PNAS PROFILE

Profile of Sangeeta Bhatia

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"Routine has never described my life," reflects Sangeeta Bhatia, a member of the National Academy of Sciences, through a full-bodied laugh. The realization comes as she finishes recounting a vast and varied career as an inventor, entrepreneur, professor, activist, physician, and engineer. Sitting behind her desk at the Massachusetts Institute of Technology (MIT), where she began as a graduate student and now runs her own lab and directs the Marble Center for Cancer Nanomedicine, her clutter-free office belies a mind overflowing with ideas and solutions for some of the most challenging questions at the nexus of medicine and engineering. The thread running through her research portfolio is the adaptation of technologies rooted in the computer industry for the advancement of human health. Her work began with liver disease and has expanded to include cancer and infectious disease.

Image credit: Len Rubenstein.

The Foundation

When Bhatia launched her lab at MIT in the early 2000s, nanotechnology was on the rise. The timing was ideal for a physician-engineer who had already devoted her graduate and postdoctoral years to studying the liver, experimenting with its cellular microenvironments, and looking for ways to enable liver cells to survive outside the human body.

Among the liver's vital functions are detoxifying blood, orchestrating metabolism, and regulating blood volume. During graduate school in Mehmet Toner's lab, Bhatia's technological goal was to put healthy liver cells in a machine that could buttress the diseased liver, much like dialysis does for the diseased kidney. For patients with liver failure, such a device would theoretically run blood from the liver through the machine, where healthy liver cells would temporarily do the work of the liver, after which the blood would be returned to the patient's body. However, realizing this goal was far from a cinch. "The cells weren't behaving once they were put into these artificial environments," Bhatia says. "So that was kind of my entry into the field. How do we make these cells behave like they [do] in the body?"

Using what she calls the "tiny technologies" born of the semiconductor manufacturing industry, she and her trainees engineered a miniature liver where, crucially, the cells were able to survive in microenvironments in which they replicated the behavior they display in the body.

Bhatia has continued to tweak the tiny livers to perform numerous functions. Her team has used them to study liver infections such as hepatitis C, hepatitis B, and malaria. They can also use them to safely test new therapeutics, such as RNA interference (1), without putting humans at risk. These so-called satellite organs can also be sent into the body to study both healthy and diseased states, much like sending a satellite into outer space to capture elusive information. The artificial livers also have future clinical applications. Through the abdomen, physicians may be able to implant such livers into patients with liver disease, either as a way of closing a functional gap that a diseased liver can no longer perform or to deliver targeted drugs.

The liver is one of few organs known to regenerate. Bhatia's next frontier is optimizing the ability of diseased livers (2) to regenerate. "I'm super excited about that, it's taken…20 y, or 15 PhDs, to get to this point," she says, beaming. Bringing this work to patients is the focus of a startup she cofounded during the COVID-19 pandemic with longtime friend and collaborator Christopher Chen. Aptly, the Cambridge-based startup is named Satellite Bio.

A Multifaceted Organ

"Liver disease has been historically underappreciated," says Bhatia. "It presents stealthily, can suffer from social stigma, and there were almost no treatments short of transplant." Lack of funding for and scientific interest in liver research abounded.

Rather than seeing this dearth of support as a drawback, Bhatia was drawn in. Her favorite space is an open one; as different facets of liver research have gotten more crowded over the last 20 y, Bhatia has tried to find a new niche each time.

After studying induced pluripotent stem cells for around a decade, she realized that her team was beginning to stray off the path of their central question: What could such cells do for engineered liver tissue? So she deftly steered the team away.

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Then came the malaria era, one of the more crowded fields Bhatia has waded into. Liver-stage malaria offered her an opportunity to collaborate closely with Maria Mota, a leading malariologist and executive director of the Institute of Molecular Medicine in Lisbon, Portugal.

"We worked on malaria for a decade. Put some…really important tools out into the world and sequenced the first transcriptome of an elusive organism [*Plasmodium vivax*] (3)," Bhatia recalls. The next stage in the research was drug and vaccine development, which was beyond what she saw as her lab's purview. "Now we offer advice but not experiments," she says, true to her conviction that knowing when to say "no" is a crucial tool in building a career.

Sense of Duty

On a Saturday night at 3 a.m., Bhatia made her way to the lab in Cambridge, Massachusetts. She had been out with friends, but she needed to feed the cell lines on which her research depended. It was her first year of graduate school, and she had something to prove. She had recently transferred from MIT's mechanical engineering program into the program in health sciences and technology, after being rejected on her first try. When she entered the lab that early morning, she was struck by the scene before her.

"The lab was full," she says, a lingering sense of disbelief still palpable, decades later.

Growing up in a high-achieving community in Lexington, Massachusetts, Bhatia was used to working hard, but she was also used to being at the top. "Even if I didn't understand something naturally, I could get there with hard work, but when I got [to MIT], everybody was brilliant *and* hard-working," she recalls. "It was just not obvious to me that I could stand out, that I could rise, and that's really stressful."

"I kind of had this 'Aha!' moment," she says now. "I was unwilling to sign up for a life of science that meant I had to be in the lab every Saturday night at 3 a.m. […] and if it meant that I wasn't going to be the best, which was something I had never until then compromised in my life, that it was okay."

Today, Bhatia has turned out at the top of her field, but in setting those boundaries from the outset, she has carved out a path where she gets to run her lab, mentor students, spend every Wednesday with her two daughters, direct a research center, be an activist for gender equity and diversity in science, have date nights on Fridays with her husband, found multiple startups, and stay nimble in charting new paths with her tiny technologies.

"In the end, I think it's probably been hugely beneficial to my creativity and to my life," she says about this balance. "I love science, but it's not my whole life."

Bhatia has passed on her style of working to her students. To provide an antidote to academia's increasingly hypercompetitive environment, she encourages them to spend 20% of their time on tinkering to remember why science can be fun despite failure or to give them a chance to stumble on an exciting finding that was not part of their planned experiments. "I worry that we're losing a lot of creative thinkers because of the way we're structurally set up right now," she says of the scientific enterprise.

The Dream Ahead

There was a moment in Bhatia's career, shortly after graduating, where she wondered whether she really could have it all. Activism in science policy enthralled her, and she considered focusing more on supporting movements to diversify the field. However, a mentor's words rang in her ears: ' "The best thing that you can do for women in engineering is stay in engineering,' which is advice I took to heart," she says.

Yet it seems that Bhatia can never fully stay away from her passion for professional advocacy. Recently, she used data to measure the gap between male and female faculty who launch new companies. Seeing how rarely female professors engage in entrepreneurial practices, she collaborated to create the Future Founder Initiative, which includes a Female Founders Bootcamp at MIT, and a competition that provides a $500,000 prize to support women faculty preparing to move their discoveries forward. This spring, an incentive prize competition awarded over $500,000 in prize money to a cohort of women faculty.

Her recent work uses nanosensors to solve intractable health problems, such as pulmonary disease and cancer. The COVID-19 pandemic put the risks of severe pulmonary disease on the map, but even before the pandemic, community-acquired pneumonia (CAP) was among the world's deadliest infectious diseases. In her Inaugural Article, Bhatia describes a nanosensor that could better diagnose and ultimately treat CAP (4).

The proof-of-concept sensor, tested in mouse models, involves a panel of nanosensors that detect abnormal protease activity in the host as a marker of infection. A urinary readout specifies whether the pneumonia is bacterial or viral. The two types of pneumonia require different treatment paths, but historically, this level of diagnostic specificity has been hard to offer patients. A simple urine test would be a boon. Notably, the same classes of enzymatic markers that distinguish the host's response to CAP are also used by tumor cells as they invade the body and spread. The similarity suggests that this kind of tool would be particularly useful in early cancer detection (5).

"The [application] I'm particularly enamored with at the moment is a breathalyzer," (6) she says. In principle, such a breathalyzer would require a patient to inhale a test solution and exhale a mix of volatile compounds into a machine that provides a cancer diagnosis. However, not all tumors are lethal, and not every patient will need such screening. She envisions that the early rollout for such a tool might come at a stage when a high-risk patient has had another diagnostic test and needs further testing to determine whether they have a lethal tumor—such as a person with a history of smoking who receives a CT scan for lung cancer and finds nodules in the lung. Currently, the next step for such a patient is an invasive, risky, and expensive lung biopsy. Using a breathalyzer with a 10-min readout would be preferable. The work, she says, is progressing in mouse models.

She adds that her vision for a cancer breathalyzer is as a tool outfitted to work in low-resource settings, where patients might be able to send a picture of their test result to a remote physician. "Those are all parts of the dream,

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but we're building the technology alongside a changing landscape," she says.

It is easy to reflect on such a varied and fruitful career and make sense of it in a chronological way. However, Bhatia says, almost every moment when those natural next steps happened in an orderly way was matched by a moment of serendipity.

"I'm really privileged, I'm so happy with this path because it's been a doorway into everything that I ever wanted, which includes collaborative research, but also includes entrepreneurship and diversity activism," says Bhatia. "Of all the things this profession has given me, the most important has been a chance to help educate the next generation."

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