



BIOASSEMBLER

Integrating bio-inspired assembly
into semiconductor manufacturing
technology for biosensors

Socioeconomic analysis of animal-to-recombinant transformation

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List of Acronyms

DNA - Deoxyribonucleic acid

R&D – Research and Development

CES – Centre for Social Studies

WP – Work Package

SSH – Social Sciences and Humanities

GMM - Genetically Modified Microorganism

GMO - Genetically Modified Organism

EU – European Union

PCR - Polymerase Chain Reaction

D – Deliverable

EURL ECVAM - EU Reference Laboratory for Alternatives to Animal Testing

SMEs – Small and Medium Enterprises

SDG – Sustainable Development Goals

UN – United Nations

TFEU - Treaty on the Functioning of the European Union

STEM - Science, Technology, Engineering and Mathematics

EIT - European Institute of Innovation and Technology

EIC - European Innovation Council

STI – Science, Technology and Innovation

STIP – Science, Technology and Innovation Policy

GDP – Gross Domestic Product

OECD – Organisation for Economic Cooperation and Development

WHO – World Health Organisation

NGO – Non-Governmental Organisation

EPO – European Patent Office

CNRS - Centre National de la Recherche Scientifique

CSIC – Consejo Superior de Investigaciones Científicas

PRO – Public Research Organisation

Summary

This document provides a comprehensive overview of the transformation of biomolecular binder production from animal sources to recombinant technology. It includes an in-depth analysis of the societal, technological, economic, and financial features that make animal-to-recombinant technology a promising innovation in the field of DNA engineering.

The reproducibility potential of recombinant binders and their flexibility of adaptation to specific uses allow for a complex diagnosis of their possible applications. This turns the advances made in big enterprises into an attractive tool ready to be applied by small and medium enterprises to increase the usage of recombinant binders. The literature review dissects the main concepts emerging in innovation and knowledge transfer in this area.

The main body of this deliverable will delve into the scientific and industrial relations between universities, R&D centres, enterprises and companies dedicated to developing recombinant technology. These mapping exercises are crucial to better understanding the degrees of innovation in the recombinant area and exploring the hubs at the crossroads of scientific development and technological advent.

Moreover, these relations came with a trade-off with societal and economic advantages and disadvantages. The positive features of recombinant technology, such as reproducibility and cost-effectiveness, have a counterpart of biological material sensitivity and ethical problems that have to be tackled to create a basis of trust from all societal actors engaging with this technology. Bringing a biological issue to the technosphere poses challenges, which will be addressed in this deliverable and must raise awareness for future partnerships among scientists, researchers, politicians and other stakeholders.

There is no one-size-fits-all solution for building an innovation ecosystem within the Recombinant DNA field capable of tackling all the Technosphere challenges. However, the growth of consortiums, particularly those joining the Natural Sciences, Social Sciences, and Humanities within an academy-government-enterprises axis, has been a significant factor in the proliferation of scientific production in recent decades. The convergence of multiple perspectives from seemingly disparate fields, united by the common goal of producing disruptive technology, offers the EU promising prospects for the future of Recombinant DNA production.

Keywords

Biosensors; Animal-to-Recombinant Transformation; Socioeconomic Analysis; Sustainable Science; Technology and Innovation

1. Introduction

The concerns about environmental protection, animal welfare and waste management had turned the animal-to-recombinant transformation into a most coveted scientific advance in biology. The ability to engineer DNA molecules without direct animal involvement or exploitation stands out as a crucial feature contributing significantly to the sustainability of technological production (Gordon, 1997). This transition in the realm of chemistry ultimately yields positive outcomes. Particularly in the biosensors field, the pursuit of more precise and compact devices has made replicating identical sets of DNA highly appealing to producers and critical players in biosensing technology (Wong et al., 2019). The BioAssembler exemplifies a commitment to innovation, evident in its efforts to integrate animal-to-recombinant transformation with synthetic photolithography, creating functional multiplex biosensors. This collaborative approach reflects a dedication to advancing technology while addressing environmental and ethical considerations.

The animal-to-recombinant transformation by editing the animal genome through synthetic methods represents cutting-edge innovation in genetic engineering—the possibility to induce specific biological matter without any animal participation. Therefore, sparing the animal suffering without impacting the quality of the science and experiments produced is a civilisational, ethical and sustainable upbringing, which is one of the priorities of the BioAssembler team. Establishing a molecular binding model to be implemented in biosensors can shape the scientific and economic landscape in DNA engineering (Zeng et al., 2012). These dynamics were analysed as part of task 5.5 of the BioAssembler project, culminating in this deliverable.

This report is part of Work Package 5, “Self-assembling molecular binders”, led by Abcalis, and aims to comprehend the models of partnerships between industry and academia in the DNA engineering field. An analysis of alliances will allow us to identify the socioeconomic consequences behind how knowledge is transferred between institutions or the hierarchical traditions when looking at consortium teams created to study the topic (Saliceti-Piazza et al., 2003). This report will use a methodology based on a structural network analysis illustrating the worldwide synergies between companies and science. The data characterising these relationships were sourced from Patent Offices, the list of projects endorsed for EU funding, partnerships documented in Web of Science/Scopus publications, and a comprehensive review

of Science and Technology studies literature. The mapping of these institutions is designed to complement the findings of Work Package 4 concerning the photolithography market and align with the objectives of Work Package 6, which seeks to establish guidelines for a comprehensive socioeconomic analysis of the biosensors field.

The approach of Social Sciences and Humanities to DNA engineering is valuable to comprehend how the natural sciences do not exist in a separate ontological world without further impacts on the other dimensions of society (Šlesingerová, 2021). Recognising that the effects of DNA engineering extend beyond its scientific realm, questions concerning limits, economic potentials, and regulatory frameworks arise in civil society. In this context, the theoretical expertise of the CES team becomes an asset, potentially enlightening members of WP5 by providing a more comprehensive understanding of innovation processes and their characteristics within the molecular binding domain.

The structure of this report unfolds in the following manner: the subsequent section explores the key attributes of the Animal-to-Recombinant transformation. Following this, a literature review delves into various perspectives within the Social Sciences and Humanities (SSH) related to the scientific domain of DNA engineering. This review precedes an in-depth examination of methodologies employed in structural social network analysis, focusing on scrutinising significant industrial-academic partnerships to build a systemic portrayal of the field. The data collected results from prior investigations into professional relationships, the production of publications, and patents associated with the Recombinant transformation theme.

Hence, the discussion highlights the central relations between contributors to steady innovation in the field and pictures future paths for industrial-academic synergies. However, the socioeconomic potential of this method might bring externalities (Jones & Brown, 2019). Therefore, before delving into the policy recommendations and conclusions, this deliverable encompasses a chapter on the possible externalities of the animal-to-recombinant transformation. This chapter includes concerns related to the several applications of this technology, the ethical issues emerging in the field, and the impacts of the process's reproducibility in future experiments. Finally, the deliverable concludes with some considerations to be addressed by the stakeholders and policymakers working in the field.

2. What is Animal-to-Recombinant Transformation?

2.1 A brief narrative

This chapter aims to understand the overall complexity of the Animal-to-Recombinant transformation and to delve into the different dimensions impacted by the progress of synthetic DNA engineering. This transformation's foundation supports the manipulation of animal genomes through advanced techniques. The first developments in this field started with the cloning experiences recurring in animals and have been evolving towards the binding of molecules using enzymes within the modified organisms (Levick, 2004). The field's constant scientific growth and the reproducibility of the recombinant will allow for more specific and targeted experiments in the genetic field (Jessop-Fabre & Sonnenschein, 2019). The intricate connections between genetic engineering and molecular biology turn the recombinant into one of the technologies more in need of drafting future paths for research with particular attention to the problems that might arise throughout the process.

The animal-to-recombinant transformation has the potential to have an impact on a multidisciplinary landscape. Editing genomes might yield agricultural progress by stimulating the growth of genetically modified organisms with nutritional profiles adequate to the population's needs or by controlling contamination in different food harvesting (Rasala & Mayfield, 2015). The reproducibility of the molecular binding process is also a promising prospect for biomedicine, healthcare or forensics, which includes the facilitation of mass commercialisation of biosensors as described in the WP4 outputs. Therefore, the industrial sector in these fields eagerly awaits the development of the animal-to-recombinant spectrum of applications. However, some challenges need to be tackled to strengthen society's trust in this technology. The control of multinational companies over seed production and modification raises issues that might significantly alter the market dynamics and the population's access to the technology, raising ethical issues regarding the late developments of the Recombinant DNA field.

Two of the most discussed applications for non-animal products since the beginning of the R&D in this field included the likes of Immunodiagnosics (Rascoe et al., 2015; Magalhães et al., 2022b) and Biotherapeutics (Jenkins et al., 2008; Carlson et al., 2021). On the one hand, immunodiagnosics started using non-animal recombinant technology to find alternative methods for antigen production, increase accuracy in serological tests, and build a more effective production process with easy reproducibility (Piazza et al., 2020). This also applies to non-structural proteins that have been researched as possible components for immunodiagnostic applications, but with few results infer generalised results success rate. On the other hand, biotherapeutics have benefited from the production of genetically modified microorganisms (GMM) similar to human characteristics that mitigates the possibility of triggering an immune response and guaranteeing the safety of therapeutic methods. The most stable models of non-recombinant production for biotherapeutics include plant-based systems, human cell lines and glycosylation control (Montero-Morales and Steinkellner, 2018).

The optimisation of DNA engineering towards the animal-to-recombinant transformation helps attain better sustainability levels in resource utilisation, waste management and biodiversity protection. The synthetic DNA mitigates the time and resources needed to maintain the biological material, and its transaction costs are lower (Chao, 2012). For example, the shipping costs, the residual waste and the sensitivity of the biological material are diminished with the mainstreaming of such innovation (Gavrilescu, 2010). Reducing chemical pesticide usage in agricultural settings, which recurs from DNA engineering, will also positively impact the biodiversity protection of the ecosystems (Hough et al., 2022).

In order to apply this technology on a larger scale, it is necessary to gather the acceptance of public opinion and guarantee that all the ethical considerations are framed by a regulatory spectrum that prevents the negative externalities that might emerge (Wolt & Wolf, 2018). The complexity of topics such as the possibility of the animal-to-recombinant transformation facilitating cloning practices (Lassen, 2005), the general mistrust in Genetically Modified Organisms (GMOs) (Wunderlich & Gatto, 2015) and room for dubious interpretations of the respective legislation requires further research, which will be addressed on this deliverable.

In the context of agriculture, the adverse effects of GMOs have increasingly burdened farmers and the global food chain. Despite being outlawed in the EU, the rise of herbicide-resistant crops and the proliferation of genetically modified patented plants have made the agricultural sector susceptible to the influence of powerful financial entities. By establishing an oligopoly in the seeds sector, these entities have assumed a pivotal role in the global food supply chain. This underscores the critical need for transparency and accountability in balancing public and private interests in regulating GMOs. These empty areas of recombinant technology need a multidisciplinary approach to understand how industrial and academic settings can collaborate to draw the red lines of DNA engineering (Heavey, 2015). These guidelines will shape the trajectory of the socioeconomic paradigm of this genetic innovation that requires efforts to balance scientific progress and industrial innovation.

2.2 Applications for the Recombinant DNA

The needs of the genetics, chemistry, health and food sectors to increase production while ensuring the sustainability of such processes have sparked a transformative era in animal-to-recombinant transformation. This has been facilitated by developing crucial synthetic proteins that, when produced on an industrial scale, can revolutionize several applications and technological devices, significantly improving human and animal lives (Kim et al., 2016). However, it's important to acknowledge the challenges that come with such innovation, as they can impact the development of the technology. The BioAssembler team, in this deliverable's section, delves into some of the areas where DNA engineering can be applied and how these challenges can be addressed and overcome, inspiring further advancements in the field.

The so-called “green chemistry” is one of the areas of expertise that the advancements in molecular bidding procedures have impacted. The chemical transformations through synthetic biological material increase stability in enzymes or microorganisms handling, and it replaces the traditional methods of chemical synthesis, which are less cost-effective, more time-consuming and with a higher waste production (Sheldon, 2017). Nonetheless, the industry should not fall for the ‘greenwashing’ trends that use labels such as green chemistry to get an unfair advantage over the competition products.

The biomaterial created through DNA can work as viable alternatives to conventional plastics, supported by the development of biopolymers that help synthesise textiles or packaging products. This feature of recombinant DNA enhances a dynamic of circular economy in scientific lab research, which has built its latest developments in the synthesis of nanomaterials (Intasian et al., 2021). Therefore, DNA engineering advances are fundamental for reducing the size of biosensing devices, in which synthetic nanomaterials can play a decisive role.

Manufacturing nanomaterials that can later be applied in wearable devices used for healthcare is one of the multiple biomedicine applications via animal-to-recombinant transformation. Tackling diabetes through synthesising proteins for insulin treatments (Vajo et al., 2001), gene therapy for cancer medical care (Schmitt et al., 2009) or viral antigen production for vaccine development are some promising achievements in recombinant technology (Oyarzún, Kboe, 2016). The increased accuracy in health diagnosis provided by biosensor devices, with the most recognisable example being the mass commercialisation of PCR assays during the COVID-19 pandemic, illustrates the financial potential of science-industry partnerships regarding DNA engineering. This progress also impacts the pharmaceutical business by tailoring medical treatments and accelerating drug development by targeting specific cells or tissues with reduced side effects while improving the accuracy and stability of the process (Tengenge et al., 2019).

The food sector has yet to have such direct synergies with the field of recombinant transformation, although DNA engineering has been trailing its path in modern agricultural practices. Including genes resistant to plagues and diseases of farm products reduces the need for chemical treatments (i.e. pesticides, herbicides, fungicides). This allows for more sustainable agriculture practices, which helps the health of ecosystems and improves the harvesting quality (Greenberg & Glick, 2018). Synthesising specific nutrients into fruits and vegetables, controlling

unwanted bolstering weed and adapting agricultural yields to adverse climate conditions (Rugini et al., 2020) are some of the benefits of DNA engineering that result in more detailed agricultural products with enhanced quality.

The DNA synthetic practices displayed above are especially relevant when facing today's issues, such as water scarcity and soil contamination. The artificial integration of organisms resistant to drought while maintaining their original essential vitamins and nutritional properties can play a role in conserving the soils and adapting the products to the population's needs. Moreover, DNA engineering is one of the primary sources for agricultural precision (Vu et al., 2020), and genetic information is now being applied to data-driven mechanisms to better monitor agricultural outcomes' natural growth process. After harvesting, the recombinant innovation can extend the products' conservation time, reduce physical damage liabilities in the storing or transportation process, and diminish residual waste. These techniques lead to eco-friendlier agriculture. However, it's crucial to note that DNA engineering still faces challenges, particularly in guaranteeing the food safety of GMOs and achieving public acceptance, as previously mentioned, with the rise of genetically modified seed patenting by 'too big to fail' companies. This awareness of the challenges is essential for a balanced understanding of the field.

Concurrently, the CES team is exploring the potential of animal-to-recombinant transformation in agriculture and forensics studies. The advancements in PCR technology have significantly improved DNA amplification and profiling in crime scenes, making it a standard procedure even when the DNA is degraded. This has led to the creation of extensive DNA databases, not without raising concerns to the privacy of personal data being handled by public entities, as BioAssembler will address and discuss in the D6.5. Moreover, the ability to detect insects and identify the approximate time of death or the presence of bacteria/viruses to reveal the existence of infectious diseases could be game-changers in forensic investigations.

2.3 Environmentally Friendly and No Animal Suffering

The industrial landscape, where several applications are envisioned for Recombinant DNA technology, can be improved by the concerns of this innovation regarding environmental sustainability and ethical research. It transforms pollutants into valuable products for a circular economy dynamic (Hasija et al., 2021). It reduces animal suffering in scientific experiments, leading to a generalisation of good practices in science, as addressed and sustained by the BioAssembler consortium.

Recombinant DNA can promote a healthier environment in contaminated sites and industrial settings by turning the contaminants into new byproducts more environmentally friendly (Kumar & Baul, 2010). DNA engineering with recombinant biological matter promotes the synthesis of

biofuels and advanced biomaterials (Pfelger and Takors, 2023), which addresses chemical waste by aligning the potential of renewable energy with the features of green chemistry.

Staying on the green chemistry expertise, we might discuss methane emissions from cattle-related activities, one of the most controversial topics when discussing the prejudicial effects of the mass creation of animal livestock. The literature supports the idea that GMOs can reduce methane emissions (Hayes et al., 2016; Honan et al., 2021).

One of the prospective uses for GMOs is to mix the diet of animals to reduce the emissions of one of the gases that negatively impacts the global environment. Mixing the diet of some animals with microorganisms (Lan and Yang, 2019; Honan, 2021) that mitigate methane production is still not fully allowed in the EU market (depending on the % of GM organisms present in it); however, the US legislation is much more flexible in the legal framework regarding microbial for methane reduction, with positive results (BioSafe, 2022).

Nevertheless, one of the most attractive features of DNA recombinant is the reduction of animal suffering for scientific progress. The application of modified enzymes, cell-based assays and tissue cultures that imitate the *in vivo* conditions to pharmaceutical endeavours is an example of the ethical effort made by researchers to avoid using animals in their experiments (Mahatthanadull and Thanaboripat, 2021). This follows a recommendation from the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) that warns of the long-term problem of exploring around one million animals per year in the EU territory for scientific purposes (Barroso et al., 2020).

Moreover, the modification of specific genes assists advances in the replication of organs and tissues similar to the animals, becoming a solution for regenerative purposes. At the same time, promoting the conservation of animal rights. Science is becoming more sustainable and humane through the significant contributions of scientists working in the animal-to-recombinant transition.

2.4 Animal-to-Recombinant and the Biosensors Production

Animal-to-recombinant technology can also benefit the production of biosensors. Using recombinant DNA allows for an increase in the sensitivity of the biosensors. For example, inserting a recombinant gene into an organism can increase the stability of the target analyte (Pedahzur et al., 2014). This will be significant when reducing the number of false diagnoses through biosensing devices. The versatility of having different recognition elements, such as enzymes or antibodies, allows this technology to be applied to other fields of study and diverse biosensing devices.

Moreover, if the extreme sensitivity of the lab components is overcome in the first stages of the experiments, the engineered proteins/antibodies can lead to more solid biosensors through

processes that make those more resistant to challenging environmental conditions (Scongamilgio et al, 2014). This might as well extend the lifetime of some of those devices. The possibility of integrating multiple recognition elements is another achievement made possible by genetic manipulation. The BioAssembler's main contribution to the field is the production of more sustainable and resistant multiplex biosensors. Therefore, recombinant technology is an essential step towards achieving the reproducibility required to be applied in multiplex biosensors to be competitive in the biosensing market.

The diversification of biosensors made possible by genetic engineering further allows for the miniaturisation of the device (Derkus, 2016) and the integration of proteins into different formats (Zhang et al., 2020). Portable devices have been the most exciting advance in the biosensors market in recent years, and the animal-recombinant transformation makes the large-scale production of these devices a reality. The reduced time and cost of production enabled by the scalability potential of genetic engineering (Fu et al., 2023) will have repercussions in the biosensors' scientific and financial domain. More sustainable, comfortable and fast-to-produce biosensors make the animal-to-recombinant technology one of the most promising prospects in the biotechnology market.

3. University-Industry Linkages in DNA Engineering

3.1 Challenges for Knowledge Transfer

The vast cooperation models in DNA Engineering illustrate the determinant role of industry-academic partnerships in genetics. As with the activities developed by the BioAssembler consortium, the knowledge transfer between academia and private or public labs increases resources, expertise and infrastructural conditions for scientific advances (Lee, 2020). The participation of industries and similar companies in the molecular binding process brings know-how to the table. It implies a model of scientific management that might be prolific in large-scale projects (Bozeman & Boardman, 2013). Reducing overlapping tasks in projects with significant participation of industrial management models diminishes the tension between work packages and facilitates trust and communication between the parties (Oliver, Montgomery & Barda, 2020).

The knowledge transfer is essential for reinforcing trust between the partners (*ibid.*). The opportunity presented by the industrial landscape to turn the scientific progress made in academia and research centres into commercialisation solutions for the outputs of DNA recombinant opens new horizons for the genetics field. The alignment of expectations and needs for the research in GMOs creates room for an interdisciplinary framework that promotes creativity and research capabilities in a dialectical dialogue for cooperation (Anderson, Michael & Peirce, 2012).

This cooperation impacts various dimensions of the industrial landscape. These partnerships increase the training available on expertise in industrial management models and science cooperation. Mutual growth happens because of this exchange of formation opportunities (Schuh et al., 2015). Moreover, citizen science is one of the BioAssembler's concerns, and the literature points out the importance of collaboration between different work settings for establishing communication strategies to gain the general public's attention (Magalhães et al., 2022A). The population's concerns are often related to environmental protection, animal welfare and ethical issues surrounding DNA engineering. Clear communication is a step towards a more straightforward implementation of innovation outside the industrial-academic nexus helping to generate interest from a larger international audience (Hooker, Capon & Leask, 2017) and to make scientists and research more aware of potential negative impacts of R&D.

The role of internationalisation in the animal-to-recombinant transformation stretches the understanding of this technological development beyond borders, allowing for diverse approaches to the same challenges (Veletanlić & Sá, 2019). However, this requires tight regulation compliance and ethical expertise when dealing with biological material within a

diverse group of international partners. The growth in global scientific-academic partnerships opens new perspectives for guaranteeing funding and financial stability for long-term collaborations (Hottenrott & Thorwarth, 2011). This might overcompensate a systemic lack of financing in academic institutions.

SMEs also have a determinant role in funding research on DNA engineering (Coghlan et al., 2020). However, a further understanding of how SMEs can economically benefit from the investment in animal-to-recombinant technology is needed. Most of the literature has focused on the development of this transition to other fields. Biopharmaceutical enterprises take comparative advantages at the innovation level by creating DNA molecules with genetic material from different sources; this legitimates the production of renewed sequences for DNA engineering (Gawad et al., 2016).

Despite SMEs not having a clear economic benefit from the DNA recombinant in the literature, the intangible assets of intellectual capital have been associated with improved performance of SMEs, more efficiency and productivity (Novotná et al., 2020; Seo and Kim, 2020). Endorsing this investment in intellectual capital requires building a structure of human resources based on specific know-how. This implies the development of training programmes established in partnership with academic environments (Padachi and Bhiwajee, 2016) and leadership practices for identifying the knowledge priorities in assuring the economic sustainability of SMEs (Akpoviroro and Amos, 2018).

3.2 The beginning of SME-Academia Partnerships in the DNA Recombinant field

DNA recombinant technology has significantly shaped the biotechnology industry, a multi-billion dollar field. This technology emerged from the healthcare sector's aspiration to bridge the gap between science and business. Its goal was to create novel, science-based drugs to attract investors and revolutionize biotechnology therapies (Liao et al., 2023; Pisano, 2006).

DNA technology has contributed to the rise of the biotechnology business, although some of its financial potential is still to be unravelled. Adopting fragile models of science management for biotechnology is pushing back the biotech industry and preventing it from taking some of the pharmaceutical industry's market share (Lazonick and Tulum, 2011). Adopting models of science-industry relationships inspired by the computers or semiconductors industry is to blame for the slow start of the biotechnology-related financial sector (Pisano, 2006).

The path to the full realization of the DNA recombinant sector involves several key strategies. These include finding solutions to better mitigate the risks associated with the development of

this innovation (see section 6.), integrating the competencies that can drive the field forward (see deliverable D4.5; Valente et al., 2023), and promoting interdisciplinarity that reflects critical perspectives on science management. These strategies aim to address the challenges that have emerged since the inception of the biotechnology industry, such as the misalignment of expectations between the time frame of scientific R&D and the product's market release, the natural formation of knowledge islands that hinder the inclusion of critical perspectives, and the intellectual property system that restricts scientists' ability to learn from tested procedures (see section 6.).

The DNA recombinant advances capture the value of science in finding new commercialisation solutions for biosensing devices. Merging science and business under the same roof opens possibilities to attract venture investors, who seek ways to bridge the technology transfer process between these two spheres to increase innovation quality (Ardito, 2018). Scientists are expected to move from universities to biotechnology companies or create their own companies. These companies do not have to go through lengthy processes of knowledge transfer. Hence, the partnerships with universities are maintained by pre-existing networks surrounding those scholars. In the DNA recombinant field, this transition usually includes the transference of concepts such as animal welfare or waste management from the university labs to the private business sector.

The first companies working on biotechnology emerged with the exploitation of innovations related to DNA recombinant, as Robert Swanson and Herbert Boyer founded Genentech with the support of a strong venture investment knowledge and a scientific community at the University of California, where Boyer worked to back it up. The model of Genentech to produce and protect its innovation property in the DNA recombinant field was based on the technology transference from universities to newly created businesses (Committee on Technological Innovation in Medicine, 1995), the search for venture capital investment to fund the first critical stages of the company establishment process and the know-how sharing between young companies and consolidated enterprises.

After a few years, Genentech reached an agreement with a relevant pharmaceutical company, which helped overcome one of the significant concerns R&D enterprises face when moving to the commercialisation stage - the high cost of sustaining the time-consuming research and production activity of producing an innovative drug (Pisano, 2006). This opened a window for long-term relationships between science-based small companies working with DNA engineering and major pharmaceutical enterprises (Bloomberg, 2024). This also turned small biotechnology companies into hot prospects for venture capitalists investing in the know-how of those small companies that could later be exported to larger companies or other sectors, such as the pharmaceutical or chemical.

Looking back to the mid-2000s, it's clear that the biotech industry has weathered significant challenges. While the costs of market entry have risen, biotech companies have managed to

consolidate themselves globally (PWC, 2010). This resilience is a testament to the industry's strength and the potential for further growth and innovation.

Academic research centres and universities play a crucial role in a business and scientific environment that constantly tackles high-risk projects (Global Health Program, 2023). The knowledge acquired in this area is still a small fraction of the field's uncertainty, underscoring the importance of solid multidisciplinary research with translational capacity for future recombinant research (Tata, 2005). This underscores the value of your contributions in deepening learning and knowledge sharing in the face of uncertainty.

The EU investment and subsidies to R&D encompass projects' criteria to engage multidisciplinary partnerships within the industrial setting. However, when applying for public funding, the assessment of the company projects by the panels of evaluators must consider that the competition has a large gap between well-established companies and SMEs (Testa et al., 2019). The small and medium enterprises' creation of values is far from the lucrative numbers achieved by the big companies that have been in the biotech market since the beginning. However, the principal value of having a significant investment in projects engaging SMEs and Universities is the new approaches to the field in the form of intellectual property. These partnerships can adjust throughout the process due to the novelty and multidisciplinary nature originally inherent (Codini et al., 2023); however, in the long run, they can benefit the overall market by producing innovative knowledge. The criteria need to open room for the intellectual assets in the form of outputs generated by these smaller companies because the capacity for implementing new processes is mitigated in the larger companies.

3.3 Evolvement of Knowledge Transfer Dynamics

3.3.1 Pioneering from scratch

Abcalis, a BioAssembler partner, is a pioneering company at the forefront of using recombinant animal-free proteins to integrate it into technological devices. Founded in 2020 in Braunschweig (Germany), Abcalis is committed to producing antibodies while advocating for animal freedom. The company's unique approach involves storing the sequences that lead to the formation of antibodies as digital data, enabling them to be reproduced in future experiments. This innovative path towards sustainable chemistry requires a new set of skills from the scientists behind the DNA recombinant, which is different from those applied in conventional chemistry (Wenzel and Zilkens, 2017). The novelty of the sequencing phenomenon derives from Phage Display Technology. This revolutionary method allows for

the display of billions of different peptides on the surface of a bacteriophage, thereby enabling the rapid screening of large peptide libraries for binding affinity. Therefore, this breakthrough form of data storage requires Abcalis's human resources to handle all the stages of this complex procedure.

In the case of Abcalis, the geographic proximity with the Institute of Biochemistry of the Technical University of Braunschweig represents a reasonable chance to build a partnership between the two working environments.

The knowledge transfer dynamics, in this case, occur in the form of traineeships from students to Abcalis, specifically designed to practice the lab techniques applied in Abcalis and co-supervised between the German enterprise and the Technical University of Braunschweig. These works both ways; the university and the students get some hands-on experience and a possible placement after finishing their degrees. At the same time, Abcalis gets to work with scientists who have experience in Abcalis's methods, which might bring some new knowledge from its studies.

As part of this partnership, Abcalis is committed to integrating new human resources from the academic environment. This process involves replicating the methods taught in their degrees as much as possible, ensuring a smooth transition for these individuals. On the other hand, the Technical University of Braunschweig is responsible for building a curriculum that

SMEs in the region can use, including Abcalis. While this transition may take time and could potentially face structural bottlenecks related to infrastructures, misfit of collaborators, and heavy competition for positions in these enterprises, it is crucial to have individuals who can fit into both contexts to balance these issues (Ulhøi et al., 2012).

One of the key mechanisms for better integration within the enterprise-academic relationship is the participation of professors or researchers from the academic environment as shareholders for SMEs like Abcalis. These individuals, with their expertise in both contexts, can provide valuable feedback on how to adapt the curriculum of the universities to match the companies' needs and attract talent from one side to the other. Their role is not only to bridge the gap between the two institutions but also to open paths for partnerships in patent applications or help produce scientific articles, thereby enhancing the overall value of the partnership.

4 Innovation Policy Interface in the EU

4.1 Policy Analysis

In the effort to invest in innovation to create cohesion mechanisms and agendas that will help meet the goals of the EU Green Deal and the SDG of the UN, animal-free antibodies have received little support from entities working in the field. The advances in engineering antibodies without animal interference during the process reinforced the potential of reproducibility of precisely designed gene sequences adapted to the respective antigen. As seen above, investment in projects in the EU has gathered more and more public and private funding for further development of this technology.

However, there has yet to be a paradigmatic change in the field in the last decades. The therapeutics sector is the only scientific area that has consistently increased its levels of animal-free antibodies. Despite the investment made by the innovation packages and agendas, animal-based antibodies are still hegemonic in the EU research arena.

The EU has pushed further towards engaging more specialists in the field by drawing Recommendations on Non-Animal-Derived Antibodies and the EU directions for alternatives to animal testing. These acts are the natural follow-up of Directive 2010/63/EU, which requires a solid justification for applying animal immunisation (Olsson et al., 2017). The long-term goal is to gradually erode the influence of animal use in the antibodies sector, estimated at around one million animals per year (European Commission, 2020).

The acute regulatory framework to expand scientific advances on non-animal antibodies is expected to reduce the number of animal-derived antibodies. The Joint Research Centre's expertise is followed by tightening the criteria for animal testing for the cosmetics industry, imitating strategies already applied in other geographical settings, such as in vitro methods (Gray, A. C. et al., 2020).

GMMs can be fundamental to ensuring a circular economy system; by using GMMs in the production process, a diversified range of sectors could produce more quickly and effectively than animal-derived solutions (Bilal and Iqbal, 2019). This economy based on GMM could be one of the most appropriate solutions to the long-term sustainability of the EU circular economy. However, the time required to implement a policy regarding GMM in the EU takes much longer than in other markets (Wessler et al., 2013). This delay can be justified by the causes inherent to researching a genetically modified product and finding a regulatory ground for harmonising a technology launch in the EU.

The regulatory postponing of the processes through maximum harmonisation processes that force the member states to comply with strict rules for non-animal products, the research schedule required to understand a new sequence reproducibility, and the compliance costs turn GMO-related activities into burdensome and time-consuming research. Therefore, firms

should carefully adjust their investments and priorities in the field to meet the needs of the EU market (Wesseler et al., 2013).

One solution proposed to increase firms' responsibility inside this regulatory framework that turns failed investments into serious harm to the EU R&D sector is the elaboration of a model for ex-post liability assessment. This would build a system of checks and balances in which the firms would be held accountable for their products. This might happen when evaluating the safety hazards of a project or its long-term economic sustainability.

4.2 EU Policy Tools

The EU has played a pivotal role in developing recombinant technology, demonstrating its commitment to innovation through substantial investments in the Innovation Policy. These investments have funded entities that strive to bring cutting-edge developments to the technological sector, addressing the complex challenges of our time. The ultimate aim is to foster an innovation ecosystem that integrates research and industrial policies, fueling a rapidly expanding market.

The legal foundations for innovation policy within the EU started with Article 173 of the Treaty on the Functioning of the European Union (TFEU); the aim was to incentivise the EU states to "ensure that the conditions necessary for the competitiveness of the Union's industry exist". The multiannual framework programme is the lead tool for promoting this competitiveness through research and development, which operates within the framework of articles 179 and 190 of the TFEU and investigates innovation and space policy. These articles aimed to frame the technological development inside the EU while increasing investment in the innovation market to build better solutions for the global marketplace.

One of this policy's objectives is to enhance the percentage of funding the EU releases to the Research and Development dimension in the health sector (Global Health Advocates, 2022), well under the likes of the US or Japan. Becoming competitive in the global innovation market implies recruiting some of the best scientists to foster greener societies (Mubareka et al., 2022), improving the quality of life for the EU citizens and building a production system where research can easily be transferred from the labs/research centres to industrial and marketable products (Dolmans et al., 2021).

Some challenges have been hindering the utilisation of innovation enterprises, primarily due to financial reasons. The more substantial investment of other markets in the R&D sector turns the brain drain effect into an issue that needs to be tackled. The more educated generation of European citizens, who took degrees in some of the world's best universities and research institutions, move abroad to other continents where their innovation value is thoroughly considered, have long-term contracts, and salaries are also comparatively higher (Khan, 2021). On the one hand, this national atomistic dynamic of the innovation sector within the EU is a

product of the competitiveness of the internal market; on the other hand, the EU has been trying to bridge the gap and foment more partnerships through new policy tools.

Some of those tools are depicted and described in this section.

The Innovation Union, part of the Europe 2020 strategy, has its principal axes of fostering collaborative projects that promote entrepreneurship, funding and education in the Science and Technology field. The goal is to be a pillar of competitiveness and sustainable, innovative practices in STEM research in the EU. One of the most pivotal financial instruments related to research in the framework of Europe 2020 is Horizon Europe, which reinforces the investment in innovation made by Horizon 2020 (2014-2020) to tackle some of the most immediate climate, healthcare and demographic needs. At the same time, funding solutions to the growing digitalisation of the EU lead to a more efficient green transition, accomplishing the goals of the New European Innovation Agenda (2022).

The European Innovation Agenda, adopted in 2022, aims to attract investment in the technological field in Europe by reinforcing the conditions for innovation in public procurement and creating more experimentation spaces; some of the most significant measures encompass the promotion of regulatory sandboxes and the expansion of living labs. New structural conditions for start-ups and tech companies within the EU regulatory framework might attract and retain talent. The idea is to create a renewed talent pool to work as an intermediate mechanism between non-EU citizens with specialisations needed in the innovation sector and newly created start-ups. This hiring process becomes more agile through the complementary activity of the European Institute of Innovation and Technology and the European Innovation Council.

The European Institute of Innovation and Technology (EIT) sets strategic knowledge areas to foster innovation in the technological ecosystem of the EU. The institute emphasises digitalisation, health innovation, urban mobility, sustainable energy, and added-value manufacturing. These axes' priorities are essential to defining the funding criteria of the Horizon Europe projects. They are significantly aided by the European Innovation Council (EIC) in transitioning the innovation from the research stage to the market. Launched in 2017, the EIC initiative works in all stages of research as an accelerator in the first steps by finding projects with the potential to be disruptive in the European market, not being averse to the high risk inherent to those projects. By offering project management services and fostering the interdisciplinarity between business and science, the goal is to scale up technological products that can tackle immediate societal challenges and expand sustainable growth.

All these tools have been followed by a legal framework that tries to keep pace with the policy tools launched by the EU and a Cohesion Policy that aims to guarantee that the interregional gap is not widened during the process. Managing new policy instruments within an ever-changing field requires a legislative effort that has seen intense legal production at the beginning of the 21st century. The resolution of 16 June 2010 on the EU 2020 strategy, the Resolution of 12 May 2011 on the "Innovation Union: transforming Europe for a post-crisis world", and the Resolution of 26 October 2011 on the Agenda for New Skills and Jobs are some of the examples of this legislative wave. The resolutions mentioned above aimed to

provide a prosperous environment for the growth of sustainable R&D inside the EU's industrial sector.

Following these amendments, in 2016, the resolution on synergies for innovation inaugurated some of the main funding programmes on technological progress within the EU, such as the European Structural and Investment Funds or Horizon 2020. These tools, with the reinforcement of the funding allocated to the European Cohesion Policy, established the pillars to the launch of the Resolution of November 2020 on a New Industrial Strategy for Europe and the Resolution of 6 April 2022, rooted in the idea of building Europe's strategy for international cooperation considering the pressing challenges of the contemporary society. The implementation of the European Innovation Council by the end of 2022 represented the constitution of an autonomous body inside the EU concerned with pushing forward the innovation agenda. The European Innovation Council manages and keeps track of the policy tools launched by the EU Commission and drafts reports on how to keep the European research-industrial paradigm at the forefront of global innovation.

Pushing forward the technology agenda in the EU requires a switch in the legal framework, citizens' engagement methods, and building the commercialisation conditions for public and private innovation centres (Jiang et al., 2015). Therefore, the next chapter balances the biotechnology features of recombinant technology and the EU contextual conditions for implementing sequencing DNA without animal use.

The case of Science and Technology investment in Finland and Germany

CONSIDERING THE CONSTITUTION OF THE BIOASSEMBLER TEAM, WHICH ENCOMPASSES RESEARCH ENTITIES FROM MANY EUROPEAN COUNTRIES WORKING IN DIFFERENT DISCIPLINES, THIS REPORT WILL BRIEFLY FOCUS ON THE STATE OF R&D IN FINLAND AND GERMANY AND ITS OPPORTUNITIES FOR SMES' GROWTH. THIS SELECTION OF CASES IS BASED ON TWO COUNTRIES REPRESENTED IN THE BIOASSEMBLER CONSORTIUM, THROUGH VTT AND BIOMENSIO IN FINLAND, AND JOBST AND ABCALIS IN GERMANY, WHICH MIGHT SHARE GREAT INTEREST IN FURTHER COMPREHENDING THE POSSIBILITIES FOR FUTURE GROWTH IN TECHNOLOGY R&D.

FINLAND

IN FINLAND, LESS THAN 4% OF ITS GDP IS CURRENTLY DEDICATED TO R&D ACTIVITIES, AND THE NATIONAL GOAL IS TO REACH THE 4% BENCHMARK AROUND 2030. THE FACTORS THAT HAVE BEEN BOTTLENECKING THE ACHIEVEMENT OF THIS GOAL ARE THE DEGRADATION OF COLLABORATION BETWEEN INDUSTRIAL AND SCIENTIFIC PARTNERS AND THE ECONOMIC TOLL CAUSED BY THE FINANCIAL CRISIS OF 2008, WHICH SLOWED THE PACE OF STI INVESTMENT IN FINLAND (SAARI, 2016).

THE LARGEST PERCENTAGE OF THE R&D EXPENDITURE IN FINLAND GOES TO THE ICT FIELD, WITH NOKIA RECEIVING A VAST SHARE OF THAT FINANCIAL MECHANISM. NOKIA WAS ONE OF THE COMPANIES THAT TURNED R&D INVESTMENT INTO A DECISIVE FACTOR IN FINLAND'S ECONOMIC GROWTH DURING THE 80S AND THE 90S (LAAMANEN ET AL., 2016). IN 2008, NOKIA RECEIVED 36,9% OF THE TOTAL EXPENDITURE OF R&D IN FINLAND AND WEIGHTED 2,6% OF THE TOTAL GDP. HOWEVER, IN THE LAST DECADE, THE FALL OF NOKIA HAS LED TO A STAGNATION OF FINNISH ENTERPRISES AND THE CEASING OF FINANCIAL INSTRUMENTS THAT WERE SUSTAINING THE QUICK PACE OF THE R&D SECTOR, SUCH AS THE SHOKS, OSKE AND INKA.

ONE OF THE GOALS OF THE RECENT STI POLICY IN FINLAND IS TO RETURN TO THE STRONG ENTERPRISE STRUCTURE OF THE BEGINNING OF THE CENTURY. THE POLICY CHOICES HAVE OPTED TO RESTRUCTURE THE R&D AND SME LANDSCAPE BASED ON INDUSTRY-ACADEMY PARTNERSHIPS (OKSANEN ET AL., 2018). THE PUBLIC POLICY PROGRAMMES PROVIDE FINNISH UNIVERSITIES WITH A NEW AUTONOMY CONFIGURATION, ENCOURAGING THE SEARCH FOR MORE DIVERSE FUNDING SOURCES. THIS AIMS TO STIMULATE INTERNATIONAL PARTNERSHIPS AND FACILITATE KNOWLEDGE TRANSFER BETWEEN SECTORS THROUGH FUNDING OPPORTUNITIES REQUIRING MULTI-SECTOR APPLICATIONS. THE FINNISH FUNDING AGENCY FOR INNOVATION, A KEY PLAYER IN THIS STRATEGY, HAS BEEN MERGED WITH PUBLIC ENTITIES THAT BASE ITS ACTIVITY ON THE INTERNATIONALISATION OF SCIENTIFIC ACTIVITY, INSTILLING CONFIDENCE IN THE FUTURE OF THE R&D SECTOR (MATEI ET AL., 2015).

ONE OF THE MAIN CHALLENGES FOR THE FINNISH R&D SECTOR IS DIVERSIFYING ITS SOURCES OF FUNDING, WHICH WOULD ALLOW IT TO REDUCE THE RISK AVERSION OF THE SECTOR. THE EU MEMBERSHIP AND THE LOSS OF COMPARATIVE POWER WITHIN THE EU MARKET WITH THE GRADUAL FALL OF NOKIA MADE THE ENTERPRISES DIMINISH THE LEVEL OF RISK TAKEN. THEREFORE, THE ACTIVITIES OF THE FINNISH ENTERPRISES HAVE BEEN MORE FOCUSED ON AN INCREMENTAL DYNAMIC OF ALREADY-EXISTENT PRODUCTS OR KNOW-HOW AREAS THAN LOOKING FOR PIONEERING INTERVENTIONS TO BUILD NEW OUTPUTS FROM SCRATCH. THIS CREATES A STRUCTURAL CHALLENGE FOR FINLAND'S R&D. ON ONE HAND, THIS RISK AVOIDANCE GRANTS SUSTAINABLE GROWTH. HOWEVER, IT MIGHT INHIBIT LONG-TERM PATHS FOR INNOVATION.

THIS LEADS TO A DISCUSSION REGARDING TECHNOLOGY PRODUCTION AND R&D THAT GRAVITATES AROUND TWO SOLUTIONS. FIRSTLY, THE INCREASE IN PUBLIC FUNDING TO THE R&D SECTOR MIGHT SURPASS THE ESTABLISHED 4%. HOWEVER, IT FACES THE DOWNSIDE OF EVENTUALLY CREATING A CULTURE OF FIRMS DEPENDING SOLELY ON PUBLIC FUNDING, CONSIDERING THE POSSIBILITY OF HAVING A LOW RATE OF RETURN. THE SECOND SOLUTION WOULD BE A REDUCTION IN CORPORATE TAX, WHICH WOULD ALLEVIATE THE FINANCIAL BURDEN OF SME ENTERPRISES (ALAJA & SORSA, 2020). HOWEVER, IT IS AN OVERARCHING MEASURE THAT NEEDS MORE SUPPORT FROM POLITICIANS, STAKEHOLDERS, AND CIVIL SOCIETY.

THE DEFINITION OF PRIORITY SECTORS IS MORE IMPORTANT THAN THE RISE OF R&D TO 4% OF THE GDP, WHICH CAN OVERCOME FINNISH ICT'S LOSS OF INFLUENCE INSIDE THE EU AND INCREASE THE QUALITY AND IMPACT OF R&D PROPORTIONALLY TO THE PUBLIC AND PRIVATE INVESTMENT EFFORT.

GERMANY

THE GERMAN ECONOMY HAS BEEN TRYING TO PUSH ITS INVESTMENT IN R&D TO AN INTENSITY TARGET OF 3.5% OF THE GDP BY 2025, FOLLOWING THE GUIDELINES LAUNCHED BY THE HIGH-TECH STRATEGY 2025, PART OF THE NATIONAL INNOVATION STRATEGY. AS IT STANDS NOW, THE INVESTMENT IN R&D ROUNDS 3% OF THE NATIONAL GDP, WITH 29% GOING TO THE PUBLIC SECTOR, AT LEAST, AS THE OECD REPORT MENTIONS FOR THE PERIOD BETWEEN 2005 AND 2018 (OECD, 2022).

UNLIKE THE FINNISH ECONOMIC STRUCTURE, THE GERMAN R&D PARADIGM IS CHARACTERISED BY A HIGH NUMBER OF SMALL AND MEDIUM CORPORATIONS THAT HAVE BEEN PRODUCING SCIENTIFIC AND INDUSTRIAL ADVANCEMENTS. HOWEVER, THIS STILL NEEDS TO BE ACKNOWLEDGED BY THE R&D FUNDING OPPORTUNITIES WITH MORE GENEROUS FUNDING ALLOCATIONS. 29% OF THE R&D BUDGET GOES TO THE PUBLIC SECTOR, AND THE LOWER PUBLIC INVESTMENT IN THE SME LEAVES WIDE ROOM FOR FINANCIAL REINFORCEMENT FOR LARGE GERMAN PRIVATE ENTERPRISES.

THIS DISPARITY BETWEEN THE R&D FUNDING FLOWS TO LARGE ENTERPRISES AND SMES PRACTICALLY ILLUSTRATES THE DIFFERENCES IN INVESTMENT ON THE EAST-WEST AND NORTH-SOUTH DIVIDES (BRITZELMAIER ET AL., 2019). IT UNDERSCORES THE IMPORTANCE OF REGIONAL BALANCE IN R&D INVESTMENT, HIGHLIGHTING THE NEED FOR EQUITABLE DEVELOPMENT ACROSS ALL REGIONS OF GERMANY.

THE REGION OF BADEN-WÜRTTEMBERG HAS BEEN EXPERIENCING A GROWTH IN INTERNAL EXPENDITURE THAT HAS CONSOLIDATED ITS POSITION AS THE GERMAN REGION WITH MORE SUBSTANTIVE INVESTMENT IN R&D, WHICH CAN BE EXPLAINED BY THE SIZE OF THE COMPANIES THAT HAVE HEADQUARTERS IN THE AREA (FIGURE A1). THE ECONOMIC ACTIVITY OF THE SOUTH OF GERMANY, PARTICULARLY OF THE CITY OF STUTTGART, BENEFITS FROM HOSTING COMPANIES SUCH AS DAIMLER AG, THE OWNER OF WELL-KNOWN BRANDS LIKE MERCEDES BENZ OR SMART IN THE AUTOMOTIVE INDUSTRY. THE PORSCHE COMPANY AND ITS SUBSIDIARIES, THE SAP SOFTWARE AND THE SCHWARZ GROUP (WITH BRANDS LIKE LIDL) ARE OTHER EXAMPLES OF CORPORATIONS THAT JUSTIFY THIS SUBSTANTIAL INVESTMENT IN GERMANY'S SOUTHERN REGIONS.

BAVIERA AND NORTH RHINE WESTPHALIA ARE OTHER REGIONS THAT ABSORB A CONSIDERABLE PERCENTAGE OF THE R&D PUBLIC EXPENDITURE, EXPLAINING THE SUPREMACY OF THE SOUTHERN AND WESTERN AXES. THE EASTERN AND NORTHERN REGIONS HAVE SIGNIFICANTLY LOWER INVESTMENTS, AND THEIR ECONOMIC ACTIVITIES PRIMARILY COMPRISE SMES.

ONE OF THE MOST CRUCIAL CHALLENGES FOR POLICYMAKERS WORKING ON R&D ISSUES IS TO FIND MECHANISMS THAT ALLOW THE GROWTH OF THE GERMAN R&D FUNDING SHARE WITHIN THE GDP VALUES WITHOUT WIDENING THE HISTORICAL GAP IN THE CORPORATION STRUCTURE BETWEEN THE AXES MENTIONED ABOVE (ARNOLD ET AL., 2015). THIS BALANCING ACT IS NOT EASY, AS IT REQUIRES A NUANCED APPROACH TO STI POLICY THAT ALLOWS FOR THE SUBSTANTIAL FUNDING ALLOCATION TO THE VAST ECONOMIC STRUCTURE OF SMES EQUITABLY WITHOUT DISREGARDING THE BIG COMPANIES AND THEIR FUNDAMENTAL IMPACT ON THE GERMAN ECONOMY. IT IS A COMPLEX TASK THAT REQUIRES CAREFUL CONSIDERATION AND STRATEGIC LONG-TERM PLANNING.

4.3 The legal-ethical international framework of Recombinant DNA

The OECD was the only institution trying to frame the application of recombinant DNA at a global scale. Due to its sensitive ethical outliers, the topic started gathering media coverage and raising awareness in civil society by the end of the last century. The OECD released a document named "Guidelines for Research involving recombinant DNA" (National Institute of Health, 2024), which established the limits for using recombinant DNA molecules in science. This document identifies the prospective risks of DNA engineering, referencing a legal

framework based on Article 15 of the Biotechnology Promotion Law and Article 15 of the Enforcement Ordinance.

Exploiting new biotechnology solutions based on recombinant DNA implies paying renewed attention to biological hazards with negative environmental consequences to the ecosystem balance. Therefore, article 15 of the biotechnology promotion law includes experimental guidelines enforcing the inclusion of "safety standards for the transfer, handling and use of genetically converted organisms".

Throughout the years, the WHO's policy has been steadfast in building safety measures and focusing on specific methods of recombinant application. In 2014, the WHO released the Technical Report Series N°987 (WHO, 2014), a significant step towards ensuring the regulatory homogeneity of nations. This report aimed to strengthen the control between manufacturers and regulatory entities, emphasising the need for constant communication from the project's early stages and detailed characterisation of every procedure during the production process. The framework established in this report applies to both clinical and non-clinical trials, with a strong recommendation for further consideration of legal requirements for antigen vaccines based on recombinant technology. This consultation is crucial before producing the designated product, ensuring its safety and quality.

The annexes to this WHO technical report support tighter regulation for the upcoming products, including recommendations for a head-to-head comparison of the criteria applied to the existing products in the market. Achieving this requires considering the importance of building on previous regulatory experiences, particularly for countries with a strong history of product manufacture. This historical knowledge forms the basis for considering the expertise of more experienced National Regulatory Authorities in addressing the clinical needs of a product. The international path to the homogenisation of regulatory directives by the WHO envisions a collaborative effort between national authorities to reevaluate products that have been approved under previous frameworks. This collaboration is crucial, as it ensures that products meet the new standards of the biotherapeutic reference products, valuing the expertise and contribution of the National Regulatory Authorities.

The latest guidelines regarding biotherapeutic products in the EU signal a bright future for recombinant technology in the pharmaceutical sector. In 2024, a European Commission document will be launched, outlining the benefits of a patient-centred approach in the pharmaceutical sector. This approach, while tightly regulating clinical trials by WHO guidelines, also promises a reduction in bureaucracy and an increase in environmentally sustainable medicines in the EU market. This policy landscape provides a fertile ground for the growth of recombinant technology, with the only missing pieces being the general acceptance of these medicines by civil society and their cost-effectiveness. That is why it is crucial to build dialogue platforms between science and society, between scientists and lay people. The urgency of overcoming the lack of trust in DNA-related technology cannot be overstated. The role of the Social Sciences and Humanities and the role of CES in BioAssembler is to comprehend understand the complexities inherent in the development and applications of new

biotechnologies, which may have an impact on their social reception. BioAssembler's Task 6.5 will delve deeper into these issues.

4.4 Society Engagement

Public attitudes towards new technological products are susceptible to misinformation and misconceptions regarding recombinant advances (Bauer, 2005). However, civil society's general opinion has gradually switched from a sceptical perspective in the last century (particularly directed to GMOs) to a more optimistic attitude about the positive effects of science and technology on humanity (Woźniak et al., 2021).

The comprehension of recombinant technology depends on the different social and age groups. Previous research stated that people with higher qualifications are keener to understand how a new technology works, namely in biology, as in recombinant innovation. The inverse was also true: the less educated groups showed a decreased understanding of its potential application to the end-user (Jelsma and Grace, 2008).

This framing of information that expands to the mainstream debate also depends on the media coverage for implementing a designated technology. The media tends to emphasise the risks of innovation launched into a market, especially in the healthcare domain. At the beginning of the Recombinant progress and to discuss its impacts on medical care, the Asilomar Conference was launched in 1975, where scientists delved into the potential and problems related to the recombinant transition (Hurlbut, 2015). Indeed, the coverage of this benchmarking conference showed that around 60% of the related news was negatively perceived, mainly devoted to discussing the risks and ethical hazards of recombinant DNA. As seen in previous communication studies, the media significantly influence public opinion.

The ethical concerns of the 70s and 80s shifted towards more environmental and institutional mistrust throughout the new century (Swazey et al., 1977; Weiner, 2020). An EU survey (2001) showed that people with environmental awareness tend to be more sceptical towards introducing new technologies and that poor trust in regulatory agencies might cause negative attitudes in civil society towards biotechnology innovation. Nonetheless, it has been noticed that public opinion has become more open to implementing new technology in recent years, and a transition in public attitudes with particular relevance to the EU general public is starting to get more profound knowledge and a higher acceptance rate of innovation-based devices. The inclusion of social scientists, NGOs and other stakeholders in developing recombinant technology, as promoted by the EU institutions, has contributed positively to bridging the innovative features with the possible societal implications.

Moreover, scientists working on biotechnology and recombinant development are becoming aware of the importance of having a transparent dialogue with citizens without embarking on an overly technical discussion (Mueller et al., 2011), which might help the goals of including citizen participation in research and innovation processes (citizen science). This social dialogue

is essential for responsible technology development. Scientists are starting to use it to anticipate unforeseen impacts of the technology, understand their consequences and other ethical issues, tackle implementation barriers and build better products that are more friendly to the end user. Public consent becomes a critical feature of a technology's success.

The role of citizens in the successful implementation of technology becomes even more critical in the animal-to-recombinant field, an ever-changing scientific area that, with the growth of animal protection movements, has seen a boom in its production in recent years. This forces biotechnology regulatory agencies to adapt constantly to new challenges and hazards. When decision-making cannot keep up with the pace of innovation, the citizens are dictating technology's success rate within its end-users (Weinberger et al., 2021) by measuring the trade-off between the benefits a new product can bring to their lives and its risks.

Throughout the decades since the recombinant DNA upbringing, efforts have been conducted to help citizens and scientists come together in defining rules when producing biotechnology-related innovations. Some relevant entities tried and succeeded in establishing a channel for communication between scientists and citizens. In the US, the Federation of American Societies for Experimental Biology and Biosafety and the National Institutes of Health's Office of Science Education (Renedo and Marston, 2015) are examples of the leading institutions trying to find points of transparent education on new technology with the participation of lay people. In the EU, there has also been an apparent effort to close the gap between technical knowledge and citizen empowerment through the engagement of civil society in open debates and consultation stages when drafting the technology. The results have been positive, given the gradual change from generalised skepticism towards more collaborative dialogues between scientists and citizens.

4.5 Economic potential

In economic terms, diverse industrial sectors might benefit from the capabilities of generating synthesised components. Genetic modification that promotes the elaboration of complex enzymes, amino acids, antibiotics, and steroids can be used in industrial settings. However, to improve market attractiveness, the cost of this production requires a scalable level until it is profitable and less time-consuming (Peterman et al., 2024). One of the main bottlenecks of genetic engineering is that the processes that lead to the production of synthetic enzymes are time-consuming, with several experiments and steps required to achieve the desirable stability - <https://www.bosterbio.com/services/recombinant-protein-expression-service>.

While industrial strain development for recombinant protein production has improved cost-reduction strategies, we must acknowledge the challenges and limitations of genetic engineering in industrial applications. The traditional process of removing the mutated gene from the original strain for future engineering of the mutated gene was resource-consuming. The alternative, a recombinant transition method, has shown promise in modifying the

mutation process to introduce a desirable gene, and the reproducibility of the sequences is seen as more cost-effective. This kind of replacement strategy was initially applied in experiences involving penicillin through the disruption of the *argB* gene (Jin et al., 2004). Other methods for cost constraint include efforts to advance nucleotide pool modification (Stovall et al., 2014). This situation occurs when there is an attempt to improve or reduce the expression of a protein through gene isolation. This knowledge allows us to find enzyme systems that enable direct modification of a gene without knowing the sequence beforehand. These challenges and limitations underscore the need for further research and innovation in the field.

Technological development plays a fundamental role in achieving higher potential gains in chemistry. It requires a significant initial investment by companies willing to promote sustainable progress through automation. However, it has been crucial for improving the accuracy and the amounts produced of animal-free PCR and DNA sequencing-related products. One of the main positive features of the technology is the simultaneous examination of polymorphism (Duan et al., 2020), a key aspect of genetic engineering that allows for quick testing of genetic hypotheses. High-throughput oligonucleotide technology allows massively parallel hybridisation of nucleic acid sequences to understand DNA profiles in an automated fashion. This technology has revolutionised molecular biology and can continue contributing to a more informed society about genetic diseases and similar outputs. This facilitates drug testing and the respective response to health conditions.

Moreover, the products and components utilised in the recombinant DNA turn it into a susceptible lab process that must be carefully handled with the high-risk tendency to the hazardous utilisation or damage to some of its components. Nevertheless, after the first stage risks are overcome, the recombinant techniques offer the possibility of manufacturing amino acids through microbial strains that will drastically reduce the cost of agriculture products such as tryptophan and threonine (Lopez-Delacalle et al., 2020). Reducing its market price from 40 dollars to 2 dollars per pound with the massification of this recombinant amino acid production would boost the cultures of corn and other agricultural products. However, it's important to note that the massification of synthetic components such as the amino acids mentioned above can have unintended consequences, including potential harm to the environment and human health, which need to be carefully considered and managed.

4.6 The process of patent attribution and commercialisation status

The universities and research centres need to find common ground to work with the business structures inside the EU to allow a multi-sectorial production of innovation. In this way, universities and research centres would be more concerned with their contributions to science, while the EU mechanisms, such as the EIC, would be accountable for these projects' profit (or lack thereof). This would facilitate more flexible access by SMEs to the knowledge developed by universities. Therefore, the EU has a fundamental role in making sure that the revenues

offered to the universities for their patents are sufficient to keep pushing innovative discoveries further while managing to build an open licensing database to help develop new knowledge (Baraldi and Waluszewski, 2011). It is crucial to understand how the universities patent their knowledge, which parts of that knowledge are the most coveted on the business side, and how we can be more flexible with this intellectual property without jeopardising academic sustainability.

The support for a system of open science has been encouraged by EU-funded multidisciplinary projects, and the role of innovation-responsible institutions is to bet on riskier and more disruptive innovation, knowing that this type of research might promote a quicker and more sustainable development of technology (Vicente-Sanchez et al., 2020). Moreover, when licenses and patents are involved, and if not working with open access sequencing, it is fundamental to concede the rights of research use to enterprises already experienced in the research sector. Advances made by research centres in very niche fields might be exploited by companies with the know-how and the facilities to conduct this research with all the caution required.

The recombinant technology to be applied in DNA and antibodies and its licensing would make sense to be attributed to a start-up focused on only working the capabilities of recombinant technology (Michelino et al., 2017). The groundbreaking research on recombinant innovation forces enterprises to work in this niche sector, finding room inside a market which needs the know-how to develop that product inside the preexisting companies. However, the licensing must be conceded only to these start-ups built from scratch if researchers want their findings' value to remain the same. An open database with several companies with access to the same technology will naturally decrease the value of those findings. A more organic form of building up valuable know-how with a solid patenting process is, as already mentioned, the academics being shareholders or founders of SMEs inside the same field of expertise (Armano and Scagnelli, 2012).

5 Structural Analysis of Research Networks: The Methodology

This deliverable focuses its methodology on analysing the research ecosystem of European biotechnology, notably the animal-to-recombinant transition. It is supported by networking data referring to recent publications, patents, and consortium constitutions' recent history. This research systematically maps knowledge sharing, collaboration dynamics, and information flow between enterprises, academic institutions and government entities.

The publications data will be collected from Web of Science and Scopus to proceed to a metadata bibliometric analysis of the literature on animal-to-recombinant transformation. The patent data are based on searches related to keywords on Recombinant DNA domains in the European Patent Office. The framing of the BioAssembler project within the Horizon programme explains the focus on EU patents. The awareness of other geographical patents and scientific consortiums will be considered a comparative frame to the EU scientific landscape. However, the core patent market to be tracked in this deliverable will be the EU patents, which are further contextualised by the political setting of the European Union on innovation within Recombinant DNA technology. The consortium research is supported by delving into a literature review, document analysis, and organisational websites (STIP, EU Horizon), which allows for categorising information on projects funded in the EU.

After the data collection stage, the three databases are merged to depict the patterns and links common to the Patents and Publications dimensions. The nodes of the networks display the metadata of patents, while the edges portray the collaboration dynamics. From there, the mapping display will allow for measuring the dispersion between central institutions and more peripheral entities and understanding the mechanisms through which the knowledge flows from the core to the outskirts of the network—applying algorithms in network software such as VosViewer and Graphi results in output in the form of quantitative data and the translation of those data into visual mapping.

The interpretation of the results establishes a general overview of the knowledge-sharing opportunities in the field, discusses the structural holes in the collaborative dynamics between SMEs and research centres/universities and draws recommendations based on metadata mapping. These results will be compared to the state-of-the-art in the field of knowledge sharing and economic opportunities for animal-to-recombinant transition to understand some gaps that must have been overseen throughout the last years of research in this scientific area.

This contribution to the literature must acknowledge and be aware of the limitations of this methodology. The choice of words to filter the metadata from the publications and patent networks influences the final results. The chosen words have been selected to refer to direct observation and participation in formal and informal meetings of BioAssembler. The team has experts on animal-to-recombinant engineering, which helped in interviews to draw the big

picture of the field and validate the word choice. A different team could have chosen other words that would slightly change the results and respective mapping.

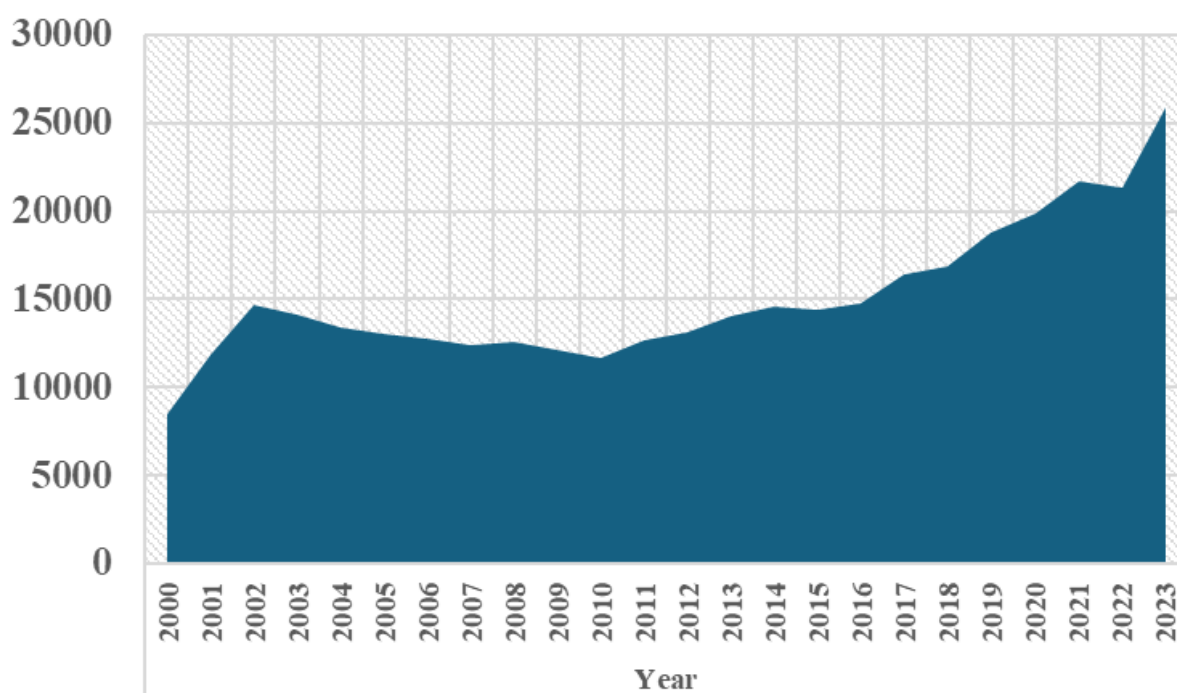
6 Research Networks & STI Priorities

6.1 Innovation Networks

Over the span of 23 years, from 2000 to 2023, the number of patents on Recombinant DNA has experienced a staggering threefold increase. The Recombinant industry, which initially began with approximately 8,000 patents licensed in 2000, reached its zenith with a remarkable 26,000 patents licensed in 2023 (Figure 1). This dramatic evolution is a testament to the substantial investment in biotechnology and R&D programmes, which have effectively fostered an environment conducive to further research in this field and have played a pivotal role in the registration of patents in the European Patent Office.

Figure 1. Recombinant DNA Patent Evolution (2000-2023)

Patent Amount



Source: Own elaboration based on European Patent Office data

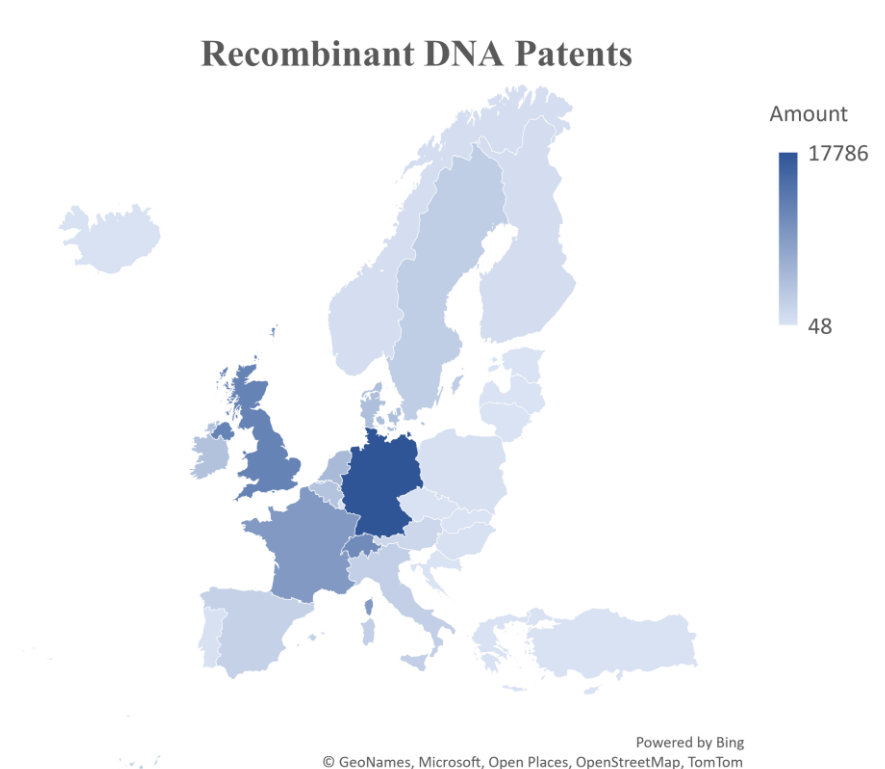
Nonetheless, this overall growth also faced challenges from macro and meso factors. At the macro level, the period between 2006 and 2010 was marked by a decrease in the quantity of patents registered in the Recombinant DNA area (Figure 1). The global crisis of the subprime, which hit the US first, where most of the institutions dedicated to building the knowledge basis (as we are going to see throughout the next section) of the recombinant field shrunk on its funding and overall cuts of public expenses launched an austerity period that had some of its

most significant impacts in the R&D due to being an activity dedicated to the long-term findings and not tailored to immediate suppression of the government/citizens demands. At the meso level, the unstable growth of the past two decades, with highs and lows that only achieved a consistent upward tendency since 2017, might be related to some bottlenecks when introducing Recombinant Technology into the civil society market that can hinder the profit potential of such industry.

The Recombinant DNA industry has not been immune to the societal and ethical challenges that have come to the forefront in the mainstream media since the advent of cloning. These issues have made the transition towards recombinant DNA an unpredictable journey regarding market acceptance. This unpredictability may have contributed to periods less attractive for investment in this area. The risk-averse nature of some funding tools and programmes, coupled with the cautious investment of private companies, the main drivers of disruptive technology, have taken a toll on the Recombinant DNA field in the first two decades of this century.

Despite the factors that potentially temporarily undermine the field's continuous development, the peak in 2023 is a promising indicator of the EPO's prosperity regarding Recombinant DNA patents for years to come.

Figure 2. Geographic Distribution of Recombinant DNA Patent Production



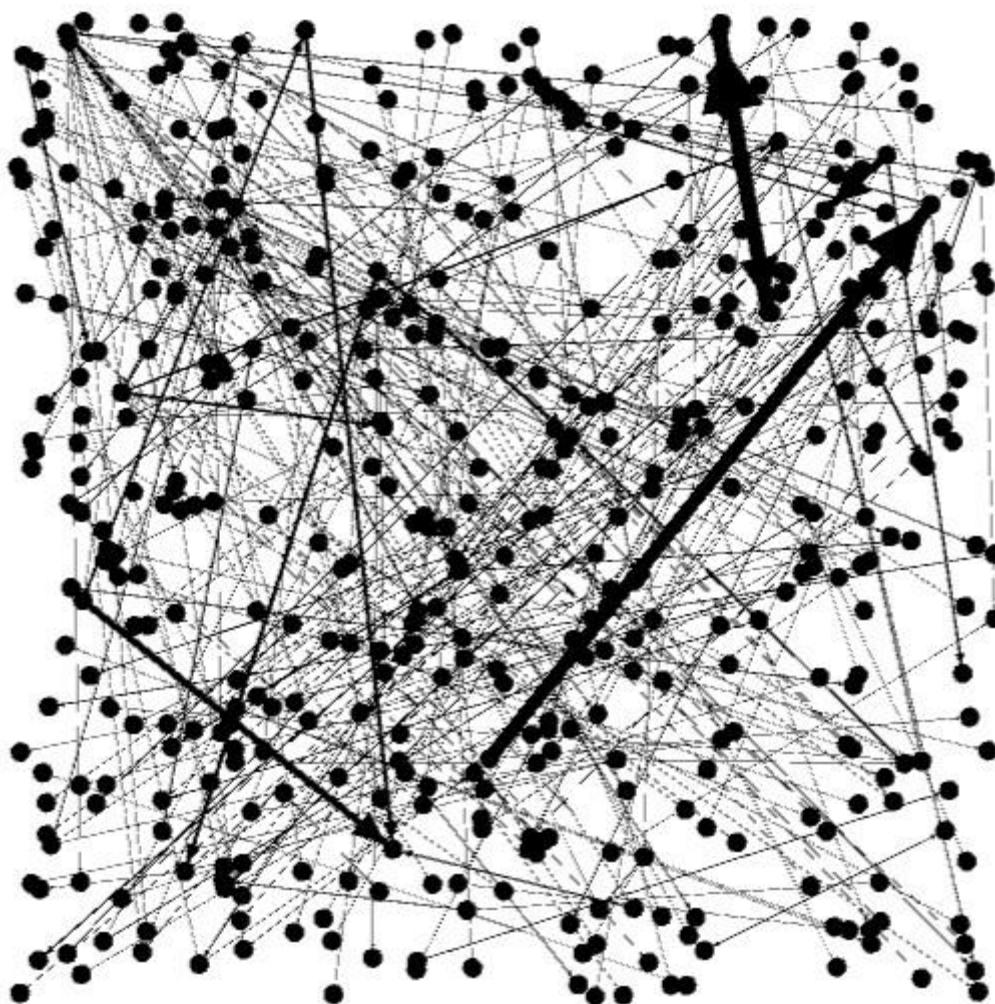
Source: Own elaboration based on European Patent Office data

Through a collaborative effort, the EU's political and funding tools have significantly improved the number of patents and the distribution of those inventions within Europe. In recent years, we have witnessed the entrance of Recombinant DNA research in countries that had very peripheral participation at the beginning of the XXI century. The EU enlargement (particularly in 2004) fostered the growth of research centres, private enterprises, and universities in countries with high levels of education but with a tradition of low funding, such as in Eastern European countries (Figure 2). This has led to an even distribution of DNA recombinant patents in southern Europe, Scandinavia, northern Europe, and the Eastern block. The continental part of Europe has the upper hand in the DNA recombinant field, reflecting the payoff of large funding and science management institutions backing up disruptive technological innovation.

The case of Germany, supported by the *Deutsche Forschungsgemeinschaft*, and of the *Centre National de la Recherche Scientifique* (CNRS) in France, are examples that have helped these countries to surpass the target of 10000 Recombinant DNA over the last 23 years. The UK, with its unique model of innovation in the field, has a historical source in the partnerships between some of the oldest universities in Europe and the first enterprises in the biotechnology sector. This resulted in long-term networks between academia and enterprises that contributed to the UK's success in patent production in this area, following the footsteps of Germany and France. Despite the Recombinant DNA and Biosensors fields not sharing most of the significant institutions in both cases, the nodes of these national funding (sometimes with executive functions within the education ministries) always had synergies across the boards, particularly with public research centres and SM private enterprises.

Moreover, Israel is a close technological partner to the EU, and those bonds are built over EU policy programmes that have been catalysers for the funding of consortiums in the recombinant DNA field, legitimating the presence of Israel on this map.

Figure 3. Innovation Map of Recombinant DNA



Source: Own elaboration (Gephi) based on European Patent Office data

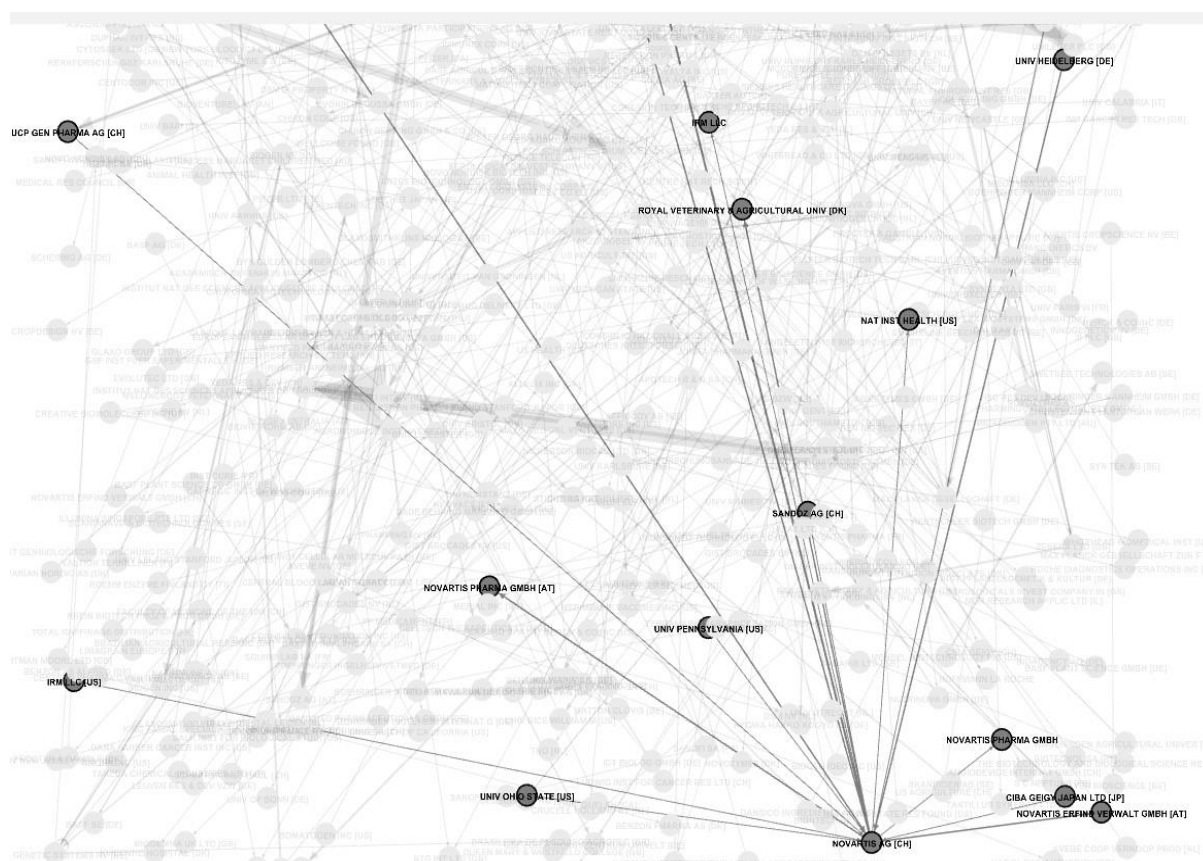
The image depicted in Figure 3 portrays the density of connections within the institutions that licensed at least one patent in the European Patent Office database regarding Recombinant DNA evolution. Recombinant DNA has a more intricate map of partnerships than the biosensors map (Figure 9), which was also tracked in this section as requested by the BioAssembler partners, who found it interesting to comprehend how these maps could intersect and share features.

This network map presents the most frequent partnerships between institutions with thicker arrows, and all the partners on patent licensing are visible for each node in the original map through the multiple links. Therefore, the following section aims to close up on the most notorious institutions on the map to unravel the connections between organisations regarding recombinant DNA innovation. The same will be compared to the research centres and enterprises pushing forward the biosensors field to understand if there have been any insightful

opportunities for the BioAssembler partners to interact with some of those companies, which could enlighten future partnerships within R&D EU-funded programmes.

The following figures (Figures 4 to 8) zoom in on the network maps (Figure 3), providing a comprehensive overview of how institutions tend to aggregate within an expanding innovation ecosystem. The second part of the analysis focuses on the diversity of connections and their intensity. The thicker arrows, which have been forming over time, represent relationships that include R&D strategies from the leading sectors in the field. This thorough analysis instils confidence in the reliability and relevance of the findings.

Figure 4. Novartis' Innovation Network



Source: Own elaboration (Gephi) based on European Patent Office data

Figure 4 represents one of the largest partnerships in the Recombinant DNA field. The heart of this network is Novartis, a long-term established company based in Switzerland. It establishes partnerships with multiple institutions, displaying its influence in the field. Moreover, these synergies happen with different models of institutions – universities, private companies and public institutions. The connection between the University of Pennsylvania and the University of Heidelberg exemplifies an intercontinental and intracontinental cooperation model within the DNA recombinant field.

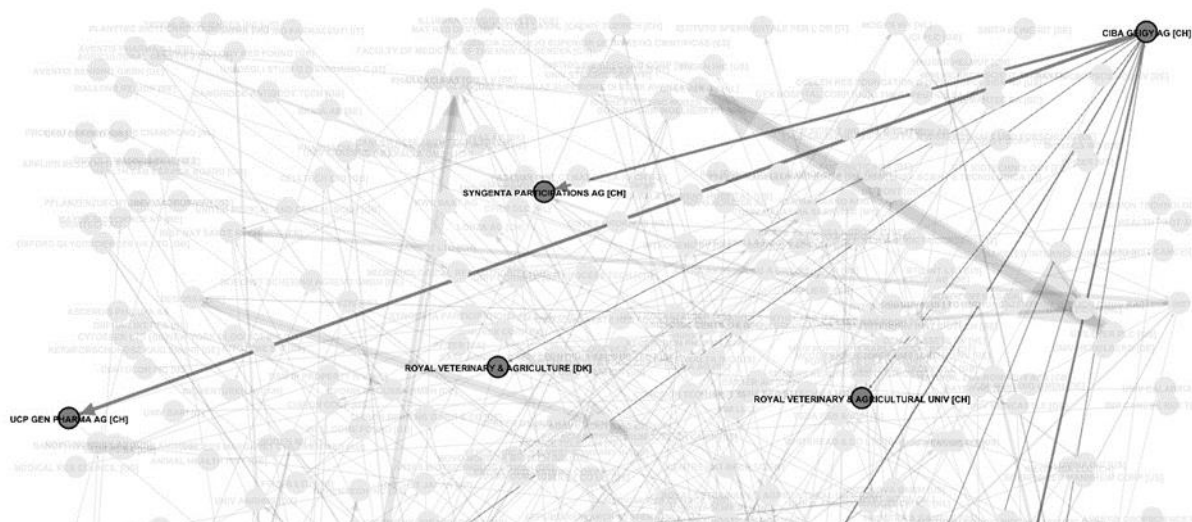
The connection between Novartis and US institutions is not just about intercontinental synergies, but also about the pivotal role that Recombinant DNA has been playing in the center of governmental investment in medical sciences and healthcare. The extensive links of the

National Institute of Health within the US position this institution as a crucial player in stimulating investment in healthcare in the US, with close ties with big companies in Europe and other continents, further emphasising the importance of its research in the global healthcare landscape.

The agricultural field is also being developed in close cooperation between private enterprises and universities. The Royal Veterinary and Agricultural University in Denmark and the Agricultural University of Athens are some of the institutions that partner with Novartis to bring new tools to tackle challenges to European agriculture. This opens the path to the application of recombinant DNA technology in the elaboration of more complex and sustainable biosensors in this field.

Switzerland has been following a steady development model for genetic research, largely driven by the contribution and collaboration between Swiss big pharma companies such as Sandoz and Novartis. The example of the following graph illustrates another pole of partnerships between Swiss private enterprises, with its core on the Ciba Geigy AG company (Figure 5). Once again, the role of universities in Swiss and Denmark to push forward the biomedical and agricultural field in straight research partnerships with commercial entities, further underlining the potential for commercialisation in this scientific field.

Figure 5. CIBA GEIGY's Innovation Network

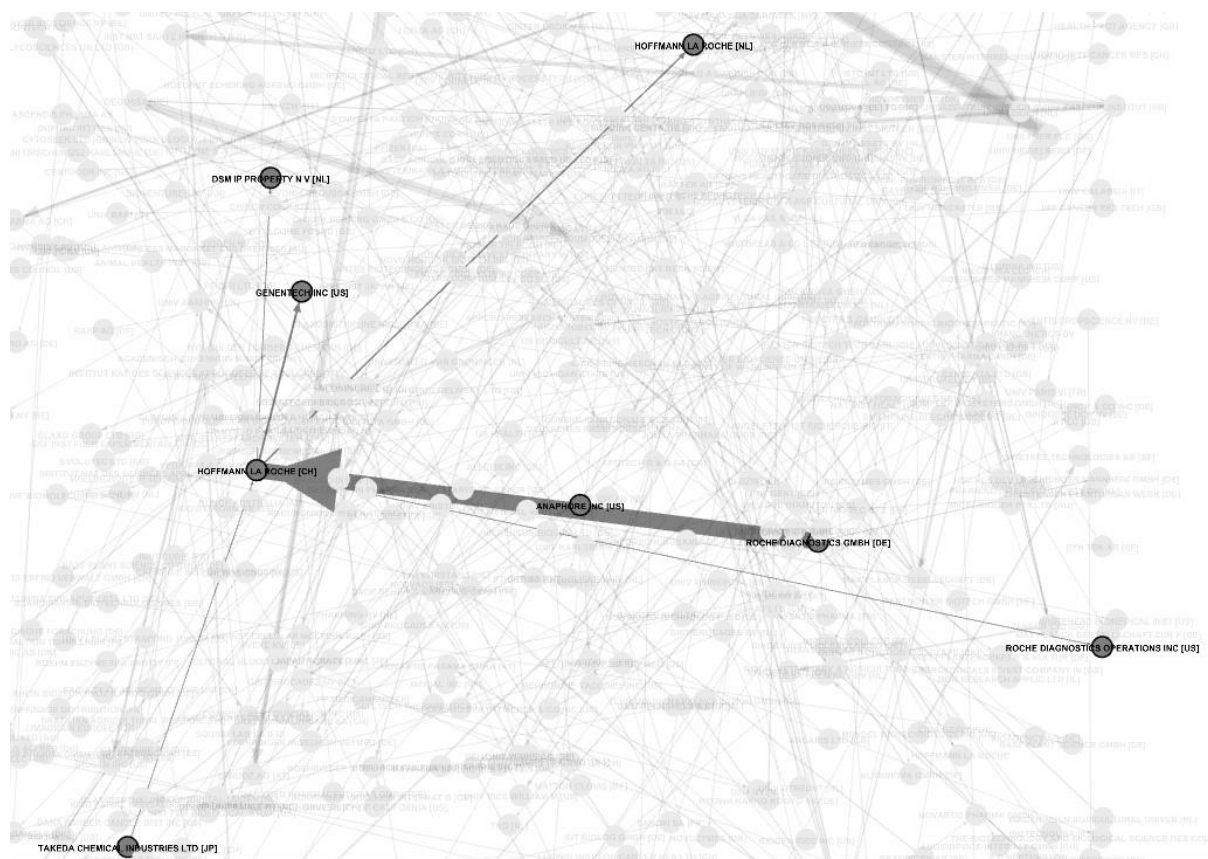


Source: Own elaboration (Gephi) based on European Patent Office data

With its extensive global reach, the Hoffmann-La Roche network is responsible for licensing the largest number of patents in Switzerland. This impressive position has been achieved through the development of several company branches in different countries, including Roche Netherlands, Roche Diagnostics for Healthcare in the US, and Roche Diagnostics in Germany (Figure 6). Roche's infrastructure spans all continents, a testament to its global presence and influence. This global reach also reduces the need to partner with universities and research centres, as Roche and its branches have similar facilities. This is one factor that explains the less intricate constitution of Roche's network, despite its high production levels. Furthermore,

Roche has strategically established connections with enterprises in Japan in the chemical industry and with genetic engineering companies in the US, such as Anaphore and Genentech, demonstrating its commitment to global collaboration and innovation.

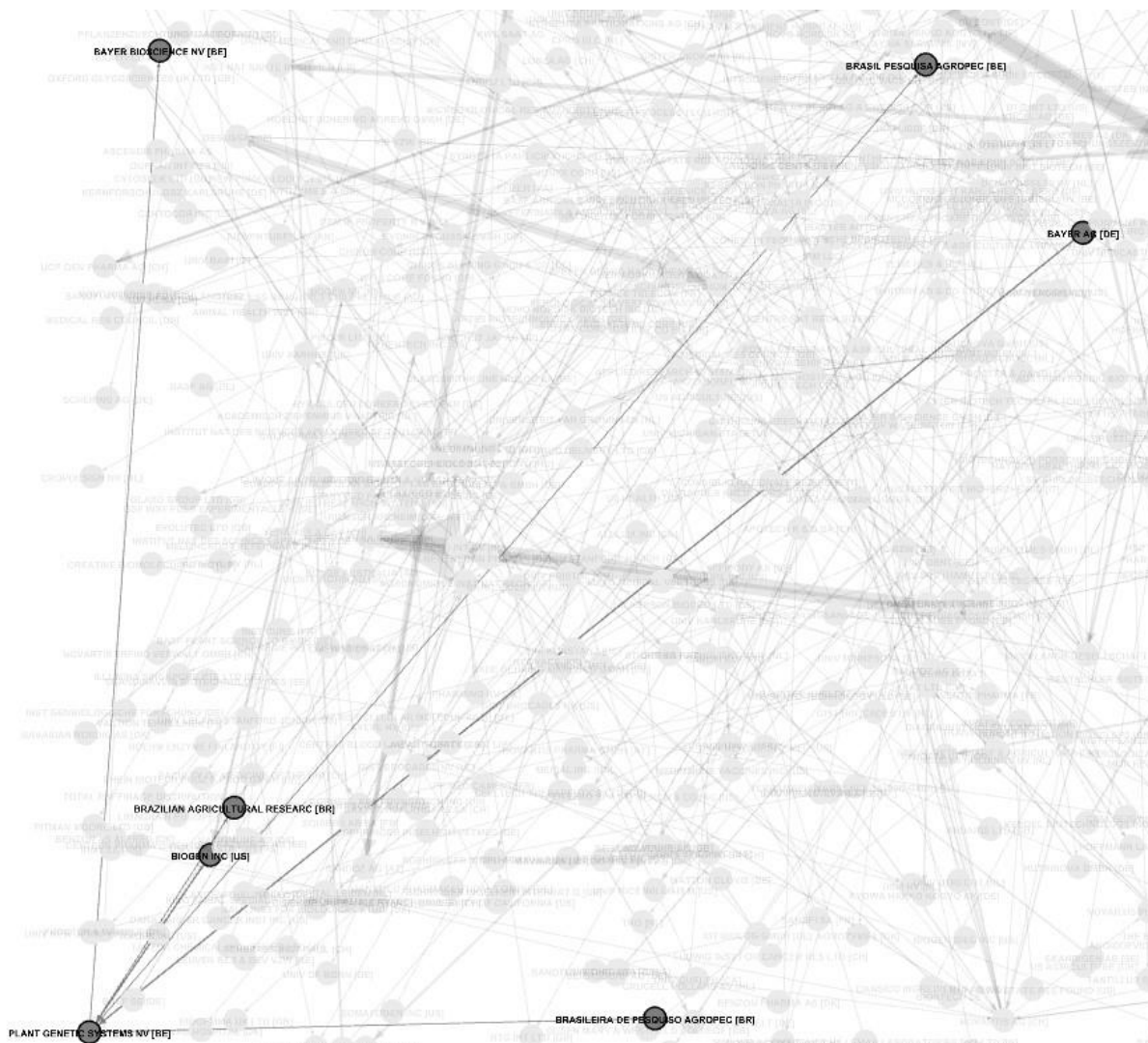
Figure 6. Hoffman La Roche's Innovation Network



Source: Own elaboration (Gephi) based on European Patent Office data

These networks reflect the intricate web of collaborations that drive recombinant DNA research forward, with the core of the partnerships established by Swiss big pharma companies. It highlights the interconnectedness of the triple helix institutions in advancing this critical area of biotechnology with intercontinental synergies. Through the partnerships, institutions from the private sector, the academic world and government-related can leverage their collective expertise and resources, leading to groundbreaking innovations and advancements in genetic engineering, medicine, and agriculture.

Figure 7. Plant Genetic Systems' Innovation Network



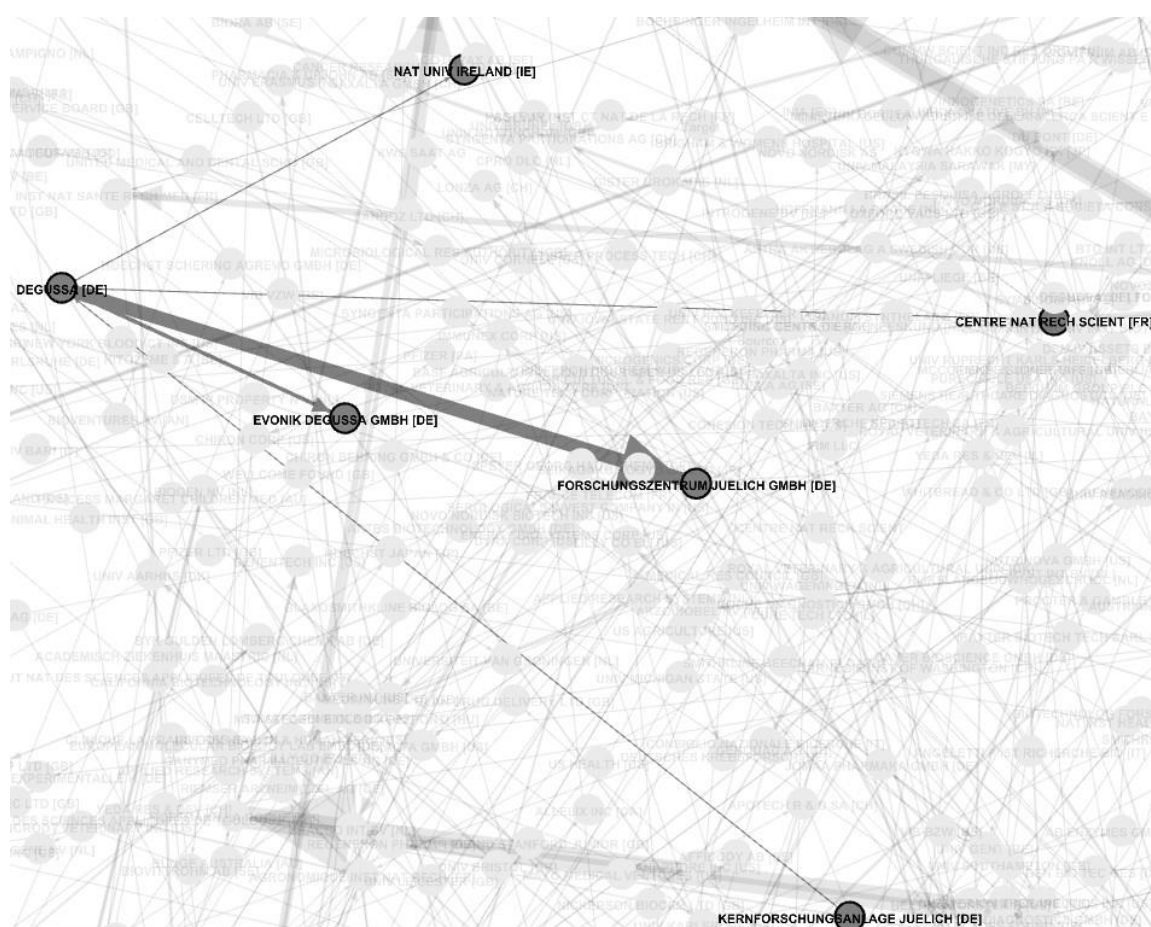
Source: Own elaboration (Gephi) based on European Patent Office data

Swiss companies, strategically leveraging their position, are expanding their influence in the pharmaceutical sector through intricate networks of partners in the research and commercialisation stages. Despite Switzerland's non-EU status, it reaps the benefits of EU-funded programmes, enhancing its competitive edge. Moreover, its well-established partnerships with EU research centres further bolster its position.

However, the EU houses clusters in the recombinant DNA sector, focusing on smaller companies operating in niche markets. A prime example is Plant Genetic Systems, a Belgian company at the forefront of DNA engineering in vegetal materials. This pioneering company has successfully tackled biological challenges in the tobacco industry, a testament to its innovative spirit. Today, it is a part of the Bayer group, as evidenced by its partnerships with Bayer Bioscience and its main branch in Germany.

The groundbreaking research in plant DNA engineering for sustainable agriculture has paved the way for fruitful collaborations. These collaborations transcend the EU, with synergies discovered in Brazilian research centres dedicated to agricultural and livestock management (Figure 7). A shining example is the partnership between the Bayer group and Brazilian Agricultural Research Centres, a beacon of intercontinental private-public cooperation. This partnership is revolutionising sustainable agricultural practices through DNA engineering, building hope for a brilliant future for green chemistry.

Figure 8. Degussa's Innovation Network



Source: Own elaboration (Gephi) based on European Patent Office data

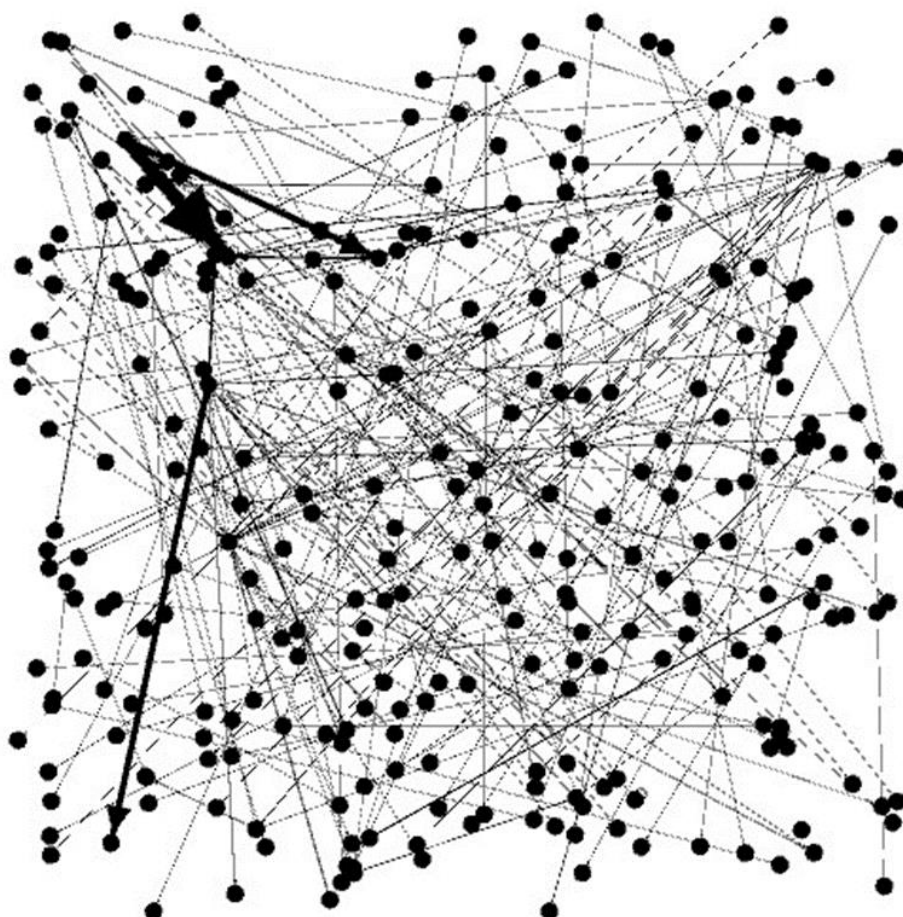
Degussa is another example of an EU-leading company in the Recombinant field, turning central Europe into a hub, particularly in the metallurgy and chemical sectors. The disruptive research of Degussa Evonik has a high percentage funded by a national German foundation in Forschungszentrum Juelich. Besides that, it also counts funding from international sources for technology and science funding, such as the French National Centre for Research (Figure 8). In the biosensors and recombinant field, the French National Centre for Research has licensed many patents registered in the European Patent Office. Many French patents in the field received funding from this public entity, and its name is included in the list of inventors.

Nonetheless, seeing the French National Centre for Research collaborate with fund enterprises outside France is not usual. However, this internationalisation of funding from public sources provides a golden parachute for more risky and time-consuming research that might need to ensure its commercialisation potential.

The association with the National University of Ireland must happen in a similar context. This helix between universities and EU companies is a win-win situation that helps the students gain more direct knowledge of laboratories and ways to make science. The companies get access to more adequate facilities to align their research activities with the commercialisation needs. Moreover, the universities are a source of creativity, leading to new approaches to including sustainability in science and technology advancements.

Even if enterprises in the recombinant DNA field have strong ties at the national and international levels, how can those patterns be shared with the biosensors area to create projects with goals similar to those of BioAssembler?

Figure 9. Innovation Network of Biosensors Production



Source: Own elaboration (Gephi) based on European Patent Office data

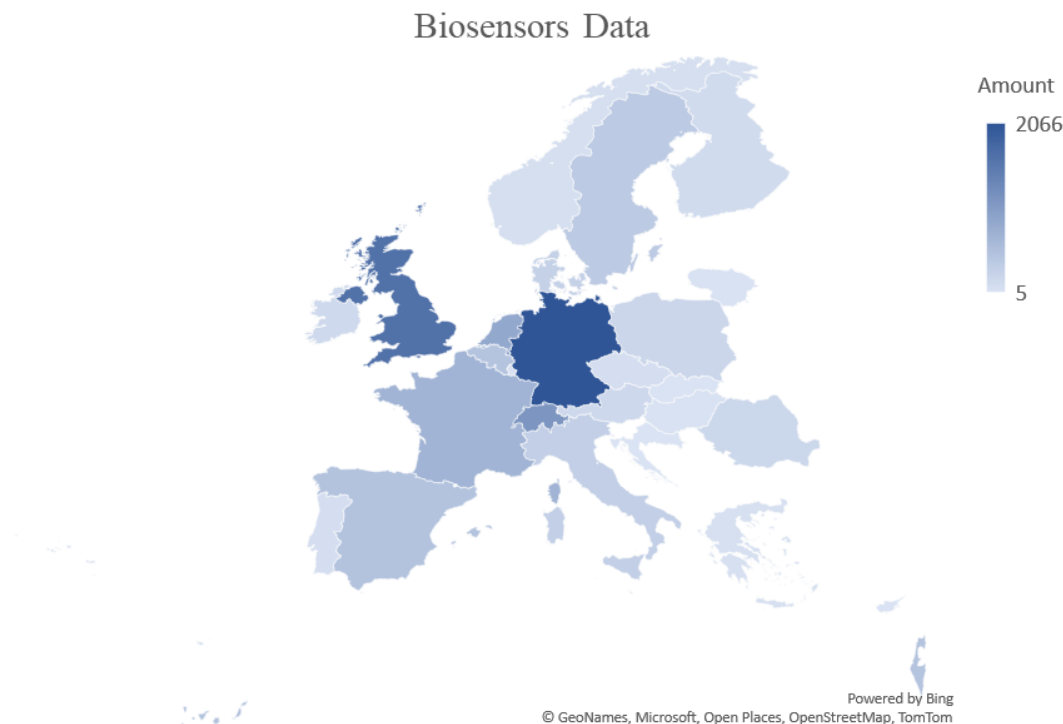
Compared with Recombinant DNA's institutional network (Figure 3), the biosensors network still has a different range of institutional partnerships concerning the patenting volume (Figure 9). However, some enterprises are simultaneously very influential in both industries. On one hand, Hoffman-La Roche and its international branches are leaders in both sectors. Moreover, the national public institutions of research (partially funded by the EU mechanisms to stimulate STI) play a much larger role in the Biosensors field when compared with the Recombinant transition. The national institutions that fund and manage R&D have organised themselves as the centre of patenting in the respective countries, allocating that investment mainly to public universities.

The French National Centre for Research (CNRS) and the Spanish Council for Research (CSIC) are two essential entities that work as the core of the Biosensors innovation ecosystem (Figure A4). The synergies established between these R&D quasi-governmental institutions and the national network of universities turn the STI systems in Spain and France heavily dependent on the priorities of these two groups. In the Spanish case, there is a wide variety and geographical dispersion of universities producing patents in the biosensors field, under the funding of the Consejo de Nacional de Investigacion. In France, the funding tends to be more centralised towards institutions located in Paris or nearby.

This hegemonic dynamic of a funding institution in the patent creation process can enhance or hinder biotechnology research within the country. On one hand, it takes off the financial burden and the pressure off the universities that rarely have full funding to buy equipment for such a sensitive field, that requires clean facilities and heavy machinery. On the other hand, as in other European countries, like Finland, as depicted by the OECD, a robust R&D national funding authority can block access to other funding models from external sources. The path dependency that might result from this is characterised by resistance to new private capital initiatives entering the biosensors field in these respective countries. Nonetheless, the core of the funding in the R&D national entity allows for the centralisation of the projects, allowing for more intranational cooperation as the applications for project funding have been trying to place requirements on the need for scientific collaboration.

Spain and France, with their collaborative model of sharing and transferring knowledge through a national entity for science management, have been patenting a significant amount of biosensors, only behind Germany and the UK (Figure 10). This model, which emphasises the power of collective knowledge sharing, is a source of inspiration. On the other hand, the UK has a slightly different model for managing science and biotechnology research. The nodes that represent the core of the UK's STI diffusion are private enterprises that look to enrich their knowledge base by partnering with national and foreign universities, with foreign national-scale science funding authorities and foreign private enterprises. Measuring the number of patents, one must say that this model was successful. One of the most notable cases is Flexanable, a catalyst of biosensor patenting that counts in its networks with several German partners, including the University of Braunschweig, a biotechnology department with close ties with BioAssembler partner Abcalis.

Figure 10. Geographic Distribution of Biosensors Patent Production



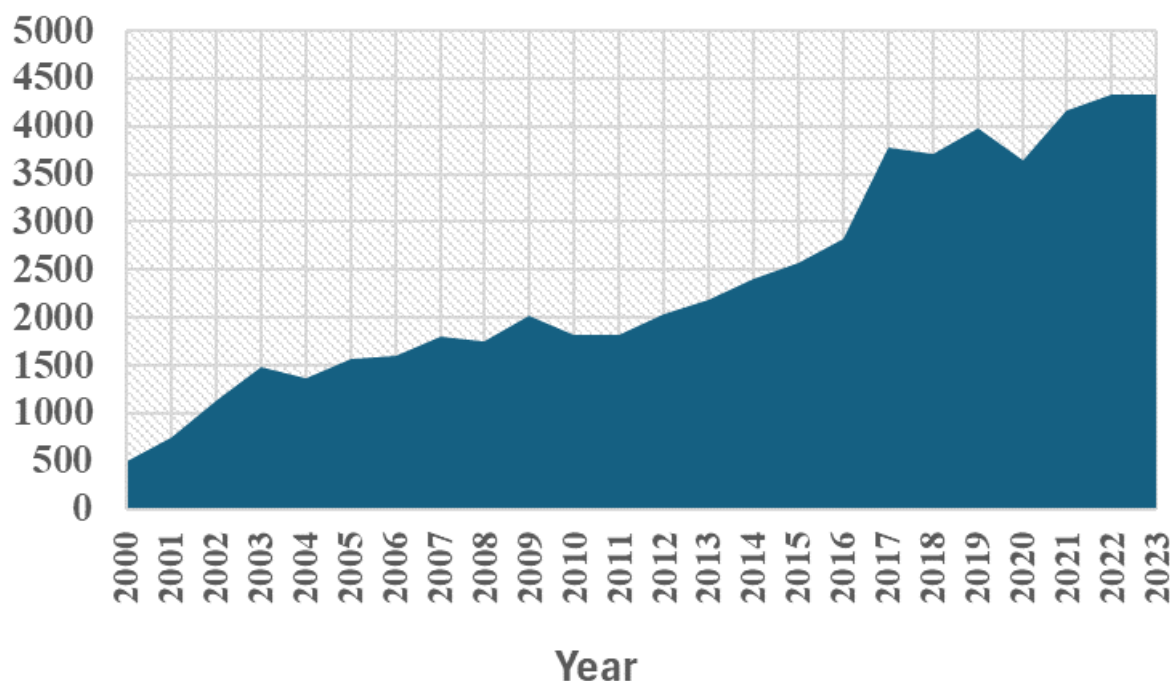
Source: Own elaboration based on European Patent Office data

As depicted by Figure 11, Biosensor technology has been growing regularly in terms of the number of patents in the European Patent Office. The trajectory is similar to the trajectory of recombinant DNA. This is mainly because the biotechnology field notices a distribution dependent on macroglobal economic tendencies. The biotechnology field needs substantial investment that requires an allocation of funding that, in an economic recession, makes it harder to hit those funding targets. This path-dependency over the global economy partially explains the fluctuation of the biosensor's patenting amounts throughout the years.

After an exponential growth tendency at the beginning of the century, from 2004 onwards, one can observe a slower growth with occasional falls in the production of Biosensor patenting. The comparison between 2003, the last moment of the constant increase in biosensors produced, and 2010, a recession that made the patents fall under almost the identical amounts as in 2003. As stated above, the lack of evolution in the amounts of biosensors patented between 2003 and 2010 is a sign of the decrease in investment allocated to biotechnology during a significant contraction of the global economy, particularly in the US, which has always played a significant role in this sector.

Figure 11. Biosensors Patent Evolution (2000-2023)

Patent Amount



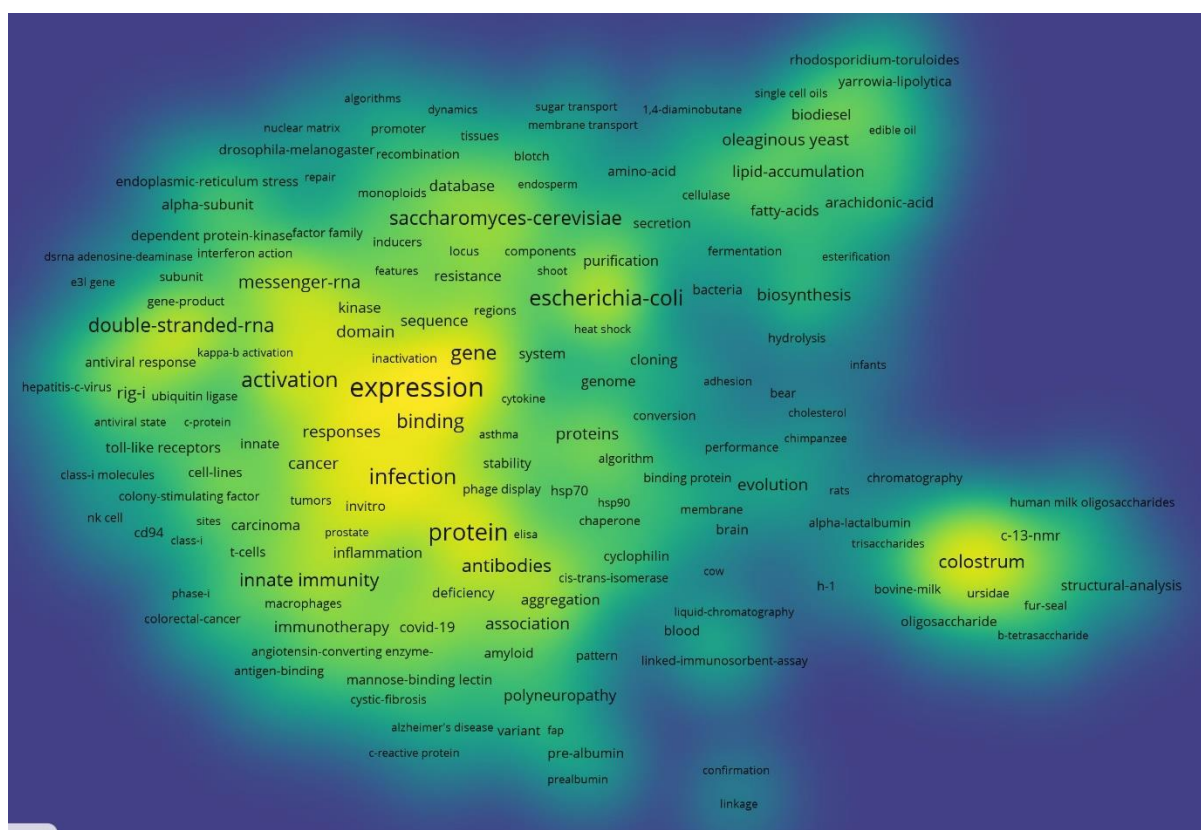
Source: Own elaboration based on European Patent Office data

From 2011 to 2020, biotechnology saw a reinvention of its market. It maintained the pace achieved at the beginning of the century, registering steady signs of a sector in permanent development, with its production being democratised to peripheral geographies. A small bump from 2020 to 2021, following unsettling times due to the COVID-19 pandemic, temporarily hindered production growth. However, from 2022 onwards, the growth tendency returned, more dedicated to developing PCR and healthcare-related challenges, as pointed out by the Task 4.5 Report of the BioAssembler project “Assessment of the Photolithographic Synthetic Chemistry Market” (Valente et al., 2023). The democratisation of biosensor production throughout the last 23 years is emphasised by the leap forward from around 500 patented biosensor inventions per year in 2000 to around 4300 in 2023, and it is expected to keep increasing in the following years and the pursuit of more sustainable technology.

6.2 Knowledge Production as Base for Innovation Networks

The recombinant DNA field, crucial for advancing the healthcare industry, is grappling with significant challenges. Based on the most frequent keywords, the heat map vividly illustrates the main concerns scientists face in this scientific domain. The challenges posed by the *Escherichia coli* infection global threat or COVID-19, prominently positioned at the centre of

Figure 12. Recombinant DNA Keywords Map



The process of innovation is a journey that spans over time, until the knowledge spreads and becomes institutionalised through the increment of stability in the scientific method. This journey is launched by words close to the core and directly related to the efficiency and stability of the Recombinant DNA transition. Inactivation, binding, phage display, cloning, and aggregation are just some of the keywords driving the development of a more accurate and generalisable production of the animal-to-recombinant transition (Figure 12). The journals that have been more cited in the field reflect the growing trend of putting biotechnology at the forefront of healthcare, underscoring the immense potential of this technology for global biomedicine, the citation network emphasises the dimensions depicted in the knowledge base.

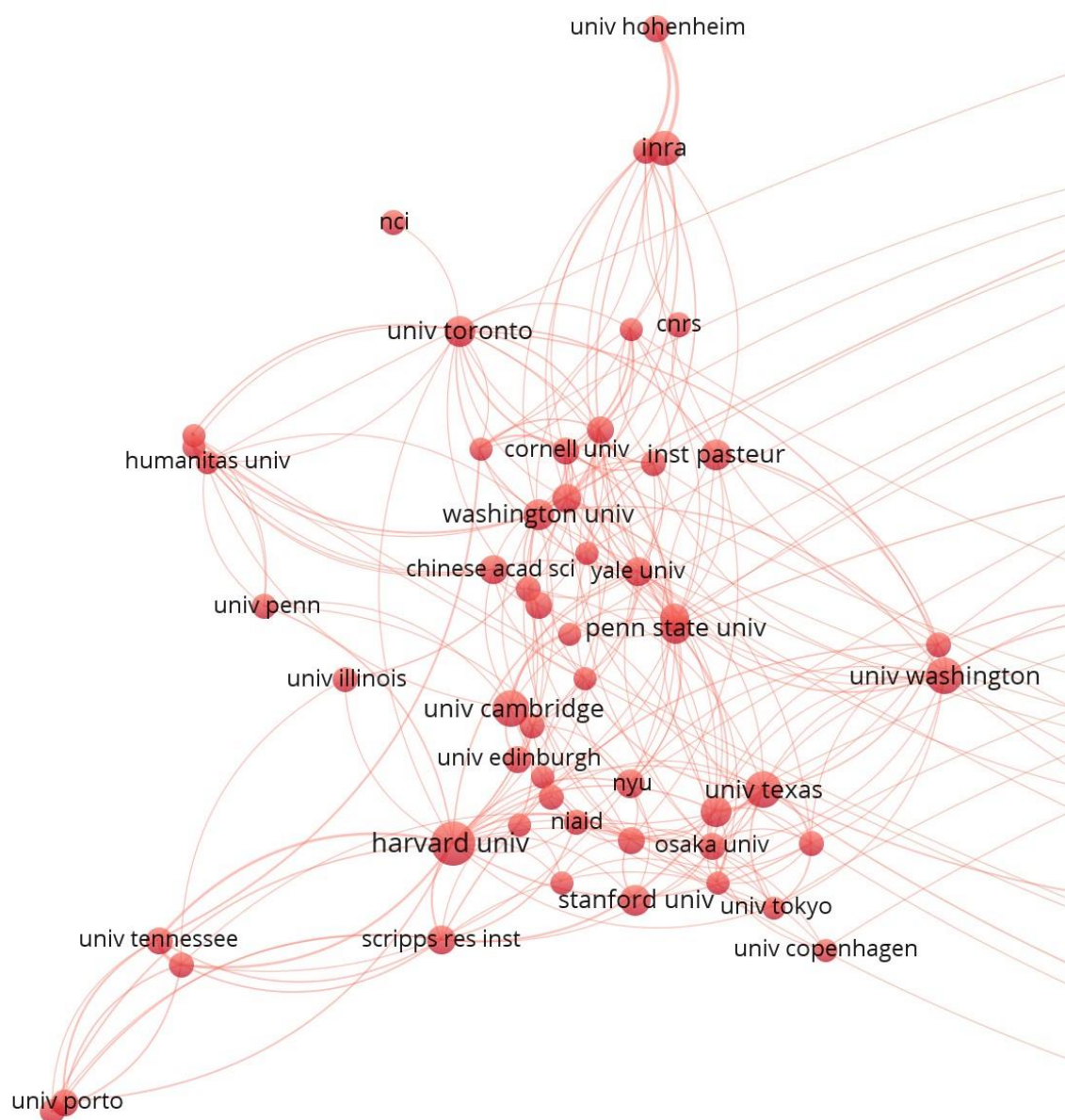
Figure 13. Most Cited Journals in the Recombinant DNA Patent Field



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composes the core of the most cited articles in the patent documents. Instead, the most influential articles on Recombinant DNA have been produced mostly in US institutions, as displayed in Figure 14. Harvard University, Washington University, and Stanford are some of the more notorious names on this list that establish connections with universities in the UK, such as Cambridge or the University of Edinburgh.

Figure 14. Most Cited Universities in the Recombinant DNA Patent Field



Source: Own elaboration (VosViewer) based on European Patent Office data

Those were the most cited institutions that have built the knowledge base in the Recombinant DNA field, making visible some patterns shared with the biosensors' networks depicted in the Task 4.5 deliverable (Valente et al., 2023; Figure 14). It is interesting to notice that those institutions in the UK, have the opposing dynamic to the German institutions mentioned above. This UK university produced some of the most influential work in this field; however, they are not among the lead patent producers in the EPO database of Recombinant DNA.

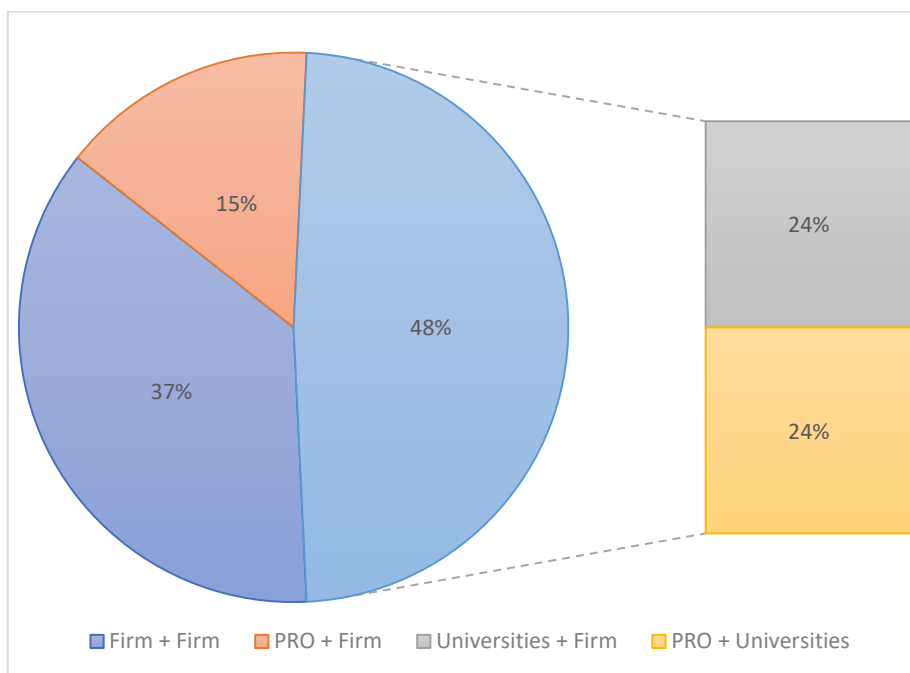
The upbringing of more European institutions outside the anglophone academic domain in the fringes of this network should be considered a study subject in the transition to recombinant DNA and more sustainable ways of producing valuable scientific achievements. The University of Copenhagen, the University of Porto, and the University of Hohenheim are among the entities that, despite not being at the core of the most significant knowledge base, have sufficient recognition from Recombinant DNA patent inventors to be some of the highly cited institutions in the field, despite not being notorious patent inventors in numbers.

Moreover, the Centre Nationale for Recherche Scientifique has seen its work rewarded once again through citation recognition, making the example of science management in a public institutional configuration in France a success. Its close ties with the Institute Pasteur are also a benchmark for the patenting process and for the production of literature to be cited by the inventors of Recombinant DNA patents.

6.3 Networks of Multi-Actors Research Consortium Constitutions

The structure of partnerships for the applicants for innovations with Recombinant technology within the European Patent Office database showed that around half of the consortiums had an academic institution as one of the applicants, and the other half was only constituted by Firms and Public Research Organisations (PRO). Two or more firms constituted Europe's most common partnership model for recombinant production. The firms with the most substantial presence in this collaboration are SMEs that produced Recombinant-related products within the scope falling under EU funding bodies. This substantial percentage of firm-firm cooperation allows for mitigating the risk of financial burden coming from a highly sensitive industry, and it counts with the funding allocation from the EU innovation programmes.

Figure 15. Collaboration Configuration in the Recombinant DNA Patent Field



Source: Own elaboration based on European Patent Office data

In the other half of the figure, 24% of the patented applications included partnerships between Universities and Private Corporations and another 24% of Universities with Public Research Organisations. This underscores the significant role of universities in the Recombinant technology sector, serving as poles of innovation and creativity. These are fundamental complementary skills to be applied in the infrastructural conditions offered by Firms or Public Research Organisations. In this department, the universities from the US have a strong presence in partnerships with European firms, which also justifies the knowledge basis of most of the patents with a heavy presence of citations from recombinant literature published by US scientists. Based on the findings of this deliverable, it is evident that the scientific knowledge produced in US universities has inspired the industrial production of recombinant in Europe, highlighting the crucial role of universities in driving innovation.

Moreover, the least observed configuration joined Public Research Organisations and Firms. This model is usually applied when firms develop a product with funding allocated from a national programme for STI and R&D. In some cases, the public research organisations, often the entity responsible for regulating and funding scientific work at the national level, are also mentioned in the applicants' group. These partnerships are usually present in research ecosystems with a long tradition of public investment in R&D and public funding bodies with a high level of autonomy (e.g. the Centre National de la Recherche Scientifique in France).

Figure 16. Patents combining the keywords “Recombinant DNA” and “Biosensors”

1	USO DE OLIGONUCLEOTIDOS MODULARES COMO SONDAS O CEBADORES EN ENSAYOS BASADOS EN ACIDOS NUCLEICOS.	DYNAL BIOTECH ASA	ES2234031T3	16/06/2005
2	MONOCLONAL ANTIBODIES TO GROWTH AND DIFFERENTIATION FACTOR 15 (GDF-15)	JULIUS MAXIMILIANS UNIVERSITÄT WÜRZBURG [DE] UNIV WUERZBURG J MAXIMILIANS [DE]	EP2900263A1 EP2900263B1	2015-08-05 2019-06-05
3	Plant haemoglobin	CROPDESIGN NV [BE] CROPDESIGN NV	CN1768077A CN1768077B	2006-05-03 2012-10-17
4	MONOCLONAL ANTIBODIES TO GROWTH AND DIFFERENTIATION FACTOR 15 (GDF-15), AND USES THEREOF FOR TREATING CANCER CACHEXIA AND CANCER	UNIV WUERZBURG J MAXIMILIANS [DE]	EP3653644A1 EP3653644B1	2020-05-20 2023-11-15
5	Protection against environmental toxicity through manipulation of the processing of messenger RNA precursors	UNIV VALENCIA POLITECNICA [ES] UNIV VALENCIA POLITECNICA	CN10139756 4A CN10139756 4B	2009-04-01 2013-07-17
6	GDF-15 AS A DIAGNOSTIC MARKER FOR MELANOMA	UNIV WUERZBURG J MAXIMILIANS [DE]	EP3356826A1 EP3356826B1	2018-08-08 2023-12-06
7	COMBINATION THERAPY USING INHIBITORS OF HUMAN GROWTH AND DIFFERENTIATION FACTOR 15 (GDF-15) AND IMMUNE CHECKPOINT BLOCKERS	UNIV WUERZBURG J MAXIMILIANS [DE]	EP3355919A2 EP3355919B1	2018-08-08 2022-12-07
8	Monoclonal antibodies to growth and differentiation factor 15 (GDF-15), and use thereof for treating cancer cachexia	JULIUS MAXIMILIANS UNIVERSITÄT WÜRZBURG [DE] JULIUS-MAXIMILIANS-UNIVERSITÄT WÜRZBURG [DE]	GB2524553A GB2524553B GB2524553C	2015-09-30 2017-06-28 2017-07-19

		JULIUS-MAXIMILIANS-UNIVERSITÄT WÜRZBURG [DE]		
9	Monoclonal antibodies to growth and differentiation factor 15 (GDF-15), and use thereof for treating cancer	JULIUS MAXIMILLIANS UNIVERSITÄT WÜRZBURG [DE] JULIUS-MAXIMILIANS-UNIVERSITÄT WÜRZBURG [DE]	GB2524552A GB2524552B	2015-09-30 2017-07-12

Source: Own elaboration based on European Patent Office data

When combining the two keywords used in this deliverable as combined filters in the European Patent Office, “Recombinant DNA” and “Biosensors”, only 9 results were obtained, as shown in Figure 15. There are some features that are worth to delve into when looking at the list. Firstly, the most recent patent in the list was registered in the EPO in 2023; however, before that, all patents in the EPO which developed biosensors with Recombinant DNA technology have four or more years since its launching. This shows that even if Recombinant DNA and the Biosensors field have been growing almost simultaneously, there is an overall stagnation in the patenting of Biosensors that use Recombinant DNA technology in their chemical processes. That is a gap that needs to be bridged in future EU research programmes. The overall expectation is that BioAssembler can sum up to this list.

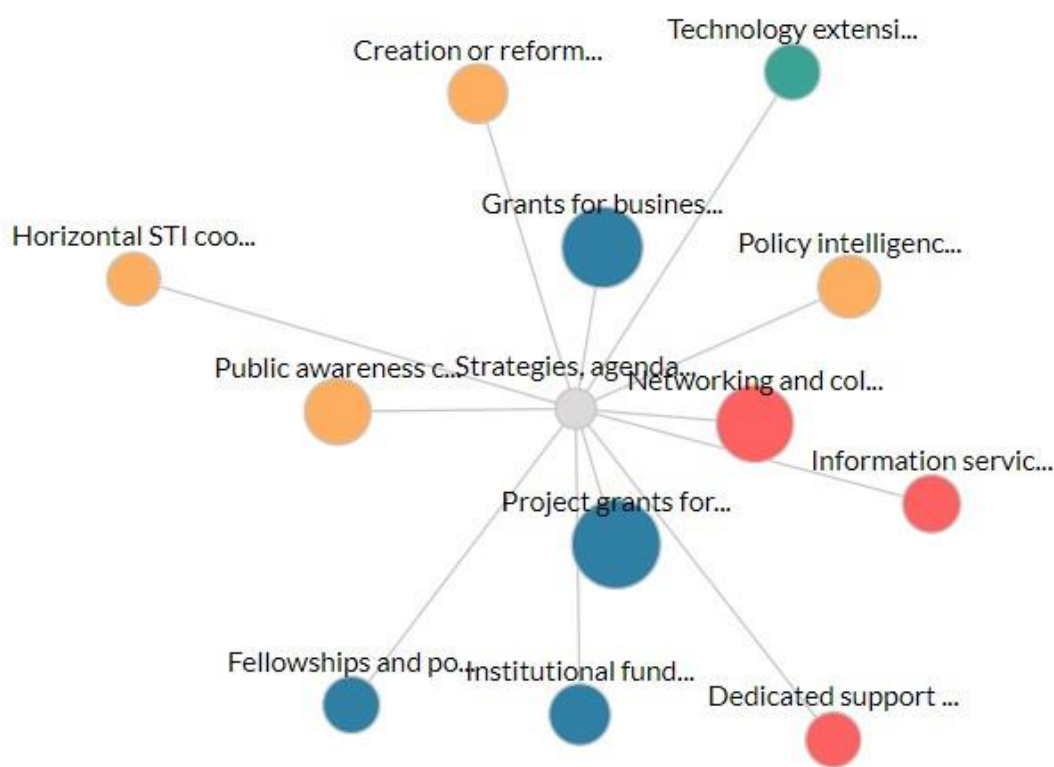
Secondly, the most approached topic in these nine patents is the assessment of cancer detection and treatment. The specificity of the topic turns this list into a niche or epistemic cluster that emphasises the role of the Julius-Maximilians-Universität Würzburg during the last decade to try to find healthcare solutions through Recombinant DNA-based biosensors. The lack of partners for the University of Würzburg in this field might indicate potential unexplored synergies waiting to be established between SMEs and the research centres developing Biosensors using Recombinant DNA technology at this university.

6.4 Priorities in EU’s STI Policy

This radial network diagram (Figure 17) was derived from the EU's recent investments in science, technology, and innovation under the Agenda 2030. This graph aims to depict the funding priorities of EU investment; the instrumental tools of this analysis are the connections between nodes and the size of those same nodes, which track the relationships between dimensions. Figure 17 shows the central node as the core point between all the dimensions present in the image. This underscores the adherence to Agenda 2030 agreements that have

been followed, prioritising two essential grant mechanisms, the Grants for Business and the Project Grants for Specific Initiatives. This factor reflects the EU's commitment to equitable financing between private enterprises and the public research sector (Alpatov et al., 2021). Horizon Europe has a budget of 95.5 billion euros until 2027 to support research in various fields.

Figure 17. EU STI Investment Priorities

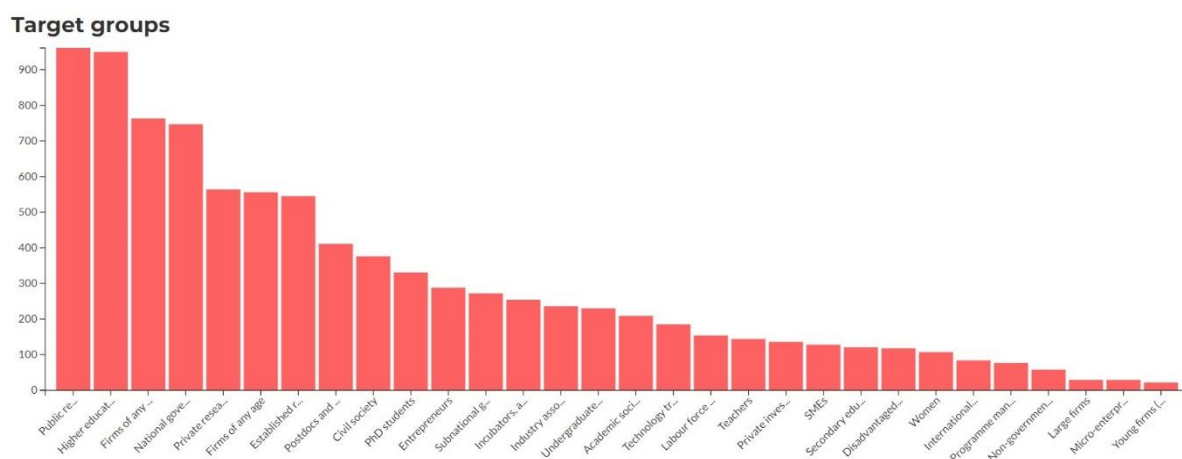


Source: EC-OECD STIP Compass

The funding allocated in this dimension has also been directed towards Institutional funding support, Fellowships, and Postdoctoral programmes. The standout grant in this investment pillar is the Marie-Sklodowska-Curie Actions (Gengnagel et al., 2022), which is well-known for helping to consolidate the careers of promising early-career researchers. This investment into public research institutions needs a scientific market that seeks to be informed about the studied topics and is eager to co-create policy based on the resulting information. Therefore, the role of Public Awareness has expanded to stimulate the practical application of scientific findings in everyday life (Riccardi et al., 2017).

This requires a more extensive network and collaboration service and more effective communication and technology playing an active part in bridging all these nodes within Agenda 2030. The inclusion of the Technology extension services results from the strong interest in funding programmes such as Horizon Europe, the European Innovation Council and the European Regional Development. Here, it is crucial to highlight the effort to democratise information through the Digital Europe Programme. There is a sense of continuity in these programmes since the funding is also dedicated to reforming policies, including improving priorities in future investment programmes to remain at the forefront of research and innovation effects.

Figure 18. Target Groups of the EU STI Investment



Source: EC-OECD STIP Compass

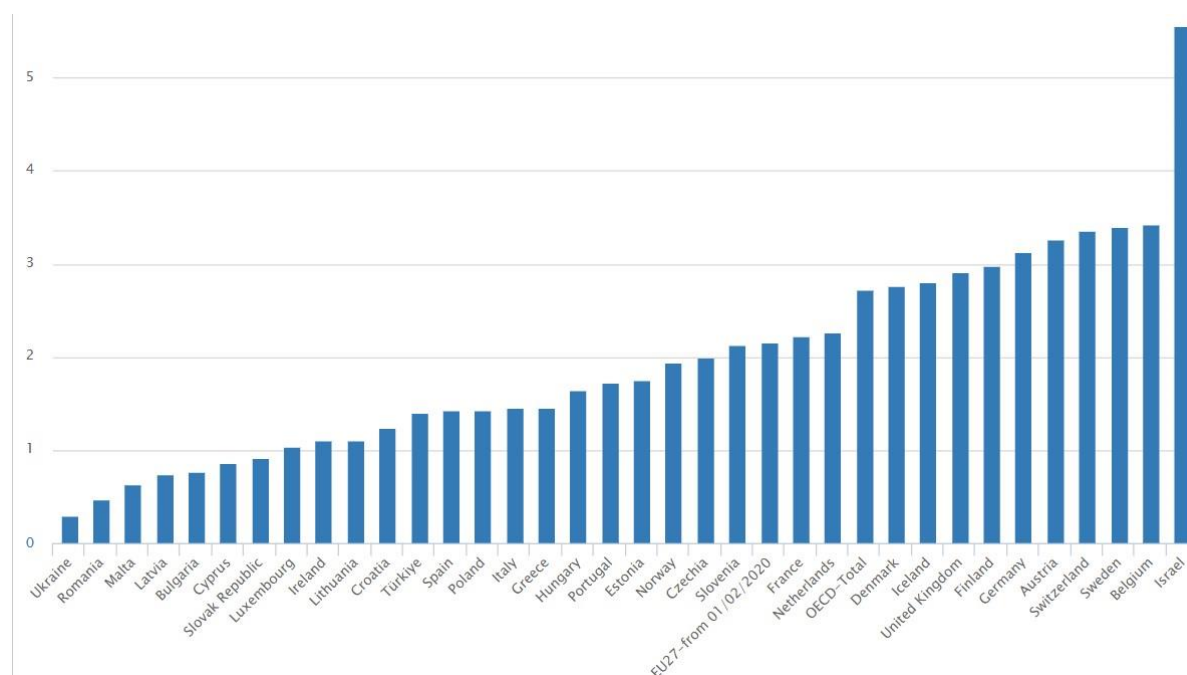
The chart presented here is a valuable tool for understanding the distribution of EU initiatives on STI funding. It offers a comprehensive view of the stakeholders involved, illustrating how the EU's STI initiatives are distributed among diverse groups. This includes the various stakeholders who benefit from funding programmes within the STI policy framework. The chart reveals a broad and robust investment in public research institutions, including the channels of funding directed to higher education institutions. The firms that follow in this hierarchy are a testament to the balanced approach of the EU in supporting both public and private entities. Mariotti and Haider (2020) underscored this connection by highlighting the pivotal role of firms and companies in providing access to new ideas and structural market knowledge.

Still in Figure 18, shortly after the Postdoctoral support, as mentioned in the radial network (Figure 17), there is civil society, representing a stretch from the EU inclusive strategy to include non-profit organisations and engage citizens with academic and SME initiatives. The projects selected to contribute to environmental initiatives reinforce the commitment of EU institutions to the EU Green Deal principles (Sengupta, 2023). This commitment promotes environmental and social and economic sustainability by empowering communities in fragile situations. Therefore, supporting disadvantaged groups is one of the most challenging tasks for EU programmes like LIFE, which guarantees long-term sustainability within the EU. The EU's dedication to the Green Deal principles is truly inspiring and sets a high standard for other funding programmes.

Another key aspect highlighted by the chart is the EU's strong emphasis on entrepreneurship. This is evident in the substantial investments in the entrepreneurial group, SMEs, incubators, and young firms. The start-up model and similar configurations of company management are reshaping the technology market worldwide, and the EU is actively embracing these changes. It offers opportunities for SME innovation enterprises through the incremental digitalisation of services, significantly reducing the bureaucratic costs for recent companies when establishing themselves (Previati et al., 2022). The COSME programme has played a pivotal role in this strategy, facilitating SME access to loans during the former European Cohesion programme period (2014-2020).

The balance between short-term profit and long-term sustainability is complex, especially when dealing with a wide variation in research areas and business fields. However, the effectiveness of EU investment is contingent upon the urgent need for individual countries to establish a complementary proportionality in funding public and private entities (Kalinowski, 2020). This crucial effort involves carefully examining the country's GDP expenditure on STI-related policy, as illustrated in Figure 19.

Figure 19. STI Investment by Countries' GDP



Source: EC-OECD STIP Compass

The percentage of Gross Domestic Product allocated to Science, Technology and Innovation (STI) within European countries sees Israel standing out, with more than 5% of its GDP going to endeavours in this area. Israel's effort to produce and commercialise its scientific findings for both the US and European Union markets needs to come from its internal budget because it does not have the funding from international institutions that the EU does; this partially explains the difference between Israel and the EU in terms of GDP invested in STI.

Israel's model of high STI investment, even when compared to the average of the Organisation for Economic Co-operation and Development (OCDE) and the European Union (EU), presents a compelling case for European countries and institutions (Trajtenberg, 2021). It prompts them to reflect on the strategies and policies necessary to increase their GDP allocation to STI. While this investment may not immediately translate into higher production in the patents or publications field, it represents a long-term commitment to gaining competitive and scientific advantages.

Within the EU, there is a wide range of GDP investment in STI projects. If we take the EU27 average investment, separating the EU into two clusters of countries it is easy to understand the formation of clusters. On the one hand, the countries under the average, almost all located in southern Europe, eastern Europe and the Balkans, have a GDP budget for STI under 2% (the exception made to Slovenia slightly above that mark). These are, in general, the countries with lower GDPs requiring different management of their state finances compared with the other half of the countries, above the EU average. The most concerning budgets for STI are in the graph's tail, where Eastern European countries such as Ukraine, Romania, Latvia or Bulgaria are recent democracies and are still looking forward to building their STI investment to surpass the 1% mark.

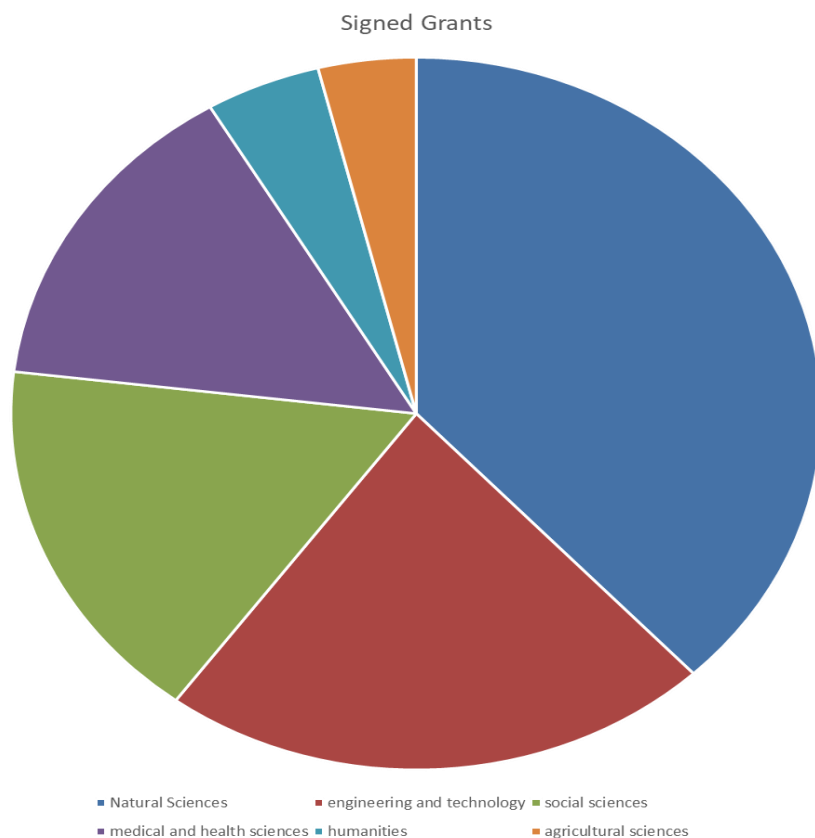
On the other end of the spectrum, the top of the graph (excluding Israel) showcases the success stories of EU countries with significant investment in STI. Belgium, Sweden, and Austria are among the countries that have a more robust allocation of their GDP to science. They are not only keeping pace with nations known for their advocacy of technological and industrial progress within the EU frameworks, such as Germany and France, but also setting new standards (Wien Büro, 2015). The Nordics and the Netherlands, with their dense investment in STI between 2% and 3%, are leading the way. Their competitiveness in the field is evident in the recombinant patents graph, with the Netherlands and Denmark securing third and fourth place in patent production in the recombinant area, respectively.

This graph mirrors a European Union with two different development paces. The differences between the two sides of the table tend to keep augmenting, while the countries with stronger scientific infrastructures continue to devote more GDPs to STI research.

The EU's investment in STI can also be split into research areas to gain a more profound understanding of the EU innovation programmes' priorities. This chart represents six dimensions: Natural Sciences, Engineering and Technology, Social Sciences, Medical and Health Sciences, Humanities, and Agricultural Sciences. The larger portion of the investment goes to the Natural Sciences, capturing around 40% of the total funding allocated to STI. Behind this substantial investment are reasons that follow the Agenda 2030, the EU Green Deal and the SDG values, aiming at tackling issues related to climate change, environmental protection and biodiversity conservation. There is an urgent need to advance scientific research to mitigate the potential aggravation of these global problems impact.

Engineering and Technology, the second-largest beneficiary of EU innovation funding, is crucial in driving future economic growth. This sector is instrumental in translating the resources derived from the Natural Sciences into practical applications. Medical and health sciences, despite not being at the top of the EU investment list, are also receiving significant attention. Their importance has been underscored since the 2019 pandemic, underscoring the need for stronger international relationships in the health sector.

Figure 20. STI Grants Signed in the EU 2023 by Field



Source: Own elaboration based on EC-OECD STIP Compass data

The distribution of EU investment in STI underscores the need for a more balanced approach. While the Natural and Medical Sciences rightly require substantial funding for infrastructure and research tools, the EU also recognises the importance of the Social Sciences and has been encouraging funding for trans-European and transdisciplinary research projects. However, the Humanities have been relegated to a residual funding amount, and the Agricultural Sciences warrant serious consideration from the decision-makers setting EU innovation priorities. Agriculture is at the forefront of defending ecosystems, conserving biodiversity, and ensuring the long-term sustainability of the EU. These are current challenges that the Natural Sciences are striving to address. The lack of funding for the Agricultural Sciences could impede the practical application of some of the findings achieved in other areas with higher levels of EU investment.

6.5 An Ever-changing Biotechnology European Research Ecosystem

This section explores the relationship between recombinant technology publications, patents, and the networks formed to build the know-how for such innovation within the EU.

There was a shift in DNA engineering scientific innovation in Europe in the 80's and 90's of the last century. The upbringing of patents in biotechnology, as a main source of diffusion and exploitation of science, turned recombinant into a priority of the sector's commercialisation actors, against the field's initial goals, which were purely scientific (Wright, 1986). The priorities changed from understanding a complex biological system and applying gene manipulation techniques to improving the organisms to a focus on the economic significance of the sector. This dynamic fomented the partnerships between public research institutions and industrial settings and a transition in its applicational and commercial goals (Khush, 2017).

The build-up of new inventions in the recombinant sector in the first trends for commercialisation around the '90s was based on an extensive publication body of literature on DNA engineering. The publication-patent ratio was highly favourable to the publication's shifts, showing an academic predominance in the field. Around this time, the EU knowledge on recombinant transition became widespread, and countries that were falling behind in the technological development in the EU turned into competitive scientific ecosystems in the field, such as Italy and Spain. These countries joined a biotechnology field in the EU, which was dominated then by partnerships in Northern European countries with the likes of the Netherlands, Germany, Sweden, and the UK. Meanwhile, the distribution of patent applications by the end of the '90s was concentrated in Germany and the UK. The differences between the northern european countries and southern european countries regarding patent applications and registrations perfectly illustrate the uneven distribution of scientific innovation in the recombinant sector during the second half of the 20th century.

At the same time, the companies that played a significant role in EU patent registration are the Dutch-based company Philips, followed by Hoffman La Roche, the ICI, Glaxo and Ciba-Geigy. This list emphasises the synergies between the chemical and pharmaceutical fields once all the companies mentioned in this list (except for Philips, which has a broader technological scope) are dedicated to finding pharmaceutical solutions through innovative products.

The UK had a slightly different model of innovation management. In the British case, the most prolific entities in the patent market are connected to government institutions and private enterprise collaborations. The Medical Research Council and the British Technology Group work closely with academic environments to turn scientific innovation into commercialised products, getting a dominant position in the medical field. In the biotechnology sector, Diamond Life Sciences and British Biotech have also registered a high level of patent registration since the beginning of DNA engineering.

7 Conclusion

7.1 What have we learnt?

The Animal-to-Recombinant transition, a technology with immense potential in the global scientific field and its commercialisation, is still in its developmental phase. However, the path taken by the European Union is promising; the increasing investment in recombinant biosensors and R&D is leading to a rise in the number of patents production, peaking in 2023 and showing a tendency to keep growing in the following years.

The models of partnership between institutions have become more diversified over time, fostering a global effort. The countries, based on their respective models of R&D management, have been increasing their investment in more disruptive technology and have been doing it to build partnerships between SMEs and larger companies, national universities and SMEs, institutions for research management and international universities and many more. All these models have successful examples and show that there is no one-size-fits-all receipt to push forward the technology advancements in the field. It always depends on a path dependency structure of the R&D investment that conditions the way science is produced and how it is made available in the market in every country. The EU investment tools are becoming more aware of distributing its STI based on the needs of every country, and the distribution of patent production within the EU is becoming widespread throughout the EU and its partners.

The obstacles mentioned by the SME enterprises in the field are related to the lack of social engagement with animal-friendly products, the high prices of specialised machinery to work DNA sequencing, the expensive facilities and the intense competition between scientists inside the same field. Moreover, there are cases when fields where genetically modified plants were cultivated were destroyed due to natural conditions or related circumstances, leading to a delay in the research on recombinants. Detailed descriptions of these factors present a social skepticism towards GMO products or non-animal organisms. The concerns related to cloning and its ethical implications might undermine the successful launching of a new product to the general public. Therefore, it does require a longer bureaucratic effort to be introduced in the EU, as seen in a previous section. After that, it faces a lack of social engagement outside the R&D environment.

The heavy machinery required for research and product development in the recombinant field is expensive (Carlson, 2003), and for SMEs, it takes work to fund the acquisition of one. Therefore, most SME labs need more equipment to automate DNA sequencing. This is a financial burden that SMEs have to carry in their first investments; the level of specialisation and cleanness of the facilities turns it into a business model with a bulky price. A reduced number of specialised machinery increases the competition between scientists from different enterprises and inside the same company. A job market for science where patent attribution is decisive in future employment prospects creates tension between peers that might do more harm than good in the long run (Van Looy et al., 2016).

While posing challenges, the research niches mentioned above also present opportunities for more intricate findings. The fragmentation of knowledge in the chemistry area can be overcome through interdisciplinary collaboration. Integrating different methodologies, theories, and methods, even with the added complexity of the business perspective during the commercialisation stage, can lead to groundbreaking discoveries. Establishing interdisciplinary departments and research centres in academic settings is a beacon of hope, a clear sign of the industry's recognition of the need for improved synergies between natural and social sciences (Sanz-Hernandez et al., 2019).

The role of big enterprises should be critically examined. The dominance of almost monopolistic health tech companies can stifle the entry of new SMEs into certain market sectors (Rikap and Lundvall, 2022). While advantageous for these companies, the established processes of knowledge sharing, bureaucratic agreements, and consolidated partnership networks can create an uneven playing field. It is crucial to ensure that while these companies are not jeopardized, opportunities are also opened up, particularly in more creative sectors, for new SME enterprises. This will foster innovation and ensure a diverse range of R&D techniques and perspectives in the market.

Moreover, a long way has been trilled since the first DNA engineering experiments, and the ethical concerns that raised some issues with the users of these products are also being tamed. The recombinant transition requires a citizen science effort logging for a change in how people perceive sustainability and how recombinant and biosensors work and how scientists perceive the socio-economic impacts of the technology. The effort made by the WHO to bring science close to the people and to limit the legal framework of how GMOs are being produced is a trust-building measure to democratise the use of such technology. The goal is to evolve towards putting these devices to good use by fragile communities, in need of assistance in healthcare or for agricultural means.

The biosphere has become a more sustainable arena without the use of animal experiences to produce scientific achievements in the DNA field. Recombinant technology's social, ethical, economic and political dimensions are evolving towards an entire epistemic community dedicated to this transition. However, the EU must solve issues regarding the patenting and intellectual property of the scientific findings. The quantification of science might hinder the establishment of more synergies and collaborative projects within the EU. There is a constant pursuit of immediate results to guarantee future funding, which can hurt the overall goal of the transition to more sustainable and cost-effective models of recombinant DNA.

The opportunities in the field are increasing, and most of the challenges have been gradually tackled by the EU's new research agendas and Green Deal. This progress should reassure the national and transnational institutions about the future of technology. Now, what is required is a continuous effort to maximise the production of the publication within the EU to build a broader knowledge base for future experiments on the recombinant transition and guarantee that the public investment in the field keeps growing to stimulate the creation of innovation ecosystems based on partnerships with several helices, which are the foundation for the upbringing and evolution of biotech SMEs in Europe.

7.2 Policy Recommendations and Future Research Path

The EU's Innovation Agenda is increasingly open to high-risk, high-reward research projects, presenting a promising future for the biotechnology sector. Start-ups and associated research centres should seize this opportunity to value their intellectual assets and explore the potential to advance the recombinant scientific field. This bold approach could lead to groundbreaking innovative products that turn EU investment into competitive global products. The resulting top-notch innovation will attract big companies, leading to more revenue and significant future funding from the EU. However, this must be complemented by close synergies with national institutions of R&D management, which have been instrumental in creating national and international networks of research and biotechnology.

The biotech SMEs might conquer something rarely achievable: combining exceptional advances in tackling social and environmental sustainability issues while supporting a profitable business model. This must consider the balance between public and private sources and ensure that these investments allow for a triple helix collaboration that has contributed to some of the most successful models of Recombinant DNA patenting with larger enterprises.

The growth of the GDP invested in STI and in promoting multiple partnerships within different institutional configurations for the recombinant DNA field must be balanced with public awareness and the need to preserve the ecosystems where this technology will be applied. Biotechnology policymaking in the EU must continue to promote the triple helix dynamics, as we have seen throughout this deliverable, how scientific and commercial partnerships have evolved from university-private enterprise models. However, the biosphere and the social sphere are becoming more and more decisive in defining the level of engagement, and a proof-of-concept needs to be approved in a specific market. Therefore, the EU, which now has good involvement with universities, private enterprises, and government entities, should look further towards a long-term quadruple or quintuple helix—merging the technology with the solutions to the factors that have hindered the EU to become more competitive in the biotechnology market.

This includes a model of technology transferring and knowledge interchange based on building social capital (the quadruple helix) and natural capital (the quintuple helix). Regarding natural capital, partnerships such as the one between Bayer and the Brazilian Research Centre for Agricultural and Livestock Management are examples of how adaptation to specific ecosystems can strengthen the technology being produced.

The principles of green chemistry and environmental conservation awareness are of utmost importance when developing innovative products in the agricultural or plant genetics fields. The protection of the population of users of such technology can drive this natural capital. Finding solutions to drop the social barriers and increase people's comprehension of the products and how those can be put to good use in their daily lives is a dimension that requires structural investment from the EU agendas. Funding allocation to citizen science, to the social sciences in consortiums mainly constituted by natural sciences institutions, to deliberative decision-making, and to customer engagement are essential to overcoming the challenges of the biosphere. This becomes even more crucial when the recombinant transition becomes more widespread, broadening its possible applications and device formats.

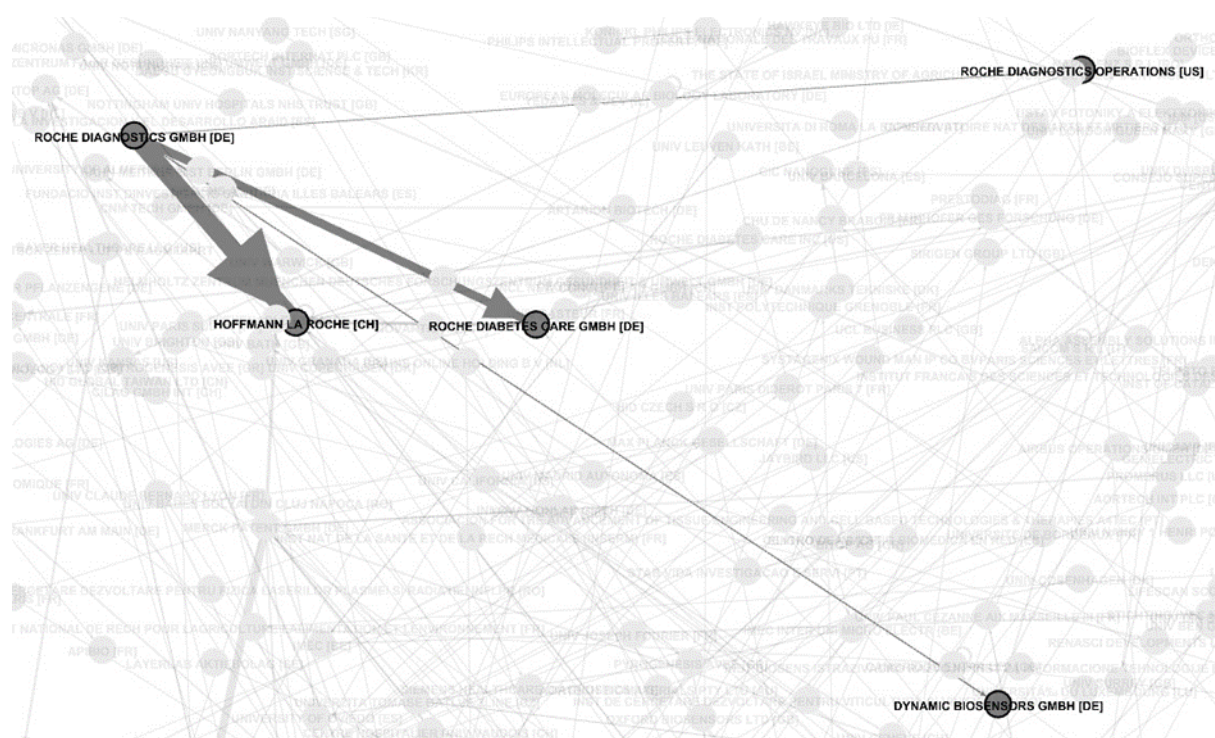
Appendix

Figure A1. Expenditure for R&D in Germany (by region)

<i>Länder</i>	Internal expenditure for research and development (million euros)			GDP share in %		
	2016	2017	2018	2016	2017	2018
Baden-Württemberg	23 451	27 910	29 179	4.93	5.64	5.68
Bavaria	18 059	18 704	19 689	3.13	3.11	3.19
Berlin	4 552	4 758	5 111	3.42	3.42	3.51
Brandenburg	1 159	1 195	1 220	1.73	1.71	1.70
Bremen	912	909	947	2.90	2.82	2.88
Hamburg	2 513	2 500	2 635	2.27	2.17	2.22
Hesse	7 752	8 182	8 622	2.85	2.94	3.02
M.burg-W. Pomeran.	759	785	810	1.85	1.79	1.81
Lower Saxony	9 156	8 928	9 316	3.27	3.12	3.13
North Rhine Westphalia	13 231	14 336	15 189	2.03	2.13	2.19
Rhineland-Palatinate	3 374	3 498	3 680	2.47	2.50	2.56
Saarland	534	619	624	1.56	1.76	1.75
Saxony	3 203	3 400	3 595	2.74	2.81	2.89
Saxony-Anhalt	860	919	980	1.46	1.52	1.59
Schleswig-Holstein	1 342	1 448	1 556	1.53	1.58	1.64
Thuringia	1 225	1 362	1 424	2.07	2.23	2.29

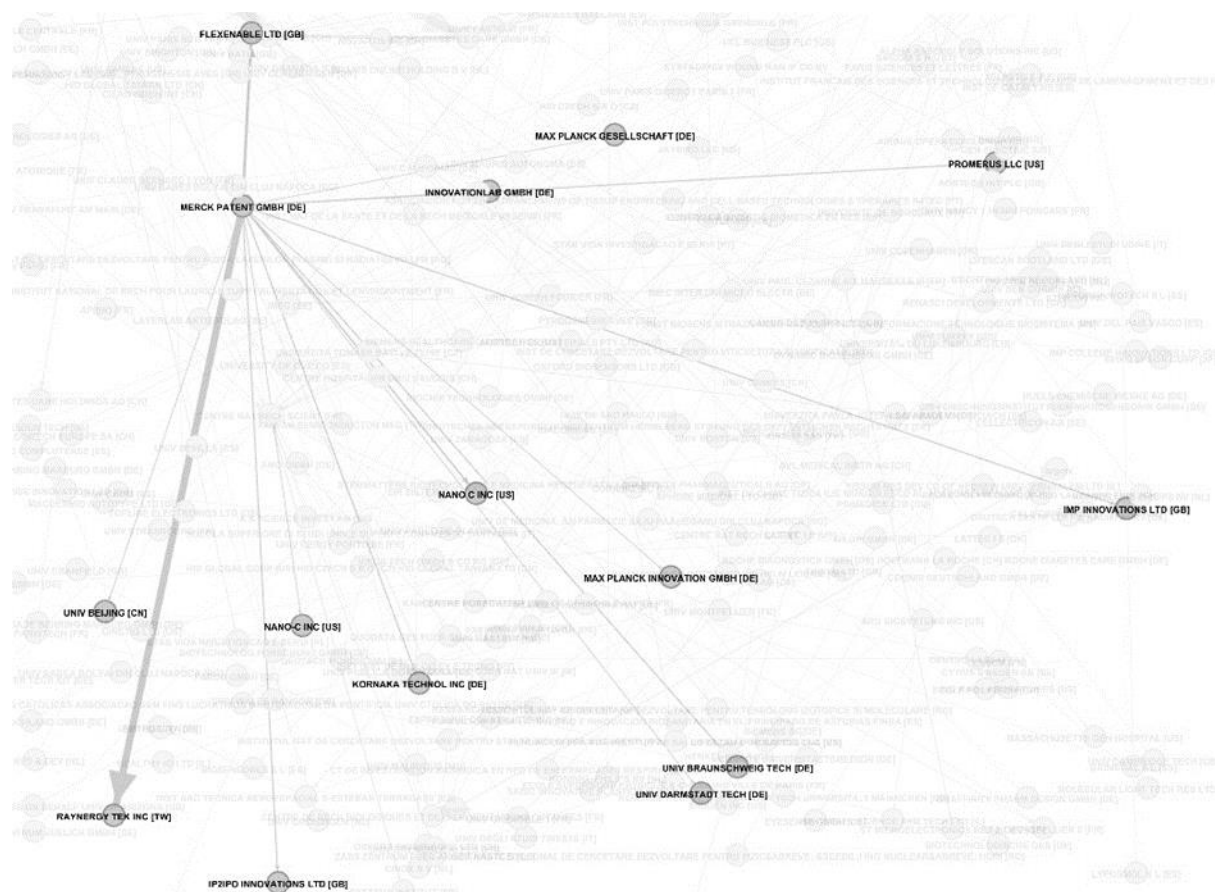
Source: OECD data

Figure A2. Hoffman La Roche's Biosensors Innovation Network



Source: Own elaboration (Gephi) based on European Patent Office data

Figure A3. Flexenable's Biosensors Innovation Network



Source: Own elaboration (Gephi) based on European Patent Office data

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CENTRE NAT RECH SCIENT [FR]

INST NAT SANTE RECH MED [FR]

Source: Own elaboration (Gephi) based on European Patent Office data

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