

# Probing Pigs

A PORCINE MODEL OF CYSTIC FIBROSIS HELPS RESEARCHERS STUDY THE DISEASE.

A new line of genetically altered piglets offers scientists a novel testing ground for the causes, progression, and treatments of cystic fibrosis. In the past, researchers relied on mice to study the disease, which in humans is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The mutation causes pancreatic failure, lung infections, and liver disease, among other problems. But mice with the flawed gene don't show humanlike symptoms of the disease, says HHMI investigator Michael J. Welsh.

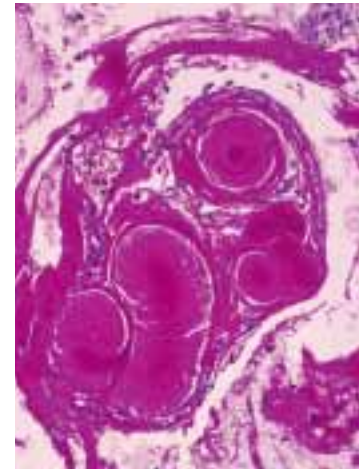
"Mice just don't develop cystic fibrosis," he says. "There are 20 theories as to why, but what it all comes down to is that if these animals don't get the symptoms, you can't use them to study the progression of the disease; you can't use them to test whether something treats the disease."

So Welsh, at the University of Iowa, and collaborators turned to pigs—closer to human in terms of anatomy, physiology, biochemistry, size, lifespan, and genetics. They engineered pig cells with mutations in *CFTR* to make piglets with one bad copy of the gene, and then mated those pigs to produce offspring with both copies of *CFTR* mutated. These piglets show many of the hallmarks of human cystic fibrosis. The results appear in the September 26, 2008, issue of *Science*.

Affected humans and piglets are born healthy but develop increasing symptoms as they age. Having the pig model will allow researchers to study how cystic fibrosis progresses over time, says Welsh. "This is a disease that affects a whole organism and now we can study it in a whole organism."

By comparing the affected pigs to mice with the same mutations, researchers may also be able to figure out why mice

don't get symptoms of cystic fibrosis. "We can look at what's different in mice and pigs that causes the mutation to have such different effects," says Welsh. "Is it gene differences? Physiological differences? Anatomical? Maybe the answer will lead us to a therapy." ■ —SARAH C.P. WILLIAMS



In humans, cystic fibrosis clogs the airways of the lungs with mucus.

## IN BRIEF

### IT TAKES TWO

The symptoms of most *Listeria monocytogenes* infections are often mild—a fever or stomachache at worst. But in pregnant women, the bacteria can be deadly to growing fetuses. Scientists long assumed that *Listeria* posed this heightened risk to a fetus because of a pregnant woman's weakened immune system. Several years ago, however, researchers found evidence that the bacteria actively target the human placenta. Now, HHMI international research scholar Pascale Cossart and colleagues at the Pasteur Institute have pinpointed two proteins involved in this targeted attack.

The team already knew that when *Listeria* infect the intestine, the organisms rely on an interaction between internalin (InIA), a protein on the bacterial surface, and E-cadherin, a receptor on human epithelial cells. To see whether this held true in the placenta, the team infected pieces of human placenta with the bacteria. They discovered that not only InIA was involved, but also a related bacterial protein, InIB.

Moreover, the researchers found that in pregnant gerbils, *Listeria* that lacked InIA, InIB, or both, couldn't infect placental tissue. And in mice—where the proteins do not normally play a role in placental infec-

tions—that were engineered to express human E-cadherin, the placenta was susceptible to the bacteria.

Cossart and her colleagues conclude in the October 23, 2008, issue of *Nature* that for *Listeria* to infect human placenta—and therefore risk harming a fetus—the bacteria must express both InIA and InIB, and that the pregnant woman's epithelial cells must express E-cadherin. Understanding this interaction could lead to ways to combat *Listeria*.

### LEARNING HOW NOT TO BE AFRAID

Like people able to keep their inner calm during stressful times, mice can be conditioned to feel safe in normally anxiety-causing situations. Researchers led by HHMI investigator Eric Kandel of Columbia University have probed the brain chemistry associated with this "learned safety."

The researchers first taught mice fear by associating a particular sound with a mild shock to their feet. Then, they changed the training conditions so mice never received the shock along with the noise. These mice learned to associate the tone with the absence of danger, and acted calmer in their surroundings than those that had learned fear.

Kandel's team next asked whether learned safety has antidepressant actions.

They placed the mice in water and used the forced-swim test, an animal model of depression in which, after awhile, animals show signs of behavioral despair and stop swimming.

"We found that the mice trained for safety could overcome their sense of hopelessness in the swim test and continued swimming," says Kandel. In fact, the mice performed similarly to mice treated with fluoxetine (Prozac).

Antidepressants such as fluoxetine mediate part of the action by regulating the production of new neurons in adulthood in an area of the hippocampus. The scientists therefore next looked at how learned safety affects the production of new neurons in adulthood. The conditioned mice had more new cells in this area. Using radiation to blunt the birth of neurons here diminished the antidepressant effects of the conditioning.

In their paper published October 9, 2008, in *Neuron*, the team also reported that learned safety ramped up expression of a factor involved in neuron growth and differentiation, and affected key components of the brain's dopamine system.

### A MOUNTAIN OF CANCER MUTATIONS

The most detailed genetic survey yet of human tumors has revealed a multitude of