How to Identify (an) Important Questions

Out of field proposal

- Out of field = an area of science that you have not, are, or will likely work(ed) on;
- nor projects that are ongoing in labs you are / have been associated with
- Nor projects that have been covered in the course

Proposal Format

1. Specific aims (1–1.5 page)
Start with a brief description of the overall objectives of the proposal, and then list the specific goals of the research proposed, e.g., to test a hypothesis, create a novel assay, solve a specific problem, etc. In general, 2-3 specific aims are recommended. Note that different aims should not go in disparate directions, but rather connect with each other cohesively to address the overall objective.

2. Background and significance.
Briefly sketch the background leading to the proposal, with emphasis on explaining the importance of the problem or critical barrier to progress that the proposal addresses.

3. Approach
Describe the strategy, methodology and analyses to be used to accomplish the specific aims of the proposal. Describe in detail the experimental design that addresses each of the specific aims in part (1), and the interpretation of potential outcomes from the experiment. Discuss potential problems and alternative strategies, if applicable.

Pick A Good Problem

- An evolutionarily conserved phenomena
- Essential or involved in pathology
- Conceptual advance – paradigm shifts that changes the way we think
- Fundamental – insights or concepts permeate a broad spectrum of phenomena or molecules
- Technological advance – enables previously impossible experiments for many scientists
- A good proposal often contain multiple of these elements

Good proposals should (if successful):

(1) clear logic and reasoning

(2) Be hypothesis driven

(3) significantly advance the understanding in a field

(4) opens up new avenues of thoughts and/or research

(5) opens a new field

Important Problems should not:

(1) Be a vague question or null hypothesis

(2) Be the obvious next step or elaboration of previous work

(3) Be anything in a currently ‘hot’ field

(4) Be a fancy tinker tool you make

(5) Be a highly esoteric problem

(6) Doing what you can do

(7) Be simple brutal force fishing

(8) Generate a stamp collection without mechanistic insight

Approach: Calculated Risk

- Start with a set of interesting observations; can you synthesize the information into interesting hypothesis?
- Ideas should be out of box but soluble
- A good question is specific enough to be broken down into a subset of complementary questions, each experimentally addressable
- Availability of accessible assays, technology, or defined model organisms
- Before the dream experiment, can you identify pilot experiments that provide proof-of-principle?
- Elegance = Simplicity and incisiveness of design

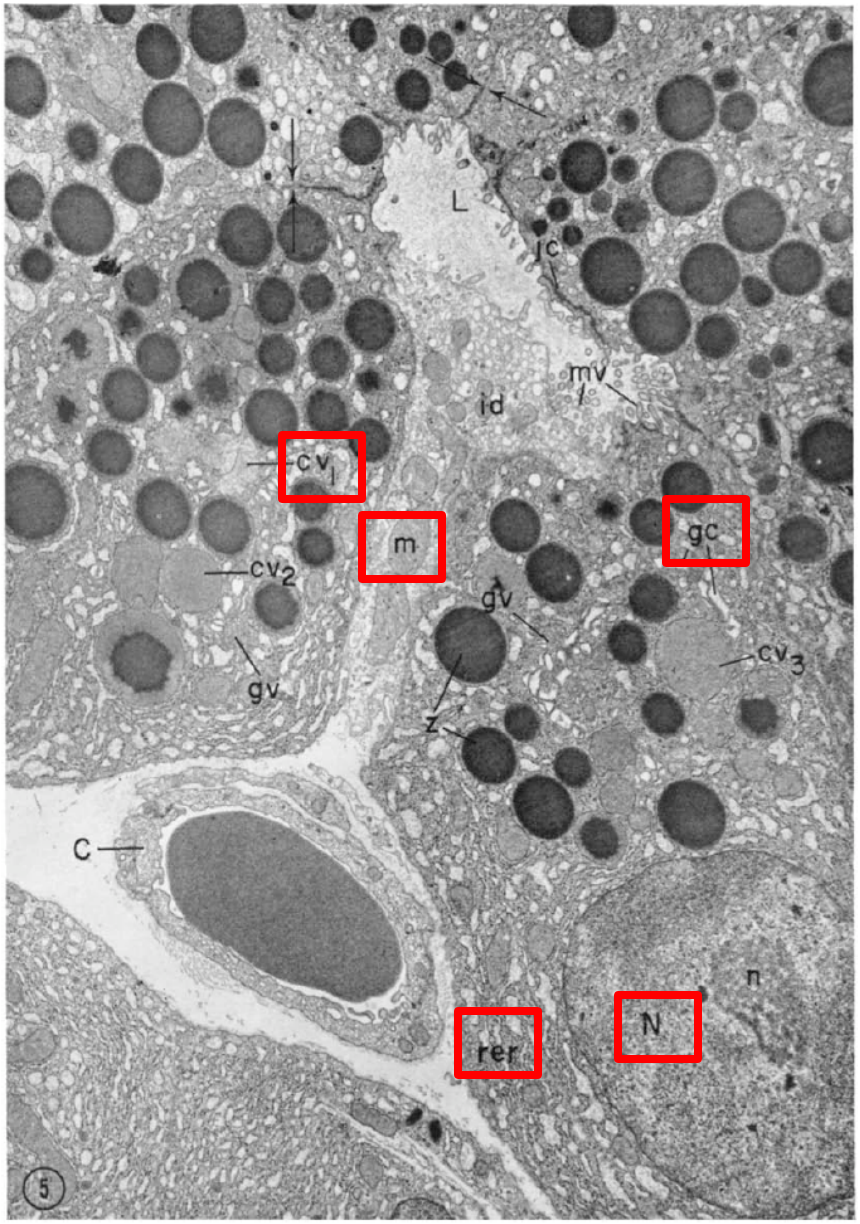
Examples

EM of pancreatic slice

George Palade
Nobel Prize 1974

Slices were cut from guinea pigs were incubated in culture media 3 hr.

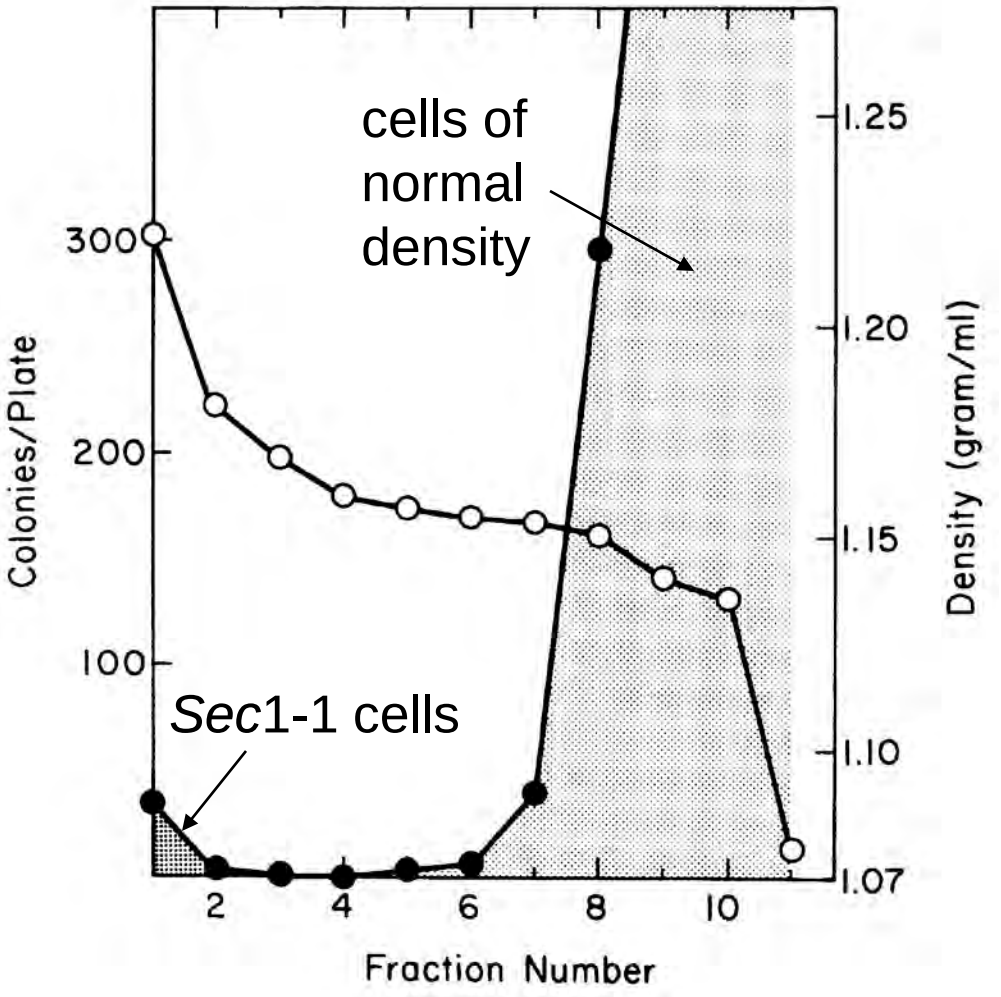
L=lumen
mv=microvilli
jc=junctional complex
id=intercalated duct cell
rer=rough ER
gc=golgi cisternae
cv=condensing vesicles
N=nucleus
n=nucleolus
C=capillary
m=mitochondria



Jamieson and Palade (1967) JCB

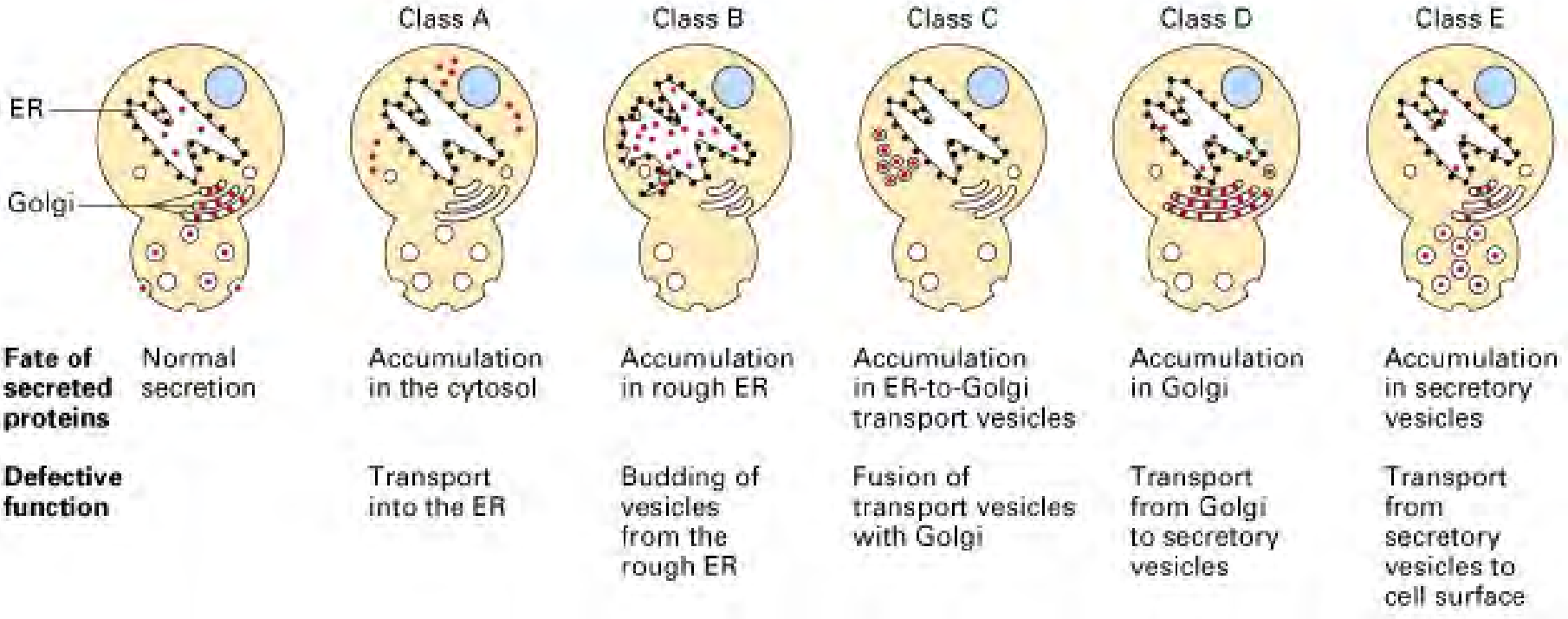
Schekman: Density gradient Separation of temperature-sensitive (ts) Secretion Mutants

secretion mutants are 5% more dense than normal cells



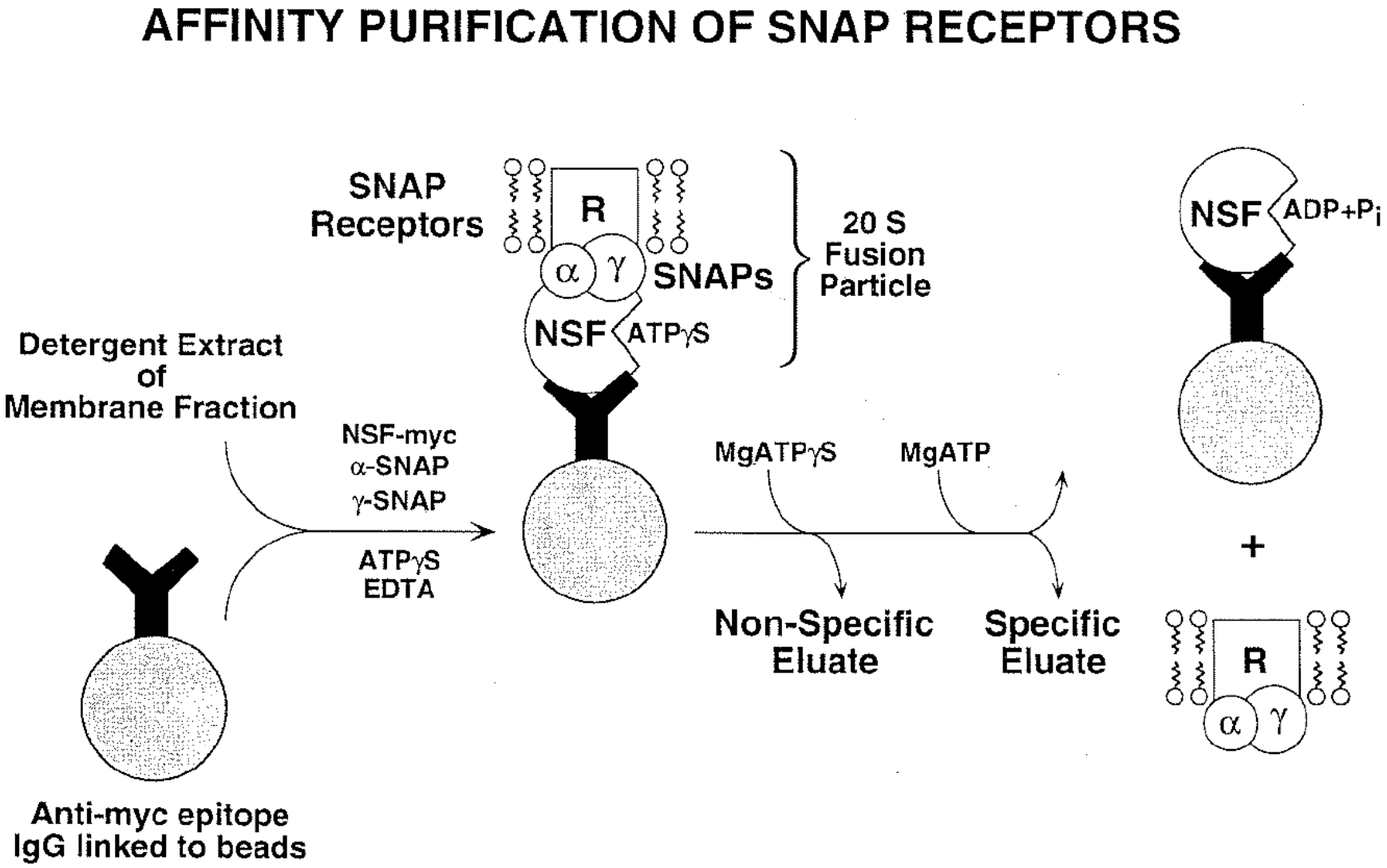
Novick et al, 1980

Analysis of yeast mutants defined the major steps in the secretory pathway



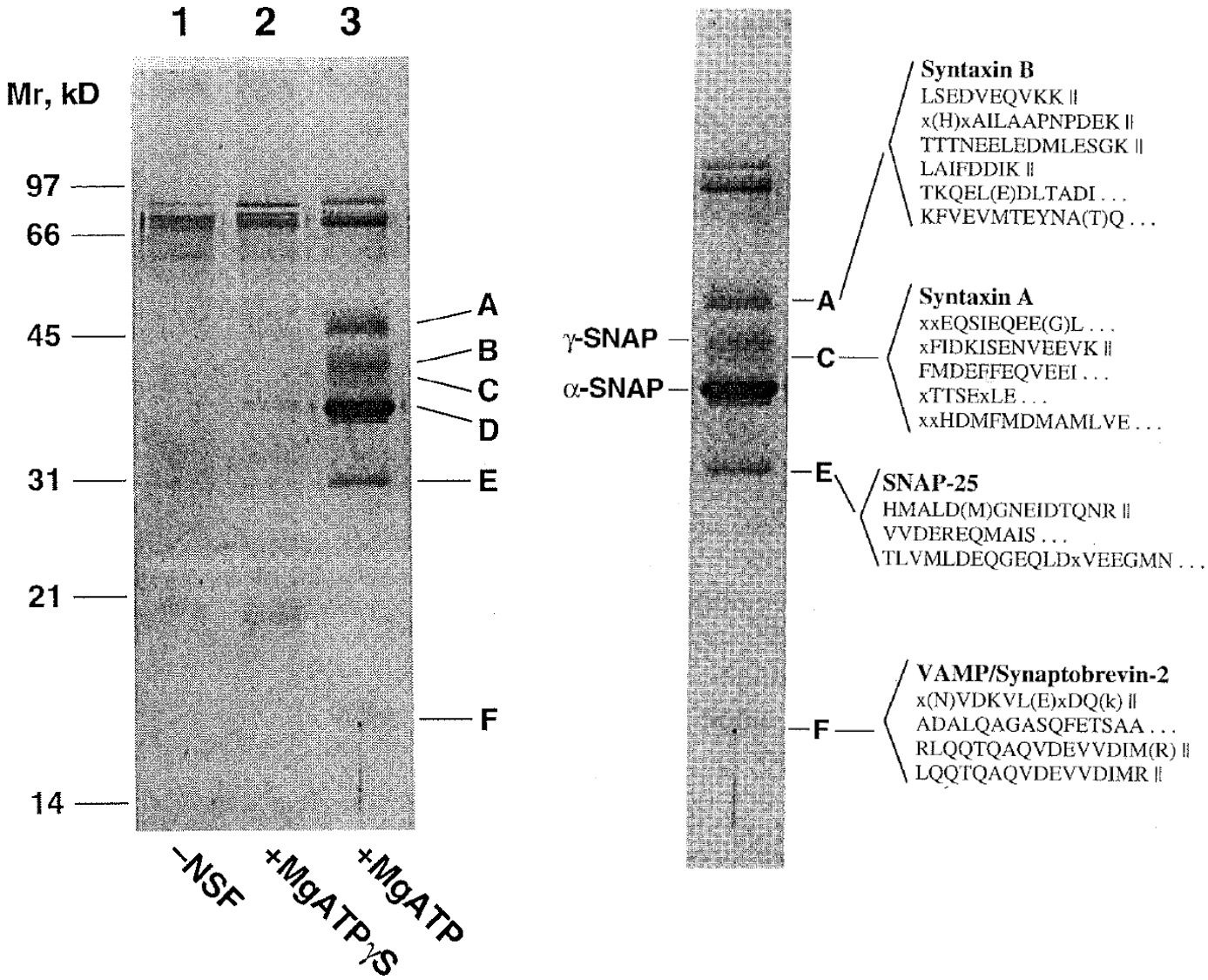
Lodish et al, 2000

Rothman:



Rothman, 1994

Purification of SNAP Receptors (SNAREs)



Rothman, 1994

Remember your reviewer

Criterion Strength	Score	Descriptor	qualification
High	1	Exceptional	Strongest, negligible weaknesses
	2	Outstanding	Extremely strong, 1-2 minor weaknesses
	3	Excellent	Very strong, 2 or more minor weaknesses
Medium	4	Very Good	Strong, 1-2 substantial weaknesses
	5	Good	Overall good, a number of substantial weaknesses
	6	Satisfactory	1-2 major weaknesses that could cripple the proposal
Low	7	Fair	Significant numbers of major weaknesses
	8	Marginal	
	9	Poor	

Proposal title:

OVERALL IMPACT/PRIORITY

Overall Impact	Please limit text to ¼ page
Strengths **Weaknesses**.	

SCORED REVIEW CRITERIA

Significance	Please limit text to ¼ page
Strengths **Weaknesses**	

Innovation	Please limit text to ¼ page
Strengths **Weaknesses**	

Approach	Please limit text to ¼ page
Strengths **Weaknesses**	