Cardiac Dysfunction Associated with Myocardial Viral Load in SIV-infected Macaques Can be Prevented by CCR5 inhibitor Maraviroc

Kathleen Kelly1,2, Carlo G. Tocchetti4, Alexey Lyashkov1, Patrick M. Tarwater5, Jami M. Karper1, Djahida Bedja1, Suzanne E. Queen1, Robert J. Adams1, David R. Graham1,4, Nazareno Paolocci4, and Joseph L. Mankowski1,2,3

1Department of Molecular and Comparative Pathobiology, 2Department of Pathology, 3Department of Neurology, 4Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, 5Division of Biostatistics and Epidemiology, Paul L. Foster School of Medicine

SIV-infected rhesus macaques develop echocardiographic abnormalities closely resembling cardiac dysfunction in HIV infected patients that is significantly correlated with myocardial viral load. In view of this association, we sought to define the molecular mechanism underlying HIV/SIV cardiac dysfunction, focusing on the role of chemokine receptor 5 (CCR5), a receptor expressed on leukocytes that serves as an important receptor mediating viral infection. Productive infection of cardiomyocytes by HIV has not been demonstrated, but cardiomyocytes may express CCR5; as the activation of signaling subsequent to interaction between chemokine receptor and HIV/SIV envelope glycoprotein gp120 or cognate chemokines presents a mechanism mediating viral damage in the absence of productive infection, CCR5 is an attractive target for further characterization in the heart. While CCR5 mRNA expression has been reported in the failing myocardium, the receptor has not previously been reported on cardiomyocytes. In our studies, we established that isolated rhesus cardiomyocytes express CCR5 (by immunostaining) and that cognate chemokines of CCR5 alter their contractility in a CCR5 dependant manner. To determine the role of CCR5 in the development and progression of SIV cardiac dysfunction, pre-infection mitral inflow and tissue Doppler echocardiography was performed in SIV infected macaques treated with Maraviroc (MVC), a small molecule inhibitor of CCR5, and outcomes compared to untreated SIV infected macaques. MVC treated macaques had lower myocardial viral loads and developed minimal echocardiographic changes from baseline to terminal timepoints with preservation of MV DT, E/A, and myoRT and improved ejection fraction compared to untreated macaques. These finding suggest the cardioprotective effects of adjunctive MVC therapy may improve treatment of cardiac disorders in HIV-infected individuals.