
CHDR
Centre for Human Drug Research
CHDR
Annual Report
2021

# Foreword

Looking back on the past year, we are proud of what has been achieved in collaboration with our clients and partners. It has been a challenging year, with the COVID-19 pandemic once again having a strong impact on planning — not only ours, but also that of our clients. However, by engaging in an open and constructive dialogue, we have managed to overcome many obstacles together. The dedication of our employees, many of whom had to work remotely for long periods, also deserves special mention: thanks to their efforts, we were able to maintain our high standards despite the inevitable setbacks due to the pandemic.

Our scientific output also remains at a high level both in quality and quantity, with 77 scientific publications and 6 PhD graduates in 2021. We are as committed as ever to our mission to develop people and cultivate talent, contributing to the training of doctors, scientific researchers and industry professionals. In the past year, four clinical pharmacologists completed their training at CHDR.

As we emerge from the global pandemic, it's also a time to regroup and look forward to the years ahead. In anticipation of further growth, we already expanded our internal clinical research unit capacity in 2020. Moreover, we are pleased to announce that in the coming years we will realise an additional clinical research unit on the premises of Leiden University Medical Center (LUMC) with a capacity of eight beds. Not only will this facilitate our continued growth as an organisation, but it will also further strengthen the long-standing partnership between CHDR and the LUMC.

We are also expanding in terms of the scope of our activities. Dr Jacobus ('Co') Bosch has recently joined our organisation as Research Director for Oncology, tasked with building an Oncology research group and cultivating a network of collaborations in this area. Meanwhile, we are responding to the increasing demand for patient studies in early drug development by establishing new partnerships with large teaching hospitals in the Netherlands. And, as ever, we are driven to explore the benefits of novel technology for pharmacological research, from remote monitoring using wearable devices to the implementation of advanced measurement techniques.

In this year's Annual Report we celebrate the innovative methods developed and implemented by researchers at CHDR, in a series of spotlight articles placed throughout the book. As a foundation, we have the freedom to reinvest our revenues into cutting-edge research and development. Five years ago, we established a formal R&D fund, which has provided the springboard for most of the methods featured in these spotlight articles. Time and again, our clients have expressed their appreciation for the innovative and science-driven approach which inspires our efforts to develop and validate new methods and biomarkers.

We look forward to a new year of innovation in 2022, strengthening our partnerships with old friends and making new friends along the way.

Leiden, June 2022

Prof. Koos Burggraaf, CEO
Prof. Geert Jan Groeneveld, CMO / CSO

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# The year in perspective

# Investing today in the innovations of tomorrow

As in the previous year, 2021 saw continued instability and uncertainty due to COVID-19, with fewer clinical studies being executed than planned. Nonetheless, the Board of Directors looks back with pride at what has been achieved in the past year. This includes sustained progress towards long-term goals despite the challenges posed by the global pandemic, and continued investment in the development of innovative methods and biomarkers.

**Prof. Koos Burggraaf,** CEO

**Prof. Geert Jan Groeneveld,** CMO / CSO

'We had hoped that in 2021 we would transition out of the global crisis to a more manageable situation with fewer difficulties, but that didn't turn out to be the case. The aftermath of the acute phase of the COVID-19 pandemic presented serious challenges,' says CEO Prof. Koos Burggraaf. 'We had to improvise and be agile and adaptive. Nonetheless, we've also seen that there is great demand for our services, so we are still confident of further growth in the coming years.' CMO / CSO Prof. Geert Jan Groeneveld shares this view: 'We have had setbacks, but we've also learned a lot. Our teams have worked very hard, and unfortunately some projects were cancelled due to factors beyond our control. As always, safety was our top priority, and we succeeded in preventing any study participants from becoming infected with COVID-19. The number of infections among staff also remained low.'

Both directors agree that the staff of CHDR have performed exceptionally well in another challenging year. Read about the year's scientific successes in Neurology and Pain (page 25), Psychiatry (page 37), Dermatology (page 51), Immunology (page 61), Internal Medicine (page 71), Biomarker research and development (pages 83 and 89), and remote monitoring with Trial@home (page 101), as well as the tenacity shown by teams working in Clinical Operations (page 107), Human Resources (page 113), Technology (page 125), QA (page 131), and Education (page 137).

## Long-term strategy

Reflecting on the setbacks of the pandemic years, the Board of Directors highlights the organisation's resilience and ability to adapt. Thanks to the renovations that were completed in 2021, the clinical capacity of the main facility has been greatly increased. In anticipation of the expected growth in coming years, the number of staff also increased slightly in 2021. Scientific output remained high, as did the number of PhD candidates and scientists undertaking clinical pharmacology training (see also pages 142 and 146). Clients and collaborators continue to value CHDR's work, and new strategic partnerships are taking shape. Burggraaf: 'Our collaboration with the Leiden University Medical Center (LUMC) is going from strength to strength. Additionally, we are exploring the possibility of forming a strategic alliance with one or more other university medical centres. Meanwhile, we're also in the process of establishing a partnership with a large teaching hospital in the region, who we've already worked with in various fields of expertise. These collaborations will provide opportunities to conduct more research in patient populations, in addition to our studies in healthy volunteers.'

CHDR's long-term strategy includes both strengthening the existing research groups and establishing two new ones: Infectious Diseases and Oncology. 'Our Infectious Diseases group has been highly active in recent years in vaccine studies and other work relating to COVID-19. This team

collaborates closely with the LUMC, which will in turn help us to grow this area further in the coming years,' says Burggraaf. 'As for oncology, in 2022 we expect to lay the groundwork for a collaborative research network in this area. In this regard, we've been very fortunate in attracting Dr Co Bosch as our Research Director for Oncology.' Read more about infectious diseases research at CHDR on page 76, and turn to page 81 to learn more about the new Oncology group.

In the course of 2022, the organisation's long-term strategy will be evaluated to see whether the focus points identified in 2020 are still relevant for the years ahead. This will include looking at recent developments at CHDR, such as the success of the Trial@home remote monitoring platform and the growth in the number of patient studies, as well as the application of new technologies such as virtual reality and machine learning.

## Innovative methods in the spotlight

'At CHDR, we distinguish ourselves from other contract research organisations by two particular characteristics: our strong emphasis on scientific insight and proof of pharmacology, and our status as a foundation,' says Groeneveld. 'And in fact, these two aspects are closely intertwined: because we don't have shareholders, we can invest our revenue back into our R&D fund, which we use to support the in-house development and validation of new biomarkers and methods.' The success of this approach can be clearly seen in the results of an evaluation carried out in 2021, which examined R&D work during the period 2017–2020. 'The evaluation showed that many of the innovations developed using the R&D fund already contribute to our turnover within four years, which is a relatively short period of time. What's more, we know that we will continue reaping the rewards of these investments for many years to come. For example, NeuroCart®, our unique CNS test battery, contains tests that we have been using and refining for more than 30 years.' To celebrate CHDR's investment in innovative research methods, a number of techniques are placed in the spotlight in this year's Annual Report. Browse through the chapters on the different research areas to learn about a range of novel approaches from the scientists who are developing and using them (for an overview, see page 5).

> 'Innovations developed using our R&D fund will yield benefits for years to come'

In 2021 the R&D fund also supported the further development of Trial@home, CHDR's remote monitoring platform, and Ready-for-Research, CHDR's approach to establishing cohorts of various patient types in anticipation of clinical studies. 'We also used our R&D fund to support a range of scientific endeavours, such as collaborative projects with our partners, or an additional study required for a PhD candidate to complete their doctoral research. After all, we strive to invest not only in science, but also in people,' says Groeneveld. The R&D fund will continue to be evaluated on a regular basis, to monitor the added value of the investments for the organisation.

## Personnel changes

2021 saw the departure of two members of the Supervisory Board who had reached the end of their terms: chairman Frans Eelkman Rooda (MSc, MBA), and Dr Jan Hendrik Egberts. 'We are grateful for their critical and constructive contributions to our organisation in the recent period of challenges and growth,' says Burggraaf. The new chair of the Supervisory Board is Prof. Willy Spaan, former chair of the LUMC and professor emeritus of Virology. Dr Jabine van der Meijs, former CFO of Amsterdam Schiphol Airport, also joined the Supervisory Board in 2021.

There were also changes among CHDR's staff, including a number of employees transitioning to new functions. Internal medicine specialist Dr Naomi Klarenbeek was appointed Medical Director (see page 72): 'Her combined expertise in internal medicine and clinical pharmacology has been invaluable during recent years,' says Groeneveld. 'During the COVID-19 pandemic, she developed and adjusted our safety policy on infections. And when the Dutch government stopped releasing data on the prevalence of the virus, she used statistical models to calculate the prevalence for us so that we could adjust our policy accordingly.'

Following her successful PhD defence in March 2021, Dr Tessa van der Kolk was appointed Senior Clinical Scientist (see page 118), and at the end of 2021, Dr Annelieke Kruithof became CHDR's first Clinical Study Manager (page 119). Meanwhile, Dr Robert-Jan Doll was appointed Associate Director for Biomarker Engineering and Analytics as of the beginning of 2022. He will continue to lead his method development team, which is now known as the Biomarker Engineering and Analytics group (page 89). In addition, Abdelrahman Elsharkawy was appointed Associate Director of Business Development.

## Looking to the future

'Although we'll still be keeping our fingers crossed, it looks like the COVID-19 pandemic is on its way out globally,' says Burggraaf. 'So in 2022 we look forward to resolving the backlog. And with public life getting back to normal, it should also become easier to recruit study participants.' To connect with potential participants, a new branding campaign is currently in the pipeline. 'This campaign profiles CHDR as a foundation focused on knowledge and innovation, with a mission to develop new medicines for unmet needs,' says Groeneveld. 'We hope this message will resonate with today's younger generation, who place great value on societal relevance.'

The lifting of the last pandemic measures in the course of 2022 will hopefully also have a beneficial effect on staff morale, which inevitably suffered due to the restrictions placed on employees during the pandemic. 'A survey we did in 2021 showed that job satisfaction

had decreased for many staff members. Unsurprisingly, working from home and reduced social interaction emerged as key causal factors,' says Groeneveld. 'With the opportunity to work in the office once again, people can reconnect face-to-face with their colleagues and rekindle their enjoyment of the work. Overall, we look forward to a reinvigorated workplace atmosphere now that things are returning to normal.'

The worldwide demand for early phase clinical trials is still growing, and Burggraaf hopes that CHDR can make an even greater contribution in the coming year. 'There were a record number of FDA approvals last year, but of course, we are yet to see the impact of the pandemic on the number of approvals in years to come,' says Burggraaf. 'Bringing potential new medicines from the lab to the market is a team effort in which the pharma industry, scientific researchers, and the public all have a role to play. So we think it's a good moment to spread the word that participation in clinical trials is a valuable contribution, an opportunity to play a part in making new drugs available to those who dearly need them.'

'Bringing potential new medicines from the lab to the market is a team effort'



## In memory of Flora van Veen (1980–2021)

It is with deep sadness that the Board announces the passing of Flora van Veen, Senior Recruitment Officer, on 29 December 2021. 'It still feels unreal for me, working here without Flora,' says head of Recruitment Herbert Anholts. 'When I started at CHDR in March 2006, Flora was already working here. In those early years, the Recruitment department was just the two of us, taking pride in our database that back then contained around 2,700 individuals. Fifteen years later, our database has grown to more than 60,000 individuals, and our team has expanded along with it. It was Flora who provided the stability and support that saw us through those years of growth. I remember how, in one of our online team events during the pandemic, we did a quiz where everyone had to write down which colleague they trusted enough to share their biggest secret with. It turned out that almost everyone had filled in Flora's name.' Flora van Veen is survived by her wife and two children.


# 2021 at a glance

# 2021 in numbers

**51**
studies

**>37,000**
volunteers available

**29**
contracts signed

**>21,000**
patients available

**77**
articles published

**16**
nationalities

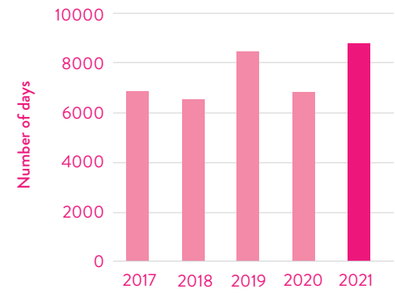
**4**
clinical pharmacology graduates

**4.8%**
turnover of clinical research staff

**6**
PhDs graduated

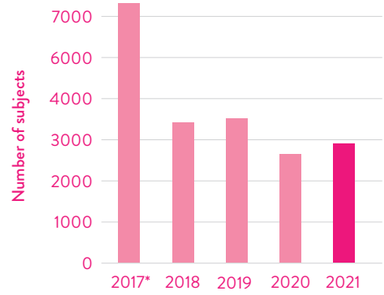
**16.8%**
growth in personnel

## CRU OCCUPANCY




Our purpose-built clinical research unit offers a dedicated first-in-human unit and private, hotel-style accommodation for study volunteers. Thanks to the unit's innovative design, we can intensively monitor subjects without compromising on comfort.

## SUBJECTS SCREENED




**includes approximately 4000 patients with Parkinson's disease*

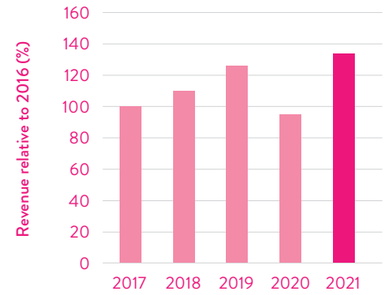
Screening at CHDR is carried out by skilled physicians in a dedicated facility next to Leiden's central train station, within easy reach for participants from the densely populated Randstad region.

## OVERALL CLIENT SATISFACTION

**8.3**/10

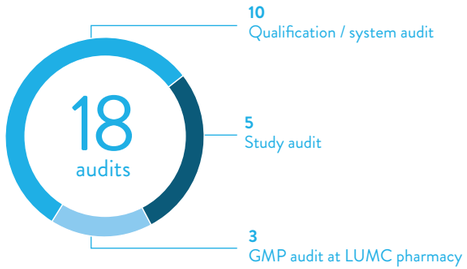
Combining scientific and operational excellence, we're driven not only to meet our clients' needs, but to also think proactively and provide added scientific value.

## CONTRACT REVENUE

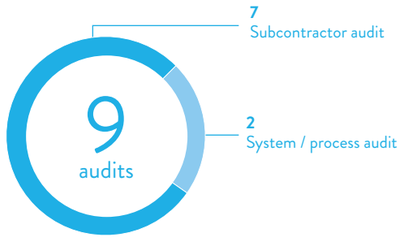



CHDR's status as a foundation has added to our financial resilience during the global pandemic, allowing us to continue supporting vital R&D.

## EXTERNAL AUDITS



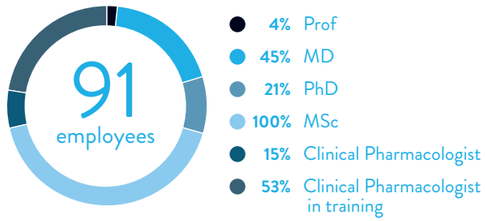

## INTERNAL AUDITS




Remote audits continued to be the norm in 2021, leveraging the possibilities offered by digital technology. Read more about Quality Assurance at CHDR on page 131.

## EMPLOYEES BY DEPARTMENT

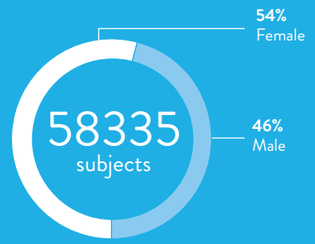

## CLINICAL RESEARCH STAFF



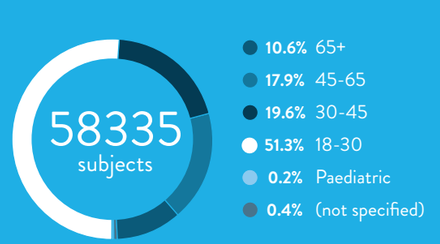

With a mission to promote education and cultivate talent, CHDR strives to offer staff in all departments opportunities for professional and personal development. Read more about Human Resources at CHDR on page 113.



## SUBJECTS BY GENDER

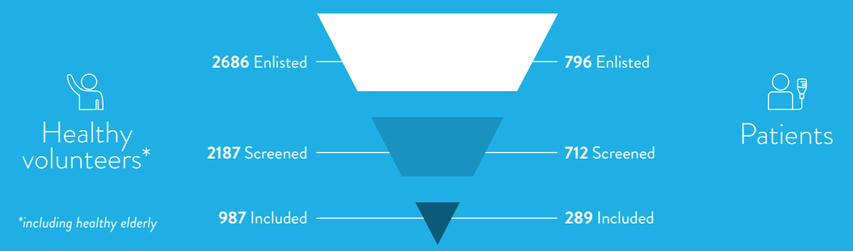



## SUBJECTS BY AGE



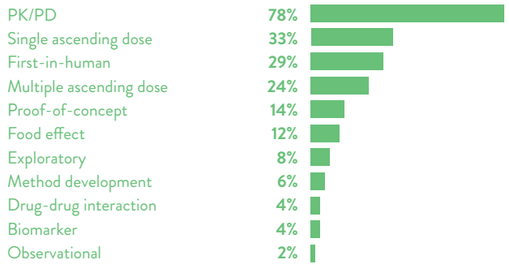

The whole lifespan – from young healthy volunteers to the elderly – is represented in CHDR's participant database. With an innovative, strategic approach, CHDR's Recruitment department rises to the challenges of recruiting healthy volunteers and patients for a wide variety of study requirements.

## SUBJECTS RECRUITED



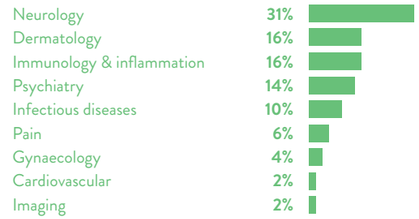

CHDR's recruiters take a proactive, social approach to study recruitment, exploiting the possibilities offered by social media, print advertisements, in-person events and more.

## TYPES OF STUDY



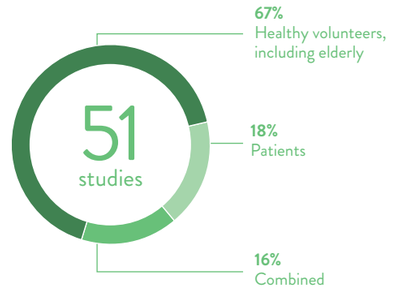

The CHDR perspective on early phase drug development is defined by the quest for both safety and insight. This integrated approach can be seen across the many types of study we perform, from classical SAD and MAD trials to studies exploring and validating novel methodologies.

## STUDIES PER RESEARCH AREA



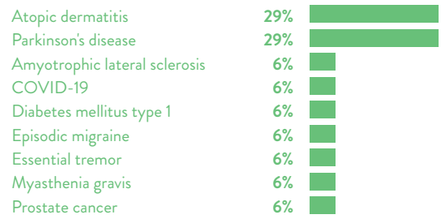

Studies at CHDR encompass a wide range of research areas. While our core research areas continue to grow, we are also expanding into new areas such as infectious diseases and oncology.

## STUDIES WITH SUBJECTS




From first-in-human safety studies in healthy volunteers to studies in patient populations or combined umbrella protocols, we offer the means to gain a comprehensive picture of a compound's properties early on in the development process.

## TYPES OF PATIENTS



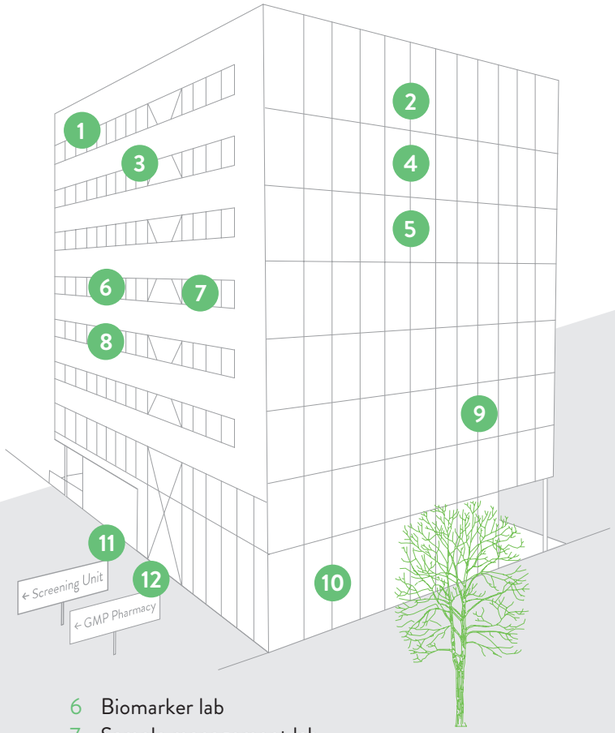

Research at CHDR spans an ever-expanding variety of patient groups. Our patient studies are supported by thriving networks of clinicians in various fields, including dermatology, mental healthcare, neurology and more.

# 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.




1 Private volunteer accommodation & research rooms
2 Volunteer relaxation area
3 CNS multifunction research rooms
4 Volunteer accommodation
5 First-in-man unit
6 Biomarker lab
7 Sample management lab
8 Multifunction research rooms
9 Open office space
10 Auditorium
11 Screening unit
12 GMP pharmacy

# Neurology and Pain

# Expanding the range of patient studies in Neurology

The number of patient studies at CHDR is increasing, in particular those that concern possible new treatments for neurodegenerative disorders. The Neurology group is supported in their work by the Research & Development lab, who are developing innovative analysis techniques to measure the effect of drugs targeting neurodegenerative processes. Meanwhile, the team also aims to study the pharmacokinetics of novel compounds in the cerebrospinal fluid.

'We're conducting more and more patient studies in diverse diseases, such as Parkinson's disease, ALS, essential tremor, and myasthenia gravis,' says Dr Philip Kremer, Research Director in Neurology. As of the end of 2021, Kremer is responsible for all neurology research at CHDR. This is part of a bigger change in the organisation: the combined Neurology and Pain group, previously led by CMO / CSO Prof. Geert Jan Groeneveld, has now grown into two distinct teams to accommodate the increasing number of studies in both fields. The new Neurology group is led by Kremer, while Groeneveld continues to lead the Pain group.

## Recruitment strategies

The growing number of studies with patients also poses new challenges for recruitment. Although the Recruitment department already has a great deal of experience in recruiting patients with various disorders, each new indication requires its own approach. Kremer: 'In the recruitment of patients with Parkinson's disease, for example, our networks with clinic-based neurologists have always played a vital role. However, we are now working on a study on essential tremor, a relatively common condition that, once diagnosed, doesn't require patients to follow up with their neurologist. So we have to find other ways to reach potential participants, such as through radio advertisements.' To support this, the Recruitment department has now appointed someone to focus exclusively on the recruitment of patients.

## Counteracting protein aggregations

New drugs for neurodegenerative diseases aim to stop the degenerative process, preferably at an early stage. One promising approach is to target protein aggregations, which occur in many neurodegenerative diseases. In Alzheimer's disease, for example, there are the well-known beta-amyloid accumulations and the plaques and tangles of the tau protein. In Parkinson's disease, multisystem atrophy, and Lewy body dementia, there are deposits of α-synuclein. Meanwhile, in ALS several protein inclusions are found, including TAR DNA-binding protein 43, which is also involved in the pathogenesis of frontotemporal dementia.

Kremer: 'The role of the various protein aggregations in the disease process is not yet entirely clear. However, it's likely that neurodegeneration is at least partly caused by a toxic effect of these protein aggregations. This view is also supported by studies of genetic risk factors. Therefore, we are now seeing the emergence of drugs that are aimed at clearing aggregated proteins via the endosomal-lysosomal system. Our Research & Development lab is now developing methods to analyse the function of cell organelles involved in the clearance of protein aggregates. In addition, they are working on other organelles involved in neurodegeneration, such as the mitochondria.' Ultimately, the team hopes to develop a complete test battery that can map cell stress and cell function in the white blood cells that serve as a proxy for the glia and neurons in the central nervous system.

## Cerebrospinal fluid and its (pharmaco)dynamics

In the past year, Kremer and his colleagues also set up a study to take a closer look at the dynamics of the cerebrospinal fluid. An increasing number of innovative treatments in neurology have to be administered in the intrathecal space — that is, via a lumbar injection into the cerebrospinal fluid. For this, it is important to know exactly how the cerebrospinal fluid moves and where it is cleared. 'If you use lumbar puncture to administer a drug that is meant to have an effect on the brain, you need to know whether it shows up in the brain in sufficient concentrations. There are more and more drugs of this kind being developed, including antisense oligonucleotides, so this knowledge will be of practical use in the near future. There are indications that cerebrospinal fluid can also leak away along the nerve roots, and we want to map this out precisely,' says Kremer. 'Overall, this is one of the many ways in which the changing pharmaceutical landscape stimulates us to explore new avenues of research and development.'

# Measuring tremor using tremography and digital spiral drawing

**Dr Kaye de Cuba,** Clinical Scientist and Research Physician

## Why was this method developed?

Essential tremor is a relatively common disorder that causes involuntary and rhythmic shaking primarily of the upper limbs. It affects about one in 20 people over the age of 65. In some cases, essential tremor also runs in the family, affecting people at a younger age. Some even develop essential tremor in their teenage years.

Essential tremor encompasses two types of tremor. There is postural tremor, which occurs especially when the patient wants to remain in a certain position, for example while holding a cup of coffee. The other type, kinetic tremor, occurs during purposeful movements, for example when the patient brings the cup of coffee to their mouth to drink. The tremor gets worse with age and most patients develop symptoms that hinder them in their daily functioning.

The drugs currently used to treat essential tremor often have unpleasant side effects and are not always effective. Therefore, there is a huge unmet need for the treatment of this condition. In 2021, we started a clinical trial for a new drug aimed at treating essential tremor. To carry out this trial, we needed an effective method of measuring tremor severity.

## What does the method involve?

To measure the effect of this candidate drug, we use a technique called tremography, which can be used to study all kinds of tremor, including Parkinson's disease and drug-induced tremor. Tremography is performed using an accelerometer, which is a small box-shaped device that measures the acceleration of movement in three directions. The accelerometer is attached to the back of the patient's hand. We perform baseline measurements prior to the administration of the drug, and at a number of intervals after drug administration. Using these data, we can then calculate the amplitude and frequency of the tremor.

CHDR has worked with tremography before, but this study was innovative in terms of procedure and data analysis. Based on the literature, we chose a position for the accelerometer which would enable optimal measurement of the postural tremor of the hand. We also introduced the use of tremography for measuring kinetic tremor: this is achieved by asking the patient to repeatedly extend their arm to the side and bend it to touch the tip of their nose.

Besides tremography, in this study we also implemented an exploratory measurement: the digital spiral drawing test. In this test, patients are asked to trace a spiral shape on a tablet computer. This is a test that is already used in pen-and-paper form by neurologists during the clinical examination of tremor. It's also a way to measure the severity of tremor while completing a specific task.

Thanks to a successful recruitment campaign, over 1,500 people registered for this trial! So we also needed to find a way to pre-screen participants. We developed a web tool based on the spiral drawing test, which enabled us to remotely evaluate tremor severity. This proved to be very effective for selecting suitable trial participants.

## What are the results?

The trial is still ongoing, but we already know from previous validation studies that tremography is a robust measure for monitoring the amplitude and frequency of tremor. Meanwhile, we're also thinking about how we can adapt our approach to enable remote monitoring for future patient studies concerning tremor. The digital spiral drawing test is very promising in this regard: it could easily be adapted for remote measurement of drug effects. For example, we could give patients a tablet or touchscreen computer to take home and ask them to complete the spiral drawing test once a day.

***Dr Kaye de Cuba** is a physician who works as a Clinical Scientist in the Neurology group: 'I previously worked in a hospital neurosurgery and neurology department. My ambition after finishing my PhD here at CHDR is to become a neurologist. I am driven to better understand why certain medicines are more effective in some patients than others. My work here as a research physician and the training I'm receiving in clinical pharmacology will give me a strong basis for a career in neurology. I'm also involved in research on myasthenia gravis and other neurological diseases. I find it fascinating to work with new biomarkers for drug effects in patients with neurological disorders.'*

# Ever smarter solutions for the complex problem of pain

Research into pain and painkillers is one of the pillars of drug development at CHDR. For the treatment of chronic and severe pain, the search is on for solutions that optimise clinical effects while reducing side effects. Besides peripheral pain stimuli from damaged tissues or nerves, complex processes in the central nervous system also play a role in the experience of pain. The Pain group is busy developing new methods that can reveal the effects of treatments that address this complexity, even in healthy volunteers.

'Pain is a multifaceted phenomenon. The experience of pain is partly influenced by emotions and other factors such as lack of sleep. We take this into account in pain treatment, but it adds to the challenge of drug development,' says Prof. Geert Jan Groeneveld, CMO / CSO and head of the Pain group. Pain research at CHDR is primarily based on PainCart®, a unique test battery developed in-house and refined over the years. Using PainCart, study participants can be subjected to different forms of pain, such as pressure pain, electrical pain, and immersion of the hand in ice-cold water.

'At present, all the PainCart pain models concern peripheral pain stimuli. Therefore, we're working to expand the test battery with tests that can influence the perception of pain at higher levels of brain functioning,' says Groeneveld. 'Our efforts in recent years are already starting to bear fruit. For example, we have shown that the experience of pain can be intensified using virtual reality technology. Meanwhile, another study has shown that sleep deprivation can lower pain thresholds. We're looking forward to exploring this further in the coming years.' Read more about the use of virtual reality in pain research on page 34.

## Chilli and mustard

The experience of pain is not only influenced by higher cognitive processes, but also by mechanisms in the lower central nervous system. For example, the descending nerve tracts in the spinal cord play a role in the development of allodynia, a hypersensitivity to stimuli that would normally not be painful. Allodynia is a known symptom in neuropathic pain. 'Central processes that influence pain perception can be tested using everyday substances that act as chemical irritants,' says Groeneveld. One of these is capsaicin, the substance that gives chilli peppers their spicy taste. When applied topically, capsaicin increases skin redness and sensitivity to pain stimuli (hyperalgesia). Around the area of application, capsaicin induces an allodynic effect, making that part of the skin sensitive to mechanical stimuli that would not normally cause pain.

Groeneveld: 'We now have a suitable and robust capsaicin model to induce allodynia in healthy volunteers, and this year it was implemented for the first time in a sponsored study. We had been experimenting with capsaicin for some time, but had been having difficulty achieving stable and reproducible allodynic effects. Hemme Hijma from our group has now succeeded in creating such a model, using an ethanolic capsaicin solution. It's a valuable addition to PainCart.' Besides capsaicin, another culinary substance being investigated by the Pain team is allyl isothiocyanate (AITC), the compound that gives mustard its characteristic pungent smell and taste. The use of AITC is currently being explored not only by the Pain group, but also by the Immunology and Cardiovascular group (see page 61).

## New horizons for opioids

For the treatment of severe pain, opioids are still the most commonly used class of analgesic drugs. This is unsurprising given the essential role that the brain's various opioid receptors play in dampening the pain stimulus. However, opioids have a number of major drawbacks. They are addictive, and their effect diminishes with regular use. Furthermore, they have use-limiting side effects such as drowsiness and constipation, and high doses may even lead to breathing difficulties (respiratory depression). Therefore, the search is on for new opioid drugs with a more favourable profile. In this area, the Pain group works closely with the department of Anaesthesiology at the Leiden University Medical Center (LUMC). In 2021, two studies began that will largely be carried out during 2022, in which the side-effect profiles of two new opioids will be investigated. The effect of one of these drugs on respiration will be tested in the clinical setting of the LUMC.

Another study in this vein will focus on so-called biased opioid agonists. Groeneveld: 'The mu receptor, which is the most important opioid receptor in the brain, sets various intracellular pathways in motion. Biased opioid agonists influence the analgesic pathway more than the pathway that is associated with side effects. We will compare these drugs with other opioids on the market that have a similar profile, in order to see how they compare. For this, we will use our NeuroCart® CNS test battery.'

The ongoing opioid crisis has also prompted pain researchers to explore a broader range of strategies for pain relief. To this end, the Pain group has joined forces with other investigators in an international consortium called QSPainRelief. This EU-funded project, led by Prof. Liesbeth de Lange of the Leiden Academic Centre for Drug Research, brings together ten institutes with the aim of developing opioid-sparing treatments for patients suffering from pain. The project implements a quantitative systems pharmacology approach involving mathematical modelling, ultimately encompassing a complete translational programme: from in silico (computer modelling) investigations to in vitro and preclinical studies, followed by trials in healthy volunteers and finally patient studies. 'The first studies in humans will start at CHDR in 2022,' says Groeneveld. 'By combining the data gathered, the hope is that this project will pave the way for new treatments with superior analgesic properties and minimal side effects.'

## THC and CBD

2021 saw the start of a joint project between CHDR and the LUMC to investigate the use of cannabis for the treatment of chronic pain. Groeneveld: 'We have received €1.9 million in government funding to establish a comprehensive evidence base for pain treatment with cannabis. We will do this by looking at the effects of two cannabinoids — THC and CBD — in both healthy volunteers and patients.' THC is the main psychoactive cannabinoid in cannabis. It binds to the CB1 receptor in the brain. CBD has no psychoactive effect, but is registered for the treatment of certain forms of epilepsy and may also have a beneficial effect on anxiety. In addition, there are indications that CBD reduces the effect of THC, possibly by influencing the CB1 receptor.

The first studies in healthy volunteers, to be completed later in 2022, aim to assess the effects of THC and CBD in a classical single ascending dose and multiple ascending dose design. The effects will be mapped using the NeuroCart and PainCart test batteries. These studies lay the foundation for a subsequent patient study involving 200 individuals suffering from chronic pain, due to begin in the second half of 2022. Groeneveld: 'In my clinical practice, I've seen that medicinal cannabis can really benefit certain patients, in addition to other medication. With these studies, we hope to identify the particular characteristics of patients who are most likely to be helped by cannabis.'



## Confirming a promising target for painkillers

Clinical Scientist Hemme Hijma and his colleagues published several articles in 2021 on research with new selective compounds that target the voltage-gated sodium channel ($Na_v$) 1.8. It has long been known that such sodium channels play a role in the transmission of pain signals in peripheral nerves. The local anaesthetic lidocaine, a non-selective sodium channel blocker, has been on the market for more than seven decades. However, lidocaine itself is not a suitable substance for systemic pain relief because it also acts on sodium channels in the heart: at the doses that would be needed to reduce pain, it causes arrhythmias. More recently, the sodium channel subtype $Na_v1.7$ was found to be an important contributor to pain signalling. Selective $Na_v1.7$ channel blockers, however, have so far not delivered on their potential.

Meanwhile, the Pain group has tested two inhibitors selective for another channel, $Na_v1.8$. One of these showed a significant effect in a PainCart study, while the other showed possible analgesic effects even at lower doses in an unpowered study. Although these two particular compounds are not currently being developed further, the studies nonetheless showed the potential of $Na_v1.8$ as a target, while also demonstrating the suitability of PainCart for profiling this class of compounds in healthy volunteers. Hijma plans to finish his PhD dissertation on these and other results in 2022.

# Pain modulation using virtual reality

**Ingrid Koopmans,** Clinical Scientist

## Why was this method developed?

Our group uses PainCart® to study new treatments for pain. This test battery is used to induce pain in healthy subjects in a controlled setting. But pain is complicated, because in addition to local pain perception, there is also a strong affective component in the experience of pain. A person who is distracted often feels less pain, as is known from stories of soldiers who don't notice they're injured until after the battle. Meanwhile, someone who is very anxious about the pain — perhaps worrying that it's a symptom of a serious illness — may experience it more intensely. Medication for the treatment of (chronic) pain may address the local transmission of the pain stimulus, or may aim to alter the pain experience by targeting higher-level processes, or both. Therefore, we wanted to find a way to include the affective component of the pain experience in our studies.

Virtual reality (VR) has been used in recent years to reduce pain. For example, there are studies where patients are provided with a distraction during painful procedures. This often results in a significant reduction of the pain experienced by the patient. The VR technique we've developed uses the same principle but in a reverse fashion: that is, to intensify the experience of pain, in healthy subjects.

## What does the method involve?

Together with a company from Eindhoven in the south of the Netherlands, we have developed a VR concept that is now almost ready to be applied in drug development. In our setup, the study participant wears a VR headset while seated on a chair, with a slider to use to indicate severity of pain on a visual analogue scale (VAS). The participant is presented with an image in VR, which shows the room and a virtual version of the participant's hands and feet, including the VAS slider. A pain stimulus is administered using electrodes applied to the lower leg, which are also represented in the VR image. The strength of the pain stimulus is gradually increased, and at the same time, the VR simulation depicts the skin burning around the electrodes. There is also a sizzling sound to further enhance the unpleasantness of the experience. The participant uses the slider to indicate how severe the pain feels. When the slider reaches its maximum, the pain stimulus stops and the image goes black.

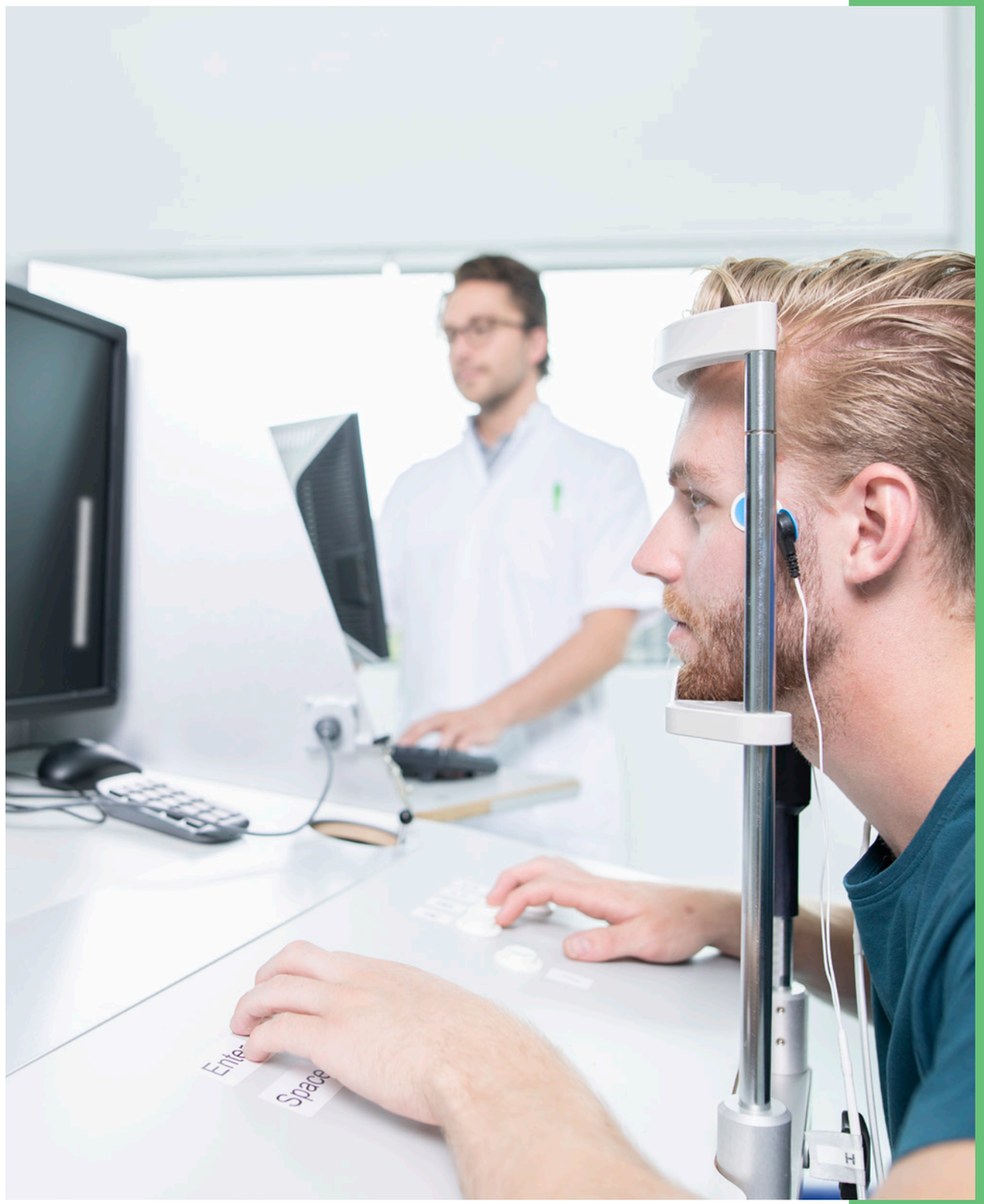
The current setup is the result of years of fine-tuning. The timing, for example, is crucial: it's vital that all subjects get to experience the visual and/or audio enhancements before they reach their pain tolerance threshold. We also found that it was important to include movement sensors on the participant's body and on the slider: this allows the participant to experience the VR simulation as interactive, which in turn makes the simulated wound process more credible.

## What are the results?

In 2021, we conducted the first study using this approach, with 24 healthy young men. We found that the wound simulation does indeed increase discomfort and intensify the perceived pain. Subjects indicated that the stimulus was painful at lower levels of stimulus intensity compared to the experience without VR, or with VR but without a simulated wound.

Now that we know that this setup intensifies the pain experience, the next step is to see whether medication that dulls the emotions can influence the outcome of the VR test. Then we will have successfully developed a biomarker for the affective component of pain. It could also be interesting to assess the importance of the affective component for patients suffering from pain syndromes such as fibromyalgia.

***Ingrid Koopmans** was trained as a technical physician and now works as a Clinical Scientist at CHDR. 'In the beginning I was hesitant about this project. Why would I want to work on a virtual reality application to make people feel more pain? I then asked Geert Jan Groeneveld, the leader of the Pain group, to introduce me to some patients with chronic pain who he treats as outpatients at the Leiden University Medical Center. Meeting them gave me a keen sense of the significance and potential of the project. More specific biomarkers for emotional aspects of (chronic) pain would be of tremendous help in the development of new treatments.'*



# Psychiatry

# Towards a new era of treatments for depression and anxiety disorders

Drug development in psychiatry presents unique challenges. Initial receptor-mediated drug action sets in motion a cascade of events, involving all levels of CNS organisation. To complement the NeuroCart® CNS test battery, the Psychiatry group is working to develop and validate additional methodologies to map potential biomarkers for CNS effects of novel compounds on (patho)physiological processes relevant to psychiatric disorders. The team focuses on both existing and novel pharmacological targets, including relatively unstudied neurotransmitter systems such as the endocannabinoid system and the hypothalamic neuropeptide orexin.

'We have achieved much in the past year, but we've also suffered a few setbacks due to the pandemic,' says Dr Gabriël Jacobs, Research Director in Psychiatry. 'Recruitment of trial participants was more difficult than in previous years. Moreover, relatively more potential participants failed to show up at appointments. Of course, some subjects could not participate for reasons directly related to the coronavirus — for example, if they had received a SARS-CoV-2 vaccination, if they had to quarantine following potential exposure, or if they had contracted COVID-19 themselves. Nonetheless, we expect things to get back to normal as public life opens up again post-pandemic. In the coming years, we look forward to using the methods we're currently developing to pursue our mission to contribute to new treatments in psychiatry.'

## Glutamate: ketamine and beyond

An ongoing line of research for Jacobs and his team concerns the effect of ketamine on depression. Central to this endeavour is the puzzling fact that patients with therapy-resistant major depression respond to a single dose of ketamine for an average of approximately 10 days, even though ketamine and its active metabolites have already disappeared from the body after 24 hours. 'We want to better understand the underlying mechanism that results from the initial receptor effect, and develop biomarkers for these sustained effects,' says Jacobs. 'Currently, several new compounds are being developed for the treatment of mood and trauma-related disorders, and we believe that such novel biomarkers might be useful in early drug development.'

In a study with healthy volunteers, the team is currently characterising the effects of a single dose of esketamine, the variant of ketamine that is already available as a medicine for depression. Combining CHDR's NeuroCart test battery with transcranial magnetic stimulation and a validated emotional test battery, the aim is to measure the effects that persist after the acute effects of ketamine have dissipated, focusing on cortical excitability as a proxy for synaptogenesis and, as a result, changes in emotional processing. 'These methods may hold promise as biomarkers for the "downstream" changes following the initial dissociative effects. We are using them to explore effects 24 hours and one week after administration. In this way, we hope to understand more about the antidepressant mechanism of ketamine. We can also potentially use these methods in early phase trials with new rapidly-acting antidepressant drugs which, like ketamine, act via the glutamate system, or other mechanisms of action that might be associated with sustained CNS effects such as $5HT_{2a}$ agonism,' says Jacobs.

'Eventually, the effects of ketamine in depression wear off. To shed more light on this, we're interested in measuring behavioural effects in this patient group at home after having responded to ketamine in a trial at our facility. For this, we can make use of CHDR's Trial@home remote monitoring platform. Using behavioural biomarkers can help us chart the return to baseline, to even better understand the whole process induced by esketamine. This knowledge will be of great value in the future, when the next generation of "psychoplastic" compounds are ready for clinical drug development.' Learn more about the Trial@home remote monitoring platform on page 101, or turn to page 44 for a case study using Trial@home in psychiatry.

## Alternatives to benzodiazepines

As a neurotransmitter, GABA is the inhibitory counterpart of the activating glutamate system. Benzodiazepines, probably the most well-known class of drug that activates the GABA-A receptors,

are often used for a wide range of disorders related to hypervigilance and/or suboptimal GABA neurotransmission. These include anxiety states and disorders, sleep disorders, epilepsy, and muscle spasms. Jacobs: 'Benzodiazepines are effective, but they have disadvantages. For example, they can be used as hypnotics, but they may disrupt sleep architecture, ultimately resulting in lower quality of sleep. In addition, the sedative effect results in reduced psychomotor function and several untoward effects on memory function, making them less useful as anxiolytic drugs. Moreover, users are known to develop tolerance, and as a consequence, benzodiazepines can be highly addictive. So we are looking for substances that act more specifically on certain subtypes of the GABA-A receptor, in the hope that we will find substances that have the desired effects with fewer undesirable side effects.'

A number of studies on such new agents were carried out at CHDR in 2021, the most interesting of which was a study aiming to demonstrate the anxiolytic effect of a novel compound using a challenge model. Jacobs: 'This compound was previously demonstrated to have a differentiated in vitro profile from a benzodiazepine, while still having the desired anxiolytic effect in non-clinical studies. To evaluate this clinically, we implemented the CO2 challenge. Inhaling carbon dioxide triggers symptoms of fear and panic in about half of healthy volunteers without a personal or family history of mood or anxiety disorder. First, we selected participants who showed sensitivity to these anxiogenic effects of CO2 at screening. These individuals were then randomly assigned to receive two different doses of the investigational compound, an active control compound — in this case, we used the benzodiazepine alprazolam — or placebo.' After several days of treatment once a relatively stable steady-state concentration was reached, the subjects underwent the CO2 challenge, during which their subjective anxiety and fear symptoms were measured using standardised questionnaires. With this approach, the team was able to demonstrate a significant anxiolytic effect of the novel compound. Jacobs: 'On certain symptoms, this effect was even more pronounced than with alprazolam. Thanks to these results, the client has increased assurance of the anxiolytic activity of the compound in the clinic, and may embark on patient trials with greater confidence.'

The Psychiatry group also participates in the development of pharmacological sleep aids based on novel pharmacological mechanisms, such as orexin antagonists. To study the potential effects of sleep aids on coordination of movement and risk of falling, the team explored a new method: the interactive walkway. Read more about this study on page 46.

## Endocannabinoid as biomarker

Endocannabinoids exert various effects in the brain. Drugs that mimic, enhance, or prolong the action of endocannabinoids are being investigated as potential painkillers and mood modulators with antidepressant and/or anxiolytic effects. Jacobs: 'A recent sponsored study offered us an opportunity to learn more about this neurotransmitter system. The emphasis was on the measurement of a molecule that might serve as a pharmacodynamic biomarker for future clinical studies with novel endocannabinoid-modulating compounds.'

> 'We look forward to using the methods we're currently developing to contribute to new treatments in psychiatry'

In this study, as well as measuring the concentration of the drug in the cerebrospinal fluid and blood, the team measured the concentration of one of the endocannabinoids in the cerebrospinal fluid. Jacobs: 'This study offered a unique chance to technically optimise this potential biomarker. We now understand the relationship between peripheral and central changes of this biomarker and how it is affected by the human diurnal rhythm. With these data, we have an important tool for studying the pharmacodynamic effects of compounds affecting the endocannabinoid system.'

## Pharmacology of psychedelics

The central serotonergic 5-$HT_{2a}$ receptor is believed to be the primary target for various substances known as psychedelics. These substances include DMT, LSD, and psilocybin, the active substance in so-called 'magic mushrooms'. In recent years, there has been growing interest in this receptor as a potential target for the treatment of mood disorders, addiction, and trauma-related disorders, especially when combined with psychotherapy during and/or after the psychedelic experience.

Jacobs: 'The first study with the psychedelic DMT was approved in 2021 and is currently underway. In this study, we integrate safety and pharmacokinetics with both subjective assessments (questionnaires probing the psychedelic experience) and objective assessments (NeuroCart and qEEG) in a single ascending dose study design. The participants are healthy volunteers with previous psychedelic experience. With this approach, we aim to understand the relationship between CNS effects and the emergence of psychedelic effects of DMT, relative to its pharmacokinetics.' The team is now preparing a number of studies with various 5-$HT_{2a}$ agonists with a similar setup and objectives, with the aim of creating a pharmacological platform for clients who are currently developing such compounds. 'It's no mean feat to maintain a rigorous scientific approach while caring for study participants undergoing a potentially intense and challenging psychedelic experience,' says Jacobs. 'We're extremely fortunate to have been trained in the preparation, support, and debriefing of trial participants in studies with psychedelic compounds by Chris Timmermann of Imperial College London, who is an expert in the field of DMT psychedelic research.'

# Developing PsyCart: how to quantify drug effects on emotional processes

**Soma Makai-Bölöni,** Clinical Scientist

## Why is this method being developed?

CHDR's NeuroCart® can be used to reliably quantify the effects of novel and existing compounds on CNS functions relevant to early drug development, such as arousal and sensorimotor function. However, NeuroCart lacks the ability to quantify drug effects on CNS functions that are of interest in psychiatry — for example, when a novel antidepressant drug is expected to optimise reward responsiveness or bolster resilience in response to adverse conditions. Our goal is therefore to develop ways to measure such effects objectively, in addition to existing methods based on self-reports. To achieve this, we seek to identify or develop assessments that reliably reflect the underlying neurobiology and the associated pharmacology of these processes.

The ideal assessment for this purpose is one that is well-characterised in terms of pharmacological sensitivity, dose-dependency and test-retest repeatability. Additionally, such tests should be cost and time efficient for clients as well as minimally burdensome for subjects. Ultimately, our aim is to demonstrate effects of novel compounds on emotional processes in early phase drug trials, as well as being able to identify the pharmacologically active dose range of such compounds. This will enable us to support clients in the development of novel compounds for the treatment of mood, anxiety and trauma-related disorders.

## How is this method being developed?

The theoretical basis of our work is the Research Domain Criteria (RDoC). The RDoC were developed by the US National Institute for Mental Health to provide a research framework in which mental health and psychiatric illness are understood in terms of varying degrees of dysfunction in general psychological/biological systems. These systems are in turn categorised into six overall domains of human functioning. At CHDR, our clinical studies in psychiatry predominantly concern mood, anxiety and trauma-related disorders, so our first step was to identify the variables that are central to these syndromes for each RDoC domain. In other words, we focus on specific clusters of emotional processes.

The next step will be to select specific assessments that quantify these variables, and to establish the optimal technical specifications for each one. Suppose, for example, that in the RDoC negative valence domain we want to map the degree of anxiety: we could do this by measuring the startle response. In that case, we first need to establish exactly how we should startle our test subjects, how we will measure their response, and how often we can repeat the procedure without habituation.

In identifying relevant assessments, we predominantly draw on existing research. However, this can be tricky, because even when a test is described in the literature, there is often insufficient detail regarding the validation of technical aspects and how exactly the test was performed. This raises the issue of standardisation and therefore reliability. So we will have to work out many things for ourselves, such as how to present a stimulus, for how long, how often, and so forth. There are also a number of different assessments of emotional processes available on the market, some of which have already been studied in a pharmacological paradigm. For example, two promising test batteries have been developed by the universities of Oxford and Cambridge, which we are now incorporating into our ketamine studies with healthy volunteers.

Once we have a basic setup, we will develop it further and validate it in healthy volunteers. In particular, we will examine whether the paradigms are sufficiently robust to be used to measure drug effects. Subsequently, we need to demonstrate that the test is also suitable for pharmacological research with healthy volunteers. We can do this by combining it with a challenge test that induces a certain symptom. Taking the startle test again as an example, we could give test subjects an anxiolytic drug and see if the startle response is reduced. Another interesting step may be to see whether the test can distinguish between healthy volunteers and patients. All in all, we are at the beginning of a fascinating quest, so we can't say yet exactly where we will end up.

***Soma Makai-Bölöni*** *came to the Netherlands from his native Hungary at the age of 19 to study psychology. After completing his bachelor's degree, he went on to gain a master's in Cognitive and Clinical Neuroscience, with a focus on drug development. 'During my master's studies, I came to CHDR to do my thesis project with the Biomarker Engineering and Analytics group, and in 2021, I joined the organisation as a Clinical Scientist. During that time, I got to know Gabriël Jacobs, and learned that there was a great need for objective measurements of emotions and behaviour. That struck me as a really interesting challenge. In addition, I'm now also setting up clinical studies with various psychedelic compounds. These hold promise as truly novel treatments in psychiatry, and it's fascinating to be involved in this process of discovery.'*

# Trial@home: real-time measurements in outpatients with depression

**Ahnjili ZhuParris,** Clinical Data Scientist

## Why was this method developed?

Currently, clinician-administered questionnaires such as the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Åsberg Depression Rating Scale (MADRS) are considered the gold standard for assessing treatment effects in trials concerning major depressive disorder (MDD). These instruments depend on subjective, retrospective reporting by patients, which may be influenced by depressive symptoms such as negative emotional bias. As such, these assessments lack objective, real-time information on behavioural changes associated with depression.

We are therefore interested in establishing biomarkers that quantify behaviour and are sensitive to pharmacological interventions. To this end, we are conducting a series of validation studies to ascertain whether data gathered using CHDR's remote monitoring platform, Trial@home, can distinguish MDD patients from healthy controls, and if we can estimate depression severity using such data.

## What does the method involve?

We conducted a self-funded, non-interventional study comparing 30 patients diagnosed with moderate to severe MDD with 29 healthy control subjects.

All subjects were monitored during their daily lives for three weeks using Trial@home. In addition, weekly in-clinic assessments were performed using the Structured Interview Guide for the Hamilton Depression Scale and Inventory of Depressive Symptomatology Clinician Rated (SIGH-D IDS-C) instruments. The remotely gathered data were collected via the sensors of a regular Android mobile phone, supplemented with data from a smartwatch, a blood pressure monitor, and smart weighing scales. Our objective was to measure sleep, social activity, and mobility patterns. We looked, for example, at the subject's location, their use of the various apps on the phone including phone calls, and whether conversations with others were detected by the smartphone's microphone. By comparing location data to information from Google Places, we were also able to determine the type of place where someone had been, for example in a supermarket or a social environment such as a theatre or cinema. The smartwatch charted physical activity, such as number of steps, as well as sleep and heart rate. Blood pressure and weight were also measured using the smart devices we provided. In order to provide regular information on the severity of symptoms, subjects completed the Positive and Negative Affect Schedule (PANAS) twice a day and the Depression, Anxiety and Stress Scale (DASS21) once a week on their smartphones, via the Trial@home electronic patient-reported outcome (ePRO) application.

## What are the results?

Based on the remote monitoring data, we identified several biomarkers that differentiate between unipolar depressed patients and healthy control subjects. In particular, we found that biomarkers related to smartphone use, social activities, and physical mobility were the best at distinguishing the two groups. In addition, we discerned biomarkers that were correlated with depression severity. For example, we found that physical activity correlated negatively with depression severity, while self-reported anxiety, depression and stress correlated positively with severity.

These results highlight the clinical relevance of monitoring depressed patients outside of the clinic. Subjective experience is an integral part of depressive symptomatology, and so these remotely monitored biomarkers cannot and will not replace in-clinic assessments. Nonetheless, we show that behaviours related to depression can be objectively, non-invasively and routinely monitored and evaluated outside the clinic. Such measures should therefore be considered in the design of future MDD trials, particularly for monitoring the effects of novel rapidly-acting antidepressants over time.

*__Ahnjili ZhuParris__ is a Clinical Data Scientist in the Biomarker Engineering and Analytics group (see also page 89). 'With Trial@home and other rich measurement methods, we are dealing with ever larger datasets. It's fascinating to see what patterns emerge from such data. In addition to the study in patients with depression described here, we've also analysed data from patients with facioscapulohumeral muscular dystrophy (FSHD), showing that Trial@home data can be used to both identify an FSHD diagnosis and estimate FSHD symptom severity.'*

# Interactive walkway to measure dynamic body stability

**Dr Rob Zuiker,** Associate Director | **Ingrid Koopmans,** Clinical Scientist

## Why was this method developed?

A new generation of sleep aids is currently being developed: orexin antagonists. These are based on a different mechanism of action from benzodiazepines, the most-used class of sleep aids. One of the known disadvantages of benzodiazepines is that they increase the risk of falling. Sleep-inducing drugs are prescribed mainly for the elderly, but if these individuals fall during the night, they may break a bone and this can really impact their quality of life and longevity. We wanted to compare an orexin antagonist with a benzodiazepine, to see if there is a reduced risk of falling. To do so, we needed a method to reliably assess fall risk, preferably in a dynamic setting. This method would complement the static body sway measurement we've been using for years in our NeuroCart® test battery.

## What does the method involve?

This research project resulted from a three-way collaboration between a pharmaceutical company, the Leiden University Medical Center (LUMC), and CHDR. The interactive walkway was originally developed by neurology researchers at the LUMC to measure dynamic body stability in Parkinson's disease or stroke patients. In this setup, virtual obstacles are presented on the ground using a projector. The test subject is given a task to complete, for example, to follow the projected path and avoid surfaces of a certain colour. Several such tasks have been validated for use in neurology research. The use of projections instead of physical objects means that the risk of stumbling is reduced, while also adding flexibility — for example, you can increase difficulty by projecting new obstacles on the floor while the subject is already walking.

To gather data on body stability, we precisely measure the position of the various joints using a Kinect sensor. This is a remote body sensor that was originally developed for the Xbox games console but is now commonly used in research. It's an elegant method that allows you to measure a person's overall performance without placing sensors on the body.

In the LUMC, where this setup is located, we had 18 healthy test subjects from 65 to 80 years old walk through this interactive walkway. These were people who had no abnormalities or limitations in their walking behaviour and no history of falling. The subjects were divided into three subgroups: one received an orexin antagonist, another received a known benzodiazepine sleep aid, and the third received a placebo. It was a crossover design, with all participants visiting three times, so that in the end every group received all three options. Measurements were taken at baseline before medication was given, and at certain times during the following nine hours.

## What are the results?

Our main finding was that the people who had been given the benzodiazepine sleep aid moved more slowly through the interactive walkway than those who had received the orexin antagonist. However, because we had excluded people with an increased risk of falling, we had probably selected a group of people who habitually reduce their speed when they sense that they are less stable. We know from the literature that the elderly people most at risk of falling are those who tend not to do this. So for future studies, it's important to first assess whether we need additional measurements besides body sway, and to possibly supplement this with the so-called Timed Up and Go test, which measures how long it takes a seated person to get up, walk three metres at a normal pace, walk back and sit down again. Together with our partners at the LUMC, we'll continue to explore the possibilities of the interactive walkway, including for research into treatments for neurological disorders.

***Dr Rob Zuiker*** *is an Associate Director at CHDR. 'I enjoy being involved with innovative approaches to measuring pharmacological action of new drugs in early phase trials. If we can show whether a compound engages its target, or has a lower adverse reaction than other compounds, we can provide valuable information that may contribute to better clinical drug development.'*

***Ingrid Koopmans*** *is a Clinical Scientist in the Biomarker Engineering and Analytics group. 'The interactive walkway had already been validated for use in neurology research, and our job was to validate it in a drug development context. We had to integrate everything we needed from our facility into the lab at the LUMC, which was an operational challenge. But interesting collaborations like this are one of the things I like most about working at CHDR.'*

‘I appreciated their motivation and dedication’

## Working with CHDR

‘We were looking for a partner who could work fast, was enthusiastic, and was willing to spend the time and effort needed to launch our study as fast as possible. CHDR ticked all the boxes.

The CHDR team was experienced, and above all I really appreciated their motivation and dedication — it was outstanding, and made a difference compared to our usual experience of working with CROs.’

Clinical Trial Manager,
Pharma Company*

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


# Dermatology

# Unleashing the potential of multimodal dermatology tools

In Dermatology, promising developments of previous years came to fruition in 2021. CHDR's multimodal DermaToolbox delivered on its potential, providing new insights into wound healing, gynaecological diseases, and skin disorders such as cutaneous lymphomas. The team also combined techniques, such as microdialysis and suction blisters in conjunction with pharmacological challenges, to conduct cutaneous biomarker assessments.

'The investments we've made in recent years to develop our methods and models are really starting to pay off,' says Prof. Robert Rissmann, CHDR's Research Director in Dermatology who also holds a professorship in Translational Dermatology at Leiden University. 'I'm proud of what we've achieved over the last few years, in collaboration with Dr Matthijs Moerland on biomarkers, Dr Martijn van Doorn on inflammatory diseases, Prof. Maarten Vermeer on cutaneous lymphomas, and Dr Mariëtte van Poelgeest in gynaecology-oncology. Our integral approach to skin research, in which we look at processes in the skin from many different perspectives, has proven to be scientifically successful and is valued by our clients.'

## Integrated approach

An integrated approach to skin processes means drawing on other sources of information beyond the standard visual and palpatory clinical assessment. These include the patient perspective, imaging, and assessment of the microbiome, as well as biophysical, molecular, and cellular analyses. To this end, Rissmann and his colleagues have developed the DermaToolbox, a state-of-the-art test battery that encompasses a range of measures to yield an integrated perspective. This includes immunological tests that were developed in collaboration with the Research & Development lab headed by Dr Matthijs Moerland. Rissmann: 'For the study of immunologically active compounds in humans, research in the skin can be an interesting first step. Local administration is safer than systemic administration, and effects in the skin are more easily detectable. What's more, the tissue can be harvested in a minimally invasive manner by means of skin punch biopsies.' Rissmann mentions the research into wound healing (see also page 58) as an example of a successful integration of different perspectives. 'That was a novel challenge, also with regard to data analysis. Thanks to the help of our colleagues from the Biomarker Engineering and Analytics group, we were able to make it a success.'

This type of integrated, comprehensive approach has come to be known as 'deep phenotyping'. Deep phenotyping in dermatology is valuable not only for studying new compounds, but also for uncovering the origins and progression of skin diseases. The value of this approach is highlighted by a recent grant proposal submitted to the Netherlands' national research fund, with the title 'Next Generation Immunodermatology'. Along with CHDR, the team behind this proposal includes all university hospitals in the Netherlands, as well as many important stakeholders and scientific opinion leaders. Rissmann: 'We've received many positive responses so far, but are still waiting to see whether the grant will be awarded. In any case, this collaboration will already improve cohesion and cooperation among academic dermatology centres in the Netherlands and, in turn, provide better access to research for patients.'

## Lesions of the vulva

In 2021, the Dermatology group conducted a deep phenotyping study in women with lesions of the vulva, in collaboration with gynaecologist Dr Mariëtte van Poelgeest of the Leiden University Medical Center (LUMC). Three groups were recruited for the study: women with high grade squamous cell intraepithelial lesions (a premalignant lesion that can develop into a vulvar malignancy), women with lichen sclerosus of the vulva, and healthy volunteers. Rissmann: 'We expected that it would be difficult to find healthy volunteers willing to have a biopsy taken from the vulva. However, recruitment proceeded smoothly.' In addition to vulvar biopsy and the various imaging techniques from the DermaToolbox, swabs were taken from all study participants in order to analyse the microbiome. 'By taking a swab at one-week intervals, we were able to gain an impression of the stability of

the vulvar microbiome,' says Rissmann. 'There has been a lot of research on the microbiome of the vagina, but much less is known about the viruses, bacteria, and fungi of the vulva.' The field is also starting to pay more attention to possibilities for prevention and treatment of vulvar carcinoma. 'Vulvar carcinoma is one of the "forgotten cancers". And yet the lesions, including the pre-stages, are potentially easy to treat.'

## New techniques and indication areas

The DermaToolbox has been expanded not only in capability, but also in capacity, so that more study participants can be examined at the same time. For example, Rissmann and his colleagues now have five laser speckle imaging devices at their disposal. Besides dermatological assessments, these devices are also used to study the skin's microvasculature, as described on page 68. In addition, Rissmann and his team are constantly exploring the possibilities to expand the applicability of the DermaToolbox. In a sponsored study in 2021, the DermaToolbox was used together with a new form of microdialysis to investigate the release of histamine into the skin following a challenge. Rissmann: 'We were able to do this thanks to our cooperation with Joanneum Research in Graz, Austria, who have experience with open flow microperfusion, an experimental method to measure active substances and endogenous molecules in the skin using sophisticated implanted catheters.'

With their collaborative, integrated approach, the Dermatology group are well-positioned to expand into new lines of research. In 2021, together with CHDR's Immunology and Cardiovascular group and the LUMC, the team conducted deep phenotyping of a specific form of cutaneous T-cell lymphoma (mycosis fungoides), using a range of approaches including suction blisters. 'We have never seen so many cells in the blister fluid,' says Rissmann. 'It turned out to be possible to do immunophenotyping of patients using this technique, in addition to the usual systemic phenotyping or pathology assessments. We're now looking further into local treatment of this form of cancer.' For Rissmann and his team, this is also an important step towards more work in the field of oncology, at the interface of immunology and dermatology. 'In that sense, "next generation immunodermatology" has already begun.'

# The skin inflammation challenge model with imiquimod

**Dr Tessa Niemeyer-van der Kolk,** Senior Clinical Scientist

## Why was this method developed?

New products are being developed for the treatment of inflammation and inflammatory skin diseases. To demonstrate the pharmacological effect of these products in healthy volunteers, a challenge model is needed, which we can use to locally induce a mild, acute inflammatory skin reaction. We must then be able to demonstrate a robust and reproducible effect of this challenge. Once this effect is well-characterised, we can use the challenge to evaluate the ability of anti-inflammatory drugs to prevent or inhibit this skin reaction.

## What does the method involve?

For this skin challenge, we use imiquimod. Imiquimod is a registered medicine that affects Toll-like receptor 7 and thus triggers an inflammatory response via two pathways: the interferon pathway and the NF-κB pathway. Clinically, one of the uses of imiquimod is to treat genital warts — activation of the interferon pathway helps to control the virus that causes the wart.

We define a number of squares on the skin of the subject's back, to which we apply imiquimod under occlusion for three to seven days. Imiquimod causes redness of the skin in a reproducible and robust manner, which we can measure in detail using various instruments from the DermaToolbox. Changes in colour, increased blood flow, and increased local temperature can all be reliably mapped.

Other substances can also be applied to the squares, in addition to different doses of imiquimod. These different squares can be used to compare the effect of various conditions, which also eliminates the need for a control group. For example, in addition to a square with imiquimod only, we can have squares where we apply a placebo and/or another active compound. In recent years, we have explored the effects not only of different drugs, but also of different sequences.

## What are the results?

In our first drug studies with the model, we explored the effects of omiganan, an antimicrobial peptide, which we used in many different combinations. We found, for example, that omiganan has the potential to enhance the beneficial effect of imiquimod on genital warts. We have also shown that systemically administered prednisolone can prevent the imiquimod inflammatory response, with a clear absence of inflammatory response after six days of oral prednisolone. Last year, we conducted a study with a new oral anti-inflammatory drug. We were able to compare that drug to prednisolone, which is one of the strongest anti-inflammatory drugs currently in clinical use. I can't say anything about the results yet, but the model has certainly proven its worth in this study.

Now, if our studies show that a new immunomodulatory compound has no effect at all when using the imiquimod challenge, that means the manufacturer has to go back to the drawing board: there would be little point in exposing patients to this new drug. And that, of course, is the purpose of our work — to collect as much information as possible in healthy volunteers, so that research with patients becomes safer and more efficient.

The next step we want to take in 2022 is to extend the imiquimod model. We're going to investigate whether long-term exposure — for seven days — also activates the complement system. That should be the case, as complement activation is part of the innate immune response, but after only three days of exposure we aren't able to detect it. We hope that this expansion will make the model suitable for studying various new drugs that are aimed at modifying the complement response.

***Dr Tessa Niemeyer-van der Kolk** is a Senior Clinical Scientist in the Dermatology group. 'We started setting up the imiquimod challenge model in 2016, and now we are finally at the point where it can be used in clinical studies with anti-inflammatory drugs. We're currently using the imiquimod challenge in a study involving a novel compound, and after all the hard work we put into developing it, it's very rewarding to see the clear results that are emerging.'*

# Profiling wound healing with the DermaToolbox

**Wouter ten Voorde,** Clinical Scientist

## Why was this method developed?

We want to characterise and understand the process of wound healing objectively and in greater detail, from a range of different perspectives. Doing so will enable us to better measure the effect of drugs on wound healing, in both healthy volunteers and patients. Some drugs have an adverse effect on wound healing, while others can be used to accelerate the healing of skin ulcers or to prevent scarring. To evaluate these drugs, we need a model that is well-characterised and maps the entire healing process in a standardised way.

## What does the method involve?

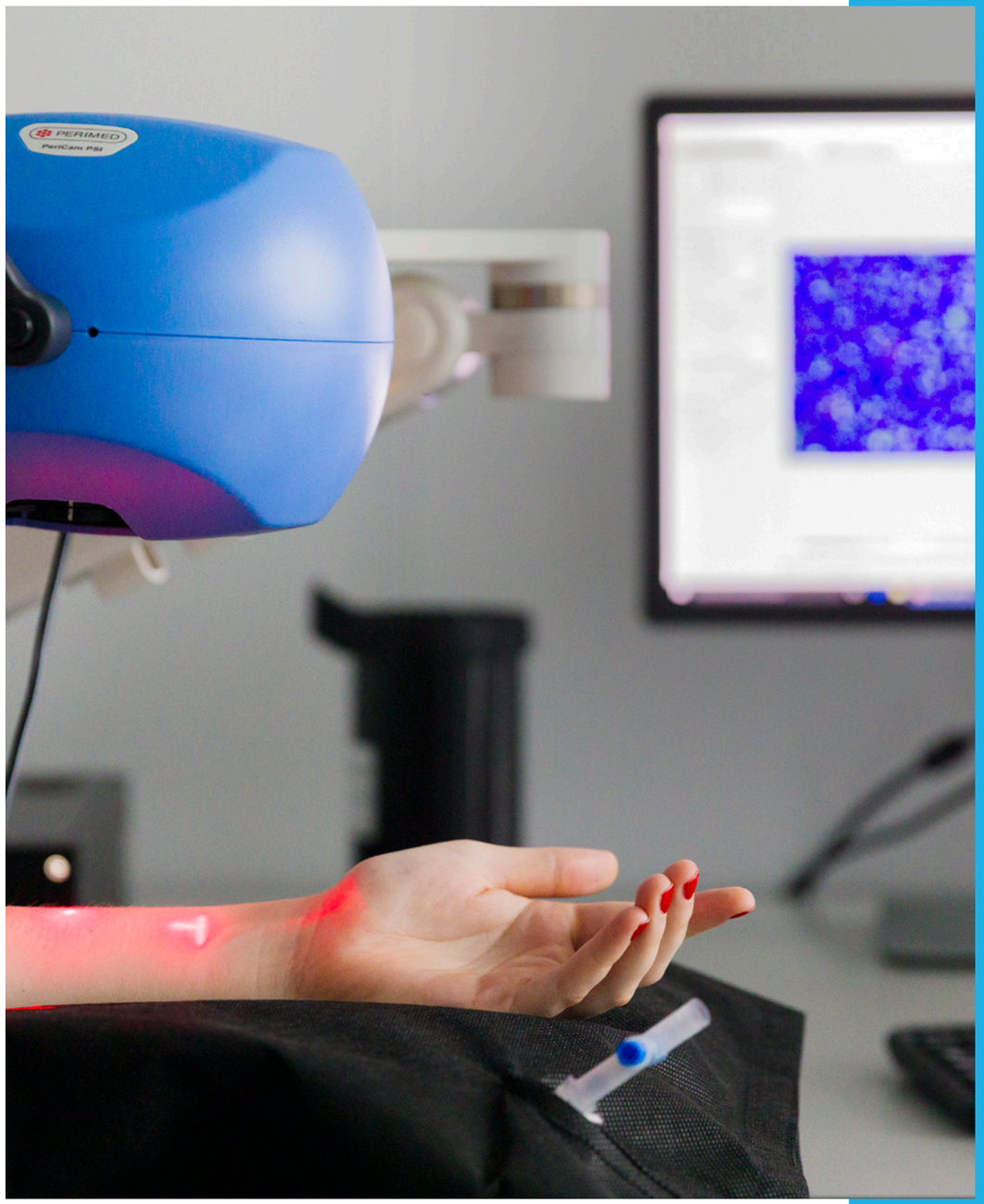
In 2021, we carried out a study in which we investigated the healing of wounds that arise after taking full-thickness skin biopsies. These biopsies involve using a punch to remove a round piece of skin about 3 mm in diameter. Another type of wound we study is an epidermal wound. In this case, we first induce a suction blister using a vacuum, and then we cut off the top of the blister. Then, over a period of several weeks, we map the wound healing process using a large number of different techniques from the DermaToolbox, our multimodal test battery for dermatological research. In the study with biopsy wounds, we used a large number of measurement methods to collect a range of data, which we then integrated. For example, we studied the blood flow and redness of the wound, and took three-dimensional images with a stereo camera to measure the cross section, size, depth, and height of the wound. We also looked at the morphology of the skin using optical coherence tomography. In addition, by measuring the skin's water permeability, we mapped its barrier function. We also took biopsies at various time points and, in addition to histopathology, we looked at inflammatory mediators and various cell types.

In about 28 days, such a wound is completely closed. However, the scarring process continues and can take years. Therefore, we also look at collagen formation. In particular, we measure the ratio between two different types of collagen, as we want to investigate whether that has predictive value for the formation of unwanted scar tissue. We're also using a number of these instruments in a longer-running study in cooperation with Dr Koen van der Bogt of the Haaglanden hospital in The Hague and the Leiden University Medical Center, in which we study diabetic foot ulcers to investigate the effects of an intervention to restore blood flow. With this knowledge we hope to translate the results from our wound healing model to the context of patient care, assessing how the two correlate.

## What are the results?

We now have a manuscript ready for publication which shows how the different modalities are consistent with each other. There is a clear correlation between the clinical evaluation, histopathology, and non-invasive readouts. We can easily recognise the different phases of wound healing described in the literature, and our study contributes important insights concerning morphology and molecular and cellular characteristics. The epidermal examination also provides useful measures for the evaluation of wounds at the boundary between epidermis and dermis. These occur, for example, in blistering diseases such as epidermolysis bullosa. All in all, we now have robust models that we plan to use in the evaluation of novel pharmacological treatments. And we'll continue to investigate specific aspects of wound healing, such as angiogenesis. Lastly, the study of diabetic foot ulcers will be finalised in 2022. In that study, there are large differences between patients which pose quite a challenge, so we need a lot of data from many different patients before we can draw robust conclusions.

***Wouter ten Voorde** is a Clinical Scientist and PhD student at CHDR. 'I studied bio-pharmaceutical sciences, partly in the same research group where Robert Rissmann and Jeroen van Smeden used to work before they joined CHDR. I first came to CHDR as an intern, helping to validate the DermaToolbox measurements that I've now also used in the research described here. I began my PhD in 2019, and fortunately, I was able to continue working on it during the coronavirus pandemic. My PhD research is broader than just wound healing: I also work on challenge models with imiquimod and LPS (see also page 65).'*




# Immunology

# Reaping the benefits of new models

The work of the Immunology and Cardiovascular group in 2021 paved the way for new studies in the years to come. By administering several challenge models to the same test subject, the team is able to gain deeper insight into the action of new agents on the immune response. At the same time, vascular tests that were validated in previous years are now delivering insights for clinical studies.

‘Over the last few years, we have developed and validated a number of challenge models that can measure various aspects of the immune response,’ says Dr Matthijs Moerland, Research Director and head of the Immunology and Cardiovascular group. ‘We’ve also seen increased interest from clients. That in turn helps us to understand our own challenge models in more detail.’ Read more about these challenge models on page 65.

## Combining challenges

In 2021, the Immunology and Cardiovascular group explored the benefits of applying challenge models in combination. Moerland: ‘We were approached by a large pharmaceutical company who had developed a number of substances with an inhibiting effect on innate immunity. Following the first studies in healthy volunteers, they wanted to know which of two potentially successful substances would be best to develop further, and for which patient population.’ To answer this question, Moerland and his team set up a study in healthy volunteers to compare four conditions: compound 1, compound 2, placebo, and prednisolone as active control. First, the imiquimod challenge test was used: imiquimod was applied locally on the subject’s back, and the inflammatory response was analysed using non-invasive methods from the DermaToolbox as well as suction blisters (see also page 56). Then, after a day of rest, an intravenous LPS challenge was applied. In addition, the subjects’ immune cells were stimulated ex vivo using various innate immune agonists.

‘The combination of challenges in the same subject proved to be feasible and not too burdensome for the individual,’ says Moerland. ‘Scientifically, the beauty of this combination is that we received information in different layers. We were not just comparing two different receptors involved in the innate immune response, but also two compartments. Immune cells in tissues, such as in the skin, sometimes behave differently from immune cells in the blood. Recently, we have seen that corticosteroids have a different effect on immune cells in the blood than those in the tissues. Obviously, most drug effects have to take place within the tissues. By administering LPS intravenously, we could also gain insight into the systemic reactions. We are currently analysing the results, but I am confident that we will be able to provide our client with useful answers. In the meantime, we have started other studies with a similar concept.’

## Intestine, nose, and lungs?

Moerland and his colleagues are now also working on ways to study immune responses in tissues other than the skin, such as the mucous membranes of the intestine and the nose. ‘In the intestine, for example, we can look at the effect of oral vaccines. Given that innate immunity is always involved in an adaptive immune response, this also gives us insight into the manner in which drugs influence the functioning of the innate immune system.’

A study conducted in 2021 involved a compound intended to activate innate immunity in the nose. If it turns out to be effective, this agent could be used as extra protection against viral respiratory diseases in situations where the infection risk is high — a possibility that is certainly attractive in light of the COVID-19 pandemic. ‘We’re also keen to see if it’s possible to develop a test like the LPS challenge in a form that is safe to apply to the lungs. Such a model would be particularly valuable for investigating drugs that aim to modify the activity of the neutrophil granulocytes in the lungs,’ says Moerland. ‘So, we’re looking forward to what we can learn by applying our existing models in sponsored studies, and meanwhile we’re busy thinking about new challenge models we could develop.’

## Blood vessels and metabolism

Alongside the application of new models in immunology, innovative studies were conducted in the field of vascular research. ‘In previous years, we had been busy validating various methods. In the past year, we were actually able to use them in clinical research, and we’re looking forward to seeing the results of the analyses,’ says Dr Pim Gal, who coordinates cardiovascular research at CHDR.

> ‘We’re looking forward to what we can learn by applying new challenge models’

One such study examined an experimental patch that creates a local increase in infrared radiation. The patch

was applied to the forearm of healthy volunteers. With various techniques, the blood flow was measured in the skin under this patch and compared with the untreated forearm. Another study was performed in collaboration with the Netherlands Organisation for Applied Scientific Research (TNO), focusing on the effects of ingesting a sweet milkshake on the (micro)vasculature in the skin. Gal: 'It is well-known that a high-calorie meal may temporarily influence the function of the endothelium. This intervention could be used in the future as a challenge test in healthy subjects.'

A third sponsored study was commissioned by a company working on a possible therapy for inherited disorders of the mitochondria. In this exploratory study, no intervention was used, but the mitochondrial function in patients was compared with that of matched healthy volunteers. 'We looked at the amount of NADH in the mitochondria, which is one of the key biomarkers to evaluate mitochondrial function, using flow-mediated skin fluorescence. This technique can be used to assess the vasculature by studying the effects of a temporary interruption of the blood flow. In addition, the technique can be used to evaluate the energy metabolism in the tissue, since NADH is used by respiratory chain complex 1 in the mitochondria. This new test has several potential applications for drugs affecting energy metabolism,' says Gal. 'Besides this, we have recently also validated a method to evaluate local oxygen consumption. In fact, there is much yet to be discovered in the area of energy metabolism.' Read more about CHDR's tools to investigate the functioning of blood vessels on page 68.



## Challenge models in clinical immunology

A challenge model mimics an aspect of a physiological response, such as an immune reaction. CHDR now offers several challenge models that focus on innate immunity. Innate immunity is the first line of defence against infections, and it is also involved in many adaptive immune reactions. One way to effectively trigger innate immunity is via the TLR4 receptor by the administration of lipopolysaccharides (LPS), substances that resemble the cell wall of bacteria.

In recent years, Moerland and his colleagues have developed several forms of LPS challenge: ex vivo (administration of LPS to blood cells outside the body), intravenous (systemic administration of LPS through a vein) and intradermal (local administration of LPS in the skin). Among these, the setup and validation of the intradermal challenge in particular has already revealed many new insights. The response to this challenge can be studied in detail thanks to CHDR's DermaToolbox, which offers several useful instruments to investigate and measure inflammatory responses in the skin.

The application of the intradermal LPS challenge involves creating suction blisters, in order to collect and study cells and cytokines in the blister fluid. Another intradermal challenge model using a similar approach focuses on innate receptor TLR7, by local application of the drug imiquimod (see also page 56). Again, the DermaToolbox and blister fluid are used to measure immune responses.

Besides innate immunity, challenge tests are also used to gain insight into adaptive immunity, particularly the cellular immune response. For this, the KLH challenge is used. This challenge leverages the immune response elicited by keyhole limpet haemocyanin (KLH), a neoantigen derived from a sea snail found near California. Read more about the KLH challenge on page 66.

# The KLH challenge as a readout for the adaptive immune response

**Dr Mahdi Saghari,** Clinical Scientist and Research Physician

## Why was this method developed?

We would like to have a reliable readout for the adaptive immune response, in addition to the various models we already have for the innate immune response. For CHDR, measuring the adaptive immune response is valuable for research into new immunomodulatory drugs, for example for the treatment of autoimmune diseases. Previously, we did not have a good measure to assess the adaptive immune response in healthy volunteers. That was the motivation to begin work on validating this method, which we did in 2017.

## What does the method involve?

Healthy subjects are given an intramuscular vaccination with a small dose of keyhole limpet haemocyanin, better known as KLH. This is an oxygen-transporting protein derived from a Californian marine mollusc. It is often used to amplify immune responses, for example in the treatment of bladder cancer. For us, it is particularly useful as a well-defined neoantigen — that is, an antigen that the test subject has never been in contact with before. We can measure the immune response to the vaccination by quantifying KLH-specific antibodies. The maximum response is reached after approximately three weeks, followed by a long-term steady-state antibody titre. After immunisation, we induce a response in the skin by injecting the KLH antigen intradermally in the subject's forearm. We measure the skin reaction, which is mediated by T cells, after 48 hours. We always compare the skin reaction with a placebo intradermal injection in the other forearm.

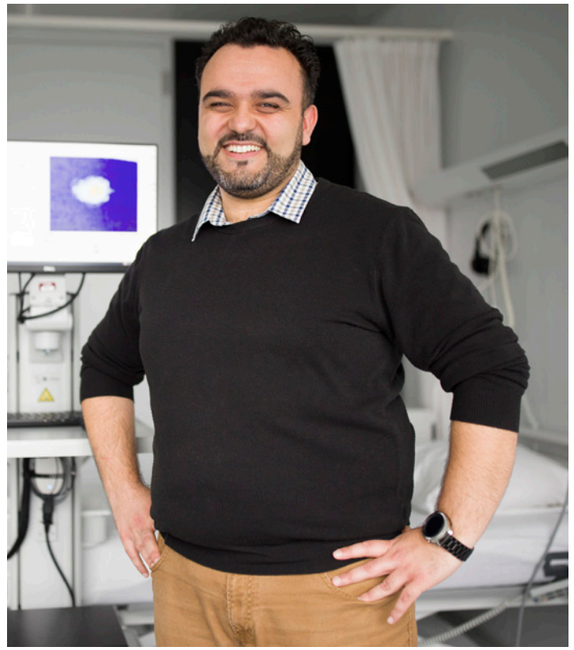
In order to better understand the role of different immune cells in the KLH response, and to further refine our KLH model, we are now conducting another study. In this study, we vaccinate subjects three times, instead of once as we did before. The idea is to then measure the activation of immune cells systemically. After just one vaccination it is not possible to find the subsets of KLH-activated immune cells — it really is like looking for a needle in a haystack! However, based on the literature we think it should be possible after multiple vaccinations. We are also taking a closer look at the skin reaction: KLH is a large protein, with many epitopes, and it seems to trigger a mixed reaction in the skin, in which the innate immune system and T helper cells also play a role. For that reason, we no longer measure only after 48 hours — we also measure shortly after administration of the intradermal antigen rechallenge and after 24 hours.

Besides the usual visual assessment, we quantify the KLH-driven skin response using techniques from the DermaToolbox, such as a multispectral camera placed on the skin to assess the lesion. In addition, we use laser speckle contrast imaging to measure changes in cutaneous blood flow. With these sensitive methods we can quantify skin responses that are not detectable by eye, and as such these methods are a critical component of the KLH model.

## What are the results?

We have carried out a number of clinical studies for clients in which we successfully evaluated the effect of a new compound based on the KLH model. Of course, we're continuing to develop and further optimise the model. In particular, we hope that the new approach of giving three vaccinations will be even more useful in revealing the effects of new immunomodulatory compounds. We're also keen to gain more insight into the immunological mechanisms involved in the KLH response: the better we understand that, the better we can interpret our results and contribute to the development of novel immunomodulatory compounds. Given the strong interest from the pharmaceutical industry in the KLH model, this should be a rich area of research in the years to come.

***Dr Mahdi Saghari** is a Clinical Scientist and Research Physician at CHDR. He hopes to obtain his PhD in the course of 2022 for his research on the KLH challenge. 'When I started here, I worked under Robert Rissmann of the Dermatology group. The original intention was to apply the KLH challenge in the context of psoriasis research. That study ultimately didn't go ahead, but there was a lot of interest in the KLH challenge from clients. So I moved to continue my research in the Immunology group. Apart from KLH-related studies, I have also led and assisted with projects in wound healing, seborrhoeic dermatitis, cardiology, and immunology. Once I've completed my PhD, I would like to become a dermatologist. I think my experience in immunology will be very useful, as the immune system plays a role in more than half of all dermatological disorders. I will also benefit from my experience with objective measurements from the DermaToolbox in my clinical work.'*



# Vascular test battery at the interface of metabolism and inflammation

**Dr Bas van Kraaij,** Clinical Scientist and Research Physician

## Why was this method developed?

Vasodilation and vasoconstriction are influenced by many systemic factors, such as metabolism and inflammation. They are therefore interesting readouts not only for therapies directly targeting the vascular tissue, but also for drugs with systemic effects, particularly those acting on the immune system and/or the metabolism. And since blood vessels are under the influence of the autonomic nervous system, blood vessel measurements could also be used to map autonomic dysfunction or autonomic side effects of drugs.

## What does the method involve?

We are developing a test battery to take a closer look at blood vessels and endothelial function in skin and mucous membranes. We usually use interventions or local challenges to induce vascular responses in healthy subjects. For example, we can heat the skin to elicit a vasodilation response. This response and the underlying mechanisms are well described in the literature. We can also temporarily interrupt the blood supply in the forearm using a blood pressure cuff on the upper arm — the response to this intervention involves other mechanisms than those involved in the reaction to heat. Challenge tests are used to induce a physiological response that temporarily throws the system off balance. For example, we are currently validating a challenge with allyl isothiocyanate, the substance that gives mustard its pungent flavour: when applied to the skin, the substance causes increased blood flow via the TRPA1 receptor.

Most of the techniques that we're using to measure blood flow have already been implemented by the Dermatology group as part of the DermaToolbox. Laser speckle imaging, for example, is a sensitive method for measuring the movement of red blood cells and thereby mapping out the blood flow. We can also film the most superficial blood vessels, for example in mucous membranes, and see how the blood cells move through them. The movement of blood cells and their distance from the vessel wall informs us about the glycocalyx, the protective layer on the inside of the endothelium. In the coming year, we expect to analyse data from a study using the LPS challenge, which challenges the immune system using lipopolysaccharides derived from the cell wall of bacteria. It is known that the glycocalyx can be damaged during sepsis, so it will be interesting to see if we can measure drug effects that way.

It's important to set up your experiments in such a way that you know which pathways are responsible for the effects you measure. In other words, you need to know how you can get from high-level readouts to the underlying mechanisms. For this, it's important to use challenges for which the mechanism is well defined. In the near future, we also want to map the effects on blood vessels of a number of existing medicines, in order to attune our test battery even better to drug effects.

## What are the results?

In recent years, we have validated a number of tests for studying the vasculature. We have found that the vascular response is reliably reproducible and that the results correspond to our expectations. We are now increasingly using our vascular test battery for sponsored clinical studies.

***Dr Bas van Kraaij*** *is a Clinical Scientist and Research Physician at CHDR. He is working on his PhD and training to become a clinical pharmacologist. 'When I came here in 2020, Pim Gal had just started setting up this type of vascular research. I am so happy to see our work already starting to pay off, both for our clients and for scientific research in general. We now have a lot of data that will help us further refine and expand the test battery.'*

# Internal medicine

# A collaborative approach to a diverse discipline

Many fields of expertise come together under the umbrella of internal medicine. For example, the study of new treatments for hepatitis B calls for a collaborative approach which integrates immunology, infectious diseases and oncology. Meanwhile, innovations such as novel drug administration routes and new fluorescent markers for surgery depend on advanced pharmacological expertise.

In 2021, internist Dr Naomi Klarenbeek was appointed Medical Director. 'In my new role, I draw on my broad experience in internal medicine,' says Klarenbeek. 'Whenever needed, I can support those Research Directors who are not themselves medical doctors, and I am the main point of contact if any unexpected situations arise during a clinical trial. For example, if a study participant suddenly develops symptoms, it's crucial to assess whether this is an unforeseen side effect or an unrelated event. During the pandemic, our clinical COVID team followed developments closely in order to ensure the safety of study participants and staff.' Alongside her various tasks as Medical Director, Klarenbeek is principal investigator for a number of studies in the field of internal medicine, while also contributing to CHDR's clinical pharmacology training programme (see page 75).

## Hepatitis B coalition

In 2021, progress was made in setting up a hepatitis B coalition with the university medical centres of Amsterdam and Leiden and a large hospital in The Hague. 'In the context of this partnership, we aim to carry out a collaborative study in patients with hepatitis B,' says Klarenbeek. 'Hepatitis B is a serious condition with a significant impact on the health and quality of life of patients. With current medicines, we're able to eliminate the virus from the bloodstream, but the disease always returns. Now, new drugs are being developed that hold promise for curing this disease or at least keeping the virus at bay for long periods, even after discontinuation of the treatment. In the past decade, we've seen a huge breakthrough in the treatment of hepatitis C, and it would be wonderful to achieve something similar for hepatitis B, which is actually far more common. We're looking forward to playing our part in the development of such novel treatments.'

Research into hepatitis B brings together various lines of research at CHDR: the field of infectious diseases (see also page 76), immunological research within the Immunology and Cardiovascular group (page 61), and even oncology (page 81). 'After all, hepatitis B is also a risk factor for developing liver cancer,' says Klarenbeek.

## New administration routes

Another of Klarenbeek's research interests concerns innovative ways of administering medicines. One such novel administration route is a ring that is inserted into the vagina, from which medication can be released into the body. What's more, the patient can control the release of the medication remotely, using a mobile phone app. 'This application has two potential advantages,' says Klarenbeek. 'First and foremost, this administration route means that the compound enters directly into the bloodstream without first passing through the liver. When drugs are administered orally, they must always pass through the liver, where metabolic changes often take place. This "first-pass effect" is a major problem for some medicines. Secondly, thanks to the possibility of controlled release, the medicine can be used on demand, which for some drugs obviously has an added value.'

In 2021, the team performed a study with the vaginal ring involving a drug that is already registered for the treatment of hyperactive bladder. Klarenbeek: 'This compound has side effects that may cause users to discontinue treatment. However, we know that the side effects are mainly caused by the metabolites of the drug, while the effect depends on the compound itself. Our research was primarily aimed at finding out — in healthy volunteers — whether administration via the vaginal ring leads to a more favourable ratio of compound to metabolites. This would make sense, because the vaginal ring circumvents the first-pass effect. We're currently planning a subsequent study to examine whether administration via the vaginal ring can achieve the same effect as oral administration with fewer side effects.'

## Green light: fluorescence in surgery

For a number of years, CHDR has been collaborating in the field of image-guided surgery with the 'Green Light' group led by surgeon Dr Alexander Vahrmeijer of the Leiden University Medical Center (LUMC). In image-guided surgery, fluorescent markers are used to make structures in the body more visible and thus improve the effectiveness and safety of surgical interventions. In recent years, for example, a substance has been developed that can visualise the ureters, reducing the risk of accidentally damaging these delicate structures during surgery. 'In 2021 we conducted some studies with a variant of this substance that has a more favourable pharmacokinetic profile,' says Klarenbeek, who is closely involved in this research alongside CEO Prof. Koos Burggraaf. 'Our primary focus is safety and pharmacokinetics. The pharmacokinetic profile of the

substance is particularly important: on the one hand, the fluorescence of the substance needs to remain visible throughout the operation, but on the other hand, it's important that it has cleared enough to avoid giving rise to interfering background signal from other tissues.' The collaborative team also completed a study involving a fluorescent marker for prostate cancer, and meanwhile, research is ongoing with tracers for GI tract malignancies. Klarenbeek: 'Our work in image-guided surgery demonstrates the diverse range of applications of clinical pharmacology in internal medicine — not only can we use our expertise to improve the treatment of a wide range of disorders, we can also contribute to improving outcomes of surgery.'



## Comprehensive clinical pharmacology training in Leiden

The Netherlands offers three tracks for clinical pharmacology training. In addition to the general training in clinical pharmacology, which is open to every physician, there is a training programme for hospital pharmacists and a training programme for internists. For several years, CHDR has provided general clinical pharmacology training, while the Leiden University Medical Center (LUMC) has provided training for hospital pharmacists. As of 2021, however, all three tracks are now offered in the Leiden region, thanks to the close partnership between CHDR and the LUMC.

Dr Naomi Klarenbeek, Medical Director at CHDR: 'The lead trainer is Prof. Teun van Gelder of the LUMC. From the CHDR side, the trainers are Jeroen van Smeden, Koos Burggraaf and myself. I'm really glad that we're now able to offer all three tracks in the Leiden region. I myself trained as an internist at the LUMC, but at that time, it was necessary to go to Rotterdam for the clinical pharmacology training. Now, Leiden-based internists can complete their training right here. What's more, our collaboration with the LUMC creates a unique opportunity for trainees to come to CHDR and learn more about drug development.'

# Joining the global fight against infectious diseases

For CHDR's infectious diseases researchers, 2021 was still very much marked by COVID-19. But regular work also got underway again, with the completion of a project investigating a treatment for malaria. In the coming year, the Infectious Diseases team hope to focus once again on their long-term strategy, including the development of challenge models for viral infections.

'For us, the pandemic was an opportunity to contribute to a number of global developments, from therapeutics to vaccines and prophylactic treatments,' says Dr Ingrid de Visser-Kamerling, Associate Director for Infectious Diseases. 'Usually, it takes years before we hear again about the compounds we test, but with COVID, things move fast! For example, we can find out very quickly which interventions are successful, and some have already become available for clinical use. It's very inspiring so see what can be achieved under such circumstances.'

## Synthetic antibodies against SARS-CoV-2

In the first half of 2021, De Visser and her team were involved in a pilot study for a new early treatment for COVID-19. The treatment is based on a revolutionary new concept called DARPins (designed ankyrin repeat proteins). 'These biotechnologically produced proteins act as antibodies, and they are already being used in research and as (experimental) drugs for various diseases. Our client wanted to set up a study among ambulatory patients who are newly infected with SARS-CoV-2, to see if DARPins protect patients against severe disease.

'We were able to successfully execute this study thanks to our cooperation with the municipal health service and the Leiden University Medical Center (LUMC). People who got a positive COVID test result were notified about our study by the municipal health service. If interested, they could contact us for more information. After the informed consent and screening procedure, participants went to the LUMC for drug administration and the collection of blood and nasal samples,' says De Visser. 'We took every possible precaution to avoid spreading the disease. It was demanding for everyone involved, including the LUMC nurses who had to adapt their working methods to adhere to our protocol. Ultimately, both the study and the cooperation were a success. We were finished just in time, before the numbers of patients started to fall sharply due to vaccination and the start of the summer season.'

Based on the results of the study, the client decided to set up a larger phase 2 study. This phase 2 study showed that the DARPins do indeed provide strong protection against severe forms of COVID-19, and the patent has since been bought by a large pharmaceutical company. Besides the study with DARPins, CHDR's infectious diseases researchers have also been involved in other projects related to COVID-19. For example, first-in-human studies were conducted with two agents that may have a prophylactic effect against infection with SARS-CoV-2 and other respiratory viruses.

## Challenge models

'It was good to contribute to international COVID-19 research. But these were ad hoc projects that did not stem from our long-term strategy,' says De Visser. 'In the coming year, we want to focus more on the big picture again: devising innovative methods for developing new vaccines and antivirals. In collaboration with Prof. Meta Roestenberg of the LUMC, we will also continue to develop new challenge models for infection.' In an infection challenge, healthy volunteers are purposely infected with a pathogen, to see if a treatment or vaccine is effective. In 2021, for example, the team completed a challenge study concerning an antimalarial drug, in which volunteers were infected with the malaria parasite. 'The study was ready to begin, and then had to be postponed due to the COVID-19 pandemic. So we were glad to be able to get back to work on it this year,' says De Visser. 'The drug that we tested had already been evaluated for the treatment of malaria. In this study, we were able to show that it also has a prophylactic effect.' Read more about the malaria challenge study on page 78.

As part of the Inno4Vac consortium, CHDR and the LUMC can draw on a large European grant that will fund work on innovative vaccines against respiratory syncytial virus (RSV) and influenza in the years to come. De Visser: 'Our clinical research unit has been remodelled to pave the way for infectious diseases research at CHDR. Now we have the facilities needed to safely conduct pathogen challenge studies. As part of this, we're able to offer study participants spacious, single-occupancy rooms in which they can isolate in comfort. We hope to start using these facilities for studies in the next year.'

# Studying antimalarial compounds using a controlled infection model

**Dr Johan van der Plas,** Clinical Scientist and Research Physician

## Why was this method developed?

Assessing effectiveness of drugs or vaccines targeting infectious diseases in early phase clinical trials in healthy volunteers can be difficult, because these compounds target (directly or indirectly) pathogens that are not present in the body under normal circumstances. To overcome this challenge, controlled human infection models, in which healthy volunteers are infected with pathogens, have been developed. Besides allowing early assessment of efficacy, controlled infections also provide opportunities to learn more about the disease process, especially the early stages, which normally take place out of sight of the clinician.

In the field of controlled human infection models, we collaborate with Prof. Meta Roestenberg, infectiologist and professor of Human Models for Vaccine Development at the Leiden University Medical Center (LUMC). Prof. Roestenberg has extensive experience with these models, especially in the field of malaria.

## What does the method involve?

We recently used a controlled malaria infection model validated by the team of Prof. Roestenberg to study a novel antimalarial drug. This model uses cultured sporozoites: these are malaria parasites, at the stage of their development when they would normally be transmitted by mosquitoes. Sporozoites are harvested from the salivary glands of the malaria mosquito, and this procedure is undertaken by a company that produces cryopreserved parasites under GMP conditions. Several hundred sporozoites are administered to each study participant intravenously, and these then migrate to the liver and develop into merozoites, the next stage of the parasite. During development in the liver, the study participants have no symptoms and can be monitored on an outpatient basis. Regular blood samples are examined using PCR tests to check the level of parasitaemia. Whenever the number of parasites in the bloodstream reaches a predetermined threshold, or if the study participant starts to develop symptoms, we immediately halt the infection by providing rescue medication in the form of registered antimalarials to which the parasite is susceptible.

In this study, we worked in close collaboration with Prof. Roestenberg's group at the LUMC. Subjects were screened by CHDR, and then went to the LUMC for administration of malaria parasites. Subsequently, every subject was randomised to receive either the novel antimalarial drug or placebo in our clinical research unit (CRU), and stayed there for the first three days of intensive sampling. After discharge from our CRU, the LUMC monitored subjects on an outpatient basis, and treated subjects who developed malaria infections.

## What are the results?

In the malaria study, the challenge model had a 100% success rate — which is not that common for controlled human infection studies — and enabled us to gain preliminary insight into the efficacy of the compound. We also gained new insight into the optimal timing and dosage for administering the antimalarial medication. In addition, the study demonstrated the synergistic collaboration between CHDR and the LUMC, and we enjoyed working with Prof. Roestenberg's group. So we're all looking forward to the opportunity to pursue the collaboration further as we begin studying respiratory viruses together.

***Dr Johan van der Plas** is a medical doctor who worked as a Clinical Scientist and Research Physician within the therapeutic area of infectious diseases at CHDR. 'I'm currently finishing my PhD thesis, which will be about various studies we performed within the area of infectious diseases. In addition, I am currently working in the Internal Medicine ward of a general hospital near Amsterdam. My plan for the future is to contribute to both patient care and drug development as a physician-scientist and clinical pharmacologist.'*

## Dr Jacobus Bosch to lead new Oncology group

The Board of Directors has appointed oncologist and early phase drug development specialist Dr Jacobus ('Co') Bosch as Research Director for Oncology, starting 1 January 2022. In fact, Bosch is not a newcomer to CHDR: in the late 1990s he worked as a research assistant at CHDR alongside his university studies, and he has kept in touch ever since. 'The philosophy of CHDR has always appealed to me. So I was immediately attracted by this new position, with the goal of establishing oncology as a distinct research area at CHDR.' Bosch's career has encompassed basic and clinical immunotherapy research in both the United States and Germany. From 2007 to 2010, he also served on the Associate Member Council of the American Association for Cancer Research (AACR). 'My experience there really showed me the value of collaborative work, and its importance for developing new therapies in oncology.'

Bosch spent much of the past decade at University Hospital Erlangen, Germany, where he combined his clinical work as a medical oncologist with translational research. In the years before joining CHDR, he was based at the Center for Clinical Trials of Hannover Medical School (MHH) in Germany, where he was clinically responsible for the early phase clinical trial unit (ECTU). In that role, he oversaw the initial studies with one of the COVID-19 vaccines, among other early phase studies.

To lay the groundwork for oncology studies at CHDR, Bosch is busy building alliances with strategic partners in Dutch university medical centres and teaching hospitals. 'We've already initiated constructive dialogues to set things in motion,' says Bosch. 'In collaboration with our partners, we look forward to contributing to the development of much-needed new therapies for cancer patients.'

# Biomarkers and Laboratory

# A renewed focus on research and development

The past year saw the transfer of advanced cellular measurements from the Research & Development lab to CHDR's operational laboratory. 'The transition has been a success,' reflects Dr Matthijs Moerland, head of the Research & Development lab. Over in the operational laboratory, the advanced cellular measurements now fall under the responsibility of Bioanalytical Scientist Pieter Hameeteman: 'We have always worked closely together, so I can count on the support of my colleagues in the Research & Development lab as we conduct these new measurements.'

'Now that we don't have to divide our time between operational work and R&D, we can invest all our energy in developing new methods,' says Moerland. The Research & Development lab is tasked with developing methods to study immune cells and measure immune responses. In addition to characterising various blood cell types (immunophenotyping), it is also possible to measure the functions of such blood cells. With a detailed understanding of the phenotype and function of circulating immune cells, it is then possible to use these cells as a proxy for those that are harder to reach: for example, joint-infiltrated immune cells in arthritis, or microglia in the brain.

## Advanced cellular measurements

The work of the Research & Development lab underlies the success of many recent clinical studies at CHDR, playing a key role in the work of the Immunology and Cardiovascular group, the Dermatology group, and the Neurology group. But recent success brought a challenge along with it: in order to complete all the advanced measurements required for clinical studies, the technicians and scientists in the Research & Development lab increasingly had to leave their R&D work to one side. Moerland: 'The more successful we were in attracting sponsored studies, the less time we had to develop novel methods.'

However, CHDR also has an operational laboratory, where blood and other materials collected in clinical studies are examined or prepared for further analysis elsewhere. Moerland: 'We decided to move the advanced cellular measurements developed in the R&D lab to the operational laboratory. These advanced analysis techniques, such as flow cytometry, now fall under the responsibility of our colleague Pieter Hameeteman, who has recently moved from the R&D lab to the operational lab.

## Handover

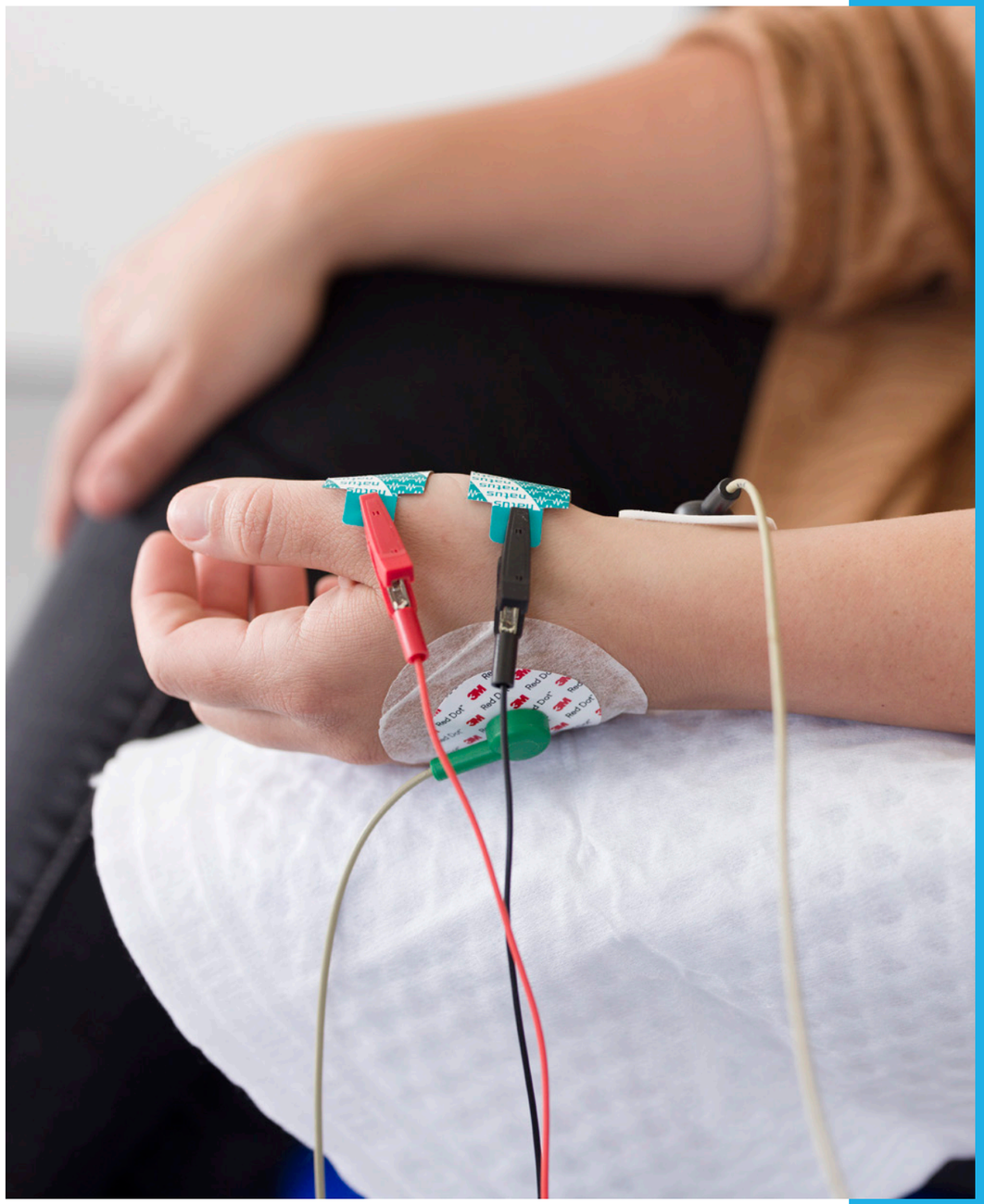
Hameeteman: 'Everything is running smoothly. The lab technicians in the operational lab have the same training as those in the Research & Development lab. Our operational lab technicians were already used to lending a hand with the R&D lab work when needed, and many of them appreciated the opportunity to broaden their experience with these more advanced techniques.' Hameeteman's new role is to carry the responsibility for the bioanalytical work conducted

by the operational lab, and to provide instruction for technicians conducting the advanced analyses. One such technique is flow cytometry, which can be used to look at subsets of immune cells and measure their activation status. By using a control sample for comparison, it can be determined whether a change has occurred due to a challenge test and/or drug treatment. ‘In flow cytometry, it is important to have sufficient insight and experience to be able to determine whether the measurements are correct. We work with fresh materials, so you don’t get a second chance — you have to be able to identify immediately if something isn’t going right.’

‘We can offer a range of advanced analysis techniques and still have capacity for innovative R&D’

Another part of the work focuses on ex vivo tests, in which fresh blood from study participants is exposed to a drug or a challenge test (such as the LPS challenge, see also page 65). ‘Technically, this is not as complicated as flow cytometry, but it still requires close attention to the protocol. Maintaining a sterile environment is critical: if a sample is contaminated, it can take quite some time before it becomes noticeable,’ says Hameeteman. Once the tests have been applied, the samples are frozen in order to be examined later by an external laboratory.

Hameeteman remains involved in the work of the Research & Development lab, so that any new techniques that are developed there can in the future be transferred to the operational lab. ‘I attend their weekly meetings, so that I always have an idea of what they are working on,’ says Hameeteman. ‘And if I ever have a question, I know exactly who to call. That’s the great thing about CHDR, you’re never working solo — there’s always someone ready to help out.’ Moerland is also pleased with the transition: ‘It’s not an easy decision, to hand over responsibility for our “brainchildren”. But with the setup now, we’re able to keep offering a range of advanced measurements and analysis techniques while also making room for innovative R&D to flourish.’



# Biomarker Engineering and Analytics

# Cradle of innovations: biomarker engineering and analytics

The Biomarker Engineering and Analytics group is engaged in the development of new measurement methods and analysis techniques to map drug effects in healthy volunteers and patients. The group consists of research professionals with a range of backgrounds, from electrical and biomedical engineering to technical medicine and data science.

'In 2021, we brought the whole group together for two strategy meetings where we aimed to formulate a common vision,' says Dr Robert-Jan Doll, Associate Director for Biomarker Engineering and Analytics. 'As a result of these discussions, we decided to change the name of our group from Method Development to Biomarker Engineering and Analytics. We were looking for a name that better aligns with the activities of our Clinical Research Engineers, Data Scientists, and Clinical Scientists. And since our goal is to introduce novel biomarkers, we thought that should be reflected in the name too.' In addition, three working groups were set up to implement the plans that emerged from these strategy meetings. 'For example, we want to take more initiative to proactively pursue new lines of enquiry, so that we can be better prepared for the research questions that our clients may have. To this end, we will also regularly invite the Research Directors of the different therapeutic areas to brainstorm together about developments in their field.'

## Engineering new measurements

As the new name already indicates, the activities of the group can be broadly divided into two areas: engineering and analytics. 'These activities overlap, of course, and it's important that the two strands align well with each other,' says Doll. 'With experts in both these fields working together within our group, we can achieve a good synergy between the two.' Engineering involves the development of new measurement setups for data collection which can then be integrated into the organisation's operational processes. In the past year, the group worked on a range of such techniques, intersecting with the full range of research areas at CHDR: the application of virtual reality in pain research (see page 34), the development of a standardised measurement method for emotions (see page 42), an interactive walkway used to map the side effects of sleep aids (see page 46), and techniques to quantify essential tremor, namely tremography and a spiral drawing task using a touchscreen device (see page 28).

In a study for a candidate drug for the neurological muscle disorder myasthenia gravis, the group demonstrated how a variety of different techniques can be combined to give in-depth insight — in this case, into the muscles of patients. Doll: 'Besides methods that had already been implemented some time ago, such as threshold tracking and muscle velocity recovery cycles, a few new methods were also introduced for this trial. The first is a measure of eye muscle exhaustion, using eye-tracking cameras. In this technique, the patient is asked to fix their gaze on a point high up, and we measure the degree to which their eyes drop down over time. Another novel technique we implemented for this study is a voluntary grip task, which quantifies the time it takes for muscles to relax. In myasthenia gravis and some other conditions, this is slower than in healthy subjects. In this method, we ask patients to grip a special device — known as a dynamometer — as hard as possible, and then measure how fast they are able to release their grip.'

## Analytics and machine learning

The analytics arm of the group aims to distil biomarkers from the vast amount of (raw) data collected. 'The data we work with vary between data collected using a single method — such as responses to stimuli and questionnaires, or electrophysiological data — and data collected from multiple methods or even multiple studies. These last two types of data are often used to build predictive machine learning models.' The analysis of EEG data provides a good example of how the group is able to obtain a number of informative biomarkers from large amounts of data collected using a single method (see also page 94). 'For five years now, we have been using a 32-lead EEG setup as standard. We therefore now have a large dataset at our disposal that includes hundreds of diverse subjects, covering both healthy volunteers and patients, which can be used in various ways. For example, we are currently using these data to train a model which is able to estimate a person's age in years based on their EEG. The model has already shown promising results, and we're now in the process of validating the model by assessing its repeatability and sensitivity to drug-induced changes,' says Doll. In other studies, the group collaborates with different universities on the processing of EEG data. 'Together with University Medical Center Utrecht, we studied EEG patterns of patients experiencing delirium, using a model derived from earlier studies in

healthy subjects who had received either placebo or amphetamine. Another example is our collaboration with the University of Twente: in a clinical trial performed at CHDR, we demonstrated that sleep deprivation affected cortical activity following electrical stimulation of nociceptive fibres.'

Meanwhile, the data scientists of the Biomarker Engineering and Analytics group work on developing models for data sets obtained from various studies. 'Recently, we've analysed data from a study where patients with depression were monitored remotely using Trial@home,' says Doll (see also page 44). 'In addition, we've developed a model to predict disease progression in patients with Parkinson's disease. In the same group of patients, we were also able to show that two simple tests — the finger-thumb test and the finger tapping task using a touch screen — were predictive of scores on the Unified Parkinson's Disease Rating Scale (UPRS).

'Due to Trial@home and other developments, such as studies of the microbiome, we are increasingly dealing with complex data sets,' says Doll. 'In this regard, we are fortunate to be able to draw on the expertise of our team members who are specialised in machine learning and other data analysis techniques. In fact, one of the great advantages of our group — indeed, of CHDR as a whole — is that it brings together professionals with very different backgrounds. With this diversity of expertise and perspectives, we're well equipped to contribute to innovation in the field of biomarker analysis techniques.'



# Growing EEG capabilities

CHDR's NeuroCart® offers a unique, standardised battery of neurophysiological tests. EEG has been an integral part of NeuroCart for many years now, meaning that research assistants can easily perform resting-state or task-specific EEG recordings using one of the many NeuroCarts available at the clinical research unit. All the software required, from stimulus presentation to data acquisition and analysis, is developed in-house. 'In addition, we're always adding new tasks and features to meet specific needs,' says Dr Robert-Jan Doll, Associate Director for Biomarker Engineering and Analytics.

EEG is part of the standard repertoire of techniques for assessing drug effects on the brain. Resting-state EEG, where brain activity is recorded while the participant is at rest, was one of the first EEG tasks to be integrated into NeuroCart®. 'If the resting-state EEG changes after administration of a drug, you can be sure that the drug is crossing the blood brain barrier. Additionally, we can use this technique to demonstrate a dose-response relationship,' says Dr Annika de Goede, Clinical Research Engineer in the Biomarker Engineering and Analytics group. Initially, we only recorded resting-state EEG with the participant's eyes closed. But since 2017, we've been including recordings with the participant's eyes open. This allows comparison between different resting conditions.'

## High gamma frequencies

In clinical drug development, there is growing interest in the gamma frequency range of brain activity, particularly the frequencies between 30 and 90 Hz. 'In preclinical animal studies, interesting drug effects are often seen in that specific range,' says Doll. 'We want to measure the activity within this range in humans, and see if the preclinical findings can be translated. However, EEG measurements in laboratory animals are often recorded directly on the brain, using electrodes implanted in the skull, while in human subjects we measure the EEG using surface electrodes. That poses a challenge when it comes to the gamma range, because this frequency range is extremely sensitive to noise.' In particular, the high gamma range overlaps with muscle activity (20–300 Hz) and with the frequency of mains electricity, which in the Netherlands fluctuates around 50 Hz. 'All in all, it is difficult to obtain clean EEG in the high gamma frequency range.'

In collaboration with academic and industry partners, Doll, De Goede, and their colleagues have been working on various adjustments to enable reliable measurements in the gamma range. Doll: 'We made various changes to the recording setup, such as ensuring minimal neck and shoulder movements, as well as co-recording eye and muscle activity and the frequency and phase of the mains electricity. We also refined the analysis pipeline, implementing advanced correction and filtering techniques.' De Goede: 'By co-recording the EMG of the most important muscle groups, we can afterwards use the data to clean the EEG, and, if necessary, to cut out highly contaminated parts. Likewise, by having an electrode that is dedicated to recording the frequency and phase of the mains electricity, we can later use mathematical processing to remove this signal from the EEG.'

## Event-related potentials

Besides recording the activity of the brain at rest, it is possible to gain insight into stimulus processing by recording brain activity before, during, and after a specific stimulus, or while performing a specific task — in other words, by recording event-related potentials (ERPs). ERPs can be used to measure the functioning of certain brain circuits and assess drug effects. The Biomarker Engineering and Analytics group has developed software for a number of such specific applications, such as the recording and quantification of potentials evoked by various types of stimuli (e.g. heat, audio, visual, and electrical stimuli). Doll: 'One method that has recently been developed is auditory sensory gating. This involves measuring the response in the EEG when the participant hears two identical tones in quick succession. In a normally functioning brain, the response to the second tone is inhibited, but in some disorders — such as schizophrenia, bipolar disorder and autism — this inhibition is impaired.'

Other auditory techniques include the well-known oddball task, in which a low-probability stimulus elicits a specific cortical response known as a P300 wave. Doll: 'Another potential evoked by auditory stimuli is mismatch negativity. To elicit this, the participant is presented with standard tones, among which a deviant tone is presented every now and then. The cortical responses to the standard and deviant tones offer a possible biomarker for cognitive processes in a variety of neurological and psychiatric disorders. In the past, we used a single deviant tone, but it turned out that this approach wasn't always sensitive enough for the drug development setting. Therefore, we're now testing a variant of this method, the Optimal-3 paradigm, which uses three deviant tones that differ in multiple characteristics from the standard tone. We hope this new paradigm will prove to be a useful tool in CHDR's psychiatry and neurology research,' says Doll.

Other EEG tasks integrated into the NeuroCart

encompass visual evoked potentials (including long-term potentiation-like effects), and the auditory steady state response (ASSR). Doll: 'The ASSR task exploits the phenomenon that a periodic sound, such as a 40 Hz square wave, causes brainwaves to synchronise within seconds. The degree of synchronisation is influenced by various factors, including sleep deprivation, and can therefore be a measure of drug effects.'

## EEG and TMS

De Goede began contributing to EEG research at CHDR even before she joined the organisation. 'As a postdoctoral researcher at the University of Twente, I validated various measurements using transcranial magnetic stimulation (TMS),' says De Goede. 'The transcranial magnetic pulse influences the brain, inducing an evoked potential which can be measured in the EEG. Alternatively, TMS applied on the motor cortex can induce motor activity — in the hand, for example — which can be measured using EMG.' Both TMS-EEG and TMS-EMG are now regularly used in clinical studies at CHDR, using a dedicated setup distinct from the NeuroCart. 'The main application of TMS in combination with EEG is to map how easily the cerebral cortex can be excited. Using this technique we have been able to show, for example, that anti-epileptic drugs decrease the brain's excitability, while antidepressant drugs increase excitability.'

Building on years of experience, the team is always busy improving or adding measurements to their EEG toolbox. Doll: 'We know our setup inside out, and we develop all our software in-house. While this is quite an undertaking, there are huge benefits in knowing precisely how data was captured and analysed, as well as having access to the unfiltered EEG data.'

‘More collaborative than a typical CRO’

## Working with CHDR

‘CHDR is more collaborative than a typical CRO, both in terms of the science and the project management. I've been working with them a long time, and we’ve built up a friendly, close relationship which translates to a high level of quality.

I think innovation is vital, and CHDR is a very important partner in that regard. They show their innovative power with the scientific expertise that goes into a study. They have a sense of curiosity that sets them apart from other CROs.’

**Senior Clinical Trial Manager, Biotech Company ***

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


No SIM
19:35
Scores
Bevestig
6
slaap
Geef een cijfer van 0 (slechtst mogelijke slaap) tot 10 (best mogelijke slaap)
7
misselijk
Geef een cijfer van 0 (niet misselijk) tot 10 (ondragelijk misselijk)

# Trial@home

# A pioneering platform ready for an expanding market

Over the past five years, CHDR has developed, validated, and perfected the Trial@home concept for remote monitoring. Using mobile devices, a range of variables can be monitored while study participants go about their daily lives. Additional well-validated measurement methods, including those from the NeuroCart®, are regularly being integrated into the platform. Trial@home is poised to take the lead in the growing market for remote monitoring in clinical trials.

‘A lot has happened in recent years, both within Trial@home and in the marketplace,’ says Dr Vasileios Exadaktylos, manager of Trial@home. ‘We have achieved a number of important milestones, both in terms of content and in terms of integrating our systems into CHDR’s operations. Meanwhile, we're seeing a growing demand for remote monitoring in biomedical research and in healthcare, so the number of competitors has also increased. That’s almost a law of nature — as soon as you bring a good idea to market, competition will soon follow. But as a pioneer, we still have an edge. Above all, we grew out of a CRO background: the Trial@home ecosystem is designed from the ground up to answer the driving questions of drug development, rather than having pivoted from gaming peripherals or similarly unrelated applications.’

## Operational integration

‘As of 2021, Trial@home is fully integrated with clinical operations at CHDR,’ says Exadaktylos. ‘Previously, we had to make some adaptations, but now, all the technical and operational issues have been ironed out. Staff across the organisation are now accustomed to working with the platform, and we’ve also finished drawing up the necessary standard operating procedures, so everything can run smoothly.’ Another milestone has been the transition to the cloud: ‘The preparations have all been completed and the transition will be implemented in the course of 2022.’

Meanwhile, the Trial@home team has also been expanded, welcoming two more staff members. This adds more flexibility and allows the team to pursue an even wider range of opportunities to apply the platform. ‘We’ve been working on approaching potential clients directly, offering remote monitoring for trials as a standalone service. A possible next step along these lines would be to offer the Trial@home platform itself for use by other researchers or CROs.’

## NeuroCart tests at home

The possibilities of the Trial@home platform are constantly expanding. In one study conducted in 2021, a task from the NeuroCart known as the ‘adaptive tracker’ was performed by trial participants at home on a laptop computer. In this test, the subject uses a joystick to move a small dot so that it stays within a continuously moving circle on a computer screen. ‘Previously, this test was always administered in-house in the presence of a measurement assistant. Now, the test can be completed at home by anyone who is able to operate a laptop,’ says Exadaktylos. ‘In this particular study, we were focusing on children with a specific congenital disorder. After brief instruction, the parents were able to help their child perform the test.’

The team expects more tests to be translated from the NeuroCart to the Trial@home platform in the coming years. One such test the team already has its eye on is the finger tapping task, which is used in clinical studies of treatments for Parkinson’s disease. Exadaktylos: ‘Adapting tests like the finger tapping task can be valuable for researching drugs whose effects only become visible after a longer period of time. If participants can carry out the tests from the NeuroCart at home, it offers opportunities for long-term follow-up without people having to come to our facility every time. We are also taking part in the ProPark study being run by the Leiden University Medical Center (LUMC), which follows and analyses a cohort of patients with Parkinson’s disease. That will likely provide interesting data for future applications.’

> ‘The Trial@home ecosystem is designed from the ground up to answer the driving questions of drug development’

## Opportunities for insight

In order to validate measurements for the Trial@home platform, the team often links up with ongoing studies within CHDR. One such example is a study in which an interactive walkway and the Timed Up and Go test were applied to measure potential side effects of sleep aids in healthy elderly subjects (see also page 46). The team used these data to validate the models from a study of the neurological condition facioscapulohumeral muscular dystrophy (FSHD). In that study, smartphone and wearable data from patients and healthy (younger) adults were used to predict the outcome of the Timed Up and Go test. The new dataset proved to be useful in validating and refining the model.

Trial@home was also used in a Psychiatry study that took place in CHDR's clinical research unit (CRU). In this study, healthy volunteers stayed a few nights at the CRU, and the sleep quality of the test subjects was measured using Trial@home technology. Exadaktylos: 'It sounds paradoxical to use Trial@home in a clinical setting – that is, not "at home". And yet, this could be a valuable application. If it turns out that sleep quality affects the outcomes of the trial, the data will be available to correct for it. Such a correction increases the power of a study and improves its scientific contribution.' Using Trial@home technology to measure participants in the CRU can also be a way to ensure continuity, for example when participants are being monitored at home and then stay at the facility for a few days.

## Expanding the possibilities

'To be able to contribute to drug development, the Trial@home platform must be robust and at the same time sufficiently versatile to integrate new measurements,' says Exadaktylos. 'To be even more versatile, we can also incorporate applications developed by others. We did so for a study in 2021 in patients with atopic dermatitis. There, we integrated a smartwatch application that was able to objectively determine how often a patient engaged in scratching.'

An area in which Exadaktylos sees great potential for the Trial@home platform is oncology. 'We are already conducting a study for the LUMC in patients who have undergone various surgical treatments for colorectal carcinoma. Trial@home is valuable here as a means to measure recovery, mobility, and sleep quality over longer periods of time. These are important outcome measures, but until now researchers have always had to rely on the subjective reports of patients.' Exadaktylos is therefore pleased with CHDR's strategic choice to carry out more studies in the field of oncology. 'I think Trial@home has great potential to contribute to future oncological studies at CHDR.'


# Operations

# Overcoming operational challenges

Businesses around the world continued to be impacted by the COVID-19 pandemic in 2021, and CHDR was no exception. Maintaining clinical operations in the face of unpredictability demanded improvisation and creativity. At the same time, it was vital to prepare for post-pandemic growth, by expanding facilities for the screening of study participants.

‘The pandemic showed clearly how interdependent we all are,’ says Clinical Operations Director Dr Ard Vink. ‘Our clients and suppliers were, of course, facing the same problems as we were: staff absences, supply chain issues, and overall increased uncertainty. For example, delays in preclinical research had a knock-on effect for first-in-human studies, making it much more uncertain than usual whether a study would go ahead at the planned time. A relatively large number of studies were postponed or even cancelled, so we needed to adjust our planning.’

## Helping each other out

CHDR had to contend with various limitations due to the pandemic. Staff absences were one of the main problems: ‘Many of our staff members have young families, who run a relatively higher chance of catching the virus. People became ill themselves, or were at home with a child who was sick or in quarantine. Fortunately, our employees were also very flexible. People were willing to take on extra shifts and cover each other's work. That helped enormously, but nonetheless, there were inevitably still some delays,’ says Vink.

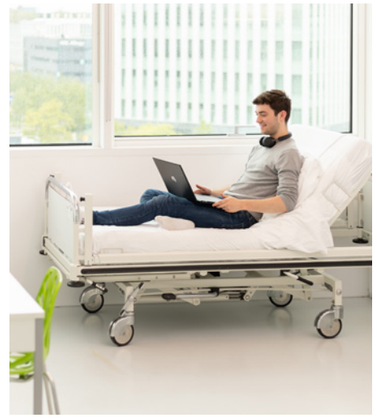
The recruitment of study participants was also hampered by the pandemic situation. The measures to reduce the spread of the virus made it more difficult for people to travel, and the restrictions on public life led to an overall reduced interest in study participation. And even if subjects were recruited, there was no guarantee that they would participate. Vink: ‘The percentage of no-shows at the screening site was considerably higher than usual. Undoubtedly in many cases this was as a result of needing to quarantine or isolate due to the coronavirus. Most of our study participants are in their twenties, and this demographic saw a particularly rapid spread of the virus in 2021.’

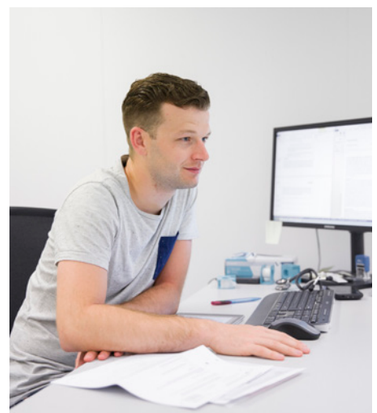
These issues had a multifaceted impact on operations, from increasing recruitment costs to hindering study execution itself. Vink: ‘In ascending dose studies, for example, you can only start on the next dose when the results from the previous group have been analysed — only then do you know whether it’s safe to increase the dose. So when a cohort is incomplete due to dropouts, you have to wait longer while the gaps are filled with new participants.’

## Screening site expansion

Despite the recent challenges, Vink is looking ahead to opportunities for further growth in the years to come. The expansion of CHDR’s clinical space, which was realised in 2020, had added benefits in 2021. ‘With more capacity, we could be more flexible. Our additional office space, which is in a building near the main facility, was put to good use during this time,’ says Vink. ‘We look forward to being able to use our expanded clinical research unit even more fully in the year ahead, when social distancing rules are lifted.’

In anticipation of post-pandemic growth, the screening location next to Leiden’s main train station was also expanded in 2021. ‘We now have extra space for the screening and training of study participants. This is particularly helpful for those studies where the participant has to be familiarised with the equipment, such as NeuroCart or PainCart,’ says Vink. ‘Increasing screening capacity is a vital step in equipping ourselves to meet the growing demand.’

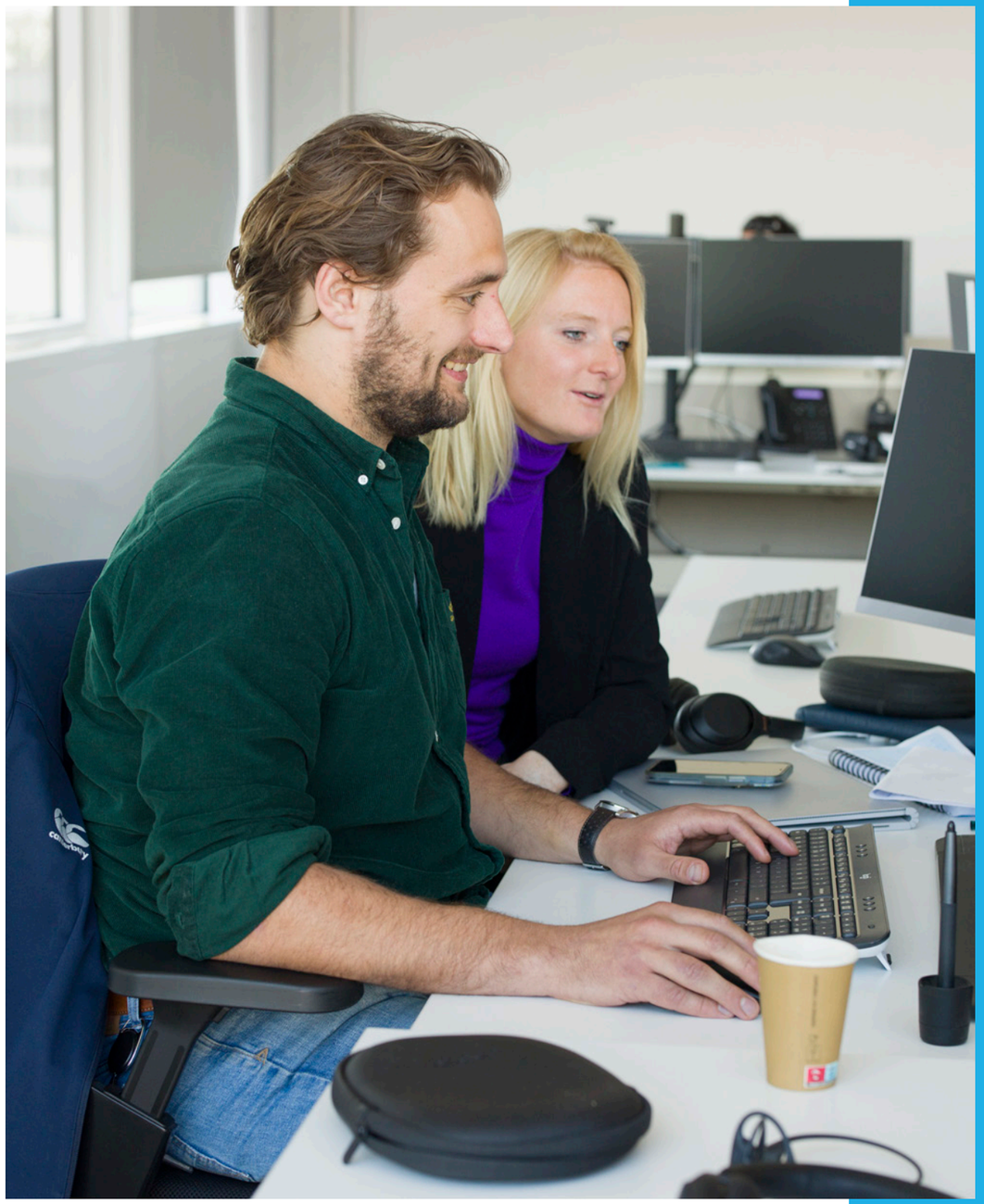


## Safety first

'Not a single subject was infected with SARS-CoV-2 at our facility in 2020 or 2021,' says Dr Ard Vink, Clinical Operations Director. 'That in itself is quite an achievement.' Safety is always top priority at CHDR, and this applied equally to the additional measures required due to the pandemic. A dedicated clinical COVID team discusses all studies with particular attention to the safety of healthy volunteers and patients in the context of the pandemic. In 2021, after careful deliberation, no (immunological) studies were cancelled or postponed due to pandemic-related safety concerns.

In response to the pandemic situation, in 2020 a standard operating procedure (SOP) was put in place describing COVID-19-related processes. This SOP is adapted regularly to reflect the changing situation and applicable government measures, and staff are trained in the new procedure. Vink: 'All subjects are tested immediately upon entry and remain in isolation until the test result is known. Thanks to the introduction of rapid tests, it is possible to know already within 15 minutes whether a study participant is infected.' Subjects who are staying in-house are then tested again 24 and 48 hours after being admitted to the unit.



# Human resources

# Flexibility, vitality, efficiency and personal development

A dynamic organisation presents many interesting challenges for human resource management. To this, the COVID-19 pandemic added a whole new layer of complexity. Nevertheless, Human Resources Director Yvette Akkermans is proud of what has been achieved by CHDR's employees in 2021. 'The main focus of HR was to increase resilience and vitality. Our staff have accomplished a great deal in the past year, benefiting both the organisation and their own professional development. As an employer, we strive to take good care of everyone and offer optimum opportunities for employees to achieve their potential.'

'The main themes of our current HR policy can be summarised in four keywords: flexibility, vitality, efficiency, and personal development,' says Akkermans. 'Flexibility and vitality are always important of course, but they were key in dealing with the challenges of the COVID-19 pandemic. Over the last year we've continued to make progress with regard to efficiency, along with further improvements in the domain of personal development.'

## Flexibility and vitality

The challenges of the past year required employees at every level of the organisation to be resilient and adapt to new and changing situations. The planning of clinical studies had to be adjusted regularly, which had consequences for everyone, whether directly or indirectly involved in the primary process. Increased staff absences due to COVID-19 meant colleagues had to go the extra mile and cover each other's work. Akkermans: 'Our staff showed great solidarity during this time. This was also reflected in a recent employee survey, which showed that our staff members value teamwork tremendously and appreciate their colleagues.' However, the unpredictability of the pandemic inevitably took its toll. 'We hoped that the vaccination campaigns would quickly bring the pandemic under control, but that didn't prove to be the case. With new waves of the virus, many employees had to go back to working from home. As an organisation we did whatever we could to support this, for example by helping people to optimise their workspaces at home.'

From a vitality point of view, the organisation invested in various training courses to support employees in dealing with the sometimes stressful consequences of the pandemic. Managers, for example, received training in how to recognise and understand stress and how to discuss absenteeism with their staff. Employees were offered mental resilience training as well as team or individual coaching. An ergonomics specialist visited CHDR regularly to discuss working posture and other aspects of health and safety. The staff association introduced a special mobile app that encouraged people to go out for a walk, whether alone or with colleagues. And, whenever possible, employees were given the freedom to arrange their working hours so that they had the flexibility to fit exercise into their schedules and to devote time to their families. 'In short, we did what we could to take care of each other and to keep everyone mentally and physically healthy,' says Akkermans.


## Efficiency and personal development

'The pandemic highlighted the importance of efficiency, and presented us with an opportunity to optimise our processes, especially in view of the organisation's growth in previous years,' says Akkermans. A good example of this concerns the authorisations, which state who is authorised to perform which activities within the organisation. 'Until recently, all authorisations were registered in a hardcopy authorisation record only. In 2021, we digitised them all and made them accessible

through our AFAS software system. It was a huge job, but now every authorisation is visible at any time in any place, making the whole authorisation process much more efficient.'

In the past year, Akkermans and her colleagues have also continued their work to update the organisation's job classification framework and role descriptions. 'Now, not only do we have a comprehensive description and classification of all functions, but it's also clearer which possibilities people have for professional and personal development. That's beneficial for our staff, because they can develop their capabilities to the full, and good for CHDR, because we can better retain talented people as they grow. It also improves our attractiveness as an employer, helping us to recruit the people we need.'

Developing people is part of CHDR's core mission, and therefore staff can follow a variety of forms of training in order to grow into new functions and to stay up-to-date in their current roles. 'We offer training on the basis of individual needs, so that each employee gets a personalised solution. That could simply be a course related to their current role, or it could be the beginning of a career switch within the organisation,' says Akkermans. A range of professional development courses are offered via the GoodHabitz online platform, which employees can also log in to from home. Akkermans: 'Staff across diverse roles within the organisation have benefited from the possibilities offered by this platform since we introduced it last year.'

Akkermans takes a moment to reflect on the organisation as a whole. 'We are fortunate to have a vibrant workplace, where we take care of one another, where social cohesion is high, and where we are dedicated to achieving our best as a team. And it's not just me who feels this way — you'll also notice it if you talk to other people around the organisation.' Turn to page 118 to hear from staff members themselves, in interviews where they describe what working at CHDR means to them.

**Dr Tessa Niemeyer-van der Kolk,** Senior Clinical Scientist

# *'I feel at home at CHDR'*

Dr Tessa Niemeyer-van der Kolk is a Senior Clinical Scientist in the Dermatology group. She received her PhD from Leiden University on 16 March 2021 for her dissertation titled 'Investigations of skin inflammation with a novel dermatology toolbox for early phase clinical drug development'. Van der Kolk: 'The ceremony had to take place online because of coronavirus restrictions. But it was still a special event. I had a glass of champagne at home with my family to celebrate the occasion. Hopefully in the coming year, when it's safe to do so, I can throw a big party!'

Van der Kolk joined the organisation in 2016. 'I was the first PhD student in this field at CHDR. There wasn't really a Dermatology group at that time — Robert Rissmann was conducting dermatology studies alongside his work as Education Director. The group was formally in created in 2017. In the past five years, the number of studies in dermatology has grown enormously and we have assembled a wide variety of instruments for measuring drug effects in the skin. Now, we have a steady stream of first-in-human and patient studies, with new topical treatments as well as systemic medications. It's been fascinating to be part of the development of this group and to have made a substantial contribution to this emerging field.

'I'm a medical doctor, and when I joined CHDR, my plan for the future was to become a clinical dermatologist. That's why I wanted to do my PhD in skin research. In recent years, in addition to my research and my training in clinical pharmacology, I worked one day a week at a dermatology outpatient clinic at the Erasmus Medical Center in Rotterdam. I really enjoyed working with patients, but I observed how hospital dermatology has a strong focus on productivity. A consultation shouldn't take more than five to ten minutes, which places a lot of time pressure on consultant dermatologists. Although I quite enjoyed the work, I couldn't see myself doing it this way for the rest of my life. Meanwhile, I really felt at home at CHDR. I could see enormous potential in our research group, and I enjoyed partnering with Robert Rissmann and Martijn van Doorn from the Erasmus MC. So when the time came to discuss my future, we were all very happy with the plan for me to continue as a clinical researcher.

'I really enjoy my current role as Senior Clinical Scientist, in which I combine my own research with PhD supervision. And of course, my work also involves conducting studies with patients. So in the end, I'm still doing clinical dermatology after all — I'm just approaching it from a different perspective.'



**Dr Annelieke Kruithof,** Clinical Study Manager

# *'My new role builds on the experience I've gained in recent years'*

At the end of 2021, Dr Annelieke Kruithof was appointed to the newly-created role of Clinical Study Manager. 'This is a new position within CHDR, and so the exact details of the role will crystallise further in the coming years. But essentially, it is my job to support the Clinical Scientists in the operational aspects of their work, in order to help ensure the quality of clinical studies,' says Kruithof. 'Most of our Clinical Scientists are also pursuing a PhD as part of their work. With clinical studies becoming increasingly complex, it's quite a challenge to take care of all the operational aspects while still fulfilling the requirements of doctoral research. So I'm going to take most of the operational work off their hands. In the future, there will likely be additional Clinical Study Managers. This is a positive development, which will improve continuity for our sponsors while attracting talented PhD candidates.

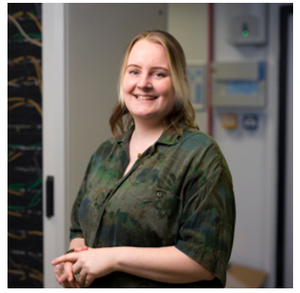
'I joined CHDR in 2011 after completing my studies in bio-pharmaceutical sciences. I started in the group led by Prof. Koos Burggraaf, and it was in that group that I eventually obtained my PhD. Over the years, I also supported other groups, and became involved in many different clinical studies. In fact, by the time I defended my PhD, I was already doing more or less what I'm doing now: facilitating project leaders in organising the operational side of their studies. And I found that I enjoyed the operational aspects of clinical trials. One of the highlights of recent years was the work we did evaluating the Janssen SARS-CoV-2 vaccine.

'When everything was locked down due to the pandemic, I decided to use the opportunity to finish my PhD dissertation. It's been a pretty intense period: during the day, I was busy working on studies with our Infectious Diseases group, and in the evening I was writing. But with social life at a standstill anyway because of the pandemic, there were far fewer distractions! When the end of my PhD came in sight, the question arose of what I would do next. And so the opportunity to become Clinical Study Manager came just at the right time.

'I really enjoy being at CHDR — I have great colleagues and I get to work on interesting projects. I also like having a broad orientation. I could have become a Senior Clinical Scientist, but that would have meant focusing on a single area of expertise. So I was very happy that this new position came up, because it really matches my interests. I'm excited to help define this new role that will improve the way we work in the long term, helping to maintain high levels of quality and efficiency for our clinical studies.'

**Kirsten Nieuwenhuizen,** Junior IT Project Manager

# *'I'm excited about my career switch to information technology'*



'At an online event in spring 2021, our CEO Koos Burggraaf stimulated us to think about our career plans. He said that CHDR takes pride in investing in its employees and he encouraged us to talk to our managers if we wanted a career change,' says Kirsten Nieuwenhuizen. 'The idea immediately appealed to me, as I was already wondering if I could do more with my growing interest in information technology. So I agreed with my manager that I would look into switching to the Technology department. I got in touch with our Technology Director Bart van der Kroef, and right away, he offered me a position as a Scrum Master starting the same autumn. Scrum is an Agile method of project management: under Scrum, the team works for short stretches of time to deliver a product or outcome, and then gathers feedback which is built upon in the next round. With this approach, the team stays better in sync with the needs of the organisation.'

Kirsten obtained her MSc in Cognitive Psychology from Leiden University in 2019. 'I didn't want to continue in that direction, so in the same year, I applied for a job in Recruitment at CHDR. They had already filled the vacancy, but I was offered a job in the admin department of the clinical research unit (CRU). I spent an enjoyable couple of years working there, and what's more, I increasingly became the point of contact for all questions relating to IT. This confirmed my gut feeling that I should pursue a career in IT. I've had an affinity with information technology for quite some time. For instance, I built my own PC at home from components — a bit like a jigsaw puzzle, but more exciting!

'Although I didn't yet have training in IT, Bart van der Kroef appreciated my enthusiasm for working with people and my willingness to learn. That's why he proposed that I could become a Scrum Master: someone who facilitates and supports a team working within the Scrum framework. When I started, we had an external coach who taught me a lot in a very short time. Thanks to him, and the courses I've done since, I now have the confidence that I can really contribute something along with my team. I still learn new things every day and I can really depend on my colleagues — we have a good team spirit.

'When I started in my new role I had to work from home. It took some getting used to, because in the CRU admin department we always worked in the office, even during the pandemic. But I soon got used to working remotely and communicating with my team online. Now that we're back in the office, we're growing closer as a team. Technology underpins so much of what we do as an organisation, and effective teamwork is key to meeting the challenges involved.'



**Sebastiaan Vonhoff,** Study Medical Assistant

# *'The opportunity to train as a nurse means a great deal to me'*

Sebastiaan Vonhoff is a doctor's assistant in the clinical research unit (CRU). In September 2021, he started studying part-time at the University of Applied Sciences Utrecht to become a nurse. 'I've been working at CHDR since September 2020. Through working in a scientific setting and interacting with my colleagues here, I realised I wanted to pursue further studies and train to become a nurse. I raised this with my superiors and I was very happy to find that they were keen for me to have that opportunity. I now work four days a week at the CRU and attend college one day a week. It's working really well so far. I've already noticed that I can put what I learn to use in my work. And in the classroom, people often turn to me when the topic of scientific research comes up. I'm pleased to say I've almost completed my first year of study, and I'm on track to become a qualified nurse in 2025.

'Of course, it's demanding sometimes. I often study in the evenings, so I regularly have to say no to my friends if they invite me to go out with them. But the people around me are really supportive, because they can see that I'm really enthusiastic about my studies. Sometimes I can even fit in some studying at work, making use of downtime during quiet evening shifts. And I spend almost two hours every day on the train commuting to and from the CRU, which is an excellent chance to get some studying done! I also have to do internships as part of my course. So far, I've been able to do these at CHDR, but later on in my training, I'll do internships in other places as well. Luckily that'll also be part-time, so I'll still be able to work at CHDR more than two days a week.

'Before I joined CHDR, I worked as a doctor's assistant in a hospital emergency department. There I also carried out all kinds of nursing activities. And in fact, there are more similarities between the hospital and the CRU than I expected — for example, in both cases, it's important to get everything done on time. Working as a doctor's assistant has been an interesting experience, but I wanted a more solid basis to build on for my career. As a nurse, I will have many more opportunities. And even though I'll be doing many of the same tasks that I do now, having more background knowledge makes the work much more engaging, especially in a research setting like CHDR.'

‘They offer valuable scientific advice’

## Working with CHDR

‘Based on our prior experience with CROs, we went into the cooperation expecting study execution, nothing more. However, it turned out that we had completely underestimated the very valuable scientific advice that the experts at CHDR could offer us. Their scientific input definitely improved our protocol.’

**Assistant Vice President, Big Pharma Company ***

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

# Technology

# Data integrity and security: a shared responsibility

The growth of CHDR and the increasing complexity of its scientific activities place high demands on the organisation's Technology team. In particular, maintaining the integrity and security of data calls for constant vigilance. Technology Director Bart van der Kroef sheds light on the procedures and systems involved, and the role that each employee plays in keeping the organisation secure.

'As an organisation, much of our wealth lies in our data,' says Van der Kroef. 'We invest a lot of energy into data collection, both in terms of the methods we use and in terms of data precision and accuracy. Behind the scenes, this means our team needs to work hard to guarantee the integrity of the data and to comply with all the relevant regulations.' Such regulations include not only privacy directives, such as the GDPR in Europe, but also the increasingly strict requirements of medicines agencies in Europe and the United States. 'In fact, this is part of a trend that goes beyond just our sector: you can see similar developments in the financial world and elsewhere.'

## More than just (fire)walls

'Long gone are the days when data security was a matter of securing the physical building and implementing a firewall,' says Van der Kroef. 'For example, we use our website to recruit study participants — any data they enter needs to be handled with the utmost care and confidentiality. Meanwhile, many of our staff want to be able to work remotely — and in the COVID-19 pandemic, we've seen that this can even be a necessity.' Many of the organisation's systems already run in the cloud, and this transition is continuing. 'These days, we all use a range of devices: from fixed workstations and laptops, to tablets and smartphones. This offers a great deal of flexibility and ease of use, which benefits the running of the organisation. However, the same development can also make the organisation more vulnerable, by offering more ways in for attackers.' The information systems themselves have also become much more complex. 'What users often do not realise is how many different layers of software have to work together for something as simple as checking your email on your phone,' says Van der Kroef. 'All those different programs and their mutual exchange of data can give rise to vulnerabilities.'

## Layered security

The measures to optimise the integrity and security of data are multi-layered. The first layer concerns the collection and input of data. Then, if any subsequent changes are made, it must always be clear who made which change and when. Authentication procedures, familiar from online banking, are used to carefully establish the identity of the user. At the same time, vulnerabilities in the device and the network need to be minimised. Besides the systems put in place by the Technology team, protecting the integrity and security of the data infrastructure requires every user to remain alert. 'As attacks become more and more sophisticated, users need to adhere to protocols and avoid falling for scams,' says Van der Kroef. 'It's also important to help employees understand why certain measures are needed, especially when they reduce ease of use.'

> 'Our team works hard behind the scenes to ensure the integrity and availability of data'

Even with the best security, however, undesirable events can still happen. 'We must always be alert to attacks. It's best to operate on the assumption that the attackers are already inside — that way, we don't risk underestimating the threat. Two things are crucial: minimising the impact and restoring any affected systems as quickly as we can.' Virus and ransomware attacks are often carried out in such a way as to infect as much of the system as possible, using so-called horizontal propagation. 'To counteract this, we use a segmentation approach, similar to the construction of a submarine: closed compartments ensure that the vessel remains intact even if one compartment is breached. Next, by using a backup that is as recent as possible, we can ensure that the system is quickly restored and able to process data again,' says Van der Kroef. 'As an organisation, we are continuously generating and storing data — not just within the building, but also with staff working from home and study participants who are monitored remotely via Trial@home. It's our job to invest in the latest systems and features to keep our data safe and available at all times.'

## Continuity and innovation at Promasys

2022 will see the retirement of Jos Hennen, the originator of the Promasys clinical data management system that was developed in-house at CHDR. ‘Promasys will remain at the heart of our data system going forward,’ says Technology Director Bart van der Kroef. ‘In the past year, we’ve worked hard to hand over Jos’ knowledge and expertise to the two new employees who will take over from him.’ Their role will include reprogramming and updating the Promasys environment to optimise the system for the future, with a focus on security, efficiency, and ease of use.



# Quality assurance

# Keeping abreast of new developments in QA

Amid pandemic restrictions, remote auditing continued to be the norm in 2021. At CHDR, this was true not only for external audits, but also for the internal and subcontractor audits conducted by the Quality Assurance department. Rebounding from 2020, the QA team also handled a record number of external audits in the past year. Meanwhile, preparations were made for the introduction of the new EU Clinical Trials Regulation.

'When the COVID-19 pandemic took hold in 2020, the European Medicines Agency called for a cautious approach to conducting audits on-site. So we started right away with facilitating remote audits,' says Margreet Rienstra, Compliance Director and head of the Quality Assurance department. 'This turned out to have been a good move, because in 2021 we had more external audits than ever before, and the vast majority of them took place remotely. The large volume was partly due to a backlog from the pandemic, but we also have new clients who need to audit us.'

## Remote external audits

For Rienstra and her team, a remote external audit is almost routine by now. The first step is to prepare all the relevant documents in a Microsoft Teams environment. The external auditors are given read-only access to these documents for a certain period of time. Next, the necessary interviews take place, also via Teams. 'This approach isn't without its disadvantages — especially when you need to plan interviews with people in completely different time zones. But overall it has advantages for the auditors, including not having to put up with jet lag,' says Rienstra. 'Of course, communication is harder when you can't meet in person and talk face-to-face. But we find that just being aware of this is already a great help, so you can remember to explicitly check whether you have understood each other correctly.'

At CHDR, the vast majority of necessary documents for auditing are already available digitally. To complement this, the QA team has devised some digital solutions to overcome the limitations of remote auditing, such as a special video presentation for auditors who want to take a look at the facilities and equipment. But some things remain offline. 'As yet, there is no digital version of the informed consent forms which study participants sign to indicate that they have understood the information and are prepared to take part. During audits, these are often the most frequently viewed documents,' says Rienstra. 'We are looking into the possibilities of recording informed consent electronically, but for the time being this is not legally permitted.'

## Towards a hybrid approach

Over the past year, the QA team has also gained broad experience performing remote audits of subcontractors, such as laboratories or IT service providers. Rienstra: 'Being able to conduct these audits remotely definitely has advantages. For example, rather than having to conduct the entire audit during a short on-site visit, we can spread the work out over more days, and consult with a colleague where necessary. This facilitates a more balanced judgment.'

Rienstra expects that in the coming years a significant number of audits — both external audits and those conducted by CHDR — will still be conducted remotely. Another likely development will be a hybrid form of auditing, whereby the majority of the audit is conducted remotely but the auditor still visits the site and examines any documents that cannot be offered in digital form. 'The choice is up to our clients,' says Rienstra. 'I would be delighted to welcome teams of auditors back to our facility in the near future.'

## European regulations

On 31 January 2022 the EU's new Clinical Trials Regulation comes into force, ushering in a new set of requirements for all drug research within the European Union. At CHDR, a special team has been working hard in recent years to inform employees about the upcoming regulations and to adapt the procedures that will be impacted. Rienstra: 'The team includes QA Officer Tanja Grobben-van de Graaf, along with colleagues from several other departments. We conducted an impact analysis to assess which processes would change, and organised courses for all employees who would be confronted with the new rules. It really is a big change, especially for multicentre studies, but also for the early phase single-centre studies that are CHDR's core business.' In addition to the online courses for staff members, the team ran three virtual meetings to update the entire organisation. 'These meetings were very well attended. It's nice that so many colleagues are keen to know about the changes, even if their work isn't directly affected,' says Rienstra. 'All in all, we are now ready for the new era of studies under the Clinical Trials Regulation. And for those clients who need more time, there is still a transition period to ensure that the implementation goes as smoothly as possible.'

‘A talent for seeing the possibilities’

## Working with CHDR

‘I see CHDR as knowledgeable, pragmatic, and scientific. What really makes a lasting impression is their scientific expertise: they have a talent for seeing the possibilities.’

Clinical Study Manager,
Big Pharma Company *

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

# Education

# National and international cooperation in pharmacology education

Both in the Netherlands and abroad, there is growing appreciation for the innovations in the field of education initiated by CHDR, which encompass academic teaching and professional development. The Teaching Resource Centre continues to attract interest, while 2021 saw progress on a promising initiative for professional training in drug development.

'Our education activities continued in 2021, albeit mainly online,' says Dr Jeroen van Smeden, Education Director at CHDR. 'Again, we reaped the rewards of our earlier investments in digital education and online training materials. But the pandemic has also taken its toll: both students and professionals have had to bear a lot of stress and isolation, sometimes even depression and overwork. Online education may work well enough for students to gain the knowledge they need, but when everything is remote you miss out on the social contact that is an important part of studying at university.'

As in previous years, CHDR taught courses on pharmacology for medical students and on drug development for bio-pharmaceutical sciences students at Leiden University. Students from various disciplines also undertook internships at CHDR. 'Thanks to the strengthened cooperation with the Leiden University Medical Center (LUMC), medical students can now choose to do their internship or co-internship with us, just the same as if the internship were in one of the LUMC's own clinical departments,' says Van Smeden. 'In the past two years, we've had far fewer interns than usual due to the COVID-19 measures. On the other hand, we have collected plenty of new data which need to be analysed, providing ample opportunities for prospective interns to learn about clinical research. So I'm glad that we'll soon be back to welcoming the same numbers as before the pandemic.'

## Teaching Resource Centre

CHDR's showpiece in the area of education is the Teaching Resource Centre (TRC), a web-based resource that serves as a pharmacology textbook and reference work for students and professionals around the world. This free resource remains as popular as ever, especially after the thorough restyling two years ago which improved and updated the TRC's graphic design, interactivity and overall coherence. Van Smeden: 'The TRC is being adopted by more and more universities, both here and abroad. In addition, every medical study programme in the Netherlands now contributes to the graphic illustrations in the TRC, as these are also used as teaching material for a drug safety test that every future doctor must pass. This is an area of crucial importance: in the Netherlands alone, about 40,000 hospital admissions each year are related to medication errors.'

> 'Our Teaching Resource Centre is being adopted by more and more universities, both here and abroad'

A recently installed editorial board moderates the content of new additions to the TRC, while graphic designer Folkert van Meurs ensures that the visual style remains consistent. Soon this editorial board will also include the British Pharmacological Society (BPS). The BPS, which collaborates with CHDR the field of education, has already adopted the TRC for use in its professional training programmes. Van Smeden: 'We are now considering how the TRC will be funded in the future, with the aim of making it self-sustaining. One possible approach is to adopt a Wikipedia-style donation model — so, keeping the main content of the site accessible free of charge, but inviting donations from users. Whichever funding model we choose, it's important to attract enough income to be able to keep the TRC up to date.'

## Teaching drug development

Besides contributing to university curricular education, CHDR's teaching activities are soon to include training for professionals involved in preclinical and clinical drug development. The plans for this training programme have been laid down in detail by a consortium of various organisations involved in drug development, ethical review, and education. Although this initiative has the support of the Dutch government, cabinet changes in 2021 meant that the associated subsidy could not yet be granted. Van Smeden: 'We did receive a starting subsidy to be able to develop a first part of the training. This was really helpful to maintain the momentum and enthusiasm within the consortium.'

This first part of the training focuses on the translation of preclinical research into first-in-human studies. At CHDR, a tool has already been developed to support this process: the IB-Derisk analyser, which helps investigators in (early) drug development to structure the relevant preclinical information. This instrument and the associated expertise are set to play a key role in the training programme. ‘A pilot version of the course has already been enthusiastically received in various places,’ says Van Smeden. ‘It also coincides with the new Clinical Trials Regulation, which applies to all drug research in the European Union from 31 January 2022. This regulation sets high standards for the medical ethics review and the expertise within medical ethics committees. Now, the European Medicines Agency wants to use a variant of our course and the IB-Derisk tool in their training activities.’ The IB-Derisk approach also featured in a recent CHDR publication about the infamous 2016 study in France in which one subject died and several others suffered neurological damage. ‘Adopting the IB-Derisk approach, we aimed to compile the information that was available from preclinical research. In the article, we make the case that the disaster may well have been prevented if that data had been analysed in a structured way. This shows the importance of CHDR’s IB-Derisk approach or a similar structured view of all available data.’



# PhD graduates

At CHDR, educating students and professionals is one of our core values. Through our Clinical Research Programme we offer ambitious young researchers and clinicians a well-defined career development path. In this rigorous five-year PhD programme, participants design and conduct several research projects while being coached by Senior Clinical Scientists and Research Directors.

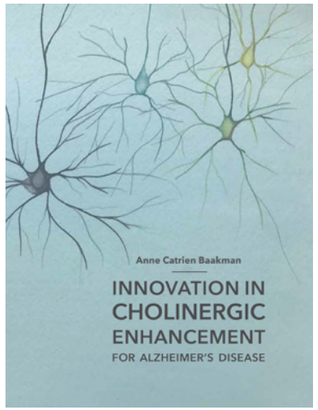
Throughout the programme, participants develop key skills and competencies in project management, clinical pharmacology, and scientific research. The programme usually culminates in the completion of a PhD thesis. In 2021, six PhD candidates successfully defended their theses. Click on each of the theses below to read more.


## Marcus van Diemen

Clinical pharmacological aspects of mithochondrial function in muscle

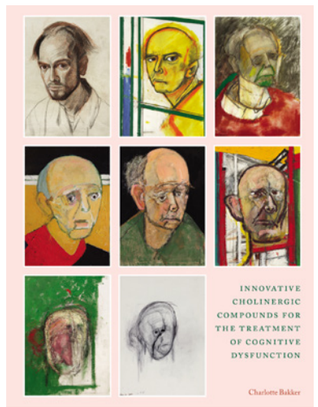

## Annelieke Kruithof

Evaluating the effects of sugammadex on coagulation in humans: reversed translational research to unravel off-target pharmacology



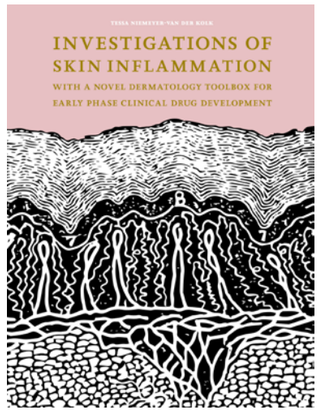

## Anne Catrien Baakman

Innovation in cholinergic enhancement for Alzheimer's disease



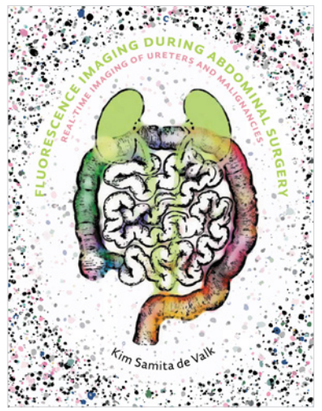

## Charlotte Bakker

Innovative cholinergic compounds for treatment of cognitive dysfunction




## Tessa Niemeyer-van der Kolk

Investigations of skin inflammation with a novel dermatology toolbox for early phase clinical drug development




## Kim Samita de Valk

Fluorescence imaging during abdominal surgery: real-time imaging of ureters and malignancies

# Scientific output

# Publications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| | Max Thijssen |
| | Rob Overmeer |
| | Jannes Linders |
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CHDR
Centre for Human Drug Research

**Centre for Human Drug Research**
Zernikedreef 8
2333 CL Leiden
The Netherlands

+31 (0)71 5246400
info@chdr.nl
www.chdr.nl


chdr.nl