close funding levels for individual investigators, but the typical award is about $1 million annually. Wiley also receives $350,625 in annual National Institutes of Health grants awarded through Harvard that don't expire until 2005 and 2006.

The news about Wiley has devastated the close-knit structural biology world. "It's a shock for everybody," says NIAID structural biologist David Garboczi, a former Wiley postdoc. But besides cooperating with the investigation, there is little that scientists can do. "Playing Hercule Poirot from one's desk in Cambridge is not very useful," says Harrison.

–JOSH GEWOLB

MICROBIAL GENOMES

New Genome a Boost To Plant Studies

Molecular biologists have bared the soul of one of nature's best genetic engineers. On pages 2317 and 2323, two teams describe the genome sequence of *Agrobacterium tumefaciens*, a soil microbe whose ability to transfer DNA into plant cells has transformed plant and crop science.

Some 25 years ago, researchers realized they could take advantage of the microbe's route of infection to ferry foreign genes into plants. *Agrobacterium* has been "the workhorse of the agrobiotech industry" ever since, says Joe Ecker, a plant scientist at the Salk Institute for Biological Studies in La Jolla, California. The new sequence data have already revealed clues about *Agrobacterium*'s astounding ability to parasitize plants and should help both academic and corporate researchers better harness its talents, says Ecker. The data also reveal unexpected hints about the microbe's origins, says Andrew Binns, a molecular geneticist at the University of Pennsylvania in Philadelphia. Binns, along with Mary-Dell Chilton, now with Syngenta in Research Triangle Park, North Carolina, and others, helped launch *Agrobacterium* as a full-fledged genetic engineer in the 1980s.

DNA transformer. Researchers have deciphered the genome of the bacterium that helped transfer herbicide resistance genes to this corn plant.

Two independent teams tackled the 5.67-million-base genome. Steven Slater, a bacterial geneticist at Cereon Genomics Inc. in Cambridge, Massachusetts, and his colleagues worked with about a dozen undergraduates at the University of Richmond in Virginia. The other effort was led by microbiologist Eugene Nester at the University of Washington, Seattle. After reading about each other's projects on the Web, both teams agreed to publish their results back to back.

Agrobacterium infects wounded plants, causing disease in some 600 species, including cherries, grapes, and roses and other ornamental plants. Infection leads to tumorlike growths called galls that typically form at the base of the plant. So-called crown gall disease "can cause very serious economic damage," says Nester, destroying whole vineyards, for example.

During the process of infection, *Agrobacterium* transfers some of its DNA to the plant host. When the bacterial DNA is incorporated into the plant's genome, the plant produces growth hormones, and these, in turn, stimulate gall formation. The tumors make novel carbon compounds—again thanks to newly acquired *Agrobacterium* genes. By feeding off these compounds, *Agrobacterium* is able to outcompete any other microbes that colonize the gall.

Although agricultural scientists have piggybacked on this process to transfer genes that make plants hardier and resistant to salt, cold, viral disease, and insect pests, a lot remains to be learned about the infection process. Often, gene transfer is not very efficient, for example. "We felt that there were many questions that could be approached only if we knew the sequence," says Nester, who recruited the University of Washington's Maynard Olson and his team to do the actual sequencing. Both Nester's and Slater's groups are combing through the newly discovered repertoire of 5400 genes looking for those involved in DNA transfer. "It's an area that's ripe for exploration that could lead to ways [to do] more efficient transformation," says Binns.

Agrobacterium's genes are distributed on four pieces of DNA: a linear and a circular chromosome that carry the run-of-the-mill housekeeping genes, and two smaller pieces of circular DNA called plasmids. "All four of these DNA molecules play a role in the interaction with the plant," Slater reports. His team was particularly intrigued by genes for enzymes that suggest *Agrobacterium* feeds off the plant's own nutrients, including cellulose and peptides. Researchers have suspected that this thievery was occurring but had lacked definitive proof. And Nester's group found that *Agrobacterium* doesn't use the usual array of genes that many plant pathogens use to gain access to their hosts. It lacks the so-called type III secretion system responsible for pathogenicity in many bacteria and instead has three versions of type IV; Nester wants to know why this pathogen is different.

The sequence also revealed a closer kinship than researchers had expected with rhizobium bacteria, symbionts that cause plants to form nodules on their roots. Rhizobium bacteria flourish in nodules, producing ammonia in return for the plant's hospitality, whereas *Agrobacterium* sponges off the plant without apparently giving anything in return. A comparison between the new sequence and that of the recently sequenced *Sinorhizobium meliloti* (*Science*, 27 July, p. 668) revealed that "big chunks of DNA are essentially the same in both," Nester reports.

Thus, the two could have a recent common ancestor and might belong to the same genus. At first glance, says Binns, because *Agrobacterium* has some of the genes needed for nitrogen fixation, it seems that it might have evolved from a primitive rhizobium. Alternatively, gene transfer between the two species might explain some of the shared genes, he adds. Whatever the explanation, these very different lifestyles "have occurred without a whole heck of a lot of change in the whole genome."

–ELIZABETH PENNISI

MAMMALIAN EVOLUTION

Placentals' Family Tree Drawn and Quartered

A nearly 240-year-old statistical technique has helped sort out the evolutionary history of the broad class of mammals that give birth to live, fully developed young. As William Murphy and Eduardo Eizirik of the National Cancer Institute (NCI) in Frederick, Maryland, and their colleagues report on page 2348, the technique places placental mammals in four major groups. The researchers propose that these groups arose in large part because of the breakup of the giant landmasses that predated modern continents, and that placental mammals in what is now Africa have the most ancient ancestors.

Those conclusions are likely to prove controversial. Researchers are sharply divided on where and when mammals arose; two distinct camps disagree by at least 35 million years. The new work "adds more ammunition" to the case for an early divergence of mammals, notes J. David Archibald, an evolutionary biologist at San

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Diego State University in California, but it is unlikely to settle the issue. The new reconstruction does help clear up some of the relationships between major groups of species, however, and "only with that [clarity] can we begin to understand how the genome evolved and focus on [subsequent changes in] form and function," says NCI's Stephen O'Brien, one of Murphy and Eizirik's collaborators.

Globe-trotting. Earth's four groups of placental mammals likely arose from an ancient southern continent.

Few dispute that the work demonstrates the power of Bayesian inference, a statistical tool developed in the 1700s for assessing how new information influences the chances that a current belief continues to be correct. It's like other statistical approaches in that "you have the same modeling assumptions," says John Huelsenbeck, an evolutionary biologist at the University of Rochester in New York. "But on top of that you have to incorporate your prior beliefs." In the past decade, researchers have coupled Bayesian inference with a simulation tool called the Markov chain Monte Carlo and applied it to many questions, from evaluating new drugs to protecting fisheries (*Science*, 19 November 1999, p. 1460). Researchers first subjected evolutionary trees to Bayesian inference in 1996.

Traditionally, researchers have built these trees by evaluating the degree of change in a given trait—limb length, for instance—or a given DNA sequence between supposed relatives. Heated debates have arisen, because the trees tend to differ depending on the data and analytical techniques used. Resolving these arguments would require the analysis of ever more species or DNA sequences, and many researchers hope that Bayesian inference will provide speedy answers. "It's fast, especially with large numbers of species or long molecules [of DNA] to be analyzed," says Sudhir Kumar, an evolutionary biologist at Arizona State University in Tempe.

Analyzing large numbers of species is exactly what Murphy and his colleagues had in mind. He and collaborator Mark Springer of the University of California, Riverside, had independently built evolutionary trees based on DNA from about the same range of species. By joining forces, "they finally have high statistical confidence to resolve the [uncertain] branches," Kumar points out. With the help of Bayesian inference, the researchers confirmed the existence of four so-called superorders, determined which superorder evolved first, and decided which orders within these larger groups shared a common ancestor. "In all respects the analysis was pretty sophisticated" and comprehensive, says Huelsenbeck.

The researchers found that placental mammals fall into one of four groups. One, called Afrotheria, includes elephants, aardvarks, and hyraxes. Another, the Xenarthra, covers armadillos, sloths, and anteaters. The much larger Euarchontoglires includes some of the more common mammals: rodents, rabbits, and primates, for example—a grouping "that's new and is strongly supported by the data," O'Brien points out. And carnivores, whales, cows, and horses make up the Laurasiatheria. Afrotheria is the oldest group, the team reports. The orders contained in this group originated in Africa, and some never left. They are followed by the Xenarthra, which live in South America, and finally by the other two superorders, which are common worldwide. Because the southern groups are the oldest, "it places the origin of the placental mammals in the south," O'Brien asserts.

The researchers also calculated that the two most ancient groups appeared a little more than 100 million years ago—during the breakup of the giant southern continent called Gondwana. "The [continental] split between Africa and South America may explain the earliest split among placental mammals," Springer suggests.

Therein lies the rub for some of their colleagues. "On one hand, what they write about higher level [evolutionary] relationships seems perfectly reasonable," comments Philip D. Gingerich, a paleontologist at the University of Michigan, Ann Arbor. "But on

CREDITS: (TOP TO BOTTOM) W. J. MURPHY *ET AL.*; NASA

ScienceScope

World-Class Headache British academics have improved the quality of their research over the last 5 years, according to a new national review released this week. But the gains may cause headaches for government funders, who will be expected to reward the most improved labs with cash.

The Higher Education Funding Council of England (HEFCE) uses expert panels to grade university departments on their work; it then uses the results to divvy up more than $1 billion in annual infrastructure funding. Higher scoring labs win more cash. This year, 64% of the reviewed work was rated of national or international excellence, up from 43% in the last review. The jump "demonstrates the value of awarding research funds selectively to reward quality," says HEFCE chief Howard Newby.

But the council now must consider whether it can feed a bigger class of ribbon winners from a fixed funding pie. It planned to meet this week to discuss options, which could include tinkering with the reward formula and asking the government for up to $240 million in new funds.

Olsen, Tarter on the Move NASA's chief scientist is slated to become a top aide at the White House Office of Science and Technology Policy (OSTP). President George W. Bush will soon nominate neuroscientist Kathie Olsen (*right*) to be OSTP's associate director for science. If confirmed by the Senate, she will be one of two top assistants to OSTP chief John Marburger. Olsen has been NASA's top scientist since 1999 and spent more than a decade at the National Science Foundation.

Bruce Tarter, for 7 years director of the Department of Energy's Lawrence Livermore National Laboratory in California, announced last week that he will step aside once a replacement is found. Tarter is credited with steering Livermore, a mainstay of the nation's nuclear weapons complex, through the end of the Cold War, forging new roles in supercomputing and environmental research. But his tenure was marred by massive cost overruns in the National Ignition Facility, a giant laser, and last year he was denied a pay raise.

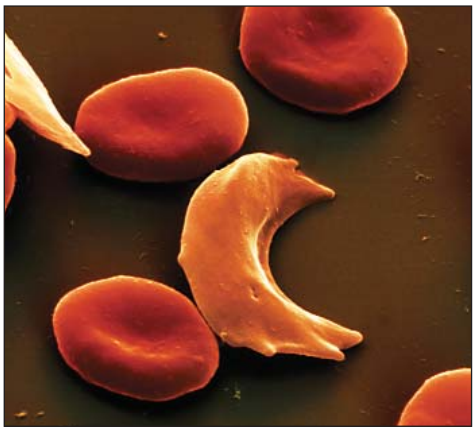
Contributors: Andrew Lawler, Jeffrey Mervis, Andrew Watson

the other hand, what they write about the timing of [mammalian] divergences seems completely unreasonable." Like many others, Gingerich thinks the fossil evidence strongly suggests that mammals diversified most after dinosaurs went extinct, only about 65 million years ago. Molecular studies by other researchers had already indicated an earlier date, which this new extensive analysis supports. The two camps are far from reaching a truce. However, O'Brien and others hope that with the help of the long-deceased Reverend Thomas Bayes, the two views will one day be reconciled. **–ELIZABETH PENNISI**

GENE THERAPY

Gene *Gemisch* Cures Sickle Cell in Mice

Twenty years ago, sickle cell disease looked like one of the few inherited disorders that might be an easy target for gene therapy. All one had to do, it seemed, was correct a simple mutation that causes red blood cells to become distorted and "sickled." As researchers dug deeper, however, they found a "nightmare" of complexity, says gene therapy researcher Philippe Leboulch of the Harvard Medical School and the Massachusetts Institute of Technology in Cambridge, Massachusetts. After a long struggle, researchers believe they've now overcome a major barrier to gene therapy: On page 2368, a team led by Leboulch reports having used an HIV-based vector to cure sickle cell disease in mice.



Sickling. Normal disc-shaped cells become elongated and block circulation.

"This is a very important advance," says Arthur Nienhuis, a leading researcher in blood disorders at St. Jude Children's Research Hospital in Memphis, Tennessee. He thinks this is one of several signs that gene therapy could become a reality for this disease, but, he adds, "there's still a lot of work to be done."

The mutation that causes sickle cell disease is a single-base defect in the human β^A-globin gene. People who inherit the mutation from both parents produce an abnormal hemoglobin that forms a polymeric fiber, making red blood cells rigid and sticky. Because having a single copy can help protect against malaria, the gene occurs widely in tropical regions. But having two copies causes red blood cells to form clumps and block circulation, damaging organs. Roughly one in 13 African Americans carries the gene, and about 72,000 people in the United States have the disease, which can be fatal.

The first attempts to cure sickle cell disease using gene therapy focused on replacing the defective β^A-globin gene in stem cells in the bone marrow, where new blood cells are produced, by using a vector made from a mouse retrovirus. The results were disappointing. But during the 1990s, the National Heart, Lung, and Blood Institute upped its funding for gene therapy in this field to roughly $13 million per year, stimulating the development of new approaches.

To boost expression of the β^A-globin gene, various researchers added a key control region to the gene package they transferred to stem cells. They tried new retroviral vectors as well. But the turning point, researchers say, came as two teams began using HIV-based vectors—one group led by Michel Sadelain of Memorial Sloan-Kettering Cancer Center in New York City and the other by Leboulch, who has ties to a Cambridge, Massachusetts, biotech company named Genetix Pharmaceuticals.

Last year, Sadelain's group used an HIV vector to insert a healthy β^A-globin gene into transgenic mice, curing them of β thalassemia, a related but milder blood disorder. Leboulch has now used an HIV vector to insert a different gene—a synthetic construct that includes parts of the β^A- and γ-globin genes—into two strains of mice with a form of sickle cell disease. Leboulch says his group decided to create this new therapeutic gene because γ-globin produces a stronger antisickling effect than β^A-globin does.

Leboulch's team focused on a critical part of the γ gene (codon 87) and added it to the sequence for the β^A-globin gene, creating a *gemisch* that they call $\beta^{A\text{-}T87Q}$-globin. They also tinkered with a control region to improve gene expression. The team then inserted the sequence into stem cells from two strains of mice with sickle cell disorders. It was a success: 99% of the red blood cells in the mice expressed the protective gene for up to 10 months, with no signs of sickling.

Before researchers try these techniques in the clinic, they must solve a couple of difficult problems, say Leboulch and Nienhuis. They must prove that HIV-based vectors are truly safe. And they must find a good way to remove unhealthy stem cells from patients' bone marrow so that new, genetically engineered cells can take over. Currently, the unhealthy stem cells would have to be removed by exposing them to destructive radiation or chemotherapy—which are life endangering.

Leboulch's group is looking into ways of giving a competitive edge to treated stem cells, such as enabling them to resist chemotherapy. If such approaches prove safe, he believes, it might be possible to begin clinical trials within a few years. **–ELIOT MARSHALL**

GENE THERAPY

Panel Reviews Risks of Germ Line Changes

A high-profile experiment using gene therapy to treat hemophilia B has been on hold for 3 months because of concerns that it might alter the inheritable, or "germ line," DNA of patients in the trial. Last week, those concerns got their first public airing at a meeting of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health. The session did not yield a clear decision, but several panel members indicated that they thought the research should be allowed to resume.

The study, led by molecular biologist Mark Kay of Stanford University, came under scrutiny in September after traces of DNA from the vector, based on adeno-associated virus, appeared in the semen of a volunteer (*Science*, 23 November, p. 1640). He is the first of nine to be enrolled. Kay and Elliott Grossbard, vice president for clinical research at Avigen Inc. of Alameda, California, which is sponsoring the clinical trial, told RAC that traces of vector were detected for 10 weeks in seminal fluid of the first volunteer. This had prompted concern that the vector could insert genes into the sperm during that time.

But one RAC member, neurobiologist Jon Gordon of Mount Sinai School of Medicine in New York City, said he believed the risks of germ line alteration are "extremely low."

On hold. Kay hopes his study will resume soon.

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