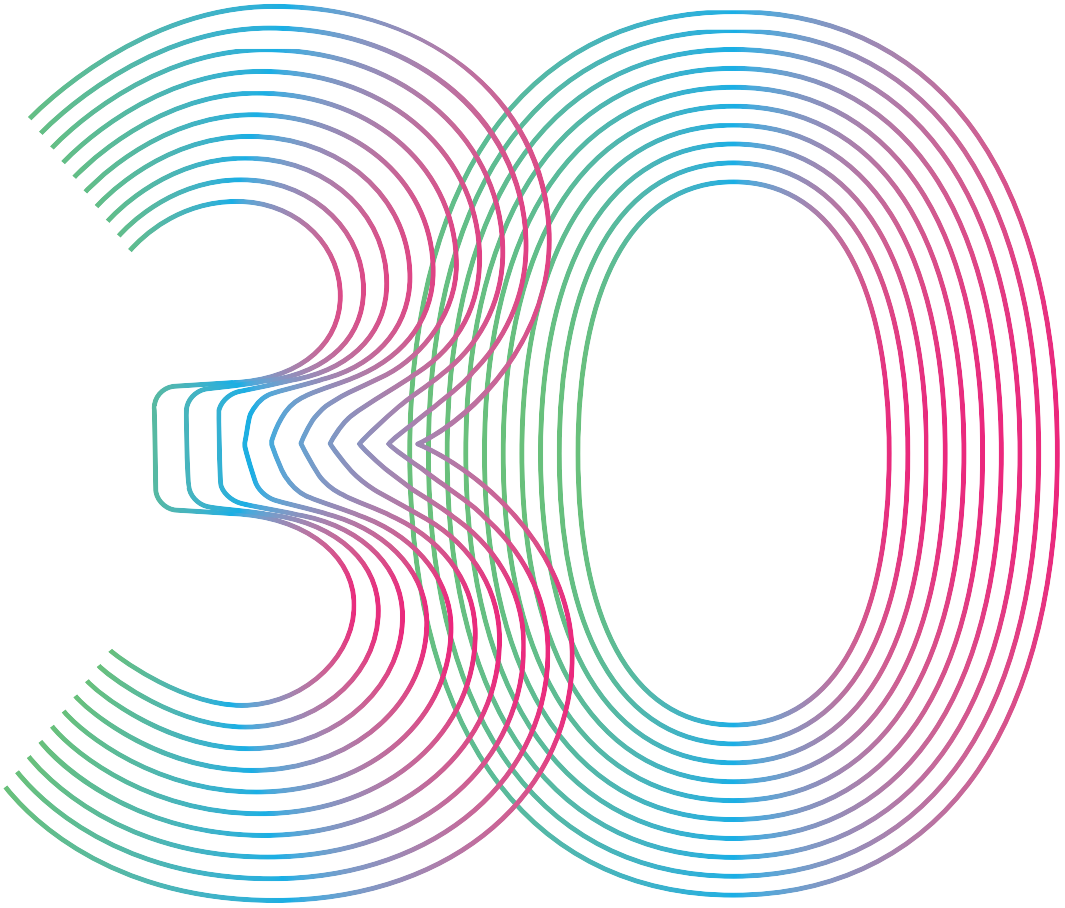

CHDR

Centre for Human Drug Research

Preface

Evolving in an ever-changing world

In 2002, when CHDR celebrated its 15th anniversary at the National Museum of Natural History in Leiden, the Netherlands, several experts in the field of drug development – including Dr Paul Janssen and Nobel laureate Jim Black – discussed the future of the pharmaceutical industry under the towering gaze of dinosaur skeletons. CHDR now celebrates its 30th anniversary, this time under the watchful eye of a nearly complete *Tyrannosaurus rex* excavated in 2013 by a Dutch team in Montana. As CEO Adam Cohen wrote back in 2002, 'Dinosaurs remind us that growing to a certain size is only possible when the world around you allows it.' This is certainly true for CHDR, whose success was both possible and facilitated by countless people and organisations.

This book is about some of the people who played a key role in helping CHDR reach this important milestone. In these pages you'll meet people who were there even before CHDR started, and you'll meet some of our recent collaborators in both academia and the pharmaceutical industry. Together, their stories help tell the tale of CHDR's evolution.

Although the giant dinosaurs of the past roamed the Earth for millions of years, they could not adapt, and they became extinct. To quote Adam Cohen once again, 'The world still needs many new drugs, and static, dinosaur-like organisations that try to single-handedly develop these drugs will be stuck in the past. The future lies with lean, effective groups of specialists who come together when needed.' This thought-provoking notion is certainly supported by biology. After all, contrary to popular belief, the dinosaurs did not become extinct; today, their descendants – modern birds – are flourishing all around us.

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‘Adam’s vision was essential to CHDR’s growth and success’

More than thirty years ago, pharmacologist Prof Douwe Breimer developed a plan to establish a clinical pharmacology unit with close connections to both Leiden University Medical Centre and Leiden University. Here, Breimer talks about how budget cuts and scarcity yielded a booming network of thriving organisations, providing a unique view of CHDR’s history through its founder’s eyes.

***Prof Douwe Breimer**, founder of CHDR and former Rector of Leiden University*

The history of CHDR began during a turbulent time for universities throughout the Netherlands. In the early 1980s, the Dutch government concluded that major budget cuts were needed in order to balance the national budget. The Dutch Ministry of Science and Education, which grew at a rate of around 14% during the 1970s, was also required to drastically reduce expenses. Universities were not spared, and the Ministry decided that major structural changes were needed. In the course of a decade, thousands of university employees lost their jobs.

Turning a budget cut into an opportunity for innovation

A major change that affected Leiden University was the government’s decision to close the university’s Pharmacy programme. Previously, four Dutch universities provided training to become a pharmacist, and the government decided to cut that number in half. Breimer, who was appointed a Professor of Pharmacology in the Pharmacy programme in 1975, remembers the response. ‘We protested, of course. Back then – just as today – I believed that pharmacists and doctors should train side by side. In practice, these seemingly different professions must work together, and I believe the best way to achieve this is to have both professionals train together at the patient’s bedside. So ideally, every medical school should also train pharmacists. Unfortunately, a government that wanted to cut the budget certainly wasn’t willing to listen to these arguments.’

Nevertheless, government officials conceded that Leiden had an extremely high-quality research programme. So when Breimer came up with a plan to save the research, they were willing to listen. ‘I remember on Father’s Day in 1983, together with Leiden University’s rector, I visited a senior official at the Ministry of Science and Education, Dr Roel in ’t Veld. We sat in Roel’s backyard drinking coffee and eating Dutch *stroopwafels*, discussing our plans to save as much of our research programme as possible. It wasn’t easy to convince Roel that we needed to engage in education as well as research, but – finally – that’s what emerged from these informal negotiations. The next day, Roel phoned to say that the Ministry had agreed to finance the transformation of our Pharmacy programme into the Institute for Bio-Pharmaceutical Sciences. Thus, we could continue to conduct research, and we could train undergraduate and graduate students in pharmaceutical science.’

The science of drug development

The Institute of Bio-Pharmaceutical Sciences, which is now the Leiden Academic Centre for Drug Research (LACDR), became a leading authority on various aspects of drug research and development. In addition, the LACDR’s Master’s and Bachelor’s programmes in biopharmaceutical sciences are now the largest programmes in the science faculty. Publications by Profs Breimer and Danhof (see also page 25) on the assessment of drug-metabolising enzyme activity and PK/PD modelling are among the most frequently cited papers by Dutch scientists. The programme included research using both laboratory animals and human subjects. However, Breimer and his colleagues were not satisfied with the relatively primitive facilities available for those early experiments. ‘We had a small room in our laboratory building where we could administer drugs to our subjects under the supervision of Dr Johan Boeijinga, a specialist in internal medicine,’ recalls Breimer. ‘But

we had no real facilities, no beds, not even the basic infrastructure needed for clinical pharmacology. We didn't have a medical ethics committee either, as clinical drug research was still in its infancy.'

In Breimer's view, it was essential to raise the quality of clinical pharmacology research and to establish a dedicated unit for early-stage clinical drug development. So Breimer approached another senior official at the Ministry of Science and Education, Mr Ed Broekhuizen, who had previously worked at Leiden University. Breimer asked Broekhuizen if there was a way to finance such a venture. In stark contrast with the trend in those days, on July 18, 1986 the Ministry granted a subsidy for a period of six years. The Leiden Clinical Pharmacology initiative was to receive an annual subsidy of at least 900,000 Dutch guilders (the equivalent of nearly 750,000 euros today), plus an up-front payment of 200,000 guilders to purchase the necessary equipment.

Why start an academic CRO?

In hindsight, it was a good move to create a clinical pharmacology unit, which soon would be officially called the Centre for Human Drug Research. But at the time, Dutch universities rarely created spin-off companies. In fact, even to this very day, CHDR has no major competitors in other universities either in the Netherlands or abroad. So why did Breimer lobby for the funding to establish CHDR? He explains: 'The transition from preclinical research to the first-in-human testing of a new compound is an extremely exciting step from a scientific point of view. In the early stage, healthy subjects receive both a single dose and multiple ascending doses, providing a unique opportunity to learn more about the effects of a new molecule in the human body, as well as the relationship between the drug's pharmacokinetics and pharmacodynamics. In addition, our new unit could gain important new information regarding currently used drugs. For the Leiden Institute of Bio-Pharmaceutical Sciences, early-stage clinical drug development was simply a logical extension of the work that we were doing in animals and our computer-based PK/PD models. So I was extremely delighted to receive that letter from the Ministry.'

Starting CHDR

Of course, this good news from the Dutch government came with the burden of responsibility, and many challenges lay ahead. The fledgling CHDR had just six years to develop into a self-supporting unit. 'It was made quite clear to us that after those six years, the subsidy would stop,' says Breimer, 'regardless of our financial need or scientific output.' To ensure the unit's future, Breimer's first task was to make a tough decision. Instead of keeping the unit under his control as part of the Institute of Bio-Pharmaceutical Sciences, he realised that it was important to have the unit close to the LUMC (then still called Leiden University Hospital). 'We felt it was safer to have the patients close to the hospital, and we wanted to achieve more synergy with the hospital, particularly at the level of forming collaborations with clinicians.'

CHDR began in a temporary building close to the LUMC Pharmacy. But it was unclear whether CHDR should remain an integral part of the university hospital, in essence just another department. 'There would have been some logic to that,' says Breimer. 'Like the staff at LUMC, the staff at CHDR were responsible for research, educating students, and caring for healthy subjects and patients. But at the same time, to become financially independent in just six years, CHDR needed freedom and an entrepreneurial spirit. The hospital's Board of Trustees was also wary of the legal aspects, particularly the hospital's liability in case anything should go wrong with a subject at CHDR.'

Given all of these considerations, it was soon clear that CHDR would need to become an independent business unit linked closely to both Leiden University and LUMC. However, all parties involved still had to decide on the governance and the form that the business would take. Again, it was not an easy task to take all of the key aspects into consideration. For CHDR's financial continuity, the unit would likely need the freedom to work with industry sponsors. But not everyone agreed with that assertion. 'In those days,' recalls Breimer, 'anything that had to do with making a profit was considered a bit tainted, and collaborating with industry was generally frowned upon. Personally, I had no objections to collaborating with the pharmaceutical industry, as I recognised that drug development is a responsibility shared by both academia and industry. But at the same time, I didn't want CHDR to become just another CRO. Eventually, we decided that the best legal structure would be a not-for-profit foundation without shareholders, and this has been the structure of CHDR ever since. It was also decided that LUMC and Leiden University would be represented among the Board of Trustees, and an independent Scientific Advisory Board would oversee the scientific quality of the research projects, including quality safeguards to ensure the safety of healthy volunteers and patients.'

'The transition from preclinical research to the first-in-human testing of a new compound is an extremely exciting step from a scientific point of view.'

Finding the right person to manage 30 years of growth

In parallel with these administrative challenges, Breimer also had to find someone with the scientific and entrepreneurial talents to run CHDR. Again, he succeeded: Breimer convinced his former PhD student, Dr Adam Cohen, to leave his job at the Wellcome Foundation in the United Kingdom and return to the Netherlands to establish and run the new unit. Cohen certainly had all the requisite credentials; he was both a physician and a pharmacist with years of experience in clinical drug development (see also page 12). So he clearly was the right man for the job. 'Without Adam,' says Breimer, 'there would be no CHDR as it is today. His independent thinking, his innovative approaches, his perseverance, his flair, and his vision have contributed greatly to CHDR's strong growth and development. Adam has also managed to remain true to CHDR's mission, developing the business side while maintaining their strong commitment to science through education and research.

'CHDR has thrived as a business,' continues Breimer, 'expanding the staff and facilities, thanks largely to a keen eye for innovative developments in drug research and the "bread-and-butter" approach to conducting research in collaboration with pharmaceutical companies. A portion of CHDR's revenues – approximately 10% overall – has always been invested back into CHDR's independent research programme. That model has worked well over the years in terms of both innovation and scientific output. At CHDR, science and business are highly complementary. For example, Adam has long been the Editor-in-Chief of the prestigious *British Journal of Clinical Pharmacology*.

'Adam has a quick and creative mind, he's always two steps ahead of the game, and he's not one to mince words. Some people can't take that, but his charm usually wins you over. He's great at motivating both staff and students, which is facilitated by the organisation's dynamics. There's always a new and exciting project to tackle. Over the years, CHDR has attracted experienced senior staff members and bright young minds, including PhD students and clinical pharmacologists-in-training, many of whom have stayed at CHDR or taken important positions elsewhere.'

'Adam has managed to remain true to CHDR's mission, developing the business side while maintaining their strong commitment to science through education and research.'

Over the past 30 years, CHDR has grown from a modest four-bed unit with a handful of employees to its current impressive size. As told by many who were interviewed at this three-decade milestone, this growth has been virtually unimpeded, appearing almost inevitable. For much of the past three decades, this may have been true; but there have also been some difficult times, as Breimer explains. 'Being entrepreneurial means taking risks. CHDR made the move to their current building in the midst of an economic crisis, at a time when banks were more strict about lending money than usual. That was a worrisome situation for quite some time. But CHDR pulled through, and now their financial situation is stronger than ever. Some critics might say that Adam was born under a lucky star, someone who's always lucky one way or another. But one of my favourite quotes – which truly applies to Adam – comes from the famous French researcher Louis Pasteur, who said *"Le hasard ne favorise que les esprits préparés"*, which translates to "Chance favours only the prepared mind."'

Coming full circle

Breimer's story of the history of pharmacology and pharmaceutical sciences in Leiden has an interesting conclusion as well. 'Even after I left LACDR to become Rector Magnificus of Leiden University in 2001, I've kept an active interest in the developments surrounding my origins in Leiden. There've been many exciting new developments connected – either directly or indirectly – to CHDR. One such development is Paul Janssen Futurelab Leiden, a new postgraduate course in which biomedical and biopharmaceutical researchers can learn how to develop new treatments more effectively and how to create and run a business. I'm glad that the programme is named after Dr Paul Janssen, who was a prominent chemist and pharmacologist, as well as a highly successful entrepreneur. Both Adam and I knew Paul personally, and he was a remarkable man and a highly creative thinker. So it's only fitting that his name is associated with this unique training programme organised by LUMC in collaboration with Leiden University and CHDR.'

Another recent development may not have a direct connection to CHDR, but it certainly fits nicely into the bigger picture. 'Since last year,' says Breimer, 'it's once again possible to receive pharmacy training in Leiden. Prof Henk-Jan Guchelaar in the Pharmacy Department at LUMC introduced a Master's programme for biopharmaceutical sciences and pharmacy students who wish to become a pharmacist with a focus in pharmaceutical care. These students train alongside medical students, which helps each profession learn to collaborate with the other. So, more than thirty years after the Ministry of Science and Education closed the pharmacy programme, it's finally back! Now we have the best of both worlds – educating pharmaceutical scientists in the science faculty, and training some of these scientists to become pharmacists in the medical faculty. Of course, it gives me great personal satisfaction to see how this story has so many happy endings, including the successes enjoyed by both the LACDR and CHDR.'

A pilgrimage to Beckenham

*Left to right: **Dr Arthur Fowle**, former Director of the Clinical Pharmacology Unit, Wellcome; **Prof Adam Cohen**, CEO, CHDR; **Dr Anthony Peck**, former Director of Psychopharmacology, Wellcome*

Once upon a time, there was a clinical research unit with a strong focus on measuring pharmacodynamics in early drug development. They had an open, informal atmosphere, and employees were encouraged to speak their minds. Staff members worked there for many years, driven by their strong sense of internal motivation. Sound familiar? Let's take a look at CHDR's roots in the Wellcome Foundation's facility located in Beckenham, England.

Our very first interview for CHDR's 30th anniversary book was also one of the most memorable. We travelled to the UK – and back on the same day – to visit the London Borough of Beckenham. For Prof Adam Cohen, CHDR's CEO, it was a trip down memory lane; in the early 1980s, Cohen was a PhD student at the Wellcome Foundation in Beckenham. On a Friday afternoon in January 2017, we were received graciously by Dr Arthur Fowle and his wife, Dr Lise Fowle, in their lovely home in Beckenham. Fortunately, Dr Anthony (Tony) Peck was also able to visit, so while we enjoyed lunch together, we could talk with two of Adam's direct superiors back in the day at Wellcome. This story is based partly on this interview, with some additional quotes from Fowle and Peck extracted from a Witness Seminar held by the Wellcome Trust Centre in London in 2007.

Back to the future of drug development

On the way to Beckenham, Cohen explained why he wanted to include an interview with both Fowle and Peck in a book celebrating CHDR's 30-year anniversary. 'You'll see how many of the things that we now take for granted at CHDR are a continuation of the things I learned at the Wellcome Foundation,' said Adam. 'And I'd also like to show you how Peck and Fowle were in many ways far ahead of their time. Sometimes when I lecture about drug development, I present our approach to developing the antiepileptic drug lamotrigine, showing parallels with cutting-edge 21st century principles of drug development.' And of course, Cohen was right. It might seem a bit far-fetched to see a novel approach to drug development in the stories and memories of two octogenarians. And some of their stories are from a different time. But their spirit and their rigorous approach to science are just as valid today as they were more than three decades ago.

Science in an old mansion

The facilities at Beckenham were housed in a 19th century mansion, with some additional buildings added after the war. The site, spanning more than a hundred acres, was purchased in 1919 by Henry Wellcome; before that, it was owned by the Langley Family for five centuries. The mansion, known as Langley Court, was built in 1886 by James Bucknall, who lived in the house with his family until the start of the first world war.

Fowle and his wife remember visiting the facilities in the 1950s, when they were both medical students. 'They had many horses back then,' recalls Fowle, 'which was essential for the production of vaccines. For decades, Wellcome was the official provider of all vaccines to the British Empire. These horses were treated quite well and were able to run freely across the meadows. The only evidence that they were being used for vaccine production was the canula placed in the jugular vein. Ironically, it was animal activists who changed these horses' lives, and for the worse. Because of their continuous protesting, Wellcome had to keep the horses locked away.'

1: Prof Sir Colin Dollery is one of the founding fathers in the field of clinical pharmacology. In recent decades, he has been involved in ground-breaking research in the development of new therapies for hypertension and other cardiovascular disorders, both in academia and with GlaxoSmithKline (GSK).

‘Many of the things that we now take for granted at CHDR are a continuation of the things I learned at the Wellcome Foundation.’

In 1965, Fowle started working as a clinical physiologist at the Wellcome Foundation; in 1968, he became the head of the clinical pharmacology unit at Beckenham. ‘I never trained formally as a clinical pharmacologist. I always thought of myself as a clinical scientist, until I read a seminal paper by Colin Dollery[1], which marked the start of clinical pharmacology as a discipline. He described what every clinical pharmacologist should do. And believe it or not, it was exactly what Colin himself had done. Both Colin and I had been housemen at the Brompton Hospital in London, and when I looked at the article I thought, “Okay, I guess I’m a clinical pharmacologist as well.” So you could say that I just copied the job title from Colin.’

Their work at the Beckenham facility led to the development of many drugs; but in a way, drug development was not the primary focus of Fowle and his colleagues. As Fowle stated in 2007 at the Witness Seminar, ‘Our outlook on success was to write papers for Clinical Science or to address the Medical Research Society. That was what gave us pleasure and nobody stopped us doing it.’

In 1969, Fowle hired Anthony Peck, who would contribute greatly to the development of new CNS drugs, particularly lamotrigine. Tony was a young doctor who felt dissatisfied with both the health service and academic research, and he had recently returned from a year in the United States. ‘I needed to do something for a living,’ says Peck. ‘I found pharmacology interesting, but Middlesex Hospital, where I had trained, didn’t have a clinical pharmacology department. So I was delighted to join the Wellcome Foundation down in Beckenham, and I had a great deal of fun for twenty-five years.’

Even today, Fowle still expresses his admiration for Tony’s dedicated approach. ‘I learned so much from Tony because he’s such a fanatic. He always insisted that absolutely everything be strictly consistent in a study. And if you do that, you can get by with only six subjects in a first-in-human experiment. So when we’d bring meals in, we made sure that everybody ate the same thing. And we even used the same car to drive them to the study. Tony was so finicky that way. But with his approach, you could have a very small number of subjects and still have reliable results.’

Pharmacodynamics and positive controls

In addition to keeping the relevant variables as consistent as possible, the Beckenham scientists had a strong interest in measuring pharmacodynamics. Early clinical drug development in the 1960s and 1970s was quite different than in later years, when pharmacokinetics became the primary focus. In fact, in those early days pharmacokinetics wasn’t even considered particularly important. Clinical pharmacologists were just beginning to see its importance, but it wasn’t until a new formulation of digoxin caused clinical problems that doctors started to recognise the relevance of pharmacokinetics. Even then, old habits died hard. ‘When we had trouble with our digoxin preparation,’ recalls Fowle, ‘I had some difficult conversations with clinicians. It soon became obvious to me that even highly trained physicians were not aware of the importance of pharmacokinetics. They didn’t think that drug dissolution and absorption really mattered.’

To study pharmacodynamics in healthy volunteers, they performed meticulous physiological measurements. ‘You were both trained as physiologists,’ says Cohen to Fowle and Peck, ‘so you were skilled at collecting these measurements. Nowadays in drug development, although we don’t use physiologists any more, those measurements are still important. That’s one of the main things I learned at Beckenham. So at CHDR, we continued collecting these precise measurements, which our sponsors value. Another lesson I learned was the importance of including positive controls. Tony, you always included a control group who received a drug with established pharmacodynamic properties similar to the variable that was being tested. For example, when we were studying a new antihistamine, we included a control group who received a well-characterised antihistamine. In short, you always tried to learn as much as possible from early studies in volunteers. And that’s also important for the subjects’ safety. Once you forget that you’re doing pharmacology, the risk of accidents increases.’

Fowle agrees. ‘We certainly did a lot of pharmacodynamics in healthy volunteers,’ he says, ‘if only to save our company from embarrassment. It was my job to keep us out of trouble. In psychopharmacology in particular, you need to be aware of all the ways in which someone can abuse or misuse a drug, for example as a recreational drug or to slip someone a “Mickey”. Such a thing would have destroyed our reputation. We had a strong reputation dating back to before the war, and I didn’t want to do anything to damage that.’

An anti-depressant, or a ‘pep pill’?

A good example of the critical pharmacodynamics research at Beckenham was a project by Peck and his colleagues in which they studied the properties of a potential new antidepressant called benzylpiperazine (also known as BZP). At the 2007 Witness Seminar, Peck recalled how Douglas Munro-Faure, the head of clinical research at Wellcome, gave him the assignment to investigate BZP’s properties. ‘Munro-Faure told me, “Here’s a compound, benzylpiperazine.

‘It was the perfect environment to do science. There was a very open and unthreatening atmosphere.’

Basic pharmacologists say it might be an antidepressant. I think it’s a pep pill. Sort it out.’” Peck told how he found it a perplexing problem, trying to figure out whether a substance is actually a pep pill. But he soon realised that he could rely on his colleagues at Wellcome and their affiliated institutions.

Using auditory stimuli to measure vigilance in volunteers (many of whom were his colleagues), he soon found that ‘of course, our benzylpiperazine was monumentally alerting.’ The next step was to determine whether BZP was as attractive to addicts as amphetamine. At Whitchurch Hospital in Cardiff, recovered amphetamine addicts compared the effects of BZP with the effects of dexamphetamine, and they preferred the new drug over dexamphetamine. As he would later write in his publication summarising these experiments, BZP ‘is a compound liable to abuse by an addict population.’

Munro-Faure had been right in suspecting that the putative antidepressant was in fact a pep pill. This should have been the end of the story. But despite the warnings from the Beckenham researchers, BZP came on the market. It took time before recreational users discovered its properties (most speed addicts do not read pharmacology journals), but once they did, BZP became a popular street drug either in its pure form or mixed with other amphetamine derivatives in so-called ‘ecstasy pills’.

CNS pharmacodynamics and the start of NeuroCart

To study the effects of drugs on the central nervous system, Peck and his colleagues obtained a series of neurophysiological and neuropsychological tests from various academic groups. At the 2007 Witness Seminar, Peck noted that ‘it’s terribly important in clinical pharmacology not to try to reinvent the wheel when there are units out there that can help you with methodology that will be useful, like Nicholson and Borland, and Wilkinson – the work had all been done before, and we used it.’

Tony Nicholson, Dick Borland, and Barbara Stone at the Farnborough RAF Aviation Medicine Unit co-developed the so-called ‘adaptive tracker’ test, which measures alertness by having the subject follow a dot on a screen using a joystick. The system was developed further at Wellcome by electronics engineers Kevin Hobbs and Alan Strutt. ‘Kevin once told me about the first time he drove to the RAF base at Farnborough to look at the prototype of the adaptive tracker,’ recalls Cohen. ‘He drove up to the gate, explained his business, and was told to drive on. But then the guard added, “Make sure you turn right at the first intersection, or you’ll be driving on the runway.” Those were certainly different times.’

Many of the tests that Peck and his team obtained from research groups throughout the UK are still being used at CHDR in NeuroCart, CHDR’s comprehensive, automated test battery used to study the pharmacodynamics of CNS drugs in healthy subjects and – increasingly – patients.

An atypical job interview

Adam Cohen’s own time at Beckenham began with a bit of serendipity. ‘My original plan was to become a paediatrician,’ recalls Adam, ‘and I intended to do my residency in Rotterdam with Henk Visser, who was the head of the paediatric department there. Even back in the early 1980s, it was Henk’s vision to conduct more pharmacological research in children, which of course has become an important topic in recent decades. So Henk pushed me to do research in clinical pharmacology. Not knowing where to start, I asked Douwe Breimer, a professor of pharmacology in Leiden who I knew from my previous studies, for advice. I followed Douwe’s suggestion to write to the Wellcome Foundation, not knowing that it would seal my fate.

‘First,’ says Cohen, ‘I was visited by one of Wellcome’s marketing reps, who invited me to interview with a delegation from the Wellcome Trust at the Marriot Hotel in Amsterdam.’ Cohen arrived at the designated date and time, prepared for a formal job interview. But he had no idea what the others looked like, and almost everyone in the bar spoke English. ‘Just when I was about to give up,’ says Cohen, ‘a trio of very British-looking fellows caught my eye. But even then, our meeting was nothing like a traditional job interview.’ While the four men drank beer, Cohen was explicitly told not to talk about himself. A few weeks later, Cohen flew to England, and the procedure was repeated at the White Bear Pub in Beckenham. Thirty-five years later, Fowle explained that he knew that the late Munro-Faure – a former Navy man – believed that a good pint of beer equalled at least one hour of psychoanalysis. Apparently, in Cohen’s case this evaluation told Munro-Faure what he needed to know, and Cohen was hired.

The open atmosphere at Beckenham

Cohen would spend the next three years in the United Kingdom, enjoying the academic freedom at the Wellcome Foundation. ‘It was the perfect environment to do science,’ says Cohen. ‘There was a very open and unthreatening atmosphere. Nobody told me what to do, but it was clear that you were expected to come up with good ideas and carry them out within a reasonable timeframe. In many respects, we had tremendous

freedom. We could develop and perform an experiment within a couple of days. There was also a free flow of ideas. We would regularly have tea with the chemists and pharmacologists in the preclinical pharmacology unit, discussing the substances they were testing and the methods they were using to measure pharmacodynamic effects in animals. I'm still convinced that this free dialogue between preclinical and clinical drug development can be very beneficial to the whole process.

'This level of informality and freedom was possible only because of the site's small scale. Mr Lapthorne, who guarded the gate, knew everybody and everybody knew him. Even Nobel Laureate Jim Black, the Director of Therapeutic Research until 1984, could be easily approached by junior staff.' But this unique atmosphere of Beckenham soon began to change. New security measures were introduced, partly due to threats by the Animal Liberation Front. ID badges were required, making it more difficult to visit other buildings. Moreover, one now needed an appointment to visit the pharmacology unit, so informal contacts became less common. After the Wellcome Trust sold part of its holdings on the Stock Exchange in 1986, a target-driven culture emerged.

How times have changed

Listening to these stories about clinical drug development in the 1980s, one almost develops a sense of nostalgia. But in many ways, it wouldn't be possible – or even advisable – to turn back the clock. Or, to put it more positively, there's been quite a bit of progress in the way that clinical studies are performed these days.

Back in those days, the facilities available at Beckenham for first-in-human studies were extremely limited. An experiment could be performed during the day, but subjects could not stay through the night. Fowle and Cohen recall the time that they studied a novel compound that had a long half-life, making it necessary to find a location where their subjects could stay overnight. A 'proto-CRU' (clinical research unit) was set up in a nearby hotel, and all of the subjects, equipment, and staff were moved there. The owner had agreed not to check-in any other guests for that night; however, because of a local sporting event, some of the rooms were given to outside guests. This led to some confusion the next morning when these guests were awakened by a nurse knocking at the door to collect blood.

Major changes also occurred with respect to medical ethics. An important change for the better was the introduction of medical ethics committees. 'Even in those early days,' says Cohen, 'we were asking for a medical ethics committee at the Wellcome Foundation. Munro-Faure and others saw the importance of thoroughly reviewing the ethical aspects of a study, but they argued that this was already being done. This was true of course, but I now believe firmly that a separate review by an independent medical ethics committee is essential.

'What intrigues me,' continues Cohen, 'is how ideas about ethics have changed over the years. When I started at the Wellcome Foundation, it was common practice to test substances on oneself, and it was considered acceptable for employees to volunteer for clinical tests. After all, these were educated people who were quite familiar with the test compound, so in a way they were ideal subjects.'

Cohen remembers one particular project from his days at Beckenham: development of the antiepileptic lamotrigine. In keeping with their tradition of using employees as volunteers, Anthony Peck was the first human to receive a dose of lamotrigine, the very drug that he ultimately

‘It was my job to keep us out of trouble. We had a strong reputation dating back to before the war, and I didn’t want to do anything to damage that.’

helped develop. ‘Tony was aware that several dogs died after receiving lamotrigine,’ says Adam. ‘But luckily, humans and dogs metabolise lamotrigine differently. At the time, we both thought that our approach was perfectly acceptable from an ethical perspective. Of course, we now recognise that some employees might not feel comfortable refusing to participate in a trial.’

Returning to the Netherlands

Cohen’s PhD thesis at Beckenham was based on the development of the antihistamine acrivastine. At the end of 1986, he received a phone call from his former advisor, Prof Douwe Breimer, who had just received approval from the Dutch government to create a new clinical pharmacology unit in Leiden (see also page 6). Breimer invited Cohen to return to the Netherlands to run this new unit. ‘I liked what I was doing in the UK,’ says Cohen, ‘but Douwe’s offer was very attractive. Plus,’ he adds, ‘our children were reaching the age where we would have to decide which primary school they would attend, and we preferred to have them at a Dutch school.’

The rest, of course, is history. For those interested in that history, the rest of this book will hopefully provide ample reading material. But the spirit of Beckenham does not lie only in the past; it’s very much alive today at CHDR. When discussing drug development, Cohen refers frequently to his experiences at Beckenham, and many of the tests that were perfected at Beckenham are used at CHDR, for example in the form of NeuroCart. But far more important than these explicit references are the parallels in the culture between those early years and CHDR as it stands today.

It’s easy to point out the obvious differences. For example, CHDR’s ultra-modern building of glass and steel looks nothing like a Victorian mansion. But when we look deeper, a familiar picture emerges. Once upon a time, there was a clinical research unit with a strong focus on measuring pharmacodynamics in early drug development. They had an open, informal atmosphere, and employees were encouraged to speak their minds. Staff members worked there for many years, driven by their strong sense of internal motivation… •

‘I thoroughly enjoy working at CHDR – that’s why I’ve stayed’

Ria Kroon has spent her entire career at CHDR, and over the years her job description has changed profoundly, from operating the HPLC analysis equipment in the lab to running a large part of CHDR’s operations. Now, CHDR’s very first employee shares some of her fondest memories.

***Ria Kroon**, Manager of Operations, CHDR*

Ria Kroon was hired in 1987 by CHDR’s founder, Prof Douwe Breimer. ‘While training to become a laboratory technician,’ says Kroon, ‘I interned at the Leiden University Hospital pharmacy and at the toxicology department. When I finished my studies, CHDR offered me a job. And I was delighted to accept, because there wasn’t much work available at the time. As things turned out, it was the perfect job for me.

‘Looking back on the past three decades, CHDR has become a completely different organisation. When I think back to those first few years, it’s almost a different world than it is today. But the changes have been relatively gradual, so we’ve all had the chance to adapt.’

Before the first building

When Kroon started working at CHDR in February 1987, the foundation existed on paper, but that was about it. ‘There was hardly anything there,’ recalls Kroon. ‘We didn’t even have our own building, and I think Adam Cohen was still in England at that time. But we did have an HPLC [high-pressure liquid chromatography] machine in the Sylvius building, where many of the basic medical laboratories were located. I performed blood analyses for the clinical pharmacology researchers, and I can remember measuring blood concentrations of drugs such as digoxin. That’s how it all began.’

A small team

A few months later, Kroon and her colleagues were working in a small building known simply as ‘Building 55’, a structure that had belonged to the Leiden University Hospital pharmacy, what is now called Leiden University Medical Centre (LUMC). The space included one room for experiments, with about four beds. ‘In the first five years or so, all the pharmacokinetics analyses were performed in our own lab, by me, that is. Today, these analyses are conducted elsewhere.’

‘Because we enjoyed a lot of freedom, we had the opportunity to develop ourselves.’

Kroon liked her job. ‘We had a small team; we knew each other extremely well, and we all knew everything that was going on at CHDR. You had to be flexible, and you had to be prepared to take on tasks that were beyond your regular job description. Because we enjoyed a lot of freedom, we had the opportunity to develop ourselves. For me, this meant that as the organisation grew, I could grow with it.’

An eight-year cycle

The first major change at CHDR came in the early 1990s, when Building 55 had become too small. CHDR looked for ways to expand, but ran into difficulties. After a failed attempt to build a new facility on the Leiden University Hospital premises, Cohen and his team turned their attention to the Leiden Bio Science Park, which had been created back in 1984. ‘About every eight years,’ says Kroon, ‘CHDR has experienced a major growth spurt.

‘Knowing that others are watching what you do keeps you alert and prevents you from settling into a routine.’

The new building was ready in 1995; in 2003, a second building was added, and we started construction on our current building in 2011.’

Moving from the lab to quality assurance

Kroon’s own career followed a similar pattern. A major change was triggered by an audit by the Healthcare Inspectorate soon after CHDR moved to its first building in 1995. This audit earned CHDR its certification for Good Clinical Practice. At the same time, the inspectorate recommended that CHDR invest more in quality assurance (QA), and Kroon became CHDR’s first QA manager. ‘At first,’ says Kroon, ‘I was able to combine these new duties with my work in the lab; but QA soon demanded all of my attention. We had to develop an increasing number of standard operating procedures, and of course our sponsors were demanding a high level of operational quality. That’s certainly a good thing. Knowing that others are watching what you do keeps you alert and prevents you from settling into a routine. After all, the safety of our subjects is our top priority and demands that we’re always alert.’

From quality assurance to running operations

About the same time that CHDR’s facility doubled in size, Kroon became responsible for operations. She now ensures that all parts of the intricate machinery operate smoothly by keeping a close watch on all aspects of operations at CHDR, starting when the contract is signed for a new study. Today, Kroon focuses on the lab, data management, subject recruitment, and the CNS research unit. Things have certainly changed since the early days when she was aware of literally everything going on at CHDR, but she’s still at the heart of the organisation. ‘I’m still involved in the vast majority of the work we do here,’ says Kroon. ‘A lot may have changed here over the years, but it’s still a great place to work.’

‘Watching everything change’

From the early days at CHDR until just three years ago, Prof Meindert Danhof served as the Chair of CHDR’s Scientific Advisory Board. Before CHDR was even founded, Danhof was involved in clinical studies at Leiden University. ‘It’s been really interesting to see all of the major advances that occurred over the years.’

***Dr Meindert Danhof**, Professor of Pharmacology at Leiden Academic Centre for Drug Research, former Chair of the CHDR Scientific Advisory Board*

‘Looking back over the years,’ says Danhof, ‘I’m amazed by how much has changed in the field of clinical pharmacology research. When I conducted my first experiments, using paradigm drugs to study drug metabolism, we used the offices next to the lab to administer the drug. If our subjects needed to stay overnight (for example, when we studied a sleeping pill), we rented rooms at the local Holiday Inn. Compared to those early days, our current facilities – with standard operating procedures, GLP conditions, and large numbers of staff – are a completely different world.’

‘Proto-CHDR’

‘I arrived in Leiden as a PhD student in 1976, after studying pharmacy and pharmacology in Groningen. My thesis supervisor was Prof Douwe Breimer, who had been appointed a professor of pharmacology just one year earlier. At the time, Douwe was busy modernising the pharmacy programme at Leiden University. He wanted future pharmacists to understand clinical pharmacology, so he organised a course in which clinicians could discuss their pharmacotherapy choices. In that context, it became increasingly important to also play an active role in clinical pharmacology research. Despite the lack of facilities, we managed to conduct some rather interesting pharmacokinetics studies. I used phenazone – also known as antipyrine – to measure the activity off various enzymes that oxidise drugs. Using blood, urine, and saliva samples, I studied the disposition and pharmacokinetics of phenazone under various conditions. That work became the basis of my thesis. In a way, what we were doing was a kind of “proto-CHDR”.’

Changes at Leiden University

‘After I obtained my PhD,’ says Danhof, ‘I went to the United States, where I was a postdoc with Professor Gerhard Levy at the State University of New York at Buffalo. I then continued my work in clinical pharmacology at Stanford University Medical Center. Later, when I returned to Leiden, I found that there had been some major changes. As a result of cuts in the national budget for higher education, Leiden University had lost its pharmacy faculty. Thankfully, though, Douwe managed to preserve much of the pharmacology research, establishing a centre for biopharmaceutical sciences in what is now the Leiden Academic Centre for Drug Research. Connected with both the science faculty and the medical faculty, this highly productive centre quickly became internationally recognised for research and education. Right around that time, when the dust from those major changes had settled, Douwe had the idea to establish CHDR.’

Different drugs

‘In the 1980s, before CHDR, we conducted clinical pharmacology research using an improvised approach in our lab. In the US, I had become interested in studying pharmacodynamics using paradigm drugs, and we continued to study this. But we also studied calcium channel blockers, beta blockers, low-molecular weight heparins, interactions between several drugs and gastric acid inhibitors – in short, we studied a wide range of compounds with a wide variety of indications. We did a bit of contract research as well, but we always wanted to add some science. Pharmaceutical companies were almost exclusively interested in their drug’s bioavailability and pharmacokinetics. But we always felt that you shouldn’t separate pharmacokinetics and pharmacodynamics; we wanted to study both. And that philosophy would become one of the guiding principles at CHDR.’

Finding the right balance between business and science

‘For more than 25 years, I served as both a member and the Chair of CHDR’s Scientific Advisory Board. And I truly enjoyed the experience, feeling that I helped contribute to CHDR’s continued success. Our job on the SAB was to ensure high scientific quality at CHDR, and this became even more important as CHDR shifted gradually from subsidised academic research to contract research. We always had to keep a close eye on the balance between business and science. We [the SAB] were critical of protocols that didn’t seem to contribute significantly to science, for example studying only the bioavailability of a new compound. Luckily, most of the projects at CHDR are in the interest of science and in the sponsor’s interests as well.’

Helping educate young scientists

‘The role of the Scientific Advisory Board has changed over the years. In the early days, we would evaluate each protocol before it was submitted to the Medical Ethics Committee in order to ensure the scientific quality of the study. Later, this became a source of tension, as our discussions regarding critical questions occasionally interfered with the planning of studies at CHDR. The SAB is comprised of clinicians and other professionals from a wide range of disciplines, and sometimes they tended to stand on a soapbox, focused on a specific agenda. Today, the role of the SAB has evolved to giving advice about a protocol, and CHDR’s Management Team usually decides whether to send the protocol to the Medical Ethics Committee.

‘Shortly after this change in the SAB’s role,’ continues Danhof, ‘we came up with the idea of involving young scientists at CHDR to participate in our meetings. SAB meetings are now open to all CHDR staff, and PhD students and other scientists are welcome to join in the discussion. Usually, the project leader would present the protocol, and then I’d ask one of the PhD students to give critical feedback before the scientific experts had their say. I understand that the SAB still operates this way, and I think it really contributes to the SAB’s educational role.’

‘Luckily, most of the projects at CHDR are in the interest of science and in the sponsor’s interests as well.’

Changes in clinical pharmacology

‘Although I’m no longer involved directly in CHDR’s research programme, it’s clear that they’re increasingly involved in research with patients. And I think that’s only logical. There were three major chapters in the history of drug development. In the first chapter, which lasted until the second half of the twentieth century, drugs were mainly symbolic in value. Of course, some effective substances such as opium were available, but most diseases could not be treated effectively using pharmacology. In the second chapter, receptor theory, pharmacology, and pharmacokinetics led to the development of a wide variety of highly effective drugs that primarily treated symptoms by changing

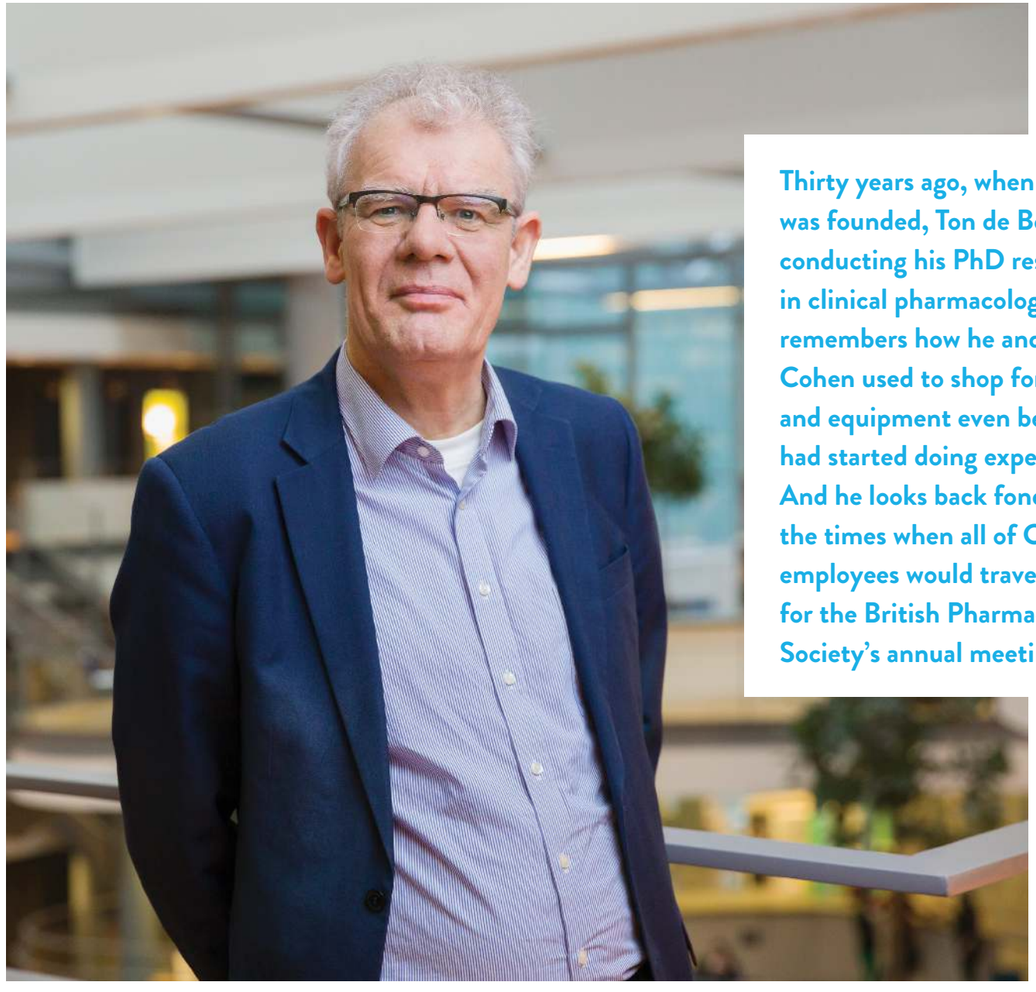
the patient's physiology. Most of these drugs also had measurable effects in healthy people, so it became possible to study pharmacodynamics in healthy volunteers. We're currently in the third chapter, and it's now possible to use pharmacology to directly interfere with pathophysiological processes. Based on insights gained from systems biology and fundamental research, many of these new drugs might not cause measurable changes in healthy people, even if they are quite effective at slowing – or even reversing – disease progression. So if you're interested in pharmacodynamics, there may not be much to see in the earliest phases of clinical drug development. That's why I think it makes sense for CHDR to conduct more research in patients.'

'Many modern drugs might not cause measurable changes in healthy people, even if they are quite effective at slowing disease progression.'

Using models

'An inherent part of this third chapter in drug development is the strong connection with molecular biology and the mechanistic approach to treating disease,' says Danhof. 'CHDR is also involved in this new approach, particularly the group studying biomarkers. And I believe they can do even more using the kind of research that my colleagues and I have done the past few decades. We've been modelling the relationship between pharmacokinetics and pharmacodynamics by creating so-called "PK/PD models". I founded LAP&P (Leiden experts on Advanced Pharmacokinetics & Pharmacodynamics), a Dutch company that provides consultancy services to pharmaceutical companies using these PK/PD models. Personally, I'd like to see CHDR and LAP&P work together more closely, as their expertise is highly complementary. Of course, they're neighbours in the Leiden Bioscience Park, so anything's possible...'

'Travelling to London with CHDR was great fun.'



Thirty years ago, when CHDR was founded, Ton de Boer was conducting his PhD research in clinical pharmacology. He remembers how he and Adam Cohen used to shop for supplies and equipment even before CHDR had started doing experiments. And he looks back fondly upon the times when all of CHDR's employees would travel to London for the British Pharmacological Society's annual meeting.

***Dr Ton de Boer**, Professor of Pharmacotherapy, Utrecht University*

Anyone who was in Leiden 30 years ago may remember the small temporary building close to the Leiden University Hospital Pharmacy; that was where CHDR started. But only a handful of people remember how clinical research was done before this dedicated unit. De Boer is one such person. 'I was doing part of my PhD research in the Sylvius Laboratory building,' he says, 'which housed most of the medical faculty's basic lab, as well as some of the science faculty's labs. There were few facilities available for administering drugs or monitoring subjects. Legend has it that one of our subjects was found in an elevator with an I.V. cannula in his arm, where he had fainted. Obviously, it was not the ideal setup for the kind of research that we were doing. One of the drugs I was testing was a low-molecular-weight analogue of the blood thinner heparin. These days, if you're testing a drug that affects blood clotting, you need to observe all kinds of safety measures. Even back then, we didn't feel good about it, so we were glad when CHDR was established and conditions improved.'

A salesman on a lie detector

'If I remember correctly,' continues De Boer, 'I was actually hired before Adam Cohen. We started the organisation from scratch, and we had to go out and buy virtually everything we needed: pencils, trashcans, you name it. I remember the time that Adam and I went to Amsterdam to look at an expensive device that could measure several cardiovascular parameters. The salesman demonstrated by hooking himself up to the device – a huge cupboard-sized machine – which showed his heart rate, among other things. When we started negotiating the price, he was still connected to the machine, and we were amused to see how his heart rate went up during the negotiations. It's not often that you can negotiate with a salesman who's connected to a basic lie detector.'
De Boer has many more fond memories of CHDR's start. There was an enthusiastic atmosphere as the team was creating this new organisation. 'For most of us, it was all rather new. But Adam's experience at the Wellcome Foundation (see also page 12) meant that he already had some very clear-cut ideas about how to conduct clinical drug research, and under what conditions. One of the things he insisted upon was that the temperature in the facility needed to be carefully regulated. But there we were, in a dark-brown wooden building that would be cold in the winter and hot in the summer. As a result, the service engineer from the air conditioning company was a regular guest at CHDR.

'Each year,' continues De Boer, 'we would all go – scientists and support staff alike – to the annual meeting of the British Pharmacological Society. Adam has always been extremely generous, and he wanted us to enjoy London. He would show us the sights, and we'd go to the opera, things like that. So it was much more than a trip to a major scientific meeting; it was also a valuable team-building experience.'

Improving methods

From the beginning, CHDR has combined contract research for pharmaceutical companies with its own science-driven approach. 'We were always looking for innovative approaches,' says De Boer. 'For our study using the low-molecular-weight heparin analogue, one of the experiments involved combining this new compound with the standard coumarin treatment regimen. The idea was to give healthy volunteers low-dose coumarin for more than a week until a steady-state level of coumarin was achieved, and then administer the heparin analogue. Even though the dose of coumarin was low, we were looking for an even safer alternative. So we decided to add an extra group in which we didn't aim for steady-state coumarin levels; instead, we gave subjects a single dose, followed by the heparin analogue. We found that this approach was just as valuable for studying the combination of these two drugs. This additional experiment wasn't financed by our sponsor, but later we used this approach to study other low-molecular-weight heparin preparations.' De Boer also remembers another example of innovative research in which they studied the effects of several drugs on pharmacokinetics, focusing on specific liver enzymes.

'In my view, CHDR has always been more than just a conventional CRO,' says De Boer. 'As an academic unit, they also conduct their own innovative research. I believe this provides added value to their sponsors. I remember how Adam once scoffed that one of their competitors had grown much too large. Today, CHDR is even larger, yet they've remained true to their roots.'

'CHDR has always been more than just a conventional CRO. As an academic unit, they also conduct their own innovative research.'

An entire trajectory

After obtaining his PhD in 1990, De Boer moved on. 'I wanted to broaden my horizons,' he explains, 'so I joined the clinical epidemiology group in Leiden, headed by Prof Jan Vandenbroucke, who'd served on the reading committee for my thesis. I knew almost nothing about epidemiology, but I learned quickly, and I soon became a pharmacoepidemiologist. In epidemiology, exposure is an important – yet often difficult to measure – variable. But in pharmacotherapy, you know exactly which molecule, and how much of it, the patient received. This can make at least one part of an epidemiologist's work easier.'

In 1994, De Boer became a registered epidemiologist; in 1996, he became a clinical pharmacologist as well. 'I was offered a position as an associate professor at Utrecht University, which I took without hesitation. At that point, the focus of my research shifted to the post-marketing phase of drug development. So now when I teach students, I can show them the entire drug development process, from preclinical drug development, through early-

stage clinical testing, up to the pharmacoepidemiology studies that we're now conducting.' In 2001, De Boer was appointed a Professor of Pharmacotherapy and became the Director of the Utrecht University School of Pharmacy.

'I can show my students the entire drug development process, from preclinical drug development, through early-stage clinical testing, up to the pharmacoepidemiology studies that we're now conducting.'

In his current research, De Boer uses large, population-based databases such as the British Clinical Practice Research Datalink and the Dutch PHARMO database, which contain pharmacy data for millions of people. Without violating patient privacy, these data can be linked to data obtained from hospitals and primary care physicians. 'These datasets are a treasure trove of information if you want to know how pharmacotherapy truly works in real-life situations,' explains De Boer. And this is of course relevant for making the right choices in pharmacotherapy. For example, if a doctor wishes to know the risks associated with prescribing a sleep aid to an elderly patient, I can calculate how much this medication will increase the likelihood that the patient will fall and possibly break a hip. Another good example is using these data to help clinicians decide between a traditional blood thinner and a new oral anticoagulant.

'So in a way, what I do now is the exact opposite of the work I did at CHDR. Today, I study extremely large groups of actual patients using population-level data; at CHDR, I tried to obtain as much information as possible from a small group of healthy volunteers. I'm glad I had the opportunity to do both, and I'm proud of CHDR's success and growth through the years. And the scale of things at CHDR has changed so much. When I think back to the way we recruited subjects in those days, posting A4-size ads on doors and bulletin boards, and I compare it with the high-tech recruitment department they have today... That's quite a transformation. And they grew gradually, but steadily. I'd say that's an impressive achievement, wouldn't you?' •

'I'm proud to see how many people at CHDR use Promasys'

Jos Hennen, Director of Software Development, OmniComm Systems

The data management system Promasys could be aptly described as the 'DNA' of CHDR. The development of this system started shortly after CHDR was founded, and even 30 years later it remains a vital part of CHDR's infrastructure. Jos Hennen, who developed Promasys, tells the story of his brainchild and CHDR.

‘I was hired in the early days of CHDR,’ says Hennen. ‘In fact, I was “employee number 5”. They needed someone to develop a data management system, and after several applicants I was the first who told Adam that such a system simply could not be ready in three months. I think that’s one of the reasons he hired me. At first, my main task was to unpack the computers – which were still in their original boxes – and build a basic network by installing the operating system, software, everything. This was all back in 1987, back in the days of monochrome monitors, MS-DOS, limited graphics, etc. Once everything was up and running, I began to develop what would later become Promasys.’

‘Because it was developed around the work itself, the staff quickly accepted the system.’

A high rate of acceptance

Hennen designed Promasys based on information he obtained from talking with CHDR’s staff. ‘My main goal was to keep everything very practical,’ he says. ‘In other words, close to the core business at CHDR. The system had to fit with the workflow that they were used to. The staff needed a system that could keep track of all the data in a study, as well as print labels for sample tubes, things like that. Because it was developed around the work itself, the staff quickly accepted the system. I remember we had an employee once who didn’t like the layout of the labels, so he tried to make something fancy using a text editor. But he soon returned to using Promasys.’

As CHDR grew, and as the needs of their sponsors changed, Promasys changed as well. Hennen made these changes personally, providing CHDR with regular software updates. For almost three decades, Mr Hennen has been ‘Mr Promasys’. In 2003, 15 years after Promasys was launched, the Management Team and Board of Trustees wanted to ensure that this system was still the best option available. Hennen has every reason to take pride in their findings: a review of other products on the market clearly showed that Promasys was still the best system for CHDR’s needs. The Management Team then came up with the idea to commercialise the data management system, selling it to CROs around the world. Thus, the next chapter in Promasys’ story began.

An international success

‘We started a new company, also called Promasys,’ says Hennen, ‘in order to capitalise on the intellectual property rights connected with our data management system. Promasys was a private company, and unlike CHDR, we could generate profits and pay dividends. We kept our close connection with CHDR of course, but we also marketed our product worldwide. My initial plan was to focus first on the European market and then gradually expand from there; but we started with six customers in South Korea, academic institutions that Adam had done business with and told about Promasys. From there, our client base began to expand rapidly. At the peak of our development, we had around 35 customers from all around the world, including Japan and the World Health Organization in Geneva. The Promasys system was used to support a wide variety of studies, from research on infants in India to drug trials in Italy. Those were really exciting times. I was still in charge of software development, and we hired Wolf Ondracek to manage the business development.’

Of course, Promasys’ international client base came with both benefits and challenges. ‘We outsourced a part of our development work to Sri Lanka,’ recalls Hennen. ‘So all of a sudden, I had to fly to the city of Colombo to train people. I barely had enough time to get all of the necessary vaccinations.’ And he remembers his first visit to Korea. ‘My doctor gave me a list of ten “dos and don’ts” if I wanted to avoid getting diarrhoea and other infections. You might know the drill: don’t eat raw vegetables that you haven’t washed yourself; only drink from a bottle that you opened yourself; never buy from the food stalls along the side of the road; those kinds of things. That’s all well and good if you’re there as a tourist; but if you’re invited as a guest, you don’t want to be rude by refusing their hospitality. So it’s almost impossible to follow all of these rules. After just the first day, I had already broken seven of the ten rules, including eating raw – but delicious – fish. Luckily, everything went fine, both with the training and with my personal health.

‘It was exciting, but sometimes it was challenging as well,’ says Hennen. ‘We often needed to improvise. I regularly found myself sitting in a hotel room preparing the slides for the next day’s training session. Some clients were quite eager to learn everything about Promasys. When I returned to South Korea years later, I met several new people who were familiar with all of the details of our system. Other clients had a more laidback approach. For example, I remember a professor from Italy who insisted on visiting our facility in Leiden. He and his team showed up several hours late for their appointment. It turned out that they had gone to the opera in Verona the evening before and were not exactly in the mood to hear all the details regarding our software. Two hours later, they left.’

‘CHDR has certainly evolved and grown in these three decades. But during all those years, they’ve always used Promasys.’

Keeping it simple

Dr Hermanus Boerhaave, the famous seventeenth century professor of medicine in Leiden, firmly believed in the Latin phrase ‘Simplex veri sigilum,’ which translates roughly to ‘Simplicity is the hallmark of truth.’ This could certainly be the motto for Promasys. ‘I’ve always advocated staying close to the core,’ explains Hennen. ‘Time and again, clients want to know if we could integrate Promasys with other software packages or devices. And time and again, we politely refuse. Not that it’s difficult,

but you have to think ahead. It may seem attractive to integrate your systems, but each link to another software package has to be tailor-made, so each client would need a new set of interfaces. And when one of the linked systems is upgraded, or if they acquire a new type of device, another interface is needed. There's simply no way to support these continuous developments, not in a niche market like ours. But of course, we always keep up with the times. For example, we created an interface for Promasys for use on an iPad, so nurses and research assistants can enter data using their tablet.'

The move to OmniComm Systems

Although they had many satisfied customers, Promasys was not a huge commercial success. 'A data management system that's tailored to the needs of early drug research is quite a specialised product, catering to a niche market,' says Hennen. 'In the beginning, we didn't even know how much to charge for the system, so pricing was a major bottleneck in the development. And we were still closely connected to CHDR, one of our major shareholders. With respect to CHDR's accounting, our estimated value was negatively affecting their financial balance. That's why in 2012, the Board of Trustees proposed that CHDR sell their Promasys stock. Promasys became a subsidiary of OmniComm, and CHDR retained the right to continue using the Promasys system.' Today, Hennen and Ondraceck – both of whom had been employees at Promasys – are now employed by OmniComm, where they continue to develop the data management system.

Maintaining close ties with CHDR

Although he's no longer a CHDR employee, Hennen still works in the same building, and he eats lunch in CHDR's cafeteria. He notes with pride that the software system that he wrote has become part of the CHDR's workflow and way of thinking. 'To give an example,' says Hennen, 'back in 1988 we had to come up with a single term that would cover the entire treatment period. So we came up with the term "occasion", which is still used today in the latest version of Promasys. For CHDR's employees, it's just the way we call it; but someone not familiar with Promasys would not know what you mean by an "occasion". CHDR has certainly evolved and grown from the small unit where I first worked, to become a large company with more than two hundred employees. But even during all those years, they've always used Promasys; it's been a constant factor at CHDR.

'In many respects, things have come full circle,' says Hennen. 'My children sometimes work part-time at CHDR, entering data into Promasys. So now, I get suggestions for improvements from my own children. And at the business level, we're now discussing a special licensing deal for CHDR, and I will remain in charge of keeping Promasys up-to-date. So in a way, Promasys has returned to its beginnings, and I'm glad for these developments. I always feel at home at CHDR, and I'm proud that I've contributed to their success.'

'CHDR is always looking for what's just around the corner'

A quarter of a century ago, a fresh PhD graduate from Switzerland arrived in Leiden to train to become a clinical pharmacologist. Now, after an impressive career in the pharmaceutical industry, Dr Andreas Wallnöfer still works closely with CHDR. 'I value our relationship, which is based on mutual trust and integrity.'

***Dr Andreas Wallnöfer**, General Partner, BioMedPartners AG and Life Science Management Consultant; Former Head of Clinical Research & Exploratory Development, F. Hoffmann-La Roche Ltd.*

'When I first came to CHDR in 1992, it was still a small organisation,' recalls Wallnöfer. 'They had only about twenty employees and just a few beds for subjects. Compared to the organisation you see today, it was a rather small-scale operation. They had a handful of dedicated investigators working on several research areas. We investigated CNS drugs, working with a battery of tests now known as NeuroCart. And Koos Burggraaf was already there as well, studying cardiovascular drugs and novel anticoagulants. At the time, I focussed on CNS drugs, but I also was involved in cardiovascular research. There was an open atmosphere at CHDR, where we could discuss anything; even when we'd have a strong disagreement, we'd still be friends. I had a very good time in Leiden.'

Developing new methods

While training in Leiden, Wallnöfer had a first-hand view of CHDR's *modus operandi*. 'Adam had a clear vision of how CHDR should develop; rather than simply trying to copy other groups, he created a new way: the CHDR way. Adam understood the importance of having validated tests for measuring pharmacodynamics, ideally in a variety of populations. When I was there, we studied the development of tolerance to several CNS drugs – particularly benzodiazepines – in various age groups of both healthy subjects and patients. Even in those early days, CHDR invested heavily in developing new methods. Although our work was not paid by a sponsor, it made CHDR more attractive to potential sponsors. If a company wanted to understand the clinical profile of their compound, we could easily compare it to the profile of a reference compound.'

After completing his training as a clinical pharmacologist, Wallnöfer returned to Basel, where he was offered a position at F. Hoffmann-La Roche. 'I continued to collaborate with CHDR, working together to develop several drugs in various research areas.'

'Adam had a clear vision of how CHDR should develop; rather than simply trying to copy other groups.'

At Roche, working in different areas, Wallnöfer benefited from what he had learned at CHDR. His first project, developing a CNS drug, was quickly discontinued when the clinical data did not support the target profile. At CHDR, he had learned that addressing key questions early in the development programme is essential. 'My second project at Roche was bosentan,' says Wallnöfer, 'which is now sold as Tracleer®. We conducted the first-in-human clinical pharmacology trials in order to investigate novel mechanisms of an endothelin antagonist. Bosentan was ultimately developed by Actelion Ltd., a spin-off of Roche, and it's now an important drug for treating pulmonary hypertension. For a drug developer, it's highly rewarding when a compound becomes an established treatment, benefitting patients.'

At Roche, Wallnöfer served as the Head of Clinical Research & Exploratory Development. He also served as a member of the F. Hoffmann-La Roche Pharma R&D Leadership and Portfolio Committee for more than 12 years, and he played a key role in integrating Genentech as a subsidiary of Roche in 2009. He later became the Head of Early Development, and later he also became the Head of the Cardiovascular & Metabolism R&D unit. Wallnöfer remained at Roche until 2015, successfully developing several drugs.

Since leaving Roche, Wallnöfer has been involved in national life science initiatives in Switzerland and has advised the Ministry of Health in Singapore. He also served as a consultant to the management and supervisory boards of several biotech companies, and Is now a partner at BioMed Partners, a Swiss venture capital firm that focusses on investments in central Europe and Benelux. Recently, Wallnöfer served as the interim Head of Development for a biotech company, helping them navigate FDA and EMA regulatory meetings for endorsement of the clinical programme.

Future-oriented

'I've always admired CHDR's dedication to scientific excellence and their passion for innovation,' says Wallnöfer. 'They're quite different from most CROs, even though other CROs have now begun including more pharmacodynamics research in early-stage clinical development. CHDR continues to look to the future, anticipating changes in the drug-development process. For example, thanks to their cutting-edge facilities and vast network, they're conducting more studies with patients in response to the growing importance of including patients in the early stages of drug development. And of course, they have highly sophisticated biomarkers for measuring pharmacological effects in distinct populations of both patients and healthy subjects. CHDR never stands still; they're always looking ahead.'

A powerhouse of knowledge

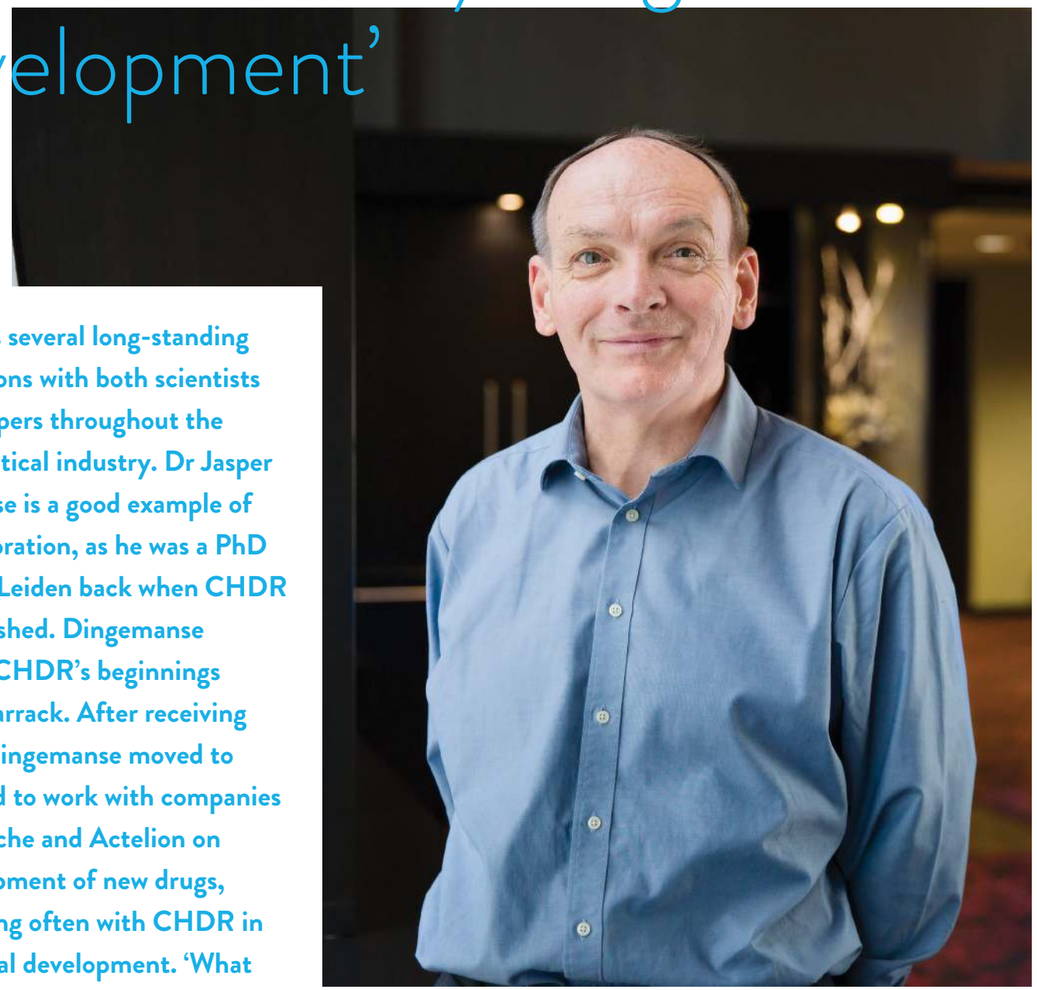
Wallnöfer was there to witness the start of CHDR and its growth through the years, and today he's able to witness their next initiative: CHDR Innovation Services. This new business unit, which is currently being developed, will provide consultancy services and strategic partnerships to biotech companies, helping young biotech companies survive the vulnerable first few years and develop their portfolio.

'CHDR has a strong connection with both academia and industry,' says Wallnöfer, 'and they're always up-to-date with respect to new developments. Because CHDR Innovation Services will be embedded within CHDR itself, they'll continuously have new input in terms of knowledge, experience, and personnel.

'CHDR continues to look to the future, anticipating changes in the drug-development process.'

'I believe that CHDR Innovation Services will help these start-up companies become highly successful. We'll have to wait to see how it works out, but one thing I know for certain is that it'll be a pleasure collaborating with my friends at CHDR. They're always very open and direct, which is the right approach for preventing misunderstandings and building a lasting, trusting relationship.' •

‘CHDR is a pioneer in pharmacodynamics research in early drug development’



Dr Jasper Dingemanse, Vice President and Head of Clinical Pharmacology, Actelion Pharmaceuticals Ltd.

CHDR has several long-standing collaborations with both scientists and developers throughout the pharmaceutical industry. Dr Jasper Dingemanse is a good example of this collaboration, as he was a PhD student in Leiden back when CHDR was established. Dingemanse witnessed CHDR’s beginnings in an old barrack. After receiving his PhD, Dingemanse moved to Switzerland to work with companies such as Roche and Actelion on the development of new drugs, collaborating often with CHDR in early clinical development. ‘What I like about CHDR is that they’re driven by scientific curiosity.’

For nearly 28 years, Dingemanse has lived in the Big Pharma hub of Basel, Switzerland. But he still likes the way Dutch scientists communicate. ‘I value the straightforward comments from my colleagues at CHDR,’ explains Dingemanse. ‘I believe that in research, it’s good to challenge each other. My German and Swiss staff members sometimes find it a little difficult – it’s largely a matter of culture, of course – but they also see the value of clear communication. If we conduct a study with CHDR, we usually write the initial draft of the protocol; but then we discuss it with CHDR, often quite extensively. Most other CROs are happy to have you write the protocol for them, but they won’t necessarily challenge you to improve it.’

Roots in Leiden

Dingemanse studied in Leiden to be a pharmacist, after which he did his PhD research in pharmacology with Prof Douwe Breimer, the founder of CHDR. ‘Soon after I defended my PhD, I moved to Switzerland to work at Roche, where I stayed for seven years. Most of my research there focused on CNS drugs, particularly sleep aids and anaesthetics. I collaborated often with Adam Cohen and Joop van Gerven at CHDR.’ In the early 90s, Dingemanse encouraged Andreas Wallnöfer, a young Swiss pharmacologist at Roche, travel to CHDR to receive training as a clinical pharmacologist. Wallnöfer would later become yet another long-term collaborator with CHDR (see also page 37).

‘Of course, a lot has changed over the years,’ says Dingemanse. ‘CHDR changed, and I changed as well, and I’m now working for another company. However, it’s satisfying that even after all those years we’re still in business together. In the beginning, I travelled regularly to Leiden; but these days, it’s usually my staff who make the trip, so my contact with CHDR is limited primarily to phone calls, the occasional trip, and seeing CHDR staff at clinical pharmacology conferences.’

To illustrate a recent project with CHDR, Dingemanse refers to the development of a new sleep medication, in which Actelion developed several antagonists of orexin, a neurotransmitter missing in patients with a specific form of narcolepsy. ‘Joop was highly enthusiastic about studying such a novel approach to treating sleep disorders and developing a novel first-in-class compound,’ says Dingemanse. ‘The first compound failed in the later phases, but we’re now working together on another compound that looks quite promising. In a few months, the results of our phase 2 studies in adults and elderly patients with insomnia will become available. These studies were designed based primarily on results obtained in studies conducted in healthy subjects in collaboration with CHDR. So it’s exciting times, both for us and for CHDR.’

Innovating drug development

When asked whether he would characterise CHDR as a CRO, Dingemanse replies, ‘In some respects, they’re a conventional CRO. But they have additional qualities as well. To begin with, they have an excellent network of clinicians and basic scientists both locally and globally. In addition, CHDR is driven by scientific curiosity, which is a quality that most CROs tend to lack. And CHDR was among the first to study pharmacodynamics in early clinical drug development. Back in the 80s and 90s, most CROs studied bioavailability and pharmacokinetics – and

not much else – in healthy subjects. So it was a novel approach to study pharmacodynamics as well. Nowadays, this approach is increasingly common, but CHDR was among the pioneers. And they've been expanding that approach over the years, always adding new measurements and biomarkers to their toolbox. Another way that CHDR stands out is that many young scientists do their PhD research at CHDR, thereby contributing to scientific progress and the development of new methodologies.'

The high number of PhD students and trainees in clinical pharmacology at CHDR is somewhat unique. 'That's special,' says Dingemanse, 'and it can be an asset, because young researchers often bring a fresh approach and provide a new perspective. Having to educate these students often challenges the regular staff to be critical of their own approach. You won't get away with the simple argument, "We do it like this because that's how we've done it the past ten years." On the other hand, the relatively high turnover at the level of project leaders can be a slight drawback for the sponsor. We might not always work with the same people, and sometimes young researchers can overstep their bounds. Thankfully, though, there's very low turnover at the top, and I admire the way Joop handles difficult situations; he's not easily upset, and he always manages to keep things in perspective. So in the end, things always turn out well.'

The advantages of early pharmacodynamics research

'From the perspective of a pharmaceutical sponsor,' says Dingemanse, 'the added value of early pharmacodynamics research is that you get additional information about your compound. I prefer to identify – as early as possible – the compounds that won't make it, so I don't waste any more precious resources on them. In many cases, early studies using healthy subjects can provide evidence to show whether a new drug will be effective or not.

'As a clinical pharmacologist, I'm a strong proponent of this approach. In my experience, though, many physicians are reluctant to accept evidence from studies using healthy subjects. "After all," they say, "we develop drugs for patients, not for healthy people who don't need the medicine." That may be true for some classes of drugs, but for other classes – for example, sleep medications – pharmacodynamics can be studied in healthy subjects quite well. For example, it might be difficult to use healthy subjects to study the efficacy of cholinergic compounds in Alzheimer's disease, but you can still collect meaningful data using a compound that temporarily reduces a healthy subject's cognitive ability. Another example is to use CO_2 inhalation to induce transient anxiety in healthy subjects, and then investigate whether your test compound reduces that anxiety. These so-called pharmacological challenge models can provide valuable indications of a compound's effect. Of course,' adds Dingemanse, 'the artificially induced symptoms may not replicate precisely the target disease state, so you should interpret the data with care. The results might not be compelling enough to stop development at that stage, but they can provide important insights.'

__Dr Peter de Boer__, Senior Director of Experimental Medicine and Neuroscience and Head of Early Development Mood Disorders, Janssen Research and Development

'We're collaborating in order to explore new territory'

Dr Peter de Boer has been developing CNS drugs with CHDR for more than 15 years, with an increasing number of studies in patients. 'Sometimes, we conduct exploratory research, following an interesting idea to see where it takes us.'

'CHDR is exceptional among contract research organisations,' says De Boer. 'With other CROs, when you ask them to do a study, they smile politely, send you a quotation, and perform the experiments – even if they think the study is utter nonsense. With CHDR, I get honest and direct input, which leads to a much better outcome. Of course, their honest approach can be a bit disconcerting at times. I remember my first visit at CHDR. I was working for PRI, which was an American subsidiary of Johnson & Johnson. My boss – who was familiar with CHDR – introduced me to Adam Cohen. I had just landed this interesting job at a prestigious firm, and five minutes into our conversation, Adam turned to me and said, "It seems to me that you don't really know what to do with your job." And in a way, he was right; I was still learning my role as an intermediary between preclinical researcher and clinical drug development, and I was probably spending too much time on data analysis and not enough on concept development. But I must say, despite the initial shock I felt from Adam's bluntness, I also realised that these are people who won't sugar-coat their comments just to get our business.'

Studies with patients

'When I first began to collaborate with CHDR,' says De Boer, 'their specialty was demonstrating pharmacodynamic effects in healthy subjects using NeuroCart, and we conducted many valuable studies with Joop van Gerven. Increasingly, though, we felt the need for more extensive studies with patients. When studying depression, data obtained from healthy subjects might give an indication of target engagement, but it's difficult to make rational decisions without knowing the drug's effects in patients.' However, demonstrating a clinical effect of an antidepressant can be challenging. Traditional tests are based on questionnaires and symptom scales such as the Hamilton scale, which are not the most sensitive instruments for detecting drug effects. Moreover, it can take up to four weeks for an antidepressant to significantly affect symptoms in patients.

'In collaboration with CHDR, we use new procedures in addition to traditional measurements.'

'In collaboration with CHDR,' says De Boer, 'we use new procedures in addition to traditional measurements. It's been an adventure, but I must say that these new methods have worked surprisingly well. We've conducted three such studies (in a multicentre setting to facilitate recruitment), and the results have improved our decision-making process with respect to the next steps in developing these drugs. I think we're onto something quite interesting here.'

Exploiting the effects of sleep deprivation

To demonstrate the effects of antidepressant drugs in early development, De Boer and CHDR developed a special trick. It's been documented that patients with depression experience a temporary improvement in mood and other symptoms after missing a night's sleep. Of course, sleep deprivation cannot cure depression, but its effects are measurable. So to study the effects of an experimental compound on depression, researchers can measure how the drug influences the effects of sleep deprivation. 'In addition to traditional symptom scales and NeuroCart,' says De Boer, 'we also use a method developed by Catherine Harmer at Oxford to investigate reward sensitivity. Harmer and her colleagues found a correlation between reward sensitivity and anhedonia, a loss of interest and responsiveness to previously rewarding stimuli and activities, which is one of the symptoms of depression. This is a novel approach, and CHDR was eager to include it in their toolbox. For me, it was a valuable opportunity to collaborate with Joop and Gabriël Jacobs in implementing this new strategy.'

Exploring the unknown

One of the main challenges in developing CNS drugs is the fact that animals cannot speak, so preclinical studies in animal models have to rely on behavioural cues in order to study the effects on the brain. This can make it more difficult to translate preclinical biomarkers into measurements that can be used in human subjects. De Boer describes how Van Gerven and his team at CHDR proposed to study such a biomarker.

'We know that administering dexamphetamine to rats increases their locomotion,' says De Boer, 'and this effect increases after several doses of dexamphetamine. In other words, the rats develop measurable sensitisation to dexamphetamine. In addition, compounds that are beneficial in conditions such as psychosis tend to counteract this sensitisation effect. So this provides an interesting preclinical model. We can measure the increase in locomotion due to dexamphetamine, and then we can measure whether the test compound affects this sensitisation.

'Dexamphetamine is a registered drug,' continues De Boer. 'So we thought it would be interesting to use this same model in human subjects to study the pharmacodynamics of test compounds. Very little has been published with respect to measuring sensitisation to psychostimulants in human subjects, so CHDR did an exploratory study – you could call it a "phase 0" study – in which they used PET to study dopamine release. It wasn't a formally sponsored study, but rather a scientific collaboration, and we learned a lot that we can use in future protocols. Although it wasn't perfect in every respect (for example, we were unable to use the outcome to adapt the dosage during the experiment), it was extremely

interesting, and I think it's important to try something new every now and then in order to improve early CNS drug development. The recent fatal incident in France taught us the importance of determining the effective dose as early as possible.'

Connected through Paul Janssen

After working for Johnson & Johnson in the United States, the Netherlands, and the United Kingdom, De Boer now works in Beerse, Belgium at Janssen Pharmaceutica, which was founded by Dr Paul Janssen, the famous Belgian physician, pharmacologist, medical chemist, and entrepreneur. '"Dr Paul", as he is referred to around here, was born in Turnhout, which is not far from Beerse. Originally, this is a rather poor region with sandy soil that's not suitable for agriculture, so starting his company here was a smart move from an economic perspective. It's a bit of a "scientific backwater", but I like what we do here.

'It's nice that Paul Janssen's legacy is continuing in Leiden,' continues De Boer, referring to the new Paul Janssen Futurelab Leiden programme. 'And I think Dr Paul would be honoured to know that his name is associated with helping teaching scientists to become biopharmaceutical entrepreneurs. In the past, most of us learned the ropes from more experienced people in the business, which is fine, of course. But I think the process can be improved through more formal education. It's a good initiative, and I think that Dr Paul's unique approach of hiring smart people and giving them wide freedom to develop new approaches is just as relevant today.'

'With CHDR, I get honest and direct input, which leads to a much better outcome.'

Dr Dana Hilt, a neurologist by training, has been involved in drug development for more than two decades. During most of that time, he's also been collaborating with CHDR on the development of a wide variety of compounds. 'When Adam first told me that they studied both pharmacokinetics and pharmacodynamics in early-stage development, it made clear sense to me. Now, increasing numbers of researchers are beginning to see the value of this approach.'

'Drug development is changing'

***Dr Dana Hilt**, Chief Medical Officer, Lysosomal Therapeutics Inc.*

‘We’re starting to realise that patients with the same clinical phenotype can have different underlying defects at the genetic level.’

‘We’re witnessing major changes in drug development,’ says Hilt. ‘What was traditionally a highly empirical process has become based more on analytics and basic science. The approach to preclinical development has become more scientific, more mechanism-driven. In the clinical phase, we also need to be more analytical, incorporating the association between pharmacokinetics and biological activity. At CHDR, they’ve always used this approach of connecting pharmacokinetics with pharmacodynamics.’

Developing a model system: the scopolamine challenge

Hilt obtained his medical degree from Tufts University School of Medicine in Boston, Massachusetts and trained in the Internal Medicine department at Harvard Medical School and the Neurology department at Johns Hopkins Hospital in Baltimore, Maryland. Hilt then joined the staff at the US National Institutes of Health, established the Clinical Neuroscience Group at Amgen, and was on the faculty at the University of Maryland School of Medicine. While working at various pharmaceutical and biotech companies, Hilt became involved in developing drugs for treating various conditions, including Parkinson’s disease, amyotrophic lateral sclerosis, schizophrenia, Alzheimer’s disease, and cancer-related conditions such as malignant glioma, chronic pain, metabolic disorder, and inflammatory disorders.

‘I’ve always enjoyed working with CHDR, particularly on new classes of drugs. For example, we collaborated to develop drugs that improve cognitive function in patients with Alzheimer’s. Because these drugs have little effect on function in healthy subjects, it would be difficult to measure a biologically relevant effect in these subjects. To overcome this hurdle, you can administer scopolamine to healthy subjects, which temporarily induces a measurable decrease in cognitive function. In this context, you can then try to determine whether your compound can improve cognitive function. It’s a nice model system that we developed with CHDR in order to investigate a specific drug’s action.’

Changing how we approach CNS disorders

Hilt has observed a radical change in the development of therapies for treating CNS disorders. ‘In neurology and psychiatry,’ he says, ‘we’re at the dawn of a new era, similar to the revolutionary changes in oncology we’ve seen over the past decade. Not long ago, all breast cancers were treated using the same approach. These days, however, oncologists can tailor the therapy to match the tumour. For example, the oncologist will measure the tumour’s receptor profile before prescribing Herceptin, which is effective only in patients with a HER2-positive tumour.

‘Now, we’re witnessing the beginning of the same approach in neurology,’ continues Hilt. ‘We’re starting to realise that patients with the same clinical condition – the same phenotype – can have different underlying defects at the genetic level. So if we want to offer patients a specific, targeted treatment, rather than just treating their symptoms, we need to address the underlying genetic defects in each individual patient. In clinical terms, this means that we’ll treat two patients with the same phenotype using two different approaches. You could compare this with aspirin, which works to lower a fever, but doesn’t treat the underlying cause of the fever. For example, if a patient has a fever due to malaria, aspirin might lower the fever, but it would not treat the malaria. In neurology, we’ve been treating malaria with aspirin. But finally, that may change. Of course, there’s still a long way to go. Four decades ago, the American government declared war on cancer. This led to significant advances in our understanding of the mechanisms underlying cancer, and – in the last decade or so – the first truly innovative treatments reached the market. Monoclonal antibodies were discovered in the late 1970s, but it took twenty to thirty years to develop them into effective therapies. So it can take a long time to translate basic data into a feasible clinical therapy. Even so, these are really exciting times. Research is literally rewriting neurology textbooks, and therapies must follow suit.’

New challenges for drug developers

‘Some of these changes have already had consequences on drug development. An interesting example is the development of anti-amyloid antibodies for treating Alzheimer’s disease. Many companies are conducting trials to test these candidate drugs in patients with Alzheimer’s disease, and they’re starting to encounter major problems. Using imaging scans, we know that up to 35% of patients who meet the clinical definition of Alzheimer’s disease do not have amyloid plaques; in other words, these patients don’t appear to have classic Alzheimers disease at all. From the perspective of drug development, this is an essential factor to consider. Very few drugs can show a positive clinical effect in a study in which 35% of the patients might not even have the disease; the effect size would have to be tremendous to overcome that handicap.

‘So we need to be aware of similar phenotypes caused by completely different underlying mechanisms at the level of genes or signalling pathways. At the same time, we’re faced with

the reverse situation: a given defect or mutation in the same pathway or gene in two patients can give rise to completely different phenotypes due to other factors such as other genetic differences, epigenetic factors, and environmental factors. So if you have a drug that you suspect might affect a specific gene or protein, you may need to investigate its effects in a phenotypically heterogeneous patient group.'

'These studies are extremely complex, so it's good to discuss them with sharp researchers who may see things that I've overlooked or hadn't fully considered.'

With respect to the early stages of drug development, these new trends indicate that it is now more important than ever to establish sensitive and specific biomarkers for measuring effects in patients, and sometimes even in healthy subjects. 'We need to develop the means to thoroughly analyse biological activity by correlating these biomarkers with exposure to the drug, the drug's maximum and minimum concentrations, and any other contributing factors.'

Changes in the business model

Clinical drug development is also evolving as a result of major changes in the pharmaceutical industry. 'Large corporations now have smaller, more focussed laboratory facilities than in the past,' explains Hilt. 'They tend to outsource the process of drug discovery and the earliest stages of development to biotech companies and academic research groups. We've seen a major change in the business model, which has also affected early clinical drug development. For example, biotech companies must now demonstrate target involvement and proof of concept as early as possible. A straightforward "vanilla" first-in-human study is no longer sufficient, as it simply doesn't give you enough key information. You need to measure effects by measuring biomarkers, and you need to correlate these effects with pharmacokinetics and exposure levels at the drug's target. The principal question is now, "What information do we need in order to encourage a large company to buy a licence to our discovery and proceed with the drug's development?"

'In this changing landscape,' continues Hilt, 'I definitely see a future for CHDR and their innovative approach. I work with many CROs; in most cases, they just want my business, so they won't criticise my protocol, even if it's necessary. But with CHDR, I always go home with a slightly different design and a new view of the problem. And that's something that I truly value. These studies are extremely complex, so it's good to discuss them with sharp researchers who may see things that I've overlooked or hadn't fully considered.'

'Working with CHDR is a true collaboration'

Brought together through serendipity, Cutanea and CHDR have begun a highly productive collaboration. Gary Feiss tells the story of how his company has benefited. 'Thanks to CHDR, one of our products has entered phase 3 trials months – if not years – earlier.'

***Gary Feiss**, Vice President of Clinical Research and Operations, Cutanea Life Sciences*

'As pharma companies go, Cutanea is a bit different,' says Feiss. 'We're based in the US, but we're a wholly owned subsidiary of Maruho Co. Ltd., a private family-owned pharmaceutical company headquartered in Osaka, Japan. Maruho recently celebrated their one-hundredth anniversary, so they've been around for a while. Today, they're the largest Japanese company focused on the field of dermatology.

'On the other hand,' continues Feiss, 'Cutanea is a relatively young company. We just launched our first commercial product. As the vice president of Clinical Research and Operations, I focus primarily on developing concepts and building the product pipeline. Most of my time is dedicated to research, preclinical development, and early clinical testing. So you can see that I have plenty of opportunities to collaborate with CHDR.'

A first meeting, almost by chance

Feiss remembers how he first came to CHDR. 'When I joined Cutanea, they had just been acquired by Maruho after several difficult years in the start-up phase. So I was looking for ways to jumpstart the development of some of our products, accelerating their transition to phase 2 clinical research. We began to collaborate with DDL Diagnostic Laboratory in Rijswijk, the Netherlands. We were developing an extremely useful biomarker based on quantitative PCR, and we were planning to conduct a clinical trial at the Dermatology department at Leiden University Medical Centre. While developing the protocol, we ran into an issue that required a pharmacokinetics approach. So Rein Willemze, the head of the Dermatology department, introduced me to CHDR. The very next day, I was sitting with Koos Burggraaf and Robert Rissmann. We discussed the issue and came up with a solution the very same day. That was really impressive, just walking in and getting straight to the heart of the matter. Together, we developed a study, which they implemented, and everything went incredibly smoothly. As a matter of fact, it worked so well that we changed the larger study that we had already planned. So "study number 1423" became our first collaborative project between Cutanea, LUMC, DDL Laboratory, and CHDR. Although it was a study with just eighty patients, it was data-intensive, and it was conducted with so much efficiency and precision that it greatly accelerated development, allowing us to move to phase 3 right away.'

Doing things differently

'This first experience was really positive for us,' says Feiss. 'It worked extremely well, so we decided to expand our collaboration with CHDR to include other areas as well. We have now done eight clinical trials in atopic dermatitis, genital warts, vulvar intraepithelial neoplasia, and many other skin conditions. The word that comes immediately to mind when I think about CHDR is "collaborative". I've been in the pharma industry for over 25 years, and although this word is used a lot, it's not implemented a lot. When we collaborate with CHDR, they usually either come to us or we go to the Netherlands, and over several productive days, all the details are hammered out. We also invite other experts from LUMC and Erasmus Medical Centre in Rotterdam, so it's a truly multidisciplinary collaboration where everyone contributes, ensuring that we'll get as much as possible from the trial. These sessions are very much like a think tank, utilising all available knowledge and expertise. We continue this approach with teleconferences and web meetings as we refine the study design, review and discuss the results, and contemplate the next steps. It's very much a real-time, continuous collaboration.

'As a result,' continues Feiss, 'we do things a bit differently than other pharmaceutical companies. Instead of conducting large, early phase 2 multicentre trials involving large numbers of patients with downstream endpoints, we prefer smaller – but still data-rich – studies. We use clinical endpoints, but we also add biomarkers to corroborate the results obtained from these endpoints. We prefer to use objective measurements, including skin swabs, histopathology, and immunohistochemistry, as well as the traditional evaluation by a dermatologist. The addition of biomarkers allows us to study dermatology objectively, without the worry of interobserver variability.

'All in all, we're not very traditional, even though we're part of a hundred-year-old Japanese company.'

Regulatory authorities

Doing things differently may sound attractive, but doesn't it complicate matters with regulatory authorities? 'We've had very positive experiences with the Dutch medical ethics authorities,' says Feiss. 'From what I've seen, it's all highly streamlined. They were quite open to our approaches, even some of which did not exactly fit with their guidelines. There's a lot of flexibility there, as long as we provide a sensible, scientific rationale. And of course, CHDR always gives the highest priority to their subjects' safety and comfort, so that's never an issue.'

And back in the US? Does the FDA accept the results obtained in the Netherlands? 'Because all of the studies we conduct at CHDR are fully compliant with ICH[2] guidelines, as well as EMA and FDA requirements,' says Feiss, 'there's never an issue from a regulatory point of view. In my experience, if you have reliable, sound data and a clear explanation for the results, the FDA tends to accept your trial dossier, even if the data were not generated in the US. The product we now have in phase 3 is a good case in point. We submitted all of the data from our study with CHDR, and it was approved for phase 3 testing in the US, thanks to the high quality, thoroughness, and clarity of the data.'

Using apps to increase understanding

In some of Cutanea's trials at CHDR, they used CHDR's Trial@home, a relatively new approach in which subjects

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2: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brings together European, Japanese, and American regulatory authorities with experts from the pharmaceutical industry in these three regions to discuss the scientific and technical aspects of pharmaceutical product registration.

participate on an outpatient basis. A crucial feature of this approach is the use of apps on a smartphone or tablet for acquiring data. 'The use of these apps was a great advantage,' says Feiss. 'We had an easy, simple way to receive much more data compared with traditional methods. These apps can be used to remind subjects to apply the study medication, and they can prompt the subjects to send us a picture of the lesion with the medication applied; this increases both subject compliance and study reliability. The app can also be used to ask subjects about their symptoms, several times a day if necessary.

'A study we conducted on atopic dermatitis stands out in my memory,' says Feiss. 'In the first week, we asked the subjects questions about some of the clinical endpoints almost every hour, and we received a lot of replies. This provided us with a more in-depth understanding of the drug's action, particularly in the first few days. I appreciated the way in which CHDR organised this, without needing to involve additional companies. It was all very efficient.'

Educating people

'Another benefit that CHDR brings to the table,' says Feiss, 'is their interest in helping researchers develop. I often collaborate with Robert Rissmann, who's also very much involved in education. CHDR's contribution to the education of medical students doesn't even exist at most CROs. And in academia, it's often the postdocs who do the heavy lifting, the non-glamorous work. It's good to see the level of dedication to personal and career development that CHDR displays.

'I think this investment in people is a key element to CHDR's success,' continues Feiss. 'I once read a quote by Adam Cohen in one of CHDR's annual reports in which he said, "If you get people with the right phenotype and put them together, then amazing things will happen." I think that's entirely true, and CHDR is clear evidence of this. They created the kind of environment that allows amazing things to happen.'

Collaboration versus a business transaction

'CHDR is also different in the way in which they collaborate with industry sponsors. Their approach is anything but ordinary. Normally, the sponsor and CRO operate using a model based on a business transaction – the sponsor gives the CRO money and receives data in return. That's fine, but working with CHDR is much more than that; it's a true collaboration where everything is shared each step of the way. We share ideas, we develop these ideas together, and after the study is completed we look at the data together and share our thoughts. This approach often raises important new questions and leads to new developments.

'From the first time I walked through the doors at CHDR, our relationship has grown organically. It just happened, and I'm sure it will continue. We have long-term plans that fit nicely with our strategic approach, which we call our portfolio enrichment process. We're not simply pushing products to the market; we're conceptualising ideas, generating data, and coming up with new ways to improve our pipeline. At Cutanea, we are committed to this approach. And given that our parent company has been around for a century already, I'm confident that we have a strong future ahead of us.' •

Dr Janneke Meulenberg, COO, and Robert Jan Lamers, CEO, Arthrogen

CHDR is collaborating with Amsterdam-based biotech company Arthrogen in a first-in-human trial to test a new gene therapy-based approach for treating rheumatoid arthritis. This one-time, local treatment may hold the key to providing a long-lasting reduction in joint inflammation. 'It's still early days, but we're all excited about the potential of this powerful new approach.'

'We develop unique gene therapy products for treating RA'

‘There’s more optimism with respect to gene therapy. In the near future, new gene therapies are expected to receive market authorisation.’

In the developed world, rheumatoid arthritis (RA) affects up to 1% of all adults. RA is a progressive, chronic disease that follows a varied course, leading to joint deterioration in some patients and more mild symptoms in others. In addition, the severity of the inflammation can vary in patients over time. In recent decades, a growing number of treatment options have been developed. ‘Although these disease-modifying antirheumatic drugs – the so-called DMARDs – can be highly effective, some patients still need to revert to using other, more invasive treatment options due to adverse effects or a lack of efficacy,’ says Meulenberg. ‘Moreover,’ adds Lamers, ‘DMARDs are expensive treatments that need to be given repeatedly over a long period of time, and they’re often associated with severe systemic off-target effects. That’s why Prof Paul Peter Tak, a rheumatologist at the Academic Medical Centre in Amsterdam, thought of using gene therapy to achieve a longer-lasting, more targeted effect with just one treatment. That was back in 2005. Today, we’re ready to test this approach in patients.’

‘The gene therapies that have been developed to date were all targeted to relatively rare diseases,’ says Meulenberg. ‘Our products have a wide market potential and would likely reduce the cost of treatment. Current therapies for RA cost about $20,000 per year, and they need to be administered every time inflammation occurs. So we designed our product to cure the affected joint using a single treatment, at a reasonable cost.’

The revival of gene therapy

The concept of gene therapy is not new. As far back as the early 1980s, the first preclinical experiments using gene therapy were conducted. In 1989, the first gene was successfully introduced into a human patient. In the 1990s, researchers conducted an increasing number of studies, with most being performed in the United States. In those days, the most common approach was to introduce a functional gene to replace a non-functional copy in patients with a genetic mutation. In nearly all cases, a viral vector was used to introduce the new gene into the target cells. In 1999, the field experienced a major setback due to the death of Jesse Gelsinger, an 18-year-old American student who developed a fatal immune reaction in response to the adenovirus used to introduce the new gene. Although it was later determined that the researchers at the University of Pennsylvania, where the trial was conducted, had violated several rules of conduct, Gelsinger’s tragic death marked the end of a period of unbridled optimism regarding gene therapy. Nevertheless, and despite headlines declaring the ‘demise’ of gene therapy, research continued. Scientists went back to the drawing board in an attempt to solve some of the more fundamental issues that emerged during the early gene therapy trials. For example, researchers developed methods to circumvent the immune system’s response to the vector and the proteins encoded by the newly introduced genes. Other improvements included the use of specific promoter regions in order to better control the gene’s expression in the target cells. In the early years of the twenty-first century, new gene therapies were developed for several hereditary disorders, but also for other diseases, including various forms of cancer. Gradually, it became clear that gene therapy could still deliver on its initial promises.

Researchers in the Netherlands were pioneers in the field of gene therapy. In November 2012, Glybera (Alipogene tiparvovec) became the first gene therapy–based treatment to reach the European market. Glybera was designed to restore the body’s ability to process fat particles called chylomicrons, which is impaired in patients with a genetic defect in the enzyme lipoprotein lipase (LPL). Patients with LPL deficiency are prone to developing severe inflammation of the pancreas (acute pancreatitis). Glybera delivers an engineered copy of the human LPL gene into the patient’s muscles using an adeno-associated virus (AAV); as a result, functional LPL protein is expressed in the muscle, where it can then enter the bloodstream.

Meulenberg was a researcher at uniQure, the company that developed Glybera, and was responsible for taking Glybera to clinical testing. ‘Developing this product was extremely interesting,’ recalls Meulenberg, ‘but it was also challenging at times. It was nice to be the first, but everything was new, even for the regulatory authorities. Now, thanks to the success of Glybera and a few other products, there’s more optimism with respect to gene therapy. In the near future, new gene therapies and other advanced therapy medicinal products are expected to receive market authorisation. This is of course for the benefit of patients who currently have no other effective treatment options available.’

‘On-demand’ therapy

Arthrogen is now developing a new therapy based on an AAV vector similar to the one used in Glybera. In many respects, this is a next-generation gene therapy. First, it’s not designed to treat an inherited genetic defect; rather, the vector introduces several copies of the gene encoding the cytokine interferon beta (IFN-ß), which plays a role in inflammation. These new copies of IFN-ß are

targeted directly to the affected joint, reducing the risk of systemic side effects. Specifically, the gene is delivered to the nuclei of the cells that line the joint, where it remains. But thanks to an ingenious addition to the vector, the gene won't be active all the time. The promoter, which controls the gene's expression, is designed to respond based on the joint's inflammatory state. During inflammation, the gene becomes activated and the synovial cells express IFN-ß. When the inflammation subsides, the gene is switched off.

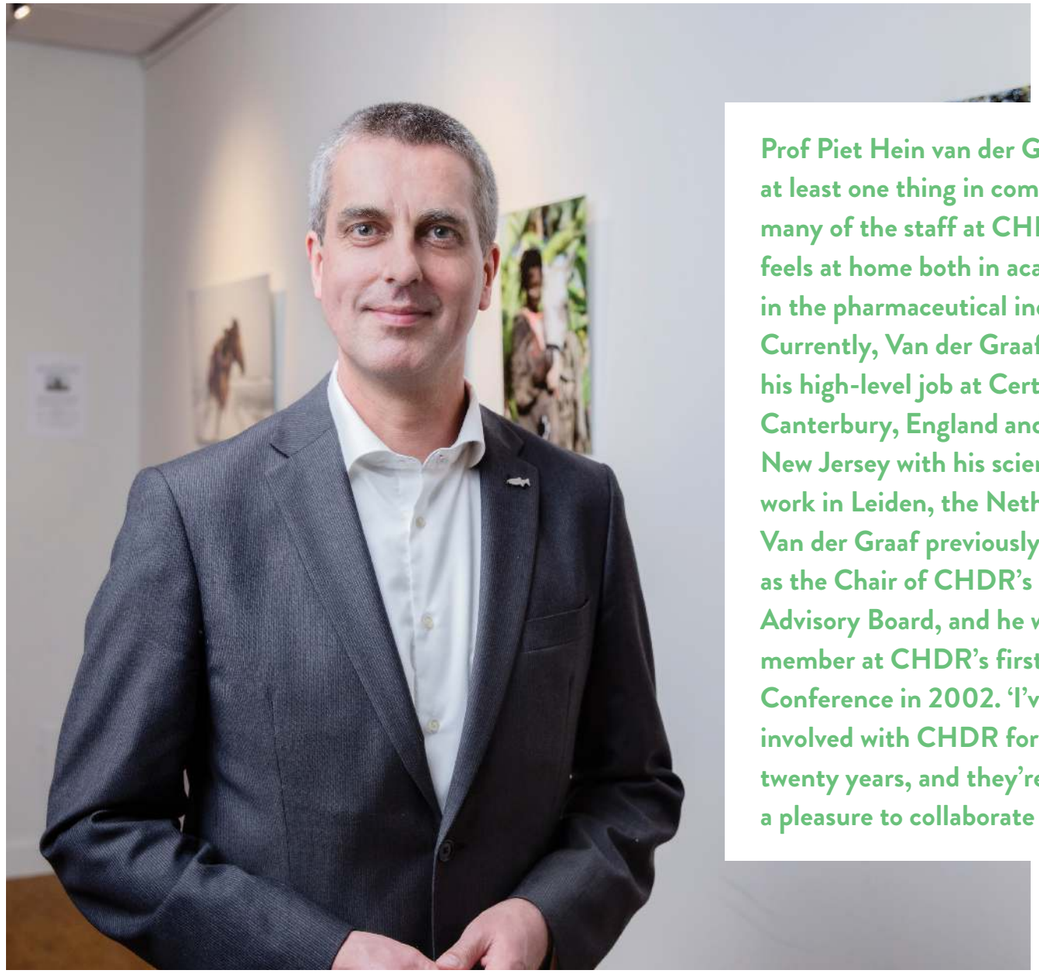
First-in-human testing

Twelve years after Arthrogen was founded, their first product is ready for testing in patients. 'With a product like this,' says Lamers, 'you can go straight from preclinical development to testing in patients. In healthy subjects with no joint inflammation, the gene won't become active. In addition, the gene is designed to stay in the synovial cells, and we don't want to introduce a lasting change in healthy subjects.'

Given the unique features of this new gene therapy product, clinical testing will be challenging. 'That's one of the reasons we're working with CHDR,' says Meulenberg. 'We developed the protocol together, using our combined expertise. I found the process – the discussions, going back and forth to come up with a feasible working protocol – to be extremely enjoyable. As the sponsor, we wanted everything to be addressed in the first trial; but with input from Koos Burggraaf and Ingrid de Visser at CHDR, we developed a more pragmatic stepwise approach, taking into consideration the burden placed on the subjects. CHDR has been eager to collaborate; for them, it's also the first time they're involved in this form of gene therapy. For us, it's extremely convenient to conduct this first study here in the Netherlands, at a single site, with Leiden University Medical Centre right next door.'

Lamers adds, 'Developing this protocol has been very intense; we collaborated with our own scientific advisers, CHDR, and rheumatologists at several academic institutes. In the gene therapy field, everything is strictly regulated, including ethics, quality assurance, and even the environmental aspects. Which is both necessary and logical, of course; after all, we're working with modified viruses and genes. So it's even more important that we work closely with professionals who have the expertise needed to deal with each of these issues.' •

'The Scientific Advisory Board has a strong educational role'



Prof Piet Hein van der Graaf has at least one thing in common with many of the staff at CHDR: he feels at home both in academia and in the pharmaceutical industry. Currently, Van der Graaf combines his high-level job at Certara in Canterbury, England and Princeton, New Jersey with his scientific work in Leiden, the Netherlands. Van der Graaf previously served as the Chair of CHDR's Scientific Advisory Board, and he was a panel member at CHDR's first Dinosaur Conference in 2002. 'I've been involved with CHDR for more than twenty years, and they're always a pleasure to collaborate with.'

***Dr Piet Hein van der Graaf**, Professor of Systems Pharmacology and Vice President and Head of Quantitative Systems Pharmacology at Certara*

Van der Graaf first came to Leiden in 1996 as a postdoc at the Leiden Academic Centre for Drug Research (LACDR). 'In those days,' recalls Van der Graaf, 'I collaborated with Rik Schoemaker at CHDR, who was doing his PhD work on PK/PD modelling and taught me how to use the NONMEM [nonlinear mixed effects modelling] software tool. We analysed datasets that I still had from my PhD days, and together we published a paper that became one of the chapters in his PhD thesis. I also had an immediate connection with Adam Cohen, in part because of our common backgrounds. I did my PhD research at King's College London with Nobel laureate Sir James Black, who was one of the heads of research at the Wellcome Foundation in Beckenham when Adam worked there in the 1980s. Adam and I were also two of the first Dutch pharmacologists to become Fellows of the British Pharmacological Society, and we both serve as the Editor-in-Chief of a clinical pharmacology journal.'

Representing the industry

A few years after arriving in Leiden, Van der Graaf returned to the United Kingdom, where he worked at Pfizer in several leadership positions. 'I headed up research and development in the field of sexual health therapies,' says Van der Graaf. 'This was shortly after the Viagra® success story, a somewhat serendipitous discovery, and Pfizer wanted to actively explore that area. Later, I also headed up the translational quantitative pharmacology section and worked in both early-stage and late-stage clinical pharmacology and pharmacometrics. These roles put me in the position to collaborate repeatedly with CHDR from the perspective of the pharmaceutical industry.

'I still remember quite vividly how I felt upon being invited to the 2002 Dinosaur Conference as a representative of the pharmaceutical industry,' says Van der Graaf. 'I didn't mind representing the dinosaurs, but I was slightly nervous when I learned that the other guests would include Sir James and Dr Paul Janssen, arguably the two most prolific pharmacologists and drug developers of the twentieth century. Even today, I can clearly see myself eating breakfast with Paul Janssen at the Oud-Poelgeest Castle, an historic hotel and conference centre in Oegstgeest; that was a somewhat surreal highlight of my career. I'm looking forward to CHDR's thirty-year anniversary, but for me personally, it will be very difficult to top that extraordinary experience back in 2002.'

At the 2002 Dinosaur Conference, Van der Graaf voiced his optimistic opinion regarding the future of drug development, which was based on the recent increase in new fundamental biomedical science and the ability of the pharma industry to convert that knowledge into effective medicines. At the conference, Van der Graaf stated that 'the number of unexploited targets greatly exceeds the number of exploited targets; so I'm optimistic, there's hope.' Looking back, Van der Graaf says, 'That statement was mainly based on my youthful optimism and naivety (and perhaps because I was there to represent Big Pharma), and it was certainly in stark contrast with the rather gloomy perspective of some of the other participants. However, fifteen years later I'm starting to think that I may have been right after all!'

Joining CHDR's Scientific Advisory Board

In 2012, Van der Graaf was appointed a professor of systems pharmacology at LACDR. A year later, he was LACDR's Scientific Director. 'I'd returned to the place where I studied as a postdoc,' says Van der Graaf. 'This also put me in even closer contact with CHDR.

'My predecessor as the Scientific Director of LACDR was Prof Meindert Danhof, who had served as the Chairman of the Scientific Advisory Board at CHDR. I was asked to succeed Meindert in that position as well, and I gladly agreed. I then became a regular visitor at CHDR. In 2013, Dr Koos Burggraaf at CHDR was appointed a professor of translational drug development at LACDR's pharmacology section. This strengthened our collaboration even further, and to this day we supervise PhD students together. I also contributed to the early plans for Paul Janssen Futurelab Leiden, and I participated in the first pilot study conducted by Saco de Visser and Marcel Kenter [see also page 91].'

According to Van der Graaf, the monthly meetings of the Scientific Advisory Board (SAB) also include a strong educational element. 'These meetings are attended by around forty people, including PhD students and clinical pharmacologists-in-training who are there to learn and to actively participate in the discussion. We always have quite a few protocols to discuss, as the SAB reviews the protocol for every study conducted at CHDR. Discussing new protocols takes up most of our time, but we also discuss studies that were recently completed. I believe that our young scientists find it highly valuable to attend these meetings. And of course, project leaders need to learn to present their protocols and results.'

The SAB itself consists of senior clinicians from various medical specialties, scientists with a more preclinical background, and researchers who specialise in drug discovery and translation. This strong combination of complementary expertise is essential for giving advice regarding early clinical studies at CHDR. 'CHDR is often the first place where a drug is administered to human subjects,' says Van der Graaf. But first, you have to establish a safe starting dose based on the preclinical data. That's why it's so important to have many people with varied scientific backgrounds evaluating the protocol. As an external reviewer, it's the SAB's job to ask critical questions and ensure that all relevant factors have been considered.

'In 2016, a tragic incident occurred during an early-phase drug trial at a CRO in Rennes, France. During the trial, several participants became hospitalised, and one participant died. At the time, I was still Chairman of the SAB, and we discussed whether such a disaster could have occurred at CHDR on our watch. It's important to realise that there's always risk involved with studying new, highly potent substances; that's why we need to scrutinise every aspect as rigorously as possible. In my opinion, that's the SAB's most important role: ensuring that everyone is alert and that we turn over every stone, no matter how small.'

In April 2016, Van der Graaf returned to the United Kingdom to join Certara. Soon after that, Dr Noortje Swart, a professor of clinical pharmacology in Amsterdam, became the new Chairman of the SAB. 'Although I was still involved in academic research at Leiden and visit on a regular basis,' says Van der Graaf, 'I felt that the SAB needed a chair who could commit fully to this important role. I'll continue to collaborate with CHDR, though, both through the university and here at Certara.'

‘We complement each other’

Dr Martijn van Doorn, a dermatologist at the Erasmus Medical Centre (Erasmus MC) in Rotterdam, works with CHDR in the clinical development of dermatological compounds. ‘CHDR has the equipment and expertise needed to perform essential measurements. In this respect, we truly complement each other.’

***Dr Martijn van Doorn**, a dermatologist at the Erasmus Medical Centre in Rotterdam, works with CHDR in the clinical development of dermatological compounds. ‘CHDR has the equipment and expertise needed to perform essential measurements. In this respect, we truly complement each other.’*

The foundation for this collaboration was first laid many years earlier, long before Van Doorn even decided to become a dermatologist. Back in 2000, Van Doorn was a resident in internal medicine, and when he was looking to take the next step in his career, an ad for CHDR caught his eye. They were looking for a clinical researcher to conduct PhD research in Clinical Pharmacology. ‘I had some experience working in a lab as a medical student,’ says Van Doorn, ‘where I studied monoclonal antibodies directed against colon cancer. But basic research didn’t really appeal to me; I wanted to do something beyond working with cells and animal models. I wanted to take the first steps towards clinical applications. Unfortunately, there weren’t many positions available that fit that description. That’s why I was glad to read CHDR’s ad and join CHDR; finally, I could conduct innovative translational research using the latest compounds and methodologies. During my PhD, I used cDNA microarrays, which were the hot trend in science at the time, so my research was both cutting-edge and highly interesting.’

Thesis work and postdoctoral training

Van Doorn’s PhD project was extremely ambitious, investigating the feasibility of using advanced molecular techniques to evaluate new drugs designed to treat type 2 diabetes. ‘We wanted to see how different drugs influence the expression of genes in various tissues,’ says Van Doorn. ‘But with the tools available at that time, we were unable to detect a significant treatment effect at the level of gene expression. Looking at metabolite profiles, however, we were able to see how one of the drugs affected metabolism in patients but not in healthy volunteers. Although it was really interesting, we couldn’t find a useful way to perform a clinical proof-of-concept study using the methods that were available at the time. I still think the approach can work, but we need more advanced techniques and bioinformatics.’

After obtaining his PhD, Van Doorn went on to train as a dermatologist. ‘Everybody expected me to return to internal medicine,’ he recalls. ‘But I knew I wanted to do something else. I’m highly visually oriented, so I was drawn to dermatology.’

A return to clinical pharmacology

‘Of course, dermatology might not be the first thing that comes to mind when you think of a clinical pharmacologist,’ says Van Doorn. ‘And at first, while training as a dermatologist, I didn’t draw much on my skills and experience in clinical pharmacology. But in recent years, there’s been a shift towards more systemic treatment approaches in dermatology. Plus, with respect to treating inflammatory skin disease, there’s considerable overlap between dermatology, rheumatology, and gastroenterology. In the past, rheumatologists and gastroenterologists had the advantage; once a new compound was found to be effective, only then would it be registered for dermatology applications (for example, moderate to severe psoriasis), and possibly for off-label uses as well, including debilitating inflammatory skin conditions. Today, however, the order is reversed, and many anti-inflammatory compounds are tested first in patients with an inflammatory skin condition. This makes sense, because the skin is visible, and it’s relatively easy to quantify a new drug’s effects on the skin. In contrast, measuring effects on the joints or internal organs is far more difficult and invasive.’

A return to CHDR

When he started working at Erasmus MC, Van Doorn was once again able to combine patient care with clinical pharmacology research. As a physician, he specialises in diagnosing and treating inflammatory skin conditions at his outpatient clinic, and he runs the dermatology ward. As a researcher, he can pursue his interests in the clinical development of new dermatology treatments. In 2012, Van Doorn visited his former boss at CHDR, Prof Adam Cohen. 'I told Adam that CHDR would be the ideal place to test these new dermatology drugs, because the infrastructure needed for conducting high-quality pharmacological research was already there. Adam put me in touch with Dr Robert Rissmann. Robert's PhD research was based on the pharmacology of skin lipids, and we quickly realised that we were a good match.'

'Many anti-inflammatory compounds are tested first in patients with an inflammatory skin condition.'

Biomarkers of inflammation

The first compound that Van Doorn and Rissmann studied was designed to disrupt the inflammatory process in psoriasis by blocking the so-called Toll-like receptors (TLRs). 'These receptors act like antennae on specific cell types,' explains Van Doorn. 'They're triggered by invading pathogens such as bacteria or viruses, forming part of the innate immune system. TLRs are involved in many inflammatory diseases, including inflammatory skin disease.'

To measure pharmacological effects on TLRs, Dr Matthijs Moerland developed a biomarker that can detect these effects in blood taken from test subjects. This first collaboration between CHDR and Van Doorn proved to be quite fruitful. 'It was a wonderful achievement when our first article was published in Clinical Immunology,' says Van Doorn. 'After that first project, our collaboration skyrocketed. Several sponsors became interested, and we're now performing studies on acne, eczema, and many other conditions. Usually, we perform the first-in-human studies here at CHDR, where we can measure all of the effects in detail. Then, when the time comes to conduct the large multicentre clinical trials, Erasmus MC is perfectly suited for the job. For pharmaceutical sponsors, this is the ideal setup – CHDR has all the experience needed for early-stage clinical development, and we're closely connected to clinical practice through my medical colleagues. For us, it's a wave we hope to ride for quite some time, because it's both fun and scientifically rewarding.' •

'Illuminating tumours and other structures from within'

Surgeon Alexander Vahrmeijer tells the story of his unique collaboration with CHDR using fluorescent markers in image-guided surgery. 'We're pioneers in this field, but it's never wise to assume that you're more than a year ahead of your competition. That's why our collaboration with CHDR is so important; it ensure that we're always moving forward, with no major bureaucracy to hold us back.'

***Dr Alexander Vahrmeijer**, Department of Surgery, Leiden University Medical Centre, and Principal Investigator, Image-Guided Surgery Group*

In 2006, when Vahrmeijer was a clinical fellow in the Department of Surgery at LUMC, he was looking for a new project. ‘I was considering going to Paris to develop my skills in hepatic surgery. But my supervisor, Prof Cornelis van der Velde, suggested that I contact Prof Clemens Lőwik, who was conducting all sorts of research, including molecular imaging. I still remember how Clemens showed me his presentation on his laptop, with fascinating colour images of tumours and other structures illuminated using fluorescence. Clemens convinced me that I was looking at the future of surgery. In those days, there was no practical application for fluorescent markers in surgery. But Clemens was in touch with Dr John Frangioni at Harvard University Medical School, who was – and still is today – a pioneer in this field. On the spot, Clemens wrote an introductory email to Frangioni, a widely-respected oncologist who dedicates his research to molecular imaging. A few months later, I was in the US for a conference in Providence, Rhode Island, after which I spent two weeks in John’s lab. I learned so many interesting things during those two weeks.’

New molecules for use in patients

Fast forward eleven years… Frangioni developed two interesting new fluorescent markers, and these markers are being produced at LUMC’s own GMP-certified facility. One is a fluorescent molecule eliminated via the kidneys, causing the ureters to fluoresce in the abdomen. For a surgeon, abdominal surgery becomes much easier when these delicate structures can be easily visualised. ‘It always takes time to locate the ureters,’ explains Vahrmeijer. ‘Sometimes, in a difficult situation we ask a urologist to run a catheter through the urethra into the bladder in order to localise the ureters. But if the urine is flowing freely from the kidneys through the ureters, this new molecule may make things much easier, preventing the need for catheterisation. If I'm confident that I can see the ureters, I can easily avoid them, making surgery faster while minimising the chance of causing damage.’

Of course, researchers cannot simply inject a newly developed substance into patients. As with any new compound for medical use, its safety and clinical value must be demonstrated first. That’s where Vahrmeijer's collaboration with CHDR comes into the picture. ‘When I went to Harvard back in 2006, I didn’t realise that we had a unique combination of facilities right here in Leiden. At the LUMC, we have a GMP-certified lab, where we can synthesise molecules under safe, reproducible conditions. And we have CHDR, which has of all the facilities we need to test new molecules in both healthy volunteers and patients. For them, it’s relatively routine to conduct first-in-human testing of a new molecule. So now, with this new molecule from Harvard, we’ll do just that. First, it will be tested in healthy volunteers. If all goes well, we’ll take it to the clinic to see how it performs during surgery in the lower abdomen.’ Another molecule developed at Harvard, designed to detect various cancers, including rectal, pancreatic, and head and neck cancer, is also being produced at LUMC’s GMP facility and will soon be tested in healthy subjects at CHDR.

Improving cancer surgery

The new molecule that makes ureters glow is just one of the latest fluorescent markers that LUMC and CHDR are investigating. In fact, just a few years after his trip to the United States, Vahrmeijer contacted Adam Cohen and Koos Burggraaf at CHDR. ‘We were in contact with several companies who asked us to help with the clinical development of their fluorescent markers,’ says Vahrmeijer. ‘But our hospital lacked the necessary infrastructure for conducting the research in healthy volunteers. That's why I was glad to get in touch with Adam and Koos. We worked well together, and I was impressed with CHDR’s facilities, the quality of their recruitment department, and of course the constructive way in which we developed our protocols together.’

One of the first fluorescent markers that Vahrmeijer and Burggraaf studied was a fluorescent analogue of folic acid (vitamin B9). Because this fluorescent analogue has high affinity for the folic acid receptor expressed in ovarian cancer, the tumour cells stand out against healthy cells. Their first step was to study the compound’s safety and pharmacokinetics in healthy volunteers. ‘For Koos and his team,’ says Vahrmeijer, ‘it must have been a rather new experience, studying a substance they could actually watch as it travelled through the circulation. Most compounds aren’t so readily visible.’ Based on the results of these studies in healthy volunteers, they calculated the optimal dose for the first trial in patients with metastasised ovarian cancer. As Vahrmeijer explains, the results were very promising. ‘Thanks to the fluorescent marker, the surgeons were able to visualise nearly 30% more cancer tissue. We first explored the area as we always do – visually and by palpating the tissues. Then, we switched off the lights and looked at fluorescence in the near-infrared spectrum. Afterwards, the pathologist confirmed that we had removed much more cancer tissue. From previous studies, we knew that prognosis is correlated with the amount of tumour tissue removed, so this was a promising start. Of course, this was a relatively small study with only twelve patients and no long-term follow-up. But for me – as a surgeon whose goal is to remove as much of the tumour as possible – a 30% increase in tumour removal was quite impressive.’

‘Image-guided surgery has considerable potential in laparoscopy, where we don’t have the ability to directly palpate the tissues.’

A logistical challenge

The two research teams are also studying another fluorescent marker with a completely different profile. This marker, an antibody, is designed to detect tumour cells in local recurrences of colorectal cancer. ‘From an early stage in development, it was clear that this molecule takes a long time to reach its target,’ says Vahrmeijer. ‘In fact, it has to be administered several days before the surgery. We’re now conducting a multicentre trial with patients who have recurrent rectal carcinoma and will undergo surgery again. This marker should be particularly useful in these patients, as their lower abdomen will have adhesions and possibly other anatomical changes from the first surgery. Recurrent rectal carcinoma is relatively rare, so we’re grateful to have our colleagues at the Erasmus Medical Centre in Rotterdam and the Catharina Hospital in Eindhoven collaborating in this study. Logistically, this trial is quite a challenge. Four days prior to surgery, each participating patient needs to come to CHDR, where they receive an infusion of the fluorescent antibody. They’re monitored at CHDR’s facility for a few hours, and then they can return home.’

The future depends on regulatory authorities and early adopters

According to Vahrmeijer, image-guided surgery has a promising future. In these early stages, however, it is highly vulnerable. ‘Nearly all fluorescent markers are developed by small companies with relatively limited funding,’ explains Vahrmeijer. ‘Much will depend upon the amount of evidence required by regulatory authorities such as the FDA in the US and the EMA in Europe. Of course, it’s reasonable for these agencies to demand that an immunological marker is safe and will have a certain level of sensitivity and specificity for detecting tumours and other structures. These issues can be addressed using the kind of research we’re currently conducting. However, if they demand evidence that a fluorescent marker significantly increases five-year survival in patients, we’ll need to conduct large clinical trials lasting many years, which most companies cannot afford. So I hope that the authorities won't set the bar too high.’

In the early-phase trials, Vahrmeijer and CHDR are testing these fluorescent markers in classic ‘open’ surgeries. However, surgeons increasingly prefer laparoscopic surgery over open surgery. ‘Image-guided surgery has considerable potential in laparoscopy, where we don’t have the ability to directly palpate the tissues,’ says Vahrmeijer. ‘Unfortunately, image-guided laparoscopy requires a dedicated system of high-quality cameras. Although these systems are now being designed, the camera industry has been reluctant because they could not foresee how this field would develop. Here at the LUMC, we recently acquired two prototypes; however, I realise this can be quite an investment for a hospital. So several barriers currently exit preventing the widespread introduction of image-guided surgery. First, the fluorescent markers have to be approved by the regulatory authorities. Second, specific camera systems are needed, and finally, some fluorescent markers require additional logistics, as they need to be administered hours – or even days – before surgery. Despite these hurdles, I hope we can soon convince surgeons and patients everywhere that image-guided surgery has valuable benefits in terms of increasing perioperative efficiency, reducing complications, and increasing long-term survival. When the benefits become clear, these hurdles can be overcome.’

30 years at CHDR: A behind-the-scenes look

5.10.87

Aan : Bestuur CHG
Van : Postma
Over: Taakomschrijving Wetenschappelijke Raad (WR)

1.1. De onderzoekstrategie van het CHG wordt neergelegd in een globaal plan van activiteiten voor een periode van bijv. drie jaar. Dit plan beschrijft researchlijnen in termen van disciplines en geneesmiddelklassen c.q. indicatiegebieden. Wat dit betreft is eerder de keuze gemaakt voor farmacodynamie en farmacokinetiek van cardiovasculaire en CNS-actieve geneesmiddelen. Uitwerking moet echter nog plaatsvinden.
Het "strategisch researchplan" bepaalt in feite de identiteit van het CHG. Dat wil zeggen dat het niet alleen betrekking heeft op het onderzoek dat m.b.v. de O&W-subsidie wordt bekostigd, maar ook het terrein afbakent waarop gesponsord onderzoek kan/zal worden uitgevoerd. In het ideale geval sluiten gesponsorde projecten zó goed aan op de CHG-expertise, dat wetenschappelijke interesse aan industriële belangen kan worden gepaard. Het zal echter ook regelmatig voorkomen dat een gesponsord project vooral dienstverlenend van aard is. Hoe dit ook zij, het strategisch plan zal niet slechts wetenschappelijke kwaliteit, maar ook relevantie voor potentiële sponsors moeten weerspiegelen.

CENTRE FOR HUMAN DRUG RESEARCH

ONDERZOEKPROGRAMMA van het C.H.G. 88003

Januari 1988

Het Centrum voor Humaan Geneesmiddelenonderzoek (CHG).

Het CHG houdt zich bezig met de humane farmacologie in de ruimste zin van het woord. Voor het optimaal uitvoeren van deze doelstelling bevind het zich in een unieke positie in de directe nabijheid van het Academisch Ziekenhuis, de Medische Faculteit en het Centrum voor Bio-farmaceutische Wetenschappen. Daarnaast zullen frequente contacten ontstaan met de farmaceutische industrie.

Human drug research

Through a joint initiative with Leiden University Hospital, a new **Centre for Human Drug Research** (CHDR) became operational in October 1987. Supported by a grant from the Ministry of Education and Sciences, CHDR concentrates on *measurement and prediction of drug effects in man*, in particular the effects of drugs acting on the cardiovascular (CVS) or the central nervous system (CNS). In addition, CHDR has a service function towards its parent organizations.

CHDR is located on the site of Leiden University Hospital and is fully equipped for studies on administration of new drugs to healthy volunteers. In addition to offices, CHDR has a main ward with central cardiac monitoring, special rooms for CVS and CNS studies, and a modest laboratory. Advanced medical equipment complements custom-built data-processing systems to create a modern facility for human pharmaco-logical research.

CHDR is a research institute which will also accommodate volunteer studies initiated by the Center for Bio-Pharmaceutical Sciences. Its drive, however, is not purely academic. Quite like the Center for Bio-Pharmaceutical Sciences, CHDR actively seeks collaboration with industry on the basis of its research capabilities.

1988
Centre for Human Drug Research

Zeildag CHG 1989.

1989
CHDR Sailing Day

1989
CHDR Sailing Day

Sinterklaas 1989.

1989
'Sinterklaas'

1989
'Sinterklaas'

Het CHG in London ; 1990.

1990
CHDR in London

1990
CHDR in London

CENTRE FOR HUMAN DRUG RESEARCH

APRIL 1990

Newsletter

P.O. BOX 9600, 2300 RC LEIDEN, THE NETHERLANDS, TELEPHONE: 071-268004. TELEFAX: 071-210293

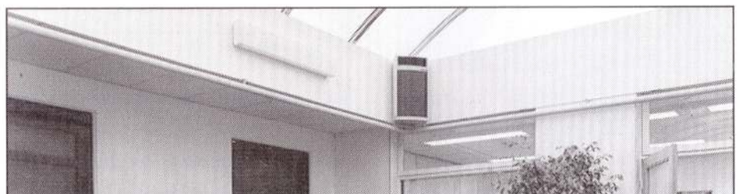
The Centre for Human Drug Research (CHDR) was established in 1987, on the joint initiative of the Center for Bio Pharmaceutical Sciences of Leiden University and the University Hospital. Its primary objective is to facilitate, expand and advance pharmacological research in man. Besides rendering services to its parent organizations, the CHDR is also developing its own research programme, supported by an innovation grant from the Dutch Ministry of Education and Sciences. In addition, collaboration with industry is pursued in areas of mutual interest.

The Centre is now well on its way to meeting its original objectives. A very competent and dedicated staff is engaged in research programmes concerning the cardiovascular system, the central nervous system and blood coagulation. Much emphasis is put on the development of a new and sophisticated methodology that is relevant to clinical pharmacological research. In general, pharmacodynamic and pharmacokinetic data are generated and evaluated in terms of a better understanding of how drugs act upon and are handled by the human body. This is of vital importance for drug innovation and development and contributes to the optimization of actual therapy in patients.

When the Centre officially opened in March 1988, a lot of plans were announced. Now, approximately two years later, we are very pleased to show you that some of these plans have indeed yielded results. Since the opening, we have performed more than forty studies. A large number of these, especially those in the clotting field, were extremely complex. The most exciting experiment was probably that of the unit itself. Establishing a new clinical pharmacology unit from scratch, on the grounds of a major teaching hospital, was a daunting task. The experiment can provisionally be called successful, not in the least part thanks to our medical, scientific and administrative colleagues at the Faculty and the Hospital. Special thanks must go to the Ministry of Education and Sciences which, by providing the grant for starting the Centre, has greatly helped to realize it.

Joint Projects

Clinical Pharmacology is a multidisciplinary subject, and setting up joint projects with colleagues of the Hospital and the Center for Bio Pharmaceutical Sciences (CBPS) was an important objective. I am very pleased that this has been



This year we have complemented our cardiovascular unit by acquiring a two-dimensional echo-Doppler instrument. It will be used in a joint project with the department of radiology to investigate drug effects on organ blood flow non-invasively. Data management remains an important area, and we will continue to improve our data management system, about which you will read more in this issue.

Ca. 1990
Laboratory at CHDR

Ca. 1991
Fun in the barracks lab

Ca. 1992
First overnight study at CHDR

1992
Clinical Pharmacology Fellows

1993
Article published in the *Leidsch Dagblad*

1994
The original CHDR office

1994
CHDR

1994
CHDR

1995
CHDR

1995
Future site of Zernikedreef 10, Leiden

1995
Early ‘construction’ at the Zernikedreef 10 site

1995
CHDR sign at Zernikedreef 10, Leiden

ACADEMISCH ZIEKENHUIS LEIDEN

Centre for Human Drug Research (CHDR)

Per onmiddellijk komen er bij CHDR twee vacatures voor:

1. verpleegkundig hoofd van de klinische research afdeling m/v
(80-100%)

Vac.nr. 96.R.23.30.LD

2. research verpleeg-kundige m/v
(50%)

Vac.nr. 96.R.24.30.LD

CHDR is het geneesmiddelonderzoekinstituut dat samenwerkt met het AZL en de Rijksuniversiteit Leiden. Bij CHDR worden effecten van nieuwe en bestaande geneesmiddelen onderzocht bij patiënten en proefpersonen. Daarbij wordt samengewerkt met een groot aantal afdelingen van het AZL. De research verpleegkundigen spelen een centrale rol in de uitvoering van deze onderzoeken en het verpleegkundig hoofd is verantwoordelijk voor de planning en organisatie van de afdeling met 16 bedden. Bij CHDR wordt gewerkt in multidisciplinaire teams. Een groot deel van de gebruikte documenten is in het Engels.

Functie-eisen:
Vac.nr. 96.R.23:
Diploma A-verpleegkundige of HBO-V met aanvullende management-/kaderopleiding. Het certificaat Brede Basis Intensive care of andere intensive care opleiding strekt tot aanbeveling met klinisch wetenschappelijk onderzoek.

Vac.nr. 96.R.24:
Diploma A-verpleegkundige of HBO-V. Onderzoek-ervaring of ervaring met speciale patiëntenpopulaties (psychiatrie of kinderen) strekt tot aanbeveling.

Salaris: Vac.nr. 96.R.23: maximaal f 4.820,- bruto per maand (schaal A8 RRAZ) bij een volledig dienstverband.
Vac.nr. 96.R.24: maximaal f 4.262,- bruto per maand (schaal A7 RRAZ) bij een volledig dienstverband.

Deze advertentie wordt gelijktijdig intern en extern geplaatst. Interne kandidaten genieten voorrang.

Informatie: nadere inlichtingen worden gaarne verstrekt door prof. dr. A.F. Cohen, directeur (071 - 524 64 00), door mevrouw A. van Vliet en door mevrouw A. van der Jagt, research verpleegkundigen (071 - 524 64 00).

Bij indiensttreding is de Algemeen Burgerlijke Pensioenwet van toepassing.
Vakantietoelage 8%.
Sollicitaties kunnen binnen 14 dagen na het verschijnen van deze advertentie worden gezonden aan: Directeur Sociale Zaken van het Academisch Ziekenhuis Leiden, Postbus 9600, 2300 RC Leiden. Graag op de brief en envelop het vacaturenummer vermelden.

AZL

Personeel Personee

CHDR
CENTRE FOR HUMAN DRUG RESEARCH

Met onmiddellijke ingang is er bij het CHDR een vacature voor een:

Klinisch (research) verpleegkundige m/v

32-40 uur per week

Bij het CHDR (Centre for Human Drug Research) wordt geavanceerd klinisch farmacologisch onderzoek verricht met nieuwe (en bestaande) geneesmiddelen. Dit onderzoek gebeurt in een nieuw, volledig uitgerust, klinisch centrum. Het CHDR werkt nauw samen met het Leids Universitair Medisch Centrum. Het onderzoek wordt veelal overdag, op doordeweekse dagen, verricht met jonge gezonde vrijwilligers in een multidisciplinaire omgeving.

Functie-eisen

Voor deze functie vragen wij:

- een enthousiaste, nauwkeurige en serieuze (BIG geregistreerde) verpleegkundige met een afgeronde HBO-V of inservice-A opleiding;
- minimaal 2 jaar ervaring als verpleegkundige;
- opleiding tot research verpleegkundige of de bereidheid deze opleiding in de toekomst te gaan volgen;
- basale PC-kennis.

Aanstelling en honorering

U wordt aangesteld volgens het CHDR functiewaarderingssysteem (pensioenfonds ABP). Secundaire arbeidsvoorwaarden als spaarloonregeling en PC-Privé behoren uiteraard tot de mogelijkheden. Naast deze zaken wordt het werk in een open en prettige sfeer verricht.

Inlichtingen

Wilt u meer informatie over de functie of het CHDR belt u dan naar de heer P. Schouten, hoofdverpleegkundige research unit (071 - 524 64 36).
Sollicitaties dienen binnen 10 dagen na het verschijnen van deze advertentie te worden gericht aan: **CHDR,** Zernikedreef 10, 2333 CL Leiden, t.a.v. personeelszaken of per e-mail: info@chdr.nl.

Ca. 1996
Telemetry device

Ca. 1996
Microfilm viewer (‘Dikke Beta’)

1996
The CHDR team

Ca. 1996
Opening ceremony at Zernikedreef 10

Ca. 1996
Opening ceremony at Zernikedreef 10

Ca. 1999
CHDR

Ca. 1999
CHDR

2000
Volunteers at CHDR

2000
Test subject at CHDR

2000
Body sway test

2000
Dinner in Oegstgeest

2000
Dinner in Warmond

2000
London

2000
Celebrating the PhD defense of Benien van Aken

Assorted Dutch newspaper headlines

Student

Medicijntesten bijverdienste voor honderden studenten

,Goed zorgen voor 'patiënten'

Nieuw Leids instituut test medicijnen op vrijwilligers

Gezonde mensen als proefkonijn

NIEUW CENTRUM VOOR HUMAAN

Geneesmiddelenonderzoek

Bejaarden moeilijk te vinden voor medicijnproeven

2000
Hockey at the Leiden Science Park

2004
Art displayed in the extension building at Zernikedreef 10
(artist: Ella Koopman)

2006
CHDR outing

CHDR
CENTRE FOR HUMAN DRUG RESEARCH

Wil jij een waardevolle bijdrage leveren aan de wetenschappelijke ontwikkeling van geneesmiddelen?

Dat kan bij het Centre for Human Drug Research (CHDR) tegen een prima vergoeding.

Het CHDR zoekt gezonde mannen en vrouwen vanaf 18 jaar voor verschillende onderzoeken. Hierbij wordt nauw samengewerkt met het Leids Universitair Medisch Centrum (LUMC). De onderzoeken worden veilig en zorgvuldig uitgevoerd en dragen bij aan de wetenschappelijke ontwikkeling van nieuwe geneesmiddelen.

Meer weten?

Bel 071 - 524 64 35

Ons adres:
Zernikedreef 10,
(Bio Science Park)
2333 CL Leiden.
E-mail: recruit@chdr.nl

Bezoek ook onze internet-site met informatie over lopende onderzoeken
http://www.chdr.nl

2006
Advertisement for test subjects

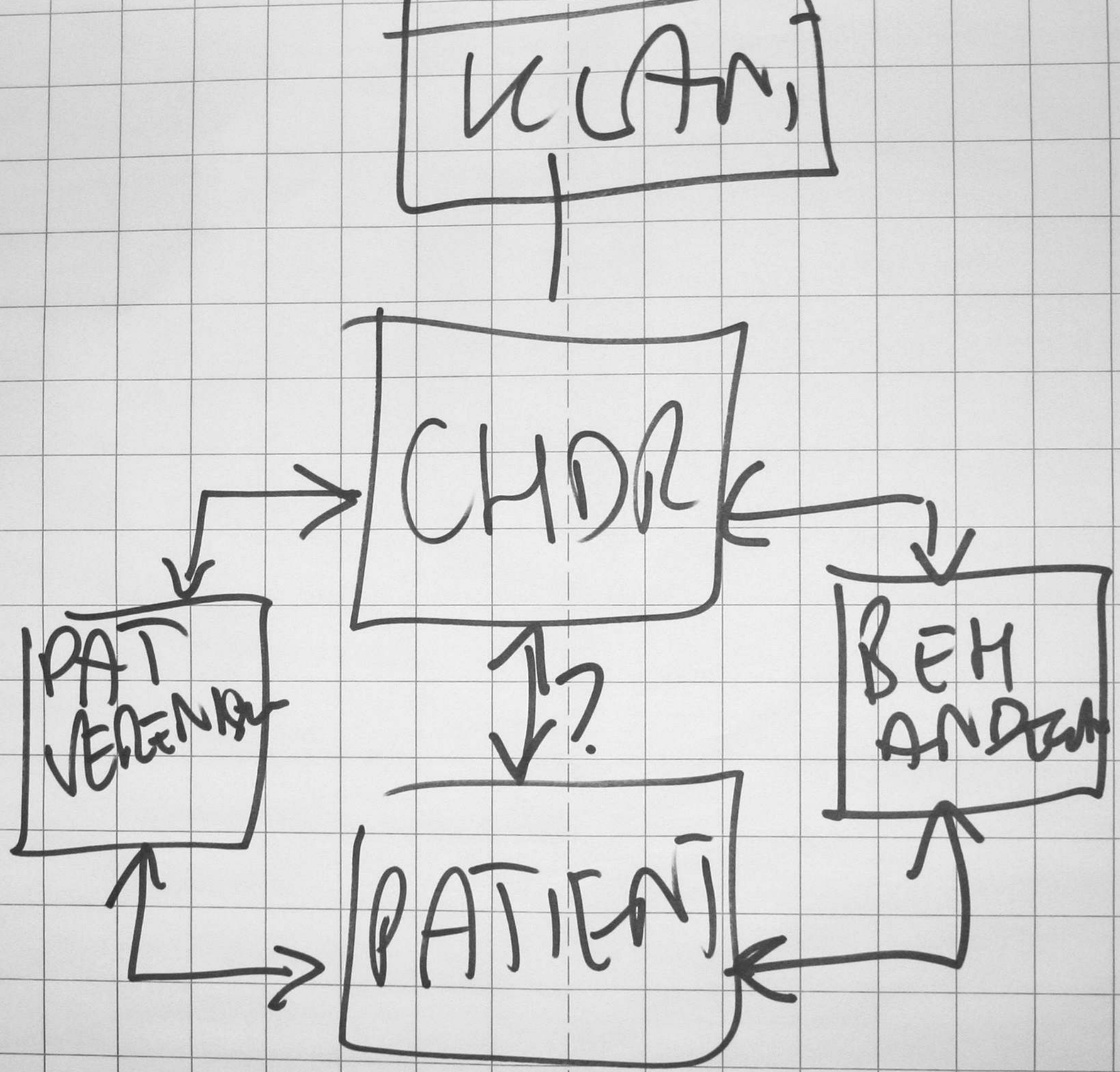
2006
NeuroCart

2007
Building extension (Zernikedreef 10)

2007
Dino meeting in Amsterdam

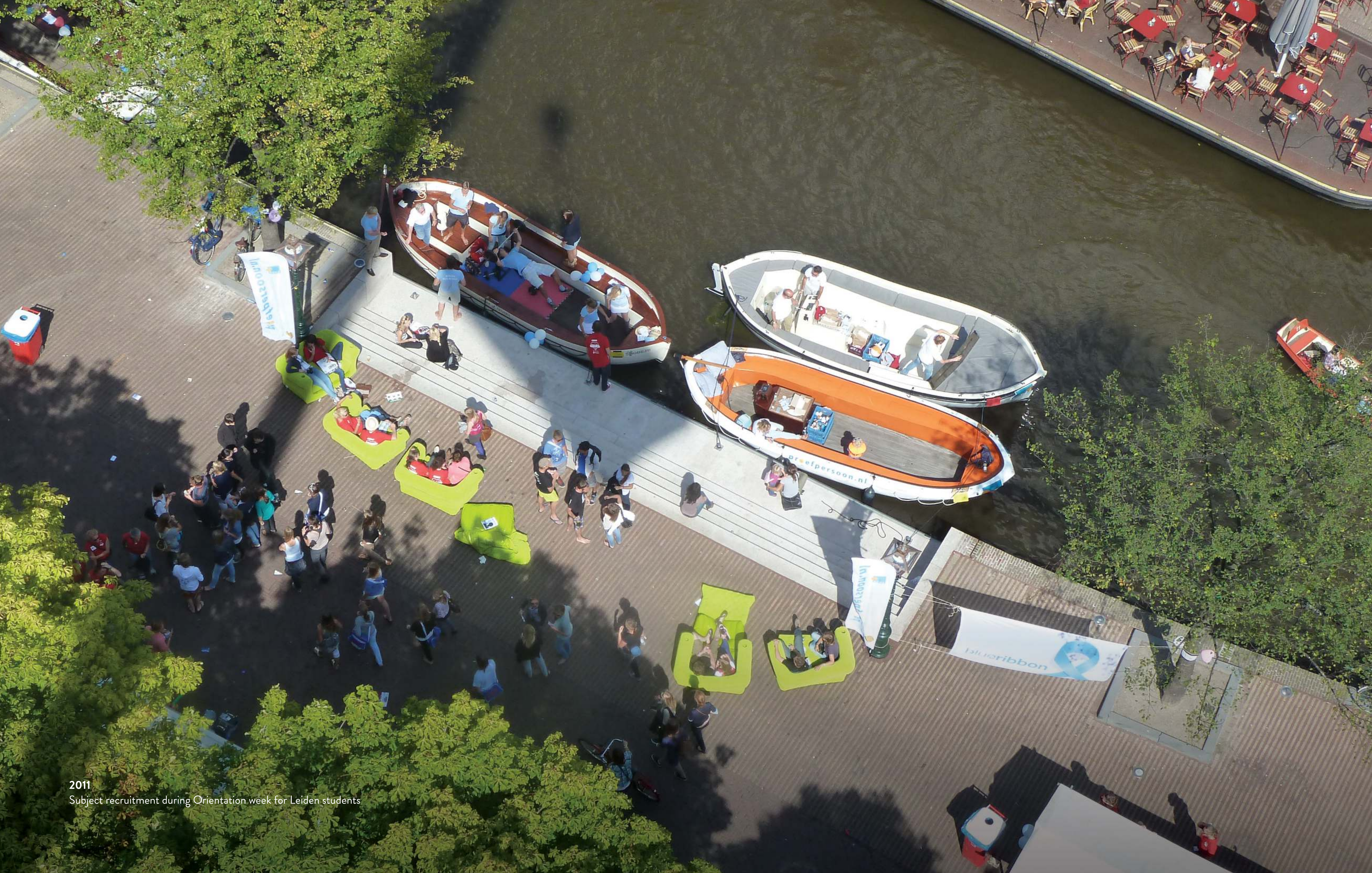
2007
Sailing weekend

2009
In Edinburgh for the European Association for Clinical Pharmacology and Therapeutics (EACPT) meeting



2009
Resaerch notes

2011
Project leader dinner in Leiden



2011
Subject recruitment during Orientation week for Leiden students

2011
Early ‘construction’ at the new site for CHDR, Zernikedreef 8, Leiden

2011
Inspecting the first support beams at the new site

2011
CHDR staff assemble at the future Zernikedreef 8 building

February 1, 2012
Construction at Zernikedreef 8

June 8, 2012
Plans of Zernikedreef 8 building

2012
Group photo at the top of CHDR

2014
Taking a break during the Leiden Singel Run

2015
Project leader weekend

2015
Farewell for Justin Hay using the PainCart cold pressor test

2015
In Madrid for the European Association for Clinical Pharmacology and Therapeutics (EACPT) meeting

2016
CHDR Ski trip

2016
EPO study in Mont Ventoux, France

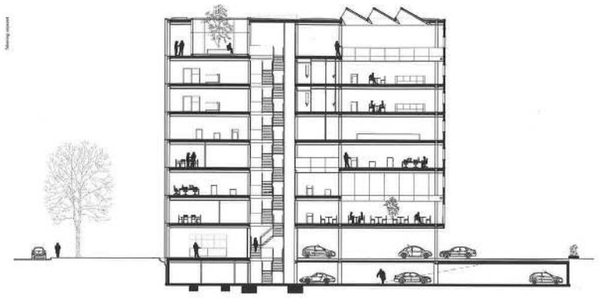
2016
EPO study in Mont Ventoux, France

2016
Christmas dinner

2016
Christmas dinner

2016
CHDR at night

Pret



Het *Centre for Human Drug Research* (CHDR) in Leiden doet onderzoek naar de (bij) werking van medicijnen. Het bedrijf begon eind jaren tachtig in een oude barak naast het Leids Universitair Medisch Centrum. In de jaren negentig betrok het een spraakmakend cepezed-gebouw op het Bio Science Park. Dit werd verschillende keren uitgebreid, maar de onderneming bleef groeien. In 2013 verhuisde zij naar een groter onderkomen direct naast het oude, wederom ontworpen door cepezed.

Boven De dwarsdoorsnede toont de ruimtelijke opzet van het pand met de drie ongelijke stroken in de diepterichting.
Midden Prof. dr. Adam Cohen, directeur CHDR: 'Door de open trappartij ben je altijd in contact met andere mensen en met wat er in het pand gebeurt.'
Links boven Aanzicht voorzijde aan de Zernikdreef. Om het volume op de gegeven kavel kwijt te kunnen is de nieuwbouw een stuk hoger dan het oorspronkelijke gebouw.
Links onder De bovenste verdieping heeft slaapruimten voor langdurig verblijf, daaronder bevinden zich de onderzoekskamers en gemeenschappelijke ruimte.

2016
Article in cepezed@work magazine

cepezed en het CHDR hebben samen een lange geschiedenis, die zich belangrijk kenmerkt door de eigenzinnigheid van beide ondernemingen. 'Toen wij in de jaren negentig een eigen gebouw wilden, werd er op het *Bio Science Park* vooral veel lelijks en dysfunctioneels opgetrokken,' vertelt professor Cohen in het hoge, lichte bedrijfsrestaurant van zijn researchorganisatie aan de Zernikedreef. 'Er waren alleen maar ontwikkelaarsgebouwen: schraal, duur en generiek. Voor je ze kon gebruiken, moest je ze eerst nog ingrijpend verbouwen. Wat heb je er dan aan?'

zelf ontwikkelen

Uiteindelijk besloot het CHDR zelf te ontwikkelen. 'We wisten alleen niet hoe dat moest, we hadden daar geen enkel verstand van,' vertelt Cohen. In zijn ogen is de pret te lezen die hij weer beleeft bij zijn rebelse aanpak van destijds. 'cepezed heeft ons toen helemaal ondersteund en begeleid. Het bureau ging bijvoorbeeld mee naar de gemeente voor de grondonderhandelingen. Dan troffen we daar toch weer zo'n ontwikkelaar, erbij gehaald door de gemeente. "Wat doet u hier?" vroeg cepezed. De inzet van de hele onderneming was immers de marge van de ontwikkelaar te elimineren en zo alle investering en ontwerpkwaliteit aan onszelf ten goede te laten komen.'
Het resultaat mocht er zijn. Voor een bescheiden budget realiseerden cepezed en het CHDR een gebouw met een verrassende typologie zoals die nog nooit eerder was gezien. Het bestaat uit twee volledig transparante, vrij indeelbare beuken met een atrium ertussen, aan de buitenkant geflankeerd door grote, zwarte schermen van geperforeerd staal. Binnen heerst zo een opvallend open en lichte sfeer, terwijl het gebouw van buitenaf grotendeels aan het oog onttrokken is. 'Zeker als je het vergelijkt met wat er voor een soortgelijk bedrag verder te koop was, was het revolutionair,' zegt Cohen. Het gebouw won zowel de Nationale als de Europese Staalprijs, is veel besproken in de internationale architectuurpers en terug te vinden in verschillende monografieën over moderne onderzoeksgebouwen. Ook was het energiezuinig nog voor dit een belangrijk thema in de bouw werd: het CHDR kreeg aanschrijvingen van de energieleverancier omdat het niet genoeg verbruikte. 'Maar bovenal,' zegt Cohen, 'paste het gebouw goed bij onze organisatie. Het reflecteerde hoe het CHDR werkt; onze multidisciplinaire activiteiten vragen om openheid en een ontmoetingsplaats. Waar andere gebouwen heel gesloten waren, vervulden die transparantie en dat atrium van ons die behoeften perfect. Die waren voor toen ook echt vooruitstrevend. Naar buiten straalde het gebouw daarnaast het beeld van een integrale organisatie uit. Dat had allemaal merkbaar effect; op klanten, maar ook op personeel. Mensen wilden graag bij ons komen werken.'

CHDR II

Voor het nieuwe gebouw volgde de tandem CHDR-cepezed een gelijke manier van werken. Weer besloot het CHDR tot zelf doen en bood cepezed inhoudelijke en procedurele begeleiding. Zo was het bureau vertegenwoordigend gesprekspartner op bijvoorbeeld het gebied van stedenbouw. 'cepezed is een gerenommeerde firma die de regels kent, voorbeelden kan aandragen en zo ook gezag uitstraalt,' zegt Cohen. 'Dat maakt dan dat de gemeente bereid is veren te laten die ze anders nooit zou laten. Ze vond de betrokkenheid van cepezed natuurlijk ook fijn; de architecten leveren een kwaliteit waar de rest van het *Bio Science Park* niet om bekend staat.'
De samenwerking tussen opdrachtgever en opdrachtnemer verliep wederom uiterst soepel. Omdat veel mensen al lang bij het CHDR werken, kostte het weinig moeite al het echt belangrijke scherp te krijgen en de benodigde informatie op te stellen. Uitgangspunt was daarnaast dat er over de toekomst weinig met zekerheid te zeggen valt en het gebouw dus superflexibel moest zijn. Eigenlijk was er maar één echt voorbehoud. 'We zeiden: "Als je weer met een zwart gebouw komt, krijg je de opdracht niet." Toen werd het een wit gebouw,' lacht Cohen.
Wederom prijswinnend ontwierp cepezed ditmaal een strak gedetailleerde toren van acht daglichtrijke verdiepingen onder meer geschikt voor Het Nieuwe Werken. Aan de voorzijde bevinden zich functies als de receptie, een auditorium en de verschillende kantoren, die deels ook zijn verhuurd aan samenwerkingspartners. In de achterzone zijn onder andere het bedrijfsrestaurant en de belangrijkste onderzoeksfuncties ondergebracht. De bovenste verdiepingen vormen een comfortabel verblijf voor de proefpersonen. Tussen de voor- en achterzone in bevindt zich een facilitaire strook die ook het trappenhuis bevat. 'Dit vind ik eigenlijk het aardigste deel van het gebouw,' vertelt Cohen daarover. 'Het is echt een ontmoetingsplek en je kunt hier overal iedereen zien. We zwaaien ook steeds naar elkaar.'
Ook nu merkt Cohen een significant effect van het gebouw op zijn bedrijf. Daar zitten veel facetten aan: 'Het zit 'm in de reacties van klanten, samenwerkingspartners en andere bezoekers, maar ook in hoe de medewerkers en proefpersonen het pand gebruiken: de manieren van werken en verblijven resoneren helemaal met de architectuur. "Dit hebben we nog nooit gezien," hoor ik vaak; qua ruimte, qua sfeer, qua wat er gebeurt. Sommige proefpersonen komen bij wijze van spreken depressief naar binnen en gaan blij weer naar buiten of willen niet meer weg. Dat zit in de aandacht die ze krijgen, maar ook in het gebouw. Het trekt ook klanten aan en goede werknemers, wat maakt dat we hier meer technologische kennis bijeenbrengen dan anderen. Sinds we hier zitten zijn we alweer zo'n 30 tot 40% per jaar gegroeid.'

2017
The CHDR Management Team

1987

CENTRE FOR
HUMAN DRUG RESEARCH

2007

CHDR
The Netherlands

1995

CHDR
CENTRE FOR HUMAN DRUG RESEARCH

2012

CHDR
Centre for Human Drug Research

2005

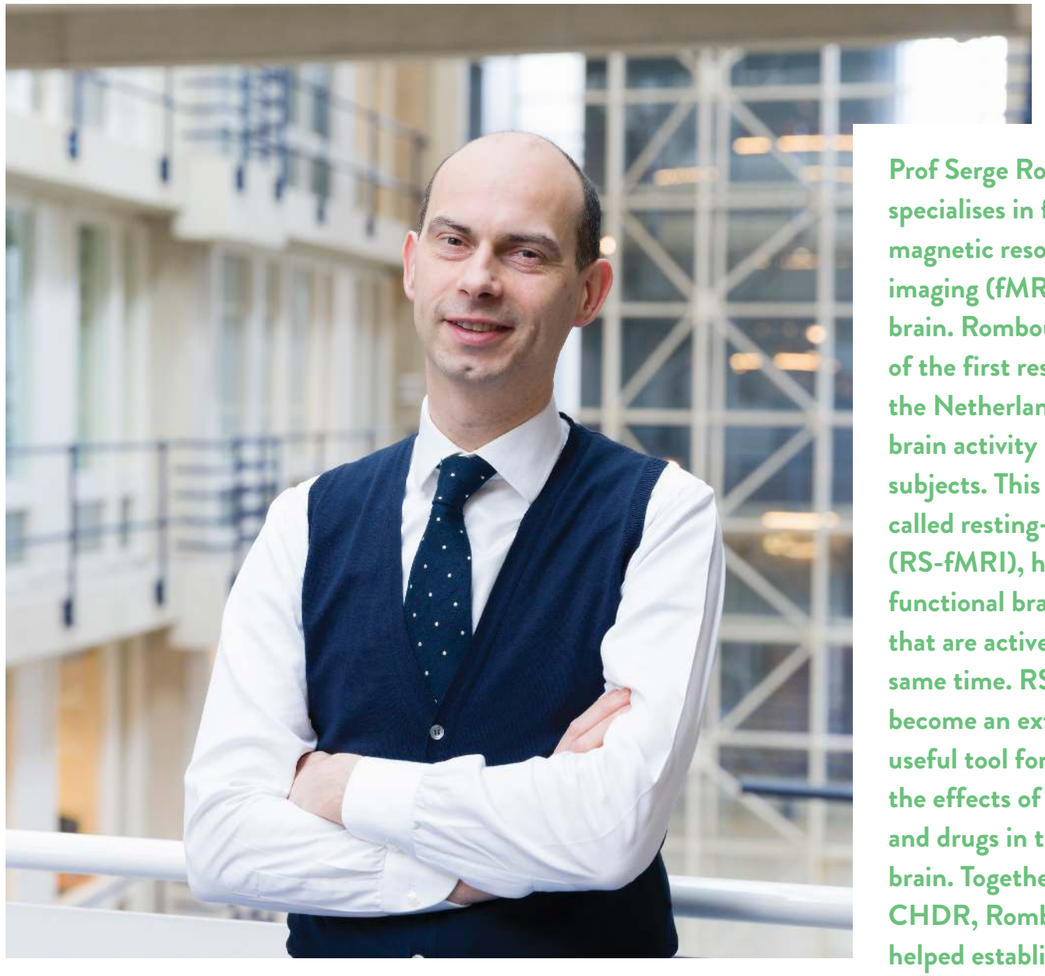
CHDR
CENTRE FOR HUMAN DRUG RESEARCH

2016

CHDR
Centre for Human Drug Research

CHDR logos through the years

‘Pharmaco-fMRI is a tool that we pioneered together’



***Dr Serge Rombouts**, Professor of Methods in Cognitive Neuroimaging at Leiden University and Leiden University Medical Centre*

Prof Serge Rombouts specialises in functional magnetic resonance imaging (fMRI) of the brain. Rombouts was one of the first researchers in the Netherlands to study brain activity in resting subjects. This approach, called resting-state fMRI (RS-fMRI), highlights functional brain areas that are active at the same time. RS-fMRI has become an extremely useful tool for studying the effects of disorders and drugs in the human brain. Together with CHDR, Rombouts helped establish a pharmaco-fMRI unit.

‘I was amazed how clearly the effects were revealed, even with relatively small groups.’

‘In 2006, when I moved to Leiden University Medical Centre from the VUmc in Amsterdam, Mark van Buchem – who now heads our radiology department – suggested that I meet Joop van Gerven at CHDR.’ This turned out to be an excellent suggestion, as Rombouts and Van Gerven quickly became both friends and collaborators, pioneering the use of RS-fMRI for use in clinical drug development. ‘We immediately realised the possibilities, and our complementary areas of expertise meant that we could achieve these possibilities by working together,’ says Rombouts.

Studying the resting state is the key to studying networks

During the 1980s and 1990s, the MRI scanner became an important imaging tool, allowing clinicians to visualise anatomical details beyond what other techniques could achieve. As the quality of these images improved and new techniques were introduced, it also became possible to visualise brain function. With fMRI measures, the signal changes in response to the change in the magnetic properties of haemoglobin when it releases oxygen. Because brain activity requires both oxygen and glucose, changes in brain activity lead to corresponding changes in the transfer of oxygen from the blood to the neurons.

In the early days, fMRI was used exclusively to measure specific changes in brain activity in subjects while performing a task; this approach helped researchers determine the functional properties of various brain areas. Rombouts and his colleagues were inspired by the work of Dr Marcus Raichle, a neurologist at the Washington University School of Medicine in St. Louis, Missouri. Raichle was studying intrinsic brain activity in subjects who were not performing any particular task during the scan. ‘It’s called the “resting” state,’ explains Rombouts, ‘but this is a bit of a misnomer, as the brain never truly rests. Our brains are always active, consuming tremendous amounts of glucose and oxygen. From an evolutionary perspective, this spontaneous activity during the resting state must be important to the organism; otherwise, our body wouldn’t waste precious resources on it.’

Observing the brain in the resting state provided highly valuable information. For example, researchers discovered that activity in different brain areas fluctuates synchronously. This synchronicity suggested connectivity. ‘Of course,’ says Rombouts, ‘it makes sense to view the brain from a network perspective, as brain function depends on interactions. So rather than studying individual brain areas, we decided to study brain networks.’

Visualising drug signatures using RS-fMRI

Rombouts recalls how Van Gerven – who was acutely aware of the limitations of conventional task-oriented fMRI in pharmacology – was intrigued by the concept of using RS-fMRI, particularly when he told Van Gerven that these networks of synchronous activity can change with ageing and in specific conditions such as depression and dementia. So Rombouts’ and Van Gerven’s teams got together and quickly found that CNS drugs can also change the activity patterns measured with RS-fMRI. Beginning with alcohol and other well-known neuroactive substances, they found that each class of CNS drug has its own RS-fMRI signature. These signatures are now used as a reference library when studying the effects of new compounds on the brain. A second frame of reference is the changes in resting-state networks induced by conditions such as depression. Thus, if a candidate drug for that condition has the opposite effect on these networks in healthy volunteers, this can be used as evidence that the compound may indeed have the intended effect in patients.

‘Working with Joop was scientific synergy at its best,’ says Rombouts. ‘Joop liked what I’d been doing, I was impressed by his knowledge and expertise in neuropharmacology, and we both had a keen interest in MRI. For example, I was familiar with the approach of giving a subject a single dose, waiting a specific amount of time, and then running a scan. Joop introduced a far more sophisticated dose-response approach. We would run up to eight scans per subject, starting with one or two baseline measurements; after each dose was administered, we’d run another scan, followed by another scan when the drug’s concentration peaked, then yet another scan after the drug had been eliminated from the bloodstream. I was amazed how clearly the effects were revealed, even with relatively small groups of twelve subjects in a crossover placebo-controlled study.’

‘It makes sense to view the brain from a network perspective, as brain function depends on interactions.’

Measuring and predicting drug effects

The pharmaco-fMRI study was a collaboration between Leiden University, LUMC, and CHDR subsidised by several grants from the NWO (the Netherlands Organisation for Scientific Research). This research resulted in several important publications, including a paper in which PhD student Bernadet Klaassens and her colleagues described how they gave healthy human subjects a single dose of the well-known antidepressant sertraline and found that the drug had widespread effects on functional connectivity in multiple networks. They also found that

for several of these networks, the effects were common to specific anatomical structures. Interestingly, fMRI was far more sensitive to the effects of a single dose of sertraline compared to both cognitive and subjective measures, which were unable to detect a difference between sertraline and placebo. Thus, RS-fMRI can likely yield more information regarding the effects of novel antidepressant drugs compared to other measuring tools.

Building on their long-standing scientific collaboration, CHDR and LUMC have also begun to collaborate at a more practical, operational level. The radiology department at LUMC acquired an additional MRI machine, which CHDR can use for pharmaco-fMRI studies using both volunteers and patients. The facility also has space available for researchers to administer compounds and perform tests such as CHDR's NeuroCart®.

Meanwhile, Rombouts and his colleagues are moving on to other forms of cutting-edge research. 'Thanks to a Vici grant from the NWO, we're now working on machine learning in which we feed large amounts of MRI and clinical data into a computer system. The computer then "learns" to recognise pathological conditions such as dementia in an early stage.' Given that CHDR is also helping develop treatments designed to slow the pathological processes that lead to dementia, it is quite likely that these two research groups will again work together on innovative research projects in the future.

'fMRI was far more sensitive to the effects of a single dose of sertraline compared to both cognitive and subjective measures.'

'I like our cross-pollination of ideas, knowledge, and information'

***Dr Bert van Hemert**, Professor of Psychiatry, Leiden University Medical Centre*

For the past 30 years, psychiatry has been one of the major areas of focus at CHDR, with a long-standing collaboration between CHDR and the Psychiatry Department at Leiden University Medical Centre (LUMC), currently headed by Prof Bert van Hemert. 'We have common ground, and I value our exchange of ideas.'

'In addition to behavioural science, neuropharmacology is a major component in psychiatric treatment,' says Van Hemert. 'Of course, we do more than just prescribe pills, but it's hard to imagine that our treatment approach would be effective without medication. Pharmacology also contributes to scientific research, helping us understand better the neurobiology of psychiatric disorders. That's why I value our collaboration with CHDR, their expertise in the field of pharmacology, and their contributions to the development of new drugs. CHDR does a great job of balancing the interests of academia with the needs of industry, all while pursuing knowledge. CHDR is always both clear and transparent regarding their activities, and they maintain a high level of quality. From what I see, CHDR plays an exemplary role in implementing good research practices and other quality standards, which benefit clinical departments, including our own.'

'Pharmacology helps us understand the underlying neurobiology in psychiatric disorders; that's why I value our collaboration with CHDR.'

The Psychiatry Department at LUMC combines patient care with educating students, training psychiatrists, and performing clinical research. Specifically, LUMC psychiatrists study mood disorders, anxiety, somatoform disorders, and dysregulation of emotions. They also study paroxysmal cerebral dysfunction and ageing. The Psychiatry Department also conducts research in neuroimaging, in collaboration with several groups at Leiden University. Many of these topics are also being studied at CHDR, providing ample opportunities for collaboration.

Pharmacology and philosophy

Recently, the collaboration between LUMC and CHDR grew even stronger. In 2016, Dr Gabriël Jacobs, a staff member at CHDR who also received training as a clinical pharmacologist at CHDR, joined the Psychiatry Department at LUMC, where he treats outpatients with severe mood disorders. 'It's good to have Gabriël on board,' says Van Hemert. 'His expertise in clinical pharmacology is invaluable in the treatment of our patients, and he shares his knowledge with the entire team, including residents, thereby contributing to their training.'

CHDR Research Director Prof Joop van Gerven has been affiliated with the Psychiatry Department since 2004. 'I've known Joop for many years,' says Van Hemert, 'and I always enjoy our lively discussions on a variety of subjects. We share an interest in studying how the brain functions under various conditions and in various disorders. Joop and I approach the same subject from different angles, which makes our discussions rewarding. Philosophically, it's the age-old problem of the brain and the mind, of matter and meaning. How can we identify connections between our subjective experiences, our language and behaviour, and our models of brain function? There's no doubt that these things are connected, but how can we exploit these connections in order to benefit our patients? In this respect, understanding how psychotropic drugs work – and identifying the neurotransmitter systems that they target – is essential to bridging these worlds. And that's where Joop comes into the picture, thanks to his expertise regarding the connections between behaviour, experience, and neurotransmitter systems. As we learn more about these systems, including their feedback loops in the brain and the way they function in patients with specific symptoms, we increase our ability to develop effective pharmacological treatments, and we can find more productive ways to understand those symptoms and the results of pharmacological interventions.'

Treating patients with depression

Van Hemert explains how his philosophical approach translates to practical consequences. 'Treating patients with depression requires a three-pronged approach consisting of medication, reactivation, and cognitive interventions. If you only give medication, the effect will be limited. Patients also need to become active again and improve their cognitive symptoms. Whenever I prescribe a medication – for example, an SSRI [selective serotonin reuptake inhibitor] – to a patient with depression, I also explain the importance of pursuing pleasurable activities. Interestingly, research at CHDR using healthy volunteers has shown that a single dose of SSRI causes a measurable change in emotional response time. Research by Joop and Serge Rombouts using resting-state fMRI has also shown that a single SSRI dose causes a measurable change in several neurotransmitter systems that play a role in depression. In the clinic, however, it takes two to four weeks of treatment before the patient's mood improves. The studies at CHDR suggest that treatment may immediately improve the patient's capacity to enjoy things again. So I now tell my patients that their treatment will likely be more effective if they get out and return to activities that they enjoy. We know that staying active is an important part of the treatment, and it motivates patients to get out of the house. After all, staying in bed with your head under the blanket almost guarantees that you'll remain depressed.'

Balancing interests

In addition to conducting research with healthy volunteers, CHDR has increased their studies using patients, including psychiatric patients. As a psychiatrist, what does Van Hemert think about allowing psychiatric patients to

participate in early-phase clinical drug trials? 'I know that some of my colleagues want to protect their patients,' he says. 'But my general view is that psychiatric patients – as competent adults – are usually fully capable of making their own decisions, provided you give them the relevant information. When I ask my patients to participate in a study, most agree. Of course, some patients do need to be protected from themselves; but these are the exceptions rather than the rule. In most cases, I see no reason to decide for my patients, and we should strive to include them in the decision-making process when it comes to their treatment. I think that is only logical; after all, if I decide for them, and they don't agree with the treatment plan, how can I expect my patients to comply with the treatment? As doctors, we sometimes forget that our patients spend the vast majority of their time away from our office.

'Through our own clinical research, and through our collaboration with CHDR,' continues Van Hemert, 'I believe we can contribute to scientific progress. Everything we do as psychiatrists isn't necessarily based on research; but I think we owe it to our patients to offer treatment options that are based on the best available evidence. As an academic psychiatry department, we have an obligation to contribute to research in order to improve patient outcome, and we should resist the temptation to act on unfounded notions and superstition.' •

'My general view is that most psychiatric patients are fully capable of making their own decisions, provided you give them the relevant information.'

'CHDR provides a strong sense of academic freedom'

Practical relevance is important to Dr José Borghans and Dr Kiki Tesselaar, academic researchers at the University Medical Centre Utrecht. Collaborating with CHDR was Borghans and Tesselaar's first experience with the pharmaceutical industry. 'We were glad to see that we could enjoy the same academic freedom. It's all about content and learning how things work.'

__Dr José Borghans__ (shown at the right) and __Dr Kiki Tesselaar__, Leucocyte Dynamics Research Group, Laboratory of Translational Immunology, University Medical Centre Utrecht

In the interdisciplinary Leucocyte Dynamics Research Group at UMC Utrecht, experimental immunologists and mathematicians work side by side to measure and model the production and lifespan of various populations of white blood cells. 'Our research focuses on analysing leucocytes in healthy individuals and in patients with HIV, leukaemia, and other diseases that affect the immune system,' says Borghans. 'We receive samples from patients who were treated either in our own hospital or in an affiliated hospital, and we return hard numbers that can be used to make sound decisions.'

'In our work,' adds Tesselaar, 'our goal is to bridge basic research with real-world clinical applications. Until recently, however, we always worked in an academic context. We had no prior experience with contract research.'

Measuring how a drug might affect lymphocyte populations

Borghans and Tesselaar were approached one day by Dr Matthijs Moerland, the research director of the Biomarkers unit at CHDR. Moerland had a very specific clinical problem, and he thought that the Utrecht researchers might have the perfect solution. Moerland wanted to determine the way in which a drug might affect the production and/or survival of specific lymphocyte subpopulations.

Moerland's request arose from a practical problem encountered by one of CHDR's sponsors. The sponsor's drug was found to cause transient lymphopenia, a temporary decrease in the number of lymphocytes. This effect was so severe in some patients that their immune system was weakened. To prevent this rare but serious complication, guidelines now call for the routine monitoring of patients while taking this drug. To identify the underlying problem and determine how it might be prevented, the manufacturer turned to Moerland at CHDR. Moerland then turned to Borghans and Tesselaar in Utrecht. 'I'm not sure how he found us,' says Borghans, 'but it was probably through our published papers. Very few groups are doing this kind of work.'

Deuterium-labelled DNA

At Utrecht, the group uses a clever approach to study lymphocyte populations – they label the cells' DNA with deuterium, a stable isotope of hydrogen with twice the mass as a regular hydrogen atom. Replacing hydrogen with deuterium in water creates D2O ('heavy water'), which looks and tastes the same as regular H2O. 'We ask subjects to drink half a cup of heavy water each morning,' Borghans explains, 'in which some of the regular hydrogen atoms were replaced with deuterium atoms. Because deuterium is chemically identical to hydrogen, it's distributed everywhere throughout the body. It's also incorporated into the DNA of dividing cells, including newly formed lymphocytes. Using a combination of gas chromatography and mass spectrometry, we can detect the ratio of deuterium to hydrogen in the DNA of lymphocytes, allowing us to monitor their production and half-life.'

Just half a cup of heavy water is relatively little compared to all of the water and other sources of hydrogen an average person consumes in a day. And because only a fraction of this is incorporated into the DNA of lymphocytes, it takes an extremely sensitive tool to detect the small number of deuterium atoms in newly formed lymphocytes. 'That probably explains why so few groups are doing this,' says Borghans. 'But we know from our own research that this is a robust method for studying the production and lifespan of these blood cells.'

The long lifespan of T cells

The subjects in the study drank heavy water for nine weeks. Blood samples were collected before the study, during the experiment, and for up to a year after. At CHDR, the relevant cell populations are extracted from the blood samples using cell sorting technology, and the DNA is sent to Utrecht to be analysed. 'We just received a new batch of DNA for analysis,' says Tesselaar, 'so this is an ongoing study. It could take until the end of the follow-up period before we can draft the first publication. This long follow-up period is important, as we know from previous research that some populations of white blood cells – particularly naïve T cells – can have an extremely long lifespan. If we follow the amount of deuterium labelling in the DNA of these cells, we see that it decreases very slowly over time, and our models suggest that these cells have a lifespan of seven to ten years. This tells us that even a one-year follow-up isn't really very long.'

Differences and similarities between academia and CHDR

When Moerland first approached Borghans and Tesselaar, they were a bit reluctant. 'We cherish our freedom in academia,' explains Borghans, 'and we were worried that working with an industry sponsor might limit that freedom. But Matthijs quickly assured us that we would be free to publish the results, regardless of the outcome. And after talking with Matthijs, we were pleased to see that he's driven primarily by scientific curiosity, not commercial gain. In fact, it felt very much like an academic collaboration.'

Their collaboration with CHDR was facilitated by the fact that the Utrecht group had already invested in a high level of operational quality. UMC Utrecht has high quality standards and is ISO-certified. 'The head of our department used to work at the biopharmaceutical company Crucell, which certainly contributed to our high level of quality,' says Tesselaar. 'Matthijs was pleased to see that our SOPs – our standard operating procedures – were all in order. And we were quite impressed with how well-organised everything was at CHDR, particularly patient recruitment. Everything went so smoothly, and now we can analyse our data and see if we can answer the underlying question. I hope that we can contribute to solving this problem by helping eliminate lymphopenia in patients who receive the drug. That's exactly the kind of clinical problem that we like to address.'

‘Leiden is a virtual pharmaceutical company’

Leiden University Medical Centre (LUMC) – and the LUMC Pharmacy in particular – plays an essential role in the daily operations at CHDR. CHDR’s study medications are prepared by the LUMC Pharmacy, and some compounds are even produced at the Pharmacy’s GMP-licenced facility. ‘As a pharmacist, scientist, and educator, I always find it interesting to collaborate with CHDR. They’re an essential component connecting a vast network of pharmaceutical experts here in Leiden.’

***Prof Henk-Jan Guchelaar**, Head of the Department of Pharmacy & Clinical Toxicology, LUMC*

CHDR’s connection with the LUMC Pharmacy dates back to CHDR’s earliest days. In 1986, shortly before CHDR was established, a part of what was then called the Leiden University Hospital moved to a new building. The hospital’s pharmacy had also moved, leaving a small building that would become CHDR’s first site. Even in those early days, the pharmacy played a key role in CHDR’s studies by supplying medications.

In a booklet memorialising the first 50 years of the LUMC Pharmacy, CHDR’s CEO Prof Adam Cohen wrote that it was clear from the beginning how the hospital pharmacy – with its impressive production capacity – was essential to the success of his newly established clinical research unit. For Cohen, it was quite an improvement compared to his days at the Wellcome Foundation in London, where he had to rely upon the local pharmacist to prepare the essential test compound. When he needed a control for his experiments with the antiepileptic drug lamotrigine, Cohen convinced a family member to bring him 2 kg of phenytoin sodium from the Netherlands. These days, he wouldn’t recommend trying to enter the United Kingdom with 2 kg of white powder in the back of a car. And a well-run pharmacy is highly preferable, even if it doesn’t give you such amusing anecdotes.

Daily collaborations

At least once a day, LUMC delivers a package to CHDR, containing all of the study medications prepared by the LUMC Pharmacy. To help make this possible, the Pharmacy is closely involved in the planning and preparation of each study at CHDR. ‘We’re involved in the early stages, when the protocol is being prepared,’ says Guchelaar. ‘We discuss our contribution to the study, and we coordinate our logistics with CHDR’s operations team.’

Although all of the medications for CHDR – including even the occasional paracetamol tablet for treating a subject’s headache – is delivered by the LUMC Pharmacy, their contributions vary. ‘Sometimes, all we do is receive the medication from the sponsor, label it, and deliver it to CHDR,’ says Guchelaar. ‘But usually, something extra is needed. For example, we might need to prepare a placebo or control compound that looks exactly like the study medication, and we might need to organise all of the logistics associated with a double-blind study. In some cases, the sponsor sends the medication in raw form, and we put it into tablet or capsule form. If a sponsor wants us to synthesise the active molecule itself, we can do that as well, using our GMP-licensed facility. These are some of the most interesting aspects of what we do here.’ A good example of the substances produced at LUMC’s GMP facility is the fluorescent markers developed for image-guided surgery, which surgeons at LUMC are studying in collaboration with CHDR (see also page 65).

Leiden, a virtual pharmaceutical company

To Guchelaar, his collaboration with CHDR is just one part of a larger network, with Leiden serving as what he calls a ‘virtual pharmaceutical company’. ‘Drug development is a chain containing many links,’ explains Guchelaar, ‘and I think we have all of these links right here in Leiden. At LACDR, the Leiden Academic Centre for Drug Research at our Faculty of Science, several groups are involved in drug discovery and early drug development. Here at LUMC, many basic science groups contribute to identifying targets and developing new treatments,

including immunotherapy and cellular therapy. In the department of Clinical Pharmacology & Toxicology, we have two GMP-licenced production facilities. CHDR specialises in early clinical development, administering test drugs to healthy subjects and patients in order to study both the pharmacokinetics and pharmacodynamics, including safety and tolerability, and LACDR is world-renowned in the field of PK/PD modelling. At LUMC, we can conduct larger studies in patients, sometimes even collaborating with other hospitals. Finally, the Leiden Bio Science Park includes more than 100 medical life sciences companies and institutions with expertise in many of the essential steps involved in developing, testing, and marketing novel drugs and advanced treatments.'

The 'Mutanome' project: towards individualised cancer treatment

An interesting example to illustrate the power of collaborating in developing a successful treatment is the Leiden 'Mutanome' project, a radical new approach to treating cancer. 'In a malignant tumour, the cells accumulate genetic mutations,' says Guchelaar. 'This can lead to the production of altered proteins that can be recognised by the body's immune system. The goal of this project is to develop personalised therapeutic vaccines based on these aberrant proteins, so-called "neo-antigens" in the patient's tumour cells. In principle, this is a highly promising approach, as the immunotherapy will be targeted specifically to proteins that are present in the specific patient's tumour cells. But it's also quite challenging in terms of developing the treatment. Essentially, we'll need to develop a new treatment for each patient. So it will be difficult to prepare an individualised therapeutic vaccine within the necessary timeframe, ideally within one to two weeks. Equally important considerations are the safety and efficacy of this individualised treatment. What antigens will be the most effective in terms of triggering an immune response? How can we prevent an immune response in healthy cells? Each of these questions – and many more – will need to be addressed. But importantly, the entire project can be performed right here in Leiden, thanks to all of the expertise available here.'

Teaching together

Guchelaar and his staff also work closely with CHDR to educate students, particularly medical students. 'In healthcare,' says Guchelaar, 'pharmacotherapy is the most common intervention. But in the medical curriculum, pharmacology receives relatively little attention. So what we're doing – teaching and developing new methods to get the message across – is extremely important. And it's not just a matter of telling our students; we're also looking for ways to make it more interesting. Although students often complain that they find pharmacology a bit boring, even dull and stuffy, we need to recognise that the patient's safety and health depend on the physician's knowledge regarding pharmacology. When teaching tomorrow's doctors, we need to make pharmacology as attractive as possible. Together with CHDR, we're now developing a highly stimulating combination of audio-visual, digital, and conventional forms of education.'

In addition to teaching future physicians and biomedical researchers, Guchelaar has another challenge. In September 2016, a new Master's programme in Pharmacy Science started, training students to become pharmacists. 'This new programme, which is designed to train students to become pharmacists, fits nicely with the idea of Leiden as an international centre for drug development. Graduates of this programme will be fully prepared to work alongside physicians and researchers in the development and application of new treatments. This pharmacological knowledge at the bedside will be essential for treating patients with complex disorders, and pharmacists will play a key role in developing and evaluating new drugs and other treatments. I'm glad we've been able to launch this new programme, and we've received many enthusiastic responses from both students and our collaborators. In the future, this may well be another opportunity to collaborate with CHDR, similar to our postgraduate training in clinical pharmacology.' •

'When teaching tomorrow's doctors, we need to make pharmacology as attractive as possible. Together with CHDR, we're now developing a highly stimulating combination of audio-visual, digital, and conventional forms of education.'

‘I enjoy combining my two passions, medicine and programming’

As a medical student, Hans Pinckaers developed an iPhone app so he could easily access the Teaching Resource Centre (TRC), CHDR’s online pharmacology tool. This attracted the attention of Dr Robert Rissmann and Prof Adam Cohen at CHDR, who asked Pinckaers to develop new apps for their outpatient studies. ‘So I became one of their providers, and I don’t think I’ve ever missed a deadline.’

***Hans Pinckaers**, pathology resident, Leiden University Medical Centre*

‘What I like most about CHDR is their open atmosphere,’ says Pinckaers. ‘They’re not hierarchical at all, and I never feel as though some people are trying to push their way to the top. They’re friendly, and they’re always willing to listen if you’ve got something to say.’ Pinckaers was quite young when he was first hired by CHDR, but in a way he came with years of experience. ‘I started writing computer programs around the age of nine. I don’t know why exactly; it was something I enjoyed, and it was something my father did as well. And I’ve been programming ever since, although in recent years I’ve focused on writing apps for the iPhone.’

Building apps for fun

‘When I was in high school, I fell in love with Apple computers,’ says Pinckaers. ‘This made things a bit complicated for me, because the Mac operating system is not an easy platform for developers. But then came the iPhone, and with it the iPhone’s operating system, iOS. In the beginning, the system was relatively simple. It didn’t allow for multitasking, so it was all very straightforward.

‘I started writing iPhone apps, which was great fun. I really enjoyed being able to make something that you can carry with you everywhere. I started with relatively simple apps, but because I like to challenge myself, I built an app to access all public libraries in the Netherlands. There’s no single source of open data for public libraries, so I had to combine the information obtained from several websites, which was a bit complicated. You’d be amazed how many different systems our public libraries have.’

The TRC app

In 2009, Pinckaers began to study medicine at Leiden University Medical Centre. ‘In my second year, Robert Rissmann from CHDR gave a lecture on clinical pharmacology, and he introduced us to the TRC, a website by CHDR for use as a teaching aid by medical students. Later, when I was preparing for my exam, I used the TRC. Although I liked the general idea, I thought the user interface was a little old-fashioned. So I wrote an app for the iPhone, using the open data available on the TRC website. It wasn’t difficult to write; in fact, it was a lot easier than the public library app. A friend of mine was quite impressed and suggested that I show it to CHDR. It didn’t take long before I was talking with Adam Cohen. That’s how things work at CHDR; even though they’re quite big, it feels like a relatively small company where the boss is easily accessible.’

Cohen and Rissmann liked Pinckaers’ work and encouraged him to perfect it. Soon after that, the first version of the TRC app was available through the App Store. A version for Android-based phones was later developed by a friend of Pinckaers. From

then on, the TRC app became a worldwide success story. At the time of this interview, the app has been downloaded more than 150,000 times by students in Europe, the US, and many other countries, including developing countries. CHDR has also invested in further developing the TRC app. In addition to the Dutch and British pharmacotherapy formularies, the app now includes access to Micromedex Ltd., one of the largest companies offering pharmacotherapeutics guidelines to thousands of university medical centres and regular hospitals around the world. Adapting the TRC app to provide access to this valuable new source was no minor task; 721 web links had to be checked manually. But the effort was well worth it, as Pinckaers explains. 'It's really amazing to realise that students on other continents are using an app I wrote, helping them become my future colleagues.'

'It's quite amazing to think that students on other continents are using an app that I wrote.'

Writing apps for clinical studies

Meanwhile, Pinckaers continued his own studies. But then, one day in 2012, his iPhone rang. Robert Rissmann was calling to ask if he had time to visit CHDR in their new building. 'They needed an app to monitor subjects at home,' says Pinckaers. 'In their first outpatient trial, they were testing a dermatological preparation and wanted to replace the usual pen-and-paper journals that patients use to record complaints such as itching and pain. Apparently, they remembered my work on the TRC app, and they asked if I could write an app that could remind subjects to record their symptoms and send the results to CHDR. The app also needed to include the ability for the subject to take a picture of the lesion after they applied the medication.'

CHDR and the study's sponsor were very happy with the app and with the data it generated. Compared to the old-fashioned handwritten journal, the app greatly increased the accuracy of the data. 'With an app,' explains Pinckaers, 'it's easy to remind the subjects to complete the questionnaire. And you always have a record of the exact time and date, something you don't have with a handwritten journal. I also like the addition of having the subjects take a picture of the lesion with the medication on it. You can then be certain that they indeed applied the medication, and you have the exact time that the picture was taken.'

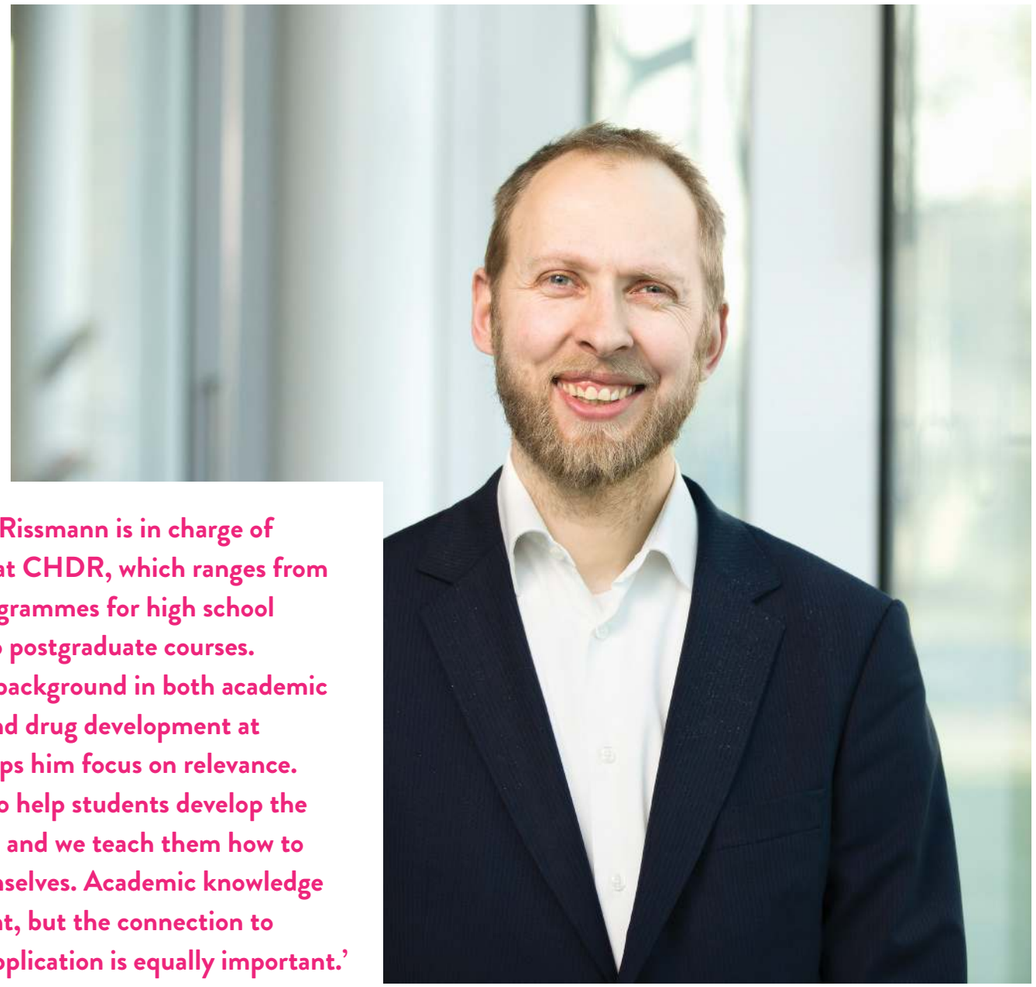
The success of his apps soon led to another request, and Pinckaers has now lost count of how many apps he's written for CHDR. Most have the same basic features: a questionnaire, the option to remind subjects to complete the questionnaire and/or apply the medication, and the option to take a picture. Pinckaers prefers to keep his apps sleek but functional. 'I don't bother with fancy designs; rather, we try to keep things simple. This adds to the app's stability and makes it easier for subjects to use. Whenever I write an app for CHDR, I test it thoroughly and then transfer it to them; the new app becomes their property and their responsibility. I know that they have their own procedures for testing and validating an app, for example checking to see what happens if a subject's phone loses its internet connection. By now, hundreds of patients have used my apps, and everyone's quite happy with the way they work.

'Rather than trying to make a fancy design, I prefer to keep my apps both sleek and functional; our users truly appreciate this approach.'

Looking towards the future

'Of course, now that I'm a pathology resident, I have less time to write new apps, so we're looking for ways to automate the process. I'm looking into ways to create a sort of template so we can easily generate most of the new apps that CHDR might need. That's fine with me, although I hope to remain involved on some level. CHDR is a nice company to work with, and I enjoy writing apps that contribute to medical research. Perhaps in the future I'll be able use my app-writing skills talent to help pathologists. But of course, I need to focus on my training first; pathology is quite a complex discipline, and there's still so much to learn.' •

‘Education is fully connected to clinical and research practice’



Dr Robert Rissmann is in charge of education at CHDR, which ranges from special programmes for high school students to postgraduate courses. Rissman’s background in both academic research and drug development at CHDR helps him focus on relevance. ‘We need to help students develop the right skills, and we teach them how to teach themselves. Academic knowledge is important, but the connection to practical application is equally important.’

***Dr Robert Rissmann**, Director of Education, CHDR*

Rissmann came to the Netherlands in 2004 to pursue a PhD at Leiden University. ‘The research climate is much more innovative here in the Netherlands compared to Germany, where I studied pharmacy science. So I was glad that I could conduct my PhD work at the LACDR [the Leiden Academic Centre for Drug Research].’ LACDR had close connections with CHDR; but when he began his basic research, Rissmann did not yet know CHDR or his future colleagues.

T-shaped education

During his PhD training, Rissmann attempted to create a synthetic version of vernix, the protective layer on the skin of newborn babies. Because of this layer’s protective properties, the idea was that an ointment comprised of the same composition might be used to treat various skin conditions. From a scientific perspective, the project was a success. But with the benefit of hindsight, Rissmann is critical of the approach they used. ‘We didn’t develop the compound the way you should develop a pharmaceutical product in a business setting,’ explains Rissmann. ‘We didn’t strive for simplicity, and we didn’t consider the costs and difficulties associated with producing the compound. My idea was to create a product that would be readily available and would sell for a few euros at the local drugstore; but what we developed was far too expensive, even for use in a neonatal intensive care unit.

‘What I missed in my academic studies was a broader perspective,’ continues Rissmann. ‘In academia, depth is what counts. In my opinion, academic training of researchers is based too heavily on an I-shaped approach – all depth and no breadth. So at CHDR, we use a T-shaped approach to education. Part of the training is highly specialised, but the top is broad, enabling you to connect with the entire landscape. Various aspects contribute to this breadth, including cost, societal issues, applicability, ethics, and different therapeutic areas.’

Teaching drug development

One of the things that Rissmann enjoyed as a lecturer at the university was being involved in the education of students in biopharmaceutical sciences. ‘We taught students the basics such as making pills and tablets. An interesting part of this was coordinating a course in drug development at the end of the Bachelor’s programme in biopharmaceutical sciences. That’s how I met Adam Cohen and Koos Burggraaf from CHDR. They were advisors and instructors in this course, and it was great fun working with them.’ One thing led to another, and when CHDR needed a new coordinator for their education activities, Rissmann gladly accepted the job.

Computer-assisted learning

Education has always been important to the staff at CHDR, primarily because they enjoy sharing their knowledge and expertise. During the 1990s, as CHDR and the number of its students grew, CHDR’s educational activities were formalised by Dr Kari Franson, a clinical pharmacologist who trained in the US. Franson also introduced computer-assisted learning. In 2008, Franson obtained a PhD for this work, particularly the Teaching Resource Centre, which was developed into an app that has become one of the hallmarks of teaching pharmacology at CHDR (see text box).

CHDR's TRC app facilitates pharmacology education worldwide

One of CHDR's major contributions to educating pharmacology students around the world is a free app called TRC (Teaching Resource Centre). This easy-to-use app provides instant access to a comprehensive pharmacology e-book based on years of experience teaching pharmacology to medical students. In the past few years, the TRC app has been downloaded more than 150,000 times by students around the world, including many students in developing countries. Thanks to recent upgrades, the app can interface with reference drug formularies in the Netherlands and the UK, as well as to Micromedex® in the US.

The TRC app is updated regularly to include the latest drugs. In the coming years, the app may need to be thoroughly upgraded in order to accommodate future changes in education and pharmacotherapy. To read more about the TRC app and its development, see page 83.

Teaching future professionals

Each year, the staff at CHDR give more than 100 hours of lectures to medical students at Leiden University Medical Centre (LUMC). 'We feel it's essential that tomorrow's doctors know their pharmacology,' says Rissmann. 'Mistakes in pharmacotherapy are a major contributor to preventable hospitalisations and even mortality. But it's no use simply cramming facts into students' heads. The field of pharmacotherapy is changing so rapidly that it's far more important – and more practical – to teach students how to think critically, showing them the basic concepts and how to find relevant information quickly, for example using the TRC app and other online resources.'

In addition to teaching medical students, CHDR also plays a role in educating the growing number of students in biomedical and biopharmaceutical sciences at Leiden University. 'Someday, these students will contribute to the development of new treatments,' explains Rissmann, 'so this is essential. For example, we developed a course specifically for Master's students in biomedical science; in this course, students receive practical, hands-on training in how to design, conduct, and analyse a clinical trial.'

A Master's level course in trial design

This three-week course, which was developed by CHDR and the LUMC Pharmacy, pushes the limits of what's possible. In the first week, the students design a study protocol. In the second week, they perform an in-class experiment based on a similar trial and using a protocol approved by the ethics committee. In the final week, the students analyse the data. 'It's truly amazing how much you can do in just three weeks,' says Rissmann. 'We tried to make the experience as realistic and complete as possible. It starts with an idea, continues with executing that idea, and ends with data analysis and reporting. The students are highly enthusiastic, and it's clear that they can learn and remember much more using this practical approach. For example, from a theoretical perspective, it's logical that students who design a study will want to obtain as much data as possible. But once they perform an actual study and analyse the data, they quickly realise how much the workload increases with each additional blood sample and measurement. And of course, collecting more blood samples adds to the burden placed of the subjects, fellow students in the course.'

Blended learning

No matter how motivated the staff at CHDR is, teaching the same course year after year can become a bit burdensome, and lecturing is not necessarily the most efficient way to involve and educate today's students. That's why CHDR is taking pharmacology education to the next level, building on the success of the TRC app and the hands-on approach discussed above. 'Together with our partners at Leiden University and LUMC, we're developing new "blended" learning concepts,' says Rissmann. 'This approach provides the ideal combination of e-learning, self-study, and direct interaction. Rather than sitting through a lecture, we believe that students learn better if they first prepare by watching digital materials in combination with books and articles. The face-to-face teaching time can then be used for reflection and discussion. Students don't need to be a walking pharmacopoeia; instead, they need to develop their professional knowledge and skills. To help us reach our goals, we recently published a strategic blueprint for pharmacology education in 2025.'

'At CHDR, we use a T-shaped approach to education. The training is highly specialised and in-depth, but the top is broad, enabling you to connect with the entire landscape.'

Clinical pharmacology and the Clinical Research Programme

Another important reason why CHDR invests heavily in education is so they can stay in touch with talented young physicians and scientists, some of whom may do an internship at CHDR or train to become a clinical pharmacologist at CHDR. 'We have a one-year programme that can be taken ether full-time or part-time,' says Rissmann. 'This allows students to combine the course with clinical work and/or other activities required for certification as a clinical pharmacologist.'

For ambitious researchers and physicians, CHDR also offers a unique career development path called the Clinical Research Programme. In this intensive five-year programme, participants conduct research projects while being coached by senior clinical scientists and research directors. Each participant is responsible for developing, leading, and reporting on clinical trials, gaining valuable experience in a specific scientific field.

During the five years, the participants develop key skills and competences, including project management, clinical pharmacology, scientific research, and personal competences. The participants also collect data for their PhD thesis, which they are expected to complete during the programme. In the final year, the senior project leader discusses the participant's future plans. Regardless of whether the participant remains at CHDR or seeks employment elsewhere, the skills and competences learned during the programme will help ensure his/her success in research, business, and/or healthcare.

Still teaching drug development

Rissmann talks enthusiastically about the drug development course offered at the end of the Bachelor's programme in biopharmaceutical sciences, which he still coordinates. At CHDR, he had the resources to expand this course into an interactive experience in which students become actively involved in the entire process of drug development. 'There are so many aspects in drug development,' says Rissmann, 'starting with drug design and preclinical testing, right up to the clinical phase. As this course is the pinnacle of the Bachelor's programme, we draw on much of the materials that the students received in previous years. And we introduce new topics such as financing, marketing, communications, ethics, guidelines, and quality assessment... In short, we cover much more than just the science. All the things that I missed during my PhD studies are taught to our students at a much earlier stage in their career.'

Using real-life data, students also write a plan for the clinical development of a promising compound. They then present and defend their plan at a symposium, culminating in a competition to decide the best plan. 'It's very intensive,' says Rissmann, 'both for the students and for the teaching staff, and it's highly rewarding. I feel honoured to be able to participate in these activities.'

Returning to science

Meanwhile, Rissmann also returned to science, albeit with a much more practical approach this time. For example, Rissman is involved in the growing number of studies in dermatology at CHDR (see page 62), and his work has helped put CHDR's Trial@home approach on the map. To date, hundreds of patients with a variety of skin conditions have participated in outpatient studies using mobile technology (see page 51). However, given that Rissmann's contributions to innovating education take much of his time, another change is in the works. 'We're now looking for someone to become the new Coordinator of Education at CHDR,' says Rissmann. 'But of course, I'll always be involved in education, which I enjoy and find highly rewarding.'

'We teach biomedical scientists to become successful entrepreneurs'

Dr Marcel Kenter, Director of Paul Janssen Futurelab Leiden

Paul Janssen Futurelab Leiden, a recent initiative by Leiden University Medical Centre developed in close collaboration with CHDR, is the first training programme specifically designed to train researchers to become entrepreneurs and Chief Scientific Officers. Named after Dr Paul Janssen, the famous Flemish physician, pharmacologist, medical chemist, and entrepreneur, the programme teaches biomedical scientists and physician-researchers the basic principles behind the development of novel, innovative medical interventions. Dr Marcel Kenter, the Director of Paul Janssen Futurelab Leiden, talks about the programme's history and future.

Kenter's own story is not just about his current passion – teaching scientists how to develop treatments and how to do business – but also about the ethics of medical experimentation and his long-standing collaboration with CHDR's CEO Dr Adam Cohen, a relationship that dates back to the time when Kenter was the director of the CCMO *(Centrale Commissie Mensgebonden Onderzoek;* in English, the Central Committee on Research Involving Human Subjects). The CCMO is the Dutch central committee for ethics in medical research and also serves as the Dutch competent authority for drug trials. 'Paul Janssen Futurelab's roots are in the CCMO,' says Kenter. 'In the CCMO, we saw the importance of correctly designing and conducting clinical trials, and – unfortunately – we also saw quite a lot of inefficiency and failures. I always wondered why people learn so little from their prior experiences. Some mistakes were quite costly financially, and some even cost lives. The least we can do is learn from these mistakes. And of course, much can be learned from new interventions that were developed successfully; in every successful development process, certain challenges must be overcome. Incorporating these successes and failures is an important ingredient in our courses.'

Even when he talks about the past, Kenter continuously returns to his current plans for Paul Janssen Futurelab Leiden. 'These are exciting times for us. We have a team of creative instructors, and we have experts designing the teaching materials and the e-learning platform. We also produced a film using professional actors, and this will be used in the first teaching module, which will launch this spring. The next modules are already in production.'

Medical research ethics in the Netherlands

Kenter notes that after the Second World War, it became gradually clearer that a high standard of medical ethics requires an independent review of the study protocols, rather than simply trusting that scientists will always do the right thing. In 1967, the first Dutch medical research ethics committee was established in Leiden by the pharmacologist Prof Erik Noach. Other university hospitals soon followed suit.

In the 1980s, the Dutch Department of Health drafted a law regulating all medical experiments with human subjects, including patients. But it took quite some time before this law finally passed. Kenter explains: 'There was a fierce political debate regarding whether we should outlaw all non-therapeutic research in children and in patients who are incapacitated, for example comatose patients and patients with dementia.' Paediatrician Prof Henk Visser – who later would become the first Chair of the CCMO – argued that a ban on all non-therapeutic research in children would be ill-advised, as it would severely limit the development of novel paediatric treatments.

Eventually, a compromise was reached. Thus, the first Dutch law regarding medical experiments prohibits non-therapeutic research in children and individuals with limited capacities, but an exception can be made if the research will benefit a specific patient group and if the risks and burden to the patients are low. In these cases, the CCMO evaluates proposals for studying non-therapeutic interventions in these vulnerable groups.

This new law on medical experimentation was signed in 1998, resulting in the creation of the CCMO. In addition to evaluating research in vulnerable groups, this new committee was also created to recognise and supervise all existing medical research ethics committees throughout the Netherlands, and to review categories of research for which expertise is relatively scarce, for example in the fields of gene therapy, xenotransplantation, and cell therapy. Kenter, a researcher in the fields of immunology and molecular biology, was the first Director of the CCMO. Adam Cohen served as a member of the CCMO in its first four years and he served as the Vice-Chair for eight years. 'Adam's expertise was invaluable,' says Kenter, 'with his strong scientific background, technical expertise, and broad experience in the pharmaceutical industry. And he was always very enthusiastic.'

Trials gone wrong

After the turn of the century, several incidents shook the world of clinical pharmacology and medical research ethics. One such incident was the tragic TeGenero event in 2006, in which six healthy volunteers in London developed severe physical damage during a phase 1 clinical trial studying TGN1412, an immunomodulatory antibody. Even at extremely low doses (which were safe when administered to cynomolgus monkeys), TGN1412 caused a severe inflammatory response in the volunteers, in some cases leading to organ failure. All six participants survived, but many were left with lasting damage. Later that year, the trial's sponsor, German biotech company TeGenero, was bankrupt, and TGN1412, which had been developed for treating rheumatoid arthritis and B cell lymphoma, was nearly shelved forever. Since then, details regarding the underlying cause of the inflammatory response emerged, thanks to excellent research conducted in the UK and Germany. Recently, a new biotech company based in Russia began taking steps to develop TGN1412 for clinical use under a new name, TAB08.

'Back in 2006, we carefully evaluated this incident in order to learn as much as we could,' says Kenter. 'This was possible only after the British authorities released the research file for the trial. Adam Cohen and I published a viewpoint in The Lancet, in which we addressed some of the lessons to be learned from this incident. One of the underlying issues was that key scientific questions were not addressed adequately during preclinical testing. TeGenero was a small biotech company, and they probably needed additional funding. They rushed to clinical development, assuming that using a low starting dose would be safe. After all, they didn't observe any serious side effects in monkeys at much higher doses, so what could go wrong? Unfortunately, they didn't base their calculation of TGN1412 dosage on the number of receptors in the human body, and it turned out that the immune system has subtle – yet critical – differences between humans and cynomolgus monkeys. That mistake nearly cost the lives of six healthy young men.' Lessons like this will of course be included in the curriculum at Paul Janssen Futurelab Leiden.

Another major incident occurred in the Netherlands during a clinical trial involving a dietary supplement. A multicentre double-blind randomised controlled trial was conducted in order to determine whether probiotics (a mixture of 'benign' Lactobacillus bacteria) in combination with parenteral feeding can improve the treatment of patients with severe acute pancreatitis. Contrary to

expectation, the mortality rate in the intervention group was considerably higher than in the placebo group (16% compared to 6%). Thus, 24 patients in the intervention group died compared to only nine patients in the placebo group. 'This was a tragic incident,' says Kenter. 'It's likely that at least some of the patients in the intervention group would still be alive today if they had not participated in that trial.' The incident also shook the world of probiotics, making it clear that these bacteria are not always harmless, particularly in intensive care patients. The incident also helped raise awareness regarding the importance of thorough preparation, carefully designing the clinical trial, and educating the clinical researchers.

'It's important to look into the history of each incident – and each near-incident – in clinical research. Not to assign blame, but to learn. I find it deplorable that we still don't know all of the details surrounding the 2016 incident in France, in which a healthy volunteer died during a phase 1 trial. Although the research file has not yet been released by the French authorities, based on what we know, I believe that this incident illustrates how CROs still study each new compound with the same routine blueprint approach, rather than attempting to predict what the specific molecule will do in the human body. That's one of the main lessons we'll try to teach at Paul Janssen Futurelab Leiden: you shouldn't design a clinical trial a certain way simply because "that's the way it's always done." You need to design each clinical trial to answer specific scientific questions. And you should always be aware that the quality of the answers will depend on the quality of your questions.'

'It's important to look into the history of each incident in clinical research. Not to assign blame, but to learn.'

A summer course develops into Futurelab

Around 2011, Dr Saco de Visser, one of Cohen's former PhD students, approached Kenter at the CCMO. De Visser was working at ZonMw, the Dutch medical research council, where he was in charge of a new programme designed to improve pharmacotherapy and the use of medicines that had already been approved by the authorities. A specific goal of this programme was to improve the national infrastructure for drug trials, and De Visser asked Kenter what he thought would be the best way to achieve that goal. Kenter advised De Visser to invest in education and training. 'I knew that no training programme was available to teach researchers and physician-researchers the development path leading from an initial idea for a new treatment through to its application in the clinic,' recalls Kenter. 'Nobody was teaching that in a comprehensive way; not in the Netherlands, nor anywhere else. I had just been to the international business school INSEAD, where I followed an intensive course based on real-world teaching cases, so I proposed something along those lines to Saco. We developed a two-week summer course in which academic scientists and researchers from biotech and pharma companies could develop their ideas for a clinical trial. The course would also include a competition in which the best idea with the best clinical protocol could receive up to half a million euros in funding from ZonMw.'

'Incorporating past successes and failures in the industry is an important ingredient in our courses.'

But things would soon become even more ambitious. Shortly after his conversations with De Visser, Kenter received a phone call from Cohen, who had been brainstorming with people at the Dutch Top Institute Pharma, in which the Dutch government, scientists, and the pharmaceutical industry collaborated on questions related to the valorisation of science. 'Adam said that he came up with a plan to establish a postgraduate drug development school, and he was looking for someone willing to invest quite a bit of time. As he put it, he was "looking for someone with enough time that he or she could start with an empty desk." So I did some initial market research, and everything looked promising. We extended the goal a bit from novel drugs to novel medical interventions. The next step was two highly successful pilot courses that we offered in the summer of 2014. These courses were based largely on the INSEAD method; they were dedicated to clinical development and intellectual property, and we used all of the expertise and experience we could find at CHDR and elsewhere. The Dutch Department of Health became interested, and we realised that our feasibility study was positive, showing that our idea met a real need for both industry professional and academics who wish to develop a novel medical intervention and/or start a spin-off company. And at the time, no such comprehensive training programme was available. So we're now developing a Master's program called "Science-driven Biomedical Entrepreneurship". But as I've always said, Paul Janssen Futurelab Leiden is Adam Cohen's brainchild. Adam even suggested that we ask the Janssen family for permission to use the name "Paul Janssen" in the programme, which Paul's widow gave in January 2016.'

Developing a new treatment is like exploring a new oil field

Not everyone will be eligible to participate in Paul Janssen Futurelab Leiden. The programme is aimed at biomedical researchers and physician-scientists who are interested in becoming biomedical entrepreneurs. Most of the participants will have a PhD. Many who applied for the first course – which will start in April 2017 – work at a biotech company or in academia and are looking for a career boost. 'The courses are about more than just drug development, says Kenter. 'These days, we see a blurring of the boundaries between drugs, cellular therapies, other ATMPs [advanced therapy medical products], medical devices, and nutritional interventions. The requirements for the registration of drugs and ATMP's are extremely strict, and the requirements for medical devices and – to a lesser extent, medicinal nutritional products – are also getting stricter.'

Developing a new treatment is complex for a variety of reasons. First, there's the challenges associated with translational research, developing a product based on discoveries made in the lab. Clinical development – i.e. testing a new treatment in human subjects – has its own complexities. Finally, there's the entire business side, which requires finding subsidies and/or investors for the initial steps, expanding the financial base to work on clinical development, securing a solid patent position, establishing production facilities, and – ultimately – serving the market.

Each of these steps must be taken with the implicit awareness that most candidate drugs and treatments fail somewhere along the line. 'We'll present our students with a decision model similar to the model used by the oil industry, in which developing an oil field can easily take ten years. During that time, investments are high, but there's no guarantee of a high yield, and there's no way to predict the price of oil when the first barrels are filled. So in both industries, you need a decision-making model that is flexible enough to account for these uncertainties and provides a solid basis for making rational decisions.'

Question-based development

The programme at Paul Janssen Futurelab Leiden was designed for international students who already have busy jobs and/or families. 'We offer blended education in which we combine distance learning with on-campus courses,' says Kenter. 'Most of the program is online. We even have an Internet-based proctoring system for our online exams. We work with a company based in Ireland that specialises in online proctoring. Their approach ensures that the student cannot cheat while taking the exam. During the exam, the student's computer is controlled by the company, and the student is monitored via the computer's webcam.'

Developing a course based largely on online learning has been quite a challenge. 'We realise that the dropout rate for online courses is usually quite high. That's one of the reasons we opted for a blended learning programme, with students coming to Leiden as well. And we tried to develop educational material that's sufficiently stimulating when you come home after a busy day at work, surrounded by everyday distractions and obligations. Of course, the proof of the pudding will be in the eating, but I believe we've designed a highly attractive set of educational materials. A good example is a movie filmed in and around Leiden. It's about a bright, young neurologist who recently left her job at a university medical centre and now works at a small biotech company. She has her own ideas about drug development, but her boss tells her to stick to the old system because according to his experience, it's much less expensive. The movie is divided into a series of episodes, with each episode ending with a 'cliff-hanger', an issue or dilemma that will be addressed in the following course week. By the way, if you're familiar with CHDR, you'll notice that many scenes were filmed at the CHDR building, which is of course the perfect setting for a movie about innovative clinical drug development.'

The fictitious neurologist represents a view towards drug development that will likely be familiar to anyone who knows CHDR. She wants to base her research on relevant scientific questions, for example whether the compound can pass the blood-brain barrier and enter the brain in sufficient quantities. She proposes including this test in the phase 1 trial, but her boss prefers the traditional phase-oriented approach, with safety and toxicity testing in phase 1, without bothering with the more difficult questions. He asks the young researcher, 'Don't you realise how much it costs to run a PET scan just to see if the drug enters the brain?' However, she realises that the cost of developing a CNS drug that doesn't reach the brain is far higher, particularly when that information emerges late in the development process. This way of thinking – the so-called question-based approach to clinical development – is a core concept at CHDR and was the principal theme in De Visser's PhD thesis. Kenter: 'Paul Janssen Futurelab Leiden is all about the future, but it also draws heavily from past experience, our work at the CCMO, and the past thirty years at CHDR.'

'We'll present our students with a decision model similar to the model used by the oil industry.'

‘CHDR is important to our university’

Willem te Beest, Deputy Chairman of the Executive Board, Leiden University

CHDR’s history is closely intertwined with Leiden University, the oldest university in the Netherlands. Willem te Beest, Deputy Chairman of Leiden University’s Executive Board, served on the Board of Trustees at CHDR for eight years. ‘We’re quite proud of CHDR’s achievements, and we’re glad we could contribute to their success when it was needed.’

In 2005, Te Beest came to Leiden after serving on the Executive Board at Twente University and a successful career as a consultant. A year later, he joined CHDR’s Board of Trustees, becoming the vice president. ‘From the beginning, I was aware of CHDR’s mission and their history. Douwe Breimer, CHDR’s founder, was Rector Magnificus when I came here, and we served together on the university’s Executive Board for nearly two years. Although CHDR originated in this university, it has always been an independent, not-for-profit foundation.’

Spin-off companies, then and now

‘It’s interesting to see how much has changed over the years with respect to the relationship between universities and spin-off companies,’ says Te Beest. ‘From what I know about CHDR’s early days, their independent status was partly the result of caution on the side of the university and the LUMC; they wanted a bit of distance in case something should go wrong. This is quite understandable when we look back at those days, but it’s quite different from our current approach.

‘These days,’ continues Te Beest, ‘we still believe that spin-off companies should be independent, but from a more entrepreneurial perspective. Running a company is quite different from governing a university. A large institution such as our university, which is run using public funds, should be a bit more conservative, avoiding unnecessary risks. Our planning needs to be long-term, and we always try to include a fall-back position, in case things don’t work out as we expect. On the other hand, an entrepreneur must be willing to take the risks associated with seizing an opportunity when it arises, for example hiring staff, investing in buildings and equipment, attracting funding, and so on. Companies also have to be willing to extend their reach, contacting potential clients and determining their current and future needs. So the entire dynamic is different.

‘Moreover, companies have specific challenges. When I look at CHDR, I see that both planning and logistics require constant attention. They have to deliver the highest quality at all times. From their samples, to their measurements, to their dossiers, everything must be done consistently and with a specific goal in mind. In contrast, in an academic lab a researcher might decide one day to do things a little differently, just to see what happens.’

‘An entrepreneur must be willing to take the risks associated with seizing an opportunity when it arises.’

‘With their vast international network, CHDR is quite an asset to Leiden.’

Operational and strategic relevance

‘So CHDR may be independent,’ says Te Beest, ‘but their well-being is quite important to our university. Operationally, CHDR contributes to our core mission, which is to provide excellent education and conduct internationally acclaimed research. CHDR continually contributes to science by training PhD students and publishing in relevant journals. They also collaborate with several research groups within Leiden University and the LUMC. Their contribution to education is invaluable, as they teach medical students, as well as students in the biomedical and biopharmaceutical sciences. I’ve attended some of their lectures, and I was impressed by the clarity of their presentation and the quality of their teaching materials.

‘Strategically, CHDR is an important link in the chain that extends from basic research to clinical application. Leiden is home to the Leiden Bio Science Park, with nearly 200 companies, organisations, and institutions in the fields of drug development, life sciences, and medical research. CHDR is housed in one of the most prominent buildings at the Bio Science Park, and as a CRO they play a key role in bridging preclinical science with the marketplace. CHDR also draws key companies to Leiden, collaborating with pharmaceutical and biotech companies from around the globe. Once those companies work with CHDR, they know where to find Leiden, which can bring business to neighbouring companies and institutions. Most people know where Amsterdam is, and they probably know that Schiphol Airport is close; but I like to make sure that people know that Leiden is even closer to the airport than downtown Amsterdam. In short, with their vast international network, CHDR is quite an asset to Leiden.’

Weathering the storm

‘Serving on the Board of Trustees at CHDR was relatively uneventful, at least until 2012,’ says Te Beest. ‘That’s when CHDR had just finished their magnificent new building. We thought we had a solid agreement with the bank regarding the mortgage. But then things started to fall apart, mostly because of the worldwide financial crisis. First, it became difficult to sell CHDR’s old building. Then we experienced a temporary dip in CHDR’s revenue. And finally, it turned out that our agreement with the bank was not as solid as we first thought. That’s how it is with banks; they can be quite pleasant as long as the sun is shining, but they tend to change the rules when it turns cloudy. By that time, the global financial “weather” had changed for the worse, so we had little room to negotiate.

‘Those were really tense times,’ continues Te Beest, ‘and we weren’t sure whether CHDR would survive. The Board of Trustees worked closely with CHDR’s Management Team. Martijn van de Mandele – who was the Chairman of CHDR’s Board of Trustees at the time – and I visited CHDR every three months to review the financial portfolio. We had some rather frank discussions with Adam Cohen and the other members of the Management Team, discussing all of the options. It was not easy, but we pulled through, and the portfolio started to grow again thanks to the efforts of everyone at CHDR.

‘At one point, though, the bank demanded a level of certainty or they would pull the plug. I felt it was crucial to step in. I wanted Leiden University to do whatever we could to keep CHDR afloat. So we came up with a practical solution: the university would give CHDR a loan, with the old building as collateral. If you’re familiar with the old CHDR building, you’ll know that it’s a beautiful, multifunctional office; so there was no real risk involved.

Still, it wasn’t easy to convince the university’s Board of Trustees. In the end, they demanded that I step down as a member of CHDR’s Board of Trustees in order to avoid any possible conflict of interest. That’s why, in November of 2014, I left CHDR’s Board of Trustees. I didn’t want to step down, as I enjoyed being involved with CHDR, but I had no choice. And luckily, thanks to the loan from the university, CHDR pulled through the crisis.

‘Although I’m no longer officially involved with CHDR,’ says Te Beest, ‘I’ve continued to watch their progress, and I’m glad to see that they’re thriving. When CHDR repaid the loan to the university, I felt vindicated. And recently, CHDR arranged a “sale-and-leaseback” contract for their current building, so their financial situation is stronger than ever. Today, it’s hard to imagine that there were times when CHDR’s future was in doubt. And now, they can look towards the future. Each year, I’m invited to the CHDR Christmas dinner, which is a truly special event. The staff are such a creative and inspiring group of people of all ages, and it’s always a pleasure to be there.’

‘CHDR’s combination of science, service, and open culture is unique’

Early in 2014, Frans Rooda joined the Board of Trustees of CHDR. In the summer of 2014, he became the chairman. ‘I’ve been quite fortunate to serve on the Board of such a thriving organisation. Over the past few years, I’ve seen nothing but growth, both in size and in depth.’

***Frans Eelkman Rooda**, Chairman, CHDR Board of Trustees*

‘When my predecessor, Martijn van der Mandele, first asked me to join the Board,’ says Rooda, ‘he didn’t mention that he was about to step down as chairman. Although it came as a bit of a surprise, my decision to replace Martijn as chairman didn’t take long. I saw a dedicated organisation with a clear mission and a strong sense of spirit. What I’ve found inspiring is the open atmosphere and high level of professionalism at CHDR. And although I can’t really compare CHDR with many other CROs, I think this is rather unique, thanks to the way they’ve successfully combined innovative research with providing high-level service to pharmaceutical and biotech companies. CHDR has a strong corporate purpose and is anchored in an academic context, which both stimulates and optimises clinical drug development.’

Not for profit

‘As I understand it, CHDR has always been unique. It is quite an accomplishment that they’ve maintained this position for three decades, given the organisation’s consistently high level of growth. It is one thing to run your organisation a specific way with just a handful of staff; but I think it is quite exceptional that here at CHDR they managed to keep up that spirit with more than a hundred employees.

‘One of CHDR’s cornerstones is the fact that it’s a not-for-profit foundation,’ says Rooda. ‘Of course, they need to maintain a healthy financial position, but there’s no pressure from shareholders. In the business world, there’s a never-ending discussion about whether to take a more long-term view or focus on the short term, and putting shareholder value first generally means favouring short-term gains. In the corporate world, the consensus is moving gradually towards long-term thinking; but at CHDR this view has always been the prevailing approach. This has had a positive outcome both financially and – more importantly – scientifically.

‘Over the years, CHDR has also placed considerable importance on educating students and research professionals. I think that makes good sense, and it’s been mutually beneficial, given the strong ties that CHDR now has with Leiden University Medical Centre and Leiden University. In the Board, we’ve always believed that education is an integral part of CHDR’s mission. The financial burden associated with education is relatively low, and on the plus side it helps CHDR attract talented students and young scientists.’

Openness and integrity

‘When I first made the rounds through the organisation,’ says Rooda, ‘I had the impression that people were encouraged to speak their minds, and I think that’s an important aspect of CHDR’s integrity. Regardless of their position, everyone at CHDR should feel free to tell a colleague when they disagree about something. When I worked at McKinsey & Company, both in Amsterdam and abroad, we were taught time and again that dissent is more than just an employee’s right; it’s an obligation. Of course, you need to be able to make your point intelligently, but you should always feel free to speak up. From a leadership perspective, it takes a high level of awareness to foster and maintain such a culture of openness. I’m convinced that encouraging everyone to take a critical role is beneficial in an organisation like CHDR. When your business activities have such significant ethical implications, integrity is paramount.

‘Society’s attitudes towards responsibility and accountability can change, particularly when things go wrong. Whether we like it or not, society is moving from “principle-based” to “rule-based” practices. Nowadays, people tend to react more quickly – and often in a negative manner – long before all the facts are in, and social media plays a role as well. This makes organisations and brands with an outstanding reputation, including CHDR, much more vulnerable. A strong reputation that’s taken years to establish can be lost in just a few hours. In this respect, I’m glad that CHDR is dedicated to quality and consistency; for example, last year we hired an outside firm to rigorously evaluate our emergency procedures. It’s good to be prepared.’

The future of CHDR

‘Now that Adam Cohen will be stepping down as CHDR’s CEO, it falls on the Board of Trustees to find his successor. We have enormous respect for everything that Adam and the Management Team have achieved over the last thirty years, and it won’t be easy to find someone to fill his shoes. Our objective is to appoint a CEO who will continue to maintain CHDR’s long-standing role in academia, as well as someone who will continue to provide the pharmaceutical industry with innovative and – in many cases – proprietary services. Together with the Management Team, the new CEO will need to maintain CHDR’s unique profile and nurture the organisation’s growth. Although not necessarily a goal in itself, growth inspires an organisation to always be on the lookout for new opportunities; good examples at CHDR include the various forms of multidisciplinary collaborations, and the new concepts such as Trial@home that developed as a result. The Board is looking forward to supporting CHDR as it enters this new chapter.’

‘Encouraging everyone to take a critical role is beneficial in an organisation like CHDR.’

***Hélène van Meir**, latest CHDR employee to receive a PhD*

An increasing number of new cancer therapies use the body’s own immune system. One such approach is a promising new therapeutic ‘vaccine’ developed at Leiden University Medical Centre (LUMC) for treating aggressive forms of cervical cancer. Hélène van Meir’s PhD research studying this innovative cancer treatment was conducted at CHDR and various Dutch hospitals, including LUMC. ‘Going back and forth between the lab and the clinic was an interesting and rewarding experience.’

‘Understanding how cancer therapies affect the immune system’

In the Netherlands, women between the ages of 30 and 60 are encouraged to receive cervical cancer screening. A recent addition to this screening programme is a free preventive vaccine against specific variants of the human papilloma virus (HPV) that cause cervical cancer. This vaccine is also offered to all girls at the age of 12. Despite the success of this programme in the Netherlands, each year nearly 700 women are diagnosed with cervical cancer and approximately 250 deaths are attributed to cervical cancer. 'Although a preventive vaccine is a good start,' says Van Meir, 'reducing mortality will require an effective therapeutic vaccine. But first, such a vaccine must be developed, and its effectiveness must be evaluated. That was the focus of my PhD project.'

Combining research with medical training

Back in 2009, when Van Meir applied for a residency in gynaecology at LUMC, she told her prospective supervisor, Prof Gemma Kenter, that she was hoping to combine her medical training with scientific research. 'Gemma suggested that I contact Adam Cohen at CHDR, as she was collaborating with Adam in the clinical development of an immunotherapy for cervical cancer. I was already familiar with CHDR, as my husband had done a student internship there, so I knew it would be a nice place to work. I was also attracted to the idea of studying cancer immunotherapies for my PhD project. Adam suggested that I also use the opportunity to train as a clinical pharmacologist; I took his advice, and last year I became board-certified in clinical pharmacology. During my years at CHDR, I collaborated primarily with Dr Koos Burggraaf. We had a good working relationship, and I learned a lot from him.'

Combining cancer treatments

The majority of women with metastatic cervical cancer are treated with either chemotherapy or radiotherapy. An experimental addition to these standard treatments is immunotherapy in the form of a therapeutic vaccine. However, whether chemotherapy and/or radiotherapy can affect the efficacy of the vaccine is unknown. In principle, both chemotherapy and radiotherapy might have a detrimental effect on immunotherapy, as both treatments target dividing cells and could impede the bone marrow's ability to produce immune cells, which are essential for effective immunotherapy.

'In patients with cervical cancer, chemotherapy actually improves the efficacy of therapeutic vaccine.'

Van Meir looked for such a detrimental effect by studying blood collected from cervical cancer patients who had been treated with chemotherapy or radiotherapy, some of whom had also received the experimental therapeutic vaccine produced at LUMC's Good Manufacturing Practice (GMP) facility. 'We found that chemotherapy actually improves the efficacy of the therapeutic vaccine,' says Van Meir. 'Although chemotherapy slightly reduces the number of "good" immune cells – cytotoxic T lymphocytes – it also reduces the number of "bad" immune cells. These bad cells include regulatory T cells and myeloid-derived suppressor cells, which protect the tumour by inhibiting the body's immune response. These inhibitory cells are often present in large numbers around a tumour, which is one of the reasons why the immune system fails to eradicate the tumour cells in the first place. So a combination of chemotherapy and immunotherapy is likely more effective than either treatment alone. In contrast, combining radiotherapy with immunotherapy does not appear to have a beneficial effect in cervical cancer. This makes sense, as irradiating a tumour in the lower abdomen means that you also irradiate the pelvis, and the pelvic bones contain large amounts of bone marrow.'

Unfortunately, the combination of immunotherapy and chemotherapy offered no hope of a cure for the patients in Van Meir's studies, as their disease had already progressed too far. 'These patients' immune system had already been weakened too much by the cancer,' explains Van Meir. 'So the next step is to determine the ideal therapeutic window in which to administer the vaccine, and to determine which patients might benefit most. And of course, we still need to determine which combination of chemotherapy and immunotherapy will yield the best outcome. Clearly, much remains to be investigated regarding this novel therapy, and I'm glad I've been able to contribute.'

Conducting a clinical trial

During Van Meir's PhD studies, Prof Kenter left Leiden to accept a position in Amsterdam, where she is now the head of the Centre for Gynaecological Oncology. For Van Meir's project, this turned out to be a double-edged sword. Although it meant spending more time travelling between Leiden and Amsterdam, it had the advantage of bringing three world-renowned hospitals to the project, greatly increasing the number of patients available for her studies. 'All of the patients were vaccinated at LUMC,' says Van Meir, 'because that's where the vaccine was produced. Moreover, we had research nurses to care for the patients and monitor for adverse reactions.' Although some patients experienced low-grade fever or a local reaction at the injection site, no other adverse reactions were observed.

'All in all,' says Van Meir, 'the logistics of the trial were challenging, but everything went according to plan, thanks largely to the many people who helped with the project. I'm particularly grateful to Sjoerd van der Burg in the immunology lab and Mariëtte van Poelgeest in the gynaecology department.' At the time of this interview, Van Meir is preparing for her PhD defence and working as a gynaecology resident in a hospital in The Hague, where she lives. Soon, Van Meir will be a registered gynaecologist and clinical pharmacologist with a PhD. What are her plans for the future? 'Right now, I want to be a physician first and foremost. But I'm glad I had the opportunity to learn to conduct research in accordance with Good Clinical Practice guidelines. At the very least, my scientific background will help me make good clinical decisions and will help me understand new technologies as they emerge. In the future, I hope to have the opportunity to conduct my own research. Although the last few years were quite intense, I'd like to draw from my experiences.'

‘I look forward to contributing to the future of surgery’

Kim de Valk, *Research Physician, CHDR*

Kim de Valk is a medical doctor who joined CHDR as they celebrate their 30th anniversary. Eventually, De Valk hopes to become a surgeon; but first she’ll do her PhD research in an exciting new field, image-guided surgery. ‘It’s a fascinating approach, and I think it has the potential to revolutionise complex surgeries, particularly in oncology.’

De Valk studied medicine in Rotterdam. Looking for a position as a PhD student, she contacted Dr Alex Vahrmeijer, a surgeon at Leiden University Medical Centre (LUMC), who was looking for someone to contribute to his ongoing research on image-guided surgery (see also page 65). In this innovative approach to surgery, fluorescent markers are used to tag specific structures such as tumours, allowing the surgeon to clearly visualise the structure’s boundaries. ‘LUMC and CHDR collaborate in this project,’ says De Valk. ‘So although I’m an employee at CHDR, my research is conducted both here and at the LUMC.’

An ongoing collaboration

De Valk’s project is an ongoing collaboration between CHDR and LUMC, which benefits both sides. Surgeons at LUMC are naturally interested in using these fluorescent markers to detect and remove tumours more effectively, as well as improving the overall quality of surgical procedures. For the surgeon, the pathologist’s report is an essential part of quality control; therefore, the Department of Pathology at LUMC also plays a key role in these studies.

At the same time, establishing the safety and primary characteristics of a new fluorescent marker is a top priority. That’s where CHDR comes into the picture, by measuring the safety and kinetics profiles of these fluorescent markers in healthy volunteers. The data obtained from these initial studies will also be used to generate a mathematical kinetics model in collaboration with Leiden University. Such models will then be used to determine the marker’s optimal dosage and timing.

A complete process

‘I’ll be involved in the entire process, including evaluating safety and kinetics, as well as testing the practical applications of a new fluorescent marker,’ says De Valk. ‘The project will be sponsored by the company that developed this new marker. So initially, I’ll spend a lot of time here at CHDR conducting research in healthy volunteers. If everything goes according to plan and we find that the marker is safe for use in humans, the focus of the project will shift to clinical applications, and I’ll spend more of my time in the operating theatre and pathology lab.’

‘Initially,I’ll be at CHDR, studying the new fluorescent marker in healthy subjects. Then, we hope to take it to the clinic at the LUMC.’

Image-guided laparoscopy

'Down the road, I hope to be a surgical oncologist,' says De Valk, 'so this project fits my interests perfectly. The markers that are currently being developed are targeted primarily at tumours. But some markers are being developed for visualising specific organs and structures, for example the ureters. Because it takes time and energy to avoid damaging these extremely delicate structures during abdominal surgery, this approach may help make surgery both faster and safer.'

Image-guided surgery is still relatively new and is now being tested in conventional 'open' surgery. With image-guided surgery, the lights are turned off, and using a near-infrared light and a special camera, the surgeon can visualise the tumour or other marked tissue. In the future, image-guided surgery will be particularly useful in laparoscopic surgery (also known as 'keyhole' surgery). De Valk explains: 'If you don't have a direct view or a way to directly touch the structure you're operating on, image-guided surgery can provide clear added value. I think that's where this technique's future lies. Minimally invasive surgery – including laparoscopic surgery – is on the rise, and image-guided surgery fits this approach like a glove. In essence, there's really only one technical hurdle remaining: the camera system needs to be adapted to meet the needs of image-guided surgery. To overcome this hurdle, Vahrmeijer and his colleagues are approaching technology companies for developing new cameras.'

A tight schedule

'I hadn't really heard of CHDR before I applied here,' says De Valk. 'To be honest, I'd never given much thought to the drug development process. But now that I work here, I keep seeing our ads, particularly for recruiting volunteers, and I'm truly fascinated by everything that my colleagues are achieving here. There are naturally many parallels between the drug-development process and my project using fluorescent markers for image-guided surgery. Just like my colleagues, I'm now involved in the entire process of organising a trial with healthy volunteers, including selecting subjects. We're on a tight schedule, and we need to put in some long hours; but being part of such an effective organisation, I'm confident that we'll meet our deadlines and reach our goals.'

Nearly 30 years after CHDR was founded, Jonas den Heijer began his first workday at CHDR, with the goal of studying several aspects of Parkinson's disease, including new treatment strategies. Den Heijer hopes to train as a neurologist, although one never knows; perhaps 30 years from now, he will still be associated with CHDR...

Jonas den Heijer, Research Physician, CHDR

'It's a privilege to study a new treatment for Parkinson's disease'

Jonas den Heijer studied medicine in Utrecht. After receiving his medical degree, he looked for an opportunity to obtain his PhD in neurology, preferably by studying movement disorders. A neurologist at the VUmc (Vrije Universiteit Medical Centre in Amsterdam) suggested that he contact Dr Geert Jan Groeneveld, a research director at CHDR and neurologist at VUmc. Groeneveld was looking for a physician who could do clinical research at CHDR.

The job interview

'I hadn't heard of CHDR before,' says Den Heijer, 'but as a medical student I was taught to be critical of anything related to the pharmaceutical industry. So, before I met Geert Jan I was uncertain about whether I should even apply for the job. It sounded so different from academia, and I wondered what I'd be getting myself into. Would I have to sell my soul to the devil? But I figured there would be no harm in just talking with Geert Jan. And I found the conversation to be truly inspiring. It soon became clear to me that CHDR is not about making money; rather, they're about pursuing science, with a focus on medical ethics. Geert Jan explained that nowadays, projects sponsored by the pharmaceutical industry are heavily scrutinised, so the subjects are often treated even better than in academic projects.'

The challenge in Parkinson's disease

As a project leader at CHDR, Den Heijer performs cutting-edge research in his favourite field, neurological movement disorders. During his PhD training, Den Heijer will assess the safety and pharmacodynamics of new compounds designed to slow the degeneration of brain cells that underlies Parkinson's disease. 'Current medications for Parkinson's disease are designed to reduce the motor symptoms,' explains Den Heijer, 'including tremors, difficulty walking, etc. But patients have many additional symptoms, including cognitive and emotional changes, as well as symptoms associated with the autonomic nervous system. These additional symptoms cannot be treated using the standard medications. In addition, until fairly recently, it has not been possible to stop the underlying pathogenesis. So I find it extremely interesting that we now have compounds that may actually address this process.'

Slowing the disease

Over the past few decades, evidence has suggested that in neurodegenerative disorders – including Parkinson's disease – several pathways can lead to the same outcome, giving rise to similar clinical symptoms. For example, the enzyme glucocerebrosidase appears to play an essential role in a subgroup of patients with Parkinson's disease. Interestingly, this enzyme is absent in patients with Gaucher's disease, a rare inherited disorder, and these patients also have a much higher risk of developing Parkinson's disease later in life.

According to Den Heijer, 'There are strong indications that decreased levels of glucocerebrosidase play a critical role in Parkinson's disease, but only in about 5-10% of patients. If you could increase the levels of glucocerebrosidase activity in these specific patients, you might be able to slow the disease. In my project, I'll be studying a candidate drug that works along these lines. If it's effective, it will be aimed primarily at this subgroup of patients.'

Taking all the right steps

Den Heijer is quite enthusiastic about the coming years at CHDR. 'It's a privilege to play a key role in the early steps of clinical drug development. I'll be testing a new compound in healthy volunteers, performing the standard single ascending dose and multiple ascending dose studies. After that, we plan to test the compound in a small group of patients with Parkinson's disease. Of course, it will be quite a challenge to find the right patients for this study. Luckily, we have an extensive network of neurologists at five university medical centres and several large hospitals in the Netherlands. I'm also in touch with an advocacy group for Parkinson's patients, to gauge their interest in this new therapeutic approach. It's such a beautiful project, and I really believe in the basic principle behind this new medication. Sometimes I find myself thinking, "This is so good, it must be effective." But then I remind myself that not every promising drug succeeds.'

'At CHDR, the money is less tight than in academia, and we enjoy the truly academic spirit of research.'

Academic freedom and funding

So, what about Den Heijer's friends and former classmates? Do they think he sold his soul to the devil? 'Oh, absolutely,' says Den Heijer with a smile, 'they joke about it all the time. But seriously, when I tell them about the freedom we have to follow up on interesting ideas, they envy me. In academic research, you usually have to specify what you want to investigate in advance, and then you cross your fingers hoping that your grant application will be among the lucky 15% or so that are approved. At CHDR, the money is less tight, and we enjoy the truly academic spirit of research. Some of this research is sponsored, and other projects can be financed by CHDR's own R&D budget. That's quite a luxury in today's environment. What I also like here is the open atmosphere. So all in all, I'm glad I took the chance and met with Geert Jan last year.'

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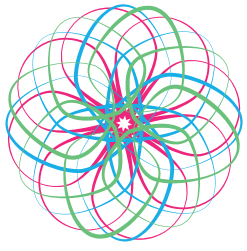

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