

ALUMNI

The Sweetest Thing

Ram Sasisekharan's research on sugar structures leads to a new biotech business—and perhaps new cures.

IN THE MID 1980S, Ram Sasisekharan, Ph.D. '92, turned to tennis to ease the pressure of his intensive graduate studies in biophysics. His search for new opponents led him to MIT, where he exchanged volleys with Ganesh Venkataraman, then pursuing a Ph.D. in chemical engineering there.

Between points, Sasisekharan and Venkataraman talked science, especially about their mutual interest in the structures of carbohydrates. Eventually, Sasisekharan turned those tennis-court discussions into a powerful technique for determining the structure of sugars, which play a major role in many cell functions, including growth, migration, and repair.

As recently as a decade ago, biologists were unable to quickly determine a sugar's structure—a step crucial to understanding how any molecule works. Since then, Sasisekharan, now a professor in MIT's biological engineering division, has developed a fast and accurate technique for determining the structure of even the most complicated sugar by identifying all its components in the correct order. As a result, he can modify sugars. That may enable the production of powerful new drugs.

In 2001, hoping to transform the research into a marketable commodity, Sasisekharan sought out an even sweeter

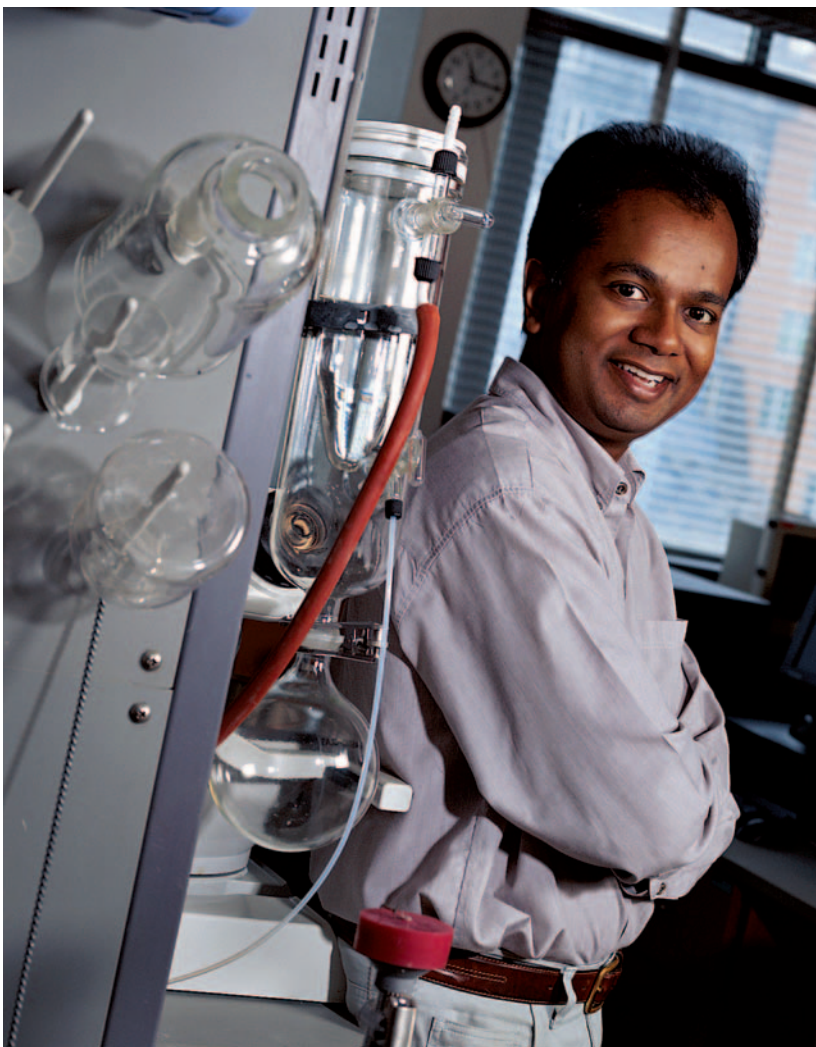
opportunity: he and several colleagues, including Venkataraman, launched a biotechnology company in Cambridge. Its goals are ambitious: "We hope to have at

least one compound in clinical trials and a product [available] in the next year or two," Sasisekharan says.

Viswanathan Sasisekharan, studied the structure of DNA and other biological molecules; he is now a visiting scientist at the Harvard-MIT Division of Health Sciences and Technology (HST). "We push each other in the ways we think and address problems," Ram Sasisekharan says about their relationship. "But more than anything, I tap his wisdom."

In 1985, Sasisekharan earned his bachelor's degree in physical sciences from Bangalore University, and then enrolled at Harvard to study biophysics. The academic environment matched his own preference for interdisciplinary research. "It's important to take a holistic approach to solving a problem," viewing it from medical, scientific, technological, and engineering perspectives, he says. "Otherwise, you get lost in the details. When you get obsessed with the decimals, you begin to lose perspective on the number." While working toward his master's, he attended a presentation by Robert S. Langer, a leading biotechnology researcher,

HST faculty member, and MIT professor of chemical and biomedical engineering. Sasisekharan was so impressed by Langer, whom he describes as "such a dynamo, such an inspiration," that he arranged to pursue his Ph.D. under Langer's direction.



Ram Sasisekharan in his laboratory at MIT, where he and his research team are finding new and healthy uses for sugars.

BORN IN INDIA, Sasisekharan grew up in a scientific environment. His father,

When Sasisekharan couldn't settle on a project for his dissertation, he asked Langer—who holds 500 issued or pending patents—for “a problem that nobody wants to work on.” Langer knew just the right challenge: it had already stymied four or five graduate students and post-doctoral researchers. He instructed Sasisekharan to sequence—or unravel the arrangement of components in—heparinase. This important enzyme cuts up sugars in the heparin family, which surround all cells. During the next few years, Sasisekharan successfully sequenced heparinase, earning his doctorate. Then he turned to a bigger job: creating a fast way to sequence sugars in general. Some colleagues tried to dissuade him. “People thought working with sugars was not only difficult, but a waste of time” because sugars simply weren't considered a research priority, he recalls. “But I had a gut feeling that something was there.”

SUGARS EXIST IN MANY FORMS. A monosaccharide consists of one carbohydrate molecule: glucose, for example. Putting together two simple sugars, such as glucose and fructose, produces a disaccharide: in this case, sucrose. Combining hundreds or thousands of monosaccharides makes a polysaccharide, such as starch.

Sasisekharan started his research with a popular blood-thinning drug, also called heparin. Heparin consists of a long string of one disaccharide that appears over and over. That sounds easy to unravel—except that each disaccharide can change just a bit. One may have a tiny bump representing an added element or two. Another may carry a different small group of elements, stuck on somewhere else. Taking all those possible minor modifications into account, heparin's disaccharide can appear in 32 varieties.

To picture that, imagine 32 different-colored beads. Now imagine putting a few hundred of those multicolored beads in a bowl, then pulling them out and stringing them together. Doing that repeatedly creates different strings of colors—or different representations of the possible structure of heparin—each time. The question, of course, is which is the *correct* structure, and how can someone find it quickly?

In the early 1990s, Sasisekharan, by then

an assistant professor at MIT, and Venkataraman, a research associate, tackled that question. They took all possible forms of the components that make up heparin and numbered them. Then they used different enzymes as chemical scissors to cut up the heparin. Returning to the image of colored beads, one enzyme might cut only between two blue beads, slicing the string into sections of various lengths and weights. Other enzymes would cut the string differently, creating a different set of sections.

Each time Sasisekharan and his team applied a specific enzyme to heparin, they recorded how many sections it produced and how much each section weighed. Then they ran a computer program that took all the potential heparin structures,

“There was definitely that ‘Aha!’ moment where you know that the puzzle is coming together,” he recalls. “You're saying, ‘This needs to go here, and this goes here, and this goes here,’ and suddenly you get the idea of what the finished picture will look like.”

chopped them exactly where the enzyme would have, and noted the results. Next, the computer compared the real experiment's results with the computer-modeled chopping. Many of the virtual forms of heparin created sections that didn't match those in the actual experiment, allowing the researchers to quickly eliminate those combinations. Eventually, only one possibility remained: heparin's actual structure.

The discovery validated Sasisekharan's gut feeling and thrilled the team. “There was definitely that ‘Aha’ moment where you know that the puzzle is coming together,” Sasisekharan recalls. “You're saying, ‘This needs to go here, and this goes here, and this goes here,’ and suddenly you get the idea of what the finished picture will look like.”

In 1999, Sasisekharan, Venkataraman, and Sasisekharan's graduate students

Zachary Shriver and Rahul Raman published an article in *Science* describing their technique for quickly and accurately sequencing a complex polysaccharide. Their method, which achieved in a day what had previously taken researchers years to accomplish, attracted attention in both the science and the business communities.

TO EXPLORE commercial possibilities of the sugar-sequencing technique, Sasisekharan, Venkataraman, and Langer teamed up in 2001 to launch Mimeon Inc., now Momenta Pharmaceuticals. Sasisekharan and Langer, both still teaching at MIT, are among Momenta's directors, while Venkataraman works solely for the company as its vice president.

“Ram and his team followed their hearts, and it worked,” says Momenta's chairman and chief executive officer, Alan L. Crane '86, M.B.A. '92. Crane came to Momenta from a major pharmaceutical company, where he negotiated more than \$2 billion in biotech deals as senior vice president for corporate development. He's shooting for similar success at Momenta, which has already raised \$25 million in venture capital, including \$10 million this year.

The company's first goal is to earn a piece of the \$3-billion annual market for heparin. The drug works well as an anti-coagulant, but it can thin a patient's blood too much, causing dangerous bleeding. Another form of the drug, called low molecular-weight heparin, causes fewer problems, but is not yet optimal at preventing clots. Momenta is using Sasisekharan's tools to make a new heparin: a better anti-coagulant with no known side effects. Meanwhile, although Sasisekharan technically doesn't work for Momenta, his team is conducting research that could turn into products for the company.

More significantly, perhaps, Uma (Narayananasami) Sasisekharan, an oncologist and an assistant professor of hematology and oncology at New England Medical Center in Boston, has helped point her husband and Momenta in another direction: fighting cancer. “As I watched my wife go through her training, I saw the challenges behind the clinical aspects of cancer, and it helped me focus on the scientific side of this battle,” Sasisekharan recalls. Anecdotal evidence, for example, suggested that

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some sugars slow tumor growth, while others accelerate it. Because heparinase releases sugars from the surface of cells, the Sasisekharans and the lab team injected a couple of versions of heparinase into mice with cancer. The researchers found that one compound, heparinase III, inhibited tumor growth because of the particular sugars it released from cancerous cells. Momenta hopes to turn that knowledge into new anti-cancer therapies.

LIKE HIS MENTOR Robert Langer, Sasisekharan, now 38, rarely slows down. This year, he has helped to launch another startup, BioScale Inc., whose purpose is to make sensors that can recognize pathogens that might be used by bioterrorists. In addition, he is involved in an international research effort to study sugars as a part of a \$35-million consortium which is funded by the U.S. National Institutes of Health. And he

continues to hope for the sweetest possible success—discovering a life-saving medical breakthrough. “I would be humbly gratified,” he says, “if one really useful product comes out of my efforts.”

~MIKE MAY

Mike May, a former associate editor at American Scientist, is a freelance writer who specializes in science and technology stories. He lives in Madison, Indiana.

Alumni Abroad

AS CLASSES RESUMED in Cambridge, alumni on both sides of the Atlantic were gearing up for the “Harvard in Europe” conference in London.

The event, to be held November 14 and 15, is part of the Harvard Alumni Association's Global Series. President Lawrence H. Summers will give the keynote address; more than a dozen other Harvard faculty members and administrators will also speak. (*Harvard Magazine* will report on the proceedings in its January-February 2004 issue.)

The conference is cosponsored by the Harvard Clubs of Europe and hosted by the Harvard Club of the United Kingdom. For additional details, visit www.haa.harvard.edu/globalseries, call Hillary Olk at 617-495-5416, or e-mail her at hillary_olk@harvard.edu.

While in London, participants may wish to visit Southwark Cathedral, on the south side of the River Thames near London Bridge. The cathedral—the city's oldest Gothic structure—houses a little-known Harvard link: in 1607, a butcher's son named John Harvard was baptized there. Nearly 350 years later, Harvard alumni helped fund repairs to the ancient structure; in gratitude, church officials renamed a chapel inside the church in Harvard's honor.

Today, the Harvard Club of the United Kingdom hopes to restore the chapel's aging stained-glass window, a 1905 gift from then-U.S. ambassador to England Joseph H. Choate, A.B. 1852. The window's imagery includes a depiction of Christ's baptism and the coats of arms of Harvard University and Emmanuel College, Cambridge, which John Harvard attended.

With restoration costs expected to reach \$15,000, the club welcomes donations. For information, e-mail HAA President James V. Baker at jvbaker@post.harvard.edu. To learn more about Southwark Cathedral and Harvard Chapel, visit www.dswark.org/cathedral.

Winning Combination

SHAKA BAHADU '04 of Dunster House and Shira Sivan Simon '04 of Leverett House are the 2003 David Aloian Memorial Scholars. They were to be honored at the fall dinner of the Harvard Alumni Association on October 23.

Established in 1988 to honor the late David Aloian '49, the former HAA executive director and master of Quincy House, the scholarships recognize two rising seniors who have made unique contributions to their Houses and to undergraduate life, thus making Harvard “an exciting place in which to live and study.”

Bahadu, of Detroit, ranks community participation and enthusiasm as the most important attributes for successful House life. He's lived his own philosophy by serving as co-chair of the Dunster House Committee, co-social chair for the House, editor and producer of Dunster's *Mooseletter* newsletter, secretary for Dunster's intramural teams, and as a cook for the Dunster Grille. He has also instituted two

enhancements to House life: an event welcoming rising sophomores with hot cocoa and s'mores, and the Dunster House Committee Handbook, which outlines protocol, procedures, and the year's events. The biological anthropology concentrator will spend a postgraduate year continuing his clinical research on cardiac allograft vasculopathy (a complication of heart-transplantation surgery), after which he hopes to attend medical school.

Simon, of West Des Moines, Iowa, dedicates much of her time to projects benefiting all Leverett House residents. Her contributions range from organizing the Leverett House '80s Dance to coordinating a clothing drive with the House and Neighborhood Development (HAND) program. She has designed Leverett apparel and gear and ordered more than 500 hamburgers for House study breaks. Outside Leverett, Simon is vice-chair of Harvard Undergraduate Council's student-affairs committee, senior editor of the *Harvard Health Policy Review*, a business associate of the *Harvard International Review*, and a member of the Harvard Hippocratic Society. A concentrator in sociology, she will attend Mount Sinai Medical School in New York City.



Shaka Bahadu (left) and Shira Sivan Simon.

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Home at Last

AFTER more than two years of construction, the Harvard Club of New York City