## Biographical Sketch of Emma Heart

Dr. Heart's research has, and continues to focus on, identifying novel metabolic signals in the pancreatic beta cells, which couple fuel metabolism with insulin secretion. Insufficient insulin secretion from pancreatic beta cells is a major contributor to the development of type 2 diabetes, which now affects over 100 million people worldwide. In order to unravel the mechanisms underlying insulin secretion, her research simultaneously drives development of novel, single-cell sensors at the BRC, where she undertakes these studies.

Insulin secretion from beta cells is contingent upon metabolism of fuel secretagogues. Fuel catabolism leads to an increase in the ATP/ADP ratio, which triggers insulin granule exocytosis via sequential closure of $K_{ATP}$ channels, plasma membrane depolarization and calcium influx. However, ample evidence suggests that the rise in intracellular calcium alone is not sufficient to account for this process and that other fuel-dependent pathways are operative in the beta cell. The goal is to identify these pathways with the help of the BRC technologies that permit assessment of metabolic parameters at the single-cell level.

The previous work has focused on the mechanism, by which non-glycolytic fuels as succinate or pyruvate, are being metabolized in the beta cell, and cause insulin release. Both oscillatory and metabolic aspect of actions of these fuels have been evaluated. This work resulted in the following publications: Heart E, Smith PJ. Rhythm of the beta-cell oscillator is not governed by a single regulator: multiple systems contribute to oscillatory behavior. *Am J Physiol Endocrinol Metab.* 292(5):E1295-300, 2007, and Heart E *et al*. $Ca^{2+}$, NAD(P)H and membrane potential changes in pancreatic beta-cells by methyl succinate: comparison with glucose. *Biochem J* 403(1):197-205, 2007. Metabolic function of GLP-1, an incretin which potentiates fuel-stimulated insulin secretion from beta cells, is being explored as a part of collaborative effort with BRC visitor Dr. Holz (Holz GG, Heart E, Leach CA. Synchronizing $Ca^{2+}$ and cAMP oscillations in pancreatic beta-cells: a role for glucose metabolism and GLP-1 receptors? Focus on "Regulation of cAMP dynamics by $Ca^{2+}$ and G protein-coupled receptors in the pancreatic beta-cell: a computational approach". *Am J Physiol Cell Physio*l. 294(1):C4-6, 2008). The effect of GLP-1 on beta cell metabolism, such as ATP production and oxygen consumption, is being explored using a low light imaging system and the self-referencing oxygen microsensors developed at the BRC.

A new focus of her research involves the development and application of sensors for direct measurement of plasma membrane electron transport (PMET). This has been catalyzed by recent findings that inhibitions of quinone reductase, a component of PMET, inhibits insulin secretion. PMET, is a ubiquitous system, which accounts for 10-20% of extra-mitochondrial oxygen consumption. PMET activity was first characterized in plants and it is now being characterized in limited number of mammalian tissues. She has demonstrated that PMET is active in insulin secreting cells and that PMET activity is crucial for insulin secretion (Heart E *et al*. Challenging the mitochondrial supremacy: Plasma membrane electron transport and insulin secretion, *manuscript in preparation*). There are many possible roles of PMET which include, but are not limited to, re-oxidation of reducing equivalents, regulation of the plasma membrane potential and intracellular pH, all of which are important for insulin secretion. Future studies will focus to address the following questions: What are the components of PMET in beta cells? How is PMET activity regulated by nutrient environment? Is there a cross-talk between PMET and mitochondrial function? These issues will be addressed using si-RNA technology to silence specific PMET components in collaboration with Dr. Joshua Gray (US Coast Guard Academy, New London). Impermeable tertrazolium compounds are available to assess PMET activity spectrophotometrically in a population of cells. However, direct measurement of PMET activity at the single cell level is a desirable goal, since it will allow assessment of coordination of PMET activity with other metabolic parameters. Single-cell measurement of PMET activity will be performed using self-referencing sensors, development of which is currently underway at the BRC. These novel sensors will be developed and tested in collaboration with Richard Sanger and Robert Lewis of the BRC, initially on cells relevant to diabetes research but then on a wider array reflecting both basic and biomedical models. Of particular interest is the role of PMET in fueling cell division.