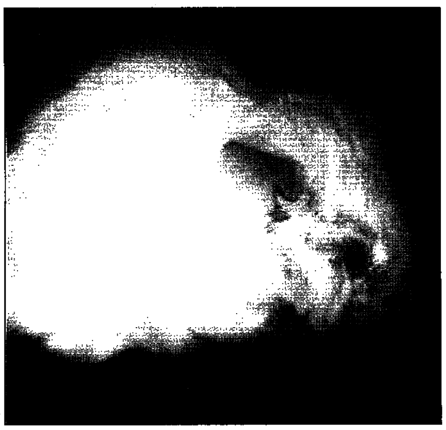
their normal counterparts. "It's really a striking result," says Matthew Scott, a developmental biologist at Stanford University School of Medicine in Palo Alto, California.

Fuchs and her university, which has applied for a patent on the work, see the finding as a possible first step toward harnessing β-catenin or the Wnt pathway to help some 30 million balding men in the United States grow new hair. That's not a sure thing, however, especially because the researchers will have to be very careful that such tinkering doesn't trigger tumors—as happened with the Fuchs team's hirsute mice.



No cue balls here. Mice with extra β-catenin grow thick coats.

Fuchs has long been fascinated by hair because it grows out of a structure, the follicle, that forms and regresses periodically, creating cycles of hair growth and loss. "It's one of the most complex forms of differentiation," she says. She suspected that β-catenin might play a role because of an observation her group made about another protein, Lef1/Tcf, in the skin of early mouse embryos. The researchers found that the protein appears in a dot pattern reminiscent of that displayed by the progenitor cells that produce hair follicles. And because Lef1/Tcf is thought to link with β-catenin to control gene expression, the finding suggested that these two molecules, and the Wnt pathway, might help regulate hair follicle development. That idea was buttressed by what Rudolf Grosschedl's group at the University of California, San Francisco, found when they knocked out the *Lef1* gene in mice: The animals had far fewer hair follicles than the controls.

To test the idea that β-catenin is also involved in hair follicle development, Uri Gat in Fuchs's lab created a new strain of mice carrying extra copies of the β-catenin gene. Before introducing the gene into the animals, Gat had linked it to a regulatory sequence that would cause it to be expressed only in skin cells. He also removed part of the gene so that β-catenin protein could not link up with proteins that would cause it to break down.

Animals carrying this gene not only were hairy critters, but they also got new hair follicles even as adults. Typically, an individual's full complement of hair follicles is set during embryonic development, but in these mice, new ones began to appear within a month after birth. They filled in the spaces between existing hair follicles, but did not form on areas, such as the foot pads, where no hair existed before. Apparently, only the cells in haired skin still had "properties that would allow them to be primed for new hair follicle [growth]," says Fuchs; these properties remain a mystery. The new hairs stuck out in many different directions, however.

The additional β-catenin had darker effects as well. As adults, the mice had hind paws three times the normal size and thickened skin, as well as ridges around the ears, eyelids, and nose. And the mice tended to develop benign tumors in the hair follicles. Humans can develop very similar tumors. Their genetic basis is not known, but the mouse results suggest that β-catenin might be involved; Fuchs is looking for signs of excess β-catenin in the human tumors.

Other goals would be to find the genes that β-catenin turns on to trigger hair follicle development in hopes that they could be activated specifically without causing tumors. Fuchs also wants to determine how β-catenin activation differs in embryonic versus tumor cells. The question is, "can we separate tumorigenesis from hair follicle morphogenesis," she says. If they can, then perhaps her ideas about manipulating the Wnt–β-catenin pathway to cure baldness won't be so hair-raising after all.

—ELIZABETH PENNISI

BIOTECHNOLOGY

Improving Gene Transfer Into Livestock

About 10 years before they startled the world by cloning Dolly the sheep, scientists at The Roslin Institute south of Edinburgh had rocked the scientific community by producing the first healthy sheep carrying a human gene. Since then, a few research groups have used similar gene transfer techniques to build herds of sheep, cattle, goats, and pigs that make human proteins, often with the goal of milking them for valuable drugs. Now, a new method developed by a team of researchers in Wisconsin and California promises to make production of such transgenic livestock much easier than it is today.

Current gene transfer procedures for large animals are time-consuming and expensive, mainly because their efficiency is low: Only 1% to 10% of the animals that develop from eggs inoculated with a foreign gene carry it, and many of those who do can't transmit it to their progeny because

ScienceScope

UN TO MOVE ON GENE RESOLUTION

The United Nations (UN) is nearing approval of a resolution calling for restrictions on human gene research and respect for genetic diversity.

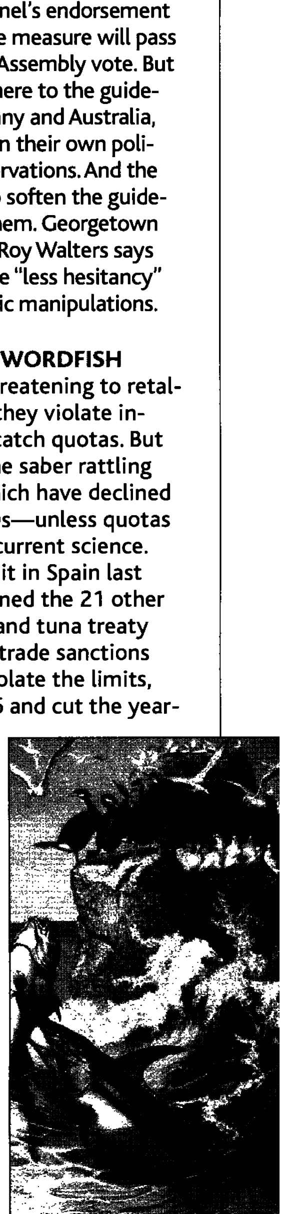
Last week, a UN committee approved the Resolution on the Human Genome and Human Rights, which calls for vigilance against discrimination based on a person's genes and recommends restrictions on human cloning and germline gene therapies, which risk introducing new genes into a population. The resolution also argues that use of human DNA "should not give rise to financial gain"—a controversial issue as companies race for lucrative gene patents.

Observers say the panel's endorsement virtually ensures that the measure will pass a 10 December General Assembly vote. But whether nations will adhere to the guidelines is uncertain. Germany and Australia, which are still working on their own policies, have expressed reservations. And the United States pressed to soften the guidelines before endorsing them. Georgetown University bioethicist LeRoy Walters says Americans generally have "less hesitancy" than others about genetic manipulations.

FENCING OVER SWORDFISH

The United States is threatening to retaliate against nations if they violate international swordfish catch quotas. But fisheries experts say the saber rattling won't help stocks—which have declined by 70% since the 1960s—unless quotas are reduced to reflect current science.

At a fisheries summit in Spain last week, U.S. officials warned the 21 other signers of a swordfish and tuna treaty that they may impose trade sanctions against nations that violate the limits, which were set in 1996 and cut the yearly kill in half. But conservationists are pushing the nations to close a loophole that allows undersized swordfish to be discarded and not counted in the catch. "Compliance with insufficient regulations is not going to solve the problem," says Lisa Speer of the Natural Resources Defense Council. Whether the treaty signers buy that argument won't be known until later this year.



CREDITS: (TOP TO BOTTOM) LINDA DEGENSTEIN AND CHUCK WELLEK; (BOTTOM) MERCURY ARCHIVES/THE IMAGE BANK they are mosaics that have the gene in some cells but not in others, including those of the germ line. Each transgenic livestock animal has cost about $500,000 to produce.

Those low success rates prompted the Roslin researchers and others to turn to cloning experiments in which they replicate individuals from somatic cells to increase the numbers of transformants. But in the 24 November issue of the *Proceedings of the National Academy of Sciences*, Robert Bremel, formerly of the University of Wisconsin, Madison, and now managing director of Gala Design, a biotech firm in Sauk City, Wisconsin, his former Wisconsin student Anthony Chan, and their colleagues report that they have achieved a transformation efficiency approaching 100%. They did this by introducing a foreign gene into cow eggs before they were fertilized rather than shortly after, as is currently done.

On the hoof. This heifer, Cressy, produces hepatitis B surface antigen in her milk.

The increased efficiency should be welcome news to researchers who want to introduce genes into livestock, either to improve the strains or to use the animals to produce medically valuable proteins, such as monoclonal antibodies or vaccine proteins. "This is good work," says geneticist Robert Wall of the U.S. Department of Agriculture's Agricultural Research Service in Beltsville, Maryland. He notes that because the gene transfer work is very costly, only about a dozen labs do it now. Improved efficiency might draw others in, however.

In the older techniques, researchers introduce a gene in a carrier, such as the DNA of a retrovirus that can insert itself into the host cell DNA, into an egg that's already been fertilized. But if the DNA doesn't insert until after the egg starts dividing, as is often the case, it ends up only in the descendants of the cell where it integrated, which might be a small minority of the total in the embryo.

To counter this problem, Bremel and his colleagues decided to use unfertilized bovine oocytes isolated in metaphase arrest, when the membrane that normally surrounds the nucleus is absent. The researchers reasoned that this would make it easier to get the foreign gene to the chromosomes so that it could integrate. In addition, putting the gene in the chromosomes of the egg itself would ensure that the gene would end up in all the cells, including the germ cells, of the animal produced when the egg was subsequently fertilized. In cows, "the DNA is incorporated better when inserted earlier," says Bremel.

And that's what the team found. First, they introduced the gene coding for the hepatitis B surface antigen into a retroviral carrier. They chose this gene, Bremel says, partly because the antigen makes an easily detected marker and partly because any transgenic animals could produce the antigen, which is used in hepatitis B vaccines. The researchers then injected the retrovirus into the oocytes, allowed them to mature, and fertilized them.

Of the 836 eggs injected, 174 developed into embryonic blastocysts, and 10 of these were implanted into five foster mothers. This yielded three pregnancies and four healthy calves, two males and two females, now about 2 years old. Tests on skin and blood cells revealed that all four animals carry the hepatitis B gene. In addition, the females, Cressy and Buttons, secrete the antigen in their milk. And mating one of the bulls, Gremlin, with a nontransgenic female produced twin offspring, both transgenic. The researchers say that this technique should work in other species, including primates, where immature egg cells can be manipulated during metaphase. Indeed, if the technique proves as efficient as it now appears, it might even make livestock cloning obsolete. —ANNE SIMON MOFFAT

NANOTECHNOLOGY

AFMs Wield Parts for Nanoconstruction

Nanotechnologists dream of creating useful machines the size of a virus, but for the time being they are in the position of a tinkerer who has a pile of parts but no workbench for assembling them. They have created a handful of molecular blocks, spheres, and rods but don't have a means of manipulating and joining the tiny components. But at the Sixth Foresight Institute Conference on Molecular Nanotechnology held in Santa Clara, California, last week, a team from Washington University in St. Louis and Zyvex, an instrument company based in Richardson, Texas, showed off their technique for wielding individual carbon nanotubes with a trio of robotic arms.

The researchers welded opposite ends of tiny, straw-shaped tubes of carbon atoms to two tiny silicon probes normally used to map surface contours by "feel" in an atomic force microscope (AFM). They then moved the probes to twist, tug, and bend the tubes and even brought in a third arm to give the nanotube a nudge in the middle. All of this was accomplished inside a scanning electron microscope (SEM), allowing them to view and control the nanomanipulation as it happened. "This is very, very beautiful work," says Anupam Madhukar, a materials scientist at the University of Southern California in Los Angeles. Cees Dekker, a nanotube researcher at Delft University of Technology in the Netherlands, says the most exciting demonstration was one showing two probe tips tugging on a nanotube until it broke. "That means they can now determine exactly how strong the nanotubes are," which has long been a goal of the community, he says.

Nanotubes, essentially just rolled-up sheets of graphite with diameters as small as 1 nanometer but lengths up to 100 micrometers, have been proposed for a wealth of jobs in the nanotoolkit (*Science*, 14 August, p. 940). Research teams have already hooked nanotubes to the apex of an AFM tip, a tiny silicon pyramid suspended from a cantilever arm, in an effort to improve the microscope's resolution, but the acrylic adhesive used to bond tube to tip has only moderate strength. For the new work, the Washington-Zyvex team had to figure out how to fasten the tube securely to two AFM tips while imaging it at the same time.

First the team developed a kind of nanoscale jig, incorporating three independently movable AFM tips in different orientations. To attach nanotubes to these tips, the team used its SEM imager as a welding gun. SEMs image an object by scanning an electron beam over its surface and detecting the reflected electrons. Previous teams had shown that an SEM's focused beam can break up stray organic molecules floating in the vacuum chamber. This creates negatively charged hydrocarbon fragments that pile up on positively charged surfaces. So graduate student MinFeng Yu decided to see if those fragments could "weld" the nanotube to their AFM tip.

Yu first dipped an AFM tip into a tiny pile of nanotubes, relying on static electricity to hold one end of a nanotube to the tip. He then focused the SEM beam so that it directed organic fragments in the vacuum toward the junction of the tube and the tip, which was given a positive charge. The result was a tiny carbon-based mound at the base of the nanotube. Then he steered a second AFM tip up next to the other end of the nanotube and repeated the nanowelding procedure. When he then moved the tips relative to one another, the nanotube curved and stretched, showing that the welds were secure—so secure, in fact, that when he pulled the tips apart with enough force, the nanotube broke. "That was a surprise, because we expected that the welds would be weaker than the nanotubes," which are theorized to be stronger than steel,

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