SUMMARY STATEMENT

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(Privileged Communication)

Release Date: 07/16/2004

Application Number: 1 R21 AR051974-01

MARSHALL, TREVOR G PHD
T G MARSHALL AND ASSOCIATES
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CALIFORNIA, CA 91360-1122

Review Group: ECDA
Epidemiology of Clinical Disorders and Aging Study Section

Meeting Date: 06/24/2004
Council: OCT 2004
Requested Start: 01/01/2005

RFA/PA: PA03-171
PCC: 1 D

Project Title: Sarcoidosis, Antibiotics and Remission Criteria

SRG Action: **
Human Subjects: E4-Human subjects involved - Exemption #4 designated
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Project Year	Direct Costs Requested
1	175,000
2	50,000
TOTAL	225,000

**NOTE TO APPLICANT: As part of the initial scientific merit review process, reviewers were asked to identify those applications with the highest scientific merit, generally the top half of applications that they customarily review. At the study section meeting, those applications were discussed and assigned a priority score. All other applications, including this application, did not receive a score. Provided is a compilation of reviewers' comments prepared prior to the meeting, without significant modification or editing by NIH staff.

NEW INVESTIGATOR

1R21AR051974-01 MARSHALL, TREVOR

CRITIQUE 1:

Significance: Sarcoidosis is a chronic, progressive, and debilitating disease that can affect multiple organ systems. The pathogenesis and etiology of the disease remains obscure. Current therapies primarily are empirical and may have little effect on the course of the disease. The investigator presents a novel alternative hypothesis to the pathogenesis of the disease. This alternative hypothesis suggests that L-form bacteria may play a role in pathogenesis of sarcoidosis and therefore antibiotics may have a role in the treatment of the disease. He presents preliminary data from a highly self-selected group of patients with sarcoidosis, treated in a non-standardized protocol, who self-report marked improvement in symptoms following antibiotic treatment. If the hypothesis proves correct and the preliminary results can be substantiated in appropriate randomized controlled clinical trials the results would change clinical practice and bring new hope to patients with sarcoidosis. However, the investigator does not adequately discuss how the results from this exploratory analysis will inform future investigations.

Approach: This application represents a request for funds to conduct an exploratory analysis of existing data as well as collection and analysis of new, follow-up data of patients previously treated with antibiotics for sarcoidosis. The application describes six specific aims; however, the research design and methods do not describe in sufficient detail how the aims will be accomplished. The investigator does not adequately address the threat to validity introduced by the selection bias in the historic cohort. The investigator states that he will identify measures, which can be used by clinicians to characterize remission from sarcoidosis, yet offers no applicable definition of remission nor does he list specific potential measures that will be evaluated. He also plans to derive a level of statistical significance for reports that antibiotic therapies are effective in inducing remission of patient-reported symptoms, yet offers no power analysis describing what level of difference might be detected in this rather small cohort of approximately 50 patients. Finally, the investigator plans to identify the roles of the hormones 1, 25-dihydroxycholecalciferol and angiotensin II in sarcoidosis; however, in a retrospective and exploratory analysis it is doubtful that any mechanism can be defined.

Innovation: The major strength of this application is the attempt to explore a very novel hypothesis regarding the etiology and pathogenesis of sarcoidosis.

Investigators: The investigator has a substantial record of success in a variety of other endeavors including biomedical technology research. However, this is his first application for NIH funding. Including a consultant or collaborator on the research team with more extensive experience in clinical and epidemiological research could strengthen the application.

Environment: The research environment raises some concern. T. G. Marshall and Associates, the Investigator Organization, appears to have adequate facilities and infrastructure to support data management; however, there is no detail describing the organization's experience managing this type of research. The application also describes Autoimmunity Research, Inc., a consortium in formation that may be able to assist with this study; however, no details are provided. The application does not name or describe the processes to gain Human Subjects Research Institutional Review Board evaluation and approval for conducting this study.

Protection of Human Subjects from Research Risks: Acceptable Risks. The investigator claimed exemption based on the use of questionnaires and general surveys and the collection and study of existing data. The justifications for these claims are adequate and supported in the application.

Inclusion of Women Plan: Adequate. Women comprised approximately 50 percent of the initial cohort.

Inclusion of Minorities Plan: Adequate. Minorities represented approximately 30 percent of the initial cohort.

Inclusion of Children Plan: Acceptable. In general, sarcoidosis is not considered a disease of childhood and therefore a plan to include children is not required.

Overall Evaluation: This application describes exploratory research to gain insight into the potential role of antibiotics in the management and treatment of sarcoidosis. The application focuses on exploratory analysis of existing data from a self-selected historical cohort of patients with sarcoidosis who apparently responded to antibiotic therapy and collection of follow-up data for analysis. The major strength of this application stems from its novel hypothesis regarding the etiology and pathogenesis of sarcoidosis. There are serious weaknesses that need to be addressed. First, the historic cohort that is the target of this application is a highly self-selected group of individuals, who have been managed without benefit of a specific protocol and who have reported data sporadically. The inherent bias in this cohort may temper the validity of any conclusions that might result from the exploratory analysis. Second, the research methods are not developed adequately nor tied sufficiently to the specific aims to provide the necessary assurances that this project has a high likelihood of success. Third, the research team and research environment may experience difficulties in completing this study. In particular, the principal investigator does not discuss limitations adequately or offer alternative approaches or strategies to overcome any anticipated problems. Despite the potential impact that could result from this study, the substantial limitations significantly limit the overall enthusiasm for this application.

Budget: The budget as presented appears appropriate for the time and effort necessary to conduct this study.

CRITIQUE 2:

Significance: Sarcoidosis is a rare disorder whose pathogenesis eludes investigators. It is a disorder with variable clinical course, often characterized by exacerbations and/or spontaneous remissions. Scattered publications over two decades have purported to identify the role of cell wall deficient bacteria and other pathogens as common antigens responsible for initiating and perpetuating the immune dys-regulation. Interesting aspects of the disease include evidence of immune activation at sites of disease, and immune suppression in the circulating immune cells. Identification of a responsible antigen would significantly advance the understanding of this disease and open new possibilities for definitive therapy.

Approach: This exploratory project proposes to do a retrospective chart /medical information review of a self-selected cohort of patients with sarcoidosis, all of whom have taken the treatment regimens in question. It appears that this will be a retrospective chart review of an unblinded, treatment cohort. There are no control groups. The study instruments and methods are incompletely developed. For example, standardized data collection sheets are not provided. A major limitation of other commonly used treatments (e.g., oral corticosteroids) is that they were not subjected to randomized placebo controlled studies. This application has not addressed this critical issue: how will the investigators be able to distinguish between spontaneous improvement and treatment associated improvement? The enthusiasm for this treatment reflected in appended documents raises additional concern as to the investigators' ability to remain impartial in the assessment of unblinded data. Case-control methodology for sarcoidosis and its clinical assessment has been recently developed in the NIH funded multi-center study of sarcoidosis. It is unclear whether the investigators propose to use this methodology so as to permit comparisons between their study population and that of other study groups.

Innovation: The treatment regimen is novel.

Investigators: The investigators do not appear to have formal training, recent publications or established collaborations with epidemiologists or biostatisticians in studies using similar methods.

Environment: It is unclear whether the investigators are in an environment for peer review and criticism; this is typically provided by an academic medical institution.

Protection of Human Subjects from Research Risks: Acceptable. No concerns.

Inclusion of Women Plan: Acceptable.

Inclusion of Minorities Plan: Acceptable.

Inclusion of Children Plan: Acceptable.

Budget: The budget is acceptable as presented.

CRITIQUE 3:

Protection of Human Subjects from Research Risk: The principal investigator provides considerable explanation for protecting patient identity and records, but there is no information about patient protection in blood draws, if they are indeed part of the follow-up evaluation.

Data Safety and Monitoring Plan: Acceptable.

Inclusion of Women Plan: Acceptable. Women are included in the study in proportion to those in the community.

Inclusion of Minorities Plan: Acceptable. The population of study is comprised of anyone interested in participating. However, the original 50 patients to be enrolled for follow-up were not broken down by ethnicity.

Inclusion of Children Plan: Acceptable. Only individuals with sarcoidosis are to be enrolled and this is generally not a disease of children.

Overall Evaluation: This is an R21 application to evaluate the remission of sarcoidosis symptoms in a cohort of 50 patients who 2 years previously had taken antibiotics for their disease. The strength of the application is that it explores the potential bacterial etiology for the development and progression of sarcoidosis. If symptoms can be alleviated with simple bacterial therapy, it could lead to new treatments for the benign inflammatory tumors that occur in various organs. There are a number of severe weaknesses in the proposed study however. The R21 mechanism is to test feasibility of new treatments, but the effectiveness of this treatment has already been established, the study is simply collecting patient records for a 2-year follow-up. Therefore, it is not clear what new data, if any, will advance the field. The application also suffers from lack of preliminary data on the patients that were treated, lack of testable hypotheses, and lack of project design to demonstrate what patient symptoms are to be evaluated, how they will control for variability in the physicians and tests of the original evaluation of the patients, what statistical tests are to be employed, or what standards are to be used in analyzing the blood and imaging data, both original and new. A mention is made of blood work for the follow-up evaluation, but no description is provided as what blood parameters are to be measured, who will conduct the laboratory analyses, and how the principal investigator will employ it in assessing remission of organ system symptoms. The principal investigator, while enthusiastic, has not demonstrated direct experience in the clinical assessment, treatment, and study of this disease. Therefore, enthusiasm is quite low for the study as proposed.

Budget: While only minimal information is given about the patient evaluations planned, the budget appears quite inflated for a review of only 50 patient records. There is no justification for so many study personnel and their amount of effort. Therefore, recommendation is made to reduce the budget to only one or two modules for one year.

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 protection of human subjects from research risk appears adequate.

NOTICE: The NIH has modified its policy regarding the receipt of amended applications. Detailed information can be found by accessing the following URL address: http://grants.nih.gov/grants/policy/amendedapps.htm

NIH announced implementation of Modular Research Grants in the December 18, 1998 issue of the NIH Guide to Grants and Contracts. The main feature of this concept is that grant applications (R01, R03, R21, R15) will request direct costs in $25,000 modules, without budget detail for individual categories. Further information can be obtained from the Modular Grants Web site at http://grants.nih.gov/grants/funding/modular/modular.htm