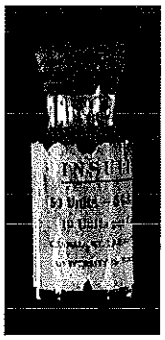
Diabetes Research and Novel Therapeutics Update

OC Collaborative Diabetes Conference
April 26, 2014
Mark Daniels, MD
CHOC Pediatric Endocrinology

Disclaimer/Disclosure

- I do not have any personal financial relationships with ANY of the companies or products presented today
- I do not have any family member's with financial relationships with the companies or products presented today
- CHOC Children's Hospital receives funding from the NIH for work on TrialNet

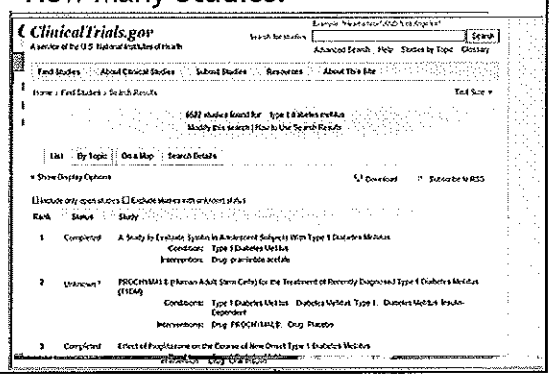
Diabetes 1921

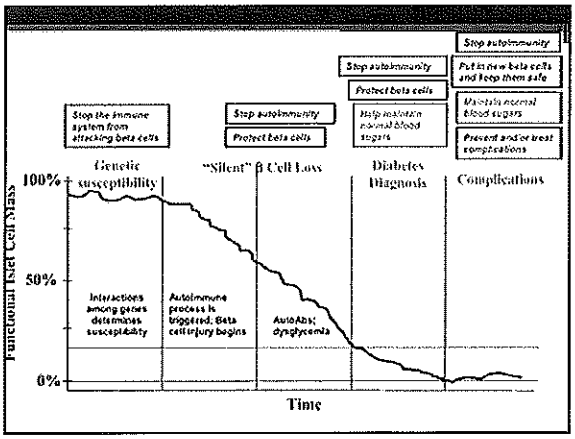


Overview

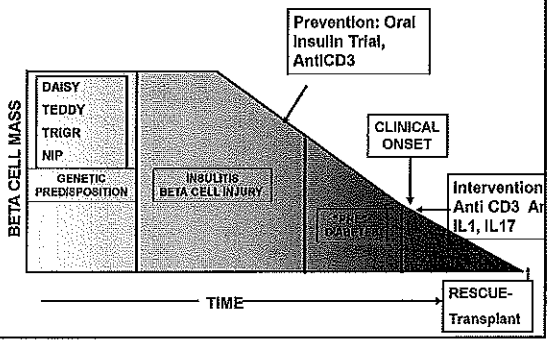
- Type 1 Diabetes Research
  - Natural History
  - Genetic and Environmental Determinants
  - The Problem of Autoimmunity
  - Transplants
- Type 2 Novel Therapeutics
  - Insulin advances
  - Non – insulin medications
- Apps

How Many Studies?





Natural History of Type 1 Diabetes

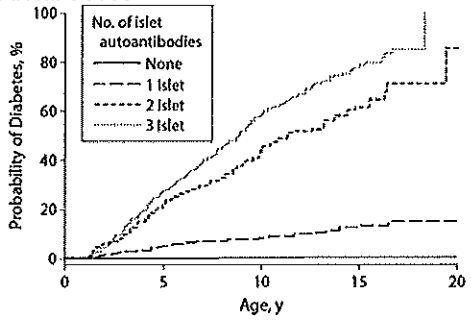


Type 1 Diabetes TrialNet

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.

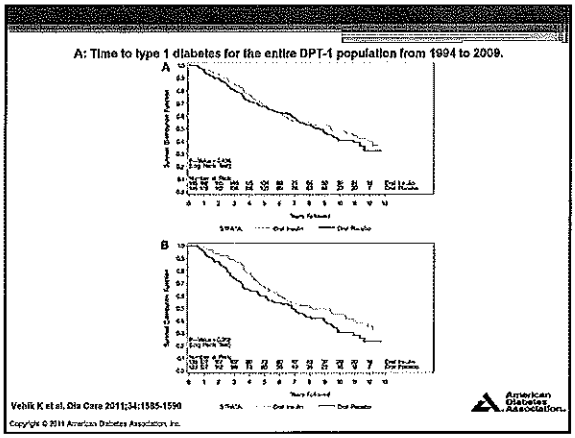
Progression to Diabetes with Islet Cell Antibodies



JAMA. 2013;309(23):2473-2479

Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children

- Progression to type 1 diabetes at 10-year follow-up after islet autoantibody seroconversion in 585 children with multiple islet autoantibodies was 69.7%
- in 474 children with a single islet autoantibody was 14.5%
- Risk of diabetes in children who had no islet autoantibodies was 0.4%
- ***JAMA*. 2013;309(23):2473-2479**



Oral Insulin in TrialNet

- Relatives of patients with type 1 Diabetes are screened for presence of antibodies.
- If + micronized Insulin Autoantibody (mIAA), and one other antibody, then randomized to receive oral insulin or placebo.
- Endpoint is development of diabetes
- Started 2007 – Still ongoing!!!

Effectiveness of Early Intensive Therapy on β-Cell Preservation in Type 1 Diabetes

	Intensive	Standard
n	47	20
C-peptide AUC (pmol/mL), geometric mean (95% CI)[a]	0.43 (0.34–0.52)	0.52 (0.32–0.75)
	N = 48	*N* = 20
HbA_{1c} (%)[b], mean ± SD	7.4 ± 1.2	7.3 ± 1.1
HbA_{1c} (mmol/mol), mean ± SD	57 ± 13	57 ± 12
CGM data median	*N* = 31	*N* = 15
Mean glucose (mg/dL)	150	152
71–180	69%	70%
<70	2.5%	0.7%
>180	27%	22%
CV (%)	35	33
	N = 48	*N* = 20
TDI (units/kg/day)	0.6 ± 0.2	0.6 ± 0.3
	N = 46	*N* = 19
BMI percentile[c]	58	62

Buckingham et al. Diabetes Care December 2013 Vol 36 No 12 4030 =4035

Genetics and Environmental Determinants

- The first questions I am ALWAYS asked after giving the news to a family is:
- WHY DID THIS HAPPEN? WHAT CAUSES DIABETES?

TEDDY

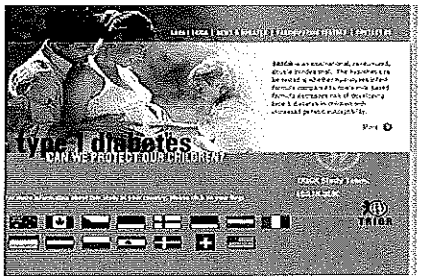
The Environmental Determinants of Diabetes in the Young

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"
- Data Collection Complete in 2025!!!

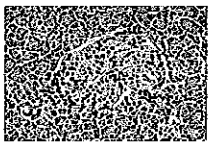
TRIGR

Trial to Reduce IDDM in the Genetically at Risk

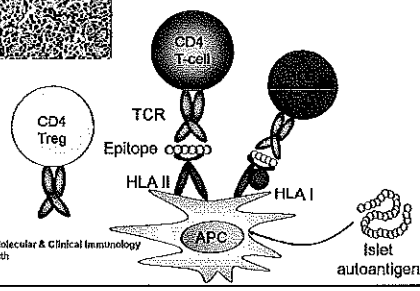


Results Expected 2017

Type 1 diabetes is T cell mediated

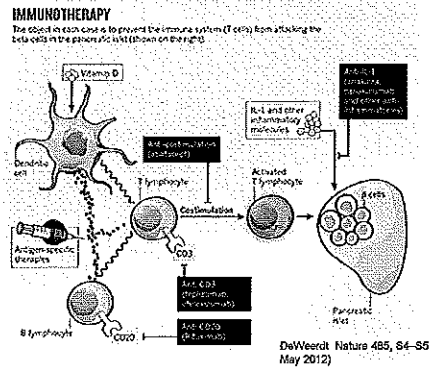


- Infiltrating CD4+, CD8+ T cells
- Anti-T cell therapies are effective
- Islet cell autoantibodies ≠ disease



Type 1 Diabetes: Cellular, Molecular & Clinical Immunology
Edited by George S. Eisenbarth
Online Edition Version 3.0

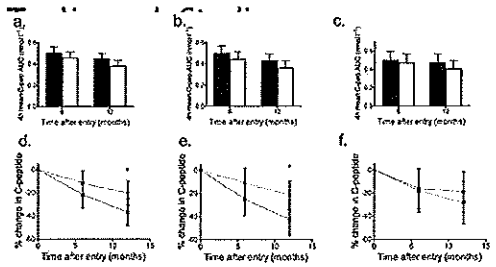
Altering the Immune Attack



DeWeerdt Nature 485, S4–S5 (17 May 2012)

Immune Targeted Therapies

- Teplizumab – Anti CD3 Ab
  - Daily Infusions for 14 days.
  - "At Risk" vs Recent Onset vs Post recent Onset
- Secukinamab Anti IL17
- Canakinumab Anti IL1 Beta
  - Monthly Subcutaneous Injections
- Imatinib – GLEEVEC ???



- At Risk – Currently Recruiting

Islet Transplants

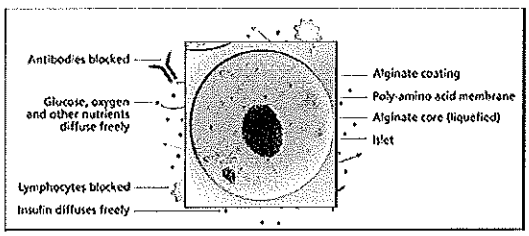
- 1893: Minkowski transplants fragments of a sheep's pancreas into a diabetic 15-year-old boy. The boy dies three days after the operation.
- 1924: Pybus tries to transplant human cadaveric pancreas tissue in an attempt to cure diabetes, grafts rejected due to lack of immunosuppression.
- 1963: The immunosuppressant Azathioprine is discovered, starting an organ transplant revolution.
- 1966: The first whole pancreas transplant is performed.
- 1974: Researchers begin the first clinical trial of islet transplantation, using steroids and azathioprine as immunosuppressants. None of these patients achieve insulin independence.
- 1990: A few islet transplant recipients achieve prolonged and consistent insulin independence using steroid-free, tacrolimus based immunosuppression.
- 1999: The Edmonton group uses a new procedure to achieve an initial 100% success rate by using tacrolimus and sirolimus rather than cyclosporine and steroids,

http://biomed.brown.edu/Courses/BI108/BI108_2004_Groups/Group09/history.htm

The Problem of Autoimmunity!

- One Solution:

Islet Cell Encapsulation



From Microislet Webpage

In

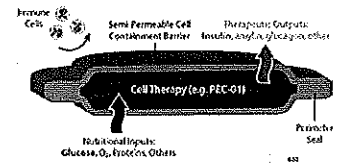
An Open Label, Pilot Investigation, to Assess the Safety and Efficacy of Transplantation of Micro-encapsulated Human Islets Within the Bioartificial Pancreas Beta-Air in Patients With Type 1 Diabetes Mellitus

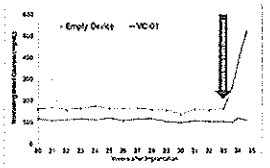
No More Frequent Glucose Monitoring & Insulin Injections

BETA-O2

ViaCyte -

Cross Section of Encaptra® Drug Delivery System





Technology

- Pumps
- Sensors
- Sensor Augmented Pumps
- Threshhold Suspend Pump
- Hybrid Closed Loop Pumps

The Effects of Lowering Nighttime and Breakfast Glucose Levels with Sensor-Augmented Pump Therapy on Hemoglobin A1c Levels in Type 1 Diabetes.

- Star 3 trial
- 196 patients analyzed
- After multivariate analysis
  - Improving Breakfast Period Glucose CGM had the largest effect on improving A1C
  - Other periods did NOT seem to affect A1C
  - Lending new credence to "Breakfast is the..."

But Is Someone Trying To "Close the Loop?" circa 2011

Inpatient Evaluation of an Automated Closed-Loop Control-to-Range System (CTR)

This study is currently recruiting participants.

Feasibility Study Assessing The Ability Of An Insulin Pump-Controlling Algorithm To Minimize Hypoglycemia And Hyperglycemia In Patients With Type 1 Diabetes In A Clinical Research Setting

This study is currently recruiting participants.

Getting Closer to Real World!

Closing the Loop in Children and Adolescents With Type 1 Diabetes in the Home Setting (APCam08)

This study is currently recruiting participants.

ClinicalTrials.gov Identifier: NCT01778348

First received: January 25, 2013
Last updated: December 19, 2013
Last verified: December 2013
History of Changes

Sponsor:
University of Cambridge

Collaborators:
Cambridge University Hospitals NHS Foundation Trust
University College London Hospitals
The Leeds Teaching Hospitals NHS Trust

Information provided by (Responsible Party):
Dr Roman Hovorka, University of Cambridge

Integration of Continuous Glucose Monitoring Into a Bi-Hormonal Closed-Loop Artificial Pancreas for Automated Management Of Type 1 Diabetes (CL2)

This study has been completed.

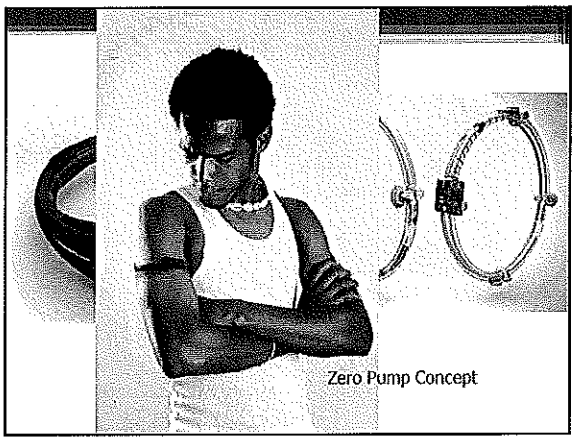
ClinicalTrials.gov Identifier: NCT01191062

First received: July 12, 2010
Last updated: October 21, 2013
Last verified: October 2013
History of Changes

Sponsor:
Boston University

Collaborators:
Massachusetts General Hospital
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Juvenile Diabetes Research Foundation
Leona M. and Harry B. Helmsley Charitable Trust

Information provided by (Responsible Party):
Edward R. Damiano, Boston University



And Now for Something Completely Different

Effects of Metreleptin in Type 1 Diabetes Mellitus

This study is currently recruiting participants.
Verified June 2013 by University of Texas Southwestern Medical Center

Sponsor:
University of Texas Southwestern Medical Center

Collaborators:
Juvenile Diabetes Research Foundation
Amylin Pharmaceuticals, LLC

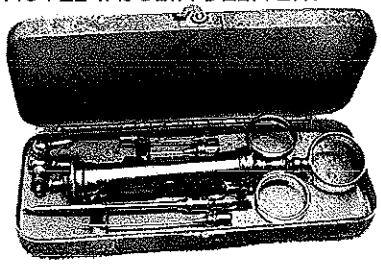
Information provided by (Responsible Party):
Aikaterini Garg, University of Texas Southwestern Medical Center

ClinicalTrials.gov Identifier:
NCT01265044

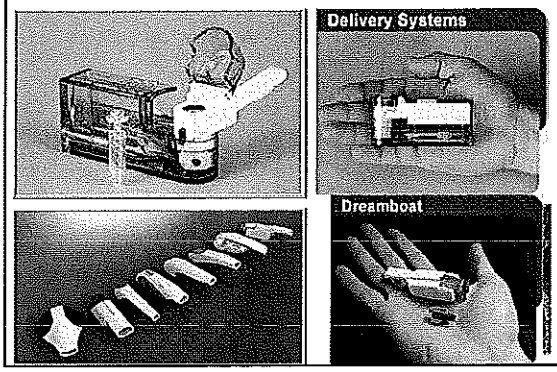
First received: December 22, 2010
Last updated: June 19, 2013
Last verified: June 2013
History of Changes

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

BIOLOGICAL SOLUTIONS And *NOVEL INSULIN DELIVERY*



MannKind And Afrezza®



AFREZZA or Technosphere Insulin (TI)

Figure 1 Technosphere inhalation insulin device.

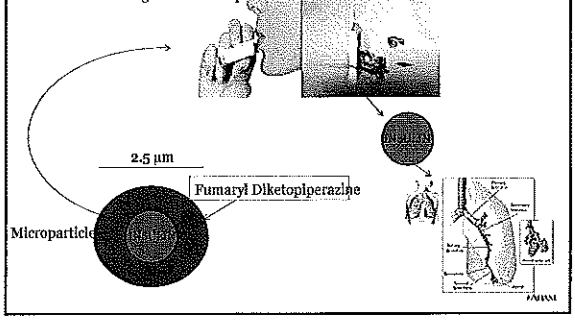
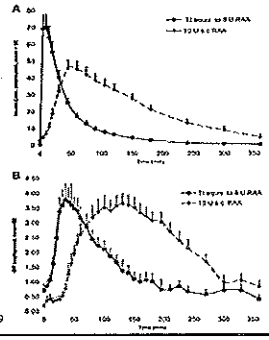


Figure 2 PK/PD profile of inhaled TI versus a Rapid Acting Analog (RAA)

A. Insulin Concentration

B. Glucose Infusion Rate (GIR)



Cassidy JP, et al. Poster presented at ADA June 5-9, 2009

Results for Change in A1c level with Technosphere Insulin (TI) vs. Aspart with Glargine.

- The initial A1C was between >7.0% and ≤11.0%
- The change in A1C was
  - -0.11% for TI and
  - -0.36% for Aspart, making TI non-inferior to Aspart.

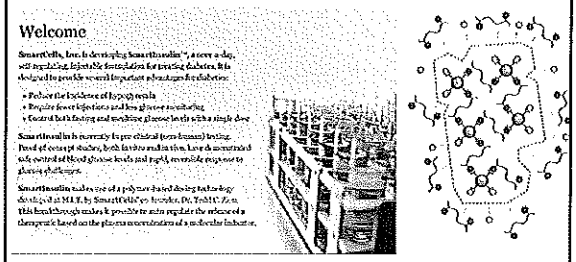
J Diabetes Sci Technol Vol 6, Issue 4, July 2012

Results for Hypoglycemia in Technosphere Insulin (TI) vs. Aspart with Glargine in Type 1 diabetes.

- TI group showed reduced incidence of mild/moderate hypoglycemia.
  - [odds ratio (OR), 0.474; 95% CI, 0.0271 to 0.831; $p = .0091$]
- TI group showed less overall hypoglycemia
  - (OR, 0.488; 95% CI, 0.278 to 0.856; $p = .0124$) compared with the Aspart group.

J Diabetes Sci Technol Vol 6, Issue 4, July 2012

SmartInsulin ™



From http://www.technologyreview.com/biomedicine/21613/?a=f

Degludec

- Insulin Degludec (Danne et. al.)
  - Ultra Long Lasting Insulin
  - Maximal concentration by 10-11 hours
  - Lasts up to 72 hours in children

Medscape Medical News > News. Approvals and Safety Changes

FDA Rejects Novo Nordisk's Insulin Degludec

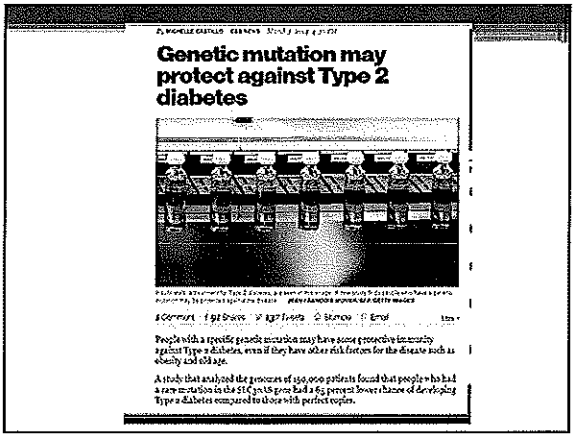
William E. Tucker | Disclosures

February 11, 2013

DRUG & REFERENCE INFORMATION

Hyperosmolar Hyperglycemic State

The US Food and Drug Administration (FDA) has declined to approve Novo Nordisk's insulin degludec, issuing instead a "complete response letter" in which it requests additional cardiovascular-outcomes data from a dedicated trial.



Incretins

- GLP-1 Agonists
- DPP-4 Inhibitors

- Recent safety concerns for pancreatitis

GLP-1 Agonists

- Exenatide
- Liraglutide
- Albiglutide – Once Weekly!!!

DPP-4

- Dipeptidyl Peptidase 4 Inhibitors
  - sitagliptin (Januvia), saxagliptin (Onglyza) alogliptin (Nesina), linagliptin (Tradjenta)
  - Prevents breakdown of endogenous GLP1

Saxagliptin vs. Placebo

- Scirica et al NEJM 2013. A randomized placebo control study of 16,492 patients showed that although the A1C was significantly improved in those using Saxagliptin (7.5% vs 7.8% at 2 years), there was NO improvement in total cardiovascular events (MI, Stroke, Cardiovascular death, etc)

Scirica B et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus . New Engl J Med 2013 Oct 3; 369 (14)5_6: 1317-26.

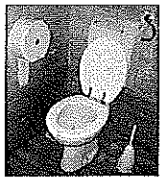
Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N = 8280)	Placebo (N = 8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke; primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization; secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	143 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.3)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.3)	176 (2.0)	1.06 (0.85–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	41 (0.5)	1.22 (0.82–1.83)	0.33

* Event rates and percentages are 2-year Kaplan–Meier estimates.

SGLT2 Inhibitors

- Canagliflozin – Invokana
- Dapagliflozin – Farxiga
  - Initial study showed increased occurrence of bladder cancer



A Big "APP"etite for Diabetes