Research and Scholarship are a cycle that define your research identity.

To accomplish a research project successfully you need resources . . .

There are key elements to writing a successful proposal:

Your proposal must have a high likelihood of producing results that will have an impact:
— Emphasize Significance, Innovation!
Your proposal must be easy to understand:
— Keep it simple, concise & logical!
You must know what is required for the proposal:
— Read the Instructions!
You must know how the proposal will be reviewed:
— Write to the Review Criteria!

It is essential to start with a good question

What is the mechanism of X?
Is this drug a better treatment?
Does this change in clinical practice improve outcomes?

For NIH research proposals high impact is determined by . . .
the likelihood for the project to exert a sustained, powerful influence on the research field

The best research questions have significance and impact

Does the project address an important problem?
A gap in knowledge or treatment?
If the goals of the project are achieved,
• how will scientific knowledge or clinical practice be improved?
• will the results exert a sustained, powerful influence on the research field

“Now you know that, what do you know?”
Floyd Bloom, MD

You must propose to answer the research question with a testable hypothesis

Funded
Good research is hypothesis driven

A hypothesis is a general statement, often describing biological mechanisms but not directly related to experiment.
Hypotheses allow you to make specific predictions that can be tested experimentally.

Hypothesis → Prediction
A hypothesis is not the same as a prediction: — don’t confuse them!

**Hypothesis:** The first step in viral infection is binding of the viral envelope protein XYZ to the cell surface receptor ABC.

**Prediction:** Treating cells with antibodies against ABC will inhibit the binding between XYZ and ABC and decrease viral infection.

**The hypothesis is NOT:** Antibodies to ABC are an effective anti-viral therapy.

Predictions define the outcomes of your proposal — “Now you know that, what do you know?”

These experiments will . . .
1. define the mechanism of virus binding to the cell surface
2. provide an opportunity for future development of anti-viral therapies

**You must state the outcomes of your proposal** — do not assume that the reviewer will

Connecting the dots: the logical framework of a research proposal

A successful proposal is an effective act of communication

Above all, remember . . .

Your goal is to excite and persuade your reviewer

How do you want the reviewer to react to your proposal?

Write simply, clearly, and logically

**Apply George Orwell’s rules for writing well . . .**

Never use a long word where a short one will do.
If it is possible to cut a word out, always cut it out.
Never use the passive where you can use the active.

Break any of these rules sooner than say anything outright barbarous.

Politics and the English Language, Orwell, 1945 [http://www.erudite.io/orwell/politics]
Image: George Orwell’s press card: http://www.netcharles.com/orwell/

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Never use a long word where a short one will do

Use short Anglo-Saxon words rather than long Latin-derived words:
- end not terminate
- start not commence

Avoid jargon
— your readers may not be experts in your field

Avoid nominalizations (nouns derived from verbs)
— use the corresponding verbs:
  - introduce not introduction
  - provide not provision

If it is possible to cut a word out, always cut it out

Most adjectives and adverbs are unnecessary
— cut them out!

Delete the “wiggle” words:
- a number of (some, several)
- in order to (to)
- is able to (can)

Remove excess modifiers:
— quite, totally, completely, absolutely

Avoid redundancies:
— (knowledgeable) experts
— (new) innovation

Never use the passive where you can use the active

Active: John kicked the ball. 4 words; 17 letters
Passive: The ball was kicked by John. 6 words; 22 letters

Do not be afraid to use “I” or “We”
say— “We will treat the cells with . . .”
not— “The cells will be treated with . . .”

Be aware that there is much confusion about the passive voice: what it is and when to use it.
Your goal should be to write clearly, concisely, directly.

What or who is more persuasive?

Screening for Prostate Cancer:
U.S. Preventive Services Task Force Recommendation

Rudy Giuliani
“The report does not make sense.”

→ the power of narrative . . .

http://commons.wikimedia.org/wiki/File:Rudy_Giuliani.jpg

Tell a good story . . .

The audience will be convinced by your evidence but excited by your narrative . . .

Narratives have three parts:
1. Set-Up (exposition)
   — the problem or question
2. Conflict/Action
   — how you will solve that problem
3. Resolution
   — the outcome you expect

The Specific Aims page will define your narrative

The Specific Aims page is the most important part of your proposal . . .

Describes concisely the goals, objectives & outcomes of the proposed studies
Is a useful summary for obtaining early feedback on your proposal (reality check!)
Is the hardest part of the proposal to write

You must devote time to draft & polish the Specific Aims!
The instructions for the thesis proposal state that the Specific Aims page should . . .

Describe the hypothesis(es) you are testing.
What are your research objectives?
What conclusions could be made from your findings?
Be concise, clear and logical. Provide an approximate timetable for accomplishing these aims. Your aims are the test of your hypothesis.

What are you planning to do?
What is your hypothesis?

A good format for a Specific Aims Page is a sandwich

First paragraph
- topic, goals, objectives, hypothesis, rationale
Set-Up
Specific Aims
- objectives, description
Action
Last paragraph
- impact, outcomes
Resolution

You must grab the reviewer’s attention at the start—consider opening lines in fiction . . .

“All happy families are alike; each unhappy family is unhappy in its own way.”
Leo Tolstoy Anna Karenina (1878)

“It was a bright cold day in April, and the clocks were striking thirteen.”
George Orwell Nineteen Eighty-Four (1949)

“We were somewhere around Barstow on the edge of the desert when the drugs began to take hold.”
Hunter Thompson Fear and Loathing in Las Vegas (1972)

Compare with . . .

“It was a dark and stormy night; the rain fell in torrents, except at occasional intervals, when it was checked by a violent gust of wind which swept up the streets (for it is in London that our scene lies), rattling along the house-tops, and fiercely agitating the scanty flame of the lamps that struggled against the darkness.”
Edward George Bulwer-Lytton, Paul Clifford (1830)

Using the Template for a Specific Aims Page . . .

The Template lists the essential elements of a Specific Aims page:
- complete each element as a sentence
- combine the sentences into a narrative
- polish
- review
- polish again
- ask for feedback
- polish again

The first paragraph provides the rationale for the proposed studies

What is the Topic?
What is the Gap in knowledge?
What is the long-term Goal of your research?
What are the specific Objectives for the proposal?
What is the Hypothesis?
What is the Evidence for the hypothesis?
What is the Rationale / Significance?

You have a half page or less (~300 words) to set the stage for the proposal & excite the reviewer!

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Infantile Respiratory Virus (IRV) is a new agent that causes a rapid inflammation of the lungs and poses an increasing health risk to young children.

Pancreatic cancer is the fourth most common cause of death from cancer in the USA; only 5% of patients survive longer than five years.

Diabetes is a major health concern in the United States.

Your turn: Compose a topic sentence for your proposal.

Although IRV resembles other adenoviruses, the exact mechanism of its pathogenesis is unknown, providing little guidance for treatment.

The majority of patients are not diagnosed until the cancer is in the later stages and there are currently no biomarkers for early detection of the disease.

But the incidence of diabetes continues to rise and the onset of disease occurs at a younger age.

Your turn: Describe the gap in knowledge or unmet need that your proposal addresses.

The long term goal of our laboratory is to develop effective therapies against infectious agents through understanding their basic biology.

Our laboratory focuses on the function of micro-RNAs (miRNAs) in the detection and treatment of cancers.

Our long-term goal is to understand how behavioral modification can prevent the early onset of diabetes.

Your turn: Describe the long term goal of your project.

This proposal will focus on understanding IRV infection through defining the mechanism of virus binding to its host cells.

I will focus this proposal on the expression of miRNAs in pancreatic cancer with the goal of developing biomarkers for early detection.

This proposal will focus on testing behavioral interventions in adolescents.

Your turn: Describe the specific objectives of your project.

In preliminary studies using an in vitro system IRV is able to infect CAR positive host cells but not CAR-negative cells.

In preliminary studies I have shown that miRNA-179A and miRNA-208D are increased in expression in pancreatic tumor cells compared to normal tissue.

On-line behavioral interventions ("mHealth") have been used successfully in adult diabetic populations; preliminary studies demonstrate that this approach can be successfully translated to adolescents.

Your turn: Define the evidence for the hypothesis.
Describe the rationale for the proposal

- This proposal will enable me to apply the expertise of my laboratory with adenoviruses to understand the pathogenesis of a novel virus.
- This proposal will apply our extensive experience with miRNAs to an important and common cancer.
- This proposal is a comprehensive assessment of the effectiveness of mHealth approaches in adolescents.

Your turn:
Define the rationale for your project.

Your Specific Aims should fit the scope of your effort

Fit the aims to the effort:
For a K Award: one person (you!) over 3–5 years
Typically no more than three aims
Avoid contingent aims (the “fatal flaw”)

Provide a timeline for your aims in the proposal

<table>
<thead>
<tr>
<th>Aim</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
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</tbody>
</table>

First define the scope of your aims

1. To determine the amino acid sequence of the IRV knob protein.
2. To characterize the regions of the IRV-knob protein necessary for binding to the host cell CAR protein.
3. To develop monoclonal antibodies against regions of the IRV-knob protein that inhibit binding to CAR.

First define the scope of your aims

1. To characterize the expression of miRNA-179A and miRNA-208D in pancreatic tumor cells.
2. To determine the relationship between expression of miRNA-179A and miRNA-208D and pancreatic tumorigenesis.
3. To measure the expression of circulating miRNA-179A and miRNA-208D in patients with pancreatic cancer.

First define the scope of your aims

1. To develop a mobile mHealth application designed to promote healthy behaviors in adolescents.
2. To assess the acceptability and behavior changes in adolescents at risk of developing early-onset type II diabetes.

Expand each specific aim to provide a short descriptive title & brief description

Aim 2. To determine the regions of the IRV-knob protein necessary for binding to the host CAR protein.

Our hypothesis predicts that alteration of the env region of the knob protein will decrease binding to the host cell CAR protein. We will test this prediction by

- a) Generating variants of the knob protein with structural alterations in env.
- b) Assessing binding to the CAR protein in vitro.

Your turn:
Write a title & description for a specific aim.
The last paragraph focuses on innovation, impact and outcomes

**Innovation:**
IRV is a recently discovered virus: these studies are the first attempt to characterize the mechanism of its infection.

This proposal applies a novel approach—miRNAs as biomarkers—to the diagnosis of pancreatic cancer.

To our knowledge, this proposal is the first attempt to use mHealth approaches for behavioral intervention in adolescents.

**Your turn:**
Describe the novel aspects of your project.

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**Outcomes & Impact:**
The proposed studies will define the mechanism of IRV infection and provide a foundation for immune therapy.

Development of biomarkers for early detection has the potential for dramatic improvement in the survival rate for pancreatic cancer.

These studies will provide a new, cost-effective approach to controlling the early onset of diabetes.

**Your turn:**
Describe the outcomes & impact of your project.

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Consider including a diagram to illustrate your specific aims

![Diagram of specific aims]

**Specific Aim # 1**

**Specific Aim # 2**

**Specific Aim # 3**

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Well written specific aims help you . . .

Sort out the logic of your proposal:
— how many aims
— dependence of aims on each other
— feasibility and scope

Identify your research priorities
— and what you may still need to learn

Take ownership of your research ideas
— an important step in building your identity as an independent investigator.

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You can also use your specific aims to . . .

Talk with a Program Officer
Test your thinking by getting feedback on your ideas in a safe and constructive manner
Open new opportunities as you develop your ideas and look for potential research collaborators.

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*Checkpoint* — check the following:

- My Specific Aims can test my hypothesis.
- They are doable within the grant period I am requesting.
- The aims are concrete and well-focused.
- I can define endpoints my peer reviewers will be able to assess.

*NIAID Grants Tutorials:*