BIOGRAPHICAL SKETCH

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NAME: **Monica J. Roth**

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

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
Barnard College, Columbia University	A.B. cum laud	05/1978	Chemistry
Albert Einstein College of Medicine	M.S.	05/1982	Biochemistry
Albert Einstein College of Medicine	Ph.D.	01/1984	Devel. Biology & Cancer
Columbia College of Physicians and Surgeons	Postdoc	06/1988	Biochemistry

A. Personal Statement

Although the COVID pause had changed our ability to perform wet bench experiments at 2019 levels, it provided a unique opportunity to examine alternative approaches to our research program. This application is the outgrowth of this re-evaluation examining new approaches/techniques that are now available to address previously difficult or unsolvable questions. We initiated studies to perform gene set enrichment analysis (GSEA) using ClusterPRofiler and Enrichr programs to apply a systems pathway analysis of the L1 receptor targets. Similarly, with NMR facilities closed and the AlphaFold2 program released, we were able to develop a putative model of the SLC35F2 protein, along with the use of Phyre2 and Evolutionary Co-variance. A third project involving the ET binding pocket developed with Drs. Gaetano Montelione (RPI) and Alberto Perez (U. Florida, Gainesville), providing a blind test of MELD to validate the two NMR solution structures of Brd3 ET bound to both the MLV IN tail peptide and the host NSD3 binding peptide. From this, we are now able to predict novel putative binding partners into this binding cleft. Based on this binding cleft, we initiated in silico drug screening with Dr. Willilam Welsh and Vlad Kholodovych at Rutgers and have three lead compounds as a new class of BET protein inhibitors. From the barriers presented by COVID arise new and exciting pathways forward.

My research has focused on the three main areas relating to retroviruses- entry, tethering, and integration. This research studies critical areas of murine leukemia virus (MLV) research defining biochemically as well as structurally how the viral p12 and IN proteins interact with host proteins and addresses the long-sought mechanism for the requirements for mitosis and subsequent target-site selection of gammaretroviruses. Our studies span both the biochemical analysis of viral proteins in vitro as well as the virology of the virus in tissue culture. Through studies of the pre-integration complex, we have expanded our research into the role in p12 in the entry process. Our collaborative studies have identified the host BET proteins as critical for the biased integration of MLV vectors at promoters. Our structural studies of the MLV IN and p12 both use solution NMR. A natural outcome of this research is the developing of viruses as nanoparticles for cargo delivery, which incorporates our long-term interest in viral entry. The convergence of these fields with our broad expertise and reagents, including RT, IN, p12, and Env proteins.

The lifespan of my research program has provided solid training to Postdoctoral fellows, PhD candidates, MD/PhD candidates, Master students and Undergraduates. My participation in service to the NIH has been throughout my career, serving as a full-member on three study sections (Virology, GDD, and AMCB) plus numerous ad hoc committees. I have also served as the Chair of the First-year Graduate Student Advisory Committee and of the Faculty Council, with a strong history of mentorship of students and faculty. I also serve on the MD/PhD admissions committee. I have always maintained an open access for students discuss questions they have. My goal is to train, mentor, and support the students in a rigorous, safe and equitable environment.

Productivity in the past 2 years has been affected by two health-related factors beyond the effect of the extended COVID pause instituted by Rutgers University and the State of NJ on bench research. The first is that I was diagnosed with cancer requiring surgery, chemotherapy and radiation therapy during this time as well as having contracted COVID. These two factors are no longer an issue going forward for this application.

Four publications that highlight my experience and qualifications for this project:

K. Bupp and M. J. Roth (2004) Targeting a retroviral vector in the absence of a known cell-targeting ligand. Human Gene Therapy 14: 1557-1564. PMID:145779717.

A. Sarangi, K. Bupp, and M.J. Roth (2007) Identification of a retroviral receptor used by an Envelope protein derived by peptide library screening. Proc. Natl. Acad. Sci. USA 104: 11032-11037. PMID: 17581869.

L. Loyola, V. Achuthan, K. Gilroy, G. Borland, A. Kilbey,.N. Mackay, M. Bell, J. Hay, S. Aiyer, D. Fingerman, R. A. Villanueva, E. Cameron, C.A. Kozak, A.N. Engelman, J. Neil and M. J. Roth. (2019) Disrupting MLV integrase:BET protein interaction biases integration into quiescent chromatin and delays but does not eliminate tumor activation in a *MYC/Runx2* mouse model. PLoS Pathogens 15(12):e1008154. PMID: 31815961; PMCID: PMC8349776.

S. Aiyer, G.V.T. Swapna, L.-C. Ma, G. Liu, J. Hao, G. Chalmers, B. C. Jacobs, G. T. Montelione, M. J. Roth. (2020) A common binding motif in the ET domain of BRD3 forms polymorphic structural interfaces with host and viral proteins. Structure, Feb 13:S0969-2126(21)00010-1. PMID: 33592170; PMC8349776

B. Positions and Honors

1978-1979	Graduate Trainee of Dr. Cheng-Wen Wu, Dept. of Biochemistry, Albert Einstein College of Medicine, N.Y.
1979-1984	Graduate Trainee of Dr. Jerard Hurwitz, Professor and Chairman, Department of Developmental Biology and Cancer, Albert Einstein College of Medicine, N.Y.
1984-1988	Postdoctoral Fellow with Dr. Stephen Goff, Department of Biochemistry, Columbia University, College of Physicians and Surgeons, New York.
July 1988	Assistant Professor, Dept. Biochemistry, UMDNJ-RWJ Medical School, Piscataway, N.J.
July 1994	Associate Professor, Dept. Biochemistry, UMDNJ-RWJ Medical School, Piscataway, N.J.
July 2000-2012	Professor, Dept. of Biochemistry, UMDNJ-RWJ Medical School, Piscataway, N.J.
July 2012	Professor, Dept. of Pharmacology, UMDNJ-RWJ Medical School, Piscataway, N.J.
April 2013	Professor, Dept. of Biochemistry & Molecular Biology, UMDNJ-RWJMS, Piscataway, N.J.
July 2013-present	Professor, Dept. of Pharmacology, Rutgers-RWJ Medical School, Piscataway, N.J.
April 2015-present	Merck Research Laboratory Professorship in Clinical Pharmacology; Endowed via Rutgers Foundation
July 2015	HERS Bryn Mawr 2015 Leadership Institute
Feb 2017	AAAS Fellow 2016
1988-present	Member: Graduate Program in Biochemistry and Molecular Biology, Rutgers School of Graduate Studies
07/1995-present	Member: Rutgers Cancer Institute of New Jersey
03/2015	Member: Rutgers BioMaPS Program

06/94, 95 3/00, 6/02 Ad hoc member Virology Study Section (NIH); **07/95-07/99 Member: Virology Study Section (NIH)**; 09/94, 06/99, 11/99Member: NCI Program Project Grants: Site visits, Subcommittee C (ad hoc); 6/00, 6/01Ad hoc member: Exp'tl Virology and Medical Biochem.Study Sections; 5/03 Program Site Visits: FDA and NCI/DRG Ad hoc Member-SSS-H(90)S-Biophysical and Chemical Sciences 6/12/03 Member: Special Study Section ZRG1 SSS-2:Gene Delivery 7/7-8/03. Member: Molecular Carcinogenesis Program Project Cluster Review NCI-C RPRB (Q2) 9/27-29/05 Chairperson: AZI1 AC-M (J2) SARS Program Project Grant Review-NIAID 9/30/04 Grant Reviewer: Fondecyt (Chile), Israel Science Foundation 2004, 2005. **Member-Genes and Drug Delivery NIH Study Section 3/2004-06/2008**. 12/2008 Ad Hoc Member GDD NIH Study Section (SBIR/STTR), 11/2009 Ad hoc Reviewer ARRA NIH Study Section.10/2010 Member PAR10-142 Study section. 2011: College of CSR Reviewers, NIH; Eureka Grant Reviews 04/2011; **Member AMCB NIH study section 07-2011-6/30/17**; Member of the Provocative Questions NIH study section 3/2012. Ad hoc Reviewer NIH ZCA1 SRLB-1 J1 R, Cancer Biology-11/2012, 4/2013 Reviewer for Israeli Science Foundation. 11/5-6/15, NICHD, NIH Intramural Site Visit; 12/2015 NIH Provocative Questions: Cancer with an Underlying HIV Infection Study Section; 4/2016, NIH NIDDK BSC Intramural Review; NIDA Avant Garde Award Program for HIV/AIDS and Drug Use Research, ZDA1 HXO-H Phase II 10/06/2017 - 12/01/2017; NIGMS ZGM1 ESI MIRA application 03/15-16/2018; CSR Anonymization Study (AARR IRG) 10/11/18; ZCA1 RPRB-L (M1) NCI Program Project II (PO1) Feb. 6-7, 2019. OSU Fall 2019/Spring 2020 Clinical/Translational, Population Science and Basic Science

Review; Dec 2019 NICHD NIH Intramural Site Visit; NIDA Avant Garde Award Program for HIV/AIDS and Drug Use Research, ZDA1 HXO-H Phase II 10/01/2019 - 12/19/2019. NIH ZRG1 AARR-B Study Section April 7, 2020. NIH/NCI Program Project IV (POI) October 21,22, 2020 (WebEX), OSU Fall 2020 Comprehensive Cancer Center IRP Basic Science Review, 10/22/2020 (Zoom). OSU OSU Spring 2021 Comprehensive Cancer Center IRP Basic Science Review 03/19/2021, NIH 2021/05 ZMH1 ERB-M Role of Myeloid Cells in Brain HIV-1 Reservoirs 03/23/2021

Honors and Awards

American Chemical Society Certified Degree in Chemistry (1978); NIH Graduate Trainee 1978-1984; NIH Postdoctoral Trainee, 1984-1985; Fellow of Leukemia Society of America, 1985-1987; Special Fellow of Leukemia Society of America, 1987-1990; Alexander & Alexandrine Sinsheimer Award, 1990; Scholar of the Leukemia Society of America, 1990-1994; UMDNJ Teaching and Service Award-1992; Stohlmann Scholar Award, Leukemia Society of America, 1994; 2001 Organizer of Retroviral Meeting, Cold Spring Harbor, NY. Editorial Board, Virology 2005-08/2013, Journal of Virology: 1/2008-12/31/2022. Foundation of UMDNJ Excellence in Research Award 2010, R. Walter Schlesinger Basic Science Mentoring Award 2010 (awarded 05/2011), 2016 Excellence in Research Award from New Jersey Health Foundation. AAAS Fellow, 2016. 2017 4th Annual Interdisciplinary Quantitation Biology Boot Camp in Single Particle Cryo-EM. July 2019 Board of Editors, mBio. 2020-Certificate in COVID Contact Tracing

Patent #4,943,531: S.P. Goff, N. Tanese and M.J. Roth "Expression of enzymatically active reverse transcriptase" (U.S.; issued 7/24/90).
Patent #6762031 (US, 07/13/04): Keith Bupp & Monica Roth “Targeting viral vectors to specific cells”.
Patent #8,450,085 B2: (US, issued 05/28/2013) Montelione; G. T., Inouye, M., Tang, Yu., Roth, M., Schneider; W. “Labeled biomolecular compositions and methods for the production and uses thereof.”
Patent # US 9,228,217 “Labeled biomolecular compositions and methods for the production and uses thereof” Issued 01/05/2016
Patent # 9,328,368 (US, 05/03/16) (application US 14/486,225) Montelione; G. T., Inouye, M., Tang, Yu., Roth, M., Schneider; W. “Labeled biomolecular compositions and methods for the production and uses thereof.”
Patent # 10,131,915 (US, 11/20/18): (US Serial No. 15/198648) Roth; Monica, Schneider; William, Montelione; Gaetano T., Inouye; Masayori, Tang; Yuefeng, “Independently Inducible System of Gene Expression for Single Protein Production (SPP)”.

PDB Structure Submissions: 2L15, 2M9U, 2FVS, 2FVR, 2FVQ, 2FVP, 7JYN, 7JYZ, 7JQ8, 7JMY, 4NZG

C. Contributions to Science

1. Viral Entry

A main area of interest of our research has been gammaretroviral entry. Early research focused on the ecotropic and amphotropic MuLV Env proteins, defining their domain structures including receptor-binding domain, the role of N-linked glycosylations, cysteines, the cytoplasmic tail and R-peptide. This research evolved into developing a system to randomize the receptor-binding domain to select for functional Env isolates that target alternative host-cell receptors. This system proved effective in retargeting viral entry to novel receptors. One modified FeLV Env utilized the SCL35F2 protein, to date, a transmembrane protein of unknown, which is the focus of this application. This application also aims to define the receptor for the L1 Env isolate. A third FeLV Env utilized the GPR172A protein as receptor, previously identified as a pig endogenous virus PERV-A receptor.

A. Sarangi, K. Bupp, and M.J. Roth (2007) Identification of a retroviral receptor used by an Envelope protein derived by peptide library screening. Proc. Natl. Acad. Sci. USA 104: 11032-11037. PMID: 17581869

P. Mazari, D. Linder-Basso, A. Sarangi, Y. Chang, and M. J. Roth (2009) Single-round selection yields a new retroviral Env utilizing GPR172A as a host receptor. Proc. Natl. Acad. Sci. USA, 106:5848-5853. PMID 19307586; PMCID: PMC2667028

P. M. Mazari, T. Argaw, L. Valdivieso, X. Zhang, K. T. Marcucci, D. R. Salomon, C. Wilson, and M. J. Roth (2012) Comparison of the convergent receptor utilization of a retargeted feline leukemia virus envelope with a naturally-occurring porcine endogenous retrovirus A., Virology 427(2):118-26. PMID: 22405627; PMCID: PMC3564632

L. T. Valdivieso, A. Sarangi, J. Whidby, J. Marcotrigiano and M. J. Roth (2015) The role of cysteines in stabilizing the randomized receptor binding domains within feline leukemia virus Envelope proteins. J. Virol., 90(6):2971-80. PMID: 26719270; PMCID: PMC4810629

2. Integration and tethering

MuLV integration requires the cells to undergo mitosis. My research focuses on the role of the MuLV IN and p12 proteins in the tethering and integration process. The Gag encoded p12 protein is required for the tethering of the pre-integrative complex (PIC) to the mitotic chromosomes, allowing for association of the PIC within the nucleus for integration to proceed. This tethering, though, has no effect on viral integration target-site selection. My initial study of viral integration identified the IN as the nuclease cleaving the terminal nucleotides from the linear viral DNA, with continued study of MLV IN both *in vivo* and *in vitro*. Our interest in defining the NMR solution structure of the MuLV IN has led to a method to label proteins using *E. coli* condensed single protein production system (cSPP), for which four patents has been issued and the structures of MuLV IN domains (NTD (PDB ID 4NZG) and CTD (PDB ID 2M9U) have been deposited in the PDB.

W. M. Schneider, J.D. Brzezinski, S. Aiyer, N. Malani, M. Gyuricza, F. D. Bushman, M.J. Roth (2013) Viral DNA tethering domains complement replication defective mutations in the p12 protein of MuLV Gag. Proc.Natl Acad Sci USA, 110 (23):9487-9492. PMID: 23661057; PMCID: PMC3677494.

J.D. Brzezinski, A. Modi, M. Liu, M. and M.J. Roth, (2016) Repression of the chromatin tethering domain of murine leukemia virus p12. J. Virol: 90 (24), 11197-11207. PMID: 27707926; PMCID: PMC5126376.

J.D. Brzezinski, R. Felkner, A. Modi, M. Liu, M., and M.J. Roth, (2016) Phosphorylation requirement of murine leukemia virus p12. J. Virol: 90 (24), 11208-11219. PMID: 27707931; PMCID: PMC5126377.

R. Guan, S. Aiyer, M. Cote, R. Xiao, M. Jiang, T. Acton, M.J. Roth, and G.T. Montelione (2016) X-ray crystal structure of the N-terminal region of Moloney murine leukemia virus Integrase and its implications for viral DNA recognition, Proteins: Structure, Function, and Bioinformatics, 85(4):647-656. PMID: 28066922; PMCID: PMC5357174.

3. Viral/Host Interaction

It was known for a long time that MuLV preferentially integrates at transcriptional start sites and CpG islands, however the molecular mechanism for this bias was not known. Through our collaborative studies, the MuLV IN protein interaction with BET proteins was validated and inhibitors of BET proteins were shown to influence MuLV integration. Based on our biochemical and structural studies of the Moloney Murine Leukemia Virus IN protein, we were able to identify the C-terminal tail of the MuLV IN as the critical domain for interaction with the BET protein ET domains. Our recent study examined the effects of the loss of the BET interaction in the MYC/Runx2 mouse model. In this system, disrupting MLV integrase:BET protein interaction biases integration into quiescent chromatin and delays but does not eliminate tumor activation. This has direct implication for the use of MLV based vectors for gene delivery. We have completed NMR based structural studies of three different structures of the Brd3 ET domain in complex with both the MLV IN domains and the host NSD3 cognate substrate. These structure identified common, yet distinct structural features utilized by both viral and host ET binding motifs.

S. Aiyer, G. V. T. Swapna, N. Malani, J. M. Aramini, W. M., Schneider, M. R. Plumb, M. Ghanem, R. C. Larue, A. Sharma, B. Studamire, M. Kvaratskhelia, F. D. Bushman, G. T. Montelione, and M. J. Roth, (2014) Altering murine leukemia virus integration through disruption of the integrase and BET protein family interaction. Nucleic Acids Research, 42(9):5917-28. PMID: 24623816; PMCID: PMC4027182

S. Aiyer, P. Rossi, N. Malani, W. M. Schneider, A. Chandar, F. Bushman, G. T. Montelione, and M. J. Roth (2015) Structural and sequencing analysis of local target DNA recognition by MLV Integrase.NAR, 43(11):5647-63. PMID: 25969444; PMCID: PMC4477651.

L. Loyola, Achuthan, V., Gilroy,K., Borland, G., Kilbey, A., Mackay, N., Bell, M., Hay, J., Aiyer, S., Fingerman, D., Villanueva, R A. Cameron, E., Kozak, C.A., Engelman, A.N., Neil, J., and Roth. M. J. (2019) Disrupting MLV integrase:BET protein interaction biases integration into quiescent chromatin and delays but does not eliminate tumor activation in a *MYC/Runx2* mouse model. PLoS Pathogens 15(12):e1008154. PMID: 31815961; PMCID: PMC8349776.

S. Aiyer, G.V.T. Swapna, L.-C. Ma, G. Liu, Ji. Hao, G. Chalmers, B. C. Jacobs, G. T. Montelione, and M. J. Roth. (2020) A common binding motif in the ET domain of BRD3 forms polymorphic structural interfaces with host and viral proteins. Structure, Feb 13:S0969-2126(21)00010-1. PMID: 33592170; PMCID: PMC8349776

4. Gene and Protein Delivery

Our research has always applied our results towards developing viral particles and viral vectors with improved, specific applications. On the basic side, we developed an ELISA assay for MuLV particles. Our interest in targeted viral entry applied the use of modified Sindbis Envelope:Antibody conjugates for gene delivery to both

early immature hematopoietic progenitor cells as well as a means of identifying iPS and hES stem cells. Additional studies identified means of increasing gene expression from non-integrating MuLV vectors. Beyond gene delivery, we have recently developed MuLV particles as a means to deliver proteins to cells. The proof-of-concept experiments have validated delivery of toxic as well as nuclear transcription factors

X. Zhang and M. J. Roth (2010) Antibody-directed lentiviral gene transduction in early immature hematopoietic progenitor cells. J. Gene Medicine, 12(12):945-55. PMID: 2110497272. PMCID: PMC3057560.
D.-T. Wu, Yasunari Seita, Xia Zhang, Chi-Wei Lu and Monica J. Roth (2012) Antibody-directed lentiviral gene transduction for live-cell monitoring and selection of human iPS and hES cells. PLos One, 7(4): e34778. doi:10.1371/journal.pone.0034778. PMID: 22536330; PMCID: PMC3334894.
X. Zhang, A. Sarangi, D.-T. Wu, J. Kanduri and M. J. Roth. (2013) Gene delivery in a mouse xenograft of a retargeted retrovirus to a solid 143B osteosarcoma. Virology J, 10:194. PMID: 23767896; PMCID: PMC3689073.
D.-T. Wu and M. J. Roth (2014) Development of MLV based viral-like particles for protein delivery of toxic protein and nuclear transcription factors. Biomaterials, 35(29):8416-26. PMID: 24997480; PMCID: PMC4139071.

5. Reverse Transcription

The studies of the viral reverse transcriptase are a seminal area of my retroviral research. My post-doctoral research started with the initial expression of an active MuLV reverse transcriptase in bacteria and resulted in a patent for this construct (Patent #4,943,531). This had widespread effects on molecular biology, allowing for commercialization of the enzyme for a variety of cDNA synthesis applications and allowed for the characterization of the termini of the full-length linear and 3' processed termini of MLV. Once independent, my laboratory focused on characterizing the RNase H activity of the HIV-1 reverse transcriptase, applying PCR to define circle-junctions and developing reagents including a Mg2+-dependent HIV-1 RNase H construct to characterize the plus-strand synthesis and second-strand transfer events.

M.J. Roth, N. Tanese, and S.P. Goff (1985) Purification and Characterization of Murine Retroviral Reverse Transcriptase Expressed in Escherichia coli. J. Biol. Chem. 260: 9326-9335. PMID: 2410413.
M. J. Roth, P. Schwartzberg, and S.P. Goff (1989) Structure of the termini of DNA intermediates in the integration of retroviral DNA: Dependence on IN function and terminal DNA sequences. Cell 58, 47-54. PMID: 2546673.
J. Puglia, T. Wang, C. Smith-Snyder, M. Cote, M. Scher, J. Pelletier, S. John, C. B. Jonsson and M. J. Roth (2006) Revealing domain structure through linker-scanning analysis of the MuLV RNase H, MuLV and HIV-1 Integrase proteins. J. Virol. 80: 9497-9510. PMID: 16973554; PMCID: PMC1617218.
R. V. Farias, D. Vargas, A. Castillo, B. Valenzuela, M. Cote, M. J. Roth, O. Leon (2011) Expression of an Mg2+-dependent HIV-1 RNase H construct for drug screening. Antimicrobial Agents and Chemotherapy, 55(10): p. 4735-4741. PMID: 21768506; PMCID: PMC3186996.

Complete List of Published Work in MyBibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/monica.roth.1/bibliography/40750136/public/?sort=date&direction=ascending

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

Active:

NIH R35GM122518 (Roth (PI) 09/30/2017-12/31/2027
"Interactions of retroviral and host proteins guided by advanced modeling"

New Jersey Health Foundation/Merck Research Laboratories 04/14/2015-present
Professorship in Clinical Pharmacology endowed fund. Roth (PI)

Completed in last 3 years

Rutgers CCRP2 award FP00021146. Roth (PI) (NCE) 07/01/2020-12/31/2020
"SARS-CoV2 Spike Protein:ACE2 interactions"
CINJ Small Molecule Screening award. Roth (PI), "Screening for small molecule anticancer inhibitors targeting a newly-defined ET domain pocket within the BET family of proteins." 02/2020-02/2021
NIH 1 RO1GM110639, Roth (PI), 05/01/2013-04/30/2020. "Interactions of MuLV IN with host proteins and DNA"