FROM RESEARCH TO CLINICAL PRACTICE:
UPCOMING ADVANCES IN DIABETES CARE
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JDRF Chief Mission Officer & VP of Research

Disclosures:
- No conflict of interests/disclosures

Where we were...

Progress – where we were and where we’re heading

Where we were...
Where we were...

Where we were...

Where we were...

Where we were...

The Artificial Pancreas!!

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The Need for Better Diabetes Treatment Options Still Exists

A Snapshot of Care of Individuals with T1D Today

Clinic Registry

TID Exchange

Clinic Registry

Biobank

Patient Webite Glu

Limited Success Achieving HbA1c Targets

A1c Goal = <7.5%

A1c Goal = <7.0%

21% 21% 17% 13% 32% 29% 0% 20% 40% 60% 80% 100% <6 6-<13 13-<18 18-<26 26-<50 ≥50

Mean HbA1c (%)
### Average Current HbA1c by Age

![Graph showing HbA1c by age](image)

*Note: *6 to 9 years and 65+ years are pooled.

### 12-month Frequency of Diabetic Ketoacidosis According to Age

![Bar chart showing frequency of diabetic ketoacidosis](image)

*1 or more events in 12 months

### 12-month Frequency of Severe Hypoglycemia According to Age

![Bar chart showing frequency of severe hypoglycemia](image)

*Seizure or loss of consciousness: 1 or more events in 12 months

### Predictive Low Glucose Suspend in Children

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Control 914</th>
<th>System Active 775</th>
<th>11-14 Year Olds</th>
<th>4-10 Year Olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nights</td>
<td></td>
<td></td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>941</td>
<td>955</td>
<td></td>
<td>0.001</td>
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</tr>
<tr>
<td>% nights &lt;60 for 120 min</td>
<td>8%</td>
<td>3%</td>
<td>&lt;0.001</td>
<td>5%</td>
</tr>
<tr>
<td>Mean Overnight Glucose (mg/dl)</td>
<td>144±18</td>
<td>152±19</td>
<td>0.004</td>
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### Outpatient Randomized Trial

**Ages 15-45 years**

% of nights with glucose level ≤60 mg/dl

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Control N=45 Participants</th>
<th>Intervention N=45 Participants</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>&lt;30 min</td>
<td>970</td>
<td>942</td>
<td></td>
</tr>
<tr>
<td>&gt;30 to 60 min</td>
<td>24%</td>
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<tr>
<td>&gt;120 to 180 min</td>
<td>15%</td>
<td>3%</td>
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<tr>
<td>&gt;180 min</td>
<td>6%</td>
<td>1%</td>
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### Looking Forward: Research is Advancing

Significant advances are improving how people live with the disease and bringing us closer to a biological cure and universal prevention.
Artificial Pancreas Systems: No longer “if”, only a matter of “when”

Evolution of AP Systems: With Entry of Technologies at ANY Stage

1. Very Low Glucose @ Insulin Off Pump
   - Drug off due to user not responding to Low-glucose alarm
2. Hypoglycemia Minimizer
   - Predicts hypoglycemia
   - Causes alarms
   - Followed by reduction in - or - cessation of Insulin Delivery below LOW THRESHOLD
3. Hypoglycemia Minimizer
   - Same as 1, but Added feature allowing Insulin dosing above LOW THRESHOLD
4. Fully Automated Insulin Closed Loop
5. Fully Automated Insulin + Anti-insulin Closed Loop
6. Automated Basal/Hybrid Closed Loop

Target Product Profile Pathway – Hypo and Hyper Minimizer

Product 3 – Same as product 2 plus mirror functionality to minimize time spent hyperglycemia

AP Systems work!

First Generation
- Threshold Suspend "LS"-er
- Hypoglycemia Minimizer "HM" "pLGS" "pLGM"

Second Generation
- Automated Basal/Hybrid Closed Loop
- Fully Automated Insulin Closed Loop

Third Generation
- Fully Automated Multi-Hormone Closed Loop

Lower/stop insulin delivery only
Lower/stop insulin delivery + automated insulin dosing

ASPIRE – LGS Reduced Nocturnal Hypoglycemia without increasing HbA1c

- 32% reduction in nocturnal hypo
- 38% reduction in hypo exposure (AUC)
- No seizure or coma in SAP-LGS but 4 in SAP (severe hypoglycemia)
VEO – LGS prevented Seizures or Coma in High-Risk Hypo Unaware Patients

- 34.2 to 9.5 reduction in incidence rate of severe + moderate hypo with LGS-SAP vs Pump (per 100 patient-months)
- No seizure or coma with SAP-LGS vs. 6 events with pump (5 and 6 events respectively at baseline)

Predictive Low-glucose Suspend:
Pump suspends insulin before glucose reaches a low number

Predictive Low Glucose Suspend in Children

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Outpatient Randomized Trial
Ages 15 – 45 years
% of nights with glucose level ≤ 60 mg/dl
Maahs, Buckingham Diabetes Care. 2014

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Notable Results
Stanford/UVA Summer Camps:
- 54 nights CL vs. 52 nights OL SAP;
- Nocturnal hypoglycemia virtually eliminated;
- Time in target range significantly increased

UVA/Padova Bedside CL Control:
- 50 nights CL vs. 50 nights OL SAP;
- New circadian reset to bring BG to 120mg/dl by the morning;
- BG by 7AM = 115.8mg/dl;
- Average BG reduced >30mg/dl, from 168 to 139mg/dl;
- Time in target increased 25%, from 60% to 85%;
- Hypoglycemia reduced 2.1% to 0.8%;
- Benefits extend into following day

Treat-to-Range:
Pump automatically increases insulin delivery if blood sugar is going too high/reduces if going too low
Insulin + Glucagon – Great control, with Caveat...

Defining value beyond A1c: burden/QoL metrics

- the nighttime security: it has given me has been even more amazing
- I have the incredible and previously unimaginable joy of waking up with a blood sugar at or around 100 nearly every single day. No waking up with extreme thirst and irritability; no waking up groggy with a low headache. When Bryan travels, I no longer run myself on the higher side of my range overnight for fear of having a nighttime low alone.
- A great deal of the burden of T1D was taken off my shoulders.
- Having Sam on the system was absolutely amazing and life-changing
- I felt confident going to sleep.
- His most recent A1C, post-honeymoon, was 5.8% with 2% hypoglycemia. What is most amazing about that A1C is how little we worked for it. We did not lose sleep over it; we did not stress over it. The system not only kept Sam’s blood sugars in range, but it kept us all feeling SAFE.

Meet the Bigfoot Family and Their Homemade Closed Loop System

- 30,000 hours of at home “AP” therapy

AP Systems are Coming...

- MDT: Hybrid CL: April 2017
- Animas HHM
- Bigfoot Biomedical: Hybrid CL
- Type Zero: Hybrid CL
- Boston University: Dual-hormone
- Inreda: Dual-hormone
- Tandem
- Insulet
- Roche

Multi-Hormone:

Insulin plus other hormones (glucagon or amylin) to more closely restore all hormones that are lost or imbalanced in type 1 diabetes
Beyond AP: Other areas of research progress

Blip
The hub of your diabetes data.
- Designed in partnership with UCIR, R&D-approved pilot study underway.
- Design process included interviews with more than 90 HCP.
- Currently in use for T1D Exchange/Juvenile Diabetes Research Institute (JDRF) study.

“Let me start by saying that Blip is 100 times better than what is currently out there...”
- Ed, Beta Participant

DexCom Share
- Better glucose control
- Lower burden

Sensors are improving rapidly

Could Silent Occlusions be Interrupting Your Patients’ Insulin Flow
- Insulin pumps are programmed to deliver the right amount of insulin, but it’s the infusion set that ensures the delivery of insulin into the body.
- All insulin pumps have a built-in alert when there is a failure to deliver insulin. Commonly known as an occlusion alarm, it is triggered when fluid pressure within the infusion set builds to a certain threshold.
- When insulin flow is interrupted, pressure rises slowly. It may take hours to trigger the alarm.
- Insulin flow interruptions, defined as a continuous rise in in-line pressure lasting at least 30 minutes without triggering an occlusion alarm, are silent occlusions.

1. Occlusion alarm thresholds vary by insulin pump manufacturer.
Introducing Infusion Set Innovations

BD FlowSmart™ technology features a unique side-ported catheter designed to improve insulin flow, potentially reducing the number of flow interruptions that result in silent occlusions.

In a clinical trial* versus a leading insulin infusion set, BD FlowSmart technology:


FDA approves MannKind’s Afrezza, partnership with Sanofi

FDA News Release

FDA approves Afrezza to treat diabetes

For Immediate Release

June 27, 2014

Sanofi and MannKind Announce Global Licensing Agreement for Afrezza (insulin human) Rapid-Acting Inhaled Insulin

Paris and Venosa, Calif. – August 11, 2014 – Sanofi (EURONEXT: SAN and NYSE: SNY) and MannKind Corporation (Nasdaq: MNKD) announced today that they have entered into a worldwide exclusive licensing agreement for development and commercialization of Afrezza (insulin human) innovation. Pioneers a new rapid-acting inhaled insulin therapy, for adults with type 1 and type 2 diabetes. The companies plan to launch Afrezza in the United States in the first quarter of 2015.

FDA approves MannKind’s Afrezza, partnership with Sanofi

Glucose-Responsive “Smart” Insulin Advancing to the Clinic

Clinical Trials Launched of Multiple T2D Therapies for Improving Management of T1D (Repurposing)

• NovoNordisk: T1D Label extension for Victoza (incretin-based therapy)
• AZ: T1D Label extension for Dapagliflozin (SGLT-2 inhibitor)
• J&J: T1D POC Phase 2a for Canagliflozin (SGLT-2 inhibitor) (n=330)

ViaCyte Launches Phase 1 Trial: First trial of human stem cell-derived islet source (islet precursor)

ViaCyte’s VC-01™ Investigational Stem Cell-Derived Islet Replacement Therapy Successfully Implanted into First Patient

SAN DIEGO, Oct. 29, 2014 /PRNewswire/ – ViaCyte, Inc., a clinical stage biotechnology company focused...
Reversal of diabetes with insulin-producing cells
derived in vitro from human pluripotent stem cells

Alireza Rezania1, Jennifer E Bruin2, Payal Arora1, Allison Rubin1, Irina Batushansky1, Ali Asadi2, Shannon O’Dwyer2, Nina Quiskamp2, Majid Mojibian2, Tobias Albrecht2, Yu Hsuan Carol Yang2, James D Johnson2,3 & Timothy J Kieffer2,3

GABA, a Nutraceutical, Promotes Human Beta-Cell Proliferation and Modulates Glucose Homeostasis

Blood Pressure Drug Verapamil May Reverse Type 1 Diabetes; Human Trials To Begin Next Year

Pre-Symptomatic T1D Can be Staged with Distinct Risk/Benefit Profiles: Sets Framework for Prevention

The PERL study is testing whether an old drug (allopurinol) might have a new use to prevent kidney problems for people with type 1 diabetes

For information about the PERL study:
www.perl-study.org
1-800-688-5252 (ext. 65630)
Diabetes – No Limits!

Thank You!
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@aaronjkowalski

Questions