New Drugs and Devices: What is In The Pipeline For Type 1 and Type 2 Diabetes

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Type 1 Diabetes
- Etiology
- Screening and Prevention
- Encapsulated islet cells
- New glucagons
- Artificial pancreas
- SGLT1&2 inhibitors
- Very smart apps

Type 2 Diabetes
- Etiology
- Screening and Prevention
- Implantable GLP-1 RA
- Oral GLP-1
- Glucagon receptor antagonists
- CGM for type 2 Diabetes
- Most powerful therapy in type 2 diabetes!

Natural History and Cause of Type 1 Diabetes

Autoimmune condition


Can We Prevent The Immune Attack On The Pancreas?

Not Yet....Very Complicated!
Using the Devices in Mice Controls Blood Sugars

STEP ONE: Demonstrated Differentiation Into Beta Cells and Potential for Prolonged Cell Survival

- Cell survival and differentiation into beta-cells 12 weeks after implant
- Appears safe and well-tolerated
- Encaptra device appears to be immune protective as designed
- Need to optimize engraftment as it relates to the foreign body response to the device

Age at Diagnosis of T1D

You can get type 1 diabetes at any age!
The most missed diagnosis in diabetes

- Type 1 diabetes can occur at any age
- Slower beta-cell destruction (may respond briefly to oral agents)
- Typically does not have features of the Metabolic Syndrome

Blood test positive for type 1 diabetes (GAD auto antibodies)

My Story with Type 1 Diabetes

Diagnosed at the age of 15 (1970) with the classic symptoms
- Thirst
- Urination
- Weight loss
- Poor wound healing
- Blurry vision
- Fatigue

My Story With Type 1 Diabetes

- No one in my family had type 1 diabetes
- I was sent home from the hospital on one shot of insulin a day (NPH/Reg)
- Urine testing only
- No A1c test
- No pumps or pens
- No insulin analogs
- No CGM

Serum Insulin Levels in Type 1 Diabetes

Blood Glucose Levels

Banting and Best
University of Toronto, 1921

LisPro

Regular

Breakfast
Lunch
Dinner

Avg A1c=6.8

90

180

270

*p < 0.05

Lispro

Regular

Breakfast
Lunch
Dinner

Arg AtC SL

0

5

10

15

210

* p < 0.05


Banting and Best University of Toronto, 1921

**Subcutaneous Insulin Has A Very Narrow Therapeutic Window**

- Too little insulin leads to postprandial hyperglycemia
- Too much leads to hypoglycemia
- Very difficult to get it just right

**Physiologic Insulin, Glucagon and Amylin Secretion**

- Systemic Circulation
- Liver
- Pancreas
- Insulin
- Amylin
- Beta Cell
- Glucagon
- Alpha Cell

**Inhaled Insulin (Afrezza)**

- Rapid on
- Rapid off
- Better post meal glucose values
- Less delayed hypoglycemia

**Faster Acting Aspart or Fiasp**

- (addition of L-arginine and niacinamide for faster absorption)

2 hour PG levels in T1D on Pump therapy after a standardized meal comparing Aspart (Novolog) with Faster Aspart (Fiasp)

**Xeris ready-to-use liquid glucagon for treatment of severe hypoglycemia**

- Could a ready-to-use liquid glucagon help address unmet need?

**Intranasal Glucagon for Treatment of Insulin-Induced Hypoglycemia in Adults With Type 1 Diabetes: A Randomized Crossover Noninferiority Study**

DOI: 10.2337/dc15-1498
Will There Be Adjustable Sizes?

What is desirable: Contextual awareness

Utilization of the sensors commonly found in today’s smartphones to tie BG to:

- Location – GPS
- Activity - Accelerometer
- Gyroscope
- Time – day – date
- Clock
- Calendar

Unmet needs – wireless sensor data aggregation with multivariate analytics

- Wirelessly interfaced metabolic sensors
- Aggregation and multivariate analytics provide deeper insights

Unmet needs – automatic food recognition

- Suggested portions
- Estimate CHO, protein and fat
- Recommended dose & testing schedule
- Postprandial BG prediction

Scan Your Plate With Your Smart Phone App!

Integrated system

Basal/Bolus or MDI Insulin Regimen

With Rapid and Long-Acting Analogs/Inhaled Insulin

BOLUS

Insulin Action

Glulisine

Or

Aspart

Or

Fiasp

Or

Lispro

or Inhaled Insulin

U-100/U-300

Glargine/Detemir

Degludec

Time

4:00

8:00

12:00

16:00

20:00

24:00

4:00

8:00

Breakfast

Lunch

Dinner

Smart Pens For You MDI (Multiple Daily Injection) Folks
Works On The iPhone XI

Artificial Pancreas

Control Algorithm
Continuous glucose sensor
Insulin pump

Insulin Pumps
- Tandem t:slim G5/X2
- Medtronic 630/670G/530G
- OmniPod

530G/630G/670G Enlite by Medtronic
Dexcom G4 & G5 Platinum
Continuous Glucose Monitoring Devices Currently Available In The United States
How CGM and Trending Information Can Affect Our Decisions (CF/I:CHO)


G5 Dexcom Now Connects Directly to the Smart Phone and Apple Watch

Dexcom CLARITY™ Diabetes Management Software

Smart Phone Clarity App

Mean glucose value
Standard Deviation
Time in Range
24 hour multiday profile

An Artificial Pancreas Is Coming Faster Than We Thought Possible

iLet • BigFoot • Tandem • Insulet • Medtronic

HOW DOES THE AUTO MODE FEATURE WORK?
AUTOMATED BASAL INSULIN DELIVERY

Auto Mode:
- 48 hours before it kicks in
- Delivers automated basal insulin doses every 5 minutes
- Automated basal target = 120 mg/dL
- Temporary target of 150 mg/dL can be used

Bolusing & Meals
- Must enter blood glucose (BG) readings and/or carbohydrate grams

670G HYBTID Closed Loop
Important to Understand what it can and cannot do

- This is a basal rate modulator
- Works well overnight
- Still requires meal boluses, correction bolus, and many fingersticks
- Diabetes tasks during the day are not decreased

670G Study Subject Download

Average glucose = 153 (eA1c = 7.5%), 1% of readings < 70 mg/dl

D.I.Y. SYSTEM

Old Medt. Pump
iPhone
Riley Loop
Always in automode
Current BS-Blue
Predicted dotted line-Blue

How much insulin orange
(Example 6 extra units last hour)
Bars above and below baseline

Exercise targets
Cut out hypos almost completely
No lows at night
More time in range

CGM Readings On and Off the Bionic Pancreas

Open Loop: Patient on their own
Closed Loop: Bionic Pancreas

Eversense Implantable CGM (under FDA review)

“Other” Therapies for People with Type 1 Diabetes
- Symlin
- Incretins (GLP–1 RA)*
- SGLT–2 Inhibitors*
- Inhaled Insulin

*Medications approved only type 2 diabetes at the current time
**Sotagliflozin: First-in-Class Dual SGLT1 and SGLT2 Inhibitor**

- SGLT1 is the primary transporter for absorption of glucose and galactose in the GI tract
- SGLT2 is expressed in the kidney, where it reabsorbs 90% of filtered glucose

**A1C and Hypoglycemia: T1D**

- Sotagliflozin significantly reduced mean A1C compared with placebo after 29 days with no increase in hypoglycemia

**Body Weight T1D**

- Patients treated with sotagliflozin demonstrated weight loss compared with weight gain in the placebo group

**CGM Time in Target, Hyperglycemic, and Hypoglycemic Ranges T1D**

**Phase 3 Program in T1DM Summary**

- **InTandem program has the largest efficacy and safety database of an oral anti-diabetic agent for T1DM**
  - Sotagliflozin significantly:
    - Reduced A1C
    - Reduced body weight
    - Reduced blood pressure
    - Reduced bolus insulin (leading to less hypoglycemia)
    - Glucose variability (more time in range)
    - Reduced severe hypoglycemia in the setting of optimized insulin setting
  - **Benefit/risk profile favorable**
    - Additional A1C efficacy on top of insulin (consistent with SGLT2 inhibition)
    - Efficacy beyond A1C
    - No increase in severe hypoglycemia, lower PPG, lower incidence of documented hypoglycemia (consistent with SGLT1 inhibition)
    - DKA is manageable with appropriate care instructions

**Type 2 Diabetes Trends Among Adults in the U.S. 1990**
Diabetes Trends Among Adults in the U.S. 2017: Over 258 billion dollars a year!

Estimate in 2050: ~33%!!!!!!

You Can Get Type 1 and Type 2 Diabetes at Any Age!

Jose diagnosed with Type 2 at age 5

Barbara diagnosed with Type 1 at age 64

Risk of Developing Type 1 And T2D

<table>
<thead>
<tr>
<th>General Population</th>
<th>0.3%</th>
<th>8–11%</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you have a sibling with T1D</td>
<td>4%</td>
<td>~30%</td>
</tr>
<tr>
<td>If your mother has T1D</td>
<td>2 – 3%</td>
<td>~30%</td>
</tr>
<tr>
<td>If your father has T1D</td>
<td>6 – 8%</td>
<td>~30%</td>
</tr>
<tr>
<td>If you have an identical twin with T1D</td>
<td>~50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

The Prevalence of Type 2 Diabetes and Obesity

The genes for type 2 diabetes and obesity are linked together.

Central or Abdominal Obesity of Type 2 Diabetes

MRI of the Belly

White is abdominal fat
Causes of Mortality in Patients With Diabetes 20 years Ago: The same Trend Exists in 2017

- **Stoke**: 55%
- **Malignant Neoplasms**: 13%
- **Pneumonia/Influenza**: 10%
- **Other**: 5%

```
Causes of Mortality in Patients With Diabetes 20 years Ago:
The same Trend Exists in 2017

55% Heart Disease
```

Most Common Causes of Death in People With Type 2 Diabetes: It is not eye, kidney or nerve disease!

- **Almost 80% die to any type of heart disease and stroke**

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Most Common Causes of Death in People With Type 2 Diabetes: It is not eye, kidney or nerve disease!

Almost 80% die to any type of heart disease and stroke
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Relatively New Class of Injectable Medications for Type 2 Diabetes

- **GLP-1 RA Agonists**

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Relatively New Class of Injectable Medications for Type 2 Diabetes
GLP-1 RA Agonists
```

Fixed Combinations Of Basal Insulin and GLP1-RA Xultophy and Soliqua

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Fixed Combinations Of Basal Insulin and GLP1-RA Xultophy and Soliqua
```

ITCA 650—Medical Device To Deliver Type 2 medication

```
ITCA 650—Medical Device To Deliver Type 2 medication
```

- **TECHNOLOGY**
  - Previously approved delivery system
  - Small micropump
  - Maintains stability at temps ∼37°C
  - Maintains stability for >12 months

- **MEDICINE-EXENATIDE**
  - Previously approved GLP1 therapeutic with demonstrated:
    - Glycemic control
    - Weight loss
    - Safety

Not yet approved by the FDA
Large Non-Insulin CVOTs in T2DM
DPP-4 Inhibitors

<table>
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<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4-i</td>
<td>saxagliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>16,500</td>
<td>5,400</td>
<td>14,000</td>
<td>6,000</td>
<td>8,300</td>
</tr>
<tr>
<td>Results</td>
<td>2013</td>
<td>2013</td>
<td>June 2015</td>
<td>2017</td>
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Large Non-Insulin CVOTs in T2DM
GLP-1 Receptor Agonists

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<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN</th>
<th>EXSCEL</th>
<th>REWIND</th>
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<tr>
<td>GLP-1-RA</td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td>exenatide</td>
<td>dulaglutide</td>
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Investigating Before Vilifying A Medication
(relative risk vs absolute risk)
(Imbalance that is statistically significant)

- Avandia (rosiglitazone): CAD
- Actos (pioglitazone): bladder cancer
- Insulin glargine (Lantus): breast cancer
- DPP-4 inhibitors: pancreatic cancer
- Onglyza (saxagliptin): hosp. for CHF
- Invokana (canagliflozin): amputation
- Ozempic (semaglutide) retinopathy/DME

Abbott FreeStyle Libre:
Now approved in the US

- Waterproof
- Lasts 10 days
- 12 hour warm up
- Swipe to get a number
- No calibration
- Low Cost

Future Developments

- Develop:
  - A simple
  - Easy to apply
  - Low cost
  - Disposable sensor
  - Integrated into a monitor or smart phone

Will give you a glucose reading every 5 minutes!
Natural History of Type 2 Diabetes Is Characterized by Progressive Loss of Beta Cell Function

Progression of Dysglycemia
- Prediabetes
- Type 2 Diabetes

Prediabetes and Early Type 2 Diabetes: Commonly Asymptomatic
- Insulin resistance
- Insulin secretion
- Fasting glucose
- Postprandial glucose

Macrovascular complications
- Microvascular complications

Insulin resistance
Insulin secretion
Fasting glucose
Postprandial glucose

Progression of Dysglycemia
- Prediabetes
- Type 2 Diabetes

Diagnosis of Type 2 Diabetes Typically Delayed Years to Decades
- Progression to Type 2 Diabetes Can be Prevented or Delayed

Adapted from Ramlo-Halsted BA, Edelman SV. Prim Care. 1999;26:771-789

Completed diabetes prevention trials

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<th>Treatment (3–4 years)</th>
<th>Relative risk reduction</th>
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<td>5.8% 31%</td>
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Developments In The Past Decade For Type 2 Diabetes

- DPP4 inhibitors (4 in the class)
- SGLT2 Inhibitors (3 in the class)
- GLP1–RA (5 in the class)
- Several positive CVOT trials
- Newer basal insulins
- Fixed combinations of GLP1–RA & basal insulins
- Insulin pumps for type 2 (Vgo and the T-Flex)
- Inhaled insulin
- Software programs and multiple apps

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Commercial HMO and Medicaid Population Results Are Even Worse

HEDIS data from >1000 health plans covering >171 million lives (2014)
- ONLY ABOUT 40% OF PATIENTS* ARE AT HbA1c <7%
- ONLY ABOUT 30% OF PATIENTS* ARE AT HbA1c <7%

Rates of Very Poor Glycemic Control in Diabetes Have Also Not Improved

HEDIS data from >1000 health plans covering >171 million lives in 2014
- % OF DIABETIC PATIENTS WITH VERY POOR GLYCEMIC CONTROL (HbA1c >8%) IN THE US
  - 2005: 29.7%
  - 2014: 31.1%
**MEDICAL COSTS OF T2D ARE INCREASING IN THE US**

Total US Medical Costs for Diabetes From 2007 to 2020 (in billion US dollars)*

>$1000 cost burden for every person in US

*Includes medical costs of type 2 diabetes and related complications.


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**DIABETES IS NOT A RARE DISEASE AND IT IS NOT AN INEXPENSIVE DISEASE**

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**Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control**

https://doi.org/10.2337/dc16-1974

Understanding the Gap Between Efficacy in Randomized Controlled Trials and Effectiveness in Real-World Use of GLP-1RA and DPP4 Therapies in Patients With Type 2 Diabetes

https://doi.org/10.2337/dc16-2725

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**POOR ADHERENCE IS THE KEY CONTRIBUTOR TO THE EFFICACY GAP: GLP-1 RAs**

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**Get Type 2 Diabetes...And Live Longer Because Of It!**
THANK YOU!
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University of California San Diego School of Medicine
Veterans Affairs Medical Center
Founder and Director, Taking Control Of Your Diabetes, a 501(c)3 Not-for-Profit Organization