one of the best selling cancer drugs worldwide. It is used to treat ovarian and breast cancer, and many breast cancer survivors take the drug to prevent recurrence of the disease. For now, there's enough paclitaxel to go around, but demand could soon grow: Investigators are testing the drug's power over other cancers, Alzheimer's disease, and multiple sclerosis, among others. If those uses pan out, supplies might become scarce. That's because paclitaxel is made by modifying a precursor compound extracted from the needles of the Pacific yew, an endangered tree that grows along the coast of the Pacific Northwest.

Angela Hoffman, a chemist at the University of Portland, Oregon, had previously looked for ways to boost paclitaxel production in yew trees. To her surprise, she found a new source of the compound while working on a completely different project. She and her colleagues were studying hazelnut trees to see why some were more susceptible than others to Eastern filbert blight, which is devastating hazelnut groves in Oregon's Willamette Valley. The researchers prepared extracts from several types of hazelnut trees, and after purifying and analyzing the samples, Hoffman noticed the familiar chemical signature of paclitaxel.

Hoffman and her colleagues determined that hazelnut trees make paclitaxel in their leaves, twigs, and nuts, although only at about 10% of the concentration in yew trees. They also found that fungi living on hazelnut trees produce paclitaxel.

Down the road, it's the fungi that could be the most valuable find, says David Houck, a natural products expert at Phytera, a drug company in Worcester, Massachusetts. Paclitaxel-producing fungi have also been isolated from yew trees, he says. If a fungus could be coaxed into churning out the drug in vats, "it would definitely have value," Houck says.

New leaf? As demand for paclitaxel grows, producers may get it from hazelnut trees.

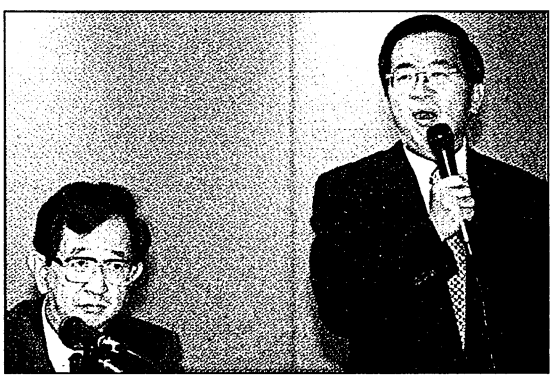
–ROBERT F. SERVICE

TAIWAN

Lee to Remain as Academy President

Scientists and staff at Taiwan's Academia Sinica are breathing a sigh of relief this week after institute head and Nobel laureate Lee Yuan-tseh decided to remain at the academy rather than join Taiwan's new administration.

Lee, who has become a major political figure since returning to Taiwan in 1994 to head the academy, endorsed Chen Shui-bian for president just a week before Chen won a narrow plurality in the 18 March election. It was a controversial move, partly because the head of Academia Sinica reports directly to the president of Taiwan.



Staying put. President-elect Chen, right, and a reluctant Y.-t. Lee.

Lee then tendered his resignation, which was rejected by outgoing president Lee Teng-hui, and went on a 2-week vacation. When Chen won, he announced that Lee was his first choice for premier.

The possibility that Lee might join the new government left a cloud of uncertainty hanging over Academia Sinica, a collection of 24 institutes that represent the island's premier research efforts. Lee is credited with garnering increased financial support, reforming advancement and research procedures, and recruiting leading scientists to key positions. But on 29 March Lee announced he would turn down Chen's offer and stay on as head of Academia Sinica, although he said he has agreed to serve as a presidential adviser.

Staff are glad to have him back. "We're really happy," says Sheng-Hsien Lin, director of Academia Sinica's Institute of Atomic and Molecular Sciences. "We think he can do much more [for Taiwan] in science than in politics."

Although the immediate question of the academy's leadership is resolved, its long-term political status remains unclear. Lee may have alienated Taiwan's National Assembly, which is still controlled by the long-ruling Kuomintang, the Nationalist Party, by criticizing its policies and endorsing Chen, a member of the Democratic Progressive Party. Some observers also wonder if Lee's support for the progressive party, the most pro-independence group in Taiwan, might affect efforts to build stronger scientific relations with China.

–DENNIS NORMILE

BIOCHEMISTRY

Chemical Tags Speed Delivery Into Cells

SAN FRANCISCO—For pharmaceutical-makers, trying to get a drug inside cells can be as difficult as meeting the Rolling Stones: You might score tickets to a Stones concert, but to party with Mick Jagger you need a backstage pass. In the case of pharmaceuticals, companies must make drugs water soluble to pass through the bloodstream on the way to their targets. Yet once the compounds have arrived at their destination, they need a very different kind of chemistry to dissolve through the fatty membrane surrounding cells. Often drugs can manage one task but not the other. But a team of California researchers may have found a way to change all that.

At a meeting of the American Chemical Society (ACS) here last week,* team leader Paul Wender of Stanford University reported that he and his colleagues have discovered a small chemical tag that appears to act as a universal pass, allowing compounds access to the interior of cells. The cellular pass is a short protein fragment, or peptide, made up of a repeating series of up to nine arginine amino acids. At the meeting, Wender, an organic chemist, reported that when the arginine peptide is linked to a variety of different drugs, it ferries its cargo into cells at unprecedented rates. When the team hooked the peptide to the powerful immunosuppressant cyclosporin, for example, the drug passed right through human skin grafted onto a mouse—an impossible feat without the peptide.

"This is an important development," says John Voorhees, a dermatologist at the University of Michigan Medical School in Ann Arbor. When physicians use cyclosporin to treat skin conditions, they give the drug in capsules in hopes that some of it will make its way from the gut to the bloodstream and eventually inside skin cells. A topical cream could be more effective for treating conditions such as psoriasis and eczema, and it

* 219th ACS national meeting, 26–30 March.

CREDITS: (TOP TO BOTTOM) AP PHOTO/WALLY SANTANA; VISUALS UNLIMITED

might carry fewer side effects, Voorhees says. "There's nothing else like it" for getting compounds into cells, he states. In fact, the new transporter group has proven so successful that the Stanford team has created a company called CellGate to commercialize the technology.

The new peptide is far from the first molecule researchers have tried to use as a chemical pass card. Researchers have long known that positively charged, or cationic, peptides and synthetic polymers make decent access keys. But progress toward a universal key has been mixed. Recently, help has come from a surprising source: the AIDS virus. In the early 1980s, researchers discovered that a protein fragment called Tat helps HIV viral proteins enter cells and initiate synthesis of RNA. And researchers at the Massachusetts Institute of Technology and elsewhere went on to show that linking HIV Tat to drugs can boost their uptake as well.

Unfortunately, HIV Tat is so complex and hard to synthesize that it is too expensive for widespread use, Wender notes. So he and his colleagues set out to find a cheaper, more effective alternative. They started by looking carefully at HIV Tat. Like other cell entry tags, HIV Tat is made up of cationic subunits—in this case six arginine amino acids, two lysines, and a glutamine. That structure initially seemed to confirm the conventional wisdom that a tag's positive charge is what gets it inside cells, says Jonathan Rothbard, head of research at CellGate. But when the researchers looked further, that turned out not to be the case. By testing a variety of cationic peptide chains, the Stanford-CellGate team found that peptides composed entirely of arginines were orders of magnitude more effective at infiltrating cells than counterparts made from leucines or glutamines. "So it's not just a cation story," Wender says.

To find out why, Wender's team synthesized short amino acid chains made from ornithine, an amino acid that differs from arginine in just one respect: It harbors a nitrogen in place of an oxygen, a change that does away with arginine's ability to form weak hydrogen bonds with its neighbors. To their surprise, the researchers found that the ornithine chains were virtually useless at shuffling drug cargo into cells, suggesting that arginine's ability to form hydrogen bonds is the key. And as it turns out, that hydrogen-bonding capability is a talent leucines and glutamines don't share.

Just what the peptides bond to and how polyarginine wends its way into cells are still mysteries. But whatever the mechanism turns out to be, it is clearly effective. At the ACS meeting, Wender reported that his team has used polyarginine tags to spirit drugs such as cyclosporin and Taxol into cells, and they are working to extend the method to other compounds. Apparently the new tags and their cargo don't just diffuse across cell membranes, Wender says; rather, it looks as if cells actively pump them inside.

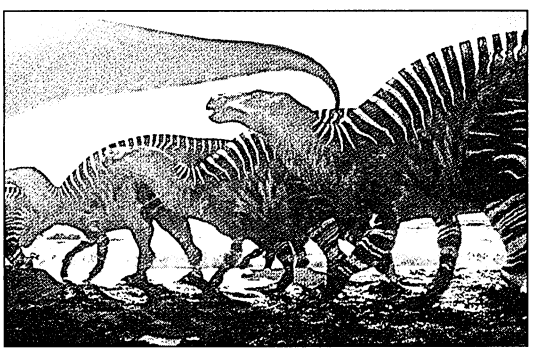
In one sense, in fact, the peptide may be too effective. "It works with every cell type we've looked at," Rothbard says. That could make it difficult to target drugs only to particular cells such as cancerous ones. For that reason, Wender says that he and his colleagues are initially focusing on linking their tag to drugs that can be applied locally, such as topical creams to treat skin diseases. Still, even if that's as far as they get—and that seems doubtful—a new access key for getting drugs into skin cells could make a profound difference for patients suffering from psoriasis and other chronic skin conditions.

–ROBERT F. SERVICE

TV CRITIQUE

Dinosaur Docudrama Blends Fact, Fantasy

Amid the majestic sequoias of what could be a state park in Northern California, the silence is broken by an unearthly, guttural bellow. An enormous beast plods across the television screen. She kicks out a shallow nest and begins to lay her eggs. Each white egg, the size of a soccer ball, slides gently down an ovipositor and comes to rest in the ground. Then, as a velvet-voiced narrator intones about the dangers that await the young hatchlings-to-be, the giant scrapes soil over the clutch and abandons her brood to their fate.



On the move. A herd of 4.5-ton iguanodons kicks up surf in the Cretaceous.

It looks and sounds just like a wildlife documentary—so much so that, if you watch long enough, you almost forget that the animals it shows have been extinct for more than 65 million years. But this is *Walking With Dinosaurs*, a sometimes stunning dino-extravaganza that uses computer animation and detailed puppets to resurrect the creatures

CREDITS: (TOP TO BOTTOM) STANFORD UNIVERSITY; BBC/DISCOVERY CHANNEL

ScienceScope

New Blood Following its history of finding new leadership within, Stanford University this week tapped Provost John L. Hennessy (below) to take over as president beginning 1 September. Hennessy, who succeeds Gerhard Casper, is expected to place the university in a strong position to reel in donations from supporters who have struck it rich in neighboring Silicon Valley.

Hennessy, a professor of electrical engineering and computer science, is also a Silicon Valley entrepreneur; he founded MIPS Technologies, which specializes in microprocessors. He was also instrumental last year in securing a $150 million donation from Netscape founder Jim Clark, who worked down the hall from Hennessy when both were Stanford professors. As president, Hennessy's early priorities are expected to include expanding interdisciplinary research and ensuring affordable housing for faculty and students.

Initial reaction to the pick was glowing. "I'm thrilled," says Richard Zare, a Stanford chemistry professor and former chair of the National Science Board. Hennessy's experience in academia and high-tech, Zare says, made him "the obvious natural choice."

Too Cautious? In what many view as a victory for science, a U.S. court last week slammed the Environmental Protection Agency (EPA) for proposing tighter guidelines for safe drinking water than its scientists thought necessary.

The case is the first test of draft risk guidelines that use molecular data to assess whether low doses of a substance can cause cancer. After reviewing studies suggesting that tiny doses of chloroform—a carcinogenic byproduct of chlorinating water—are harmless, EPA scientists in 1998 proposed increasing the goal for maximum tap-water levels from 0 to 300 parts per billion. But under pressure from environmentalists, the agency nixed the change. The Chlorine Chemistry Council sued, claiming EPA had violated a law that requires it to base decisions on the best science.

On 31 March, a federal judge agreed, finding that EPA "openly overrode" the scientific evidence. Toxicologist Jay Goodman of Michigan State University in East Lansing says the ruling should be "a wake-up call to EPA," which now plans to reevaluate its stance.

Contributors: Andrew Lawler, Eliot Marshall, Adrian Cho, David Malakoff, Robert F. Service, Jocelyn Kaiser