Session Hematologic & Immunologic Diseases I

Add To Itinerary

187 - Prevalence of Neutralizing Antibodies Targeting Two Novel Clade F AAV in Human Sera

May 10, 2017, 5:30 - 7:30 PM | Exhibit Hall A & B South

Keywords
Vector Immunology/Host Responses,AAV Vectors,Pharmacology/Toxicology,Neutralizing Antibodies

Authors
Jeff L. Ellsworth, Hillard Rubin, Albert Seymour, Michael O'Callaghan

Homology Medicines, Inc., Bedford, MA

Disclosures
J.L. Ellsworth: 1; Commercial Interest ***i.e. Company X***; Homology Medicines, Inc.. 1; What was received? ***i.e. Honorarium***; salary, stock options. 1; For what role? ***i.e. Speaker***; Employment.

Abstract
A novel group of adeno-associated viruses have been cloned from human CD34+ hematopoietic stem cells (AAVHSC). Capsid sequence analysis has shown that these vectors map to AAV Clade F of which AAV9 is the prototypic member. Since Clade F viruses are emerging as key vectors for gene therapy, it is imperative to understand the factors that regulate their pharmacokinetics and bio-distribution in the intact animal. One such factor is the presence of neutralizing antibodies (Nab) within the blood that may opsonize the vectors and block AAV-mediated cellular transduction. Depending on the dose of AAV administered, even low titers of Nab can reduce AAV-mediated gene delivery. In the present study, the human prevalence and titers of Nab that block the transduction of cells by AAVHSC15 and AAVHSC17 were assessed in a representative human population and compared to those of AAV9. Nab levels were measured in a set of 100 unique mixed-race (34:33:33, Black:Caucasian:Hispanic) and sex (49% female, 51% male) human sera collected within the United States. All sera were heat-inactivated by incubation prior to assay. Two cellular assays at two separate laboratories were used to measure Nab: 56 unique sera were tested in HuH7 cells and 44 unique sera were tested in 2V6.11 cells with vectors packaging either a chicken beta actin (CBA)-promotered ***LacZ*** or a Firefly Luciferase transgene, respectively. A ten-sample overlap of sera was also included to test concordance between the two laboratories. Nab prevalence was assessed using 1/16-1/64 dilutions of each serum sample whereas Nab titers of positive samples were assessed using a two-fold dilution series (1/5 to 1/1280) of each sera. Concordance of Nab levels measured in the two cell assays was 100%. For AAVHSC15, AAVHSC17, and AAV9, 24/100 (24%) , 21/100 (21%), and 17/100 (17%), respectively, of all sera tested were seropositive for Nab. Over a wide range of dilutions, each Nab positive sera (24 in total) blocked, by cross-reactivity, the transduction of each AAV with titers for 50% neutralization falling equally into four groups: less than or equal to 1/25, 1/50, and 1/100, and greater than or equal to 1/150 for all three vectors. In the latter group, which represented 6% of Nab positive sera, Nab titers of 1/150 (lowest) to 1/340 (highest) were observed indicating that the majority of Nab positive sera were of low titer. These data demonstrate that approximately 80% of sera in the human population tested were seronegative for Nab to Clade F AAV, enabling the use of AAVHSC as therapeutic vectors for human diseases.