Harnessing Patient's Immune System To Fight Cancer

St Jude Children's Research Hospital

For patients with leukemia or lymphoma, today's treatments can fall short. If a patient's cancer recurs, sometimes It can be more aggressive and more difficult to treat. Even when treatments are successful, therapies often have dangerous side effects with long-term consequences, particularly in children. In response, researchers from St. Jude Children's Research Hospital have developed an alternative treatment to harness the power of patients' immune systems that could lead to better therapies for some cancers, including leukemia and lymphoma.

This therapy "provides a new treatment option for patients whose cancer does not respond to standard treatment," said former St Jude researcher and co-inventor Dario Campana, MD, PhD, noting that it may become part of the standard-of-care arsenal to treat cancer, and could even replace some or all of the existing therapies for leukemia and lymphoma. "Hopefully, as similar methods are being developed, patients with other forms of cancer will also benefit from these technologies."

In the Beginning

In the early 2000s, Campana and fellow St. Jude researcher Chihaya Imai, MD, PhD, began working to stimulate patients' immune cells to fight cancer — a method known as immunotherapy. To achieve that, they enlisted the help of white blood cells called T-cells (the "T" is for thymus, the gland where these immune-system cells develop). Infusions of T-cells had already helped a few leukemia patients, but the resulting side-effect outweighed the benefits. The treatments required T-cells from donors, and those donor cells would sometimes attack patients' tissues and organs. Campana and Imai needed a way to control the T-cells' search-and-destroy activity, to kill cancer cells while leaving healthy cells intact.

They found the answer by improving an existing T-cell therapy, called chimeric antigen receptor or CAR. A version of the therapy uses a patient's own cells instead of donor cells. How? After T-cells are removed from the patient, they are genetically engineered to attack specific cancer cells. This is done by modifying the T-cells to target proteins expressed on the surface of cancer cells. For their treatment, the researchers programmed T-cells to target a protein called CD19, which is found in leukemia and lymphoma cells. After the T-cells are genetically engineered, they are returned to the patient's bloodstream. Because donor T-cells can be too destructive, the patient's T-cells represent a useful alternative. "Our own T-[cells] do not attack our own tissues," says Campana.

To improve the strength of CAR treatment, the St. Jude researchers added a molecule (4-1BB) that not only induces T-cells to kill the targeted cancer cells, but also causes T-cells to proliferate.

When the researchers tested this modified treatment in the lab, the results were encouraging. "I was amazed by how powerful they were," says Campana, who now works at University of Singapore. "This incredible capacity to eliminate target cells within minutes was something that I had never seen before."

In 2003, the researchers presented their findings at the American Society of Hematology conference, which attracted about 20,000 scientists and physicians — but only about 20 people attended their presentation. Interest from pharmaceutical companies and investors was essentially non-existent, says Campana. Ten years later- after this CAR T-cell therapy achieved its first clinical results and the promise of immunotherapy began to be realized - interest increased significantly.

From Lab to Marketplace

The basic idea behind immunotherapy has existed for many decades. As far back as the 1890s, doctors attempted to fight cancer by stimulating patients' immune systems. Sometimes those experiments worked, but researchers often struggled with a lack of knowledge about the immune system. That changed over the last 15 years, with advances in genetics that revealed key information about the body's natural defenses. "[Immunotherapy] is something that's come of age," says Chad Riggs, a marketing associate for technology licensing at St. Jude, which filed a patent application in 2003 based on Campana and Imai's T-cell work. A patent was issued in March 2013.

> *It wasn't long before St. Jude heard from Juno Therapeutics, a Seattle-based biopharmaceutical company that focuses on immunotherapy treatments for cancer, and is one of a small number of companies working to bring CAR T-cell therapies to market.*

“We identified the St. Jude technology as a good fit,” said Hans Bishop, Juno’s CEO, who credits St. Jude’s technology transfer office, which supports the commercialization of research innovation, as “critical to a positive outcome.” Licensing negotiations were completed in December 2013.

A drug candidate, JCAR017, is currently being evaluated in clinical trials directed at CD19, a known antigen associated with certain leukemias and lymphomas. Juno has announced that its collaborator, Celgene Corporation, has exercised an option to commercialize Juno’s CD19 program outside of North America and China.
There are no CAR T-cell treatments commercially available yet, but Bishop says that they expect their product candidate could be on the market as early as 2018. It’s too soon to know if that will be JCAR017 — but based on early clinical results, JCAR017 received designations from both the FDA and the European Medicines Agency (EMA) that make it eligible for expedited approval assessment. Still this does not guarantee approval.

Bishop is confident. "This product candidate has the potential to provide a life-saving treatment option for patients,” he said.

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