Woong-Ki Kim, Ph.D.
Eastern Virginia Medical School

CHRB Grant Title: ***Targeting of CD16+ Monocytes in HIV NeuroAIDS***

CHRB Project Summary:

The HIV epidemic is still raging in the United States, and the State of Virginia is not immune to this threat. Virginia State ranks 12th in number of reported AIDS cases in the country, and currently 18,425 persons are estimated to be living with HIV and AIDS in Virginia. While deaths associated with HIV infection have decreased thanks to effective antiretroviral treatment, dementia developed in HIV-infected patients continues to increase because individuals are living longer. Recent reports provide evidence that CD16+ monocytes, a type of white blood cell, emerge during HIV infection and that these cells correlate with cognitive impairment and HIV-associated dementia. To directly assess a pathogenic role of these cells, we propose the selective depletion of CD16+ monocytes with anti-CD16 antibody treatment in our well-characterized monkey model of HIV CNS disease. Our novel approach to selectively target CD16+ monocytes could lead to an effective immunotherapy for HAD.

CHRB Project Outcome:

This project was designed to demonstrate the role of CD16+ monocytes/macrophages in the pathogenesis of brain disease associated with HIV infection (neuroAIDS). A subset of blood monocytes expressing the CD16 antigen expand dramatically in HIV infected patients with neuroAIDS. The CD16+ monocyte subset preferentially harbors HIV in infected patients. Furthermore, perivascular CD16+ monocytes/macrophages are a major reservoir of virus in the brain. We hypothesized that the infection and traffic of CD16+ monocytes play a central role in driving neuroAIDS.

In this CHRB–funded project, we have succeeded in demonstrating such a role using the SIV/macaque model of neuroAIDS (rhesus monkeys that are SIV infected, CD8 lymphocyte depleted). These experiments have demonstrated the selective suppression of the CD16+ monocytes/macrophages inhibits development of SIV encephalitis (SIVE) and may be neuroprotective in neuroAIDS.

We have successfully demonstrated the importance of CD16+ monocytes/macrophages as therapeutic targets of neuroAIDS. Despite the use of highly active antiretroviral therapy, neuroAIDS remains prevalent. Since many HIV infected patients here in Virginia (18,425 living with HIV/AIDS in 2006 presently) and elsewhere are now living longer, a population of aging HIVA patients with neurological disorders will expand. Our findings point out that system suppression of monocyte turnover and/or local inhibition of CD16+ macrophage proliferation may be the effective treatment options for neuroAIDS.

Comments regarding CHRB Grant Funding

My efforts to obtain federal funding have finally paid off and initial funding from the CHRB was instrumental in this. CHRB grant also helped me get through the difficult funding situation in the U.S. I am very grateful and indebted to the CHRB for its support.

Leveraged Funding as a result of CHRB Grant Award: $4,918,632

Awarded:

Project title: *Targeting Brain Macrophage Reservoirs of Infection in Pediatric NeuroAIDS*
Principal Investigator: Woong-Ki Kim, Ph.D.
Funding agency: NIH NIMH
Awarded: June 26, 2015 to May 31, 2017
Amount awarded: $441,500

Project title: *Targeting Brain Macrophage Reservoirs of SIV during HAART*
Principal Investigator: Woong-Ki Kim, Ph.D.
Funding agency: NIH Office of the Director
Awarded: July 2014
Amount awarded: $3,137,369

Project title: *Effects of Opioids on SIV Reservoirs in Brain Macrophages of Rhesus Macaques*
Principal Investigator: Marcelo J. Kuroda (Woong-Ki Kim, Ph.D., PI of subaward)
Funding agency: NIH NIDA
Submitted: September 30, 2015 to July 31, 2018
Amount requested: $1,043,695

Project title: *Brain Macrophage Reservoirs of HIV during Suppressive ART*
Principal Investigator: Woong-Ki Kim, Ph.D.
Funding agency: NIH/NIMH
Awarded: July 14, 2016 to June 30, 2019
Amount awarded: $296,068

Publications

Holder GE, McGary CM, Johnson EM, Zheng R, John VT, Sugimoto C, Kuroda MJ, Kim W-K (2014) Expression of the mannose receptor CD206 in HIV and SIV encephalitis: a phenotypic switch of brain perivascular macrophages with virus infection. J Neuroimmune Pharmacol 9:716-726.
http://link.springer.com/article/10.1007%2Fs11481-014-9564-y

Cai Y, Sugimoto C, Liu DX, Midkiff CC, Alvarez X, Lackner AA, Kim W-K, Didier ES, Kuroda MJ (2015) Increased monocyte turnover is associated with interstitial macrophage accumulation and pulmonary tissue damage in SIV-infected rhesus macaques. J Leukoc Biol 97:1147-1153.
http://www.jleukbio.org/content/97/6/1147.long

Kim W-K, McGary CM, Holder GE, Filipowicz AR, Kim MM, Beydoun HA, Cai Y, Liu X, Sugimoto C, Kuroda MJ (2015) Increased expression of CD169 on blood monocytes and its regulation by virus and CD8 T cells in macaque models of HIV infection and AIDS. AIDS Res Hum Retroviruses 31:696-706.
http://online.liebertpub.com/doi/10.1089/aid.2015.0003

Sugimoto C, Hasegawa A, Saito Y, Fukuyo Y, Chiu KB, Cai Y, Breed MW, Mori K, Roy CJ, Lackner AA, Kim W-K, Didier ES, Kuroda MJ (2015) Differentiation kinetics of blood monocytes and dendritic cells in macaques: insights to understanding human myeloid cell development. J Immunol 195:1774-1781.
http://www.jimmunol.org/content/195/4/1774.long

He Z, Allers C, Sugimoto C, Ahmed N, Fujioka H, **Kim W-K**, Didier ES, Kuroda MJ (2018) Rapid Turnover and High Production Rate of Myeloid Cells in Adult Rhesus Macaques with Compensations during Aging. J Immunol 200:4059-4067. http://www.jimmunol.org/content/200/12/4059.long

Filipowicz AR, McGary CM, Holder GE, Lindgren AA, Johnson EM, Sugimoto C, Kuroda MJ, **Kim W-K** (2016) Proliferation of Perivascular Macrophages Contributes to the Development of Encephalitic Lesions in HIV-Infected Humans and in SIV-Infected Macaques. Sci. Rep. 6, 32900; doi: 10.1038/srep32900. https://www.nature.com/articles/srep32900

Cai Y, Sugimoto C, Arainga M, Midkiff CC, Liu DX, Alvarez X, Lackner AA, **Kim W-K**, Didier ES, Kuroda MJ (2015) Preferential destruction of interstitial macrophages over alveolar macrophages as a cause of pulmonary disease in simian immunodeficiency virus-infected rhesus macaques. J Immunol 195:4884-4891. http://www.jimmunol.org/content/195/10/4884.long