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Fox Chase clinical trial tests first of its kind antibody

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Patients with HER2-positive cancers can have dramatic responses to HER2-targeted drugs but eventually develop resistance to the agents. With that problem in mind, Fox Chase Cancer Center researchers are testing a novel type of antibody called MM-111 in patients with HER2-positive disease who have progressed on standard therapy.

Unlike natural antibodies, which have two arms that recognize the same antigen, the new MM-111 antibody has one arm that binds the HER2 receptor on the cell surface and a second arm that binds the HER3 receptor and blocks signaling through HER3.

"This is the first-in-human bi-specific antibody that targets the HER2/HER3 pathway," says Crystal Denlinger, M.D., a medical oncologist who is leading the phase I/II trial at Fox Chase. "It uses the HER2 target to deliver a punch to the HER3 pathway." Denlinger will present the phase I/II study design and background data at the 46th Annual Meeting of the American Society of Clinical Oncology on Monday, June 7.

Scientists have recently found that HER3 (also called ErbB3) signaling is an important therapeutic target in HER2-positive cancers. HER3 is the preferred binding partner for the HER2 receptor and together they promote tumor growth. In tumors that have become resistant to HER2-targeted drugs, the HER3 receptor may become highly active and appears to contribute to the resistance.

"With MM-111, we now have the technology and ability to exploit this pathway and provide an additional therapeutic target within the HER2 pathway," Denlinger says.

Enrollment in the phase I portion of the trial is complete with 11 advanced breast cancer patients and one HER2-positive gastric cancer patient. The final safety analysis for the phase I portion is on-going, and the team anticipates beginning enrollment of patients in the phase II portion of the trial later this summer. Advanced breast cancer patients with HER2-positive disease who have progressed on standard therapy and have adequate performance status, bone marrow reserve, and organ function will be eligible for the phase II trial.

"I am really excited about this drug," Denlinger says. "It is a fascinating mechanism, certainly a novel mechanism, and I think the concept of using HER2 as a target to bring a therapeutic intervention to HER3 makes a lot of sense. Many HER2-positive patients develop resistance to their HER2-directed therapies, so if we can find an alternative means to block that pathway by targeting HER3 that would be a clinically meaningful step forward for the HER2 population in breast cancer and in other HER2-positive cancers."

The trial is sponsored by Merrimack Pharmaceuticals, Inc. (Cambridge, Mass.), which is developing the antibody.

The general concept behind the new drug was first developed at Fox Chase in collaboration with researchers at the University of California, San Francisco. Both institutions joined to license the intellectual property for the bispecific antibody to Merrimack, which further refined the antibody and made it more suitable for use as a drug in humans.

The origin of the double-headed antibody has its roots in a conversation between Louis Weiner, M.D., then-chair of medical oncology at Fox

Chase, and Greg Adams, Ph.D., an antibody engineer and Co-Leader of Fox Chase's Molecular and Translational Medicine Program. Weiner and Adams took the concept of an anti-ErbB2/ErbB3 bispecific antibody to their long-term collaborator James Marks, M.D., Ph.D., of the University of California, San Francisco. The Adams lab used recombinant DNA technology to engineer the ErbB2 and ErbB3 targets which the Marks lab then used to isolate the antibodies that the Adams lab used to engineer the prototype bispecific antibodies. The exquisite ability of these prototype bispecific antibodies to target and treat breast cancer cells was then determined in the laboratory by Matthew Robinson, Ph.D., a Fox Chase associate member.

After licensing the intellectual property, Merrimack scientists further refined the concept to create a new drug. Its antibody arms bind more tightly to their targets and its linker chain is derived from a human protein, which allows the drug to survive in the bloodstream longer. According to Merrimack, MM-111 is the first bispecific antibody binding two different receptors on the same cell to enter clinical development.

Provided by Fox Chase Cancer Center