BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Almo, Steven C.

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

POSITION TITLE: Professor of Biochemistry

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	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	B.S.	1982	Biology
Harvard University, Boston, MA	Ph.D.	1990	Biophysics
Johns Hopkins School of Medicine, Baltimore, MD	Postdoc	1992	Cell Bio/Biophysics

A. Personal Statement

For the past three decades, the major scientific focus of my laboratory has been on enzyme functional annotation and the functional dissection of cell surface immune receptors. My laboratory has been directly involved in a number of large-scale programs involved in technology development and high-throughput applications. I am the Director of the Einstein Macromolecular Therapeutics Development Facility, which provides a wide array of proteins services to the Einstein community, and served as PI of the New York Structural Genomics Research Consortium (NYSGRC), one of the four large-scale high-throughput structure discovery centers supported by the NIGMS Protein Structure Initiative. I served as Director of the Protein Expression Core for the Northeast Biodefense Center (one of the NIAID-funded Regional Centers of Excellence) and was a major participant in the Immune Function Network, an NIGMS-funded program on the mechanistic dissection of innate and adaptive immunity. I also served as co-PI of the Enzyme Function Initiative, an NIGMS-supported Glue Grant focused on the development, implementation and dissemination of strategies for the large scale annotation of enzyme function. My laboratory has made extensive contributions to the structural, functional and mechanistic analysis of the cell surface and secreted proteins that modulate adaptive and innate immunity (including structures of TIM-3, TIGIT, CRTAM and the CTLA-4:B7, PD-1:PD-L, CTLA-4:ipilimumab, LIGHT:DcR3, TL1A:DcR3, FasL:DcR3 complexes). My laboratory has deposited over 1800 structures to the PDB, including the HVEM:CD160 and HVEM:LIGHT binary complexes and the HVEM:LIGHT:CD160 ternary complex important for the proposed work. Notably, Dr. Herold and I have coauthored a number of papers directly relevant to the current proposal (see below), involving the role of HVEM in HSV biology, including our most recent report that describes the cryo-EM structures and associated mechanistic insight on the complexes formed by HSV gB with protective and non-protective mAbs. Based on my experience with protein expression/purification and biochemical, biophysical, structural, functional and mechanistic analysis, I am well qualified to contribute to the proposed work.

Recent publications with Dr. Herold that I would like to highlight:

A non-neutralizing glycoprotein B monoclonal antibody protects against herpes simplex virus disease in mice. Kuraoka M, Aschner CB, Windsor IW, Mahant AM, Garforth SJ, Kong SL, Achkar JM, Almo SC, Kelsoe G, Herold BC. J Clin Invest. 2023 Feb 1;133(3):e161968. doi: 10.1172/JCI161968. PMID: 36454639

Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients.
Pierce CA, Preston-Hurlburt P, Dai Y, Aschner CB, Cheshenko N, Galen B, Garforth SJ, Herrera NG, Jangra RK, Morano NC, Orner E, Sy S, Chandran K, Dziura J, Almo SC, Ring A, Keller MJ, Herold KC, Herold BC. Sci Transl Med. 2020 Oct 7;12(564):eabd5487. doi: 10.1126/scitranslmed.abd5487. Epub 2020 Sep 21. PMID: 32958614

Cell-impermeable staurosporine analog targets extracellular kinases to inhibit HSV and SARS-CoV-2.
Cheshenko N, Bonanno JB, Hoffmann HH, Jangra RK, Chandran K, Rice CM, Almo SC, Herold BC.

Commun Biol. 2022 Oct 16;5(1):1096. doi: 10.1038/s42003-022-04067-4. PMID: 36245045

HVEM signaling promotes protective antibody-dependent cellular cytotoxicity (ADCC) vaccine responses to herpes simplex viruses.
Burn Aschner C, Loh LN, Galen B, Delwel I, Jangra RK, Garforth SJ, Chandran K, Almo S, Jacobs WR Jr, Ware CF, Herold BC. Sci Immunol. 2020 Aug 14;5(50):eaax2454. doi: 10.1126/sciimmunol.aax2454. PMID: 32817296

A Herpes Simplex Virus (HSV)-2 Single-Cycle Candidate Vaccine Deleted in Glycoprotein D Protects Male Mice From Lethal Skin Challenge With Clinical Isolates of HSV-1 and HSV-2.
Burn C, Ramsey N, Garforth SJ, Almo S, Jacobs WR Jr, Herold BC. J Infect Dis. 2018 Feb 14;217(5):754-758. doi: 10.1093/infdis/jix628. PMID: 29216362

Ongoing and recently completed projects that I would like to highlight include:

P30 CA013330 Goldman PI, Almo Co-PI 06/01/1997 – 06/30/2028
"The Montefiore Einstein Cancer Center"

R01 AI123730 DiLorenzo, Almo MPIs 02/08/2018 – 01/31/2024
"Structural, functional, and mechanistic analysis of autoreactive CD8 T cells"

P30 AI124414 Goldstein PI, Almo Co-PI 05/01/2017 – 04/30/2027
"Einstein-Rockefeller-CUNY Center for AIDS Research"

R01 AI172607 Goldstein, Almo, MPIs 06/03/2022 – 05/31/2027
"Amplifying and Redirecting CMV-specific CD8 T cells to provide sustained control of HIV infection"

R01 AI145024 Goldstein, Almo MPIs 04/01/2019 – 03/31/2024
"Novel Biologics Designed to Mobilize HIV-specific CTL for Sustained HIV Remission"

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2017 – Present	President, Institute for Protein Innovation (July 2017 – July 2019); SAB & Board member (2017 – Present)
2017 – Present	Scientific Advisory Committee, Advanced Photon Source, Argonne National Laboratory
2016 – Present	Board of Directors, New York Structural Biology Center
2015 – Present	Chairman, Department of Biochemistry, Albert Einstein College of Medicine
2015 – 2016	Senate Council
2014 – Present	Scientific Advisory Board, Institute for Bioscience and Biotechnology Research, U. of Maryland
2014 – 2016	Linac Coherent Light Source Proposal Review Panel; SLAC National Accelerator Laboratory
2012 – Present	Wollowick Family Foundation Chair in Multiple Sclerosis and Immunology
2012	Organizer, Keystone Meeting "Structural Biology of Cellular Processes: From Atoms to Cells"
2010 – Present	Science Council
2010	College of CSR Reviewers
2009 – Present	Beamline Advisory Team, Advanced Beamlines for Biological Investigations with X-rays (ABBIX) Project for the NSLS-II BNL [Chair 2013 – Present]
2009 – Present	Scientific Advisory Committee, PXRR (Robert Sweet, PI; BNL) [Chair 2011 – Present]
2009 – Present	Scientific Advisory Committee, Case Center for Synchrotron Biosciences (Chance, PI; CWR)
2009 – 2014	Director, Eukaryotic Expression Core for the Northeast Biodefense Center
2009 – 2012	Scientific Advisory Committee, HIVRAD (Michael Cho, PI; Iowa State)
2009	NIH CSF Study Section, Ad hoc
2009	NIH ZRG1 BST-D (50) Technology Centers for Networks and Pathways
2009	ZRG1 BCMB-B (99) R Review Panel
2009	Faculty of 1000, Electronic Reviews, Biology Reports Ltd.
2007 – Present	Director, Albert Einstein Macromolecular Therapeutic Development Facility (MTDF)
2007	Chair, Strategic Planning Committee on Structural Biology and Proteomics
2006 – Present	Director of Structural Proteomics, New York Structural Biology Center
2006	NIH ZRG1 IDM-G (02) Drug Development

2005 Chairman, NIH ZRG1 CB-B 02 S, Review Panel (Bioengineering Research Partnership)
2005 – Present Tenure Committee
2005 NIH ZRG1-SBMI Review Panel, Ad hoc
2005 NIH IDM-G (2) Review Panel, Ad hoc
2004 – 2006 NIH Admin. Chair of Division of Molecular and Cellular Mechanisms Special Emphasis Panel
2004 – 2005 NIH Scientific Advisory Board, Epitope Discovery Working Group, NIAID
2003 – Present Professor of Physiology & Biophysics, Einstein, Dept of Physiology & Biophysics
2002 NIH CDF-4 Study Section, Ad hoc
2002 – 2004 Professor Promotion Committee
2002 – 2006 NIH CSF (formerly CDF-4) Study Section
2001 – Present Professor of Biochemistry, Albert Einstein College of Medicine, Dept. of Biochemistry
2001 – 2007 User Executive Committee, National Synchrotron Light Source, BNL
2001 National Center for Research Resources Review Panel ZRG1 BBCA
2000 – Present Advisory Committee, Analytical Imaging Facility
2000 NIH Physical Biochemistry Study Section, Ad hoc
1999 – Present Proposal Study Panel, Brookhaven National Laboratory (BNL)
1998 – 2001 American Cancer Society, Peer Review Committee on Cancer Drug Development
1998 – 2000 Editorial Board, International Archives of Allergy and Immunology
1998 National Center for Research Resources Special Emphasis Panel ZRR1 BRT-1
1998 Special NCI Study Section for Program Project Review
1998 NIH BBCB Study Section, Ad hoc
1997 – 2010 Molecular Biophysics Training Grant Steering Committee
1997 – 2006 Associate Director for Crystallography, Center for Synchrotron Biosciences
1997 – 2001 Associate Professor of Biochemistry, Albert Einstein College of Medicine, Dept. of Biochemistry
1997 – 2000 Associate Professor Promotion Committee
1997 Special NCI Study Section for Program Project Review
1996 – Present Member, Albert Einstein Cancer Center
1996 – Present Medical Scientist Training Program (MSTP) Steering Committee
1993 – 1996 Sue Golding Graduate Admissions Committee
1993 – Present Faculty Senate (1993-1995, 1998-2007, 2014-present)
1993 – Present Reviewer for J. Biol. Chem., Biochem., Science, Nat. Struct. Biol., Biophys. J., Structure, Acta. Cryst, Chem. & Biology, Nature, Proc. Natl. Acad. Sci., J. Cell Biol., Protein Science, Proteins
1992 – 1997 Assistant Professor of Biochemistry, Albert Einstein College of Medicine, Dept. of Biochemistry
1990 Instructor, Woods Hole Marine Biology Laboratories, Physiology Summer Course
1988 – 1989 Instructor in Molecular Graphics Course, MIT, Department of Chemistry
1983 – 1985 Teaching Assistant, Harvard University, Dept. of Biochemistry and Molecular Biology
1982 Teaching Assistant, Stanford University Medical School, Dept. of Biochemistry, September

Honors

2005 The LaDonne Schulman Faculty Recognition Award for Graduate Teaching at Einstein
2004 AMGEN Award, American Society for Biochemistry and Molecular Biology
2000 – 2004 Irma T. Hirschl/Monique Weill-Caulier Career Development Award
1988 Recipient, Institute for Biological Recognition and Catalysis, Inc., Travel Grant (Nov. and Mar.)

C. Contributions to Science

I. Strategies for Functional Annotation and Metabolism Discovery. The number of newly reported protein sequences inferred from genome sequencing continues to grow at a rate that severely outpaces the assignment of function through comparative genomics or direct biochemical analysis. This situation results in a large proportion of unannotated and misannotated protein sequences precluding the discovery of novel enzymes, activities, and metabolic pathways important to (1) understanding the contributions of the gut microbiome to human health, (2) the realization of new chemical processes for industry, and (3) our understanding of critical environmental issues, including global nutrient cycles and the evolution of complex microbial communities. To address these challenges our laboratory is devising experimental strategies based on the solute binding protein (SBP) components of small molecule transport systems, since the first step in a catabolic pathway is frequently the passage of a metabolite across the cellular membrane by SBP-dependent transport machinery. The ability to identify the initial reactant (or a closely related molecule) for a catabolic pathway provides an immediate toe-hold by placing significant constraints on the regions of chemical space that need to be considered and, in

conjunction with knowledge of colocalized and coregulated genes, begins to define details of the *in vivo* biochemical transformations operating within the metabolic pathway. Using our high-throughput infrastructure we produced and screened 158 TRAP SBPs against a small molecule library by differential scanning fluorimetry (DSF). These efforts led to the identification of 40 new TRAP SBP ligands, the generation of experiment-based annotations for 2084 individual SBPs in 71 isofunctional clusters, and the definition of numerous metabolic pathways, including novel catabolic pathways for the utilization of ethanolamine as sole nitrogen source and the use of D-Ala-D-Ala as sole carbon source[1]. Other comparable large scale functional annotation studies were performed for the Isoprenoid Synthase[2] and Haloacid Dehalogenase[3] Superfamilies.

1. Vetting MW, Al-Obaidi N, Zhao S, San Francisco B, Kim J, Wichelecki DJ, Bouvier JT, Solbiati JO, Vu H, Zhang X, Rodionov DA, Love JD, Hillerich BS, Seidel RD, Quinn RJ, Osterman AL, Cronan JE, Jacobson MP, Gerlt JA, Almo SC. (2015) "Experimental strategies for functional annotation and metabolism discovery: targeted screening of solute binding proteins and unbiased panning of metabolomes." Biochemistry. 54(3):909-31. PMCID: PMC4310620
2. Wallrapp FH, Pan JJ, Ramamoorthy G, Almonacid DE, Hillerich BS, Seidel R, Patskovsky Y, Babbitt PC, Almo SC, Jacobson MP, Poulter CD. (2013) Prediction of function for the polyprenyl transferase subgroup in the isoprenoid synthase superfamily. Proc Natl Acad Sci U S A. 110(13):196-202. PMCID: PMC3612614
3. Huang H, Pandya C, Liu C, Al-Obaidi NF, Wang M, Zheng L, Toews Keating S, Aono M, Love JD, Evans B, Seidel RD, Hillerich BS, Garforth SJ, Almo SC, Mariano PS, Dunaway-Mariano D, Allen KN, Farelli JD. (2015) Panoramic view of a superfamily of phosphatases through substrate profiling. Proc Natl Acad Sci U S A. 112(16):74-83. PMCID: PMC4413258

II. High-throughput Protein Production Infrastructure. Despite a multitude of recent technical breakthroughs speeding high-resolution structural and functional analysis of biological macromolecules, production of sufficient quantities of well-behaved, active protein continues to represent the rate-limiting step in many structure discovery and functional annotation efforts. These challenges are amplified when considered in the context of ongoing large scale efforts to systematically define structure, function and mechanism of a wide range of macromolecules including multi-domain eukaryotic proteins, secreted proteins, and ever larger macromolecular assemblies. As part of our programs at Einstein, we have established robust bacterial expression platforms for the high-throughput discovery of new metabolism. Unique to the Almo group is the world's first integrated system for high-throughput functional and structural biology of oxygen sensitive proteins. This resource has allowed for the recapitulation of the entire high-throughput protein production and crystallization pipeline within an oxygen-free environment. We have also established high-throughput eukaryotic expression platforms, including insect and mammalian-based systems, which represents a unique resource in academics. We have extensively described the capabilities of our protein production platforms in the literature[4]. These capabilities are being leveraged to realize a wide range of cutting-edge platform technologies, including receptor-ligand deorphaning, epitope discovery, the generation of novel biologics and the development of new clonal-specific T cell strategies for the treatment of malignancies and autoimmunity[5].

4. Almo SC, Garforth SJ, Hillerich BS, Love JD, Seidel RD, Burley SK. (2013) Protein production from the structural genomics perspective: achievements and future needs. Curr Opin Struct Biol. 23(3):335-44. PMCID: PMC4163025
5. Samanta D, Mukherjee G, Ramagopal UA, Chaparro RJ, Nathenson SG, DiLorenzo TP, Almo SC. (2011) Structural and functional characterization of a single-chain peptide-MHC molecule that modulates both naive and activated CD8+ T cells. Proc Natl Acad Sci U S A. 108(33):13682-7. PMCID: PMC3158197

III. Structural, functional and mechanistic analysis of the cell surface and secreted proteins that modulate adaptive and innate immunity. Cell surface receptors and adhesion molecules are the gatekeepers of cellular function, and are responsible for the detection of signals arising from developmental, morphogenetic and environmental cues central to normal physiology and pathology. Notably, these receptors and ligands are not only therapeutic targets, but soluble versions of these molecules are themselves widely exploited therapeutics for the treatment of autoimmune diseases, infectious diseases and malignancies. High resolution structural characterization and biochemical analyses of these complexes are mechanistically invaluable as they define the chemical and physical determinants underlying receptor:ligand specificity, affinity, oligomeric state, and valency. We have made significant contributions in these areas, including the structures of complexes of CTLA-4:B7-2[6], PD-1:PD-L2[7], DcR3:TL1A[8], DcR3:LIGHT, DcR3:FasL and HVEM:LIGHT, as well as B7-H3, B7-H4[9], TIM-3, NTB-A, CD84, GITRL, TIGIT, CRTAM, nectins and CD160, all of which are potential/proven targets for immunotherapy. These structures defined the determinants responsible for receptor:ligand recognition, which are being leveraged to generate a wide range of variants with altered biochemical properties (e.g., affinities, selectivities) to probe mechanism and provide new functional/therapeutic insights. A major challenge in these efforts is the fact that many, if not most, receptor:ligand pairs remain undefined and thus cannot be structurally characterized or exploited for immunotherapy. To address this bottleneck, we are developing experimental platform technologies for the rapid, systematic and affordable identification of cell surface protein-protein

interacting partners and the mapping of protein interaction interfaces. This same platform provides powerful approaches to generate costimulatory receptors and ligands with a wide range of affinities and selectivities, which can be leveraged for the design of “tunable” immune modulators.

6. Schwartz J-C, Zhang X, Fedorov AA, Nathenson SG & **Almo SC** (2001) Structural Basis for Costimulation by the Human CTLA-4/B7-2 Complex. *Nature* **410**, 604-608. PMID: 11279501; DOI: 10.1038/35069112
7. Lázár-Molnár E, Yan Q, Cao E, Ramagopal U, Nathenson SG & **Almo SC** (2008) Crystal structure of the complex between programmed death-1 (PD-1) and its ligand PD-L2. *Proc Natl Acad Sci* U S A. **105**:10483-8. PMCID: PMC2492495
8. Zhan C, Patskovsky Y, Yan Q, Li Z, Ramagopal U, Cheng H, Brenowitz M, Hui X, Nathenson SG, **Almo SC** (2011) Decoy Strategies: The Structure of TL1A-DcR3 Complex. *Structure* **19**:162-71. PMCID: PMC3065972
9. Jeon H, Vigdorovich V, Garrett-Thomson SC, Janakiram M, Ramagopal UA, Abadi YM, Lee JS, Scandiuzzi L, Ohaegbulam KC, Chinai JM, Zhao R, Yao Y, Mao Y, Sparano JA, **Almo SC** & Zang X (2014) Structure and cancer immunotherapy of the B7 family member B7x. *Cell Rep* **9**, 1089-98. PMCID: PMC4250833

MyBibliography: 394 author entries (491 total including NIH grant acknowledgments):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1-CTfoJ579o5l/bibliography/45940359/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Betsy C. Herold

eRA COMMONS USER NAME (credential, e.g., agency login): herolb01

POSITION TITLE: Chief, Division of Pediatric Infectious Diseases, and Vice Chair for Research, Dept. of Pediatrics, Albert Einstein College of Medicine and Children's Hospital at Montefiore

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
Brown University	B.A.	1978	Biology
University of Pennsylvania	M.D.	1982	Medicine
Northwestern University	Intern & Resident	1982-1985	Pediatrics
Northwestern University	Chief Resident	1985-1986	Pediatrics
Northwestern University	Fellow	1987-1990	Infectious Diseases
Northwestern University	Postdoc	1988-1992	Virology

A. Personal Statement:

Dr. Betsy Herold is Professor of Pediatrics and Microbiology-Immunology and chief of the division of pediatric infectious diseases. She directs a translational research laboratory focused on viral-host interactions and their impact on disease progression and clinical outcomes. Dr. Herold has extensive experience leading multidisciplinary translational research programs focused on the prevention of herpes simplex virus (HSV), HIV and, more recently SARS-CoV-2, through vaccine and antiviral development and identifying the molecular mechanisms underlying antibody-dependent cell-mediated cytotoxicity (ADCC). The focus on ADCC emanates from ongoing studies of a novel, paradigm-shifting candidate vaccine for HSV. The vaccine (designated ΔgD-2) is a single-cycle virus deleted in glycoprotein D (gD), the primary target of neutralizing antibodies. Deletion of gD results in a vaccine that provides complete protection against multiple clinical isolates of HSV-1 and HSV-2 in mice and guinea pigs following active or passive immunization. The protection is mediated by antibodies that mediate ADCC. More recently, Dr. Herold and colleagues isolated and characterized HSV-specific monoclonal antibodies (mAb) from ΔgD-2 vaccinated mice. One of the mAbs, BMPC-23, has no neutralizing activity but activates FcγRs to mediate ADCC. A single dose of the mAb prevents HSV disease when administered before or after viral challenge when configured as mouse IgG2c and protected mice expressing human Fc**γ**RIII when engineered as a human IgG1. BMPC-23 binds to domain IV of glycoprotein B. In studying why ΔgD-2 vaccination elicits a predominant ADCC response whereas neutralizing antibodies are elicited in response to acute infection and other failed candidate vaccines, the lab uncovered a previously unknown immune evasion strategy and a pivotal role for TNFRSF14, also known as HVEM, in ADCC. Vaccination of *TNFRSF14*$^{-/-}$ mice resulted in a significant loss of protection, which was associate with both a decrease in the generation of ADCC-mediating antibodies as well as an impairment in effector cell killin. The importance of TNFRSF14 in ADCC is generalizable; similar results were obtained when we immunized mice with VSV-pseudotyped virus expressing SARS-CoV-2 spike protein or using human *TNFRSF14*$^{-/-}$ effector reporter cells in ADCC assays with rituximab (anti-CD20 ADCC-mediating mAb) and B cells as the target. Clinical studies conducted by the Herold lab have further demonstrated the protective role of ADCC and other nonneutralizing antibody functions (e.g., antibody-dependent phagocytosis, complement mediated cytolysis) in protecting against HSV and CMV. The lab has also conducted clinical studies to evaluate placental transfer of protective ADCC-mediating antibodies.

Dr. Herold has been overall PI on 3 U19 and Project Leader on 7 projects focused on the development of pre-exposure prophylaxis (PrEP) for the prevention of HIV and HSV-2 highlighting her ability to lead and contribute to multicentered projects. Dr. Herold is also the Associate Director of the Einstein-Rockefeller-CUNY Center for AIDS Research (CFAR) and her lab provides several Core services including multiplex assays for

measurements of cytokines, chemokines and phosphorylated signaling proteins, Ongoing NIH funded projects include:

R01AI134367
Herold (PI)
012/5/2017-11/30/2028
Mechanisms Underlying the HIV-HSV 2 Syndemic

R01AI177673
Herold, Kuraoka, (MPI)
06/06/2023-05/31/2028
Optimizing the generation of monoclonal antibodies for prevention and treatment of HSV disease

R01AI159684
Steinbach, Englund, Herold, Tuomanen (MPI)
09/17/21-08/31/26
Multicenter evaluation of the threat of established and emerging respiratory viral infections in pediatric transplant recipients

R01HD98977
Herold (PI)
04/12/2019-3/31/2024
Impact of the vaginal microbiome on topical HIV pre-exposure prophylaxis (PrEP)

Citations:

a. Kuraoka, M., Burn Achner, C., Windsor I.W., Mahant, A.M., Garforth, S., Kong, S.L., Achkar, J.M., Almo, S.C., Kelsoe, G., and **Herold, B.C**. A non-neutralizing glycoprotein B monoclonal antibody protects against herpes simplex virus disease in mice. *JCI* 2023 Feb 1;133(3):e161968 PMC9888390
b. Burn Aschner, C., Loh, L.N., Galen, B., Delwel, I., Jangra, R.K., Garforth, S.J., Chandran, K., Almo, S.C., Jacobs, W.R., Ware, C. F., and **Herold, B.C**. HVEM signaling promotes ADCC vaccine responses to herpes simplex viruses. *Science Immunology*, 2020, Aug 14;5(50): eaax2454. doi: 10.1126 PMC7673108
c. Pierce CA, Sy S, Galen B, Goldstein DY, Orner E, Keller M, Herold KC, **Herold B.C.** Natural mucosal barriers and COVID-19 in children. *JCI Insight*, 2021. May 10;6(9):e148694. PMC8262299
d. Pierce, C.A., Preston-Hurlburt, P, Dai, Y, Burn Aschner, C., Cheshenko, N., Galen, B., Garforth, S.J., Herrera, N.G., Jangra, R.K., Morano, N., Orner, E., Sy, S., Chandran, K., Dziura, J., Almo, S.C. Ring, A., Keller, M.J., Herold, K.C, and **Herold, B.C**. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. *Sci Transl Med* 2020 Sep 21;eabd5487do10.1126/ PMC 7658796

B. Positions and Honors

Positions:

1992-1998	Assistant Professor, Pediatric Infectious Diseases, University of Chicago, Chicago, IL
1998-2004	Associate Professor, Pediatric Infectious Diseases, Mount Sinai School of Medicine, NY
2002-2007	Chief, Division of Pediatric Infectious Diseases, Mount Sinai School of Medicine, NY
2005-2007	Professor with Tenure, Department of Pediatrics, Mount Sinai, NY
2007-present	Professor of Pediatrics, Microbiology-Immunology and Obstetrics, Gynecology & Women's Health, Albert Einstein College of Medicine (Einstein), Bronx, NY
2007-present	Vice Chair for Research, Dept. of Pediatrics, Einstein-Children's Hospital at Montefiore
2013-present	Harold and Muriel Block Chair in Pediatrics, Einstein
2013-present	Director,Translational Prevention Research Center, Einstein
2014-present	Chief, Pediatric Infectious Diseases, Einstein-Children's Hospital at Montefiore

Honors: Alpha Omega Alpha Honor Medical Society (1981); Henry and Jacob Lowenberg Prize in Pediatrics, Univ. of Penn. (1982); Pediatric Infectious Disease Society Young Investigator Award (1995); IDSA/ Burroughs Welcome Young Investigator Award in Virology (1995); The U. of Chicago, Dept of Pediatrics, Outstanding Teacher Award (1996); Society for Pediatric Research (1997); American Pediatric Society (2003); Council,

Pediatric Infectious Disease Society (2007-2011); Council, Office of AIDS Research (2007-2011); Tenure, Albert Einstein College of Medicine, Yeshiva University (2009), Fellow Infectious Disease Society of America (2010), Faculty Clinical Sciences Mentoring Award, Albert Einstein College of Medicine (2012); Secretary-Treasurer, Pediatric Infectious Disease Society (2013-2015); Chair, NIAID AIDS, Clinical Studies, & Epidemiology (ACE) Study Section (2014-2016); Einstein-Montefiore Presidential Lecture Award (2018); Leo M. Davidoff Society, Einstein College of Medicine (2020); Saul R. Korey Award in Translational Science and Medicine, Einstein-Montefiore (2021); 2021 Caroline B. Hall Lectureship. Infectious Disease Society of America.

C. Contribution of Science

1) Development of a novel vaccine candidate for HSV prevention: HSV-2 vaccine efforts have been dominated by the presumption that neutralizing antibodies (Abs) to glycoprotein D (gD-2) alone or in combination with other glycoproteins would be protective. However, the clinical trial outcomes have been uniformly disappointing. Thus, we adopted a radically different strategy. Rather than focusing on gD-2 as the primary immunogen, we generated a single-cycle vaccine strain by deleting the *gD-2* gene (HSV-2Δ*gD*), which is essential for HSV entry and cell-to-cell spread. We found the following: (i) HSV-2Δ*gD* is safe, does not induce disease or establish latency in immunodeficient mice, and no recombinants have been detected; (ii) HSV-2Δ*gD* induces robust cellular and humoral immunity following prime-boost vaccination providing complete protection from high dose lethal challenges with clinical isolates of HSV-2 and HSV-1 and prevents the establishment of latency; (iii) HSV-2Δ*gD*-induced Abs provide passive protection and promote antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent phagocytosis. Passive immunity is decreased in neonatal FcR or FcγR knockout mice. Mechanistic studies demonstrate that ΔgD overcomes a novel immune evasion strategy that acts to prevent the generation of ADCC Abs. The findings challenge the paradigm that high titer neutralizing anti-gD Abs are required and highlight the central role of FcR functions in mediating HSV protection.

a. Mahant, A.M, Estrada Trejo, F., Aguilan, J.T., Sidoli, S., Permar, S.R., and Herold, B.C. Antigenic target, glycans, affinity for and placental expression of Fc receptors modulate HSV IgG transfer. *iScience*, 2023 Aug 15; 26(9):107648 PMC10475509
b. Mahant, A.M., Guerguis, S., Blevins,T., Cheshenko, N., Gao, W., Anastos, K., Belshe, R. and **Herold, B.C**. Herpes Simplex Virus Glycoprotein D Antibodies Fail to Elicit Antibody-Dependent Cell-Mediated Cytotoxicity: Implications for Future Vaccines. *J Infect Dis* 2022; 226:1489-1498 PMC10205893
c. Burn Aschner, C., Knipe, D. and **Herold, B.C**. Model of vaccine efficacy against HSV-2 superinfection of HSV-1 seropositive mice demonstrates protection by antibodies mediating cellular cytotoxicity. *NPJ Vaccines*. 2020 May 7;5:35. PMC767310
d. Petro, C.D., Weinrick. B., Khajoueinejad, N., Burn, C., Seller, R., Jacobs, WR. and **Herold, B.C**. HSV-2 ΔgD Elicits FcγR-Effector Antibodies that Protect Against Clinical Isolates. *JCI Insight*. 2016 Aug 4;1(12). PMC4985247

2. Uncovering molecular mechanisms that contribute to the HIV/HSV syndemic: The Herold lab has identified several novel mechanisms that contribute to the syndemic interactions between HIV and HSV using cell and tissue cultures, novel murine models, and clinical samples. Specifically, we found that defensins and secretory leukocyte protease inhibitor (SLPI) inhibit HSV and HIV infection in vitro and contribute to the endogenous antiviral activity of genital tract secretions. However, HSV-2 down-modulates the expression of these antimicrobial peptides, which may facilitate HIV and HSV infection and spread. In addition, HSV-2 induces the expression of proinflammatory cytokines and recruits immune cells to sites of HSV replication to promote HIV acquisition and transmission. HSV also has immunomodulatory effects on immune cells. HSV-2 interferes with dendritic cell (DC) function in vitro by inducing apoptosis, which may allow HSV to escape immune surveillance, but the cytokines and chemokines secreted by DCs in response to HSV promote HIV replication. Many of the in vitro and murine findings were recapitulated in clinical samples comparing genital tract mucosal immunity (genital tract secretions, cytobrushes, and vaginal or skin biopsies) in HIV-infected women who are HSV-2 seropositive or seronegative. Surprisingly, we also found that coinfection with HIV and HSV-2 is associated with significant changes in the phenotype and function of peripheral blood CD4 T cells that may contribute to the HIV reservoirs. Moreover, we found that IL-32, which is decreased in HSV-2+ vs HSV-2 seronegative women, blocks the effects of latency reversal stimuli being studied for HIV eradication and cure.

a. Murphy, K, Gromisch, M., Srinivasan, S., Wang, T., Wood, L, Proll, S., Liu, C. Fiedler, T., Valint, D.J., Fredricks, D., Keller, M.J., and **Herold, B.C**. IgA coating of vaginal bacteria is reduced in the setting of bacterial vaginosis (BV) and preferentially targets BV-associated species. *Infection and Immunity*, 2023, Dec 15:e0037323, in press.

b. Keller, M.J., Huber, A., Espinoza, L., Serrano, M.G., Parikh, H.I., Buck, G.A., Gold, J.A., Wu, Y., Wang, T. and **Herold, B.C**. Impact of herpes simplex virus type 2 and HIV dual infection on female genital tract mucosal immunity and the vaginal microbiome. *J. Infec Dis, 2019* . 2019 Jul 31;220(5):852-861 PMC6667798

c. Mesquita, P.M.M., Preston-Hurlburt, P., Keller, M.J., Vudattu, N., Espinoza, L., Altrich, M., Anastos, K., Herold, K.C. and **Herold, B.C**. Role of IL-32 in HIV Reactivation and its Link to HIV-HSV Coinfection. *J Infect Dis.* 2017 Feb 15;215(4):614-622 PMC5388286

d. Nixon, B, Fakioglu, E, Stefanidou, M, Wang, Y, Dutta, M, Goldstein, H and **Herold, BC**. Genital herpes infection of humanized HIV transgenic mice triggers HIV shedding and is associated with greater neurological disease. *J. Infec Dis*, 2014 Feb 15;209(4):510-22. PMC3903370

3) Development of topical pre-exposure prophylaxis products (PrEP) for HIV and HSV prevention: The Herold lab is actively engaged in HIV and HSV prevention through the development and evaluation of pre-exposure prophylaxis (PrEP) products as well as vaccines and mAbs. In collaborative studies (funded by several U19 that Dr. Herold led), the team has developed an intravaginal ring that delivers tenofovir disoproxil fumarate, the more potent prodrug of tenofovir. The greater potency reflects significantly increased tissue and cellular uptake of TDF. The TDF ring prevented 100% of macaques from SHIV infection and retained activity when macaques were pretreated with high dose medroxyprogesterone, which provides a rigorous model of SHIV Infection by increasing susceptibility of NHP to Infection. Notably, a 0.3% TDF gel provided significantly greater protection than 1% tenofovir gel against HSV-2 in wild-type mice and against HIV and HSV-2 in transgenic mice (expressing human CD4, CCR5 and cyclin T1 to render them susceptible to HIV). In a Phase 1 clinical trial in the Bronx, the TDF ring was safe and the tissue drug levels exceeded those associated with protection against HIV. Howver, in the followup clinical trial, which included sexually active young women, a subset developed vaginal lesions, which self-resolved but raised concerns about a potential safety signal. Ongoing work focuses on different strategies including the role of Abs for treatment and prevention.

a. Keller, M.J., Wood, L., Billingsley, J.M., Ray, L.L., Goymer, J., Sinclair, S., McGinn, A.P., Marzinke, M.A., Frank, B., Srinivasan, S., Liu, C., Atrio, J.M., Espinoza, L., Mugo, N., Spiegel, H.M.L., Anderson, P.L., Fredricks, D.N., Hendrix, C.W., Marrazzo, J., Bosinger, S.E., and **Herold, B.C**. Tenofovir disoproxil fumarate intravaginal ring for HIV pre-exposure prophylaxis: a Phase 1 randomised controlled trial in sexually active women. *Lancet HIV*, 2019, Aug;6(8):e498-e508. PMC6719300

b. Taneva, E., Sinclair, S., Mesquita, P.M.M., Weinrick, B., Cameron, S.A., Cheshenko, N., Reagle, K., Frank, B., Srinivasan, S., Fredricks, D., Keller, M.J. and **Herold, B.C**. Vaginal microbiome modulates topical antiretroviral drug pharmacokinetics. *JCI Insight*, 2018 Jul 12;3(13). PMC6124523

c. Keller, MJ, Mesquita P.M., Marzinke, M.A., Teller, R., Espinoza, L., Atrio, J.M. Lo, Y. Frank, B., Srinivasan, S., Fredricks, D.N., Rabe, L., Anderson, P.L., Hendrix, C.W., Kiser, P.F. and **Herold, B.C.** A phase 1 randomized placebo-controlled safety and pharmacokinetic trial of a tenofovir disoproxil fumarate vaginal ring. *AIDS* 2016 Mar 13;30(5):743-51. PMC4767579

d. Smith, JM, Rastogi, R, Teller, RS, Srinivasan, P, Mesquita, PM, Nagaraja, U, McNicholl, JM Hendry, RM, Dinh, CT, Martin, A, **Herold, BC** and Kiser, PF. An intravaginal ring eluting tenofovir disoproxil fumarate completely protects macaques from multiple vaginal SHIV challenges. *Proc Natl Acad Sci U S A*. 2013 Oct 1;110(40):16145-50. PMC3791780

4) Development of novel preclinical and clinical assays for assaying the safety and efficacy of PrEP: The Herold lab has played a major role in developing novel cell culture and animal models for studying PrEP efficacy and safety, including a dual-chamber culture system to study the impact of drugs on the epithelial barrier and an expanded murine safety model. Dr. Herold also conducted the first study demonstrating the importance of delivering virus in semen (or seminal plasma) to assess efficacy and found that seminal plasma proteins interfered with the antiviral activity of several polyanionic drugs. Subsequent Phase I clinical studies that she led demonstrated a significant decrease in drug levels and antiviral activity of genital tract secretions in samples collected from women following barrier unprotected sex compared to in the absence of sex. This work has led to changes in the recommended algorithm for preclinical assessment of microbicide efficacy and safety. Most recently, Dr. Herold was the Protocol Chair for a Microbicide Trials Network study (MTN011) designed to test the PK/PD of tenofovir gel following barrier-unprotected sex. There was a significant decrease in tissue and genital tract drug levels following sex when gel was administered either 1 h before or 24 h prior to sex, highlighting the importance of sustained drug delivery or postcoital dosing.

a. Serebrenik Sultan, J, Wang, T, Hunte, R, Srinivassan, S., McWalters, J, Tharp, G.K., Bosinger, S.E., Fiedler, T., Atrio, J.M., Murphy, K., Barnett, R., Ray, L.R., Krows, M.L., Fredricks, D.N., Irungu, E., Ngure, K., Mugo, N., Marrazzo, J., Keller, M.J., **Herold, B.C**. Differences in vaginal microbiota, host transcriptome and proteins in women with bacterial vaginosis are associated with metronidazole treatment responses. *J Infect Dis.* 2021;224(12):2094-2104. PMC8672760

b. Nakra, N., Madan, RP, Buckley, N, Huber, AM, Freiermuth, JL, Espinoza, L, Walsh, J, Parikh, UM, Penrose, KJ, Keller, MJ, and **Herold, BC**. Loss of innate host defense following unprotected vaginal sex. *J Infec Dis.* 2016 Mar 1;213(5):840-7. PMC4747617

c. **Herold, BC**, Dezzutti, C, Richardson, BA, Marrazzo, J, Mesquita, PMM, Carpenter, C, Huber, A, Louissaint, N, Marzinke, MA, Hillier SL and Hendrix, CW. Antiviral activity of genital tract secretions following oral or topical tenofovir pre-exposure prophylaxis for HIV-1. *J Acquir Immune Defic Syndr*. 2014 May 1;66(1):65-73. PMC3981887

d. Mesquita, PM, Srinvasan, P, Johnson, TJ, Rastogi, R, Evans-Strickfaden, T, Kay, MS, Buckheit, KW, Buckheit, RW, Smith, JM, Kiser, PF, and **Herold, BC.** Novel preclinical models of topical PrEP pharmacodynamics provide rationale for combination of drugs with complementary properties. *Retrovirology* 2013;10:113. PMC3827994

5) Identifying signaling pathways that HSV-2 usurps for entry and immune evasion: Genital herpes infections are a major global health problem and a substantial co-factor for HIV infection. Development of new approaches to prevent and ultimately eradicate HSV requires an understanding of the molecular and cellular events critical for the establishment of infection and latency and how the virus evades host immunity. To identify novel targets, the Herold lab has focused on cellular signaling pathways usurped by the virus to promote infection. Current work from the laboratory demonstrates that HSV activates Akt and calcium signaling pathways and these signaling pathways play critical roles in the establishment of infection and in cell-to-cell spread. Notably, HSV triggers the translocation of Akt from the inner to the outer plasma membrane where it interacts with the viral envelope glycoprotein B to activate calcium signaling and promote viral entry. In immune cells, viral induced Akt activation promotes apoptosis. We recently identified several drugs that block HSV-induced Akt signaling and prevent infection in vitro including a cell-impermeable analog of staurosporine.

a. Cheshenko, N. Bonanno, J.B., Hoffmann, H-H., Jangra, R.K., Chandran, K., Rice, C.M., Almo, S.C. and **Herold, B.C**. Cell-impermeable staurosporine analog targets extracellular kinases to inhibit HSV and SARS-CoV-2. *Nature Communications Biology*, 2022;5(1):1096. PMC9569420.
b. Cheshenko, N., Pierce, C., and **Herold, B.C**. Herpes simplex viruses activate phospholipid scramblase to redistribute phosphatidylserines and Akt to the outer leaflet of the plasma membrane and promote viral entry. PLoS Pathog. 2018 Jan.2;14(1):e1006766 PMC5766253
c. Cheshenko, N, Trepanier, JB, Gonzalez, PA, Eugenin, EA, Jacobs WR and **Herold, BC**. Herpes simplex virus type 2 glycoprotein H interacts with integrin αvβ3 to facilitate viral entry and calcium signaling in human genital tract epithelial cells. J Virol 2014 June 18. PMC4136333
d. Cheshenko, N, Liu, W, Satlin, LM, and **Herold, BC**. Multiple receptor Interactions trigger release of membrane and intracellular calcium stores critical for HSV entry. Molecular Biology of the Cell 2007 8(8): 3119-30. PMC1949381

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/betsy.herold.1/bibliography/40769123/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Bonanno, Jeffrey B.

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

POSITION TITLE: Research Assistant Professor

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
Alfred University, Alfred, New York	B.A.	1990	Chemistry
Cornell University, Ithaca, New York	Ph.D.	1995	Chemistry
Columbia University, New York, New York	Postdoctoral	1996	Chemistry

A. Personal Statement

The focus of my research efforts has, for the last 25 years, been combining chemical and biochemical observations with structural analysis to more fully understand the structure/function relationship which controls the activities of biological macromolecules. The bulk of this work was with the NYSGRC supported by the Protein Structure Initiative (PSI), in which I served as crystallographer, program manager, and principle investigator (2001-2002). This allowed me to both address a broad range of problems from the perspective of three dimensional protein structure and also gain experience in development, operation and management of multi-investigator programs. I have also collaborated closely with the enzymologists, protein chemists and structural biologists engaged in the Enzyme Function Initiative (EFI) project. Following the PSI project, my focus has shifted to advancing high-impact collaborative projects which benefit strongly from HTP biophysical methods employed at Einstein. Given my experiences with the programs described above, and my position at Einstein as co-Director of the Macromolecular Structure Core Facility, I will be able to meaningfully serve this project with management, grid preparation, screening, data collection, and particle reconstruction.

B. Positions

Employment

09/90 – 05/92 Teaching Assistant, Cornell University, Ithaca
09/95 – 08/96 Postdoctoral Research Associate, Columbia University, New York
09/96 – 04/02 Research Specialist, Howard Hughes Medical Institute, New York
09/96 – 10/01 Research Associate, Rockefeller University, New York
11/01 – 12/02 Research Assistant Professor, Rockefeller University, New York
01/03 – 04/05 Senior Scientist, Structural GenomiX, Inc., San Diego
09/05 – 08/06 Deputy Director NYCOMPS, New York Structural Biology Center, New York
09/05 – 08/06 Regional Coordinator NYSGXRC, Columbia University Medical Center, New York
09/06 – 09/15 Associate, Albert Einstein College of Medicine, New York
09/15 – present Research Assistant Professor, Albert Einstein College of Medicine, New York

C. Contributions to Science

High-throughput Protein Expression and Structure Determination. As a direct result of many of the high-impact contributions of the Protein Structure Initiative (for which I played a variety of roles over 15 years), we now possess the ability to rapidly prosecute targets for gene-to-structure-to-function via bioinformatics target selection, orthologue expansion, domain and construct design, expression, purification, structure determination and biophysical analysis for functional annotation and inhibitor design. These achievements have expanded the approaches researchers will consider in experimental design to address biophysical research problems. The PSI, the EFI, and other structural genomics programs in the US and worldwide have generated an enormous amount of primary data and materials which are now routinely mined in the advancement of ongoing research. Likewise, the methods development which was integral to these projects has resulted in a manifold of accessible techniques for the parallel prosecution of multiple target proteins in structure determination, functional assessment, and inhibitor discovery. This is borne out by the numerous collaborative publications resulting from the support of the biological community by the PSI and EFI investigators and infrastructure (for two examples, see references 1 and 2). Additional studies on biologically focused projects resulted in remarkable discoveries (see references 3 and 4, for example). Finally, a large number of contributions arising from the PSI, EFI and other efforts, detailing powerful methods advancements have been published (see references 5 and 6, for example). See the full list of publications for many more examples in each category.

1. Sampathkumar P, Kim SJ, Upla P, Rice WJ, Phillips J, Timney BL, Pieper U, Bonanno JB, Fernandez-Martinez J, Hakhverdyan Z, Ketaren NE, Matsui T, Weiss TM, Stokes DL, Sauder JM, Burley SK, Sali A, Rout MP, Almo SC. (2013) Structure, dynamics, evolution, and function of a major scaffold component in the nuclear pore complex. *Structure* 21(4), 560-571.
2. Ho MC, Wilczek C, Bonanno JB, Xing L, Seznec J, Matsui T, Carter LG, Onikubo T, Kumar PR, Chan MK, Brenowitz M, Cheng RH, Reimer U, Almo SC, Shechter D. (2013) Structure of the arginine methyltransferase PRMT5-MEP50 reveals a mechanism for substrate specificity. *PLoS One* 8(2):e57008.
3. Kim J, Xiao H, Bonanno JB, Kalyanaraman C, Brown S, Tang X, Al-Obaidi NF, Patskovsky Y, Babbitt PC, Jacobson MP, Lee YS, Almo SC. (2013) Structure-guided discovery of the metabolite carboxy-SAM that modulates tRNA function. *Nature* 498(7452), 123-126.
4. Vladimirova A, Patskovsky Y, Fedorov AA, Bonanno JB, Fedorov EV, Toro R, Hillerich B, Seidel RD, Richards NG, Almo SC, Raushel FM. (2015) Substrate distortion and the catalytic reaction mechanism of 5-carboxyvanillate decarboxylase *J. Am. Chem. Soc.* Dec 30. Epub ahead of print, PMID: 26714575
5. Liu W, Vigdorovich V, Zhan C, Patskovsky Y, Bonanno JB, Nathenson SG, Almo SC. (2015) Increased Heterologous Protein Expression in Drosophila S2 Cells for Massive Production of Immune Ligands/Receptors and Structural Analysis of Human HVEM. *Molecular Biotechnology* 57(10), 914-922.
6. Zhao S, Kumar R, Sakai A, Vetting MW, Wood BM, Brown S, Bonanno JB, Hillerich BS, Seidel RD, Babbitt PC, Almo SC, Sweedler JV, Gerlt JA, Cronan JE, Jacobson MP. (2015) Discovery of new enzymes and metabolic pathways by using structure and genome context. *Nature* 502(7473), 698-702.

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

Research Support

N/A

NCBI Bibliography:

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