

## Absent mouse gene leads to no-brainer

Scientists who shut off a certain gene in developing mice got a bizarre result: The mice look normal from tail to neck, but for a head they have only a stump tipped with ears.

These mice “unambiguously show that this is an essential gene” for early embryo development, says developmental biologist William Shawlot. The work by Shawlot and Richard R. Behringer of the University of Texas’ M.D. Anderson Cancer Center in Houston also verifies a 70-year-old notion that a tiny region of the embryo touches off changes in neighboring tissue that cause it to grow into a major part of the neural system.

An embryo begins as a clump of identical cells, but soon control genes switch on, setting off reaction cascades that cause this bit of tissue to become the heart, that bit a limb, and so on.

Scientists have begun unraveling how control genes work by seeing what happens when they “knock out,” or disable, them. Shawlot and Behringer knew from work on a similar gene in *Xenopus* frogs that a mouse gene called *Lim1* probably plays a role in head development.

They replaced *Lim1* in immature mouse cells, called stem cells, with a non-functional gene. They then inserted the cells into mouse embryos and eventually bred mice that carried two copies of the gene.

Most of these mice died as embryos at about 10 days of gestation, the scientists report in the March 30 *NATURE*. The embryos had a normal tail, trunk, and limbs but lacked most of the head. A more graphic demonstration of the gene’s effect came from a handful of headless mice (4 of more than 1,000 born) that survived the 19 days until birth, when they emerged stillborn.

The mice had most of the hindbrain but lacked forebrain and midbrain. Possession of those areas distinguishes vertebrates, including fish, reptiles, and people, from other animals.

The *Lim1* result jibes with Nobel prize-winning work by German embryologist Hans Spemann in the 1920s. Spemann transferred a patch of tissue from one newt embryo to another and caused the second embryo to form an extra central nervous system. Realizing that the transplanted tissue could direct how adjacent cells develop, he called the potent region it came from the “organizer.”

“The important point is that this embryological concept developed by Spemann is, in fact, true,” Shawlot says.

“The organizer has been considered the soul of the vertebrate embryo,” notes Eddy M. De Robertis of the Howard Hughes Medical Institute at the University of California, Los Angeles. “These are



Two stillborn mouse pups lacking the *Lim1* gene lie under a normal pup. Arrows mark the pups’ ears.

very old problems in biology and very fundamental ones. Now new progress is

being made. A biochemical pathway is now being established as to how this organizer works.” De Robertis wrote a commentary accompanying the paper.

Scientists have knocked out several organizer genes in mice in recent years but saw mostly trunk or tail effects. “A headless embryo like that has not been seen,” De Robertis says. “It suggests that there is a different regulatory pathway to the formation of the head than to the formation of the trunk-tail. This we didn’t know — that there could be two genetic mechanisms.”

The *Lim1* gene probably has no connection with such human defects as babies born with only part of a brain, a result of the neural tube failing to close properly. But, De Robertis says, “this is the type of thing that will tell you about how Siamese twins occur.”

Shawlot and Behringer write that the headless mouse “will be an important genetic tool for the molecular and cellular analysis” of neural development in vertebrate embryos. — J. Kaiser

## Ibuprofen stalls advance of cystic fibrosis

Heavy daily doses of a leading over-the-counter drug for arthritis can dramatically retard the progressive and ultimately lethal lung deterioration that characterizes cystic fibrosis, a new study finds. However, the novel treatment’s benefits appear to be restricted largely to children.

Respiratory infections plague individuals with cystic fibrosis (CF), a genetic disease that fills the lungs with mucus. To fight the bacteria and other microbial invaders behind those infections, the body recruits a host of different agents, including neutrophils — a class of white blood cells that functions as the immune system’s rapid-deployment commandos. Unfortunately, lung tissue often succumbs to friendly fire from those neutrophils.

About 10 years ago, a team of Cleveland-based researchers began investigating the potential for ibuprofen, a non-steroidal, anti-inflammatory drug, to shield the lungs of CF patients from the neutrophils’ ravages. In the March 30 *NEW ENGLAND JOURNAL OF MEDICINE*, they report its success in a double-blind study involving 85 patients between the ages of 5 and 39.

Reasoning that the anti-inflammatory therapy would work best where little permanent structural damage had occurred, the researchers restricted their trial to patients with only mild lung deterioration. Throughout the 4-year study, they charted lung function with a series of assays. Chief among them was FEV<sub>1</sub>, the volume of air an individual can forcefully expel in 1 second.

Healthy children should experience no FEV<sub>1</sub> change from year to year, notes pediatric pulmonologist Michael W.

Konstan of Case Western Reserve University in Cleveland, but “most CF patients have close to a 4 percent decline per year.” That’s about the rate of FEV<sub>1</sub> decline his team witnessed in that half of the patients who received up to 16 inactive tablets daily (molded to look like the real drug). Declines were much smaller among those who received ibuprofen for 4 years — 88 percent smaller for patients who were under 13 when the study began.

“We don’t know if this treatment will benefit patients with more severe disease,” Konstan says. But he says the findings “look promising enough that most CF centers are going to institute this as a therapy.” The Bethesda, Md.-based Cystic Fibrosis Foundation, which helped fund the research, is drawing up guidelines to help physicians determine daily dosages of the drug.

While ibuprofen’s long-term benefit “can only be surmised” from a 4-year trial, the new data strongly support the drug’s efficacy, argues Harvey R. Colten of Washington University in St. Louis in an accompanying editorial.

In the United States, CF is the most common fatal genetic disorder. Some 1,000 new cases are diagnosed each year. Gene therapy to cure the disease (SN: 9/3/94, p.149) — currently the holy grail of CF research — will likely benefit only those patients with mild lung damage, Konstan believes.

“What’s so nice about ibuprofen therapy,” he says, “is that it will delay the progression of the disease so that when gene therapy becomes a reality, more patients will be able to benefit from it.”

— J. Raloff