parasite's life cycle," says Stephen Hoffman, a malaria researcher at the Naval Medical Research Center in Silver Spring, Maryland.

But does that phase serve a purpose? Rodríguez can only speculate. Perhaps the parasites like to shop around to find a "good" liver cell to infect, she says. Or maybe passing through multiple liver cells somehow activates the parasite, preparing it for the real thing. Rodríguez's first priority now is to find out why parasites show this behavior and how they do it. Watch for the sequel.

–MARTIN ENSERINK

CANCER RESEARCH

Preventing Hair Loss From Chemotherapy

The images are painful: a cancer patient, perhaps a child without hair, or a woman wearing a scarf or all-too-obvious wig to disguise the hair loss caused by chemotherapy. Although this loss may seem trivial—it's likely to be temporary and the chemotherapy may well save the patient's life—it's not. "After nausea and vomiting, one of the harder side effects of chemotherapy is loss of image," says cancer researcher Stephen Friend of Rosetta Inpharmatics in Kirkland, Washington. "Keeping that image intact," he adds, "has a lot to do with fighting the disease." Now, researchers may be on the way to developing a drug that can prevent chemotherapy-induced hair loss.

Many chemotherapeutic agents cause hair loss because they are aimed at rapidly dividing cells—one of the defining characteristics of cancer cells. The problem is that these drugs also kill normal dividing cells, including those of the hair follicle. On page 134, Stephen Davis and his colleagues at Glaxo Wellcome Research and Development in Research Triangle Park, North Carolina, report that they can prevent chemotherapy-induced hair loss in rats by rubbing the animals' skin with a newly developed drug before administering the chemotherapy.

The new drug targets an enzyme called cyclin-dependent kinase 2 (CDK2), which drives a key step in the cell division cycle. Many researchers in both industry and academe are looking for CDK inhibitors, mainly in hope of developing agents to block the growth of cancer cells. But William Kaelin of the Dana-Farber Cancer Institute in Boston, who is among those doing this work, points out that CDK inhibitors offer two possibilities. They can be used, he says, to find "either smarter ways to kill cancer cells or smarter ways to protect normal cells."

In the current work, the Glaxo Wellcome group focused on the latter goal. They began by determining the x-ray crystallographic structure of CDK2 bound to a previously identified, but relatively weak, inhibitor of the enzyme. They then used this structural information to design a modified form of the inhibitor that would bind more tightly to the enzyme, making it a more effective inhibitor, and that would also be suitable for topical application. Tests with cultured cells showed that their design strategy worked: The modified inhibitor blocked the division of the cells at just the point where CDK2 comes into play. What's more, Davis says, it "protected the cells from a panel of currently used chemotherapeutic agents."

The team went on to test the prospective drug in two animal models. In one, the researchers transplanted human scalp hair onto immunodeficient mice that can't reject the foreign tissue. When they applied the CDK2 inhibitor to the actively growing hair transplants, Davis says, it reversibly inhibited hair follicle cell division.

In the second model, the researchers treated newborn rats with the CDK2 inhibitor, followed by either the chemotherapeutic drug etoposide or a cyclophosphamide-doxorubicin combination. Control animals subjected to the chemotherapies without the CDK2 inhibitor lost all their hair. But when applied to the heads of the rats before they were given etoposide, the inhibitor completely prevented hair loss at the application site in 50% of the animals and partially prevented it in another 20%. It was less effective against the drug combination, protecting 33% of the animals from hair loss. But the researchers were thrilled to see the hair still growing on many treated animals. "There's nothing better than visual proof," Davis says.

Because the CDK2 blocker inhibits cell growth, the team checked to see whether it interferes with the ability of the chemotherapeutic drugs to kill cancer cells in animal tumor models. Davis says that they didn't detect any such interference, and the fact that the drug is applied externally should also limit any potential

Hair preserver. The CDK2 inhibitor, when rubbed on the heads of mice (bottom), prevented the hair loss caused by etoposide.

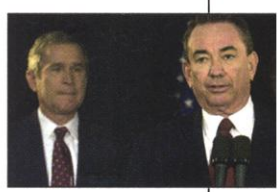
CREDITS: (LEFT TO RIGHT) S. DAVIS *ET AL.*; KENNETH LAMBERT/AP

ScienceScope

THE YEAR TO COME

With a new U.S. president and a host of hot global R&D issues in play, 2001 should be an eventful year for science. A few areas to watch:

Decisions, Decisions The incoming George W. Bush Administration has many R&D–related choices to make, including picking a White House science adviser and deciding biomedical research policy. At the **National Institutes of Health** (NIH), observers are wondering what the selection of Wisconsin Governor Tommy Thompson (right) to head the Department of Health and Human Services will mean for research using **stem cells** derived from human embryos. Last August, the Bush campaign criticized NIH's plan to fund such work, but Thompson's appointment has cheered some scientists. Although antiabortion groups that oppose stem cell funding consider Thompson an ally, he has praised groundbreaking stem cell work by scientists in his home state.



Antiabortion politics could also complicate the selection of a **new NIH director,** prompting some observers to recall a similarly prolonged hunt during the last Bush presidency. Whoever succeeds Harold Varmus, who left 13 months ago, will have to satisfy both conservatives and moderates. Also look for new heads at two institutes—eye and neurological disorders—and at the Office of AIDS Research.

At the **National Park Service,** Bush has pledged to undo a Clinton-era shift that sent the agency's 100 research scientists to the U.S. Geological Survey. Bush wants to return them to shore up protection for park resources.

Pay Hikes Look for the **National Science Foundation** (NSF) to propose higher stipends for graduate students and postdocs in its 2002 budget request, due out early this year. NSF officials calculate that it will take $52.4 million to raise postdoc pay under research grants to $40,000, a 45% hike, and another $30 million to boost grad student stipends from $18,000 to $25,000.

Director Rita Colwell is also hoping to launch a math initiative in 2002 that would triple or quadruple the division's current $130 million budget over 5 years. NSF is also searching for a catchy name for a social science initiative that it hopes to begin in 2003. "It's got to have 'human' in it, be short, and include the idea of technological change," says NSF's Norm Bradburn.

interference with chemotherapy.

Oncologist David Fisher, also at Dana-Farber, describes the work so far as an "enormous advance." He speculates that it might also be possible to design inhibitors to protect other normal tissues that are damaged by chemotherapeutic drugs. The lining of the gut—where damage causes nausea and vomiting—is one possibility, if a non-absorbable version can be produced.

Davis says he doesn't know how long it might take to bring the current CDK2 inhibitor to market, as the drug is just beginning preclinical testing. But if it does eventually move into human trials, Fisher predicts, "the clinical community will pound on the door to test it." –JEAN MARX

EVOLUTION

Tooth Theory Revises History of Mammals

To paleontologists who study mammals, you are what you eat with. Teeth are often the only remains of tiny, extinct mammals, but they can reveal an animal's diet as well as its place on the family tree. The most important advance in mammalian dental evolution has long been regarded as the tribosphenic molar—a Cuisinart-like tooth that could both slice and grind. This was considered a key innovation, shared exclusively by placental mammals and marsupials, that helps explain their extraordinary success ever since the Cretaceous period.

Now three paleontologists propose that the tribosphenic molar evolved not once, but twice—a highly provocative idea. "It shakes a bedrock principle that we've held for a long time," says Andy Wyss of the University of California (UC), Santa Barbara. In the 4 January issue of *Nature*, the trio argues that this kind of molar independently appeared in the Southern Hemisphere in fossil relatives of the monotremes, an extremely ancient group of mammals that includes the platypus. Because the hypothesis is based on extremely limited evidence, many paleontologists are reacting cautiously. "I think many people would tend to take it with a grain of salt right now," says Michael Woodburne of UC Riverside. But Bill Clemens of UC Berkeley adds, "It's going to be very, very stimulating."

Mammal teeth have come a long way in the past 220 million years. The earliest relatives of placental and marsupial mammals had molars that sliced like pinking shears—good for chopping up insects but not for crushing tougher food. The tribosphenic molar, however, also incorporates a grinder: a cusp (called the protocone) on the upper tooth that fits like a pestle into the mortar-like basin (known as the talonid) of the lower tooth. This action allows tribosphenic mammals to crush seeds, pulp fruit, and grind up leaves.

For most of this century, all known Mesozoic fossils of placental and marsupial mammals had tribosphenic teeth. The fossils came from Asia, Europe, and North America and showed a clear step-by-step progression toward more and more tribosphenic features. Paleontologists concluded that mammals with this type of tooth most likely had arisen from a common ancestor that lived in the Northern Hemisphere during the Early Cretaceous. Meanwhile, they thought, the more primitive, nontribosphenic monotremes had evolved in the southern continents.

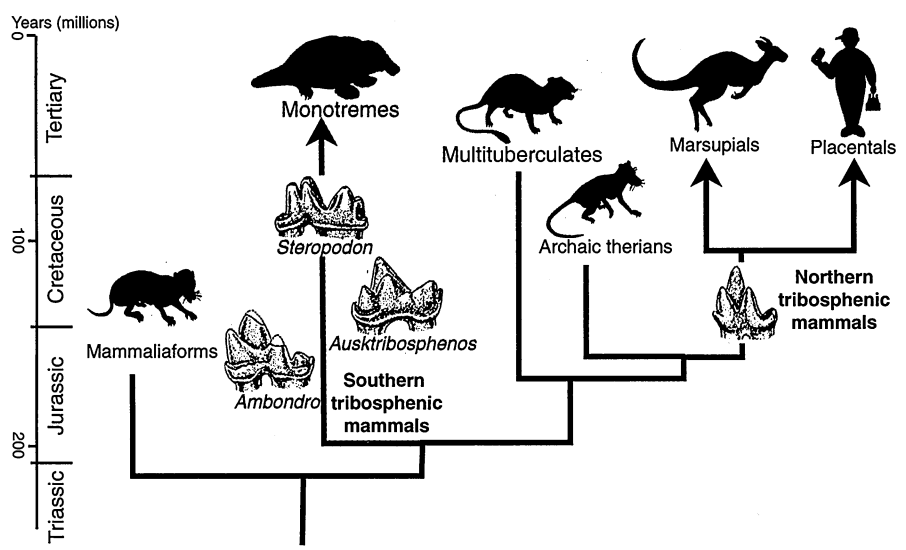
Cracks in the theory appeared in 1985, with a report of the jaw of a fossil mammal, called *Steropodon*, from Early Cretaceous rocks in Australia. The jaw clearly belonged to a monotreme, but it bore relatively advanced teeth that vaguely resembled tribosphenic molars. "This came as a tremendous surprise," says Richard Cifelli of the Oklahoma Museum of Natural History in Norman. Even bigger surprises were to come. In the late 1990s, unquestionably tribosphenic molars belonging to animals called *Ausktribosphenos* and *Ambondro* turned up in Australia and Madagascar, respectively. What's more, *Ambondro* was found in mid-Jurassic rock—evidence that the tribosphenic molar had originated not only in the "wrong" hemisphere, but at least tens of millions of years earlier than transitional molar forms in the north. By this time, Cifelli says, "the contradiction had become absolutely impossible to ignore."

Trying to resolve the puzzle, Cifelli teamed up with Zhexi Luo of the Carnegie Museum of Natural History in Pittsburgh, Pennsylvania, and Zofia Kielan-Jaworowska of the Polish Academy of Sciences. The trio picked 21 living and fossil mammals, examining the widest suite of features yet. They concentrated on 55 characteristics preserved in the teeth and jaws of the three new fossils from the Southern Hemisphere.

From similar features, the paleontologists divided the fossils into two distinct tribosphenic clans: the southern australosphenidans, which include *Ausktribosphenos*, *Ambondro*, *Steropodon*, and living monotremes; and the northern boreosphenidans, which include placental mammals and marsupials. The tribosphenic molar originated independently in both, they propose. By making that assumption, they say, paleontologists can continue to classify monotremes and other primitive mammals as distant cousins of marsupials and placentals, without having to assume that fully tribosphenic Jurassic mammals in the south somehow gave rise to later, less tribosphenic mammals in the north.

Not everyone is convinced. "I think they're sticking their necks out pretty far," Wyss says, noting that the remains of the southern fossils include only teeth and jaws—no upper teeth, skulls, or other bones. "There's a tremendous amount of missing information here." And the existing data haven't thoroughly convinced other experts, either. "Some of the characters that Luo and company have been using to link *Steropodon* with *Ambondro* and *Ausktribosphenos* may be suspect," Woodburne says.

But, if true, the hypothesis also robs paleontologists of a long-standing touchstone. "The tribosphenic molar has been something that we have hung our hats on forever because it is so distinctive," Cifelli says. Now, he adds, it may be time to admit that "we can have no more sacred cows"—or at least no more holy molars. –ERIK STOKSTAD



Coinci-dental? "Unique" mammalian molars actually may have evolved twice.

ILLUSTRATION: ADAPTED FROM Z. LUO ET AL.