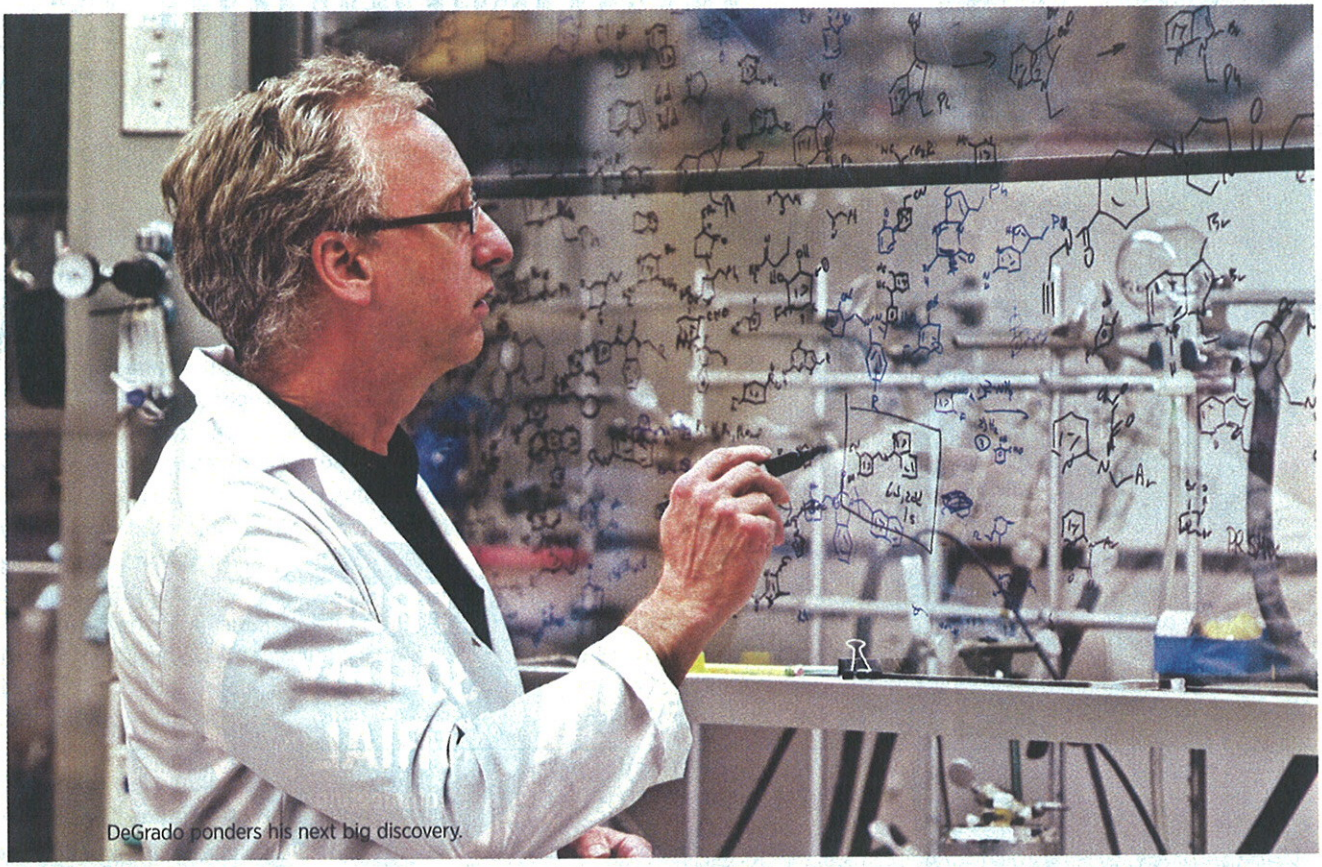

DeGrado ponders his next big discovery.

Antibiotic Artisan

Using supercomputer simulations, chemist William DeGrado is crafting potent new drugs that mimic nature's own defenses.

BY ROBERT LANGRETH

The biotech industry creates new drugs by making tweaks to natural proteins. University of Pennsylvania chemist William DeGrado is more of an artist than a tweaker. He has spent much of his career designing new proteins from scratch, a three-dimensional engineering task so complicated that until recently few scientists bothered to try. His goal is to create molecules unknown to nature but adept at serving humans by absorbing environmental toxins, fighting cancer or extending Moore's Law down to the atomic scale.

These applications are years away. But DeGrado's interest in creating artificial molecules that mimic more complex natural ones may have a more immediate payoff: a powerful new generation of antibiotics.

Scientists have known for decades that organisms as diverse as insects, frogs, pigs and humans make natural protein-based antibiotics to ward off microbes. These chemicals are one of

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life's most ancient defenses. They attack microbes in a unique way that makes it hard for resistance to develop.

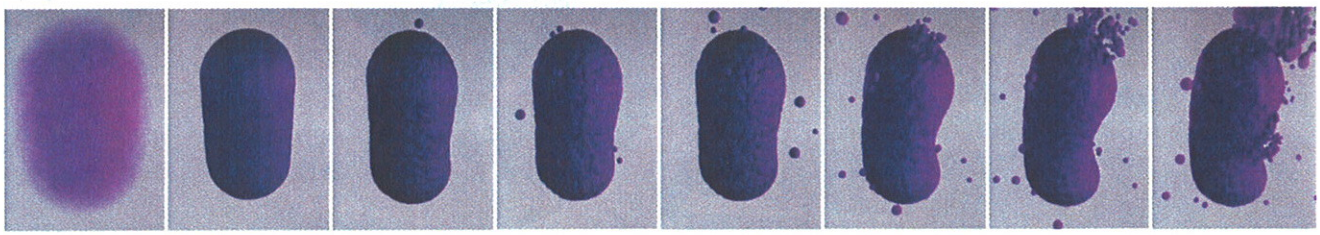
Drugmakers have tried to bottle their power, but the compounds, known as antimicrobial peptides, have proven to be poor drugs. They are difficult to manufacture, unstable in the bloodstream and prone to toxic side effects. A drug based on pig chemicals failed to prevent pneumonia in hospital patients in a 2006 study. Another drug, from the African clawed frog, was rejected in 1999 by the FDA as a treatment for diabetic foot ulcers. Because of the peptides' high cost and unclear safety profile, "Big Pharma has abandoned them," says Georgetown University researcher Michael Zasloff.

DeGrado, with the help of a powerful supercomputer simulation, has created new antibiotics that mimic natural ones but are far simpler to produce and more stable. They capture the essence of animal antibiotics in molecules that are one-quarter the size and can be made with standard chemistry techniques. The supercomputer work "was absolutely critical" in crafting the antibiotic, says DeGrado. "It narrowed the choices tremendously [and converted it] from an intractable problem to a feasible one."

other things, helps it to distinguish bacteria from human membranes, which have a less negative charge. The other side of the antibiotic contains an oily surface that is attracted to the greasy interior portion of the membrane.

Doodling on a scrap of paper with postdoctoral student Gregory Tew (now a professor at the University of Massachusetts), DeGrado came up with a crescent-shaped molecule that was somewhat similar to the polymer Kevlar used in bulletproof vests. He wasn't sure it would work, so he took it across the campus to molecular modeling expert Michael Klein. Klein took one look and was convinced that DeGrado was on to something. "I was so excited that I got [DeGrado] to sign and date the paper and gave it to my secretary" for safekeeping, recalls Klein, now at Temple University.

Klein devised a supercomputer simulation to predict in practically atomic detail what would happen when DeGrado's molecule collided with a bacterium's membrane. Each "frame" of the movie represents a fraction of a nanosecond and involves 1 million calculations. The simulation took nearly three months to perform at the Pittsburgh Supercomputing Center and revealed that DeGrado's instincts were on target. "What we discovered with the simulation is that these things dive into the membrane and swim around underneath," says Klein. "When there is enough of them they make their way to the other side of the membrane and make a pore." The bacterium's contents leak out. Lab experiments confirmed that this is what happens.



After a bacterium is hit by PolyMedix's new antibiotic, its membrane is compromised and the contents leak out. This artist's rendition is based on an electron microscope's image of an E. coli bacterium. This mechanism should be less vulnerable to resistance.

The first antibiotic from this work is now in human trials at the biotech firm PolyMedix, which DeGrado cofounded in 2002. In animal tests PolyMedix's drug PMX-30063 is at least as powerful as the gold standard hospital antibiotic vancomycin at killing key strains. The initial effectiveness trial in staph skin infections could yield results this year.

New antibiotics are badly needed as bacteria become resistant to existing drugs. Because existing antibiotics target specific bacterial molecules, a mutation in the bacterium can render the drugs ineffective. One nasty bug inhabiting American hospitals, methicillin-resistant *Staphylococcus aureus,* is linked to 18,650 deaths each year, a 2007 study concluded. In contrast, the peptide antibiotics are less vulnerable to resistance because they infiltrate and damage the membrane that holds the bacterium together.

In 2000 DeGrado became curious about what was the simplest possible molecule that could mimic this membrane-infiltrating ability. He realized that the key was a two-sided structure. One side is attracted to negatively charged molecules on the surface of bacterial membranes. This, among

DeGrado and Klein published their initial results in 2002 and cofounded PolyMedix the same year. It took six years to design and test a molecule safe and effective enough to go into human trials. No resistance to PolyMedix' drug has emerged in standard lab tests. Klein says the continuous simulations give chemists confidence they are on the right track. "Our role is often psychological. A good scientist has intuition. If we can build a model that reinforces that intuition, they have confidence to extrapolate to the next level."

Wall Street remains skeptical. PolyMedix shares hover around a dollar. A key question is whether the drug will be able to distinguish bacteria from host as it goes about its killing business. PolyMedix Chief Executive Nicholas Landekic is optimistic—there have been no showstopper safety problems so far—but only big human trials can tell for sure.