PHILIPS

Technology Backgrounder

THE SONODRUGS PROJECT

Cancer and cardiovascular disease are two of the world's biggest killers. In the European Union alone, deaths from cardiovascular disease in 2003 numbered 1.9 million, while the 2004 figure for cancer deaths was 1.2 million. The cost associated with treating and managing these diseases and the impact they have on sufferers' quality of life are enormous, as is the economic cost due to lost working hours. It is widely accepted that earlier diagnosis and treatment of these diseases, using targeted drugs and minimally invasive or non-invasive procedures, is the key to reducing their mortality rates as well as their human and economic burden.

The SonoDrugs project aims to develop image-guided drug delivery techniques that use ultrasound-activated particles to deliver drug doses directly to diseased tissue. By locally delivering appropriate drugs only where they are needed, these new drug delivery techniques could increase the therapeutic efficiency. In addition, they may reduce the side effects currently associated with 'whole-body' dosing (typically caused by uptake of the drugs by vital organs).

Two types of drug delivery particle

The drug delivery technology being developed in the SonoDrugs project will utilize drug-loaded particles, typically between 100 nm and 2000 nm in diameter that are designed to carry drugs to the site of disease via the bloodstream. It is known that at these very small diameters the particles are easily transported by normal blood flow through the finest capillaries in the vascular system and can therefore penetrate deep into diseased tissues. The drug payload will be inside the particles or attached to the shell.

Arrival of the particles at the disease site is detected using the real-time medical imaging techniques Magnetic Resonance Imaging (MRI) or ultrasound (see below). The drug is then locally released from the particles by subjecting them to focused ultrasound pulses. For this purpose, the SonoDrugs project will aim to develop two different types of particle:

The first of these will have a shell made of a material, such as a phospholipid, that melts or becomes porous at a temperature that is just a few degrees above normal human body temperature. The temperature rise required to melt or increase the porosity of their shell in order to release the contained drug will be provided by the local heating effect of the focused ultrasound.

The second type of particle, which will be larger in diameter (up to 4 µm), will have a shell made of a material such as albumin, a phospholipid or a polymer, that ruptures due to pressure-induced stresses generated by the focused ultrasound pulses. Often referred to as microbubbles, gas-filled particles of this type are already used as a contrast agent for ultrasound imaging. Philips Research has actively been investigating their use as a drug delivery mechanism for several years. Moreover, the SonoDrugs project can build on the results of the recently-completed Dutch BURST (Bubbles for Ultrasound and Therapy) project.

Guidance by MRI or ultrasound

In order to monitor the arrival of the drug-loaded particles at the disease site and accurately focus ultrasound pulses onto them, real-time image guidance is an essential part of the drug delivery process. The SonoDrugs project will examine the use of MRI and ultrasound imaging (two widely available imaging modalities for cancer and cardiovascular disease) for this purpose.

MRI is ideal for use with thermally activated particles because of its ability to measure local tissue temperatures. It is also a good technology for imaging soft tissues and has the ability to locate particles labeled with MR contrast agents such as gadolinium or manganese. MRI could therefore provide all the information required for lesion location, accurate ultrasound focusing and controlled drug release (using the tissue temperature measurements in a controlled feedback loop). Philips has already integrated the necessary ultrasound hardware and feedback mechanisms into its HIFU (High Intensity Focused Ultrasound) MRI research system using its phased-array ultrasound transducer technology. SonoDrugs project activities in MRI-guided ultrasound-induced drug delivery will focus primarily on the treatment of cancers.

For potential applications in the treatment of cardiovascular disease the project will focus on the use of ultrasound as the real-time imaging modality as well as the means of releasing drugs from pressure-sensitive nanoparticles. This is facilitated by the fact that gas-filled or partially gas-filled microbubbles show up well in ultrasound images. In fact, they are already used in clinically-approved ultrasound contrast agents.

Sonoporation

As a parallel thread in its research, the SonoDrugs project will also investigate the use of ultrasound-activated gas-filled microbubbles to increase the uptake of drugs into target tissue – a process known as sonoporation. When microbubbles are bombarded by ultrasound at their resonant frequency they rapidly expand and contract in size, often resulting in fragmentation of the microbubbles when the stresses in their walls become too great. If the microbubbles involved are close to a cell wall, the effect of their physical deformation is known to increase the porosity of the cell wall to extra-cellular material such as drug molecules. The exact mechanisms involved are not yet fully understood, but it may be that the oscillating microbubbles induce cavitation or microscopic water jets in the surrounding fluid, while fragmentation of the microbubbles may create ballistic fragments that pierce the cell walls.

Sonoporation does not necessarily involve drug-filled nanoparticles. It can be achieved during co-administration of existing drugs and ultrasound contrast agents. Although the drug would still need to be administered as a whole-body dose, increasing its uptake rate in the target tissue could mean an increased therapeutic efficiency without increased side effects.

Philips' HIFU-MRI research system will also be used as a platform for the SonoDrugs project's investigations into sonoporation effects.

Project organization

The SonoDrugs project is divided into several work packages. These include a major work package to develop new particles with the necessary size, structure, physical behavior and biocompatibility; a work package to undertake in-vitro testing of the derived particles; and work packages to assess the in-vivo bio-distribution and effectiveness of the drug delivery techniques. Philips will act as the overall project coordinator.

The project will run for four years and has a budget of €15.9 million, €10.9 million of which is being funded under the EU's 7th Framework program. The SonoDrugs project consortium consists of the industrial partners Philips (The Netherlands, Germany and Finland), Nanobiotix (France) and Lipoid (Germany); the university medical centers Erasmus Medical Center (The Netherlands) and Universitäts Klinikum Münster (Germany); and the academic institutions University of Cyprus (Cyprus), University of Ghent (Belgium), University of Helsinki (Finland), University of London (United Kingdom), University of Tours (France), University Victor Segalen (France), University of Technology Eindhoven (The Netherlands) and the University of Udine (Italy).