BIOGRAPHICAL SKETCH

NAME: Nilles, Matthew

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
North Dakota State University, Fargo, ND	BS	12/1987	Biotechnology
North Dakota State University, Fargo, ND	MS	08/1990	Microbiology
Washington State University, Pullman, WA	PHD	05/1995	Microbiology
University of Kentucky, Lexington, KY	Postdoctoral Fellow	08/1998	Bacterial pathogenesis

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 an analyze of 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.

1. Matson JS, Durick KA, Bradley DS, Nilles ML. Immunization of mice with YscF provides protection from Yersinia pestis infections. BMC Microbiol. 2005 Jun 24;5:38. PubMed PMID: 15978133; PubMed Central PMCID: PMC1168899.
2. Jessen DL, Osei-Owusu P, Toosky M, Roughead W, Bradley DS, Nilles ML. Type III secretion needle proteins induce cell signaling and cytokine secretion via Toll-like receptors. Infect Immun. 2014 Jun; 82(6):2300-9. PubMed PMID: 24643544; PubMed Central PMCID: PMC4019191.
3. Osei-Owusu P, Jessen Condry DL, Toosky M, Roughead W, Bradley DS, Nilles ML. The N terminus of type III secretion needle protein YscF from Yersinia pestis functions to modulate innate immune responses. Infect Immun. 2015 Apr;83(4):1507-22. PubMed PMID: 25644012; PubMed Central PMCID: PMC4363447.

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.

    a. Nilles ML, Williams AW, Skrzypek E, Straley SC. Yersinia pestis LcrV forms a stable complex with LcrG and may have a secretion-related regulatory role in the low-Ca2+ response. J Bacteriol. 1997 Feb; 179(4):1307-16. PubMed PMID: 9023216; PubMed Central PMCID: PMC178830.

    b. Matson JS, Nilles ML. LcrG-LcrV interaction is required for control of Yops secretion in Yersinia pestis. J Bacteriol. 2001 Sep;183(17):5082-91. PubMed PMID: 11489861; PubMed Central PMCID: PMC95384.

    c. Matson JS, Nilles ML. Interaction of the Yersinia pestis type III regulatory proteins LcrG and LcrV occurs at a hydrophobic interface. BMC Microbiol. 2002 Jun 28;2:16. PubMed PMID: 12102728; PubMed Central PMCID: PMC117220.

    d. Hamad MA, Nilles ML. Structure-function analysis of the C-terminal domain of LcrV from Yersinia pestis. J Bacteriol. 2007 Sep;189(18):6734-9. PubMed PMID: 17644582; PubMed Central PMCID: PMC2045164.

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.

    a. Nilles ML, Fields KA, Straley SC. The V antigen of Yersinia pestis regulates Yop vectorial targeting as well as Yop secretion through effects on YopB and LcrG. J Bacteriol. 1998 Jul;180(13):3410-20. PubMed PMID: 9642196; PubMed Central PMCID: PMC107298.

b. Fields KA, Nilles ML, Cowan C, Straley SC. Virulence role of V antigen of Yersinia pestis at the bacterial surface. Infect Immun. 1999 Oct;67(10):5395-408. PubMed PMID: 10496922; PubMed Central PMCID: PMC96897.

3. 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.

   a. Matson JS, Durick KA, Bradley DS, Nilles ML. Immunization of mice with YscF provides protection from Yersinia pestis infections. BMC Microbiol. 2005 Jun 24;5:38. PubMed PMID: 15978133; PubMed Central PMCID: PMC1168899.

4. 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.

   a. Jessen DL, Osei-Owusu P, Toosky M, Roughead W, Bradley DS, Nilles ML. Type III secretion needle proteins induce cell signaling and cytokine secretion via Toll-like receptors. Infect Immun. 2014 Jun; 82(6):2300-9. PubMed PMID: 24643544; PubMed Central PMCID: PMC4019191.
   b. Osei-Owusu P, Jessen Condry DL, Toosky M, Roughead W, Bradley DS, Nilles ML. The N terminus of type III secretion needle protein YscF from Yersinia pestis functions to modulate innate immune responses. Infect Immun. 2015 Apr;83(4):1507-22. PubMed PMID: 25644012; PubMed Central PMCID: PMC4363447.

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

   a. Jessen DL, Bradley DS, Nilles ML. A type III secretion system inhibitor targets YopD while revealing differential regulation of secretion in calcium-blind mutants of Yersinia pestis. Antimicrob Agents Chemother. 2014;58(2):839-50. PubMed PMID: 24247143; PubMed Central PMCID: PMC3910845.

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