Novel Antibodies Beat Bacterial Toxins

An experimental drug that quenches microbial poisons can save the lives of patients with severe bacterial infections, new research indicates. If the findings convince the FDA to approve the compound later this year, as some physicians expect, the drug will become the first of a new family of medicines – called human monoclonal antibodies – to advance from the research arena into the clinic.

In the United States each year, as many as 300,000 people acquire severe blood infections from gram-negative bacteria. Many of these microbes, including the large-intestine inhabitant *Escherichia coli,* are normal tenants of the human body. But when an individual's immune system becomes suppressed (by disease or chemotherapy, for instance) or when protective tissue-barriers get breached (as in surgery), the otherwise benign organisms can enter the bloodstream and go on a rampage.

Most important, they secrete potent compounds called endotoxins, which trigger a cascade of life-threatening reactions in the body. Under the influence of endotoxins, pulse and respiratory rates increase, the coagulation system falters and kidneys begin to fail. The syndrome can progress rapidly to septic shock, in which blood pressure drops radically. About one-third of those diagnosed with this microbial poisoning, called gram-negative bacteremia, die from the infection despite massive doses of antibiotics, which kill the offending bacteria but leave the endotoxin intact.

The new drug, called HA-1A, consists of antibodies produced by laboratory-reared human cells isolated nearly a decade ago by researchers at Stanford University and the University of California, San Diego. The antibodies bind to endotoxins, inactivating them.

In its first large-scale human tests, HA-1A seems to have worked exactly as it should. The trial, described in the Feb. 14 NEW ENGLAND JOURNAL OF MEDICINE, involved more than three dozen U.S. and European medical centers and included 543 patients with various blood infections. All patients received standard antibiotic therapy. In addition, about half the patients received an intravenous infusion of HA-1A while the rest received a placebo infusion.

In the 200 patients with gram-negative bacteremia, infection-related mortality was 39 percent lower among those receiving HA-1A than among those on placebo. That's impressive, considering the severity of these patients' illness, comments Harry L. Malech, a bacterial disease specialist at the National Institute of Allergy and Infectious Diseases in Bethesda, Md., who is familiar with the work. "The beauty of this study is that the product was helpful even after the bacteremia had progressed," he says. "This is a marvelous example of a drug whose performance in the clinic matches what we'd hoped for from theory."

The drug caused no significant side effects and, as expected, didn't help patients with blood infections due to microbes that don't secrete endotoxins.

In an editorial accompanying the report, Sheldon M. Wolff of the Tufts University School of Medicine in Boston cautions that the promising findings should be confirmed by additional studies. But he foresees a time when physicians may routinely treat gram-negative bacteremia not only by targeting the microbes with antibiotics but also by blocking the fatal effects of endotoxins with antibodies such as HA-1A and other novel compounds now under development.

– R. Weiss

One researcher's DNA is another's unicorn

It looks like a DNA molecule. It meanders like a DNA molecule. It even appears to twist like a DNA molecule. But that doesn't mean it is one, warn two chemists at the University of Utah in Salt Lake City.

In the Feb. 8 SCIENCE, Thomas P. Beebe Jr. and Carol R. Clemmer caution that researchers using scanning tunneling microscopes (STMs) to image biological molecules deposited onto a commonly used graphite substrate often mistake biological-looking features of the graphite surface for the biomolecules they aim to study.

Since their introduction in the early 1980s, STMs and related "scanning probe" instruments have provided researchers with observational revelations and unprecedented manipulative powers, even at the atomic level. Scientific journals now teem with striking STM images. "Awash with enthusiasm, the first pretty picture [that seems to show a biomolecule] gets published," says biophysicist and STM researcher Stuart Lindsay of Arizona State University in Tempe.

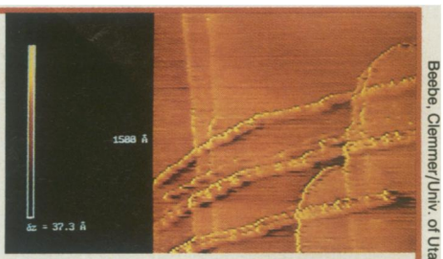
But pitfalls lurk for the unwary. Last August, several speakers at an STM conference in Baltimore remarked that features of a substrate called highly ordered pyrolytic graphite (HOPG) can muddle interpretations of biomolecular studies. "People have been talking about [this problem] for a while, but until now no one had actually addressed it in a paper," Clemmer says.

She and Beebe used their STM to examine hundreds of blank HOPG surfaces. They found numerous features resembling what they would expect to see if they had deposited DNA or other biomolecules onto the blanks. Beebe admits he has fallen prey to these ambiguities in the past.

Looking at HOPG under an STM is "like looking at a marble floor in a bathroom: You can see anything you want to in it," Lindsay notes.

On HOPG surfaces, the Utah scientists and others have observed linear, periodic features easily mistaken for a chain-like DNA or protein molecule. Sometimes these features "meander" over atomic steps on the substrate, giving the false impression that they are independent of the surface. Some even appear to have a left-handed twist remarkably similar to the helical pitch of many biomolecules.

Beebe acknowledges a "very small probability" that his team's observations resulted from unexpected DNA contamination on the supposedly naked graphite. However, he says, "I strongly feel that that's not the case."



Beebe, Clemmer/Univ. of Utah

Graphite surface features look deceptively like DNA.

Graphite's propensity for harboring long, twisting, polymer-like features that match textbook representations of molecules like DNA can create a dangerous decoy for scientists who hunt for such molecules. "There are many reports due to come out which we think could be vulnerable to these problems," Beebe says.

He and Clemmer urge biomolecular researchers to abandon graphite for substrates less likely to mimic biological molecules. Some STM users, they note, are turning to gold, often deposited onto a mica surface, as a preferred substrate for such studies. *– I. Amato*