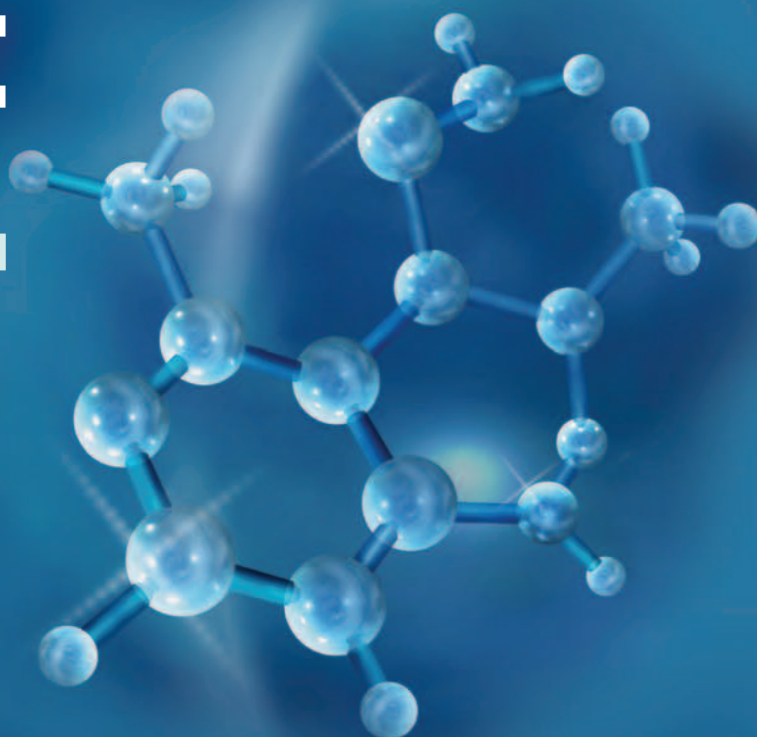


ALL IN THE DETAIL

Molecular imaging is allowing pharmaceutical researchers to improve drug development at the molecular level, enabling earlier disease diagnosis and better follow-up care. Holger Grüll and Oliver C Steinbach of the department of bio-molecular engineering at Philips Research Laboratories outline some of the ways in which molecular imaging is making a difference.



Progress in pharmaceutical research has brought relief to millions of patients. The average cost of bringing a drug to market, however, has escalated to more than \$1 billion and the process typically takes ten to 15 years. Despite the high investment in research and development, the US Food and Drug Administration (FDA) estimates that a drug entering clinical trial today has only an 8% chance of reaching the market. Common reasons for this, such as inefficacy or undesirable side effects, are even more prominent when novel targets (whose biology is often insufficiently explored) are introduced into the research and development drug pipeline. Clearly this is disappointing for patients needing new treatments for life-threatening diseases such as cancer. It is also detrimental to the pharmaceutical industry, which needs to generate sufficient profits to develop the drugs of tomorrow.

How can molecular imaging help?

The clinical applications of molecular imaging range from earlier disease diagnosis to better staging, and more accurate therapy planning to improved follow-up care. Using molecular probes, molecular imaging is also expected to aid in many steps of the drug-development process. By measuring drug effects at the molecular level, molecular imaging can identify drug responders that will benefit from drugs acting on targets that exist only in a sub-group of patients. The following demonstrates the range of uses of molecular imaging.

Improving predictivity for clinical trials

The potential of and need for molecular imaging in the preclinical stage is significant. As a non-invasive technique, it can be repeated many times to provide both spatial and temporal dimensions to the understanding of disease or



Authors

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As a department head for bio-molecular engineering, Oliver Steinbach and his team are focusing on molecular imaging applications to generate new business opportunities, by exploring combinations of new or existing imaging modalities and novel imaging contrast agents for diagnostic and therapeutic applications.

KEY POINTS

- The average cost of bringing a drug to market is \$1 billion.
- Only 8% of drugs entering clinical trial reach the marketplace.
- Medical imaging can help ensure the success of investment in drug development.

therapy in animal models. The fact that molecular imaging detects early changes at the cellular level and can even visualise biological processes, makes it much more sensitive than conventional medical imaging.

Specifically, preclinical small-animal imaging provides the capability to, for example, visualise and quantify metabolic activity, gene expression,

cell proliferation, apoptosis, angiogenesis, receptor status and immunoreactions, and hypoxia, among other relevant biological processes. Optical imaging is most common and has the advantage of high temporal and spatial resolution, but gives little quantitative information. Increasingly popular are designated preclinical nuclear imaging systems, such as PET/CT and SPECT/CT scanners that provide quantitative tomographic *in-vivo*

information with cross-correlated anatomical details using CT. As research moves from describing systems to measuring systems, the quantification of biological processes is extremely important.

Preclinical imaging can be used for:

- Snapshot measurements on single subjects
- Longitudinal studies of single individuals across multiple imaging sessions
- Group studies with multiple subjects in same laboratory
- Population analysis across multiple distributed studies and/or methodologies

Appropriate software applications supporting the analysis of each experiment replace the time-consuming and error-prone manual methods to lead to more reproducible standardised studies that can be compared across different laboratories.

Microdosing for smarter selection

Many factors lead to the creation of a successful drug. However, the way in which the human body absorbs and metabolises the drug is critical. This area of drug development (known as pharmacokinetics (PK) and pharmacodynamics (PD)) defines the drug's absorption, distribution, metabolism and excretion (ADME) characteristics. Inappropriate ADME parameters can lead to up to 40% of drug candidates failing to make it past the first human studies (Phase I).

At present, methods to define the ADME characteristics of a molecule include *in vitro* and *in vivo* studies using a range of experimental models. However, moving from animal data to humans is often misleading. Moreover, a number of lead candidates might come out of a drug-screening programme with similar pharmacological activities and identical animal ADME parameters, leaving open the question of which of these leads would result in the best drug.

A new method of obtaining human metabolism data, known as microdosing, has been developed, which will permit smarter candidate selection by introducing investigational drugs earlier into humans. In microdosing, a compound is administered at such a low dose that toxic effects are very unlikely, while the ADME parameters and compound target interaction can still be monitored. Microdosing, or tracer dose ADME screening, can be considered as human Phase 0 trials, in contrast to Phase 0 studies that refer to preclinical studies in animals.

The steps before human microdosing involve identifying one or more drug candidates with high affinity to the target protein and demonstrating pharmacological activity in *in vitro* and animal models. The next step is conducting limited animal safety testing and chemically synthesising the appropriate isotopically labelled drug molecule, typically using PET radioisotopes with a rather short half-life between minutes (C-11, 20min, for example) up to hours (F-18, 2h).

After administering a sub-pharmacological/sub-therapeutic dose of the novel drug candidate to human volunteers, real-time disposition data are collected in order to gain essential PD and PK information, rather than efficacy or safety

THE STRONGHOLD OF MOLECULAR IMAGING

The underlying ideas of molecular imaging are not new and were already applied to some extent in nuclear medicine as early as the 1940s. However, thanks to more sensitive imaging methods, better radio labelling techniques and new biological insights, molecular imaging is rapidly growing in scope and influence.

The first driver was the demand for better and more specific diagnostic methods; the first applications are now in the clinic. When the value of molecular imaging in drug development and screening is more widely accepted by pharmaceutical companies, drug development will be the next driver to push molecular imaging ahead.

The shift in recent drug discovery towards novel compounds focused on specific molecular targets, highlights the need for techniques to visualise and follow drug-target interaction and biological processes *in-vivo* on a molecular level. This is a discipline commonly denoted as molecular imaging.

Molecular imaging visualises agents with the help of imaging systems, such as positron emission tomography, single-photon emission computed tomography, molecular magnetic resonance imaging, magnetic resonance spectroscopy, optical bioluminescence and fluorescence, and ultrasound.

data. This contrasts with conventional Phase I studies in which the aim is to demonstrate tolerability and safety in a small number of subjects starting with a relatively low drug exposure.

NS and cancer

Microdosing is particularly useful for studying central nervous system (CNS) drugs, where PET is used to assess drug passage across the blood-brain barrier and follow uptake in different brain regions. Drug binding to receptors can be quantified to correlate receptor occupancy with pharmacodynamic responses. To follow disease progression and to monitor the outcome of new treatments, PET also facilitates longitudinal studies of biomarkers of pathophysiology, such as amyloid plaque load in Alzheimer's disease. In addition, combining genomic knowledge with PET neuroreceptor imaging is expected to facilitate the search for genetic predictors of drug response.

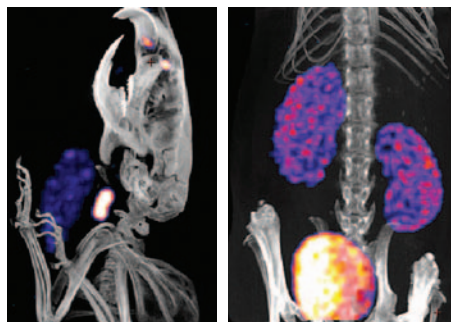
Nuclear imaging techniques are also used in cancer treatment to directly monitor the drug concentration in blood, normal tissue and the tumour. Anatomic and functional imaging modalities, such as computed tomography, MRI and US, have been used to assess tumour size and structure in response to treatment. They can also provide valuable information on:

- Tumour perfusion
- Integrity of the blood-brain barrier
- Vessel density and permeability
- Multi-parameters of the blood, such as oxygenation level, volume, flow, velocity and flow resistance

With the recent shift from conventional, cytotoxic compounds to novel drugs against specific molecular targets, therapies become much less toxic, and may not lead to anatomical changes of tumours in a short time. Molecular imaging can help in evaluating treatment efficacy *in vivo* much earlier.

Another promising area is in tumour angiogenesis imaging. The formation of new blood vessels from pre-existing blood

vessels is a fundamental process occurring during tumour progression. Tumour growth depends on the balance between proangiogenic and antiangiogenic molecules that can be used as molecular imaging markers.



Uptake of a radio-labelled compound in the thyroid of a mouse (left) and renal excretion (right).

New generations of cellular therapeutics, such as those based on dendritic cells or stem cells, show great promise for the treatment of diseases and are currently in preclinical and clinical trials. However, few non-invasive techniques exist for monitoring the cells after implantation. Recent data show the use of Fluorine-19 MRI technology in selectively tracking perfluoropolyether (PFPE) labelled cell migration, while the conventional proton image provides the anatomical context. Future studies are needed to evaluate the efficacy of these approaches in a clinical setting.

The future

While economic, scientific and regulatory questions still need to be answered, imaging technologies undoubtedly have the potential to increase efficiencies in many areas of drug research. To foster the expansion of molecular imaging, cooperative efforts are needed from molecular biologists, chemists and medical physicists to develop the technology further. We are at the threshold of a very exciting and innovative time in drug development. Many advances in molecular imaging are anticipated over the next decade and are likely to expand significantly in the future. **END**

CASE STUDY: MOLECULAR IMAGING AND BREAST CANCER

Innovative, targeted drugs, such as Herceptin, Gleevec and Velcade, have performed sub-optimally, as non-responder patient groups could not be distinguished a priori from responders. For example, only 30% of all breast cancer patients show over-expression of ErbB2 and can benefit from Herceptin treatment.

So far, variations in the ErbB2 receptor status over time, which can be used to predict the efficacy of treatment with Herceptin, have been neglected in patient management. This is largely because monitoring by repeat biopsies (as in certain new guidelines) is not feasible. Here, non-invasive imaging technologies, such as PET or SPECT, can be used to customise treatment programmes, thereby improving drug effectiveness, patient comfort and, ultimately, accelerating therapy outcomes.

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