BIOGRAPHICAL SKETCH

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NAME: David M. Markovitz

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

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
University of Minnesota, Minneapolis, MN	B.A.	08/1976	Middle Eastern Studies
University of Minnesota, Minneapolis, MN	M.D.	06/1981	Medicine
University of Rochester, Rochester, NY	Resident	06/1984	Internal Medicine
University of Rochester, Rochester, NY	Fellow	06/1986	Infectious Diseases
University of North Carolina, Chapel Hill, NC	Post-Doc	06/1988	Virology

A. Personal Statement

My research, training experience, and ability to put together and lead teams of scientists position me very well to advance new and innovative approaches to developing therapeutic agents for cancer. I head a laboratory group that includes other faculty members and uses diverse experimental modalities to investigate issues in basic molecular virology and cell biology, specifically the interaction between viruses and human cells, projects that have also evolved into a strong interest in the molecular biology of malignancy and cancer therapeutics. Recent projects in our research group have used such diverse modalities as NMR, crystallography, molecular dynamics modeling, glycoclusters, next-generation sequencing, bioinformatics, atomic force microscopy, glycobiology, and animal models to work out mechanisms of pathogenesis and to design new agents to attack cancer and viral diseases. Interdisciplinary work in my group has resulted in 114 publications, and I have supervised doctoral students (including six MSTP graduates), post-doctoral fellows, medical students, masters students, undergraduates, and high school students. I have a history of putting teams of investigators together to pursue projects in areas that have been previously unexplored. Our work on a molecularly modified banana lectin (H84T BanLec) led to the first demonstration that the functions of a lectin (in this case mitogenicity and antiviral activity) can be separated through targeted molecular engineering, and we went on to explain the atomic level basis for this divergence. This work, the result of the efforts of 26 authors from five different countries, was published in *Cell*. Subsequent studies showing the safety, specificity, mechanism of action, and anti-influenza and anti-coronavirus activity of H84T BanLec in vitro and in vivo were published in *PNAS* and *Cell Reports Medicine,* again with an international team of investigators. We have also worked with our collaborators at Baylor to show that H84T BanLec can be expressed in a CAR construct and that the resultant CAR T cell is well-tolerated and highly potent against pancreatic ductal adenocarcinoma (PDAC) in vitro and in vivo, attacking both the cancer cells and the stroma surrounding the tumor (*Journal for ImmunoTherapy of Cancer*). Combining my interests and strengths in cancer biology, immunology, and glycobiology with the ability to forge scientific teams from diverse disciplines will allow me to successfully lead the proposed project, which aims to target tumor-specific glycans in the therapy of hepatocellular carcinoma and ultimately other solid tumors.

Ongoing and recently completed projects that I would like to highlight include:

National Institutes of Health (NIAID/NIH)
R01
Markovitz (PI)
03/01/2023-02/28/2028
Molecularly Engineered Lectins for Intranasal Prophylaxis and Treatment of Coronaviruses

Frankel Innovation Initiative, University of Michigan
Markovitz (PI)
Dates: 10/01/22-09/30/23
Sweet CARs: Attacking Gylcans to Treat Pancreatic Cancer

Department of Defense
Wilcox (PI); Co-I: Markovitz
03/01/23 – 02/28/26
Targeting T-Cell Lymphomas with a Novel Lectin

Citations:

a. Swanson, M.D., Boudreaux, D.M., Salmon, S., Chugh, J., Winter, H.C., Meagher, J.L., Andre, S., Murphy, P.V., Oscarson, S., Roy, R., King, S., Kaplan, M.H., Goldstein, I.J., Tarbet, E.B., Hurst, B.L., Smee, D.F., de la Fuente, C., Hoffman, H-H., Xue, Y., Rice, C.M., Schols, D., Garcia, J.V., Stuckey, J.A., Gabius, H-J., Al-Hashimi, H.M., and Markovitz, D.M. Engineering a Therapeutic Lectin: Uncoupling Mitogenicity from Antiviral Activity. *Cell.* 2015; 163:746–758. PMID: 26496612.
b. Raglow, Z., McKenna, M.K., Bonifant, C.L., Wang, W., Pasca di Magliano, M., Stadlmann, J., Penninger, J.M., Cummings, R.D., Brenner, M.K., Markovitz, D.M. Targeting Glycans for CAR Therapy: the Advent of Sweet CARs. *Mol Ther*. 2022 Jul 11:S1525-0016(22)00427-0. 10.1016/j.ymthe.2022.07.006. Epub ahead of print. PMID: 35821636.
c. Chan, J., Oh, Y., Yuan, S., Chu, H., Yeung, M.L., Canena, D., Chan, C., Poon, V., Chan, C.Y., Zhang, A., Cai, J.P., Ye, Z.W., Wen, L., Yuen, T., Chik, K., Shuai, H., Wang, Y., Hou, Y., Luo, C., Chan, W.M., Sit, K.Y., Au, W.K., Legendre, M., Zhu, R., Hain, L., Seferovic, H., Tampé, R., To, K., Chan, K.H., Thomas, D.G., Klausberger, M., Xu, C., Moon, J.J., Stadlmann, J., Penninger, J.M., Oostenbrink, C., Hinterdorfer, P., Yuen, K.Y., Markovitz, D.M. A Molecularly Engineered, Broad-spectrum Anti-coronavirus Lectin Inhibits SARS-CoV-2 and MERS-CoV Infection In Vivo. *Cell Reports Medicine.* 2022; Oct 18;3(10):100774. doi: 10.1016/j.xcrm.2022.100774. Epub 2022 Sep 29. PMID: 36195094; PMCID: PMC9519379.
d. McKenna, M. K., Ozcan, A., Brenner, D., Watanabe, N., Legendre, M., Thomas, D., Ashwood, C., Cummings, R., Bonifant, C., Markovitz, D. M., Brenner, M. K. Novel Banana Lectin CAR-T cells to Target Pancreatic Tumors and Tumor-Associated Stroma. *J Immunother Cancer*. 2023 Jan;11(1):e005891. doi: 10.1136/jitc-2022-005891. PMID: 36653070; PMCID: PMC9853244.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2002-present Professor (with tenure), Division of Infectious Diseases, Department of Internal Medicine University of Michigan Medical Center, Ann Arbor, Michigan
1994-2002 Associate Professor (with tenure), Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan
1988-1994 Assistant Professor, Division of Infectious Diseases, Department of Internal Medicine University of Michigan Medical Center, Ann Arbor, Michigan

Other Experience and Professional Memberships

American Society for Clinical Investigation; Association of American Physicians; American Clinical and Climatological Association; Editorial Board – Journal of Virology, 2002-2007; FDA Vaccines and Related Biological Products Advisory Committee, 2002-2006; Research Committee, Infectious Diseases Society of America, 2009-2014 (Chair of the Committee 2011-2014); Board of Directors, American Physician Scientist Association, 2012-2024

Honors

University of Minnesota, B.A., Magna Cum Laude 1976; National Cancer Institute – Clinical Investigator Award, 1990; Life and Health Insurance Medical Research Fund Scholar, 1991; American Society for Clinical Investigation, 1997; Burroughs Wellcome Clinical Scientist Award in Translational Research, 2003; Association of American Physicians, 2004; Transformative R01, Office of the Director, NIH, 2009; American Clinical and Climatological Association, 2012; Fellow, American Association for the Advancement of Science, 2024

C. Contributions to Science

1. Throughout my career as a trainee and then as an independent investigator, much of my work has either directly focused on, or interconnected with, the pathogenic retroviruses that cause AIDS, HIV-1 and HIV-2. As I emerged as an independent investigator, I focused on the differences in the regulation of HIV-2 transcription as compared to HIV-1, as both viruses cause AIDS but HIV-2 much more slowly. These studies identified distinct differences in the enhancer elements of HIV-2 that mediate its response to T-cell activation, suggesting important ways that the two viruses could exhibit differential courses of disease causation. This work was also aimed at identifying the key cellular factors that mediate transcriptional activation following immune stimulation and therefore are likely to be involved in the immune response. Through these studies, we were able to clone an important, previously identified cellular factor, DEK, showing that it interacted with a key enhancer element that mediates HIV-2 transcriptional activation. It was through this line of investigation that our efforts to understand the biology of the DEK protein, detailed below, were launched.

    a. Gartner, S., Markovits, P., Markovitz, D.M., Kaplan, M.H., Gallo, R.C., Popovic, M. The Role of Mononuclear Phagocytes in HTLV-III/LAV Infection. *Science* 1986; 233:215-219.
    b. Markovitz, D.M., Hannibal, M., Perez, V.L., Gauntt, C., Folks, T.M., Nabel, G.J. Differential regulation of Human Immunodeficiency Viruses (HIVs): a Specific Regulatory Element in HIV 2 Responds to Stimulation of the T-cell Antigen Receptor. *Proc. Natl. Acad. Sci*. USA 1990; 87:9098-9102.
    c. Fu, G.K., Grosveld, G., Markovitz, D.M. DEK, an Autoantigen Involved in a Chromosomal Translocation in Acute Myelogenous Leukemia, Binds to the Human Immunodeficiency Virus Type 2 Enhancer. *Proc. Natl. Acad. Sci*., USA 1997; 94:1811-1815.
    d. Faulkner, N.E., Hilfinger, J.M., Markovitz, D.M. Protein Phosphatase 2A Activates the HIV-2 Promoter Through Enhancer Elements That Include the Pets Site. *J. Biol. Chem*. 2001; 276(28):25804-25812.

2. The DEK protein is a biochemically distinct factor that has been implicated in the pathogenesis of cancer and, in its pro-inflammatory role, in the pathogenesis of juvenile arthritis. We have detailed the complex life cycle of DEK, wherein it serves as a crucial chromatin factor, is secreted and acts as a chemotactic factor, and can then be taken back up by other cells in a bioactive manner wherein it corrects the chromatin and DNA repair defects seen in cells that do not contain DEK. We have proven at the genetic level that DEK is vital to inflammation and is key to neutrophil extracellular traps (NETs) and have developed an anti-DEK aptamer that has pronounced anti-inflammatory activity in a mouse model. Most recently, we have shown that DEK is a key factor in hematopoiesis.

    a. Kappes, F., Waldmann, T., Mathew, V., Yu, J., Zhang, L., Khodadoust, M.S., Chinnaiyan, A.M., Luger, K., Erhardt, S., Schneider, R., Markovitz, D.M. The DEK Oncoprotein is a Su(Var) That is Essential to Heterochromatin Integrity. *Genes Dev*. 2011; 25:673-678. PMCID: PMC3070930.
    b. Saha, A.K., Kappes, F., Mundade, A., Deutzmann, A., Rosmarin, D., Legendre, M., Chatain, N., Al-Obaidi, Z., Adams, B.S., Ploegh, H., Ferrando-May, E., Mor-Vaknin, N., Markovitz, D.M. Intercellular Trafficking of the Nuclear Oncoprotein DEK. *Proc. Natl. Acad. Sci*., USA. 2013; 110(17):6847-52. PMCID: PMC3637753.
    c. Mor-Vaknin, N., Saha, A., Legendre, M., Carmona-Rivera, C., Amin, M.A., Rabquer, B.J., Gonzales-Hernandez, M.J., Jorns, J., Mohan, S., Yalavarthi, S., Pai, D.A., Angevine, K., lmburg, S.J., Knight, J.S., Adams, B.S., Koch, A.E., Fox, D.A., Engelke, D.R., Kaplan, M.J., Markovitz, D.M. DEK-targeting DNA Aptamers as Therapeutics for Inflammatory Arthritis. *Nature Communications* 2017; Feb 6;8:14252. doi: 10.1038/ncomms14252. PMID: 28165452; PMCID: PMC5303823.
    d. Capitano, M., Mor-Vaknin, N., Saha, A., Cooper, S., Legendre, M., Guo, H., Contreras-Galindo, R., Kappes, F., Sartor, M., Lee, C., Huang, X., Markovitz, D.M., Broxmeyer, H. Secreted Nuclear Protein DEK Regulates Hematopoiesis Through CXCR2 Signaling. *J Clin Invest*. 2019[; May 20;130. pii: 127460. doi: 10.1172/JCI127460. eCollection 2019 May 20.

3. Vimentin is a very highly-expressed cellular protein that has been termed the “conundrum of the intermediate filament family” because of its great abundance but unknown function. Indeed, Vimentin knock-out mice were, very surprisingly, not found to have a phenotype at first. In the process of studying the secretion of DEK, we made the paradigm-shifting observation that the vimentin intermediate filament

protein is actually a secreted inflammatory factor. Using a mouse model, we went on to demonstrate that this protein plays a vital role in a key clinical setting involving unwanted inflammation: inflammatory bowel disease.

a. Mor-Vaknin, N., Punturieri, A., Sitwala, K., Markovitz, D.M. Vimentin is Secreted by Activated Macrophages. *Nat. Cell Biol*. 2003; 5:59-63. doi: 10.1038/ncb898. PMID: 12483219.
b. Mor-Vaknin, N., Legendre, M., Yue, Y., Serezani, C.H.C., Garg, S.K., Jatzek, A., Swanson, M.D., Gonzalez-Hernandez, M.J., Teitz-Tennenbaum, S., Punturieri, A., Engleberg, N.C., Banerjee, R., Peters-Golden, M., Kao, J.Y., Markovitz, D.M. Murine Colitis is Mediated by Vimentin. *Sci. Rep*. 2013; 3:1045. PMCID: PMC3540396.
c. Russo, B.C., Stamm, L.M., Raaben, M., Kim, C.M., Kahoud, E., Robinson, L.R., Bose, S., Queiroz, A.L., Herrera, B.B., Baxt, L.A., Mor-Vaknin, N., Fu, Y., Molina, G., Markovitz, D.M., Whelan, S.P., Goldberg, M.B. Intermediate Filaments Enable Pathogen Docking to Trigger Type 3 Effector Translocation. *Nat Microbiol*. 2016; Mar 7;1:16025. PMID: 27572444.

4. Eight percent of the human genome is, surprisingly, made up of ancient retroviruses that have insinuated themselves into our genetic inheritance. These retroviruses, termed human endogenous retroviruses (HERVs), have traditionally been thought to be genetic fossils that are incapable of replication. We have shown that they can package and transmit viral RNA from one cell to another. Further, we have found that, surprisingly, contrary to other known retroviruses, these viruses assume both an RNA and DNA form, and both are infectious. In studying the blood of patients with HIV, we uncovered two completely new members of the HERV-K family. These particular HERVs were found to be in centromeres and to have spread from one centromere to the next. These and subsequent findings have given us new "bar-codes" to study specific centromeres as well as allowing us to make the ground-breaking discovery that genetic exchange, probably due to homologous recombination, takes place between different centromeres. We recently showed that abnormal centromeres and nuclei are found in scleroderma, likely triggering the cGAS-STING inflammatory pathway.

   a. Contreras-Galindo, R., Kaplan, M.H., He, S., Contreras-Galindo, A.C., Gonzalez- Hernandez, M.J., Kappes, F., Dube, D., Chan, S.M., Robinson, D., Meng, F., Dai, M., Gitlin, S.D., Chinnaiyan, A.M., Omenn, G.S. and Markovitz, D.M. HIV Infection Reveals Wide-Spread Expansion of Novel Centromeric Human Endogenous Retroviruses. *Genome Res*., 2013; 23(9):1505-13. PMCID: PMC3759726.
   b. Contreras-Galindo, R., Fischer, S., Saha, A.K., Lundy, J.D., Cervantes, P.W., Mourad, M., Wang, C., Qian, B., Dai, M., Meng, F., Chinnaiyan, A., Omenn, G.S., Kaplan, M.H., and Markovitz. D.M. Rapid Molecular Assays to Study Human Centromere Genomics. *Genome Res*. 2017 Dec;27(12):2040-2049. doi: 10.1101/gr.219709.116. Epub 2017 Nov 15. PMID: 29141960.
   c. Saha, A.K., Contreras-Galindo, R., Niknafs, Y.S., Iyer, M., Qin, T., Padmanabhan, K., Siddiqui, J., Palande, M., Wang, C., Qian, B., Ward, E., Tang, T., Tomlins, S.A., Gitlin, S., Sartor, M.A., Omenn, G.S., Chinnaiyan, A.M., and Markovitz, D.M. The Role of the Histone H3 Variant CENPA in Prostate Cancer. *The Journal of Biological Chemistry*. 2020 Jun 19;295(25):8537-8549. doi: 10.1074/jbc.RA119.010080. Epub 2020 May 5. PMID: 32371391; PMCID: PMC7307189.
   d. Paul, S., Kaplan, M. H., Khanna, D., McCourt, P. M., Saha, A. K., Tsou, P. S., Anand, M., Radecki, A., Mourad, M., Sawalha, A. H., Markovitz, D. M., Contreras-Galindo, R. Centromere Defects, Chromosome Instability, and cGAS-STING Activation in Systemic Sclerosis. *Nat Commun*. 2022 Nov 18;13(1):7074. doi: 10.1038/s41467-022-34775-8. PMID: 36400785; PMCID: PMC9674829

5. Lectins have the potential to be used as antiviral agents due to their ability to bind sugars, especially high mannose, on the surface of multiple pathogenic viruses and thus block their ability to attach to cellular receptors. We demonstrated that a lectin from bananas, termed BanLec, is a potent inhibitor of HIV infection. However, BanLec as it is naturally derived from bananas is highly mitogenic, making it undesirable for use as either a systemic therapy or for blocking vaginal transmission of HIV. We overcame this problem by making a single amino acid mutation that totally disrupts mitogenicity while preserving broad-spectrum antiviral activity against HIV, hepatitis C virus, influenza, and all pathogenic coronaviruses, including SARS-CoV-2, SARS-CoV-1, and MERS-CoV. This compound, termed H84T BanLec because the histidine at position 84 has been changed to a threonine, has now been patented in the United States and China and in several countries in Europe. We have now applied this compound to the therapy of pancreatic ductal adenocarcinoma and more recently to hepatocellular carcinoma which, unlike healthy tissues, have high mannose on their surfaces and hence can be targeted by H84T BanLec.

a. Swanson, M.D., Boudreaux, D.M., Salmon, S., Chugh, J., Winter, H.C., Meagher, J.L., Andre, S., Murphy, P.V., Oscarson, S., Roy, R., King, S., Kaplan, M.H., Goldstein, I.J., Tarbet, E.B., Hurst, B.L., Smee, D.F., de la Fuente, C., Hoffman, H-H., Xue, Y., Rice, C.M., Schols, D., Garcia, J.V., Stuckey, J.A., Gabius, H-J., Al-Hashimi, H.M., Markovitz, D.M. Engineering a Therapeutic Lectin: Uncoupling Mitogenicity from Antiviral Activity. *Cell* 2015; 163:746–758. PMID: 26496612.
b. Covés-Datson, E.M., King, S.R., Legendre, M., Gupta, A., Chan, S., Gitlin, E., Kulkarni, V., Pantaleón García, J., Smee, D.F., Lipka, E., Evans, S.E., Tarbet, E.B., Ono, A., Markovitz, D.eM. A Molecularly Engineered Antiviral Banana Lectin Inhibits Fusion and is Efficacious Against Influenza Virus Infection In Vivo. *Proc. Natl. Acad. Sci*. *USA* January 2020; pii: 201915152. doi: 10.1073/PNAS.1915152117. PMID: 31932446.
c. Chan, J., Oh, Y, Yuan, S., Chu, H., Yeung, M.L., Canena, D., Chan, C., Poon, V., Chan, C.Y., Zhang, A., Cai, J.P., Ye, Z.W., Wen, L., Yuen, T., Chik, K., Shuai, H., Wang, Y., Hou, Y., Luo, C., Chan, W.M., Sit, K.Y., Au, W.K., Legendre, M., Zhu, R., Hain, L., Seferovic, H., Tampé, R., To, K., Chan, K.H., Thomas, D.G., Klausberger, M., Xu, C., Moon, J.J., Stadlmann, J., Penninger, J.M., Oostenbrink, C., Hinterdorfer, P., Yuen, K.Y., Markovitz, D.M. A Molecularly Engineered, Broad-spectrum Anti-coronavirus Lectin Inhibits SARS-CoV-2 and MERS-CoV Infection In Vivo. *Cell Reports Medicine* 2022; Oct 18;3(10):100774. doi: 10.1016/j.xcrm.2022.100774. Epub 2022 Sep 29. PMID: 36195094; PMCID: PMC9519379.
d. McKenna, M. K., Ozcan, A., Brenner, D., Watanabe, N., Legendre, M., Thomas, D., Ashwood, C., Cummings, R., Bonifant, C., Markovitz, D. M., Brenner, M. K. Novel Banana Lectin CAR-T cells to Target Pancreatic Tumors and Tumor-Associated Stroma. *J Immunother Cancer*. 2023 Jan;11(1):e005891. doi: 10.1136/jitc-2022-005891. PMID: 36653070; PMCID: PMC9853244.

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