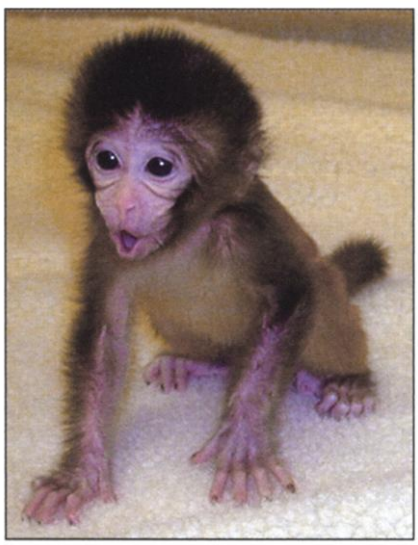
TRANSGENIC ANIMALS

Infant Monkey Carries Jellyfish Gene

Efforts to make a fluorescent green monkey are not quite a glowing success—yet.

In an attempt to create the first transgenic primate, scientists at the Oregon Regional Primate Research Center in Beaverton have produced a rhesus monkey that carries the gene coding for green fluorescent protein (GFP). This gene, first isolated from glowing jellyfish, has been inserted into a host of experimental species, including plants, frogs, and mice. Although he is not green, the 3-month-old monkey named ANDi, described on page 309 of this issue, is something of a proof of principle. The achievement could lead to valuable experimental models for certain diseases and a better understanding of primate and human development, say other biologists. But the cumbersome technique is not likely to lead to transgenic humans, green or otherwise.

To produce ANDi, reproductive biologists Anthony Chan, Gerald Schatten, and colleagues injected a genetically modified virus into the unfertilized eggs of rhesus monkeys. A few hours later, they injected sperm into the oocytes to fertilize them. As with other in vitro fertilization (IVF) procedures in nonhuman primates, this one was relatively inefficient. Half of the fertilized eggs developed into embryos, and five pregnancies resulted from 20 embryo transfers, including one set of twins, which were miscarried.



Close, but no glow. ANDi, the first transgenic rhesus monkey, carries the gene for green fluorescent protein but does not glow green.

Three healthy monkeys were born, but the team has detected the GFP gene only in ANDi. The miscarried twins also carried the GFP gene, but unlike ANDi, their hair follicles and toenails did glow under fluorescent light. Schatten attributes the miscarriage to the fact that rhesus twins are rare, but the team is investigating whether it might be related to the inserted gene. So far, the team doesn't know whether ANDi's cells are expressing the protein. But Schatten says other transgenic animals have delayed producing their transgene for up to a year after birth.

Although the gene transfer techniques the researchers used are routine in other organisms, reproductive biologist Ted Golos of the Wisconsin Regional Primate Research Center in Madison says the birth of ANDi is the first demonstration that a primate egg can develop normally after such manipulations.

"We've made an incremental step from one species to another," Schatten says. And even that small step involved multiple hurdles. Whereas the experiment "is essentially several days' work in transgenic mice," Golos notes, monkey eggs are difficult to collect, and primatologists do not know how to artificially control a monkey's reproductive cycle. That meant the researchers had to time the experiment precisely so that an embryo was ready when a surrogate mother was at the right stage of her reproductive cycle. In fact, ethics considerations aside, the project might have been easier to achieve in humans, for whom IVF technology is much more advanced.

Even so, the work will not inspire fertility doctors to try the technique with human embryos anytime soon, Schatten predicts. Scientists can't control where the modified virus enters the genome, so the risk of an inserted gene interrupting an important gene would be relatively high. "I don't see an immediate therapeutic application," says bioethicist LeRoy Walters of the Kennedy Institute of Ethics at Georgetown University.

And until researchers find more efficient ways to create specific genetic changes, says Schatten, transgenic monkeys will not be common research tools. Even if those techniques were feasible, expense and ethical considerations would limit the use of transgenic monkeys as medical models, he says: "We don't need a knockout monkey for every disease."

But for questions that are difficult to study in rodents, such as those related to aging, neurodegenerative diseases, immunology, and behavior, transgenic primates could prove a plus, Golos says. Schatten predicts that genetically altered monkeys could be a boon to developmental biologists as well. Because monkeys are large enough to fit into magnetic resonance imaging machines, researchers might be able to introduce gene markers and track organ development by noninvasive means. "ANDi and his future cousins and brothers and sisters will help us bridge that gap between what we know in the mouse and what we're keenly interested in in human development," he says.

–GRETCHEN VOGEL

CIRCADIAN RHYTHMS

Mutant Gene Speeds Up the Human Clock

"Early to bed and early to rise, makes a man healthy, wealthy, and wise," advised Benjamin Franklin in his *Poor Richard's Almanack for the Year 1757*. Today, as then, people assume that self-discipline is the key to following such counsel. But in a paper published online today by *Science* (www.scienceexpress.org), a team led by Ying-Hui Fu and Louis Ptáček at the University of Utah in Salt Lake City shows that a person's genes may be more important. The researchers have identified a mutation that causes people to be extreme early birds, rising, say, at 4:00 a.m. The discovery opens a window into the genetic basis of the human circadian clock, which keeps body activities such as sleeping and eating running on a roughly 24-hour rhythm.

Researchers have identified genes that drive the circadian clocks in fruit flies, mice, and other species. They have also found what seem to be the human equivalents of some of those genes, but they've had no direct proof that those genes are in fact part of the human clock machinery. The Utah team has now provided that proof for one of the human genes, known as h*Per2*, by showing that a mutation in the gene speeds up the circadian clock. "It's the first example of a circadian clock gene in a human," says Joseph Takahashi, a geneticist at Northwestern University in Evanston, Illinois.

It's also one of the first times that researchers have linked a single gene to a complex human behavior. Ultimately, the work could lead to treatments for patients affected by the mutation, which causes a disease called familial advanced sleep-phase syndrome (FASPS), and perhaps even for people with more common sleep disturbances.

FASPS is an inherited disorder discovered just last year by Utah's Christopher Jones and colleagues. The internal clocks of these patients appear to run fast, shifting their sleep schedules ahead by about 4 hours. Fu and Ptáček's team set out to find the genetic cause of this circadian shift by combing through the DNA of members of a large family afflicted by the disorder, searching for genetic variations associated with the disease.

They ultimately homed in on the end of chromosome 2 as the likely site of the defec-

CREDIT: CHAN *ET AL.*