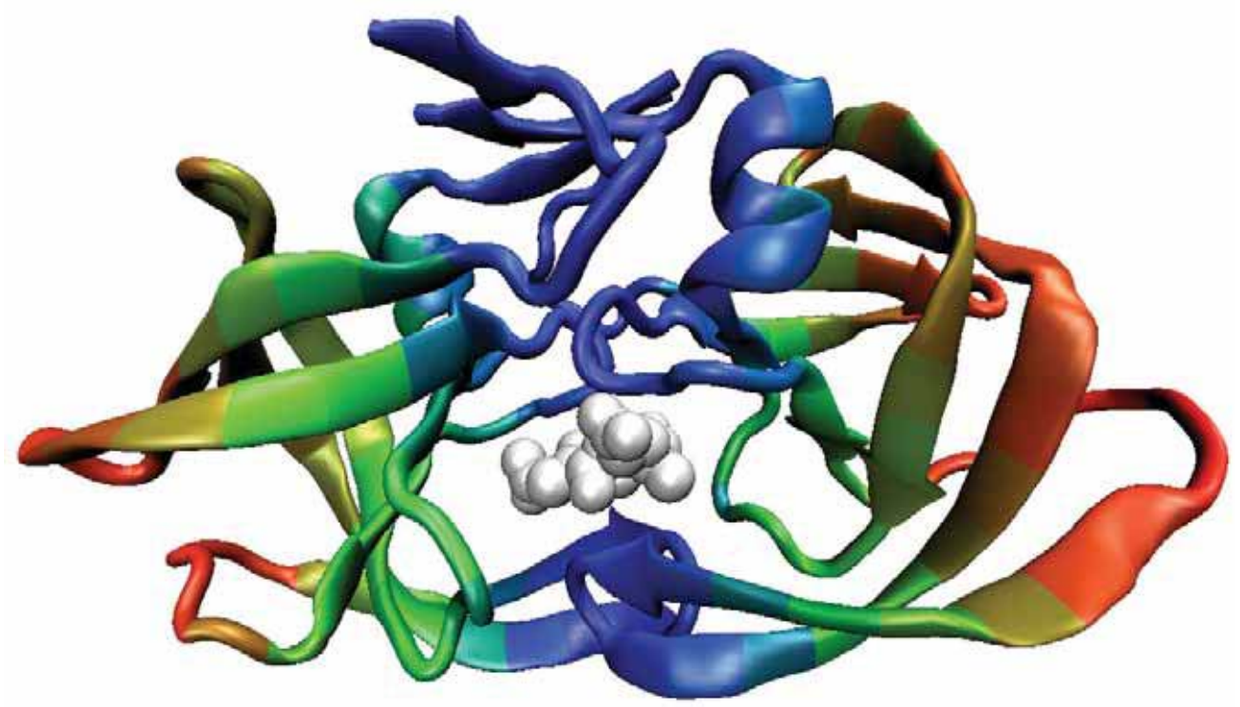
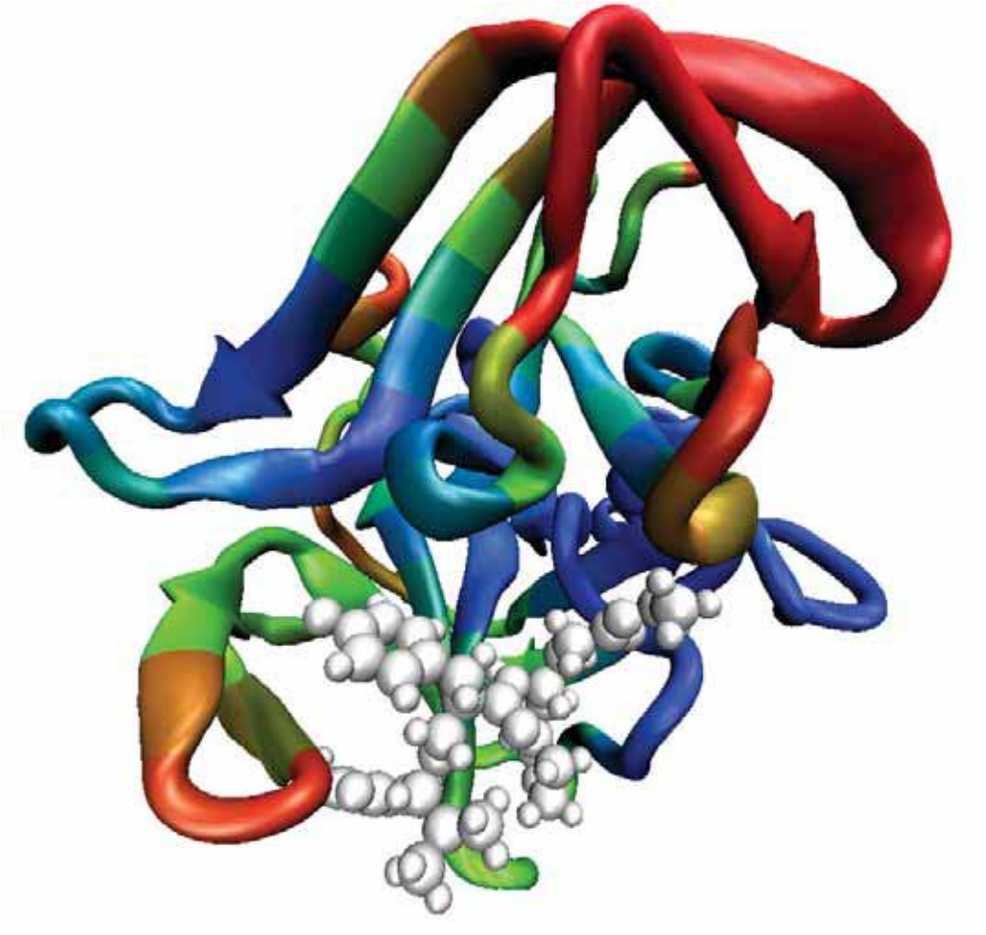




Ivet Bahar and Lee-Wei Yang made the connection between the architecture and stability of proteins and their function. Both figures here show the propensity of enzymes to bind ligands at highly stable regions. TOP: This HIV-1 protease is color coded by its ability to change structurally. Blue represents the most stable region. A binding molecule sits in the blue area at the bottom of the image—that's where the reaction that accounts for the protein activity occurs. BOTTOM: Similar features are illustrated for another enzyme (type 2 rhinovirus 3c protease) bound to an inhibitor (white).

COURTESY LEE-WEI YANG

IN SHAPE

RESEARCHERS SEEK LINK BETWEEN FORM AND FUNCTION | BY SHARON TREGASKIS

In 1913, biochemist Maud Menten—who would later spend four decades on the University of Pittsburgh School of Medicine faculty—copublished the Michaelis-Menten equation for predicting the rate of chemical reactions spurred by enzymes. Before the equation became standard, the pace at which any particular reaction might occur was a mystery. Even the most sophisticated scholars were stumped when it came to anticipating the speed at which the body's various biochemical feedback loops operated, and drug development was largely a game of chance.

In the intervening decades, the understanding of proteins and their functions has grown exponentially. Advanced imaging techniques reveal the molecular twists and turns of proteins, while the increasing speed and sophistication of computer processing allow for analysis of massive amounts of data. Yet, a clear conception of the relationship between a protein's chemical function and its shape has remained elusive. According to Pitt's Ivet Bahar, that means the basic science behind drug development really hasn't evolved much since Menten's day.

"Most drug discoveries are made through a kind of trial and error," says Bahar, the chair of the Department of Computational Biology, who is also a professor of molecular genetics and biochemistry.

"There are libraries of compounds that are screened against proteins to see which ones produce an effect."

A more rational—and effective—approach, she suggests, would allow researchers to identify optimal drug candidates in advance of experimentation, anticipating the molecular reactions they might initiate. Such capacity would save vast quantities of time and money.

But that means understanding both the rate at which any given reaction will proceed and how the structure of a particular enzyme influences its interactions.

Bahar, a PhD in chemistry, has dedicated her career to crafting sophisticated computer simulations that reveal the connection between form and function.

"Michaelis-Menten is useful and still widely used in experimental data," says Bahar, "but it doesn't provide a molecular understanding of what's happening."

In a June 2005 paper in the journal *Structure*, Bahar and postdoctoral research associate Lee-Wei Yang published their analyses of a set of two dozen proteins, examining both the chemical properties and physical dynamics of each.

"When we analyzed a whole bunch of proteins and identified their mechanical key regions—forget the chemistry, look at the mechanics—we identified key regions that act as a hinge," says Bahar.

Those hinge regions tended to be near the places where chemical reactions took place.

In the same issue of *Structure*, University of Wisconsin, Madison, biochemists Dimitry Kondrashov and George Phillips noted that the Pitt findings added a new dimension to the field of protein dynamics and would likely ease the job of solving protein structures.

The findings led Bahar and postdoctoral research associate Dror Tobi to investigate how chemical interactions between proteins relate to the shapes of increasingly complex macromolecules, such as immunoreceptors and muscle filaments.

Previously, scientists imagined proteins bound as interlocking rigid structures, much like a gate latch snapping down.

Bahar and Tobi's findings, published in the December *Proceedings of the National Academy of Sciences*, suggest that the architecture of a single protein—in its unbound state—provides clues as to where and how it will ultimately couple with other molecules.

Their studies suggest a more flexible coming together than the gate-latch model. Remember the popular Transformers toys from the '80s with multiple hinges and joints? They were two or three toys in one. (Like the "prehistoric pterodactyl" that became an "evil robot with snap-out attack blades.") Proteins also possess an "ensemble of conformations," says Bahar. One form best suits any given biological function, she explains, and binding stabilizes that particular shape.

As the name suggests, research in Bahar's department relies heavily on sophisticated algorithms and detailed computer coding. But the underlying conceptual framework takes precedence.

"First, we need to understand the fundamental phenomenon," she says. ■

DATA PLEASE

The Howard Hughes Medical Institute has honored the School of Medicine's new doctoral program in computational biology with a $1 million grant to develop a course to give students hands-on training in wet labs. More than 130 institutions across the country contended for the awards, intended to bolster interdisciplinary efforts. Ten programs received funding.

"There's a real necessity for closely coordinating experimental and computational approaches," says program codirector Ivet Bahar, who chairs Pitt's Department of Computational Biology.

She notes students can do *in silico* (her term for computational) studies to assess what might be eliminated from an experimental task. "That saves time and funds," she says. "On the other hand, computational biologists need data—all of our calculations are based on a repository of experimental results." —*ST*

One student is writing a medical thriller for her scholarly research project.

BRIDGET LASCH

A RESEARCHER IS BORN

STUDENT PROJECTS OPEN DOORS TO ACADEMIC MEDICINE

BY HATTIE FLETCHER

The young doctor, fresh out of residency, suspects something fishy at the sports center where she just started a new job. Some athletes connected to the center's clinic are performing very well—almost too well. Their drug tests come back negative, but the young doctor is starting to wonder: What's going on in the lab late at night? And why do the mysterious men in military uniforms who visit the clinic have access to the athletes' medical records?

Intrigued? If you want to get to the bottom of things, you'll have to wait. The young doctor, the sports center, and the athletes currently exist only in the imagination of Giselle Aerni (Class of '08).

Aerni plans to have a draft of *Adrenaline Rush*, a mystery/thriller in the mold of a Robin Cook or Patricia Cornwell novel, completed by March 2008. That's when she, along with all of her Pitt med classmates, will hand in the final report for a scholarly project.

At first blush, writing a thriller might not seem like the most scholarly of projects, but it will require Aerni to learn a great deal, not only about chemistry and the development of undetectable and illegal supplements, but also about the daily practice of sports medicine.

Performing such independent and self-motivated research is exactly the point of the scholarly project, a new addition to the curriculum, beginning with the Class of '08.

The school asks each student to design and carry out a long-term, in-depth study requiring logical decision making and analyses, notes Nina Schor, who helped design and oversee the program. Schor, an MD/PhD, believes the project also will help students develop their verbal skills as they articulate the goals of their projects and explain the results to classmates, mentors, and an executive committee of faculty members and deans.

These are essential skills. But there's another motive behind the program. The requirement is one way the school has responded to the need for more academic physicians. Schor hopes it will inspire some students to consider careers in academic medicine.

The first set of project proposals reflects the diversity of Pitt student interests. For example, there's an interactive Web site for diabetic children and a short documentary about an uncommon genetic disorder. And many students have opted to work on more traditional projects, often diving into research the summer after the first year. The program requires students to stay involved throughout med school, analyzing data, building relationships with mentors, and putting their research into a larger context for a paper or presentation.

For Joan Striebel (Class of '08), a former elementary school teacher, the project offered a welcome opportunity to develop her lab skills. After she realized teaching children was not her calling, Striebel headed back to college. Then in medical school she felt at a slight disadvantage compared to students who had already done research.

"My idea was to find someone established in lab work and have [her] show me how to ask questions and analyze data," Striebel says.

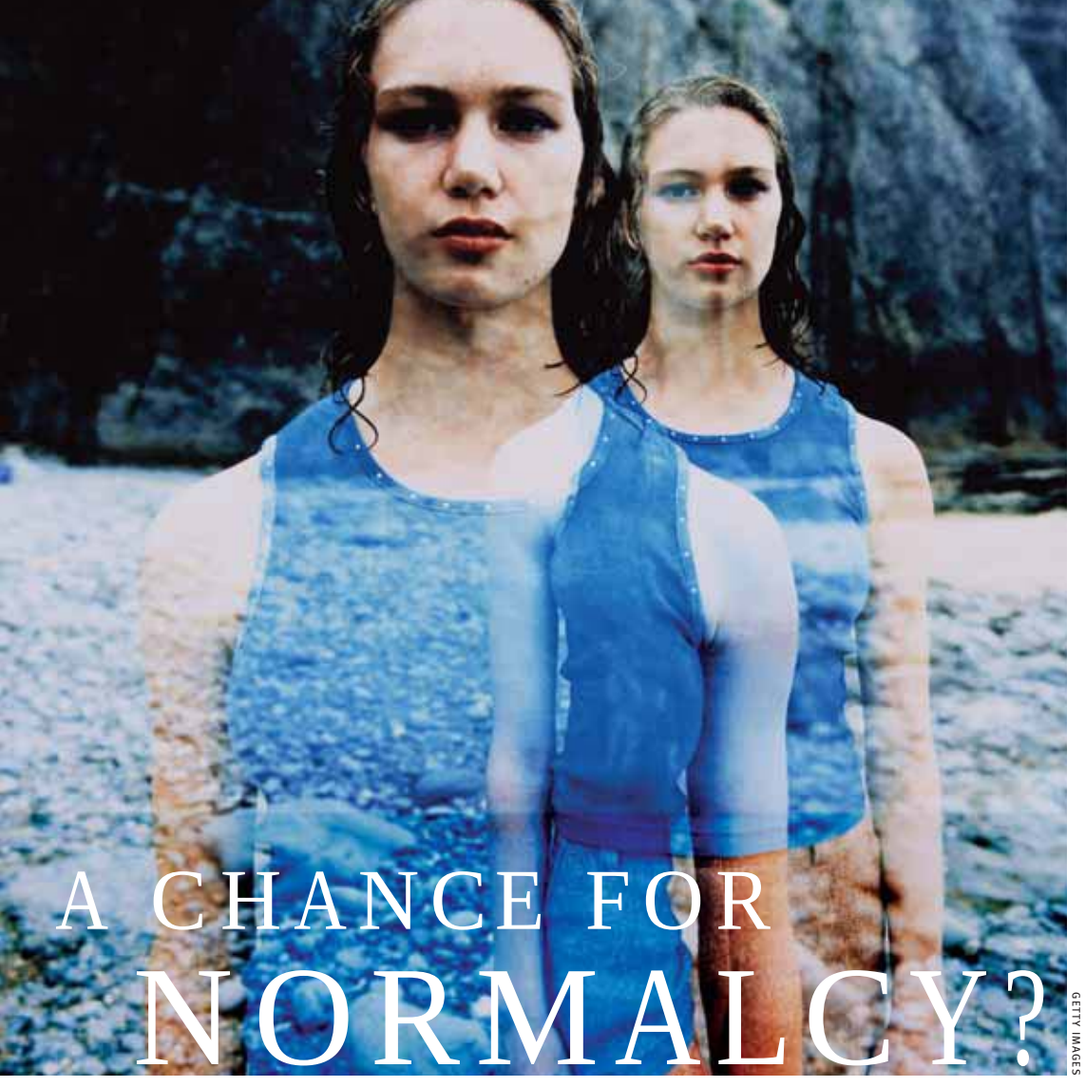
She found a willing mentor in Edith Tzeng, who suggested Striebel consider several projects relating to carbon monoxide and the vascular system. The student did preliminary work last summer; now she's seeking funding so she can take a leave during her third year to run the data again and continue the research.

Striebel is hooked. In part, she thinks it's because the project allowed her some independence at an otherwise very structured point in the curriculum. She's also grateful for the mentorship.

Perhaps the biggest thrill has been how much she enjoyed the lab work itself. On her return from a summer vacation, Striebel was surprised at her excitement to see "her" blood cell slides again. Now she's considering a career in pathology.

Schor says some students initially came to the project "kicking and screaming." But many of those students have stopped by Schor's office to offer sheepish apologies for being so resistant. *This has turned out to be the best thing I've done in medical school so far,* they tell her. ■

Watch future issues for more stories about how students shape their scholarly research projects.



GETTY IMAGES

A CHANCE FOR NORMALCY?

A NEW SCHIZOPHRENIA DRUG ON THE HORIZON | BY JOE MIKSCH

When David Lewis was growing up in Ohio, he had a favorite aunt. Both his mother and father were the youngest of seven. Lewis is the youngest of four. This meant, in Lewis' words, he was "the young cousin kind of left out" at densely populated family gatherings. This aunt took pity on the boy whose older cousins found better things to do than hang around with little David. She occupied his time and entertained him.

But, on occasion, his aunt wouldn't be around. No one talked about where she went or what she did when she was absent. She always came back; but when she did, Lewis perceived her to be out of sorts, different, not the same aunt he knew before. Gradually, she'd become her old self again, and the two would return to their usual relationship: kindly aunt and a young boy who otherwise would have been lonely.

As he got older, Lewis became aware that his aunt was mentally ill. Today, as director of the Translational Neuroscience Program and the Conte Center for the Neuroscience of Mental Disorders as well as professor of psychiatry and neuroscience at the University of Pittsburgh, it's his life's work to understand the mechanisms and costs associated with major psychiatric disorders.

"I really liked her," he says of his aunt. "I felt badly, though. I couldn't understand it at all. I didn't say, 'Okay, well, I'm going to go do research to try and solve this problem.' But it created within me a concern, a desire, compassion, and awareness."

Lewis, an MD who has been on the School of Medicine faculty since 1987, is in the midst of running a phase II clinical trial of a drug that may help subdue cognitive defects associated with schizophrenia, such as dysfunction of working memory.

The drug targets a class of GABA neurons (GABA is a kind of amino acid) that regulates working memory. Working memory is what healthy people draw on to briefly retain and use information. People with schizophrenia are likely to have certain neurons that don't produce enough GABA.

Yet, says Lewis, "If it were possible to just rev up the activity [of a GABA-producing cell] and make it kick out GABA more often, well, that would probably be worse than the situation is now. We want to preserve the timing but boost the signal."

He thinks he's found a way to do that.

In addition, he believes the drug will "boost GABA signaling just at the location where the signaling is deficient and not boost it at locations where things seem to be normal."

Lewis says that most schizophrenia drugs are directed toward controlling psychosis—the delusions and hallucinations commonly associated with the disease. Although these drugs help keep people with schizophrenia out of the hospital, they don't do anything to restore normal thought processes.

A combination of Lewis' yet-to-be-named experimental drug, antipsychotics, and cognitive and social rehabilitation training may ease a patient's reintegration into society.

It's also possible that the drug could be effective in treating teens and young adults at the onset of symptoms.

"There could be a treatment intervention," Lewis says.

"You could get involved early to enhance cognitive capacity. Could you delay or postpone or reduce the severity of the more evident clinical features of the illness? It's the grand target."

Lewis expects that trial results will be available toward the end of this year. If the trial volunteers don't show great improvement, the study still could be considered a success from Lewis' perspective.

"The hope is, even if we can't detect a clinical improvement, we will see a change in biology. That will at least let us know we're on the right track." ■