GOALS?

- **Produce insulin, cure diabetes?**
- **Reverse Complications?**
- **Prevent Complications?**
- **Eliminate metabolic memory?**

Stem Cell Defects in Diabetes

- **Acquired vs. Genetic, do they predate the development of hyperglycemia?**
- **Role of inflammation vs. hyperglycemia in observed defects.**
- **Should you select or enrich?**
- **Do you need to pre-treat ex vivo with growth factors, small molecules, etc?**

Retinopathy

- **Only 15-20% of DM RD will progress, is this stem cell related?**
- **EPCs (CD 34, VEGFR-2) will home to injured retinal vasculature**
- **Integrate less well with cells isolated from diabetics**
- **Can defects be corrected? Blocking TGF-β1?**

Define Pathophysiology vs. Develop Therapeutics

- **Do cells regenerate tissue or act as supportive cells?**
- **Do they release differentiation blockade?**
- **Do they recruit endogenous tissue specific stem cells?**
- **Organ System vs. General mechanisms?**

Cell Types

- **Embryonic Stem Cells**
- **iPS**
- **Adult stem cells (bone marrow, adipose, tissue specific)**
- **Differentiated**

Cell Sourcing

- **Autologous-*Problems:* cells are dysfunctional in DM, Diabetes decreases circadian release of EPCs,**
- **Allogeneic**
- **Xenogeneic**
- **iPS-safety concerns**
- **ESCs-safety concerns**
- **Small molecules /growth factors to precondition and/or reprogram cells**

Question #1: Current Status

- **Extensive basic and translational literature supports the concept that a variety of stem cell populations are dysfunctional in diabetes**
- **Mechanistic understanding is lacking**
- **Clinical research is proceeding without this, which is a risk**
- **There is some risk of creating problems and further complications**

Question #2: Potential Impact

- **Would curing diabetes with stem cells eliminate complications? Probably not…**
- **However, understanding stem cell biology will help us understand diabetic complications better**
- **Short term, adult stem cells may be more approachable in the clinic, but iPS cells are probably the future**

Question #3: Technical Barriers

- Relative importance of acquired vs. genetic defects in observed stem cell defects
- Could stem cell treatments make things worse (i.e., retinopathy with EPCs secreting VEGF)
- Some fields are using old data with respect to markers, selection, etc.
- May need to understand the function of the cells to select the correct indication

Question #3: Technical Challenges (cont'd)

- Cell delivery to retina and kidney and nerve are a challenge
- What cells to use?
- How to prevent ongoing damage from underlying diabetic states
- How to translate into the clinic

Question #4: Are there clear objectives that can be achieved?

- Yes, the pathophysiology can be understood
- Clinical trials can be done with adult cells and are being done now
- Can look at iPS and ESCs in diabetic animals and humans and may be different because of epigenetics

Question #5: Biomarkers

- **No.**
- **Maybe. Retinopathy, could segregate progressors and treat more aggressively.**
- **Would require long term trials and is not “low hanging fruit”.**
- **Urine still unknown.**

Question #6: Leveraging existing NIH and other resources

- NHLBI Cell Therapy Networks
- NIH Bio-Bank?
- Should there be a workshop or shared facility to work with iPS, etc.
- Partner with NHLBI (**P**roduction **A**ssistance for **C**ellular **T**herapies)
- New models within consortium allow teasing out of inflammation, human vs. mouse, etc.

Question #7: Broader Understanding

- **Each complication has different mechanisms but stem cells are probably involved in all complications.**
- **Thus, both fundamental and translational research in this are likely to lead to advances in understanding diabetic complications.**