Douglas T Golenbock

Address: University of Massachusetts Medical School

Country: USA

Position Title: Chief, Division of Infectious Diseases and 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	Completion Date	Field of Study
University of Michigan , Ann Arbor, MI	BS	05/1975	Zoology
University of Michigan , Ann Arbor, MI	MD	05/1980	Medicine

A. Personal Statement
My lab has a long - standing interest in innate immune activation. Our group was one of the first in the world to study Toll receptors. Subsequently, our group has developed one of the largest and best reagent collections of any lab in the world to investigate issues related to innate immunity, including over 120 knockout mouse lines (not including mice with multiple KOs and transgenes), hundreds of transformed macrophage cell lines, cDNAs, purified ectodomains of TLRs and more. Although I am an adult Infectious Diseases specialist, my major interests are in the mechanisms of inflammation, such as the nature of the LPS receptor, the role of LPS/LOS in gonoccocal infections , nucleic acid recognition in both bacterial infections and malaria, and beta amyloid induced inflammation in Alzheimer's disease. I am particularly interested in pursuing the AD work because of its potential translational value, both with respect to the progression of Alzheimer's Disease and AD-related seizures. Indeed, I am working with a pharmaceutical company that is developing NLRP3 inhibitors.

One aspect of my work is that it has alw ays been highly collaborative. It is worth noting that Dr. Futai and I have recently submitted a manuscript together, Dr. Heneka and I have published 6 papers together with 2 manuscripts under review and that Dr. Kurt Jones and I have published 20 papers together, hold joint lab meetings and sha re two NIH grants.

B. Positions and Honors
Positions and Employment

1999 – 2001 Professor, Dept. of Medicine and Microbiology, Boston Univ. School of Medicine, Boston, MA
1980 – 1983 Internal Medicine Residency, The George Washington University Hospital, Washington, DC
1984 – 1987 Fellow, Infectious Diseases, University of Wisconsin Hospital and Clinics, Madison, WI
1987 – 1990 Post- doctor ate, Dept. of Biochemistry, Univ. of Wisconsin, Madison, WI

1990 – 1995	Assistant Professor, Dept. of Medicine & Microbiology, Boston Univ. School of Medicine, Boston, MA
1995 – 1999	Associate Professor, Dept . of Medicine & Microbiology, Boston Univ. School of Medicine, Boston, MA
2001 – present	Professor of Medicine (tenured); Microbiology and Physiological Systems, Univ. of Massachusetts Medical School, Worcester, MA
2001 – present	Chief, Division of Infectious Diseases and Immunology, Univ. of Massachusetts Medical School, Worcester, MA

Organizer for international meetings

1994 Organizer and Chair, "Sepsis", Woods Hole, MA
1998 Organizer and Chair, International Endotoxin Society Meeting, Santa Fe, NM
2004 Organizer and Chair, Toll 2004, Taormina, Italy
2006 Organizer and Chair, Toll 2006, Salvador, Brazil
2008 Organizer and Chair, Toll 2008, Cascais Portugal
2011 Organizer, Toll2011, Riva del Garda, Italy
2015 Organizer and Chair, Toll2015, Marbella, Spain
2018 Organizer and Chair, Toll2018, Porto Portugal

Honors

1986 Squibb Award, National Foundation for Infectious Diseases
1993 Junior Faculty Award, American Cancer Society
1997 Elected to the American Society for Clinical Investigation
2007 Elected to the Association of American Physicians
2011 Elected to the Fellowship, American Society of Microbiology
2014 Sheldon Greisman Award recipient, International Endotoxin and Innate Immunity Society
2014 Elected to the Brazilian Academy of Sciences, Brazilian Academy of Sciences
2015 Awarded the Pillar Chair for Biomedical Sciences, UMass Medical School

Languages

English (primary language)
Spanish (fluent)
Portuguese (fluent)
French (conversational)

C. Contribution to Science

1. Identification of the "LPS Receptor": I began my scientific career 30 years ago in aneffort to find the receptor for LPS, which at the time was considered to acti vate cells "non - specifically." The existence of an LPS receptor was thought to require faith, and some thought the searc h would prove to be fruitless. Before the discovery of TLRs, for example, my work was instrumental in changing this dogma, and was particularly effective in providing evidence that the LPS receptor was a transmembrane signal transducer that bound ligand on the cell surface. Perhaps the most influential of my reports relates to the tetraacylated lipid A precursor known as lipid IVa, which has species - specific effects. We proposed at the time that the true LPS receptor (which was unknown) would be responsible for this species specificity. Indeed, CD14 failed this test (a) Delude et al., but TLR4 did not (b). Another controversy about the LPS receptor related to a paper in Nature suggest ing that TLR2 was the LPS receptor (Godowsky et al, Nature. Sept 17, 1998; 395:284- 288); this

finding differed markedly from the Nobel prize winning paper by Beutler published a few months later in Science. We found that Chinese hamsters (as well as CHO ce lls) were actually null for TLR2 expression and yet responded to LPS by producing cytokines and prostaglandins (c). This was conclusive evidence that TLR2 was not needed for LPS responses, and led to our current appreciation of the role of TLR4. Finally, our group provided the first evidence that MD - 2, which was first identified by Miyake et al. and said to be a chaperone for TLR4, was actually an essential part of the LPS receptor (d).

a. Delude RL, Savedra R Jr, Zhao H, Thieringer R, Yamamoto S, Fenton MJ, Golenbock DT. CD14 enhances cellular responses to endotoxin without imparting ligand - specific recognition. Proc Natl Acad Sci U S A. 1995 Sep 26;92(20):9288 - 92. PubMed PMID: 7568119 ; PubMed Cen tral PMCID: PMC40970.

b. Lien E, Means TK, Heine H, Yoshimura A, Kusumoto S, Fukase K, Fenton MJ, Oikawa M, Qureshi N, Monks B, Finberg RW, Ingalls RR, Golenbock DT. Toll- like receptor 4 imparts ligand- specific recognition of bacterial lipopolysaccharide. J Clin Invest. 2000 Feb;105(4):497 - 504. PubMed PMID: 1 0683379 ; PubMed Central PMCID: PMC289161.

c. Heine H, Kirschning CJ, Lien E, Monks BG, Rothe M, Golenbock DT. Cutting edge: cells that carry A null allele for toll- like receptor 2 are capable of re sponding to endotoxin. J Immunol. 1999 Jun 15;162(12):6971 -5. PubMed PMID: 10358136.

d. Schromm AB, Lien E, Henneke P, Chow JC, Yoshimura A, Heine H, Latz E, Monks BG, Schwartz DA, Miyake K, Gole nbock DT. Molecular genetic analysis of an endotoxin nonresponder mutant cell line: a point mutation in a conserved region of MD - 2 abolishes endotoxin - induced signaling. J Exp Med. 2001 Jul 2;194(1):79- 88. PubMed PMID: 11435474; PubMed Central PMCID: PMC2193443.

2. When TLRs were discovered, there was clarity only with respect to the LPS response. An important question was whether other microbes were sensed by TLRs. My group was the first to demonstrate that TLR2 was the TLR primarily responsible for recognition of Gram- positive bacteria (a).

a. Yoshimura A, Lien E, Ingalls RR, Tuomanen E, Dziarski R, Golenbock D. Cutting edge: recogniti on of Gram- positive bacterial cell wall components by the innate immune system occurs via Toll - like receptor 2. J Immunol. 1999 Jul 1;163(1):1- 5. PubMed PMID: 10384090.

3. Our group has made several other important discoveries with respect to TLRs which, more or less, filled in big gaps in the basic understanding of TLRs at the beginning of the 2000s. The first of these discoveries was the identification of the TLR - adapter that we called TRAM (a) . Until we reported on TRAM, it was clear that at least one more TLR adapter must exist, and that this adapter was critical for the generation of type I interferons in response to LPS, which is a major part of the role of TRAM. Another central contribution we made to the field of innate immunity was the first description of an endolysosomal TLR, i.e., TLR9. At the time, TLRs were thought to be surface receptors, and we identified how TLR9 is induced to translocate from the endopl asmic reticulum to the lysosomal compartment when cargo is internalized in macrophages and dendritic cells (b,c).

a. Fitzgerald KA, Rowe DC, Barnes BJ, Caffrey DR, Visintin A, Latz E, Monks B, Pitha PM, Golenbock DT. LPS - TLR4 signaling to IRF - 3/7 and NF- k appaB involves the toll adapters TRAM and TRIF. J Exp Med. 2003 Oct 6;198(7):1043 - 55. PubMed PMID: 14517278; PubMed Central PMCID: PMC2 194210.

b. Latz E, Schoenemeyer A, Visintin A, Fitzgerald KA, Monks BG, Knetter CF, Lien E, Nilsen NJ, Espevik T, Golenbock DT. TLR9 signals after translocating from the ER

to CpG DNA in the lysosome. Nat Immunol. 2004 Feb;5(2):190- 8. PubMed PMID: 14716310.

c. Latz E, Verma A, Visintin A, Gong M, Sirois CM, Klein DC, Monks BG, McKnight CJ, Lamphier MS, Duprex WP, Espevik T, Golenbock DT. Ligand - induced conformational changes allosterically activat e Toll-like receptor 9. Nat Immunol. 2007 Jul;8(7):772 - 9. PubMed PMID: 17572678.

4. A fourth area in which we have recently contributed concerns the innate immune response to malaria, which we now believe involves a response to microbial DNA and hemozoin. Until we began our work, it was established dogma that the innate immune response in malaria was driven by the recognition of surface lipids such as glycosylphosphatidyl inositol anchors. Althou gh we found that GPI anchors were innate immune activators, it was clear that this dogma was wrong. In the middle part of the last decade, Akira et al. claimed that this was indeed incorrect, and that the innate immune response was due to direct interactio ns of TLR9 with hemozoin, a malaria crystal. Our work showed that this new dogma was incorrect as well, in that hemozoin does not bind DNA nor activate it directly. Rather, hemozoin has the capability of carrying DNA into cells where it can interact with TLR9 in the phagolysosome (a,b). We have subsequently found that hemozoin, whether it enters macrophages alone or as part of the food vacuole in intact schizonts, results in phagolysosomal deterioration, and the movement of DNA into the cytosol where AT - rich motifs (c) from Plasmodial DNA activate cytosolic DNA receptors. Hemozoin itself activates the NLRP3 inflammasome, while p lasmodial DNA activates AIM2 (b). Most importantly, nearly all of our findings in mice (or with mouse cells) seem to hold up with hu man cells. Thus, we have established parasite DNA and hemozoin as major activators of phagocytes in malaria.

a. Parroche P, Lauw FN, Goutagny N, Latz E, Monks BG, Visintin A, Halmen KA, Lamphier M, Olivier M, Bartholomeu DC, Gazzinelli RT, Golenbock DT. Malaria hemozoin is immunologically inert but radically enhances innate responses by presenting malaria DNA to Toll - like receptor 9. Proc Natl Acad Sci U S A. 2007 Feb 6;104(6):1919-24. PubMed PMID: 17261807; PubMed Central PMCID: PMC1794278.

b. Kalantari P, DeOliveira RB, Chan J, Corbett Y, Rathinam V, Stutz A, Latz E, Gazzinelli RT, Golenbock DT, Fitzgerald KA. Dual engagement of the NLRP3 and AIM2 inflammasomes by plasmodium- derived hemozoin and DNA during malaria. Cell Rep. 2014 Jan 16;6(1):196- 210. PubMed PMID: 24388751; PubMed Central PMCID: PMC4105362.

c. Sharma S, DeOliveira RB, Kalantari P, Parroche P, Goutagny N, Jiang Z, Chan J, Bartholomeu DC, Lauw F, Hall JP, Barber GN, Gazzinelli RT, Fitzgerald KA, Golenbock DT. Innate immune recognition of an AT- rich stem- loop DNA motif in the Plasmodium falciparum genome. Immunity. 2011 Aug 26;35(2):194-207. PubMed PMID: 21820332; PubMed Central PMCID: PMC3162998.

5. Finally, we were the first group to identify beta amyloid as an activator of the NLRP3 inflammasome. This work began with the recognition that beta amyloid directly activates the NLRP3 inflammasome in vitro (a), followed by our report that NLRP3 and caspase- 1 KO mice are protected from memory loss and associated pathology in the APP/PS1 model of disease (b).

a. Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, Fitzgerald KA, Latz E, Moore KJ, Golenbock DT. The NALP3 inflammasome is involved in the innate immune response to amyloid- beta. Nat Immunol. 2008 Aug;9(8):857 - 65. PubMed PMID: 18604209; PubMed Central PMCID: PMC3101478.

b. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira - Saecker A, Griep A, Axt D, Remus A, Tzeng TC, Gelpi E, Halle A, Korte M, Latz E, Golenbock DT. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013 Jan 31;493(7434):674- 8. PubMed PMID: 23254930; PubMed Central PMCID: PMC3812809.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/douglas.golenbock.1/bibliography/40625194/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

U19 AI089681- 08 Gazzinelli PI; UMASS Subcontract 07/01/17 - 03/31/24
NIH/NIAID
Amazonian International Center of Excellence on Malaria Research
This project aims to evaluate innate and acquired immunity in asymptomatic malaria.
Role: Co - I

R01 AI079293- 07 Douglas Golenbock/Katherine Fitzgerald (PI) 09/01/14 - 08/31/19
NIH/NIAID
Innate Immune Activation in Malaria
The ultimate goal is to define the relative role of malarial DNA in mediating innate immune responses during malarial infection and to definitively identify related DNA receptors.
Role: MPI

R37 G M54060- 20 Douglas Golenbock (PI) 07/01/13 - 04/30/18
NIH/NIGMS
Phagocyte Receptors for Lipid A
The major goals of this project are to identify elements of LPS signaling pathways in transfected cell lines
Role: PI

R21AI122160 Douglas Golenbock (PI) 05/31/2016- 05/30/18
NIH/NIAID
Recognition of Group B Streptococci by Innate Immune Sensors
The purpose of this grant is to define how GBS activates the type I interferon response.

R21AI124171 Douglas Golenbock (PI) 04/20/2016- 04/19/18
NIH/NIAID
Role of the cytosolic DNA sensor cGAS in malaria
The purpose of this grant is to determine the role of intracellular plasmodial DNA in activating the innate immune response in Colombian patients with P falciparum malaria.

Completed Research Support

R03 TW009007- 03 Douglas Golenbock (PI) 01/1 3 /13 - 02/29/16
NIH/NIAID – Fogarty International Center
Innate Immune Activation in Malaria

The purpose of this project is to gain a better understanding of why malaria causes disease in the hopes that better therapies can be devised, including an effectiv e vaccine
Role: PI

Life Science Moment Fund Douglas Golenbock/Garth Hall (PI) 07/01/13 - 12/31/15
UMASS
The role of Tau in inflammasome activation in Alzheimer's Disease
The goal of the project is to determine the role that exosomally secreted tau plays in inflammation - induced neurotoxicity in AD and in non AD tauopathy. It will be done in inducible tauopathy mutant mice 4510 crossed (b y Dr. Golenbock's lab) with NLRP3 and Caspase 1 knockout mutant mice. Parallel work will be performed on neuroblastoma cell lines via transient transfection and induction of stable tau lines currently in use in Dr. Hall's lab. The work at UML will consist of preparing exosomes from cell culture preparations in which human tau is overexpressed and also exosome preps fr om mouse tissue samples take at Dr. Golenbock's lab.

U19 AI084048 Douglas Golenbock (PI) 09/25/09 - 08/31/14
NIH/NIAID
Innate and Adaptive Immunity in Experimental and Human Gonoccocal Infection
The main objective is to be responsible administratively for all aspects of the Sexually Transmitted Diseases Cooperative Research Centers (STD- CRCs).

R01 AI079293 Douglas Golenbock/Katherine Fitzgerald (PI) 09/24/09 - 08/31/14
NIH/NIAID
Innate Immune Activation in Malaria
The ultimate goal is to define the relative role of malarial DNA in mediating innate immune responses during malarial infection and to definitively identify related DNA receptors.

U24 AI082663 Neal Silverman (PI) 04/01/09 - 03/31/14
NIH/NIAID
TLR Ectodomains for Microbial Detection and Therapeutics

R21 AI09587 - 01 Douglas Golen bock/Katherine Fitzgerald (PI) 07/01/11 - 06/30/13
NIH/NIAID
Role of PSTPIP1 in a Mouse Model of PAPA Syndrome

R37 GM54060 Douglas Golenbock (PI) 06/01/08 - 04/30/13
NIH/NIGMS
Phagocyte Receptors for Lipid A

R01 AI052455 Douglas Golenbock (PI) 08/15/02 - 03/31/13
NIH/NIAID
Group B. Streptococci and Toll - like Receptors
The major goal of this project is to determine the molecular basis of innate immune recognition of Group B. Streptococci.