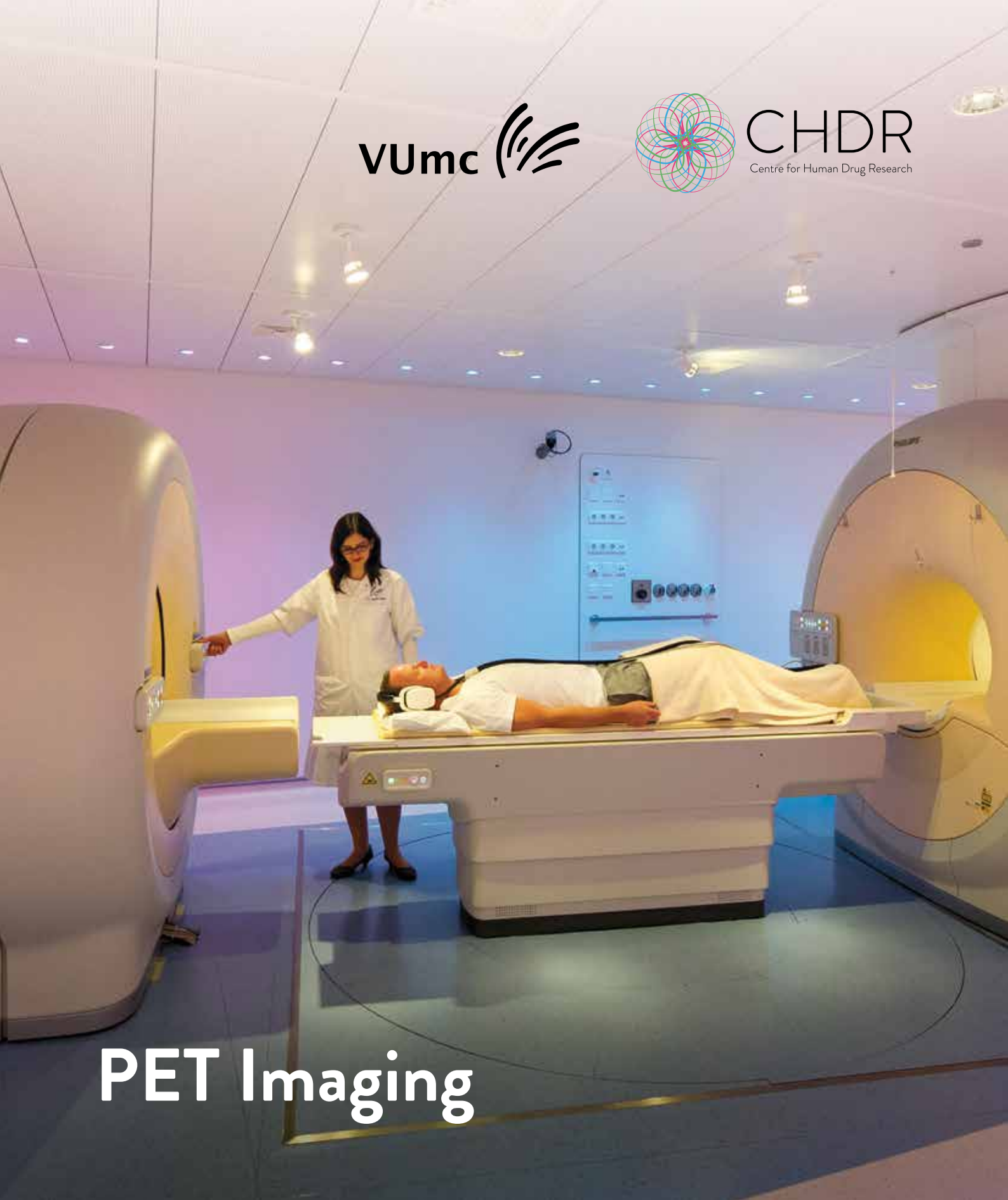

PET Imaging

A clear picture of a drug's action within the brain

Positron emission tomography (PET) provides researchers the ability to perform 'precision' pharmacology by combining the measurement of a variety of biological processes involving receptors, enzymes, and transporters with the measurement of the biodistribution of a labelled drug. Because pharmacological applications for PET are based on the availability of specific probes at the imaging centre, CHDR collaborates with one of the largest PET facilities in the world — the VU University Medical Centre (VUmc) in Amsterdam — to conduct a wide range of cutting-edge PET studies. In addition, our Clinical Research Unit at VUmc provides sponsors with state-of-the-art clinical imaging services for use in early clinical drug development.

At CHDR, we can combine quantitative PET imaging with intensive pharmacokinetics sampling, pharmacodynamics tests such as NeuroCart and PainCart, and 'wet' biomarkers. PET can be used to answer key questions in drug development by providing information regarding successful target binding based on measurable changes in protein density, receptor occupancy, glucose metabolism and perfusion, oxygen utilisation, and/or blood-brain barrier integrity.

Practical answers to important research questions

Does our test compound pass the blood-brain barrier and bind its target?

Studying the biodistribution of a drug labelled with a positron-emitting radioisotope can reveal the drug's ADME (administration, distribution, metabolism, and elimination) profile. In addition, using a labelled tracer that binds specifically to the drug's target can help confirm the interaction between the study drug and its target by showing changes in radiotracer binding; this approach is similar to competitive antagonism.

How can we determine the optimal dose of our test drug?

Using PET imaging, researchers can estimate the optimal dose of a test compound for further clinical development. For example, CHDR recently studied a novel, low-affinity dopamine D_2 receptor antagonist that was being developed as an antipsychotic drug. Healthy subjects were given a fixed dose of ^{11}C-labelled raclopride, a synthetic D_2 receptor antagonist, followed by various oral doses of the test compound. The relationship between the dose of the test drug and [^{11}C]raclopride binding — combined with plasma levels of the test dose — allowed our researchers to determine the drug's safety, tolerability, and CNS pharmacodynamics, thereby providing key information regarding the optimal dose for use in clinical development.

What is the relationship between the dose of the drug, receptor occupancy, and pharmacological effects?

CHDR has extensive experience developing and performing functional testing, particularly in the CNS. For example, both NeuroCart® and PainCart® can be used to measure a drug's effects on a variety of neurophysiological parameters, including attention, memory, and psychomotor performance. Researchers at CHDR recently combined PET imaging with NeuroCart to show that increased levels of dopamine in the brain following amphetamine administration are correlated with improved impulse control. With respect to new compounds, a wealth of information for use in future studies can be obtained using analytical models to correlate dose, blood concentration, functional effects, and receptor occupancy.

Highlights

- PET imaging provides unique insights into the interaction between a test compound and specific molecules in the body, helping bridge preclinical and early clinical drug development.
- VUmc has a dedicated radiochemistry facility for producing a wide range of radiotracers in accordance with GMP regulations.
- CHDR's Clinical Research Unit at VUmc meets pharmaceutical grade GCP standards and has access to all necessary facilities. Moreover, the unit can be used for studies involving both patients and healthy volunteers.
- The Clinical Research Unit can perform functional CNS and electrophysiology testing both before and after PET imaging.
- The VUmc PET imaging centre has more than two decades of experience using PET data to model tracer kinetics.
- Our expertise with PK/PD modelling allows us to study the relationship between plasma drug levels and drug binding in the target tissue.
- Our ability to visualise and quantify immune reactions using PET has led to the development of new antibody-based drugs in a variety of clinical fields, including oncology.

CHDR and VUmc: a closer look

Researchers at CHDR work closely with VUmc staff to development new treatments for several neurological disorders. For example, the Alzheimer Centre at the VUmc Department of Neurology is one of the world's leading research centres for studying Alzheimer's disease. Pharmacological imaging approaches using PET and fMRI also provide exciting new opportunities to study promising new targets such as the mitochondrial translocator protein TSPO, tau and amyloid, which have led to phase 1 and phase 2 trials.

PET imaging has a wide range of applications in early-phase drug development, including:

- Translational imaging to help select candidate drugs or to identify and validate biomarkers.
- Studying a drug's biodistribution in order to confirm that the drug reaches its target site in sufficient concentrations.
- Studying drug–target interactions (for example, receptor occupancy) as a guide for selecting the optimal dose.
- Measuring the compound's half-life in order to determine the best dosing regimen.
- Using pharmacodynamic biomarkers for proof-of-concept studies.

PET applications beyond the CNS

CHDR has always played a role in drug development in a wide range of medical fields, including cardiology, endocrinology, immunology, oncology, dermatology, and haematology. In many of these fields, PET imaging has contributed significantly to the development of new compounds. For example, VUmc is a global leader in the field of 89Zr-immuno-PET, which uses 89Zr-labelled monoclonal antibodies, peptides, or other molecules to study mechanisms in the immune system. This approach played an important role in the development of therapeutic monoclonal antibodies for use in oncology and in the treatment of autoimmune diseases. A clear advantage of PET imaging is that it provides both high spatial resolution and a highly quantitative measure of target binding.

Research conducted at the VUmc Department of Radiology and Nuclear Medicine has greatly facilitated the use of PET imaging in the field of oncology, both in terms of diagnosing cancer and in terms of developing and testing new treatments. For example, micro-dosing with a labelled chemotherapeutic agent (e.g., ^{11}C-labelled docetaxel) can be combined with PET imaging in order to measure tumour uptake. A robust model developed from these data is now being used to predict chemotherapy outcome.

A stable, state-of-the art research infrastructure

CHDR works closely with VUmc researchers and staff at both the scientific and practical levels, including patient recruitment. The neurology ward at VUmc houses CHDR's Clinical Research Unit (CRU), which includes a dedicated soundproof room for testing. This patient-friendly CRU gives our researchers easy access to PET and MRI facilities, neurophysiology equipment, certified diagnostic laboratories, and a GMP-approved pharmacy.

Why choose the VUmc and CHDR for your PET imaging needs?

VUmc has been a pioneer in PET imaging for decades. Together with the VU's Cyclotron Production Facility, the Department of Radiology and Nuclear Medicine has extensive experience developing tracers for both PET and SPECT (single-photon emission computed tomography). Our expertise includes the production of radionuclides, development and preclinical evaluation of new tracers, as well as developing novel clinical applications for new and existing tracers in a multidisciplinary environment. All practices are performed in accordance with established standards and regulations. In addition, our facilities are inspected at regular intervals by the Dutch Healthcare Inspectorate and are fully licensed to manufacture radiopharmaceuticals for use in humans.

The VUmc Radionuclide Centre within the Department of Radiology and Nuclear Medicine has decades of expertise developing and producing radiopharmaceuticals and tracers for use in animals and humans. The Radionuclide Centre is one of the largest in the world, with a growing library of ^{11}C- and ^{18}F-labelled tracers available for clinical use. As they become available, newly developed radiotracers can be quickly implemented for use in preclinical and clinical studies. In addition, the PET methodology group develops powerful PET data modelling techniques that are used by research groups around the globe. Thanks to our close relationship with the VUmc, sponsors who are interested in molecular imaging have direct access to our wide range of radiotracers and robust data analysis methods.

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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