Project title: Mayo CRM-original iPSC-derived islet product in a retrievable, encapsulation device

Grant Number: RMM-2017-BB-05

Requester: Yasuhiro Ikeda, Ph.D., D.V.M.

Project Timeline: 5/30/2017-5/29/2018

Brief description of project:

Diabetes represents a continuing massive health care problem. Our goal was to develop Mayo CRM-original iPSC-derived islet cells for diabetes therapy. We have optimized iPSC differentiation protocols and tested the functionality of iPSC-derived islets in vitro and in vivo. We have established a new protocol, which facilitates regeneration of functional islets in vitro. Transplantation of derived islets significantly reduced blood glucose levels in diabetic mice. Our results therefore demonstrate the feasibility of regenerating functional islets from iPSC in vitro.

Where did this project take place?

Mayo Clinic Rochester (Center for Regenerative Medicine)

People impacted by project and where they are from:

Yasuhiro Ikeda, DVM, PhD (Center for Regenerative Medicine, Mayo Clinic)
Zachary T. Resch, Ph.D. (Biotrust, Center for Regenerative Medicine, Mayo Clinic)
Yaxi Zhu, PhD (Molecular Medicine, Mayo Clinic)
Jason Tonne (Molecular Medicine, Mayo Clinic)

What was the outcome of the project?

Through optimization of differentiation conditions and addition of multiple essential beta cell transcription factors, we have established a protocol, which allowed regeneration of glucose- and GLP1-responsible beta cells in vitro in 3 weeks. Further optimization led to regeneration of over 20% of insulin-positive beta-like cells from multiple iPSC lines,

including Mayo CRM iPSC lines, under serum-free conditions. Unexpectedly, however, insulin-positive beta cells from four Mayo Clinic iPSC lines secreted insulin independently of glucose concentrations. In sharp contrast, a commercially available iPSC line showed reproducible production of glucose-responsive beta cells. After transplantation into diabetic mice, BM9-derived islets, but not Mayo iPSC-derived islets, reversed diabetes. We speculate that uncontrolled insulin secretion from Mayo iPSC-derived islets might be responsible for insulin resistance and no therapeutic effects of the non-glucose-responsive islets. Nevertheless, our data clearly demonstrated the feasibility of regenerating functional islets with robust glucose- and GLP1-responsiveness from iPSCs. Based on our promising results, we are in the process of discussing with FDA for further studies required for an IND application. Our new differentiation protocol will also advance diabetes research through in vitro disease modeling and drug screening of iPSC-derived functional beta cells.

Publications and/or manuscripts submitted for publication:

"Regeneration of glucose- and GLP-1-responsive beta cells from iPSCs in vitro" by Zhu et al. is currently under review.

Responsible spending:

We used the funding to support scientists' salary and to purchase reagents to maintain and differentiate iPSCs and characterize iPSC-derived islets.