A living biological substitute for treatment of insulin-dependent diabetes has significant potential in providing a less invasive, more physiologic regulation of blood glucose levels than insulin injections. The critical technologies needed for such a substitute depend strongly on the type of cells used. With cells from another individual (allogeneic) or another species (xenogeneic), encapsulation in semipermeable barriers improves immune acceptance, as it inhibits passage of antibodies and excludes cytotoxic cells of the host. However, immune acceptance is not complete, and immune suppression may still be needed to prolong survival of the implant. Non-pancreatic cells from the same patient (autologous), targeted by gene transfer vectors or retrieved surgically and genetically engineered ex vivo, may relax the immune acceptance problems but pose challenges regarding the amount and kinetics of insulin secretion in response to physiologic stimuli. Stem and progenitor cells constitute another promising cell source, however, their differentiation into pancreatic cells presents significant challenges.

In our laboratory, we focus on encapsulated allogeneic pancreatic cells and on non-pancreatic cells genetically engineered to secrete insulin in response to physiologic stimuli. With encapsulated cells, we are developing methods to cryopreserve them for off-the-shelf availability and to monitor them noninvasively using nuclear magnetic resonance imaging and spectroscopy. With non-pancreatic cells, we genetically engineer hepatic and intestinal endocrine L cells for insulin secretion. Methods to improve the kinetics of insulin release include the use of glucose-responsive promoters and of mRNA destabilization. It may be possible to combine such cells to further improve the insulin secretory kinetics. The importance of pursuing these research directions in parallel and in an integrated systems fashion will also be discussed.