EPIGENETICS AND DEVELOPMENT

Corina Lesseur and Carmen Marsit are intrigued by the effects of epigenetics on the development of infants.

A CLOSE LOOK AT THE HORMONE LEPTIN has revealed a connection between methylation of the leptin gene and the development of male infants. The study, which was led by Geisel associate professor of pharmacology and toxicology Carmen Marsit and former graduate student Corina Lesseur, both confirms earlier findings made in studies of mice and offers a potential mechanism to explain differences by sex in environmental effects on development. The research was published in the journal *Psychoneuroendocrinology*.

Leptin is commonly known for its role in regulating appetite and weight, but it is also involved in fetal development, including the development of the brain. Methylation can prevent expression of the leptin gene (*LEP*), leading to lower levels of the hormone and potentially affecting development.

Marsit, Lesseur, and colleagues analyzed the methylation of *LEP* in 444 placental samples and measured the expression of leptin in a subset of those samples. They found that a 10 percent increase in *LEP* methylation was associated with a 90 percent increase in the risk that an infant would display signs of delayed development, such as low muscle tone and lethargy.

The study is part of Marsit's ongoing work in the field of epigenetics, which focuses on heritable changes in gene expression rather than on the DNA sequence itself. "You're born with some genetics, but that alone doesn't tell you what your outcome is," Marsit explains. "Your genetics are not everything."

Marsit and Lesseur were excited by the findings because they parallel other research in mice that found a similar relationship between leptin and development. "It's really translation," Marsit says of the new study. "It's taking what has been found in a very basic model . . . and showing that in people you can see similar behavior."

Lesseur, who earned a medical degree in her native Venezuela before coming to the U.S. to study at Dartmouth, has long been interested in how leptin—and, more generally, obesity—affect early development. She graduated last spring and is now a postdoctoral fellow at the prestigious International Agency for Research on Cancer in Lyon, France.

Although the study involved both male and female infants, the effect of leptin methylation on development was seen only in males. Even more intriguing, Marsit says, is that even in females with high levels of methylation, the leptin gene was still expressed. So the difference wasn't just the result of differences in methylation but of differing effects of methylation.

"YOUR GENETICS ARE NOT EVERYTHING."

STIMULATING BRAIN RESEARCH

Researchers at DHMC and Geisel are playing a key role in a multicenter $22.5 million, four-year effort to develop next-generation technologies to restore memory function in individuals who suffer from memory loss. The project, which is in support of President Obama's BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative, will combine research on the basic mechanisms of memory function with the development of systems designed to electrically stimulate discrete regions of the brain. The research team hopes that the project will lay the groundwork for a fully implantable neural monitoring and stimulation system that could be used to treat memory loss.

Lesseur says that many studies have now found sex-specific effects of epigenetic factors, which might help to explain differences in health and disease by sex. "We're looking at a mechanism now," Marsit says. "What we're getting at are potential mechanisms behind these differences. That could start to explain some of these findings that people have seen for years and never understood."

The researchers are continuing this line of research by studying other hormones related to metabolism and how the metabolic status of the mothers affect methylation levels. "What you experience *in utero* can set you up for very different outcomes," Marsit says.

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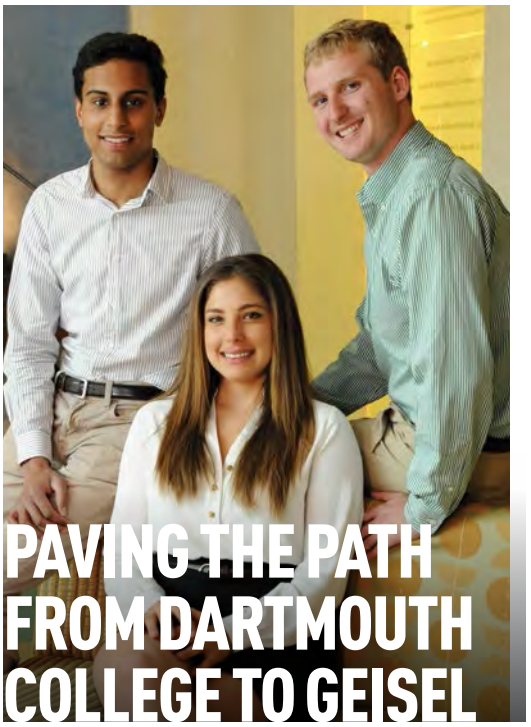
HELPING PHYSICIANS HELP PATIENTS

Over the next year, Dartmouth researchers will carry out a pilot study to determine if training physicians in a standardized protocol can help smokers with vascular disease quit smoking. The trial will be led by Philip Goodney, an assistant professor of surgery at Geisel, and Emily Spangler, a resident in vascular surgery at DHMC. They were recently awarded a grant of $100,000 from the Society for Vascular Surgery to carry out the study.



Three first-year medical students—Sunil Bhatt (left), Nayrana Carneiro, and Matthew Sattler—are the first Dartmouth College graduates to matriculate at Geisel as part of an early assurance admissions program.

PAVING THE PATH FROM DARTMOUTH COLLEGE TO GEISEL

GEISEL'S EARLY ASSURANCE ADMISSIONS PROGRAM is smoothing the way to medical school for a few fortunate—and talented—Dartmouth College undergraduates. The program allows Dartmouth students to apply to Geisel at the end of their sophomore year and waives the requirement of taking the Medical College Admission Test (MCAT), and it also offers students the chance to defer admission for one year after completing their undergraduate work.

"The idea behind the program is to offer undergraduates an inducement to stay with us," says Joseph Schwartzman, a professor of pathology and past chair of the admissions committee. "Recommendations and grades from Dartmouth professors allow us to forgo the MCATs."

But the program is by no means an easy pass into medical school. Early assurance applicants are part of a highly competitive pool of candidates who are considered alongside all medical school applicants throughout the interview process—with only five undergraduates accepted for admission to Geisel.

"All of the early assurance applicants are very accomplished, and they've all done something that is unusual at their level of study," Schwartzman says. "We want people who have enough experience to *know* that they really want to be doctors."

Julia Berkowitz, Sunil Bhatt, Nayrana Carneiro, Emily Dollar, and Matthew Sattler are the first five Dartmouth undergraduates admitted to Geisel through the program, and while Dollar and Berkowitz have deferred for one year, Bhatt, Carneiro, and Sattler are now first-year Geisel students.

"I am very passionate about science and about helping people, which I think is common among all medical students," Carneiro says. "But I do believe that if you want to be a doctor, you have to have it in your heart that you really want to help others."

As an undergraduate, Carneiro worked at a clinic in a tough Philadelphia neighborhood with limited access to health care. A significant number of the population struggles with diabetes, HIV, and other serious health issues. Scared and vulnerable, many of the clinic's patients were unpleasant and resistant to help.

Carneiro was unfazed. "That internship was life-changing," she says. "It was there that I learned the importance of showing patients love, compassion, and understanding. It confirmed my desire to become a physician."

Long interested in health care, Sattler, a licensed emergency medical technician (EMT), began volunteering with Dartmouth Emergency Medical Services, the college's student-run basic life support squad, during his freshman year.

"While working as an EMT it became clear to me that I wanted to continue working in that environment but to provide consistency of care beyond on-call emergencies," he says.

"I came to Dartmouth because of its rural environment and I'm staying for medical school because I really like what I've found here—a school that's focused on patient care," Sattler adds.

In high school, Bhatt traveled to India with his father, a physician, who established an ear, nose, and throat (ENT) service at a charity hospital there. "I was able to help set up a simple telemedicine system that allowed my father, and another ENT doctor in the U.S., to evaluate transmitted images of patient exams and provide feedback on the diagnoses," Bhatt recalls. "I had the capacity to make a difference and to see a patient through the course of their treatment no matter where they were from. It's what led me down the path to Dartmouth and to global health."

Schwartzman says he's confident that all of the students will do well at Geisel. "Dartmouth College students who are admitted through the regular process are very strong and I expect these students will be great medical students as well."

SUSAN GREEN