ActoGeniX, a small Belgian biotech company, is breaking new ground in developing a new class of drugs to treat gastrointestinal, immunological and metabolic diseases (such as Type 1 diabetes) which afflict millions. Established in 2006 as a spin-off from research carried out at the University of Ghent and the Flanders Institute of Biotechnology (VIB), ActoGeniX’s technology, known as Actobiotics™, promises to revolutionize treatment of these chronic conditions. Emil Pot, General Counsel at ActoGeniX, explains how the technology works and why intellectual property (IP) is so important for the growth of the company’s business.

**ACTOBIOTICS™: A PROMISE OF MORE EFFECTIVE TREATMENT**

ActoGeniX’s core technology, TopAct™, was developed by scientists at the University of Ghent in 1994 and was first patented in 1996. TopAct™ transforms the non-pathogenic food bacterium *Lactococcus lactus* into a delivery vehicle for a therapeutic protein which can induce healing in the body. Using sophisticated genetic engineering techniques, a gene that is essential to the survival of the bacterium outside the body is removed and replaced with one that contains the code (or recipe) for secreting the desired therapeutic protein. In this way a so-called ActoBiotic™ is produced. “We basically engineer food-grade bacteria which have been used for millennia in cheese-making and encode it with a therapeutic protein. Once a patient swallows it, it starts producing the therapeutic protein of interest,” Mr. Pot explains. “It has got very broad application and can be used, in principle, for any DNA-based polypeptide – antigens, allergens, cytokines and antibodies.”

**ADVANTAGES OF THE TECHNOLOGY**

This pioneering technology offers exciting possibilities for treating a wide range of diseases. ActoBiotics™ can be taken orally and are safer and more effective than drugs administered by injection. “The big advantage is that because of its oral application, it locally targets specific diseased areas. For example, if you have mouth ulcers resulting from radiotherapy, you can apply the medication directly to the inflamed area instead of applying it systemically, and thereby avoid a lot of side effects. It is very safe,” Mr. Pot explains.

“Our manufacturing approach differs from other biologics companies in that whereas they discard the bacteria once the therapeutic proteins are isolated, we throw away the proteins and keep the engineered bacterial cells. These then act as vehicles that can carry a whole range of therapies to a specific treatment area.”

ActoBiotics™ are very cheap to produce, compared to other biologics which can involve complex and costly processes. “We simply ferment, harvest and formulate the bacteria either as a capsule for intestinal delivery or as a mouth rinse for buccal applications,” Mr. Pot notes.
WHAT ROLE FOR INTELLECTUAL PROPERTY?

Intellectual property has been at the heart of the company’s business strategy from the outset. During the company’s incubation, where efforts focused on broadening the technology’s application, the emphasis was on ensuring adequate IP protection was in place. By its launch in 2006, ActoGeniX already boasted 12 patent families covering different aspects of its technology. “When we decided that the technology was mature enough to get sufficient financing, we had 12 patent families already. That is quite a lot for a spin-off company.”

This approach, however, made it possible for the company to attract the necessary finance to go forward. “This strong patent portfolio was instrumental in obtaining a substantial first round of financing of 30 million euros.” Seven years on, the company has some 32 patent families comprising more than 150 individually granted patents in major markets (e.g. China, Europe, Japan and the US) with around 50 patent applications still pending.

“IP management is a very important aspect of the company’s business strategy, because we are developing drug products based on a unique platform for the oral delivery of therapeutic proteins and antibodies which are normally administered by injection. In order to maintain our competitive advantage and create value for our shareholders it is extremely important to have an active IP management strategy in place,” he explains.

DEALS WITH BIG PHARMA

Developing a drug and taking it all the way through clinical trials to market approval can cost well over a billion dollars. “For clinical development of drug products you need a lot of money, so we need to partner with the big pharmaceutical companies. Our strong focus on IP management supports our business strategy to enter into valuable deals and collaborations with such companies.”

This approach is already bearing fruit. In November 2012, ActoGeniX sealed a research collaboration agreement with Merck (known as MSD outside the US and Canada) to develop antibodies for an undisclosed indication using its ActoBiotics™.

A year later, in December 2013, the company joined ranks with Stallergenes, a global leader in allergen immunotherapy, to develop and commercialize novel allergy drugs based on its technology. Worth an estimated 170 million euros, this partnership promises to significantly increase the efficacy of treatments for indoor (mites, dust, etc.) and outdoor (birch, ragweed, grass) allergies as well as food allergies with a reduced doses of allergens. “The people at Stallergenes really believed in the application of our technology platform in the field of allergies,” Mr. Pot notes.

Under the terms of the deal, ActoGeniX will use its technology to create and deliver clinical product candidates that express and secrete a range of allergens to treat some of the most prevalent allergies. If Stallergenes exercises its option on any of these product candidates, it will have full development and exclusive worldwide commercialization rights on them. ActoGeniX will be eligible for milestone payments and tiered royalties on future net sales of products according to a company press release.

“Without a strong IP portfolio we would never be able to execute such agreements, or secure the financing we need to move forward,” Mr. Pot observes.

A MULTI-LAYERED APPROACH TO IP

ActoGeniX has adopted what might be termed a belt and braces approach to IP protection. “We have adopted a multi-layer strategy. Each product is protected by multiple patents covering different aspects of our technology. This means that anyone that wants to copy our product will infringe a whole bunch of patents and will have to invalidate a whole series of patents in court. It is pre-eminent for all our potential partners that our IP is very strong. Without IP they wouldn’t be willing to invest so much money in the company,” he explains.

In a competitive market, ActoGeniX’s survival hinges on its ability to continually stay ahead of the curve in developing its technology. The first patents on the technology will expire in 2016; and the company’s ability to attract high-value licensing deals depends on the continued development and protection of its technology offering. “We try to constantly file patents to extend the protection available to a product. In the world of drug development, it can take between 8 and 10 years to develop a product. That means that a significant chunk of the life of your patent is consumed without you ever seeing a return. That is why it is important to keep filing patents on new developments so you can get a return on the huge investments made,” Mr. Pot explains.

IP EXPERTISE IS ESSENTIAL

“A correct understanding of IP is essential because you need to make sure IP covers all future product strategies. There are also important decisions to make in relation to the territories in which to file and validate patents to make sure proper IP protection is maintained,” he said underlining the importance of assigning responsibility for IP management to a qualified IP professional.
THE CONCEPT OF ACTOBIOTICS™

Genetic engineering of *Lactococcus* to create an ActoBiotic™ by chromosomal insertion of one or multiple genes

Coated capsules with freeze-dried Actobiotic™ are taken orally by the patient

Containment system preventing survival of excreted bacteria outside of the human body

ActoBiotic™ released in gut and locally secreting therapeutic at site of disease

PERSPECTIVE ON OPEN INNOVATION

As a small company with just 22 employees, ActoGeniX lives by open innovation. “Open innovation is very important to us because we don’t have everything in-house,” notes Mr. Pot. “We believe we are the world experts in the area of genetic engineering, so we keep this core technology in-house, but work relating to pre-clinical studies or toxicity studies we farm out to other companies that are far more experienced than we are and can do the job faster. In this respect, open innovation saves us time and money, but the challenge, of course, is to ensure that contracts are in place that secure our IP rights and ensure we are fully entitled to use any results of work undertaken at our own discretion. With IP you are always looking around the corner.”

THE PCT: SUPPORTING SMES

A small company, with a global reach, ActoGeniX uses WIPO’s Patent Cooperation Treaty (PCT) to file its patent applications internationally. “The PCT buys us time to determine whether it is really worth pursuing a patent at the national level. This can be a costly affair, so the PCT offers us valuable time and cost savings.”
CHALLENGES

While ActoGeniX’s IP-intensive strategy is central to its business strategy, securing sufficient financial resources for filing and validating the patents is a constant challenge. “It is critical to educate company managers and investors about how important IP is for an innovative company so they release sufficient funding for filing and maintaining the company’s patent portfolio,” he says.

External challenges relate to the need for a more supportive environment for SMEs. Tax breaks and the need for companies to be able to acquire IP rights at reasonable cost and to effectively enforce their rights are important ways in which governments can support small businesses, Mr. Pot believes.

Patent quality is another key area of concern, given the increasing threat of patent trolls. Policymakers “need to be sure that patent quality is improved and that there is increasing legal certainty. Young innovative companies rely heavily on patents and can face devastating consequences under the threat of a damaging lawsuit or if their patents are invalidated by the court,” he explains. Many IP-related challenges confronting SMEs, he believes, could be addressed through more and better training programs for SMEs to raise IP awareness, improve intellectual asset management and create opportunities for engagement with IP officials.

On top of the need to address patent quality, “all kinds of other practices and rules put pressure on the alleged infringer to settle with a patent troll,” Mr. Pot notes. Take, for example, a pharmaceutical company that, after obtaining approval to market a potential multi-billion dollar product, receives a letter from a patent troll claiming infringement and threatening a lawsuit unless a hefty licensing fee (in the hundreds of thousands of dollars) is paid. Under such circumstances, he explains, the alleged infringer is likely to settle out of court rather than delay getting his product to market and face uncertainties associated with a complex and lengthy trial. “This all puts pressure on the alleged infringer and favors the patent troll. Incentives need to be put into place to make it less favorable for patent trolls to bring cases, but as long as trial costs are not attributed to trolls when they lose, the situation is unlikely to change.”

THE FUTURE

With a number of products in the early stages of clinical research, the company is seeking partners that can help it further develop, expand and commercialize its product range. “There are a lot of indications that we can address but we only have so much time and so much money. We could partner with companies to develop therapies for allergies, auto-immune diseases, rheumatoid arthritis and Type 1 diabetes while we ourselves focus on developing inflammatory bowel disease therapy.”

As the incidence of non-communicable diseases rises, so too does the need for safer and more effective treatments. As a pioneer and dominant player in the delivery of a new class of orally administered, locally acting, biological drugs, the prospects for ActoGenix look very promising. IP has played a central role in establishing the company and in fueling the continuous development of its technology. IP will, no doubt, continue to shape the company’s fortunes and help meet medical needs for better and more effective treatments for a broad range of chronic diseases.