



CHDR
Centre for Human Drug Research

Annual Report

2018

Foreword

CHDR's strategy is based upon three intertwined principles: the development of medical interventions, through the use of innovative methods, under the guidance of expert staff. With this approach we provide our clients with information-rich answers to the most important questions in the early phases of clinical development. To continue to provide an efficient, innovative service, we must also strive to maintain our position as an attractive employer, where education and professional development are paramount.

To map a sustainable path forward, we began 2018 by recalibrating our strategy. The result of this was the establishment of three programmes: *commercial excellence*, *operational excellence*, and *people excellence*. These programmes are designed to sustain CHDR's role as a leader in the field, and to equip us to deal proactively with the challenges that the next five to ten years will bring.

This approach is already bringing tangible results. These include the opening of a new screening unit – a move which has also freed up additional research space in our main building, thereby allowing us to better accommodate the substantial expansion of our scientific and operational staff. Alongside this, we have established innovative consultancy services on a broad range of subjects related to (early) development of therapeutic interventions, as well as investing in the use of wearable technology to collect naturalistic, real-world data. We've also launched an IT transformation project: aimed at future-proofing our operations, the new infrastructure will also facilitate complex data analyses and improve overall efficiency.

Financially, 2018 was also a year of stable development: revenues have seen double-digit growth, further strengthening our already solid financial position. As an organisation with research and development at the core, we continued to allocate a fixed percentage of our annual revenue to our own R&D activities. Although the return on this investment is likely to be in the long term rather than the short term, we believe that this commitment to R&D is what sets CHDR apart from the rest. It not only allows us to remain competitive as a service provider, but also positions us as an attractive employer for top research talent. It is with this model that we can create most value for our clients. Evidence of this approach in 2018 can be seen in our work on the development and validation of 15 different methods to measure drug effects. Alongside this, we have published more than 40 peer-reviewed articles on a variety of topics in clinical pharmacology, which yield benefits for our clients and our staff, while also serving as recognition of the quality of our work within the field.

We are proud to present this Annual Report highlighting CHDR's achievements in 2018. It is our strong conviction that our staff are our greatest asset in delivering our services, and so in this Annual Report we turn the focus to the individuals and teams that make up CHDR. We hope you will share our pride in the drive and capabilities of our talented people, as they strive to provide the best service possible.

We would like to thank CHDR's staff for their dedication, and we look forward to successful collaborations with current and new clients in the years ahead.

The Executive Board

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The background of the slide is a collage. On the left, a large portion is occupied by a close-up of a modern building's facade, characterized by a grid of windows. Some windows are tinted with a warm, orange-pink light, while others are clear, reflecting the sky and surrounding environment. To the right of this, and below it, are several smaller, rectangular inset images. These insets show various interior office spaces, including desks with computers, ergonomic chairs, and open-plan areas with glass partitions. The overall color palette is a mix of cool blues and purples from the building's reflection and warm oranges and yellows from the interior office lights.

Message from the Executive Board

Building a strong launch pad for the future



Dr Pierre Peeters, Prof. Koos Burggraaf and Dr Geert Jan Groeneveld, CHDR's Executive Board

In 2018, CHDR invested more than ever in people and method development. The number of sponsored studies was on par with the year before, while the number of self-financed projects grew. Human Resources was a key focus, with more staff being hired across the organisation. 'The industry we're part of is in the middle of ground-breaking changes,' says CEO Prof. Koos Burggraaf. 'We're pioneers, so it's in our nature to keep a step ahead. As we see the traditional drug development process being challenged and even disrupted, we are busy building a strong foundation for our future.'

'Wherever I look at CHDR, I see new developments,' says Dr Geert Jan Groeneveld, Chief Scientific Officer / Chief Medical Officer. 'Our Method Development group, which also includes data scientists, is busy

developing new ways to study the effects of pharmacological compounds on human physiology. Meanwhile, our Biomarker group is equally active in the field of immunology and other "wet" biomarkers. All these new methods need to be thoroughly validated, to understand them fully before implementing them in sponsored studies.'

'CHDR is a financially healthy not-for-profit organisation, so we can afford to invest time and resources in developing methods and expanding staff capabilities,' says Dr Pierre Peeters, Chief Operations Officer. 'Our legal status as foundation means we are free to grow at our own pace. At the same time we're also a business, so we are always aiming to develop and expand our activities.'

Paradigm shift

Talking to the Executive Board, a vision emerges of CHDR's integral role in the paradigm shift taking place in the process of drug development. The organisation's unique model – a foundation run as a business, with close ties to academia and a focus on innovation – underpins its role as a pioneering force in the field. The question-based drug development (QBD) approach, which helps to find the optimum design for the early stages of drug development, originated at CHDR and was first described in the PhD thesis of Saco de Visser in 2003. Now, this approach, albeit under different names, is standard in many pharmaceutical companies.

So, where is CHDR headed next? ‘We have always been an agile organisation, adapting swiftly to a rapidly-changing environment without losing sight of stability and continuity,’ says Burggraaf. ‘As you know, drug development continues to grow more complex. We need to expand our toolkit with novel approaches such as the use of wearable technology for data collection, or machine learning techniques for the analysis of large datasets.’ An example of this is how CHDR is responding to the demand for more naturalistic data by developing Trial@home, which enables the collection of rich data via remote monitoring equipment and mobile devices. This Annual Report contains many examples of the ongoing technological and scientific developments at CHDR, as explained by Dr Robert-Jan Doll (page 30), Dr Robert Rissmann (page 54), and Dr Matthijs Moerland (page 80) among others.

‘We see great benefit in continuing to strengthen the interaction between the preclinical and early clinical phases of drug development, to better anticipate risks and gain as detailed a picture as possible at these early stages,’ says Burggraaf. ‘This is even more important for compounds aimed at relatively small markets where there is a high unmet medical need. There are currently initiatives exploring the possibility for early market authorisation to be granted based on information-rich phase 1 and phase 2 trials. The result of this is that patients can begin to benefit from new drugs while these are still under evaluation. Such initiatives align well with our approach, but they do imply a stronger degree of responsibility. We need to deliver high-quality, validated, information-rich dossiers that the authorities can base their decisions on. In this context,

it’s interesting that the European Medicines Agency (EMA) is currently building its new headquarters here in the Netherlands, less than half an hour by train from our facility.’

Focus on people

Early-stage drug development is an intricate and complex undertaking, which calls for dedicated and capable individuals with the newest tools at their disposal. That’s why one of the main points in CHDR’s strategy is a focus on people. ‘Our people are our main asset,’ says Burggraaf, ‘so we need to be a good employer, attracting and retaining the best and brightest in the field.’ In reflection of this, 2018 saw the reorganisation of the Human Resources department. Professional development, which has always been an important factor, now receives more systematic attention: career paths are provided for different roles, at both the general and individual level. Alongside this, all employees are invited to develop themselves through ongoing education. The Executive Board has also implemented new measures to position CHDR as an attractive employer for all kinds of professionals: among other benefits, scientific staff now have the freedom to devote 20% of their time to reading and writing articles, protocols and reviews, and operational staff have the opportunity to follow advanced professional training courses.

To develop and apply new methods, it’s necessary to recruit a range of new people in addition to the nurses, physicians and pharmacists who have always played a foundational role in our research. The organisation

is now home to a wide variety of professionals, with a greater breadth of expertise than ever before. Throughout this Annual Report, the reader will meet a cross-section of CHDR’s diverse workforce, from data scientists to technical medical professionals, highly-trained lab technicians and even an anthropologist with a knack for planning complex clinical trials. Groeneveld: ‘For young professionals, this kind of environment is particularly stimulating. Especially if you’re at the beginning of your scientific career, it is inspiring to come into contact with people from completely different backgrounds studying the same phenomena as you.’

Operations, planning and IT

As CHDR has grown over the years, the operational aspects have become more complex. Therefore, the organisation has hired additional staff to better support the work of those involved in the primary process of conducting clinical trials. Departments such as finance, quality control, quality assurance, and planning have all expanded in recent years with the aim of facilitating operations. ‘In the past, we were able to manage operations with a small core of support staff,’ says Peeters. ‘As operations increase in complexity, I’m glad that we have the capacity to continue growing in a sustainable way.’

In addition to recruiting and retaining the right people, having the right information technology infrastructure is essential to operational success. CHDR’s planning software, implemented in 2016, has been adjusted and adapted to the needs of the organisation. Peeters: ‘The

next item on our wish list is a direct link between our planning capabilities and our protocol management system, which also contains our clinical data. We look forward to eventually having an integrated data infrastructure that combines planning and study data.’

Another major change afoot in terms of IT infrastructure is the transition to ‘the cloud’. With the increase in large data sets and the use of mobile technology, a cloud-based system will allow the organisation to adapt and grow in new directions. Of course, transitioning to the cloud requires thorough planning. The team tasked with navigating this transition is led by project manager Edgar Nettl, in collaboration with LINKIT. The team has begun with a pilot project, using two studies funded by CHDR’s R&D Fund as a basis to explore the best way to use Microsoft’s cloud-based Office 365 suite. At the same time, a cloud services infrastructure is under development which will serve as a platform for the software applications that are used at CHDR. The goal is to create an IT infrastructure that will allow employees and their collaborators the freedom to work anywhere using their favourite devices, while still ensuring that data is secure.

Space to expand

In 2013, when CHDR moved into its current building, no one could have predicted how fast the organisation would outgrow its new home. But now, it is obvious that the building has reached its limits. Peeters: ‘We have grown fast and taken on many new challenges, which were not foreseen when the building was designed. To give an example: when we moved here, we had

a small laboratory for processing materials, with measurements being done elsewhere. Fast forward to now, and we have a state-of-the-art bioanalysis lab.'

To accommodate this growth, CHDR has been on the lookout for ways to expand beyond the main facility. The first step was taken in 2018, when the screening of potential study participants was moved to a new facility located next to Leiden's main train station, where it's easily accessible for volunteers and patients. It's also just a five-minute bicycle ride from the main facility. Although this means that staff working at the Screening Unit are now no longer working side-by-side with their colleagues in the main facility, they are still very much part of the CHDR family.

Opportunities to grow

Challenges such as these are the natural result of successful developments over the past few years. And for an innovative organisation like CHDR, challenges are the source of new opportunities. CHDR Innovation Services (InnoS), the organisation's new consultancy branch, will provide a channel for our scientists to make a greater contribution to solving current challenges in the pharmaceutical industry. One area of particular opportunities is the increasing role of vaccines and immunotherapies in a wide variety of diseases, including cancer. There's even the possibility that CHDR could be involved in the development of similar institutions in other countries. Burggraaf: 'Due to changes in the pharmaceutical and

biotech industries, the CHDR concept of creating value for drug developers has become more attractive to universities abroad. Our lean organisation model, our not-for-profit approach, our focus on education, our track record of innovation, the strong link between science and method development – all these characteristics together have put us at the leading edge. In the past year, we've been approached by universities from abroad to explore the potential for collaboration, raising exciting possibilities for the future.'

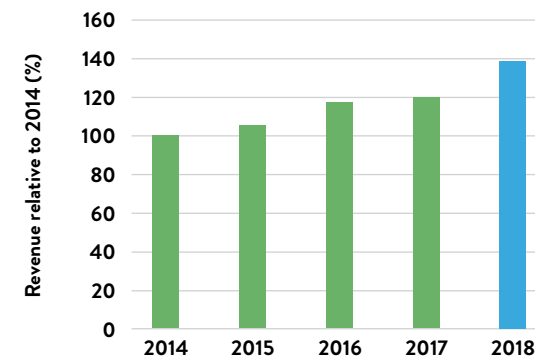




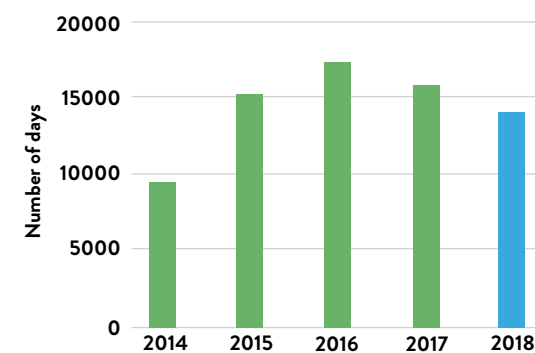
2018 at a glance



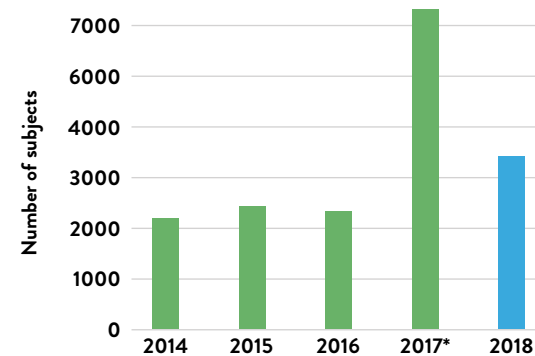
Contract revenue



Accommodation days



Subjects screened



*includes approximately 4000 patients with Parkinson's disease

Overall client satisfaction



9.1



2018 at a glance



52 studies



31 contracts signed



45 articles published



5 PhDs graduated



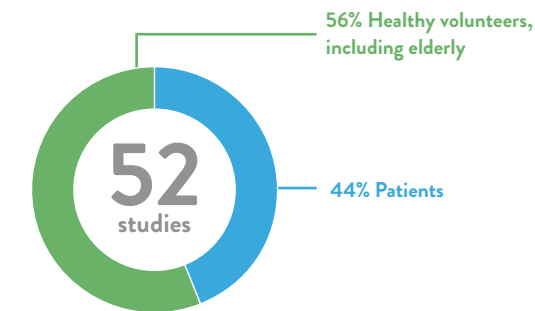
> 50,000 volunteers available



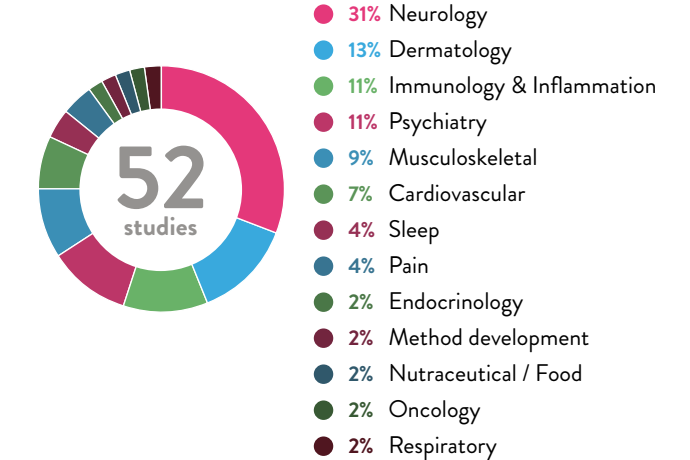
> 22,000 patients available



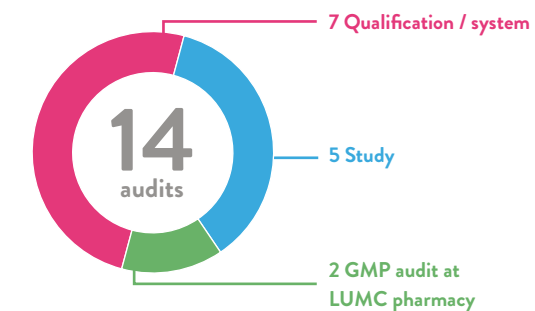
Studies with subjects



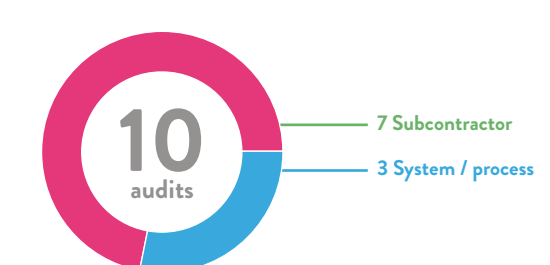
Studies per research area



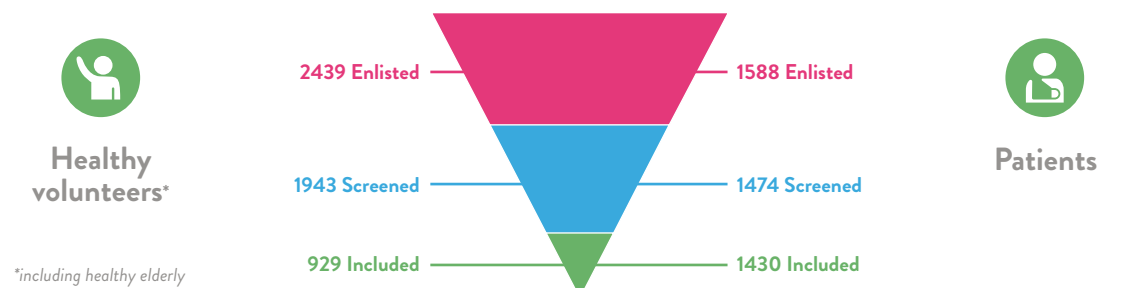
External audits



Internal audits

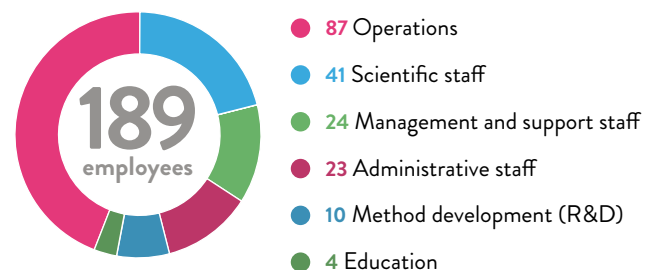


Subjects recruited

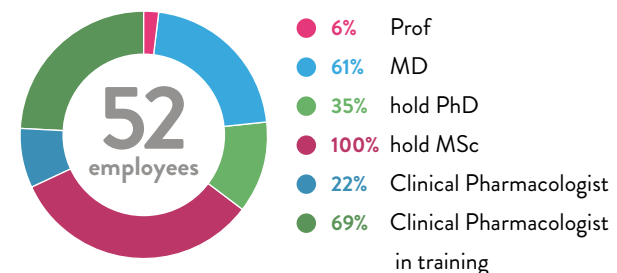


*including healthy elderly

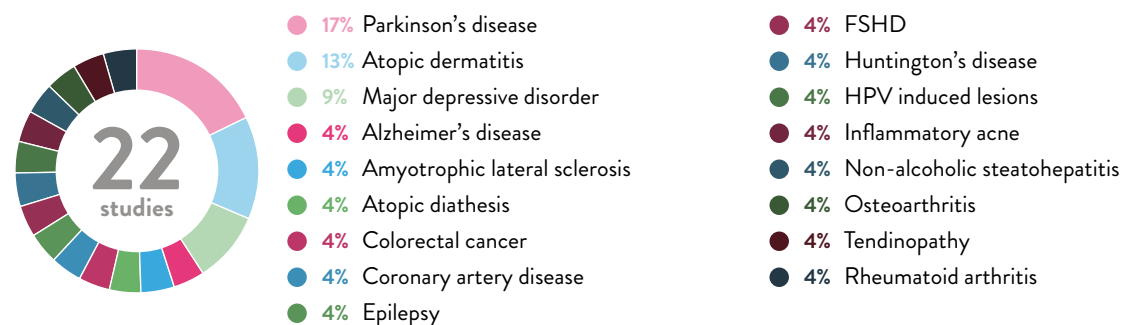
Employees by department



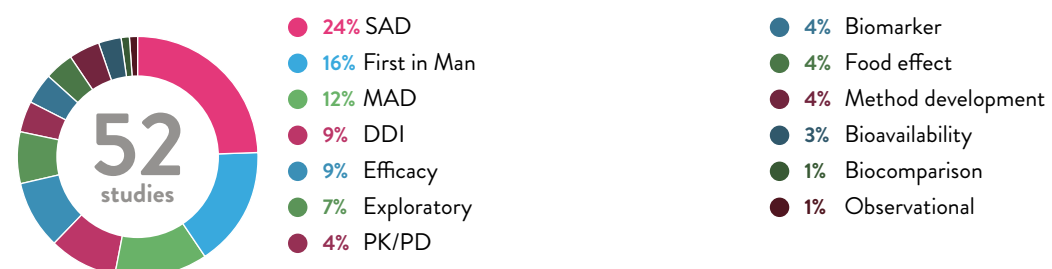
Clinical research staff



Types of patients



Types of study



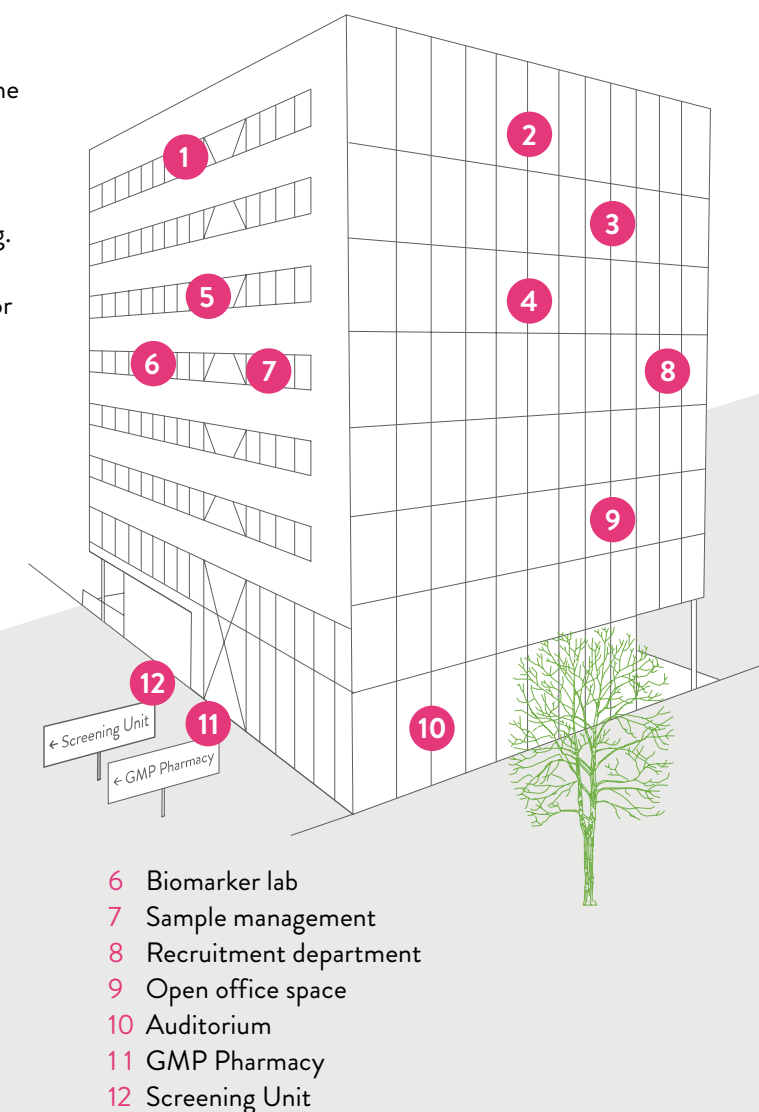
Designed to facilitate research

Our facility is purpose built to streamline everything we do. From our modern First-in-Man unit and top-notch volunteer accommodation, down to dedicated research rooms and efficient sample management, our key processes inspire the unit's design.

With a light and open work environment, we aim to stimulate collaboration and innovative thinking. Our modern office space offers flexible working and meeting areas, and a dedicated auditorium for educational activities.

Let us show you around.

[Start the video tour](#)





Neurology and Pain



Dr Geert Jan Groeneveld, Chief Scientific Officer / Chief Medical Officer

Parkinson's, pain and method development

Over the past year, CHDR's Neurology and Pain group has performed a number of successful clinical studies, and invested in the future in a variety of ways. A study conducted in Parkinson's disease patients with a specific genetic mutation paves the way for future studies in patients with this debilitating neurological disease. New pain models have been added to CHDR's PainCart®, offering the possibility for new insights into central pain regulation.

'My work here at CHDR has always been interesting, but my current combination of responsibilities is more challenging and rewarding than ever before,' says Dr Geert Jan Groeneveld, who is CHDR's CSO/CMO as well as the principal investigator for neurology and pain studies. 'I'm still very much involved in the work of our Neurology and Pain group, but due to my CSO/CMO role, I naturally have to delegate more to our senior scientists and project leaders. And they have been doing a marvellous job, both from an operational

and a scientific point of view. Currently, there are very interesting developments in neuropharmacology, with new compounds that promise to address the underlying pathophysiology of neurodegenerative diseases rather than just reducing their symptoms. With our future-oriented approach, we are poised to play our part in the clinical development of these compounds.'

Parkinson's disease

'As you'll remember from last year's report, we had taken on quite a challenge: the early phase development of a new candidate drug for the treatment of Parkinson's disease,' says Groeneveld. 'The bulk of that study has been completed in the past year, and everything went well, even exceeding our expectations.' The investigational compound in this study aims to restore the function of an enzyme called glucocerebrosidase in a subgroup of patients with Parkinson's disease who have mutations in the GBA1 gene, which contains the code for this enzyme. To recruit these patients, CHDR first had to find a large number of patients with Parkinson's disease, and then screen their DNA for GBA1 mutations. Thanks to the collaboration of several large neurological clinics in the Netherlands, 3,500 Parkinson's patients were found who were willing to send a saliva sample to CHDR.

After these samples had been tested by GenomeScan, a genetic analysis lab located nearby in the Leiden Bio Science Park, patients carrying the mutation were invited to participate in the clinical study. This early-

stage study was too short to expect any clinical effects, given that the aim with this compound is to slow down the progression of the disease. However, together with the sponsor, CHDR performed an analysis to indirectly quantify enzyme activity, which showed that the compound influenced substrate levels. Project leaders Jonas den Heijer and Annelieke Kruithof were the ones tasked with performing this study, and Groeneveld is extremely proud of their accomplishments. 'It was quite a complex study, and they conducted it flawlessly and right on schedule.' Read more about this study in the interview with Den Heijer and Kruithof on [page 26](#).

Ready-for-Research strategy

According to the literature, an estimated 5-10% of patients with Parkinson's disease carry the GBA mutation. Remarkably, CHDR found that in the Netherlands the percentage is much higher, at around 15%. Of course, this still means that the majority of the patients who contributed to the DNA study do not have this specific mutation. Nonetheless, these patients will be extremely valuable for future studies. Groeneveld: 'Research into Parkinson's is of course broader than just this study: besides another study involving patients with Parkinson's that was conducted at CHDR in 2018, we know that the search is on for other compounds to slow down the progression of the disease. As a result of this study, we now know 3,500 patients who have been diagnosed with Parkinson's disease and who have already shown their willingness to be involved in research by sending us a saliva sample.'

This cohort of patients is a great illustration of CHDR's Ready-for-Research strategy: by gathering well-defined groups of patients, specific (sub)groups can be recruited swiftly and efficiently as soon as specific protocols are established.

Understanding pain

In 2018, several clinical studies made use of the PainCart, CHDR's unique combination of validated pain models. Groeneveld: 'Using PainCart, we can show the effects of pain medication in healthy subjects. There have been several cases in which we were able to predict the success or failure of a compound in the clinical target groups, based on our research in healthy subjects. However, from a scientific point of view, there are some additional complexities. Evoked pain models are based on nociceptive stimuli. Putting it simply: to cause pain, you have to hurt someone by stimulating peripheral tissues. Chronic pain, however, is much more complicated: it may begin in peripheral tissues, but leads to secondary changes in the central nervous system that may become more important in maintaining the pain. Nociceptive stimuli will of course also be processed centrally, so we can also measure the effects of a centrally-acting compound by using peripheral nociceptive tests. But we are also looking for additional models to directly address central processing. After all, chronic pain is one of the largest unmet needs in medicine.'

There are several ongoing studies on central pain processing at CHDR, supported by the R&D Fund. For example, one study measures pain perception and pain thresholds to investigate the effects of sleep deprivation. Another study, investigating the effects of systemic administration of bacterial lipopolysaccharides (LPS) in healthy subjects, also pays special attention to effects on pain perception. Groeneveld: 'I don't expect sleep deprivation or LPS to ever become part of our routine set of pain models, but we can learn a lot from these studies. There are bound to be effects on central pain processing from lack of sleep: we know from clinical experience that patients who sleep badly report more pain. Effects on central pain processing are also bound to result from a systemic activation of the inflammatory response. These studies will help us to quantify these effects and give us more insight into the underlying mechanisms. Ultimately, we hope to gain a better understanding of the role of the central nervous system in pain perception.' Find out more about the sleep deprivation study on [page 34](#).

In the future, virtual reality (VR) may be added to the PainCart test battery, to involve the affective component of pain perception. Studies in healthcare – in the care of burn victims, for example – have shown that a pleasant VR experience can have a positive effect, reducing the amount of pain experienced during a painful procedure. CHDR is currently investigating the opposite approach, using VR to induce a stronger pain response to electrical or pressure-based stimuli. Groeneveld: 'First, we will conduct a study in healthy subjects to establish if and how we can obtain

reproducible results. The next step will then be to evaluate how we can use such reproducible endpoints in clinical studies of various analgesics, to explore the effects they have on the affective component of pain.'

Developing methods

Augmenting the PainCart with VR capabilities is just one of many methodological developments happening at CHDR. Other innovative approaches include new techniques using EEG, such as the combination with transcranial magnetic stimulation (TMS-EEG) and sophisticated evoked-response measurements. Groeneveld: 'Our Method Development group has grown and diversified in the last few years. We started three years ago with just two people. Now, one of those first two pioneers, Robert-Jan Doll, oversees a diverse team of 10 people. The team would not be complete without our data scientists, who are busy developing ways to deal with the tremendous datasets that are generated by our new, data-rich methods. Of course, the Method Development group is not only developing new approaches, but also validating them in collaboration with our clinical researchers. This is crucial in contemporary drug development: we are all working together to use validated, standardised approaches to arrive at a dossier that is based on rich, robust data.' Read more about the work and ambitions of the Method Development group on [page 30](#).

‘The study with Parkinson’s patients was a very rewarding experience’



Dr Jonas den Heijer, Research Physician and Annelieke Kruithof, Clinical Scientist

‘Overall, the project has been a real success,’ says Jonas den Heijer, Research Physician involved in a recent study in Parkinson’s disease (PD). ‘Thanks to the collaboration of neurologists across the country, we managed to find 3,500 PD patients who were willing to send in a saliva sample for screening. We were looking for a mutation in the GBA1 gene, and we managed to find a large number of patients who displayed this mutation. In 2018, we conducted a clinical study with 40 of those patients.’ Annelieke Kruithof, Clinical Scientist also involved in the clinical study: ‘I had done quite a few studies in healthy volunteers already, in the Neurology and Pain group and in the Internal Medicine group. But the Parkinson’s study was the first that either of us had ever done with patients, and it was on a much larger scale, too.’

In the clinical study, PD patients with a mutation in the GBA1 gene received either placebo or one of three different doses of a compound aimed at restoring the function of the enzyme glucocerebrosidase (see also [page 23](#)). The patients were asked to take this medication for 28 days. They were evaluated clinically using a number of tests, including the NeuroCart test battery. In addition, blood samples were taken and lumbar punctures performed at the beginning and the end of the study period. Participants visited CHDR twice more during the study period, with further monitoring being done by means of a phone call from

Den Heijer: ‘We wanted to check how our patients were doing, but we didn’t want to burden them with more travel than necessary.’

Kruithof joined the project a few months before the start of the clinical study. ‘We took great care to make the patients comfortable while they were here. Some of them had to travel quite a distance to reach us, which is even more demanding for people suffering from Parkinson’s disease. We tried to accommodate them as best as we could, offering a taxi ride to CHDR, or a place to stay the night. Participants were also welcome to bring along their partner or a close friend.’ Den Heijer: ‘Even before the study started, we did what we could to reduce the burden for patients. We eliminated everything we considered unnecessary, and we decided to have just four patients visiting at a time, to be able to give each one our full attention.’

Den Heijer, who had also conducted the saliva test study, was in charge of recruitment: ‘I called the patients to tell them the results of the DNA test, and I invited eligible participants to come and be screened for the clinical study. I was also in charge of most of the screening. I was very glad I had Annelieke by my side to take care of the logistics, so I could focus on my duties as study physician.’ Kruithof adds: ‘Jonas and I tried our best to be present on all the days that participants were at the facility. Tin Nhi Truong, our research nurse,



‘We took great care to make the patients feel welcome and ensure that they were comfortable. It paid off: all the patients remained in the study until the end.’

was also very dedicated and was another familiar face for the patients. I found it really rewarding to see that participants appreciated our efforts, that they felt at home here. Some of them even brought us chocolates or cake to say thanks!’ The hard work to accommodate patients paid off, with every participant remaining in the study until completion.

‘After obtaining my PhD, I hope to become a neurologist,’ says Den Heijer, who studied medicine in Utrecht. ‘I’m learning so much here about Parkinson’s disease, both clinically and scientifically. Thanks to genetic research, several potential drug targets have been established, and there are many promising compounds currently in the pre-clinical and clinical phases of development. It will be really interesting to see how things progress – I believe that what we are doing now is the future of treatment for this disease. I hope one day we will see better treatments for PD patients, for the motor symptoms as well as for the debilitating symptoms that arise in the later stages of the disease.’

Den Heijer and Kruithof are currently working on another project, which aims to describe the course of the disease in the same subgroup of patients. ‘Our plan is to go through the files of all the patients from the saliva test study who display the GBA1 mutation. But there are a number of legal and regulatory hurdles we need to clear first, especially with the recent tightening of privacy regulations in Europe.’ Kruithof, who studied Bio-Pharmaceutical Sciences at Leiden University, has plenty to keep her busy in the meantime: she is currently finishing her PhD thesis on haemostasis. ‘I really like doing research, but I enjoy being involved in the operational side of clinical studies even more. The great thing about working at CHDR is that I can combine the two.’



Ghobad Maleki, Clinical Scientist, **Ahnjili Zhuparris**, Data Scientist and **Dr Robert-Jan Doll**, Clinical Research Engineer

‘Innovative method development is all about teamwork’

‘Our group is really dynamic,’ says Dr Robert-Jan Doll, who leads CHDR’s Method Development group. ‘It’s a collaboration between people who have such different backgrounds. Sometimes there are different points of view, which can spark interesting discussions. But the bottom line is that everyone is open to new ideas and works together towards a common goal. It makes me proud to lead a group like this.’ In conversation with team members Ahnjili Zhuparris and Ghobad Maleki, a picture emerges of a vibrant team with a diverse range of profiles and interests.

Zhuparris is one of the group’s data scientists. She studied Biomedical Sciences at the University of Edinburgh, initially with a focus on neuroscience. During her studies, she became increasingly interested in artificial intelligence and machine learning approaches. After a short stint in a digital marketing consultancy (‘very boring!’), she was glad of the chance to get back into doing science, joining CHDR in 2018. With her data science expertise, she helps the team navigate the large datasets generated by new data-rich methods, such as the MORE platform for remote monitoring. ‘I’m really glad to be working here, as part of this team. The questions we address are so much more compelling than the problems I worked on in marketing. For example, we’ve developed an algorithm which can automatically detect whether, and how frequently, a baby is crying. We scoured the internet to gather a set of audio files: sounds of babies crying,

other infant sounds such as babies making happy noises, and lastly, just normal background noises. We then trained the system to distinguish between these different types of audio until it was able to successfully identify the sound of babies crying. The system is now being validated with the help of audio recordings from nursing wards in the Juliana Children’s Hospital in The Hague.’

Another project Zhuparris is working on uses machine learning to try and predict the risk of an individual developing Alzheimer’s Disease (AD). ‘This project ultimately aims to correlate biomarkers from spinal fluid with the cognitive status as measured by NeuroCart. My goal is to develop an algorithm based on less-invasive biomarkers for AD pathology, with the aim of being able to use it to identify subjects who may be prone to developing AD. If we can classify subjects reliably using this method, it will remove the need to perform lumbar punctures as part of the screening process – that is, on people who ultimately won’t be part of the study. So, in a nutshell, you could say we’re using machine learning to reduce the number of lumbar punctures.’ This kind of approach holds potential for tackling a whole host of questions. Zhuparris’ colleague Onno Elzinga, for example, is using clinical data from patients with Parkinson’s Disease to predict the progression of the disease based on the findings from their first visit to the neurologist.

Ghobad Maleki is a medical student who has been working at CHDR for the past two years, developing the MORE remote monitoring system (see also [page 100](#)). He is collaborating with Zhuparris on two studies which will be conducted in 2019. One of these is an observational study in patients with depression, the other an observational study in patients with the neurological condition facioscapulohumeral muscular dystrophy (FSHD). In these studies, MORE will be used to remotely monitor the patient's social activity and movements based on phone usage and GPS. The data will be gathered by means of regular upload from subjects' mobile devices. 'Those datasets will be relatively large, calling for a Machine-Learning approach,' says Maleki. 'Ahnjili and I wrote the protocol together, and as soon as the first data are in, we will start the preliminary analysis.' To handle this complex task, CHDR is collaborating with Landscape, a company specialised in the analysis of big datasets. Zhuparris will act as a point of liaison between Landscape on the one hand, and Maleki and colleagues on the other.

In addition to these large datasets, the studies will also yield clinical data, such as readings from NeuroCart and results of traditional questionnaires. These data are imported into Promasys, CHDR's clinical database, for analysis by CHDR's own Statistics group and the group involved in modelling the relationship between a drug's pharmacokinetics and pharmacodynamics (PK/PD modelling). Some of the more complex data, however, must first be prepared for inclusion in Promasys. Doll: 'In many of our projects, we focus on the hardware, the software, and the analysis that is needed to convert raw data into meaningful endpoints for import into Promasys. In that sense, we are a kind of filter between the raw data and Promasys.'

Doll, who oversees this dynamic team, came to CHDR in 2016. He had trained as an electrical engineer specialising in biomedical signals and systems. He wrote his PhD thesis on the topic of pain, developing new methods to observe nociceptive processing. 'In those days, I collaborated with CHDR's Neurology and Pain group. After I got my PhD, I did contract research for a US-based company on a volume conduction model for neuronal activation during spinal cord stimulation. I also worked at a Dutch hospital, setting up clinical trials. One day I got a call from Geert Jan Groeneveld: he wanted me to be involved in establishing a new Method Development group at CHDR.'

The group started off with just two people, expanding to ten people in just two years. 'For me, that means that I increasingly need to delegate to my team members,' says Doll. 'I think that people work best when they can focus on just a couple of projects at a time, giving them the chance to effectively apply their particular expertise.' The projects that are close to Doll's own interests and experience include work on analysing complex datasets, such as evoked potentials in EEG, and the development of new neurophysiological paradigms as upgrades for the NeuroCart and PainCart. 'Other times, we work more efficiently by pooling our resources to look for solutions. We can also cast our net wider to draw on knowledge from beyond our group. For example, we have been working on a method to quantify tremor severity during daily activities in essential tremor patients, using accelerometers. It became clear that the expertise required to achieve this was more wide-ranging than any of us had. Therefore, we opened it up to our colleagues outside the group, and now it's a collaborative project between three departments. This way, we're not only capitalising on the range of expertise within our team, but on the diverse experience across the whole of CHDR.'





Hemme Hijma and Ingrid Koopmans, Clinical Scientists

‘We use sleep deprivation to study pain perception and driving performance’

Ingrid Koopmans and Hemme Hijma are working together on a project financed by CHDR’s R&D Fund, exploring the effects of sleep deprivation on a wide variety of brain functions, including driving skills and pain perception. ‘The project has got off to a great start,’ says Koopmans, who studied Technical Medicine at the University of Twente before joining CHDR’s Method Development group. ‘Since 2017, I have been involved in developing and validating an on-the-road driving test, using a car with state-of-the-art measuring equipment. To validate the measurements obtained with this car, we’ve decided to run a clinical study using sleep deprivation. It’s common knowledge that skipping a night’s sleep will affect your driving skills, yet it’s perfectly legal to get behind the steering wheel after being awake for 24 hours, as long as you feel capable of driving safely. So we’ve written a protocol combining NeuroCart, our Green Dino driving simulator and our on-the-road test car to measure the performance of healthy volunteers before and after a night without sleep.’

Hijma is a Clinical Scientist doing his PhD research on novel analgesic compounds and the role of (evoked) pain models in drug development. ‘My main focus

is central hyperalgesia, that is, increased pain and a lowered pain threshold caused by changes in the central nervous system,’ says Hijma. ‘There are a number of highly selective and potent centrally-acting analgesics currently being developed. There is an urgent need for such drugs, especially since opioids – the classical centrally-acting analgesics – are highly addictive. We are looking for models to study specific mechanisms of central control. For example, we are updating one of our pain models, conditional pain modulation (CPM), in order to increase its applicability in drug development.’

The collaboration between Hijma and Koopmans came about when Dr Geert Jan Groeneveld (leader of the Neurology and Pain group, interview [page 22](#)) saw the opportunity to investigate the effects of sleep deprivation on pain perception. ‘To assess the analgesic potential of these novel centrally-acting compounds, we are looking into sleep deprivation as a model to complement the range of PainCart tests,’ says Hijma. ‘It will also be interesting to gain a deeper understanding of the relationship between sleep deprivation and pain perception, because many patients with pain syndromes also suffer from sleep problems.’

The combination of all these measurements – from NeuroCart, PainCart and driving tests – has made for a complex study, which will therefore now be conducted in two parts. Hijma will be in charge of the second part of the study, in which EEG and (laser) evoked potentials will be used to ascertain the effects of sleep deprivation on signal processing in the brain. In addition, the full PainCart test battery will be applied, including the most recent additions such as intra-epidermal stimulation (IES), a method to establish pain thresholds. IES was developed at University of Twente by Dr Robert-Jan Doll, who now leads CHDR's Method Development group (see also [page 30](#)). Hijma: 'I'm excited about the opportunity to learn more about the underlying mechanisms involved.'

'There are so many opportunities here for academic and professional development.'

'When I arrived here two years ago, genetics and immunology were my main areas of interest,' says Hijma, who gained his BSc in Biomedical Sciences at the Free University in Amsterdam, followed by an MSc in Science and Business Management at Utrecht University. 'However, I soon became involved with the Neurology and Pain group, and was project leader for several of their clinical studies. Now, I play a role in most of CHDR's pain research – even my PhD thesis will now be in this area.' Koopmans has also

found opportunities to develop professionally and academically while at CHDR: 'I'm currently involved in a wide range of projects, working on the development of several new technical biomarkers. The sleep deprivation study is the first clinical project I've led, so I'm really glad to be able to draw on Hemme's experience.'

In 2018, Koopmans took the decision to start working towards her own PhD. 'Ever since doing an internship at the European Space Agency in Bonn, I've been fascinated by the topic of applying clinical measurements in space. I'm intrigued by the extreme challenges involved, such as preparing astronauts for weightlessness and dealing with the time delays in long-distance communication. CHDR has no plans as yet to do space medicine, but nonetheless, my supervisors Geert Jan Groeneveld and Robert-Jan Doll have supported me to pursue my ideas. We're currently brainstorming to find a scientific problem that is both relevant to space medicine and interesting to CHDR, and we've already come up with a lot of really interesting possibilities. When I first came here, I wasn't sure I'd find an opportunity that would suit me. Now, I have the opposite problem – I'm spoilt for choice!'



Working with CHDR

‘Approachable and insightful’

‘I’m very satisfied with our relationship with the CHDR team. They are approachable and insightful. The communication was very straightforward. They made sure to be available for us throughout the study, planning meetings at short notice where needed. A fair number of problems cropped up during the study, mostly from our side, and CHDR dealt with them wonderfully.’

Director, Experimental Medicine, Top 10 Big Pharma Company*

**The views expressed here are the sole opinion of CHDR’s sponsors.*





Psychiatry



Dr Gabriël Jacobs, Research Director Psychiatry

Advancing the pharmacological treatment of depression and anxiety disorders

Developing new drugs for the treatment of mood and anxiety disorders presents psychopharmacologists with unique challenges. CHDR is increasingly performing studies in patients with such disorders, using a variety of new and existing methods to demonstrate pharmacological effects. For CHDR's project leaders, such studies are complex and challenging, offering a unique opportunity to hone their skills in the field of clinical CNS drug research.

'Within the CNS division at CHDR, my group focuses on drug development for psychiatry,' says psychiatrist and clinical pharmacologist Dr Gabriël Jacobs. 'At present, we mostly study new treatments for depression and anxiety. However, we collaborate regularly with our CHDR colleagues who study neurodegenerative disorders and pain. Since both groups are involved in developing drugs for the treatment of CNS disorders, such collaboration is not only logical but also makes cross-pollination possible.'

In the past few years, CHDR has performed an increasing number of studies in patients with mood disorders. CHDR's nurses and staff have been trained to provide a safe and welcoming environment for psychiatric patients. Scientifically and logistically, these studies in patients present far more challenges than the studies in healthy volunteers that CHDR has been conducting for more than 30 years. Jacobs: 'Although we still perform several complex trials in healthy volunteers every year, patient studies are becoming increasingly important. Since these studies have different dynamics from trials in healthy volunteers, they typically take longer, which raises challenges with regard to other issues such as patient recruitment

and retention. But I think it's worth it in terms of our contribution to the drug development process and the science of psychiatric pharmacology.'

Intranasal esketamine

A good example of such a complex patient study is the work of Francis Dijkstra and the rest of the study team, with an intranasal formulation of the ketamine isomer, esketamine. Although repeated intravenous esketamine infusion has been demonstrated to have antidepressant effects in patients with treatment-refractory depression, repeated injections are burdensome for patients and present challenges with regard to accessibility, convenience, and logistics. Jacobs: 'That's why we were really interested when a sponsor approached us during the development of esketamine nasal spray, especially considering its potential advantages as a form of antidepressant maintenance treatment.' Administration of esketamine by nasal spray also allows relevant drug exposure comparable with intravenous administration. CHDR already had experience with esketamine in studies with both healthy volunteers and patients suffering from depression. This was the second study at CHDR using the intranasal formulation.

In 2018, CHDR completed an on-the-road driving study in 23 patients with treatment-refractory depression. Patients were recruited and enrolled by CHDR, while the on-road driving test took place in collaboration with Dr Joris Verster's team at Utrecht University. The study focused on the effects of esketamine on driving ability in the hours following either a single or repeated administration. Jacobs: 'One of the things we wanted to know is how long it takes before the patient is able to safely drive a car.

This is particularly important because esketamine as maintenance treatment will probably be applied in the outpatient setting.'

The study was complex in a variety of ways. The first challenge was recruitment. Jacobs: 'Luckily, thanks to our network of psychiatrists and with the help of our excellent recruitment department, we generally were able to meet our recruitment targets within the defined timelines.' The study design itself was fairly complex as well, involving 11 visits to CHDR over the course of three months. Subjects spent a day and a half at CHDR and received either ketamine or a placebo, after which they were transferred to Utrecht for the on-road driving test, where alcohol was used as reference compound. Jacobs: 'During the three months the study took for each participant, we managed to retain most of the patients who had been enrolled in the study. The collaboration with our colleagues at Utrecht University meant an extra layer of logistical complexity. So I'm really proud of everyone involved that we managed to successfully perform this study with such a high retention rate.' The outcomes of the study are currently being analysed and will be published in the near future.

Future developments

Developing new drugs for psychiatric disorders is notoriously difficult. In spite of the great unmet clinical need, the past decade has not seen many new compounds enter clinical development, and there have been even fewer successful market introductions of new pharmacological treatments. This problem has its roots in a number of contributory factors, including the fact that most animal models for human psychiatric disorders are known to be unreliable. Perhaps the most important hurdle is the

'translational gap' between neurobiological research and neuroscience on the one hand, and clinical psychiatry on the other. Jacobs: 'Neurobiological research has identified a variety of both central and peripheral pathophysiological processes that putatively underlie the individual symptoms that are clustered together and classified as major depressive disorder. Since the Diagnostic and Statistical Manual of Mental Disorders (DSM) is used to classify psychiatric symptoms and, as a consequence, select patients for clinical trials, a group of patients selected as having major depressive disorder is in fact relatively heterogeneous in terms of their underlying pathophysiology. Suppose a compound could successfully restore healthy functioning by targeting one of those pathophysiological pathways: if it is tested in a heterogeneous group of patients, the compound's therapeutic effect may be diluted or even obliterated. We therefore need to identify common pathophysiological processes in subgroups of patients or even specific processes in the individual patient, and select the compound that targets those specific processes.'

This ambitious approach has already been introduced as part of the Research Domain Criteria project of the National Institute for Mental Health (NIMH) in the United States. The aim is to systematically identify the biology of psychiatric disorders on the genetic, pharmacological, neurocircuit and behavioural level. Jacobs: 'I hope this approach will contribute to addressing the discrepancy between clinical diagnosis and the varying dysfunctions in biological systems, and as a consequence, lead to better-informed drug development and clinical trials.'

Over the years, CHDR has developed different methods, including NeuroCart and PainCart, to study specific CNS functions and the pharmacological effects

of CNS active compounds in healthy volunteers and patients. Depending on the specific compound under investigation, these tools are combined with methods such as resting-state fMRI and quantitative EEG. Jacobs: 'In addition, we plan to introduce and validate new methodologies that are currently applied in preclinical and clinical research to study the effects of compounds with novel mechanisms of action. That way, if a sponsor needs these new methods in their clinical development programmes, we will be ready to use them.' For example, the Neurology and Pain group has further validated the use of transcranial magnetic stimulation combined with EEG (TMS-EEG) for studying the effects of various CNS inhibitory compounds on human cortical excitability. The Psychiatry group is now using the same method to study the effects of a range of CNS stimulatory compounds, including ketamine. 'Hopefully this will raise the interest of sponsors who are currently developing compounds that target the central glutamate system,' says Jacobs. 'I look forward to updating you on this next year!'

Digital technology

Another promising methodology is so-called 'digital phenotyping' or 'biotyping'. Using common digital technologies, such as smartphones or wearable devices, it's possible to gather data about the day-to-day behaviour of patients. These measurements could prove to be sensitive to the effects of CNS drugs on a behavioural level. CHDR is pioneering this approach in the Trial@home programme (see also [page 56](#)). Jacobs: 'Traditionally in psychopharmacology, we use validated psychiatric questionnaires such as the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Åsberg Rating Scale for Depression

(MADRS) to enquire about patients' mood, cognition and behaviour during the preceding two weeks or so. Needless to say, people find it rather difficult to remember details about how they felt over the past two weeks, meaning that the answers to such questions are of limited value. Such scales are also associated with unintended therapeutic effects when administered by researchers – in particular, that they tend to over-predict therapeutic effects in research settings compared to naturalistic settings. In addition, assessments using rating scales are time-consuming, adding a burden to patients and unnecessarily increasing the logistical complexity and cost of laboratory-based clinical trials. And as depression negatively colours one's memories, depressed patients have a tendency to remember only their worst moments.'

Clearly, then, it makes much more sense to ask about a patient's mood on a daily basis, perhaps even several times a day. In addition, rather than asking patients how forgetful or how active they have been over the past two weeks, we can instead measure patient behaviour objectively – this could be through measuring their movements, the amount of time they spend talking on their mobile phone, and so forth. It was for this purpose that CHDR developed its MORE platform (previously REMOS; see [page 100](#)). 'We will conduct a first study in depression this year in collaboration with a local mental health centre in Leiden. In this study, we will cross-sectionally characterise a cohort of patients with major depressive disorder using both smartphones and wearable technologies (such as smart watches or blood pressure monitors) that are validated for use at home. We will then correlate these characteristics with the HAM-D and MADRS. 'I think we will see interesting developments in the coming years, which have the potential to revolutionise both the drug development process and clinical practice in psychiatry.'

Keeping colleagues in the loop

With the Research Domain Criteria paradigm likely to drive psychopharmacological research in the coming years, there's a risk that clinical psychiatry will be left behind. Researchers like Jacobs and his team also need clinicians on board to help with finding patients willing to participate in scientific studies and to provide ongoing clinical care while patients are participating in the study. Jacobs, who still is involved in clinical work at the Psychiatry department of the Leiden University Medical Center, has set up a network of psychiatrists who are interested in collaborating on drug trials. 'In the past year, we have also established a collaboration with a mental health care organisation in our region,' says Jacobs. 'This enthusiastic team of psychiatrists and psychologists provide outpatient care for a growing number of psychiatric patients in our region. Since drug trials are rather new to them, we organised an educational event for them to get acquainted with our organisation and the kind of work we do. It was a unique experience for CHDR's project leaders too: they not only got the chance to present their ongoing studies, but also benefited from the opportunity to interact with clinicians who deal with the complexities involved in the clinical care of psychiatric patients.'

In a similar vein, CHDR organised a symposium on drug development in psychiatry at the Dutch Psychiatric Association's Annual meeting last spring. 'As a drug researcher, I believe that engaging with clinicians on an ongoing basis is crucial to prevent polarisation between research and practice,' says Jacobs. 'What's more, CHDR's 30-year history puts us in a prime position to demonstrate how scientific collaboration with both industry and clinicians can help to bridge the gap between clinical work and drug research, despite the challenges in psychiatric drug development.'





Dr Vincent Aalten, Research Physician

‘Patients who participate in trials enjoy staying at CHDR’

‘This is my last day at CHDR,’ says Dr Vincent Aalten, as we sit down for the interview. ‘I’ve spent a year here doing a research internship as part of my training to become a psychiatrist. Next week, I’ll continue my training in a community outreach team in The Hague.’ As a psychiatry resident, Aalten has been a member of Dr Gabriël Jacobs’ team. He joined the team as study physician for the duration of his internship, and in this capacity has been involved in preparing and performing clinical studies, screening patients for clinical trials, and writing protocols, among other tasks. In the beginning, it was challenging to work in a setting so different from his usual clinical work in psychiatry. ‘I chose to do this internship because I wanted something new, but especially in the beginning, it was almost more novelty than I had bargained for. To add to that, the pace is pretty fast here at CHDR. It was a challenge to get my head around all the rules, regulations and standard operating procedures surrounding clinical drug research. For example, the exact time at which a screening interview is conducted is so important that I’m supposed to double-check that it’s correctly recorded, even though it takes place three weeks before the actual study.’

Aalten quickly came to value the in-depth scientific discussions with his colleagues. ‘People here really think critically, which makes it a very stimulating place to work. I particularly enjoyed being involved in

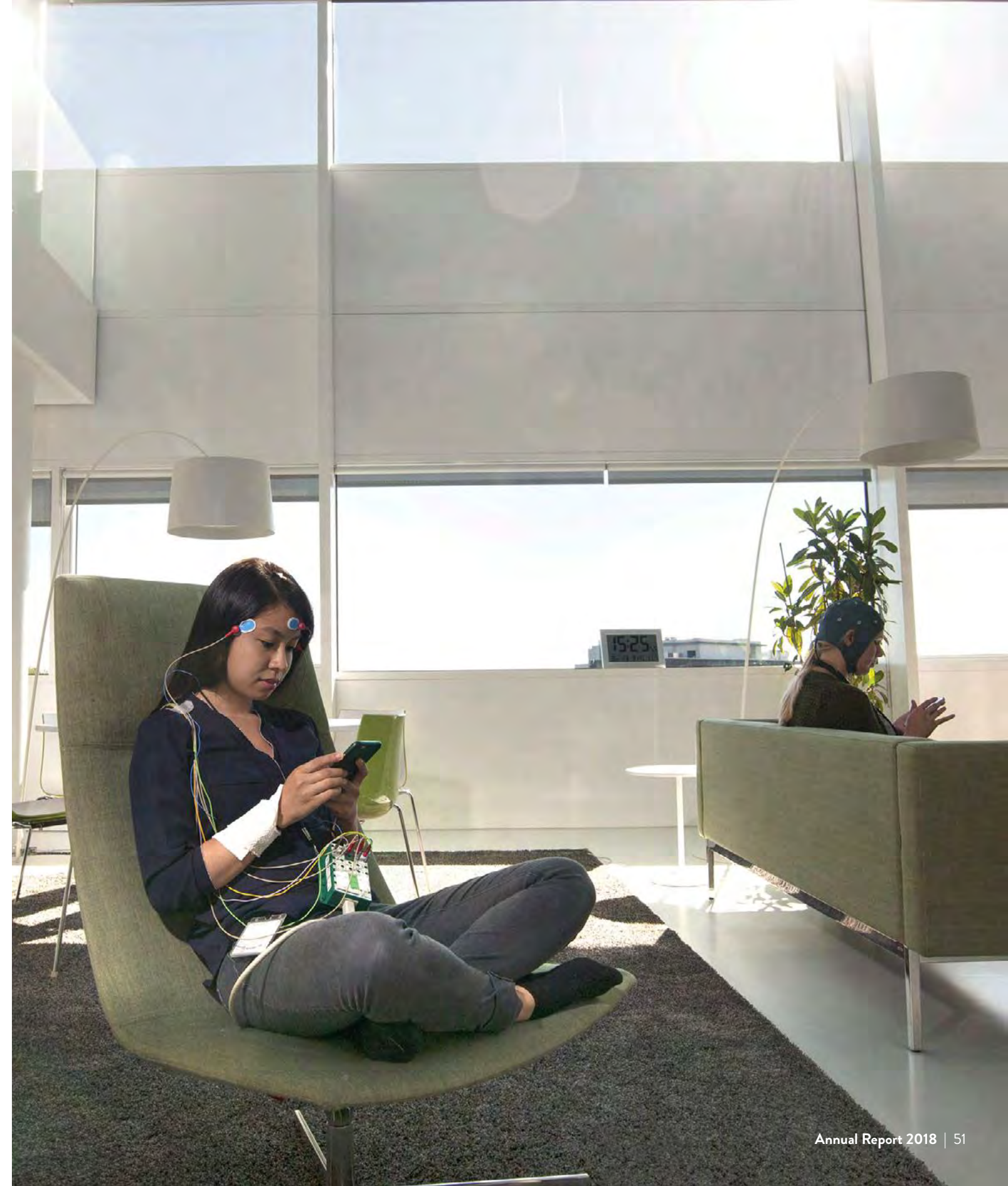
a study on one of the new orexin antagonists, a new class of drugs with potential effects on both sleep and mood.’ Another study that Aalten helped to set up and conduct was part of CHDR’s method development programme. Using smartphone apps in conjunction with the MORE platform, this study aimed to explore the value of naturalistic data for measuring the severity of symptoms in patients with depression. ‘I think remote monitoring offers exciting new opportunities to study the behaviour of psychiatric patients objectively, instead of relying on patients’ retrospective evaluations of their own mood and behaviour. It may even provide new means to quantify the effects of drugs or psychotherapy. Of course, it’s crucial to first validate these methods and establish their value, both for drug development and for clinical applications. Being involved in the implementation of this new approach was a great experience. In the coming years, I look forward to seeing the benefits this technology will bring.’

A large part of Aalten’s work at CHDR concerned screening patients with depression and providing them with the necessary information about the trial. ‘It’s all very methodical. We use a set of questionnaires and structured interviews to systematically evaluate a patient’s symptoms and see if they fit our inclusion criteria. Most of the time, it’s also necessary to liaise with their psychiatrist or GP to clarify some point in

their file or verify something they said. We do our best to take good care of our patients, and we never include anyone in a clinical trial if we think that doing so might be unwise in terms of safety or suitability. And from what I've seen, patients benefit from the attention and care they receive here at the facility.'

What does the future hold for Aalten, as he moves on from CHDR? 'For the next one and a half years, I'll be busy doing my residency. I do it on a part-time basis, to have more time for my family. I have two young daughters, and it's so important to spend time with them and see them grow up. Beyond that, nothing is set in stone – there are always a lot of interesting jobs out there for a psychiatrist, so I can keep my options open. I've really enjoyed being involved with scientific research here, so I may come back to it at a later stage, ideally combining it with my clinical work.'

'People here really think critically. It's a very stimulating place to work.'





Dermatology



Dr Robert Rissmann, Research Director Dermatology

Increasing the diversity and depth of dermatology research

Dermatology is one of the fastest-growing research areas within CHDR. Thanks to a strong collaboration with the Immunology, Neurology and Pain, and Method Development groups and a growing network of external collaborators, the range of scientific questions being addressed is becoming ever more diverse. At the same time, CHDR's researchers are devoting themselves to a deeper understanding of underlying mechanisms, building a solid foundation for the personalised medicine approach of the future.

'For me personally, 2018 was the first time I had the freedom to focus on my research,' says Dr Robert Rissmann, Research Director for Dermatology. 'Until then, I was combining my scientific work and clinical

studies in dermatology with my role as Education Director. In 2017, Jeroen van Smeden took over most of my educational responsibilities. He's been doing an excellent job, so I'm really happy. I still enjoy being involved with education, but it's also good to have time to focus on new developments: not only the development of new methodologies and drugs, but also professional development for our staff members, especially our PhD students. There are now eight of them conducting research in my area, so there's a lot going on.'

Pioneering dermatology

From the perspective of drug development, the skin is an interesting organ for several reasons. In the first place, it's easily accessible. Most changes in its physiology and pathophysiology are readily visible, or can be straightforwardly measured using dedicated equipment. The skin reacts to systemic drugs, but in most cases, a topical or intradermal application of a compound will also cause measurable changes. For early-stage clinical experiments with a new compound, such local applications may represent a safe first step. For the growing number of novel immunomodulating agents for the treatment of autoimmune diseases, cancer, infections and other disorders, the skin is therefore interesting as a first organ in which to try out a new compound.

In addition, the skin is interesting for the possibilities it offers as an administration route. All these aspects of dermatological research feature in CHDR's work.

In recent years, much effort and resources have been invested in the development of a range of dermatological measurements, coming together to form the DermaToolbox. Rissmann: 'In 2018, we added more methodologies and evaluated them thoroughly in both diseased skin and challenge models. For instance, to study wound healing we can now apply thermography, perfusion assessment by laser speckle contrast imaging, transepidermal water loss and 3D imaging. The outcomes were aligned with the molecular and cytological markers in the biopsies including mRNA and protein profiles. Additionally, we can now use optical coherence tomography for non-invasive monitoring of cutaneous morphology over time.'

The high-tech approach to dermatology at CHDR is attractive to scientists interested in studying the skin and its disorders, with the goal of contributing to better treatments. Besides clinical studies, CHDR also contributes to the work of Prof. Joke Bouwstra at Leiden University who studies skin lipidomics, using liquid chromatography mass spectrometry (LC-MS) to establish lipid profiles from both healthy people and patients with various skin disorders. Rissmann: 'We integrated the tape-stripping method into this project, using adhesive tape to collect a sample of the outer layer of the skin. In collaboration with Professor Bouwstra, we explore specific biomarkers that could be used in the future to follow a specific pathophysiological process in eczema. If we find useful biomarkers, they could also contribute to the development of personalised treatments.'

And then there's the sort of high-tech we're all carrying in our pockets nowadays: the smartphone. Rissmann's group has been pioneering the implementation of CHDR's Trial@home approach, using apps on a smartphone or tablet to collect measurements in an outpatient setting. 'Most of the patients who participate in our study never stay in our clinical research unit for longer than a few hours. We monitor their skin lesions through pictures they send us from their mobile devices. We also use the platform to remind them to apply their medication or to ask them questions about symptoms such as itching or pain. Only if we want to conduct a more detailed investigation of their skin and their lesions do we invite them to CHDR,' says Rissmann.

Intradermal administration

The skin can also be useful as an administration route for systemic medication. For example, transdermal patches are used to deliver drugs such as opioids or medication for motion sickness over longer periods of time. But not all compounds can be transported through the skin. Peptide-based compounds or proteins such as monoclonal antibodies consist of molecules that are too large to effectively permeate the stratum corneum (the outer layer of the skin, which forms the main barrier). In 2018, CHDR studied another route to administer a treatment for juvenile idiopathic arthritis: intradermal injection using micro-needles. Rissmann: 'The usual administration route for this treatment is subcutaneous injection. However, repetitive injections can be a source of stress, and even more so when the patients are children. For this reason, paediatricians have been seeking alternative ways to deliver the drug.' In healthy adult volunteers, CHDR investigated if intradermal administration was efficient enough in

delivering the drug to the system. 'The outcomes of the study were mixed: it is possible to use this route, but we'll need further research to find the optimal volume for administration,' says Rissmann. 'In the future, I hope that this line of research will lead to an improvement in the therapy for these young patients.'

Collaborations

The clinical studies conducted at CHDR in 2018 in the field of dermatology covered a wide range of skin conditions. Rissmann: 'There are a number of topics that we have been studying for quite some time now. Among them are infections with human papilloma viruses – both the viruses that cause benign lesions, such as warts, and the HPV strains that are associated with malignant growth, such as carcinoma of the vulva and cervix. This work has benefited from the input of gynaecologist Dr Mariëtte van Poelgeest, who joined us recently (interview on [page 58](#)). Alongside this, we have been studying treatments for common dermatological conditions such as psoriasis and various forms of eczema. Yet another line of research is focused on inflammatory skin conditions, in collaboration with the Immunology group (led by Dr Matthijs Moerland, interview on [page 80](#)). These have been the key themes over the last few years, but we are always looking for interesting new treatments that we can help develop using our DermaToolbox.'

In addition to work with sponsors, CHDR also collaborates on an academic front with clinical dermatologists and other researchers, to foster the development of new therapies. 'One of the important things our PhD students need to learn is not just how to ask the right questions, but how to connect with others who have the expertise to help you answer

those questions. In science nowadays, it's naive to think you can answer all the questions by yourself.' A recent example of such an academic collaboration is work on the treatment of cutaneous T-cell lymphomas. The Leiden University Medical Center (LUMC) is home to the specialised centre for the diagnosis, treatment and research of this rare malignancy in the Netherlands. Patients with cutaneous T-cell lymphomas from all over the country are referred to the LUMC. In 2018, two intriguing new potential treatments were investigated at CHDR, in close collaboration with the LUMC's clinical dermatologists. 'It was a win-win collaboration,' says Rissmann. 'The LUMC hospital doesn't have sufficient resources for conducting this kind of clinical experiment. So the LUMC patients came to our clinical research unit and we carried out the experiments together.' One of the two treatments was an immunomodulating compound, the other involved the intravenous infusion of an investigational treatment.

CHDR also has a long-standing collaboration with the Dermatology department at the Erasmus University Medical Center in Rotterdam, in particular with their staff dermatologist Dr Martijn van Doorn (interview on [page 62](#)). Dr van Doorn is well-known to CHDR from his time here training as a clinical pharmacologist and writing his PhD thesis. Rissmann: 'Together with Martijn we are building a network of dermatologists interested in clinical research, which we call CONNECTED (Clinical Network for Trials in Dermatology). Clinicians participating in this network will be co-creators of clinical studies, providing their expertise and helping to recruit patients with specific skin conditions. It's another example of a collaboration that's beneficial to all parties: we share expertise and information at the same time as facilitating clinical studies. And in the end, it's the patient that benefits most of all.'



Dr Mariëtte van Poelgeest, gynaecologist specialised in oncology at LUMC and CHDR

‘I want to contribute to the wellbeing of patients, both as a physician and as a researcher’

‘I spend two days a week here at CHDR’, says gynaecologist Dr Mariëtte van Poelgeest, who is also based at the Leiden University Medical Center (LUMC). ‘I wouldn’t want to miss the time I spend with my patients at the hospital, so for me this is the best of both worlds.’ The collaboration with CHDR started back in 2005, when PhD student Hélène van Meir began studying a therapeutic vaccine for carcinogenic strains of the Human Papilloma Virus (HPV), for the treatment of cervical cancer. Van Meir was based at CHDR, but did much of her research at the LUMC. Van Poelgeest: ‘My own PhD thesis was about immune reactions to HPV, which is the cause of most cervical cancers and some vulvar carcinomas. Within gynaecology, I specialise in treating cancer, especially lesions of the vulva. I have also continued my research work, investigating HPV-related tumours and premalignant lesions.’

Van Poelgeest’s collaboration with CHDR intensified when Robert Rissmann from the Dermatology group and Matthijs Moerland from the Biomarker group began a study to investigate agents which can be used to treat premalignant lesions caused by HPV. ‘These preparations, which can be applied locally, cause a controlled inflammatory response. This can be enough

to remove the viruses from the lesion, stopping the transition towards cancer,’ Van Poelgeest explains. ‘We conducted that study here at the facility. I was involved in writing the protocols and, together with the project leader, I recruited and screened all the patients who participated.’ Since October 2018, Van Poelgeest has been seconded from the LUMC to CHDR to pursue collaborative work. ‘We started small, with studies focused on HPV-related cancers. Now, we are expanding towards other oncology-related studies. We are currently planning to study a new approach to immunotherapy, injecting immunotherapeutic agents into different types of tumours. And of course, there is a close collaboration with researchers from the Dermatology department at the LUMC whose main focus is the treatment of T-cell lymphomas of the skin.

‘Research is teamwork, especially in oncology. In our collaboration, we complement each other’s expertise. What I love here at CHDR is that everyone is dedicated to research. Because it’s a relatively small organisation, it’s easy to meet up with each other, to discuss essential details at short notice, all of which contributes to propelling a research project forward. I’m also very interested in the image-guided surgery project led by CHDR’s Prof. Koos Burggraaf and

Dr Alexander Vahrmeijer, a surgeon at the LUMC. They are world leaders in the development and testing of immunofluorescent markers, with the goal of improving surgical treatment, especially in cancer. In the vulvar lesions I am treating, one of the major problems is that it's often very difficult to see the boundaries of the lesion. I've applied for funding for a project to identify antigens which are specific to these premalignant or malignant lesions. These can be used to develop specific fluorescent markers so that we can treat these lesions effectively without causing more damage than strictly needed.

'With the development of immunofluorescent markers, we hope to minimise the damage caused in the surgical treatment of lesions.'

'Treating patients with vulvar carcinomas and other lesions of the vulva is challenging, but also very rewarding. Unfortunately, there is a high level of recurrence, necessitating a long follow-up. That means I see these patients many times over the years and end up forming a personal connection with them. For me that's very valuable, and it's a major motivating force to keep searching for effective treatments. Where we stand now, surgical removal can be effective, but it is also mutilating and the tumour tends to recur. The other option is radiotherapy, but once a patient has received curative radiotherapy treatment, she is not allowed to receive it again even if the tumour recurs, because of secondary damage to healthy tissues. Chemotherapy is not effective for vulvar carcinoma. For these reasons, we're currently exploring other options, one of which is immunotherapy. We have shown that, contrary to what was believed, vulvar carcinoma can cause an immune response.'

Another line of enquiry concerns the difference between patients in the typical age range for this condition and the minority of younger patients, who mostly have HPV-related cancer of the vulva. Van Poelgeest: 'Under current guidelines, all patients are treated the same. However, we have shown that these younger patients have a far better prognosis, so it may make sense to treat them differently. It may be a relatively rare type of tumour, but there's a lot to be done, both scientifically and clinically. Going back and forth between CHDR and the LUMC, I am in a key position to be able to contribute to the treatment of these patients in particular, as well as other patients with different types of cancer.'





Dr Martijn van Doorn, dermatologist at Erasmus Medical Center, Rotterdam

‘We are connecting clinicians and researchers via our fast-growing network’

A dynamic network is growing in the field of dermatology, promising a greater cross-pollination between research and clinical practice. At its heart is a collaborative exchange between specialists at CHDR, the Erasmus Medical Center Rotterdam, and the Leiden University Medical Center. ‘Everyone involved benefits from the collaboration,’ says Dr Martijn van Doorn, dermatologist based at the Erasmus MC. ‘CHDR offers us cutting-edge research facilities and expertise, while my colleagues and I can reciprocate with our clinical experience, especially concerning inflammatory skin conditions. As more dermatologists from Leiden University Medical Center join the collaboration, we also gain from their specialist knowledge about HPV-related skin lesions and cutaneous lymphoma.’

It’s this collaborative exchange that has given rise to the Clinical Network for Trials in Dermatology (CONNECTED), for which Van Doorn is the driving force. ‘The name says it all: we’re aiming to connect dermatologists working in general hospitals with our clinical and academic research. We want to establish a dialogue, where we can ask our clinical colleagues for input on research questions and protocols, and where they get the opportunity to play a greater role

in scientific research.’ The network also provides a way to improve recruitment for clinical trials, by involving doctors more directly in the process. Van Doorn: ‘For clinical research, recruitment is always a bottleneck. I know from personal experience that, even with the best of intentions, doctors often forget to ask their patients if they want to participate in a trial. As part of CONNECTED, we are developing an app that should help overcome this. Once dermatologists have indicated their wish to be involved in a study, the app will send them a notification before they begin their clinic, to remind them to ask patients if they would like to participate in the trial. If a patient is willing to be screened, the same app can then be used to look up inclusion criteria and to fill in a sign-up form.’

For a hospital to participate in CONNECTED, two or more dermatologists need to register. They can then select from a range of clinical studies which ones they would like to be involved in. Van Doorn: ‘We’ll also be having regular meetings to keep our colleagues in the loop about ongoing projects, and to update them on any results.’ The network is already growing in the south-west of the Netherlands, and Van Doorn hopes it will expand to include all Dutch university medical centres and major hospitals within the next few years.

Van Doorn's own dermatology practice specialises in inflammatory skin conditions. 'Our clinic has become a tertiary referral centre for patients with chronic urticaria, as part of the Urticaria Centre of Reference and Excellence (UCARE) network. We have recently run a project aiming to optimise the treatment of patients with chronic spontaneous urticaria, which benefited from the involvement of Tessa Niemeyer-van der Kolk, a PhD student at CHDR who did her clinical pharmacology internship at our clinic. The current therapy for chronic spontaneous urticaria is with the biologic omalizumab (anti-IgE). However, it's very expensive. Tessa has helped us to retrospectively evaluate a new personalised treatment algorithm, with the goal of reducing the treatment frequency in patients who are in complete remission. This would not only make treatment more cost-effective, but would also reduce the burden for the patient. Our work was recently published in a high impact journal. Now, together with CHDR, we have applied for funding to conduct a prospective randomised clinical trial.'

At CHDR, Van Doorn also plays a role in overseeing ongoing work in dermatology, helping to coach the Clinical Scientists as they lead new projects. 'Some of them are hoping to qualify as dermatologists, too, so they enjoy the chance to discuss the clinical aspects of their work with me.' Van Doorn's affiliation with the organisation goes back to 2001, when he started here as a PhD student investigating new therapies for diabetes. Having finished his clinical pharmacology training and obtained his PhD, he went on to train as a dermatologist: 'I think my affinity with dermatology comes down to the fact that I'm a really visual person.' In 2012, he returned to approach Prof. Adam Cohen

with a proposal for a collaborative study, to take place at CHDR. Along with his colleague Deepak Balak, Van Doorn conducted a first phase 2 study in psoriasis patients, evaluating a novel anti-inflammatory compound aimed at toll-like receptors 7, 8 and 9. The collaboration also involved Dr Robert Rissmann, who now heads the Dermatology group (see interview [page 54](#)).

'In the space of a few years, things have really flourished. Dermatology is now one of CHDR's fastest-growing research areas.'

'In the space of just a few years, things have really flourished,' says Van Doorn. 'Now, dermatology is one of CHDR's fastest-growing research areas. Many of my colleagues from the Erasmus MC, both from clinical practice and basic research, also play a role in our collaborative projects. I'm proud of what we have already achieved, and I'm confident that our collaboration will be fruitful for years to come.'



Working with CHDR

‘A stimulating collaboration’

‘We have really enjoyed working with the team at CHDR. We’ve had valuable exchanges with the PI, and the project manager has also been a pleasure to work with. What really elevated the partnership was the input of senior scientific staff. Having additional brains in the conversation, going beyond the purely operational side of things, made this a really stimulating collaboration.’

CEO and Co-Founder, Biotech Company*

**The views expressed here are the sole opinion of CHDR’s sponsors.*





Internal medicine



Prof. Koos Burggraaf, Chief Executive Officer

Expanding the frontiers of internal medicine

Internal medicine has always been CHDR's most diverse research area, and 2018 continued this trend. Activities ranged from innovations in cardiology, to gene therapy, vaccine development and image-guided surgery. With the help of cutting-edge technology, the Internal Medicine group performed several ground-breaking studies and laid foundations for future developments.

'Thanks to the efforts of our Senior Clinical Scientists, the Internal Medicine group can look back on a very fruitful year,' says Prof. Koos Burggraaf, CEO and former Research Director for Internal Medicine. 'Our team has done a wonderful job, not only in managing ongoing projects, but also in pursuing a range of new activities. It will take some time before all of these new developments are ready for use in clinical studies, but it's important for us to anticipate future needs in the industry and in medical practice.'

Some of the group's activities, such as CHDR Cardiology Services, are concerned with improving and

enhancing the standard process of drug development. Other activities go beyond drugs in the traditional sense, developing vaccines and Advanced Therapy Medical Products (ATMPs), or fluorescent markers for use in image-guided surgery. In order to be able to cover such a wide range of research themes, collaboration is key. In-house collaborations with the Biomarker group (led by Dr Matthijs Moerland) and the Method Development group (led by Dr Robert-Jan Doll) are complemented by external collaborations, such as those involving scientists and clinicians at the Leiden University Medical Center (LUMC).

ATMPs and vaccines

2017 saw exciting advances at CHDR in the development of ATMPs, including studies with genetically modified viruses. This work has continued apace in 2018, with Senior Clinical Scientist Dr Ingrid de Visser-Kamerling and her team studying a vaccine for respiratory syncytial virus (RSV). 'In most healthy adults, RSV is relatively harmless, causing an upper respiratory tract infection – the common cold. In premature or malnourished babies and people with immune deficiencies, however, the same virus is associated with serious health problems and even death. Especially in developing countries, RSV is a cause of child mortality,' explains De Visser. 'It's not easy to develop a vaccine for RSV. Decades ago, it was tried with a formalin-inactivated virus, but this turned out to potentiate the infection instead of preventing it. Moreover, the immunity induced by the naturally-

occurring virus disappears quickly. So people get infected time and time again, sometimes even more than once a year. The vaccine we have been studying in 2018 was based on a genetically modified virus, which we hope will be effective in preventing RSV infection.’ ATMP studies, including those concerned with gene therapy, can be particularly tricky to navigate due to a range of legal requirements and regulations. De Visser: ‘This kind of work certainly brings with it an extra layer of complexity. Nonetheless, the regulations are there to help us ensure the safety and well-being of our subjects – and that’s always our highest priority.’

Research into vaccine development at CHDR is set to continue in the coming years. In collaboration with the LUMC, De Visser and her colleagues are exploring the possibility of developing challenge tests for vaccines. Pharmacological challenge tests are already used in many other areas, allowing researchers to study effects in healthy volunteers. In the case of a vaccine, a challenge test would involve exposing healthy volunteers to the germs to assess whether the vaccine protects against infection. De Visser: ‘Dr Meta Roestenberg at the LUMC has already used this approach with malaria. In the case of malaria, there is effective medication that can be administered to subjects at the first sign of an infection, meaning that it is ethically acceptable to perform such a challenge test. With RSV and similar viruses, a healthy subject may contract an upper respiratory tract infection, which is again ethically acceptable.’ Find out more about De Visser’s work in the interview on [page 140](#).

The study of vaccines and infections is closely related to the study of immunologically active compounds. In collaboration with the Biomarker group, a vaccine with the neoantigen KLH was used to study an investigational immunomodulating compound. This compound influences the interaction between antigen-presenting cells and T cells, a mechanism of action that can be of interest for the treatment of autoimmune diseases, as well as in oncology. Burggraaf: ‘Thanks to the expertise of Dr Matthijs Moerland and his group, we have an expanding toolkit for studying immunomodulating compounds. Immunomodulation has great potential for the treatment of a wide variety of diseases, including cancer. Many novel compounds targeting the immune system are currently under development, so I’m glad we can offer cutting-edge tools to study them.’ Read more about the neoantigen study, and the work of the Biomarker group, on [page 80](#).

Cardiology

2018 was also a busy year in cardiology at CHDR. In collaboration with the Amsterdam University Medical Center, the safety and tolerability of a candidate drug for the treatment of atrial fibrillation was studied in healthy volunteers. Dr Pim Gal, Senior Clinical Scientist: ‘Atrial fibrillation is quite common, with a prevalence of two to three percent. It increases the risk of thrombus formation, causing stroke and dementia, so it needs to be treated effectively. Most current treatments lower the heart rate, which helps to prevent atrial fibrillation, but at a cost. The candidate drug we have been investigating aims to restore a normal sinus

rhythm without lowering the heart rate.’ The trial at CHDR was successful, which means the compound can now be taken forward for testing in patients.

While novel compounds in cardiology are relatively rare, Gal and his colleagues regularly study the cardiac effects of compounds as part of CHDR Cardiology Services. A key question in drug development concerns the effects of a compound on the heart rhythm, specifically on ventricular repolarisation time, also known as the QT interval in the ECG. It’s important to confirm that a compound will not cause a specific ventricular arrhythmia known as torsade de pointes, which can be fatal. For this reason, regulatory authorities have strict rules on testing for prolongation of the corrected QT interval. For almost 15 years now, this has been done by means of a thorough QT study. However, this method is costly and can even lead to the exclusion of compounds that are in fact perfectly safe – meaning that promising new compounds could be unnecessarily ruled out. ‘Recently, scientists associated with the US Food and Drug Administration (FDA) published an article outlining how we can evaluate the risks more precisely,’ says Gal. ‘We know that a blockade of some ion channels, such as hERG, is associated with ventricular arrhythmias. On the other hand, a blockade of other ion channels may have no such effect – or may even protect against the effects of hERG blockade. With a more detailed analysis of the ECG, we can identify which ion channels are involved.’ Based on this article, Gal and colleagues have developed a method to evaluate the risk of serious ventricular arrhythmias already in the early stages of clinical drug development. ‘We can use this method to reliably assess if the compound is safe in terms of the risk of

ventricular arrhythmias. We plan to publish a white paper about this in 2019.’

Gal and his colleagues have also been studying the effects of other variables on cardiac (electro) physiology. In 2018, they investigated the influence of fasting on the ECG. Subjects in early drug development trials are almost always asked to fast for several hours before the start of the trial, because food may interfere with the pharmacokinetics of the compound. But fasting itself has physiological consequences. Gal: ‘We have a large collection of screening data and ECG data from hundreds of subjects, which we can use for research purposes. We regularly ask our subjects to remain fasted for 4 hours before the medical screening, and before the actual study we ask them to fast for 10 hours. Using this database, we compared the effects on the ECG of 4 hours versus 10 hours of fasting. We found an even larger effect than we expected.’ The ECG changes Gal and his colleagues found after 10 hours versus 4 hours of fasting included a reduced wave amplitude and duration, as well as increased isoelectric interval duration. Gal: ‘These findings are not only scientifically interesting, but also relevant to early drug development trials, as they indicate that the influence of fasting needs to be taken into consideration when examining QT intervals.’ Read more about Gal’s work on [page 152](#).

Image-guided surgery

Another theme of ongoing research at CHDR is image-guided surgery, in close collaboration with Dr Alexander Vahrmeijer from the Department of

Surgery at the LUMC. This technique uses fluorescent markers to increase the visibility of tumours and other structures, enabling greater precision and efficacy of surgery. The past few years have seen an emphasis on using this technique to discern tumour tissue, paving the way for more effective cancer surgery. In 2018, a number of successful studies took place using a fluorescent marker to increase the visibility of ureters. Burggraaf: 'Causing accidental damage to a ureter is every surgeon's nightmare. These structures, which run from the kidney to the bladder, are thin and vulnerable, and it can be really hard to identify them during surgery. In patients who have had lower abdominal surgery before, it can be even more of a challenge to recognise them because of adhesions and scar tissue.' The numbers speak for themselves: as many as one in ten women suffer damage to a ureter during gynaecologic oncological surgery. In other types of oncological surgery the percentage is much lower, but still significant.

To increase the visibility of ureters during surgery, the LUMC-CHDR team used a fluorescent compound from a novel class of near-infrared fluorophores, which has a low affinity for healthy tissue and is exclusively cleared through the kidneys. Another advantage of the new compound is that it remains in the body for several hours, so a single administration may be enough for a regular surgical procedure. Just as with pharmacologically active compounds, the new fluorophore was first tested in healthy volunteers at CHDR for safety and tolerability. In those studies, fluorescence in the skin was measured to gain insight into the pharmacokinetics of the compound. Subsequently, the compound was tested in patients

undergoing surgery at the LUMC. During surgery, the compound showed a very promising profile. Burggraaf: 'The surgeons could see the ureter clearly, watching a bolus of fluorescent urine travel all the way from the kidneys to the bladder. So the compound can be used not only to visualise the ureter, but also to assess its functioning and see whether it is intact. Even when the ureters were hidden in scar tissue or under the peritoneum, they could be clearly seen. It was checked using several different camera systems, and even with the da Vinci robot, so the use of this compound is compatible with robotic surgery.'

Burggraaf, Vahrmeijer and their teams see a promising future ahead for their collaboration in image-guided surgery. Their work also forms part of CHDR's growing involvement in the field of oncology. Burggraaf: 'In the past, CHDR did not actively contribute to cancer research. Now, with our work on image-guided surgery and our studies in immunology, we are playing an increasingly important role in this vital area of work.'





Dr Naomi Klarenbeek, Research Physician

‘As a general internist, I can make a broad contribution’

‘At the moment, I’m still a resident in internal medicine,’ says Dr Naomi Klarenbeek. ‘I’m completing my training in clinical pharmacology, here at CHDR and at both the Leiden University Medical Center and the Erasmus Medical Center in Rotterdam. In the summer of 2019, I’ll be a registered internist and I’ll join the staff at CHDR. It’s important to stay in touch with clinical practice, so I’ll also continue to work in the hospital setting.’

Klarenbeek studied medicine at Erasmus MC, before coming to Leiden to write her PhD thesis on treatment strategies in rheumatology, especially in rheumatoid arthritis. ‘I analysed the results of a multicentre trial comparing four different treatment strategies. The most important conclusion was that it’s important to have a clear goal, and to keep adjusting the treatment until you have achieved that goal. We call this “treat-to-target”. The results showed that beginning with combination therapy led to earlier clinical improvement.’ It was during her training in internal medicine that she decided to specialise in clinical pharmacology.

When she joins the staff at CHDR, Klarenbeek is looking forward to a dynamic and varied role. ‘Internal medicine has always been an important area for CHDR. Over the past three decades, Prof. Koos Burggraaf and his team have contributed to the clinical development of drugs in cardiology, endocrinology, coagulation and several other fields. CHDR’s Cardiology Services have innovated the whole procedure of safety testing from a cardiological perspective. Matthijs Moerland has

built a state-of-the-art immunology lab, allowing us to participate in the development of immunologically active compounds. The field of immunology in particular is currently seeing a lot of growth. We’re already studying immunological treatments in dermatology and in autoimmune diseases; in the near future, we may focus more on immuno-oncology, infectious diseases and geriatric diseases, building on the experience we’ve gained in these areas in recent years. Overall, I’m looking forward to the chance to contribute to this wide range of fields. As an internist I’ve always kept a broad perspective, and in my clinical practice I’ll also be working across the whole spectrum of internal medicine.’

In addition to pursuing her training and teaching students, Klarenbeek has been conducting studies as a project leader. ‘Last year, we studied the effect of a novel compound for the treatment of non-alcoholic steatohepatitis. We also performed multiple studies with innovative immunological treatments for musculoskeletal diseases. When I’m working here in a more supervising role, it’ll be great to have these experiences to draw on.’ She is looking forward to spending more of her time at CHDR. ‘It’s such a dynamic environment, with a strong focus on service and scientific quality. Working here is a great way to contribute to the future of medicine.’



Biomarkers and Laboratory



Dr Matthijs Moerland, Research Director Translational Biomarkers

Future-focused bioanalysis and biomarker development

CHDR's laboratory for biomarker development and bioanalysis – the R&D lab – has grown in the past years. In 2018, the lab was restructured and audited to achieve optimal functioning. Methods research continued apace with the development of dedicated T cell methodology. Meanwhile, several clinical studies focusing on immunologically active compounds took place. Research Director Dr Matthijs Moerland reflects on another dynamic year.

‘When I spoke to you last year, we were focused on expanding our laboratory facilities and hiring new staff members. In 2018, we invested in creating a better organisational structure for our team,’ says Moerland. The team used to be small, with a flat structure. As the number of members grew, it became necessary

to rethink the way the team was organised, introducing a structure to facilitate supervision and reporting. The group now consists of two Bioanalytical Scientists (Wieke Grievink and Diana Pereira) who oversee the day-to-day work of seven research technicians and scientists.

The new organisational structure makes the laboratory more efficient, also contributing to the education of new personnel and the introduction of new procedures. ‘Our lab team is now a dynamic mix of experienced technicians and young professionals. We realised that the younger members of the team learn best from people who are a few years ahead of them in terms of lab experience,’ explains Moerland. ‘I don’t always have time to answer all their questions, and for many questions, a lab technician may actually be better qualified to answer them.’

Audit

Following the rapid growth and the restructuring of the team, it was time to take a critical look at the results. CHDR therefore organised an internal laboratory audit, inviting auditors from Profess® Medical Consultancy to take an in-depth look at the bioanalysis laboratory. The objective was to assess ICH GCP compliance, with emphasis on the development of bioassays and

biomarker research. The auditors decided to zoom in on two projects in particular, evaluating the way the laboratory handled them. The results were encouraging. Moerland: ‘The auditors told us that we had been too modest in the past about our bioanalytical capabilities and performance. I have always told sponsors we are primarily a research lab – we don’t claim to be more. However, according to the audit, with some minor improvements our work aligns fully with the guidelines described by the FDA and EMA in their opinion papers, including the training of personnel, the introduction of new procedures, data streams and storage, and so forth. This is of course good news for our sponsors, but it’s also reassuring for the team to know that their work conforms to official standards. Two and a half years ago we were mainly a sample handling lab which outsourced almost all bioanalysis. Since then we’ve grown into to a state-of-the-art bioanalysis laboratory, specialised in advanced cell-based analysis. It’s really encouraging to hear from experts in the field that we are on the right track – a great motivation to keep developing further in the coming years.’

Towards a T cell laboratory

Moerland and his colleagues also have taken further steps in the development of immunological biomarkers. ‘In the last few years, we have set up various methods to investigate the innate immune system, which we have now been using in our clinical studies. In 2018, we took the first steps towards realising our ambition to develop and validate methods to assess the functioning of the B cells and the T cells of the adaptive immune system. We established methods to quantify the effects of immunosuppressant drugs targeting the T cell non-specifically, and successfully performed the first clinical study with the well-known immunosuppressant drug

tacrolimus in healthy volunteers. Eventually we hope to be able to monitor specific immune reactions.’

After administering a dose of tacrolimus, the researchers took samples to establish serum concentrations. Additionally, T cells were gathered using a cell sorter, and the tacrolimus concentration in these target cells was measured. Finally, using a functional assay, the activity of T cells was studied. Moerland: ‘The experiments were a success. In the coming year, we plan to study two more registered compounds before doing our first study in patients who are on immunosuppressive medication following a kidney transplant. Currently, alongside monitoring kidney function, clinicians only measure blood concentrations of the immunosuppressant drug. We think our approach makes more sense, because we “bridge the gap” between drug dose and clinical effect: we quantify the actual level of target inhibition, the target being the T cell itself. And of course, we could pursue the same trajectory with a new compound aimed at T cell-mediated immunity.’

Building on this experience, CHDR has now also embarked on new methodology for the quantification of antigen-specific T cell responses. This will be critical for future clinical trials evaluating the effects of immunomodulatory compounds for oncological conditions or autoimmune diseases. Moerland: ‘An important future goal for us will be monitoring antigen-specific immune reactions, both cellular and antibody mediated. It may take some time to get there, but we have already taken some important initial steps.’ In addition to the work on T cells, CHDR focuses on B cell function in collaboration with the laboratory of Prof. Johan Kuiper at the Leiden Academic Centre for Drug Research (LACDR). One of the team’s members, Wieke Grievink, has begun her doctoral research on this

topic, combining preclinical research at LACDR with clinical research at CHDR: a truly translational PhD project. For more about Grievink’s work, see [page 88](#).

Tailored methodology

According to current scientific views, immunological factors play a role in the initiation or progression of almost all diseases. This insight is being translated into product development, meaning that the pipelines of the biotech and pharmaceutical industries are full of promising new immunomodulatory compounds. In anticipation, CHDR is developing tailored methodology that facilitates the clinical investigations of such compounds. The immunological and cell-based techniques developed by CHDR’s R&D lab will be a critical component of such clinical studies. However, state-of-the-art lab-based methods may not suffice to demonstrate drug effects in healthy volunteers who don’t have active inflammations. The workaround for this is to induce an immune response in these volunteers. In 2018, CHDR invested in two such models: the intradermal LPS challenge, and the challenge with KLH, a neoantigen.

Intradermal LPS

In the past, CHDR successfully qualified and applied the intravenous low-dose LPS challenge. In this procedure, a low dose of lipopolysaccharide (LPS) is injected initiating a significant but transient and controlled innate immune response via toll-like receptor 4 (TLR4). The drawback of this intravenous approach is that it can only be performed once per volunteer, due to the long-lasting effects of LPS on the immune system. In 2018, an interesting new

approach was developed that circumvents this problem. Moerland: ‘In the skin, an LPS challenge causes a much more localised reaction. Therefore we have been undertaking some clinical studies to validate and use the LPS challenge in the skin.’ For more on this project, see the interview with Dr Thomas Buters on [page 84](#).

Neoantigen challenge

Novel compounds acting on adaptive immunity are also being studied at CHDR, some of which have quite sophisticated mechanisms of action. ‘An interesting new compound we studied last year targets the interaction between antigen-presenting cells and T cells in the skin, reducing T cell reactivity and inflammation. Potentially, it could be used in the treatment of various inflammatory skin conditions. The challenge for us was to find a way to monitor the intended pharmacological effect in healthy volunteers,’ says Moerland. ‘In 2017, we had validated a new approach, based on vaccination with a neoantigen. We use KLH: it’s an antigen derived from a limpet that lives in the Pacific Ocean, so we can be certain that our volunteers’ immune systems have never encountered it before. If we vaccinate volunteers with this antigen, we can monitor the antigen-specific adaptive immune response, and the potential effect of an investigational compound developed to modulate this response. The first KLH vaccination study an investigational compound, executed last year, was very successful. I’m confident that future studies will show that this vaccination challenge model provides useful additional information about the effects of other immunomodulating compounds.’



Dr Thomas Buters, Research Physician

‘Using our skin inflammation model, we can now effectively test immunomodulatory compounds’

Scientific careers can really take off at CHDR. In the space of less than two years, Dr Thomas Buters has gone from intern to Research Physician and contributed to the development of a challenge model to study anti-inflammatory compounds in dermatological research. ‘I studied both medicine and biomedical sciences,’ says Buters. ‘By the end of 2016, I had almost finished my medical training and was looking for an internship in biomedical sciences, so I got in touch with Dr Robert Rissmann. He was a familiar face for us medical students – in those days, he was the one leading our pharmacology course. He agreed to help me find a suitable project to do at CHDR. A few months later, I graduated from medical school, which meant that I was in a position to be able to take on the role of study physician in a clinical trial with eczema patients. Following that study, I was hired as a Research Physician.’

Buters’ next step was to work on a project developing an immunological challenge test, a collaboration between Rissmann’s Dermatology group and Dr Matthijs Moerland’s Biomarker group. The aim

was to induce a temporary inflammation in the skin of healthy volunteers, enabling researchers to then measure the effects of anti-inflammatory compounds. ‘Matthijs and his colleagues already had a lot of experience studying inflammation in the laboratory, using lipopolysaccharide (LPS), a component of bacterial cell walls. LPS triggers an inflammatory response through the toll-like receptor, or TLR. This response can be seen when you add LPS to white blood cells in a test tube; when you then add your compound, you can see the response subside. Matthijs and colleagues also conducted a clinical trial where LPS was administered to subjects intravenously, triggering a systemic inflammatory response which caused flu-like symptoms. With the project I was involved in, we wanted to use LPS in an intradermal challenge test. This application is, of course, more controlled. I reviewed the literature, but there weren’t many examples of LPS being used in an intradermal setting. What I did find, though, was a study conducted in Prof. Derek Gilroy’s lab at University College London, using killed E. Coli bacteria instead of LPS.’

It soon became clear that Buters was onto something. Thanks to his discovery, a collaboration developed between CHDR and University College London, allowing both sides to benefit from one another's expertise and resources. One of the most important gains for CHDR was the introduction of suction blisters. Buters: 'By applying suction to an area of skin, we can easily cause a blister. This is a method that has been used in dermatology for decades, as a method of obtaining small skin grafts, or in order to measure drug concentrations in the fluid inside the blister.

In our application, we analyse the blister fluid to examine inflammatory skin responses, by measuring immune cells and cytokines. Since our laboratory is equipped with flow cytometers, we can now perform the inflammatory challenge and measure the immunological skin response within the same day. This is a vast improvement over biopsy analysis, which typically takes a long time and is only performed after the clinical study has been completed.' Buters' literature review also turned up a commercially available blister-inducing device. 'We already had a device, which was custom-made at the Leiden University Medical Center. The advantage of a commercially-available device, however, is that the manufacturer is also able to provide a list of publications that demonstrate the device's safety. This made for a much smoother process with the medical ethics committee and the health inspector.'

'Skin conditions are such a burden for patients. The possibility of improving their quality of life is a strong motivator for me.'

In 2018, the intradermal LPS challenge model was fully validated, using suction blisters, biopsies and a variety of measurements from the DermaToolbox to characterise the skin's response to the intradermal injection of LPS. Buters: 'We now know the dynamics of the inflammatory response and how to measure them. We have also shown the effects of topical and systemic corticosteroids on this induced inflammation. This all means that we are now ready to study novel compounds in healthy volunteers.'

Buters plans to write his PhD thesis on the development of therapies for inflammatory skin conditions, and hopes to eventually become a dermatologist. 'Skin conditions are such a burden for patients. They not only have to live with symptoms such as pain and itching, but they also suffer psychologically from the negative reactions of people around them. The desire to help improve the quality of life of dermatology patients is a strong motivator for me.' Even with such a glowing track record, getting a position as a dermatology resident will not be easy. 'The fact that there are few places and many applicants means there is intense competition. But I don't want to worry about that just yet. At CHDR I already have the opportunity to do research that contributes to the wellbeing of dermatology patients – and I will benefit, too, from the chance to be involved in this exciting work.'





Wieke Grievink, Bioanalytical Scientist

‘I’m excited to be part of cutting-edge scientific research’

Wieke Grievink, Bioanalytical Scientist in the Biomarker group, started her career studying to be a lab technician at the Saxion University of Applied Sciences in Enschede. ‘Back then, I only had a vague idea what I wanted to do and where my talents lay. Now I’m starting my PhD research, both here at CHDR and the Leiden Academic Centre for Drug Research (LACDR). The fact that I’m also able to continue my work here as a Bioanalytical Scientist means I get the best of both worlds.

‘When I first came to Leiden I worked at Good Biomarker Science, which happens to be in the same building as CHDR. Then, in 2016, I joined CHDR as a member of the Biomarker group – in fact, I was one of the first people Dr Matthijs Moerland hired when he was setting up his bioanalytical lab here. One of my first assignments was a trip to Cologne, Germany, to take a course in flow cytometry. We had just bought our first flow cytometer then, and I had the honour of being the first to use it. It was quite challenging in the beginning, though, because the technique was new for us and it was up to me to get to grips with it. But the lab has gone from strength to strength: we’re now in the process of purchasing a third cytometer, with even more colour channels, so that we can study more cell subsets.

‘In the years after I graduated, I worked in a number of different roles. It was during that time that I became increasingly drawn to the idea of pursuing my own research career. When I joined CHDR, Matthijs was very encouraging of my plans, and we began to discuss the possibility of me doing a PhD here. There was one problem: since an MSc is normally required before beginning a PhD, I needed a waiver from the Dean. Thanks to a letter of recommendation from Prof. Koos Burggraaf, I eventually received the Dean’s approval to proceed. That’s how, in September 2018, I began my research in the BioTherapeutics lab led by Prof. Johan Kuiper at LACDR. I’m working with a mouse model to study the role of B cells in atherosclerosis, and the plan is to study the same phenomena in both mice and humans.’

At CHDR, Grievink will be examining immune cells in peripheral blood and adipose tissue, comparing healthy volunteers from younger and older age groups, smokers from younger and older age groups, and patients with coronary heart disease. ‘This first part is an observational study, which repeats and extends what has been done in previous research. By comparing these five subject groups, we can distinguish between normal ageing and pathological changes due to atherosclerosis. The smokers are included in the study because they are already at risk of developing atherosclerosis, but they don’t get all the

medication that patients with coronary heart disease receive.’ The next step will be to design and perform an intervention study, based on the results of the animal research and the observational study. Grievink: ‘It’s exciting to be part of a collaboration between LACDR and CHDR, going back and forth between basic research and clinical applications. This translational research is important for CHDR, since it drives the development of new bioanalytical methodology for a cell-based characterisation of immune responses. Such techniques can be implemented in our future clinical studies.’

Grievink will be balancing her PhD research with her regular work as Bioanalytical Scientist. ‘Depending on what studies are going on, either my focus will be on my responsibilities in the lab, or I’ll be able to devote more time to doing my own research.’ She is glad to have found such an opportunity to develop both academically and professionally – especially given the route she has taken to arrive at this point. ‘When I was in high school, I barely even knew what a PhD was, and I didn’t know anyone who was a scientist. Then, while training as a lab technician, I almost quit – I did an internship in a large clinical chemistry lab in a hospital, and the pace and repetitiveness of the work didn’t suit me at all.’ Things changed when she found an internship in a research lab, and discovered her affinity for this kind of work. ‘Now, at CHDR, I get to be involved in cutting-edge science – and I can even combine it with working towards my own PhD.’

‘Thanks to the collaboration between CHDR and the Leiden Academic Centre for Drug Research, I get to be involved in both basic research and clinical applications.’



Working with CHDR

‘The relationship has worked very well’

‘I’m very happy with the CHDR team. The contact structure worked very well for me. The project leader is very responsive and has done an excellent job managing our studies. I feel connected to CHDR on a personal level, and I trust their clinical and scientific judgment very much. Even with the nine-hour time difference between the Netherlands and California, the relationship has worked very well.’

Medical Expert, Biotech Company*

**The views expressed here are the sole opinion of CHDR’s sponsors.*





Tech and InnoS



Prof. Adam Cohen, Director of CHDR InnoS

State-of-the-art technology meets professional development

A growing number of experts from universities and hospitals across the globe are joining the network of CHDR InnoS™, CHDR's consultancy department for innovation services. Their aim: to support decision-making across the industry, from large organisations to small biotech start-ups. Meanwhile, enthusiastic scientists and technicians in CHDR's Technology group are laying the foundations for radical future innovations in research.

‘In the past year, I have gained a whole new perspective on the organisation I had been leading for the previous 30 years,’ says Prof. Adam Cohen, CHDR's former CEO, who currently leads InnoS (Innovation Services) and the Technology group. ‘And I can tell you, it's been a very interesting and sometimes humbling experience. I may be one of the most experienced members

of the organisation, but I'm also a newcomer in my current role. Over the past year, I've been inspired by discussions with a range of people, from ambitious young scientists to my colleagues at the helm of the organisation. When I ask people about their activities over the last few years, and what they see as their main needs for development and skills going forward, the theme that emerges time and time again is technology. More than ever before, professionals need good tools if they are to develop their skills.’

Into the cloud

Transitioning to cloud-based computing is one of the necessary technological developments afoot at CHDR. In the past, a localised IT infrastructure was a good fit for the organisation. All studies were performed at the Clinical Research Unit, and almost all the data were generated, stored and analysed within the walls of the building. However, this situation has already begun to change and will continue to do so in the near future. The innovative Trial@home approach means that an increasing amount of data is being generated off-site by subjects who automatically upload gigabytes of data from their mobile phones, augmented by the use of wearables and other devices. This approach, along with other new data-rich technologies, means that the volume of data that CHDR systems need to handle is expanding dramatically.

InnoS, too, will benefit from a different approach to data – especially data sharing. Cohen: ‘The information that clients provide us with is largely confidential. We need an IT infrastructure that enables us to safely store this information and to easily share it with trusted experts for as long as the consultancy relationship lasts. Where consultancy is concerned, flexibility and agility are also paramount. When you do a clinical study that takes a year, a few days extra to prepare a report isn’t such a problem. In consultancy, however, the whole process may take no more than two weeks from start to finish: in that context, a delay of a few days is a real pain.’

Effective communication

‘Professional development is one of the core values of CHDR, and communication with others is essential for developing professional skills,’ says Cohen. ‘We need to facilitate interaction on many levels, looking both at the tools we use to communicate and at the way we approach our work.’ Besides modernising internal communication and collaboration by moving away from email to apps such as Slack and Microsoft Teams, CHDR has invested in improving another major aspect of scientific professional development: the process of writing scientific papers. Cohen: ‘You know how it goes in scientific institutions, and we were no exception. A young scientist first gathers a lot of data, and then sits at their desk to write it all down. Most people don’t know how to proceed, so they end up procrastinating in all kinds of ways, and a month later, there’s still no draft. After a serious conversation with the thesis adviser, the poor scientist gets down to work. Another month passes and finally a draft materialises. But the adviser and other reviewers are really busy, so it’ll be another month before they look at the draft. And then they

conclude that it needs major restructuring. Need I go on? We decided that this process could be made far more efficient. To start with, we changed the sequence. Instead of first doing all the research and then writing it down, we work towards what we call “concurrent design”: envisaging what you will write while you’re collecting your data.’

Another facet of this new approach is the introduction of ‘design meetings’, in which science writer Karin Broekhuizen gathers researchers and advisers around a whiteboard to first design a general outline of a new publication. Based on this, a researcher can use their time more effectively to fill in the outline and come up with a draft much sooner. The advisers, who were involved in designing the outline, know what to look for and how best to contribute. Cohen: ‘We are already seeing more papers being produced, and we have only just started with this new approach.’ To further stimulate professional development and scientific output, staff members can set aside one fifth of their time to work on publications. This means that people who work full time can devote a whole day each week to writing papers and articles.

The rise of technology

Just a few years ago, no one would have associated drug development with fields like artificial intelligence, data science, or mobile technology. Nowadays, however, CHDR is investing in just such fields, alongside technological innovations such as transcranial magnetic stimulation electroencephalography (TMS-EEG), which is currently being explored by the Technology group. Cohen: ‘Facilitating a growing team of brilliant, motivated people from many different backgrounds is an inspiring experience. Together, we can come up with

solutions for a whole host of challenges in our current and future drug development programmes. One of the areas I find most exciting is remote monitoring, using mobile phones and wearables, and the new possibilities it brings. MORE, our remote monitoring platform, is now fully operational. It’s currently being tested in a children’s hospital, to explore the possibility of monitoring the recovery of children after surgery and other interventions. We are also planning to test the feasibility of using this platform to monitor patients with depression, objectively measuring their behaviour and regularly asking them about their wellbeing. In short, we are gearing ourselves up for the next step in gathering naturalistic data from study participants as they go about their daily lives, a trend which I’m convinced will revolutionise clinical trials. And of course, at the same time, we are educating pharmacologists and other scientists in the use of these new technologies, so that they too are ready for what the future has to offer.’

CHDR InnoS™

‘The development of the InnoS consultancy is progressing well,’ says Cohen. ‘We have been busy planning and building our team. The first 10 consultants have signed their contracts and we are expanding our base. We are set to grow over the course of 2019, becoming fully operational in 2020.’ Like all CHDR departments, InnoS works for clients worldwide, and draws on the expertise of medical and pharmacological specialists from across the globe. Cohen: ‘Our main contribution will be to connect people. Experts from different fields, or from different institutions, rarely communicate with each other. They are keenly focused on the work of their own departments – after all, that’s what makes them such good experts to begin with. Our position as outsiders means that we can easily

connect people, because we’re not affiliated with one specific institution. Moreover, we have a broad network to draw on. Traditionally, the pharmaceutical industry has tended to rely on a handful of experts who are highly visible within their fields. There’s no doubt that their expertise is valuable, but it’s still dangerous for a whole industry to rely on just one or two experts in a given area. There’s the potential for one person’s error of judgement to propagate through the industry without being challenged. Our mission is to add a wider range of expert voices to ongoing discussions about drug development. With three decades’ experience connecting with people across the industry, we’re in a key position to make this happen.’ Cohen has no doubt that there is a growing need for the kind of consultancy he and his colleagues have to offer. In addition to the ever-present demand for consulting services among large pharmaceutical companies, there’s a growing number of biotech firms and other start-ups whose contributions to medical innovation will only increase in the coming decades. Cohen: ‘We’re even seeing it on our doorstep. Not so long ago, everyone was saying that the Netherlands no longer contributed to medical innovation. Today, I can see many start-up firms from the windows of our own building. Medical science in the Netherlands has always been strong, and now all this knowledge is coming to the market. Of course, not every idea becomes a product and not every start-up has what it takes to be successful. Often it’s the investors who call in our expertise to assess the potential of a new company.

‘As we look forward to 2019, the coming year will see the European Medicines Agency headquarters relocate to Amsterdam, which is just half an hour by train from here. As they settle in to their new home, CHDR InnoS will be on hand to contribute to their work and to facilitate innovative drug development.’



Ghobad Maleki, Clinical Scientist and **Dr Matthijs Kruizinga**, Research Physician

‘The MORE platform can facilitate better paediatric studies and even improve care’

‘Our work represents a major step in the development of the MORE remote monitoring platform,’ says Ghobad Maleki. MORE, CHDR’s platform for collecting naturalistic data from subjects as they go about their daily lives, is his focus within the Method Development group. Dr Matthijs Kruizinga, his colleague, spends most of his time at the Juliana Children’s Hospital in The Hague, using remote monitoring technology and the MORE platform to gather data on the behaviour of children with various medical conditions, as well as healthy children.

‘My current studies are part of a larger PhD project about the use of non-invasive measurements in children,’ says Kruizinga. ‘A major challenge when doing clinical studies in children is minimising the added burden of the study. A medical ethics committee won’t allow you to perform invasive measurements unless it’s necessary for diagnostic purposes – in other words, unless the child directly benefits. On the other hand, clinical studies are essential for evidence-based paediatric care. That’s why we need to develop procedures that make it very easy for children and their parents to participate in clinical studies.’

Kruizinga and Maleki are collaborating on a large study, which will involve 270 paediatric patients and 150 healthy children, of various ages. Their main goal is to help validate the MORE platform, by assessing its capabilities for measuring health-related parameters in children. Paediatricians at the Children’s Hospital help to enrol patients suffering from asthma, obesity, fatigue or sickle-cell anaemia. Kruizinga: ‘These are all chronic conditions, with a variable impact on the health and activities of children. Until now, we’ve had no way to objectively monitor their health on a day-to-day basis. We’re asking these children to wear a smartwatch, which is able to register their heartbeat and their movements and allows us to see when the child sleeps. Additionally, using peripheral devices, parents will be asked to measure their child’s blood pressure and do a full pulmonary function test every day, as well as weighing the child every week. To validate our measurements, the parents are also asked to keep a diary about the health of their child.’

Children who enrol in this study participate for a month. Once children and their parents have agreed to participate, Kruizinga or his colleague Esmeessers (a Bio-Pharmaceutical Sciences master’s intern at CHDR) visit them at their home to instruct them

how to use the equipment. ‘Parents appreciate the fact that we visit them at home. I think that sparing them unnecessary visits to the hospital aligns with our overall philosophy of minimising the burden for children and their parents,’ says Kruizinga. In a related study, Kruizinga is also investigating the recovery of children who are hospitalised with pulmonary complaints such as asthma or pneumonia. In that study, measurements start while the child is still at the hospital, and continue for at least two weeks at home until the child has fully recovered.

‘We’re excited about the possibilities that remote monitoring will bring to both research and clinical practice.’

The data yielded by these studies – that is, the data from all the remote devices, along with the parent diaries – are collected by means of regular upload via the MORE platform. ‘In this study, MORE basically functions as a data hub which allows us to integrate naturalistic data from a range of sources and devices,’ Maleki explains. ‘Most of the data are collected using commercially-available apps and devices. MORE ensures that all the data are entered smoothly into our clinical database. In other studies using MORE, such as a study with adult depression patients and a clinical study in neurology that we’re setting up right now, the platform will serve other purposes. For example, we can

use MORE to monitor the patient’s social activity and movements based on phone usage and GPS.’

Maleki has been involved in the development and validation phase of MORE, and he hopes to eventually write a PhD thesis about remote monitoring – but first, he has to complete his medical training. ‘I came here two years ago during my medical studies to do an internship. I liked it so much that I decided to stay on here as an employee. In October 2019, I’ll start with the last phase of my medical studies, doing my rotations in the hospital. My plans for the future? I want to be a neurosurgeon. So, for the final stage of my PhD thesis, I’m really keen to do one or two studies investigating how remote monitoring could be used in neurosurgery.’ For Kruizinga, his current work is also an important stepping stone towards realising his ambitions. ‘I want to be a paediatrician. Just like in neurosurgery, only a very limited number of residents are allowed to start every year. That’s why I grabbed the opportunity when I heard about this project at CHDR, which will allow me to write a PhD thesis in the field of paediatrics. I hope that will help me on the path to becoming a paediatrician. I look forward to the possibility of using remote monitoring to better care for my patients. For every doctor, it’s a challenge to understand what happens at home, between visits to the outpatient clinic. For a paediatrician, there’s an extra layer of difficulty, because you have to largely rely on the observations of parents. I think, for children as well as adult patients, remote monitoring could contribute to better care.’





Operations



Giel Borsboom, Planning Officer

‘Good planning is about effective communication’

In 2018, CHDR completed 52 studies. ‘To manage all our resources and make sure that everything runs smoothly, we obviously need quite a sophisticated approach to planning,’ says Giel Borsboom, CHDR’s Planning Officer. ‘We start months in advance, knowing that we will have to change about two thirds of our initial planning in the course of time. There are always unforeseen developments – for example, due to external circumstances such as a delay in the delivery of test medicines, or because unexpected results require us to pause a study. Other times, it’s simply delays that arise in the long chain of events from planning to concluding a study. It’s important that project leaders, senior staff members and others keep me in the loop about anything that could affect the planning: I can only be as good as the input I get! Now that I’ve been working here for over a year, I know people well. That makes my work easier, because I know what to expect from my colleagues, and when I need to give that extra nudge to keep things progressing smoothly.’

Borsboom joined the organisation in 2017, and his enthusiasm shows that he still enjoys his job as much as he did back then. ‘I’m the first dedicated planning officer that CHDR has had. Before I came here, the planning was managed by Emilie Jonxis, who leads the Clinical Research Unit, and Peter Schouten, our Logistics and Training Officer. The planning software that we currently use was implemented shortly before I joined. It has taken some time to adapt the software package to the specific needs of the organisation, and there are still many items on our wish list. Nonetheless, it does give me a handle on all the different components

that need to be managed. For example, we can see if a CNS study needs NeuroCart or PainCart, if there are subjects staying overnight in the unit, what moment of the day a certain dose will be administered, and so forth. Thanks to the clear visual overview the software gives us, we can keep tabs on all the facilities. For example, we can see at a glance if there are any NeuroCarts available next month.’

In an organisation full of pharmacological, medical and healthcare specialists, Borsboom is an exception: ‘I studied Public Administration at Leiden University, before doing my master’s in Organisational Anthropology at the Free University in Amsterdam. It’s a fascinating subject – you learn all about company cultures, including the stories and symbols that give meaning to organisations and their constituent parts. This background gives me a special kind of insight into how CHDR functions as an organisation, and the contributions that all the different groups make to the whole.’ In his role as Planning Officer, Borsboom can also draw on his experience working for a national supermarket chain, where he was responsible for inventory management and personnel planning. ‘Of course, CHDR was a whole new level of complexity, especially considering the additional time I needed to learn all the technical terms and to get a feeling for the research that’s done here. Now I have the experience to be able to support staff in their planning and to understand what they need in terms of equipment and personnel.

‘The great thing about my work is the variety. Some days, I’m working flat out just to get the planning right. Other days, I have the flexibility for extra tasks, such as advising members of staff, or working on side projects together with Emilie, my manager. We are also in the process of adapting the way we use our software. For example, the screening unit still uses a separate system for planning, so I’m working on trying to integrate their planning with ours to form one overall system. Another interesting project was a study involving Huntington’s Disease patients: the study participants needed to be visited at home, and I was tasked with helping to plan all those home visits.’

Borsboom works part time, taking one day a week to work on his own company, doing audio production and creating music. ‘At CHDR, I have even been able to offer my services as a musician: I composed the music for the company video. Maybe in the future, there’ll be another role for me, as an organisational anthropologist. In such a dynamic environment, you never know what opportunities lie around the corner.’

‘In such a dynamic environment, you never know what opportunities lie around the corner.’





Herbert Anholts, Head of Recruitment

‘With the right strategies, we can recruit participants of all ages and backgrounds’

CHDR already has contact with thousands of people who are willing to participate in drug trials, but Herbert Anholts and his team are always on the lookout for more potential subjects. ‘Recruitment can easily become a bottleneck in the progress of a study, so we work hard to try and make sure that we can deliver. In 2018, we planned and launched a nationwide billboard campaign featuring a positive, science-oriented message. We’re inviting people to join us on a scientific journey.’ In addition to advertisements in traditional media, the recruitment department also has a strong presence on social media. ‘Lisette Mastenbroek, one of our senior recruiters, works full time managing our social media presence. Social media can be instrumental in reaching specific groups, such as asthma patients or people with depression. Increasingly, we also try to monitor the response to the different approaches. For example, we have done billboard campaigns both with and without an accompanying social media campaign, in order to be able to get an idea of the differential effects that the two methods have.’

With the organisation growing as a whole, the recruitment department has expanded too. Anholts: ‘I’ve been working here for almost 13 years now. Back when I started, it was just me and Flora van Veen. She is still with us now, as one of our team of six senior recruiters. A lot of the legwork – such as contacting lists of potential subjects by phone – is done by our

junior recruiters, who are usually students who come to work here on a temporary basis.’ Anholts clearly is proud of his team and their spirit. ‘Most of our senior recruiters originally came here looking for temporary work, but liked it so much that they stayed on. The main quality I look for in a recruiter is their dedication to the work. And when a team is dedicated, it’s fun to work together.’

The recruitment team spans a range of educational backgrounds, with a leaning towards the humanities and social sciences. Anholts himself studied communication science, while Flora van Veen originally trained to be a physical therapist. Lisette Mastenbroek studied economics, management and law. The other senior recruiters are Kimberley Boender, a human resource manager by training, Laura van der Togt, a philosopher with an MA in political science, and Ruben Groenendijk, an ex-soldier who is currently concluding his degree in psychology, writing a thesis about senior participants in clinical studies with Anholts as his supervisor.

The variety of clinical studies conducted at CHDR calls for a flexible approach to recruitment. ‘If it’s healthy volunteers we need, our recruiters can do everything themselves. If we need patients for a specific study, it depends: we’re not medically trained, so we’re not allowed to ask medical questions. But on the other

hand, you don't want people to go to all the trouble of visiting the screening facility for nothing. Our approach is to be very clear about the exclusion criteria. For example, we can already let people know that they won't be able to participate if they've had a previous diagnosis of cancer, or if they have a history of heart problems. If we do need specific medical information from a patient or a healthy volunteer, we arrange for them to have a second phone call with the study physician.'

Anholts is especially proud of the successful efforts of his department to recruit healthy volunteers from older age groups. 'We have contact details for about 2,500 people between 65 and 75 years old who are not on any medication. In my experience, these older participants are a pleasure to work with: on the whole they are friendly, polite, and punctual. They rarely fail to show up – if they're unable to attend, they make sure to give us a call. Some of the people in our database even call me now and then to check whether there are any studies they can participate in.'

This large cohort of healthy older people has been recruited partly by means of a social programme. Every Wednesday morning, CHDR organises a free boat trip through the canals of Leiden for senior citizens. 'It's been a huge success,' says Anholts. 'People enjoy it so much that we continue the programme even when we have enough subjects: it helps us maintain contact with potential participants and spreads a positive message about what we do. We don't bore our guests with lectures or anything like that, though. We just give a short introductory talk and provide them with our contact details. It may seem like a big investment, but in

fact it costs far less than a page in a national newspaper. Not to mention that the return on the investment is far better – and it's fun, too. The personal touch means we also have a much better chance of expanding our network to recruit specific elderly populations, such as individuals with Alzheimer's disease.'

'Through our social programme, we can maintain contact with potential participants and spread a positive message about what we do.'

One of the major achievements of 2018 was the recruitment of 3,500 patients with Parkinson's disease to submit saliva samples for DNA testing (see also [pages 23](#) and [27](#)). Anholts: 'The project leader, Jonas den Heijer, was quite confident that by contacting neurologists we would be able to find enough patients. I almost laughed – I told him I'd heard that story before, and that for recruitment on that scale we would need to start a social media campaign. But it turned out Jonas was right: thanks to the collaboration of neurology departments across the country, thousands of patients were found, many of them willing to send in a saliva sample.'

In fact, the success of this initial approach was where the real work for Anholts and his team began: 'The patients received a letter from their neurologist, informing them about our study, and asking them to phone us. When 1,600 letters went out in a single day, our switchboard almost had a meltdown! After that, we asked our partners to send the invitations in batches of about a hundred letters at a time. Even then, it was quite a job to inform all the participants, and then to send out thousands of envelopes each containing a saliva sampling kit.' These samples were screened for a specific genetic mutation, to identify subjects for the next part of the study. Anholts: 'To our surprise, nearly everyone with the mutation was willing to participate in the next stage. What I learned from that trial was that people are much more willing to continue participating in research when they've already made an initial step, such as sending in a saliva sample. It's thanks to challenging projects like this that we are able to continually refine and improve our strategies for recruitment.'





Raymond van Teijlingen, QA & ICT Validation Specialist and Margreet Rienstra, QA Manager

‘A thoroughly validated ICT system benefits everybody’

‘ICT is part of everything we do these days,’ says Margreet Rienstra, who has been running the QA department for over 12 years. ‘Back when I worked here as a nurse, we wrote the data on paper forms, which were then entered into our Promasys clinical database by typists. Nowadays, the nurses all work with iPads and everything is uploaded automatically.’ Advances in information technology have brought huge benefits, but the more dependent we become on these systems, the more vital it is to ensure that the systems are valid, reliable, and secure.

‘I was hired as a dedicated QA ICT validation specialist in 2018,’ says Raymond van Teijlingen. ‘Part of my work involves validating existing systems, but I’m also called on to advise on upgrades and changes to the system. I am also tasked with making contingency plans, should things go wrong. Part of the QA puzzle is simply raising awareness among the people using the system. Whenever a new application or piece of software is introduced, people should be automatically asking themselves: “Has it been validated for the purposes I’ll be using it for? And if someone wants to know how it was validated, can we show the documentation?” After all, nobody wants to do a study and then discover that their results are worthless because an application may have corrupted the data.’

‘I’m really glad Raymond has joined our team,’ says Rienstra. ‘I used to do system validation alongside my other QA work, collaborating with other departments to validate the most important systems, such as Promasys. But this part of the job has grown in importance, even more so now that we are transitioning part of our ICT infrastructure to the cloud. This is the ideal moment to review and improve our approach to system validation. When setting up a new system, a thorough validation procedure can be executed from the start. It’s much harder to do it when everything is up and running.’ Van Teijlingen: ‘A transition also offers new opportunities to straighten things out and redesign the whole information flow in a more rational way. Systems grow organically, with patches being used to fix problems, rather than structural solutions. A system transition is like moving house: a golden opportunity to have a good clear-out and a tidy-up. I’m also on board to help make sure that the systems we design now are sustainable for the years to come.’

A cloud-based ICT infrastructure offers new tools and opportunities to get a clearer insight into day-to-day operations and to design new ways of communicating, both internally and externally. ‘Last year, we had a remote audit by a sponsor. Since the auditor couldn’t visit our facility in person, we provided her with all the information digitally, by sending huge batches of pdf files,’ says Rienstra. ‘It worked, but it required quite a

bit of effort. In the future, it will be possible to share the necessary files with just a few clicks of the mouse. And the recipient will only be able to read them as long as they need them, so that no sensitive information remains on their systems.’ Van Teijlingen: ‘Contrary to what some people think, cloud-based ICT actually offers more possibilities for ensuring privacy and confidentiality of data.’

Van Teijlingen can easily appreciate things from a sponsor’s perspective, thanks to his 18 years of experience working in the laboratory of a pharmaceutical company. ‘I’m a bioanalytical scientist. In the lab where I worked I had several tasks, including setting up very sensitive measurements of compounds using liquid chromatography mass spectrometry (LC-MS). My work then had many connections to early clinical drug development, so I’m familiar with most of the terms and methods that are used at CHDR. During that time, I became increasingly involved in validating ICT systems. I ended up being the administrator of the laboratory information management system (LIMS). That experience is certainly useful now, as we are implementing our LIMS here at CHDR.’

Rienstra’s history at CHDR goes back to 1998, when she joined the Clinical Research Unit (CRU) as a nurse. ‘I was familiar with the routine at the hospital, and I wanted something different. The organisation was on a much smaller scale back then. Many more of the tasks were done at the CRU, including the screening and planning of subjects. If things weren’t too busy, we also helped out with data entry. I did some additional training to become a research coordinator, and was then offered the opportunity to become a data manager.

After a while, I wanted to explore new opportunities, so I took a job as a research coordinator at a university medical centre. Two years into that role, I was offered the opportunity to return to CHDR. Ria Kroon, then responsible for Quality Assurance, had been promoted to head of operations, and I was invited to take over her QA role. And that’s what I’ve been doing since 2006. In 2015, I was joined by my colleague Tanja Grobben, followed by Raymond in 2018. That’s what’s exciting about working at CHDR: things are always changing. Sometimes it’s the world around us that requires us to adapt, sometimes we initiate the change ourselves. But as long as there is change, there will be opportunities to refresh and improve both our systems and our work.’

‘Cloud-based ICT provides new tools and opportunities. Contrary to what people think, it also offers better possibilities for ensuring confidentiality of data.’





Dr Afke Mevius, Screening Unit Team Leader



Emilie Jonxis, Clinical Unit Manager

‘The new location is ideal, both for our participants and our team’

An average of 65 potential study subjects are screened each week at CHDR, most of them healthy volunteers. In March 2018, the Screening Unit moved out of the main facility to a new location close by Leiden’s central train station. Emilie Jonxis, Manager of the Clinical Research Unit and Dr Afke Mevius, Screening Physician and Team Leader, reflect on the move and the benefits it has brought to their work.

‘For us, this is the perfect location,’ says Mevius. ‘We now have a dedicated office space, and everything here is focused on optimising the screening process. The team as a whole has really benefited from the move. We may be in a separate building, but we’re still very much part of CHDR. All screening physicians visit the main unit on a regular basis as part of their recruitment duties. Our medical assistants also go back and forth regularly between the two locations – they handle almost all of the transportation between the units, and help out at the Clinical Research Unit when needed.’

When the decision was taken in 2017 to relocate the Screening Unit, Jonxis, who is in charge of both the Clinical Research Unit and the Screening Unit, began scouting for a location. From a number of possible locations in the vicinity, one emerged as the most suitable: located right next to the central bus and rail stations and a large parking garage, it is also a stone’s throw from both CHDR’s main facility and the Leiden University Medical Center.

‘It was a very dynamic, interesting time,’ Jonxis says, reflecting on the transition. ‘Luckily, we were able to call on the same architects who designed our main building, CEPEZED. Thomas, their building coordinator, played a key role in the success of the renovations. We even managed to stay within budget. But of course, there are always unforeseen hitches in a project like this. One of the hurdles we faced was getting our data connection in place. We required a direct fibre-optic cable connection with the main facility, to ensure smooth and secure data transfer. It took ages to get all the necessary permits, and then we ended up having to wait even longer due to winter frost. Luckily, the thaw came just in time.’ Mevius: ‘After all that, the move itself took only one day. We packed our things on the Friday and were already screening people at the new location the following week.’

On a tour through the new unit, Jonxis and Mevius point out the consultation rooms, the rooms for taking ECGs and collecting blood, a small laboratory with a centrifuge for the preparation of blood and urine samples, and rooms containing NeuroCarts, PainCarts, and even a Green Dino driving simulator. Subjects can also be trained or pre-tested at this facility, which is sometimes crucial for selecting the right participants for a study. Mevius: ‘Especially for the PainCart, we have to test people beforehand. In all the pain models we use, we’ve defined a maximum, a cut-off point, to eliminate the risk of physical damage. If a subject’s

pain threshold is higher than 80% of our cut-off, they can't participate in the trial because of ceiling effects. Unfortunately, many people who sign up for pain research seem to see it as an opportunity to prove themselves. We regularly have to send away more than half of our potential subjects just because they want to show how much pain they can take!

In addition to all the spaces devoted to screening and testing, there's also a larger room used for participant information meetings. Jonxis: 'In all studies with patients, it's the project leader who provides subjects with information about the study. For studies in healthy volunteers, it's the screening physicians who inform the potential participants.' Recently, the tasks of screening physicians have been expanded, to bring more challenges and variety to their work. Mevius: 'When you're just screening volunteers, you see up to 12 people per day. If you have to do that every day, it becomes tedious – asking the same questions, making the same joke every time. Nowadays, we do much more, including reviewing all the lab results and actually deciding who will be included and who won't. In short, we take care of everything that's needed to get a healthy volunteer ready to begin a study. The job is much more interesting as a result, and it pays off: people who come to work here tend to stay on for longer. Most of our screening physicians are young doctors who come here while waiting to be able to start their residency. Once they're here, they find that the job is more than just a stepping stone – it's a positive experience that they want to make the most of. This benefits us too: the longer people stay, the more expert they become in their work.'

Mevius first started working at CHDR in 2003, when she was still a medical student. 'I worked as a research assistant, operating the NeuroCart and PainCart. In those days the organisation was much smaller, so I was called on to do all kinds of additional tasks. I even worked on the reception when the regular receptionist was on vacation!' After finishing medical school she worked in several roles, including another year at CHDR as a screening physician in 2011, followed by a period living in the UK. 'I took on my current role in 2014, after being convinced by my old boss, Esther Davidse, to come back to CHDR. I still enjoy working here, especially being part of such a great team. There are always chances to develop and take on new challenges, so staying here never means standing still.'

'Our screening physicians now have more varied and rewarding roles. It benefits us too, as they remain with us for longer.'

'I was 60 years old when I came to work here,' says Jonxis. 'I used to work as a nurse practitioner at a hospital here in Leiden, and I initially applied for a similar job at CHDR. But the organisation was growing fast, and I was invited to take on the role of managing the Clinical Research Unit – a role which now also encompasses the Screening Unit. It was quite a challenge to transition from working in individual

patient care to a managing role. But I've always been glad that I took the leap: it's a great job, and I'm involved in a wide range of different duties, from picking out uniforms to managing staff matters. Last year, with the relocation of the Screening Unit, was a particular highlight. I'm really proud of what we've accomplished, and we had so much fun in the process, too.' You only have to walk around the new unit, with its welcoming atmosphere and state-of-the-art facilities, to see what a positive move it has been.





Education



Dr Jeroen van Smeden, Education Director

Connecting through education

Making connections is a key theme driving CHDR's educational activities. CHDR staff teach in a range of educational settings, putting them at the heart of a thriving academic network. Students learn to connect theory and practice, while CHDR's project leaders draw on their practical experiences to feed back into the learning environment. Meanwhile, the development of modern and innovative teaching approaches allows experts to connect more effectively with a wider audience.

'I've been coordinating CHDR's education activities for one and a half years now, and it's a role that just keeps on getting more interesting,' says Dr Jeroen van Smeden, Education Director. 'I love teaching. It's so direct. Every hour you spend in front of a class, you're impacting on the future development of many people. Writing scientific articles requires hours of effort for a single manuscript, but one hour in a

classroom can benefit literally hundreds of students.' Van Smeden's enthusiasm is contagious, and people at all levels of CHDR share his passion for education. CHDR staff regularly teach bachelor's and master's students at Leiden University, the Leiden University Medical Center (LUMC) and the Leiden University for Applied Sciences. They also participate in providing postgraduate training, for example in collaboration with the Paul Janssen Futurelab Leiden, teaching the biotech entrepreneurs of the future how to run an innovative company. Students from a range of disciplines come to CHDR to undertake internships and traineeships. Almost all of CHDR's project leaders complete a PhD thesis during their time here, with most of them becoming clinical pharmacologists as well.

Learning from each other

Every Thursday lunchtime, the auditorium at CHDR is buzzing with project leaders, senior scientists, interns and other staff members, gathered for a meeting that's dedicated to education in clinical pharmacology. 'We call it the education hour,' says Van Smeden, 'and it's a way for project leaders to be able to contribute to our educational activities. Take, for example, a project leader who has been advising clinicians about the best medication for an elderly patient with many comorbidities, as part of their clinical pharmacology training. From this, they can come up with a case study for a student discussion group on geriatric care. At CHDR we believe that teaching and learning should feed into one another as much as

possible: if you want to find out if you really understand something, try explaining it to someone else! A positive by-product of this is that developing the skill of communicating complex ideas also leads to more successful teamwork.'

The education hour is designed to be interactive, with the idea that everyone, including the project leaders themselves, should gain something from the experience. Instead of just presenting a case to their peers every once in a while, project leaders are invited to be actively involved in every meeting. Van Smeden: 'Every project leader has a slightly different background, so each individual has something unique to bring to the table. These meetings are lively and illuminating for everyone who joins.'

Cultivating experts

Pharmacology is a key component in the education of medical students and other future clinical professionals. Through university teaching, CHDR plays a crucial role in educating students about the basics of pharmacology, such as pharmacokinetics and pharmacodynamics. Additionally, in courses on specific subjects such as inflammation or cardiovascular diseases, CHDR staff are on hand to teach the pharmacology of the specific drugs used in that field. 'We see our educational role as key to our mission to improve pharmacology and drug development in general,' says Van Smeden. 'Of course, we have a reciprocal relationship with the departments we collaborate with. Many of the LUMC teachers are doctors themselves, who are experts in their respective fields. They in turn help us to keep our materials up to date. Naturally, all of this is of great benefit to our students.'

That the students appreciate the educational efforts of CHDR is clear from the positive evaluations they give. Van Smeden: 'Every year, the medical students go on an excursion to a company or institution. This year, they opted to visit CHDR. That was a great compliment: it shows that they're interested in our work and are curious to go beyond what we've discussed in the classroom.'

Updating the TRC

CHDR's educational impact is not limited to students in Leiden. Across the globe, hundreds of thousands of students and residents have been benefiting from CHDR's Teaching Resource Centre (TRC) online platform for learning pharmacology and applying it in clinical practice. Since its introduction in the 1990s, the TRC has been updated regularly. However, it is now time for it to be rebuilt, to meet the standards and demands of the 21st century.

'TRC in its current form is still essentially a book that has been adapted to the digital environment,' says Van Smeden. 'We are now developing a more dynamic, interactive resource that is visually attractive and offers more possibilities for educating students at different levels. Teachers will be able to use the resource to identify materials appropriate to the course level, so that students can study in preparation for class. This approach also ties in with our teaching philosophy: students are required to take an active role in their own education, instead of being passive consumers of knowledge. If students come to the classroom with enough basic knowledge to participate in an intelligent discussion with the teacher, the experience is far more valuable for them.' To learn more about the redesign

of the TRC, see the interview with the design team on [page 128](#).

Engaging with students

One of the courses CHDR has been running for many years is the final course for students in the BSc Bio-Pharmaceutical Sciences at Leiden University. It used to comprise a series of lectures covering the process of drug development, from early preclinical studies to market introduction and pharmacovigilance. Van Smeden and his colleagues are busy rethinking the way this material is presented, to stimulate and engage students right from day one. 'At the beginning of the course, students sign up as if they are participants in a clinical trial. They receive the kind of information that a volunteer would get. Next, we show them a short documentary about the notorious TeGenero trial, in which several subjects experienced severe adverse effects, some of them with lasting consequences. This might seem unsettling, but the intention is to bring home to the students just how critical it is to be alert and to use all the available information from the preclinical phase when designing first-in-human studies.'

Students in this course will be assigned a candidate drug, for which they have to write a protocol for a first-in-human clinical study. To do this, they will use CHDR's IB-Derisk analyser to structure all the information from preclinical trials. The IB-Derisk tool, which was launched in 2017, provides a systematic view of all the available preclinical data, as a way to assess the risks and caveats for the clinical development of a compound. Next, students will role-play reviewing the protocol, taking on the roles of the scientific advisory board and the medical ethics committee. In addition,

students have to perform the health technology analysis (HTA) for the market launch of the drug they were assigned. Over the duration of this eight-week course, the students will therefore experience each step of the drug development process. Van Smeden: 'In the past, we often heard from students that they did not grasp what drug development really involved until after the exam. With this new hands-on approach, they will gain deeper insight much earlier, and at the same time learn the material in a more stimulating, and thus more effective way. Ultimately, they will attain a much higher level of knowledge. The exam will also be tougher, but due to the improved approach, we are confident that we'll see at least as many students successfully completing the course.'

Lifelong learning

This student-centred approach to education, where students are encouraged to take an active role in their learning process, also prepares them for a professional future in which continual development is key. For those who choose careers in (or related to) pharmacology, CHDR provides advanced education in the form of courses within postgraduate programmes, or in collaboration with partners such as the Paul Janssen Futurelab Leiden. And of course, talented individuals who come to work at CHDR will discover many different opportunities to keep learning. Van Smeden: 'It works both ways. By sharing our expertise and experience in the university context, we in turn attract bright, dedicated people with innovative ideas who see CHDR as an opportunity to grow further in their careers. But it doesn't stop there. From talking about drug development to primary school kids, to offering refresher courses for retired clinical pharmacologists, we are passionate about truly lifelong learning.'

‘We put creativity to work to develop innovative teaching resources’



Folkert van Meurs, Graphic Designer (CHDR), **Sanne Fennema**, Graphic Designer, **Dr Saco de Visser**, Head of Education (Paul Janssen Futurelab) and **Thijs van Iersel**, Multimedia Designer (Paul Janssen Futurelab)

In 2018, Paul Janssen Futurelab Leiden and CHDR assembled a creative team to remodel the Teaching Resource Centre (TRC) website, a vital resource in the pharmacology education of students around the world. The website, which started life in the 1990s, is being completely overhauled, making the most of the possibilities offered by modern technology. Members of the project team reflect on their work, and the collaboration with CHDR.

TRC could be said to be CHDR’s gift to pharmacology students and medics across the globe: an estimated more than two hundred thousand of people have accessed TRC via their phones or computers whether to cram for exams or to look up crucial information about medicines for a patient. But the website, originally built in the 1990s, is starting to look a bit dated. ‘I was setting up a course in pharmacology at Paul Janssen Futurelab Leiden, where we teach biomedical scientists how to develop therapies in a business setting,’ says Dr Saco de Visser, who is Head of Education at Paul Janssen Futurelab. ‘I wanted to use the TRC, but it really needed a makeover. I discovered that CHDR were indeed thinking about updating it, and so we decided to collaborate.’

‘I have great respect for the original TRC,’ says independent graphic designer Sanne Fennema, who managed the project. ‘There was so much in it already, and it was really well designed. We kept some of

the original designs, and remade many others.’ The designers’ work included updating 825 illustrations, to present pharmacological concepts in a format that is consistent throughout the resource. Fennema: ‘We soon discovered it was impractical to redesign each illustration in turn. The different parts of the TRC are interrelated, so we needed to adopt an iterative approach to the work. We would redesign a few illustrations, go back to CHDR to review them, implement changes, and later review them again, eventually combining everything into a consistent whole. There were some illustrations that we ended up redesigning three or four times – but, as we kept saying to ourselves, work done twice is still work done! For me, it was an interesting new experience to manage a project like this, collaborating so closely with the client. I’m really proud of what my team achieved in a relatively short period of time.’

‘The original mission of the TRC was to establish a graphic language to discuss pharmacological concepts. We wanted to stay true to that mission, but to do so using a style that would resonate better with a 21st-century audience,’ says Folkert van Meurs, graphic designer and animator at CHDR. ‘This graphic language comprises over 600 different symbols representing all kinds of concepts, ranging from organs to cellular components, from receptors to ligands. These symbols form the building blocks for the illustrations in the TRC.’

An important aspect of the redesign was the transformation of the book-like TRC into a truly interactive digital resource. Thijs van Iersel, Multimedia Designer at Paul Janssen Futurelab Leiden: 'The illustrations in the original were just pictures. Now, as you move over an illustration with the mouse, the symbols are highlighted and their names appear. Clicking on a symbol brings up more extensive information and allows you to see other parts of the TRC featuring that element. The old illustrations were also completely static, meaning that even sequential processes had to be represented as fixed images. Now, we can include animations, meaning that processes can be explained and illustrated with much more clarity.' Another feature that will really bring the TRC up to date is the possibility to embed topics on external websites. 'Educators can now share specific topics from the TRC via their own websites. We hope this will contribute to even more people using the TRC, and lead to a wider uptake of our graphic language for sharing and discussing pharmacological concepts.'

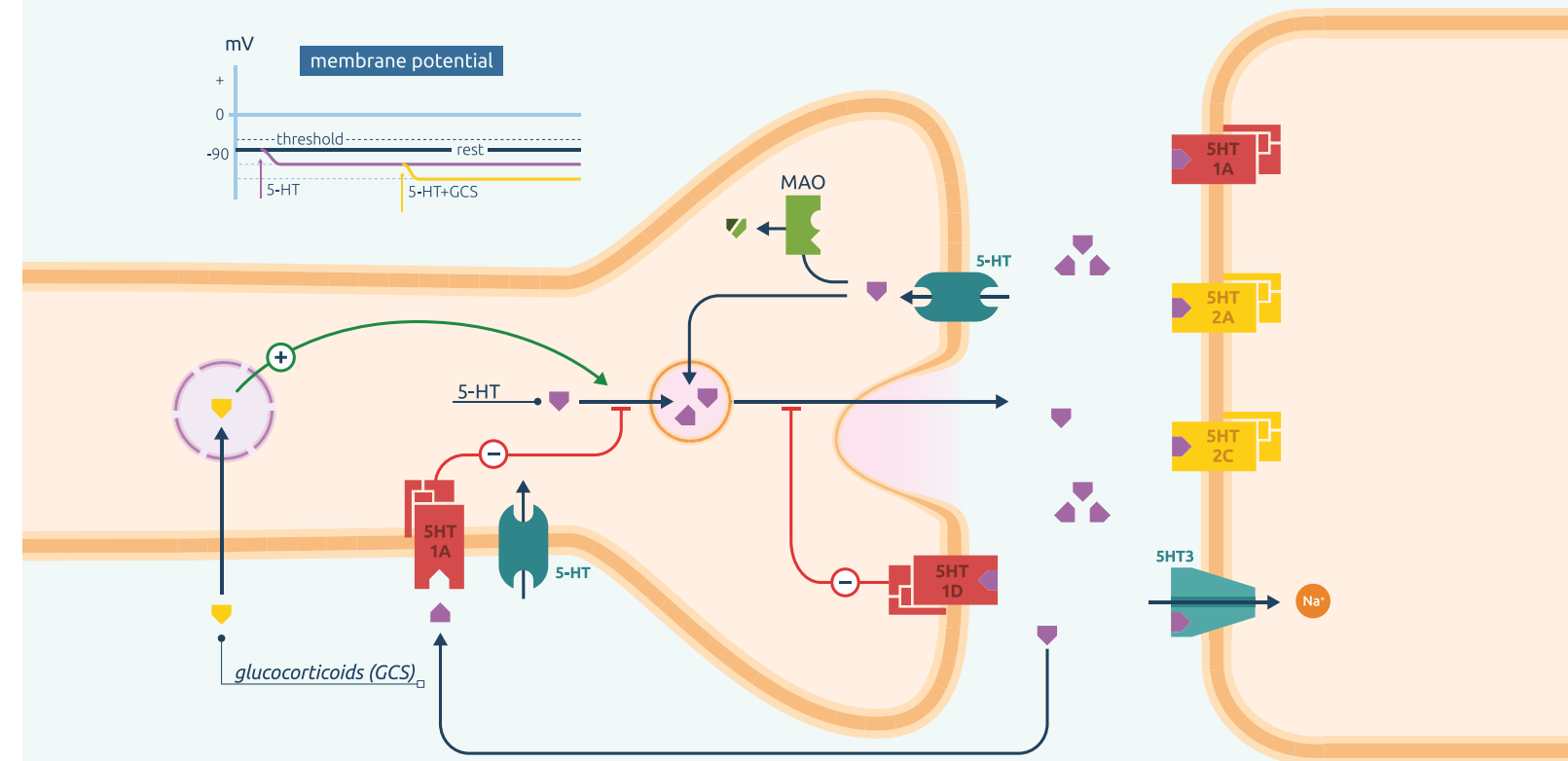
‘The newly-transformed Teaching Resource Centre provides a strong basis for the future.’

At the time of the interview, the team is awaiting a thorough review by about 30 physicians, scientists and educators, who will comb through the new TRC to ensure that the content is correct down to the smallest details. And while the team have completed their mission to remodel and refresh the TRC, this is only the beginning for the newly-renovated resource.

De Visser: 'As new treatments and innovative drugs are constantly under development, a course in pharmacology is never finished. But we have a strong basis now, and we're looking forward to sharing it with the world soon.'

De Visser is one of the founders of the Paul Janssen Futurelab Leiden, where he is Head of Education, developing and teaching courses in clinical development and pharmacology. It was at CHDR that he did his PhD research, developing the concept of question-based drug development (QBD). 'My passion: improving the development of treatments, and the ways that we can deliver them to those who need them.' In line with De Visser's twin affiliations, the design team included members of both CHDR and the Paul Janssen Futurelab, alongside independent graphic designers. Van Meurs was studying animation at Willem de Kooning Academy in Rotterdam when he did an internship at CHDR, which led to his current role: 'It's a lot of fun to put creativity to use in an innovative environment like CHDR, where learning and research feed into one another.' The combination of education and creativity also appeals to Van Iersel, working at the Paul Janssen Futurelab: 'I love the academic environment here, and the chance to use my skills to help create teaching materials that really engage students.' And when developing a resource like this, the learning experience is not only for the end users: 'I knew almost nothing about pharmacology when I started, and it's opened up a whole new world for me,' says Fennema. 'Now, I think I could almost pass an exam in it!'

Serotonin neurons and glucocorticoids



Working with CHDR

‘I can rely on them to provide honest and useful input’

‘What’s really important for me about CHDR is their capacity to think critically. Right from the start of a collaboration, I can rely on them to provide honest and useful input. CHDR stands out from other organisations working in early phase drug development. They aren’t just bringing in volunteers, giving them drugs and drawing blood. They actually engage in depth with the study, thinking about the scientific objectives. Because CHDR is not-for-profit, they can focus on the science, technology and implementation. In the beginning phases of a project we communicate frequently, even across different time zones. That makes you more than a vendor – it makes you a partner.’

VP Clinical Research and Operations, Biotech Company*

*The views expressed here are the sole opinion of CHDR’s sponsors.





Senior scientific staff



Jules Heuberger, Senior Clinical Scientist

‘I hope that doping will one day be investigated with the same rigour as drug development’

‘In 2013, I was an intern at CHDR, during my MSc in Bio-Pharmaceutical Sciences,’ says Jules Heuberger, Senior Clinical Scientist. ‘We were still in the old building and due to the lack of space, there was a separate, temporary building where we interns used to sit. Prof. Adam Cohen, who was then our CEO, used to join us from time to time, looking for a quiet spot to work. One day, he had an interesting question for us. He wanted us to review the literature about doping in sports, especially about the effectiveness of erythropoietin (EPO).’

At that moment in 2013, Heuberger had no idea that this question would eventually be the main theme of his PhD thesis. He went off to the United States to do another internship, graduated, and returned to CHDR as a project leader. ‘My internship here really kindled my interest for the type of work done at CHDR. I like doing scientific research, but I didn’t want to work in a university lab. Here, you’re also dealing with operational challenges, and there is a clear link to social and economic impact. So, I was happy that I was offered a

job here. My work is now primarily in the area of CNS research, especially neurodegenerative disorders.’

At the company’s Christmas celebration in 2014, Cohen told Heuberger that CHDR would sponsor a study on the effects of EPO on the performance of cyclists – and that he wanted Heuberger to be the project leader. Being an avid cyclist himself, Heuberger embarked on the project with great enthusiasm. ‘We approached the study of EPO as we would any other pharmacologically active compound. We did a placebo-controlled study over several months, with regular measurements in the laboratory and performance tests of participants, who were all high-level amateur cyclists.’ The culmination of this study was a Tour-de-France style race to the top of Mont Ventoux in the French Alps. ‘We showed, both in the lab and on Mont Ventoux, that EPO does not make you cycle any faster.

‘It will take some time to convince the people who engage in this kind of doping that it really doesn’t increase your chances of winning. But in any case,

it's about time we took a more rational and transparent approach to doping. By going about things in such a cryptic way, the authorities tasked with eliminating the practice only succeed in adding to its mystique. In addition, doping tests are a methodological minefield. For many tests, the specificity and sensitivity are not even publicly known. Why not investigate doping using the same toolkit that we use to investigate drugs, as we did in this study? By using pharmacological common sense, we can bring a lot more rationality to the table – for authorities and athletes alike.'

Heuberger has almost finished his thesis and hopes to obtain his PhD in 2019. He was already promoted to Senior Clinical Scientist in 2018. 'It's an interesting new challenge, a chance to further develop myself,' he says. 'It helps that I know first-hand how it is to be a project leader – I can easily recognise potential pitfalls and notice when things need my attention. Of course, my new role brings new challenges, such as supporting project leaders without taking over their work. I've learned a lot just through experience already. In 2019, I will follow a management course to further develop my leadership skills.'

'The best aspect of every role I've had at CHDR is the combination of operational challenges with cutting-edge science. I enjoy sitting down with my project leaders to discuss their plans, their PhD theses, their future ambitions. Another high point has been the chance to contribute to CHDR's method development. For example, one of our PhD students, Titia Ruijs, is using transcranial magnetic stimulation in combination with EEG and EMG to study the phenomenon of hyperexcitability, which is prominent in conditions such

as epilepsy and ALS (amyotrophic lateral sclerosis). I've been involved in several ALS studies already, and I find it fascinating to observe her work. Having validated this method, we will use it to study compounds that might be useful in the treatment of ALS and other neurological disorders. That's typically CHDR: always on the lookout for potential biomarkers for early pharmacological effects. There will always be new developments, new challenges, and that's exactly what makes working here so rewarding.'

'By using pharmacological common sense, we can bring a lot more rationality to the table – for doping authorities and athletes alike.'





Dr Ingrid de Visser-Kamerling, Senior Clinical Scientist

‘It’s uplifting to see people growing into their roles’

‘In 2007, I was one of the first three people appointed as Senior Clinical Scientist at CHDR,’ says Dr Ingrid de Visser-Kamerling. ‘Up till then, the three research directors at the time had been directly responsible for the project leaders. But as the organisation grew, they needed us – as intermediaries, in effect. We were tasked with providing support for project leaders, helping them to solve their own problems as far as they could, so that only a few urgent questions needed to be put to the research directors. That’s still a fundamental part of our job, and in fact we provide support on a range of levels: scientific, operational and sometimes personal.’

In addition to coaching project leaders, Senior Clinical Scientists are also involved in the development of the organisation. ‘For us, this is often a chance to develop our own skills and knowledge,’ says De Visser. ‘Over the past few years, I’ve been busy preparing and conducting two studies involving genetically-modified organisms (GMOs). One was a gene therapy study with a viral carrier in patients with rheumatoid arthritis, the other a GMO-based vaccine for respiratory syncytial virus (RSV), which is a major cause of serious health problems in premature babies and people with immune deficiencies. For CHDR, working with GMOs was uncharted territory. I soon found out that the regulations are far more complicated than I had thought. For example, one of the first major hurdles

I came across was the fact that any institution that wants to do a GMO study in the Netherlands is legally required to have a biosafety officer – that is, someone who has been specially trained to supervise labs where there might be biohazards. Luckily, the biosafety officer at the Leiden University Medical Center (LUMC) was willing to expand his activities to include CHDR and help me with some parts of the environmental permit.

‘Vaccines are another area where we hope to make a greater contribution in the near future,’ says De Visser. ‘We have a state-of-the-art immunology lab now, so we have a lot of expertise that’s applicable to vaccine development. For some viral infections, such as RSV, we will develop challenge tests to demonstrate the effects of vaccines in healthy volunteers. RSV produces symptoms of the common cold in adults, so it’s ethically acceptable and practically feasible to expose healthy volunteers to the virus, giving some volunteers a placebo and others the vaccine and seeing how many people in each group develop symptoms. It’s a fascinating new field to explore. An added bonus is that, due to my work in this field, I’ve been invited to be on the board of the Netherlands Society of Gene and Cell Therapy.’

De Visser studied Medical Biology at Leiden University. ‘My final internship was in the Gastroenterology department in the LUMC. Around the time that

I was finishing, Adam Cohen happened to ask my supervisor if he knew someone who could conduct a gastroenterology study for CHDR.’ The supervisor recommended De Visser, and so she worked at CHDR for five years, studying the effects of the gut hormone motilin and an investigational motilin receptor antagonist, ultimately writing her PhD thesis on these studies. ‘I met my husband Saco here, and we obtained our PhDs on the same day in 2003. I then took a job at the Netherlands Heart Foundation, because we didn’t want to both work at the same organisation. A few years later, shortly after Saco had got another job, I ran into Adam Cohen. I told him I missed CHDR. He simply said, “why don’t you come back, then?”.’ That’s how De Visser returned to CHDR in 2007, first as interim Education Coordinator, then as Senior Clinical Scientist.

‘CHDR takes pride in developing people, and that’s also a crucial part of my job. Often, project leaders go from one Senior Clinical Scientist to another, depending on the specific project they’re involved in. However, we increasingly share notes about our various project leaders, in order to better follow and support their professional development. Personal coaching, noticing when someone needs a bit extra, is something I care deeply about. It won’t raise my H-index, it may even go unnoticed, but it can have a great impact. And it’s so gratifying to see people develop and thrive in their professional lives. Alongside the scientific and operational challenges, it’s an important part of what gives me satisfaction in my work.’

‘We are looking forward to contributing more to vaccine development in the future. With our state-of-the-art immunology lab, we have a lot of relevant expertise.’





Dr Rob Zuiker, Senior Clinical Scientist

'I love the variety in my work, all the different things I can do'

'It was eleven years ago that I first came here for my job interview, hoping to become a project leader and work towards my PhD,' says Dr Rob Zuiker, Senior Clinical Scientist. 'At the time, I had a steady job at a pharmaceutical company, with a nice car and everything. But I wanted to be in a role where I could develop, and where I could get a PhD. My original plan was to only stay here for a few years, and then go back to a business career, with an extra focus on science.' But Zuiker ended up staying on at CHDR, as many people do, attracted by the dynamic atmosphere and the breadth of opportunities on offer. Even before receiving his PhD, Zuiker was promoted to Senior Clinical Scientist.

'Nowadays, I'm a senior project leader for many studies – some of them sponsored, others financed by our R&D fund. The best thing about my job is the variety of roles I take on as part of my work. I'm a member of a team, working together to develop drugs in psychiatry. I'm a principal investigator, overseeing the development of our on-the-road driving test. I'm an educator, coaching young scientists and teaching university students. And I'm a board member of ACRON, the Association of Contract Research Organisations in the Netherlands. Even just one of those projects would be fun to do – and I get to do them all.'

Zuiker's career path has taken some interesting turns over the years. 'I trained as a physician, but I didn't want to work in a hospital. So after graduating, I became a medical officer in the Navy, joining the Dutch marines. It was a wonderful period of my life, and I learned a lot during those years. But the Navy mostly consists of young people, and after five years, I felt it was time to move on. In the meantime, I had studied business administration and got an MBA. So, a career in business beckoned. For seven years, I worked at a well-known, large pharmaceutical company. It was a tough environment, where you had to compete to keep your job – not so different from the military, after all! Every few years, you were supposed to switch jobs, to keep you from stagnating. CHDR is very different. It's warmer, more welcoming, and people tend to stick around for quite a long time. This creates a different climate, with a different kind of work culture.'

'For many young people, CHDR is an excellent place to start their career. They are really encouraged to develop their talents. They're encouraged to take responsibility, too, but they're given the chance to learn from experience, rather than being made to fear for their jobs.' As a Senior Clinical Scientist, an important part of Zuiker's role is to coach project leaders. 'Especially in the earlier phases of your professional career, it can really help to have someone support you in managing the operational side of things. Coaching project leaders

and helping them to thrive is one of the most fulfilling aspects of my work here. I've learned to see the differences between people and use this insight to tailor my style of coaching to their needs. For some people, a word of praise every now and then is enough. Others require a more intensive approach. As a senior, you eventually develop a sort of radar for when things need your attention. And then when you see them becoming self-sufficient, doing things for themselves – it's a source of great satisfaction.'

'At CHDR, young scientists are really encouraged to develop their talents. With so many exciting projects to pursue, as a senior member of staff I am constantly learning and growing too.'

The organisation, too, has grown and developed in the eleven years that Zuiker has been working here. 'Back when I joined, things were simply on a different scale. We were still based in the old building then. During my PhD in asthma research, I would do spirometry sessions with subjects, encouraging them to breathe out as much as they could. Apparently I could be heard yelling encouragements all through the building – people used to have to close their doors! When it was my birthday, I celebrated by ordering cream puffs for everyone in the company: that's not really realistic these days. Nowadays, the informal and friendly atmosphere still exists, but as part of a more formal, structured approach. For example, back when I had my job interview, it was just me and Adam Cohen. These days, job applicants talk with a number of different colleagues and complete an assessment as well. Although I have fond memories of how things used to be, the changes that have taken place are what's allowed us to pursue so many exciting projects. Against this backdrop of new developments, I am constantly learning and growing too.'





Dr Rik Stuurman, Senior Clinical Scientist

‘Pursuing research and coaching scientists - I can’t think of a better job’

‘In the five years that I’ve been working at CHDR, I’ve been involved in all kinds of studies,’ says Dr Rik Stuurman, Senior Clinical Scientist. ‘Studies in internal medicine, immunology, CNS, psychiatry, you name it. I’ve worked with a lot of different project leaders over the years, supporting them in both the operational and scientific aspects of their work. By helping them to improve, I can also help them to develop professionally. So that’s what I do, and I really love it.’

After studying pharmacy at Groningen University, Stuurman trained as a clinical pharmacologist at the Netherlands Cancer Institute in Amsterdam, where he also did his PhD research. ‘We developed oral formulations for several classical cancer drugs. My studies aimed to bridge the preclinical work in mice with the clinical application in humans. So even before I came to CHDR, I was involved in first-in-man, early clinical drug development.’ After obtaining his PhD in 2013, Stuurman worked for another Dutch CRO for about a year. ‘Then Adam Cohen invited me to come and work here. I accepted gladly, because I knew that at CHDR there would be more opportunity to focus on the science.’

At the time of this interview, Stuurman is in Brisbane, Australia, for nine months. He is there to accompany his wife who is pursuing her own research career. Although he is on the other side of the globe, he is still working part time for CHDR. ‘Some of my time is devoted to writing: scientific articles, standard operating procedures, and so on. I’m also coaching Matthijs Kruizinga, one of our project leaders, whose work looks into the use of non-invasive procedures in paediatrics. Matthijs is running an observational study, using remote technology to monitor children with various diseases, based at the Juliana Children’s Hospital in The Hague (interview on [page 100](#)). He is very enthusiastic, really ambitious, so it’s a pleasure to work with him – even at moments when things don’t work out as we had hoped. That’s an important quality: if you’re working at the cutting edge, especially when you’re doing so using newly-developed technology, you can’t expect everything to run smoothly.

‘I am confident that remote monitoring can contribute a great deal to drug development, and maybe even to patient care. It is especially promising for paediatrics, where using non-invasive techniques and reducing the frequency of hospital visits can really lessen the burden that children have to bear. Prof. Adam Cohen is our

principal investigator, and his enthusiasm about this approach is an inspiration to us too.

‘In the past few years, I’ve seen CHDR grow and expand. Not just in terms of the number of studies or the increase in staff, but in terms of the diversity of scientific fields. When I arrived, there were two key areas: CNS and Internal medicine. Now, we have research directors for Dermatology, Immunology and Psychiatry as well, and each of those fields are growing rapidly. Maybe, some day, I could even be involved in oncology again, coming full circle back to the topic of my PhD.

‘Going to Australia has been a valuable experience, both for me personally and for my family. Leaving all our friends and relatives behind wasn’t easy, but it has brought us closer together. Even so, I’m looking forward to returning to the Netherlands in the summer of 2019. I’m excited to see what opportunities there are for me back in Leiden. I’ll always be grateful to CHDR for supporting me in making this move, to have this experience. When they say they care about people at CHDR, they really mean it.’

‘Remote monitoring has great potential for improving drug development and patient care – especially in paediatrics.’





Dr Pim Gal, Senior Clinical Scientist

‘It’s inspiring to be around so many smart people’

‘When I first came here in 2015, I knew right away that this was where I wanted to be,’ says Dr Pim Gal, Senior Clinical Scientist. ‘And I still feel at home here. It’s the perfect balance between routine activities and interesting challenges – and even the routine stuff at CHDR keeps you on your toes.’ After becoming a physician, Gal originally wanted to be a cardiologist. During his residency, however, he realised that he had more affinity with scientific research. He wrote his PhD thesis on atrial fibrillation, and then started looking for a research position. An acquaintance happened to forward him a CHDR job advertisement on social media. He came for a job interview with Prof. Koos Burggraaf (at that time Research Director for Internal Medicine, now CEO) and the rest, as they say, is history.

Cardiology, especially cardiac electrophysiology, remains Gal’s main research interest. He played a key role in the development of CHDR’s Cardiology Services, which provides sponsors with detailed information on cardiac safety of investigational compounds. Screening for potential adverse effects on the heart rhythm is vital in the development of any new drug. This need to monitor cardiac effects relates to the discovery that certain drugs cause a specific arrhythmia called torsade de pointes, resulting in sudden cardiac death. A hallmark of this particular arrhythmia is a prolongation of the corrected QT interval in the ECG. Gal: ‘The standard procedure is to do a thorough QT study. However, this is quite expensive and typically exposes participants to supratherapeutic exposures of new drugs. At CHDR, we’ve adopted a method

of concentration-effect modelling that uses ECG extractions from Holter data and correlates the blood concentration of the compound with the QT effect.’ The US Food and Drug Administration has reviewed this procedure, and it can be used to obtain a waiver for the thorough QT study, if the outcomes are within a specified range.

‘CHDR has also adopted an approach to differentiate between harmful and harmless QT prolongation,’ says Gal. ‘The type of QT prolongation that is harmful results from hERG blocking. However, prolongation of the QT interval can also be induced by non-HERG blockers, which is typically harmless. With the ability to distinguish harmless from harmful QT prolongation, we can better support our sponsors in making the necessary decisions about how to proceed with their compounds. We’re currently writing a white paper specifying our procedures.’

Gal is also involved in a project using a machine-learning approach to see what insights can be gleaned from a veritable treasure trove of data: ‘We’ve combined the screening data of more than 6,000 subjects, including healthy volunteers of all ages as well as patients with various disorders. By applying machine learning techniques, we hope to identify specific parameters that indicate cardiac ageing, which could then be used to study compounds that improve cardiac function. From the screening data, there are about 400 parameters per individual, and our standard ECG analysis provides more than 700 parameters. So there’s certainly plenty of data to work with.’

As one of CHDR's Senior Clinical Scientists, Gal is responsible for coaching and supporting project leaders. 'Initially, I found it harder than I had thought it would be, but I've started to get the hang of it. You can even adopt a systematic approach here, too: I've recently become interested in psychological classification, and how we can use a framework such as the Myers-Briggs Type Indicator to help us understand how different characters deal with challenges and setbacks.' The more that project leaders progress in their roles, the more they themselves must learn how to delegate tasks and supervise others in the day-to-day tasks of running a project. Gal: 'In coaching project leaders, one of the main challenges is encouraging them to stretch themselves, supporting them as they expand their professional skills. In my role I'm constantly shifting gears: from science, to operations, to people. And that's what I love about my job.'

'Thanks to improved insight into cardiac effects, we can better support sponsors in making the necessary decisions about how to proceed with their compounds.'



Working with CHDR

‘Everyone has been very friendly and easy to work with’

‘CHDR comes across as scientific and professional. They deliver high quality work and I was very impressed with the facility. The personal attention from their staff was excellent. The relationship with the CHDR team has been very positive. They are very effective and reply promptly to questions. Everyone has been very friendly and easy to work with.’

Executive Vice President, Biotech Company*

**The views expressed here are the sole opinion of CHDR's sponsors.*





Scientific output

Publications

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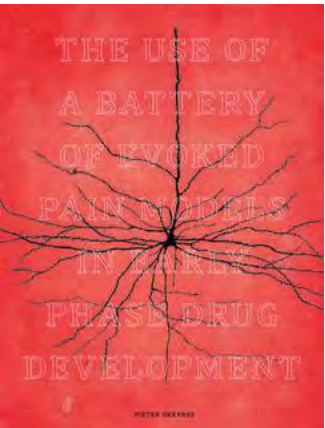
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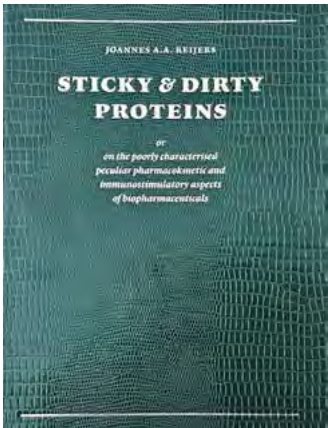
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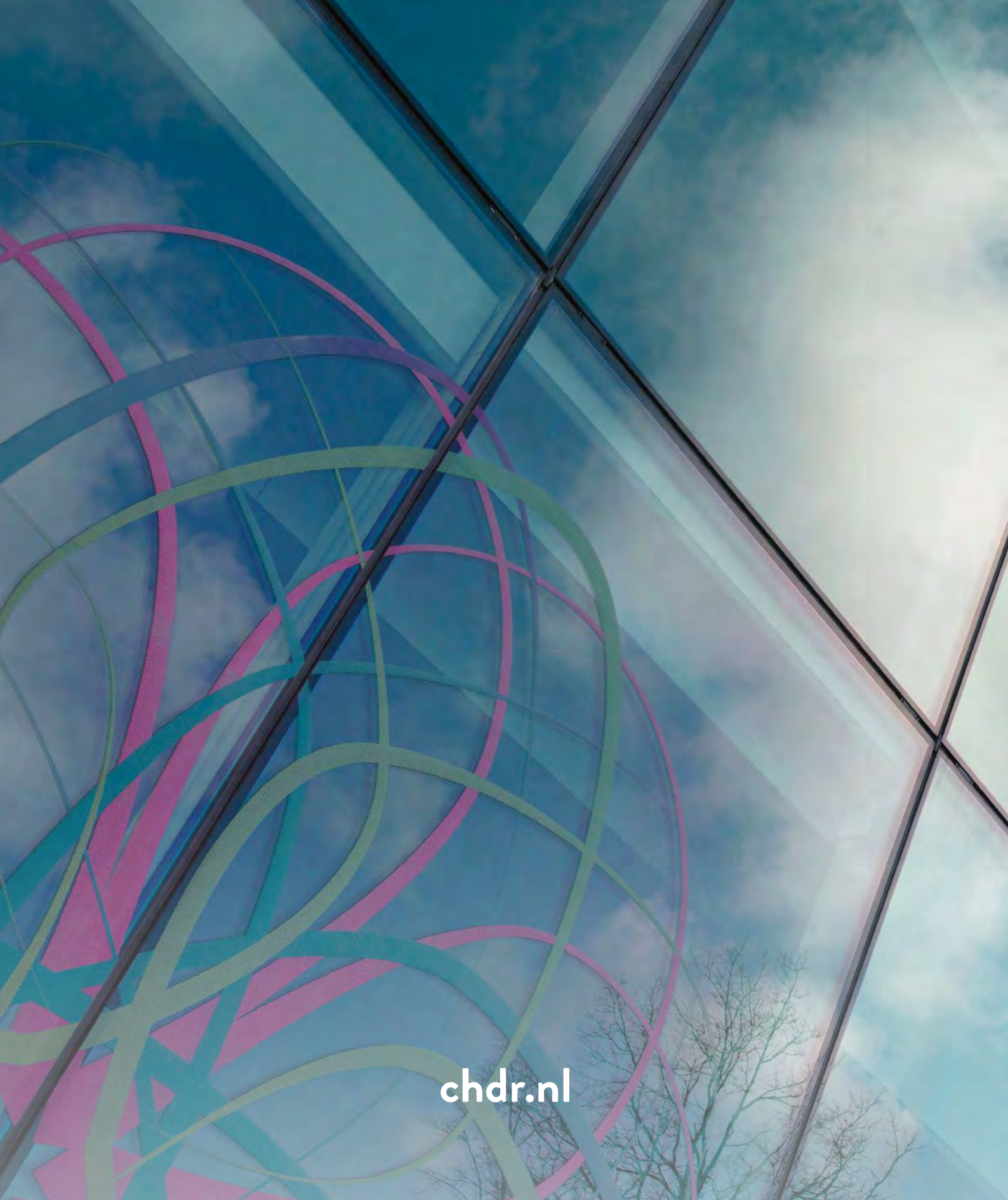
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