KUMC student's research may lead to understanding of colorectal cancer

Anand Venugopal's study of cancer stem cells catches the NIH's attention.

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Even as a kid, Anand Venugopal was at home in the laboratory, and a regular fixture at his mother's plant biology research group meetings. He especially liked helping her mash up leafy samples with a mortar and pestle, since the task involved liquid nitrogen — which gives off that icy, smoke-like vapor even grownups find fascinating.

Now in his fourth year of the MD-PhD program at the University of Kansas School of Medicine, Venugopal manages his own laboratory research project, one that recently attracted federal funding through an F30 fellowship grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This grant category is exclusively for MD-PhD students, and Venugopal's is the first for KUMC. It represents national-level endorsement of the school's young MD-PhD program and its training capabilities in translational, bench-to-bedside science.

Venugopal's research spotlights colorectal cancer, the second most common cause of cancer-related deaths nationwide. The colon consists of a series of crypts, or pockets, each containing a few adult stem cells that can divide to regenerate the colon's lining. "The thinking is that in cancer, similar populations of stem cells exist, with many of the same properties," Venugopal explains. These cancer stem cells are a select but critical group capable of endlessly replacing themselves and forming other tumor cell types.

"Because adult stem cells are important for the self-renewal of tissues, they're naturally protected from insults like chemotherapy and radiation," Venugopal adds. "So cancer stem cells, being similarly protected, are really tough to treat."

While the scientific community has largely caught on to the notion of cancer stem cells, a precise definition remains elusive. Some scientists think tumors originate from these cells; others describe

them as specialized cells that help maintain tumors.

"The important thing is that they exist," Venugopal says, "We need to figure out how to selectively target these cells so they're eliminated, or at least neutralized. This would help reduce disease recurrence, one of the biggest challenges in cancer."

Venugopal's work will build on that of his mentor, Shrikant Anant, PhD, associate director of cancer prevention and control at The University of Kansas Cancer Center. Anant's research group previously uncovered a possible link between a protein called RBM3 and stem-like characteristics in several types of solid tumors, including colorectal cancer. Exactly how RBM3 works is unclear, although it likely involves cross-talk between this protein and one named Notch, which directs signals guiding the self-renewal of cells all along the gastrointestinal tract.

With this newly funded grant, Venugopal plans to eavesdrop on the conversation between RBM3 and Notch, to better understand how RBM3 confers or enhances "stemness." He can readily distinguish between normal and stem-like cells in the laboratory; the latter have the ability to grow into round clumps, or spheroids — balls of cells resembling pinheads, and visible to the naked eye. They also express another protein, DCLK1, well-established as a marker of "stemness." And they're remarkably resilient when zapped with 12 Gray of radiation — what Venugopal's mentor Anant calls "crazy levels," far higher than any cancer patient would ever receive. Illuminating the vagaries of stem cells' ability to resist radiation may eventually help scientists predict the outcomes of treating specific tumor types with radiation.

In addition, a class of drugs called gamma-secretase inhibitors — tested as potential treatments for Alzheimer's disease, albeit with mostly dismal results — could gain fresh purpose. These drugs, says Venugopal, selectively target the Notch pathway and could hit aggressive tumors with out-of-whack RBM3 levels and stem-like properties. First, though, he'd like to better understand the biology of these proteins, and transcribe what he can of their ongoing chatter.

"We were looking for a single magic bullet when we declared war against cancer some 40 years ago, but we're never going to find one," Anant remarks. He often compares cancer to a beehive, with cancer stem cells analogous to the queen bee. "For most of this time, we've been going after the worker bees," he elaborates. "But the hive will collapse only if the queen is destroyed; otherwise she'll simply repopulate her colony." In other words, getting to the root of cancer will likely involve two sets of treatments: classic chemotherapy to shrink most of a tumor, and new therapies aimed at cancer stem cells. Venugopal's task — helping to clarify how and why cancer stem cells do what they do — is crucial.

Both Anant and Venugopal are careful to emphasize that there are different types of stem cells, given some of the public's visceral reaction against research involving those from embryos. "I explain that adult stem cells can't be used to create another living being; they're already differentiated," Anant

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says. "As for cancer stem cells, they can make people die. This usually gets the public's attention."

Given that cancer stem cells are probably as diverse as cancer itself, "it's very apparent, at least to me, that personalized medicine is the only way to a cure," Venugopal says. "Out of 100 different signaling pathways in any given cell, it might take just 10 pathways running amok to cause cancer, but what are the chances that every patient has the same 10 taken out of commission? Or that they'll all respond to the same molecule or drug targeting those pathways?"

"This is why the concept of a magic bullet has failed," Anant adds. "We really need to take the variability within patient populations into account. The pharmaceutical industry has some big adjustments to make. It's hardly useful treating thousands of people with one drug and having just a fraction respond."

Venugopal credits team effort — his mentor, and his laboratory colleagues — for his successful grant application. "I don't think this has set me apart in any distinctive way," he says. "The data everyone else contributed were so much more significant."

"It's why he'll be a star someday," Anant says. "Because he's not only smart, with a real love for the academic enterprise — he also knows that research takes a village, and he gives credit where it's due."

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