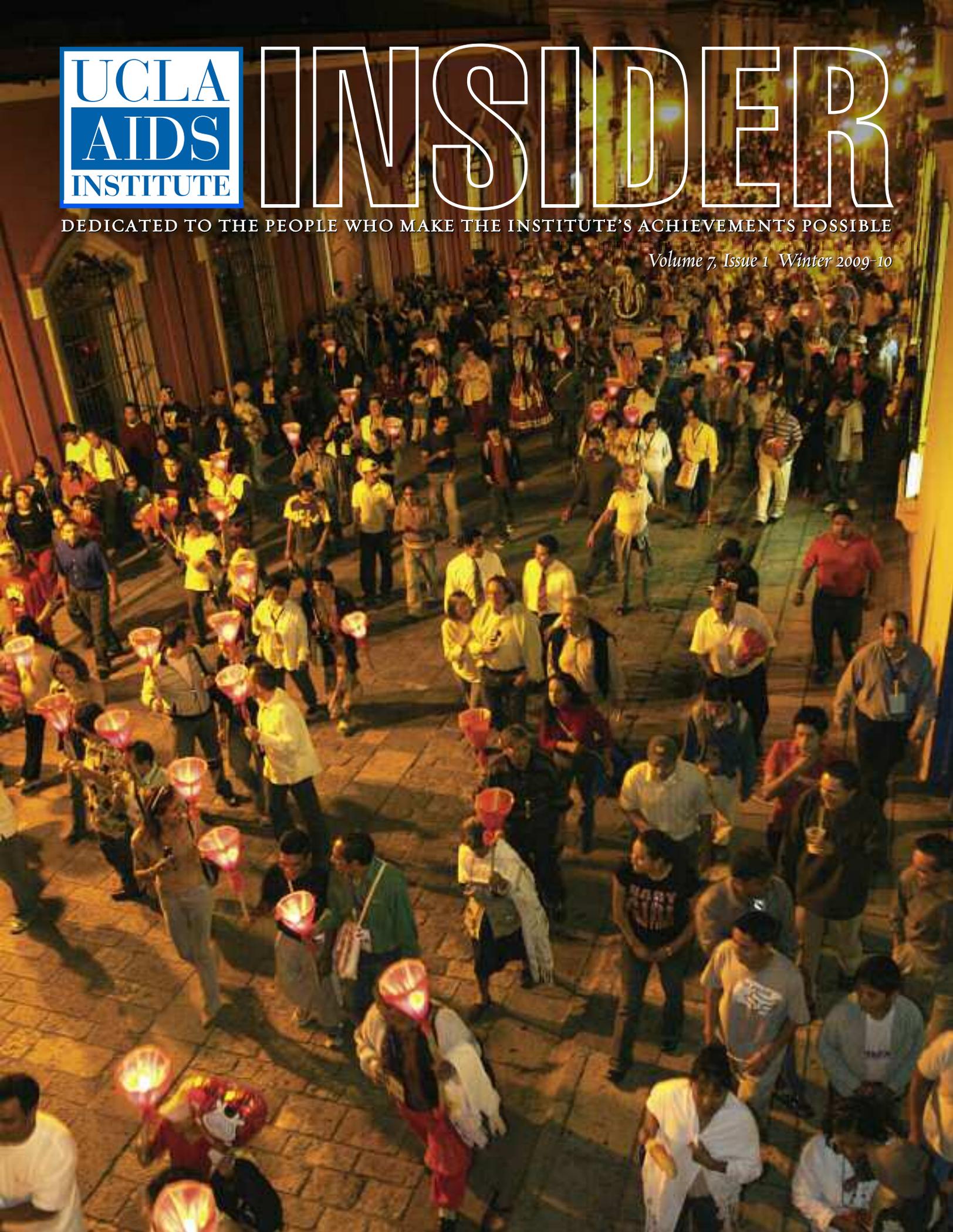




INSIDER

DEDICATED TO THE PEOPLE WHO MAKE THE INSTITUTE'S ACHIEVEMENTS POSSIBLE

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Programs to Contain the Epidemic, Progress in Vaccine Research

Interventions along our border with Mexico, and novel approaches to preventing new infections from occurring



Nothing exemplifies the diversity of the research being conducted by members of the faculty of the UCLA AIDS Institute better than the work represented in the two major articles in this issue of *Insider*. The first, “Hand Across the Border” (pages 4–15), demonstrates the Institute’s commitment to AIDS education and treatment—in this instance in the form of a cross-border collaboration with the government of Mexico that is helping to map, and contain, the HIV epidemic that moves back and forth across the common border with our southern neighbor as part of the human traffic, legal and illegal, that characterizes our region.

“Hands Across the Border” demonstrates the Institute’s capacity to mobilize, on short notice, the considerable resources of the institution to address a specific problem—in this case the near-absence, in the mid-1990s, of a comprehensive, Spanish-language prevention, diagnosis, and treatment program in Mexico. Under the inspired leadership of Dr. Octavio Vallejo, UCLA created, in less than a month, a teaching module that has, over the last decade, been successfully delivered to doctors, nurses, and clinical technicians in more than 20 of Mexico’s 32 states. “It was a real scramble,” Dr. Vallejo reports, “but we put together a faculty and fielded a team of bilingual volunteers. We pulled together a four-day training program that covered education, prevention, program development, clinical management, strategies to ensure long-term survival, as well as information about nutritional and psychological support of patients.”

In every respect Dr. Vallejo was the ideal person to lead this effort, beginning with the fact that he is a bilingual Latino whose medical specialty is infectious disease. He is also a long-term survivor of HIV disease and an openly gay man. As a result, his very presence at training sessions in Mexico was a source of inspiration to the providers and activists who participated in these intensive sessions. (Octavio Vallejo’s personal story was the subject of a photo-essay and article in the February 2004 issue of *Insider*; his work with HIV-infected members of the Latino community was covered, in both English and Spanish, in the January 2006 issue. Both are available online at www.uclaidsinstitute.org under the heading PUBLICATIONS.)

The second article, “The Great Dismal Swamp” (pages 16–19), examines the mire of AIDS vaccine research, explains why every vaccine trial has ended in disappointment, and describes the novel approaches that Institute researchers are taking to resolve a conundrum almost as old as the AIDS epidemic itself: How do you develop a vaccine that will prevent HIV infection, when the human body cannot prevent such infection? All vaccines, after all, replicate the mechanism by which the body thwarts disease, and in the case of HIV there is no obvious protective mechanism to mimic.

As most AIDS researchers now realize, there is little likelihood that any traditionally formulated vaccine will be effective against HIV, thanks in large measure to the sheer mutability of the virus—which changes its generic makeup far faster than vaccines can be developed to squelch it. We have therefore asked ourselves, If standard approaches to fostering immunity to HIV infection do not work, what will? One approach is to stop thinking in terms of sterilizing vaccines—given in advance of exposure to a virus, and 100% effective in preventing infection—and start thinking in terms of therapeutic vaccines—given to those already infected, in lieu of toxic drug regimens. A research team at the Institute is exploring this approach.

Another method involves harnessing the very latest technological breakthrough in gene therapy to engineer a new and novel method of vaccination. This approach uses a discovery, made only last year, that mature, well differentiated cells—in this case skin cells—can be induced to un-learn the genetic instructions that have turned them in skin cells and revert back to stem cells. The great challenge before us—and the principal work of the UCLA AIDS Institute in the years to come—is to use the same technological breakthrough to reprogram human T cells, with the objective of creating lines of CD8 cells that, far from being uniquely vulnerable to HIV, kill the virus whenever they encounter it.



Irvin S.Y. Chen
Director, UCLA AIDS Institute

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Hands Across

UCLA spearheads a crossborder program to equip Mexican healthcare providers with the training and tools they need to cope with their AIDS epidemic

Politicians and self-styled patriots are going to extraordinary efforts to prevent Mexican migrants from reaching the United States. The former want to see a multibillion-dollar fence constructed along our common border with our southern neighbor; the latter have formed vigilante groups to patrol the trackless expanses of sage and seguardo that make up much of that border. Meanwhile, another migrant moves regularly across the border, unseen and largely unchecked. That stealthy traveler is HIV, which occasionally comes north in the bloodsteam of an infected migrant worker... and much more regularly heads home with a worker who has spent the harvest season picking crops in California's Central Valley and is bound for his native village with as much hard-earned cash as he has been able to save.

One of the enduring myths of the immigration conundrum—which boils down to “Don't want to let 'em in, but can't run the state's vast agribusiness without 'em”—is that migrant workers want to settle permanently in the United States. The truth is that the vast majority spend their time in el Norte dreaming of home, and think of their time here as a kind of indentured servitude, lucrative but lonely. To ease that ache, some pay for sex; others, both male and female, take money in exchange for sex. All too often these transactions involve more than the exchange of cash. No one knows how many migrant workers are infected with HIV while they are in the States, because only the most desperately ill risk deportation by seeking medical help, but the results of this cross-border trafficking in sex has resulted in a rash of infections in young Mexican women who were virgins when they married and have been entirely faithful to their husbands during the long months those men are north of the border, seeking better-paying work... and seeking solace in the arms of strangers.



the Border



Billions for a fence to keep migrant workers from coming north... and practically nothing to keep them from taking HIV home with them. Like every other country in this hemisphere, Mexico was slow to recognize the extent of its epidemic, and there, as elsewhere, the shaming, silencing stigma associated with HIV infection, coupled with frank discrimination directed against early victims of the epidemic, contributed to the government's tardy response.

UCLA's involvement in efforts to teach Mexican doctors, nurses, and other healthcare providers how to diagnose and treat HIV infection began in 1995, when Dr. Octavio Vallejo, a fellow of the Fogarty International Training Program at the UCLA Center for Health Promotion and Disease Prevention, got a call from a group of researchers who had received a grant from the United States Agency for International Development to provide training in HIV/AIDS care to Mexican medical personnel.

The first of these trainings had already occurred in the United States, and the group was desperately trying to organize a more intense follow-up training in Mexico. Could Dr. Vallejo put together a training program for 25 physicians, nurses, psychologists and social workers who would be meeting in Hidalgo, Mexico, in less than a month? He could, and did. "It was a real scramble, but with my connections in Mexico—and with the support of Dr. Charles Lewis at UCLA and Dr. Richard Beach, who then had one of the largest HIV practices in Miami—we put together a faculty and fielded a team of bilingual volunteer trainers from UCLA and AIDS Project Los Angeles. We pulled together a four-day training program—entirely in Spanish, of course—that covered education, prevention, program development, clinical management, strategies to ensure long-term survival, as well as information about nutritional and psychological support of patients."

In every respect Dr. Vallejo was the ideal person to lead this effort, beginning with the fact that he is a bilingual Latino whose medical specialty is infectious disease. He is also a long-term survivor of HIV disease and an openly gay man. As a result, his very presence at training sessions in Mexico was a source of inspiration to the providers and activists who participated in these intensive sessions. (Octavio Vallejo's personal story was the subject of a photoessay in the February 2004 issue of *Insider*; his work with HIV-infected members of the Latino community in Los Angeles was covered, in both English and Spanish, in the January 2006 issue. Both are available online at www.uclaidsinstitute.org under the heading PUBLICATIONS.)

Despite a lack of formal funding—and any guarantees that future training sessions would be funded—this first cross-border foray was a resounding



Dr. Octavio Vallejo put together UCLA's first training session for Mexican healthcare providers in less than a month's time. To help UCLA sustain and broaden this educational effort, Vallejo's Mexican colleagues donated rooms and meals to members of the faculty, and provided the high-quality printed materials that were handed out at the meetings.



Competition for Yanqui dollars takes many forms south of Mexico's common border with the United States. Panhandling, both active and passive (lower right), is commonplace. Musicians, like the one at upper right, and street buskers hope to convert a moment or two of diversion into a modest gratuity. Come nightfall, these supplicants are replaced by commercial sex workers, like the leggy transsexual below, whose age-old profession has become a conduit for HIV transmission on both sides of the border.





success. By the end of the four days the team had invitations to repeat and expand the training in several of the participants' home states, and later that year a second four-day training took place, this one in Guerrero with support from local university and business leaders. More than 300 healthcare providers and people living with AIDS participated in the event in Guerrero, at which some of the first support groups for people living with HIV were established in Mexico. The team then traveled to San Luis Potosí and conducted a training session for some 250 doctors, nurses, and lab workers. "By going to two cities in one trip we were able to maximize the impact of the donated airfares and utilize much of the same curriculum. Local organizers and attendees alike were so grateful and enthusiastic about our programs that they often donated rooms, meals, television and radio time, and significant quantities of high-quality printed materials to our program," says Dr. Vallejo.

It was at San Luis Potosí that the UCLA representatives got a sense of the enormity of their task—and the necessity for continuing to conduct such trainings—when they heard a local doctor, one who held a high position in the city's public health department, encourage attendees to "burn the sheets and blankets of AIDS patients after they die." In the absence of hard clinical facts, such ignorance flourishes, and part of what the UCLA team has sought to do in Mexico is supplant such misinformation without offending local organizers, while demonstrating that physical contact with infected individuals is not only safe but is an essential element of the comprehensive care of AIDS patients. As Vallejo and his colleagues came to realize, their mission in Mexico involved equal parts diplomacy and scientific instruction.

By 1996, the UCLA team had more requests for trainings than it could fill. This was a time when the world was first hearing about the possibility of "eradicating" HIV in infected individuals through the use of multi-drug combinations that included a potent new class of antiretrovirals, the protease inhibitors. In the United States this euphoria would fade within 18 months, as patients put on these two- and three-drug combinations began to develop drug-resistant strains of HIV, but in the interim UCLA was flooded with requests from Mexican healthcare providers desperate to get these new medications, not yet available south of the border, for their patients.

Although all of the UCLA-sponsored training sessions included local experts, a five-day training session held in Michoacan towards the end of 1996 was the first such session to feature more local speakers than Norteamericanos, and it was the first to secure financial support from both sides of the border—from the Elton John AIDS Foundation and the University of California





In the absence of an effective vaccine against HIV infection, the only way the AIDS epidemic can be contained is through a simple and highly accurate blood test (above) and candid, confidential post-test counseling (top)—to reduce the likelihood that people living with HIV will transmit the virus to their sexual partners.



Institute on Mexico as well as from the University of Michoacan and CONASIDA, Mexico's National AIDS Program. More than 150 healthcare providers participated directly in the training, and hundreds more participated through special call-in television and radio shows or through satellite events held at local schools of medicine, nursing and law. Over the next decade similar training programs were held in Jalisco, Chihuahua, Mexico City, Oaxaca, Puebla, Yucatan, Sonora, Quintana Roo, and Baja California.

In all, more than 20 of Mexico's 32 states have been reached through these programs, and thousands of healthcare providers across Mexico have been trained to provide state-of-the-art care for people living with HIV infection, thanks to an army of volunteers, who collectively donated thousands of hours to this educational effort. "We were able to utilize much of the bilingual curriculum that we developed here at UCLA," Dr. Vallejo notes, "and although we never received a grant for more than \$5,000, that shortfall was compensated for by the willingness of people to donate their time and skills to the project, and by the significant support we received from our colleagues at Mexican universities, government health agencies, and non-governmental organizations. It was a true example of binational cooperation at its very best."



In countries that do not provide free, anonymous, routine HIV testing, infected individuals are often unaware that they harbor the virus until they develop one or more of the serious infections that are associated with the final stage of HIV disease. The patient shown opposite, a Mexican migrant worker in his mid-thirties, came to the hospital with shortness of breath, developed full-blown AIDS-related pneumonia within 48 hours (above), died three days later, and was buried alongside other victims of the epidemic (left).

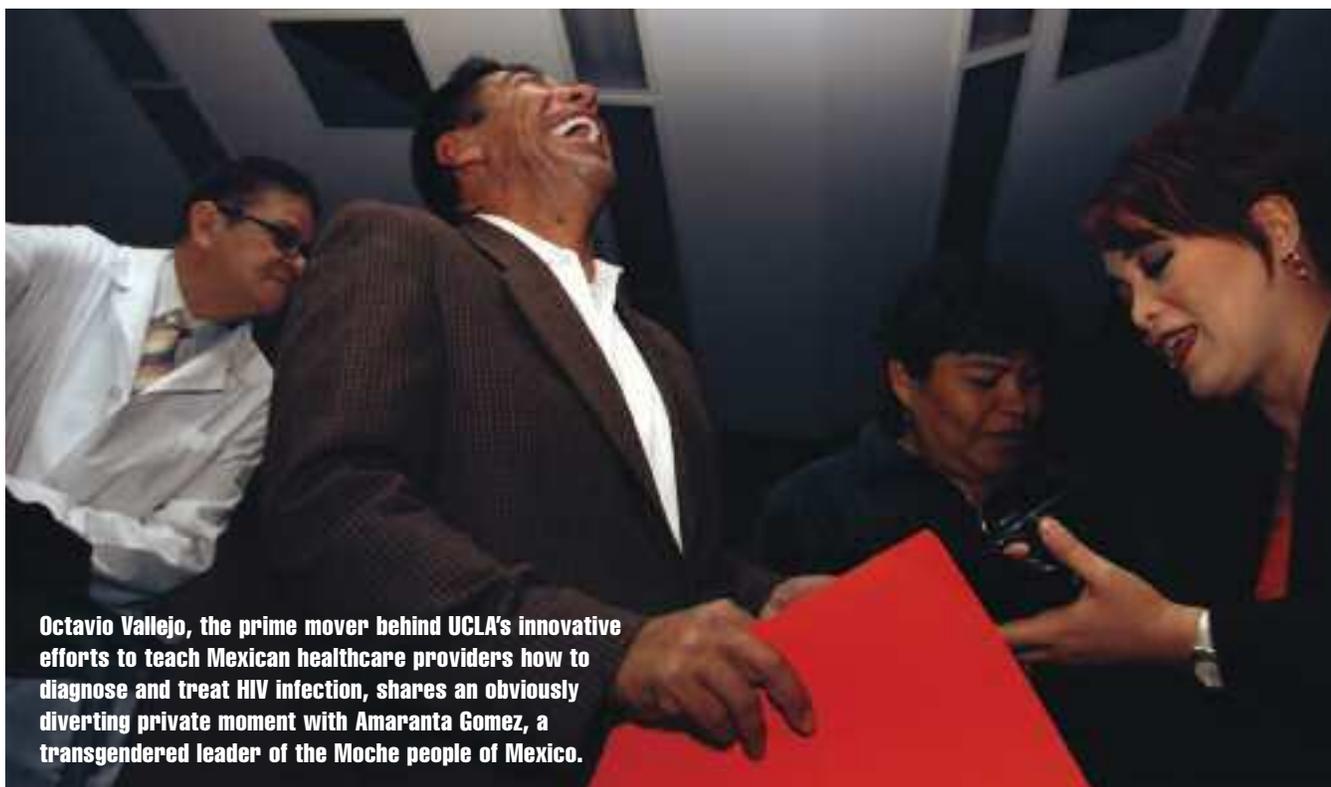
The collaboration continues

In November and December of 2005 the North American Treatment Advocates Forum conference was held in Oaxaca, Mexico—the first time this meeting had ever been held south of the border. Some 500 participants attended from the U.S., Canada, and Mexico. Dr. Vallejo and members of his staff conducted workshops a wide variety of topics. Each session was team-taught with co-presenters from Mexican AIDS organizations. The conference ended with a massive World AIDS Day celebration in the *zocalo*, or town square, of Oaxaca. Dr. Jorge Saavedra, Director of CENSIDA, the Mexican Secretary of Health, Dr. Julio Frenk, and the city's medical and political leaders all took part in a celebration outside the city's main cathedral, and more than 1,000 of the town's students marched through the streets in support of people living with HIV. Many of Mexico's indigenous populations sent delegates, and the Moche tribe was represented by Amaranta Gomez, a transgendered tribal leader who formally introduced the governor of Oaxaca at the forum.

Dr. Saavedra's relationship with UCLA dates back to 2004, when he was invited to meet with the leadership of all programs that serve the U.S./Mexico border. In February of 2006 he delivered an address at UCLA entitled "Update on HIV in Mexico: Fighting Stigma and Discrimination, Fighting Homophobia." Dr. Saavedra discussed the challenges and successes of his HIV work in Mexico and screened three government-funded public service announcements currently being aired on television

and radio in Mexico. These PSAs primarily address homophobia, which underlies so much of the stigma associated with HIV infection. Each of these announcements ends with the same voice-over: "Homophobia is intolerance of homosexuality. Equality starts when everybody recognizes that everyone has the right to be different. For a tolerant, inclusive and plural Mexico." With Dr. Saavedra's encouragement, these ads are now being aired on Spanish-language TV and radio stations in San Diego and Los Angeles counties at no cost to local AIDS organizations.

There is no doubt that the work done by UCLA was instrumental in changing Mexican healthcare providers' attitudes toward HIV disease and AIDS. The trainings that Octavio Vallejo and his coworkers conducted across Mexico, beginning in the mid-1990s, were not only informational but inspirational—encouraging participants to fight the silence, stigma and fears associated with this disease. With few resources and very limited funding, UCLA's volunteers made a huge impact in the HIV epidemic in Mexico. Because of those programs, Mexico now has healthcare providers advocating for their HIV-infected patients and HIV-infected people advocating for their peers—and California has culturally appropriate Spanish-language materials and messages about HIV and AIDS to distribute to its huge Latino population. The UCLA AIDS Institute hopes that these binational interventions will keep occurring, with the philosophy that guided them from the outset— a passion for teaching, caring and sharing.



Octavio Vallejo, the prime mover behind UCLA's innovative efforts to teach Mexican healthcare providers how to diagnose and treat HIV infection, shares an obviously diverting private moment with Amaranta Gomez, a transgendered leader of the Moche people of Mexico.

A thousand local students joined medical and political leaders on a march through Oaxaca to support people living with HIV.



The Great Dismal Swamp

UCLA AIDS Institute researchers hope to end the protracted, thus-far futile search for a safe, successful HIV vaccine

The history of HIV vaccine development is a two-decade-long tale of frustration, disappointment, and dashed hopes. Time and again candidate vaccines have failed to confer protection on those vaccinated—a dismaying record that culminated, in September of 2007, in the sudden discontinuation of a huge vaccine trial being conducted by Merck and Co. Merck had spent a decade developing its vaccine—which was based on a virus that can cause the common cold, onto which parts of three crucial HIV genes had been spliced. Many thought that the Merck vaccine, because it contained genetic material from the *gag*, *pol*, and *nef* proteins of HIV, would succeed where its predecessors had failed: by teaching the sentinel cells of the immune system to recognize those key components of HIV, Merck’s vaccine would equip those cells to identify, isolate, and kill the actual virus, should it invade a vaccinated individual.

Instead, the Merck vaccine proved to be a failure. Not only did this promising candidate fail to protect those who got the active agent in Merck’s placebo-controlled trial, the vaccine appears to have made some of those volunteers *more* susceptible to HIV. Whatever the explanation for this disastrous outcome, one thing is now abundantly clear: Traditional approaches to vaccine development are highly unlikely to yield an HIV vaccine that is both safe and broadly effective. Consequently, we need to reconsider what it is that we hoped to achieve through vaccination—and develop altogether new ways of attaining that end. That is precisely what researchers at the UCLA AIDS Institute are doing.

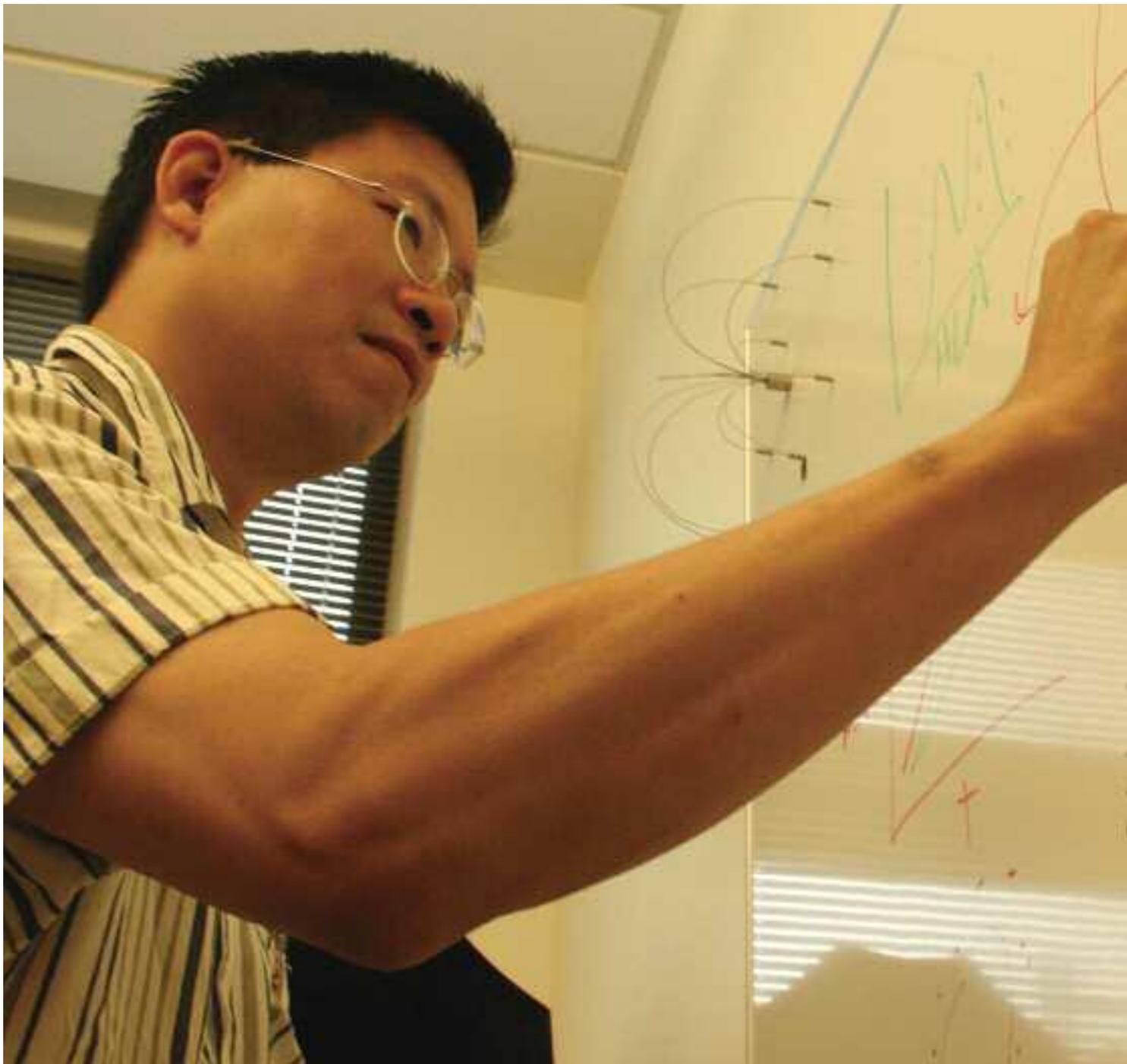
In a sense, the fact that every HIV vaccine trial to date has ended in disappointment should come as no surprise. The function of traditional vaccines—like those

that protect us against smallpox, measles, and polio—is to confront the immune system with a facsimile of one of those potentially deadly viruses and induce the system to develop antibodies to that virus... so that if, at some future date, the body’s defenses are breached by the actual virus, the immune system already knows how to respond. The problem is that there is very little that is traditional about HIV infection. For one thing, its target is the immune system itself. And although the body does eventually learn to combat HIV infection, by the time it does so the immune system is in tatters, and incapable of mounting an effective counterattack. The result is a desperate war of attrition, and in the absence of life-prolonging medications, the virus always wins the battle.

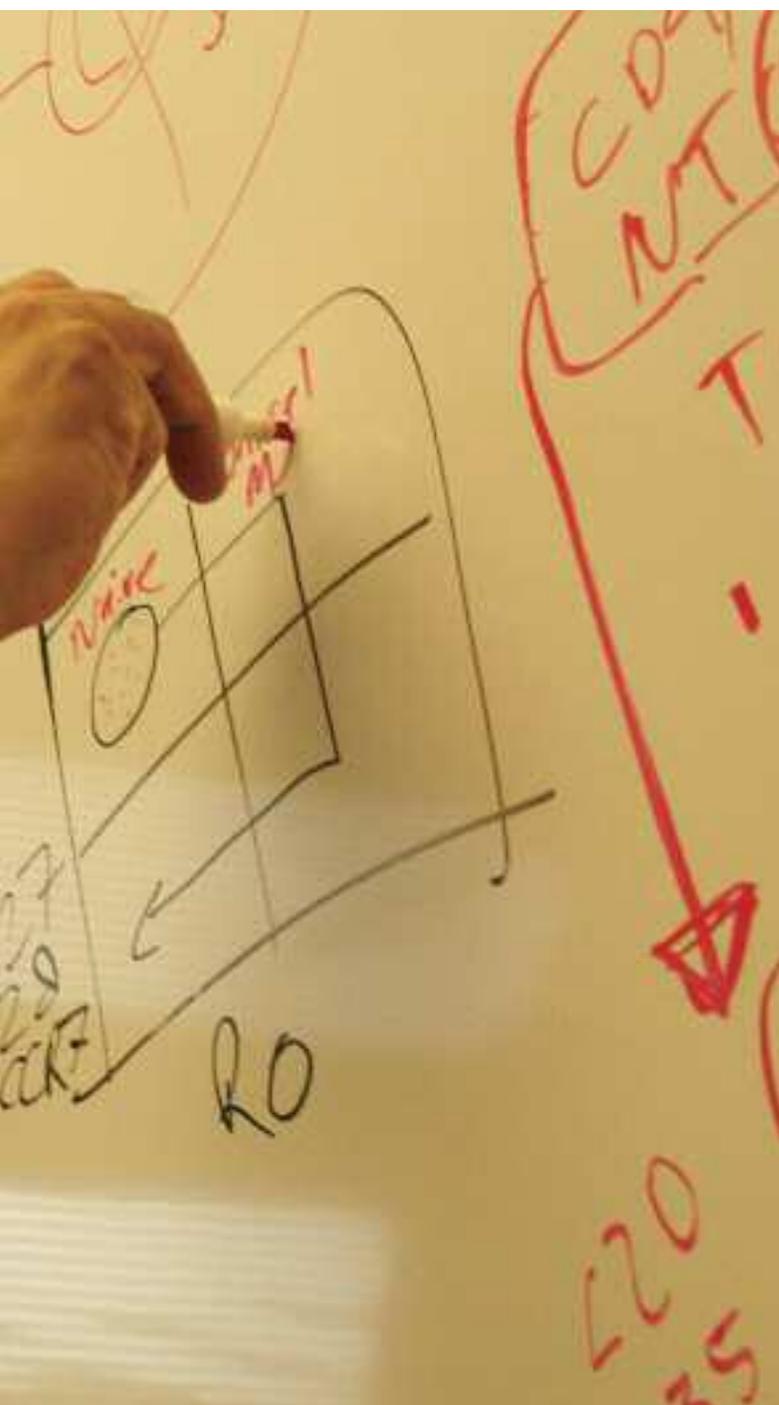
Historically, successful vaccines have been derived by developing agents that mimic successful natural responses to infection. The problem, when dealing with HIV infection, is that the body’s natural response is one that fails to contain the virus. As Dr. Otto Yang, an Associate Professor and a member of the Institute’s faculty, puts it, “We have never known exactly how vaccines work—and we have never needed to know. It was enough that we were able to induce the immune system to produce protective antibodies to a particular virus.” But as Dr. Yang notes, there is no cure for HIV infection, so even if antibodies are produced, the best we can hope for is slower disease progression. The immune system cannot be taught to generate a sufficient number of virus-killing antibodies to extinguish infection when an individual is exposed to HIV, because it has never been able to do that naturally. There is, in short, no effective mechanism for the immune system to mimic.



“We have never known exactly how vaccines work—and we have never needed to know. It was enough that we were able to induce the immune system to produce protective antibodies to a particular virus.” —DR. OTTO YANG



KATRINA CHEN



This already complicated picture is further clouded by what scientists call the “incompetence” of HIV. It takes only a single mutation for HIV to evade the drugs used to treat it—and any vaccine used to prevent it. And because HIV, the largest and most complex of all known viruses, makes countless errors every time it replicates—and it undergoes replication a *billion* times every day—the statistical likelihood is that the virus will generate every known mutation *every single day*. Therefore, no vaccine based on a set sequence of surface proteins can ever hope to identify, and kill, this shape-shifting virus.

Over the years Dr. Yang has developed a healthy skepticism about the likelihood that any traditionally formulated vaccine will be effective against HIV. His pessimism extends to the findings of a vaccine trial recently concluded in Thailand. The media—following the lead of the trial’s chief investigators—hailed that trial as a modest success, one that seemed to confer protection against HIV infection on roughly 31.2% of those vaccinated. Although this is hardly the level of efficacy that researchers were hoping for, it does represent the first positive result from any AIDS vaccine trial—too modest to make the vaccine a serious candidate for widespread use, but not too modest to encourage some researchers in the field. After all, saving 31% of a given population is better than saving none at all, and in some parts of sub-Saharan Africa, that may be the alternative. The problem is that the data from Thailand can be read many ways, and if you exclude from consideration any study subjects who did not rigorously adhere to their vaccination regimen, the findings cease to be statistically significant.

It is, in the end, a mark of how desperate AIDS researchers are to find an epidemic-ending vaccine that they would even consider launching a trial, at a cost of more than \$125 million, that combined two older vaccines, both of which had been abysmal failures when given separately. No one could say why these two vaccines, when used together, would achieve an efficacy that neither could on its own, but this did not stop the U.S. Army from recruiting 16,000 at-risk Thais to participate in the trial. It is fair to wonder, at this point, how many times it will be possible to enroll more than 10,000 Thais, or 10,000 Ugandans, in a vaccine trial

that yields statistically equivocal results or proves to be an outright failure.

If traditional approaches to fostering immunity to HIV infection do not work, what will? One approach is to rethink the whole role of vaccines. The smallpox, measles, and polio vaccines are all what are known as sterilizing vaccines: they protect 100% of those vaccinated from ever contracting the disease. But what if we think of vaccine not as a means of preventing disease but as a means of treating it? That is precisely the tack that Dr. Kathie Grovit Ferbas, an Associate Professor of Medicine in the Division of Hematology and Oncology at the David Geffen School of Medicine and the Greater Los Angeles VA Healthcare System, has taken. Dr. Ferbas, who has been conducting AIDS vaccine research at the UCLA AIDS Institute since 1996, first became interested in AIDS research as a summer intern working in the infectious disease department at Memorial Sloan-Kettering in New York in the early 1980s, during the first, devastating wave of the AIDS epidemic. “I had lots of time on my hands,” she recalls, “because I was a volunteer, so I would visit with the patients. Many had been ostracized by their families out of homophobia and fear, and I said to myself, ‘People shouldn’t die like this.’”

When she arrived at the UCLA AIDS Institute, Dr. Ferbas knew that she wanted to pursue vaccine research. She set out to look at the envelope, the outside shell of the AIDS virus that is the first point of contact when the virus is infecting a cell. What she discovered was that if she heated the envelope, parts of it appeared to open up, and these parts were especially good targets for antibody responses.

When she presented this early data in a meeting at the AIDS Institute, Dr. Judith Currier, the co-director of the Clinical AIDS Research and Education Center at UCLA, approached her with a novel idea. Dr. Currier speculated that it might be possible to take the HIV virus from a person who is already infected, heat it, and infuse it back into them in the form of a therapeutic vaccine. The first step would be to inactivate HIV by removing some of its genetic material, so that it was no longer capable of causing infection, and then heat-treating it. These processes turned HIV into a pseudovirion, which the two women gave a female name: “Pseu.”

Their plan was to take an HIV-positive patient on

antiretroviral therapy and vaccinate them with Pseu. The patient would then be taken off antiretroviral therapy, and vaccination would be repeated until the virus was cleared from the patient’s body. The goal of such therapy is not to eradicate the patient’s HIV infection but, ideally, to take patients off of antiretroviral therapy for long periods of time—thereby sparing them the toxic side effects of prolonged multidrug treatment. Patient would return at regular intervals for monitoring and, as necessary, for follow-up vaccinations.

Dr. Yang’s observations about the extreme mutability of HIV have led him in another direction. He thinks it has been a mistake to focus on the best-known proteins on the surface of HIV—*gag*, *pol*, and *nef*—because these proteins are also among the most genetically volatile. Instead, he proposes to concentrate on the *least mutable* regions of the virus; those regions, which scientists call “highly conserved,” are least prone to mutation and therefore best suited as targets for an HIV vaccine. They are, in a sense, HIV’s Achilles’ heel. Interestingly, this approach improves on the body’s own response to HIV: the immune system begins by attacking all parts of the virus envelope, and by the time it learns to attack only the highly conserved regions of the virus, the system is so weakened that it can no longer mount an effective attack against the virus.

What the immune system needs is a leg up in this war of attrition—and CD8 cells that are already programmed to kill HIV would provide that crucial advantage. Dr. Yang has already created an extensive library of HIV-specific killer CD8 cells lines—cells that can do what the Merck vaccine was supposed to teach such cells to do: identify, isolate, and kill HIV. Dr. Yang’s cell lines are derived from CD8 cells taken from people with advanced HIV infection. These individuals have developed CD8 cells that destroy HIV, but that process has taken such a toll on their immune systems that they do not possess enough of these cells to eradicate the virus in their bodies.

A team of researchers at the UCLA AIDS Institute, led by the Institute’s longtime director, Irvin S.Y. Chen, propose to exploit a recent scientific breakthrough that will, they hope, lead to a novel way of using Dr. Yang’s library of HIV-specific cell lines to confer lasting immunity against HIV infection.

This all-new approach to protective immunization



When what you do is HIV vaccine research, it helps to have a more immediately satisfying hobby—and Dr. Yang does: he collects vintage fountain pens such as this one, which he uses to sign his official correspondence.

is based on work done over the past year by four research teams, one of them right here at UCLA. The basis of this pioneering work is the discovery that mature, fully differentiated cells—in this case fibroblasts, or skin cells—can be induced to revert to their immature, undifferentiated embryonic progenitors. These are what are commonly called pluripotent stem cells, meaning that they have the capacity to mature into any kind of cell—a process that is guided by the genetic instructions they receive. What these four research teams have succeeded in doing is, in effect, reversing the sequence of genetic signaling, thereby inducing mature cells to shed their defining characteristics and reassume their original form. This process is known as the creation of *induced* pluripotent stem cells, or iPS cells.

It is hard to overestimate the implications, and potential clinical applications, of iPS technology. For one thing, it overcomes the ethical objections that some have raised to using embryonic stem cells for gene-based therapies. For another, it eliminates the risk of graft-versus-host reactions to genetic therapies like bone-marrow transplants, which often depend on donors who are not perfect genetic matches to the recipients.

Dr. Chen and his colleagues at the UCLA AIDS Institute plan to use this brand-new iPS technology to create killer CD8 cells that contain HIV-specific antigens. In the human body, CD8 cells are the first line of defense against HIV infection—and, as the natural history of HIV infection makes painfully clear, they are not up to the task. By the time CD8 cells have learned how to attack HIV, there are too few of them left to protect the body against the so-called opportunistic infections that overwhelm

individuals with HIV-ravaged immune systems.

The idea behind the work that Dr. Chen and his collaborators are undertaking is to isolate these killer CD8 cells and generate highly effective anti-HIV CD8 cell lines using iPS technology. These cloned lines of killer CD8 cells could be used in people infected with HIV as immunotherapy—to reconstitute these patients' battered immune systems by replacing the depleted CD8 reservoir with cells that can kill HIV when they encounter it. These same cloned lines could be used to confer genetic immunity on uninfected individuals—by augmenting their immune systems with cells that can kill HIV.

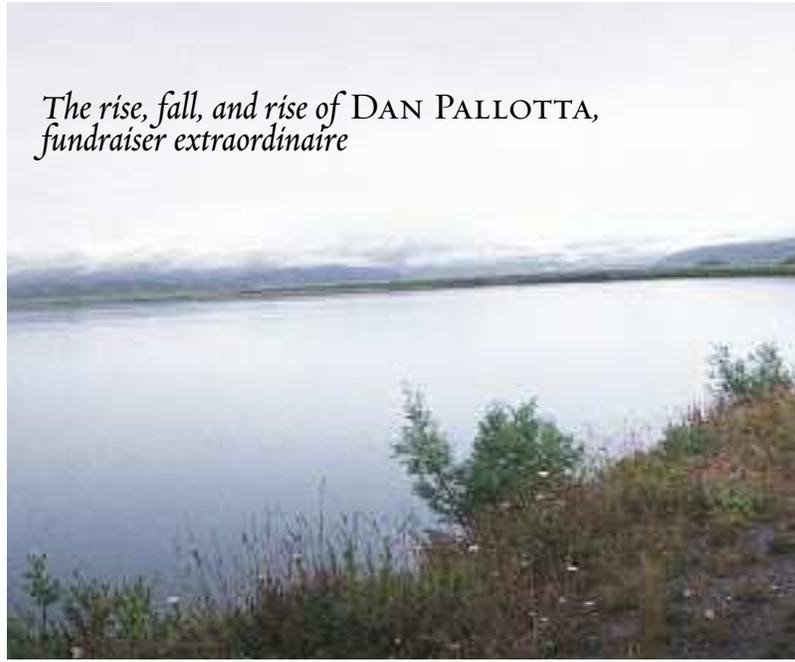
Dr. Chen and his team anticipate that it will take six months to a year to establish conditions for effective, efficient reprogramming of primary human CD8 cells to pluripotent stem cells through iPS technology. It will take roughly the same length of time to fully characterize the capacity of these iPS cells for pluripotency and for their ability to achieve differentiation into specific stem cell lines. The third and final step of this five-year program will be to clone killer CD8 cell lines and demonstrate that these lines are indeed comparable to Dr. Yang's original cell lines in their ability to target and destroy HIV. At present iPS technology has advanced only to the stage where cells called fibroblasts—which are composed to cells found in flesh wounds and scar tissue—can be induced to revert back to stem cells. The great challenge before us is to use the same technological breakthrough to reprogram human T cells, with the objective of creating lines of CD8 cells that, far from being uniquely vulnerable to HIV, kill the virus whenever they encounter it.

White Knight, Dark Horse

Dan Pallotta is the most successful AIDS fundraiser of all time. He is also, almost certainly, the most controversial. Indeed, even as Pallotta's serial successes in the late 1990s and early 2000s were transforming the landscape of fundraising in general and AIDS research in particular, a vocal minority was railing against his entrepreneurial, unorthodox approach to promoting and producing charitable events. Worse, calumnies that had no basis in fact sprung up, fed as much by the sour-grapes attitude of less successful rivals than by anything else. It was said that Pallotta was pocketing the bulk of the funds he raised, enriching himself at the expense of the AIDS patients who were the putative beneficiaries of his charitable enterprise. In truth, his firm's fees for creating and producing these events, and for taking on the liability of administering all of the expenses involved in them—a liability which, on several occasions, involved Pallotta's putting up his home up as collateral—represented just 4.01% of the total dollars raised, an amount roughly comparable to the fee that a credit card company would charge for merely processing a donation to such an event.

It was said that Pallotta TeamWorks, the remarkably effective engine of his enterprise, refused to open its books to outside inspection, to conceal the extent to which Pallotta was profiting from his supposedly "charitable" enterprises. In reality, the firm was a model of transparency, publishing all expenses and even the company's fees on an event-by-event basis, both in hard copy and on the Web, for all to see—a disclosure standard that is a model for non-for-profits everywhere. (You can find all of these numbers at www.pallottateamworks.com). Pallotta's own salary never came close to approaching the

The rise, fall, and rise of DAN PALLOTTA, fundraiser extraordinaire



multi-million dollar amounts his critics accused him of siphoning off these events. His salary peaked at around \$425,000 in 2001—which was roughly \$27,000 for each of the sixteen multi-million dollar events he created and produced that year alone. It was even said that Pallotta stayed in hotel penthouse suites, while his volunteers slept in tents. In fact, Pallotta himself rode the entire distance in many of the rides, including the AIDS Vaccine Ride across Montana, which he did with his father, and the Breast Cancer Three-Day Walk in Boston, which he did with his mother and two sisters. He slept in a tent like everyone else, and he ate with the participants. What many people do not realize is that the whole enterprise got its start when Pallotta himself bicycled 4,256 miles across the United States with 38 of his college classmates, to raise money for world hunger in an event that was his brainchild. Out of 69 nights the group spent on the road, they stayed in a hotel only once.

Over time the misinformation and rumor-mongering took their toll, and in 2002 TeamWorks, which had raised a staggering *half billion* dollars for a range of charities over a mere nine years, was put out of business. Dan Pallotta had become a prophet without honor in his own country. Ironically, that final year was the company's most successful ever: it netted \$82 million for charity *after all expenses*, an amount equivalent to more than half the annual giving of the Rockefeller Foundation. To set the record straight, Pallotta has written a book (see excerpt, pages 24–25). Given what was done to him and to his organization, *Uncharitable: How Restraints on Nonprofits Undermine Their Potential* could easily have been a very angry book. What righteous wrath there is in Pallotta's book, however, is all contained in a single



LEFT: PAWEI WE BELOW LEFT: MATT MENDELSON

chapter—and it is in the appendix at that. In that section he details the origins of the whispering campaign that ultimately brought Pallotta TeamWorks down, and without attributing sinister motives to his adversaries, he suggests why they may have been initially alarmed,



and ultimately confused, by his radical approach to fundraising. The bulk of *Uncharitable* is given over to a riveting analysis of the dysfunctional way our culture has been taught to think about social change, and any fair-minded reader will conclude that while Pallotta's thinking is indeed radical, it also makes eminent sense.

Reviewers across the country seem to agree. In the year since Pallotta's book appeared, it has been hailed as long overdue, clearheaded thinking on a formerly sacrosanct subject. The *Stanford Social Innovation Review* said that the book "deserves to become the nonprofit sector's new manifesto." Former U.S. Senator Gary Hart wrote that, "*Uncharitable* should make us all take two steps back and imagine a new philosophy and theory of charity itself. This is nothing less than a revolutionary work." *The New York Times* called it "powerful," and the head of Oxfam said, "If this is heresy, we need more of it." Indeed, Pallotta's

The Alaska AIDS Vaccine Ride (top) that Pallotta TeamWorks conceived and produced netted \$1.3 million for researchers at the UCLA AIDS Institute. As Irvin Chen, the director of the Institute, says, it is almost impossible to tally the number of promising ideas—and young careers—that have languished as a result of the demise of the TeamWorks rides. Many of the participants rode in memory of someone they lost to AIDS.

book has been endorsed by former Harvard President Derek Bok and the heads of Save the Children, the Southern Poverty Law Center, the Cato Institute, the Hewlett Foundation, Share Our Strength, and *Time* magazine's man of the Year, Dr. David Ho, among others.

Pallotta says that his experience raising hundreds of millions of dollars gave him a unique perspective on the way the donating public thinks about charity. He saw that the nonprofit ethic, which he describes as a religion, forces charities to obsess over keeping overhead low, even if it means they don't have the organizational strength to solve community and social problems as a result. "If what we tell charities is that, more than anything else, what we want is low overhead, then that's what we will get," he declares. "Or at least we will get the appearance of it. And if we say nothing about the fact that we want to solve problems, then solving problems will become a secondary concern. Is it any wonder, then, that our problems aren't getting solved?"

Pallotta also points out that, because of the fixation on overhead, many charities game the system, broadening their accounting definition of "the cause" so that they can tell donors that even higher percentages of their dollar go to the cause. "This makes the overhead measure utterly unjust and completely useless," he notes. "A charity that



LEFT: PAWEI WE OPPOSITE COURTESY OF PETERANTON

does middling work but does really aggressive ‘cause accounting’ can end up looking better on paper than a charity that does great work but uses a more conservative accounting approach. Donors are unaware of this.”

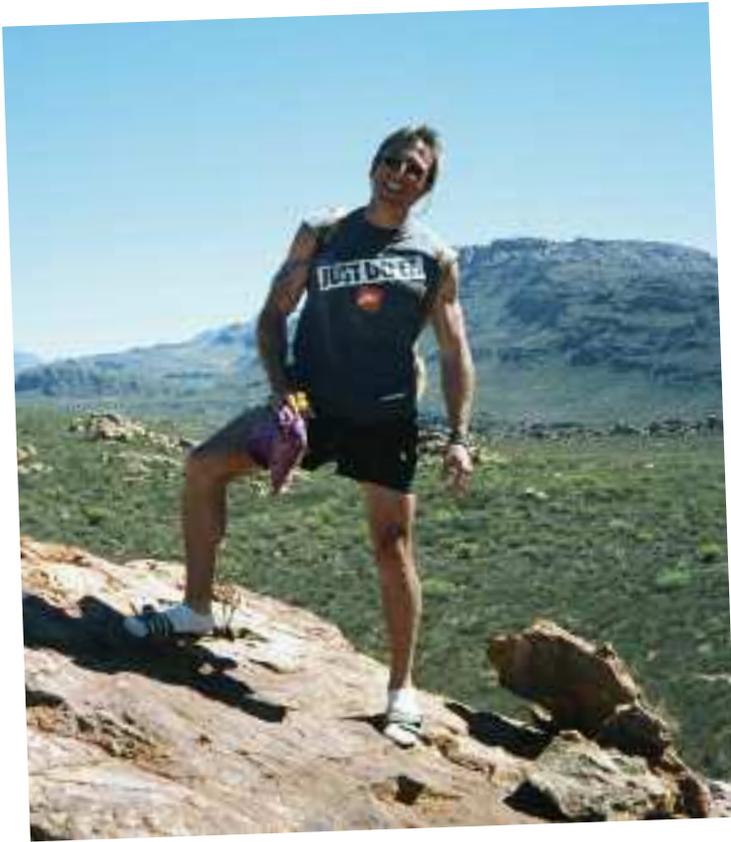
Pallotta surveyed this scene and realized that the notion of asking highly talented professionals to work for a pittance, just so a given charity could say they’re returning 85% on every dollar donated to it, was in keeping with the widely-held notion of how a charity should operate, but this logic, while internally consistent, was “externally nonsensical.” Why would Harvard’s newly-minted MBAs go to work for, say, the Gay Men’s Health Crisis, when they could make four or five times as much money in the private sector? “It gives our best and brightest stark and mutually exclusive choices between doing well and doing good, and it sends them marching into for-profit careers because they can’t afford the economic sacrifice the nonprofit ethic demands. How is that helping the poor, or people with AIDS?”

What charities need, Pallotta concludes, is the freedom to use the tools of capitalism as liberally as the for-profit sector does. “We shoot ourselves in the foot. We let the for-profit sector feast on the tools of capitalism—compensation, capital, risk, advertising, you name it—and

we deny these tools to charity.” Charity is being suffocated with the reverence paid to the idea of charity, and this attitude puts the nonprofit sector at an extreme disadvantage. “The very ethic we think is helping people is in fact undermining them. Charities must be given the freedom to use the tools of the market, or they will never achieve the scale needed to solve the massive social problems that confront us,” he says.

And that is precisely what he did at Pallotta TeamWorks, which used gorgeous graphics and handsomely produced videotapes to promote its events, and provided logistical support for those events that was unprecedented in the history of fundraising: the riders who participated in Pallotta TeamWorks’ events to raise money for AIDS vaccine research, for example, ended each day’s ride at a neatly laid out tent city, ate professionally prepared food, and listened to entertainment—and exhortations—produced especially for them.

No one had ever attempted events on this scale before. Pallotta literally created the multi-day event concept and experience. Prior to the advent of Pallotta TeamWorks,



Dr. Peter Anton, who heads rectal microbicide research at the UCLA AIDS Institute, rode in the very first TeamWorks event, a ride from San Francisco to Los Angeles (left), and he joined Pallotta for the African AIDS Trek as well (above).

such events simply did not exist. Within nine years TeamWorks was raising \$169 million annually, and today the multi-day event industry to which Pallotta gave birth raises some \$225 million a year for charity in the U.S. and Canada alone.

Pallotta's genius lay in rethinking charitable events in commercial terms—by using the tools of free-market capitalism to change the scale, and the scope, of fundraising events. What if the place where the ride was held were itself a destination? This thinking led to AIDS rides in Africa and in Alaska. And what if spending as much as \$500,000 promoting an event meant it netted \$12.5 million for medical research, as was the case with his Chicago Breast Cancer Three-Day Walk in 2002? That is fundraising on the scale that is needed to fund productive research against deadly diseases.

There was another difference, as it turned out. Because these rides were so epic, so exciting, so amped-up—because they asked participants to do the most they could do instead of the least, participants came home saying the same thing: “It was a life-transforming experience.” Dr. Peter Anton, the head of the AIDS Institute's rectal microbicide program, uses precisely those words to

describe the very first TeamWorks AIDS ride, from San Francisco to Los Angeles in 1994. So enthused was Anton by this experience that he also took part in the cross-Montana AIDS vaccine ride in 2001 and the Africa AIDS Trek in 2002. These were, in Anton's words, “the most exhilarating life- and hope-affirming human bonding experiences I've ever known” (see picture at left).

Not surprisingly, many groups sought to emulate Pallotta's success, including several that had, until then, been TeamWorks clients. One such group was the Avon Products Foundation. In 2002 Pallotta's team raised \$142 million for the foundation through a series of three-day walks. The following year the foundation undertook to produce these events on its own, in the interest of lowering overhead, and fundraising plunged by over \$100 million, to just \$28.5 million. And, ironically, overhead actually went up, not down.

The AIDS Institute was not a disinterested spectator during this period. A major beneficiary of the TeamWorks vaccine rides, the Institute stood helplessly by in 2002 while the hen that laid gold eggs for the members of its faculty was slowly smothered. Pallotta TeamWorks, which presented a check for \$1.3 million to the AIDS Institute in 2001, was out of business by the following year, and the Institute had nowhere to turn to make up the shortfall.

“We cannot help but wonder,” says Dr. Irvin S.Y. Chen, the director of the Institute, “what might have been.” Where, for example, might we now be in the long struggle to develop a safe, cheap, effective vaccine against HIV if Pallotta TeamWorks had not been put out of business by an informal coalition of well-intentioned AIDS activists, who thought they were serving the community by assailing Dan Pallotta's unorthodox—but hugely successful—approach to fundraising. “The money that Pallotta TeamWorks raised for vaccine research at UCLA and elsewhere—an astonishing \$8.7 million *net* in a mere three years—helped to jump-start our work on a number of promising ideas,” Dr. Chen declares—“many of which we were subsequently obliged to put on hold for lack of continued funding. At the moment, our best guess is that it will take another 15 to 20 years to develop an effective vaccine against HIV. With Dan's continued help, we might have been able to cut that development time in half.”

But it isn't just vaccine development that has suffered since the demise of Pallotta TeamWorks. As Dr. Chen notes, “It is almost impossible to tally the number of promising ideas—and young careers—that have languished as a result. And it is hard to avoid asking ourselves, ‘What might have been?’”



An excerpt from

Uncharitable:

How Restraints on Nonprofits Undermine Their Potential

“What if a system that frowns on self-interest turns out to be an inferior way of serving the interests of others? What if a system that allows people to satisfy their own self-interest as well as the interests of others turns out to be a much more effective way of helping those in need?”

From: *Uncharitable: How Restraints on Nonprofits Undermine Their Potential* (Tufts University Press, 2008).

The fact that charity exists at all is a testament to the tenderness of the human soul. We feel for others. When someone else is suffering, we suffer ourselves, and we have a powerful and emotional need to help. The very fact that charity is an emotional subject is further testament to our love for one another. On the question of whether or not mankind is basically good, this reality speaks for itself.

The system we have to channel this inner charity is itself called “charity,” and just as we all have a desire to make a difference, we have all been taught by this system how best to do it. But as we look around at the continuing persistence of poverty and need, of disease and suffering, in a world of unimaginable affluence and productivity, we have to ask ourselves, does the system work? Is it the best system we could have? What other systems are available? It is to these questions that this book is addressed. The possibility that there is another system that could take our love for one another and leverage it into a kind of social progress on a scale we never even considered must be examined.

Like most people, I never asked questions about our system of charity. Why would I? Who was I to question a system that had been around for centuries? It never dawned on me to ask questions about it. Then I spent two decades working inside the system. During that time an observation was gathering momentum—this system doesn’t work. Another observation was gathering momentum about a system that does...

Whenever I told people I was writing a book about freeing charity to use the tools of capitalism they would nod their heads, believing they were in total agreement, and proceed to say that we absolutely need to put more restraints on charity. This response was consistent. This made me realize something else—that the only way most of us can even conceive of improving charity is by constraining it further. I could see that this belief was so ingrained that it had compromised my friends’ hearing—literally. Our nonprofit ethos is a kind of religion on which we have all been raised, and it doesn’t easily suffer the bigger picture. In fact, like most religion, it obscures the big picture. Suffice it to say, this book is not about adding constraints. It is about removing them, in the interest of the bigger picture.

For example, after explaining to a friend that we need to let charities hire the most talented people in the world, he wholeheartedly agreed, and then said something that didn’t logically follow: “It makes me angry to see people making high salaries in charity.” “Even if they’re worth it?”

Why?” I asked. “Because it’s supposed to be nonprofit,” he replied. Right there he gave expression to the entire problem. His logic was internally consistent but externally nonsensical. Still, I understood where he was coming from. Twenty years ago I felt the same way. In fact, I remember thinking it was unconscionable that a charity event producer I knew about was making a profit “off of,” as I thought of it at the time, people’s compassion. “Nonprofit” means you don’t seek gain for yourself. So, when someone wants a high salary, of course it makes us angry. It is a violation of the fundamental basis of the system.

But what if the fundamental basis of the system is the problem? What if a system that frowns on self-interest turns out to be an inferior way of serving the interests of others? What if a system that allows people to satisfy their own self-interest as well as the interests of others turns out to be a much more effective way of helping those in need? In other words, what if the whole system should not be nonprofit in the first place? Then my friend’s logic, and the whole of society’s, is rotten at the core, and everything we have come to believe about helping the needy is as well.

From a system that starts with an illogical premise will come a series of illogical rules. Such is the nature of the nonprofit dilemma today. For instance, the great suffering masses of the world would no doubt benefit from the full-time services of the brightest graduates coming out of the nation’s top MBA programs. However, society’s nonprofit thinking refuses to allow them to earn anywhere near the kinds of salaries they can command in the for-profit sector. Predictably then, they march off into the for-profit sector, steering clear of its nonprofit stepsister. People continue to die as a result. This we call morality.

The same is true of the issue of investment capital. If we allowed the average investor to make as much of a financial return by investing in their favorite charity as they can by investing in Toyota, people would send investment capital to their favorite charity. They would have money to experiment and to grow. Alas, society’s nonprofit commandment prohibits it. So all the investment capital goes to the for-profit sector. Our favorite charities are starved for new capital. This we call benevolence.

Same with advertising. No doubt, the Leukemia Society would get more donations if they paid for advertising on the Super Bowl. Our nonprofit mindset

prohibits it, on the grounds that it is wasteful, and that people should give without having to be asked. So Budweiser advertises on the Super Bowl instead and reaps the sales bump that might otherwise have gone to the Leukemia Society. This we call charity. The very system we have cherished as the hallmark of our compassion is in fact what undermines it.

The more I began to write about these irrationalities, the more I was stalked by an obvious question. From where could these errors possibly have come? We are not irrational by nature. In the depths of our hearts, we want to do whatever will most help the needy. How could we possibly have become religious about a belief system that undermines those we most want to help?

I began looking for the answer by studying the earliest formal constructions of charity in America, beginning with the early Puritan settlers to New England. Having grown up there, I was familiar with the Puritan gestalt, and the nonprofit gestalt felt uncannily similar. I am not a historian, but nevertheless, I found what I was looking for. It was as fundamental as things can get. It was the Puritans’ religious belief that human beings are evil, that we are obnoxious to God, and that the self is depraved. Logically, this meant that the self had to be negated. Charity became the monument to this belief, a compensation for human depravity. From that core belief grew a complex array of rules and secondary beliefs designed to preserve it. As a result, the merchants, farmers and carpenters of the world got an economic system that indulged self-interest—they got free market capitalism. The needy got a religion—charity—where the merchants, farmers and carpenters could do penance for their self-interest. By and large, that is still what the needy have today.

Most of the efforts to improve the current situation are careful not to offend the underlying religion. Thus, they are necessarily complex, and can only hope to have an impact at the margins, if at all. But this is not a complicated problem to solve. Remove the error, and you remove the problem. What we are left with is this shocking reality: that the way to alleviate suffering on earth is to use the same system which satisfies every other human need, and which heretofore has been prevented from doing so by the religion. That system is free market capitalism. If we surrender our nonprofit dogma, we bring economic freedom to the causes and charities we love, and we make rapid progress toward solving the most vexing problems facing humanity. It is to this radical thesis that this book is addressed.



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UCLA spearheads a crossborder program to equip Mexican healthcare providers with the training and tools they need to cope with their AIDS epidemic



The Great Dismal Swamp page 16

UCLA AIDS Institute researchers hope to end the protracted, thus-far futile search for a safe, successful HIV vaccine



White Knight, Dark Horse page 22

The rise, fall, and rise of Dan Pallotta, fundraiser extraordinaire