Writing Successful Grant Proposals for Surgical Research During Residency

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Scientific Publications Manager
Department of Surgery

1. The purpose of a research fellowship
2. Finding funding
3. Planning the application
4. The basic structure of the application
5. Career goals & training plan
6. Research plan
7. Revising and getting feedback

The purpose of a postdoctoral fellowship is to move you further along the path to becoming an independent researcher.

- Gain needed knowledge in specific areas (through coursework, tutorials)
- Learn and apply research skills, techniques (through hands-on, mentored/supervised work carrying out the aims of the proposed study)
- Understand how collaborative science works
- Publish the results; establish “track record” (essential “product” of grant funding)

Do you know what's expected of you?

http://residentresearch.surgery.ucsf.edu/objectives--policies/policies/general-policies--procedures.aspx

Frequently Asked Questions

Do I have to apply for grants?

Yes, grant writing is an integral component of the training program. Grants should be written with guidance from the research mentor. The Department of Surgery Scientific Publications Office (Pamela Derish) provides guidance in scientific writing. The Department of Surgery Contracts and Grants Office provides guidance in the nuts-and-bolts of grant submission.

What happens if I don't apply for grants?

You will not be allowed to participate in a research training program.

How many grants do I need to apply for?

Residents typically apply for multiple grants. Usually, the same application can be submitted to several agencies (although funding from only one agency is allowed – unless permitted by the funding agency (sometimes one grant will fund salary and another will fund research costs).

What happens if I am unsuccessful at obtaining grant funding?

You will be eligible to be considered for funding from the Department of Surgery or your research mentor. See Policy on Lab Selection and Funding.

http://residentresearch.surgery.ucsf.edu/objectives--policies/policies/general-policies--procedures.aspx

Can I moonlight?

Yes, provided that this does not detract from your training program, which is your primary responsibility. Moonlighting must be discussed with your research advisor **at the start of your training program**.

What if I want to do something for which there is no grant funding available?

You have chosen the wrong project and should select a different research topic.

What if I want to obtain an additional degree?

This is possible at UCSF and elsewhere, but you will usually have to fund this activity yourself.

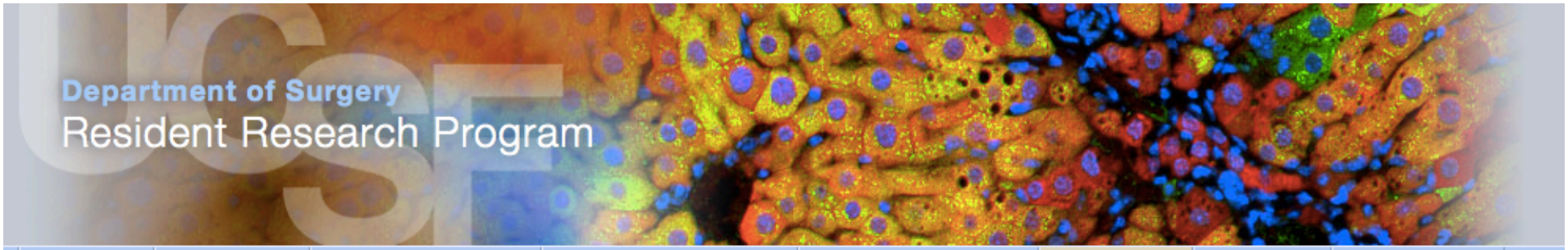
Will the department fund research at a different institution?

No. See Policy on Lab Selection and Funding

What do I do if I have problems – if I have selected the wrong research program or mentor, or if my research is going nowhere?

First, immediately contact one of the research resident ombudsman,Peter G. Stock, M.D., Ph.D. If so desired, these discussions will be kept in the **strictest confidence**. The Research Committee can intercede on your behalf and help you and your mentor negotiate suitable outcomes. Under exceptional circumstances, the Research Committee can reassign you to an alternative training program.

http://residentresearch.surgery.ucsf.edu/resources/resources/grant-writing--publications.aspx



Resources
- Grant Writing & Publications
- Fellowships & Grant Opportunities

Related Sites and Programs
Department Websites

Contact Us
FAQ & Links
Resident Portal

Chair of Research Committee

Resources for Grant Writing, Publications and Research

A successfully funded grant proposal is far more than a piece of writing. It is often the culmination of months of preparation and requires a collaborative effort between you, your mentor(s), UCSF Research Administration, and others. Spend a few hours learning more about what's involved in preparing a successful grant application. You will save yourself time and grief.

Note: The new Department of Surgery Resident Research Program website replaces the spiral-bound "UCSF Department of Surgery Research Resource Guide 2012". All content in that booklet has been moved to this website in an updated form.

The Big Picture

If you need to start with a "research roadmap" that lays out how to find a research mentor, conceive of the research question, do the literature review, design the study, write the proposal, conduct the research, and report the results, then by all means download an example here of the *"The Research Guide: A Primer for Residents, Other Healthcare Trainees, and Practitioners" (from The Royal College of Canadian Physicians and Surgeons).* Please contact the Residency Education Office to obtain a complete copy.

Preparing a Grant Application

Writing Successful Grant Proposals for Surgical Research During Residency (slide presentation from workshop given by Pamela Derish, the Department of Surgery's editor and scientific writing instructor)

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Tips for Writing Successful Grant Proposals During Surgical Residency (Pam's text summarizing the slide presentation, including how to work with UCSF Grants Administration—essential information.)

Funding Sources

- Fellowship & Grant Opportunities
  This searchable table is sorted by deadline.
- Pivot™ Funding Opportunity Database
  Get acquainted with Pivot, one of the most comprehensive searchable funding opportunities databases available, with approximately 40,000 opportunities that are private, federal and international in nature. Pivot allows researchers to search funding opportunities, save results, set automated funding alerts, and identify potential collaborators. Please see Pivot Training Powerpoint Slides for further details and then get started on tailoring your searches.

Once You Are Ready to Write (and Revise!) the Proposal

Fundamentals of Writing a Successful Grant Proposal, J Hand Surg, 2008

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Department of Surgery's Resource Guide for Scientific Writing (Pam Derish's writing guide for everything from writing papers to the peer review process to giving talks; for grants, see the sections on "Grant Proposals", "Revising Your Prose" and "CVs and Personal Statements"

Sample Grant Proposals

(generously provided by past research residents)

California Institute for Regenerative Medicine (A. Nijagal)

American College of Surgeons (S. Wang)

Generic – adapted for multiple agencies (J. Carter)

NIH NRSA (S. Wang)

Society of University Surgeons (J. Harbell)

Ask for Help

Are you planning to submit a grant proposal for an upcoming deadline? Do you need help staying on track with regular feedback on your writing in order to prepare the best possible proposal? If so, it's a good idea to start at least 4 months before the grant is due. To make steady progress, it's important to set aside time each week to work on the proposal and to write. As the Department's scientific editor, Pamela Derish can set up a regular "tutorial" time to meet with you in order to break the writing task down into manageable chunks, give you editorial feedback, and help you prepare the research plan (and career development or training plan if you are seeking a mentored award) for review by your mentor(s) and others with time to spare before the deadline.

Need help with a paper for publication?

Pamela can help with that too. To learn more, visit Editorial Consultation & Review at the Scientific Publication Office website.

- Finding funding

Fellowships & Grant Opportunities

Due Date	Funding Agency	Duration/Amount	Grant/Award Mechanism	Description
March 1	American Society of Colorectal Surgeons	1-2 years. $20,000	ASCRS Grants & Awards	The purpose of the General Surgery Resident Research Initiation Grant is to attract General Surgery Residents or recent Graduates of such programs into the field of Colon and Rectal Surgery by providing opportunities to engage in clinical or laboratory-based research focused on diseases of the colon, rectum and anus.
April 20, 2015	Society of University Surgeons	1 year. $30,000 for salary or other costs.	SUS Resident Scholar Award	Intended for surgical residents in any of the surgical disciplines who have completed two years of training and agree to spend one or two years in full-time research in the laboratory of an SUS member. Co-mentoring by a non-SUS member is acceptable providing there is clear documentation of a collaborative relationship between the SUS research mentor and the non-SUS research mentor.
May 1	Northwestern University	2 Years - a funded two-year onsite fellowship	Surgical Outcomes and Quality Improvement Center (SOQIC)	Northwestern University's Surgical Outcomes and Quality Improvement Center (SOQIC) is offering a funded two-year onsite fellowship in surgical outcomes, health services, and health care policy research for surgical residents to pursue during their research years. This position begins July 1, 2016 with space available for two residents. Applications are due May 1, 2015.

*see full table at http://residentresearch.surgery.ucsf.edu/resources/resources/fellowships--grant-opportunities.aspx

For Pivot training, see http://residentresearch.surgery.ucsf.edu/resources/resources/grant-writing--publications.aspx

Find Appropriate Funding Opportunities

Pivot training is also available “in person” through the Library:
http://calendars.library.ucsf.edu/calendar/classes#!/month/2015/10/01/21499/

In determining appropriateness of a funding source, consider:

- How many years of research do you plan to do?
- How much money do you need? Salary support? Travel costs? Tuition? Project costs?
- Where will the research take place?
- Prestige versus likelihood of funding.

Important distinctions about funding mechanisms:

- Student-held awards (e.g., NIH F32, awarded to the trainee)
- Institution-held awards (e.g, T32, awarded to a Department or Program; selection process for fellows)
- Investigator-held awards (e.g., P.I's NIH R01 grant provides funding)

What area of research interests you?

American Society of Colorectal Surgeons
1-2 years. $20,000.
http://www.fascrs.org/physicians/research_foundation/grants/

The purpose of the General Surgery Resident Research Initiation Grant is to attract General Surgery Residents or recent Graduates of such programs into the field of **Colon and Rectal Surgery** by providing opportunities to engage in clinical or laboratory-based research focused on diseases of the colon, rectum and anus.

What area of research interests you?

American Society of Transplant Surgeons

1-2 years. Stipend awarded to a total of $40,000-$42,500/ year.

http://www.asts.org/Awards/AnnualAwardsEligibility.aspx

Awards support **basic and clinical research in the field of transplantation and transplant immunobiology** in the laboratory / clinical service of an ASTS member. Eligibility for specific awards is defined by period of training or career status, and with some awards by age, academic degree, membership in the Society (or sponsorship by a member), and other criteria.

- Planning the application

Reviewers want the proposal to convey the applicant's potential and the mentor's guidance.

- Is the mentor a good fit (*is there a track record of mentoring success, evidence of mentor guidance in preparing a solid proposal*)?

- Is the training or career development plan carefully thought out (*not just "off the shelf" MPH*) and feasible in terms of the time-frame and budget?

- Is the proposed research (the Aims) feasible in terms of the time-frame and budget?

- How will the combination of training and hands-on experience impact the trainee's path to eventually becoming an independent investigator?

- Is the institutional environment suitable for the training and research proposed?

Do you know who the reviewers are?

The goal is to minimize the risk that a reviewer will misunderstand you!

NIH and Surgical Society Awards (SUS, AAS, etc):

Proposal is looked at by a committee of members.

Disease Foundations (American Heart Association, American Cancer Society, etc):

Proposal will be assigned to scientific reviewers AND a "lay" person.

What are the reviewers looking for?

- Candidate's potential
  - track record so far, publications
  - good grades, etc.
  - stellar letters of recommendation

- Mentor qualifications
  - record of effectiveness as a research mentor
  - track record of funding, publication
  - good fit with you and your proposed research

What are the reviewers looking for?

- Training plan
  - well organized, detailed, tailored to applicant's needs and goals

- Research plan
  - high impact, novel, integrated with training goals, feasible

How much will the applicant learn through the combination of training and research?

Make it easy for reviewers to champion your proposal!

- should be able to grasp your ideas quickly, not do mental manipulations to understand your message.
- should be able to find the statements in your proposal that address specific review criteria (significance, innovation, feasibility, mentor involvement, training plan)
- should easily make their way through the text & figures
  - ✓ leave white space
  - ✓ Include legible figures
  - ✓ Use informative subheadings
  - ✓ highlight important key points **using bold-face type**
  - ✓ edit & proofread

Allow Enough Time to Prepare a Great Application

Timeline and Checklist for Grant Submissions

6 months before grant deadline:

- ❑ Identify a mentor and discuss grant opportunities and proposal ideas

3 months before grant deadline:

- ❑ Complete a draft of your research (and training) plan and have your mentor/PI review it
- ❑ Ask Pam Derish to review and edit your research (and training) plan – allow plenty of time to revise per her and mentor's feedback

2-3 months before grant deadline:

- ❑ Contact Pre-Award Analyst to assist with your grant submission **(all applications must be submitted through UCSF Office of Sponsored Research)**

As Soon as You Think You Want to Apply for a Grant, Contact UCSF's Office of Sponsored Research.

All applications for extramural (= outside of UCSF) funding must be formally reviewed and approved by the Department Chair and by an official in UCSF's Office of Sponsored Research (OSR). *Therefore,* as soon as you think you'd like to submit a research proposal, contact a Research Services Coordinator in the OSR who works with the Department of Surgery:

If you are working with a mentor in the division of Cardiothoracic, Vascular, or Transplant Surgery, contact Mayumi Cutler mayumi.cutler@ucsf.edu.

If you are working with a mentor in any other division within Surgery, contact Paul Tang Paul.Tang@ucsf.edu.

They will assist you in completing all ***administrative*** (as opposed to scientific) components of your application and will read the agency guidelines and let you know exactly the sections you will need to complete for your application and which sections they will complete for you. They will also complete all internal forms, obtain approval signatures, make copies of hard-copy submissions and submit your final application for UCSF's Internal Review (formerly known as the Office of Contracts & Grants) or directly to the funding agency.

2 months before grant deadline:

- ❑ Find out the OSR deadline for your grant **(usually at least 5 working days before the actual grant deadline!)**
- ❑ Review submission requirements with your assigned Analyst. Gather supporting materials:
  - ❑ CV/biosketch for you & your mentor
  - ❑ Letters of recommendation
    - ❑ Mentor
    - ❑ Department chairperson
  - ❑ Other required documents

1-2 weeks before grant deadline:

- ❑ Confirm your letters of recommendation have been received, or send reminders
- ❑ Submit your final, complete grant application

The biggest mistake a first time investigator makes is thinking a proposal can be put together at the last minute.

Mistake #1: No mastery of the literature

The applicant has not considered the recently published research on determinants of risk behaviors predicting graft survival in transplant patients who have HIV/ AIDS infection, whereas the much older literature has been discussed.

Mistake #2: The Research Plan is overly ambitious

There are some concerns as to the likelihood of completing Aims 2 and 3 within the allotted time given the pilot nature of the work and the number of techniques that need to be mastered.

Mistake #3: There are problems with the hypothesis, study design, experiments, data analysis…

- Hypothesis is ill-defined, lacking, faulty, diffuse
- Methodology is questionable, unsuited or flawed
- Inconsistency in level of detail from one experiment to the next
- Agents, clinical interventions, high tech procedures are not adequately described
- Are there alternatives worth mentioning?
- Data collection procedures are not clear
- Power calculation isn't included
- Data management plan is unclear

It is unclear whether the analytic techniques will yield the anticipated outcomes.

Mistake #4: Resources and/or mentorship not adequately described

It appears that the lab does not have established techniques, models related to the applicant's training and research goals. There is insufficient supervision by the mentor.

Mistake #5. The proposal is messy, ergo the research will be messy too.

The committee commented on the less than stellar grantsmanship throughout the proposal. There were many misspellings, typos, and grammatical errors. Some members commented on whether the investigator would approach research and publication in a similarly sloppy fashion.

- The basic structure of the proposal

Proposal format (& content): variations on a theme

If you apply to > 1 agency, prepare a "generic" version and adapt very specifically for each agency.

Follow each agency's requirements *to the letter*. *That means font size, margin size, page limits, names of sections, letters of recommendation, description of training plan, etc.*

Agencies may reject an application because it didn't adhere to the required format.

"Reviewer friendly" applications are appreciated! Attempts to circumvent font size, etc. are not!

Resident Research Grants from Surgical Societies & Disease Foundations

- **Career goal/academic academic development plan** for the period of research funding (1-2 years) your short and long-term career goals, and any other relevant information. *This may be part of the proposal itself or will go in a cover letter.*
- **Letters of recommendation** from the "sponsoring" mentor (e.g., AAS, SUS, other society) and Department Chair
- **Mentor letter** describes the applicant's training plan in detail.
- **Your CV or NIH biosketch** (more and more agencies want NIH biosketch) *and probably your mentor's as well.*
- **Research Plan**, including abstract and/or specific aims, background, significance (sometimes innovation too), preliminary data, & experimental plan.
- Research approvals (animal, human)

See proposals (AAS, SUS, Crohns Colitis Fdn, others) from DOS residents on the Resident Research Website

NIH Postdoctoral Fellowship (F32, NRSA) Grant Application

F32 is NIH's way of designating postdoctoral rather than predoctoral fellowship.

NIH fellowship grants are also known by the acronym NRSA, which means National Research Service Award.

Major Sections of Individual NIH Fellowship (F) Proposals

[see SF424 for additional details]

- □ Project Summary/Abstract (30 lines)

Biosketches (trainee, mentor and co-mentor, consultants, advisory committee); form; 5 pages

- □ Research Training Plan
  1. Introduction, *only if revision/resubmission* (1 page)
  3. Specific Aims (1 page)
  4. Research Strategy (6 pages)
     - A – Significance
     - B – Innovation
     - C – Approach

     Bibliography (no page limit)
- □ Facilities and Other Resources (no page limit)
- □ Resource Sharing Plan (if applicable)
- □ Application for Concurrent Support (if applicable)

NIH Postdoctoral Fellowship (F32, NRSA) Grant Application

Special Additional Parts:

2. Applicant's Background and Goals (6 pages)
    - A – Doctoral Dissertation and Research Experience
    - B – Training Goals and Objectives
    - C – Activities Planned Under This Award
5. Respective Contributions (1 page)
6. Selection of Sponsor & Institution (1 page)
8. Training in the Responsible Conduct of Research (1 page)
9. Sponsor & Co-Sponsor Statements (6 pages)
    - A – Research support
    - B – Prior fellows/trainees
    - C – Training Plan, Environment, Research Facilities
    - D – Number of Fellows/trainees during fellowship
    - E – Applicant's qualifications & potential
10. Letters of Support from Collaborators, Contributors, and Consultants (6 pages)
11. Description of Institutional Environment and Commitment to Training (2 pages)

NIH Postdoctoral Fellowship (F32, NRSA) Grant Application

Appendix items:

- ☐ Copies of accepted manuscripts, abstracts, and patents (if not publically available)

Other 'stuff':

- ☐ Cover letter (from applicant) to indicate the individuals (in a list) who will provide letters of recommendation
- ☐ Institutional letter if application requests consideration as a diversity application

More complex, more time to prepare, write, and refine, but very prestigious!

See the Resident Research Website for…

- *NIH NRSA proposals written by DOS residents*
- *Specific resources for preparing NIH NRSA proposals*

AAS/AAS Trainee Research Fellowship Awards

Application Deadline: August 15, 2016
Apply online at http://grants.aasurg.org/

Eligibility/Application:

- Applicants must be residents or fellows who are currently enrolled in an accredited training program and have completed at least two years of postgraduate training in a surgical discipline.
- The awardee must be a candidate member or an active member of the AAS.
- There must be at least one mentor who is an active or senior member of the AAS *(applicants with AAS membership applications in process are also eligible)*.
- Applicants submit the following materials:
    1. A Cover Letter outlining their academic development plan for their one-year research period, their short and long-term career goals, and any other relevant information that they wish the committee to consider with their application.
    2. Applicant's curriculum vitae or NIH-Style Biosketch - not to exceed 5 pages.
    3. Lay Summary of the project (200-300 words only)

    - Comprehensive Research Plan - This should be no more than five (5) [single-spaced, Arial 11pt, 1" margin] pages inclusive of the following items:
        - abstract for research proposal
        - significance of research
        - background information
        - preliminary observations
        - experimental plan (methods, materials, potential limitations and pitfalls)
        - references

    (Applications which exceed the page limitations WILL NOT BE REVIEWED.)

AAS/AAS Trainee Research Fellowship Awards

Application Deadline: August 15, 2016
Apply online at http://grants.aasurg.org/

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4. Evidence of institutional approval (IRB, IND, University Animal Use Committee, etc.) (Please note: Approval need only be pending at the time of submission, as long as the study is approved at the time the funding is awarded.)
5. Letter of support from sponsoring AAS mentor.
6. Letter of support of protected time from the chair of your department. The letter must guarantee that the applicant will spend the entire funding period in the research fellowship and that the department is committed to providing the additional support necessary to ensure completion of the project.
7. NIH-style Biosketch from your AAS mentor – not to exceed 4 pages.

1. RESEARCH APPLICATION

Applications must use either 11 pt. Arial or 12 pt. Times Roman font. There is a 4.5 page limit with standard one-half inch margins (top, bottom, left, and right) for all pages, including continuation pages. No information should appear in the margins, including the PD/PI's name and page numbers. The research application should be structured as follows:

- Hypothesis and Specific Aims (1 page)
- Significance and Innovation (1/2 page)
- Approach (2 pages)
- Career Plan (1/2 page)
- References (1/2 page)

Preliminary data can be included in the Approach Section; however, this section must not exceed 2 pages. Grants which are incomplete or do not follow the page limits or formatting guidelines above will not be reviewed.

2. INSTITUTIONAL AUTHORIZATION FORMS

Approvals must be submitted from the Chairman of the Department and the administration (Dean or Fiscal Officer) of the institution in which the research will be performed verifying various institutional requirements and approvals (e.g. research, administration, human subjects and animal care committee, approvals etc.). Please download and print a hard-copy of the Award Authorizations Form, available on the Dashboard page once you have validated your application. **NOTE**: Validation and Submission of your application are 2 separate activities. **Validate** will tell you what your application is missing and **Submit** will mark it as complete and ready to submit to the Scholarship Committee. You may validate as often as you like, it will not change or submit your application.

3. ANIMAL OR HUMAN SUBJECT AUTHORIZATION

Approvals must be submitted for the use of animal or human subjects, if appropriate. The SUS would not fund a project which might not receive animal use committee approval. IRB and IACUC can be stated as pending, but would need to be approved and submitted prior to the start of the award funding (by June 30). An approved IRB may be submitted as the “human rights” authorized officer.

4. LETTERS OF RECOMMENDATION:

THREE letters of support must be included with your application:

A. SUS MEMBER SPONSOR: The letter from the SUS member sponsor should cover the basics of recommendation-why they have chosen to be your mentor/sponsor, their thoughts on your proposal, research, honors, publications, etc. They should indicate the value they feel in your participation/application and may choose to include comments regarding your abilities and your potential contributions to the field. Please note: To meet the eligibility requirements, the SUS Member Sponsor must be a member in good standing. The SUS Member sponsor may check their member status by contacting Ochun Farlice at the SUS Membership Department at ochun@susweb.org.

B. RESEARCH MENTOR: A letter from a research mentor or collaborator familiar with your research describing his/her own mentorship track-record and outcome of previous trainees. The research mentor's letter should provide the mentorship plan, including information on research environment, plan for supervision, and other educational activities during the course of the award period.

*If the Research Mentor and SUS Member Sponsor are the same person, we request that you submit a second faculty recommendation letter that comments on your candidacy for the award, ability to complete the proposed work and, overall research aptitude.

C. DEPARTMENT CHAIR: The letter from the Chairman (whether or not he/she is an SUS member) should indicate the research capability of the applicant and the institutional support for the applicant in terms of salary, laboratory space, and protected time available for the pursuit of research and confirmation that the institution will not subject the award to an indirect costs tax.

Letter from Sponsoring Mentor

Describes mentor's past mentoring experience and track record. **May need to describe training plan** for applicant.

Letter of Support from Department Chair

Contact the Chair's Office at least **6 days** before the agency deadline. **Usually, you will need to provide a draft of the letter**.

How to Ask for a Recommendation

And how to supervise the faculty member writing it

Brian Taylor

http://www.chronicle.com/article/How-to-Ask-for-a/235968

DOS Transplant T32 Application

Appendix A: FAVOR T32 Initial Proposal

Please review each section (12 total) carefully and provide the requested information.
The Concept Sheet should be 2-4 pages long in 12-point font size. Upon completion, please submit electronically in Microsoft Word format to Susanna Cheng at Susanna.Cheng@ucsf.edu.

1. **Study Title:**
   [Descriptive title of the proposed project/work]

2. **Proposing Trainee Investigator:**
   [Name, title, address, telephone number, and e-mail address]

3. **Clinical Mentor/Principal Investigator:**
   [Name, title, address, telephone number, and e-mail address]

4. **Scientific Mentor/Principal Investigator:**
   [Name, title, address, telephone number, and e-mail address]

5. **Study Rationale, Background, and Preliminary Data:**
   [Complete, concise discussion of the study rationale, including sufficient background information (e.g., data, references) to support the study's scientific merits and importance]

6. **Hypothesis and Study Objective(s):**
   [The hypothesis to be tested should be clearly stated. A clear and thorough description of all study objectives should be provided]

7. **Study Design and Methodology:**
   [Provide a clear and thorough explanation of study design and analysis methods – full description of how the critical research questions will be answered, and justification of all statistical components. Include sample size estimate and duration of follow-up]

8. **Anticipated Challenges:**
   [Describe what possible challenges you might face with your study, if any]

9. **Tentative Budget for Project Completion:**
   [Provide an approximated budget for assay cost(s), reagent/supply cost(s), etc. Note that funds are not available from the T32 grant – PI will be responsible to cover costs]

10. **Expected Outcome and its Impact on Transplantation:**
    [Describe your expected outcome from your study and how it will impact Transplantation]

- Career goals and training plan

Resident's Career Plan

I have completed three years of General Surgery residency, and I plan on pursuing additional training and a career in transplantation after completing residency. As a surgical resident interested in transplantation and academic surgery, skills enabling me to contribute to the field of transplantation in the form of basic and translational research are very important to me. Stem cell research, in particular if using iPS cells derived from patient biopsy specimens, offers exciting new opportunities for liver disease modeling and therapy. Academic surgeons trained in techniques related to stem cell research will be instrumental in translating research advances into clinical applications. By carrying out the proposed project, I will receive training relevant to both basic and translational research. Therefore, I will not only have the immediate opportunity to contribute to advancing the field, but will also be a strong candidate for future career development and research funding from the National Institutes of Health and the California Institute for Regenerative Medicine. In summary, I hope this award will allow me to begin to contribute to the field of liver cell therapy in a significant way, and act as a stepping-stone to a successful career as a surgeon/scientist and principal investigator.

DOS resident Jack Harbell, SUS proposal

If you are asked for a detailed training plan, e.g, for NIH NRSA:

Consider writing the training plan first. Then you can point to the specific aims in the Research Plan that will help you accomplish the training goals.

Develop a training plan that matches your needs exactly (not "off the shelf"). Propose a combination of didactic and "hands-on" research experiences. A degree-granting program (MPH) may be appropriate, but should still be "personalized".

See examples:

NIH NRSA grants on Resident Research Website

More examples at

http://accelerate.ucsf.edu/files/TICR_GrantWritingPt1Examples.pdf

Activities Planned Under This Award

Year 1: July 2016 – July 2017
Research, Didactic Learning: 90%; Presentations, Career Development, Manuscript Preparation: 10%

Research: The majority of my efforts during my first year of fellowship will be dedicated to the Transplant Immunology lab. My role as a resident researcher will involve both didactic education in laboratory, translational and clinical research, as well as bench research training by conducting the experiments proposed in this fellowship application. I plan to begin acquiring the technical skills necessary to perform the mouse hindlimb transplants prior to the start of the fellowship period so that I am proficient and able to work on study animals early in the year. I expect to generate the necessary data for Parts I and II of Aim 1, as well as begin aim 2, during this first year. I will have direct guidance with my labwork under Dr. Tang, and we will have weekly one-on-one meetings with me to discuss experimental plans, analyze results, and troubleshoot problems. I will also participate in weekly lab meetings and present my work as data becomes available.
Didactic Learning: I will take advantage of formal and informal didactic teachings in the form of online and classroom courses. At the start of my research time, I will begin by auditing graduate level courses in immunology to obtain fluency in the vernacular of the lab environment. I will also register and take the UCSF Training in Clinical Research (TICR) Program, which provides coursework in clinical research design and biostatistics.
Presentations: I will attend and present preliminary data at the Plastic Surgery Research Council meeting in May 2017. Additionally, I will attend the American Transplant Congress (ATC) in May 2017. I will have the opportunity to present ongoing research for a broad surgical audience at UCSF as part of our Grand Rounds series in December 2016 and our Resident Research Symposium in June 2017. Additionally, I hope to attend and submit some of my clinical projects for local and regional society meetings.
Career Development: I will interact with the Transplant Surgery division through the Transplant Seminar Series, a year-long curriculum designed for current fellows and residents in transplantation. I will continue to participate in our Plastic Surgery educational program, consisting of weekly service and teaching conferences. I will continue to participate in clinical research projects with the division of Plastic Surgery. I will meet regularly with my clinical advisor to help focus my efforts toward achieving my future academic career goals.
Manuscript Preparation: As we gather data, I will begin to prepare manuscripts for publication. I anticipate at least two publications may be generated from completion of Parts I and II of Aim 1. I will continue to refine my technical skills, and I will take advantage of my peers, mentors, and formal writing workshops to bring our work to publication.

DOS resident Nicole Conkling, NIH NRSA

Year 2: July 2017 – July 2018
Research: 75%; Presentations, Career Development, Manuscript Preparation: 25%

Research: In the second year of research, I will complete the intervention studies described in Aim 3. I will also explore further directions, including changing the dose of administered T-regs and using other immunosuppressive adjuncts if necessary. I will continue and complete the data analysis and compile my work for lab meeting presentations and manuscript submission.
Presentations: I plan to attend and present my work at Plastic Surgery the Meeting in October 2017, and at the 2018 Plastic Surgery Research Council. I also hope to travel to and present my work at the International Confederation of Plastic, Reconstructive, and Aesthetic Surgery in 2018. Additionally I plan to attend present at Immunology and Transplant society meetings in order to gain a broader interdisciplinary perspective and cultivate useful professional connections.
Career Development: I will continue to attend weekly division meetings and work on clinical research projects, as well as meet regularly with my clinical mentor. In particular, I plan to apply my newly acquired knowledge and interdisciplinary connections toward helping to establish a VCTA clinical program at UCSF.
Manuscript Preparation: As I approach my return to clinical duties in July 2018, I will focus on manuscript preparation for the final portion of the fellowship. I will continue to make revisions to pending manuscripts as required, and will prepare data from Aim 2 for publication. I anticipate two publications from this aim of research. I will also prepare any additional manuscripts and reviews as appropriate from existing data.

For NIH NRSA grants, the Mentor Statement *also* **describes the Research Training Plan** for the applicant…including

- nature and frequency of meetings
- relationship of training to applicant's career goals
- how the current application will aid the applicant in pursuing an academic career/ develop an independent line of investigation

The mentor & applicant descriptions of training activities must be in synch! No raising of reviewers' eyebrows over inconsistencies. Takes time to revise & refine.

For the DOS Transplant T32 application, you also need to include a training plan

11. Coursework Plan (100 hours per year):

[See **Appendix B** for list of courses available and provide an outline of curriculum coursework concurrent with clinical-translational research projects]

Look at training descriptions in the sample grant applications from DOS residents:

Cohan J. Crohns Colitis Foundation of America (CCFA). *Implementation and effectiveness of a decision aid for patients with ulcerative colitis considering surgery*

Conkling N. NIH NRSA. *Allograft rejection and salvage therapy with chimeric antigen receptor T-regulatory cells in murine hindlimb transplant*

Moses W. NIH Diversity Supplement. *Evaluating hemofilter biocompatibility as it pertains to surgical implantation factors*

Wisel S. American Society of Transplant Surgeons (ASTS). *The effects of nutrient and oxygen supply on h-ESC-derived islet survival*

Wisel S. Broad Institute of Regenerative Medicine. *Inducing immune tolerance in hESC islet transplantation*

- Research plan

The Research Plan for Most Agencies

Each section describes an important aspect of the proposed research:

Specific Aims: research steps for testing your hypothesis or accomplishing your objective

Background and Significance: concise description outlining the important need addressed by your research, its scientific merit, and the impact of the research to the field of science and to public health (tailored to your research focus)

Preliminary Studies: data showing the viability of your proposal

Research Design and Methods: detailed description of your planned experiments or intervention (including statistical analyses & sample size calculations); expected outcomes; anticipated problems & alternative approaches

The Research Plan for DOS Transplant
T32 Application

5. **Study Rationale, Background, and Preliminary Data:**
   [Complete, concise discussion of the study rationale, including sufficient background information (e.g., data, references) to support the study's scientific merits and importance]

6. **Hypothesis and Study Objective(s):**
   [The hypothesis to be tested should be clearly stated. A clear and thorough description of all study objectives should be provided]

7. **Study Design and Methodology:**
   [Provide a clear and thorough explanation of study design and analysis methods – full description of how the critical research questions will be answered, and justification of all statistical components. Include sample size estimate and duration of follow-up]

8. **Anticipated Challenges:**
   [Describe what possible challenges you might face with your study, if any]

10. **Expected Outcome and its Impact on Transplantation:**
    [Describe your expected outcome from your study and how it will impact Transplantation]

The Research Plan for NIH NRSA

SPECIFIC AIMS (1 page)
RESEARCH STRATEGY (6 pages), includes:
- Significance (0.5-0.75 pages)
- Approach
  - For each aim:
    - Rationale
    - Research design
    - Methods (including statistical)
    - Expected outcomes
    - Potential problems and alternative strategies

NIH Research Strategy: Organizing the Approach Section

"Unitary" (if there's one overall study and one study population)

- Introduction
- Background
- Preliminary Studies
- Research Design
  - Overview of study design
  - Study population
  - Study procedures
  - Study measurements
  - Data quality and management
  - Data analysis
- Expected Outcomes
- Potential Problems & Alternative Approaches
- Timeline
- Future Directions

Source: Tom Mitchell, UCSF (used with permission)

NIH Research Strategy: Organizing the Approach Section

"Modular" (if each aim is it's own separate "story")

For each specific aim, include the following subsections:

- Introduction
- Background
- Preliminary Studies
- Research Design & Methods
- Expected Outcomes
- Potential Problems & Alternative Approaches

- Timeline
- Future Directions

Source: Tom Mitchell, UCSF (used with permission)

For All Funding Agencies, the Research Plan Provides Answers…

1. What do you intend to do?
2. Why is this worth doing? How is it innovative?
3. What has already been done *in general*, and what have other researchers done in this field?
4. What will this new work add to the field of knowledge and to public health?
5. What have you (and your mentor/collaborators) done to establish the feasibility of what you are proposing to do?
6. How will the research be accomplished?

Use these questions to set up an outline for drafting the research plan.


DEEP
DIVE

Within the Research Plan, the Specific Aims Section…

- introduces **the problem** you are addressing; indicates if your research has contributed
- identifies the **specific gap** in knowledge that the proposed research will fill.
- identifies the long-term goal (beyond the current proposal).
- introduces hypotheses to be tested; describes the basis for the hypothesis.
- states the **aims or objectives** of project
- briefly **describes the main techniques** you will use to answer questions;
- highlights your qualifications to do the research (space permitting)
- describes **the advance** your study represents.

The Specific Aims Section Must Hook the Reader

In several paragraphs (NIH)

1. "Set-up" (Introductory) Paragraph
2. Hypothesis Paragraph
3. Specific Aims Paragraph
4. "Pay Off" Paragraph (emphasize significance, innovation, and insuring research training/contibution to career development

…or less (most societies)

If you've got ½ a page, you can't have 4 paragraphs; instead, think of 4+ sentences:

1. 1 or 2 sentences of introduction
2. 1 sentence of hypothesis.
3. Aims statements
4. Maybe a short concluding sentence about significance, innovation, contribution to career development (if that isn't a separate section)

Specific Aims: NIH Template

Source: *NIH F-Award (NRSA) Handbook, UT Austin (see link on Resident Research Website)*

Overview/construction of typical Specific Aims page

Specific Aims

40,000 foot view

Succinct statement regarding the overall research area in relation to human health and disease. For example: Cardiovascular disease is the leading cause of death and disability in developed countries and is highly associated with numerous risk factors. These factors include genetics, diet, obesity, cigarette smoking, hypertension, blah blah blah.

What's known (this section should include references!)

~3/8 page

Gap in knowledge (*i.e.*, what's missing). For example: Despite advances in the diagnosis and treatment of occlusive cardiovascular disease, the mechanisms involved in _____ remain to be established.

The proposed studies will address this gap by _____. The combined results of these investigations will _____.

The long-term goal of these research efforts will examine the hypothesis that _____. The following Specific Aims will address this hypothesis as follows:

~3/8 page

Specific Aim #1: To _verb_ (define, establish, elucidate etc)

Hypothesis:

Rationale and/or Approach:

Specific Aim #2: To _verb_ (define, establish, elucidate etc)

Hypothesis:

Rationale and/or Approach:

Specific Aim #3: To _verb_ (define, establish, elucidate etc)

Hypothesis:

Rationale and/or Approach:

~1/4 page

Summary paragraph with restatement of the problem to be addressed and the area/approach of study. For example: In summary, the proposed studies will _____. The proposed studies are *significant* because_____. The planned approach is *innovative* because _____. As a result, these studies will have a significant *impact* on our understanding/approach to _____.and will lead to improved treatments for _____ to reduce the death and disability associated with these devastating disorders. Completion of the proposed studies will also insure the comprehensive research training of the applicant and contribute to the development of a successful career as an independent (clinician) investigator.

Specific Aims: NIH

Source: DOS Resident Nicole Conkling

Specific Aims

Vascularized composite tissue allotransplantation has revolutionized reconstructive microsurgery, finally enabling surgeons to not just recreate but to truly replace what has been lost to burns, trauma, or tumor extirpation. Despite the growing clinical experience with VCTA, there is much that remains to investigate about composite transplant's unique immunogenicity and the frequency of allograft rejection. Acute rejection has been reported to be nearly universal in clinical VCTA, even with excellent HLA matching and immunosuppression adherence (1). These episodes, while responsive to treatment, require temporary increases in immunosuppression and may have subsequent long-term consequences for graft survival by triggering chronic rejection (3). There is little published evidence of clinical chronic rejection in VCTA, but case reports and clinical observation suggest it may be more common than previously thought, and it contributes to insidious graft loss. Prior histologic studies in animal and human tissue have described not only tissue architectural changes during rejection but also mononuclear cell aggregates rich in cytotoxic T cells and relatively poor in T-regs (15,20). Thus, the presence and abundance of T-regs are believed to be instrumental in promoting long-term graft survival (12).

T-regs are demonstrated actors in long-term allograft survival, and may comprise a new era of cellular therapy for graft tolerance. Their ability to prevent acute and chronic rejection in animal organ transplant models is well-established (10-14). Cultivation of these cells for practical use is challenging, however. Donor-specific T-regs have greater potency than their polyclonal counterparts, but they are more tedious to harvest and selective expansion is constrained by the availability of donor antigen presenting cells (a significant limitation in deceased donor transplant). Chimeric antigen receptor (CAR) T-regs, alternatively, can be expeditiously expanded *in vitro* using beads coated with the target antigen. Thus, the application of engineered T-regs with CARs will enable a more efficient and targeted use of cellular therapy. We hypothesize that the histology of rejection in a murine hindlimb transplant model will be consistent with an environment that is hostile to, and/or depleted of T-regulatory cells. In addition, graft-specific T-regs can be an effective salvage treatment to reverse chronic rejection and ensure long-term stable graft acceptance.

Aim 1: Define the kinetics and immunological characteristics of allograft rejection following vascularized composite tissue allotransplantation in a mouse hindlimb transplant model.
We hypothesize that in VCTA displays characteristic clinical and histologic changes in a predictable sequence. We plan to demonstrate this using a murine allogenic hindlimb transplant model, first by studying the kinetics of rejection after immunosuppression withdrawal, and second by analyzing the composition of graft cellular infiltrates at the onset and peak of rejection.

Aim 2: Evaluate CAR T-regs as a salvage treatment for rejection in mouse hindlimb transplant.
The administration of graft-specific CAR T-regs to mouse hindlimb transplant recipients with biopsy-proven allograft rejection should arrest or reverse this process. We will produce this effect by infusing anti-human HLA-A2 engineered CAR T-regs into transplanted mice that are recipients of allografts from HLA-A2 transgenics. We expect to see clinical and/or histologic stasis or improvement in the rejection process, and find biochemical evidence of CAR T-regs' cellular effect using gene analysis.

Successful completion of this study will not only contribute to the body of knowledge of the histologic characteristics and cellular processes of rejection in VCTA, but it will help to validate the use of CAR T-regs as a potential therapy for allograft rejection. This technology, already broaching on clinical application, could feasibly be applied to treat rejection in VCTA while minimizing toxic immunosuppression, ultimately preventing the morbidity of graft loss. By conducting this study, I will gain hands-on experience on preclinical modeling of a clinical problem, immunological basis of VCTA rejection, and novel cell therapy development in preclinical models. These skills and insights will valuable for my development as a surgeon scientist.

Template for ½ Page Aims Section

Succinct statement regarding the unmet need and/or gaps in our knowledge and why this is an important topic of study. *Our overall goal* is to understand _____. *The specific objective* of this proposal is to _____. *The central hypothesis* is that _____. We formulated this hypothesis, in part, based upon our strong preliminary data, which shows that _____. The rationale for the proposed research is that once it is known how _____ we can _____. We will pursue these studies in three Specific Aims:

Aim 1. *To verb (define, establish, determine, etc).*

Our *working hypothesis* for this Aim is that _____.

Aim 2. *To verb (define, establish, determine, etc).*

Our *working hypothesis* for this Aim is that _____.

Aim 3. *To verb (define, establish, determine, etc).*

In these studies, we will examine the *prediction* that _____. The proposed work is significant because it_____, and is innovative because it capitalizes on _____. We expect that the combined work proposed will establish _____. By conducting this study, I will gain hands-on experience in ___, _____, and _____, as well as _____, all of which will provide a valuable foundation for my development as a surgeon' scientist.

Understand what a Specific Aim is

A specific aim should *describe concisely and realistically what the proposed research is intended to accomplish*:

- 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 a field
- develop a new technology

The overall goal of the proposal is not the same thing as a specific aim:

General goal:
To improve the quality of alcoholism treatment

Specific aim:
To determine the relative efficacy of Treatment A vs. Treatment B for increasing abstinence by a measurable %

The overall goal is not the same thing as a specific aim:

General Goal: Our *long-term goal* is to elucidate the molecular basis for suppression of innate immunity by type III effectors.

Specific Aims:

1. Determine the molecular consequence of ADP-ribosylation on the function of *At*GRP7 and elucidate the role this protein plays in innate immunity.

2. Identify additional substrates of HopU1 and verify their involvement in innate immunity.

3. Analyze the affect that HopU1 has on host-microbe interactions.

Source: NIAID

If your aims are testing a hypothesis or accomplishing an objective, that hypothesis or objective must be

- ✓ Logical
- ✓ Relevant to a gap in recent scholarship and/or assessed needs
- ✓ Feasible
- ✓ Stated precisely

The Logical, Testable, Feasible Hypothesis

For more advice on developing a solid hypothesis, go to the NIH:

http://funding.niaid.nih.gov/researchfunding/grant/cycle/pages/part03.aspx#e

Evolution from description to what is clearly a testable hypothesis

1. **We hope to observe how** tumor cells respond to TGF-beta and if the responses promote angiogenesis and tumor growth.

2. **We propose to determine how** tumor cells respond to TGF-beta and if the responses promote angiogenesis and tumor growth.

3. **We propose to determine the mechanisms by which** tumor cells respond to TGF-beta and if the responses promote angiogenesis and tumor growth.

4. **We will test the hypothesis that *x* is the mechanism by which** tumor cells respond to TGF-beta and if the responses promote angiogenesis and tumor growth.

based on Israel Goldberg, PhD, Health Research Associates

Evolution from description to what is clearly a testable hypothesis

1. **We hope to observe that** HPV infection is a risk factor for heterosexual HIV infection among women in Zimbabwe.

2. **We propose to establish a relationship between** HPV-mediated cervical lesions and the incidence of HIV infection among women in Zimbabwe.

3. **We will test the hypothesis that HPV-mediated cervical lesions are not only more prevalent but enhance** the acquisition of HIV in HIV+ women.

*based on Sarah Averbach, MD, "the effect of cervical HPV infection on HIV acquisition among women in Zimbabwe (UCSF Pathways to Discovery Program, 2009)

Specific Aims Section: Remember…

YOUR GOAL: Convince *every* reviewer that the problem or need that you identify is *relevant to the mission of the funding agency.*

Provide an overview that frames the problem or need and establishes its significance.

Make sure to make it clear what is *known* and what is *unknown*.

Make it clear that your aims are focused, clearly conceptualized, and feasible, (and in many cases, will test a hypothesis).

Organization, brevity, and clarity are critical.

Write your Aims and plan to rewrite them. Send them to whoever is willing to review them. Allow enough time for this iterative process.

The Rest of the Research Plan

Background and Significance: importance of the research to science and public health

Preliminary Studies: data showing the viability of your proposal

Research Design and Methods: detailed description of your planned experiments/intervention

Background and Significance

Background:

1) Brief and focused recent history of what has been done about the problem, emphasizing current state of knowledge in the field
2) Gap(s)in the field that your project will fill *(the ones that you highlight in your narrative should be the ones you address in your proposal!)*
3) Theories and concepts that will guide your approach

Significance:

Why the study is important.

Background and Significance

Position your project in relation to other efforts and show how your project:

- will extend the work that has been previously done
- will avoid the mistakes and/or errors that have been previously made
- will serve to develop stronger collaboration between existing initiatives

or

- is unique since it does not follow the same path as previously followed

Background and Significance

<u>Not</u> an exhaustive literature review!

You don't need to show that you've read everything.

Be selective, deal with contradictions, cite your own work and that of the reviewers.

Outline for Organizing the Key Information

	Importance	Existing Knowledge	Gaps to be Filled	Innovation
Specific Aim 1				
Specific Aim 2				
Specific Aim 3				

"Research Image", N. Bell

Background: It's about synthesis

There is **much** more background material than can possibly be included.

Content depends on precisely what hypothesis is to be tested, or what objective is to be attained. Be sure to…

1. Define the current state of knowledge in the field (using current, appropriate citations; *refer to recent reviews*).

2. Identify important gaps, discrepancies, questions.

3. State how the proposed research will address these gaps and increase knowledge by weaving your specific aims into the narrative.

Don't just *rehash* what's been written—*interpret* it!

Background: Synthesis not Rehash

Example: Topic sentence first, then details:

Currently, the standard treatment for congenital hematopoietic stem cell disorders is postnatal bone marrow transplantation. The treatment efficacy using this approach is often limited by transplantation complications, such as graft versus host disease and graft rejection, by the availability of few HLA-matched donors, and by the morbidity of host myeloablation preceding transplantation (reviewed in [2]). The induction of donor-specific tolerance to transplanted allogeneic stem cells without long-term immunosupression would therefore have important clinical applications.

Background: It's about synthesis

- ✓ **Focus on the ideas, not the names & dates**

  Example

  Numerous studies have shown that inflammation increases SQ RBC adhesion (5, 30, 34, 40) but few have provided direct evidence linking inflammation to vaso-occlusion. **In the most convincing study to demonstrate this link** (30), platelet activating factor increased SQ RBC-endothelial adhesion and vaso-occlusion in the artificially perfused trat mesentery, and blockade of the pro-adhesive integrin c5b3 attenuated these events.

Background: It's about synthesis

Example: Tying it all together (paragraph with topic sentence, supporting sentences, transition words/phrases), explicit link to the proposed work. NOTE: No names & dates!

Regulatory T cells (Tregs) have been implicated as critical regulators of the immune system, responsible for maintaining immune self tolerance [9]. Through the production of inhibitory cytokines and/or direct inhibition with cell to cell interactions, Tregs function to inhibit immune activity and thereby maintain self tolerance. Furthermore, recent evidence has demonstrated the ability of Tregs to promote tolerance following allogeneic postnatal bone marrow transplantation[10]. Little is known, however, regarding their involvement in allogeneic IUHSCTx and this proposal will address the application of Tregs to improve host engraftment after IUHSCTx.

Source: sample grant from resident Amar Nijigal

Background: Illustrate

Use figures to make key points, illustrate hypotheses and aims (many reviewers are "visual").

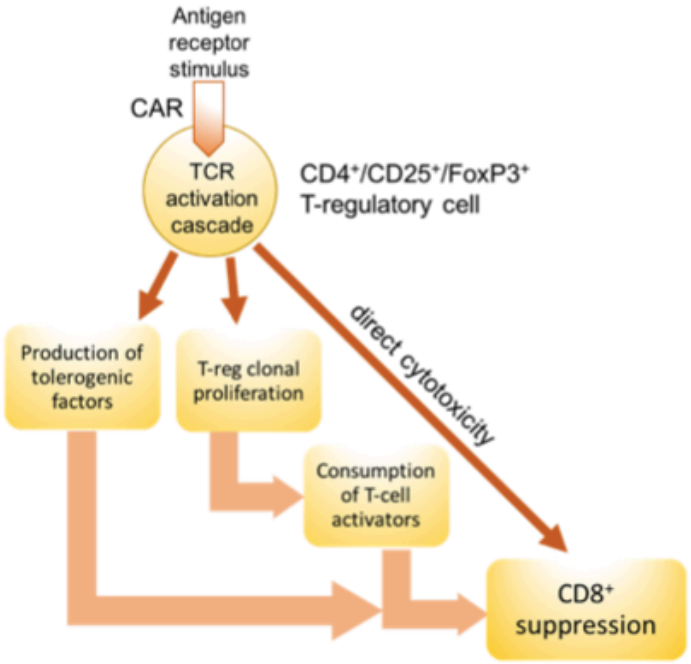


Fig. 1. Schematic of hybrid T-regulatory cell chimeric antigen receptor (CAR) activation and proposed mechanism of allograft tolerance.

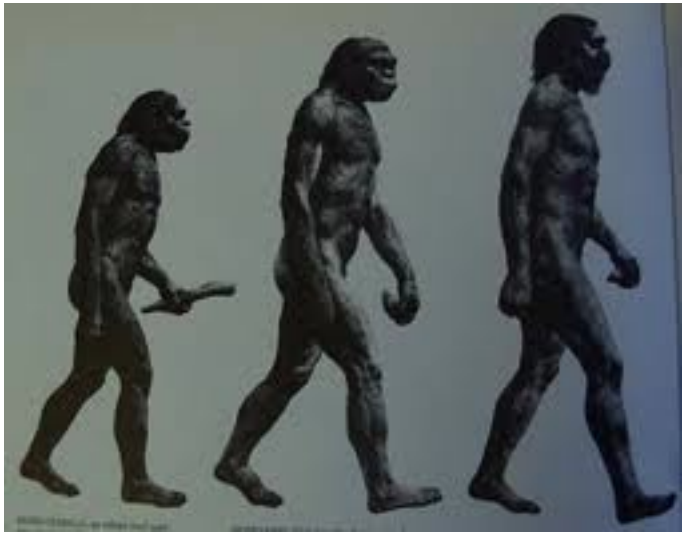
The therapeutic use of T-regs, while important and effective in mitigating allograft rejection, is not without challenges. Donor-specific T-regs, while more difficult to cultivate, have greater potency in protecting an allograft than polyclonal T-regs. An exciting and innovative technology in cell engineering that attempts to obviate these challenges is the development of hybrid T-cells, notably those with chimeric antigen receptors (CARs). Hybrid T-cells are engineered, typically using a viral vector, to contain cell-activating receptors designed to respond to an immunologic trigger of choice. These cells have an extracellular domain responsible for antigen recognition, and an intracellular signal transduction domain of T-cell receptor zeta chain that activates the T-cell effector responses (Fig. 1). Hybrid T-cells have been in clinical use in the field of oncology and have demonstrated great success with the treatment of hematologic malignancies that have failed all other therapies (17). By engineering donor-specific T-regulatory cells, their immunomodulatory potential can be harnessed and targeted toward the cellular processes responsible for rejection of donor tissue. While T-regs have previously been proposed as an approach to prevent rejection in VCTA, CAR T-regs have not yet been investigated as a salvage method for allograft rejection (7). Given their potential for success and the availability of necessary biotechnology, demonstrating their usefulness in chronic

DOS resident Nicole Conkling, NIH NRSA

Significance

Can your research move the field forward?

Will progress in this endeavor make a difference in human health?



Significance

Convinces reviewers that your research addresses an important, clearly defined question that pertains to health/mechanisms of disease.

Explains why your proposed experiments are an important extension of your preliminary studies.

Significance of your research **is not the same** as significance of the disease!

How to Communicate Significance

Establishing the source of tumorigenesis is a fundamental and unresolved issue in pancreatic cancer research. The cells of origin may solely determine pancreatic tumor phenotype. Alternatively, it may be the unique combination of genetic "hits" amassed by pancreatic cells, rather than the cells of origin, that determines tumor phenotype. It is the goal of my proposal to distinguish between these possibilities.

Source: Sample grant provided by Sam Wang

How to Communicate Significance

If successful, this work will facilitate the generation of new accurate human liver disease models and provide an in vivo assay to test the efficacy of iPS cell-derived hepatocytes for human liver cell therapy.

Source: Sample grant provided by Jack Harbell

Preliminary Studies

Lets reviewers evaluate the basis of your project:

Shows that you (and your mentor) know what you're doing

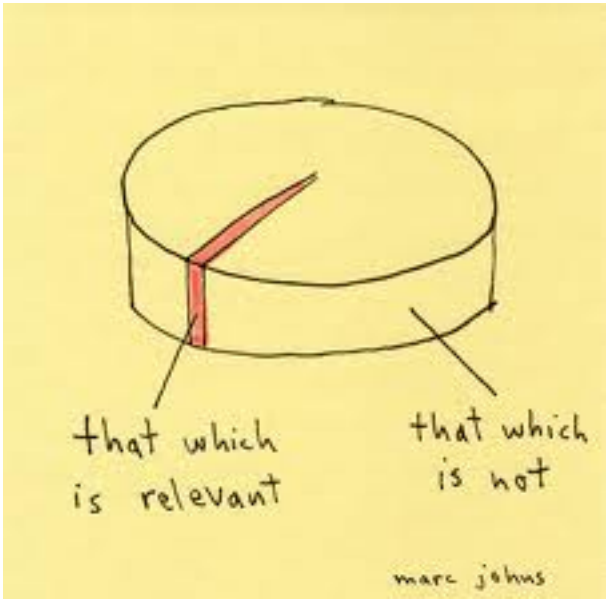
- ability to develop/test hypotheses
- expertise to design/conduct/analyze results of rigorous experiments
- ability to interpret findings and present them clearly and effectively

Shows that the proposed techniques are feasible

For clinical studies, shows pilot data on proposed intervention and availability of study participants

Preliminary Studies

- ✓ Show only data that is relevant to the current proposal. Make it obvious how the data is relevant to what you propose to do.



1. Begin with a brief introduction that gets right to the gap in knowledge and an overall statement of what you (or your lab) did in the preliminary studies for the current grant**:**

Both Hedgehog (Hh) and Wnt have long been known to play an important role in embryonic development, but the exact nature of their contributions to cancer development remains obscure. Previous histological studies on human tumor samples **and recent work from our laboratory** have implicated the Hh and Wnt signaling pathways in pancreatic tumorigenesis [6, 7]. Based on this work, we have developed mouse models of several pancreatic tumors.

This and following slides taken from sample grant provided by Sam Wang

2. Next, describe in detail what you did and your interpretation of what it means, and refer to tables and figures as needed to show your data:

In PanIN-PDAC lesions, we found that k-ras activation led to Hh signaling, that in turn activated the Wnt pathway. These results imply a step-wise relationship from k-ras activation to PDAC formation, via Hh and Wnt signaling (Figure 1) [8]. This model suggests that Hh or Wnt activation would also produce PanIN-PDAC. While simultaneously activating k-ras and Hh (via GLI2, a downstream mediator of Hh) resulted in PanIN-PDC, triggering Hh alone led to only undifferentiated tumor formation [9] (Table 1).

3. More about what you did and what it means**:**

When we perturbed the Wnt pathway, the results were also confounding. Triggering Wnt alone via an activating mutation of β-catenin (β-cat^{ex3}), which is the downstream effector in the Wnt pathway, led to formation of solid pseudopapillary tumors (SPT), a rare and indolent type of pancreatic neoplasm, without evidence of PanIN-PDAC. More interestingly, when k-ras and Wnt were activated together, acinar cell carcinoma-like tumors (ACC) formed without PanIN-PDAC (unpublished data, Table 1).

Like SPT, ACC is rare and comprises less than 1% of pancreatic tumors. However, it is more malignant in nature. This finding is notable because k-ras activation in the absence of exogenous Wnt activation results in PDAC formation.

4. Summarize…and end at the "doorstep" of your first specific aim (or the proposed study).

Even though our early work suggested that Hh and Wnt act as intermediaries in a k-ras-PanIN-PDAC progression model, our recent studies suggest a more complicated relationship. Currently, it is unknown whether each type of pancreatic tumor arises from a unique cell type that is transformed when certain signaling pathways are perturbed. Alternatively, the tumors may originate from the same cells but the phenotype is determined by the combination of genetic changes. The objective of the proposed study is to establish the role that each pancreatic cell type plays in the formation of various pancreatic tumors.

Preliminary Studies: Details

All tables and figures necessary for the presentation of preliminary results must be included in this section.

Legibility is critical or figures are a waste of space and source of frustration for reviewers.

A figure or table that accompanies the text should be inserted ***after*** referring to it in the text. If there's no room at the bottom of the page after a table or figure is first mentioned, moved it to the top of the next page, with a note on the preceding page that says *'(see Figure 6, top of next page)'*.

Preliminary Studies: Details

Figures should include legends and footnotes.

The first part of the legend should include whatever description is relevant to making the figure intelligible and include the meaning of all symbols, including error bars.

The second part of the legend can take advantage of the fact that figure legends (and footnotes for tables) can often be in smaller font than text (9 pt vs 11 pt for NIH). You can therefore provide methodologic summaries in figure legends and table footnotes. That way, reviewers can read it if they want to, but you don't take up a lot of text space.

Source: *"The Grant Application Writer's Workbook. A Guide to a Successful Proposal, National Institutes of Health (Beta Edition), by SW Russell and DV Morrison. 2009*

Research Design and Methods

- Describes *how* you will carry out your specific aims.

- Usually the longest section (~ half the research plan).

Rationale. Describe the overall concept of your proposal and the principles and ideas underlying its design and topic.

Methods. How will carry out your aims? Mention any new methods & why they are better. Describe experiments, intervention(s), data collection, statistical analysis (sample size calculation). *Provide enough detail for reviewers to determine what you are proposing to accomplish.*

Anticipated Outcomes/ Pitfalls/Alternative Approaches. State the expected outcome for each experiment (or aim), and why it is interesting & important; briefly discuss the limitations of each approach, how they may affect your results and data, and propose alternatives.

Aim 1. Determine the optimal nutrient supply for h-ESC-derived islet survival.

Rationale: Experience from clinical islet transplantation shows that at least 5,000 islet equivalents (IEQ) per kilogram are required for insulin independence in humans. If islets are to be transplanted in an iPhone-sized device, with a 400um thickness to the subcutaneous space in humans, islets will require packaging at a density of ~250 islets per uL. Achieving h-ESC-islet transplantation on the human scale will therefore require h-ESC-derived islet survival in high-density conditions. To determine islet tolerance to high-density packing, the Tang lab has cultured mouse islets in vitro at various densities and observed density dependent islet death. At a density of 1 islet/uL, 80% of the islets died within 12 hours of culture (Fig 2). Islet death occurred independent of oxygen concentration or glucose supplementation, which suggests nutrient deprivation as a cause of cell death. Islet cell death can be prevented in vitro following supplementation of glutamine to the culture medium, highlighting glutamine as a limiting nutrient in these cultures (Fig 3). The impact of nutrient deprivation on h-ESC-derived islets is not widely recognized and has not been investigated in depth. Experiments proposed in this aim will identify nutritional substrates most effective at promoting islet survival and function in high-density packing scenarios.

Experimental Design: Studies in Aim 1 will focus on comprehensive dose response and kinetic response profiles of all 20 amino acids to determine the optimal amino acids, concentrations, and durations of exposure for islet survival. Subsequent analysis will further include candidate metabolites as suggested by known biochemical pathways. Candidate nutrients will be added to h-ESC islet culture medium at multiple concentrations. Effects of nutrient supplementation will be assessed by:

a. Islet cell survival using propridium iodide (PI) and fluorescein diacetate (FDA) staining, followed by microscopy and flow cytometry;
b.Beta cell function by glucose stimulated insulin secretion (GSIS), percentage of GFP+ cells using the insulin reporter h-ESC line, and flow cytometric analysis of C-peptide production; and
c. Differentiation state of the cells, which will be assessed by qPCR analysis of insulin, Glut-2, Pdx1, Mafa, NKx6.1, Ngn3, and Sox9 gene expression, in addition to immunofluorescent analysis of insulin and Sox9 protein expression.[10]

DOS resident Steve Wisel, ASTS

Expected Results: For Aim 1, I expect to observe glutamine, in addition to several other candidate amino acids, as limiting nutritional reagents in culture. I expect to see a cluster of amino acids, known to play a central role in aerobic metabolism and the TCA cycle, as effective nutritional supplements to prevent cell death. Alternatively, glutamine is known to confer protective benefit to islets through an antioxidant mechanism.[11,12] If control of oxidative stress is the mechanism of action, I would expect sulfur-containing amino acids other metabolites such as glutathione, taurine, and N-acetylcysteine to confer protective benefit.[13]

Pitfalls and Alternative Strategies: h-ESC- derived islets may behave differently than mouse islets, although preliminary data in the Tang lab shows that glutamine supplementation can rescue h-ESC islets cultured at high density. It is possible that other amino acids do not have the same effect on overall survival. With this in mind, I will evaluate wider concentration ranges and include metabolic intermediates, such as pyruvate, acetyl-CoA, and TCA cycle in my analyses. Additional experiments may be continued with metabolites playing a role in antioxidant pathways.

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Writing About Methods: Some Rules of Thumb

- ✓ Describe in detail all methods that have not been published.
- ✓ Give a brief overview of methods that have been fully described previously in published articles and cite the reference.
- ✓ Write short paragraphs.

Design and Methods for Clinical Studies

Very different from describing individual experiments for a basic science proposal:

- Study population
- Subject recruitment, enrollment, and retention
- Study procedures
- Study measurements
- Data quality & management

But… as with basic science, also describe:

- Data analysis (including sample size calculation)
- Potential problems and alternative approaches

Design and Methods: Examples to Follow

- See Inouye and Fiellin article for clinical proposals (citation is in Pam Derish's *Resource Guide for Scientific Writing*, available on the Research Website)

- See sample grant proposals from other residents (on the Resident Research Website)

- See sample grant proposals at NIAID website (link is in Pam's *Resource Guide for Scientific Writing*, available on the Resident Research Website)

The Abstract

1) brief background of the project
2) hypothesis and specific aims
3) the unique features of the project
4) the methods to be used
5) expected results
6) description of how results will affect other research areas
7) the significance and health relevance of the proposed research (for NIH, this goes in the separate *Project Narrative*.

The Abstract

View the abstract as your advertisement.

Be complete, but brief –takes time to get it right.

Use active voice and strong action verbs.

Write it so it can be made public without revealing intellectual property.

Use all the space allotted.

NIH Template

Source: *NIH F-Award (NRSA) Handbook, UT Austin (see link on Resident Research Website)*

Overview/construction of typical Project Summary/Abstract

SELF-CONTAINED, CONCISE, AND POWERFUL SUMMARY; must fit within the space limitations in the form (30 lines)

****

Introduction - ~2-3 sentences to set the stage about the area of research and the nature of the problem to be studied, i.e., why do we care about the problem? <<<THESE FEW SENTENCES MUST ADDRESS THE IMPORTANCE OF THE AREA TO BE EXAMINED IN THE PROPOSED STUDIES>>>>>>>>

Statement of the problem / gap in knowledge that will be filled in the planned studies, i.e., what do you want to learn?)

Overall hypothesis

The following aims will address this hypothesis:

Specific Aim #1

Specific Aim #2

Specific Aim #3.

<<<<Methods/approaches to be used to address the Specific Aims are usually BRIEF (or not mentioned) and are summarized at the end of the aims, e.g., molecular and genetic studies will be accomplished using an *in vitro* cell culture system, i.e., primary cultures of human umbilical vein endothelial cells

blah blah blah)>>>>>

Implications of the results to be obtained: **Significance/Innovation/Impact**, *e.g.*, a statement of how will the results of the planned studies add to the body of knowledge to potentially change our understanding. For instance, 'these studies are significant because ' or 'these studies are innovative because ' or 'these studies will have impact because '

And, brief concluding comment regarding how this training will prepare you for the next step in your career development, *e.g.*, faculty or postdoc, towards your ultimate goal to become an independent investigator

Brief Synopsis of Research:

Although islet transplantation has shown great progress in the treatment of diabetes mellitus, broader application of the technology is limited by the scarcity of human donor tissue and the massive islet loss in the peri-transplant period. Human embryonic stem cell (h-ESC)-derived islets hold great promise as a robust option for clinical application, providing an unlimited source of beta cells with the ability to recover cell mass over time and more durable response to hypoxia.[1-4] However, these h-ESC-derived islets remain susceptible to primary graft failure (PGF), with death of 60-80% of islets in the first 3-5 days prior to revascularization.[5-7] Early clinical trials with h-ESC islets will take place within an encapsulation device in a subcutaneous location, providing immunoprotective barrier function and protection against malignant transformation. The Tang lab at UCSF has observed that the high density packing required for encapsulation further exacerbates PGF. Optimizing graft survival remains the central challenge to establishing islet transplantation as a feasible therapeutic option. As PGF mainly occurs in the early transplant period prior to revascularization, I hypothesize that nutrient deprivation and hypoxia are two independent primary triggers of PGF. I will test this hypothesis with h-ESC-derived islets in vitro and in a humanized mouse model. Successful completion of this study will help to optimize early h-ESC islet survival, decrease encapsulation device size, and make h-ESC islet transplantation a viable clinical therapeutic option on the human scale.

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The Abstract

Look for examples!

- ✓**Your mentor's proposals**
- ✓**NIH:** http://projectreporter.nih.gov/reporter.cfm/

Excellent guidance:

http://blog.citizen.apps.gov/NIAIDFunding/2011/02/tips-for-other-application-parts/

The Title

Research intent and value should be communicated clearly, in plain English:

Before: G-PROTEIN SIGNALING IN SYMPATHETIC OVEREXCITABILITY

HUH?

After: THE ROLE OF ABNORMAL G-PROTEIN SIGNALING IN HEART DISEASE

Template*: The role/effect/appropriate noun of X on Y in Z"*

Look for examples: http://projectreporter.nih.gov/reporter.cfm/

Mentors do not want to “heavily revise” a disorganized document that doesn’t follow the agency’s format & guidelines.

Revising: big things first

First, make sure the various parts of the proposal are in synch with each other.

- Is everything in the proper place?
- Is each part accomplishing what it's supposed to?
- Reorder things, restructure things, draw arrows, cross out.

Revising: big things first

Second, read through the proposal, putting yourself in the position of a reader who knows nothing about your work.

- Is everything clearly and logically arranged?
- Are there any gaps in the logic or the story you're telling?
- Are there places where the reader might get bogged down in excessive detail?
- Are there internal inconsistencies?

Revising: big things first

- Check each figure and legend against the text.
  - ✓ Are they working synergistically, or is there excessive overlap?
  - ✓ Are all the figures cited in the text?
  - ✓ Do the figures/panels cited actually support the statements made in the text?

Revising: smaller things after

- Write structured paragraphs
  - Use topic sentences
  - Focus on 1 topic
  - Use transitions

- Write well-designed sentences;
  - write short sentences
  - write clear comparisons
  - avoid writing errors
  - use passive voice selectively

Revising: smaller things after

"A scrupulous writer, in every sentence that he writes, will ask himself at least four questions, thus:

1. What am I trying to say?
2. What words will express it?
3. What image or idiom will make it clearer?
4. Is this image fresh enough to have an effect?"

— George Orwell

Use tools to help you revise

Derish PA and Eastwood S. *A Clarity Clinic for Surgical Writing*. J Surg Res 2008, 147:50-58. Learn several techniques for achieving clarity in your writing, including choosing words carefully, designing well-constructed sentences, building structured paragraphs, and displaying your thinking clearly by using topic sentences and transitions http://www.ncbi.nlm.nih.gov/pubmed/17655864

Zeiger M. *Essentials of Writing Biomedical Research Papers* (second edition). New York: McGraw-Hill, 1999. Indispensible and authoritative. Available at Amazon.com

Use tools to help you revise

Resource Guide for Scientific Writing and Presentations

UCSF Department of Surgery

Pamela Derish
Scientific Publications Manager & Writing Instructor
Department of Surgery, UCSF
tel 415.885-7686
Pamela.Derish@ucsf.edu
http://sciencepubs.surgery.ucsf.edu

Get editing help

- Help with developing the Research Plan component of your proposal so that you make a straightforward case for your work
- Help with your Biosketch and Training Plan
- Help with wrestling the abstract to meet the word/space limit; taming the technical language for lay abstracts.

Most authors find it easiest to e-mail a file to me at pamela.derish@surgery.edu. I'll need to know what agency you are applying to, the deadline, and who your mentor is. If you have any questions, call me at 415.885.7686 or send an email message.

Read more at http://sciencepubs.surgery.ucsf.edu

Eliciting feedback from mentors & others

1. Get an explicit commitment

2. Specify the purpose of asking for a review at this time
   - General review?
     - Broad-based (does the argument flow, is the content understandable?)
     - Fine (stylistic issues; grammar and typos)
   - Focused expert review?
     - Technical questions (is this an adequate description of logistic regression?)

3. Be courteous
   - Double or triple-spaced draft (ask in advance – see #1)
   - Include page numbers (can consider using line numbers too)
   - Everyone works on the same draft at the same time

4. Arrange to have a conversation to receive the feedback

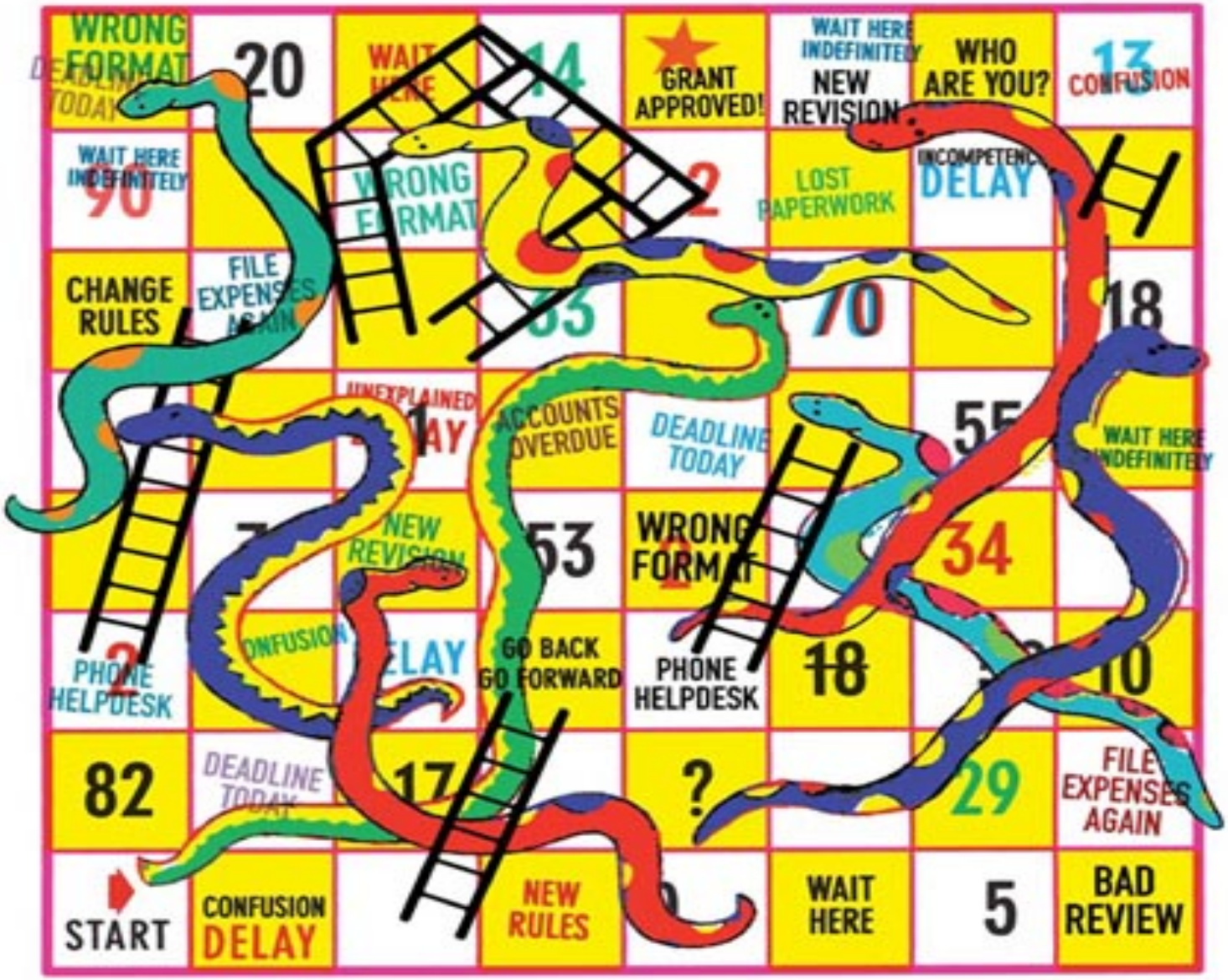
Dealing with feedback from your mentor (& others)

"Here it is—my novel. I'll be interested to hear your compliments."

1. Don't be defensive (most important, that is why it's #1).

2. Try to understand the reason for the concern.

3. View the suggestions you receive critically.


WRONG FORMAT
20
GRANT APPROVED!
WAIT HERE INDEFINITELY
NEW REVISION
WHO ARE YOU?
13
CONFUSION
WAIT HERE INDEFINITELY
90
LOST PAPERWORK
DELAY
CHANGE RULES
FILE EXPENSES AGAIN
70
18
ACCOUNTS OVERDUE
DEADLINE TODAY
55
WAIT HERE INDEFINITELY
NEW REVISION
53
WRONG FORMAT
34
PHONE HELPDESK
GO BACK GO FORWARD
PHONE HELPDESK
18
82
DEADLINE TODAY
17
?
29
FILE EXPENSES AGAIN
START
CONFUSION DELAY
NEW RULES
WAIT HERE
5
BAD REVIEW