Development and Evaluation of a Novel Gene Delivery Vehicle Composed of Adenovirus Serotype 35

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Adenovirus (Ad) vectors, which are commonly composed of the subgroup C Ad serotype 5 (Ad5), are highly promising; however, Ad5 vectors do not efficiently transduce cells lacking the primary receptor, coxsackievirus-adenovirus receptor (CAR). In addition, more than 50 % of adults are seropositive for Ad5. On the other hand, Ad serotype 35 (Ad35), which belongs to subgroup B, infects various types of cells, including CAR-negative cells. Anti-Ad5 antibodies do not inhibit Ad35 infection. Furthermore, the seroprevalence of Ad35 is significantly lower than that of Ad5 in adults. Therefore, we developed a novel Ad vector, which is fully composed of Ad35.

1) *Development of Ad35 vectors and their in vitro transduction efficiencies*; Ad35 vectors exhibited a broad tropism, including CAR-negative cells. In addition, anti-Ad5 serum did not inhibit Ad35 vector-mediated transduction.
2) *Evaluation of Ad35 vectors using genetically modified animals and nonhuman primates*; CD46, which is a receptor for Ad35, is ubiquitously expressed in primates, but expression of rodent CD46 is limited to the testis. Therefore, we evaluated the transduction properties of Ad35 vectors using CD46-transgenic mice and nonhuman primates, which express CD46 in a pattern similar to humans.
3) *Elucidation of mechanism of Ad35 vector-mediated transduction*; we found that Ad35 vectors bind to short consensus repeats 1 and 2 in human CD46, and that the interaction between integrins and the penton base Arg-Gly-Asp (RGD) motif is crucial for infection with Ad35 vectors.
4) *Ad35 vector-mediated transduction in hematopoietic stem cells*; Ad35 vectors efficiently transduced human bone marrow-derived $CD34^+$ cells, which is a fraction containing human hematopoietic stem cells.