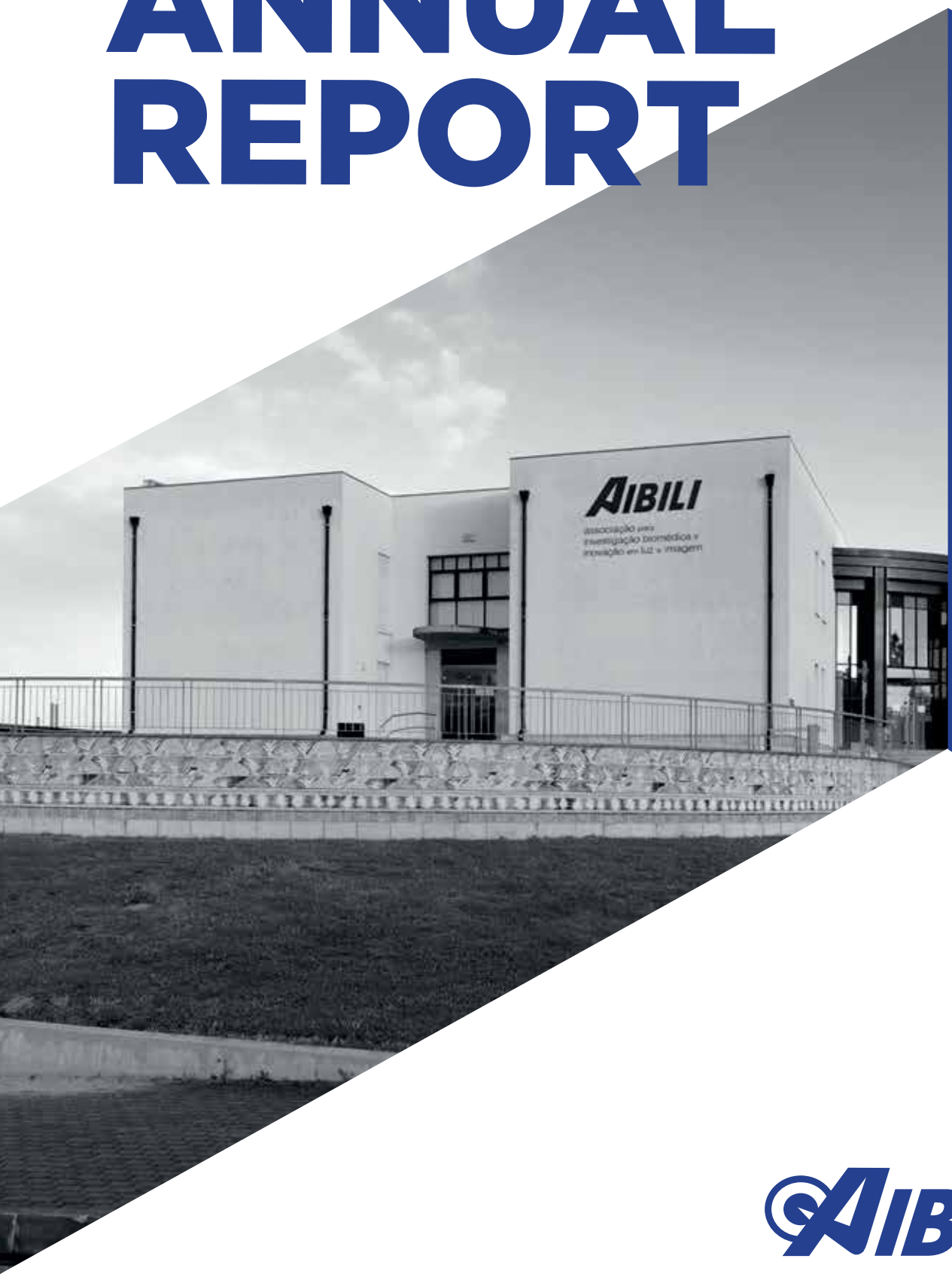
2022

ANNUAL REPORT



AIBILI

AIBILI

association for innovation and biomedical research on light and image

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MESSAGE FROM THE PRESIDENT

AIBILI is a reference ophthalmology research institution recognized nationally and internationally with more than 30 years of experience supporting translational research and technology transfer in the health area. It is the only Interface Centre in Portugal with focus on Human Health. In 2022 AIBILI obtained again the recognition by the Portuguese Ministry of Economy as a Technology and Innovation Centre (CTI), the new designation of entities dedicated to the production, dissemination, and transmission of knowledge, with relevance for the creation of economic value, contributing to the pursuit of public policy objectives, in specific priority areas.

The last two years were challenging years. AIBILI Units had to adapt to market priorities, namely the Clinical Trial Centre (CEC) and in the Reading Centre (CORC), where there was an impact on ongoing activities and planned clinical studies. However, in the last recent months, we are seeing again a growing demand due to the continued recognition of excellent studies performance and the high quality of the services provided.

The Coimbra Coordinating Centre for Clinical Research (4C) maintained their activities as supporting the development and coordination of Investigator Initiated and Industry Sponsored clinical research studies and the management of the EVICR.net, the network of Ophthalmological Clinical Research Sites. The EVICR.net is considered a successful network with growing demand in the last years due to its recognition in strengthening the European Union capacity to perform multinational clinical research activities. Presently EVICR.net has 95 Clinical Site Members from 17 European countries envolving more than 800 investigators.

The Data Centre (DC) increased its activity to improve AIBILI's information security, cybersecurity and privacy protection, guaranteeing the safety and integrity of the data collected for clinical research. AIBILI Data Centre is compliant with GCP Guidelines, US FDA 21 CFR part 11 (Guidance for Electronic Records) and ISO 27001 (Information Security Management) and is an ECRIN Data Centre certified since 2016.

The Centre for New Technologies in Medicine (CNTM) is particularly dedicated to the development of new methodologies for early identification of alterations and disease biomarkers that can facilitate targeted clinical interventions. CNTM works in partnership with relevant international companies, and through projects based on artificial intelligence dedicated to the diagnosis of retinal changes in age-related diseases promoting precision medicine.

With the integration of the knowledge generated by the different Units, the contribution of highly qualified and dedicated team, AIBILI is successfully achieving its main objective, which is to convert basic knowledge into innovative applications that impact and improve health care and the human well-being.

Conceição Lobo
President

Association for Innovation and Biomedical Research on Light and Image

INTRODUCTION

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 clinical research of new products for medical therapy and diagnostic imaging.
AIBILI is a private not-for-profit organisation, founded in 1989, established to support technology transfer and translational research in the health area. It is a Technology and Innovation Centre (CTI) in the health area of the National Network of the Economy Ministry.

AIBILI main areas of activity are:

- **Performance of Clinical Studies**
- **Planning, Coordination, Monitoring of Clinical Research Activities**
- **Health Technology Assessment**
- **Grading of Eye Exams**
- **Research and Development in New Technologies for Medicine in the areas of Imaging, Optics and Photobiology**
- **Data Centre**

AIBILI is ISO 9001:2015 certified for all its activities. Clinical research is performed in accordance with ICH - Good Clinical Practice (GCP) Guidelines and national and European regulatory requirements, as well as personal data protection legislation. AIBILI Data Centre is certified by ECRIN - European Clinical Research Infrastructures Network since 2016.

AIBILI is located in the Coimbra University Health Campus since 1994 and has its own building with 1.454 m2 and state-of-the-art equipment.

Regarding human resources it has a permanent staff of 53 including medical doctors, researchers, engineers, pharmacologists, technicians, project managers, statisticians, data managers, quality managers, study coordinators and administrative personnel. Another 43 professionals collaborate regularly in research activities.

In order to promote science and technology advancement and bring potential new treatments and diagnostic tools to the market, AIBILI has assumed an integrated Strategic Scientific Research Plan 2020-2025 with five main Research Programs: Diabetic Retinopathy; Age-Related Macular Degeneration; Imaging Biomarkers; Drug Evaluation; and Translational Vision. The outcome of this Strategic Scientific Research Plan will be a key element to enable AIBILI to maintain its excellence in health innovation: by increasing the number and quality of research projects, as well as their funding; to promote AIBILI as an added-value to clinical development and innovation; to promote technology transfer and translational research, and to stimulate novel national and international collaborations, focusing on the improvement of health research and life quality.

The main goals of AIBILI are translational research and innovation contributing to the conversion of basic research knowledge into practical applications in order to improve human health and wellbeing.

2022 HIGHLIGHTS:

Participation of Carlos Domingues in the celebration of the Clinical Trials Day organised by AICIB where AIBILI Data Centre was presented.

Publication of the Patent US 11,2354,591 B2. The team lead by the inventors José Cunha-Vaz and Torcato Santos has developed a method and device that detects and quantifies abnormal increases of retinal extra cellular space using sites of low optical reflectivity from optical coherence tomography OCT.

ARVO 2022 MIT Outstanding Poster Award Retina Section attributed to Cláudia Farinha with the project "AMD_Metab - Metabolomics, Genetics and Environment - A novel integrative approach to Age-Related Macular Degeneration".

Participation of Conceição Lobo in the Azores Health Summit to share AIBILI's experience in the development and implementation of diabetic retinopathy screening programmes using artificial intelligence (complemented by João Diogo Ramos from our partnering company Retmarker SA).

José Cunha-Vaz honored during the XXX Coimbra Ophthalmology International Meeting for his outstanding contributions in the field of ophthalmology.

José Cunha-Vaz received the Arnall Patz Medal during the 45th Congress of the Macula Society in Berlin, Germany, distinguishing outstanding contributions to the study of retinal vascular diseases.

In June 2022, AIBILI's External Scientific Council met, comprised by: Prof. Morton Goldberg, John Hopkins Hospital, Baltimore, USA; Prof. Francesco Bandello, University Vita-Salute Scientific Institute San Raffaele, Milan, Italy; and Prof. Carlos Marques Neves, University of Lisbon – Faculty of Medicine, Lisbon, Portugal. AIBILI obtained a classification of Excellent. The External Scientific Council recommendations are reflected in AIBILI Strategic Scientific Research Plan.

Recognition of AIBILI as a Technology and Innovation Centre (CTI) by the Portuguese Economy Ministry, identifying AIBILI as a facilitating partner between scientific institutions, enterprises and industry in order to bring novel solutions to the health market.

EURETINA Retinal Medicine Clinical Research Award 2022 attributed to the study "AMD_LifeGene - Diet, lifestyle, systemic medication and genetics: can the risk for AMD be modulated?" proposed by Cláudia Farinha.

Organization together with the Coimbra University of the Health Technology Show on 16/09/2022.

Participation in the National Pharmacovigilance Day organised by INFARMED. AIBILI is one of the Regional Pharmacovigilance Units and its Coordinator Dr. Lisete Lemos presented a talk dedicated to the challenges and opportunities for the Regional Units.

Patrícia Barreto received the Plácido Prize by the Portuguese Ophthalmology Society, during the 65th Portuguese Congress of Ophthalmology with the work "Genetics and the Mediterranean diet: What is the risk for Age-Related Macular Degeneration".

AIBILI participation in CR-INOVE, a CCDRC initiative to foster innovation and competitiveness in the Centre Region of Portugal.

Development of the EVICR.net Eye Platform which will gather high quality ophthalmology data and allow the re-use of data in performing large data analysis and foster clinical research. A pilot study in AMD will kick of the Eye platform and funding was attributed by Boehringer Ingelheim.

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TECHNOLOGY AND INNOVATION CENTRE IN THE HEALTH SECTOR

AIBILI is a Technology and Innovation Centre (CTI) in the Health Sector of the National Technology Network of the Economy Ministry. This recognition identifies AIBILI as the facilitating partner between scientific institutions, enterprises and industry in order to bring novel solutions to the health market.

In order to promote research of excellence and science innovation, AIBILI has established the following priorities:

- Maintain a critical position in clinical and translational research allowing the creation of new knowledge in collaboration with other reference institutions and participation in international consortia;

- Increase research in the areas of diabetes, neurology and cardiology, taking advantage of the articulation with primary health care units and the established capacities to study the retina-brain relationship;

- Develop new imaging biomarkers to support the diagnosis and identification of disease stages and facilitate the analysis for risk of development and progression of disease;

- Increase AIBILI's technological strength through the qualification of human resources, the use of state-of-the-art equipment and research collaborations.

With these priorities and participation in international reference networks following the Strategic Scientific Research Plan and the quality management system, AIBILI is positioned to achieve excellence in research and innovation that will benefit the society through the contribution of improvements in clinical practice.

BIOTECHNOLOGY AND LIFE SCIENCES FOCUS: HUMAN HEALTH

FINANCIADO POR

FITEC Fundo de Inovação, Transferência de Tecnologia e Economia Circular

PROGRAMA INTERFACE

Programa Nacional de Reformas

REPÚBLICA PORTUGUESA

ASSOCIATES

Founding Associates

- FLAD - Fundação Luso-Americana para o Desenvolvimento (Honorary Associate)
- IAPMEI - Instituto de Apoio às Pequenas e Médias Empresas e à Inovação
- José Cotta - EMS, S.A.
- José Cunha-Vaz
- Laboratório EDOL - Produtos Farmacêuticos, S.A.
- Biofísica da Faculdade de Medicina da Universidade de Coimbra
- Farmacologia da Faculdade de Medicina da Universidade de Coimbra
- Serviço de Dermatologia do Centro Hospitalar e Universitário de Coimbra
- SUCH - Serviço de Utilização Comum dos Hospitais

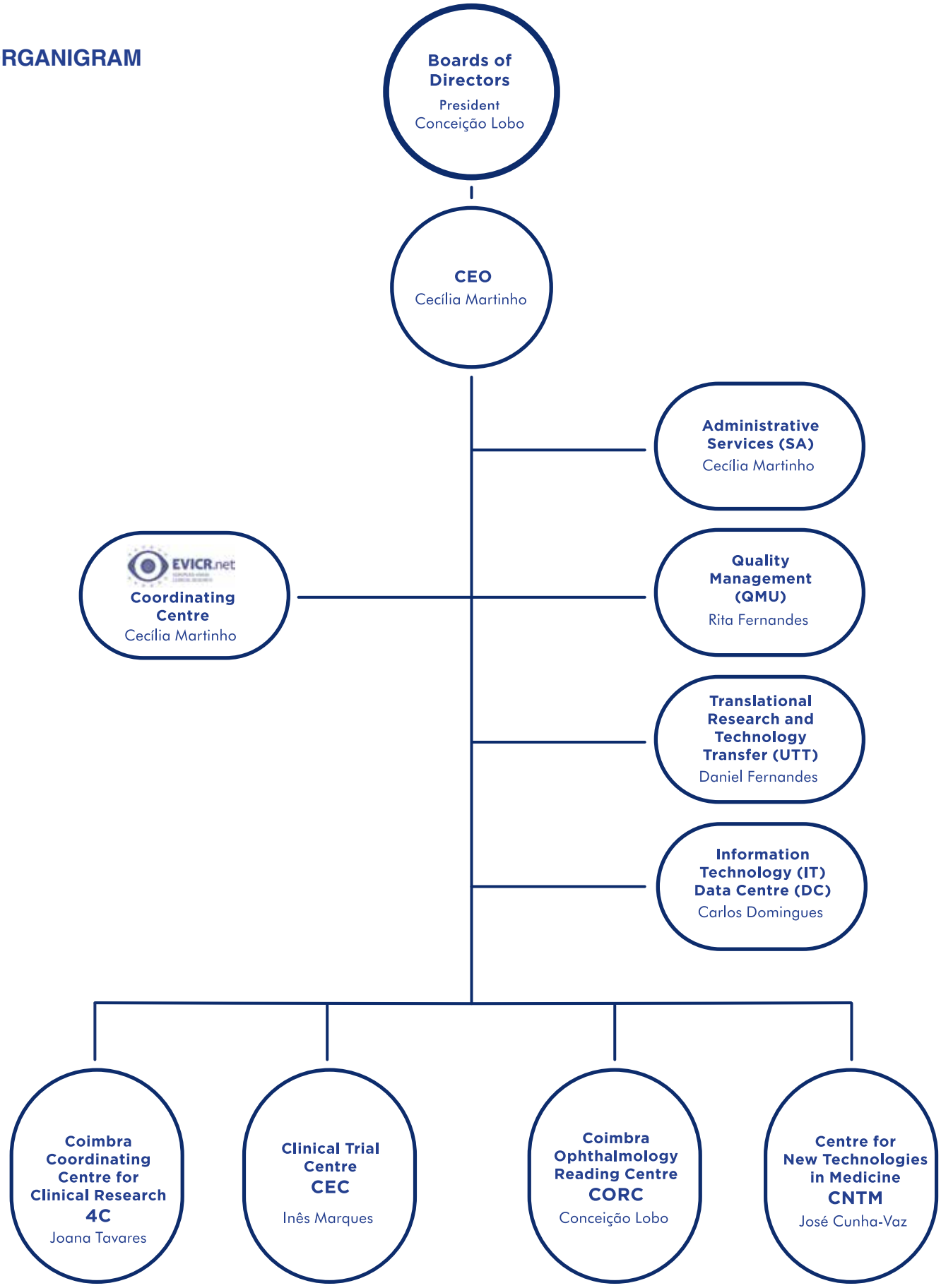
Other Associates

- Universidade de Coimbra (Honorary Associate)
- Fundação Champalimaud (Honorary Associate)
- Alcon Portugal - Prod. e Equip. Oftalmológicos, Lda.
- BIAL - Portela & Cª., SA
- Cecília Martinho
- Centro de Oftalmologia da Universidade de Coimbra
- Conceição Lobo
- Francisco Batel Marques
- Hospital CUF Coimbra / José de Mello Saúde
- Laboratórios Pfizer, Lda.
- Novartis Farma, SA

BOARD OF DIRECTORS
(2020-2023)

- Conceição Lobo, President
- António Parreira (Rep. Fundação Champalimaud), Vice-President
- Nuno Pires (Rep. BIAL - Portela & Cª, SA)
- Gonçalo Pimpão (Rep. Laboratórios EDOL - Produtos Farmacêuticos, S.A.)
- Margarida Gonçalo (Rep. Serviço de Dermatologia do Centro Hospitalar e Universitário de Coimbra)
- António Cotta (Rep. José Cotta - EMS, Lda)
- Cecília Martinho, CEO
- José Cunha-Vaz, Honorary President

ORGANIGRAM


Boards of Directors
President
Conceição Lobo
CEO
Cecília Martinho
Administrative Services (SA)
Cecília Martinho
EVICR.net
Coordinating Centre
Cecília Martinho
Quality Management (QMU)
Rita Fernandes
Translational Research and Technology Transfer (UTT)
Daniel Fernandes
Information Technology (IT) Data Centre (DC)
Carlos Domingues
Coimbra Coordinating Centre for Clinical Research
4C
Joana Tavares
Clinical Trial Centre
CEC
Inês Marques
Coimbra Ophthalmology Reading Centre
CORC
Conceição Lobo
Centre for New Technologies in Medicine
CNTM
José Cunha-Vaz

AIBILI IN NUMBERS

AIBILI Foundation
1989

1991
Public Utility recognition

1994
1ST Building in the Coimbra University Health Campus

1999
Good Laboratory Pratices certification

2004
ISO 9001 certification
+
Coordinating Centre

2008
Expansion of AIBILI CORC and CHAD

2009
Official market launch
+
Expansion of AIBILI 4C

2010

European
C-TRACER
Member

Champalimaud Foundation

2016

Data Centre
certification

ecrin

2017

Establishment of

DruSERONet

+

CIT
Centro Interface

Recognition by
Ministry of Economy

2019

AIBILI 30 YEARS OF EXCELLENCE

2021

ecrin

Data Centre
Recertification

2022

CTI CENTROS DE TECNOLOGIA E INOVAÇÃO

Recognition by
Ministry of Economy

Fulltime Staff	**53**
N° of PhD	**18**
N° of Consultants	**43**
N° of Ongoing studies, services, projects, contracts	**122**
N° of Patents	**3 (USA) + 1 (Europe)**
N° of European Union funded projects (ongoing)	**3**
N° of Publications (2021-2022)	**45**
N° of Publications / PhD (2021-2022)	**2,5**

AIBILI RESEARCH CENTRES AND UNITS

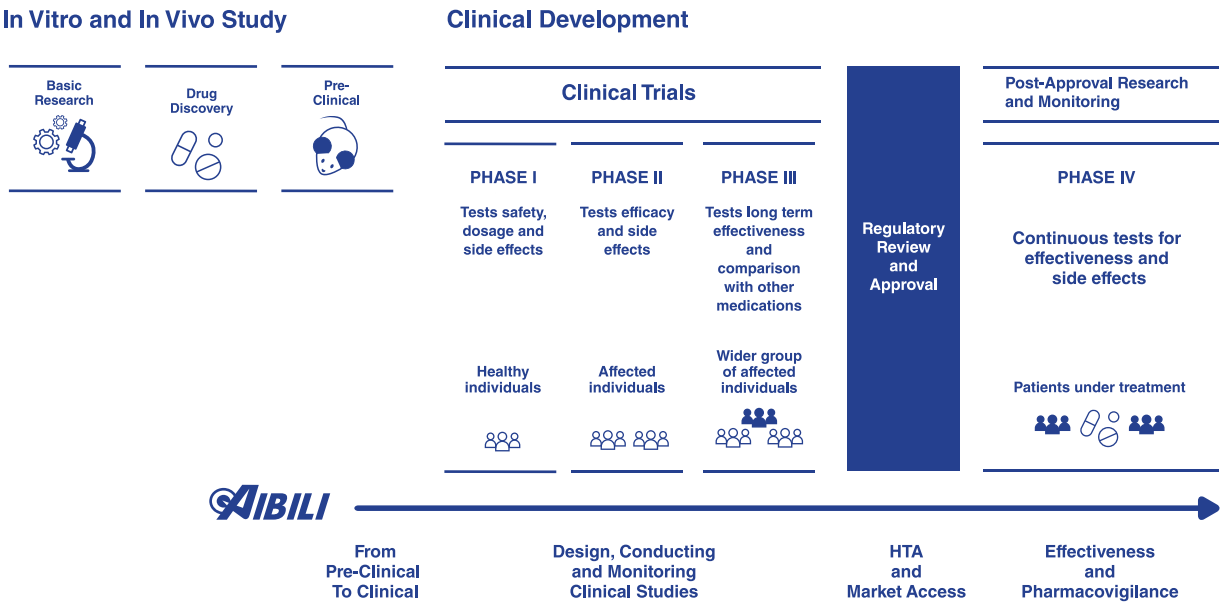
AIBILI is organized in Research Centres and Organizational Units.

The Research Centres are:

- Coimbra Coordinating Centre for Clinical Research (4C)
- Clinical Trial Centre (CEC)
- Coimbra Ophthalmology Reading Centre (CORC)
- Centre for New Technologies in Medicine (CNTM)
- Data Centre (DC)

Organizational Units are:

- Administration (SA)
- Quality Management Unit (QMU)
- Translational Research and Technology Transfer Unit (UTT)
- Information Technology Unit (IT)



4C - COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH

Director: **Joana Tavares, PhD**

Staff: Ana Fernandes, Cecília Martinho, Conceição Lobo, Daniel Fernandes, Daniel Figueiredo, Débora Ferreira, Fábio Mesquita, Laura Seco, Inês Aires, Inês Tavares, Joana Abrantes, Liliana Carvalho, José Cunha-Vaz, Pier Basile, Raquel Branco, Rita Coimbra, Rita Fernandes, Sara Carvalho, Sónia Simões

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

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E-mail: jftavares@aibili.pt

PRE-STUDY

- Study Design
- Statistical Plan
- Protocol and Informed Consent Development
- eCRF Development
- Database Validationsand Implementation
- MF and Site File Development
- Clinical Centre Selection
- Regulatory Affairs
- Contracts and Insurance
- Monitoring Plan

IN-STUDY

- Study Coordination
- IMP Management
- eCRF Management and Support
- Data Management
- Monitoring
- Pharmacovigilance and Risk Management

POST-STUDY

- Data Base Lock
- Biostatistics
- Final Report
- Medical Writing
- Publication
- Archiving

4C uses a Clinical Management System (CMS), a computer database system, developed by AIBILI Data Centre (AIBILI-DC), used for an effective planning, management and monitoring of clinical studies.

4C is compliant with ICH GCP - Good Clinical Practice Guidelines and European regulations, namely Clinical Trials Regulation (Regulation (EU) No 536/2014), Medical Devices Regulation (Regulation (EU) No 2017/745) and ISO 14155.

The 4C also supports industry on evaluation of medicines and other medicinal products for market access purposes by providing the following services:

MARKET ACCESS	PRIMARY RESEARCH	SECONDARY RESEARCH
• Early advice to develop a value strategy for market access • Supporting strategic value enhancements through expertpanels and advisory boards • Core vaule dossier elaboration • HTA, pricing and reimbursement submissions	• Patient-reported outcomes (PROs) • Real world effectiveness studies	• Literature searching and evaluation • Systermatic reviews • indirect/mixed trestment comparisons according to methodological guidelines • Comparative Effectiveness studies • Expert reports

Nº of Clinical Studies / Projects at 4C (2020-2022)

	Coordination of Clinical Studies (nº)					
Year	Investigator Initiated	Industry Sponsored	Market Access	Drug Safety	Other	Total
2020	13	2	16	8	4	43
2021	15	3	15	9	5	47
2022	**18**	**2**	**8**	**8**	**4**	**40**

Representative Publications

Farinha C, Barreto P, Coimbra R, Cachulo ML, Melo JB, Cunha-Vaz J, Lechanteur Y, Hoyng CB, Silva R. **Common and rare genetic risk variants in age-related macular degeneration and genetic risk score in the Coimbra eye study**. Acta Ophthalmol. 2022 Aug 29. doi: 10.1111/aos.15232.

Farinha C, Barreto P, Coimbra R, Iutis A, Cachulo ML, Cunha-Vaz J, Lechanteur YTE, Hoyng CB, Silva R. Phenotypic **Expression of CFH Rare Variants in Age-Related Macular Degeneration Patients in the Coimbra Eye Study.** Invest Ophthalmol Vis Sci. 2022 Aug 2;63(9):5. doi: 10.1167/iovs.63.9.5.

Marques, I. P.; Ribeiro, L.; Santos, T.; Mendes, L.; Carvalho, S.; Santos, A. R.; Lobo, C.; Cunha-Vaz, J.: **Different risk profiles for progression of nonproliferative diabetic retinopathy.** Ophthalmology and Therapy 10 December 2022; doi: 10.1007/s40123-022-00623-7.

Mauschitz MM, Verzijden T, Schuster AK, Elbaz H, Pfeiffer N, Khawaja A, Luben RN, Foster PJ, Rauscher FG, Wirkner K, Kirsten T, Jonas JB, Bikbov MM, Hogg R, Peto T, Cougnard-Grégoire A, Bertelsen G, Erke MG, Topouzis F, Giannoulis DA, Brandl C, Heid IM, Creuzot-Garcher CP, Gabrielle PH, Hense HW, Pauleikhoff D, Barreto P, Coimbra R, Piermarocchi S, Daien V, Holz FG, Delcourt C, Finger RP; European Eye Epidemiology (E3) Consortium. **Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans.** Br J Ophthalmol. 2022 Nov 7:bjo-2022-321985. doi: 10.1136/bjo-2022-321985.

Ribeiro L., Marques I. P., Santos T., Carvalho S., Santos A. R., Mendes L., Lobo C., Cunha-Vaz J.: **Characterization of two-year progression of different phenotypes of nonproliferative diabetic retinopathy.** Ophthalmic Res. 2022 Sep 28. doi: 10.1159/000526370.

CEC - CLINICAL TRIAL CENTRE

Director: **Inês Marques, MD, PhD**

Staff: Aida Vitorino, Ana Almeida, Ana Rocha, Ana Rita Santos, Catarina Eloy, Cláudia Farinha, Céu Simões, Conceição Lobo, Filipe Martins, Isabel Pires, Joana Abrantes, Luisa Ribeiro, João Figueira, João Pedro Marques, José Cunha-Vaz, Maria da Luz Cachulo, Marcela Pascoal, Marta Lopes, Patrícia Barreto, Paulo Marques, Pedro Faria, Rufino Silva, Sandra Pardal

Contacts
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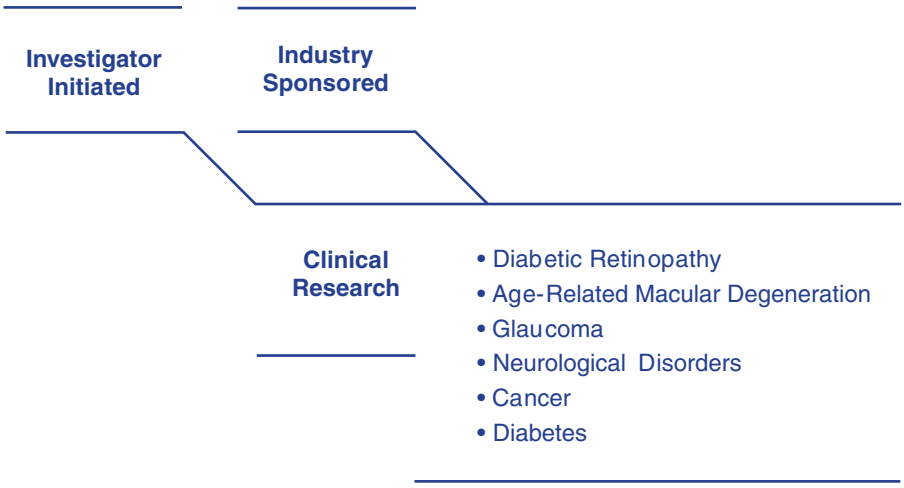
The Clinical Trial Centre (CEC) performs clinical trials and studies with special emphasis on ophthalmology, focusing on patient's wellbeing.

Clinical patient-oriented research involves characterizing disease progression and testing new discoveries by carrying out controlled research studies in patients, i. e., clinical trials. This includes testing not only new drugs, but also new methods, devices, imaging and surgical procedures as well as well-designed prospective, non-interventional, longitudinal studies.

Our research is focused on age-related eye diseases with special emphasis on diabetic retinopathy and age-related macular degeneration.

CEC has proven expertise with relevant scientific publications in these areas and is a certified Clinical Site of Excellence by the EVICR.net - European Vision Institute Clinical Research Network since 2006.

CEC has experienced and qualified staff and dedicated facilities to perform clinical research according to ICH GCP Guidelines and Data Protection compliant. In its daily routine, CEC uses an Electronic Medical Record integrated with the equipment's imaging allowing a quick and easy access to the patient's data.



Nº of Investigator Initiated and Industry Sponsored Studies Performed at CEC (2020-2022)

	Nº of Clinical Studies		
Year	Investigator Initiated	Industry Sponsored	Total
2020	5	10	15
2021	8	10	18
2022	**11**	**8**	**19**

Investigator Initiated Clinical Studies

Diabetic Retinopathy

1. CORDIS - Characterization of retinal vascular disease in eyes with mild to moderate Nonproliferative diabetic retinopathy in Diabetes type 2, using novel non-invasive imaging methods, in a longitudinal and prospective clinical study with 2 years of duration
ClinicalTrials.gov nº: NCT03696810
Financial support: Portugal 2020 - 02/SAICT/2017 - Project nº 030375

2. RECOGNISED - Retinal and Cognitive Dysfunction in Type 2 Diabetes: Unraveling the Common Pathways and Identification of Patients at Risk of Dementia
ClinicalTrials.gov nº: NCT04281186
Financial support: European Union - H2020-SC1-BHC-01-2019-847749

3. PROGRESS 10 - Progression of Diabetic Retinopathy. Identification of Signs and Surrogate outcomes -10-year follow-up
ClinicalTrials.gov nº: NCT04650165

4. CHART - Characterization of Retinal disease progression in eyes with NPDR in diabetes Type 2 using non-invasive procedures
ClinicalTrials.gov nº: NCT04636307
Financial support: IIR Grant from Bayer

5. RICHARD – Retinal Ischemia characterization in diabetes
ClinicalTrials.gov nº: NCT05112445
Financial support: IIR Grant from Boehringer Ingelheim

6. Exploratory project – Diabetic Retinopathy: from clinical to cellular phenotyping
Financial support: AIBILI

7. PREDICTION – Prediction of Retinal Ischemia in Diabetes
ClinicalTrials.gov nº: NCT05581225

Age-Related Macular Degeneration

8. MACUSTAR - Intermediate AMD: Development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention
ClinicalTrials.gov nº: NCT03349801
Financial Support: European Union and EFPIA - Innovative Medicines Initiative 2 Joint Undertaking - Grant Agreement nº 116076

9. AMDMetab - Metabolomics: An Integrative Tool for Investigating the Pathogenesis of Age-related Macular Degeneration
Partner: Massachusetts Eye and Ear Infirmary (MEEI) and the Harvard Medical School, Boston, USA
ClinicalTrials.gov nº: NCT04241536
Financial Support: EURETINA Clinical Research Award

Retinal Degenerative Diseases

10. STAR - Development of a Model for Advanced Screening for Timely Treatment of Age-Related Eye Diseases

11. EYEMARKER - Characterization of potential biomarkers of Eye Disease and Vision Loss
ClinicalTrials.gov nº: NCT02500862

Industry Sponsored Clinical Trials

Diabetic Macular Edema

1. A two-year, three-arm, randomized, double-masked, multicentre, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL)
EudraCT nº: 2017-004742-23

2. A Multicenter, Open-Label Extension Study To Evaluate The Long-Term Safety And Tolerability Of Faricimab In Patients With Diabetic Macular Edema (Rhone-X)
EudraCT nº: 2020-000402-29

3. A Phase 2 Randomized, Placebo-controlled, Double-masked Proof-of-concept Study to Investigate the Efficacy and Safety of Runcaciguat (BAY 1101042) in Patients With Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NEON)
EudraCT nº: 2020-002333-15

Age-Related Macular Degeneration

4. A 52-week multicenter, randomized, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea®, administered intravitreally, in patients with neovascular age-related macular degeneration (Mylight)
EudraCT nº: 2019-004838-41

Glaucoma

5. Long-Term Surveillance Study of Latanoprost to Monitor Hyperpigmentation changes in the eye in Pediatric Populations (A6111144)

Neurological Disorders

6. A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis (EXPAND)
EudraCT nº: 2012-003056-36

7. Multicenter, non-comparative extension to study AC-058B301, to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg in subjects with relapsing multiple sclerosis (OPTIMUM)
EudraCT nº: 2016-004719-10

Oncology

8. A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib Versus Gemcitabine With Cisplatin in Subjects With Advanced/Metastatic or Inoperable Cholangiocarcinoma With FGFR2 Gene Fusions/Translocations: the PROOF Trial (PROOF)
EudraCT nº: 2018-004004-19

Representative Publications

Farinha C, Barreto P, Coimbra R, Cachulo ML, Melo JB, Cunha-Vaz J, Lechanteur Y, Hoyng CB, Silva R. **Common and rare genetic risk variants in age-related macular degeneration and genetic risk score in the Coimbra eye study.** Acta Ophthalmol. 2022 Aug 29. doi: 10.1111/aos.15232.

Farinha C, Barreto P, Coimbra R, Iutis A, Cachulo ML, Cunha-Vaz J, Lechanteur YTE, Hoyng CB, Silva R. **Phenotypic Expression of CFH Rare Variants in Age-Related Macular Degeneration Patients in the Coimbra Eye Study.** Invest Ophthalmol Vis Sci. 2022 Aug 2;63(9):5. doi: 10.1167/iovs.63.9.5.

Lobo C, Santos T, Marques IP, Madeira MH, Santos AR, Figueira J, Cunha-Vaz J. **Characterisation of progression of macular oedema in the initial stages of diabetic retinopathy: a 3-year longitudinal study.** Eye (Lond). 2022 Jan 22. doi: 10.1038/s41433-022-01937-3.

Marques IP, Ferreira S, Santos T, Madeira MH, Santos AR, Mendes L, Lobo C, Cunha-Vaz J.: **Association between Neurodegeneration and Macular Perfusion in the Progression of Diabetic Retinopathy: A 3-Year Longitudinal Study.** Ophthalmologica. 2022;245(4):335-341. doi: 10.1159/000522527.

Ribeiro L, Marques IP, Santos T, Carvalho S, Santos AR, Mendes L, Lobo C, Cunha-Vaz J.: **Characterization of two-year progression of different phenotypes of nonproliferative diabetic retinopathy.** Ophthalmic Res. 2022 Sep 28. doi: 10.1159/000526370.

CORC – COIMBRA OPHTHALMOLOGY READING CENTRE

Director: **Conceição Lobo, MD, PhD**

Staff: Alda Baltar, Ana Catarina Almeida, Ana Cláudia Rocha, Ana Paula Pascoal, Ana Raquel Branco, Ana Rita Santos, Ana Sousa, Carla Castro, Carla Sofia Gomes, Catarina Neves, Christian Schwartz, Cláudia Farinha, Cláudio Mendes Ferreira, Diana Ramos, Inês Marques, Isa Sobral, Isabel Pires, João Gil, João Pedro Marques, José Cunha-Vaz, José Filipe Costa, Jorge Simão, Lara Portugal, Márcia Ferreira, Marco Marques, Maria Filipa Ponces, Mariana Costa, Maria da Luz Cachulo, Marta Lopes, Miguel Raimundo, Renata Castanheira, Rui Pita, Sílvia Simão, Telmo Miranda

The Coimbra Ophthalmology Reading Centre (CORC) is a central reading centre for multinational and multicentric clinical studies as well as for the Diabetic Retinopathy Screening Programmes of the Central and South Regions of Portugal.

It is a qualified provider for multinational studies, contributing to high quality data/results in clinical trials.

CORC focus its activities on grading of ophthalmic exams for characterization and quantification of ophthalmic disease, mainly of the posterior segment/retinal diseases.

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Posterior segment / Retinal Diseases	• Diabetic Retinopathy (DR) • Age-Related Macular Degeneration (AMD) • Retinitis Pigmentosa (RP) • Retinal Vein Occlusion (RVO)
Anterior Segment Diseases	• Neurotrophic Keratitis

Ophtalmic Exams	• Retinal Fundus Images
	  • Fundus Photography (FP)
	  • Fluorescein Angiography (FA)
	  • Ultrawide field (UWF) imaging (UWF FP and UWF FA)
	  • Indocyanine-green Angiography (ICG)
	  • Fundus Autofluorescence (FAF)
	• Optical Coherence Tomography (OCT)
	• Optical Coherence Tomography Angiography (OCTA)
	• Anterior Segment Photography
	• Functional examinations: Perimetry, Microperimetry, ERG

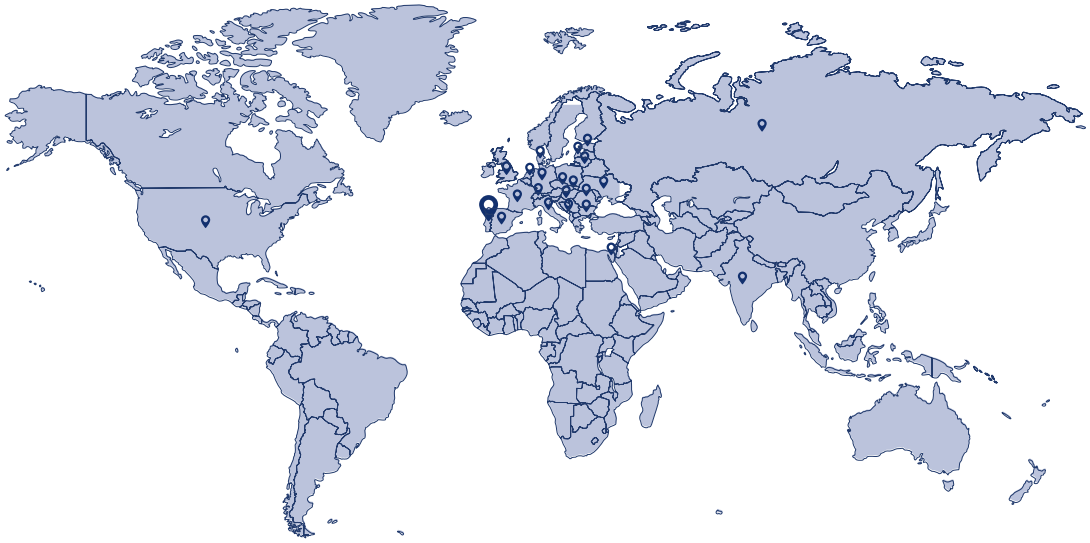
CORC provides the following services:

Study Development	• Study-specific Acquisition Protocols Development • Web-based platform for exams' submission • Study-specific Grading Protocols Development
Training and certification	• Equipment • Technicians
In-study services	• Grading of ophthalmic exams • Eligibility criteria review and confirmation • Quality check of functional objective examinations • Management and monitoring of exams received and results • Exploratory analysis under sponsor request • Data backup procedures and Disaster Recovery Plan • Secure long-term archiving of study materials, both digital and hardcopy

CORC uses the following IT systems:

IT Systems:	• Secure custom-designed web based tool to transmit images between Clinical Sites and CORC (https://studies.corc.pt/). (hosted in the AIBILI's Data Centre)
	• Digital grading forms using a secure web application (hosted in the AIBILI's Data Centre)
	• For grading CORC uses:
	  • Licensed software from the equipment suppliers (e.g., Cirrus (Carl Zeiss Meditec), Heidelberg Eye Explorer (Heidelberg Engineering), Topcon (Topcon Corporation), ReVue/iVue software (Optovue) Navis-EX (Nidek CO), Optopol OCT (Optopol), OptosAdvance (Optos), etc)
	  • Common applications for imaging edition and analysis (e.g., GIMP, XnViewer, ImageJ, etc)

Receive and grade exams from



- BULGARIA
- CZECH REPUBLIC
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- ESTONIA
- FRANCE
- GERMANY
- HUNGARY
- INDIA
- ISRAEL
- ITALY
- LATVIA
- LITHUANIA
- MONTENEGRO
- NETHERLANDS
- POLAND
- **PORTUGAL**
- ROMANIA
- RUSSIA
- SLOVAKIA
- SPAIN
- SWITZERLAND
- UK
- UKRAINE
- USA

Nº of Projects per Scientific Area at CORC (2020-2022)

	Nº of Projects			
Year	Diabetic Retinopathy	AMD	Other	Total
2020	9	5	2	16
2021	12	2	4	18
2022	**11**	**3**	**6**	**20**

Representative Publications

Farinha C, Barreto P, Coimbra R, Cachulo ML, Melo JB, Cunha-Vaz J, Lechanteur Y, Hoyng CB, Silva R. **Common and rare genetic risk variants in age-related macular degeneration and genetic risk score in the Coimbra eye study.** Acta Ophthalmol. 2022 Aug 29. doi: 10.1111/aos.15232.

Farinha C, Silva AL, Coimbra R, Nunes S, Cachulo ML, Marques JP, Pires I, Cunha-Vaz J, Silva R. **Retinal layer thicknesses and neurodegeneration in early age-related macular degeneration: insights from the Coimbra Eye Study.** Graefes Arch Clin Exp Ophthalmol. 2021 Sep;259(9):2545-2557. doi: 10.1007/s00417-021-05140-0.

Lobo C, Santos T, Marques IP, Madeira MH, Santos AR, Figueira J, Cunha-Vaz J. **Characterisation of progression of macular oedema in the initial stages of diabetic retinopathy: a 3-year longitudinal study.** Eye (Lond). 2022 Jan 22. doi: 10.1038/s41433-022-01937-3.

Marques IP, Kubach S, Santos T, Mendes L, Madeira MH, de Sisternes L, Tavares D, Santos AR, Lewis W, Lobo C, Durbin MK, Cunha-Vaz J. **Optical Coherence Tomography Angiography Metrics Monitor Severity Progression of Diabetic Retinopathy-3-Year Longitudinal Study.** J Clin Med. 2021 May 25;10(11):2296. doi: 10.3390/jcm10112296.

Silva R, Arias L, Nunes S, Farinha C, Coimbra R, Marques JP, Cachulo ML, Figueira J, Barreto P, Madeira MH, Pires I, Sousa JC, Distefano L, Rosa P, Carneiro Â, Vaz-Pereira S, Meireles A, Cabrera F, Bures A, Mendonça L, Fernandez-Vega-Sanz A, Barrão S, Koh A, Cheung CMG, Cunha-Vaz JG, Murta J; EVICR.net ATLANTIC Study Group. **Efficacy and Safety of Intravitreal Aflibercept Treat and Extend for Polypoidal Choroidal Vasculopathy in the ATLANTIC Study: A Randomized Clinical Trial.** Ophthalmologica. 2021 Jul 13. doi: 10.1159/000518235.

CNTM - CENTRE FOR NEW TECHNOLOGIES IN MEDICINE

Director: **José Cunha-Vaz,** MD, PhD

Staff: Cátia Gonçalves, Celina Cangueiro, Francisco Ambrósio, Luís Mendes, Raquel Santiago, Rufino Silva, Telmo Miranda, Torcato Santos

The Centre for New Technologies in Medicine (CNTM) develops new medical diagnostic techniques with special emphasis on the area of eye fundus imaging.

The eye offers unique opportunities to obtain in a non-invasive manner information on the body, in general and of the retina and brain in particular. It is, in fact, a window to the body. CNTM is particularly interested in developing non-invasive methodologies that allow repeated observations and measurements in order to identify early alterations that may allow timely therapeutic interventions, e.g., precision medicine.

CNTM has been able to patent novel biomarkers of disease progression, such as microaneurysm turnover in diabetic retinopathy identified automatically by software developed in-house, the Retmarker®, developed in a partnership with Retmarker SA., and fluid quantification in the retinal diseases by identifying non-invasively changes in the Blood-Retinal Barrier in the retina, using a novel algorithm, the OCT-Leakage. CNTM is also engaged with EVICR.net in the development of the EVICR.net Eye Platform. This platform, composed of several components and microservices, will explore the Cloud computing capabilities for gathering high-quality ophthalmology data generated in Europe to allow the re-use of data and foster clinical research.

A major effort is also being made in the validation and development of Optical Coherence Tomography Angiography for diagnosing progression of diabetic retinopathy and to develop methods involving artificial intelligence.

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Research Focus

- Multimodal imaging of retinal disease
- Characterization of capillary closure as the main alteration that identifies diabetic retinopathy progression
- OCT-Leakage. Layer by layer fluid analysis of the retina and identification of extracellular fluid accumulation
- Characterization of prognostic biomarkers of retinal disease progression using artificial intelligence
- Characterization of response to anti-VEGF treatment in Diabetic Macular Edema

Nº of Projects at CNTM (2020-2022)

Year	Nº of Projects		Total
	Imaging/ Artificial Intelligence	Diabetic Retinopathy	
2020	8	4	12
2011	9	6	15
2022	**11**	**6**	**17**

Representative Publications

Lobo C, Santos T, Marques IP, Madeira MH, Santos AR, Figueira J, Cunha-Vaz J, **Characterization of progression of macular oedema in the initial stages of diabetic retinopathy: A 3-year longitudinal study.** Eye 2022. Doi: 10.1038/s41433-022-01937-3.

Marques IP, Ferreira S, Santos T, ·Madeira MH, Santos AR, Mendes L, Lobo C, Cunha-Vaz J. **Association between neurodegeneration and macular perfusion in the progression of diabetic retinopathy. A 3-year longitudinal study.** Ophthalmologica. 2022;245(4):335-341. doi: 10.1159/000522527.

Marques IP, Ribeiro L, Santos T, Mendes L, Reste-Ferreira D, Santos AR, Lobo C, Cunha-Vaz J. **Different risk profiles for progression of nonproliferative diabetic retinopathy: a two-year study.** Ophthalmology and Therapy. December 2022; doi: 10.1007/s40123-022-00623-7

Mendes L, Marques IP, Cunha-Vaz, **Comparison of Different Metrics for the Identification of Vascular Changes in Diabetic Retinopathy Using OCTA.** Front Neurosci. 2021 Nov 30;15:755730. doi: 10.3389/fnins.2021.755730.

Santos T, Lewis W, Santos AR, Marques IP, Kubach S, Mendes L, Sisternes L, Madeira MH, Durbin MK, Cunha-Vaz J. **Swept source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR.** Br J Ophthalmol. 2022 May;106(5):712-718. doi: 10.1136/bjophthalmol-2020-317890.

DC – DATA CENTRE

Director: C**arlos Domingues, BSc**

Staff: Celine Cangueiro, Fábio Mesquita, Hugo Morgado, PierBasile, José Monteiro, Rafael Santos, Telmo Miranda
Consultant: Torcato Santos

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AIBILI Data Centre was built specifically to support AIBILI's information systems as well as to store clients/partners data and information. Inside the Data Centre, the server racks are connected to two separate power circuits, protected by two redundant Uninterruptable Power Supplies (UPS). These redundant power supply units ensure that a failure of one power supply unit does not cause any problems and that power is always supplied to servers. The UPS also ensures that the quality remains constant. It compensates for voltage and frequency fluctuations and thereby effectively protects sensitive computer electronic components and systems. Block batteries ensure that all operating applications can run for almost three hours. For Data Centre cooling AIBILI has implemented a cold air container solution with redundant air conditioning units. The air is directed to the container through the floor and flows through the racks, dissipating the heat produced by servers and providing adequate temperature and humidity for electronic equipment's. Water detection sensors on the floor and automatic fire extinguisher (based on gas-based suppression system FM200) complements the Data Centre asset-protection.

Presently Information Technology Unit maintains more than 70 servers, either virtual or physical supported on different operating systems and technologies. There are specific Standard Operating Procedures (SOPs) in place, developed according to IT best practices such as Information Technology Infrastructure Library (ITIL), and project management standards such as recommended by the Project Management Institute (PMI). All changes in the production environment are preceded by testing and validation processes, according to GAMP5 V-model and methodology. This Unit is responsible to guarantee the safety and integrity of the data and images collected all in compliance with GCP Guidelines and applicable national legislation. AIBILI specific SOPs for Information Technology and Data Centre also comply with US FDA 21 CFR part 11 (Guidance for Electronic Records) Regular internal audits and penetration tests are performed to ensure the safety and integrity of data. AIBILI has been implementing the best practices in compliance, server management and information system security and is presently working to be certified by ISO 27001 (Information Security Management).

All this information is categorized with specific backup policies defined according to information value. Long term storage procedures are in place to assure the whole information lifecycle. Information Technology Unit manages over than 80 TB of useful information/data (clinical images and databases, administrative information, project information and long-term storage).

AIBILI Data Centre is certified by ECRIN - European Clinical Research Infrastructure Network (www.ecrin.org) version 3 since April 2016 and recertification (in version 4) was achieved in February 2021. This Data Centre is the only one certified in the Peninsula Iberia. ECRIN Certification confirms AIBILI capacity to provide appropriate and effective data management services for multinational, randomised controlled studies as well as clinical studies.

Main Activities	• CDMS (Clinical Data Management System) validation, implementation and support • eCRF (Electronic Case Report Form) development and management • eCRF users helpdesk • Data export and biostatistics support • Long Term Storage • Software development • CORC platform support and digital grading forms development

Nº of Projects at DC (2020-2022)

	Nº of Projects	
Year	Projects/Services	Total
2020	17	17
2021	27	27
2022	**26**	**26**

ORGANISATIONAL UNITS

ADMINISTRATIVE SERVICES

CEO: **Cecília Martinho, BSc**

Staff: Laura Seco, Mara Miraldo, Marco Santos, Paulo Barros, Sandra Jesus, Tânia Melro

The Administrative Services (SA) are responsible for the management of AIBILI and to perform all the necessary administrative tasks, including finances and accountability, human resources management, as well as maintenance of infrastructure according to the institution's needs and in compliance with national legislation and requirements. The Administrative Services establishes a direct liaison between the Board of Directors of AIBILI and its Centres and organisational Units.

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QUALITY MANAGEMENT UNIT (QMU)

Quality Manager: Rita Fernandes, BSc

Staff: Rita Fernandes, Marta Ventura

The Quality Management Unit (QMU) is responsible for the Quality Management System (QMS), which is in accordance with ISO 9001:2015, Principles of Good Clinical Practices, requirements for Certification of ECRIN Data Centre and General Data Protection Regulation (EU) 2016/679, Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, Regulation (EU) 2017/745 on medical devices as well as other regulatory requirements applicable to AIBILI activities, to ensure continual improvement through regular support to Unit´s activities and internal audits.

Internal auditing is a guarantee that procedures are followed and the QMS is in continual improvement to enhance Client's satisfaction by meeting Clients´ requirements. This year an information security internal audit was also performed by QMU to assess the employees´ behaviour regarding security issues and their compliance with the internal Policies, as well as, to prepare them for the current implementation of stricter procedures.

AIBILI is incorporating in AIBILI´s Quality Management System the ISO 27001 — Information security management systems — Requirements and other ISO 27000 family of standards to improve its information security, cybersecurity, and privacy protection.

The QMU assures that the Quality Management System (QMS) is maintained effective and efficient permitting continual improvement and has the necessary resources to provide the services and meet the needs of its Clients and interested parties. AIBILI QMS is in digital format streamlining approvals, records and archiving as well as giving permanent access to all information.

AIBILI is ISO 9001 certified for all its main activities. AIBILI Data Centre is certified by ECRIN Data Centre requirements (https://ecrin.org/data-centre-certification).

The QMU performs external Quality Assurance (QA) services. The QMU also performs internal and external training on quality and regulatory requirements applicable to clinical research activities.

The QMU, as Personal Data Privacy Committee, is responsible for promoting compliance and awareness of applicable personal data protection laws, advising on the implementation of data protection standards and monitoring compliance in AIBILI.

The QMU has also a Compliance Committee, since June 2022, which is responsible for managing and processing whistleblower breach reports in a work-related context submitted through an internal channel available at www.aibili.pt.

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TRANSLATIONAL RESEARCH AND TECHNOLOGY TRANSFER UNIT (UTT)

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Director: Daniel Fernandes, BSc

Staff: Cecília Martinho, Daniel Fernandes

The Translational Research and Technology Transfer Unit facilitates the development of research activities and promotes translational activities by establishing the connection between the different stakeholders. It identifies opportunities for creating new knowledge and transferring technology, by supporting contracting with industry an searching for financing programs.

The UTT is also responsible for promoting and disseminating AIBILI activities, being the main point of contact for partnerships and collaborations.

Following the implementation of the AIBILI Strategic Scientific Research Plan 2020-2025, UTT coordinates the activities of the different lines of research, supporting the conceptualization and elaboration of different projects and applications. It also promotes the integration of multidisciplinary concepts from the different scientific areas with the aim of creating new knowledge bases that contribute in a relevant way to innovative research.

INFORMATION TECHNOLOGY UNIT (IT)

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IT Manager: Carlos Domingues

Staff: Carlos Domingues, Celina Cangueiro, Hugo Morgado, José Monteiro, Telmo Miranda, Rafael Santos
Consultant: Torcato Santos

The Information Technology Unit is responsible for the management and maintenance of AIBILI Data Centre, IT networks and information systems. The Data Centre, built in 2014 for storing AIBILI's critical information, houses all AIBILI servers/systems: the Electronic Medical Record that is daily used to collect patient clinical information at CEC; the custom-designed web based platform used to exchange grading data and images by CORC (https://studies.corc.pt/); the Clinical Data Management System that is used in the development of eCRFs and Grading Forms for each clinical study; as well as the Clinical Management System (CMS) used for the management of multiple multinational clinical studies by 4C. There are also other administrative information systems supported in AIBILI's Data Centre. AIBILI Data Centre also houses EVICR.net website (www.evicr.net), EVICR.net Educational Programme webinar platform (https://cloud.aibili.pt/evicrnet_webinars) and supports other administrative/office information systems. IT has been implementing the best practices in server management and information system security and is presently working to be certified by ISO 27001.

ETHICS COMMITTEE

AIBILI has an Independent Ethics Committee (IEC/IRB) that is responsible for protecting the rights, safety and wellbeing of human subjects involved in clinical studies (not involving Investigational Medicinal Products (IMP) or medical devices) performed by AIBILI according to the Portuguese Decree Law nº 80/2018 of October 15th. AIBILI Ethics Committee is available to be called upon National Ethics Committee for Clinical Research (CEIC) request, in case it is needed for the review of ophthalmology clinical trials or studies since it has expertise in this scientific area.

For more information regarding the AIBILI Ethics Committee you may consult https://www.aibili.pt/units-centres/ethics-committee/.

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MEMBERS

President

André Dias Pereira, PhD

Director of the Centre for Biomedical Law of the University of Coimbra and Professor at the Faculty of Law, University of Coimbra

Vice-President and Secretary

Margarida Duarte Ramos Caramona, PhD

Emeritus Professor at the Faculty of Pharmacy, University of Coimbra

Members

José António Moura Pereira, MD

Ophthalmologist at the University Hospital of Coimbra

Maria Elizabete Batista Geraldes, MD

Endocrinologist at the University Hospital of Coimbra

Paulo Simões, BSc

Father, Director of University Institute of Justice and Peace, Coimbra

Filomena Maria Ferreira Ramos Mena, BSc

Nurse at the National Institute of Forensic Medicine, Coimbra

Maria Cecília Martinho, BSc

AIBILI CEO

RESEARCH AND INNOVATION

Throughout its more than thirty years of existence, AIBILI has created an excellence track record in ophthalmology clinical research, being internationally recognized for its innovation in the area of imaging biomarkers and diagnostics.

With the huge acceleration in innovation in the past years, and the increased complexity in medical needs, it has become crucial to science to escort this acceleration. Researchers must provide more insight on disease understanding and deliver more healthcare solutions to promote and protect human health. Likewise, AIBILI also needs to keep up its pace in innovation.

In order to promote science and technology advancement and bring potential new treatments and diagnostic tools to the market, AIBILI has assumed an integrated Strategic Research Program 2020 - 2025 with five main Research areas:

- Diabetic Retinopathy
- Age-Related Macular Degeneration
- Imaging Biomarkers
- Drug Evaluation
- Translational Vision

AIBILI Strategic Research Program aims to achieve four main goals, to stimulate the complementarity of our dedicated research areas:

Integrate science and medicine development

- Support the development of precision medicine, biomarkers
- Create integrated evaluation pathways for assessment of medical devices and innovative products

Improve research quality

- Foster innovation in clinical trials
- Exploit digital technology and artificial intelligence (AI)
- Expand benefit-risk assessment and communication

Advance in patient-centred access to medicine

- Contribute to HTA decision-making in innovative medicines
- Promote high-quality real-world data
- Deliver improved products, targeted on earlier stages and precision medicine

Leverage research and innovation

- Foster collaboration between academia and other research institutes to address critical research innovation questions in our dedicated Research Programs
- Contribute to better healthcare and personalized medicine

DIABETIC RETINOPATHY RESEARCH PROGRAM

Coordinator: **João Figueira, MD, PhD and Inês Marques, MD, PhD**

Research Team: Ana Rita Santos, Conceição Lobo, Débora Ferreira, Inês Aires, Inês Marques, Joana Tavares, José Cunha-Vaz, Luis Mendes, Luisa Ribeiro, Pier Basile, Rita Coimbra, Torcato Santos

Diabetic retinopathy (DR) remains a major cause of blindness as the prevalence of diabetes is expected to approximately double globally between 2000 and 2030. DR progresses over time at different rates in different individuals with only a limited number developing significant vision loss due to the two major vision-threatening complications, clinically significant macular edema and proliferative diabetic retinopathy.

Good metabolic control is important to prevent and delay progression, but whereas some patients escape vision loss even with poor control, others develop vision loss despite good metabolic control. Our research group has been able to identify three different DR phenotypes characterized by different dominant retinal alterations and different risks of progression to vision-threatening complications. Microaneurysm turnover (MAT) has been validated as a prognostic biomarker of development of clinically significant macular edema, whereas subclinical macular edema identified by Optical Coherence Tomography (OCT) appear to be also a good candidate as organ-specific biomarker of DR. Haemoglobin A1c (HbA1c) remains the only confirmed systemic prognostic biomarker of DR progression.

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Main Goals

Identify new biomarkers of DR progression and their correlation with different risks for development of vision-threatening complications, offering new perspectives for understanding DR and for its personalized management.

Ongoing Projects

PROGRESS – Progression of Diabetic Retinopathy. Identification of Signs and Surrogate outcomes
ClinicalTrials.gov nº: NCT03010397
Sponsor: AIBILI

PROGRESS is a clinical study dedicated to characterise the 5-year progression of mild non-proliferative DR (NPDR), in patients with diabetes type 2, to vision-threatening complications.

Through this study, the predictive risk of ocular and systemic markers was accessed to identify prediction methods for disease development and progression. Moreover, visual acuity and retinal neurodegenerative changes in different stages of DR are explored.

PROGRESS 10 – Progression of Diabetic Retinopathy. Identification of Signs and Surrogate outcomes -10-year follow-up
ClinicalTrials.gov nº: NCT04650165
Sponsor: AIBILI

PROGRESS 10 is the continuation of the PROGRESS study (NCT 03010397), a prospective non-interventional longitudinal clinical study designed to follow type 2 diabetic individuals with non-proliferative diabetic retinopathy, in a 10-year period of follow-up.

Patients have a complete annual ophthalmological examination, including standard methodologies as color fundus photography (CFP), visual acuity, optical coherence tomography, and also taking advantage of recent and innovative approaches as Spectral domain OCT-angiography (SD-OCTA) and Swept-source OCT (SS-OCTA).

CORDIS - Characterization of retinal vascular disease in diabetes type 2, using novel non-invasive imaging methods
ClinicalTrials.gov nº: NCT03696810
Sponsor: AIBILI
Financial support: Portugal 2020 - 02/SAICT/2017 - Project nº 030375

The main objective of this project is to better characterize, using new methods, OCTA and OCT-Leakage, the evolution and progression of phenotypes B and C of DR identifying eyes that show worsening and disease progression to sight-threatening DR (progression phenotypes), allowing for a better characterization of the two main features of the leaky or ischemic progressor phenotypes, using non-invasive methodologies.

RECOGNISED - Retinal and cognitive dysfunction in type 2 diabetes: unravelling the common pathways and identification of patients at risk of dementia
ClinicalTrials.gov Number: NCT04281186
Sponsor: VHIR, Barcelona, Spain
Financial support: Horizon2020 – H2020-SC1-BHC-01-2019-847749

RECOGNISED is a multicentre, multinational study that aims to investigate the common mechanisms involved in the pathogenesis of DR and cognitive impairment in the type 2 diabetes (T2D). The main goal is to use the retina as a tool to identifying individuals with T2D at a higher risk of developing cognitive decline or dementia.

CHART - Characterization of Retinal disease progression in eyes with NPDR in diabetes Type 2 using non-invasive procedures
ClinicalTrials.gov nº: NCT04636307
Sponsor: AIBILI
Financial support: IIR Grant from Bayer

This is a multicentre two-year observational study that aims to better characterize the retinal changes that occur during a 2-years follow-up period in patients with the initial stages of NPDR and at higher risk for sight-threatening complications (ETDRS 35, 43, 47 and 53), allowing better characterization of eyes at risk of progression (phenotypes B and C).

The main aim is to identify biomarkers, obtained using non-invasive procedures, that can predict disease progression and progression to sight-threatening stages of the disease and to characterize the retinal changes that occur in NPDR.

RICHARD - Retinal ischemia characterization in diabetes
ClinicalTrials.gov Number: NCT05112445
Sponsor: AIBILI
Financial support: IIR funding from Boehringer Ingelheim

RICHARD will use these state-of the art methodologies to perform a complete, accurate and non-invasive evaluation of retinal ischemic events associated with diabetes, aiming on having a precise characterization of Diabetic Macular Ischemia (DMI) and its microvascular mechanisms, which can have critical importance in clinical practice allowing a more precise medicine.

Representative Publications

Cunha-Vaz J. and Mendes L. **Characterization of Risk Profiles for Diabetic Retinopathy Progression.** J Pers Med. 2021 Aug 23;11(8):826. doi: 10.3390/jpm11080826.

Figueira J et al. **Guidelines for the Management of Center-Involving Diabetic Macular Edema: Treatment Options and Patient Monitorization.** Clin Ophthalmol. 2021 Jul 30;15:3221-3230. doi: 10.2147/OPTH.S318026.

Lobo C, et al. **Characterisation of progression of macular oedema in the initial stages of diabetic retinopathy: a 3-year longitudinal study.** Eye (Lond). 2022 Jan 22. doi: 10.1038/s41433-022-01937-3.

Marques IP, et al. **Different Risk Profiles for Progression of Nonproliferative Diabetic Retinopathy: A 2-Year Study.** Ophthalmol Ther. 2022 Dec 10. doi: 10.1007/s40123-022-00623-7.

Marques IP, et al **Optical Coherence Tomography Angiography metrics monitor severity progression of Diabetic Retinopathy – 3-year longitudinal study.** J Clin Med. 2021;0(11):2296. doi: 10.3390/jcm10112296.

Marques IP et al, **Retinopathy Phenotypes in Type 2 Diabetes with Different Risks for Macular Edema and Proliferative Retinopathy,** J. Clin. Med. 2020, 9(5), 1433; https://doi.org/10.3390/jcm9051433.

Marques IP, et al. **Multimodal Imaging of the Initial Stages of Diabetic Retinopathy: Different Disease Pathways in Different Patients.** Diabetes. 2019 Mar;68(3):648-653. doi: 10.2337/db18-1077.

Martinho, A. C.-V. et al. **Ocular and Systemic Risk Markers for Development of Macular Edema and Proliferative Retinopathy in Type 2 Diabetes: A 5-Year Longitudinal Study.** Diabetes Care dc201125, (2020).

Ribeiro L, et al: **Characterization of 2-Year Progression of Different Phenotypes of Nonproliferative Diabetic Retinopathy.** Ophthalmic Res 2022. doi: 10.1159/000526370.

Santos, A. R. et al. **Microaneurysm turnover in mild non-proliferative diabetic retinopathy is associated with progression and development of vision-threatening complications:** A 5-year longitudinal study. J. Clin. Med. 10(10):214, (2021). doi:10.3390/jcm10102142.

Santos, T. et al. **Swept source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR.** Br J Ophthalmol. 2022 May;106(5):712-718. doi: 10.1136/bjophthalmol-2020-317890.

Santos, A. R. et al. **Microperimetry and mfERG as functional measurements in diabetic macular oedema undergoing intravitreal ranibizumab treatment.** Eye 2020. doi:10.1038/s41433-020-1054-2.

AGE-RELATED MACULAR DEGENERATION RESEARCH PROGRAM

Coordinator: **Rufino Silva, MD, PhD**

Research Team: Cláudia Farinha, Inês Laíns, Joana Tavares, José Cunha-Vaz, Luis Mendes, Patrícia Barreto, Rita Coimbra, Torcato Santos

Age-related Macular degeneration (AMD) is the leading cause of adult blindness in developed countries, which affects almost 30% of the older population. In fact, with the aging of population, AMD will become globally an increasingly important and prevalent disease worldwide.

The hallmark of the early phases of AMD are macular drusen and pigmentary changes, and it progresses slowly from early AMD to intermediate AMD (iAMD) and ultimately late-stage AMD with severe manifestation and frequently irreversible lesions. Of note, it is probable that the early and intermediate forms of AMD do not represent a single disease, but rather a collection of subtypes, which ultimately progress to the advanced forms. Therefore, elucidating these subtypes and their underlying pathogenesis will be critical in developing effective therapies for these earlier stages of AMD.

The ethiology of AMD is complex, and although genome-wide and gene-candidate studies have been enabled to identify genetic variants associated with AMD pathogenesis, studies on gene-environment interactions have gain increased relevance on the disease onset. Hence, maintenance of healthy diet, with the use of nutritional supplements has raised as a strategic preventive measure for personalized medicine in AMD.

The AMD multifactorial nature is currently well-established; however, how these factors interact to promote the development and progression of this condition remains largely unknown. This leads to a current lack of treatments for dry AMD and to halt its progression to AMD late blinding forms. Identification of progression biomarkers would be a major advance that could greatly improve patient care.

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Main Goals

Contribute to the understanding of the pathophysiology of AMD, and to identify novel targets for future treatments of this condition and innovative diagnosis methods, focusing on:

- Structure and function relation in AMD
- Genomics and metabolomics of AMD
- Lifestyle and genetics interplay in AMD onset and progression
- Drug safety and effectiveness in AMD
- Development of innovative approaches, based on Artificial Intelligence, to facilitate AMD diagnosis
- Correlation of genetics, pathophysiology and phenotype

Ongoing Projects

AMD Metab - Metabolomics, Genetics and Environment - A novel integrative approach to Age-Related Macular Degeneration ClinicalTrials.gov nº: NCT04241536
Sponsor: AIBILI
Financial support: EURETINA Retinal Medicine Clinical Research Award 2020

In collaboration with Massachusetts Eye and Ear Institute and the Harvard Medical School, Boston, USA.
This clinical study will elucidate the role of metabolomics in the understanding of AMD and will also identify potential biologically robust biomarkers that can address the problem of predicting progression. It has the central hypothesis that patients with progression of AMD have a distinct metabolomic profile compared to patients in who AMD remains stable. Likewise, this study seeks to achieve the following aims:

- To characterize the metabolome of AMD progression over six years.
- To evaluate the relationship between metabolomics and genetics in AMD and identify new candidate AMD-metabolite associations.

COIMBRA EYE STUDY - Epidemiological study of the prevalence and incidence of Age-Related Macular Degeneration in Portugal
ClinicalTrials.gov nº: NCT01298674 and NCT02748824
Sponsor: AIBILI

Age-related Macular Degeneration in Portugal - Prevalence, incidence and risk factors in the era of multimodal imaging

The main objective of this clinical study is to take advantage of multimodal evaluation of possible risk factors and biomarkers, demographic factors, genetics and structural markers, to evaluate a possible progression biomarker and infer on an association with fast progressor AMD phenotype or another particular phenotype.

Age-Related Macular Degeneration: Genetic susceptibility, Nutrition and Lifestyle
The purpose of this project is to determine the effect modification on the risk of AMD onset and progression of high-risk-patients due to nutrition and lifestyle. It will assess on what grounds food, nutrients and lifestyle protect or not patients at genetic risk for AMD.

MACUSTAR - Intermediate AMD: Development of Novel Clinical Endpoints for Clinical Trials in Patients with a Regulatory and Patient Access Intention
ClinicalTrials.gov nº: NCT03349801
Sponsor: UKB, Bonn, Germany
Financial Support: European Union and EFPIA - Innovative Medicines Initiative 2 Joint Undertaking - Grant Agreement nº 116076

MACUSTAR is a multinational clinical study which the major objective of is to develop novel clinical endpoints for clinical trials with a regulatory and patient access intention in the area of functional, structural, and patient-reported outcome measures in patients with intermediate age-elated macular degeneration (iAMD). MACUSTAR will also characterize visual impairment in iAMD and its progression, as well as identify risk factors for progression to late-stage AMD.

Representative Publications

Farinha C, et al. **Genetic Associations with Age-related Macular Degeneration and Genetic Risk Score in the Epidemiologic Coimbra Eye Study.** Revista da Sociedade Portuguesa de Oftalmologia Vol. 46 N.º 1 (2022). doi.org/10.48560/rspo.25959.

Farinha C, et al. **Phenotypic Expression of CFH Rare Variants in Age-Related Macular Degeneration Patients in the Coimbra Eye Study.** Invest Ophthalmol Vis Sci. 2022 Aug 2;63(9):5. doi: 10.1167/iovs.63.9.5.

Farinha C, et al. C**ommon and rare genetic risk variants in age-related macular degeneration and genetic risk score in the Coimbra eye study.** Acta Ophthalmol. 2022 Aug 29. doi: 10.1111/aos.15232.

Farinha C et al. **Retinal layer thicknesses and Neurodegeneration in Early Age-related Macular Degeneration – insights from the Coimbra Eye Study.** Graefes Arch Clin Exp Ophthalmol. 2021 Mar 18. doi: 10.1007/s00417-021-05140-0.

Farinha et al, A**ge-Related Macular Degeneration Staging by Color Fundus Photography vs. Multimodal Imaging—Epidemiological Implications (The Coimbra Eye Study—Report 6**) J. Clin. Med. 2020, 9, 1329; doi:10.3390/jcm9051329.

Farinha C, et al. **Optical Coherence Tomography Leakage In Neovascular Age-Related Macular Degeneration: Identification of Choroidal Neovascularization Activity by Location and Quantification of Abnormal Fluid Under Anti-Vascular Endothelial Growth Factor Therapy.** Retina. 2019 Jan 24. doi: 10.1097/IAE.0000000000002470.

Laíns I, et al. **Human Plasma Metabolomics in Age-Related Macular Degeneration: Meta-Analysis of Two Cohorts.** Metabolites. 2019 Jul 2;9(7). pii: E127. doi: 10.3390/metabo9070127.

Laíns I, et al **Urine Nuclear Magnetic Resonance (NMR) Metabolomics in Age-Related Macular Degeneration.** J Proteome Res. 2019 Mar 1;18(3):1278-1288. doi: 10.1021/acs.jproteome.8b00877.

Laíns I, et al. **Urinary Mass Spectrometry Profiles in Age-Related Macular Degeneration.** J Clin Med. 2022 Feb 11;11(4):940. doi: 10.3390/jcm11040940.

Mauschitz MM, et al. **Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans.** Br J Ophthalmol. 2022 Nov 7:bjo-2022-321985. doi: 10.1136/bjo-2022-321985.

Thee EF, et al. **The Phenotypic Course of Age-Related Macular Degeneration for ARMS2/HTRA1: The EYE-RISK Consortium.** Ophthalmology. 2022 Jul;129(7):752-764. doi: 10.1016/j.ophtha.2022.02.026.

IMAGING BIOMARKERS RESEARCH PROGRAM

Coordinator: Conceição Lobo, MD, PhD

Research Team: Ana Rita Santos, Débora Ferreira, João Figueira, José Cunha-Vaz, Luis Mendes, Torcato Santos

The eye offers unique opportunities to obtain in a non-invasive manner information on the body, in general, and of the retina and brain in particular. It is, in fact, a window to the body. The retinal circulation and the retina can be examined using a variety of methods.

Fundus Digital Photography, Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA) are non-invasive examinations that offer extremely promising perspectives as the data 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 identify non-invasively changes in the Blood-Retinal Barrier in the retina, using also a novel AIBILI patented algorithm, the OCT-Leakage.

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Main Goals

Development of new imaging techniques of the eye fundus for diagnosis and risk progression.
Particular interest is given to non-invasive methodologies that allow repeated observations and measurements in order to identify early alterations and their degree of activity.

Ongoing Projects

Identification of Capillary Closure in using Optical Coherence Tomography Angiography
Sponsor: AIBILI
Financial Support: Partnership with Carl Zeiss Meditec (CA, USA)

The major goal is to identify reliable methods to quantify retinal vascular alterations, which allow disease characterization and identification of the different disease progression groups. As ultimate goal, we aim on facilitate disease stage identification in clinical practice, as well as to facilitate the identification of patients with higher risk for progression.

OCT-Leakage. Layer by layer fluid analysis of the retina
Sponsor: AIBILI

Our group is developing applications that result to advanced imaging algorithms to enable analysis of OCT data, focusing on the segmentation of the different layers of the retina and the permeability of the Blood-Retinal Barrier. A novel analysis “Method and device for the non-invasive indirect identification of sites of alterations of the Blood–Retinal Barrier” was published under the Patent Cooperation Treaty number WO2016/174637A1 and US 11,2354,591 B2.

Retinal-FluidMAPPING - Development and validation of OCT-based Abnormal Retinal FluidMapping
Sponsor: AIBILI
Financial Support: FCT PEX grant - EXPL/EMD-EMD/1402/2021

In this project we propose to further explore the potential of OCT-Leakage and develop a more refined system to enable 3-dimensional visualization of extracellular fluid

accumulation. This will allow mapping of microcystic and cystoid changes and therefore identify the distinctive features that characterize different responses to treatment.

The project Retinal FluidMAPPING has the goal of developing a software prototype tool that maps and quantifies abnormal accumulations of abnormal fluid to be used as a DME prognostic biomarker, facilitating a personalized ophthalmological healthcare and consequent reduction of societal and economic burden of DME treatment.

Ultra-widefield CFP vs ETDRS

This study is expected to confirm the need for widefield imaging in more advanced stages of DR. Examination protocols are expected to be developed and tested.

The microvascular disease that plays a central role in the evolution of DR is expected to be better characterized by identifying the location and correlations of the different vascular alterations: microaneurysms, capillary closures, haemorrhages, venous abnormalities and neovessel formation.

Artificial intelligence for characterization of retinal biomarkers

The purpose is the development, testing, and validation of cognitive computing methods applied to state-of-art imaging data to be used in the screening and management of eye diseases.

FILTER - Framework to Develop and Validate Automated Image Analysis Systems for Early Diagnosis and Treatment of Eyes at Risk in Blinding Age-Related Diseases

Financial support: Portugal 2020 - 02/SAICT/2017 - Project nº 032412

FILTER aims the development and validation of a prototype to be used in the screening and management of blinding age-related diseases.

The prototype will allow the detection, characterization, and follow- up of lesions associated with AMD and DR. Novel methods will be developed for the analysis of OCT imaging data and CFP images.

ADRIAN - Development and Validation of a Machine Learning Algorithms for Automated Prediction of Diabetic Retinopathy Progression
Sponsor: Roche, Switzerland

With this collaboration, ROCHE and AIBILI expects to develop and validate a machine learning (ML) algorithm that automatically predict Diabetes Mellitus patients that are at high risk for progression in Diabetic Retinopathy severity and vision-threatening conditions.

Research Contracts and Partnerships

Quantification of Retinal Microvasculature in Retinal Disease
Sponsor: Carl Zeiss Meditec, USA

ADRIAN - Development and Validation of Machine Learning Algorithms for Automated Prediction of Diabetic Retinopathy Progression
Sponsor: Roche, Switzerland

Representative Publications

Cunha-Vaz J, et al. **Agreement between OCT Leakage and Fluorescein Angiography to Identify Sites of Alteration of the Blood-Retinal Barrier in Diabetes.** Ophthalmol Retina. 2017 Sep - Oct;1(5):395-403. doi: 10.1016/j.oret.2017.02.002.

Durbin MK, et al **Quantification of Retinal Microvascular Density in Optical Coherence Tomography Angiography Images in Diabetic Retinopathy,** JAMA Ophthalmol. 2017, vol. 135, N 4, pp 370-376.

Farinha C, et al. **OCT-Leakage Mapping: A New Automated Method of OCT Data Analysis to Identify and Locate Abnormal Fluid in Retinal Edema.** Ophthalmol Retina. 2017 Nov - Dec;1(6):486-496. doi: 10.1016/j.oret.2017.03.004.

Marques IP, et al. **Multimodal Imaging of the Initial Stages of Diabetic Retinopathy: Different Disease Pathways in Different Patients**. Diabetes. 2019 Mar;68(3):648-653. doi: 10.2337/db18-1077.

Mendes L, et al. **Comparison of Different Metrics for the Identification of Vascular Changes in Diabetic Retinopathy Using OCTA.** Front Neurosci. 2021 Nov 30;15:755730. doi: 10.3389/fnins.2021.755730.

Pappuru RKR, et al. **Microaneurysm turnover is a predictor of diabetic retinopathy progression.** Br J Ophthalmol. 2019 Feb;103(2):222-226. doi: 10.1136/bjophthalmol-2018-311887.

Santos AR, et al. **Microaneurysm Turnover in Mild Non-Proliferative Diabetic Retinopathy is Associated with Progression and Development of Vision-Threatening Complications: A 5-Year Longitudinal Study.** J Clin Med. 2021 May 15;10(10):2142. doi: 10.3390/jcm10102142.

Santos, T. et al. **Swept source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR. Br. J. Ophthalmol.** Br J Ophthalmol. 2022 May;106(5):712-718. doi: 10.1136/bjophthalmol-2020-317890.

Santos AR, et al. **Characterization of Initial Stages of Diabetic Macular Edema.** Ophthalmic Res. 2019;62(4):203-210. doi: 10.1159/000499117.

Santos AR, et al. **Measurements Of Retinal Fluid By Optical Coherence Tomography Leakage In Diabetic Macular Edema: A Biomarker of Visual Acuity Response to Treatment.** Retina. 2019 Jan;39(1):52-60. doi: 10.1097/IAE.0000000000001905.

Santos AR, et al; **Functional and Structural Findings of Neurodegeneration in Early Stages of Diabetic Retinopathy: Cross-sectional Analyses of Baseline Data of the EUROCONDOR Project.** Diabetes. 2017 Sep;66(9):2503-2510. doi: 10.2337/db16-1453.

Vujosevic S, et al. **Standardisation of Optical Coherence Tomography Angiography Imaging Biomarkers in Diabetic Retinal Disease.** Ophthalmic Res. 2021 Jul 30. doi: 10.1159/000518620.

DRUG EVALUATION RESEARCH PROGRAM

Director: **Joana Tavares, PhD**

Research Team: Daniel Figueiredo, Inês Tavares, Lisete Lemos, Joana Abrantes

The demand on health services and the challenges of drug development, in the light of increased aging of population, changing patterns of disease and increased costs of medicines, creates the need for research on the effectiveness, safety and economics of drugs R&D and reimbursement. Research, through several interconnected ongoing projects, aimed at real world outcomes, safety, economics and market access of drugs.

Main Goals

To strengthen the evaluation of medicines for the benefit of public health, through research and development of methodologies to assess their safety, effectiveness, and efficiency.

Contacts

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Ongoing Projects

DruSER.Net – Drug Safety and Effectiveness Research Network
Sponsor: AIBILI

The DruSER.Net is a research network of Hospitals and Primary Healthcare Centres, which is coordinated by the Pharmacovigilance Regional Unit of Coimbra. The main objective of the DruSER.Net is to investigate and monitor safety and effectiveness of medicines used in routine clinical practice and therefore contributing for patient safety through the conduction of research projects using real-world data.

Probabilistic Models for Health Technologies Assessment (ProMoHTA)
Sponsor: AIBILI

The aim of this project is to quantify underreporting of suspected adverse drug reactions (ADRs) in the clinical practice of family physicians in Portugal. Primary care physicians will actively and continuously report clinical events (i.e., cases) that occur during a calendar year.

Coimbra Pharmacovigilance Regional Unit of the Portuguese Pharmacovigilance System
Sponsor: INFARMED, IP

The main aim is to validate the post-marketing adverse drug reactions reported to the Coimbra Regional Unit of the Portuguese Pharmacovigilance System, by assessing causality, seriousness and previous knowledge. Different techniques for safety signals generation are being tested and applied.

Covid Vaccine Monitor: Safety monitoring of SARS-CoV-2 vaccines in EU Member States
Sponsor: Universiteit Utrecht, Netherlands

The Coimbra Pharmacovigilance Regional Unit together with two other regional centres (Lisbon and Porto) of the Portuguese Pharmacovigilance System comprise the CLPP Vaccines Network, which participates in a consortium of 8 European countries (Ireland, Italy, Portugal, Romania, Slovakia, Spain, Switzerland, and the Netherlands) to carry out the Work Package (WP) 1 “Cohort Event Monitoring of safety of COVID-19 vaccines in special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection)” of the Covid Vaccine Monitor (CVM) project, which is coordinated by the University of Utrecht. The study is funded by the European Medicines Agency (EMA). The primary aim of the WP1 is to generate and compare incidence rates of patient-reported adverse reactions of different COVID-19 vaccines in special populations.

Representative Publications

Alves C, et al. **Risk of Cardiovascular and Venous Thromboembolic Events Associated With Janus Kinase Inhibitors in Rheumatoid Arthritis: A Systematic Review and Network Meta-analysis**. J Clin Rheumatol. 2021 Nov 3. doi: 10.1097/RHU.0000000000001804.

Alves C, et al. **The Risk of Infections Associated With JAK Inhibitors in Rheumatoid Arthritis: A Systematic Review and Network Meta-analysis.** J Clin Rheumatol. 2021 Apr 24. doi: 10.1097/RHU.0000000000001749.

Alves C, et al. **Risk of infections and cardiovascular and venous thromboembolic events associated with JAK inhibitors in rheumatoid arthritis: protocols of two systematic reviews and network meta-analyses.** BMJ Open. 2020 Dec 31;10(12):e041420. doi: 10.1136/bmjopen-2020-041420.

Alves C, et al. **Fluoroquinolones and The risk of tendon injury: a systematic review and meta-analysis.** Eur J Clin Pharmacol. 2019 Oct;75(10):1431-1443.

Batel Marques F, et al. **Effectiveness in clinical practice versus efficacy of dipeptidyl peptidase-4 inhibitors in clinical trials for type 2 diabetes: protocol for systematic review.** BMJ Open 2019;9:e032522.

Mendes D, et al. **Real-world intensive safety monitoring of biosimilars rituximab and trastuzumab in a Portuguese oncology hospital.** J Oncol Pharm Pract. 2021 Sep;27(6):1432-1438. doi: 10.1177/1078155220957079.

Mendes D, et al. **Rectus sheath hematoma in patients receiving subcutaneous enoxaparin: A case series of five patients.** Clin Case Rep. 2020 Oct 27;8(12):3432-3439. doi: 10.1002/ccr3.3427.

Mendes D, et al. **Intensive safety monitoring program of antineoplastic medicines: A pilot study in a Portuguese oncology hospital.** J Oncol Pharm Pract. 2020 Jan;26(1):133-140. doi: 10.1177/1078155219849277.

Mendes D, et al. **Spontaneous reports of hypersensitivity adverse drug reactions in Portugal: a retrospective analysis. Expert Opinion on Drug Safety** 2020, DOI: 10.1080/14740338.2020.1743262.

Penedones A, et al. **Risk of nonarteritic ischaemic optic neuropathy with phosphodiesterase type 5 inhibitors: a systematic review and meta-analysis.** Acta Ophthalmol. 2020 Feb;98(1):22-31. doi: 10.1111/aos.14253.

Penedones A, et al. **A comparison between two recommendations to conduct and report systematic reviews on drug's safety.** Syst Rev. 2019 Oct 16;8(1):238.

Ribeiro I, et al. **A Systematic Review of Economic Studies Evaluating Ophthalmic Drugs: An Analysis of the Health-state Utilities.** Ophthalmic Epidemiol. 2020 Oct;27(5):325-338. doi: 10.1080/09286586.2020.1792938.

Ribeiro I, et al. **An analysis of the effectiveness outcomes of economic studies evaluating ophthalmic drugs: a systematic review.** Acta Ophthalmol. 2020 Jan 30. doi: 10.1111/aos.14362.

TRANSLATIONAL VISION RESEARCH PROGRAM

Director: **António Francisco Ambrósio, PhD**

Research Team: Ana Paula Silva, Ana Raquel Santiago, Henrique Alves, José Cunha-Vaz, Rosa Fernandes, Raquel Boia

AIBILI and the Faculty of Medicine of the University of Coimbra have a historical relationship, particularly with the Coimbra Institute for Clinical and Biomedical Research (iCBR, former IBILI). This represents an excellent and strategic opportunity for the facilitation of Translational Research and of innovation based on knowledge gathered from fundamental research on vision science.

This research area at AIBILI, named 'Translational Vision Research', results from the previous and fruitful collaboration with the Retinal Dysfunction and Neuroinflammation Lab, a Group from iCBR headed by the coordinator of this Program, Francisco Ambrósio.

Contacts

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Main Goals

To promote innovative translational vision research, not only by translating laboratory science into new therapeutic strategies, but also by finding new biomarkers of disease, disease progression and response to therapy.

Ongoing Projects

Biomarkers of disease, disease progression and response to therapy.

With a clear translational perspective, and with the aim of bridging the gap between fundamental and clinical research and finding new biomarkers, the aim is to analyse ocular fluids (tears, aqueous humour, vitreous humour) and blood, namely at a molecular level, to access proteins, microRNAs, mitochondrial DNA and antimicrobial peptides (AMPs).

New links between tears composition and Diabetic Retinopathy

Cross-sectional, non-interventional study including healthy controls and T2D patients without and with NPDR or PDR from both genders and between 40-75 years, which aims to evaluate changes in tear protein profiles that can act as early biomarkers for diagnosis Diabetic Retinopathy onset and be useful do predict or monitor its progression. Further this study aims to establish associations between changes in the composition and stability of the tear fluid, as well as, with DR progression.

The retina as a window to the brain or a mirror of the brain

Taking advantage of the communication between retina and brain, we will assess structural, functional, cellular and molecular changes in the retina and will try to establish correlations with changes occurring in the brain in the context of Alzheimer's disease, and Attention Deficit Hyperactivity Disorder (ADHD).

Development of new potential therapeutic strategies for retinal diseases

Target the unmet need for novel potential advanced therapeutic strategies to retinal degenerative diseases, focusing on testing the efficacy of molecular entities that have been selected based on our studies focused on the mechanism of disease, and new delivery routes, such as biodegradable implants or microparticles loaded with drugs of interest.

hiPSCs derived endothelial cells to identify novel mechanism of disease and drug targets in diabetic retinopathy

We are establishing human induced-pluripotent stem cell (hiPSCs) technology derived from skin fibroblasts of diabetic patients, with or without diabetic retinopathy, and controls, and also implementing protocols for the differentiation of hiPSCs into endothelial and RPE cells. These cells will then be used to investigate mechanisms of disease in diabetic retinopathy and to identify potential novel therapeutic targets.

Representative Publications

Aires ID, et al. **Exosomes derived from microglia exposed to elevated pressure amplify the neuroinflammatory response in retinal cells.** Glia. 2020 Dec;68(12):2705-2724. doi: 10.1002/glia.23880.

Amorim M, et al. P**utative Biomarkers in Tears for Diabetic Retinopathy Diagnosis**. Front Med (Lausanne). 2022 May 25;9:873483. doi: 10.3389/fmed.2022.873483.

Boia R, et al. **Intraocular implants loaded with A3R agonist rescue retinal ganglion cells from ischemic damage.** J Control Release. 2022 Mar;343:469-481. doi: 10.1016/j.jconrel.2022.02.001.

Campos A, et al. **Choroidal and retinal structural, cellular and vascular changes in a rat model of Type 2 diabetes.** Biomed Pharmacother. 2020 Dec;132:110811. doi: 10.1016/j.biopha.2020.110811.

Campos A, et al. **Inflammatory cells proliferate in the choroid and retina without choroidal thickness change in early Type 1 diabetes.** Exp Eye Res 2020 Oct;199:108195. doi: 10.1016/j.exer.2020.108195.

Chiquita S, et al. **Retinal thinning of inner sub-layers is associated with cortical atrophy in a mouse model of Alzheimer's disease: a longitudinal multimodal in vivo study.** Alzheimers Res Ther. 2019 Nov 13;11(1):90. doi: 10.1186/s13195-019-0542-8.

Martins B, et al. **Extracellular Vesicles and MicroRNA: Putative Role in Diagnosis and Treatment of Diabetic Retinopathy.** Antioxidants (Basel). 2020 Aug 4;9(8):705. doi: 10.3390/antiox9080705.

Quinn PMJ, et al. **PINK1/PARKIN signalling in neurodegeneration and neuroinflammation.** Acta Neuropathol Commun. 2020 Nov 9;8(1):189. doi: 10.1186/s40478-020-01062-w.

Rodrigues-Neves AC, et al. **Retina and Brain Display Early and Differential Molecular and Cellular Changes in the 3xTg-AD Mouse Model of Alzheimer's Disease.** Mol Neurobiol. 2021 Jul;58(7):3043-3060. doi: 10.1007/s12035-021-02316-x.

Santiago AR, et al. **Keep an eye on adenosine: Its role in retinal inflammation.** Pharmacol Ther. 2020 Jun;210:107513. doi: 10.1016/j.pharmthera.2020.107513.

Socodato R, et al. **Microglia Dysfunction Caused by the Loss of Rhoa Disrupts Neuronal Physiology and Leads to Neurodegeneration.** Cell Rep. 2020 Jun 23;31(12):107796. doi: 10.1016/j.celrep.2020.107796.

Vieira M, et al. **Lab-on-a-chip technologies for minimally invasive molecular sensing of diabetic retinopathy**. Lab Chip. 2022 May 17;22(10):1876-1889. doi: 10.1039/d1lc01138c.

Promoting excellence in clinical research

INTERNATIONAL NETWORKING

EVICR.net - EUROPEAN VISION INSTITUTE CLINICAL RESEARCH NETWORK

AIBILI is the Coordinating Centre of EVICR.net, that is responsible for the management of the Network, coordination of multinational clinical research studies as well as developing training activities in ophthalmology clinical research.

The EVICR.net is a network of European Ophthalmological Clinical Research Centres, dedicated to perform multinational clinical research in ophthalmology, following the European and International Directives for Clinical Research.

At present, EVICR.net has 95 Clinical Ophthalmological Research Centres members from 17 European countries.

EVICR.net strengthens the capacity of the European Union to explore the determinants of ophthalmic diseases and to develop and optimise the use of diagnostic, prevention and treatment strategies in ophthalmology, by performing multinational clinical research.

It is a platform for ophthalmology multinational clinical research in Europe and a structure to support multinational Investigator-Initiated Research (IIR). EVICR.net is also a resource for Industry in the development of new drugs and medical devices in ophthalmology.

In order to become a member of EVICR.net, each Clinical Research Centre must apply to the Network and fulfil basic requirements such as dedicated space to perform clinical studies, qualified and experienced personnel, experience of multinational clinical research and to agree to implement organisational SOPs according to ICH – GCP Guidelines.

Once a member, the Clinical Site adopts/harmonises EVICR.net SOPs with the help of the Coordinating Centre in order to become a EVICR.net certified Clinical Site of Excellence.

Scientifically it is organised by ophthalmology subspecialty Expert Committees namely: Age-Related Macular Degeneration; Retinal Dystrophies; Diabetic Retinopathy and Vascular Diseases; Glaucoma; Anterior Segment; and Ocular Surface, Inflammation, Dry-Eye & Allergies. It also has Transversal Sections in Rare Diseases, Medical Devices and Reading Centres.

Chairman: Prof. Hendrik Scholl, CS nº 110, University Hospital Basel, University Eye Clinic, Basel, Switzerland.

Clinical Studies and Registries

AIBILI as EVICR.net Coordinating Centre, assumes the coordination and management of Investigator Initiated Research (IIR) in ophthalmology across Europe through the Network. EVICR.net Members have the opportunity to participate in IIR as well as to submit abstracts for IIR to the Coordinating Centre in order to be evaluated by a specific Expert Committee. When approved, they will have access to support in coordinating and implementing the IIR. All information is available at www.evicr.net.

EVICR.net Investigator Initiated Research (IIR) has been growing in the last years, giving the opportunity for investigators to perform multinational clinical research of high quality in compliance with ICH-GCP Guidelines assuming that the rights, safety and wellbeing of the trial subjects are protected and that the clinical data are credible.
EVICR.net has contributed to the improvement of diagnostic, prevention and treatment strategies in ophthalmology. In 2022 there were five ongoing multinational clinical research studies of which 3 are European Union funded.

More information:
www.evicr.net

Ongoing Clinical Studies and Activities

Age-Related Macular Degeneration

- MACUSTAR - Intermediate AMD: Development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention

  ClinicalTrials.gov nº: NCT03349801

  Financial Support: European Union and EFPIA - Innovative Medicines Initiative 2 Joint Undertaking - Grant Agreement nº 116076

Retinal Dystrophies

- 2nd IRD Survey - Current management of Inherited Retinal Degenerations (IRD) patients in Europe

  Financial Support: Novartis

Diabetic Retinopathy

- RECOGNISED - Retinal and Cognitive Dysfunction in Type 2 Diabetes: Unraveling the Common Pathways and Identification of Patients at Risk of Dementia

  ClinicalTrials.gov nº: NCT04281186

  Financial support: European Union - H2020-SC1-BHC-01-2019-847749

- CHART - Characterization of Retinal disease progression in eyes with NPDR in diabetes Type 2 using non-invasive procedures

  ClinicalTrials.gov nº: NCT04636307

  Financial support: IIR Grant from Bayer

Anterior Segment

- ANIRIDIA-NET

  Financial support: European Union - COST Action CA18116

Educational Programme

EVICR.net has developed a continual training and educational programme with webinars on ophthalmology clinical research. The Educational Programme is organised in modules each with three webinars of one hour.
Currently the following modules are available at www.evicr.net/webinars/webinars/ to the whole community:

Educational Programme Module	Dry Eye Diagnosis and Treatment	Unmet needs in Glaucoma		Retinal Dystrophies	
Webinars	**Webinar #11** Dry eye syndrome: signs and symptoms	**Webinar #14** Patient compliance & IOP telemetry	**Webinar #17** Inherited Retinel Dystrophies: Overview Causative Genes and Diagnostic Apprach	**Webinar #20** Macular Dystrophies	**Webinar #23** Genetic Diagnostics in IRDs
	Webinar #12 Diagnosis in dry eye syndrome	**Webinar #15** Non-IOP dependent strategies	**Webinar #18** Retinitis Pigmentosa and Gene Therapy	**Webinar #21** Functional Diagnostics of The Retina in IRDs	
	Webinar #13 Treatment of dry eye syndrome	**Webinar #16** Surrogate markers and outcome measures & Early diagnosis	**Webinar #19** Differential Diagnostics of Juvenile and Childhood Genetic Diseases of The Retina	**Webinar #22** Retinal inaging in IRDs	

Representative Publications

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C-TRACER - CHAMPALIMAUD TRANSLATIONAL CENTRE FOR EYE RESEARCH

AIBILI is recognized as a C-TRACER - Champalimaud Translational Centre for Eye Research by the Champalimaud Foundation for its activities in translational eye research.

This Network is of great relevance 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.

The C-TRACERs Network brings together the LV Prasad Eye Institute in Hyderabad, India; AIBILI in Coimbra, Portugal and the Institute for Vision at the Federal University of S. Paulo in S. Paulo, Brazil.

ECRIN - EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK

ECRIN-ERIC is a network dedicated to improving the health of patients and citizens across the world through clinical research. ECRIN-ERIC supports multinational collaboration in clinical research, acting through correspondents hosted in national clinical research hubs and networks. ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research.

AIBILI as Coordinating Centre of EVICR.net, a disease-oriented network clinical research in ophthalmology, is an Affiliate Partner of ECRIN-ERIC. Thus, EVICR.net serves as a resource to ECRIN-ERIC in the area of vision and ophthalmology multinational clinical research, particularly by providing scientific and medical expertise, access to patients and research capacity whereas, ECRIN provides support in the submission and coordination at national level. The MACUSTAR clinical study is as example of this collaboration where the overall clinical study coordination is performed by EVICR.net under the leadership of Prof. Frank Holz, University Hospital Bonn, Germany (Sponsor), and the submission and monitoring activities are performed by ECRIN.

More information:
https://www.ecrin.org

EATRIS - EUROPEAN INFRASTRUCTURE FOR TRANSLATIONAL MEDICINE

EATRIS is a client driven, non-profit organization comprising European academic centers of excellence in translational research. EATRIS partner institutes support in bringing innovative ideas for novel preventive, diagnostic or therapeutic products towards first in human application and on to clinical proof of concept. EATRIS partner institutes provide services and expertise in the following areas: Advanced therapy medicinal products and biologics, Biomarkers, Imaging and tracing, Small molecules, and Vaccines.

AIBILI, is member of EATRIS and has capacities in the **Biomarkers** and **Imaging and Tracing** platforms.

More information:
https://eatris.eu/

ERN-EYE - EUROPEAN REFERENCE NETWORK ON RARE EYE DISEASES

The European Reference Network on Rare Eye Diseases (ERN-EYE) is led by Prof. Hélène Dollfus (Strasbourg, France) and is composed of 64 health care providers (HCP) in 23 countries across European Union. ERN-EYE is organised in thematic groups: Retinal, Neuro-ophthalmology, Paediatric Ophthalmology and Anterior Segment.

EVICR.net is a member of the Scientific, Medical and Ethical Advisory Board (SMEAB). EVICR.net collaborates with ERN-EYE through the Rare Diseases Transversal Section and with its long experience in Quality Systems and certification of Clinical Sites as well as by providing overall management and logistical support needed in multinational investigator-initiated studies in rare eye diseases.

The 2nd IRD Survey - Current management of Inherited Retinal Degenerations (IRD) patients in Europe, performed in 2022, was a collaborative work of EVICR.net with ERN-EYE.

More information:
https://www.ern-eye.eu/

PARTNERS

ARSC – HEALTH ADMINISTRATION OF THE CENTRE REGION OF PORTUGAL

ARSC regulates the organization and functioning of healthcare institutions and services in the Centre Region of Portugal.

The Protocol between AIBILI and ARSC is of great relevance as the area of primary healthcare is a major research interest as screening and prevention are priorities for AIBILI research particularly in imaging diagnostics.

Since 2011, AIBILI-CORC is the Reading Centre for fundus images of Centre Region of Portugal Screening Programme for Diabetic Retinopathy.

ESENFC - NURSING SCHOOL OF COIMBRA

ESEnfC is a public institution of national and international reference, dedicated to the education of nurses in health education, research and innovation. AIBILI and ESEnfC signed a partnership agreement for the development of clinical research activities that brings together two institutions in the city of Coimbra. This partnership includes the promotion of training activities focused on clinical research, as well as strengthening the international presence through the networks in which both institutions are involved.

FMUC – FACULTY OF MEDICINE OF THE COIMBRA UNIVERSITY

The Faculty of Medicine of the University of Coimbra (FMUC) is one of the most important schools of medicine in Portugal due to its vast research areas. The partnership between AIBILI and FMUC allows AIBILI to support FMUC investigators in the overall development and coordination of clinical research studies.

HCP – HEALTH CLUSTER PORTUGAL

AIBILI is member of the Health Cluster Portugal (HCP) whose 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.

ICBR – COIMBRA INSTITUTE FOR CLINICAL AND BIOMEDICAL RESEARCH

Coimbra Institute for Clinical and Biomedical Research (iCBR) is a multidisciplinary research unit from the Faculty of Medicine, University of Coimbra (FMUC). Research at iCBR aims to investigate molecular and cellular mechanisms underlying the pathophysiology of chronic diseases, to identify innovative therapeutic strategies and disease biomarkers, as well as to unveil and implement new approaches to promote the quality of life and wellness.

The partnership between AIBILI and iCBR aims to establish the link between pre-clinical and clinical research, setting the ground for the development of innovative research projects, translating basic science into new therapeutic strategies, but also by using human samples to find new biomarkers of disease, disease progression and response to therapy.

I3S – INSTITUTE FOR RESEARCH AND INNOVATION IN HEALTH OF THE UNIVERSITY OF PORTO

The i3S merges three institutes and researchers from several schools of the Porto University, thus consolidating an extensive collaboration between all institutions. This wide participation of schools, research institutions and hospitals in a research institute is unique in Portugal and is a valuable asset for science and technology development, while creating an environment that feeds real breakthrough research and translation of discoveries into the clinic.

The partnership between AIBILI and i3S increases the participation in innovation and translational projects as well as to have a more complete and robust value chain for their clients, particularly, for companies.

BIO – PORTUGAL'S BIOTECHNOLOGY INDUSTRY ORGANIZATION

P-BIO is the only association that brings together the vast majority of companies linked to the biotechnology and life sciences sector. P-BIO seeks to develop an environment that is favourable to the creation and growth of start-ups, promoting their corporate development domestically and internationally.

The partnership with AIBILI allows P-BIO companies to have access to differentiated support to evaluate the economic viability of medicines, value strategy design, regulation and translation of technology, market access and effectiveness after commercialization as well as to the coordination and overall management of clinical research studies.

INFOCUS CLINICAL RESEARCH

INFOCUS is an ophthalmology focused full-service contract research organization (CRO) based in the USA.

AIBILI and INFOCUS are currently providers of ophthalmology clinical research development support services, respectively, in Europe and North America and together they are able to provide a global ophthalmology clinical research support to industry.

SPO – PORTUGUESE OPHTHALMOLOGY SOCIETY

SPO was founded with the aim of promoting and contributing to the development of Ophthalmology in its different aspects: community and prophylactic, care and curative, scientific, educational and research, with respect for ethics and professional deontology professional ethics; defend the interests of its members, particularly in the exercise of the profession the exercise of the profession; to contribute to the correct conception of a health policy in the Ophthalmology, ensuring standards of quality and competence in accordance with the requirements of medical science. requirements of medical science.

A Protocol between ABILI and SPO is in place allowing the mutual collaboration in clinical research activities, namely training, reinforcement of existing collaboration networks and support to investigator-initiated studies promoted by SPO associates.

HOSPITAL CUF COIMBRA - JOSÉ DE MELLO SAÚDE

The CUF Coimbra Hospital provides access to excellent health services, both inpatient and outpatient with a comprehensive and innovative offer in diverse medical-surgical areas.

The partnership between AIBILI and CUF Coimbra Hospital main goal is the development and coordination of clinical research activities facilitating the exchange of scientific and technical knowledge and taking advantages of the expertise and resources of each institution.

PTCRIN – PORTUGUESE ACADEMIC CLINICAL RESEARCH INFRASTRUCTURES NETWORK

PtCRIN is the national clinical research network aiming to facilitate and improve quality in clinical research and to increase national and international research collaboration for the benefit of patients, citizens and the healthcare system.

PtCRIN is the Portuguese member of ECRIN-ERIC.

AIBILI is a founding member of the PtCRIN and is a Clinical Trial Unit as well as a Clinical Research Centre. AIBILI has the only ECRIN Certified Data Centre in the Iberian Peninsula since 2016 and recertified in 2021 by ECRIN.

UA – AVEIRO UNIVERSITY

The UA is a public foundation under private law whose mission is to contribute to and develop graduate and postgraduate education and training, research and cooperation with society. This partnership with AIBILI allows to cooperate in clinical research activities as well as to students from the Master in Medical Statistics of UA to perform internships at AIBILI.

CHUC - COIMBRA UNIVERSITY HOSPITAL

CHUC is the largest Hospital Center in Portugal playing a central role in the hospital structure of the Center region of Portugal. The CHUC is a regional and national reference hospital center for a significant number of highly complex pathologies and has the recognition, by the competent bodies, of a large number of reference centers for complex and/or rare pathologies that require a degree of professional, technical and scientific differentiation.

AIBILI and CHUC have a Protocol in place that allows the performance of ophthalmology clinical research through clinical trials as well as observational studies.

INFARMED - NATIONAL AUTHORITY OF MEDICINES AND HEALTH PRODUCTS, I.P.

INFARMED, IP is a Government agency accountable to the Health Ministry, that evaluates, authorises, regulates and controls human medicines as well as health products, namely, medical devices and cosmetics for the protection of Public Health.

AIBILI has a protocol with INFARMED to collaborate in the framework of the national strategy for the development of clinical research in the pharmaceutical sector.

Since 2008 that AIBILI has been responsible for a Pharmacovigilance Regional Unit of the National Pharmacovigilance System contracted with INFARMED, IP.

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