PROJECT INFORM FACT SHEET

AL-721 (active lipids 7:2:1)

What is It?

AL-721 is a substance with anti-viral properties discovered at the Weizman Institute in Israel. It is said to act by changing the characteristics of the membrane (outer shell) of certain types of cells and viruses, making them more fluid, or softening them up. AL-721 is thought to act on viruses which have a rigid outer shell, including, among others, the HIV, or AIDS virus.

HIV attaches itself to human T-cells much in the way pieces of a puzzle line up with each other. Attachment points (called "activity sites") on the virus line up with receptors sites on the membrane of T4 cells. The virus and the cell, in effect, link up in a docking maneuver, after which the virus takes over the cell, using it as a factory to produce new virus. One theory says that when AL-721 fluidizes the outer shell of the HIV virus, the attachment points no longer align with the receptors on the cell, thus preventing the virus from taking over the cell. When the virus can't link up with T4 cells, it is unable to reproduce. There are alternate theories of how AL-721 may function, but all of them suggest that it appears to affect the ability of the virus to enter and damage T4 cells.

AL-721 consists of 3 ingredients joined in a 7:2:1 ratio: 7 parts neutral lipids, 2 parts phosphatidyl choline (PC), and 1 part phosphatidyl ethanolamine (PE). In theory, this particular ratio is what gives the substance its fluidizing properties. In practice, it is unknown how critical the actual ratios are. Most commercial AL-721 "workalikes" (generic equivalents) sold in the U.S. differ somewhat from this ideal 7-2-1 ratio.

What does the Research Show?

To date, reported research has been encouraging but inconclusive. One widely quoted study (11/14/86, NEJM), reported that it reduced viral activity *in vitro*. Robert Gallo, disputed discoverer of HIV, is one of the scientists whose names appear on this study. However, Gallo now reportedly holds that these preliminary findings were "overreported."

Initial studies in Israel treated a small number of AIDS patients and reported clinical improvements. Formal reports were never made of this work, so its methodology and conclusions are unclear. Some U.S. AIDS patients who took part in the study, however, attest to the benefit of the treatment. Recently, the Israeli correspondent of The Baltimore Jewish Times reported that 48 of 60 patients treated in Israel have shown improvements. Three patients described as near "terminal" were said to be "in remission." Other unnamed tests concluded that the virus had become "less infective" at some point during treatment. Although such news is good to hear, it is an anecdotal report of treatment efforts and does not constitute a research study. Like the other Israeli research, these findings are unpublished in scientific journals and thus may or may not meet the test of peer review.

Phase I research on 7 people at St. Luke's Hospital in New York reports that AL-721 reduced the level of viral activity in 6 of 7 patients, as measured by reverse transcriptase levels. Late reports from this on-going study suggest that the anti-viral effect is dose dependent, and that a dose of 20-30 grams daily produces the best results. The study also reported improvements in some immune functions (but not in T-4 cell counts). Although this data has been presented at a scientific conference, it has not been published in scientific journals.

N.I.H. sponsored tests have been promised for many months and should commence in late 1987 or early 1988 after repeated delays. AL-721's manufacturer and patent holder, Ethigen Corporation, claims it will start large scale clinical trials in 1988. It remains a major question why such tests have been put off for so long.

A few grassroots surveys have been conducted of people using various AL-721 "workalikes." These subjective surveys have been relatively positive. About half the participants report a sense of feeling "better" while the rest say they aren't sure yet. Unfortunately, surveys have measured mostly short term use of a wide variety of products. PI is currently conducting a long-term survey which measures symptomatic changes and lab measures as well as subjective assessments. (Please call for survey forms to participate!)

In total, the research completed on this substance, although encouraging, is still minimal and preliminary. No double-blind studies have been conducted, and no studies with large numbers of people.

What About Side Effects?

This is one of AL-721's strongest suits: no side effects of any kind have been reported, other than the strange taste of some of the commercial "workalikes."

Perhaps the greatest concern voiced about AL-721 is the rumoured "rebound effect" reported by some sources. This is based on an observation that some people in the small U.S. trial of AL-721 seemed to get worse after going off treatment. This has lead some to conclude that once AL-721 is taken, a person must con-

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AZT – RETROVIR (Azidothymidine)

What is It?

AZT, probably the best known of all AIDS drugs, is the only drug which has been approved as a treatment for the HIV infection. AZT was discovered in the 1960's and originally researched as a cancer treatment, for which it proved ineffective. In 1984, the Centers for Disease Control identified AZT as one of the first substances found to act against the virus *in vitro*.

Burroughs Wellcome was given special rights to develop and market AZT under the Orphan Drug Act in late 1984. Working in close cooperation with the National Institutes of Health, AZT was quickly guided into Phase I and II testing. The study was ended early (after 19 weeks) when it seemed clear that people using the drug were doing far better than those on a placebo. For a short period afterwards, AZT was distributed in a limited fashion to about 5000 people under a new step in drug development called a Treatment IND. Although little data was collected during this period, the drug was approved for marketing in record time. Since coming into use, a broader picture of AZT has developed, leading many to conclude that it is both the most effective and the most toxic treatment currenlty available.

AZT is commonly used today by PWAs of all classifications, PWARCs. with low T4 counts, and increasingly by people without symptoms who test positive for the virus (often called "seropositives"). This last group uses it in hopes of preventing the occurrence of illness, although there is no proof yet that it can do this. There is some information that it may slow or prevent progression of ARC patients to AIDS, so a similar benefit is reasonably expected by seropositives. AZT is a controversial drug with all groups due to the seriousness of it side effects.

How Does It Work?

In scientific terms, AZT is said to "inhibit reverse transcriptase," an enzyme or protein which is critical to the reproduction of the virus. AZT does this by providing an attractive substitute for one of the proteins the virus seeks out and joins with during its reproductive cycle. When the virus joins with the substitute provided by the drug–instead of the real enzyme it seeks–the chain of reproduction is broken. Since other cells need these same enzymes to reproduce, it is critical for a drug to be selective. It must interfere more effectively with reproduction of the virus than with the reproduction of other cells. The side effects of AZT are due to its interference with cell reproduction. AZT sometimes damages the production of red blood cells, and sometimes white cells, both of which are produced in bone marrow. At its best, AZT does more damage to viral reproduction than to red and white cells and the precursors in the bone marrow..

AZT appears to slow or prevent production of new virus, but it has no affect on cells which are already infected. It can only prevent them from putting out new virus. Since infected cells themselves can attack other T-cells, it is clear that AZT alone cannot solve all the problems associated with AIDS. It does, however, cross the blood-brain barrier, meaning that it gets into the brain and spinal fluids. Thus, it can be effective in slowing the spread of the virus in these areas as well.

What Does the Research Show?

Soon after AZT was shown to act against HIV *in vitro,* a small human study showed that it was well tolerated for six weeks (*Lancet, 1986*). Some subjects experienced increased T4 cell counts, weight gain, and other improvements. Afterwards, a larger placebo-controlled study tested the safety and effectiveness of the drug in AIDS and ARC patients. The study was prematurely concluded when, after 19 weeks, people taking the drug clearly had a higher survival rate than those on placebo.

The study concluded that AZT increased the short-term survival rate in AIDS patients. At the conclusion of the study, 19 had died in the placebo group, versus only 1 on AZT. Those receiving AZT experienced fewer opportunistic infections, although only after they had used the drug for more than 6 weeks. Although ARC patients on AZT experienced no infections after the first six weeks, some AIDS patients experienced new bouts of PCP. AZT patients also gained weight, while the placebo group lost weight. Long-term follow-up showed continued advantages for patients taking AZT, although the benefits were not as dramatic as they had appeared at the early conclusion of the study.

AZT's effect on T4 cell counts was puzzling. For AIDS patients, T4 cells increased early in the study, but by the 19th week, the gains had reversed and the numbers were, on average, lower than at the start. ARC patients also showed an initial increase followed by decline, but their average numbers remained just slightly above their starting points. The increase in T4 counts for ARC patients averaged only 22 cells, a clinically insignificant improvement. Researchers theorized that the falling T4 counts in both groups may be the result of drug toxicity, rather than a decline in the drug's effectiveness. Some also point out that the actual decline of T-cells may be worse than the numbers cited by this trial, since patients who suffered serious illnesses were excluded from the data as

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DTC – IMUTHIOL (Diethyldithiocarbamate)

What Is It?

DTC (diethyldithiocarbamate), sold in France under the tradename Imuthiol}, is a complex chemical with several different actions. It is claimed to be an immune modulator and has been shown to have a limited degree of anti-viral action against HIV *in vitro*. It is a metal chelating agent (a substance which attracts metals to itself, and thus draws them out of other solutions). Metal chelators are believed to have anti-viral properties.

How Does It Work?

DTC is believed to work by stimulating the liver to produce a thymic hormone-like activity called hepatosin. It is claimed to: (1) speed the maturation of T4 cells, thus increasing their total number; (2) enhance overall T cell functions; (3) improve T4/T8 ratios; (4) improve NK (Natural Killer) cell response; and (4) to slow reproduction (*in vitro*) of the AIDS virus (as measured by the level of reverse transcriptase, a common measure of the level of HIV activity). It is said not to cause new reproduction of T cells, but only to help existing cells reach maturity and become effective. It thus avoids theoretical, and some say unreasonable, concerns about producing "additional food for the virus."

What Does the Research Show?

In Vitro Study:

In a French study (reported in The Lancet (12/21/85), DTC reduced reverse transcriptase levels in an HIV culture by 67%, a considerable amount. The test compared DTC against Isoprinosine, which achieved a 48% reduction. Researchers concluded that this effect was most likely to occur, for either drug, only at early stages of infection and may or may not be duplicated *in vivo*.

Clinical (in vivo) studies:

Several initial studies have been completed or are underway. In a French study of 6 people (Lancet, 11/9/85), (a) all but one showed increased T4 cells and improved T4/T8 ratios, (b) 3 showed increased sensitivity in skin tests, and (c) all showed "slow clinical improvement). No patients showed decline of T4 counts after the improvement, indicating that the T4 cells were not later taken over by virus. Two patients retested 3 months after discontinuing the drug showed lower T4 counts and lowered skin sensitivity.

A study at the University of Arizona on 26 people concluded that DTC slowed the progression of ARC, but few details were published.

A multi-center placebo-controlled trial in France of 80 people with ARC, sponsored by the manufacturer, showed overall improvements, fewer opportunistic infections, and an average increase of 169 in T4 counts. (against an increase of 38 in the placebo group). The only side effects were some stomach pain, nausea and a metallic taste in the mouth. After withdrawal of the drug, patients showed decline. This results of this trial, however, were not as carefully scrutinized as a typical U.S. trial would be by the FDA.

Ongoing studies at 4 U.S. centers include some AIDS patients as well as ARC and seropositives.

What Does All This Suggest?

DTC *might* be the first drug proven to consistently improve T4 counts (neither AZT, AL721, Ribavirin, etc. have done this across the board to the satisfaction of researchers). Informal conversations with researchers at a participating hospital suggests that, although the studies are still going on, the drug appears to be providing some benefits. Some, but not all, patients appear to experience a significant T4 rise. The T4 counts, though, don't keep going up indefinitely, instead reaching a plateau in a few months. The higher the starting number, the better a response can be expected. For people with very low counts, the increase may not be enough to make much difference clinically. The drug appears to help make the most of whatever immune capability a person has left. No miracles should be expected.

Where and How to Get DTC

DTC is available, but not easily. There are 4 ways:

- Join a clinical trial. See the AMFAR directory for a list of U.S. trials.

- Buy it as a raw chemical in the U.S. Be forewarned, though, that the raw chemical cannot be taken orally, but must be taken rectally or in specially coated capsules. DTC, called *diethyldithiocarbamate* or *sodium diethyldithiocarbamate* is available inexpensively from chemical supply houses. A 500 gram jar, good for at least 1000 doses costs about $60.00. This purest form, called *"reagent grade"* is at least 99% pure, some suppliers as high as 99.6% pure. No none knows what the other 1% is, but there are no reports yet that it is harmful. Experienced buyers order the *"tri-hydrate"* version of the chemical. The FDA warned suppliers not to sell to AIDS patients, since the chemical is not certified for human use, but later retracted the warning. Some suppliers require a "resale" tax number to prove the buyer is a business; others will take your word. Some ask what you're going to do with it. Suggestions: order through someone who already has an account with the supplier. Some companies selling it offer other health products, such as vitamins. Use a phony business name,

RIBAVIRIN (Vilona)

What Is It?

Ribavirin is a U.S. made wide-spectrum anti-viral substance which is sold in many other countries, where it is used for a variety of viral conditions, including herpes, flu, colds, and viral illnesses common in the tropics. It is licensed for use as a pharmaceutical product in the United States for treatment of respiratory synctal virus, a viral lung infection with afflicts infants. It is also under study as a possible treatment against AIDS and ARC.

Ribavirin is one of the class of drugs called *nucleoside analogues*. AZT and Acyclovir are also *nucleoside analogues*. These drugs work by creating an artificial substitute, in effect a decoy, for one of the proteins the virus attaches to in completing its reproductive cycle. One group of these proteins the virus must link up with are called *nucleosides*. Anti-viral drugs such as AZT and ribavirin are substances, called *nucleoside analogues*, which look to the virus like one of the nucleosides it needs to reproduce. When such a drug is used, the hope is that the virus joins up with the decoy, the nucleoside analogue, instead of the real protein it was looking for. When this happens, the chain of reproduction is broken, since the decoy doesn't really have what the virus needs to complete the process. AZT, ribavirin, and other nucleoside analogues differ in regards to which nucleoside they imitate, and thus what stage of the virus's reproduction they interfere with.

Ribavirin is considered a "wide spectrum" anti-viral because is produces an analogue of an protein which is needed by many viruses, including HIV, the retrovirus responsible for AIDS.

In the early years of the epidemic, from 1984 through 1987, ribavirin was the most widely used treatment for HIV infection, although it was never approved for this use. There were several reasons for its popularity: there were no other anti-virals which worked against HIV *in vitro* available; many patients reported significant improvements while taking it; and early studies supported the belief that it could be helpful. In 1987, ribavirin became the subject of great controversy in a public battle between its manufacturer, ICN Pharmaceuticals, and the FDA.

What Does the Research Show?

Because it has been around for more than 15 years, more than 600 scientific papers have been written about the effects of ribavirin. Only a few, however, address its use against HIV. Shortly after discovery of the HIV virus, ribavirin was identified by the Centers for Disease Control as having activity against the virus *in vitro*. These findings were confirmed by the work of Richard Roberts at Cornell University (The Lancet, 12/15/84), who concluded that the drug halted reproduction of the virus in concentrations which could be attained in human use. A later, Phase I study by Roberts demonstrated clinical benefits in human subjects, primarily some increase in immune response and a reduction in viral activity as measured by reverse transcriptase levels. This study served as the basis for dosage selection for later, larger clinical trials.

A researcher at the Harvard Medical School reported in 1986 that ribavirin crosses the "blood-brain" barrier. Thus, the drug may be capable of suppressing the virus in the brain and spinal fluids where the virus is known to do significant damage. This ability is believed to be key to the success an AIDS-related drug.

Two multi-center clinical trials, sponsored by the manufacturer, were conducted in 1986 at key hospitals working in the NIH AIDS Treatment program. These studies, one with patients with LAS (lymphadenopathy syndrome or swollen lymph nodes) and one with patients with more advanced ARC, proved controversial. The LAS study appeared to show that the drug reduced the progression to AIDS. Ten people in the placebo group came down with an AIDS-defining illness during the study, as did six in a group receiving 600 mg of ribavirin daily. None receiving 800 mg. of the drug came down with AIDS, although no other important benefits, either in virus reduction or immune system response, were measured for this group. FDA later disputed these findings, charging possible improprieties in the assignment of patients with more severe illness to the placebo group. These charges were later withdrawn when an FDA investigation found no evidence (or possibility) of such tampering. Although there is no remaining accusation of wrong-doing, FDA still argues that the study was inconclusive.

In the study with ARC patients, no benefits were demonstrated to a statistically significant degree, although trends toward increased longevity and reduced viral activity were noted by some researchers. In its most serious charge, FDA originally claimed that there was a disproportionate number of deaths among patients who had received ribavirin in the ARC study. Furthermore, FDA suggested that the drug perhaps had caused to get worse rather than better. Thus, the drug was put on clinical hold, stopping further research. However, when the full FDA investigation was completed, no statically significant evidence of harm was noted and the clinical hold was released. FDA blamed its flip-flop on the manufacturer, saying that it had not originally supplied the agency with the full data it needed to make an accurate judgment. This point continues to be debated, as the company has shown evidence that FDA

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DEXTRAN SULFATE

What is It?

Dextran Sulfate is a chemical believed to have anti-viral activity against HIV. Dextran sulfate was first produced during the 1950's and has been used for more than 20 years in Japan and elsewhere to lower blood cholesterol levels and as an anti-coagulent (a drug which thins the blood). Some forms of dextran sulfate are sold over the counter in Japan. Another version is sometimes used with blood transfusions to minimize blood clots.

How Does It Work?

Dextran sulfate may act against HIV in two ways. First, it inhibits production of reverse transcriptase, a protein required for the virus to reproduce (AZT produces a similar effect). This prevents the virus in the blood from reproducing and attacking new T-cells. However, this is not the only way in which HIV attacks. Infected T-cells often remain active, linking up with and attacking other T-cells. This cell-to-cell infection is unaffected by AZT and similar drugs. There is some evidence that dextran sulfate also acts against this second type of infection. If it works this way in the body, not just the laboratory, dextran sulfate is a very active anti-HIV agent.

Other evidence suggests that dextran sulfate may interfere with the attachment of HIV to T-4 cells (AL-721 produces a similar effect). If this is dextran's manner of action, it would be inherently safer than anti-virals such as AZT which interfere with cell reproduction.

For the moment, the mechanism by which dextran sulfate produces its anti-viral effect must be considered unproven. The researcher who has submitted evidence of its effectiveness as an anti-viral believes that its anti-viral properties are closely related to the compound's sulfur content ratio. There are conflicting opinions regarding the drug's ability to cross the blood-brain barrier. As yet, there is also little proof that it is capable of crossing the blood brain barrier. Some feel this is unlikely because of the large size of the dextran sulfate molecule. No studies have been conducted in this regard using the anit-HIV version of dextran sulfate. However, animal studies of a different version suggest that the drug gets into almost all body tissue.

What Does the Research Show?

In Vitro Studies:

Dextran sulfate attained worldwide attention in 1987 when a letter describing its *in vitro* activity against HIV was published in the Lancet. The first of four letters on the subject reported that dextran sulfate, when added to T-cells cultures, prevented their infection and destruction by HIV. This occurred at concentrations easily attained in the body. A second letter from the same source indicated that the compound worked synergistically with AZT when the two were added in certain proportions. The researcher, Ryuji Ueno, claimed that an optimal combination of the two drugs resulted in better protection against HIV than either drug could achieve alone without using much higher concentrations. This claim of synergistic action was later disputed by another writer, who claimed the case was not proven by the data supplied. In response, Ueno supplied additional data which appeared to answer the criticism.

Drs. Broder and Mitsuya at the National Cancer Institute have duplicated and confirmed the initial experiments which showed anti-viral activity. They also claim to have demonstrated it's ability to inhibit cell-to-cell infection Because of these findings, the National Institutes of Health has given dextran sulfate its top priority.

Clinical (human) Studies:

Prior human studies of dextran sulfate indicate that it may activate the immune system, increasing the number of T-lymphocytes. Its ability to suppress blood clotting is well established, as is its ability to reduce the cholesterol levels in the blood. To date, no human studies have measured its affects against HIV.

A single U.S. study testing dextran against HIV has been conducted in a pioneering effort by Dr. Donald Abrams at San Francisco General Hospital. This Phase 1 study measured toxicity and tested dosage levels. The study conlcuded that the drug was generally well tolerated, with only minor toxicity. Although not designed to measure effectiveness, the the study reported a trend toward T-cell increases at the higher doses (2700 to 5400 mg.) P24 antigen tests were meaningless, as only 2 patients were p24 positive to begin with. Lab analysis, however, did suggest that cell-to-cell infection was reduced. A Phase 2 study is scheduled to begin shortly which will look for evidence of effectivenss.

A small number of physicians are monitoring patients using available Japanese dextran sulfate. Most use it in combination with AZT, Acylovir, AL721 or other available treatments. These physicians report that some patients have experienced lowered p24 antigen levels and significant T-cell improvements after 9 to 12 weeks. Two physicians have concluded that doses of 1800 mg and below are not effective. Since these are reports of patient use and not controlled studies, the information must be considered anecdotal. Some physicians are beginning to collect data in a uniform manner. If this effort is successful, it will add credence to any data reported.

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NALTREXONE (Trexan™)

What Is It?

Naltrexone is an existing pharmaceutical product used in the treatment of opiate (heroin) addiction. It is classified as a "narcotic antagonist" and interferes with the body's normal response to opium-derived drugs. In recent years, some researchers have come to believe that naltrexone may also play a role in regulating the immune system. This theory has since been tested in clinical trials, in which naltrexone has been shown to regulate some aspects of immune function.

How Does It Work?

Naltrexone's activity on the immune system is indirect and not easily understood. Those who are unconcerned with the way it works may skip ahead to the upcoming sections on "Research to Date" and "How to Use It." Those with unswerving curiousity may continue below.

When used as a narcotic antagonist, the naltrexone interferes with the action of narcotics and is used to help people overcome drug dependence. The body produces substances called endorphins which act to regulate nervous system activity. These endorphins, which are sometimes called the body's natural pain killers, attach to *opiate receptor sites* on certain cells of the nervous system. When the proper levels of endorphins are present at these receptor sites, the nervous system is balanced, pain and sensation levels are normal, and the body is signaled that it can stop further endorphin production. Opiate drugs, such as heroin and morphine, are chemically very similar to endorphins and attach to the same receptor sites, substituting for the endorphins. When the level of the drug is high, it exceeds the natural endorphin levels and the addict feels no pain –or anything else. This produces the high associated with drug use. However, since the drugs take the place of the endorphins, the body stops producing endorphins as they no longer seem needed. Later, if the addict tries to stop using the drug, neither the drug nor the endorphins are present at the receptor sites, and the addict begins to feel the great pain of withdrawal. This continues until the body eventually begins to produce normal endorphin levels again.

Naltrexone stimulates the production of natural endorphins and, in high doses, blocks reception of opiates.

What does this have to do with the immune system? Researchers believe that the endorphins also provide an important link between the immune system and the central nervous system. Some white blood cells have receptor sites which are very similar to the opiate receptors on nerve cells. Thus, they attract endorphins. By interacting with these receptor sites, endorphins also appear to regulate certain immune functions.

There is evidence that AIDS is accompanied by lowered endorphin levels and decreased sensitivity of the receptor sites on immune system cells. Whether this is a cause or an effect is uncertain. Some believe it is related to the fact that many AIDS patients show abnormally high levels of natural alpha-interferon, which itself has some endorphin-like activity. This high level of alpha interferon appears to signal the brain to lower or shut down production of endorphins and decrease receptor site sensitivity, resulting in poorly regulated immune response.

Some researchers believe that using small amounts of naltrexone may help re-establish the normal regulation of certain immune functions by increasing endorphin levels and the sensitivity of the endorphin receptor sites on white blood cells. They also have noted that the drug appears to reduce chronically high levels of alpha interferon for many patients.

Research to Date

Most research to date has been conducted by a single researcher and his colleagues. Their studies, whcih have been presented at international AIDS conferences but have not yet been published, indicate positive responsive to the use of naltrexone. The study group, which was compared against a control group on placebo, showed changes which indicate improved immune response. including improved helper/suppressor cell ratios. People were considered "responders" to the therapy if their level of alpha interferon declined while using the naltrexone. In the clinical trials, these responders also experienced a significantly lower rate of opportunistic infections. Preliminary data suggests that those who responded to the use of naltrexone survived for longer periods, but it is uncertain whether this was due to the use of naltrexone.

Checking each person's alpha interferon level seems to be the only way of knowing who is responding to the therapy. Unfortunately, there is no simple or inexpensive way to measure this, so it is difficult to determine which patients are likely to benefit from naltrexone.

Although these researchers remain enthusiastic about naltrexone's use, others show no interest and little other research in underway. There are, however, many well-qualified researchers who support its theoretical basis, and many private physicians have experimented with it, To date, there seems to be no consensus either way regarding the use of naltrexone except that it is harmless