The Ins and Outs of NIH Grants
R01, R21, R15 and R03
Understanding NIH Requirements, Impressing Reviewers and Writing a Competitive Proposal!
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Best Regards,

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MODERATOR:

It is my pleasure to introduce Dr. Christopher Dant. Dr. Dant is a faculty instructor at Dartmouth Medical School. His PhD work was concentrated in cellular and molecular biology. Early in his postgraduate career he apprenticed with a senior editor at JAMA and went on to work as a biomedical writer for life sciences investigators in academia, private industry and government agencies.

Before going to Dartmouth, Dr. Dant was projects director at the Stanford Medical School for grants and manuscripts and served as the Director of Medical Publications at Genentech in California. At Dartmouth he worked with investigators in developing grant proposal and programmatic initiatives, and educates faculty in grant and manuscript writing skills. He has worked with investigators at the NIH, NSF, NASA, DOE and other federal agencies.

DR. DANT:

What do Peer Reviewers Want to See in Your Application?

Today, I want to talk about a program that we developed at Dartmouth, and previously at Stanford, to inform investigators on the best way to reach peer reviewers. This is a bit tricky because it is impossible to know how peer reviewers will react to each grant proposal, but we’ve developed some information that I think will inform each of you on how peer reviewers react to most grants R grants, what they do or do not want to see, and how this influences their decisions. Much of this evidence that I’m going to present comes directly from research carried out by myself on peer reviewer focus groups, and from reviewing a number of grants and summary sheets from a large range of grants from many different fields, with a wide range of scores. Some of the evidence and some of the advice I’m going to give you is what many program officers and peer reviewers at the NIH have told me...What is important to them, and what influences their decisions.
NIH Institutes

I want to talk a little bit about the NIH, its culture and the things I think are important to consider when you’re writing a grant. First of all as many of you probably already know there are 27 institutes at the NIH, and each of the institutes has their own mission, their own budgets, their own activities, the way they do things and their own personality. I think you would notice that by looking at any of the institute websites, they are all very different. When you’re planning to submit a grant the first thing you should do is check with the program officers from institutes you think would be interested in your research to determine their specific policies and interest in your science. You’ll learn a great deal by doing that. I’m going to talk today essentially about the R21 and the R01 which are two different types of grants, each with its own emphasis. For example, the R21 is not a mini R01. It is really an exploratory developmental grant that has a fair amount of innovation and has potential for high impact. Therefore, it is looked at a little differently than the standard R01.

One of my main points here is that really there is no grantsmanship, or a way to write a grant, that will turn a bad idea into a good idea. However, there are many ways to disguise a good idea, and that’s the point I want to make in this presentation. If you are going to submit a grant the first thing you should be doing is looking at the NIH Institute’s website, here showing the National Heart, Lung and Blood Institute and the NCI, National Cancer Institute. Each one of them has a listing of what their research priorities are. It’s more overt in one website than the other. They all have research priorities and in addition there are RFAs and PAs, Request For Applications and Program Announcements. You should look at those to see the kind of research that the NIH at that institute is sponsoring.

In addition, another extremely valuable tip, and I recommend this to every PI that does a grant, is to look at the RePORTER (see http://www.projectreporter.nih.gov/), which is the research portfolio online reporting tool from the NIH. This is a very powerful way of searching the database of all funded grants and through this tool you can search by...
keywords. So if you happen to know the areas that you want to search for, you can use a Boolean search using and/or. For keywords you can put in a PI’s name if you want to know of a grant similar to the one you want to submit, which had a particular PI. Or you can do it by institution or project number, or a type of award. You can filter it out to only include career awards, program projects, research grants, fellowships etcetera. Few people know that you actually can search by the study section, so all the study sections are listed in the reporting tool. You can by itself just look at what that study section has funded in the last few years to get a sense of what kinds of things they’re looking at. You can do it by study section and then by institute so it’s very helpful.

5 NIH Review Criteria

So in order to understand how peer reviewers look at a grant you have to understand fundamentally what criteria they review the grant against. For an R grant it’s a series of five criteria, it’s different for a K Award, but we’re going to concentrate on the R. Essentially these are:

- **Significance:** Relevance to human health and disease
- **Innovation:** Originality of approach
- **Approach:** Feasibility of your methods
- **Investigator:** PI training and experience
- **Environment:** Suitability of facilities and adequacy of support from your institution

Significance: What is its relevance to human health and disease, its significance? Innovation: How original is the approach? How new, and how novel is the approach? Approach: how feasible are your methods to answering the Aims that you proposed? Investigator: what is your training and experience against what you’re studying? Then, lastly, Environment: what is the suitability of your facilities and support from your institution that will support that grant? These are the five central review criteria that are used.

When peer reviewers review a grant they give you an overall impact score, usually from one to nine. The overall impact, I’m going to repeat this because this is central to understanding how grants are reviewed, the overall impact is the likelihood for your project to exhort a sustained powerful influence on the research fields. It is important that you understand how the reviewers look at your application, how they use that application and extract from it these five review criteria and I’ll show you how they do that.

**Review Criteria Alignment**

First of all, as you all know research grants changed in about 2010 and changed structures slightly. The **Significance** has its own section. The **Investigators** now have a personal statement on their biosketch, which
tells them why they’re the best person to do the study. In the Approach section you should have a section that outlines how you and your team are best suited to do this study. Innovation has its own section and the Approach has its own section. The Environment is still under resources. The main ones are significance, innovation and approach. Although the other two, investigators and environment, are important but you would have to pretty much ignore those to get bad scores on them. Because presumably you’re presenting a grant to the NIH because you think you’re the best person to do it and you have the environment and the resources to do this work.

What are each of these? And I’m going to give you what the NIH wants to see.

**Significance**

The first thing under significance is “does this project that you’re presenting address an important problem or barrier to progress in the field?” If your Aims are achieved, “how will the knowledge, technical capability, and other, perhaps clinical practice at the clinical study, be improved?” And lastly, “how will the successful completion of the Aims change the concepts, methods, technologies, treatments, services and preventive interventions that drive the field?” These are not words I choose, these are the actual words that the NIH chooses, so I would recommend when you write your Significance section that you use these words. For example you might say “our research, our four year project, will use technologies and methods that drive the field and are intended to target this specific problem and we will show how the completion of our Aims will change those methods and technologies or those treatments or those concepts.” I would use those words when you’re writing your Significance section and when you’re writing your Aims section.

**Investigators**

The next section is Investigators. They want to know things like: “Are you well suited to do this project?” If you’re early stage or new, and within the first few years of doing your work, and some of that is defined by whether you ever had an R01 before, “do you have the appropriate experience and training?” If you’re established, “have you demonstrated ongoing records of accomplishments that have advanced the field?” That will be shown in your biosketch as well as some of the work that you’ve published. Lastly, if it’s a collaborative multi-PI study, “do they have the complementary and integrated expertise to do the work?” “Is their leadership approach governance and organizational structure appropriate for the project?” A lot of times they aren’t appropriate for the project. They’ll have some groups in there that maybe don’t have complementary skills or
it appears as though the one PI is doing all the work and the other PIs are really doing nothing more than say being your collaborators and not actual PIs on the project.

**Innovation**

As you’re considering Innovation, that’s one of the hardest parts to address, and here’s what the NIH is looking for: “Are you challenging and seeking to shift current research or clinical practice paradigms by using a novel theoretical concept, approach, methodology, instrumentation or intervention?” In other words, “are you challenging and shifting the research paradigm that exists today by using a new approach or method or new instruments or interventions?” “Are these novel to one field the research or novel in a broad sense?” You have to address that, so, “are these concepts, approaches, methods or instrumentation or interventions novel to just one field of researcher or novel in a broad sense?” They also want to know “is there a refinement, improvement or new application of theoretical concepts, approaches, methods, instrumentation or intervention, proposed?” “Are you proposing a refinement or improvement or new application of these things?” Those are actually the things that the NIH is asking you to address.

I read many, many grants. I just read an R21 grant this morning that did not address these points. They start talking about the background, and how important it is to study, and other items of Significance but do not address the Innovation. I recommend that when you’re writing this Innovation section, it is not enough to tell the reviewer your study is innovative in several aspects, and then not go into how each of the aspects are innovative and in what way are you challenging or shifting paradigms. Address specifically how it’s innovative.

**Approach**

Talking about, now, the Approach, what they basically want to know is: “Are your overall strategies, methods and analyses well-reasoned?” “Is there a rationale that says it’s clear and appropriate to accomplish the Aims?” Reviewers want to know if there are potential problems, alternative strategies and benchmarks for success presented. In every grant that you write, in the approach section, you should address what you think might be potential roadblocks and how you’re going to get around that. They want to know, especially if it’s in a new phase of development, “will the strategy establish feasibility and will particularly risky aspects be managed?” You have to address that, so for anything that’s really new and novel you need to address how you’re going to establish the feasibility with that. A lot of times that could include using collaborators that have some knowledge of say a novel method, or a new type of strategy that they’ve used.
If you’re doing clinical work, “are there plans to protect your subjects, inclusion of minorities, both sexes and genders as well as the inclusion of children, and is it justified?” As you all know, if you do involve humans you must write a human study section. This is fairly extensive and they take it very seriously. Basically, they will not review your grant if it’s not fully addressed.

**Environment**

Looking at your Environment section, in the scientific environment where you do the work, “how will it contribute to the probability of success?” “What labs are you using what kinds of instruments perhaps are shared under shared resources?” “How are you set up and is the institution equipment and other physical resources available to you adequate for the proposal?” A lot of times letters will come from the head of the division where you’re doing the work, that will tell the NIH “we intend to get doctor X an office, we intend to give them lab space, we intend to support them financially in some ways,” whatever it might be, but any support from the institution, any equipment or other physical resources must be addressed. “Will your project benefit from any unique features of the scientific environment, populations or collaborative arrangements?” So you have to consider that.

**Scoring**

Then each of these five criteria are addressed and considered when assigning an overall score weighing them as appropriate. The application does not need to be strong in every category to be judged likely to have a major impact, and therefore deserve a high priority score. For example you might propose important work that is not particularly innovative but it’s essential to drive the field. The scoring is a 9-point scale using whole numbers and there’s no formula used for an overall impact score, in other words they don’t take all the five criteria and add them up and then divide by five. Reviewers weigh criteria as they see fit to drive the scores. They score the application as a whole, they can’t modify their score on the assumption that some of the work proposed will be deleted or modified according to the recommendation.
One key thing to remember is that **Overall Impact is not a sixth review criteria**. It is not an additional criteria, and reviewers, when they read your application, will write a paragraph that summarizes the factor that informed their score. It’s not intended to be a summary or restatement of the strengths and weaknesses, but it addresses the underlying rationale for why they gave you that score. As I said, the overall impact score is not necessarily the arithmetic mean of the scores. I have seen an application that received, in some areas, a five, which is not particularly a good score, in say Innovation, but ones and twos in Significance and Approach perhaps. They may have gotten a very, very good score despite the fact that some of the areas were not seen as strengths.

Read the NIH Reviewer Guidelines here:


Overall Impact takes into consideration the score review criteria but it is distinct from it. Again I want to make this point, the reviewers make an assessment of your study and the likelihood for that study to exhort a sustained powerful influence on the research fields involved. That’s really the key phrase there and I’ll talk a little bit about what that means.

**What is “Impact”?**

What is Impact? It is the likelihood or the probability for the project to exert a sustained powerful influence on the field. Likelihood is derived from you, that means “are you trained, do you have the background to do this work?” “What is your approach? Is that approach strong, and very likely that you’ll get the answers?” “What are your preliminary findings?” If you have some good preliminary data, that will tell the reviewer “yeah they’ve done some of this work already. It looks like they’re on the right track, it looks like they’re poised to do this work.” And lastly, your environmental criteria, that is your labs and your institution.

The sustained powerful influence derives from Significance and Innovation and the research fields might vary, so you have to be clear about what fields you believe are influenced by your project. You could be looking at a very, very specific cancer such as caused by say HER2 positive gene, like for breast cancer. Your work might influence say estrogen receptor positive breast cancers in addition, or it might influence research on a wider variety of cancers that may identify say certain key points that the researchers can use to broaden their
research, so you might identify certain receptors on the cell that might also be receptors on cells of other types of cancers. It may vary, it may be more broad than what you’re looking at.

**Specific Aims: What Do I Intend to Accomplish and Why is It Worth Funding?**

I want to talk a little bit about the Specific Aims and each of the research sections because this is really important. If you don’t get this right the reviewers will not give any kind of a good score, and the aims page is critical. So they want to know “what are the goals, these are your Aims, of your proposed research?” Summarize the expected outcomes, including the impact, and this is a little confusing because that word impact is a little different than impact scores. “What is the impact that your results will exert on the field?” So “what impact or what influence will this work have on the research field?” They want to know the objectives of your research and there are six points the NIH makes: “Are you testing a hypothesis?,” Most research does; “Are you creating a new design, a novel design;” “Are you solving a particular problem;” “Are you challenging a paradigm?;” “Addressing a barrier to the field?”; or “Are you developing a new technology?” You might be doing all six of those things, and it’s important that you read this and use those buzz words. Say for example “In this research we are creating a novel research design to test pregnant mice to understand the problems of X,Y and Z.” You have to say you’re creating a novel design, you are challenging an existing clinical practice paradigm, or you are addressing this critical barrier. They want to know how you are going to make that leap across that barrier and what is the barrier…what is the problem. That’s every critical to address in the Aims.

**Specific Aims: Structure**

So the first paragraph must define the problem or the need, and the gaps in knowledge. This is the short background leading up to the stated problems. What is your solution to that problem and how you’ll fill that gap? by proposing your hypothesis. Hypotheses are really important to list in the Aims page. Then your Aims are your objectives and you have to make them very specific:

- “Are you measuring something?
- “Are you identifying a particular cell surface antigen, are you developing something?”

I see a lot of grants that say “we will explore” or “we will study” or “we will investigate” or “we will consider” and these aren’t the ways that you should list your Aims. You can list an aim by saying “we will test the hypothesis that …” so that’s another way of doing it.
“What are your expected outcomes that lead to the impact?” And then, “what is the probability your study will be successful and exert a sustained influence in the field?” If it doesn’t work it will have no impact even if it has high significance, and what you want to address here is the immediate problem in your long range goals. “Where are you going with this research?” This should be the ending paragraph on your Aims page.

Your hypothesis should be clear, it should be understandable, it should be testable and it should be very specific. The most important thing is: “Are the aims obtainable within the stated time frame?” You need to focus your research and it’s probably best in the areas you have strong supporting data. The Aims should be related, cohesive, and I’ll talk a little bit about that. For example, if the focus of your grant is to “identify lymph node metastases in patients with resected lung cancer,” that’s the basic idea. Let’s look at this first opening sentence on an Aims page: “Lung cancer is the leading cause of deaths among men and women in the US. In 2008 109,000 men were diagnosed and 88,000 died. In addition 93,000 women were diagnosed with lung cancer and 70,000 died.” Equating disease and the devastation of the disease with significance is a mistake. This is stating material that is available to anybody. It’s obvious and it’s not focused, it doesn’t tell me what the grant is about. However, if I were to say “Failure to identify regional lymph node metastases in 40,000 US patients each year with surgically resected lung cancer associated with the three fold increase in recurrence and decreased overall survival. This research will deliver novel nanotechnology methods to identify and to prevent lymph node metastases.” This is focused on what you’re grant is about, it adds information, it identifies the problem and it relates actually to the mission of the NCI. Which in this case is actually looking at identifying lymph node metastases in patients with resectable lung cancers, and if you actually can, you should try to focus your grant in the areas that the NCI or the NHLBI, or whatever institute you’re going for is interested in. State that in the grant “this research addresses two key areas of research priorities for the NCI namely…” That’s a very important thing to do and the reviewers will really pick up on that.

Here’s an example of a specific aim:

• “We hypothesize that functional nanoparticles, which undergo cellular uptake and cause endosomal rupture, will afford enhanced targeted delivery of paclitaxel, which is a drug, for the prevention of nodal metastases in lung cancer.

Our Aims are: first, to identify the key molecular nanoscale characteristic of nanoparticles required for controlled release of the paclitaxel; second, characterize the efficacy of nanoparticle delivery for tumor cytotoxicity and lymph node trafficking in vitro; and third, measure the ability of the drug loaded functional
nanoparticles to arrest the development of nodal metastases in lung cancer in vivo.” This is a good example of three clear Aims.

**Specific Aims: Common Errors**

One of the things that most reviewers say about the Aims page is that they don’t have any innovative ideas. What I mean is they’re not focused and they’re not realistic so that’s the first question they’re going to ask: “Are the Aims very specific and focused?” If there are risks, “why is it important to pursue, and how knowledge will be moved forward if the aim was not met?” Reviewers also say that Aims aren’t justified clearly: “What is the relationship to what we already know and what we don’t yet know?” It should be clear. If there are gaps in knowledge, “how are you addressing those?” Lastly, reviewers say that the Aims do not demonstrate to be hypothesis driven. You don’t want to get back a review that says “this proposal looks more like a cohesive set of experiments in which the applicants are simply listing experiments according to their expertise and techniques instead of testing an underlining hypothesis.” Or one like this “our enthusiasm was dampened by a lack of a hypothesis, driven by a specific mechanism.” It should be hypothesis based. Reviewers say that lack of cohesiveness is common and that the Aims must be somatically based and form a cohesive unit. That is, a central hypothesis that unifies them.

“Is one aim is totally dependent on the other?” Say you propose to identify and clone the cellular receptor that restricts a certain virus infection in humans in aim one, but in aim two there are plans to construct transgenic mice expressing that receptor to develop a model. What will happen if you’re not successful in identifying the receptors, and what if there’s more than one receptor?” **If one aim is totally dependent on the other, that will be a big red flag for a reviewer.** Generally there are 2 Aims or 3 or 4 Aims in the R01, 1-2 in an R03 or an R21. Too many will give them the impression you are not focused, and that you really haven’t thought it through. Lastly, if there is no impact on the field, even if the Aims are achieved, that’s really a big problem for a reviewer.

There was a study done in 2005 in the Annals of Internal Medicine where they looked at a series of 66 grants, and of these 66 grants half of them had overstated goals and they where overambitious, or they were unrealistic. Thirty-eight percent of them were poorly focused or inadequately conceptualized, and in half of the grants that they looked at, the hypothesis was not clearly articulated. To read more on this manuscript visit: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3052777/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3052777/)
On your Aims page you must have a sentence like “Our hypothesis is” or “We are testing the hypothesis that.” That has to be clear. One of my mentors at Stanford, Alan Reiss, MD, said that “most reviewers will form a general conclusion or make up their mind after reading this page. They’ll then read the rest of the proposal looking for support of their opinion.”

**Approach: NIH Requirement**

Let’s talk about what Significance is. I mentioned these before. There are three things that the NIH actually asks. “Are you addressing a barrier?” “How will you improve scientific knowledge?” And “how these concepts, technologies, methods and so forth that drive the field, be change if your Aims are achieved?” That’s sort of in a sense the impact. You need to address each of these.

**Significance: Why is This Work Important?**

Recommendations I would make based on reviewing a number of grants and based on peer reviewers is, you have to make a compelling case here. “Why is this research important to this field?” This is a review of published and unpublished work including your own. “How will your research fill the knowledge gaps?” You need to show that you are aware of the opportunities to end gaps and road blocks in the research you’re doing. Then try, as I mentioned, to tie the mission of the NIH institute that you’re addressing to your research. “What are their priorities?” You can do this by checking their websites as I mentioned for RFAs, PAs, as well as their research priorities.

**Significance: Common Errors**

The common errors that peer reviewers say; “it’s too diffuse and long.” This used to be called background and significance and it was often an exhaustive review of the literature and you don’t want to do that. I would say your Significance and your Innovation section alone should be no more than a page for a six page R21, and for a 12 page R01, it should be no more than two pages. It’s really important to keep it short. Significance is not related to the stated problem, that’s extremely important. That seems obvious, but a lot of times the Significance isn’t directly related to the problem you’re studying. If you follow your Aims you will keep yourself focused. As I mentioned earlier, you don’t want to equate significance with illness. Don’t argue that a disease is significant. Significance is what you will do to treat or diagnose the disease or change in some way how it’s treated or diagnosed. Lastly, another common error is that your work is incremental. It’s not really
driving the field that much, its confirmatory research, its duplicated research, it’s been done before.


**Innovation: How is This Work Novel?**

Innovation is one of the hardest things to understand: “How you’re seeking to shift current research”; “How any novel concepts, approaches, methods will be changed”; “What is their advantage over existing methods.” You need to say “why am I using this new technique to look at this?” “How is it going to be more important, what is it going to give me over the current way of doing it?” “What are your refinements, improvements and so forth that you’re addressing?” It’s really important that you read these things and think about how you will address these in your research. You need to understand what it means for an NIH grant application, and this is particularly important for an R21.

**What is Innovation?**

Your research doesn’t have to create a new paradigm to be innovative. To be innovative it can shift a paradigm, it can offer a combination of the known methods leading to a new perspective in addressing a problem, or it can refine an existing model and technology. It doesn’t necessarily mean you’re using a brand new method or tool. It can be shifting the way something is done, slightly. You can look at a combination of known, kind of non-innovative ways, that are tried and true but you’re using them in a new way. So being innovative and knowing how your research is innovative is critical. It’s less risky to use an innovative approach to solve an existing problem than to take on a problem that’s highly innovative. For the reviewers, it’s going to be harder to gain acceptance if your ideas are outside the mainstream, especially if you’re not experienced. You’ll need to make a strong case for why you’re challenging the existing paradigm and have data to support that. You need to show how you will break new ground. I mean it is a review criteria and this work should have should have some novelty to it.
**Approach: NIH Requirement**

In the Approach section, the NIH wants to know “what strategy, methods, and analyses you are going to use to accomplish the Aims.” “How you’re going to collect, analyze and interpret your data and what potential problems and alternatives strategies and benchmarks that you have to achieve the Aims.” These are three areas that are important to address. Especially if you’re a new investigator, you have to describe how you are going to establish feasibility and address the management of high risk aspects of your work. If it’s highly innovative you’re going to need to convince them that it will have a high probability of success even though it’s innovative.

**Approach: Organization**

I will share the best way to engage reviewers, and what they like to see. First you want to address your preliminary studies in your approach. You also want to put what your study design is. You want to put what your approach is for each Aim, then you want to emphasize in there, any unique methods. You may want to spell out a little bit more and talk about it but also abbreviate standard methods. If you are using methods that you’ve never used before you should use collaborators. **Use tables and figures to illustrate complex experiments.** That’s very, very helpful to the reviewers, to see a picture or a table that describes your study design.

“How will you interpret the results?” The interpretation is vital to the reviewers, and you want a link that interpretation back to your Aims and hypothesis. You want to tell them what your pitfalls are and an alternative approach, how you adjust the Approach. If you don’t see the pitfalls and you don’t mention them that may give the reviewer the impression that your Approach is careless, and that you don’t see the weak points. I mention this, again, for any early stage PI, you’re given some leeway with some aspects of the grant, such as preliminary data but you’re not given any leeway with Approach, anticipated results and lack of plans for possible problems. Those have to be addressed. Any future directions that you’re going to take need to also be addressed and then, give quantitative benchmarks for assessing the progress over the grant years. For each Aim, “what are some of the milestones that you might reach and how you will get to that Aim?” It would be helpful even for you to outline that for yourself.

Approach: Common Errors

Some of the common problems that peer reviewers see is excessive detail on approaches or inconsistency in detail. The level of detail should be proportional to the novelty of it. How that happens is that investigators start writing a grant from a blinking cursor and they don’t outline it first, which I strongly recommend you do. Then they get up to near the end, and they say “oh my god I haven’t even addressed Aim two and I only have two more pages.” Then they start writing Aim two in an abbreviated way, and when the grant is looked at as a whole it looks inconsistent in the amount of detail, which is not favorable. Standard techniques don’t need to have a lot detail you can reference them or show them in preliminary studies. The next error is how you’re going to get to each Aim, and it not being clear. This is a common error. Your experiments have to be tied to the Aims or that will kill your grant otherwise.

The next common error is a lack of pitfalls and alternative approaches. It scores big with reviewers if you show how if your Aims fail, or what the potential roadblocks are, how you are going to go in a new direction if you need to revise your approach. Another error: it’s too ambitious. This is a very common problem and if your Aims or certain studies are not achievable in the time frame this may become future work. Another error is a lack of a section on “interpretation of results.” This is very important because it’s not always clear to the reviewers. You need to show that you can predict your results, consider alternative results, refine the stated hypothesis, adjust your overall research plan and assess the impact of the data. Last common error: There is a lack of clear logistical organization and a plan for the grant period. This has to be very clear to the reviewer, so providing a time line for completing the Aims is very helpful, even if it is sentence forms and sentences.

Approach: Quantitative Milestones

A Quantitative benchmark is helpful for assessing the annual progress of your project, not just a restatement of the Aims. A time line and a pathway for the development of the proposed technology is helpful. For example:

- Detect one cancer cell in 106 normal blood cells.
- Increase the therapeutic index of an agent >3-fold by nanoparticle-based therapeutic solution relative to the non-nanoparticle bound agent.
- Achieve >95% selectivity in targeting mixed cell populations in vitro.

So it will be good for the reviewers to see some of these, to say these are some of our milestones that we hope to achieve.
Your Overall Impact Score

For the overall impact score, reviewers are essentially asking you to answer these questions: “Why is my research important to health and human disease?” Plus “can I do it and am I qualified to do it?” Plus “will it have a significant impact on the field?” Those three things are probably at a 50,000 foot view. They are the most important things to consider when you are putting together your grant as they address the Significance, Innovation, you the Investigator, your Environment and the Approach.

Overall Reviewer Advice on Grants

Let me share some advice from NIH reviewers:

“The most common error, particularly with new investigators, is over ambitiousness—trying to cover too much territory with the time allotted.”

- Keith Yamamoto, Chair, University of California San Francisco, Executive Vice Dean Schools of Medicine.

“If you do not convey the essence of the idea clearly, then no matter how good the idea is, it’s lost!”

“Use grantsmanship—conveying clearly and repetitively what you want to do, what you will do, and how it will advance the science.”

“There are 3 elements of a proposal that excite me: The major hook for me is first, how it’s presented: how clear is the language, how well do the ideas follow from one to another? Second, what is the quality of the idea? The third is Innovation--how much will this study advance our knowledge of something that has eluded our understanding for some time?”

- Martin Philbert, University of Michigan School of Public Health, Professor of Toxicology and Senior Assoc. Dean for Research.
“Seek outside help before you submit the grant—there are things you miss all the time—and take any reviews seriously and revise many times before you submit your grant application.”

- Kate Bent, Center for Scientific Review, NIH, Chief, Healthcare Delivery and Methodologies RG.

“You can read many proposals and one stands out as being a wonderful piece of writing—for me these contain a lucid style, a compelling scientifically creative idea, and especially this idea of IMPACT—moving science forward towards a clinical end that is credible with a boost of capability to a patient population with an unmet need.”

- David Grainger, University of Utah, Professor of Bioengineering and Pharmaceutical Chemistry.

“You have a bunch of peer reviewers looking at your proposal who want to find an exciting idea and good science that is supported... so tell them a good story.”

- Brian Hoffman, Northwestern University, Professor of Chemistry.

**Specific NIH Peer Reviewers Advice**

In this next section, I’m going to give you the results of some of the peer reviewer advice provided by about 100 peer reviewers, and these are the kinds of things that they said that they want to see, that they don’t want to see, and the advice they give, that I think is important. Again, as I said over and over again the major criterion is future Impacts, and Significance plus feasibility. “How feasible is your study?” “Is it an important study and will it have impact?” These are really the main criteria. The “so what?” factor is so predominant that solid science proposed by productive investigators didn’t always get favorable reviews because the work wasn’t seen as ground breaking. Scientists that are focused on basic applications that were weakly linked to human health, or added a weak Aim to the effect, did not succeed.
Peer reviewers say that you want to find a good idea that’s significant, innovative and impactful, and you want to concentrate on areas of expertise that will make a broad impact. Make sure your idea fills a clear gap in the research, that you’re stating that gap on your Aims page and that you’re filling it, this has to be crystal clear to the reviewer. “Does it fit the mission of the center that you’re proposing it to?” Don’t try to go it alone. Most reviewers’ say “build a team that strengthens an application, and that may be with collaborators or other co-investigators.” You want to seek collaboration opportunities to fill the gaps in your own expertise. Consider multidisciplinary approaches. You want to make sure that your proposal is extremely well written, that it doesn’t contain errors because that’s a real turnoff to most reviewers.

Propose a scope of work that is appropriate to your track record. They’ll look at your biosketch’s publication records, and your personal statement to get a sense of how experienced you are and what you’ve done. Make sure that the application is not overly ambitious or lacks focus, that’s really important. Lastly, it should be clearly defined and narrow in focus. It should be defined, and particularly, defined in the area that you have some supporting data, and it should be focused in a specific area. You have to make sure that it is very doable. The flow of logic in your application must be very, very clear and compelling.

Reviewers said that the production of numerous publications was not necessarily seen as sufficient, particularly if the impact wasn’t high. They sometimes describe these proposals as “cluttering” the journals. There was one example where there were over 250 publications. The lack of relevant publications was seen as a deficit, if there were already noted problems with the Impact. The most successful proposals were those that took the research out of the PI’s comfort zone, and collaborations may be required to push the project beyond the PI’s traditional approach. For example, if the PI were a geneticist doing experiments in yeast, proposing only continued yeast genetics experiments was not favorable. You should collaborate with somebody who can approach the question perhaps in a different way, using biochemistry or physiology to move into different models. Scientists should move from cell culture and yeast experiments into animals for example. That is researchers should not keep using the same mouse models over and over again.

If you’re doing a renewal, the bar is going to be higher. This is the way the NIH is now setup. I would say that if you’re going for a renewal, you’re going to have a tougher time getting it renewed as in the past. A lot of times the people at the NIH, in particular the peer reviewers, want to see new approaches. So you want to think about new versus continuing. I would say if your grant is going in for a competitive renewal, you have to make sure that you have compelling, really compelling evidence that shows you’ve met the Aims in your last five years and this is moving you now into a new field. Into a new series of questions and here are the
new questions that we’re going to be asking, instead of just continuing to gather data. You want to summarize critiques and look at the big picture to make reviewers feel as if as if the critiques are evaluated carefully. The most useful part of the review for those concerned with resubmissions: separate the responses to significance from the responses to approach.

Using too little preliminary data was a negative. Including enough context is the key. PIs must assure that there is enough information for reviewers to understand what they’ve done and how it’s key to your Aims, this is really important. The best formats on the grant were treating each Aim like a story integrating background and preliminary data into the approach. If you don’t have figures or you have very little white space this equates to the reviewer that you are having difficulty with the new format, which is a six or twelve page shorter format, and it’s negatively viewed. Include solid collaborations with PIs who have expertise in areas you don’t. I mentioned this several times as this is really critical. The quality of the Approach draws the overall impact score for many peer reviewers. The quality of the Approach includes: “For the experiments that you propose, the way you’re going to do them, the way you’re going to analyze the data, the problems you anticipate and how you’ll get around that; is the reviewer convinced you’re going to get there?” You need to say “I’ve already done some of this work, here is my outline plan.” If it looks very solid, and there are no holes in it, that drives the impact score, very strongly.

Reviewers usually read through the grant and then they go back with the review sheets. Innovation is the hardest for them to evaluate. They’re looking for flagged statements such as:

- “The proposed research is innovative because …”
- “This problem [gap in knowledge] is significant and this is what they are and this is why it is significant.”
- “The impact of this research will allow scientists…”

You want to use some of these words, flag them in your proposal. The personal statement on your biosketch is extremely important particularly when reviewers don’t know you. Standard statements versus tailored statements are really important. If you put a tailored statement in there similar to an application, it’s negatively reviewed. Do not put down some sort of general background; you have to tailor every single personal statement for every single grant and what your role is and why your background is particularly suited for that role. Don’t say:
• “We have sufficient energy and enthusiasm for the project” or
• “We have a strong desire to undertake this research.”

This isn’t stuff you want to say. It is meaningless to a reviewer and it upsets them when they see these things.

Detail your training or your publication experience on your biosketch, that’s important. In basic science, grant Aims that were highly innovated had a higher bar for preliminary data. Early stage investigators seem to have leniency that varied. In some study sections there’s a third reviewer outside of the field, usually called the discussant, which makes it imperative to write a comprehensive application. What that means is the discussant usually looks at the application for its Significance and Impact. They’re looking to see a very strong, clear statement of Significance and Impact. I would say use NIH RePORTER to find keywords for funded applications similar to yours and study sections, particularly, and what they fund.

To view study sections visit: http://public.csr.nih.gov/StudySections/Pages/default.aspx.

**Common Grant Mistakes**

Common grant mistakes that reviewers find include:

• **Vague, unfocused writing:** “It took me too long to figure out what they wanted to do.”
• **Too densely academic:** “Written like a journal paper….wading through tedious detail and unnecessary academic rhetoric.”
• **Incomplete response to program announcement:** “I kept looking through the proposal for direction on key objectives…”
• **Too ambitious, too global in scope:** “Clearly, in 2 years, it would not be possible to accomplish these broad goals.”
• **Research plan too vague:** “I couldn’t conceptualize the specific objectives.”
• **PI lacks proven competence to do the work:** “No clear evidence in preliminary data that the PI has the knowledge of these novel methods.”

**What Does an Outstanding Proposal Include?**

What peer reviewers say about outstanding proposals is:
• “They clearly follow the RFA or PA and demonstrate how the work will achieve the specific goals that they want.”
• “They’re fresh, novel insights into a clearly important problem.”
• “The writing highlights the impact.” I cannot stress this enough. If I said any one thing today, that you should remember, it is that you must clearly nail this part, “what is the impact?” I read some grants and I say “what is the impact of the work?” and they can’t articulate it. That’s a really big mistake. The data that you have already that shows how you understand the methods, that your Aims are feasible and that you have knowledge of the field. That’s very important.
• “The overall application is neat, organized and it’s very easy to read.” One of the things that a grant reviewer said; “psychological mechanisms came into play… once I lost patience with an applicant for writing a disorganized section I was much more likely to notice other faults. Also when the proposal was sloppy, it was difficult not to extrapolate that to the applicants lab work as well.” “At the other extreme, the easier the applicant made it for me to get the information necessary to assess it, the more likely I was, if the science was sound, to have a positive feeling about the proposal.”

This last point is very true, I think, for many peer reviewers. When I read applications that are clear, that are addressing all the things that are important to the review, and applicants don’t stumble over things, then you feel positive about it. You say this person has really written a very clear, very compelling argument which I find very important. The same reviewer said “bad organization could mislead the reviewer. If the topic sentence of the paragraph’s full of unimportant words, I would move on to the next paragraph. This is detrimental for the applicant, as well as embarrassing for me when I learned from my peers that important information had been buried down in one of those paragraphs.” “My suggestion to proposal writers: once you think it’s finished go through it to see if you told the reviewer up front what’s important in these paragraphs.”

In college, you’ll remember, you learned how to write a good paragraph. You have a topic sentence that addresses a central idea, and then you tell them more details about it in the paragraph. I always liked to, at the end, especially if there are several paragraphs, to summarize what you just said to the reviewer. This is complicated stuff you want to keep it as easy to understand as possible. One the grant reviewer said “the best guide proposal presentation is to think about what the reviewers need to know, and to remember they are real people. They’re overworked, they are pressured and they want to do a good job. It’s hard for them not to be favorably inclined towards those who save them time and make their lives easier.” That is all the things that I mentioned before…make the grant clear. Put all the important things in there and make sure that you are identifying them in the grant. In the next page is a copy of a grant that shows how neat some of them are. All of
the figures, for example, on this page are in a box. You see the captions so you don’t get confused where the captions and figures are, and it has a fair amount of white space in there.

**What Annoys Reviewers?**

The reviewers are annoyed by the following things:

- **Errors such as punctuation, grammar and spelling.**
- **Cutting and pasting portions of the document.** I have seen grants over and over again that from the Aims page they just cut and pasted material from Significance, they’ve cut and pasted a section from Innovation, they cut and paste in whole sentences back and forth, you should never do that.
- **Inconsistent formatting and writing styles.**
- **Illogical and confused paragraphs that wander through and include unconnected thoughts.** That is why you need to outline your grant.

Reviewers say “if the PI can’t take time to do it why should I do it right?” “The PI takes way too long to get serious about writing their grants and they don’t allow enough time to polish the document,” that’s very true. I get calls from investigators saying I’m going for this R21 then I look at it and say well the deadline is in two weeks. “Well I haven’t quite finished it yet” and said you should be finished with it by now, and you should have it out for review. A lot of times people do this at the last minute and again they don’t realize how important this is.
What do you consider to be the most important criterion by which peer reviewers judge your R grant application?

Dr. Dant: Well, I hope that you all know pretty much what those are, but I would say again when you get an impact score, what that score is that it basically ranks your application against the others. It will determine whether you are funded or not. Essentially the most important criteria that peer reviewers want to see are those of significance, feasibility and impact, I would say those are the three main ones. I mean there are other obviously important things, but reviewers want to see that this is an important problem to study. Clearly there are gaps in our knowledge that have eluded us for some time and I’m proposing a study that is very doable and it’s doable because you looked at my biosketch you’ve seen what my background is. You’ve looked at my publications and seen what I’ve done. We’ve proposed a very, very compelling Approach to each of these Aims and that we believe that based on this we will get there. When we do get there this is the great pay off, this is that impact. The impact statement probably is the most important thing to articulate, that’s really what they will be looking for.

You may, as I say, have a study that is not particularly innovative but it is really going to have a big impact, it’s going to move the field forward in a way that really is necessary. This is stuff that we are doing that we feel is going to bridge some of these really important treatment gaps, and maybe provide patients with a new targeted therapy that has eluded our understanding for some time. It’s a medical need, it’s providing a brand new model that has never been looked before that will really give us some great ideas that will go on to clinic trials. It has to have very, very clear and strong impact otherwise, that’s the most important criteria I would say… impact.

Can you reiterate your comment about what should be the last part or sentence of the specific Aims?

Dr. Dant: In the last sentence in the Aims you have stated what the problem is that you are studying, and again the problem is not that lung cancer kills a million people a year. Your problem that you are studying is that there is a gap in our knowledge that we don’t quite yet know, and I am addressing that by hypothesis based research. I’m giving you my Aims of how I’m going to get over that gap to the other side and answer the questions. The last paragraph on that page answers two specific questions, the first one is “what do I expect to
find?” A lot of PIs miss this; you have to tell them. This is NIH mandated information. If you don’t tell them, the reviewers will throw their hands up and say I don’t know what they expect to find with this. Then maybe you say “oh that’s buried in page six of my research plan.” No. That’s got to be up front.

The other important thing is “what do I expect to find leading to impacting the field?” It’s an Impact statement. The impact statement or statements need to be very clear about how this is going to change research in the field, and it has to be realistic. I mean you are not obviously going to say something like “we are going to move the field forward so we can cure a specific kind of cancer.” Don’t say something obviously stupid like “that it’s got to be very specific to what you are doing and you believe that this is how we will move the field forward.” That is the paragraph in your Aims page, that’s got to be there. If they read your Aims and there’s nothing beyond that, they are going to wonder what do they expect to find with this and what impact will it have. Then, they have to sort of theorize what that might be, and then look through the rest of application for support of that, that would be a big mistake.

Do I have to have preliminary data to apply for the R21?

Dr. Dant: The NIH actually says it’s not required in the R21. If you read the unsolicited RFA for the R21, it says primarily data is not required. However, and this is only one institute, the NIAID in 2010 or 11 somewhere in there did a study on 200 R21 grant applications. They found that over 90% of them had preliminary data, whether they were new PIs or not new PIs. I would say and you’re going to be up against all the other applications that do have preliminary data. The R21 for example is not a grant mechanism that is intended to collect preliminary data, an R03 is but an R21 is not. The R21 mechanism is actually exploratory, developmental and you are going to be collecting data in that grant obviously. Because it is somewhat exploratory and they place a high emphasis on innovation, you’re going to need to back up your Aims somehow and that hopeful will be in form of preliminary data.

It doesn’t mean that they will reject it immediately but it is going to be up against others that do have preliminary data, so I would say that it’s important to have it in there. You can certainly submit without it and it won’t be rejected on that basis, but it will be up against some that do have preliminary data. I would just say that if you don’t have preliminary data you are proposing a novel idea you should have a lot of collaborators and a lot of co-investigators that will bolster your application. That will give them the feeling like, “well okay he/she doesn’t have the data to support this but he/she does have a team and that team is very clearly outlined.”
I would say be very clear in your Approach section that you have expressed who you are, who your team is, why this combination of expertise is going to drive the success of your application. They’re going to say “well he doesn’t have preliminary data so we don’t know if you can do this and second of all he’s just going this alone.” I would say that would immediately be a death to your application, so it’s got to be really bolstered. Hopefully that answers your question.

**Should all preliminary data be placed in the approach section?**

**Dr. Dant:** Yes, your preliminary findings, your preliminary studies that you’ve done go under section 3C approach. So in your research plan its section two is your Aims, section one is introduction of the application, that’s not unless you are doing a revision or you doing answers to critiques. Section two is aims. Section three is what they call research strategy where part A is significance, part B is innovation and part C is approach. Under part 3C the first thing is your preliminary data and if it’s easier or more logical to put that preliminary data by Aim, in other words, the data that you’ve collected so far, the studies that you’ve done so far, what you’ve found can be easily categorized by Aim than do it that way. Here’s Aim one, preliminary data and then approach, here’s aim two preliminary data and approach, if doesn’t follow into a neater category then you put in 3C, approach and the first thing is preliminary data.

What would be helpful for you to do in the preliminary data section is to say what you have found so far that relates to your Aims and what aim relates to it? “Well this relates to Aims one and two, but in this particular section what we found is particularly significant for Aim one.” Tell the reviewer why this data is important for these aims because they’re looking at feasibility and bolstering your approach. I mean you are basically saying “we’ve done this work we can do it again and that this data has shown that this is an important problem.” It also addresses significance and innovation, if you’re using a highly innovative method or tool or whatever it might be, you’ve used it once before or you’ve had people help you with it, that will help the innovation. It all goes under approach and it should be very specific to your Aims.

**Can preliminary data be published?**

**Dr. Dant:** Absolutely and I would say that preliminary data that’s published adds credence to the data, it’s been peer reviewed and published. Hopefully it is published, but make sure that you’re not signing published work that don’t really relate directly to the Aims that you’re addressing. It may relate directly to the methodology that you’re doing, but it absolutely should ideally be published. I mean the peer reviewers
who look at your work are going to wonder if this work is published. “Has it been subject to a review by his peers?” That’s I think it’s a very important thing that you should consider. If it isn’t published you can make the statement “our preliminary findings, which are still being fleshed out, we’re still doing these experiments and we hope to publish this year.” Don’t list something as submitted; some people think that adds credence but actually it isn’t published.

If a journal takes your paper and they say “yes, I think, once you’ve addressed these problems, then we would like to publish your paper.” Then it’s not considered published, but it is considered in press, so you can list that as in press, but you’ve got to make sure that the journal has accepted the paper. Also I would recommend that you think a little bit more widely about your data. If you went to a scientific conference such as ASCO or AACR or whatever it might be, and you presented an abstract that was accepted by that conference, that is published piece of work. That is a peer reviewed, published piece of work so you should list that. If you gave a presentation at that meeting or you gave a poster that should be listed, so those are all legitimate publications.

If you have published a book on a subject that’s a legitimate publication, although it’s probably not waited as heavily as a journal article. These are all things that if it’s in the public domain, it’s been published, then yeah. I would say it’s very important to have this stuff out there and it should be published as much as possible.

**How long should the innovation and the approach section be in an R01 application?**

**Dr. Dant:** The NIH used to suggest how many pages that you put this in, they don’t do that anymore, they just say that whole section should be six or 12 pages. I would say first of all the tendency for most investigators is to, unfortunately, make it too long. I would say the majority of the space in your research strategy should be to your approach, because there you are showing them, this is how I’m going to get from A to B. This is how I’m going to get to these questions. For an R21 that has only six pages for that section I would say it shouldn’t be longer than a page, or a little longer than a page. Certainly two pages for those two sections and then four pages for your approach may be too unbalanced. An R01 versus an R21, the innovation and significance really isn’t any different right, I mean they are both legitimate questions it maybe more complicated in R01 and you are asking more questions.

For an R01, I would say if you have more than two pages for those two sections, it is too long. Do not think about Significance as “Background and Significance” that’s what it used to be called. The NIH said, “we used
to wade through these tedious long paragraphs of background that were unnecessary to understanding why this is an important problem.” You need to be really clear and really succinct about why this is an important problem to study for human health and disease.

When you write your grant there’s a section called project narrative and the project narrative is the second part of the abstract, the project abstract is the first part that’s three lines and it’s like an abstract. The project narrative is written to the layperson and the project narrative says “in two to three sentences describe why this study is important to human health and disease and tell me as the layman”, and this goes to congress okay. This is important to be able to nail and I would say that you should go on to NIH reporter, and look up similar projects to your own and in there they will show the abstract and the project narrative. Read some of those narratives and get a sense of the succinctness of them. Some of them are beautifully worded. I would say you really need to focus your significance section on why this is important to study. Most studies you could do that in a half a page.

Your innovation section should not be long either. It should be very clear on how it’s innovative and you should address specifically the questions I posed for the areas I posed. Otherwise the reviewers will not be aligned with what they are expecting to see and you are likely to get a low score. The more you can align your applications with the expectations of the reviewers, the better of you will be. In terms of the length, however, certainly no more than a page for an R21 and maybe a couple for an R01.

**What if there is a competitor on the study section or someone else with a conflict of interest assigned to your grant review, what would you do?**

**Dr. Dant:** I believe, and I’m not really that familiar with this because I haven’t done it, but I believe you can address that very much like a journal. If you know who the journal reviewers are, you can ask they be excused and not included on the study section. As you know there’s a roster of maybe 15 people that they choose from and if there’s somebody on that panel, and you can look up those panels and find out who they are, you can ask if that particular reviewer be excused from the review because you believe that there’s a conflict of interest, or some other reason that would bias their review. Usually the NIH will exclude those people. I’m not sure of the exact mechanism of how to do that, I think a letter to the NIH. You can call your scientific program officer, for the MTI or whatever it is, and ask them how to do that, but there’s a method to do that. You don’t necessarily have to get always the reviewers that they pick you can ask them to be excused. You have to have a good reason for it though.
How do you weigh going for a renewal versus a new R01?

**Dr. Dant:** I mentioned this a bit earlier, so the way NIH pay lines are now and the way that the NIH is looking at renewals versus new, is that you should think about what you’ve done in the last five years on your grant. I would say unless it’s extremely clear to you, and to your investigators that you are doing the work with, that you’ve made highly significant progress in five years, that you have answered your original Aims for the most part and that it has given you new knowledge to go into new areas that will go farther in this research that will have even bigger impact and lead you to your final goals of your research or lead you to making a big breakthrough; then you should go for the renewal. But you have to make it very clear in the renewal what you found. In other words it’s a progress report, so you would tell the reviewers under the approach section, this is what we found, this is where we’ve gone, this what we’ve seen and these are the new questions that we are answering because we believe that this is now moving this field forward. If, on the other hand, you’ve done five years of work and it’s been somewhat ambiguous, what you’ve found, there’s been conflicts, there’s been a lot of things held up, you need new data, you want to go for the same aims then I would recommend you write a brand new R01, and that you use what you found in the last five years as preliminary data.

I realize that it’s all the same thing. I mean your preliminary data is what you’ve found in the last five years, but you are asking a brand new set of questions. A lot of reviewers say that this is probably a better idea, than trying to go for a renewal. The renewals are important too. I mean we’ve had one grant where it was so clear that the field was moved forward, they’ve answered a lot of questions with the original Aims and now they are taking it and shifting it in a slightly different direction. They’re wanting to get some more data but they are asking new questions beyond this. They can show tremendous progress towards what they’ve done then they went out for a renewal. I think it really depends on what you’ve done in the last five years and what you think.

I would say you err in the side of new versus renewal. I don’t know if there’s money set aside for renewals versus new, I think there might be, but I know that it’s much harder to get a renewal today than it used to be. It used to be that what we’ve done five years of this work and we can renew this for five more years. There are many grants that don’t get renewed. As you know an R21 cannot be renewed only an R01 can. Also the R03 cannot be renewed.
**Should you discuss your proposal with the program officer beforehand?**

**Dr. Dant:** Absolutely! This is the way you focus it right, you start off with an idea that you have and you say well I think NCI might be interested in this. I had one investigator for example who was studying, I can’t quite remember the project, but they were studying a certain type of cancer that is predominant in young children that affects the head and neck and that had some implications for both the NCI as well as the NICHD, which is National Institutes of Child and Human Development. He didn’t know whether to go to for the NCI or the NICHD. Also it was very important in neurological terms so it was a cancer that affected the spinal cord and peripheral nerves. He said maybe the National Institute of Stroke and Neurological Diseases would be another place he could go. So he called all three program officers of those institutes and said here’s my idea, I’m going to email you my specific Aims page, it’s not finished bur here’s the idea what do you think? This is critical to do because like in this case the NINDS, Neurological Diseases and Stroke said, “yeah it does involve neurological diseases and stroke but we don’t study cancers, or children. We would refer you to the NCI. They would be more interested in those.” I think it’s important to first read the priorities of the institutes, and then second look at what other proposal similar to yours, either by study section or by key words, are being funding and what institutes those are at and then try to narrow it down. Then call them and say here’s my idea, and here’s the Aims page, I’m going to send it to you. What do you think?

This is absolutely important to do before you ever go anywhere with it. Whether it goes to the NICHD, Child and Human Development, or the NCI or say this neurological diseases, I think you’ll certainly write it the same way but you may emphasize certain things in the grant that are more important to one of those institutes. If it’s affecting human development, or it’s affecting a certain type of cancer that has eluded us for sometimes, or that cancer affects nerves and we want to look at the mechanism of how nerves or whatever they might be, then you want to focus it for that institute and what those institutes’ priorities are. So that I think critical to make a lot of phone calls and discuss it to start off, yes.
It is my pleasure to introduce Dr. Christopher Dant. Dr. Dant is a faculty instructor at Dartmouth Medical School. His PhD work was concentrated in cellular and molecular biology. Early in his postgraduate career he apprenticed with a senior editor at JAMA and went on to work as a biomedical writer for life sciences investigators in academia, private industry and government agencies.

Before going to Dartmouth, Dr. Dant was projects director at the Stanford Medical School for grants and manuscripts and served as the Director of Medical Publications at Genentech in California. At Dartmouth he worked with investigators in developing grant proposal and programmatic initiatives, and educates faculty in grant and manuscript writing skills. He has worked with investigators at the NIH, NSF, NASA, DOE and other federal agencies.

Today, I’d like to talk about what the R21 Research Grant from the NIH is, what it is not, and how it differs from other grants that are similar to it.

There are actually several different types of R Grants that the NIH offers, and I’m not going to discuss all of these. We’re focusing on the R21. The 3 common ones that you’re all familiar with are the standard large 5-year R01 Grant; which is very common throughout all of the NIH institutes; the R03, which is a small pilot type of award; and then the R21, which is exploratory and developmental in nature and it’s a 2-year grant like the R03.
If you were to look at the R01 versus the R21, I think it’s important to point out some differences because there’s a fair amount of misconceptions about what the R21 is and what it is really not. This implies all agencies at the NIH, not just NIAID, which puts out a lot of data about the R21.

**What’s an R21?**

First of all, the purpose of the R21, and I’m going to repeat this several times because it’s so important, is really to introduce novel scientific ideas, model systems, tools, any model agents or novel agents, targets, and technologies that will substantially advance research. The R01 supports a discrete, specified project, in an area representing the specific interest of the investigator as well as in their competencies based on the NIH mission.

For the R21, the grant duration is 2 years, as opposed to up to 5 years for the R01. The budget for an R21 is up to $275,000 directs over a 2-year period, whereas for the R01 it’s unlimited. Most new PIs submit modules of 250K or less each year for the R01. The one thing is that the R21 is not renewable, as opposed to the R01, and we’re going to talk about preliminary data. It says on the NIH website that it’s not required for the R21. The R01 requires it.

If you are a new PI, meaning you have not submitted an R01, you don’t get any benefit from submitting an R21 but you do on your first R01. With the R01 new PIs have a higher pay line. The other important point is that the research strategy on the R21 is 6 pages, as opposed to 12 pages in the R01.

I’m going to say something here because I understood there was somebody in the audience who is interested in resubmitting their R01 as an R21. It isn’t a good strategy to take an R01 that has been rejected and then just rewrite it to be an R21. First of all, the R21 is half the number of pages for the research strategy. You can’t edit a grant down half the amount of material by just editing it. The other reason you wouldn’t want to do that is because the strategy for an R21 is different. R21s are very exploratory and developmental in nature. They break new ground. They look at novel new ways of doing things.

The things you stressed in an R21 are different, and there’s a different amount of detail obviously. There’s not as much detail on methodology. There’s more detail on conceptual design, on how things are looked at. We’ll talk a little bit about that, but I just want to warn you. I think it’s bad advice to have anybody say, “Just edit your R01 as an R21.” Some of you may remember back in 2010 when the NIH came
out with a new research strategy that went from 25 pages down to 12 in the R01, and a lot of investigators tried to unsuccessfully edit their 25-page research strategy to 12 pages. It’s just not advisable.

The R21, and this is the NIH language and I want to emphasize, “encourages exploratory, developmental and novel research that provides support for early and conceptual stages of the project.” This is a high-risk, high-reward research grant that may lead to a breakthrough in an area that results in novel strategies, agents, methods, models, or applications that will have big impacts on biomedical and clinical research. It’s a very distinct mechanism from the traditional R01.

In an R21, you basically are exploring novel concepts and methods, previously understudied problems or gaps in knowledge. It explores the feasibility and applicability of a research idea. The idea in an R21 is that you are going to develop a new technique and approach or new models, methods or applications. When you write the strategy of this grant, you’re going to have to talk about how the models, how the methods, how the applications, how the paradigm that you’re challenging to shift are better than the old ones, and why you’re doing this, what new techniques and approaches you’re going to use. Therefore, it’s a high risk but high reward. You have to convince the reviewer that you can establish feasibility with the methods you propose, that they are new. That’s part of the problem with this type of grant.

**What the R21 is NOT**

For the R21, what a lot of investigators think it is, it really isn’t. If you’re thinking I need a project of limited scope or cost using a widely accepted approach and method within an established field, this is really not what the R21 is. That’s what an R03 is, a small grant. A small grant is more established of fields, you’re just collecting some pilot data and that’s what the R03 is. Long-term projects that are projects designed to increase knowledge in a well-established area are not the R21, that’s an R01.

The R21 is not a mini R01. It’s not a maxi R03. No way is it intended to provide training for anyone, and it is not generally used to generate preliminary data. A lot of investigators feel like, “This is my entry level into an R01. I’ll get my preliminary data and then I’ll write my R01.” That is not the way to think. Generally speaking if you want some pilot data and you aren’t sure of a new method or something, but it’s an established area, you might go to an R03 or find other ways to generate your preliminary data if you haven’t already gotten some. We’ll talk a lot about preliminary data because that’s the biggest controversy in this.
If you were to look at the success rates across some of the more common institutes, you’ll see that except for a couple of the institutes, such as the NIG and the General Medical Sciences and NIDDK, that the R21 is not as successful and some institutes don’t encourage this mechanism, whereas some do. Those who do are particularly the NIAID, the National Institute of Allergy and Infectious Diseases; the NINDS, Neurological Diseases and Stroke; NHLBI, the National Heart, Lung, and Blood Institute; and to some extent NCI although the NCI lets out an RFA or a request for application for the R21 that’s specialized. It’s not part of the parent announcement.

**New R01s vs. R21s Success**

Looking at success rate percentages, for 2013, it was 17.5% for the R01, and 16.8% for the R21 across all NIH Institutes. These are not pay lines. These are not any indication of where the cutoff is. It’s just showing that approximately 16% to 17% of all R21s or R01s are accepted at the NIH.

**R21 RFAs**

Here are three R21 RFAs, just to give you an idea of the kinds of things that they are looking for and these are in different institutes:

- Innovative approaches for the identification of mitochondrial-cell signaling networks and response to environmental stress;
- Disseminating and implementing evidence from patient-centered outcomes research in clinical practice using novel mobile health technology; and
- Novel research in the pathogenesis of HIV-related heart, lung, and blood diseases in adults and children.

They are very different areas but the one thing that you obviously see from these 3 is the word “innovative” and “novel,” and that’s precisely what they’re looking for. Again, the innovation of this is very large.
R21 Applications: The Basics

Now, the basics of the R21 is that it’s 2 years. It’s up to $275,000 for total direct cost, which is a maximum of $200,000 in a given year. It’s a modular budget as opposed to an R01. It’s a 6-page limit as opposed to 12. Like all R grants, it’s submitted electronically and they’re due February, June, or October 16 for unsolicited applications, so that’s the new application. Just about all NIH branches support the R21, but there are a couple that don’t. NCI, National Cancer Institute, is not listed in the parent request for application on the R21, but they do have an R21 mechanism that they let separately.

Preparing an R21

These are 3 questions that a lot of investigators ask me. “Does the research plan follow the same format as in R01?” “Do I need preliminary data; do I need pilot data to write it?” “Do I need to have a clear testable hypothesis?” The answer to these questions is; one, yes, the research plan follows the R01 format. Two, yes, you do need to have a hypothesis that’s testable and clear. Three, regarding the pilot data, the preliminary data, The NIH says, “Preliminary data is not required.” If you were to submit an R01 for consideration and you didn’t have any preliminary data, they wouldn’t even look at it. If you submit an R21 without preliminary data, they will look at it. They will evaluate it, but it is advised to have preliminary data, and I’ll tell you why. You’ll not have an easy time getting funded if you’re applying for an R21 to gather preliminary data, that’s not the purpose of the R21 and even if you succeed, you may come up short because it’s a 2-year grant, and we’ll talk a little bit about timing because a lot of investigators get caught on that.

Preliminary Data

Let’s talk a little bit about what preliminary data is and why it’s important to the NIH. First of all, it establishes credibility of you and your collaborators. The data that you put forth shows that you have the necessary skills and experience to do the work. Obviously, the NIH wants to know can you do it.

Preliminary data establishes project feasibility. It assesses the likelihood of research being done in the time frame of the grant. If you show that over a period of time you’ve done some of this work and you are familiar with some of the work, and I realize this is exploratory, but you’ve done some of the up front work, you are familiar with how long it takes and that is important.
It also educates the reviewer; “what’s been done in the field, especially by you,” that’s presumably what preliminary data is, it’s your data; “what preliminary data is novel and advances the fields;” and “why the proposed work is important.” Really, “what questions that are raised by the preliminary data will the proposed experiment answer?” That gives the reviewer some education as to why it’s important or significant. 

It also demonstrates the continuity of your research that led to the proposal. It follows logically from what you have published, what you have done before up to now. It demonstrates continuity, and it supports significance and your hypothesis. It also impresses the reviewers and shows that you are uniquely qualified.

Preliminary data has a number of positive things. For one, it gives you credibility beyond your statement in the biosketch, and beyond whatever you say in the research strategy about you and your team. It shows you have the unique skills and you’re an expert. This is a very, very strong thing in a grant to have any preliminary data toward the end of what you’re studying.

### 2012 R21s from New/Non-New PIs

The NIAID, the National Institutes of Allergy and Infectious Diseases, did a number of studies in 2012 and I’m going to talk about some of these because they illustrate certain things on the R21. It may not apply necessarily to other institutes, but this is the only institute that did these studies.

First of all, they look at R21s from new investigators, those who had not had a major research grant, and non-new PIs, those that had major research grants or R01s, and here are the results:

- NIAID funded 13 of 69 *new PI* applications, a **success rate of 18.8%**
- NIAID funded 46 of 131 *non-new PI* applications, a **success rate of 35.1%**

They funded 13 of 69 new PI applications, which was a success rate of 18.8%, but they funded 46 of 131 with non-new PIs which is a higher success rate of 35%. That’s a little discouraging if you’re new.

### 2012 Preliminary Data in 200 Grants

Then they wanted to know, “Was the presence or absence of preliminary data a factor?” What they did was they looked at 200 grants and the NIAID funded 59 of those, which is a 29.5% success rate. 13, or 6.5%,
had no preliminary data and 46, or 93.5%, did have preliminary data, so it was overwhelming that the ones that were funded had preliminary data. **It appears that the preliminary data strengthens their case to be doable.** Reviewers now expect to see some data that you’ve generated. Even though it says you don’t require it, I think this is really a disconnect between the NIH and investigators.

The NIAID study found that more applications from new PIs lacked preliminary data compared to the cohort as a whole. Out of the 13 applications that had no preliminary data, 53.8% were from new investigators, none of which were funded.

Essentially, this counters a belief among new investigators that seeking an R21 as a very first grant is an easier route to take than applying for an R01. In fact, the R01 is a better choice for a first independent grant because you benefit from the special pay line for new investigators and the R01 is a more robust award.

I think the bottom line in all of the investigators I’ve ever spoken with and especially peer reviewers, they say, “You don’t need as much preliminary data. We don’t expect that especially a new investigator is going to have tons of data and really back up their questions, but it’s very helpful for us to evaluate if this is doable or not.”

**Do Multiple PIs Make a Difference?**

If you put multiple PIs on your grant, does that make a difference? In the NIAID study:

- Of 200 applications, 47 (23.5%) were from multiple PIs and they did about the same as those from single PIs:
  - Of 47 multiple PI applications, NIAID funded 14 or **29.8% success**
  - Of 153 single PI applications, NIAID funded 45 or **29.4% success**

Of 153 single PI applications, they funded 45 or 29.4% so it’s about the same. That doesn’t really seem to make a difference, which is surprising to me because I believe that if you have multiple PIs, and particularly if it’s exploratory in nature and you’re developing novel methods or anything innovative, it’s very helpful to have a big team or a stronger team. Having consultants, in particular, who can help you with some of the new methods or interpret maybe, say for example, you’re doing diffusion tensor imaging analysis which is a type of analysis of an MRI study and you don’t have expertise in that, you can get an investigator on your team or consultant that can help you with that.
New vs. Experienced PI

In considering New vs. Experienced PI:

- Presence of 1 or more experience PI was positive:
  - For applications with all new PIs, funded 1 of 10 applications, a success rate of 10%
  - For applications that were mixed (one or more but not all PIs were new), funded 4 of 17 applications, a success rate of 23.5%
  - For applications with no new PIs, funded 9 of 20 applications, a success rate of 45%

The presence of experienced investigators was positive so if you’re a brand new PI, meaning you have not had an R01, I would suggest you put some investigators who are experienced or not new, or those who’ve had R01s, on your team.

The other problem is that you have a 2-year grant and a lot of researchers find that it’s just not long enough to complete a project that yields enough data for publication or for an R01. When you have a 2-year grant, you need to avoid the gap in funding because the R21 is not renewable so that’s a problem. If you’re applying for the follow-on R01, that takes more time than most PIs anticipate. In fact, you should estimate anywhere from 5 to 20 months from application to award, especially if you need to resubmit. The R21 you cannot renew.

The R21 won’t benefit, again, from the higher pay lines for ESIs or early stage investigators like in an R01. I don’t want to confuse people, an early stage investigator is within 10 years of their PhD or their residency, a new investigator is somebody who has never had an R01. They could have had another R21 or an R03 or a K award.
Your R21

Here are the questions you must answer before you start an R21:

- What truly new knowledge might this yield?
- What’s unique about how I’m going about generating that knowledge?
- How will this work prepare me to conduct similar, larger-scale research?
- What is my game plan for next steps once the R21 is completed?

You have to think well ahead of time on these before you even start applying.

Preparing an R21: Common Errors

Some of the common errors while preparing an R21 include:

- Not conveying how the work is exploratory/developmental
- Trying to do too much
- Too much structure (the “mini R01”)
- Too little structure (“trust me”)

Trying to do too much, that’s a big problem. If you have too much structure, it’s the mini R01. Too little structure, it’s like saying, “trust me, I know how to do this.” If it’s exploratory, developmental, you’re doing something as novel. You’re breaking new ground. It’s a little tough because you have to show you can do it, that’s why the preliminary data is important, and you’ve got to have a good team. I would suggest you’ll have some preliminary data. I would suggest that you also put consultants and non-new PIs or somebody that’s had an R01 on your grant as a co-investigator.

How do Reviewers Ideally View R21s?

How do reviewers in a peer review panel ideally review the R21s? They’ll focus essentially on the conceptual framework. What that means is not so much the “detail of experimental detail” but more like “what is the concept here, what is the overarching thing you’re going to be looking at, what is your overall design, what are your long-range goals, what does this going to inject in general do, and what are the concepts that you’re studying?”
They’re going to look at the level of innovation. As I mentioned, that’s going to be a very big part of it so that scored criteria is going to count a lot. The potential to significantly advance our knowledge, and I’ll talk a little bit about what that is, is the impact. Reviewers will place less emphasis on methodological details and certain indicators traditionally used in evaluation the scientific merit of R01 applications, including supportive preliminary data.

**How do Reviewers Actually View R21s?**

A lot of reviewers actually view the R21 as a great first step for new investigators with a clear long-range research plan. It’s good for studying less well-studied areas. The one thing that R21 reviewers said is that “they do not hold PI to R01-level methodological standards.” That doesn’t mean you’re experimental approach can be sloppy, weak or nonexistent. It doesn’t hold it to the same standard. This is a short grant. You’re trying to break new ground but it has to be doable and it has to convince them that this will yield data. **It’s very, very important that you don’t overstep what you can do in a 2-year period.**

Again, even though the NIH says they don’t require data, most applications include it and reviewers tend to expect it. The R21 is really not for an entry-level grant for investigators who are just getting started. Really if you’re going for this grant, it should be because your ideas and your project are good match for the high-risk/high-reward, exploratory nature of your program.

I would encourage you all to look at the institutes that most likely are going to sponsor your research and look at the RFAs, MPAs that they list to see if anything is a match for what you’re doing.

**R21 Review Criteria**

Let’s talk a little bit more about the nitty-gritty of your R21, which is the research strategy section of your grant. First of all, these are the 5 review criteria, and these are the same review criteria for R03 and R01:

- **Significance**: relevance to human health and disease
- **Innovation**: originality of approach
- **Approach**: feasibility of your methods
- **Investigator**: PI training and experience
- **Environment**: suitability of facilities and adequacy of support from your institution
I would just say in general, investigator and environment are numerators. You should have the experience and be able to support that strongly in your application and the environment should be very strong. You should not get anything less than 1 or 2 on those 2 criteria.

It’s the Significance, the Innovation and Approach that are really scrutinized heavily. Then the reviewers will give you an overall impact score. It’s a synthesis or integration of these 5 criteria from 1 to 9. Overall, and I’ll repeat this again, it’s the likelihood of your project to exert a sustained powerful influence on the research field, in consideration of these 5 criteria and others if they’re applicable. There may be others, but these are the 5 elements talked a little bit about.

Remember that the Significance goes on your aims page as well. The Investigator is under the Approach and personal statement. Innovation has its own section, and research strategy and Approach have their own sections. The 3 most important ones have their own section. Resources and facilities, the environment, are in their own sections.

**Specific Aims**

On the specific aims, this is really where the rubber meets the road for most reviewers and if any of you are reviewers, you know this. Essentially, you’re asking the question, “What do I intend to accomplish and why is it worth funding?” Here are the instructions from the NIH and I put this here because most investigators missed this and I don’t understand exactly why. Every grant that I read, and I read many, many grants in a course of the year, miss this, and I point out to the investigators in lectures, I lecture all over the country about what this is. **On this page, the NIH wants you to state concisely the goals of the proposed research.** That’s no brainer. Those are your aims. Then summarize the expected outcomes, including the impact the results of the proposed research will exert on the field. The 2 things that people missed the most are expected outcomes and impact, so I want to concentrate a little bit on that.

These 6 bullets show you what your objectives are:

- 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 the field, or
• develop new technology

“Are you testing a hypothesis?” Every aims page will have a hypothesis statement. “Are you creating a new design?” “Are you solving a specific problem?” “Are you challenging a paradigm?” “Are you addressing a barrier?” “Are you developing new technology?” Likely, you’re doing all of those things, or some of them. Those are the words the NIH chooses and I think it’s important for you to read those and to internalize them so when you write your aims page it is very clear.

**Specific Aims Structure**

This is the way I would recommend you write an aims page:

- **FIRST** paragraph – Define the problem/critical need and gap(s) in knowledge—short background leading up to the stated problem and knowledge gap
- Proposed **solution** to problem and gap by proposing hypothesis(es)
- Specific Aims – **Objectives** that test the hypotheses addressing the critical need
  1. e.g., to measure, develop, identify…
  2. Avoid vague aims, e.g., “to explore” “to study/investigate”
- **Expected Outcomes** leading to impact on the field
- **Impact** – probability your study will be successful and will exert a powerful sustained influence on the field
  1. If it won’t work, it has no impact, even with high significance
  2. Address the immediate problem AND your long-term goals

Your first paragraph should define the problem and the critical need and the gaps in knowledge. This is a short background that leads up to the stated problem. Then you put your proposed solution to the problem that’s stated in the gap by proposing a hypothesis-based solution.

Then your aims, these are the objectives that test your hypothesis. You are going to measure something. You are going to develop something. You are going to identify something. A lot of investigators when they first start out write aims and say, “We will explore. We will investigate. We will study.” These are not specific enough. You have to have an aim that’s very, very testable in the time frame and it’s very important
that these aims are spot on in terms of what you are going to do and that it is doable. Probably 95% are too broad and they’re not specific enough and they are not doable.

Then your expected outcomes. “We expect to find.” “This is what we would expect.” Then impact, the probability that your study will be successful and exert a powerful sustained influence on the field. If it won’t work, it won’t have any impact even if it has a high significance. It may be a very important thing to study but if it doesn’t work, you don’t get data. It really probably doesn’t have the impact.

Then in your aims page you should address the immediate problem that you have stated and your more long range or long-term goals, so what are you looking at beyond this. Because this is an R21, you’re going to be looking obviously beyond this. You’re going to go for 2 years and then what is the continuum of a research that you envisioned, that’s very important to state on this page.

**R21 Research Strategy**

Here we go. This is section 3; Significance, Innovation, and Approach. The Approach now includes the preliminary data, the preliminary studies. A lot of investigators still don’t understand that. It goes under C, Approach. Why is this work important to human health and disease? Again, this is for human health and disease. This is the NIH, not the NSF or the DOD or any other. The purpose of these grants is to improve human health and disease.

**Significance**

Here are the 3 NIH stated requirements:

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

In a sense, that third bullet is actually the impact, that’s part of the significance. That is really the question
you need to answer very clearly and write up on your aims page as well as in this section on significance. That’s extremely important. The NIH is going to give you $275,000 for a 2-year project, and they want to know if this is really an important problem to study, and will it drive the field forward.

My recommendation on this is to really make a compelling case. “Why is this research important for the fields, maybe broadly and more specifically?” This can be a review of published or unpublished work, including your own. Then you want to show how your work will fill knowledge gaps, that you are aware of the opportunities, the gaps or roadblocks, and the research being done.

The third thing is that if possible, you want to try and tie the significance of your work to the mission of the NIH at that institute. This is very important, if you look at the institute websites, study it and look for what their objectives are, what their mission is. They will all be in different places. This is the frustrating aspect of the NIH because all the websites are different for each of the institutes, but what are their missions? A lot of them will be very detailed. The NCI has a section called provocative questions, 5 provocative questions they want answered. Find some commonality between what you’re doing and maybe the broad mission of the NIH institutes and state that right up front in the significance. You say, “Our research addresses two central missions of the NIAID namely, A and B.”

The other thing you want to do is check the institute’s program announcements and request for applications. This will give you an idea of what they are interested in funding. The other thing you want to check is the NIH RePORTER (see http://www.projectreporter.nih.gov). There you can do searches by peer review panels. You can do searches by PI. You can do Boolean searches for different areas of research for different mechanisms, and you can find out what the NIH is funding in certain areas. That’s a very powerful thing.

**Innovation**

This section is extremely important for the R21. “How is this work novel?” The NIH wants to know 3 things:

• Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
• Describe any novel theoretical concepts, approaches or methodologies, instrumentation or intervention(s) to be developed or used, and any advantage over existing methodologies, instrumentation or intervention(s).
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation or interventions.

First, explain how you are challenging in seeking to shift current research or clinical practice paradigms; “how are things done now; how are you going to do that; and why is it better than how it’s being done now?”

Second, describe novel concepts, approaches, methods, instruments, interventions that you will develop and/or use, and any advantage over existing methods, instrumentation or intervention. That’s extremely important to put in there. How are your methods or instrumentation going to be better? How are they going to serve research?

Then, third, what are the refinements, improvements, or new applications of concepts, approaches, methods, instrumentation or interventions that you’re going to use, so any refinements. It’s important in an R21 to really clearly understand what innovation means because I will tell you reviewers have the hardest time with this section. This is something you really need to think about when you’re writing an R21 because they are looking for innovative approaches.

Your research doesn’t necessarily have to create a brand new paradigm or a brand new method, but it can shift the current paradigm, offer a new combination of known methods leading to a new perspective or refine an existing model or technology. For example, you might be looking at compounds, new antibiotic compounds, that will kill methicillin-resistant Staph aureus, MSRA, which is a very deadly thing. Actually, this example is from a grant that I helped to write. You are thinking, “I want to look at 5 labs.” I’ve got 5 labs lined up across the United States. One of them is looking at medicinal chemistry. In other words, they are actually creating molecules that we think will be very, very toxic to this deadly disease and there’s a medicinal chemistry lab.

There’s another one that’s looking at PK and PD analysis; pharmacokinetics, pharmacodynamics. It looks at that in animal models. There’s another with an in vitro testing that uses certain assays in a laboratory setting with MSRA in place and it does some initial in vitro testing. Then there’s another lab that does in vivo testing in rats and mice. Then there’s another lab that is looking at this in hospital settings for some pilot data in early clinical design.

Each of those labs have been operating for many years. They published tons of papers that got grants.
They have existing methodologies that work beautifully and it’s a very, very doable system. The key is nobody has ever looked at developing compounds in this way with those 5 types of approaches looking at a molecule and passing it back and forth, with better pharmacokinetics, trying to make it more potent to increase the killing capacity and increase the safety. They want to make it more efficacious and less toxic.

There is an application that showed how they are going to move a compound from one lab to the other and that was extremely novel. That was a combination of known methods. That’s another way of looking at innovation. It doesn’t have to be brand new or create a brand new way of doing something in of itself. It was a very doable study in terms of the methodologies but very unique in the way it suits design, so the design may be very innovative.

**Approach**

Your approach section is really the major part of your grant and really is “what I’ve already found in my preliminary studies,” and “how will I accomplish my specific aims.”

Preliminary studies go in 2c. Approach. For each aim, describe not only your research approach but what preliminary studies you have, or include all your data in one section.

This is what the NIH wants to know:

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project.
- How will data be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate?
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high-risk aspects of the proposed work.
They want you to describe by aim. “What is your strategy, method and analyses that you will use to accomplish your research and answer the aims;” “how will you collect, analyze and interpret the data as well as any resource sharing plans if that’s appropriate;” and then “what potential problems do you anticipate and what are the alternative strategies that you will use to overcome those problems and what are your benchmarks for success?”

If your project is in the early stages of development, and R21s by nature are; you need to describe strategies to establish feasibility and address management of high-risk aspects of the work. You have to convince the reviewer you can do it and you convince them in a couple of ways.

One is preliminary data, you’ve done some of this work already, and the other way is using consultants and co-investigators that have expertise in the areas that you don’t or can strengthen. If there’s any question where they say, “Gee, this is really a significant study. It has huge potential impact. I just don’t think they’re going to get there. It’s early in the stages of its development. They haven’t done a lot of work, it’s just too risky. We can’t fund this.” That’s unfortunate.

On your approach, you want to look at your preliminary data and also the study design. This is very important for an R21 because you want to look at overarching, overall design. “What is your strategy?” and then “what are your experiments that you will do to address each aim?” Again, in an R21, as opposed to an R01, you don’t need as much methodological detail but you do need to show how you are going to get there. You want to emphasize anything that’s unique but you can abbreviate standard methods especially if they are used in preliminary studies.

For methods that were not previously used, or that you haven’t done, collaborators are necessary. I would say in an R21 it’s good to use tables and figures to illustrate perhaps your approach. Complex experiments that might have multiple arms or repetitions under different conditions would be helpful to have a figure or a table. Then even if the experiment is well designed, you must show that you can interpret the data, what it means, and that should be linked back to your specific aims and hypothesis. You have to have in there a section on interpretation of results.

Your Overall Impact Score

When you get a score in each of the 5 review criteria given a 1 to a 9, most of the time their given score
is like 2, 3, 4, or something in there, rarely do you see a lot of 1s. You do see occasionally 1s. You might see 1s for an investigator and/or environment, but the approach, innovation and significance are really where it’s important. Essentially, all those 5 review criteria boil down to this: “Why is my research important or significant to human health and human disease, plus can I do it and am I qualified to do it, and plus will it have a significant impact on the field?” The two things that are important in there are “why is it important to study and will it have impact?” In an R21, the other thing, again they look at is “is this novel?”, “are you doing something that’s really ground breaking, exploratory or new that hasn’t been done before?”

In an R21 proposal, your score will not be the arithmetical means of those scores on the 5 review criteria.

**An Outstanding R21 Proposal**

An outstanding proposal depends on what institute it’s coming from and what their pay lines are, etcetera. All the study sections do is triage your grant, either they don’t give you a score and they just triage it or they score it and give you comments. If your score, say, a 30 or 28, which is pretty reasonably good, but the pay lines are being paid for and only in scores below, say, 25 then you’re not going to get funded unfortunately. The pay lines could be very low and as you know there’s a lot of competition and unfortunately not a lot of money going to the NIH.

The outstanding proposal has the following: it follows the RFA that you might apply for, showing how the work will achieve specific program goals. It has exploratory and novel insights into a clearly important problem with a large payoff. It has writing that clearly highlights the innovation and impact of the work. Then it has convincing data that shows you could understand the methods, that they’re feasible, that what you’re doing is feasible and there’s knowledge in the field. Lastly, then, in general I would just say it’s neat, it’s organized, and it’s easy to read. It should look really easy to read. You shouldn’t have to turn the page and see blocks and blocks of text.
Could you go over the biggest difference between an R21 and an R03 please?

Dr. Dant: The R03 by nature is entitled to a small grant program. First of all, the big difference is the R03 only pays up to 50,000 per year. They only take new applications, and the R03 is really for pilot or feasibility studies, it might be secondary analysis of existing data that you already have so they’re small self-contained research projects. You might develop a research methodology in a 2-year period. You might develop new research technologies. It does not require preliminary data. The R03 is one of the grant mechanisms that does not truly require preliminary data.

It’s different from the R21 in that the R21 is really for research that is looking at doing something developmental or exploratory and it’s in the early stages of development. So, ”if it’s in early stages, then why would I have preliminary data?” That’s why they say you don’t need it, but you do have to have something there if you really want to have a chance to get a good score. The R21 does involve considerable risk, the R03 doesn’t. The R21 supports developing novel techniques, agent’s methods as I said. It breaks new ground, extends previous discoveries.

The other big difference is the R03 is not a very widespread program of the NIH. There were very few institutes that offer the R03. You don’t see many if any request for applications for R03s, most are R21s and R01s. I would say if you just want to do a short, small feasibility study to gather preliminary data, R03 would be an adequate thing. Again, there are only certain institutes that offer it and will take it. If you go to grant mechanisms of the NIH and look at the R03 RFA, the parent announcement, it will show you which institutes support it. I don’t off hand remember, but it’s only maybe 4 or 5 of the 21 institutes so it’s very limited. A lot of people don’t feel it is a very useful mechanism but it is if you’re collecting some preliminary or pilot data.

How many aims should I have for my R21?

Dr. Dant: Of course, there is no perfect answer for that is there? You have two years to do the work, I think that’s the key. There are certain people who say, “Oh, you should have 1 aim per year.” That’s a ridiculous point. I would say that certainly no more than 2 aims and I’ve seen some R21s with just 1 aim. The other thing that is important here is you don’t want to try and put in sub-aims. When you say Aim 1 and then you say
sub-aim 1A, 1B, 1C, it gives the reviewers the impression that you aren’t very focused and it’s way to overly ambitious.

I would say a good thing to do, and I really suggest all investigators do this, is when they write their aims page, generally that aims page will be revised once you go back after you’ve written your research strategy because a lot of investigators say, “Gee, I don’t think I can get there from here now that I’ve tried to write some of the detail.” One of the ways to look at it, and bigger grants require this, and I recommend you do it but you don’t include it in your grant, you might include it in an R01, is to put a milestone chart in there and your milestones are not aim 1 or aim 2. Your milestones are discrete, measurable objectives that you reach in pursuit of that aim. You should sit down, and investigators have a hard time doing this, but write out what you need to do. “What milestones do you need to reach to get to that aim?” Then look at how long you think it’s going to take you to do that. A lot of milestone charts will show by month, maybe 24 months or whatever, they’ll show how long they think it will take to get there when they think they can accomplish it.

A lot of program project grants, or U mechanisms, or NIH cooperative agreements, require this in their grant. What that does is it reverse engineers your R21 grant and you can start looking at, “Here are the milestones. This is too ambitious. I need to narrow my scope.” Again, the number of aims is not probably the right question. It’s like “what is the scope of your work?” “Are the aims specific enough and can you obtain the data in two years?” If you already have preliminary data and you’ve done some of this work, you should be able to answer that.

Is it usual and/or allowed for PI’s to seek funding from more than two centers? If all mission statements from all 3 are aligned with your population, age, demography and clinical issues, is it acceptable to request funds in your cover letter from 3 of them, say, the NIMH, the NIA, and the NINR?

Dr. Dant: First of all, when you write your cover letter you can say, “We believe that this research answers the central missions of two of the NIH institutes, namely the National Institutes of Mental Health and the National Institutes of Neurological Diseases and Stroke.”

What institute it’s sent to is not necessarily up to you, but I think before you get to that point what you need to do is to call the program officer at the institute you’re thinking and say, “Here’s my research. Let me email
you my aims page.” “This is what we’re thinking of doing. What do you think in terms of how this would be aligned with the NIMH’s mission or do you think it’s more appropriate for the National Institute of Neurological Diseases and Stroke or whatever the other institute?”

It would be pretty hard for me to imagine any research that would align to more than 2 or 3 actual institutes because they’re fairly discrete. First of all, the overall mission of some institutes is very broad. When I say mission I mean, what are their objectives, what are the research objectives, what kinds of areas are they most interested in studying?

If you look at the National Institute of General Medical Sciences, it’s all over the board. That’s actually a very good one if you’re not sure where to go because that really funds a lot of very basic research that can be translatable. I would say the best thing to do is call the program officer and discuss it at the institute.

I don’t believe that you should be writing a letter saying, “This covers several institutes,” because it sounds like you really don’t know what the purpose of your own research is and I think that’s important to target.

For example, you’re looking at mechanisms of gliomas in children and this is a terrible brain cancer, and you’re looking for ways of understanding the mechanisms to develop targeted therapies, the NCI might be very interested in that, the National Cancer Institute, because it’s a cancer but also the National Institute of Neurological Diseases and Stroke are very interested in that because it’s a neurological disease. In fact, one of their missions is to study brain cancer.

By the way, the Shriver National Institute of Childhood and Human Development, the NICHD, is also interested in childhood diseases. The specific thing that you’re looking at really should be targeted to only one of those things and you have to find out what it is, where is it most likely that they will be interested. You do that by talking to the officer. You do that by going on NIH RePORTER (see http://www.projectreporter.nih.gov/) and looking at what they’re already funded in those, say, in the various review panels or the various institutes. You look at their RFAs and PAs as well as their missions. If you do a lot of that up front work, you’ll answer a lot of those questions.
Dr. Dorothy Lewis, Professor of Internal Medicine and Infectious Diseases at the University of Texas Health Science Center, has a 25-year history of writing grant applications including vast experience with the new scoring system. Her successful track record for winning grants has given her a valuable “in the trenches” perspective that can benefit you, at whichever stage you find yourself. She received her PhD in Microbiology in 1978 from the University of Arizona in Tucson. She then pursued an NIH-supported postdoctoral fellowship at the University of New Mexico School of Medicine in Albuquerque. In 1985, she published her first paper related to T-cell subset changes in HIV patients and acquired her own independent NIH funding. She has maintained continuous NIH funding since 1985, experiencing both times of multiple grants and times of reduced funding. She is former chair of the AIDS Immunology and Pathogenesis study section (2009-2011).

The purpose of today’s webinar is to really give you an overview of the R01 process.

Getting Started

Okay so how do you get started? The first step really is to have a good idea or a good hypothesis to test. Without that, it’s really hard to write an R01 and not only that but the research should be important to do and fill a gap in the understanding of the topic. So you have to have a reason to get started. In addition, you have to think that you and your team are the best ones to do the work. You have the tools to do the work. You have the expertise to do the work. And then you have to think about the approaches for each of the aims that you’re going to generate. And it must be doable, possible to do and when you do them and get results, those results should be meaningful so that you can find out where the research is headed. Finally the most important thing before you get started is that the work that you propose is going to have high impact or else it doesn’t really have a good chance of getting funded.
So another key thing is to allow sufficient time. This is two to three months. Most of us don’t have that kind of time nor do we allow enough I think. But really the whole process takes a while to do and the key thing is not just writing it. It’s the thinking about it. You know, what’s the best strategy to do this? What do I really want to test? What do I really want to know? And another key thing is try not to wait until the last minute. A lot of us are procrastinators.

If you can create a schedule, and follow it… Easy to say, harder to do… And then also, I think it’s really important to work on it but then know when to step back from it to take a break because if you don’t do that, then your mind doesn’t have any time to kind of wander. Usually what it needs to do is wander a bit in order to make it success of it.

**Is the R01 Mechanism Right for You?**

So the first thing you really need to consider is whether or not the R01 mechanism is really right for you. Is this the best place for your research? First of all, just some details about that, you need an advanced degree and an institution that has resources that support research and you should have a position at that research institution that’s beyond a postdoctoral fellowship or beyond a fellowship. It should be that you are actually a faculty member at the institution.

Then second of all, you need preliminary data or papers published related to the topic. Really without that it’s hard to get going on an R01. It’s hard to think that you’re going to be funded. And then you need a longer period of time, an R01 is just destined to be a longer period of time, three to five years. And because of that time frame, there’s going to be a bigger budget to accomplish the work that you want to accomplish.

**TIP 1: Determine if the Work is Hot!**

The key thing here is determine whether or not your work is hot. What I mean is, “is the research hot?” “Is that really something that’s at the forefront of things?” It really increases your chances of funding if this is a hot topic. Truth be told, much of the science that’s done is done in kind of waves and so it’s important for you to place your work into context. The first tip is trying to determine if what you’re doing is a hot area that NIH is interested in supporting.
The way I would do this is look for similar papers that go along with your own papers. Look for similar grants. The key thing here is to find a niche where there’s not that much information known about the topic and you would consider yourself at the forefront of accomplishing, of pushing the edge if you will. That’s what I mean by hot, hot, hot!

**TIP 2: Rules, Rules, Rules**

You need to pay attention to the format of the grant. This has to do with length and the length of an R01 these days is a page for specific aims and 12 pages for all the rest. And then you need to pay attention to whether or not you’re going to use human subjects. You need to document that. You need to document the vertebrate animals and the budget. All of those you have to follow rules.

So the way to do this is to consult with your administration people as to their requirements and deadlines. Every institution is going to have different ways of doing this but you need to contact them and make sure that you understand what their process is. Usually, once you finish a grant, it really takes weeks for the institution to get it into stages where they want to see it so that’s another reason why it takes 2 or 3 months to do this. It’s hard to do it, write a grant, write an R01 on a short time frame.

So pay attention to the format. You need to pay attention also to the font and to the margins. Some of the key features of grants that get noticed or graded, you’re graded on this, “is this a hot hypothesis about a hot area.” You have believable data. You have papers to go with that, that’s actually a key. And then how good a scientist you are. Your way to tell the story and sell the story that you’re going to tell. And then of course the all-important impact that the work will have. And then the approaches that you will take to get to that impact. All of these are important things that will get your grants noticed, and you are graded on these things.

**TIP 3: Make Specific Aims Count**

Make your specific aims count. These aims are kind of a first place in a page where you can tell the reader why it’s important to do, and in a nutshell what your approaches are. These are the things you are going to accomplish with these approaches. So the aims that you write whether they be 2 to 4 aims, they should relate to each other but not depend on one another. And what I mean by that is, you don’t want Aim 1 to have to get an answer before you do Aim 2. If you do, then that’s a problem because what if Aim 1 does not work, well then, you’re not going to do Aim 2. So you have to have them related but not dependent, so related around
the seams. So each one of the aims that you propose should be done regardless of the others. So even if Aim 1 turned out that it might not be true or you got different results, you would still do Aim 2 because it’s related to Aim 1 but it’s not dependent on Aim 1.

And then what I like to do is have data for each aim that I present. And that just shows the reader that I have thought about it sufficiently so that I’ve generated data in support of my aims. Aims can be more imaginative. Maybe you have less data, more out on a limb in the third aim. So the idea that the reader gets is, okay aims 1 and 2 are really likely to be accomplished and are going to have impact. The third aim is more risky but it’s very imaginative and if it works, it will be great. So I always try to put something like that in a grant because I think that helps sell it.

Now the specific aims are only a page but they must contain your central ideas and the overall plan. So what you want to do is set up the work sufficiently so that the reader can understand what the aims are about. And here’s what you don’t do. You don’t take that opening paragraph and use the same paragraph in your background and significance. That’s cutting and pasting and that’s just lazy on your part. This beginning paragraph should say enough that the reader knows what you want to do and why you want to do it and why it’s important to do. Making these aims really requires honing. Most of us just can’t spit it out. It requires time to go back, go over and back and forth. You might even have to revisit the aims after you do your approaches.

So the way I like to write specific aims. There’s a number of ways to do this, that’s not the only way to do it. Just me, I like to say ‘specific aim will test the hypothesis that’. A lot of people write ‘specific aim one will determine…’ But I like to put my hypothesis right up front. And because I always take a stand on my hypothesis, then the reader knows exactly what I think and what I expect to get in that aim.

So the basic strategy is given in each aim. So “I’m going to test the hypothesis that something happens using flow cytometry,” whatever. So you give them a little bit of detail about how you’re going to do it but not detail that you would in an approach section. Just so that the reader has a flavor of how you are going to do each of the aims.

**TIP 4: Impact, Impact, Impact**

This would have to do with making sure that your application has impact. And here is where you need
to tell the reader why the work is important to do, why are you the one to do the work, what the results will mean and put this in the context of not just “you’re going to find these results out,” but the big picture, “what it will mean for human health, how it will allow you to go forward and develop a cure, how it will allow you to understand the development of some disease.” So the reader needs to know that. The reader can’t judge it in a vacuum because what you’re looking for and what the new system has given us is the key thing that the research that you do is going to have impact, that’s the key thing.

So impact, it’s important to remember, is not significance. That’s confusing but it’s not. Impact means that if you do the work with the approaches that you’re going to use, the results will have great meaning. They’ll be shape shifting, they’ll change the way we do things, they’ll change our understanding. The significance is whether the work is important to do at all. So what I mean is, it’s important to work on something like Type 1 Diabetes to understand how it develops and that’s of great significance but if you propose something that in your approaches it indicates that your direction forward is not going to work, then even though it’s a significant problem to go after, the work might not have significance. I hope that’s clear because it’s confusing. So you’re trying to build a case for significance but only through the way you go about doing the work will it actually have impact.

**TIP 5: Highlight Eureka!**

I found it. You need to point out how innovative the work actually is. There are several ways to do this. In a separate section in the background and significance area and the research strategy area, you actually say “innovation” and then you tell the reader why the work you propose is innovative. You do this here and then you have a personal statement in the biosketch. You could also do it there. So you have in that personal statement, you’re going to point out your credentials but you’re also going to say ‘this grant does…’, ‘I propose this…’ and ‘it’s innovative because this…’. And it doesn’t hurt because lots of people that will review the grant, even if they’re not one of the three reviewers, they will look at your biosketch so why not have the innovation there pointed out because you have enough space to do that. And then at the end of the grant, you really need to point out both the impact and the innovation. Why is this innovative strategy, innovative thought process, whatever, you need to point it out wherever you can. Because this is actually a very hard thing for reviewers to foresee so it doesn’t hurt for you to actually tell them this. It’s really hard for most reviewers to judge this so take the initiative and I’ve given you three places where you can do it. Tell the reader why the work is innovative, okay? So make sure this comes across because it’s an important aspect upon which a grant is judged.
The approaches are really one of the most important parts of the grant because you can have a great idea of high significance. It can be innovative, but if you go down to the point where you’re going to have actually strategies to perform each aim, that’s where you can fall down. That’s actually where I have my greatest weaknesses usually. So approaches actually will determine your final score.

Make sure that your approaches answer questions and are not just experiments. And what I mean by this is you can mention the five experiments you’re going to do, but unless you tie them into your specific aims and the hypothesis that you’re testing, they come across sounding just like experiments. So in your approaches you should make the readers see how you’re thinking about the problem, how are you going to solve that specific aim. And usually there’s 3 to 4, 3 to 5 kind of experimental approaches to solving each aim, not experiments.

And then the way I like to do it is to follow rules of presentation and the rules I use is, first of all, I introduce my aim with a rationale. And the rationale means, based on my aims, my hypothesis is this. So the reason I want to test it this way as my rationale and I spell that out. Make the reader see your mind. Then you say what the experiments are: Experiment 1, Experiment 2, Experiment 3, whatever and then the expectations. So what do you expect to find in each of those experiments? And then for each of the experiments that you’re going to run for that aim, you need alternative approaches or pitfalls. So that’s the kind of presentation style that I prefer because then the reader looks at the way you’ve written it and understand that your mind is organized. You know, you can see how the work is going and you can see into the future so that even if your expectations turn out to be wrong, you’ve thought of alternative ideas about the work that you’re going to do.

So make sure that reader sees how you’re thinking that’s really critical and really hard to do. Most of us have trouble showing another person how we think. I personally find it much easier to do that when I’m talking to somebody in person. It’s much harder for me to write that out.

I don’t think you need to spell out the methods in great detail but in generalities. Rather the most important thing in approaches is the strategy, and why you want to do it, and why the strategy will give you the answers that will go with that aim. So you look ahead and make the reader know that you will be able to interpret the experiment planned. And actually part of this process is, in the preliminary data, you have shown the reader that you know how to interpret your own data. And so that’s an important part of convincing the
reader that your approaches are going to be strong. Let the reader see your mind. It’s the hardest thing to do but actually the most important aspect of this.

**TIP 6: Highlight Your Credentials**

Make sure that your credentials are highlighted. Use the personal statement to point what you have done that makes you perfect for the work that you propose. List the papers that support the work in the grant. So if you published a couple of papers and now you want to move forward with this new grant, make sure that the reader knows that Paper 1 and Paper 2 directly relate to what you’re proposing or that your preliminary data, part of what’s in Paper 1, Paper 2. That’s really important.

In a personal statement, here’s your chance to really get the reviewer on board. So remember that each grant that you write needs a different one that’s customized, that’s tailored to the grant proposal that you’re writing. So in addition, if you have other key personnel on the grant, you need their biosketches, correct? So each one of those needs a different one. Don’t use a standardize one. What that looks like is, it looks like you have not paid attention to this. That you don’t think the reader’s going to read this. It could indicate laziness on your part. So make sure, especially for each person on the grant that’s listed as a key personnel, has a different one so make sure that that’s done.

And then now, NIH wants you to cite a PMCID number. The number that you get from PubMed that’s called the PMID, that’s not the one they want. What they want is the publication information that has been submitted to the NIH website and you can actually find that out by using a PMID to PMCID converter.

**TIP 7: Data, Data, Data**

A key thing as I mentioned even for the approaches section is data, data, data. A key thing is that if you show the data, in support of your aims, it must be believable. I can’t tell you how many grants get shot down because of this. And one of the reasons they might not believe it is, it’s not big enough to read. So you need to make the information that you use, in support of the work that you propose readable. So remember, a lot of grant reviewers, they are past 40 and their eyes have changed so they need to see bigger letters. And so remember that the font is Arial 11. So you really shouldn’t go below that and especially in the legend areas where a grant reviewer will read the legend and every figure needs to have a legend. If you don’t put the
legend in, then the reader can’t interpret what you’ve done. So it’s just laziness on your part. So don’t make the reader work.

And then what I like to do is of course, each piece of data should stand alone just like in a poster. I like to have a title. I like to have a legend with basic details and then I like to have conclusions or interpretations of that data just like you would in a poster. And if you don’t do that, then the reader thinks maybe you don’t understand. So always interpret the data. Don’t leave it to the reader to interpret the data. And this is the biggest mistake made by both new and old investigators. That everything else can be okay. But if the reviewer actually looks at your data and they don’t believe it, it’s like a fatal flaw. It’s going to shoot down the work that you propose.

So if you don’t interpret the data, here’s what the reader thinks. “You don’t know what the data means. If you don’t know what your own data means, how am I going to trust you to go forward with the next five years of funding.” So you need to interpret the data for the reader and you need to make sure that the reader is on your side in that interpretation. And part of that is the reader can actually see the data.

Another thing that the reader might think is that you’re just too lazy. I mean you just don’t have time, you put it together in such a short amount of time that you don’t have the time or the space to tell the reader.

And then another thing which is evil, that the reader thinks, “well, your mind is just, you know, it skips over these types of details and that’s indicative of what might happen with the rest of the grant that you wouldn’t pay attention if you got the money.” So all of that, when they look at your data makes the reader really weary of the rest of the grant. So I think it’s really important in your preliminary data to do a good job.

**TIP 8: Writing Style Matters**

So Tip 8. Your writing style really matters. I can’t tell you how many times I’ve heard reviewers say, “oh the reading, this is so hard, it was so dense I had to skip around different places to find out what they meant…da…da…da…da.” So this behooves you to try to use words sparingly. What I always try to do once a year is go over that tiny book Elements of Style. So this allows me to think again about how I use words and the brevity and conciseness of words.

In addition, it emphasizes what I want to do is use action words. So verbs that purport something being
done. This makes you sound more proactive. At the same time, you need to be succinct and you can’t be too flowery. I just edited a fellow’s personal statement and it started out being five pages long and it had all these extraneous stuff and that flowery language, and I even find flowery language in novels, sort of, over the top so I edited it. I have edited it and then I gave it back to him and he edited it again and he cut 3 and a half pages out.

So what I like to tell people to do is to channel Mark Twain, my letter would have been shorter but I ran out of time. So the more you go over something, the shorter you can make it because the more concise and to the point you can be.

So you need to go over and over the grant. Think about different ways to say the information. Sometimes at the end of the grant, you’re over the 12 page limit so you need to reduce it so I’ve become pretty good at wordsmithing and saying the same things in different ways with shorter language.

Make it an active style and avoid the passive voice. So what’s the active voice? Active style emphasizes the performer of the operation. So it goes performer- verb-receiver, performer-verb-receiver. ‘We have analyzed the results’, not the passive voice which is ‘The results were analyzed by us’. You see the former is much more forward thinking it. The words make you think forward. The passive voice emphasizes the receiver of the action. Thus the receiver, verb and performer. You want to flip it the other way around and this is something that’s emphasized in Elements of Style.

So here’s what can happen in the awkward passive voice. You can sound like your hedging. That’s when the receiver of an action is an ‘it’ and we all do this. ‘It is concluded that squirrels hide nuts in pots’. Why not just ‘Squirrels hide nuts in pots’. That’s what they do. So the whole ‘it is concluded’ is just not a good thing to, it’s not the most efficient way to say something. You don’t need that first part of that sentence. And so if you are short on words, you could reduce that sentence by 40% just by taking out that superfluous stuff at the beginning which makes you sound like you’re hedging anyway.

Another thing is dangling. So you put a verb at the end of the sentence instead of declare a verb and then…Okay so instead of saying ‘To investigate mechanisms, cells were compared’, you say, ‘to investigate mechanisms, we compared cells’. Okay, so that’s putting the verbs before the… what you’re comparing of so try to avoid the awkward passive sense.
So here’s a brilliant example from 1953, it starts, ‘We wish to suggest a structure for the salt of dioxynucleic acid’. It’s just straight to the point and you get the meaning right away. It’s a hypothesis still but there’s a structure and it’s a salt of DNA. Well what if you said instead: In this paper, a structure is suggested for salt of DNA. Doesn’t that sound kind of weak? Doesn’t the first sentence sound better? Which one sounds like a better sell? This actually is the opening sentence of the Watson and Crick’s Classic Paper. ‘We wish to suggest a structure for the salt of DNA’. In this paper, a structure is suggested’. Oh that’s weak. That’s passive.

**TIP 9: Special Considerations**

So Tip 9, the special considerations. These are things that you need to do in order to finish the grant that are sort of outside the specific aims and the research strategy but still need to be done. That is, if on that front page, you say that you are using humans or animals in the work, you need to attend to that with special documents that you upload when you submit the grant. You must have a description of that.

So for human work, you absolutely need an enrollment table. This means you know how many people you will use for whatever you got to do. For the mouse work, you need to tell the reader how many animals you will use and their purpose. You relate it to the experiments that you propose. So you need to pay attention to this because your grant can get downgraded based on not doing this.

You must also tell the reader if the work involves select agents. And there’s a website to look at whether or not the agents you’re going to work on is a select agent. In addition, if there’s bio hazardous material to be used or generated, you need to tell the reader about the precautions that are going to be taken to use that material. That needs to be spelled out in the document.

Now, all the special considerations are not part of the page numbers. They’re extraneous. They’re considered separate documents and they’re not part of the 12-page limit. So you also might need a data sharing plan. Usually this is how you will disseminate the information. And usually that’s writing papers or maybe you’re going to generate some G-sequences. You need to say that they’ll go into this data bank, stuff like that, which you need to share with the world. This actually is much more applicable for larger grants where there are more players but it is something that you might have to consider in your grant.
**TIP 10: Go Over, Then Let It Go**

You need to go over the grant again and then let it go. Go back over the grant until you have a good gestalt about it and then it’s really a good idea to have others read it. When others give me something to read, what I like to have is the whole thing to read so I can see how everything really relates. I can see the big picture of it and then I like to have enough time to respond to the feedback that I give. It’s really good to give feedback and if you give it to a colleague and you get that feedback, especially if their critiques are helpful, it can really make a difference in how your grant comes off.

So that’s another reason why you need to give yourselves enough time to actually change the grant. If the grant is due on Friday and you give a colleague it Monday, unless they are somebody like me that reads fast, it’s not going to be enough time for most friends to get it back to you with any kind of reasonable suggestions. So that’s why you need really to think about this as a 2 or 3 month project.

So go over it again. I emphasize this is really why you need a lot of time to do this. And not many of us can keep going on one thing for weeks or months because we have other things to do right? We teach or we’re trying to run the lab at the same time and we have meetings to go to, etcetera. But also, it’s not just the other things you do, you need some time to get away from it. And that allows you to see it in a new light. And you need that kind of downtime. If you are pressed for time, you won’t have the time you need to kind of ruminate about it as you’re writing it. So that’s another reason to get started early and to give yourself enough time.

And then, the advice I would give you is to psyche yourself up. If you really care about this work, you think you have good ideas and you have good ways to accomplish those ideas, then this is a perfect opportunity that you’re going to put all that down on paper and you’re going to make a product. You know like this is your, almost like having a child. This is the product of your intellect is coming out on the paper.

Make sure you put your work or your ideas in the context with the field that you’re in. That’s why if you think of it as “I’m spending time thinking about the field and how I fit into it,” that’s a good thing to look at it. My philosophy on life is that all learning that you do has payoffs. It might not be intermediate. I mean, you’ll never know when you’re going to need something but eventually you might. And I can give you an example.
In the 90s I wrote a big chapter on tissues and cells of the immune system. Well, in the writing of that I learned a lot about tissues that I didn’t know before. Well, then years later, that information pays off because I have an understanding of lymph nodes and where they are in position to fat which is something I’m working on right now. So the big picture is, I think that no matter when you do this work of synthesis that eventually it will pay off.

Also, finally give yourself a break. When your grant is submitted, get away from it awhile. This will actually help you deal a lot with the critique when you get it back. If you get away from it awhile and then come back to it say in a month and reread it, then you can identify where it’s good and where it’s bad. So that when you get the critique, you’re not so shocked, maybe, maybe not. That’s kind of what I do. These are places where people could criticize it. I never, never expect to be funded the first time. It just really doesn’t happen. It’s just a rare thing. And don’t be intimidated. Keep your eyes on the thing that you really want. You want to do this work because you have good ideas and you need to get this money to do the work. Just hang in there. Give yourself a break.
Q&A

What if you are not certain that the work will have impact or is innovative?

Dr. Lewis: We all have doubts about what we do but I think that if you spend the time, the 2 or 3 months thinking about your own work and how you want to carry it forward, many of those doubts will go away. And the key thing in the grant is to come up with an innovative angle. Sometimes grants are not necessarily innovative in the topic but they’re innovative in the way you think about the topic or you’re putting X with Y together, nobody’s done that.

So think of innovative ways to say things so that the reader will think that what you’re doing is important to do. Now, one of the hardest things for us to know is whether or not what we’re going to do has impact or will have impact but I think if you don’t have that confidence, it’s hard to sell it to another person. And if you talk to somebody in person, it’s hard if you don’t have the confidence in what you’re saying, it’s hard for that to come across, the same way with your writing. So I think you need to get yourself into a place where you feel confident that the work that you propose is going to have an impact. If you’re not there yet, maybe you need some more time before you submit.

I plan to use some new techniques that my lab hasn’t published before for the approaches section. How should I handle that?

Dr. Lewis: Well, it’s a tricky thing because if you haven’t published on something, it’s easy for the reviewers to say, “oh they don’t know how to do that.” I mean, how many times have I heard that. So there’s a couple of ways you could handle.

One, you could get a collaborator that has expertise in it and they could write you a letter and then something to the effect that they will help you with the strategy and they have the stuff working in their lab and the blah, blah, blah… An alternative to that is that you’re going to have to be in the section, in the approach section. You’re going to have to be a little bit more specific about the actual technique of doing something than you would ordinarily if it was something that you had published on. So two ways, you could get a collaborator. Second, you can have more detail in the strategy section. In addition, another thing you could do is do some experiments and have some preliminary data then it’s harder for the reviewer to say “oh they can’t do that.”
Writing a Winning R03 Proposal: Making a Powerful Impact with a Small Budget

Presented by Dorothy Lewis, PhD

MODERATOR:

Dr. Dorothy Lewis, Professor of Internal Medicine and Infectious Diseases at the University of Texas Health Science Center, has a 25-year history of writing grant applications including vast experience with the new scoring system. Her successful track record for winning grants has given her a valuable “in the trenches” perspective that can benefit you, at whichever stage you find yourself. She received her PhD in Microbiology in 1978 from the University of Arizona in Tucson. She then pursued an NIH-supported postdoctoral fellowship at the University of New Mexico School of Medicine in Albuquerque. In 1985, she published her first paper related to T-cell subset changes in HIV patients and acquired her own independent NIH funding. She has maintained continuous NIH funding since 1985, experiencing both times of multiple grants and times of reduced funding. She is former chair of the AIDS Immunology and Pathogenesis study section (2009-2011).

DR. LEWIS:

Today I’m going to talk about the R03 proposal.

R03’s: Brief and Focused

The key thing to remember with the R03 is that they’re very brief and very focused. They’re not so brief in the space. It’s still the six pages that you would get with the R21, but they are very focused and that is because they should have a limited scope because you really have a limited budget. So there’s only so much you can do with the money that you can get with this mechanism.

As Cicero said, brevity is a great charm of eloquence, and that’s what you need to think about most in terms of your writing, and in terms of the scope of the work. What I’d like you to think about is focusing.
So what are the criteria for deciding if the R03 is your best option? What you want to ask yourself is, “does the work involve a very focused project that requires little money, but is important to do and you can accomplish it in one or two years?” What you really need to convince yourself of, and then convince the reader, is that you can get significant data on this limited budget in that amount of time. And it’s difficult to do.

**R03 vs. R21**

If you’re going to compare the small funding mechanisms, you might want to think about comparing the R03 to the R21. The R03 is smaller and it’s a more focused idea. It’s less money even than the R21, although it’s the same amount of time, one to two years. But the key thing is that the R21 is for exploratory grants, really, not small projects. The money really is the main limitation of an R03. You’ll only get $50,000 per year. That’s it. And at least in my institution, that’s not much to pay a full-time person and buy supplies at the same time. I might be able to pay for an entry-level technician or maybe a little above that and supplies, but I wouldn’t be able to, on $50,000 a year, pay for a post doc, for example, and buy supplies.

What really determines whether or not the R03 is your mechanism is the scope of the work. That’s what really determines the choice. So I think it’s really important to keep in mind that the R03 is not a funding mechanism for new investigators. So you might think, “Well, I’m a new investigator. I’ll just go for a little bit of money.” It turns out that, as I said before, the choice is really the scope. It must be minimalistic and in point of fact, I think that if you are not an established investigator, you wouldn’t have the likelihood of getting funded by this mechanism. If you’re a new investigator, then you don’t have a piece of work that you could pull out and do for $50,000 a year usually.

So if it’s a very limited funding mechanism you have to kind of put yourself within the limits of the scope. And it’s not – keep in mind – the R03 is not a mechanism to fund what we call high-risk, high-reward science. That is the R21. So this R03 is not going to be something that’s kind of “pie in the sky type research.” It’s going to be something that’s really doable and focused. You’re going to get results. They’re much more focused. They’re not necessarily high-risk and probably the antithesis of high-risk, but they’re also worthy of doing. So you have to be able to convince somebody that you need this money to do the work and it will have some impact.
So the R03 can be a better approach and that’s, again, if there’s a limited scope in the budget. Say, you use more established procedures to get your end point. You might use the R03 to get innovative data for a future R01. In fact, that’s a really good way to sell it. Say, “I don’t have enough data in this project X and if I just had this little bit of money more, I’d be able to do one, two, three experiments and that would give me the data that I need to go forward for an R01.”

**Some NIH Institutes Don’t Fund R03s**

So keep in mind that actually the restrictions on the R03s are smaller than for R21. So some NIH institutes just don’t fund the R03s. Participating institutes are: NHGRI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIEHS, NIMH, NINDS, and NINR.

NIH institutes that do not participate are: FIC, NCATS, NCCAM, NCI, NEI, NHLBI, NIMHD, NCRR, NHLBI, NIAMS, NIDCR, NIDDK, NIGMS, NLM and ORIP.

Some of the non-participating institutes might fund R03s related to their own specific announcements. So they won’t participate in a general R03 announcement but they might have their own particular announcements. For example, the NCI funds a number of R03 mechanisms but only when they issue the announcement by themselves. The NIMHD does not use the R03 mechanism. So what you want to do is go and see if your research falls within the scope of one of these institutes because these are the ones that really take the general R03s.

**Scope of R03 Grants**

So what are the scopes of R03 grants? You want to do a pilot or feasibility study. I have a friend of mine that just got an R03 and what she wanted to do is, and she has some experiments in mice already, so she had some existing data and what she wanted to do was compare the existing data she had to a knockout of a gene of interest. So that’s clearly something she can write a whole grant for, but she convinced the study section that if she did these two years of experiments with this small amount of money, then that might lead to more money. So it’s kind of like a pilot study based on an idea that these knockout mice that she was going to use would give her some interesting data. So that’s how she sold it and she got funded.
Let’s say you have some nice existing data and maybe it’s 10 years old, but you really haven’t analyzed it in depth and that could be believable only because 10 years ago, maybe you got some microarray data or some data from a sophisticated analysis, except that you didn’t have the tools 10 years ago by using bioinformatics to actually analyze the data and now you do. So you could probably convince the study section that, “Gee, I have this great database I can mine, and now, I have a great tool with which to mine it. So I need the money in order to buy a computer and pay for a graduate assistant, etcetera, to do the work.” So that’d be an example of an R03, a small or self-contained research project.

So from my own experience, what I wanted to do was just this small study to develop a methodology that I could use to diagnose pre-eclampsia. It was very small, but if I got the markers working, then I could apply it to a bigger dataset and I could write an R01, etcetera. Or let’s say you actually have a research methodology that you think you can sell and it’s worthy of developing. You have the expertise to develop it and it will just require some expenditures, some technical help to get that research methodology up and going. That could be a technique; it could be an analysis technique to analyze existing data. So maybe you don’t just have the data but you have a method to analyze the data. That’s something that can be sold as an R03.

Next, then, let’s say you want to develop a new research technology. $50,000 is not a lot of money to do that. So it would have to be very limited in scope, but if you could think of something like that, a new technology that you could develop with a small amount of money, the R03 is a good choice.

**Examples of R03 Topics**

So what are some examples of topics? For example, you have a dataset that needs one or two years to analyze. You need to convince the study section that right now you don’t have any money to mine the data. You don’t have the time. You don’t have the computers. You need the money to pay somebody to help you analyze the data. Or let’s say you have a procedure like I described with my technique to look at pre-eclampsia. You have a procedure that you want to perfect and you need this procedure developed or you’re not going to be able to convince anybody that you can go forward with an R01. That’s a perfectly great R03 topic. You have to write it in a way that you can convince the readers that with the limited scope and budget, you can move forward. So, again, if you have a focused question that requires limited money to perform, that’s the kind of topic for an R03.
R03 Stipulations

So here are the stipulations. As I said, it’s a $100,000 direct for two years. The page limitations are the same as an R21, it’s six pages of the approach. It’s one page for the specific aims. About seven pages total. That’s not much room to make arguments. So you have to keep everything concise and focused. You don’t need a justification and you don’t need any data.

What? No data? Well, they say no data, but really the arguments that you’re going to make as to why you should do this R03 are going to be more persuasive if you have that data. But please don’t show data that’s weak or don’t show data that you don’t interpret because if you put it in, the reviewers can actually then judge it and use it against you to denigrate the grant.

Another caveat with the R03, just like the R21, is that they aren’t renewable. So typically, if you get an R01, you can keep going. You resubmit. You make a progress report and you go on to the next question or next hypothesis. But with an R03 or an R21, you’re expected to generate the interesting data, analyze the dataset, whatever. Then in order to continue, you’ll have to submit an R01 which then would have an expanded scope or it’s possible that after you analyze that data that needed to be analyzed in the two years, or you tested your hypothesis in a knockout mice that you’re at the end of work. The hypothesis didn’t pan out. So these grants, the R03 and the R21, are designed to be terminal. They’re designed to end.

So the R03 has page limits for a reason. You need to live within the six-page approach limit and it’s also really unwise to propose more experiments than it’s possible with the time or a budget. For two years, $50,000, you have to be very focused. It can’t be over-the-top, too many experiments. It’s probably what a half-time person can do in those two years. With the supply budget, just with the money you have, you’re limited.

How to Deal with Page Limits

So how to deal with the page limit? The research strategy is six pages. You have to get to the point early. So the aims, and set-up for them, needs to be concise. Say, that would be two pages max. I wouldn’t have any more than two aims. Maybe even one aim for an R21. If you have two aims, they should be interrelated but not dependent on another. So you don’t set that up to where Aim 1, you make a reagent and then you need that to do Aim 2. That won’t cut it.
Then you could have preliminary data as one to two pages or not and then that leaves two to three pages for approaches because you have about, six pages for the research strategy and you have one page for the specific aims.

**Submit a Former R01/R21 as an R03?**

Should you take a former R01 or R21 and resubmit it as R03? Actually, that is something that I just did because I had an R21 that I thought was high-risk, high-reward but there was a methodology in there that I needed to develop and it turns out I could do that for the small amount of money. So that might be the answer to get some preliminary data that has a finite goal. And here is the best of advice I could give you. You really need to ask the program officer what they think. So you need to have a relationship with them and if you’re a new investigator you won’t. So that puts you in the disadvantage with respect to this mechanism.

So you want to formulate your idea about what you do with the $50,000 per year for two years. It has to be finite, concrete, and ask the program officer if that’s something that he or she thinks would be worthy of going after. If you don’t have this buy-in, I think it’s a harder mountain to climb to get this funded.

So in my own experience, when you write a grant, any grant, it’s the approaches that make or break the grant. You need to have a finite outcome and the best advice is to spend most of your time and most of the space on approaches and that’s especially critical for an R03 because you’re asking for the money to do a finite series of experiments which you expect to have outcomes.

**What Sells a Grant?**

So what sells the grant? Really a good and significant idea, in this case, it’s going to be a finite idea. If you have a good strong preliminary data and actually for an R03, like I said, you don’t need that, you have rationale for doing the aims and design of approaches, and the questions you need to ask yourself are, “will you test the most important outcome and will the results be significant and definitive?” For an R03, these are especially important because they have a very focused direction and a very limited budget.

So keep in mind, the only prudence in life is concentration. And so, take a look at this picture. I’m afraid of heights so you wouldn’t find me up here but what could this lady focus on? Well, if I was up there, I’d be focused on keeping my balance and maybe that is what helps her to focus because she’s got her one hand on
her leg and the other hand up in the air. She struck a pose. So she’s very limited in the scope. She’s standing on a very small amount of ground. And then what could she see to focus on?

Well, she might focus down below since that’s sort of in her line of sight. And maybe if she looked over to the side, to this cloud mist, that would take her off the subject or if she looked down into the water, that would take her off her subject. She certainly can’t look behind her unless she lowers her head and looks between her legs. That’s not wise in this situation. So probably what she’s doing is she’s focusing on the posture and she’s focusing on this ledge or the rock down here. So she’s got a very focused composure because she has to keep her balance on this limited stand and she has to keep what she’s doing in tight focus. Or what’s going to happen? She’s going to fall off this ledge.

**From the Cloud Level**

So from the cloud level, although in that picture you’re not supposed to look at the clouds, some people flood your data with detail. So you can’t see the forest either. It’s so much detail. “I’m going to put half a mil into 50 mil conical tube.” That’s too much detail. You’re not helping your cause if you give so much kind of intricate detail. Sometimes, it’s useful but most of the time it’s a hindrance because you want to sell the reader on that you know how to do the work but you have some concepts of why you want to do the work, how you’re going to do the work, and what your work is going to need.

Most of reviewers actually will assume the technical detail. Now, of course, if you purport in this R03 to develop a procedure, you’re going to have to spend some time on the technical details. If you’re going to develop a procedure you will have to spell it out. But even then, most reviewers are going to be more interested in why you’re doing each experiment. So even if you’re developing a technical R03 to develop some technique, they’re going to need to know why you have X control, Y control, and why this is your test, and what the test will mean, what do you expect to get, and what the data is going to mean, what are your results, so what are you actually going to measure, and what the data is going to mean when you get it. This is especially important for an R03 because it shouldn’t be really exploratory because it’s very focused. In other words, it’s really not like an R21 that’s high-risk, high-reward, but it could be exploratory in the sense that there’s some concrete thing that you want to develop. But it should ultimately be feasible to do and very focused.
**Parts of the R03, Similar to R01**

We are going to go over the parts of the R03. They are very similar to the R01 and to the R21. Also these are things that you’re graded on by the reviewers. The first is the significance, which leads to the impact that your work’s going to have, the innovation, you as the investigator, the approaches you’re going to take, and the environment in which you’re going to do these things. The most important of these is the approach. Then you have to tell the reader that the work you’re going to do is going to have some impact because it has significance for a problem. And then you should be the one to do the work.

**Significance**

So what is significance? What you have to do is say to yourself “what’s the ultimate goal?” If it’s to develop a procedure, if it’s to mine a piece of data that you generated 10 years ago, you need to tell the reader why that’s important to do and you need to do that in a succinct and convincing way. Then tell the reader how this R03 with a small budget and scope is going to get you there. So the scope of the work should reflect the funds available. So like I said, with $50,000 you could pay for a part-time person, maybe a full-time graduate student and $15,000 of supplies. So what can you do with that money? Not a lot of things. So that’s why your experiments have to be really focused and direct, but at the same time you should be able to convince anybody, “If you give me this money, I can do the work and I can get a significant result.”

Build a case for this, set up why the work is important to do and why you need this little bit of money to go forward. In the case of the example I gave before, this friend of mine got the R03 because she had work already published in a mouse strain and she wanted to test an idea in a knockout mouse along a similar component. Then she had an idea about what would happen, so she convinced the study section that it was a really interesting take on things and worthy of doing.

So what you want to do is make an outline of the key facts that the reader needs to know to understand why the work is important to do, not a book report, but the key facts that are necessary to understand the importance of the work. What I try to do is weave the impacts throughout the documents. So wherever you can say to the reader, “this is important because…” use it to remind the reader of the importance, that constant reminder helps to sell your grant.
So remember that the R03s are focused; they have focused goals with less money. For the innovation section you want to make the reader see that you have a novel aspect to solve a problem. Like that friend of mine did, she thought that her work would apply to this knockout mouse that nobody else had thought of so it was a reasonable question to ask. It could be, like I said, a new method that you’re trying to develop. Some way of analyzing old data with the a new technique or maybe you have just a dataset you’ve acquired and you ran out of funds and you have a great way to analyze it that maybe you didn’t think about before. This might be a mechanism; you have a new technique or refinement of an old technique that’s going to have a significant impact.

**Innovation**

So there are many ways the proposal could be innovative, and what I like to do in this section is make sure that I tell the reader why it’s innovative. Don’t leave it for them to guess because it’s hard for any of us to know why something is innovative. You have to tell the reader this. It should be novel but it should ultimately be feasible. This is very, very important for an R03. This is not high-risk, high-reward stuff. This is limited scope, limited budget stuff. You could propose something entirely new and amazing if it proved to be true. However, it needs to be feasible and your number one limitation here is really the money. You don’t have a lot of money to propose something entirely new, I don’t think.

The scope is limited. You need to remind the reader of this. So since they’re reading it amongst other grants – so there’s not an R03 study section, they go to the same study sections that where the R01s and the R21s go. Remind the reader that it’s a limited scope. Remind them that you only have so much money; you only have so much technical help. So it’s best in an R03 to be very specific about what you will accomplish. It can’t be pie in the sky. It’s kind of the antithesis of the R21.

**Approach**

In the approach section you will tell the reader how you will study each aim. This should include some experimental designs, some methods, and some preliminary data to support each aim if it’s possible. Some put all the preliminary data at the beginning of the approach and some put pieces of the data with each aim. It doesn’t really matter, either way can work. For an R03, you don’t have much scope, right? So I would limit it to one or maybe two pieces of data, max. So if you have a new spin on an old technique, give them
the old technique and give them a hint of how the new technique might work better or how the new analysis might work better with another piece of data, for example.

Since the approach is so important for the score, how do you best set up the approach section? The first paragraph should describe the key area you are focusing on and highlight your new approach or new analysis of old data. So the idea would be “we understand this and recent evidence suggests this but the mechanism is not understood or the proposed mechanism doesn’t make sense.” So because of your data, it makes you think of another mechanism, perhaps. You need to state that. Or you have this old data and now you have a new, great analysis method you didn’t have 10 years ago. This is why I think it would be advantageous to run the old data through this new analysis program.

If you showed the data, like I said before, be sure the reader can see it. Don’t make it miniscule. Remember, reviewers have more than 40-year old eyes. Most of us do anyway. Put in the legend what the data means to you. Always, always, always interpret the data or else the reviewer will think, “This person doesn’t even know what it means!” or “They put the grant together hastily.” It creates a bad impression if they think you don’t know what it means. This turns out for any grant to be the most common mistake because lots of times we’re so close to our own data. We believe our own data. We think it is self-explanatory and that anybody that sees the data will be able to interpret it, but that’s not the way to think about it. A better way to think about it is “I’m trying to communicate why my data is so important. I’m going to show the data and I’m going to tell the reader what I think it means.” Then the data better say that or it will be easy for the reviewer to say, “Well, I don’t see that out of that data.” So if you’re going to show data, it really needs to make the point and you need to always, always, always interpret the data.

How to set up the approach section? Remember, that what you write is contextual and you need to place it in the context. The reader needs to know that you are confident, that you’re telling them what they need to know so that they understand what you want to do. You need to tell them enough information to make it clear what you’re going to test. You want to tie the preliminary data or the published work to the big picture and show how this leads your mind to the next step in approach, “Because I understand this, I’m going to do this and this is why.”

Is the approach section technical? Yes, it’s technical. But it also allows the reader to see your mind and how you approach problem-solving. That’s why the approach is such an important section of any grant, because that lets the readers see how you do problem-solving.
So anticipate the things that could happen, and the things reviewers could say about your approaches. You need to emphasize the section about why you need to do the work. You need to do this work and this is why this is important to do. You need to reassure the reader that you’re actually the one to do the work. You have the flow cytometry background or you have the data analysis background that if you do the work, you will get some answers.

Then remember that alternative ideas and approaches are pretty limited in an R03. You don’t have much room or time to say, “Well, if this set of experiments doesn’t work, I’m going to do this set of experiments.” So it has to be a very small problem scope and has to be feasible. You’re going to get answers without too much of a it-might-not-work type of thing.

So the experiments you propose must be doable but they also must be critical to do. So the key thing here is don’t just do experiments to do experiments, that is try this, try that. And in R03, you can’t do that. You don’t have enough space. You don’t have enough money. Don’t list the battery of 10 things you want to try. This isn’t a strategic way to do anything and this is a huge mistake for an R03 because remember it speaks to your realization of the scope and the amount money.

What I would do is always list just a few approaches. We’re going to use our primary method. It’s this and we will confirm with another approach, maybe two things. Tell the reader what you would expect and what it means. Just like the data, when you present data, you need to tell the reader what you think it means. When you present approaches, you need to tell the reader what to expect and what you think it will mean.

A Common Mistake in Strategy

So a common mistake in the strategy for approaches is to list all the things you will measure. So you’ll do westerns, you’ll do flow cytometry, you’ll examine cell death, you’ll do calcium flux experiments. So you make a list of all the things you’re going to do to develop some technique. So you do all these tests and you think, “Well, if I do all these things, I will understand how the cells or how the system works.” But here’s what the reader really thinks, “What’s the importance in doing all these tests? I don’t understand why you need to do all these tests. What’s the critical information that each one of these tests will do that’s different? So what will it mean?” And especially for an R03 because of the scope, the experiments are limited. So you don’t really have the time or the personnel or the money to examine 10 things. And I’m telling you it’s a mistake because each experiment and each technique you do should be set up so that it’s designed to answer
critical questions, to give you critical answers. So that’s especially important because of the scope and your budget in an R03.

What you need to do is instead of make a strategy to find out an answer, perform those critical experiments that will tell you the answer and convince the reviewer, but really you have to convince yourself first, that what you propose is a critical experiment. So each thing that’s in the grant, you should be able to tell your mother or whoever, “Mom, I’m going to do this experiment because it’s a critical experiment to do and here’s why.” So then anybody could understand why it’s a critical experiment.

*What are Critical Experiments?*

So what are those critical experiments? In the previous example, ask yourself, do you need to know what cell type is involved? Maybe yes, maybe no. Do you need to know what the cell type actually does, i.e. the function? Do you need to know the calcium thing? Why is that important to know? So they might be interesting to do and can be done. So just because something can be done doesn’t mean it should be done. So especially in an R03, you have to convince yourself and you have to convince the reader that each one of the things you propose to do is important to do. Tell the reader why what you were doing is a critical experiment to do.

*Strategy for Each Aim*

So the strategy for each aim, what I’d like to do is state the rationale, why the work in this aim is important to do, how you think about the problem and what you think is the best experimental approach. So let’s say there are three main experiments you will do: Aim 1, state them in broad strokes with greater detail to follow and then give expectations, outcomes and then pitfalls or alternative approaches. In an R03, you’re kind of limited there, so this has to be pared down. Remember; the rationale, experimental design in detail, outcome or the expectations, and the pitfalls or alternative approaches.

Really for an R03, you should have 80 to 90 percent likelihood of success because they shouldn’t really be high-risk, high-reward. They should be feasible to do and you will get results. For your rationale, what you want to tell the reader is “what’s the big purpose of the aim?” To find out how something works, to test the new computer, say, bio-informatics on my old data, to characterize something in detail, to ask if these knockout mice do what I think they’re going to do; to find out what? What’s the big question? You need to think beyond individual experiments.
So let’s say for each aim you have three main types of experiments. You can designate them. Say, 1A, 1B, 1C. You can use a narrative for each. “These are the experiments. How many wraps the critical detail and expectations? If I do experiment X, this is what I expect to get, but if I don’t get this, then I have a back-up plan.” But an R03 scope limits your back-up plan, so it should be very straightforward and concise. You’re going to get answers 80 to 90 percent of the time.

**Pitfalls/Alternative Approaches**

In the pitfalls or alternative approaches, it could be that aims—1A, 1B—impact each other or will be used to guide other experiments. Do a careful analysis to examine the data for dependent variables. If I find that my data leads in another direction, I can adopt a new strategy in future experiments. In an R03, as I’ve said again and again, there is limited room for back-up plans because of the limited scope. So you just need to remind the reader of that.

**Go Back and Check**

So what I would do is go back and check that the reader has enough background and preliminary data to understand the significance. This will be hard because you really only have that six pages for the research approach. Make sure that each aim is separate and not dependent on each other; that the design for each aim yields meaningful data; and that each experiment is necessary and critical to do; and that you describe your unique skills, whatever you bring to bear to answer the problem.

So go back and check and see if the data, if it’s presented, is clear and is interpreted. Make sure that the experiments are described with expectations and implications; that alternatives and pitfalls are mentioned but, of course, realize that the scope of the R03 really limits you. Try to eliminate extraneous information. Always ask, “Does the reader need to know this information?” If they don’t need it to understand what you want to do, take it out. Lastly for an R03, it’s really important that you ask yourself, “Can I do the work in the time with the budget that’s limited for an R03?” A reality check really needs to be done.

**R03 Guidelines**

So for an R03, I’d say make sure the project is contained and it’s doable. It really should be feasible. It shouldn’t be pie in the sky type stuff. Because of the space limitation, you must be a wordsmith. So I find...
myself going back over and over and over a grant to make sure that my words are brief, that I say something in the least possible number of words, that it’s concise and clear. If you show the data, it must be convincing. One or two pieces of data, that’s it.

Experimental approaches must be feasible, this is very important for an R03. The outcomes must be finite and it is still important to have impact. The work still must be significant to do even though it’s a small amount of money.

Q&A

**What is the current funding level for R03s? Are they better than the R21 and the R01?**

**Dr. Lewis:** Well, that’s a really good question because it turns out that the R03s really are funded at a higher score than the R21s or R01s.

So it really is if you have a small thing you want to do, and it’s going to have impact, it really behooves you to do this mechanism because you have a better chance of getting funded. For example, something like the NCI that doesn’t do by the regular R03 mechanism but by their own, they had a 71 percent increase in the funding of R03s in 2011. They had all these little projects that they thought were worthy to give us small amount of money to. So it really, even though it’s a small amount of money, it might be in your best interest to apply.

**How can such a small amount of money produce such a high impact?**

**Dr. Lewis:** Well, that’s a difficult question – important but difficult. If you’re going to develop a new technique to do something, you know, translational like I was going to do, it could have a big impact since what I proposed was to develop a non-invasive way to predict pre-eclampsia. So you have to take what work you’ve done and what you think you could do with a small amount of money and turn it into something that might have a big impact. It really depends on what your idea is.
I am a post doc, how can I show independency in my proposal from my PI’s R01 project? Do you just list different specific aims or is there a more efficient way?

**Dr. Lewis:** Yeah. I’m going to assume you have a faculty position. However, even if you have a faculty position or you are promised one, I’m not sure that the R03 is the best mechanism for you simply because you need to establish a relationship with the program officer and that’s unlikely. You’ll be unlikely to do that unless you have a grant already. I don’t think this is a mechanism for the first time investigator. I think a better mechanism might be to try to write one of those K03, or K12 that allow you to establish independence. There are a number of those mechanisms I would check into before writing an R03.

Now, if you still insist upon doing that, you’re going to have to make sure that it’s separated from your mentor’s R01 enough. There are aspects that are not in that grant. So what you can do – I assume your mentor’s given you a copy of their grant– you can look in their aims. If not, you could always go on the query and type in your mentor’s name and look for his or her funded grant and then look at the abstract. In the abstracts, there should be specific aims there so you could match. But, make sure that your aims are not part of their aims. They have to be different.

**To clarify the 50K budget limit is per year, meaning, you could get a 100K for two years total?**

**Dr. Lewis:** Yes, that’s right. It’s 50K per year for two years.

**I have research fellows in my practice. Could I apply for an R03 in order to increase the payroll for them so they can dedicate specific time to a specific R03 proposal?**

**Dr. Lewis:** It’s possible. That might be possible to do. Then it depends on what you want to do, what the scope is. You’ll have to make it clear that these people are going to be paid from this R03, but they’re going to accomplish something. So I don’t think it’s a way to get salary kind of like for fellows or whatever. You have to have a scientific question that you’re going to ask and answer.
I am a mouse researcher interested in kidney function. Is the R03 mechanism a good one for proof of concepts in animal experiments?

Dr. Lewis: Oh, I think it’s an excellent one especially if you’re already established as a mouse researcher doing kidney research. So you have a reputation for doing that. Now you have a new idea or there’s a new mouse model. Say, there’s a transgenic mouse that has its kidneys reversed or developed polycystic kidney, maybe you want to ask your question in this new mouse and I think it would be pretty easy to convince a reviewer that that was an interesting experiment to do. So I think it is a mechanism with a small amount of money and limited scope that you could do mouse research with it.

What level of risk would be suitable for an R03?

Dr. Lewis: I think the level of risk should be pretty minimal and that I think there should be 80 to 90 percent chance of it working. I don’t think it should be like an R21 at all because that’s high-risk, high-reward. Here’s the dilemma. You have to make it so it’s going to be significant and have impact, but at the same time, it needs to be able to be done. So it needs to be feasible and that’s especially important I think for an R03.
Academic Research Enhancement Award: R15 Grants

Presented by Dr. Sridhar Mani

MODERATOR:

Dr. Sridhar Mani is a professor of Medicine and Genetics at the Albert Einstein College of Medicine in Bronx, New York. He was the founding director of the Phase I Experimental Therapeutics Program at the Montefiore Einstein Cancer Center. He received MD degree from the Mount Sinai School of Medicine New York, New York, followed by further postdoctoral training in Internal Medicine and Hematology Oncology at Yale New-Haven Hospital at Yale University School of Medicine. He is the recipient of the Clinical Investigator Award from his Damon Runyon Foundation and presently is an NIH funded investigator on the role of Orphan Nuclear Receptors and Metabolism. He is a permanent member of the Developmental Therapeutic Study Section of NCI and serves as an editorial board member for Cancer Research, Clinical Cancer Research and Molecular Cancer Therapeutics. He has more than 100 peer-review papers in journals like Science, Cancer Research, Clinical Cancer Research, Molecular Pharmacology, Molecular Endocrinology, Molecular Cancer Therapeutics and Journal of Clinical Oncology.

DR. MANI:

How-to for R15 Applications

So the first question comes to mind is to why apply? In 2010, 923 new R15 applications were submitted, of which 158 were funded for a total funding of over $45 million, which represents a 17.1% funding rate. For renewal R15s, the rate has been higher, fewer people apply, 69, of which 27 got funded and that gives you a 39% funding rate.

Of course some institutes gets fewer applications than others, but the success rate has been dropping over the number of years from 2001 to 2010, but the success rate is still 19% and over. So it is very competitive in terms of the success rate in comparison to the other grants such as the other R Grants as R21s and R01s. So it is clearly important to use this funding mechanism if you are legible. Now, for the R15 also known as the Academic Research Enhancement Award or the AREA Award, and you can get more details here
http://grants.nih.gov/grants/funding/area.htm, you must check the eligibility, one. Two, you must also know that if you’re doing meritorious research, it must foster a student learning environment as tied into your specific research. And three, students especially undergraduates and others but includes graduate students, must be recognized by meritorious research by publications, peer-reviewed publications or other recognition that’s impactful in the field and you must be able to show that.

What are the Intended Goals for the R15?

And the goals that NIH intended for the R15 were the following:

• That the R15 focuses on meritorious research, so that is very important. That that research then peer-reviewed should be viewed as a renewable form of investigation and that the research should have impact to peer-reviewed contributions.
• The second goal is that students should be exposed to this research with the evidence of them performing the research of clear learning environment and of the students co-authoring publications and presentations, which are very important for this R15 program to continue.
• And then finally that there’s an enrichment of the institutional research environment by giving the seed money you could foster more investigation and more long term investigation, sustainable investigation. So the most important thing I mentioned before was checking your eligibility.

Before you apply you must prepare a short summary of your research. Add in your resources and keep a checklist on the side to make sure that, yes you can include all these things, if indeed you were to apply. And on one page you should present this to your grant officer and then the program official at NIH. And I’ll get to how you can get the information or the exact NIH institute and the grants officers and the program official later in this broadcast. But what’s important in the eligibility, that you are or you come from a baccalaureate or advance degree granting institution. And that your institution should not have more than $6 million in NIH grants documented each year over the past 4 consecutive years over a 7 year block, over a given a 7 year block. And some types of awards are included in this, for example clearly the R, activity code designates like R, the R01s, the R21s, P or program projects are all included. But what’s excluded from this are the CS and G designations. And so it’s very important for you to check with your grants office whether indeed your institution qualifies for an R15.
And even if you qualify, I must emphasize, you must cross check your institution against the list of area eligible and ineligible institutions under the R15 homepage. So if you go to the eligibility under the R15 homepage (see http://grants.nih.gov/grants/funding/area.htm), you will see a point where they actually give you a URL to check whether your institution is listed as area eligible or not. Okay, so you must double check that. And I would caution that you should then take that information back to your grant’s office to make sure that indeed, if your institution is listed, that you are currently at the time of application still eligible. Okay. And the final point here about eligibility is that you must demonstrate that the majority of the work would be done at the home institution, that’s at your institution.

R15 Key Features

Right, so the key features of the R15: that the grant is renewable with competing continuations just like your other grants, like the R Grants for example. And that there are some special supplements allowed. For example if you have students with disability or minority students who qualify, additional supplements are allowed to the grant. The second point is that only up to a maximum of $300,000 direct costs per project period up to 3 years is allowed. And then the indirect cost is obviously added on to this. But you’d have to give a detailed budget unless your total direct cost is $250,000 or less than whatever budgets are acceptable. Now there’s a standard 5 NIH criterion rule that applies which is how your application is assessed. That includes the impact of your grant, the significance, the investigators, the environment and the approach. But in addition, you need to specify how you will satisfy area specific goals of the program and we will come on to this a little later on. There’s a 12 page limit for research strategy, and then there defined electronic receipt dates which are February 25th, June 25th and October 25th.

Format for Application

Our format for the application is a specific aims page, which is one page in length, a research strategy page which is 12 pages in length, which comprises of key subsections that include significance, innovation, approach, preliminary data and progress report in case you are submitting a renewal application. In addition, if you’re going to do a resubmission, you need to put in a one page introduction that addresses the critiques of the prior application. There’s a Biosketch, and here I bolded this because it’s very important, in the assessment for R15s it **is very important that your personal statement emphasizes the area specific goals.** “Why are you well suited to be the PI especially in training students?” Furthermore, the resource page is critical for the description of the environment so as to satisfy reviewer questions about whether the
students and whether the research can get done and whether the students will enhance their learning and contribute in that environment.

**Institutional Commitment and Support**

Now, the institutional commitment on support is paramount because a lot of these applications are sent to study sections where a host of applications that have to do with R01s and R21s are presented and then the R15s are discussed. And often the mind-set is well you know the resources aren’t there. And it’s very important to show that there’s institutional commitment and support for your success. So you need to identify a faculty mentor, a senior president, a business office administrator who has some experience with NIH grants and a clerical staff in the Dean’s Office where previously supported and submitted NIH grants. And you must go through the guidelines, the checklist, the deadlines for submissions and corrections process and the review of criteria with them before you even contemplate putting an application together.

The second point is, does your institution provide and support an environment that facilitates faculty success? And this is very important to bring out both in your resource page and the student profile which is in the environment section. And this means, “what does your institution do in terms of start-up packages, student environment, the course working credits, faculty promotions, and in particular protection of faculty when they are funded in order for them to do research, tenure decisions that are based on independent and or collaborative research.” This will all aid the reviewer in assigning a high score if they feel that you have the right supports in place. And you must be able to directly help with the resource page equipment and student profiles. And the institution must contribute to your writing of this page. And encourage restrained submissions.

Now, the institutional commitment and support can also be reflected within the design and crafting of cover letter to NIH. This is very important because you need to get a personnel at your institute who have done this before to suggest, besides you having to discuss this application with your program officer, to suggest which NIH institute is the most applicable to your area of research and which NIH study section would be most favorable to your area of research.

Review the areas of expertise and potential review conflicts within those committees because they could be one of many things that precludes an application from getting a high score. You want to make sure that you have all the right pieces in place. Then, finally you want to give a brief description of that research in
that one page cover letter to NIH so that in the receipt and referrals the officers sees this application without even having to come through or print to some electronic process or assignment, study section assignment that they would then say look this is rightfully goes to this particular study section and they had made the case. And certainly the institution needs to encourage mentorship and you need to bring that up in the application, provide a platform for faculty interactions and research, submit NIH workshop attendance, encourage pre-submission contact with NIH staff by email and submission of specific aims page.

Application Preparation

Now, when you are preparing the application I would advise you to familiarize yourself with NIH, the institute, and the appropriate CSR research goals and focus. “Does your research fit this?” Because that’s where it’s going to be scored. So, you’d like to look at any research and define your research as any research impacting health to get broadly what is covered under this definition (see http://www.nih.gov/about/mission.htm). Then you want to also look up specific research missions by institutes. So, if you click on the NIH webpage you will see institutes at NIH, you click on the institutes of NIH icon and you will get a whole description of specific institutes with their research mission. Then I would look up the Center for Scientific Review, the CSR, which is at http://public.csr.nih.gov/Pages/default.aspx. This will allow you to look at review group descriptions. This is the study section that’s going to review your application. So you click on the peer-review meeting icon on the right corner and then on the review group descriptions and you’ll come unto all the study sections that you want to list your application.

Note the special area applications review sections, and see if your chosen preferred study section has reviewed R15s before. And that’s why it’s important, when you get a review study group or review group that you’ve chosen like for example Developmental Therapeutics, you want to talk to the scientific review officer to see whether that study section has reviewed R15s before. If they have not, their mind set is going to probably be very different and may not be the best to encompass and to give you a fair evaluation. So it’s very important to select the right review group using these criteria also. Then finally, you want to look at a study section expertise that would cover your area. So once you’ve done all this, you have a very good idea of the 1 or 2 or 3 institutes and/or CSR review groups that could potentially review your application. All that information goes into your cover letter. Then you want to generate preliminary data supportive of both your research and preferably the students.

So it’s not enough to just say well I’ll have a student do this and demonstrate that in the past that has
been done. But it is very helpful to have students ongoing that are doing part of the research that makes it very attractive. Show that all tools and reagents are readily available. And this is very important because this comes on the approach where reviewers might feel that the aims are laudable, the research goals are laudable but the tools aren’t there. And this may well not be done within the 1 to 3 year window period that’s given. Finally, you want to focus on student recruitment and training. There has to be enthusiasm and a commitment factor that you have to bring out almost as if you’re writing a training grant.

**Research Strategy**

Now, it’s very important when you formulate your initial research proposal that you know you’re potentially eligible, and you have a specific aims page that you should send to your mentor at your institute, and also to the appropriate NIH program official or scientific review officer. In fact, I would encourage you to do that because they can give you a lot of information about the suitability of your research. The second point is you need to focus the impact of your research throughout your application. And this is a tough term for those who have not applied for NIH grants. Let me explain this to you.

The NIH reviews your application based on 5 NIH criteria: First, approach, innovation, significance, investigator, environment. That is, “what is your approach? And how feasible is it to get work done? What is the innovative potential of the work being proposed? What is the significance of the work?”

Significance covers the importance of the proposed research to the field of science. If successful, it also means that the research is cutting-edge. However, impact is a more global term and that includes not only the importance of the goal, but also the likelihood of successfully meeting them. The overall impact indicates the potential likelihood for the project to exert a powerful influence in the field. So, impact is a separate overall criteria okay, which is what guides your final score.

It’s not necessary for you to believe that your grant has to be so innovative that it will go through to the NIH grants process because the way NIH grants are scored it’s not all about innovation. It’s about the total package of trying to do a forward moving research that would be impactful for the field. This is critical when you’re writing your R15. So that research strategy is where reviewers get their review criterion satisfied. For example, scoring on the significance they would look for the significance subsection in your application. So scoring on the investigators or the potential of having the right investigators will come from the biographical sketch personal field. And this has to be especially strong for R15 applications. The
innovation will come from the research strategy subsection innovation. The approach will come from the approach subsection. And environment will come from facilities and the other resources, environment subsection. Investigators and environment are key points for R15 applications. Not to ignore the others but a weak investigator section and environment section is surely to lower the R15 score.

Now, getting a little more in depth into research strategy. So as we discussed your specific aims page is one page. It has an introductory paragraph with a hypothesis and then you know the rationale for the aims, you put down your aims and then at least one line that suggests what you’re going to do if this grant was successfully completed, sort of a forward thinking statement. The research strategy on the other hand is 12 pages. And I put here an outline that I have used, successfully used, in writing my grants. The significance page is about 3 quarters of a page max. If you go above 3 quarters of a page, then your diluting out the significance. It’s not coming out. It should be very crisp and clear what it is, why it is that your research will be significant in the field that you’re proposing. Second point, innovation should be fairly straightjacketed within half to a 3 quarters page max. And it should be a crisp statement about what is the innovation in your research.

The approach can be 10 pages maximum. And under each specific aim in the identical format for each aim I have the following breakdown. You have an introductory paragraph about the aim, a justification and feasibility of why that aim is proposed. So you review the literature and background here and you’ll also present preliminary data here. It’s better if you have manuscripts published because you can save a lot of space here. Finally you’d have a research design section where you’d propose the exact design, your approach. Then you should have a section of expected outcomes and potential pitfalls and solutions. Now, for an R15 this is critical because you’re seeing expected outcomes for you, your research and that of the students. The student is critical in the entire construction of the aim especially where you talk about “well these are the expected outcomes of the research that my student will and blah, blah, blah.” And “the potential pitfalls and solutions are that if we are unable to do this, we will do this, this, this, this, that the student is familiar with and will proceed in this fashion.” And so you bring together the whole training aspect within the approach part of the application itself.
Then you should have a timetable page which is a quarter page and a future discussion of direction, it’s optional but it’s recommended if you have a quarter page there. It’s important that in your approach you are self-critical, rigorous and persistent. That is propose less, be very finite about the research being proposed but going to depth. Be critical about the expected outcomes and the potential problems. This is where you should be self-critical, rigorous and persistent.

**Significance**

The significance that you need to bring out in your significance paragraph must address “does this project address an important problem or critical barrier in the field?” “If the aims of the project are achieved, how will it further drive scientific knowledge, technical capability or and of clinical practice, depending on the type of grant you propose?” “How will successful completion of aims change existing knowledge driving that particular field?” You have tricky questions that you need to address within the body of that significance paragraph.

**Investigators**

In the Investigator section, you need to address the program directors and principal investigators, the collaborators and key personnel well suited for the project. You need to bring that out through their Biosketch.

Remember that the R15 award does not recognize early stage investigators and new investigators. There’s no point trying to emphasize that as you do in R01s. There should evidence for balance of research and teaching over the past 5 years, this is key. Not only that, you should also show that there’s been successful research mentoring over the past 5 years. And finally, that multiple PI program director grants must show complementarity and expertise. This is very important. If you have the same expertise, that could be a significant negative for scoring the investigator section.
Innovation

Now innovation is always brought up as a point of debate in study sections as whether a grant is innovative or not. But you know you’re talking about novelty, not just something that’s new. And you can craft novelty even if it were moving the field incrementally forward but it was a necessary set of experiments that needed to be done to move the field forward. It does not have to be vertically innovative. It’s helpful to have that of course but it does not have to be. If it is to change current paradigm in the field and also the substantial refinement of existing methods and paradigms that would be necessary for changing research direction. So, any of these could fit the definition of innovation or innovativeness of your research proposal.

Approach

The approach should be well reasoned, logical, feasible, given your resources. And you must always demonstrate that in your approach. Building step wise is appropriate to accomplish project goals, they should be independent. Linked aims such that “if the first aim doesn’t work or the reviewer sees it as that one cannot succeed in doing the first thing, well the second and the third aim are linked to the first aim then I think you know the whole grant falls apart.” So you have independent but linked aims. Each aim should have a section dealing with expected results and potential problems and solutions. This is very important in judging the rigor with which you’re going to conduct that research. And if the project is early in development and there’s high risk but also high reward, will the strategy used establish feasibility in your environment. This is very important because this money is being given to institutions where the resources may not be so plentiful and they’re excellent investigators but they need the resources. So you need to show that. And then for clinical projects to be very careful to spell out the protection of human subjects and the minority of gender, children including section. This is where the institution can help you.

Environment

The environment is the key, you need to demonstrate appropriate scientific environment which is included in the facilities and resources page. You need institutional support and commitments. Letters are great especially from the Dean or the Dean of Research with regards to the student research and teaching and that you will have access to all of this. Spell out unique features. For example “the Dean allows you to focus teaching for the first year in support of developing your project, yet pays your salary.” From your
institution you need support letters and why your institution feels that you are deserving of this R15. Profile student data, on the bachelor degrees that have been given or a valedictorians that have come out from your lab, post baccalaureate degrees over the past 5 years, all this is data compiling that’s very useful to you, in the setting environment. Describe impact of the R15 or the principal investigator program director development and the research environment of the school and academic component. That is if you got this R15 and if the school got this money that it would foster 5 more grants in the next 10 years because you will have X, Y, Z collaboration. That’s an example. Description of the university, it’s mission, it’s demographics, degree programs with URLs that reviewers may be able to click on will be most useful. And you could expand the support by paragraphs in two.

The environment also should include a paragraph on the number of graduates enrolled in the graduate program, medical program, dentistry, pharmacy and so forth. And expectations for future growth if applicable, and you may get these projections from the Dean’s Office. The environment also should have a description of the university level programs for faculty undergraduate teaching recognized by the highest office at your institute. An example is the new university wide internal grants program to encourage interdisciplinary research by faculty who are primarily engaged in teaching. And having that information on a letterhead or that information on a website that one can go to is very useful in reviewing this section.

Departmental environment, student researchers, active student chapters, presence of scholarships and grants for students, student presentation, available equipment to them and opportunities for interdepartmental or university collaborations, all are a big plus for this section. And I put here a summary paragraph that you may look at your leisure.

Modify this and embellish it as you write your own grants. That kind of gives a sense of the teaching institution, the incentive, faculty incentive grants they give, their...
commitment. And so I’ll let you look at that at your own leisure. And same with the institutional summary, this is X, Y, Z, as X this college has grown into a competent university and so on and so forth. You could still embellish that and use this in your summary statements within the environment health section.

**R15 Specific Review Emphasis**

Now, as I told you the R15 specific review emphasis is not only on the research, but also “is the research project meritorious and appropriate for available students and is the environment likely to have this whole thing succeed?” So, you need to remember this, just keep that in your mind as you’re writing this application.

**INSTITUTIONAL SUMMARY**

As XYZ has grown into a comprehensive university, the ABC College has recognized the importance of research to an outstanding undergraduate science education and has sought to enhance faculty research and research opportunities for undergraduates by making significant investments to improve the research environment. The need for extramural support has grown commensurately. An AREA award would be a primary support for Dr. P&Q’s research, strengthen the research environment, expose more undergraduates to research and enhance their prospects for health-related careers.
Q&A

You said impact of the research is important but for R15 training is part of the impact. Is the impact on the field or the number of citations of your pub the only impact that matters or is the impact on student learning considered?

**Dr. Mani:** Both, and that’s a very good question, both. In contrast to R01s where the impact really from your own research in terms of the number of publications and high level publications that you have, is the sole criteria. In R15s it’s both the impact on student learning that you can show as well as some degree where you have peer-reviewed publications so that indeed your proposal you know stands external peer-review. So the answer is both. There is a skewing towards, clear skewing towards being back on student learning. That’s a heavy emphasis and that’s something that should really be the first thing you want to maximize and show in your application.

You said we should plan which institute to send to and which study section to go to. Does one study section cover more than one institute? Or one institute cover more than one study section?

**Dr. Mani:** Well, typically one study section is covered under one institute. But there are some study sections where you know depending on if you assign it to one institute it will still be reviewed under that study section from there to another institute. So I think you’d have to discuss the details exactly with your SRO and your program official. So you get the names of these individuals from that URL and you would say well my grant is applicable, it’s under the mission covered by NIDDK and NCI as an example. But from a study section point of view it’s most applicable to say developmental therapeutics. Okay. And if the grant is slanted towards cancer, okay, it will go to NCI DT. If it’s slanted towards aspect that’s more covered under NIDDK, it’ll be assigned primarily to NIDDK, reviewed under a DT. So I think that you have to discuss your exact mission with the program officer in writing your cover letter.

Am I correct that there should be a separate institutional profile of students and a PI lab profile of students?

**Dr. Mani:** Yes, correct. That is very helpful to the reviewer because as a reviewer if I were looking at an R15 I would want to know what does the institution as a whole do with students and how does this individual
lab do with students. First of all I’d like to know that both missions are indeed you know congruent. And I’d like to know also whether the institution supports the PI in furthering their goals with their students. And this could be done in many ways but both descriptions are necessary, at least in my view.

**Does the faculty mentor or senior need to be from the same institution? Or can it be an outside member?**

**Dr. Mani:** It’s advisable in my view to have the mentor from the same institution because you want to be mentored in the process of R15. However having said that, lot of junior faculty moved from one institute where they did their PhD or their initial postdoctoral training to another institution where they are submitting, to which they are submitting their R15. It’s okay to have a mentor from the previous institute recognizing that they can only give you certain structural advice. They can’t obviously talk about your institutional support.

**Can you speak about the balance between the faculty member’s teaching and research responsibilities? Is there an optimum balance that is desirable to demonstrate?**

**Dr. Mani:** There’s not an optimal balance because you can find individuals with a heavy teaching load who also carry a very active laboratory. It does not give them any more of an edge than another applicant you know with a good amount of research load but much less of a teaching. To all school it’s dependent on how they craft that particular schedule. What is important is that the grant requires that the research will be protected. And so you must show, I think it’s very important to show that the school recognizes that and, gives certain allowances to the researcher if they were to get such an award to protect that time and that research capability. That could be protecting your teaching time, curving your teaching time, reassigning you to classes that don’t require much your preparations but are consonant with your skills. That could be pre-screening students to come to your lab with the right expertise to help you conduct the research. See, these are all new answers but if they go in a letter they are very, very strongly supportive of the fact that you have institutional commitment.