Subcutaneous Epithyme™ —

The FIV Connection

Why Cats May Be The Purr-fect Model For HIV Infection

by Peter Hale

Lessons From The Cat

Feline immunodeficiency virus (FIV) is a retrovirus and a member of a group of known immunosuppressive lentiviruses like SIV and HIV-1. FIV infection in cats causes a severe, chronic immunodeficiency-like syndrome which leads to feline AIDS. Like human AIDS, FIV disease is characterized by a progressive depletion of $CD4^+$ T cells, as well as macrophages and other cells that coordinate the activities of the immune system leading to immune system collapse and increased susceptibility to a host of opportunistic infections.

The recent findings that Epithyme™ has been shown in several *in vivo* cat studies to enhance the immune responses of FIV-infected cats and provide increased protection against opportunistic infections, as well as significantly prolong survival, provide tantalizing evidence of the safety and efficacy of Epithyme™ in an animal model system that closely mimics human AIDS.

Moreover, based upon the biological, clinical and immunological similarities of FIV and HIV disease, the results of these clinical studies suggest that Epithyme™ might be safely and effectively used in humans for the treatment of HIV.

The FIV Discovery

Feline immunodeficiency virus was first identified by scientists at the University of California at Davis in 1987 as a causative agent for a generalized immune deficiency syndrome in cats.[1] The new feline lentivirus was brought to their attention by a peculiar outbreak of disease in a large colony of pet cats in Petaluma, CA. Based upon their initial observations, the new virus was tentatively designated "feline T-lymphotropic lentivirus," abbreviated to FTLV.

"Feline immunodeficiency virus infection in cats is an excellent non-primate, small animal model. As a retrovirus and lentivirus (member of the AIDS virus family), many biochemical, clinical and immunological events that occur during FIV infection mimic HIV infection. Like HIV, a hallmark of FIV infection includes $CD4^+$ cell loss which leads to loss of immune function and immune suppression."

—Janet K. Yamamoto, Ph.D.
University of Florida

From the outset, scientists thought FTLV might provide a useful model for the study of human AIDS. The virus seemed more closely related to HIV-1 in terms of disease pathogenesis than to other known lentiviruses, such as the equine lentiviruses, which are not T lymphotropic and do not induce chronic immune suppression. As a highly T-lymphotropic virus with immunosuppressive properties, the newly discovered feline lentivirus appeared to be very similar to the primate T-lymphotropic retroviruses, such as SIV and HIV-1.

As soon as it was established that the newly discovered virus was a major cause of a chronic acquired immunodeficiency-like syndrome in cats, the FTLV virus was renamed FIV by its discoverers in 1988. Now recognized as morphologically and biochemically similar to HIV but antigenically distinct, FIV is considered an excellent model for HIV basic virological research. Moreover, since primates are difficult to obtain, it was realized that the naturally-occuring FIV in cats could provide an excellent, small animal model for HIV research.

Since FIV has been genetically sequenced, its position in the evolutionary tree of lentiviruses has become more clear. As a distinct lentivirus, FIV shares sequence homology with many other lentiviruses, but most closely with equine infectious anemia virus.

Originally believed to have evolved in parallel with HIV, most experts now believe that FIV evolved earlier. Across the globe, FIV is fairly well distributed geographically and is now believed to be widespread among the cat family. For example, African lions (but not Asian) have recently tested positive for FIV seroreactivity.

The discovery that there are fewer FIV strains than HIV-1 around the world also suggests that FIV may be more highly evolved than HIV. The number and wide variety of HIV-1 strains suggests that HIV is still evolving at a fast rate in the human and, as such, is probably the younger lentivirus.

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While lentiviruses are found in many species of animals, there appears to be a great deal of species specificity. The human lentivirus, HIV-1, appears more closely related to SIV than FIV. However, because of the limited availability and high cost of primates, scientists have discovered that FIV-infected cats can serve as an excellent, alternative *in vivo* animal model in which to study human AIDS.

Epidemiological studies suggest that the incidence of FIV is greater than 10% in areas of the U.S. and Canada, based upon the presence of serum antibodies to the virus core protein.[2] Overseas, FIV is apparently widespread occurring in both Europe and Asia. In Japan, the rate of infection is almost twice as high.

Experimental studies have indicated that biting is a highly efficient mode of transmission—and probably the most common. For this reason, feral cats are at higher risk than indoor domestic cats. There has never been any evidence that FIV can infect humans.

FIV Pathogenesis

Immunopathologic 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 lymphocytes 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, chronic gingivitis, upper respiratory infections, dermatologic lesions, diarrhea, loss of appetite, and anemia.[3]

In FIV disease, $CD4^+$ T cells are reportedly depleted by many of the same mechanisms as HIV in humans: FIV-infected $CD4^+$ T cells, as well as many uninfected bystander cells, are induced to die of apoptosis; FIV infection also induces giant cell formation similar to HIV syncytium formation.

> ***"The most compelling evidence of the efficacy of Epithyme is the fact that we have seen cats survive for five years with full-blown FIV disease with both increases in CD4 counts and clinical improvements in symptomology."***
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> ***—Terry Beardsley, Ph.D.***

Regarding host cell range, early *in vitro* studies demonstrated that FIV can replicate in primary feline blood mononuclear cells, thymus cells, and spleen cells, as well as in feline T-lymphoblastoid cell lines. Unlike feline leukemia virus (FeLV, see page 24) which can infect human cells, FIV has not infected any of the human cells tested thus far.

Thymus Atrophy

Studies conducted to date demonstrate that the thymus in FIV infection is progressively altered or damaged by FIV in much the same way as the thymus is damaged in HIV disease. Early studies in FIV-infected cats have shown that lymph nodes are also infected and damaged much like in HIV infection.

While FIV infection and depletion of intrathymic progenitor cells has not yet been demonstrated, mature thymocytes are productively infected and depleted in FIV disease. Like HIV, it is possible that thymic epithelial cells are also infected and damaged which could disrupt the production of growth factors normally secreted by these cells, thus providing a maturational block on developing thymocytes in the thymus.

Currently, there is no effective treatment for FIV infection or its symptoms. FIV disease is chronic and progressive, and invariably fatal. Cats seen in the animal hospital or clinic are usually in the later stages of the disease. As with human AIDS, antiretroviral therapy has been attempted experimentally using AZT, and alpha-interferon. In most cases, veterinarians can only prescribe supportive care, isolation, and ultimately euthanasia.

SQ Epithyme™

However, a series of clinical studies has shown that a putative thymic stromal cell derived growth factor, Epithyme™, is useful in the symptomatic treatment of FIV-infected cats *(Beardsley T, McDaniel W, et al. Manuscript in preparation. See Epithyme™, pages 8–10).*

Three separate studies conducted by Vicel Incorporated, Bonsall, CA, the biotechnology company that discovered and is now developing Epithyme™ for HIV infection, have demonstrated that Epithyme™ enhanced the immune status of FIV-infected cats with a corresponding, significant improvement in clinical

symptoms. Moreover, the therapeutic effect under experimental conditions appeared to be long-lasting.

A total of 22 FIV-infected cats to date have been treated with Epithyme™ and have responded to treatment. In the first study, seven of eight FIV-infected cats are still doing well after 4-5 years of treatment. Maintenance doses were variable, but not more frequent than once per month.

"Cats with FIV-related disease demonstrated benefit when treated with Epithyme. We saw improvements in symptomology as well as prolonged survival. Most of these cats were severely immune compromised when brought into the clinic and suffering from numerous complications associated with FIV."

—Alice Villalobos, D.V.M.

Success in the Cat

Combined with a second group of 14 cats with late-stage FIV infection, long-term data have been compiled on 22 cats maintained on Epithyme™ treatment for between 3 and 5 years.

The combined data from these 22 cats showed a significant increase in both CD4 lymphocyte percentage and total lymphocyte count.

All cats showed positive clinical responses, in many cases greater than the increases reflected in their lymphocyte counts, as reported by veterinarians.

To date, there have been no reported adverse reactions attributable to Epithyme.™ Despite repeated injections over a long period of time, the product appears to be well tolerated and has been found to induce no undesirable side effects.

Role Model

In FIV-infected cats, Epithyme™ has been shown to significantly enhance both cellular and humoral immune responses as measured by clinical and laboratory parameters, including responses to infectious agents, diminished disease symptoms, prolonged survival, and increased laboratory lymphocyte values.

These improvements in immunocompetence have translated into increased protection of cats from the infectious complications of FIV disease. In the cat, Epithyme™ appears to be safe, and has shown striking efficacy against the clinical complications and lymphopenia that are characteristic of FIV infection, both in experimentally-infected animals and in late-stage animals with naturally-acquired disease.

Can these results be duplicated in humans?

In the case of Epithyme™, it is hoped that the answer will soon be forthcoming as a result of the first proof of concept study of Subcutaneous Epithyme™ announced in this issue of *SEARCHLIGHT*.

This clinical trial will be conducted among seven (7) HIV-infected individuals with fairly advanced HIV disease. The four-month study will track T-cell proliferation, HIV viral load, and other immunological parameters to determine whether this novel thymic derived growth factor can achieve the same cellular and humoral immune responses in humans as it did in cats.

Based upon the virological, immunological and clinical similarities of FIV and HIV disease, especially the loss of $CD4^+$ T cells, thymus atrophy, and other aspects of FIV disease, many scientists believe that cats could turn out to be the perfect role model to test other concepts for HIV disease.

Future Uses

In addition to Epithyme™, there are many other novel immune-based therapies for HIV that could be tested in the cat, both for the treatment of primary HIV infection, as well as for more advanced HIV disease.

One program already under way using the cat model is a bone marrow transplantation study in FIV-infected cats. This study will use bone marrow from healthy cats (i.e., using allogeneic system) and not from another species. However, like the Jeff Getty experiment, this will be combined with radiation (Yamamoto, personal communication), as well as triple-drug antiretroviral therapy. Current plans are to use total body radiation and not just lymphoid radiation.

Moreover, the promise of a successful FIV vaccine (*see page 25*) suggests that FIV and cats can provide a valuable source of new ideas for developers of more effective AIDS vaccines.

In this exchange of ideas, cats can also benefit. Since HIV infection mimics FIV disease in cats, many of the advances in the treatment of HIV, such as antiretrovirals and new treatments for opportunistic infections, could lead to new therapies for the treatment of FIV in cats.

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