Current Status Basic, Translational, and Clinical Research in Genetics and Epigenetics

- Many candidate gene associations reported for diabetic complications, particularly nephropathy and retinopathy
- GWAS have identified multiple QTLs for nephropathy phenotypes; so far no potential causal variants identified
- Epigenetic modifications (ie, changes in DNA methylation, etc) have been identified as mechanisms for “metabolic memory”; role in complications not clear
- Models emerging from AMDCC have demonstrated: (a) strong effects of genetic background on severity of various complications (b) strong effects of environment on complication severity with fixed genetic background

Potential impact/significance

- Identifying genetic variants and epigenetic modifications affecting susceptibility to complications would be significant advance in understanding disease mechanisms and identifying new diagnostic and therapeutic approaches
- Heritability of complication susceptibility clear, but specific causal genes not yet identified
- Clear evidence for gene-environment interactions in DM complications, but specific mechanisms unknown

Barriers

- Relevance of genetic findings in mice to humans?
- Modest differences in some strain-specific phenotypes
- Access to bioinformatics resources
- Cost
- Evolving epigenetic methodology
- Impact of tissue heterogeneity
- Inherent difficulties in disease gene identification

Objectives

- Susceptibility gene identification
  - Integration of other approaches: genomics, metabolomics, etc
- Identify environmental factors with strong effects on phenotypes
- Role of epigenetics as mechanism for environmental influence on complications
- Generate mice with humanized susceptibility/resistance alleles
- Take greatest advantage of existing AMDCC models and phenotype data

Biomarkers

- Risk allele identification from PBMCs
- Epigenetic markers in cells from blood and urine

Assist understanding of all diabetic complications?

- Similar mechanisms of response to metabolic stress across different organ systems
- Gene identification approaches only amenable to complications with heritable patterns of susceptibility
- Epigenetic mechanisms likely important across many complications