

# Injecting Enthusiasm Into the Future of Type 1 Diabetes Research



Mark Daniels, MD  
CHOC Children's  
Diabetes Symposium  
January 22, 2011

The logo for Type 1 Diabetes TrialNet features the text "Type 1 Diabetes TrialNet" in a bold, blue, sans-serif font. A large, red, curved swoosh graphic is positioned behind the text, starting from the right side and curving upwards and then downwards to the left, partially overlapping the letters.

**Type 1  
Diabetes  
TrialNet**

**TrialNet is a network of 18 Clinical Centers and 150 affiliates in the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia, and New Zealand.**

**TrialNet is dedicated to the study, prevention, and early treatment of type 1 diabetes.**

# Points of Discussion

- Identify the similarities and differences between type 1 and type 2 Diabetes Mellitus
- Note Increasing Incidence of Type 1 Diabetes
- Identify Areas to Intervene
  - Genetic Predisposition + Environmental Triggers
  - Pre-Diabetes
  - At Diagnosis
  - Years Post-Diagnosis
- Technological Solutions
- Biological Solutions
- There is HOPE

# Type 1 vs. Type 2 DM

- AKA Juvenile-Onset, or Insulin Dependent Diabetes Mellitus
- Rapid progression –weeks to months
- Absolute need for insulin from outset
- Autoimmunity in 90% (GAD65, ICA, IAA)
- May present in Diabetic Ketoacidosis
- Obesity is NOT protective
- Usually childhood, but ANY age
- AKA Adult Onset and Non-insulin dependent Diabetes Mellitus
- Usually insidious onset-months to year
- May be treated with orals, or need insulin
- Antibody negative (usually)
- Unlikely to present in DKA
- Usually with Obesity
- Usually adulthood, but also adolescence

# Multifaceted Approach to Type 2 prevention and treatment

- Behavioral
  - Community/Population Based
  - Individual Based
  - Motivational
- Medication
  - Incretins
  - Standard “Adult” medications

# School/Community Based HEALTHY

- HEALTHY is a primary prevention trial conducted in 42 middle schools at 7 locations across the US to impact risk factors for **type 2 diabetes** in adolescents. Students are recruited at start of 6th grade (fall 2006) and followed to end of 8th grade (spring 2009). Half of the schools are randomized to receive an intervention that integrates four components: the school nutrition environment, physical education class activities, behavior change initiatives, and educational and promotional communications activities

# Individual Based Studies

- Circuit Training and Motivational Interviewing to Reduce **Type 2 Diabetes** in Youth (Jaimie Davis – USC)
- Partners for Better Health in Adolescent **Type 2 Diabetes**: The Buddy Study (NIH)
- Situational Problem Solving in Adolescents With **Type 2 Diabetes**: Enhancing a Randomized Controlled Trial (Vanderbilt)

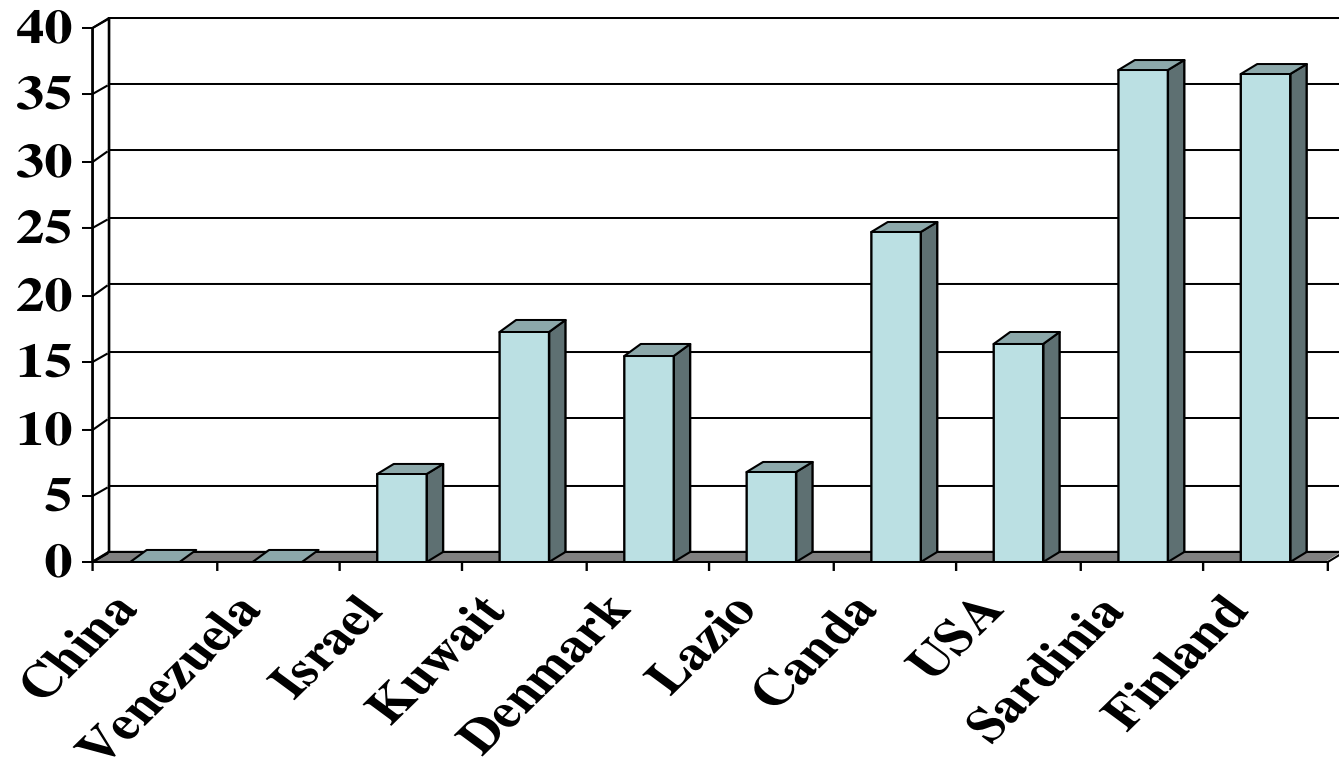
# Medication Interventions in Type 2 DM

- A Study of ...Exenatide in Adolescent Subjects With **Type 2 Diabetes Mellitus**
- A Prospective, Observational Study to Assess and Evaluate the Use of Glucophage XR Therapy in the Management of Patients With **Type 2 Diabetes**
- Colesevelam Pediatric **Type 2 Diabetes Mellitus Study (WELKid DM)**

# Type 1 Diabetes is out there!!!

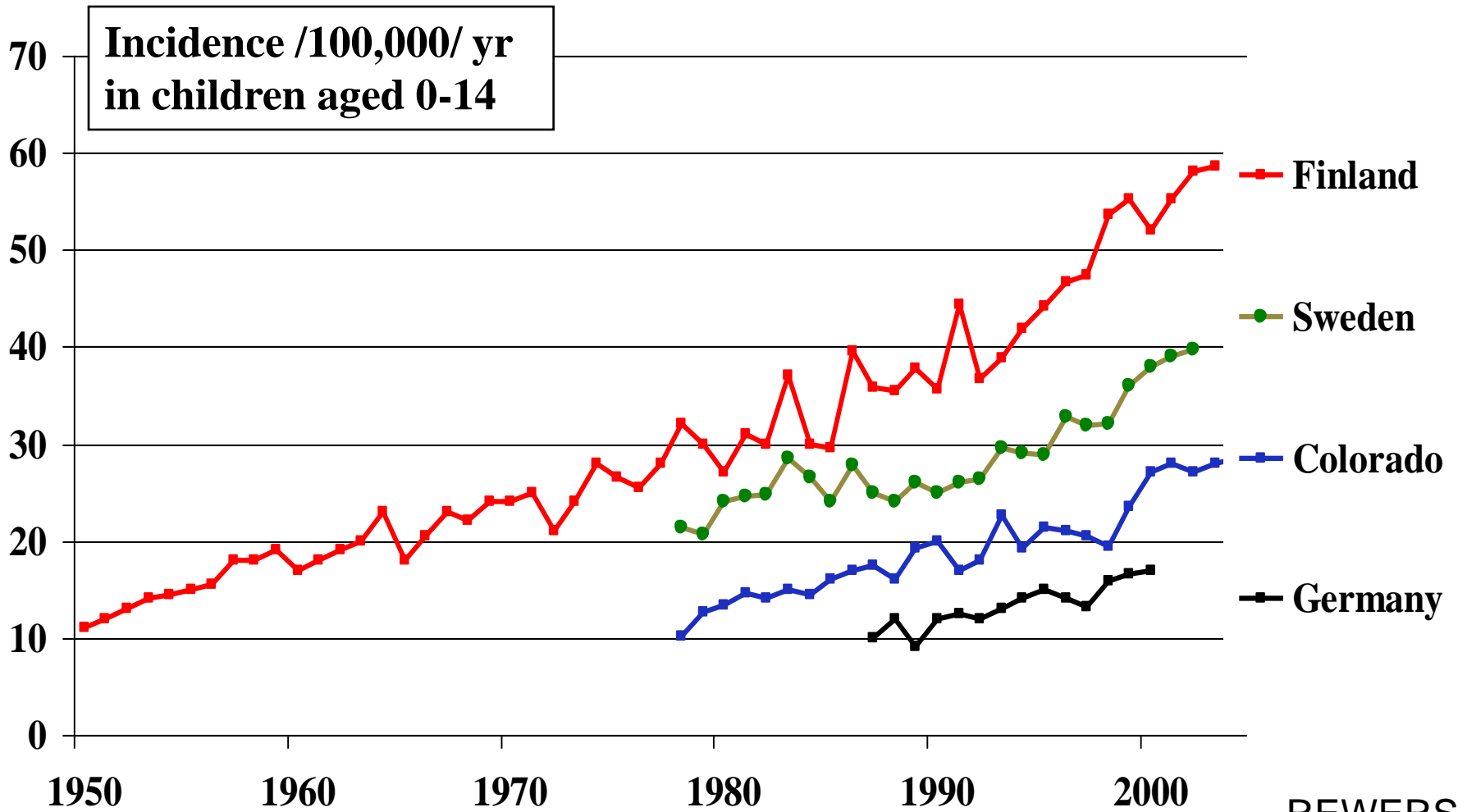
- **Approximately one in 300 children under the age of 18 has type 1 DM.**
- **~1 million Americans have type 1 DM**

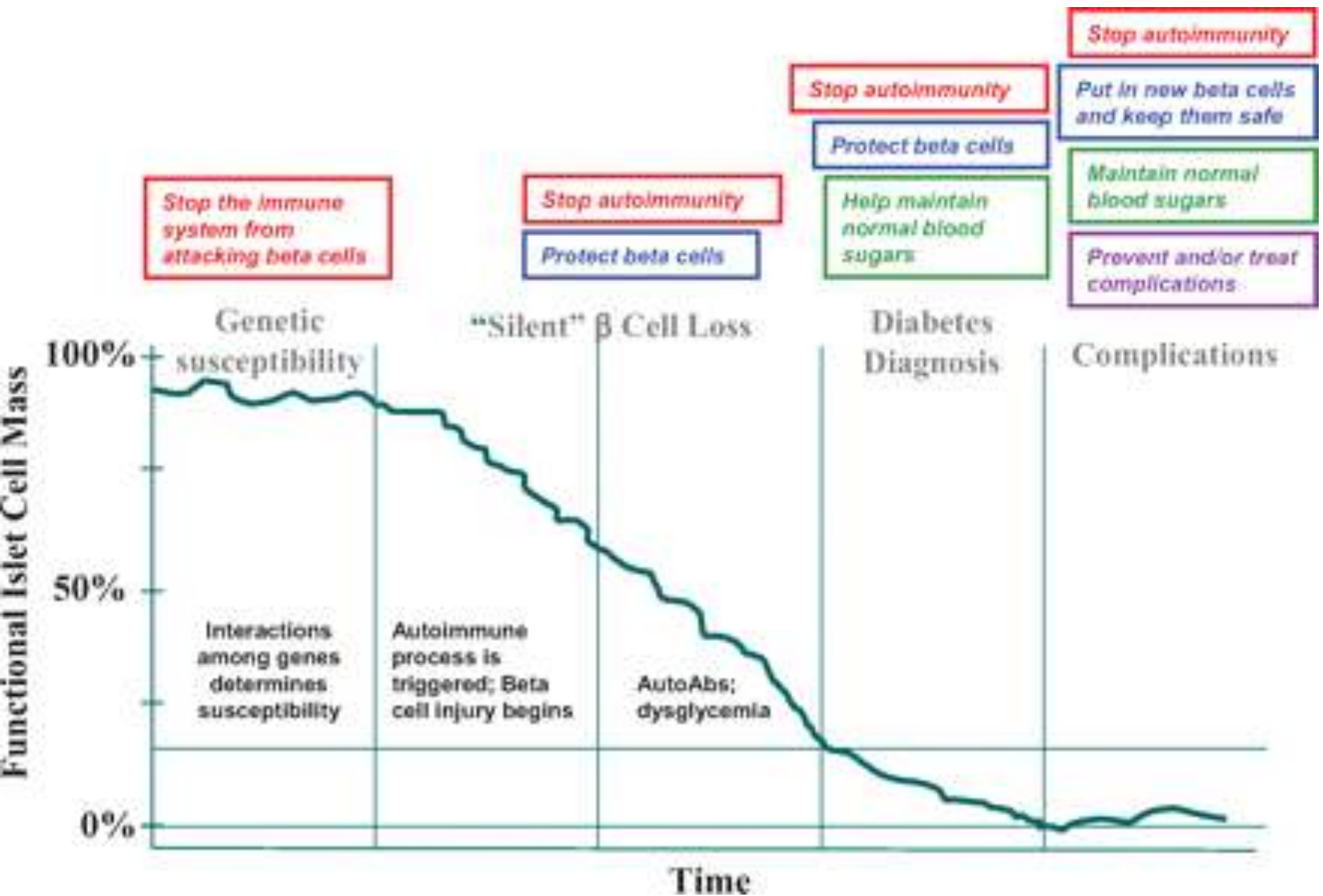
# Incidence Type 1 Diabetes per 100,000 per year Children $\leq 14$ (As of 2000)



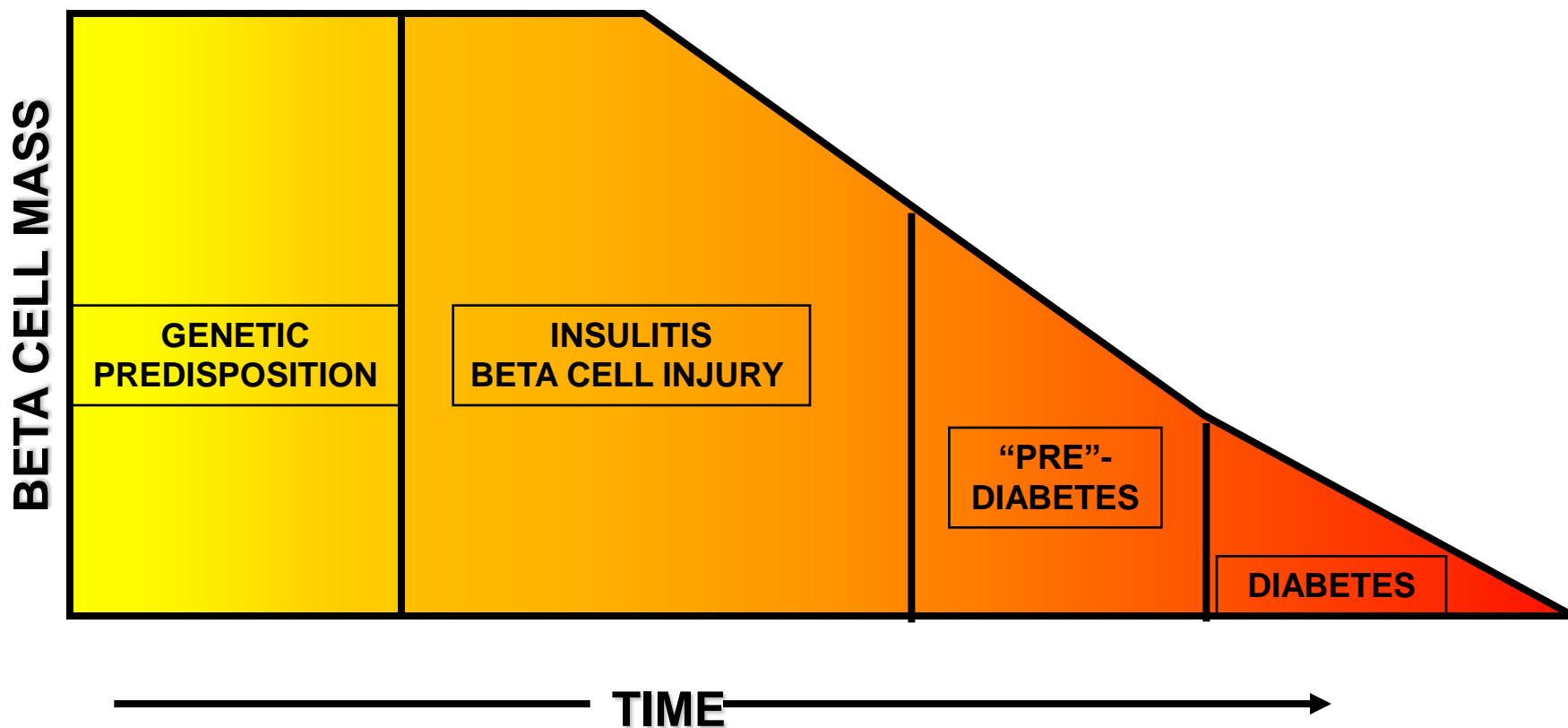
# T1D incidence is rising 3-5% per year

## Due to environmental cause(s)

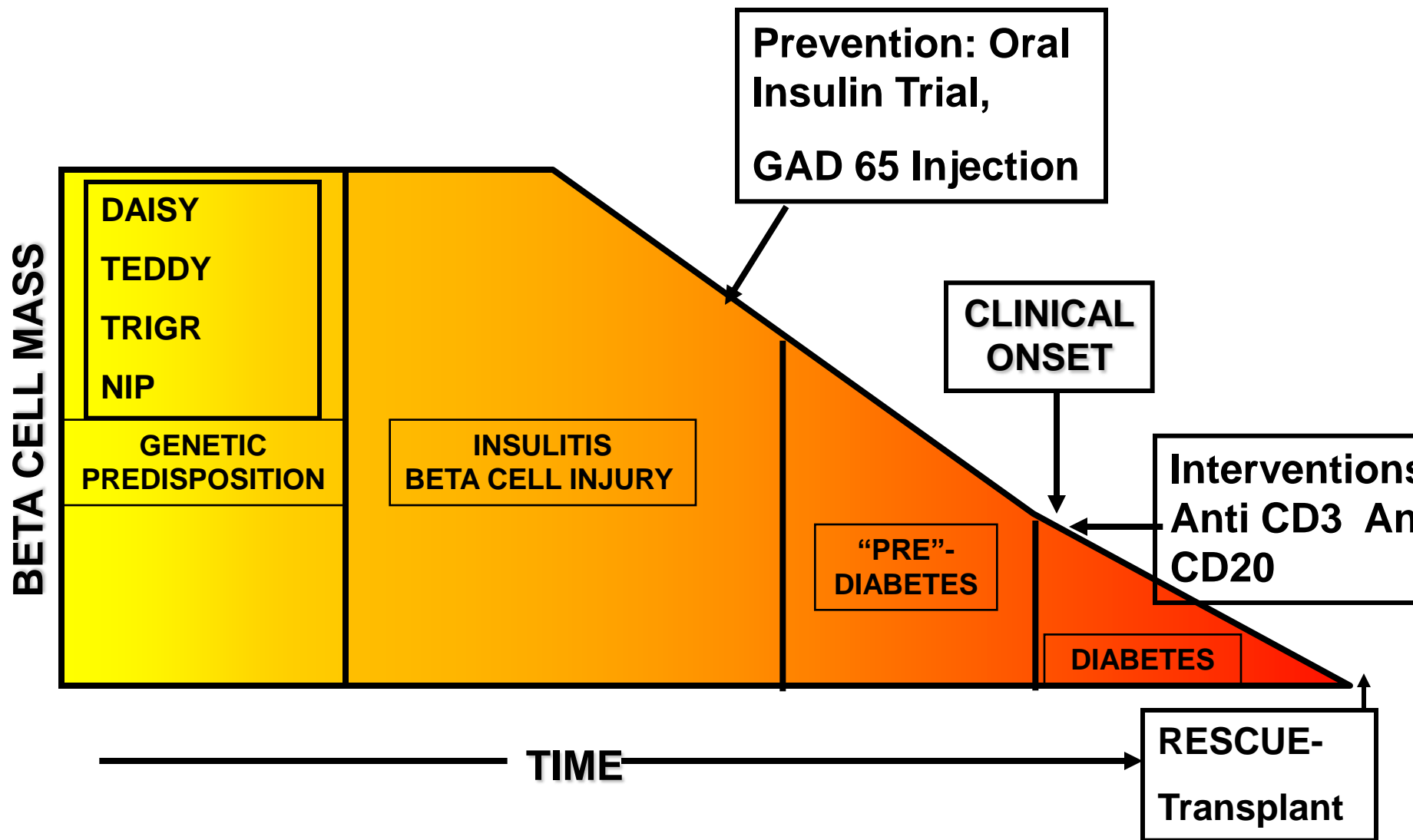




# Natural History of Type 1 Diabetes



# Natural History of Type 1 Diabetes



# NIP

- Nearlyborns and Newborns who have a family member with Type 1 Diabetes Mellitus are eligible
- Offered a common Dietary Supplement, DHA (an Omega-3 fatty acid) in hopes of “resetting” the immune system and preventing self-attack
- Results are pending publication

## Nutritional Intervention to Prevent (NIP) Diabetes



A Research Study for  
Infants at Increased Risk  
for **Type 1 Diabetes**



The Environmental Determinants of Diabetes in the Young

[What is Type-1 Diabetes?](#)

[What is the TEDDY Study?](#)

[How to Join?](#)

[Clinical Centers](#)

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[Contact Us](#)

Already a Participant in the TEDDY study? Visit the [MyTEDDY](#) Web site.



Finding diabetes early can prevent serious illness and complications.

Most of the new cases of type 1 diabetes occur in children who have **no family history** of the disease.

Learn more about [Type 1 Diabetes \(T1D\)](#) and what you can do to help our research.



**Are you Pregnant?**

Do you have a newborn?

**Every child in the TEDDY study helps us come closer to preventing this disease.**

[We invite you to take a part in helping us reach this goal!](#)

<http://teddy.epi.usf.edu/>

- “The long-term goal of the TEDDY study is the identification of infectious agents, dietary factors, or other environmental agents, including psychosocial factors, which trigger type 1 diabetes in genetically susceptible individuals or which protect against the disease”

# TRIGR

## Trial to Reduce IDDM in the Genetically at Risk

[ABOUT TRIGR](#) | [NEWS & UPDATES](#) | [PARTICIPATING CENTRES](#) | [CONTACT US](#)

**TRIGR** is an international, randomized, double-blinded trial. The hypothesis to be tested is whether hydrolyzed infant formula compared to cow's milk-based formula decreases risk of developing type 1 diabetes in children with increased genetic susceptibility.

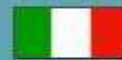
[More](#) 

**type 1 diabetes**  
CAN WE PROTECT OUR CHILDREN?

For more information about this study in your country, please click on your flag:

TRIGR Study Team:

[LOG IN HERE](#)



# Oral Insulin

- Previous Study (DPT-1) suggested that diabetes could be delayed or prevented in certain high risk individuals with an Insulin Pill
- This study will look at this group specifically.
- Insulin pill does not lower blood glucose, but may change immune system attack

If Someone In Your  
Family Has

**Type 1 Diabetes**

You May Be At Risk

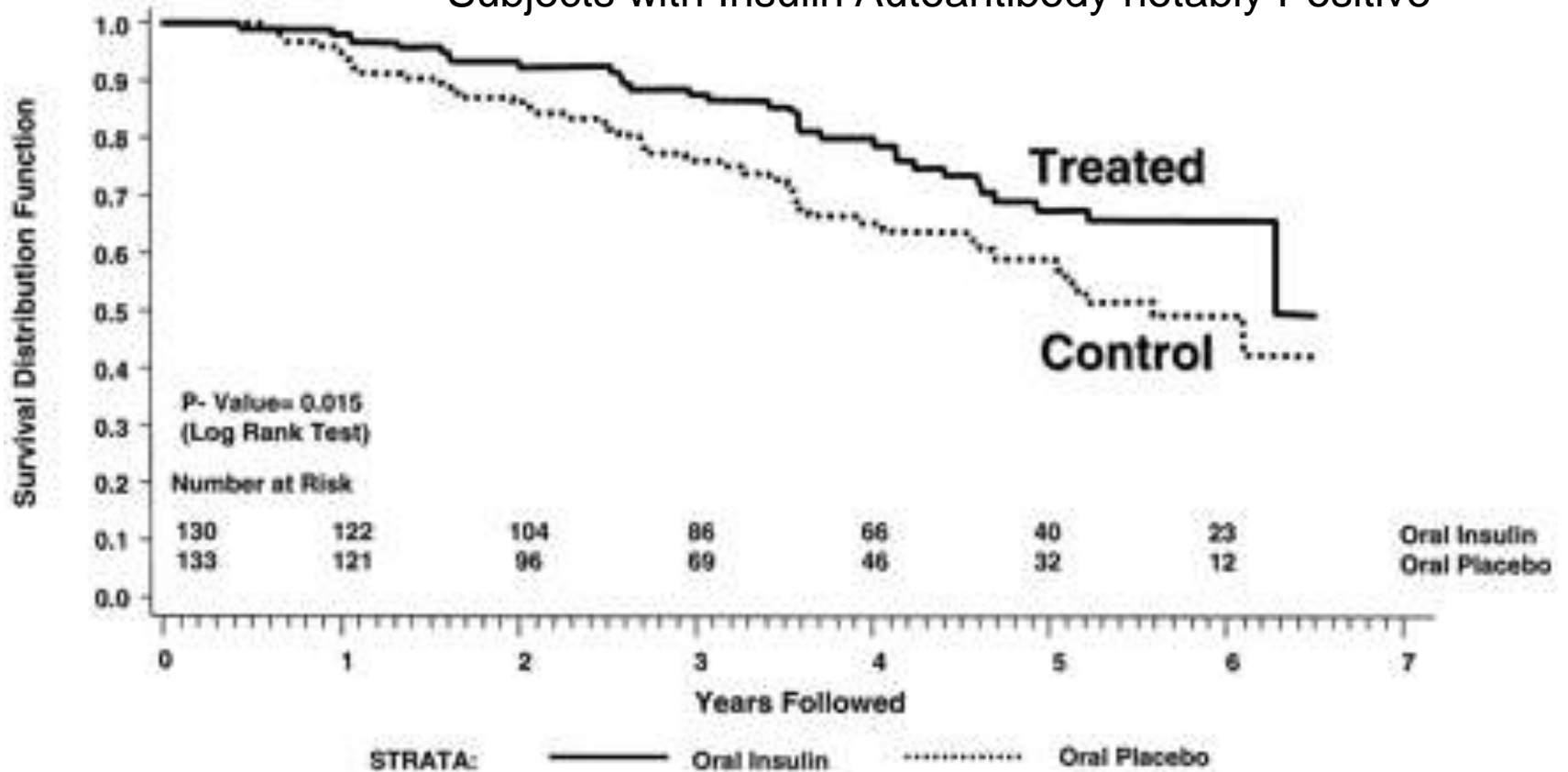


Can Type 1 Diabetes  
Be Prevented?

You Can Help Answer  
This Question

# Oral Insulin

Subjects with Insulin Autoantibody notably Positive



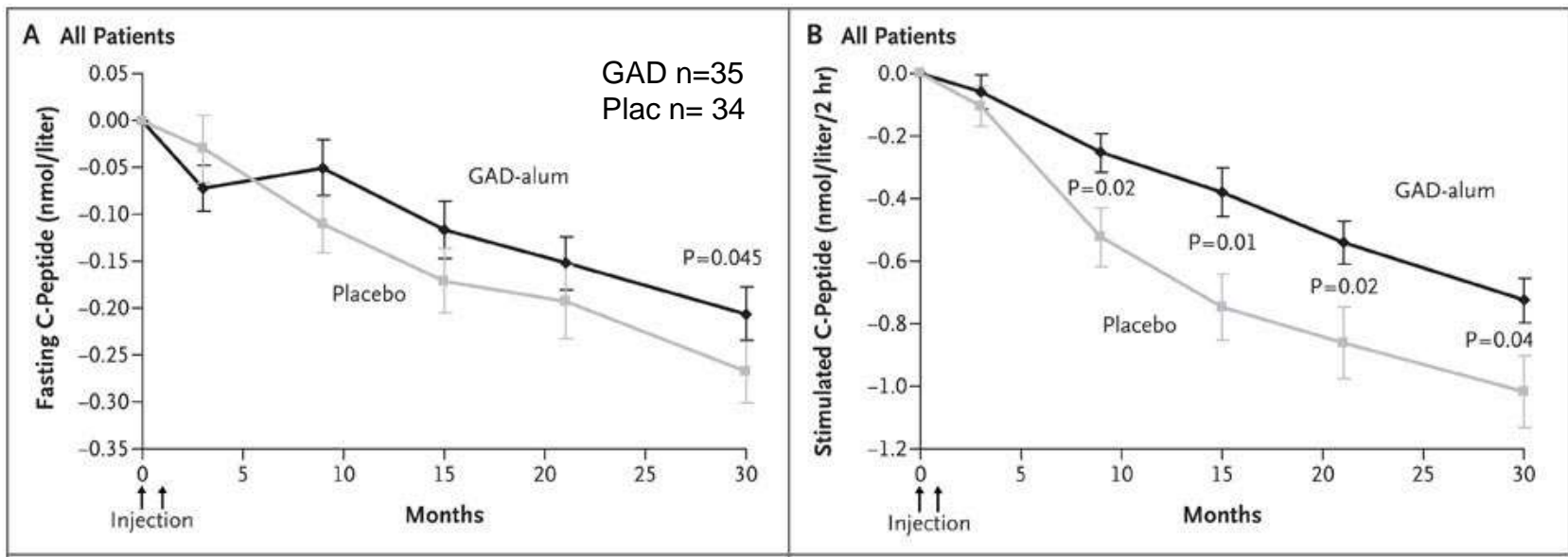
# Diabetes Vaccination Under Investigation



- GAD 65-Alum Injection
  - May lead to tolerance/immunomodulation
  - Ludvigsson et al. Diabetologia 2010 Nov 30
  - Shows continued safety and apparent efficacy in preserving beta cell function.
  - Larger studies underway



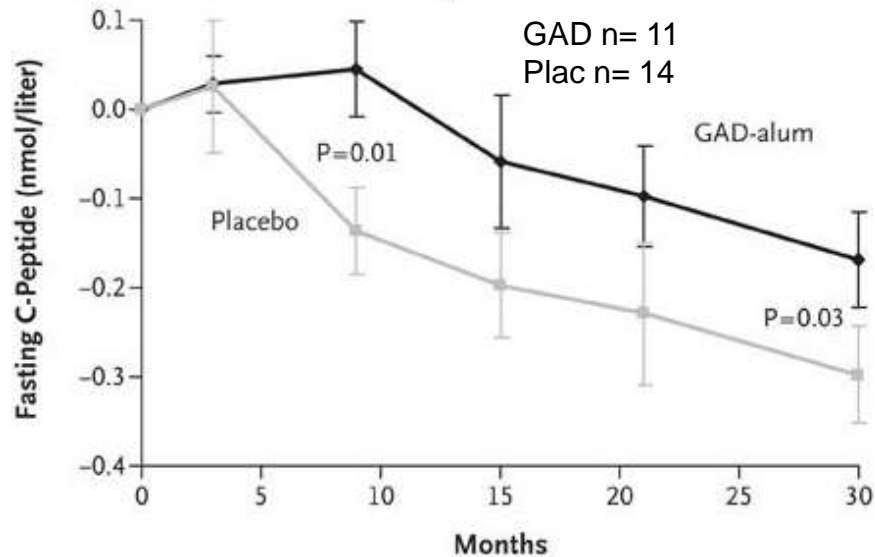
# C-Peptide Levels in GAD treated vs. Placebo



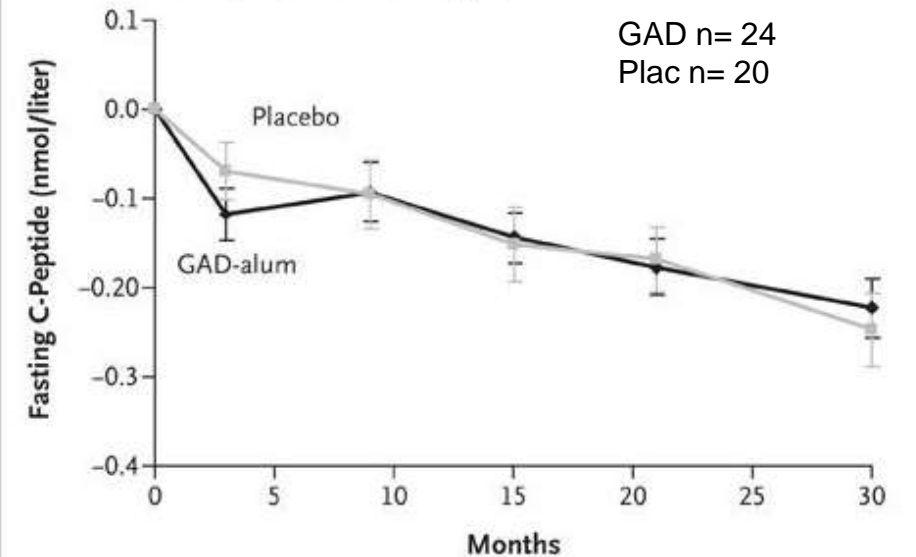
Ludvigsson et al. 359 (18): 1909-20 NEJM October 30, 2008

# Fasting C-Peptide Levels by duration of Diabetes at time of study

C Patients Treated <6 Mo after Diagnosis



D Patients Treated ≥6 Mo after Diagnosis





ORIGINAL ARTICLE

[◀ Previous](#)

Volume 352:2598-2608

June 23, 2005

Number 25

[Next ▶](#)

## Insulin Needs after CD3-Antibody Therapy in New-Onset Type 1 Diabetes

*Bart Keymeulen, M.D., Ph.D., Evy Vandemeulebroucke, M.D., Anette G. Ziegler, M.D., Ph.D., Chantal Mathieu, M.D., Ph.D., Leonard Kaufman, Ph.D., Geoff Hale, Ph.D., Frans Gorus, M.D., Ph.D., Michel Goldman, M.D., Ph.D., Markus Walter, M.D., Sophie Candon, M.D., Ph.D., Liliane Schandene, Ph.D., Laurent Crenier, M.D., Christophe De Block, M.D., Ph.D., Jean-Marie Seigneurin, Ph.D., Pieter De Pauw, Ph.D., Denis Pierard, M.D., Ph.D., Ilse Weets, M.D., Ph.D., Peppy Rebello, B.Sc., Pru Bird, Ph.D., Eleanor Berrie, Ph.D., Mark Frewin, Herman Waldmann, M.D., Ph.D., Jean-François Bach, M.D., Ph.D., Daniel Pipeleers, M.D., Ph.D., and Lucienne Chatenoud, M.D., Ph.D.*

### ABSTRACT

*Background* Type 1 diabetes mellitus is a T-cell-mediated autoimmune disease that leads to a major loss of insulin-secreting beta cells. The further decline of beta-cell function after clinical onset might be prevented by treatment with CD3 monoclonal antibodies, as suggested by the results of a phase 1 study. To provide proof of this therapeutic principle at the metabolic level, we initiated a phase 2 placebo-controlled trial with a humanized antibody, an aglycosylated

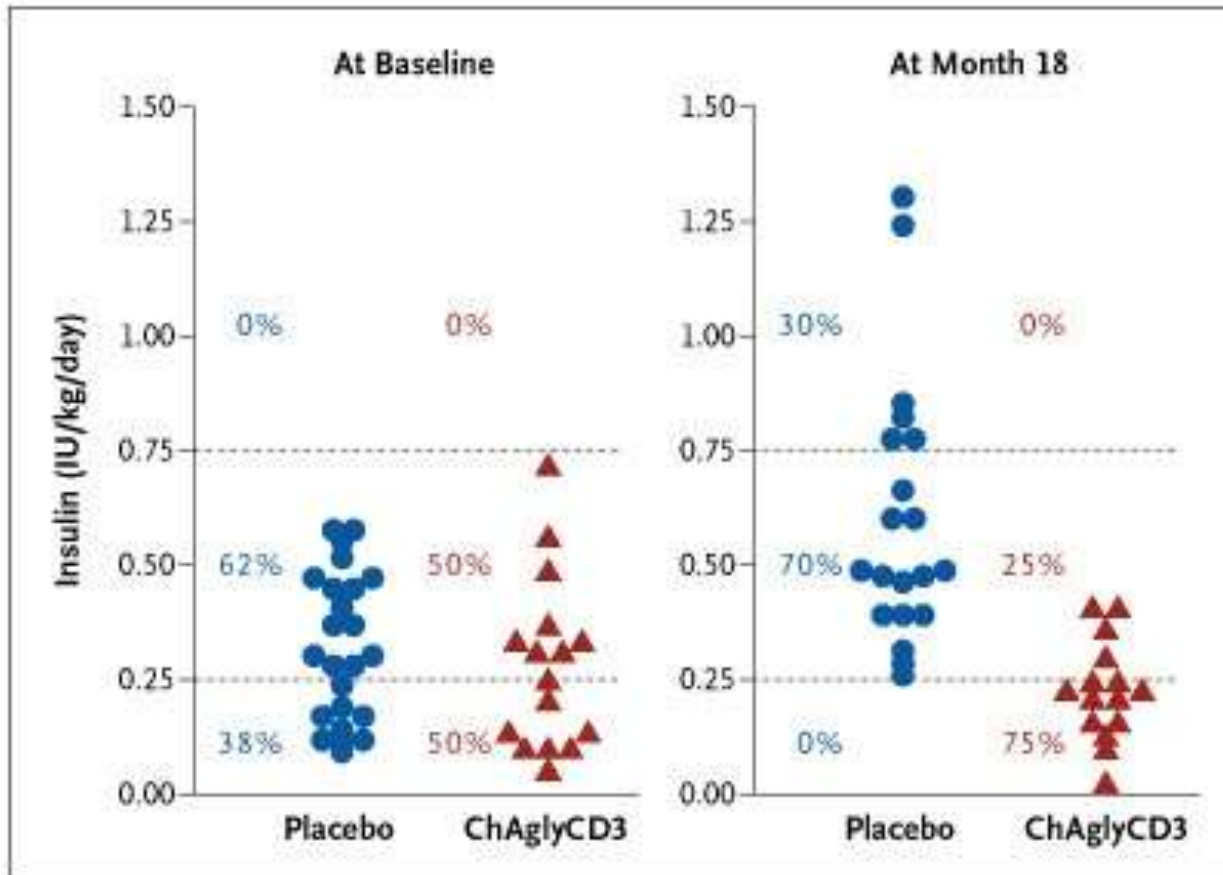
#### THIS ARTICLE

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- ▶ [Supplementary Material](#)

#### COMMENTARY

- ▶ [Editorial](#)

# Use of Anti-CD3



Comparison of Individual Insulin Doses at Baseline and 18 Months in Patients with an Initial Secretory Response at or above the 50th Percentile

# 4 Year Followup of Anti-CD3 treatment

- Keymeulen et al. continued to see a difference in insulin needs at 4 years post infusion
  - (Placebo 0.32 units/kg/day, study subjects 0.09 units/kg/day)
  - No long term adverse events

## Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus

Júlio C. Voltarelli, MD, PhD; Carlos E. B. Couri, MD, PhD; Ana B. P. L. Stracieri, MD, PhD; Maria C. Oliveira, MD, MSc; Daniela A. Moraes, MD; Fabiano Pieroni, MD, PhD; Marina Coutinho, MD, MSc; Kelen C. R. Malmegrim, PhD; Maria C. Foss-Freitas, MD, PhD; Belinda P. Simões, MD, PhD; Milton C. Foss, MD, PhD; Elizabeth Squiers, MD; Richard K. Burt, MD

*JAMA.* 2007;297:1568-1576.

### ABSTRACT

**Context** Type 1 **diabetes** mellitus (DM) results from a cell-mediated autoimmune attack against pancreatic beta cells. Previous animal and clinical studies suggest that moderate immunosuppression in newly diagnosed type 1 DM can prevent further loss of insulin production and can reduce insulin needs.

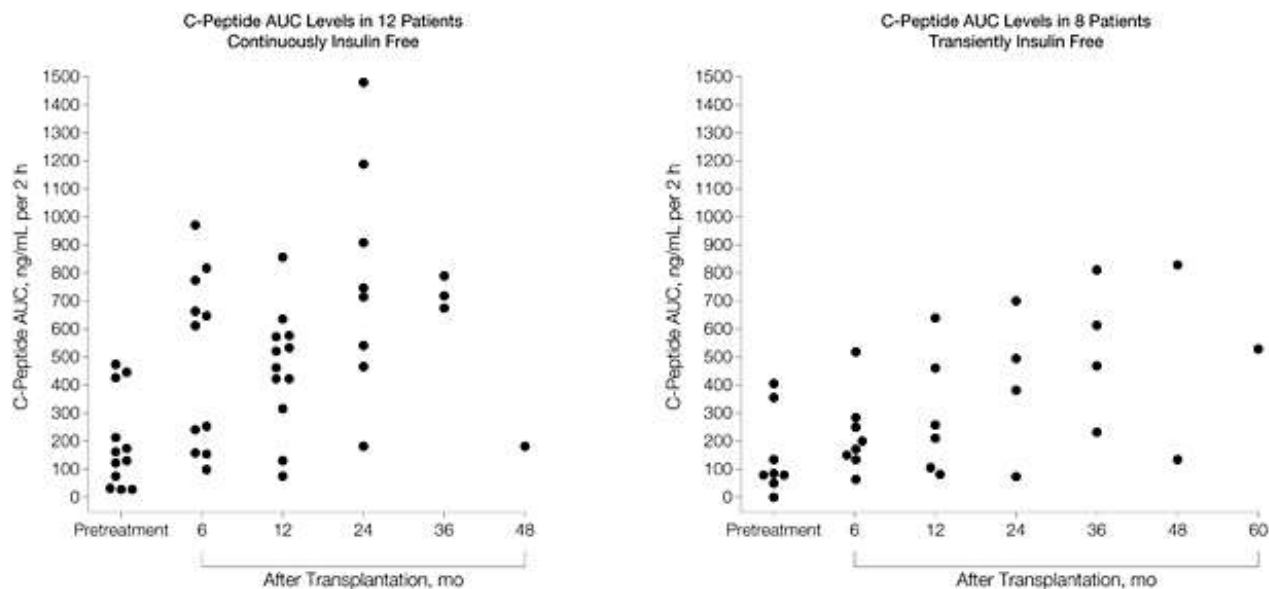
**Objective** To determine the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) in newly diagnosed type 1 DM.

**Design, Setting, and Participants** A prospective phase 1/2 study of 15 patients with type 1 DM (aged 14-31 years) diagnosed within the previous 6 weeks by clinical findings and hyperglycemia and confirmed with positive antibodies against glutamic acid

# The Brazil Experience

- The researchers enrolled 15 patients aged 14 to 31 (mean 19.2) between November 2003 and July 2006. All patients had been diagnosed with type 1 diabetes mellitus within the prior six weeks.
- All patients were first given an immune ablative conditioning regimen (Cyclophosphamide and Antithymocyte globulin)

# Time Course of Total Area Under the Curve (AUC) of C-Peptide Levels During Mixed-Meal Tolerance Test in 12 Patients Continuously Insulin Free and in 8 Patients Transiently Insulin Free



Couri, C. E. B. et al. JAMA 2009;301:1573-1579.

# Transplantation Complications

**Table 2.** Transplantation Complications

Patient No.	Mobilization Complications	Minor Conditioning Complications <sup>a</sup>	Major Conditioning Complications	Late Complications
1	Nausea, vomiting, pyoderma	Anorexia, fever, catheter infection	None	None
2	Dysuria		Bilateral pneumonia (from day -2 to day +14)	Graves disease ( $\geq 2.8$ y) <sup>b</sup>
3	None	Diarrhea, sinusitis, rash, fever	None	Rhabdomyolysis, hypothyroidism ( $\geq 1$ y)
4	Nausea, vomiting	Fever, catheter infection, herpes simplex, right cephalic vein thrombosis	None	Leukopenia, oligospermia
5	None	Anorexia, fever, urticaria	None	Oligospermia
6	None	Anorexia, fever, rash, hypokalemia, mucositis	None	None
7	None	Rash, diarrhea, fluid overload	None	None
8	None	Rash, anorexia, diarrhea	None	Oligospermia
9	None	Diarrhea, anorexia, fever	None	None
10	None	Rash	None	Transient hypogonadism ( $\geq 1$ y)
11	Fever	Anorexia, fever	None	None
12	None	Epistaxis	None	None
13	Fever	Diarrhea, rash	None	Oligospermia <sup>c</sup>
14	Sialorrhea	Rash, fever, fluid overload	None	Oligospermia
15	Nausea, vomiting, anorexia	Rash, fever	None	Oligospermia
16	Purulent amigdallitis	Anorexia	None	Oligospermia
17	Fever	Fever, rash	None	Oligospermia
18	None	Rash	None	Oligospermia
19	None	Headache, bradycardia	None	None
20	None	Urticaria, fever	None	None
21	None	Urticaria	None	None
22	Folliculitis	Rash, epistaxis	Bilateral pneumonia (from day +1 to day +11)	None
23	None	Urticaria, fever	None	None

<sup>a</sup>All patients except 4, 5, 7, and 8 presented with nausea; vomiting presented in all patients except 4 and 6; and all presented with alopecia.

<sup>b</sup>Patient 2 fathered a child 2 years after transplantation.

<sup>c</sup>Patient 13 fathered a child 2 years after transplantation.

Couri, C. E. B. et al. JAMA 2009;301:1573-1579.

# The Brazil Experience

## Concerns

- Cyclophosphamide – toxic to gonads
- 2 patients had Bilateral pneumonia – resolved
  - Could there be worse side effects –worth it?
- Not placebo controlled
  - Good honeymoon?
- Final Results **REMAIN TO BE SEEN**

# Very Early Concepts

- Leptin
  - Blocks Lipogenesis (fat breakdown) and excess glucagon secretion
  - Thus, can help smooth out the variability/hyperglycemia seen in insulin treated patients

# Generation of pluripotent stem cells from patients with type 1 diabetes

René Maehr<sup>a</sup>, Shuibing Chen<sup>a</sup>, Melinda Snitow<sup>a</sup>, Thomas Ludwig<sup>b</sup>, Lisa Yagasaki<sup>a</sup>, Robin Goland<sup>c</sup>, Rudolph L. Leibel<sup>c</sup>, and Douglas A. Melton<sup>a,1</sup>

<sup>a</sup>Department of Stem Cell and Regenerative Biology, Howard Hughes Medical Institute, Harvard Stem Cell Institute, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138; and <sup>b</sup>Department of Pathology and Cell Biology, and <sup>c</sup>Division of Molecular Genetics and Naomi Barrie Diabetes Center, College of Physicians and Surgeons, Columbia University, New York, NY 10032

Contributed by Douglas A. Melton, July 8, 2009 (sent for review May 18, 2009)

Type 1 diabetes (T1D) is the result of an autoimmune destruction of pancreatic  $\beta$  cells. The cellular and molecular defects that cause the disease remain unknown. Pluripotent cells generated from patients with T1D would be useful for disease modeling. We show here that induced pluripotent stem (iPS) cells can be generated from patients with T1D by reprogramming their adult fibroblasts with three transcription factors (OCT4, SOX2, KLF4). T1D-specific iPS cells, termed DiPS cells, have the hallmarks of pluripotency and can be differentiated into insulin-producing cells. These results are a step toward using DiPS cells in T1D disease modeling, as well as for cell replacement therapy.

$\beta$  cell | disease model | autoimmune | directed differentiation | endoderm

reactions and the autoimmune response that caused the initial  $\beta$  cell destruction.

Mouse and human fibroblasts can be used to generate iPS cells (14–16). Recently, iPS cells have been generated from fibroblasts obtained from patients with various diseases (4–7), but not for T1D. T1D-specific iPS (DiPS) cells derived from patients offer several significant advantages. First, DiPS cells would unquestionably contain the genotype responsible for the human disease. Second, DiPS cells would provide an immunologically matched autologous cell population, although dependent on improvements in differentiation protocols. Third, and the present focus of our work, patient-specific cells make possible patient-specific disease modeling wherein the initiation and

# Many More Studies!!!

List Results

[Refine Search](#)

[Results by Topic](#)

[Results on Map](#)

[Search Details](#)

Found 3228 studies with search of: **type 1 diabetes mellitus**

[Hide studies that are not seeking new volunteers.](#)

Rank	Status	Study
1	Active, not recruiting	<a href="#">PROCHYMAL® (Human Adult Stem Cells) for the Treatment of Recently Diagnosed Type 1 Diabetes Mellitus (T1DM)</a> Conditions: Type 1 Diabetes Mellitus; Type 1 Diabetes; Diabetes Mellitus, Insulin-Dependent; Juvenile Dia Interventions: Drug: PROCHYMAL®; Drug: Placebo
2	Completed	<a href="#">A Study to Evaluate Symlin in Adolescent Subjects With Type 1 Diabetes Mellitus</a> Condition: Type 1 Diabetes Mellitus Intervention: Drug: pramlintide acetate
3	Recruiting	<a href="#">Sleep and Glucose Regulation in Youth With Type 1 Diabetes Mellitus</a> Conditions: Type 1 Diabetes Mellitus; Sleep Intervention:
4	Recruiting	<a href="#">Effect of Pioglitazone on the Course of New Onset Type 1 Diabetes Mellitus</a> Condition: Type 1 Diabetes Mellitus Interventions: Drug: pioglitazone; Drug: Placebo control
5	Active, not recruiting	<a href="#">Islet Transplantation for Type 1 Diabetes Mellitus</a> Condition: Type 1 Diabetes Mellitus Intervention: Procedure: Islet Transplant
6	Completed	<a href="#">T Cell Validation Study Using Blood Samples From Subjects With Recent Onset Type 1 Diabetes Mellitus</a> Condition: Type 1 Diabetes Mellitus Interventions: Procedure: T Cell Proliferation and Autoreactivity Assays; Procedure: Cellular Immunoblot Assay Procedure: Tetramer Studies; Procedure: Cytokine ELISPOT intervention: Drug: Oral insulin

# Natural History of Type 1 Diabetes



# Pumps



# Sensors/CGMS

- Embedded in Pump
  - Medtronic
- Stand Alone
  - Medtronic Guardian RT
  - DexCom
  - FreeStyle Navigator



# Super Computer



# How Do We Close the Loop?



From Medtronic UK Website

# The Path to Clinical Use

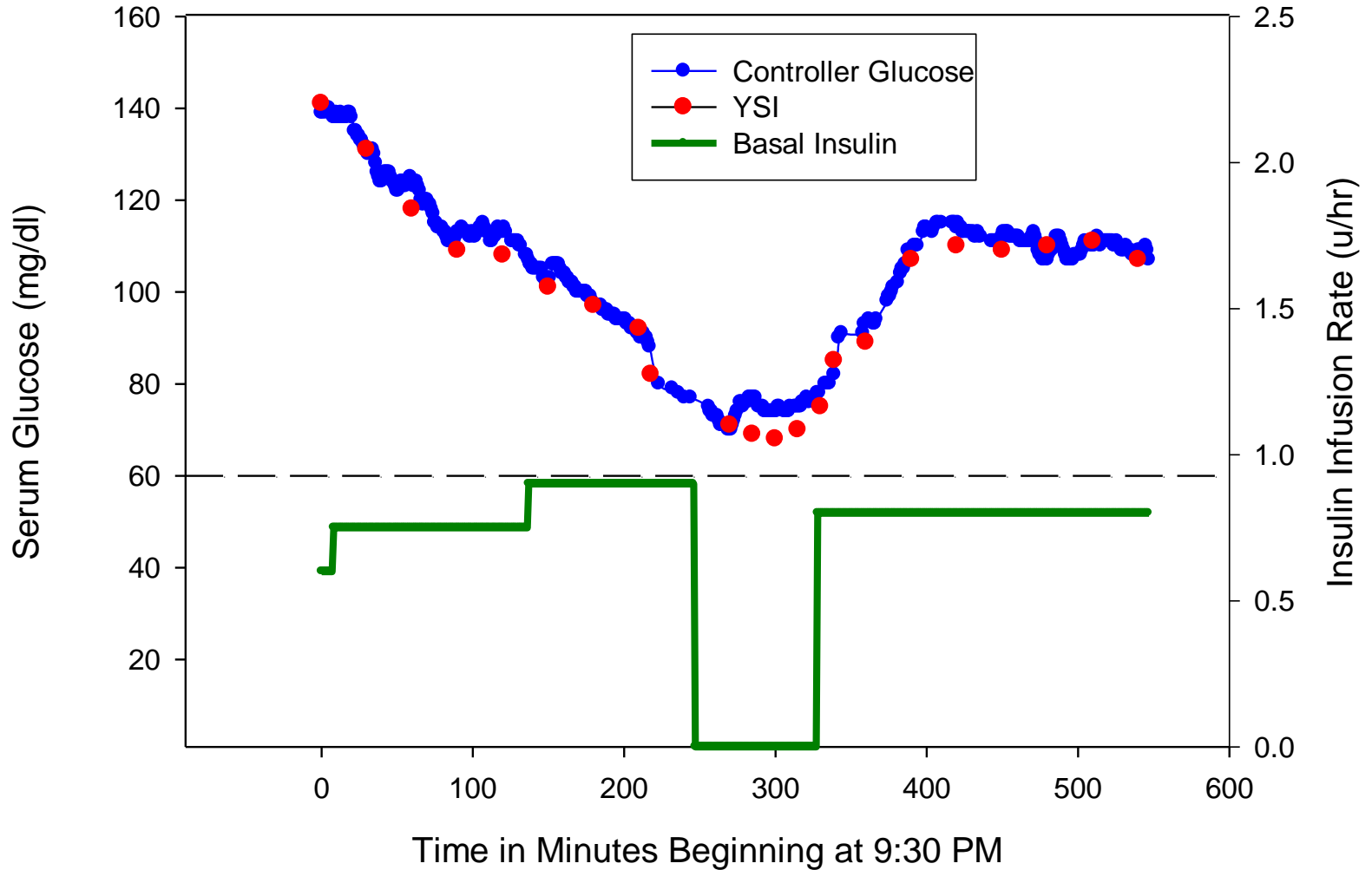
- Low Glucose Auto-suspend
- Hypoglycemia Prevention
- Treat-to-Range – closed-loop control to prevent extremes
- Full closed-loop
  - Inpatient
  - Outpatient

# A Closed-Loop System Should:

- Detect the onset of eating
- Detect Sensor Failure
- Detect Infusion Set Failure
- Prevent Hypoglycemia/Hyperglycemia
- Be small and lightweight
- “Auto-insertion” of sensors and infusion sets
- Be user friendly

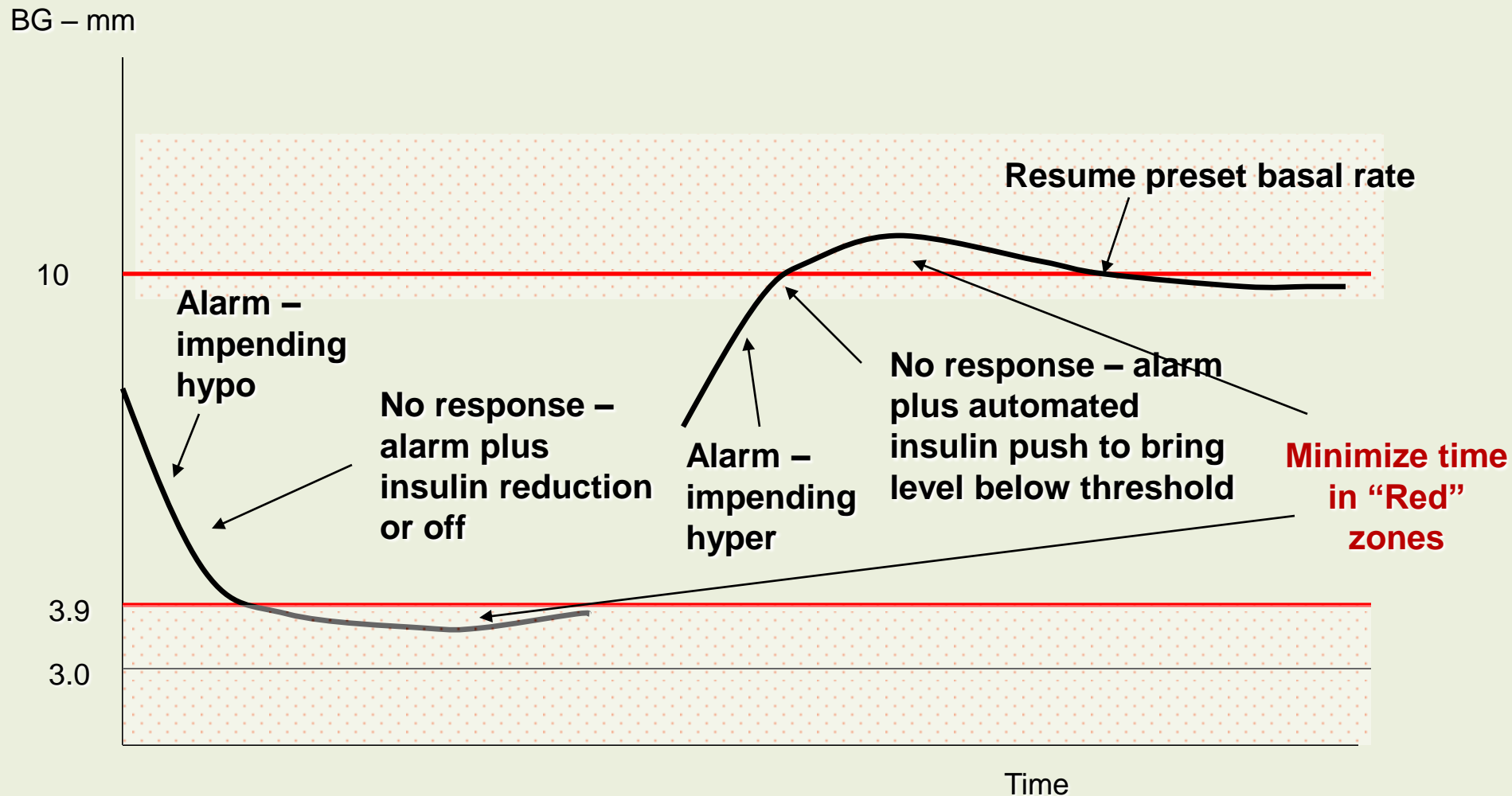
# CL2-MW 9-3-08

3 Alarm, Threshold 80 mg/dl, Horizon 35 min



Patient Data from Personal Communication, Dr. Buckingham

# Target Product – Hypo & Hyper Minimizer



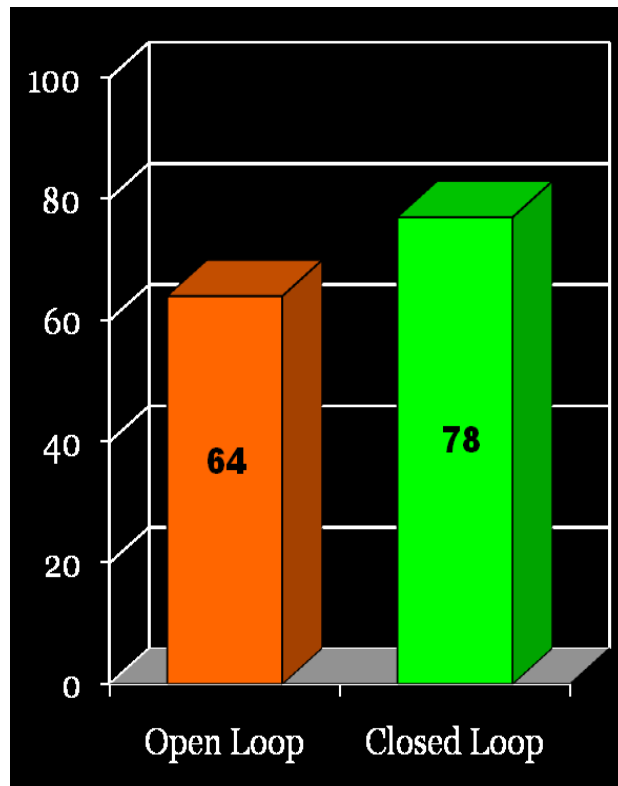
But Has Someone “Closed the  
Loop?”

# Closed Loop at UVA/Padova/Montpellier

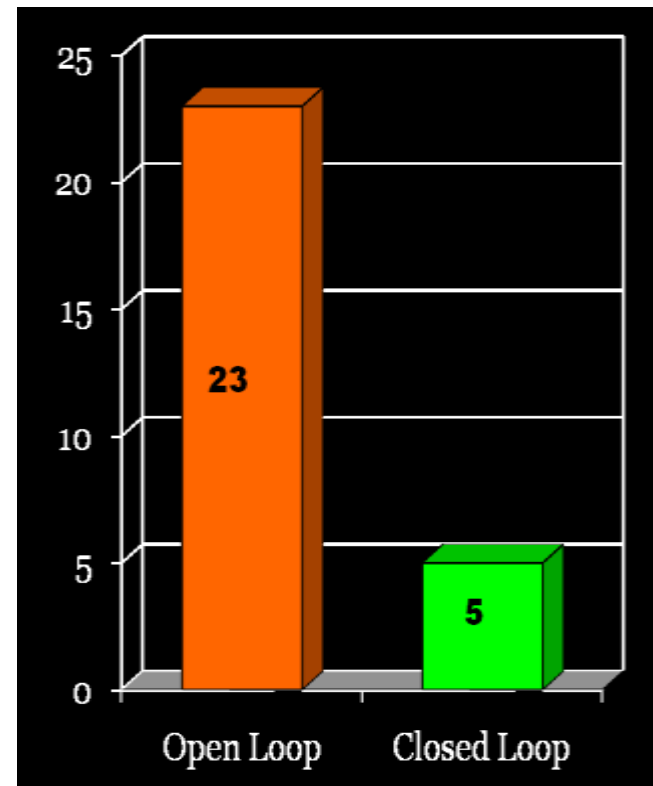
N=20 subjects completed study

Primary Outcome: Reduction in Nocturnal Hypoglycemia with better overall glucose control within target range:

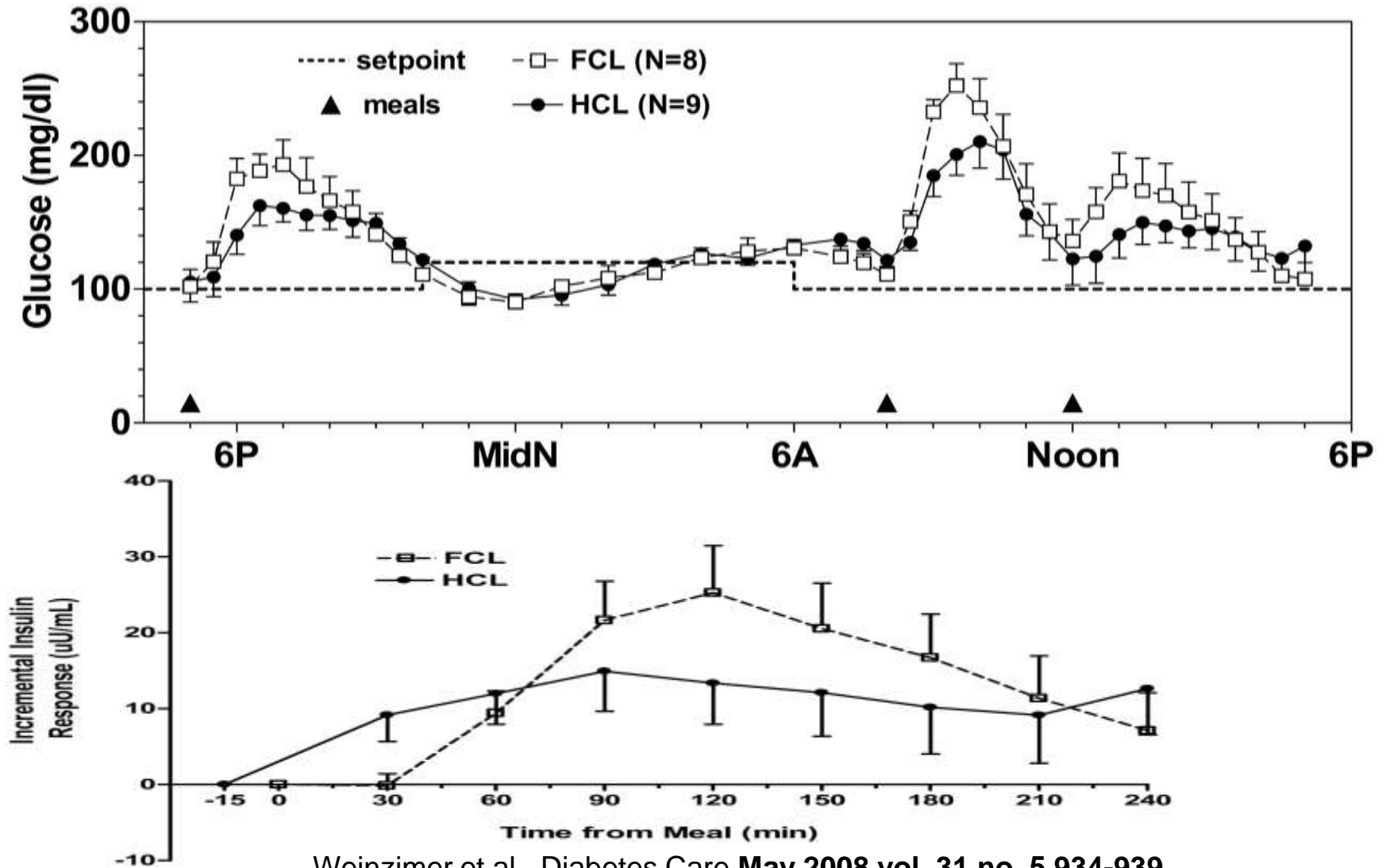
Overnight percent time within Target range of 70-140 mg/dl



Nocturnal Hypoglycemic Episodes (BG < 70 mg/dl)



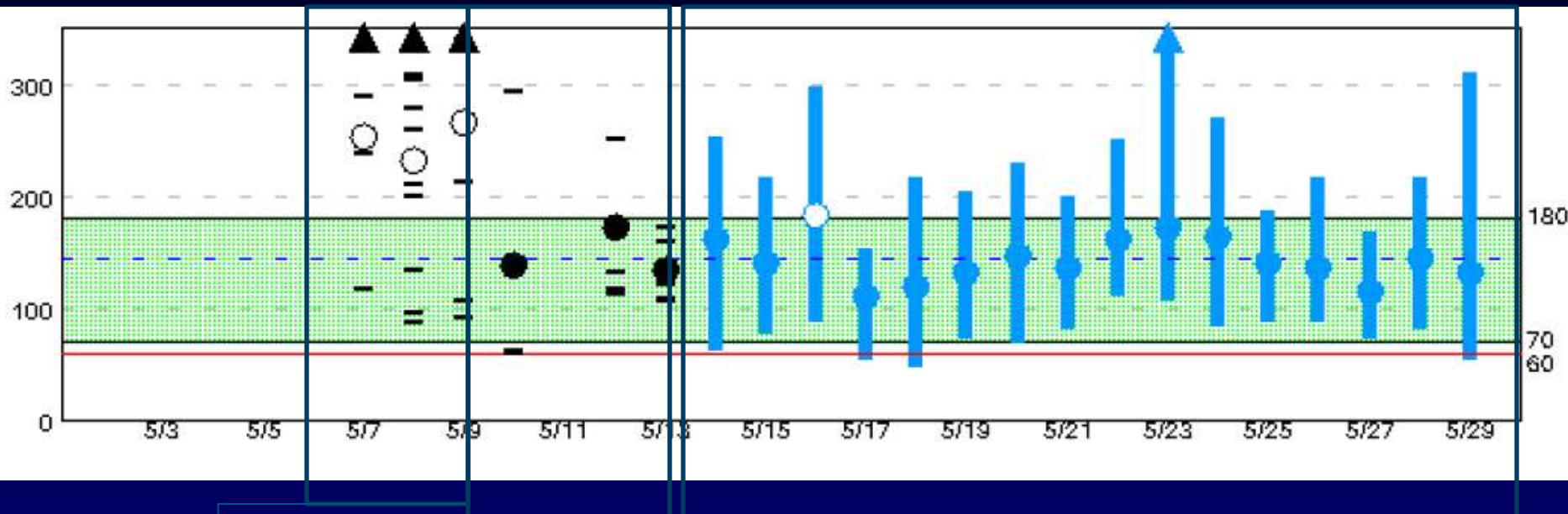
# Full Closed Loop Vs. Hybrid



# Glycemic Control Parameters

	FCL mean ± SD	HCL mean ± SD	P value
Daytime plasma glucose (mg/dl)	159 ± 59	149 ± 47	0.03
Nighttime plasma glucose (mg/dl)	111 ± 27	112 ± 28	0.81
Peak Postprandial glucose (mg/dl)	226 ± 51	194 ± 47	0.04
Nocturnal glucose nadir (mg/dl)	72 ± 16	79 ± 20	0.48

# Metabolic Control Closed-loop Subject 1

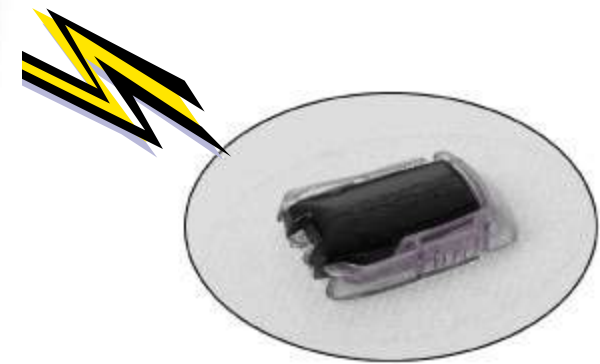
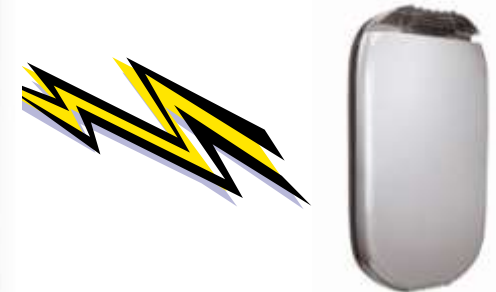


Post-DKA  
Humalog  
And  
Lantus  
Mean  
 $245 \pm 111$

3-day  
closed  
loop  
Mean  
 $138 \pm 50$

At home on Sensor Augmented Pump  
Mean  $145 \pm 50$

# Pumps and Sensors Communicate to a Shared Platform



Buckingham, 2009

# Some Pig



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## Nine-year survival of transplanted pig islet cells in a diabetic patient

Main Category: [Diabetes](#)

Article Date: 09 May 2005 - 10:00 PST

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Living Cell Technologies Ltd today reported the long-term survival of encapsulated pig islets in a man with type 1 diabetes. The cells were retrieved after being in the patient's abdomen for almost nine years.

A 40 year old man with Type 1 diabetes received a transplant of an early prototype of LCT's DiaBCell in 1996, as part of an approved clinical trial. Type 1 diabetics are not able to produce sufficient insulin of their own. The pig islet transplants were intended to release insulin and restore control of blood glucose levels.

The pig islets were prepared in an alginate capsule to protect them from immune rejection and no immune suppressive drugs were needed for this transplant.

"For about one year, his insulin dosage was reduced by as much as 34 per cent and control of his diabetes improved," said Professor Bob Elliott, LCT Medical Director. "However, by two years the daily insulin requirement returned to the pre-transplant dose. Nevertheless, he has insisted that over the next seven years continued benefit from DiaBCell helped him control his diabetes better than before the transplant," continued Professor Elliott. Professor Elliott said, "The patient insisted that the site of the transplant (the abdominal cavity) be examined. We were pleasantly surprised to see a small number of intact capsules. The capsules contained live pig cells. A few were removed and produced a detectable amount of insulin in culture when stimulated with glucose. Analysis using microscopy further indicated that these few cells contained insulin."

"I have always thought the transplant has helped me manage my blood glucose levels better, especially overnight. I am looking forward to another transplant," the patient told LCT. "This is one patient's experience," said David Collinson, Chief Executive Officer of LCT, "but it shows that pig cells within capsules, when placed in the abdomen, can be protected for a long period of time and, continue to produce small amounts of insulin. This is potentially great news for diabetics."

"We have taken the best features of this prototype islet preparation, advanced our encapsulation technology and

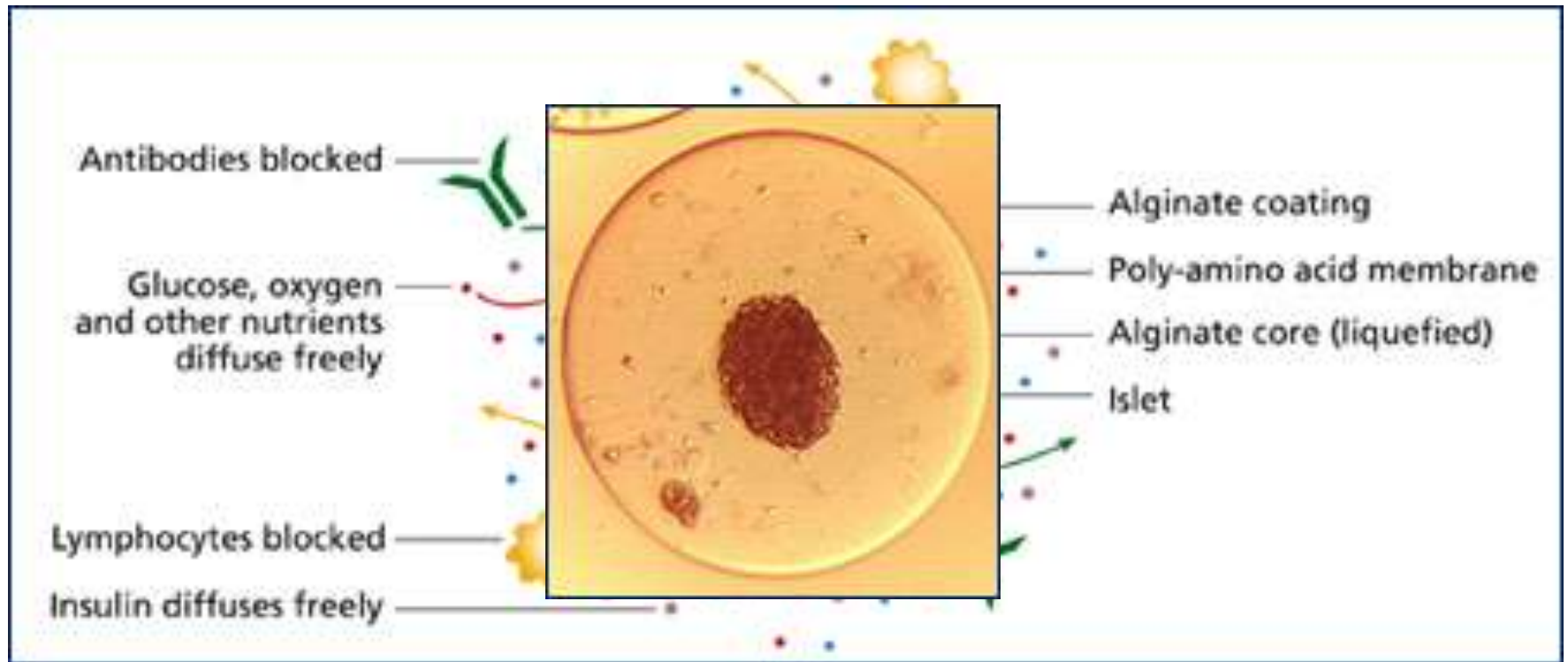
*Living Cell Technologies NZ Limited*

**DIABECCELL®**  
ENCAPSULATED  
PORCINE ISLET CELLS

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Manukau 2155, Auckland, New Zealand  
ph +64 9 276-2690 fax +64 9 276-2691

QA 011

# Islet Cell Encapsulation



From MicroIslet Webpage

# MannKind And Afresa®

