SPOTLIGHT ON THE NETHERLANDS

Going Dutch

How a tradition of easy collaboration is helping start-ups and small companies drive a new wave of biotech innovation in the Netherlands.

"Everyone was in uproar when Organon closed. In fact, the Dutch paradigm of mobilising new innovative start-ups that eventually get bought by larger companies was already emerging."

Saco de Visser, director of cluster development at Leiden Bio Science Park

THE DEATH KNELL for the pharmaceutical industry in the Netherlands sounded in 2010. In July, 2,175 employees including 1,100 researchers were made redundant with the closure by MSD of its Dutch subsidiary Organon, in Oss. In September another 500 posts were cut when US giant, Abbott Laboratories, announced it was closing the R&D facilities of its new acquisition, Solvay Pharmaceuticals, in the town of Weesp.

These were just two of many restructuring operations that followed a wave of mergers and acquisitions globally in big pharma. In the Netherlands, which has a population of just 16.8 million, many saw them as devastating blows that signalled the end of an industry.

But six years on, Dutch biotechnology is thriving. A new 35-company science park — Pivot Park — has sprung up on the former Organon site, and university spin-outs and small companies are growing rapidly and taking on employees. A series of recent big deals and acquisitions highlight the health of the sector. This remarkable turnaround provides wider lessons for organisations and individuals buffeted by the uncertain winds of economic and technological change beyond Holland's borders.

Pivot Park is the best place to start learning the secrets of the Dutch recovery. In the summer of 2010, as politicians blamed MSD and Abbott for their job-shedding restructuring plans, and industry figures accused the Dutch government of failing to create an attractive investment climate, others were looking to the future. Groups of soon-to-be-unemployed MSD scientists began negotiating agreements that allowed them to continue working on promising concepts within their own spin-out companies.

MSD held discussions with local and provincial governments and they agreed to make use of the existing facilities and infrastructure to establish Pivot Park, which opened for business in February 2012. One MSD spin-out was BioNovion, a company specialising in immune oncology antibody discovery. The work there by former Organon scientists led to the development of the drug pembrolizumab (Keytruda), to treat melanoma and non-small cell lung cancer. The US company Aduro Biotech bought BioNovion for €29 million in September 2015.

"Our experience showed the resilience of the people working here," says Mirjam Mol-Arts, the managing director of Pivot Park. "We started off with companies set up by former MSD scientists who were able to go back into their labs and continue with what they were doing before. We've grown considerably since then."

Today some 400 people work at the park in new product development, pharmaceutical contract research, manufacturing and support services. Another significant tenant is Acerta Pharma, a US-Dutch company for which AstraZeneca paid $2.5 billion for a 55% stake in December 2015.

A growing proportion of the companies based at Pivot Park are spin-outs that originated in university incubators. Each of the country's 12 publicly funded

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Equipment at Pivot Park

The Leiden Bio Science Park campus

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Development taking place at Leiden Bio Science Park

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Top ten institutions, 2015

Dutch institutions are heavily involved in collaboration and research commercialization — it's paying off.

	INSTITUTION	WFC	AC
1	Utrecht University	103.17	498
2	University of Groningen	91.15	441
3	Leiden University	82.09	596
4	Delft University of Technology	64.47	161
5	Radboud University Nijmegen	60.92	523
6	University of Amsterdam	58.38	584
7	Eindhoven University of Technology	37.88	88
8	VU University Amsterdam	37.04	319
9	University of Twente	23.62	56
10	Wageningen UR	21.18	108

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research universities have set up incubators since 2005, and it's an area in which the Netherlands is receiving growing international recognition. In November 2015, YES!Delft and UtrechtInc, the incubators of the Delft University of Technology and Utrecht University, came 9th and 11th respectively in a global ranking of university incubators published by UBI Global.

Since launching in 2005, YES!Delft has worked with more than 160 start-ups, which it estimates have attracted at least €300 million in investment and created more than 1,000 jobs. Success stories include Eternal Sun, which makes solar simulators for uses such as solar panel and paint testing, and i-Optics, which specialises in eye diagnosis technology.

"In other countries you have one city that's really leading, like Berlin or London." says Pieter Guldemond, YES!Delft managing director. "In the Netherlands we have a network of 12 hubs that are increasingly co-operative, and performing on a global level."

If the university incubators dotted across the Netherlands are important drivers of innovation, the pioneering and still most significant force in the life sciences is the Leiden Bio Science Park. Home to the science departments of Leiden University and Leiden University Medical Centre, it was set up in 1984 with land set aside for private industry and institutes.

Many years later, this matchmaking of university researchers with private industry would become far more common. In 2011 there were 147 organisations employing 15,000 people at the park. This has risen to 16,900 people employed by 173 organisations in 2014. "The sector is doing very well," says Annemiek Verkamman, managing director of the biotechnology industry association HollandBIO. "We're seeing a lot of interest from international parties in biotech in the Netherlands and last year saw a lot of deals and acquisitions."

Although collaboration between the public and private spheres has become something of a mantra in many parts of the world, it's a concept the Dutch take further than most. One example is the Centre for Human Drug Research (CHDR), a contract research organisation (CRO) also based at the park that runs early-phase drug trials. Unusually, its senior management is dominated by professors and medical doctors.

"Americans might find the idea of having a professor or a practicing doctor as a CEO of a CRO disturbing," says Saco de Visser, the director of cluster development at Leiden Bio Science Park. "But this blended situation is very common here."

Then, there's the new advanced part-time master's degree being offered from this year by the Leiden University Medical Center. Established in partnership with the CHDR, Leiden University, and a number of pharmaceutical and biotech companies at the park, it is aimed at biomedical scientists from industry or academia with entrepreneurial ambitions.

"It's unique," says de Visser. "Scientists elsewhere who are interested in the business side of developing novel therapeutics would have to do an MBA (Master's of Business Administration). This truly tears down the walls between the public and private sectors."

While few who went through the traumas of the 2010 closures would wish to repeat the experience, some believe it brought long-term benefits. "Everyone was in uproar when Organon closed," says de Visser. "In fact, the Dutch paradigm of mobilising new innovative start-ups that eventually get bought by larger companies was already emerging."

Those who have ridden the ups and downs of the Dutch pharmaceutical and biotech sectors in recent years agree on the importance of effective public-private partnerships.

"On the one hand universities have realised they can make money from their basic research and have become much better at spinning out their ideas," says Mol-Arts. "On the other, big pharma companies are scaling down their early R&D efforts, and becoming more dependent on the output of smaller companies and universities."

Most of those who run major pharmaceutical companies realised years ago that they needed fresh ideas from academia and smaller, more dynamic commercial players

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to help them innovate. "The larger companies have evolved into machines with linear processes, from discovery to phase one, two, three and then to market," says de Visser. "What's needed today is a more agile approach based on better understanding of disease, so academia is being integrated more into drug development."

Guldemond agrees. "Big corporates are slow," he says. "A start-up can focus on innovating and getting their product to customers, without all the procedures, speaking to shareholders and managing of egos that a large company has to deal with."

The Dutch talent for cross-sector collaboration is exemplified by the work of Lygature, a not-for-profit organisation that seeks to drive the development of new medical solutions by managing joint projects between government, industry and academia. Its flagship project is the European Lead Factory (ELF), which helps researchers test their new drug targets against a huge compound library they would not usually have access to (see **Bridging the innovation gap**). Lygature played a central role in setting up the 30-partner collaboration and runs the selection process that determines which research groups get screening time.

"If you have one academic group working with one company, you don't necessarily need an independent third party," says Jorg Janssen, managing director of Lygature. "But if you have a complex agreement between 10-20 players, you need an honest broker with no interests other than keeping everyone focused on the agreed goals."

Some argue that the Dutch talent for collaboration can be explained by aspects of national character and social structure.

"The Dutch are direct, and the lack of hierarchy means you can easily have a frank discussion with your manager," says Verkamman. "It means big ideas don't have to come from the top." Verkamman believes all of HollandBIO's 130 members, covering healthcare, agriculture, food and industry, are engaged in collaborations with at least one university.

De Visser agrees the straightforward approach has been important in facilitating public-private partnerships. "The Dutch way of interacting between academia and companies is very direct and open-minded," he says. "We can walk into a professor's office without feeling the embarrassment that might be a hurdle elsewhere."

The ultimate origins of the collaborative spirit that has served the Dutch drug discovery and biotech sectors so well in recent years may have started more than 1,000 years ago. Without the complex combination of dykes, canals, levees and dams that surround the country, almost half of the Netherlands would be underwater.

"Some say we had to collaborate because it doesn't make sense if I make a dyke but my neighbour is under water," says Verkamman. "The theory is that our collaborative nature came from all of us working together against the water. I don't know if it's true, but there could be something in it."

Bridging the innovation gap

Chris Schofield

Some call it the innovation gap. Academics and researchers from small and medium-sized enterprises (SMEs) have promising ideas for new drugs, but lack the means to develop them. Large pharmaceutical companies have money and equipment to throw at a problem, but lack the basic biological research expertise and creative thinking required to find new solutions.

Enter the European Lead Factory (ELF), set up in 2013 with the goal of accelerating the hunt for new therapies by helping to bridge this gap.

ELF offers researchers from European academic institutions and SMEs the ability to screen novel drug targets against a library of 400,000 chemical compounds. It also provides technical expertise in the design, running and analysis of screening experiments, and access to state-of-the-art screening facilities at the Pivot Park Screening Centre, in Oss, the Netherlands.

Some 300,000 of its compounds have been provided by seven large pharmaceutical com-panies, and academic and SME groups will have added another 200,000 by the end of 2017.

A group, led by Chris Schofield, head of organic chemistry at the University of Oxford, ran a screen at the ELF in 2013 to identify potential inhibitors of a protein they had identified as a target for novel drugs to overcome multi-drug bacterial resistance.

After 50 candidate compounds were identified, their chemical structures were supplied to the team, which then carried out further analysis in collaboration with ELF scientists in Oss and at the Scottish city of Dundee.

"The outcomes exceeded our expectations," says Schofield. "From the proposal submission process to help with developing the screening assay, validating the results, and chemical synthesis work, we were extremely impressed both with the technical competence and commitment of the ELF teams."

So far the ELF has carried out 65 drug target screens which have resulted in more than 3,000 potential compound hits and 30 journal publications. It has funding until the end of 2017, and is seeking to secure its future beyond then.

This content was commissioned and edited by the Naturejobs editor

MIRJAM MOL-ARTS

A Pivot Park lab

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