GENE THERAPY FOR TYPE 1 DIABETES

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In a normal individual, blood glucose levels are determined by insulin that is produced by the \( \beta \)-cell of the pancreas.
POSSIBLE THERAPIES (1)

Insulin Therapy

Does not provide a cure and patients develop the chronic complications of diabetes.

- Retinopathy → Blindness
- Nephropathy → Kidney Failure
- Neuropathy → Nerve Degeneration
- Macrovascular → Stroke
- Cardiovascular disease
- Gangrene
POSSIBLE THERAPIES (2)

Transplantation of Insulin-Secreting pancreatic tissue
- Too few donors
- Patients must be immunosuppressed

Stem Cells
- May be prone to autoimmune attack
- Immunosuppression

Gene Therapy
- Production of replacement $\beta$-cells by genetic engineering
WHAT DOES AN ARTIFICIAL BETA CELL NEED TO FUNCTION CORRECTLY?

- The ability to accurately sense glucose levels
- The ability to metabolise glucose
- The ability to store insulin for later secretion

Liver cells have:

- Similar glucose-sensing apparatus to pancreatic β cells
- Synthesise and secrete complex proteins
- Ability to undergo differentiation into β-like cells that possess storage granules
ALTERNATIVE GENE THERAPY SOLUTIONS

• Insulin-secreting liver cell line that can be encapsulated and used as a treatment

• Direct delivery of genes to the liver curing the disease
CREATION OF MELLIGEN CELLS

- As an alternative to the transplantation of islets, a human liver cell line has been genetically engineered to reverse type 1 diabetes.
- Melligen cells which express β cell transcription factors store insulin in granules and secrete insulin to glucose correctly, reversing diabetes.
MELLIGEN CELLS: REVERSAL OF DIABETES

- Capsules are made of bio-inert material (cellulose/cotton)
- Capsules have pores for nutrient and waste transfer
- Pores are too small for immune system cells to enter or encapsulated live cells to leave
- Long-term (5+ years) frozen storage of encapsulated live cells with more than 95% viability of cells upon thawing
- Manageable logistics and long shelf-life
- Cell-in-a-Box® encapsulation performed in a cGMP-compliant facility
- Other live cell encapsulation technologies use alginate (derived from seaweed). All are far less robust and stable. None can be frozen to ship
- Cell-in-a-Box® capsules shown to be safe, effective and durable

http://pharmacyte.com/diabetes/
DIRECT DELIVERY OF INSULIN TO LIVERS

Human insulin is delivered directly in a viral vector to animal livers by a surgical technique that isolates the liver from the circulation

REVERSAL OF DIABETES IN NON OBESE DIABETIC (NOD) MICE

Storage granules
REVERSAL OF DIABETES IN NOD MICE

Spontaneous expression of β-cell transcription factors
FUTURE DIRECTIONS/ PARTNERING

Different Cell Types
- Bone marrow mesenchymal stem cells
- Human islet progenitor cells
- Gall bladder cells

Pre-clinical Animal Models: Direct delivery of insulin
- Humanised FRG mice
- Large animal models
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