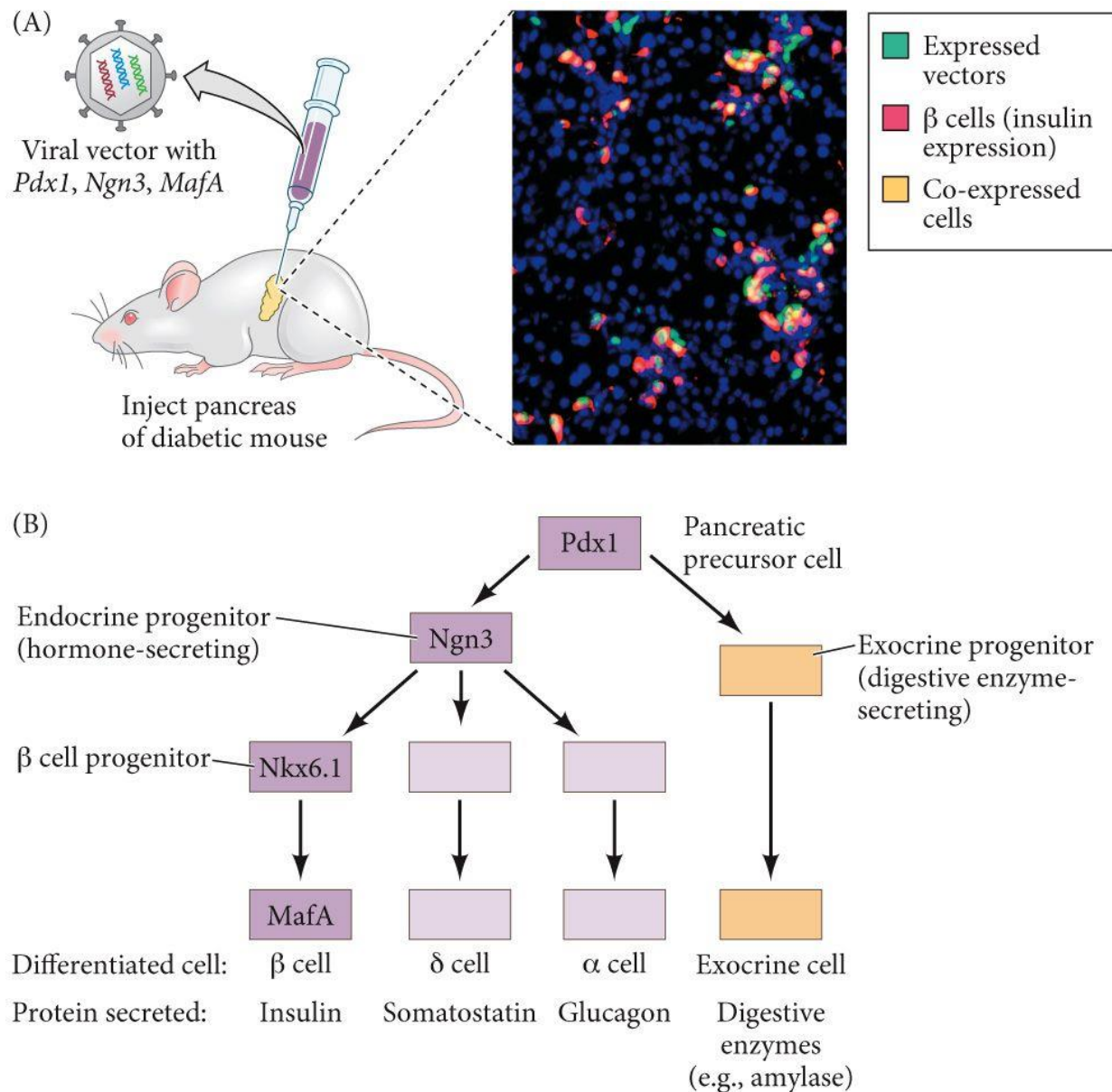


# Transcription Factors with the Power to Cure Diabetes

An intriguing example of pioneer transcription factor control over cell fate came from Doug Melton's lab, which tested whether select transcription factors could convert pancreatic cells of a diabetic mouse into insulin-producing  $\beta$  cells. The researchers infected the pancreatic cells with harmless viruses containing the genes for three transcription factors: Pdx1, Ngn3, and MafA (Figure 1; Zhou et al. 2008; Cavelti-Weder et al. 2014; Melton 2016). In early development, Pdx1 protein stimulates the outgrowth of the digestive tube that results in the pancreatic buds. This transcription factor is found throughout the pancreas and is critical for specifying that organ's endocrine (hormone-secreting) cells and activating genes that encode endocrine proteins. Ngn3 is a transcription factor found in endocrine, but not exocrine (digestive-enzyme secreting), pancreatic cells. MafA, a transcription factor regulated by glucose levels, is found only in insulin-secreting  $\beta$  cells and activates transcription of the insulin gene. During normal development, Pdx1, Ngn3, and MafA activate other transcription factors that together work to turn a pancreatic endodermal cell into an insulin-secreting  $\beta$  cell. After experimentally inducing production of these three transcription factors in the pancreas cells of the diabetic mice, Zhou and colleagues saw that the non-insulin-secreting cells had been converted into insulin-secreting  $\beta$  cells. The converted cells looked identical to normal  $\beta$  islet cells and cured the mice of their diabetes.

These studies have opened the door to a new field of regenerative medicine, illustrating the possibilities of changing one adult cell type into another by using the transcription factors that had made the new cell type in the embryo. In some instances, the developmental histories of the cells can be very distant. For instance, adult mouse skin fibroblasts (the mesodermally derived connective tissue of the skin) can be transformed into endodermal hepatocyte-like cells by the addition of only two liver transcription factors (Hnf4 $\alpha$  and FoxA1). These induced hepatocytes make several liver-specific proteins and are able to substitute for liver cells in adult mice (Sekiya and Suzuki 2011). Indeed, several laboratories (Caiazzo et al. 2011; Pfisterer et al. 2011; Qiang et al. 2011) have been able to "reprogram" adult human and mouse fibroblasts into functional dopaminergic neurons (i.e., the type of nerve cell that degenerates in Parkinson disease) by the addition of three particular transcription factor genes to adult skin cells. Other laboratories (Son et al. 2011) have used a different mix of transcription factors to convert adult human fibroblasts into functional spinal motor neurons (of the type that degenerate in amyotrophic lateral sclerosis, or ALS also known as Lou Gehrig disease). These "induced neurons" had the electrophysiological signatures of spinal nerves and formed synapses with muscle cells. The cell type conversions in these studies have helped reveal the role that pioneer transcription factors play in differential gene expression. *How is it that only a few transcription factors can initiate cell type specific gene expression? Who controls gene expression? When in doubt, who do you blame?*



Photograph courtesy of D. Melton

**Figure 1** Pancreatic lineage, transcription factors, and direct conversion of β cells to treat diabetes. (A) New pancreatic β cells arise in adult mouse pancreas in vivo after viral delivery of genes for three transcription factors (*Pdx1*, *Ngn3*, and *MafA*) into a diabetic mouse model. Virally infected exocrine cells (shown in the photo) are detected by their expression of nuclear green fluorescent protein. Newly induced β cells are detected by insulin staining (red). Their overlap (co-expressed cells) produces yellow. The nuclei of all pancreatic cells are stained blue. (B) Simplified depiction of the role of transcription factors in pancreatic islet β cell development. *Pdx1* protein is critical for specifying a certain group of endodermal cells as pancreas precursors (dark purple lineage). Those descendants of *Pdx1*-expressing cells that express *Ngn3* become the endocrine (hormone-secreting) lineages (shades of purple), whereas those that do not express *Ngn3* become the exocrine (digestive enzyme-secreting) lineage of the pancreas (gold). Types of hormone-secreting cells in the pancreatic islets include the insulin-secreting β cells, the somatostatin-secreting δ cells, and the glucagon-secreting α cells. Those cells destined to become β cells express the *Nkx6.1* transcription factor, which in turn will activate the gene for the *MafA* transcription factor found in the insulin-producing β cells. (Photograph courtesy of D. Melton.)

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