

CHAPTER 5

Blind Them with Science—The Research Training Plan

The third major component used to evaluate a Ruth L. Kirschstein training grant is the Research Training Plan, in which you present the scientific project that will be undertaken during the training period. Unlike the R-series grants, that focus entirely on the quality of the science and the overall experimental design of the project, the Research Training Plan focuses more on how the quality of the science, the significance of the project, and logic of the experimental design contribute to the overall training potential. This subtle shift in focus does not mean that less care can, or should, be given to designing the project. A poorly laid out research plan indicates poor mentoring by the sponsor in preparing the application, which indicates a poor potential for training. However, this subtle shift in focus does mean that some things commonly viewed as “fishing expeditions” (such as large-scale genomics screens) are tolerated more in the Research Training Plan than they would be in the R-series of research grants. Despite this “increased” tolerance, these so-called “fishing expeditions” still must be justified by preliminary data or literature evidence and provide evidence that clearly demonstrate a significant contribution to the overall training. Further, although innovation is not explicitly required for the Research Training Plan, the use of what are considered “standard” procedures may detract from the perception of the training potential, unless these “standard” procedures provide the applicant with training in a new field, discipline, or technology.

The Research Training Plan contains all of the components that are present in any standard NIH research grant *except* for the inclusion of an Innovation section. In general, innovation is not a consideration when evaluating the Research Training Plan. Overall the science portion can be broken down into the following sections:

- Specific Aims (1 page)
- Research Strategy (6 pages)
 - Significance

- Approach, in which each Aim is broken down into the following sections:
 - Rationale
 - Preliminary Data
 - Experimental Design
 - Expected Outcomes
 - Potential Problems and Alternatives.

The following descriptions are recommendations on how to construct each of the sections for the Research Training Plan. These recommendations derive from a basic understanding of the purpose each section and subsection plays in the overall grant. The structure and key phrases that are described in the examples below are intended to help focus the writer on the purpose of each section, which should allow you to impart clarity to the reader. It is important to note that the examples that follow are simply recommendations and not intended to be the “perfect” format for writing an exceptional grant. Nor are these recommendations intended to serve as the only way to write a clear, focused, and detailed Research Training Plan. Instead, the following discussion is meant to provide an understanding of the purpose that each section of the Research Training Plan plays in the overall presentation of your project, and to provide key phrases and ideas to help direct your writing while you develop your own writing style.

5.1 SPECIFIC AIMS (1 PAGE)

In the pre-Internet, pre-electronic submission days, the only reviewers that saw the entire grant package for any individual application were the three assigned reviewers of that grant. All of the other study section members received the Project Summary (Abstract) and the Specific Aims page. Therefore, the Specific Aims was the most important part of a science-oriented grant because this was the only part of the application that every member of the study section would see. Since the advent of the Internet and electronic submission, all study section members, regardless of whether they were assigned the application for full review or not, have immediate access to every single grant is under consideration in their study section. Therefore, during study section, instead of simply having the Specific Aims page, each reviewer can quickly and easily pull up an application being discussed to read individual sections, scan the entire

document, or just read the Specific Aims or Project Summary. Although the easy access to the entire application in some ways minimizes the original importance of the Specific Aims page, it does not alter the fact that great care must be taken when constructing this section as it serves as a one-page overview of the entire project.

Because the Specific Aims page serves as an overall summary of the scientific project, it must contain all of the elements of the entire Research Training Plan, which includes background of the field, identification of the gap in knowledge, significance of the project, a statement of your hypothesis, literature and preliminary data evidence to support the hypothesis, explicit aims that will address this hypothesis, and how your results will impact the field. Conceptually the Specific Aims page can be broken down into four sections, which may visually appear as four distinct paragraphs.

Paragraph #1: Conceptually, the first paragraph of the Specific Aims serves as the background and significance. You need to establish the importance of the disease and or scientific question that you are investigating, which is usually established by utilizing statistics of disease mortality or morbidity. Once you establish the health relevance, provide the reader with enough evidence to identify a gap of knowledge in the field. Once you've identified this gap in knowledge, state why it is a problem with advancing of the field, which may include developing effective or novel treatments for the disease state under study. For example: "Although some of the molecular mechanisms regulating the biological activities of the key factors are known, at present the exact role of posttranslational modifications, particularly phosphorylation, in regulating both proteins has yet to be elucidated. The absence of this knowledge will greatly impact the ability to develop novel therapies to treat the disease." Then conclude this paragraph by explicitly stating how the long-term goals of the lab or the explicit goals of your project will address this gap and thereby advance the field: "Therefore, it is *the long-term goal of this lab* to understand how phosphorylation of the key factors regulate their biological activity, how this regulation contributes to normal development, and how this regulation is altered to contribute to the development of the disease."

Paragraph #2: This paragraph is where you describe the objectives of the project and state the central hypothesis of your proposed research. For example: "In keeping with the long-term goals of the lab

the central hypothesis of this project is....” Follow this statement with a detailed and explicit description of your hypothesis: “...differences in the phosphorylation of the key factors throughout early differentiation contribute to alterations in gene expression, thereby contributing to the development of disease phenotypes.” Reviewers like to see what is commonly termed “hypothesis-driven research,” in which there is a *very clear and direct hypothesis* that is driving the overall project. Many times a Research Training Plan will suffer because the applicant does not formulate an explicit hypothesis or central driving question or this hypothesis is stated in broad generalities and not detailed specifics.

After the statement of hypothesis, provide a description of the literature evidence that supports this hypothesis: “This hypothesis was formulated from the following literature evidence...” with a concise, yet detailed description, properly referenced, of the literature evidence that supports your hypothesis. In addition to literature evidence, the reviewers also like to see preliminary data that not only supports the hypothesis but also supports the feasibility of the proposed studies. Therefore, state: “In addition to this literature evidence I present preliminary data that further supports the idea that (or provides feasibility for the studies)...” again with a concise, yet detailed description of the data you will present in the Research Training Plan. Finally, wrap up this paragraph by leading into the statement of your specific aims: “We will test our central hypothesis through the following two/three specific aims.”

Alternatively, many people start this second paragraph with a description of the literature evidence that they used to develop their central hypothesis. This statement is then followed by a description of the preliminary data that supports the hypothesis and/or the feasibility of the studies. Finally, tie these two different lines of supportive logic together to lead into the statement of your central hypothesis: “Therefore, taken together, this information allows me to propose ***the central hypothesis that....***” As with the example above, the statement of the hypothesis leads into the statement of the Specific Aims as described above. It is important to note that bold and italic fonts are purposefully used to highlight the statement of the hypothesis. The use of a different style draws the reader’s eye to those words and makes it easy for the reviewer to see that you have a very defined, clearly stated hypothesis driving your work.

Paragraph/section #3: Explicitly state your specific aims in bold letters. This is a 2–3 year project so two to three aims are appropriate. In some cases, a brief one- to two-sentence description of the importance of the aim and the methods that will be used to test the aim can be included:

“Specific Aim 1: To examine the role of the phosphorylation of key factors in development and as a contributor to the pathology of the disease. We will use the physiologically relevant primary cells or disease-derived cell lines stably expressing the key factor or mutants in which the identified sites of phosphorylation are mutated to phospho-incompetent or phospho-mimetic amino acids. We will determine how phosphorylation at these sites contributes to normal development and the development of disease by examining cellular functions, such as growth, migration, differentiation, and by performing an unbiased survey to analyze changes in the transcriptome profiles during early myogenesis.”

When constructing the specific aims for your project, great care needs to be given to ensure that the aims you are proposing are interrelated but not interdependent. What this means is that you want to have all aims contribute to addressing the central hypothesis of your project. However, you don’t want the feasibility of one aim to be directly dependent on the success of a prior aim. For example, suppose you propose in Aim 1 to identify and characterize the sites of phosphorylation on a transcription factor. Then in Aim 2 you propose to generate explicit mutants that target the identified sites in order to determine the role they play in biological functions. In this example, although these aims are obviously interrelated, the feasibility of Aim 2 directly depends on the ability of being able to identify the sites of phosphorylation. If you are unable to identify these sites in Aim 1, then Aim 2 is not possible and half of your project is a bust. In contrast, assume you have preliminary data that identifies the only sites of phosphorylation on your protein of interest. Given this knowledge you propose in Aim 1 to determine the effects of these mutations on biological events (e.g., proliferation and differentiation) and in Aim 2 you propose to determine the effects of these mutants on the molecular activities (e.g., DNA binding, transcriptional activity, expression of target genes). In this illustration, both aims focus on the effects of the identified sites of phosphorylation have on the molecular and biological functions of the protein. However, the success of the second aim is not dependent on the success of a previous aim.

Paragraph #4: Finally, you want to provide a summary for the reader, which is the conceptual basis of this final paragraph. Tell the reviewer what each aim will achieve and how the successful completion of this aim will provide information that will advance the field: “The research accomplished in Specific Aim 1 will provide an understanding for how changes in the phosphorylation of key factors contributes to both normal differentiation and the development of the disease. Completion of Specific Aim 2 will provide an understanding of the role that phosphorylation plays in regulating the transcriptional and biological activities of the key factors.” Also, it is important to tell the reviewer exactly how these results could be used for future studies or what you visualize the long-term impact of this project to be. “Therefore, by understanding the mechanism by which phosphorylation of this protein affects tumor development, we will be able to identify novel molecular targets that can be used for the creation of new pharmaceutical therapies for the treatment of this cancer.” Although this scientific program is part of a training plan, the reviewers like to see that you are able to think past the present work and that you understand the potential impact of your results. Many times a grant will not be considered as strong as it possibly could be because the applicant did not adequately demonstrate that they understand the implications of their work to the larger field and future experiments.

It is advisable to include a statement of the contributions that the proposed research will make to the training potential of the individual: “The applicant, an MD/PhD candidate, will develop the necessary technical and critical thinking skills, including the development and analysis of behavioral and molecular studies, to ensure success in a translational research career under the mentorship of the sponsor, an established researcher and MD/PhD scientist in the field of research.” Although not essential for a successful application, this final statement summarizes for the reader exactly how the applicant will obtain key training for them to obtain their career goals.

5.2 SIGNIFICANCE (≈ 0.5 PAGES)

In January 2010, the NIH implemented a new, shorter format for grant submissions. This shorter format modified subsections of the grant to provide a different focus than the original, longer form. One of the sections that changed was switching from a “Background and

Significance” section to a section entitled “Significance.” In the original format the Background and Significance consisted of an extensive, multipage review of the literature that described the field in which the proposed research was being conducted. This section also contained a statement, within the context of the large literature review, of why the research described in the proposal was significant. In the new format, however, the purpose of the Significance section (note the lack of the word Background in the section heading) is to focus entirely on the just that... the significance that the research presented in the Research Training Plan has to impact the field of study. *This section is not intended to replace the Background and Significance section from the old format!* Therefore, the inclusion of a several page discussion of background information is not required, and within the shorter format, which for a Ruth L. Kirschstein NRSA training grant is only six pages, the luxury of having such an extensive discussion is not feasible.

The purpose of the “Significance” section is to explicitly state why your work is significant in relation to your field of study and how the results from the proposed project will impact the field. The absence of the word “Background” in this new format is not meant to imply that this section does not contain any background information. Background literature is essential to provide the reader with enough context about the field of study so that they can evaluate your interpretation of how the proposed research is significant. In contrast, this background information should encompass only a few sentences and not several paragraphs, or even pages. In many respects, this section will provide essentially the same information found in the first paragraph of the Specific Aims page (see above), and in fact it is advisable to paraphrase the first paragraph of the Specific Aims page. However, you will provide more detail in the Significance section in discussing the literature evidence that creates the foundation of your proposed work and how your work is essential for advancing the field.

Once you have provided enough evidence to create a solid background foundation, identify the gap in knowledge in the field: “Despite this information, the mechanism by which X does Y to contribute to disease progression is not yet known.” Once you have identified the deficiency, explicitly state why this is a problem to advance the field: “Without understanding the mechanism by which X does Y, it will be difficult to develop novel therapies for the treatment of the

disease.” Then explicitly state in ***bold, underlined, italics***: “***Therefore, the contributions of the present proposal are significant because it will be the first study to...***” As in every other important statement within the Research Training Plan (hypothesis, objective, long-term goals, etc.), be explicit and detailed in your statement. Again, the use of bold, underlined, italics draws the reader’s eye and makes it easier for a potentially tired reviewer to see that you have explicitly stated the significance of the work. Finally, as with the Specific Aims, end the Significance section with a statement that informs the reader exactly how the successful completion of the proposed research will push the field forward and could be used for future studies: “By understanding the mechanism by which X does Y we will be able to identify new molecular targets to be used for the development of novel pharmaceutical therapies for the treatment of the disease.” As with the Specific Aims, the reviewers like to see that you are able to think past the present project to see the overall implications of the work and that the project is not simply “research for research sake.”

5.3 APPROACH (≈ 5.5 PAGES)

The old NIH grant format contained sections for Background and Significance, Preliminary Studies, and Research Design. The new, shorter format contains two sections: Significance (which was discussed above) and Approach. Therefore, the background, preliminary data, and research design are all encompassed within the new Approach section, in essence condensing nearly 10–15 pages of writing into an approximately 5.5 page space. This may at first seem like an insurmountable task. However, the purpose of creating the new format was to help facilitate the review process by decreasing the amount of time a reviewer spent reading an application. Therefore, the new format condenses the writing from a broad-spectrum document to a more focused work that is meant to contain only information that is absolutely essential to support and describe the proposed project.

To condense and focus your writing, it is often beneficial to think of the Approach section in terms of the Specific Aims. What this means is that instead of providing background information and preliminary data *for the entire project*, separate the Approach into parts that correspond to the number of aims that you have proposed and then provide the background information and preliminary data essential to

support that individual specific aim. Within each section, or specific aim, organize the writing to include three subsections entitled Rationale, Preliminary Data, and Experimental Design. For example, if you are proposing a project with two specific aims, the Approach will be separated into two parts, one part for each aim. The title of each section will be the title of the Specific Aim, *exactly as written on the Specific Aims page*, followed by subheadings for each part:

“Specific Aim 1: To examine the role of the phosphorylation of key factors in development and as a contributor to the pathology of the disease.”

Rationale: This section includes the *literature evidence* that supports the objective and working hypothesis *for this aim*.

Preliminary Data: This section includes the *preliminary data obtained by the applicant* that supports the hypothesis and the feasibility of the project *for this aim*.

Experimental Design: This section describes the experiments and analyses that you propose to address the working hypothesis *for this aim*. This section also includes a description of the expected results, potential problems, and alternatives should problems arise.

5.3.1 Rationale

About one paragraph in length, the Rationale provides background that supports the working hypothesis *for each individual aim*. It is in this section that you discuss the *literature evidence* that was used to support the objective of the aim. Much of the same literature evidence mentioned in the first paragraph of the Specific Aims page and in the Significance section will be used in the Rationale. However, the most detail is used here to describe the specifics of the literature. You want to explicitly describe the results in the literature that you have used to support your working hypothesis for this aim. Once you have described the literature evidence, summarize what you have just written by explicitly stating how this evidence supports the hypothesis or the feasibility of the aim: “Taken together, this evidence shows that....” After this, as with the Specific Aims and the Significance, state what the gap in knowledge is *as it relates to the aim under discussion*: “However, despite this knowledge, the mechanism by which phosphorylation contributes to the molecular mechanisms of disease pathology is not yet known.” Follow this statement with a clear and explicit statement of the objective and working hypothesis *for this aim*.

again written in ***bold, underlined, italics***: “Therefore, the objective of *this aim* is to test the working hypothesis that....”

5.3.2 Preliminary Data

In addition to solid literature support, reviewers almost always want to see preliminary data that supports the hypothesis you have proposed. Through the preliminary data you also give the reviewer confidence that you are technically capable of performing the proposed research and that your model system and/or hypothesis are valid and functional. The validity and functionality of your model system are important. Your training period, regardless of the granting mechanism (F30, F31, or F32), will be about 2–3 years. Therefore, the reviewers do not want to see a proposed project in which you will spend a majority of your time developing or validating a novel model system. They want to see an experimental model in place and know that you are capable of using this model to obtain viable data to address a specific question.

After beginning this section by stating; “In addition to published reports, my preliminary data supports the hypothesis that...” systematically present *your* preliminary data. If you include unpublished data from another member of the lab, it is essential that you identify this fact. Confusion among the reviewers regarding who actually did the work presented in the Research Training Plan will affect the score of this section and may affect the overall impact score. In addition, it is critical that the inclusion of the figures be presented in an ordered, logical, and neat manner. Many times an application will be submitted in which the figures appear to have been haphazardly imported into the document with no apparent logic for where and how the figures were placed. Visually this gives the impression of sloppy work and results in a poor first impression, which may suggest to the reviewer that the lack of attention to detail in putting together the application may be indicative of the type of science the applicant will perform or the training that they will receive. Remember, the first impression a reviewer will have is the visual impression. The appearance of sloppy work or a document with no “white space” to provide rest for the eye may predispose a potentially tired reviewer to a negative impression before they even begin to read your science.

When discussing your data, it is recommended to use one paragraph for each experiment, point, or conclusion that you are presenting.

This physical and visual separation of experiments allows the reviewer to focus on one thought and idea at a time and gives a visual impression of discrete conceptual units. Also, by devoting one paragraph to each experiment it is easy to import the figure illustrating this data so that it is embedded within the paragraph in which the data is being discussed. In addition, you want to make the basic assumption that the person reading your application will know nothing about your field of research and therefore may not implicitly understand why you performed each experiment or why the results are important to support your hypothesis. It is more than likely that the reviewer reading your grant may be familiar with the techniques you are using, but they will know very little about the field in which you are working. Therefore, you must be explicit, detailed, but yet concise as you describe the thought processes underlying each experiment. In essence, walk the reviewer through each experiment starting with why the experiment was performed, how the experiment was performed, what the results looked like, and the conclusions drawn from these results.

The following rubric can serve as a model for the construction of each individual paragraph of the Preliminary Data section. First, tell the reader exactly what the purpose of the experiment is, how it derived from literature evidence or unpublished data, and how it relates to the hypothesis or model system. “Literature evidence suggests that phosphorylation of the transcription factor is important for regulating differentiation. However, to date, no experiments have been performed to test this idea. Therefore, to determine how phosphorylation at specific sites affects the functions of the transcription factor we tested the ability of different phospho-mutants to alter DNA binding.” Once you have established the reason for performing the experiment, provide them with just enough information, usually one to three sentences, to understand how the experiment was performed. This description does not need to include minute details, such as buffers used or concentrations of reagents but should be broader strokes that include the experimental system used, the read out that provided the data, and how the data was analyzed.

After discussing the experimental system you next want to describe the results of the experiment. Do not assume that the reviewer will understand or be able to interpret the data simply by looking at your figure! Too many times an applicant will simply write “As evident in

Figure X, treatment of cells with the drug inhibits differentiation,” without providing an explanation of what the figure is showing, what the control is, what differentiation of this cell type looks like, etc. As stated repeatedly, the reviewer will most likely not be versed in your field of research, let alone be able to interpret data without at least a minimal explanation. Making the assumption that the reader may have an expertise that they might not truly have will only frustrate and anger your reviewer. Therefore, be sure to describe the data to the reader so they can make an intelligent evaluation of the data for themselves. Also, it is important to point out exactly what it is about the results that you want the reviewer to focus on. For example, “We observed the elongation of cells with fusion into multinucleated myotubes, which was confirmed by quantification of the percentage of nuclei present in multinucleated myotubes (Figure X). Further, the presence of the phospho-mutant inhibited differentiation, as evidenced by a decrease in elongation and percentage of multinucleated cells relative to cells expressing the wild-type transcription factor.” In general, it is not a good strategy to assume the reader will see exactly what you see in the data.

Finally, spell out your conclusions from the experiment and describe why these conclusions are important to support your hypothesis for the aim or to provide feasibility for the experimental model. “This data demonstrates that the ectopic expression of the phospho-mutant inhibits myogenesis, supporting the idea that the non-phosphorylated form is essential for differentiation. Therefore, this conclusion supports our hypothesis that....” If the data provides feasibility or validity of the new experimental model system, state this fact as follows: “This data demonstrates that we have all of the reagents required for the successful completion of this Aim and that the model system utilized for all experiments is valid to study our working hypothesis.” Once you have discussed all of your preliminary data for that specific aim, provide a summary statement to further highlight how, when examined as a whole, the mass of data you presented supports the idea that your project has a high level of feasibility and the hypothesis is sound. “Taken together, published reports combined with our preliminary data demonstrate that the expression of the oncogenic protein results in distinct morphological and biological effects on primary cell differentiation. These observations, which most likely result from global changes in transcriptional regulation, provide solid evidence to support the idea

that the presence of the oncogenic protein is capable of altering global transcriptional regulatory networks to result in the observed changes in differentiation, proliferation, and cellular movement.”

5.3.3 Experimental Design

After establishing the feasibility of your hypothesis and the validity of your experimental model through literature evidence and preliminary data, you next logically lay out the series of experiments that you will use to address the working hypothesis of this Aim. As with the Preliminary Data section, each individual experiment will be described in its own paragraph or sentence with the experiments being numbered in sequential order (i.e., Experiment #1, Experiment #2, etc.). **Begin each experiment with a descriptive title that tells the reader the purpose of this experiment:** “Experiment #1: Determining the effects of phosphorylation of the transcription factor on cellular proliferation.” **Follow this title with an introductory sentence to tell the reader how this experiment fits into context of the larger scope of the aim:** “Literature evidence demonstrates that the transcription factor is involved in multiple aspects of cellular functions, including proliferation. Our preliminary data demonstrates that phosphorylation of the transcription factor contributes to some of these phenotypes. Therefore, this experiment directly tests the role that phosphorylation of the transcription factor plays in cellular proliferation.”

After placing the experiment in context, provide several sentences detailing the experimental design itself. As with the Preliminary Data, it is not necessary to provide the minute details of the experiment (i.e., buffer concentrations, reaction volumes, incubation times, etc.). **However, it is essential to provide significant details that will allow the reader to evaluate the construction of the experiment and the analysis of the results.** This means you should **detail the technique** that you will be using to perform the experiment. You also need to **describe what samples you will use within the experiment and why you are including them**, what are the **positive and/or negative controls** that will be included, what are the **time points** that will be used (if appropriate) and exactly why are you choosing those time points, and what is the **output that you will use to determine the results**. Finally, you must include a description of **how you will analyze the results, reproducibility, and statistics**: “To determine how the phospho-mutant alters

cellular proliferation, we will compare the results obtained with the mutant to those of cells expressing the wild-type factor. We will perform all experiments in triplicate and normalize values for the negative control of cells not expressing either protein.” It is not necessary to discuss the expected results from the analysis at this stage. This information will be provided later in its own section (see below).

One question that arises in the construction of the Experimental Design component of the Research Training Plan is whether a section detailing the exact methods to be used should be included. In the old grant format, where an applicant had fewer space constraints, it was possible to dedicate a full page or even more describing the minutiae of the experimental details in a discrete section dedicated to methods. However, the new format does not allow for such usage of space. The reviewers generally make the assumption that a trainee will be experienced enough to know the details of an individual experiment or if they don't, that they will have the intellectual resources in the laboratory to troubleshoot and learn these details. The reviewers are interested in seeing the “bigger picture” of the experimental design, as described above, and that the applicant understands why they are doing the experiment, what are the essential samples to be used in the experiment, what is the basic assay and read out for the assay, and how will they analyze the results. Therefore, it is usually not recommended to include a specific section of the Experimental Design dedicated to a description of the methods.

5.3.4 Expected Results

To convince the reviewers that you will be capable of interpreting the results of your experiments, you need to provide them with a description of what you expect your results to look like, and how you will interpret them, should your hypothesis be correct. You want to include brief descriptions of the expectations you have for all of the experiments included in the Experimental Design. This section can be difficult to write given the simple fact that sometimes the reason you are doing the experiment in the first place is to determine what will happen. In some cases, you might have preliminary data that will give you very solid groundwork to predict what you will see: “Based on our preliminary data in which the mutation of the transcription factor resulted in an inhibition of the effect, we expect to observe a decrease in our

experimental output with our mutant when compared relative to the wild-type control.” Sometimes, too, you just don’t know what you will see and you have no preliminary data or literature evidence to allow you to make an educated guess. However, you can supply the reader with a *hypothetical* situation that is based on your hypothesis, being very careful to explicitly tell the reader that it is just that... a hypothetical situation: “At present, it is difficult to determine how mutation of the transcription factor will affect cellular biology. However, assuming the *hypothetical* situation in which loss of the site is essential for proliferation, then we would expect to observe a decrease in proliferation rate of the mutant relative to the wild-type control.” In essence, prove to the reader that once you get the data and the results from the experiments that you will know how to evaluate them and to interpret them based on your hypothesis.

5.3.5 Potential Problems and Alternatives

Finally, the reviewers want to see that you, the applicant, are aware that problems can, and most likely will exist in the project and that you have alternative methods should you encounter these problems. Remember, if successful, the federal government will be giving you upwards of \$100,000–\$150,000 in total for your training. They want assurance that if you run into problems that derail your project that this money will not be wasted. Many Research Training Plans suffer from the very simple fact that the applicant did not include any description of potential problems and alternatives to these problems. What is important is that you *do not state that you expect no problems!* This is science. The people reading your application are scientists, many of whom have been working in research for years if not decades. They all know that research is fraught with problems both technical and intellectual. Therefore, the statement that there should be no problems will be viewed for what it is... a naïve statement. However, if there is a technique that you are using that is standard practice in the lab in which you are working you can state the following: “The techniques described in this aim are routinely performed within the lab and as such are not expected to present any major *technical* difficulties.” You must be sure to follow this statement up by identifying some valid problems (e.g., transfection efficiencies are inadequate and limits of detection are not feasible) and provide descriptions of viable experimental alternatives to these problems.

Most importantly, unless you have solid evidence that supports your hypothesis incontrovertibly, consider very hard the simple fact that your hypothesis may be wrong. Hypotheses are developed specifically to be tested through experimentation in order to achieve an answer. Part of your training in basic research is to learn that sometimes the answer to these questions are “no” and that your hypothesis as originally constructed is incorrect. Therefore, you must provide the reader with a solid description of what you intend to do should your hypothesis be incorrect, either in part or in its entirety. Are there other pathways that may be considered? Are there other explanations that could lead to the same phenotype that could then be tested? Let them see that if your hypothesis is incorrect, that you know what to do, and that you have alternative options or explanations to test so that the money given to you by the federal government will not be wasted. You don’t want to undersell or undermine your hypothesis, as that is the cornerstone of your project. However, recognize the fact that hypotheses may not necessarily be correct as constructed.