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Primary Research Interest:	Internal Medicine
Description of Research:	Hepatic insulin gene therapy has the potential to improve glycemic control in patients with diabetes. In rodents, delivery of a metabolically responsive insulin transgene produces near normoglycemia. However, the impact in non-rodent animals remains unclear. We propose to demonstrate HIGT efficacy in pigs, and examine HIGT effects on whole body carbohydrate metabolism by nuclear magentic resonance spectroscopy (NMRS). We will administer sufficient adenovirus to obtain ~25% hepatocyte transduction, and deliver a metabolically responsive insulin transgene to diabetic pigs. Efficacy will be tested using intravenous glucose tolerance testing. Then, the effect of HIGT on hepatic glucose fluxes will be evaluated by serial 13-C NMRS, providing quantification of HIGT in pigs. Successful completion of these studies will provide an important model system for human diabetes, and may advance hepatic insulin gene therapy toward human studies.
Relevance to VA:	The disease burden of diabetes mellitus among the veteran population is tremendous, costing the VA health system $1.5 billion each year. Approximately 20% of veterans have diabetes, and 70% are overweight,predisposing them to developing type 2 diabetes. The majority of veterans with diabetes will succumb to cardio- or cerebral vascular disease. HIGT inhibits endothelial dysfunction, an early marker of atherosclerotic vascular disease, in rats. However, whether HIGT can control glycemia and induce similar vascular effects in large mammals is disputed. Our research utilizes STZ-diabetic pigs, a disease model with similarities to both type 1 and type 2 DM. Moreover, HIGT is effective in lowering BG in hyperglycemic Zucker rats (unpublished data), an accepted model of type 2 DM. Successful completion of our research will determine the efficacy of HIGT in pigs, and propel HIGT toward human trials, and potentially the treatment of tens of thousands of veterans.