BMSC 8219 Specific Aims & Significance
February 1, 2021

Peer group discussion: draft Specific Aims page

What makes a specific aims page strong?

Next, discuss with mentor? Revise, revise.

***

Introduce Research Strategy/Approach (6 pages)

- Significance ½ page, Innovation ½ page
- Working model figure
- Aim 1, Aim 2
- Summary

Peer Discussion: Specific Aims Page

Discuss:

- First line "hook"
- Paragraph on what is known
- Paragraph on the gap you will address/ your approach
- Paragraph on why address this question now
- Your hypothesis
- Aim 1 statement and paragraph description of approach
- Aim 2 statement and paragraph description of approach
- Paragraph on the impact of your study

Consider:

- Was each element present?
- Was the document one page?
- Active tone? Easily understood?

- Compare main sections for R01/ fellowship
  - Significance
  - ~~Innovation~~
  - Approach
- Preliminary Studies
  - You can either include this information as a subsection of Approach or integrate into ea aim.
- Address Rigor and Reproducibility by describing the experimental design and methods you propose and how they will achieve robust and unbiased results.

Research Strategy (6 pages total)

Fellowship: Significance 0.5 p

- Describe the importance of the problem or barrier to progress that the proposed project addresses.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice
- Describe how the concepts, methods, technologies, treatments, or preventative interventions that drive this field will be changed.
- Use a model concept figure/ working model

Remember professional tone…

1-Review groups often include patients or laypeople with a personal interest to assist with review. Your reviewer may be a scientist with that disease/disorder

Person (first)…with disease

a person who had a stroke (not stroke victim)

a man with paraplegia (not paraplegic)

We are not defined by our diseases, but are people who happen to be living with and managing them.

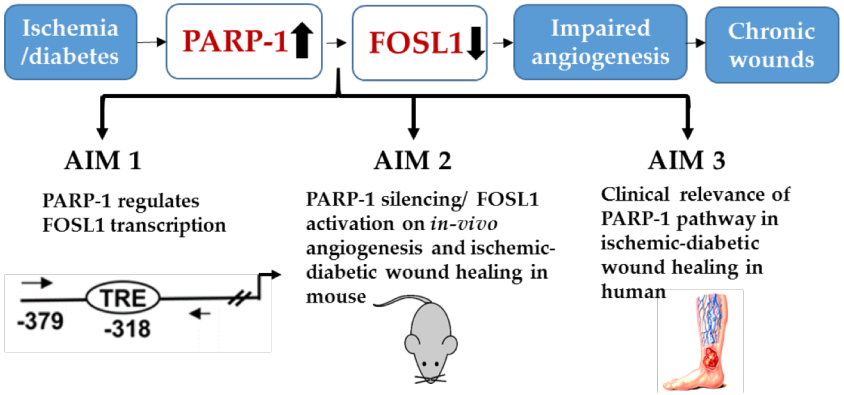
2-Research is supported by taxpayers

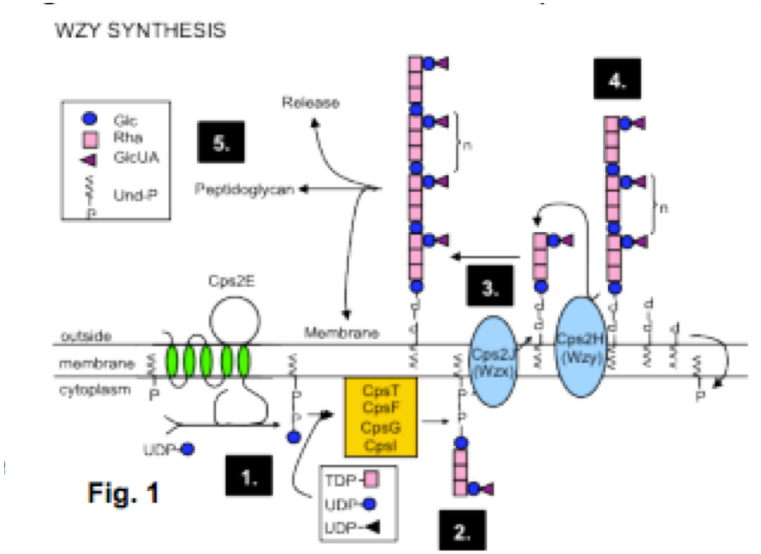
3-Newspapers and representatives seek answers & expertise

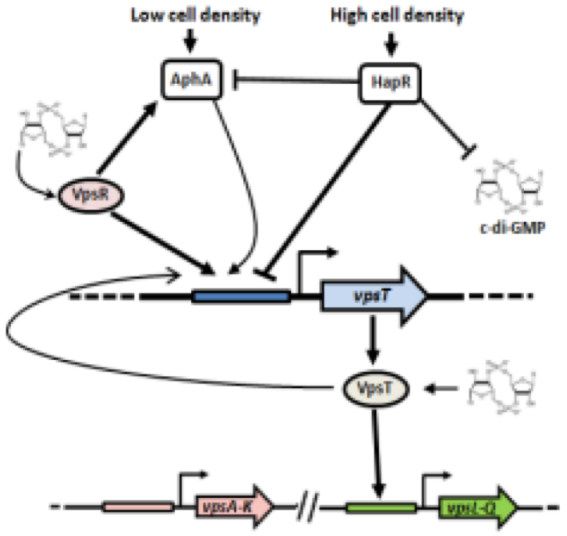
When reviewers read your application, they'll look for the answers to three basic questions:

1. Can your research move your field forward?
2. Is the field important—will progress make a difference to human health?
3. Can you and your team carry out the work?

Model Figure, Concept, Examples







First Draft Specific Aims

1st paragraph-what is known and the gap

Capture reader's attention

Gap you will address

Critical need

Viruses are thought to be involved in 15% to 20% of human cancers worldwide, thus providing critical tools to reveal common mechanisms involved in human malignancies. As the etiologic agent of adult T cell leukemia/lymphoma (ATLL), human T cell leukemia virus type I (HTLV-1) is just such a virus. HTLV-1 encodes a potent oncoprotein, Tax, which regulates important cellular pathways including gene expression, proliferation, apoptosis, and polarity. Over the years, Tax has proven to be a valuable model system in which to interrogate cellular processes, revealing pathways and mechanisms that play important roles in cellular transformation. **Although the Tax oncoprotein has been shown to transform cells in culture and to induce tumors in a variety of transgenic mouse models, the *mechanism by which Tax transforms cells is not well understood*.** A large number of Tax mutants have been generated and their biological activities have been thoroughly characterized, primarily in cell culture systems. ***Currently, a major obstacle in the field*** is that the transforming activity of Tax mutants cannot be compared using available transgenic models due to random transgene integration sites, variable transgene copy number, and inconsistent transgene expression levels, making it difficult to link the biological activities of Tax mutants with their transforming potential.

What readers are thinking about

- Will the investigators be able to get the work done within the project period, or is the proposed work over-ambitious?
- Did the PI describe potential pitfalls and possible alternatives?
- Will the experiments generate meaningful data?
- Could the resulting data prove the hypothesis?
- Are others already doing the work, or has it been already completed?

Research Strategy
(6 pages, including S & I and rest of the approach)

- Brief context, may have preliminary data
- Describe how any results in literature lead to your hypothesis (think about premise)
- Organize by aim
  - -Restate your aim, then build rationale, approach, anticipated results, alternatives for each
- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project.
- Include how the data will be collected, analyzed, and interpreted; sample size, power, significance of outcomes
- Describe expected results
- Always have a paragraph on potential problems and alternative approaches

2nd paragraph-introduce the solution

Hypothesis

Approach

How your work will advance the field

Keep your wording simple, relevant, and to the point.

strong, testable hypothesis

Remember that a hypothesis is a statement, not a question

(Seu) AIM 1 To determine the origin and functional significance of lung resident memory B cells (BRMs). Since we observe an early seeding of lung BRMs we hypothesize that the BRMs in the lung should maintain their mutation pattern and proportion early and late during the response, due to early seeding and establishment. Further, the GC derived CD73+swig+ subset should be the most protective, as they have gone through rigorous selection and differentiation through (SHM and AM) in the GC. We will test these hypotheses by analyzing the repertoire of the B cell population in the lung, which should remain constant if our hypothesis is correct. To identify the lung BRM with the greatest inclination to form ASCs, we will image live BRMs post challenge from Blimp-YFP reporter mice (YFP+ will be ASCs) to determine ASC formation. (Model1)

We investigated the mTOR pathway as a potential mechanism for the phenotype of progranulin-deficient mice based on reports of altered S6 kinase expression and phosphorylation in progranulin-deficient model systems, and of interaction of progranulin with insulin/IGF-1 signaling. We found increased phosphorylation of Akt and ribosomal protein S6 in the amygdala of Grn+/– mice relative to wild-type, which suggests increased signaling through the mTOR pathway. Elevated mTOR signaling causes abnormal social behavior in several genetic mouse models of autism, and mTOR signaling may also be involved in conditioned fear memory. **We therefore hypothesize that progranulin deficiency causes abnormal social behavior, conditioned fear, and amygdala dysfunction through elevated mTOR signaling.** We propose to investigate this hypothesis with the following specific aims.

Specific Aim 1 **will test the hypothesis that subjects with schizophrenia have increased dopaminergic inputs in the nucleus accumbens core and shell compared to normal** control cases by measuring the density of immunolabeling of tyrosine hydroxylase, a synthesizing enzyme of dopamine, using (SA1.1) optical densitometry, and (SA1.2) measuring protein levels using western blot assays.
Specific Aim 2 **will test the hypothesis that subjects with schizophrenia have increased synapses, both symmetric (inhibitory) and asymmetric (excitatory), in the nucleus accumbens core and shell** using stereology at the electron microscopic level to determine density of synapse types.

Add emphasis—selected italics or bold

- While describing a method, state their or collaborators' experience with it.
- Point out that they have access to a necessary piece of equipment.
- When explaining their field and the status of current research, they weave in their own work and their preliminary data.
- They delve into the biology of the area to make sure reviewers will grasp the importance of their research and understand their field and how their work fits into it.

Observations from draft Aims

Opening paragraph should make a point; not list a series of facts. Lead the reader through your study.

Introduce any major approaches in significance and first paragraph-not only in aim

Look for ways to establish feasibility. State using "established techniques" and include a ref from lab.

Always describe expected outcomes

Some of the aims were not discovery questions but applications of techniques