CLEANING UP BLOOD

A NEW DEVICE GETS NASTY STUFF OUT

BY TRINA WOOD

Medics struggle to lift the inert body of the young soldier onto a stretcher, then pause to take a pulse and measure other vital signs—he is still alive, yet unconscious, with no external sign of injury. Quickly, they set up a blood pump and begin running his blood through a baton-sized filter. Until the medics can reach a hospital and figure out what chemical or biological agent was used in the attack, this small device may keep enough toxins out of the soldier's bloodstream to keep him alive.

While this scenario may seem straight out of a science-fiction novel, John Kellum, associate professor of critical care medicine in the School of Medicine, says the reality of being able to use such technology may only be a few years distant.

His team of basic scientists and clinical researchers, including Mingchen Song and Ramesh Venkataraman, is developing a device that shows promise in clearing noxious substances from blood, including those brought on by biological weapons. Specifically, this device reduces the concentration of inflammatory mediators known as cytokines, produced primarily by white blood cells as a response to illness or trauma. Normally present in small quantities, these proteins cause damage to cells and tissue when present in high levels. Throughout the past decade, researchers have tried to find ways to either stop the overproduction of these mediators or remove them from the blood. None of their efforts worked very well—until now.

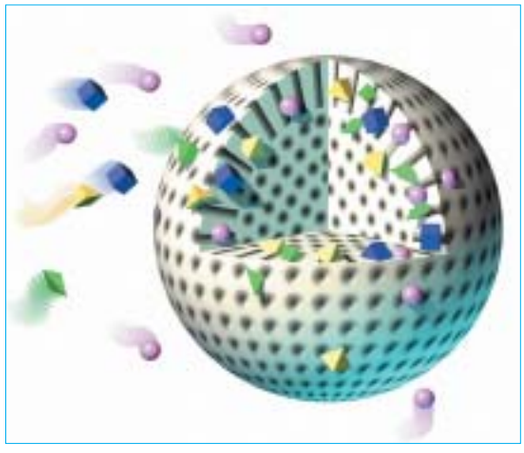
Nearly two years ago, Kellum was working late in his office when an e-mail came through at 2 a.m. Thinking it might be a colleague from the other side of the planet, Kellum read it immediately. To his surprise, the e-mail came from a company called RenalTech in New York. Scientists at RenalTech had read a paper of his describing how inflammatory mediators may be best removed from the blood by absorption. Their chemists had recently developed BetaSorb, a cartridge-shaped device undergoing testing in clinical trials for hemodialysis patients. BetaSorb was designed to remove a class of toxic molecules from the blood (molecules similar in size to cytokines) not efficiently removed by standard dialysis. (These molecules jeopardize the health and quality of life for chronic renal-failure patients.) With a few bioengineering modifications, they felt Kellum could use this existing technology to remove large volumes of cytokines from acutely ill patients.

Joined by collaborators at RenalTech, Kellum's team set to work on a new evolution of BetaSorb specially designed to absorb cytokines. The end result is CytoSorb, a cartridge about 12-inches long by 3-inches wide, packed with a column of tiny beads (each about 500 microns) covered with pores like a Wiffle ball. Kellum notes this device is novel because each bead is made from a highly absorbent polymer and coated with a biocompatible surface, so that white blood cells don't react to the beads. As blood flows through the device, small to mid-size molecules can get inside the beads where all the absorption occurs, but larger molecules and cells can't.

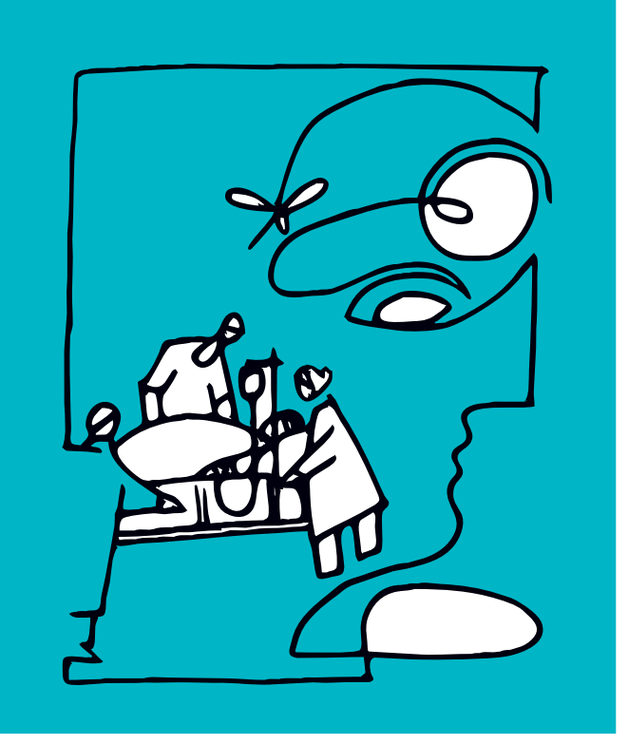
Within the next several months, CytoSorb will be used in clinical trials for patients undergoing cardiopulmonary bypass. These patients typically experience an inflammatory response owing to stresses of surgery and the bypass machine. Though inflammation is often a normal response to infection, the response in these cases only causes harm because it triggers a massive release of cytokines. Reducing these harmful levels of cytokines may result in better patient outcomes, says Kellum.

CytoSorb could also be used in treating severe sepsis. Transplant recipients whose new organs are suffering from reperfusion injury could also benefit. And victims of bioterrorism or biological weapons are potential target patients, because the low-tech, portable device can be used to purify the blood during evacuation, even before doctors identify the harmful agent.

"This device is potentially cheaper and more effective than drug therapy with a much broader applicability," Kellum says. ■



John Kellum and colleagues' CytoSorb is designed to remove harmful levels of cytokines from blood. It will soon be tested in clinical trials. What looks like a Wiffle ball (right) is actually a 500-micron-size bead. CytoSorb is filled with such beads, which absorb only small and mid-size molecules, notably cytokines.



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PATIENTS WITH THE SAME CONDITION MAY REQUIRE DIFFERENT TREATMENTS | **BY KRISTIN OHLSON**

Imagine that two people have survived a car crash and are rushed to the same emergency room. They present the same mix of physiological red flags: Both have suffered trauma to the body and blood loss. Both have similarly abnormal readings for blood pressure, respiration, heart rate, and other factors. The ER team rushes to set their bones, close their wounds, give them blood, and offer other standard treatments. Both patients seem to be stable after 24 hours. Yet days later, one dies in the ICU of multiple organ failure and the other survives.

When faced with trauma or severe infection, the body unleashes a fusillade of cellular and molecular events to reduce blood loss, fight pathogens, and eliminate damaged tissue. Sometimes, though, the response is so overwhelming that it destroys the body it is trying to protect. Why does one patient's inflammatory response save him, while that of another leads to systemic shock or multiorgan failure?

"The inflammatory response is like a game of chess," says Gilles Clermont, assistant professor of critical care medicine at the University of Pittsburgh and an attending physician at UPMC Presbyterian. "We're very good at knowing exactly how the pawn moves and how the queen moves, but we are still not good at knowing how the whole game works." In other words, critical care specialists may know what a certain enzyme is doing but don't understand overall how individual patients will fare in this high-stakes game. "It all has to do with one genetic makeup compared to another," Clermont adds.

Before Clermont joined what's now Pitt's Department of Critical Care Medicine in 1994, he had done graduate work in physics and never lost his interest in that subject, especially in the study of complex systems. This field of study examines how dozens of processes create a global system that is dauntingly more complex and mysterious than the sum of its parts; in particular, researchers in this field look at the indirect effects resulting from the interdependence of many seemingly unrelated or distantly related processes. The study of complex systems has been applied to diverse areas—from environmental woes to economic cycles. Clermont's own graduate thesis discussed complex systems in language formation. At some point in the ICU, he looked at a patient in the throes of inflammation and realized that here, too, was a complex system. He began to imagine a diagnostic tool that could assess the integrated effect of all the inflammatory processes at work in an individual patient and offer custom therapies.

With the help of a National Institutes of Health grant, Clermont and Pitt specialists in mathematics, immunology, surgery, and statistics began developing software that uses mathematical modeling to simulate the interaction of more than 20 key processes involved in the inflammatory response. When this tool receives its final tweaks, emergency and ICU physicians will prepare data for it by taking blood samples from a patient at several timed intervals, even as they begin treatment, and measuring the patient's changing levels of immune cells and cytokines. As they feed this data into the computer model, it will gauge the action and energy of patients' inflammatory responses over time and reactions to treatments.

"The model 'learns' you as it gathers information," explains Clermont. "When we take your last blood sample, it will have zeroed in on who you are as an individual and what will drive your outcome many days down the road." He believes the model will not only be able to determine what kind of drug or combination of drugs a particular patient needs, but it also will be able to determine the best time to administer the dose.

Clermont and his team are still developing the model with animal and human data; a working clinical version probably won't be ready for another three years. However, a partnership between the Pitt team and LaunchCyte, a company that commercializes biotechnology breakthroughs, may deliver another promising application sooner. The partners have founded Immunetrics, a company that markets a version of the software designed to reduce the cost of drug development as well as speed the development of drugs for inflammation-related diseases like sepsis, a frequently fatal response to infection that afflicts 750,000 Americans every year. Using this tool, pharmaceutical and biotech companies could test the action of promising compounds before they ever reach the stage of costly animal trials. In addition, they may be able to run virtual clinical studies that account for the millions of combinations of criteria—the type of patient enrolled, the timing of the drug administration, the dose, etc.—to design more productive human trials.

"This method will replace a lot of trial and error," says Tom Petzinger Jr., CEO and chair of LaunchCyte. "And with the computer, you can do a lot of marginal experiments, too—the ones no one wants to try because they're such long shots." ■