Dr. Jain and his research colleagues at Mass General’s Steele Lab have investigated the causes and consequences of abnormalities in tumor vessels with the ultimate goal of finding ways to repair them so that drugs to eliminate them can be delivered more effectively.

Rakesh K. Jain, PhD, director of Mass General’s Edwin L. Steele Laboratory for Tumor Biology and the A. Werk Cook Professor at Harvard Medical School.

RAKESH K. JAIN, PHD, HAS MADE GROUNDBREAKING DISCOVERIES ABOUT CANCER TUMORS THAT UNDERSCORE THE POWER AND PROMISE OF BASIC RESEARCH.

Early in the pursuit of groundbreaking research, encouragement can be hard to find. Just ask Rakesh K. Jain, PhD, director of Mass General’s Edwin L. Steele Laboratory for Tumor Biology and the A. Werk Cook Professor at Harvard Medical School. At the start of his career, he faced the same struggle to find research funding as many young cancer researchers. Moreover, he was a chemical engineer, not a biologist or a medical doctor, and some of his novel ideas about tumors flew in the face of the prevailing wisdom of the time.

Yet today, Dr. Jain is recognized as one of the pioneers of his field. His research has transformed the current understanding of the inner workings of tumors and their treatment, provided key insights into other diseases and inspired numerous scientists to pursue significant cancer research of their own.

Dr. Jain’s career offers a powerful example of how today’s medical breakthroughs are often deeply rooted in basic research that might have once seemed too abstract or theoretical to matter. His success also reflects Mass General’s reputation for attracting and nurturing innovative researchers and supporting their efforts to translate laboratory findings into new treatments that can save and improve the lives of patients with cancer, diabetes, cardiovascular disease and other maladies.

Indeed, over the course of nearly four decades of research, Dr. Jain has published 580 scientific papers that have been cited more than 56,000 times. He is the only Mass General faculty member ever elected to the National Academy of Sciences, the National Academy of Engineering and the Institute of Medicine. In 2012, the American Society of Clinical Oncology — the largest professional organization of cancer doctors — awarded Dr. Jain its Science of Oncology Award in recognition of his contributions to the field.

During more than two decades at the helm of the Steele Laboratory, Dr. Jain has also served as a mentor to nearly 200 doctoral and postdoctoral students, many of whom have become leaders in academia, government and industry.

Pursuing New Ideas Passionately

Biologist Dan G. Duda, DMD, PhD, has been a Steele Lab colleague ever since Dr. Jain was his postdoctoral advisor more than a dozen years ago. Also an associate professor at Harvard Medical School, Dr. Duda admires Dr. Jain’s continued passion for research after nearly four decades in the field. “He continues to generate new and innovative ideas and pursues them passionately,” Dr. Duda marvels. “Especially in an environment like Harvard, the expectations are very high. He continues to be a star here after 22 years.”

Melody Swartz, PhD, is the director of the Institute of Bioengineering at the Swiss Federal Institute of Lausanne, as well as a professor there. She is also head of its Laboratory of Lymphatic and Cancer Bioengineering. A 2012 recipient of the prestigious MacArthur Foundation Fellowship, Dr. Swartz attributes much of her own success to the mentorship she has received from Dr. Jain while she was earning her doctoral degree in chemical engineering.
from the Massachusetts Institute of Technology. “His lab was, and continues to be, truly unique,” Dr. Swartz says. “I have always been very inspired by his ability to bring together different types of scientists and clinicians to think about problems in totally new ways.”

Massachusetts General Hospital is an exceptional place where scientists who explore the mechanics of disease on the cellular level can collaborate with physicians who treat patients every day. Ideas flow freely, resulting in patients gaining access to cutting-edge therapies and receiving care backed by rigorous research. Mass General has a long list of medical discoveries and firsts, including the first public demonstration of ether as general anesthesia and the first use of X-rays in the United States.

Mass General receives more research funding from the National Institutes of Health than any other independent U.S. hospital.

Revolutionary Ideas from Unlikely Sources

But in recent years, continued cuts in federal research funding have made it necessary for Mass General to rely more heavily on charitable giving to support such research. Launched in 2011, the MGH Research Scholars Program was designed to signal Mass General’s determination to support extraordinary MGH scientists who are deemed likely to make transformative advances in scientific thinking and medical practices. Funded by charitable gifts, the program provides recipients with five years of support at $100,000 per year.

Such programs have a pressing need for philanthropic donors with a long-term view. For example, cancer research was not part of the early medical faculties of Columbia University and the University of Pennsylvania. But in the 1970s, after cancer research was added to the curriculum, it began to receive more funding, and many medical schools now have a strong cancer research program.

In the pursuit of game-changing medicine, failures far outnumber successes. Even for ideas that show great promise, the path forward is seldom straightforward or quick. One small lab finding leads to another and an observation along the way can steer the work in an unconventional direction. Sometimes, the most revolutionary ideas come from the least likely sources.

For example, cancer research was not part of Dr. Jain’s personal plan when he came to this country from India in 1972. For his masters’ thesis in chemical engineering at the University of Delaware, he used mathematics to model the flow of pollutants in the Delaware River.

Dr. Jain’s academic pursuits might have continued in the same vein if his PhD advisor, James Wei, PhD, had not introduced him to the late Pietro M. Gullino, MD, a distinguished cancer researcher at the National Cancer Institute. They were working on flow issues of a different sort, namely how the course of drugs injected into cancer patients kills tumors. How was it, they wondered, that powerful chemotherapy drugs could often pass through a tumor without having a substantial impact on the malignancy?

Dr. Jain pursued his cancer research while serving on the chemical engineering faculties of Columbia University and Carnegie Mellon University. As the years passed, Dr. Jain’s engineering focus spawned a series of findings that cumulatively began to reshape scientists’ understanding of how tumors survive and grow in the body. After discovering that solid tumors had high fluid pressure inside, Dr. Jain and his colleagues began searching for the reason. They learned that, as tumors grow, the blood vessels inside them grow increasingly disorganized and leaky. That means the flow of oxygen and nutrients through them is less efficient than in normal tissue. Coupled with the resulting high pressure outside the blood vessels, the chaotic vasculature also hinders the efficient and effective delivery of drugs designed to kill the tumor.

“You can’t say the component of a tumor is abnormal,” says Dr. Jain, who began to think about
WITH FUNDING AND ENCOURAGEMENT FROM THE NATIONAL CANCER INSTITUTE, OTHER INSTITUTIONS HAVE EMBRACED THE SORT OF SCIENTIFIC COLLABORATION BETWEEN ENGINEERS AND CANCER RESEARCHERS PIONEERED BY THE STEELE LAB.

opportunistic ways to repair or “normalize” the tumors’ blood vessels to make it easier to deliver a more definitive knockout punch with drugs.

The 1990s saw increasing discussion among cancer researchers about “antiangiogenic” drugs, which block the formation of blood vessels, as a potent new weapon. Early on, many scientists believed such drugs could single-handedly choke a tumor to death by cutting off its blood supply and thereby eliminating its source of oxygen.

Dr. Jain saw some flaws in that logic. The doses probably needed to eliminate a tumor completely could damage healthy tissue, particularly in a patient’s cardiovascular system. And given the tumor’s nonuniform circulatory system, there was the question of whether, on its own, the antiangiogenic drugs could be counted upon to kill all cancer cells. If that didn’t happen, he reasoned, the malignancy might flare up again with renewed intensity.

Today, the Steele Lab’s 80 scientists and support staff — including four associate professors — are taking a different approach. Instead of simply cutting off blood vessels, their team has tested the process of “opportunistic ways to repair or normalize some of the tumor’s leaky blood vessels, lowering the fluid pressure outside the blood vessel and making it easier to deliver oxygen and various treatments.”

The lab was established in 1975 through a gift from the late Jane Bancroft Steele Cook. Named in honor of her husband, Edwin L. Steele, the lab continues to receive generous support from the Steele family. The lab is devoted to charting the functional changes that cancer causes in the human body and finding ways to prevent or reverse them.

With funding and encouragement from the National Cancer Institute, other institutions have embraced the sort of scientific collaboration between engineers and cancer researchers pioneered by the Steele Lab.

In recent years, Johns Hopkins, Princeton, Stanford and the Massachusetts Institute of Technology are among those that have launched programs to combine the principles of engineering with oncology research.

A Key Change in Blood Vessels

Today, the Steele Lab’s 80 scientists and support staff — including four associate professors and four assistant professors — have expertise in a dozen different disciplines, including engineering, physics, genetics, molecular biology, immunology, and radiation-, medical-, neuro-, pediatric- and surgical oncology. This array of specialties allows laboratory discoveries to undergo clinical tests more quickly than they might elsewhere. “We are very fortunate to have the convergence of so many different disciplines and people that enables rapid translation of our discoveries from bench to bedside,” Dr. Jain says.

That convergence proved pivotal in the Steele Lab’s work on the antiangiogenic drugs. Dr. Jain and his researchers pursued the issue on multiple fronts. In laboratory tests, they found that, after initially shrinking, tumors in mice treated with the antiangiogenesis drugs eventually began to grow again. On their own as a cancer treatment, the antiangiogenesis drugs did not seem to be the magic bullet some had hoped.

But subsequent tests with mice and cancer patients revealed another curious phenomenon: although some blood vessels inside the tumor were indeed destroyed by the new treatment, those that survived functioned more normally. In effect, the antiangiogenic drugs actually repaired or “normalized” some of the tumor’s leaky blood vessels, lowering the fluid pressure outside the blood vessel and making it easier to deliver oxygen and various treatments.

“This discovery had implications for almost every tumor type and every type of treatment — chemotherapy, radiation, immunotherapy,” Dr. Jain says, noting that their team has tested the process of normalizing tumor vessels with antiangiogenic drugs in more than 20 human trials in the last decade. Some of the results have been remarkable. For instance, in two trials involving patients with a particularly aggressive type of brain tumor, those whose tumor blood flow and oxygenation increased — due to vascular normalization by antiangiogenic drugs — lived up to six to nine months longer than those whose blood flow did not increase.

These days, Dr. Jain is focused on why the blood flow increases in certain patients and not in others. Is it something in their blood that could be measured ahead of time so that doctors could better personalize cancer treatments and extend survival times?

The research for answers is aided by innovations developed by the Steele Lab’s own researchers. They include special microscopes that produce 3-D images of tissue in living lab animals and tiny window-like devices that, when implanted in mice, allow researchers to see cancer cells in action.

Meanwhile, the research itself has branched off in new directions, including using stem cells to engineer blood vessels that could be used to treat certain types of vascular disease. Dr. Jain says he is sometimes disheartened by concerns that cuts in federal research funding will impede progress toward getting important new therapies from laboratories like his to the bedside of patients. But the scientist doesn’t allow himself to dwell on such negatives for long.

“The excitement of discovery is so profound,” he says “But more importantly, I hope our work makes a difference for cancer patients.”

To learn how to support research at Mass General Hospital, please contact Deborah Farr at dfarr@partners.org or (617) 726-0839. For information about supporting research at the Massachusetts General Hospital Cancer Center, contact Sara Kelly at (617) 643-0410 or skelly14@partners.org.