

SEARCHLIGHT

QUARTERLY NEWS FROM AIDS RESEARCH ALLIANCE OF AMERICA

The National Leader in Fast-Track AIDS Research

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What's News—

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Clinical Research

Pharmacia & Upjohn has selected AIDS Research Alliance of America to participate in a Phase II multi-center study of **tipranavir** in HIV-infected individuals failing their current single protease inhibitor (PI) containing regimen. Tipranavir is a protease inhibitor that remains active against highly drug resistant HIV strains in test tube experiments.

(Article on page 3)

Gut Inflammation Targeted in UCLA/Procter & Gamble HIV Study

ARAA consults on study design, aids enrollment

LOS ANGELES, DECEMBER 1—Drs. Peter Anton and Michael Poles of UCLA Medical School are collaborating with Procter & Gamble Pharmaceuticals in a safety and feasibility study of the of the anti-inflammatory medication, Asacol[®], in reducing inflammation in the gut of HIV infected individuals. Asacol[®] is already FDA-approved for use in patients with ulcerative colitis, a form of inflammatory bowel disease. ARAA is contributing trial design expertise and aiding in identification and enrollment of study participants.

Dr. Anton, a member of ARAA's Medical Executive Committee, has a long-standing interest in the involvement of gut-associated lymphoid tissue in the natural course of HIV infection. As detailed in the previous issue of *Searchlight*, his lab has been developing techniques to measure HIV within gut tissue, as well as to assay immune activation markers.

The gut, which contains the majority of the body's immune cells, is thought to be significantly inflamed in HIV-infected individuals. Inflammation in turn both promotes the ongoing replication of HIV and increases the number of cells that can be infected by the virus. This permissive environment for continuous viral expansion very likely represents a substantial impediment to the success of treatment with antiretroviral therapy.

In theory, an anti-inflammatory treatment for the gut, provided as an adjunct to conventional anti-HIV "cocktail" therapy, would provide improved control of HIV replication. This therapeutic approach could potentially also address symptoms associated with inflamed bowels, such

Also in this Issue

Although in recent years we have seen substantial progress towards achieving a vaccine to prevent the transmission of HIV, answers to very basic scientific questions are needed to inform vaccine designs. In an interview with *Searchlight*, vaccine specialist Dr. David Hone of the Institute of Human Virology in Baltimore, MD, shares his insights into the state of HIV vaccine development.

(Coverage begins on page 9)

Many potentially useful compounds are currently in the HIV/AIDS drug pipeline; one source recently listed 49 anti-HIV agents currently in some stage of clinical investigation. Freelance writer David S. MacDougall reviews some of the more hopeful HIV/AIDS drugs for the new millennium.

(Article begins on page 7)

In Spotlight

After more than six years as our CEO, **Gregory S. Britt** is moving on to a new job opportunity in the corporate sector. On behalf of all the staff, we wish him well in his new position.

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SEARCHLIGHT

QUARTERLY NEWS FROM AIDS RESEARCH ALLIANCE OF AMERICA

A National Leader in Fast-Track AIDS Research

ARAA envisions a future in which HIV and its effects are eliminated from infected individuals, and a vaccine preventing new cases eradicates the virus.

ARAA's mission is to find and accelerate the development of effective treatments for HIV and its complications. We do this by conducting cutting edge research and clinical trials in order to improve the longevity and quality of life for all people with immune deficiency.

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Fighting a Dangerous Notion—

For Some, The Equation Is Zero Sum

Zero sum thinking is the belief that every time you gain something, I lose something. Adherents to this paradigm live in a world in which the sum of all equations equals zero, and we have to always fight for our own piece of the pie in order to gain anything. It is NOT the world that I live in and is not the type of thinking that rules my thought process.

There is a dangerous notion that is spreading across the country. The notion is that because there are finite financial and scientific resources, various major disease groups have to compete with each other for these resources in order to make scientific advances in their disease area. Other major disease groups have coined the term "AIDS Exceptionalism" to attack the amount of federal (and private) funding that has been garnered by the AIDS epidemic. They argue that in a "dollars per death" analysis, AIDS research gets far greater resources than, say, heart disease or certain cancers. Some advocate for a wholesale recalculation of federal research dollars using the "dollars per death" equation.

This is a scary argument and is a very slippery slope to travel down. It ignores the fact that AIDS receives so much attention and resources because it is widely recognized to be the greatest worldwide public health crisis of the modern age. AIDS is an infectious disease that kills people of all ages, decimates those in the prime of their life, and leaves a wake of economic hardship and millions of orphans in heavily impacted communities.

"Dollars per death" also ignores the way scientific progress is made.

Biomedical science is becoming increasingly inter-disciplinary, and one can no longer expect that advances in one field are applicable to that field alone. AIDS research has probably added more to our understanding of the human immune system than any other disease research in history, enhancing our understanding of human health on many levels. And because retroviruses cause cancers, AIDS research has improved the outlook for cancer research as well.

The incredible synergy that occurs everyday among various major disease research programs works both ways. The protease inhibitors that revolutionized the care of people living with HIV was made possible in large part by information accumulated by research into hypertension, a biological system involving a protease similar to that of HIV.

To me, "AIDS Exceptionalism" should mean that AIDS research has shown how passion, fierce commitment and collaboration has yielded EXCEPTIONAL results, to date. We welcome the opportunity to join hands with our brothers and sisters who are passionately committed to fighting other major disease challenges that threaten our global community. Let's all advocate for more resources, because we have proven that resources can make a real difference.

But if we bicker and fight for our piece of what we perceive as a finite pie, we will lose the infrastructure that has and continues to yield so much. If we can all recognize that there is synergy in collaboration and partnership, then we will find that the whole is greater than the simple sum of its parts.

Gregory S. Britt
Chief Executive Officer

The next generation of protease inhibitors—

Pharmacia & Upjohn's Tipranavir

Tipranavir: An open-label, randomized study comparing combination therapy (tipranavir and ritonavir vs. saquinivir and ritonavir) used with two nucleoside reverse transcriptase inhibitors in single protease inhibitor-experienced HIV-1 patients.

LOS ANGELES, September 15—Pharmacia & Upjohn has selected AIDS Research Alliance of America to participate in a Phase II multi-center study of tipranavir in HIV-infected individuals taking a protease inhibitor (PI) containing regimen that is failing to control their viral loads.

Because of the need to ensure that participants are not experiencing drug resistance to any of the drugs used in this trial, the inclusion/exclusion criteria for study entry are stringent with respect to the medications that potential volunteers have used. Participants must be currently on a regimen that incorporates one of the following three PIs: indinavir (Crixivan™), nelfinavir (Viracept™), or amprenavir (Agenerase™). Additionally, there must be at least two nucleoside reverse transcriptase inhibitors (NRTIs) that participants have yet to use.

Widespread use of PIs in the treatment of HIV infection has led to the rapid emergence of viral resistance to these agents. Estimates of the frequency of resistance vary, but range from 30% to 50% of patients treated with the currently marketed PIs. Since virus resistant to one compound from this class is likely to be resistant to other members of this class (currently marketed PIs all belong to a single category of compounds, "peptidic"

molecules that mimic the natural substrate of the HIV protease), the development of a new type of PI can be expected to dramatically improve treatment options for many infected people.

The primary objective of this study is to evaluate the safety and efficacy of each dose of tipranavir enhanced by ritonavir as compared to saquinivir in combination with ritonavir.

Tipranavir is a member of a new class of nonpeptidic HIV PIs discovered through structure-based design. Results from *in vitro* studies demonstrate that tipranavir is active against virus resistant to a broad range of antiretroviral agents, including currently approved PIs (see the accompanying box, "Tipranavir active against highly resistant strains", page 5). These data suggest that tipranavir can be useful for treating HIV infection in patients currently being treated unsuccessfully with a PI containing regimen.

Small doses of the FDA-approved PI ritonavir (Norvir®) substantially elevate the levels of tipranavir in blood. The present study compares three groups of volunteers. Two groups will receive doses of tipranavir and

ritonavir that are designed to produce two different blood levels of tipranavir. These two groups will be compared to a third group receiving a conventional "second line" dual PI regimen of saquinivir (Fortovase™) and ritonavir.

Thus, the primary objective of this study is to evaluate the safety and efficacy of each dose of tipranavir enhanced by ritonavir as compared to saquinivir in combination with ritonavir. In addition, other endpoints—such as immunological and metabolic changes that might be associated with these regimens—will also be monitored.

Medications and Dose

Participants in this study will be randomly assigned to one of three groups that will differ in terms of the PI component of the anti-HIV regimen they will receive. All participants will be changed from their current PI-containing therapy (that is failing to control viral load), to one of these three possible new regimens:

Ritonavir will be prescribed as the FDA-approved formulation, Norvir®. Saquinivir will be prescribed as the FDA-approved soft-gel cap formulation Fortovase™.

In addition to the PIs, all participants will also receive two NRTIs. These must be NRTIs that the participant has not pre-

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Pharmacia & Upjohn's Tipranavir—

continued from page 3

GROUP

-
- 1) **Tipranavir** 500 mg twice daily plus **Ritonavir** 100 mg twice daily plus **2 NRTIs**.

 - 2) **Tipranavir** 1250 mg twice daily plus **Ritonavir** 100 mg twice daily plus **2 NRTIs**.

 - 3) **Saquinavir** 400 mg twice daily plus **Ritonavir** 400 mg twice daily plus **2 NRTIs**.

viously been treated with. The NRTIs can be chosen from the following list: abacavir (Ziagen™), adefovir (Preveon™), didanosine (Videx®), lamivudine (EpiVir®), stavudine (Zerit®), zalcitabine (Hivid®), and zidovudine (Retrovir®). Participants who become intolerant or exhibit toxicity to their originally prescribed study NRTIs may switch to other NRTIs if the option is available (if there remain NRTIs for which that participant has not received prior exposure).

Side Effects

Tipranavir is an experimental drug, and there may be side effects associated with its use that are still unknown. However, the safety of tipranavir has been assessed in over 120 healthy subjects at doses up to 2000 mg twice daily and in 40 HIV-infected volunteers at doses up to 1500 mg twice daily.

Tipranavir has been well tolerated in the doses and regimens used in both populations. The safety profile of this drug is similar in both populations: the most frequently reported adverse events have primarily been related to the gastrointestinal tract and include diarrhea, nausea, vomiting, flatulence, abdominal cramping and decreased appetite.

All of the other study medications are also associated with potential side effects. Furthermore, adefovir (Preveon®), one of the possible NRTIs, is still an experimental compound.

Testing

An initial screening visit (not more than 21 days before the start of therapy) will include a medical history as well as a blood draw for determining T cell counts and viral load measurements. A subsequent screening visit will include a chest X-ray as well as a

blood draw for determining T cell counts, viral loads and blood chemistry. Therapy will commence from 2 to 14 days following the screening visit.

Participants will receive therapy for 24 weeks. Visits will be scheduled at weeks 2, 4, 8, 12, 16, 20 and 24. Those who meet specified response criteria at the completion of week 24 may participate in an optional 24-week long extension phase (in which participants continue to receive their study medications) that will include visits at weeks 32, 40 and 48. All such visits will involve blood draws (including monitoring of T cell counts and viral loads) and assessment of any adverse effects.

Inclusion Criteria (partial list)

- 1) Clinical failure (defined as unsuccessfully controlled viral load) while taking a PI-containing regimen of indinavir (Crixivan™), nelfinavir (Viracept™) **or** amprenavir (Agenerase™).
- 2) At least 6 months exposure to the present PI therapy.
- 3) HIV RNA (viral load) at least 5,000 copies/mL at initial screen.
- 4) CD4 cell count at least 50 cells/μL at initial screen.
- 5) No prior experience with at least 2 of the NRTIs allowed in this study (see "Medications and Dose", above).
- 6) At least 13 years of age.

Exclusion Criteria (partial list)

- 1) Treatment with more than one PI-containing regimen.
- 2) Clinically significant active and/or acute (onset within the past month) medical problems.
- 3) Prior exposure (more than 7 days) or hypersensitivity to tipranavir, saquinavir or ritonavir.

Patient Slots

4

Status

Soon to enroll.

Principal Investigator

Stephen J. Brown, M.D.

For information about participation in this study, contact Corigan Castro at (310) 358-2429.

Outlook improves for fighting drug resistant HIV— **Tipranavir active against highly resistant strains**

Tipranavir can fight drug-resistant HIV isolated from infected individuals—at least in test tube experiments, as a new report indicates.

The tendency of HIV to become resistant to antiretroviral drugs severely limits the effectiveness of conventional anti-HIV cocktail therapy for a number of individuals. In the case of protease inhibitors (PIs), this problem is exacerbated because resistance to any one of the currently approved PIs (all of which share a common mode of action) often confers resistance to the other members of this drug class.

Tipranavir belongs to a different class of PI, making it potentially active against HIV that has become resistant to currently approved PIs. To find out how active, the drug was screened with the experimental "phenotyping" resistance test Antivirogram™.

The Antivirogram™, currently being developed by the Belgian company Virco, is designed to predict patient responses to anti-HIV regimens. For the assay, HIV is

isolated from infected individuals, grown in test tubes, and tested for its susceptibility (and conversely, its resistance) to antiretroviral drugs. In theory, a physician should be able to use this information to select a potent regimen for each patient, avoiding all drugs to which the virus has become resistant.

In the present study, the Antivirogram™ was applied to the question of whether tipranavir could suppress PI-resistant virus. If so, then HIV with such resistance patterns would not grow well in test tubes when treated with tipranavir.

Tipranavir performed well in this study. 87% of the viruses tested remained fully susceptible to tipranavir, and only 4% of virus were more than 10-fold less sensitive to tipranavir. This is important because the majority of these viruses had more than 10-fold resistance to four other PIs—these being indinavir (Crixivan™), ritonavir (Norvir™), nelfinavir (Viracept™) and saquinavir (marketed as Invirase™ and as

Fortovase™).

These results—presented in June by Dr. Brendan Larder, Vice President of Research at Virco, in collaboration with researchers from Pharmacia & Upjohn at the 3rd International Workshop on HIV Drug Resistance and Treatment Strategies—can only predict, and cannot prove, the effectiveness of tipranavir in reducing viral load in patients whose virus has become resistant to existing PIs. The usefulness of tipranavir for such people will not be known until clinical studies to investigate this have been completed.

The results of this experiment are cause for hope for patients with antiviral-resistant HIV, however. In a press release to announce the findings this past summer, Dr. Larder said, "since considerable numbers of patients failing HAART harbor PI-resistant strains of the virus, the development of new agents active against these variants is an urgent priority."

Gut Inflammation Targeted in UCLA / Procter & Gamble HIV Study—

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as diarrhea, that are frequently presented by HIV-infected individuals.

Asacol® is the brand name for mesalamine, a compound related to aspirin, but in a form that is generally non-absorbed, topically active and has minimal side effects. Currently, Procter & Gamble markets it for the treatment of inflammatory bowel disease.

The present study is designed primarily to assess the safety of Asacol® as an adjunctive therapy in an HIV-infected population. However, some efficacy data will also be gathered, particularly on the viral responses in both the gut and the blood of participants. These data will then be used to design a subse-

quent trial to statistically test the efficacy of Asacol® in a larger study population.

Consistent with its role as a specialized "niche" contract research organization, ARAA has been helping to design the present trial, in addition to spearheading patient enrollment, and will likely do so again in subsequent trials as well. Furthermore, this study has been largely enrolled with volunteers who participate in ARAA's Clinical Trials Priority Notification Program.

The trial is still open to enrollment.

For more information, call Marie Fuerst, R.N. at (310) 825-9254.

Looking ahead—

Coming down the HIV/AIDS drug pipeline

Tipranavir is only one of many new drugs being developed to fight HIV.

How full is the HIV/AIDS drug pipeline? The June 1999 issue of the magazine R & D Directions lists 49 separate products currently at some stage of clinical investigation for the prevention or treatment of HIV infection. Yet more compounds are being tested for the treatment of various complications and conditions associated with HIV. And the candidates that make it to clinical trials represent only the tip of iceberg; many more are being prepared in preclinical work for future study in human subjects.

It would obviously be impossible to cover each and every one of them. Freelance writer David S. MacDougall takes a look at some of the "stand-out" compounds in the drug pipeline (see facing page).

* * *

You can't tell the players without a scorecard...

Our discussions of Pharmacia & Upjohn's tipranavir and the drug pipeline refer heavily to the existing drugs and drug classes. Recognizing that not all our readers keep a chart of the existing HIV/AIDS drugs handy, we have compiled this table listing those drugs currently approved by the FDA for the treatment of HIV infection:

	BRAND NAME	GENERIC NAME	ALSO CALLED...
NRTIs <i>(nucleoside RT inhibitors)</i>	Epivir	lamivudine	3TC
	Hivid	zalcitabine	ddC
	Retrovir	zidovudine	AZT, ZDV
	Videx	didanosine	ddI
	Zerit	stavudine	d4T
	Ziagen	abacavir	--
NNRTIs <i>(non-nucleoside RT inhibitors)</i>	Viramune	nevirapine	NVP
	Rescriptor	delavirdine	--
	Sustiva	efavirenz	--
Protease inhibitors	Crixivan	indinavir	--
	Fortovase	saquinavir	soft-gel cap
	Invirase	saquinavir	hard-gel cap
	Norvir	ritonavir	--
	Viracept	nelfinavir	--
	Agenerase	amprenavir	--

Hope on the Horizon—

AIDS Drugs of the New Millennium

BY DAVID S. MACDOUGALL

The clock is ticking, and not just for those counting the days to the biggest New Year's Eve celebration in modern history. A somber fact of life for those with HIV infection is that the relentless destruction of immune system cells begins at the moment of infection and continues throughout life. This life-and-death struggle can often be slowed by medication, and the health of the immune system can be substantially restored, but HIV/AIDS remains incurable. The outcome of this struggle is influenced by a host of factors, and is never certain.

So where does this leave persons with HIV infection in 1999? A wide range of anti-HIV drugs are currently available, and these drugs are sometimes effective but always difficult to take. Even if the current batch of anti-HIV drugs were completely non-toxic, they can lose some of their therapeutic punch as the virus mutates. Many of these drugs are prohibitively expensive, and compliance with the demanding treatment regimens is notoriously poor. How much longer before something better comes along?

The fact is, a host of promising anti-HIV drugs are currently in various stages of development. Some are still in the preclinical stage, while others are in late clinical trials and close to final approval. Some are members of existing therapeutic classes, and others are the first of their kind. The one thing they all have in common, however, is that the current batch of investigational anti-HIV drugs stems from a foundation of knowledge about HIV dynamics that was unavailable only a few years ago. The identification of the cascade of events in HIV replication has provided a variety of potential targets for therapeutic intervention (see fig-

ure). Similarly, the characterization of the host response to HIV infection has yielded invaluable information about the optimum timing and duration of anti-HIV therapy. Taken together, these

The next generation of anti-HIV drugs promises fewer pills, less toxicity, and more bang for the buck.

recent insights offer hope for the discovery and development of a new generation of anti-HIV drugs with increased potency, easier administration, and better side effects profiles than those currently available.

Nucleoside RTIs: New and Improved

Nucleoside reverse transcriptase inhibitors (RTI) are the cornerstone of anti-HIV therapy, and all of these drugs share common chemical and structural elements. Several promising and newly approved or soon-to-be-approved drugs are members of this therapeutic category.

The newest member of the nucleoside RTI class of anti-HIV drugs is abacavir (ABV), a product of Glaxo Wellcome that was approved by the FDA in

December, 1998. The approval of ABV was unique in that it marked the first time in history that a nucleoside RTI was approved on the basis of its safety and efficacy when used as part of a combination regimen limited to RTIs only. In the pivotal clinical trial that sealed the approval of ABV, the three-drug combination of ABV, lamivudine (3TC), and zidovudine (ZDV) proved therapeutically equivalent to the combination of 3TC and ZDV with the protease inhibitor (PI) indinavir in reducing viral load for up to 24 weeks in previously untreated persons with HIV infection.

A strong scientific rationale exists for investigating the three-drug combination of ABV, 3TC, and ZDV, said M. Lynn Smiley, MD, Vice President of HIV Clinical Development, Glaxo Wellcome. "ABV is synergistic with ZDV and additive with 3TC," she said. "There are no pharmacokinetic interactions or overlapping toxicities among the three drugs, and there are no dietary and fluid restrictions associated with the three-drug combination. Another advantage of the combination is that the regimen is relatively simple and could involve taking only two pills twice daily."

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AIDS Drugs of the New Millennium—

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ABV is not without its drawbacks. Hypersensitivity reactions occurred in 2-3% of patients exposed to ABV in clinical trials. ABV-related hypersensitivity is a multi-organ reaction that usually occurs within the first six weeks of therapy. Continued treatment with ABV in the face of ABV hypersensitivity can result in worsening of symptoms, and restarting ABV after stopping for a hypersensitivity reaction may lead to more severe and potentially life-threatening events, including death. Despite this caveat, ABV is still considered an exceptionally safe drug, and its most common side effects are mild nausea, fatigue, headache, and diarrhea.

Emtricitabine, formerly known as FTC, is another investigational nucleoside RTI with activity against both HIV and HBV. A product of Triangle Pharmaceuticals, Durham, North Carolina, emtricitabine is structurally similar to 3TC but up to 10 times more potent. HIV resistant to 3TC will likely be resistant to emtricitabine as well. Pivotal clinical trials of emtricitabine are currently underway, and the dosage under investigation is 200 mg taken once daily.

Several investigational nucleoside RTIs are still in the early stages of development, and not much is known about these drugs beyond their pharmacologic properties and effects in laboratory animals. However, the preliminary findings have been encouraging enough to support their contin-

ued development. One drug with particular promise is PZT, also known chemically as 3'-azido-2', 3'-dideoxythymine-5'-H-phosphate. PZT has potent anti-HIV activity and a resistance profile similar to that of ZDV. Researchers at Montreal General Hospital recently administered PZT to 42 treatment-inexperienced persons with HIV infection, and viral load levels decreased significantly within two weeks. No major toxicities were observed, and the response to treatment was maintained for a minimum of 12 weeks.

The names of other promising candidates in the nucleoside RTI

The fact is, a host of promising anti-HIV drugs are currently in various stages of development. The one thing they all have in common, however, is that the current batch of investigational anti-HIV drugs stems from a foundation of knowledge about HIV dynamics that was unavailable only a few years ago.

category make up an alphabet soup of letters and numbers including DAPD, PMPA, DMP-450, and L-FMAU. These and other investigational nucleoside RTIs have some exciting properties, but their clinical track records are still unproved. Some of these drugs will probably find their way into routine HIV management, while others might be delegated to specific therapeutic niches like post-exposure prophylaxis or prevention of HIV transmission from mother to infant.

Nonnucleoside RTIs: The Mixed Bag

Nonnucleoside RTIs (NNRTIs) are a diverse group of compounds that inhibit HIV RT in a different manner than the NRTIs. Whereas the NRTIs mimic the ingredients for new viral DNA, NNRTIs bind elsewhere on the enzyme to block its function.

NNRTIs are often discovered by screening large numbers of chemical compounds for HIV inhibitory effects, and then selecting compounds that specifically target the isolated HIV RT enzyme. All of these seemingly unrelated compounds are potent inhibitors of HIV and constitute a generally less toxic class of antiretroviral drugs; most are also highly active against ZDV-resistant HIV strains. A main drawback of NNRTIs is that resistance to these drugs is quick to develop.

Emivirine (EMV), also known as Coactinon, is a lead contender in the NNRTI category of investigational anti-HIV drugs. According to Triangle's Cary Moxham, PhD, EMV is actually a nucleoside analog that functions as a NNRTI in view of where it binds to the enzyme. EMV is considered a potent and specific inhibitor of HIV that is highly synergistic with ZDV, moderately synergistic with ddI, and additive with zalcitabine (ddC).

The combination of EMV and ZDV appears to offer a unique advantage; that is, the dose of ZDV required to inhibit HIV is reduced to 10% of the usual level

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HIV vaccine development—

The hurdles faced by scientists

The reasons why we still do not have a vaccine to stop the spread of HIV are complex and varied, and go beyond the scientific hurdles. But these obstacles are themselves immense.

Effective vaccines for some infectious diseases work because they present the immune system with antigens to which antibodies are produced. However, many researchers do not believe that merely inducing antibodies against HIV would prevent the virus from establishing an infection.

Such pessimism for an antibody-based approach stems in part from what has been learned about the role of antibodies against HIV on the natural course of an infection. Within weeks of HIV infection, the amount of virus in the blood (viral load) reaches extremely high levels. Several weeks later, the viral load falls dramatically to a much lower level. Only after this reduction has occurred do antibodies that effectively neutralize HIV appear in the blood. This suggests that some other kind of immune reaction is responsible for the initial control of viral load. Furthermore, neutralizing antibodies in the blood of infected individuals do not seem to greatly influence the subsequent course of infection (i.e., the length of time before CD4 counts fall and AIDS-defining symptoms are seen in the absence of treatment).

Finding correlates of protection

If neutralizing antibodies will not do the trick, some other immune response must be employed. A wide spectrum of possible antiviral responses are available to the immune system, and scientists have been attempting to correlate them with protection against HIV infection in animal models. Unfortunately, in part because these responses can be difficult or impossible to measure, these so-called “correlates of protection” are still undefined.

For example, antibodies produced at mucosal surfaces—as opposed to antibodies circulating in the blood—may have more impact on HIV transmission, because the majority of new infections occur at the mucous-coated surfaces of the uro-genital tract and the gastrointestinal tract. Much work has been going into the development of a mucosal HIV vaccine, but since there is little precedence in vaccinology for such approaches, researchers still lack basic information about them.

Many scientists believe that the dramatic albeit incomplete immune control of HIV seen shortly after infection (as discussed above) is due to the activity of CD8 cells, sometimes referred to as CTLs (though

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Using bacteria to vaccinate against a virus






Although scientists have been pessimistic about antibodies in the blood preventing HIV transmission, some think that antibodies against HIV can work well if present in the mucosal regions of the gut (as discussed in the body of the interview with Dr. Hone). The problem is, antibodies generated within the blood do not work their way into the mucous. For antibodies against HIV to be present in the mucous, viral proteins must be presented to the immune system there.






Certain bacteria are naturally adept at colonizing our gut, and Dr. Hone and associates attempted early on to engineer bacteria to express small bits (peptides) of viral envelope protein gp120, in the hope that they would then present these peptides to the immune system at the best location—the gut.

Unfortunately, bacteria cannot add sugars to any of the proteins they produce (a process known as glycosylation); this is a trick of mammalian cells. And the immune system will not generate the appropriate antibodies unless it sees a properly glycosylated gp120 protein. It began to look as though one could not use bacteria as a kind of mucosal HIV vaccine.

But the bacteria can transfer DNA to host cells. By splicing genes for gp120 into bacteria, and allowing them to colonize mammalian gut, Hone's group was able to show that mammalian cells would produce the peptides. Since these cells add sugars onto the peptides, they were able to produce antibody-generating HIV proteins within the gut, leading to evidence of mucosal immunity.

C L I N I C A L T R I A L S

STUDY	SPONSOR	DESCRIPTION	STATUS
Tipranavir™	Pharmacia & Upjohn	An open-label, randomized study comparing combination therapy (tipranavir and ritonavir vs. saquinavir and ritonavir) used with two nucleoside reverse transcriptase inhibitors in single protease inhibitor-experienced HIV-1 patients.	Currently enrolling
Remune™	Agouron Pharmaceuticals 	A randomized, double-blind, adjuvant-controlled, multicenter study to compare the virologic and immunologic effect of Highly Active Antiretroviral Therapy (HAART) plus REMUNE™ versus HAART plus Incomplete Freund's Adjuvant (IFA) on antiretroviral-naïve patients infected with HIV-1.	Currently enrolling
Zerit® (Stavudine)	Bristol-Myers Squibb 	Evaluation of the safety and antiviral activity of stavudine <u>extended release</u> formulation as compared to stavudine <u>immediate release</u> formulation, each as part of potent antiretroviral combination therapy.	Currently enrolling
Neurontin® (gabapentin)	Parke-Davis 	A randomized, double-blind study assessing "low dose" versus "high dose" gabapentin for the treatment of painful HIV polyneuropathy.	Enrollment complete, study ongoing
Anticort™	Steroidogenesis Inhibitors, Inc. 	A pharmacokinetic and safety study of Anticort™ (an oral procaine formulation) in HIV-infected patients.	Currently enrolling
Hydroxy-chloroquine (in combination with hydroxyurea and didanosine)	AIDS Research Alliance of America 	An open-label, Phase I/II study of the safety and antiviral efficacy of hydroxy-chloroquine in combination with hydroxyurea and Videx® (ddl or didanosine) in HIV-1 infected patients.	Currently enrolling

STUDY	SPONSOR	DESCRIPTION	STATUS
PMPA Prodrug	Gilead Sciences, Inc. 	A Phase II, randomized, double-blind, placebo-controlled study of the safety and antiviral activity of the addition of PMPA Prodrug to combination antiretroviral regimens in treatment-experienced HIV-infected patients.	Enrollment complete, study ongoing
AIDSVAX™ B/B	VaxGen, Inc. 	A double-blinded, placebo-controlled, Phase III trial to evaluate the efficacy of the AIDSVAX™ B/B vaccine in adults at risk of sexuality transmitted HIV-1 infection.	Enrollment complete, study ongoing
Ziagen™ (abacavir): Cognitive impairment	Glaxo Wellcome 	A Phase III, randomized, double-blind study to evaluate the safety and efficacy of Ziagen™ in patients with HIV-associated neurocognitive impairment.	Enrollment complete, study ongoing
Ziagen™ (abacavir): combination	Glaxo Wellcome 	A Phase III, randomized, double-blind study to evaluate the safety and efficacy of 3TC/AZT/1592U89 vs. 3TC/AZT/Crixivan in HIV-infected antiretroviral-naïve subjects.	Enrollment complete, study ongoing
Nelfinavir™ (viracept)	Agouron Pharmaceuticals 	A Phase II/III placebo-controlled study of Nelfinavir™ in combination with AZT+3TC versus AZT+3TC alone.	Long-term extension phase continuing

For information about enrolling in any of our studies, contact Corie Castro at (310) 358-2429. Transportation to our clinical research facility is available upon request. For priority notification of new/enrolling clinical trials, sign-up for our Priority Notification Program.

The hurdles faced by scientists—

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the terms are not synonymous). Could CD8 cellular activity represent a necessary correlate of protection? CD8 cells in fact perform a number of antiviral activities, but whether these cells can sufficiently protect against infection remains an open question. Still, researchers have been paying greater attention to the effects of HIV vaccine candidates on CD8 cell functioning.

Other immune responses might also have an impact on HIV infection. Many kinds of immune cells secrete chemicals into the blood that strongly affect the response to microbial infections. One such class of chemical, called chemokines, has been associated with protection in animal models of HIV vaccine candidates.

HIV vaccine development suffers from an incomplete understanding of how these various immune responses can impact HIV transmission.

HIV diversity yet another hurdle

The global epidemic involves not a single virus, but a genetically diverse family of HIV. It remains unknown how this will impact vaccine development. The predominant type, or “clade”, of virus in North America and Europe is clade B, but in many Third World countries, non-B clades predominate. Clade C, in fact, now is responsible for the majority of new infections. For this reason,

some scientists have been calling for a greater allocation of resources towards the development of a vaccine appropriate for protecting against transmission of clade C virus.

Can an HIV vaccine be developed that protects against multiple clades of virus? Some experimental vaccine candidates are capable of inducing immune responses effective against HIV of several clades—so-called “cross-clade” protection. But without knowing what constitutes the cor-

A wide spectrum of possible antiviral responses are available to the immune system, and scientists have been attempting to correlate them with protection against HIV infection in animal models. Unfortunately, in part because these responses can be difficult or impossible to measure, these so-called “correlates of protection” are still undefined.

relates of protection against HIV infection, one cannot be certain in advance how cross-clade protection can be achieved in practice.

Attacking the immunosuppression

The entire problem can be viewed at another level. What if there are immune responses that could protect against infection, but HIV prevents them from being activated? Even within the first years of the epidemic, it was becoming clear that the impairment of the immune system can be out of proportion to the loss of immune cells. Immunosuppression by HIV is not just a matter of how many cells it kills, it seems.

Data have been accumulating to suggest that the HIV protein Tat is a toxin that is at least partially responsible for this immunosuppression. In infected individuals, Tat can be found dissolved in the blood, independent of the virus. Though probably still a minority view amongst researchers, it has been suggested on this basis that Tat will be a necessary component of a preventative HIV vaccine. The argument (still controversial) is that the long-sought immune correlate of protection against HIV is inhibited by Tat. If so, then a Tat vaccine might permit these responses to emerge. The vaccines against several infectious diseases actually do consist of inactivated toxins produced by the microbes, so that this approach has some precedence.

Prospects

The very nature of HIV infection requires new thinking about vaccine approaches. HIV presents issues that have not necessarily been encountered before with other diseases. They will have to be resolved by focused and continued effort.



Current issues in HIV vaccine development—
An interview with Dr. David Hone

David M. Hone, Ph.D., is Associate Professor in the vaccine division of the Institute of Human Virology in Baltimore, MD. His laboratory has been developing novel vaccine systems for HIV. To learn more about current trends in the science underlying the search for a preventative HIV vaccine, Searchlight recently interviewed Dr. Hone.

Searchlight: What information is needed for designing new HIV vaccine candidates?

Hone: When we're talking about Tat and rev and other regulatory proteins being candidate vaccine antigens, it's a travesty that after 15 years of the AIDS epidemic, I can't sit here and tell you much about the immunogenicity of those proteins, and the natural history of the immune response of infected individuals to those proteins. There have been some studies in Europe, but they're very limited in their scope.

And so if I were to say that I'd like to design a vaccine that had tat and rev as components of a multi-antigen vaccine, I couldn't at the same time tell you what type of immune response would be most beneficial, since I'm not armed with that information. I can take guesses based on other antigens and what appears to be beneficial in the context of an infection and say that those immune responses might also be useful against Tat and rev, but I can't in an absolute sense. I think that's a sad indication of where this whole vaccine effort has gone really.

Searchlight: How important will it be to have that kind of information to rationally design a vaccine considering that so many other vaccines were developed with an empirical approach?

Hone: Vaccines for diseases such as hepatitis or polio were designed with an empirical approach but we had a clear-cut indication that, say, neutralizing antibodies had a potent antiviral effect. We know with HIV that CD8 T cells have effector functions that are antiviral, but we don't know what specific functions matter. We only know this limited information in the context of gag and envelope, which have been sort of the staple antigens that are being used in clinical tri-

Institute of Human Virology

The Institute of Human Virology (IHV) at the University of Maryland in Baltimore is dedicated to research into, and the eventual treatment and prevention of, chronic viral diseases and virally linked cancers. Its director, Dr. Robert Gallo, was one of the discoverers of HIV, and remains at the forefront of HIV/AIDS research.

als where people have looked at correlates [*of protection*]. I think we really need to know at the front end a lot about the correlates of protection against HIV-1. If we had a better idea what those correlates might be, one could then use that measure up front in vaccine trials as a go-ahead/discontinue parameter.

Searchlight: Vaccine candidates have been studied in numerous experiments. What has been learned from all that work?

Hone: One thing that stands out in recent times is the notable effect that chemokines appear to have against HIV. We are very interested in looking at [*at the Institute of Human Virology, IHV*] in clinical trials with our bacterial vaccine vectors, the type of effector cells we induce that produce beta-chemokines, as well as looking for CTL function and neutralizing antibodies, of course. However, we think that beta-chemokines are going to play a major role in antiviral protection.

Searchlight: What has been seen so far in terms of antiviral effects of beta-chemokines?

Hone: Tom Lehner made a major contribution with his mucosal challenge model and

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An interview with Dr. David Hone—

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showed that there was indeed a correlation between beta-chemokine producing cells and protection. It was also notable that he saw a correlation in addition to the beta-chemokines with antibody-secreting cells, particularly those that would target the mucosal compartment. So, another aspect of our approach [*at the IHV*] is to induce immune responses in the mucosal compartment, which in a sense acts as a “protected” site immunologically—not in the classical sense but in a vernacular sense. If one were to vaccinate parenterally, one typically does not induce a very strong mucosal response. That creates a scenario that upon challenge, the virus can get into a compartment where there is very little T cell immunity, and so any breakthrough virus essentially would have a compartment where it could replicate more or less freely, in the early stage after infection.

We also know that the mucosal compartment is a site of very early replication. So when you put those things together, mucosal

immunity has to be a consideration [*see side-bar, “mucosal immunity”*].

Searchlight: I guess there’s really not enough known about mucosal immunity with HIV vaccines.

Hone: Yes, I think it is very sad that we haven’t really made any leaps and bounds towards understanding much about mucosal T cells against HIV. We certainly know a lot about mucosal antibody. We also know systemic antibody can get into certain mucosal compartments, in particular the genital-urinary tract. The studies that have been done provide limited information and I think again that there is a sadness that we don’t get much help from that information.

Searchlight: Is sterilizing immunity both plausible and necessary in a vaccine strategy against HIV?

Hone: There are two schools of thought here. I would say that sterilizing immunity is our

priority. Obviously, one would want sterilizing immunity. We don’t want to run the risk that we induce some type of partial immunity that 10 or 20 years from now results in the manifestation of a different epidemic in vaccinated cohorts. In other words, where the virus percolates along in a quiescent and silent manner but still retains this capacity to transmit itself. So I believe that sterilizing immunity against HIV really still has to be a goal.

Having said that, I don’t think we should turn a blind eye to the possibility that an HIV vaccine that induces some form of non-sterilizing immunity could be useful in the short-term. That is, a highly contained infection. But again, what that type of immunity would be really I couldn’t answer except to say that it would have to be the type of immunity that restricts the virus from being shed into the blood or mucosal secretions.

Searchlight: What do you think of the state of the art in recombinant envelope vaccine design?

Hone: I think it’s an exciting new area. For the first time we are seeing neutralization of primary virus with HIV subunit vaccines, particularly the complexes. The notable individuals in this area are of course Jack Nunberg, but before him and I think someone that has been overlooked a little bit has been Tony DeVico, who’s now at the Institute of Human Virology. I’m not beating our drum; it’s just that Tony has a very strong [*vaccine*] candidate. His is

Mucosal immunity

As has been reviewed in previous issues of *Searchlight* (Winter 98/99, Fall 99), immunity at mucosal surfaces is separate from systemic immunity. Systemic immunity, which involves blood-borne antibodies and immune cells, is effective against many com-

municable diseases, but prevention of HIV infection of mucosal surfaces may require specific mucosal immunity as well. The majority of new HIV infections occurs at mucosal surfaces in the urogenital or gastrointestinal tracts.

a soluble complex that is made by covalently linking CD4 to gp120, and it induces the same types of antibodies that Jack Nunberg has seen. Tony has conducted some limited monkey studies, and they're immunogenic in monkeys. He also knows that the antibodies elicited by his vaccine do not bind to CD4 expressed on CD4-positive cells, so that the antibodies are probably envelope-specific.

Searchlight: Let's talk about your work then.

Hone: We're developing a bacterial DNA vaccine vector system. [see the side-bar, "Using bacteria to vaccinate against a virus", page 12] What that means is that we are using human-specific bacteria, Salmonella type B and Shigella, to introduce DNA vaccines by the oral route. In a sense that constitutes a mucosal vaccination strategy, because it's oral, and we're accessing the gut-associated lymphoid tissue. And, as I said earlier, our major emphasis is to induce mucosal immunity.

The bacterial DNA vaccine technology stems from work in our lab where we were developing strategies to induce antibodies against conformational epitopes of the envelope protein gp120. At first, the V3 peptides were thought to be the principal neutralizing epitope and we thought we could express it bacteria. It turned out later on, of course, through Kathy Steimer's work that the neutralizing epitopes of HIV-1 are more complex and require glycosylation. Bacteria don't glycosylate proteins, so we were pondering—this was back in 1992—as to how to make those discontinuous epitopes.

Searchlight: Just so I have the explanation: glycosylation refers to the addition by the cell of sugars onto gp120, which causes the

If I were to say that I'd like to design a vaccine that had tat and rev as components of a multi-antigen vaccine, I couldn't at the same time tell you what type of immune response would be most beneficial, since I'm not armed with that information ... I think that's a sad indication of where this whole vaccine effort has gone really.

protein to fold differently. The epitope—a term referring to what the antibody recognizes—is not therefore a continuous portion of the protein but a structure produced only by the proper folding of the protein.

Hone: That's exactly right. It's a three-dimensional structure. And glycosylation plays a critical role in its formation. Its main function is to enable viral binding to CD4, as well as CCR5, and without glycosylation one does not the appropriate structures to allow this.

Now, having said that, we typically use in vitro neutralization as our measure of a potent antiviral antibody, but mucosal antibody, especially IgA [*Editor's note: a form of mucosal antibody*], can strongly associate with the glycocalyx.

Searchlight: What is the glycocalyx?

Hone: The glycocalyx is the stream of mucous that is constantly being flushed out of our body.

IgA associates with that mucous barrier and binds to antigens found there. So neutralization in the mucosal compartment should

be thought of in a different context: if a mucosal antibody binds to an antigen, it will cause the antigen to associate with the glycocalyx and slow down its diffusion into the host.

Searchlight: So the bar is a little lower in terms of what an antibody needs to do there.

Hone: Right, an antibody in the mucosal compartment may not have what we call neutralizing activity in a test tube, but may nevertheless bind to and thus flush the virus from the body. Plus there are several antiviral molecules present in the glycocalyx; there's lysozyme, there are RNAses, in the gut there are deoxycholate and other molecules; stalling of the virus in that compartment probably would have a potent antiviral effect in and of itself. So mucosal antibodies probably may have antiviral effects without mediating neutralization in a classical sense.

Searchlight: So neutralization in the test tube refers to whether the antibodies, when they bind to the virus, will prevent the virus from being infectious anymore?

Hone: That's right. What I'm talking about is essentially restricting the virus from ever getting to the target cell. Which is a step earlier than stopping it from fusing with the cell after it has entered the host.

Searchlight: So, getting back to the previous point: you were trying to figure out how to produce the epitope in bacteria?

Hone: So this line of reasoning resulted in us concluding that

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AIDS Drugs of the New Millennium—

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when ZDV is administered in combination with EMV. This feature alone makes EMV an attractive partner in combination therapy regimens including ZDV. Also important is the fact that EMV is active against both ZDV-sensitive and ZDV-resistant HIV strains.

Monotherapy with NNRTIs is not recommended in the real world setting, but is used for short periods in preliminary clinical trials to evaluate new experimental medications. EMV monotherapy in one such study was associated with substantial decreases in viral load after only one week. Resistance to EMV is quick to develop, Moxham noted, and the most common adverse effects are transient headache and rash. Over 800 patients are currently enrolled in Phase III studies of EMV used in combination with other anti-HIV agents, and the dosage of EMV currently under investigation is 750 mg taken twice daily.

The investigational NNRTI SJ3366 is distinct from other NNRTIs in that it effectively inhibits both HIV-1 and HIV-2 at low serum concentrations. The anti-HIV activity of SJ3366 is additive with that of PIs and other RTIs except ddI, where a synergistic interaction has been observed. Developed by Samjin Pharmaceuticals, Seoul, Korea, SJ3366 inhibits HIV RT and interferes with the attachment of HIV to target cells. SJ3366 shows early promise for the treatment of HIV infection, and preclinical trials of SJ3366 are currently underway.

The macromolecule DNP-poly A, another investigational NNRTI,

was designed to fill the entire binding gap of HIV RT. According to Jui Wang, PhD, State University of New York, Buffalo, DNP-poly A has been shown to inhibit HIV-1, HIV-2, ZDV-resistant HIV, and nevirapine-resistant HIV. DNA-poly A injected 3 times per week over a 3-week period protected susceptible blood cells from HIV infection and decreased viral load to undetectable levels in a mouse model of HIV infection. Surprisingly, HIV RNA remained undetectable four months after the discontinuation of treatment. Definitely a drug to watch, DNP-poly A has demonstrated favorable pharmacologic properties and low toxicities in preclinical studies.

Newer PIs

The newest member of the protease inhibitor (PI) class of anti-HIV compounds is amprenavir (AMP), approved this past April. AMP is the first PI to be approved in over two years. Developed and launched by Glaxo Wellcome, AMP features twice-daily dosing, an easier side effects profile, and activity against drug-resistant HIV strains.

In clinical trials, patients who took AMP in combination with other anti-HIV drugs achieved undetectable viral loads for at least 24 weeks. AMP can be taken with or without food, but a high fat meal decreases the absorption of AMP and should be avoided. AMP capsules and solution contain large amounts of vitamin E, and persons taking AMP should not take additional vitamin E.

A promising investigational PI is ABT-378, a second generation

PI from Abbott with potent anti-HIV activity and favorable pharmacologic properties, particularly when administered in combination with Abbott's ritonavir. ABT-378 is 10-fold more active than ritonavir in cell culture assays and remains active against mutant HIV strains that emerge during ritonavir therapy. ABT-378 may also suppress the emergence of HIV resistance against ritonavir when both drugs are used in combination.

The combination of ABT-378 and ritonavir is particularly potent for a simple reason. In the body, the metabolism of ABT-378 is regulated by a family of enzymes called the cytochrome P450 3A enzyme system. Ritonavir is a strong inhibitor of chemical reactions regulated by the P450 3A enzyme system. In the presence of ritonavir, ABT-378 gets a free metabolic ride, so the effective doses of ABT-378 can be much lower when the drug is administered in combination with ritonavir. And lower doses usually means fewer side effects.

Other investigational PIs are in various stages of development and will likely be launched in the not-too-distant future. Among these is tipranavir, which is now in clinical trials. DMP-450 is a urea-based PI that has been licensed to Triangle by Dupont Pharmaceuticals. Preliminary findings with DMP-450 and another experimental PI, Bristol-Myers Squibb's BMS-232,623, are particularly encouraging.

Hold the Fusion

A whole new class of anti-HIV drugs is based on a simple thera-

peutic strategy: block the fusion of HIV to the surface of host cells, and you can prevent HIV from gaining entry and replicating.

The prototype HIV fusion inhibitor is known as T-20, a protein that corresponds to a section of the HIV envelope protein. T-20, also known as pentafuside, was discovered by Duke University researchers who were looking for new HIV vaccine candidates. The idea was to use parts of HIV that vary little from strain to strain, thereby creating a vaccine that would be effective against HIV variants from different parts of the world. The search uncovered a protein sequence composed of 36 amino acids that is highly conserved, meaning the protein is present in the same form in virtually all known strains of HIV. The protein failed to work as a vaccine, but it was found to be highly effective in preventing HIV from infecting new cells.

Clinical studies of T-20 have been carried out by researchers from the University of Alabama and Trimeris, a small biotechnology company located in Durham, North Carolina. In these studies, T-20 was injected intravenously, twice daily, for 14 days to 16 patients with HIV infection. At the highest dose tested (100 mg twice daily), viral load became undetectable and CD4 cell counts increased. No toxicity of T-20 was observed. Trimeris is planning to start large scale studies of T-20 at multiple locations in the near future.

T-20 is not without its drawbacks. Being a protein, T-20 cannot be taken orally. T-20 may be delivered intravenously or subcutaneously by a portable infusion pump, similar to the type used to deliver continuous insulin thera-

py. Eventually, orally bioavailable compounds similar to T-20 with the same mechanism of action may be developed.

T-20 is an exciting compound because it attacks HIV from a whole new angle. Patients with HIV resistant to RTIs and PI and few remaining therapeutic options may still respond dramatically to treatment with T-20. Multiple daily injections are no picnic, but the apparent lack of toxicity and effectiveness against resistant mutant HIV strains may be enough to offset this drawback. Trimeris recently signed a pact with pharmaceutical giant Roche to work collaboratively on the development and eventual marketing of T-20 and a second investigational HIV fusion inhibitor, T-1249.

Experimental agents which block the fusion of HIV envelope proteins with the CD4 cell surface receptors are also under develop-

The anti-HIV drug development pipeline is full, almost to the point of bursting. A host of investigational anti-HIV drugs and strategies are in the works, and most of these interventions show great potential.

ment. Among these is a compound called PRO 542, a product of a collaborative effort between Progenics Pharmaceuticals, Tarrytown, New York, and Pharmacopeia, Inc., Princeton, New Jersey. PRO 542 has proven safe in patients treated in early studies, and additional trials are currently underway.

The Third Enzyme

About 10 years ago, when researchers first figured out the genetic structure of HIV, it became apparent that three

enzymes were critical for HIV infection and replication. The structures and functions of two of these enzymes—reverse transcriptase and protease—have been well studied, and inhibitors of these enzymes currently form the backbone of anti-HIV treatment strategies. The third and final essential enzyme, HIV integrase, is another attractive target for therapeutic intervention.

HIV integrase regulates the cutting of host cell DNA and the insertion of HIV's proviral DNA into the genetic material of the host cell. Only upon this insertion of HIV genetic material can the machinery of the host cell be reprogrammed to produce the RNA and proteins needed to make multiple copies of HIV for eventual release from the host cell. HIV integrase acts at a point in the HIV life cycle in between that of the reverse transcriptase and protease enzymes. Inhibiting HIV integrase, like inhibiting any of the other critical HIV enzymes, is an effective means of shutting down the process of HIV replication.

Another reason that HIV integrase is an attractive therapeutic target is that, like reverse transcriptase, no integrase activity is normally present in human cells. The activity of integrase is unique to HIV, and inhibition of this enzyme has little chance of disrupting the normal function of cells in the body. This fact alone could dramatically reduce the incidence and severity of side effects associated with HIV integrase inhibitors.

The development of HIV integrase inhibitors with therapeutic potential has proven a formidable challenge, however. Scientists

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An interview with Dr. David Hone—

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we would want to express the envelope protein the same way as a human cell would express it. This resulted in our turning our attention to a DNA vaccine and the possibility that bacterial vectors may be suitable delivery vehicles for them.

But not only did it turn out that we could effect transfer of DNA from a bacteria to the mammalian host, and induce immune responses against those proteins including mucosal antibodies, but that it was better than if the bacteria just expressed the protein by itself as a denatured structure. We're using the strategy not just to deliver envelope, but other antigens of HIV, notably as I mentioned earlier, proteins like Tat and rev, that are what we call "early antigens" because of the role they play very early in the replication cycle of HIV.

Searchlight: How far away are you from clinical trials?

Hone: Currently, my collaborator for over 10 years, Dr. George Lewis, and I are planning to initiate clinical trials within the next 18 months. We have an advantageous situation at the University of Maryland in that we collaborate with Drs. Carol Tacket and Myron Levine at the Center for Vaccine Development, who are experts in bacterial vector technology and have a longstanding set of clinical protocols for vaccinating individuals using bacteria that are essentially harvested directly off an agar plate.

Searchlight: More is known about HIV than any other virus, and a lot is being learned about

immune responses in general from the study of HIV. How do you think that will impact vaccine development for other diseases?

Hone: Undoubtedly it will strongly benefit the vaccine community in general. We're having to learn how to induce immune responses, not just in the systemic compartment as we've done traditionally with injected vaccines, but for the first time we are really having to develop effective mucosal vaccines. That will have benefits downstream, because by far the majority of infectious agents are acquired at mucosal surfaces.

In addition, we're learning a lot more about how the effector arm of cellular immunity clears and eliminates viruses and we can only benefit from that information in the broader context of other viral infections such as papilloma virus and hepatitis B and C viruses, which are other notable problems that we face on the horizon.



Active virus despite effective therapy—

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have mapped the three-dimensional structure of the active site of HIV integrase, but it appears that clinically useful drugs with anti-integrase activity are still a long way off. "Integrase inhibitors have been very slow in coming, and I don't see any particular light at the end of the tunnel," said Anthony Fauci, MD, Director of the National Institutes of Allergy and Infectious Diseases. "The problem has simply been in the development of specific inhibitors that work."

One of the obstacles to the development of effective integrase inhibitors has been the lack of correlation between integrase inhibition assays in the laboratory and the effects of the same compounds on HIV replication in cell culture systems. Purified HIV integrase has been exposed to vast numbers of potential inhibitors in laboratory screening studies, and dozens of potential drug candidates have been identified. The problem is, many of these putative integrase inhibitors have proven very nonspecific; that is, they inhibit other purified enzymes in addition to HIV integrase. Other promising candidates have simply proven deadly to normal healthy cells.

Despite these hurdles, optimism remains high that safe and effective HIV integrase inhibitors will eventually be developed. The most promising candidate to date is zintevir, a product of Anorex Pharmaceuticals, The Woodlands, Texas. Also known as AR-177, zintevir is actually a synthetic form of DNA that inhibits both purified HIV integrase and the replication of HIV in cultured cells. Curiously, while zintevir inhibits

purified integrase in the laboratory, that is almost certainly not how the compound blocks HIV replication in cells. Rather, in cell culture studies, zintevir appears to prevent the binding of HIV surface proteins to CD4 receptors on cells. Of course, this finding does not affect the drug's potential value as an HIV inhibitor. If clinical trials currently underway show zintevir to be safe and effective, the mechanisms of HIV inhibition can be figured out later. But for the time being, researchers must continue to struggle with the irksome discrepancies between the effects of HIV integrase inhibitors in test tubes and living cells.

Novel Agents and Strategies

There is no shortage of novel approaches to the identification and development of potential therapeutic agents and strategies for the treatment of HIV infection. Not all of these strategies will ultimately prove useful, and not all of these experimental drugs will find their way into clinical practice. An important point to remember, however, is that the anti-HIV drug development pipeline is full, almost to the point of bursting. A host of investigational anti-HIV drugs and strategies are in the works, and most of these interventions show great potential. There is no question that in the new millennium, the treatment of HIV infection will become simpler, less toxic, and more effective. And that alone is something to celebrate.



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❖ Hydroxychloroquine (in combination with hydroxyurea and didanosine): A study to determine the antiviral activity & safety of hydroxychloroquine in combination with hydroxyurea and Videx® (ddl or didanosine).

❖ Tipranavir™: A study to determine the safety & effectiveness of a new kind of protease inhibitor.

❖ Zerit® (stavudine, d4T): A study to determine the antiviral activity & safety of extended-release d4T compared with standard Zerit®.



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For further information on trial enrollment or joining the Priority Notification Program, please call Corie at 310/358-2429.

*ICCAC, abstract 1-179, 1997.

Para información en español, llame al 310/360.3876.