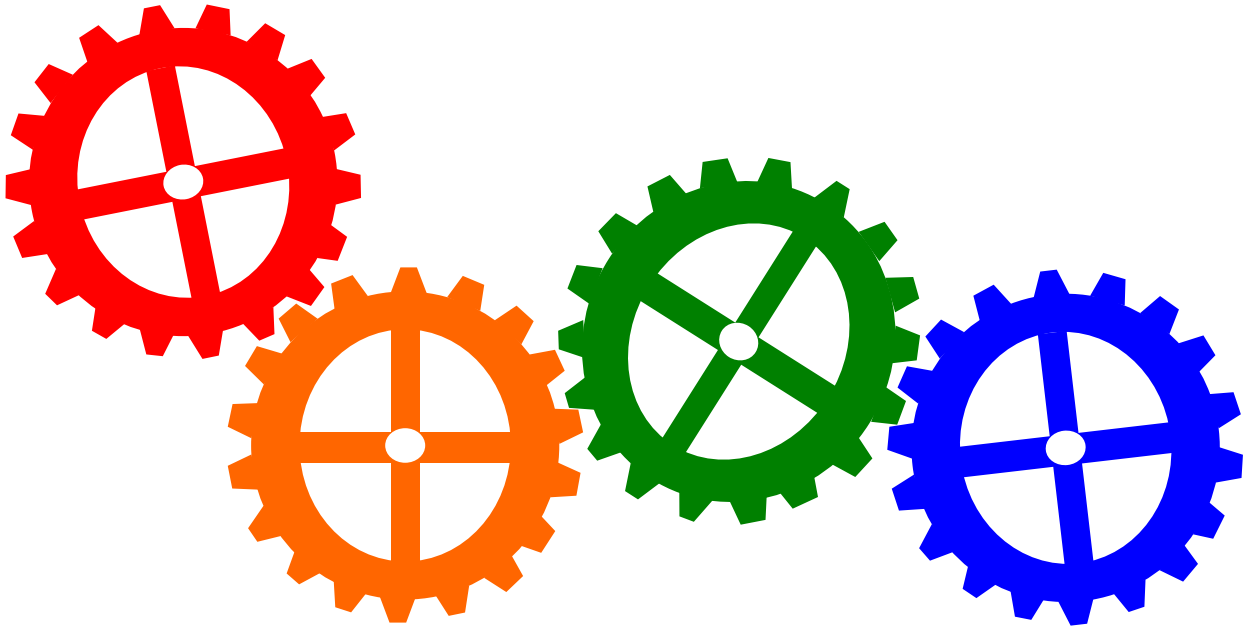
Writing the Specific Aims

Crystal Botham, PhD



Why is the Specific Aims document important?

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Perfect for eliciting feedback!

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It is a roadmap!

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Reviewers will read it!

Specific Aims Instructions

National Institute of Health (NIH)
*** 1 page ***

State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.

List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.

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Key Questions

Is the question important?

What specifically will be done?

What is the overall goal?

What is the expected payoff?

Gearing Up

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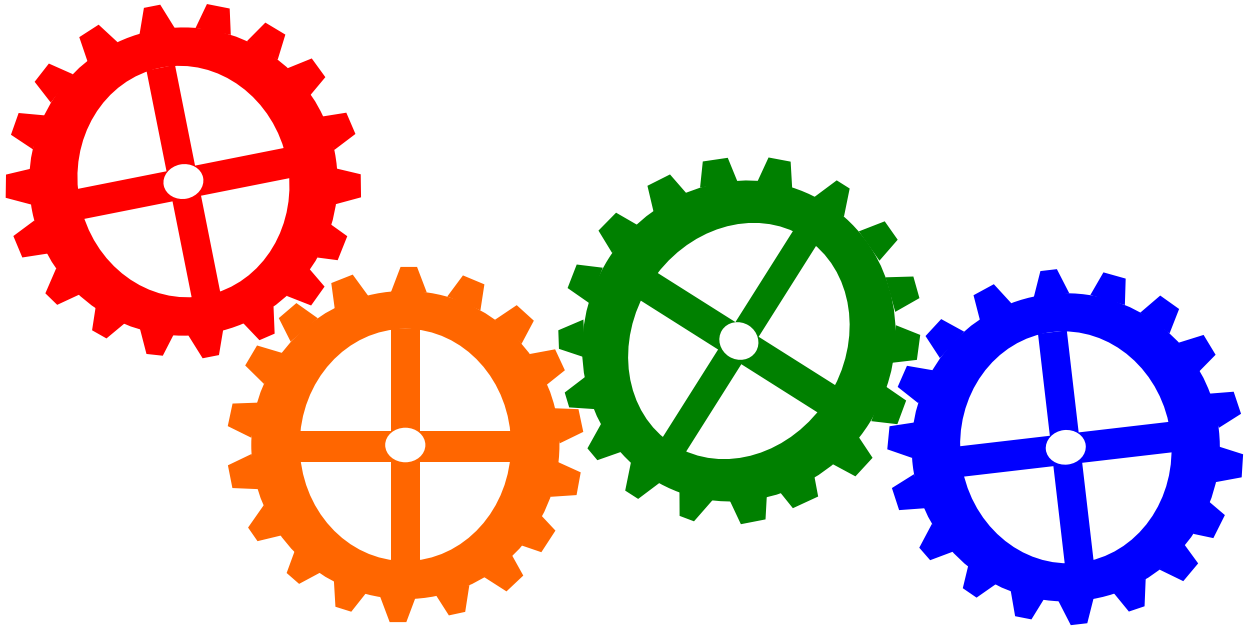
Use the answers to the 4 key questions to organize your Specific Aims document!



Specific Aims

1) Is the question important?

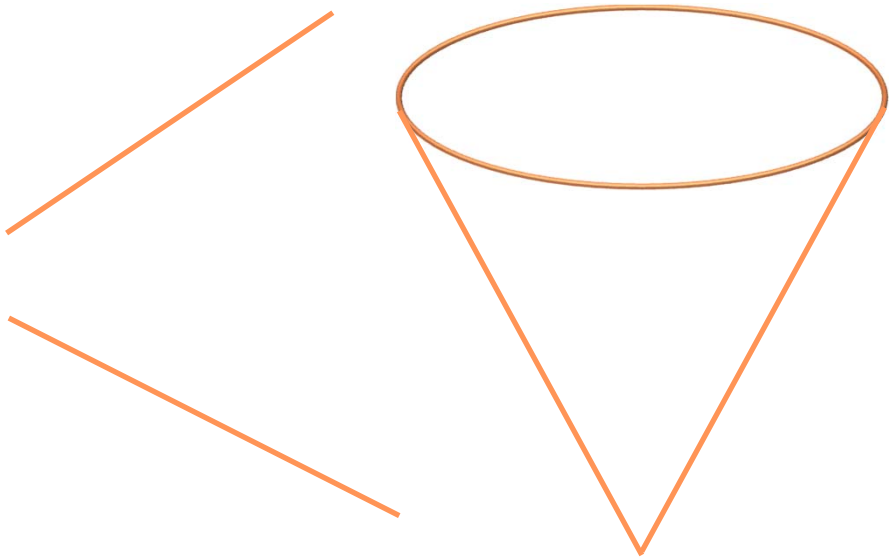
- Attention grabbing first sentence
- Bring reviewers up to speed
- Frame the knowledge gap/need

Specific Aims

1) Is the question important?

2) What is the overall goal?

knowledge gap



specifics

Specific Aims

1) Is the question important?

2) What is the overall goal?

- Big-picture goal
- Objective of this proposal
- Best bet / hypothesis
- Supportive preliminary data

Specific Aims

1) Is the question important?

3) What specifically will be done?

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- Aims
- Working hypotheses
- Methods

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- Return on investment
- Related to goals of the funding announcement

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SPECIFIC AIMS CONFIDENTIAL - DO NOT COPY

The demand for donor hearts for transplantation far outstrips the supply. With a growing population of patients living with end-stage heart disease in the U.S., waiting times for transplantation are increasing, thereby placing a large number of potential recipients at risk for adverse outcomes. Despite this donor organ shortage, *only one in three available donor hearts are currently accepted for transplantation, which greatly limits heart transplant rates nationwide*. There are many donor predictors of organ non-acceptance, but previous studies have failed to demonstrate consistent associations among these donor characteristics and adverse recipient outcomes. Prior studies are limited by (1) lack of detailed data on donor characteristics, (2) lack of carefully adjudicated data on donor heart function, and (3) lack of detailed data on reasons for donor heart non-acceptance. *Thus there is a critical need to standardize how donor hearts are evaluated and accepted for transplantation.*

Is the question important?

←Knowledge Gap

Our *long-term goal* is to safely expand the use of available donor hearts without adversely affecting transplant recipient outcomes. We propose to carefully characterize the current population of organ donors, particularly with regards to cardiac function; to examine how decisions are made regarding donor heart acceptance for transplantation; and to develop evidence-based tools to assist with real-time acceptance decisions. Our *central hypothesis is that acceptable hearts for transplantation are being unnecessarily discarded*. The establishment of an evidence-based process for cardiac donor evaluation and acceptance will increase donor heart acceptance rates while maintaining excellent clinical outcomes. In response to this need, we propose a collaborative study with organ procurement organizations representing distinct regions of the U.S. to address the following three *specific aims*:

What is the overall goal?

AIM 1. To identify clinical correlates of cardiac function in potential donors being evaluated for heart transplantation. An existing database will be expanded for standardized collection of detailed data on donor characteristics, especially as pertains to cardiac function. We will perform expert core review of donor transthoracic echocardiograms (TTEs), including serial TTEs in donors with cardiac dysfunction. We will also study serial electrocardiograms (ECGs) and cardiac biomarkers (Troponin I and B-type natriuretic peptide) (see **Figure 4**).

Hypothesis 1a: Left ventricular dysfunction (left ventricular ejection fraction <50%) is common in brain dead organ donors without pre-existing cardiac pathology and is largely reversible during the donor management period.

Hypothesis 1b: ECG abnormalities and elevated cardiac biomarkers are often transient during donor management, and are not necessarily associated with cardiac dysfunction in potential organ donors.

AIM 2. To prospectively study reasons for non-acceptance of hearts offered for transplantation. Real-time surveys will be conducted on specific reasons for non-acceptance of hearts offered for transplantation in order to study donor heart acceptance practices and variation in acceptance nationwide.

Hypothesis 2a: There will be variability among heart transplant centers in donor heart acceptance and clinical predictors of non-acceptance, such as advanced donor age, left ventricular dysfunction, and left ventricular hypertrophy.

Hypothesis 2b: Systems-based factors, including the day and time of organ offer, and the qualifications of the transplant center personnel evaluating the offer, will also be associated with non-use of donor hearts.

AIM 3. To develop clinical tools to assist transplant centers with real-time decisions regarding donor heart acceptance. Data will be collected on recipient re-hospitalization and survival to identify associations among donor characteristics and recipient outcomes. We will then develop a report that evaluates the quality of an offered donor heart with respect to other historically available hearts and anticipated recipient outcomes.

Hypothesis 3a: Specific donor characteristics, such cause of death and history of hypertension, are not strongly associated with adverse recipient outcomes after transplantation.

Hypothesis 3b: A "donor heart report" that summarizes the key donor characteristics predictive of heart acceptance and recipient outcomes will be created to aid transplant centers in real-time decision making.

What specifically will be done?

Completion of the proposed study may have an important *positive and immediate impact* by (1) defining how to optimize the evaluation and use of available donor hearts for transplantation and (2) safely expanding the donor pool by providing evidence supporting the use of organs previously felt to be unacceptable.

What is the expected payoff?

SPECIFIC AIMS

Understanding the basis of an immune response that controls infection or provides sterilizing immunity remains a major goal in the search for effective vaccines or immunotherapies for HIV. Antibodies (Abs) induced by candidate vaccines to the surface envelope glycoprotein have not neutralized a broad array of primary virus isolates. For this reason, eliciting a cytotoxic cellular response has been the primary goal in most recent vaccine trials. However, this approach has not been successful in containing viral replication in vaccinees that have become HIV-infected. Antibody-dependant cellular cytotoxicity (ADCC) has been shown to mediate sterilizing immunity against challenge with pathogenic simian immunodeficiency virus [Hessel 2007]. In ADCC, Fc-bearing Abs bind viral epitopes coating an infected CD4+ target T cell and an Fc receptor bearing effector, most commonly natural killer cells (NKs), bind the Ab and use perforin to deliver granzymes which induce apoptosis in the target. We want to study ADCC in infected patients to understand the magnitude and characteristics of the best responses achieved by natural infection. First, we will compare ADCC mediated by the sera of a cohort of patients using a granzyme B cytotoxicity assay developed in our lab. Based on these findings, we will select the sera of patients with the most ADCC, generate monoclonal Abs (mAbs), and characterize the mAbs based on epitope specificity, affinity, potency, breadth, IgG isotype, and Fc type. We wi also evaluate whether ADCC is disparate from classical neutralization. Finally we will use microscopy to examine the synapse between effectors, Abs, and targets. The outcome of this research will provide insight into the characteristics of Abs that mediate ADCC that are likely important goals in the design of HIV vaccines or immunotherapies.

Hypothesis: Antibody-dependent cellular cytotoxicity (ADCC) is a function that has been shown to mediate protection from lentiviral infection. We hypothesize that variations in ADCC activity of sera are dictated by the amount, specificity, and subclass of HIV-specific antibodies.

Aim 1: Characterize the potency of sera of HIV-infected individuals in ADCC.
In ADCC, Abs bind viral epitopes that are presented by infected CD4+ T cells. NKs expressing an Fc receptor bind the Fc domain of the Ab and use perforin to deliver granzymes to the HIV-infected cell. Subsequently, granzymes induce apoptosis within the cell. Our lab has developed a flow cytometric assay that measures granzyme B delivered to an HIV-infected CD4+ target T cell. We will classify ADCC by the percent of target cells receiving granzyme and the elimination of targets as defined by residual percent of targets expressing p24, HIV capsid.

a. Compare the serum of HIV+ individuals with various rates of progression and viral loads to determine which contain Abs capable of mediating the highest levels of ADCC.
b. Compare the ADCC and neutralizing activity of patient sera.

Aim 2: Characterize the specificity and breadth of antibodies with ADCC activity.
Our laboratory has panels of NAbs derived from patients with known serum neutralizing or ADCC-mediating activity.

a. Determine whether recognition of specific epitopes is required for ADCC.
b. Define the breadth of the polyclonal sera by its ability to mediate ADCC in CD4+ T cells infected by different clades of HIV.
c. Titer serum total IgG, IgG1, and IgG3 binding infected CD4+ T cells.

Aim 3: Characterize the structure and function of the target-effector synapse.
Using both fixed and live cell laser scanning confocal microscopy (LSCM), transmission electron microscopy (TEM) and cryo-electron microscopy (cryo-EM) and tomography, we will examine the synapse formed between NK and other cells with potential ADCC activity (macrophages and neutrophils) and infected target cells. We will specifically investigate:

a. The structure of a functional ADCC synapse.
b. The kinetics of ADCC function in real time and its relation to antibody type and specificity.
c. A role for antibody-dependent cell-mediated phagocytosis (ADCP) in elimination of HIV-infected cells.
d. Receptors and effector molecules central to ADCC activity against HIV infected cells.

Adjoa R. Smalls-Mantey (Columbia University Health Sciences) – 1F31AI098409 (NIAID)

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←Knowledge Gap

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←Central Hypothesis

What specifically will be done?

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FEEDBACK IS CRITICAL

Resources

Hollenbach, Andrew. *A Practical Guide to Writing a Ruth L. Kirschstein NRSA Grant*. Amsterdam: Academic Press, 2014. [ISBN 978-0-12-420187-3]

Russell, Stephen W. and David C. Morrison. *The Grant Application Writer's Workbook: National Institutes of Health Version*. Los Olivos, CA: Grant Writers' Seminars and Workshops, LLC, 2016. <www.grantcentral.com>

Yang, Otto O. *Guide to Effective Grant Writing: How to Write an Effective NIH Grant Application*. New York: Springer US, 2012. [eBook ISBN 978-1-4614-1581-7]

Sample NIH applications and summary statements are available here: https://www.niaid.nih.gov/grants-contracts/sample-applications