BIOGRAPHICAL SKETCH

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NAME: **Harry B. Greenberg, MD**

eRA COMMONS USER NAME (credential, e.g., agency login): **GREENBERG.HARRY**

POSITION TITLE: **Professor of Medicine; Microbiology 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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Dartmouth College, Hanover, NH	B.A.	1966	Medicine
Columbia College of Physicians & Surgeons, New York, NY	M.D.	1970	Medicine
Stanford Univ. School of Medicine, Stanford, CA	Fellowship	1972-74	Medicine (GI Div.)

A. Personal Statement

I have devoted my research career to the study of medically important viral pathogens. My specific interests have focused on viral infections of the GI tract, liver and the respiratory tree. These interests have centered on viruses associated with substantial morbidity and/or mortality in both developed and less developed countries and range from basic studies of innate and acquired immunity and pathogenesis in cell culture and animal model systems to more translational investigations of antiviral immunity in animal model systems and people. Recently, my research efforts on rotavirus (RV) have centered on better defining the mechanistic role of innate and acquired immune mechanisms in regulating host range restriction and protection from reinfection in humans. These studies take advantage of several novel technologies including the ability to grow human intestinal enteroid cultures, simplified approaches to isolating human neutralizing monoclonal antibodies to rotavirus from human small intestine and the recent availability of a tractable reverse genetics system for rotavirus. On a more practical level, I have had a long-term interest in human vaccine development and this has allowed me to actively participate in the early development and ultimate licensure of two live attenuated orally administered human rotavirus vaccines and a live attenuated intranasally administered influenza vaccine.

1. Ding S, Mooney N, Li B, Kelly MR, Feng N, Loktev AV, Sen A, Patton JT, Jackson PK, Greenberg HB. Comparative Proteomics Reveals Strain-Specific β-TrCP Degradation via Rotavirus NSP1 Hijacking a Host Cullin-3-Rbx1 Complex. PLOS Pathog. Oct 5; 12(10): e1005929. doi: 10.1371/journal.ppat.1005929. PMID: 27706223, 2016.

2. Zhu S, Ding S, Wang P, Wang G, Lei X, Palm NW, Pan W, Zheng Y, Feng N, Lu J, Shan L, Abraham C, Fikrig E, Greenberg HB, Flavell RA. Nlrp9 inflammasome recognizes and restricts enteric viral infection in intestinal epithelial cells. Nature. Jun 29;546(7660):667-670. doi: 10.1038/nature22967. Epub 2017. PMID: 28636595

3. Nair N, Feng N, Blum LK, Sanyal M, Ding S, Jiang B, Sen A, Morton JM, He X, Robinson WH, Greenberg HB. VP4- and VP7-specific antibodies mediate heterotypic immunity to rotavirus in humans. Sci Transl Med. Jun 21;9(395). pii: eaam5434. doi: 10.1126/scitranslmed.aam5434, 2017. PMID: 28637924

4. Ding S, Diep J, Feng N, Ren L, Li B, Ooi YS, Wang X, Brulois KF, Li X, Kuo CJ, Solomon DA, Carette JE, Greenberg HB. STAG 2 deficiency induces IFN responses via cGAS-STING pathway and restricts virus infection. Nature Communications. 9: 1485. Published online 2018 Apr 16.

doi: 10.1038/s41467-018-03782-z, 2018. PMCID: PMC5902600

B. Positions and Honors

B.1. Positions and Employment

1972-1974	Research Associate, USPHS, NIAID, LID, NIH, Bethesda, MD
1976-1983	Medical Officer, USPHS, NIAID, LID, NIH, Bethesda, MD
1983-1989	Associate Professor of Medicine and Microbiology and Immunology, Stanford University
1988-1998	Chief, Division of Gastroenterology, Stanford University School of Medicine, Stanford, CA
1989- present	Professor of Medicine and Microbiology and Immunology, Stanford University
1991-1997	Medical Investigator, VA Palo Alto Health Care System, Palo Alto, CA
1996	Acting Chairman, Department of Medicine, Stanford University School of Medicine
1997-2000	Associate Chief of Staff for Research, VA Palo Alto Health Care System, Palo Alto, CA
1999-2000	Senior Associate Dean for Research, Stanford University School of Medicine, Stanford, CA
2000-2002	V.P. for Research, Medimmune Vaccines, Mountain View, CA. (LOA, Stanford University)
2002- 2017	Senior Associate Dean for Research, Stanford University School of Medicine, Stanford, CA
2002- present	Staff Physician, Medical Service, VA Palo Alto Health Care System Palo Alto, CA
2005-2006	Acting Co-Chairman, Department of Medicine, Stanford University School of Medicine
2008- 2018	Director of Spectrum, the NIH funded CTSA at Stanford University
2018-	Co-Director of Spectrum, the NIH funded CTSA at Stanford University
2018-present	Associate Dean for Research, Stanford University School of Medicine, Stanford, CA

B.2. Other Experiences and Professional Memberships

1980	American Society of Clinical Investigation
1992	Association of American Physicians
1991-1997	VA Medical Investigator Award
1994-2004	NIH Merit Award (R37)
2003-	Fellow, American Association for the Advancement of Science (AAAS)
2008-2009	President, American Society of Virology
2009-	Fellow, American Academy of Microbiology
2011- 2014	Co-Chair, NIAID, NIH Board of Scientific Counselors
2016-2017	Chair, Section on Medical Sciences, AAAS

B.3. Selected Honors and Awards

1966	Rufus Choate Scholar, Dartmouth College
1997	Public Health Service Commendation Medal
1997-2000	Member and Chairperson, Vaccines and Related Biologic Advisory Committee, FDA
2007	American Gastroenterology Association Mentors Award
2008	Walter Albion Hewlett Award, Stanford University
2015	Robert Chanock Lectureship, NIAID, NIH
2015	Distinguished Alumni Researcher Award, Columbia College Physicians and Surgeons

C. Contributions to Science

A). Rotavirus: Rotaviruses (RV) are the single most important cause of severe gastroenteritis in young children and the leading cause of diarrhea related infant mortality. Over the past 40 years my research group has investigated many aspects of RV biology, immunology and pathogenesis using *in vitro* cell culture systems, a tractable suckling mouse model that employs wild-type homologous murine RVs and heterologous non-murine RVs and a variety of immunologic, cell biologic, high throughput technologies as well as vaccine studies in people. Our findings have expanded many critical areas of RV biology as well laying the groundwork for developing several successful vaccines.

1) *RV gene coding assignments and the targets of neutralizing immunity*. We used classic viral genetics, murine and human monoclonal antibodies, molecularly expressed RV proteins and murine RV infection model systems to demonstrate that the two RV surface proteins (VP4 and VP7) were the only targets of neutralizing antibody in vitro, that passive or active delivery of antibodies to either protein *in vivo* was protective, that VP4 was the viral attachment protein and that dimeric IgA monoclonal antibodies to the major internal structural protein (VP6)

of the RV protected suckling mice, presumably via an intracellular neutralization process. The studies below and others have been pivotal to the field. They demonstrated for the first time a method to genetically manipulate RVs by gene reassortment and used viral genetics, murine and human monoclonal antibodies and an animal model system to identify the targets of protection. These findings provided much of the basic scientific ground work for subsequent vaccine development.

a) Greenberg HB, Kalica AR, Wyatt RG, Jones RW, Kapikian AZ, Chanock RM. Rescue of noncultivatable human rotavirus by gene reassortment during mixed infection with its mutants of a cultivatable bovine rotavirus. Proc. Natl. Acad. Sci. USA 78:420-424, 1981. PMID 6264442

b) Burns JW, Siadat-Pajouh M, Krishnaney A, Greenberg HB. Protective effect of rotavirus VP6-specific IgA monoclonal antibodies that lack neutralizing activity. Science 272:104-107, 1996. PMID 8600516

c) Feng N, Lawton JA, Gilbert J, Kuklin N, Vo P, Prasad BVV, Greenberg HB. Inhibition of rotavirus replication by a non-neutralizing, rotavirus VP6-specific IgA Mab. J Clin. Invest. 109:1203-1213, 2002. PMC 150959

d) Zhu S, Ding S, Wang P, Wang G, Lei X, Palm NW, Pan W, Zheng Y, Feng N, Lu J, Shan L, Abraham C, Fikrig E, Greenberg HB, Flavell RA. Nlrp9 inflammasome recognizes and restricts enteric viral infection in intestinal epithelial cells. Nature. Jun 29;546(7660):667-670. doi: 10.1038/nature22967. Epub 2017. PMID: 28636595

2) *Studies of acquired immunity to rotavirus.* Virtually every mammalian species is infected with its own distinct family of RVs and in these species, infection causes diarrheal disease in the young. Murine RVs were the first members of the RV family to be discovered. The availability of highly tractable, homologous and heterologous infection models of RV in mice greatly facilitated studies of viral immunity and pathogenesis. In a series of studies to clarify the role of humoral and cellular immunity in RV infection we discovered that CD8/CD4 T cells assist in and hasten the resolution of infection but have limited ability to prevent reinfection. We also examined the role of lymphocyte homing in modulating infection and characterized the role of several trafficking receptors in modulating infection. Finally, we examined the role of the innate immune system in modulating the acquired mucosal antibody response. These studies provided a scientific basis for vaccine development and some of the first demonstrations of the importance of lymphocyte trafficking to microbial immunity in the GI tract.

a) Franco MA, Greenberg HB. Role of B cells and cytotoxic T lymphocytes in clearance of and immunity to rotavirus infection in mice. J. Virol. 69:7800-7806, 1995. PMC 189723

b) Feng N, Jaimes MC, Lazarus NH, Monak D, Zhang C, Butcher EC and Greenberg HB. Redundant Role of Chemokines CCL25/TECK and CL28/MEC in IgA Plasmablast Recruitment to the Intestinal Lamina Propria After Rotavirus Infection. Journal of Immunology.176:5749-59, 2006. PMID: 16670280

c) Deal E, Lahl K, Narvaez CF, Butcher E, Greenberg H. Plasmacytoid dendritic cells promote rotavirus-induced human and murine B cell responses. JCI. 123 (6): 2464-74. 2013. PMID: 23635775. PMC 3668833

3) *Studies of the rotavirus tissue tropism and host range restriction and their relationship to innate immunity.* RV infection is substantially, but not exclusively, restricted to the small intestine and is host range restricted (HRR) in the intestine- that is a homologous host RV (human rotavirus in a human) replicates much more efficiently than a heterologous RV (bovine RV in a human) in the intestine. We carried out an important series of studies to better define the mechanistic and genetic determinants of these restrictions. We found that RV replication was at least 1000-fold more efficient in the small bowel than at systemic sites such as MLN or liver, but that replication did also occur systemically. We determined that host range restriction was much less apparent at systemic sites than in the gut. Using genetic studies, we found that the RV VP4 (the RV receptor), NSP1 (a viral poly-functional IFN inhibitor) and VP3 (the viral capping enzyme) were important determinants of replication restriction both in the gut and systemically and that HRRs were primarily abrogated when IFN signaling was interrupted. These studies were seminal in identifying the genetic basis for cell tropism and HRR and demonstrating the pivotal role of viral entry and host specific interferon responses in regulating replication.

a) Feng N, Kim BK, Fenaux M, Nguyen H, Vo P, Omary B, Greenberg HB. The role of interferon in homologous and heterologous rotavirus infection on the intestines and extra-intestinal organs of suckling mice. J. Virol. 82(15): 7578-90, 2008. PMC 2493311

b) Feng N, Sen A, Wolf M, Vo P, Hoshino Y, Greenberg HB. Roles of VP4 and NSP1 in determining the distinctive replication capacities of simian rotavirus RRV and bovine rotavirus UK in the mouse biliary tract. J. Virol. 85 (6): 2686-2694, 2011. PMID: 21191030. PMC 3067955

c) Feng N, Yasukawa L, Sen A, Greenberg HB. Permissive replication of homologous murine rotavirus in the mouse intestine is primarily regulated by VP4 and NSP1. J Virol. 87(15):8307-16, 2013. PMID: 23698306. PMC 3719818

4) *Studies of the mechanistic basis for interferon stimulation and antagonism by RV.* More recently we carried out a series of *in vitro* and *in vivo* studies to examine the mechanisms by which RV NSP1 inhibits the inductive and amplification phases of the interferon response. Since several of the currently licensed RV vaccines are based on HRR and the differential effects of homologous and heterologous NSP1s on restricting RV replication are substantial, these studies have provided fundamental insight into the basis for attenuation of several vaccines.

a) Sen A, Dermody T, Pruijssers AJ, Garcia-Sastre A, Greenberg H. The early interferon response to rotavirus is regulated by PKR and depends on MAVS/IPS-1, RIG-I, MDA-5, and IRF3. J.Virol. 85 (8): 3717-32, 2011. PMID: 21307186. PMC 3126121

b) Sen, A., Rothenberg, M.E., Mukherjee, G., Feng, N., Nair, N. T., Johnstone, I. M., Clarke, M. F., and Greenberg, H. B. Innate immune response to homologous rotavirus infection in the small intestinal villous epithelium at single-cell resolution. PNAS, 109(50), 20667-20672, 2012. PMID: 23188796. PMC 3528539

c) Sen, A., Rott, L., Phan, N., Mukherjee, G., and Greenberg, HB. The rotavirus NSP1 protein inhibits IFN-mediated STAT1 activation. J Virol 88(1):41-53, 2014. PMID: 24131713. PMC 3911692

d) Lin JD, Feng N, Sen A, Balan M, Tseng HC, McElrath C, Smirnov S, Peng J, Yasukawa LL, Durbin RK, Durbin JE, Greenberg HB, Kotenko SV. Distinct roles of type 1 and type III interferons in intestinal immunity to homologous and heterologous rotavirus infections. PLOS Pathogens. 2016 April; 12(4): e1005600. Published online 2016 April 29. doi: 10.1371/journal.ppat.1005600. PMCID: PMC4851417

e) Ding S, Mooney N, Li B, Kelly MR, Feng N, Loktev AV, Sen A, Patton JT, Jackson PK, Greenberg HB. Comparative Proteomics Reveals Strain-Specific β-TrCP Degradation via Rotavirus NSP1 Hijacking a Host Cullin-3-Rbx1 Complex. PLOS Pathog. Oct 5; 12(10): e1005929. doi: 10.1371/journal.ppat.1005929. PMID: 27706223, 2016.

f) Sen A, Sharma A, Greenberg HB. Rotavirus degrades multiple type interferon receptors to inhibit IFN signaling and protects against mortality from endotoxin in suckling mice. J Virology. Doi:10.1128/JVI.01394-17. Posted online October 2017. 2017 Oct 25. pii: JVI.01394-17. 2017. [Epub ahead of print] PMID:29070687

B) Influenza: Annual and pandemic influenza virus (IV) infection creates a very large mortality and/or morbidity burden on all age groups worldwide. We have had IV vaccines available for over 60 years but they are not optimal, especially in the elderly and very young. We are examining the immune response to influenza vaccination (live and inactivated) in healthy adults and the elderly with a focus on the B cell plasmablast response. These studies have demonstrated that the decreased vaccine response in the elderly is not due to decreased secretion of IV specific antibody from individual B cells but to a decreased total B cell response. Other findings relate to the mechanism by which the novel pH1N1 pandemic IV elicited increased heterotypic responses and the fact that live attenuated and wild type infections are more efficient at inducing heterotypic antibodies than inactivated vaccines.

5) *Studies of Immune responses to Influenza vaccination and infection in people.*

a) Sasaki S, Sullivan M, Narvaez CF, Holmes T, Furman D, Zheng N-Y, Nishtala M, Wrammert J, Smith K, James J, Dekker C, Davis MM, Wilson PC, Greenberg HB, and He X-S. Limited efficacy of inactivated influenza vaccine in elderly individuals is associated with decreased production of vaccine-specific antibodies. JCI. 121 (8): 3109-3119, 2011. PMID: 21785218. PMC 3148747

b) He XS, Sasaki S, Baer J, Khurana, S, Golding H, Treanor J, Topham D, Sangster M, Jin H, Dekker C, Subbarao K, Greenberg H. Heterovariant cross-reactive B-cell responses induced by the 2009 pandemic influenza A/H1N1 vaccine. JID. (207): 288-296, 2013. PMID: 23107783. PMC 3532823

c) Sasaki S, Holmes TH, Albrecht RA, García-Sastre A, Dekker CL, He XS, Greenberg HB. Distinct cross-reactive B-cell responses to live attenuated and inactivated influenza vaccines. J Infect Dis. 2014 Sep 15;210(6):865-74. Epub 2014 Mar 27. PMID: 24676204. PMC 4200073

d) Xiao-Song He, Tyson H. Holmes, Mrinmoy Sanyal, Randy A. Albrecht, Adolfo GarcÃa-Sastre, Cornelia L. Dekker, Mark M. Davis, and Harry B. Greenberg. Distinct patterns of B-cell activation and

priming by natural influenza infection versus inactivated influenza vaccination. J Inf Dis. 2014 Oct 21. pii: jiu580. [Epub ahead of print] PMID: 25336731. PMC 4366605

List of Published Work in NCBI:

http://www.ncbi.nlm.nih.gov/pubmed/?term=greenberg+hb

Ongoing Research Support

UL1 TR001085 Greenberg (Co-PI) 9/26/13–12/30/18
NIH / NCATS (no cost extension)
Stanford Center for Clinical & Translational Education and Research (Spectrum)
This CTSA transforms clinical and translational research and education at Stanford. It consists of 12 interrelated programs focused on ensuring that discoveries get translated into health improvements
Role: Principal Investigator

GRH0022 Greenberg 7/1/10 – 12/31/18
VA Merit Review Award
Rotavirus: Studies of Intestinal Tropism and Innate and Heterotypic Immunity
This award examines two separate but related components of the rotavirus-host interaction: 1) Characterize *in vivo* the effects of homologous murine and heterologous simian RV infection on STAT3 related transcription factors; 2) Determine the basis for heterotypic immunity following RV infection.

U19 AI057229 Davis 4/1/09 – 3/31/19
NIH / NIAID
Influenza Immunity: Protective Mechanisms against Pandemic Respiratory Virus
The major goal of this project is to use vaccine-induced and naturally acquired influenza A immunity as a model for comprehensive, integrated analyses of adaptive and innate immune mechanisms and antimicrobial protection of the respiratory tract in children and adults. The primary goal of Project 1 is to study B cell immunity to influenza.
Role: Project 1 Leader and Co-Director

U19 AI116484 Kuo 5/1/15 – 4/30/20
NIH / NIAID
Stanford Cooperative Research Center for Novel, Alternative Model Systems for Enteric Diseases
Project 2: The Determinants of Rotavirus Host Range Restriction in Human Intestinal Organoids
In this project we propose to employ human organoid technologies incorporating epithelial-only or epithelial/mesenchymal components to create a human intestinal tissue-specific model of human rotavirus replication focusing on the genetic determinants of host range restriction of human rotaviruses in human IECs.
Role: Project 2 Leader

1R01 AI125249 Greenberg 2/15/17 – 2/14/22
NIH/ NIAID
Regulation of Rotavirus Replication, Virulence and Host Range Restriction by the Innate Immune System
The specific aims are to: 1) Determine the structural basis and *in vivo* activity of NSP1-mediated **β-TrCP** degradation. 2) Identify the molecular mechanisms underlying MAVS inhibition by VP3 in a strain-and host-specific fashion both *in vitro* and *in vivo*. 3) Identify the mechanism of RV NSP1-mediated inhibition of STAT1 activation and the intestinal cell origin of the IFN responses to RV infection.

Recently Completed Research Support

U01 AI115715 Greenberg 1/1/15 – 12/31/17
NIH / NIAID
Mucosal and Systemic Immune Responses to Influenza Virus
These studies are expected to generate new knowledge on the underlying mechanism for protective immunity against wild-type influenza viruses through collaboration with investigators at the NIH clinical Center involving a human challenge model of WT influenza. The findings will guide the development of improved seasonal and pandemic flu vaccines.