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Q1 Faculty Information:

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Q2 Type of Research?

Basic Science Research

Q3 Please describe your research interests:

Dendritic cells (DCs) biology and immunotherapeutic potential against human chronic viral infections (HTLV-1, HIV-1, and HIV/HCV co-infection) as well as neuroinflammatory diseases associated with retroviral infection (HAM/TSP), HAND) or inflammation (multiple sclerosis).

Q4 Please provide a brief description of research opportunity/project(s):

1) Title of project(s):	**Restoring anti-viral immunity during HTLV-associated cancer and neuroinflammatory disease.**

Brief Description:	**Worldwide, 20 million people are infected with HTLV-1, a majority of which remain asymptomatic carriers (ACs), while a few develop ATL or HAM/TSP with no effective treatment or vaccine for either disease state. The exact mechanism(s) of disease pathophysiology remain unresolved with a big question of high proviral load in HAM/TSP patients despite vigorous cellular immune response (primarily directed towards viral transactivator protein Tax). Our initial studies implicated programmed death (PD)-1 receptor and its ligand, PD-L1 as potential underlying factors for observed immune cells' dysfunctions leading to viral persistence and disease progression, primarily in HAM/TSP patients. Thus far, PD-1 and CTLA-4 pathways have been extensively studied; and blocking antibodies against these have shown clinical benefit in the setting of cancer. However, the clinical applicability of PD-1 and CTLA-4 remains to be tested with respect to human chronic viral infections as well as neuroinflammatory diseases, such as HAM/TSP, NeuroAIDS, etc. Interestingly, HTLV-1 provides a good model for both and thus, we find it significant to investigate the role of key inhibitory receptors/ligands in HTLV-1 infection and test their combined blockade as potential immunotherapeutic strategy to restore immune cell functions in HAM/TSP patients. While this approach should help in restoring functions of pre-existing antiviral immunity in patients, activating new CTLs to mimic polyclonal CD8 T-cell response found in ACs will be the key for a successful immunotherapeutic intervention of HTLV-associated diseases. Therefore, this project will systematically identify T-cell epitopes presented by HTLV-1-infected cells that define protective immunity in silent carriers alongside blocking co-inhibitory pathways in order to fully restore T-cell functions in chronically infected patients.**
Time commitment:	**Student will be associated with a senior researcher in the laboratory who will oversee his/her full time activity. PI will meet with both of them routinely and be available as needed.**
Specific Requirements:	**While not needed, prior laboratory work experience and basic understanding of Biology/Immunology will be beneficial**
Funded or unfunded (yes or no):	**Funded**
Brief Description:	**Dendritic cells (DCs) are the most potent antigen presenting cells and an important myeloid cell components with proven role in the pathogenesis of Multiple Sclerosis (MS). This is by their ability to enter into the central nervous system (CNS) at a much greater**

extent compared to any other immune cell types as was demonstrated by our previous in vivo imaging studies. Lectins and integrins are the two major groups of receptors on myeloid cells that are involved in cell trafficking. Thus far, transmigration of DCs across the inflamed blood brain barrier (BBB), and the importance of lectins in the adhesion of DCs to BBB have been least explored. During preliminary studies, we showed that accumulation of DCs within the CNS corresponds to the severity of inflammation through in-vivo near infrared imaging of EAE (experimental autoimmune encephalomyelitis) mice. The demyelinating lesions in these mice showed increased presence of chemokine CCL2 with DCs transmigrating into the perivascular spaces, which was found to be mediated by ERK 1/2 phosphorylation (Sagar et al., Journal of Neuroinflammation, 2012). We then studied the importance of surface C-type lectin receptor (CLRs) on DCs for their role in adhesion and transmigration across the BBB. We were able to identify a specific type of CLR, CLEC12A on the surface of DCs, which is an immunoreceptor tyrosine – based inhibitory motif (ITIM) that recruits Src homology region 2 domain-containing phosphatase (SHP) on activation. SHP1/2 phosphorylation was found to facilitate polymerization of actin in DCs thus helping in transmigration across BBB. Most importantly, we showed that by administering blocking antibody to CLEC12A, we could reduce the disease severity and restore body weight as well as overall health of mice in both progressive and relapsing models of MS. The observations correlated with reduction in demyelination and reduced infiltration of exclusively myeloid cells into the CNS. Moreover, there was accumulation of DCs in the peripheral circulation and in spleen. Based on these findings, we hypothesize that inhibiting the adhesion and transmigration of DCs across the inflamed BBB by administering blocking antibodies to CLEC12A could be a novel therapeutic approach for MS. For this we need to characterize the various ligands of CLEC12A and the mechanism of action of anit-CLEC12 antibody before proceeding with the Phase I clinical trial with this new target. CLRs are glycan-binding receptors present on the surface of DCs. The amino acid triplet sequence in the carbohydrate recognition domain determines the glycan-binding specificity of these receptors. Even though, CLEC12A shares many features of the CLRs, it lacks calcium binding residues and homologous with the C-type lectin-like receptors on Natural Killer cells. Hence we would like to identify those ligands and determine its glycosylation. Following this we would like to find out

	the mechanism of action of the blocking antibody to CLEC12A. Theoretically, a blocking antibody could either neutralize the receptor after binding to it or activate the receptor upon binding and internalization. We believe that, the mechanism of anti-CLEC12A antibody is by activating the receptor upon binding and internalization.
Time commitment:	**Student will be associated with a senior researcher in the laboratory who will oversee his/her full time activity. PI will meet with both of them routinely and be available as needed.**
Specific Requirements:	**While not needed, prior laboratory work experience and basic understanding of Biology/Immunology will be beneficial**
Funded or unfunded (yes or no);	**To be funded**

Q5 Please indicate the specific level of experience required, if applicable:	**Open to all medical students**