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## Original Article

# Biotechnology in the capital region of Europe

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**ABSTRACT** It has never been as challenging in biotechnology as today. Convergence is the key word, forcing alliances between pharmaceuticals and biology, and new economic opportunities arise from the growing interface between biotechnology and nanotechnology, nanobio. The challenges to bring such disruptive technologies to the market are unprecedented, ranging from truly multidisciplinary research to matching totally different business models among the various industries. In Flanders, Belgium, the message has been understood already 20 years ago.

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### FROM SOLVAY TO ABLYNX

Flanders, state in Belgium, lies in the heart of Europe. It encompasses Brussels, capital of the European Union (EU). Flanders is a small state, only 13700 km<sup>2</sup>, about two-thirds the size of New Jersey, USA. The region is home to a tremendous number of European policymakers, lobbyists, regulatory affairs and related offices, but is also home to a fast growing high-tech industry (see Box 1). Being a small state, Flanders has always been internationally oriented, even from the Middle Ages where cities like Ghent, Bruges and Antwerp were continuously on the European map. Today, our most famous painters such as

Rubens, Van Eyck and Breugel are still witnesses to that era. In the past 30 years, the region has become Europe's capital region, with major European headquarters, the European government, NATO and international media such as the *Wall Street Journal*, and in the past 100 years, a hub in science and technology. Perhaps even more known, the region is known for the most famous biotechnology application in the world: its Belgian beers, hosting the Trappist beers and the world's largest brewer ABInBev, so called after Belgian InBev took over US' Anheuser-Bush. This 'traditional' biotechnology industry has thrived since more than 1500 years in this region, mainly stimulated by the monks in the Middle Ages producing excellent cheese, specialty beers and even wine. Gradually, these products became

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**Box I: Flanders**

1. Flanders is located at the center of the wealthiest and most populated area of Europe.
2. Belgium's Top five business attractions: quality of life, quality of the labor market, excellent telecommunications infra structure, stability of social climate and transport and logistics infrastructure.<sup>1</sup>
3. Flanders has four ports, including Antwerp the world's fifth largest, Europe's fifth ranked freight airport, inland waterways and one of the world's highest density networks of road and rail
4. Brussels, capital of both Flanders and Belgium as well as administrative capital of the European Union, is one of the most cost-effective cities in northern Europe with an index rating of 87.2 using New York as the base at 100.<sup>2</sup>
5. The Flemish workforce is productive, multilingual and loyal. With US productivity as the base at 100, Belgian productivity is 109 in GDP per hour worked, ranked number three in OECD.<sup>3</sup>
6. The communications infrastructure is highly developed: 96 per cent of Belgian companies are Internet-connected (70 per cent broadband) compared with the EU average of 89 per cent (53 per cent broadband).<sup>4</sup>

industrialized, and today, apart from a few very specialty products, all cheese and beer are produced by modern manufacturing facilities. Today, these products are not cataloged as biotechnology products, and fall under the food and beverages classification.

Meanwhile, during the past four decades, this 'traditional' biotechnology industry has been increasingly supplemented with modern biotechnology.

The most pronounced pioneer in international high tech in the early twentieth century was without doubt Solvay. Today one of Belgium's forerunners in biotechnology and chemicals, at that time, the multinational company was famous for pushing innovation forward, with the world renowned Solvay Conferences. The most notable was certainly the fifth conference that was held in Belgium in October 1907 on electrons and photons, with leading figures participating such as Albert Einstein and Niels Bohr.

Today, Flanders has one of the most successful biotechnology industries in Europe. The government of Flanders, from its inception with the creation of states in the late 1970s, chose new technologies as the backbone for its industrial strategy: micro- and nanotechnologies, biotechnology and new materials. This resulted in a number of initiatives, ranging from supporting R&D to the availability of venture capital and financial incentives to attract companies from abroad. New highly successful companies have emerged from this strategy, like Ablynx, Tigenix and Thrombogenics.

## A COMPLETE AND DYNAMIC ECOSYSTEM

Flanders hosts around 200 life sciences companies, including over 80 biotechnology, 40 pharma and 40 medical devices companies. Science and technology breakthroughs from three research centers, five universities and a highly R&D intensive industry is continuously translated in commercial success. As a result, more than 90 per cent of all biotechnology companies are R&D intensive. They rely on partnerships with big pharma to further develop their biotechnology drugs into marketable products. Companies such as Ablynx, a developer of nanobodies, a novel class of antibody-derived proteins, work extensively with major pharma companies such as Boehringer-Ingelheim and Wyeth, to finance further development into clinical trials. An interesting example is Galapagos, a biotechnology company that has successfully deployed a hybrid business model. As other relatively small biotechnology companies, Galapagos relies on big pharma to further develop its new drug discoveries. But thanks to these alliances (such as with Merck), they are able to develop in-house a limited number of proprietary drugs, and likely to bring them to market themselves.

One of the flagships of the region, Janssen Pharmaceuticals, one of Johnson & Johnson major research and manufacturing facilities in the world, is a major driver of the life sciences industry in the region. Other bio- and pharma giants in Flanders include Pfizer, GlaxoSmithKline, Genzyme, UCB Pharma

(the largest biotechnology company in Europe), Solvay (that recently acquired biotechnology company Innogenetics), AstraZeneca and Amgen. Together with a very dense network of university and city hospitals and the European headquarters, they are responsible for Belgium's number one position in Europe on clinical trial intensity.

This success has been highly dependent on a number of factors. A sustainable industry needs a full ecosystem ranging from high-quality R&D to the presence of venture capital and an entrepreneurial spirit.

Of utmost importance is a clear, focused and long-term strategy of the regional government to stimulate and support the biotechnology industry. This should be done in all aspects of the ecosystem, including incentives and budgets for R&D, infrastructure, workforce development, incentives and co-financing mechanisms.

Today, the Flemish state is famous in Europe for its excellent R&D climate, actively supporting R&D partnerships and innovation. Through its IWT agency (the Institute for the Promotion of Science and Technology in Industry), companies can submit R&D proposals for product development that result in co-financing of the project up to 80 per cent! In addition, tax incentives are especially supporting R&D activities, such as the R&D staff deduction, allowing companies to deduct up to 75 per cent on the salary withholding tax of R&D workers, or the patent income deduction (taxed to only 6.8 per cent).

## VIB

As part of a large stimulus project, in 1996, the Flanders' Government decided to establish VIB, the Flemish Interuniversity Institute of Biotechnology. This decision was based on the good reputation the region had in molecular biology, from renowned scientists such as Desiré Collen and Marc Van Montagu. Flemish scientists were the first to unravel the chemical structure and functional meaning of a gene and then of a complete genome. They developed the *Agrobacterium*

transformation system, a technique of inserting genes in plants currently used worldwide. With the establishment of the VIB, research at the different Flemish universities became concentrated into one center, that takes care of the research coordination and – equally important – of the commercialization process.

In fact, this project was part of a strategy that the regional government devised in the beginning of the 1980s. At that time, the reform of the country of Belgium came into a new phase in which extensive responsibilities were transferred from the federal level to the regions Flanders, Wallonia and Brussels. In Flanders, the newly established government decided to establish a number of instruments to make the Flemish economy a knowledge economy in the twenty-first century. This action, called DIRV, a Dutch abbreviation for Third Industrial Revolution Flanders, aimed to stimulate three strategic technologies: microelectronics (and later nanotechnology), biotechnology and new materials. From the microelectronics objective came amongst others IMEC, today one of the world's largest nanotech R&D centers (see below). Out of biotechnology came a few years later VIB, the Flemish Institute of Biotechnology.

Today, VIB has become one of the largest independent R&D centers in biotechnology in Europe. With its 1100 scientists in molecular and cell biology, VIB puts breakthrough after breakthrough on its resume, in domains including genetics, cancer, neurobiology, Alzheimer's disease, gene expression and regulation, functional genomics and proteomics, plant systems biology and so on. The business development department is highly developed and takes care of R&D cooperation agreements with for example, large pharma companies and small biotechnology players. If new technology breakthroughs are ready for commercialization into a new technology platform, they become the basis for new bio high-tech companies: Ablynx, Actogenix, CropDesign, DevGen, Pronota and SoluGel. Their activities range

from antibody development over protein biomarker analysis to plant biology.

VIB is mainly a virtual center grouping eight university departments. Instead of physically integrating the Flemish R&D groups into one location, the Flemish Government drew out an innovative concept. The intention of this concept was to strengthen international competition of the Flemish excellence via structural long-term financing and combining competence, while maintaining a close relation with the local university. Specific framework agreements were set up between VIB and each local university to ensure this strategy. Being an administrative office, the VIB staff in the headquarters (HQ) take care of daily management of the center, public relations and public awareness and of business development. An Institutional Advisory Board of prominent international scientists and science managers assists VIB management in its activities. This board is highly independent and does not interfere with the operation of VIB as such. Its purpose is to give direction to the scientific strategies of the VIB departments by giving recommendations, and works as a sounding board for important questions regarding which scientific pathways to take. These recommendations are included in the VIB scientific strategy that is defined by the Group Leader Committee, consisting of one group leader from each department, coordinated by an integration manager from HQ.

As VIB receives an annual grant from the Flemish Government, this investment comes with some strings attached. As stipulated in the management agreement, the Flemish Government has very precisely described expectations of this investment in terms of scientific productivity and industrial and social benefits. As a result, VIB gets evaluated every 5 years on a number of key performance indicators (KPIs). These KPIs are a mix of scientific, economical and societal parameters. They range from the number of scientific publications and citations, the number of invited talks and the number of patents to the

amount of contract research income from industry cooperation and the number of spin-offs generated during the agreement period, to the number of actions taken to educate the general public (for example on genetically modified food). As a measure of its growing success, the Flemish Government decided, on the basis of a highly positive evaluation, to increase the annual grant with more 20 per cent, to €38 million. The continued support from the Flemish Government in the past 13 years is admirable, not only because of the continuous success of the VIB, but equally taking into account the 4-year term of the Government itself, with changing political power over the years, delivering a true long-term approach.

## SUPPORT INFRASTRUCTURE

Studies have proven without doubt that having excellent R&D and having great business development people is not enough to create and sustain a vivid high-tech industry. As mentioned above, a large number of factors should be fulfilled: entrepreneurship, continuous and innovative education for new generation of scientists and engineers, serial entrepreneurs who lead new companies in their early years and/or have a mentorship role based on their extensive experience and indispensable network, real estate and other infrastructure, venture capital and business angels, and last but not least, the continuous presence of government support, including incentives.

VIB has always been very committed to answer to these challenges. One of the objectives VIB is actively pursuing is bio-infrastructure. The success of a highly dynamic biotechnology cluster depends to a large extent on the presence of adequate bio-incubators. Today, three bio-incubators exist, located in the technology parks of Ghent and Leuven, two cities that are often called 'smart hubs'. In a bio-incubator, next to the specialized infrastructure typical for biotechnology, companies can benefit from additional services ranging from environmental

permits, recruiting staff, accounting and patent filings. Flanders is going even one step further with the creation of a so-called 'bio-accelerator'. This bio-incubator encompasses a venture fund that supplies the necessary capital to establish the company's presence in the incubator.

## **PARTNERING FOR GROWTH**

The past couple of years saw many large partnering deals, with major deals in Flanders, highlighting the success of its fast growing biotechnology companies (for example Ablynx, Galapagos).

The growing interest in partnering is a necessary evolution for both the pharma and bio industry. Biotechnology companies need money to finance the development of their products. Pharma companies are experiencing increasing difficulties to feed their product pipelines and are extremely active in looking for partnering deals or acquisitions of biotechnology companies. In these times, they are sitting on a pile of cash to spend, and have excellent clinical test, sales and distribution networks to offer to biotechnology companies. The tight connection of Flemish biotechnology companies with excellent research centers such as VIB and a long-standing clinical trial track record is an additional bonus that makes Flemish biotechnology extremely popular.

## **NANOELECTRONICS RESEARCH FLANDERS, A UNIQUE ENDEAVOR**

The trends towards a more fundamental understanding of diseases, triggered by the advances in genomics, proteomics and systems biology has increased the need for a more multidisciplinary approach. Thanks to new molecular diagnostics and therapeutics techniques, personalized medicine starts to become a reality. These disciplines often require the combination of large set of scientific and technological domains, even between biotechnology as such and

nanotechnologies. This growing convergence is already starting to spur new industry applications in molecular diagnostics, bioelectronics, microfluidics, nanomedicine and so on. The Flemish Institute for Biotechnology VIB has teamed up with its sister institute IMEC, one of the world's largest R&D centers in nanotechnology and nanoelectronics, and the University of Leuven. The new NanoElectronics Research Flanders (NERF) R&D center focuses on neuroelectronics for brain-computer interfaces and fighting neurodegenerative diseases. It is a unique experiment in Europe, combining electrical engineers with biochemists, physicists with physicians, forming a true multi-disciplinary team of nearly 40 people.

The presence of a sister institute, IMEC, which is world leader in R&D on nanotechnologies, is of utmost importance to the region. In their own domain, the institute has created a tremendous economical impact in Flanders. Today, the center, with a staff of 1600 and a budget of US\$300 million, performs joint R&D with roughly 1000 companies from all over the world, including the leaders in semiconductors, such as Intel, Texas Instruments, Panasonic and Philips. Interestingly, their business model, a model in which R&D is done in a true co-operation scheme, has been highly successful. R&D programs are set up in which companies are invited to join and form a true mixed R&D team. Program results are in general co-owned. This co-ownership model is sustainable only because the program results cover mostly generic technologies, that is technologies that are basic and common to all design and manufacturing processes for semiconductors. More and more, IMEC employs its expertises in nanoelectronics and semiconductors to new devices and systems other than the typical microprocessors and memory chips: biosensors, lab-on-a-chip, bio-micro-electromechanical systems, neuron interfacing, nanoparticles for medical imaging and drug delivery and so on. It is precisely the interfacing between the different

disciplines, bio and nano, that holds the most promises. They are the fundamentals for new discoveries and disruptive technologies, and should be stimulated as much as possible. The establishment of the NERF Institute, with the support of the Flanders Government, is a key example for this strategy. The uniqueness of NERF resides in the fact that both R&D centers, VIB and IMEC bring leading skills and technology platforms to the table into one center. Their success will highly depend on the mix of scientists and technologists from physics, engineering, chemistry, biochemistry, medicine and biology into joint R&D programs run by principal scientists that will be recruited globally. Even today, the structure (including the government grant, complemented with contract research income) and the results that come out of the R&D programs of its modest predecessor render, the Neuroelectronics Laboratory unique in Europe.

As partnering is more and more recognized to be the only way to bring emerging

bio- and nanotechnologies to market, the question arises: is each industry domain ready to transform its business model into a collaborative business model, tuned to the needs of each partner? In Flanders, VIB and IMEC take a leading role to commercialize multi-disciplinary technologies into the global market. More and more companies start to work in a collaborative model, with clearly defined ownership on intellectual property and the rights to commercialize.

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