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Adeno-associated virus (AAV) for immuno-gene therapy

AAV has proven itself to be an outstanding vector, well used in liver, in brain, in eye, in muscle, and in cardiovascular gene delivery. However this has not been the case for immuno-gene therapy with only a few laboratories using AAV. In fact, the AAV research community as a whole is fixated on the opposite trajectory, how the immune system recognizes and responds to AAV, itself, and how this response may limit AAV-transgene delivery. However, there are multiple reasons why the author considers AAV to be an outstanding vector for immuno-gene therapy. First, it was shown in published studies that AAV (AAV2 have been used) transduces both human dendritic cell (DC) precursors and T cells at high levels (>80% at MOI 1000). Second, it was shown by vector-chromosome junction PCR amplification/Southern blot analysis that AAV chromosomally integrates at significant levels in both primary human DC precursors (monocytes, Mo) and in T cells. Consistent with this, AAV vector DNA has been shown surviving out to 6-7 weeks in ex vivo treated T cells which were then injected back into rhesus monkeys. Third, transduction of Mo/DC by AAV results in the up-regulation of multiple important DC markers, including CD80, CD86, CD83, HLA-DR, and others, and is consistent with superior antigen presentation and T cell stimulation, by these AAV-transduced DC. Fourth, the transduction of either antigen genes into human DC, or Th1 response cytokine genes into human DC and T cells results in improved, robust cytotoxic T lymphocyte (CTL). Not only should AAV-based immuno-gene therapy be useful in the development of clinical protocols against cancer, but AAV gene delivery is a novel approach for studying the basic functions of cytokines. Most cytokines have a short half-life (eg. IL-2 $t_{1/2}$ = 10 minutes) and AAV transduction of cytokine genes can circumvent this issue. As an example, through this methodology we recently uncovered an intracrine activity for IL-12 in human DC. AAV transduction of antigen genes into DC is also highly useful as HLA Class I molecules, on which antigenic epitopes are displayed, have a half-life of about 1 day or less. While AAV2 has proven effective in transducing human DC and T cells, the many new AAV types and capsid modifications that are now available can only serve to improve AAV-based human immuno-gene therapy even further. In addition to all that mentioned, AAV has an outstanding track record for safety and long term gene delivery. Taken together, all these proven attributes indicate that AAV's future in DC and T cell gene delivery is bright and that the use AAV for immuno-gene therapy needs to be promoted, increased.

Biography

Paul L Hermonat completed his PhD at the University of Florida in 1984, and Postdoctoral studies at the National Institutes of Health. He is Research Career Scientist at the Central Arkansas Veterans Healthcare System, and a Professor of Internal Medicine and OB/GYN at the University of Arkansas for Medical Sciences. He mapped mutationally AAV's genes, determined their functions, was the first to generate recombinant adeno-associated virus (AAV/NeoR) and to transfer genes into cells via this method, and has over 140 manuscripts published. From his first study on AAV-based gene therapy in 1984 there are now over 2,400 papers on the topic. He now continues studies on AAV genetics and helper genes, and on gene therapy for cardiovascular disease and cancer.

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