FREQUENTLY ASKED QUESTIONS RE: ALVAC/IL-2 CLINICAL TRIAL

- **What is a clinical trial?**

Before the U.S. Food and Drug Administration (FDA) approve a new drug or new treatment it must be shown to be both safe and effective. Typically, this is accomplished via clinical trials- carefully controlled studies designed to test and evaluate new drugs and new treatment plans. These trials are carried out to learn more about new treatment and to find better therapies.

- **What is informed consent?**

Before enrolling in a clinical trial, the doctors and coordinators will discuss with all potential volunteers the possible risks and benefits involved. These issues are summarized in a lengthy form that explains the trial procedures and the possible side effects. This is called an informed consent form and all clinical trial participants are asked to read, understand, and sign it before beginning treatment. It is important to ask the doctor or coordinator to explain any part of the form that is unclear.

- **Can volunteers leave a trial after enrolling?**

Yes. Even though someone has agreed to participate in a trial by signing the informed consent form, they are free to leave the trial at any time.

- **What is interleukin 2 (IL2)?**

Like most parts of the body, the immune system functions by producing chemical substances so that cells can communicate with one another. These chemicals have been called ***hormones*** if they serve to excite or arouse cells, and in the immune system they have been given the name ***cytokines*** or ***interleukins.***

IL2 is one of the first of now more than 20 interleukins that have been discovered in the past 25 years. Only T cells produce it, particularly "helper" T cells. Therefore, IL2 is especially important in infection by the Human Immunodeficiency virus (HIV), since these are the very cells that HIV infects.

- **How does IL2 work normally in the immune system?**

The immune system is made up of several different types of White Blood Cells (WBCs) that circulate in the blood and can be found in the lymph nodes (glands) that are distributed all over the body. Most of the WBCs of the immune system are called lymphocytes, of which there are 3 major types: T cells, B cells, and Natural Killer (NK) cells.

Normally these cells remain quiet and are thought to be resting. However, if a germ gets into the body, the T cells become activated and begin to make and release IL2. At the same time,

activated T cells, B cells and NK cells become responsive to IL2 by placing IL2 ***"receptors"*** on their surface.

When IL2 binds to IL2 receptors, the cells are signaled to grow and divide. In a very short time, these cells multiply so that many more cells are created. Afterwards, these cells, especially the "killer" T cells, recognize and kill germ-infected cells. Therefore, IL2 is necessary for the multiplication and function of the cells of the immune system that fight infections.

- **Why is IL2 used in the therapy of HIV infection?**

Most people do not know when HIV infects them because usually HIV causes no symptoms when it enters the body. Also, HIV remains silent for a long time, months and even years. During this time, the immune system fights the infection and keeps it under control. However, as the killer T cells and NK cells kill the HIV-infected helper T cells, the number of helper T cells (which make most of the IL2) gradually drops. Eventually, the number of helper T cells becomes so low that the immune system is crippled, and cannot react to germs that usually it can remove rapidly. When this happens, the Acquired Immunodeficiency Syndrome (AIDS) is recognized and diagnosed.

Because of the central role that IL2 plays in the immune system, functioning to stimulate the multiplication of killer cells, and because the IL2 producer CD4+ T cells eventually decrease to very low numbers leading to a deficiency of IL2, it is logical to try to replace the IL2 by giving it as a medicine.

- **How is IL2 used in the therapy of HIV?**

Since IL2 is a protein molecule, it must be injected, either underneath the skin (subcutaneous, SC) or into the blood stream (intravenous, IV). It cannot be taken as a pill, because the stomach will digest it.

IL2 is being tested for use in HIV infection as a medicine to boost the general function of the immune system, especially to raise the number of helper T cells. It is also being tested to boost the immune reaction to HIV itself, so that the ability of the body to control HIV is improved.

- **What are the different IL2 doses and regimens?**

There are 3 different doses of IL2 that are being tested as general immune stimulants, the so-called high and intermediate doses that are given for 5 days every 2 months, and the low dose that is given daily. The high dose is 15 million Units (U), the intermediate dose is 6-9 million U, and the low dose is 2 million U.

- **How do these doses and regimens differ?**

These doses and regimens differ in 2 ways: therapeutic effects and side effects. The high and intermediate doses of IL2 are only given for 5 days because if administered longer they cause

unacceptable toxic whole body (systemic) side effects. By comparison, the low dose has been adjusted so that there are no systemic toxic side effects.

The systemic side effects associated with the high and intermediate doses of IL2 are flu-like symptoms, such as fatigue, muscle aches, fever, and chills. In addition, theses doses of IL2 cause the WBCs and plasma (the liquid part of the blood) to leak from the blood into the tissues, leading to a drop in blood pressure. This can be counteracted by the administration of fluids, which result in the accumulation of fluid in the tissues (edema) and a weight gain that can be as much as 10-20 pounds. This fluid and weight gain is then lost when the administration of IL2 is discontinued.

The therapeutic effects of the high and intermediate IL2 doses are an immediate decrease in the number of WBCs in the blood while the IL2 is administered, followed by a "rebound" increase in the number of WBCs after IL2 is discontinued. In particular, helper T cells increase dramatically, as much as 10-fold, then gradually decline until the next dose of IL2.

The low dose of IL2 causes no systemic side effects, and results in a rapid increase in NK cells, and a gradual increase in helper T cells over the course of several months.

- **Why should IL2 help control HIV after interruption of the antiviral drugs?**

When the antiviral drugs are discontinued, viral replication resumes. In a preliminary study, we found that when low dose daily IL2 therapy was continued, there was an increase in the killer T cells that occurred at the same time that the HIV concentration decreased. Therefore, it appears that IL2 may be beneficial when the antiviral drugs are withdrawn, helping the immune system to control the virus. Therefore, IL2 therapy can be used to try to add to the way that IL2 functions normally during an immune reaction, to stimulate the multiplication and function of lymphocytes.

- **What are Therapeutic Vaccines?**

Vaccines are substances that are similar to germs but are non-infectious, non –harmful. They can be weakened or killed forms of viruses or bacteria. They are designed to stimulate your immune system to recognize and react to the germs that they resemble. When we think of vaccines we normally think of them in a prophylactic sense, in which they are administered to prevent infections with microorganisms such as bacteria or viruses. We have many such prophylactic vaccines against childhood diseases, including measles, mumps, rubella and chicken pox, among others. Therapeutic vaccines however, are for people already infected with a disease-causing germ, such as HIV.

- **Why use Therapeutic Vaccines in the Treatment of HIV?**

The investigation into HIV therapeutic vaccines is now more important than ever. This is based upon our understanding that the elimination of the very last HIV infected cell is impractical, and as well, the continued long-term use of antiviral drugs may give rise to severe toxicity, such as the lipodystrophy syndrome.

Therefore, attempting to harness the body's own immune resources becomes an important strategy. This is the goal of therapeutic HIV vaccines. They aim to boost immune responses in persons already infected with HIV, when the HIV virus is maximally suppressed with antiviral drugs. Therapeutic vaccines employ non-infectious HIV proteins to activate the immune system, especially the T cells, which can then become killer cells, capable of killing HIV-infected cells.. These cells recognize HIV, and when activated by the vaccine, they can multiply and become effective killer cells. Ideally, these vaccine-boosted immune responses would help your body control or abort the HIV infection.

- **Types of HIV Vaccines**:

There are many types of HIV vaccines currently in development. They are classified into several broad categories, named for the methods used to create them. For example, there are whole killed HIV vaccines like Remune, in which HIV is killed and fixed with formaldehyde. "Naked DNA" vaccines are another type. These vaccines are constructed from bacterial viruses that cannot replicate in human cells, and into which several HIV genes are inserted. A third type of vaccine is made from poxviruses. The poxvirus family includes viruses such as small pox, cowpox and canary pox.

- **How is the ALVAC HIV Vaccine made?**

The vaccine to be used in this trial is called ALVAC vCP1452. This is constructed from the canarypox virus. The name ALVAC is derived from where the canarypox vaccine was first made, Albany, NY at the New York State Health Labs. The number vCP1452 indicates that this HIV Canarypox vaccine has been developed after several other generations of ALVAC vaccines.
Canarypox is a virus that infects birds but not mammals, and it cannot replicate in human cells. This is important from a safety standpoint, so that there is no danger that the vaccine itself can cause disease.

To make this vaccine specific for HIV, scientists have inserted several HIV genes into the canarypox virus. These genes include the HIV-1 envelope (*env*) and major structural (*gag*) genes, the protease (*p15*) and synthetic genes (*nef*) that encode the "negative effect" and (*pol*) that encodes RNA polymerase.

This vaccine is administered while patients continue to receive HAART, to maximally activate the HIV-specific T cells before the antiviral drugs are withdrawn. In this way it is hoped to help the immune system to control viral replication so that plasma HIV remains undetectable, and the progression to AIDS is prevented.

- **Why combine IL-2 and Therapeutic Vaccine?**

The trial is based upon the hypothesis that to generate maximal HIV immune-reactivity or immune control of the HIV virus, we will need two signals. HIV antigens supply one signal and IL-2 supplies the other. The HIV antigens will be presented in the form of the therapeutic vaccine (ALVAC) and will select HIV specific T cells, while the IL-2 will promote the growth

and function of these HIV specific cells. The idea is to improve both the quality and the quantity of the immune response, to prevent viral relapse upon discontinuation of HAART.

- **What are the side effects of IL-2 and the Vaccine?**

The side effects of IL-2 are dose dependent, that is, the higher the dose the more severe the side effects. However, with the low dose used in this trial the side effects are mild and easily managed. The details regarding these side effects will be discussed in great detail with you at your screening visit.

The side effects associated with the administration of the vaccine again are minimal and mainly consist of tenderness at the injection site (similar to flu- vaccine injection). A list of the most common risks of the vaccine is outlined in the consent form and all will be discussed at the screening visit.

- **How long is this study?**

Each patient's participation in the study will last a minimum of six months. During step 1 you will be required to attend the clinic either once or twice a month, depending on the group you have been randomized to. During step 2, when anti-viral therapy is discontinued, weekly visits to the clinic are required. At the end of the six months, if certain criteria are met (i.e. viral load below 30,000 and CD4 greater than 250) you may be eligible to remain off HAART and continue in the study.

- **Will hospitalization be required?**

No, this trial is conducted on an outpatient basis.

- **Can clinical trial participants still see their regular doctor?**

Yes. Clinical trials do not replace normal health care. In fact, your regular doctor (primary care physician) will be updated regularly of your progress by the trial coordinators.