# Creating your Specific Aims: the key to a successful grant

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Are those really my *peers*??

# What you are scored on

- Overall impact
- 5 criteria
  - Significance
  - Investigator
  - Innovation
  - Approach
  - Environment

# Cover the "easy ones" first market the novelty and impact

- Overall impact
- 5 criteria
  - Significance
  - Investigator
  - Innovation
  - Approach
  - Environment

# Approach is where the bulk of the critique will focus upon

- Overall impact
- 5 criteria
  - Significance
  - Investigator
  - Innovation
  - Approach
  - Environment

# "Problem solving" versus "problem finding"

- Choose an interesting/important question!
- It is possible to write a "perfect grant" on an unimportant problem that lacks novely and will not truly advance the field

#### THEORETICAL NOTES

#### Problem Finding: a Theoretical Note

#### J. W. GETZELS

#### The University of Chicago

Despite the self-evident role of problems in initiating thought and the function of new problems in guiding thought toward new solutions, very little is known about how problems are found and formulated. Although there are dozens of theoretical statements, hundreds of psychometric instruments, and literally thousands of empirical studies of problem solving, there is hardly any systematic work on problem finding (Getzels, 1964; Getzels, 1975; Henle, 1975; Getzels & Csikszentmihalyi, 1976). Indeed, *Cognitive Science* itself, to cite it as an instance of many other journals in the field of cognition, informs potential contributors that it publishes articles ''on such topics as the representation of knowledge, language processing, image processing, question answering, inference, learning, problem solving, and planning'' (see ''Information for Authors''), but fails to make any mention of ''question asking'' or ''problem posing''—as if questions and problems, like the weather, were just there naturally.

The purpose of this note—and it is to be taken only as a note—is to call attention to the relative neglect of the 'problem of the problem' by offering some tentative observations regarding the significance of problem finding in thought, the nature and variety of problems, and the human being as problemfinder.

#### ON THE SIGNIFICANCE OF PROBLEM FINDING

Need problems be *found*? Is not the world already teeming with problems and dilemmas at home and in business, in economics and in education, in art and in science? The world is of course teeming with dilemmas. But the dilemmas do not present themselves automatically as *problems* capable of resolution or even sensible contemplation. They must be posed and formulated in fruitful and often radical ways if they are to be moved toward solution. The way the problem is posed is the way the dilemma will be resolved (Getzels, 1975).

### **Scoring Descriptions**

Impact	Score	Descriptor	Additional Guidance on Strengths/Weaknesses
High Impact	1	Exceptional	Exceptionally strong with essentially no weaknesses
	2	Outstanding	Extremely strong with negligible weaknesses
	3	Excellent	Very strong with only some minor weaknesses
Moderate Impact	4	Very Good	Strong but with numerous minor weaknesses
	5	Good	Strong but with at least one moderate weakness
	6	Satisfactory	Some strengths but also some moderate weaknesses
Low Impact	7	Fair	Some strengths but with at least one major weakness
	8	Marginal	A few strengths and a few major weaknesses
	9	Poor	Very few strengths and numerous major weaknesses

Minor Weakness: An easily addressable weakness that does not substantially lessen impact

Moderate Weakness: A weakness that lessens impact

Major Weakness: A weakness that severely limits impact

# Create a proposal that causes endorphin release for your reviewers!





"IT'S NOTHING SERIOLS . HIS ENDORPHINS HAVEN'T KICKED IN YET."

# A few positive features in grants

- Pleasure to read
- Logical and organized
- Sometimes less is more—don't over cram
- Don't cheat on font size or spacing
- Figures and legends should be legible
- Cool and novel techniques/innovative
- Strong preliminary data that demonstrate key concepts and feasibility
- Interesting and important ideas

# **Specific Aims**

- Succinct and unambiguous questions/goals
- Aims should be inter-related, not dependent
  - Success with Aim 1 can't be necessary in order to execute Aim 2
- State what performing each Aim will accomplish
- Conclude: What will be the impact in the field
- Sweet spot for quantity: an aim shouldn't be one big experiment, but on the other hand shouldn't be enough for a complete grant on its own

#### **Specific Aims**

Checkpoint blockade immunotherapies have demonstrated remarkable therapeutic success by overcoming tumor-induced T cell inhibition. Although durable clinical responses occur in a subset of patients, efficacy is poor when patients lack evidence of a spontaneous T cell response. Overcoming key deficiencies in the tumor microenvironment that result in lack of immune infiltration may be critically important for generating an anti-tumor T cell response and improving response rates to immunotherapy. Previous work from our laboratory has shown that tumors in mice which generate a spontaneous T cell response activate the innate immune system through CD103<sup>+</sup> dendritic cells (DCs) and the STING pathway. In all transplantable tumor models tested, STING agonists promote DC activation and the subsequent priming and recruitment of T cells, leading to significant tumor control. These findings have led to the rapid clinical development of therapeutic STING agonists. However, preliminary clinical trial results suggest that STING agonists have clinical activity in only a minority of patients, and have limited efficacy in non-inflamed tumors, which represent the largest unmet clinical need.

STING agonists may fail in non-inflamed tumors because those tumors also lack the required CD103<sup>+</sup> DC subset for T cell priming and recruitment. This notion suggests a need to more closely study the non-inflamed tumor microenvironment, and understand which innate immune cells and signaling pathways are required for driving tumor-specific T cell priming and recruitment in this context. We hypothesize that these questions may be addressed using the BRAF-activated, PTEN-deleted, β-catenin-stabilized (BPC) genetic mouse model. Our lab has previously shown that tumors induced in these mice lack a spontaneous CD103<sup>+</sup> DC and T cell infiltration and have low expression of the chemokines known to recruit these cells, namely CCL4 and CXCL9/10. We hypothesize that if we can recruit and activate CD103<sup>+</sup> dendritic cells in these tumors, we will induce a tumor-specific T cell response and promote tumor control either alone or in combination with checkpoint blockade in this non-inflamed model. Such findings could be rapidly translated to the clinic.

Aim 1: Identify and overcome barriers to dendritic cell recruitment and activation in a non-inflamed tumor model in order to prime tumor-specific T cells. Our working model is that both recruitment and activation of CD103<sup>+</sup> DCs is lacking in cold tumors. Regarding recruitment, DC103<sup>+</sup> DC entry depends on specific chemokines (e.g. CCL4), but also can be driven by the hematopoietic growth factor Flt3L. To overcome the known defect in CCL4 expression in BPC tumors, I will inject mice intravenously with CCL4 linked to a collagen binding domain (CBD-CCL4), which drives tumor localization. As an alternative, we will administer Flt3L, either intratumorally or systemically. For DC activation, the STING agonist DMXAA will be administered. Additional innate immune activators may be explored based on initial results. CD103<sup>+</sup> DC recruitment and activation status will be assessed, along with CD8<sup>+</sup> T cell recruitment and tumor control. If a T cell-inflamed tumor microenvironment is successfully generated, then anti-CTLA-4 +/- anti-PD-L1 Abs will be administered to investigate optimal tumor regression.

**Aim 2: Elucidate the requirements for tumor-specific T cell recruitment and effector function in a non-inflamed tumor model.** We will evaluate whether STING agonists alone induce T cell recruitment in a non-specific manner by treating BPC-SIY tumors with a STING agonist then injecting a mixture of tumor-specific pre-activated 2C T cells and non-tumor-specific pre-activated P14 T cells. The ratio of the two T cell populations will be measured in the tumor. We will determine whether the combination of improved DC recruitment plus activation with a STING agonist is sufficient to favor tumor-specific T cell priming and recruitment. To test if CXCL10 is required for tumor-specific T cell recruitment, mixed bone marrow chimeras will be generated with CD11c DTR and CXCL10<sup>-/-</sup> bone marrow, followed by diphtheria toxin treatment. T cell recruitment and tumor outgrowth will be evaluated. The phenotype and functional status of recruited T cells will be assessed, to consider alternative immune checkpoint antibodies for improving therapeutic efficacy.

#### Emily Higgs, MD/PhD candidate

# **Define the problem**

#### **Specific Aims**

Checkpoint blockade immunotherapies have demonstrated remarkable therapeutic success by overcoming tumor-induced T cell inhibition. Although durable clinical responses occur in a subset of patients, efficacy is poor when patients lack evidence of a spontaneous T cell response. Overcoming key deficiencies in the tumor microenvironment that result in lack of immune infiltration may be critically important for generating an anti-tumor T cell response and improving response rates to immunotherapy. Previous work from our laboratory has shown that tumors in mice which generate a spontaneous T cell response activate the innate immune system through CD103<sup>+</sup> dendritic cells (DCs) and the STING pathway. In all transplantable tumor models tested, STING agonists promote DC activation and the subsequent priming and recruitment of T cells, leading to significant tumor control. These findings have led to the rapid clinical development of therapeutic STING agonists. However, preliminary clinical trial results suggest that STING agonists have clinical activity in in only a minority of patients, and have limited efficacy in non-inflamed tumors, which represent the largest unmet clinical need.

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# Begin with conceptual framework, then describe key experiments emphasizing novelty

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### **Background / Rationale**

- <u>Not</u> an exhaustive literature search
- Build a story to form compelling support for the studies
  - Make it seem like a historical imperative that your proposed experiments are the next logical and mission-critical step
- Highlight key concepts (possibly by bold, italic text)
  - But don't annoy reviewers by over-using these highlights!

## How much preliminary data?



## **Preliminary results**

- You don't need to have "already performed the grant"
- Show key data supporting <u>feasibility</u> and <u>rationale</u> (especially if a new technique or model)
- Preliminary results should be solid and interpretable (including statistics)

### Goldilocks concept: finding the sweet spot for optimal amount of preliminary data



## **Experimental Approach**

- Emphasize the rationale
- Clarify and justify (defend) the choice of models (e.g. specific animal models)
- Design experiments to determine mechanism (think Koch's postulates)
- Clearly describe interpretation of results
- Don't waste too much space describing detailed methods—refer to published papers and show preliminary data for key techniques
- Clearly describe interpretation of results

# Feasibility!

- Demonstrate that you can do this (yourself and/or with appropriate collaborators/coinvestigators)
  - Preliminary data with challenging techniques helps
  - Does not mean including extensive and tedious methodology
- Key relationship between feasibility and impact!

### **Pitfalls / Alternative Approaches**

- Be your own best critic!
- What can go wrong and what you do about it?
- What if you don't get the expected results?
- Consider alternative approaches and future directions
  - Can be conditional based on types of initial results obtained (if this then that)

## **General Conclusions I**

- Clearly answer: So What?
- Do I have a clear and important question/hypothesis?
  - descriptive/confirmatory experiments with no mechanism are not enough
- Can I convince the reader that I can do this?
- Do both 'positive' and 'negative' results have meaning?
  - difference between testing a hypothesis versus trying to demonstrate only one viewpoint

## **General Conclusions II**

- 'Cosmetics' matter: Carefully put together and edit
- If necessary, have someone review the English language usage
- Be explicit regarding conclusions (experimental or conceptual): Not 'results will lead to new directions in the field'......What does that mean?
- A summary paragraph at the end of a grant can help: "After completion of these aims, we will have learned whether..."

