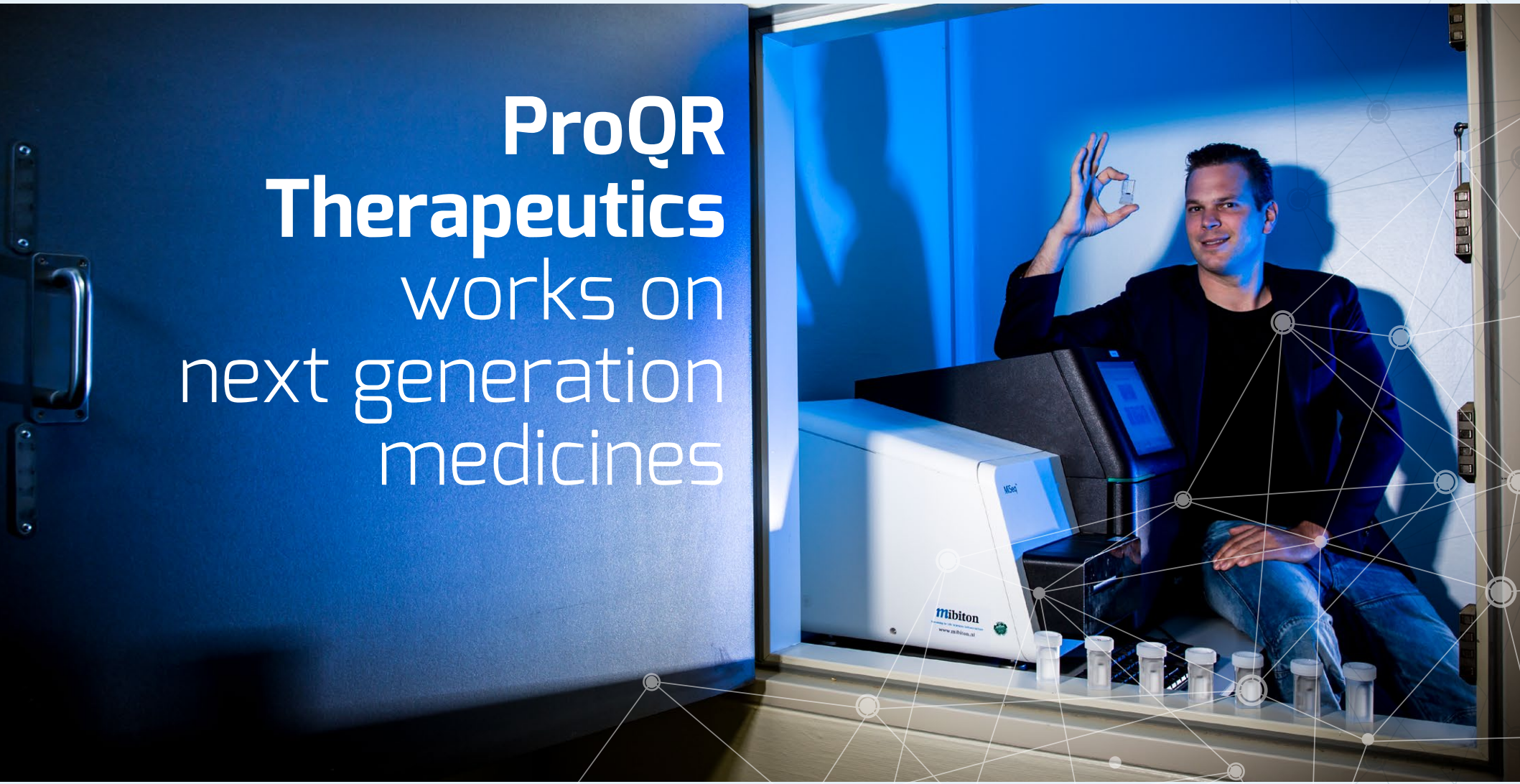
ProQR Therapeutics works on next generation medicines



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"As a new Life Sciences company, it is difficult to get funds. You still need to prove that a new technology or therapy actually works. Success rates are low and thus financial risks are high. At this stage, *enabling cash* is incredibly important. For ProQR Therapeutics, the initial loan from Mibiton for valuable equipment in addition to starting capital was therefore more than welcome. Mibiton has certainly contributed to the fact that our company has been able to get off the ground quickly over the last four years."

Spokesman is **Daniel de Boer, CEO of ProQR** (pronounced: pro-q-r). When his son was born seven years ago, it quickly became apparent that he had cystic fibrosis, an inherited disorder with an average life expectancy of 27 years. More than 70,000 people worldwide suffer from this condition. De Boer who was then an ICT entrepreneur, decided to sell his business and to devote all of his time to searching for a panacea against this disease. He travelled around the world for two years, attended conferences and was extensively educated by scientists and companies about what is scientifically known about the disease and how far one had come with treatment of this disease. "At a certain point it became clear to me that I could best support this development by starting a private company in order to develop a new medicine against the disease", said De Boer.

He obtained support from famous people such as Dinko Valerio (founder of Crucell), Henri Termeer (ex-CEO of the American company Genzyme) and Gerard Platenburg (founder of Prosensa and CIO of ProQR since 2014). Together they founded ProQR in 2012. De Boer managed to gather even more people with proven knowledge and experience around him. "I asked them, 'what is happening and what is showing the most promise?'. We arrived at a method used at the Massachusetts General Hospital in Boston in the United States and procured a license on this."

Cystic fibrosis (cystic fibrosis CF) involves mutations in the CFTR gene, resulting in a protein in the membrane of certain cells no longer being able to transport chloride ions to the outside. This causes an accumulation of thick mucus in vital organs: not just in the lungs, but also in the kidneys and intestines. ProQR is working on QR-010, an oligonucleotide in the form of a short single-strand RNA molecule, which will eventually make the cells of these organs pump chlorine ions to the outside again, so that mucus no longer accumulates.

"Soon we will be presenting the initial data from clinical studies and next year the results of the two studies, with an emphasis on *proof of concept*. After this, more years of research are needed to be able to determine whether the therapy is safe and effective", said De Boer.

In 2012, only four or five people worked for ProQR Therapeutics. Meanwhile the company has been listed on the US technology stock exchange NASDAQ and 150 people are working there, some in North America. "This would never have succeeded if we had had no support initially", said De Boer. "In order to check the quality of the RNA-constructs, we had to be able to determine their sequences. Initially we sent samples to laboratories abroad, but it took months before we saw the analysis results. That put huge delays on development."

"In order to progress, we would have needed access to a *deep sequencer*, a device that determines the base sequence of DNA and RNA molecules within half a day", De Boer adds.

"However, this would have cost about 160,000 euros, an amount we could not possibly fund from our cash flow. However, we received help from PROXY Laboratories. This company offered us space and facilities in the Bio Science Park in Leiden, which we could rent for a reasonable amount, so we could start immediately. PROXY was also willing to acquire and use the *deep sequencer* together with us, and teach

"During the first four years, ProQR's workforce grew from five to 150 employees."

us to use this device. Together as SMEs we were eligible for a loan from Mibiton Share that would enable us to finance the purchase. The loan would need to be repaid within a maximum of five years. Initially, PROXY owned three quarters of the device and ProQR owned one quarter. After some time, we took over the device and the loan is now completely paid off. The Mibiton system works very well and the Government should definitely continue with this. Continuity of this policy is very important", De Boer stresses.

"Without the *enabling* cash from Mibiton and other financiers, this company would never have been able to get off the ground. As a start-up company, you need tangible capital; that is essential. This capital has enabled us to quickly move forward and ensure that by 2014, we have been able to get listed on the NASDAQ in New York, so we could suddenly invest much more capital into medication development", De Boer added.

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Apart from developing a medication against cystic fibrosis (CF), ProQR now also develops RNA-based drugs for other diseases. There are now seven or eight development programs, such as, for example, for a medicine, QR-110, against Leber's congenital amaurosis (LCA), a genetic defect that causes blindness in children in their first years of life. There are ca. 15,000 LCA patients in the world. With QR-110, ProQR hopes to have a compound, with which 2,000 of these patients with LCA Type 10 can be treated in due course. The company is also working on QRX-411, a medication against the Usher syndrome, a genetic disorder that causes blindness and deafness, and QRX-504, against a condition affecting the cornea (Fuchs endothelial corneal dystrophy). The company is also developing a compound (QR-313) against a genetic disease that causes children to lose their epidermis, leaving open wounds. The Mibiton equipment is also being used in the development of drugs against these other conditions.

How unique is all of this? De Boer: "RNA technology is a new and promising field. There are also other companies working on it. Previously, companies have tried to combat *cystic fibrosis*, with gene therapy for example, but that didn't work because it involved using much larger molecules. Oligonucleotides are smaller and penetrate mucus around the cells more easily".

According to him, ProQR is and will continue to be a Dutch company. Whether or not the company will ever be taken over is of no interest to him: "the important thing is that there are new drugs available for patients. Whether this happens via our ProQR as an independent company or as part of a larger whole does not really matter that much".

Finally, De Boer still has two wishes regarding the Dutch business climate. "Recruiting here is very difficult and inhibits our growth. We have needed to

attract a lot of talent from abroad. So now we are working with thirty different nationalities. Attracting talent from abroad, however, is not easy either. For example, it is quite a big step for a researcher from Milan with a family to move over here.

Furthermore, the Government should make more funding available so that we can start more programmes, develop new drugs faster and thus also grow into a large company that offers many more jobs."

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Treating cystic fibrosis with QR-010

ProQR is working on QR-010, an oligonucleotide in the form of a short single-strand RNA molecule. This synthetic RNA section ensures that the CFTR protein becomes active again and that chlorine ions can be actively transported again. Patients who participate in clinical research, have the RNA administered via a saline solution spray through an inhaler so that it reaches the lungs, where it is finally absorbed into the cells. A proportion of the drug also reaches the intestines and kidneys via the blood. In the cells, the oligonucleotide QR-010 repairs the active CFTR protein, so that the cells can pump out the chlorine ions again and no more mucus accumulates. Tests on mice have shown that this method resulted in 80% of the protein function being temporarily restored. It is hoped that a large proportion of patients will benefit from treatment with QR-010 in a few years' time. They will need to inhale this drug regularly.

Currently two global clinical trials with QR-010 are being conducted. The first study in 64 patients concerns studying the effects of the intake of a single or a multiple dose via inhalation for up to four weeks. This includes researching the safety of the new CF drug, the tolerance to it and whether patients derive benefit from the treatment.

In the second study a small electrode is placed in the noses of 16 patients to measure the electrical voltages before and after administering the medication. This provides a measurement of chlorine ion-transport. This is designed to detect if the CFTR protein is more active and can thus reflect the drug's efficacy (*proof of concept*). A total of 80 patients in 27 hospitals in North America and Europe are enrolled in this research.

QR-010

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