



BUILDING A
CELL BLOCKER

USC Norris scientists lead clinical trial of innovative cancer therapy that stops tumor growth. BY HOPE HAMASHIGE



ONE OF THE CLINICAL TRIALS UNDERWAY AT USC NORRIS IS OF THE HOMEGROWN VARIETY, THE RESULT OF YEARS OF RESEARCH BY ONE OF THE CENTER'S SCIENTISTS, PARKASH GILL, MD, PHD. GILL, PROFESSOR OF MEDICINE IN THE DIVISION OF HEMATOLOGY AND PATHOLOGY AT THE KECK SCHOOL OF MEDICINE OF USC, DEVELOPED AN EXPERIMENTAL TREATMENT FOR PATIENTS WITH A VARIETY OF CANCERS THAT IS BEING TESTED IN A PHASE I CLINICAL TRIAL UNDER THE LEADERSHIP OF ANTHONY EL-KHOUEIRY, MD, DIRECTOR OF THE PHASE I DRUG DEVELOPMENT CLINICAL PROGRAM AT USC NORRIS.

The treatment attacks cancer in multiple ways — by halting the ability of tumor cells to grow the blood vessels they need to strike and later spread cancer, by shutting off some of the pathways that promote growth inside the cancer cell, and by recruiting the immune system to assist in fighting the cancer.

The clinical trial is the result of more than 15 years of research by Gill, holder of the Renette and Marshall Ezralow Family Chair in Cancer Therapeutics, who is one of the few people in the medical field who has extensive experience in both treating patients and in conducting basic research in drug development.

Throughout his career, Gill's research has focused on a process known as angiogenesis, a physiological process through which new blood vessels form. It is also a step in the transition of a tumor from a benign to a malignant state. He has spent years in his laboratory studying key proteins involved in angiogenesis in an attempt to identify the most important contributors to blood vessel development in cancerous tumors.

Gill developed a treatment based on the basic research conducted in his laboratory, which is currently in its second year of a phase I clinical trial at USC Norris. But it was no easy feat. The basic research alone was painstaking, assessing tiny proteins to learn if they played key roles in angiogenesis and how they interacted with other proteins to try to find the interactions that seemed most critical to spark angiogenesis in cancer.

Over time, Gill and the research team in his laboratory have made many important discoveries that have illuminated the process of angiogenesis. They identified proteins that played roles in inhibiting angiogenesis and even engineered a recombinant protein to selectively kill newly forming blood vessels as well as tumor cells.

More than a dozen years ago, he honed in on one particular protein called EphB4, which is a receptor protein that sits on the surface of tumor cells. They later uncovered that EphB4 is present on many types of tumors, it is expressed from the very first stage of cancer formation and that it sends signals for more blood vessels to grow.

Many proteins interacted with EphB4 and after studying the relationship between EphB4 and several of those proteins, Gill learned that it was the interaction between EphB4 and another protein, Ephrin-B2, that played a critical role in the development of blood vessel growth in cancer. They developed a protein to block the interaction between EphB4 and Ephrin-B2 that they hoped might inhibit the growth and spread of cancer.

That protein, called sEphB4-HSA, appeared in laboratory tests to prevent tumor cells from multiplying and blocked several compounds that promoted the growth of blood vessels that bring nutrients to the tumor. It was later tested in mice and shown to shrink colon, lung, breast, glioma, melanoma, prostate and Kaposi's sarcoma tumors.

Some treatments that work on mice do not work at all on humans, explains El-Khoueiry, associate professor of medicine in the Division of Medical Oncology at the Keck School, and so while the team at USC Norris wanted to push Gill's research to the next phase, there was no guarantee it was going to be effective in humans.

Two years into the clinical trial of sEphB4-HSA, which is being overseen by El-Khoueiry, the results are encouraging.

For one thing, the treatment appears to be safe for use in humans and it is easily administered and remains stable once it is given to patients. It also appears to be living up to its promise of inhibiting tumor growth in patients with a variety of tumor types. "We have had patients whose tumors progressed on chemotherapy and then go on the treatment and it stops growing," reports El-Khoueiry. "There have been actual shrinkages that we can measure and that is rare."

At present, the drug is being tested on patients with non-small cell lung cancer, pancreatic cancer, colorectal cancer, head and neck cancer, mesothelioma, hepatocellular carcinoma and gallbladder cancer. There are plans to begin studying the drug in a subtype of leukemia and also in combination with chemotherapy.

"We don't want to get ahead of ourselves and be unfairly biased, but we have seen some really exciting signals," says El-Khoueiry.