BIOGRAPHICAL SKETCH

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NAME: **LIEBERMAN, Paul M.**

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

POSITION TITLE: **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
Cornell University, Ithaca, NY	B.A.	06/1983	Chemistry
The Johns Hopkins University, School of Medicine, Baltimore, MD	Ph.D.	12/1988	Virology/Pharmacology
University of California, Los Angeles, CA	Postdoc	06/1993	Molecular Biology

A. PERSONAL STATEMENT

Human tumor viruses are responsible for ~17% of all human cancers. I have been investigating the molecular virology and pathogenesis of Epstein-Barr Virus (EBV) since my PhD work with Gary and Diane Hayward, and then post-doctoral work with Arnie Berk on basic mechanisms of transcriptional activation using EBV Zta as a model transcriptional activator. My present research focuses on the mechanisms controlling viral latency and how they impact oncogenesis. We have found that EBV and KSHV genomes are tightly regulated by viral and cellular factors involved in chromatin structure and genome maintenance. My present research focuses on the mechanisms controlling viral latency and how they impact oncogenesis. We have found that EBV and KSHV genomes are tightly regulated by viral and cellular factors involved in chromatin structure and genome maintenance. We now pursue understanding how these host-viral interactions regulate the viral episome during latency and the establishment of a tumorigenic phenotype. We focus on basic mechanisms of viral proteins, like EBNA1 and LANA, control viral latency and promote host-cell survival. The information generated is required for better understanding of how EBV and KSHV contributes to diverse human cancers, and how to target these factors for therapeutic intervention. To this end, we have used structure-based drug design to develop small molecule inhibitors of EBNA1, the key viral protein sustaining EBV tumor growth and survival. With funding from the Wellcome Trust Seeding Drug Discovery and in collaboration with structural biologists and medicinal chemists, we are approaching the final stages of an IND application to the USFDA and planning for a Phase I clinical trial in 2018 for a First-in-Class new chemical entity to treat EBV-associated malignancies.

B. POSITIONS AND HONORS

Professional Experience:

1993-1995	Assistant Member I, Roche Institute of Molecular Biology
1993-1995	Assistant Adjunct Professor, Department of Biological Sciences, Columbia University, NYC
1995-1999	Assistant Professor, The Wistar Institute, Philadelphia, PA
1995-Present	Adjunct, Department of Microbiology, University of Pennsylvania, Philadelphia, PA
2000-2005	Associate Professor, The Wistar Institute, Philadelphia, PA
2005-Present	Professor, The Wistar Institute, Philadelphia, PA
2008-2017	Scientific Director, Protein Expression and Libraries Facility, The Wistar Institute Cancer Center, Philadelphia, PA
2009-Present	Director, Center for Chemical Biology and Translational Medicine, The Wistar Institute, Philadelphia, PA
2010-2013	McNeil Professor of Molecular and Translational Medicine
2013-Present	The Hilary Koprowski, M.D. Endowed Professor
2014-Present	Program Leader, Gene Expression and Regulation Program, The Wistar Institute

Honors and Awards:

1981	National Science Foundation Undergraduate Summer Fellowship, Cornell University
1988	California Institute of Cancer Research Fellow
1989	National Research Service Award
1989-1992	American Cancer Society Fellow
1992-1993	Leukemia Society Special Fellow
1997	Leukemia Society Scholar
1999	Malinkrodt Foundation Award Recipient
2000	W.W. Smith Foundation Award Recipient
2001	American Cancer Society Investigator Award
2010-2012	President, Association for Research on Epstein-Barr Virus and Associated Diseases
2012-2018	Wellcome Trust Seeding Drug Discovery Award Recipient
2018	Henle Lectureship. EBV-KSHV International Symposium, Madison, WI

Review Panels/Study Section:

2005-2012	American Cancer Society (MPC Study Section)
2010	Ad-Hoc VirB 2010, P01 NIAID/ZA
2011	Ad-Hoc NASA
2011	Ad-Hoc ZRG1
2011,12	Ad-Hoc ZRG1 AARR-K
2011	Ad-Hoc Chronic Fatique and Immune Disease Association
2012-2018	Ad-Hoc ZRG1 AAR (VirB), AARREO2, ZCA1 SRB-2 (O1), ZCA1 SRLB-1, Swiss Science Foundation, IMM Portugal, AIDS Malignancies ZCA1
2018	Panel for NCI's Important Questions in HIV/AIDS Cancer Research- Invited Speaker

Editorial Boards:

2013	Associate Editor, *PLoS Pathogens*
2013	Associate Editor, *Journal of Virology*

C. CONTRIBUTIONS TO SCIENCE

Early career investigating basic mechanisms of transcriptional regulation by viral immediate early proteins

My early independent research focused on the mechanism of transcription activation of EBV-encoded immediate early protein Zta, and how it stimulates viral reactivation from latency. We discovered that Zta interacts with general transcription factors TFIIA and TFIID to form a stable preinitiation complex at viral promoter start sites with extended downstream interactions. This was one of the first demonstrations that transcription activators could induce conformational changes in TFIID promoting TBP-associated factors (TAF)-DNA interactions.

1. Lieberman PM, Berk AJ. 1994. A mechanism for TAFs in transcriptional activation: activation domain enhancement of TFIID-TFIIA-Promoter DNA complex formation. ***Genes Dev*** 8:995-1006. PMID: 7926793.
2. Ozer J, Moore PA, Bolden AH, Lee A, Rosen CA, Lieberman PM. 1994. Molecular cloning of the small (gamma) subunit of TFIIA reveals functions critical for activated transcription. ***Genes Dev*** 8:2324-2335. PMID: 7958899.
3. Chi T, Lieberman P, Ellwood K, Carey M. 1995. A general mechanism for transcriptional synergy by eukaryotic activators. ***Nature*** 377:254-257. PMID: 7675113.
4. Moore PA, Ozer J, Salunek M, Jan G, Zerby D, Cambell S, Lieberman PM. 1999. A human TBP related protein (TRP) with altered DNA binding specificity inhibits transcription from multiple promoters and activators. ***Mol Cell Biol*** 19:7610-7620. PMCID: PMC84787.

Epigenetic regulation of Epstein-Barr Virus (EBV) latency and reactivation in viral cancers

The regulation of EBV latency depends on epigenetic modifications of the viral chromosome. We have used biochemical and computational methods to investigate the EBV epigenome during latency. Using both ENCODE data and experimentally generated genome-wide data sets we found that EBV genomes have chromatin boundaries and DNA conformations that are mediated by CTCF and cohesin binding sites. We also

identify host chromosome binding sites for the episome maintenance protein EBNA1 that can modulate host cell gene expression, and epigenetic modifications. These latter findings have implications for how EBNA1 may provide a host-survival function by altering host gene expression and chromatin organization.

5. Lu F, Wiedmer A, Martin KA, Wickramasinghe PJMS, Kossenkov AV, Lieberman PM. 2017. Coordinate Regulation of TET2 and EBNA2 Control DNA Methylation State of Latent Epstein-Barr Virus. ***J Virol*** pii:JVI.00804-17. PMCID: PMC5625499.
6. Lu F, Chen HS, Kossenkov AV, DeWispeleare K, Won KJ, Lieberman PM. 2016. EBNA2 Drives Formation of New Chromosome Binding Sites and Target Genes for B-Cell Master Regulatory Transcription Factors RBP-jκ and EBF1. ***PLoS Pathog*** 12:e1005339. PMCID: PMC4709166.
7. Arvey A, Tempera I, Tsai K, Chen HS, Tikhmyanova N, Klichinsky M, Leslie C, Lieberman PM. 2012. An atlas of the Epstein-Barr Virus transcriptome and epigenome reveals host-viral regulatory interactions. ***Cell Host Microbe*** 12:233-245.
8. Tempera I, Klichinsky M, Lieberman PM. 2011. EBV Latency Types Adopt Alternative Chromatin Conformations. ***PLoS Pathog*** 7:e1002180. PMCID: PMC3145795.

Regulation of Kaposi's Sarcoma-Associated Herpesvirus (KSHV) latency and chromatin structure

KSHV persists as a chromatinized episome that can spontaneously and sporadically reactivate. This dynamic toggling between latent and lytic gene expression is thought to be critical for the strategy of viral persistence, oncogenic pathogenesis, and immune evasion. We have used biochemical and functional genomic approaches to understand the mechanisms regulating KSHV gene regulation during latent infection in various cell types and tumors. We have also use X-ray structural biology to understand the molecular details of LANA function in episome maintenance, chromatin assembly, and viral gene regulation.

9. De Leo A, Chen HS, Hu CA, Lieberman PM. 2017. Deregulation of KSHV latency conformation by ER-stress and caspase-dependent RAD21-cleavage. ***PLoS Pathog*** 13(8):e1006596. PMCID: PMC5595345.
10. Chen HS, De Leo A, Wang Z, Kerekovic A, Hills R, Lieberman PM. 2017. BET-Inhibitors Disrupt Rad21-Dependent Conformational Control of KSHV Latency. ***PLoS Pathog*** 13:e1006100. PMCID: PMC5287475.
11. Domsic JF, Chen HS, Lu F, Marmorstein R, Lieberman PM**.** 2013. Molecular basis for oligomeric-DNA binding and episome maintenance by KSHV LANA. ***PLoS Pathog*** 9:e1003672. PMCID: PMC3798644.
12. Dheekollu J, Chen HS, Kay KM, Lieberman PM. 2013. Timeless-dependent DNA replication-coupled recombination promotes KSHV episome maintenance and terminal repeat stability. ***J Virol*** 87:3699-3709. PMCID: PMC3624199.

Mechanisms of telomere chromatin dysfunction in cancer

We have found that telomeric factors assemble with EBNA1 at the DS element of OriP. How telomeric factors contribute to episome maintenance, and how viruses utilize telomeric mechanisms to maintain their genome integrity is an important area of investigation, having implications for viral latency and telomere biology.

13. Tutton S, Azzam GA, Stong N, Vladimirova O, Wiedmer A, Monteith JA, Beishline K, Wang Z, Deng Z, Riethman H, McMahon SB, Murphy M, Lieberman PM. 2016. Subtelomeric p53 binding prevents accumulation of DNA damage at human telomeres. ***EMBO J*** 35:193-207. PMCID: PMC4718461.
14. Wang Z, Deng Z, Dahmane N, Tsai K, Wang P, Williams DR, Kossenkov AV, Showe LC, Zhang R, Huang Q, Conejo-Garcia JR, Lieberman PM. 2015. Telomeric repeat-containing RNA (TERRA) constitutes a nucleoprotein component of extracellular inflammatory exosomes. ***Proc Natl Acad Sci U S A*** 112:E6293-6300. PMCID: PMC4655533.
15. Deng Z, Kim ET, Vladimirova O, Dheekollu J, Wang Z, Newhart A, Liu D, Myers JL, Hensley SE, Moffat J, Janicki SM, Fraser NW, Knipe DM, Weitzman MD, Lieberman PM. 2014. HSV-1 remodels host telomeres to facilitate viral replication. ***Cell Rep*** 9:2263-2278. PMCID: PMC4356630.
16. Deng Z, Glousker G, Molczan A, Fox AJ, Lamm N, Dheekollu J, Weizman OE, Schertzer M, Wang Z, Vladimirova O, Schug J, Aker M, Londoño-Vallejo A, Kaestner KH, Lieberman PM, Tzfati Y. 2013. Inherited mutations in the helicase RTEL1 cause telomere dysfunction and Hoyeraal-Hreidarsson syndrome. ***Proc Natl Acad Sci U S A*** 110:E3408-E3416. PMCID: PMC3767560.

Small molecule drug discovery to treat viral cancers

We have established multiple different approaches to identify small molecule inhibitors and regulators of EBV and KSHV infection and tumorigenesis. These include assay development for high-throughput screening, structure-guided fragment-based drug design, computationally directed drug design, and phenotypic assay development and screening. We have used these to target EBV latency protein EBNA1, KSHV latency protein LANA, lytic inducing pathways for EBV, and identification of targets for bioactive small molecules. Development of new small molecules with better understanding of target interaction is a major focus for future research, with great potential for therapeutic impact.

17. Tikhmyanova N, Tutton S, Martin KA, Lu F, Kossenkov AV, Paparoidamis N, Kenney S, Salvino JM, Lieberman PM. 2017. Small molecule perturbation of the CAND1-Cullin1-ubiquitin cycle stabilizes p53 and triggers Epstein-Barr virus reactivation. ***PLoS Pathog*** 13:e1006517. PMCID: PMC5531659.
18. Tikhmyanova N, Schultz DC, Lee T, Salvino JM, Lieberman PM. 2013. Identification of a new class of small molecules that efficiently reactivate latent Epstein-Barr virus. ***ACS Chem Biol*** 9:785-795. PMCID: PMC4159771.
19. Li N, Thompson S, Schultz DC, Zhu W, Jiang H, Luo C, Lieberman PM. 2010. Discovery of selective inhibitors against EBNA1 via high throughput in silico virtual screening. ***PLoS One*** 5:e10126. PMCID: PMC2853575.
20. Thompson S, Messick T, Schultz DC, Reichman M, Lieberman PM. 2010. Development of high throughput screen for inhibitors of Epstein-Barr virus EBNA1. ***J Biomol Screen*** 15:1107-1115. PMCID: PMC2853575.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/paul.lieberman.1/bibliography/40832602/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT
ACTIVE

P30 CA010815 (PI, Altieri) 03/01/14-02/28/19
NIH/NCI
Consolidated Basic Cancer Research Program
Role in Project: Co-Program Leader for Gene Expression and Regulation Program
Note: This is the Cancer Center Support Grant (CCSG) that supports basic cancer research at The Wistar Institute.

P01 CA174439 (PI, Robertson) 07/01/13-04/30/19
NIH/NCI
Early Events in KSHV Infection of Primary B-Cells
Project 3: Chromatin Dynamics of KSHV Primary Infection (Core Director)
This project investigates the role of chromatin assembly on the fate of de novo KSHV infection. This work will provide new insight into the mechanism of chromatin control of viral gene expression and genome propagation, and may reveal new targets for therapeutic intervention in KSHV-associated disease and cancers.

R01 CA186775 (PI, Lieberman) 06/01/14-05/31/19
NIH/NCI
Development of a Small Molecule Inhibitor for KSHV LANA
The goal of this research program is to develop and characterize novel small molecule inhibitors of latent Kaposi's Sarcoma Associated Herpesvirus (KSHV) infection.

R01 CA140652 (PI, Lieberman) 05/19/15-04/30/20
NIH/NCI
Epigenetic Regulation of Human Telomeres
We propose to use genomic and proteomic methods to investigate telomeric chromatin in normal and pathogenic states, including proliferation stress and cancer. These studies will provide important new information on human telomere chromatin control and epigenetic programming, as well as identify new biomarkers and therapeutic targets for human diseases associated with telomere dysfunction.

R01 DE017336 (PI, Lieberman) 02/01/16-01/31/21

NIH/NIDCR
Epigenetic Regulation of Epstein-Barr Virus
In this proposal, we will test the hypothesis that EBV gene expression and replication programs are coordinately regulated with host cell information through complex epigenetic mechanisms. The studies will provide important new information on how EBV gene expression programs are coordinated with host-cell biology, and also provide new insights into the epigenetic control of viral genes associated with EBV carcinogenesis.

R61 AI133696 (MPI: Collman and Lieberman) 08/01/17-07/31/20
NIH/NIAID
Epigenetic HIV Silencing in Macrophages
In Phase 1 of this project, we will establish a robust high-throughput primary cell-based screen as well as orthogonal validation assays to confirm on-target hits. In Phase 2, we will complete a high-throughput screen of several structurally diverse small molecule libraries, identified and validated hits, and selected advanced lead candidates.

R01 CA117830 (PI, Lieberman) 12/01/17-11/30/22
NIH/NCI
Epigenomic Control of KSHV Latency
In this application, we investigate the mechanisms regulating gene expression from Kaposi's Sarcoma (KS)-Associated Herpesvirus (KSHV) latent genomes, and how this process may be deregulated in KS.

R01 CA193624 (MPI: Lieberman, Salvino, and Keeney) 05/19/15-04/30/19*
NIH/NCI
Development of a Novel Inducer for EBV Lytic Therapy
This proposal aims to optimize this newly identified class of chemical probe using medicinal chemistry principles to enhance drug-like properties predictive of in vivo efficacy. We will also develop probes and methods to understand the biochemical mechanism of action of these EBV lytic activating agents. Finally, we will use animal models of EBV-associated cancer to test the in vivo efficacy of advanced probes and lead compounds to reactivate the EBV lytic cycle more efficiently and with a significantly improved safety profile compared to HDAC inhibitors and phorbol esters.
*1 yr no cost extension

COMPLETED
096496/Z/11/Z (PI, Lieberman) 11/18/11-03/31/18
WELLCOME TRUST
Development of a Small Molecule Inhibitor of EBNA1 to Treat Epstein- Barr Virus (EBV) Infection and Associated Disease
The primary objective of the proposal is to develop a safe and efficacious clinical candidate to treat oncogenic Epstein-Barr Virus (EBV) and associated disease.

R01 CA093606 (PI, Lieberman) 05/01/14-04/30/18
NIH/NCI
Regulation of EBV Latency by EBNA1
Elucidation of the mechanism of EBV plasmid maintenance and DNA replication during latency. This grant focuses on the interactions of EBNA1 with cellular telomere repeat binding factors and poly-ADP ribose polymerases