Hitting the right spot

Image-guided drug delivery. These four words could one day revolutionize the way diseases like cancer and cardiovascular disease are treated. For patients, it could change lives: more effective treatment, lower systemic toxicity and new drug possibilities.

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Cancer and cardiovascular disease affect millions of people around the world. They’re also two of the most deadly and difficult-to-treat diseases. Currently, most treatments involve powerful drugs that are distributed passively throughout the body – all for a disease that may be limited to one spot.

Doctors are left without an efficient way to ensure the treatment gets to where it’s needed most. This ‘whole-body’ dosing also limits a doctor’s ability to ensure the treatment is as effective as possible. Due to the inherently toxic nature of treatments like chemotherapy, doctors have to work within a tight margin – called the therapeutic window – to make sure the amount of treatment given is enough to have a positive effect while keeping side effects and toxicity to a minimum. Usually, this means the doctor has to limit treatment doses and spread them over a period of time. It’s definitely not the powerful punch doctors – and patients – are hoping for.

Right on target

One solution is to deliver the treatment right to the target spot. Right now, the best way to do this is through injectable drug-loaded carrier particles, which already exist for the treatment of some diseases, such as breast cancer. But they aren’t as effective as they could be. The current generation of carriers localizes treatment but only in a passive manner, with drugs released as a slow diffused leakage over time. Ideally, there would be a better way to control – or trigger – the release of drugs right at the disease site.

Triggered release

With the goal of giving patients more benefit from potentially life-saving treatment, Philips Research began to develop localized drug-delivery techniques that aim to release treatment locally using an external trigger, such as ultrasound pulses or heat. The concept involves tracking the path of the drug through the body and then triggering its release from the carrier particles at the target spot – potentially making...
Novel techniques

The potential of image-guided drug delivery has not gone unnoticed. In fact, Philips is heading a €15.9 million project focused on furthering the novel techniques. The Sonodrugs’ project, which is partially funded by the European Union, draws on the expertise of 15 partners, including medical centers and academic institutions from throughout the EU.

The project will run for four years and work will focus on a number of different areas, including the development of new particles with the right size, structure, physical behavior, half-life and bio-compatibility, as well as exploring the bio-distribution and effectiveness of the drug-delivery techniques in-vitro and in-vivo.

the uptake of treatment into disease cells more controlled and, therefore, more powerful.

“New options that involve externally triggered treatment at the specific site of disease could really change patient care for the better,” notes Klaus Tiemann, Professor of Cardiology at the University of Münster, Germany. This is because triggered local delivery means a higher concentration of the drug reaches the disease site. This may result in fewer side effects for patients and give doctors the option of increasing dosage in an effort to hit the disease harder straight away, possibly improving treatment efficacy.

Visual delivery

Not wanting to limit the possibilities, Philips is working on two different image-guided delivery techniques that could one day change the way these diseases are treated. The first technique, developed for the treatment of cancer, involves drug-loaded particles mostly made of phospholipids – called liposomes. Typically just 100 to 200 nanometers in diameter, liposomes are tiny enough to travel through small capillaries in the vascular system and penetrate deep into diseased tissue. After injection, the particles are tracked using MRI and once they’re at the target site, a small amount of heat is applied using ultrasound, causing the heat-sensitive particles to release the treatment drugs on the spot.

Since damage can occur when tissue is overheated, MRI is ideal because it can be used to monitor local temperature changes in the body. “The physiological range of heating body tissue is very small,” explains Holger Gruell, project leader at Philips Research. “You shouldn’t heat body tissue much above 42°C. Beyond 44°C, you can do permanent damage. So the heating effect that releases the drug must occur within a certain temperature range, which requires a precise finetuning of the particles. It’s a balance that we’re still working on. But this is where the combination of ultrasound and MRI has a big advantage because MRI can monitor the subtle ultrasound-induced temperature changes very precisely.”

MRI is also capable of imaging soft tissues and organs, as well as detecting the arrival of the drug-loaded particles at the disease site using contrast agents.

A burst of bubbles

The other method for image-guided drug delivery involves larger particles, up to two micrometers, often called ‘microbubbles’, which can be adapted to rupture when exposed to ultrasound pressure waves – or pulses. Philips is exploring ways to fill these microbubbles, currently used as contrast agents for ultrasound imaging, with treatment drugs and use them to deliver precise doses exactly where needed in the body. Ultrasound imaging would track the microbubbles in the

bloodstream
and when they reach the target site, a high-energy ultrasound pulse would shatter the microbubble shells – releasing the drugs right at the disease site.

“When microbubbles are exposed to ultrasound pulses, they rapidly expand and contract in size eventually causing them to explode,” notes Marcel Bohmer, who’s responsible for microbubble development at Philips Research. “But actually one of the most exciting aspects of microbubble drug delivery is the aftereffect of that bubble burst.”

Researchers have found that when microbubbles burst, the explosion somehow pierces nearby cell membranes making them more porous and, therefore, more susceptible to drugs. This phenomenon is called sonoporation and could allow for new treatment possibilities. In fact, there’s a whole range of new drug therapies based on genetics and DNA that may prove to be the most powerful and tolerable treatments yet for diseases such as cancer and cardiovascular disease. But there’s one main obstacle: getting the treatments into the disease cells.

Sonoporation may just offer a solution. The controlled opening of the cell membrane caused by the microbubbles may not only increase the local drug concentration but also facilitate the uptake of drugs that would never otherwise be able to enter cells.

There are still many rounds of testing and many issues to be resolved before image-guided drug delivery hits the clinical setting – no sooner than five to ten years from now. But it may one day offer doctors more localized ammunition in the fight against two of the deadliest diseases known to man.

For more information, go to www.research.philips.com/password

**Particle particulars**

Temperature-sensitive liposomes are formed by arranging different lipids into a bi-layer about five nanometers thick, which encircles a tiny reservoir that’s filled with highly concentrated drug treatment. Liposomes have membranes that closely resemble that of natural cells but are 50-100 times smaller. When heated from 37°C to 42°C, the bi-layer develops pores that readily release the drug. The research process also involves fine-tuning the design and selection of lipid materials to ensure a precise drug-release temperature.

Microbubbles are currently used as contrast agents in ultrasound imaging. They have a gas core and a shell consisting of phospholipids, proteins or a biodegradable polymer. But for drug delivery purposes, the more robust polymer shell is preferred. These shells are formed around oil droplets containing the treatment drugs. The oil is then partially removed and a capsule with a polymer shell is the result. The oil acts as a liquid reservoir for the drug, whereas the gas helps trigger its release during the ultrasound application.