



MIA Portugal
Multidisciplinary
Institute of Ageing

**Translational & Clinical Research
for MIA-Portugal M29**

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This document describes MIA-Portugal M29 Report on translational and clinical research for MIA-Portugal.

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1. Summary

This report describes in generic terms the Coimbra translational and clinical research ecosystem and in detail the 2020-2022 initiatives that are relevant to MIA's investigational activity, namely : 1) healthy leaving community programmes in partnership with Ageing@Coimbra; 2) creation of a new collaborative laboratory for ageing (Colab4Ageing), involving academic researchers and industrial partners; 3) a new Academic Clinical Centre (CACC) for coordinating and facilitating transfer of knowledge; 4) a Biobank with capacity to store over 400,000 biological samples.

Considering that the MIA scientific director, CEO and group leaders have been hired recently or are being hired and installed, the priority on translational and clinical research has been to establish the intramural network to leverage MIA's translational and clinical research on ageing. MIA is working closely with the Ageing@Coimbra consortium and joint community initiatives are described in detail in this report. The sophistication and critical mass of the Coimbra translational and clinical research ecosystem as well as the ongoing initiatives make us confident that MIA will be in a strong position to translate its research results to the clinic in the near future in a smooth and productive way.

2. Coimbra translational and clinical research ecosystem.

Coimbra has a dense and sophisticated biomedical and clinical research ecosystem that will help MIA's mission at various levels, from basic biomedical, to translational and clinical research. The main components of this ecosystem are : 1) the Associated Laboratory CIBB (<https://www.cibb.uc.pt/>), a consortium of the Centre for Neurosciences (CNC; <https://www.cnc.uc.pt/en>) and the Institute for Clinical and Biomedical Research (ICRB; <https://www.uc.pt/en/fmuc/icbr>), which enrolls over 600 researchers, 2) the University of Coimbra Hospital Centre (CHUC; <https://www.chuc.min-saude.pt/>), which is one of the biggest hospitals in Portugal with 18 clinical reference centres), 3) the Coimbra Institute for Biomedical Imaging and translational Research CiBiT; (<https://www.uc.pt/en/uid/cibit>), 4) the Institute for nuclear sciences applied to health (ICNAS; <https://www.uc.pt/icnas>), 5) the healthy living community consortium Agein@Coimbra (<https://ageingcoimbra.pt/>) and 6) the Coimbra Biobank located at CHUC. A new collaborative laboratory on ageing (Colab4Ageing) involving academic and industrial partners has been created recently by MIA's ERA-Chair on Ageing Lino Ferreira, and an application to create an academic clinical centre to leverage translational and clinical research has been submitted to the national agency for biomedical and clinical research (AICIB; <https://aicib.pt/en/home-en/>). These two initiatives have been promoted in close collaboration and are of crucial importance to MIA, and are described in detail in this report.

3. Translational and clinical research initiatives

3.1 Evaluation of healthy lifestyles in collaboration with Ageing@Coimbra.

Ageing@Coimbra¹ became one of the most relevant European Innovation Partnership on Active and Healthy Ageing Reference Sites. Ageing@Coimbra has been ranked 4 starts in 2019 evaluation exercise (maximum ranking)². As part of the strategy of the region and MIA-Portugal to embrace healthy living and active ageing as a priority for the Center Region of Portugal, the regional authority CCDRC included this thematic priority as a key element for the region's Smart Specialization Strategy (RIS3). MIA-Portugal, in close connection with Ageing@Coimbra, contributed to build a toolkit for the assessment of population healthy

lifestyles³. The toolkit has been build following a multidisciplinary focus group that developed a science-based product instrumentalized with innovative technologies to interact with the citizens in a user-friendly way. This exercise has been implemented by an EIT Health funded project (HeaLIqs4Cities) in

Lifestyles assessment Toolkit



two complementary activities: 1) Praça Vida+; 2) Vida+ Móvel. The two activities were implemented in Coimbra and in low-density territories of the Centro Region⁴ and further replicated in Porto, Seville, Paris and Groningen.

¹ Malva JO, Amado A, Rodrigues A, et al. The Quadruple Helix-Based Innovation Model of Reference Sites for Active and Healthy Ageing in Europe: The Ageing@Coimbra Case Study. *Front Med (Lausanne)*. 2018 May 8;5:132. doi: 10.3389/fmed.2018.00132. PMID: 29868588; PMCID: PMC5952223.

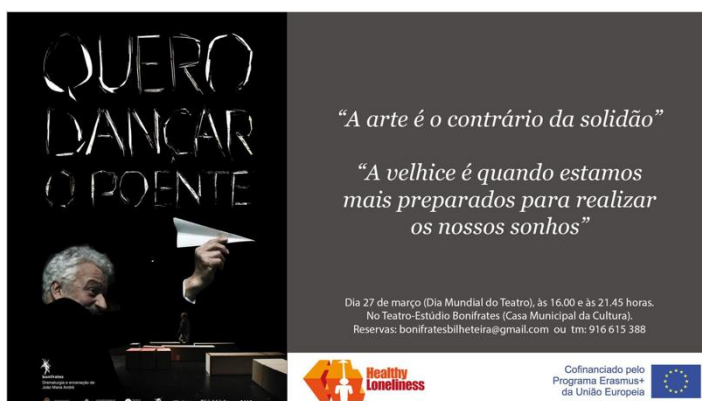
² Malva et al. Chapter 3 – Flagship initiatives for healthy living and active ageing in Europe: the European Innovation Partnership on Active and Health Ageing and the Reference Sites; In: “Aging: from fundamental biology to societal impact”. Ed Oliveira P and Malva J, Academic Press 2022 (In Press)

³ Azul AM, Almendra R, Quatorze M, et al; HeaLIqs4Cities consortium. Unhealthy lifestyles, environment, well-being and health capability in rural neighbourhoods: a community-based cross-sectional study. *BMC Public Health*. 2021 Sep 6;21(1):1628. doi: 10.1186/s12889-021-11661-4. PMID: 34488709; PMCID: PMC8422758.

⁴ <https://www.youtube.com/watch?v=5Co6pN9wAkA>

Recently, the healthy lifestyle assessment toolkit was adapted to the new context of COVID-19 lockdown and loneliness faced by many older persons. The interlink between loneliness and frailty of older persons was dissected in the EIT Health funded project and the ERASMUS+ project Healthy Loneliness. The new healthy lifestyle assessment toolkit was offered through web and also by direct interviews reaching 950 participants. A strong correlation between low education levels and poor health status of older adults highlighted the need to educate the Portuguese population to adopt healthy lifestyles in order to support healthy living in all ages. Moreover, the frailest citizens also demonstrate poor outcomes concerning mental health parameters, including fear about COVID-19, and fear about loneliness and its adverse health-related consequences.

Healthy loneliness project will deliver education materials to support and empower professionals to recognize and manage people suffering from loneliness, including flyers and a book. In partnership with a theater



company in Coimbra (Bonifrates) healthy loneliness project and Ageing@Coimbra inspired the script of “Quero Dançar o Poente”, a theater event to value older adults.

The healthy lifestyle assessment toolkit has been the source of inspiration to build a proposal for Horizon Europe “Excellence Hubs” based on healthy lifestyles associated with Mediterranean Diet. This proposal (CHANGing Excellence Hubs) is a partnership between two Reference Sites, Ageing@Coimbra, in Portugal and FORTH in Crete, Greece.

3.2 A new collaborative laboratory for ageing - Colab4Ageing

A successful application coordinated by Lino Ferreira (ERA-CHAIR Ageing), was submitted to the Portuguese Agency for Innovation (ANI; <https://www.ani.pt/>) and to the main national research funding agency (FCT; <https://www.fct.pt/>), resulted in a new Collaborative Laboratory on Ageing (Cola4Ageing) in Coimbra. Collaborative laboratories are consortia of Academic Research Institutes and industry to leverage innovation and technology transfer.

The objective of the Colab4Ageing is to address a complex societal/demographic/economic problem about ageing that requires the contribution of several stakeholders including universities, companies, hospitals, municipalities, primary care and social providers, among others. To address this objective, the **Colab4Ageing will accelerate the transformation of Portuguese health system** by: (i) creating a strategic alignment between all the stakeholders, (ii) creating the ground for a geriatric culture at scientific, technological, entrepreneurial and clinical levels, (iii) nurturing new leadership approaches based on a system approach, (iv) increasing patient and public engagement so they become co-producers of health and (v) supporting evidence-informed policy that is timely and relevant. The **Colab4Ageing will demonstrate the transformation in 2 areas**: (i) active healthy ageing and (ii) Patient Centered care & multimorbidity. These two areas accommodate a large number of individuals and have the interest of the partnering companies in the areas of IT, food, medical devices and pharmacology. In all the 2 areas, the CoLab will develop market-driven products and services supported by an international recognized research team in the area of ageing or age-related diseases. The strategic vision of the CoLab4Ageing is to enhance the cooperation between companies (NOS Comunicações, S.A; Linde Saúde, Lda; Outsourcing, Lda; Tecnimede; ICNAS produção), a higher-education institution (Universidade de Coimbra), a technological interface center

(Instituto Pedro Nunes), hospitals (Centro Hospitalar e Universitário de Coimbra, EPE; Instituto Português de Oncologia de Coimbra, EPE), primary care and social providers (Caritas Diocesana de Coimbra; Infosaude - Instituto de Inovação e Formação em Saúde, S.A.), and municipalities (Câmara Municipal de Penela) and to contribute for an integrated platform in the area of healthy ageing.

3.3 A new Academic Clinical Centre in Coimbra (CACC) and a new Biobank.

The Faculty of Medicine in collaboration with the Coimbra University Hospital (CHUC) and the Coimbra Institute for Clinical and Biomedical Research (iCBR; <https://www.uc.pt/en/fmuc/icbr>) - the main strategic partners of MIA-Portugal for translational and clinical research - submitted to the national agency for clinical and biomedical research (AICIB; <https://aicib.pt/>) and application to create a Clinical Academic Centre in Coimbra (CACC) to leverage translational and clinical research. If successful, it will have major impact on Coimbra's and MIA's capacity to develop clinical research projects promoted by academic researchers.

The Coimbra CACC aims at creating new models for care, education, research, while departing from the traditional organizational siloes that have prevented the development of integrated approaches to deliver innovative solutions for health care. The new CACC will be a comprehensive hub that congregates researchers devoted to different areas of research, thus bringing complementarity and transversality to topics elected by the consortium as being of strategic importance. Identification of the strategic topics considered existing resources, capabilities and competencies, and the strategy of the founder members and associated partners, as well as the following specific criteria: 1) their value as "Reference Centre" assigned by DGS, 2) the maturity of the areas concerning the effective articulation between education, research and health care, 3) the existence of

competencies and resources to successfully implement a strategy from the bench to bedside and return, that can ultimately benefit citizens and patients and 4) previous outstanding research and ongoing collaborative projects that can be effectively potentiated by CACC. This exercise resulted in the identification of the following topics : Ageing, Neurosciences, Vision Sciences, Cardiovascular Sciences, Metabolic Disorders, Transplantation, Advanced Therapies and Medical Imaging. On the other hand, the areas of Oncology and Palliative Care were considered as emergent, of undoubtedly relevance for human health and also of great cohesive capacity within the ecosystem, since they can transversely overarch several fields.

The CACC has some transversal projects already in place, involving research groups from different areas, including basic scientists and clinicians. We have identified unifying topics, such as iPSC-based therapies, metabolism, and ageing, that comprehensively cross different projects.

The success of pre-clinical studies largely relies on advanced models that mimic key aspects of disease onset and development. We are deeply involved in generating novel, improved disease models for genetic disorders, by taking advantage of the reprogramming technique of patient fibroblasts and epithelial cells collected from patient's urine into iPSC, that allow a thorough cellular, molecular and mechanistic characterization of the disease, as well as the high-throughput screening for the identification of innovative therapeutic strategies. With the main goal of unveiling the molecular basis of disorders the CACC members have implemented two cutting-edge technologies: a) the generation of human iPSC, generated from patient fibroblasts and b) the use of viral vectors for modelling and therapy, the main approach used currently in gene therapy. With the local resources and competencies available, the CACC has privileged conditions to conduct research with clinical impact and application, namely the discovery of new biomarker and innovative pharmacological, gene and cell therapies.

A complementary and crucial initiative was the implementation of the CHUC-UC Biobank for collecting carefully characterized human biologic samples and the associated data. This is an essential resource for approved clinical uses and research projects, promoting basic, translational, and clinical research between CACC members and partners. The biobank was installed inside the CHUC campus, ensuring proximity to the clinical facilities so that new samples can be easily collected. The biobank has all the technology for the automatic extraction, quality testing and archive of genetic material as well as the secure storing of the associated digital data. All samples are encoded and positioned by an automatic system, thus ensuring the highest level of data safety and the complete prevention of human error. The current equipment allows for the housing of more than 400.000 samples, but this capacity will be increased using new solutions for sample storage at room temperature which are already under local testing. Important future developments include database compliance with GDPR, high density genotyping and/or genome sequencing of disease cohorts for supporting next generation clinical studies, pharmacogenomics, personalized and preventive medicine approaches, in close collaboration with MIA-Portugal.

3.4 Examples of ongoing translational and clinical work promoted by both MIA-researchers and MIA-support researchers.

The ERA Chair on Ageing (Lino Ferreira) is participating in a clinical trial to treat patients with stroke. It is the first researcher-driven clinical trial in cell-based therapies in Portugal. The clinical trial has been covered by the national press (<http://sicnoticias.sapo.pt/pais/2018-01-31-Uso-de-celulas-estaminais-pode-vir-a-ser-usado-para-recuperar-doentes-de-AVC>). The clinical trial has been approved by CEIC (national ethics commission) and is currently under evaluation by INFARMED (national medicines regulatory agency) a decision is expected in the next 3 months. The clinical trial



required a INFARMED certified laboratory facility to process stem cells (i.e. isolation and purification). The clinical trial has the coordination of Dr. João Sargento Freitas (Coimbra University Hospital, CHUC), the director of the stroke unit at CHUC, and the participation of the University of Coimbra, Hospital Rovisco Pais and the company Crioestaminal. The clinical trial is supported by previous data showing that after stroke there is an increase in the mobilization of CD34⁺ cells from the bone marrow into the periphery which correlated with higher clinical recovery (Dunac A et al., J Neurol., 2007; Moniche F et al., Stroke, 2012). In addition, Lino Ferreira has identified a set of miRNAs expressed in CD34⁺ cells that predict the outcome of the functional recovery after transplantation (Sargento-Freitas J et al., Neurology. 2018). The novelty of this clinical trial is based in a combination of variables: (i) cells will be administered by intra-arterial injection, (ii) inclusion of patients at subacute phase, and (iii) inclusion of a control group of patients. Previous studies have evaluated CD34⁺ cell-based therapies in the context of stroke (George PM et al., Neuron, 2015); however, they have not used intra-arterial administration (and thus not explored cell delivery in the proximity of the ischemic area) and/or did not include patients at a subacute phase (who present less cellular plasticity and are often in large number for advanced therapies). A randomized controlled phase IIa will be performed in 30 patients to detect a difference in 3 months infarct volume (Sargento- Freitas J, et al., Front Neurol., 2018). Treatment will involve bone marrow aspiration, selection of CD34⁺ cells, and their administration intra-arterially in the symptomatic MCA by angiography.

The clinical trial has been followed by the approval of other important translational projects supported by EC in the context of stroke. For example, a Marie Curie Innovative Training Network entitled NanoStem was funded by the European Commission through the Horizon 2020 Research and Innovation program. The project started in June 2018 and will last for 4 years. The consortium is formed by 9 beneficiary partners from 7 different

countries, including the teams of the ERA Chair Lino Ferreira and João Sargento Freitas. The project addresses brain drug delivery to target neurogenic niches. The level of expression of transferrin receptor in the ischemic region of stroke patients will be quantified for the first time by positron emission tomography. Moreover, the work has also laid the background for two European projects in the setting of INTERREG and POCTEP calls that have been recently funded (NeuroAtlantic and 2IQBIONEURO).

The former scientific coordinator of MIA-Portugal (Prof. Rodrigo Cunha) engaged in a collaborative effort with the Neurology Department of the Coimbra University Hospital, led by Dr. Isabel Santana, to probe if polymorphisms of the A2A receptor gene are predictive of the development of psychiatric comorbidities in demented patients. Prof. Rodrigo is also running a translational project with the Instituto de Medicina Legal – Coimbra to characterise modifications of the properties of the adenosine A2A receptor in human brain samples collected from suicide completers with a pre-record history of depressive conditions. These studies are a follow up of ontogenetic studies that revealed that the activation of adenosine A2A receptors in the lateral septum trigger depressive-like behaviour.

The MIA support group coordinated by Prof. Teresa Gonçalves setup laboratory conditions to recreate viral contaminated environments using aerosol generators, air sampling systems and air disinfection devices, and established a collaboration with general and family doctors to quantify SARS-CoV-2 in the air of rooms and public areas in nursing homes and day care centers for elderly. The same group started a new study to identify specific IgEs of novel allergens in allergic patients attending the Immunoallergology and Othorrinolaringology services at the University Hospital in Coimbra (CHUC). Another project aims at studying novel allergens for diagnosis and for immunotherapy of respiratory allergies. This

project is being done in collaboration with Dr. Jay E. Slater (<https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/improving-safety-and-potency-testing-allergen-extracts>), the Director of the Division of Bacterial Parasitic and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration Food and Drug Administration(FDA) , an immunobiochemist, specialist and regulator in allergens and in immunotherapy of allergies.

The MIA-Portugal support group led by Prof. Carlos M. Palmeira has established a collaborative project with the Department of General Surgery of the Coimbra University Hospital (CHUC) on liver regeneration; a unique biological phenomenon on which liver surgery is crucial for good clinical outcomes and relies on the energetic capacity of liver cells. In this translational project the team is documenting the adaptations in liver energy metabolism after resection, the impact of preoperative chemotherapy on liver mitochondrial function and the development of therapeutic strategies aiming at improving liver regeneration in young and aged patients.

The MIA-Portugal support group led by Prof. Claudia Cavadas has established a collaborative project with the Sleep Unit of the Coimbra University Hospital (CHUC) on Obstructive Sleep Apnea (OSA) - a highly prevalent but undiagnosed sleep disorder that accelerates functional decline and increases the risk of several diseases that have age as risk factor (metabolic and cardiovascular diseases, neurodegenerative disorders, cancer). This translational project (SleepApneaID) aims to contribute to the development of early OSA diagnosis, patient stratification and treatment monitoring. The team showed that, using blood samples and patients data from a cohort of OSA patients, long-term treatment with CPAP (2 years) re-establishes several markers of circadian rhythm dysfunction (Gaspar et al, 2021; EBiomedicine). Additionally, the results

suggest that Long-term CPAP treatment re-establishes some hallmarks of ageing observed in blood cells of OSA patients. The project is moving to the validation in a larger cohort and development of an algorithm for data analysis that ultimately, by the development of SleepApnealD prototype, will contribute to improve OSA diagnosis, patient stratification and treatment monitoring.

The MIA-Portugal partner institute ICRB (Coimbra Institute of Clinical and Biomedical Research) has multiple initiatives and translational and clinical projects, including :

- 1) NANOSTEM – New nanomaterials for neural stem cells drug delivery. the NANOSTEM project (Marie Skodowska-Curie Innovative Training Network) addresses brain drug delivery to target specifically neurogenic niches
- 2) EOLinPLACE – Choice of where we die”, focused on palliative care. ERC grant ERC-StG “ awarded to Barbara Gomes.
- 3) CALMA – Training and support to calm and raise awareness of dyspnea crisis
- 4) Expert 3D (EIT Health) - Transversal Programme in Medical image postprocess, training professionals: 3D printings to research
- 5) PATHWAYS – Data-rodeo for a better healthcare: clinical pathways and process mining (EIT Health)
- 6) VALUE – Value based healthcare supported by process mining tools (EIT Health)
- 7) RIGHT – 2H: On the right side – unveiling the mechanisms of pulmonar hypertension reversability and heart failure progression (FCT)
- 8) GLORIA – Comparing the effectiveness and safety of additional low-dose glucocorticoid in treatment strategies for elderly patients with rheumatoid arthritis (H2020)

- 9) VEMoS – Virtual eye model system for personalised refractive surgery treatment (H2020)



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