

BIOGRAPHICAL SKETCH

NAME Leonid B. Margolis		POSITION TITLE Section Chief, Senior Investigator	
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Moscow State University, Russia	M.S.	06/1970	Mathematics, Biology
Moscow State University, Russia	Ph.D.	05/1974	Oncology
Moscow State University, Russia	Dr. Sci (advanced degree)	08/1985	Biophysics, Cell Biology

A. Personal Statement

The general goal of my studies is to understand mechanisms of cell-cell interactions in the context of human tissues in health and disease. Towards this goal, my colleagues and I developed a system of human tissues ex vivo that support replication of HIV and of other viruses without artificial activation or stimulation. We are able to maintain ex vivo many human tissues, including cervico-vaginal, placental, gastro-intestinal, and lymphoid ones. These tissues preserve their cytoarchitecture and some functions. In such in vivo-like system that faithfully reproduces many of in vivo aspects of pathogenesis, we studied mechanisms of HIV-1 induced immunodeficiency and the role of host and viral factors in this process. We found, that among host factors, long-term tissue immune activation plays a critical role. Non-HIV viruses as well as vaginal microbiota are important host factors that trigger immune activation and affect HIV infection. We hypothesized that interactions of various pathogens in the context of human tissues determine the course of the disease. My objective is to decipher the mechanisms of these interactions and to develop ways to manipulate them in order to prevent disease progression. In the course of my studies, I became interested in virions' heterogeneity and we developed a flow technique for analysis of antigenic composition of individual viral particles. In applying this technique, we found that what we and other considered to be viral preparations are in fact mixtures of infectious viruses and various extra-cellular vesicles (EVs) that carry cellular and viral proteins. The difference between defective virions and such EVs is purely semantic. Extracellular vesicles turned out to be important factors in cell-cell communications in health and are altered in disease, and we now study the role of these vesicles in various pathologies. In particular, we found that cytokines, the classical soluble signal molecules, can be carried by EVs constituting a system of cell-cell communications. We focus on the role of EVs in various viaral pathologies, including ones triggered by vHIV, CMV, and SARS-CoV-2 in the context cardiovascular pathologies, and complicated pregnancies. Our current studies are designed according to the NICHD Strategic Goals on reproductive health, healthy pregnancies, life-long wellness, and sex-based health disparities

1. S. Glushakova, J.-C. Grivel, W. Fitzgerald, J. Zimmerberg, L. B. Margolis (1998). Evidence for the HIV-1 phenotype switch as a causal factor in acquired immunodeficiency. *Nature Med.* 4:346-349.
2. J.-C. Grivel, S. Santoro, G. Faga, M. Malnati, Y. Ito, W. Fitzgerald, P. Lusso, L. Margolis (2001) Suppression of CCR5- but not CXCR4-tropic HIV-1 replication in lymphoid tissue by human herpesvirus 6. *Nature Medicine* 7 :1223-1235.
3. L. Margolis (2003) Chemokines: strategic weapons in germ warfare: Microbes as antimicrobials (2003) *Nature Biotechnology* 21,1: 15-16.
4. L. Margolis, R. Shattock (2006) Selective transmission of CCR5-utilizing HIV-1: the "gatekeeper" problem resolved? *Nature Microbiology* 4: 312-317.
5. J.-C. Grivel, and L Margolis (2009) Culture of human tissue explants to study human infectious agents. *Nature Protocols* 4:256-69.
6. E. Nolte-t Hoen,, R. Gallo , L Margolis (2019) Extracellular vesicles and viruses: Are they close relatives? *PNAS* 113 (33) 9155-9161 |
7. R.Sadovsky, L.Margolis (2019) "The biology of extracellular vesicles: The known unknowns" *PLoS Biology* DOI: 10.1371/journal.pbio.3000363
8. R.Palomino,C Vanpouille, P.Costantini, L Margolis (2021) Microbiota–host communications: Bacterial extracellular vesicles as a common language. *PLOS Pathogens* doi.org/10.1371/journal.ppat.1009508

Multiple plenary presentations including keynote once at National and International Meetings, including Keystone symposia, International Microbicide Conferences, International AIDS Conferences, International Conference on Extracellular Vesicles, etc.

B. Positions and Honors

Institutes Positions

1970-1980 Junior Researcher, Senior Researcher, Lomonosov Moscow University, Russia
1980-1991 Leading Researcher, Lomonosov State University, Russia
1991-1995 Chief Scientist, Professor, Head of the Laboratory (1993), Lomonosov Moscow University, Russia.
1994-1995 Fogarty Scholar-in-Residence, National Institutes of Health,
1995-2001 Head of a Unit, Laboratory of Cellular and Molecular Biology, National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)
1995-2010 Deputy Director, NASA/NIH Center for Three-Dimensional Tissue Culture
2000-active Senior Investigator, NICHD, NIH
2001-active Head, Section of Intercellular Interactions, NICHD, NIH
2007-2008 International Professor to India, American Society for Microbiology
2009 International Professor, Erevan, Armenia,
2011-active Adjunct Professor, Department of Bioinformatics and Biotechnology, Lomonosov Moscow University
2011 Visiting Professor, Ilia University, Republic of Georgia
2015-active Adjunct Professor, Department of Medicine, University of Maryland, Baltimore
2018-active Honorary Visiting Professor Moscow University of Medicine (Russia)
2016-active Honorary Visiting Professor Charles University, Prague (Czech Republic)

Editorial Boards

1991-1993 Member of Editorial Board, "Membrane and Cell Biology" Biological Membranes
1993-1998 Deputy-Chief Editor of the Journal " Membrane and Cell Biology
1992 -2013 Member of the Editorial Board " Animal Biology"
1999-2013 Reviewing Editor "In Vitro Cellular & Developmental Biology.
2009-active Member, Advisory Board "The Journal of Laboratory Physicians"
2014-active Member of the Editorial Board "Creative Cardiology"
2015-active Member of the Editorial Board "Infectious Diseases: News and Opinions"
2015-active Member of the Editorial Board "Frontiers Microbiology"
2015-active, Editor "Pathogens and Immunity "
2015-active Academic Editor, "PLoS ONE"
2018-active Editor "Scientific Research"

Committees

1988-1994 Member, Scientific Council, Belozersky Institute of Lomonosov Moscow University
 1990-1993 Member, Promotion Committee of the Scientific Council of the Belozersky Institute of Lomonosov Moscow University
 1991-1996 Member, Scientific Council on Physics of Biological Membranes
 1991-1995 Member, Scientific Council on Structure and Function at the Russian Academy of Sciences
 1999-active Member of the NIH AIDS Interest Group Stirring Committee.
 2000, 2005 Panelist, Special Emphasis Panel for Grant Review.
 2000-2002 Member of the NICHD Contraceptive Microbicide Coordinating Subcommittee.
 2007-active Leader, NIH AIDS Interest Group.
 2009-active Member of the NIH Intramural Sub-Committee for the U.S.-India collaboration on prevention of sexually transmitted diseases and HIV/AIDS
 2016-2018 Member of the NICHD Committee for Hiring Strategy
 2009-2018 Co-Chairman of the Advisory Committee, Trans-NIH Center for Human Immunology

Awards

1991-1994 Biomedical Award of Russian Ministry of Higher Education
 1993 Outstanding Scientist Award, Ministry of Science, Russia
 1993 Fogarty International Research Collaboration Award, National Institutes of Health
 1992-1994 Welcome Trust Award (UK)
 1991-1992 Yamagava-Yoshida Memorial International Cancer Research Award, International Union Against Cancer (Switzerland)
 1999 National Institutes of Health Intramural AIDS Targeted Antiviral Program Awards.
 2001-05 National Institutes of Health Intramural AIDS Targeted Antiviral Program Awards
 2011 NIH Office of AIDS Research Award
 2010-2011 NIH- India Award
 2013-14 NIH-Russia Award
 1991-active Elected Member of Russian Academy of Natural Sciences
 2006, 2009 NIH Director Award
 2010 St. Petersburg University Biomedical Center Award
 2002, 2003, 2009, 2016, 2020, 2022 National Institute of Child Health and Human Development Director Awards
 2016-active Honorary Visiting Professor Charles University, Prague (Czech Republic)

Contributions to Science

At the **early stages** of my career I studied the problems of cell adhesion. These problems are directly linked to tissue morphogenesis and designing of non-adhesive materials that can be used in human bodies. Together with my colleagues we found that phospholipid liquid-crystalline surface is un-adhesive for various cells including platelets. In a surface formed by phospholipids but in a gel state becomes adhesive. contrast phase. By forming domains in different states cells my control it adhesiveness, in particular unadhesiveness of endothelial cells for platelets.

1. O.Ivanova, L.B.Margolis. (1973) Use of phospholipid film for shaping cell cultures. *Nature* 242:200-1.
2. L.B Margolis, Yu.Vasiliev, I.Gelfand. (1979) Upper surface of epithelial sheets and of fluid lipid films are unadhesive for platelets. *Proc. Natl. Acad. Sci. USA* 76:2303-05.
3. L.B Margolis, A.N Tikhonov, E.Vasilieva. (1980) Platelet adhesion to fluid and solid phospholipid membranes. *Cell* 19:1996-9.

II. In my **laboratory at the NIH** we developed a system of human lymphoid tissue in which HIV pathogenesis is now widely studied. This system preserves its cytoarchitecture and many of important aspects of tissues *in vivo*. Since the critical events of HIV infection *in vivo* occurs in tissues, this system allows one to address important problems of HIV transmission and pathogenesis in *in vivo*-like system under controlled laboratory conditions. Various antivirals can be tested in this pre-clinical system.

1. S. Glushakova, B. Baibakov, L.B. Margolis (corresp. author), and J. Zimmerberg. (1996). Infection of tonsil histocultures: a model for HIV pathogenesis. *Nature Med.* 1:1320-1322.
2. J-C. Grivel, and L Margolis. (2009) Culture of human tissue explants to study human infectious agents. *Nature Protocols* 4:256-69
3. E. Saba, Grivel JC, C. Vanpouille, B. Brichacek, W. Fitzgerald, L. Margolis (corresponding author), A. Lisco. (2010) HIV-1 sexual transmission: early events of HIV-1 infection of human cervico-vaginal tissue in an optimized ex vivo model. *Mucosal Immunol.* 3: 280-90.
4. A. Introini, C. Vanpouille, A. Lisco, J-C. Grivel, L. Margolis. (2013) Interleukin-7 facilitates HIV-1 transmission to cervico-vaginal tissue *ex vivo*. *PLoS Pathogen* 9(2): 1-10. e1003148. doi:10.1371.
5. A. Introini, W. Fitzgerald, C. Vanpouille, L. Margolis (2018) Histoculture and Infection with HIV of Functional Human Lymphoid Tissue. *Meth Mol. Biol* 1760:187-197

III. In the system of human tissues *ex vivo* we investigated the difference in pathogenesis between CCR5-tropic and CXCR4-tropic HIV-1 variants. It was thought that the former variant typical for the early stages of HIV infection is less pathogenic for cells than the latter which is often found at the late stages of the HIV disease. We found that both variants are equally pathogenic but the CCR-5 tropic variant has fewer cell targets in human lymphoid tissue.

1. J-C. Grivel, L.B. Margolis. (1999) CCR5-tropic HIV-1 isolates are highly cytopathic but only for CCR5+/CD4+ T cells in human lymphoid tissue *ex vivo*. *Nature Med.* 5:344-346. (See comment *Nature Med.* 5: 592-593)
2. S. Glushakova, Y. Yi, J-Ch Grivel, A. Singh, D. Schols, E. De Clercq, R.G. Collman, L. Margolis. (1999) Preferential usage of CCR5 or CXCR4 co-receptors by dual-tropic HIV-1 in human lymphoid tissue *ex vivo*: Consequences for cytopathicity. *J. Clin. Inv.* 104: R7-R11. (See comments *J. Clin. Inv.* 104: 531-532).
3. M. Penn, J-C. Grivel, B. Schramm, M. Goldsmith, L.B. Margolis. (1999). CXCR4 utilization is sufficient to trigger CD4+ T cell depletion in HIV-1 infected human lymphoid tissue. *Proc. Natl. Acad. Sci. USA* 96: 663-668.
4. N. Malkevich, N.C. Womack, A. Fauci, L. Margolis. (2001) Human Immunodeficiency Virus Type 1 (HIV-1) Non-B Subtypes Are Similar to HIV-1 Subtype B in that coreceptor specificity is a determinant of cytopathicity in human lymphoid tissue infected *ex vivo*. *J. Virol.* 75:10520-10522.
5. V. Mercurio, W. Fitzgerald, C. Vanpouille, L. Margolis (2021) Mechanisms of residual immune activation in HIV-1-infected human lymphoid tissue *ex vivo* *AIDS* 35(8): 1179-1190

IV. My laboratory was one of the first to focus on the mechanisms of interactions of HIV co-pathogens with HIV itself. In particular, we found that common HIV co-pathogens herpesviruses may significantly affect HIV infection. Molecular mechanisms of these interactions involve chemokines and other soluble factors as well as interactions between pathogens' cell targets. This effect first discovered in our *ex vivo* tissue system was confirmed in a clinical trial in the framework of the NIH Bench-to-Bed Program. Recently we found that Lactobacilli suppress HIV infection mediated by EVs

1. J-C. Grivel, S. Santoro, G. Faga, M. Malnati, Y. Ito, W. Fitzgerald, P. Lusso, L. Margolis. (2001) Suppression of CCR5- but not CXCR4-tropic HIV-1 replication in lymphoid tissue by human herpesvirus 6. *Nature Medicine* 7:1223-1235.
2. A. Lisco, C. Vanpouille, E.P. Tchesnokov, J-C. Grivel, A. Biancotto, B. Brichacek, J. Elliott, E. Fromentin, R. Shattock, P. Anton, R. Gorelick, J. Balzarini, C. McGuigan, M. Derudas, M. Gotte, R. F. Schinazi, L. Margolis. (2008) Acyclovir is activated into a HIV-1 reverse transcriptase inhibitor in herpesvirus-infected human tissues. *Cell Host & Microbe* 4:260-270.

3. G.Andrei, A.Lisco, C.Vanpouille, A.Introini, E.Balestra, J van den Oord, T.Cihlar, C.Perno, R.Snoeck, LB Margolis (corresponding author), J. Balzarini. (2011) Topical tenofovir as dual-targeted anti-humanimmunodeficiency virus and anti-herpesvirus microbicide. *Cell Host&Microbe* 10:1-11.
4. C. Vanpouille, A. Lisco, J-C. Grivel, L. Bassit, RC.Kauffman, J. Sanchez, M.Lederman, RF. Schinazi, B.Rodriguez, L.Margolis. (2015) Valacyclovir decreases plasma HIV-1 RNA in HSV-2 Seronegative Individuals: A randomized placebo-controlled crossover trial. *Clin Infect Dis.* 60, 11: 1708–1714, <https://doi.org/10.1093/cid/civ172>
5. C.Vanpouille, J.A.Bernatchez, A. Lisco, A. Arakelyan S. Saba, M. Götte, L. Margolis. (2017) A common anti-cytomegalovirus drug, ganciclovir, inhibits HIV-1 replication in human tissues ex vivo. *AIDS.* 17;31(11):1519-1528. doi: 10.1097/QAD.0000000000001532.
6. R.Ñahui Palomino, C.Vanpouille, L. Laghi, C. Parolin, K.Melikov, P. Backlund, B.Vitali , L Margolis (2019). Extracellular vesicles from symbiotic vaginal lactobacilli inhibit HIV-1 infection of human tissues. *Nature Commun* 10, 5656 <https://doi.org/10.1038/s41467-019-13468-9>

V. We developed a new a nano-technique, flow virometry that permits analysis of single virions stained with fluorescent antibodies. A similar technique we developed for analysis of antigenic composition of extra-cellular vesicles that seem to constitute a general system of cell-cell-communication in norm and pathology. Using magnetic nano-particles we can now characterize antigenic composition of individual virions and relate it to viral biological features. Also, analysis of EVs in different pathologies may reveal their role in pathogenesis and serve as a diagnostic tool.

1. A. Arakelyan, W. Fitzgerald, L. Margolis (corresponding author), J.-C. Grivel. (2013) Nanoparticle based flow virometry for the analysis of individual virions. *J Clin Invest* 123(9):3716-27. doi: 10.1172/JCI67042.
2. M.Vagida, A. Arakelyan, A. Lebedeva, JC.Grivel, A.Shpektor, E.Vasilieva, L.Margolis.(2017) Flow analysis of individual blood extracellular vesicles in acute coronary syndrome. *Platelets* 28,2165-173. doi:1080/ 09537104.
3. A.Arakelyan, W.Fitzgerald, D. King, P.Rogers, H. Cheeseman, J-Ch.Grivel, R Shattock, L. Margolis. (2017). Flow virometry analysis of envelope glycoprotein conformations on individual HIV virions. *Scientific Reports* 7;948: 1-14, doi:10.1038/s41598-017-00935-w.
4. W Fitzgerald, ML Freeman, MM Lederman, E.Vasilieva, R.Romero, L. Margolis. (2018). A system of cytokines encapsulated in extracellular vesicles. *Sci Rep*, 8(1):8973.doi: 10.1038/s41598-018-27190-x.
5. L.Margolis, Y.Sadovsky. The biology of extracellular vesicles: The known unknowns. (2019) *PLoS Biol* 7(7):e3000363. doi: 10.1371/journal.pbio.3000363
6. R.Ñahui Palomino, C.Vanpouille, L. Laghi, C. Parolin, K.Melikov, P. Backlund, B.Vitali , L Margolis. (2019). Extracellular vesicles from symbiotic vaginal lactobacilli inhibit HIV-1 infection of human tissues. *Nat Commun* 10, 5656 <https://doi.org/10.1038/s41467-019-13468-9>.
7. R.Romero ,W.Fitzgerald, Adi L. Tarca ,L. Margolis. (2020). Compartmentalized profiling of amniotic fluid cytokines in women with preterm labor *PLoS ONE* <https://doi.org/10.1371>.
8. C.Vanpouille, A.Wells, T. Wilkin T, S. Morris Margolis L*, S.Gianella. (2022) .Sex differences in cytokine profiles during suppressive antiretroviral therapy. *AIDS* 36(9):1215-1222. doi: 10.1097/QAD.0000000000003265.

1999-Active Intramural NICHD Program
2010-2011 NIH-India Office of AIDS Research Award
NIH Office of AIDS Research Awards
2011-2014 NICHD Bench-to-Bed Program Award
2008-2012 NIH Office of AIDS Research Awards
NICHD Scientific Director's Award; NIH
2015-2022 Office of AIDS Research Awards

Role: PI