CHDR
Centre for Human Drug Research

The keyhole limpet haemocyanin (KLH) challenge model

What CHDR offers:

- A KLH model developed in-house, driving an adaptive immune response without inducing adverse events
- Response quantification at different levels: blood-based antibodies, circulating T cells, or skin response after local re-exposure to the antigen
- Evaluation of the immunomodulatory effects of investigational compounds in healthy volunteers
- An experienced and enthusiastic research team consisting of clinical pharmacologists, molecular scientists and immunologists, committed to characterising the KLH challenge response in greater detail, further increasing its applicability

The keyhole limpet haemocyanin (KLH) challenge model

CHDR's keyhole limpet haemocyanin (KLH) challenge model holds promise for evaluating the pharmacological activity of immunomodulatory agents, already at the earliest stages of clinical development. Developed in-house in 2016, this model has been applied in a number of trials, demonstrating its ability to detect pharmacodynamic effects of novel compounds, as well as its safety and the absence of systemic adverse effects.

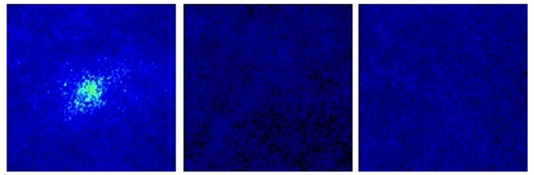
The KLH challenge

The immune system in healthy volunteers is not sufficiently active to allow measurement of the desired pharmacodynamic effects of immunomodulatory compounds. This complicates the clinical evaluation of novel drugs targeting the immune system. The KLH challenge triggers the immune system with a novel antigen, resulting in a quantifiable immune response that can be pharmacologically modified. Previous studies have reported that immunomodulatory agents such as cyclosporine, methotrexate, rituximab and co-stimulation blockers can modify responses driven by KLH. KLH drives a humoral and a cellular response, so the model is applicable for the pharmacodynamic evaluation of a wide range of immune-targeted drugs, modulating processes such as T cell and B cell activity, antigen presentation, and support by innate immune responses.

The KLH model at CHDR: a case study[1]

CHDR initially developed the KLH challenge model in 2016, in order to investigate a novel compound modulating T cell activation. Healthy volunteers were vaccinated with low molecular weight KLH, which is registered under the trade name Immucothel® and used in routine clinical practice in many countries (including the Netherlands). The antigen-driven response was evaluated by quantification of KLH-specific antibodies in the circulation. In addition, three weeks after vaccination a low dose of KLH was injected intradermally, driving a local inflammatory response. This response was quantified using sensitive imaging techniques: high-tech cameras, optimised to quantify skin response with the greatest accuracy, were used to measure local redness (by multispectral imaging) elevated skin perfusion (by Laser Speckle Contrast Imaging) driven by KLH (figure 1). In the subsequent first-in-human study evaluating the novel compound (a co-stimulation blocker), the KLH model was applied with success. Based on the KLH challenge model, the pharmacologically active dose of the novel compound could be identified, and this dose was further evaluated in the subsequent phase 2 trial.

Image right: Antera 3D - Multi-spectral imaging



i.m. KLH i.d. KLH | **i.m. Placebo i.d. KLH** | **i.m. KLH i.d. untreated**

Figure 1. Illustrations of laser speckle contrast imaging (LSCI) basal flow 2 days after intradermal keyhole limpet haemocyanin (KLH) administration of a subject treated with intramuscular KLH immunization and intradermal KLH administration (left image), intramuscular placebo immunization and intradermal KLH administration (middle image) and intramuscular KLH immunization and untreated control arm (right image).

[1] https://chdr.nl/library/a-randomized-controlled-trial-with-a-delayed-type-hypersensitivity-model-using-keyhole-limpet-haemocyanin-to-evaluate-adaptive-immune-responses-in-man

The KLH model and delayed type hypersensitivity (DTH) test

The KLH protein is unfamiliar to the human body, so an adaptive immune response develops following vaccination with KLH. This adaptive immune response includes antibody formation (both IgM and IgG). In addition, KLH drives a cellular response that can be detected and quantified by a local re-challenge of the skin: a few weeks after the initial vaccination, a low dose of KLH is injected intradermally. The immune system, trained by the vaccination, recognises the injected antigen, and an immune response evolves: cytokines and chemokines are produced and effector immune cells are attracted. Locally released immunogenic agents induce vasodilation and vascular permeability. This results in increased blood perfusion, erythema and swelling which can be accurately measured using advanced imaging techniques.

Choosing the KLH challenge model for your study

The KLH challenge is a valuable tool for detecting drug activity that could otherwise only be evaluated in a patient population. Implementing the KLH challenge model in early-phase studies with healthy volunteers may avoid the need for complex and expensive dose-finding studies in patient populations at a later stage. Moreover, our researchers are continuing to further characterise and refine the KLH model. We encourage you to reach out to us to discuss the potential value of the KLH challenge model for the evaluation of pharmacological activity of your novel immunomodulatory drug.

Image: PeriCam PSI System - Laser Speckle Contrast Imaging

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.

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