SUMMARY STATEMENT

Dr. Diane Sayre
301-496-8866
SAYRED@CTEP.NCI.NIH.GOV

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Application Number: **1 R03 CA78345-01**

WESTCOTT, THOMAS K MD
NIELS BOHR COLLEGE OF MED
DEPARTMENT OF SURGERY
1100 CENTRAL AVE
NEW YORK, NY 10461

Review Group: **NCI-D (O2)**
National Cancer Institute IRG D

Meeting Date: **08/03/1998**
Council: **OCT 1998**
Requested Start: **07/01/1998**

RFA/PA: **PAR97-006**
PCC: **A2HP**

Project Title: **ANALYSIS OF A CANARYPOX VACCINE EXPRESSING CEA AND B7**

SRG Action: **Priority Score: 211**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **1A-Both Children and Adults, scientifically acceptable**
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	50,000	50,00
2	50,000	50,00
TOTAL	100,000	100,000

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

RESUME AND SUMMARY OF DISCUSSION: This application was submitted in response to Program Announcement Request (PAR) PAR-97-006, "Small Grants for Therapeutic Clinical Trials of Malignancies." The goal of this project is to evaluate the clinical and immunological effects of a recombinant canarypox virus (ALVAC) expression human carcinoembryonic antigen (CEA) and the co-stimulatory molecule B7- 1 in patients with advanced CEA-expressing tumors. The addition of B7-1 to the vaccine is predicted to enhance the generation of CEA-specific T-cell responses and thus break tolerance to the weakly immunogenic CEA. The optimum tolerated dose, clinical toxicity, and anti-tumor activity of the vaccine will be determined in a dose escalation phase I clinical trial. The application is somewhat innovative in the addition of CD80 to CEA in an ALVAC vector. Both the antigen and vector, however, have been studied in humans. The major weaknesses of the proposal are in the lack of detail and proven feasibility of the Principal Investigator to perform the detailed cellular analysis proposed, as well as issues with the patient population being studied. Support at the requested level is recommended for this very good application for a period of two years.

DESCRIPTION (provided by applicant): Nearly 500,000 patients are diagnosed annually with solid tumors that express carcinoembryonic antigen (CEA). Recent studies suggest that CEA may be a useful target for vaccine development and could, thus, benefit a large number of cancer patients. However, CEA is a self-antigen and avoiding or breaking tolerance may be required for effective anti-tumor immunity. Activation of T-cells requires both the interaction of a peptide-MHC complex with the corresponding T-cell receptor and the interaction of co-stimulatory molecules on antigen-presenting cells (APCs) with the appropriate T-cell ligand. The goal of this project is to evaluate the clinical and immunological effects of a recombinant canarypox virus (ALVAC) expressing human carcinoembryonic antigen (CEA) and the co-stimulatory molecule B7-1 in patients with advanced CEA-expressing tumors. The addition of B7-1 to the vaccine is predicted to enhance the generation of CEA-specific T-cell responses and thus break tolerance to the weakly immunogenic CEA. The optimum tolerated dose, clinical toxicity, and anti-tumor activity of the vaccine will be determined in a dose escalation phase I clinical trial. Since patients in this trial will have advanced disease and the effectiveness of a vaccine may be limited, the patients will be evaluated for evidence of humoral and cellular immune responses as proof of vaccination. Evaluation of anti-CEA immunity will include serum CEA and cytokine levels, anti-CEA and anti-viral antibody titers by standard ELISA assays. Cellular immunity will be determined by using an intracellular interferon-gamma assay or, alternatively, by ELISPOT or in vitro stimulation assays to determine the change in CEA-reactive precursor frequency T-cells through the course of multiple vaccinations in individual patients. The phenotype of reactive Tcells will be determined and long-term cultures established. The results of this project should provide insights into the immunologic and clinical effects of this new vaccine and guide future strategies for the application of tumor vaccines.

CRITIQUE

The comments in the CRITIQUE Section were prepared by the reviewers assigned to this application and are provided without significant modification or editing by staff. The RESUME AND SUMMARY OF DISCUSSION section documents the final outcome of the evaluation by reviewers and is the basis for the assigned priority score.

CRITIQUE 1:

Significance: The study addresses an important problem which is the development of vaccines for colon cancer, an important tumor for which therapy improvements are needed. If the aims are achieved, this will provide (a) toxicity and clinical response information in the context of a phase I trial, on the effects of a novel canarypox vaccine construct that encode genes for both CEA and B7, and (b) the activity of this vaccine in terms of its ability to generate CEA specific cellular and humoral responses. These studies should be able to show whether the canarypox dual construct is well tolerated and whether it can generate responses that are at least equivalent to what has been observed in previous studies with the previous human vaccinia CEA and possibly better. This is a nonreplicating virus which has low immunogenicity and therefore may be more efficient than the human vaccinia construct. These studies may determine whether effective T-cell responses or antibody responses can

be generated as well with repeated vaccinations, and might open the way to definitive trials for these agents. The study represents a new approach with a viral vector construct that could possibly be safer, less immunogenic (in terms of the vector) and with enhanced immunogenicity related to the effects of the costimulatory ligand B7.

Approach: The clinical trial is well designed and the aims are appropriate to the aims of the project. The intent of the project is to determine an optimum tolerated dose. It may also detect clinical effects with the accrual of up to 18 patients. Specific Aim 1 will determine the "degree" of host immunity against CEA. There is some lack of clarity as to what outcome measures are to be used to measure success or failure from the immunologic standpoints. In other words, do the investigators have in mind a certain "degree" of specific responses, either cellular or humoral, as a target for their studies? It should be possible to design a reasonable statistical approach to examine this issue with the numbers of patients expected for accrual.

The investigator acknowledges potential problems with assays such as the ELISA spot assay, and provides some alternatives such as the intracellular FACS, although they may have their own problems. The proliferation assays proposed with T2 lines presumably will be for A2+ patients, although this is not clearly stated, nor is it stated whether alternative methods will be used for non-HLA-2+ patients.

Innovation: The aims and design are innovative and original and provide a new approach to the development of vaccines for colon cancer that could also impact on the development of vaccines for cancer generally.

Investigator: The investigator had an extensive experience as a Fellow at the NCI in the Surgical Branch and is publishing well in his area. Moreover, he has been actively involved in both the development of the constructs, and in the conduct of earlier trials.

Environment: The environment is outstanding and he continues a useful collaboration with Dr. J. Abraham, and has identified clinical collaborators who will be important for the project.

OVERALL EVALUATION: Overall, this is a very good proposal and seeks to evaluate a new viral vector construct that encodes the gene for CEA and B7 in the treatment of colon and other CEA exposing cancer patients. The strength of the proposal includes a well written protocol with laboratory studies that should provide some correlative data on the immunological efficiency of this approach and perhaps lead to definitive clinical trials. Possible weaknesses include a lack of discussion of the endpoints and statistical approach to the analysis of these endpoints in the laboratory studies. They also do not address the possibility that CTLA-4 or molecules associated with induction of apoptosis may also be induced. While weaknesses stand out, they are reparable and given the experience of the investigators and collaborators and the numbers of patients available these weaknesses are expected to be overcome.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISKS: Adequate Risks and/or Adequate Protections – no concerns. Data safety and monitoring plan is included and is acceptable.

GENDER, MINORITY AND CHILDREN SUBJECTS: G1A, M1A, C1A – The clinical trial will include men and women age 18 and over. Minorities and non-minorities will be included - acceptable.

ANIMAL WELFARE: Not applicable.

BIOHAZARD: No concerns.

BUDGET: No concerns.

CRITIQUE 2:
Significance: CEA expressing tumors are some of the most common cancers found in humans and so targeting CEA as a immunogenic model for cancer vaccines is common. Several strategies have been used by multiple investigators to elicit immunity against CEA; CEA in vaccinia virus, peptide immunization, and CEA peptides loaded onto dendritic cells to name a few. The strategy presented here is to use CEA in canarypox virus. The canarypox vector has been used in several phase I studies and has been shown to have limited toxicity. In addition, CEA has been immunized against in a variety of vectors, including vaccinia, a similar strategy to canarypox. Therefore, the significance as a toxicity study is rather limited as both the antigen and vector have been used extensively. The proposal may attain greater significance due to the addition of CD8O to improve the immunogenicity of the vaccine. Therefore, the significance of the proposal is in (1) the evaluation of immunity to CEA, especially from a T-cell standpoint, (2) some comparison of the level of immunity generated to the "first generation" CEA vaccine-CEA in vaccinia, which has not been proposed.

Approach: Strengths: The protocol in terms of evaluating toxicity and safety is well written. The concept and plan of evaluation is well organized. The plan of analysis of the CEA antibody responses is well written and thought out including analysis for immune complexes.

Weaknesses: A weakness of the proposal is in the lack of detail and preliminary results of the immunologic monitoring for T-cell activity. The use of virus or pox constructs allows the theoretical generation of CTL responses. The ability to induce cytotoxic T lymphocytes by vaccination is still a major pitfall of cancer vaccine design. The Principal Investigator discusses that one of the potential problems is in the assays to measure CTL activity and proposes to use two newer assays which are being investigated by several groups as readouts for vaccine trials; ELISPOT and intercellular cytokine production by FACS analysis. Both ELISPOT and FACS analysis have sensitivity problems of their own and have been difficult to translate to clinical trial use. The Principal Investigator shows one example of an ELISPOT analysis from a previous trial with very little regarding method. Page 15, paragraph 1 he states "...the assay is cumbersome, laborious to reproduce, and has high background making analysis difficult to interpret...." This can be true, yet, in Specific Aim 1, this assay will be a baseline of comparison to the FACS based analysis? It is very unclear whether the Principal Investigator has the expertise in either of these difficult cellular analyses. The data shown in the preliminary results demonstrating IFNg production as measured by FACS were performed after a mitogenic stimulation. This is very different from antigen-specific stimulation. A better control to prove the ability to perform the method would be an example with CEA (surely there is some data from the vaccinia studies). Since the grant is based largely on immunologic monitoring (Specific Aim 1), and the Principal Investigator has published little to demonstrate proficiency in these studies, the Preliminary Results should do a better job in proving feasibility of accomplishing these analyses.

In addition, while the Principal Investigator states that the potential long term use of the vaccine is in patients with minimal disease, that is why there is a heavy concentration on surrogate endpoints such as immunologic analysis, the study will be run in patients with existing metastatic disease. The protocol states that patients should have evidence that they can mount an immune response as based on normal WBC, no evidence of infection, and no immunosuppressive disorder. These criteria are poor means of judging immunocompetence. Other strategies such as neoimmunization or skin testing with recall antigens may be better predictors of the ability to generate an immune response in this high risk group for anergy. Therefore, this calls into question the second specific aim, evaluation of toxicity. If the majority of the toxicity you intend to evaluate is due to the immunogenicity of the antigen or the vector and the patient can not mount an immune response, then the vaccine will be non-toxic. The reason the vaccine is well tolerated, however, is because it is not effectively immunizing.

Innovation: The use of the canarypox vector encoding both the tumor antigen, CEA, and CD8O is novel. The few reports of immunity generated to CEA with various vaccine strategies have shown that

the immunity (CTL) is most likely low level. Supplying accessory molecules for improving T cell interaction may increase the immunogenicity of the vaccine.

Investigator: The Principal Investigator has a strong clinical background and has been involved in clinical trials with CEA based vaccines. It is not clear how much background he has in running a laboratory for the analysis of immunologic responses. There are no publications re: immunologic analysis.

Environment: The interaction with Dr. Abraham is important, but it is unclear how much participation he will have as a consultant beyond supplying reagents.

OVERALL EVALUATION: Level of merit, very good.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISKS: Adequate Risks and/or Adequate Protections – no concerns.

GENDER, MINORITY AND CHILDREN SUBJECTS: The issue of gender, minorities and children is adequately addressed – G1A, M1A, C1A (Age 18 and over).

ANIMAL WELFARE: Not applicable.

BUDGET: The budget is appropriate.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW ADMINISTRATOR TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE
The applicant has addressed all of the issues regarding protection of human subjects and the committee has no concerns for the protection of human subjects in the proposed studies.

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE
G1A – The committee felt that an adequate number of women would be included in the proposed studies.

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE
M1A – The committee felt that an adequate number of minorities would be included in the proposed studies.

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE
C1A – Patients age 18 and over are eligible for the proposed studies and the committee felt that this was acceptable.

VERTEBRATE ANIMAL (Resume): NOT APPLICABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.
(Roster not included for this mock study section)