SOUTH KOREA

Institute Helps Spread Use of Vaccines in Asia

The International Vaccine Institute hopes that research collaborations will make vaccines more available in the developing world

SEOUL, SOUTH KOREA—Vietnam is providing Indonesia with technology to produce a low-cost oral cholera vaccine. And China is sharing with India and Vietnam its technology on a typhoid fever vaccine. These and other collaborations are fruits of a new program, called Diseases of the Most Impoverished (DOMI), dedicated to improving the health of nearly half the world's population. The program is the largest undertaken by the fledgling International Vaccine Institute (IVI), which takes a novel approach to stimulating research, training, and technical assistance on vaccines in developing countries.

IVI's goal is to escape the Catch-22 that hinders health research throughout the developing world: Cash-strapped governments don't have enough information about infectious disease killers to know how best to fight them, but they are reluctant to spend scarce resources to get that information because the payoff isn't clear. "We're trying to evaluate the magnitude of the problem and, just as importantly, show that there is a market for vaccine producers," says IVI director John Clemens, a U.S.-trained epidemiologist who has spent 20 years working on vaccines for the developing world. Collaboration also offers member countries a chance to advance more quickly than if they worked on their own. "Typhoid fever and cholera vaccines have been available for 15 years," says Clemens, "but they were not used in most developing countries. We're telescoping that introduction process."

The institute is the creation of the United Nations Development Programme; it set up shop here in 1997 (*Science*, 16 April 1999, p. 410). South Korea has made room for it on the campus of Seoul National University and is building a five-story laboratory and headquarters that the small but growing scientific staff hopes will be ready by the end of the year.

IVI's first project, begun in 1999, tackled bacterial meningitis in Vietnam, Korea, and China. But DOMI, a 5-year, $40 million effort funded by the Bill and Melinda Gates Foundation, is by far its largest initiative. Seven countries—China, India, Indonesia, Bangladesh, Pakistan, Vietnam, and Thailand—have declared war on cholera, typhoid fever, and shigellosis, which together kill nearly 2 million people a year and afflict 200 million in the seven countries. Last year DOMI supported more than 40 projects, including disease-burden studies, vaccine demonstration projects, training, and socioeconomic surveys.

A team approach. Vietnamese health workers administer a domestically developed killed oral cholera vaccine (*above*), while Zulfiqar Bhutta (far right) meets with collaborators in Sultanabad, Pakistan, a DOMI study site.

In addition to the formidable scientific and technical challenges they face, scientists must also grapple with obstacles less visible but just as crippling. "There is a large-scale denial of the existence of cholera as a major public health problem in Pakistan," says Zulfiqar Bhutta of the Aga Khan University in Karachi. The same is true for shigellosis, he says. A lack of data initially blunted his attempt to start a typhoid fever vaccination program, he recalls. But once he had enough information for a presentation to policy-makers, "the reaction was a mixture of surprise and shock."

Clemens says that Bhutta's tale is not unusual in DOMI countries, where the concerns of the poor take a back seat to those of the wealthy and politically influential. "If these diseases affected the middle class," he says, "we wouldn't have a problem." DOMI helps scientists level the playing field by offering policy-makers what Clemens calls "a constellation of different kinds of evidence."

The first steps are disease-burden studies. Simply determining how many people are suffering from these diseases is a challenge for countries with large gaps in their health care systems. Poor populations are highly mobile (especially refugee populations), are not well enumerated, and lack the resources to help themselves.

The next step is to evaluate the effectiveness of existing vaccines and develop new strains tailored to the local population. "The results from several countries using standardized protocols will have a much greater impact on regional policy than would individual studies in individual countries," Clemens says. The third step is helping each country gain reliable access to the vaccines. Throughout the process, social scientists are needed to educate the public about the cost-effectiveness of the vaccines and to deal with people's concerns.

Although DOMI was launched just 2 years ago, it has already made an impact on health care in the region. Bio Farma, Indonesia's only vaccine producer, has built facilities for local production of Vi typhoid fever vaccine, a subunit of a live, attenuated oral vaccine, and a killed oral cholera vaccine developed in Vietnam that's less expensive than the Western version. Shantha, a major vaccine producer in India, is receiving help from China's Lanzhou Institute to produce the Vi vaccine for both the public and private sectors. Vietnam's National Institute of Hygiene and Epidemiology in Hanoi has taken out a low-interest loan from South Korea to build modern facilities, with design help from DOMI, that can produce the oral cholera

CREDITS: IVI

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

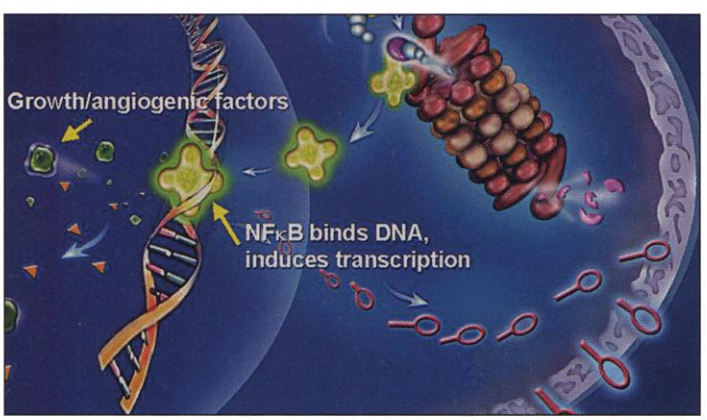
The proteasome is the cell's garbage shredder, a barrel-shaped enzyme that sucks in damaged or short-lived proteins and dismembers them for eventual disposal or recycling. It's absolutely essential for survival. So when ProScript, a tiny, privately held company leasing a basement office in Cambridge, 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.

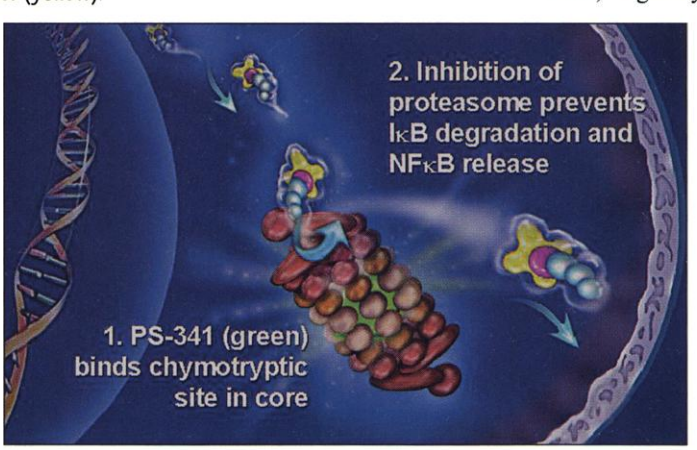
PS-341 is generating interest largely because it works in a completely new way. Cancer drugs, with few exceptions, go after predictable targets: DNA replication (cisplatin), microtubules (Taxol), growth signaling pathways (Gleevec), and angiogenesis (for example, endostatin). Proteasome inhibitors are "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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