Vital signs

New, exciting developments in molecular healthcare

The exciting new science of molecular medicine, which focuses on the molecular processes underlying disease, offers tremendous potential for early detection and diagnosis of medical conditions. It also provides what many clinicians see as the 'holy grail' of therapy assessment – a quantitative, explicit measure of a therapeutic drug's effectiveness, allowing for more targeted, more effective therapy. Although still in its infancy, this new branch of medicine is developing rapidly thanks to major advances in medical imaging by companies such as Philips.

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A powerful medical tool

Molecular medicine describes a generalized molecular approach to screening and assessment, diagnosis, disease tracking and treatment. It encompasses a whole range of techniques that make use of molecules tagged with a contrast agent and which bind to target molecules in the body. The target molecules are keyed in some way to a specific cellular activity or disease process and the contrast medium carried by the molecular agents allows biochemical processes, including the presence and extent of disease, to be visualized and even quantified using conventional imaging techniques. If bound to a drug, molecular agents can provide targeted therapy.

Major developments in molecular medicine in recent years have provided a much deeper understanding of the underlying molecular mechanisms controlling disease. In particular, advances in molecular target identification have led to the development of new contrast agents and targeted drugs. Moreover on the imaging front, resolution is constantly improving in virtually all imaging modalities with some systems already achieving microscopic-resolution capabilities and sensitivities that would have been unattainable only a few years ago.

Bringing disease into focus

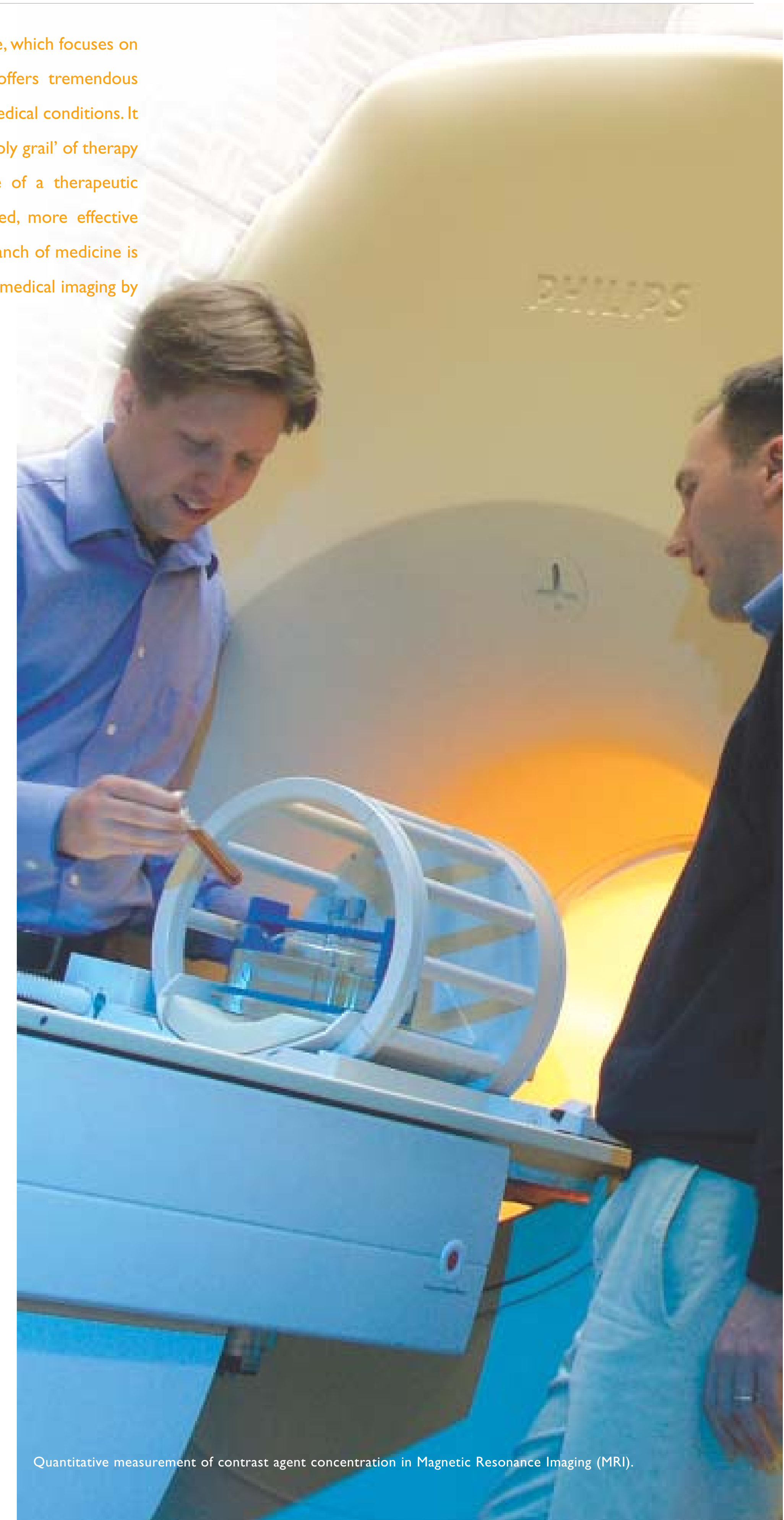
As an established manufacturer of medical imaging systems with many years' experience in clinical science, Philips is ideally placed to become one of the principal players in the emerging science of molecular medicine. The company recently formed a dedicated Molecular Imaging business unit. Its major strategic aims include supporting R&D in molecular medicine through the development of new ultra-sensitive imaging systems with exceptional sensitivity capable of observing phenomena at the molecular level, supporting academic groups working on new biomarkers, and forming alliances with contrast-agent and pharmaceutical companies.

In realizing its goals, Philips Medical Systems (PMS) is also supported by Philips Research, which has a whole range of R&D programs covering all imaging modalities. What's more, PMS and Philips Research are active in developing combined systems for molecular imaging, including X-ray/MRI systems, PET/CT systems, SPECT/CT systems and ultrasound/CT systems. Allowing for fast switching between modalities, these systems combine excellent anatomical detail for accurate drug administering using for example X-ray's high spatial resolution, with high sensitivity using for example nuclear imaging to observe the drug's effect.

Therapy evaluation

Much of Philips Research's current R&D work on molecular imaging focuses on quantification, specifically on quantifying contrast-agent concentration. This is important for disease staging and therapy monitoring since it gives an objective measure of a treatment's efficacy. It also facilitates faster, more cost-effective drug development as quantitative results, statistical evidence and repeatability form the only bases on which new drugs receive approval by the national drug authorities (such as the US Food and Drug Association).

A valuable tool for objectively assessing drug transfer between blood and tissue is pharmacokinetic (PK) modeling in which mathematical schemes are developed that represent complex processes within the body. Accurate PK modeling is important for precise determination of drug take-up rate. Recent work by Philips Research Aachen has been directed towards the use of PK modeling techniques to quantify contrast-



Quantitative measurement of contrast agent concentration in Magnetic Resonance Imaging (MRI).

agent and drug diffusion rates between blood vessels and tissue. Results of this work include a new parameter-mapping program currently in the qualification phase that generates 2D maps of exchange rates and computes the variation of these parameters in the time domain to provide a clear and objective measure of a molecular agent's delivery and take-up rates.

Quantitative MRI

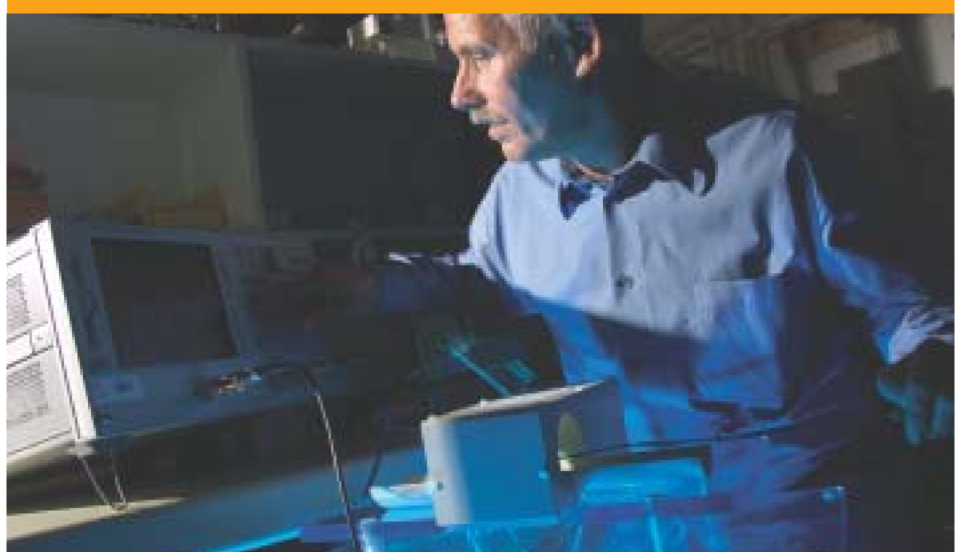
Classical Magnetic Resonance (MR) imaging deals with the interaction of a radio-frequency field with protons (water molecules) precessing in a large magnetic field. The MR-images obtained depend on the density of the protons and the tissue-dependent relaxation times. These MR-images can be enhanced with gadolinium- or iron-oxide-based contrast agents that locally influence the T1 and or the T2/T2* relaxation times. Usually (T1, T2 and T2*) weighted images are obtained that allow only qualitative assessment of the pathology. Philips Research, however, has developed new (T1, T2 and T2*) mapping techniques for Philips' MRI systems that provide a quantitative indication of pathology based on a pixel-by-pixel measurement of the relaxation times during post-processing. The numerical output of the mapping technique allows MRI to provide information down to the bio-molecular level by, for example, comparing the behavior of a tumor (uptake rate) before and after targeted therapy to provide objective evidence of the effectiveness (or otherwise) of the therapy.

> "And by providing objective, measurable evidence of the effectiveness of new treatments, it will create a route to faster, more cost-effective drug development and therapy."
>
> Tobias Schäffter, Philips Research Hamburg.

Other developments include a new software evaluation tool that corrects for errors introduced into (T2*) relaxation times by susceptibility effects at tissue-air boundaries. By eliminating these errors, more reliable comparisons of T2* values between different locations within the body and even between different subjects become possible, allowing contrast agent concentration within tissue to be accurately measured. Standard (or classical) methods, usually based on exponential fitting algorithms, introduce large errors into the quantification of contrast agents and show lower sensitivity. Philips' technique provides an accurate measure of low contrast agent concentrations. This is important in stem-cell research, for example, since it allows the detection and tracking of small amounts of stem cells that are labeled with an iron-oxide contrast agent.

Animal imaging supports R&D

One of the major focuses of Philips' new Molecular Imaging business unit is the development of equipment to support the R&D chain from development of targeted contrast agents and drugs in the laboratory, through pre-clinical animal trials towards early clinical human trials. Philips now offers researchers in this field specially-developed animal-imaging equipment including Optical Imaging, PET, CT, MRI with dedicated animal coils, and animal probes for ultrasound. Many of these systems are based on the same back-ends as the company's established clinical-imaging systems. They therefore offer the important advantage of allowing protocols developed during pre-clinical animal-testing phases to be transferred directly to the clinical testing phases, saving time and costs in drug and contrast agent development. This is in marked contrast to current specialized animal-testing equipment in which transfer from pre-clinical to clinical trails requires the time-consuming development of completely new protocols for testing on humans.



Development of a dedicated small-animal RF-coil for MRI

Advances in nuclear imaging

New developments by Philips Research have also led to major advances in the performance of SPECT (Single Photon Emission Computed Tomography) cameras including improvements in spatial resolution and sensitivity. With a unique Sky Light feature, Philips' new SPECT camera incorporates two detectors that can arbitrarily move around a patient and make close approaches to increase spatial resolution. What's more, the camera features a new multi-acquisition window allowing for multi-tracer studies using several nuclear tracers with different energies, e.g. technetium which is taken up fast into tissue and indium which is taken up more slowly. This allows simultaneous acquisitions to be performed focusing on different clinical phenomena, for example, blood flow (perfusion) and controlled cell death (apoptosis) following a cardiac event.

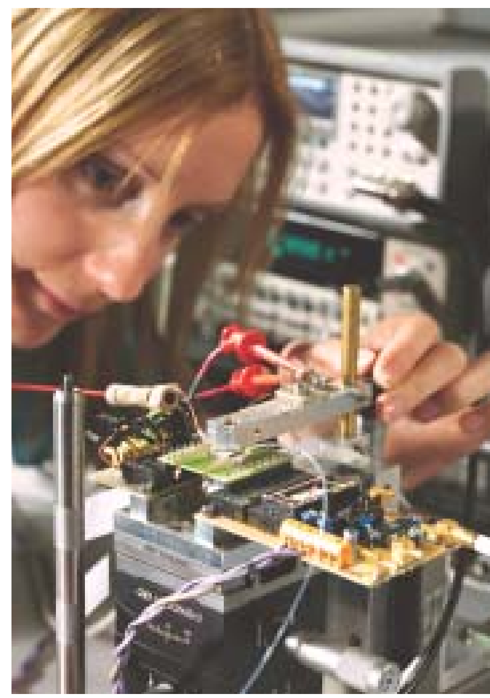
> "By dramatically improving the power of diagnosis and therapy, molecular imaging is becoming one of the most important tools of modern medicine."
>
> Tobias Schäffter, Philips Research Hamburg.

Ultrasonic molecular imaging and therapeutics

Ultrasound has been traditionally known for its real-time imaging capability of anatomical features as well as functional changes in blood flow. For this, ultrasonic contrast agents consisting of micro-bubbles have become the industry standard for increasing the signal from the blood pool. A leader in the development of imaging techniques for contrast agents, Philips is currently extending its expertise from blood-pool contrast agent imaging to molecular imaging and has formed several collaborations with leading academic institutions for the advancement of targeted ultrasonic contrast agent development. We have made significant advances in the imaging of newly formed blood vessels around tumors by targeting to the specific angiogenesis marker integrin with ultrasonic contrast agents, along with several important characterizations of the necessary conditions for successful binding of contrast agent to specific molecules. Philips is also actively engaged in what's known as 'ultrasonic-mediated molecular therapeutics' – the use of appropriate biochemical delivery mechanisms to control the delivery of a therapeutic intervention to allow user-controlled release of pharmaceuticals and immediate assessment of the effect of a chosen intervention.

Creating a new world of healthcare

Molecular medicine has been described as a medical breakthrough as fundamental and as significant as Harvey's discovery of blood circulation and the discoveries of antibiotics and the structure of DNA. Its development will revolutionize clinical practice. Molecular-based screening will provide information about a patient's predisposition to particular diseases that will allow clinicians to employ preventive care designed to help a patient combat risk factors. And in cases where disease is discovered, molecular-based techniques will allow specific imaging, identification of pathology and treatments. The advances currently being made by Philips Research are making a vital contribution towards turning these visions into reality to create a new world of healthcare in which many of today's most debilitating diseases will be consigned to history.



New biosensors for molecular diagnostics

Philips Research is investigating a new biosensor technology based on magneto-resistive sensors that promises to radically improve the speed, sensitivity and reliability of biomolecular diagnostics for applications such as protein and pathogen monitoring, near-patient testing in medical centers (blood, urine, saliva tests etc.), and ultimately home testing by individuals. Philips' biosensor measures the magnetic field created by magnetic nano-particles that bind to target molecules in a biological assay. Compared with optical sensing methods, the use of magnetic nano-particles not only eliminates the additional steps required to bind optical labels to the target molecules, it also results in biosensors that are up to a hundred times more sensitive than existing devices.

Philips' next step in the development of such systems is to demonstrate dose-response curves for relevant biological molecules and the company expects the technology could be ready for industrialization in about four to six years.