OUR ROOTS ARE GROWING after page 12

Summer, 1996

SEARCHLIGHT

QUARTERLY NEWS FROM AIDS RESEARCH ALLIANCE

The National Leader in Fast-Track AIDS Research

What's News—

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Clinical Research

VICEL INCORPORATED gives AIDS RESEARCH Alliance the go-ahead for the first human clinical trial in the nation of **Subcutaneous Epithyme™**, a whole protein, thymic stromal cell derived immune stimulant that has been shown to restore immune function in FIV-infected cats.

(Article on Page 3)

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New immune-based therapy moves into preclinical development. AIDS RESEARCH Alliance will be the trial site for first proof-of-concept study of the **CDR1 peptide**. Immunization with this peptide has been shown in mice to reverse the aberrant cytokine production of retroviral infection. A related peptide is being investigated for the treatment of **multiple sclerosis**, an autoimmune disease.

(Article on Page 7)

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22 volunteers have been enrolled by AIDS RESEARCH Alliance in the nationwide Phase III clinical trial of **Remune®**, the HIV-1 immunogen developed by Dr. Jonas Salk at **The Immune Response Corp**. AIDS RESEARCH Alliance was first in the U.S. to enroll patients among 30 sites chosen.

(Article on Page 6)

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Chinese Government will collaborate with AIDS RESEARCH Alliance in an expanded, dose-escalating Phase II study of **Allicin** for the treatment of *Cryptosporidium parvum* diarrhea. Results of the Phase I study were presented at the **XI International Conference on AIDS** in Vancouver, B.C.

(Article on Page 4)

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Combination cytokine study concepts, based upon **IL-2** and **IFN-γ** pilot study results, move forward in preclinical development. Details are being sorted out with **Chiron Corp.**, **Genentech**, and **Immunex Corp**. AIDS RESEARCH Alliance expects to make announcement soon regarding an innovative series of combination cytokine studies for patients with advanced HIV disease.

(Article on Page 4)

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Fund-raising & Development

UNCLE SAM employees pledge over $333,000 to support AIDS RESEARCH Alliance. Pledges were made via the **Combined Federal Campaign**, the workplace giving program run by the government to make it easier for federal employees to support charitable causes. This represents our first year in the campaign and will help us fund several critical new research programs.

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"A Cocktail Party Among Friends" held April 16 was a great success and a first for AIDS RESEARCH Alliance. Hosted by Board member **Matt Redman** at his beautiful Hollywood Hills home, this event was an entertaining and informative evening drawing over 75 guests.

(Article and Photos on Page 18)

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Celgene Corporation, Warren, NJ, was the first to start the ball rolling and offer to share in the cost of a full-page ad for AIDS RESEARCH Alliance in the National Edition of the **New York Times** on July 9 to coincide with the opening of the XI International Conference on AIDS in Vancouver, B.C. **Cel-Sci Corp.**, **Immune Response Corp.**, **Immunex Corp.**, and **Agouron Pharmaceuticals** generously joined in to ensure all costs were covered.

(See Centerfold and Article on page 16)

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Let There Be Hope—AIDS RESEARCH Alliance co-sponsored with the Anti-viral Research Institute a seminar at the Pacific Design Center on April 28 focused on **Immune Restoration for HIV**. This well-attended event was well received and follows last year's participation in a similar seminar.

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AIDS RESEARCH Alliance participated in **Bill Rosendahl's** Public Affairs ***"AIDS Update"*** TV Special on Century Cable Channel 10 Los Angeles which aired during the week of June 14–22. The one-hour show tackled the latest developments in AIDS research, with political and health provider segments.

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Immune-based Therapy —

Subcutaneous Epithyme™ Debuts in Proof of Concept Phase I Clinical Trial

A Pilot Study to Evaluate Safety and HIV-1 Directed Immune Responses in Severely Immune-Compromised HIV-1 Infected Subjects.

In HIV infection the progressive depletion of $CD4^+$ cells and other cells (macrophages, dendritic cells) that are integral to the proper functioning of the immune system may be secondary to the destruction of lymphatic tissues, including the thymic gland tissues which are known to be selectively targeted, damaged or involuted directly by the virus.[1,2]

While combination antiretroviral and prophylactic therapy has extended life expectancy and improved quality of life for persons infected with HIV, a new and growing patient population has emerged that comprises people with significantly depleted immune systems. Although these patients may have recurrent clinical manifestations of minor opportunistic infections accompanied by fevers, they are otherwise relatively healthy. However, the considerable degree of immunologic dysfunction caused by HIV disease has led to increased interest in methods of immune stimulation and reconstitution.

Role of the Thymus

The thymus is responsible for the differentiation, specialization, maturation and activation of thymocytes, or T lymphocytes (hence T cell, to denote thymus-derived lymphocyte). The thymus is also a primary site of age-related atrophy, and necrosis caused by direct infection with HIV-1.[2] Immune dysfunction may result from the lack of or alteration of specific thymic proteins required in the thymus for the natural developmental processes.

Epithyme™ thymic stromal cell derived immune stimulant has been studied over the past fifteen years for its potent immune stimulatory effects. Epithyme™ is a large (50K Dalton) protein derived from cloned epithelial cells from the bovine thymus. Similar activity from mouse[3] and human[4] thymic stroma has been described. Further characterization of a putative thymic stromal cell growth factor, its mode of action, and distinction from other known lymphokines has been published by two different groups.[5,6]

"The thymus is an essential organ for development of cells of the immune system. This development is controlled by humoral factors and cytokines produced in thymic stromal and lymphoid cells. The developing cells of the thymus are susceptible to infection with HIV. Treatment with thymic factors could be useful in regeneration of the immune system from uninfected early progenitors in patients whose viral load has been markedly reduced by antiviral therapy."

—Esther F. Hays, M.D.

Thymic stroma derived immune stimulant may play an essential role in intrathymic T-cell development in the context of T-cell growth promotion and T-cell repertoire selection, including clonal elimination of autoreactive cells.

Loss Of Immune Function

In a successful immune response, the destruction of HIV-infected cells by Cytotoxic T Lymphocytes (CTL) relies on the successful engagement of the T cell receptor (TCR) with a complex formed by viral peptide bound to a Human Leukocyte Antigen (HLA) Class I molecule on the infected cell surface. Researchers have demonstrated the potent ability of naturally occurring viable HIV to inhibit CTL activity by causing an unproductive but specific engagement with the TCR.[7]

This inhibition of CTL activity is greatly facilitated by the number of viable HIV mutants[7]—a pervasive mechanism of escape allowing viral persistence in the face of an otherwise active and effective immune response.[8] However, many experts believe that this process may also be related to thymic dysfunction. While the effects of HIV infection on the thymus, the thymic microenvironment, and the development of the T-cell lineage have been difficult to study, new data have shown that, regardless of CD4 count, the T-cell regenerative capacity of cells by HIV-infected patients *in vitro* is diminished.[9] In this case, the immune response and the rate of T-cell regeneration could theoretically be positively impacted by the replacement of thymic maturation product(s).

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Subcutaneous Epithyme™ —

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Among these natural thymic products, Epithyme™ appears to represent a major regulatory protein that contributes to the process of driving new progenitor cells.

Theoretical Rationale

Epithyme™ has been shown in animals to greatly enhance cytolytic T-cell responses to alloantigens.[5,6] Studies have suggested that a primary mechanism of action is the stimulation of $CD4^+$ T cells to produce interleukin-2 (IL-2).

"Treating AIDS solely with antiretroviral drugs has the same limitations as treating cancer with chemotherapy and X-ray alone. In both diseases, boosting T-cell immunity with a drug like Epithyme gives the body a far greater chance to conquer the invader without the development of drug resistance."

—Bill McDaniel, M.D.

However, unlike IL-2, Epithyme™ apparently needs to be present only for the initial 24 hours of the immune response. This finding suggests that Epithyme™ effectively enhances the amplification of T4 cell function, providing a possible explanation of its effects after only bi-weekly injections, both *in vitro* and *in vivo*.

A weak immune response (or lack of an immune response, or anergy) is a common manifestation in individuals with advancing HIV disease. Clonal deletions may also contribute to the loss of immune function and an increased susceptibility to opportunistic infections.

Epithyme™ may have the ability to improve or reverse both of these defects, amplifying the functionality of the T-cell population and providing the necessary signaling for the correct T-cell growth promotion and T-cell repertoire expansion. This would provide for an increase in the functionality and total population of T cells, partially as a result of the cellular expression of IL-2 by T lymphocytes in the presence of Epithyme™.

Naive Vs. Memory T Cells

Recent flow cytometric studies have identified several phenotypically and functionally distinct subsets of $CD4^+$ and $CD8^+$ T cells. Functional studies have assigned specific roles to some of these subsets. In particular, the terms "memory" and "naive" distinguish subsets which either contain or do not contain long-lived cells capable of mounting an immediate response to a specific antigen.

In vitro studies have also demonstrated that these subsets (CD45 RA and CD62L) have distinct functional capacities: in general, the memory subsets do not proliferate as well as naive subsets in response to generic mitogenic stimuli; however, the memory subsets produce a wider variety and greater amounts of many cytokines.[10]

Epithyme™ may have the ability to increase the naive population of both $CD4^+$ and $CD8^+$ T cell subsets and thus improve or correct a defect which effects both potential and functionality.

Viral burden in long-term survivors of HIV infection is a determinant of anti-HIV $CD8^+$ lymphocyte activity, including secretion of soluble antiviral factors, and, as such, is a viable marker to determine the progression of HIV disease.[11,12] It would be expected that an increase in the number and functionality of both T-cell lineages would provide for more effective direct clearance of HIV-infected cells and would thereby provide a corresponding reduction of the viral load.

Animal Studies

In a series of clinical studies,[13] Epithyme™ has been shown to be useful in the symptomatic treatment of FIV-infected cats (see article on page 21). First identified in 1987, feline immunodeficiency virus (FIV) causes a generalized immune deficiency syndrome in cats. Recent studies indicate that FIV disease shares many similarities with HIV-1 disease. After an initial mild, transient leukopenia, fever, and lymphadenopathy, remission occurs for 4-5 years.

Like HIV-1, FIV infects $CD4^+$ T helper cells which causes drops in white blood cell (WBC) counts and an increased susceptibility to opportunistic infections. Clinically, the disease is characterized by below normal WBC and a host of opportunistic infections that, like HIV, take advantage of a weakened immune system. Like HIV, FIV disease is chronic and progressive, and invariably fatal.

In early studies with cats, it has been shown that Epithyme™ thymic stromal cell-derived immune stimulant can enhance the immune status of FIV-infected cats with a significant improvement in clinical symptoms. The therapeutic effect under experimental conditions appears to be long-lasting.

Animal Vaccine Studies

A series of vaccine studies conducted in dogs (rabies and distemper vaccines) and cats (FIV vaccines) subsequently suggested that Epithyme™ could be used as a stand-alone immunotherapeutic for treatment of immunocompromised hosts.

Long-term Cat Studies

In a feasibility study, eleven (11) experimentally FIV-infected cats were given either placebo or Epithyme™ 1cc subcutaneously (under the skin) on a bi-weekly basis during a 5-week period. Blood samples were taken weekly and clinical observations were made daily.

Within 72 hours of the initial injection, cats in the treatment group showed marked improvement in respiratory symptoms. At weeks 1, 2, and 3 post initiation of treatment, lymphocyte counts were significantly enhanced in treatment versus control groups ($p<0.05$).[15]

Based upon these results, a larger study using field cats was begun in the spring of 1991. As observed in the feasibility study, cats improved significantly within 72 hours, as reported by the owners and confirmed by their vetrinarians upon the second visit two weeks later. At 4 weeks, a second blood sample was taken before the third injection of the initial three-dose regimen.

Follow-up injections were given at bi-monthly intervals or as needed. After 9-12 months, blood samples were obtained for long-term evaluation of lymphocyte levels and a follow-up exam was conducted to determine long-term effects of therapy.

Seven of eight cats are doing well after 4-5 years of treatment.

The Epithyme™ Story

The thymus gland is essentially the "heart" of the immune system. It is responsible for maturing and specializing cells, such as T cells (the T stands for thymus-derived), to perform their many different duties in the immune system. HIV directly infects and atrophies the thymus—making it impossible for the body to mature and replace T cells and other immune system cells as fast as it would like.

HIV infection damages key compartments of the thymus. Although the thymus naturally tends to shrink in size after puberty, HIV infection accelerates this process. After many years of infection, thymic function is diminished or marginalized as the course of HIV disease progresses.

"Man has never conquered a viral disease by antiviral agents alone. The only two that have, smallpox and polio, have been conquered by immunological means. The combination of antivirals and immune-based therapies may represent the best hope for the eradication of HIV."

—Terry Beardsley, Ph.D.

New antiretroviral drugs used in combination can already effectively reduce HIV viral load—the amount of virus circulating in the blood—to nearly undetectable levels. However, the damage already done to the immune system has been irreversible to date. Despite some low viral levels, HIV-infected patients continue to decline—partially, it is believed, as a result of a damaged thymus gland.

A therapeutic whole thymic protein, Epithyme™ has been studied over the past several years for its immune stimulatory effect. This protein, which is highly conserved among humans and animal species, is derived from a cell line recovered from the core of the thymus (hence, thymic stromal cell derived immune stimulant).

Researchers believe that Epithyme™ may play an essential role in T-cell development. For example, when a person is born with or develops diabetes, that person's pancreas is no longer able to produce insulin and insulin replacement is begun. As HIV disease progresses, the human thymus may no longer be able to produce the thymic proteins needed for T-cell maturation. Epithyme™ may replace one of these proteins. As a growth factor that may be needed for thymic maturation, Epithyme™ is distinguished from all known cytokines and lymphokines, hormones or other growth factors.

Epithyme™ has demonstrated benefit in cats with feline immunodeficiency virus (FIV). As FIV and HIV share many characteristics, FIV-positive cats provide an excellent animal model to evaluate new treatments for HIV. The typical survival time for cats at end-stage FIV is 3-4 months. Of the 22 cats, all with advanced FIV disease, treated with Epithyme™ for 3-5 years, all but one are still alive and healthy today.

AIDS RESEARCH Alliance will study Epithyme™ in seven individuals with HIV-induced immune dysregulation and suppression in an attempt to restore immune function, regain the ability to mature bone marrow-derived precursor cells into functional $CD4^+$ and $CD8^+$ T cells, as though the host's own thymus had produced these restricted and differentiated T cells.

—Peter Hale

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Maintenance doses are variable, but not more frequent than once per month.

An additional 14 cats with late-stage FIV infection have since been treated, thus providing long-term follow-up data on 22 cats who have been maintained on Epithyme™ treatment for between 3 and 5 years. After the initial induction phase, all animals have received injections at 30-60 day intervals. The combined data from these 22 cats showed a significant increase in both lymphocyte percentage and total lymphocyte count.[13]

All cats showed positive clinical responses—which, in many cases, appeared greater than the increases reflected in their lymphocyte counts. Among these 22 cats, all have been maintained on monotherapy with Epithyme.™

Safety

In all the animal studies performed to date, no adverse reactions have been observed or reported either at the local site of injection or systemically. As a highly purified natural product which appears to be very homologous among species, no serological responses have been observed across species. Mice do not respond *in vivo* to canine, human, or feline thymic stromal cell protein. In fact, several bovine thymic-derived peptides have an extensive clinical history, and despite no evidence of clinical efficacy, no serious side effects have been reported.[14,15] Despite repeated injections over a long period of time, Epithyme™ appears to be well tolerated and has been found to induce no undesirable side effects.

Reductions In Viral Load

In a study completed in 1994, a group of eleven FIV-positive cats which had been experimentally infected and observed in a university laboratory were treated with three weekly injections of 1 microgram of Epithyme™. These animals had only been infected with FIV for approximately 2 years and were all therefore in a latent stage of the disease.

Many cytokines and lymphokines, such as IL-2, IFN-γ, and IL-12, are being intensely studied for their potential to restore the immune balance disrupted by HIV infection. Among these, Epithyme is a novel protein that may go far beyond the others in helping to regenerate the effective immune response needed for recovery from HIV infection.

—George C. Fareed, M.D.

While hematologic parameters did not change in these clinically healthy cats during the four-week study period, viral load by FIV RNA PCR showed that four of the six treated cats had a reduction in their PCR value by an average of 46%.[13] Combined with the results from previous studies, this finding suggests that Epithyme™ has striking efficacy against FIV disease.

Based upon the similarities of FIV and HIV disease, including the loss of $CD4^+$ T cells and other aspects of the disease, these findings may have important implications for the treatment of HIV infection.

Study Objectives

1. To determine if Epithyme™ can safely be used in persons with HIV/AIDS when given by subcutaneous injection.
2. To determine if Epithyme™ may lead to improvements in immune function.
3. To determine if these improvements lead to a reduction in HIV viral load.
4. To determine, if these changes occur, whether they also lead to an improvement in clinical status.

Clinical Endpoints

1. Toxicity monitoring abnormalities as defined by: Amylase, CBC, Urinalysis, RNA PCR for HIV-1, and Chemistry panel 24.
2. Disease progression as defined by significant increases/decreases in the following laboratory parameters: RNA PCR, Thymocyte enumeration panel, HIV-specific CD4/CD8 CTL, CD4 and CD8 naive/memory cells(CD45RA and CD62L), and Short Form Health Survey.

Study Design

This Phase I clinical trial is a proof of concept (POC) and safety study. Seven (7) individuals that meet the inclusion/exclusion criteria of the protocol will receive five (5) doses of Epithyme™ as determined by their weight according to the dosage schedule. The minimum dose is 36 mcg. and the maximum dose will be 48 mcg. All treatments will be administered as subcutaneous injections over seven weeks/43 days and followed for eight weeks/56 days.

On Day One, a 4 mcg. test dose will be administered intradermally, 1 hour prior to the treatment dose and the study participant will be monitored for hypersensitivity as an indicator of potential systemic anaphylaxis.

One individual will receive treatment and will be followed for one week (through study Day 8) before the second individual will begin treatment. After the second individual has been followed for one week, enrollment will be open until the study is fully accrued.

The principal investigators will review all laboratory data from Day 1 and Day 4 on study participant One (1) and Two (2) before any additional participants are administered drug.

Materials

A 50K Dalton bovine protein expressed by thymic stromal epithelial cells, Epithyme™ is derived from live cells, under sterile laboratory conditions. It is harvested, purified and tested for biologic activity and filled in compliance with GMP standards. These precautions, however, do not preclude that another pathogen could be transmitted from the live culture via the supernatant harvested protein (Epithyme™) and infect the recipient.

Study Group

Seven (7) participants will be enrolled with $CD4^+$ cell counts of no less than 100 and no more than 250, and no major ongoing opportunistic infection(s). All participants should be on a stable antiretroviral regimen for 60 days or longer (or no antiretroviral treatment) combined with standard of care (SOC) prophylactic therapy.

Inclusion Criteria

1. A Karnofsky score of at least 65.
2. Life expectancy greater than 6 months.
3. Man or woman at least 18 years old and not older than 50, known to be infected with HIV-1 (measured by ELISA).
4. $CD4^+$ count greater than or equal to $100/mm^3$ and less than or equal to $250/mm^3$.
5. Have no prior history of clinically significant cardiac, pulmonary, neurologic, blood, liver, kidney dysfunction or hematologic problems and are in good general health as determined by a medical history, physical examination and laboratory tests which indicate lab values fall within pre-defined values.
6. Available to participate in this study for 4 months.
7. Have not received any other immunization, including influenza vaccination, within 4 weeks of study entry or any vaccine during study.
8. Have key baseline laboratory values within normal ranges.
9. Agree to use suitable contraception to prevent pregnancy.

Exclusion Criteria

1. Active or ongoing major opportunistic infection.
2. History of drug or alcohol abuse within the 12 months prior to study entry.
3. Currently taking corticosteroids, anabolic steroids, hormones, Human Growth Hormone, testosterone, cytokines such as interleukin-2 (IL-2), immune suppressants or any other immune altering agents including any vaccinations.
4. Have not been on a stable antiviral treatment regimen for the last 60 days.
5. Currently receiving chemotherapy to treat any type of cancer.
6. Participation in a clinical trial within the last 3 months.
7. Pregnant, breast feeding, or plan on becoming pregnant during the course of the study.
8. Use of immune modulating therapies within 8 weeks of screening.
9. Use of any thymic-derived proteins including Epithyme™ within 8 weeks of screening.
10. Score of more than 100 or less than 50 on SFHS.

Monitoring

Baseline evaluation will consist of a complete medical history including detailed information about the course of the patient's HIV infection, previous/current medications/treatments and a physical exam. On each visit, the patient will also complete a quality of life instrument, the Short Form Health Survey. Physician will assess the patient's general health status using the Karnofsky scale on every visit.

Patients will be asked to record any changes or event(s) out of the normal or of interest, that reflect a change in their clinical status related or unrelated to the study drug.

Flow Cytometry Analysis

In addition to viral load testing, the following laboratory tests will be performed:

- Thymocyte Maturation/ Enumeration Panel (3-Color Flow Cytometry)
- CBC
- CD3/CD4/CD8
- CD3+CD8+S6F1+
- CD4/CD45RA/CD62L
- CD8/CD45RA/CD62L

All flow data will be captured in list mode for future analysis.

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Side Effects

The side effects and adverse reactions of administration of Epithyme™ may include: anaphylaxis, fever, chills, fatigue, nausea, vomiting, headache, flushing, tightness of the chest, back pain, myalgia, sweating and hypotension, serum sickness, muscle weakness.

As with any foreign protein, Epithyme™ may produce an allergic or anaphylactic reaction. Anaphylaxis is the term used to denote the immediate, transient kind of immunologic reaction characterized by contraction of smooth muscle and dilation of capillaries due to release of pharmacologically active substances (e.g., histamine, serotonin), classically initiated by the combination of antigen (allergen) with mast cell-fixed, cytophilic antibody (chiefly IgE).

Anaphylactic reaction can also be initiated, by large quantities of serum aggregates (antigen-antibody complexes, and others) that activate complement leading to production of anaphylatoxin, a reaction termed "aggregate anaphylaxis." This reaction could be life-threatening.

Participants receiving SQ injections of Epithyme™ will be carefully observed for signs of anaphylaxis, such as syncope, hypotension and bradycardia. If any of these events occur, therapy will be terminated immediately and measures for resuscitation will be available for immediate use.

Data Evaluation

In this proof of concept/safety study, assessment of the efficacy of this therapy will be based upon percentage differences between baseline and interim values and baseline and final values.

A forty (40%) increase in $CD4^+$ cells and a fifty (50%) decrease in viral load by HIV RNA PCR will be determinants of benefit. The goals of the research protocol are to determine safety and efficacy and determine whether the results revealed from this study are encouraging enough to proceed to a larger scale clinical trial.

Modification Of Protocol

There may be indications for the modification of this protocol as the study proceeds. These indications will be documented as they occur but they will be reported to the Study Monitor within 48 hours of their occurrence.

Status

This study is currently enrolling.

Principal investigators:

George C. Fareed, M.D.
David Hart, M.D.
Robert Winters, M.D.

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