BIOGRAPHICAL SKETCH

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NAME: Gelbard, Harris A.

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POSITION TITLE: Professor and Director, Center for Neurotherapeutics Discovery

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
Northwestern University, Evanston, IL	B.S.	06/1976	Medical Sciences (Honors Program in Med. Education)
Northwestern Univ. Med. School, Chicago, IL	M.D.	06/1983	Medicine
Northwestern University, Chicago, IL	Ph.D.	06/1983	Pharmacology

A. Personal Statement

Role in T32: Mentor

I am the Director of the Center for Neurotherapeutics Discovery, a new division in the Department of Neurology, as well as Professor of Neurology, Pediatrics and Microbiology and Immunology, and Neuroscience at the University of Rochester Medical Center. As a molecular neuropharmacologist, I have worked primarily with experimental models of neuroAIDS and HIV-1 induced neuroinflammation since 1992. After working with members of the Experimental Therapeutics faculty in Neurology at URMC to repurpose already FDA-approved medicines for neurologic disease, my team has developed new therapies for HIV-associated neurocognitive disorders (HAND) since 2005. Our laboratory has a preclinical focus on neuroinflammation and synaptic plasticity with an overarching translational goal of restoring synaptic plasticity (the basis for learning and memory) in neuroinflammatory conditions. Our major research goal is to develop protective approaches by targeting mixed lineage kinase (MLK3) that regulates neuroinflammation in CNS-resident and peripheral immune effector cells and neuronal function/fate through effects on downstream kinases that include Jun N-terminal kinase (JNK). With multiple cycles of PO1, RO1 and SBIR support, we have developed a library of >200 novel small molecules that efficaciously inhibit MLK3, and we have tested these new inhibitors in *in vitro* and *in vivo* models for HAND, with the goal of filing an investigational new drug (IND) application with the FDA. MLK3 is a pathologic target with therapeutic implications in a broad range of diseases that are also problematic for people living with HIV-1. Serendipitously, our broad spectrum MLK3 inhibitors have demonstrated disease-modifying outcomes in *in vivo* studies of non-alcoholic steatohepatitis (NASH), multiple sclerosis (MS), perioperative neurologic dysfunction (formerly post-operative cognitive dysfunction or POCD), Alzheimer's disease (AD), Parkinson's disease (PD) and HAND. Our lead compound, URMC-099, protected with 43 national and international composition of matter and method of use patents, is now being tested in additional models of disease, including amyotrophic lateral sclerosis (ALS) and sepsis associated encephalopathy (SAE). URMC-099 is now approximately halfway through successful completion of preclinical safety and toxicokinetic IND-enabling studies, with an anticipated IND filing by 4th quarter of 2019.

I have a strong interest in interdisciplinary training for residents, postdocs, medical and graduate students, and have emphasized ongoing collaborations with faculty from Neurology, Neuroscience, Toxicology, Microbiology and Immunology, Pharmacology, Chemistry, Optics and Electrical Engineering, sharing trainees over the past 25 years. During this time, I have trained 32 undergraduates, 2 masters students, 5 PhD students (2 of which have been MSTPs) (with an additional 2 predoctoral trainees currently in my lab) and 12 postdoctoral fellows. One postdoctoral fellow trained in my laboratory and remaining with our group is currently an Assistant Professor of Neurology with a research interest in MS. Thus, my laboratory is an ideal translational

environment for trainees who are interested in experimental therapeutics, the intersection of basic science focused on neuroimmunology and preclinical/clinical development of new therapeutic agents for neuroinflammatory disease. Trainees fill an important role in executing the multitude of research avenues and I welcome the opportunity to train them in sound experimental design and supporting methods, as well as activities that are integral to a career in translational research. My laboratory provides an ideal and unique environment for trainees to fulfill their early investigator career goals and secure subsequent funding.

B. Positions and Honors

Positions and Employment

1983-1984	Intern, Pediatrics; Children's Memorial Hospital, Chicago, IL.
1984-1985	Resident, Pediatrics; Children's Memorial Hospital, Chicago, IL.
1985-1987	Resident, Neurology; Longwood Neurology Program, Boston, MA.
1987-1988	Chief Resident, Child Neurology; The Children's Hospital, Boston, MA.
1988-1990	Postdoctoral Fellow; Mailman Res. Center, Mass. Gen. Hosp., Boston, MA.
1990-present	Assistant Professor (1990-95); Associate Professor (1995-2000); Professor with unlimited tenure (2000-present) of Neurology & Pediatrics; Professor (2001-) of Microbiology & Immunology; Professor (2016-) of Neuroscience; Member (1999-2007), Center for Aging & Developmental Biology, Kornberg Med. Res. Inst., University of Rochester Medical Center.
2007	Interim Director, Ctr. for Neural Dev. & Dis., Kornberg Med. Res. Inst., Univ. of Rochester.
2008-present	Director, Center for Neurotherapeutics Discovery (previously known as the Center for Neural Development & Disease), Kornberg Med. Res. Inst., University of Rochester Medical Center.

Other Experience and Professional Memberships

2017-present	ZTR1 DP1-7(02)1 Study Section, Member
2015-present	1PO1MH105303--"NeuroAIDS Therapeutics – Targeting Immune Polarization of Macrophages in CNS," P.I. J. Rappaport, Temple University.
2009-present	Neurology Scientific Leadership Group, The Pediatric HIV/AIDS Cohort Study (PHACS) network (NICHD U01 HD052104), Russell Van Dyke, P.I.
2008-present	Co-chair, ZRG1 AARR-D (05) M
2003-present	Ad hoc Member, NIH NIMH/NINDS SEPs for PO1 PPGs/R21/RO1 on NeuroAIDS
2009-2014	1UO1-MH090325-01-Anti-HIV Neuroimmunomodulatory Therapy. Children's Hospital of Pennsylvania, S. Douglas, P.I.
2003-2012	Chair, External Advisory Committee for CNS HIV Anti-Retroviral Therapy Effects Research ("CHARTER"), NIMH and NINDS N01 MH22005, Igor Grant, P.I.
2007-2012	Diagnostic Safety Monitoring Board (DSMB) for the Neurologic AIDS Research Consortium (NARC) (NINDS UO1 NS32228) for clinical trials for adjunctive neuroprotective therapies, Washington Univ. in St. Louis, MO, David Clifford, P.I.
2007-2012	External advisory committee, The Johns Hopkins NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders (5P30MH075673), Justin McArthur, P.I.
2003-2007	ZRG1 AARR5 Study Section, Permanent Member

Honors and Awards

1980-1981	NIMH NRSA Predoctoral Fellowship Grant
1988-1990	Dana Foundation Fellowship and Grant, Massachusetts General Hospital, Boston, MA
1989	First Prize, Wyeth-Ayerst New Res. Award, VIII World Cong. of Psychiatry, Athens, Greece
1990	Child Neurology Young Investigator Award
1990	Buswell Memorial Fellowship, University of Rochester
2015	Translational Research in NeuroVirology Lectureship, 13th International Society for Neurovirology, San Diego, CA
2016	Hilary Koprowski Prize in Neurovirology, 2016 International Symposium on Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, PA
2019	2019 Herman and Gertrude Silver Award on Children, Youth and HIV, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

C. Contributions to Science

1. My early contributions discovered the existence of a nuclear receptor for calcitriol in the pituitary and investigated the link between early brain injury to dopaminergic neurotransmitter systems in the mammalian forebrain, focusing on the role of dopamine as a trophic factor for development of the D_1 receptor subtype.
    a. Gelbard, H.A., Stern, P.H. & U'Prichard, D.C. (1980). 1 alpha, 25-Dihydroxyvitamin D3 nuclear receptors in pituitary. Science, 209(4462), 1247-1249.
    b. Gelbard, H.A., Teicher, M.H., Faedda, G. & Baldessarini, R.J. (1989). Postnatal development of dopamine D1 and D2 receptor sites in rat striatum. Brain Research: Developmental Brain Research, 49(1), 123-130.
    c. Gelbard, H.A., Teicher, M.H., Baldessarini, R.J., Gallitano, A., Marsh, E.R., Zorc, J. & Faedda, G. (1990). Dopamine D1 receptor development depends on endogenous dopamine. Brain Research: Developmental Brain Research, 56(1), 137-140.
    d. Teicher, M.H., Gallitano, A.L., Gelbard, H.A., Evans, H.K., Marsh, E.R., Booth, R.G. & Baldessarini, R.J. (1991). Dopamine D1 autoreceptor function: possible expression in developing rat prefrontal cortex and striatum. Brain Research: Developmental Brain Research, 63(1-2), 229-235.
2. Influenced by the epidemic proportions of HIV-1 infection in the late 80's and early 90's, coupled with the unique opportunity to investigate "bench-to-bedside" experimental therapeutics of HIV-1 associated dementia (HAD), I refocused my research program to a neuropharmacologic approach to investigating neuroimmunologic disease associated with HIV-1 infection. In particular, I investigated the role of excitatory neurotransmitter signaling in a neuroinflammatory milieu as a major contributory factor to HAND.
    a. Gelbard, H.A., Nottet, H.S., Swindells, S., Jett, M., Dzenko, K.A., Genis, P., White, R., Wang, L., Choi, Y.B., Zhang, D. & et al. (1994). Platelet-activating factor: a candidate human immuno-deficiency virus type 1-induced neurotoxin. Journal of Virology, 68(7), 4628-4635. PMCID: PMC236390.
    b. Talley, A.K., Dewhurst, S., Perry, S.W., Dollard, S.C., Gummuluru, S., Fine, S.M., New, D., Epstein, L.G., Gendelman, H.E. & Gelbard, H.A. (1995). Tumor necrosis factor alpha-induced apoptosis in human neuronal cells: protection by the antioxidant N-acetylcysteine and the genes bcl-2 and crmA. Molecular Cellular Biology, 15(5), 2359-2366. PMCID: PMC230464.
    c. Perry, S.W., Hamilton, J.A., Tjoelker, L.W., Dbaibo, G., Dzenko, K.A., Epstein, L.G., Hannun, Y., Whittaker, J.S., Dewhurst, S. & Gelbard, H.A. (1998). Platelet-activating factor receptor activation. An initiator step in HIV-1 neuropathogenesis. Journal of Biological Chemistry, 273(28), 17660-17664.
    d. New, D.R., Maggirwar, S.B., Epstein, L.G., Dewhurst, S. & Gelbard, H.A. (1998). HIV-1 Tat induces neuronal death via tumor necrosis factor-alpha and activation of non-N-methyl-D-aspartate receptors by a NFkappaB-independent mechanism. Journal of Biological Chemistry, 273(28), 17852-17858.
3. Contemporaneously, I demonstrated that HIV-1 infection of the developing central nervous system resulted in neuronal apoptosis.
    a. Gelbard, H.A., James, H.J., Sharer, L.R., Perry, S.W., Saito, Y., Kazee, A.M., Blumberg, B.M. & Epstein, L.G. (1995). Apoptotic neurons in brains from paediatric patients with HIV-1 encephalitis and progressive encephalopathy. Neuropathology and Applied Neurobiology, 21(3), 208-217.
    b. Krajewski, S., James, H.J., Ross, J., Blumberg, B.M., Epstein, L.G., Gendelman, H.E., Gummuluru, S., Dewhurst, S., Sharer, L.R., Reed, J.C. & Gelbard, H.A. (1997). Expression of pro- and anti-apoptosis gene products in brains from paediatric patients with HIV-1 encephalitis. Neuropathology and Applied Neurobiology, 23(3), 242-253.
    c. James, H.J., Sharer, L.R., Zhang, Q., Wang, H.G., Epstein, L.G., Reed, J.C. & Gelbard, H.A. (1999). Expression of caspase-3 in brains from paediatric patients with HIV-1 encephalitis. Neuropathology and Applied Neurobiology, 25(5), 380-386.
4. Because premortem neurologic disease associated with HIV-1 infection of the central nervous system did not correlate with the level of observed postmortem neuronal apoptosis, I then investigated whether reversible vs. irreversible synaptodendritic injury might be the substrate for HIV-1 associated neurocognitive deficits (HAND) and demonstrated potential mechanisms for these types of injury in *in vitro* and *ex vivo* models of HAND as well as multiple sclerosis (MS).
    a. Bellizzi, M.J., Lu, S.M., Masliah, E. & Gelbard, H.A. (2005). Synaptic activity becomes excitotoxic in neurons exposed to elevated levels of platelet-activating factor. Journal of Clinical Investigation, 115(11), 3185-3192. PMCID: PMC1265873. doi: 10.1172/JCI25444
    b. Norman, J.P., Perry, S.W., Reynolds, H.M., Kiebala, M., De Mesy Bentley, K.L., Trejo, M., Volsky, D.J., Maggirwar, S.B., Dewhurst, S., Masliah, E. & Gelbard, H.A. (2008). HIV-1 Tat activates neuronal

ryanodine receptors with rapid induction of the unfolded protein response and mitochondrial hyperpolarization. PLoS One, 3(11), e3731. PMCID: PMC2579580. doi: 10.1371/journal.pone.0003731

c. Perry, S.W., Barbieri, J., Tong, N., Polesskaya, O., Pudasaini, S., Stout, A., Lu, R., Kiebala, M., Maggirwar, S.B. & Gelbard, H.A. (2010). Human immunodeficiency virus-1 Tat activates calpain proteases via the ryanodine receptor to enhance surface dopamine transporter levels and increase transporter-specific uptake and Vmax. Journal of Neuroscience, 30(42), 14153-14164. PMCID: PMC2972730. doi: 10.1523/JNEUROSCI.1042-10.2010

d. Bellizzi, MJ, Geathers, J, Allan, K and Gelbard, HA. Platelet-activating factor receptors mediate excitatory post-synaptic hippocampal injury in experimental autoimmune encephalomyelitis. J. Neurosci. 2016 Jan 27;36(4):1336-46. PMID: 26818520. PMCID: PMC4728729. doi: 10.1523/JNEUROSCI.1171-15.2016.

5. We demonstrated that mixed lineage kinase type 3 and leucine rich repeat kinase type 2 play pivotal roles in mediating neuroinflammation and synaptodendritic damage associated with HAND, using a variety of *in vitro* and *in vivo* models of HAND. Additionally, we designed and validated a small molecule "selectively non-selective" inhibitor of MLK3 with a favorable CNS profile to advance to adjunctive therapy for HAND.

a. Marker, D.F., Tremblay, M.E., Puccini, J.M., Barbieri, J., Gantz Marker, M.A., Loweth, C.J., Muly, E.C., Lu, S.M., Goodfellow, V.S., Dewhurst, S. & Gelbard, H.A. (2013). The new small-molecule mixed-lineage kinase 3 inhibitor URMC-099 is neuroprotective and anti-inflammatory in models of human immunodeficiency virus-associated neurocognitive disorders. Journal of Neuroscience, 33(24), 9998-10010. PMCID: PMC3682381. doi: 10.1523/JNEUROSCI.0598-13.2013

b. Goodfellow, V.S., Loweth, C.J., Ravula, S.B., Wiemann, T., Nguyen, T., Xu, Y., Todd, D.E., Sheppard, D., Pollack, S., Polesskaya, O., Marker, D.F., Dewhurst, S. & Gelbard, H.A. (2013). Discovery, synthesis, and characterization of an orally bioavailable, brain penetrant inhibitor of mixed lineage kinase 3. Journal of Medicinal Chemistry, 56(20), 8032-8048. PMCID: PMC4032177. doi: 10.1021/jm401094t

c. Gnanadhas, DP, Dash, PK, Sillman, B, Bade, AN, Lin, Z, Palandri, DL, Gautam, N, Alnouti, Y, Gelbard, HA, McMillan, JE, Mosley, RL, Edagwa, B, Gendelman, HE and Gorantla, S. Autophagy facilitates macrophage depots of sustained release nanoformulated antiretroviral drugs. J. Clin. Inv. 2017 Mar 1;127(3):857-873. Epub 2017 Jan 30. PMID:28134625. PMCID: PMC5330738. doi: 10.1172/JCI90025

d. Bellizzi MJ, Hammond JW, Li H, Marker MAG, Marker DF, Freeman RS, Gelbard HA. The mixed-lineage kinase inhibitor URMC-099 protects hippocampal synapses in experimental autoimmune encephalomyelitis. 2018 Dec 3;5(6). Pii. ENEURO.0245-18.2018. eCollection 2018 Nov-Dec. eNeuro. PMID: 30627663. PMCID: PMC6325567. doi:10.1523/ENEURO.0245-18.2018

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/harris.gelbard.1/bibliography/41146597/public/?sort=date&direction=ascending

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

Ongoing Research Projects

R01MH104147 Gelbard (PI) 07/16/2014-06/30/2020
Novel Kinase and Nanoformulated Protease Inhibitors for Eradication of CNS HIV-1
The goal of this project is to investigate mechanisms for synergy between MLK3 inhibition and nanoformulated antiretroviral therapy on eradication of persistent HIV-1 infection in cellular reservoirs.

Michael J Fox Fdn for Parkinson's Disease Gelbard (PI) 09/01/2018-11/30/2019
URMC-099 In *in vivo* AAV-hSYN and *in vitro* Dopaminergic Neuron Models
Major goal: To investigate whether URMC-099 can reverse the disease course of PPD.

University of Rochester Gelbard (PI) 11/01/2017-10/31/2019
Technology Development Fund
URMC-099 and disease modifying outcomes for ALS in a new transgenic model
The major goal of this project is to address the lack of disease-modifying therapeutic agents available for amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease that typically leads to death from respiratory compromise within 10 years or less of diagnosis.

University of Rochester Gelbard (PI) 03/01/2015-02/31/2020

Technology Development Fund
IND-Enabling Studies for a First-In-Class Treatment for NeuroAIDS
The major goal of this project is conduct IND-enabling studies for URMC-099.

R01AG057525 Subaward Terrando (PI, Duke University) 09/15/2017-04/30/2022
Neurovascular dysfunction in delirium superimposed on dementia
The major goal of this project is to investigate interactions between infiltrating inflammatory leukocytes, perturbation of the blood-brain barrier after sterile trauma from tibial fracture and deposition of amyloid in the neurovascular unit, broadening the utility of mixed lineage kinase inhibition (URMC-099) as a therapeutic approach for the treatment of post-surgical delirium and dementia in the aging population.
Role: Co-Investigator and PI, subaward

R01NS066801 Maggirwar (PI) 02/15/2010-01/31/2021
Platelet-mediated neuroinflammatory response to HIV
Major goal: To test whether activation of peripheral platelets by HIV-1 elicits abnormal effects on brain micro-vascular endothelial cells, thereby altering blood-brain barrier integrity and exacerbating inflammation in the CNS. Role: Co-Investigator

R21NS111255 Hammond (PI) 04/01/2019-03/31/2021
Role of the Sez6 family in synapse pruning
The goal of this proposal is to investigate the role of the Sez6 family in complement-mediated synaptic pruning to gain insight into how Sez6 family proteins may contribute susceptibility to ASD. Role: Co-Investigator

P30AI078498 Dewhurst (PI) 05/01/2013-04/30/2020
University of Rochester Center for AIDS Research
Major goal: to develop a Center for AIDS Research at the U of Rochester, and to provide support for institutional HIV/AIDS researchers. Role: Investigator, Executive Committee (prev. Director of CNS SWG)

R01NS094037 Birbeck (PI) 10/01/2015-09/30/2020
Cohort of HIV-Associated Seizures and Epilepsy in Zambia (CHASE)
The goal of this project is to investigate the HIV-associated seizures and epilepsy in Zambia. Role: Consultant

T32AI049815 Maggirwar (PI) 07/01/2011-06/30/2021
Training in HIV replication and pathogenesis (renewal)
Major goal: to train predoctoral students for careers as outstanding research scientists in the field of HIV/AIDS.
Role: Mentor

U01HD052104 Van Dyke (PI) 09/01/2005-07/31/2020
Coordinating Center for the Pediatric HIV/AIDS Cohort Study (PHACS)
The major goal of the Pediatric HIV/AIDS Cohort Study (PHACS) network is to address the long-term safety of fetal and infant exposure to prophylactic antiretroviral (ART) chemotherapy, and the effects of perinatally acquired HIV infection in adolescents. Role: Unpaid Consultant (previously Investigator)

Completed Research Support

NMSS RG-1607-25423 Bellizzi (PI) 04/01/2017-03/31/2018
Modulating microglial activation for gray matter neuroprotection in multiple sclerosis. Role: Investigator

P01MH064570 Gelbard (PI) 06/01/2002-05/31/2017
Novel Adjunctive Therapies for NeuroAIDS

R01NS054578 Maggirwar (PI) 06/15/2012-05/31/2017
Inflammatory Mechanisms Associated with HIV-1 Dementia (renewal). Role: Investigator

R44MH092137 Gelbard (PI) 07/01/2015-06/30/2016
MKLi Therapy for Cognitive Impairment in Multiple Sclerosis
Subaward via Califia Bio Inc.