BIOGRAPHICAL SKETCH

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NAME: Margolis, David M.

eRA COMMONS USER NAME: margolis

POSITION TITLE: Sarah Graham Kenan Distinguished Professor of Medicine, Epidemiology, and Microbiology and Immunology; Director, UNC HIV Cure Center

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Harvard University, Cambridge, MA	AB	06/1981	Biology
Tufts University School of Medicine, Boston, MA	MD	06/1985	Medicine
Tufts-New England Medical Center, Boston, MA	Residency	06/1988	Internal Medicine

A. Personal Statement

My laboratory has a long history of translational HIV research: investigating basic molecular, virological, and immunological phenomenon, and leveraging insights to develop new interventions in HIV disease. While my work has involved many aspects of HIV science and medicine, for the last two decades a central focus of has been the study of molecular mechanisms of HIV proviral latency [1] and persistence despite potent antiretroviral therapy (ART). We have begun to define the role of epigenetic factors in the restriction of HIV expression, and this has led to diverse, multidisciplinary collaborations and translational clinical studies resulting in discovery and high-impact work [2]. I am the principal investigator for CARE (Collaboratory of AIDS Researchers for Eradication), an NIH-funded research organization that seeks to develop the tools to bring an HIV cure from the bench to the clinic [3, 4]. I am the principal investigator of two NIH-funded studies to combine biologics (broadly-neutralizing antibodies or antiviral T cell infusions) and small-molecule anti-latency agent (HDAC inhibitor) in FDA-approved investigations to attempt to precisely document the depletion of persistent HIV infection. Finally, I direct the UNC HIV Cure Center, created to support novel and impactful research needed to advance towards therapies to induce an HIV remission. We currently support 7 junior faculty scientists in a multidisciplinary environment ideal for training and translational research.

1. Margolis, DM, Somasundaran, M, Green, MR. Human transcription factor YY1 represses HIV-1 transcription and virion production. J. Virology 1994; 68:905-910. PMCID: PMC236527.
2. Archin NM, Liberty AL, Kashuba AD, Choudhary SK, Kuruc JD, Crooks AM, …, Margolis DM. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature. 2012; 487(7408): 482-5. PMCID: PMC3704185
3. Denton PW, Long JM, Wietgrefe SW, Sykes C, Spagnuolo RA, Snyder O, ..., Margolis DM, Garcia JV. Targeted cytotoxic therapy kills persisting HIV infected cells during ART. PLoS Pathog. 2014; 10(1):e1003872. PMID:24415939
4. Spina CA, Anderson J, Archin NM, Bosque A, Chan J, Famiglietti M, Greene WC, …, Margolis DM, et al. An in-depth comparison of latent HIV-1 reactivation in multiple cell model systems and resting CD4+ T cells from aviremic patients. PLoS Path 2013; 9(12): e1003834

B. Positions and Honors

1985-88: Tufts-New England Medical Center, Boston, Mass: Residency in Internal Medicine
1988-91: National Institute of Allergy & Infectious Diseases, NIH, Bethesda, MD: Medical Staff Fellow and Clinical Associate, Laboratory of Clinical Investigation (Stephen E. Straus MD)
1991-94: University of Massachusetts Medical Center, Worcester, MA:
Program in Molecular Medicine: postdoctoral fellowship (Michael R. Green, MD, PhD)
1994-99: University of Maryland, Baltimore, MD:
Assistant Professor: Institute of Human Virology and School of Medicine
1999-2005: University of Texas Southwestern Medical Center at Dallas, Dallas, TX:
Associate Professor, Department of Medicine, Division of Infectious Diseases

Section Chief, Infectious Diseases, Dallas VA Medical Center
2005-present: The University of North Carolina at Chapel Hill, Chapel Hill, NC: Director, UNC HIV Cure Center and Kenan Distinguished Professor of Medicine, Epidemiology, Microbiology and Immunology

Magna Cum Laude, Harvard College, 1981
Amer. College Physicians Associates award, 1988
NIH Physician-Scientist award (K-11), 1991-94
Fellow, American College of Physicians, 1996
IDSA young investigator, 1997
Fellow, Infectious Dis. Society of America, 2000
amfAR Basic Science award, 2001
WJ Way Visiting Professor, Duke CFAR, 2005
Am. Society for Clinical Investigation, 2005
M. Glenn Koenig Visiting Professor, Vanderbilt 2011
Tim Gill Visiting Professor, U Colorado Denver, 2013
Sarah Graham Kenan Distinguished Professor of Medicine, UNC Chapel Hill, 2018
Association of American Physicians, 2019
Web of Science Highly Cited Researchers, 2019

Selected Committees: NIAID AIDS Research Advisory Committee 2004-2008; AIDS Clinical Trials Strategic Working Group 2006-2008; IDSA Research Committee 2008-2011; NIAID ACTG Research Agenda Committees 1999-present; V.A. Merit Review 2000-04; NIAID AIDS Clinical Studies and Epidemiology Study Section 2010-14; amfAR Scientific Advisory Committee (since 2002); other *ad hoc* review panels for NIH, ANRS, MRC, Deutsche Forschungsgemeinschaft, AIDS Fonds. ***Editorial Boards:*** AIDS (2006-12), J Virology (2008-15), J. Infect. Dis. (2015-present), Retrovirology (2017-present).

C. Contribution to Science

1. ***The molecular basis of HIV latency:*** For over 25 years we have studied the regulation of expression of HIV proviral genomes, following an initial discovery that HIV transcription could be suppressed as well as activated [1]. Attempts to define the mechanism of action by which host factors could repress HIV transcription and viral production led to the first definition of a complex of host factors that specifically recruited a chromatin-modifying enzyme to the HIV promoter [5 and others]. Our studies led to an emerging understanding of a dynamic interplay between restrictive and activating influences [6], and of overlapping influences that may contribute to HIV latency, forming a complex and dynamic view of the state of HIV latency. Recent work has revealed specific mechanistic insights into the enforcement of latency by other mechanisms such as histone methylation and crotonylation [7, 8 and others], suggesting novel, selective strategies to disrupt latency.
    5. Coull, J, Romerio, F, Sun, J-M, Volker, JM, Galvin, KM, Davie, JR, Shi, Y, Hansen, U, Margolis, DM. The human factors YY1 and LSF repress the human immunodeficiency virus type-1 long terminal repeat via recruitment of histone deacetylase 1. J. Virology 2000; 74:6790–6799. PMCID: PMC112196.
    6. He, G, Margolis, DM. Counter-regulation of Chromatin Acetylation and Histone Deacetylase Occupancy at the Integrated Promoter of Human Immunodeficiency Virus Type 1 by the HIV-1 Activator Tat and the HIV-1 Repressor YY1. Mol. Cell. Biol. 2002; 22:2965-2973. PMCID: PMC133763.
    7. Tripathy MK, McManamy MEM, Burch BD, Archin NM, Margolis DM. H3K27 demethylation at the proviral promoter sensitizes latent HIV to the effects of vorinostat in ex-vivo cultures of resting CD4+ T cells. J. Virol. 2015; 89(16):8392-405. PMID: 26041287 PMCID: PMC4524215
    8. Jiang G, Nguyen D, Kim PL, Archin NM, Elsheikh M, Lagares GM, Thompson III GR, Hartigan-O'Connor D, Margolis DM, Wong JK, Dandekar S. Histone crotonylation is a novel epigenetic mark that regulates HIV latency. J Clin Invest. 2018; 128(3):1190-1198. doi: 10.1172/JCI98071. PMID: 29457784

2. ***Developing tools to reverse HIV latency:*** Studies of the molecular basis of HIV latency have more recently led to efforts to develop tools to specifically disrupt HIV latency, as part of an emerging strategy to clear persistent HIV infection. A potent histone deacetylase (HDAC) inhibitor, a pre-clinical candidate drug at the time, was shown to disrupt HIV latency at clinically attainable exposures [9], and selected isoforms [10] shown to be most relevant. As bromodomain inhibitors were also shown to have potential for translational use in HIV latency disruption strategies [11]. Recently non-canonical NF-kB agonists have shown remarkable unprecedented latency reversal activity in both the humanized mouse and SIV model systems, and related compounds are being prepared for first-in-human studies [12].
    9. Archin NM, Espeseth A, Parker D, Cheema C, Hazuda DJ, Margolis DM. Expression of Latent HIV Induced by the Potent HDAC Inhibitor Suberoylanilide Hydroxamic Acid. AIDS Res Hum Retro. 2009; 25:207-212. PMID: 19239360; PMCID: PMC2853863

10. Keedy KS, Archin NM, Gates AT, Espeseth AS, Hazuda DJ, and Margolis DM. A limited group of class I histone deacetylases act to repress human immunodeficiency virus type-1 expression. J Virol. 2009; 88:4749–4756. PMID: 19279091; PMCID: PMC2682072
11. Banerjee C, Archin N, Michaels D, Belkina AC, Denis GV, Bradner J, Sebastiani P, Margolis DM, Montano M. BET bromodomain inhibition as a novel strategy for reactivation of HIV-1. J Leukoc Biol. 2012; 92(6):1147-54. PMID: 2280244
12. Nixon CC, Mavigner M, …, Margolis DM, Dunham RM, Wahl A, Silvestri G, Chahroudi A, Garcia JV. Systemic HIV/SIV latency reversal via activation of the non-canonical NF-κB signaling pathway *in vivo*. Nature 2020; 578(7793):160-165. PMID:31969707

3. ***Pilot studies to disrupt HIV latency:*** As the success of potent and durable ART became more fully realized in the prior decade, we began to explore the potential to directly attack replication-competent genomes that persist despite ART. The demonstration that HIV latency could be reversed by a clinically available HDAC inhibitor [13] led to a proof-of-concept study in man [14] that suggested depletion of latent infection. However, as further studies [15 and others] showed only a marginal effect on persistent infection, we designed and implemented new clinical assays to directly measure expression of cell-associated HIV RNA in the resting CD4+ T cells of HIV-infected, ART-suppressed study participants. Using a new and more potent HDAC inhibitor [9], at the time an investigational drug, we directly documented the disruption of HIV latency [2]. However, subsequent study revealed complexities and potential limitations in the serial administration of HDAC inhibitors as latency reversing agents [16 and others], a challenge now under intensive study in our group.

13. Ylisastigui, L, Archin, N, Lehrman, G, Bosch, RJ, Margolis, DM. Coaxing Human Immunodeficiency Virus Type 1 from Resting CD4+ T Cells: histone deacetylase inhibition allows latent viral expression. AIDS 2004; 18:1101-1108. PMID: 15166525.
14. Lehrman, G., Hogue, I.B., Palmer, S., Jennings, C., Spina, C.A., Wiegand, A., …, Margolis, D.M. Depletion of latent HIV infection in vivo. Lancet 2005; 36:549-555. PMCID: PMC1894952
15. Archin NM, Bateson R, Tripathy M, Crooks AM, Yang KH, Dahl NP, …, Margolis DM. HIV-1 Expression within Resting CD4 T-Cells Following Multiple Doses of Vorinostat. J Infect Dis 2014; 210:728-35. PMID:24620025
16. Archin NM, Kirchherr JL, Sung J, Clutton G, Sholtis K, Xu Y, …, DM Margolis. Interval Dosing Allows Effective Reversal of HIV Latency by Vorinostat. J Clin Invest. 2017; 127(8):3126-3135. PMID: 28714868

4. ***Understanding persistent HIV infection:*** The sources and origins of persistent HIV infection are incompletely defined. Over the last several years, in painstaking studies of samples obtained from HIV-infected participants in clinical trials or study protocols, we have studied the founding of the latent reservoir during acute HIV infection, the sources of residual viremia, and the cell subpopulations that are persistently infected with replication-competent provirus. We have defined the resting central memory CD4+ T cell as the primary reservoir of latent, persistent infection, but ongoing studies are defining the frequency and durability of latent infection in other cell population in durably ART-treated patients.

17. Anderson J, Archin NA, Ince W, Parker D., Wiegand A, Coffin J, Kuruc J., Eron JJ, Swanstrom R, Margolis DM. Clonal sequences recovered from plasma from patients with residual HIV-1 viremia and on intensified antiretroviral therapy are identical to replicating viral RNAs recovered from circulating resting CD4+ T cells J. Virol. 2011; 85(10):5220-3. PMCID: PMC3126162
18. Archin NM, Vaidya NK, Kuruc JD, Liberty AL, Wiegand A, Kearney MF, …, Margolis DM, Perelson AS. Immediate antiviral therapy appears to restrict resting CD4+ cell HIV-1 infection without accelerating the decay of latent infection. Proc Natl Acad Sci U S A. 2012; 109(24):9523-8. PMCID: PMC3386138
19. Crooks AM, Bateson R, Cope AB, Dahl NP, Griggs M, Kuruc JD, Gay CL, Eron JJ, Archin NM, Bosch RJ, Margolis DM. Precise Quantitation of the Latent HIV-1 Reservoir: Implications for Eradication Strategies. J Infect Dis. 2015; 212(9):1361-5. PMID: 25877550 PMCID:PMC4601910
20. Bradley T, Ferrari G, Haynes BF, Margolis DM, Browne EP. Single cell analysis of quiescent HIV infection reveals host transcriptional profiles that regulate proviral latency. Cell Rep. 2018; 25(1):107-117.e3. PMID:30282021

5. ***Developing immunotherapies to eradicate HIV infection***: The nascent research effort towards an HIV cure has required focus and effort in new areas. Over the last several years, we have participated in the

development of humanized mouse models for use in these efforts, Most recently, we have begun to explore novel immunotherapies as a tool to clear persistent HIV infection following the disruption of latency.

21. Denton PW, Long JM, Wietgrefe SW, Sykes C, Spagnuolo RA, Snyder O, ..., Margolis DM, Garcia JV. Targeted cytotoxic therapy kills persisting HIV infected cells during ART. PLoS Pathog. 2014; 10(1):e1003872. PMID:24415939
22. Sung JA, Pickeral P, Liu L, Stanfield-Oakley SA, Lam C-YK, Garrido C, …, Margolis DM, Ferrari G. Dual Affinity Re-Targeting (DART) proteins direct T cells to mediate cytolysis of patients' latently HIV-infected cells. J Clin Invest. 2015; 125:4077–4090. PMID: 26413868
23. Sung JA, Patel S, Roesch L, Kuruc JD, Clohosey ML, Archin NM, …, Margolis DM. HIV-specific, Ex-Vivo Expanded T-Cell Therapy (HXTC): Feasibility, Safety, and Efficacy in ART-suppressed, HIV-infected Individuals. Mol Ther. 2018; 26(10):2496-2506. doi: 10.1016/j.ymthe.2018.08.015. PMID:30249388. PMC 6171327.
24. Tuyishime M, Garrido C, Jha S, Mielke D, Moeser M, Haynes B, Joseph S, Margolis DM, Ferrari G. Improved Killing of HIV-infected Cells by a Combination of Three Antibodies: implications for clearing persistent infection. J Clin Invest. 2020: doi: 10.1172/JCI135557. PMID: 32584790

List of Published Work (211 total publications/chapters/in press, 4 manuscripts in review):
https://orcid.org/0000-0001-5714-0002

D. Research Support

Ongoing Research Support

R01 HL132791 Margolis (PI) 07/15/16-03/31/21
HIV-specific ex-vivo expanded T cell therapy (HXTC) to deplete the Latent Reservoir of Persistent HIV Infection: This project aims to investigate HIV-specific ex vivo expanded T cells (HXTCs) alone and in combination with the latency reversing agent, vorinostat, for induction of latent virus expression and depletion of the latent reservoir. Role: Principal Investigator

UM1 AI126619 Margolis (PI) 07/14/16-06/30/21
Collaboratory of AIDS Researchers for Eradication (CARE)
Extending and redirecting the work initiated in 2011-2016, the reorganized Collaboratory of AIDS Researchers for Eradication (CARE) brings together scientists from UNC, Duke, Emory, and UCSD, and from Merck Research Laboratories, Qura Therapeutics, and Macrogenics, to seek therapies to eradicate HIV infection. Role: Principal Investigator

U01 AI117844 Margolis (PI) 03/01/15-02/28/21
A Pilot Trial of the effect of Vorinostat and AGS-004 on Persistent HIV-1 Infection: This is a proof-of-principal study to measure the potential of VOR and AGS-004 to: a) induce expression of persistent proviral HIV, b) induce an HIV-specific immune response, and c) clear persistent infection in HIV+ patients in whom viral replication, evasion, and spread is inhibited by uninterrupted ART. Role: Principal Investigator

Qura Therapeutics Margolis (PI) 10/01/15-12/31/5
A joint academic/industry partnership dedicated to finding a cure for HIV/AIDS and created to pool the best expertise of industry (product focus, discovery and development expertise) and academia (basic research, translational medicine, clinical trials implementation). Role: Principal Investigator

R61 DA047023 James (PI) 09/01/18-08/31/23
Polycomb Repressive Complexes as Key Regulators of HIV Latency and Targets for Latency Reversal
The overarching objective of this proposal is to apply genetic, biochemical, and chemical biology approaches to study the role of the Polycomb Repressive Complexes, PRC1 and PRC2, in HIV latency. Role: Co-Investigator

R01 AI134363 Archin (PI) 08/08/17-07/31/21
The HIV Reservoir in Women: Implications for HIV Cure interventions
This project seeks to rigorously characterize the distribution of the replication competent HIV reservoirs in T-cell subpopulations in the periphery and in tissues of women, assess the stability of the reservoir and identify factors that establish this reservoir, and evaluate approaches to disrupt latency in women. Role: Co-Investigator

HHSN272201500032C Koenig (PI) 01/01/16-08/31/22
Immune-Based Antiviral Products for Suppression/Elimination of HIV-1 To perform product development and advance therapeutic products, Dual Affinity Re-Targeting (DART®)-1 and DART-2, into Phase 1/2 Clinical Trials for use as therapeutic agents, in combination with latency reversing treatments, and to deplete human immunodeficiency virus (HIV) infection that persists despite the presence of existing combination anti-retroviral therapy. Role: Co-Investigator

U01 AI131310 Goonetilleke (PI) 07/15/17-06/30/22
Phase I therapeutic testing of viral-vectored vaccines that shift CD8+ T cell immunodominance to conserved regions of HIV-1
This project proposes a first-in-human trial of a novel vaccine regimen which aims to elicit an arm of our immune response, called CD8+ T cells. Role: Co-Investigator

UM1 AI124436 Amara, Hunter (co-PIs) 06/01/2017-05/31/2021
Consortia for Innovative AIDS Research in NHP
This project aims to develop advanced vaccines that provide sustained protection from retroviral infection. In addition, they aim to refine existing "shock and kill" approaches that seek to eliminate the virus from latent reservoirs in people who are infected with HIV, enhancing the possibility of a cure. Role: Co-Investigator

R01AI123010 Wahl (PI) 03/01/2016- 02/29/2021
The role of human gut microbiota in HIV-1 rectal acquisition, replicaton, and pathogenesis
This study will utilize a novel and innovative in vivo humanized mouse model that is colonized with human gut microbiota to establish the role of human gut microbiota in rectal HIV-1 acquisition, replication, and pathogenesis. Role: Co-Investigator

U01 AI103390 Adimora (PI) 01/01/19-12/31/25
UNC MACS/WIHS Combined Cohort Study Clinical Research Site: The Multicenter AIDS Cohort Study (MACS)/Women's Interagency HIV Study (WIHS) Combined Cohort Study (CCS) is a longitudinal, observational cohort study of persons with HIV and a demographically matched cohort of men and women at risk for HIV infection. The CCS supports basic, clinical, and contextual research on HIV disease across the lifespan, including HIV-related chronic comorbidities and health disparities. Role: Co-Investigator

H76HA08949-12 Farel (PI) 4/01/20-3/31/21
DHHS/HRSA
Ryan White Part C Outpatient EIS Program: This project provides financial support for indigent HIV medical care at UNC, Moses Cone and Randolph County Hospitals. Role: Co-Investigator

R01 AI152703 Ke (PI) 7/01/2020-6/30/2025
NIH/NIAID
Modeling the HIV latent reservoir, latency reversal and immunotherapeutics for HIV cure: The goal of this project is to provide a theoretical framework to understand HIV control and rebound, estimate the impact of therapeutic interventions and predict effective approaches for a functional cure. Role: Co-Investigator

U54 CA260543 Baric, Walett (co-PIs) 10/01/20 -9/30/25
NIH/NIAID
North Carolina Seronet Center for Excellence:The Center uses basic and applied research strategies to improve our understanding of the molecular and cellular mechanisms driving immune responses after SARS-CoV2 infection. Role: Co-Investigator

Pending
UM1 (NIAID) Margolis (PI) 07/01/21-06/30/26
Collaboratory of AIDS Researchers for Eradication (CARE): Extending and redirecting the work initiated in 2011, the reorganized Collaboratory of AIDS Researchers for Eradication (CARE) brings together scientists from UNC, Duke, Emory, Scripps FL, The Gladstone Institute/UCSF, Fred Hutch/UWa and from Merck Research Laboratories, Qura Therapeutics, ViiV Healthcare and Macrogenics, to seek therapies to eradicate HIV infection. Role: PI