CHDR
Centre for Human Drug Research

Translational biomarkers

Finding biomarkers to predict clinical success by combining knowledge, subjects and data analysis

When a sponsor wants to discuss early-stage clinical drug development, a commonly encountered challenge finding a way to reliably predict the candidate drug's effects in a clinical setting. CHDR Research Director Dr Matthijs Moerland explains the solution: 'At CHDR, we have the knowledge, laboratory capacity, and access to human samples needed in order to develop customised biomarkers for addressing answer specific questions. Our expertise allows us to turn preclinical questions into clinical research, ultimately predicting post-marketing issues.'

CHDR Research Director Dr Matthijs Moerland explains the solution

Moerland's research specialty, translational biomarkers, overlaps with all of CHDR's other, disease-based research areas. To complement existing functional measurements such as blood pressure monitoring and test batteries (e.g. NeuroCart® and PainCart®), biomarkers are gaining increasing attention in early-stage drug development. The term translational refers to the translation from preclinical development to early clinical drug development. Moerland explains: 'It's only logical that sponsors want to know as early as possible whether their compound has – or will have – the desired effect on its target. Because clinical biomarkers are often not suited to early-phase drug development, I look for biomarkers that can reveal an effect on the target pathway in both healthy individuals and patients after just a single dose.'

Integration

'Many of the things we do may not be unique, but we add value to the process because we bring it all together,' says Moerland. 'It's my job to integrate pathophysiology, biology, infrastructure, and bioanalytical capacity. In this way, we can easily transition from in vitro studies to ex vivo/in vivo studies to studies involving human subjects. And we're in close contact with the research community and with several university medical centres. This means that, for example, if we need cells and/or tissue samples from patients with inflammatory bowel disease in order to answer a specific question, CHDR is part of a large network that can obtain these biological samples, as well as expert advice from gastroenterologists.'

A nice illustration of this integrated approach is a recent study measuring the turnover rate of lymphocytes (white blood cells). Moerland: 'Our goal was to determine if – and how – a new drug might cause lymphocytopenia (reduced numbers of lymphocytes in the blood). We performed a study using deuterium-labelled water (D2O) to label newly synthesised lymphocytes in patients who were taking the drug. For this study, we collaborated closely with the referring physicians; in addition, we worked with a high-tech laboratory that uses cell sorters and mass spectrometers, and we worked with biomathematicians who created complex models of the study data. It was particularly rewarding to see first-hand the power of this collaborative effort.'

In the spotlight

Biomarkers can be used to study a wide range of biological processes. One such process that has long been in the spotlight of biomedical research is inflammation; indeed, many new drugs are being developed in an attempt to prevent or reduce the effects of inflammation in a variety of conditions, including classic inflammation disorders such as rheumatoid arthritis and Crohn's disease, as well as other diseases such as atherosclerosis, cancer, and even depression. At CHDR, biomarkers for several inflammation pathways have been studied intensively. One such pathway is the Toll-like receptor (TLR) pathway, which is activated by bacterial lipopolysaccharide (LPS). Moerland and his team performed a comprehensive series of experiments to measure the efficacy of a new TLR blocker. Moerland explains: 'First, we studied the effect of the drug on LPS-induced inflammation in patient blood. Next, we administered the drug in increasing doses to healthy subjects and measured the LPS-induced response ex vivo. Finally, we gave healthy subjects an infusion of LPS and measured the response both with and without the drug. Of course, before we started, we determined the dose of LPS that was sufficient to trigger an inflammatory response in our subjects, but was still safe. It was particularly interesting to correlate in vitro data with both ex vivo data and clinical measurements, which allowed us to identify the optimal dose level of TLR blocker with the intended effect in the target population. We're now using similar approaches to study the effect of other compounds on inflammatory pathways, coagulation, and fibrosis.'

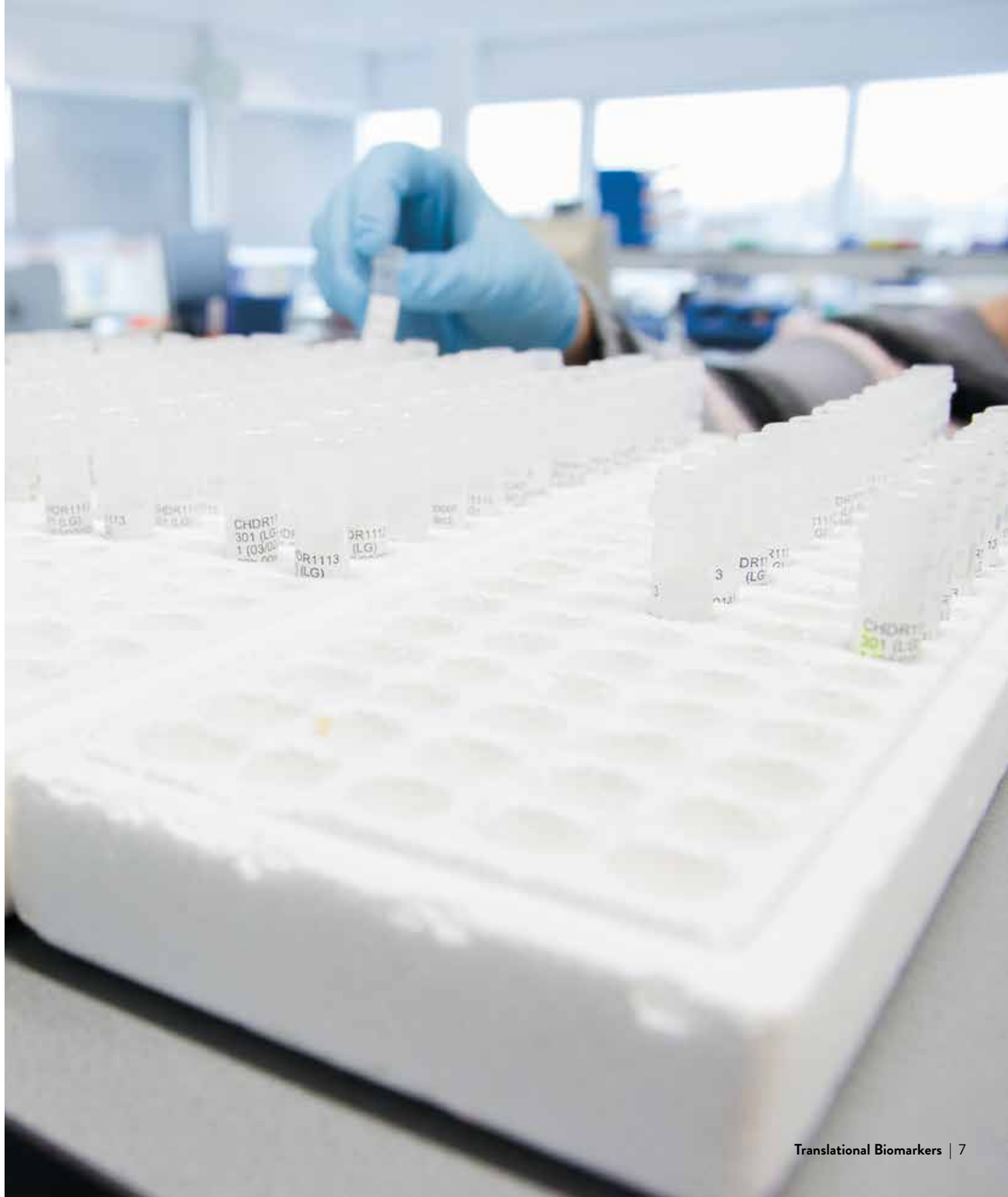
'Because clinical biomarkers are often not suited to early-phase drug development, we look for biomarkers that can reveal an effect on the target pathway in both healthy individuals and patients after just a single dose.'

From preclinical research to post-marketing data... and vice versa

In many cases, Moerland starts by studying the compound's preclinical dossier to determine which biomarkers might be useful for studying the compound's effects in human subjects, or to determine which assays might be needed in order to detect any unintended effects. The ability to predict unintended effects particularly relevant for biotherapeutics, an emerging field that includes proteins synthesised by bacterial systems and human monoclonal antibodies. Even if all required tests have been passed, suggesting the compound is ready for release, these proteins can – at least in principle – retain their undesired immuno-stimulating activity, potentially resulting in inflammatory responses in early clinical studies. Together with our partner Good Biomarker Sciences, CHDR has developed a test battery that can be used to detect the immuno-stimulating activity of biotherapeutics in whole blood samples before the compound it tested *in vivo* in subjects. The boundaries associated with drug development have become increasingly flexible, with increasing interaction between the researchers who perform the preclinical studies and the researchers who perform the clinical phases. Moerland explains: 'It can be extremely useful to think about biomarkers in the preclinical phase, so you can use the same biomarkers in both animals and human subjects. This approach facilitates the process of biomarker-driven drug development, resulting in a faster, more economical, and more rational way of developing new compounds .'

'We are driven by the challenge of developing reliable ways to study drug effects, including both desired effects and adverse side effects.'

Biomarkers can also be extremely valuable even when a drug is already on the market. For example, if post-marketing studies reveal minor side effects, a sponsor may want to examine the underlying mechanism in order to address the problem. CHDR can design and perform dedicated in vitro and clinical experiments in order to select appropriate biomarkers and/or bioassays. Moerland: 'I'm driven by the challenge of developing reliable ways to study drug effects, including both desired effects and adverse side effects.'



Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact

To learn about CHDR's full range of services, contact us today.

+31(0)71 524 64 00

info@chdr.nl

www.chdr.nl