**Targeted AAV delivery to improve beta-cell therapies**

***Background/Aims***: Beta-cell transplantation is a promising therapy for diabetes, but islet grafts suffer significant beta-cell death post-transplant, often necessitating multiple donors to attain sufficient beta-cell mass. Inducing beta-cell proliferation is a potential solution, however in humans, this is extremely low in adulthood (<0.1%).

Recombinant adeno-associated viral vectors (rAAVs) offer a low-immunogenic, long-lasting gene-delivery method. However, achieving islet-specific targeting has been challenging. Here, we aimed to develop beta-cell targeting rAAVs to promote beta-cell proliferation.

***Methods****:* To test beta-cell specificity, Ai9 reporter-mice were injected rAAV expressing Cre recombinase. In Ai9 mice, Cre deletes a floxed stop sequence, enabling TdTomato expression in transduced cells. Pancreases were imaged in vivo and ex vivo one-week post-injection.

Following confirmation of islet specificity, C57Bl/6 mice were injected with rAAVs overexpressing a candidate gene to promote beta-cell proliferation. Mice were sacrificed 1 week after injection.

***Results***: Intraperitoneal rAAV injection led to strong tdTomato fluorescence in beta-cells in Ai9 mice. Isolated islets showed red fluorescence, indicating successful transduction. Overt tdTomato expression was not seen in other tissues, and particularly, not in the liver.

Overexpression of our gene of interest in C57BL/6J mice markedly increased beta-cell proliferation, evidenced by 1-3 dual Ki67+ insulin-positive cells per islet, compared to 1 per 3-10 islets in controls.

***Conclusions:*** We have developed rAAV which efficiently target beta-cells after an intraperitoneal injection. Our candidate gene induces strong beta-cell proliferation at 1 week. Our results suggest rAAVs may be used to enhance beta-cell mass, making them an attractive tool for improving beta-cell function and glucose tolerance in diabetes.