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A two-fisted blow against a deadly cancer


Wayne Marasco

Patients with a rare, often incurable malignancy known as cutaneous T cell lymphoma (CTCL) develop disfiguring tumors caused by cancerous cells from the person's immune system that migrate through the bloodstream and accumulate in the skin.

CTCL cells not only "home" in on the skin as if drawn by a magnet; they also suppress the body's natural means of detecting and attacking tumors. Unless CTCL is caught early, it tends to spread to other parts of the body and, in advanced cases, is often lethal.

Dana Farber sees an increasing number of these patients every year from all over the world as a result of a multidisciplinary Cutaneous Lymphoma Clinic established in the 1990's.

Wayne Marasco, MD, PhD, Thomas Kupper, MD, and their colleagues have devised and tested a novel strategy that deploys a designer monoclonal antibody to fight CTCL on both fronts. Antibodies are proteins made by the immune system to recognize and bind to foreign invaders. Monoclonal antibodies are identical copies, made in the laboratory, of a single, specific antibody that binds to a particular protein on a cancer cell.

The antibody designed by the Marasco team binds to a receptor on the malignant CTCL T cells discovered by Kupper's team, causing them to ignore the chemical signals summoning them to the skin. The antibody fights the CTCL tumors in a second way: It prevents the cancer cells from suppressing the patient's immune defenses in the area of the tumor. As a result, the immune system is better able to recognize and attack the CTCL cells.

In experiments reported in two journal articles earlier this year, the monoclonal antibody showed activity against a mouse model of CTCL, and increased the animals' survival. The Marasco team used a virus carrier to insert the antibody – called mAb h1567 – into the mice, where it was continuously produced and active for months.

"We remain hopeful that additional studies will support this humanized mAb 1567 moving from bench to bedside," says Marasco, of Cancer Immunology and AIDS. Kupper is chair of Dermatologic Oncology and Director of the Cutaneous Lymphoma Clinic at Dana-Farber.

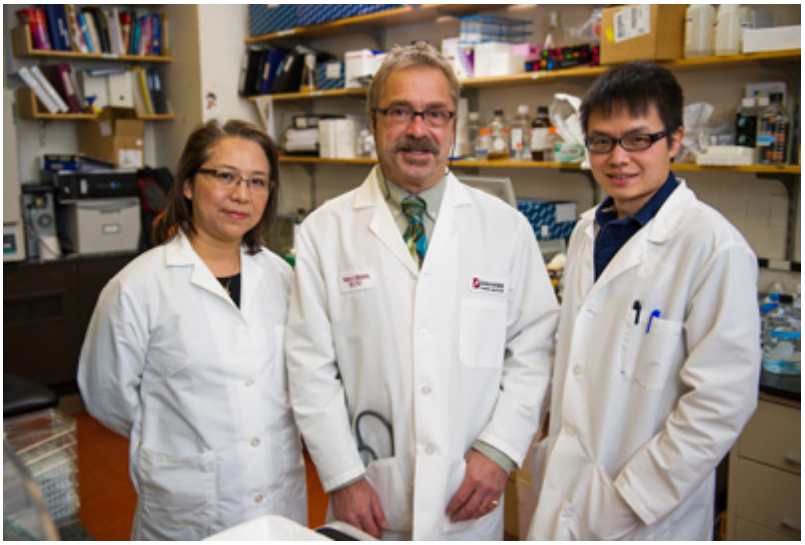
The antibody was designed to home in on a signal-receptor molecule, called CCR4, which is present both on CTCL cells and on some T regulatory cells. CCR4 responds to chemical signals called chemokines. In CTCL, skin cells transmit chemokine signals that trigger CCR4

receptors on the CTCL cells and attract them to the skin to form tumors. The cancer also activates CCR4 receptors on T regulatory cells – whose normal job is to turn off an immune response after its mission is accomplished – which suppresses the patient's immune defenses in the skin, helping the tumor survive.

By targeting the CCR4 receptor, therefore, the mAb 1567 antibody both blocked the migration of the lymphoma cells to the skin and prevented T regulatory cells from dampening the immune response to the cancer. In addition, the antibody activated other T cells to kill the CTCL cells.

"This is a very exciting development in the field of cancer immunotherapy," says Marasco. Further work is ongoing, which could lead to clinical trials to test the antibody in patients with CTCL, he says, adding that the strategy holds promise for immunotherapy of other solid tumors.

–*Richard Saltus*



Quan Karen Zhu, Wayne Marasco, De-Kuan Chang, and their colleagues have devised and tested a novel strategy that deploys a designer monoclonal antibody to fight CTCL.

Photos by Sam Ogden