MANUFACTURING CELLS THAT FIGHT CANCER

Steve Kemper writer, Peter Baker photographer

The new Advanced Cell Therapy (ACT) Laboratory widens Yale Cancer Center's horizon of possibilities for developing cutting-edge therapies. "It's a state-of-the-art facility," said Diane Krause, MD, PhD, Medical Director of the lab; Professor of Laboratory Medicine, Cell Biology, and Pathology; Associate Director of Yale Stem Cell Center; and Medical Director of the Clinical Cell Processing Laboratory. "Only the top cancer centers have a laboratory like this. Yale needs this lab to do clinical trials using cells."

The facility is a Class 10,000, Good Manufacturing Practices (GMP) laboratory with three ISO 7 rooms. Those specs are required to manufacture cells that can be transferred into patients. In lay terms, the specs signify a super-clean sterile environment. The air is HEPA-filtered, which means that 99.97 percent of all airborne particles are removed. Everyone in the lab wears hats, gloves, booties, and coveralls made of particle-free materials. "A lot of effort goes into maintaining that clean-room atmosphere," said Dr. Krause, "and we test it daily to prove that it's clean."

The lab allows Yale's scientists to create cellular therapies that go far beyond the type familiar to most people—bone marrow transplantation. In that treatment, a cancer patient gets high doses of chemotherapy to destroy the blood-making stem cells in their bone marrow. These cells are replaced by cancer-free bone marrow, either from the patient or from a donor, which is infused back into the patient.

New cellular therapies take a huge leap beyond that. One of the most exciting innovations is to inject a patient with manufactured cells that recognize cancer and supercharge the immune system's response against it. These cells may be from the patient or from someone else. "It's huge," said Dr. Krause, "and it's where the field is now."

While the physical space for the Advanced Cell Therapy Laboratory is new, the team under Dr. Krause has been working at the cutting edge of Cell Therapy and Regenerative Medicine for many years at Yale. At the moment, Dr. Krause's laboratory team is assisting two immunotherapy clinical trials at Yale for metastatic melanoma. Both trials are
invaded into the cancer itself. It turns out that these cells are the most active against the cancer, which makes sense because they're found at their target sites inside the tumor.” The problem occurs when cancer cells overpower these TILs and begin spreading.

The Yale trial will test TIL therapy against metastatic melanoma. First, under absolutely sterile conditions, Dr. Hurwitz’s team will remove the main tumor, which isn’t usually done with metastatic cancer. From there, the highly trained team in the ACT Laboratory will take over. The tumor will be dissected into small bits, and enzymes will be added to break down those bits into what Dr. Krause calls “a single-cell slurry.” The lymphocytes—the immune cells—will be separated from the cancer cells and then put into an incubator, where they will be expanded with help from growth factors.

“We nurse them for about two weeks,” explained Dr. Krause, “and then we rapidly expand them for another two weeks, to get a 6,000-fold expansion. So we're manufacturing the patient’s own immune cells from the patient’s own tumor. Then the clinicians infuse those cells back into the patient immediately following a high dose of chemotherapy to suppress their immune system. The 6,000-fold expansion of the lymphocytes overwhelms any inhibitory effects of the immune system and destroys the cancer. And the patients achieve long-term cures. The process is widely known but not widely performed, because the work is so involved. Only four or five other centers can do it.”

“This is very complex and requires a lot of coordination,” said Mario Sznol, MD, Professor of Medicine (Medical Oncology); Program Leader of the Melanoma Program; and Co-Director of the Yale SPORE in Skin Cancer, which is providing some of the clinical trial’s funding. “It’s impossible to do without people like Diane and without a facility that can generate these cells, and also without having someone like Mike [Hurwitz] interested in being the lead. The lab’s success also depends on Alexey Bersenev, MD, PhD, Technical Director of the ACT Lab and Associate Research Scientist, who’s a world expert in the production of these cells and the expertise of cellular immunologist Marina Komarovskaya. None of it is possible without all of this collaboration.”

Dr. Hurwitz expects to enroll 10 patients in the trial. In addition to demonstrating Yale’s ability to provide TIL therapy, he and Dr. Krause will be looking for ways to improve it, perhaps by enhancing the generation of cells or, once the cells are infused, the conditions inside the patients, perhaps by using drugs to boost the TILs aggressiveness and distribution.

The trial also will open up other avenues of research. For instance, Dr. Hurwitz expects to analyze the removed tumors to see if some are more susceptible to treatment than others. Dr. Kluger also sees many possibilities. “Once the whole operation is running,” she said, “it opens the door for experimental interventions. For example, we can do genetic engineering of the immune cells before we infuse them. We can expand the cells in the petri dish and expose them to cancer cells. We can make new cancer-specific immune cells. The Advanced Cell Therapy Lab provides us a lot of opportunity to be at the cutting edge of immunotherapy for solid tumors and liquid tumors.”

Drs. Hurwitz and Kluger both hope to run clinical trials in the near future that use TILs against kidney cancer. Dr. Hurwitz also mentioned bladder cancer and lung cancer, and added, “And I think the list will grow.”

Dr. Krause is eager to jump into the manufacture of other innovative cell therapies that use dendritic cells, natural killer cells, and lymphocytes expressing chimeric antigen receptors (CARs). Her new lab can handle all of those processes. “We’re just waiting for the opportunity,” she said.

Drs. Hurwitz, Kluger, and Sznol all are certain that such opportunities are around the corner, thanks to the new facility. “Once you have it in place, it’s like Field of Dreams,” said Dr. Sznol. “If you build it, they will come.”