



Strength From Within

Researchers are increasingly looking to the body's immune system to beat cancer

By Nicolas Heffernan

www.biobusinessmag.com

www.alpha-cancer.com

IS THERE A SCARIER DIAGNOSIS THAN CANCER? IT'S ALMOST BECOME SYNONYMOUS WITH A DEATH SENTENCE.

Despite seemingly daily reports of the newest wonder drug that shrinks tumours, gene therapies or even a vaccine there really hasn't been much progress treating the disease over the last half-century. In 1960, the mortality rate for all cancers combined in the United States was 194 deaths per 100,000 people. In 2009, the mortality rate was 174 deaths for every 100,000 persons.

“The number of people dying from cancer per 100,000 is still pretty much the same as it was 50 years ago,” says Igor Sherman, CEO of Alpha Cancer Technologies, a Toronto-based company developing a targeted cancer platform. “So despite all the advances we have made, what happens is people live a little longer with cancer but the quality of life is horrible. I sometimes doubt whether it's worth the prolonged life and very rarely do we actually succeed in curing the disease.”

....

From Fetus to Cancer Cure

It's one of nature's ironies that the vessel that brings nutrition to a fetus could also be the way to cure cancer.

Alpha fetoprotein (AFP) is a protein produced by the embryo so nutrients can be delivered to the zygote. This protein carries nutrients and circulates in the mother's bloodstream until it encounters an embryonic cell, which has specific AFP receptors. It turns out that almost 80 per cent of all cancer cells express AFP receptors as well. Sherman, Alpha Cancer's CEO, found predominantly Russian research that suggested loading AFP with chemotherapy drugs could provide targeted treatment for cancer.

But the research petered out in the early 2000s in Russia. After a long search via Russia and eventually Montreal, Sherman found an American company, Merrimack Pharmaceuticals, was working with AFP to treat rheumatoid arthritis. Merrimack received confirmation that its stage two trials into AFP had failed the day Sherman called so Alpha Cancer's CEO was able to secure a licensing agreement on “very favourable terms. I acquired this technology that had a huge amount of money already invested in it that already had the manufacturing for the key protein going on,” he says.

Sherman started repeating the experiments he had seen in the Russian literature and found that he could load AFP with cytotoxic drugs. Sherman chose generic taxol as the chemotherapy agent of choice. “In principal, you can cure any cancer with taxol,” says Sherman. “The problem is you have to kill the patient first.” The drawback with taxol like all other chemotherapy agents is its toxicity, but since AFP allows you to target the cancer alone, the dose can be significantly reduced.

Alpha Cancer has demonstrated in animal studies that a dose that is significantly lower than the maximum tolerated dose allows better survival. “We believe that we actually have something that can be potentially revolutionary in terms of treating cancer,”

says Sherman. “We might be able to treat not all, but most patients with cancer... with low dose chemotherapy that wouldn’t cause systemic toxicity but can potentially over the long term cure those patients who today are incurable and certainly prolong survival significantly without all the associated toxicity and the misery that comes with chemotherapy.”

Cure All?

The company is looking for approval for ovarian cancer first, which means Alpha Cancer would benefit from an FDA program for orphan treatments that allows businesses to start marketing drugs after phase two trials, cutting years off the approval process. The company still has to complete phase three trials that confirm phase two results and if the outcome isn’t the same, the drug is removed from the market. “A lot of companies are using this as a first entry into the market because that proves the principal,” says Sherman. “And in the U.S., when the drug is on the market, physicians are allowed to prescribe for any indication, it doesn’t have to be ovarian cancer.”

A recent study found that one-third of all chemotherapies are used to fight off-label indications. Another regulatory advantage of Alpha Cancer’s platform is that the two key molecules are already well known to the FDA. AFP might have failed to fight arthritis for Merrimack but their trials proved it was just as safe as the placebo. Taxol is the standard of care in platinum resistant ovarian cancer which also makes for a very clean trial where Alpha Cancer compares standard Taxol versus AFP Taxol. Unfortunately, the survival rate for ovarian cancer is typically six to eight months so the trial by design will also be very short.

The question is, can every patient benefit from this type of approach? Alpha Cancer estimates 80 per cent of all cancers express the receptor. A recent Japanese study looking at gastric cancer showed that the majority of these cancers express the receptor, however about half of the cancers express the receptor uniformly and the other half express it heterogeneously. “Under those circumstances when every cell has the receptor that’s an ideal candidate and I think we can even talk about cure,” says Sherman. “When it’s patchy, when there are areas that don’t have the receptor, we can expect to shrink the tumour significantly. Now you have a much smaller tumour which can be amenable to other means such as surgery or conventional chemotherapy.”

Another benefit of Alpha Cancer’s strategy is it lessens the disease’s ability to develop resistance. Typically, a patient with chemotherapy receives a single dose that will kill much of the tumour but since it’s so toxic and attacks healthy tissue as well, the patient becomes very sick and usually requires about three weeks before the next dose. If the next dose is given in a shorter interval it will kill the patient. “You have to wait for the patient to recover but during that time cancer recovers as well and those cells that survived are a little less sensitive to chemo,” says Sherman. Practically all cancer cells have pumps on the cell membrane that siphons chemotherapy agents out. At the beginning of treatment the cancer doesn’t have as many pumps so the chemo overwhelms the defence mechanism. After each course of treatment the surviving cells express a larger and larger numbers of pumps on the surface until eventually chemotherapy has no chance of getting into the cell. “That’s why all chemotherapy fails ultimately,” says Sherman. “It takes time to kill the cancer and if you don’t kill it with the first one or two treatments the cells become more and more resistant and over seven or eight treatments which is typical for chemotherapy they become completely resistant unless you eradicate all of the tumour. Then nothing works.” However, when AFP binds to the receptor on the surface the drug is released inside the cell bypassing the membrane and the membrane pumps. “It probably will change the whole treatment paradigm,” says Sherman.

Since Alpha Cancer’s system is non-toxic, doctors don’t have to wait weeks for the patient to recover so they can administer the next dose. Instead, doctors would maintain a plasma level of the drug that would continuously enter the cells and keep on killing them for as long as the cells have the receptors on the surface. Alpha Cancer think the total number of doses might be the same or higher than currently used but will be delivered over a much shorter period of time.

The potential for Alpha Cancer’s drug, ACT-901 is huge. The best comparison is with Celgene’s Abraxane, which the American company bought for \$2 billion. Abraxane is a very similar concept to Alpha Cancer’s molecule except it uses albumin instead of an AFP platform. By using albumin as a delivery system, Celgene reduced the toxicity of Taxol by 20 to 30 per cent allowing a higher dose with greater efficacy. Its value in the Celgene portfolio is \$6 billion. “Our drug is a third generation Taxol in a way,” says Sherman. “It will definitely replace Abraxane and that’s already \$6 billion being displaced and it can displace a lot of other chemotherapies as well.”

