ISRAEL21c A Focus Beyond www.israel21c.com

HEALTH

Israeli 'guided missiles' induce cancer cells to commit suicide

By Nicky Blackburn November 21, 2007

For a moment, Dr. Shai Yarkoni, president and CEO of biotechnology start-up Target-In, appears to veer off on a tangent. "There's something very interesting in the terms we take from the military to the medical world and vice versa," he says contemplatively. "Surgical strike, magic bullets, these are all phrases that pass from one industry to the other."

People call what Target-In is doing 'guided missiles', and in a way that's exactly what the company's technology is: a guided missile that can recognize and kill inflamed cells from tumors and other diseases. But Target-In's technology is more sophisticated than that. The technology doesn't just shoot diseased cells down, it makes them commit suicide.

Target-in was founded in 2002 and stems from over 10 years of academic research by Prof. Hiya Galski, a leading academic in the field of immunotoxins at Hebrew University, and Yarkoni, who was her PhD student. The pair had been looking for a human toxin that could be used to kill off diseased human cells.

The problem was, however, that no creature on the planet will create a toxin for itself because basically it's suicide to do so. Instead doctors were using alternative man-made toxic compounds like radioactivity, chemotherapy and antibodies to treat diseased cells. Then the researchers had a bright idea.

Cell apotosis (programmed cell death) is one of the pivotal mechanisms through which an organism can control its cells. It enables an animal or human to induce suicide in cells that no longer serve appropriately and is a physiological, rather than pathological response. It is also used actively in the development of a fetus. Yarkoni holds out his arm as an example.

"As long as it the shaft of the arm that is developing, everything is fine. But what happens when you get to the fingers?"

He touches the creases of skin between his fingers. "In the fingers the cells have to keep on growing, but where the creases are it has to stop. The way it does this is through the cells committing suicide.

"The whole idea of modern medicine is to imitate the processes that happen naturally in the body. In one bright moment we realized that the cell suicide mechanism is the toxic compound we were looking for," Yarkoni told ISRAEL21c.

Targeted cell death is only possible because of advances that have taken place in targeted therapies over the last few years. Antibodies, hormones and growth factors, are already being used to treat diseases by targeting the specific cells that cause the illness. The only problem with these therapies, however, is that they don't kill the cells and have little biological effect.

Target-In aims to change that. The company has so far created eight molecules that can be combined with the molecules of proven targeted therapies to create a single small protein with two functional domains.

"This protein acts through using the targeting molecule to get to the right cells, and then

once there, initiates the physiological effects of cell suicide," explains Yarkoni.

"Think of it like a key in a keyhole," he adds. "Antibodies match certain receptors of the cell the way a key matches a key hole. But getting a key into a hole doesn't always open the door. We have to add something to make it more effective and kill the cells. We take the small molecule or key, fuse to it a protein that causes cell suicide and get a molecule that preserves the specificity of the target while making the killing very effective. And it does this with little, if any, side effects and no effect on safety."

The apotosis protein will not destroy healthy cells, for example, because outside the cell it cannot have any impact. The only way for it to enter the cell is through the targeting molecule. In addition only small amounts of the protein are needed. "We imitate the physiological process and the cell doesn't know that the process is artificial," says Yarkoni. "There's no collateral damage."

This all sounds very innovative, but the company's goal is not to waste time pioneering anything that doesn't need to be pioneered. As a result, the company plans to only use antibody targets that have already been proven by other companies - treatments like Herceptin, an antibody used to treat breast carcinoma cells. This treatment sells for more than $2 billion, according to Yarkoni, but doesn't cure the patients.

"It merely prolongs the remission time," he said. "The market of targeted therapies has to be upgraded and we are bringing the solution."

The company has now taken five prototypes through successful animal studies which indicate that the treatment is a generic solution. The company's lead compound, the IL2-Caspase3, now has full proof of concept. In studies this receptor proved to have a clear beneficial effect on animal models of Crohn's disease and Diabetes Type 1. This receptor is currently used in three products on the market - two antibody treatments, Simulict and Zenapax, and one immunotoxin, Ontak, which are used to treat cancer and transplantation rejection.

"The existing treatments suffer major drawbacks," says Yarkoni. "The antibodies have low efficacy and the immunotoxin has high toxicity inducing many side effects."

The company now plans to add its protein to these three compounds and test them in a clinical setting. Trials will begin in one year. The goal, to show that the new drug is safer than Ontak, and more efficacious than the antibodies.

To do this as quickly and efficiently as possible, Target-In has signed two licensing agreements with an Indian active pharmaceutical ingredient (API) company, Century Pharmaceutical, which develops anti-allergens and asthma therapies; and a US company based in Palo Alto in San Francisco, which is developing a product for leukemia. Target-In will co-develop its treatment with Century Pharmaceuticals.

Yarkoni, who worked as CTO at Collguard before joining Target-In, is expecting to receive fast-track status from the FDA to develop the new treatments at a faster rate than normal. This will enable the company to carry out Phase I clinical trials and then pass directly to a pivotal study with fewer patient numbers than normal Phase II and III trials.

Once the first treatments have gone through clinical trials and proved safe, the company intends to expand the indications to address other diseases.

Target-In is a small company employing six; most of the work is sub-contracted out. It received $200,000 in seed money from the Hebrew University of Jerusalem. "This was very unusual," says Yarkoni. "It was the first time that the university had invested money directly into a company. The head of Yissum Technology Transfer company (the commercial

arm of the Hebrew University), strongly believed in us."

Since then the company has raised more than $4 million from private investors, and is now gearing up for its second round. The aim is to raise $10 million. Already Century Pharmaceutical has pledged $1 million, and Yarkoni says the company has also received a firm commitment for a further $3 million from a Japanese company. Further negotiations are taking place with US and Japanese venture capital companies.

This money will get the company through two clinical trials and proof of concept.

"For me this is déjà vu," says Yarkoni. "I remember the antibodies industry in the late '80s. No one believed in it. In 1997 the whole worldwide market of antibodies was $250 million. In 2007, it's worth $20 billion. I think this is going to happen once again. We expect to revolutionize the whole concept of targeting therapy."


Slashdot It!