

PROTOCOL FOR ANIMAL USE AND CARE*Handwritten forms are not accepted***CNPRC**

EH&S USE ONLY

PROTOCOL # 10794**EXPIRES: 9/10/04**

| Investigator | | Contact | |
|---------------|--|---------------|--|
| Last Name: | | Last Name: | |
| First: | | First: | |
| Middle: | | Middle: | |
| email: | | email: | |
| Department: | | Department: | |
| Phone / Fax: | | Phone: | |
| After hrs. #: | | After hrs. #: | |

| Species (common names): | Number: | Source: |
|-------------------------|---------|---------|
| Rhesus macaques | 18 | CNPRC |
| | | |

| | | | |
|--------------------------------|---|----------------|--|
| Project Title | Effects of IL-2SA therapy on viral replication and CD4 T cell counts in SIV-infected macaques. | | |
| Overnight housing location:: | CNPRC | Day use only : | |
| Animals will be maintained by: | <input checked="" type="checkbox"/> Vivarium <input type="checkbox"/> Investigator <i>(If investigator maintained, attach husbandry SOP's.)</i> | | |

Procedures: Provide a one or two sentence layman's description of the procedures employed on the animals in this project. This information will help the animal care staff understand any conditions they may encounter while caring for your animals.

This study will investigate the effects of IL-2SA on SIV infection. Eighteen animals will be infected with SIV_{mac251} and monitored for 6 months. The SIV infected animals will be divided into 2 groups: nine animals each will be treated with twice daily for 5 days with IL-2 SA, the other 9 monkeys will be treated the same way, but with placebo (saline). The treatment will be repeated 3 times in 4-week intervals. Animals will undergo phlebotomy for clinical measurements, as well as immunologic and virologic parameters. At approximately week 24, all surviving animals will be euthanized and undergo necropsy.

Special Husbandry Requirements: Describe any special requirements your animals have with respect to **food, water, temperature, humidity, light cycles, caging type, bedding**, or any other conditions of husbandry.

Infectious housing after SIV inoculation

Other instructions for animal care staff: (check applicable entries)

| Sick Animals | Dead Animals | Pest Control |
|---|---|--|
| <input checked="" type="checkbox"/> Call Investigator | <input checked="" type="checkbox"/> Call Investigator | <input checked="" type="checkbox"/> Call Investigator |
| <input type="checkbox"/> Clinician to treat | <input checked="" type="checkbox"/> Save for Investigator | <input checked="" type="checkbox"/> OK to use pesticides |
| <input type="checkbox"/> Terminate | <input type="checkbox"/> Bag for disposal | <input type="checkbox"/> No Pesticides in animal area |
| <input checked="" type="checkbox"/> Necropsy | <input checked="" type="checkbox"/> Necropsy | |

Hazardous Materials *(only if in the animal room):*

| | | | |
|-----------------------|---|-----------|--|
| Infectious Agents? | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | Agent(s): | Simian Immunodeficiency Virus-mac ₂₅₁ |
| Radioisotopes? | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | Agent(s): | |
| Chemical Carcinogens? | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | Agent(s): | |
| Toxic Chemicals? | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No | Agent(s): | |

| | | | |
|--------------------------------|---|------------------------------------|---|
| Funding source: | Bayer | Previously approved? | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| Is the project already funded? | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | Previous protocol number (if any): | |

What Veterinarian or veterinary clinic will provide care for your animals? (check one)

| | | | |
|--------------------------|--|-------------------------------------|---|
| <input type="checkbox"/> | Lab Animal Health Clinic (2-0514) | <input checked="" type="checkbox"/> | California Primate Research Center (2-0447) |
| <input type="checkbox"/> | VMTH Large Animal Field Service (2-0292) | <input type="checkbox"/> | Another Veterinarian |

If you checked "Another Veterinarian", please provide:

| | | | |
|------------------|--|----------|--|
| Veterinarian: | | Address: | |
| Day phone: | | | |
| Emergency phone: | | Email: | |

If your veterinarian is not affiliated with one of the three service units listed above, please contact the campus veterinarian, 2-2357 (email pctlillman@ucdavis.edu) for current information about training and record keeping requirements.

Summary of Procedures:

a) Briefly describe the **overall intent** of the study. Include in your description a statement of your hypothesis, the objectives and significance of the study. Your target audience is a faculty member from a discipline unrelated to yours. Do not use jargon.

Hypothesis: It is proposed that IL-2 SA treatment of SIV-infected rhesus macaques results in improved CD4 T cell numbers, and thus better preservation of cellular immune responses necessary to control and limit SIV replication. **Objectives:** Antiretroviral therapy (HAART) is routinely used to suppress viral replication in HIV-1 infected patients. However, some patients don't respond to HAART therapy. Thus, there is a need to combine HAART therapy with immunomodulatory molecules that can increase the effectiveness of HAART. Cytokines that promote T helper functions are candidates for such immunomodulators. Interleukin-2 is a cytokine that promotes CD4 proliferation. CD4 T cells are the main cell type infected by HIV-1, and loss of CD4 T cells results in progression to AIDS. Thus, an increase in CD4 T cell numbers after IL-2 treatment should be beneficial to the patient. IL-2 treatment in humans was often accompanied by toxic side effects. IL-2SA is a modified IL-2 that contains a single amino acid change. This mutation prevents binding of IL-2 SA to Natural Killer cells (NK cells) without affecting its binding to T cells. Many of the toxic side effects of IL-2 have been attributed to massive activation of Natural Killer (NK) cells. IL-2SA is a modified IL-2 that contains a single amino acid change. This mutation prevents binding of IL-2 SA to NK cells without affecting its binding to T cells. Thus, it should have all the beneficial effects of IL-2 without severe adverse effects. **Significance:** An effective immunomodulatory therapy, like the one proposed in this study, could have multiple applications in the treatment of HIV disease. It could be beneficial in prolonging treatment free periods in strategic treatment interruption (STI) regimens, or it could be added as part of an antiretroviral regimen. As there is no vaccine available, the boosting of host immune responses in HIV-1 infected patients is needed to control virus replication and thereby improve their quality of life and their overall life expectancy. The results of this study could suggest novel approaches for future non-human primate and human clinical trials. The authors are in the process of designing a clinical trial treating HIV-infected subjects with IL-2 SA.

b) Procedures employed in this project:

Please check the appropriate boxes if any of these procedures will be employed in your project:

| | | |
|---|---|---|
| <input type="checkbox"/> Monoclonal Antibody Production ** | <input type="checkbox"/> Food or water restriction | <input type="checkbox"/> Special diets; food or water treatment. |
| <input type="checkbox"/> Polyclonal Antibody Production ** | <input type="checkbox"/> Non-recovery surgical procedures | <input checked="" type="checkbox"/> Induced illness, intoxication, or disease |
| <input type="checkbox"/> LD 50 or ID50 studies. | <input type="checkbox"/> Survival surgical procedures | <input type="checkbox"/> Death as an endpoint (see i below) |
| <input checked="" type="checkbox"/> catheters, blood collection, intubation | <input type="checkbox"/> Multiple survival surgery | <input type="checkbox"/> Trapping, banding or marking wild animals |
| <input type="checkbox"/> Prolonged restraint. (8 hrs+) | <input type="checkbox"/> Behavioral modification. | <input type="checkbox"/> endoscopy |
| <input checked="" type="checkbox"/> Fasting prior to a procedure. | <input type="checkbox"/> Aversive conditioning. | <input type="checkbox"/> |

** If this protocol only describes antibody production, you may use the attached antibody production page in lieu of completing section c below.

c) Describe the use of animals in your project in detail, with special reference to any of procedures checked above. Include any physical, chemical or biological agents that may be administered. List each study group, and describe all the specific procedures that will be performed on each animal in each study group. Use terminology that will be understood by individuals outside your field of expertise. (Note: This cell will expand to whatever length you require. You may make this section as long as you wish, but try to be concise. Some projects may require one or two pages.)

Experimental Design: Following baseline measurements, 18 macaques will be infected with 1 ml of 1000 TCID₅₀ (tissue culture infectious dose causing 50% cell death) SIVmac₂₅₁ intravenously and monitored for SIV disease progression. Peripheral blood will be collected on days 7, 14, and 28 p.i., and monthly thereafter (10 mls) up to the time of euthanasia (6 months after the first IL-2SA treatment). Blood samples will be used for the determination of virus replication levels, peripheral blood lymphocyte (PBL) subset analysis and Chem20 panel analysis. At the time of viral set-point (around 10 weeks p.i., no later than 6 months p.i.), blood and CSF (1 ml) samples will be obtained for each animal and IL-2 SA treatment will be started. Nine animals (placebo group) will receive subcutaneous injection twice daily (8 hours apart) of saline (1 ml). The other 9 monkeys will receive subcutaneous injection twice daily (8 hours apart) of IL-2 SA (6.7 mcg/kg) for five consecutive days (Bayer). The treatment will be administered for 5 consecutive days in 3 treatment cycles that are 4 weeks apart. All animals will be bled before each treatment cycle (10 ml), and 3 days (10 ml) after each treatment cycle. Samples will be analyzed for SIV plasma viral RNA, CBC, and a blood chemistry panel. In addition, T cell proliferative responses will be measured. The primary safety laboratory measurements will be complete blood cell counts and the liver transaminase ALT. Dose adjustment of IL-2 SA will be made as necessary. Six months after the start of IL-2 SA treatment, all animals will undergo necropsy. The lymphoid (spleen, lymph nodes, thymus) and non-lymphoid tissues (liver, kidney, heart, adrenals, gall bladder, jejunum, ileum, stomach, cecum, pancreas) will be collected to analyze the effect of IL-2 SA on SIV viral RNA levels in plasma and tissues as well as to assess histological changes due to IL-2 SA treatment: blood, CSF, thymus, lymph nodes and spleen. Parameters of host immune responses to be measured include SIV specific immunity for CD4+ T-cell function (lymphocyte proliferation responses) and lymphocyte subset analysis and distribution by FACS analysis (flow cytometry). Virologic, pharmacokinetic and pharmacodynamic parameters will also be measured to establish dose effect relationships. **Data analysis:** Each animal will serve as its own control. In addition, animals will be grouped by treatment intervention. The primary endpoint is the assessment of viral RNA levels and SIV-specific CD4 T cell immune responses in blood and lymphoid tissues. Tissue and plasma samples will be preserved for additional evaluation.

All animals will have weekly weight determination according to CNPRC guidelines. Daily CNPRC staff observation of the specially housed, infected animals will be utilized to monitor the animals. All animals will be euthanized 3 months after the last treatment cycle and CSF, blood and lymphoid tissues will be collected. Animals will be euthanized as specified in the CRPRC guidelines "criteria for euthanasia of retrovirus infected macaques". A complete necropsy will be performed for each animal and peripheral and systemic lymphoid tissues will be prepared for histological, immunohistochemical, flow cytometric, bDNA and PCR analysis.

Note:

All animals will be fasted before blood and CSF collection and anaesthetized for blood draws and CSF collection. The blood volume will be adjusted according to each animal's weight as not to exceed the allowed blood volume of 12.5 ml/kg/month.

CSF collection: After anesthesia (ketamine), the anterior dorsal rim of the iliac crest or head of humerus is identified by palpation. An 18 or 20 gauge 1-1 1/2 inch bone barrow aspiration needle is advanced in a rotating manner 5-15 mm depending on the size of the animal. The stylet will be removed and a syringe will be attached to the aspiration needle. Suction will then be applied. Note that after each pull, the needle should be rotated 90 degrees to redirect the direction of aspiration. Not more than 1 ml of CSF will be collected. Post-procedure analgesics will be applied at the veterinarian's discretion.

d) **Study Groups and Numbers:** Define, in the form of a table, the numbers of animals to be used in each experimental group described above. The table may be presented on a separate page as an attachment to this protocol if you prefer. The Normal format should be three columns: Study Group, Procedure, Number of animals. The number of rows should follow from the number of study groups; **you may add as many rows as you require.** The chart must fully account for the number of animals you intend to use under this protocol. Assign each group to an invasiveness category according to the chart below.

| Group | Procedures / Drugs | Number of Animals | Category |
|-------|---|-------------------|----------|
| 1 | After 10 –24 weeks of SIVmac ₂₅₁ infection, subcutaneous injection of placebo. Placebo treatment will be administered twice daily subcutaneously for 5 consecutive days in 3 cycles, each 4 weeks apart. Pretreatment phlebotomy and CSF collection to measure status of SIV infection. Pre- and post treatment blood collection, necropsy at 3 months after last treatment cycle. | 9 | 3 |
| 2 | After 10 –24 weeks of SIVmac ₂₅₁ infection, subcutaneous injection of IL-2 SA. IL-2 SA treatment will be administered | 9 | 3 |

| | | | |
|--|--|--|--|
| | twice daily subcutaneously for 5 consecutive days in 3 cycles, each 4 weeks apart. Pretreatment phlebotomy and CSF collection to measure status of SIV infection. Pre- and post treatment blood collection, necropsy at 3 months after last treatment cycle. | | |
|--|--|--|--|

Categories of invasiveness

| Category | Description |
|----------|--|
| 1 | Little or no discomfort or stress Examples: domestic flocks or herds being maintained in simulated or actual commercial production management systems; the short-term and skillful restraint of animals for purposes of observation or physical examination; blood sampling; injection of material in amounts that will not cause adverse reactions by the following routes: intravenous, subcutaneous, intramuscular, intraperitoneal, or oral. |
| 2 | Minor stress or pain of short duration Examples: cannulation or catheterization of blood vessels or body cavities under anesthesia; minor surgical procedures under anesthesia, such as biopsies or laparoscopy; short periods of restraint beyond that required for simple observation or examination, but consistent with minimal distress |
| 3 | Moderate to severe distress Examples: major surgical procedures conducted under general anesthesia, with subsequent recovery; prolonged (several hours or more) periods of physical restraint; induction of behavioral stresses such as maternal deprivation |
| 4 | Severe pain near, at or above the pain tolerance threshold Examples: exposure to noxious stimuli or agents whose effects are unknown; exposure to drugs, chemicals, or infectious agents at levels that markedly impair physiological systems and which cause death, severe pain, or extreme distress; Surgical experiments which have a high degree of invasiveness. |

Further descriptions of these categories are included in the instructions following this document.

e) **Rationale for species and numbers:** How did you determine that 1) the species choice was appropriate and 2) the number of animals in each study groups was the minimum number necessary to achieve sound scientific results?

SIV and SHIV infection of nonhuman primates remains the optimal model for studying HIV immunopathogenesis and for testing novel therapeutic strategies. Access to large numbers of lymphoid tissue cells during and after treatment will afford extensive and detailed analysis of the immune response in the setting of IL-2 SA. The results of this study could suggest novel approaches for future non-human primate and human clinical trials. A group number of 9 animals is necessary to obtain data that can reveal statistically significant differences between the IL-2SA treated and placebo group (see et al., 2001).

f) **Surgery:** If the project involves survival surgery, where will the surgery be conducted?

Building:

Room:

Who will be the surgeon?

g) **Anesthetics, Analgesics, Tranquilizers, Neuromuscular blocking agents:**

Post procedural analgesics should be given whenever there is possibility of pain or discomfort that is more than slight or momentary. If postoperative analgesics are not to be given, justify the practice under part (i) below.

Provide the following information about any of these drugs that you intend to use in this project.

| Species | Drug | Dose (mg/kg) | Route | When and how often will it be given? |
|----------------|---------------|---------------|-------|--|
| Rhesus macques | Telazol | 5 mg/kg | IM | before biopsy procedure |
| Rhesus macques | Ketamine | 10 mg/kg | IM | as analgesic before blood draws and CSF collection |
| Rhesus macques | Buprenorphine | 0.1-0.3 mg/kg | IM | BID for 3 days, discretion of CNPRC vets |
| | | | | |

h) **Neuromuscular blocking agents** can conceal inadequate anesthesia and therefore require special justification. If you are using a neuromuscular blocking agent, please complete the following:

Why do you need to use a neuromuscular blocking agent?

What physiologic parameters are monitored during the procedure to assess adequacy of anesthesia?

Under what circumstances will incremental doses of anesthetics-analgesics be administered?

i) Adverse effects:

Describe any potential adverse effects of the experiment on the animals (such as pain, discomfort; reduced growth, fever, anemia, neurological deficits; behavioral abnormalities or other clinical symptoms of acute or chronic distress or nutritional deficiency)

Discomfort may accompany CSF collection, however animals are anesthetized during the entire procedure.

Blood collection may be associated with minimal discomfort.

IL-2 SA treatment may lead to increased pathology in SIV infected monkeys. However, preliminary studies performed by Bayer did not show any severe side effects of the proposed dose in monkeys. In some human patients, skin rashes have been observed and required treatment with Motrin/ Benadryl.

Toxic side effects observed with IL-2 treatment are reduced using IL-2SA due to a single amino acid change in IL-2 SA that greatly reduces the potential toxic side effects of IL-2.

Animals will be euthanized according to CRPRC criteria for euthanasia of SIV infected macaques. This would include weight loss of >15% in 2 weeks, persistent leukopenia, total WBC<3,000, opportunistic infections that do not respond to therapy, dehydration >7% and not responsive to oral hydration therapy for 3 days, lymphopenia, abdominal lesions and severe depression (obtusion).

How will the signs listed above be ameliorated or alleviated? If signs are not to be alleviated or ameliorated by means of post-operative analgesics or other means, explain why this is necessary.

Analgesics or any post-operative procedures may be utilized as deemed necessary by the attending veterinarian.

Note: if any unanticipated adverse effects not described above do occur during the course of the study, a complete description of those effects and the steps taken to mitigate them must be submitted to the committee as an amendment to this protocol.

Is death an endpoint in your experimental procedure? Yes No

(Note: "Death as an endpoint" refers to acute toxicity testing, assessment of virulence of pathogens, neutralization tests for toxins, and other studies in which animals are not euthanized, but die as a direct result of the experimental manipulation). If death is an endpoint, explain why it is not possible to euthanize the animals at an earlier point in the study. If you can euthanize the animals at an earlier point, describe the clinical signs which will dictate that an animal will be euthanized.

j) Literature search for alternatives and unnecessary duplication:

This section is specifically required by Federal law. You are required to conduct a literature search to determine that either 1) there are no alternative methodologies by which to conduct this study, or 2) there are alternative methodologies, but these are not appropriate for your particular study. "Alternative methodologies" refers to reduction, replacement, and refinement (the three R's) of animal use, not just animal replacement. You must also show that the study is not unnecessarily duplicative of other studies.

What was the date on which you conducted this search?

July, 2003

List the databases searched or other sources consulted (there should be more than one). Include the years covered by the search.

| Database Name | Years Covered | Keywords / Search Strategy |
|---------------|----------------|--------------------------------------|
| PubMed | 1990 - present | Non-human primates, IL-2, HAART, SIV |

| | | |
|------------------|----------------|--------------------------------------|
| Current Contents | 1990 - present | Non-human primates, IL-2, HAART, SIV |
| | | |

What were your findings with respect to alternative methodologies?

There are no known alternatives to the procedures used in this study.- IL-2SA is related to IL-2, but is a novel compound (see section 2a) that has not been tested in clinical trials.

Has this study been previously conducted?

Yes No

If the study has been conducted previously, explain why it is scientifically necessary to replicate the experiment.

k) **Disposition of animals:** At what point in the study, if any, will the animals be euthanized?

All animals will be euthanized 3 months after the last treatment period. If an animal develops SAIDS before the end of this period, the animal will be euthanized at that time.

l) **Methods of euthanasia:** Even if your study does not involve killing the animals, you should show a method that you would use in the event of unanticipated injury or illness. If anesthetic overdose is the method, show the agent, dose, and route.

| Species | Method | Drug | Dose (mg/kg) | route |
|------------------|---|----------------------|--------------|-------|
| rhesus macacques | deep ketamine anesthesia followed by barbiturate overdose | Sodium pentobarbital | 60 mg/kg | I.V. |
| | | | | |
| | | | | |

m) **Surplus animals:** What will you do with any animals not euthanized at the conclusion of the project?

N/A

ANIMAL ROOM SAFETY INFORMATION

Complete this form if you will be using biohazards, radioisotopes, carcinogens, or toxic chemicals in the animal room.

PROTOCOL # 10794**EXPIRES:** _____

RUA#: _____

BUA#: 0669

CCA#: _____

Identity of Hazard:

SIV

Investigator Last Name:

Department:

First Name:

Phone:

Email:

Fax:

Provide a short description of the agent:

SIV (simian immunodeficiency virus) is a blood born lentivirus that causes fatal immunodeficiency (AIDS) in rhesus macaques. It is genetically similar to HIV. SIV can infect humans but it is unknown whether it can cause disease.

This agent / material is hazardous for: Humans only Animals only Humans and Animals
For which Animal Species? **Non-human primates**

The agent can be spread by: Blood Feces/urine
 Saliva/nasal droplets Does not leave animal
 Other: mucosal contact (eye/ mouth/nose/ genital)

Describe any human health risk associated with this agent:

SIV can infect humans; thus, it could possibly cause fatal AIDS-like disease in humans. SIV-infected humans have generated infectious virus and antibodies to SIV. There have been no reports of disease seen in SIV-infected humans.

The precautions checked below apply to this experiment:

- The researcher or his/her technicians are responsible for the feeding and care of these animals.
 The following items must be assumed to be contaminated with hazardous material and must be handled only by the researcher or his/her technicians.
 Cage Stall Water Bottle Animal Carcasses
 Bedding Other:
 Cages must be autoclaved before cleaning.
 Label cages and remove label after decontamination.
 Animal carcasses must be labeled and disposed of as follows:
 Incineration Biohazardous Waste Container
 Bag and Autoclave EH&S will pick-up (2-1493).
 All contaminated waste (soiled bedding or other animal waste) must be properly labeled and disposed of as follows:
 Incineration Biohazardous Waste Container
 Bag and Autoclave EH&S will pick-up (2-1493).

Personal Protective Equipment Required:

- The following personal protective equipment must be worn/used in the room:
 Lab Coat/Coveralls Shoe Covers/Booties
 Disposable Gloves Head Cover
 NIOSH Certified Dust Mask Disinfectant footbath
 Eye Protection/Face Shield
 Fitted Respirator Type:
 Other: Describe: **disposable gown/coveralls**
 Personal protective equipment must be removed before leaving the room.
 Personal protective equipment must be discarded or decontaminated at the end of the project
 Hands, arms, and face must be thoroughly washed upon leaving the room
 Full shower, including washing of hair, must be taken upon leaving the room.
 Decontaminate Room (Inform ARS area supervisor when cage and/or room can be returned to general use).

Provide any other information needed to safely work in this room:

Biosafety level 2+ (BSL2+) precautions must be followed at all times

Date: Tue, 02 Sep 2003 10:52:56 -0700
 To:
 From:
 Subject: Fwd: Re: AUC 10794

Hi,

please find enclosed the revised AUC 10794. Do you look this over or should I send this message directly to ?

The following points have been addressed:

Protocol 10794 () Effects of IL-2SA therapy on viral replication.....

1. On page 1, in the procedures section, there appears to be an incomplete sentence with information missing. Please review the third sentence and provide the missing information.

Additional information was provided in sentence 3.

2. In section c, the following questions need clarification:

a. How much (cc or ml) of the SIV will be administered IV?

1 ml SIV will be administered. This information has been added to section c.

b. You mention that blood samples will be collected monthly after the first 28 days of sampling. How many months will the collections be taken?

All animals will be euthanized 6 months after the first treatment, and thus monthly blood collection will taken an additional 5 months.

c. You go on to mention the collection of CSF samples. How much CSF will be collected at each time point? Will this be performed under anesthesia? Please expand to include whether the animal is fasted for the procedure and anesthesia used or if no anesthesia, how will the animals be restrained?

1 ml of CSF will be collected.

All animals will be fasted before blood and CSF collection, and all animals will be sedated for these procedures. This information has benn added to section c.

3. In section e, you state that this protocol is a pilot project, but you are using 9 animals per group. Why do you need 9 animals per group for a pilot project? Please clarify.

While 9 animals per group may seem large at first glance, this number is necessary to detect statistically significant differences between the IL-2SA treated and placebo treated animals.

4. In section g, you list buprenorphine and oxymorphone as analgesics, but have not mentioned their use in section c. Please expand section c to include a discussion about the possible use of analgesics post procedure.

Section c now contains a sentence stating that animals will be sedated before blood and CSF collection.

suggested that we remove oxymorhane from the protocol and add ketamine as analgesics for blood and CSF collection (see sectiong).

5. In section j, you have only listed one database, when the instructions for this section state that "Federal law specifically requires this section be complete" and asks you to provide "more than one" source. Please expand this section to include at least one additional database.

An additional database was checked and added to section j.

Please let me know if you need any further info,

Thanks.-



9/8/03
Pre review questions protocol 10794 from
Hi ,

I have received the following committee questions for protocol 10794, which is on this week's committee agenda.

Please return the questions with the response on or before Thursday noon.
(Note: since there have been a request to revise sections of the protocol, I have attached a copy of the protocol to make the appropriate revisions for the committee.)

Thanks,

Protocol 10794 ()

1. Page 2 - The summary is not really a summary, rather it has the details for the experimental design. Please provide a summary to reflect what is requested: the overall intent with hypothesis, objectives, and significance.
2. In section e, although a rationale was provided for the numbers when asked (reflecting the need for statistical significance), the total numbers and the rationale provided indicate this is not a pilot study. This may be an initial study for the investigators to determine outcome, but not what the Committee has considered a pilot in the past. Please clarify.
3. Section c - The investigator indicates juvenile monkeys without the weight range; will the total volume proposed for blood collection be within the acceptable limits per month based on body weight? This is not clear. Please clarify.
4. In section j, the investigator does not indicate/cite other published literature in rhesus on SIV infection and treatment with IL-2, and indicate the difference with the study proposed (thus supporting lack of redundancy). Phase II and III trials with IL-2 in HIV-infected human patients have been done, thus this is not a unique approach, and the difference with the proposed studies should also be highlighted to emphasize lack of redundancy. This should be addressed in the revised Summary of Procedures (a).
5. Section k-Disposition - sentence appears incomplete.

Date: Wed, 10 Sep 2003 11:06:08 -0700
To:
From: >
Subject: Fwd: AUC#10794

Date: Wed, 10 Sep 2003 09:19:51 -0700
To:
From:
Subject: AUC#10794

Hi ,

attached is the revised AUC #10794. The following changes have been made to answer questions:

The summary in section 2a has been rewritten. It now also includes a description of IL-2SA.

The term "pilot study" has been eliminated from section 2e. It is a first study that we will use to obtain future grant support. Further, a reference has been cited to justify the relatively large number of animals needed to detect statistically significant differences between the 2 treatment groups.

In section 2c, a sentence has been added stating that the blood volume will be adjusted according to each animal's weight, so that the maximum allowed blood draw volume will not be exceeded.

In section 2j, the novelty of IL-2SA compared to commonly used IL-2 is mention, but the reviewers are referred to section 2a where the differences between IL-2 and IL-2SA are explained.

Regards,