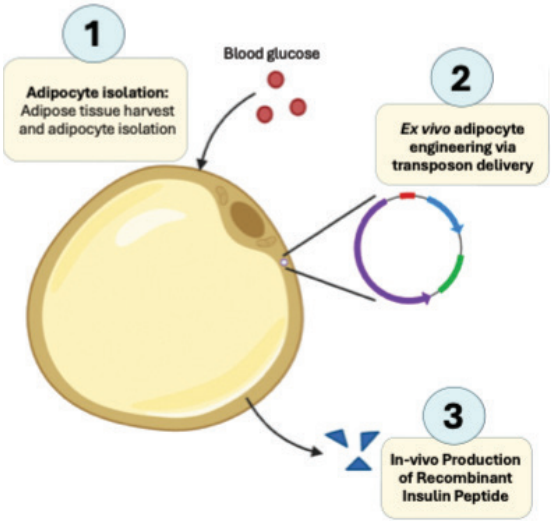

Figure 1.

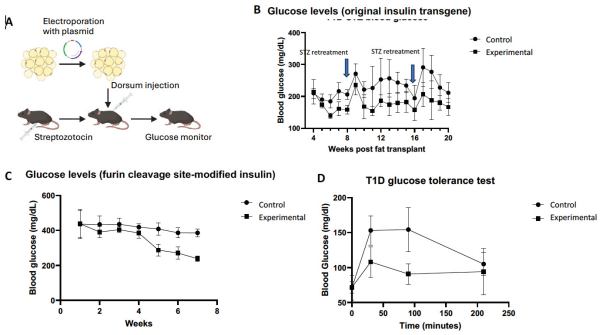

Figure 2.

Closed-loop Cell Therapy to Restore Normoglycemia in Types 1 Diabetes

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Type 1 diabetes (T1D) affects over 2 million individuals in the US and is caused by autoimmune destruction of pancreatic islet cells. This leads to chronic cardiovascular, cerebrovascular, ophthalmologic, and renal complications that severely limit quality of life and reduce life expectancy. Current treatments rely on exogenous insulin delivery using subcutaneous injections or infusion pumps; however, these strategies are marred by missed doses, pump malfunction, and loss of access to insulin. Strategies to enable long-term endogenous insulin production have focused on restoring pancreatic cells; however, this approach is complicated by recurrent autoimmune destruction of the reconstituted cells. A cell therapy that restores closed-loop insulin production while evading autoimmune destruction would be transformative to T1D, and potentially myriad other medical conditions.

Our team at the BWH has developed a point-of-care cell therapy using a patient's own fat cells (adipocytes) modified to enable glucose-responsive insulin production. Fat cells are removed and modified with a transcriptional circuit which includes a glucose-responsive promoter element and a modified insulin transgene. The modified fat cells are then directly re-implanted into the subcutaneous tissues. The procedure is designed for the clinic setting under local anesthesia or moderate sedation and takes approximately 90 minutes.

We engineered and validated a transcriptional circuit enabling glucose-responsive insulin production in a T1D mouse model. All mice received subcutaneous injections of adipocytes; treated mice received modified fat cells from same-strain mice. These mice exhibited improved glucose control, with levels dropping to ~200 mg/dL compared to ~400 mg/dL in mice receiving unmodified fat cells. Glucose tolerance testing confirmed better glycemic response within 60 minutes after glucose load. In addition, no episodes of hypoglycemia were observed, and treated mice exhibited improved weight gain, as expected with repletion of insulin therapy.

Our approach combines two innovative strategies: 1) permanent modification of adipocytes using point-of-care ex vivo genetic techniques for safe, durable gene delivery and 2) transcriptional circuits that leverage the cell's own environmental sensing to drive expression and secretion of the desired payload. Our strategy is applicable beyond T1D providing an attractive platform technology with a tangible first-use case. We are seeking strategic partners for continued T1D development in T1D and for expansion to additional indications.