A. Personal Statement

The proposed research will investigate the induction of pro-inflammatory cytokines by YscF and T3S needle proteins. YscF was identified by my lab as a modest protective antigen for plague. Subsequent work in the lab to improve YscF as a vaccine component led to our novel observation that exposure of human and mouse cells to YscF results in the production of pro-inflammatory cytokines. Interestingly, we also found that deleting the N-terminus of YscF resulted in increased amounts of cytokines from cells exposed to the truncated protein. In this proposal we seek to define structure-function relationships and to analyze the biological role of needle protein induced cytokine expression. Additionally, we will analyze the signaling pathways and receptors involved in sensing YscF. My lab has extensive experience in bacterial genetics and in structure/function analysis of protein interactions. Previous NIH funded research in my lab demonstrated the role of the LcrG/LcrV protein-protein interaction in controlling the activity of the T3S of Y. pestis. The preliminary data leading to this proposal and our publications on cytokine induction by needle proteins, on a novel plague resistant mouse model, and the work demonstrating that YscF is a protective antigen demonstrates that my lab has acquired the techniques necessary for this proposal. My lab is transitioning from a bacterial genetics focused lab to a broader focus concentrating on innate immune responses in plague. The combination of a successful track record in structure function experiments and my data with YscF induction of cytokines in vitro and ex vivo demonstrate that this project will be successful.

B. Positions and Honors

Positions and Employment

1987 - 1990  Research Assistant, North Dakota State University, Department of Veterinary and Microbiological Sciences, Fargo, ND
1990 - 1995  Teaching Assistant, Washington State University, Department of Microbiology, Pullman, WA
1995 - 1995  Postdoctoral Fellow, University of Kentucky, Department of Microbiology, Lexington, KY
1998 - 2005  Assistant Professor, University of North Dakota, School of Medicine and Health Sciences, Grand Forks, ND
2005 -       Associate Professor, University of North Dakota, School of Medicine and Health Sciences, Grand Forks, ND

Other Experience and Professional Memberships

1987 -       Member, American Society of Microbiology
1998 -       Member, American Association for the Advancement of Science

Honors

C. Contribution to Science

1. My early work on Yersinia pestis centered on the understanding of protein:protein interactions involved in the activation of the Ysc Type III secretion system. While I was a post-doc with Susan Straley at the University of Kentucky I discovered a novel interaction between a positive (LcrV) and and a negative regulator of secretion (LcrG). This work led to the LcrG-titration model of T3S regulation. Further work on this model at the University of North Dakota led to structure/function analysis of the LcrG/LcrV interaction, and a demonstration that is the interaction were disrupted, the T3S system could not be activated.

   
   
   

2. LcrV (V antigen) is a well known virulence factor and protective antigen of Yersinia pestis. Work I was involved with at the University of Kentucky led to the first demonstration that LcrV was required for translocation of effectors into eukaryotic cells and that LcrV was found on the surface of Y. pestis prior to contact with eukaryotic cells. Additionally, we demonstrated that LcrV was required for YopB to leave Y. pestis to complete the translocon.


Yersinia pestis is known to have 3 protective antigens: the F1 capsule, LcrV (the V antigen), and YscF, the T3S needle protein. My laboratory established that YscF is a protective antigen for Y. pestis.


Interactions between pathogenic type III secretion systems and the innate immune system are poorly understood. My lab has discovered that T3S needle proteins are pathogen associated molecular patterns that interact with TLR2 and TLR4 to induce the innate immune system. We have also demonstrated that some type III needle proteins have N-terminal modifications that influence the interaction with the innate immune system.


The T3S system has emerged as a target for small molecule therapeutics. My lab has identified the translocon protein YopD as a target for one small molecule inhibitor.

D. Research Support

Completed Research Support

R01 AI051520-05
Nilles, Matthew L. (PI)
02/01/03-01/31/09
Protein Interactions in Type III Secretion in Y. pestis
Role: PI

R01 AI051520-01A1
Nilles, Matthew L. (PI)
02/01/03-01/31/08
Protein Interactions in Type III Secretion in Y. pestis
Role: PI

R01 AI051520-02
Nilles, Matthew L. (PI)
02/01/03-01/31/08
Protein Interactions in Type III Secretion in Y. pestis
Role: PI

R01 AI051520-03
Nilles, Matthew L. (PI)
02/01/03-01/31/08
Protein Interactions in Type III Secretion in Y. pestis
Role: PI

R01 AI051520-04
Nilles, Matthew L. (PI)
02/01/03-01/31/08
Protein Interactions in Type III Secretion in Y. pestis
Role: PI

1, Novadigm Therapeutics
Nilles, Matthew (PI)
04/01/11-05/31/12
YscF as an adjuvant
The project was to examine the use of YscF to boost heterologous immune responses.
Role: PI

188354, Air Force Research Laboratories/Defense Threat Redyction Agency
Matthew Nilles (PI)
01/01/08-12/31/10
Use of epitope-directed nanobodies as passive immunotherapeutic agents against Yersinia pestis
Role: PI

U54-AI065357, NIH
John Belisle (PI)  
11/01/05-10/31/07  
YscF as a vaccine candidate for the Plague  
National Institute of Allergy and Infectious Disease. Region VIII Rocky Mountain Regional Center for Excellence in Biodefense Research, Developmental project; “YscF as a vaccine candidate for the Plague.” Dr. John Belisle, CSU is the RCE PI. Dr. Matthew Nilles was the PI of the Developmental project, Dr. David Bradley was the Co-PI.  
Role: CPI

U01-AI54815, NIH

Brian Green (PI)  
08/01/03-01/31/07  
Characterization of Proteomes of Category A Pathogens  
Role: CPI