Prospects for inducing endogenous beta-cell regeneration in the pancreas, one of the most attractive approaches to reverse type 1 and type 2 diabetes, have gained substantially from recent evidence that cells in the adult pancreas exhibit more plasticity than previously recognized. There are two major pathways to beta-cell regeneration, beta-cell replication and beta-cell neogenesis. Substantial evidence for a role for both processes exists in different models. While beta-cell replication clearly occurs during development and early in life, the potential for replication appears to decline substantially with age. In contrast, we have demonstrated that the exocrine compartment of the adult human pancreas contains a facultative stem cell that can differentiate into beta-cells under specific circumstances. We have favoured the idea that, similar to models described in liver regeneration, beta-cell mass can be increased either by neogenesis or replication, depending on the intensity of different stimuli or stressors. Understanding the nature of endocrine stem/progenitor cells and the mechanism by which external stimuli mobilize them to exhibit endocrine differentiation is central for success in therapeutic approaches to induce meaningful endogenous beta-cell neogenesis.