



# ALPHA CANCER TECHNOLOGIES

## The pharma company on a path to help cancer patients beat cancer and not worry about toxic side effects of chemotherapy

by Alexander Kuklin, Ph.D., *Managing Editor*

The biotech community and the media knew Adriana Jenkins for years as competent PR professional. What many people did not know was her long battle with breast cancer. Adriana Jenkins died at 4:30 PM on February 9, 2011. Mrs. Jenkins published an article in *Forbes* before her death, which was a “dying cancer patient’s plea for personalized medicine.” Among many important issues that Adriana addressed in her last article, she wrote, “The result of the focus on testing cancer drugs on all patients is painful trial and error. Chemotherapy is prescribed with no guarantee of effectiveness and can cause wretched, and sometimes fatal, side effects. But cancer patients like me don’t have time to waste. How do we convince drug makers to focus their shrinking R&D budgets on this area of scientific discovery?”<sup>[1]</sup>

A Canadian pharmaceutical company is trying to change the current reality of chemotherapy and its side effects on suffering patients. The company is Alpha Cancer Technologies Inc., which is based in Toronto, Canada. I had the opportunity to meet with its founder and CEO, Igor A. Sherman, PhD (*Figure 1*) and discuss his vision of the next generation cancer therapy and the future of his company. Dr. Sherman pointed out that Alpha Cancer Technologies was born “out of frustration, which built up over many years of working in large pharma and small biotechnology companies.” Dr. Sherman saw very little progress in the desired outcome for drug development and “whatever progress was made it offered only marginal benefit for patients at a cost of significant toxicity.” He asked himself many times, “Is it really progress if the patient’s suffering is extended for a few more months as a result of treatment?”

Pharmaceutical companies understand that path to success has to involve targeted therapy with lower toxicity and better efficacy than current drugs. The field of targeted cytotoxins is an area of active research and development with such companies as Genentech, Seattle Genetics, Medarex (now owned by Bristol-Myers Squibb), Roche and many others funding major efforts in this area. The targeting concept is rational and conceptually very attractive - by carrying cytotoxic drugs selectively and specifically to targets on cancer cells, cancer cell killing should be increased and systemic toxicity should be reduced. However, as Dr. Sherman explained, success in this field has been hampered by four major obsta-

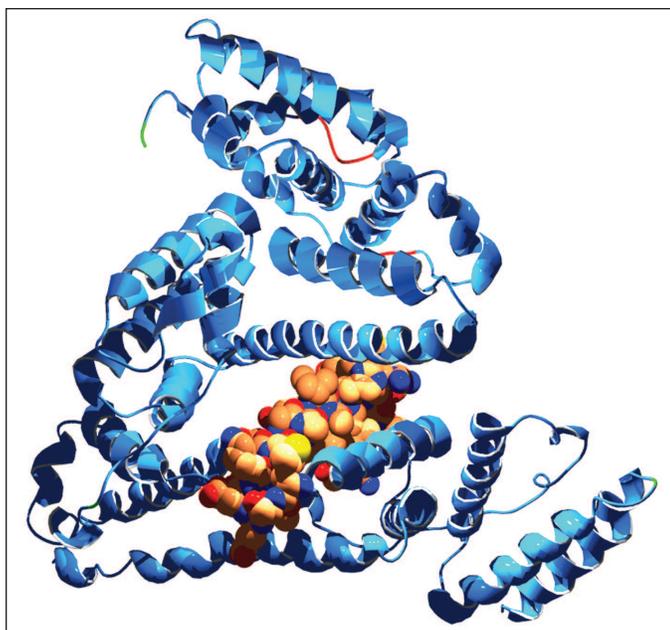


**Figure 1** Igor Sherman, Ph.D., CEO and Founder of Alpha Cancer Technologies, Inc..

cles: a) difficulties in identifying targets that are unique to the cancer and absent from normal cells; b) serious toxicity caused by immune reactions to the targeting agent which is a foreign protein (usually a monoclonal antibody or a fragment of an antibody); c) lack of targets that are expressed on most cancer cell types in the majority of patients; and d) need to use extremely potent toxins because of limitations on the amount of targeting protein that can be administered and the fact that usually only one toxin molecule can be conjugated to a targeting protein.

Dr. Sherman was very excited when he came across an opportunity that addressed all of the above limitations and thus offered a potential breakthrough of effective therapy without toxicity (and possibly even a cure for many patients). He immediately jumped on it.

The technology that Dr. Sherman and his team, as well as investors, are betting on is utilizing recombinant human alpha-fetoprotein (AFP) conjugated cytotoxins. No wonder the company’s name is Alpha Cancer Technologies! Recombinant human alpha-fetoprotein (AFP) is a single chain glycoprotein with a molecular mass of 69 kD or greater depending on the carbohydrate (glycan) content (*Figure 2*)<sup>[2]</sup>. This protein is encoded by the AFP gene and is produced by the yolk and the liver during fetal life. The fetus has the highest levels of AFP, which decreases after birth and is hardly

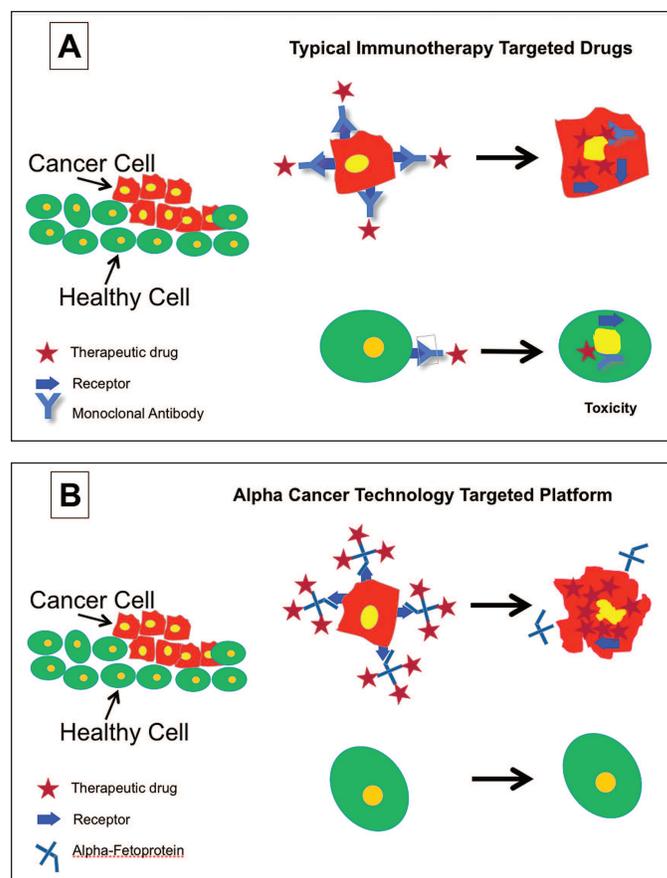


**Figure 2** A three-dimensional (3-D) helical/ribbon model of human AFP was created with commercially available software from a structure of the AFP protein in the Protein Data Bank. Human AFP is known to contain 60% alpha-helices, an ideal topology for receptor binding.

detectable after that. It has no known function in adults. However, studies during the last few decades have implicated AFP in carcinogenesis (reviewed in reference 2). AFP was reported to play a role in both inhibiting and stimulating the growth of cancer cells. AFP has also been reported to promote growth via up-regulation of the PI3K/AKT and cyclin AMP/protein kinase A (PKA) pathways (see reference 2).

The advantage of the approach employed by Alpha Cancer Technologies is that AFP binds to cells through specific receptors. These receptors are not present on normal cells in adults but they do show up on most tumor cells. Therefore, AFP will bind only to tumor cells. The uptake of AFP into cells is carried out through receptor-mediated endocytosis<sup>[2,3]</sup>. Endocytosis is the process by which cells absorb molecules by engulfing them. It has been demonstrated that AFP was taken up by cells undergoing differentiation, whereas undifferentiated and fully differentiated cells did not incorporate AFP<sup>[2]</sup>.

The Alpha Cancer Technology scientists are working on conjugation of therapeutic drugs with AFP with the goal to target only cancer cells (*Figure 3*). Conjugation of the antibiotic carminomycin to AFP has been previously shown to inhibit tumor growth and increase the mean life span of experimental animals<sup>[4]</sup>. Another study demonstrated that doxorubicin conjugated to AFP overcame the multi-drug resistance of the human ovarian carcinoma cell line SKVLB and the human breast carcinoma cell line MCF-7 AdrR<sup>[5]</sup>. Dr. Sherman's scientific team is developing novel conjugation



**Figure 3** Effect of typical Immunotherapy Targeted Drugs (Panel A) and Alpha Cancer Technologies Inc. (ACT) platform (Panel B) on cancer and normal cells. Typical immunotherapy drugs bind not only to cancer cells but also to many normal cells, causing serious side effects. Drugs based on the ACT platform achieve greater effect on cancer cells by delivering more cytotoxic drugs to them and have almost no effect on normal cells (Panel B). The AFP comes out of the cancer cell after unloading the drug.

methods to increase the efficacy of the drug-AFP complex. Igor Sherman also pointed out that previous work with AFP conjugates (references 4 and 5) had been carried out with fully human AFP derived from aborted fetuses. “Both ethical and practical considerations prevent the use of fully human AFP for commercial purposes,” explained Dr. Sherman. “Our company uses recombinant human AFP and thus has a viable alternative for large scale production of AFP-conjugated drugs.”

“Using AFP we can develop targeted therapies that are non-toxic to normal cells,” explains Igor Sherman. Without AFP, chemotherapeutic drugs enter both normal cells and cancer cells damaging normal cells (the phenomenon referred to as “off-target toxicity”) and causing nasty side effects in the patient. The Alpha Cancer Technology's drugs can enter only cancer cells because they are the only ones expressing the receptor for AFP.



Alpha fetoprotein has the potential to be a class leading targeting agent because it addresses all key hurdles that have limited full exploitation of the targeting concept:

- AFP receptor has a uniquely optimal pattern of expression - high levels present on almost all cancers, near absence on most normal cells;
- Is non-immunogenic since it is a normal human protein to which every human is exposed in utero, eliminating the risk of anaphylaxis and production of neutralizing antibodies;
- Is taken up by cancer cells expressing the receptor and its uptake circumvents membrane pumps which are the most frequent reason for resistance to chemotherapy; and
- The molecule has several potential binding sites for cytotoxins, which will cut the amount of protein required (reducing cost and dosing volumes) and allow the use of conventional chemotherapies instead of potentially more dangerous very potent toxins such as ricin.

The Alpha Cancer Technologies team believes that their drug products have the potential to significantly improve cancer outcomes for the majority of patients by providing superior efficacy and much better safety and tolerability than currently used therapies. In fact, the company says that this is “a disruptive technology that could displace most chemotherapy products for the majority of cancer patients”. This is good news for patients and medical providers as well as for investors.

Igor Sherman elaborated further that the technology being developed by his company is particularly exciting and promising because it enables the development of drugs that can reach cancer patients who need it in a very short time. Alpha Cancer Technology has designed a rapid clinical development plan, which benefits from the significant investments already made by Merrimack Pharmaceuticals (Cambridge, MA) in conducting human trials of recombinant human AFP and setting up the FDA-compliant manufacturing process for the production of recombinant human AFP (Merrimack is the company that licensed the technology to Dr. Sherman’s company). Additionally, clinical trials conducted by Merrimack demonstrated remarkable safety profile of AFP<sup>[6]</sup>. Dr. Sherman and his team think that only 1/10th of the conventional chemotherapy dose will be required to kill most cancer cells, which express the receptor that binds AFP. “Due to the targeted approach, almost all of the drug will end in cancer cells and none of the drug will be wasted harming normal cells since they do not express the AFP receptor,” explains Dr. Sherman.

Furthermore, AFP-conjugated toxins have been shown to overcome multi-drug resistance mechanism and can therefore be used to effectively treat patients that failed previous chemotherapy. These products clearly address an unmet need in cancer therapy and if approved, will become a new standard of care.

Between 60% and 90% of liver, prostate, breast, ovarian, pancreatic, lung, stomach, colorectal, and germ cell tumors and some leukemias express AFP receptors. This translates into a big market potential for drugs that are based on the Alpha Cancer Technology’s platform. The US sales of oncology drugs (excluding hormonal therapies and vaccines) reached US\$18.5 billion in 2009<sup>[7]</sup>. This is a growth of ~11% compared to the cancer drug sales in 2008.

Alpha Cancer Technology is well positioned to successfully ride the wave of targeted approach to drug delivery that is the greatest promise of the 21st century. The company has more than 20 international patents covering the technology. In the era of Personalized Medicine (PM), which emphasizes the customization of therapy for each patient, Alpha Cancer Technology has a lot to offer. PM drug targeting employs a combination of diagnostic test and the drug (called also combination products by the FDA). The therapeutic drugs developed by Alpha Cancer Technology will be administered only to patients with cancers, whose cells express receptors. Diagnostic tests for AFP receptor presence are available and new ones are being developed.

The finishing paragraph of Adriana Jenkins’ last article said, “I am so grateful for the extra time a PM drug gave me. My hope is that future patients have the same chance to benefit from personalized medicine.<sup>[1]”</sup> Dr. Sherman is optimistic that the cancer drugs his company is working on will not only extend cancer patients lives but will actually lead to cure for many of them.



## Alpha Cancer Technologies

**Location:** Toronto, Ontario, Canada  
**Telephone:** 1 (416) 826-6626  
**Website:** <http://www.alpha-cancer.com>  
**Principals:** Igor Sherman, Ph.D.  
*Founder and Chief Executive Officer*  
 Richard Potts  
*Chairman*



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