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Nagarajan, Uma M

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BIOGRAPHICAL SKETCH

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NAME: Nagarajan, Uma M

eRA COMMONS USER NAME (credential, e.g., agency login): NAGARAJANUMA

POSITION TITLE: Assistant Professor of Pediatrics and Microbiology/Immunology

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Madras, Madras, India.	B.S.	06/1986	Chemistry
University of Madras, Madras, India	M.S.	06/1988	Biochemistry
Madurai-Kamaraj University, Madurai, India.	Ph.D.	11/1997	Biochemistry
Case Western Reserve University, Cleveland, OH	Post doc	03/96-04/97	Immunology
Emory University, Atlanta, GA	Post doc	05/97-06/00	Immunology

A. Personal Statement

Chlamydia trachomatis infection contributes significantly to the $16 billion total medical costs of treatment. Rates of infection in young women (<16 y) of age have been steadily increasing over years and currently no vaccines are available. Infection can lead to pelvic inflammatory disease (PID) and infertility in some women, resulting from an inflammatory response. My research is focused on the inflammatory response to infection and its contribution to oviduct pathology. I have about 14 years of experience studying chlamydial pathogenesis and the studies have been funded largely by the NIAID. We have examined the contribution of cell death pathways; specifically, type I IFNs, caspase-11, and IL-1R signaling in oviduct pathology during *Chlamydia* infection using a mouse model and human cell lines. We have established that innate immune signaling pathways are the major contributors of host pathology during *Chlamydia* infection by identifying specific molecular pathways leading to disease in animal models. We are currently working on therapeutically blocking these pathways without affecting protective response to infection.

In my career in science, I have been very fortunate in having the right mentors at the right times. I wish to pass this on and serve as a good mentor for my students, trainees and post-doctoral fellows. I believe that in addition to the science, one of the most satisfying parts of academic research is the opportunity to interact with fellow scientists, graduate students and post-doctoral fellows. Along these lines, I hope to play an integral role in teaching, training and mentoring graduate students, post doctoral fellows and clinical research fellows in UNC. My goal is to help in growing them into independent thinking scientists with exceptional analytical skills and technical rigor.

B. Positions and Honors

Positions and Employment

2000-2002 Senior Associate, Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta GA.
2002-2004 Research Assistant Professor, Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR.
2004-2007 Instructor, Department of Pediatrics, Division of Pediatric Infectious Disease, and Department of Microbiology and Immunology, UAMS, Little Rock, AR.
2007-2012 Assistant Professor, Division of Pediatric Infectious Disease, and Department of Microbiology and Immunology, UAMS, Arkansas Children's Hospital Research Institute, Little Rock, AR.
2012-2013 Assistant Professor, Division of Infectious Disease, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.
2013- Assistant Professor, Division of Pediatric Infectious Diseases, Department of Pediatrics and Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Honors and Awards

1986 B.S. Chemistry, Top Ranked student, University of Madras, Madras, India
1986 Certificate of Merit awarded by The Royal Society of Chemistry, London
1988 M.S. Biochemistry, Top Ranked student, University of Madras, Madras, India
1989 Competitive award for Junior and Senior Research Fellowship, Council of Scientific & Industrial Research, India 2003-
2008 Reviewer on Special Emphasis Panel 2 for RFA AI-08-005- NIAID "Development of Novel interventions and tools for the control of Malaria, Neglected Tropical diseases and their vectors".2007-11
2009 Reviewer on Special Emphasis panel for RFA#AI-08-020-NIAID "Immune defense mechanisms at the Mucosa (R21)

2010 Reviewer on F13 Infectious Diseases and Microbiology Fellowship Review Panel (NIAID

C. Contributions to Science

1. **Regulation of MHC class II gene expression:** Major histocompatibility complex class II proteins play a pivotal role in the generation of CD4 T cell responses. The importance of MHC class II expression is exemplified in the bare lymphocyte syndrome (BLS). Patients with BLS have severe primary immunodeficiency and fail to mount T cell-mediated immune responses. BLS patients cannot transcribe MHC class II genes due to mutations in one of four transcription factors (CIITA, RFX5, RFXAP, and RFX-B/ANK) required for MHC class II expression. In my post-doctoral work, I made seminal contribution to this field by identification, cloning, and characterization of RFX-B/ANK, one of the essential transcription factors that regulate MHC class II expression. The novelty of this finding and importance led to a cover page article in the leading journal, *Immunity*. Subsequently, I have identified novel mutations within the RFX-B gene that cause BLS and determined its association with other BLS factors. Subsequent work mapped the nuclear localization signals of RFX-B and its binding partners. This work was also chosen as a cover page article in *Journal of Immunology*.

   a. Nagarajan UM, Louis-Plence P, DeSandro A, Nilsen R, Bushey A, Boss JM. RFX-B is the gene responsible for the most common cause of the bare lymphocyte syndrome, an MHC class II immunodeficiency. *Immunity*. 1999 Feb;10(2):153-62. PubMed PMID: 10072068.
   b. Nagarajan UM, Peijnenburg A, Gobin SJ, Boss JM, van den elsen PJ. Novel mutations within the RFX-B gene and partial rescue of MHC and related genes through exogenous class II transactivator in RFX-B-deficient cells. *J Immunol*. 2000 Apr 1;164(7):3666-74. PubMed PMID: 10725724.
   c. Nagarajan UM DeSandro AM, Boss JM. Associations and interactions between bare lymphocyte syndrome factors. *Mol Cell Biol.* 2000 Sep;20(17):6587-99. PubMed PMID: 10938133; PubMed Central PMCID: PMC86141.
   d. Nagarajan UM, Long AB, Harreman MT, Corbett AH, Boss JM. A hierarchy of nuclear localization signals governs the import of the regulatory factor X complex subunits and MHC class II expression. *J Immunol.* 2004 Jul 1;173(1):410-9. PubMed PMID: 15210800

2. **Chlamydia genital infection and type I IFN response:** *Chlamydia trachomatis* is a common sexually transmitted bacterial pathogen that can cause oviduct inflammation and subsequent tubal infertility. At University of Arkansas for Medical Sciences, I initiated an independent study on the role of type I IFNs during chlamydial pathogenesis, as type I IFN-inducible genes predominated in a micro-array analysis of RNA from *Chlamydia*-infected cells. The first line of

defense against chlamydiae is the innate immune response. Using type I interferon deficient mice, we reported that type I IFNs exacerbate *C. muridarum* genital infection through an inhibition of the chlamydial-specific CD4 T-cell response. Next, to identify how *Chlamydia* infection triggers type I interferon response, the contribution of different pattern recognition receptors was studied. This work ruled out the role for known TLRs and RNA sensors that contribute to type I interferon response. We identified that the protein STING is essential for IFNβ induction during *Chlamydia* infection. This paper was accepted "as is" without any modifications by the Editors and was featured as one of the top 8 articles for "In this issue" section in the same issue of Journal of Immunology. Very recently, at University of North Carolina, we identified the PRR essential for IFNβ expression as cGAS, a DNA sensor, upstream of STING in Chlamydia-induced IFNβ response. This was the first report of the role for cGAS in a bacterial infection. This paper was also featured by the Editors of *Journal of immunology* for "In this issue" section, as one of the top 10% of the article of that issue. (***** indicates corresponding author)

a. Nagarajan UM*, Ojcius DM, Stahl L, Rank RG, Darville T. Chlamydia trachomatis induces expression of IFN-gamma-inducible protein 10 and IFN-beta independent of TLR2 and TLR4, but largely dependent on MyD88. J Immunol. 2005 Jul 1;175(1):450-60. PubMed PMID: 15972679.
b. Nagarajan UM*, Prantner D, Sikes JD, Andrews CW Jr, Goodwin AM, Nagarajan S, Darville T. Type I interferon signaling exacerbates Chlamydia muridarum genital infection in a murine model. Infect Immun. 2008 Oct;76(10):4642-8. PubMed PMID: 18663004; PubMed Central PMCID: PMC2546839.
c. Prantner D, Darville T, Nagarajan UM*. Stimulator of IFN gene is critical for induction of IFN-beta during Chlamydia muridarum infection. J Immunol. 2010 Mar 1;184(5):2551-60. PubMed PMID: 20107183; PubMed Central PMCID: PMC2863030.
d. Zhang Y, Yeruva L, Marinov A, Prantner D, Wyrick PB, Lupashin V, Nagarajan UM. The DNA sensor, cyclic GMP-AMP synthase, is essential for induction of IFN-β during Chlamydia trachomatis infection. J Immunol. 2014 Sep 1;193(5):2394-404. PubMed PMID: 25070851; PubMed Central PMCID: PMC4212656.

3. **Role of IL-1β and inflammasome during chlamydia infection.** IL-1β is secreted at high levels in the genital secretion during *Chlamydia muridarum* genital infection in the mouse model. The goal of this study was to characterize the role of IL-1 signaling and the inflammasome-activation pathways during genital chlamydial infection. Our findings demonstrate that IL-1β is secreted by macrophages and neutrophils. Additionally, prestimulation of macrophages by chlamydial ligands may account for the elevated levels of pro-IL-1β mRNA observed in vivo in this cell type. *Chlamydia* infection weakly activates inflammasome by NLRP3 pathway. However, inflammasome activation play

minimal role in development of pathology during infection. A major finding from this study was that IL-1 signaling played a major role in development of oviduct pathology. Our current findings suggest that the pathology associated with IL-1 signaling during infetcion is largely driven by IL-1α and not IL-1β.

a. Prantner D, Nagarajan UM. Role for the chlamydial type III secretion apparatus in host cytokine expression. Infect Immun. 2009 Jan;77(1):76-84. PubMed PMID: 18852236; PubMed Central PMCID: PMC2612240.
b. Prantner D, Darville T, Sikes JD, Andrews CW Jr, Brade H, Rank RG, Nagarajan UM. Critical role for interleukin-1beta (IL-1beta) during Chlamydia muridarum genital infection and bacterial replication-independent secretion of IL-1beta in mouse macrophages. Infect Immun. 2009 Dec;77(12):5334-46. PubMed PMID: 19805535; PubMed Central PMCID: PMC2786476.
c. Lacy HM, Bowlin AK, Hennings L, Scurlock AM, Nagarajan UM, Rank RG. Essential role for neutrophils in pathogenesis and adaptive immunity in Chlamydia caviae ocular infections. Infect Immun. 2011 May;79(5):1889-97. PubMed PMID: 21402767; PubMed Central PMCID: PMC3088137.
d. Nagarajan UM, Sikes JD, Yeruva L, Prantner D. Significant role of IL-1 signaling, but limited role of inflammasome activation, in oviduct pathology during Chlamydia muridarum genital infection. J Immunol. 2012 Mar 15;188(6):2866-75. PubMed PMID: 22331066; PubMed Central PMCID: PMC4321901.

Complete List of Published Works in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1ZmZDXYRHdeAJ/bibliography/40221422/public/?sort=date&direction=ascending.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

2R01AI067678-07A1 Nagarajan (PI)
4/1/07 – 3/31/19.
Title: “Mechanism of *Chlamydia*-induced type I IFN response”. The goals of the Project are to delineate the mechanism by which caspase-11 activation, alarmins, and IL-1 signaling lead to oviduct pathology during *Chlamydia* infection and to develop therapeutic interventions of these pathways in a mouse model.
Role: PI

1R21AI124010-01 Nagarajan (PI)
7/1/16-6/30/18
Title: “IRF3 is a novel mediator of cell death during Chlamydia infection”. The goals of the project are to investigate the cell-intrinsic nature of IRF3-dependent cell death response to infection in vivo and the potential mediators of IRF3-mediated response during infection.
Role: PI

Intramural:
UNC-TTSA Phase II grant application Darville/Randell (PI)
08/15/09-08/14/15
Title: "Primary human fallopian tube cell models for research on *Chlamydia trachomatis* - induced disease"
Role: Co-PI

Completed Research Support

U19 AI084024-01 Darville (PI)
09/30/13-08/31/14
The UPMC Sexually Transmitted Infections Cooperative Research Center- Project (4) Determine protective T cell responses to Chlamydia trachomatis infection.
Role: Co-I

Supplements for
Collaborative Science (SCS) Lupashin (PI)
06/01/11 to 05/31/2013
R01 GM083144 09
Title: "Role of Golgi trafficking during *Chlamydia trachomatis* infection".
Role: Co-PI

R01 (CA143130-A1) Nakagawa (PI)
06/01/10 to 05/31/12
Title: "Understanding and Enhancing T-Cell Responses to High Risk Human Papillomaviruses". The major goal of this project is to develop therapeutic vaccine for HPV. The adjuvant Candin enhances the T cell response significantly. My specific role was to determine the pathogen recognition receptor used by the adjuvant Candin in human Langerhans cells.
Role: Co-I