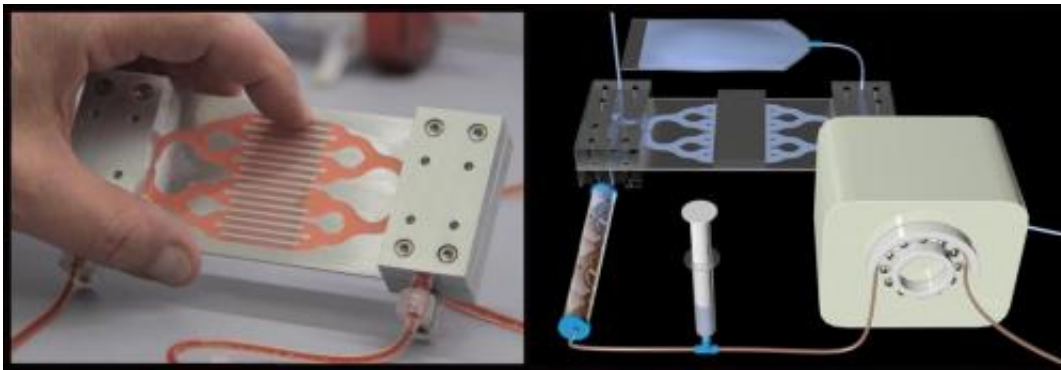


Blood-cleansing biospleen device developed for sepsis therapy

September 14 2014



The Wyss Institute's spleen-like blood-cleansing device makes use of genetically modified blood proteins coated on magnetic nanoparticles and magnetic forces to pull a variety of pathogens from the blood. Credit: Harvard's Wyss Institute

Things can go downhill fast when a patient has sepsis, a life-threatening condition in which bacteria or fungi multiply in a patient's blood—often too fast for antibiotics to help. A new device inspired by the human spleen and developed by a team at Harvard's Wyss Institute for Biologically Inspired Engineering may radically transform the way doctors treat sepsis.

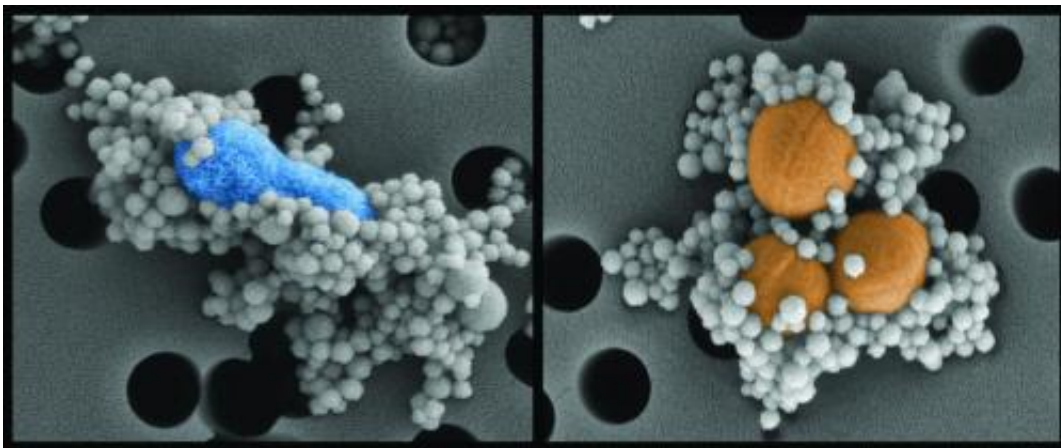
"Even with the best current treatments, [sepsis](#) patients are dying in intensive care units at least 30 percent of the time," said Mike Super, Ph.D., Senior Staff Scientist at the Wyss Institute. "We need a new approach." Sepsis kills at least eight million people worldwide each year

and it's the leading cause of hospital deaths.

The device, called a "biospleen," exceeded the team's expectations with its ability to cleanse human blood tested in the laboratory and increase survival in animals with infected blood, as reported in *Nature Medicine*. In a matter of hours, it can filter live and dead pathogens from the blood, as well as dangerous toxins that are released from the pathogens.

Sepsis occurs when a patient's immune system overreacts to a bloodstream infection, triggering a chain reaction that can cause inflammation, blood clotting, organ damage, and death. It can arise from a variety of infections, including appendicitis, urinary tract infections, skin or lung infections, as well as contaminated IV lines, surgical sites, and catheters.

Identifying the specific pathogen responsible for sepsis can take several days, and in most patients the causative agent is never identified. If doctors are unable to pinpoint which types of bacteria or fungi are causing the infection, they treat sepsis patients empirically with broad-spectrum antibiotics – but these often fail in many cases and they can have devastating side-effects. The sepsis treatment challenge continues to grow more complex as the prevalence of drug-resistant bacteria increases while the development of new antibiotics lags.



This picture demonstrates the effectiveness of the genetically engineered protein-coated magnetic beads binding to pathogens. Here, the magnetic beads (128 nm) are bound to two pathogens (*E. coli* on the left and *S. aureus* on the right) Credit: Harvard's Wyss Institute

"This is setting the stage for a perfect storm," said Super, who was part of a team led by Wyss Institute Founding Director Don Ingber, M.D., Ph.D., that also included Wyss Institute Technology Development Fellow Joo Kang, Ph.D., and colleagues from Boston Children's Hospital, Harvard Medical School, and Massachusetts General Hospital.

Kang, who is also a Research Associate at Harvard's School of Engineering and Applied Sciences (SEAS) and Research Fellow in the Vascular Biology Program at Boston Children's Hospital, set out with the team to build a fluidic device that works outside the body like a dialysis machine, and removes living and dead microbes of all varieties—as well as toxins. They modeled it after the microarchitecture of the human spleen, an organ that removes pathogens and dead cells from the blood through a series of tiny interwoven blood channels.

The biospleen is a microfluidic device that consists of two adjacent hollow channels that are connected to each other by a series of slits: one channel contains flowing blood, and the other has a saline solution that collects and removes the pathogens that travel through the slits. Key to the success of the device are tiny nanometer-sized [magnetic beads](#) that are coated with a genetically engineered version of a natural immune system protein called mannose binding lectin (MBL).

In its innate state, MBL has a branch-like "head" and a stick-like "tail."

In the body, the head binds to specific sugars on the surfaces of all sorts of bacteria, fungi, viruses, protozoa and toxins, and the tail cues the immune system to destroy them. However, sometimes other immune system proteins bind to the MBL tail and activate clotting and organ damage – so Super used genetic engineering tools to lop off the tail and graft on a similar one from an antibody protein that does not cause these problems.

The team then attached the hybrid proteins to magnetic beads 128 nanometers in diameter approximately one-five hundredths the width of a human hair to create novel beads that could be added to blood of an infected patient to bind to the pathogens and toxins without having to first identify the type of infectious agent. The sepsis device then has a magnet that pulls the pathogen-coated magnetic beads through the channels to cleanse the blood flowing through the device, which is then returned to the patient.

The team first tested their blood-cleaning system using human blood in the laboratory that was spiked with pathogens. They were able to filter blood much faster than ever before, and the magnets efficiently pulled the beads – coated with the pathogens – out of the blood. In fact, more than 90 percent of key sepsis pathogens were bound and removed when the blood flowed through a single device at a rate of about a half to one liter per hour, and many devices can be linked together to obtain levels required for human [blood](#) cleansing at dialysis-like rates.

Next they tested the device using rats that were infected with *E. coli*, *S. aureus*, and toxins – mimicking many of the bloodstream infections that human sepsis patients experience. Quite similar to the tests on [human blood](#), after just five hours of filtering, about 90 percent of the bacteria and toxin were removed from the rats' bloodstream.

"We didn't have to kill the pathogens. We just captured and removed

them," Super said. What's more, 90 percent of the treated animals survived compared to 14 percent of the controls—and sure enough, thanks to the team's modified MBL, the [immune system](#) had not overreacted.

"Sepsis is a major medical threat, which is increasing because of antibiotic resistance. We're excited by the biospleen because it potentially provides a way to treat patients quickly without having to wait days to identify the source of infection, and it works equally well with antibiotic-resistant organisms," said Ingber, who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital, as well as Professor of Bioengineering at SEAS. "We hope to move this towards human testing to advancing to large animal studies as quickly as possible."

More information: An extracorporeal blood-cleansing device for sepsis therapy, *Nature Medicine*, [dx.doi.org/10.1038/nm.3640](https://doi.org/10.1038/nm.3640)

Provided by Harvard University

Citation: Blood-cleansing biospleen device developed for sepsis therapy (2014, September 14) retrieved 27 April 2024 from <https://medicalxpress.com/news/2014-09-blood-cleansing-biospleen-device-sepsis-therapy.html>

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