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Chemically Modified AAV Capsids for Targeted Pancreatic Gene Delivery

Researchers from Stanford developed chemically modified adeno-associated virus (AAV) capsids that enable selective gene delivery to either exocrine or endocrine pancreatic cells through unnatural amino acid incorporation and peptide conjugation.

Gene therapy is a promising therapeutic modality for treatment of pancreatic disorders, including Type 1 and Type 2 diabetes. However, gene transfer into specific pancreatic cell populations can be limiting. Traditional AAV vectors lack the specificity needed to distinguish between exocrine and endocrine compartments of the pancreas, leading to potential off-target effects. Administration of conventional AAVs can result in broad tissue distribution, limiting therapeutic efficacy, and potentially causing unwanted immune responses or toxicity in non-target cells. There is a critical need for AAV vectors that can selectively target pancreatic cell types in vivo while minimizing off-target transduction.

To address these limitations, the inventors developed a chemically modified AAV platform. The technology utilizes site-specific insertion of unnatural amino, enabling click chemistry conjugation exclusively at the capsid position. This modification serves a dual purpose: it reduces non-specific AAV transduction of cells in general while allowing precise attachment of targeting peptides. By conjugating specific peptides to the modified capsid, the AAV selectively targets exocrine pancreatic cells containing the respective receptors. Alternatively, conjugating a endocrine pancreatic cell-specific peptide directs the AAV to those cells specifically. This approach provides enhanced specificity for pancreatic gene delivery, limiting transduction to cells expressing the appropriate receptor while avoiding off-target effects in other tissues.

Applications

- Gene therapy for Type 1 and Type 2 diabetes
- Treatment of genetic disorders of the pancreas
- Targeted delivery of therapeutic genes

Advantages

- Selective targeting of either exocrine or endocrine pancreas
- Versatile platform adaptable to different targeting ligands
- Reduced off-target transduction in non-pancreatic tissues

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