A Message from the Director

Far Afield, and Close to Home

The UCLA AIDS Institute conducts vital HIV prevention and treatment programs—and cutting-edge research—in venues as remote as East Africa and as familiar as Westwood.

Nothing illustrates the remarkable diversity—and geographic range—of the research being conducted by members of the faculty of the UCLA AIDS Institute than the first and last articles in this issue of Insider. Although our principal scientific laboratories are located on the university’s Westwood campus, over 200 MDs and PhDs affiliated with the Institute have undertaken programs in virtually every corner of the globe: an intervention to teach ayurvedic nurses how to provide optimal clinical care for AIDS patients in India; an assessment of potential risk factors for HIV infection among young, single, female factory workers in China; a culturally sensitive outreach to at-risk men who have sex with men in Peru. It is said that at any given time perhaps a third of our faculty is doing research overseas.

“Hope for Malawi,” on pages 4–9, describes the fruitful partnerships that the AIDS Institute has established on the ground in Malawi, under the stewardship of Dr. Thomas Coates, who is an Associate Director of the Institute and the head of the UCLA Program in Global Health. Malawi is one of the poorest countries in Africa. It is thought that one in every four adults in the capital city of Lilongwe is HIV-positive, and one in every three pregnant women is infected. Although the principal thrust of Dr. Coates’s efforts has been to establish a comprehensive HIV prevention and treatment program through the country’s university system—one that will mobilize both faculty and students to address AIDS-related issues while providing free HIV testing and offering post-test counseling and support services—Coates is also working with Partners in Hope, the first state-of-the-art AIDS clinic in Malawi, to train a cadre of native-born HIV specialists.

In keeping with the AIDS Institute’s stated mission to “develop more effective education and prevention strategies for at-risk communities around the world, and better treatments for all people living with HIV,” there is also a research component to the multidimensional program that Dr. Coates has put in place in Malawi. This research, which is being conducted by Drs. Otto Yang and Chris Tymchuck, will examine interactions between the type of drug treatments being used in Malawi and the genetic background of the Malawan people, in an effort to elucidate the clinical significance of particular variants of drug-resistant HIV. Most of this work will be done in the modern laboratory that UCLA has equipped and staffed at the Partners in Hope medical center in Lilongwe—where the UCLA team will have a unique opportunity to conduct its research in a largely unstudied region of Africa.

“Stem Cells: A New Avenue of HIV Research,” on pages 23–27, reports on intriguing research that is being conducted much closer to home—in the labs of the Institute’s new research facility on the Westwood campus. Although UCLA investigators have been trying to harness the potential of stem cells for some time now, the thought that these shape-shifting, miraculously regenerating cells might be useful in treating—or even preventing—HIV infection is a rather more recent concept. To assess those possibilities, the AIDS Institute recently convened the first symposium devoted exclusively to the potential application of gene-based therapies to the management of HIV disease. (An approach to “vaccinating” at-risk individuals against HIV infection using stem cells is described on pages 20–21 of the Winter 2009–2010 issue of Insider, which is available online at the Institute’s Web site, www.ucliaidsinstitute.org.)

In my opening remarks at the Institute’s groundbreaking symposium on the role that stem cells may one day play in treating and preventing AIDS, I observed that “HIV infection is particularly vulnerable to stem cell-based therapies because the targets of such therapy, CD4 cells, circulate in the blood, where they can be easily accessed. Protecting these cells from infection, by genetically modifying them with anti-HIV genes, should prevent the virus from attacking the immune system.” In the long run, this approach may prove to be the best hope for patients who come to our clinic in Westwood—and those who come to our satellite clinic in Lilongwe, Malawi.

June 5, 2011, was the thirtieth anniversary of the publication—by Dr. Michael Gottlieb and a group of his colleagues at UCLA—of the first description of AIDS to appear in the medical literature. The hundreds of men and women who work at the UCLA AIDS Institute marked this solemn occasion by rededicating themselves to finding better means of preventing HIV infection; to developing less toxic, more potent treatments for those who are infected; and to the eventual eradication of AIDS through safe, inexpensive vaccines.

Irvin S.Y. Chen
Director, UCLA AIDS Institute
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Hope for Malawi

The UCLA Program in Global Health is helping to bring state-of-the-art HIV testing and treatment to one of Africa’s poorest nations

Once each month, Melida walks seven miles to the free clinic. Sometimes as she walks she thinks, “I will do this for the rest of my life.” At 36, the opportunity for a full life hinges on her commitment to this walk. At home there is a child to feed, a small garden—her family’s only source of food—to tend, and a daily trip to the borehole to fill her bucket with water. Melida knows that if she wants to be able to grow enough food to last until the next rains, to ensure her daughter is able to go to school, to provide her aging relatives the care they need, it is imperative that she takes this walk to the clinic each month.

Melida’s story is similar to thousands of Malawians living with HIV/AIDS, although she is more fortunate than some because she can access a clinic that provides free, high-quality HIV/AIDS care, including life-saving antiretroviral drugs (ARVs). The clinic is the Partners in Hope Medical Center in Lilongwe, Malawi’s capital city. Since 2006, the UCLA AIDS Institute has collaborated with Partners in Hope, and the success of this partnership can be seen as a model for academic engagement in Malawi and other low-income countries.

Located in southern Africa, Malawi is one of the world’s most densely populated countries, with more than 15 million people living in an area slightly smaller than Pennsylvania. It is also one of the world’s poorest countries, with over 40% of the population living on less than US$1 per day. Population density and poverty have contributed to making Malawi a particularly challenging environment for preventing and treating HIV.

Malawi has lived with the specter of HIV since the country’s first case was diagnosed in 1985. Within ten years, prevalence of the disease climbed to 26% of the population. In 2007, 68,000 deaths a year were attributed to HIV/AIDS, a rate of 186 per day. Malawi is one of a cluster of sub-Saharan African countries that have the highest prevalence of HIV on the planet.

It was in this setting that Dr. Perry Jansen, a Penn State and UCLA-trained family medicine physician, made his first visit to Malawi in 1999. There, he saw firsthand the devastating impact of HIV as he cared for mothers too sick to nurse their babies, emaciated men reduced to begging for food on street corners, teachers unable to conduct classes, and farmers too wasted by illness to tend their crops. Dr. Jansen and his wife Brenda were deeply affected by what they saw, and decided to respond by moving their family to Lilongwe to set up a mission-based HIV/AIDS practice.

Soon after they arrived, the Jansens launched Partners in Hope, a Malawian NGO with the primary goal of bringing people and resources together to help Malawians living with HIV. Motivated by his faith and a desire to help those in need, Dr. Jansen established a collective of individuals, churches, civic organizations, and charities that shared a desire to respond to the AIDS crisis in Malawi. In 2002, Partners in Hope started a small HIV/AIDS clinic and became one of the first sites in the country to offer ARVs to people with AIDS. The impact was immediate—many patients who had been so sick they were unable to feed themselves or get out of bed rapidly regained weight and the ability to resume family and community life. The Jansens
A Malawian woman and her child present for care at the Partners in Hope clinic.
Above: Patients complete intake forms in the clinic’s waiting area.

Right: UCLA Resident Bijal Surti examines a young girl with HIV infection and malnutrition.

Opposite: UCLA Resident Mike Shino initiates a patient with HIV infection and Kaposi sarcoma on antiretroviral therapy (ART). The clinic has initiated more than 5,000 patients on ART since 2006.
witnessed these miraculous restorations again and again.

In 2004, Dr. Jansen began looking for a larger facility to meet the growing demand for care. He found an abandoned factory in the southern part of the city and began to envision it as a medical center. He pictured three units—a private general clinic, a public HIV specialty clinic, and an in-patient ward. Revenue from the private facilities would fund free services for Malawians living with HIV/AIDS. Remarkably, in seven short but hectic months, the Partners in Hope Medical Center opened and this vision became reality.

This swift realization of a new health facility in Malawi resulted from the collective effort of dozens of people, both in Malawi and in the United States. One of these persons was John Hamilton, then UCLA's Assistant Provost. Mr. Hamilton met the Jansens at a social gathering in 2001, and contributed to efforts to finance the purchase and renovations of the medical center building in Lilongwe. He also introduced Dr. Jansen to the incoming director of the UCLA Program in Global Health, Dr. Thomas Coates. Subsequently, Dr. Coates invited Perry Jansen to speak at an AIDS Institute-sponsored symposium on HIV/AIDS in Africa entitled “Integrating HIV Prevention and Care in Africa: Existing Challenges and Innovative Solutions” (for a full description of this event, see the January 2006 issue of *Insider*, pages 22–27, available online at the Institute’s Web site, www.uclaaidsinstitute.org).

This groundbreaking gathering was underwritten by UCLA's Center for AIDS Research and the AIDS Institute. Recognizing that the epidemic, in Africa and elsewhere, can only be contained through the coordinated efforts of all those who have a stake in the outcome, the organizers made a particular point of inviting treatment activists, socially engaged artists, and representatives of corporations that do business in Africa to join the symposium’s distinguished panel of academic experts.

Dr. Jansen’s presentation was a highlight of the symposium and so impressed those in attendance that Dr. Coates decided to travel to Malawi with John Hamilton and a group of UCLA physicians, researchers, and donors.
After visiting Partners in Hope, the group immediately recognized that the site was an excellent opportunity for UCLA to collaborate with an African NGO, to the mutual benefit of the university and the people of Malawi. Within two months, Dr. Coates raised $250,000 to fund a seed program for a UCLA initiative in Malawi and recruited John Hamilton to move to Lilongwe to lead it.

One of the most exciting components of the initiative is a clinical training program established through the UCLA Program in Global Health that brings 10–12 senior UCLA medical residents to Partners in Hope Medical Center for a one-month rotation each year. During their time in the country, UCLA residents have the opportunity to teach their Malawian colleagues, learn more about HIV in a resource-limited setting, and see a plethora of diseases that would be considered rare in Southern California. Now in its third year, this program has become a highly sought-after experience for UCLA residents. For many, the experience is life changing.

As the AIDS Institute broadened and deepened its involvement in Malawi and solidified its relationship with Partners in Hope, members of the UCLA community began to launch research projects in the country. These investigators include Chris Tymchuk, MD, PhD, a resident in medicine, and Otto Yang, MD, a senior member of the Institute faculty whose work on HIV vaccine development was the subject of a profile in the Winter 2009–2010 issue of Insider. Drs. Tymchuk and Yang are attempting to determine if there has been a change in baseline resistance to antiretroviral drugs since Malawi started providing these drugs to HIV-infected individuals in 2005.

Last year, the Partners in Hope-UCLA collaboration received a major five-year grant of $12 million from USAID/PEPFAR to enhance high-quality HIV/AIDS care at other hospitals in the country. This project, called EQUIP-Malawi (Extending QUality ImProvement for HIV/AIDS in Malawi) is already working in eight hospitals and health centers in the central and northern regions of Malawi.

A Co-Director of EQUIP-Malawi, Dr. Risa Hoffman, a member of the faculty in the UCLA Department of Medicine, Division of Infectious Diseases, has been intimately involved in the development and implementation of the project. In addition to designing and conducting trainings for Malawian clinical trainers, Dr. Hoffman has taken the lead in an upcoming research project involving reproductive desires and access to family planning services for HIV-infected women in Malawi.

What began as an idea and aspiration on the part of a single physician visiting a small country in southern Africa has evolved into a multifaceted collaboration with UCLA that is helping to improve the health care of a nation. Only a decade ago, many experts questioned whether providing ARVs for people in sub-Saharan Africa would ever be possible. While an enormous amount of work remains to be done—there are approximately one million Malawians living with HIV, and several hundred thousand of them will need access to ARVs in the next year—Partners in Hope was able to evolve rapidly into a major ARV-providing clinical site in Malawi, and is now taking the lead in building the capacity of other clinical sites in the country. This collaboration between Partners in Hope and UCLA points to the success—and hope—that is possible when people work together to improve the health and well-being of those in need.

For more information about the Partners in Hope Medical Clinic, please visit http://www.partnersinmalawi.org

*Dr. Jon Fielder, a physician working at Partners in Hope, examines a patient.*

*Opposite, top: The staff of Partners in Hope with UCLA Medicine residents.*

*Opposite, bottom: Walking to the clinic from the road in Lilongwe.*
Legions of African children—many of them barely more than toddlers, most of them unschooled and unskilled—are struggling to hold their families and their cultures together against overwhelming odds.

How do you measure the true cost of the AIDS epidemic in sub-Saharan Africa? One obvious way is to count the corpses, but in a country like Malawi, where infrastructure is rudimentary and large areas of the country are accessible only on foot, this method will give you only an approximation of the death toll—because many of those with end-stage HIV infection succumb without ever receiving treatment and die without ever being diagnosed. Any count, then, is by definition an undercount, and in any case the numbers that UNAIDS makes available can only tell us how bad the epidemic was three or even four years previously—because it takes that long to collect, tally, and interpret the data on mortality rates in the most afflicted areas of Africa.

Malawi has a total population of less than 15 million people—and close to a million of them are orphans. Two out of every three of these children are so-called AIDS orphans, meaning that they have lost one or both parents to the virus. And of the 650,000 AIDS orphans that Malawi is struggling to support, roughly 120,000 are themselves HIV-positive. Most of them will not live into adolescence. For those who do reach adulthood, the prospects are very bleak: many of the teachers who might have taught these children how to read and write are dead or dying, and so are many of the policemen whose job it is to maintain civil order.

In Africa, in particular, the transmission of culture is in the hands of mothers and grandmothers, who teach the next generations how to croon the lullabies and cook the traditional dishes that distinguish their tribe from all others. In Africa today, this oral tradition is dying with the women who learned it from their mothers and grandmothers. In the words of Laurie Garrett, a Senior Fellow for Global Health at the Committee on Foreign Relations, this is a form of “cultural genocide,” and any reckoning of the true cost of the AIDS epidemic in sub-Saharan Africa must take into account that it is not just people who are dying as a result of HIV, whole cultures are dying as well.

The sheer magnitude of the numbers numbs the senses: UNAIDS estimates that there are 14.8 million AIDS orphans in sub-Saharan Africa today—and that this number will top 20 million before 2020. Experts have identified at least 2.5 million cases of pediatric AIDS in the region, and they estimate that some 570,000 new infections occur in African infants each year, leading to roughly 350,000 deaths. Laurie Garrett, who has won Pulitzer, Polk, and Peabody prizes for her reporting on health issues, says that there is a better way to understand the devastation that AIDS has brought to the youngest generation of Africans. Forget the statistics. Forget the imprecision of the data. Focus instead on this single, unassailable fact: Uganda, which is home to 1.2 million AIDS orphans, is so overwhelmed by the task of caring for these children that state-run orphanages look after abandoned infants only until the reach the age of two. After that, they are fostered to 10-year-olds, “because there are no longer adults to look after children of any age.”

Dreadful as this situation is, it is made even worse by the belief, widely held in East Africa, that having sex with a virgin will cure a man of AIDS. This practice has cured no one, needless to say, but it has resulted in countless cases of sexually transmitted HIV infection in pubescent girls. The 11-year-old pictured here is one such victim of this pernicious myth. Her 9-year-old sister is another.

As the Honorable Stephen Lewis, the former United Nations Special Envoy for HIV/AIDS in Africa, has put it, “all of the natural rhythms of life have been damaged” by the African epidemic. In particular, Lewis cites grandmothers, whom he dubs the heroes of the pandemic: “These extraordinarily brave women bury their children, and then they raise the children those children left behind.”

Lewis also cites the phenomenon of “child-headed households,” where there are no adults left. “What distinguishes AIDS orphans from other orphans is that these children become orphans not when their parents die, but while their parents are dying,” he notes. “They look after their parents, and then they stand in the hut and watch their parents die. How do you deal with the intensity of trauma of that kind?”
Children are children the world over: give them a rubber ball, and a tamped-mud floor to bounce it against, and they will improvise a game to divert themselves (lower left). These particular children are all AIDS orphans, and they are cared for, from dawn to dusk, in what amounts to a government-subsidized day-care center. The center provides each child with a single meal, which is served at midday—a mélange of corn and beans, which the youngsters must scoop up with their hands (below) because there is no money for utensils. Two of these orphans are themselves HIV-positive: the pensive little girl seen at right (and on the previous spread), and her younger sister, seen at lower left in the yellow skirt. Both were raped by their own grandfather, a subscriber to the misbegotten notion that sex with a virgin will “cure” AIDS. This infamous act of incest did not save him, but it almost certainly doomed his granddaughters.
The day-care center featured on the previous pages consists of only two rooms, one of which serves as a rudimentary kitchen where powdered milk can be reconstituted (right) and cracked-corn samp can be warmed up over a wood fire (below). Samp is typically paired with dried beans in southern Africa, and it is a staple of these orphans’ diet. (In South Africa, samp and beans, known as umngqusho, is a traditional dish of the Xhosa people, and Nelson Mandela has said that it was one of his favorite childhood meals.) Primitive as this center is, it represents a genuine refuge for these youngsters. They are safe so long as they remain at the facility; physical and sexual abuse occur when they are forced to join their foster families at the end of each day… which explains why they often leave the day-care center in tears.
The Pediatric AIDS Coalition at UCLA raises more than $400,000 for research and treatment through Dance Marathon 2011, and makes the AIDS Institute one of its beneficiaries

by Helen J. Brown, Ph.D., Administrative Director, UCLA AIDS Institute

The global effort to contain—and ultimately extinguish—the AIDS epidemic is most often described as a battle. Doctors and healthcare workers battle to identify and treat new infections; newly-infected people battle to sustain their health as the virus takes hold; researchers battle to develop more potent, more effective, less toxic, less expensive antiretroviral drugs and continue the battle to develop vaccines against HIV infection. It’s an apt description for a formidable enemy. But because we commonly use martial language to describe our relationship with this virus, you may be surprised to learn that a committed contingent of UCLA undergraduates has made dancing their weapon of choice in the war against pediatric AIDS.

This slightly irreverent association isn’t lost on UCLA Dance Marathon Executive Director, Erin Ward, but she makes the connection seamlessly: “Kids living with HIV fight their whole lives, not only battling the physical obstacles that come with the disease but the social stigma as well, so the least we can do is literally take a stand for them.” And dance Ward and her colleagues and friends did, not just for an evening or even all night, but for a marathon 26 hours, from 11:00 A.M. on Saturday, February 19th, to 1:00 P.M. on Sunday the 20th, 2011. In response to this lofty goal, more than 2,000 enthusiastic participants packed the Ackerman Grand Ballroom at the heart of the UCLA campus, full of energy and excitement, with a commitment to raise more money than any previous UCLA Dance Marathon had on behalf of children living with HIV.

You may reasonably wonder whether it is possible to dance for 26 hours without a break. After all, at some point the need for rest and refreshment would overcome even the fittest and most dedicated of dancers. But lack of stamina was no excuse to avoid signing up for this event, because, in truth, every one of the participants took dance breaks, even if the music never stopped. A lack of dancing skills was no excuse either: enrollment was open to all those who could commit to staying on their feet for 26 hours—never mind what they did with those feet in the intervening time. At the event itself, there was a clear commitment to this goal, evidenced by the lack of chairs, stools or any piece of furniture likely to support the weight of a weary reveler. Instead, the Grand Ballroom was transformed into a high-energy nightclub with a large dance floor in front of a stage flanked by screens projecting larger-than-life music videos. Dancers were sustained by a stream of entertainment: pumping music from a DJ and his team of laptop-bound assistants; live rock-band performances; games and skits; and inspiring speeches.
Above: Actress Kate Flannery takes some time away from "The Office" to show her support. Below: Campers from "One Heartland" get into the groove.

This year’s Dance Marathon theme was “Power Up,” which was broken down into eight re-energizing three-hour shifts. Each shift change was marked by the on-stage arrival of the “moralers,” an imaginatively-dressed group whose task it was to lead the crowd, in unison, through the “morale dance.” And if that wasn’t enough of a boost, each shift also had its own “Power Up”/AIDS education theme, among which were “Powertools” (building a better future), “Power-outage” (don’t be in the dark, get tested), “Get charged” (take charge of your AIDS Education), “Superpowers” (because “Pediatric AIDS needs more superheroes”) and “Powernap” (which explains why so many dancers were planning to stay up all night but were nonetheless wearing pajamas). Clearly everything possible had been done, not only to keep the participants energized but to remind them of the reason they were there.

Dance Marathon at UCLA began in 2001, with 180 dancers and a respectable $27,000 in proceeds to donate to its sole beneficiary, the Elizabeth Glaser Pediatric AIDS Foundation. Although not the first charity dance marathon—Pennsylvania State’s Dance Marathon, “THON,” began in 1973—the UCLA event has grown, over the past ten years, into the largest student-run philanthropic event on the West Coast. A steady increase in revenue each year has also allowed the students to increase their beneficiaries, from one in
2001 to four in 2011. In 2007 two children’s summer camps, “One Heartland” and “Project Kindle,” were added to the list. Both camps provide free recreation opportunities (“camping and care”) for children with HIV. Many children from the camps come to the Dance Marathon each year with their counselors, and they speak to the students about the physical and emotional challenges of living with HIV as well as their appreciation for the group’s fundraising efforts.

The emotional connection between the UCLA students and young people with HIV is very evident, and is no doubt a source of encouragement for both sides in their shared goal to battle the virus in different ways. At one point during the 2011 event, the room went silent for a “candlelight vigil” as participants were asked to raise a “candle” (in the form of a glow stick) if they had ever “lost someone to HIV/AIDS,” “felt helpless, as if they hadn’t done enough,” or “are going to continue to fight for this cause”—queries that were followed by a moment of silence. This year, the vigil was followed by the on-stage arrival of children from Camp Kindle, who talked to the dancers about their hopes and fears for the future, some with songs and poems. Executive Director Erin Ward describes this as a defining moment for this year’s event: “It was incredible and I think it moved everyone in the room. That is what defined Dance Marathon 2011 for me.”

Over the years Dance Marathon has also welcomed celebrity guests, whose presence helps to draw more dancers to the event as well as guaranteeing a higher level of media attention. This year’s event drew a cluster of stars, including “Modern Family”’s Rico Rodriguez, “The Office” actress Kate Flannery, comedian Patrick Warburton (“Family Guy,” “Seinfeld,” “Rules of Engagement”) and “NCIS” star Pauley Perrette. Through simple appearances, photo opportunities and meet-and-greets with the students, celebrities have their own electrifying effect on the event. And in many cases, the event itself appears to be a welcome regression back to student days for these celebrities—to a time before the constraints of fame and the demands of production schedules took center stage.

This year’s event marked a milestone for Dance Marathon: a full decade at UCLA, with, in 2011, a record 120 student organizers, some 2,000 participants, and $410,530 raised, bringing the fund-raising total over the past 10 years to close to $3 million. With its continued success comes the addition, this year, of the UCLA AIDS Institute as a beneficiary. The Institute and Dance Marathon are natural partners, since both share a commitment “to the eradication of HIV infection worldwide.” The Institute also adds a powerful research component to Dance Marathon’s fundraising impact. In fact, with its four current beneficiaries, the event has the capacity to affect every aspect of the fight against pediatric HIV/AIDS,
from the most basic of research into how the HIV virus operates, to cutting-edge stem cell therapies to fight the disease, to expanded opportunities for testing and treatment, to support for children and their families affected by HIV, all the way to prevention through education programs, both in the US and abroad.

Attracting donations of this magnitude in the context of a global recession is no small task. Charities and non-profits across the nation are struggling to sustain support as people tighten their belts and cut down on “discretionary spending,” which is charity’s lifeline. Dance Marathon Fundraising Director Natalie Battilana admits that the economic climate in recent years has placed more pressure on the committee and the students to reach their fundraising goal. But instead of lowering their expectations, Battilana and her committee were challenged to think of new and creative ways to raise money. “As students ourselves we know that a lot of UCLA’s students are struggling financially with tuition payments and are initially discouraged by the dollar goal we set for dancers. However, the organizing committee does a really good job of providing support for dancers and creating a dynamic approach to fundraising.”

The relentless encouragement provided to each participant in Dance Marathon helps them reach their personal fundraising goal of $219 (an easy-to-remember “219 by 2/19,” the date of this year’s event). Asking for donations, although known to induce a cold sweat in even the most passionate of advocates, is promised to be “efficient and stress free,” according to the Bruin Dance Marathon Web site (www.bruindancemarathon.org), where even the most introverted participant can find out how to be the BEST (Break down your fundraising goal into small pieces, plan Events, write Solicitation letters, and be sure to Thank your supporters). And if this list of helpful suggestions is too impersonal, each student is also contacted regularly by e-mail in the

months leading up to the event, by their designated Dancer Captain, who is responsible not just for leading them on the dance-floor but for shepherding them all the way to the Big Day.

Lead-off events like a basketball tournament fundraiser and Club Night help kick-start the annual fundraising efforts for Dance Marathon and build some early confidence, and as the day draws near, weekly e-mails from the dancer captains offer additional encouragement and suggestions to keep the ball rolling. “The number one things we tell our dancers is to ask, ask, ask, and don’t let the economy deter you from sending a simple e-mail as a way of reaching out for additional help, because every single dollar counts,” says Battilana. It is clear that this approach works: the fundraising totals posted by successive Dance Marathons at UCLA, instead of following general economic trends, have actually increased every year, including 2011. Indeed, there is every indication that the UCLA Pediatric Coalition will continue to be a fundraising force-to-be-reckoned-with. And they invite you to join their fight. “If anything, Dance Marathon has proved that, despite this economic downturn, people still care about helping others.”

The foot-weary participants in Dance Marathon 2011 will doubtless be pleased to know that every dollar they donate to the AIDS Institute will go to support pediatric HIV patients and their families through the “Care4Families” program at UCLA and to provide HIV research scholarships to UCLA students.

7 year old Basia, a “One Heartland” camper, joins in to show the students how it’s done.
A Tickle, Not an Elbow in the Ribs

Dr. David Brooks returns to UCLA to develop therapies that alleviate immune suppression while reinforcing positive stimulation of the immune system

David Brooks is living proof that you can go home again—if “home” is the UCLA AIDS Institute, and if you leave such an indelible mark, the first time around, that your UCLA colleagues make it their mission to find a way to bring you back into the fold. Dr. Brooks did his doctoral work, in the Department of Microbiology, Immunology and Molecular Genetics at UCLA, under the direction of Dr. Jerome A. Zack—who is, among other things, the director of UCLA’s Center for AIDS Research, which is housed within the AIDS Institute. After David completed his Ph.D., he accepted a position at The Scripps Institute in La Jolla, California, to study the interaction of viruses and the immune system with one of the leaders in the field, Dr. Michael Oldstone. But Dr. Zack and UCLA never completely let go of Dr. Brooks, and apparently the reverse was true as well, because in the fall of 2008 Dr. Brooks did indeed come home again. We will save that story, with its happy ending, for the end of this profile—because first you need to know why the AIDS Institute has such high regard for David Brooks, and why such an effort was mounted to bring him home.

Dr. Brooks began working in the Zack lab in the late 1990s, at a time when Dr. Zack was interested in a novel compound called prostratin, which is found in the bark of the mamala tree of Samoa. Native healers on the island—which will forever be associated with Margaret Mead’s pioneering work on cultural diversity, Coming of Age in Samoa—had long known that tea brewed from mamala bark was an effective treatment for hepatitis, which they called “yellow fever” because the severe jaundice associated with the disease turns the skin and the whites of the eyes a distinctive yellow shade. What interested Drs. Zack and Brooks, however, was a more recent discovery about prostratin, one that might prove to be useful in the treatment of HIV infection: this botanical compound was found to possess the capacity to flush HIV out of so-called sanctuary sites in the body, like the brain and central nervous system, where the virus is able to hide from the drugs that are so effective at killing it in the bloodstream.

This discovery was made not by a virologist but by an ethnobotanist named Paul Alan Cox and a team from the National Cancer Institute, who were assessing the knowledge of traditional Samoan healers, hoping that the lore those healers had accumulated over the centuries might lead to botanically-based treatments for cancers and other diseases. Dr. Zack’s excitement over this unanticipated discovery was fueled by his keen interest in the problem of what is known as latent virus—HIV particles that sequester themselves in compartments of the body that are inaccessible to even the most potent combinations of anti-HIV drugs. These HIV-infected cells can remain dormant for long periods of time, only to emerge and begin to multiply when suppressive drug therapy is halted. They are the chief reason why it has never been possible to completely clear a body of virus and pronounce a patient cured. (The lone exception to this rule, which has held for three long, frustrating decades, is the remarkable case of the so-called Berlin patient, whose radical, and near-miraculous, cure is described on page 24.)

The immune system, when it is functioning as it should, operates in exquisite equipoise: it attacks invading pathogens aggressively, but only aggressively enough to destroy them. That is to say, it produces no more firepower than is needed to do the job, and it shuts itself down the minute that job is done. From the moment of infection, the race is between the wildly replicating invading virus and the body’s antiviral immune responses. In the case of all infections that are resolved, immune responses are successful in clearing the virus efficiently and effectively, leaving behind no residual virus and no toxic by-products. However, when the initial viral attack is overwhelming, or the virus is especially efficient at evading the body’s
immune response, the immune system is unsuccessful in eliminating the pathogen.

This situation, which results in the enduring infection seen in AIDS patients, leads to prolonged activation of the immune system. And this, in turn, results in chronic inflammation, the biological equivalent of a never-ending, five-alarm fire. Worse, the body’s own response to this fire, which it cannot put out, may result in chronic activation of the B–cell component of the immune system—which can lead to the development of non-Hodgkin’s lymphoma and other malignancies. For obvious reasons, the body’s responses to chronic infection must somehow be attenuated, to avoid such catastrophic developments. Unfortunately, all efforts to date to repress undesired immune outcomes have led to a concomitant attenuation of virus-specific responses.

What Drs. Zack and Brooks hoped to do, with prostratin, was to nudge latent HIV particles out of their hidey-holes and into the bloodstream—where they would be vulnerable to anti-HIV drugs circulating in the blood. The aim was to activate the latent cells without setting off a five-alarm fire in the immune system, and the highly technical term used by Dr. Zack for this maneuver was to “tickle” the latent cells just enough to induce them to emerge from their Rip van Winkle state and slip into the bloodstream.

In the end, prostratin proved to be effective in this role but, like many botanicals, hard to control and quantify. If you can never be sure just how much pharmacologically active drug you are administering, it is hard to know how much is an effective dose—a “tickle,” as opposed to an elbow in the ribs.
Dr. Zack continues to explore the unique properties of prostratin, and his willingness to investigate its merits serves as a reminder of how widely the members of the faculty of the AIDS Institute will range in an effort to develop better means of preventing and treating HIV infection. But in 2003 Dr. Zack’s collaboration with Dr. Brooks came to an end, when the younger researcher joined the staff of The Scripps Institute. Dr. Brooks moved on—from UCLA and from prostratin—but he remained vitally interested in the mechanisms by which virus-specific cells lose their functional capacity and permit viral persistence to develop. He simply found a new model for investigating this phenomenon.

That model is lymphocytic choriomeningitis virus (LCMV) infection in mice, and it has proven enormously useful in the study of a wide range of persistent viral infections, among them HIV. One of the key discoveries about LCMV is that nearly identical virus variants are capable of inducing very different clinical outcomes. One variant produces a rapid expansion of virus-specific killer cells, which clear the infection in a bit more than a week’s time. By contrast, infection with a slightly different variant rapidly suppresses the immune response in order to facilitate the establishment of persistent infection.

Significantly, the second set of responses mirrors the cellular reactions seen in chronic HIV infection, particularly the inability of such cells to proliferate and produce HIV-killing cytokines, even when the immune system recognizes HIV-infected cells. In both conceptual and therapeutic terms, then, the LCMV model of persistent infection is an invaluable experimental tool for studying aspects of immunity to HIV. What Dr. Brooks and others are looking for is how to induce the protective antiviral immune responses, while avoiding the suppression. One answer seems to lie in combining immune regulating components—in much the way that combination drug therapy suppresses HIV replication at several points simultaneously. In this instance, stimulatory agents, such as cytokines or vaccines, may enhance immunity by simultaneously alleviating suppression and rendering cells susceptible to the stimulatory signals that elicit long-lasting immunity.

Dr. Brooks is still tinkering with this combination—but for the last two years he has been doing that tinkering at the UCLA AIDS Institute. His former colleagues at the Institute were able to put together a recruitment package in 2008, to lure him home. Academic salaries are disgracefully modest, so the bulk of this package went not to compensation but to providing Dr. Brooks with the requirements to outfit a lab. In a world in which a single piece of laboratory equipment—say, a machine that recognizes only certain types of blood cells, and only the positive cells at that—can cost five times a professor’s annual salary, this is no small consideration. In putting this package together, the Institute got considerable help from a longtime friend, the James B. Pendleton Charitable Trust. (For more information about James Pendleton, see page 14 of the July 2003 issue of Insider, which is available on-line at www.uclaaidsinstitute.org.)

Funds from the Pendleton grant were used both to equip Dr. Brooks’ new laboratory and to help launch two important projects there. The first of these projects sought to define how the suppressive factor interleukin-10, alone and in combination with another suppressive factor, prevents the immune system from clearing a chronic virus infection. This work led to the important discovery that multiple factors, separately yet concurrently, suppress the immune response during chronic infection, and that therapies that simultaneously disrupt multiple immunosuppressive pathways are substantially better at restoring immune function and controlling persistent infection than any single agent. In a second set of studies, Dr. Brooks and his team identified the novel role of the stimulatory factor interleukin-21 in sustaining immune activity throughout persistent virus infection. Unlike interleukin-10 and other suppressive factors that diminish immunity, antiviral immune cells required interleukin-21 to continue fighting virus infection. Interestingly, the loss of interleukin-21 stimulation led to an outcome similar to that observed in patients with AIDS-ravaged immune systems. Excitingly, the suppressive role of interleukin-10 and the stimulatory role of interleukin-21 have recently been extended from the LCMV system and implicated in controlling antiviral responses during HIV infection, suggesting that these mechanisms, which restore and sustain antiviral responses against LCMV, may also form the basis for novel therapies to enhance HIV-specific immunity.

Taken together, these studies greatly enhance our understanding of the mechanisms that regulate the immune system, both positively and negatively, during viral infection. This is, of course, precisely what Dr. Brooks was seeking to find when he began looking at the differing impact of nearly identical variants of LCMV. Interest in the interleukins—and awareness of their potency as immune regulators—has been high among researchers for years, but results from early studies of these powerful cytokines have proved equivocal—so much so that interleukins have been dubbed a miracle cure in search of a disease. In Dr. Brooks’ hands, that search may be nearing its end. It is our hope that these studies will ultimately lead to the development of therapies that alleviate immune suppression while reinforcing positive stimulatory signals—to prevent, and eventually eradicate, persistent virus infections such as HIV.
Spotlight On...

Stem Cells: A New Avenue of HIV Research

The UCLA AIDS Institute convenes the first-ever scientific symposium on the role that stem cells may play in preventing—and treating—HIV infection

No one knows when the concept of mortality first entered human consciousness, but from the time man first understood that dying is inevitable, he has been searching for a means of prolonging youth and postponing death. The ancient Chinese had more than a thousand names for magic libations that were said to confer immortality on those who drank them. In one of its earliest forms this concoction involved ground-up jade and cinnabar, mixed with liquid gold. By the time the Tan Chín Yao Chêh (“Great Secrets of Alchemy”) was published in the seventh century A.D., the preferred recipe involved mercury, sulfur, and salts of arsenic—a frankly counterintuitive remedy for aging, given that all these ingredients are highly toxic to humans.

By the Middle Ages, the great age of alchemy, the portmanteau term for all such potions was elixir of immortality. The word elixir comes from Arabic—al-Ikseer means a mixture—and indeed these nostrums could, and often did, consist of virtually anything. (One Medieval recipe for eternal life instructed aspirants to “begin by collecting May-dew from sprouting corn with a cloth of pure white linen.”) At some point the Irish abandoned alchemy as a means of conjuring “the breath of life,” and found a more practical answer in uisce beata, which means both “the breath of life” and “whiskey” in Gaelic.

The millennia-old quest for the elixir of immortality may help to explain the hold that stem cell therapy has on the practical imagination. Here at last is a scientific breakthrough that seems to hold promise of delivering what alchemists never could: a means of retarding the aging process and eluding death. According to early proponents of stem cell therapy, this advance would soon permit us to cure cancers and congestive failure, abolish autoimmune diseases like lupus and rheumatoid arthritis, and eliminate such genetic disorders as Down syndrome, sickle-cell anemia, and Alzheimer’s disease.

It seemed too good to be true—and, unfortunately, it was.

The first dramatic cures attributed to stem cell-based therapy were reported in 1999, when a group of French researchers announced that they had used the technique to treat five male infants, all of whom were born with profoundly compromised immune systems. After two years of follow-up, four of the boys had functioning immune systems, and the fifth had experienced partial immune reconstitution. A year later the same researchers were obliged to report that three of the boys had developed a leukemia-like blood disorder. The bitter lesson of this experience is that genetic manipulation requires enormous skill and great delicacy, lest the process inadvertently induce the activation of oncogenes, which cause cancer.

The French experience, which cast a pall on stem cell research worldwide, did little to diminish popular enthusiasm for the process. It was evident that the mythic Phoenix, rising reborn from its own ashes, could no longer serve as a symbol of the regenerative powers of stem cell therapy, but a replacement was a hand: the salamander, which Medieval alchemists believed was also born in fire. (This misbegotten notion probably derived from the fact that salamanders like to hibernate in hollow logs... and when those logs were tossed onto a roaring fire, the prudent
salamander beat a hasty retreat across the inglenook.) What is not myth but irrefutable fact is that salamanders, and their close cousins newts and skinks, are unique among vertebrates in their ability to regenerate limbs, tails, jaws, eyes, and a number of internal structures. Indeed, these little creatures routinely use their regenerative capacity to escape would-be predators: they rapidly shed their tails, and escape while the predator is focused on the sloughed-off but still-twitching appendage. These resourceful amphibians then grow a new tail, which is identical to the old one.

Clearly, then, the mechanism for regeneration exists—not as an elixir but as an integral component of the salamander’s genome. The issue is how to elucidate, and mimic, that process. Science is part way toward solving this conundrum, through a technique known as autologous stem cell transplantation, which involves harvesting so-called pluripotent hematopoietic stem cells from a patient’s own bone marrow. These are immature stems cells that have yet to differentiate into blood cells, bone cells, or brain cells. In theory, they can be “directed,” through a series of chemical manipulations, to evolve into any of these cell types. (This, presumably, is what the salamander’s body does in response to the loss of a limb.) Once they have been imbued with new genetic information, these stem cells are transfused into the patient, where they soon supplant older, defective cells and, in effect, eliminate the source of the medical malady. For a more detailed explanation of this process, as it applies to the prevention and treatment of HIV infection, see the schematic diagram opposite.

Although stem cell therapy has yet to live up to the exaggerated expectations that have been generated by the lay press, real progress is in fact being made in the field. This progress was the theme of a symposium that the UCLA AIDS Institute recently convened—the first such scientific conference to focus specifically on the potential uses of stem cell therapy to prevent, treat, and even cure HIV infection. As Dr. Irvin S.Y. Chen, the director of the Institute, noted in his opening remarks at the conference, “HIV infection is particularly vulnerable to stem cell-based therapies because the targets of such therapy, CD4 cells, circulate in the blood where they can be easily accessed. Protecting these cells from infection, by genetically modifying them with anti-HIV genes, should prevent the virus from attacking the immune system.”

As Dr. Chen pointed out, the fact that the immune system is incapable of eradicating HIV infection on its own argues forcefully for the use of gene-based therapies to treat carriers of the virus. Chemotherapeutic regimens, while effective in retarding the progression of HIV infection and the concomitant destruction of the body’s immune system, require lifelong, multidrug therapy, are highly toxic, and produce a range of serious side effects. What is needed, he emphasized, is an immune–based therapeutic strategy that will produce long-lived, renewable immune responses capable of generating the quantity and quality of antiviral cells needed to completely eliminate HIV from infected individuals.

Interestingly enough, we already have compelling evidence that this approach can work. It comes from the unique experience of the man known as the “Berlin patient”—who is, in fact, a 44-year-old, HIV-positive American living in Germany. When this patient, who had previously been treated for acute myeloid leukemia, a potentially fatal cancer of the immune system, relapsed in February 2007, his doctors determined that he would need a bone-marrow transplant to survive. Rather than simply performing a transplant that would increase the patient’s chances of surviving his cancer, the man’s doctors opted to perform a transplant that might also increase the patient’s chances of surviving HIV. They asked the blood and tissue bank at their medical center if any of its stem cell donors had a particular genetic defect known as the CCR5-delta-32 deletion. Carriers of the delta-32 deletion are born without the protein CCR5, a protein that enables HIV to enter cells and turn them into incubators for new virus particles.

This genetic anomaly occurs naturally in about 1% of Caucasians, mostly those of Northern European descent. It is not known to have any deleterious effects, but its does protect those who carry the mutant allele from HIV infection. (More specifically, it provides substantial protection to those who have inherited the delta-32 deletion from both parents. Those who inherit the deletion from only one parent do become infected, but they are what are known as long-term non-progressors, meaning that they can live for decades without developing symptomatic disease.) The researchers in Berlin were able to identify a stem cell donor who was both a good genetic match with their patient and a carrier of the delta-32 deletion, and after the patient’s own bone marrow was completely ablated through radiation and drug treatment, he received stem cells from this donor. Bone marrow transplants are both hugely expensive and extremely dangerous—roughly a third of transplant recipients die from their underlying disease or from the procedure itself—so transplantation is not a feasible option for the millions of people living with HIV infection worldwide. But in the case of the Berlin patient, it achieved exactly what his doctors hoped it might: four years after the procedure, the patient exhibits no evidence of his leukemia, and even the most sensitive assays cannot detect HIV anywhere in his body. He is, for all intents and purposes, the only individual ever cured of AIDS, albeit at enormous cost and risk.

Not illogically, considerable interest has focused on how stem cell therapy might be used to confer the benefits of the CCR5-delta-32 deletion on those who
**Eradicating AIDS: A Stem Cell-Based Approach**

**STEP 1** Identify, isolate, purify, and amplify a factor that will prevent HIV from entering cells, as T20 does, or will kill HIV that has invaded cells, as antiretroviral agents do. Although the best factors for both of these tasks have yet to be identified, a number of candidates exist, and some of them are already being studied for safety and efficacy.

**STEP 2** Synthesize a vector that can be used to deliver the anti-HIV factor to cells, a process known as transduction. Vectors, by definition, must be safe, non-toxic, and stable in order to perform their assigned function, and researchers rely on so-called lentivirus vectors for this purpose because these vectors have the unique capacity to integrate into the target cells’ genome. As the cells divide, the vector, carrying the anti-HIV factor, becomes part of all of the daughter cells, an important feature of a successful stem cell strategy.

**STEP 3** Harvest CD34-positive cells from the patient. The presence of the CD34 protein on the surface of a cell is a good indicator that the cells is a hematopoietic stem cell—so by collecting cells that are positive for CD34, researchers can be assured that they have identified stem cells. The first phase of this process is to stimulate the bone marrow to release excess stem cells, after which CD34-positive cells can be isolated in the blood through a technique known as apheresis.

**STEP 4** Transduce the collected CD34-positive cells, with the anti-HIV factor. This process involves using the vector (developed in Step 2) to transport the anti-HIV factor (developed in Step 1) into the nucleus of the CD34 cells (harvested in Step 3). Each CD34 cell now contains new antiviral DNA, which incorporates itself into the genome of the cell and alters its preordained biological purpose.

**STEP 5** Reinfuse the genetically altered CD34 cells into the patient. The human body cannot distinguish the transduced CD34 cells (with the red horizontal bars) from untransduced CD34 cells because they both originated from the same individual, so it will not reject the cells that carry the anti-HIV factor.

**STEP 6** Multiply cells that contain the anti-HIV factor “in vivo” (in the body). Once they have been reinfused into the patient, the transduced CD34 cells will naturally migrate to the bone marrow, where they will become long-term progenitors of stem cells, and produce blood cells carrying the transduced gene. Because these transduced cells are, in effect, resistant to HIV, they will be protected from HIV infection, and as the unprotected cells become infected and die, these protected cells should become the dominant cells in the treated patient.

**STEPS 7A AND 7B** Protect cells vulnerable to HIV infection, or destroy of HIV-infected cells. Depending on the anti-HIV gene chosen, the genetically modified CD34-positive cells (red horizontal bars) will be protected from HIV infection (for example, if their expression of the CCR5 gene is blocked) (7a) or they will destroy freely circulating HIV and/or HIV-infected cells (7b). The anticipated result of the therapy is an immune system that is able to resist HIV infection.

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Adapted with permission from “Stem cell-based anti-HIV gene therapy,” Kitchen et al., *Virology* 2011.
are not born with this fortunate genetic abnormality, and two of the presentations made at the UCLA AIDS Institute’s symposium dealt specifically with this issue. Dr. Dong Sung An of UCLA presented data showing that levels of the CCR5 receptor protein could be depleted, using a technique known as “RNA interference”—which blocks production of the protein inside the cell. Importantly, his studies in mice that have been genetically altered so that they harbor a human immune system—and are therefore known as humanized mice—demonstrate that the cells treated by RNA interference to deplete their levels of CCR5 can also protect the mice from HIV infection.

Dr. Paula Cannon of USC also presented work examining the effects of depleting the CCR5 receptor protein, this time using a zinc-finger nuclease enzyme to remove the CCR5 gene itself. Like Dr. An, Dr. Cannon was able to show effective depletion of CCR5 in hematopoietic stem cells and protection of the cells from HIV infection in humanized mice. A key finding of both studies was that the protected cells have a survival advantage; in fact, they appear to divide more readily than the unprotected cells, which are killed by HIV.

Another novel genetic reagent that blocks HIV infection is the entry inhibitor T-20, also known by its trade name, Fucis. It has been known for some time that HIV carries the protein gp41 on its surface, and that this protein is one of several that HIV uses to gain entry into cells. The function of the peptide T-20 is to flood the circulatory system with small pieces of gp41. These snippets of protein mask the genuine gp41 protein on the surface of the virus, preventing it from fusing with its target cells. T20 therefore diverts the virus, in much the way that chaff, discharged from Allied bombers during World War II, provided an alternative target to Axis antiaircraft gunners. Dr. Dorothée von Laer of the Georg-Speyer-Haus Institute in Frankfurt, Germany, reported at the symposium that she and her colleagues have engineered a form of this peptide that can embed itself in the cell membrane at the point where HIV binds to it. This genetically engineered reagent no longer needs to flood the circulation in order to have its effect, and as a result, it may be effective in much smaller amounts. This modified peptide can be utilized safely in human cells. Dr. von Laer’s data showed.

Although the famous Berlin patient is unique in the annals of HIV treatment, he is one of thousands of HIV-positive individuals who develop malignancies that are associated with immune deficiency. Two linked presentations at UCLA’s symposium dealt with the treatment of HIV-positive patients who develop one of the most common of these cancers, lymphoma. Dr. John Burnett of City of Hope in Los Angeles presented preliminary results from a phase I clinical trial based on the hypothesis that targeting HIV and restoring immune function will also halt the progression of
lymphoma in patients suffering from both. Dr Burnett presented data showing that hematopoietic stem cells can be genetically modified to express three different forms of RNA, which will attack HIV at three different stages of its lifecycle. This combination of anti-HIV RNAs is more effective in blocking HIV than when the RNAs are used individually—a finding that echoes what we know about the efficacy of using three or more classes of antiretroviral drugs to treat HIV infection. Early results from this ongoing clinical trial suggest that transplanted cells carrying these three RNA genes continue to express the genes for long periods of time and that this method has no adverse effects on normal blood cell development, both of which are important criteria for any potential stem cell-based treatment.

As a follow-up to Dr Burnett’s presentation, City of Hope’s Dr. David DiGiusto examined the same study from a different perspective: how to improve the efficiency of the transplant procedure itself. This procedure requires delicate handling of the cells while they are removed from the patient and transfused with the anti-HIV genes, and only a fraction of the cells survive to take up the new genes. Monitoring the process and ensuring that the patient receives healthy cells is therefore a very significant burden on the investigators performing the procedure. In light of these challenges, Dr. DiGiusto demonstrated ways to increase the yield and the purity of the modified cells before they are transferred back into the patient. He also presented data comparing different ways to deliver the anti-HIV genes into the cells. The ill-fated French trial in 1999 demonstrated the rare but significant risk of cancer when the genes are delivered in a lentivirus, which integrates into the cells own genome, and disrupts other healthy genes. Dr. DiGiusto compared this method to delivery of the same genes inside an adenovirus, which does not integrate into the cell’s own genome. His results suggested that, although the adenovirus vector circumvents problems that are associated with integration of the new genetic material into cells, it presents its own challenges for gene delivery.

In the final presentation of the day, Dr. Jerome A. Zack, who is the director of the Center for AIDS Research within the UCLA AIDS Institute, described the success that his lab has had in using genetically-modified hematopoietic stem cells to target and kill cancer cells. These stem cells have been given new genes which allow them to recognize and kill melanoma cancer cells. Dr. Zack demonstrated that these modified cells, when given to humanized mice with melanoma tumors, were able to decrease the size of the tumor. Dr. Zack concluded the meeting by emphasizing the broader potential of stem cell therapy to strengthen the immune system, providing hope not only for HIV patients but for those afflicted with a range of debilitating autoimmune diseases.
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A research star returns to UCLA to develop therapies that reinforce positive stimulation of the immune system

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