THE ANSWER IS NO

NITRIC OXIDE DISCOVERIES UNRAVEL PATHWAYS LEADING FERID MURAD TO THE NOBEL PRIZE — AND GW

The question had puzzled doctors for more than 100 years: How did nitroglycerin — the same explosive compound Alfred Nobel famously tamed in his invention of dynamite — work as a therapeutic? They knew it flushed blood into the heart, alleviating painful conditions like angina, but how? That was the million-dollar question.

For Ferid Murad, M.D., Ph.D., now University Professor and professor of Biochemistry and Molecular Biology in the GW School of Medicine and Health Sciences (SMHS), the answer struck like a lightning bolt. He was a young faculty member at the University of Virginia (UVA) when he realized nitroglycerin and other blood vessel-widening drugs (which he dubbed nitrovasodilators) were being converted to nitric oxide (NO) in the body.
“That was heresy,” says Murad. After all, NO was best known as a toxic gas and environmental pollutant — not as a molecule with beneficial biological functions. But when Murad and his team linked lab-generated NO with a family of enzymes called guanylate cyclase (GC), they successfully mimicked the lock-and-key combination nitroglycerin uses to make blood vessels relax, expand, and encourage blood flow.

“We did that experiment on Dec. 2, 1976 — I’ll never forget it,” he says. “It was one of those ‘eureka’ moments.” And it wouldn’t be the last. Two years later, Murad postulated that nitrovasodilators work not by being converted to NO in the body, but by prompting smooth muscle cells to create the gas themselves. NO, he thought, was behaving as a messenger molecule — one uniquely capable of both carrying messages between cells (i.e., a first messenger) and entering the cells to regulate their functions (i.e., a second messenger). And though it took years to prove it, and even longer for the scientific community to accept it, Murad was right.

AN INTELLECTUAL BRIDGE

The memory of a molecule once outcast seems distant to Murad now — 35 years since the discovery of NO’s first biological effects and 13 since he and two colleagues won the Nobel Prize in Physiology or Medicine for it. Today, the study of NO is one of the most popular in biology, generating about 130,000 academic papers each year. Murad estimates the molecule has influenced breakthroughs in cardiovascular disease, cancer, and arthritis, and — Murad proudly reports — formed the basis for Viagra. “It’s just remarkable what it can do,” he says. “If you were asked: Does it do this? Does it do that? Chances are, the answer is ‘yes.’”

The same could be said of Murad, who has served as chief of Medicine at Palo Alto Veterans Hospital, chair of Medicine at Stanford University, and most recently director emeritus of the Institute of Molecular Medicine at the University of Texas Health Science Center at Houston. He’s founded several biotechnology companies, served as an advisor to city and government leaders on technology development, and lectured around the world. In June, he became the namesake of a hospital in Macedonia — the same hospital where his Albanian father sold candy as a teenager.

Through it all, Murad’s philosophy has remained the same. “I like to chase problems,” he says. “You have to do whatever it takes to answer the most important questions.”

Most recently, “whatever it takes” comes in the form of GW, where, as University Professor — the institution’s highest academic title — Murad teaches an undergraduate course, mentors medical and doctoral students, and leads a lab program at SMHS’s Department of Biochemistry and Molecular Biology, where he is a full professor. “Something significant is happening at GW, and it’s fun to be a part of it,” he says.

And according to University and SMHS leadership, Murad’s not just a part of it — he’s driving it. “Dr. Murad’s presence on our faculty immediately catalyzes and elevates our strategic efforts in advancing scientific discovery, educating the next generation of physicians and scientists, and improving the health and lives of the people we treat,” says Jeff Akman, M.D. ’81, G.M.E. ’85, interim vice provost for Health Affairs and dean of SMHS. “In many ways, he is an intellectual bridge between the University and SMHS.”

Rakesh Kumar, Ph.D., professor and Catharine Birch & William McCormick Endowed Chair of the Department of Biochemistry and Molecular Biology, and long-term collaborator of Murad’s, agrees. “Dr. Murad is a compassionate colleague and mentor whose infectious intellectual curiosity is sparking a fresh spirit of creativity on our campus.”

ONE PERVERSIVE PATHWAY, THREE IMPORTANT PROJECTS

When Murad joined the GW faculty in April, he unpacked three nagging questions: Can deadly tumors be treated with minimal side effects? How can stem cells be manipulated to grow into certain tissue types? Is there a cheap and portable way to save the millions of lives lost each year to diarrhea? While ostensibly quite distinct, each project stems from the cellular signaling pathway that begins with NO and ends with cyclic guanosine monophosphate (cGMP), a second messenger that is released inside a cell after GC is activated by NO (i.e., the lock and key).

“NO and cGMP reprogram genes that influence the differentiation and proliferation of cells,” explains Murad of project number one. “Because some of these effects are related to cancer proliferation, interrupting that process can be a novel way to treat cancers.” It’s a thought that’s been simmering in Murad’s mind since the 1970s, when his work with liver and renal tumor models first indicated a relationship between cGMP and tumor proliferation. After several years exploring this relationship — and even demonstrating that cGMP excretion in the urine of rats correlated with the size of their tumors — Murad and his colleagues tabled the project because their ambitions exceeded the day’s technologies.

In recent years, Murad has returned to the pursuit, this time focusing on glioblastoma, a “very aggressive, nasty” type of brain cancer that Murad estimates kills up to 80 percent of its victims in less than three years. His goal, in broad terms, is to enhance the expression of a certain subtype, or isoform, of the receptor GC and its product cGMP so that the message “grow” cannot be received by the tumor cells. So far, Murad and his team of investigators have successfully quadrupled the life span of mice injected with manipulated tumor cells. “Can we do that with humans? I don’t know, but I hope so,” he says.

Murad’s second project, regenerative therapy, goes hand in hand with his first. Like cancer cells, embryonic stem cells are
proliferating and differentiating systems whose growth and change is dependent upon the messages they receive. If Murad can understand whether and how much NO and cGMP dictate the messages that tell embryonic stem cells what kind of tissue to become, he might also be able to swoop in and tell them to be something else.

So far, Murad and his colleagues have coaxed cell lines toward futures as hearts and brains. But, of course, cGMP and NO are only part of the story, Murad cautions. “It’s going to be a complicated cocktail of goodies you put in your cultures to become this or that, and I think part of the story will be cGMP or NO.”

In 20 or 30 years, he predicts, the “organ transplant program won’t be necessary anymore. Wouldn’t that be wonderful?”

The third research goal also dates back to the 1970s, when Murad helped a colleague at JVA reveal that a bacterial toxin in Bangladesh was causing diarrhea by increasing cGMP production, similar to how cholera causes diarrhea by increasing the production of another second messenger, cyclic adenosine monophosphate (cAMP). The pair demonstrated that the only isofrom of GC found in the intestinal mucosa, particulate GC, is the receptor for the bacteria’s heat-stable strain. When that strain interacts with the particulate GC, the lock-and-key match unleashes cGMP and prompts diarrhea — an illness responsible for the death of about 2 million children worldwide each year.

Ever since, Murad has been on the hunt for the perfect compound that plugs the lock between the toxin and the particulate GC receptor. He and colleagues have already found one particularly promising molecule that works with both the bacterial toxin and the cholera toxin. And while there is still “homework to do” on the compound, including clinical trials for toxicity, Murad is optimistic that a marketable therapeutic will be developed in his lifetime. “If we can make an impact on cancer, if we can make an impact on stem cells, and if we can figure out a way to treat infectious diarrhea in third-world countries, I will turn my toes and feel blessed,” he says.

A PRODIGY OF NATURE AND NURTURE

Even as a “youngster,” Murad knew he would go to medical school. He had always been smart — remaining at the top of his class from grade school through high school, despite rarely doing homework — but his desire for higher education was as attributable to nurture as it was to nature, he says. Raised in a small town in Indiana, Murad learned the value of hard work and education from his restaurant-owning parents, neither of whom had completed elementary school. “I knew that when I grew up, I wanted to accomplish more than my parents,” he recalls. The other important component of success, says Murad, “is identifying that teacher or professor who will get you excited about something, guide you, and keep you going.”

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For him, there were many — high school teachers who were regulars at his parents’ restaurant, professors during his undergraduate years at DePauw University, doctors in residency at Massachusetts General Hospital, and scientists at his fellowship at the National Institutes of Health. But it was while achieving one of the nation’s first dual M.D./Ph.D. degrees at Case Western Reserve University that Murad met his two most influential mentors: Earl Sutherland Jr., M.D., chair of the Department of Pharmacology, and Theodore Rall, M.D., a young faculty member in the same lab.

Murad joined their lab shortly after it had discovered cAMP as the first intercellular second messenger — a finding for which Sutherland later won a Nobel Prize. “What a wonderful and exciting time ... watching a new area of biology develop and actively participating in the work,” writes Murad on the Nobel Foundation website. He has studied cellular signaling ever since.

Murad has also embraced the opposite side of the mentorship dyad, training about 150 medical students and fellows in his lab over the course of his career. Many have become department chairs, several are company presidents, and one is the president of a Japanese university, but none have won the Nobel Prize ... yet. “One of my students has to win the prize because I don’t want this lineage in cellular communication disrupted in any way,” says Murad, half-joking and alluding to the three-generation trend that began with Sutherland’s mentor, Carl Cori, who won the prize in 1947 for describing how the body uses glycogen for energy. “One of my goals is to identify that next generation here at GW.” But even more than the Nobel trait, Murad hopes he can pass down his passion for research and penchant for problem solving. After all, if conducting one revolutionary experiment was his only goal, Murad could have stopped that winter night in 1976. But “quitting while you’re ahead” is an idea that’s never made much sense to Murad. “I hope I never retire,” he says. “I really love what I do — solving problems. How long I can go, I don’t know. But I am willing to find out.”