## BIOGRAPHICAL SKETCH

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NAME: Eric Murnane Poeschla

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

POSITION TITLE: Professor of Medicine

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 |
|---|---|---|---|
| Franklin & Marshall College | B.S. | 05/1980 | Biology |
| Yale Medical School, New Haven, CT | M.D. | 06/1985 | Medicine |
| UCSF Internal Medicine Residency | | 07/1988 | Internal Medicine |
| Tropical I.D. Fellow, Staff Physician, Kundiawa General Hospital, Papua New Guinea | | 06/1999 | Infectious Diseases |
| UCSD I.D. & Molecular Virology Fellowship | | 06/1993 | Infectious Diseases, Molecular Virology |

### A. Personal Statement

I am a virologist, innate immunologist, and physician-scientist with three decades of experience in RNA viral replication and in intrinsic and innate host defenses. I have concentrated on host dependency and restriction factors, innate immunity, and the roles of nucleic acids in pathways that affect viral life cycle and autoimmune pathways. I did basic research in college and medical school, but my virology and innate immunity vocation began for me when I was a house officer at UCSF School of Medicine in the grim days (1985-1988) when we had no effective antiviral therapy and our HIV patients died week after week, often after much suffering. Those years convinced me that basic science was where the game would be won in solving the dire HIV-1 problem (which turned out to be the case, most notably in the triumph of small molecule antiviral therapy for HIV disease). It led me to choose a curiosity-driven, basic science career in virology and innate immune defense. My group's HIV research has concentrated on basic aspects of the viral life cycle. We contributed foundational work on the HIV provirus integration cofactor LEDGF/p75 and other host factors involved in the viral life cycle. We continue to be strongly interested in post-entry events and innate immune responses, e.g., viral PAMP sensing, restriction factors, and IFN-stimulated gene (ISG) function. We collaborated with the lab of Mamuka Kvaratskhelia to characterize small molecules – lenacapavir(GS-6207), ALLINIs – and proteins e.g., Sec24c, that affect proper assembly, bind the HIV-1 capsid core post-entry, or affect HIV-1 pre-integration complex integration.

My lab subsequently extended our work to the innate immune response to other positive-strand RNA viruses, which led to focus on the viral dsRNA sensing, MDA5-MAVS pathway, MDA5-MAVS downstream ISGs, and ADAR1. This also now has good relevance to HIV-1 given the MDA5 sensing of the unspliced genome that has been reported. We were drawn to this pursuit of new directions by our investigation of cell-intrinsic innate immune response to viral dsRNAs in a unique mouse model that transgenically expresses – outside the viral life cycle – the RdRp enzyme of a picornavirus. That drives dsRNA duplex synthesis that mimics viral replication intermediates, leading to very high, life-long elevations of many ISGs (mirroring picornavirus sensing itself, it is essentially a pure MDA5 constitutive activation state, no RIG-I involvement). It is strongly antivirally protective yet – strikingly and unexpectedly – tolerated by the mice with no evidence for autoimmune or autoinflammatory disease. We have published four papers from this project in high-quality journals.

I am committed to graduate education and training the next generation of scientists. Eleven Ph.D. degrees have been earned by graduate students in my laboratory. Six have gone on to careers in academic science and are currently publishing papers, two to industry, two to academic administrative roles, and one to a senior research assistant role. Numerous clinical fellows and post-baccalaureate students have worked in the lab and sixteen of the latter went on to graduate school and/or medical school.

**B. Positions, Scientific Appointments, and Honors**

| | |
|---|---|
| 2023-present | World Health Organization (WHO) Expert Committee on Retroviruses, Process for Prioritization of Pathogens of Epidemic and Pandemic Threat |
| 2016 | Elected to American Association of Physicians (AAP) |
| 2014-present | Tim Gill Professor of Medicine, Division of Infectious Diseases, University of Colorado School of Medicine |
| 2014-2024 | Chief, Division of Infectious Diseases, University of Colorado School of Medicine |
| 2011 | Organizer, 36th Annual Cold Spring Harbor Meeting on Retroviruses |
| 2013-present | Editorial Board, Journal of Virology |
| 2008-present | Editorial Board, Viruses |
| 2006-2021 | Editorial Board, Virology |
| 2006-2014 | Professor of Molecular Medicine, Mayo Clinic College of Medicine |
| 2002-2005 | Associate Professor of Molecular Medicine, Mayo Clinic College of Medicine |
| 2000-2002 | Assistant Professor of Molecular Medicine, Mayo Clinic College of Medicine |
| 1993-1999 | Assistant Professor of Medicine, University of California at San Diego |
| 1990-1993 | Infectious Diseases Fellow, University of California at San Diego |
| 1988-1989 | Staff Physician, Simbu Province Provincial Hospital, Kundiawa, Papua New Guinea |
| 1985-1988 | Resident, Internal Medicine, University of California San Francisco |
| 1985 | Yale Medical School Peter F. Curran Graduation Research Prize |

**C. Contributions to Science**

My interests are in the cell biology of viral replication, innate immunity with a special focus on dsRNA sensing and MDA5, and the determinants of viral tropism and viral emergence. Our research has primarily focused on viral interactions with host cell factors, including host dependency factors, e.g., the role of the pre-integration complex chromatin docking factor LEDGF/p75 in HIV integration (Section C.1), restriction factors (C.2) and more recently, non-HIV positive-strand RNA viruses and the innate immune system (C.3-C.4). We have collaborated with the adjacent Kvaratskhelia lab to characterize proteins such as Sec24c and small molecules (lenacapavir, ALLINIs) (C.5).

The animal-human interface and species barriers has been a theme since my career began. We study how positive-strand RNA viruses such as retroviruses, picornaviruses, and coronaviruses are sensed and interdicted by cell-intrinsic innate immunity mechanisms including interferon- stimulated genes (ISGs). We have established a good collaboration with M. Santiago on interferon responses related to SARS-CoV-2.

We have investigated how RNA species generated by viral RNA-dependent RNA polymerases (RdRps), as well as the products of retroviral reverse transcription, are sensed as pathogen- associated molecular patterns by nucleic acid sensors such as MDA5 and RIG-I and how viral DNAs are metabolized by TREX1. Four papers have provided a compellingly unique mouse model ($RdRp^{tg}$ mouse) that has raised new possibilities for focused, controlled study of MDA5-MAVS, and for augmenting innate immunity while also preventing autoimmunity/ interferonopathy. Thus, we have excellent experience with maintaining mouse colonies and in experimentation, including surgery, solid organ and hematopoietic lineage tissue analyses, breeding, genotyping, colony maintenance.

**C.1. HIV-1 replication (host dependency factors).** These papers concern dependency factors (co-factors, such as LEDGF/p75 and CPSF6) that HIV-1 depends on to complete its life cycle. We established the role of LEDGF as an integration co-factor in key papers below. This protein functions as the ‘tether’ that links the incoming pre-integration complex that contains the reverse-transcribed genome to the chromosomal target. We proved its function, mapped key domains, and showed that we could replace the chromatin binding domain with alternative proteins. Other proteins of interest to us have been nucleoporins and CPSF6.

a. Llano, M., D.T. Saenz, A. Meehan, P. Wongthida, M. Peretz, W.H. Walker, W. Teo, and **E.M. Poeschla**. An Essential Role for LEDGF/p75 in HIV Integration. Science, 2006, 314(5798): p. 461-4. PMID: 16959972
b. Ciuffi, A., M. Llano, **E. Poeschla*,** C. Hoffmann, J. Leipzig, P. Shinn, J.R. Ecker, and F. Bushman*. A role for LEDGF/p75 in targeting HIV DNA integration. Nature Medicine, 2005, 11: p. 1287-9. *Co-corresponding authors. PMID: 16311605
c. Meehan, A.M., D.T. Saenz, J.H. Morrison, J.A. Garcia-Rivera, M. Peretz, M. Llano, and **E.M. Poeschla**. LEDGF/p75 proteins with alternative chromatin tethers are functional HIV-1 cofactors. PLoS Pathogens, 2009, 5(7): p. e1000522. PMID: 19609362
d. Achuthan V, Perreira JM, Sowd GA, Puray-Chavez M, McDougall WM, Paulucci-Holthauzen A, Wu X, Fadel HJ, Poeschla EM, Multani AS, Hughes SH, Sarafianos SG, Brass AL, Engelman AN. Capsid-CPSF6 Interaction Licenses Nuclear HIV-1 Trafficking to Sites of Viral DNA Integration. Cell Host and Microbe. 2018 Sep 12;24(3):392-404. PMCID: PMC6368089

**C2. Lentiviral restriction mechanisms (host restriction factors).** Restriction factors mediate 'intrinsic immunity,' or immediately acting innate immunity by binding to viral components or otherwise impeding critical life cycle steps. They often display positive selection. These papers concern either natural or engineered mechanisms that constrain the lentiviral life cycle in a virus and species-specific manner.

a. Morrison J, **Poeschla EM**. The Feline Immunodeficiency Virus Envelope Signal Peptide is a Tetherin Antagonizing Protein. mBio, 2023 April vol. 14(20:e0016123. PMID: 36927083.
b. Morrison J, Miller C, Bankers L, Crameri G, Wang L-F, **Poeschla EM**. 2020. A Potent Post-Entry Restriction to Primate Lentiviruses in a Yinpterochiropteran Bat. mBio 11(5): e01854-20. doi: 10.1128/mBio.01854-20. PMID: 32934084
c. Meehan, A., D. Saenz, R. Guevara, J. Morrison, M. Peretz, H.J. Fadel, H. Mazuka, J.M. van Deursen, and **E.M. Poeschla**. A cyclophilin homology domain-independent role for Nup358 in HIV-1 infection. PLoS Pathogens, 2014 Feb 20;10(2):e1003969. PMID: 24586169
d. Meehan A, Saenz D, Morrison M, Hu C, Peretz M, **Poeschla EM**. LEDGF dominant interference proteins demonstrate pre-nuclear exposure of HIV-1 integrase and synergize with LEDGF depletion to destroy viral infectivity. Journal of Virology, 2011 Apr;85(7):3570-83. PMID: 21270171

**C.3. Innate immunity and other positive strand RNA viruses, MDA5, dsRNA.** Four papers on the picornaviral RdRp-transgenic mouse, which is (**i**) MDA5- and MAVS-dependent (and not RIG-I dependent), (**ii**) dsRNA-driven, and (iii) in contrast to GOF models, is wild-type for all host proteins (MDA5, etc.).

a. Painter M, Morrison JH, Zoecklein L, Rinkoski T, Watzlawik J, Papke L, Warrington A, Bieber A, Matchett W, Turkowski K, **Poeschla EM*,** Rodriguez M. Antiviral Protection via RdRP-Mediated Stable Activation of Innate Immunity. PLoS Pathogens, 2015 Dec 3;11(12):e1005311. *The corresponding author. PMID: 26633895
b. Miller C, Barrett B, Chen J, Morrison JH, Santiago M, **Poeschla EM.** Systemic expression of a viral RNA- dependent RNA polymerase protects against retrovirus infection and disease. Journal of Virology, 2020 Feb 12. pii: JVI.00071-20. doi: 10.1128/JVI.00071-20. PMID: 2051266
c. Bankers L, Miller C, Liu G, Thongkittidilok C, Morrison J, **Poeschla E**. Development of interferon-stimulated gene expression from embryogenesis through adulthood, with and without constitutive MDA5 pathway activation. Journal of Immunology, 2020 May 15;204:2791-2807. PMID 32277054
d. Miller C, Morrison J,H Bankers L, Dran R, Kendrick J, Briggs E, Ferguson V, **Poeschla EM**. ADAR1 haploinsufficiency and sustained viral RdRp dsRNA synthesis synergize to dysregulate RNA editing and cause multi-system interferonopathy. mBio 2025. PMID: 40693792

**C4. Collaborative work on HIV-1 host factors, ultra-potent capsid inhibitor (lenacapavir, aka GS-6207) & integrase inhibitors, SARS-CoV-2.**

a. Bester S, Wei G, Zhao H, Adu-Ampratwum D, Iqbal N, Courouble V, Francis A, Annamalai A, Singh PK, Shkriabai N, Van Blerkom P, Morrison J, **Poeschla EM**, Engelman A, Melikyan G, Griffin P, Fuchs JR Asturias F, Kvaratskhelia M. 2020. Structural and mechanistic bases for a potent HIV-1 capsid inhibitor. Science, vol. 370 (6514):360-364), 2020. PMID: 33060363

b. Rebensburg S, Wei G, Larue R, Lindenberger J, Francis A, Annamalai A, Morrison J, Shkriabai N, Huang S, KewalRamani V, **Poeschla EM**, Melikyan G, Kvaratskhelia M. 2020. Sec24C contains a capsid-binding FG-motif and is a critical cytoplasmic co-factor for HIV-1 infection. Nature Microbiology April, 2021 (vol. 6: 434-444). doi: 10.1038/s41564-021-00868-1. PMID: 33649557.
c. Sharma, A., A. Slaughter, N. Jena, L. Feng, J. J. Kessl, H. J. Fadel, N. Malani, F. Male, L. Wu, **E. Poeschla**, F. Bushman, J. R. Fuchs, and M. Kvaratskhelia. 2014. New Class of Multimerization Selective Inhibitors of HIV-1 Integrase. PLoS Pathogens, 2014 May 29;10(5):e1004171. PMID: 24874515
d. Guo K, Barrett S, Morrison JH, Mickens K, Vladar EK, Hasenkrug K, **Poeschla EM*,** Santiago ML*. Interferon resistance of emerging SARS-DoV-2 variants. Proceedings of the National Academy of Sciences USA, 2022 (August), 119(32):e2203760119. PMID: 35867811. *Co-corresponding authors.

**C5. Lentiviral and other gene expression vectors, FIV, feline transgenesis**

As a fellow I constructed the first non-primate lentiviral vector system, from feline immunodeficiency virus (FIV, first paper below) with it and the second paper below showing that when I stripped out the U3 element (which is the promoter in a retrovirus) and replaced it with the hCMV promoter, the entire FIV production cycle is exuberantly enabled in human cells (while the FIV U3 promoter is dead in human cells; we also showed FIV uses CXCR4 for entry). These FIV vectors are now used all by labs over the world for basic virology work, especially species-specific innate immunity mechanisms where HIV and other primate lentiviruses are compared to FIV and EIAV to map restriction differences that are informative. Neither FIV nor other non-primate lentivirus-based vectors (or simian lentivirus vectors) have become clinically applied human gene therapy vectors of much note simply because later generation HIV-1-based lentiviral vectors are excellent, are perfectly safe, and are not restricted post-entry in human cells (as noted above, one can now make FIV vectors to high titer in human cells, but FIV is in various complex ways post-entry restricted in human primary cells, which has been valuable in our and many other labs for deciphering human restriction factor mechanisms). Thus, the work has been valuable for mapping species-specific barriers to retroviruses in many studies worldwide now.

An offshoot of this, done when we were given special-interest donor funding at Mayo Clinic to do so, was to devise a method for effective feline transgenesis, which we published in Nature Methods (Wongsrikeao P et al.) in 2011. We have not pursued the latter further but could readily do so if it became scientifically informative.

a. **Poeschla, E**, Wong-Staal, F., & Looney, D. J. Efficient transduction of non-dividing human cells by feline immunodeficiency virus lentiviral vectors. Nature Medicine 4 (3):354-357, 1998.
b. **Poeschla, E**, Looney, D. J. CXCR4 is required by a nonprimate lentivirus: heterologous expression of FIV in human, rodent and feline cells. Journal of Virology 72:6858-6866, 1998.
c. Kemler, I., I. Azmi, and E. M. **Poeschla.** The critical role of proximal gag sequences in feline immunodeficiency virus genome encapsidation. Virology 327:111-20, 2004.
d. Morrison, J.H., R.B. Guevara, A. Marcano, D.T. Saenz, H.J. Fadel, D.K. Rogstad, and **E.M. Poeschla**. (2014) FIV Envelope Glycoproteins Antagonize Tetherin through a Distinctive Mechanism that Requires Virion Incorporation. Journal of Virology, 88(6):3255-72.