Writing Competitive Grants: Significance and Innovation
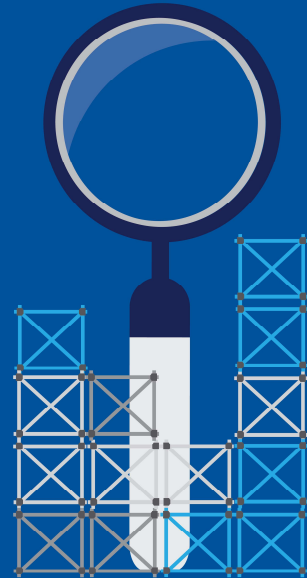
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Hello and welcome to "Writing Competitive Grants: Significance and Innovation." I am Lauren Anderson, Director of Research Development for the Department of Surgery.

I am here today to review two sections of the research strategy: Significance and Innovation.
These two sections are independently scored, and a such you will want to make sure you are clearly and directly addressing the necessary items.

NIH Grant Components

- Specific Aims
- Research Strategy
  - Significance
  - Innovation
  - Approach
- Bibliography
- Summary Documents (abstract and project narrative)
- Supporting Documents (vertebrate animals, human subjects, facilities, resource sharing, etc.)

Briefly, among the scientific portions of the grant application, which include Specific Aims, the Research Strategy, Bibliography, summary documents (abstract and project narrative), and the more technical supporting documents (vertebrate animals, human subjects, etc.). Significance and Innovation lies within the research strategy.

Even though reviewers can get some of the information covered in these two sections from other places in the grant, they are looking specifically for the review criteria to be addressed in these sections. Today, I'll go through the instructions and review criteria of these sections and discuss a couple of approaches you can take in writing these components. Let's start with Significance.
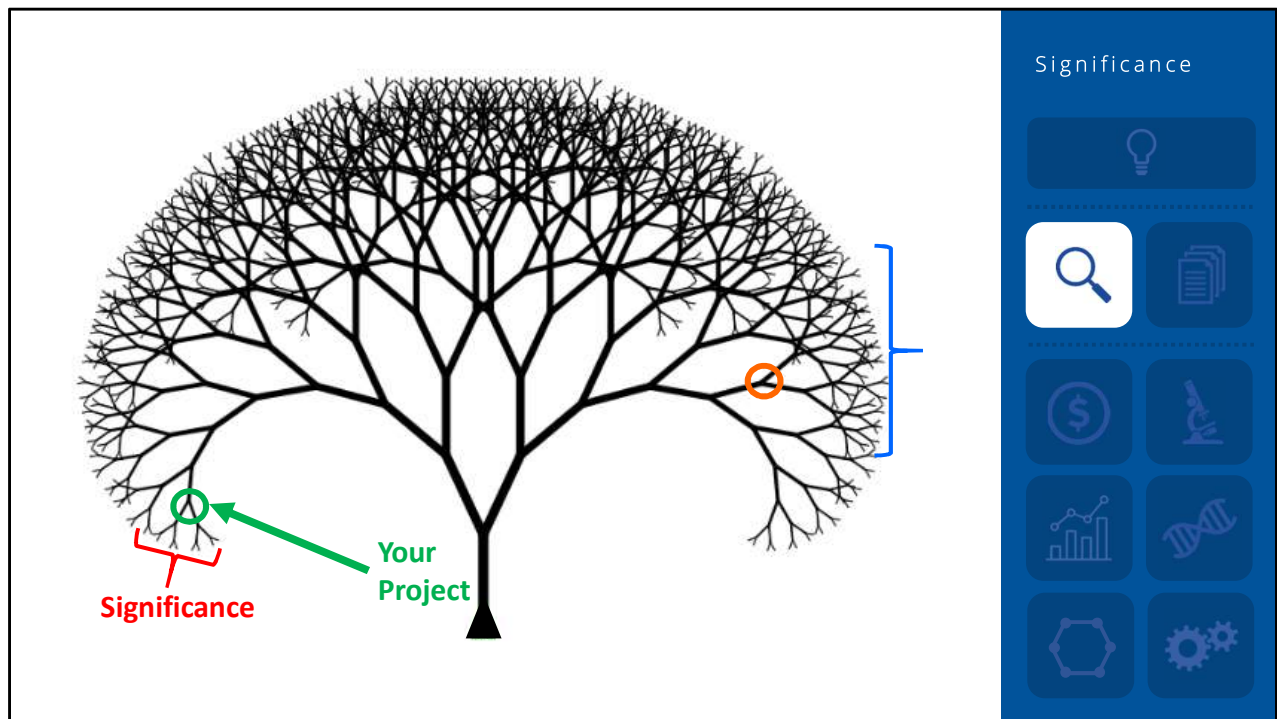
The Significance section continues to evolve and NIH refines the understanding of how your research within the field.

If you think of the science as a branch on the scientific tree, you may just be the tip of a branch on a well developed tree, so the significance really may only be to this particular branch or the sister branches.

Or perhaps you're forging a new major branch or are tackling a pathway that is shared by a number of different conditions in which case the significance may be more broad.

There's no right or wrong, good or bad, what you want to consider when you're thinking about the significance of your project is: where does your project fit in the bigger scheme of things?

Significance - Instructions

- Explain the importance of the problem or critical barrier to progress that the proposed project addresses.
- Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.
- Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

The SF424 instructions will help you hone in on this point and identify four requirements for the Significance section:

1) **THE PROBLEM:** Explain the importance of the problem or critical barrier to progress THAT THE PROPOSED PROJECT ADDRESSES.
2) **WHAT'S KNOWN/UNKNOWN RELATIVE TO YOUR QUESTION:** Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the KEY SUPPORT for the proposed project.
3) **POTENTIAL IMPACT ON THE FIELD:** Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields. And
4) **HOW WILL IT IMPACT THE PROBLEM:** Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

Not only are we talking about what will be possible following the successful execution of your project, but what will be alleviated in the field by doing so? If those sound like the same thing to you, we'll dig in a bit more so that you'll understand not only the difference between those last two, but also why that distinction matters.

So let's take a closer looks at the review criteria to get a better idea of how you may want to write this section.

Significance – Review Criteria

1. Does the project address an important problem or a critical barrier to progress in the field?
2. Is the prior research that serves as the key support for the proposed project rigorous?
3. If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
4. How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

The scored review criteria identifies four points that will contribute to you score….

1. THE BARRIER: Does the project address an important problem or a critical barrier to progress in the field?

2. THE GAP: Is the prior research that serves as the key support for the proposed project rigorous?

3. NEW POSSIBILITIES: If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

4. PROGRESS TOWARDS A SOLUTION: How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
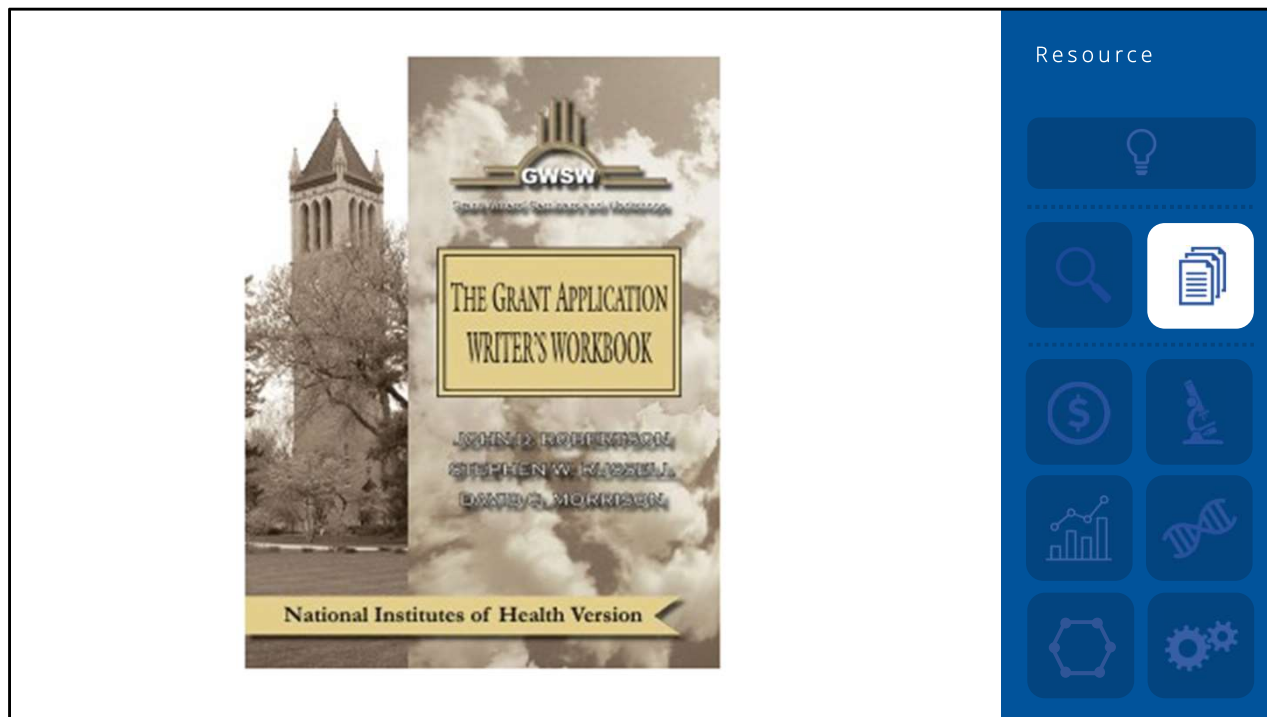
If you've followed the Russel & Morrison "Writing Winning Grants" approach, you may come to the significance section already knowing how you want to start this section.

My recommendation is to not start this section off with the same sentence or initial paragraph that you used on your Specific Aims page. The Russell & Morrison method will have you tackle these questions in the stated order. In fact, if you've followed their method for developing your specific aims page, the significance section will just have you expand on the points you made in Specific Aims to address the review criteria.

So this can seem like a lot things to address if you're following the instructions and addressing the review criteria, so let's simplify this.

Draw the Connection

Instructions		**Review Criteria**
• The problem	➡	• The barrier
• Known/Unknown relative to your question	➡	• The gap
• Potential impact on the field	➡	• New possibilities
• Impact on the "problem"	➡	• Progress towards a "solution"

Ultimately, in the significance section you're drawing connections.

(click) The instructions have you describe the problem, the review criteria is looking for identification of the barrier. The clearer this is, the easier it is to address the second item.

(click) What is known or unknown relative to the question you're asking? You're doing this to identify and clarify the gap in knowledge, an element of the review criteria.

(click) Once we know the problem and the environment around the problem, now we're looking to state what this project is going to do for the field, that is, what new possibilities or opportunities will exist when you're done. This is a type of "where do we go from here."

(click) And you'll close with how you're project addresses the gap. You'll SHOW progress towards a solution. Your project is part of the solution to overcome the barrier in the field.

For our purposes today instead, let's use this opportunity to check that you've provided the reviewer with the information they need in order to understand your aims, while also confirming that you've started your proposal off "in the right spot."
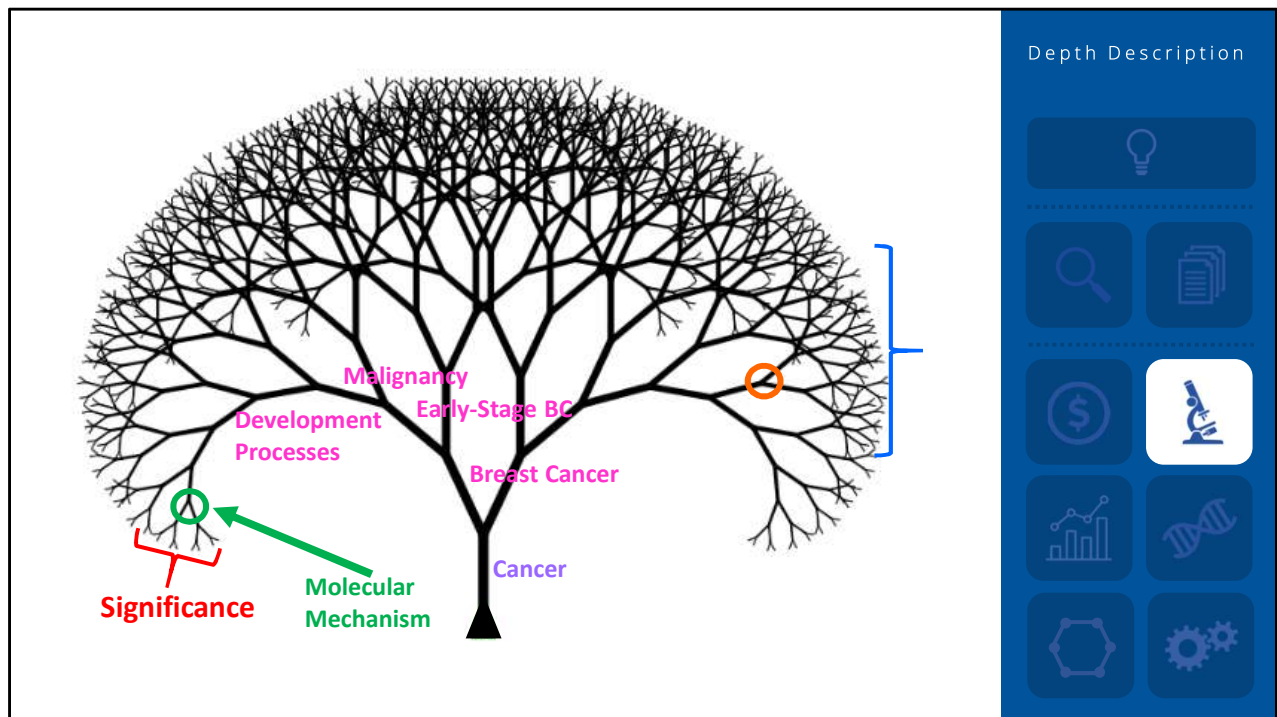
What I mean by "the right spot" lets com back to our scientific tree. Here's a very simple demonstration.

Let's say you're studying cancer, that's entirely too broad to serve as the starting point for describing your project.

Okay, so you're studying Breast Cancer. -- Again, still too broad. -- Let's say you're studying early-stage breast cancer. Okay, but is it DCIS, Stage 1 or 2. Still too broad. -- So you're interested in malignant early-stage breast cancer. Okay, sounds closer. -- You're looking at the processes that lead to the development of malignancy. Bingo.

That's where the mechanism you're studying comes into play.

So do you really need to go all the way back to a general statement about any of these earlier, broader points? Not likely. Depending on how robust the research is in the development processes your project is based on, you might not need to go further back than that, or perhaps an orienting statement regarding malignancy.

Where as, what if you're looking at a new branch in the development process? Well, the range of down stream things that could be impacted by your work could be a bit more expansive. So perhaps you need to go a bit further back on the tree to find the right orienting statement. It's possible you may not need to go any further back than the relevance to malignancy to orient your reader to the significance of the project.

So, in order to do this type of checking, I would suggest working backwards through these

questions.

Again, there's no right or wrong, but what starting point does the clearest job or orienting the reader to where your project fit in the scheme of things?

The "Problem"

- Instructions
  - Explain the importance of the problem or critical barrier to progress that the proposed project addresses.

- Review Criteria
  - Does the project address an important problem or a critical barrier to progress in the field?

So let's go through the 4 points and provide some very simple examples of how you might outline your significance section.

The first element of the significance section asks about the importance of "the problem" or barrier being addressed by the project.

The "Problem" ➡ The Barrier

- Original Sentence
  - Despite important recent advances in the treatment of metastatic melanoma, several limitations still exist.

- Revised Sentence
  - **Despite newly developed therapies for metastatic melanoma, there is an urgent need to develop safe and effective therapies that potentiate <u>durable</u> anti-tumor efficacy.**

So what's in the way AND why is it important. For example, an initial draft of a grant defined the problem this way *(click, read original sentence).*

I think we can agree this sentence does not clearly define the problem, nor does it convey the importance of the barrier. After some revising and development of the thought process for the proposal, the investigator ultimately included the revised sentence *(click, read revised sentence).*

Here they are stating the problem: need for safe and effective therapies, the importance that these therapies need to potentiate durable anti-tumor efficacy, and the sentences preceding this one demonstrated the importance of the durable quality.

There is even a "booster" clause here that notes DESPITE new therapies, so there are things being done, however, they are still falling short. That clause directly relates to the second element of the Significance section, the key support. For example, what the new therapies have accomplished, yet important elements remain to be resolved.

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Key Support

- Instructions
  - Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project.

- Review Criteria
  - Is the prior research that serves as the key support for the proposed project rigorous?

So Key Support comes next. What do we know, what do we not know, and what's missing.

Key Support ➡ The Gap

- Original Sentence
  - Despite the growing older adult trauma population, there is a gap in the understanding of their long-term outcomes.

- Revised Sentence
  - **There is a _critical need_ for a comprehensive understanding of all aspects of these patients long-term health care trajectories, including outcome metrics important to both patients and their caregivers, and the diversity of these patients' pathways.**

Key support is looking to frame the gap. So let's look at another simplified example. _(click, read original sentence)_
Similar to the example framing the importance, if this is how the gap is defined, how clear is the problem being addressed?
(click, read revised sentence) The revised sentence clearly defines the gap. Further, the sentence also gives you a hint of what types of information may have preceded this to define the gap. Perhaps each of these features have been addressed individually, in different populations, but never connected to one another in a single, well-defined population.

Impact on the Field

- Instructions
  - Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.

- Review Criteria
  - If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

The third element of the Significance section address the impact of THE PROJECT on the field. I want to pause here to emphasize the element to be highlighted here is what successful completion of THE PROJECT will do.

Our objective here is to make clear what will be possible once the project is completed. What are the new possibilities, what will be clarified, what will be improved.
So let's look at this a little differently. Does the project make it possible to address the gap? In this case, using an underutilized approach at a few stages in the process directly addresses the gap and makes it possible use that same approach to look at 3 or 4 things that they haven't been able to look at before.

So now that we know what will be possible if the aims are completed, we must now consider what the new knowledge or understanding will be. Ultimately, what will change? What will be improved?

Impact on the Problem

- Instructions
  - Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

- Review Criteria
  - How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Lastly, the impact of the project on the "Problem"

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Impact on the "Problem" → Progress towards a "Solution"

- The gap
  - A therapy that inhibits [reagent] activity would preserve the structural integrity of all three barriers to T cell invasion of the transplant graft.

- The advance
  - The benefit of our strategy over the current standard of care is that it <u>preserves the barriers to graft invasion by T cell</u>, rather than causing global suppression of T cells function. This approach offers the advantage of <u>limiting off-target effects and maintaining T cell functions</u> important for host immunity against pathogens and tumor suppression.

Our objective here is to make clear the progress that will have been made once the project is completed. How does this get closer to the solution?
So let's look at this a little differently. Does the project help close the gap? In this case the approached used by the project directly addresses the gap (it preserves the barriers) and it limits undesired effects and maintains desired effects. Steps that will need to be achieved if they are to continue developing a therapy based on the reagent's activity.

Considering all the things you're proposing to do, what will be possible that is not currently possible?

This should be focused directly on the project, not the larger "we'll cure cancer in 10 years" pie in the sky dreaming. What would be the next scientific step or milestone after you complete the proposed project?

Significance

Instructions

Review Criteria

What needs to be known in order to recognize something is missing?

- The problem
- The barrier

Why is something missing?

- Known/Unknown relative to your question
- The gap

What do you need to know/do?

- Potential impact on the field
- New possibilities

What do you want to be able to do next?

- Impact on the "problem"
- Progress towards a "solution"

So let's work backwards to make sure we've addressed the review criteria, provided the required information, and importantly, start our presentation in the right spot. Why? You want to give the reviewer the information they need to understand your project. No less, no more. The slight caveat here being, if you're challenging a long-held belief. You may need to acknowledge you're going against the grain and are aware of the ramifications in doing so.

If you've address the impact on the problem and the progress that will be made towards a solution, then you will have answered *(click)* what do you want to be able to do next.
In order to do that, what needs to be possible? *(click)* What do you need to know or known how to do?
If there's something you need to know or know how to do, why is that missing? *(click)* What's known/unknown?
And lastly, if this is missing, *(click)* how would someone have known it was missing? What would they have needed to know in order to see the hole that your project is filling?

If you're able to move through the instructions and review criteria and back through the connections between these elements, then you should have a compelling, responsive significance section that directly addresses each element of the review criteria. In fact, you may have some direct quotes reviewers can use in support of their scores.

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Next up. Innovation.

The SF424 instructions will help keep you focused when writing the Innovation section:

1) **THE SHIFT:** Explain how the application challenges and seeks to shift current research or clinical practice paradigms.

2) **WHAT'S CHANGED/DIFFERENT:** Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions. *(I use Changed here over Different, because innovation is indicative of a change. Difference implies that's it's always been there, but has yet to be revealed. If your project is revealing something, what is that? What is hidden and unseen that can't help but be seen once your project is done)?*

3) **WHAT'S NEW/IMPROVED:** Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions

So we're not talking about what you're doing, that comes next in the Approach section. What innovation is doing is setting the stage, building the excitement. What's the new, shiny, bells, and whistle that your project will shine and light on and ring?

So let's take a closer looks at the review criteria to get a better idea of how you may want to write this section.

Innovation – Review Criteria

1. Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?

2. Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?

3. Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

The scored review criteria identifies three points that will contribute to you score….
1. **THE METHOD.** How is the shift accomplished?
2. **HOW NOVEL?** This is scope, and ties back to where on that significance tree you are. Are we interrogating a development process or are we defining a new type of malignancy? Where is this applicable? Is it limited to just a few processes, or does this potentially challenge how we look at a whole branch of research?

Similar to significance, there is no good or bad, more or less important. What is the degree of advancement that will be achieved, simply, where is the innovation?
3. WHAT IS IT? Again, we can keep this rather simple, what is the new thing being proposed? A method, intervention, application? Animal, vegetable, mineral? You're putting everything in perspective.

I'll pause here, because if you've followed the Russel & Morrison "Writing Winning Grants" approach, they note that it's important to emphasize what is new about this particular application. While it may be part of a larger innovation, in this section you are to focus specifically on WHAT YOUR PROJECT will be contributing.

You'll no doubt make reference to a larger approach, which may or may not already be fully established, but it is your job in the innovation section to draw out what the current project

is contributing to that larger vision/goal/approach.

Here I revert back to R&M's method and suggest you tackle this section in order. If you do this section correctly, it should drop you off at the front door of your approach section, with no need for a major transition or re-telling of information provided earlier.

Draw the Connection

Connections

Instructions	Review Criteria
• The shift	• The method
• What's changed/different	• How novel?
• What's new/improved	• What is it?

You're welcome

Again, let's draw some connections.

(click) The instructions have you describe the shift, the review criteria is looking for HOW you plan to accomplish the shift. Again, the clearer this is, the easier it is to address the second item.

(click) What's changed/different about your project? This will give perspective to how novel your project is. Not every project needs to be revolutionarily novel. Each project DOES need to do SOMETHING. Is it changing something, is it filling a need? You want to make sure it's clear where the innovation will be noticed.

(click) Once we know how you're making the shift and where the shift will be noticed, now bring it home. WHAT IS IT?! What is the "tangible" result of this project that is unlike anything that is currently out there? Is it an idea, a method, a feature? That is, define WHAT the innovation is. This is a type of "present wrapped in a bow." Hey reader, once the project is done, you're welcome.

AH! So THAT'S what the project is giving me. Okay. Now I'm ready to see the details of how you plan to do this.
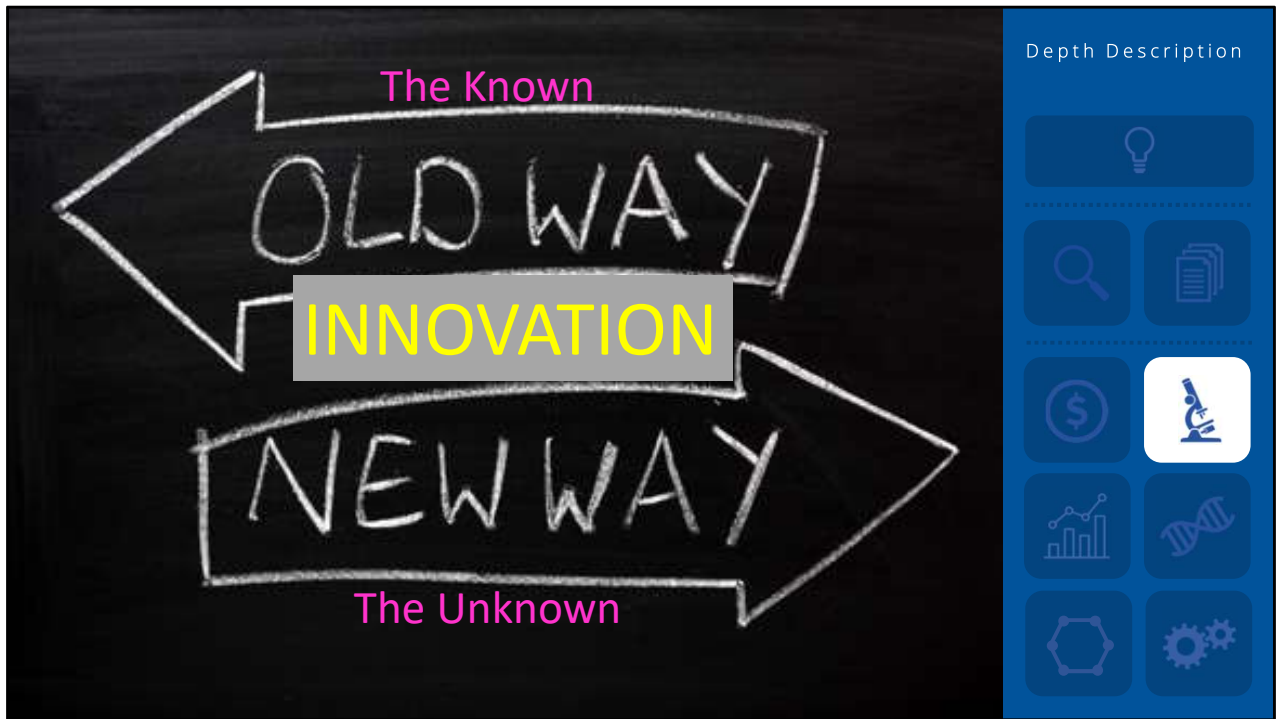
Simply put, Innovation sets up how you, through your project, are getting from the known to the unknown.

The Shift

- Instructions
  - Explain how the application challenges and seeks to shift current research or clinical practice paradigms.

- Review Criteria
  - Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?

So let's go through the 3 points and provide some very simple examples of how you might outline your Innovation section.

The first element of the innovation section asks about the shift your project is proposing and where that shift takes place.

The Shift ➡ The Method

- Original Sentence
  - [The approach] suggests synergistic potential for agents that selectively disrupt impediments to T cell function such as PD-1 blockade.

- Revised Sentence
  - This proposal is a comprehensive evaluation of a promising oncolytic virus including tumor analysis from a Phase I trial that could lead to a *meaningful treatment impact for patients with [cancer type] and further elucidate the mechanism of action of oncolytic virotherapy*.

Our objective here is to make clear the what the project is changing. How is it different? So let's look at this a little differently. Do we know how the shift will happen?

We had a proposal that started out saying that their approach was the shift and then told us what their approach would revel or could be used to reveal how agents selectively disrupt impediments to cells that target and destroy cancer cells.

This was remarkably far from what the project was actually doing. This project was actually testing a novel intervention. Was any of that in the original explanation of the innovation of the project? Right.

When you're thinking about the shift. What are you doing? What are you trying to accomplish? How are you planning to get there. What are you trying to change? How are you trying to change it?

What's changed/different?

- Instructions
  - Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.

- Review Criteria
  - Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?

Innovation Element

So now that we know how we plan to accomplish the shift. How changed or different will it be?

The second element of the innovation section asks you to put your innovation in perspective. Who will see it? What is making it different?

I'll keep this one simple.

Investigators will frequently just tell you what they're doing in the innovation section. Well, that's coming later in the approach. Unless your approach is the innovation, you shouldn't be using this section to describe what you're doing. Even if your approach IS the innovation, you STILL don't use this section to describe what you're doing. This section is for you to tell the reviewer what is new and improved. In our previous example a contrast was set up. This is how it currently is being done and this is what we're doing differently.

This example had the benefit of being something that had not been done in their patient population before and was reinforced by the significance section because this project FILLED THE GAP. There was no available data.

Additionally, this investigator reiterated the impact of what is lost if this project wasn't completed. Further driving home the point of not only what the innovation and contribution is, but also why it's important. How innovative is it? There's currently something we can't do for out patients BECAUSE this hasn't been done.

What's new/improved?

- Instructions
  - Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.

- Review Criteria
  - Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Innovation Element

Lastly, if you haven't gotten to it by now. What's new and/or improved?

What's new/ improved ➡️ **What is it?**

Significance Detail

- Current state
  - Although the field of regenerative medicine has largely focused on stem cell therapies and tissue engineering, the scope of cell-based therapies may be limited in affecting complex tissue injury or chronic wounds.

- What's changing?
  - The proposed research is innovative because it departs from retrospective studies of cell positions in fixed tissue specimens and instead employs live imaging of [specific cells] as they participate in the regeneration process in real-time. *[3 additional examples]*.

If it wasn't already clear, this is the proverbial "last chance". What is YOUR PROJECT doing that hasn't been done before?

In this example the current state doesn't work as well for a complex type of wounds. This investigator's project was using a new/atypical method to evaluate a phenomenon with the added benefit of being in real time. They then provided 3 examples that their project would be contributing to.

Innovation

Instructions	Review Criteria
What is changing?	
• The shift	• The method
How is it different (and relative to what)?	
• What's changed/different	• How novel?
What will exist or happen that hasn't before?	
• What's new/improved	• What is it?

Summary

Again, let's work backwards.
What will exist on happen that hasn't before?

How is that different from today? Who will it matter to/relative to what?

The opportunity for a strong innovation score acknowledges that while an approach might not be novel in a broad sense, it may be novel in a specific context. For example, gene therapy my not be a novel approach in virology or cancer biology, but it may still be a relatively new approach in transplant immunology.

and if you know that, then it should be clear, what is changing.

In summary, Significance and Innovation lay the path for your approach.
The Specific Aims sets up the destination.
Significance shows you why you need to get there (who it's important to) and what you'll need to get there.
Innovation shows us how you plan to get what you need.

Next stop, the open road. I'll take any questions.

Thank you!