vaccine under internationally recognized good manufacturing conditions.

"There were collaborations before IVI," says Vietnam's Thu Van Nguyen. "But each institute has its strengths and weaknesses. IVI spreads the strengths around more widely then ever before," he adds, through the meetings, workshops, and collaborations it sponsors. Wang Bing-rui of the Lanzhou Institute is quick to agree: "DOMI has helped us increase vaccine yield, with improved quality."

IVI's success has also caught the eye of scientists from the industrial world, who are eager to work more closely with large afflicted populations. "I came here because of their experience with clinical trials in the Third World," says Hans G. Kreeftenberg of the National Institute for Public Health and the Environment in the Netherlands, who visited Seoul recently for a workshop on technology transfer. "These diseases have a major public health impact, but they don't get priority from drug companies because of the low return on investment."

IVI can also play a positive political role, says Bhutta: "It recognizes that the diseases are the real enemy." And it's a foe that can't be ignored. "Officials often say that these problems will go away when a country gets good clean water," says Clemens. "But that might take 50 years. We need to do something now."

—MARK RUSSELL

Mark Russell writes from Seoul.

CANCER RESEARCH

Taking Garbage In, Tossing Cancer Out?

Working in a novel way—blocking the cell's garbage disposal or proteasome—a new class of compounds is showing promise in clinical trials

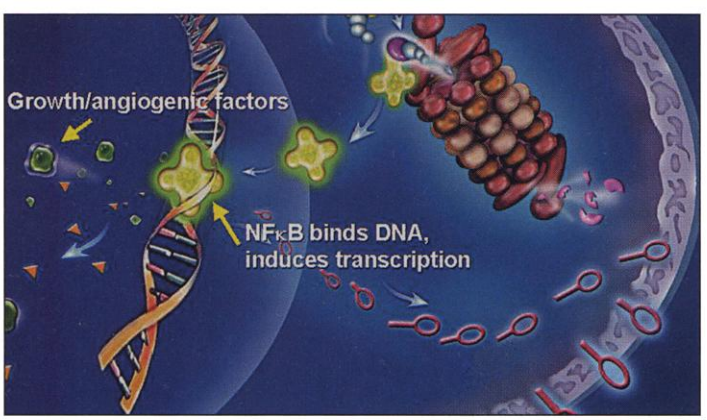
The proteasome is the cell's garbage shredder, a barrel-shaped enzyme that sucks in damaged or short-lived proteins and dismembers them for eventual disposal or recycling. It's absolutely essential for survival. So when ProScript, a tiny, privately held company leasing a basement office in Cambridge, Massachusetts, discovered a drug in 1995 that could treat cancer by blocking the proteasome, the idea met with almost universal skepticism: The treatment seemed likely to kill patients along with their tumors. The company persevered, however, getting encouraging results in animals and eventually persuading the National Cancer Institute (NCI) to fund clinical trials of its drug, PS-341. "Our budgets were strapped," recalls Julian Adams, ProScript's former chief scientist and now senior vice president for drug discovery at Millennium Pharmaceuticals, also in Cambridge. "We were down to fumes."

ProScript's tenacity may be paying off. First, Millennium acquired the company in 1999, providing badly needed capital. And now, clinical results in multiple myeloma, presented at December's meeting of the American Society of Hematology (ASH), demonstrate that blocking the proteasome may actually work. "There has been very impressive antimyeloma activity even … when no other available therapy is effective," says oncologist Ken Anderson of the Dana-Farber Cancer Institute in Boston, who is directing a phase II trial of the drug. "That accounts for our excitement." But side effects remain an issue, and Dave McConkey of the M. D. Anderson Cancer Center in Houston points out that PS-341's mechanism of action is complex and still poorly understood. "I don't think it's the magic bullet," he says.

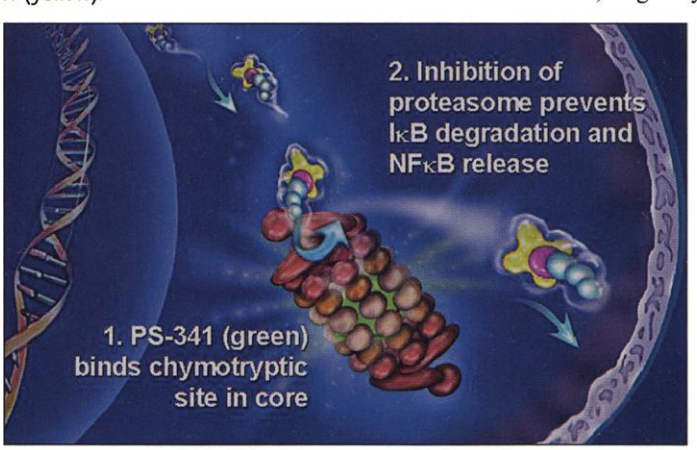
PS-341 is generating interest largely because it works in a completely new way. Cancer drugs, with few exceptions, go after predictable targets: DNA replication (cisplatin), microtubules (Taxol), growth signaling pathways (Gleevec), and angiogenesis (for example, endostatin). Proteasome inhibitors are "a new group of agents aimed at a novel target," says John Wright, a senior investigator in NCI's Cancer Therapy Evaluation Program. Still, NCI took a gamble in funding clinical trials, because protein breakdown, or proteolysis, is so central to normal cell function. "I think luck has to be on your side" for this approach to work, says British cell biologist Paul Nurse, co-recipient of this year's Nobel Prize in physiology or medicine.

How does PS-341 work? When the proteasome is blocked, proteins, instead of disintegrating, build up in the cell. This is ultimately fatal, because constant protein degradation, or "turnover," is necessary for proper cell function. Proteins called cyclins, for example, must disappear for the cell cycle to proceed through cell division. Adams, a medicinal chemist and veteran of industry giants Merck and Boehringer Ingelheim, originally expected that his drug, by allowing cyclin buildup, would arrest cell division and halt tumor growth. PS-341 does seem to do this, but it seems to kill tumors in a variety of other ways as well.

"The most important mechanism is likely to be NFκB inhibition," says McConkey. NFκB is a transcription factor that triggers expression of proteins that promote tumor and



New agent, new target. Transcription factor NFκB (green, shown leaving the proteasome, red) triggers expression of proteins that promote tumor growth (*above*). Proteasome inhibitors (shown binding a site inside the proteasome) block the cancer-promoting effects of NFκB by preventing breakdown of its precursor (yellow).



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tumor blood vessel growth. It also blocks apoptosis, or programmed cell death, perpetuating cancer cells. By forcing the buildup of a protein that prevents NFκB activation, PS-341 seems to starve tumors of their blood supply and growth stimuli, thereby promoting their self-destruction.

On a cellular level, blocking the proteasome generally stresses cancer cells by jamming them with proteins. Adams believes that cancer cells may be selectively vulnerable to PS-341 because they can't handle the stress of the protein buildup as easily as normal cells can. This stress causes "catastrophic signaling events, which drive the tumor cell to die," explains Adams. "A normal, untransformed cell can withstand the stress response, at least for short periods of time." For that reason, intermittent dosing—once or twice weekly, for a limited time—is crucial. The rest periods are designed to allow the proteasome in normal cells to recover. "We keep patients' dose below a level of 80% proteasome inhibition," says Adams. "There's a stress to the host, but a tolerable stress."

The clinical results, from a multicenter trial sponsored by Millennium and headed by Dana-Farber, announced at ASH seem to bear this out. Of 54 myeloma patients, more than half experienced major tumor shrinkage, and the drug halted tumor growth in most of the others. Because myeloma is currently incurable, oncologists are jubilant, although they express some misgivings. "We have something to whack myeloma with we didn't have a year ago," says James Berenson, director of myeloma programs at Cedars-Sinai Medical Center in Los Angeles. "That's pretty cool." But, he adds, "this is not an easy drug." Some patients experience such severe pain after taking PS-341 that they refuse to continue treatment. But enough have benefited that more than 30 separate clinical trials are now under way, sponsored by the NCI and by Millennium, in a wide range of cancers, including breast, colon, lung, and prostate.

Even if acute side effects can be managed, the long-term effects of partial, periodic proteasome inhibition in humans are unknown. "We definitely need to understand the effects of partial inhibition before we can make sweeping statements about why it's not toxic to normal cells," says McConkey. Primate studies have only gone out 3 months.

Already, it's clear that PS-341 is not the ideal proteasome inhibitor, because the drug indiscriminately raises levels for hundreds of proteins without regard to their anticancer effect. Millennium is now trying to develop inhibitors upstream of the proteasome, by tagging proteins for survival even before they're sent to the proteasome for destruction. If a drug could inhibit specific enzymes that attach ubiquitin to individual proteins (ubiquitin chains mark proteins for destruction in the proteasome), it could, in theory block degradation of only those proteins thought to have a direct anticancer effect—for example, tumor suppressor gene products.

So proteasome inhibition, in all its guises, has arrived as an anticancer strategy, although no one, including Millennium, is quite sure how best to apply it. "They have a golden nugget, but they're going to have to figure out how to make it into a golden ring," says Berenson. Only time will tell if PS-341 ultimately proves useful in the clinic, but the drug has already shown that playing with garbage has its rewards.

–KEN GARBER

Ken Garber is a science writer in Ann Arbor, Michigan.

MEETING PRIMATE ORIGINS

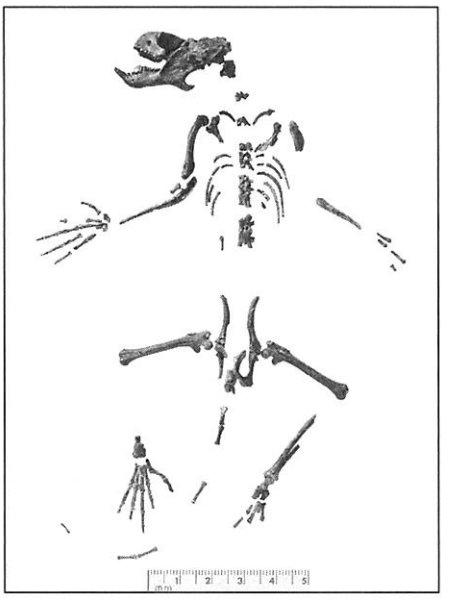
New Fossils and a Glimpse of Evolution

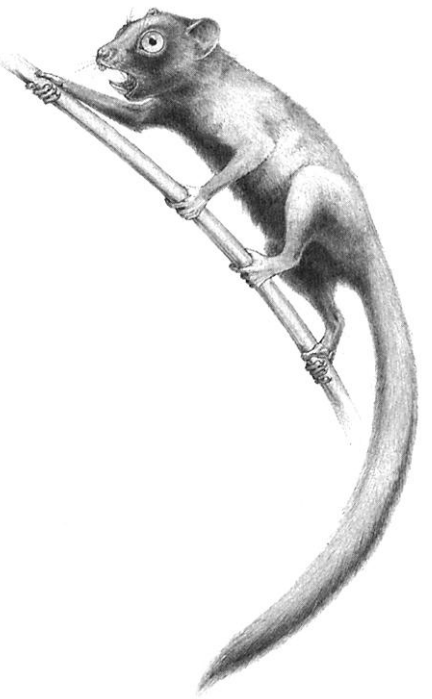
CHICAGO—In an all-too-rare occurrence, paleontologists and molecular biologists met here 13 to 15 December 2001 to share their data and their often very different perspectives. The gathering, the "First-Ever International Conference on Primate Origins and Adaptations: A Multidisciplinary Perspective," was organized by the Field Museum and Northwestern University. Hot topics included descriptions of six exceptionally well-preserved fossils of archaic primates and of how primates evolved color vision.

Fresh Look at Primate Ancestors

Small, furry, with large eyes, grasping hands, and a fondness for hunting insects: That's one of several popular images anthropologists have painted of the ancestors to primates. The first undisputed primates appear in the fossil record about 55 million years ago in the Eocene. The problem, however, has been a dearth of fossils before that time, in the Paleocene, to back up conjectures about primate ancestors. Vast movements of rock, earth, and water over tens of millions of years crushed the fragile fossils, usually leaving only scattered bones and teeth as evidence. Worldwide, less than a half-dozen incomplete Paleocene primate skeletons have been described.

Now, vertebrate paleontologist Jonathan I. Bloch and undergraduate Doug M. Boyer of the University of Michigan, Ann Arbor, and their colleagues have added considerably to this data bank. At the meeting they described their full cache of six exceptionally well-preserved, complete skeletons, dissolved out of freshwater limestone in the





Arborealist. Fossils of *Carpolestes simpsoni* suggest that it had specialized tactile and grasping abilities, necessary for a life in the trees.

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