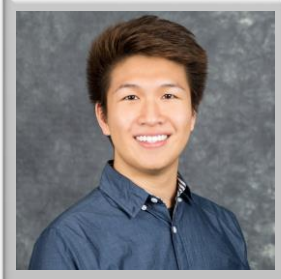

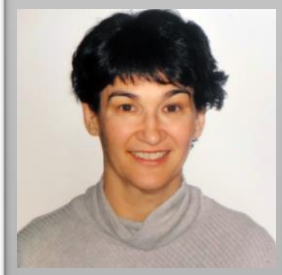

LAMININS AS A POTENTIAL ENHANCER OF BETA CELLS: PROLIFERATION AND SUBSEQUENT GENE EXPRESSION FOR THERAPEUTIC TREATMENT OF DIABETES MELLITUS

Vincent Fu (Anna Gooch, Ph.D.)

Department of Biology

Islet of Langerhans transplant is a proven treatment for autoimmune Type 1 Diabetes mellitus (T1DM), as has been demonstrated both pre-clinically in mice, rats and dogs, and clinically in humans. When administered as a treatment those affected with T1DM, these islets are potent enough to eliminate the patient's need for insulin for up to five years, albeit with the need for immunosuppression. One challenge faced by investigators, however, is the lack of abundance of islets for treatment due to donor scarcity. Islets must be harvested from the pancreata of deceased organ donors, and up to five donors are needed to cure a single patient. Thus, many researchers are currently focused on effectively proliferating the insulin-producing islet beta cells. Beta cells are difficult to culture and tend to proliferate slowly, even in very rich growth mediums. Passaging multiple times to exponentially expand these cells is one solution to the problem of low cell counts, but another issue arises: the potency of the beta cells decreases as the passage number increases.

Islet beta cells are understood to have reduced gene expression after each successive passage (i.e. using small volumes of one culture to seed multiple new cultures, thus increasing overall cell yield exponentially). This reduced gene expression is particularly observed in genes relating to T1DM, namely the genes for insulin, glucagon, and others. In past experiments, it has been determined that islet cells tend to lose both growth and treatment potency around the third or fourth passage—or in other words, around the fourth or fifth successive culture grown from harvested cells.

In this study, both technical challenges—low cell count yields and loss of potency in later passages—were addressed by studying the effect of human recombinant laminin-511 on the proliferation and gene expression of dog islet beta cell cultures. SymbioCellTech, located in the University of Utah Research Park, has developed a therapeutic that, after a single treatment, has been shown in pre-clinical testing in both immune-competent, non-obese diabetic (NOD) and non-obese diabetic, severe combined immunodeficient (NOD/SCID) mice to be a lifelong functional cure for diabetes. This treatment was developed using wild-type Islet of Langerhans cells harvested from both mouse and domestic dog pancreata.

In aggregate, the present data demonstrate that there is no statistically significant difference in the growth rate, gene expression, or potency between cultures expanded from the same dog. Disproving our hypothesis about laminins, we conclude that r-laminin-511 does not bear significant benefits or enhancing effects on the growth of SCT dog islet beta cell cultures under our growth conditions.