



BY STEPHANIE ROBERTS

IN
FOCUS

IMAGE-GUIDED

SOUND

WAVES WILL

CHANGE MEDICINE;

HERE'S HOW

THE LATIN OF THE
poet Virgil dignifies
the medals
awarded to that rare
creature, the
Nobel Laureate.

In four of the prize's five categories, the inscription reads *Inventas vitam juvat excoluisse per artes*. It means, "And they who bettered life on earth by their newly found mastery;" or, more literally, "Inventions enhance life which is beautified through art." There is a less well-known phrase of Virgil's, however, one that as easily could have been chosen to express what marks those who achieve greatness in discovery: *Possunt, quia posse videntur*—"They can because they think they can."

Dr. Kullervo Hynynen heads imaging research at Sunnybrook Research Institute (SRI) and is a professor at the University of Toronto. He wanted only to be a scientist. "I never really thought about anything else," he says. "I always did experiments." Some time after he retired his Meccano kit what he did think about was how to invent a technology that renders the impenetrable penetrable and redefines surgery as scalpel-less.

Most of us will be familiar with ultrasound as a tool used either for diagnosis or, during pregnancy, to see inside the uterus. Ultrasound works by producing sound waves, the echoes of which are translated into "pictures" of internal structures. In this way, a doctor can see

if blood is flowing through an artery or measure the size of a fetus.

Therapeutic focused ultrasound is grounded in the same physics principles, but works differently: it harnesses sonic energy to effect a change in biological tissue. High-intensity focused ultrasound, or HIFU (pronounced hi-foo), generates heat to ablate, or destroy, tissue, like a tumour, inside the body. Lower-intensity focused ultrasound, which (so far) doesn't have a catchy acronym, is used in the brain, where high temperatures are not feasible. In addition, focused ultrasound is being explored as a way to deliver drugs and other biological agents into the brain.

The history of using ultrasound to destroy tissue goes back a long way—the first study to show that ultrasound could alter tissue biologically was in 1926, and a 1942 article established that it could be focused—but the path has not been smooth, even up to recently. Some of the glazier issues pertain to control: achieving the precision needed to heat only the target and not the healthy tissue surrounding it; knowing when the right temperature for ablation has been reached, and for the right length of time; and, in the case of the brain, training ultrasound through



LEFT TO RIGHT: DRs. GREG CZARNOTA, YUEXI HUANG AND KULLERVO HYNYNEN

the skull without the beam scattering or becoming distorted.

Hynynen says he first saw the therapeutic promise of ultrasound as a doctoral student in Aberdeen, U.K., where he landed after completing a master's in physics in Finland, his birth country. He was exploring the use of microwaves to heat and destroy tumours. One day he attended a meeting at which he was assigned to review the literature on ultrasound. He did the review and switched gears. "From that, it was obvious ultrasound would be better," he says. Obvious, because ultrasound can penetrate deep and be focused, whereas microwaves can do one or the other singly, but not both at the same time. Less clear, however, was how to achieve the control needed to exploit the full potential of ultrasound as a therapy. After some work (simplifying the plot somewhat), he deduced that bringing magnetic resonance (MR)—with its superb capacity to display high-quality images of internal structures in real time—into the equation might be just the ticket, and in 1991 invented an MR-guided focused ultrasound system. Eight years later, GE Healthcare, then GE Medical Systems, formed a company to commercialize the system. That company, InSightec, has since worked with Hynynen to refine and develop further the system.

Twelve years on, punctuated by study after study establishing feasibility, safety and even clinical effectiveness, it does, indeed, appear to be just the ticket. If you haven't heard of it yet, you soon will. Focused ultrasound surgery, as it is also called, is an approved therapy for select conditions in the U.S., Europe and Canada. Many more applications are in clinical trials, edging closer to approval and promising to provide options where none exist, as in inoperable brain cancer, or where the best alternative—"traditional" surgery—is de facto highly invasive, not to mention risky and expensive.

Focused ultrasound surgery, which relegates the scalpel to the bottom of the surgeon's tool kit, is ushering in a paradigm shift in

medicine, says Hynynen. "It's disruptive technology. It's going to change the way people think," he says.

How does it work? Let's take uterine fibroids as an example. In 2003, Hynynen was part of a clinical team at Harvard's Brigham and Women's Hospital, where he was then located, that was the first to show using MR-guided HIFU to treat symptomatic fibroids is safe and feasible. These benign lesions affect up to 25% of women of childbearing age. Symptoms include heavy bleeding and pain. Many treatments are invasive; the most common one, hysterectomy, removal of the uterus, renders a woman infertile.

During the procedure, the woman lies prone on a table that has ultrasound transducers built into a cradle at the pelvic level, and that can be rolled into an MR scanner. First, doctors plan the treatment. They use MR to verify the location and size of the fibroids, position the transducer robotically, and map the starting temperature of and around the lesions, displaying these data in 3-D on monitors. Treatment then begins. The transducer focuses sound waves onto a fibroid in 15-second pulses. The energy from these sonications causes the targeted tissue—and only that tissue—to heat up and coagulate, or solidify. This is repeated until all targeted fibroids have been treated. Throughout, doctors use MR to guide the sonications and map the temperature changes, which tell them when the tissue has attained sufficiently destructive heat.

Treatment takes two to three hours. No anesthesia is needed. Tylenol may be given to reduce discomfort. Adverse effects are infrequent and rarely serious—skin burn, perhaps. After the procedure, the woman rests for an hour or two, and then goes home; usually she can return to work the next day. Success is measured by symptom reduction, which Hynynen says is "almost right away." The uterus is spared.

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Making temperature maps inside the body is called thermometry. “MR is the only imaging modality that can do thermometry quantitatively over the range of temperatures that we need to do for these treatments,” says Dr. Rajiv Chopra, an imaging scientist at SRI and assistant professor at U of T. “With focused ultrasound, you can control the heating, plus you can measure temperature in the body with imaging and do better targeting.”

Therein lies the power of the technology: its precision and immediacy. With brain cancer, for example, Chopra notes standard protocol goes something like this: diagnosis with MR, then treatment with radiation or chemotherapy, followed by another MR scan eight weeks later to see if the treatment is working. He contrasts this to focused ultrasound surgery: “Within minutes after the treatment you can see if you’ve coagulated the tissue or not. It’s a very different paradigm—you have measurements that tell you with certainty [if] the tissues are dead or alive, and what’s been spared.”

The treatment for uterine fibroids is approved for specific indications in more than 20 countries, including in Canada; study on it continues, for example, to treat large fibroids or to test new systems. Sunnybrook Research Institute is conducting trials in this area, led by interventional radiologist Dr. Elizabeth David. In 2010, SRI opened an MR-guided HIFU research facility in the Odette Cancer Centre, part of a collaboration with Thunder Bay Regional Research Institute, which also has a focused ultrasound surgery suite. At SRI, the facility is part of the Centre for Research in Image-Guided Therapeutics.

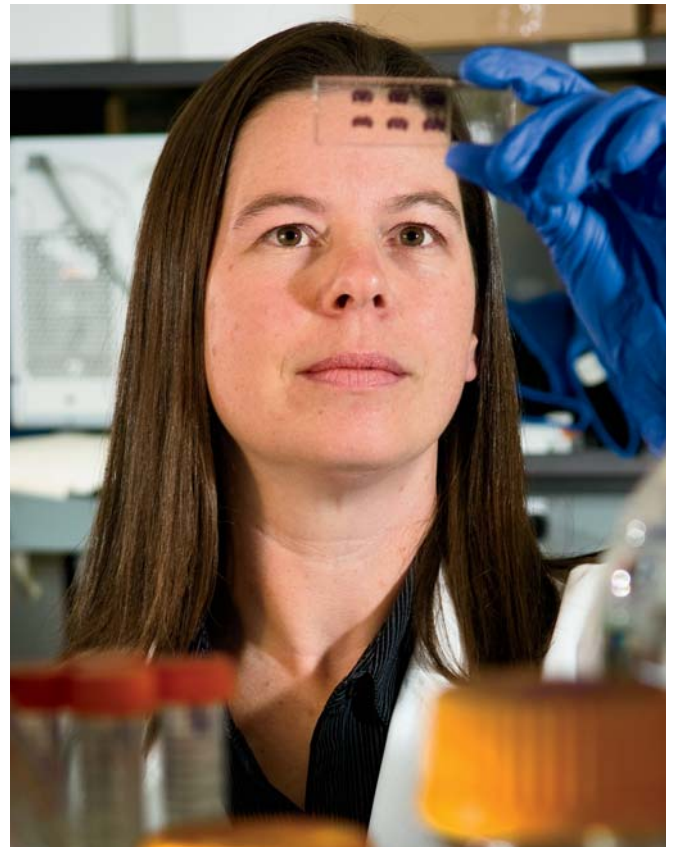
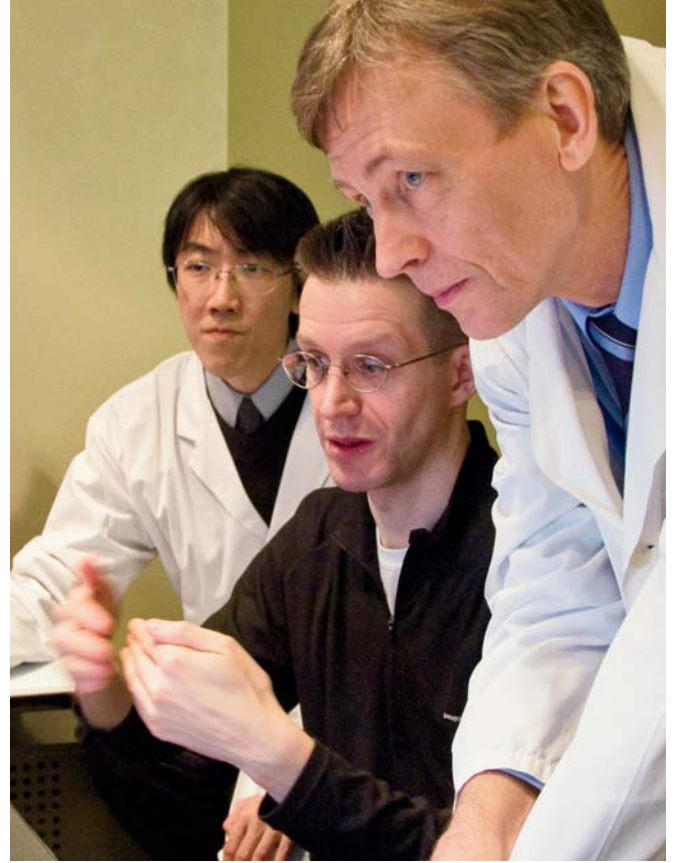
Focused ultrasound surgery for uterine fibroids is compelling as an example of this therapy’s power, but its potential in other areas is more gripping still. Of these, conditions that imperil the brain surely rank at the top: cancer, dementia, stroke—these shatter countless lives. The brain is devilishly difficult to treat,

encased as it is by the skull and further guarded by the blood-brain barrier, densely packed cells that bar entry to 95% of drugs, including most chemotherapeutics. Hynynen and his team, working with industry, developed a device that overcomes these obstacles. It enables even the most deeply nested lesions to be destroyed without opening the skull, and smuggles drugs past the blood-brain barrier to where they are needed.

The device resembles a clunky helmet. The transducer comprises more than 1,000 elements that are arrayed inside the device; roughly the size of dominoes, they look like black backsplash tiles, only uneven. In the case of lesions, the procedural principles are the same as for uterine fibroids—MR guides and monitors the focused ultrasound to heat and kill diseased tissue—with crucial differences to account for the challenges of the brain.

Bone gets hotter, and faster, than does soft tissue—not a good thing for delicate grey and white matter. In addition, individual skulls vary in shape and thickness, so while the helmet may be one-size-fits-all, treatment must be bespoke. Solving each of these problems was a technical masterwork by Hynynen and his team.

Spanning a years-long looping process of numerical modelling, computer simulation, prototype development and preclinical testing, they adjusted the frequency so that the device would generate a lower-frequency beam than that used for body tissue, and designed the multi-element transducer as a hemisphere, to distribute heating more widely. The half-circle shape and large number of transducer elements permit the therapy to be customized to individuals. This is done by using computed tomography imaging during treatment planning to take scans of the patient’s head. These scans provide data in 3-D on skull shape and density, which are then linked with transducer information and MR data on the structure of the targeted tissue. Altogether,



TOP TO BOTTOM: DRs. YUExI HUANG, GREG CZARNOtA AND KULLERVO HYNENEN; DR. ISABELLE AUBERT

this provides a patient-specific “picture” that enables the neurosurgeon to calculate the beam path and make any corrections needed to ensure the beam does not scatter as it passes through the skull, but instead converges to focus with millimetre exactitude on the target. During the therapy MR maps the temperature changes, telling the surgeon when ablation has been achieved.

InSightec commercialized this device, too; research on it is advancing rapidly and has moved into patient trials. In 2010, Hynynen and a clinical team published the first evidence showing that ultrasound can be focused in the human brain noninvasively without cracking open the skull. Since then, groups in Boston and Switzerland have launched phase I clinical trials in brain conditions. At SRI, Hynynen will work with colleagues at the Odette Cancer Centre and other institutions to test the therapy in patients who have brain tumours or movement disorders.

Also exciting swelling interest is research into the nonthermal applications of the technology: manipulating it to transport drugs or other agents into the brain. About five years ago, Hynynen approached Dr. Isabelle Aubert, an SRI neuroscientist and assistant professor at U of T studying Alzheimer’s disease, to talk about it.

“When I first heard about it, I was, ‘Wow. Really? That will work?’” says Aubert, recalling the meeting that spawned their collaboration. She was instantly intrigued.

As Aubert explains, the use of antibodies to clear the brain plaques that feature in Alzheimer’s disease (these are large deposits of a protein called amyloid beta) is being studied in clinical trials. Therapy, however, is not being targetted to the brain, owing to the blood-brain barrier. Instead, researchers are injecting anti-amyloid antibodies into the bloodstream, hoping that they will pull the plaques from the brain and draw them to the blood, essentially neutralizing them.

“But Kullervo and I were thinking, the pathology is in the brain, so why not get in there? The clearance of the plaques by the current mechanism, just by the periphery, is really slow, and our thinking is that if you have Alzheimer’s disease, you don’t want to wait 12, 18 months before you see an effect,” she says.

Get in there is what they did, as published in the journal *PLoS One* in 2010. Aubert, Hynynen and graduate student Jessica Jordão used MR-guided focused ultrasound to deliver an anti-amyloid agent into the brains of mice with Alzheimer’s disease. Just days



TOP TO BOTTOM: DR. KULLERVO HYNYNEN; DR. RAJIV CHOPRA

later they found that plaque deposits had shrunk, effectively altering the disease's progression. "What was amazing is that within four days it reduced the plaque deposits; usually it takes at least a month to clear the plaques if you put it into the periphery," says Aubert.

How did they deliver the antibodies into the brain? Via the Ali Baba-esque power of microbubbles, harmless particles of gas that when injected into the bloodstream and paired with MR-guided focused ultrasound have an "open sesame" effect of disrupting the blood-brain barrier just long enough to let biological

agents slip in, before the barrier closes to resume its guard role. Guided by MR, ultrasound then conveys the drugs precisely to the target—the plaques, tumour or other tissue of interest.

Aubert and Hynynen are doing further study, including testing the effect of leaving the antibodies in longer and exploring gene therapy. The aim, says Aubert, is not only to clear the plaques, but also to repair damage and restore function. "The ultimate goal is to make people live better, longer," she says.

It's an aim that applies to all diseases for which therapeutic focused ultrasound shows promise, including stroke, which kills 14,000 Canadians a year and hobbles tens of thousands more. Hynynen and other researchers at SRI, including Dr. Sandra Black, director of the Brain Sciences Research Program, and Dr. David Goertz, an imaging scientist, are experimenting with MR-guided focused ultrasound to deliver and enhance the effect of clot-busting agents in the brain.

"Stroke will be a big application. I've got no doubt about it," says Hynynen. The main problem (apart from getting into the brain) is timing, he says. "With stroke, you have a window of opportunity of two to three hours where you have to get the treatment—everything has to be really quick—whereas with a brain tumour, you can plan it for days beforehand."

With so many applications for the technology, it's not surprising that some are closer than others to clinical translation (assuming regulatory approval, which is a whole other story). The technology for dementia and stroke has a way to go before it hits a hospital near you. For the disease that kills one in four Canadians, however, the timeline is shorter.

"Particularly in cancer, the technology is at the stage where it has gone out of the lab and into the hands of the medical manufacturer, and it's being deployed around the world in various

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sites. That’s why it stands to have impact quickly,” says Dr. Greg Czarnota, director of the Odette Cancer Research Program at SRI. He and Hynynen are building a program that brings together scientists and clinicians to evaluate HIFU applications that Hynynen has developed. The role suits Czarnota, who alone at SRI is both an imaging scientist and a radiation oncologist. “You can call me the marriage broker,” he says.

He’s assembled about 10 clinicians and their staff into teams to evaluate the technology for brain tumours, bone metastases, recurrent breast cancer, liver metastases and rectal cancer. These trials will happen in the new focused ultrasound surgery facility. Many will be first-in-human trials, evaluating feasibility and safety. Czarnota, who is also an assistant professor at U of T, notes that for some cancers HIFU could become the brass ring of care.

“Think of it—if you can ablate a tumour completely, why have someone go for a month of radiation or chemotherapy that’s not necessarily going to work for a big tumour?” he asks.

He points to prostate cancer, specifically to a therapeutic device for this cancer that Chopra and Dr. Mike Bronskill, another SRI imaging scientist, invented. “It has the power to replace surgery and to replace radiation,” says Czarnota.

Chopra and Bronskill spent 10 years inventing the device. It fits inside the urethra and uses MR-guided HIFU to ablate tumours in the prostate gland in a 30-minute procedure. It aims to be as effective as surgery, with none of surgery’s harmful effects, like urinary dysfunction or impotence. The device has earned its stripes in preclinical studies, and was recently evaluated in a first-in-man study at Sunnybrook led clinically by Dr. Laurence Klotz, chief of urology. Chopra is encouraged by the results. “It confirmed that the technology worked as expected in humans, and that it could be an efficient, precise treatment for localized prostate cancer,” he says.

The next major step will be a phase I clinical trial. In parallel, the technology was commercialized in 2008 and spun-off into a company, Profound Medical Inc., which is developing a clinical system for transurethral ultrasound therapy for widespread use.

Time is especially relative in the world of science where delayed gratification is the norm, but each researcher interviewed for this story agreed that MR-guided focused ultrasound will shift the paradigm for patient care. For his part, Hynynen is not resting on his laurels. There is much more to do, he says, with help from a global research community. “The field is in expansion phase, and having more and more systems around the world, and more and more people working on it, the pace is accelerating. It has taken 20 years to get to this point, but the next, similar advances will be made in a much, much shorter time,” he says.

Standing on a path littered with progress, then, how far, really, is therapeutic focused ultrasound from changing medicine? Hynynen counsels patience: “It will take time.” With that qualification, however, he says he is confident in the technology’s capacity “to better life on earth,” as Virgil might have put it. “It will happen—50 years from now, there is no doubt that this will be the way to treat patients. Is it going to happen in the next five years? I don’t know. But it will happen—there is nothing else that can do this noninvasive surgery.”

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Dr. Hynynen holds the Canada Research Chair in Imaging Systems and Image-Guided Therapy.