Review of Literature

Reprogramming to Beta Cells for Type 1 Diabetes

# History of reprogramming stem cells to beta cells

The main approach for differentiating stem cells into beta cells is by adherent cell culture with progressive, stepwise lineage commitment while using combinations of cues added to the culture medium. Using such an in vitro lineage differentiation approach, D’Amour et al. were the first to succeed in robust induction of definitive endoderm differentiation [[47](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B47-cells-10-00191)], with subsequent generation of pancreatic endocrine hormone-producing cells [[48](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B48-cells-10-00191)]. However, the endocrine cells that were generated were mainly polyhormonal (e.g., insulin and glucagon co-expressing cells) that are more akin to immature islet cells [[49](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B49-cells-10-00191)]. The resulting insulin-expressing cells also lacked the essential beta cell transcription factors NKX6.1 and PDX1 [[50](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B50-cells-10-00191)]. Over the ensuing years, strategies have been devised and optimized in order to generate monohormonal insulin-expressing cells that co-express NKX6.1 and PDX1 by modifying the composition and timing of growth factor and small molecule addition [[51](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B51-cells-10-00191),[52](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B52-cells-10-00191),[53](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B53-cells-10-00191)]. In 2014, Rezania et al. [[53](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B53-cells-10-00191)] and Pagliuca et al. [[52](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B52-cells-10-00191)] reported the successful generation of functional stem cell-derived beta-like cells that possessed many beta cell-specific traits, including glucose-responsive insulin secretion. Importantly, the transplantation of these cells was able to reverse diabetes in mice. However, the beta-like cells that were generated by these protocols [[52](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B52-cells-10-00191),[53](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B53-cells-10-00191)] and follow-up studies [[51](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B51-cells-10-00191),[54](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B54-cells-10-00191),[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B55-cells-10-00191),[56](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7835995/#B56-cells-10-00191)] still displayed poor glucose-induced insulin secretion when compared to human islets.