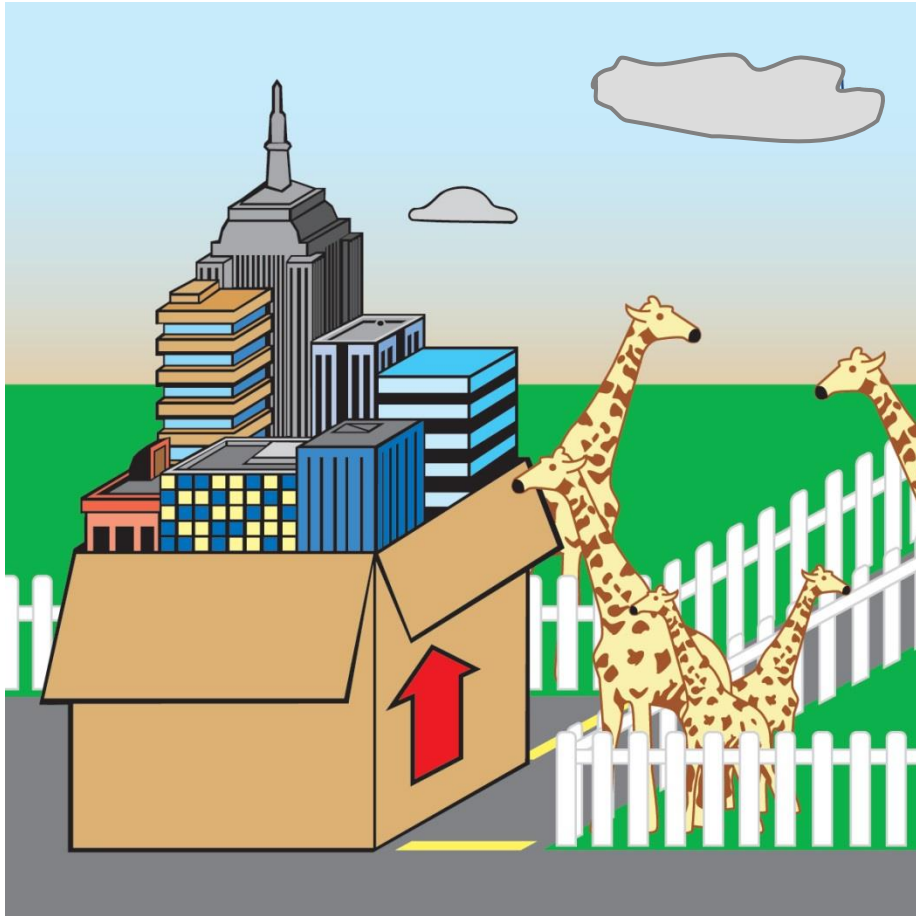


# Anatomy of a Specific Aims Page

*(limit – 1 pg)*



- This section is a microcosm of the grant proposal
  - All the elements should be present
    - ✓ Significance
    - ✓ Investigator
    - ✓ Innovation
    - ✓ Approach
    - ✓ Environment
- IMPACT** – score driving

# The Specific Aims are One of the Keys to Success



- Most reviewers focus first and foremost on the specific aims page
- If a reviewer is confused about your aims it's likely 'game over'
- Don't be discouraged by how difficult it is to formulate a single page – it's hard for everyone!

# Purpose of Specific Aims

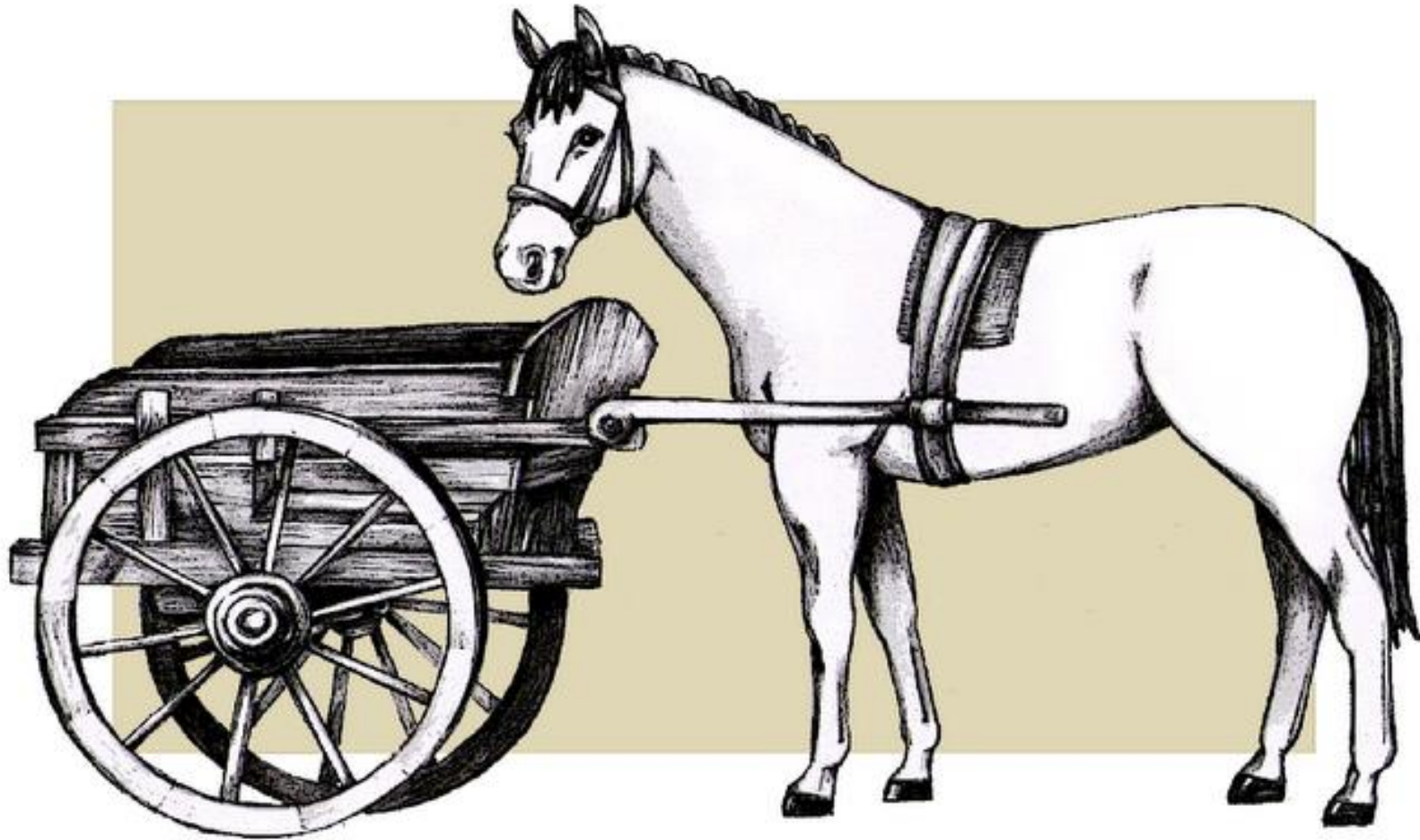
- To test the hypothesis
- The central hypothesis must be tightly linked to the aims
- Concepts that should be covered in this section
  - ✓ Gap
  - ✓ Overall objective
  - ✓ Central hypothesis
  - ✓ Rationale for the research – based on literature and highlight your (lab's) findings that led to this question (don't show data)
  - ✓ Specific aims
  - ✓ Broad significance

# Analogy Between Specific Aims Page & a First Date.....



- Strive to make a great first/lasting impression
- Opportunity to put your best foot forward
- While the project may have flaws (they all do), minimize them in the proposal
- Goal is to have the reviewer want to know more

# Avoid The Cart Before the Horse Phenomenon (*model drives the question*)



# Outline for the Specific Aims Section



- 2-4 paragraphs
- Use a template
- Introductory paragraph
- What/why/who paragraph
- Specifics paragraph
- Payoff paragraph

# Introductory Paragraph



- Opening sentence
  - ✓ Must be compelling
  - ✓ Grab the reader
  - ✓ Relate to the agency's mission
- Current knowledge
  - ✓ 3-5 sentences, set the stage
- Gap or need
  - ✓ Must be important
- Tell your story
  - ✓ Don't start in the middle....
  - ✓ How does your research address next step in the scientific process?

# What / Why / Who Paragraph



- State the long-term goal of the research (not the application)
- How will this research take you one step closer to the long-term goal?
- State gap in the field and your central hypothesis – must be directional/focused
- Describe rationale for doing study

# Specific Aims Paragraph



- The aims are the *foundation* of the application
- 2-4 aims (at the most)
- Brief, focused
- Use ‘eye-catching’ headline
- Conceptual, not descriptive – give sense of approach
- Must collectively test all parts of the hypothesis

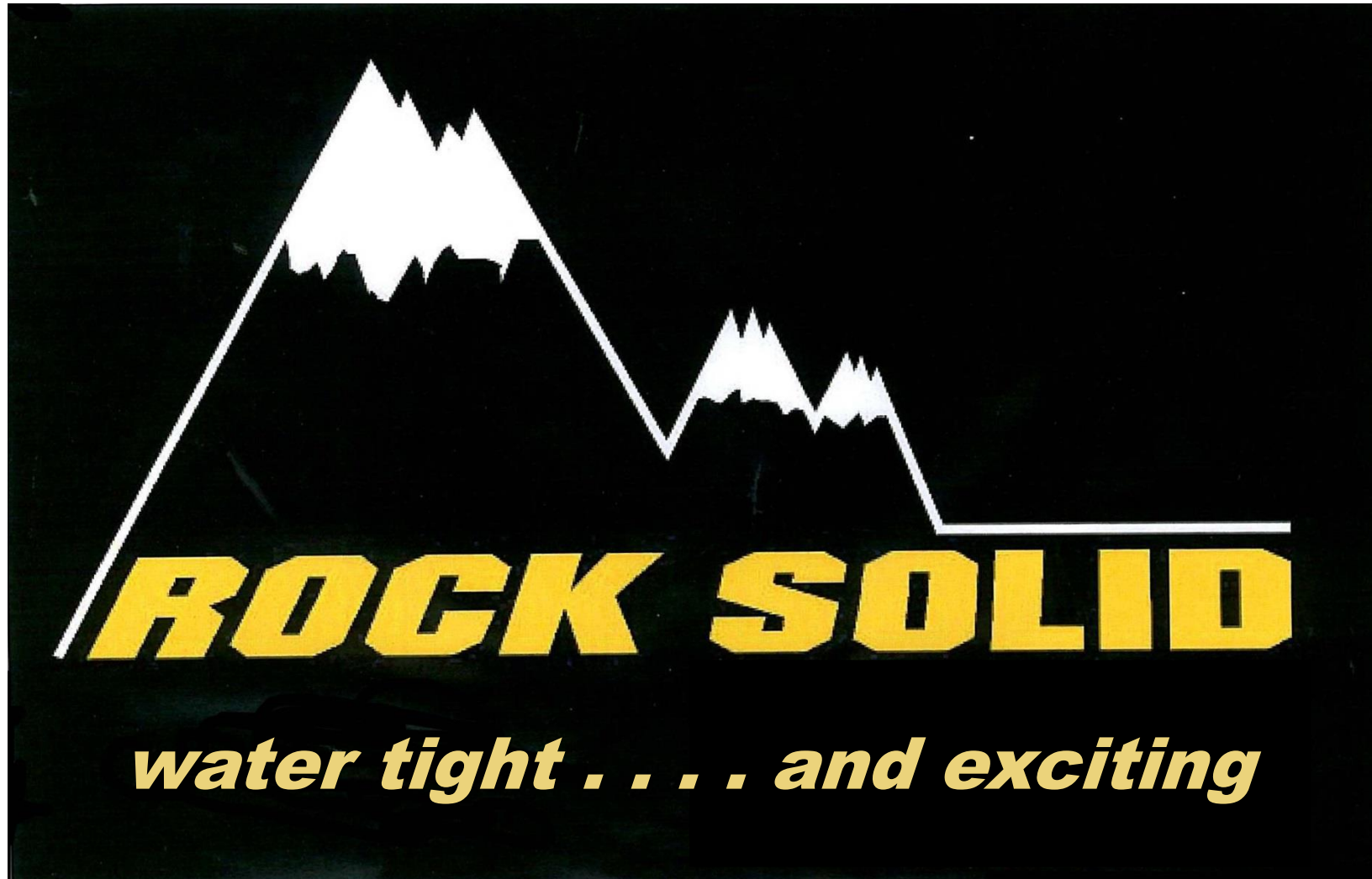
# Specific Aims Paragraph

- It should be implicit in Aim why you are doing this research

*Show, don't tell.....*



Don't bother working on the rest of the proposal until the aims are .....



# Avoid Shaky Aims at All Costs



- Avoid having one aim dependent on outcome of an earlier aim ('house of cards' common mistake)
- Just one weak aim is fatal – reviewers zoom in on flaws
- Don't propose more than one aim per year

# Payoff Paragraph



- Expected outcomes
  - ✓ Return on investment in this research
- Positive impact
  - ✓ How will this research move the field forward

# Example Specific Aims Page

Grant: 1F30CA177210-01

PI: Mikucki, Maryann  
(mentor: Evans, SS)

Study Section: CSR Special Emphasis  
Panel Fellowships:  
Oncological Sciences

Funding Agency: NIH/NCI

Title: Chemokine Scavenging as a  
Mechanism of Tumor  
Resistance to Immunotherapy



# Introductory Paragraph

While overall cancer patient outcome has improved dramatically within the past 30 years, the 5 year survival rate for metastatic melanoma remains less than 15%. Limitations of standard therapies have renewed interest in identifying immune-based strategies that hold the promise of durable and site-specific responses. The suitability of these approaches is supported by studies linking high levels of tumor-infiltrating CD8 effector T cells with overall patient survival in melanoma and other cancers. Therapeutic interventions such as adoptive cell transfer (ACT) are designed to boost circulating levels of CD8 T cells, but the frequency of clinical cures remains low. Our laboratory has recently identified limited T cell trafficking across tumor vessels as a major barrier to successful anti-tumor immunity and an overlooked component of poor clinical response.

# What / Why / Who Paragraph

Migration of blood-borne CD8 effector T cells into inflamed tissue is governed by vascular display of the interferon- $\gamma$  (IFN- $\gamma$ )-inducible chemokines CXCL9/10/11. These chemokines interact with their cognate receptor, CXCR3, on T cells to direct trafficking into tissues in a site-specific manner. CXCR3 expression on peripheral blood lymphocytes from melanoma patients predicts improved survival and preliminary work from our laboratory has demonstrated its obligate role for CD8 T cell trafficking into tumor tissues. Paradoxically, recent studies have revealed that the same chemokine receptor, CXCR3, is also expressed on melanoma cells where it is implicated in metastatic spread and poor prognosis. An unresolved question is whether CXCR3+ melanoma cells actively compete with CXCR3+ CD8 effector T cells over chemokine availability in the tumor microenvironment. Here, we propose to test the central hypothesis that ***melanoma cells evade CD8 T cell-mediated anti-tumor immunity by sequestering locally produced inflammatory chemokines.*** This hypothesis will be addressed by two complementary but independent specific aims:

# Specific Aims Paragraph

**Aim 2. To investigate the contribution of CXCR3 expression on melanoma cells to poor T cell trafficking in the tumor microenvironment.** We propose to test whether CXCR3 on melanoma cells impacts T cell trafficking in the tumor microenvironment by inhibiting its expression using stable shRNA knockdown (B16shCXCR3). We will adoptively transfer tumor-specific CD8 effector T cells into mice bearing B16 or B16shCXCR3 tumors and quantify CXCR3-dependent T cell trafficking using state-of-the-art intravital microscopy and short-term (1h) homing assays. To determine whether elevated CXCR3L bioavailability within tumors is linked with improved T cell trafficking to B16shCXCR3 tumors, we will measure CXCR3L concentrations in tumor extracts as well as the intraluminal display of CXCR3L on the surface of tumor vessels in orthotopic B16 or B16shCXCR3 tumors. Since increased functional CXCR3L could impact the intratumoral localization of T cells via mechanisms affecting entry we will also evaluate retention, survival and proliferation of adoptively-transferred T cells in B16 or B16shCXCR3 tumors. The consequence of improved trafficking of adoptively transferred T cells in B16shCXCR3 tumors on antitumor immunity will be examined by quantifying apoptosis of B16 or B16shCXCR3 tumor targets in vivo. We expect that inhibition of CXCR3 on tumor cells will improve CXCR3L bioavailability in vivo, leading to enhanced T cell trafficking and subsequent immune-mediated destruction of tumor cell targets.

# Payoff Paragraph

**Overall Significance:** Chemokine-driven trafficking of T cells to tumor sites is a critical requirement of many cancer therapies in clinical practice today. The identification of novel mechanisms whereby expression of chemokine receptors by tumor cells limits cytotoxic T cell trafficking is expected to further our understanding of immune evasion and suggest new treatment options for melanoma and other cancer types.

# Take home message.....



- There's no magic formula
- Develop strategy that works for you
- Hone your personal style
- Clarity is key
- Work at it!