At the University of Texas Southwestern Medical Center at Dallas, human geneticist Glenn Evans is investigating just how useful various rough drafts would be. "The issue of completeness and utility has never been determined," says Richard McCombie, a sequencer at Cold Spring Harbor Laboratory in New York. "We don't know anything about intermediate sequencing products," notes Jane Peterson, an NHGRI cell biologist who oversees the human genome sequencing effort. "We have to be sure it will be useful." And the first requirement, adds Lander, is that a draft "can't impede our ability to finish."

In early September, NHGRI will evaluate the results of these efforts and decide whether to proceed with its original plan—to produce a detailed sequence over the next 6 years—or shift gears to focus on an interim rough draft. The awards announced last week (see table) are based on the original plan. They assume that the seven centers—which include all those that took part in earlier phases, except for TIGR—will be generating 117 million bases of detailed, finished sequence. If the program is refocused, next year's sequence output should be considerably higher.

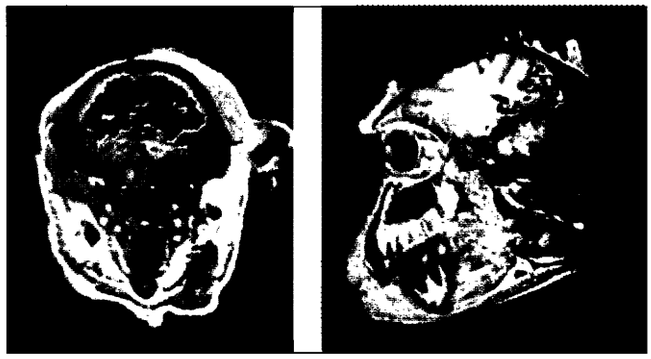
That possibility pleases Evans. His team was dismayed by the prospect of being beaten to the complete genome by Venter, and he says doing a rough draft would be "a legitimate way of not being scooped." And, he adds, "it's politically the right thing to do."

–ELIZABETH PENNISI

NEUROSCIENCE

First Images Show Monkey Brains at Work

Monkey brains have gotten plenty of close scrutiny from researchers studying functions such as perception and memory. But monkey researchers have been unable to use one promising technique: functional magnetic resonance imaging (fMRI), which maps out active brain areas and has revolutionized the study of human brain function. The problem is convincing a monkey to sit perfectly still and perform a thought task inside the claustrophobic banging magnet that creates the magnetic resonance images. Now Tom Albright and his colleagues at the Salk Institute and the University of California, San Diego, have overcome the difficulties. In the June issue of *Neuron*, they have published the first fMR images of activity in a monkey's brain. A second team, headed by Richard Andersen at the California Institute of Technology (Caltech) in Pasadena, has a similar study coming out next week in *NeuroReport*.



L. STEFANACCI *ET AL., NEURON*

Mind of a monkey. The colored patches show activity detected by functional magnetic resonance imaging in the visual areas of the brain of a rhesus monkey as it watched a children's cartoon.

These successes, achieved by patiently training the monkey and designing a special seat to restrain it in the magnet, could ultimately help neuroscientists get more out of human fMR images. This noninvasive technique, based on the magnetic signal of oxygen in the blood, records the increases in blood flow that result from changes in neural activity. But what individual neurons are doing in the areas that light up on an fMR image is open to interpretation, because researchers can't stick electrodes into the brains of healthy humans. "Monkey fMRI will allow us to test our interpretations," says neuroscientist Robert Desimone, who directs intramural programs at the National Institute of Mental Health.

The technique should also benefit traditional electrode studies of monkey brain activity. "Say I am interested in a perceptual phenomenon, but I don't have much evidence about the part of the brain that underlies it," says Albright. "fMRI gives me a way of identifying the relevant parts of the brain, which will then guide my microelectrode studies."

The first monkey fMR images, which show activation of the visual system as the animal watched a children's cartoon, don't offer any new scientific insights—just a proof of principle. To make them, both Albright's and Andersen's groups designed chairlike apparatuses made of nonmagnetic materials that hold the monkey still inside the magnet, in variations of a position Andersen describes as "sphinxlike," on haunches and elbows and looking forward, down the length of the magnet. "We worried that it would be difficult to get the monkey to cooperate," says Albright, but they found that by rewarding the monkey with juice, they were able to train it to relax in the magnet.

Both groups worked with ordinary hospital MRI machines—horizontal magnets designed to accommodate a prone human. But several labs, including those of Nikos Logothetis at the Max Planck Institute in Tübingen, Germany, and Carl Olson at Carnegie Mellon University in Pittsburgh, are working with manufacturers to develop a new generation of MRI machines specifically for monkey research. The magnets are vertical, allowing the monkey to sit upright, and have greater magnetic fields, which will increase the resolution of the images, says Andersen, who hopes to have such a facility at Caltech within 2 years.

In the meantime, Albright's and Andersen's teams are using the hospital magnets to test the relation of fMR images to neural activity in monkey brains and look for new brain areas to explore with electrodes. Eventually, Albright says, the researchers will need the better resolution—and the additional research time—available with the dedicated machines. But for now, he says, "the important thing was to show we could do it."

–MARCIA BARINAGA

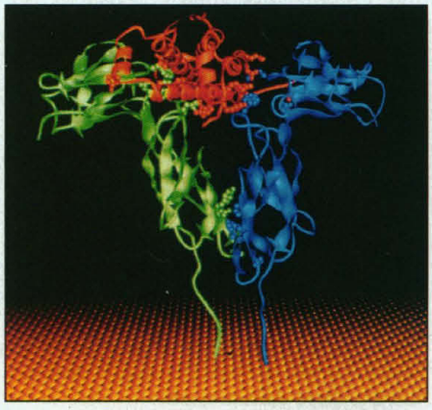
DRUG DEVELOPMENT

Small Molecule Fills Hormone's Shoes

As diabetics who must inject themselves daily with insulin know only too well, a major disadvantage of protein drugs is that they can't be taken orally. Drug companies would love to find small compounds that mimic the effects of these drugs yet evade breakdown in the digestive tract. But for many protein drugs—including insulin and other hormones known as cytokines—that has seemed a forlorn hope. These proteins stick snugly to large surfaces on their receptors, and small chemicals—which might be just 1/50 of a protein's size—seemed too puny to turn on such receptors. "People didn't feel that a

small molecule would have enough contact points," says James Ihle, who studies cytokine receptors at St. Jude Children's Research Hospital in Memphis, Tennessee.

But on page 257, researchers at Ligand Pharmaceuticals in San Diego and SmithKline Beecham Pharmaceuticals in Collegeville and King of Prussia, Pennsylvania, prove the skeptics wrong. They report their discovery of a small molecule that activates the receptor for granulocyte–colony-stimulating factor (G-CSF), a cytokine that triggers the growth of white blood cells. G-CSF is commonly used to boost patients' immune systems after chemotherapy, which kills off immune cells. Although the new compound works in mice but not humans, it is being heralded as evidence that the right small molecule can indeed fill a protein hormone's shoes.



A. M. DE VOS, M. ULTSCH, A. A. KOSSIAKOFF, *SCIENCE*

Togetherness. Two receptors for the cytokine growth hormone (blue and green) are held together by the growth hormone protein (red). Small molecules may produce the same effect.

"A lot of people have been trying to do this," says Alan D'Andrea, who studies cytokine receptors at the Dana-Farber Cancer Institute in Boston, "and this is proof that it really can happen. It has generated a lot of excitement." The discovery will also spur the pharmaceutical industry's search for protein-mimicking drugs, says Mark Goldsmith, who studies cytokine receptors at the University of California, San Francisco. It suggests, he adds, that with small molecules, "we can mimic many interactions that just a few years ago would have been expected to be much more difficult."

The Ligand–SmithKline Beecham team had some grounds for optimism when they began their search for a G-CSF mimic. When cytokines bind to their receptors, they drag the receptors together into pairs called dimers. That aggregation seems to be what turns on a receptor, as researchers have shown by using antibodies to bind receptors together or mutating the receptors so that they stick together of their own accord. And linking receptors was a job that a small molecule might be able to do.

In the past 2 years, moreover, two research teams showed that peptides—small fragments of proteins—can activate the receptors for the blood cell cytokines thrombopoietin and erythropoietin. Peptides can't be given orally, but they are considerably smaller than proteins. That peptide finding was "encouraging," says Ligand researcher Peter Lamb, who with his teammates was already at work to find a small molecule that could link G-CSF receptors.

To speed the search, the team had engineered a line of mouse cells as a biological test for G-CSF–like activity. When G-CSF activates its receptor, a cascade of cellular events begins that ultimately activates proteins called STATs, which turn genes on and off to stimulate growth or cause other changes in the cell. To monitor STAT activity in their test cells, the team added a gene for the light-generating protein luciferase, engineered to be turned on by STATs. They then treated the cells with thousands of compounds and picked out the ones that made the cells literally light up.

After further tests to make sure that the candidate compounds really were activating STATs and that the G-CSF receptor was playing some role, the group was left with a small organic compound called SB 247464. This compound actually stimulated the growth of mouse white blood cells in culture and in living mice. "As far as we know, this is the first example of a [nonpeptide] cytokine mimic," says Lamb. The data suggest that the compound binds and dimerizes the G-CSF receptor, but more tests are needed to prove that is actually how it works.

The researchers admit that they were disappointed to find that the compound works in mouse but not human cells. It remains to be seen whether chemical alterations will make the compound capable of acting on the human receptor. "That is a lesson about the importance of using human [receptor] molecules for screening for human compounds," says Goldsmith. But despite that weakness, he says, the paper has taken the field "a quantum leap" along the path toward developing oral substitutes for protein drugs.

Ligand plans to use luciferase-gene assays to search for substitutes for other cytokines that work through STATs, Lamb says. And the drug industry as a whole is likely to mount a broader search. "The insulin receptor is fundamentally no different" from the G-CSF receptor, Goldsmith notes, pointing out that it too is activated by dimerization. "Why not consider [searching for] a synthetic compound that can be taken as a pill and will activate your insulin receptors?" If drug companies aren't looking already, it certainly won't be long before they start.

–MARCIA BARINAGA

ScienceScope

COW DONE DOLLY-STYLE?

Japanese scientists say they have replicated in cattle the technique used to produce Dolly, the sheep that was the first mammal cloned from adult somatic cells. Twin calves were born on 5 July; their mother reportedly died unexpectedly the next day. The research group won't release further details until it completes a DNA analysis to confirm the calves' origin.

A team at the Ishikawa Prefectural Livestock Research Center and the Kinki University School of Agriculture in Nara put cells from a cow's uterine tube into eggs stripped of their nuclei and implanted the resulting embryos into surrogate mothers. Team leader Yukio Tsunoda says a second birth is expected in the next few weeks. The news was released prematurely, he says, in accord with new government guidelines requiring prompt disclosure of cloning research.

It was the second report of Dolly-style cloning in 2 weeks. On 26 June, Ryuzo Yanagimachi of the University of Hawaii, Manoa, claimed his group had cloned mice using adult somatic cells.

BAIKAL JAM SESSION

Hoping to save the world's largest freshwater lake from the depredations of industrial pollution, tourists, and exotic species, U.S. and Russian researchers and policy experts plan to meet next month in Irkutsk, Russia, to plot joint studies and to draft legislative initiatives geared toward protecting Lake Baikal.

Sponsored by the nonprofit Tahoe Baikal Institute, the forum aims to learn from alterations wrought by 40 years of development around California's Lake Tahoe, including a dimming of its stunning water clarity. "Baikal is now at the stage that Tahoe was in the 1950s, just before development really got under way," says UC Davis limnologist Charles Goldman, a forum participant.

Lake Baikal

Goldman and Valentin Brovchak, chair of the Baikal Commission, hope the forum will lead to the establishment of a government agency to defend Baikal's interests, along the lines of the Tahoe Regional Planning Agency. Future forums will be hosted at UC Davis's planned Lake Tahoe Center for Environmental Research, slated to open by summer 2000.