Pathways to Achieving a Bionic Pancreas

Jay S. Skyler, MD, MACP

Professor, Division of Endocrinology, Diabetes, and Metabolism
and Associate Director, Diabetes Research Institute
University of Miami Miller School of Medicine

Adjunct Professor, Barbara Davis Center for Childhood Diabetes
University of Colorado
Disclosure of Relevant Financial Relationships

- **Was on Board of Directors of Minimed, Inc. (prior to acquisition by Medtronic) at time of development of the first subcutaneous continuous glucose monitoring system**
- **Currently on Board of Directors of DexCom, Inc – “the Glucose Sensor Company”**
“The Beginnings”
1960s
Glucose Enzyme Electrode

- *Nature*; volume 214; 986-988, June 3, 1967
- SJ Updike and GP Hicks
Concept of Miniaturization
Essential Components

- Glucose Measurement
- Algorithm for Regulation
- Insulin Delivery
Bedside “Artificial Pancreas”
1970s
Success in developing GCIIS was achieved nearly simultaneously in the 1970s by groups in:

- Toronto, Canada
- Ulm, Germany
- Montpellier, France
- Sydney, Australia
- Osaka, Japan
Biostator
Glucose Controlled Insulin Infusion System
Nikkiso  STG-22
New Hope
Cures for Diabetes
Appear on the Way,
Researchers Report
Prospects Include Implant
Of an Artificial Pancreas
And Transplants of Cells

Hold out promise of cure for "juvenile" cases
Transplants offer hope for diabetics

"Artificial Pancreas" Makes Debut

New Machine To Aid Diabetics
Continuous Subcutaneous Insulin Delivery (CSII) 1980s
Implantable “Artificial Pancreas”
1990s
Physiologic Insulin Delivery
## Peritoneal Insulin Absorption

**Absorption following 1 u/kg IP injection**

*Double tracer method in dogs*

<table>
<thead>
<tr>
<th></th>
<th>Portal</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Absorption</td>
<td>20 min</td>
<td>28 min</td>
</tr>
<tr>
<td>Proportion Absorbed</td>
<td>51%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Implantable Insulin Pump
Implantable Insulin Pump & External Controller
Implantable Glucose Sensor
Implantable Glucose Sensor
Implantable Glucose Sensor

Implanted Closed Loop
“Moon” – The First Implantable Closed Loop System
Closed Loop Glucose Regulation with Implanted Pump & Implanted Glucose Sensor

Pancreatectomized Canine

![Graph showing glucose levels over time with manual and automatic control phases highlighted.]

- **Manual Control** begins and ends.
- **Automatic Control** is indicated by a shaded area.

**Glucose (mg/dL)**

**August 2000**
Subcutaneous Continuous Glucose Monitoring (CGM) 2000s
Continuous Glucose Monitoring System (CGMS)
Guardian Telemetered Glucose Monitoring System
MiniLink Transmitter
GlucoWatch® Biographer
DexCom Seven Plus
Continuous Glucose Monitor
Navigator Continuous Glucose Monitor

Receiver

Transmitter

Sensor Delivery Unit
Current Glucose Sensors
External “Artificial Pancreas”
2000s
External Closed Loop Delivery
External Closed-Loop Setup for Canine Studies
Closed Loop Glucose Regulation with CSII & Subcutaneous Glucose Sensor

Pancreatectomized Canine

- **Recalibration**
- **Meal**
- **Manual**
- **Closed-loop**

**Graph Details**
- **Y-axis (GLUCOSE (mg/dl))**
  - 0 to 500
- **X-axis (Time)**
  - 6am to 6am
  - Noon to诺on
  - 6pm to midnight

**Legend**
- Red dots: Plasma Glucose
- Blue line: Sensor Glucose
Glucose Control During Closed-Loop

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Daytime</th>
<th>Peak PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>142 ± 53</td>
<td>148 ± 54</td>
<td>207 ± 54</td>
</tr>
</tbody>
</table>

Weinzimer et al. Diabetes Care 31:934 May 2008
# Reference Glucose Levels in Closed Loop vs. Hybrid Control

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Daytime</th>
<th>Peak PP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full CL</strong></td>
<td>147 ± 58</td>
<td>154 ± 60</td>
<td>219 ± 54</td>
</tr>
<tr>
<td><strong>Hybrid</strong></td>
<td>138 ± 49</td>
<td>143 ± 50</td>
<td>196 ± 52</td>
</tr>
</tbody>
</table>

Weinzimer et al. Diabetes Care 31:934 May 2008
In Silico Experiments allow for:

- Testing of the robustness and sensitivity of control algorithms
- Experiments with extreme scenarios that cannot be tested in vivo
- Accelerated development of closed-loop control

![Graph showing glucose concentration over time](image)

**Acknowledgment:** B. Kovatchev and C. Cobelli
Realistic Virtual Clinical Trials

- A complete artificial β-cell system testing platform, allowing:
  - Systematic analysis
  - Component Verification and Validation
  - Complete system V&V
  - PnP for *in silico* patients
  - PnP for control algorithms

Boston closed-loop BG control
Next Step: Automatic Shut Off for Projected Hypoglycemia

• All automatic pump suspensions ≥ 60 min during prior CL study

• Plasma and sensor glucose at the time of suspension

• Nadir plasma and sensor glucose for each suspension event
Pathway to a Closed-Loop Artificial Pancreas

1. Very Low Glucose $\Rightarrow$ Insulin Off Pump
   - Shuts off due to user not responding to low-glucose alarm

2. Hypoglycemia Minimizer
   - Predictive hypo alarms $\Rightarrow$ reduction or cessation of insulin delivery below LOW THRESHOLD

3. Hypo/Hyper Hyperglcemia Minimizer
   - Same as (2), but allows insulin dosing above HIGH THRESHOLD (ie above 200mg/dl)

4. Automated Basal / Hybrid Closed Loop
   - Fully closed loop with meal-time manual assist bolusing

5. Fully Automated Insulin Closed Loop

6. Fully Automated Insulin + Anti-insulin Closed Loop
Issues to Be Resolved

- Current insulins work too slowly and last too long
- Amylin – the second $\beta$ cell hormone – is missing in people with type 1 diabetes
- Glucagon may be needed to obviate hypoglycemia