



Sangeeta
Bhatia

Photo by Flynn Larsen

THE MULTIMODAL INVENTOR

Sangeeta Bhatia has harnessed an enduring fascination with getting synthetic things to infiltrate and talk to tissues to devise new approaches to diagnosing and treating cancer.

Ludwig MIT investigator Sangeeta Bhatia was only in high school when she decided to become a bioengineer. But it wasn't until her junior year at Brown University, during an internship in the laboratory of the prominent tissue engineer Patrick Aebischer, that she figured out what exactly she would do with that expertise.

Bhatia was trying to accelerate nerve regeneration by guiding growing nerves to muscles with an electromagnetic field induced by piezoelectric materials, which generate a current when deformed. "I was fascinated by the work," she recalls. "It was the perfect marriage of engineering and cell biology, and it was applied science, but it had some pretty fundamental interdisciplinary pieces. I realized I was interested in getting materials to talk to cells, and to do it in a way that would help patients."

And that is precisely what Bhatia—bioengineer, inventor, physician, cancer researcher, entrepreneur—has been doing in one way or another ever since, contributing significantly to fields ranging from infectious disease to tissue engineering to cancer research and care. In that last category, Bhatia published a study in *Nano Letters* in 2016 describing injectable nanosensors for profiling colon tumors that are activated by targeted magnetic fields and provide a read-out in a simple urine test. In another

paper, published in *Nature*, her team and their longtime collaborators at the University of California, San Diego, reported how they engineered bacteria that, when fed to mice, made their way to liver tumors and produced three distinct molecules in consistently timed pulses to help destroy the malignancies.

DOING IT ALL

Bhatia's parents immigrated out of what is now Pakistan during the 1947 partition of India and met in Mumbai. Her father had just received his engineering degree, and her mother was among the first women in India to obtain an MBA. The couple immigrated once again in the 1960s, this time to the US, where Bhatia's father, a budding entrepreneur, had been accepted into an MBA program. They eventually moved to Boston, where they started a business together importing metallurgical components, boat parts and the like. "I was born in Brigham and Women's Hospital, which is kind of funny because I'm on the faculty there now," says Bhatia. "I've come full circle."

After obtaining her engineering degree at Brown and taking a gap year doing drug formulations at a pharmaceutical company, Bhatia got her PhD from the Harvard-MIT Health Sciences and Technology (HST) program, where she now teaches. "I remember I had to sit my dad down and break it to him that I was going to graduate school,"



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she recalls. “He was, like, ‘oh, ok, when are you going to start a company?’” He would not be disappointed. Over the years, Bhatia has put her name on more than two score patents, and collectively, she and her trainees have launched ten startup companies.

The HST program required its engineering students to take a full year of classes at Harvard Medical School. Bhatia, who says she “fell in love with the human body”, decided to stick around for a second year. Meanwhile, her PhD training was proceeding apace in the laboratory of Mehmet Toner, a biomedical engineer at Massachusetts General Hospital who was trying to do for liver disease what dialysis had done for ailing kidneys.

After obtaining her PhD, pioneering the use of microchip fabrication tools to grow liver tissue on a chip, Bhatia took a faculty position at the University of California, San Diego, completing her medical schooling as she set up her new lab (her MD is from Harvard). Her schedule was grueling, but she was

having fun. “Within a year I realized this was the perfect place for me,” she says. “I loved academia, loved idea creation and training young minds.”

MATERIAL CONCERNS

Bhatia pressed ahead with her work on liver tissue engineering at UCSD. “That had been my window into how cells communicate with materials,” she says. “We were going to use these tiny tools to make materials that pattern and organize cells and interact with them.” But the field was changing. Around the turn of the century, it became possible to make remarkably small and smart materials. “I got really excited about moving from the microscale, where we could build tissues, to the nanoscale, where we could make materials that could enter tissues,” she says. Bhatia started a group in her lab to investigate nanotechnology applications for cancer, and began a collaboration with the cancer researcher Erkki Ruoslahti of the University of California, Santa Barbara, who she says shepherded her into tumor biology.

The pair worked together to devise targeted nano-probes for medical imaging.

Bhatia also got promoted and had the first of her two daughters in San Diego. In 2005, looking to live closer to family, she and her husband Jagesh Shah, who was at the time affiliated with the laboratory of Ludwig San Diego’s Don Cleveland, moved to the Boston area. (Shah, an electrical engineer by training, is an associate professor of systems biology at Harvard.)

Bhatia’s tissue engineering has since progressed from success to success. Her lab’s human “microlivers”—miniature representatives of the organ suited to basic scientific and pharmacologic research—have been put to work to explore the pathology of malaria and Hepatitis C, and implanted successfully in mice. A biotech company launched by Bhatia already sells the technology to scores of pharmaceutical companies, which use it to analyze the metabolic processing and toxicity of experimental drugs.

Her lab at the Ludwig Center at MIT has, meanwhile, branched out in multiple directions. Her graduate students are all engineers because, she says, she understands how to direct their doctoral training. “But the postdocs are very diverse, and deliberately so,” she says. “We have chemists, physicists, allergists, developmental biologists, and we have some engineers.” The engineers are warned they’ll have to get their hands dirty. “It’s great if you can derive elegant systems of equations on the board,” she explains. “But if you come to our lab, you should know that we’re going to push everything *in vivo*. You have to be willing to apply that thinking in a translational way.”

GLOWING SUCCESSES

That principle has paid dividends for both Bhatia’s lab and biomedicine. When Bhatia first got excited by nanomaterials as a tool for tumor imaging in the year 2000, her lab

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worked on targeting nanomaterials called quantum dots to tumors. When exposed to UV light, the quantum dots glow in different colors depending on their size.

By the early years of this decade, her lab was trying to make nanoparticles that, instead of just revealing tumors, would reveal something about them as well. One approach was to use small protein molecules that are specifically snipped by a class of enzymes known as matrix metalloproteinases (MMPs), which are expressed in distinct patterns in different stages and types of tumors. The pattern of snipping would then serve as a signature of a tumor’s type or stage.

“One of the students noticed serendipitously that whenever we administered these materials to a tumor-bearing mouse, there

was an organ lighting up in the abdomen of these animals,” recalls Bhatia. The organ in question was the bladder, indicating that the snipped protein fragments were being cleared from the body via the urine. In 2014, Bhatia’s team harnessed that insight to create a paper-strip urine test for tumors.

That achievement opened up other opportunities as well. “We wanted to see whether we could profile the proteolytic environment of tumors, recognizing that there’s more than one protease expressed as the tumors progress through different stages,” says Bhatia. That would require isolating the signal from the chosen tumor alone. The trouble was that MMPs are also found in the bloodstream, and their activity would cloud signals from the test.

Working with the laboratory of MIT colleague Polina Anikeeva, Bhatia’s team devised a method to control the activation of their sensors in space and time. To do so, as they reported in *Nano Letters* in 2016, the researchers encapsulated their nanosensors in a heat-sensitive coating along with small magnetic particles. When a focused magnetic field was then aimed at the tumor, the particles heated up and the coat melted away, exposing the nanosensors to MMPs solely within the tumor. The researchers showed that the test allowed them to distinguish between two different types of colon tumors in mice using a paper strip test devised to detect specific MMP signatures.

BUGGING CANCER

In 2011, on a social visit back to San Diego, Bhatia found herself discussing how bacteria might be engineered to report on and treat tumors with an old friend, the synthetic biologist Jeff Hasty, whose own lab was moving in that direction. “There are many bacteria living in and on our body,” says Bhatia. “You can take native strains like *Escherichia coli* that exist in the gut, or the oral, genetically engineered probiotic versions of them, and engineer them further

to report on a tumor, or deliver therapeutic cargo.”

Soon, Hasty and Bhatia were collaborating on a project to that end. It was primarily led by Tal Danino, a graduate student in Hasty’s lab who moved over as a postdoc to Bhatia’s group as the work evolved.

In 2015, Bhatia, Hasty and their team described in *Science Translational Medicine* how they had engineered a widely used probiotic, *E. coli* Nissle 1917, to report on the presence of liver tumors. Fed to mice with intact immune systems, the bacteria traveled from the stomach to the liver through a major blood vessel and selectively accumulated in liver malignancies. Once there, they secreted an enzyme that, when exposed to its injectable target, generated a luminescent chemical detectable by both imaging and urine tests.

“The cool thing about that study was that we discovered, using immune-competent mice, something that we hadn’t previously appreciated so acutely,” says Bhatia. “If you give bacteria systemically, they are privileged in the tumor, where the immune system is suppressed.” When they traveled to other parts of the body, it appeared, the immune system would simply clear them away.

This meant that with the right dose and route of administration, bacteria would infect tumors but spare healthy tissues. And that, in turn, suggested they’d make great vehicles for the delivery of therapies. “If they grew selectively in the tumor,” says Bhatia, “they’d selectively kill tumor cells.”

Building on that insight, the researchers devised an elegant system for not only delivering multiple anti-tumor payloads in bacteria, but also getting those bacteria to deliver them in regularly timed pulses. First, they engineered the bacteria to express a protein that prompts them to self-destruct when their population reaches



Photo by Flynn Larsen

a certain density. They also programmed the bacteria—a variety of *Salmonella*—to produce one of three different anti-tumor agents: one that stimulates an immune response, one that pops cancer cells open, and a third that prompts them to commit suicide.

As the team reported in their *Nature* paper in 2016, the system worked like a dream in their animal models. Fed to mice bearing colon cancer metastases in their livers, the *Salmonella* traveled like the *E. coli* through the portal vein and thrived within the metastatic tumors. When their cancerous housing got a bit too crowded, the bacteria self-destructed on cue—releasing their anti-tumor agents into the heart of the malignancy. But a few remained to rebuild the bacterial colony, reinitiating the cycle of growth and self-destruction. The researchers found that though the combination arrested tumor growth

moderately, it did so more dramatically when it was combined with a standard chemotherapy.

Bhatia and her colleagues have spun off their nanosensors as a biotech startup that hopes to have its product in clinical trials by next year. As for the bacterial work, Bhatia says her collaborators are thinking about translating that research as well. For now, she’s mainly intrigued by the trafficking of the bacteria within the body, especially since their migration seemed to be augmented by chemotherapy.

“The bugs had to cross the gut, get into the portal circulation and travel into the liver and then set up shop there,” says Bhatia. “It’s important to understand the fundamentals of how that happened to determine which patients this will be most relevant in.”

It’s a fair bet she’ll let us know soon. ■