SARAH MICHEL

Researcher Unravels Biochemical Enigma

BY RANDOLPH FILLMORE

At the University of Maryland School of Pharmacy, one of the nation's innovative leaders in drug discovery, development, and delivery, researchers are focusing on challenging questions about human health today, so they can translate their discoveries into new and better ways to fight disease tomorrow.

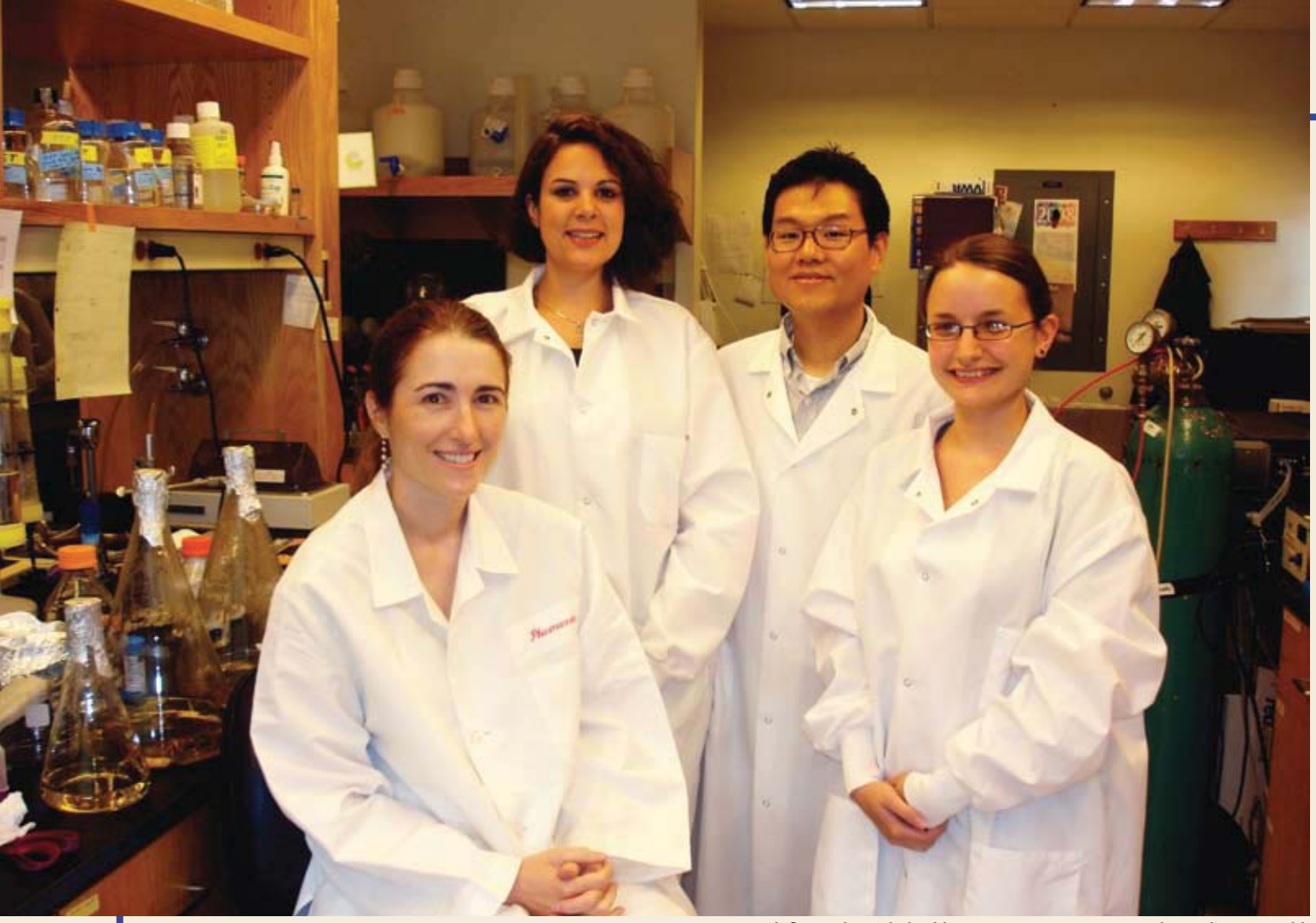
Critical, however, to the School's efforts in this area is the ability of the School's talented and top-level researchers to bring in the grants that facilitate such studies. In Fiscal Year 2007, the School received more than $16 million in contract and grant awards.

In January 2008, Sarah Michel, PhD, assistant professor in the Department of Pharmaceutical Sciences (PSC), received a prestigious five-year, CAREER award (Faculty Early Career Development Program) from the National Science Foundation (NSF) to investigate a biochemical enigma—what are the toxic consequences when iron, rather than zinc, binds to specific proteins in the body that control how different genes are expressed?

Michel was awarded the NSF grant for her work studying two zinc finger proteins, proteins that use zinc to regulate the expression of a wide range of human genes. Many of these genes encode proteins that are an integral part of the body's defense against infection. However, if not regulated effectively, these same proteins may be involved in chronic inflammation and may contribute to neurodegenerative diseases such as Alzheimer's, as well as to arthritis and cancer.

"Iron and zinc are the most abundant metals in the human body, and each metal ion binds to a specific protein, with zinc

Photograph by Robert Burke



From left: Sarah Michel, Abby West, Seung Jae Lee, and Angelique Besold

commonly binding to zinc finger proteins," says Michel.

Work in Michel's laboratory has shown that an abundance of iron in cells causes some zinc finger proteins to bind to iron instead of zinc. Identifying the physiological consequences of the iron substitution is an issue with ramifications in the development of some serious diseases, such as Alzheimer's and Parkinson's, and, yet, may hold the key to preventing or treating those same diseases.

"This substitution with iron may disrupt proper gene regulation and lead to diseases such as cancer, arthritis, and neurodegenerative diseases," explains Michel, who is assisted in the lab by graduate students Seung Jae Lee and Abby West, postdoctoral fellows Robert diTargiani and Nuvjeevan Dosanjh, lab tech Angelique Besold, and summer student Sarah Wasink. "If on the molecular level we can understand the role of iron in disrupting gene regulation, we can begin to design drugs to target the diseases associated with this disruption."

In her groundbreaking work, Michel is looking at two specific zinc finger proteins; one that activates the cell's response to inflammation, called "TTP," and another, "NZF 1," that facilitates the proper development of nerve cells. She is particularly interested in the role that TTP might play in the development of serious diseases such as arthritis and various types of cancer.

According to Michel, if iron—the wrong metal—rather than zinc—the right metal—binds to the zinc finger protein TTP, for example, the result can be cellular inflammation not only related to the serious diseases mentioned, but also septic shock, which can be fatal.

Her studies demonstrate that iron can bind to TTP and that these iron-substituted proteins selectively recognize a physiologically relevant RNA [ribonucleic acid] sequence with "affinities" similar to the zinc-bound form of TTP.

Direct translation of these findings to health care may be a few years away, but a "target" may have emerged.

"TTP is a therapeutic target for the development of novel anti-inflammatory drugs to treat other diseases, such as arthritis and cancer," Michel says. "By understanding the role of iron in TTP's function, we will be better positioned to iden-

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tify potential drugs that target this protein and the diseases associated with its function.

“Although zinc is presumed to be the correct metal ion for zinc finger proteins to properly regulate genes in the body,” explains Michel, “we want to understand the consequences of this substitution. Our studies not only teach us new fundamentals of inorganic chemistry and help us better understand the roles of iron and zinc in gene regulation, but will provide us with new drugs to combat many serious diseases.”

When she says “we” she is referring not only to herself and her School of Pharmacy colleagues, but also to undergraduate chemistry students at Morgan State University, who, through their chemistry department, will be collaborating with her in the Spring Into Maryland Science (SIMSI) Program. This program allows chemistry students a first glimpse at how their education can lead to a career in health sciences research and practice.

SIMSI, due to kick off in January 2009, is a weeklong graduate school immersion program that also provides additional short- and long-term research opportunities for Morgan State undergraduates in their freshman year. The goal is to inspire undergraduates from underrepresented groups to follow science careers at the very beginning of their college experience.

The research and the relationship will be mutually beneficial, says Holly Cymet, PhD, the assistant professor in the Morgan State Department of Chemistry who is serving as the SIMSI coordinator.

“We have a number of undergraduate chemistry students interested in pursuing the pharmacological sciences,” says Cymet. “SIMSI will provide an excellent opportunity to connect these students with the field early in their college careers.”

Alvin Kennedy, PhD, professor and chair of Morgan State’s Department of Chemistry, concurs.

“This partnership will greatly enhance our efforts to support undergraduate research here at Morgan,” says Kennedy. “It is especially important to note that the experience for the undergraduates is during their first year, when they are enrolled in general chemistry.”

A goal of SIMSI is to expose undergraduate students to PhD-level research and offer them the opportunity to connect with PSC graduate students who will serve as mentors. Cymet’s lab has had an ongoing interest in NZF 1.

Michel has been collaborating with Cymet for two years, and further collaboration through SIMSI will help the chemistry students at Morgan State and also enhance the training of Michel’s graduate students who will serve as mentors.

“Both sets of students will get great experiences at the interface of inorganic chemistry and biology,” says Michel. “Students are learning the techniques and gaining the skills required for scientific research, including how to ask the right questions, design the right experiments, and develop ideas based on experimental results.”

Finally, Michel promises that students also will learn to communicate their results, both via publications in scientific journals and by presenting their data at scientific conferences.

During collaborative research, additional questions will be posed and answers unraveled by the graduate student mentors working with the Morgan State undergraduate chemistry students. Then the Morgan State undergraduates will actually perform cutting-edge research, far beyond what they would normally encounter in a general chemistry course.

Andrew Coop, PhD, professor and chair of the Department of Pharmaceutical Sciences, raves, “The outstanding basic research performed in Sarah’s lab coupled with the training of undergraduates from Morgan State lays the foundation for new therapeutic agents for numerous disease states and trains the next generation of scientists, with the aim of discovering new medications for improvement of public health.”