The POZ 50 Most Innovative AIDS Researchers

A survey of the American scientific landscape

August 1, 1996 By Bob Lederer and Patrick Pacheco

To the extent scientific progress has been made in understanding and fighting the AIDS pandemic, it is largely due to bold, innovative thinking. While this often involves building on a large body of established work, sometimes the most important advances come from those willing to take a leap of faith -- regardless of their peers' skepticism.

So *POZ* takes great pride in presenting the 50 Most Innovative U.S. AIDS Researchers. They represent a cross-section of the most exciting, cutting-edge projects along the major highways and byways of AIDS research today -- including basic science, clinical studies, prevention and epidemiology. The *POZ* 50 includes scientists ranging from the internationally famous to those unknown to the public. Yet all were selected because they dared to move in new directions that have been intellectually influential, inspiring colleagues to further investigation and advances.

Although *POZ* consulted a wide range of scientists, journalists and advocates in developing this list, the ultimate choices are -- of necessity -- subjective. We strove for a broad mix of fields and disciplines, large and small institutions, well-established and newcomer faces. We focused on those whose innovative research continues today, rather than on ones whose main contributions were early in the epidemic. We were determined to break with the narrow view that the only important AIDS research is about viruses, immune cells, drugs, vaccines and safer-sex education. Equally key areas such as nutrition, alternative medicine, psychotherapy, social support and community cohesion all have outstanding, recognized scientists doing vital but grossly underfunded (and underreported) investigations.

And because AIDS research, like biomedical science in general, continues to under-study the differing needs of disenfranchised populations -- especially women, adolescents, drug users and people of color -- we made it a point to include groundbreaking scientists in each of these areas. Still, even on this "enhanced" list, the face of U.S. AIDS research is largely white and male, reflecting the prevailing dominance in this country's higher education and scientific research institutions. Note also that we have included eight two-person teams, since many advances are the products of collaboration, a fact often obscured when the spotlight falls on a better-known team member.

Reluctantly, we limited the list to researchers in the U.S. Unquestionably, brilliant AIDS researchers elsewhere -- from the world-renowned Luc Montagnier of the Pasteur Institute to many less-known but important scientists on every continent -- are at the frontiers of scientific discovery. In several fields, American experts told us that non-U.S. researchers are the clear leaders; they are not as hobbled by a conservative peer-review process or by the major pharmaceutical company influence on grants which can make or break careers here.

Finally, you will note that two researchers on the list -- Carlton Hogan and Walt Senterfitt -- are themselves living with HIV. These two remarkable scientists have brought invaluable insights to their work gained from longtime involvement in community-based AIDS organizations. Indeed, perhaps the most important innovators are not on this list at all: The thousands of people with HIV worldwide who have heroically done their own self-experiments, set up information-sharing networks and -- through unrelenting creativity and activism -- inspired and cajoled the research establishment to try new approaches that will some day end this horrible nightmare. We dedicate this list to all of them.

VIROLOGY

Dr. Yuan Chang

Columbia College of Physicians and Surgeons

Dr. Patrick S. Moore

Columbia University School of Public Health New York, New York

“Spectacular work” is how Dr. Harold Jaffe of the Centers for Disease Control and Prevention (CDC) greeted the discovery early last year by a team headed by Dr. Yuan Chang and her husband, Patrick S. Moore. Kaposi’s sarcoma, a curious cancer especially associated with gay men since the outset of the epidemic, had been tentatively found to be caused by what the Columbia research team dubbed “KSHV” -- Kaposi’s Sarcoma-Associated Herpes Virus. Although a virus had long been suspected, scientists were divided between believing that the cause of KS was an infectious agent or a behavior, namely the use of nitrites, which were popular recreational drugs among gay men. “It was very clear that the cause of KS was a factor other than HIV,” says Chang, adding that the first indication of it’s being a virus came when the team discovered herpes-virus-like DNA in 25 out of 27 PWAs’ lesions. Once mapped out, similar sequences were found in both AIDS KS and non-HIV-related KS. Though some scientists remain skeptical, Chang is optimistic: “The research is going very well. To know the mechanism of its pathology is the first step in terms of treatment.”

Dr. Max Essex

Chairman, Harvard AIDS Institute
Harvard School of Public Health Cambridge, Massachusetts

“I think it’s better to move rapidly and risk being wrong than to be so conservative that relatively little progress is made,” says Dr. Max Essex. The discoverer of HIV-1’s cousin viruses, the human HIV-2 and the simian SIV, accuses some scientists of just “filling data banks,” but he is moving

rapidly to develop a vaccine. Says Essex, “We’re at the dawn of a new era in vaccine research.” Essex is building on the pathogenic clues provided by the close genetic similarities between HIV-1 and 2, as well as his lab’s identification of protein products linked to HIV-1’s lethal effects. Among these are nef and gp120, a protein on the surface of HIV that provides the most likely target for a vaccine. He speculates that vaccine trials two or three years down the road will offer only “modest protection” at first but become more effective in time. A bigger stumbling block is “a lack of serious international collaboration” due to Western racism against Africa and Asia, where Essex has done considerable research. “The same people too bigoted to recognize the importance of AIDS on a global level are also incapable of recognizing the importance of a vaccine for everyone in the U.S. and Western countries,” he says.

Dr. Robert C. Gallo

Director, Institute of Human Virology
University of Maryland
Baltimore, Maryland

Robert Gallo says he’s perceived as either “the Angel Gabriel or Lucifer.” To supporters, he’s the genius who discovered HIV, developed the HIV antibody test kit and has now made a new discovery that could help slow AIDS progression. To detractors -- including several federal investigative panels -- the former National Cancer Institute (NCI) official is a ruthless competitor who steals other scientists’ findings, refuses to share his cell lines and has cashed in on taxpayer-funded research (all charges he strongly denies). Recently, Gallo’s lab, pursuing Dr. Jay Levy’s leads, isolated three chemokines (chemicals released by killer T-cells) shown in test tubes to block HIV replication. Could this lead to drugs that mimic their action or boost natural production? Gallo is optimistic, but other scientists are skeptical. “These natural approaches to control HIV replication and help the immune system are now our major focus,” he says. Another area of his work has been researching the theory that human herpes virus 6 is a cofactor in AIDS progression. “Preliminary studies suggest the hypothesis may be correct. If so, we’d certainly argue that it becomes a priority to develop drugs against herpes 6.” Meanwhile, Gallo’s recent transition to a Maryland state-funded virology lab has brought new controversy. Several scientists protested the state’s waiver of conflict-of-interest rules allowing Gallo to get 50 percent of profits on sales from products developed at his lab. Gallo rejects the charges as “trumped-up nonsense.…As a state scientist in an academic center. I can do whatever I want,” he says. “The state asked us to form a company to create jobs and fund the institute. If I made profit out of it, would that be wrong? Absolutely not.”

Dr. David Ho

Director, Aaron Diamond AIDS Research Center
New York, New York

Science Watch ranked it No. 1 of “The Red Hot Research Papers of 1995”: Dr. David Ho’s assertion that the virus replicates from the moment of infection, even during clinically silent periods, while the immune system is continually being destroyed. In this view, the AIDS battle is a titanic struggle

in which a crafty and relentless foe eventually wears down the marshaled forces of the immune system, with billions of casualties on both sides each day before HIV ultimately triumphs. The implications of Ho's discovery were immediate and dramatic: They argued for early intervention to hit HIV hard from the outset. It meant a shift in emphasis from T-cell reconstitution to attacking HIV with powerful combinations of drugs. "Based on numbers alone, we knew that using a single drug wouldn't work," says Ho. "We had to corner the virus using multidrugs simultaneously to create more antiviral pressure." The theory also explains one of the central mysteries of AIDS -- how so much destruction could be caused by what was thought to be so little detectable virus. "That led many scientists to adopt convoluted theories based on autoimmunity," says Ho, "which are less convincing now that we have this very simple explanation."

Dr. Konstance Knox

Senior Research Associate Immunotherapy Research and Treatment Institute

Dr. Donald Carrigan

Associate Professor of Pathology
Medical College of Wisconsin
Milwaukee, Wisconsin

Dr. Konstance Knox calls human herpes virus 6 variant A "a big, dumb brute destroyer of tissue," which she and collaborator Dr. Donald Carrigan have in their crosshairs. Their recent finding, which she calls "revolutionary" if confirmed, is that HHV-6A is the cofactor needed for HIV to do its most damaging work. Studying the lymph nodes of 10 HIV positive people with CD4 counts from 200 to 700 and no serious infections, they found all had degenerating tissue containing the herpes virus. Thus, the two doctors have proposed that "active HHV-6 infection appears relatively early" in HIV infection. Adds Knox, "We believe the two are interactive and that if you could suppress the HHV-6A infection, HIV levels would go down dramatically." Many scientists have long dismissed the role of HHV-6 in AIDS, noting that almost everyone carries the virus. "But that's strain B, not A, and the epidemiology of A has never been done," counters Knox, adding that funders with careers focused on HIV have a vested interest in limiting competing research. "They want us to prove the virus' cofactor role, but then they dismiss our proposal. It's a catch-22." Knox and Carrigan want to study long-term nonprogressors, theorizing they won't find HHV-6A in their tissue. The next step will be finding the best drugs to break up this destructive viral team. Two anti-CMV drugs, foscarnet and ganciclovir, suppress HHV-6 in test tubes, and an experimental antiviral, ampligen, seems to work against it in PWAs. "We can't get rid of it, but we can control it," says Knox.

Dr. John P. Moore

Staff Investigator, Aaron Diamond AIDS Research Center
New York, New York

"Sometimes you have to look at failure and see from that how to succeed," says Dr. John P. Moore, who is frustrated by recent setbacks surrounding the search for an effective vaccine against HIV. Most of that effort, including his own, has focused on the gp120 subunit, since HIV's attack on the

immune system involves binding of the gp120 to the cells' CD4 receptor. Followed by fusion of virus and cell, it is the first step in the viral replication process. "Since the gp 120 is central to the process," says Moore, "using gp 120 subunit vaccines to generate neutralizing antibodies against HIV-1 has been at the forefront of vaccine strategies for the past 10 years." Now some of Moore's work is showing how difficult it is to penetrate the virus's defense. Do we try to blast through the barriers? Subtly undermine them? Or choose another route altogether? "We're at the crossroads in vaccine development," he says. "We're going down the wrong road. We have to stop in our tracks and take the right road." Does Moore resent going back to the basics? Says Moore with a shrug, "The life of a researcher is to take three steps forward and four steps back."

Dr. George Shaw and Dr. Beatrice Hahn

Center for AIDS Research
University of Alabama at Birmingham

In January 1995, two independent studies -- one by a team headed by David Ho, the other by Dr. George Shaw (and his wife, Dr. Beatrice Hahn), stemming from their previous work to develop HIV clones -- made surprising discoveries that seemed to fly in the face of received wisdom. Using new anti-HIV drugs as probes, the researchers revealed that billions of virus particles were continuously being produced by newly infected cells and then rapidly cleared. No longer was drug resistance necessarily due to HIV's high mutation rate; it was actually the high rate of replication that was the engine driving CD4 depletion. Hahn's work is now centered largely on recombinant strains of HIV -- hybrid viruses that she says can create drug-resistant mutants and, in one case, have been found to "go through populations like wildfire." Shaw is continuing to look at the fallout of his work, including the critical and controversial question of whether the rapid turnover of virus and CD4 cells leads to death or merely suppression. The latter carries encouraging "implications for the regenerative capacity of the immune system," says Shaw. "Re-trafficked cells could play a role in the reconstitution."

IMMUNOLOGY

Dr. Arthur J. Ammann

Director of Research
Pediatric AIDS Foundation
Novato, California

"If we can identify the causes of maternal-infant transmission, we could virtually eradicate it," says Dr. Arthur Ammann, the founding head of the Ariel Project, a scientific team searching hard for the answers. Is it high viral load (as some studies suggest), an immune mechanism, a genetic factor or, as Amman believes, a combination of all three? Those are the major focuses. The project's goal, Ammann says, is to drive down the transmission rate -- which a famous 1994 federal study said AZT could lower from the U.S. average of 25 percent to 8 or 10 percent. (These hopeful results led Ammann to support calls for mandatory counseling and offering of voluntary HIV testing of pregnant women.) "We can and must lower that figure to under one percent in the next five years," says Ammann, pointing to the promise of protease inhibitors. But some scientists

challenged the AZT study's methods, and the drug's long-term side effects remain unknown. "Clearly, there are problems with AZT," says Ammann, "and if we're to control the epidemic, particularly in developing countries, we need a less toxic and less expensive treatment." He criticizes drug companies for rarely spending the extra money to design drug trials for pregnant women and children. "It's frustrating that discoveries that have been made can't be put into action because of economics," he says.

Dr. Anthony Fauci

Director, National Institute of Allergy and Infectious Diseases
Bethesda, Maryland

"Could I have done better? Sure," says Dr. Anthony Fauci, reflecting on his own high profile -- as hero or lightning rod- -- in the fight against AIDS. "But I've listened and I've learned." His various leadership positions at the National Institutes of Health (NIH) have put Fauci in the political hot seat from time to time, but he has also greatly influenced the direction of AIDS research through his own work -- namely in seeking to uncover the complex mechanisms of the immune system, especially endogenous cytokines, to develop strategies for immune reconstitution in HIV positive people. "The virus is modulated very tightly by cytokines, and this has created a whole new field of AIDS research," says Fauci. His lab has also begun exploring the process by which HIV moves from acute to chronic infection. "We think the virus is resulting in the deletion of the initially responding clones of cells that could suppress the virus," he says. Fauci says the coming year may turn out to be the most promising yet. "I'm sure the criticism of me will continue," he says, "but I've learned not to take it too personally. It's good to remember that what you think is the wrong path may lead to good research down the road. That's the beauty of science."

Dr. Janis V. Giorgi

Professor of Medicine
UCLA School of Medicine
Los Angeles, California

Developed in the late '70s, "flow cytometry" plays an increasingly important role in cellular immunology. "It's a rapid and precise tool to measure the cellular basis of immune deficiency and determine what goes wrong when people get infected," says Dr. Janis V. Giorgi, who has used the technology to study the "crucial role" of CD8 cells in the fight against HIV. These cells are on the front line of defense against infections, but research has shown that in people with advanced HIV, the CD8 cells produce a substance that actually promotes viral replication. "By knowing that the CD8 cells can be detrimental, we can attack the fundamental mechanism of pathogenesis," says Giorgi. Flow cytometry has also led to a more accurate measure of CD8 activation, a marker that Giorgi claims will predict viral activity more accurately and determine whether or not AIDS will develop in a particular person who has HIV. "We will know if and when to begin antiviral medication," says Giorgi, who believes intervention should begin early, with flow cytometry tracking both the decline and repair of the immune system. "We have drugs that can successfully suppress viral replication," Giorgi says. "Flow cytometry can show us what's happening in terms of

repair."

Dr. Russell Jaffe

Director, Serammune Physicians Lab
Reston, Virginia

"Think of your immune system as an engine pulling the train of your health," urges diagnostic immunologist Dr. Russell Jaffe. "The lighter the load, the more robust your immune system remains to 'pull you through' assaults of toxic and infectious agents commonly encountered by PWAs." Jaffe's research suggests that people with HIV should begin a regimen of nutritional, attitudinal and movement therapies -- and find nurturing time. "If your immune, hormonal, neurochemical [impulse transmitter] and digestive systems all stay strong, it will greatly reduce your risk of illness progression," he says. Jaffe has found evidence that both newer and established lab tests have good predictive value for PWAs, offering windows into each system's health and suggesting possible interventions. For the immune system, Jaffe has developed a lymphocyte response test measuring hypersensitivity to common foods, food preservatives, medications and chemicals. Other useful tests, Jaffe says, include the cortisol/DHEA ratio (hormonal), adrenaline/seratonin ratio (neurochemical) and secretory-IgA/digestive-transit-time ratio (digestive). "But most doctors' practices lag five to ten years behind many advances in laboratory medicine applicable to chronic diseases," he says. Still, he's hopeful the word will spread. "These breakthroughs in monitoring and therapeutic goal-setting hold promise for improving quality, and maybe even length, of life," Jaffe concludes.

Dr. Jay Levy

Research Associate, Cancer Research Institute
University of California,
San Francisco

Back in the '80s, Dr. Jay Levy's tenet that long-term survivors might well supply the key to developing effective treatments for AIDS led him and his collaborators to an important discovery: That the CD8 cells, virus-controlling lymphocytes, secrete a substance that appears to halt replication of HIV. Their research was even able to demonstrate that this cytokine -- common in long-term survivors -- was actually "turning off" HIV without killing the cell. "But we had to figure out what the substance was," says Levy, who along with Robert Gallo and Luc Montagnier, was one of the first to isolate HIV. A proposal to the NIH for grant money was turned down as too iffy, and other researchers were skeptical. "It was a new discovery and, because it was new, not very popular," says Levy, whose findings have now been confirmed in other studies. Though Levy's work is impeded by the lack of funding for basic science, which he feels has hit an all-time low, he perseveres. "We are looking at various compounds that will allow a person's own CD8 cells to increase the factor in a way that will maintain the CD8 antiviral response over a long period of time," says Levy.

Dr. Joseph "Mike" McCune

Associate Investigator, J. David Gladstone Institute
University of California,
San Francisco

Dr. Mike McCune calls it a “wild-ass experiment” he thought of on a commute from Stanford to San Francisco eight years ago, but his development of the SCID-hu mouse has been an invaluable, versatile and fairly accurate model of HIV pathogenesis and drug therapy. McCune has used his animal model to formulate and test various hypotheses as head of the Gladstone viral pathogenesis lab and antiviral drug research division. The mouse, implanted with tissues from the human immune system, has proved to be useful in the analysis of cytokine dysregulation, in the study of CMV as a cofactor in HIV progression and, in particular, in gauging the impact that HIV has on the thymus and bone marrow, two central organs involved in human hematopoiesis, the formation of blood. McCune has also tested drug combinations in the SCID-hu mouse. “I’m worried, as we all are, about how to figure out which combination is best,” says McCune, who recommends that his patients contact advocacy groups, such as San Francisco’s Project Inform, for the latest information on HIV treatment and drug therapy. “We can and will use the mouse in preclinical evaluations of therapeutic modalities, especially in the little-tested immune-based therapies.”

Dr. Mario Roederer

Research Associate, Department of Genetics
Stanford University
Palo Alto, California

Research by Dr. Mario Roederer challenges the consensus that AIDS is primarily caused by the loss of CD4 helper cells. Roederer’s compelling evidence suggests that “naive T-cells,” a subset of CD4 and CD8 cells that were previously thought to remain steady or perhaps increase in the course of HIV, are instead decimated. “It was fun publishing a black-and-white result that contradicted previous papers,” says Roederer. In addition to providing a more accurate prognostic marker, Roederer’s discovery has far-reaching implications, not the least of which is the need -- and Roederer’s wish -- to shift research emphasis from antivirals to the restoration of immunocompetence by study of the mechanism that causes the depletion of naive T-cells, which are essential for fighting off new infections. “A good hypothesis is that the thymus, the primary source of T-cells, is destroyed early by HIV, shutting off the production of naive T-cells,” he says. “This could account for a lot of the immunodeficiency we see in HIV.” Though critics maintain that the harmful impact of no naive T-cells has yet to be demonstrated, Roederer feels strongly that understanding AIDS progression requires an in-depth analysis of this phenomenon. But getting funding is tough in a field dominated by virologists. “It’s frustrating, but very exciting,” he says. “It’s unexplored territory.”

Dr. Robert Root-Bernstein

Associate Professor of Physiology
Michigan State University
East Lansing, Michigan

Ask Dr. Robert Root-Bernstein into which category he'd place his work and he quips, "Crackpot?" The maverick researcher says that if he's had any influence at all in the scientific community, it's to have pointed out the importance of cofactors and the role of autoimmunity in the progress of AIDS. Root-Bernstein says that current research takes into account the factors he's been screaming about for years: The study of long-term survivors and specific cases of PWAs who've eliminated all traces of HIV, as well as autoimmune diseases, which he has researched at his own expense. "If cofactors are intrinsic, even if only to the rate at which HIV progresses, then each cofactor must be targeted." Root-Bernstein is also skeptical about the ability of protease inhibitors to withstand resistant viral strains. "I think we're going to have to work out some way to enhance or reconstitute the immune system and keep it under control," he says. "Bob Gallo used to say, 'Multifactorial means multi-ignorance,' but that's just the point. If we had the answers, we'd have cured AIDS."

Dr. Paul A. Sandstrom

Visiting Fellow, Retrovirus Diseases Branch
Centers for Disease Control and Prevention
Atlanta, Georgia

"If you're facing an enemy that's stronger than you, then use its strength to your advantage," says Dr. Paul Sandstrom, who has been investigating the role of oxidative stress -- the generation of cell-damaging free radicals -- in HIV positive people. Noting that his current hypothesis is not CDC policy, Sandstrom is looking into the possibility of shifting cells toward apoptosis, in which the cell effectively commits suicide before it can produce large amounts of virus. Previous research seemed to indicate that the reverse was called for: Blocking apoptosis through the use of antioxidants -- such as the drug NAC -- would seemingly slow the depletion of CD4 cells and viral replication. But Sandstrom and his collaborators -- chiefly Tom Folks, Alan Diamond and Tom Buttke -- discovered that over-expressing bcl-2, a much-investigated anti-apoptosis gene, caused acute infections to run through the cells more rapidly, and higher levels of virus were produced. Since HIV-infected people have accelerated apoptosis going on already, Sandstrom and his group theorized, "Why not try pushing it a little bit further to reduce the cell's ability to produce functional virus"? Sandstrom hopes that modulating any of a number of check points in the process of apoptosis might lower the viral load.

Dr. Gene Shearer

Chief, Cell Mediated Immunity Branch
National Cancer Institute
Bethesda, Maryland

In 1990 an NCI team headed by Dr. Gene Shearer and his then colleague, Mario Clerici (now in Italy), studied a group of people -- gay men, IV drug users, newborns of hiv positive women and health care workers stuck by needles -- who had shown no signs of infection by HIV, although some had clearly been exposed. There was even a suggestion that in some people the virus may have been destroyed or at least controlled. The results led them to think that the key to protection

against HIV, and to a possible vaccine, might be the cellular immune response -- in which the body itself recognizes and destroys the very cells infected with a virus -- rather than the antibody immune response. Much of this groundbreaking research stemmed from the scientists' previous investigation of cytokines, proteins regulating the immune system. They found evidence that just before some HIV positive people progressed to AIDS, a shift occurred in their production of cytokines from Th1 -- which produce a cellular response -- to Th2 which in turn is responsible for antibody production. "The notion of a type 1-to-type 2 shift has stimulated research to test new ways of treating people," says Shearer, who says the take-home message is simple: "We've got to start looking for people who've dodged the bullet," he says. "In all the history of medicine and vaccinology, there are people who've escaped. We can learn a lot from them."

NUTRITION/GASTROENTEROLOGY

Dr. Peter Anton and Dr. Ian McGowan

UCLA School of Medicine
Los Angeles, California

AIDS takes guts, and that's what Dr. Peter Anton and Dr. Ian McGowan study, plumbing the many mysteries behind wasting and chronic diarrhea. "Forty percent of the body's immune system is in the gut," says Anton, "which is also one of the earliest major sites of infection." Because the causes of diarrhea are complex, Anton warns that any investigation requires thorough evaluation and follow-up to ensure that no treatable factors are missed, but doctors should not wait for results to start vital nutritional supplementation. "Because the mucosal barrier of the gut is always revved up, our theory is, the virus is having a field day," he says. "By studying the intestinal tract, we can detect progression of the disease much earlier." That means testing the viral load in biopsied intestinal lining and examining immune dysregulation in the stomach and, in the process, providing crucial education to researchers about the importance of the mucosal barrier. PWAs need little education; they feel it in their guts. "It's ironic, but the patients understand this at once," says Anton. Yet little basic research has been done in this area. Anton hopes to establish a federally funded clinical and research center for HIV-related gut problems at UCLA.

Dr. Marianna Baum

Chief, Nutrition Division
Department of Epidemiology and Public Health
University of Miami School of Medicine
Miami, Florida

If acknowledging the role of nutrition in fighting HIV has become more acceptable in the last few years, says Dr. Marianna Baum, it is because PWAs have demanded that their physicians take it into account. "There's little money in nutritional supplementation," she says. Early on in the epidemic, Dr. Baum was among the first to do broad nutritional surveys of HIV positive gay men, finding that despite excellent diets -- many of which were highly supplemented after diagnosis -- at least two thirds had one nutritional deficiency and one third had two or more. Subsequent studies have shown that over a two-year period, vitamin therapy has had "a statistically significant impact

in slowing AIDS progression," says Dr. Baum. On the other hand, deficiencies of some nutrients, especially vitamins A and B-12 and zinc, are associated with early mortality. Determining the safest and most effective way of bringing HIV positive people to what she calls "normal nutritional status" has been the focus of Baum's work. "I think too much of a good thing can be toxic as well," she says, "but our studies suggest that supplementation is indicated."

Dr. Howard Greenspan

Medical Director,
LGD Biomedical Group
Annandale, New Jersey

"I'm a firm believer in taking from whatever body of knowledge you can," says Dr. Howard Greenspan, a researcher focused on the role of oxidative stress in immune-cell death and viral replication. "There's a great deal to be learned from the Ayurvedic." This reference to the traditional medicine of Middle Asia reflects Greenspan's studies there and his interest in using certain plant extracts in HIV treatment to counteract the cell damage inflicted by free radicals of oxygen -- highly destructive, unstable molecules. "Oxidative stress" occurs when HIV blocks the body's defenses -- antioxidants such as beta carotene and vitamins A, C and E, which become deficient in people with HIV. "This may be a major factor in killing off the immune system," says Greenspan, who proposes clinical studies of plants with antioxidant systems -- to get cumulative benefits -- rather than of single nutrients, helpful though they are. But drug companies rarely invest in trials of unpatentable substances, and Greenspan says large, established scientific organizations don't support such nutritional immunology. "They say they haven't seen a lot of substantiation," he says. "But they're overlooking a lot of evidence." In 1993, Greenspan chaired an NIH conference on oxidative stress and HIV, with numerous papers offering basic science and clinical data. He says the scientists there agreed that stepped-up research was needed. "But despite activist pressure, the powers that be retain their conservative biases," Greenspan says.

Dr. Donald P. Kotler

Director of Gastrointestinal Immunology
St. Luke's-Roosevelt Hospital
New York, New York

Dr. Donald Kotler thinks of his gastrointestinal tract research as detective work. "People don't automatically lose weight -- they do so for a reason," he says. "If somebody has diarrhea, I look for the cause. I'm basically sleuthing." Though Kotler describes the nutritional effects of HIV infection on the intestine, and the mucosal and lymphatic mechanisms of immune dysfunction in AIDS patients, he's acutely aware of wasting as a quality of life issue and is heralding a predigestive diet as a possible breakthrough. "It'll allow us to get away from Hickman catheters to feed people in a way that costs less and is less dangerous. I'm looking at nutritional therapies to see how they can be used in the most effective and efficient way," says Kotler of his work measuring the impact of growth hormones and testosterone on body mass, and the use of anti-cytokines, like thalidomide, to inhibit the excessive muscle breakdown caused by the wasting syndrome. Kotler stresses that

eating a lot is not, in itself, a solution. “Dealing with the viral burden may take care of the problem,” he says, “but simply stuffing in more food, especially if the body is in a catabolic mode, is not likely to do a damn thing.”

Dr. Kathleen Mulligan

Assistant Professor of Medicine
University of California at San Francisco Medical School

“When you’re losing weight, ’I don’t feel like eating’ is not an option,” says endocrinologist Dr. Kathleen Mulligan, who argues that “aggressive nutritional care is as important as prescription drugs, even in early HIV infection.” Mulligan, with her mentor and coinvestigator, Dr. Morris Schambelan, closely studies hormonal and metabolic factors in wasting and tests anabolic therapies to reverse or halt the process. Contrary to the prevailing wisdom that wasting stems mainly from muscle breakdown, their research shows that when PWAs lose weight, they’re losing both lean tissue and fat. Mulligan maintains that wasting is neither inevitable nor irreversible, but intervention is crucial during acute infections when weight loss occurs most rapidly. Her studies have largely focused on growth hormones and less expensive anabolic therapies, including the famed former morning-sickness pill, thalidomide. A current project is evaluating the effects of a male hormone, nandrolone decanoate, on wasting in women -- an often ignored population. “We’ll look carefully at safety issues,” she says. “Next we’ll be studying how to use these agents -- say, combining a steroid with an appetite stimulant.” Mulligan culls many of her ideas from her patients. “Both lab and clinical investigators must look not only to each other but to the community as a rich source of new research directions.”

CLINICAL PHARMACOLOGY

Dr. Barry R. Bloom

Professor of Microbiology and Immunology
Albert Einstein College of Medicine
Bronx, New York

Tuberculosis is the most lethal of opportunistic infections (OIs) among HIV positive people, says Dr. Barry Bloom. Together with colleagues at Albert Einstein College, Bloom has recently developed a new vaccine against TB that could provide protection for HIV positive people and prevent them from infecting others. BCG, the anti-TB vaccine now in use, employs a live virus that can actually cause TB in those with weakened immune systems. The new vaccine is a genetically altered form of BCG that generates a protective immune response while preventing mutant BCGs from living long enough to cause the disease in susceptible people. “TB is the sentinel in much of the world for AIDS,” says Bloom. “We don’t know how to deal with drug-resistant TB, and there are no drugs in the pipeline,” he says, linking the research inertia to TB’s lack of “trendy disease” status. “When major outbreaks of TB occurred in 1989, it took three years to fund TB research. If Ebola fever had hit the U.S., the money would have been there without having to steal it from other programs. It’s bizarre to have researchers competing with each other for funds.”

Dr. Wafaa El-Sadr

Director, Division of Infectious Diseases
Harlem Hospital Center
New York, New York

While many people believe that the war against HIV-related OIs has been largely won, Dr. Wafaa El-Sadr is still on the front lines, coping with what she sees as acute problems among the Latino and African American populations in Harlem. “We have major problems with large numbers of OIs that we don’t have the answer for, like diarrhea,” says El-Sadr, who has been studying prevention of TB, CMV, PCP and other infections which have hit hard at inner-city minorities. She has also worked towards the development of an HIV nutrition program and investigations into fungal and bacterial infections among women, who continue to be underrepresented in clinical trials. With her colleagues she has focused on recruitment and retention of minorities in trials, overcoming a long tradition of mistrust and establishing a clinical trials unit in Harlem close to where the patients receive their primary care. More research is urgently needed, and El-Sadr is worried that spending cuts may weaken the foundations of solid primary care which are essential to clinical research. “If you weaken public assistance programs and social services, it’ll have a devastating effect on research. It’s crucial for the poor, but it’ll impact on everyone.”

Dr. Emilio Emini

Executive Director, Department of Antiviral Research
Merck & Co., Inc.
West Point, Pennsylvania

Protease inhibitors are touted as the hope of anti-HIV treatments, but experience persuades Dr. Emilio Emini that “there should always be caution until hopes are fulfilled.” That said, the man who spearheaded the development of Merck’s protease inhibitor believes that the optimism surrounding the newest breakthrough is justified. “We tried to have a reasonable base of knowledge before proceeding forward,” says Emini. Still, Emini sees room for improvement. “Certainly in terms of short-term studies, we’re seeing much better results than with reverse transcriptase inhibitors [the earlier class of antiretroviral drugs].” One of the first scientists to study cross-resistance to protease inhibitors, Emini reported that resistant viral variants have emerged in PWAs, suggesting that combination therapy may not prevent loss of antiviral activity. “The data argue in favor of biochemically divergent, as opposed to convergent, strategies for combination therapy of HIV-1 infection,” he says, although some scientists disagree. Together with colleagues, Emini is also developing novel anti-HIV agents targeting integrase, another enzyme on the virus. Emini touts HIV as the best organism to demonstrate survival of the fittest. “You’ve just got to take a stake, drive it to the heart [of the virus] and pin it to the floor,” he says.

Dr. Alexandra Levine

Chief, Division of Hematology
USC School of Medicine
Los Angeles, California

When the AIDS epidemic first hit, oncologist Dr. Alexandra Levine realized that the high doses of chemotherapy usually prescribed for lymphoma were far too toxic for her HIV positive patients. A study of low doses of chemo over a shorter period of time yielded impressive results. The remission rate was 51 percent, and most patients didn't relapse when chemo was stopped. "As a woman, I was particularly pleased that a light touch was effective," says Levine. Although low-dose chemo is becoming standard practice in many parts of the country, she encountered strong resistance from skeptics. "The typical response is that more is better," she says. Levine is presently working with Dr. Dan Von Hoff on a new drug, Mitoguazone, which in combination with low-dose chemo may be helpful to those with relapsed AIDS lymphoma who've failed other regimens. "Mitoguazone is not significantly toxic to bone marrow and also crosses from the bloodstream to the brain." Levine sees urgency in studying interactions that may occur -- either positive or negative -- when chemo for lymphoma is combined with protease inhibitors. "I think this is an extraordinarily exciting time in the history of the epidemic."

Dr. James Oleske

Professor of Pediatrics
New Jersey Medical School
Newark, New Jersey

Immunization has always had a special place in pediatrics, and Dr. James Oleske believes that if he is going to make a contribution in the war against HIV, it will be as a proponent of therapeutic vaccines. For the past couple of years, he has been working in his lab on an autogenous (self-produced) whole vaccine using cellular and viral antigens of people who are already infected, largely designed for his patient load of children, teens and women. "I think we've given up too quickly on therapeutic vaccines, and we've been too much in love with high technology in our quest for a preventivevaccine," he says. "We went too fast in trying to make a safe, targeted immunogenic preventive vaccine. We've got to go back to basics on vaccines." The pediatrician has also designed pilot studies on nutrition; pain management and other quality of life issues are top priority to Oleske for children in trial studies. "Pediatrics is not paid attention to," says Oleske, who hasn't turned his back on children and others with HIV in his search for a preventive vaccine. "We have to pay attention to people who are already infected."

Dr. William Powderly

Co-Director, Division of Infectious Diseases
Washington University School of Medicine
St. Louis, Missouri

"We're potentially one step away from disaster," says Dr. William Powderly, underlining the urgent need to develop innovative drugs to provide both treatment and prophylaxis for OIs. Powderly himself has focused on acute and long-term crypto-meningitis and fungal infections and is now studying resistant forms of candidiasis. He has also helped develop new drugs, which he calls macrolytes. Although adequate treatment exists for many OIs, there is little available to control diarrhea, CMV and other resistant organisms, and getting funds isn't easy: Powderly labels OIs a

“stepchild,” given the focus on finding a cure. “Thanks to community activism and lobbying, there has been an acceleration of funding for research that may give us more options,” he says. “But it’s too early to tell if it’s enough.” Part of the problem is that prophylaxis continues to be controversial, considering questions of cost-effectiveness and, especially, the idea of administering toxic medications to prevent infections that people don’t yet have and that not everybody is going to get. “It’s something that every physician has to weigh against the benefits,” concedes Powderly. “But there’s no question we have to optimize those prevention strategies that we know improve quality of life and actually extend survival.”

Dr. Richard Price

Vice Chair, Department of Neurology
University of California, San Francisco

The incidence of HIV-related dementia complex is declining, and experts aren’t sure why. “It’s possibly the result of the use of antivirals,” says Dr. Richard Price, who was analyzing the pathology of neurological problems associated with HIV before the virus was even named. Though recent studies indicate that AZT could ameliorate or even reverse the syndrome, little is known about dementia, a complicated and underfunded area of HIV research. “What’s wily about dementia is how it comes about,” says Price, “and how the brain is injured as a result of infection.” Price is focusing on the establishment of a theoretical framework to clarify pathogenesis. “We need to know why it occurs in some people and not in others,” he says. “We still can’t predict who will or won’t develop dementia.” Price and his colleagues do know that the syndrome is caused by indirect mechanisms of infection and is, paradoxically, related to immune responses triggered by HIV. “This idea provides targets for intervention to reduce the damage,” he says, suggesting that treatments already exist that can improve the quality of life for PWAs with neurological impairments. Adds Price, “It’s also important for us to understand how to prevent it from developing in those infected.”

Dr. Douglas Richman

Professor of Pathology and Medicine
University of California San Diego School of Medicine

Dr. Douglas Richman maintains that the media hype surrounding AIDS research has put the public on an emotional roller coaster. As one of the first to study viral resistance to anti-HIV drugs (specifically AZT), his focus through ups and downs has been on the efficacy and toxicity of these antiretrovirals and developing non-nucleoside inhibitors of reverse transcriptase. But while Richman maintains that viral resistance is a serious and ongoing concern -- now in connection with protease inhibitors -- what is key is how the antiretroviral drugs affect viral replication. “There are theoretical mechanisms by which these drugs can sustain activity in the face of drug-resistant virus,” he says, citing the maintenance of plasma concentrations that exceed the susceptibility of drug-resistant virus or two drugs that target the same viral protein, with mutations in one drug, conceivably sensitizing the virus to the other, or preventing the emergence of viable mutants. “Drug resistance is always going to be a problem, but one that we can contend with,” he says.

“Given that some people with long-term HIV infection have not developed AIDS, we know that a significant but incomplete suppression of virus replication is a reasonable initial aim.”

Dr. Stephanie Seremetis

Director, Women’s Health Program
Mount Sinai School of Medicine
New York, New York

In the early ’90s, the development of genetically engineered very-high-purity blood products presented clinicians with yet another option in choosing factor VIII concentrates for HIV positive hemophiliacs. With an eye toward determining the impact on the immune system of these clotting factors, Dr. Stephanie Seremetis spearheaded a three-year-study comparing high-purity vs. intermediate-purity factor VIII concentrates among symptom-free HIV positive hemophiliacs. “We saw very significant differences in the rates of decline in terms of changes in the CD4 lymphocyte counts,” says Seremetis. “The genetically engineered products that didn’t include proteins had essentially stable counts, while there was a drop of about 80 per year in the group receiving intermediate-purity factor VIII.” The research seemed to indicate that various proteins in the lesser-purity products were stimulating an immune response that resulted in a proliferation of HIV-infected cells, thus acting as a cofactor in HIV progression. “If we minimize coexistent infections and other antigens,” reasons Seremetis, “there is likely to be a salutary effect.” Now that more than 90 percent of hemophiliacs are receiving the higher-purity clotting factors, the researcher says that she has shifted to studying viral load among her patients and ways to reduce transmission to partners.

COMMUNITY-BASED RESEARCH

Dr. Donald L. Abrams

Chairman and Principal Investigator
Community Consortium
San Francisco, California

“You can do research in a doctor’s office that’s important and useful,” says Dr. Donald Abrams, a San Francisco physician on the front lines since the early days of the epidemic. Sounds like common sense, but when Abrams and other Bay Area health care providers founded the Community Consortium to conduct research doctor by doctor, rather than relying on university-based research, it was trailblazing. “In 1985 a group of us thought, ’Instead of just listening to what everybody else thinks might work, let’s collect some data ourselves.’” The consortium’s initial studies included aerosolized pentamadine as an effective prophylactic against PCP, with data gathered from 74 physicians at 12 different sites around the city. The results, along with parallel findings by New York’s Community Research Initiative, led to FDA approval. The Consortium is currently fighting the blockage by the powerful Drug Enforcement Administration of an FDA-approved proposal to compare marijuana with Marinol as a treatment for wasting. The illegal weed is just one of the herbal and nutritional therapies Abrams has helped study. “I’m willing to investigate alternative treatments,” says Abrams, who is gay. “I’ve lost a number of

lovers, and I’m not going to stop short of finding a drug that will actually prolong survival.”

Dr. Misha Cohen

Clinical Director, Quan Yin Healing Arts Center
San Francisco, California
