OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Genetic Syndromes & Gene Therapy

November 19-21, 2012 Hilton San Antonio Airport, USA

Evaluating immune profile of next generation AAV viral vectors

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Latest research shows improved generations of AAV vectors show promise for long-term treatment of hemophilia B, while vector capsid immunity has become a hurdle for maintaining hFIX expression in human trials. Our work assessed immune responses to variations in the AAV capsid and vector genome. A self complimentary vector (scAAV) genome rapidly increased innate signaling in the liver. Infection with either scAAV2 or scAAV8 vector increased liver gene expression of: TNF-α, MCP-1, IP-10, IFN-α/β, IL-6, IL-12α, MIP-1, RANTES from a range 2 to 4 fold over a standard AAV vector genome (ssAAV) 2 hrs after injection. Additionally, elevated protein levels (IL-6, MCP-1, TNF-α) and proinflammatory infiltration in liver tissue was observed. Furthermore, the scAAV vector increased capsid specific adaptive responses. Next, the potential of AAV2-(Y-F) capsid mutants to bypass $CD8^+$ T cell responses due to decreased vector shuttling to proteasome was tested. In vitro data demonstrated that AAV2-(Y-F) vector has reduced capsid presentation on MHC-I molecules and suppresses cytotoxicity of AAV infected liver cells when co-cultured with capsid specific $CD8^+$ T-cells (cap-$CD8^+$). Adoptive transfer of cap-$CD8^+$ cells in RAG-/- deficient mice following liver infusion of an AAV2-hFIX vectors showed a 3 fold increase in liver transaminitis and 4 fold decease in hFIX transgene expression; these results were not observed from the AAV2 (Y-F) vector. These data demonstrate that the use of AAV2-(Y-F) vectors have capacity to bypass immune responses and increase transgene expression while the use of scAAV2 vectors, especially at higher doses, may illicit inhibitory immune responses.

Biography

Ashley T Martino, PhD served in the US Air Force; 1996 – 2000. He received his BS from Cal State Northridge in 2002 and PhD from University of Florida in 2007; mentored by Terence Flotte, MD. Post doctoral work was done at University of Florida; directed by Roland Herzog, PhD, 2008-2011. He was recently appointed Assistant Professor at St John's University within the department of Pharmaceutical Sciences. His research involves AAV gene therapy for liver and lung treatments and extends into immune responses to vectors and transgene products. He has 7 first author publications and has contributed too many others.

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