

THINK CLINICALLY, ACT COMMERCIALY

Two SRI physicists develop and market a novel treatment for prostate cancer

In spring 2007, Raphael Ronen was looking into the commercial potential of several medical science technologies that had emerged from research at the University of Toronto (U of T). A number of the projects looked promising, but one—magnetic resonance image (MRI)-guided ultrasound therapy for prostate cancer—left him particularly excited and puzzled. “It seemed too good to be true,” recalled Ronen in an airy conference room at the MaRS Centre, the glass, steel and brick hub of Toronto’s medical science-meets-biotech Discovery District. “I felt there had to be something wrong with it, because it was such a good technology. I was really blown away.” Ronen, a life sciences commercialization manager at The Innovation Group, which handles technology transfer for U of T and some of its affiliated research institutes, including Sunnybrook Research Institute (SRI), examined the new concept closely. Looking for flaws, assessing its patents and patent space (competing patents for similar technology, of which there were few), he concluded the technology was sound.



The only explanation he could see for why such a well-developed system wasn't already commercialized was that its inventors—SRI imaging physicists Drs. Michael Bronskill and Rajiv Chopra—hadn't been exposed to the investment community. "Where other people might have been promoting their technology, looking for partnerships," Ronen explained, "Mike and Rajiv were just working away below the surface. They're very, very low key." That was good news for Ronen. "It's probably the biggest undiscovered gem I've found," he says.

Magnetic resonance imaging-guided transurethral ultrasound may prove even better news for men with localized prostate cancer. The technology, which Bronskill and Chopra developed over 12 years at SRI, enables precise, MRI-guided focusing of heat-generating ultrasound to coagulate targeted cells while leaving surrounding healthy tissue intact. Bronskill and Chopra are working to translate the technology for clinical use via Profound Medical Inc.—a startup company formed in 2008—to offer patients a therapy with fewer side effects than those associated with existing clinical options, particularly prostatectomy (surgical removal of the prostate), and external-beam radiation therapy. Those treatments often result in side effects that significantly disrupt life after treatment for many men.

Statistics vary depending on the nature and degree of treatment, but most men who undergo prostatectomy will have erectile dysfunction, and about one in three will suffer urinary or bowel incontinence, diarrhea or rectal bleeding. Drug therapy, physiotherapy and other rehabilitation techniques can relieve these side effects, but with limited success. A large *Journal of the National Cancer Institute* study published in 2004 found that 79% of men treated with prostatectomy and 63% given radiation had some form of impotence five years after treatment; 15% of the prostatectomy patients were incontinent, as were 4% who received radiation.

Adding urgency to this quality-of-life issue is a surge in the number of men diagnosed with prostate cancer, owing in part to more screening and better detection techniques. Diagnoses, based primarily on biopsies, jumped fourfold from 1983 to 1992, according to a 1995 study in *The Journal of the American Medical Association* that looked at rates before and after widespread implementation of the prostate-specific antigen test (a standard screening tool, as is digital rectal exam). The study found a dramatic rise in diagnoses among younger men, especially those in their 50s. Prostate cancer is now the most common cancer in Canadian men, an estimated 24,700 of whom will be diagnosed with it in 2008.

The growing cohort diagnosed with the disease at a relatively young age has complicated physicians' treatment decisions. "When it was a disease of someone 75 or 80 years old—not that it was acceptable—it was less of a dilemma to deal with," says Chopra, in his office at SRI. "Whereas with someone in their 50s or 60s, the prospect of wearing absorbent pads or having bowel problems for the rest of their life—that can't be ignored." Consequently, patients and clinicians are facing a predicament: most men diagnosed with prostate cancer will not die from it, because usually it's slow-growing and remains localized in the

gland; yet, roughly 90% choose some form of aggressive treatment, risking distressing side effects. There is swelling clinical interest in "watchful waiting," which foregoes invasive treatment while the disease remains low-risk, but this shift hasn't greatly affected the number of men who choose more aggressive treatment.

Chopra, a young scientist with a brisk but gentle manner, has studied ultrasound and its potential for cancer therapy since he was a graduate student in Bronskill's lab in the mid-1990s. He acknowledges the rationale for treating prostate cancer aggressively, given the dire consequences of metastases, but he says there is growing interest in treating only parts of the gland—an approach that the precision of the transurethral ultrasound applicator may bring to fruition. The applicator is inserted into the urethra through the penis and into the prostate gland. Its end contains a column of transducers, powered electronically to emit high-intensity ultrasound. "By adjusting the number and size of transducers, rotating the device, and modulating the power and frequency of each transducer," says Chopra, "we control for length and depth to create a 3-D pattern of energy and heating. That's where the precision comes in."

The treatment is performed inside an MR imager, a technical advance that Chopra says took years of experimentation, given that ultrasound and MRI are disparate technologies that typically interfere with each other. During treatment, magnetic resonance imaging provides noninvasive 3-D temperature images of the prostate every five seconds. A separate computer system automatically analyzes and processes those temperature images, and incorporates them into algorithms that in turn control and adjust the device, under supervision by the treatment team. The system creates what Chopra calls a feedback loop—sophisticated, elegant and precise. Additionally, MRI profiles the treated gland right after treatment using contrast agents to detail coagulated tissues and halted blood flow, providing immediate treatment validation.

Compared with transrectal ultrasound, a similar first-generation technology approved by Health Canada and offered at some clinics in Toronto, this new treatment has several advantages. It's faster (about 30 minutes versus three hours for transrectal ultrasound) and provides real-time visualization of the heating generated in the prostate gland and surrounding tissue. The scientists foresee the treatment requiring only a spinal block, which would make it a day procedure. Also, the older technology is delivered somewhat blindly. Using pretreatment ultrasound images, the transrectal technology coagulates tissue about the size of a grain of rice, waits for several seconds, moves, and then targets another area of similar size, hundreds of times. The device is unable to adjust for swelling and gland movement during the procedure, so treatment tends to cover a larger area, running greater risk of damage to healthy tissue. Chopra and Bronskill have



Dr. Rajiv Chopra, Raphael Ronen and Dr. Michael Bronskill

Prostate cancer is now the most common cancer in Canadian men, an estimated 24,700 of whom will be diagnosed with it in 2008.


shown in preclinical models that their technology accurately targets tissue to within one millimetre, which should mean fewer side effects. Moreover, it costs less than transrectal ultrasound.

Picking up a prototype applicator from a bench in his lab at SRI, Bronskill moves toward an adjustable MRI-compatible brass and plastic mount. "We can't at this point claim side effects are lower because we have no clinical data yet," he says. "One of our goals with Profound during the next year is to get this therapy to a clinical trial. Envisage—whoops!" Water streams out the probe's end onto the floor near an empty seat. "Aaron will want to know why there's a puddle by his chair," says Bronskill, as members of his lab look on. "It'll be dry by the time he shows up," he chuckles.

Bronskill is affable, especially with his lab group, as at ease discussing the breezy hotspots that fuel his windsurfing passion as the technology of ultrasound, and that quality serves him well as an academic physicist. Matthew Asselin, a research assistant responsible for software and hardware integration who has worked for Bronskill for two years, says he is easy to approach and doesn't run his lab as a hierarchy. "He affords us a good amount of experimentation, probably more than we'd get in the private sector," says Asselin, who adds that at first he found the hands-off approach too loose, but now believes it produces results, especially when shaped by Bronskill's guidance at weekly lab meetings.

Bronskill studied math and physics before doing a PhD in the department of medical biophysics at U of T in the early 1970s. Now a professor in that department with cross-appointments in medical imaging and physics, he wasn't always keen on commercialization. "Fifteen years ago, I probably couldn't have seen myself involved in a venture like this," says Bronskill of Profound. "What I've learned in the interim—and you might argue I've been a slow learner," he laughs, "is that there's really only one road for taking a new medical device or technology through to clinical application, and that is through commercialization."

The target when he and Chopra began their project 12 years ago, with basic-science funding from the Terry Fox Foundation, was not the medical device market or prostate cancer specifically. That early-stage high-risk funding enabled them to explore the feasibility of this concept as a general therapeutic tool. Then, as the technology matured, it became clear that commercialization was the only way to get their innovation to patients. A \$500,000 commercialization grant from the Ontario Institute for Cancer Research (OICR) that triggered immediate venture capital interest in the formation of Profound drove the point home. "Basic scientists tend to regard commercialization as a bad word," says Bronskill, "but the harsh realities are that no hospital will take the financial risks of implementing a clinical trial with a new technology, whereas a startup company will."

Back at MaRS, Ronen, who was instrumental in securing the OICR grant, says that Bronskill and Chopra "get" commercialization. They had already pushed the physics of their technology beyond early prototypes when Ronen first saw their work, incorporating miniaturization and human factors to make the whole therapeutic system function effectively. "That's rare in an academic setting," he says. "Many scientists lose interest before that point, because it's not about publishing key papers." Bronskill and Chopra are still focused on publishing, but see it and commercialization as two halves of the same whole. "Research is about testing new ideas and hypotheses, demonstrating if they work," says Chopra. "But we can't get to patients without commercialization, so I'm happy about Profound. It's enabling us to see the fruits of our research." 

The Canadian Institutes of Health Research, Ontario Institute for Cancer Research, Ontario Research Fund-Research Excellence, Ontario Research and Development Challenge Fund and the Terry Fox Foundation through the National Cancer Institute of Canada funded this work. The Canada Foundation for Innovation and Ontario Innovation Trust provided infrastructure support.