by INFARMED).



Contacts

Francisco Batel Marques

PhD

Phone: +351 239 480 138

E-mail: hta@aibili.pt

PROJECTS

1. Evaluation of therapeutic value and economic value of Apixabano® in the prevention of venous thromboembolism

Sponsor: Bristol-Myers Squibb

Principal Investigator: Batel Marques and Óscar Lourenço

2. Evaluation of therapeutic value of Livopan® for treating pain of short duration

Sponsor: Linde

Principal Investigator: Batel Marques

3. Evaluation of therapeutic value and economic value of Fingomilod® in multiple sclerosis relapsing-remitting

Sponsor: Novartis

Principal Investigator: Batel Marques and Óscar Lourenço

4. Pharmacokinetic assessment of ceftriaxone (Betaspantina®) or clavulanic acid or ceftriaxone plus clavulanic acid administered by the endovenous route

EudraCT n° 2011-005089-39

Sponsor: Laboratórios Atral

Principal Investigator: Carlos Fontes Ribeiro

5. Evaluation of therapeutic value and economic value of Neupro® in Parkinson Disease

Sponsor: UCB Pharma

Principal Investigator: Batel Marques and Óscar Lourenço

6. Evaluation of therapeutic value and economic value of Apixabano® in the prevention of stroke in patients with atrial fibrillation

Sponsor: Bristol-Myers Squibb

Principal Investigator: Batel Marques and Óscar Lourenço

7. Budget Impact Model for Eviplera®

Sponsor: Gilead

Principal Investigator: Batel Marques and Óscar Lourenço

8. Evaluation of therapeutic value and economic value of Sativex® as an add-on to the spasticity due to multiple sclerosis

Sponsor: Almirall

Principal Investigator: Batel Marques and Óscar Lourenço

9. Survey of therapeutic practices of VEGF-Trap-Eye®

Sponsor: Bayer

Principal Investigator: Batel Marques and Óscar Lourenço

10. Evaluation of therapeutic value of Perjeta® in combination with Herceptin (trastuzumab) and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

Sponsor: Roche

Principal Investigator: Batel Marques

11. Evaluation of therapeutic value of BG-12® in the Treatment of Relapsing-Remitting Multiple Sclerosis

Sponsor: Biogen

Principal Investigator: Batel Marques

12. Evaluation of economic value of Tepadina®

Sponsor: Adienne

Principal Investigator: Batel Marques and Óscar Lourenço

13. Evaluation of therapeutic value, economic value and budget impact model for Lyxumia®

Sponsor: Sanofi

Principal Investigator: Batel Marques and Óscar Lourenço

14. Evaluation of therapeutic value, economic value and budget impact model for Zaltrap®

Sponsor: Sanofi

Principal Investigator: Batel Marques and Óscar Lourenço

B

Clinical Vision Research

RESEARCH PROGRAMMES IN VISION AND IMAGING

Age-related eye diseases affect more than 10% of the western world population. The most common eye diseases are macular degeneration, diabetic retinopathy and glaucoma. Diabetic retinopathy is the most frequent cause of new cases of blindness in individuals aged 20-74 (working age years) resulting in most disability and person-years of vision lost than other diseases.

Clinical patient-oriented research involves characterizing disease progression and testing new discoveries by carrying out carefully controlled investigations in patients, well-known as clinical trials. This includes testing not only new drugs, but also new methods, devices, imaging and surgical procedures.

Our research is focused in age-related eye diseases with special emphasis on diabetic retinopathy and age-related macular degeneration. The results of our research have had impact worldwide with frequent international publications and our translational research programme has contributed to improving management of these diseases.

Our research interest has been particularly focused on development of biomarkers of disease activity and progression as well as early detection. Early detection and validation of biomarkers of disease progression allow timely intervention and open much needed opportunities for new models of prospective health care and ultimately better patient care.

Finally, our research programme is looking at stem cells to repair advanced stages of anterior segment and retinal disease.

Our research group is involved in a large number of investigator-driven clinical trials, three of them funded by the 7th European Union Research Framework Programme.

B1

BIOMARKERS OF PROGRESSION OF DIABETIC RETINOPATHY

José Cunha-Vaz MD, PhD

Other Research Personnel: Ana Rita Santos, Conceição Lobo, Isabel Pires, Luisa Ribeiro, Rui Bernardes, Sandrina Nunes, Sérgio Leal, Sílvia Simão



Contacts

José Cunha-Vaz
MD, PhD

Phone: +351 239 480 100

E-mail: cunhavaz@aibili.pt

Diabetic Retinopathy remains the most frequent complication of diabetes and the main cause of vision loss in the professionally active age-group 24-70 years of age. Today, despite the goal of tight blood glucose control and the use of retinal photocoagulation and new drugs, blindness still occurs. Therapies targeted at the earliest stages of retinal disease, involving necessarily the demonstration of efficacy of a new drug are needed and remain a priority for eye research. To achieve this goal is urgent to identify biomarkers of disease progression that can be accepted as surrogates for generally accepted endpoints. Our research group identified a biomarker of diabetic retinopathy progression: microaneurysm turnover. Microaneurysm turnover on fundus photographs using the Retmarker®, taking into account their exact, specific location in the eye fundus has the potential to become an extremely valuable biomarker of the overall progression of diabetic retinal vascular disease.

Microaneurysm turnover rate appears to be a direct indication of the progression of retinal vascular damage and activity of disease. Reduction in macular thickening by measuring the changes in retinal thickness with dedicated instrumentation is another promising alternative for another biomarker. The measurements are reliable, and changes in retinal thickness are a direct indication of macular edema and breakdown of the blood-retinal barrier. Another promising examination procedure is multifocal ERG. Our research group is collaborating with a number of clinical research centres from Europe and India to test these potential biomarkers. Our research group also found that there is great individual variation in the presentation and course of diabetic retinopathy. We were able to identify three major phenotypes of diabetic retinopathy progression with different risks for vision loss that need different personalized treatment.

INVESTIGATOR-DRIVEN CLINICAL TRIALS

Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures
ClinicalTrials.gov n° NCT01145599

Protocol n° ECR-RET-2010-02

Participating Centres (19): Amsterdam, Antwerp, Barcelona, Bonn, Coimbra, Glostrup, Leipzig, Lisbon, London (2), Milan, Padova, Paris (3), Valência, Rome, Rotherdam, Surrey.

EUROCONDOR – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy

EudraCT n°: 2012-001200-38

ClinicalTrials.gov n° NCT01726075

Participating Centres (11): Barcelona, Birmingham, Cheltenham, Coimbra, Liverpool, London, Milan, Odense, Padova, Paris, Ulm.

Financial Support: European Union 7th Framework Programme – Call Health 2011 – Project n° 278040-2

C-TRACER Project n° 1 – Biomarkers of Diabetic Retinopathy Progression

ClinicalTrials.gov n° NCT01607190

Protocol n° 4C-2012-02

Participating Centres (2): Coimbra, Hyderabad (India).

Grant: Champalimaud Foundation

SELECTED PUBLICATIONS

Cunha-Vaz J., Bernardes R.: Nonproliferative retinopathy in diabetes type 2. Initial stages and characterization of phenotypes. *Progr Retin Eye Res* 2005; 24:355-377.

Cunha-Vaz J.: Characterization and relevance of different diabetic retinopathy phenotypes. In: *Diabetic Retinopathy*. Lang GE. Ed. Basel, Karger. *Dev Ophthalmol* 2007; 39, 13-30.

Lobo CL, Bernardes RC, Figueira JP, Faria de Abreu JR, Cunha-Vaz JG: Three-year follow-up of blood retinal barrier and retinal thickness alterations in patients with type 2 diabetes mellitus and mild nonproliferative retinopathy. *Arch Ophthalmol* 2004; 122: 211-217.

Bandello F, Cunha-Vaz J., Chong N., Lang G., Massin P., Michell P., Porta M., Prunte C., Schlingensmann R., Schmidt-Erfurth U.: New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. *Eye* 2012; 26(4):485-93.

Simó R., Hernández C.; on behalf of the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR): Neurodegeneration is an early event in diabetic retinopathy: therapeutic implications. *Br J Ophthalmol* 2012;96(10):1285-1290.

PHENOTYPE/GENOTYPE CORRELATIONS IN DIABETIC RETINOPATHY

B2

Conceição Lobo, MD, PhD

Other Research Personnel: Carlos Faro, Conceição Egas, Isabel Pires, José Cunha-Vaz, Luísa Ribeiro, Maria José Simões, Mário Soares, Rui Bernardes, Sandrina Nunes, Torcato Santos

Several studies have provided evidence that good diabetes control is important to prevent progression of diabetic retinopathy, but it is clear that some patients develop a rapidly progressing retinopathy despite good control, while others escape the development of severe retinopathy despite poor control. The onset, intensity and progression of diabetic complications show large interindividual variations (Lobo et al, 2004). There is evidence from aggregation in families and specific ethnic groups, together with lack of serious complications in some diabetic patients with poor metabolic control that there is a genetic predisposition to develop some diabetic complications such as retinopathy (Warphea and Chakravarthy, 2003). Our research group has initiated a research programme trying to associate candidate genes to

well defined phenotypes of diabetic retinopathy progression. Preliminary results obtained in 236 patients with diabetes type 2 and categorized in different phenotypes showed promising results (Lobo et al, 2012).

The candidate genes tested based on gene organization and Single Nucleotide Polymorphisms (SNPs) density were: ALR (AKR1B1), VEGF, TNF- α , NOS-1, RAGE, ICAM-1 and ACE.

A statistically significant difference between the 3 phenotypes was found for NOS-1 – rs4519169 ($p=0.031$).

Considering only the eyes that developed clinically significant macular edema during the 2-year follow-up period and eyes that did not develop statistically significant differences were also found for AKR1B1 – rs759853 ($p=0.034$) and ICAM-1 RS 1801714 ($p=0.044$).



Contacts

Conceição Lobo
MD, PhD

Phone: +351 239 480 108

E-mail: clobo@aibili.pt

CLINICAL TRIALS

Correlation phenotype/genotype in diabetic retinopathy

ClinicalTrials.gov n° NCT01228981

Protocol n° CEC/120

Financial Support: Foundation for Science and Technology, Portugal – PTDC/SAU-OSM/103226/2008

DIAMARKER Project: Genetic susceptibility for multi-systemic complications in diabetes type-2: New biomarkers for diagnostic and therapeutic monitoring

ClinicalTrials.gov n° NCT01440660

Protocol n° 4C-2011-01

Financial Support: QREN – Quadro de Referência Estratégico Nacional – Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico – Project n° 13853

SELECTED PUBLICATIONS

Lobo C., Bernardes R., Figueira J., Faria de Abreu J., Cunha-Vaz J.: Three-year follow-up of blood retinal barrier and retinal thickness alterations in patients with type 2 diabetes mellitus and mild nonproliferative retinopathy. *Arch Ophthalmol* 2004; 122: 211-217.

Lobo C., Pires I., Cunha-Vaz J. Diabetic Macular Edema. In: *Optical Coherence Tomography: A Clinical and Technical Update*. Rui Bernardes and José Cunha-Vaz al., Ed. Springer. 2012: 1-21.

Cunha-Vaz J., Bernardes R., Santos T., Oliveira C., Lobo C., Pires I., Ribeiro L. Computer-Aided Detection of Diabetic Retinopathy Progression. In: *Digital Telerecinal Screening*. K. Yogesana al, Ed. Springer-Verlag Berlin Heidelberg. 2012:59-66.

Cunha-Vaz J., Bernardes R., Lobo C. Clinical Phenotypes of Diabetic Retinopathy. In: *Visual Dysfunction in Diabetes*. Springer New York, 2012, 53-68.

Lobo C., Ribeiro L., Bento G., Nunes S., Simoes M., Miranda T., Bernardes R., Faro C., Cunha-Vaz J.: Patterns of Progression in Diabetic Retinopathy. Correlation Between Phenotypes and Genotypes. *Inv. Ophthalmology Vision Sciences*, 2012 53:2849.

B3

NOVEL TREATMENT OPTIONS FOR COMPLICATIONS OF DIABETIC RETINOPATHY

João Figueira, MD

Other Research Personnel: Ana Rita Santos, Isabel Pires, Luísa Ribeiro, Pedro Serranho, Rufino Silva, Rui Bernardes, Sérgio Leal



Contacts

João Figueira, MD

Phone: +351 239 480 128

E-mail: joaofigueira@oftalmologia.co.pt

Macular edema is a nonspecific sign of ocular disease and not a specific entity. It should be viewed as a special and clinically relevant type of macular response to an altered retinal environment. In most cases, it is associated with an alteration of the blood-retinal barrier (BRB). Starling's law, which governs the movements of fluids, applies in this type of edema. Multimodal macula mapping uses a variety of

diagnostic tools and techniques to obtain additional information. These imaging techniques are essential to guide the indications for current treatment and to assess the response to treatment. Our research group is using novel imaging technologies to test different approaches to treatment of diabetic macular edema, such as intravitreal injections of anti-VEGF agents and/or thrombolytic agents.

INVESTIGATOR-DRIVEN CLINICAL TRIALS

Prospective, randomized, open label phase II study to assess efficacy and safety of Macugen® (pegaptanib 0.3 mg intravitreal injections) plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy
EudraCT n° 2009-016760-36
ClinicalTrials.gov n° NCT01281098
Protocol n° CC-02-2009
Grant: Pfizer

Prospective, randomized, multicenter, open label phase II study to assess efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis® plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy
ClinicalTrials.gov n° NCT01280929
Protocol n° CRFB002DPT04T
Grant: Novartis

PROTEUS - Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy
Project Coordinator: José Cunha-Vaz
Participating Centres (12): Alicante, Cheltenham, Coimbra, Dijon, Liverpool, London, Milan, Padova, Paris, Porto, Rome, Valencia.
Grant: Novartis

SELECTED PUBLICATIONS

Figueira J., Khan J., Nunes S., Sivaprasad S., Rosa A., de Abreu JF, Cunha-Vaz J., Chong N.: Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. *Br J Ophthalmol* 2009;93(10):1341-4.

Figueira J., Cunha-Vaz J.: Severe macular ischemia in a poorly controlled diabetic patient. *Diabetes Management* 2012;2(1):21-23.

Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, Tolentino M, Gupta A, Duarte L, Madreperla S, Gonder J, Kapik B, Billman K, Kane FE and FAME Study Group: Long-term Benefit of Sustained-Delivery Fluocinolone Acetonide Vitreous Inserts for Diabetic Macular Edema. *Ophthalmology* 2011; 118(4):626-635.

Franqueira N, Cachulo ML, Pires I, Fonseca P, Marques I, Figueira J, Silva R.: Long-Term Follow-Up of Myopic Choroidal Neovascularization Treated with Ranibizumab. *Ophthalmologica* 2012;227(1):39-44.

EARLY MARKERS OF WET AGE-RELATED MACULAR DEGENERATION

B4

Rufino Silva, MD, PhD

Other Research Personnel: Ana Rita Santos, João Figueira, Maria Luz Cachulo, Rui Bernardes, Sérgio Leal

Age-related macular degeneration (AMD) causes loss of visual acuity by progressive destruction of macular photoreceptor cells and retinal pigment epithelial cell function. These features are commonly referred to as dry AMD or age related maculopathy (ARM). Dry AMD affects ~6% of Caucasian individuals aged 65-74 and rises to 20% of those aged >75.

In some people neovascularization is stimulated from the choriocapillaris, perhaps by vascular endothelial growth factor (VEGF) and/or other local inflammatory cytokines, to grow through a fragmented Bruch's membrane under the RPE and/or under the retina. When neovascularisation is present the condition is termed wet, exudative or neovascular AMD. Neovascular AMD occurs in ~10-20% of people with dry AMD and causes accelerated and severe visual loss by leakage of serum and blood and then scarring under the macula. Increased longevity in developed countries has already made AMD the dominant cause of visual disability, and the numbers projected to be visually disabled by this condition may substantially increase in the future.

It is crucial to understand the natural history of

the conversion from dry to neovascular AMD, to characterize the different phenotypes of AMD and to identify markers of this conversion.

Identification of such markers would enhance our ability to identify the earliest signs of neovascular AMD, which is currently limited by the inadequacies of existing diagnostic imaging modalities. Identification of a patient population at high risk for conversion to neovascular AMD will allow for an appropriate clinical trial to evaluate the possibility of improved outcomes with prevention or early treatment of neovascularization. Also, the identification of predictive markers for choroidal neovascularization (CNV) will allow efficient targeting and testing of new therapies with a higher probability of success.

Our research is looking to identify the sequence of changes in the chorioretinal interface during the development of CNV and the progression from dry to neovascular AMD, to identify the morphological features that define the earliest identifiable CNV lesion that may be appropriate for treatment with an anti-VEGF therapy, and to evaluate the sensitivity of quantitative image analysis relative to clinical observations and evaluation of the images.



Contacts

Rufino Silva MD, PhD
Phone: +351 239 480 128
E-mail: rufino.silva@oftalmologia.co.pt

INVESTIGATOR-DRIVEN CLINICAL TRIALS

Early Markers of choroidal neovascularization (CNV) in fellow eyes of patients with age-related macular degeneration (AMD) and CNV in one eye

ClinicalTrials.gov n° NCT00801541

Protocol n° A9010002

Participating Centres (3): Coimbra, Belfast and Milan

Epidemiological study of the prevalence of Age-Related Macular Degeneration in Portugal

ClinicalTrials.gov n° NCT01298674

Protocol n° CC-01-2009

Grant: Novartis

Life style and food habits questionnaire in the Portuguese population aged 55 or more

ClinicalTrials.gov n° NCT01715870

Coordinating Investigator: Rufino Silva

Grant: Novartis

SELECTED PUBLICATIONS

Silva, R., Figueira, J., Cachulo, M.L., Duarte, L., Faria de Abreu, J.R., Cunha-Vaz, J.G.: Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. *Graefes Arch. Clin. Exp. Ophthalmol.* 2005, 24, 973-979.

Silva, R., Cachulo, M.L., Figueira, J., Faria de Abreu, J.R., Cunha-Vaz, J.G.: Chorioretinal anastomosis and photodynamic therapy: a two-year follow-up study. *Graefes Arch. Clin. Exp. Ophthalmol.* 2007; 245:1131-1139.

Silva R, Cachulo ML, Fonseca P, Bernardes R, Nunes S, Vilhena N, Faria de Abreu JR. Age-related macular degeneration and risk factors for the development of choroidal neovascularisation in the fellow eye: a 3-year follow-up study. *Ophthalmologica.* 2011;226(3):110-8.

Silva R, Axer Siegel R, Elden B, Guimer R, Kirchof B, Papp A, Seres A, Gekkieva M, Nieveg A, Pilz S, for the Secure Study The SECURE Study. Long-Term Safety of Ranibizumab 0.5 mg in Neovascular Age-Related Macular Degeneration. *Ophthalmology.* 2013; 120:130-9.

Silva R, Ruiz-Moreno JM, Gomez-Ulla F, Montero JA, Gregório T, Luz Cachulo M, Pires I, Cunha-Vaz JG, Murta JN. Photodynamic therapy for chronic central serous chorioretinopathy: a 4-year follow-up study. *Retina.* 2013;33(2):309-315.

B5

RETINAL NEURODEGENERATION IN AGEING AND DISEASES OF BRAIN AND GLAUCOMA

Lúisa Ribeiro, MD, MSc

Other Research Personnel: Aldina Reis, Ana Rita Santos, Inês Marques, Sérgio Leal, José Cunha-Vaz, Miguel Castelo-Branco, Pedro Guimarães, Pedro Faria, Pedro Fonseca, Pedro Rodrigues, Rufino Silva, Rui Bernardes, Sílvia Simão



Contacts

Lúisa Ribeiro, MD, MSc

Phone: +351 239 480 128

E-mail: lr@aibili.pt

Glaucoma is a progressive neurodegenerative disease characterized by pathologic loss of ganglion cells, optic nerve damage and visual field defects. A major risk factor for blindness is often the late detection of the disease.

Glaucomatous optic neuropathy is biologically identified by the death of retinal ganglion cells. Ganglion cell axons are slowly lost, leading to thinning of the Retinal Nerve Fibre Layer (RNFL) and thinning of the neuroretinal rim.

Optical Coherence Tomography (OCT) provides quantitative and objective measurement on RNFL and optic nerve head with high resolution and enables the detection of glaucomatous optic neuropathy. The incorporation of spectral

domain OCT (SD-OCT) offers significant advantages for identifying glaucomatous changes. Brain degenerative diseases such as multiple sclerosis, Parkinson's disease and Alzheimer are characterized by early changes in the ganglion cell layer of the retina that may be quantified. These changes occur with absence of cognitive changes and also with absence of visual loss. Our research group is using now automated software analytical approaches of the Optical Coherence Tomography (OCT) information to characterize these retinal changes. Our work is integrating this information in the context of ageing of the retina in close collaboration with the Diagnostic Imaging research programme.

INVESTIGATOR-DRIVEN CLINICAL TRIALS

Data analysis regarding OCT and Color Fundus Photography in patients with Multiple Sclerosis

Principal Investigator: Luisa Ribeiro

STRONG – Early onset of Neovascular Glaucoma

Coordinating Investigator: Norbert Pfeiffer (Mainz, Germany)

Financial Support: European Union 7th Framework Programme – Call Health 2012 - Project n° 305321

SELECTED PUBLICATIONS

Miglior S, Zeyen T., Pfeiffer N., Cunha-Vaz JG., The European Glaucoma Prevention Study. Design and Baseline Description of the Participants. The European Glaucoma Prevention Study Group. *Ophthalmology* 2002, 109:1612-1621.

The European Glaucoma Prevention Study Group (EGPS): Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005; 112: 366-375.

The European Glaucoma Prevention Study Group (EGPS): Clinical and therapeutic intercurrent factors associated with the development of open angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. *Ophthalmology* 2007; 114(1):3-9.

The Ocular Hypertension Treatment Study Group and the European Glaucoma Prevention Study Group: The Accuracy and Clinical Application of Predictive Models for Primary Open-Angle Glaucoma in Ocular Hypertensive Individuals. *Ophthalmology* 2008-Nov; 115(11):2030-2036.

STEM CELLS IN THE TREATMENT OF EYE DISEASES

B6

Joaquim Murta, MD, PhD

Other Research Personnel: Andreia Rosa, Esmeralda Costa, Maria João Quadrado

This research programme is directly related to a joint effort performed between AIBILI (C-TRACER 2) together with the Department of Ophthalmology of the University Hospital of Coimbra, the LV Prasad Eye Institute, India (C-TRACER 1) and the Institute for Vision at the Federal University of S. Paulo, Brazil (C-TRACER 3).

C-TRACER 1, in Hyderabad, has been able to set up an outstanding and innovative stem cell research programme. It has offered limbal stem cell therapy to a large number of patients in India, whose corneal surface had been damaged by burns. C-TRACER 1 long-term results on this procedure (designated as cultivated limbal epithelial transplantation or CLET) has been internationally recognized. More recently, C-TRACER 1 has also moved to study the applications of stem cell biology to retinal disorders, this is being done by using human embryonic stem cells (HESCs) and differentiating them to certain retinal cells (e.g. retinal pigment epithelium (RPE)) and also to generate induced pluripotent cells (iPSCs) from skin fibroblasts and differentiating them to RPE cells.

C-TRACER 3, in S. Paulo, has set a cell biology lab where it has been possible to cultivate human limbal epithelial, conjunctival epithelial,

endothelial and keratocytes stem cells. C-TRACER 3 also started a very exciting project with dental pulp stem cells for ocular surface reconstruction which may together with conjunctival epithelial ex vivo transplantation be excellent options for recovering vision in bilateral cases of limbal stem cell deficiency, without the need of systemic immunosuppression. These last techniques have already been approved for patients and are in the process of publishing the first clinical results.

C-TRACER 2, in Coimbra, has also initiated stem cell research, cultivating human limbal epithelial cells and establishing primary cultures of human corneal endothelium (hCE), understanding its physiology and therapeutic potentialities. The three C-TRACERs are starting autologous ex vivo transplantation of conjunctival and oral mucosal epithelial stem cells for ocular surface reconstruction in bilateral total limbal stem cell deficiency. They are also developing a multicentric protocol using dental pulp stem cell transplantation for this group of patients.

Finally, the three C-TRACERs are working together to share and develop new cell biology technology for retinal diseases with the support of the Champalimaud Foundation.



Contacts

Joaquim Murta, MD, PhD

Phone: +351 239 480 100

E-mail: jmurta@netcabo.pt

PROJECTS

C-TRACER Project - Use of stem-cells in the repair of corneal and retinal diseases

Participating Centres (3): Coimbra, Hyderabad (India), S. Paulo (Brazil).
Champalimaud Foundation

SELECTED PUBLICATIONS

Mariappan I, Maddileti S, Savy S, Tiwari S, Gaddipati S, Fatima A, Sangwan VS, Balasubramanian D, Vemuganti GK: In vitro culture and expansion of human limbal epithelial cells. *Nat Protoc.* 2010 Aug;5(8):1470-9. doi: 10.1038/nprot.2010.115. Epub 2010 Jul 29.

Sangwan VS, Basu S, MacNeil S, Balasubramanian D: Simple limbal epithelial transplantation (SLET): a novel surgical technique for the treatment of unilateral limbal stem cell deficiency. *Br J Ophthalmol.* 2012 Jul;96(7):931-4. doi: 10.1136/bjophthalmol-2011-301164. Epub 2012 Feb 10.

Ricardo JR, Cristovam PC, Filho PA, Farias CC, de Araujo AL, Loureiro RR, Covre JL, de Barros JN, Barreiro TP, Dos Santos MS, Gomes JÁ: Transplantation of conjunctival epithelial cells cultivated ex vivo in patients with total limbal stem cell deficiency. *Cornea.* 2013 Mar;32(3):221-8. doi: 10.1097/ICO.0b013e31825034be.

Gomes JA, Geraldes Monteiro B, Melo GB, Smith RL, Cavenaghi Pereira da Silva M, Lizier NF, Kerkis A, Cerruti H, Kerkis I: Corneal reconstruction with tissue-engineered cell sheets composed of human immature dental pulp stem cells. *Invest Ophthalmol Vis Sci.* 2010 Mar;51(3):1408-14. doi: 10.1167/iovs.09-4029. Epub 2009 Nov 5.

Costa E, Quadrado MJ, Rosa A and Murta JN: A insuficiência límbica e os transplantes de limbo. In: *Superfície Ocular de SPO*, 2012.

There are ongoing industry-sponsored clinical trials on: Diabetic Retinopathy, Age-Related Macular Degeneration, Glaucoma, Retinal Vein

Occlusion, Ophthalmic Safety and Neurological Disorders.

DIABETIC RETINOPATHY

1. 3-year, phase 3, multicenter, masked, randomized, sham-controlled trial to assess the safety and efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) applicator system in the treatment of patients with diabetic macular edema (POSURDEX)

EudraCT n° 2004-004996-12

Sponsor: Allergan

2. A 2 year Randomized, single-masked, multicenter, controlled phase IIIb trial assessing the Efficacy and safety of 0.5 mg ranibizumab in two “treat and extend” Treatment algorithms vs. 0.5 mg ranibizumab as needed in patients with macular edema and visual impairment secondary to diabetes mellitus (RETAIN)

EudraCT n° 2010-019795-74

Sponsor: Novartis

3. A Multicenter, Open-label, Randomized Study Comparing the Efficacy and Safety of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) to Ranibizumab in Patients with Diabetic Macular Edema (POSURDEX)

EudraCT n° 2011-005631-20

Sponsor: Allergan

AGE-RELATED MACULAR DEGENERATION

4. A multicenter, patient-masked, safety extension study to evaluate the biodegradation of the brimonidine tartrate posterior segment drug delivery system (Brimo 33)

EudraCT n° 2010-019079-32

Sponsor: Allergan

5. The safety and efficacy of AL-8309B ophthalmic solution for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) (C-08-36)

EudraCT n° 2008-007706-37

Sponsor: Alcon

6. Investigational Observational Portuguese Project with Lucentis in Age Macular Degeneration (AMD) among 50 ophthalmologic Centers for 12 months (PICO)

Sponsor: Novartis

7. Safety and Efficacy Study of ESBA1008 versus LUCENTIS® for the Treatment of Exudative Age-Related Macular Degeneration (SEE)

EudraCT n° 2011-000536-28

Sponsor: Alcon

8. Study to observe the effectiveness and safety of ranibizumab through individualized patient treatment and associated outcomes (Luminous)

ClinicalTrials.gov n° NCT01318941

Sponsor: Novartis

9. A Retrospective non-interventional study to assess the effectiveness of existing anti-vascular endothelial growth factor (anti-VEGF) treatment regimens in patients with wet age-related macular degeneration (Review)

ClinicalTrials.gov n° NCT01447043

Sponsor: Bayer

GLAUCOMA

10. A phase III, randomized, double-masked 6-month clinical study to compare the efficacy and safety of the preservative-free fixed dose combination of tafluprost 0.0015% and timolol 0.5% eye drops to those of tafluprost 0.0015% and timolol 0.5% eye drops given concomitantly in patients with open angle glaucoma or ocular hypertension (N.201051)

EudraCT n° 2010-022984-36

Sponsor: Santen

11. Safety and IOP-Lowering Efficacy of Brinzolamide 10 mg/mL / Brimonidine 2 mg/mL Fixed Combination Eye Drops, Suspension compared to Brinzolamide 10 mg/mL Eye Drops, Suspension and Brimonidine 2 mg/mL Eye Drops, Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension (C-10-40)

EudraCT n° 2010-024512-34

Sponsor: Alcon

12. Prospective, Non-Interventional, Longitudinal Cohort Study to evaluate the long-term safety of XALATAN® Treatment in Pediatric Populations (Xalatan Pediatrico)

Sponsor: Pfizer

RETINAL VEIN OCCLUSION

13. A 24-month, phase IIIb, open-label, randomized, active-controlled, 3-arm, multicenter study assessing the efficacy and safety of an individualized, stabilization-criteria-driven PRN dosing regimen with 0.5mg ranibizumab intravitreal injections applied as monotherapy or with adjunctive laser photocoagulation in comparison to laser photocoagulation in patients with visual impairment due to macular edema secondary to branch vein occlusion (BRVO)

EudraCT n° 2011-002859-34

Sponsor: Novartis

14. A 24-month, phase IIIb, open-label, single arm, multicenter study assessing the efficacy and safety of an individualized, stabilization criteria-driven PRN dosing regimen with 0.5-mg ranibizumab intravitreal injections applied as monotherapy in patients with visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO)

EudraCT n° 2011-002350-31

Sponsor: Novartis

OPHTHALMIC SAFETY

15. Randomized, open label multi-center study comparing cabazitaxel at 25 mg/m² in combination with prednisone every 3 weeks to Docetaxel in combination with prednisone in patients with metastatic castration resistant prostate cancer not pre-treated with chemotherapy (Firstana)

EudraCT n° 2010-022064-12

Sponsor: Sanofi

16. Long term (3 years) ophthalmic safety and cardiac efficacy and safety of ivabradine administered at the therapeutic recommended doses (2.5/5/7.5 mg b.i.d.) on top of anti anginal background therapy, to patients with chronic stable angina pectoris. An international, double-blind placebo controlled study (Ivabradina)

EudraCT n° 2006-005475-17

Sponsor: Servier

17. A single arm, open-label, multicenter study evaluating the long-term safety and tolerability of 0.5mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis (FTY 720 2399)

EudraCT n° 2010-020515-37

Sponsor: Novartis

NEUROLOGICAL DISORDERS

18. A Multi-Center, Open-Label Extension Study to Examine the Safety and Tolerability of ACP-103 in the Treatment of Psychosis in Parkinson's Disease

EudraCT n° 2007-003035-22

Sponsor: Acadia

19. Efficacy and safety of Eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, double-dummy, randomized, active-controlled, parallel-group, multicenter clinical study

EudraCT n° 2009-011135-13

Sponsor: Bial

20. Efficacy and safety of BIA 9-1067 in idiopathic Parkinson's disease patients with "wearing-off" phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomised, placebo and active-controlled, parallel-group, multicentre clinical study.

EudraCT n° 2010-021860-13

Sponsor: Bial

21. A multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the effect on cognitive performance, safety, and tolerability of SAR110894D at the doses of 0.5 mg, 2 mg, and 5 mg/day for 24 weeks in patients with mild to moderate Alzheimer's Disease on stable donepezil therapy.

EudraCT n° 2010-022596-64

Sponsor: Sanofi

22. A Phase 3, 12-Week, Double-Blind, Double-Dummy, Placebo- and Active-Controlled Efficacy and Safety Study of Preladenant in Subjects with Moderate to Severe Parkinson's Disease

EudraCT n° 2009-015161-31

Sponsor: Shering-Plough

23. A multicenter, double-blind, double-dummy, randomized, positive-controlled study comparing the efficacy and safety of lacosamide (200 to 600 mg/day) to controlled release carbamazepine (400 to 1200 mg/day), used as monotherapy in subjects (f116 years) newly or recently diagnosed with epilepsy and experiencing partial-onset or generalized tonic-clonic seizures.

EudraCT n° 2010-019765-28

Sponsor: UCB

24. A Phase 3, 40-Week, Active-Controlled, Double-Blind, Double Dummy Extension Study of Preladenant in Subjects with Moderate to Severe Parkinson's Disease.

EudraCT n° 2009-015162-57

Sponsor: Schering-Plough

25. Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) versus placebo in patients with mild to moderate Alzheimer's disease. A 24-week international, multicentre, randomised, double blind, placebo-controlled phase IIB study followed by a 24-week extension period.

EudraCT n° 2010-024626-37

Sponsor: Servier

26. A multicenter, double-blind, double-dummy, follow-up study evaluating the long-term safety of lacosamide (200 to 600mg/day) in comparison with carbamazepine (400 to 1200mg/day), used as monotherapy in subjects with partial-onset or generalized tonic-clonic seizures f116 years of age coming from the SP0993 study.

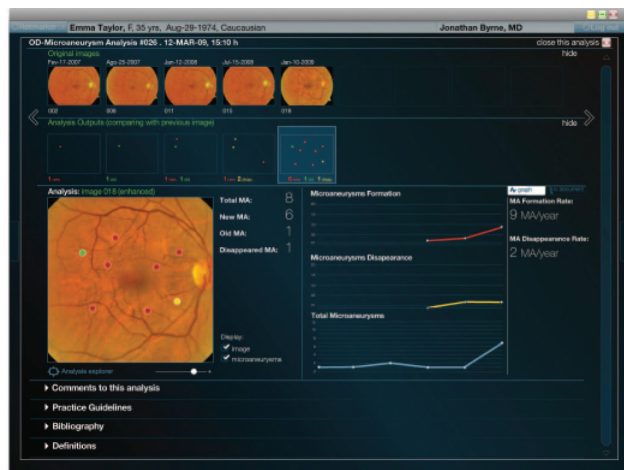
EudraCT n° 2010-021238-74

Sponsor: UCB

27. Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) versus placebo, in co-administration with donepezil (10 mg/day) in patients with moderate Alzheimer's Disease. A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIB study.

EudraCT n° 2011-005862-40

Sponsor: Servier



Diagnostic Imaging through the Eye

C

RESEARCH PROGRAMMES IN VISION AND IMAGING

The eye offers unique opportunities to obtain in a non-invasive manner information on the body, in general, and of the brain in particular. The retinal circulation and the retina can be examined using a variety of methods. Our research group has focused on development of new imaging techniques of the eye fundus without disturbing in any way the ocular and body environment. We are particularly interested in methodologies that allow repeated observations and measurements in order to identify early alterations and the degree of activity of these alterations when present over time. Fundus Digital Photography and Optical Coherence Tomography are non-invasive examinations

that offer extremely promising perspectives as the information collected can be analysed automatically. The analysis of the data can also be tailored to specific purposes, allowing validating imaging biomarkers of disease. These imaging biomarkers may give information on retinal and eye disease but also may serve as indicators of systemic disease, such as brain degenerative diseases and circulatory disorders. Our group has been able to identify biomarkers of disease progression, such as microaneurysm turnover in diabetic retinopathy identified automatically by software developed in house, the Retmarker®, and quantify changes in the blood-retinal barrier and inner retinal layers.

PATENTS AND PRODUCTS

1. Retmarker®

Partner: Critical Health, Portugal

Retmarker® is a software that provides information to monitor the progression of retinal diseases, which are the leading causes of blindness in the Western world. Monitoring of progression of retinal diseases is much needed to gather information to support diagnosis, definition of treatment strategies and to evaluate the treatment's effectiveness.

The RetmarkerC® is a innovative software solution that uses image processing technology and the latest medical research to deliver a product that detects retinal changes automatically, effectively and effortlessly.

The RetmarkerDR® is a software solution for predicting Diabetic Retinopathy (DR) progression from its Nonproliferative stage to Clinically Significant Macular Edema (CSME), a sight-threatening stage.

The RetmarkerAMD® Research is a software solution for the assisted grading of retinographies from patients with Age-Related Macular Degeneration (AMD).

Product available / More information:
www.retmarker.com

2. Ocular Fluorometer

Partner: OverPharma, Portugal

Measurement of fluorescence in the cornea, aqueous, lens and anterior vitreous. It is used to measure natural autofluorescence of these sites of the eye and to measure the penetration of fluorescein into the aqueous after local or systemic administration.

C1

FUNCTIONAL IMAGING WITH OPTICAL COHERENCE TOMOGRAPHY

Rui Bernardes, PhD

Other Research Personnel: Ana Rita Santos, António Correia, Conceição Lobo, Dan Brudzewsky, Francisco Ambrósio, Francisco Caramelo, José Cunha-Vaz, Luís Pinto, Miguel Morgado, Paulo Menezes, Pedro Guimarães, Pedro Rodrigues, Pedro Serranho, Pedro Tralhão, Sílvia Barbeiro, Torcato Santos



Contacts

Rui Bernardes, PhD

Phone: +351 239 480 108

E-mail: rcb@aibili.pt

Changes in the permeability of the Blood-Retinal Barrier (BRB) have a major impact in disease process of the retina and have major relevance for systemic drug delivery to the retina. Any alteration of the BRB implies a change on the optical characteristics of the retina as an increase in the permeability of the BRB allows an abnormal influx of substances from the blood to the retina. The high sensitivity of the Optical Coherence Tomography (OCT) to refractive index changes allows to detect these changes in a very sensitive manner. Functional imaging of

the retina, in vivo and non-invasively, is, therefore, possible. This rationale is being explored in several research projects such as non-invasive assessment of the BRB and characterization of neuronal degeneration/ageing of retina as an extension of the brain in age-related diseases. Our group has already demonstrated the possibility to discriminate between different age groups, solely based on OCT data of the human macula. It thus suggests the possibility that OCT embeds information on the central nervous system ageing process.

PROJECTS

Development and clinical applications of a system with adaptive optics for ocular tomography and high-resolution retinal imaging

Financial Support: Foundation for Science and Technology, Portugal - PTDC/SAU-BEB/72220/2006

Evaluation of blood-retinal barrier alterations using non-invasive optical coherence tomography

ClinicalTrials.gov n° NCT01220804

Financial Support: Foundation for Science and Technology, Portugal - PTDC/SAU-BEB/103151/2008

Optical Modelling of the Human Retina in Health and Disease: from structure to function

Financial Support: Foundation for Science and Technology, Portugal - PTDC/SAU-ENB/119132/2010

Determination of retinal changes in brain degenerative diseases

Financial Support: This project assembles data and developments made under a set of research projects, namely the PTDC/SAU-BEB/103151/2008, the PTDC/SAU-ENB/11139/2009 and the PTDC/SAU-ENB/119132/2010 of the Foundation for Science

SELECTED PUBLICATIONS

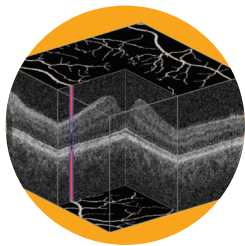
Rodrigues, P. & Bernardes, R. 3D Adaptive Nonlinear Complex-Diffusion Despeckling Filter IEEE Trans Med Imaging, 2012, 31, 2205-2212.

Bernardes, R. & Cunha-Vaz, J. Bernardes, R. & Cunha-Vaz, J. (Eds.) Optical Coherence Tomography: A Clinical and Technical Update Evaluation of the Blood-Retinal Barrier with Optical Coherence Tomography Springer, 2012, 157-174.

Bernardes, R.; Santos, T.; Serranho, P.; Lobo, C. & Cunha-Vaz, J. Noninvasive Evaluation of Retinal Leakage Using Optical Coherence Tomography Ophthalmologica, 2011, 226, 29-36.

Bernardes, R.; Maduro, C.; Serranho, P.; Araújo, A.; Barbeiro, S. & Cunha-Vaz, J. Improved adaptive complex diffusion despeckling filter. Opt. Express, OSA, 2010, 18, 24048-24059.

Bernardes, R.; Dias, J. & Cunha-Vaz, J. Mapping the human blood-retinal barrier function IEEE Trans Biomed Eng, 2005, 52, 106-116.



STRUCTURAL IMAGING OF THE RETINA WITH OPTICAL COHERENCE TOMOGRAPHY

C2

Pedro Serranho, PhD

Other Research Personnel: Ana Rita Santos, João Figueira, Pedro Guimarães, Pedro Rodrigues, Rui Bernardes, Sílvia Simão, Torcato Santos

We followed an original approach towards the segmentation of the human retina and to the reconstruction the vascular network of the human retina in 3D. This reconstruction will play a major role in the localization and quantification of the focal areas of ischemia that characterize diabetic retinopathy and other retinal vascular diseases. It is now possible to demonstrate perfused and non-perfused vessels in an

automated way without the need for injection of contrast material.

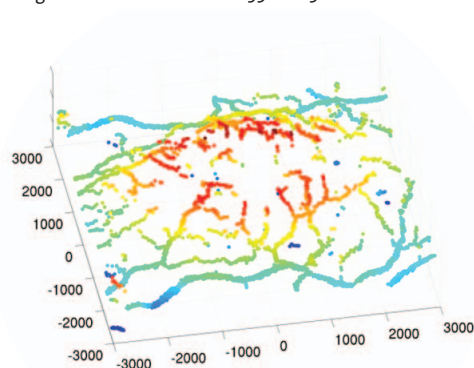
From the structural information provided by the Optical Coherence Tomography (OCT) data, and through automated classification systems, we have derived a method that is capable of identifying the fellow eyes of patients with idiopathic macular holes which are at increased risk for macular hole formation.



PROJECTS

3D retinal vascular network from Optical Coherence Tomography data

Financial Support: Foundation for Science and Technology, Portugal - PTDC/SAU-ENB/111139/2009



SELECTED PUBLICATIONS

Serranho, P. A hybrid method for inverse scattering for sound-soft obstacles in R_3 . *Inverse Probl. Imaging*, 2007, 1, 709-730.

Ivanyshyn, O.; Kress, R. & Serranho, P. Huygens' principle and iterative methods in inverse obstacle scattering. *Adv Comput Math*, 2010, 33, 413-429.

Serranho, P.; Maduro, C.; Santos, T.; Cunha-Vaz, J. & Bernardes, R. Synthetic OCT data for image processing performance testing Proc. of 18th IEEE International Conference on Image Processing (ICIP), 2011, 409-412.

Guimarães, P.; Rodrigues, P.; Serranho, P. & Bernardes, R. 3D Retinal Vascular Network from Optical Coherence Tomography Data Image Analysis and Recognition, Lecture Notes in Computer Science. *Image Analysis and Recognition*, Springer Berlin/Heidelberg, 2012, 7325, 339-346.

Serranho, P.; Guimarães, P.; Rodrigues, P. & Bernardes, R. On the relevance of the 3D retinal vascular network from OCT data, *Biometrical Letters*, 2012, 49(2), 95-102.

Contacts

Pedro Serranho, PhD

Phone: +351 239 480 108

E-mail: pedro.serranho@uab.pt

AUTOMATED ANALYSIS OF DIGITAL FUNDUS PHOTOGRAPHS OF THE HUMAN MACULA

Luísa Ribeiro, MD, MSc

Other Research Personnel: Ana Rita Santos, Catarina Neves, João Figueira, José Cunha-Vaz, Rufino Silva, Conceição Lobo, Rui Bernardes, Sandrina Nunes, Torcato Santos, Pedro Melo, Sílvia Simão



Contacts

Luísa Ribeiro, MD, MSc
Phone: +351 239 480 128
E-mail: lr@aibili.pt

Diabetic retinopathy and age-related macular degeneration are chronic retinal diseases that may eventually progress to develop sight-threatening complications and even blindness. Our group has shown that the evolution and progression of these diseases vary between different individuals.

It is, therefore, of fundamental importance to monitor the progression of the disease in an individual patient and identify the patients that are “progrisors”, i. e, showing signs of rapid disease progression. We have introduced the concept of velocity of progression in retinal disease management. Using fundus digital photography, a simple, non-invasive examination, our group has developed the RetmarkerDR[®], a new

methodology of automated analysis capable of identifying changes occurring in the eye fundus, by comparing successive visits to the reference image based on co-registration and exact co-localization of the changes.

The methodologies developed by our group opened also new perspectives for improved screening of diabetic retinopathy working together with the Coimbra Ophthalmology Reading Centre who is responsible for the Diabetic Retinopathy Screening Program in the Central Region of Portugal.

Methods for reliable measurement of retinal vascular diameter are also being developed as promising tools to identify risk of stroke and cardiovascular disease.

PROJECTS

Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures
ClinicalTrials.gov n° NCT01145599

Protocol n° ECR-RET-2010-02

Participating Centres (19): Amsterdam, Antwerp, Barcelona, Bonn, Coimbra, Glostrup, Leipzig, Lisbon, London (2), Milan, Padova, Paris (3), Valência, Rome, Rotherdam, Surrey.

EUROCONDOR – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy

EudraCT Number: 2012-001200-38

ClinicalTrials.gov n° NCT01726075

Participating Centres (11): Barcelona, Birmingham, Cheltenham, Coimbra, Liverpool, London, Milan, Odense, Padova, Paris, Ulm.

Financial Support: European Union 7th Framework Programme – Call Health 2011 - Project n° 278040-2

C-TRACER Project n° 1 - Biomarkers of Diabetic Retinopathy Progression

ClinicalTrials.gov n° NCT01607190

Protocol n° 4C-2012-02

Participating Centres (2): Coimbra, Hyderabad (India).

Grant: Champalimaud Foundation

Diabetic Retinopathy Screening – Central Region of Portugal

Coordination: Helder Ferreira (ARSC)

Financial Support: Health Administration of Central Region of Portugal (ARS Centro).

SELECTED PUBLICATIONS

Bernardes R, Nunes S, Pereira I, Torrent T, Rosa A, Coelho D, Cunha-Vaz J: Computer-Assisted Microaneurysm Turnover in the Early Stages of Diabetic Retinopathy. *Ophthalmologica* 2009; 223:284-291.

Nunes S, Pires I, Rosa A, Duarte L, Bernardes R, Cunha-Vaz J: Microaneurysm Turnover is a Biomarker for Diabetic Retinopathy Progression to Clinically Significant Macular Edema: Findings for Type 2 Diabetics with Nonproliferative Retinopathy. *Ophthalmologica* 2009; 223:292-297.

Oliveira CM, Cristovao LM, Ribeiro ML, Faria Abreu J: Improved Automated Screening of Diabetic Retinopathy. *Ophthalmologica* 2011;226(4)191-197.

Ribeiro L, Nunes S, Cunha-Vaz J: Microaneurysm Turnover in the Macula is a Biomarker for Development of Clinically Significant Macular Edema in Type 2 Diabetes. *Current Biomarkers Findings* 2013;3 11-15.

Ribeiro L, Cunha-Vaz J.: Surrogate Outcomes for Progression in The Initial Stages of Diabetic Retinopathy. *Immun., Endoc. and Metab. Agents in Med. Chem.*, 2013, 13, 25-34.

D

Pre-Clinical Research – Associate Unit

RESEARCH PROGRAMMES IN VISION AND IMAGING

Retinal degenerative diseases affect millions of patients worldwide. In the last decade, basic and clinical scientific research gathered a huge amount of data that allowed better insight into the pathogenesis of these diseases, at both molecular and cellular level. Despite these advances, and the identification of potential therapeutic targets and a few biomarkers, the translation of this knowledge into effective treatments for patients suffering from retinal degenerative diseases is still limited. Therefore, efforts aimed at identifying new therapeutic targets and new therapeutic modalities are clearly needed.

In our research, we have focused in the pathogenesis of two retinal degenerative diseases: diabetic retinopathy and glaucoma. Regarding diabetic retinopathy, we have been interested in understanding both blood-retinal barrier dysfunction and neural dysfunction and degeneration. In glaucoma research our main goal is the neuroprotection of retinal ganglion cells. In fact, neuroprotection can be also viewed as an additional therapy in diabetic retinopathy. Moreover, it has been proved that neuroinflammation has a key role in the pathogenesis of both diseases, and the development of therapies targeting neuroinflammatory processes can be also considered.

Regarding potential targets, we have been interested in three neurotransmitter systems, namely neuropeptide Y, adenosine and endocannabinoids.

To achieve our goals we have developed several *in vitro* models, such as primary mixed retinal cultures, primary microglial retinal cultures, cultured retinal explants, and endothelial and microglial cell lines, as well as several animal models: type 1 diabetes animal model (streptozotocin model), elevated intraocular pressure models (episcleral vein cauterization model and microbeads model), ischemia-reperfusion model and excitotoxic models (intravitreal injection of excitotoxic drugs). In our studies, we use biochemistry and cell and molecular biology techniques, bioimaging (fluorescence and confocal microscopy), as well as functional observations including ocular coherence tomography and electrophysiology and visual evoked potentials.

D1

DIABETIC RETINOPATHY

Francisco Ambrósio, PhD

Other Research Personnel: Andreia Gonçalves, Dan Brudzewsky, João Martins, Maria Madeira, Raquel Santiago, Rosa Fernandes, Tiago Martins



Contacts

Francisco Ambrósio, PhD
Phone: +351 239 480 093
E-mail: afambrosio@fmed.uc.pt

Diabetic Retinopathy is a leading cause of vision loss and blindness worldwide in working age adults. Despite being considered a microvascular disease, evidence gathered during the last 15 years clearly indicates that the neural components of the retina are also affected by diabetes. Moreover, it has been claimed that inflammation plays a critical role in the pathogenesis and progression of the disease, which may affect both blood-retinal barrier and neural components. Despite recent advances in the treatment of diabetic retinopathy, these are still not very effective and are directed to the later stages of the disease. Taking this into account, the development of new treatments for diabetic retinopathy is needed. We have been investigating the molecular and cellular mechanisms underlying the pathogen-

esis of diabetic retinopathy, namely the mechanisms underlying endothelial, glial and neuronal cell dysfunction/death. We have identified potential molecular targets involved in inflammatory processes in the diabetic retina, namely the inducible nitric oxide synthase (iNOS) and the atypical protein kinase C isoforms. Our ultimate goal is to identify potential therapies targeted for the early stages of the disease, aiming to prevent or delay the blood-retinal barrier breakdown and neurodegenerative processes. Presently, we are testing the NPY system as a potential therapeutic target for the treatment of diabetic retinopathy, and also evaluating if inhibitors of dipeptidyl-peptidase IV have potential for the treatment of this disease, independent of their known effects on glycemic control.

PROJECTS

Neuropeptide Y system: a new potential therapeutic target in diabetic retinopathy

Financial Support: Foundation for Science and Technology, Portugal - PTDC/NEU-OSD/1113/2012

SELECTED PUBLICATIONS

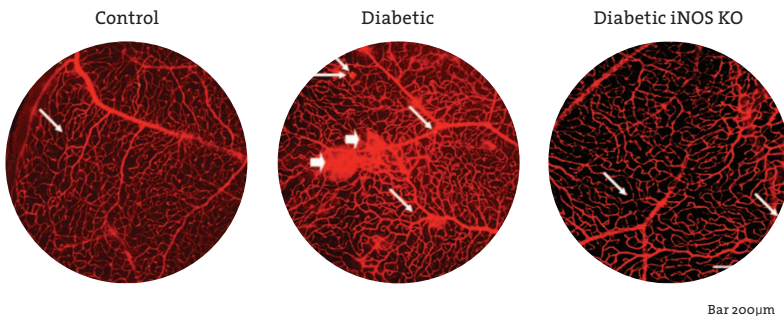
E.C. Leal, A. Manivannan, K.-I. Hosoya, T. Terasaki, J. Cunha-Vaz, A.F. Ambrósio and J.V. Forrester. Inducible nitric oxide synthase isoform is a key mediator of leukostasis and blood-retinal barrier breakdown in diabetic retinopathy. *Invest. Ophthalmol. Vis. Sci.* 2007, 48:5257-5265.

E.C. Leal, J. Martins, J. Liberal, P. Voabil; C. Chiavaroli, J. Bauer, J. Cunha-Vaz and A.F. Ambrósio. Calcium dobesilate inhibits the alterations in tight junction proteins and leukocyte adhesion to retinal endothelial cells induced by diabetes. *Diabetes* 2010, 59:2637-2645.

C.A. Avelaira, C.-M. Lin, S.F. Abcouwer, A.F. Ambrósio and D.A. Antonetti. TNF- α signals through PKC ζ /NF- κ B to alter the tight junction complex and increase retinal endothelial cell permeability. *Diabetes* 2010, 59:2872-2882.

G.N. Costa, J. Vindeirinho, C. Cavadas, A.F. Ambrósio and P.F. Santos. Contribution of TNF receptor 1 to retinal neural cell death induced by elevated glucose. *Mol Cell Neurosci.* 2012, 50: 113-123.

A. Castilho, C. A. Avelaira, E. C. Leal, N. F. Simões, C. R. Fernandes, R. I. Meirinhos, F. I. Baptista and A.F. Ambrósio. Heme oxygenase-1 protects retinal endothelial cells against high glucose- and oxidative/nitrosative stress-induced toxicity *PLoS One.* 2012;7(8):e42428. Epub 2012 Aug 3.



Nitric oxide, originated from the inducible nitric oxide synthase isoform, mediates the increase in leukostasis and blood-retinal barrier permeability.

GLAUCOMA

Ana Raquel Santiago, PhD

Other Research Personnel: Dan Brudzewsky, Francisco Ambrósio, Joana Galvão, Joana Martins, João Martins, Maria Madeira, Pedro Tralhão, Raquel Bóia, Tiago Martins

D2

Glaucoma is a progressive and non-curable retinal degenerative disease and is the second cause of blindness worldwide, affecting approximately 70 million people. The disease is characterized by retinal ganglion cell degeneration and optic nerve damage. Elevated intraocular pressure (IOP) is considered a major risk factor for glaucoma and treatments are mainly focused on decreasing IOP. However, despite good IOP control, the disease still progresses. Therefore, other therapies are needed, and neuroprotection has been claimed to offer potential as a complementary therapy to save retinal ganglion cells. Chronic neuroinflammation has

been also considered to be involved in the pathogenesis of glaucoma, and its prevention might be an additional strategy to rescue retinal ganglion cells. Using *in vitro* and animal models we have been testing the potential neuroprotective effects against retinal ganglion cells degeneration due to the manipulation of several neurotransmitter systems: neuropeptide Y, adenosine and endocannabinoids. These systems offer potential for neuroprotection and can also exert anti-inflammatory effects. Endocannabinoids are also able to decrease the IOP. The ultimate goal is to find new molecular targets that can be translated into new therapies to treat glaucoma.



Contacts

Ana Raquel Santiago,
PhD

Phone: +351 239 480 226

E-mail: asantiago@fmed.uc.pt

SELECTED PUBLICATIONS

A.R. Santiago, M.J. Garrido, P.F. Santos, A.J. Cristóvão and A.F. Ambrósio. High glucose and diabetes increase the release of [³H]-D-aspartate in retinal cell cultures and in rat retinas. *Neurochem. Int.* 2006, 48:453-458.

A.R. Santiago, S.C. Rosa, P.F. Santos, A.J. Cristóvão, A.J. Barber and A.F. Ambrósio. Elevated glucose changes the expression of ionotropic glutamate receptor subunits and impairs calcium homeostasis in retinal neural cells. *Invest. Ophthalmol. Vis. Sci.* 2006, 47:4130-4137.

A.R. Santiago, A.J. Cristóvão, P.F. Santos, C.M. Carvalho and A.F. Ambrósio. High glucose induces caspase-independent cell death in retinal neural cells. *Neurobiol. Dis.* 2007, 25:464-472.

A.R. Santiago, J.M. Hughes, W. Kamphuis, R.O. Schlingemann and A.F. Ambrósio. Diabetes changes ionotropic glutamate receptor subunit expression level in the human retina. *Brain Res.* 2008, 1198:153-9.

A.R. Santiago, J.M. Gaspar, F.I. Baptista, A.J. Cristóvão, P.F. Santos, W. Kamphuis and A.F. Ambrósio. Diabetes changes the levels of ionotropic glutamate receptors in the rat retina. *Mol. Vis.* 2009, 15:1620-1630.

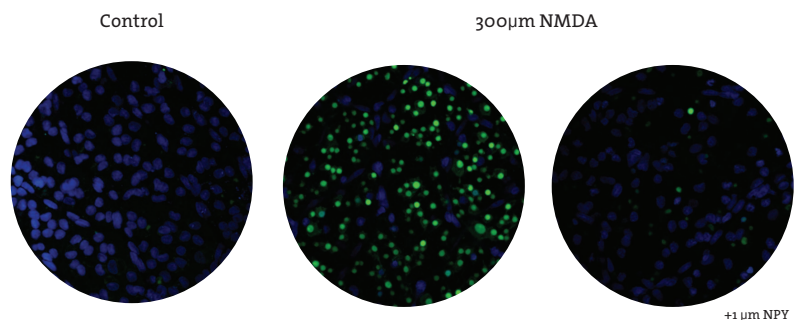
RESEARCH CONTRACTS

Endocannabinoid Inhibitors: evaluation of their potential to reduce intraocular pressure
Sponsor: BIAL, Portugal

PROJECTS

Life and death of retinal ganglion cells: unmasking the neuromodulatory and neuroprotective roles of Neuropeptide Y
Financial Support: Foundation for Science and Technology, Portugal - PTDC/SAU-NEU/99075/2008

From neuroinflammation control to neuroprotection: blocking adenosine A_{2A} receptor for the treatment of glaucoma
Financial Support: Foundation for Science and Technology, Portugal - PTDC/BIM-MEC/0913/2012



Neuropeptide Y exerts a potent neuroprotective effect against excitotoxicity-induced apoptosis (evaluated by TUNEL assay) in the ganglion cell layer in cultured retinal explants.

4

CHAMPALIMAUD TRANSLATIONAL CENTRE FOR EYE RESEARCH – C-TRACER 2

AIBILI was recognized in 2010 as a Champalimaud Translational Centre for Eye Research (C-TRACER) by the Champalimaud Foundation for its activities in translational eye research. The work of AIBILI and particularly of the Coimbra Coordinating Centre for Clinical Research in the coordination of the European Vision Institute Clinical Research Network (EVICR.net) were very relevant for this recognition.

The Champalimaud Foundation has been progressively establishing a Network of C-TRACERs involving major eye research centres looking for collaborations in a global perspective to improve patient eye care worldwide.

This Network is of great relevance to AIBILI because it brings together under the Champalimaud Foundation three major eye research institutions in the world and creates links between three major continents, Asia, Europe and South America.

AIBILI is C-TRACER 2 in the C-TRACERs Network. It brings together the LV Prasad Eye Institute in Hyderabad, India, C-TRACER 1, and the Institute for Vision at the Federal University of S. Paulo at S. Paulo, Brazil, C-TRACER 3.

The research of the C-TRACERs Network is at present, focused on identification of biomarkers of disease progression with particular impact on the prevention and personalized management of diabetic retinopathy, one of the major causes of vision loss, and on the use of stem-cells in the repair of corneal and retinal diseases. New methodologies of stem-cell preparation and conditioning developed at C-TRACER 1, LV Prasad Eye Institute, are expected to contribute to more efficient corneal repair in situations of previously irreversible vision loss.

The first multinational project funded by the Champalimaud Foundation within the C-TRACERs Network is focused on the characterization of different phenotypes of progression of diabetic retinopathy using the RetmarkerDR® developed at C-TRACER 2, AIBILI. It is expected to predict the individual cases that are at risk to develop clinically significant macular edema. This approach will contribute to establish personalized management of diabetic retinopathy and will also reduce the costs involved in the treatment of diabetes.

Another areas of major relevance are the development of stem cells to treat anterior segment and retinal disorders and the development of teleophthalmology using automated image analysis and centralized reading centres creating the conditions for more efficient ophthalmological care and making it possible to reach isolated/inaccessible populations/communities. Improved access to expert eye care and strategies of mass screening are goals of the C-TRACERs Network to translate their research activities into clinical practice always taking into account patient needs and contributing to improved health care at reduced costs.

PROJECTS

C-TRACER Project nº 1 - Biomarkers of Diabetic Retinopathy Progression

ClinicalTrials.gov nº NCT01607190

Protocol nº 4C-2012-02

Participating Centres (2): Coimbra, Hyderabad (India).

Grant: Champalimaud Foundation

C-TRACER Project - Use of stem-cells in the repair of corneal and retinal diseases

Participating Centres (3): Coimbra, Hyderabad (India), S. Paulo (Brazil).

Champalimaud Foundation

STRUCTURAL UNITS

5

Contacts

Cecília Martinho,
BSc Econ

Phone: +351 239 480 100

E-mail: cvm@aibili.pt

5.1 ADMINISTRATIVE SERVICES

Staff: Cecília Martinho, Paulo Barros, Élia Gomes, Sónia Simões, Maria do Céu Fidalgo, Marco Santos

The Administrative Services is responsible for the management of AIBILI and to perform all the administrative tasks, including finances and accountability, human resources manage-

ment, as well as maintenance of infrastructure. The Administrative Services establishes a direct liaison between the Board of Directors of AIBILI and its Centres.

5.2 QUALITY MANAGEMENT

Staff: Cecília Martinho, Rita Fernandes, Teresa Morgadinho

AIBILI is certified by ISO 9001 for the activities of: research and development in new technologies for medicine with particular emphasis in the areas of imaging, optics and light; preclinical studies of new molecules of potential medical use; performance of clinical trials; clinical pharmacology studies; planning, coordination, execution and monitoring of clinical research activities and health technology assessment.

AIBILI has a Quality Manual stating its quality management system, that it has the necessary resources to provide the services and meet the needs and expectations of our clients.

It has a Standard Operating Procedure (SOP) Manual which contains general organizational SOPs and specific SOPs for each process, in compliance with ISO 9001, ICH GCP - Good Clinical Practice Guidelines, OECD Principles of GLP - Good Laboratory Practice and national legislation.

The Quality Management Unit aims to assure that the quality management system is maintained effective and efficient permitting a continual improvement and that data obtained in AIBILI is valid and reliable.

Internal auditing is a guarantee that quality procedures are followed at AIBILI.

Contacts

Rita Sousa Fernandes,
BSc

Phone: +351 239 480 101

E-mail: anarf@aibili.pt

5.3 TRANSLATIONAL RESEARCH AND TECHNOLOGY TRANSFER

Staff: Daniel Fernandes

The Translational Research and Technology Transfer Unit is responsible to provide all the administrative support to facilitate and promote the transfer of R&D activities and preclinical studies, to the development of clinical trials and to enhance the adoptions of best practices in the community. This Unit is responsible to identify and apply for external funding, namely R&D programs for the health market. It is responsible also for promoting AIBILI and the activities of its Centres.

This Unit collaborates closely with the Technology Transfer Office of the Coimbra University (DITS) and with the Knowledge Valorization and Innovation Department of the Instituto Pedro Nunes (IPN).

AIBILI participates with the Instituto Pedro Nunes and the Universities of Coimbra, Aveiro and Beira Interior in a project called DHMS under the QREN Program that aims to enhance synergies between the various players in the Centre Region in the area of the healthcare and medical solutions.

More information: <http://dhms.ipn.pt/>

AIBILI is member of the Health Cluster Portugal (HCP) which main objective is the promotion and implementation of initiatives and activities leading to the consolidation of a national cluster for competitiveness, innovation and technology in the health area.

More information: <http://healthportugal.com/>

Contacts

Daniel Sanches Fernandes,
BSc

Phone: +351 239 480 116

E-mail: danielsf@aibili.pt

Contacts

Torcato Santos, BSc

Phone: +351 239 480 108

E-mail: torcato@aibili.pt

5.4 INFORMATION TECHNOLOGY

Staff: Joana Ecsodi, Rui Bernardes, Telmo Miranda, Torcato Santos, José Monteiro

AIBILI has an Information Technology Unit responsible to guarantee the safety and integrity of the data and images collected all in compliance with GCP Guidelines and applicable national legislation.

The Information Technology Unit is responsible for the management/maintenance of the electronic medical records of the Clinical trial Centre that is daily used to collect patient data as well as for the management and maintenance of the platform of the Coimbra Ophthalmology Reading Centre used to exchange data and images for central grading.

It is also responsible for the management and maintenance of the Coimbra Coordinating Centre for Clinical Research Data Center when developing CRF Databases for clinical trials. This Unit is also applying for Data Centre Certification in 2013 by ECRIN - European Clinical Research Infrastructure Network.

All AIBILI intranet, management and maintenance are guaranteed by the IT Unit.

EDUCATION, TRAINING, MEETINGS

6

JUNE, 28TH

2ND ANNUAL COIMBRA CHAMPALIMAUD SYMPOSIUM

Opening words by the Champalimaud Foundation

Leonor Beza (Champalimaud Foundation, Lisbon, Portugal)

Diabetic Retinopathy Clinical Research Network (DRCR.net)

Neil Bressler (Johns Hopkins University, Baltimore, USA)

European Vision Institute Clinical Research Network (EVICR.net)

Cecília Martinho (AIBILI)

Developments of Fundus Imaging at AIBILI

José Cunha-Vaz (AIBILI)

C-TRACER Project n° 1 – AIBILI

Luisa Ribeiro (AIBILI)

C-TRACER Project n° 1 – LV Prasad

Ajit Babu Majji (LV Prasad Eye Institute, Hyderabad, India)

Update on our stem cellwork

D. Balasubramanian (LV Prasad Eye Institute, Hyderabad, India)

Current perspectives of stem cell transplantation

Esmeralda Costa (CHUC – Faculty of Medicine, Coimbra, Portugal)

UT DSAEK. How thin should we go

Maria João Quadrado (CHUC – Faculty of Medicine, Coimbra, Portugal)

Perspectives for a Teleophthalmology collaboration

Michel Eid Farah (IPEPO, S. Paulo, Brasil)

Financial Support: Champalimaud Foundation

NOVEMBER, 16TH

INVESTIGATOR DRIVEN CLINICAL TRIALS. RELEVANCE OF NEW STRUCTURES IN PORTUGAL

Investigator-Driven Clinical Trials in Portugal – Researchers' Perspective

Rufino Silva (CHUC / AIBILI)

Hugo Prazeres (IPO, Coimbra, Portugal)

Academic CRO – Logistic Support

Sandrina Nunes (AIBILI)

EVICR.net – Disease-Oriented Network

Cecília Martinho (EVICR.net)

PtCRIN – Portuguese Representation of ECRIN Network

Pedro Caetano (Univ. Nova, Lisbon, Portugal)

PNEC – National Platform for Clinical Trials

Ana Isabel Severiano (INFARMED, Lisbon, Portugal)

Financial Support: Bayer

NOVEMBER, 30TH

NEW TECHNOLOGIES IN MEDICAL IMAGING

Vascular Network of the Human Macula from Optical Coherence Tomography

Pedro Rodrigues (AIBILI)

3D Blood Vessels Segmentation from Optical Coherence Tomography

Pedro Guimarães (AIBILI)

Correlation phenotype / genotype in Diabetic Retinopathy

Conceição Lobo (AIBILI)

Adelphic eyes of macular holes

João Figueira (AIBILI)

7

ETHICS COMMITTEE

Contacts

Maria do Céu Fidalgo

Phone: +351 239 480 100

E-mail: secsa@aibili.pt

AIBILI has an Independent Ethics Committee (IEC/IRB) that is responsible to protect the rights, safety and wellbeing of human subjects involved in observational studies performed at AIBILI.

Regarding observational studies the AIBILI Ethics Committee has reviewed and approved five studies in ophthalmology to be performed in AIBILI.

Regarding interventional clinical trials, which are reviewed by the National Ethics Commit-

tee for Clinical Research (CEIC), the IEC/IRB of AIBILI was informed of the approval of eight new interventional clinical trials, four in the area of ophthalmology, three in neurology and one in Bioavailability/Bioequivalence before they started at AIBILI as well as on the already ongoing interventional clinical trials.

AIBILI Ethics Committee is available to be called upon CEIC request, in case it is needed for the review of ophthalmology clinical trials since it has expertise in this scientific area.

MEMBERS

President

Francisco Manuel Corte-Real Gonçalves, MD, PhD
(Vice-President of the National Institute of Forensic Medicine and Professor at the Faculty of Medicine, University of Coimbra)

Vice-President

André Dias Pereira, BSc
(Investigator and Scientific Secretary at the Centre for Biomedical Law of the University of Coimbra and Assistant Professor at the Faculty of Law, University of Coimbra)

Secretary

Margarida Caramona, PhD
(Director of the Pharmacology Laboratory and Professor at the Faculty of Pharmacy, University of Coimbra)

Members

José Rui Faria de Abreu, MD, PhD
(Ophthalmologist at the University Hospital of Coimbra)

Maria Elizabete Batista Geraldês, MD
(Endocrinologist at the University Hospital of Coimbra)

Jorge António Lopes Feio, BSc
(Hospital Pharmacist at the University Hospital of Coimbra and Assistant Professor at the Faculty of Pharmacy, University of Coimbra)

Filomena Maria Ferreira Ramos Mena
(Nurse at the National Institute of Forensic Medicine)

PARTNERSHIPS

8

VICT – VISION AND IMAGING CONSORTIUM FOR TRANSLATIONAL RESEARCH

A Vision and Imaging Consortium for Translational Research (VICT) is in the process of being created bringing together the following institutions: IBILI - Institute for Biomedical Imaging and Life Sciences of the Faculty of Medicine, AIBILI - Association for Innovation and Biomedical Research on Light and Image, ICNAS - Institute for Nuclear Sciences Applied to Health, and CRIO - University Clinic of Ophthalmology of the Coimbra University Hospital.

The VICT aggregates institutions covering the entire translational process in Vision and Imaging, from the molecular development to clinical practice and patient care.

The VICT has complementary areas of competence in each of the four members of the consortium:

- 1. IBILI** offers laboratory research and experimental development in vision and imaging areas, from cell to tissue and organism level (animal and human). IBILI has expertise on basic molecular processes underlying visual disorders, as well as on pharmacology and experimental therapeutics, with the main goal of identifying potential molecular targets to treat diseases of vision. To achieve these goals, forefront engineering and imaging techniques are also being used to study vision and brain in health and disease. Collaborations with industry in pre-clinical studies in the area of visual sciences have been conducted in recent years.

- 2. AIBILI** is a Clinical Trial Centre dedicated to perform clinical trials in ophthalmology since 1994 and a Research Technology Organization providing services of an Academic CRO essential to support the development and management of multicentric clinical research compliant with ICH-GCP Guidelines. It is the Coordinating Office of EVICR.net, a European Network of 79 Clinical Research Centres in Ophthalmology from 16 European countries. AIBILI also has a Reading Centre for Ophthalmology Images. It has a Unit dedicated to development of new technologies and a Health Technology Assessment Unit providing services to the Health Industry. AIBILI is the European C-TRACER - Champalimaud Translational Centre for Eye Research of the Champalimaud Foundation.

- 3. ICNAS** has unique expertise and equipment for development of imaging markers and studies in vision and brain imaging. ICNAS runs pre-clinical trials and Phase 0 microdosing studies, and imaging clinical trials. It also develops new imaging techniques in partnership with the industry and labels candidate drugs for scientific and industry studies.

- 4. CRIO** is a reference Hospital for Ophthalmology in Portugal and Europe with a large clinical staff, access to a large patient population and a varied ocular pathology. It has a strong permanent and active collaboration with AIBILI especially in the area of clinical research and with IBILI in the area of pre-clinical research.

ARSC - HEALTH ADMINISTRATION OF THE CENTRAL REGION OF PORTUGAL

The Protocol between AIBILI and ARSC is of great relevance to AIBILI. The area of primary health care is a major research interest of AIBILI. Screening and prevention are priorities for AIBILI research particularly in the area of imaging diagnostics. The Reading Centre for fundus images of the Central Region of Portu-

gal Screening Programme for Diabetic Retinopathy is located at the Coimbra Ophthalmology Reading Centre (CORC) of AIBILI. A series of epidemiological studies have been taking place in the Central Region of Portugal as a result of this partnership in an effort to map the incidence of age-related eye disease in Portugal.

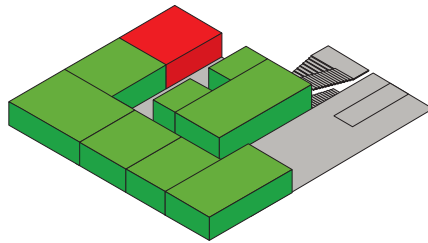
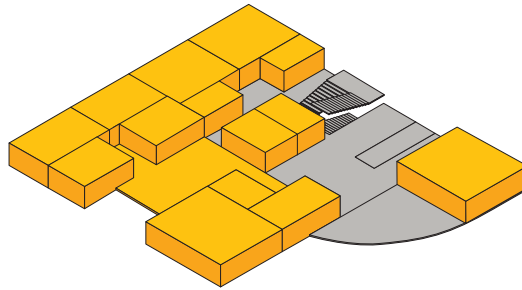
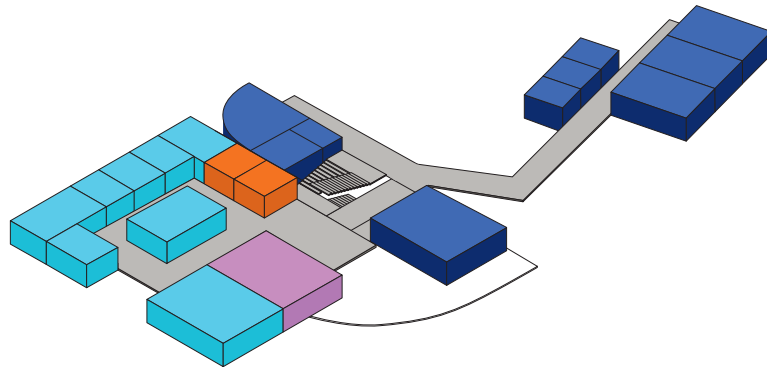
INFARMED - NATIONAL AUTHORITY OF MEDICINES AND HEALTH PRODUCTS

AIBILI has a Protocol signed with INFARMED since 2001 with an addendum signed in 2010 to collaborate in the areas of pharmacovigilance; pharmaco-economics, studies of market moni-

toring and drug utilization; bioavailability/bioequivalence studies and central fundus image classification and grading.

9

AIBILI BUILDING



3rd floor

- SA – Administrative Services
- 4C – Coimbra Coordinating Centre for Clinical Research
- CHAD – Centre for Health Technology Assessment and Drug Research
- EVICR.net Coordinating Centre

2nd floor

- CEC – Clinical Trial Centre

1st floor

- CNTM – Centre of New Technologies for Medicine
- CORC – Coimbra Ophthalmology Reading Centre



CONTACTS

AIBILI

Azinhaga de Santa Comba
 Celas, 3000-548 Coimbra
 Portugal
 Phone: +351 239 480 100
 Fax: +351 239 480 117
 E-mail: aibili@aibili.pt
 Website: www.aibili.pt

4C – COIMBRA

COORDINATING CENTRE FOR CLINICAL RESEARCH

Sandrina Nunes
 Phone: +351 239 480 137
 Fax: +351 239 480 117
 E-mail: sandrina@aibili.pt

CEC – CLINICAL TRIAL CENTRE

Luísa Ribeiro
 Phone: +351 239 480 128
 Fax: +351 239 483 593
 E-mail: lr@aibili.pt

CNTM – CENTRE OF NEW TECHNOLOGIES FOR MEDICINE

Rui Bernardes
 Phone: +351 239 480 106
 Fax: +351 239 480 117
 E-mail: rbc@aibili.pt

CORC – COIMBRA OPHTHALMOLOGY READING CENTRE

Conceição Lobo
 Phone: +351 239 480 135
 Fax: +351 239 480 134
 E-mail: seccorc@aibili.pt

CHAD – CENTRE FOR HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH

Francisco Batel Marques
 Phone: +351 239 480 138
 Fax: +351 239 480 117
 E-mail: hta@aibili.pt

SA – ADMINISTRATIVE SERVICES

Cecília Martinho
 Phone: +351 239 480 100
 Fax: +351 239 480 117
 E-mail: cvm@aibili.pt



association for
innovation and biomedical
research on light and image