An incubator of medical innovation

Zapping tumours with focused ultrasound and putting new cancer drugs to the test: just two of Sunnybrook's life-saving research projects

Health care is being reinvented at Sunnybrook Research Institute's $160-million Centre for Research in Image-Guided Therapeutics (CeRIGT).

"CeRIGT brings together scientists, clinicians and industry to make discoveries and get them to patients. This work will replace generalized therapy with targeted treatment based on a person's genetic makeup and medical history. We will be able to tell within weeks, not months, if a therapy is working. To do this, we're developing gene-screening technology and inventing imaging tools to visualize the 'invisible,' guide therapy delivery and monitor outcomes," says Dr. Michael Julius, vice-president, research, Sunnybrook.

Targeting disease at the molecular level

A traditional microscope helps scientists see things that are too small to see with the naked eye. But scientists peering through those lenses are imperfect observers, because the human brain interprets what is seen and attention drifts over time.

To address these drawbacks, Dr. David Andrews, director of biological sciences at Sunnybrook Research Institute, collaborated with industry to develop a high-content screening microscope called the FLIM Opera. It takes more than 300 measurements per cell and processes more than 100,000 images a day without supervision. Sunnybrook is the only academic site in North America to have the $2-million device.

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'FLIM' stands for fluorescence lifetime imaging microscopy. It measures tiny interactions where proteins bind together on cell membranes by analyzing changes in fluorescent light.

Dr. Andrews' work focuses on a pair of specific proteins which work like master control programs to determine whether cells grow out of control, as with cancer, or die prematurely, in cases such as dementia.

For cancer research, Dr. Andrews' team is using the FLIM Opera to work with live cells to identify possible molecules to target, and to test the efficacy of experimental chemotherapy drugs. "It allows us to identify therapeutic targets that were previously inaccessible, at high speed, and to test whether a drug is working. Drug companies can use our findings to develop new drug candidates. This was more difficult in the past, because you couldn't get the numbers," says Dr. Andrews.

"We examined a promising new cancer drug and we showed that for the most part it does what it was designed to do. However, in the process, we identified two new binding sites between two specific proteins that may represent new drug targets, and that had not been identified previously," says Dr. Andrews. Beyond cancer applications, "We are also working on ways to test if inhibiting specific proteins may be a useful treatment for retinal degenerative diseases, and validating a pharmaceutical target for stroke," says Dr. Andrews.

New ways to heal the brain

The blood-brain barrier (BBB) is the tightly connected network of cells in the blood vessels of the brain that prevent foreign molecules from entering, making it next to impossible to deliver drug treatments.

Dr. Kullervo Hynynen has invented a way to sneak past the BBB, using magnetic resonance image (MRI)-guided focused ultrasound. "Our work is going to revolutionize how brain disease is treated. Right now about 98 per cent of potential medications cannot enter. We have a tool that can allow these treatments into the brain," says Dr. Hynynen, director of physical sciences at Sunnybrook Research Institute and project lead for CeRIGT.

Microbubbles and therapeutic agents are injected into the blood stream. The expansion and contraction of the bubbles in the focused ultrasound beam, operating at a frequency of one-half million times per second, pry apart the tightly bound cellular junctions at a specific site, temporarily opening a tiny space for the molecules to enter. Remarkably, the space heals within a few hours.

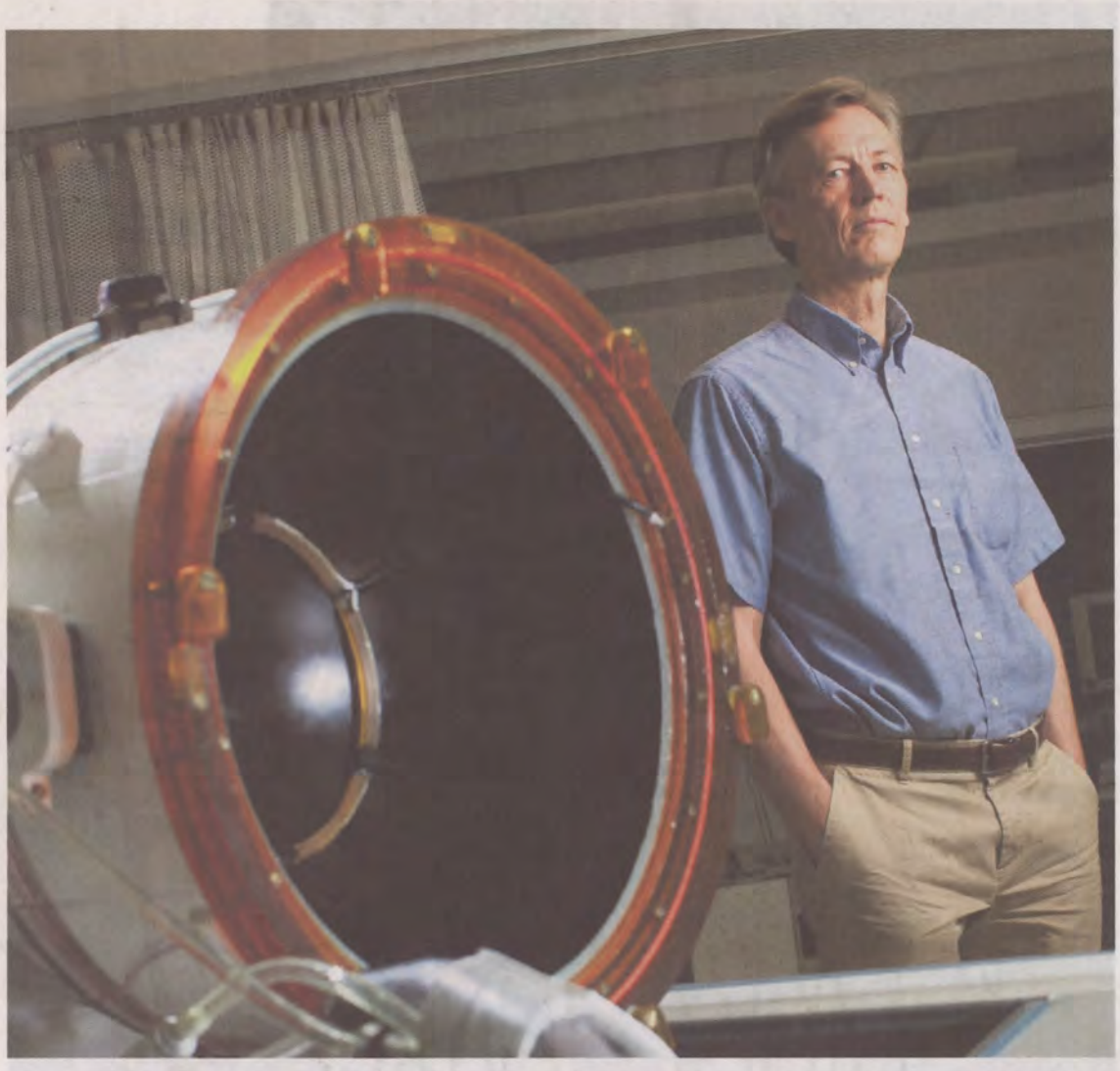
Dr. Hynynen's team has successfully used this method to deliver targeted chemotherapy directly to brain tumours in preclinical models. For human applications, Dr. Hynynyen invented a special transducer helmet, which allows precise placement of the ultrasound beam through the human skull.

Focused ultrasound is already in use in a clinical trial at Sunnybrook for patients with essential tremor, a movement disorder caused by a brain-signalling malfunction. A world's-first clinical trial has also just opened for brain cancer patients, where MRI-guided focused ultrasound will be used to ablate or 'cook' brain tumours without invasive brain surgery.

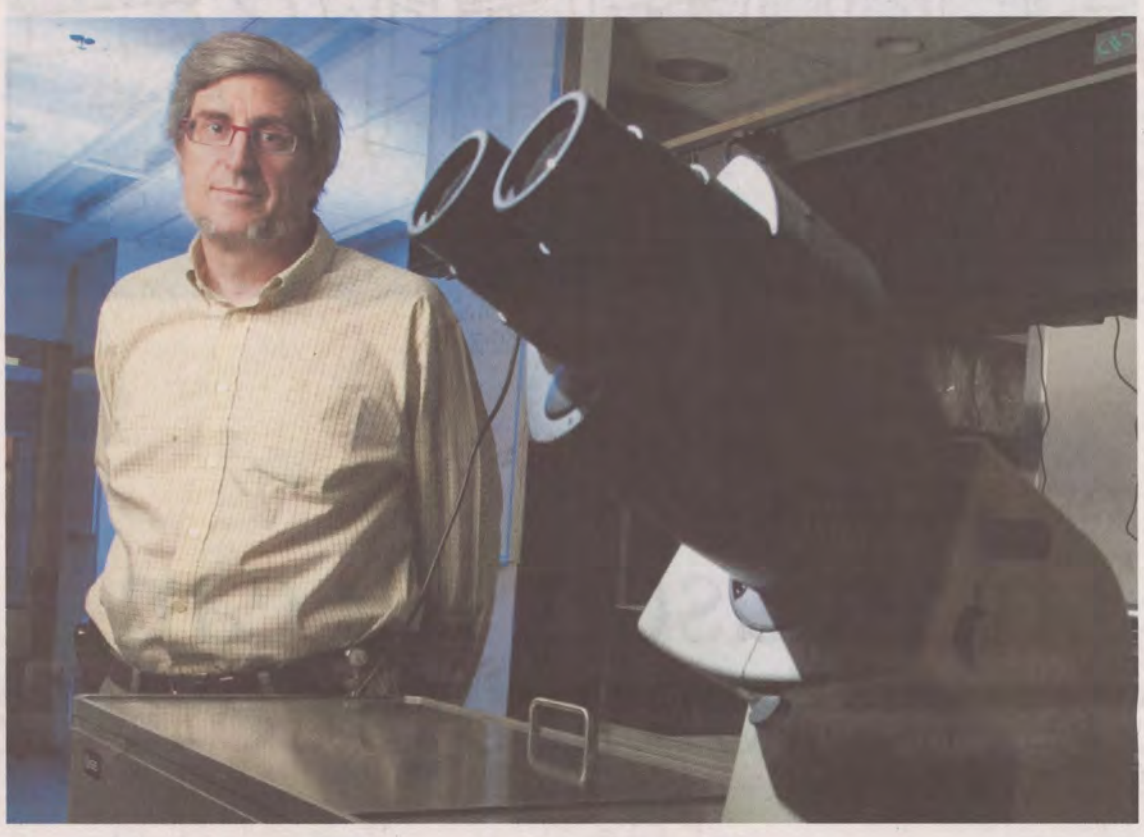
Opening up the BBB, however, offers an incredible opportunity to target therapies directly to specific areas of the brain, like chemotherapy for tumours or therapeutics to treat areas of brain damage in dementia patients: "The nice thing about this technology is that it's a universal tool to get any kind of molecule, natural killer cells or stem cells into the brain," says Dr. Hynynen.

Dr. Isabelle Aubert, senior scientist at Sunnybrook Research Institute, studies ways to halt the decline and promote regeneration of brain cells in cases of Alzheimer's disease. In collaboration with Dr. Hynynen's group, her team has successfully used focused ultrasound to reduce amyloid beta plaques associated with Alzheimer's disease in mice.

"By using focused ultrasound, the delivery of therapeutics to the brain is localized and noninvasive. The hippocampus, which is responsible for memory, is affected in the disease, so that's an area we could target," says Dr. Aubert.



Dr. Kullervo Hynynen has pioneered the use of MRI-guided high-intensity focused ultrasound to treat brain conditions such as tremors and tumours that were previously tough to target. TIM FRASER



Dr. David Andrews with the FLIM Opera microscope, a powerful tool for identifying better drug treatments. TIM FRASER

Connecting the dots between Alzheimer's and stroke

Someone in Canada develops dementia every five minutes, a rate that is projected to more than double over the next thirty years.

Sunnybrook's internationally renowned stroke expert, Dr. Sandra Black, is investigating a promising new area of brain research — the relationship between vascular disease, cognitive function and Alzheimer's disease.

"Canadians often punch above their weight when it comes to neuroscience research, especially for dementia and stroke. The brain imaging facilities at CeRIGT have provided us with important physics and analytical expertise, allowing us to take up new research opportunities quickly and use them in clinical settings," says Dr. Black, director of the Brain Sciences Research Program at Sunnybrook Research Institute.

At CeRIGT, researchers can spot irregularities in the brain's blood vessels, from silent strokes that show up as little holes to white spots or patches that indicate other areas of damage, long before dementia sets in. White spots or patches (called white matter disease) are present in 95 per cent of those aged over 65 years.

People who have had silent strokes are much more likely to become cognitively impaired and to have a future stroke. Silent strokes are present in about 28 per cent of people over the age of 65, making them at least 10 times as common as clinically overt stroke.

One of the hallmarks of Alzheimer's disease, the most common cause of dementia, is a buildup of plaque made of amyloid-beta peptides. In the inherited form of the disease, a genetic mutation causes overproduction of amyloid, and in later-onset disease, the brain's inability to clear away amyloid is the main culprit in causing brain damage.

Small blood vessels in the brain (small arteries and veins) are susceptible to scarring as people age, causing resistance, back flow and leakage of blood fluid and proteins into the brain. This back-up can prevent amyloid removal from the brain along these vessels. Such amyloid build-up can make vessels burst and bleed, or cause a stroke through blockage of the arteries. It may also cause more amyloid plaques to deposit. "Believe it or not, Alzheimer's disease is a key cause of hemorrhagic stroke, which is becoming more common in our aging society as we get better at treating hypertension, the more traditional cause. Amyloid is emerging as a major cause of brain hemorrhage in older people," says Dr. Black.

Dr. Black's team is conducting multiple intervention studies among stroke and dementia patients. "Our role in the Heart and Stroke Foundation Centre for Stroke Recovery is to provide the leadership in brain imaging and analysis on physical and cognitive aspects of recovery, including gait, balance and exercise, as well as in preclinical models. We are also investigating new ways to use infusion therapies with antibodies," she says.