

SEPTEMBER 26, 2008

New Pig Model Could Improve Understanding of Cystic Fibrosis

For more than a decade, researchers have turned to mice to learn how cystic fibrosis develops and progresses. Although the mouse model of the disease has led to important insights into the molecular roots of cystic fibrosis, researchers have long felt they needed a model that more closely resembles the disease typically seen in humans.

Now, Howard Hughes Medical Institute (HHMI) researchers have developed a new model of cystic fibrosis in pigs that more accurately mimics features of the disease observed in human infants.

"I am hopeful that this model will help us devise improved tests, mechanism-based therapies, and strategies for prevention."

— **Michael J. Welsh**

HHMI investigator Michael J. Welsh at the University of Iowa and collaborators at the University of Missouri reported the development of the porcine model of cystic fibrosis in the September 26, 2008, issue of the journal *Science*.

At least in the newborn, the porcine model seems to mirror the disease in people, Welsh says. He hopes the new model will enable biomedical scientists to understand the disease better.

I am hopeful that this model will help us devise improved tests, mechanism-based therapies, and strategies for prevention, Welsh said. He added that a more aggressive approach to therapy has already improved the lives of patients with cystic fibrosis. Things have gotten much better, but we still have a long way to go.

Cystic fibrosis was first identified as a clinical syndrome in 1938. In 1989, researchers showed that the disease is caused by mutations in the gene that encodes the protein CFTR, the cystic fibrosis transmembrane conductance regulator. CFTR is a chloride channel that controls the movement of salt and water across cells that line the body's surfaces.

In humans, symptoms of cystic fibrosis often manifest in infancy and childhood. The disease affects the lungs, pancreas, intestines, and liver causing progressive disability as those organ systems fail. Without working CFTR channels, the body cannot perform the normal process of moving chloride and bicarbonate ions into and out of cells lining organs affected by cystic fibrosis. In the lungs, loss of normal salt transport disrupts the defense system that protects the airways from bacterial infection. As a result, bacteria thrive in the thick mucus.

As soon as the gene mutation underlying cystic fibrosis was discovered in the 1980s, scientists began using that information to create mouse models to study the disease in the lab. If you want to understand cystic fibrosis, you need good models, said Welsh.

Scientists' understanding of the disease has been aided greatly by mouse models and elegant clinical studies, according to Welsh. But the mouse model never faithfully reproduced the symptoms of the disease seen in humans. And clinical studies are limited in their ability to assess the etiology and progression of cystic fibrosis in human patients.

The mouse has taught us a tremendous amount, Welsh explained. But mice don't get pancreatic disease. Mice don't get cystic fibrosis lung disease. Mice don't get liver disease, and on down the list. Why the mouse doesn't have a typical cystic fibrosis phenotype is unknown.

He and others felt that a porcine model could be a significant improvement over the mouse and human tissue models of cystic fibrosis that are currently used in the lab, because pigs are closer to humans in terms of anatomy, physiology, biochemistry, size, lifespan, and genetics than mice.

To develop the new model, Welsh and colleagues from the University of Iowa and the University of Missouri disrupted the *CFTR* gene in pig cells and then cloned the altered cells to produce piglets with one bad copy of the gene, mimicking the genetic background of human carriers. Using conventional breeding techniques, they produced piglets with two mutated genes and many of the hallmarks of cystic fibrosis, including impaired ion channel function and a type of bowel obstruction often observed in newborn infants with cystic fibrosis. Like people, the piglets also showed an abnormal pancreas, liver, and gallbladder.

Welsh said the pig model may permit researchers to track progression of the disease, a feat that can't be accomplished in human patients. The piglets with cystic fibrosis are born with healthy lungs. Humans with cystic fibrosis are also born with normal lungs, but then they develop progressive infection and inflammation. Welsh hopes that as the pigs are exposed to the environment and bacteria and viruses it will be possible to identify how the pulmonary system is affected and discover the initiating factors responsible for disease.

At birth, the lungs of these pigs are fine, Welsh said. We'll have to see what happens over time. We don't yet know if they will develop lung disease.

With the pig, scientists will have better odds of tracking the disease as the animals age, Welsh said. We want to understand better the pathogenesis of the disease. We hope that knowledge will lead to improved therapies and preventions for people with cystic fibrosis.