

Stephen Galli '70: A scientist and a limericist

By Laura Stephenson Carter

Pathologist Stephen Galli, M.D., a world-renowned expert on mast cells and the chair of the Department of Pathology at Stanford, often laces his talks at research meetings with clever limericks that he's written about his work. Here's a sample:

*The mast cell has earned a bad name,
Because for wheezing it's partly to blame.
But it also keeps us all healthy,
Despite pathogens stealthy,
By helping us win in the host-defense game.*

"Sometimes people come up to me and say, 'I remember you. You told those limericks about mast cells,'" Galli says, joking that he figures it's better to be remembered for *something* than to be forgotten.

But Galli will hardly be forgotten. He is well known for his research on the role that mast cells and basophils play in allergic and other immunological or inflammatory responses. Mast

cells and basophils are types of white blood cells that when activated by allergens release histamines, which in turn cause tissues to swell, make eyes water, and trigger other equally unpleasant symptoms associated with allergic reactions. Recently Galli and his team discovered a protein, called RabGEF1, that may help keep allergic reactions in check—in mice, anyway. That study was published in the August issue of *Nature Immunology*.

Galli has been working with mast cells and basophils for about 30 years, ever since he did his residency in pathology at Massachusetts General Hospital (MGH) in Boston in the 1970s. But he can trace his interest in science even further back. "I have an essay I wrote in the—maybe it was the third grade," he says, "in which I said I wanted 'to be a scientist when I grow up.'" Back then he was interested in bugs and snakes, though, and at one point considered a career in wildlife management. But by his junior year at Harvard, he'd decided to go to medical school instead.

He got hooked on research during his residency. He recalls doing an experiment to determine whether basophils make their own histamine or whether it is absorbed from the environment. It was already known that mast cells make their own histamine, so Galli figured it was likely that basophils do, too. He painstakingly went through all the steps—purifying basophils from guinea pigs; separating the precursor, histidine, from the product, histamine; dropping the histidine into the medium; recovering the histidine at different intervals; and preparing the recovered specimens with thin-layer chromatography. "And you would simply wait as this dye developed to find out . . . whether basophils were making histamine from what you gave them," Galli explains. He then scraped out the material from the plate and

put it into a machine that counted radioactivity. If the histamine showed the same radioactivity as the histidine, it would mean that the basophils had indeed made their own histamine. And they had.

"I remember getting those data from the machine and realizing," he says, "that I was the first person in the world who knew this . . . tiny piece of information. I can assure you that no one was waiting by the phone at the *New York Times* to find out that basophils made histamine . . . but it was so exciting to have discovered this myself that I thought, 'This really is a lot of fun—and can you imagine if you discovered something *really* important, how that would feel?'"

It takes a certain kind of person to be willing to spend countless hours, days, weeks, and years doing research for the sheer joy of it. Be-

havioral psychologist B.F. Skinner once said there are two types of human activity where, as Galli paraphrases the point, "you might invest a little effort or a lot of effort, for a short period of

time or a long period of time, and get either a big reward or a small reward." One is fishing and the other is scientific research, says Galli, who loves both activities, though he hasn't fished in years.

It's impossible to know at the start of your career "whether you're going to be fortunate enough to make a really important discovery," explains Galli. "So it's very important . . . to enjoy the process. Because if you don't enjoy the process, and it's all about making a big discovery, then you could very well be terribly disappointed."

Luckily for Galli, he's enjoyed the process and, as it turns out, made some important discoveries along the way, too. He's been elected to such prestigious societies as the Collegium Internationale Allergologicum, of which he is president-elect, and the Accademia Nazionale dei Lincei, an organization that counts Galileo Galilei among its former members. He is also vice-president-elect of the American Society for Investigative Pathology. Among his many honors is the Scientific Achievement Award, bestowed by the International Association of Allergy and Clinical Immunology in 1997.

In fact, when Galli was in medical school—two years in DMS's pre-clinical program and two years at Harvard—he did not intend to become a pathologist. Instead, he was interested in tumor immunology. He even took a year off from medical school to work in a tumor immunology lab at what is now the Dana-Farber Cancer Research Institute. When it came time to choose a residency, however, he realized he still didn't know what he wanted to specialize in. His advisor suggested that he do a year of pathology—it would give him an excellent background in medicine as well as provide him with more time to make up his mind. Galli wound up at MGH—his first choice because he wanted to work with Benjamin Castleman, M.D., MGH's chair of pathology and the editor of a series of case reports in the *New*

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Laura Carter is the associate editor of DARTMOUTH MEDICINE magazine.

England Journal of Medicine. Each case “was kind of a medical riddle,” explains Galli, and would be discussed first by a clinician who didn’t know the final diagnosis and then by a pathologist.

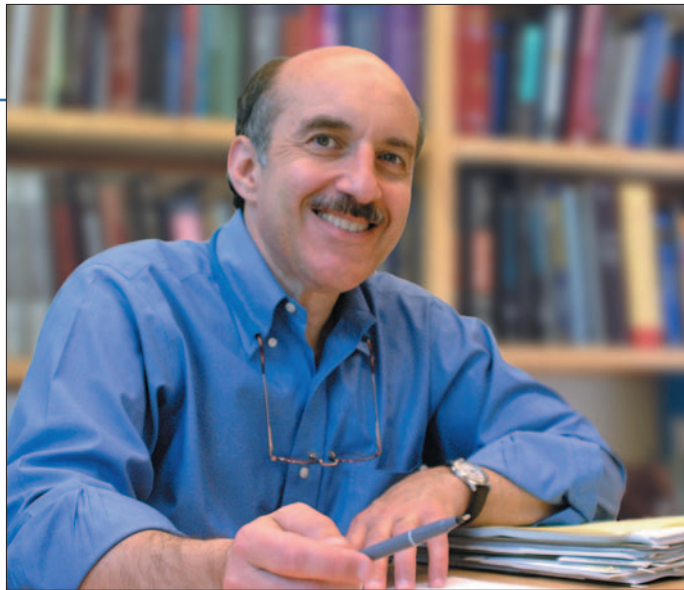
When Galli interviewed with Castleman, he explained that he was planning to do only one year of pathology. Castleman told him that was fine. But in the middle of the year, “Dr. Castleman went walking through the lab, the place where the residents sat,” Galli says. “I felt him squeeze my shoulder and he said, ‘What are you doing next year? Are you

staying or are you leaving?’ So I said, ‘Well, I haven’t made up my mind, Dr. Castleman,’ because I’d decided I really liked it and I was learning a lot. . . . And he says, ‘Well, think about this. If you stay for two years then you’ll be able to go on an NIH training grant.’” Castleman said Galli could work with whomever he wanted.

So Galli decided to stay. He chose to work with someone he deemed to be the smartest and most productive of MGH’s investigators—Harold Dvorak, M.D., who was studying basophils. “I had no particular interest in basophils,” says Galli. But “I thought I’d learn the most from him.” That turned out to be a wise choice. Dvorak soon discovered a major factor involved in angiogenesis, the formation of blood vessels, in tumors. During his residency and a subsequent post-doctoral research fellowship at MGH, Galli grew more fascinated with basophils and mast cells. He was also fascinated by a young woman he met over a microscope—a fellow researcher named Anne Stuart, whom he eventually married and even coauthored papers with.

Galli knew that he needed to establish his own research identity, which would be hard if he stayed at MGH. For scientists, “one of the challenges of establishing their own independent laboratory, and their own research identity, is to differentiate themselves from their mentor. And that can be especially difficult if one elects to stay in the same institution as a mentor.” In 1979, however, Dvorak left MGH to be the chief of pathology at Beth Israel, another Harvard-affiliated institution. He invited Galli to follow him, saying his new administrative responsibilities would limit his time for research, and he’d decided to focus on just one of his interests—tumor biology. “This would leave to me the field of basophils and mast cells, since he wouldn’t be working on that any more,” says Galli. “So I had the advantage of being in a supportive environment with my former mentor, but not directly competing with my mentor in his area of interest.”

Galli spent the next 19 years on the Harvard faculty and as the di-



CAROLINE TUDOR

When Stanford pathologist Steve Galli picks up a pen, it may be to jot down a research finding, but it’s just as likely to be to turn out a clever limerick—about science.

rector of Beth Israel’s autopsy services, pathology research laboratories, and division of experimental pathology. His research shifted from basophils to mast cells. His team developed a way to grow mast cells *in vitro* from either hematopoietic progenitors (cells, like bone marrow, that produce blood cells) or embryonic stem cells. Thanks to his work, scientists now know that mast cells are involved in allergic reactions but also help maintain homeostasis by eliminating toxic substances from the body.

One of Galli’s papers “showed that by selectively expanding mast cell populations, using their major growth factor, you could enhance the ability of the mouse to resist bacterial infection,” explains Galli. “So this suggested a therapeutic possibility that in subjects [with] impaired resistance to bacterial infection, if you could safely expand mast cells, you could enhance the ability . . . to resist bacterial infection. But that would have to be done very carefully so as not to increase their susceptibility to asthma or other negative consequences of having too many mast cells.”

While it had once been thought that mast cells “were bad guys—driving allergic reactions, anaphylaxis, [and] asthma,” Galli’s work showed that mast cells “had a good side as well, in that they contributed to innate immunity, or resistance to infection.” And because mast cells are close to the surfaces exposed to the environment—the skin, as well as the intestinal, respiratory, and genital tracts—they serve as “a sort of early warning system when . . . there might be some sort of infection,” mobilizing the body’s defenses earlier than might otherwise be the case.

In 1999, Galli left Harvard for Stanford, where he is now the Mary Hewitt Loveless, M.D., Professor as well as the chair of pathology. But he returns to the East Coast every summer and spends a month with his wife and son at the family’s 1813 cottage on the shores of Squam Lake in Center Sandwich, N.H. He loves hiking and canoeing there and hopes to one day find time to take up fishing again.

But he’ll always find time for his limericks—like this thoroughly tongue-in-cheek one about how to be a successful researcher:

*To win in science, the rules are quite few;
Listen now while I tell them to you:
Make your own work sound great,
Publish ere it’s too late,
And then earnestly hope that it’s true. ■*