Docket #: S17-319

Pancreatic islet cell-specific rAAV vectors for more efficient gene therapy or research

Researchers in Prof. Mark Kay's laboratory have developed variant AAV (adeno-associated virus) vectors with specificity and high transduction efficiency for pancreatic alpha- and beta- islet cells. AAV vectors are recognized as the gene transfer vectors of choice for therapeutic application because they have the best safety and efficacy profile for the delivery of genes *in vivo*. However, they require high levels of transduction to be used in pancreatic cells (including the insulin-producing cells associated with diabetes). Furthermore, the vectors need to target the diseased cells specifically and efficiently.

To address this problem, the inventors employed directed molecular evolution to generate and identify rAAV vectors with enhanced ability to transduce human islet cells. These AAV vectors with superior human pancreas transduction could require lower doses and fewer injections to achieve therapeutic relevance. They could be used for basic research into pancreatic cells function or in gene therapy to treat endocrine disorders, particularly type 1 or 2 diabetes.

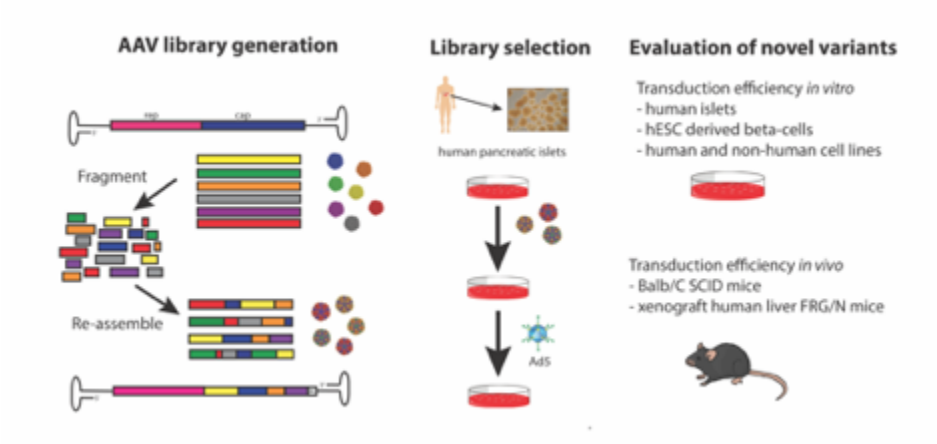

Figure description - Graphical Abstract

Stage of Research

The inventors have performed directed evolution and identified several candidate variant AAV capsid polypeptides with relative transduction efficiencies 10 times more robust than previous gold standard (LK03). The inventors demonstrated the performance of these candidates *in vitro* (human, mouse, monkey, rat and hamster cells, including primary cells), *in vivo* (mouse liver transduction) and *ex vivo* (human islet cells). Another laboratory that used the AAV variant materials transduced over 90% of beta and 99% of alpha-cells using intact human islets in culture.

Applications

- **Gene therapy** - treatment of endocrine disorders, specifically diabetes type 1 and 2
- **Research** - basic studies of pancreatic function, particularly in relation to diabetes

Advantages

- **High gene transfer:**
  - relative transduction efficiencies to islet cells were 10 times more robust than previous gold standard vectors
  - for gene therapy applications, superior transduction efficiency could result in lower doses and fewer injections for patients
- **Cell-type specific transduction** for alpha- or beta- islet cells specific

Publications

- Pekrun, K., De Alencastro, G., Luo, Q. J., Liu, J., Kim, Y., Nygaard, S., Galivo, F., Zhang, F., Song, R., Tiffany, M. R., Xu, J., Hebrok, M., Grompe, M., Kay, M. Using a barcoded AAV capsid library to select for clinically relevant gene therapy vectors. JCI Insight. 2019;4(22).

Patents

- Published Application: 20200024616
- Published Application: WO2019191701
- Published Application: 20230304039
- Issued: 11,608,510 (USA)

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