

**CURRICULUM VITAE - Alan D. Levine, Ph.D.**

**Professional Preparation:**

- 1971 B.S., Summa cum Laude, Mathematics, Physics, French; Union College, Schenectady, New York.  
1973 Masters of Philosophy, Physics, Yale University, New Haven, Connecticut.  
1975 Masters of Philosophy, Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut.  
1978 Ph.D., Molecular Biophysics and Biochemistry, Thesis Advisor: Dr. W. Dean Rupp, Yale University, New Haven, Connecticut.  
1978 Postdoctoral Fellow, Department of Molecular Biophysics and Biochemistry, Mentor: Dr. W. Dean Rupp, Yale University, New Haven, Connecticut.  
1979 - 1982 Postdoctoral Fellow, Department of Cell Biology, Mentor: Dr. Roger D. Kornberg, Nobel Laureate, Stanford University School of Medicine, California.

**Appointments:**

**Present Position:** **Primary Appointment:** Professor of Molecular Biology & Microbiology

**Secondary Appointments:** Professor of Medicine - Division of Gastroenterology and Liver Disease, Pathology, Pharmacology, Pediatrics, and Hematology/Oncology (General Medical Sciences) at the Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, and Professor of Biological Sciences, Case Western Reserve University School of Dental Medicine

- 2016- present Director, Training Program in HIV Cure, NIH NIAID 1T32 AI 127201  
2016- present Graduate Program Director – Cell Biology, Molecular Virology, Molecular Biology and Microbiology  
2014- present Chief Operating Officer, Case Western Reserve University, Center for AIDS Research (CFAR)  
2011-present Professor of Biological Sciences, Case Western Reserve University School of Dental Medicine, Cleveland, Ohio.  
2011-present Professor of Pediatrics  
2011-present Professor of Molecular Biology and Microbiology  
2011-2012 Past-Chair, Faculty Senate, Case Western Reserve University, Cleveland, Ohio.  
2010-2011 Chair, Faculty Senate, Case Western Reserve University, Cleveland, Ohio.  
2009-2010 Chair-elect, Faculty Senate, Case Western Reserve University, Cleveland, Ohio.  
2004-2005 Sabbatical leave. Department of Biochemistry, University of Florence, Italy. Mentor: Professor Paola Chiarugi (Cancer biology).  
2002-present Professor of Medicine, Pathology, Pharmacology, and Oncology (General Medical Sciences) at the Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, Ohio.  
2002 Award of Tenure, Case Western Reserve University, School of Medicine, Cleveland, Ohio.  
1999-2002 Associate Professor of Pharmacology, Case Western Reserve University, School of Medicine, Cleveland Ohio  
1997-2002 Associate Professor in Division of General Medical Sciences – Oncology at the Case Comprehensive Cancer Center, School of Medicine, Cleveland, Ohio.  
1995-2002 Associate Professor of Medicine, Case Western Reserve University, School of Medicine, Cleveland, Ohio.  
1995-2002 Associate Professor of Pathology, Case Western Reserve University, School of Medicine, Cleveland, Ohio.  
1994-1995 Research Scientist II, Department of Immunology, Searle Research and Development, St. Louis, Missouri.  
1988-1994 Senior Research Specialist, Molecular Immunology, Monsanto Corporate Research, Department of Biological Sciences, Monsanto Company, St. Louis, Missouri.  
1985-1988 Research Specialist, Molecular Genetics and Mammalian Biology Section, Department of Biological Sciences, Monsanto Company, St. Louis, Missouri.  
1983-1985 Senior Research Biologist, Molecular Genetics Group, Monsanto Company, St. Louis, Missouri.

- 1974-1976 Instructor, Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut.
- 1973-1974 Instructor, Physics Department, Yale University, New Haven, Connecticut.
- 1971 Instructor, Physics Department, Union College, Schenectady, New York.

**Publications:**

1. Le, N., Mazahery, C., Nguyen, K., Levine, A.D. (2021). "Regulation of Intestinal Epithelial Barrier and Immune Function by activated T cells." *Cell Mol Gastroenterol Hepatol* (2021) **11**(1), 55-76. doi: <https://doi.org/10.1016/j.jcmgh.2020.07.004>. (PMID: 32659380; PMCID: [PMC7596298](https://pubmed.ncbi.nlm.nih.gov/PMC7596298/))
2. Mazahery, C., Valadkhan, S., and Levine, A.D. "Transcriptomic Analysis Reveals Receptor Subclass-Specific Immune Regulation of CD8+ T Cells by Opioids." *ImmunoHorizons* (2020) **4** (7) 420-429; doi: <https://doi.org/10.4049/immunohorizons.2000019> PMID: 32675085
3. Mazahery, C., Benson, B.K., Cruz-Lebrón, A., and Levine, A.D. "Chronic Methadone Use Alters the CD8+ T Cell Phenotype In Vivo and Modulates Its Responsiveness Ex Vivo to Opioid Receptor and TCR Stimuli." *J. Immunol.* (2020) **204** (5) 1188-1200. doi:10.4049/jimmunol.1900862. (PMID: 31969385; PMCID: [PMC7757720](https://pubmed.ncbi.nlm.nih.gov/PMC7757720/))
4. Cruz-Lebrón, A., D'argenio Garcia, L., Talla, A., Joussef-Piña, S., Quiñones-Mateu, M.E., Sekaly, R-P., Inacio Ladislau de Carvalho, K., and Levine, A.D. "Decreased enteric bacterial composition and diversity in South American Crohn's disease vary with the choice of treatment strategy and time since diagnosis." *J. of Crohn's and Colitis* (2020) **14**, (6), 791–800. <https://doi.org/10.1093/ecco-jcc/ijz189>. (PMID: 31758685; PMCID: [PMC7346893](https://pubmed.ncbi.nlm.nih.gov/PMC7346893/))
5. McCausland, M.R., Cruz-Lebron, A., Pilch-Cooper, H.A., Scott Howell, S., Albert, J.M., Park, Y.S. and Alan D. Levine, A.D. "Toll-like receptor distribution in colonic epithelium and lamina propria is disrupted in HIV viremic, immune success, and failure." *AIDS* (2020) **34** (6):815-826. DOI:10.1097/QAD.0000000000002499. (PMCID: [PCM8139559](https://pubmed.ncbi.nlm.nih.gov/PMC8139559/)).
6. Chung C.Y., Alden S.L., Fu P., Funderburg N.T., Levine A.D. "Progressive Proximal-to-Distal Reduction in Expression of the Tight Junction Complex in Colonic Epithelium of Virally-suppressed HIV+ Individuals." *PLoS Pathog* (2014) 10:e1004198; doi: 10.1371/journal.ppat.1004198. PMID: 24968145. PMCID: [PMC4072797](https://pubmed.ncbi.nlm.nih.gov/PMC4072797/)
7. Funderburg, N.T., Stubblefield Park, S.R., Sung, H.C., Hardy, G., Clagett, B., Ignatz-Hoover, J., Harding, C.V., Fu, P., Katz, J.A., Lederman, M.M., Levine, A.D. "Circulating CD4+ and CD8+ T cells are activated in IBD and are associated with plasma markers of inflammation." *Immunology* (2013) 140, 87–97; doi: 10.1111/imm.12114. Published online 22 April 2013. PMID: 23600521. PMCID: [PMC3809709](https://pubmed.ncbi.nlm.nih.gov/PMC3809709/).
8. Meisch, J.P., Vogel, R.M., Schlatzer, D.M., Li, X., Chance, M.R., Levine, A.D. "Human  $\beta$ -defensin 3 induces STAT1 phosphorylation, tyrosine phosphatase activity, and cytokine synthesis in T cells." *J Leukoc Biol* (2013) 94, 459-471; doi:10.1189/jlb.0612300. Published online June 26, 2013. PMID: 23804808. PMCID: [PMC3747125](https://pubmed.ncbi.nlm.nih.gov/PMC3747125/).
9. Gill, T., Levine, A.D. "Mitochondrial derived hydrogen peroxide selectively enhances T cell receptor-initiated signal transduction." *J. Biol Chem* (2013) 288, 26246-26255; doi: 10.1074/jbc.M113.476895. Published online July 23, 2013. PMID: 23880762. PMCID: [PMC3764828](https://pubmed.ncbi.nlm.nih.gov/PMC3764828/).
10. Das, L.M., Torres-Castillo, M.D.L.A., Gill, T., Levine A.D. "TGF- $\beta$  conditions activated CD4 T cells to express increased levels of endogenous miR-155, destabilizing IL-2 and itk mRNA." *Mucosal Immunology*. (2013) 6, 167–176. doi: 10.1038/mi.2012.60. Epub July 11, 2012; PMCID: [PMC3504619](https://pubmed.ncbi.nlm.nih.gov/PMC3504619/)

**Research Leadership:**

P30 AI 03219 (PI- Karn)	07/01/1994 – 06/30/2021	1.8 calendar
NIH / NIAID	\$1,106,494	
Case Western Reserve University / University Hospitals Center for AIDS Research (CWRU/UH CFAR)		
Role: Chief Operating Officer		
DP1 DA 037997 – Avant Garde Award (PI - Levine)	02/01/2015 – 01/31/2022	4.2 calendar
NIH / NIDA	\$500,000	
Repairing the intestinal epithelium from the dual action of HIV and drug use		
DP1 DA 037997-04S1 (PI - Levine)	02/01/2018 – 01/31/2021	0.0 calendar
NIH / NIDA	\$ 48,000	
Avant Garde Award Diversity Supplement		
Repairing the intestinal epithelium from the dual action of HIV and drug use		

T32 AI 127201 (PI - Levine) NIH / NIAID Training Program in HIV Cure	07/01/2016 – 06/30/2021 \$227, 904	0.0 calendar
IPAS 204493 Alliance Investment Fund (PI - Levine) Provost, Case Western Reserve University Impact of Drug Abuse on Infectious Disease	07/01/2011 – 06/30/2022 \$50,000	0.0 calendar
R01 DA 043253 (PI - Levine) NIH / NIDA Identification of immune protective pathways dysregulated by opioid use in HIV infection, using a systems biology-based approach, toward the goal of pharmacological restoration of immune function	09/01/2016 to 05/31/2021 \$513,431	2.4 calendar
R01 DA 043253-03S1 (PI - Levine) NIH / NIDA Diversity Supplement Award Identification of immune protective pathways dysregulated by opioid use in HIV infection, using a systems biology-based approach, toward the goal of pharmacological restoration of immune function	09/01/2018 – 05/31/2021 \$ 48,000	0.0 calendar
University Hospitals Cleveland Medical Center Department of Medicine (PI – Levine) Roe Green Center for Travel Medicine	09/01/2018-08/31/2021 \$25,000	0.0 calendar
CWRU/UH CFAR Uganda Research Travel Award (PI - Levine) Internal funding Establish a research program at the JCRC on mucosal immunity and the microbiome in HIV co-infections.	\$10,000	0.0 calendar
CWRU School of Medicine (PI - Levine) Case Western Reserve University Task Force Fund Impact on the GI tract from the triple action of HIV, SARS-CoV-2, and opioid use	07/01/2020 – 06/30/2021	0.0 calendar
BFA2013-003 (Levine) CWRU Office of the Dean Mutualism between host and microbial during intestinal trauma initiated by HIV and drug abuse	04/01/2013 – 03/31/2015 \$100,000	2.4 calendar
P01 AI 076174 (Lederman) NIH/NIAID (Project 2 - Levine) Defining the Pathogenesis of Immune Deficiency in Chronic HIV Infection	08/01/2008 – 07/31/2013 \$249, 507	3.2 calendar
R01 DA-021525 (Levine – supplement)) NIH/NIDA (Wood PI parental grant) Impacts of universal access to HIV/AIDS care among HIV+ injection drug users	09/01/2009 – 08/31/2012 \$199,334	3.0 calendar
R21 AI083609 (Levine) NIH/NIAID Redox regulation of intestinal T cells	09/01/2009 – 08/31/2012 \$125,000	1.6 calendar
R01 DK 054213-10 (Levine) NIH/NIDDK The Extracellular Matrix in Inflammatory Bowel Disease	09/01/1998 – 08/31/2012 \$242,500	2.4 calendar
P20 DA-026133 (Chance) NIH/NIDA (Project 1 – Levine) Case Proteomics Center for HIV/AIDS and Drug Abuse	04/15/2009 – 03/31/2012 \$102,045	1.8 calendar
R21 NR010781-01 (Winkelman) NIH/NINR Dose of Early Therapeutic Mobility: Does Type or Frequency of Activity Matter?	05/01/2009 – 04/30/2011 \$150,000	0.6 calendar

### **Leadership and Professionalism: Synergistic Activities:**

- 2015 Carl F. Wittke Award for Excellence in Undergraduate Teaching
- 2012-present Academy of Scholar Educators, CWRU School of Medicine
- 2012-present Chair, Human Health Alliance, Case Western Reserve University
- 2009-2011 Chair-elect, Chair, and Past Chair, Faculty Senate, Case Western Reserve University
- 2010-present Chair, Addiction Initiative, Case Western Reserve University

### **Commitment to Diversity and Inclusiveness:**

I am currently Graduate Program Director for the Molecular Virology program, with a focus on HIV/AIDS research. In the past decade, of our 33 students studying HIV, we have trained or are training a total of 10 students of color (30%). Past trainees from the Virology / Immunology pre- and postdoctoral program include Drs. Moses Joloba (Dean, School of Biomedical Sciences, Makerere University College of Health Sciences, Kampala, Uganda), Angel Luciano (Associate Professor, Pediatrics, University of Southern Florida), Anthony Stallion (Chief of Pediatric Surgery, Carolinas Healthcare System), Bernard Bagaya (Senior Scientist & Deputy Executive Director of the International AIDS Vaccine Initiative-Uganda Unit at the Makerere University College of Health Sciences), Virginia Baez-Socorro (Assistant Professor, Pediatrics, Rainbow Babies and Children's Hospital), Immaculate Nankya (Core Director of the CFAR Uganda Laboratory at the Joint Clinical Research Centre, in Kampala), and Ann Vazquez (Research Scientist, Quidel Corporation, Athens, OH). I also direct the NIH-funded T32 Training Program in HIV Cure. In the current 5-year funding cycle this training program has supported 71% people of color. Importantly, our attrition rate for students of color in the HIV virology and immunology training program for the past decade is ZERO. The University of Puerto Rico campuses represent a major undergraduate origin for Latino students who subsequently earn a Science and Engineering doctorate. I have developed very amicable relationships with several academic advisors at these campuses and will continue to target Puerto Rican institutions for CWRU programs. I am particularly active in the University of Puerto Rico recruitment visiting program, having traveled, before the pandemic lockdown, to four universities in November 2019 to publicize graduate training and invite applications. I served as thesis committee chair for both Drs. Reyes-Rodriguez and Valentin-Torres, and doctoral mentor for Dr. Cruz-Lebrón, three Case PREP and now graduated doctoral students. I also trained a 2005 MSTP graduate, Dr. Brenda M. Rivera Reyes who graduated from the University of Puerto Rico, Mayaguez campus in 2001. Furthermore, two other Latinx predoctoral students, Braulio Llorens and Michelle Cruz, are currently completing their doctoral degrees in my laboratory.

### **Mentoring:**

I am extensively committed to research training programs, currently serving as Program Director of an NIH-funded T32 on HIV Cure, as a preceptor on multiple T32 training grants, and on the steering committee of the MSTP program, the Neonatology training grant, and the Pharmacology training program and grant. He has supported graduate student education university-wide by serving on and then chairing the Faculty Senate Graduate Studies Committee. As Chair of the University Faculty Senate, he furthered the design and implementation of Graduate Student guidebooks on Mentoring and Being a Mentee and formed a Case Western Reserve University Mentoring Training program for junior and senior faculty. He led the Senate toward passage of new advising and mentoring criteria for Promotion, Tenure, and Appointment, modifying the By-Laws in the process. Dr. Levine has graduated a doctoral student every other year of the past two decades, has chaired over 68 graduate student thesis committees, and served on another 62 as a committee member. He is currently Graduate Program Director for the Cell Biology, Molecular Biology and Microbiology, and Molecular Virology programs.

### **Major Awards, Fellowships, Invited Lectureships, and Honors:**

- 2002 Crohn's and Colitis Foundation of America Student Research Fellowship Mentor
- 2003 NRSA General Medical Sciences Student Research Fellowship Mentor
- 2007 Waldron Roll, Union College, Schenectady, NY
- 2012 Undergraduate's Favorite Professor, Case Western Reserve University, Cleveland, OH
- 2013 Undergraduate's Favorite Professor, Case Western Reserve University, Cleveland, OH
- 2014 Undergraduate's Favorite Professor, Case Western Reserve University, Cleveland, OH
- 2016 John S. Diekhoff Award for Distinguished Graduate Teaching
- 2019 Case Western Reserve Univ. John S. Diekhoff Nominee: Distinguished Mentoring Award
- 2020 Case Western Reserve Univ. John S. Diekhoff Nominee: Distinguished Mentoring Award
- 2021 Case Western Reserve Univ. John S. Diekhoff Nominee: Distinguished Mentoring Award

### Major Career Contributions and Legacy:

- My research interests include investigations on immunopathogenesis of the intestinal innate and acquired immune response in inflammatory bowel disease and during an HIV-1 infection, further complicated by substance use disorder. My laboratory focuses on the mechanisms that regulate a complex multi-tiered host defense system of the intestinal mucosa, the largest lymphoid organ of the body. I have a broad background, training, and expertise with publications in molecular immunology, mucosal immunology and biology, cell biology, molecular biology, biochemistry, cytokine biology, inflammatory diseases, and animal models.
- I have served on review committees and other national panels for the Crohn's and Colitis Foundation, the American Cancer Society, NIH/CSR, NIDA, NINR, NCI, NIDDK, and NIAID.
- I have extensive leadership and experience in furthering interdisciplinary research at Case Western Reserve University and between his institution and other academic centers, such as the NIH, University of North Carolina, the Catholic University of Rome, George Mason University, Drexel Medical Center, the University of Florence, the University of Pittsburgh, and the University of British Columbia. I have successfully administered these projects (e.g., staffing, research projections, budget), collaborated with other investigators, and produced several peer-reviewed publications from each funded project.
- In the mid 1980s immunology was abuzz with the potential isolation and characterization of the "infamous" IJ region-associated antigen-specific immune suppressor factors, whose basic science and clinical impact was boundless. In collaboration with the leading cellular immunologists in this discipline, my laboratory set out to clone and characterize the genes coding for these suppressor factors. Using new technology, we successfully cloned and sequenced the first gene coding for a suppressor factor. This sequence was mapped to the genome of a contaminating mycoplasma in the T cell culture. Since publication of that observation would likely shatter the career of a very well established cellular immunologist, the work was not reported, although the observations were universally distributed and the spurious field was rapidly dismissed. It took immunology almost 20 years to return to immune suppression, renamed as the regulatory T cell.
- The immune mediator critical to the diseases of allergy and asthma is the antibody isotype IgE, and our laboratory was the first to clone, sequence, characterize, and patent the human cytokine, Interleukin 4 (IL-4), as the switch factor for IgE secretion. In collaboration with eminent immunologists in allergy, William Paul, Fred Finkelman, and Rebecca Buckley, we demonstrated in mouse that blocking IL-4 or its receptor inhibited IgE class switch and human IL-4 regulated human B cell maturation to IgE production. We also demonstrated and patented, precedent to a clinical trial, that the proprietary prostaglandin analogue, misoprostol, blocked IL-4-mediated IgE production *in vitro* and *in vivo*. My former employer, Monsanto, initiated a 120-person project team to pursue a clinically effective, orally deliverable anti-asthmatic/allergy pharmaceutical, a project that continued until I left the company.
- Helper CD4+ T cells orchestrate an adaptive immune response after activation by a specific antigen, through its T cell receptor (TCR), and secondary stimulatory pathways initiated by a variety of environmental cues that include cytokines, extracellular matrix via integrins, and co-stimulatory receptors. Using purified human T cells we established an *in vitro* cell culture model to characterize (i) the signaling pathway induced by the co-stimulatory receptor ICOS, (ii) the ability of an effector T cell migrating through tissue engaged by the extracellular matrix to modulate its state of activation, (iii) the contribution of lipid rafts to coordinate TCR activation, and (iv) the role for tyrosine phosphatases, regulated by endogenous reactive oxygen species, to tune T cell activation and modulate immune responses. Together these studies demonstrate the intricate regulatory network at play within a T cell during the activation process and the critical role played by environmental factors in shaping an immune response.
- Chronic inflammation in the wall of the Inflammatory Bowel Disease (IBD) GI tract is associated with immune dysfunction in the epithelium and among mucosal T cells. Our studies in murine models of IBD revealed the molecular events that regulate mucosal tolerance, and that immune pathology evolves with time as the disease progresses and treatments relevant early in the disease process are ineffective late, and *vice versa*.
- Development of the mucosal immune system in the wall of the GI tract is regulated by the commensal microbiome and *vice versa*. Very early after an HIV infection or the onset of IBD, we observed an increase in paracellular permeability due to changes in gene expression, assembly, transport, and composition of the epithelial tight junctional complex. This permeability is associated in both diseases with microbial translocation, whose products circulating in the blood lead to systemic immune activation. We propose that systemic inflammation in HIV and IBD lead to subsequent non-mucosal organ dysfunction including cardiovascular disease.