A Pathway Towards Better Therapies FOR T-CELL LYMPHOMA

A nti-immunoblastic T-cell lymphoma (AITL) is a rare, fast-growing cancer typically diagnosed at an advanced stage. Treatment options have not improved in two decades. The consequence: a poor prognosis and survival rate.

Two scientists at Yale are working to change that outcome. Francine Foss, MD, Professor of Medicine (Hematology) and of Dermatology, and Elias Lolis, PhD, Professor of Pharmacology, are looking for ways to subvert and defeat AITL.

“Basically, we’re trying to develop novel targeted therapies for T-cell lymphomas,” said Dr. Foss, an internationally known expert on T-cell lymphomas. “As a first step, we are attempting to develop small molecule inhibitors,” explained Dr. Foss. “Our second step will be to develop other targeted therapies for AITL that kill the malignancy by a different mechanism, making drug resistance more difficult.”

Dr. Foss and Lolis are interested in two particular proteins because their interaction seems to promote cancer. Every AITL cancer cell secretes a type of protein known as a chemokine, specifically CXCL13 that binds to a receptor protein called CXCR5 on the same cell, which stimulates the cell to survive. In normal cells, the relationship between CXCL13 and CXCR5 is healthy and eventually leads to antibodies that fight invaders such as bacteria and viruses. But in AITL cells, the interaction sends signals that spur the growth of cancer.

The chemistry between these proteins in AITL cells may also have another effect. “Chemokines basically make cells move,” said Dr. Lolis, a structural biochemist. “Cells in lymph nodes also secrete CXCL13, and create a concentration gradient as it diffuses away. A tumor cell with the receptor CXCR5 senses differences in CXCL13 concentrations and moves toward increasing CXCL13 concentrations, which may lead to metastasis into other lymph nodes.”

Dr. Foss and Lolis believe that interrupting the CXCL13/CXCR5 pathway can slow or stop AITL’s spread and kill the cancer cells.

They first began discussing a collaboration in 2012 after a colleague, Demetrios Braddock, MD, PhD, Associate Professor of Pathology, suggested that Dr. Foss discuss her interest in cancer and chemokine receptors with Dr. Lolis, an expert in these proteins. They finally secured funding and the right mouse model, and are about to test their hypothesis in three experiments. Most of the work will be done in Dr. Lolis’ lab.

The first experiment involves a mouse model of AITL identified by an Australian lab. Left alone, about half of the mice in this model develop lymphomas within 4-6 months. Dr. Lolis developed genetic experiments to test the role of CXCR5 in AITL. “The first thing we’re going to do is delete the CXCR5 gene in young mice,” explained Dr. Lolis, “and then we’ll see what happens in six months. We want to know if CXCR5 is involved in development of the cancer. Our assumption is that it is.”

For the second experiment, the researchers will wait until the mice develop AITL, and then delete CXCR5 to see what happens to the lymphoma. “In the best case,” said Dr. Lolis, “it will disappear. Or the tumor could shrink. In the worst case, nothing will happen. It’s going to take one or two years to work this out in the mice.”

The third experiment will be an AITL PDX study to test a small molecule antagonist (inhibitor) against human CXCR5 in mice. PDX stands for patient derived xenograft. In a PDX test, tumor tissue from a human patient is put into mice, where researchers can study how human cancer responds to various treatments. “In this case, the tumor tissue will contain AITL, and the small molecule antagonist will prevent CXCL13 from binding to CXCR5 and having any pro-survival effects. Drs. Foss and Lolis are also working on other molecules that target AITL through a different mechanism. The human cells will sur vive in the mice for a couple of months, long enough to do experiments and gather data in a short time.

“We have collaborations with institutions that have different types of mice with T-cell involvement,” said Dr. Foss, “so we can test the compounds we’re developing with these other labs.”

Dr. Foss added that targeting these pathways in AITL might work because a similar approach has been successful against B-cell lymphomas and leukemia using a small molecule drug called ibritunib. “It targets B-cell receptors,” she said, “so the paradigm for doing this already exists, but there are no drugs like that for T-cell lymphomas. This would be one of the first ones to be developed.”

She and Dr. Lolis are initially concentrating on T-cell lymphomas that express CXCR5, but they believe their findings may be relevant to other cancers that also express it, such as prostate cancer. Dr. Lolis mentions a study that showed that people with cutaneous T-cell lymphomas whose tumor cells don’t express CXCR5 live longer than patients who do make CXCR5. “So basically it’s an adverse prognostic factor,” said Dr. Foss, “which means we would be targeting the worst lymphomas with this new therapy.”

Looking ahead, Dr. Foss thinks a clinical trial is probably two or three years away. Despite the rarity of AITL, she doesn’t anticipate any trouble in filling a trial because there are no good options for AITL patients, who would eagerly come from all over to Yale or collaborating institutions for the treatment.

Dr. Foss describes her partnership with Dr. Lolis as “a great example of how synergy can develop. We were brought together by a colleague from pathology. It’s a good paradigm for translational science at Yale, bringing clinicians together with researchers.”

Dr. Lolis agreed. “It’s a true collaboration where basic biology has led to a preclinical trial and translational research.”

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