

I am happy to report that funding from DRC has enabled successful completion of this project. Our previous research had demonstrated the feasibility of reversing type 1 diabetes (T1D) without insulin in mouse models, through subcutaneous transplantation of embryonic brown adipose tissue (BAT). Euglycemia following BAT transplants is rapid and long-lasting, accompanied by decreased inflammation and regenerated healthy white adipose tissue (WAT).

The major goal of the current project was to establish better alternatives to embryonic tissue, practical for use in human patients. As previously described, BAT-derived stem cell lines or adult BAT transplants alone fail to reverse T1D, presumably due to the lack of growth factors abundant in embryonic tissue. We hypothesized that adding growth factors would enable transplants to survive and vascularize in the recipients' subcutaneous space as well as stimulate adipogenesis and decrease inflammation in the surrounding host tissue. Preliminary data point to insulin like growth factor 1 (IGF-1) as a possible candidate. IGF-1 is expressed more abundantly in donor embryonic BAT and in newly-formed WAT in transplant recipients than it is in the WAT of diabetic or normal controls. Plasma IGF-1 levels increase soon after transplant placement, and continue to increase in negative correlation to pro-inflammatory cytokines.

Here we tested the ability of adult BAT transplants to correct T1D aided by temporary supplementation with exogenous IGF-1 in nonobese diabetic (NOD) mice, a mouse model closely related to human T1D. Fresh BAT from healthy adult CB7BL/6 donors were transplanted in the subcutaneous space of NOD recipients. Exogenous IGF-1 was administered daily for a week following transplant, at 100 $\mu\text{g}/\text{Kg}$ SC. Adult BAT transplants with IGF-1 supplementation resulted in rapid and long-lasting reversal of T1D at a 61% success rate, in contrast with no recovery in the control groups who received adult BAT alone, IGF-1 alone, or no treatment (Figure 1). As before, the euglycemia occurred independent of insulin. Insulin was not detectable by immuno-staining in the pancreas of the transplant recipients post-mortem, in contrast to normal non-diabetic controls (Figure 2).

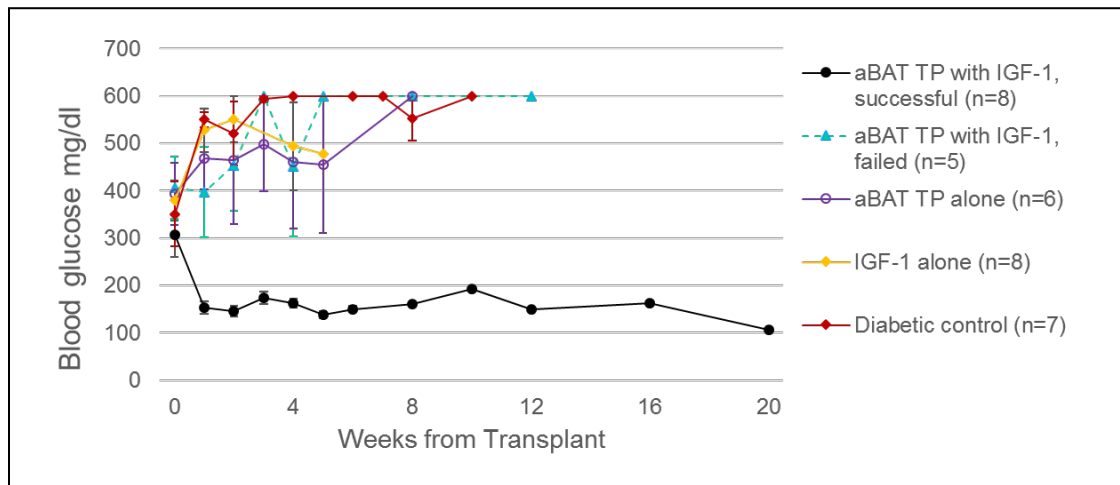


Figure 1. IGF-1 supplementation enables adult BAT transplants to correct T1D in NOD mice: Non-fasting blood glucose levels before and after adult BAT (aBAT) transplants followed by temporary supplementation with exogenous IGF-1 (100 $\mu\text{g}/\text{Kg}/\text{day}$ SC for 5-7 days), compared with different control groups. Adult BAT transplants combined with IGF-1 corrected T1D at a 61% success rate.

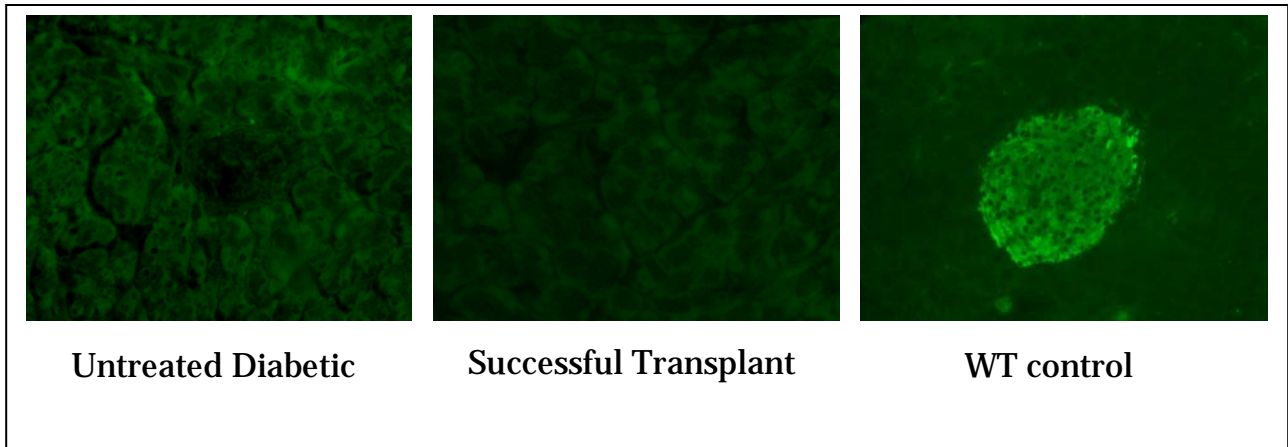


Figure 2. Effects are independent of insulin: Lack of insulin immuno-staining in the pancreata of NOD mice with or without transplants, in comparison with non-diabetic WT controls

While more time is needed to verify whether this effect is permanent and to improve success rates, these findings provide a strong foundation for eventual translation of this approach to human patients. To that end, we now seek to reproduce the results with human adipose tissue transplants, and to document the underlying mechanisms of insulin-independent glucose regulation.