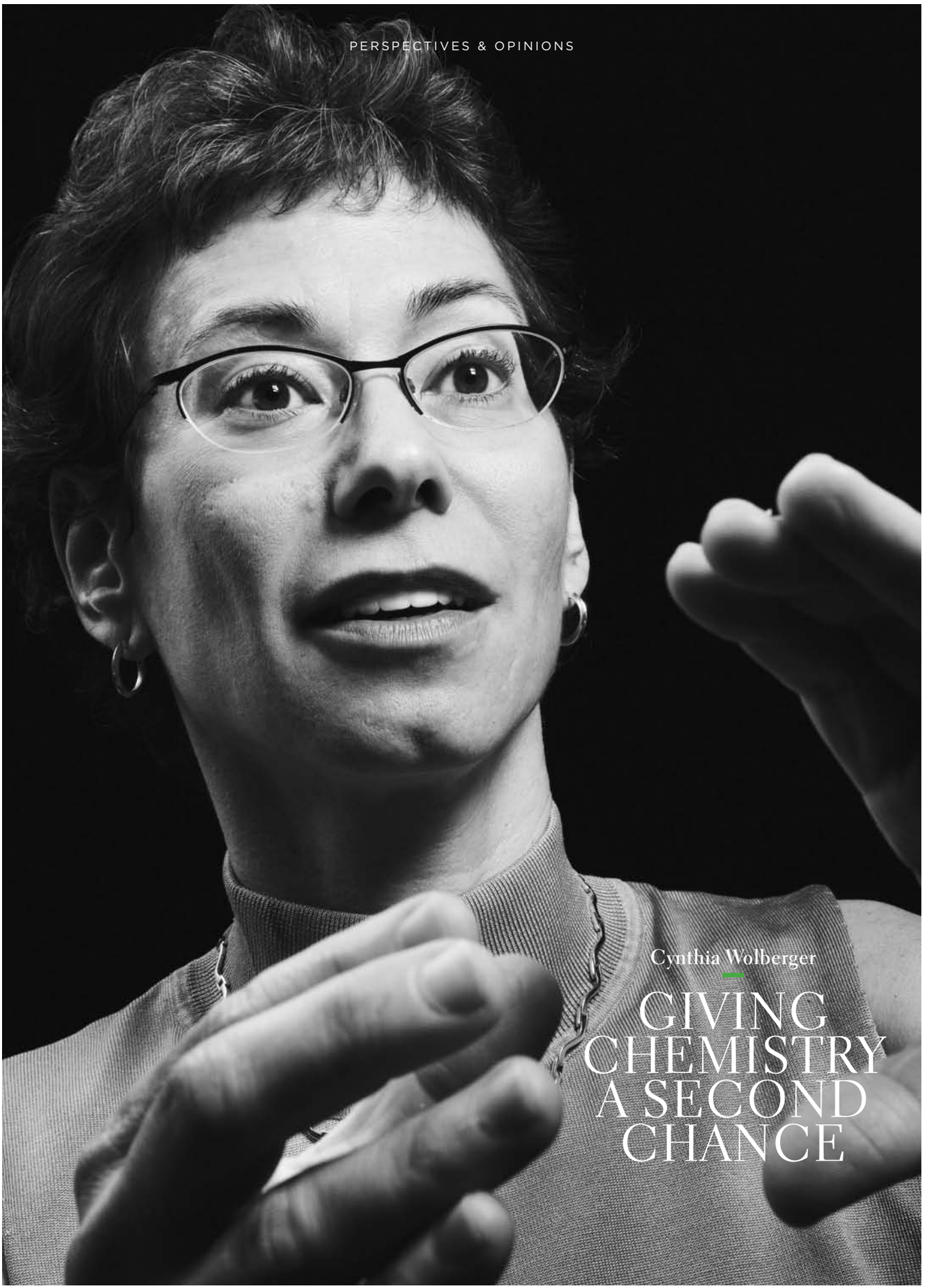

Cynthia Wolberger

GIVING CHEMISTRY A SECOND CHANCE

Paul Fetters

Structural biologist Cynthia Wolberger has spent much of the last decade trying to understand the behavior of Sir2 enzymes, also called sirtuins, which affect gene expression, metabolism, and aging. The key to understanding Sir2's biology, says Wolberger, an HHMI investigator at the Johns Hopkins University, is its unusual chemistry. To dig deeper, she dusted off her college notebooks and made some new friends.

What is it about Sir2 that caught your attention and inspired you to expand your knowledge of chemistry?

My lab has always concentrated on gene regulation, especially on proteins that bind DNA and control transcription. I was thinking of further aspects of transcriptional regulation that might be amenable to the tools of structural biology—my field—when I encountered sirtuins. I focused on the Sir proteins because they can shut down whole regions of a chromosome and turn off all genes located there. Sir2 in particular stands out because it makes life more difficult for itself. Instead of taking a more direct route to cleaving the appropriate molecules, it uses a more complex, energy-costly method. I wanted to explore the unusual chemistry of this process. When nature doesn't settle on the most efficient pathway to carry out a particular task, there must be a reason. Understanding Sir2's unique chemistry will be key to understanding its function and regulation. And the fact that it is universal—all organisms have at least one, if not several, sirtuins—means that its chemistry is important to all forms of life.

In what ways are you learning the chemistry you need?

Having had only the courses that most people took in college and graduate school—maybe fewer, as my background is in physics and biophysics—I'm basically playing catch-up. So I've been getting an education in chemistry and enzyme mechanisms in a number of ways, including by doing it. I asked my students to recommend some textbooks on enzyme mechanisms. I keep them here on my desk. This is a switch for me. When I first presented my work on these enzymes at an HHMI meeting, a friend came up to me afterward and said, "I can't believe you talked about enzyme mechanisms. As a student, you used to say it was so boring." It's true. My focus was thermodynamics. I was actively uninterested in chemistry back then. But it turns out to be the heart of the matter. Even though I was dragged into it by the necessities of my work, now I'm fascinated by it. Why does this enzyme do this baroque chemistry, how does it do it, and how is it being exploited by the cell? I spend time talking to different people as well. Now I tend to gravitate to enzymologists at meetings. This bouncing of ideas off people who have thought about enzyme chemistry for years has proven invaluable. Like anything in science, if there's something you need to learn, you go and learn it. A good scientist is a lifelong student.

How are you applying your new dexterity in chemistry and enzymology?

In my lab, we are learning about Sir2's chemistry in particular by visualizing structures of enzymes bound to a variety of substrates and intermediates, and by trying to trap the enzyme in the crystal at different stages of the reaction. Also, we are using proteomics approaches to identify new substrates and to characterize the substrate requirements for the reaction. That, together with standard enzymology of normal and mutant proteins, allows us to put together a picture of how sirtuins work.

What is the payoff?

Besides just understanding the fundamental nature of this fascinating chemistry, there are implications for human health. One sirtuin, SirT1, seems to regulate the p53 tumor-suppressor pathway. Sirtuins have also been implicated in the insulin-signaling pathway in diabetes. In lower organisms such as yeast, losing a copy of Sir2 shortens life span and getting extra copies of the enzyme makes them live significantly longer. Restricting calories extends life span in many organisms, including mammals (though it's never been proven in humans), and Sir2 may mediate that process. Much remains to be learned about Sir2's potential role in longevity. We're constantly finding out new things about them. Giving chemistry a fresh look is a big help.

INTERVIEW BY STEVE BENOWITZ. *Cynthia Wolberger is Professor of Biophysics and Biophysical Chemistry at the Johns Hopkins University School of Medicine.*

Q&A

What field of science do you struggle hardest to understand?

Students aren't the only ones who may find science challenging. Scientists themselves wrestle with particular aspects — even entire fields — of science. Here, four HHMI investigators reveal some of the things that stump them. Where is the late, great astronomer Carl Sagan when you need him? – EDITED BY KATHRYN BROWN

Natalie G. Ahn

ASSOCIATE PROFESSOR OF CHEMISTRY AND BIOCHEMISTRY, UNIVERSITY OF COLORADO AT BOULDER

"There are many fields that I find difficult, but at the moment I am struggling to understand neural networks and machine-learning algorithms. The applications of computational sciences to biological problems are tantalizing, but their language, conceptual processes, strategies for validation, and controls are very different from those of experimental biology. Luckily, we have good collaborators to interact with, but we do spend a lot of time just trying to figure out if we're really talking about the same thing!"

Nipam H. Patel

PROFESSOR OF INTEGRATIVE BIOLOGY AND MOLECULAR CELL BIOLOGY, UNIVERSITY OF CALIFORNIA, BERKELEY

"For me, bioinformatics is now particularly challenging. With the current flood of genome sequencing and analysis, researchers are drowning in data. Although scientists have found countless molecular differences between even closely related organisms, it's difficult to know how to sort through all these data and then build on them with further experiments that really capture evolution at the molecular level and explain the diversity of life."

Helen M. Piwnica-Worms

PROFESSOR OF CELL BIOLOGY AND PHYSIOLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE IN ST. LOUIS

"Discussions about the big bang and related topics come up in social gatherings with close professional colleagues or when my children ask me questions related to the origins of life. But cosmology is a field that is not intuitive to me. Theories like the big bang create uncertainty in my world ... in a Heisenberg sort of way."

Morgan Sheng

PROFESSOR OF NEUROSCIENCE, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

"Astronomy is the hardest for me to understand, due to my weakness in math and physics. Still, concepts like 'black holes,' 'supernovae,' and 'big bangs' are intellectually seductive and hard to resist. It is also healthy to feel 'small' sometimes, and nothing makes you feel small like the universe."

Ahn: Paul Fetters Patel: Todd Buchanan Piwnica-Worms: Mark Katzman Sheng: Jason Grow