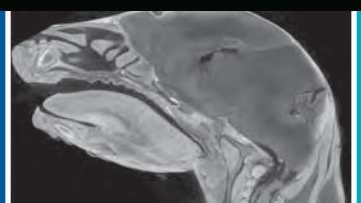
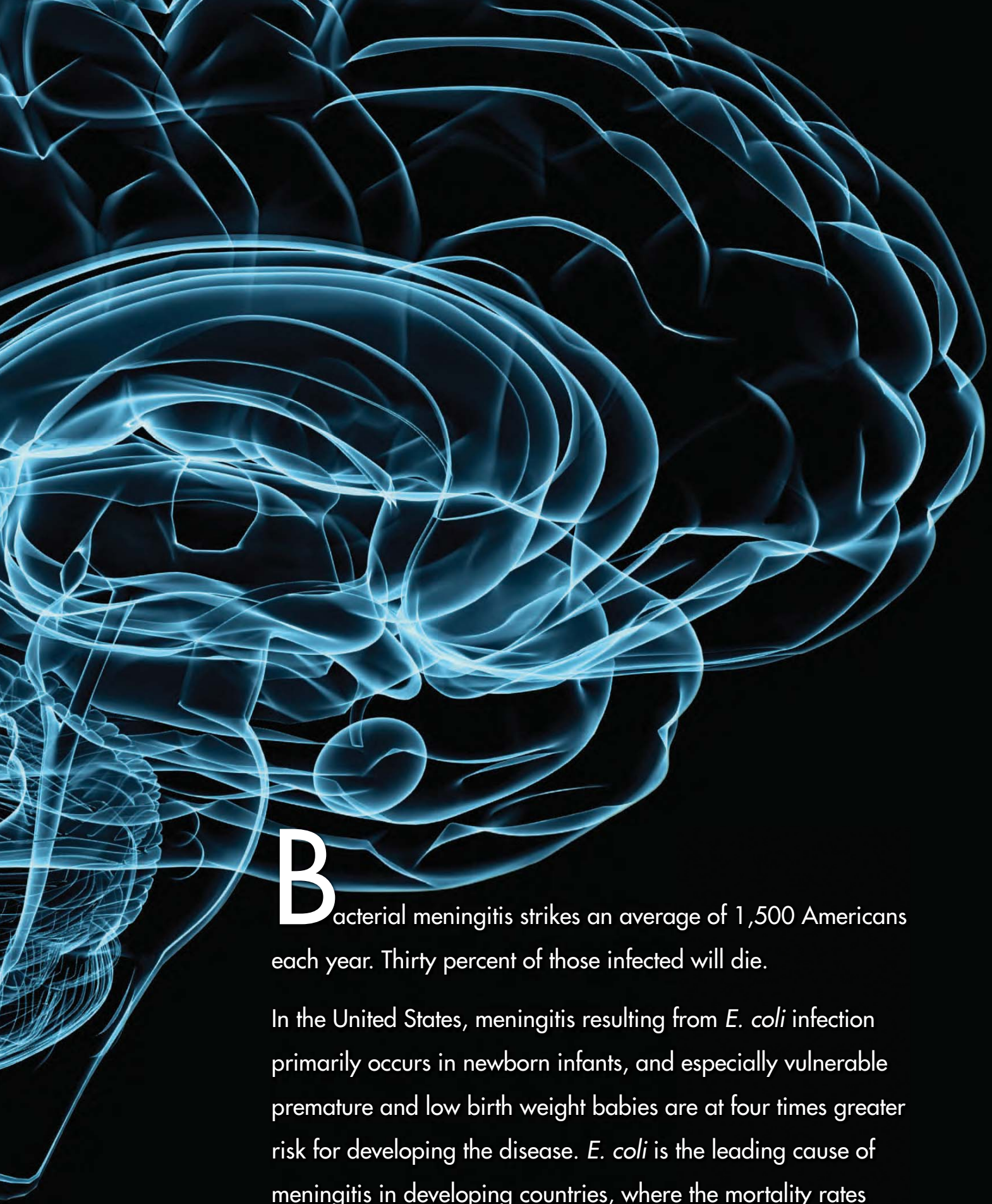
NOVEL THERAPY AT A LOW COST

In pursuit of an effective, inexpensive treatment for meningitis





Bacterial meningitis strikes an average of 1,500 Americans each year. Thirty percent of those infected will die.

In the United States, meningitis resulting from *E. coli* infection primarily occurs in newborn infants, and especially vulnerable premature and low birth weight babies are at four times greater risk for developing the disease. *E. coli* is the leading cause of meningitis in developing countries, where the mortality rates are higher than in the U.S.

"I wanted to make a significant impact on this worldwide health problem," says Prasadarao V. Nemani, PhD, a researcher in the Microbial Pathogens and Immunology program at The Saban Research Institute. "We set the bar high—not only did we need a new way to treat meningitis, but it had to be inexpensive. Novel therapy and low cost don't usually go together."

Without treatment, the mortality rate approaches 100 percent. Even with effective therapy, 15 to 30 percent of affected babies will die. The majority of those who survive face lifelong consequences, including loss of vision, loss of hearing and brain damage.

The disease occurs when bacteria replicate and eventually break through a physical structure called the blood-brain barrier. Comprised of a single layer of specialized cells, the blood-brain barrier is normally very effective in protecting the brain against invading bacteria.

SO WHAT GOES WRONG?

"There is a type of white blood cell, a macrophage, that typically removes bacteria from the bloodstream," Nemani explains. "But something happens—the cell becomes a traitor. Instead of killing the bacteria, the macrophage helps it survive in the blood and enter the brain. We need to find out what causes that change. Once we know that, we have the basis for preventing meningitis."

Nemani and his group not only are working to prevent the disease, but they're also exploring truly innovative strategies for treatment.

"Meningitis is generally diagnosed when bacteria are present in cerebrospinal fluid," he explains. "By then, brain damage is already occurring. And with large numbers of circulating bacteria, introducing antibiotics causes dead bacteria to release toxins, resulting in septic shock and organ failure. Clearly, we need a better way."

They may have found it. One of a class of proteins known as cytokines, IL-10 is a molecule normally present in the body that is involved in immune function. Not only does IL-10 eliminate bacteria, but it also appears to repair the first signs of damage to the brain. Results of this study were reported in *The Journal of Experimental Medicine*.

"We found that during an episode of bacteremia, when a large number of bacteria are circulating in normally sterile blood, IL-10 acts to clear antibiotic-sensitive and antibiotic-resistant *E. coli* from the circulation of infected mice," says Rahul Mittal, PhD, a post-doctoral fellow in Nemani's lab.

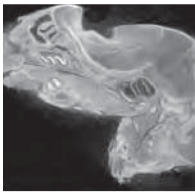
Nemani and Mittal have determined that *E. coli* infection causes damage to the mouse brain comparable to that seen in humans. Three-dimensional imaging studies of infected animal and human infant brains showed similar gross morphological changes.

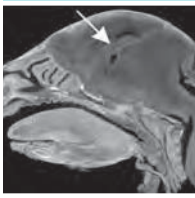
"When we gave IL-10 to mice 48 hours after infection, those changes to the brain were reversed," says Mittal. "Since diagnosing meningitis is difficult until bacteria reach the central nervous system, finding an agent that can clear the bacteria while also preventing or restoring the damaged brain is very exciting."

Nemani returns to the other part of the problem: price. "We could produce IL-10 using recombinant technology and inject it," he explains. "But that would be expensive. So we began looking for an alternative."

Together with his team, Nemani, an associate professor of Research at the Keck School of Medicine of the University of Southern California, has identified a receptor on white cells that controls the production of IL-10 during *E. coli* infection. Using an inexpensive small molecule medication, the team believes that they can stimulate the patient's immune system to increase production of IL-10 by manipulating expression of this receptor and allowing the patient to heal on his or her own.

An effective, low-cost treatment to battle the ravages of meningitis? Sounds like just what the doctor ordered.





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