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REVIEW



Treatment innovation for patients: a collaborative network in the Benelux and an inside view of 20 years of Galapagos

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ABSTRACT

A better understanding of disease pathology, improvements in relevant disease outcomes, better treatment strategies and the development of novel therapies all contribute to improving healthcare and treatment options. However, the global drug development model today is under increasing pressure, with very high drug development costs. Collaborative research is critical for bringing together different capabilities and expertise to increase the success of drug development, and large-scale collaborations with multiple partners are becoming increasingly common. Research clusters supported by local governments play an important role in bringing together academic centres, hospitals, scientists, and pharmaceutical and biotechnology industries. The 'triple helix' model, with academia, industry and governments working together, has been an important factor in the successful development of novel therapies. During the past 20 years, Galapagos has worked closely with academic centres, hospitals, governments and pharmaceutical companies to conduct innovative research and to develop a novel therapy for rheumatoid arthritis. These collaborations have brought unique knowledge, expertise and skills together, as well as crucial funding at various stages. Local governments in the Benelux have operated in this triple helix model to provide the necessary environment and to stimulate companies to achieve innovation through collaboration. Although the triple helix has already proved successful, evolution to a quadruple helix that includes patients and patient representatives could be the next step to ensure innovation remains transformational.

KEYWORDS

Innovation; collaboration; research and development; triple helix

1. Introduction

Over the last few decades, important progress has been made in providing therapy for patients with diseases previously seen as very difficult to treat and with high morbidity and mortality. A better understanding of underlying pathology, improvements in relevant disease outcomes, better treatment strategies and the development of novel therapies have all led to a better quality of life for many patients, including those with rheumatoid arthritis (RA). Nevertheless, the global drug development model today is under increasing pressure. The cost of developing a new molecular entity (small-molecule compound) or a new biological entity (antibody, protein, gene therapy or other biological medicine) up to the approval phase has been estimated to be US\$2.6 billion, on average [1]. It takes about 12–15 years to develop a new drug entity from early discovery to registration (Figure 1), and the risk of failure is high, with an estimated success rate of only 10% of those entered into clinical development [2].

Often, basic research from academic centres will increase knowledge of disease pathways and generate insights that can be developed further by industry through the different phases of drug development, leading to a new medicine. However, such a segregated approach remains suboptimal for meeting increasingly demanding research and regulatory requirements, as well as for transformational innovation of novel therapies [3]. Collaborative research is vital for bringing together different capabilities and expertise to increase the success of drug development [4,5].

Collaborations are indeed becoming increasingly common but usually tend to be small scale and involve only two parties, such as an individual academic institute or a healthcare organization in conjunction with an industry partner. For example, in the field of rheumatology, the discovery of the first fully human antibody drug adalimumab by Cambridge Antibody Technology (CAT) was through collaboration with the Medical Research Council and the Babraham Institute in Cambridge, UK. In recent years, a transition to large-scale collaborations has been observed across the biomedical and

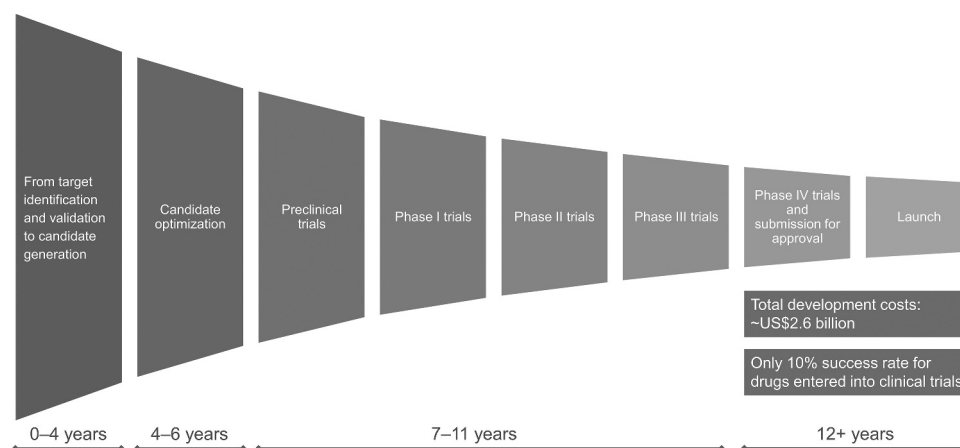


Figure 1. The drug development process is long and complicated with a high risk of failure.

pharmaceutical industries leading to centres such as the collaboration between Imec (research in nano and digital technology) and Janssen Pharmaceutica in the Benelux [6]. Collaborations with more than two stakeholders often fall within the ‘triple helix’ model comprising academia, industry and government [7].

Triple helix collaborations are considered critical to overcome the innovation deficit and to bring novel discoveries to the patient [8]. A recent European Union (EU) report highlighted that researchers from across academia, healthcare and industry must work towards an environment that nurtures innovation and supports the sharing of expertise, capabilities and early-stage research data [9]. For collaborations to be effective and productive, appropriate processes and governance frameworks need to be established. By enabling and stimulating the different sectors with financial incentives, governments have the opportunity to be a key element in innovation and collaboration. As such, government investments have the potential not only to create job opportunities and investments but ultimately to benefit patients through innovative therapies that would not be possible without extensive collaboration.

In the Benelux, with a population of approximately 28 million, a unique ecosystem has been developed, with multiple world-class academic and research centres. Belgium and the Netherlands combined have 13 academic hospitals, over 200 hospitals providing high-quality patient care, more than 10 private or hospital phase 1 units, in excess of 500 small- and medium-sized enterprises (SMEs) in healthcare, larger companies, more than 20 venture capital funds actively engaging with start-up companies and at least 10 business incubators active in life sciences. All of these hospitals, companies, institutes and agencies operate in close proximity, facilitating collaborations and the exchange of ideas.

In addition to academic centres and biotech science parks, cluster organizations – such as *flanders.bio*, *BioWin* and *Bio.be* in Belgium and *Health~Holland* and *HollandBIO* in the Netherlands – play an important role in supporting the triple helix by organizing network events and advocating for collaboration. The Flemish government (of the Flanders region in Belgium) was instrumental in the establishment of *flanders.bio* and supported the network organization with more than €2.5 million in the first 5 years. These clusters with support of local governments are hugely important for bringing together academic centres, hospitals, scientists, and pharmaceutical and biotechnology industries. By working closely together, each partner has the opportunity to bring their knowledge and expertise to each stage of drug development, from translational research through to clinical studies.

2. The triple helix: an ecosystem of academia, industry and government

Belgium and the Netherlands both have a strong research and development (R&D) ecosystem, consisting of world-class academic research, high-performing healthcare systems with high standards of patient care and a strong and lively industry presence comprising a dynamic mix of start-ups, SMEs, and pharmaceutical and biotechnology companies.

The Flemish government has developed extensive measures designed to incentivize the collaboration between industry and academia for the benefit of transformational innovation, because ultimately, patients will benefit from novel therapies resulting from combining the knowledge, skills and tools available in these different sectors. A scheme known as Belgian Innovation Income Deduction has led to an influx of pharmaceutical and biotechnology companies into the region, particularly benefitting Flanders [10]. The scheme provides a tax deduction of up to 85% of revenue from patents, creating an incentive for

pharmaceutical and biotechnology companies to establish themselves in Flanders and to collaborate with academic institutes to develop innovative therapies [10]. Further incentives include tax deductions and exemptions specifically focused on R&D investments and employment, aimed at attracting the best and brightest scientists.

R&D grants from Flanders' Agency for Innovation and Entrepreneurship (VLAIO), with a subsidy rate of almost 60%, have played an important role in the establishment of new consortia working on highly experimental and risky targets. Following EU state aid rules, VLAIO aims to give the maximum allowed subsidy. This subsidy programme is stable and there have been no major changes in the R&D grant system over the last 20 years, making the Flemish government a very reliable partner. The creation of the Flanders Institute for Biotechnology (VIB), a research institute linked to five Belgian (Flemish) universities, was initiated by the Flemish government as part of their ongoing efforts. The VIB has a strong focus on translating scientific results from basic research into pharmaceutical, agricultural and industrial applications [11]. The VIB has become an integral part of the Flanders ecosystem and encourages the quick and efficient translation of scientific inventions into viable products or therapies [11,12].

Academic centres in the Benelux are known worldwide for their extensive expertise in clinical trials. In particular, the fast review and approval of clinical trials in Belgium have been an important cornerstone of clinical research for many years. Whereas new EU clinical trial regulations impose harmonization of approval timelines for all multi-country clinical studies [13], Belgian law stipulates a 15-day approval time for national Phase 1 trials, guaranteeing fast review and approval of Phase I studies performed in Belgium [14,15]. Traditionally, most clinical trials are sponsored by a pharmaceutical company. To also stimulate large investigator initiated research focusing on strategy trials and cost-effectiveness studies, the Belgian Health Care Knowledge Centre (KCE), a governmental organisation, set up a programme to provide advice and funding [16]. This programme is part of a close international collaboration between the Belgian KCE and the Dutch Organisation for Health Research and Development (ZonMw) [17,18].

Overall, the financially, scientifically and clinically stimulating ecosystem in Flanders is a substantial contributor to the fact that Belgium has the highest percentage worldwide of biotechnology R&D investments [19].

The government in the Netherlands has opted for a different approach to that of Belgium: in the Netherlands, the Top Consortia for Knowledge and Innovation (TKI) are at the centre of cooperation between academia, industry and government.

Operating in the triple helix model, the Dutch government stimulates collaboration between academia and industry by adding 30% to each Euro invested by industry in public-private R&D projects [20]. In addition to this allowance, the government also provides tax benefits for investments (including employment benefits) in the R&D sector. Significant investments have been made in the Netherlands, with the emergence of large science parks in close proximity to academic centres. For example, the Leiden BioScience Park and the Amsterdam Science Park allow innovative start-up companies to connect emerging talent with cutting-edge science easily [21,22].

In this overview, we describe how a government-supported ecosystem aimed at encouraging innovation contributed to collaborations between Galapagos (a biotechnology company founded and headquartered in Belgium, with R&D operations in Belgium, the Netherlands and France), academic and medical centres in the Benelux and regional governments. We also look ahead to what can be done to encourage innovation through collaboration further.

3. Galapagos and filgotinib

Founded in 1999, Galapagos NV (Galapagos) is a biotechnology company with a strong presence in Belgium (headquarters in Mechelen), the Netherlands (Leiden BioScience Park) and France (Romainville). Throughout the past 20 years, part of Galapagos' innovative research can be linked to the R&D ecosystem in the Benelux.

In its early years, Galapagos primarily conducted fee-for-service research, operating R&D activities on behalf of clients, using a technology platform investigating novel mechanisms of action. This proprietary platform for target discovery provides a significant advantage in identifying potential drug candidates with novel modes of action [23]. The target discovery platform closely mimics the situation *in vivo*, with relevant trigger and readout for a specific disease phenotype through the use of primary human cells from patient samples provided by academic centres and biobanks [23]. A collection of modified adenoviruses acts as the vector to introduce short hairpin RNAs that will knock down specific disease pathways. The collection covers approximately 6000 drug targets, and the screening of this collection allows rapid analysis of the druggable genome by the function of each target in a disease. Galapagos has been operating this target discovery system since 2003 and has been able to select pharmaceutically tractable protein targets directly by their ability to regulate key disease biology [23]. In the early stage, the Flemish government supported Galapagos to develop its proprietary discovery platform, and in the first 5 years, the company received

€8 million of non-dilutive funding from VLAIO, making VLAIO a key collaborator for the company.

Galapagos invested the revenue from their fee-for-service model in its own R&D activities, but an additional approach was needed to expand their drug development further. Galapagos was able to achieve this thanks to the supportive surrounding ecosystem for collaborations and partnerships in the Benelux. From the beginning, Galapagos fostered relationships with leading academic researchers and rheumatologists. Academia was involved through an advisory board to assist with the design of the first RA trials at a time when the company did not yet have any in-house expertise in organizing clinical trials. This early collaboration between clinicians and Galapagos researchers focusing on clinical study design allowed for the fast conduction of a Phase 2 clinical study in patients with RA [24]. The academic and clinical input into the specific design for this trial allowed for timely conclusions to be drawn while minimizing unnecessary patient exposure. Long-term collaborations have ultimately led to innovations that go beyond a single study or project. Current, long-standing collaborations include top academic centres such as the Catholic University of Leuven (KU Leuven), Leiden University Medical Center (LUMC) and University of Louvain (UCL) in Brussels.

Galapagos' discovery and development of filgotinib for the treatment of patients with RA is an example of an efficacious, innovative therapy resulting from the successful collaboration. However, the long road to drug development required various partners along the way. As a key collaborator, VLAIO supported Galapagos at this research stage, with approximately €4.5 million in non-dilutive funding. In 2003, Galapagos developed assays for inflammatory disorders, based on patient cells and expertise obtained from academic collaborators in the Netherlands and Belgium. This led to the discovery that the family of Janus kinases (JAKs) plays a key role in inflammatory disorders. Galapagos discovered that one specific member of the JAK family, JAK1, is primarily responsible for the inflammatory effects. As such, research was targeted at the development of a chemical compound with specific JAK1 inhibitory activity. Collaborative efforts were subsequently focused on the development of filgotinib, a selective JAK1 inhibitor for RA.

In 2006, a large pharmaceutical partner was needed to continue developing filgotinib and to move forward with preclinical candidate testing. Before the start of Phase 1 trials, however, collaboration with this first pharmaceutical partner ended because of the perceived risks. Nevertheless, Galapagos started a Phase 1 trial in 2010, followed in 2011 by a proof-of-concept study including patients. A new partner was found in 2012 to allow Galapagos to progress to large Phase 2 and Phase 3 studies. DARWIN 1 and DARWIN 2 were

the first large Phase 2 trials conducted by Galapagos [25,26]. As with the previous trial, the trials in the DARWIN program were designed and developed in collaboration with academic researchers and clinicians.

This second collaboration also ended prematurely, for similar reasons, after completion of the DARWIN trials, and a third partner was needed to continue with the Phase 3 trials (FINCH 1, FINCH 2 and FINCH 3), as well as to progress to the commercial phase [27–29]. As such, Gilead Sciences, Inc. (a US-based biopharmaceutical company) and Galapagos have been developing the later phases of the programme together. The Phase 3 trials showed that filgotinib significantly improves signs and symptoms in individuals with RA at various stages of the disease. Both doses of filgotinib demonstrated favourable benefit–risk profiles, with low rates of treatment-related adverse events (such as serious infections, herpes zoster infection and deep venous thrombosis or pulmonary embolism) [27–29]. This finally led to submission for marketing authorization in Europe, USA and Japan, which is expected in 2020. In the second quarter of 2020, Gilead and Galapagos announced positive Phase 3 data for filgotinib in patients with the inflammatory bowel disease ulcerative colitis (UC), the second indication for filgotinib.

As described earlier, only a small proportion of potential novel therapies get through development, clinical trials, market approval and ultimately reach patients, and strong collaborations have been a cornerstone of the development of filgotinib. The difficulties in finding suitable industry partners throughout the drug development and the associated delays in R&D highlight the importance of the triple helix system.

This example clearly demonstrates both the financial risk involved in developing innovative therapies and that the driving factors behind innovation have historically been academia and (small) biotechnology companies. Major pharmaceutical concerns tend to be more risk-averse, as illustrated during the development of filgotinib when two partners discontinued their collaboration with Galapagos. In addition to vital long-term academic collaborations for drug development, the continued collaborative effort with Gilead is now key to help to bring filgotinib to patients.

After nearly 20 years of extensive collaborations and partnerships since the very start of the journey of target discovery, filgotinib has now been submitted for marketing approval. The knowledge and expertise brought in through these collaborations have been key in reaching this milestone for filgotinib, but the financial investment should not be overlooked. Meanwhile, the use of filgotinib is being explored in other indications, including Crohn's disease, psoriatic arthritis and ankylosing spondylitis. An estimated total of €2.5 billion will be required from the first discovery all

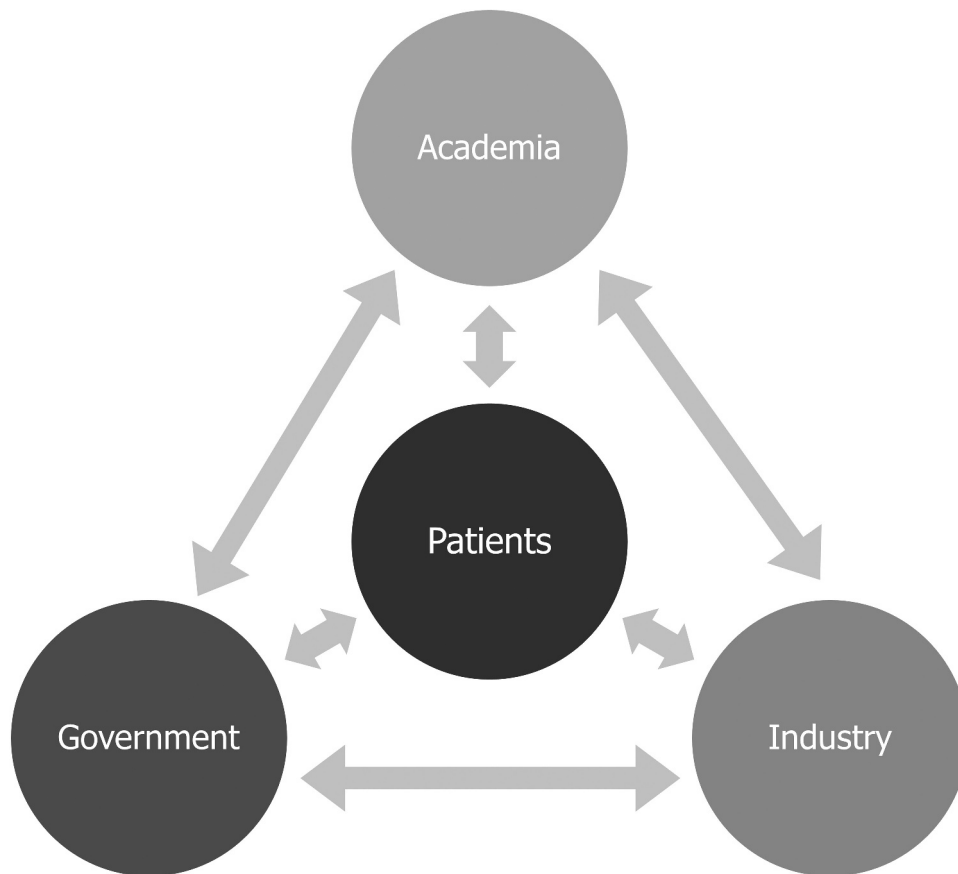


Figure 2. The quadruple helix, which includes patients at the centre of collaborations.

the way through to its availability for patients with rheumatoid arthritis, though this estimate also includes the ongoing development of filgotinib for other disease indications. Investments of this magnitude are not possible for a small company or academic centre. Large, continuous investments are needed from other partners and from government support. During the past 20 years, Galapagos has received €38 million in non-dilutive financial support from VLAIO, including €8 million for development of the discovery platform, and almost €5 million for R&D related to filgotinib. This support from government agencies has translated into substantial investments from Galapagos over time anchoring its presence and activities in Belgium.

Reaching this significant milestone leads Galapagos into a new era. For the first time, Galapagos is entering into the marketing and commercialization phase. During the next part of the filgotinib journey, collaborations and partnerships with academic institutes and clinicians will remain important cornerstones. Additional data collected in real life via Phase 4 studies, registries or investigator-initiated research will help to address remaining data gaps and can provide guidance for correct use [30]. The innovative approach demonstrated during the discovery and development of filgotinib should also be maintained during the commercialization phase.

The growth of Galapagos has been linear with the development of filgotinib. Galapagos began as a small start-up focused around their target discovery platform. As the development of filgotinib evolved, other capabilities and departments were created, ultimately resulting in the current, fully integrated biotechnology company with end-to-end in-house capabilities, from early discovery to commercialization.

Evidently, drug development is a long road, starting with drug target discovery, through preclinical testing, clinical pharmacological investigations and proof-of-concept studies, and culminating in large-scale Phase 3 trials. Making it all the way to regulatory approval is fraught with uncertainty. This is exactly why large-scale and, perhaps more importantly, long-term collaborations between different institutes and companies are so valuable, and why continued support from all sectors, including the government, is so essential to maximize available expertise, minimize risk and increase efficiency. Thanks to the ecosystem in the Benelux region, companies such as Galapagos can continue their collaborations with academic institutes, hospitals and pharmaceutical partners, ensuring that the right partner is selected for each discovery so that efficient and timely clinical trials can be conducted.

4. Lessons learned and future directions

The Department of Economy, Science and Innovation in Flanders, Belgium, is suggesting a next step to stimulate innovation: to move from the triple helix to a 'quadruple helix' [31], which would incorporate citizens and target audiences (Figure 2). Likewise, the European League Against Rheumatism (EULAR) recommends the inclusion of patient representatives in scientific projects [32]. The King Baudouin Foundation has gone even further in their recommendations, stating that a move is needed from a system of informal recognition and funding to a more formal arrangement, with the necessary political support, for patient associations to be more effective in their social role [33]. This would transform the innovation process into a fully collective process, in which patients are part of the development of innovative therapies. Ideally, the inclusion of patient organizations in drug development should be done at an early stage, ensuring that unmet patient needs are incorporated from the discovery phase onwards and that patient-important outcomes are central. Including patients and patient advocacy groups at the start of drug research would hopefully benefit the development of successful novel therapies. EU regulation further requires clinical trial sponsors to provide summary results of their trials in a format understandable to laypersons, which may increase the opportunities for collaboration with patient representatives [13]. Patient involvement in the drug life cycle remains challenging, and gaps remain between theory and practice, as shown by a recent Belgian survey [34]. Involving patients and patient perspectives in the design of studies that include patient-reported outcomes is an important step [35]. In this example, patient involvement was in line with EULAR recommendations. In addition, patients have been trained as 'research partners' in an initiative from EULAR, and ReumaNet (a Belgian patient organization for rheumatic diseases) and the Koninklijke Belgische Vereniging voor Reumatologie (KBVR; Royal Belgian Society of Rheumatology) have implemented this in Belgium. Future studies should not only include patient-reported outcomes but focus more on patient-important outcomes, i.e. outcomes that are valued by patients and make a difference in their daily quality of life. Organising the quadruple helix is necessary to address patients' unmet needs and to create the required organizational and legal frameworks so that patients can fully collaborate with companies and authorities at every stage of the drug development life cycle.

Involving the key collaborative stakeholders at the right time is essential to avoid slowing down drug development. As shown in Figure 1, the drug development process is long, complex and costly, therefore it could be argued that all relevant parties should be

included as early as possible, to optimize available knowledge, expertise and funding. For example, relevant authorities may be vital at an early stage to validate patient-reported outcome measures for access and reimbursement purposes. Authorities could also play a valuable role to ensure innovative treatments enter the healthcare system and reach the patient early. The Belgian government has created an annual priority list of rare diseases or diseases with high unmet need, with the aim to have a program in place stimulating research in these fields providing early access and early treatment reimbursement. The criteria for this priority list are based on unmet healthcare needs of patients and society [36]. A current challenge where the government could play an important role is to encourage further research into the use of existing medications in additional (rare) indications.

Collaboration with clinicians remains important during the continuous life cycle of a drug, for example, by collecting adverse events and collecting real-world evidence, via investigator-initiated research or in co-creation during the set-up of medical education programmes. The challenge is to continue with an innovative collaborative approach during all phases and to gain as much information as possible from all partners and loop back to R&D and incorporate into new drug development. For example, real-world clinical data from patients enrolled in a compassionate-use programme can help to detect safety signals, whereas information from patients with therapy resistance can provide valuable insights for target discovery and initiate a new drug development process.

Finally, the commitment from partners should not be underestimated, nor should the motivation – that comes from collaboration – to not give up when you hit a bump in the road. A novel finding does not automatically lead to a success story if there is no passion and belief, which are needed to get other partners in the innovation process fully on board and to continue with determination.

5. Conclusion

Collaboration across sectors is both key to success and necessary to address the need for innovation and increasingly demanding research and regulatory requirements [3]. The ecosystem that has been developed in the Benelux region comprises five key factors: a consistent financial and reliable grant system, cutting-edge academic research, access to patients and patient data, proximity of industry partners in clusters, and financial or tax incentives. These factors have led to a major influx of R&D activities and companies in life sciences, pharmaceutical and biotechnology industries, which will ultimately benefit the patient with innovation through collaboration [10]. The Benelux

R&D ecosystem has contributed significantly to the story of Galapagos, and in recent years, it has become evident that biotechnology companies in the region are leading to further transformational innovation. The ecosystem described here has been established to benefit patients and to address many unmet needs that still exist. The examples provided here that have been seen in the Benelux should perhaps be the envy of other countries. As well as novel therapies for patients, major investments made by academia, industry and governments have resulted in job opportunities and economic growth. The continued success of these ecosystems relies upon the commitment and support of all partners involved in the triple or even quadruple, helix; it will require all of these partners and sectors to invest together and to keep pushing for innovation through collaboration.

Disclosure statement

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Conflict of Interest statement

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