ON THE FRONT LINES of battle

The photograph of a single chromosome that hung on a wall at the Los Alamos National Laboratory captivated Kevin Pruitt's attention. One particular gene on this chromosome, he learned, had the ability to repair damaged DNA. The concept fascinated Pruitt and became the game changer in his career.

It was the summer of 1994, and Pruitt was at Los Alamos for an undergraduate research internship. The experience, he said, radically changed his career trajectory from chemical engineering to biomedical science. "I discovered that, for me, engineering was a challenging and safe career choice, but personally not intriguing.

"The idea of becoming a biomedical research scientist, on the other hand, was an allure that could not be resisted because you get to peer into what is hidden and, in most cases, open that up and study it; and then when you see a connection between two things no one has described before, it's just absolutely fascinating."

Pruitt now leads a team of researchers in the School of Medicine Department of Immunology and Molecular Microbiology. They investigate molecular pathways that contribute to tumor growth and look for novel therapies to stop it. Their research is grounded in epigenetics—an area Pruitt studied initially toward the end of his Ph.D. studies at the University of North Carolina at Chapel Hill and continued during his postdoctoral studies at Johns Hopkins University School of Medicine. This line of investigation was continued later at Louisiana State University Health Sciences Center-Shreveport, where he established his first lab.

Cancer epigenetics is the research of the future, Pruitt said, "Advances in this field are now bringing to light concepts that were really only glimpsed in the previous decade. For example, the causes of cancer have become clearer now that we realize that there are both genetic and epigenetic alterations contributing to the etiology."

BY DANETTE BAKER | PHOTOS BY NEAL HINNKLE

PRUITT LEADS RESEARCH TEAM EYEING BIOLOGICAL MECHANISM TO COMBAT CANCER GROWTH

Epigenetics, in simplified terms, is the study of biological mechanism(s) that cause the thousands of genes in every cell in your body to switch on and off. Even if cells in the human body have the same genome, depending on the organ in which the cell resides, they do not express the same genes, which is a good thing, Pruitt said. A distinct pattern of gene expression is what makes tissues, organs, and ultimately, each of us unique.

The process of controlling gene expression, however, doesn't always occur as it should. For example, small modifications to DNA, known as DNA methylation, can control which genes get expressed. In cancer, this DNA modification may be acquired by genes where it shouldn't. This mark can then serve as a docking site for proteins that bind to them and inappropriately turn off the gene even though the genetic sequence is normal.

By identifying how cancer alters those marks, Pruitt said, they can then use a variety of therapies—molecular inhibitors or other medications known to have anticancer properties—to counteract them.

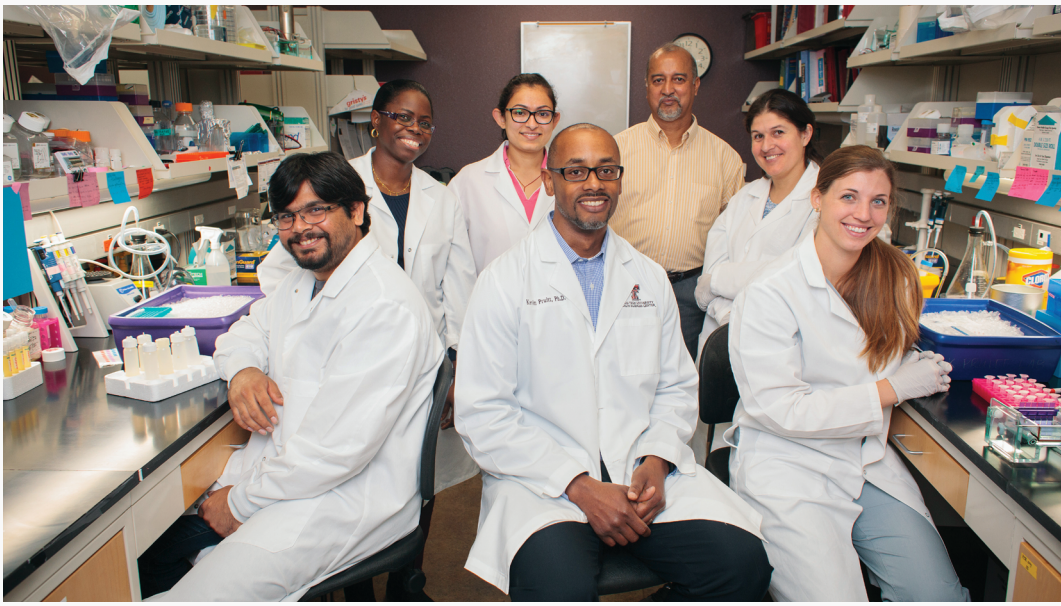
Success stories from this work have produced clinical therapies that reverse DNA methylation and thereby enable the expression of diverse genes that suppress tumor growth. However, continued investigation is important because many therapies don't just target rogue cancer cells; they affect the normal ones as well.

"One of our newest research projects aims to understand how epigenetic therapies impact the body's immune system which is the ultimate way to fight cancer. If epigenetic therapies can help cancer cells become less resistant to the defense of the body's immune system and become subject to apoptosis, or programmed cell death, while not harming the normal cells, this would be a major breakthrough."

In addition to DNA methylation, Pruitt's team also studies epigenetic enzymes, whose role is to modify histone proteins. These histone proteins help package the immense quantity of DNA into the cell, similar to how wrapping paper is packaged on its cardboard tube. These histone proteins, however, can be modified, causing that neatly wrapped roll to look more like the discarded wrapping paper on Christmas morning.

"When a cell tries to turn on a gene that blocks its ability to invade surrounding tissue, when it should stay put, depending on the nature of the packaging or wrapping of this gene, it may or may not adhere to cellular instructions. The packaging of DNA, which is controlled by DNA methylation and histones marks, will either enable or disable the cell to respond to growth control cues. If the "wrapping" of the DNA is all wrong, certain tumor suppressor genes may be turned off incorrectly, and the cell will be deaf to the signals that tell it to halt its growth."

Pruitt's work in cancer epigenetics took on a new meaning when his mother died from breast cancer around the time he was establishing his lab at LSU. "Purely from a scientific standpoint, you can't help but be intrigued by something that defies all kinds of normal biological controls," Pruitt said. "My mom was diagnosed with cancer when I was in graduate school, and she put up a good fight for a while, so when you experience something like that, you become even more devoted to understanding the molecular basis of cancer," Pruitt said. Other family members including his father and brother also died from cancer.



Researchers working with Kevin Pruitt, PhD, are, from left: David Vartak, research assistant; Deborah Molehin and Monica Sharma, research technicians; Pulak Manna, research associate professor; Isabel Castro-Piedras, PhD, postdoc research associate; and Megan Waterman, research technician.

TTUHSC President Tedd L. Mitchell, MD; Wendy Pruitt, PhD; Kevin Pruitt, PhD, associate professor of immunology and molecular microbiology; Celeste and Joe Fralick, donors; and Steven L. Berk, TTUHSC vice president and provost and School of Medicine dean

It's a story that could be told by many, and one Celeste and Joe Fralick know all too well. She is a survivor of stage 4 breast cancer; her mother and her cousin, Diane Childers, died from cancer, lung and breast, respectively. In fact, almost 40 percent of all men and women in the U.S. will be diagnosed with cancer at some point during their lifetimes, according to data published by the National Cancer Institute.

The Fralicks are scientists—she has a PhD in biomedical engineering, and he is a professor of immunology and molecular microbiology—and know the invaluable role of research in medical maladies. They wanted to honor Childers' desire for her trust bequest to support cancer research and chose TTUHSC at which to establish an endowed chair position in cancer research. Pruitt was named to the position. (Read more about the Childers-Fralick Basic Cancer Research Endowed Chair on Page 4 of this issue).

"Celeste and Joe gave us a choice to recruit someone new or find someone within the institution to hold the chair position. When they described their ideal candidate, Kevin immediately came to mind," said Matthew Grisham, PhD, chair of the Department of Immunology and Molecular Biology. "They said the investigator should be a rising star, someone whose career was continuing to progress in leaps and bounds.

"Their hope was through his or her investigations, the possibility of new drug therapies for the treatment of these devastating disorders could greatly be increased."

Pruitt has received numerous research awards during his career, some of which include the Hoechst-Celanese Corporation Research Scholarship Award, Graduate School Excellence Award, American Association for Cancer Research Scholar in Training Award, National Science Foundation pre-doctoral fellowship and American Cancer Society postdoctoral fellowship.

His lab, supported by National Institutes of Health R01 funding, is focused on out-of-the-box approaches to finding novel therapies for treating cancer. In fact, the Cancer Prevention Research Institute of Texas (CPRIT) recognized his work with the Rising Star Award, as part of a recruitment effort for Pruitt to relocate his lab to TTUHSC in 2014. When Pruitt, a native Texan, was presented with the opportunity to return to his home state, he was thrilled.

Pruitt said he is honored to hold the newly endowed chair position. Having the Fralick's generous support, he said, allows for the aggressive investigation toward significant, novel discoveries and allows his team to generate preliminary data that can then be used to submit for larger extramural grants, such as from the National Institutes of Health or Department of Defense.

Currently, Pruitt's team has multiple investigations, primarily focused on breast and colon cancers, each with ties to cancer epigenetics. They are studying the overproduction of estrogen within tumors and have gathered evidence of surprising ways breast cancer cells increase estrogen production using a mechanism typically employed by the placenta. "This means of estrogen production should only be activated by the placenta during pregnancy, but we are deciphering how tumor cells gain the capacity to ramp up estrogen production in this unexpected way," Pruitt said. "It's like you have a combination that should only work on one lock, yet to your surprise you find it works on several others as well.

"We have some really cool insights that might be causing this. Once those factors are identified, some of them will be druggable targets, amenable to therapy. This is one of our newest, most exciting findings that we think will make a major impact on cancer treatment."

Members of Pruitt's lab also study a specific protein that impacts the epigenetic function when physiological stresses attack cells and the role this protein plays in the immune system's signaling structure to sustain cell growth or initiate cell death.

Information uncovered in each study, Pruitt said, has the potential to provide targeted novel therapies for treating cancer with increased responses and fewer negative side effects.

"The studies are all novel, cutting edge and hopefully we think we are going to make a nice splash both in scientific terms of new discoveries but also from a translational standpoint in at least laying the foundations for what might be new strategies to combat cancer resistance or some type of clinical relevance."