Serving up cancer cells

An antibody that counters cancer’s “don’t eat me” signal is all set to be tested as a therapy

Irving Weissman is wary of the pitfalls of drug development.

Over decades of research, the Ludwig Stanford director has launched three biotechnology companies, and has set up many partnerships with large pharmaceutical firms. These are often the only ways to move products through the expensive clinical trial process. The experience has changed Weissman’s mind about how best to get major discoveries to the clinic. All too often, he says, promising therapies are shelved at early stages because of business decisions. And he is determined not to let that happen to his latest endeavor. Weissman and his colleagues aim to hold onto this latest project longer, proving its worth before seeking the appropriate venue for clinical and commercial application.

Weissman’s team has developed a therapeutic antibody against a key protein found on the surface of essentially all tumor cells, CD47, and is preparing it for human studies. After years of labor, including readying paperwork and lining up patients, human studies are set to begin this summer at Stanford. The researchers will examine the safety and appropriate dosage of the antibody therapy against a variety of solid tumors. This will be followed by a similar trial for acute myeloid leukemia centered at the University of Oxford. If all goes as planned and hoped, the antibody will be tested against a broad spectrum of cancers in more advanced trials.

In addition to tapping Weissman’s extensive experience in launching biotech firms, the project bridges his three primary domains of scientific expertise: stem cells, cancer and immunology. Last year his team also made strides with basic research studies that could refine the therapeutic targeting of CD47 and create opportunities for new therapeutic candidates down the line.

Road to immunotherapy

CD47 first caught Weissman’s interest when his team found that it coated the surface of cells they had been studying for years, stem cells in the blood and bone marrow that give rise to leukemia. Intrigued, the researchers investigated how widespread the phenomenon might be. “We found that it is highly expressed in every type of cancer we examined,” says Weissman.

CD47, it turns out, is critical to tumor survival. It tells macrophages, immune cells that patrol the body and engulf diseased cells, to cease and desist. “Every cancer cell seems to transmit this ‘don’t eat me’ signal to help it avoid elimination by macrophages,” Weissman says.

Weissman and his colleagues have tested their antibody against CD47 in immune-deficient

Recruiting the immune response
mice bearing transplanted tumors taken directly from patients, and found that it blocks the “don’t eat me” signal. As a result, macrophages consume cancer cells, dramatically reducing tumor size. What’s more, the anti-CD47 antibodies synergize with therapeutic antibodies such as rituximab, which is used to treat certain blood cancers. This synergy, the team found, leads to the complete elimination of most human tumors in these mice, and the elimination of all metastatic tumors evaluated so far.

HONING THE APPROACH
Meanwhile, Weissman and his team have gone back to the bench to take a closer look at how the anti-CD47 antibody operates. In July 2013, his team showed in mice that the antibody not only prompts macrophages to eat tumors, but also activates killer T cells. Their studies revealed that these immune cells, which can attack cancer cells, prevent human tumors from taking hold when implanted into mice. The new findings have led to a planned scientific collaboration with Alexander Rudensky and Jedd Wolchok of Ludwig MSK, who are also running immunotherapy trials.

Together, the researchers plan to monitor the immune responses of patients in the upcoming clinical trial. They will investigate whether the patients’ T cells are activated by anti-CD47 antibodies, as they are in mice. The scientists are also planning animal studies to examine whether anti-CD47 antibody treatment can be powered up by drugs that activate T cells—such as murine versions of the experimental drug nivolumab, one of several “immune checkpoint blockers” that modulate the immune response.

In 2013, Weissman’s team also found an alternative way to target CD47, using a small protein molecule based on a natural binding partner for CD47 on macrophages. The new protein synergized strongly with rituximab and other tumor-targeting antibody therapies, enhancing their tumor-busting capability in experiments in mice. “This new agent is about
a year and a half from moving into clinical trials,” says Weissman. “But it could be an alternative first-line therapy, and certainly has potential as a backup therapy if resistance evolves to the CD47 antibody.”

IN THE HOUSE
Weissman leads a group of Ludwig-funded principal investigators at Stanford with a wide range of expertise. “Weissman has made an antibody himself, and it is now poised for evaluation in clinical trials without the help of a commercial entity,” says Jonathan Skipper, who leads Ludwig’s technology development program. “That is a major accomplishment.”

If the phase 1 trials show that the antibody is safe, and if the experiments show synergy of anti-CD47 treatments with immune checkpoint blockade antibodies, Weissman plans to carry out preclinical tests to optimize the combination and test its safety. If these are successful, he hopes to launch clinical trials to test whether the optimized combination has synergistic effects on tumors. He has already begun discussions with Skipper’s team, which will bring expertise in immunotherapy to guide the trials.

Weissman is confident that his team’s work on CD47 will, with Ludwig’s support, be judged worthy (or not) of further investment on the basis of its scientific merit, independent of commercial considerations. “If all of this works out,” he says, “we can move forward with this whole package of immunotherapies in a way that will be of maximum benefit for patients.”

REFERENCES

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