AUTOMATED INSULIN DELIVERY DEVICES STATE OF THE FIELD: WHERE ARE WE? WHERE ARE WE GOING? WHEN WILL WE GET THERE?

Aaron Kowalski, PhD, Chief Mission Officer
Aaron 1984
OUR PURPOSE

JDRF is committed to driving forward T1D research and policy

- Invested nearly $2 billion in research since 1970
- Leverages resources from governments, other foundations
- Influences policy and commercial landscape to accelerate therapies

$1.9 billion
TOTAL JDRF SUPPORT FOR WORLDWIDE T1D RESEARCH PROJECTS
- JDRF is currently funding 45 human clinical trials

Source: Click to edit source for this chart
OUR MISSION
Accelerating Life-Changing Breakthroughs

CURE
Restoring Insulin Independence

PREVENT
Preventing Symptomatic T1D

TREAT
Improving Glucose Control
WE’VE COME A LONG WAY...
We used to measure urine glucose, there was no home blood glucose testing!
This was my first lancet device!
And my first test strips...
One of the first commercial insulin pumps, the “blue brick”
BUT NOT FAR ENOUGH...
Limited Success Achieving HbA1c Targets

A1c Goal = <7.5%

A1c Goal = <7.0%
Average Current HbA1c by Age

*≤2 years old and ≥80 years old are pooled
Hypo is still common – even with incredible efforts to avoid it.

### Predictive Low Glucose Suspend in Children

<table>
<thead>
<tr>
<th></th>
<th>11-14 Year Olds</th>
<th>p</th>
<th>4 – 10 Year Olds</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>System Active</td>
<td>Control</td>
<td>System Active</td>
</tr>
<tr>
<td># nights</td>
<td>941</td>
<td>955</td>
<td>755</td>
<td>769</td>
</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>&lt; 0.001</td>
<td>153 ± 14</td>
</tr>
</tbody>
</table>

Buckingham et al. 2015.
THE ROAD TO AN ARTIFICIAL PANCREAS SYSTEM
The JDRF Artificial Pancreas Launched in 2005
JDRF Partnerships in Artificial Pancreas Research and Development
A 2009 Roadmap to AP System Development

1. Very Low Glucose \(\Rightarrow\) Insulin Off Pump
   (Shuts off due to user not Responding to Low-glucose alarm)

2. Hypoglycemia Minimizer
   Predictive hypoglycemia Causes Alarms
   Followed by reduction in - or - Cessation of Insulin Delivery below LOW THRESHOLD

3. Hypoglycemia
   -AND – Hyperglycemia
   Minimizer
   Same as (2), but Added feature allowing Insulin dosing above HIGH THRESHOLD
   (ie above 200mg/dl)

4. Automated Basal / Hybrid Closed Loop
   Closed loop at all times -With – Meal-time manual assist Bolusing

5. Fully Automated Insulin Closed Loop

6. Fully Automated Insulin + Anti-insulin Closed Loop

START

END

Kowalski DTT 2009
Target Product Profile Pathway – Hypo and Hyper Minimizer

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

BG – mg/dL

Time

Resume preset basal rate

No response – alarm plus automated insulin push to bring level below threshold

Alarm – impending hypoglycemia

No response – alarm plus insulin reduction or off

Alarm – impending hyperglycemia

Minimize time in “Red” zones
POLICY & ADVOCACY

JDRF Success: CGM Coverage

“The most important milestone towards getting broad reimbursement for CGM is the … randomized, 450-patient CGM trial by the Juvenile Diabetes Research Foundation.”

JDRF Funded Trial to Demonstrate CGM Effectiveness
Major Diabetes Clinical Guidelines Include CGM
Majority of Private Health Plans Cover CGM for T1D

Lobby your House Representative to support the bill for Medicare CGM access
http://jdrf.org/take-action/advocacy/cgm-medicare-coverage/
POLICY & ADVOCACY

JDRF Success: Artificial Pancreas FDA Pathway

- JDRF led process to define FDA pathway for artificial pancreas studies and product review
- Final guidance issued which reflected JDRF goals and clinical recommendations
- As results, new systems and components have been approved and are in development
STATUS UPDATE: 2016
It’s an Exciting Time for Artificial Pancreas Development

- JDRF spent $100MM on research over 10 years
- Medtronic 670G Approved in US!
- Multiple other manufacturers in Development – see table for sample
- Like 1\textsuperscript{st} Generation Cell phones, 1\textsuperscript{st} Generation AP systems will make a tremendous difference, but not euglycemia
- JDRF AP program is now looking at what is needed for 2\textsuperscript{nd} (less intrusive) & 3\textsuperscript{rd} Generation (near Fully automated) AP systems

<table>
<thead>
<tr>
<th>Who</th>
<th>Product</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic</td>
<td>670G</td>
<td>FDA Approved. Soft Launch 2Q17</td>
</tr>
<tr>
<td></td>
<td>690G (Auto-Correction) using DreaMed algorithm</td>
<td>Feasibility Study completed; Pivotal TBD</td>
</tr>
<tr>
<td>Animas (JDRF Partner)</td>
<td>Treat to Range with Dexcom G5</td>
<td>Pivotal starts 4Q16, Launch 1Q18</td>
</tr>
<tr>
<td>Tandem</td>
<td>Predictive Suspend with Dexcom</td>
<td>Pivotal starts 1Q17, Launch late 2017</td>
</tr>
<tr>
<td></td>
<td>Treat to Range with Dexcom using UVA/TypeZero Algorithm</td>
<td>Pivotal starts late 2017, launch in 2018</td>
</tr>
<tr>
<td>Bigfoot Biomedical</td>
<td>Closed Loop system, details TBD</td>
<td>Feasibility under way; Pivotal start 1H17, launch by end 2018</td>
</tr>
<tr>
<td>Insulet</td>
<td>Closed Loop POD with UCSB/Doyle Algorithm</td>
<td>Feasibility under way; Launch late 2018</td>
</tr>
<tr>
<td>Beta Bionics</td>
<td>Insulin Only iLet</td>
<td>Pivotal starts 3Q17; launch late 2018</td>
</tr>
<tr>
<td></td>
<td>Bihormonal iLet</td>
<td>Pivotal starts 1H18, launch TBD</td>
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</tbody>
</table>
FIRST STUDIES – SHORT DURATION, FEW PATIENTS AND LIMITED TO HOSPITAL BED

Artificial Pancreas

- CGM
- INSULIN PUMP
- LAPTOP (glucose control software)
Overnight Closed-Loop Camp Studies

- Study Participant age 10-35 years
  - Initial inpatient study with 12 participants
  - 20 participants completed Camp study
- Randomized to Closed loop or Sensor Augmented Pump (SAP)
- 73% time in range (70-150mg/dl) vs 52% SAP

Figure 4—Per-protocol analysis of sensor glucose values over 8 h during OCL (n = 41) versus sensor-augmented pump nights (n = 39). Results are mean ± SD.

TT Ly, Diabetes Care 2014;37:2310–2316
Overnight Closed-Loop Home Studies
Presented at EASD, Sep 2015

- Cambridge have collected 12 years of data on unsupervised home use
- APCAM08 Study, JDRF Funded
  - 33 Adults (Day/Night),
  - 25 Children>10 years Closed loop at Night only
  - 12 week study
- Results
  - Average night time glucose reduced by 29mg/dl
  - HbA1c reduced by 0.3%
  - Time in range (70-180 mg/dl) in Child/Teen group increased by 25%
JDRF Multi-Center 6 month trial of 24/7 Closed Loop Control at Home
Presented at ATTD, Feb 2016

- 2 stage study with 30 subjects in Stage 1 for 1 month, 14 subjects in Stage 2 for 6 months
- During overnight use, time in hypoglycemia reduced significantly
- Time in target (70-180 mg/dl) increased to 77% overall from 64%, and 84% at night

- Next steps: Awarded NIH grant for $12.7 Million for 6 month randomized control trial in 240 participants

Time in Hypoglycemia Reduced uniformly across all sites
3 month at home study in 124 subjects (94 adults, 30 adolescents)
0.5% Average reduction in A1c from 7.4 to 6.9%
In those with A1c > 7.5% at start, showed 1% reduction in A1c
Time < 70mg/dl decreases by 44%
Time in range (71-180mg/dl) increases from 67 to 72%
Looking at the plots: extremes are reduced – less severe highs & lows
80% of subjects opted to keep using the device post study (special FDA)
Multi-Hormone:

Is there a role for other hormones in AP systems?
Insulin + Glucagon – Great control, with Caveat

A

- CGMG (N=1409, 118±39 mg/dl, [45, 249]; 2.0% <60 mg/dl, 7.4% <70 mg/dl; 85% in 70-180 mg/dl)
- PG (N=165, 114±41 mg/dl, Projected A1c ~ 5.6%, [42, 273]; 2.3% <60 mg/dl, 9.5% <70 mg/dl)

B

- Insulin (Total = 171.75 U ~ 0.43 U/kg/day, bolus ~ 0.29 U/kg/day, basal ~ 0.14 U/kg/day)
- Glucagon (Total = 4.5370 mg ~ 0.9074 mg/day ~ 11.26 μg/kg/day)
DIY: #OPENAPS #WEARENOTWAITING
Meet the Bigfoot Family and Their Homemade Closed Loop System

- 30,000 hours of at home “AP” therapy
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**.
I love you, #DIYPS closed loop!
Pic.twitter.com/BLjHTP3FMJ
While using OpenAPS, self-reported outcome measures showed median HbA1c dropped from 7.1% (SD 0.8%) to 6.2% (SD 0.5%), and median percent time in range (80-180 mg/dL) increased from 58% (SD 14%) to 81% (SD 8%). All but one respondent reported some improvement in sleep quality, and 56% reported a large improvement.
MOVING FORWARD: JDRF FOCUS ON IMPROVED AUTOMATION, BIG DATA, EASE OF USE/MINIATURIZATION
PATHWAY TO AP SYSTEMS

Artificial Pancreas

530G/Veo-world wide

1. Suspend
   - Next steps: Clinical adoption

2. Predictive Suspend
   - Next steps: U.S. approval, reimbursement, clinical adoption

3a. Automated Insulin Delivery (AID)
   - Next steps: Faster insulin action, miniaturization, integration, individualized control

3b. Multihormone (MH)
   - Next steps: Glucagon: Soluble pumpable glucagon, chronic glucagon exposure studies, dual-chamber pump development, algorithm finalization, head-to-head vs. AID
   - Amylin: Coformulation vs. dual-chamber pump, ratio determination, algorithm finalization, head-to-head vs. AID

640G Australia, Denmark UK

670g Approved, Soft Launch 2Q17
Moving Forward, New Therapies Must Improve Diabetes Health and Diabetes Happiness!

Diabetes Health

Work/Effort/Burden

ROI

Diabetes Happiness (QoL)
Tidepool Uploader

- Dexcom
- TANDEM Diabetes Care
- OmniPod
- Asante Snap

+ Medtronic CareLink Compatible

Development made possible by JDRF

IMPRESSING LIVES CURING TYPE 1 DIABETES.
Blip

The hub of your diabetes data.

- Designed in partnership with UCSF, IRB-approved pilot study underway
- Design process included interviews with more than 90 HCP
- Currently in use for T1D Exchange / Jaeb Center “ReplaceBG” study

“Let me start by saying that Blip is 100 times better than what is currently out there...”

- Ed, Beta Participant
DexCom Share

- Partially JDRF-funded
DexCom - Google

Google Partnership Objectives

Develop a simple, low-cost, disposable body-worn sensor system integrated into an advanced data analytics platform to drive entry into Type 2 market and to expand CGM use in Type 1 market.
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:

Daytime Closed-Loop

What Are the Problems?

▪ Time Delays
  ▪ SQ sensor lag times
  ▪ Onset of SQ Insulin Action

▪ Accuracy & Convenience of Sensors

▪ Biologic Variability
  ▪ Immune Response – infusion sets
  ▪ Speed of Insulin action
  ▪ Meal absorption

▪ Exercise
  ▪ Type
  ▪ Intensity/Duration
We need Faster Insulin…

Today’s insulin arrives too slowly and stays around too long after the meal – Hyper followed by hypoglycemia.
BUILDING OUT LANDSCAPE FOR 2ND & 3RD GENERATION AP SYSTEMS

Reduce Burden: Smaller Form Factor, Longer Wear

NEW PROJECTS IN 2016

- Making 1st Gen AP work Better
  - Dr Perkins, Toronto – SGLT2
  - Dr Cengiz, Yale - Afrezza
  - Dr Rebasa-Lhoret – Exercise & bi-hormonal AP
- 7 Day Infusion Sets
  - Capillary Biomedical, Irvine
  - Dr Meyerhoff, Michigan
  - Dr Ratner, Washington
- 2nd Gen – Smaller Systems
  - Dr Botvinick – Continuous Insulin sensing
  - Arecor – U1000 Insulin for miniature devices
  - Dr Pennathur, UCSB – Miniature Pumps
  - Pacific Diabetes – Single port CGM/Infusion set
- 3rd Gen – Near Full Automation
  - Fully Implantable systems may be a way to achieve near full automation & convenience
  - Dr Guo, Ohio State – Novel pumps/catheters
  - Dr Renard, Montpelier – catheter failure

PROJECTS IN THE PIPELINE FOR 2017

- User Centric AP systems
  - Encourage Industry to Innovates, developing smaller, more convenient AP system
  - e.g. Integrated CGM/Patch pump
  - e.g. Less invasive sensing
- Additional Sensor for Gen 2-3 AP
  - Identify other signal which may be useful to inform AP algorithms
  - E.g. lactate for exercise detection
  - GPS for restaurant detection
- Evaluate AP in Sub-groups
  - Pregnancy, V Young, Seniors
- Decision Support for MDI users
  - Automated Analysis for Endo’s
  - Prediction & dose recommendation for PWD
What’s Next for AP - In Summary

- Amazing progress has been made in 10 years in the AP space
  - on the cusp of true (hybrid) closed loop AP systems being available to people with T1D

- Large opportunities on multiple fronts: enabling smaller systems, increasing automation, improving reliability, and reducing day to day burden
  - Ultimate Aim is to deliver “Fit & Forget” AP systems

- JDRF Advocacy is working hard to make sure PWD have access to this technology, lobbying Insurance, Medicare, Congress
  - What are Barriers to Adoption: Endocrinologist prescribing AP system, PWD switching & remaining on AP systems, and Insurers looking beyond A1c & seeing True value in these systems
Diabetes – No Limits!
Acknowledgments:

JDRF Team
Thank You
akowalski@jdrf.org
@aaronjkowalski