Simplifying Oncology Care

Philips Research focuses on ultrasound-mediated drug delivery
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Philips Research and its academic partners explore the efficacy of pressure-induced microbubbles and temperature-sensitive liposomes for localized drug delivery.

First introduced to the medical world in the 1960s, ultrasound imaging has been cited as one of the most widely used diagnostic tools in modern medicine, second only to conventional X-ray. The non-invasive characteristics of ultrasound have made it an ideal technique for viewing the unborn fetus and for visualizing what goes on inside the patient during certain minimally invasive procedures. Hoping to take ultrasound to the next level of patient care, scientists at Philips Research are exploring how the modality may also play a role in the localized delivery of anti-cancer drugs or other therapeutic molecules to targeted areas of cancerous tumors.

Putting on the pressure: microbubbles

The microbubbles that Philips Research is evaluating are typically less than 5 µm (micrometers) in diameter, approximately the size of a red blood cell. Philips microbubbles are made of a biodegradable polymer that carries drugs inside them. The drugs are released by using a focused ultrasound pulse to rupture the microbubbles.

“The ultrasound is used to burst the bubble at the precise location where the drug needs to go—into an organ, a tumor, or where a higher uptake of the drug is needed—and does so non-invasively,” notes Ralf Seip, PhD, Director of Ventures, Ultrasound Imaging & Therapy, Philips Research.

To deliver the drug where it is required, these microbubble-rupturing ultrasound pulses must be accurately targeted at the site of the disease. To achieve this, Philips Research has developed a special phased-array transducer designed to focus ultrasound pulses into a small ellipsoidal volume up to 8 cm deep in the target tissue. In the experimental prototype, this phased-array applicator is co-aligned with a standard clinical imaging transducer so that ultrasound imaging and drug delivery can be performed simultaneously.

“Collaborating with Philips in the area of ultrasound is very exciting,” says Alexander Klibanov, PhD, Associate Professor, Cardiovascular Division, University of Virginia. “Our patients are tumor-bearing mice. The tumor is grown on the mouse’s hind leg and our goal is to inhibit tumor growth,” explains Dr. Klibanov. “When we can see the tumor with a normal ultrasound imaging system, we inject the drug-laden microbubbles into the mouse’s bloodstream, fire up the Philips therapeutic transducer, and observe the microbubbles as they travel to their target. Once they reach the vasculature of the desired target, we deliver a strong ultrasound pulse that bursts the microbubbles, thereby releasing the drug. A side transducer allows us to visualize our target throughout the entire process and monitor the drug delivery.” Dr. Klibanov continues, “We are definitely in the beginning stages of the process and some experiments are more successful than others but we remain hopeful.”

**Turning up the heat: liposomes**

Philips Research is also exploring the viability of temperature-induced drug delivery with liposomes. Smaller than 0.5 µm, the tiny, spherical liposome capsules, made of the same material as a cell membrane, contain the drugs. The drugs are released inside the tumor by a slight local temperature increase mediated by a focused ultrasound wave that causes the liposomes to become leaky. MRI imaging is used to image and guide the process.

“Offering new non-invasive therapeutic options would be the main reason for healthcare facilities to provide this therapy.”

*Klaus Tiemann, MD, PhD, Professor of Medicine/Cardiology, University of Münster, Münster, Germany*
Subtle heating above body temperature triggers the release of an anti-cancer drug and an MRI contrast agent from a nano-sized liposome. The MRI agents provide the ability to visualize and quantify the amount of released drugs.

Illustration

Holger Gruell, PhD, Department of Bio-Molecular Engineering, Philips Research and Professor, Department of Bio-Molecular Engineering, Eindhoven University of Technology, leads the Philips research efforts on drug delivery agents. “One of the areas we’re studying requires us to pair MRI contrast agents with anti-cancer drugs into the liposome. As the temperature rises, the liposome breaks down, thereby releasing the drug and sending out a signal that can be seen on the MRI system.” Dr. Gruell continues, “Theoretically, we look at the MRI image and we see that the signal change is correlated with the amount of drug released in the tumor—it’s really quite a breakthrough if it works the way we think it will.”

According to Dr. Gruell, heat-sensitive liposome drug delivery has the potential of allowing clinicians to offer a more flexible, personalized treatment option for their patients. “Currently, the dosing rate of chemotherapeutic therapy is based on body weight. The problem is that weight is just one element. Every patient is different. One may have a faster metabolism than the other, which means we may compromise efficacy if the drug is metabolized too quickly. Additionally, there are patients who can tolerate a higher dose without side effects. If we know how much drug were sending and how much is actually hitting the target, we have the power to personalize treatments, which in return, gives us more control over the outcome.”

Considering the potential

“Offering new non-invasive therapeutic options would be the main reason for healthcare facilities to provide ultrasound-mediated therapy,” notes Klaus Tiemann, MD, PhD, Professor of Medicine/Cardiology, University of Münster. Over the last 10 years Dr. Tiemann’s focus has been on tissue perfusion imaging and the use of contrast microbubbles for ultrasound-mediated drug delivery. “We’re looking at prevention of re-stenosis after stent implantation and the improvement of stem cell delivery, which can be optimized by bioeffects, induced by insonification with contrast microbubbles and focused ultrasound. We have already demonstrated in a preclinical setting that the efficacy of stem cell transplantation can be improved by utilizing the Philips Therapy and Imaging Probe System (TIPS) to deliver the high-frequency pulse needed to rupture the microbubbles. In contrast to regular stem cell transplantation, this is a very exciting and cost-effective option,” reports Dr. Tiemann. “It is possible that we may have many indications for this therapy. Cancer therapy is very obvious because it’s easier to destroy cells than to repair any kind of damage (e.g. myocardium after infarction).”

“Breast cancer treatment may be a good initial application of the technology, as ultrasound-mediated delivery can be used to deliver and activate the agents only where required, reducing the side effect profile of current chemotherapeutic treatments,” says Dr. Seip. “The breast also presents an ideal acoustic window to the applicator, as its entire volume is accessible to the therapeutic pulses used to deliver the agent, while ultrasound imaging technology can be used to guide the tumor targeting.”

“My dream is that therapeutic ultrasound becomes a commonplace treatment option, and we are working hard to turn this dream into reality.”

Ralf Seip, PhD, Director of Ventures, Ultrasound Imaging & Therapy, Philips Research, Briarcliff Manor, New York, USA
The Philips Therapy and Imaging Probe System (TIPS) is an advanced preclinical research tool that enables scientists to investigate and develop potential therapies through either the pressure- or temperature-mediated mechanisms provided by therapeutic or high-intensity focused ultrasound. To learn more about TIPS, visit www.research.philips.com/TIPS or call 914.945.6188.

“Ultrasound imaging combined with ultrasound therapy has the potential of being quite accessible for clinicians concerned with maintaining quality patient care while balancing economic considerations.”

Alexander L. (Sasha) Klibanov, PhD, Associate Professor, Cardiovascular Division, University of Virginia, Charlottesville, Virginia, USA

“The idea is to stop cancer and to do so without large doses of therapeutic drugs toxic to normal tissues,” says Dr. Klibanov. “Ultrasound-mediated drug delivery, whether we use microbubbles or liposomes, has the potential of allowing us to effectively treat patients without surgery, without radiotherapy, and with less harm and more localized treatment.”

Looking to the future
Early results from experimental set-ups for ultrasound-mediated drug delivery, using both microbubbles and liposomes, is promising, but there is still some way to go in fully developing the technology. “It’s important to remember that we are in the very early phase of research,” notes Dr. Gruell. “If everything works out the way we hope, we are probably 10 to 15 years away from making our preclinical research a clinical reality.” Dr. Klibanov agrees, “If the situation is such that we achieve all of the aspirations we hope for, we will have the ability to point toward a metastasis, hit it with the ultrasound, and then send and release the drug directly to the target. And that will be cause to celebrate.”

Looking to the future

The Philips Therapy and Imaging Probe System (TIPS) is an advanced preclinical research tool that enables scientists to investigate and develop potential therapies through either the pressure- or temperature-mediated mechanisms provided by therapeutic or high-intensity focused ultrasound. To learn more about TIPS, visit www.research.philips.com/TIPS or call 914.945.6188.

“Medicine is about evolutions rather than revolutions. We’re simply taking the non-invasive nature of ultrasound to the next level of patient care.”

Holger Gruell, PhD, Department of Bio-Molecular Engineering, Philips Research, and Professor, Department of Bio-Molecular Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands

To learn more about Philips Research and its developments in ultrasound-mediated drug delivery, please contact Dr. Ralf Seip at ralf.seip@philips.com or Dr. Holger Gruell at holger.gruell@philips.com.