Reversing HIV-induced B cell dysfunction with bisphosphonates

Due in large measure to the success of combination antiretroviral therapy (ART), HIV-infected individuals are living longer than ever before, although life expectancies for HIV-infected individuals remain lower than in the general population. It is estimated that over half of the HIV/AIDS population in the US is now over 50 years of age. This increased longevity is accompanied by increased prevalence and earlier incidence of non-AIDS age-related comorbidities including neurocognitive, renal, hepatic, cardiovascular and skeletal disease. Enduring chronic immune activation that drives inflammation, even in the context of otherwise successful ART contributes significantly to the development of these comorbidities. Preventing and/or mitigating HIV/ART-related comorbidities is increasingly becoming a major challenge in HIV disease management. The overarching goal of this study is to investigate a novel therapeutic approach to ameliorate or reverse B cell dysfunction driving inflammation in patients with HIV infection on chronic ART. HIV infection leads to severe phenotypic and functional impairment of the B cell compartment, which is not effectively reversed by ART and manifests as: (i) expansion of abnormal B cell subsets including immature and pro-inflammatory memory B cells; (ii) hyper-activation characterized by polyclonal B cell activation with increased expression of pro-inflammatory cytokines including IL-6, IFN-γ, TNF-α and RANKL; and (iii) increased autoantibody production (including anti-nuclear antibodies (ANA)). These B cell secreted inflammatory cytokines promote a systemic inflammatory environment that is further augmented by autoantibody driven adaptive immune responses that together contribute significantly to multiple end organ damage. Consequently, pharmacological amelioration of these B cell pathologies would be an optimal strategy to alleviate systemic inflammation and downstream end organ damage. The goal of this project is thus to demonstrate the utility of a novel therapeutic agent for reversing B cell dysfunction in human subjects with HIV-infection on ART. Bisphosphonates, such as Zoledronic Acid (ZA) are small-molecule inhibitors of bone resorption and are the mainstay of fracture prevention in osteoporotic conditions. Importantly, studies in bisphosphonate-treated mice unexpectedly found increased generalized antigen (Ag)-specific humoral immune responses, suggesting an enhancement of B cell functions. Bisphosphonates may thus be attractive agents for mitigating B cell dysfunction, attenuating inflammation and ameliorating end-organ complications in HIV-infection. Interestingly, a few studies have demonstrated that BPs are able to significantly decrease the titers of pro-inflammatory markers including C-reactive protein, IL-6, IL-1 and TNF-α, suggesting an effective anti-inflammatory effect of BPs in rheumatoid arthritis. We hypothesize that ZA can ameliorate or reverse HIV-induced B cell dysfunction, and as such the global inflammatory environment that leads to end-organ damage. Moderating and/or reversing this B cell dysfunction will mitigate or prevent organ damage in the aging HIV/AIDS population.