New Center Offers Novel Treatment Options

Cancer patients may now have new treatment options with this year’s opening of the Ravitz Foundation Phase 1 / Translational Research Center.

Type 1 drug trials represent the first step along the path from scientific laboratory to medical clinic. They’re “where science really comes together with the development of clinical medicine,” explains David Smith, MD (below far left), clinical director of the center, which he leads with Moshe Talpaz, MD (below left), associate director of translational research for the University of Michigan Comprehensive Cancer Center.

“What the Ravitz Center is designed to do is allow us to offer patients access to some of the cutting-edge drugs being developed by pharmaceutical companies and new agents developed in U-M Cancer Center laboratories,” adds Dr. Smith.

Such agents include experimental primary targeted therapies as well as new combination treatments with standard chemotherapeutic agents in conjunction with targeted agents. “The drugs which are being—and will be—tested in the phase 1 center include tyrosine kinase inhibitors and inducers and activators of the apoptotic cellular machinery (which lead to cancer cell death),” explains Dr. Talpaz. “We’re also looking at molecules that interfere with proteins involved in cell cycle navigation and in novel inhibitors of cancer stem cells.”

In addition to its four infusion chairs and two beds with ample space for close patient monitoring, the center includes a nearby translational research laboratory that conducts intensive, sophisticated cellular and molecular analyses of how these therapies act within the body. The approach translates to highly personalized care for each patient. Many have advanced disease and have not responded to standard therapies, or no known therapy exists. “These drugs, which are being tested as new in humans, have already been tested extensively in pre-clinical studies, and most have unique mechanisms of actions and may provide hope in desperate situations,” says Dr. Talpaz.

Five phase 1 trials are already underway, and Dr. Smith expects to double the number of patients participating in center studies within the coming year. Those studies will encompass novel agents for both solid tumors and hematologic cancers.

In addition, center investigators are collaborating with the biostatistics department within the School of Public Health on novel trial design methods. Their goal is to more rapidly determine biologically effective as well as maximum safe doses for patients.

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Striking a Balance to Stop Graft Versus Host Disease

Bone marrow transplantation is an effective treatment for—and often curative of—many hematological cancers. That’s due to the graft versus leukemia (GVL) effect, the ability of transplanted donor cells to seek out and destroy cancer cells.

Prior to transplant, clinicians check donors and recipients for histocompatibility, that is, that the donor-recipient pair have the same or very similar gene alleles for human leukocyte antigens (HLA). These receptor proteins help the immune system determine which cells of the body are “self” and which are “other.” In this way, prospective donors and frequently unrelated recipients are “matched.”

But it’s impossible to match all antigens, and even with immunosuppressive drugs, donor cells can go on a rampage against the recipient’s body. That’s desirable when the rampage is against cancer cells, but dangerous when donor cells target other cells and tissues. This response, known as graft versus host disease (GVHD), occurs in chronic form in some 50 to 60 percent of bone marrow transplants between related pairs; it occurs in almost 70 percent of transplants between unrelated pairs. GVHD can cause a range of dangerous complications in many organ systems and can even lead to death.

The crux of bone marrow transplant therapy is to “enhance the GVL effect without triggering GVHD,” says Pavan Reddy, MD (left), associate professor. Dr. Reddy investigates the immunobiology of GVHD—why and how it occurs—primarily in animal models. Recent work published this year in the Journal of Clinical Investigation confirmed some new and important findings in human cells as well.
The work focuses on a group of anti-tumor agents, HDAC inhibitors, which control the expression of several genes and have been used to treat different types of cancer. Experimental studies have shown that HDAC inhibitors also can affect immune responses and have anti-inflammatory properties in doses much lower than those needed for anti-tumor effects.

A few years ago, Dr. Reddy and colleagues found that very low doses of one HDAC inhibitor, suberoylanilide hydroxamic acid (SAHA), altered the function of certain immune cells and reduced inflammation in mice. Using these agents in low doses lessened the severity of GVHD. Since then he and his team have continued their work, trying to understand the mechanisms underlying the beneficial effect. From more recent research, his laboratory has discovered that SAHA and other HDAC inhibitors affect dendritic cells, a type of antigen presenting cell. Antigen presenting cells "tag" foreign cells so that the host immune system can recognize and destroy them. Dendritic cells are the most significant type of antigen presenting cell.

Dr. Reddy’s work has shown that SAHA and other HDAC inhibitors suppress the activity of dendritic cells (below), likely through an enzyme called IDO. As a result, dendritic cells are less capable of activating donor immune system T cells to attack host cells, thereby reducing the GVHD response.

But what about the GVL response? Does inhibiting dendritic cell activity mean a less effective attack on cancer cells? The good news is, “we still found enough donor T cell activity to retain the GVL effects,” Dr. Reddy says. Others have looked at using HDAC inhibitors in mice models of different autoimmune diseases. They’ve found that these drugs can turn down the severity of both lupus and type 1 diabetes, too. In addition, HDAC inhibitors appear able to prolong the life of transplanted solid organs including the heart and kidneys.

In addition to mice models, Dr. Reddy also has looked at the effect of HDAC inhibitors on dendritic cells in healthy human cells in vitro. He is now designing a new study to demonstrate similar effects in patients who are about to undergo a bone marrow transplant. Along with the standard immunotherapy given prior to transplant, some patients will also receive SAHA, which has been shown to be well tolerated. Patients would take the drug for up to 100 days post-transplant as well, the timeframe within which GVHD typically develops. The endpoints of the study will be a lower incidence and severity GVHD. “We’re hoping to see a reduction of about 20 percent or more,” Dr. Reddy says.

This study and other ongoing research will allow Dr. Reddy and his group to gain added insights into the precise molecular mechanisms and specific genes at work. “From an experimental standpoint, it’s exciting to connect the dots,” he says. “From a translational standpoint, we have to restrain our excitement until we have further results. But if the therapy has some anti-GVHD activity, it would be a dream for many patients.”

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