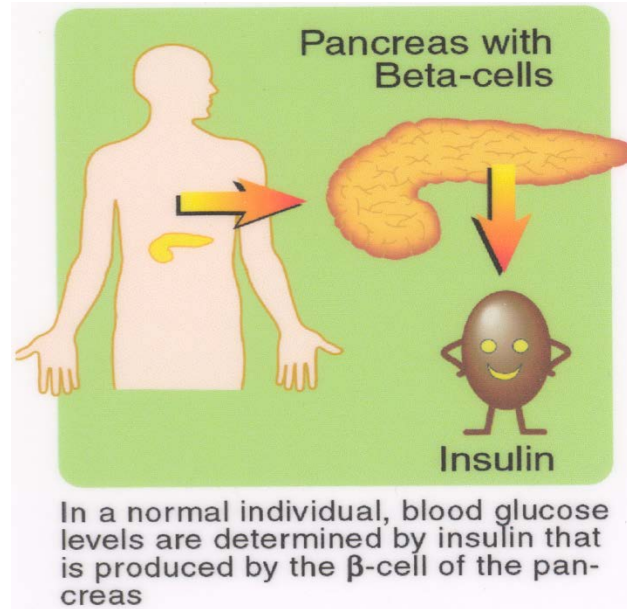


## **GENE THERAPY FOR TYPE 1 DIABETES**

Ann M. Simpson  
Centre for Health Technologies



# NORMAL INDIVIDUAL

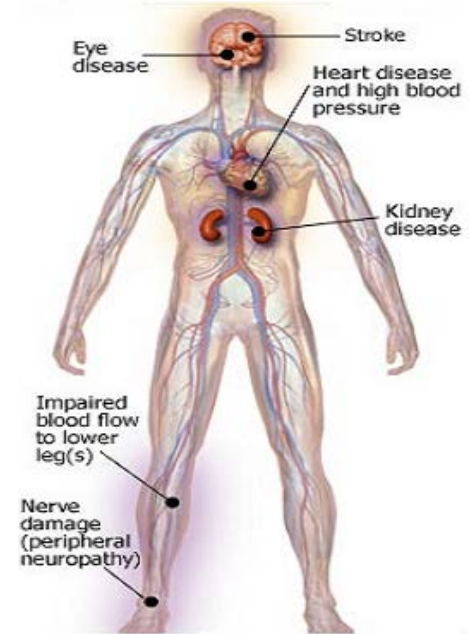


# POSSIBLE THERAPIES (1)

## 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

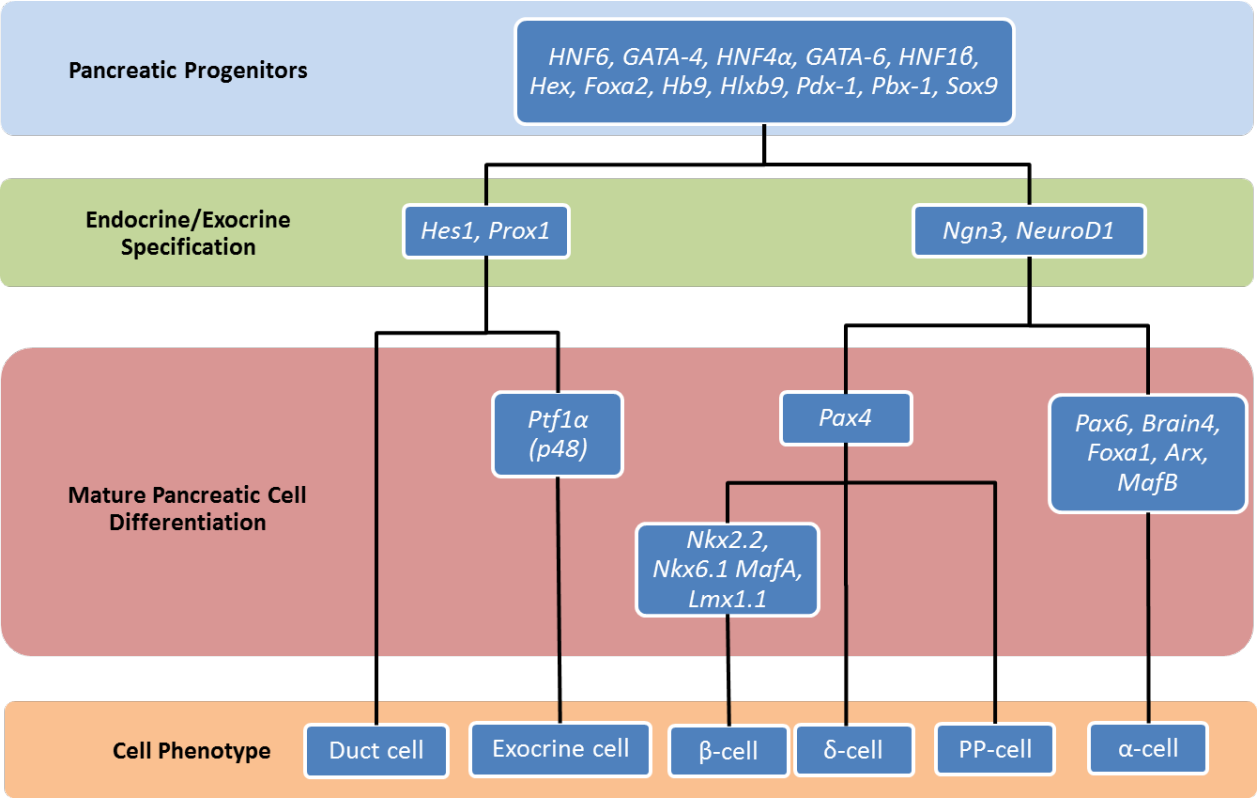
# WHAT DOES AN ARTIFICIAL BETA CELL NEED TO FUNCTION CORRECTLY?

- 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  $\beta$  cells
- **Synthesise** and **secrete** complex proteins
- Ability to **undergo differentiation** into  $\beta$ -like cells that possess storage granules

# BETA CELL TRANSCRIPTION FACTORS

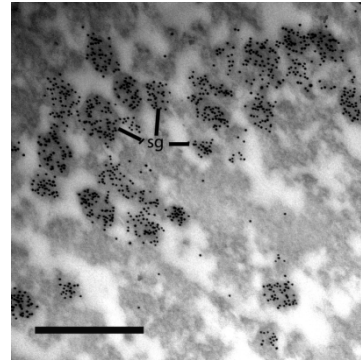
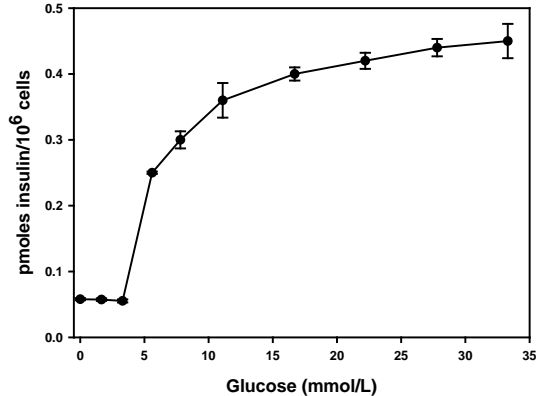


# ALTERNATIVE GENE THERAPY SOLUTIONS

- Insulin-secreting liver cell line that can be encapsulated and used as a treatment
- Direct delivery of genes to the liver curing the disease

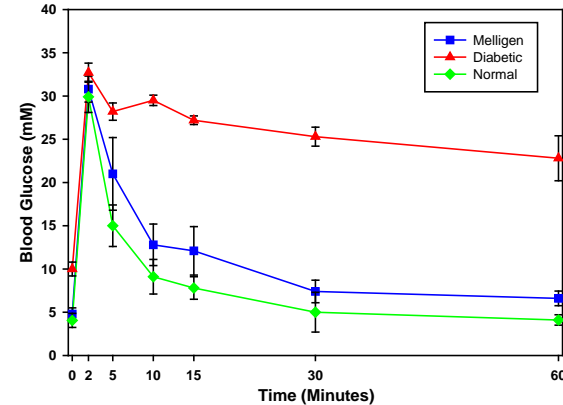
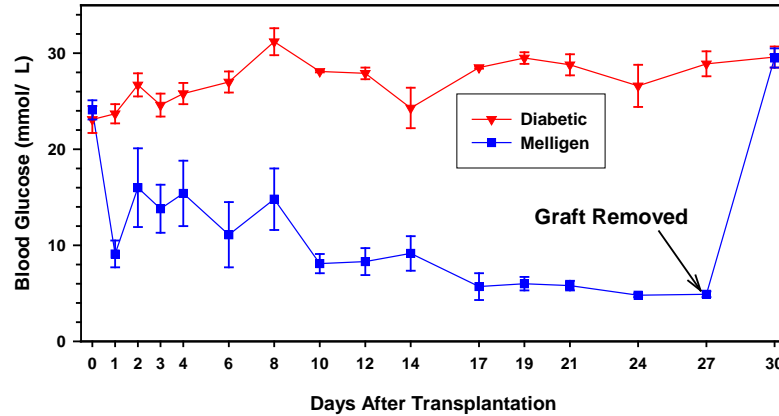
# CREATION OF MELLIGEN CELLS

- 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  $\beta$  cell transcription factors store insulin in granules and secrete insulin to glucose correctly, reversing diabetes.



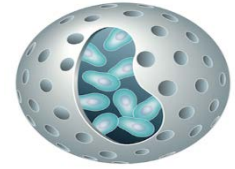
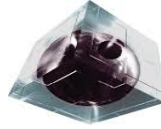


# MELLIGEN CELLS: REVERSAL OF DIABETES



Lawandi et al (2015) *Molecular Therapy- Methods & Clinical Development* 2, 15011; doi:10.1038/mtm.2015.11.

<http://newsroom.uts.edu.au/news/2014/11/breakthrough-diabetes-research-be-commercialised>  
<http://ir.pharmacytebiotech.com/press-releases/detail/108/pharmacyte-biotech-receives-patent-protection-of-the>



- 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<sup>®</sup> 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<sup>®</sup> capsules shown to be safe, effective and durable

# DIRECT DELIVERY OF INSULIN TO LIVERS

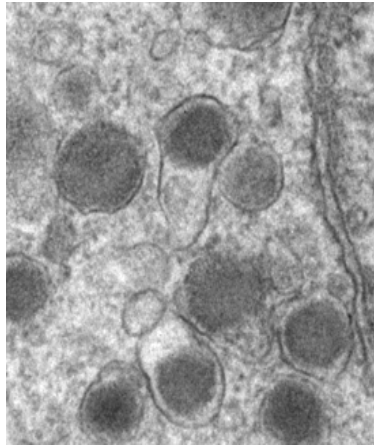
Human insulin is delivered directly in a viral vector to animal livers by a surgical technique that isolates the liver from the circulation

*Ren B et al (2007) Diabetologia 50: 1910-1920.*

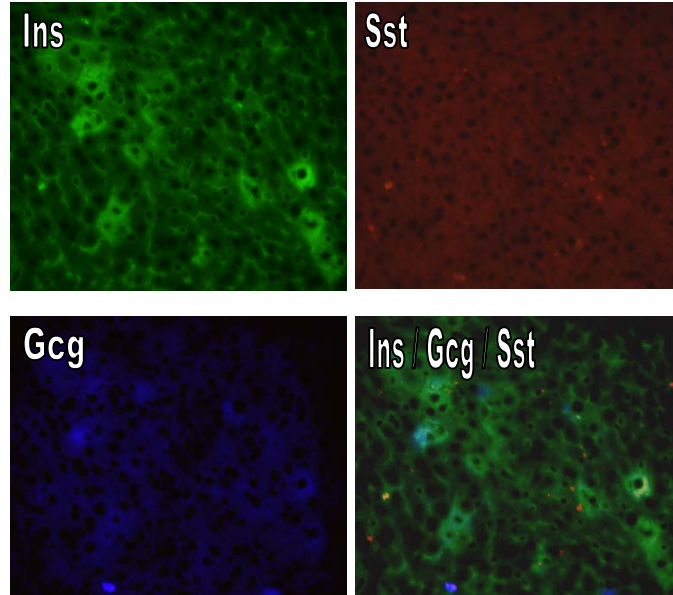
*Ren B, et al (2013) J Gene Medicine 15: 28-41*

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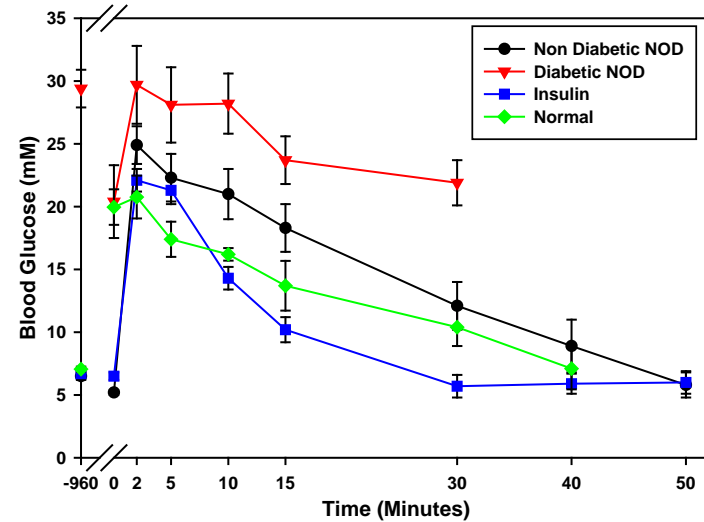
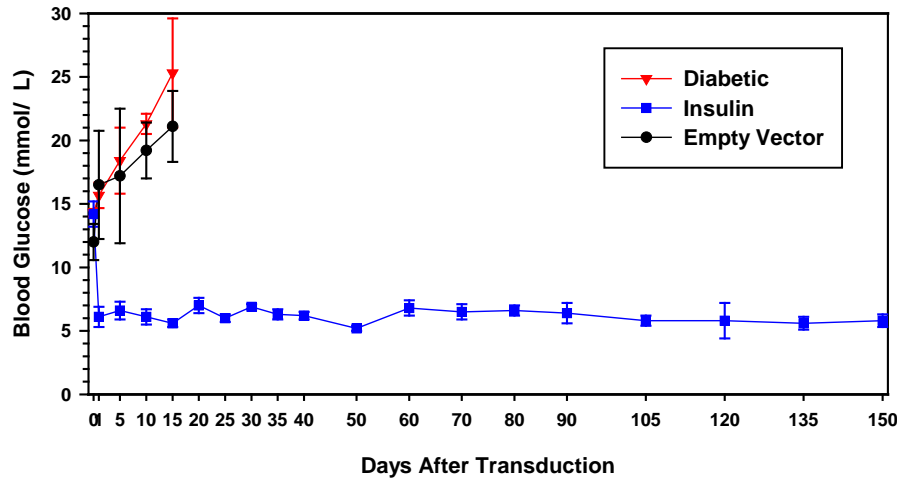
# REVERSAL OF DIABETES IN NON OBESE DIABETIC (NOD) MICE



Storage granules



# REVERSAL OF DIABETES IN NOD MICE



Spontaneous expression of  $\beta$ -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**

# ACKNOWLEDGEMENTS

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