Heart of the Matter

Prototype drug targets cell's nucleus to stop heart failure

by Kate Rein

A master of multi-tasking, professor, cardiologist and researcher Saptarsi M. Haldar, MD, can start a conversation about his research, leave to address alerts from his beeper about his patients in the cardiac intensive care unit, and minutes later return to the sentence where he left off. Hearing him list disease stats can quicken your pulse.

But what really energizes Haldar is discussing heart failure, which he and many other medical professionals deem one of the greatest medical challenges for the 21st century.

"Heart failure is a big, big problem and is very, very common. About 6 million Americans have it—500,000 new diagnoses each year," said Haldar, assistant professor of medicine at Case Western Reserve University School of Medicine and cardiologist at University Hospitals Case Medical Center. "Despite current standards of care, patients have only a 50 percent chance of being alive five years after diagnosis. That's worse than a lot of cancers. It is imperative that we do better."

Heart transplants are a "boutique" practice, he said, serving only a tiny fraction of patients. That's why Haldar has spent the past decade pursuing the discovery of new heart failure drugs.

Currently used medications work on the outer surface of heart cells, defending them from harmful hormones such as adrenaline. But Haldar and other researchers suspect that the best offense could happen inside a cell's nucleus, its "command center." The nucleus, which holds a cell's DNA, can tell a healthy heart cell to morph into a sick heart cell. If researchers could only find a drug to reach the nucleus and stop that deadly conversion…

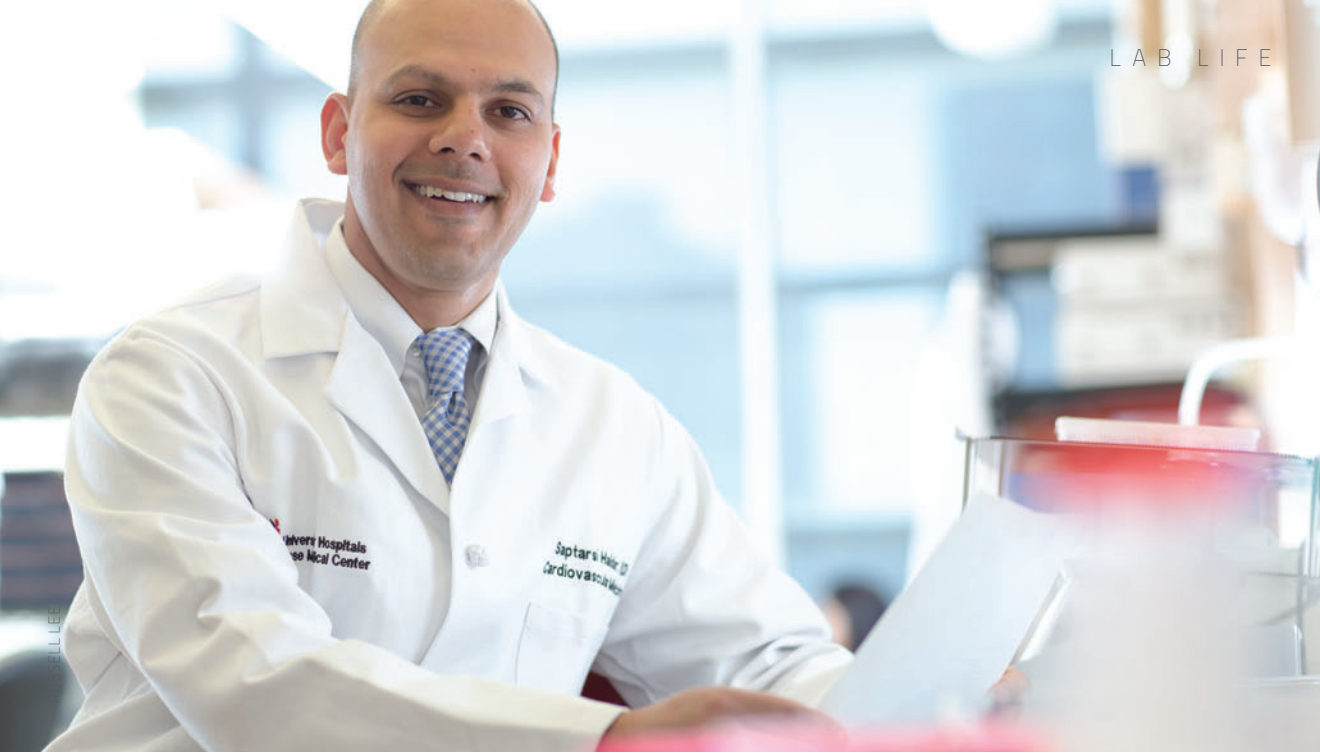
Reprogramming the Nucleus

That's what Haldar was discussing with his good friend Jonathan Brown, MD, cardiologist and physician-scientist at Brigham and Women's Hospital in Boston. They'd met as medical students in 1998 during a research fellowship.

"We were both at a scientific meeting in Washington, D.C., in 2010, and we were out having a beer one evening," remembered Haldar. "We started talking about an exciting paper that had just been published in *Nature* by our mutual colleague Dr. James Bradner, and the light bulb went on."

James Bradner, MD, an oncologist and researcher at Dana-Farber Cancer Institute, had trained with Haldar and Brown at Brigham and Women's Hospital in the early 2000s. He had helped discover that a family of genes, BET bromodomains, drove some common cancers. Then he invented a prototype drug, JQ1, that could turn off these cancer-causing genes. It was a landmark innovation—a drug that could reprogram a cell's nucleus and potentially stop cancer progression.

"We wondered if the same nuclear events triggering cancer could also be triggering heart failure," said Haldar. "I got back to Cleveland from that meeting on a Sunday night and immediately emailed Bradner. He FedExed me a sample of JQ1 right away and we have been closely collaborating ever since."



Stopping Heart Disease in its Tracks

It started off as a fun side project, he said. During a summer research program funded by the Case Western Reserve School of Medicine dean's office, two first-year medical students, Kareem Alazem and Jace Bullard, studied the effect of JQ1 on heart cells in a petri dish. The results were promising. Next, Haldar's lab tried JQ1 on mice that had classic features of human heart failure, including enlarged hearts and poor pumping function.

For four weeks, research scientist Priti Anand tracked two groups of mice, one in which she injected a daily solution of JQ1 and one in which she injected a placebo. Each week she checked their heart function by a cardiac ultrasound (echocardiogram) and recorded the findings. At the end of the study, she harvested the hearts and compared them visually.

"I still remember that day," says Anand. "We expected the results to be good because we were tracking them by ultrasound, but when we actually saw the hearts, we knew we had found something big. We were telling everyone in nearby labs. Everyone was excited."

The hearts of mice that received JQ1 weren't as enlarged and diseased as those that received placebo. Some looked completely healthy. According to the echocardiograms, the hearts of mice in the JQ1 group had been pumping 60 percent stronger by the end of the study.

"This was one of the most striking findings in my career," says Haldar. "We couldn't believe the test had worked so well."

JQ1 had stopped heart disease in its tracks.

More to Learn

Today, Haldar's team is actively investigating if the drug also can reverse heart damage. Additional laboratory studies will be underway and will hopefully pave the way for human trials.

There's more to learn about the potential toxicity of JQ1-like drugs in humans and for what clinical scenarios they'd be appropriate. However, information will be coming quickly as Bradner forges ahead, studying the effect of JQ1-like drugs in cancer.

"Lots will depend on what we see in the early-phase cancer trials. But if they look promising, we may be developing new applications for human heart disease within five years," predicts Haldar.

That should keep his lab buzzing.

"We have a collaborative, engaging environment where we work together to crack tough problems in human health," he said. "I'm enthusiastic about our research, and I hope the excitement is contagious."

Researchers like Haldar are exploring potential heart failure treatments that target the nucleus of a heart cell, rather than working on the cell's outer surface like current medications. Haldar cites the Case Cardiovascular Research Institute (CVRI) and the Harrington Heart & Vascular Institute (HHVI) as the primary organizations supporting this important research.