Exhibit 7 – Part 2 of 2

ble at the cell surface and are released by budding. Interferon α (IFNα) can inhibit HIV replication in vitro,[19,209,210] and it is believed that it may act at least in part at this step. IFNγ and IFNβ have also been shown to have partial anti-HIV activity in vitro.[211,212] These agents have been shown to have activity both in reducing HIV production by chronically infected cells as well as reducing de novo infection. IFNα also has some clinical activity against Kaposi's sarcoma, and there is some evidence that it may have some anti-retroviral activity in a subset of patients with high numbers of CD4 cells.[213] As will be discussed below, the anti-HIV of IFNs is synergistic with that of the dideoxynucleosides,[210] and this combination is now being tested in several clinical trials.

COMBINATION THERAPY OF HIV INFECTION

So far, this discussion has focused on single agents for the therapy of AIDS and related disorders. However, it may be an unreasonable expectation that any single agent will be the optimal approach for the treatment HIV infection. Instead, combinations of agents will probably be found to be superior to any available single agent. There are a number of potential benefits of carefully selected combination regimens. One benefit is the reduction of toxicity. For example, taking advantage of the different toxicity profiles of AZT and ddC, our group has initiated a trial of alternating AZT and ddC therapy.[10] Preliminary results from this trial, which is still ongoing, suggest that some patients can have a sustained anti-HIV effect and that the toxicity from either drug may be reduced as compared to full-dose single-agent therapy.[214] Other regimens exploring alternating or simultaneous AZT and ddC are now being tested by the ACTG.[215] Also, Pizzo et al have found that a combination regimen can provide a sustained anti-HIV effect in children.[216] By analogy with the multiple-drug treatment of tuberculosis, another potential benefit of combination therapy may be to prevent or delay the development of HIV resistance. This may apply in combinations of dideoxynucleosides because HIV isolates resistant to AZT appear to preserve their sensitivity to other dideoxynucleosides (vide supra). Indeed, we have preliminary evidence that HIV isolates from some patients on an alternating AZT and ddC therapy for up to 18 months preserve their sensitivity to both drugs.[99] Our group is presently exploring a four-drug alternating regimen of AZT with acyclovir, ddC, and ddI.

Certain combinations of anti-HIV agents may have synergistic activity when used together,[173,177,210,217,218] and this may provide yet another rationale for combination therapy. One might expect synergistic interactions to occur particularly with agents that act at different steps of the HIV life cycle. For example, in vitro synergy against HIV has been demonstrated when dideoxynucleosides are used with rCD4 or IFNα.[210,217,218] Indeed, such synergy may serve to increase interest in the development of agents that work at different steps in the HIV life cycle. Extending this approach, Johnson and Hirsch have shown that complete suppression of HIV replication in vitro for 28 days using a three-drug regimen of AZT, rCD4, and IFN[219]; this represented an improvement over the results obtained with two-drug combinations of those agents. However, it is worth noting that not all drug combinations are synergistic, and in fact, antagonistic interactions can sometimes be observed. For example, ribavirin blocks the anti-HIV activity of AZT in vitro[220] by reducing its phosphorylation. This observation serves as a warning against the ad hoc use of drug combinations without in vitro testing.

Although not strictly combination anti-HIV therapy per se, it may be desirable to administer drugs that suppress certain opportunistic infections along with anti-HIV agents. The regulatory proteins produced by certain herpes viruses or adenovirus, for example, can transactivate HIV.[221] In addition, infection of CD8-positive cells with herpes virus 6 has been shown to induce CD4 expression on those cells and to render them susceptible to infection by HIV.[222] Thus, suppression of these other viruses might indirectly help to suppress HIV replication.

Finally, now that it is possible to suppress HIV replication in patients (with antiretroviral therapy), it is worth considering therapies that may serve to boost their immune system. Immunostimulatory drugs or other maneuvers that may stimulate the immune system of such patients may in the future be found to offer an advance over the results that can be obtained with anti-HIV drugs alone. The use of bone marrow-stimulatory cytokines in this setting has already been discussed. Some of the other approaches being studied include bone marrow transplantation,[223] infusion of anti-HIV antibodies from patients whose HIV infection appears to be well controlled,[148] or infusions of expanded populations of CD8 cells. Ideally, one would aim at effecting a complete reconstitution of the patients' immune system. However, there is recent data to indicate that, at least in a research setting, patients with HIV infection rarely die unless their CD4 count decreases below 50 CD4 cells/mm^3.[224] This correlation was statistically very unlikely to have occurred by chance alone ($P < 10^{-10}$).[224] Thus, it is possible that maintaining the CD4 count above 50 CD4 cells/mm^3 may permit a substantial improvement in survival.

It is possible that combination therapy of HIV infection may prove to be a substantial advance over the results obtainable with any single agent. Such has been the case in certain other settings; the curative therapy of certain childhood leukemias, for example, was made possible only with combinations of agents. This is now an area of active research in HIV disease. However, in a practical sense it will be difficult to prove the efficacy of a given agent solely based on its contribution to a combination regimen. Thus, making drugs available for combination therapy may be one of the main benefits of getting such drugs approved as single agents.

HIV-ASSOCIATED MALIGNANCIES

It has been appreciated for some time that patients with immunodeficiency have a high risk of developing certain tumors, particularly non-Hodgkin's lymphoma. In addition, various retroviral infections have long been studied as models of tumorogenesis. It is therefore not surprising that

malignancies are frequently observed in HIV-infected individuals. Indeed, the appearance of Kaposi's sarcoma in individuals in certain risk groups was one of the first signs of the AIDS epidemic. Also, certain high grade B-cell lymphomas are associated with HIV infection[225] and are now considered in the surveillance definition of AIDS. Maiman et al have recently reported an association between HIV seropositivity in women and cervical carcinoma.[226] In addition, cervical carcinoma is often of advanced stage in HIV-infected women. For these reasons, annual Pap smears are now recommended in HIV-infected women. In addition to these, the incidence of certain other cancers, such as squamous cell or cloacogenic carcinoma of the ano-rectal area, appears increased in certain groups of patients at risk for AIDS.[227] Clinicians should be vigilant for other unusual tumors as well (Fig 9). Overall, tumors are a major cause of morbidity and mortality in HIV-infected patients, and, in fact, their clinical significance may be increasing with the devleopment of antiretroviral chemotherapy and prophylaxis for certain opportunistic infections.[228,229]

Milder or localized forms of Kaposi's sarcoma can be treated with radiation therapy, IFNα, or cytotoxic chemotherapy. However, the therapy of aggressive Kaposi's sarcoma is often unsatisfactory; while it may respond to cytotoxic chemotherapy, toxicity in the form of bone marrow suppression and immunosuppression is often limiting. Recent studies have suggested that a cascade of cellular and biochemical events may be involved in the pathogenesis of Kaposi's sarcoma.[181,230,231] As part of this process, Tat protein released from HIV-infected cells may enhance the proliferation of key Kaposi's sarcoma cells.[192-194] Specific inhibitors of Tat may, therefore be worth exploring for anti-Kaposi's sarcoma activity. In addition, there is evidence that a variety of other factors, including fibroblast growth factor, interleukin-6 (IL-6), or other cytokines may act as paracrine or autocrine factors for Kaposi's sarcoma cells and may thus be targets for attack.[181,182,193,194,232] It is conceivable that inhibitors of these cytokines may halt disease progression rather than destroying existing lesions. As mentioned above, our group is now testing whether pentosan polysulfate, an inhibitor of basic fibroblast growth factor,[182] has activity in patients with Kaposi's sarcoma.

Non-Hodgkin's lymphoma been recognized for some time as being associated with HIV infection.[233] These lymphomas usually present in extranodal sites, particularly the central nervous system. The majority are high grade, either small noncleaved cell or large cell immunoblastic. At a chromosomal level, many resemble Burkitt's lymphoma in having translocations involving the *c-myc* oncogene and Ig loci; t(8:14) translocations are the most frequent observed.[233] It has been proposed that HIV-associated lymphomas may be like endemic Burkitt's lymphoma in having Ig-variable, Ig-diversity, or Ig-joining segment rearrangement but no rearrangement of the *c-myc* oncogene.[234] Patients with HIV-induced lymphoma often cannot tolerate cancer chemotherapy, and this diagnosis usually carries a poor prognosis. There is some evidence that the incidence of HIV-associated lymphomas may be higher than previously appreciated.[228,229] Of the first 55 patients with AIDS or AIDS-related complex treated with AZT or AZT-containing therapy at the NCI, eight have developed non-Hodgkin's lymphoma.[228] When this group was first analyzed in March 1990, the risk of lymphoma developing after 3 years, as estimated by the method of Kaplan and Meier, was 46% (95% confidence interval, 20% to 76%). No lymphomas developed during the next 6 months, and the revised estimate for the development of lymphomas is 31% (95% confidence interval, 16% to 52%) after 3.5 years of follow-up (Fig 10) (J. Pluda, R. Yarchoan, D. Venson, S. Broder, unpublished observation, October 1990). The pa-

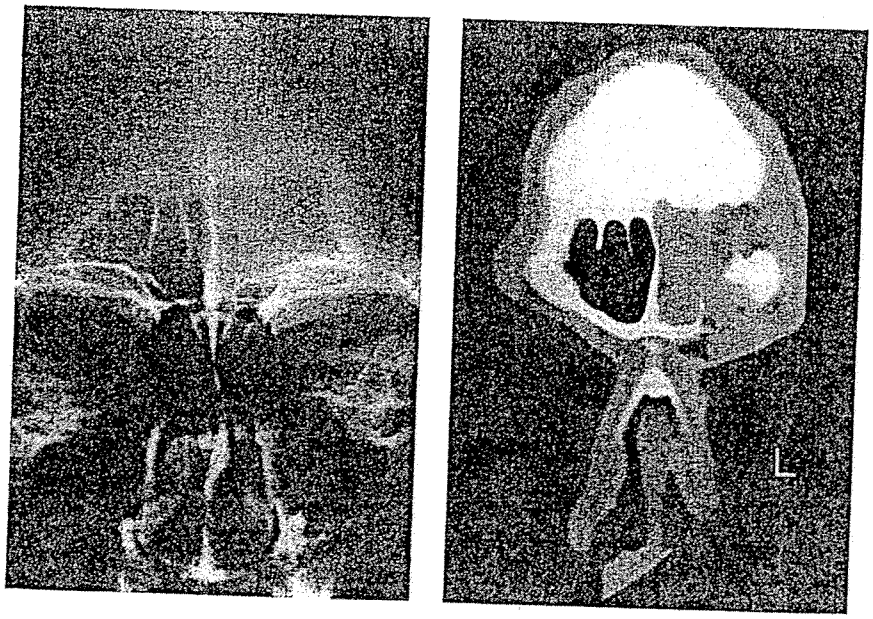

Fig 9. Sinus X-ray (left) and magnetic resonance imagery study (right) of an ARC patient with a history of sinusitis who developed a squamous cell carcinoma of the left maxillary sinus. As the AIDS epidemic matures, physicians should be alert for unusual tumors developing in HIV-infected individuals.

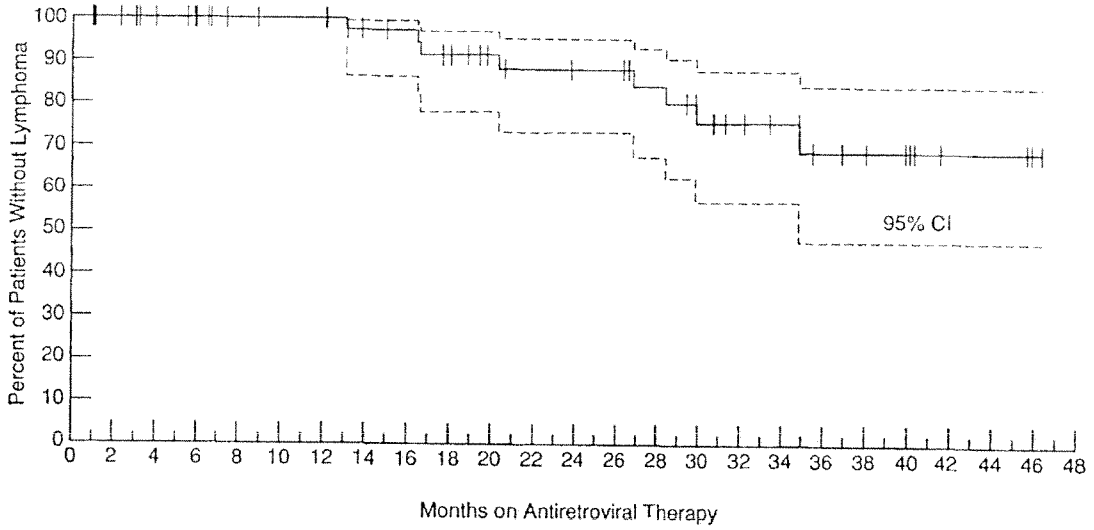

Fig 10. Kaplan Meier plot of the estimated development of non-Hodgkin's lymphoma in a cohort of 55 patients receiving AZT or combination therapy including AZT in the NCI. Time is measured from the entry onto the protocols; all patient had either AIDS or severe ARC (with either oral candidiasis or weight loss) at entry. The dotted lines show the 95% confidence interval. The development of lymphoma in this same cohort, examined at an earlier time, had previously been reported in Pluda et al.[228] Since that report, none of the 12 surviving patients have developed lymphoma (J. Pluda, D. Venzon, S. Broder, R. Yarchoan, unpublished observation, October 1990).

tients who developed lymphoma were extremely immunosuppressed (median, 6 CD4 cells/mm^3 at the time of their lymphoma), and it is likely that the prolongation of their survival by AZT increased the cumulative number who developed this complication. Two of the patients in this cohort developed cerebral lymphoma in the site of preexisting toxoplasmosis (Fig 11). Whether or not the toxoplasmosis may have contributed to the malignant transformation in such patients (eg, by causing local B-cell proliferation) is unclear. Physicians should be alert for lymphoma of the brain in patients who do not appear to be responding to appropriate therapy for cerebral toxoplasmosis.

It is possible that by prevention of profound immunosuppression in HIV-infected patients it might be possible to reduce the incidence of lymphoma. It may also be possible to target other factors involved in the pathogenesis of these tumors. B-cell hyperproliferation, which occurs in HIV-infected patients, may increase the chance of a malignant transformation occurring. There appear to be a number of causes for this B-cell activation. AIDS patients have increased numbers of circulating EBV-infected B cells,[235,236] and EBV sequences have been identified in approximately 40% of the cases of HIV-associated non-Hodgkin's lymphoma. In a majority of the cases where it has been examined, there is evidence that EBV infection of the HIV-associated lymphomas has preceded clonal expansion, suggesting that EBV may have contributed to the lymphomagenesis.[237] HIV can directly stimulate B cells[236,238,239] and this may have increased the probability of a malignant transformation occurring. Finally, HIV infection can lead to increased IL-6 production,[240-242] and this in turn can stimulate B cells and lead to tumor-like proliferation.[243,244]

It may be possible to interfere with certain of these steps. Could the likelihood of malignant B-cell transformation be reduced by blocking the effects of IL-6, for example, with an inactive, modified IL-6? It has been reported that IL-4 can reduce the production of IL-6 by monocytes,[245] and this modality may be worth exploring. Finally, there is evidence that IL-10, also known as cytokine synthesis-inhibitory factor, can suppress certain T-cell responses and thus permit the outgrowth of EBV-transformed cells or lymphoma cells. Interestingly, there is recent evidence of sequence homology between this cytokine and the BCRF1 gene of EBV.[246] Either IL-10 or a BCRF1 gene product could thus potentially act to suppress the immune response to transformed B cells, and it is conceivable that suppression of these substances may reduce the incidence of lymphomas. It is likely that lymphomas will be an increasingly important limitation of survival in AIDS, and the prevention and treatment of these tumors will be an important area for future research.

CHALLENGES FOR THE FUTURE

As we have seen, therapy of HIV infection that is directed at the causative agent is now a reality; AZT has already been shown to improve both survival and the quality of life in HIV infection, and other active drugs are now undergoing widespread clinical testing. However, the results attained so far represent only a first step, and much more needs to be accomplished. Patients still progress to frank AIDS and death despite the best available therapy. We need to develop more effective and less toxic agents and combinations of agents. No therapy, either under develop-

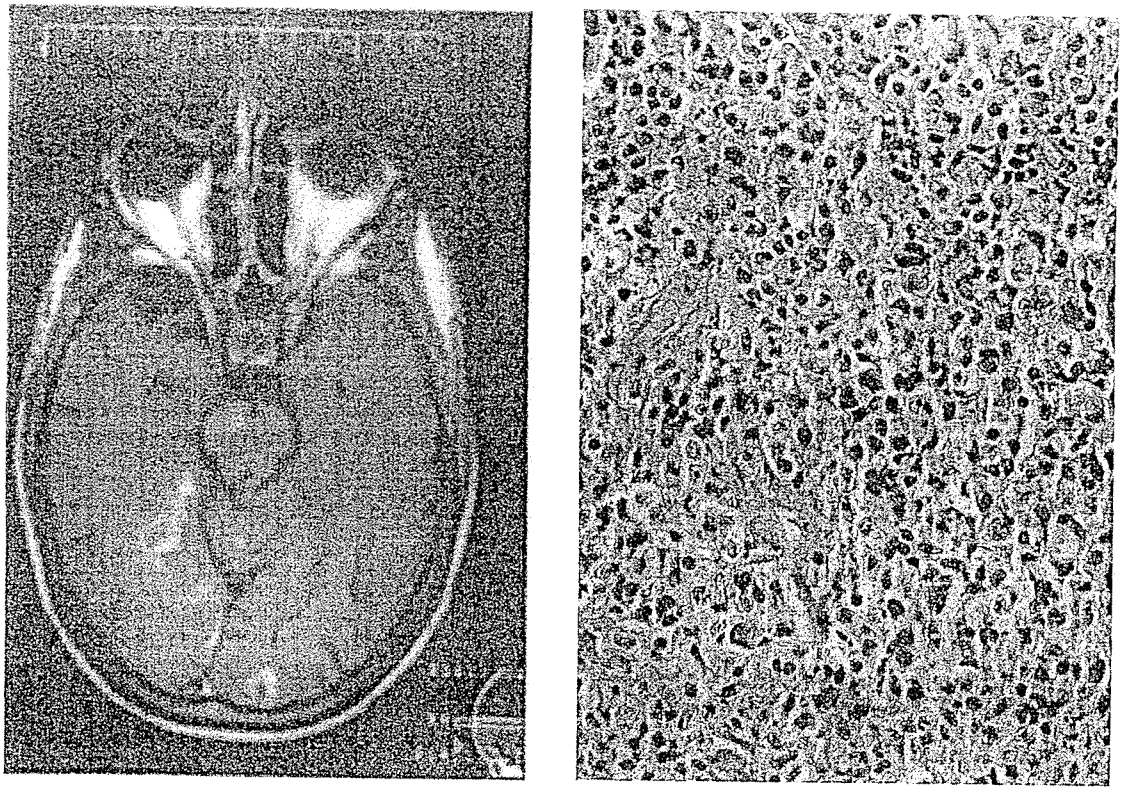

Fig 11. Patient with toxoplasmosis of the brain on prolonged therapy with an alternating regimen of AZT and ddC who subsequently developed primary central nervous system lymphoma. The patient's toxoplasmosis initially responded to therapy with pyramethamine and sulfa. However, this neurologic symptoms subsequently worsened, and magnetic resonance imaging showed new lesions (left). Biopsy of the brain at this time showed a small non-cleaved cell lymphoma (right).

ment or on the drawing board, is curative, if we define a "cure" in the strict sense of ridding the body of every infectious virion. However, this is not necessarily our first goal. Many persons are chronically infected with a number of viruses (eg, EBV) that rarely pose clinical problems. Thus, it may be an attainable goal to control HIV infection to the extent that the expected survival of individuals infected with HIV coincides with the actuarial survival of age-matched uninfected controls.

We have already discussed the matter of drug resistance. The replication of HIV is an error-prone process,[97] and while resistance has not formally been proven to have clinical significance, it is likely that the emergence of drug-resistant variants is clinically important and will pose a problem for long-term therapy.[7] Combination therapy may be one approach to this problem. If nothing else, the emergence of resistant strains of HIV may provide a rationale for developing a variety of anti-retroviral drugs, some of which may not necessarily be superior to available therapies.

Another issue is the failure of available anti-HIV therapies to effect sustained and complete immunologic reconstitution in patients with advanced AIDS. This failure may in part reflect the inability of drugs such as AZT to completely halt viral replication at the doses used, or alternatively a toxicity of such drugs for the immune system. Also, while the load of HIV generally correlates with disease progression,[247] it has been hypothesized that T-cell depletion in AIDS occurs in part because of indirect mechanisms, such as gp120-specific cytotoxic T cells killing normal T cells with gp120 absorbed on to their surface.[248-250] If such mechanisms prove to be of clinical significance, they may have to be specifically addressed. Thymic damage in AIDS patients may also pose a barrier for immunoreconstitution. HIV can infect thymic cells,[251,252] and patients with advanced AIDS generally have pathologic abnormalities of the thymus.[253,254] It will be important to understand the mechanisms for the incomplete immunologic reconstitution observed and to learn how to improve on the present results.

Yet another issue is how to best define the efficacy of antiretroviral drugs with both speed and accuracy. With AZT, this was accomplished by a randomized, placebo-controlled trial in patients with established AIDS.[3] However, because AZT has been found to prolong survival, doing such a placebo-controlled trial in patients with fulminant AIDS is unethical. One can, of course, do large

studies to show equivalence or superiority to AZT in the same population, but such studies require large numbers of patients and may take 2 or more years to complete. Long-term AZT recipients, particularly those with AIDS, provide an intriguing group for the comparative study of new drugs, because these patients are likely to have developed some resistance to AZT.[96] As noted above, AZT has been shown to be efficacious for at least 2 years in patients with 200 to 500 CD4 cells/mm^3 (and one can argue for 1 year even in AIDS patients), so equivalence to AZT may perhaps be viewed as sufficient to define efficacy in such populations. Finally, the use of endpoints other than survival or serious complications to define efficacy may help speed the process. In particular, certain laboratory markers of disease activity (such as CD4 counts, p24 antigen, or other markers of viral load) may have usefulness. For example, having less than 50 CD4 cells/mm^3 may be viewed as a "mortality risk indicator"[224] and, as such, may be a useful endpoint for clinical trials.

Finally, as discussed above, it will be important to learn how to prevent and treat the tumors that arise in patients with HIV infection. Thus, while we have accomplished much, many problems need be solved. In addition, the large number of patients expected to progress to AIDS in the next several years adds an extreme sense of urgency. It is quite possible that effective therapy for HIV infection will be multifaceted, comprising both antiretroviral agents as well as specific therapies to address the immunodeficiency and development of tumors. Alternatively, it is possible that with early intervention using effective anti-HIV agents such additional approaches will be unnecessary. Through a concerted effort targeting many steps, it should be possible to substantially improve on existing therapies in the not too distant future.

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