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Inês Isabel Sobral Escoval

Overcoming the "Valley of Death" in Healthcare A Study of Factors That Influence the Licensing of Healthcare Technologies From R&D Centres in Portugal

Dissertação de Mestrado na área científica de Biotecnologia Farmacêutica co-orientada pela Senhora Doutora Catarina Cunha Santos e pelo Senhor Professor Doutor João Nuno Moreira e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Outubro de 2021

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"Innovation happens when people are free to think, experiment and speculate"

Matt Ridley

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Resumo

Para ultrapassar o "Vale da Morte" falta-nos conhecimento relativamente aos fatores que influenciam o licenciamento de tecnologias da saúde provenientes de Centros de Investigação e Desenvolvimento (I&D) portugueses. Neste estudo identificámos e analisámos os fatores e problemas que afetam a transferência de tecnologia em saúde em Portugal, assim como as soluções mais promissoras no melhoramento deste ecossistema. Começámos por criar uma lista compreensiva de 511 entidades nacionais que operam no ecossistema de investigação em saúde – a Base de Dados CNCHealthPT. Através de entrevistas com alguns destes intervenientes (Centros I&D, empresas, parques tecnológicos e incubadoras, *Venture Capitalists*, agentes de patentes, e associações de apoio e regulamentação), seguidas por um inquérito nacional, identificámos sete fatores, 93 problemas e 93 soluções que afetam o licenciamento de tecnologias de Centros de I&D em Portugal. Os principais problemas e soluções relacionam-se com o financiamento, conhecimento e competências, diretrizes, recursos humanos em transferência de tecnologia e a colaboração entre a academia e a indústria. Com base nestes resultados, desenvolvemos um estudo-de-caso no Centro de Neurociências e Biologia Celular (CNC) da Universidade de Coimbra relativamente ao maior problema (e solução associada) que afeta o fator 'investigadores de Centros I&D': a falta de conhecimento e/ou alienação para tópicos relacionados com Transferência de Tecnologia e Empreendedorismo. O estudo-de-caso do CNC demonstrou que investigadores possuem reduzidos níveis de formação académica e experiência em transferência de tecnologia apesar de demonstrarem um interesse elevado nestes tópicos. Este estudo vem colmatar uma falha que existe no ecossistema português de transferência de tecnologias da saúde e providencia orientações nos passos que podem ser tomados para melhorar este ecossistema para todos os intervenientes envolvidos.

Palavras-Chave: 'Vale da Morte', Transferência de Tecnologia em Saúde, Ecossistema de Saúde, Licenciamento, Comercialização, Tecnologias da Saúde.

Abstract

As we work to easily cross the "Valley of Death", we lack knowledge about the factors that influence the licensing of healthcare technologies from Portuguese Research & Development Centres (R&D Centres). In this study, we identified and analysed the factors and problems that affect the healthcare technology transfer (TT) in Portugal as well as the most promising solutions that can improve this ecosystem. We started by creating a comprehensive list of 511 national entities that operate on the healthcare research ecosystem—the CNC HealthPT Database. Through interviews with some of these players (R&D Centres, enterprises, technological parks and incubators, Venture Capitalists, patent agents, and support & regulatory associations), followed by a national survey, we identified seven factors, 93 problems, and 93 solutions that affect the licensing of healthcare technologies from R&D Centres in Portugal. The main problems and solutions are related to funding, knowledge and skills, guidelines, human resources in technology transfer, and collaboration between academia and industry. Based on these results, we performed a case study on the Center for Neuroscience and Cell Biology (CNC) of the University of Coimbra regarding the major problem (and associated solution) that affect the 'R&D Centres researchers' factor: the lack of knowledge and/or alienation for topics related to TT and entrepreneurship. The CNC case study showed that researchers have a low level of academic background and experience in TT although they have a high interest in these topics. This study will fulfil a gap that exists in the knowledge of the Portuguese healthcare technology transfer ecosystem and it will provide insights on the steps that we can take to improve this ecosystem for all the players involved.

Keywords: "Valley of Death", Healthcare Technology Transfer, Healthcare Ecosystem, Licensing, Commercialisation, Healthcare Technologies

Index

Index of Figures

Index of Tables

Abbreviations

A4TEC - Association for the Advancement of Tissues Engineering and Cell-Based Technologies & Therapies

AIBILI - Association for Innovation and Biomedical Research on Light and Image (*Associação para Investigação Biomédica em Luz e Imagem*)

AIPPI - *Association Internationale pour la Protection de la Propriété Intellectuelle*

ANI – National Innovation Agency (*Agência Nacional da Inovação*)

ARIPO - African Regional Industrial Property Organization

ASTP – Association of European Science and Technology Transfer Professionals

ATC - Anatomical Therapeutical Chemical Code

ATTP – Alliance of Technology Transfer Professionals

AUTM – AUTM (previously known as Association of University Technology Managers)

BICs - Business Innovation Centres

BLA - Biologics License Application

CCDRN - Norte Portugal Regional Coordination and Development Commission (*Comissão de Coordenação* e *Desenvolvimento Regional do Norte*)

CENTITVC – Centre for Nanotechnology and Smart Materials (*Centro de Nanotécnologia* e *Materiais Técnicos Funcionais* e *Inteligentes*)

CERN – European Organization for Nuclear Research (Conseil Européen pour la Recherche Nucléaire)

CHLN – Lisbon North Hospital Centre (*Centro Hospitalar Lisboa Norte*)

CHLO - Lisbon West Hospital Centre (*Centro Hospitalar de Lisboa Ocidental*)

CHUC – Coimbra Hospital and University Centre (*Centro Hospitalar* e *Universitário de Coimbra*)

CHUSJ – São João Hospital and University Centre (*Centro Hospitalar e Universitário de São João*)

CIBB - Centre for Innovative Biomedicine and Biotechnology

CICS-UBI – Health Research Centre of University of Beira Interior (Centro de Investigação em Ciências da Saúde da Universidade da Beira Interior)

CITS – Centros de Interface Tecnológica (Interface Centres')

CNC – Center for Neuroscience and Cell Biology (Centro de Neurociências e Biologia Celular)

COFAC - Cooperativa de Formação e Animação Cultural

CoLabs – Collaborative Laboratories

COTEC – Associação Empresarial para a Inovação

CPIs - Corporate Private Incubators

CRIA – Centro Regional para a Inovação do Algarve

DGES – Direção Geral do Ensino Superior

DGEEC- Direcção-Geral de Estatísticas da Educação e Ciência

DSECTSI - Direção de Serviços de Estatísticas da Ciência e Tecnologia e da Sociedade de Informação

EAO - Euroasian Patent Office

EAPO - Euroasian Patent Office

EATRIS - European Infrastructure for Translational Medicine

EC – European Commission

ECRIN-European Clinical Research Infrastructure Network

EMA – European Medical Agency

EMBL - European Molecular Biology Laboratory

EMID- Equipa para a Monitorização da Investigação e Desenvolvimento

EPC - European Patent Convention

EPO – European Patent Office

ERIC - European Research Infrastructure Consortium

ESA - European Space Agency

ESO – European Southern Observatory

ESRF - European Synchrotron Radiation Facility

EU – European Union

EuropaBio - European Association for Bioindustries

FCT –Fundação para a Ciência e Tecnologia (Foundation for Science and Technology)

FDA – Food and Drugs Administration

Fundação AEP – Fundação da Associação Empresarial de Portugal (Portugal Business Association)

GAPI – Network of Support Offices for the Promotion of Industrial Property (Gabinetes de Apoio à Promoção da Propriedade Industrial)

GCC Patent Office - Patent Office of the Cooperation Council for the Arab States of the Gulf

GDMF – Pharmaceutical and Medical Device Group (Grupo do Dispositivo Médico e da Farmacêutica)

GDP – Gross Domestic Product

GMP – Good Manufacturing Practice

HCP - Health Cluster Portugal

3S – Instituto de Investigação e Inovação em Saúde da Universidade do Porto

IAPMEI – Agency for Competitiveness and Innovation (Agência para a Competitividade e Inovação)

iBET – Instituto de Biologia Experimental e Tecnológica

IBMC – Institute for Molecular and Cell Biology (Instituto de Biologia Molécular e Celular)

iCBR - Coimbra Institute for Clinical and Biomedical Research

IEEPI – Institut Euroéen Entreprise et Propriété Intellectuelle

IGCF – Gastão da Cunha Ferreira Index (Indicator Gastão Cunha Ferreira)

IMM – Instituto de Medicina Molecular João Lobo Antunes

IND - Investigational New Drug

INEGI – Science and Innovation in Mechanical and Industrial Engineering (Instituto de Ciência e Inovação em Engenharia Mecânica e Engenharia Industrial)

INESC MN – Instituto de Engenharia de Sistemas e Computadores Microsistemas e Nanotecnologias

INFARMED – National Authority of the Medicament and Health Products (Autoridade Nacional do Medicamento e Produtos de Saúde)

INL - International Iberian Nanotechnology Laboratory

INPI - National Institution for Industrial Property (Instituto Nacional de Propriedade Indústrial)

IP – Intellectual Property

IPATIMUP - Instituto de Patologia e Imunologia Molecular da Universidade do Porto

IPC - International Patent Classification

IPEA - International Preliminary Examining Authority

IPI - Independent Private Incubators

IPN –Instituto Pedro Nunes

ISA - International Search Authority

ISR - International Search Report

ISSO - International Organization for Standardization

IT - Instituto de Telecomunicações

KET - Key Enabling Technologies

MIA - Market Introduction Authorization

MIT – Massachusetts Institute of Technology

NA – Non-Applicable

NASA - National Aeronautics and Space Administration

NIS – National Innovation System

NRP - National Reform Programme

OAPI - African Intellectual Property Organization

PACT – Parque do Alentejo de Ciência e Tecnologia

P-BIO – Portuguese Association of Bioindustry Enterprises (Associação Portuguesa de Empresas de Bioindústria)

PCT - Patent Cooperation Treaty

PoC- Proof-of-Concept

R&D – Research and Development

RISE - Health Research Network

RTTP - international accreditation of the Technology Transfer Professionals

S&R – Support and Regulatory

SME – Small and Medium Enterprise

TLA – Technology Licensing Agreements

TP – Technological Parks

TRL – Technology Readiness Level

TTOs – Technology Transfer Offices

TTTs – Technology Transfer Technicians

UA – University of Aveiro

UAlg – University of Algarve

UBIs – University Business Incubators

UCP – Portuguese Catholic University (Universidade Católica Portuguesa)

UÉ – University of Évora

UPIN – Universidade do Porto Inovação

VCs – Venture Capitalists

VoD – Valley of Death

WHO - World Health Organization

WIPO - World Intellectual Property Organization

Glossary

Business Angel – A type of private investor that supports rising business opportunities (e.g., start-ups or early-stage businesses) with 'smart-money' (financial resources plus expertise and business networking).

Darwinian Sea - Metaphor for the crossing of the critical phase in technology development, commonly known as the 'Valley of Death'. In contrast with the 'Valley of Death', the 'Darwinian Sea' has a positive perspective. The successful crossing of this phase is based on the presence of more adequate characteristics for the technology establishment in the market.

Innovation – Original or enhanced technology (in form of a product, process, or a combination of both) that differs significantly from the unit's previous versions and has been introduced in society or unit.

Industrial Property – A subdivision of Intellectual Property. Group of measures that legally protect exclusive rights over inventions, signs for commerce, or article appearances. These measures can be patents, industrial designs, trademarks or geographical indications.

Intellectual Property – Category of property that refers to creations of the mind. Intellectual Property can be focused on literary or artistic aspects (Copyright) or industrial aspects (Industrial Property).

Intellectual Property Rights – The legal rights associated with Intellectual Property protection.

Invention – Materialization of the creation of the mind in the form of a new solution for a specific technical problem or a new way of doing something.

Inventive Step – A patentability requirement based on the non-obvious nature of an invention.

Know-how – It refers to disclosed information combined with obtained skills and expertise that can be used to create a competitive benefit.

Technology Transfer - The process of sharing skills, knowledge, technology, and facilities between entities (such as academia, industry or government) enabling the development and exploitation of the shared resources.

Licensing agreements – Formal contracts between two parties regarding the rights of use of a specific Intellectual Property.

National Innovation System – Set of interactions exercised by the various players involved in the innovation process within a country.

Novelty - A patentability requirement based on whether a technology is considerably different from the state-of-the-art.

Patent – Group of legal rights on the usage of a said invention issued by a governmental authority in the form of a document.

Patent Claims – Most relevant sector of a patent application. Here, the patent applicant defines the extent of protection they intend to pursuit in their patent.

Patent Rights – Legal rights granted by a governmental authority through a patent to the holder of a technological invention in a limited geographical area and time frame.

Patent Cooperation Treaty– International patent law treaty that allows the filing of patent applications in multiple countries (that signed this treaty) through a single application.

Proof-of-Concept (PoC) – Collection of evidence demonstrating that certain technology meets its intended requirements.

Portal da Inovação - Public database created by ANI in 2021, which integrates several entities that integrate the Portuguese National System of Innovation, allowing the centralisation of information concerning the players of this system.

Spin-Off - Enterprise created within the R&D Centre and financed and managed mostly by it. The technology that originated the spin-off is owned by the R&D Centre.

Start-Up - Enterprise created outside of the R&D Centre and financed and managed mainly by outsider funders/investors. The technology that originated the spin-off, although owned by the R&D Centre, is licensed by it to the start-up.

Trade secret – Competitive advantage that is not public knowledge obtained by the safekeeping of critical information. No legal protection rights are associated with this practice, although is maintained through a series of measures (such as non-disclosure agreements). The disclosure of this information is considered an unethical practice and classified as a trade secret violation.

Technology Readiness Level– Scale that measures the level of maturation that a technology presents at a certain stage of its development.

Valley of Death (VoD) – Critical phase in a technology development process in which a turning point occurs that may result in the demise of the technology. It is a negative perspective of this phase, also named 'Darwinian Sea'.

Venture Capitalist (VC) – A type of private investor that temporarily finances rising business opportunities (e.g., start-ups or early-stage businesses). These businesses are usually associated with risky investments and high profitability potential.

Introduction

1.1. Healthcare Research

1.1.1. Healthcare Research in Portugal

Until the 1990s, the scientific research in Portugal presented limited resources (lack of qualified professionals, facilities, and institutions), low internationalization, and deficient legal organization and supervision with the scientific institution's jurisdiction distributed through several governmental bodies. The entrance of Portugal into the European Union (in 1985) gave accessibility to European funds, which lead to a significant increase in international scientific collaborations, the attraction of qualified researchers, and the emergency of novel programmes and research activities. Between 1995 and 2005, several steps were taken to overcome the scientific delay of Portugal in comparison with the EU. For example, institutions tasked with the coordination, funding, and execution of research activities were organized under a unique jurisdiction of the newly created Science and Technology Ministry, scientific career status was reviewed, the number of Research and Development (R&D) units was increased, the concept of Associated Laboratories (excellence and funding label attributed to R&D Centres alone or in a consortium in Portugal) was created, and the funding process became competitive with core and specific programmes. Portugal became a scientific member of several European entities, such as the European Molecular Biology Laboratory (EMBL), the European Synchrotron Radiation Facility (ESRF), and the European Space Agency (ESA)(Vieira *et al.*, 2019).

Between 2006 and 2010, strategies were set up to prioritize science such as qualification of scientific human resources mainly through doctoral fellowships and promotion of scientific employment, competitive funding programmes, and creation of a specific entity for the promotion of research and innovation of excellence towards its internationalization, the R&TD Framework Programme Promotion Office (*Gabinete de Promoção do Programa Quadro de I&DT*). For the first time, the national expenses in R&D were superior to 1% of the Gross Domestic Product, getting to a maximum of 1,59% in 2009. The next 5-year period (2011-2016) was a rough phase for the scientific sector in Portugal due to the negative repercussions of the financial crises that befallen the country. The funding to the qualification of human resources was reduced (hitting the lowest point in 2013 with the number of available scholarships retracted to numbers of 2003), funding programmes for scientific research projects and technological development became inconsistent in periodicity, and the number of approved projects diminished due to a reduction and restriction in the attribution of national funds for R&D. However, positive aspects were maintained such as the advanced training programmes in collaboration with international prestigious institutions: laboratories and observatories (e.g., International Iberian Nanotechnology Laboratory, CERN, and ESO); agencies (e.g., ESA) and higher education institutions (e.g., MIT, Harvard University, and Austin University in the USA)(Vieira *et al.*, 2019). In December 2016, the creation of a major industrial program (INTERFACE) (Presidência do Conselho de Ministros, 2016), integrated into the National Reform Programme (NRP), with three main initiatives to support technology transfer, contributed significantly to the boost of the Portuguese scientific panorama: Clusters (in the health sector - Health Cluster Portugal); Collaborative Laboratories, and Interface Centres (Programa Interface- Home, [s.d.]).

Despite the temporary reduction of funds allocated to science (due to the financial crisis mentioned above), scientific production has managed to maintain itself. One of the tools that allow us to assess scientific production is the number of scientific publications. Between 2009 and 2019, the number of scientific publications in healthcare increased on average 10% *per* year, jumping from 3847 to 10014 publications (2,6 times the initial value). In 2019, 46% of the scientific publications were developed in collaborations with international institutions, which represents an 11% increase compared to the 35% registered in 2009. Between 2009 and 2019, the TOP10 countries that collaborated with Portugal were Spain, UK, USA, France, Germany, Italy, Brazil, the Netherlands, Switzerland, and Belgium (Direção-Geral de Estatística da Educação e Ciência and Direção de Serviços de Estatísticas da Ciência e Tecnologias e da Sociedade de Informação, 2020).

1.1.1.1. The INTERFACE Programme

A. Health Cluster Portugal

Created in 2008 by several entities (Bial, IPATIMUP, IBMC, I3S, INL, CNC, IMM, Hovione, CCDRN, and GDMF), the Health Cluster Portugal (HCP) was recognized in 2016 (through the creation of the INTERFACE program) as a health competitiveness cluster (Health Cluster Portugal [s.d.][a,b]) . In 2019, the HCP counted 175 associates, 115 enterprises, 23.6 thousand working posts, 3 776 Million Euros in business volume, and 493 Million Euros in exportations making Portugal a competitive player in the research, design, development, manufacturing, and marketing of products and services associated with health through the transformation of knowledge into value (IAPMEI, [s.d.][a]). This association contributes to healthcare provision improvement through the promotion of socio-economic development (regional and national) and the increase of business volume, exports, and qualified employment in the healthcare sector. As main strategic areas, HCP elects active ageing and wellbeing, health tourism, e-health, and preventive, personalised, and participative medicine (with special focus on neurodegenerative, oncologic, metabolic and infectious diseases), taking into consideration other structural aspects such as innovation, clinical and translational research, Intellectual Property, technology transfer and entrepreneurship, intelligent specialisation, and internationalisation (Health Cluster Portugal [s.d.][c]).

B. Interface Centres

Interface Centres (Centros de Interface Tecnológica - CITs) strengths the connection between higher education institutions and enterprises through academic products valorisation. They were created to empower their participants in R&D activities and innovation, facilitating access to highly qualified human resources, promoting scientific and qualified jobs, and increasing access to knowledge(ANI, [s.d.][a,b]). Currently, of the 31 CITs, 16 are in the 'health, chemistry and biotechnology' category eight located in the Centre Region of Portugal, five in the North region, and three in the Lisbon and Tagus Valley region (Agência Nacional de Inovação [s.d][a]) . A Table with all the existing CITS in the area of health constitutes Annexe A.

Within the 'health, chemistry, and biotechnology' category, we can identify nine CITs operating in the healthcare niche: AIBILI; CENTITVC; iBET; INESC MN; INL; IPN; IT and INEGI. AIBILI is the only CIT focused exclusively on the healthcare area (Agência Nacional de Inovação[s.d.][a.b]).

AIBILI is a private non-profit institution focused on clinical research, namely on the development of medical imaging technologies. Its R&D activities focus mainly on the development of ophthalmological biomarkers and automatic image analysis through the application of artificial intelligence in preventive diagnosis and personalized medicine. It is associated with 19 entities from enterprises to public entities. AIBILI is the Coordinating Centre of the EVICR.net - European Vision Institute Clinical Research Network (a group of European Ophthalmological Clinical Research Sites dedicated to multinational clinical research in ophthalmology) that gathers 96 centres from 14 European countries. AIBILI is also integrated into the following networks: C-TRACER (from Champalimaud Foundation), European Reference Network for Rare Eye Diseases, and medical research infrastructures such as ECRIN-ERIC and EATRIS-ERIC (AIBILI, [s.d.]; Agência Nacional de Inovação[s.d.][a]). The remaining CITs of the healthcare niche are all private institutions, except the INL that is an intergovernmental organization legally constituted by the governments of Portugal and Spain—the only organization in Europe with an international legal status solely focused on research in the nanotechnology and nanoscience fields. CENTITVC develops nanotechnologies and smart materials such as medical textiles (sutures, biocompatible tissue implants, textile-based biosensors, textiles with antimicrobial, anti-inflammatory, and anti-oedema properties, biometric sensors for wearables devices) (Agência Nacional de Inovação[s.d.][a]; CeNTI, [s.d.]). IBET focus on the pharmaceutical and agro-industry areas (Agência Nacional de Inovação[s.d.][a]; iBET, [s.d.]). INESC MN develops micro-and nanotechnologies to apply in electronic, biological, and biomedical devices such as biochips, biosensors, and Lab-on-a-Chip (miniaturize devices that integrate into a single chip several analyses usually done on a laboratory setting) (Agência Nacional de Inovação[s.d.][a]; INESC MN, [s.d.]). IPN provides R&D and technology transfer, consulting, and specialized services with six in-house laboratories in the following areas: materials, informatics, automation and robotics, geotechnics, electroanalysis and corrosion, and phytosanitary. Although not directed linked to the area, the results of some of these topics (e.g., informatics and automation and robotics) have healthcare usage. IPN also develops activities in innovation management, supporting new products development, performing technological brokerage initiatives, and promoting and managing Intellectual Property. IPN has also an important role as a business incubator/accelerator (Agência Nacional de Inovação[s.d.][a]; IPN, [s.d.]). IT creates and disseminates new knowledge in the telecommunications field with licensing of patent portfolios to enterprises, some of them in the healthcare area such as CardioID (spin-off that develops innovative devices to process heart signals from hands) (Agência Nacional de Inovação[s.d.][a]; CardioID, [s.d.]; IT, [s.d.]). INEGI focus on materials, mechanical, and industrial engineering. For example, INEGI acts within the biomechanics area by re-evaluating and treating pathologies and developing personalized diagnoses and therapeutics (Agência Nacional de Inovação[s.d.][a]; INEGI, [s.d.]).

C. Collaborative Laboratories

The Collaborative Laboratories (CoLabs) mainly create qualified and scientific employment in Portugal by implementing and promoting research projects and lines focused on the creation of socioeconomic value (Agência Nacional de Inovação[s.d.][c]). The CoLab status is granted by Fundação para a Ciência e a Tecnologia (Foundation for Science and Technology, FCT) and CoLab agenda implementation (in research and innovation) is monitored by Agência Nacional de Inovação (National Innovation Agency, ANI). These CoLabs include private, non-profit institutions or associations and enterprises. From the 35 existing CoLabs, ANI recognizes seven as operating in the healthcare research sector: Value4Health.CoLAB; Vector2B; 4LifeLab; BioScale; Healthy Ageing@LAB; Aquavalor and CoLAB TRIALS (ANI, FCT and Programa Interface, 2019; FCT, [s.d.][a]).

Value4Health.CoLAB measures outcomes versus costs of novel technologies to calculate their value for the healthcare system, involving medical professionals and society. It is a partnership among Nova University Lisbon, CUF, Vodafone, and Fraunhofer Portugal Association (ANI, FCT and Programa Interface, 2019; VoHColab, [s.d.]).VectorB2B focuses on drug discovery and development providing specialized services in drug screening, in vitro and in vivo efficacy tests, manufacturing, and clinical trials. It is a partnership among Coimbra and Lisbon Universities (Faculties of Medicine, Pharmacy, and Veterinary Medicine) and the Technophage and Medinfar Group enterprises (ANI, FCT and Programa Interface, 2019; VectorB2B, [s.d.]). The available information for the remaining four CoLabs is scarce, as well as for the CoLabs operating details in general. 4LifeLab focuses on technological knowledge for better health and is coordinated by Centro Hospitalar Universitário São João E.P.E. in Oporto(FCT, [s.d.][a]). BioScale promotes the discovery and translation of pharmaceutical products and is coordinated by Institute for Molecular Medicine João Lobo Antunes in Lisbon(Fundação para a Ciência e Tecnologia, [s.d.][a]). Healthy Ageing@LAB focuses on innovative products and services regarding ageing and is coordinated by Coimbra University(FCT, [s.d.][a]). Aquavalor acts in the various aspects of the water subject, namely in the increasing of knowledge about its therapeutic and prevention benefits and health promotion of thermal waters. It is a partnership among a large number of institutions such as the Polytechnic Institute of Bragança, the University of Vigo (Spain), and the Centro Hospitalar de Trás-os-Montes e Alto Douro(AquaValor, [s.d.]; Fundação para a Ciência e Tecnologia, [s.d.][a]). CoLab TRIALS focuses on creating a unique framework of excellence in clinical research to increase innovation in the healthcare sector through strengthening multidisciplinary team skills and is coordinated by the Nova University Lisbon(Fundação para a Ciência e Tecnologia, [s.d.][a]).

1.1.2. Healthcare Research Players

In 2019, healthcare constituted 11% of the total R&D costs of enterprises, between 29% and 13% of higher education institutions, 34% of government, and 90% of private non-profit institutions. In this section, we overview the healthcare research players in Portugal that are categorized in Research and Development (R&D) Centres (including universities, polytechnics, research institutions, and foundations), enterprises and associations and other relevant organizations (associations, clusters, and other organizations that support and regulate the healthcare research ecosystem)(DGEEC, DSECTSI and EMID, 2020).

1.1.2.1. R&D Centres

It is difficult to identify the number of institutions focused on healthcare research in Portugal. A total of 42 R&D institutions operate in this area according to the Innovation Portal (Portal da Inovação)1. However, this database depends on auto-registration, which can bias the real number. On the other hand, FCT has available information on national research institutions (providing documents with information on funding, strategic projects, among others) but lacks a detailed and updated compilation of all the research institutions in Portugal. In May 2021, FCT published the updated list of 45 associated laboratories (in form of both individual research institutions and consortia) valid for a maximum period of 10 years(Fundação para a Ciência e Tecnologia,[s.d.][b]). This information complements a recent list divulged by FCT identifying a list of 312 research centres with approved funding for the period 2020-2023, 35 of which are in the healthcare area (Fundação para a Ciência e Tecnologia, [s.d.][c]). From these identified 35 R&D Centres, 31 are associated with higher education institutions, two with major research foundations (Champalimaud and Calouste Gulbenkian Foundations), one with an association (Cooperativa de Formação e Animação Cultural, COFAC), and one with a hospital (the Portuguese Institute of Oncology of Oporto); their locations are mainly in Lisbon and Tagus Valley, North and Centre regions. Several of these R&D Centres (associated with the Faculty of Medicine of the Lisbon University Faculty of Medicine of Oporto University, NOVA Lisbon University Aveiro University, Nursing School of Oporto, and Portuguese Institute of Oncology of Oporto) form a 'Health Research Network' (RISE) to develop translational and clinical research of non-communicable diseases (not passed from person to person) such as cardiovascular, oncological, inflammatory and degenerative ones. The RISE initiative aggregates more than 220 healthcare professionals among PhD researchers, nurses, physicians, biologists, nutritionists, and psychologists (Schmitt, 2021).

As we verify an information gap regarding the general status and activities of healthcare R&D Centres, we can infer their improvement indirectly by analysing one of their main outcomes, scientific publications, which we previously approached in the introduction of this section 1.1.1 Healthcare Research in Portugal.

[1] In March 2021.

One of the R&D Centres in healthcare is the Center for Neuroscience and Cell Biology from Coimbra University, which we will focus our analysis on and will be described furthermore in this section.

1.1.2.1.1. Center for Neuroscience and Cell Biology

The Center for Neuroscience and Cell Biology (CNC) is an R&D centre that fosters biomedical and biotechnological research and post-graduate teaching within the Coimbra University. CNC in conjunction with the Coimbra Institute for Clinical and Biomedical Research (iCBR) form the Centre for Innovative Biomedicine and Biotechnology (CIBB). CNC has +490 researchers distributed through three main research areas: Neurosciences and Disease (9 research groups); Metabolism, Aging and Disease (6 research groups), and Biotechnology (20 research groups)(CNC UC, [s.d.][a]). In terms of technology transfer, CNC currently detains 19 patent applications/patents and 10 licensing agreements that originated 10 start-ups (one of which is still under development) based on knowledge/technologies developed at CNC, including MitoTAG, TREAT-U, and Exogenus Therapeutics (data from 2020) (CNC UC, [s.d.][b]). CNC has collaboration agreements with national and international big pharmacological enterprises such as Bial, Bluepharma, and Crioestaminal (national) and Bioblast, Merck, and Innotech (international). Within a clear stimulus to technology transfer and bio-entrepreneurship (creation of biomedical and biotechnological enterprises), CNC was a founding partner of the BioCant Park, the only science and technology park in Portugal specialized in biotechnology, and the Health Cluster Portugal (more information on HCP in sector 1.1.A)(CNC UC, [s.d.][c]).

1.1.3. Enterprises

Similarly to the R&D Centres, it is difficult to identify the enterprises operating in the healthcare research area in Portugal. In the TOP50 of R&D costs by national enterprises are three big players in the healthcare area: Bial, Bluepharma Group, and Hovione (DGEEC, 2020). These three enterprises mainly produce generic pharmaceutical products or develop novel pharmaceutical products for disorders such as Parkinson's Disease, diabetes, and cancer. Bial was founded in 1924 and is based in Oporto with a recently created filial in the USA (Bial Biotech) to develop novel therapeutics for genetic mutations associated with Parkinson's Disease (Bial, [s.d.]). Bluepharma Group was founded in 2001 and is based in Coimbra, integrating four innovative enterprises: Luzitin - solutions in photodynamic therapy and diagnosis (Luzitin, [s.d.]); TreatU - targeted nanotechnology-based platforms for the delivery of pharmaceutical products in the oncology area (TREAT U, [s.d.]); BSIM Therapeutics - design of biotechnological products to treat amyloid diseases (BSIM Therapeutics, [s.d.])) and TechnoPhage - development of biological molecules (mainly bacteriophages and antibody fragments) as therapeutic agents in neuroscience, infection, and ophthalmology (Bluepharma, [s.d.]; Technophage, [s.d.]). Hovione was founded in 1959 and is based in Loures with an initial focus on the development of tetracyclines and anti-inflammatory corticosteroids. Currently, it develops and produces innovative compounds and generic active principles for pharma enterprises and develops proprietary drug products and medical devices with a licensing goal (Hovione [s.d.]).

1.1.4 Associations and other relevant organizations

In Portugal, several organizations support innovation in different aspects: coordination and funding of the R&D (FCT), IP protection (GAPI), or industry development (P-BIO, ANI, and Fundação AEP). These organizations have a global focus on innovation, except P-BIO that supports exclusively the biotechnology industry (one of the topics related to healthcare). Their headquarters locations vary between North, Centre and Lisbon and Tagus Valley regions, except for GAPI that works as a national network. Some of these associations are described in more detail:

A. Foundation for Science and Technology – FCT

The Foundation for Science and Technology (Fundação para a Ciência e Tecnologia) is a public national agency that provides support to scientific and technological research and innovation. This foundation was created in 1997 and is coordinated by the Science, Technology and Higher Education Ministry. The FCT intends to make Portugal an international reference in science, technology, and innovation, and to translate the knowledge generated by scientific research into socio-economic growth. To achieve this vision, FCT endowments research (through opening peer-reviewed calls, grants, and researcher's recruitment), develops projects that support competitive R&D Centres and cutting-edge research infrastructures, ensures the national participation in international scientific organisations, promotes the participation of the national scientific community in international projects, and stimulates the transfer of knowledge between research centres and industry. These actions promote scientific and technological advances and their dissemination and contribution to society and implement the highest international standards of quality and competitiveness in Portugal (Fundação para a Ciência e Tecnologia, [s.d.][d]).

B. Network of Support Offices for the Promotion of Industrial Property – GAPI

In 2001, The National Institution for Industrial Property (INPI)—an entity that protects and promotes industrial property rights in Portugal—created a network of support offices named GAPI (Rede de Apoio à Propriedade Indústrial) to establish knowledge centres in Intellectual Property close to the citizens. These offices promote strategic partnerships, boost cooperation between entities of the National Innovation System, and promote and disseminate Intellectual Property. They are spread across the country and are associated with higher education institutions, business associations, and technological parks helping citizens to obtain specialized information on Intellectual Property and related rights (INPI, [s.d.][a]).

C. *Portuguese Association of Bioindustry Enterprises – P-BIO*

The Portuguese Association of Bioindustry Enterprises (Associação Portuguesa de Empresas de Bioindústria; P-Bio) congregates biotechnology and life sciences enterprises in Portugal. This association is a key element in the support and development of this industrial sector in our country by promoting their national and international business development and by pursuing the development of a favourable environment for the creation and growth of start-ups. P-Bio functions as a connection between industry and higher and relevant authorities (such as government, investors, regulatory agencies) and enhances their role as members of EuropaBio. P-Bio presents three main focus groups: industrial biotechnology, diagnostics and precision medicine, and rare diseases. Recently, P-BIO presented a strategic plan known as BioSaúde 2030 that aims to position Portugal as a research and development centre and a strategic pillar of the production capacity in the biotechnology and life sciences areas in the EU, making our country the 'Factory of Europe for Health' (P-BIO, [s.d.]).

D. *National Innovation Agency – ANI*

The National Innovation Agency (Agência Nacional de Inovação- ANI) supports technological and entrepreneurial innovation in Portugal by contributing to the consolidation of the National Innovation System (NIS) and by reinforcing the competitiveness of the national economy in global markets. ANI follows the guidelines set by the resolution of the council of ministers (RCM 25/2018) for a technological and business innovation strategy for Portugal. This resolution highlights the promotion of innovation (in the economic, social, environmental, and cultural domains) and set guidelines based on collaboration and internationalisation, ensuring a more structured and informed monitoring of the players and the actions involving them (ANI, [s.d.]d; Presidência do Conselho de Ministros, 2018).

E. Portuguese Business Association – Fundação AEP

The *Fundação AEP* or *Associação Empresarial de Portugal* (AEP foundation or Portuguese Business Association) is a private legal entity created in 2009 (and recognized in 2010) that responds to job needs in the creation, innovation, growth, and economic development of the business sector. This association aims to value and disseminate knowledge in the business area (through the development of studies and/or research work), to present proposals of different procedures to competent official bodies and entities, to acknowledge and award companies and entrepreneurs, to promote the improvement of skills for the labour market among young people (enabling access to training through scholarships and professional internships), and to hear the needs of business people (concerning the modernisation and internationalisation of enterprises). One of the studies developed by this foundation is Desafio 2030 that evaluates collaboration and knowledge transfer between the entities integrated into the National Scientific and Technological System (Fundação AEP, [s.d.]).

1.2. General Concepts in Technology Transfer

Technology Transfer (generally known as tech transfer) is the process of sharing knowledge, technologies, or other assets (such as facilities or skills) among distinct institutions (research institutes, governments, industries, universities, or citizens) to enable further scientific and technological development and exploitation (European Commission, [s.d.]). In the context of R&D Centres (as defined above in section *1.1.2- Healthcare Research Players*). Technology transfer transforms results from scientific research activities into innovations. According to the 2018 Oslo Manual, innovation is a 'new or improved product or process (or a combination thereof) that differs significantly from the unit's previous products or processes and that has been made available to potential users (product) or brought into use by the unit (process). It is important to clarify that the generic term of 'unit', in this definition, is used to describe the player responsible for the innovations, this term refers to an institutional unit in any sector, including the institution and its members.' In summary, for a particular scientific result to be considered an 'innovation,' it has to be new and made available for use (implemented). This implementation can be reviewed and undergo updates (major or minor) that can result in additional innovations or the resignation of the existing one (mostly due to lack of commercial value) (OECD and EUROSTAT, 2018).

Known as a catalyst to academic technology transfer, the Bayh-Dole Act (P.L. 96-517, Patent and Trademark Act Amendments of 1980) was enacted in the USA in December 1980 and implemented a standard in patent policy that allowed non-profit organizations (e.g., universities or R&D institutions) and small businesses to retain the title of novel technologies developed with governmental funding. This act encouraged academia to use these novel technologies to combat industry gaps and to license them to small businesses. Although this act was based on USA legislation, it opened doors to similar initiatives around the world, namely in Europe (AUTM, [s.d.][a]).

1.2.1. Advantages of Technology Transfer

The technology transfer process presents several benefits for all the players involved (R&D Centres, industry, general public and scientific community, and the local area):

- increases reputation and recognition and generates revenues for further finance the scientific and technological development – R&D Centres;
- reduces risks and costs with the R&D process, especially with the development of high-gain/high-risk technologies – Industry;
- allows the practical use of the technologies developed and leads to the creation of qualified jobs – General Public and Scientific Community;
- promotes the economic development of the local area where the technology transfer process occurs through the commercialization of innovative technologies – Local Area.

Technology Transfer also encourages collaborations between public and private entities regarding further scientific and technological development, which leads to sharing of resources such as technical expertise and facilities that the players would have a hard time accessing otherwise and the creation of platforms that allow and simplify the exchange of ideas and technologies(USGS, [s.d.]).

1.2.2. The Technology Transfer Process

To simplify the long road of the technology transfer process, we can start by defining its cycle (Fig. 1). The technology transfer cycle starts with the **Research and Development (R&D**) phase that consists in the creation of scientific results with potential commercial interest. The **Evaluation** phase consists of analysing the possibility of intellectually protecting the scientific results and is performed by a Technology Transfer Technician. If the scientific results meet the requirements needed, they will be submitted to **Intellectual Property (IP) Protection**, followed by **Marketing** procedures, and passed on to an entity through **Selling** or **Licensing**. This entity will complete the **Product Development** to fit commercialization needs, if necessary, and finally will put the scientific results available for **public use** in the form of a product, contributing in this way to the **Economic growth** (University of Toledo, [s.d.]).

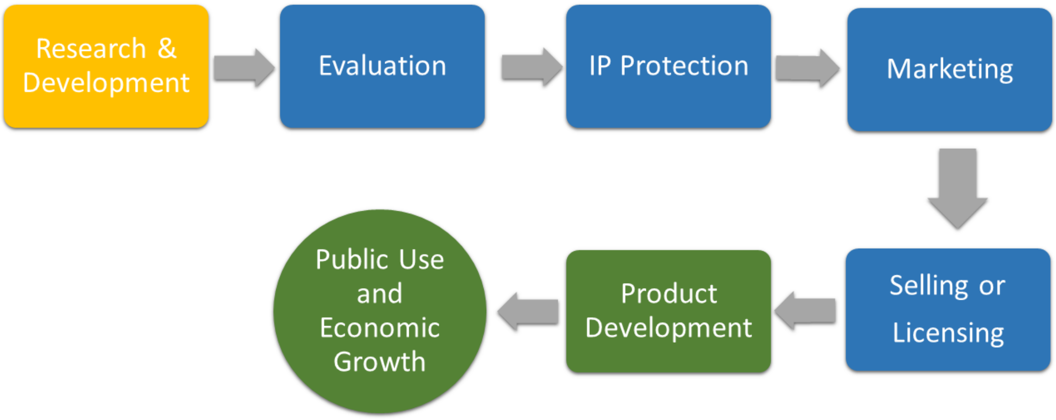


***Figure 1** - The Technology Transfer Cycle from R&D Centres to enterprises. Orange: scientific and technological development phases performed by researchers; Blue: technology transfer core phases performed by a Technology Transfer Technician; Green: post-licensing phases performed by the Licensee. Adapted from: (University of Toledo, [s.d.]).*

This thesis will focus on Evaluation, IP Protection, Marketing, and Licensing (represented in blue in Fig. 1) as the core phases of the technology transfer cycle. These phases are constituted by six key steps: Technology Scouting; Technology and Market Assessment; IP Protection and Management; IP Promotion; Negotiation and Commercialization. These steps are divided according to the core phases mentioned above and their goal (protection or valorisation) regarding the technology being assessed (Fig. 2) (European Commission, [s.d.]).

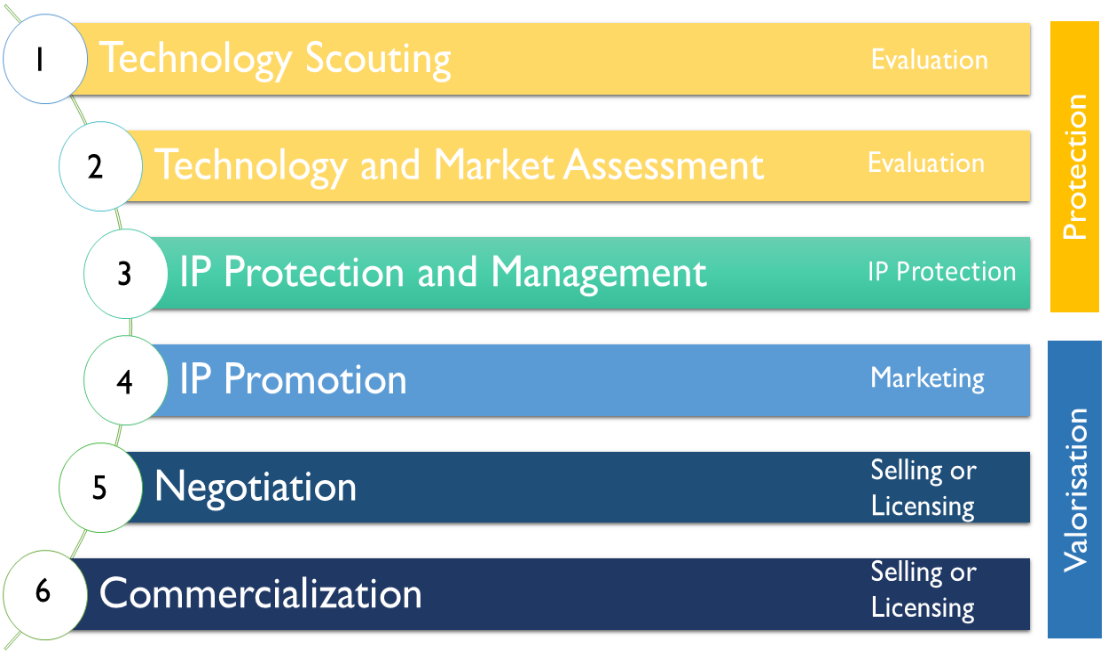


***Figure 2 -** The six steps of technology transfer core phases and their relationship with the different phases of the technology transfer cycle from R&D centres (Adapted from: (European Commission, [s.d.]; University of Toledo, [s.d.])).*

Technology Scouting is the process of identifying scientific results that have the potential to be transformed into innovations early in the R&D process (emerging technologies) by performing regular reviews (formal or informal), as well as doing the first assessment in the commercialization value of these potential innovations (European Commission, [s.d.]).

Technology and Market Assessment is a market screening, where a global overview of the market sectors where the new technologies can be commercialized is identified. This assessment intends to recognize innovation trends and potential competitor technologies, leading players, and clients.

Intellectual Property (IP) Protection and Management have two distinctive steps:

A. The **protection** step is needed for securing the new technologies as intellectual assets that can be commercialized. This step protects the investment in the scientific research, supports business strategies, provides competitive advantages, and unlocks the potential of the technologies. The IP topic will be discussed further in section 1.3.
B. The **management** step ensures the procedures and vigilance necessary to secure IP protection through the appropriate time (European Commission, [s.d.]).

Intellectual Property Promotion is the step necessary for the dissemination of the protected technology. This advertising can be made, for example, by contacting potential buyers/clients (identified in the technology and market assessment step), by organizing promotional events, or by publicizing the technology in proper databases(European Commission, [s.d.]).

Negotiation is the step where the technology valorisation will be discussed among the parties involved. This step has to comply with two major aspects: goal and confidentiality. This compliance can be achieved by the following steps:

A. Define specifically the objective of the technology transfer deal that can be to maximize revenues, to increase the reputational impact of the research activities, or to keep control of the future development of the technology.
B. Define the level of confidentiality within the team, organization, and partners.

Commercialization is the step to decide the better path for the technology to reach the market: (A) selling or (B) licensing.

A. Selling: The new owner will have all rights over the IP assets. After the ownership is transferred, the seller has no further claim to it.

B. Licensing: This commercialization type is based on a technology licensing agreement (TLA) that grants the licensee the right to a certain parcel of the IP rights owned by the licensor. The owner of the IP rights is still the licensor.

1.2.2.1. Licensing of technologies

The licensing of a technology is made through technology licensing agreements (TLAs). These are formal contracts between two parties regarding the rights of use of a specific Intellectual Property. In these agreements, the individual or entity that provides the Intellectual Property rights of a specific technology is the **licensor** and the individual or entity to which is granted the right of usage of said technology is known as the **licensee.** The key elements to a licensing agreement are based on conditions such as the exclusivity degree, the territorial scope, the financial conditions, the duration of the contract, and confidentiality (WIPO, 2015). The licence agreements parameters can vary between:

(1) *Total or partial*. The part of the technology that will be included in the contract. The contract is applied to the entire technology or only a part of it.

(2) *Onerous title or free of charge*. The financial scope of the contract. The existence or lack of any kind of payment for the licensing of the technology.

(3) *Partial territory or entire territory*. The territorial scope of the contract. The contract is applied in a specific or the entire territory where the technology was protected.

(4) *Perpetual licensing or term licensing.* Temporal scope of the contract. The contract is permanent or time-limited.

(5) *Exclusive or non-exclusive*. Exclusivity degree. The contract blocks the licensing of the technology to another party (exclusive) or not (non-exclusive).

(6) *Alienable or non-alienable.* Contract with or without the possibility of the licensee to grant sub-licenses.

The capitalization of these licensing agreements can also vary between:

(1) *Royalties.* Legally binding payment made to the entity that owns an asset for their ongoing use.

(2) *Shares.* Offering the licensor a stake/share in the licensee's equity;

(3) *Milestone payments.* Payment of specific amounts corresponding to the achievement of certain objectives set by the parties;

(4) *Lump-sum payments.* Payments made to the licensor in one or more instalments;

(5) *Cross-licensing agreements (with or without additional payments).* The entities grant licensing agreements to each other where the payment of one licensing agreement is made

through other(s) licensing agreement(s). Both parties benefit from a *quid pro quo* payment and possibly avoid litigation or an infringement dispute while fulfilling their commercial interests. In these agreements still exist the possibility of additional payments.

The licensee can be an enterprise created on purpose for the commercialization of the technology, named a spin-off or a start-up. Although the different meanings associated with these designations, 'University Spin-off or Start-up' is the branch of this concept more relatable to this study. Several authors (such as Roberts and Malonet (1996) and Steffensen, Rogers and Speakman (1999) define it as a new enterprise created by a faculty member or student (the scholar) who left the university to start the enterprise or started the enterprise while still affiliated with the university or an enterprise that is based on a technology or idea transferred from the university.

a. **Spin-Off:** enterprise created within the R&D Centre and financed and managed mostly by it. The technology that originated the spin-off is owned by the R&D Centre.
b. **Start-Up:** enterprise created outside of the R&D Centre and financed and managed mainly by outsider funders/investors. The technology that originated the spin-off, although owned by the R&D Centre, is licensed by it to the start-up. As independent from the R&D Centre, funding is needed to cover premises, materials, and initial costs such as payrolls and operating expenses. According to Nicolaou and Birley (2003) with Start-ups can be categorized in:
    i. **Orthodox.** The technology and the scholar depart from the R&D Centre. There is a severing in the connection with the R&D Centre.
    ii. **Hybrid**. The technology departs from the R&D Centre but is not entirely scholarly. The scholar maintains his/her position at the R&D centre, adding a new function on the board or scientific council of the start-up;
    iii. **Technologic.** The technology departs from the R&D Centre but not the scholar. The scholar maintains his/her position at the R&D Centre but severs the connection with the start-up.

As mentioned in *Manual do Empreendedor* (IAPMEI, [s.d.][b]), these enterprises have various funding sources available:

(1) idea contests. Contests created specifically to support innovative and disruptive ideas.

(2) private and public funding programmes. Funding programmes (created by public or private entities) that aim to fund promising R&D projects or enterprises.
(3) loan banks. Bank loans with the goal of financing enterprises.
(4) business angels. Individual private investors that support rising business opportunities (e.g., start-ups or early-stage businesses) with 'smart-money'—besides the financial investments they contribute with expertise and business network.
(5) venture capitalists. Collective private investors with legal personality (a form of business investment) that finance and support enterprises development. These investors constitute a main source of funds for new enterprises, start-ups and risk investments with high profitability potential, as it provides these businesses with stable funds to manage their development. Their involvement is temporary, once the enterprise reaches a specific level, they look to withdraw the finances invested with a substantial return on investment.

Often, spin-offs and start-ups are inserted into structures that provide resources and support to their development, the incubators. According to Grimaldi and Grandi, (2005), there are four types of incubators:

(B) **Business Innovation Centres (BICs).** Public incubators that aim to reduce business costs by providing free tangible goods such as infrastructures and facilities and access to technical knowledge and management skills. Their main profit derives from service provision and public funding from local, national, and international projects.

(C) **Independent Private Incubators (IPIs).** Private incubators that aim to assist the creation of new enterprises in exchange for fees. They usually provide intangible, high-value goods with a short-term orientation through the realisation of business models, validation and control, access to networks where strategic partners of interest are found, technologies that allow business acceleration, and contact with specialists linked to the entrepreneurial area. These incubators are owned by an individual or a group of individuals to assist new entrepreneurs in the creation and growth of their businesses being able to maintain an equity stake in these businesses. They can also be known as 'accelerators'.

(D) **Corporate Private Incubators (CPIs).** The CPIs are similar to the IPIs, except in ownership. The CPIs are maintained by large enterprises to assist the development of new independent businesses, being able to maintain an equity stake in these businesses.

(E) **University Business Incubators (UBIs).** Public incubators in terms of funding and access to academic infrastructures, however, are similar to private incubators in promoting continuous access to highly technical knowledge and networks of interest to the company that the university possesses.

Although with common points with the Grimaldi and Grandi study, in 2006, Becker and Gassmann released alternative categories for incubators according to their financial goal as non-profit or for-profit. Non-profit incubators are driven by the creation of jobs, regional development, and the formation of an innovation and technology cluster; for-profit incubators are driven by the creation of business, enterprise development, and the formation of a business cluster. In this categorization, UBIs are englobed in the non-profit incubator category, being supported by public funds with the objective of social improvement.

1.2.3. Technology Transfer Offices and Technicians

Technology Transfer Offices (TTOs) are organizations or specific units that handle the Intellectual Property and the remaining technology transfer process for the institutions they represent or are inserted (R&D Centre, enterprise, or other). The main activities of these Offices are the protection of research results, the assessment of the commercial potential and target markets of new technologies, and the promotion and commercialization of these technologies (Young, 2007).

According to the latest ANI report regarding the Knowledge Transfer and Valorisation Network in Portugal, 31 TTOs are associated with higher education institutes (51,6% universities and 48,4% polytechnic institutes); research centres TTOs were not included in this report. From the TTOs enlisted, 32,3% are located in the Lisbon and Tagus Valley, 25,8% in the Centre, 22,6% in the North, 9,7% in the Alentejo, and 3,23% in each of the following regions: Algarve, Azores, and Madeira. The majority (48%) are focused on the 'Health and Life Sciences' area, followed by 37% on the 'Biotechnology' area. From the TTOs enlisted, 93% offer support and management of Intellectual Property, 89% dissemination of information on IP rights and entrepreneurship, 79% creation and support of spin-offs/start-ups, 79% preparation of applications for incentives/subsidies, and 75% management of material transfer or confidentiality agreements (Agência Nacional da Inovação, 2021).

The complexity of the technology transfer process requires specialized human resources within an organization or unit, the Technology Transfer Technicians (TTTs, also known as Technology Transfer Officers). Considering the multiplicity of tasks (IP protection and management, entrepreneurship and spin-off/start-up support, connection with enterprises, fundraising, technology assessment and scouting, among others), TTTs require expertise in areas so distinct as patent law, economy and management, and scientific and technological knowledge in the areas where the technologies being developed are inserted. According to the same 2020 ANI report, 31% of the TTTs enlisted are responsible for incentives/subsides attraction, 26% for Intellectual Property-related activities, 17% for connection with enterprises/industry, 13% for entrepreneurship and spin-offs/start-ups support, 7% for coordination functions, and 7% for other functions(Agência Nacional de Inovação, 2021).

In Portugal, as in the rest of Europe, specialized education and training in technology transfer are scarce. In consequence, the most common situation constitutes an academic researcher who gains interest in technology transfer and branch to train on specific areas such as IP protection, management, and valorisation. This training can be in the form of workshops, networking sessions, summits, or non-degree courses. For example, the National Institute for Intellectual Property (*Instituto Nacional de Propriedade Intelectual - INPI*) provides a catalogue of annual courses in IP protection and valorisation (INPI, [s.d.][b]). National higher education institutions and associations (e.g., Coimbra and Aveiro Universities, HCP, ANI) offer training in the form of presential or online courses (e.g. in the areas of knowledge transfer and IP valorisation strategies and good practices in technology and knowledge transfer). Online courses are always an option for further training of Portuguese TTOs through foreign institutions such as EPO, WIPO, foreign universities (e.g., Cambridge University, Copenhagen Business School,), educational enterprises (e.g., Coursera, edX), and technology transfer associations (e.g., Alliance of Technology Transfer Professionals, AUTM, Association of European Science and Technology Transfer Professionals). A collection of educational and training programmes and courses can be found in Appendix A.

In Portugal, master and doctoral degrees are unavailable for the technology transfer area. Regarding technology transfer related topics such as innovation and entrepreneurship, more training is available. In the ‘innovation’ topic, we can find 13 higher technical professional courses (e.g., Technology Management for Innovation in the Polytechnic Institute of Oporto, or Endogenous Product Management and Innovation in the Polytechnic Institute of Guarda), two bachelor degrees (i.e., Creativity and Business Innovation in the Politechnical Institute of Oporto, or Industrial Management and Technological Innovation in the Higher Institute D. Dinis), 28 master degrees (e.g., Economics and Management of Science, Technology and Innovation in the University of Lisbon, Innovation and Technological Entrepreneurship in the University of Oporto), and four doctorate degrees (e.g., Governance, Knowledge and Innovation in the University of Coimbra, or innovation in business in the University of Aveiro) distributed through 33 higher education institutes. In the entrepreneurship topic, we can find one higher technical professional course (i.e., SME Management and Entrepreneurship in the Higher Institute of Administration and Languages), two bachelor degrees (e.g., Entrepreneurship in Higher Institute Miguel Torga and Development and Social Entrepreneurship in Polytechnic Institute of Beja), 20 master degrees (e.g., Engineering and Innovation Management and Entrepreneurship in the Higher Technical Institute, Management or Entrepreneurship and Innovation in Univerity of Algarve), and one doctorate degree (i.e., Technological Change and Entrepreneurship in the Higher Technical Institute), distributed through 20 higher education institutes (DGES, [s.d.]).

1.2.4. Technology Transfer Community

Worldwide, there are 14 professional associations in technology transfer that form the Alliance of Technology Transfer Professionals (ATTP). Some of these associations, as well as others associated with Intellectual Property and related topics, are discussed below. Portugal has still no association for technology transfer professionals.

1.2.4.1. Worldwide

A. Alliance of Technology Transfer Professionals

The Alliance of Technology Transfer Professionals (ATTP) is a union of 14 knowledge and technology transfer associations worldwide. It was founded by the Association of European Science and Technology Transfer Professionals, the Association of University Technology Managers (USA), the Knowledge Commercialization Australasia, and the PraxisAuril (UK). The ATTP was founded in 2010 and since then joined by associations of technology transfer from countries such as Japan, Turkey, Italy, and Sweden. It promotes and maintains global standards in knowledge and technology transfer by providing support in international accreditation of the Technology Transfer Professionals (RTTP), a recognized title provided to professionals in knowledge transfer and commercialization, which at the beginning of August 2021 counted with 638 professionals across 40 countries (ATTP, [s.d.]).

B. AUTM

AUTM, formerly known as the Association of University Technology Managers, was created in 1974 in the USA and is focused on inspiring, educating, and promoting professionals to support the development of academic research based on innovation and world changes. Currently, it is a community of 3000 members worldwide, associated with 800 R&D Centres (including universities and research centres), hospitals, governmental organizations, and enterprises. From 1980 to 2017, AUTM was associated with the development of more than 200 pharmaceutical products through public-private partnerships (AUTM, [s.d.][b,c]).

C. Association of European Science and Technology Transfer Professionals

The Association of European Science and Technology Transfer Professionals (ASTP), founded in 2000, is a pan-European organization that promotes the knowledge transfer practice and its professionalization, for example, by offering high-quality training in this area. Its main objective is to improve the impact of public research on the economy and society and counts with more than 800 members from 41 countries (ASTP, [s.d.]; Innoget, [s.d.]).

D. *Association Internationale pour la Protection de la Propriété Intellectuelle*

The *Association Internationale pour la Protection de la Propriété Intellectuelle* (AIPPI) was founded in 1897 and its current headquarters are located in Zurich, Switzerland. AIPPI is the world lead non-profit association committed to the development and improvement of laws related to Intellectual Property protection. Their associates represent several professions related to the IP area, such as lawyers, patent agents, patent attorneys, judges, and even scientists and engineers. This association currently has over 8000 members, distributed by 68 national and 2 regional groups, representing a total of 131 countries (AIPPI, [s.d.]). The Portuguese faction of this association (included in the national groups identified) was created in 1975 and is located in Lisbon(Grupo Português da AIPPI, [s.d.]).

E. EuropaBio

The European Association for Bioindustries (EuropaBio) was created in 1996 and represents the interest of the European biotechnology enterprises (over 2600, including the ones focused on the ‘red biotechnology’, healthcare within the biotechnology topic) in communicating with the top European governance. Among other goals, EuropaBio intends to promote the biotech industry based on innovation, coherence, and dynamism and to remove European competitive barriers in this area (EuropaBio, [s.d.]).

1.3. Intellectual Property

According to the World Intellectual Property Organization (WIPO), Intellectual Property (IP) protects 'creations of the mind – everything from works of art to inventions, computer programs to trademarks and other commercial signs'. Depending on the nature of the creation, IP can be classified into two main types: Copyright (and Related Rights) and Industrial Property (Fig. 3). Less known IP types exist such as trade secrets, new plant varieties protection, and unfair competition.

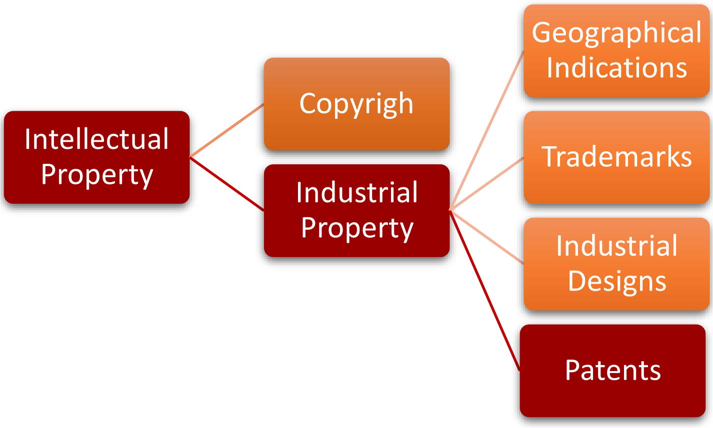


Figure 3 - *The main types of Intellectual Property. Highlighted in red is the IP pathway discussed in this study.*

Copyright protects literary and artistic works (writings such as books and presentations, music, works of the fine arts such as paintings and sculptures, technology-based works such as computer programs and electronic databases). Industrial Property protects inventions (patents), distinctive signs for goods or services related (geographical indications) or not related (trademarks) with a specific geographical origin, and article appearances (industrial designs). A creation can be protected by more than one IP type and subtype simultaneously. According to the focus of this study, we will further explore the most common IP subtype for protecting healthcare innovations: patents (WIPO, [s.d.][a]).

1.3.2. Patent

According to the WIPO definition, a patent is 'an exclusive right granted for an invention, which is a product or a process that provides, in general, a new way of doing something or offers a new technical solution to a problem'. For a patent to be conceded, technical information about the invention must be disclosed in full to the public in a patent application. Three requirements must be fulfilled by the technology to be patentable: **novelty** (non-identical to prior art available on the matter); have an **inventive step** (non-obvious to experts in the area) and **applicability in the industry** (susceptible to be used or made in some kind of industry). The patent rights are territorial, meaning that patent protection can only apply to the country or region where the application process was made, being possible to extend it to other territories (e.g., through the Patent Cooperation Treaty). The patent application generally is a long (from the application submission to the patent grant can pass four to five years), bureaucratic, and expensive process (WIPO, [s.d.][b]).

1.3.2.1. Patent Application Routes

The applicant, the entity that owns the patent, has several routes available for patenting its inventions depending on the country(ies) selected for protection and the costs and timeline of the patent process. In Europe, three main routes for patent application are considered (EPO, [s.d.][a]):

A. Direct National Application (focused on Paris Convention).
B. Direct European Application – EPO (European Route);
C. Patent Cooperation Treaty – PCT (International Route);

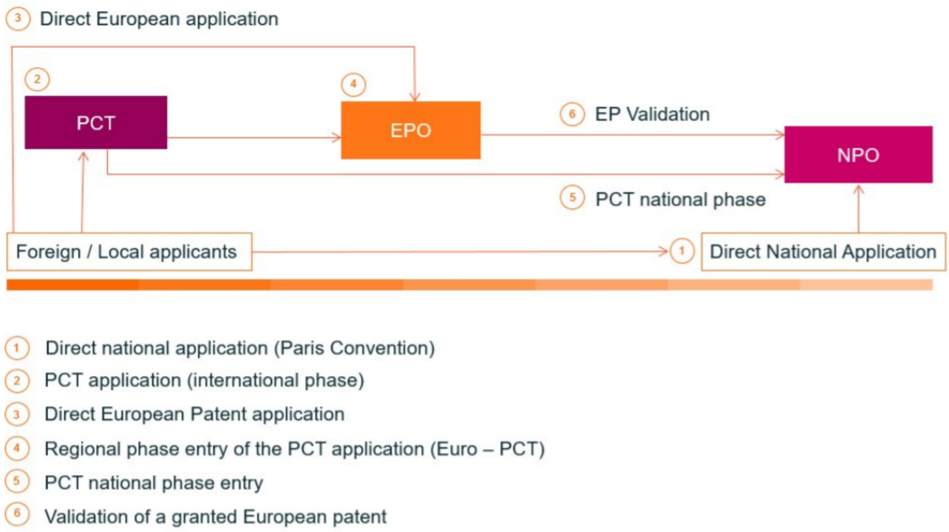


Figure 4 - *Patent application routes in Europe. Source: (Chatel, [s.d.]). PCT: Patent Cooperation Treaty; EPO: European Patent Office; NPO: National Patent Office.*

1.3.2.1.1. Direct National Application (focused on Paris Convention)

The Paris Convention for the Protection of Industrial Property establishes a union for the protection of industrial property (including patents) and was signed on March 20th 1883 in Paris. This Convention stipulates that each signatory country must grant the same protection to nationals of other signatory countries as grants to its own. Individuals of non-signatory countries are allowed the national treatment under the convention if the individual resides or have a real and established industrial/commercial establishment in a signatory country. Paris Convention stipulates a right of priority, meaning that the patent applicant may apply for protection in any of the other signatory countries within a certain period (12 months in case of patents), as these subsequent applications will be considered as if they were filled on the same date as the first application. Paris Convention stipulates common rules that all signatories must follow (WIPO, [s.d.][c]), being the most relevant in the context of this study:

A. Patents: Patents granted in the different signatory countries for the same invention are independent of each other. This means that despite the patent being granted in one signatory country, other signatory countries are not obliged to grant the patent, and a patent cannot be refused, annulled or terminated on the basis that it has been refused in another signatory country.
B. Inventor: The inventor has the right to be named as such in the patent.
C. Patent grant: The grant of a patent might be refused, and a granted patent might be invalidated on the basis that the transaction of the patented product or of a product that was achieved by the means of the patented process is subject to restrictions/limitations resulting from the respective national law.
D. Compulsory License: Each signatory country is required to have legislative measures to act in the prevention of abuses that might arise from exclusive rights associated with a patent. These measures include the grant of compulsory licenses.

Besides Paris Convection, National Patent Offices must consider national laws.

1.3.2.1.2. Direct European Application – EPO

The regional entity responsible for IP protection in Europe is the European Patent Office (EPO). The European Patent Organization integrates 38 countries (named member states): all 27 European Union member states, Albania, Iceland, Liechtenstein, Monaco, North Macedonia, Norway, San Marino, Serbia, Switzerland, Turkey, and United Kingdom. Some countries have an extension (Bosnia and Herzegovina and Montenegro) or validation (Cambodia, Morocco, Republic Moldova, and Tunisia) agreements with EPO regarding the patent application process, as shown in Fig. 5 (EPO, [s.d.][b]).

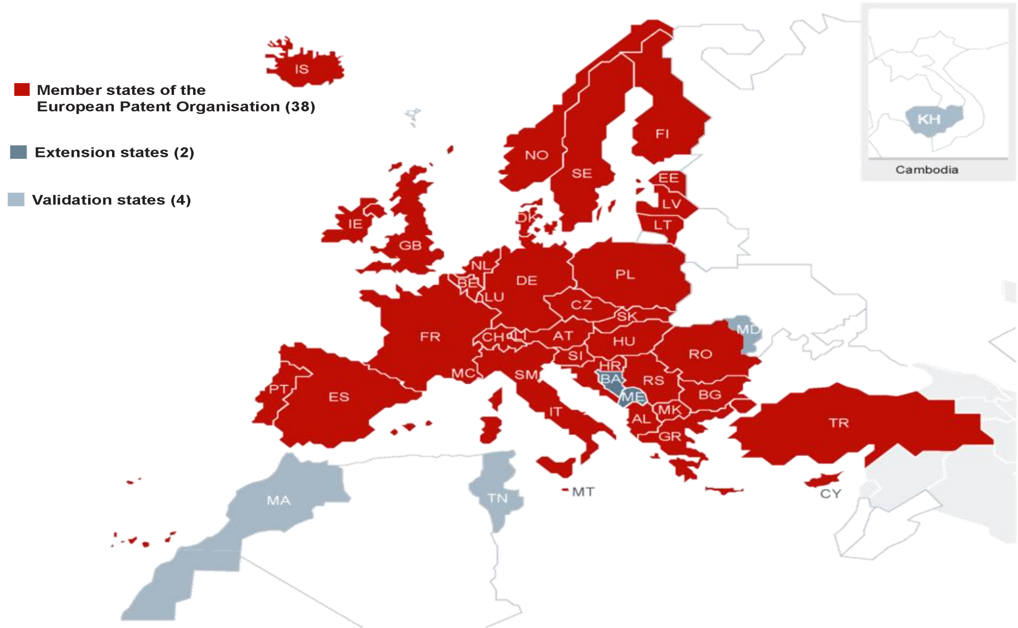


Figure 5 - *Member, extension, and validation states of the European Patent Organization. Source: (EPO, [s.d.][b])*

The EPO patent process begins with the provision of a documentation list according to the EPO guidelines such as a request for a patent, details of the applicant, claims, drawings, and an abstract in one of the three official EPO languages: English, French, or German. As the documentation is classed as correct, a filing date (also known as priority date) for the application is granted, followed by formal examinations. The applicant has the option to file for patent protection in other signatory countries within 12 months of the filing date. After the formal examination, a list of prior art documents relevant to the invention is sent to the applicant in the form of a search report that constitutes an initial opinion on the invention patentability. Eighteen months after the filing date, the patent application is published and available in databases worldwide, acting this application as prior art against any future patent applications. Within six months, the applicant can request a substantive examination for EPO to determine whether the invention and application meet the requirements of the European Patent Convention (EPC). If the EPO examiners favour the grant of the patent, all fees have been paid, and claim translations filed, the decision to grant a patent is reported in the European Patent Bulletin and validated in each designated country/state within a time limit. Third parties may file a notice of opposition to the granted patent (normally, competitors of the invention), within nine months from the patent publication that results in an examination of the appeal by three EPO examiners. After the EPO decision, there is a chance to appeal to independent boards (EPO, 2020).

EPO is one of the regional patent offices inserted on the PCT system.

1.3.2.1.3. Patent Cooperation Treaty - PCT

As previously referred, the patent process is territorial, which means that is geographically bound to the specific country/region where is submitted. However, the applicant can file a patent in multiple countries worldwide (signatory countries) within a single procedure through the Patent Cooperation Treaty (PCT). The PCT is an international patent law treaty established in 1970 that became operational in 1978, currently signed by 153 member states (represented by national patent offices in Fig. 6) (WIPO, [s.d.][d]) and working with five regional patent offices: the European Patent Office (EPO); the Euroasian Patent Office (EAPO); the African Intellectual Property Organization (OAPI), the African Regional Industrial Property Organization (ARIPO), and the Patent Office of the Cooperation Council for the Arab States of the Gulf (GCC Patent Office)(WIPO, [s.d.][e]). A patent application filed under this treaty is known as an international application or a PCT application. The PCT system does not grant or refuse patent applications, it only redirects the application process towards the national/regional offices, providing a preliminary analysis on the invention patentability. Each PCT contracting State has to appoint a national/regional patent office to integrate the International Search Authority (ISA) and the International Preliminary Examining Authority (IPEA).

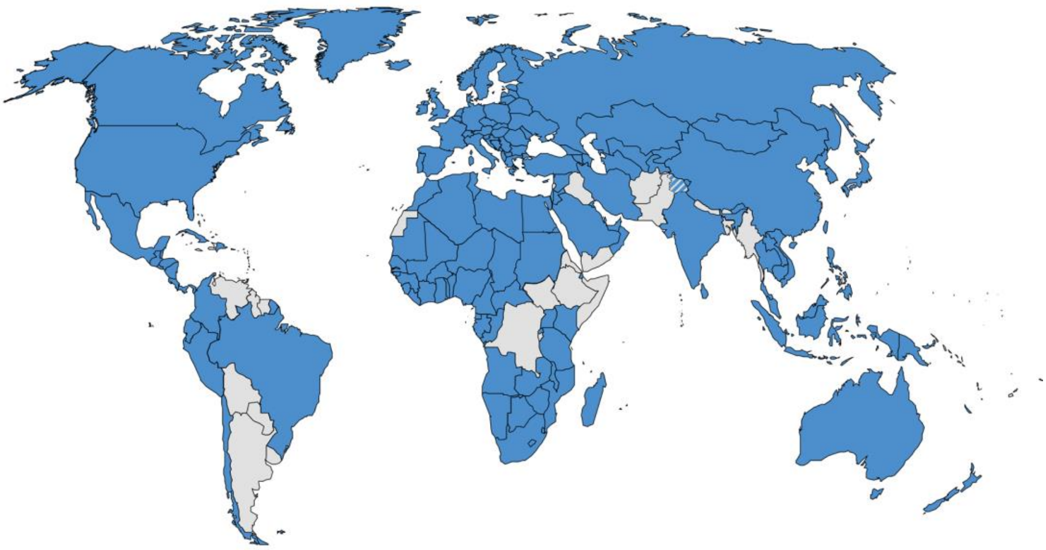


Figure 6 - *World map with the current (June 2021) PCT signatory countries represented in blue. Source: (WIPO, [s.d.][d]).*

The PCT application occurs up to 12 months after the application in the national office (also known as priority date) and presents the international and the national/regional phases. The international phase starts with the PCT application (until 12 months of the priority date). Within 16 months of the priority date, the national/regional office appointed by the International Searching Authority (and selected by the applicant in case there is more than one competent authority appointed) will issue an International Search Report (ISR), comprehending citations of patent documents and other technological references as state-of-the-art, and a written opinion analysing the patentability of the PCT application. After 18 months of the priority date, the International Bureau of WIPO will publish the PCT application in a database referred has 'PATENTSCOPE' to ensure the invention technical disclosure. After 30 months of the priority date, the patent application entries into the national/regional phase. In this national phase, there will be applicable the national procedures for patent applications. An overview of the PCT system is shown in Fig. 7(EPO, 2021).

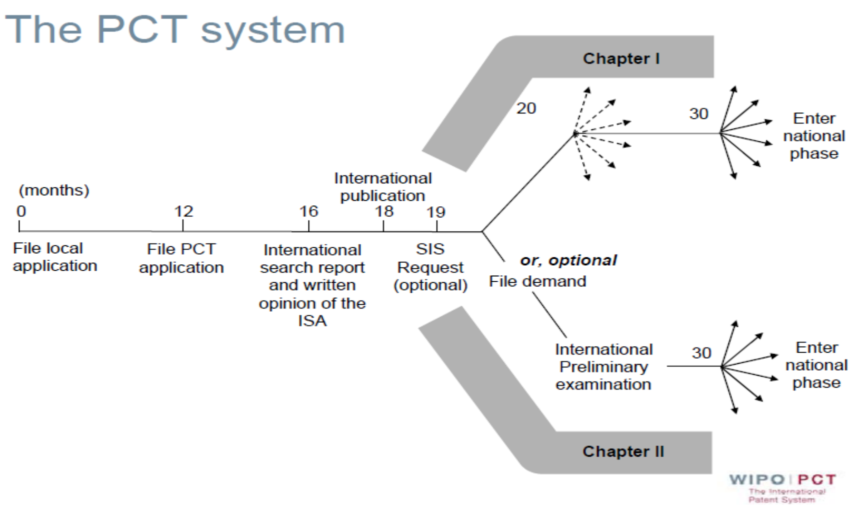


Figure 7 – *Overview of the PCT system. Source: (MPEP, [s.d.]).*

1.3.3. Patent Status in Portugal

In 2020, Portugal granted 203 patents and registered 391 patent, 552 provisional patent, 91 utility model—a type of protection similar to the patent but that presents a shorter protection period and a more limited thematic scope where this model excludes, among others, inventions on biological matter, chemical, and pharmaceutical substances—72 supplementary protection certificate—a supplementary type of protection that extends the protection period of a patent of pharmaceutical products in 5 years to counteract the effects of potential delays associated with regulatory approval processes for these type of products—and 18 PCT system (that entered the national phase) applications. Concerning the different types of applications, provisional patents represented 49,1%, patents 34,8%, utility models 8,1%, supplementary protection certificates 6,4%, and PCT system (that entered the national phase) 1,6% of the total. Overall, Portugal presented an increase in the number of granted patents (0,5% more than in 2019) and invention requests (16,5% more than in 2019). In particular, there were an increase in patent applications (~72,2%), utility model applications (~8,3%), and supplementary protection certificate applications (~10,8%) and a decrease in provisional patent applications (~3%) and PCT system applications that entered the national phase (~10%) (Instituto Nacional da Propriedade Industrial, 2021). In terms of classification (set by the International Patent Classification (IPC) (WIPO, [s.d.][f]), 'A – Human Necessities' (that includes healthcare products) represented 28,3%, of the invention requests. In terms of regional distribution, inventions requests were originated from (in decreasing order) Lisbon and Tagus Valley, North, Centre, and Madeira regions (Fig. 8B)(INPI, 2021). This list differs from 2019, which had requests from (in decreasing order) North, Lisbon and Tagus Valley, Centre, Algarve, Azores, and Madeira regions (Fig. 8A)(INPI, 2020). According to the *Índice ClarkeModet de Propriedade Industrial e Inovação Tecnológica* (2021), hygienisation products and devices, medical devices, protection equipment, and other similar products presented an increase regarding IP applications due to the COVID-19 pandemics. Corporate bodies were the major patent applicants with 52,9% (more 12% than 2019), followed by independent inventors with 27,9% (minus 7% than 2019), higher education institutes with 14,8% (minus 3,6% than 2019), and research institutions with 4,4% (minus 1,6% than 2019). Overall, it was verified a decrease in all categories in relation to the 2019 year, except for corporate bodies that increased 12,3% (ClarkeModet, 2021). The TOP10 entities in applications for national inventions in 2020 were constituted by six higher education institutions (the Oporto, Minho, Aveiro, Beira Interior, Coimbra, and Évora Universities), three enterprises (with no relation with the healthcare sector) and one R&D Centre (the Association for the advancement of tissues engineering and cell-based technologies & therapies – A4TEC). In the overview of industrial protection of inventions, the 'A – Human Necessities' (the category set by IPC in which medical products are inserted) was the area with more representation (28,3%), followed by the 'C - Chemistry' area with 23% (INPI, 2021).

Portugal had 249 European patent applications, occupying the 34th position in the ranking of patent applications by country, according to the EPO European Overview of 2020. The TOP3 areas of the European patent applications from Portuguese applicants were healthcare-related areas (representing 39% of the TOP15): 'medical technologies', 'pharmaceuticals', and 'biotechnology' (ClarkeModet, 2021).

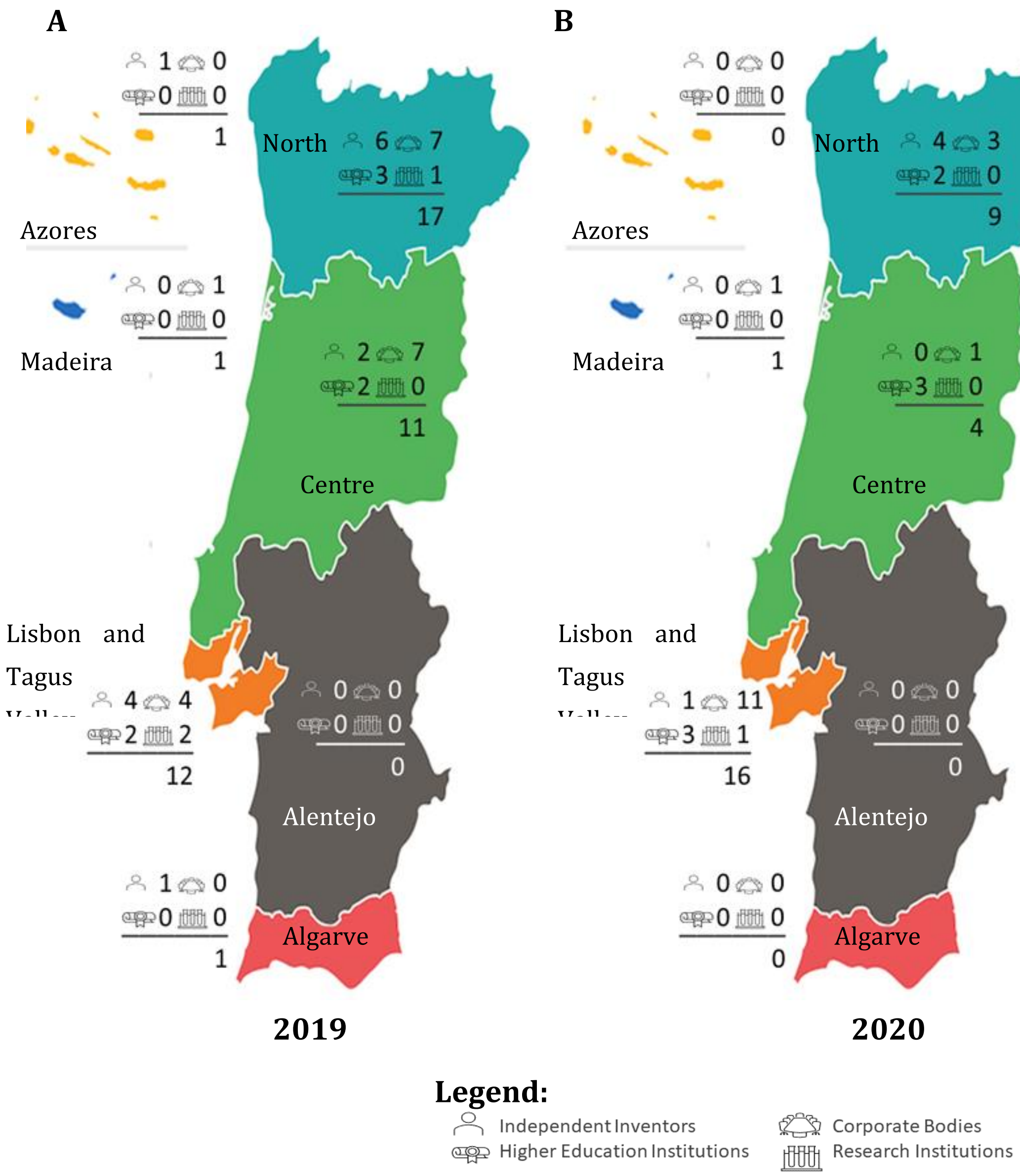


Figure 8 - *Representation of the different regions and types of applicants (i.e., independent inventors, higher education institutions, corporate bodies, and research institutions) of the granted patents in 2019 and 2020 in 'Human Necessities' A. In 2019 (Adapted from: INPI, 2020; B. In 2020 (Adapted from: INPI, 2021).*

According to the 2016-2020 *Indicator Gastão Cunha Ferreira* (IGCF), a ranking that measures international patent activity from Portuguese institutions, two of the TOP5 enterprises that presented more international patent applications operate in the healthcare area: Hovione (3rd position) and Bial (5th position), two of the biggest pharmaceutical enterprises in Portugal. Regarding the TOP5 of Portuguese Universities (and associated research centres), during the 2016-2020 period, the University of Oporto occupies the first position, followed by the University of Minho, both in the North region (Fig. 9)(Cruz, 2021).

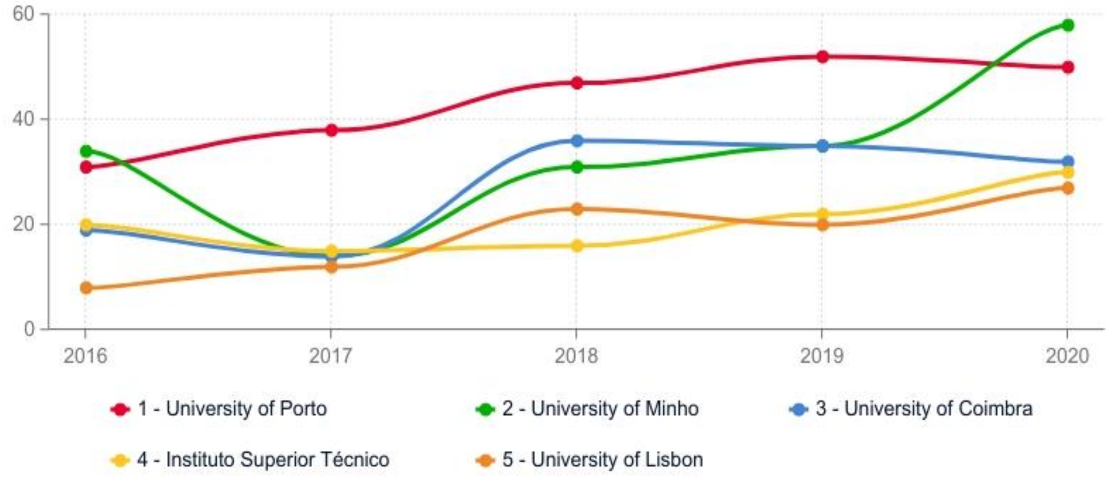


Figure 9 - *Evolution of the international patent activity of the TOP5 Universities according to IGCF through the number of international patents in a specific university between 2016 to 2020. Adapted from: (Cruz, 2021).*

International Overview (WIPO)

According to the WIPO International Overview of 2019, Portugal had 2252 patent applications, 615 granted patents, and a total of 40 052 patents in force. Regarding the patent applications via the PCT System in 2020, Portugal had 269 patent applications, which represents an increase in comparison with the 196 PCT system patent applications in 2019. The TOP10 of Portuguese international patent applicants include three enterprises (one in the healthcare area, SWORD Health S.A.) and seven R&D Centres (four universities – Oporto, Minho, and NOVA Lisbon Universities and Higher Technical Institute - and three research centres - INL, INESCTEC, and RAIZ). From these research centres, only one (RAIZ - *Instituto de Investigação da Floresta e do Papel*) has no focus on healthcare (WIPO, [s.d.][g]).

1.4. Technology Maturation

The technology development stage affects the process of technology transfer. In 1974, Stan Sadin— a National Aeronautics and Space Administration (NASA) researcher—developed a scale to assess the maturity level of a particular technology, named Technology Readiness Level (TRL)(Sadin, Povinelli and Rosen, 1989). The original scale was composed of seven levels of technology maturation (being 1 the lowest and 7 the highest), being later (around the 1990s) modified to nine levels. In 2013, the TRL scale became a guideline adopted by the International Organization for Standardization (ISO). In 2010, the European Commission identified Key Enabling Technologies (KETs)—specific investments and technologies with the potential to capitalize on new markets and retain competitiveness in markets already set such as nanotechnology, advanced materials, and biotechnology—and following a demanding trend (due to contact with governmental organizations) started to widely use the TRL concept

(Héder, 2017). Being originally developed to be applied in aerospatial/aeronautical technologies, TLR is currently used in a broad spectrum of areas. Although respecting the maturation level of each stage, a TLR scale should be designed for each scientific area.

1.4.2. Technology Readiness Level Scale in Healthcare

Considering this thesis topic, we will detail a TLR scale appropriate for pharmaceutical and medical developments (Notander, [s.d.]). The stages of the TLR scale (Fig. 10) are the following:

TRL1 – Ideation. Identification of the market need and study of the technology basic principles.

TLR 2 – Proof-of-principle. Formulation of the technology concept (hypothesis) and development of research ideas and protocols. Development of core individual components.

TRL3 – Experimental proof-of-concept. Performance of analytical and laboratory studies (hypothesis testing) for initial tests of the technology. Limited *in vitro* and *in vivo* studies.

TRL4 – Laboratorial validation. Validation of the technology in the laboratory by completion of laboratory studies (efficacy and safety studies in an *vivo* model). Development of a functional prototype/system.

TRL5 – Environmental validation. Lab-scale prototype/system testing. Approval for Phase I clinical trials.

TRL6 – Environmental demonstration. Commercial-stage prototype/system testing. Phase I clinical trials completed and approval for phase II clinical trials.

TRL7 – Late-stage validation. Testing of commercial prototype/system in an appropriate environment. Phase II clinical trials completed and approval for phase III clinical trials.

TLR8 – Pre-commercialization. Final product ready for the market. Phase III clinical trials completed and approval for market introduction.

TLR9 – Commercialization. The commercial launch of the product. Postmarketing studies and surveillance.

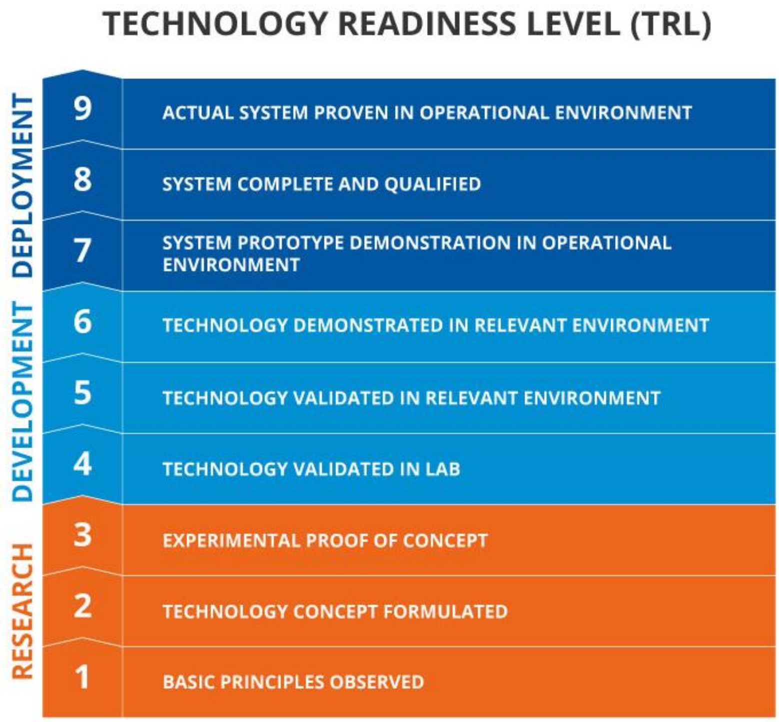


Figure 10 - *Technology Readiness Level scale with the description of each phase. Source: (TWI, [s.d.])*

1.4.3. Clinical Trials: Pharmaceutical Development

This sector will approach aspects of the general process of the development, review, and approval of pharmaceutical products.

Usually, clinical trials constitute an obligatory process for the market introduction of pharmaceutical products. They are constituted by three phases (Phases I, II, and III) and inserted into a long chain of events (Fig. 11). The pharmaceutical product development starts with the strategic and applied research, where the product is discovered, followed by a Phase 0 (also known as a pre-clinical phase) that comprises *in vitro* and *in vivo* tests and preliminary safety, pharmacokinetics, and pharmacodynamics studies and can last from 3 to 6 years. If positive, a request is submitted for an Investigational New Drug (IND) that once approved culminates in the initiation of the clinical trials. Phase I has a duration of weeks to months and is performed in 20-80 healthy volunteers (except for severe pathologies, such as oncological diseases or Acquired Immunodeficiency Syndrome – AIDS, where the pharmaceutical products are too risky to be tested in healthy individuals, compromising the underlining ethics of the clinical trials). Phase I evaluates the product safety and ADME (absorption, distribution, metabolism, and excretion) profile. Phase II has a duration of ~2 years and is performed in 100-300 participants that suffer from the disease targeted by the product being analysed, with restrictive criteria for patient's selection. Phase II evaluates the short-term efficacy and safety and the most beneficial dosage for treatment of the pharmaceutical product. It also evaluates endpoints for the study, assesses the therapeutic regime, and identifies a new population for the next phase. Phase III has a duration of months to years and is performed in 1000-3000 patients with selection criteria close to the real-life application. It evaluates long-term efficacy and safety, interactions, and contraindications of the pharmaceutical product (by developing comparative studies between the experimental and the standard pharmaceutical product or a placebo). After Phase III, a request for a commercial authorization (named Market Introduction Authorization – MIA in Europe and Biologics License Application - BLA in the USA) is submitted to an official authority that reviews and approves (if compliant with regulatory criteria) the trial results. The official authority differs according to the geographic location of the new product target market: Europe - European Medicines Agency (EMA) and the USA - Food and Drugs Administration (FDA). Phase IV (also known as Post-Approval Research and Monitoring Phase) evaluates the long-term safety and secondary effects of the product during its commercialization. On average, 10-15 years pass from the pharmaceutical product discovery to the market (Apifarma, 2013; Quintela Da Luz, 2016).

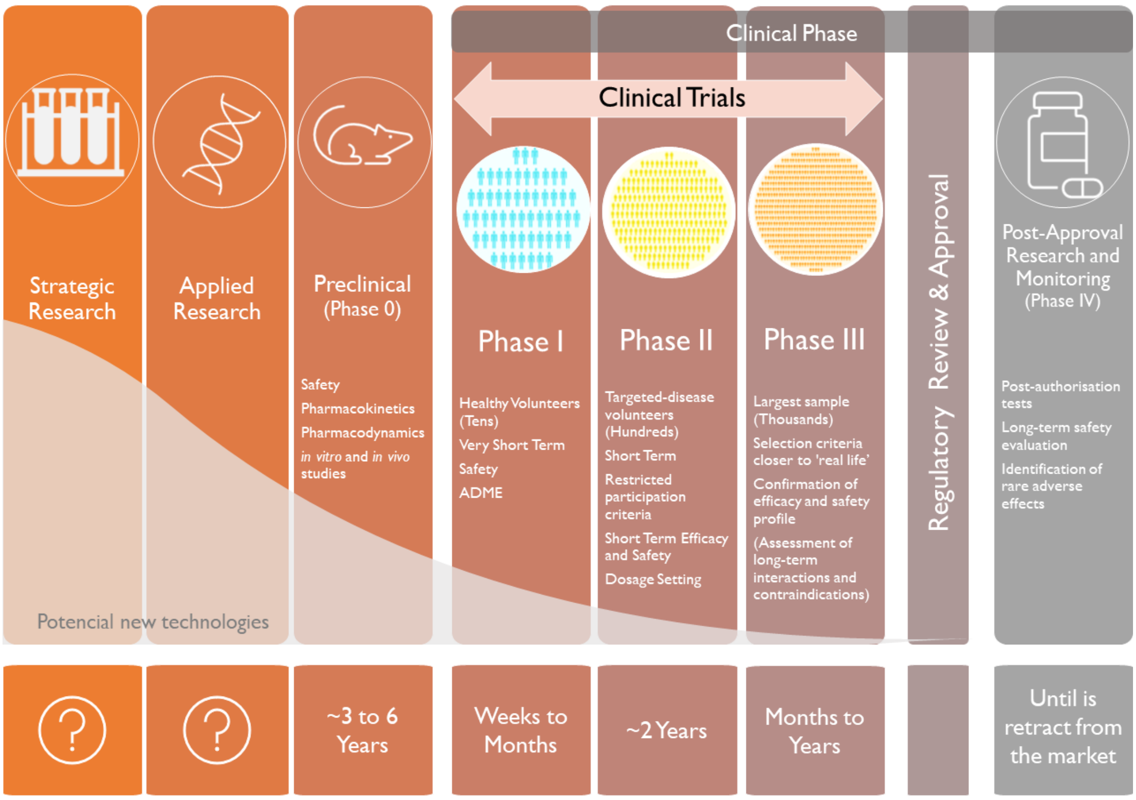


Figure 11 - *The path of pharmaceutical products from the discovery to the market.*

1.4.3.1. Clinical Trials in Portugal

In Portugal, clinical trials are regulated by the *Autoridade Nacional do Medicamento e Produtos de Saúde* (National Authority of the Medicament and Health Products, INFARMED) according to national and European laws (e.g., *Lei nº21/2014, de 16 de Abril* that was modified by the *Lei nº73/2015, de 27 de julho* and the European Council and Parliament guideline 2001/20/CE). In the year 2020, INFARMED had 187 clinical trial applications (30% higher than the previous year), 155 of them were approved. Of these 187 applications, 41 were to Phase I, 36 to Phase II, 99 to Phase III, and 11 to Phase IV. The industry submitted 167 of these clinical trial applications, being the remaining 20 submitted by academia (INFARMED, 2021; LUSA, 2021). The major clinical trial applications were in the 'antineoplastic and immunomodulating agents' (81 applications), the 'nervous system' (27 applications), the 'antiinfectives for systematic use' (13 applications), and the 'cardiovascular system' (13 applications) clinical areas as defined by the Anatomical Therapeutical Chemical Code (ATC) of the World Health Organization (WHO). The year 2020 was only surpassed by 2006 with the historical number of 160 approved clinical trial applications Currently, clinical studies in Portugal occur essentially in four main hospitals: *Centro Hospitalar e Universitário de Coimbra* (Coimbra Hospital and University Centre, CHUC), *Centro Hospitalar e Universitário de São João* (São João Hospital and University Centre, CHUSJ, in Oporto), Centro Hospitalar Lisboa Norte (Lisbon North Hospital Centre, CHLN), and *Centro Hospitalar de Lisboa Ocidental* (Lisbon West Hospital Centre, CHLO). These clinical trials are focused on oncology, neurology, and infectious diseases, mainly antiretroviral pharmaceutical products for HIV and Hepatitis C. To improve clinical trials, Portugal joined the European Infrastructure for Translational Medicine (EATRIS), a consortium that assists its members in the development of diagnostic and therapeutic programmes, reducing the risk and increasing the value of novel health products (LUSA, 2019).

1.5. 'Valley of Death' in Healthcare

The concept of the 'Valley of Death' (VoD) describes a critical phase in the development of a technology that occurs at a turning point where overlap between the final stages of the scientific research and the commercialization process is verified (Ellwood, Williams and Egan, 2020). A representation of this can be found in Fig. 12.

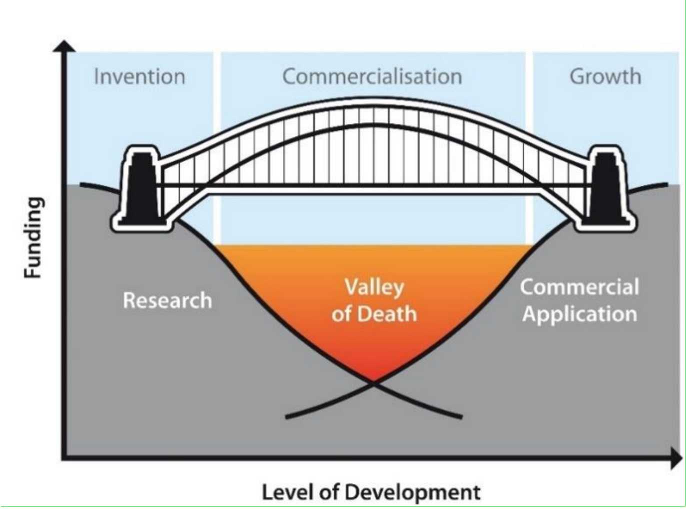


Figure 12 – *General visualization of the concept of the 'Valley of Death' (VoD). Source: t.ly/NB4u*

When studying the VoDin the healthcare context, the literature is scarce and mostly refers to case studies of specific or type-specific technologies rather than general studies (e.g., Silver et al., 2015; Fritzler et al., 2021). Steven Reis (2006) and the Canadian Institutes of Health Research (2011) identify not one but two 'valleys of death', as shown in Fig. 13. The first occurs in the transition from the basic to the clinical research (referring to a transition from TLR4 to TLR5) when difficulties are encountered to move the health technology from the discovery and development in a laboratory setting to the development in a clinical setting (clinical trials). The second occurs in the transition from clinical research to clinical practice (referring to a transition from TLR6 to TLR7) when moving the technology from clinical validation to the market and consequent use in the clinical practice. For example, the study of Silver et al. (2015) describes the path and challenges that preclinical innovations in acute kidney injuries go through to reach clinical applications, demonstrating this 'double valley' phenomenon.

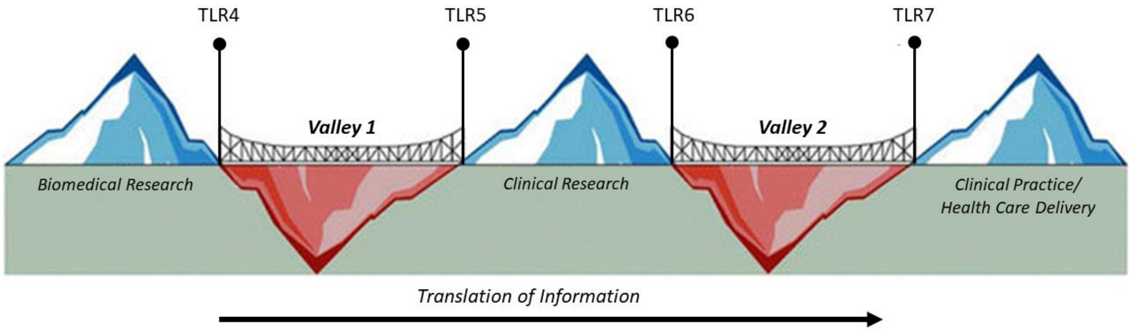


Figure 13 – *The 'Valleys of Death' in the healthcare context. Adapted from: Silver et al., 2015*

Although there is no definitive clarification nor a consensus for solutions to be reached according to Ellwood, Williams and Egan (2020), there are several studies (regarding general and healthcare contexts of the VoD) that analyse/present various perspectives on these factors. These factors are funding, technology, Intellectual Property, TTO, commercialization and academia-industry collaboration. Examples of these studies are: a) Maia and Claro (2013) analysed the creation of a Proof-of-Concept Centre (in the Centre region of Portugal) as a possible solution for the existing gap in the funding of proof-of-concept studies; b) Khademi and Ismail (2013) analysed the factors for successful commercialization of university technologies; c) Hugget (2014) present an overview of TTOs status in the US; d) Roll, Lerner and Gimmon(2015) identified barriers that Israelis medical centres (e.g., hospitals) face in the healthcare technology transfer process (e.g., the lack of training and expertise of medical centres TTTs, funding options, regulatory measures, and collaboration with TTOs, the scattered geographical location of the different medical centres, and the academic 'publish-or-perish culture'); and (e) Davey and colleagues (2018) studied the relationship status between academia and industry in the European countries. A brief general description of these studies and related factors is shown in Table 1.

Table 1 – Review of the state-of-art factors associated with the bridging of the 'Valley of Death' (VoD) in technology transfer.

Identified factor	General description of the study	Reference
Funding	Analysis of the technology transfer process funding: from basic research to successful commercial innovations	Auerswald and Branscomb (2003)
	Analyse and categorise barriers in entrepreneurship in healthcare organizations	Phillips and Garman (2006)
	Commercialization Success Factors of University Research Output	Khademi and Ismail (2013)
	Study of a proposal to combat a gap in proof-of-concept studies in the Centre region of Portugal	Maia and Claro (2013)
	The effect that public science policies have on the success or failure of crossing the VoD.	Meslin, Blasimme and Cambon-Thomsen (2013)
	Analysis of the role of the university and PRO-oriented seed funds as tools to address funding gaps and facilitate the commercialization of academic technologies.	Munari et al. (2014)
	Analyses the barriers in technology transfer from medical centres in Israel	Roll, Lerner and Gimmon (2015)

Table 1 – Review of the state-of-art factors associated with the bridging of the 'Valley of Death' (VoD) in technology transfer.

Identified factor	General description of the study	Reference
Funding	Analysis of proof-of-concept studies and university-oriented seed funds in the technology transfer process as a funding gap aid	Munari, Sobrero and Toschi (2015)
	Analyses and categorises the barriers and challenges associated with the technology transfer of technologies from R&D centres.	Mazurkiewicz and Poteralska (2017)
	An overview of the problems and possible solutions associated with the VoD of pharmaceutical products	Seyhan (2019)
	Review of the development pathway of biomarker-based diagnostic tests: from discovery, validation, regulation to approval	Fritzler et al., (2021)
	Review on successfully crossing the VoD	Kampers et al., (2021)
Technologies	Literature review on the academia-industry relationship for the commercialisation of research and technologies	Markman, Siegel and Wright, (2008)
	Study on assessing prospects for crossing the VoD	Coller and Califf, (2009)
	Analysis of the technology transfer process funding: from basic research to successful commercial innovations	Auerswald and Branscomb (2003)
	Commercialization Success Factors of University Research Output	Khademi and Ismail (2013)
	An overview of the problems and possible solutions associated with the VoD of pharmaceutical products	Seyhan (2019)
	Review of the innovation processes of technology development across the VoD	Ellwood, Williams and Egan (2020)
	Review of the development pathway of biomarker-based diagnostic tests: from discovery, validation, regulation to approval	Fritzler et al., (2021)
University Technology Transfer: Commercialization	Commercialization policies	Goldfarb and Henrekson (2002)
	Analysis of the main considerations for commercialization in neurosciences.	Caulfield and Ogbogu, (2008)
	Analyses the impact that patenting and commercialization have in the stem cell research community	Caulfield et al., (2008)
	Analysis of the difficulties faced by R&D Centres in the commercialization path.	Markman, Siegel and Wright (2008)
	Commercialization Success Factors of University Research Output	Khademi and Ismail, (2013)

Table 1 – Review of the state-of-art factors associated with the bridging of the 'Valley of Death' (VoD) in technology transfer.

Identified factor	General description of the study	Reference
University Technology Transfer: Commercialization	Analyses and categorises the barriers and challenges associated with the technology transfer of technologies from R&D Centres.	Mazurkiewicz and Poteralska (2017)
University Technology Transfer: Intellectual Property	Review on IP protection of scientific and biotechnological technologies from academia.	Kesselheim and Avorn (2005)
	Analysis of the main considerations for commercialization in neurosciences.	Caulfield and Ogbogu (2008))
	Analyses the impact that patenting and commercialization have in the stem cell research community	Caulfield et al., (2008)
	IP practice in pharmaceutical innovation	Grootendorst (2009)
	Innovation performance assessment based on different IP outcomes	Balas and Elkin (2013)
	Analyses the barriers in technology transfer from medical centres in Israel	Roll, Lerner and Gimmon (2015)
	Analyses and categorises the barriers and challenges associated with the technology transfer of technologies from R&D Centres	Mazurkiewicz and Poteralska (2017)
	Analyses the effect that government funding has on the valorization of the patents (through patent renewal)	Tahmooresnejad and Beaudry (2018)
	Analyses the influence that TTOs (with a specific role in the IP national support) have in entrepreneurial universities in Portugal	Mascarenhas et al., (2019)
University Technology Transfer: TTO	Literature review on entities involved in the commercialisation of technologies from academia	Siegel and Phan (2004)
	Analyses the role of business schools have in technology transfer	Wright et al., (2009)
	Analysis of the role of TTOs in the academia-industry interface in the northeast of Italy	Comacchio et al. (2012)
	Analysis of the roles of inventors and TTOs in the licensing process	Ismail, Omar and Ayunniza, (2012)
	Commercialization Success Factors of University Research Output	Khademi and Ismail, (2013)
	Review of the TTOs status in USA universities	Huggett, (2014)
	Analyses the barriers in technology transfer from medical centres in Israel	Roll, Lerner and Gimmon (2015)

Table 1 – Review of the state-of-art factors associated with the bridging of the 'Valley of Death' (VoD) in technology transfer.

Identified factor	General description of the study	Reference
University Technology Transfer: TTO	Analyses the influence that TTOs (with a specific role in the IP national support) have in entrepreneurial universities in Portugal	Mascarenhas et al. (2019)
	Analysis of TTOs strategies in commercialization based on their demographics	Pitsakis and Giachetti (2019))
	Analyses the TTOs involvement in science and technology entrepreneurship education	Bolzani et al. (2020)Bolzani et al. (2020)
	Analyses the TTTs behavioural patterns needed for the commercialization of academic technologies in Japan	Takata et al. (2020)
	Analyses the effect that TTTs academic background has on the commercialisation outcome	Soares and Torkomian (2021)
Academia-Industry Collaboration	Analyse and categorise barriers in entrepreneurship in healthcare organizations	Phillips and Garman (2006)
	Study on assessing prospects for crossing the VoD	Coller and Califf (2009)
	Analysis in knowledge transfer between university and industry in Canada	Bramwell, Hepburn and Wolfe (2012)
	Analysis of the role of TTOs in the academia-industry interface in the northeast of Italy	Comacchio et al. (2012)
	Literature review on academia-industry interactions	Perkmann et al. (2013)
	Analyses the barriers in technology transfer from medical centres in Israel	Roll, Lerner and Gimmon (2015)
	Case-study in university-industry interactions in a researcher centre perspective in Malaysia	Mansor et al. (2015)Mansor et al. (2015)
	Academia-pharma partnerships for new drugs development	Palmer and Chaguturu (2017)
	Analysis on university-business cooperation among European countries	Davey et al. (2018)
	An overview of the problems and possible solutions associated with the VoD of pharmaceutical products	Seyhan (2019)
	Review on successfully crossing the VoD	Kampers et al. (2021)

It is also important to refer that, in 2001, Branscomb, Auerswald and Chesbrough introduced a new perspective in the VoD concept, the 'Darwinian Sea' (Fig. 14B). Whereas the VoD is a metaphor for an area of extreme conditions in the Mojave Desert, USA, the 'Darwinian Sea' is a metaphor for Charles Darwin natural selection theory. This alternative concept seeks an approach of the 'survival of the fittest', where the most capable technologies survive due to their outstanding characteristics, in a vast ecosystem that faces several adversities (like a sea), instead of a sterile area with clean edges (like the 'valley of death' desert).

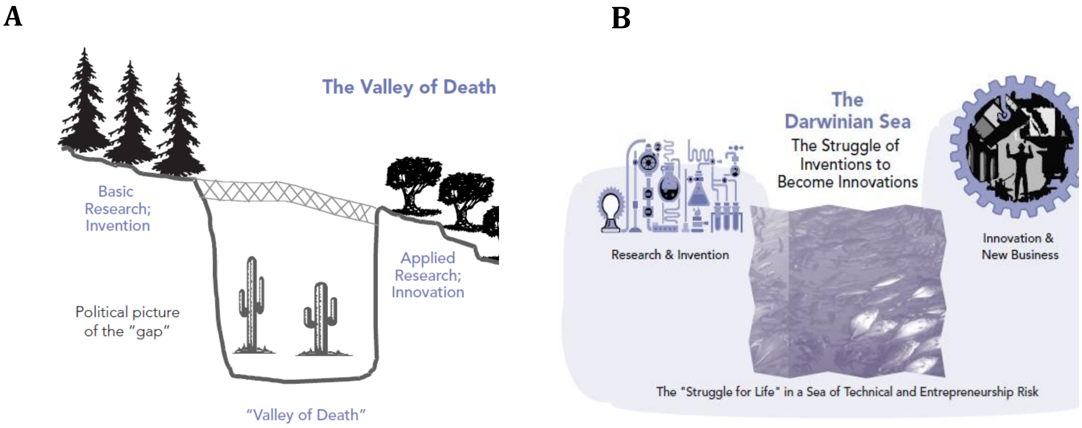


Figure 14 - *Comparison between the two concepts: the 'Valley of Death' and the 'Darwinian Sea' A. Schematic representation for the 'valley of death' concept (Source: Ehlers, 2000 in (Branscomb et al., 2002); B. Schematic representation for the 'Darwinian Sea' (Source: Branscomb et al., 2002).*

2. Objectives

As technology transfer begins to improve in Portugal, we still verify low numbers in the licensing of healthcare patents from R&D Centres; the 'Valley of Death' (VoD) constitutes a major hurdle regarding healthcare technologies developed at R&D Centres. This study aims to identify and analyse the factors that influence the transferring through licensing of healthcare technologies from R&D Centres to the market and to propose solutions to tackle them (Fig. 15). For achieving these major goals, we propose to identify and categorize the players in the healthcare research innovation ecosystem in Portugal, to identify and categorize the factors, associated problems, and possible solutions that influence the licensing process in R&D Centres, and to evaluate the relevance of each identified factor, problem, and solution from the perspective of the different healthcare players according to their business type and region location. In the first part, we will carry out a bibliographic survey and interviews with representative players of the healthcare innovation ecosystem in Portugal (venture capitalists, R&D Centres, enterprises, technological parks, incubators, and associations) to exhaustively identify and categorize the factors, problems, and solutions that influence the licensing of healthcare technologies from R&D Centres. In the second part, we will elaborate and distribute a questionnaire comprehensively through the national players of the healthcare innovation ecosystem to evaluate the importance of each identified factor, problem, and solution in the context of our country. To finalize this work, we will analyse one of the most voted solutions and present a case study based on the opinions of researchers from the R&D Centre - Center for Neuroscience and Cell Biology (CNC). This study will allow us to delineate strategies for improving the valorisation of healthcare technologies from academia.

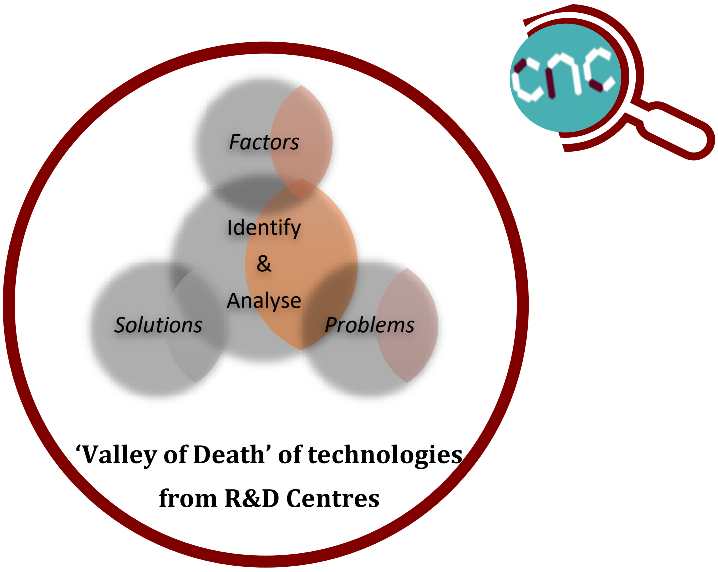


Figure 15 - *Resume of the main objectives of this study: to identify and analyse factors, problems, and solutions related to the 'Valley of Death' of healthcare technologies from R&D Centres in Portugal and to develop a case study based on our results at the Center for Neuroscience and Cell Biology (CNC).*

3. Methods

To achieve the objectives we set ourselves, we first needed a comprehensive and updated list of players in the healthcare research innovation ecosystem (e.g., enterprises, R&D Centres, associations, etc.) operating in Portugal. As we found a lack of a functional database for this purpose, we started this thesis project by creating a one that we named CNCHealthPT Database. Through this database, we were able to carry out interviews with representatives of healthcare players from distinct categories (business types) and regions of Portugal. We collected their opinion on factors that influence the licensing of health technologies from R&D Centres, on problems faced with this type of licensing, and on possible solutions to mitigate and solve these problems. With a list of problems and solutions identified, we evaluated their importance for the licensing process of heath technologies from R&D Centres at a national level with the dissemination of an online survey. We terminated this thesis project with a case study at the Center for Neuroscience and Cell Biology (CNC), where we evaluated researchers' interest in entrepreneurship and innovation topics and technology transfer training and awareness initiatives. The following schematics (Fig. 16) resume the main steps and topics that were taken in this study.

***Figure 16 -** Schematic overview of the study methodology.*

3.1. Construction of the CNC HealthPt Database

To compile a comprehensive list of players in the national landscape of healthcare research, we performed an extensive online search based on the RACIUS website (www.racius.pt, this website gathers data on all the companies that act in Portugal), the Health Cluster Portugal (HCP) database (http://www.healthportugal.com/, an association that promotes and implements initiatives and activities towards competitiveness, innovation, and technology in the healthcare area), the recent '*Portal da Inovação*' database (http://portaldainovacao.pt/) from *Agência da Nacional de Inovação* (ANI), and the official websites of institutions as shown in Fig. 17). The data collected consisted of the legal name, Tax Identification Number, and main contacts such as headquarters address, phone number, website, and e-mail of the institutions. For some, we identified also a representative focused on the technology transfer or innovation departments/functions. This research resulted in the creation of a network database on healthcare research that was named: CNC HealthPT Database.

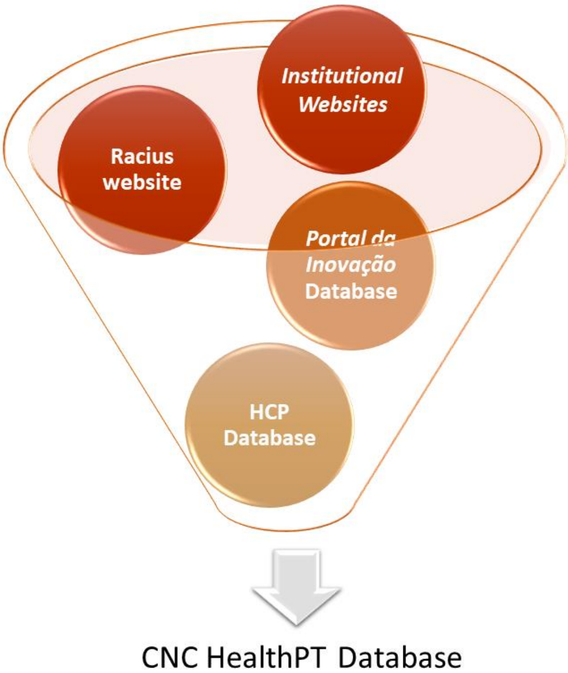


***Figure 17 -** Resources consulted for the creation of the CNC HealthPT Database.*

In the CNC HealthPT database, institutions were categorized according to two features: the region of Portugal where their headquarters are located (A) and the business type in healthcare research (B).

A - Region of Portugal

- Insular Portugal
    - a) Azores;
    - b) Madeira.
- Portugal Mainland
    - a) Algarve;
    - b) Alentejo;

c) Lisbon and Tagus Valley;

d) Centre;

e) North.

B – Business type

- R&D Centres (including research institutions, higher education institutions such as Universities and Polytechnic Institutes, and foundations);
- Enterprises (including national and big pharma - the latest including Portuguese branches of international pharmaceutical enterprises);
- Technological Parks (TP) and Incubators;
- Venture Capitalists (VCs);
- Patent agents and S&R associations (support and regulatory associations).

3.2. Identification of the factors that influence the licensing of technologies from R&D Centres: The interview processes

To identify factors that influence the licensing of technologies from R&D Centres in Portugal, we conducted interviews with players from distinct categories of the CNC HealthPT Databases. For the player's selection, we employed a stratified sampling method—proportional selection from sub-groups with different representations—considering each player's business type and headquarters location to ensure a more realistic and accurate representation of each category and to avoid over-representation of some. We aimed to interview 10% of the total number of players for each category business type in proportion to their regional distribution. For example, if the R&D Centres category had 100 entities in total, 50 in the Centre region and 50 in the Algarve region, we aimed to interview at least 10 institutions in total, 5 from the Centre region and 5 from the Algarve region. In cases where this sampling was not possible, we used convenience sampling by selecting participants based on their availability and willingness to participate in this study.

A formal invitation explaining the aim and context of the interview was sent by email to the institutional (general) contact or, if possible, to a specific technology transfer or innovation department/representative according to the information collected on the CNCHealthPT Database. The interviews were hosted through the online Zoom platform due to the COVID pandemics for approximately 1 hour and recorded with the authorization of the interviewee with the sole purpose to be analysed in more detail in the context of this thesis.

We started by collecting information about the interviewees to set some context for the interview, followed by a group of questions on the topic that we aimed to analyse. The questions were the following:

A. In their professional experience, what difficulties did they face when applying the technology transfer process in the healthcare area?
B. In their view, which factors affect the licensing of technologies from R&D Centres in the healthcare area?
C. What can be done to improve the licensing of patents from R&D Centres in the healthcare area?

There was room for any subject or comment that they wished to address regarding the topic. From these interviews, we extensively identified the factors and problems that in the experience and opinion of these players most influence the process of licensing technologies from an R&D Centre. We also gathered suggestions of what could be done to improve this process. When analyzing the information gathered, we categorized the problems and solutions identified into seven correspondent factors.

3.3. Identification of the factors that influence the licensing of technologies from R&D Centres: The National Survey

After reviewing and further analyzing the answers provided in the interviews, we summarized all the factors, problems, and solutions provided by the interviewees and created an online survey that was distributed by all the entities that integrated the newly created CNCHealthPT Database, as in March 2021. To reach a larger number of players, the survey was divulged in social media groups of technology transfer professionals or focused on technology transfer and innovation topics such as the Facebook group 'PIC' (a Professionals' discussion group on the interface areas of science) and the LinkedIn group 'Rede TechTransferPT'. The 'Rede TechTransfer PT' was created in the context of this thesis project to facilitate communication between professionals of the technology transfer area and at the same time to disseminate various information such as job opportunities, funding programmes, and activities in this area. This network, currently, integrates 63 members among technology transfer technicians, industry professionals, entrepreneurs, venture capitalists, and patent attorney professionals.

The online survey consisted of 30 to 33 questions (depending on the type of player) distributed by five sections with an approximate time for answering of 20 minutes. The survey was constituted by the following sections:

1. general characteristics;

2. technology transfer in Portugal;
3. factor relevance assessment;
4. problems in technology transfer;
5. solutions to the problems of technology transfer.

3.3.1. Section 1 - General characteristics

This first section was constituted between six and eight questions (depending on the type of player), inquiring the players' category according to the definition set on the CNCHealthPT database, headquarters location in terms of regions of Portugal, technology transfer unit or organization within the entity and entity dimension (in employees or enterprises, the latter in the case of technological parks and incubators), main scientific focus, investment values in the past 2 years and percentage of these values that correspond to healthcare investments (only to Venture Capitalists), interest in healthcare investments (only to Venture Capitalists), number of enterprises in healthcare and how many of these are considered R&D Centres start-ups/spin-offs (only to technological parks and incubators).

3.3.2. Section 2 – Technology transfer in Portugal

Section 2 was constituted by four questions and inquired R&D Centres and enterprises about the technology transfer status of the players as in March/April 2021 regarding the number of patents/patent applications, number of patents/patent applications in healthcare, number of licensed patents/patent applications, and number of licensed patents/patent applications to Portuguese enterprises according to the scale: 0; 1-4; 5-10; 11-20; 21-50 and >50.

3.3.3. Section 3 – Factor Relevance Assessment

Section 3 was constituted by eight questions (one for each factor and an additional one) where the players were asked to evaluate the relevance of each factor previously identified during the interview phase) in influencing the licensing of healthcare technologies from R&D Centres (Methods, section 2 - Identification of the factors that influence the licensing of technologies from R&D Centres: The interview processes). This relevance was evaluated on a scale from 1 to 5: *1 - Nothing relevant; 2 – Slightly Relevant; 3 – Relevant; 4 – Highly Relevant; and 5 – Extremely Relevant*. An option was also given to the player for adding a non-mentioned factor considered relevant and to evaluate it according to the scale mentioned above.

3.3.4. Section 4 - Problems in technology transfer

Section 4 was constituted of eight questions (one for each factor and an additional one) where the players were asked to select the ~1/3 of the problems (the number of selected options varied *per* question according to the number of problems identified within each factor) they considered to have the most impact in the licensing process within each factor. An option was also given to the player for selecting a non-mentioned problem considered relevant.

3.3.5. Section 5 - Solutions to the problems of technology transfer

Section 5 was constituted of eight questions (one for each factor and an additional one) where the players were asked to select the ~1/3 of the solutions (the number of selected options varied per question according to the number of solutions identified within each factor) they considered to be the most suitable for improving the licensing process within each factor. An option was also given to the player for selecting a non-mentioned solution considered relevant. At the end of the survey, there was a space for comments on the topic. This survey was in Portuguese language and its layout and the English translation can be found in Appendix B.

3.4. Case Study: CNC-UC

After analyzing the answers regarding the relevance of the factors, problems, and solutions provided in the online survey, we conducted a case study at the Center for Neuroscience and Cell Biology from the University of Coimbra (CNC), on one of the most relevant problems identified. In this case (due to time constrictions and accessibility), we have chosen to act on of the most selected problem related to the factor 'R&D Centre researchers' (fourth position within the TOP10 of the general problems - the *'lack of knowledge and/or alienation for topics such as Intellectual Property, technology transfer, patents, licensing and commercialization of technologies, and entrepreneurship'* - B1) by acting on the correspondent solution (second position within the TOP10 of the proposed solutions): *'Increase the number of training, awareness-raising actions, and programs in the areas of technology transfer; Intellectual Property; valorization and licensing of technologies, among others'* - b1. To do so, we developed an online survey to be distributed in the CNC community, where we analysed previous training, interest, and motivation in themes such as entrepreneurship, technology transfer, and Intellectual Property and preferences in different training actions and available time to do so. To reach all of the CNC community, the online survey was distributed through institutional personal e-mails with the support of the CNC Science Communication Office. The online survey consisted of 36 questions distributed by five sections with an approximate time for answering of 15 minutes. A template of the online survey can be found in Appendix C. The survey was constituted by the following sections:

1. description;
2. patent and licensing at CNC;
3. technology transfer and entrepreneurship;
4. training in technology transfer and entrepreneurship;

3.4.1. Section 1 - Description

This first section was constituted of seven questions, inquiring the researchers' demographics (such as gender, age range, highest academic degree and in which country was obtained), main research area, and research group.

3.4.2. Section 2 - Patent and licensing at CNC

Section 2 was constituted of six questions where the researchers were asked about their job position, number of patent/patent applications (during their career and at the moment of the survey), number of licensed patents, and number and name of start-ups they are associated with.

3.4.3. Section 3 - Technology Transfer and Entrepreneurship

Section 3 was constituted of seven questions where the researchers were asked about their previous training, general interest, and need to update their knowledge in entrepreneurship, patents, and technology transfer topics. They were also inquired about their possible interest in being involved in the creation of an enterprise based on research developed by themselves and their plans to take the path of entrepreneurship in the future.

3.4.4. Section 4-Training in Technology Transfer and Entrepreneurship

Section 4 was constituted of five questions where the researchers were asked about previous training in entrepreneurship, Intellectual Property, and/or technology transfer, the time they were willing to spend in technology transfer training, and their preference in several types of training actions.

4. Results

4.1. CNC HealthPT Database

The first step in our study was the creation of a contact network in the healthcare technology transfer area in Portugal, the CNC HealthPT Database. After intensive research, we identified and gathered information on 511 players that constitute the technology transfer ecosystem of healthcare research in Portugal (Fig. 18). These players were classified into six categories according to their business type: **R&D Centres** (including research institutions, higher education institutions such as Universities and Polytechnic Institutes, and foundations); **Enterprises** (including national enterprises and big pharma); **Technological Parks** (TP) **and Incubators**; **Venture Capitalists** (VCs); **Patent Agents,** and **S&R Associations** (support and regulatory associations). Of these players, 242 (the majority with ~47,4%) are enterprises, mainly small and medium-sized (212), followed by 125 R&D Centres that constitute ~24,5%. Surprisingly, Portugal presents 54 TPs and Incubators, 63 Venture Capitalists, 8 patent agents, and 19 S&R associations operating in the healthcare area.

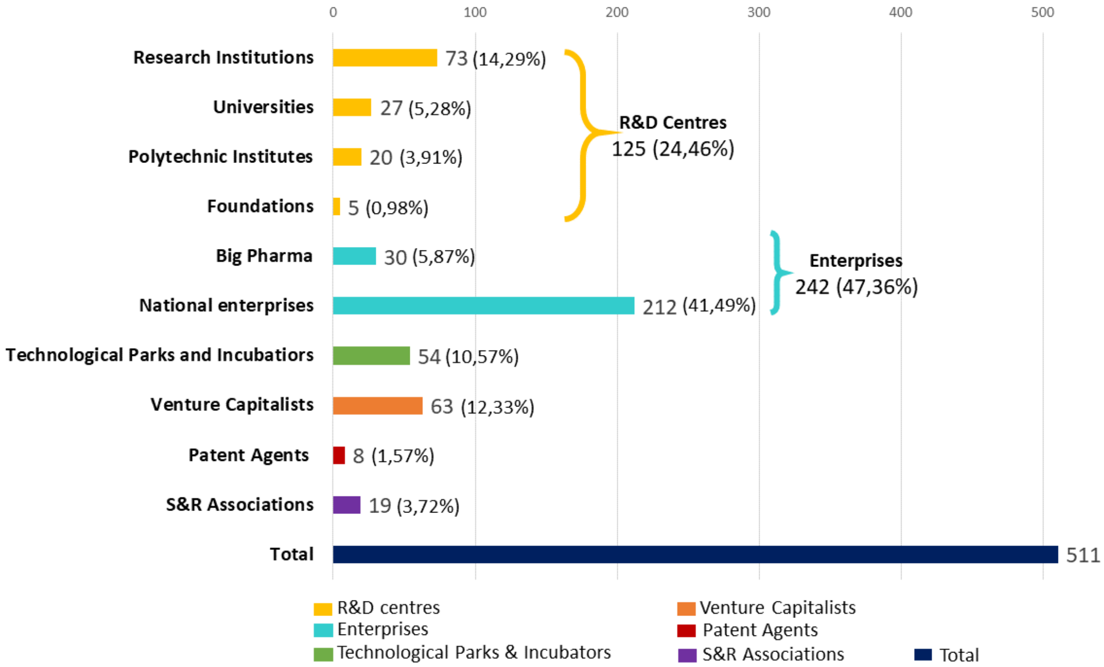


Figure 18 - *Composition of the CNC HealthPT database in terms of players categories in December 2020. The official six categories as defined in the context of this thesis are highlighted. The dark blue bar represents the total number of players.*

The institutions of the CNC HealthPT Database are scattered among the country, except for Patent Agents and S&R Associations with headquarters only in the North and Lisbon and Tagus Valley regions, Venture Capitalists with headquarters only in the North, Centre, and Lisbon and Tagus Valley regions, and enterprises that have no representation in the Azores region (Fig. 19). The Lisbon and Tagus Valley region presents a higher number of players, both in total and in each category. The Autonomous Regions present the lower number of players with a total of four for each archipelago. They also present the lower number of players in each category, except for the TP and incubators (in this case, the Algarve region).

Focusing on the representation of R&D Centres (Fig. 20A) and enterprises (Fig. 20B) categories in the TOP3 most represented regions, we verify that the R&D Centres in the Lisbon and Tagus Valley region are concentrated almost exclusively in the Lisbon county with ~81,7% of the regional healthcare R&D Centres. The enterprises representation is more scattered, although Lisbon county still presents ~45,7% of the regional healthcare enterprises. The North and Centre regions present a broader geographical distribution. In the Centre region, Coimbra county present ~52% of the regional healthcare R&D Centres and, together with Cantanhede, ~80,8% of the regional healthcare enterprises (~42,3% in Coimbra and ~35,9% in Cantanhede). In the North region, Oporto county is the most represented in both categories, with ~67,4% of the regional healthcare R&D Centres and ~32,8% of the regional healthcare enterprises. These data show that R&D Centres and enterprises are more concentrated in the district capitals, being these values higher in Lisbon county. In general, a more concentrated pattern exists in Lisbon and Tagus Valley region in comparison with a more scattered pattern in the Centre and North regions, as shown in Fig. 20.

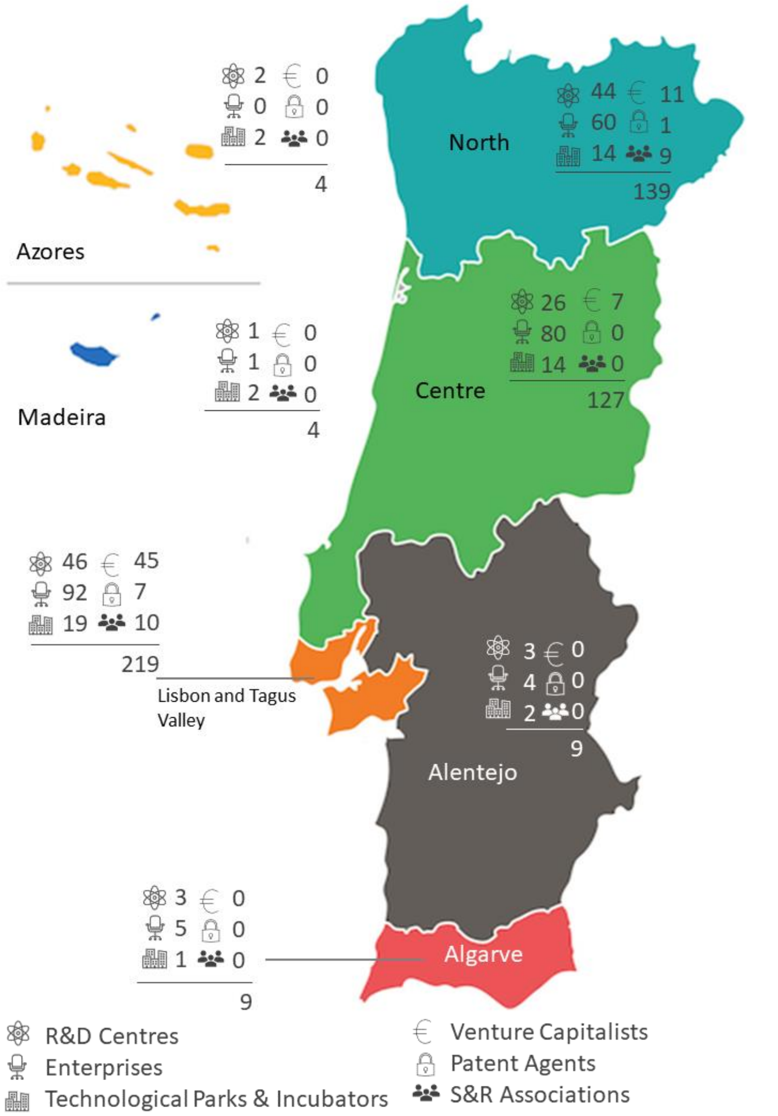


Figure 19 - *Regional distribution of human health research players identified at the CNC HealthPT Database (December 2020).*

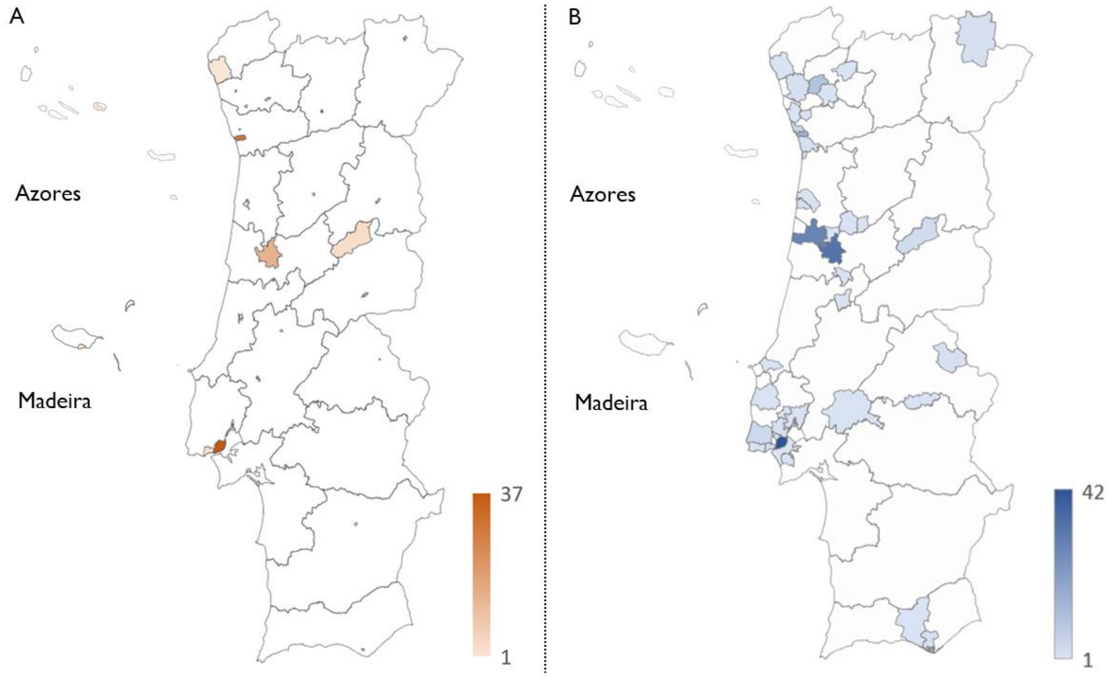


***Figure 20 -** Geographic incidence of R&D Centres and enterprises inserted in the CNCHealtyhPT Database based on their county location. a. Geographic incidence of R&D Centres (in orange); b. Geographic incidence of enterprises (in blue). Note that the maximum number in a single county is 37 R&D Centres and 42 enterprises.*

Although this study refers to the available data on December 2020, it is important to note that this database is in constant update.

To eliminate the regional size variant, we confronted the number of players at the CNCHealthPT with the number of inhabitants per region (Table 2). We verified the existence of a national average of 4,9 players per 100K inhabitants, with an average of 5,1 players in the Portugal mainland and 1,6 players in the Portugal Autonomous Regions. The only regions that surpass the national and mainland averages are the Lisbon and Tagus Valley (1,6 times more) and the Centre regions (1,2 times more). The Alentejo presents the low national numbers with 1,3 players per 100K inhabitants. Comparing the regional GDP per capita with the regional number of players in healthcare, an overlap in their ranking only occurs in the Lisbon and Tagus Valley (in the first place) and Madeira (in the sixth place) regions, with the remaining regions shifting positions, with a highlight for the Alentejo region that ranked fourth in the regional GDP per capita and last in the regional number of healthcare players. This data suggest that although healthcare represents a relevant economic sector in more developed regions, the same does not happen in less developed regions, which are majorly associated with other economic sectors (e.g., agriculture, marine resources, among others).

Table 2- Number of players in the healthcare research on CNC HealthPT DataBase per 100K inhabitants.

Region	Inhabitants per region in 2021*	Percentage (%) of GDP per capita (2019) in the region**	Healthcare Research players	Healthcare Research players per 100K inhabitants
Portugal	**10.347,892**	100	**511**	**4,9**
Mainland	9.860175	95,6	503	5,1
North	3.588,701	29,7	139	3,9
Centre	2.227,912	18,8	127	5,7
Lisbon and Tagus Valley	2.871,133	36	219	7,6
Alentejo	704,934	6,3	9	1,3
Algarve	467,495	4,8	9	1,9
Autonomous Regions	487,717	4,5	8	1,6
Azores	236,657	2,1	4	1,7
Madeira	251,060	2,4	4	1,6

Note: The difference between the years presented in the columns 'inhabitants ***per*** region' and 'GDP ***per*** capita' is since these refer to the last years for which information was available. **In addition, is important to note that.**
Legend: NA – Non-Applicable
*Information on the number of inhabitants per region available at INE - Censos 2021
** **The more recent data regarding the GDP per capita is classified as provisional by the source** (Gabinete de Comunicação e Imagem do Instituto Nacional de Estatística (2020))

4.2. Identification of factors that influence the licensing of technologies from R&D Centres in Portugal – interview processes

After we identified the players in the healthcare innovation ecosystem of Portugal, we proceed by comprehensively identifying the factors that may influence the licensing process of healthcare technologies from R&D Centres in Portugal. We interviewed several players of the business type categories and regions identified in the CNCHealthPT Database.

Regarding the selection process, we aimed to interview at least 10% of the players from each business type category also considering headquarters location (to have all the regions represented). We were able to interview the number of players we set ourselves, except for the enterprises and VCs categories due to lack of answer to or rejection of our invitation to conduct the interview (Table 3). We conducted a total of 47 online interviews: ~12% of the R&D Centres; ~6,2% of the enterprises; ~7,9% of the VCs; ~13% of the Technological Parks and Incubators; 12,5% of the patent agents; and ~21,1% of the S&R Associations. More information about the regional distribution of the number of interviews (whether proposed, realized, or non-realized due to refusal or no response) can be found in Appendix D.

Table 3- Distribution of the interviews conducted regarding the players in healthcare research on CNC HealthPT DataBase.

	Identified on CNCHealthPT	Realized	
		n	%
General	**511**	47	9,18
R&D Centres	**125**	15	12,00
Enterprises	**242**	15	6,20
Venture Capitalists	**63**	5	7,94
Technological Parks & Incubators	**54**	7	12,96
S&R Associations	**19**	4	21,05
Patent Agents	**8**	1	12,5

From these interviews, we identified factors, as well as problems and solutions associated with these factors, that in the player's opinion and/or experience could influence the licensing of healthcare technologies from R&D Centres. To each identified factor was attributed a capital letter (*e.g.*, A: R&D Centres, B: R&D Centres Researchers, C: Technologies, D: Technology Transfer Offices and Technicians, E: Technology Transfer Process: Patent, F: Technology Transfer Process: Licensing, G: Industry/Investors) as stated in Table 4.

Table 4- Resume of the factors and number of problems and solutions identified during the interview phase.

Factor	Designated Letter	Number of problems identified	Number of solutions identified
R&D Centres	A	15	15
R&D Centres Researchers	B	15	15
Technologies	C	15	11
Technology Transfer Offices and Technicians	D	16	21
Technology Transfer Process: Patent	E	8	6
Technology Transfer Process: Licensing	F	14	13
Industry/Investors	G	10	12
	TOTAL	**93**	**93**

From these data, we obtained a list of problems (Table 5) and solutions (Table 6) that resulted in the construction of an online survey that will be discussed below. To each problem was attributed a capital letter, corresponding to the factor category, followed by a number (*e.g.*, A1, A2, A3 … B1, B2, B3… C1, C2, C3 …); to each solution was attributed a lowercase letter, corresponding to the factor category, followed by a number (*e.g.*, a1, a2, a3 … b1, b2, b3 … c1, c2, c3 …).

Table 5– Resume of the problems gathered during the interview phase of this project

Factor	**Ref.**	**Problem**
R&D Centres	A1	The geographic isolation of R&D Centres in relation to other players in the health innovation ecosystem (*e.g.,* R&D Centres located in low populated areas);
	A2	Existence of a culture of start-ups creation to licensing technologies, when this type of licensing is not always the most appropriate;
	A3	Lack of reputation and recognition of R&D Centres in the global and often European context;
	A4	Research lines of the R&D Centre not focused on market needs (the objects in studies do not address any permanent market necessities);
	A5	Lack of human and other resources allocated to technology transfer tasks;
	A6	Lack of human resources with specific training in technology transfer;
	A7	Deviation of human resources in technology transfer to tasks in other areas;
	A8	Lack of openness/willingness to adapt technologies developed in a given scientific area to other areas with more commercialization opportunities;
	A9	Alienation for the logic and/or commercial value of the patent;
	A10	Lack of incentives for the development of an entrepreneurial mindset among researchers;
	A11	Lack of metrics in technology transfer or metrics that promote the quantification of the number of patents instead of their value (their real impact/commercialization);
	A12	Time-consuming and bureaucratic technology transfer processes;
	A13	Lack of knowledge (on the part of the R&D Centre) of the market needs in the scientific areas in which they operate;
	A14	Lack of collaboration, coordination, and communication between the R&D Centre and the industry;
	A15	Lack/limited advertising of the technologies to be licensed and of the R&D Centres and its research;

Table 5– Resume of the problems gathered during the interview phase of this project

Factor	Ref.	Problem
R&D Centres Researchers	B1	Lack of knowledge and/or alienation for topics such as Intellectual Property, technology transfer, patents, licensing and commercialization of technologies, and entrepreneurship;
	B2	Lack of time to dedicate to technology transfer processes due to the multiple functions/positions assigned to the researchers at the same time;
	B3	Lack of proactivity in technology transfer;
	B4	Higher prevalence of the 'researcher' personality at the expense of the 'entrepreneurial' personality;
	B5	Researchers' expectations for the transfer of their technologies not aligned with reality (e.g., simplistic view of the technology transfer process, the real impact of the results less than expected);
	B6	Majority/Exclusive focus on ad hoc scientific research in detriment of a focus on market needs;
	B7	Focus limited to the submission of patent applications instead of the whole process of technology transfer, in particular, the valuation/licensing phase;
	B8	Alienation to the logic/value of the patent;
	B9	Lack of strategy at the beginning of the development of a project/technology regarding its final goal: scientific dissemination versus commercialization;
	B10	An installed mindset of giving priority to the number of patents submitted (mere metric) instead of the number of licensed patents (with potential for commercialization and, therefore, real impact);
	B11	Installed mindset for creating start-ups as a way of licensing technologies, when this type of licensing is not always the most appropriate;
	B12	Lack of clarification as to whether the patent property belongs to the institution (in this case to the R&D Centres) and not to themselves, researchers are only inventors (difficulty in distinguishing between inventor versus patent holder);
	B13	Lack of openness for restructuring the team that develops the technology according to its valorization needs (necessity to add/replace members to/from the team, sometimes external to the institution, during the technology valorization process);
	B14	Desire/Expectation of the researcher who developed the technology to become an entrepreneur without having the proper profile for it;
	B15	Researchers are afraid to disclose the technologies they develop/are developing to potential licensees, even if the technologies are already patented or there is a confidential agreement in place;
Technologies	C1	Limited financing for R&D activities in general;
	C2	Lack of specific funding for proof-of-concept and prototypes;
	C3	Lack of funding for scale-up studies;
	C4	Immaturity of the technology when the patent was submitted (low TLR);
	C5	Lack of prototyping;
	C6	Inadequate proofs-of-concept studies (in terms of robustness and design) for pursuing the technology transfer process, are only suitable for the scientific dissemination;
	C7	Scientific experiments carried out to develop the technology were inadequate for its potential commercial applications;
	C8	Reduced technology commercialization potential (the technology does not meet market needs or there are better solutions already available);
	C9	The level of novelty of the technology is not sufficient for its successful commercialization;
	C10	Lack of market studies before and during the development of the technology (e.g., lack of cost-benefit studies);

Table 5– Resume of the problems gathered during the interview phase of this project		
Factor	**Ref.**	**Problem**
Technologies	C11	The long and expensive regulatory process for entry into the market of technologies in the area of healthcare;
	C12	Lack of involvement of industry/investors in the development of the technology;
	C13	Lack of involvement of technology transfer offices in the development of technology;
	C14	Reduced scientific quality of the idea/development of the technology;
	C15	Little involvement of opinion leaders in technology validation studies;
Technology Transfer Offices and Technicians	D1	Lack of diversity in the specialities of human resources in the technology transfer offices;
	D2	Lack of training and professional experience in the technology transfer process of the human resources of the technology transfer offices;
	D3	Lack of human resources with specific training for writing patents in technology transfer offices (*e.g.*, lawyers specialized in Intellectual Property);
	D4	Lack of human resources with specific training and experience in valuing/licensing technologies in the technology transfer offices;
	D5	Reduced/Non-existent funds available to technology transfer offices to assess the patentability and commercial potential of technologies, as well as other studies necessary for the technology transfer process;
	D6	Immaturity of the technology transfer area in Portugal;
	D7	Lack of sensitivity on the part of technology transfer technicians when evaluating technology due to a low level of knowledge of the market;
	D8	Little involvement of opinion leaders in technology assessment studies;
	D9	Dependence and partiality of the technology transfer technician regarding the entity that he/she represents at the expense of the technology;
	D10	Ignorance of the technology transfer ecosystem in Portugal;
	D11	Ignorance of the existence of organizations in the technology transfer ecosystem at national and international levels;
	D12	Lack of a national network dedicated to the general technology transfer ecosystem;
	D13	Lack of a national network dedicated to technology transfer offices;
	D14	Lack of communication between the various players in the technology transfer process;
	D15	Lack of critical mass in the technology transfer ecosystem, specifically in the area of healthcare, in Portugal;
	D16	Lack of uniformity in technology transfer processes between faculties at the same university (*e.g.*, medical school ≠ pharmacy school ≠ science and technology school);
Technology Transfer Process: Patents	E1	Patent writing not suitable (*e.g.*, poorly written, written by unqualified people...);
	E2	Lack of human resources with specific training for writing patents at R&D Centre (*e.g.*, specialist lawyers with extensive experience in Intellectual Property);
	E3	Limited specific funding for maintenance and obtaining of patents;
	E4	Problems in the sharing agreements of results between patent holders that result in the lack of clarification regarding the patent's ownership;
Technology Transfer Process: Patents	E5	Immaturity of the technology when submitting the patent application (*e.g.*, early patent application regarding the maturity of the technology);
	E6	Limited patent claims (sometimes they do not cover all potential applications);
	E7	Poor advice on the type and strategy of intellectual protection;
	E8	Lack of uniformity in technology transfer processes between faculties at the same university (*e.g.*, medical school ≠ pharmacy school ≠ science and technology school);

Table 5– Resume of the problems gathered during the interview phase of this project

Factor	Ref.	Problem
Technology Transfer Process: Licensing	F1	Search for licenses in the scientific area where the technology development was based, in detriment of possible adaptations to other areas with more market opportunities;
	F2	Lack of human resources with specific training and experience in valuing/licensing technologies;
	F3	High values and early payment dates of milestones and/or royalties defined in the licensing contracts with start-ups, not in line with the company's maturity;
	F4	Lack of guidelines in the negotiation process within an R&D Centres (similar to what already exists in other renowned institutes such as MIT and Harvard University);
	F5	Insecurity in licensing processes due to a lack of trust between the parties involved;
	F6	Use of a single language for writing legal documents rather than having documents written in 2 or more languages (*e.g.,* Portuguese and English);
	F7	Poorly executed licensing agreements that do not provide for all possible situations;
	F8	Lack of perception of the value of technology in the market;
	F9	The final decision on the negotiation process is dependent on the administration/management council of the R&D Centres that do not have the know-how/expertise necessary;
	F10	The negotiation process is slow and bureaucratic;
	F11	Commercial targets not defined when designing the strategy for technologies development;
	F12	Preference for licensing to new enterprises (start-ups) instead of enterprises that are already established in the market, when this is not always the best solution;
	F13	Lack of knowledge of the players in the industry (*e.g.,* possible licensees, competitors);
	F14	Lack of knowledge on the part of potential licensees of the existence of the technology to be licensed;
Industry/Investors	G1	Lack of headquarters/enterprises/decision-making centres in Portugal;
	G2	Lack of proactivity in the search for new technologies by enterprises and investors;
	G3	Lack of investors (venture capitalists and others) in the area of healthcare in Portugal;
	G4	Lack of collaboration, coordination, and communication between the R&D Centre and the industry to promote more licensing contracts;
	G5	Lack of specific and accessible contacts on the part of the enterprises for R&D Centre to establish first contacts regarding a licensing opportunity (technology transfer technicians or equivalent in human resources of the industry);
	G6	Lack of investment to attract international enterprises in healthcare to Portugal (potential licensees of technologies from R&D Centre);
	G7	Limited economic support to incubators and technology parks, hampering the creation of new start-ups and, consequently, new licensees;
	G8	Limited financial support to start-ups to encourage their creation and to increase their capacity to license more technologies;
	G9	'Prejudice' of enterprises towards R&D Centre (especially public universities) being the patents holders (enterprises and investors perceive it as a threat/risk);
	G10	Lack of knowledge of the portfolio of technologies to be licensed from R&D Centre by enterprises and investors;

Table 6– Resume of the solutions gathered during the interview phase of this project

Factor	Ref	Solution
R&D Centre	a1	Promote physical proximity between R&D Centre and enterprises (centres and enterprises with some joint spaces or in the vicinity to reinforce communication between them);
	a2	Change the evaluation metrics in technology transfer of the R&D Centre, promoting the valorization of the technologies (*e.g.,* number of licenses, income, and commercialization) instead of technologies protection (*e.g.,* number of patents);
	a3	Promote the reputation and recognition of R&D Centre (*e.g.,* providing high-quality services; creating biobanks; etc.);
	a4	Promote/Optimize the 'parent institution' support to the R&D Centres in the process of protecting and licensing technologies (if applicable);
	a5	Encourage an increase in the number of technologies/projects developed within an R&D Centres in collaboration/partnership with enterprises, for example by including this factor in its assessment (if applicable taking into account the R&D Centres' mission and vision);
	a6	Create regulations for the formation of start-ups from an R&D Centres;
	a7	Publicite R&D Centre, as well as their scientific areas and activities, at national and international events (*e.g.,* trade fairs, congresses, conferences, workshops, lectures, among others);
	a8	Integrate R&D Centre in national and international networks in the different areas of healthcare (*e.g.,* P-Bio; European networks; etc.);
	a9	Promote and invest in scientific research in specific areas of healthcare that capitalize on pre-existing economic advantages derived from the geographic localization of the R&D Centres (*e.g.,* R&D Centre located in the Algarve/coastal region: health solutions based on aquatic products; R&D centres located close to reference hospitals in certain areas of medicine: health solutions for these specific areas of medicine);
	a10	Create synergies between R&D Centre and centralized technology transfer structures (e. associations, technology parks, incubators, among others);
	a11	Bet on expertise and know-how that does not exist in the industry, to promote your interest (*e.g.,* pre-clinical tests, GMP, etc.)
	a12	Create collaboration protocols in technology transfer between R&D Centre to help each other in good practices and attract investment;
	a13	Create 'Open Days' in the R&D Centre for the industry;
	a14	Define and implement good technology transfer practices within an R&D Centres (*e.g.,* research, regulation, industry input, etc.) based on international guidelines;
	a15	Promote the dissemination of a complete, clear and accessible form of technology transfer practices to researchers within the R&D Centre;
R&D Centre Researchers	b1	Increase the number of training, awareness-raising actions, and programs in the areas of technology transfer; Intellectual Property; valorization and licensing of technologies, among others;
	b2	Work the entrepreneurial profile with specificity for the healthcare area of researchers through mentoring actions and programs;
	b3	Increase training in technology transfer in the different academic degrees (bachelor, master, doctorate);
	b4	Develop awareness actions, specifically for the licensing of technologies;
	b5	Determine early a specific goal for the technology in development: scientific dissemination versus commercialization;
	b6	Create 'Open Days' in the industry for researchers;
	b7	Streamline researchers' access to patent databases to anticipate the process of assessing the novelty of the technology they have developed;

Table 6– Resume of the solutions gathered during the interview phase of this project

Factor	Ref	Solution
R&D Centre Researchers	b8	Grant access to and encourage the use of databases that disseminate the existing needs in the market for a given technology;
	b9	Create incentives for researchers based on qualitative results (*e.g.*, licensed technologies) instead of (only) quantitative (*e.g.*, publications/patents);
	b10	Encourage the creation of multidisciplinary/hybrid research teams (*e.g.*, include people with a background in the industry, experience in entrepreneurship, etc.);
	b11	Train the researcher to include the technology transfer technician as early as possible in the development of the technologies (*e.g.*, in the design and writing of the project);
	b12	Encourage the researcher to reassess the main objective/area of expertise of the technology whenever necessary in the detrimental of scientific curiosity (*e.g.*, very innovative technology in an area not related to the initial objective, but unable to be commercialized in the original area in which it was developed because of market saturation);
	b13	Include early in the recruitment/integration process of a new researcher clear and concise information on technology transfer, namely in the rules and procedures in place in the R&D Centres where the researcher is being integrated;
	b14	Promote the increase in the number of opportunities for doctorates/internships in collaboration with the industry;
	b15	Include and encourage researchers to participate in the process of technology valorization, namely in the search for collaborators/stakeholders in the industry;
Technologies	c1	Submit the patent only when the technology is sufficiently mature, even if against the researcher's expectations;
	c2	Define the value and objective of the technology early in the development process: scientific communication versus commercialization;
	c3	Create exclusive financing programs for scale-up/prototyping studies;
	c4	Create and disseminate databases that identify existing needs in the market for a given technology, as well as existing solutions (competitors);
	c5	Create consistency in the team that develops and represents the technology throughout the process (*e.g.*, members of the original team that actively accompany the technology throughout the technology transfer process and engage in the start-up creation by being part in the management of the start-up created);
	c6	Promote the involvement of industrial partners from the beginning of the technology development (*e.g.*, creation of multidisciplinary teams; design of technology development adapted to a commercial application from the beginning);
	c7	Create exclusive funding programs for proof-of-concept studies;
	c8	Increase the number and quality of the studies in the assessment of the commercial potential and socio-economic impact of the technology before and during its development (preferably as early as possible);
	c9	Base the research on a pressing problem or need of the market;
	c10	Increase funding for R&D activities as a whole;
	c11	Increase the involvement of opinion leaders and clinicians in the development of technology as early as possible;
Technology Transfer Offices and Technicians	d1	Create more technology transfer offices within R&D Centre and increase their funding;
	d2	Increase the number of highly qualified, specialized human resources with a diversity of backgrounds in technology transfer offices (*e.g.*, 'in-house entrepreneur', manager, patent attorney, economist, a specialist in a particular area of research) in technology transfer offices;

Table 6– Resume of the solutions gathered during the interview phase of this project		
Factor	**Ref**	**Solution**
Technology Transfer Offices and Technicians	d3	Assign specific tasks/functions to each human resource that constitutes the technology transfer office (patents, valuation, market assessment, communication with enterprises);
	d4	Assign tasks exclusive to the area of technology transfer to human resources in the technology transfer offices;
	d5	Invest in training and updating the skills of technology transfer technicians;
	d6	Create an official network of technology transfer offices in Portugal;
	d7	Create highly-qualified regional technology transfer offices;
	d8	Create highly-qualified regional technology transfer offices with an exclusive focus on a specific area according to the region's strengths;
	d9	Create an Advisatory Council (of various actors in the ecosystem: venture capitalists, industry, researchers) to provide consultancy services on protection and enhancement of technologies, helping critical decisions in this process;
	d10	Invest in the marketing area through the participation of technology transfer technicians in trade fairs and events to publicize the portfolio/research of the R&D Centres;
	d11	Create a national network of technology transfer offices to share knowledge and best practices;
	d12	Increase the possibility of subcontracting specialists to assist in decision-making regarding the submission and maintenance of patents;
	d13	Create teams that are transversal to the technology development (teams that follow the entire technology process: from its creation in the laboratory to its commercialization);
	d14	Share portfolios and network of contacts between technology transfer offices;
	d15	Create specific human resources within the R&D Centres to communicate with other R&D Centre or enterprises on matters related to technology transfer;
	d16	Improve the access of technology transfer technicians to work tools in this area (*e.g.,* access to paid databases; dissemination platforms; etc.);
	d17	Assign/Increase the decision autonomy to/of technicians of technology transfer in relation to the management and direction councils of the R&D Centre in licensing contracts;
	d18	Bet on strong networking with other players in the ecosystem (to function as interlocutors of the technologies developed);
	d19	Create forms of exclusive investment in technology transfer (*e.g.,* state funds);
	d20	Monitor the market in which the R&D Centres operates (potential customers, technologies, competitors, etc.);
	d21	Create exclusive financial support for technology transfer offices/interface centres;
Technology Transfer Process: Patents	e1	Reinforce exclusive funding (from state and European funds) for patent submission and maintenance;
	e2	Create clear guidelines for decision-making on patenting or maintaining a patent;
	e3	Define strategies for patenting technologies to optimize the costs of maintaining and/or submitting patents and not carrying out ad hoc costs;
	e4	Enhance accessibility to reference law firms for the patent writing and submission process;
	e5	Create a national network/office with specialized skills in assisting writing, submission and other matters related to patents;
	e6	Limit the submission of patent applications when the technologies do not have sufficient maturity, interest to the market or competitiveness with existing solutions;

Table 6– Resume of the solutions gathered during the interview phase of this project

Factor	Ref	Solution
Technology Transfer Process: Licensing	f1	Create exclusive financing programs for the valorization of technologies;
	f2	Increase the network of brokers to facilitate licensing agreements;
	f3	Adopt international guidelines in the technology licensing negotiation process;
	f4	Increase the quality of the drafting of the licensing contracts to safeguard the interests of the R&D Centre (*e.g.*, reduce access to technologies/know-how other than the licensed ones);
	f5	Negotiate licensing contracts with realistic economic terms favourable to the technology commercialization (*e.g.*, avoid including premature milestones/royalties when the licensee is a start-up);
	f6	Restructure the team that develops the technology according to its valorization needs (*e.g.*, against the version of the patent owned by the researcher);
	f7	Prepare bilingual legal documents (Portuguese + English) in detriment of only in Portuguese;
	f8	Create a structured portfolio(s) for technology assessment (available technologies; technologies already licensed; the number of start-ups that have resulted);
	f9	Disseminate the technology portfolio at events (national and international) in the healthcare innovation ecosystem;
	f10	Consider the different technology transfer regimes: technology licensing, technology sale, or hybrid regime in detriment only to technology licensing;
	f11	Stimulate the increase in risk capital;
	f12	Create interface programs to support the contact between R&D Centre and the industry;
	f13	Implement hybrid valuation strategies with venture capitalists (*e.g.*, in addition to the typical investment in the creation and development of start-ups to act as licensing agents);
Industry/Investors	g1	Attract international investors to the Portuguese technology transfer ecosystem;
	g2	Increase incentives for the creation of start-ups;
	g3	Create a national entity specialized in the process of writing and submitting patents, as well as in solving problems related to these issues;
	g4	Create public policies to benefit foreign enterprises that license technologies from Portugal;
	g5	Create a Portuguese association in technology transfer for industry and venture capitalists to deal with technology transfer;
	g6	Create 'Open Days' in the industry for researchers;
	g7	Create/Finance more technology development programs in basis on the industry - R&D Centre collaboration;
	g8	Create 'Open Days' in the industry for technology transfer technicians and representatives of R&D Centre;
	g9	Stimulate the increase of risk capital;
	g10	Encourage hybrid valuation strategies with venture capitalists (*e.g.*, in addition to the typical investment in the creation and development of start-ups to act as licensing agents);
	g11	Assign to specific human resources within the company the responsibility of receiving contacts from R&D Centre to establish possible collaborations and/or licensing agreements and disseminate these contacts in a clear and accessible way to R&D Centre;
	g12	Assign specific human resources within the company the responsibility to search for technologies that can be licensed from R&D Centre;

4.3. Evaluation of factors that influence the licensing of technologies from R&D Centres in Portugal – online survey

An online survey was constructed and disseminated by our entire CNC HealthPT Database to evaluate the relevance of each factor, problem, and solution identified in the previous task. The survey was answered by a total of 45 entities (8,8% of the entities identified in the CNCHealthPT) from different business type categories and regions within our country. We obtained a minimum representation of ~3,3% (enterprises) and a maximum representation of ~60% (patent agents) regarding the entities identified in the CNCHealthPT database, with a medium representation of ~19,3%. A more detailed statistical report regarding player classification and regional distribution can be found in Appendix E.

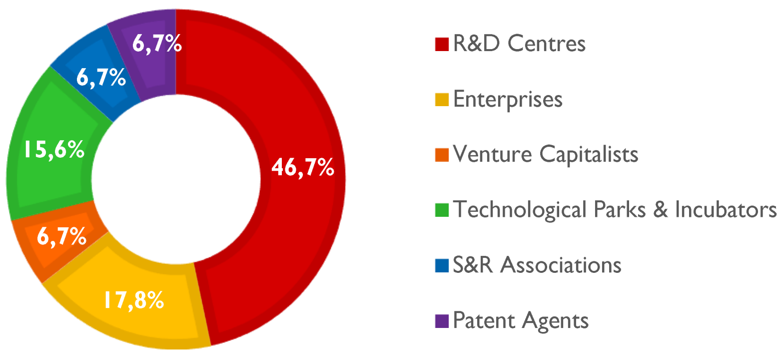
Table 7-Distribution of the answers to the online survey according to the business type categories of the CNC HealthPT database.

	Identified on CNC HealthPT Database	Answers gathered in absolute number and percentage regarding the specific type of entities identified in the CNCHealthPT	
		n	%
R&D Centres	125	21	16,8
Enterprises	242	8	3,3
Venture Capitalists	63	3	6,4
Technological Parks &Incubators	54	7	13
S&R Associations	19	3	15,8
Patent Agents	8	3	60
Total	511	**45**	8,8

4.3.1. Demographics of the participants

From a demographic point of view, our inquired can be described according to player category and headquarters location within the country regions. We gathered answers from 48 professionals within 45 different entities. The demographics that we will present are relative to the entities that the professional represented. The majority of the entities represented are R&D Centres (46,7%), followed by enterprises (17,8%), as shown in Fig. 21A. In terms of regional representation, the Centre region is the most represented with 33,3% of the inquired, followed by the Lisbon and Tagus Valley region with 26,7% (Fig. 21B).

A



B

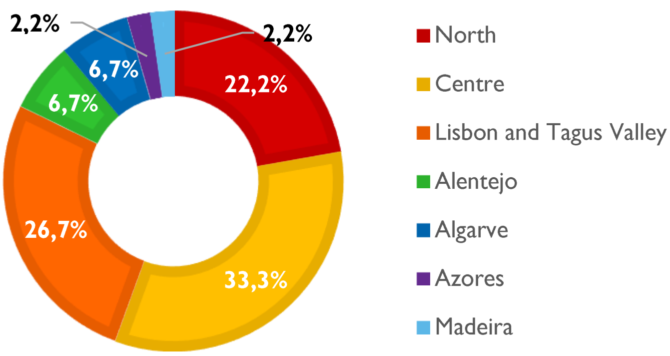


Figure 21 *- Demographics of the inquired A. Regarding the player category; B.Regarding the headquarters location within the country regions.*

4.3.1.1. R&D Centres

Regarding the characterization of the R&D Centres that answered the survey, the majority (28,6%) have 1-50 employees as shown in Fig. 22A. The main healthcare research topics of these centres are 'Bioinformatics/Machine learning' and 'Microbiology and/or Infectious Diseases' (both with 42,9% of participation each), followed by 'Development and/or manufacture of pharmaceuticals products' (38,1%), as shown in Fig. 22B.

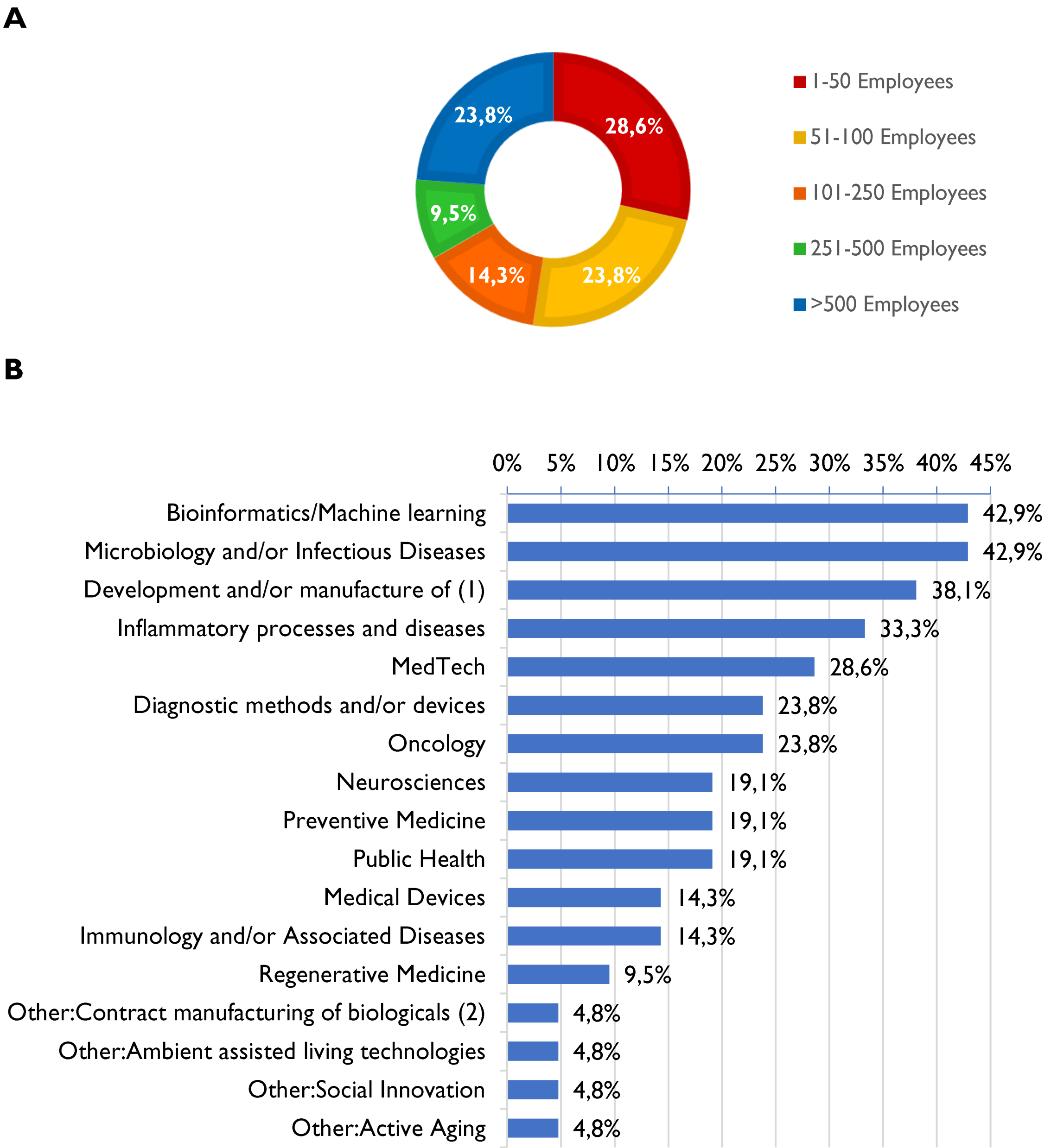


Figure 22 – *Characterization of the R&D Centres that answered the online survey. A. Regarding their size; B. Regarding their research topics were (1) means 'pharmaceutical products', and (2) means 'for clinical trials'.*

4.3.1.2. Enterprises

Regarding the characterization of the enterprises that answered the survey, the majority (50%) are micro-sized (1-10 employees), as demonstrated in Fig. 23A. The main healthcare research topics of these enterprises are the 'development and/or manufacture of pharmaceuticals' (37,5%), followed by 25,0% on 'microbiology and/or infectious diseases' (Fig. 23B).

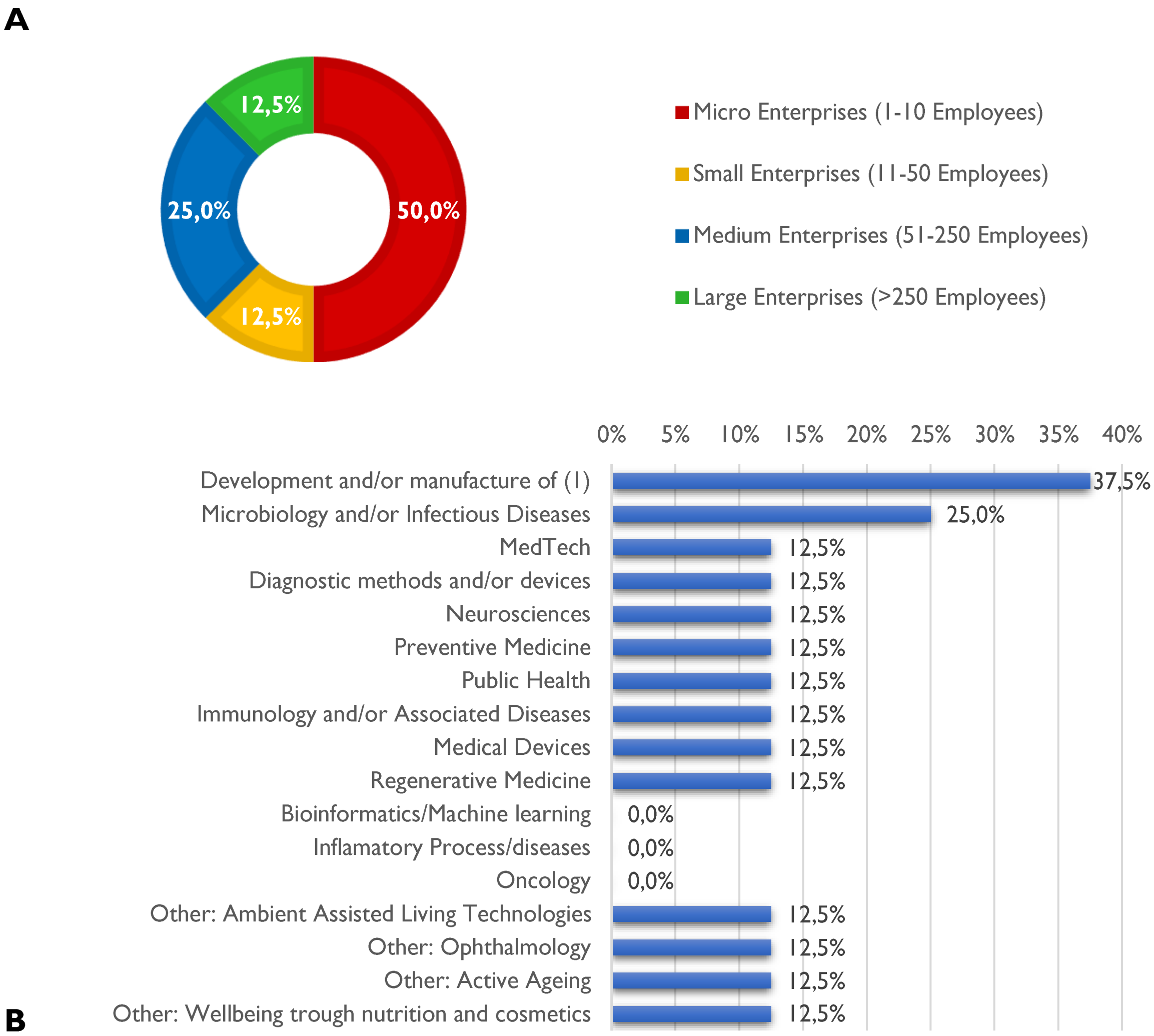


Figure 23 *- Characterization of the enterprises that answered the online survey. A. Representation of the enterprise size; B. Representation of the healthcare areas where these enterprises operate, were (1) means 'pharmaceutical products'.*

4.3.1.3. Venture Capitalists

Regarding the characterization of the Venture Capitalists that answered the survey, all present 11-50 employees and 50-200 million euros available in investment capital. In the last two years, they invested up to 40 million euros (with a total combined of 69,5 million euros) and up to 60% of this value in healthcare technologies. On a five-value scale from '1 - nothing interested' to '5 - highly interested', 25% of the Venture Capitalists answered to be '4 - very interested' and 75% to be '5 - highly interested' in healthcare investments. These results indicate that issues with funding in the leverage of healthcare technologies are not related to a lack of interest in this research area from the Venture Capitalists.

4.3.1.4. Technological Parks & Incubators

Regarding the characterization of the technological parks & incubators that answered the survey, they are composed of 30 to 130 enterprises with a medium of 4% operating in the healthcare area, except one technological park that presents a percentage of 78%. Regarding the healthcare enterprises, all technological parks present ~41,7% of start-ups from R&D Centres, except one that presents 67%.

4.3.1.5. S&R Associations & Patent Agents

Regarding the characterization of the S&R associations that answered the survey, the answers gathered represent both regions where they are located: North (75%) and Lisbon and Tagus Valley (25%) regions. Regarding the characterization of the patent agents that answered the survey, they are located in Lisbon and Tagus Valley (75%) and North (25%) regions.

4.3.2. Technology Transfer of healthcare in Portugal

Regarding the patent status of the inquired (only for R&D Centres and enterprises), 48,3% has between 1-4 ongoing patents/patent applications at the time of the survey and 13,8% more than 50 patents/patent applications. Of note, 13,8% of enterprises and R&D Centres have no patent/patent application. From the entities that have patents/patent applications, ~75,9% of them are in the healthcare sector, with the large majority (63,6%) presenting between 1-4 patents (Fig. 24). Of the entities that have patents/patent applications, 13,6% present none in the healthcare sector.

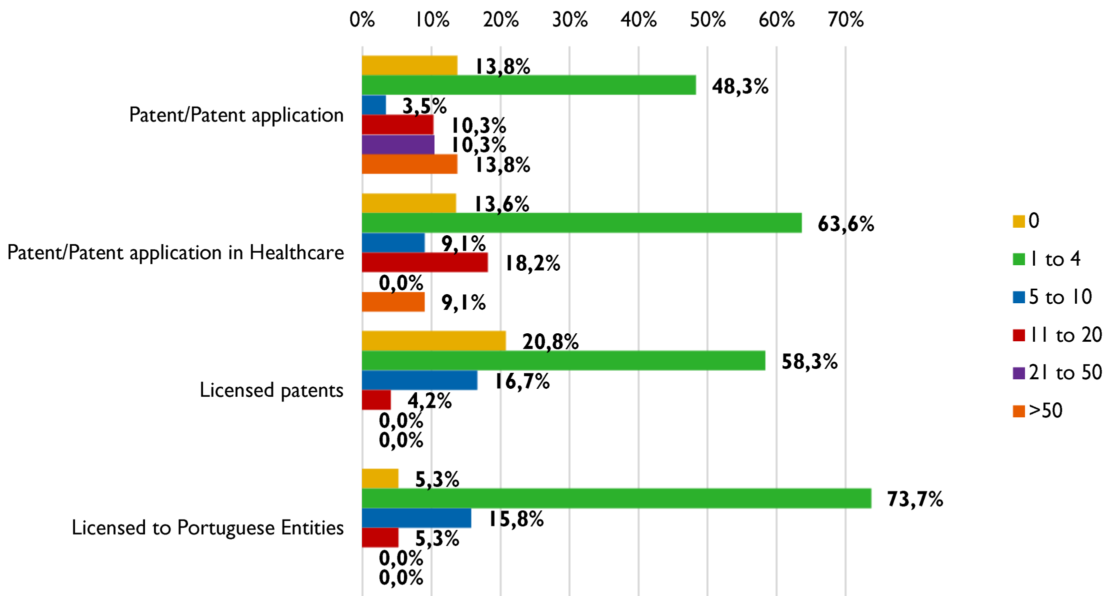


Figure 24 - *Evaluation of the entities status regarding the number of patents/patent applications hold in general and in the healthcare sector, number of licensed patent/patent applications, and number of licenses to Portuguese enterprises.*

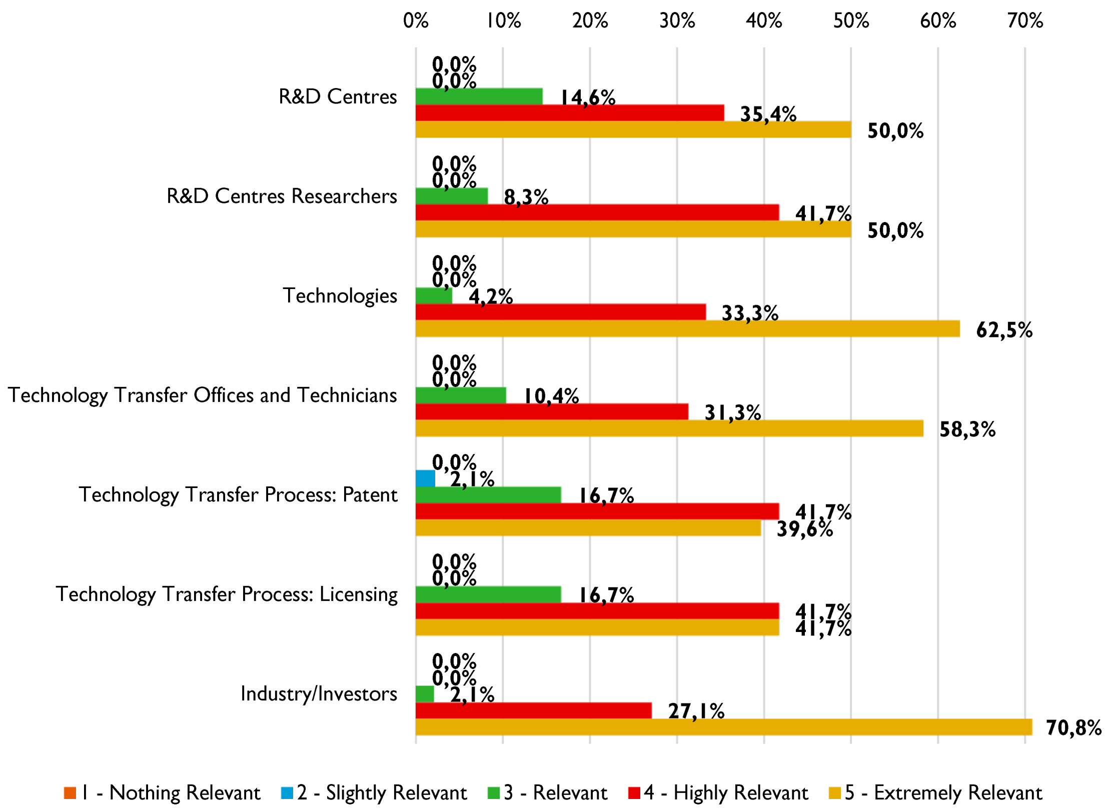
Regarding the commercialization status of the patents, most of the entities with patents/patent applications (58,3%) has 1-4 patents with a current licensing contract, followed by 16,7% with 5-10 licensed patents. In contrast, 20,8% of the entities have no single patent licensed and no entity presented more than 11 to 20 licensed patents/patent applications. Of the entities with licensing contracts, 73,7% have 1-4 patents/patent applications licensed to Portuguese enterprises, followed by 15,8% entities with 5-10. In contrast, 5,3% of the entities do not have a single patent licensed to Portuguese enterprises.

4.3.3. Factors That Influence the Licensing of Healthcare Technologies

From this point forward, the data shown are relative to the professional's individual opinion. To evaluate the data gathered during the interviews in the previous task, we asked the inquired to classify the factors on a scale from one to five according to their relevance (from nothing relevant to extremely relevant). The list of factors was the following: (A) R&D Centres; (B) researchers from R&D Centres; (C) technologies; (D) technology transfer offices and technicians; (E) technology transfer process: patent; (F) technology transfer process: licensing and (G) industry/inventors.

All the factors were classified between 3-relevant and 5-extremely relevant with an exception for the factor technology transfer process: patents that 2,1% of the participants grated as only 2-slightly relevant. The inquired could also add missing factors. The following factors were added and classified: ‘Role of training/acceleration programmes in the teams’, classified as ‘extremely relevant’ and ‘Effective means of communication that allows the standardization of the language used for the different stakeholders involved’ which was not classified. No factor in any player’s category was classified as 1- nothing relevant and almost all of them were mainly classified as 5-extremely relevant, except the ‘technology transfer process: patents’ that was mainly classified as 4-highly relevant and the ‘technology transfer process: licensing’ that was equally mainly classified as 4-highly relevant and 5-extremely relevant. These results demonstrate the adequacy and importance of all identified factors for the technology transfer process, especially the licensing of healthcare technologies (Fig. 25A). Based on the statistical analysis (Fig. 25B), the order of the relevance of the identified factors is the following: Industry/Investors; Technologies; Technology Transfer Offices and Technicians; R&D Centre Researchers; R&D Centres; Technology Transfer Process: Licensing and Technology Transfer Process: Patents.

A



B

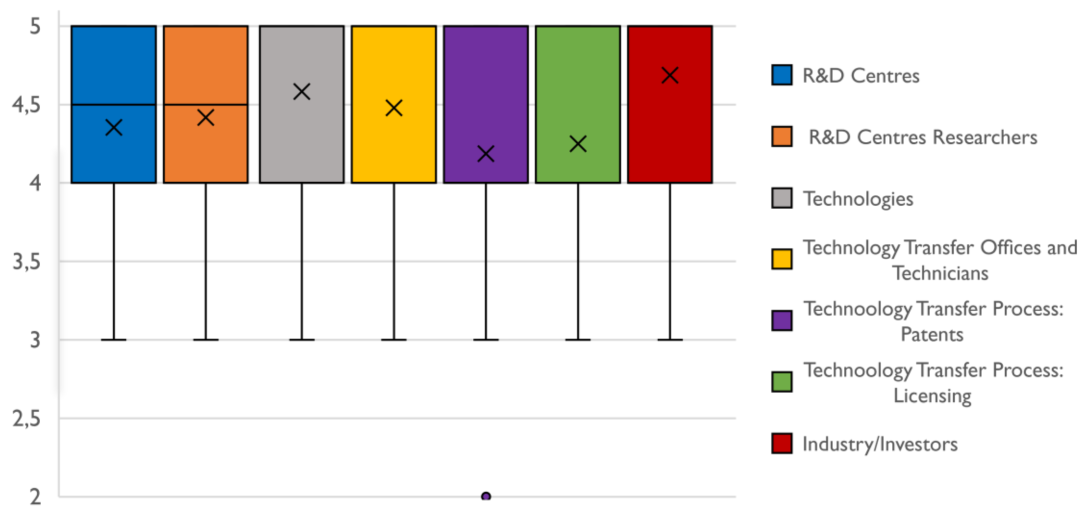


***Figure 25** – Statistical evaluation of the relevance of the identified factors in the study. a. Relative frequency representation of the relevance of the factors identified in the study; b. Box-plot analysis of the relevance of the factors identified in the study. Note that the median of the Technologies, Technology Transfer Offices and Technicians, Technology Transfer Process: Patent, Technology Transfer Process: Licensing and Industry/Investors is not noticeable in the figure since it coincides with the maximum values (in the Technologies, Technology Transfer Office and Technicians, and Industry/Investors) and with the minimum values of the interquartile range (Technology Transfer Process: Patent and Technology Transfer Process: Licensing).*

4.3.4. Problems That Influence the Licensing of Healthcare Technologies

In total, we identified 93 problems (Table 5), categorized into the mentioned seven factors, as previously described in (Methods 3.3.4.). From this list of problems, we asked the inquired to select a specific number (about 1/3 of the total gathered) from a list associated with each factor (with an option to add one if not specified).

R&D Centres (Fig. 26) selected the following problems as the most relevant:

- A6- **Lack of human resources with specific training in technology transfer** with 56,3% of the votes;
- A4- **Research lines of the R&D Centre not focused on market needs** (the objects in studies do not address any permanent market necessities) with 50% of the votes;
- A5- **Lack of human and other resources allocated to technology transfer tasks** with 47,9% of the votes;
- A10- **Lack of incentives for the development of an entrepreneurial mindset among researchers** with 43,8% of the votes;
- A14- **Lack of collaboration, coordination, and communication between the R&D Centre and the industry** with 43,8% of the votes.

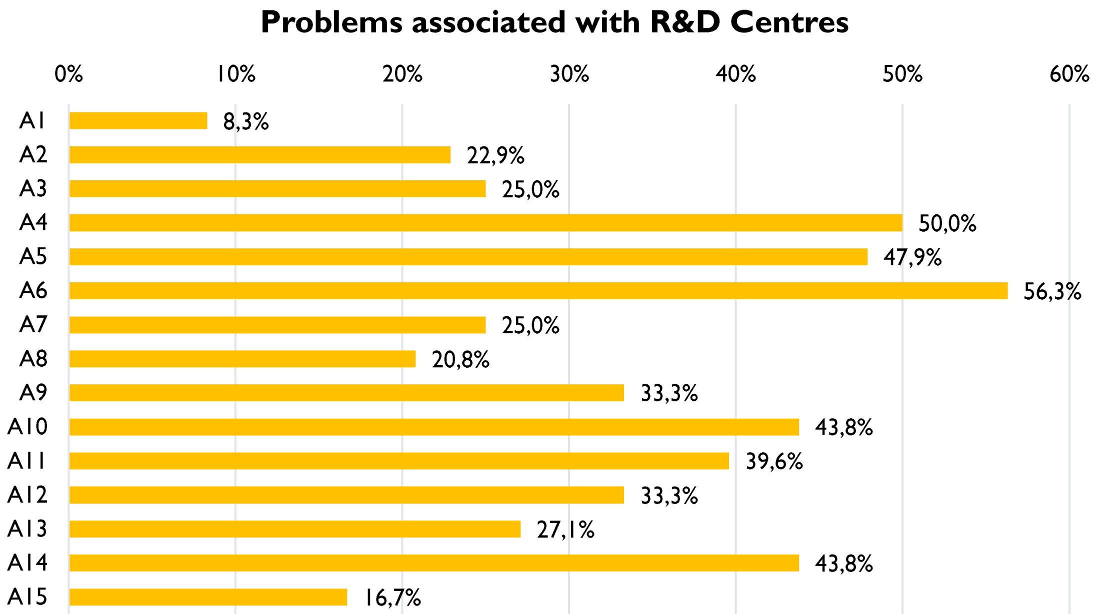


Figure 26 – *Prevalence of the most voted problems within the 'R&D Centres' factor.*

R&D Centres Researchers (Fig. 27) selected the following problems as the most relevant:

- B1- **Lack of knowledge and/or alienation for topics such as Intellectual Property, technology transfer, patents, licensing and commercialization of technologies, and entrepreneurship** with 58,3% of the votes;
- B2- **Lack of time to dedicate to technology transfer processes due to the multiple functions/positions assigned to the researchers at the same time** with 56,3% of the votes;
- B9- **Lack of strategy at the beginning of the development of a project/technology regarding its final goal: scientific dissemination versus commercialization** with 54,2% of the votes;
- B4- **Higher prevalence of the 'researcher' personality at the expense of the 'entrepreneurial personality** with 52,1% of the votes;
- B6– **Majority/Exclusive focus on ad hoc scientific research in detriment of a focus on market needs** with 43,8% of the votes.
- B5- **'Researchers' expectations for the transfer of their technologies not aligned with reality (e.g., simplistic view of the technology transfer process, the real impact of the results less than expected)** with 41,7% of the votes;

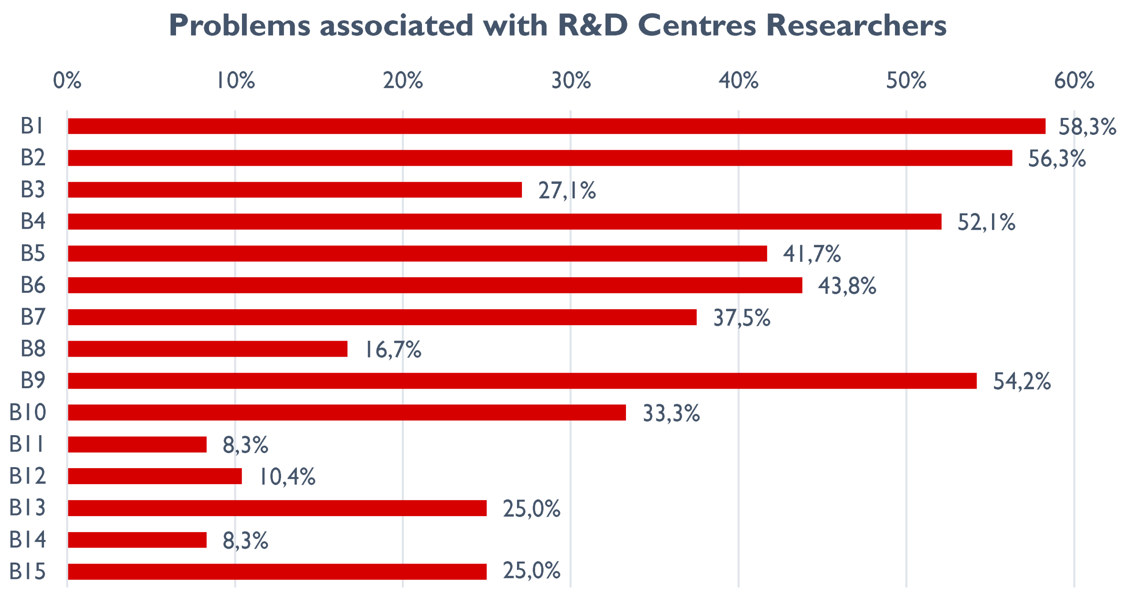


Figure 27 - *Prevalence of the most voted problems within the R&D Centres Researchers factor.*

Technologies (Fig. 28) selected the following problems as the most relevant:

- C10- **Lack of market studies before and during the development of the technology (e.g., lack of cost-benefit studies)** with 56,3% of the votes;
- C1- **Limited financing for R&D activities in general** with 54,2% of the votes;

- C2- **Lack of specific funding for proof-of-concept and prototypes**, with 54,2% of the votes;
- C12- **Lack of involvement of industry/investors in the development of the technology** with 54,2% of the votes.
- C3- **Lack of funding to scale up studies** with 52,1% of the votes;

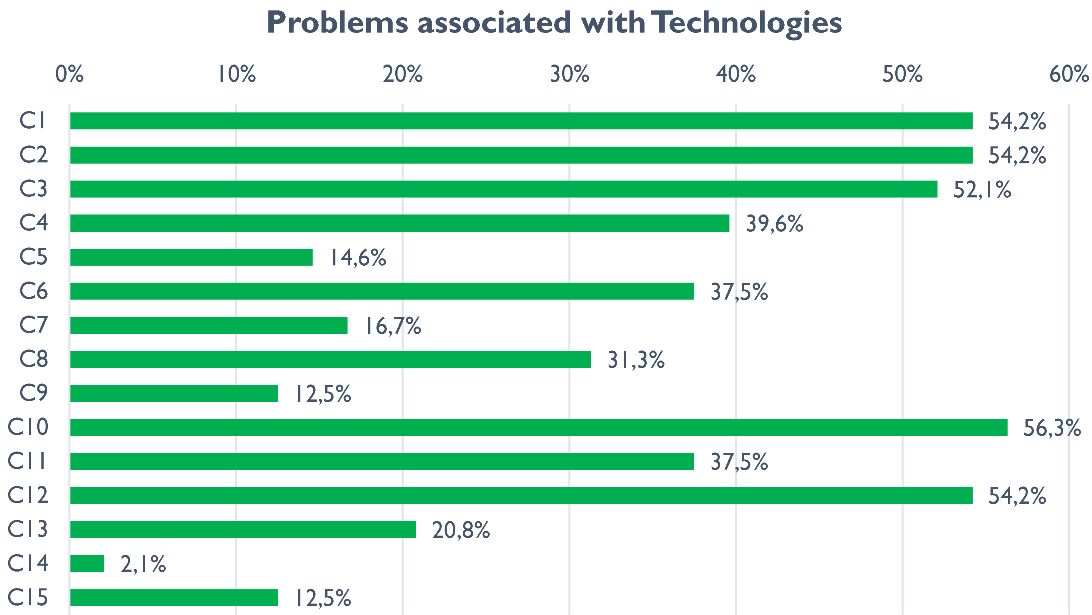


Figure 28 - *Prevalence of the most important problems within the Technology factor.*

Technology Transfer Offices and Technicians (Fig. 29) selected the following problems as the most relevant:

- D5- **Reduced/Non-existent funds available to technology transfer offices to assess the patentability and commercial potential of technologies, as well as other studies necessary for the technology transfer process** with 61,7% of the votes;
- D4- **Lack of human resources with specific training and experience in valuing/licensing technologies in the technology transfer offices** with 48,9% of the votes;
- D6- **Immaturity of the technology transfer area in Portugal** with 48,9% of the votes;
- D2- **Lack of training and professional experience in the technology transfer process of the human resources of the technology transfer offices** with 44,7% of the votes;

- D3- **Lack of human resources with specific training for writing patents in technology transfer offices (e.g., lawyers specialized in Intellectual Property)** with 38,3% of the votes.

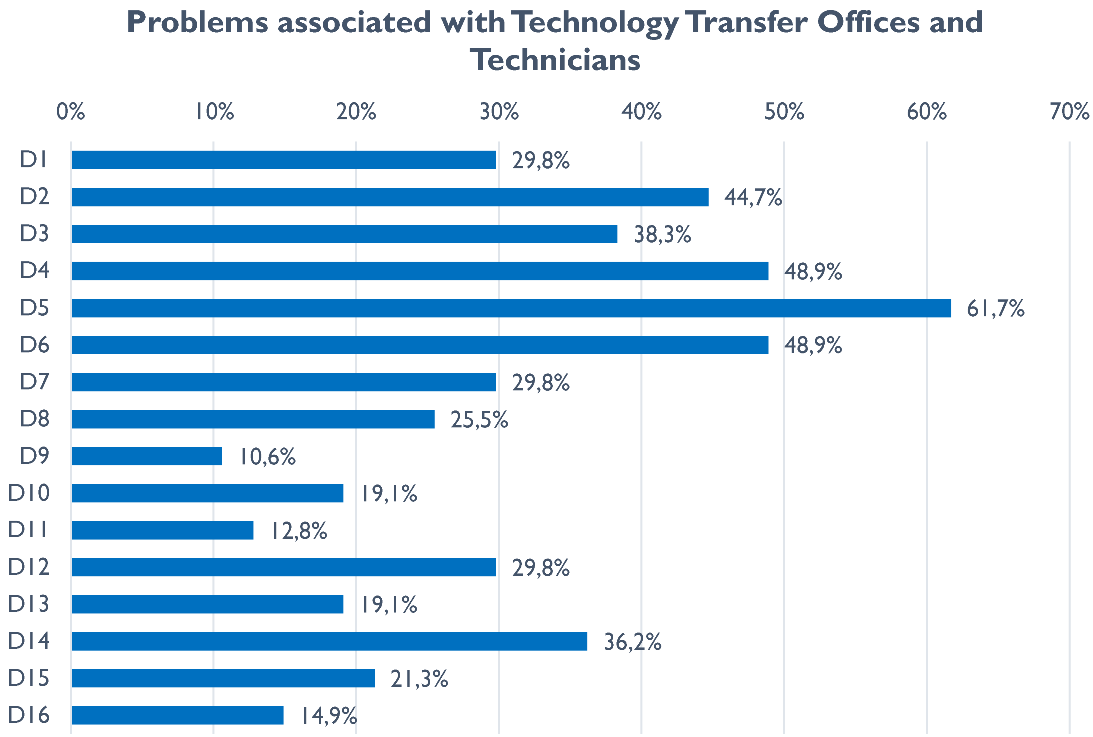


Figure 29 - *Prevalence of the most important problems within the Technology Transfer Offices and Technicians factor.*

Technology Transfer Process: Patent (Fig. 30) selected the following problems as the most relevant:

- E3- **Limited specific funding for maintenance and obtaining of patents** with 66,7% of the votes;
- E2- **Lack of human resources with specific training for writing patents at R&D Centres (e.g., specialist lawyers with extensive experience in Intellectual Property)** with 43,8% of the votes;
- E5- **Immaturity of the technology when submitting the patent application (e.g., early patent application regarding the maturity of the technology)** with 39,6% of the votes.

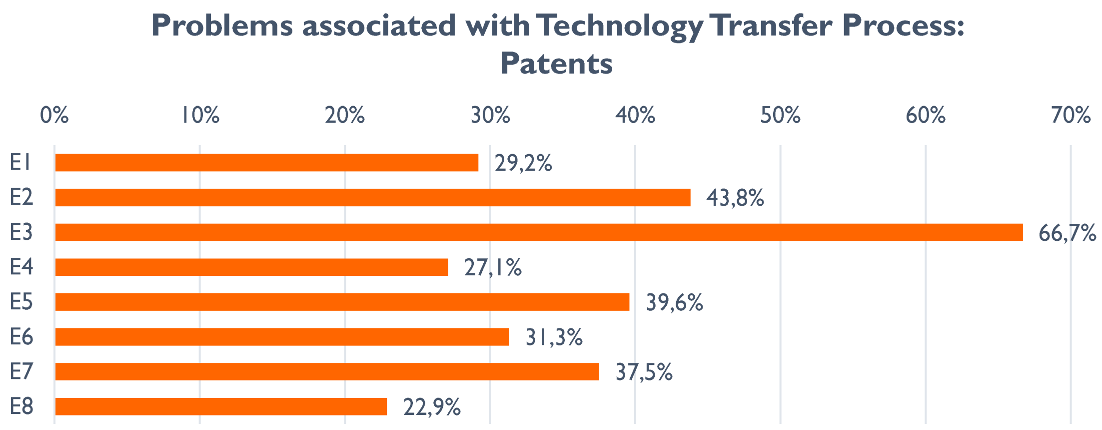


Figure 30 - *Prevalence of the most important problems within the Technology Transfer Process: Patents' factor.*

Technology Transfer Process: Licensing (Fig. 31) selected the following problems as the most relevant:

- F4- **Lack of guidelines in the negotiation process within an R&D Centre (similar to what already exists in other renowned institutes such as MIT and Harvard University)** with 64,6% of the votes;
- F8- **Lack of perception of the value of technology in the market** with 58,3% of the votes;
- F2- **Lack human resources with specific training and experience in valuing/licensing technologies** with 56,3% of the votes;
- F13- **Lack of knowledge of the players in the industry (e.g., possible licensees, competitors)** with 39,6% of the votes;
- F14- **Lack of knowledge on the part of potential licensees of the existence of the technology to be licensed** with 37,5% of the votes.

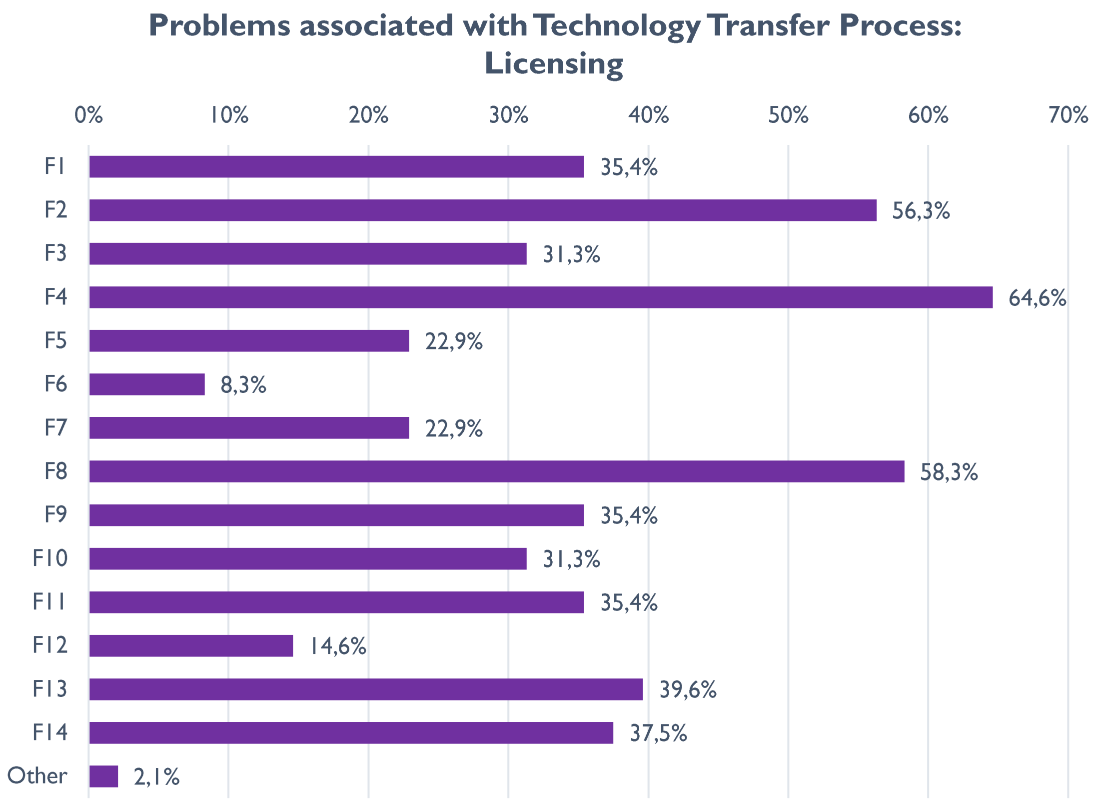


Figure 31 - *Prevalence of the most important problems within the Technology Transfer Process: Licensing' factor. The 'Other' problem is identified as a lack of involvement of the Technology Transfer Technicians in the licensing process.*

Industry/Inventors (Fig. 32) selected the following problems as the most relevant:

- G4- **Lack of collaboration, coordination, and communication between the R&D Centres and the industry to promote more licensing contracts** with 50% of the votes;
- G3- **Lack of investors (venture capitalists and others) in the area of healthcare in Portugal** with 41,7% of the votes;
- G2- **Lack of proactivity in the search for new technologies by enterprises and investors** with 35,4% of the votes.

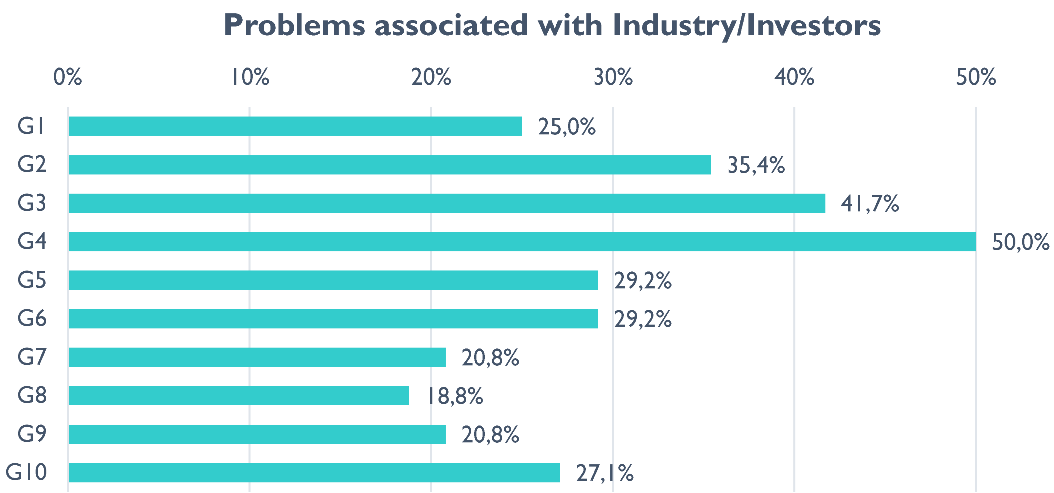


Figure 32 - *Prevalence of the most important problems within Industry/Investors' factor.*

4.3.5. Solutions

In total, we identified 93 possible solutions, which were categorized into seven factors with which they are associated (as shown in Table 6), as previously described in (Methods 3.3.5.). We followed the same method previously used for the problems and asked the inquired to select a specific number (about 1/3 of the total gathered) of the solutions (that were proposed during the interview phase) from a list associated with each factor (with an option to add one if not specified).

R&D Centres (Fig. 33) selected the following problems as the most relevant:

- a5- **Encourage an increase in the number of technologies/projects developed within an R&D Centre in collaboration/partnership with enterprises, for example by including this factor in its assessment (if applicable considering the R&D Centre's mission and vision)** with 66% of the votes;
- a2- **Change the evaluation metrics in technology transfer of the R&D Centres, promoting the valorization of the technologies (e.g., number of licenses, income, and commercialization) instead of technologies protection (e.g., number of patents)** with 55,3% of the votes;
- a14- **Define and implement good technology transfer practices within an R&D Centre (e.g., research, regulation, industry input, etc.) based on international guidelines** with 46,8% of the votes;
- a8- **Integrate R&D Centres in national and international networks in the different areas of healthcare (e.g., P-Bio; European networks; etc.)** with 42,6% of the votes;

- a10- **Create synergies between R&D Centres and centralized technology transfer structures (e.g., associations, technology parks, incubators, among others)** with 36,2% of the votes.

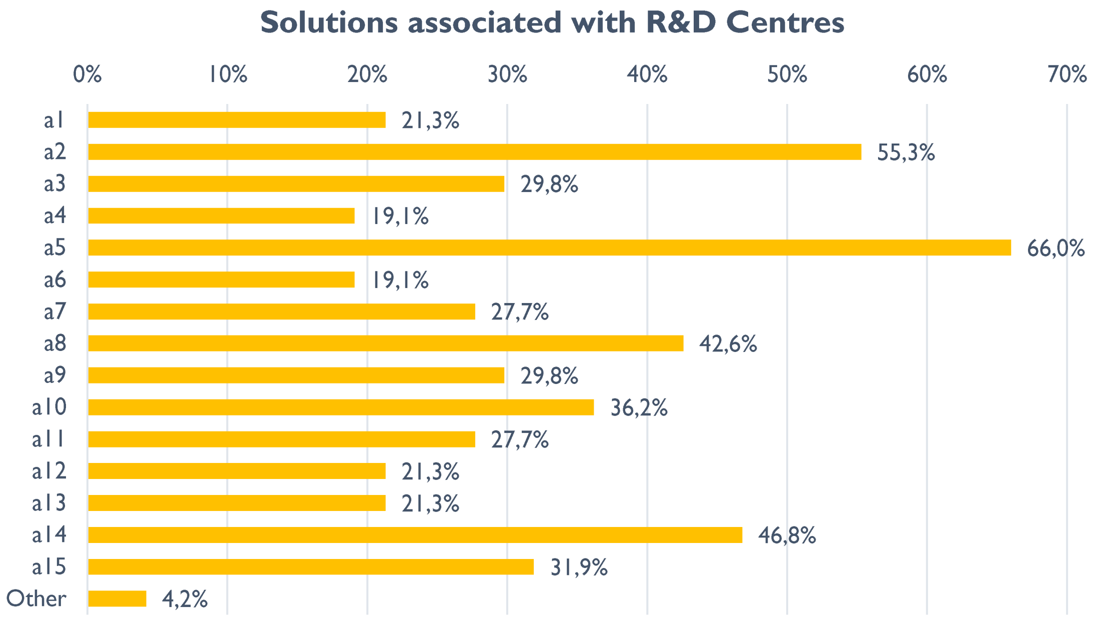


Figure 33 - *Prevalence of the solutions identified within the R&D Centres factor and an additional solution, the 'other' option – the 'creation of financial support for proof-of-concept and creation of connection with experienced executives'.*

R&D Centres Researchers (Fig. 34) selected the following problems as the most relevant:

- b1- **Increase the number of training, awareness-raising actions, and programs in the areas of technology transfer; Intellectual Property; valorization and licensing of technologies, among others** with 68,8% of the votes;
- b10- **Encourage the creation of multidisciplinary/hybrid research teams (e.g., include people with a background in the industry, experience in entrepreneurship, etc.** with 45,8% of the votes;
- b3- **Increase training in technology transfer in the different academic degrees (bachelor, master, doctorate)** with 43,8% of the votes;
- b9- **Create incentives for researchers based on qualitative results (e.g., licensed technologies) instead of (only) quantitative (e.g., publications/patents)** with 39,6% of the votes;
- b2- **Work the entrepreneurial profile with specificity for the healthcare area of researchers through mentoring actions and programs** with 37,5% of the votes;
- b6- **Create 'Open Days' in the industry for researchers** with 33,3% of the votes.

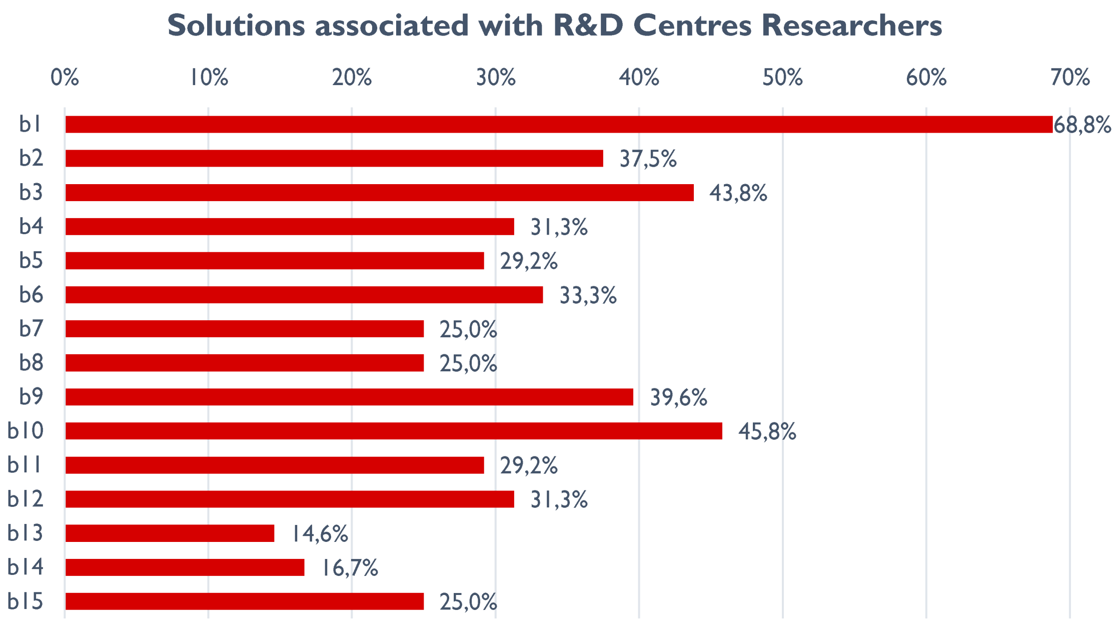


Figure 34- *Prevalence of the solutions identified within the R&D Centres Researchers factor.*

Technologies (Fig. 35) selected the following problems as the most relevant:

- c6- **Promote the involvement of industrial partners from the beginning of the technology development (*e.g.,* creation of multidisciplinary teams; design of technology development adapted to a commercial application from the beginning)** with 56,3% of the votes;
- c3- **Create exclusive financing programs for scale-up/prototyping studies** with 50% of the votes;
- c7- **Create exclusive funding programs for proof-of-concept studies** with 50% of the votes;
- c5- **Create consistency in the team that develops and represents the technology throughout the process (*e.g.,* members of the original team that actively accompany the technology throughout the technology transfer process and engage in the start-up creation by being part in the management of the start-up created)** with 39,6% of the votes.
- c1 – **Submit the patent only when the technology is sufficiently mature, even if against the researcher's expectations** with 37,5% of the votes;
- c2 - **Define the value and objective of the technology early in the development process: scientific communication versus commercialization** with 37,5% of the votes.

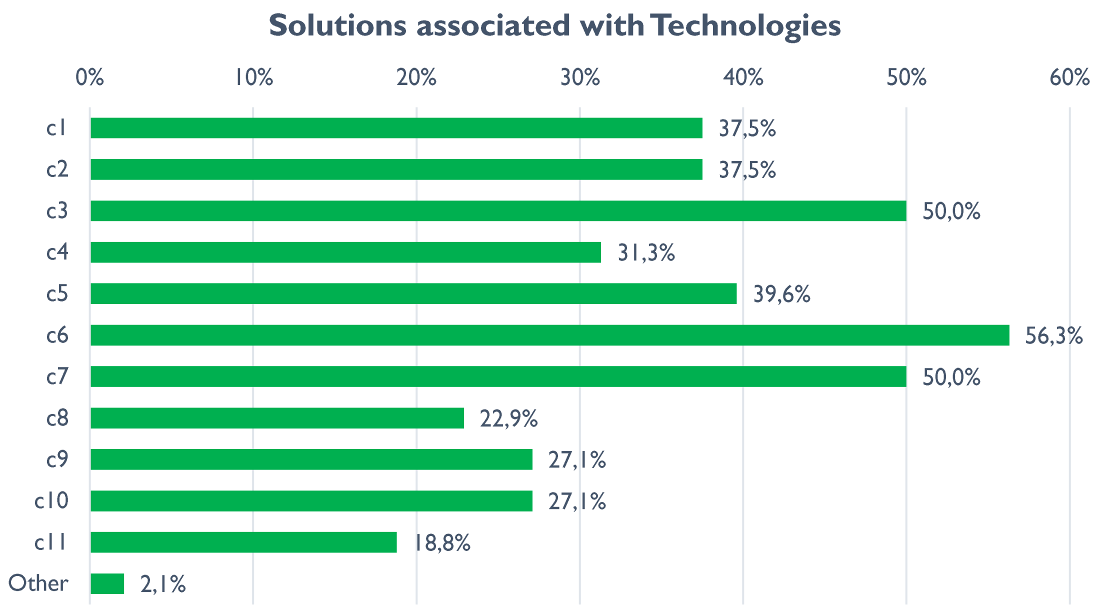


Figure 35 - *Prevalence of the solutions identified within the Technologies factor, and the 'other' suggested option the 'proceeding with a technology evaluation when still in development to support the decision making for the ongoing investment'.*

Technology Transfer Offices and Technicians (Fig. 36) selected the following problems as the most relevant:

- d2- **Increase the number of highly qualified, specialized human resources with a diversity of backgrounds in technology transfer offices (e.g., 'in-house entrepreneur', manager, patent attorney, economist, a specialist in a particular area of research) in technology transfer offices** with 64,6% of the votes;
- d5- **Invest in training and updating the skills of technology transfer technicians** with 58,3% of the votes;
- d3- **Assign specific tasks/functions to each human resource that constitutes the technology transfer office (patents, valuation, market assessment, communication with enterprises)** with 41,7% of the votes;
- d6- **Create an official network of technology transfer offices in Portugal** with 39,6% of the votes;
- d9– **Create an Advisatory Council (of various actors in the ecosystem: venture capitalists, industry, researchers) to provide consultancy services on protection and enhancement of technologies, helping critical decisions in this process** with 39,6% of the votes;

- d13– **Create teams that are transversal to the technology development (teams that follow the entire technology process: from its creation in the laboratory to its commercialization)** with 39,6% of the votes;
- d12– **Increase the possibility of subcontracting specialists to assist in decision-making regarding the sub-commission and the maintenance of patents** with 37,5% of the votes;
- d16- **Create more technology transfer offices within R&D Centres and increase their funding** with 37,5% of the votes;

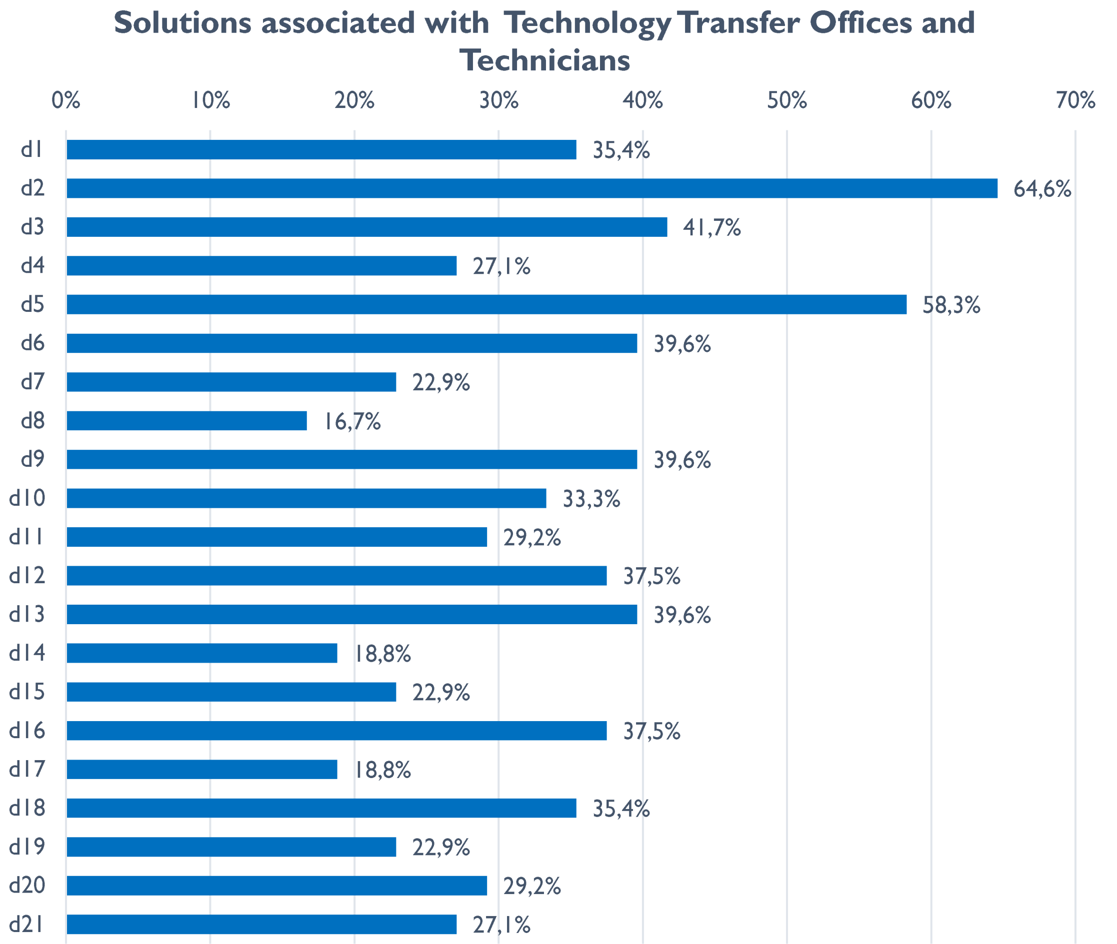


Figure 36 - *Prevalence of the solutions identified within the Technology Transfer Offices and Technicians factor.*

Technology Transfer Process: Patents (Fig. 37) selected the following problems as the most relevant:

- e2- **Create clear guidelines for decision-making on patenting or maintaining a patent** with 43,8% of the votes;

- e3- **Define strategies for patenting technologies to optimize the costs of maintaining and/or submitting patents and not carrying out ad hoc costs** with 43,8% of the votes.

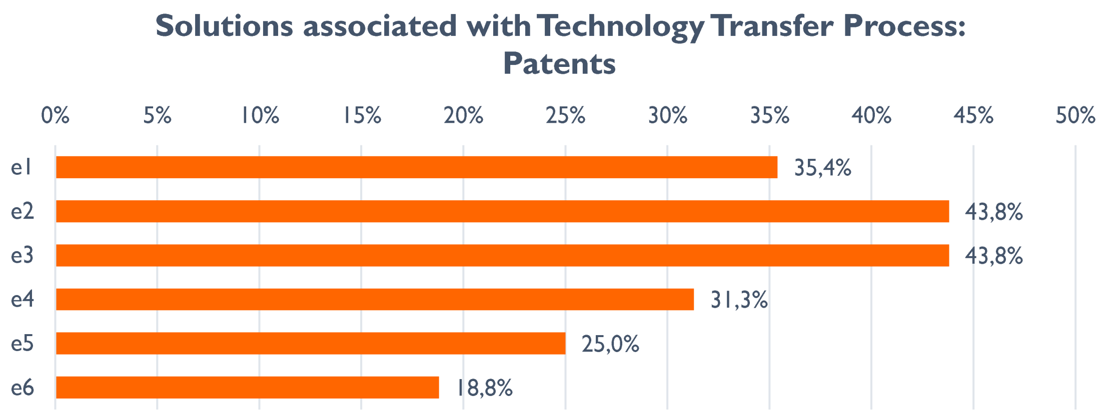


***Figure 37 -** Prevalence of the solutions identified within the Technology Transfer Process: Patents factor.*

Technology Transfer Process: Licensing (Fig. 38) selected the following problems as the most relevant:

- f1- **Create exclusive financing programs for the valorization of technologies** with 45,8% of the votes;
- f8- **Create a structured portfolio(s) for technology assessment (available technologies; technologies already licensed; the number of start-ups that have resulted)** with 43,8% of the votes;
- f12- **Create interface programs to support the contact between R&D Centres and the industry** with 43,8% of the votes;
- f5- **Negotiate licensing contracts with realistic economic terms favourable to the technology commercialization (e.g., avoid including premature milestones/royalties when the licensee is a start-up)** with 39,6% of the votes.

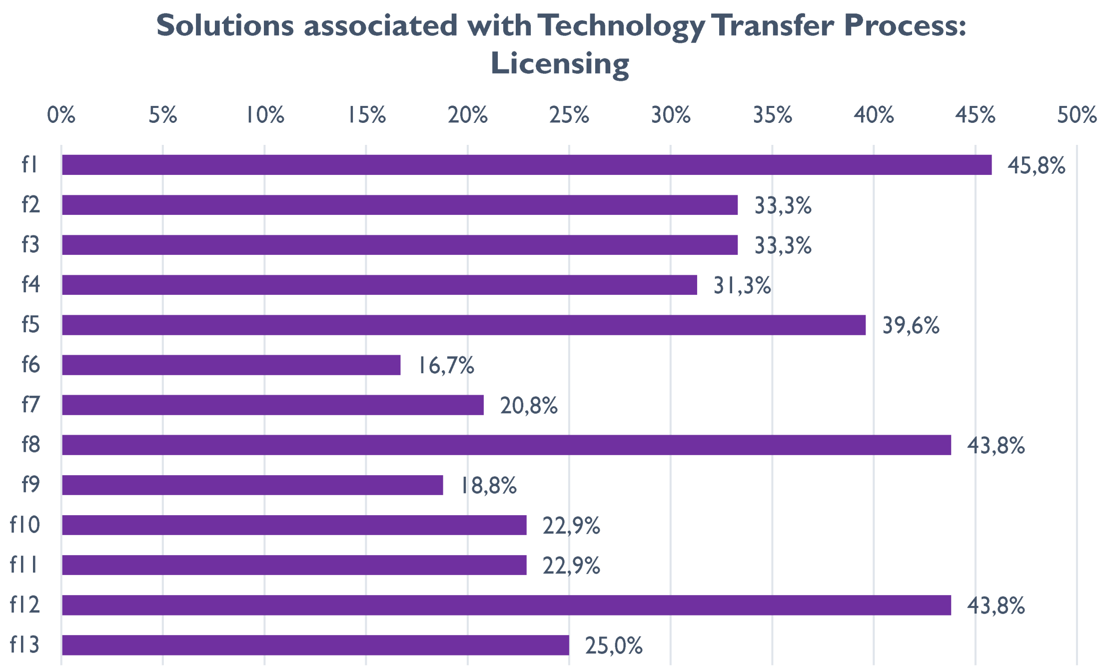


Figure 38 - *Prevalence of the solutions identified within the Technology Transfer Process: Licensing factor.*

Industry/Inventors (Fig. 39) selected the following problems as the most relevant:

- g1- **Attract international investors to the Portuguese technology transfer ecosystem** with 72,9% of the votes;
- g7- **Create/finance more technology development programs in basis on the industry - R&D Centres collaboration** with 45,8% of the votes;
- g10- **Encourage hybrid valuation strategies with venture capitalists (e.g., in addition to the typical investment in the creation and development of start-ups to act as licensing agents)** with 37,5% of the votes;
- g4- **Create public policies to benefit foreign enterprises that license technologies from Portugal** with 35,4%
- g11- **Assign to specific human resources within the company the responsibility of receiving contacts from R&D Centres in order to establish possible collaborations and/or licensing agreements and disseminate these contacts in a clear and accessible way to R&D Centres** with 35,4%.

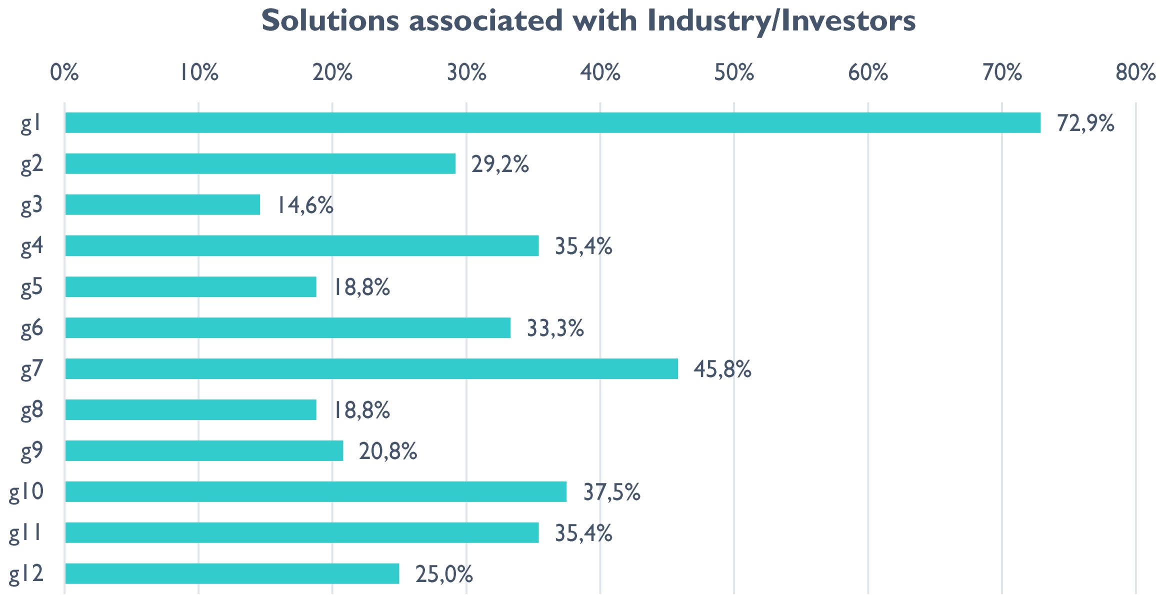


Figure 39 - *Prevalence of the solutions identified within the Industry/Investors factor.*

4.3.6. Main Results

From the total 93 identified problems (Table 5), the TOP10 most voted are associated with six of the seven identified factors, being the exclusion the industry/investors factor (Table 8). The TOP3 most voted problems are the limited funding for patents submission and maintenance, the lack of guidelines for the negotiation process within the R&D Centres, and the limited or non-existing funding for the analysis of patentability, commercial potential, and other studies related to the developed technology by the TTOs. The remaining TOP10 voted problems are related to a lack of knowledge, time, training, and awareness by researchers for topics related to technology transfer, a lack of training and experience in the different steps of the technology transfer process by technology transfer technicians, and a lack of funding, market studies, and specialized human resources in different steps of the technology transfer process. The TOP10 is composed of 12 problems because associated with the last position are three problems with the same percentage of votes, as shown in Table 8.

Table 8 – TOP10 most voted problems regarding the licensing of technologies from R&D Centres.

'TOP10'	Associated Factor	Ref	Problems	Vote percentage
1	**Technology Transfer Process: Patents**	**E3**	Limited specific funding for maintenance and obtaining of patents;	66,7%
2	**Technology Transfer Process: Licensing**	**F4**	Lack of guidelines in the negotiation process within an R&D Centre (similar to what already exists in other renowned institutes such as MIT and Harvard University);	64,6%
3	**Technology Transfer Offices and Technicians**	**D5**	Reduced/Non-existent funds available to technology transfer offices to assess the patentability and commercial potential of technologies, as well as other studies necessary for the technology transfer process;	61,7%
4	**R&D Centres Researchers**	**B1**	Lack of knowledge and/or alienation for topics such as Intellectual Property, technology transfer, patents, licensing and commercialization of technologies, and entrepreneurship;	58,3%
5	**Technology Transfer Process: Licensing**	**F8**	Lack of perception of the value of technology in the market;	58,3%
6	**R&D Centres**	**A6**	Lack of human resources with specific training in technology transfer;	56,3%
7	**R&D Centres Researchers**	**B2**	Lack of time to dedicate to technology transfer processes due to the multiple functions/positions assigned to the researchers at the same time;	56,3%
8	**Technologies**	**C10**	Lack of market studies before and during the development of the technology (e.g., lack of cost-benefit studies);	56,3%
9	**Technology Transfer Process: Licensing**	**F2**	Lack of human resources with specific training and experience in valuing/licensing technologies.	56,3%
10	**R&D Centres Researchers**	**B9**	Lack of strategy at the beginning of the development of a project/technology regarding its final goal: scientific dissemination versus commercialization	54,2%
11	**Technologies**	**C1**	Limited financing for R&D activities in general	54,2%
12	**Technologies**	**C2**	Lack of specific funding for proof-of-concept and prototypes;	54,2%

From the total 97 solutions proposed (Table 6), the TOP10 most voted are associated with five of the seven identified factors, being the exclusion the 'Technology Transfer Process: Patents' and the 'Technology Transfer Process: Patents' factors (Table 4). The TOP3 most voted solutions are the attraction of international investors to the Portuguese technology transfer ecosystem, the increase in the number of awareness-raising actions and training in technology transfer topics for researchers, and the encouragement of the increase in the number of R&D Centres projects developed in collaboration with the industry. The remaining TOP10 voted solutions are associated with the improvement of human resources in technology transfer (in their number, training, and background diversity), the improvement of industrial partners since the beginning of the technology development, the creation of exclusive funding for the different steps of the technology transfer process, the definition and implementation of good technology transfer practices, and the promotion of researchers evaluation metrics focused on the quality of the technologies developed in R&D Centres. The TOP10 most voted solutions is shown in Table 9.

Table 9 – TOP 10 most voted solutions regarding the licensing of technologies from R&D Centres.

'TOP10'	**Associated Factor**	**Ref.**	**Solutions**	**Vote percentage**
1	**Industry/ Investors**	**g1**	Attract international investors to the Portuguese technology transfer ecosystem	72,9%
2	**R&D Centre researchers**	**b1**	Increase the number of training, awareness-raising actions, and programs in the areas of technology transfer; Intellectual Property; valorization and licensing of technologies, among others;	68,8%
3	**R&D Centres**	**a5**	Encourage an increase in the number of technologies/projects developed within an R&D Centre in collaboration/partnership with enterprises, for example by including this factor in its assessment (if applicable taking into account the R&D Centre's mission and vision);	66%
4	**Technology Transfer Offices and Technicians**	**d2**	Increase the number of highly qualified, specialized human resources with a diversity of backgrounds in technology transfer offices (*e.g.*, 'in-house entrepreneur', manager, patent attorney, economist, a specialist in a particular area of research) in technology transfer offices;	64,6%
5	**Technology Transfer Offices and Technicians**	**d5**	Invest in training and updating the skills of technology transfer technicians;	58,3%
6	**Technologies**	**c6**	Promote the involvement of industrial partners from the beginning of the technology development (*e.g.*, creation of multidisciplinary teams; design of technology development adapted to a commercial application from the beginning);	56,3%
7	**R&D Centres**	**a2**	Change the evaluation metrics in technology transfer of the R&D Centres, promoting the valorization of the technologies (*e.g.*, number of licenses, income, and commercialization) instead of technologies protection (*e.g.*, number of patents);	55,3%

Table 9 – TOP 10 most voted solutions regarding the licensing of technologies from R&D Centres.

‘TOP10’	Associated Factor	Ref.	Solutions	Vote percentage
8	**Technologies**	**c3**	Create exclusive financing programs for scale-up/prototyping studies;	50%
9	**Technologies**	**c7**	Create exclusive funding programs for proof-of-concept studies;	50%
10	**R&D Centres**	**a14**	Define and implement good technology transfer practices within an R&D Centre (*e.g.*, research, regulation, industry input, etc.) based on international guidelines	46,8%

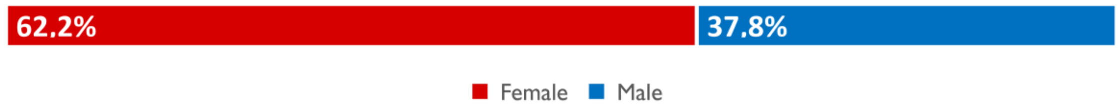
4.4. CNC Inquire: ‘What is your opinion on tech transfer?’

As we identified that the most voted problem associated with the R&D Centre researcher factor was their training, we developed a case study for researchers of the Center for Neuroscience and Cell Biology (CNC). Our choice of this R&D centre was based on their focus and expertise in healthcare research and accessibility (since the CNC is the institution that hosted our project). With this, we developed the online survey presented below.

4.4.1. Inquired Description

The survey conducted on CNC was answered by a total of 37 individuals with different academic degrees and positions within the different research groups. From a demographic point of view, our sample can be described according to their age, gender, highest scholar degree, research area, and position within the research group. From the answers, we gathered more females than males (62,2% vs 37,8%) (Fig. 40 A) with the majority (32,4%) being between 41 and 50 years old (Fig. 40B), although all group ages are fairly represented.

A.



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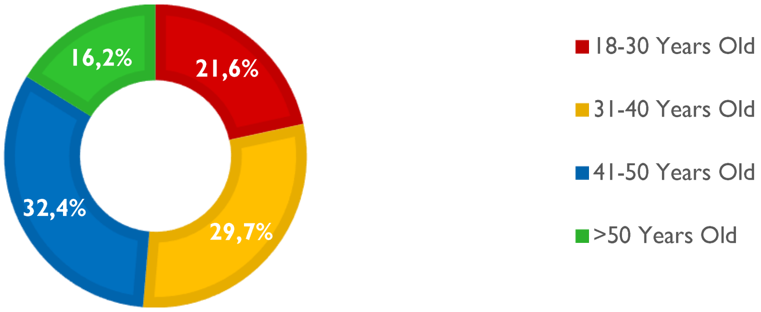

Figure 40 - *Demographic description of the inquired. A. Gender; B. Age groups.*

Relatively to the highest academic degree, there are two representations: doctorate and master's degrees, where the majority has a doctorate degree (73%). Of note, one of the options was 'other' and the answer gathered was 'aggregation', we considered this answer as a doctorate degree, as 'aggregation' is an academic title and not an academic degree in which a doctorate degree is a requirement (UC, [s.d.]).

Within the three main study subjects of CNC, the majority (64,9%) of the inquired are inserted into the 'Neuroscience and Disease' group whereas the remaining are distributed similarly through the two remaining groups – 'Metabolism, Aging and Disease' (13,5%) and 'Biotechnology' (16,2%). There is also a 5,4% representation from support professionals in 'Scientific Platforms/Services/Infrastructures' (Fig. 41A). As of the position of the inquired within the research group, the responses variated between 27% as post-doctorate researchers and 2,7% as Laboratory Technicians (Fig. 41B).

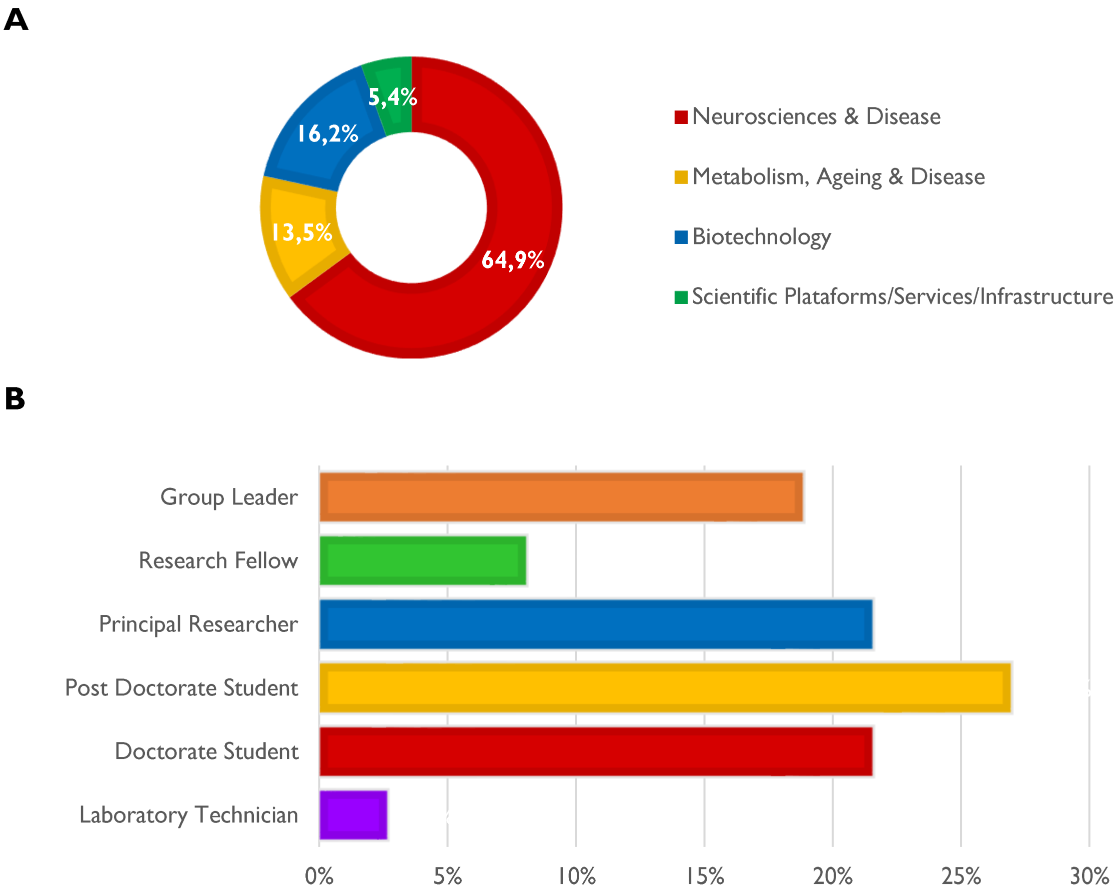

***Figure 41 -** Inquired demographics. A. Representations of the main study subjects at CNC; B. Representation of the different positions within the groups.*

4.4.2. Patents and Licensing at CNC

In this section of the survey, we intended to evaluate the status of patents/patent applications and licensing of the same within researchers at CNC. Note that these data are referring to the first fortnight of April 2021.

The majority (78,4%) of CNC inquired have no association present or past with a patent/patent application (Fig. 42A), with 62,5% of the remaining inquired being associated with 1-2 patent/patent applications (Fig. 42B). Of the individuals with a patent/patent application, 37,5% belong to the 'Metabolism, Aging and Disease' research area, 37,5% to the 'Neuroscience & Disease', and 25% to the 'Biotechnology'. According to the Technology Transfer Office of CNC, this institute currently detains 17 patents/patent applications and five licensed patents.

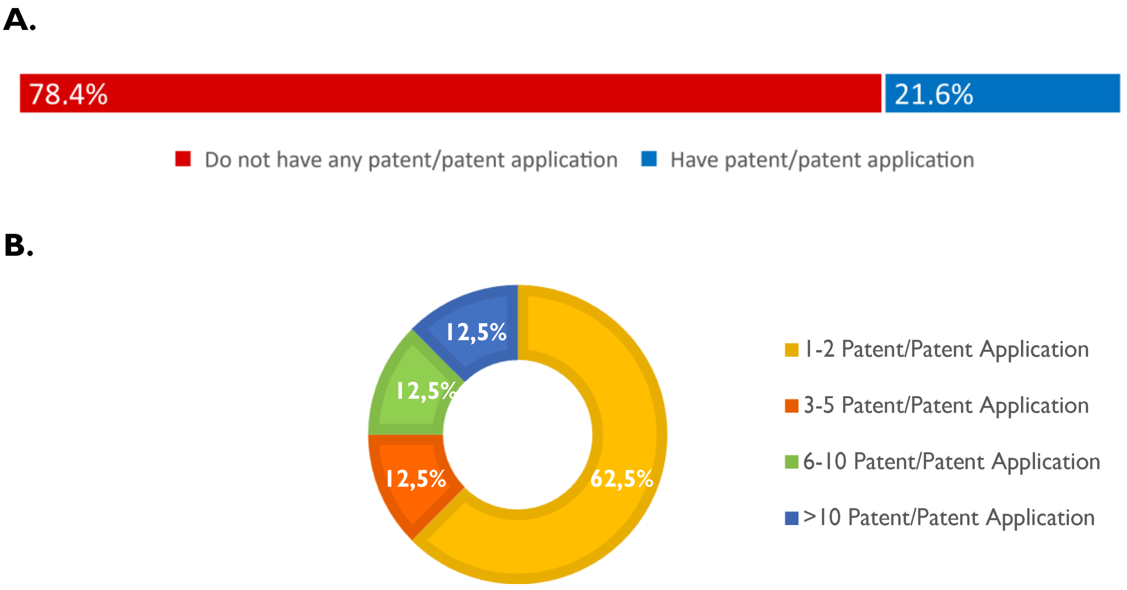

Figure 42 *- Current patent ownership (in percentage) by CNC researchers. A General overview of the patents/patent applications associated with CNC researchers; B. Representation of the different quantitative ranges regarding the total number of researchers who stated that they were associated with patent/patent application.*

Regarding the commercialization through licensing, only 8,1% of the inquired present licensed patents (Fig. 43A). In terms of the individuals with licensed patents, 66,7% of them have 51 to 75% of their patents licensed and the remaining (33,3%) 26% to 50% (Fig. 43B).

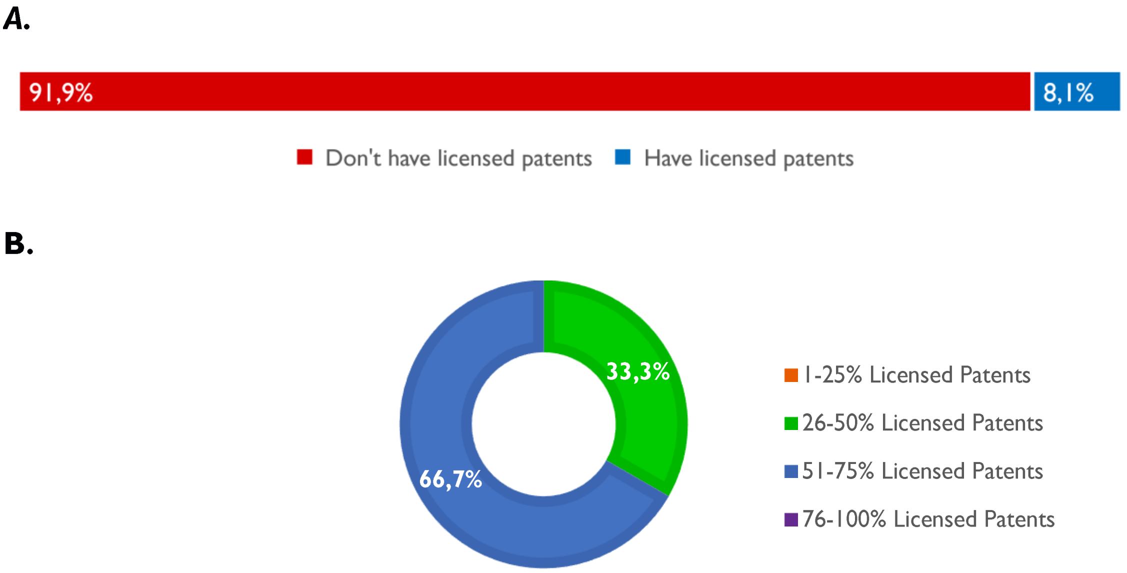

Figure 43 *– Licensing status of patents/patent application from CNC researchers. A. Percentage of researchers associated with licensed patents versus researchers that do not have licensed patents (including those who do not have a patent/patent application). B. Representation of the licensed patents within their patent/patent application 'portfolio' regarding the researchers who claimed to be associated with patents.*

Only 8,1% of the researchers answered to be associated with CNC start-ups. These start-ups are Toxfinder, MitoTag, and Healper (the latter still under development).

These results show, in general, no or a low number of patents (either as applications or conceded) and licensed patents among the researcher.

With this survey, we also aimed to evaluate the background and interest of the researchers in the topics of tech transfer and entrepreneurship. In the following questions, we will approach previous education on the subjects of technology transfer and entrepreneurship, the level of interest in these subjects, the need for an educational update on the topic of technology transfer, entrepreneurship, or patents, and the willingness/intention on following the path of commercializing their technology.

4.4.3.1. Technology Transfer and Entrepreneurship during academic training

Only 27% of the inquired answered that they had contact with the tech transfer topic during their training (Fig. 44A), with 50% of them finding this training 5-very interesting and none of them answering that it was not interesting at all ('1-nothing interesting'), as stated in Fig. 44B. Regarding the topic of entrepreneurship during their training, more researchers had contact with this topic (32,4%) (Fig. 44A), with 41,7% of these finding this training very interesting but, in this case, with 16,7% founding it nothing interesting (Fig. 44B). These results demonstrate a clear insufficient academic training in technology transfer and entrepreneurship topics in Portugal, although general interest in these topics is demonstrated by the healthcare researchers.

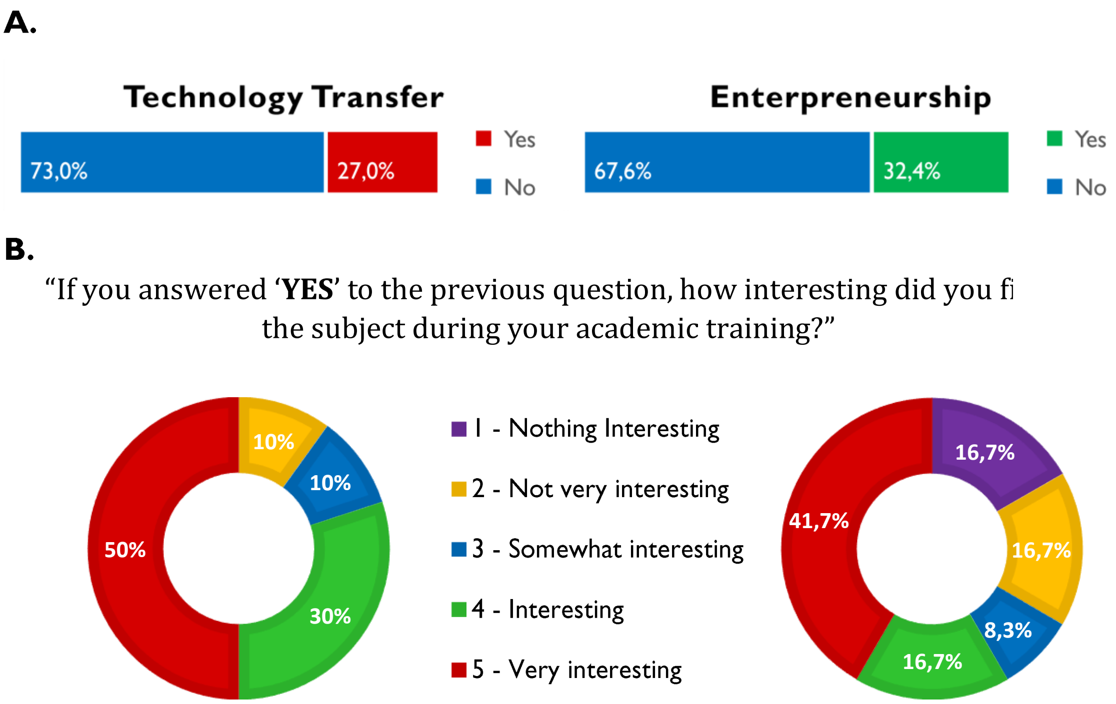

Figure 44 *– Academic training and interest shown by researchers regarding the topics of technology transfer and entrepreneurship. A. Approach to the topic during academic training; B. Interest in the topic during academic training.*

After establishing the interest among the researchers, we evaluated the need for an academic update on the topics of entrepreneurship, technology transfer, and patents. From the inquired,

~78,3% feels a need to update their knowledge in entrepreneurship, technology transfer, or patents, with 48,6% of the inquired feeling a lot or a great need, as shown in Fig. 45. These results demonstrate that there is an urgent need for training in technology transfer and entrepreneurship topics among healthcare researchers and, as such, the necessity to include these topics in academic and training programmes within our R&D Centres and educational institutions.

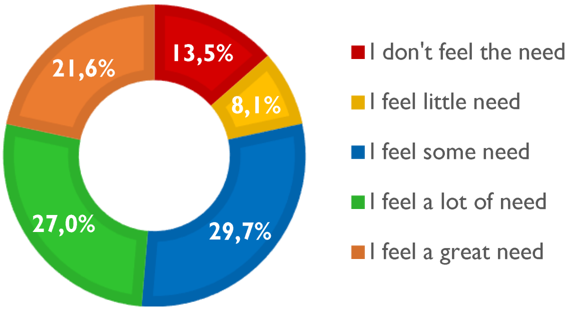

Figure 45 – *Status of the inquired need (in percentage) for a knowledge update on the entrepreneurship, patents, and technology transfer topics.*

The majority of the inquired answered that they did not have any specific training in the entrepreneurship topic whatsoever on entrepreneurship (59,5%), as demonstrated in Fig.46A, or IP and/or technology transfer (56,8%), as demonstrated in Fig.46B. These results also demonstrate insufficient training in entrepreneurship, IP, and technology transfer among healthcare researchers in a general manner, raising the necessity for more awareness in these topics.

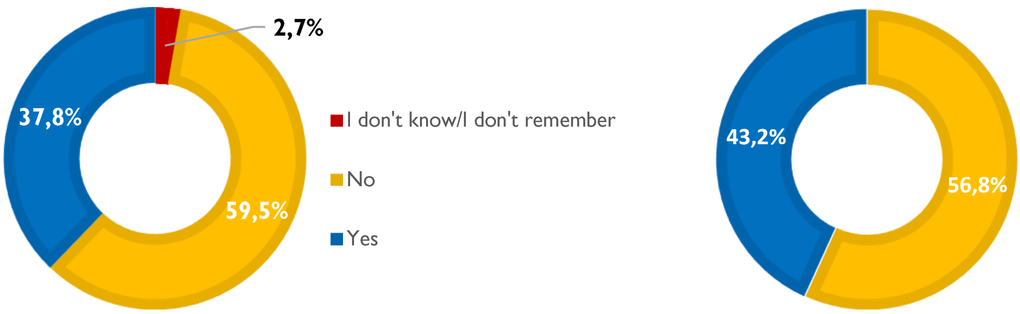

Figure 46 – *Status of the inquired background (in percentage) in entrepreneurship and IP and/or Technology Transfer. A. Background specific training on entrepreneurship; B. Background specific training on IP and/or Technology Transfer (B).*

4.4.3.2. Entrepreneurship Career

Regarding a career path in the 'Entrepreneurship' area, ~67,6% of the inquired never experienced the creation of enterprises based on their technology, followed by 10,8% that had a brief experience (Fig. 47A). When asked for a hypothesis in an entrepreneurship path, approximately half (51,4%) of the inquired consider this a hypothesis, with only 2,7% being certain to go through this path (Fig. 47B). These results demonstrate a clear misalignment between the number of researchers that never had an experience in entrepreneurship (67,6%)

with the number of researchers that consider it a hypothesis at least (64,9%). These results demonstrate that more should be done to motivate, assist, and support healthcare researchers that desire to be entrepreneurs.

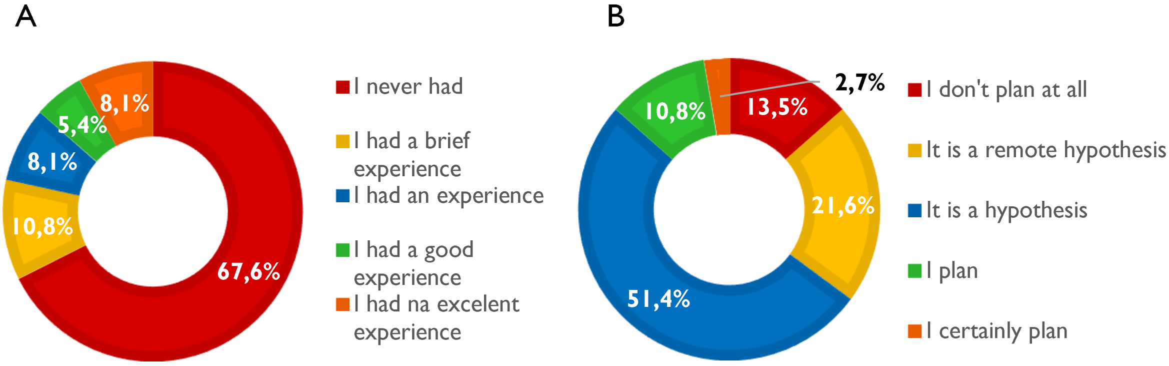

Figure 47 *– Experience and future perspectives in entrepreneurship by CNC researchers. A. Level of experience by the inquired (in percentage) in the creation of enterprises based on technologies developed on their research; B. Status of the inquired (in percentage) in the intention of pursuing an entrepreneurship* ***path.***

4.4.3.3. Future awareness-raising and training activities preferences

Optimistically, the large majority (73%) of the CNC researchers are willing to spend until two hours per month, on average, on technology transfer training, as shown in Fig. 48.

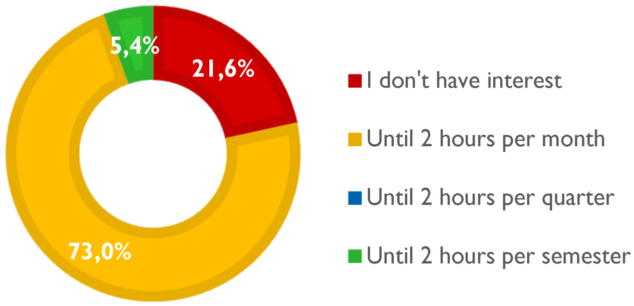

Figure 48- *Average time (in percentage) CNC researchers are willing to spend in technology transfer training sessions per year.*

Among the awareness-raising actions and training activities, the majority of the researchers preferred the 'Open days at the CNC to the industry' (43,2%) and an online course (43,2%), as shown in Fig. 49.

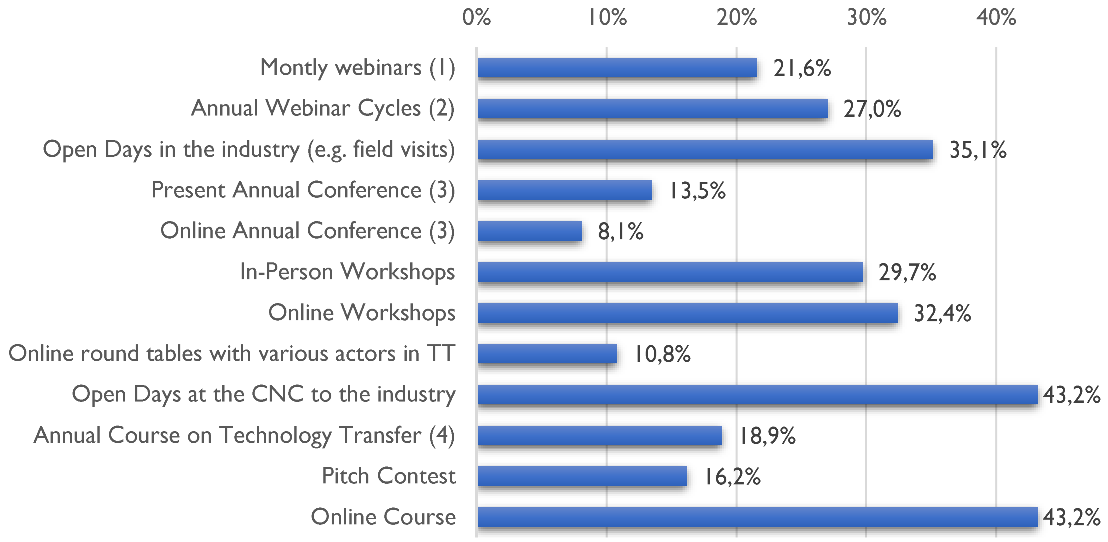

Figure 49 - *Preference (in percentage) regarding the types of the training/awareness-actions of CNC researchers. Note that the referred activities would present the following durations: (1) up to two hours per month, (2) between four to five webinars per year, (3) between one to two days; (4) between two to four days.*

The most voted actions (i.e., the creation of an online course and the realization of an Open day at the CNC to the industry) are currently being implemented at CNC. These actions will be followed by an analysis of their efficiency in improving researchers' knowledge on the subjects of technology transfer and entrepreneurship, as well as their intentions to consider following an entrepreneurial pathway by comparison of the answers to a form realized before and after these activities.

5. Discussion

In this project, we identified and analysed the factors that influence the licensing of healthcare technologies from R&D Centres in Portugal. First, we identified the players of the healthcare research innovation ecosystem in Portugal and then comprehensively identified the factors, associated problems, and possible solutions for the low number of technologies licensed from R&D Centres and evaluated their relevance from the perspective of the different healthcare research players according to their business type and region location in Portugal. We were also able to develop a case study at the CNC regarding the most relevant problem related to the R&D researchers' factor.

5.1. CNC HealthPT Database

We started by creating a database of healthcare research players because organized information about the total number of institutions that operate in this area in Portugal was lacking, especially regarding R&D Centres and enterprises. Regarding the R&D Centres, two main sources can be found: *Portal da Inovação* from ANI and FCT website. Regarding the enterprises, two main sources can be found: *Portal da Inovação* from ANI and HCP website. In December 2020, we had identified 73 research institutions and 47 higher education institutions. In March 2021, Portal da Inovação had identified 42 research institutions and 77 higher education institutions in the category named 'medical and health sciences'. The *Portal da Inovação* database requires auto registration, which could underestimate the number of players and was publicly launched in February 2021 (several months after the time we started this thesis study). The fewer number of identified higher education institutions in the CNC HealthPT Datase is due to criteria divergencies (for example, the inclusion of different locations associated with the same institution as different higher education institutions). The FCT website has available information on national research institutions (through the provision of various documents) but lacks the reference to their work areas in some of these documents. Recently, FCT divulge a list of 312 research centres with approved funding for the period 2020-2023, 35 of which are in the healthcare area (Fundação para a Ciência e Tecnologia, [s.d.]). In addition, in May 2021, FCT published the updated list of 45 associated laboratories (including both individual research institutions and consortia) valid for a maximum period of 10 years (Fundação para a Ciência e Tecnologia, 2021). The fewer number of identified research institutions in the CNC HealthPT Datase is due to criteria divergencies (i.e., the FCT list includes non-healthcare R&D Centres and consortia, not only individual centres, and only considers the R&D Centres who were granted funding support, a criteria that the

CNCHealthPT does not take into consideration). Portal da Inovação database identified 22 enterprises in 'medical and health sciences' versus the 242 enterprises identified in the CNC HealthPT Database. This high discrepancy in the number of enterprises is probably related to the auto-registration necessity of the *Portal da Inovação* as mentioned above. The information available on the HCP website regarding the number of enterprises operating in the healthcare research is overdue (from 2015). This database identifies 88.909 enterprises/institutions in the health sector in Portugal, a significantly higher number compared to the 242 enterprises identified by the CNCHealthPT database. The discrepancy in the number of healthcare enterprises is related to the fact that the HCP database includes institutions on human health service provision (e.g., hospitals, clinics, private practices, pharmacies, among others) that were excluded from our CNCHealthPT database(Health Cluster Portugal, [s.d.]).

Comparing the regional GDP per capita, we verify that the healthcare sector plays an important role in the economic development of the most developed regions. In terms of the enterprises' distribution within the TOP3 most developed regions in healthcare, we verify that they are almost exclusively concentrated in the bigger urban centres of these regions. For example, Lisbon and Tagus Valley region present only 3,3% of enterprises located outside of the Lisbon metropolitan area. The same is verified for the R&D Centres, where 91,3% of the regional R&D Centres are located in Lisbon county. In the Centre region, the majority of R&D Centres (~52%) and enterprises (~42,3%) are located in Coimbra county. In the North region, the majority of the R&D Centres (~67,4%) and enterprises (~32,8%) are located in Oporto county.

5.2. Identification of factors that influence the licensing of technologies from R&D Centres in Portugal – interview processes

We verified difficulties to identify and reach the person with the most appropriate position within the entities to answer our request for an interview since the majority lacks a professional exclusively dedicated to the technology transfer/innovation topic.

From the 47 interviews that we performed, we gathered a total of 93 problems and 93 solutions categorized into seven factors: (1) R&D Centres, (2) R&D Centres researchers, (3) Technologies, (4) Technology Transfer Offices and Technicians, (5) Technology Transfer Process: patent, (6) Technology Transfer Process: licensing, and (7) Industry/Investors. These factors are associated with themes often debated in international literature as barriers that contribute to the VoD in the development of technologies, both in the general and in the healthcare contexts. Examples of these studies in healthcare are (a) Phillips and Garman (2006) categorizes several problems to entrepreneurship in healthcare organizations within structural, economic, organizational, and behavioural barriers (e.g., lack of financial resources, misalignment of organizations mission with a financial interest, lack of entrepreneurial behaviour, and an incompatibility between the professionals' motivation and entrepreneurship); (b) Caulfield and Ogbogu (2008) reviews problems associated with the commercialization (e.g., patenting, technology maturation, and validation) of products in neurosciences; (c) Caulfield et al., 2008 analyses the problems associated with patenting and commercializing research within the stem cells topic; (d) Khademi and Ismail (2013) reviews the state-of-art of several factors (e.g., researchers, networking, technology maturation, funding, TTOs, market research, entrepreneurial team, among others) that can influence the success of the commercialization of technologies from R&D Centres. Some of the studies covered in this review meet the problems and solutions we have collected in our study. They identify these factors as the ones that most influence the success of the commercialization process of university research: the researchers' engagement (that depends on their perception of the commercialization process), the timing for commercialization (the holdback in the commercialization in hope for a better deal is risky), the implementation of 'entrepreneurial teams', the technology maturation level, the importance of funding (that is crucial in the early stages of the process), the importance of market research, and the existence of a TTO; and (e) Fritzler et al., (2021) reviews the process for the development of biomarker-based diagnostic tests, approaching different aspects such as regulamentation, cooperation, and factors that can influence the VoD of these technologies (other examples can be found in Table 1).

5.3. Evaluation of factors that influence the licensing of technologies from R&D Centres in Portugal – online survey

Regarding the online survey, most of the inquired entities (70,8%) has ranked the 'industry/investors' as the most relevant factor in the licensing of healthcare technologies from the R&D Centres, followed by the technologies, the technology transfer offices and technicians, the R&D Centres Researchers, the R&D Centres, the Technology Transfer Process: Licensing, and the Technology Transfer Process: Patents (Fig. 50).

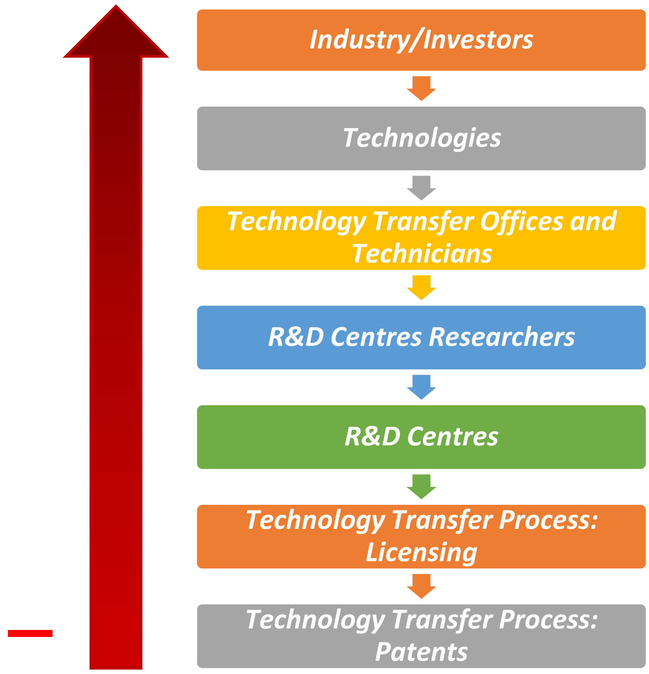

Figure 50 - *The identified factors based on their 'relevance' classification. Their relevance increases in the orientation of the arrow (from the bottom to the top).*

The problems associated with the VoD topic that we identified are in line with the ones identified by others in national and international contexts. **The lack of funding for patents application and maintenance** is supported by Tahmooresnejad and Beaudry (2018) that shows how funding programmes in valorization have a positive effect on patent renewal and also highlights the need for the government to intensify the funding of inventive activities and to create supporting policies regarding long-term funding mechanisms for the innovation of academic inventors (in a Canadian context); **the lack of a strategy at the beginning of a project/technology development regarding its final goal and a lack of time by the researcher** to pursue the technology transfer path are also problems identified by Kampers et al., (2021). In this study, Kampers and colleagues deliver an overview of crossing the VoD in biotechnology, where one of the topics approached is the mindset of the researchers, as they are focused on teaching, conducting research, publishing their work, and pursuing funding. The association of these focuses with the lack of commercialization incentives leads researchers away from a path aimed at the commercialisation of their technologies. We also identify the **lack of human resources with specific training and/or experience in value/license technologies**, which is mentioned by Hugget (2014). From a survey for VCs (and other investors) performed in the context of this study, it is claimed that TTOs over evaluate their Intellectual Property (although, the author cautiously notes that this could be a biased vision by the VCs mindset). This study suggests a lack of perception of the technology value in the market and points to a need for improvement in the TTOs valorization (and consequently negotiation) skills. This problem relates with another one identified in this study that is the **lack of guidelines in the negotiation process by R&D Centres**. The identification of **a lack of specific funding for proof-of-concept and prototypes** is supported by Maia and Claro (2013) as they concluded that the creation of a proof-of-concept centre associated with the University of Coimbra can have a very relevant impact on the commercialization of technologies within the Centre region of Portugal. This problem is also identified by Munari et al. (2015) that when analysing determinants and consequences of funding programmes (through university seed funds and proof-of-concept programmes) in Europe and their gaps and disparities, they identified that these programmes are well-established in the Nordic and Western Europe and scarce or absent in the Southern and Eastern Europe. Munari et al. (2015) also correlate the minimum level of TTOs development (i.e., staff, resources, and expertise) to the existence of these gaps, and the need to manage the available financial instruments more scrupulously as they are more dependent on them. The **lack of human resources with specific training in technology transfer** is supported by (a) Takata and colleagues mention that TTTs need to understand how to manage the VoD in addition to possessing skills related to legal management, project management, negotiation, licensing, and experience in specific fields of business and sciences (amongst others) and (b) Soares and Torkomian (2021) refers that the TTTs background can have an effect on the technology transfer process: TTTs with a research-oriented background presented a positive effect on the discloser of new technologies and conclusion of licensing agreements (and are also more likely to overcome barriers associated with conflicting goals and interest of TTOs and researchers); TTs with a marketing-oriented background presented a positive impact on the licensing agreements (as their mindset is commercially focused, they can better interpret the commercial and strategic perspective of industry representatives). In addition, this study also refers that TTTs specialized in licensing have a positive effect on the disclosure of new technologies and licensing agreements. The remaining problems we identified are highly linked to the policies (or lack of) enforced in Portugal, such as **the low funding for R&D activities and the lack of available funds for TTOs to assess the potential of the technology and to develop market studies during the development phase.**

From the data we gathered, one of the more voted solutions points towards the **increase of the number of training, programmes and awareness-raising opportunities in the technology transfer process, Intellectual Property, valorization and licensing of technologies, directed to researchers**. This solution is approached also by (a) Barr et al. (2009) that proposes entrepreneurship training based on real case scenarios (problems) and by (b)Bolzani and colleagues (2020) that identify the TTOs and TTTs as actors capable to contribute significantly to entrepreneurship education and training (due to their privileged position at the interface academia-industry). In addition, the authors also identified the need for an action-oriented approach (e.g., through case studies, projects, simulations, internships, and/or other interactive activities). **The encouragement in the increase in the number of technologies (within an R&D Centre) in collaboration with enterprises** is also referred to by Kampers et al. (2021) that mentions the need to include the preparation of product development right from the start of the technology development. **The importance of the involvement of industrial partners from the beginning of the technology development** is shown by (a) Barr et al. (2009) that observed that work teams with a heterogeneous background (with professionals in management and science/engineering) had better performances and (b) by Seyhan (2019) that in its review (of problems and solutions for overcoming the VoD in pharmaceutical development) identified the adoption of a multidisciplinary team (concerning both the professionals background and institutions involved in the project) as essential to the success of the technology. **The need for definition and implementation of good technology transfer practices by the R&D Centres** is also referred to by (a) Munari et al. (2015), which proposes the definition of clear guidelines regarding the ownership of Intellectual Property rights to (among others) avoid conflict during the licensing process and (b) by Mascarenhas et al. (2019) that identified the existence of royalties guidelines as one of the most important factors that contribute to the increase of patent applications. **The creation of proof-of-concept funding** has already been approached by Maia and Claro (2013) that study the possibility of the creation of a Proof-of-concept Centre in the University of Coimbra that would positively impact the commercialization of technologies, not only from the university but also from the regional R&D Centres. **The investment in training and updating skills in technology transfer technicians** is supported by (a) Wright et al., (2009) that highlights the relevance of negotiation and business skills in TTTs' ability to exploit opportunities and to improve entrepreneurship and (b) by Mom et al. (2012) that defends the importance of TTTs' to acquire both soft and hard skills in technology transfer. **The creation of specific funding programmes for scale-up and prototyping** is highlighted by Tufféry (2015) that refers to the proof-of-concept as one of the more financially pressured phases to achieve results. Similarly to the identified problems, the remaining proposed solutions are related to specific policies enforced in Portugal, such as the **improvement of the available conditions to attract international investors** and the **change on the evaluation metrics of the**

researchers (that currently privilege quantity over quality). We also identified the **diversification of TTOs by employing highly qualified human resources with diverse backgrounds** (e.g., patent attorney, economist, or research specialist) which is supported by (a) Siegel and Phan (2005) who, as referred above, identify the need to improve the capacities (e.g., negotiation and marketing skills) of the various participants (e.g., researchers, administrators, and other actors) in academic entrepreneurship, (b) Bolzani and colleagues (2020), as mentioned above, identify the TTOs and TTTs as actors capable to contribute significantly to entrepreneurship education and training (due to their privileged position at the interface academia-industry), and by (c) Soares and Torkomian (2021) that, as mentioned above, indicates that the TTTs background can have positive effects in the outcome of the technology transfer process.

The most prominent problems point to an immature healthcare technology transfer ecosystem, where its actors are still somewhat isolated and quite dependent on public funds for its operation. This points to an obvious need for a paradigm shift. Following this need to change and improve in this ecosystem, the solutions we identified can help players to make necessary changes based on a global ecosystem perspective.

5.4. Case-study: the CNC

As we identify several problems and solutions involved in the technology transfer ecosystem, we applied a case study at the CNC where we selected the higher-ranked problem and the correspondent solution among R&D Centres researchers: improving training, awareness actions and programs in technology transfer related themes to counter the lack of knowledge this area from the researchers. For the development of a possible training program and awareness-actions, we needed to set a baseline for CNC researchers' knowledge and interest in entrepreneurship and technology transfer topics through an online survey. The CNC researchers showed a well-developed 'academic status' but a low 'technology transfer status', where the vast majority of the inquired did not present any contact with a patent/patent application (of note: several researchers work on fundamental research, which justifies their lack of contact). We also noted a gap in their academic training regarding entrepreneurship and technology transfer topics with the researchers recognizing a need to create/update their knowledge in these topics with approximately half considering the possibility of crossing their professional path with entrepreneurship. To the best of our knowledge, this study is the first to perform a case study in Portugal that addresses interest and academic training in entrepreneurship and technology transfer by healthcare researchers. However, we found multiple international studies that link knowledge, behavioural, and motivational, traits of the researchers with the eventual success of their technologies such as (a) Magnusson, McKeley and Versiglioni, (2009)., and Escobar et al., (2017). The first study recognizes a positive attitude of researchers towards commercialization, however, they lack time and knowledge (in entrepreneurship and commercialization areas) to perform these activities. Furthermore, the researchers say they do not feel supported or encouraged by the university to pursue this path and refrain from doing it because they believe they are not skilled to do so. In light of these findings, the authors suggest granting researchers more freedom to perform mutual roles in academia and industry, keeping in mind that the commercialization route should be seen as a complement to the research activities but not a substitute. The authors also propose to implement formal training in entrepreneurship and business and commercialization skills and experience of researchers as criteria for promotions and hires.

The second study conducted at Catalunya Polytechnic University concludes that the involvement of researchers in knowledge and technology transfer is often associated with an emotional tie with academia and their commitment to pursue the university mission (intrinsic motivations). The authors propose to improve the participation of researchers in technology transfer activities (and consequently academia-industry relationships), by increasing extrinsic motivations (i.e., monetary and career progression incentives). Although the need to improve researcher's participation in technology transfer, authors also acknowledge that a positive attitude towards the knowledge and technology transfer path is negatively affecting the R&D, as researchers are focused on these processes they tend to reject or diminish the time they spent in new projects, as well as being more selective towards the ones they participate. On the other hand, the communication between researchers and industry (e.g. through industry-academia collaborations) promotes a positive culture towards entrepreneurship within the University, positively influencing the researchers to participate in knowledge and technology transfer activities.

These data support the identified problem of a 'researcher' mindset in detriment of an 'entrepreneurial mindset, the importance of the inclusion of themes such as IP, technology transfer, and entrepreneurship in the core background, and the realization and promotion of training/ awareness activities in areas such as entrepreneurship, Intellectual Property, and technology transfer to stimulate an entrepreneurial culture within an R&D Centre.

6. Conclusion

With this study, we were able to obtain a better overview of the healthcare research innovation ecosystem, namely the factors, problems, and solutions that affect the licensing of healthcare technologies from R&D Centres. This ecosystem is concentrated in three main regions: Lisbon and Tagus Valley, North, and Centre. The Lisbon and Tagus Valley has an outstanding number of big pharma enterprises and R&D Centres, which contributes to their regional leadership in the healthcare sector. We acknowledge the fact that the results of this study could be improved by raising the number of collected answers. This study has also brought light to issues that healthcare researchers have with the topics such as entrepreneurship, innovation, and/or technology transfer.

We conclude that the main factors impacting the licensing of healthcare technologies from R&D Centres are the Industry and/or Investors, the Technologies, and the Technology Transfer Offices and Technicians. The main problems we identified are associated with the lack of funding for several steps of the technology transfer process and specialized professionals in these steps, an alienation from the technology transfer professionals to the functioning of the valorization process, and an alienation from the researchers regarding the technology transfer process. The main solutions we identified are related to the internationalization of the technology transfer process (by improving the attractiveness of the Portuguese technology transfer ecosystem to international investors), the training of healthcare researchers in entrepreneurship, innovation and/or technology transfer related themes, and the increase of projects in collaboration with industry partners. Although we identified an immature technology transfer ecosystem, with a high number of problems, we were also able to identify a vast spectrum of possible solutions that vary from simple actions of individual players (for example researchers can carry out training in entrepreneurship/innovation or consider the inclusion of industry partners in a project) to structural improvements by entities (with the creation of technology transfer guidelines by R&D Centres or the improvement in cooperation/communication between academia and industry), to the revision of public policies (from national funding programmes to the attraction of international investment). One common aspect that is highlighted is the excruciating need for the improvement of academia-industry collaborations. This relationship has been proven crucial for the successful transferring of technologies and their benefit for society, which was reinforced by the COVID-19 pandemics with the collaboration between researchers and industry in the development of vaccines (Nature, 2021).

The importance of our study lies in the need to assess the impact of each factor and to provide solutions that could improve the Portuguese healthcare technology transfer ecosystem as well as allow each player to become aware of the role they can play in improving this area. Despite having filled this gap, this study would benefit from a more depth national analysis through the recollection of a higher number of answers to the 'Overcoming the "Valley of Death" survey and the translation of CNC case study to others R&D Centres. The study will also benefit from a more thorough analysis of the most voted problems and solutions. The study will be continued by introducing training activities in technology transfer in CNC to analyse their effect of on the interest, knowledge, and general technology transfer of the CNC researchers and institute standard international guidelines (based on successful examples) to the technology transfer process.

We hope that this study can ignite the changes needed to improve the healthcare technology transfer ecosystem and demonstrate our capabilities as health technology providers worldwide.

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Appendix A

Examples of the different training programmes and awareness-actions in technology transfer and related thematics available both online or presential.

Appendix A - Examples of the different training programmes and awareness-actions in technology transfer and related thematics available both online or presential.

Entity	Type	Thematic	Name
ANI	Online	Innovation	Innovation Talks
ASTP	Online	Technology Transfer	Fundamentals of Technology Transfer
	Online	Technology Transfer	Finalising negotiations: the contract
	Online	Technology Transfer	Financial Tools of KTOs
	Online	Technology Transfer	Developing KT Strategy & Policy
AUTM	Online	Technology Transfer	Essentials of Academic Technology Transfer Virtual Course
	Online	Technology Transfer	The Basics of Technology Transfer
	Online	Technology Transfer	Promoting Inclusivity and Diversity in Patenting and Innovation
	Online	Technology Transfer	Tech Transfer In The Crosshairs: How to Help Your University Make Its Case
	Online	Technology Transfer	Building a Career in Technology Transfer
Cambridge University	Online	Technology Transfer	Research Commercialisation and Technology Transfer
	Online	Technology Transfer	Business from Bioscience
Catalent	Online	Technology Transfer	Effective Scale-Up and Technology Transfer Strategies for Spray Dried Amorphous Dispersions
	Online	Technology Transfer	Scale Up & Tech Transfer of Fluid Bed Coating Processes
CITI program	Online	Technology Transfer	Technology Transfer
Coursera	Online	Healthcare Innovation Intellectual Property	Patenting in Biotechnology by Danmarks Tekniske Universitet and Copenhagen Business School
	Online	Healthcare Innovation	Pharmaceutical and Medical Device Innovations by University of Minnesota
	Online	Healthcare Innovation	Medical Technology and Evaluation by University of Minnesota
	Online	Innovation	Innovation Management by Erasmus University Rotterdam
	Online	Healthcare Innovation	Intellectual Property in the Healthcare Industry by University of Pennsylvania

Table A - Examples of the different training programmes and awareness-actions in technology transfer and related thematics available both online or presential.

Entity	Type	Thematic	Name
Coursera	Online	Technology Transfer	Transferencia tecnológica: De la investigación al mercado by Pontificia Universidad Católica de Chile
	Online	Healthcare Innovation Technology Transfer	Healthcare Entrepreneurship: Taking Ideas to Market by Imperial College of London
	Online	Healthcare Innovation	Drug Commercialization by University of California San Diego
edX	Online	Healthcare Innovation	Innovating in Health Care by HarvardX
	Online	Healthcare Innovation	Healthcare Finance by MIT
	Online	Innovation	Innovation and Entrepreneurship by University of Maryland
	Online	Innovation	Policy for Science, Technology and Innovation by MIT
	Online	Innovation	Technology Entrepreneurship: Lab to Market by Harvard University
EPO	Online	Healthcare Innovation Intellectual Property	How to get patents in healthcare
	Online	Healthcare Innovation Intellectual Property	Patentability in healthcare, biotechnology and chemistry
Higher Education Institutions	Presential	Innovation	Technology Management for Innovation by Polytechnic Institute of Oporto
	Presential	Innovation	Endogenous Product Management and Innovation by Polytechnic Institute of Guarda
	Presential	Innovation	Creativity and Business Innovation by Polytechnic Institute of Oporto
	Presential	Innovation	Industrial Management and Technological Innovation by Higher Institute D. Dinis
	Presential	Innovation	Economics and Management of Science, Technology and Innovation by University of Lisbon
	Presential	Innovation	Innovation and Technological Entrepreneurship by University of Oporto
	Presential	Innovation	Governance, Knowledge and Innovation by University of Coimbra
	Presential	Innovation	Innovation in business by University of Aveiro
	Presential	Entrepreneurship	SME Management and Entrepreneurship by Higher Institute of Administration and Languages
	Presential	Entrepreneurship	Entrepreneurship by Higher Institute Miguel Torga
	Presential	Entrepreneurship	Development and Social Entrepreneurship by Polytechnic Institute of Beja

Table A - Examples of the different training programmes and awareness-actions in technology transfer and related thematics available both online or presential.

Entity	Type	Thematic	Name
Higher Education Institutions	Presential	Entrepreneurship	Engineering and Innovation Management and Entrepreneurship by Higher Technical Institute
	Presential	Entrepreneurship	Management or Entrepreneurship and Innovation by Univerity of Algarve
	Presential	Entrepreneurship	Technological Change and Entrepreneurship by Higher Technical Institute
IEEPI	Online	Technology Transfer	Enhanced Negotiating Strategies
	Online	Technology Transfer Licensing	Best practices of international licensing agreements
	Online	Technology Transfer Licensing	Patent Licensing: Strategy and negotiation
	Online	Technology Transfer Intellectual Property	Certified Patent Valuation Analyst
	Presential	Technology Transfer	Master in Knowledge and Technology Transfer by University of Strasbourg and Solvay Brussels School
	Online	Technology Transfer Intellectual Property	Certified Patent Valuation Analyst
	Presential	Technology Transfer	Master in Knowledge and Technology Transfer by University of Strasbourg and Solvay Brussels School
INPI	Online	Innovation	Integration Courses on Value Creation through Innovation
	Online	Intellectual Property	General Course on Intellectual Property
	Online	Intellectual Property	Course in writing patent applications
	Online	Intellectual Property	Defence of industrial property rights
	Online	Technology Transfer Valorisation	Knowledge transfer and IP valorisation strategies
Instituto Pedro Nunes	Presential	Intellectual Property	IP Fundamentals
	Presential	Intellectual Property	IP Advanced
	Presential	Licensing	Licensing and Technology Transfer and the management of Science/Company relations
	Presential	Technology Transfer	The management of Science/Company relations
	Presential	Intellectual Property	Searches in patent databases
WIPO	Online	Intellectual Property	Primer on Intellectual Property
	Online	Innovation Technology Transfer	Promoting Access to Medical Technologies and Innovation - WHO, WIPO, WTO Executive Course on the intersections between public health, Intellectual Property, and trade

Table A - Examples of the different training programmes and awareness-actions in technology transfer and related thematics available both online or presential.

Entity	Type	Thematic	Name
WIPO	Online	Intellectual Property	Patents
	Online	Intellectual Property	Patent Information Search
	Online	Intellectual Property	Basics of Patent Drafting
	Online	Intellectual Property	Specialized Course on the Essentials of Patents
	Online	Intellectual Property	General course on Intellectual Property
	Online	Intellectual Property	Intellectual Property Management
	Online	Intellectual Property	Introduction to the patent cooperation treaty

Appendix B

Template of the national online survey: Overcoming the 'Valley of Death': Study of Factors That Influence the Licensing of Healthcare Technologies from R&D Centres in Portugal

A. General Characteristics

1. What is the geographical location of the headquarters of the institution to which you belong?
    a. Algarve
    b. Alentejo
    c. Lisbon and Tagus Valley
    d. Centre
    e. North
    f. Azores
    g. Madeira
2. Which entity is currently responsible for the technology transfer process in your institution?
3. What is the name of the entity you represent?
4. Which category of the technology transfer ecosystem does your institution fall into?
    a. Enterprises
    b. Venture Capitalist
    c. Technological Parks
    d. Incubator
    e. R&D Centres
    f. Universities
    g. Polytechnic Institutes
    h. Associations
    i. Patent Agent
    j. Other

4.1. Enterprises

i. Classify the company to which you belong in terms of its size.
    a. Microenterprise [1-10 employees]
    b. Small enterprise [11-50 employees]
    c. Medium enterprise [51-250 employees]

d. Large enterprise [>250 employees]

ii. Within the area of human health, what are the focuses of your institution?

a. Development and/or manufacture of pharmaceutical products
b. Microbiology and/or Infectious Diseases
c. MedTech
d. Diagnostic methods and/or devices
e. Neurosciences
f. Preventive Medicine
g. Public Health
h. Immunology and/or Associated Diseases
i. Medical Devices
j. Regenerative Medicine
k. Bioinformatics/Machine learning
l. Inflammatory Process/diseases
m. Oncology
n. Other

4.2. Venture Capitalist

i. What is the size (in terms of members) of the entity you work for?

a. 1-5 employees
b. 6-10 employees
c. 11-50 employees
d. >50 employees

ii. What is the enterprise available investment capital?

iii. What is the value of the capital invested in the last 2 years?

iv. Of the amount of capital invested in the last 2 years, what percentage was invested in human health?

a. 0%
b. 1-25%
c. 26-50%
d. 51-75%
e. 76-90%
f. 91-100%
g. Other

v. What is your interest as a Venture Capitalist to invest in healthcare technologies?

a. 1: Not at all interested;

b. 2: Not very interested;

c. 3: Interested;

d. 4: Very interested;

e. 5: Very interested

4.3. Technological Parks and Incubators

i. What is the total number of enterprises that make up your entity?

ii. How many enterprises in healthcare constitute your entity?

iii. How many of these enterprises are considered start-ups of R&D Centres in healthcare?

4.4. R&D Centres

i. What is the number of associates of the R&D Centre (researchers, scholarship holders, technicians, among others)?

a. 1-50 employees

b. 51-100 employees

c. 101.250 employees

d. 251-500 employees

e. >500 employees

ii. What are the research focus (within healthcare) of your institution?

a. Development and/or manufacture of pharmaceutical products

b. Microbiology and/or Infectious Diseases

c. MedTech

d. Diagnostic methods and/or devices

e. Neurosciences

f. Preventive Medicine

g. Public Health

h. Immunology and/or Associated Diseases

i. Medical Devices

j. Regenerative Medicine

k. Bioinformatics/Machine learning

l. Inflammatory Process/diseases

m. Oncology

n. Other

B. Technology Transfer in Portugal (This section aims to collect data on recent technology transfer results in Portugal for statistical purposes. These data will not be treated individually for each institution but as a whole.)

1. The number of patents currently in force (application or granted format) in your institution:
    a. 0
    b. 1-4
    c. 5-10
    d. 11-20
    e. 21-50
    f. >50
2. Number of patents in the field of human health currently in force (application format or granted) at the institution to which it belongs:
    a. 0
    b. 1-4
    c. 5-10
    d. 11-20
    e. 21-50
    f. >50
3. The number of licensed patents (with licensing agreement currently in force) at the institution to which it belongs:
    a. 0
    b. 1-4
    c. 5-10
    d. 11-20
    e. 21-50
    f. >50

4. Of the patents licensed, how many of these were licensed to Portuguese entities (with a licensing contract currently in force) at the institution to which you belong:
    a. 0
    b. 1-4
    c. 5-10
    d. 11-20

e. 21-50
f. >50

C. Factor relevance assessment (In this section, select from 1 to 5 the relevance that, in your opinion, each of the following factors has for the success of the technology transfer process in Portugal.)

1. The role of R&D Centres
    a. 1. Nothing relevant;
    b. 2. Slightly relevant;
    c. 3. Relevant;
    d. 4. Highly relevant;
    e. 5. Extremely relevant;
2. The role of R&D Centres Researchers
    a. 1. Nothing relevant;
    b. 2. Slightly relevant;
    c. 3. Relevant;
    d. 4. Highly relevant;
    e. 5. Extremely relevant;
3. The role of Technologies
    a. 1. Nothing relevant;
    b. 2. Slightly relevant;
    c. 3. Relevant;
    d. 4. Highly relevant;
    e. 5. Extremely relevant;
4. The role of Technology Transfer Offices and Technicians
    a. 1. Nothing relevant;
    b. 2. Slightly relevant;
    c. 3. Relevant;
    d. 4. Highly relevant;
    e. 5. Extremely relevant;
5. The role of the Technology Transfer Process: Patents
    a. 1. Nothing relevant;
    b. 2. Slightly relevant;
    c. 3. Relevant;
    d. 4. Highly relevant;

    e. 5. Extremely relevant;

6. The role of the Technology Transfer Process: Licensing
    a. 1. Nothing relevant;
    b. 2. Slightly relevant;
    c. 3. Relevant;
    d. 4. Highly relevant;
    e. 5. Extremely relevant;
7. The role of the Industry/Investors
    a. 1. Nothing relevant;
    b. 2. Slightly relevant;
    c. 3. Relevant;
    d. 4. Highly relevant;
    e. 5. Extremely relevant;

D. Problems in technology transfer (This section aims to assess the importance of each factor identified as a contributor to problems in the technology transfer process in this area according to the various players of the technology transfer ecosystem in human health in Portugal.)

1. R&D Centres (From the following factors related to R&D Centres, please select the 5 that, in your opinion, most contribute to problems in the process of technology transfer in human health in Portugal.)
    a. A1-The geographic isolation of R&D Centres in relation to other players in the health innovation ecosystem (e.g. R&D Centres located in low populated areas);
    b. A2-Existence of a culture of start-ups creation to license technologies, when this type of licensing is not always the most appropriate;
    c. A3-Lack of reputation and recognition of R&D Centres in the global and often European context;
    d. A4-Research lines of the R&D Centres not focused on market needs (the objects in studies do not address any permanent market necessities);
    e. A5-Lack of human and other resources allocated to technology transfer tasks;
    f. A6-Lack of human resources with specific training in technology transfer;
    g. A7-Deviation of human resources in technology transfer to tasks in other areas;

h. A8-Lack of openness/willingness to adapt technologies developed in a given scientific area to other areas with more commercialization opportunities;
i. A9-Alienation for the logic and/or commercial value of the patent;
j. A10-Lack of incentives for the development of an entrepreneurial mindset among researchers;
k. A11-Lack of metrics in technology transfer or metrics that promote the quantification of the number of patents instead of their value (their real impact/commercialization);
l. A12-Time-consuming and bureaucratic technology transfer processes;
m. A13-Lack of knowledge (on the part of the R&D Centres) of the market needs in the scientific areas in which they operate;
n. A14-Lack of collaboration, coordination, and communication between the R&D Centres and the industry;
o. A15-Lack/limited advertising of the technologies to be licensed and of the R&D Centre and its research;
p. Other

2. R&D Centres Researchers (Within the following factors related to researchers, please select the 5 that, in your opinion, most contribute to problems in the process of technology transfer in human health in Portugal.)

   a. B1-Lack of knowledge and/or alienation for topics such as Intellectual Property, technology transfer, patents, licensing and commercialization of technologies, and entrepreneurship;
   b. B2-Lack of time to dedicate to technology transfer processes due to the multiple functions/positions assigned to the researchers at the same time;
   c. B3-Lack of proactivity in technology transfer;
   d. B4-Higher prevalence of the 'researcher' personality at the expense of the 'entrepreneurial' personality;
   e. B5-Researchers' expectations for the transfer of their technologies not aligned with reality(e.g. simplistic view of the technology transfer process, the real impact of the results less than expected);
   f. B6-Majority/Exclusive focus on ad hoc scientific research in detriment of a focus on market needs;

g. B7-Focus limited to the submission of patent applications instead of the whole process of technology transfer, in particular, the valuation/licensing phase;
h. B8-Alienation to the logic/value of the patent;
i. B9-Lack of strategy at the beginning of the development of a project/technology regarding its final goal: scientific dissemination versus commercialization;
j. B10- Installed mindset of giving priority to the number of patents submitted (mere metric)instead of the number of licensed patents (with potential for commercialization and, therefore, real impact);

k. B11-Installed mindset for creating start-ups as a way of licensing technologies, when this type of licensing is not always the most appropriate;
l. B12-Lack of clarification as to whether the patent property belongs to the institution (in this case to the R&D Centre) and not to themselves, researchers are only inventors (difficulty in distinguishing between inventor versus patent holder);
m. B13-Lack of openness for restructuring the team that develops the technology according to its valorization needs (necessity to add/replace members to/from the team, sometimes external to the institution, during the technology valorization process);
n. B14-Desire/Expectation of the researcher who developed the technology to become an entrepreneur without having the proper profile for it;
o. B15-Researchers are afraid to disclose the technologies they develop/are developing to potential licensees, even if the technologies are already patented or there is a confidential agreement in place;
p. Other

3. Technologies (Within the following factors regarding technologies, please select the 5 that, in your opinion, most contribute to problems in the process of technology transfer in human health in Portugal.)

a. C1-Limited financing for R&D activities in general;
b. C2-Lack of specific funding for proof-of-concept and prototypes;
c. C3-Lack of funding for scale-up studies;
d. C4-Immaturity of the technology when the patent was submitted (low TLR);

e. C5-Lack of prototyping;
f. C6-Inadequate proofs-of-concept studies (in terms of robustness and design) for pursuing the technology transfer process, they are only suitable for the scientific dissemination;
g. C7-Scientific experiments carried out to develop the technology were inadequate for its potential commercial applications;
h. C8-Reduced technology commercialization potential (the technology does not meet market needs or there are better solutions already available);
i. C9-The level of novelty of the technology is not sufficient for its successful commercialization;
j. C10-Lack of market studies before and during the development of the technology (e.g. lack of cost-benefit studies);
k. C11-Long and expensive regulatory process for entry into the market of technologies in the area of human health;
l. C12-Lack of involvement of industry/investors in the development of the technology;
m. C13-Lack of involvement of technology transfer offices in the development of technology;
n. C14-Reduced scientific quality of the idea/development of the technology;
o. C15-Little involvement of opinion leaders in technology validation studies;
p. Other

4. Tech Transfer Offices and Technicians (Within the following factors regarding tech transfer offices and technicians, please select the 5 that, in your opinion, most contribute to problems in the process of technology transfer in human health in Portugal.)

   a. D1-Lack of diversity in the specialities of human resources in the technology transfer offices;
   b. D2-Lack of training and professional experience in the technology transfer process of the human resources of the technology transfer offices;
   c. D3-Lack of human resources with specific training for writing patents in technology transfer offices (e.g. lawyers specialized in Intellectual Property);

d. D4-Lack of human resources with specific training and experience in valuing/licensing technologies in the technology transfer offices;
e. D5-Reduced/Non-existent funds available to technology transfer offices to assess the patentability and commercial potential of technologies, as well as other studies necessary for the technology transfer process;
f. D6-Immaturity of the technology transfer area in Portugal;
g. D7-Lack of sensitivity on the part of technology transfer technicians when evaluating technology due to a low level of knowledge of the market;
h. D8-Little involvement of opinion leaders in technology assessment studies;
i. D9-Dependence and partiality of the technology transfer technician regarding the entity that he/she represents at the expense of the technology;
j. D10-Ignorance of the technology transfer ecosystem in Portugal;
k. D11-Ignorance of the existence of organizations in the technology transfer ecosystem at national and international levels;
l. D12-Lack of a national network dedicated to the general technology transfer ecosystem;
m. D13-Lack of a national network dedicated to technology transfer offices;
n. D14-Lack of communication between the various players in the technology transfer process;
o. D15-Lack of critical mass in the technology transfer ecosystem, specifically in the area of human health, in Portugal;
p. D16-Lack of uniformity in technology transfer processes between faculties at the same university (e.g. medical school ≠ pharmacy school ≠ science and technology school);
q. Other

5. Tech Transfer Processes: Patents (Within the following factors regarding patents, please select the 3 that, in your opinion, most contribute to problems in the process of technology transfer in human health in Portugal.)

    a. E1-Patent writing not suitable (e.g. poorly written, written by unqualified people...);
    b. E2-Lack of human resources with specific training for writing patents at R&D Centres(e.g., specialist lawyers with extensive experience in Intellectual Property);
    c. E3-Limited specific funding for maintenance and obtaining of patents;

d. E4-Problems in the sharing agreements of results between patent holders that result in the lack of clarification regarding the patent's ownership;
e. E5-Immaturity of the technology when submitting the patent application (e.g. early patent application regarding the maturity of the technology);
f. E6-Limited patent claims (sometimes they do not cover all potential applications);
g. E7-Poor advice on the type and strategy of intellectual protection;
h. E8-Lack of uniformity in technology transfer processes between faculties at the same university (e.g. medical school ≠ pharmacy school ≠ science and technology school);
i. Other

6. Tech Transfer Processes: Licensing (Within the following factors, please select the 5 that, in your opinion, most contribute to problems in the process of technology transfer in human health in Portugal.)

a. F1-Search for licenses in the scientific area where the technology development was based, in detriment of possible adaptations to other areas with more market opportunities;
b. F2-Lack of human resources with specific training and experience in valuing/licensing technologies;
c. F3-High values and early payment dates of milestones and/or royalties defined in the licensing contracts with start-ups, not in line with the company's maturity;
d. F4-Lack of guidelines in the negotiation process within an R&D Centre (similar to what already exists in other renowned institutes such as MIT and Harvard University);
e. F5-Insecurity in licensing processes due to a lack of trust between the parties involved;
f. F6-Use of a single language for writing legal documents rather than having documents written in 2 or more languages (e.g. Portuguese and English);
g. F7-Poorly executed licensing agreements that do not provide for all possible situations;
h. F8-Lack of perception of the value of technology in the market;
i. F9-The final decision on the negotiation process dependent on the administration/management council of the R&D Centre that does not have the know-how/expertise necessary;
j. F10-The negotiation process is slow and bureaucratic;

k. F11-Commercial targets not defined when designing the strategy for technologies development;
l. F12-Preference for licensing to new companies (start-ups) instead of companies that are already established in the market, when this is not always the best solution;
m. F13-Lack of knowledge of the players in the industry (e.g. possible licensees, competitors);
n. F14-Lack of knowledge on the part of potential licensees of the existence of the technology to be licensed;
o. Other

7. Industry/ Investors (Within the following factors regarding industry/investors, please select the 3 that, in your opinion, most contribute to problems in the process of technology transfer in human health in Portugal.)

    a. G1-Lack of headquarters/companies/decision-making centres in Portugal;
    b. G2-Lack of proactivity in the search for new technologies by companies and investors;
    c. G3-Lack of investors (venture capitalists and others) in the area of human health in Portugal;
    d. G4-Lack of collaboration, coordination, and communication between the R&D Centres and the industry to promote more licensing contracts;
    e. G5-Lack of specific and accessible contacts on the part of the companies for R&D Centres to establish first contacts regarding a licensing opportunity (technology transfer technicians or equivalent in human resources of the industry);
    f. G6-Lack of investment to attract international companies in human health to Portugal(potential licensees of technologies from R&D Centres);
    g. G7-Limited economic support to incubators and technology parks, hampering the creation of new start-ups and, consequently, new licensees;
    h. G8-Limited financial support to start-ups to encourage their creation and to increase their capacity to license more technologies;
    i. G9-'Prejudice' of companies towards R&D Centres (especially public universities) being the patents holders (companies and investors perceive it as a threat/risk);
    j. G10-Lack of knowledge of the portfolio of technologies to be licensed from R&D Centres by companies and investors;

k. Other

8. In this section, you can indicate other factors that in your opinion affect the technology transfer processes.

E. Solutions to the problems of technology transfer (This section aims to assess the importance of each solution identified to problems in the technology transfer process in this area according to the various players of the technology transfer ecosystem in human health in Portugal.)

1. R&D Centres (Within the following actions regarding R&D Centres, please select the 5 that, in your opinion, most contribute to the improvement of the technology transfer process.)

   a. a1-Promote physical proximity between R&D Centres and companies (centres and companies with some joint spaces or in the vicinity to reinforce communication between them);
   b. a2-Change the evaluation metrics in technology transfer of the R&D Centres, promoting the valorization of the technologies (e.g. number of licenses, income, and commercialization) instead of technologies protection (e.g. number of patents);
   c. a3-Promote the reputation and recognition of R&D Centres (e.g. providing high-quality services; creating biobanks; etc.);
   d. a4-Promote/Optimize the ‘parent institution’ support to the R&D Centre in the process of protecting and licensing technologies (if applicable);
   e. a5-Encourage an increase in the number of technologies/projects developed within an R&D Centre in collaboration/partnership with companies, for example by including this factor in its assessment (if applicable taking into account the R&D Centre's mission and vision);
   f. a6-Create regulations for the formation of start-ups from an R&D Centre;
   g. a7-Publicite R&D Centres, as well as their scientific areas and activities, at national and international events (e.g. trade fairs, congresses, conferences, workshops, lectures, among others);
   h. a8-Integrate R&D Centres in national and international networks in the different areas of human health (e.g. P-Bio; European networks; etc.);

i. a9-Promote and invest in scientific research in specific areas of human health that capitalize on pre-existing economic advantages derived from the geographic localization of the R&D Centre (e.g. R&D Centres located in the Algarve/coastal region: health solutions based on aquatic products; R&D Centres located close to reference hospitals in certain areas of medicine: health solutions for these specific areas of medicine);
j. a10-Create synergies between R&D Centres and centralized technology transfer structures(e.g. associations, technology parks, incubators, among others);
k. a11-Bet on expertise and know-how that does not exist in the industry, to promote your interest (e.g. pre-clinical tests, GMP, etc.)
l. a12-Create collaboration protocols in technology transfer between R&D Centres to help each other in good practices and attract investment;
m. a13-Create 'Open Days' in the R&D Centres for the industry;
n. a14-Define and implement good technology transfer practices within an R&D Centre (e.g.research, regulation, industry input, etc.) based on international guidelines;
o. a15-Promote the dissemination of a complete, clear and accessible form of technology transfer practices to researchers within the R&D Centres;
p. Other

2. R&D Centres Researchers (Within the following actions R&D Centre Researchers, please select the 5 that, in your opinion, most contribute to the improvement of the technology transfer process.)

   a. b1-Increase the number of training, awareness-raising actions and programs in the areas of technology transfer; Intellectual Property; valorization and licensing of technologies, among others;
   b. b2-Work the entrepreneurial profile with specificity for the human health area of researchers through mentoring actions and programs;
   c. b3-Increase training in technology transfer in the different academic degrees (bachelor, master, doctorate);
   d. b4-Develop awareness actions, specifically for the licensing of technologies;
   e. b5-Determine early a specific goal for the technology in development: scientific dissemination versus commercialization;

f. b6-Create 'Open Days' in the industry for researchers;
g. b7-Streamline researchers' access to patent databases to anticipate the process of assessing the novelty of the technology they have developed;
h. b8-Grant access to and encourage the use of databases that disseminate the existing needs in the market for a given technology;
i. b9-Create incentives for researchers based on qualitative results (e.g. licensed technologies) instead of (only) quantitative (e.g. publications/patents);
j. b10-Encourage the creation of multidisciplinary/hybrid research teams (e.g. include people with a background in the industry, experience in entrepreneurship, etc.);
k. b11-Train the researcher to include the technology transfer technician as early as possible in the development of the technologies (e.g. in the design and writing of the project);
l. b12-Encourage the researcher to reassess the main objective/area of expertise of the technology whenever necessary in the detrimental of scientific curiosity (e.g. very innovative technology in an area not related to the initial objective, but unable to be commercialized in the original area in which it was developed because of market saturation);
m. b13-Include early in the recruitment/integration process of a new researcher clear and concise information on technology transfer, namely in the rules and procedures in place in the R&D Centre where the researcher is being integrated;
n. b14-Promote the increase in the number of opportunities for doctorates/internships in collaboration with the industry;
o. b15-Include and encourage researchers to participate in the process of technology valorization, namely in the search for collaborators/stakeholders in the industry;
p. Other

3. Technologies (Within the following actions regarding technologies, please select the 4 that, in your opinion, most contribute to the improvement of the technology transfer process.)

   a. c1-Submit the patent only when the technology is sufficiently mature, even if against the researcher's expectations;
   b. c2-Define the value and objective of the technology early in the development process: scientific communication versus commercialization;

c. c3-Create exclusive financing programs for scale-up/prototyping studies;
d. c4-Create and disseminate databases that identify existing needs in the market for a given technology, as well as existing solutions (competitors);
e. c5-Create consistency in the team that develops and represents the technology throughout the process (e.g. members of the original team that actively accompany the technology throughout the technology transfer process and engage in the start-up creation by being part in the management of the start-up created);
f. c6-Promote the involvement of industrial partners from the beginning of the technology development (e.g. creation of multidisciplinary teams; design of technology development adapted to a commercial application from the beginning);
g. c7-Create exclusive funding programs for proof-of-concept studies;
h. c8-Increase the number and quality of the studies in the assessment of the commercial potential and socio-economic impact of the technology before and during its development(preferably as early as possible);
i. c9-Base the research on a pressing problem or need of the market;
j. c10-Increase funding for R&D activities as a whole;
k. c11-Increase the involvement of opinion leaders and clinicians in the development of technology as early as possible;
l. Other

4. Tech Transfer Offices and Technicians (Within the following actions regarding tech transfer offices and technicians, please select the 7 that, in your opinion, most contribute to the improvement of the technology transfer process.)
    a. d1-Create more technology transfer offices within R&D Centres and increase their funding;
    b. d2-Increase the number of highly qualified, specialized human resources with a diversity of backgrounds in technology transfer offices (e.g., 'in-house entrepreneur', manager, patent attorney, economist, a specialist in a particular area of research) in technology transfer offices;
    c. d3-Assign specific tasks/functions to each human resource that constitutes the technology transfer office (patents, valuation, market assessment, communication with enterprises);

d. d4-Assign tasks exclusive to the area of technology transfer to human resources in the technology transfer offices;
e. d5-Invest in training and updating the skills of technology transfer technicians;
f. d6-Create an official network of technology transfer offices in Portugal;
g. d7-Create highly-qualified regional technology transfer offices;
h. d8-Create highly-qualified regional technology transfer offices with an exclusive focus on a specific area according to the region's strengths;
i. d9-Create an Advisatory Council (of various actors in the ecosystem: venture capitalists, industry, researchers) to provide consultancy services on protection and enhancement of technologies, helping critical decisions in this process;
j. d10-Invest in the marketing area through the participation of technology transfer technicians in trade fairs and events to publicize the portfolio/research of the R&D Centre;
k. d11-Create a national network of technology transfer offices to share knowledge and best practices;
l. d12-Increase the possibility of subcontracting specialists to assist in decision-making regarding the submission and maintenance of patents;
m. d13-Create teams that are transversal to the technology development (teams that follow the entire technology process: from its creation in the laboratory to its commercialization);
n. d14-Share portfolios and network of contacts between technology transfer offices;
o. d15-Create specific human resources within the R&D Centre to communicate with otherR&D Centres or companies on matters related to technology transfer;
p. d16-Improve the access of technology transfer technicians to work tools in this area (e.g.access to paid databases; dissemination platforms; etc.);
q. d17-Assign/Increase the decision autonomy to/of technicians of technology transfer in relation to the management and direction councils of the R&D Centres in licensing contracts;
r. d18-Bet on strong networking with other players in the ecosystem (to function as interlocutors of the technologies developed);
s. d19-Create forms of exclusive investment in technology transfer (e.g., state funds);
t. d20-Monitor the market in which the R&D Centre operates (potential customers, technologies, competitors, etc.);

u. d21-Create exclusive financial support for technology transfer offices/interface centres;
v. Other

5. Tech Transfer Processes: Patents (Within the following actions regarding patents, please select the 2 that, in your opinion, most contribute to the improvement of the technology transfer process.)

a. e1-Reinforce exclusive funding (from state and European funds) for patent submission and maintenance;
b. e2-Create clear guidelines for decision-making on patenting or maintaining a patent;
c. e3-Define strategies for patenting technologies to optimize the costs of maintaining and/or submitting patents and not carrying out ad hoc costs;
d. e4-Enhance accessibility to reference law firms for the patent writing and submission process;
e. e5-Create a national network/office with specialized skills in assisting writing, submission and other matters related to patents;
f. e6-Limit the submission of patent applications when the technologies do not have sufficient maturity, interest to the market or competitiveness with existing solutions;
g. Other

6. Tech Transfer Processes: Licensing (Within the following actions licensing, please select the 4 that, in your opinion, most contribute to the improvement of the technology transfer process.)

a. f1-Create exclusive financing programs for the valorization of technologies;
b. f2-Increase the network of brokers to facilitate licensing agreements;
c. f3-Adopt international guidelines in the technology licensing negotiation process;
d. f4-Increase the quality of the drafting of the licensing contracts in order to safeguard the interests of the R&D Centres (e.g. reduce access to technologies/know-how other than the licensed ones);
e. f5-Negotiate licensing contracts with realistic economic terms favourable to the technology commercialization (e.g. avoid including premature milestones/royalties when the licensee is a start-up);

f. f6-Restructure the team that develops the technology according to its valorization needs(e.g., against the version of the patent owned by the researcher);
g. f7-Prepare bilingual legal documents (Portuguese + English) in detriment of only in Portuguese;
h. f8-Create a structured portfolio(s) for technology assessment (available technologies; technologies already licensed; the number of start-ups that have resulted);
i. f9-Disseminate the technology portfolio at events (national and international) in the human health innovation ecosystem;
j. f10-Consider the different technology transfer regimes: technology licensing, technology sale, or hybrid regime in detriment only to technology licensing;
k. f11-Stimulate the increase in risk capital;
l. f12-Create interface programs to support the contact between R&D Centres and the industry;
m. f13-Implement hybrid valuation strategies with venture capitalists (e.g. in addition to the typical investment in the creation and development of start-ups to act as licensing agents);
n. Other

7. Industries/Investors (Within the following actions regarding industry/investors, please select the 4 that, in your opinion, most contribute to the improvement of the technology transfer process.)

a. g1-Attract international investors to the Portuguese technology transfer ecosystem;
b. g2-Increase incentives for the creation of start-ups;
c. g3-Create a national entity specialized in the process of writing and submitting patents, as well as in solving problems related to these issues;
d. g4-Create public policies to benefit foreign companies that license technologies from Portugal;
e. g5-Create a Portuguese association in technology transfer for industry and venture capitalists to deal with technology transfer;
f. g6-Create 'Open Days' in the industry for researchers;

g. g7-Create/Finance more technology development programs in basis on industry-R&D Centres collaboration;
h. g8-Create 'Open Days' in the industry for technology transfer technicians and representatives of R&D Centres;
i. g9-Stimulate the increase of risk capital;
j. g10-Encourage hybrid valuation strategies with venture capitalists (e.g. in addition to the typical investment in the creation and development of start-ups to act as licensing agents);
k. g11-Assign to specific human resources within the company the responsibility of receiving contacts from R&D Centres in order to establish possible collaborations and/or licensing agreements and disseminate these contacts in a clear and accessible way to R&D Centres;
l. g12-Assign specific human resources within the company the responsibility to search for technologies that can be licensed from R&D Centres;
m. Other

8. In this section, you can indicate solutions that you think are feasible to apply and that are not identified above.

Appendix C

Template of the Online Survey regarding the CNC case study: What is your opinion on tech transfer?

A. Description (Demographic survey of respondents.)

1. Gender :
   a. Female
   b. Male
   c. Other
   d. Prefer not to discloseDescrição |
2. *Age:*
   a. 18-30
   b. 31-40
   c. 41-50
   d. >50
3. What is the highest academic degree you have?
   a. No degree
   b. Bachelor Degree (Pre Bologne)
   c. Bachelor Degree (Post Bologne)
   d. Master Degree
   e. Doctorate Degree
   f. Other
4. Did your academic degree was obtained in a Portuguese higher education institution?
   a. Yes
   b. No
5. If you answered 'No' to the previous question, please indicate the country where you obtained your degree.
6. In what area does your research group belong?
   a. Neurosciences and Disease
      i. Mitochondria and Neurodegenerative Diseases
      ii. Synapse Biology
      iii. Neurotrophin signalling and synaptic dysfunction
      iv. Neuroendocrinology and Aging
      v. Redox Biology and Neurochemical Dynamics
      vi. Neuronal circuits and behaviour

vii. Biomarkers in Neuropsychiatric Diseases: From molecules to diagnosis and intervention
viii. Neuromodulation

b. Metabolism, Aging and Disease
   i. Obesity, Diabetes and Complications
   ii. Reproduction Biology and Stem Cells
   iii. Intermediate Metabolism
   iv. Blood-brain barrier immunometabolism
   v. Cell Signaling and Metabolism in Disease
   vi. Mitochondria, Metabolism and Disease

c. Biotechnology
   i. Rational protein engineering
   ii. RNA & Infection
   iii. Computational and Systems Biology
   iv. Life Sciences Mass Spectrometry
   v. Cellular reprogramming and hematopoiesis
   vi. Microbiomes, metabolites and omics
   vii. Nanosystems and targeted anti-tumour strategies
   viii. Molecular data design
   ix. Molecular and Microbial Biotechnology
   x. Medicinal Chemistry and Drug Discovery
   xi. Tumour microenvironment and targeted therapies
   xii. Biomaterials and Stem Cell-Based Therapies
   xiii. Gene and stem therapies for the brain
   xiv. Therapies targeting brain diseases: genomic and lipidomic approaches
   xv. Cell Mechanobiology
   xvi. Functional Genomics and RNA-Based Therapies
   xvii. Molecular Mycobacteriology and Microbiome
   xviii. Nanotechnology-based vaccine adjuvants
   xix. Structural Biotechnology
   xx. Medical Microbiology

d. Platforms/Services/Infrastructures

B. Patents and Licensing at CNC

1. What is your position in the research group?
    a. Group Leader
    b. Principal Researcher
    c. Post Doctorate Researcher
    d. Research Fellow
    e. Laboratory Technician
    f. Doctorate Student
    g. Master Student
    h. Bachelor Student
2. In how many patent applications do/did you have your name associated with as an inventor?
    a. 0
    b. 1-2
    c. 3-5
    d. 6-10
    e. >10
3. In how many patent/patent applications are you currently an inventor in?
    a. 0
    b. 1-2
    c. 3-5
    d. 6-10
    e. >10
4. Of the patent applications in which you were/are an inventor, what percentage has been licensed?
    a. Don't have patents
    b. 0 %
    c. 1-25 %
    d. 26-50 %
    e. 51-75 %
    f. 76-100 %
5. Are you associated with any CNC start-up?
    a. Yes
    b. No

6. If you answered 'Yes' in the previous question, what is the name of the company and its current status(closed, sold, active...)?

C. Technology Transfer & Entrepreneurship (In this section, we will briefly approach your opinion/vision about technology transfer and entrepreneurship.)

1. Was the topic of technology transfer addressed during your academic training?
   a. Yes
   b. No
2. If you answered 'YES' to the previous question, how interesting did you find the topic of technology transfer during your academic training?
   a. 1: Nothing interesting;
   b. 2: Not very interesting;
   c. 3: Somewhat interesting;
   d. 4: Interesting;
   e. 5: Very interesting
3. Was the topic of entrepreneurship addressed during your academic training?
   a. Yes
   b. No
4. If you answered 'YES' to the previous question, how interesting did you find the subject of entrepreneurship during your academic training?
   a. 1: Nothing interesting;
   b. 2: Not very interesting;
   c. 3: Somewhat interesting;
   d. 4: Interesting;
   e. 5: Very interesting
5. Do you currently feel the need to update yourself on the topics: entrepreneurship, patents, technology transfer?
   a. 1: I don't feel the need;
   b. 2: I feel little need;
   c. 3: I feel some need;
   d. 4: I feel a lot of need;
   e. 5: I feel a great need
6. During your career, have you had experience with the creation of companies based on technologies developed from your research?

a. 1: I never had;
b. 2: I had a brief experience;
c. 3: I had an experience;
d. 4:I had a good experience;
e. 5: I had an excellent experience

7. In the future, do you see the hypothesis or do you plan to take the path of entrepreneurship?
    a. 1: I don't plan at all;
    b. 2: It is a remote hypothesis;
    c. 3: It is a hypothesis;
    d. 4: I plan;
    e. 5: I certainly plan

D. Training in Technology Transfer & Entrepreneurship

1. Have you had specific training in the areas of Intellectual Property and /or technology transfer?
    a. Yes
    b. No
    c. I don’t remember/I don't know
2. Have you had specific training in the area of entrepreneurship?
    a. Yes
    b. No
    c. I don’t remember/I don't know
3. How much time on average would you be willing to spend on technology transfer training?
    a. I don't have interest
    b. Until 2 h per month
    c. Until 2 h per quarter
    d. Until 2 h per semester
4. According to your level of preference and availability to participate in possible events in the area of technology transfer (eg presentation of open programs, topics related to Intellectual Property, technology transfer, case studies, etc.), select the three types of events you would rather participate in.

    a. Monthly Webinars (up to 2 h per month)

b. Annual Webinar Cycles (4 to 5 webinars distributed throughout the year)
c. Open Days in the industry (e.g. field visits)
d. Present Annual Conference (1-2 days)
e. Online Annual Conference (1-2 days)
f. In-Person Workshops
g. Online Workshops
h. Online round tables with various actors in technology transfer
i. Open Days at CNC to the industry
j. Annual Course on Technology Transfer (average of 2 to 4 days)
k. Pitch Contest
l. Online Course

5. You can leave your suggestion here for events in the area of technology transfer that you might be interested in.

Appendix D

Appendix D - Distribution of the interview status regarding the players in Healthcare Research on CNC HealthPT DataBase and their distribution per region (Part 1 of 2)

Region		General		R&D Centres		Enterprises		Venture Capitalists		Technological Parks & Incubators		S&R Associations		Patent Agents	
Portugal	**CNC**	**511**		**125**		**242**		**63**		**54**		**19**		**8**	
	Prop	*151*		*54*		*50*		*21*		*14*		*6*		*6*	
		Realized	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**
	n	47	104	15	39	15	35	5	16	7	7	4	2	1	5
	%C	9,18%	20,35%	12%	31,2%	6,20%	14,46%	7,94%	25,40%	12,96%	12,96%	21,05%	10,53%	12,5%	62,5%
	%R	31,12%	68,87%	27,78%	72,22%	30%	70%	23,81%	76,19%	50%	50%	66,67%	33,33%	16,67%	83,33%
Lisbon and Tagus Valley	**CNC**	**219**		**46**		**92**		**45**		**19**		**10**		**7**	
	Prop	*63*		*15*		*24*		*12*		*3*		*2*		*5*	
		Realized	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**
	n	12	51	2	13	4	20	3	9	1	2	1	1	1	4
	%C	5,48%	23,29%	4,34%	30,23%	4,35%	6,52%	6,67%	20%	5,26%	10,53%	10%	10%	14,29%	57,14%
	%R	19,05%	80,95%	13,33%	86,67%	16,67%	25%	25%	75%	25%	75%	50%	50%	20%	80%
North	**CNC**	**139**		**44**		**60**		**11**		**14**		**9**		**1**	
	Prop	*43*		*16*		*13*		*7*		*2*		*4*		*1*	
		Realized	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**
	n	13	30	6	10	3	10	1	6	0	2	3	1	0	1
	%C	9,35%	21,58%	13,64%	22,73%	5%	16,67%	9,09%	9,09%	0%	14,29%	66,67%	33,33%	0%	100%
	%R	30,23%	69,77%	37,5%	62,5%	23,08%	76,92%	14,29%	14,29%	0%	100%	75%	25%	0%	100%
Centre	**CNC**	**127**		**26**		**80**		**7**		**14**		**0**		**0**	
	Prop	*30*		*15*		*9*		*2*		*4*					
		Realized	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**	**Realized**	**NA**				
	n	14	16	5	10	5	4	1	1	3	1				
	%C	11,02%	12,60%	19,23%	38,46%	6,25%	5%	14,29%	14,29%	21,43%	7,14%				

Appendix D - Distribution of the interview status regarding the players in Healthcare Research on CNC HealthPT DataBase and their distribution per region (Part 2 of 2)

		General		**R&D Centres**		**Enterprises**		**Venture Capitalists**	**Technological Parks and Incubators**		**S&R Associations**	**Patent Agents**
Alentejo	**CNC**	**9**		**3**		**4**		**0**	**2**		**0**	**0**
	Prop	*7*		*3*		*2*			*2*			
		Realized	**NA**	**Realized**	**NA**	**Realized**	**NA**		**Realized**	**NA**		
	n	5	2	1	2	2	0		2	0		
	%C	55,56%	22,22%	33,33%	66,67%	50%	0%		**100%**	0%		
	%R	71,43%	28,57%	33,33%	66,67%	100%	0%		**100%**	0%		
Algarve	**CNC**	**9**		**3**		**5**		**0**	**1**		**0**	**0**
	Prop	*4*		*2*		*1*			*1*			
		Realized	**NA**	**Realized**	**NA**	**Realized**	**NA**		**Realized**	**NA**		
	n	3	1	1	1	1	0		1	0		
	%C	33,33%	11,11%	33,33%	33,33%	20%	0%		100%	0%		
	%R	75%	25%	50%	50%	100%	0%		100%	0%		
Azores	**CNC**	**4**		**2**		**0**		**0**	**2**		**0**	**0**
	Prop	*3*		*2*					*1*			
		Realized	**NA**	**Realized**	**NA**				**Realized**	**NA**		
	n	0	3	0	2				0	1		
	%C	0%	100%	0%	100%				0%	50%		
	%R	0%	100%	0%	100%				0%	100%		
Madeira	**CNC**	**4**		**1**		**1**		**0**	**2**		**0**	**0**
	Prop	*3*		*1*		*1*			1			
		Realized	**NA**	**Realized**	**NA**	**Realized**	**NA**		**Realized**	**NA**		
	n	0	3	0	1	0	1		0	1		
	%C	0%	100%	0%	100%	0%	100%		0%	50%		
	%R	0%	100%	0%	100%	0%	100%		0%	100%		

Legend: CNC - HealthPT Database; n-Number of proposals; %R-Percentage regarding proposes by region; %C-Percentage regarding identified entities in CNCHealthPT; NA- Non-Applicable (due to reject or no response).

Appendix E

Appendix E - Distribution of the online survey answers regarding the players identified in Healthcare Research on CNC HealthPT DataBase

		General		R&D Centres		Enterprises		Venture Capitalists		Technological Parks and Incubators		S&R Associations		Patent Agents	
Portugal	**CNC**	**511**		**125**		**242**		**63**		**54**		**19**		**8**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
		45	8,80%	21	16,8%	8	3,31%	3	4,76%	7	12,96 %	3	15,79 %	3	37,5%
Lisbon and Tagus Valley	**CNC**	**219**		**46**		**92**		**45**		**19**		**10**		**7**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
		11	5,02%	3	6,52%	2	2,17%	2	4,44%	1	5,26%	1	10%	2	28,57 %
North	**CNC**	**139**		**44**		**60**		**11**		**14**		**9**		**1**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
		11	7,91%	5	11,36 %	1	1,67%	1	9,09%	1	7,14%	2	22,22 %	1	100%
Centre	**CNC**	**127**		**26**		**80**		**7**		**14**		**0**		**0**	
		n	**%**	**n**	**%**	**n**	**%**	n	%	**n**	**%**				
		15	11,81%	8	30,77%	4	5%	0	0%	3	21,43%				
Alentejo	**CNC**	**9**		**3**		**4**		**0**		**2**		**0**		**0**	
		n	**%**	**n**	**%**	**n**	**%**			**n**	**%**				
		3	33,33%	2	66,67%	0	0%			1	50%				
Algarve	**CNC**	**9**		**3**		**5**		**0**		**1**		**0**		**0**	
		n	**%**	**n**	**%**	**n**	**%**			**n**	**%**				
		3	33,33%	2	66,67%	1	20%			0	0%				
Azores	**CNC**	**4**		**2**		**0**		**0**		**2**		**0**		**0**	
		n	**%**	**n**	**%**					**n**	**%**				
		1	25%	0	0%					1	50%				
Madeira	**CNC**	**4**		**1**		**1**		**0**		**2**		**0**		**0**	
		n	**%**	**n**	**%**	**n**	**%**			**n**	**%**				
		1	25%	1	100%	0	0%			0	0%				

Annexe A

Annexxe A - Interface Centres on the 'health, chemistry and biotechnology' category according to ANI (ANI, 2021)

Health	Abbr.	Denomination		Region
		Original (Portuguese)	Translation (English)	
✔	AIBILI	Associação para Investigação Biomédica e Inovação em Luz e Imagem	Association for biomedical research and innovation in light and imaging	Centre
✔	CENTITVC	Centro de Nanotecnologia e Materiais Técnicos, Funcionais e Inteligentes	Centre for Nanotechnology and Technical, Functional and Intelligent Materials	North
✔	iBET	Instituto de Biologia Experimental e Tecnológica	Institute of Experimental and Technological Biology	Lisbon and Tagus Valley
✔	INEGI	Instituto de Ciência e Inovação em Engenharia Mecânica e Engenharia Industrial	Institute of Science and Innovation in Engineering Mechanical and Industrial Engineering	North
✔	INESC MN	Instituto de Engenharia de Sistemas e Computadores, Microsistemas e Nanotecnologias	Institute for Systems and Computer Engineering, Microsystems, and Nanotechnologies	Lisbon and Tagus Valley
✔	INL	Laboratorio Ibérico Internacional de Nanotecnologia	International Nanotechnology Laboratory	North
✔	IPN	Instituto Pedro Nunes	Pedro Nunes Institute	Centre
✔	IT	Instituto de Telecomunicações	Institute of Telecommunications	Centre

Legend:

Abbr. – Abbreviation

✔ - Inserted in the 'Health' category