BIOGRAPHICAL SKETCH

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NAME: Tracy Fischer, Ph.D.

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POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Ohio Northern University, Ada, OH	B.M.	05/1992	Vocal Performance
Rider University, Princeton, NJ	M.M.	05/1994	Vocal Performance and Pedagogy
Temple University, Philadelphia, PA	Ph.D.	01/2005	Biology

A. Personal Statement

I am a basic scientist with expertise in HIV neuropathogenesis, HIV infection of macrophages, and macrophage/microglial function in the context of chronic inflammation. During the early stages of my career, my work on immunomodulatory changes associated with HIV encephalitis helped to focus my research interests toward uncovering the mechanisms underlying chronic inflammation in the brain and its influence on neurocognitive and/or neuropsychiatric function. This is an important issue in HIV infection, as CNS disorders remain a significant concern, even among patients on suppressive combination antiretroviral therapy (cART).

We previously found that inflammation and impaired microglial function are a common complication of HIV, even among individuals who had been on suppressive cART. In addition to the anticipated inflammatory changes, we also identified altered expression of several transcripts involved in neuroprotection and brain homeostasis, suggesting a more complex role for microglia in the context of chronic inflammation.

In this R21 application, we will utilize SIVmac251-infected and uninfected rhesus macaques to test our hypothesis that inflammation in the brain allows greater penetrance of efavirenzv (EFV) into the CNS compartment. In the brain, EFV can promote the development of neuropsychiatric adverse events (NP-AEs) by competing with 5-HT (serotonin) receptors, which may be seen through increased concentration of the inactive serotonin metabolite, 5-HIAA, in blood and urine. We will also explore a potential role for peripheral EFV in BBB perturbances that impair integrity through an *in vitro* model of the BBB. We anticipate this work will yield potential predictors of individuals at risk for developing ART-induced NP-AEs and key insights into the mechanisms of ART-accumulation in the CNS for potential exploration in a future R01.

B. Positions and Honors

Positions and Employment

1998-2000 Veterinary Technician, Stoney Creek Veterinary Hospital, Springfield, PA
2005-2007 Post-Doctoral Fellow, Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA
2007-2008 Associate Scientist, Department of Neuroscience, Center for Neurovirology, Temple University, School of Medicine, Philadelphia, PA
2008-2019 Assistant Professor, Department of Neuroscience, Center for Neurovirology, Temple University School of Medicine, Philadelphia, PA
2019-present Associate Professor, Division of Comparative Pathology, Tulane National Primate Research Center, Covington, LA

Honors

2002 Temple University Excellence in Neuroscience Award in Recognition of Outstanding Research
2003 Temple University Excellence in Neuroscience Award in Recognition of Outstanding Research

2004 Keystone Symposia Scholarship for the Keystone Symposium on Molecular Mechanisms of HIV Pathogenesis
2004 Investigators in Training Travel Award for the 6th International Symposium on NeuroVirology HIV Neuroprotection Workshop
2004 Outstanding Graduate Student Research Award, "HIV infection and invasion of perivascular macrophages in HIV induced CNS disorder," Temple University
2004-2007 Post-Doctoral Fellowship, School of Pharmacology, Temple University, awarded through National Institute on Drug Abuse/National Institutes of Health
2005 Travel Award for the 11th Society on Neuroimmune Pharmacology Conference
2006 Keystone Symposia Scholarship for the Keystone Symposium on Molecular Mechanisms of HIV Pathogenesis
2006 Arthur Falek Young Investigator Award for excellence in poster presentation, Society for Neuroimmune Pharmacology
2006 Post-Doctoral Research Award, Philadelphia Area Chapter Society for Neuroscience

C. Contributions to Science

1. **Demonstrated that CNS inflammation and impaired microglial function is a common feature of HIV infection, regardless of the presence of productive virus.** It has been suggested that human immunodeficiency virus-1 encephalitis (HIVE) is no longer a significant concern, since the introduction of combination antiretroviral therapy (cART) has reduced its incidence and severity in the few individuals who go on to develop encephalitis. Although less severe than the frank dementia associated with HIVE, neurocognitive disorders in the setting of HIV infection persist and greatly impact the quality of life of individuals living with HIV. To gain insight into the processes that might contribute to neurocognitive impairment in HIV infected persons, we performed an immunohistochemical (IHC) study on brain tissue from HIV infected neurocognitively-impaired individuals with and without HIVE, as well as seronegative individuals without cognitive impairment. This study revealed marked neuroinflammation in frontal white matter and basal ganglia in HIV infection, regardless of detectable virus production. Although less severe than that seen in HIVE, HIV infected persons without encephalitis had similar activation marker upregulation and/or increased frequency, as well as morphological alterations in microglia and astrocytes that indicate an activated state. In a separate study investigating RNA expression of laser-capture microdissected microglia from autopsy brain of the same seronegative, HIV/noE and HIVE patients, we found several classes of microglial transcripts in HIVE and HIV/noE were altered, relative to HIV^- subjects. This includes factors related to cell stress, immune activation, and apoptosis. Together, these studies suggest that the microglial activation/dysfunction in the context of chronic inflammation contributes to HIV neuropathogenesis in the absence of significant (detectable) virus replication in brain.
    a. Tavazzi E, Morrison D, Sullivan P, Morgello S, **Fischer T**. Brain inflammation is a common feature of HIV-infected patients without HIV encephalitis or productive brain infection. Curr HIV Res. 2014 Mar 1;12(2):97-110. PMCID: PMC4152918
    b. Ginsberg SD, Alldred MJ, Gunnam SM, Schiroli C, Lee SH, Morgello S, **Fischer T**. Expression profiling suggests microglial impairment in human immunodeficiency virus neuropathogenesis. Ann Neurol. 2018 Feb;83(2):406-17. PMCID: PMC5822676

2. **Identified the sources of M-CSF in the brain in SIVE and demonstrated that HIV production is reduced when signaling through the M-CSF receptor is inhibited.** Macrophage colony stimulating factor (M-CSF) has been implicated in the development and maintenance of long-lived macrophage reservoirs of HIV infection. M-CSF promotes HIV infection of macrophages through upregulation of receptors the virus uses for cell entry and virus production by upregulating factors that act on the viral LTR. In turn, HIV infection of macrophages promotes M-CSF production, producing a positive feedback loop of HIV replication and M-CSF production. Through its normal biological function as a macrophage survival factor, M-CSF may make HIV infected macrophages resistant to cell death. Although M-CSF has been proposed to significantly contribute to HIV infection in the brain, the cellular source of M-CSF in the CNS was unclear. Through immunohistochemical analyses of brain tissues from rhesus macaques with and without SIV infection and with and without SIVE, we demonstrated that $CD163^+$ macrophages, which comprise perivascular cuffs and nodular lesions and are the principal reservoir of productive SIV in brain, are also the primary source of M-CSF in SIVE. We further demonstrated that M-CSF and IL-34,

which signal through the same receptor, cFMS, enhances HIV-1 production in microglia *in vitro*. This is attenuated by the addition of a receptor tyrosine kinase inhibitor with high specificity for cFMS, GW2580. We also demonstrated that cFMS inhibition reduces $CD16^+CD163^+$ monocyte frequency, which is expanded by both M-CSF and IL-34. Together, these data suggest cFMS signaling may be an attractive target for eliminating long-lived macrophage reservoirs of HIV infection in brain, as well as other tissues.

a. Gerngross L, **Fischer T**. Evidence for cFMS signaling in HIV production by brain macrophages and microglia. J Neurovirol. 2015 Jun 1;21(3):249-56. PMCID: PMC4305491
b. Gerngross L, Lehmicke G, Belkadi A, **Fischer T**. Role for cFMS in maintaining alternative macrophage polarization in SIV infection: implications for HIV neuropathogenesis. J Neuroinflammation. 2015 Dec;12(1):58. PMCID: PMC4381451

3. **Provided clear evidence that $CD14^+CD16^+$ monocytes/macrophages that accumulate perivascularly and within nodular lesions are derived from the peripheral blood and serve as the principal reservoir of productive HIV in brain.** The importance of the $CD14^+CD16^+$ monocyte subset in HIV infection and HIV dementia (HIV-D) was suggested based on increases in the frequency of this monocyte subset in patients with HIV and associated neurological disorders. However, there had been no studies in human brain tissue to directly examine this hypothesis. We provided clear evidence that $CD14^+CD16^+$ monocytes/macrophages comprise perivascular cuffs and nodules in HIV encephalitis (HIVE) and are a significant source of productive HIV in the brain. Using a series of lineage-specific immunohistochemical markers, alone and in combination, we also demonstrated the most likely source of these accumulating cells is the peripheral blood. This is further supported by our immunohistological investigation of macrophage/microglial proliferation in brain of HIV infected persons, which revealed little evidence this occurs in the setting of HIV or in HIVE. This suggests $CD14^+CD16^+$ monocytes represent a more invasive subset able to invade the brain. In support of this hypothesis, we also demonstrated that, in individuals with HIV infection, $CD14^+CD16^+$ monocytes/macrophages accumulate in other tissues outside of the CNS compartment, including liver, spleen, lymph node, and kidney. This is even greater in individuals who develop encephalitis, suggesting a greater disease process in the periphery, as well as the brain.

a. **Fischer-Smith T**, Croul S, Sverstiuk AE, Capini C, L'Heureux D, Régulier EG, Richardson MW, Amini S, Morgello S, Khalili K, Rappaport J. CNS invasion by CD14+/CD16+ peripheral blood-derived monocytes in HIV dementia: perivascular accumulation and reservoir of HIV infection. J Neurovirol. 2001 Nov 1;7(6):528-41. PMID: 11704885
b. **Fischer-Smith T**, Croul S, Adeniyi A, Rybicka K, Morgello S, Khalili K, Rappaport J. Macrophage/microglial accumulation and proliferating cell nuclear antigen expression in the central nervous system in human immunodeficiency virus encephalopathy. The Am Pathol. 2004 Jun 1;164(6):2089-99. PMCID: PMC1615769
c. **Fischer T**, M Wyatt C, D D'Agati V, Croul S, McCourt L, Morgello S, Rappaport J. Mononuclear phagocyte accumulation in visceral tissue in HIV encephalitis: evidence for increased monocyte/macrophage trafficking and altered differentiation. Curr HIV Res. 2014;12(3):201-12. PMCID: PMC4314220

4. **Identified the $CD16^+CD163^+$ monocyte ($CD14^+$) as having a potential role in HIV production and disease progression, as a potential useful biomarker in HIV infection and AIDS progression, and a possible target for therapeutic intervention.** We posited that dysregulation of monocyte/macrophage activation and differentiation may promote immune dysfunction in HIV infection and contribute to AIDS pathogenesis. Using flow cytometry, we analyzed the frequency of monocyte subsets in HIV-1 infection relative to seronegative controls, focusing on the $CD16^+CD163^+$ monocyte as a likely precursor of the "alternatively-activated" (M2) macrophage. Individuals with detectable HIV in plasma showed an increase in the frequency of $CD16^+/CD163^+$ monocytes (identified as $CD14^+$) when compared to seronegative or HIV infected persons with undetectable viral loads. A positive correlation was revealed between increased $CD163^+/CD16^+$ monocyte frequency and viral load that was not seen between viral load and the number of $CD4^+$ T cells or frequency of $CD16^+$ monocytes (without CD163 sub-typing). We also found strong inverse correlations between $CD16^+$ monocytes ($r=-0.71$, $r^2=0.5041$, $p=0.0097$) or $CD163^+/CD16^+$ monocytes ($r=-0.86$, $r^2=0.7396$, $p=0.0003$) and number of $CD4^+$ T cells below 450 cells/µl. An inverse relationship between $CD163^+/CD16^+$ and $CD163^+/CD16^-$ monocytes suggests the expanded $CD163^+/CD16^+$ population is derived exclusively from within the M2 subset.

Interestingly, the $CD16^+$ monocyte/macrophages that accumulate in brain of individuals with HIVE are also $CD163^+$, suggesting an M2-polarized immune environment in the CNS in HIVE.

a. **Fischer-Smith T**, Tedaldi EM, Rappaport J. CD163/CD16 coexpression by circulating monocytes/macrophages in HIV: potential biomarkers for HIV infection and AIDS progression. AIDS Res. Hum. Retroviruses 24(3): 417-421. PMCID: PMC4420148
b. **Fischer-Smith T**, Bell C, Croul S, Lewis M, Rappaport J. Monocyte/macrophage trafficking in acquired immunodeficiency syndrome encephalitis: lessons from human and nonhuman primate studies. J. Neurovirol. 14(4):318-26. PMCID: PMC2728912

Complete list of published work: https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40017385/

D. Research Support

Ongoing Research Support

NIH/NIMH **P01 MH105303** (MPI: Tracy Fischer, Ph.D., Steven Douglas, M.D.) 06/01/14-05/31/19
Title: NeuroAIDS Therapeutics - Targeting Immune Polarization of Macrophages in CNS
Project 2 Goal: Investigate the effect of cFMS inhibition for preventing the development of CNS disease in SIV infected rhesus macaques.
Roles: Administrative Core Leader, Histopathology Core Leader, and Project #2 Principal Investigator

Completed Research Support

NIH/NIMH **P30 MH092177** (PD: Kamel Khalili, Ph.D.) 08/01/11-05/31/21
Title: Comprehensive NeuroAIDS Center (CNAC): Clinical and Behavioral Core
Core Goal: To bridge the gap between clinical, behavioral and basic research activities in neuroAIDS and develop strategies to integrate behavioral science and biomedical approaches in HIV care.
Role: Core Co-Leader; responsibilities transferred with move to Tulane.

NIH/NIMH **R01 MH090910** (PI: Jay Rappaport, Ph.D.) 07/01/10-03/31/15
Title: Monocyte/Macrophage Dynamics in NeuroAIDS
Goal: Investigate kinetics of monocyte/macrophage expansion and trafficking in SIV infected rhesus macaques.
Role: Co-Investigator

NIH/NINDS **R01 NS063605** (PI: Tracy Fischer, Ph.D.) 04/10/08-03/31/14
Title: Role of Monocytes/Macrophages in CNS Disease in the HAART Era
Goal: Investigate alterations in monocyte/macrophage homeostasis in HIV associated CNS disease in the HAART era.
Role: Principal Investigator

NIH/NIDA **P01 DA023860** (PD: Thomas Rogers, Ph.D.) 07/01/08-4/30/14
Title: Drugs of Abuse Affecting AIDS Pathogenesis
Goal: To investigate the effect of opioids on the development of CNS disease in SIV infected rhesus macaques.
Roles: Leader, Core B Histopathology and Co-Investigator, Project #2: Opioids in AIDS progression and neuropathogenesis of SIV infected macaques