Testing Chemotherapy's Effectiveness Early In Treatment

Laurentian University

For cancer patients and their doctors, chemotherapy often poses a high-stakes gamble. Although the treatment can destroy some tumors and dramatically extend patients' lives, that's not the outcome for all. Chemotherapy has little or no effect on some tumors, but it still wreaks havoc on healthy tissues — and in extreme cases, the side effects can be life-threatening.

During early stages of chemotherapy treatment, doctors haven't been able to predict whether a patient's tumor will likely die or survive after treatment. But at Laurentian University in Sudbury, Ontario, a serendipitous discovery may have changed that. The resulting test, licensed to Toronto, Canada-based Rna Diagnostics Inc., analyzes RNA to assess chemotherapy's effectiveness. It would allow doctors to identify patients who aren't benefiting from a specific chemotherapy regimen, and switch those patients to another treatment — instead of continuing on a path that won't lead to improved health.

A "Weird" Result Yields Exciting Developments

“Like a lot of discoveries, people like to think that we planned these things,” says Amadeo Parissenti, Ph.D., a chemistry and biochemistry professor at Laurentian University. That certainly wasn’t the case in 2006, when Parissenti was working on a large clinical trial — one that became pivotal in unexpected ways. Parissenti is a tumor geneticist with a keen interest in the role genes play in patients’ response to chemotherapy. In the clinical study, he and his colleagues assessed whether certain genes might be associated with chemotherapy resistance in breast tumors.

For some subtypes of breast cancer, the survival benefit of chemotherapy may be as little as about 25 percent, and the remaining 75 percent of patients get no survival benefit, says Parissenti. “What's horrible about that is they get all of the toxicities associated with chemotherapy, and there are many.” The 75 percent of patients who do not benefit from the chemotherapy may still get the side effects of hair loss, nausea, heart problems, neuropathy, accelerated blood clots, and increased infections. In some elderly patients, chemotherapy itself can contribute to a higher death rate.

> *The researchers hoped the clinical study could lead to more targeted and safer treatment for a disease that affects millions of people worldwide.*

About 1.7 million women received a breast cancer diagnosis in 2012, according to the World Health Organization — a 20 percent increase compared to 2008 figures.

In the clinical study, administered by the NCIC (National Cancer Institute of Canada) Clinical Trials Group, researchers focused on active genes (humans have tens of thousands of genes, but not all of them are turned on). To identify active tumor genes in the breast cancer patients, they looked for an important indicator: ribosomal RNA.

Parissenti and others have successfully isolated RNA from tumors prior to treatment on many occasions. But this study was a bit different, because the researchers also tested tumor samples that had undergone chemotherapy treatment specifically to see changes in gene activity.

Parissenti remembers the eureka moment that occurred during that study. His postdoc, Baoqing Guo, Ph.D., was analyzing tumor samples from patients in the midst of chemotherapy treatment, but there seemed to be a problem. “He told me, ‘It’s really weird, but I’m not getting good RNA quality from some patients,’” says Parissenti. The RNA for some samples appeared to be degraded. At first, Parissenti thought it might be a technical problem — sometimes tumor samples are processed differently, which leads to variation in RNA quality. “In fact, one thing you learn early in research is often, something that looks really exciting can be explained by mundane factors,” says Parissenti. He finally determined that a technical problem wasn’t the explanation.

Instead, Parissenti suspected that if a patient's tumor RNA was degraded, that tumor was probably dying. If the tumor RNA quality was high, the tumor was probably surviving and resisting the chemotherapy drugs. So he chose several patient tumor samples with high quality RNA — then called Maureen Trudeau, M.D., who was leading the study and had access to patient records. Parissenti then asked her a simple question: "Is there anything special about these patients?" The response: “How did you do that? These are some of our worst performing patients. Some have already died.”

That wasn’t enough to prove he had a valid method for testing chemotherapy effectiveness — additional studies followed, with early funding from Aventis Pharmaceuticals Inc. and a grant from the Cancer Research Fund of the Ontario Institute for Cancer Research. Still, it was an exciting phone call, says Parissenti. “It was our first indication that we were on to something."

A Looming Patent Deadline

In 2007, Laurentian University filed a U.S. provisional patent application for the RNA test — then a year later, it filed an application under the Patent Cooperation Treaty (PCT). “That covers you worldwide, for 18 months, and at the end you have to decide in which country you will apply for a patent,” says Gisele Roberts, MBA, research activities manager for Laurentian University's Intellectual Property and Partnerships. "If the deadline lapses, you lose your patent application and you can’t get it back.” That created an urgent timeline for finding investors. Roberts helped contact about eight companies, but they weren’t ready to commit.

Then in 2009, she encouraged Parissenti to present his idea at a biotech conference for investors. His pitch caught the attention of Ken Pritzker, M.D. At the time, Pritzker was a partner at York Medtech, a venture capital firm in Toronto. “We were looking selectively to invest and manage an early stage biotech,” he says. “We’d looked at over 100 opportunities during the past year.” As a former chief of pathology at Mount Sinai Hospital in Toronto, Pritzker appreciated the potential implications of Parissenti’s findings. But that wasn’t enough — not then, anyway. “We were busy evaluating a lot of investment opportunities, and we hadn’t thought through the business model [for Parissenti’s test,],” says Pritzker. So they parted ways, with no investment deal.

Then about six months later, Pritzker and his colleagues received an urgent call from Ontario Centres of Excellence, a government organization that partners with industry to help fund and commercialize research from universities. The 18-month PCT patent application for Parissenti’s innovation was about to expire in three months, and Laurentian University couldn’t cover the cost to file the PCT application in individual countries. It was seeking an investor to fund a portion, with the rest of the application fees covered by Ontario Centres of Excellence.

In December 2009, Pritzker and his colleagues signed a nondisclosure agreement. In February 2010, the license agreement between the new company, Rna Diagnostics Inc, and the university was signed. It represented Laurentian University’s first licensing agreement, and only took about three months to complete. “You have to appreciate the speed at which this occurred,” says Pritzker, now CEO of that Toronto-based company where Parissenti is chief scientific officer. “This meant the university’s [intellectual property office] and its management team came to an agreement on licensing in a very short period of time — a shorter time than you could even get a call back from some universities.”

The test the company plans to sell is called the RNA Disruption Assay. The diagnostic test will be provided as a service for labs: Tumor samples will be sent to Rna Diagnostics, which will test the biopsies at its Canadian facility, then send results back to the lab. A set of patent-protected algorithms provides an objective, quantitative way to assess RNA quality from tumor biopsies, to determine whether chemotherapy is working for a patient.

So far, the company has filed for additional patents in Canada, the United States, and Europe. Patents have been awarded already in Japan and Australia, and the company expects a European Union patent to be awarded soon — Pritzker says the company should begin selling the RNA Disruption Assay in Europe in 2015.

Meanwhile, trials are under way to further explore the technology’s potential. That includes a trial with 220 patients, sponsored by MaRS EXCITE, an Ontario government agency, and others. “The trial is part of a program that looks at groundbreaking new technologies that have the prospect of strongly affecting patient care, and possibly save money with personalized care,” says Parissenti.

Assessing Chemotherapy During the First Treatment Cycle

If doctors know early that chemotherapy won’t destroy a tumor, the benefits are two-fold — it helps the patient, and it

can also lead to more effective use of healthcare dollars. The greatest benefits will occur when doctors can identify nonresponding patient tumors as early as possible. Chemotherapy usually involves six to eight cycles of treatment, each lasting two to three weeks. Parissenti already has data showing the RNA Disruption Assay can identify nonresponding tumors during the midpoint of chemotherapy. But that can be nine weeks into treatment.

Parissenti thinks the RNA Disruption Assay can reveal chemo effectiveness much earlier in treatment. A recent study has demonstrated reliable data during the first or second cycle of chemotherapy. "That's where the value of the test is," he says. "If you can show no survival benefit from certain chemotherapy drugs, then you can get patients early on to other treatments that can work." That minimizes exposure to toxicity that's only harming healthy cells, not the tumor.

At a breast cancer conference in 2013, Parissenti reported findings that showed a correlation between patients who had poor RNA quality in tumors after receiving chemotherapy, and a longer disease-free survival rate. That suggests the RNA Disruption Assay could be a much more reliable indicator of whether chemotherapy is effective, compared to tracking how much a tumor shrinks. "It's always better to have shrinkage than not, but that doesn't show if the tumor is responding to chemo, in terms of enhanced survival," says Pritzker. "The tumor might shrink 100 times, but there can still be billions of cancer cells left."

The benefits of the RNA Disruption Assay aren't limited to breast cancer, says Pritzker. He notes the company has preliminary data from other studies that show the test could work for other cancers, including ovarian cancer and lymphoma.

Before Parissenti's work that led to the RNA Disruption Assay, there was no mention in cancer chemotherapy scientific literature about a connection between dying tumors and degraded RNA. Pritzker says he's not surprised by this. "I've come across a lot of stuff before that was plainly evident, but nobody paid attention to it," he says. "That's actually the story of science, in many ways. You only see what you know, or what you think you know."

It's the sort of scientific discovery that, for years, was hiding in plain sight. "From the start, we had a lot of support, but as you would expect, there were also people who said there's nothing in this, it's an artifact — anything but that it's real," says Pritzker. "We're long past that stage. They were wrong. This is real."

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