Re-dosing AAV gene therapy vectors – the elephant in the room

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The immunogenicity of adeno-associated virus (AAV) vectors is a key challenge for gene therapy, particularly for systemic applications. AAV vectors are non-replicating and consequently transgene expression is expected to wane over time, particularly in pediatric patients. It would be desirable to be able to readminister AAV vectors in pediatric patients and to boost expression in patients who have inadequate transgene expression. However vector re-administration is limited by the formation of neutralizing antibodies to AAV, which mediate vector clearance and inhibit efficacy. Additionally, CD8 immunity against the AAV capsid can induce liver inflammation resulting in loss of transgene expression. We have recently developed a novel strategy to induce immune tolerance to protein biotherapeutics based on the co-administration of biodegradable synthetic vaccine particles containing rapamycin (SVP-Rapamycin; Kishimoto et al., Nature Nanotechnology, 2016, Melani et al, Nature Communication, 2018). SVP-Rapamycin has been shown to mitigate the formation of anti-drug antibodies (ADAs) against pegylated uricase enzyme in patients with hyperuricemia in an ongoing Phase 2 clinical trial. Here we demonstrate that SVP-Rapamycin added on to AAV8-base gene therapy inhibits the formation of anti-AAV8 antibodies and enables successful re-dosing of AAV8 resulting in therapeutic levels of Factor IX protein directed by a second AAV injection in both mice and nonhuman primates. The effect of SVP-Rapamycin was antigen-specific, as treated mice showed normal immune responses to subsequent challenge with other antigens. In addition, co-administration of AAV with SVP-Rapamycin effectively inhibited T-cell responses to AAV. In conclusion, SVP administration at the time of in vivo gene transfer is a promising approach to enable effective redosing of AAV vectors.

Biography

Kishimoto is the Chief Scientific Officer of Selecta Biosciences, a biotechnology company developing synthetic vaccines based on a novel self-assembling nanoparticle technology. Prior to joining Selecta, Kishimoto was Vice President of Research at Momenta Pharmaceuticals where he led multidisciplinary teams in inflammation, oncology, and cardiovascular disease. Previously he was Senior Director of Inflammation Research at Millennium Pharmaceuticals, where he provided the scientific leadership for four programs in clinical development, and an Associate Director of Immunology at Boehringer Ingelheim. Kishimoto received his doctoral degree in Immunology from Harvard University and his post-doctoral training at Stanford University.

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