Rational Design Capsid Engineering for AAV Functionalization

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Adeno-associated virus (AAV) has yet to reach its full potential as a gene vector due to several critical challenges such as its limited packaging capacity, immunogenicity, restricted tropism, low tissue specificity, not to mention its low resistance towards neutralizing antibodies from hosts. In addressing these challenges, capsid engineering play a crucial role in the optimization of AAV. Herein, we attempted to diversify AAV's functionality through rational design capsid engineering. In this study, we exposed cysteine residues onto AAV capsid surface through site-directed mutagenesis, where the cysteine residues can be utilized as tethers for additional functional biomolecules. We demonstrated that non-native cysteine exposure on AAV capsid surface through mutagenesis did have its impact on AAV's viral assembly and infectivity. Furthermore, we also successfully linked cysteine-specific oligonucleotide onto mutant AAV, a proof of concept that such a mechanism allows for biomolecular tethering onto AAV capsid surface, ultimately granting AAVs with further functionalities.