Inventing a medical device is a rare accomplishment. Rarer still is getting that invention into the global medical marketplace. Here's how two Sunnybrook Research Institute startups did just that, and became in-demand multinational acquisitions

By Jim Oldfield

Catch a Rising Star

On July 6, 2010, Cameron Piron, president of Sentinelle Medical, a Toronto-based developer of magnetic resonance imaging (MRI) equipment for the early detection of breast cancer, sold his company to U.S.-based women's health corporation Hologic for $85 million.

The deal included an "earn out"—an additional sum equal to a multiple of Sentinelle's revenue growth over the next two years—that will make it one of the biggest in the history of Canada's medical device industry.

Though success was rapid—Piron founded Sentinelle just five years ago, based on research he did at Sunnybrook Research Institute (SRI) in the imaging lab of senior scientist Dr. Donald Plewes—it was not easy. Medical device startups in Canada must meet the rigorous demands of skilled and busy clinicians; navigate tight safety regulations and testing requirements; and deal with scarce venture capital and banks that don't lend freely to startups.

Overcoming these and other challenges required a timely convergence of government funding for innovative research at SRI, economic opportunity and sound decision-making. Perhaps most critical to Sentinelle's success, however, was a passion to make breast cancer screening for women better. "I can't say enough about how Cameron and the others associated with Sunnybrook worked their hearts out," says Plewes, who is also a professor of medical biophysics at the University of Toronto and a silent partner in Sentinelle. "This was more than an opportunity—it was a clarion call to participate in the breast cancer agenda, from a commercial perspective, and it was genuine."

That clarion call was based on a pressing clinical need.

In the late 1990s, Plewes and colleagues at SRI had begun a clinical trial using MRI to screen women at high risk for breast cancer. As BRCA1 and BRCA2 gene carriers, these women had a lifetime risk of breast cancer approaching 85%, versus 11% for most women. Moreover, their cancers were aggressive and often fatal. The best that clinicians could offer these women were X-ray mammograms, which did not catch small tumours and produced false positives, leading to high rates of preventive mastectomy (breast removal).

Magnetic resonance imaging potentially offered increased detection and the confidence to avoid unnecessary mastectomies, but it had been developed to scan patients lying on their backs, which made breast imaging difficult. Plewes gave Piron, then a graduate student in his lab with a background in systems design engineering, the job of creating a better MRI system for breast imaging. Through several iterations, they honed a dramatically new prototype: patients lay face down on a detachable table, breasts neatly cupped in customized magnetic coils. Radiologists could gather high-resolution images with MRI, then quickly move patients to ultrasound, co-register the data in the system's software and perform a biopsy if necessary. The process reduced patient time in the magnet by almost two-thirds, making MRI cost-competitive with mammography while providing more accurate results.

CAMERON PIRON

By 2003, radiologists and oncologists were so impressed with the prototype that they began asking Plewes and Piron how they could get one. Shortly thereafter, results from the Sunnybrook trial showed MRI could detect breast tumours with more than twice the sensitivity of other screening methods. The challenge then became how to commercialize and distribute the technology.

Though Piron had been exposed to business through his father, who was an entrepreneur, he had no training for starting a company. Plewes says that at that point, passion was again vital. "I think Cameron realized we were ahead of the curve—the clinical need—that we could see was going to spike. The passion to meet that need added enormously to the tenacity he and the others showed, in those days, to make it happen."

The standard model for starting a company based on research innovation is to solicit venture capitalists, who invest expecting the company will generate short-term revenue with a single product that enables them to "exit"—get their money back quickly, with a profit.

Instead, Piron and his colleagues, with zero fundraising experience, raised the dollars privately by growing a network of donors among family, friends and radiologists excited about the technology. "There is a lot of private money out there," says Piron. "People are uncertain where to put it, and they feel good about investing in a new technology for better detection of cancer."

This approach proved crucial, says Piron, because it enabled the company to think long-term and invest in developing a rich pipeline of products. By the time Sentinelle was ready for the acquisition by Hologic—largely because they needed a sales force of hundreds to meet demand, which Hologic could offer—their products were best in class.

Dr. Ken Brooks is the vice-president of new technology development at Hologic. He has evaluated about 200 potential acquisitions during his four years with the company, and was instrumental in the purchase of Sentinelle.

"Two things impressed me most about Sentinelle," says Brooks. "The first was their ability to meet a clinical need for breast MRI that was unmet by the large vendors. This involved patient workflow, coil design, microdynamics, Monte Carlo modeling, etcetera—they just knocked that out of the park. Second, their software made the whole system integrated, which was very impressive."

Brooks expects Hologic will eventually adapt Sentinelle's software for most of their product areas, which cover mammography, women's bone health, preterm birth care and gynecology. Near-term, Brooks and Piron say the hottest synergy will emerge in integrating Hologic's interventional biopsy technology with Sentinelle's software, for better breast cancer screening. "No company has owned development in those areas until now, so we're well-positioned going forward," says Piron.

Regarding hardware, Brooks says Hologic could use Sentinelle's coil technology for imaging the female abdomen, head and neck, and they have long-term plans to apply that hardware to men's health, for earlier detection of and treatment guidance in prostate cancer.

Piron credits his time in the lab of Plewes for shaping the mentality that enabled Sentinelle to produce a pragmatic line of products. "'Apply what you think in practice or it's no use.' Don instilled that in everyone who worked with him," says Piron. "It drove the technology development cycle in an incredibly rewarding way." Clinicians now use Sentinelle's system in over 200 North American sites, and the technology will soon be available around the world.

Concurrent with an applied focus and passion, a Canadian paradox may have shaped Sentinelle's global competitiveness. The obstacles to starting a medical device company in Canada can spur a sink-or-swim approach that results in high-performing and cost-efficient products—unlike in the U.S., where easier access to capital can undermine efficient design and production. As the device market becomes more international, Canada is honing its production of increasingly saleable products. "It's an interesting subtlety," says Piron, "but a lot of Canadian companies are able to expand globally, because they have the right product to offer."

No Borders

On September 9, 2009, Anil Amlani walked into the Bristol Lounge at the Four Seasons Hotel in Boston for a meeting he hoped would alter the future of his company.

Amlani, president and CEO of Toronto company VisualSonics, had secured a meeting with Kevin Goodwin, president and CEO of SonoSite, a Seattle-based firm with a global presence in hand-held clinical ultrasound.

Amlani was excited because he knew SonoSite was the ideal partner to adapt VisualSonics' preclinical high-frequency ultrasound imaging system—invented by physicists at Sunnybrook Research Institute (SRI)—for use in patients. Goodwin, however, had granted Amlani only 25 minutes between presentations at the investment and health care conference the two were attending to pitch VisualSonics as a potential acquisition.

Over coffee, Amlani outlined the clinical possibilities of the Vevo, VisualSonics' real-time device, which can image tissue microscopically up to three centimetres inside the body. Those potential applications included precise guidance for inserting intravenous lines in infants, a painful procedure that can require multiple needle jabs; early detection of rejection in skin grafts, enabling more effective alterations in treatments; better detection and characterization of skin cancer and diseases of the eye; and noninvasive imaging of blood flow in the hearts of newborns.

Goodwin, an ultrasound aficionado with 22 years in the business, was impressed. "After 15 minutes, he got it," recalls Amlani. Nine months later, SonoSite finalized a $71-million deal to acquire VisualSonics, sealing one of the largest sales in the history of Ontario's medical imaging industry and putting micro-ultrasound on a fast track to transform radiology and improve care.

Behind the headlines of this success story is a lengthy and frequently unappreciated process of scientific discovery and commercialization known as the "research pipeline." The metaphor fits VisualSonics, whose origins can be traced back over 20 years to the lab of Dr. Stuart Foster, a senior scientist at SRI who holds the Canada Research Chair in Ultrasound Imaging.

In the late 1980s, with funding from the Terry Fox Foundation and other organizations with visionary mandates to support early-stage research, Foster, who is also a professor of medical biophysics at the University of Toronto, began tinkering with high-frequency ultrasound transducers. Just out of curiosity, Foster says, he and his lab were able to fashion the devices to perform reliably in imaging experiments; they discovered subsequently that the transducers could usefully image human anatomy, in particular the eye and skin. In the early 1990s, in collaboration with Toronto physician Dr. Chuck Pavlin, Foster and SRI licensed a system based on those curiosity-driven experiments to Carl Zeiss Inc., which made the technology available globally for diagnosis of eye conditions including cancer, glaucoma and corneal disease.

By the mid-1990s, it was clear the human genome project was progressing rapidly and that once the genome was mapped, questions of what genes do would proliferate. This piqued Foster's interest and altered his focus. There were no good ways of showing the results of adding or knocking out genes in experiments, a process known as phenotyping, but Foster thought imaging might help solve that problem. Experimenting with mice that lacked a gene called Wnt-1, Foster's lab noninvasively captured clear images showing that the brains of the mice had developed without a tiny part. "That was a definitive moment, in terms of understanding that high-frequency ultrasound allowed us to see a lot of interesting things that would have been impossible with any other technology," says Foster.

Because the equipment they used for the gene knockout experiment was mostly cobbled together, Foster and his lab regrouped and designed a completely new machine dedicated to mouse imaging. They considered the functions researchers might need, and what new technologies they should therefore incorporate. They produced a prototype, and with essential investment from Canadian venture capital firms VenGrowth Asset Management and Hargan Ventures, Foster formed VisualSonics to commercialize and distribute the technology.

Scientists in research organizations quickly expressed interest in the machine for studies of embryonic development, cardiovascular disease and cancer. Where early versions of the technology could image six frames per second, by 2004 the system was operating at 100 to 200 frames per second—viable for cardiology research. Over the next two years, VisualSonics grew to employ over 100 people and became the industry leader in high-frequency, real-time microultrasound, manufacturing more than 600 systems for research organizations around the world.

Spurred by new revenue, Foster and VisualSonics steered the technology through several more iterations.

The resulting linear array system, which VisualSonics released in December 2008, was a defining moment for the company and the history of ultrasound. Until that point, microultrasound systems were built around single-element transducers. The new system used 256 transducers in a linear array; by phasing the signals from each transducer, it produced a greater depth of field and enabled focusing at multiple points, which produced a better image. Because the transducers were fixed, there was no mechanical movement, which meant the system could achieve frame rates above 500 per second. Moreover, and critically, elimination of liquid from the machine's design made it safe for clinical use.

According to Amlani, four factors fomented the conditions for VisualSonics' scientific and commercial success: basic-science innovation at SRI; modest yet critical Canadian venture capital investment; funding from government and tax-incentive programs; and the availability of highly qualified engineers and application specialists from the university cluster in southern Ontario. "Those four things were essential and attractive, from a business perspective, and that's why [VisualSonics] is a great story for Canada," says Amlani.

For critics who note that SonoSite represents yet another U.S. company buying out a Canadian business, Amlani has a quick response. "There is no such thing as borders for financials and financing these days. Canadians sell to Americans; Americans sell to Canadians. The question becomes, 'What is the best way to take this technology to the human market, to lessen suffering?'"

With the clinical potential of VisualSonics' technology manifest, the answer to that question came down either to raising capital—which Foster estimates would have been up to $50 million—privately or through an initial public offering on the stock market, or to finding a corporate partner with clinical capacity.

The latter option was more attractive for three reasons. First, the economic downturn meant securing capital had become especially difficult. Second, despite its profitability, VisualSonics was under pressure to sell from the venture capital firms that had supported it. Third, SonoSite could provide the ideal mix of technical know-how and financial and regulatory resources to push the technology into the clinic.

With profits from multiple products, SonoSite could fund VisualSonics' continued expansion into the preclinical medical device market, forecasted to grow from 8% to 15% annually over several years. They also had experience with regulatory approvals from the U.S. Food and Drug Administration (FDA). More importantly, they had a proven ability to compress large-footprint ultrasound systems, such as the 350-pound Vevo, for point-of-care clinical medicine.

"It was a perfect marriage," says Amlani.

SonoSite liked the deal because VisualSonics had a healthy, profitable business model, with further potential in the preclinical research market, and what Goodwin calls a "strong group of people who accomplished a lot with limited resources." Goodwin was confident that SonoSite could converge VisualSonics' technology with his company's silicon application-specific integration circuit technology to produce a cost-effective, convenient device weighing less than 15 pounds. "We got very excited about what we thought we could do with that technology, between expanding it in the preclinical world of research and bringing it into clinical medicine," says Goodwin.

In the global clinical market, Goodwin expects revenues for the new technology could approach $1 billion. It's a big opportunity, he says, because it brings physicians something they can't have today, and it fits into the cost-safety paradigm toward which medicine is moving.

SonoSite will put that new technology into their manufacturing and supply chain, then attempt to get FDA approval, which Goodwin anticipates will be quick. "Then I think it's 'Katie bar the door,'" he says. "There are a lot of people very interested in this technology for very good reasons. It has the potential to completely transform one's ability to look from the skin line to three centimetres deep in the body, and as the saying goes in our industry, 'Get the anatomy books out again.'"

Foster, for his part, is now focusing his research on photoacoustics, which also holds huge potential for medicine. The idea is that light can be converted into sound, and as it enters the body in nanosecond-length laser pulses, it creates an ultrasound signal. The result is an imaging hybrid that combines the sensitivity and specificity of optics with the readout of ultrasound.

Foster will maintain a scientific advisory role with SonoSite while pursuing photoacoustics research, and he isn't ruling out another commercial venture. Overall, he says he's "quite positive" about the trajectory of his research and the deal with SonoSite, which he calls educational. "I've learned a lot about business and how ideas get translated into things people can use," he says. "And I've come to appreciate what people do in creating commercial instrumentation. There's a lot more to it than straightforward engineering."

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