Forum for Collaborative HIV Research

Immunologic Markers to Evaluate Immune-Based Therapies in HIV Disease
Meeting Report

February 6, 2001

Chicago, Illinois

Scientific Chair:

Alan Landay, Ph.D.

The Forum for Collaborative HIV Research, a project of the Center for Health Services Research and Policy at the George Washington University School of Public Health and Health Services, was founded in 1997. The goal of the Forum is to facilitate discussion regarding emerging issues in HIV clinical research and the transfer of research results into care.

The Forum is a coalition of government agencies, clinical researchers, health care providers, pharmaceutical companies, and patient advocates. The Forum is governed by an Executive Committee made up of representatives from each of the above named constituency groups. The Executive Committee determines the subject and scope of the Forum projects. The Forum brings these constituencies together to identify gaps and impediments in the understanding of the medical management of HIV disease and develops recommendations to fill those gaps. The Forum is a public/private partnership, which receives financial support from its governmental and industry members and with in-kind support from its membership within the academic research, patient care, and advocacy communities.

For more information about the Forum or to download reports from this meeting or prior ones, visit the Website at

www.hivforum.org

Several people assisted in making this meeting possible and provided invaluable input. The Forum first would like to thank the Scientific Chair, Alan Landay, Ph.D. for his time and effort in planning this meeting. Mark Mascolini did a wonderful job of writing up the notes from the meeting and preparing this report and Forum staff member Houtan Movafagh patiently handled all the meeting logistics.

We would also like to thank Agouron Pharmaceuticals and GlaxoSmithKline for providing unrestricted grants to support this meeting.

David Barr – Executive Director
June Bray, Ph.D – Deputy Director

The Forum for Collaborative HIV Research convened a meeting to discuss ways to promote the selection, refinement, and evaluation of immunologic markers used to assess immune-based therapies in people with HIV infection. Attendees included immunologists and other scientists and clinicians from academia, industry, and federal agencies. Alan Landay (Rush Medical College) chaired the meeting. Several points emerged from the discussion:

- Immunologists should identify and validate surrogate markers of efficacy for immune-based therapies instead of relying on the FDA for direction in selecting markers.
- A few key efficacy markers of immune therapies should be selected for intense scrutiny rather than diluting the effort by pursuing scores of markers.
- Consensus emerged that a good marker to study is the ability to mount an immune response to a scheduled immunization with an immunogen that evaluates the individual response to an opportunitstic pathogen.
- Attention should focus on whether an absolute rise in CD4 cells is an appropriate efficacy marker for immune therapies, or whether trials will also have to demonstrate the functionality of those CD4 cells.
- A better assay of the lymphoproliferative response to antigen must be developed.

After a welcome and introduction by June Bray, Deputy Director of the Forum, Dr. Landay offered a brief summary of the December 7-8, 2000 meeting of the Forum to discuss immune-based therapies and related issues. He characterized those sessions as an excellent culmination of the past decade's work in the area of immune reconstitution, immune therapy, and immune markers. One outcome of that meeting was the suggestion to hold smaller, more focused meetings that concentrate on well-defined topics. The February 6, 2001 meeting was the first of those more focused sessions.

Dr. Landay summarized several other recommendations made and goals set at the December 7-8 meeting:

1. Examine obstacles to immune-based therapy development, including lack of structure from bench to bed, pathogenesis research, study section education, new mechanisms for RO1-like research, and incentives for industry.
2. Convene a selection committee to identify immune-based therapies ready for development.
3. Establish guidelines for development of new immune-based therapies to help determine when work should continue with a specific therapy.
4. Identify alternatives to clinical endpoints to evaluate immune-based therapies.
5. Determine what immune markers can be used in trials of immune-based therapies.
6. Select assays ready for further development, refinement, and evaluation.
7. Develop timelines and commit resources.

The December 7-8 meeting reached a consensus that work should focus on the most promising candidate assays rather than attempting to evaluate a wide range of assays.

These issues have gained urgency, Dr. Landay said, because recent research demonstrates that HIV cannot be eradicated with antivirals. As a result, work must move forward on alternative strategies—including adjunctive immune-based therapies. ***Identifying and validating immune markers are essential first steps in studying immune agents in humans.***

"The answer lies in this room"

Speaking for the FDA, Linda Forsythe said the agency's position on regulatory approval of immune-based agents had not changed since the December Forum meeting: The FDA wants to see reductions in plasma HIV RNA (viral load) as an efficacy marker for immune therapies.

Fred Valentine (New York University) reminded colleagues of a dichotomy in responses to immune agents. Vaccines can reasonably be expected to exert an effect on plasma viral load, he said, but other agents may only stimulate cytokines. The difficulty facing the group, as Dr. Valentine saw it, was defining what cytokine changes may signal efficacy.

Brenda Lein (Project Inform) noted that her discussion with the FDA indicated an openness to consider markers other than plasma viral load—if the HIV immunology community can reach some consensus on the issue. Lein argued that "the answer doesn't lie with the agency; the answer lies in this

room." If certain markers can be validated, she believes the FDA would endorse those markers. So immunologists must determine what markers to assess and then must convince their peers to help confirm those markers.

Richard Ginsburg (Wyeth-Lederle Vaccine) endorsed that opinion. He objected to what he sees as over-reliance on the FDA "to try to determine where science is." Dr. Ginsburg strongly doubts that the FDA will fail to accept evidence of immune function derived from scientifically sound studies.

Dr. Forsythe (FDA) confirmed the impression that the FDA remains open to evidence about immune markers. "We want to hear what people have to say at these meetings," she maintained. "We're very open. We're looking to all of you for the answers, in one sense."

Seeking a broad model of immune protection

Jonathan Kagan (National Institute of Allergy and Infectious Diseases) argued that studies should seek to validate markers that are known to confer clinical benefit. "The best immune-based therapy," he maintained, "is the best antiviral therapy." More attention should focus on what happens to the immune system when antiretrovirals lower viral load, and on how those changes account for improved immunity. Dr. Kagan urged colleagues to be "humble" about soluble immune products and to "look to efficacious [antiviral] therapy for guideposts to future immune therapies." He maintained that any immune marker can be validated in the context of phase I/II immune-based intervention trials.

Pat Bucy (University of Alabama at Birmingham) reiterated the "fundamental distinction" between lowering viral load through direct intervention (such as with a vaccine) versus general immune stimulation, for example, with interleukin 2 (IL-2). Current antiretroviral therapies are so potent that clinical endpoints can be used to evaluate immune-based therapies only in large and long trials. At this point, though, Dr. Bucy believes the FDA will still consider only clinical endpoints and viral load in considering new products.

Gail Skowron (Brown University) framed the same point in a different way. Antiretroviral therapy, she said, does two things: It lowers viral antigen and raises CD4 T-cell counts. One of those effects, probably raising CD4 counts, has reduced HIV-induced morbidity and mortality. The best-studied immune-based agent, IL-2, has only one of those effects, boosting CD4 counts.

Because of these realities, Bucy continued, one pivotal question is whether a general immune modulator can be used not as stand-alone agent, but to amplify efficiency of the immune response. In that context, one could "fall back on viral load" as the primary endpoint of a clinical trial.

Michael Lederman (Case Western Reserve University) noted that, for an HIV-specific intervention, some aspect of virologic control is a legitimate and valid readout. But that effect must be placed in context. For example, someone might be treated with "a very aggressive drug" that blocks viral replication but may not be in the patient's interest because of unwanted effects. The challenge, he maintained, is to "try to develop agents that enhance the immune responses in a more general way. And that's going to be tough because we don't have an easy way of getting clinical endpoints yet."

Proving the functionality of CD4 T cells

David Sahner of Chiron, which makes the IL-2 product, agreed with the distinctions others made between types of immune products. For antiretrovirals, he said, both viral load and CD4 counts have been validated as type II surrogate markers. Because IL-2 also raises CD4 T-cell counts, the question becomes whether those T cells are functional. If they are, "that would be good fodder for discussion," he argued, because studies show that IL-2 has no deleterious impact on viral load when given with antiretrovirals. Thus he believes the critical issue is how to define functionality of CD4s.

Merril Gersten (Agouron Pharmaceuticals, La Jolla) and Dr. Valentine noted that several studies demonstrate the safety of stopping prophylaxis for opportunistic infections when potent antiretrovirals control viral replication and boost CD4 counts. It should be possible, they reasoned, to demonstrate the activity of IL-2-induced CD4 gains when such prophylaxis stops in these patients.

Dr. Lederman agreed with the concept of evaluating CD4 cell function in that way, but he worried that such a trial would be difficult because it would be hard to determine what a reasonable control arm would be.

Dr. Valentine noted that CD4 function can now be assessed in two ways, by their response to antigens of opportunistic pathogens and by restoration of T-cell receptor repertoire. He argued that any agent shown to raise CD4 levels and restore repertoire should be considered immunologically effective.

Dr. Lederman voiced concern over whether measuring T-cell receptor repertoire expansion would prove a universal marker because some agents may have certain immune benefits without

expanding the repertoire. He observed that assessing immune function could prove as difficult as clinical endpoint studies. But he believes the problem can be addressed in stages. Natural history studies have already been done, as have a few cross-sectional studies of patients who don't sustain a CD4 rise. The third step will be to use enhancement of immune responses as a means to help develop novel agents. Demonstration of enhanced responses would not necessarily be sufficient for approval of new agents, but as a "green light" for subsequent stages of analysis.

Is there a valid marker besides CD4 and RNA?

Donna Mildvan (Beth Israel, NY) recalled that CD4 count was among the first surrogate markers. Although the FDA granted antiretrovirals accelerated approval on the basis of CD4 increases, investigators learned that CD4 counts did not completely explain an agent's immune-enhancing effects. For example, Dr. Mildvan recounted, an analysis by Harvard statistician Stephen Lagakos showed that the survival benefit in an early AZT trial greatly exceeded what could be explained solely by a CD4 increase.

What was the *X* factor that explained the additional benefit? Attempts to find out led many to advocate one marker or another as this additional factor. But, Dr. Mildvan argued, "I don't have any evidence from my clinical perspective at the bedside that there *is* another marker waiting to be discovered besides CD4 and RNA." Cohort studies and clinical observations indicate that patients with viral suppression but persistently low CD4 counts don't do well. That raises a basic question, she suggested: "Do we need another marker to tell me this patient needs another intervention or a better antiviral?"

Dr. Landay sought to focus the discussion of this point with a few questions: Where are we with immune-based therapy? Antiviral therapy has worked well, but no one knows how long patients can be maintained with current antiretrovirals. If they cannot be maintained for more than a few years, will patients need immune therapies to continue doing well clinically?

Richard Pollard (University of Texas) proposed that one goal may be to identify an immune agent that would allow clinicians to delay starting antiretrovirals for a substantial period, perhaps 3 years. He suggested that such an agent would stand a good chance of winning a license from the FDA.

An immunization-based response model

If the goal is to develop immune-based therapies that enhance responses in a general immune-enhancing way instead of via an HIV-specific path, said Dr. Lederman, then research must identify "a final common pathway that reflects protection against opportunistic infections." But since there are few opportunistic infections in 2001, immunologists must devise some model that will reflect protection from those infections. That model must not be specific to any one intervention, but must be broadly applicable to immune-based therapies, according to Dr. Lederman, "otherwise we're going to be reinventing the wheel with every immune-based therapy."

Dr. Lederman encouraged discussion of whether "a first-pass at a model for opportunistic infection" might be the ability to mount an immune response to a scheduled immunization. As a measure of adaptive immunocompetence, "I propose this because it's the closest thing I can think of to an opportunistic infection," Dr. Lederman explained, "and there are a variety of reasons why such a protein might be feasible." The difficulty would come in determining how much of a response should be considered sufficient to confer clinical benefit.

Several attendees agreed that Dr. Lederman's model is a reasonable way to assess or validate immune responses. Dr. Valentine noted that opportunistic infections do develop in occasional patients whose CD4 counts increase during antiretroviral therapy. What distinguishes those patients is their lack of lymphocyte proliferative responses to that particular antigen, for example, *Pneumocystis carinii*. The opportunistic infection then stimulates the missing antigen response. If enough of these rare individuals could be studied, Dr. Valentine proposed, the ability to gain such responses could be taken as a measure of immune function.

Dr. Sahner raised another stumbling block to the study of immune stimulation: the lack of a standardized assay for lymphoproliferative responses. "I'm struck by the heterogeneity of the lymphoproliferative assay [LPA] data," he said. Chiron is anxious to collect as much data as possible in its clinical endpoint study of IL-2, he added. But the LPA results he's seen from other studies make it difficult to know how useful those data are.

On the other hand, Dr. Sahner continued, antibody titers generated in vaccine studies can be correlated with clinical protection. If a certain immune-based therapy does generate such antibody

responses, he wondered, "would that constitute a meaningful argument that you've done something good for the patient?"

Dr. Valentine strongly encouraged Chiron to track as many laboratory markers as possible in its clinical endpoint trial of IL-2. In that way, the study may be able to validate certain of these markers because the study will have clinical endpoints.

Clinical endpoints or CD4 gains?

Ronald Mitsuyasu (University of California, Los Angeles) argued that demonstration of clinical benefit remains the sine qua non of any agent proposed for the treatment of HIV infection. That clinical benefit can be broadly conceived, he noted. Besides the obvious benefit of prolonged survival, a trial might also measure endpoints such as reduced rates of opportunistic infection, or decreased reliance on antiretrovirals with their accompanying toxicities. But some clinical benefit must be demonstrated before he would feel comfortable routinely prescribing any agent.

"I don't think we're going to get around clinical endpoints," Dr. Mitsuyasu concluded. "If [immune therapies] don't have clinical benefit, you don't move them forward into practice."

Brenda Lein concurred that, with IL-2, clinical endpoints are essential. "There's not a consensus on what the compelling evidence should be short of that," she maintained. But she suggested that the two ongoing clinical endpoint studies of IL-2 needn't conclude before the FDA is asked to consider accelerated approval of IL-2 based on data collected to date.

Dr. Bucy argued, though, that a case can be made for functional CD4 gains with IL-2, and that such functional improvement would be a strong signal of clinical benefit from IL-2. To make his point, Bucy invoked the train wreck metaphor posited by retrovirologist John Coffin of Tufts University. If an infected person is a train approaching a ravine with a washed-out bridge, viral load represents the speed of the train and CD4 count represents the distance to the ravine. Bucy proposed that antiretroviral therapy only stops the train, and it doesn't stop if forever because resistance and toxicity limit its durability. IL-2, on the other hand, may *back up* the train from the ravine by adding substantially more CD4 cells.

If that CD4 "cushion" adds another 5 years of health, "I think it's an excellent assumption that the CD4s are functional," Bucy said. No one has turned up any evidence, he added, that "CD4s grown

in the hothouse of IL-2 are not as good as" CD4 cells not expanded by IL-2 therapy. "How does a CD4 cell know where it was grown?" he wondered.

But Dr. Skowron warned that relying solely on absolute CD4 changes could prove a "house of cards" because if one study participant with a CD4 count of 500 cells/µL comes down with *Pneumocystis carinii* pneumonia or lymphoma, it will appear that the CD4 cells are not functional and the house of cards could collapse. A marker of functionality, she argued, would protect from such a collapse.

Suboptimal lymphoproliferative assays

Dr. Lederman proposed that one of the more important populations to study consists of people who have a good virologic response to antiretrovirals but gain few CD4 cells. Their CD4 count probably stays flat because they don't have a functional thymus. Such individuals deserve special research attention because strategies must be devised to enhance their immune responses.

He also stressed the urgency of developing a better assay of lymphoproliferation. Current assays, he said, are suboptimal. The ability of CD4 cells to react to antigen is not necessarily a marker of function, if those cells don't proliferate. A better lymphoproliferation assay could verify restoration of CD4 cells against opportunistic pathogens.

Dr. Sahner suggested convening a special working group to devise a standard methodology for lymphoproliferation assays. But Dr. Bucy argued that the problem is not methodological. The heterogeneity of T-cell function is more complex than most virologists realize, he maintained. Proliferation per se is not the issue as much as effector mechanisms, because those are the deficient mechanisms in a poor immune response.

Dr. Landay closed the meeting by reiterating the Forum's plan to hold small meetings focused on just a few questions. This session suggested that a key issue for future discussion is whether CD4 increases alone should be further evaluated as a marker of immune therapies, or whether it is also necessary to demonstrate CD4 cell function. He re-emphasized that a few key markers should be selected for intense scrutiny rather than diluting the effort by pursuing scores of markers.

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