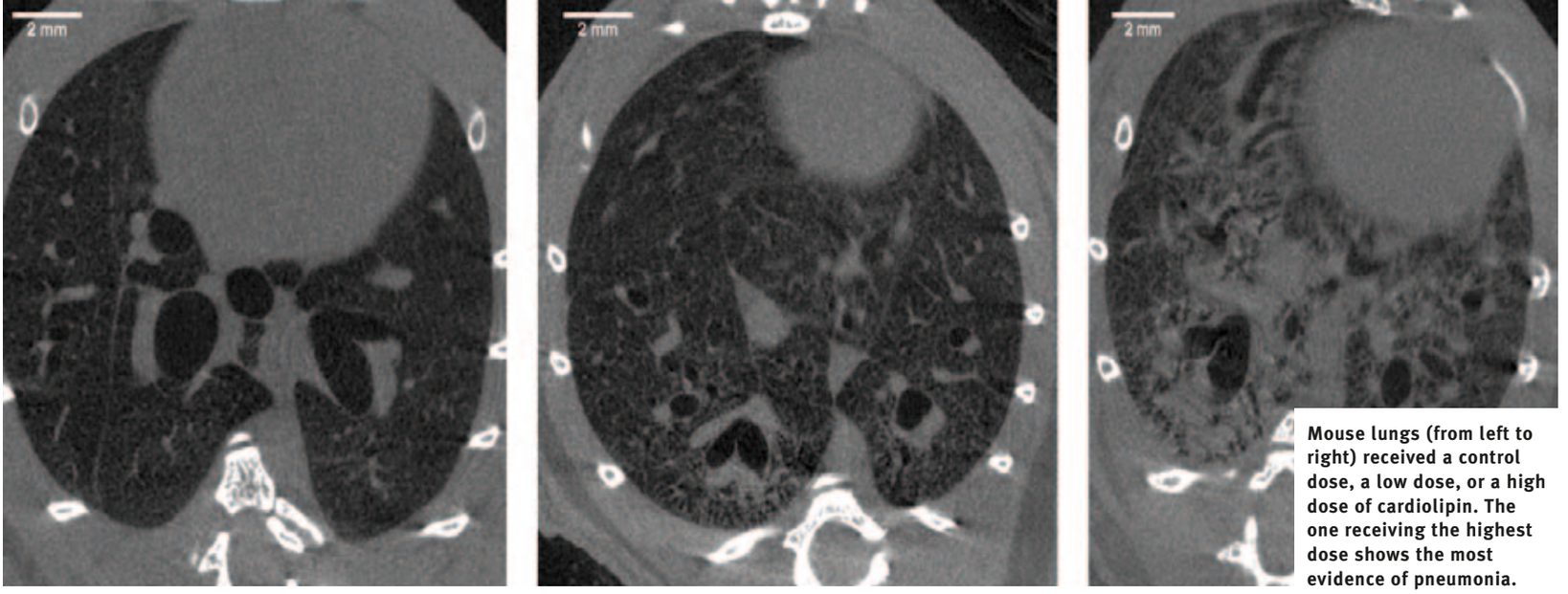

RAMA MALLAMPALLI

Mouse lungs (from left to right) received a control dose, a low dose, or a high dose of cardiolipin. The one receiving the highest dose shows the most evidence of pneumonia.

A VISCOUS CYCLE

STEPPING UP THE "MOTOR OIL" OF THE LUNGS TO TREAT PNEUMONIA

BY JOE MIKSCH

Under the best circumstances, typical bacterial pneumonia can be a rough road. In the course of about two weeks, a person with pneumonia will cough, have trouble breathing, and develop shaking chills and fever. For the lucky ones, antibiotics and rest will restore health over time.

But for some people—particularly those with weakened immune systems, smokers, the very old, and the very young—pneumonia can require hospitalization. And, in more than 10 percent of cases, it can lead to death. The Centers for Disease Control and Prevention reports that in 2007, 1.1 million people in the United States were hospitalized with pneumonia and more than 52,000 died.

But why does pneumonia hospitalize or kill some and spare others, regardless of these risk factors? Rama Mallampalli—Pitt professor of medicine, chief of the pulmonary division of the VA Pittsburgh Health Care System, and director of the Acute Lung Injury Center of Excellence at the University of Pittsburgh—thinks a process involving a structural molecule called cardiolipin might be key.

Mallampalli, an MD, and Pitt colleagues Bill Chen, Bryan McVerry, and Valerian Kagan—along with faculty from the University of Iowa School of Medicine—recently published a paper in *Nature Medicine* that reports that cardiolipin is found in unusually high concentrations in the lung fluid of mice and people infected with bacterial pneumonia.

Under normal circumstances, cardiolipin plays a role in mitochondrial-energy metabolism—a good thing, obviously, because mitochondria provide the power that keeps our cells, and therefore us, alive. So the questions become: Why is there so much cardiolipin in the lung fluid of pneumonia sufferers? And why does it seem to be such a bad actor when let loose in the lungs? "You and I normally have very low concentrations of [cardiolipin] in our lung-fluid secretions," Mallampalli says. "We hypothesized that there may be a protein that basically eliminates or removes [cardiolipin], and there might be a problem related to it."

As the investigation progressed, Mallampalli and his team identified a carrier protein called Atp8b1. They learned it transports cardiolipin, essentially acting as a pump that controls levels of the molecule.

With cardiolipin and Atp8b1 in his sights, Mallampalli traced their interaction: As pneumonia progresses, lung cells die. And as they perish, these cells release their components, including cardiolipin, into the lung fluid. At a point, Atp8b1 is faced with much more cardiolipin than it can process. As cardiolipin levels build, the molecule begins to disrupt the function of surfactant, a lubricant that is essentially the motor oil of respiration. As surfactant fails to work properly, respiration falters, and lung cells acquire even more damage—and a conventional case of pneumonia becomes more severe.

Mallampalli says he intuited that Atp8b1 might play a role here because of earlier work done by others on a rare and very serious liver condition called Byler's disease. Byler's disease patients have a mutation in Atp8b1 and an unusually high incidence of pneumonia in addition to liver failure.

Mallampalli is optimistic that this discovery offers the potential for new anti-pneumonia drugs. "All treatments for pneumonia are antibiotics," Mallampalli says. "This has been a good thing in that we've saved a lot of lives; but on the bad side, this has led to the emergence of drug-resistant bacteria."

Now, Mallampalli says, it may be possible to design drugs that either bind to cardiolipin, rendering it impotent, or that activate Atp8b1, making it a more robust cardiolipin "pump."

"For the first time, we have a new paradigm or model for pneumonia, and it will lead to a nonantibiotic approach to alter the host response to the infection," he says. ■