COMPONENTS OF A GOOD GRANT PROPOSAL

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RESEARCH PLAN

GOOD IDEAS

- OVERALL GOAL
- SPECIFIC AIMS
- PRELIMINARY DATA

- HYPOTHESIS-DRIVEN GRANT
  - –ASK QUESTIONS IN TERMS OF A TESTABLE HYPOTHESIS

RESEARCH PLAN

- START WITH AN OUTLINE
- INCLUDE SUFFICIENT INFORMATION NEEDED FOR EVALUATION
- GRANT SHOULD STAND ALONE
- BE SPECIFIC AND INFORMATIVE
- TELL THE REVIEWER WHAT YOU ARE GOING TO DO AND HOW YOU ARE GOING TO DO IT

RESEARCH PLAN

- WHAT DO YOU INTEND TO DO?
- WHY IS THE WORK IMPORTANT?
- WHAT HAS ALREADY BEEN DONE?
- HOW ARE YOU GOING TO DO THE WORK?

GRANT PROPOSAL

- **SPECIFIC AIMS**
- **BACKGROUND AND SIGNIFICANCE**
- **PRELIMINARY DATA**
- **RESEARCH DESIGN AND METHODS**
- **LITERATURE CITED**

SPECIFIC AIMS

- **LIST LONG TERM OBJECTIVES**
- **WHAT IS THE SPECIFIC RESEARCH THIS APPLICATION IS INTENDED TO ACCOMPLISH**
- **STATE HYPOTHESES TO BE TESTED OR QUESTIONS TO BE ANSWERED**

HOST GENETIC CORRELATES IN SCHISTOSOMIASIS

- **A. SPECIFIC AIMS:** The overall goal of this grant is to define the contribution of host genetics to the initiation and outcome of infection with *Schistosoma mansoni*. To accomplish our goals we will identify relevant immunological phenotypes by their responses to defined schistosome antigens and use these phenotypes to identify loci (genes) involved in determining resistance/susceptibility to re-infection and the host contribution to different clinical forms of schistosomiasis. These studies are best performed on subjects from endemic areas, who are exposed to the parasite under natural conditions of transmission. Although experimental infections provide important information, they are not able to reproduce the complex interactions between genetic, immunological and environmental factors that determine patterns of disease epidemiology in human populations. The overall focus of this grant is to develop immunological phenotypes (variables) involved both in resistance/susceptibility to re-infection and development of different clinical forms of schistosomiasis and then to identify the genetic determinants (loci) of these immunological phenotypes. We will study large well-characterized extended families from endemic areas to address the following specific aims:

SPECIFIC AIMS

A.1. Develop immunological phenotypes by studying the B and T cell response to defined and crude antigens in a longitudinal study of extended pedigrees residing in areas endemic for S. mansoni.

A.2. Determine the contribution of environmental factors to the observed phenotypes as they relate to susceptibility/resistance to re-infection and disease states.

A.3. Using methods of quantitative genetics partition the variance of immunological phenotypes related to susceptibility/resistance to re-infection or disease state into genetic and non-genetic components.

A.4. To perform linkage analysis and combined linkage/disequilibrium analysis to determine the contribution of candidate genes involved in determining the expression of immunological phenotypes related to susceptibility/resistance to

re-infection and disease outcomes.

A.1. Develop immunological phenotypes by studying the B and T cell response to defined and crude antigens in a longitudinal study of extended pedigrees residing in areas endemic for S. mansoni.

The purpose is to evaluate the longitudinal humoral and cellular immune response of extended pedigrees residing in endemic areas as they correlate with reinfection and clinical schistosomiasis. After demographic, parasitological, and genealogical characterization of extended pedigrees residing in endemic areas, all pedigree members (egg-positive and egg-negative) will be asked for a blood sample prior to treatment and 6, 12, 24, and 36 months after treatment. We will focus on immunological phenotypes identified from previous human and animal studies to determine which humoral and cellular immune responses to defined schistosome antigens associate with the initiation and outcome of infection. The patients plasma will be analyzed for (a) specific isotypes (IgE, IgG1, IgG2, IgG3, IgG4, IgM, and IgA) against various crude antigens (adult worm, SWAP; egg, SEA) and defined antigens (p40, Sm20.8) and (b) levels of circulating cytokines (sIL-5, sTNF), receptors (sTNFR-1, sTNFR-II) and adhesion molecules (sICAM-1). We will also measure the proliferation of T cells to crude and defined schistosome antigens and the production of selected T cell-derived cytokines (IL-2, IFN-γ, IL-4, IL-5, IL-10, IL-13, TNF-α) in response to antigen stimulation. The results of this analysis will provide us with a panel of immune markers to defined *S. mansoni* antigens which will then undergo quantitative genetic analysis.

D.1. AIM 1. Develop immunological phenotypes by studying the B and T cell response to defined and crude antigens in a longitudinal study of extended pedigrees residing in areas endemic for S. mansoni.

- **Hypothesis:** That the immune response determines susceptibility/resistance to reinfection and disease outcome and selected phenotypes will associate with intensity of infection after re-exposure and/or disease. Therefore, we intend to define and develop quantitative immunological phenotypes related to schistosomiasis in extended pedigrees residing in areas endemic for *S.mansoni*.

- **Overview of experimental design:** Villages in endemic areas will be identified where transmission rates are high, transmission sites are limited, and treatment has not occurred previously or in the past 5 years (for example Melquíades). The immunological phenotypes will be taken from extended pedigrees residing in endemic areas of the Marilac region of Minas Gerais. They will be enrolled in a 3-year longitudinal study to assess reinfection with *S. mansoni* and changes in clinical forms of schistosomiasis. We will perform quantitative genetic studies in three independent areas. This will allow us to confirm the role of genetics and environment in determining the initiation and clinical outcome of schistosome infection. Some of the concepts such as heritability are population specific and by necessity need to be confirmed in independent environments and populations. In addition to Melquíades, a second area will contain members of the same pedigree as Melquíades but represent an independent environment. The third area will contain a different pedigree(s) and new environment.

BACKGROUND AND SIGNIFICANCE

- OUTLINE THE BACKGROUND LEADING TO THE PRESENT APPLICATION
- CRITICALLY EVALUATE EXISTING KNOWLEDGE
- IDENTIFY GAPS THAT THE PROJECT IS INTENDED TO FILL
- STATE IMPORTANCE OF RESEARCH DESCRIBED IN THE APPLICATION
- RELATE SIGNIFICANCE TO SPECIFIC AIMS

PRELIMINARY DATA

- SUPPORT THE AIMS OR HYPOTHESES
- DEMONSTRATE EXPERIENCE OR COMPETENCE OF PI
- DEMONSTRATE ABILITY TO PERFORM PROPOSED METHODS
- PROVIDE PUBLISHED AND UNPUBLISHED RESULTS

RESEARCH DESIGN AND METHODS

- SPECIFIC AIM

- PROVIDE HYPOTHESIS OR RATIONALE
- OVERVIEW OF DESIGN

- TECHNIQUES (METHODS) USED TO TEST HYPOTHESIS
- HOW WILL DATA BE COLLECTED, ANALYZED, AND INTERPRETED

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RESEARCH DESIGN AND METHODS

- DISCUSS EXPECTED OUTCOMES
- DISCUSS PROBLEMS, PITFALLS, LIMITATIONS OF THE PROPOSED PROCEDURES
- ALTERNATIVE APPROACHES
- TENATIVE TIMETABLE FOR PROJECT

OUTLINE

OVERALL GOAL

- **AIM 1:**
- **AIM 2:**
- **AIM 3:**

AIM 1:

- **HYPOTHESIS**
- **BACKGROUND AND SIGNIFICANCE**
- **PRELIMINARY DATA**
  - **IF NONE, DO I NEED TO GENERATE SOME**
- **RESEARCH DESIGN AND METHODS**

OUTLINE CONTINUED

AIM 1:

- **HYPOTHESIS**
- **BACKGROUND AND SIGNIFICANCE**
- **PRELIMINARY DATA**
  - **IF NONE, DO I NEED TO GENERATE SOME**
- **RESEARCH DESIGN AND METHODS**
  - **METHODS**
  - **CONTROLS**
  - **ANALYSIS (STATISTICS)**
- **EXPECTED OUTCOMES**
- **ALTERNATIVE APPROACHES**

OUTLINE CONTINUED

RESEARCH DESIGN AND METHODS

- **METHODS**
- **CONTROLS**
- **ANALYSIS (STATISTICS)**
- **EXPECTED OUTCOMES**
  - **IF I PERFORM EXPERIMENT, WHAT WILL HAPPEN**
  - **IS THIS THE BEST APPROACH, LIMITATIONS**
- **ALTERNATIVE APPROACHES**

AIM 2

AIM 3

OUTLINE

- OVERALL GOAL
  - AIM 1:
  - AIM 2:
  - AIM 3:
- AIM 1:
  - HYPOTHESIS
  - BACKGROUND AND SIGNIFICANCE
  - PRELIMINARY DATA
  - RESEARCH DESIGN AND METHODS
    - METHODS, CONTROLS, ANALYSIS
      EXPECTED OUTCOMES
    - ALTERNATIVE APPROACHES

INSTRUCTIONS

- COVER PAGE
- BIOGRAPHIC SKETCH
  - RECENT AND RELEVANT PUBLICATIONS
- BUDGET
  - REALISTIC
  - JUSTIFICATION
- REFERENCES
  - RELEVANT ONES
- LETTERS
  - COLLABORATORS
  - REAGENT PROVIDERS

FOLLOW INSTRUCTIONS

- **FONT SIZE**
- **MARGINS**
- **SPELL CHECKER AND GRAMMAR**
  - **HELP FROM COLLEAGUE**
- **PAGE LIMITATIONS**

OTHER ISSUES

- HUMAN SUBJECTS
  - INSTITUTIONAL REVIEW BOARD (IRB)
  - OFFICE FOR PROTECTION FROM RESEARCH RISKS (OPRR)
- ANIMAL WELFARE
  - INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)
- APPENDIX
  - SPECIAL FIGURES
  - MANUSCRIPTS: PUBLISHED AND IN PRESS

HAVE KNOWLEDGABLE COLLEAGUES READ PROPOSAL FOR SCIENCE AND FOR PROPER ENGLISH

WEBSITES

- http://nccam.nih.gov/nccam/fi/research/guidelines/firsttimers/index.html
- http://www.niaid.nih.gov/ncn/ap-bettr.htm
- http://nccam.nih.gov/nccam/fi/research/guidelines/firsttimers/quick-guide.html
- http://www.niaid.nih.gov/ncn/pdf/howto.pdf
- .niaid.nih.gov/ncn/toolmain.htm
- http://www.grantsnet.org