Project Updates

Update on 7-16-17

Video Update

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 newlyformed 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 proinflammatory 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 µg/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).

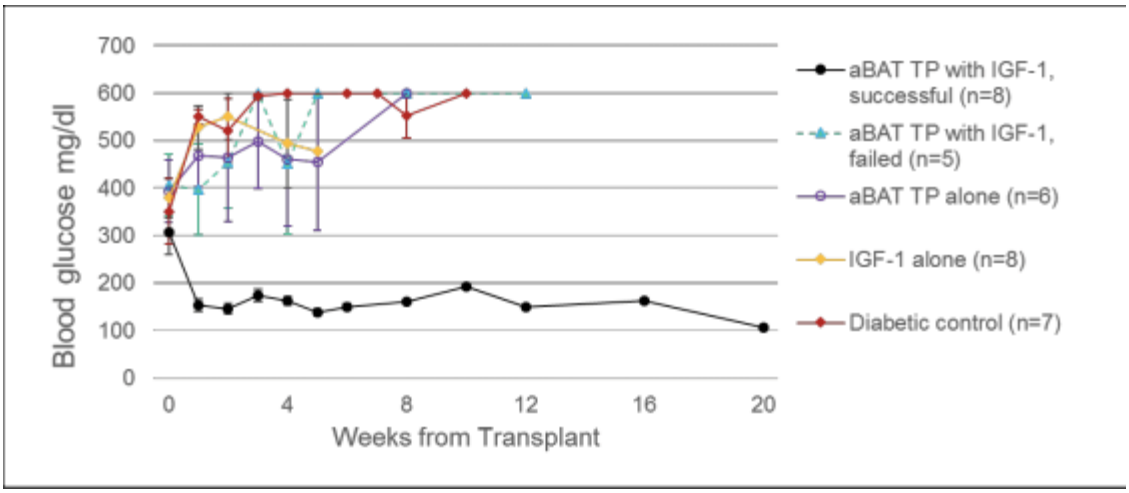

Figure 1. IGF-1 suplementation enables adult BAT transplants to correct T1D in NOD mice: *Nonfasting blood glucose levels before and after adult BAT (aBAT) transplants followed by temporary supplementation with exogenous IGF-1 (100 ug/Kg/day SC for 5-7 days), compared with different control groups. Adult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

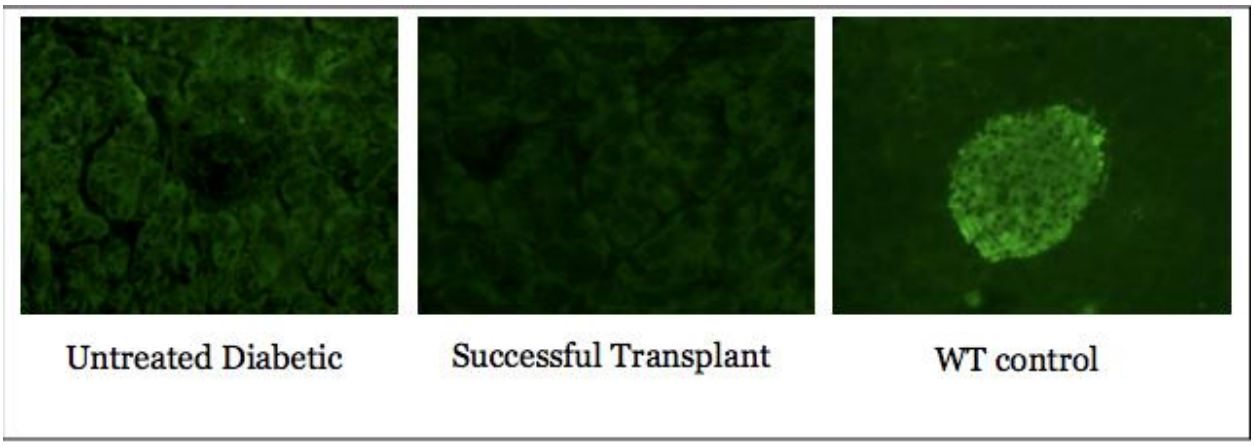

Figure 2. Effects are independent of insulin: *Lack of insulin immuno-staining in the pancreata of NOD mice with or without transplants, in comparison with non-diabetic WT controls.*

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.

Update on 11-10-16

Video Update

Update on 09-01-16

Aided by funding from DRC, we are researching suitable alternatives for embryonic tissue in order to customize the BAT-transplant technique for human patients. In the past few months, we have performed several transplants with healthy adult BAT on T1D mice, with and without temporary administration of IGF-1 (insulin-like growth factor). IGF-1 is a growth factor abundant in embryonic BAT but absent or deficient in adult adipose tissue. Preliminary results are promising, showing significant improvement of diabetes in some of the recipients who received IGF-1 supplementation. We are in the process of adjusting the dosage and duration of IGF-1 supplementation in an attempt to improve success rates. In addition, we plan to test other growth factors which may enable adult adipose tissue transplants to reverse diabetes and to investigate the molecular mechanisms underlying the insulin-independent glucose regulation produced by BAT transplants.