

Evaluation of Cell Replacement Therapy for Type 1 Diabetes in Mice

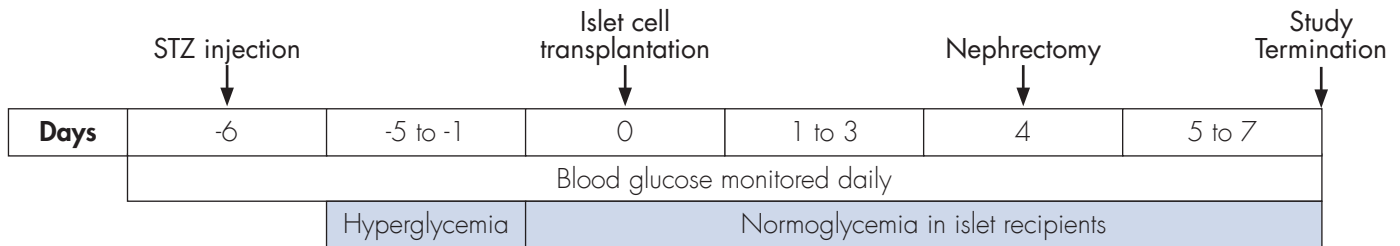
Type 1 diabetes, or insulin dependent diabetes mellitus, is characterized by the autoimmune destruction of pancreatic beta cells. As a result, patients produce inadequate amounts of or no insulin. Replacement of the insulin-producing pancreatic islet beta cells represents the ultimate treatment for type 1 diabetes. Recent advances in stem cell research underscore the urgent need for diabetic animal models that will support the engraftment of the insulin producing cells (Chen *et al.*, 2009).

The alkylating agent streptozotocin (STZ) causes pancreatic necrosis, leading to elimination of insulin production and development of hyperglycemia. Administration of STZ in mice results in a synchronous and reproducible experimental model for the end stages of type 1 diabetes. NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ mice (NSG; Stock Number 005557) are susceptible to the effects of streptozotocin and highly permissive to engraftment with human and mouse cells. STZ-treated NSG mice represent an *in vivo* model for testing cell-based therapies for type 1 diabetes (King *et al.*, 2008).

Study Design

- Adult NSG male mice are rendered diabetic by a single IP injection of STZ
- Pancreatic beta cell islets isolated from healthy C57BL/6J (Stock Number 000664) mice
- NSG mice transplanted with islets under subrenal capsule
- Nephrectomy on islet recipients
- Blood glucose monitored throughout

Experimental Timeline



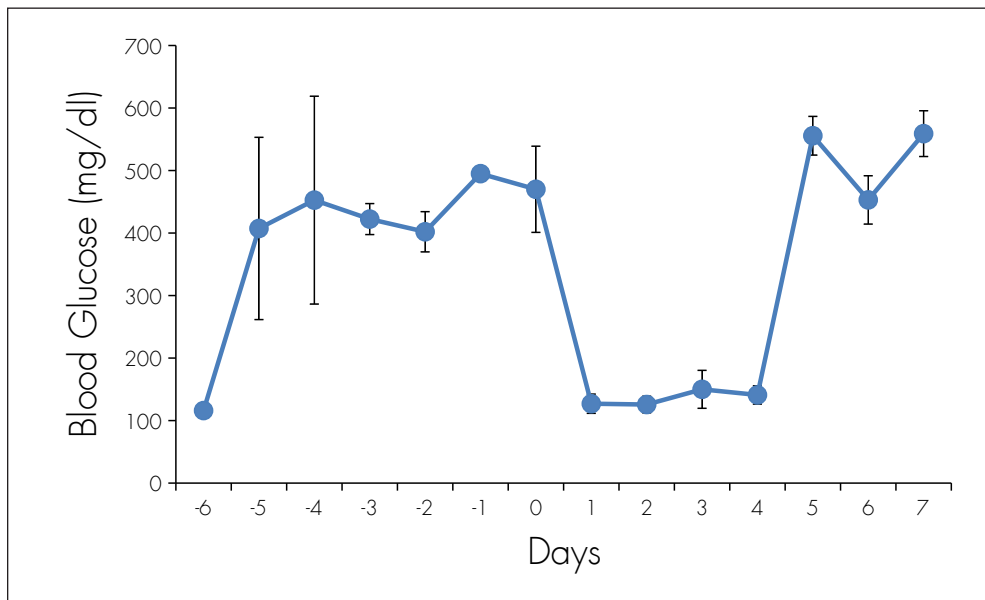
Deliverables

1. Blood (serum or plasma)
2. Histology blocks and slides
3. Written report providing the following information:
 - a. Blood glucose levels
 - b. Histological verification of subrenal beta cell engraftment by aldehyde fuchsin staining or insulin immunostaining upon request

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Representative data



NSG mice (N=3) were injected with STZ to induce hyperglycemia (Day -6). Mice received beta cells from a healthy donor (Day 1), and were later nephrectomized (Day 4). Error bars report standard deviation.

Conclusions

1. STZ administration leads to synchronous, reproducible hyperglycemia in NSG mice that mimics the end stage of type 1 diabetes.
2. Hyperglycemia can be rescued by subrenal transplants of beta cells from a healthy donor.
3. The reversion to hyperglycemia after nephrectomy demonstrates therapeutic effect of donor cells.

References

King M, *et al.* 2008. A new Hu-PBL model for the study of human islet alloreactivity based on NOD-scid mice bearing a targeted mutation in the IL-2 receptor gamma chain gene. *Clin Immunol* 126:303-314.

Chen S, *et al.* 2009. A small molecule that directs differentiation of human ESCs into the pancreatic lineage. *Nat Chem Biol* 5:258-265.

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