2016 PATH awardee Amariliz Rivera has allowed us to share her pre-proposal as an example.

Burroughs Wellcome Fund
Investigators in the Pathogenesis of Infectious Disease
Five Critical Questions

This award provides $500,000 over a period of five years to support accomplished investigators at the assistant professor level to study pathogenesis, with a focus on the interplay between infectious agents and their hosts, shedding light on how both are affected by their encounters. The awards are intended to give recipients the freedom and flexibility to pursue new avenues of inquiry and higher-risk research projects that hold potential for significantly advancing understanding of the pathogenesis of infectious disease.

What is your proposed research question? Up to 50 words/~250 characters

Diminished neutrophil or monocyte counts place patients at high risk to invasive fungal infections. Is this enhanced susceptibility due only to the absence of essential antifungal effectors or does absence of one innate cell affect the function of another? Our central hypothesis is that bidirectional innate cell licensing critically controls antifungal immunity. In this process antifungal innate effector mechanisms are regulated by the continuous interactions between monocytes and neutrophils. We propose that this process can be targeted to boost antifungal immunity in susceptible populations.

Why is the work you propose *interesting* and *important*? How will it change our understanding of how disease unfolds?" Up to 200 words/~1000 characters

The number of patients susceptible to invasive fungal infections across the world continues to rise at an alarming pace yet current antifungal drugs are often inadequate. Immune-based interventions hold the promise of significantly improving patient outcomes however our understanding of relevant targets for antifungal defense is limited. Innate cells are important direct effectors of fungal pathogen eradication and low numbers of neutrophils or monocytes results in enhanced susceptibility to invasive fungal infections. It has thus been assumed that enhanced susceptibility to fungal infections in patients with low innate cell counts is due only to the absence of effector cells. Recent findings from my lab indicate that monocytes and their derivative cells are direct antifungal effectors as well as regulators of neutrophil antifungal function. We find that in the absence of monocytes, neutrophils are less capable of inactivating fungal cells. Similarly we find that in the absence of neutrophils, monocytes are less capable of eliminating fungal cells. We propose that monocytes and neutrophils engage in bidirectional innate cell licensing for optimal fungal pathogen eradication. This is a novel conceptual advance that may change the way we understand risk factors to fungal infection. We propose that cytopenic patients are at high risk for fungal infection due to the lack of important antifungal effectors as well as impaired response of the remaining innate cells. By deciphering the factors that mediate this pathway we will identify novel immune-based therapeutic targets.

How will you do it? What is your approach? Up to 200 words/~1000 characters

Using a combination of methods perfected in my lab to measure antifungal immunity and a discovery-based systems biology approach we have developed a platform to identify novel factors in antifungal immunity. We employed this unbiased platform to discover a group of novel candidate factors that might control bidirectional innate cell licensing. Our goal is to test systematically and rigorously the effects of these factors in innate cell antifungal responses and to establish whether human innate cells can similarly be activated by analogous factors. We have strong preliminary data validating the importance of two new pathways in antifungal innate responses in mice. We will test whether these factors activate antifungal activities in human innate cells. We will also validate the importance of other factors in mice and human cells. The identification of bidirectional innate cell licensing as a central pathway that controls antifungal immunity represents a novel conceptual advance that will change the way we think about risk factors to fungal infection. Moreover, our mechanistic studies on factors that mediate bidirectional innate cell licensing will validate novel targets with potential therapeutic benefit for susceptible patient populations.

What about your outlook/background/training gives you great insight into this problem?
Up to 100 words/~500 characters

I have been studying host immune responses to fungal pathogens for over 10 years. As a postdoctoral fellow in the laboratory of Dr. Eric Pamer I gained significant expertise on immunity to infection with a focus on fungal pathogens. I was the first to generate a CD4 T cell receptor transgenic mouse to model fungus-specific T cell responses. With this tool I was able to show that monocyte-derived dendritic cells were essential for the activation of fungus-specific CD4 T cells and dissected the distinct contributions of Dectin-1 and TLR/MyD88 innate activating signals to T cell differentiation. I have built upon this expertise in my independent research program and recently published that monocytes are essential innate effectors that regulate neutrophil function in defense to aspergillosis. I bring to this project extensive relevant expertise and a global view of the host immune system and how it specifically responds to fungal pathogens.

How is this work innovative and different from that supported by your other external funding?
Up to 100 words/~500 characters

In these studies I will lead my research group to undertake a series of more high-risk experiments than those supported by our current federal funding. I seek to expand my laboratory's strong expertise in fungal immunology in mouse models to human responses. I am very excited by the potential clinical implications of our ongoing unpublished findings and with support from this BWF award we would be able to attain the necessary resources to validate our exciting findings in mice to human cells. Furthermore, this award would support the validation of novel factors not currently covered by our grants. In addition to building a strong and unique research program on antifungal immunity I strive to provide guidance and support to young scientists from disadvantaged backgrounds. As a female scientist of Hispanic origin I'm uniquely poised to encourage and aid other women and minority students in their quest to become independent scientists. An award from the BWF would provide recognition and financial support to further my scientific aspirations.

2016 BWF Investigator in the Pathogenesis of Infectious Disease Amariliz Rivera, PhD at Rutgers New Jersey Medical School has allowed us to share the pre-proposal she submitted as the first part of her successful application. Her application shows **one** way to approach it. There are many other ways to answer the 5 questions.