SPRING 06 **PROSTRATIN UPDATE:**

AN INDEPENDENT RESEARCH PROJECT OF AIDS RESEARCH ALLIANCE

What is Prostratin?

Natural Compound Holds Promise as Adjunctive Therapy for Eradicating HIV

Prostratin was initially isolated by the National Cancer Institute (NCI) in 1992 as the active constituent of extracts of the tropical plant, *Homalanthus nutans*, used in Western Samoa to treat viral diseases such as hepatitis. Prostratin exhibits two anti-HIV activities. It interferes with HIV infection by decreasing the expression of HIV receptors on the surface of healthy cells. More importantly, it activates HIV-1 expression from cells that are infected with latent HIV, forcing them to produce new virus. These latently infected cells form "reservoirs" of HIV hidden throughout the body, including the brain, lymphoid tissue and genital tract. Because HIV is dormant within these cells they escape the reach of current anti-HIV drugs and the immune system. HIV reservoirs are the major stumbling block to the eradication of HIV.

People currently infected with HIV could remain so for life without strategies to eliminate the reservoirs. One possible strategy involves activating the HIV virus in the reservoirs, making the cells more detectable by the immune system, and rendering them susceptible to targeted destruction by other anti-HIV drugs. Prostratin's ability to stimulate HIV production from latently infected cells is an important feature that could be exploited as an effective therapy to target latent reservoirs for patients using Highly Active Antiretroviral Therapy (HAART), commonly referred to as the "drug cocktail".

In 2001, AIDS Research Alliance (ARA) applied to the National Institutes of Health (NIH) for the exclusive license to develop prostratin as an anti-HIV drug. This was granted based on our track record in community-based research and our reputation for collaboration, making this the first time NIH has in-licensed a drug to a non-profit. Over the past few years, ARA has conducted preclinical research on prostratin, with the help of an NIH grant worth nearly $950,000 under the DART program and collaborations with some of the most prominent AIDS scientists worldwide. A complete account of these studies is available in previous issues of *Searchlight* which can be found at www.aidsresearch.org.

Currently, ARA is in the final pre-clinical toxicology experiments necessary to start testing the drug in humans.

Samoan healer Ake Lilo prepares an extract from the bark of the *mamala* tree, from which the chemical prostratin, was isolated. *(Photo: Paul Cox and Patricia Stewart)*

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On-Going Studies

Last summer, AIDS Research Alliance engaged one of the world's largest pharmaceutical research and development services companies to complete pre-clinical research on prostratin. The experiments included in the study are required for submission of an Investigational New Drug (IND) application to the Food and Drug Administration (FDA) and initiation of a Phase I clinical trials. The preclinical research, at a projected cost of $1.2 million, is scheduled to be concluded by Fall 2006.

Currently, two kinds of studies are underway. The first are **"drug distribution" experiments to determine where prostratin goes in the body** once it is ingested. The first step in this process involved hiring a firm in England to create prostratin infused with a radioactive form of hydrogen that is visible when exposed to X-Ray film. The labeling process took five weeks and Whole Body Radiography experiments began in early March. **The second set of experiments will help us learn what other compounds are created** as rat, monkey and human liver cells (hepatocytes) break down the prostratin compound. The goal is to have the fewest number of compounds – or metabolites – created because each new metabolite must also be tested for toxicity. These experiments have already begun and we have preliminary information, although we must wait for definitive results.

Interest Across the State

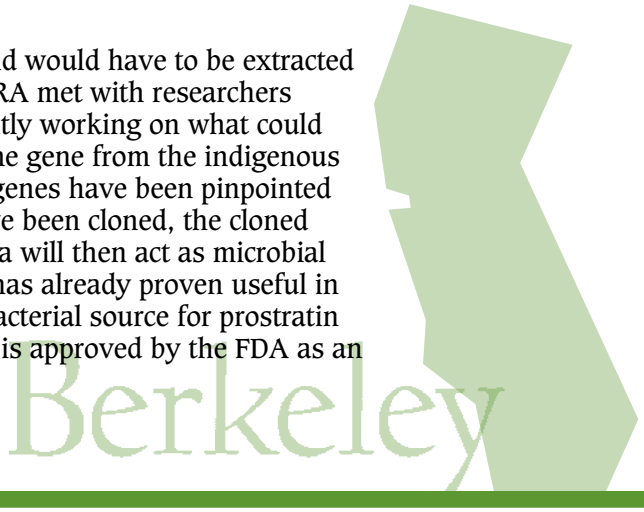
At the beginning of 2006, ARA participated in several meetings with major research institutions interested in – and investigating – the mechanism of prostratin's activity. A few highlights include:

ARA Contacted by Stanford Area Pharmaceutical about Prostratin Analogues

In December 2005, a start-up pharmaceutical company that develops novel drugs from small molecular compounds used in traditional Chinese medicines, contacted ARA Scientific Director, Marjan Hezareh, Ph.D. The company presented data on several compounds derived from modification of prostratin's chemical structure that have different pharmacokinetics and absorption characteristics. As ARA does additional work on prostratin's mechanisms of action, we may be able to structurally modify a "second generation" version of prostratin that retains the desirable characteristics we want – like increased solubility which is helpful for an oral dosage – while eliminating the undesirable ones like toxicities.

UC Berkeley: Supply to Meet Future Demands

Prostratin's supply is tightly limited by the fact that the compound would have to be extracted from the bark and stem wood of the mamala tree. In January, ARA met with researchers in the UC Berkeley laboratory of Dr. Jay Keasling, who are currently working on what could become a supply problem. Keasling's group is trying to isolate the gene from the indigenous plant that actually builds the prostratin molecule. Once the key genes have been pinpointed through an arduous gene sequencing process, and the genes have been cloned, the cloned genes will be inserted into a strain of E. coli bacteria. The bacteria will then act as microbial factories, producing large quantities of prostratin. This method has already proven useful in producing precursors of the anti-malarial drug artemisinin. "A bacterial source for prostratin will ensure a plentiful, pure and inexpensive supply if Prostratin is approved by the FDA as an anti-AIDS drug," said Dr. Stephen Brown, ARA Medical Director.



Big Pharma To Research Drugs That Will Eliminate HIV Reservoirs

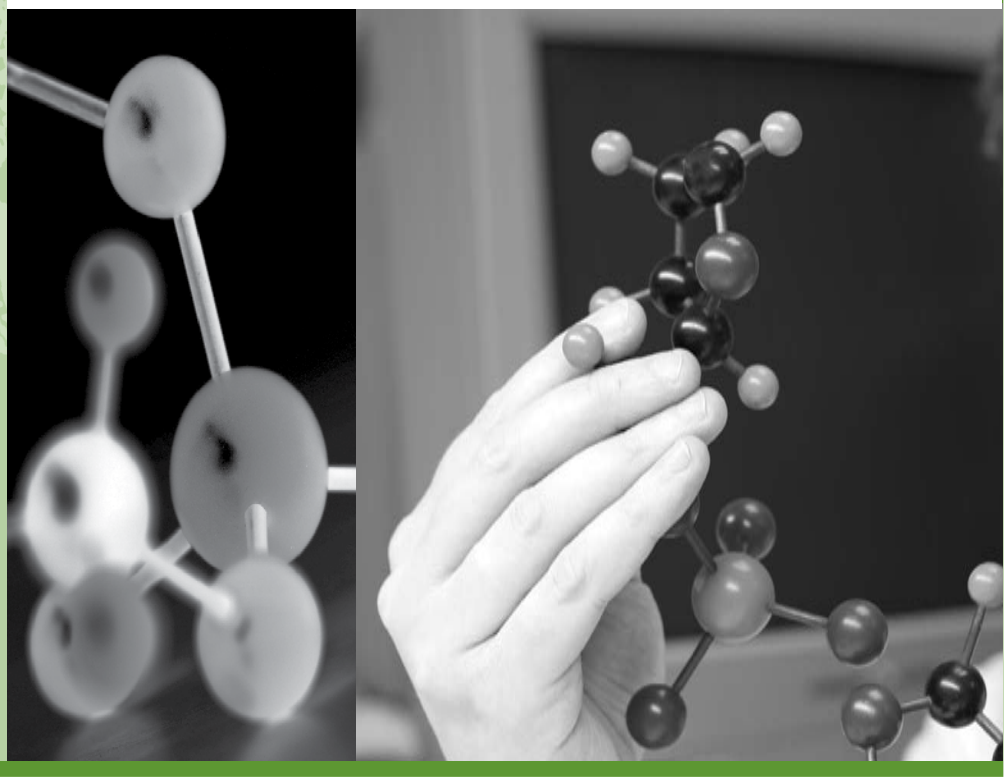
For many years, the pharmaceutical industry was disinterested in strategies to deplete viral reservoirs, instead focusing its research on new generations of anti-HIV drugs. The data that ARA and its collaborators have published on viral elimination strategies has finally caught the eye of big Pharma. At CROI, researchers from Merck presented a new system to screen for drugs that activate HIV from latency simultaneously in 3 cell lines: T-cells, macrophages, and microcytes. These cells are thought to be able to harbor HIV in its latent form. Merck hopes to find genes involved in activating HIV common to all 3-cell types, and to target the gene products for drug development. ***This is the first major pharmaceutical company to enter into the HIV reservoir arena.*** The process will take years, but if successful it will facilitate efficient selection and screening for potential drug candidates. Preliminarily, Merck has indicated an interest in screening prostratin through this process. ARA's persistence in this area of the science has shifted the conversation and is advancing a promising new strategy for eradicating HIV.

A Combination of Strategies to Eliminate HIV Reservoirs

Researchers in Texas reported in the fall issue of Lancet an attempt to eliminate the HIV reservoir using valproic acid on four HIV+ individuals with undetectable plasma viral loads (plasma RNA <50 copies/ml over a tow-year period). Valproic acid, an anti-convulsant, is a drug in wide use for epilepsy and bipolar disorder that has shown the ability to block the system that cells use to keep DNA "quiet." In blocking the "quieting" mechanism, valproic acid could mimic prostratin's ability to activate DNA. The researchers observed a statistically significant decrease in frequency of infection in resting CD4+ cells in three of the four patients.

The Free University of Brussels presented data at the 12th Annual Conference on Retroviruses and Opportunistic Infections (CROI) in December 2005, looking at the combination of prostratin with valproic acid that shows that **prostratin and valproic acid combined was more active than either compound alone**, and significantly greater than mere addition of their effects. This means that it may be feasible to administer much smaller doses and shorter exposures of prostratin, thus decreasing any difficulties with toxicity.

After the conference, ARA's team met with researchers from the UCSF based Gladstone Institutes, including the Immunology and Virology Institute Head Warner Greene Ph.D, M.D., and researchers from the UC Davis Primate Research Center. Gladstone scientists presented test-tube data on prostratin that confirmed the activity of prostratin and showed that, when paired with another activating compound, created a measurable synergistic effect.



Nurturing Prostratin Research:
ARA Donors Meet the Challenge

ARA faces the exciting prospect of developing a drug that may actually make the eradication of HIV a possibility, but this exciting work has not come cheap. Last year, Douglas M. Kinney – a partner at Palmer Capital in Chicago and the former board chair of the National Tropical Botanical Garden in Hawai'i – issued a challenge gift of $250,000 to fund the pre-clinical work on prostratin. A number of very generous donors – both long-term supporters and new members of ARA's family – met that challenge without pause, adding $500,000 to help move prostratin towards human clinical trials.

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