Writing Effective Grant Proposals

❖

SUPPLEMENTAL HANDOUT

EXERCISES
(*to accompany powerpoint slide presentation*)

Pamela Derish
Scientific Publications Manager
Department of Surgery, UCSF
tel 415.885-7686
Pamela.Derish@ucsfmedctr.org

Review the following goal statements and try to answer the following questions:
- What verbs are used to indicate the long-term goal?
- Is there a time-frame or end-point implied in the goal?
- One of these statements could be confused with another component of the proposal. Which one is it? Why can it be confused with another component?

Examples

1. Our long term goal is to determine the diagnostic and prognostic utility of genetic markers of thyroid cancer.

2. We aim to analyze the structural and molecular composition of SFG rickettsial antigens and to determine which components stimulate protective immunity.

3. The long term objectives of this project are to define mechanisms of transcriptional regulation in metazoans, to understand how a regulatory factor specifies programs of gene expression as a function of developmental, cellular or physiological cues, and to decypher gene regulatory circuits.

EXERCISE 2: The Logical, Testable, Feasible Hypothesis

What are the problems with the following hypotheses? (Too broad? Not logical? Not testable?) Can you revise them?

1. Analogs to chemokine receptors can be biologically useful.

2. A wide range of molecules can inhibit HIV infection.

EXERCISE 3: Revise your one-sentence specific aim <u>so that the language is very precise</u>.

EXERCISE 4. Reviewing a Sample Specific Aims Section

LIPOPROTEINS AND MICROBIAL IMMUNITY
(Kindly provided by Dr. Hobart Harris, Department of Surgery, UCSF)

SPECIFIC AIMS

Exposure to pathogenic microbial lipids, like lipopolysaccharide (LPS), triggers a complex and coordinated protective response by the immune system. A growing body of evidence indicates that triglyceride-rich lipoproteins and apolipoprotein E (apoE) play an integral role in host defense against bacterial infection. Yet, how these non-traditional elements of the immune system contribute to host immunocompetence is unclear. Published data indicate that apoE is protective against bacterial infection and injury. Accordingly, infusion of apoE has been shown to decrease LPS-induced morbidity and mortality in rodents. [2, 3] Also, apoE-deficient mice have an increased susceptibility to lethal infection when injected with live bacteria. [4, 5] But, unexpectedly, our laboratory has recently discovered that infusion of apoE *increased* rather than decreased mortality after cecal ligation and puncture, an *in vivo* model of polymicrobial sepsis. [1] We believe that this discordant observation highlights a novel activity for apoE in regulating the host response to pathogenic microbial lipid antigens through activation of thymus-derived lymphocytes (T cells). Consequently, uncovering the role that triglyceride-rich lipoproteins, apoE and T cells play in the mammalian response to infection simultaneously assigns important new biological functions to plasma lipoproteins, further blurs the boundary separating innate and adaptive immunity, and provides unique insights into the host response to infection that could yield innovative therapies for sepsis. This proposal will investigate how apoE and natural killer T (NKT) cells, a sub-population of T lymphocytes, contribute to the host response to severe sepsis following cecal ligation and puncture in mice. Furthermore, we will test the hypothesis that modifying the expression or activity of apoE can protect against sepsis.

Our working hypothesis that triglyceride-rich lipoproteins are integral components of the immune system is supported by the following observations. First, the synthesis and secretion of triglyceride-rich lipoproteins is dramatically increased during clinically significant infections, an observation termed "lipemia of sepsis." Second, triglyceride-rich lipoproteins bind various microbial lipids and thus protect against shock and death in rodent models of sepsis. [6-9] Third, triglyceride-rich lipoproteins clear LPS from the circulation and deliver it to the liver [7, 10], where lipoprotein-LPS complexes subsequently modulate the hepatic immune response to infection. [11-14] And, fourth, apoE has recently been shown to bind and deliver microbial lipids to antigen-presenting cells, a critical step in activating NKT cells and the immune system. [15]

The specific hypothesis driving the proposed research is that apoE, a key constituent of triglyceride-rich lipoproteins, regulates the host response to severe infection through its effects on NKT cell activation and cytokine production. By examining the effect of apoE on an *in vivo* model of polymicrobial sepsis in mice, we aim to uncover the regulatory impact of apoE on the immune response to infection. **Our long term goal** is to identify how plasma lipoproteins contribute to host immunocompetence and apply this knowledge to the development of novel and effective treatments for severe bacterial infections.

The specific aims of the proposal are therefore:

1. To demonstrate that serum apolipoprotein E (apoE) concentrations correlate with morbidity and mortality in a murine model of polymicrobial sepsis.
   A. show that apoE increases mortality following cecal ligation and puncture (CLP) sepsis in mice in a dose-dependent manner;
   B. show that apoE increases CLP-induced morbidity via changes in Th1 cytokine secretion, liver injury and bacterial clearance;

2. To demonstrate that apoE promotes the activation of natural killer T (NKT) cells during CLP-induced sepsis.
   A. delineate the effect of apoE on NKT cell frequency, proliferation, cytokine expression and cytotoxic effector functions in the liver, spleen and thymus following CLP in mice;
   B. show that apoE-mediated immune regulation during sepsis is dependent on NKT cell activation using immunodeficient mice;

3. To test the hypothesis that inhibition of apoE activity protects against the morbidity and mortality of sepsis.
   A. show that the biochemical, immunologic or genetic inhibition of apoE activity protects against sepsis;
   B. examine the effect of modifying apoE activity during the early versus late phase of sepsis.

Examples of Abstracts

ABSTRACT (H. Harris)

Exposure to pathogenic microbial lipids, like lipopolysaccharide (LPS), triggers a complex and coordinated protective response by the immune system. Our laboratory investigates the novel postulate that triglyceride-rich lipoproteins and apolipoprotein E (apoE) have been co-opted to play an important role in host defense against bacterial infection, in addition to their well-established roles in lipid metabolism. Yet, precisely how these non-traditional elements of the immune system contribute to host immunocompetence is unclear. Published data indicate that apoE is protective against bacterial infection and injury as injection of this apolipoprotein has been shown to decrease LPS-induced morbidity and mortality in rodents. Also, apoE-deficient mice have an increased susceptibility to lethal infection when injected with live bacteria. But, unexpectedly, our laboratory has recently discovered that infusion of apoE *increased* rather than decreased mortality after cecal ligation and puncture, an *in vivo* model of polymicrobial sepsis. We believe that this apparent dichotomy highlights the existence of a novel activity for apoE in the sequestration and delivery of pathogenic microbial lipid antigens to thymus-derived lymphocytes (T cells). **Specifically, we hypothesize that apoE, a key constituent of triglyceride-rich lipoproteins, regulates the host response to pathogenic bacterial lipids through its effects on natural killer T (NKT) cell activation and cytokine production.** Through three specific aims, this proposal will investigate how apoE and NKT cells contribute to host defense against toxic bacterial lipids after cecal ligation and puncture in mice. **In Aim 1**, we will demonstrate that serum apoE concentrations correlate with morbidity and mortality in a murine model of polymicrobial sepsis. **In Aim 2**, we will demonstrate that apoE promotes the activation of NKT cells during sepsis. Lastly, **in Aim 3**, we will test the hypothesis that inhibition of apoE activity protects against the morbidity and mortality of sepsis. Results of our studies will yield considerable insight into the role of triglyceride-rich lipoproteins, apoE and T cells in the mammalian response to microbial infection. Moreover, our studies will simultaneously assign important new biological functions to plasma lipoproteins, further blur the boundary separating innate and adaptive immunity, and provide unique insights into the host response to infection that could yield innovative therapies for sepsis.

Development of a Continuity of Care Record: Bridging the Medication Use Gap from Hospital to Home

Principal Investigator: Kim C. Coley, Pharm.D., FCCP

Abstract

The U.S. health care system is multifaceted and complex with patients commonly receiving care from several providers in various locations. Despite efforts to emphasize care driven by a primary care provider and a focus on medication safety, little attention has been given to the problems faced by patients and providers as patients transition across settings. It is recognized that problems with medication reconciliation and adverse drug events after discharge from the inpatient setting occur commonly. Community-based pharmacists frequently don't have the information or tools necessary to ensure appropriate medication use and follow-up monitoring for patients recently discharged from the hospital. In 2003, the ASHP House of Delegates approved the Continuity of Care Policy Statement which aims to strongly encourage pharmacists to assume responsibility for ensuring the continuity of pharmaceutical care as patients move from one setting to another. With this goal in mind, the purpose of this study is to develop a consensus-based Medication Continuity of Care (MCOC) Record to communicate medication-related clinical information from the point of hospital discharge to the point of community-based pharmaceutical care. Furthermore, we seek to determine the effects of the MCOC Record under different provision of pharmaceutical care practices, including community-based medication therapy management (MTM), in high risk patients following hospital discharge compared to usual care.