BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Ralph Steven Baric	Co-Investigator
eRA COMMONS USER NAME (b) (6)	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
North Carolina State University, Raleigh, NC	BS	1977	Zoology
North Carolina State University, Raleigh, NC	Ph.D.	1982	Microbiology
University of Southern CA, School of Med, (Los Angeles, CA)	Post-Doc	1986	Microbiology

A. Personal Statement: The Baric laboratory uses genetic, biochemical, molecular and immunologic approaches to study the molecular mechanisms regulating viral evolution, virus immunity, virus-host interactions and vaccine mediated protective immunity using coronaviruses (CoV), noroviruses and flaviviruses (Dengue) as models. SARS-CoV and MERS-CoV are used as models to address fundamental questions in genetics, structure-function analyses, entry and cross species transmission, fidelity regulation, host susceptibility allele mapping, pathogenesis as well as therapeutic design and testing. Synthetic genomics and reverse genetics are used to create a panel of CoV molecular cDNA clones for SARS-CoV, SARS-like bat coronaviruses (SL-CoV), MERS-CoV, several human coronavirus, Dengue 1-4 and Zika virus. The Baric laboratory has developed key animal models of human disease, including SARS-CoV and SL-CoV pathogenesis in young and aged mice, and CRISPR gene edited mice encoding permissive mutations in the murine dipeptidyl peptidase receptor, making the animals permissive for MERS-CoV infection and disease.

The Baric laboratory has longstanding expertise in CoV evolution and emergence, replication, virus-receptor interactions, genetics, animal model development and pathogenesis. Not only has the Baric laboratory made fundamental breakthroughs in all aspects of CoV genetics, biology and immunology, but it has designed, developed and tested small molecule inhibitors and vaccines against emerging CoVs. Our group has collaborated with Drs. Daszak, Shi and Wang on SARSr-CoVs for the past 3 years, and this R01 is a natural development of this collaboration.

***Qualifications by Publication*: : >314 total publications, >120 since 2013, H-index: 84.**
http://www.ncbi.nlm.nih.gov/sites/myncbi/ralph.baric.1/bibliography/40583903/public/?sort=date&direction=ascending.

Key Manuscripts

1. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS (2017). Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. **Science Translational Medicine**, 9(396). eaal3653. PMC5567817.
2. Scobey T, Yount BL, Sims AC, Donaldson EF, Agnihothram SS, Menachery VD, Graham RL, Swanstrom J, Bove PF, Kim JD, Grego S, Randell SH, Baric RS (2013). Reverse genetics with a full-length infectious cDNA of the Middle East respiratory syndrome coronavirus. **Proceedings of the National Academy of the Sciences**, 110(40):16157-62. PMC3791741.
3. Menachery, VD, Yount, BL, Debbink, K, Agnihothram, S., Gralinski, LE, Plante, JA, Graham, RL, Scobey T, Ge SY, Donaldson EF, Randell SH, Lanzavecchia A, Marasco WA, Shi Z, Baric RS (2015). A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. **Nature Medicine**, Nov 9. doi: 10.1038/nm.3985. [Epub ahead of print]. PMID:26552008.

4. Cockrell AS, Yount BL, Scobey T, Jensen K, Douglas M, Beall A, Tang XC, Marasco WA, Heise MT, Baric RS (2016). A Mouse Model for MERS Coronavirus Induced Severe Respiratory Distress Syndrome. **Nature Microbiology**, 2:16226. PMC5578707.

B. Positions and Honors.

Employment Experience:

1986-92 Assistant Professor, Department of Parasitology and Laboratory Practice and Department of Epidemiology, University of North Carolina (UNC), Chapel Hill, NC
1992-2001 Associate Professor, Departments of Epidemiology and Microbiology & Immunology, UNC Chapel Hill
2001- Professor, Departments of Epidemiology and Microbiology and Immunology, UNC Chapel Hill

Selected Awards/Honors:

2018 US Natl. Acad. Sci. "China-US Workshop on Challenges of Emerging Infections, Laboratory Safety and Global Health Security, Jan 2018, Galveston, Tx.
2015 US Natl. Acad. Sci./UK Royal Society Workshop: Sackler Scientific Forum on the Trends in Synthetic Biology and Gain of Function and Regulatory Implications, U.K.
2015 US Natl. Acad. Sci. "China-U.S. Workshop on the Challenges of Emerging Infections, Laboratory Safety, and Global Health Security" September 28-30 in Beijing, China
2015 MERS-CoV Stakeholders Workshop, invited panelist, NIH
2014 National Academy of Sciences: Working Group on Risks and Benefits of Gain of Function Research
2005-15 Review Board, *J. Virology*
2008-15 Senior Editor, *Plos Pathogens*
2008 US Natl. Acad. Sci. Working Group: Gene Sequence Methods for Classification of Select Agents
2007-08 Associate Editor, *Plos Pathogens*
2005-09 Permanent Member, NIH VirB Study Section
2003 Finalist/Runner-up, World Technology Award
1989-94 Established Investigator: American Heart Association
1984-86 Harvey Weaver Scholar, National Multiple Sclerosis Society

C. Contributions to Virology: The Baric laboratory has made significant contributions to our understanding of all aspects of CoV biology, including: i) CoV genetics and reverse genetics for SARS-CoV, MHV, MERS-CoV, HCoV NL63, PEDV, TGEV, bat SARS-like CoV (SL-CoV), BtCoV HKU-5 and others, ii) demonstration of proof-reading activities in the CoV genome, iii) identification and characterization of bat SL-CoV with prepandemic potential, iii) coronavirus transcription mechanisms, iv) mechanisms of interferon antagonism and interferon stimulated gene expression control, v) virus host susceptibility allele mapping, vi) epitope mapping of human monoclonal antibodies, vii) identification of broad spectrum human monoclonal antibodies against SARS-CoV and MERS-CoV, viii) mouse models of human disease (MERS-CoV and SARS-CoV), ix) aging and emerging coronavirus vaccine efficacy, and x) live and attenuated vaccine design in young and aged animal models of human disease. The Baric laboratory has also made major contributions to norovirus immunology and flavvirus reverse genetics and the human immune responses after infection.

Some representative major contributions outside and within the CoV field include:

1. (b) (4)

2. Gralinski LE, Ferris MT, Aylor DL, Whitmore AC, Green R, Frieman MB, Deming D, Menachery VD, Miller DR, Buus RJ, Bell TA, Churchill GA, Threadgill DW, Katze MG, McMillan L, Valdar W, Heise MT, Pardo-Manuel de Villena F, Baric RS (2015) Genome Wide Identification of SARS-CoV Susceptibility Loci Using the Collaborative Cross. **PLOS Genetics,** 11(10): e1005504. PMID:26452100.
3. Lindesmith L, Moe C, Marionneau S, Ruvoen N, Jiang X, Lindblad L, Stewart P, LePendu J, Baric R (2003). Human susceptibility and resistance to Norwalk virus infection. **Nature Medicine**, 9(5):548-53. PMID:12692541.

4. Lindesmith LC, Donaldson EF, Lobue AD, Cannon JL, Zheng DP, Vinje J, Baric RS (2008). Mechanisms of GII.4 norovirus persistence in human populations. **PLOS Medicine**, 5(2):e31. PMC2235898.

C.1. Coronavirus Pathogenesis and Virus Immunity. Our group has studied the role of virus-immune interactions in coronavirus and other emerging virus pathogenesis mechanisms.

1. Rasmussen AL, Okumura A, Ferris MT, Green R, Feldmann F, Kelly SM, Scott DP, Safronetz D, Haddock E, LaCasse R, Thomas MJ, Sova P, Carter VS, Weiss JM, Miller DR, Shaw GD, Korth MJ, Heise MT, Baric RS, de Villena FP, Feldmann H, Katze MG (2014). Host genetic diversity enables Ebola hemorrhagic fever pathogenesis and resistance. **Science**, 2014 346(6212):987-91. PMC4241145.
2. Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, Leist SR, Whitmore A, Heise MT, Baric RS (2018). Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis. **mBio**, 9(5). e01753-18. PMC6178621.
3. Menachery VD, Eisfeld AJ, Schäfer A, Josset L, Sims AC, Proll S, Fan S, Li C, Neumann G, Tilton SC, Chang J, Gralinski LE, Long C, Green R, Williams CM, Weiss J, Matzke MM, Webb-Robertson BJ, Schepmoes AA, Shukla AK, Metz TO, Smith RD, Waters KM, Katze MG, Kawaoka Y, Baric RS (2014). Pathogenic influenza viruses and coronaviruses utilize similar and contrasting approaches to control interferon-stimulated gene responses. **mBio**, 5(3): e01174-14. PMC4030454.
4. Graham RL, Becker MM, Eckerle LD, Bolles M, Denison MR, Baric RS (2012). A live, impaired-fidelity coronavirus vaccine protects in an aged, immunocompromised mouse model of lethal disease. **Nature Medicine**, 18(12):1820-6. PMCID: PMC3518599.

C.2. Coronavirus Innate Immunity/Animal Models. The Baric laboratory group has studied CoV host range expansion using experimental evolution and SARS-CoV, MERS-CoV, civet SL-CoV, bat SL-CoV, and bat CoV HKU5 as models. This includes synthetic reconstruction of civet and bat CoV from *in silico* sequence, the first reported recovery of recombinant bat viruses, and characterization of host range phenotypes *in vitro* and *in vivo*. Applications of experimental evolution have focused on molecular mechanisms associated with virus-receptor interactions in viral persistence, virus innate immune interactions, and increased virulence in mice.

1. Agnihothram S, Yount BL, Donaldson EF, Huynh J, Menachery VD, Gralinski LE, Graham RL, Becker MM, Tomar S, Scobey TD, Osswald HL, Whitmore A, Gopal R, Ghosh AK, Mesecar A, Zambon M, Heise M, Denison MR, Baric RS (2014). A mouse model for Betacoronavirus subgroup 2c using a bat coronavirus strain HKU5 variant. **mBio**, 5(2): e00047-14. PMC3977350.
2. Sheahan T, Rockx B, Donaldson E, Corti D, Baric R (2008). Pathways of cross-species transmission of synthetically reconstructed zoonotic severe acute respiratory syndrome coronavirus. **Journal of Virology,** 82(17):8721-32. PMC2519660
3. Becker MM, Graham RL, Donaldson EF, Rockx B, Sims AC, Sheahan T, Pickles RJ, Corti D, Johnston RE, Baric R*, Denison MR* (2008). Synthetic recombinant bat SARS-like coronavirus is infectious in cultured cells and in mice. **Proceedings of the National Academy of the Sciences**, 105(50):19944-9. PMC2588415. (* = co-first authors)
4. Menachery VD, Schäfer A, Burnum-Johnson KE, Mitchell HD, Eisfeld AJ, Walters KB, Nicora CD, Purvine SO, Casey CP, Monroe ME, Weitz KK, Stratton KG, Webb-Robertson BM, Gralinski LE, Metz TO, Smith RD, Waters KM, Sims AC, Kawaoka Y, Baric RS (2018). MERS-CoV and H5N1 influenza virus antagonize antigen presentation by altering the epigenetic landscape. **Proceedings of the National Academy of the Sciences**, 115(5): E1012-E1021. PMID: 29339515.

C.3. Virus Genetic Platforms. The Baric laboratory has pioneered reverse genetic analyses of CoVs and DENVs. Several CoV infectious cDNA clones are available in the lab, including SARS-CoV, MERS-CoV, conventional human and model CoVs, and several bat CoVs with pandemic potential. The availability of these genetic platforms allows for detailed studies into the role of viral genes in pathogenesis, innate immune antiviral immunity, vaccine performance and design, virus-receptor interactions, entry and virus evolution.

1. Yount B, Curtis, K, Fritz L, Hensley L, Jahrling P, Prentice E, Denison M, Geisbert T, Baric RS (2003). Reverse Genetics with a full length infectious cDNA for the SARS Coronavirus. **Proceedings of the National Academy of the Sciences**, 100(22): 12995-13000. PMCID: PMC240733.

2. Rockx B, Sheahan T, Donaldson E, Harkema J, Sims A, Heise M, Pickles R, Cameron M, Kelvin D, Baric R (2007). Synthetic reconstruction of zoonotic and early human severe acute respiratory syndrome coronavirus isolates that produce fatal disease in aged mice. **Journal of Virology** 81(14):7410-23. PMC1933338.
3. Widman DG, Young E, Yount BL, Plante KS, Gallichotte EN, Carbaugh DL, Peck KM, Plante J, Swanstrom J, Heise MT, Lazear HM, Baric RS (2017). A Reverse Genetics Platform that Spans the Zika Virus Family Tree. **mBio**, 8(2): e02014-16. PMC5340872
4. Donaldson EF, Yount B, Sims AC, Burkett S, Pickles RJ, Baric RS (2008). Systematic assembly of a full-length infectious clone of human coronavirus NL63. **Journal of Virology**, 82(23):11948-57. PMC2583659.

C4. Virus Vaccine Design and Antiviral Immunotherapy. Viruses are major causes of morbidity and mortality globally. The Baric laboratory has used structure-guided immunogen design and epitope exchange to build multivalent immunogens to increase vaccine breadth and diagnostic potential.

1. Deming DJ, Sheahan T, Heise M, Yount B, Davis N, Sims A, Suthar M, Whitmore JH, Pickles R, West A, Donaldson E, Curtis K, Johnston, RE, Baric RS (2006). Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. **PLOS Medicine**, 3(12): e525 PMCID: PMC1716185.
2. Tang XC, Agnihothram SS, Jiao Y, Stanhope J, Graham RL, Peterson EC, Avnir Y, Tallarico AS, Sheehan J, Zhu Q, Baric RS, Marasco WA (2014). Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution. **Proceedings of the National Academy of the Sciences**,111(19):E2018-26. PMC4024880
3. Lindesmith LC, Ferris MT, Mullan CW, Ferreira J, Debbink K, Swanstrom J, Richardson C, Goodwin RR, Baehner F, Mendelman PM, Bargatze RF, Baric RS (2015). Broad blockade antibody responses in human volunteers after immunization with a multivalent norovirus VLP candidate vaccine: immunological analyses from a phase I clinical trial. **PLOS Medicine**, 12(3):e1001807 PMC4371888.
4. Bolles M, Deming D, Long K, Agnihothram S, Whitmore A, Ferris M, Funkhouser W, Gralinski L, Totura A, Heise M, Baric RS (2011). A double-inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. **Journal of Virology**, 85(23):12201-15. PMC3209347

D.Research Support.

U19 AI 100625 Baric/Heise (MPI) 09/01/17-08/31/22
Systems Immunogenetics of Biodefense Pathogens in the Collaborative Cross
The Collaborative Cross is a mouse resource for study of complex genetic interactions in diverse populations, to identify novel polymorphic genes regulating immune responses to SARS, influenza and WNV, analyze genetic underpinning of immune phenotypes in mice and humans, and generate panels of genetically defined mice to probe polymorphic gene control of immune responses against a pathogens or other immune stimuli.

R01 AI108197 Denison/Baric (MPI) 05/01/18-04/30/23
Determinants of Coronavirus Fidelity in Replication and Pathogenesis
Experiments in this aim will test the hypothesis that nsp14 functions in maintaining high replication fidelity and viral RNA synthesis are coupled and that targeted engineered mutations across nsp14 alter: a) RNA fidelity outcomes; b) sensitivity to nucleoside mutagens and polymerase inhibitors; c) sensitivity to innate immunity.

HHSN272201000019I-HHSN27200003 Baric (PI) 09/30/17-03/31/24
MERS-CoV Mouse Model for Vaccine & Therapeutic Testing (Task Order A57)
Use generation of transgenic mice and modifications to the MERS-CoV genome to identify a mouse model for MERS-CoV that recapitulates human disease phenotypes for evaluating vaccine platforms and therapeutics.

U19 AI 109680 Whitley (PI) 03/01/14-02/28/19
Antiviral Drug Discovery and Development Center
The specific aims of the proposal will identify small molecule inhibitors of CoV fidelity and RNA capping, define their mechanism of action, and determine their efficacy against SARS-CoV and across CoV families using in vivo mouse models of acute and persistent CoV disease. Role: Co-Investigator

U19 AI 109761 Lipkin (PI) 03/01/14-02/28/19
Diagnostic and Prognostic Biomarkers for Severe Viral Disease
The goal is to develop new platform technologies that use functional genomics as diagnostic and prognostic indicators of severe end stage lung disease, systemic and enteric diseases following virus infection, including coronaviruses, flaviviruses and noroviruses. Role: Project Leader

R01 AI110700 Baric (PI) 04/20/15-03/31/20
Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis
The overall goal is to build a comprehensive understanding of the molecular mechanisms guiding group 2c CoV receptor recognition, entry and pathogenesis.

(b) (4) Baric (PI) (b) (4)
Breadth of Blockade Antibody Responses Following Norovirus Vaccination.
(b) (4) and UNC will collaborate to evaluate the breadth of the antibody blockade response following norovirus vaccination in various human volunteer populations.

P01 AI106695 Harris (PI) 07/1/2015-6/30/20
Protective immunity following dengue virus natural infections and vaccination
Project 2: Aravinda deSilva and Ralph S. Baric (Co-PI).
The goal is to identify natural correlates of protective immunity following natural infection and or vaccination.
Role: Co-Investigator

R01-AI125198 de Silva (PI) 05/01/16 – 04/30/21
Preclinical assays to predict dengue vaccine efficacy
We use samples from DENV tetravalent Sanofi Pasteur vaccine clinical trials to identify mechanisms and correlates of protective immunity or breakthrough infections in vaccinees. Role: Co-investigator.

R01 1AI132178 Baric/Sheahan(MPI) 08/15/17-8/14/22
Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV.
The goal of this proposal is collaborate with Gilead Inc. and obtain GS-5734 preclinical data for IND development and translational studies, all designed to move the therapeutic into human trials.

(b) (4) Breuer (PI) (b) (4)
Why do Norovirus pandemics occur and how can we control them?
The program uses hospital and community cohorts of NoV infected individuals to ask fundamental questions into the molecular and evolutionary epidemiology of human NoV infections, focusing on the GII.4 strains, leading to new models of virus emergence and disease prevention. Role: Co-Investigator:

R01 AI 089728 Li (PI) 07/01/16-06/30/21
University of Minnesota/NIAID
Receptor recognition and cell entry of coronaviruses
The program studies receptor usage and cell entry mechanisms of emerging coronaviruses, focused on PEDV, MHV and SARS-like Coronaviruses. Role: Co-Investigator

R21 AI135682 Georgiou (PI) 04/01/18-03/30/20
UT Austin/NIAID
Molecular Analysis of Serum Antibody Constituents in Zika Virus Infection.
The goal of this application is to identify antibodies that make up the serologic repertoire after Zikv infection of naive and DENV preimmune individuals. Role: Co-investigator.

R21 AI137887 Moorman/Heise (MPI) 02/05/18-01/31/20
NIH/NIAID $150,000
Molecular Characterization of Functional RNA Structures in the ZikV genome
The goal of this project is to study the RNA Structure of Zika virus. Proposed studies will identify new viral virulence determinants that can be targeted to generate safer and more effective Zika virus vaccines and therapeutics. Role: Co-Investigator.