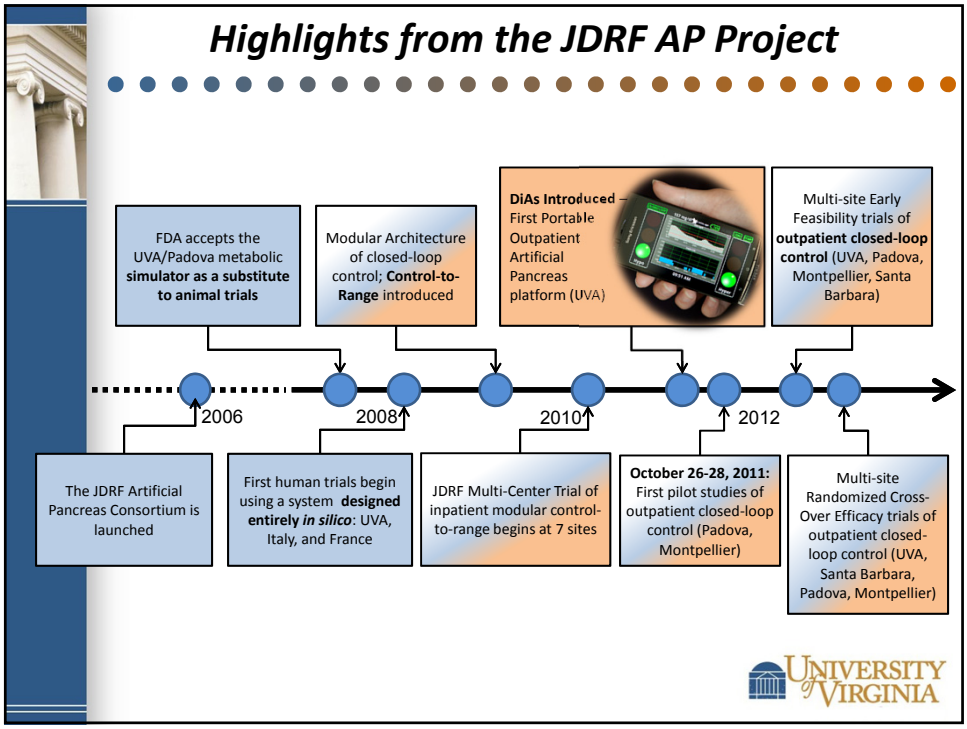
Artificial Pancreas Components

Continuous Glucose Monitor

Closed-Loop Control Algorithm

Insulin Pump

Highlights from the JDRF AP Project



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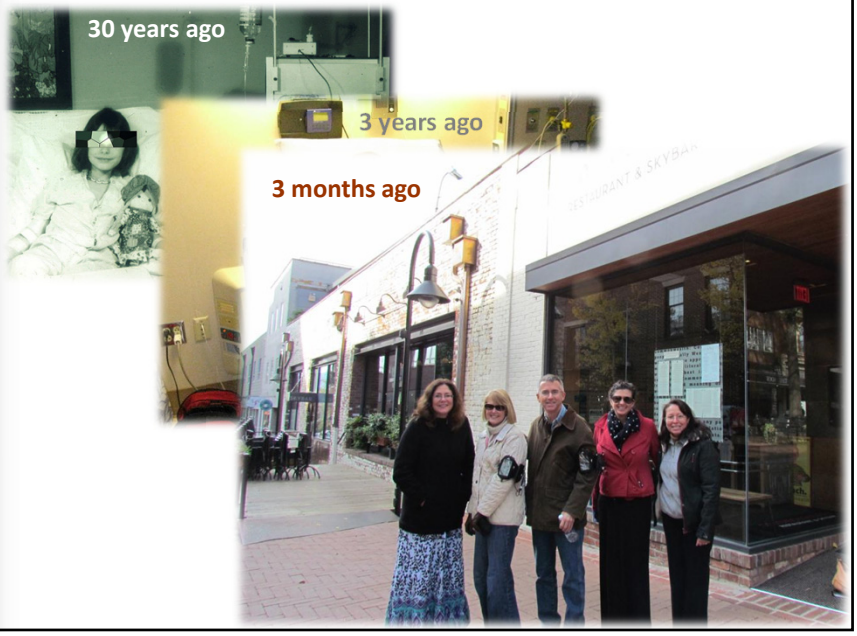
Milestones



PERSPECTIVES IN DIABETES

Artificial Pancreas: Past, Present, Future

Claudio Cobelli,[1] Eric Renard,[2,3] and Boris Kovatchev[4]

The artificial pancreas (AP), known as closed-loop control of blood glucose in diabetes, is a system combining a glucose sensor, a control algorithm, and an insulin infusion device. AP developments can be traced back 50 years to when the possibility for

control (MPC), avoid these limitations by using a mathematical model of the metabolic system of the person being controlled in their calculations. Many of these MPC algorithms are based on another 1979 milestone, the Minimal Model of Glucose Kinetics (17). Thus, since the early years of AP development, glucose sensing and insulin delivery technologies were accompanied by computer modeling

hinder their use in subcutaneous systems because of unavoidable time lags in subcutaneous glucose sensing and insulin action. Newer controllers, known as model-predictive

critical problems in AP development and to outline possible solutions and a pathway toward the clinical acceptance of ambulatory closed-loop control.

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DOI: 10.2337/db11-0654

LIMITATIONS OF CURRENT GLUCOSE SENSORS

CGM technology was introduced 10 years ago, initially as a method for retrospective review of glucose profiles (34–36). Shortly after, real-time devices came about, providing online glucose readings (37). These first devices had limited performance, particularly in the hypoglycemic range (36,38,39). Since then, significant progress has been made toward versatile and reliable CGM; a number of studies

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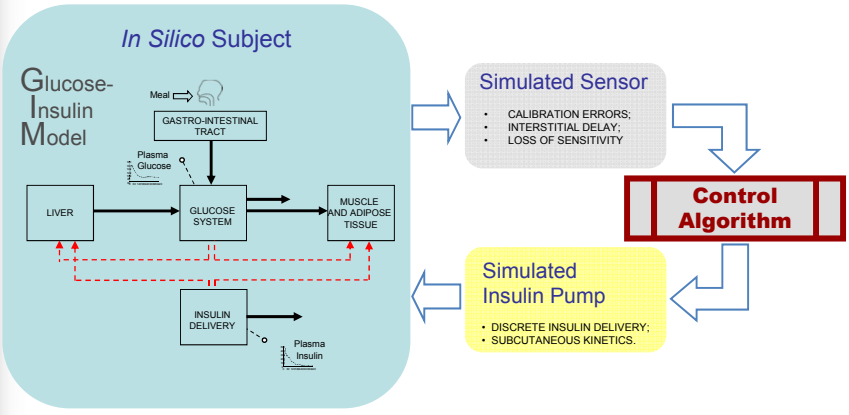
2008: *In Silico* Model of Type 1 Diabetes

Kovatchev, Breton, Dalla Man & Cobelli, 2008



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The In Silico "Subjects"

$$\dot{G}_p = -k_2.G_p + k_1.G_t - U_{ii} - E_t + k_{p1} - k_{p2}.G_p - k_{p3}.I_d + \frac{f.k_{abs}.Q_{gut}}{BW}$$

$$\dot{G}_t = -k_1.G_t + k_2.G_p - \frac{(V_{m0} + V_{mX}.X)G_t}{K_{m0} + G_t}$$

meal

Biometric Characteristics of the Population of N=300 *In Silico* "Subjects"

	Adults			Adolescents			Children		
Parameter	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Mean (SD)	Min	Max
Weight (kg)	79.7 (12.8)	52.3	118.7	54.7 (9.0)	37.0	88.7	39.8 (6.8)	27.6	60.7
Insulin (U/day)	47.2 (15.2)	21.3	98.4	53.1 (18.2)	22.6	141.5	34.6 (9.1)	17.6	56.1
Carb ratio (g/U)	10.5 (3.3)	4.6	21.1	9.3 (2.9)	3.2	19.9	14.0 (3.8)	8.0	25.5

$$\dot{Q}_{sto1} = -k_{gri}.Q_{sto1} + M(t)$$

$$\dot{Q}_{sto2} = -k_{empt}.Q_{sto2} + k_{gri}.Q_{sto1}$$

$$\dot{Q}_{gut} = k_{abs}.Q_{gut} + k_{empt}.Q_{sto2}$$

insulin → I_{sc1} → I_{sc2}

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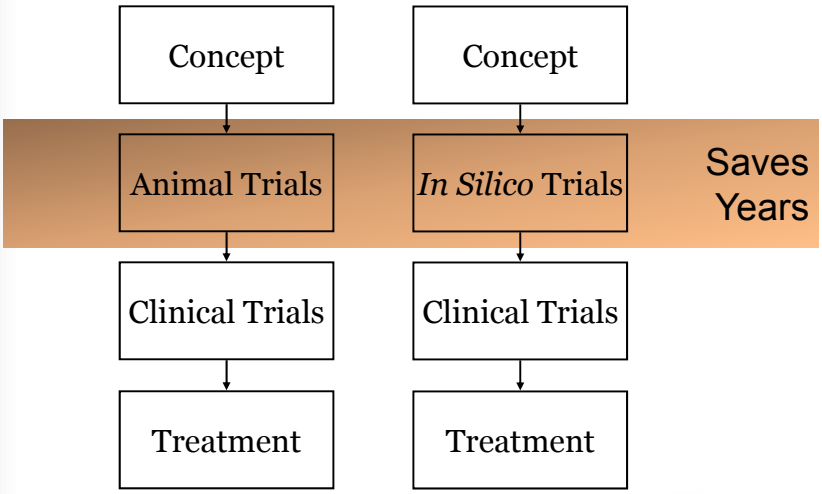
Paradigm Change: In Silico Experiments Replacing Animal Trials



FDA Master File MAF 1521, February 2008

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2009-2012:

IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 59, NO. 11, NOVEMBER 2012

Modular Closed-Loop Control of Diabetes

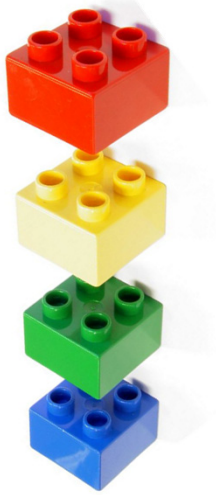
S. D. Patek*, L. Magni**, E. Dassau**, C. Hughes-Karvetski, C. Toffanin, G. De Nicolao, S. Del Favero, M. Breton, C. Dalla Man, E. Renard, H. Zisser, F. J. Doyle, III, C. Cobelli, and B. P. Kovatchev, and International Artificial Pancreas (iAP) Study Group

Control Module 3: Meal Control
Fully automated control action; multi-hormone meal control (e.g. insulin + amylin)

Control Module 2: Range Correction
Acts episodically as needed to correct hyperglycemia

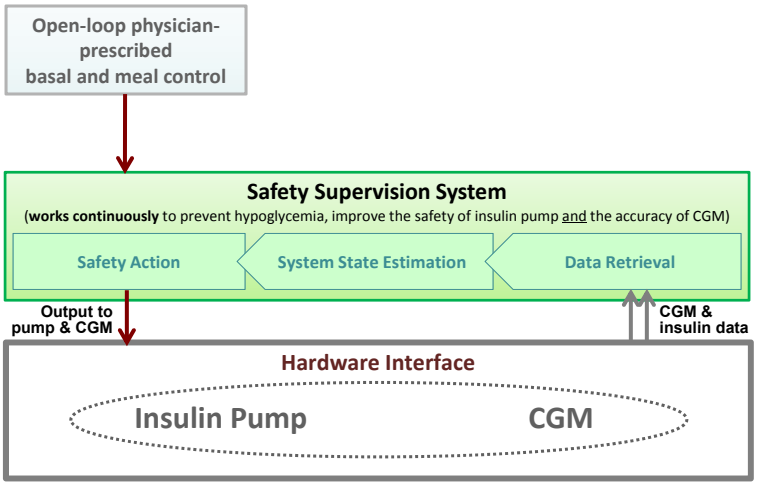
Control Module 1: Safety Supervision
Acts continuously to prevent hypoglycemia by smooth attenuation of insulin delivery and preventive warnings/actions if needed.

AP Operating System: Specific built of mobile OS that allows a system to function as a Class 3 medical device;
Comm drivers and patient-oriented user interface.



Safety First!

- ***Adjunct to*** sensor-augmented pump therapy;
- Supervises the ***safety of insulin delivery*** to prevent hypoglycemia;
- Supervises the ***accuracy of the sensor*** to detect sensor failure.



Defining Control-to-Range

Open-loop physician-prescribed basal and meal control

- ***Adjunct to*** sensor-augmented pump therapy;
- ***Silent*** if open-loop therapy is optimal.

Post-Meal Correction Algorithm

(**works when needed** in advisory or atomatic mode to correct postprandial hyperglycemia)

Correction Action | System State Estimation | Data Retrieval

Safety Supervision System

(**works continuously** to prevent hypoglycemia, improve the safety of insulin pump and the accuracy of CGM)

Safety Action | System State Estimation | Data Retrieval

Output to pump & CGM

CGM & insulin data

Hardware Interface

Insulin Pump | CGM

2011: Portable Artificial Pancreas Platform

DiAs (the Diabetes Assistant) introduced by Patrick Keith-Hynes

Key specifications:

- **Based on smart phone;**
- **Runs various control algorithms, open-loop, or sensor-alone modes;**
- **Connects to remote monitoring site through WiFi or 3G;**
- **Android OS modified to meet medical application standards.**

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The Technology to Date

- *In silico* experiments replaced animal trials;

- Modular architecture enabled easy configuration of control algorithms;

- Medical Android OS was designed to run artificial pancreas applications;

- DiAs was introduced by UVA as the first portable outpatient artificial pancreas system;

- Total outpatient use of DiAs so far: 2,600 hours in the U.S. and Europe.

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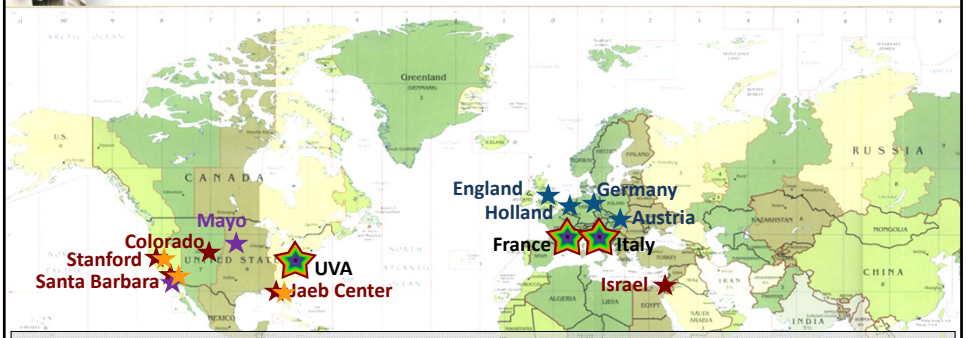
2008-2013: An International Consortium



The JDRF AP Project at UVA-Padova-Montpellier (2008-2010)

The JDRF Multi-Center Trial of Control-to-Range (2009-2012)

The NIH Bio-Behavioral AP Project (2009-2014)

The European AP@Home Project (2010-2014)

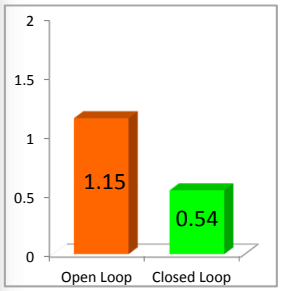
The JDRF CTR at Home Project (2011-2013)

The NIH DP3 AP Project (2011-2016)

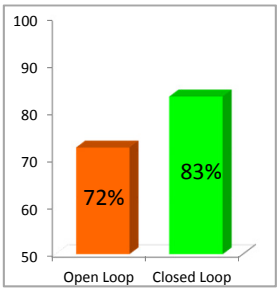
2008-2011 In-Clinic Feasibility Studies:

60 Subjects – 48 Adults and 12 Adolescents
UVA (N=30); Montpellier, France (N=18); Padova, Italy (N=12)
Randomized Cross-Over Design; Moderate Exercise (2 Studies)

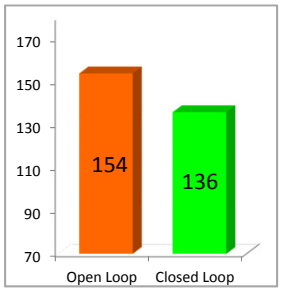
 # Hypoglycemic episodes /subject <70mg/dl



Percent time within target range 70-180 mg/dl



Average Glucose (mg/dl)
(translates into A1c change 7.0→6.36)



Open-loop physician-directed control

Closed-Loop Control

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ORIGINAL ARTICLE

Fully Integrated Artificial Pancreas in Type 1 Diabetes

Modular Closed-Loop Glucose Control Maintains Near Normoglycemia

Marc Breton,[1] Anne Farret,[2] Daniela Bruttomesso,[3] Stacey Anderson,[1] Lalo Magni,[4] Stephen Patek,[1] Chiara Dalla Man,[5] Jerome Place,[2] Susan Demartini,[1] Simone Del Favero,[5] Chiara Toffanin,[4] Colleen Hughes-Karvetski,[1] Eyal Dassau,[6,7] Howard Zisser,[6,7] Francis J. Doyle III,[6] Giuseppe De Nicolao,[4] Angelo Avogaro,[3] Claudio Cobelli,[5] Eric Renard,[2] and Boris Kovatchev,[1] on behalf of The International Artificial Pancreas (iAP) Study Group

Integrated closed-loop control (CLC), combining continuous glucose monitoring (CGM) with insulin pump (continuous subcutaneous insulin infusion [CSII]), known as artificial pancreas, can help optimize glycemic control in diabetes. We present a

Department of Computer Engineering and System Sciences, University of Pavia, Pavia, Italy; the [3]Department of Information Engineering, University of Padova, Padua, Italy; the [4]University of California Santa Barbara, Santa Barbara, California; and the [7]Sansum Diabetes Research Institute, Santa Barbara, California.
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This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db11-1445/-/DC1.
M.B., A.F., and D.B. contributed equally to this study.

See accompanying editorial, p. XXX.

The maintenance of close-to-normal blood glucose (BG) levels slows the onset and progression of

However, to date, there are no randomized crossover studies of fully integrated CLC, defined as having all of the following three components: *1*) automated data transfer from the CGM to the controller, *2*) real-time control action, and *3*) automated command of the insulin pump. Only one previously reported study has a state-of-the-art randomized crossover design (18), but it lacks automated data transfer (15). Conversely, the studies that use fully integrated glucose control (13,14,17,19–22) do not follow a randomized crossover design.

We have developed a novel approach to CLC algorithm design based on a modular architecture concept (7,23,24).

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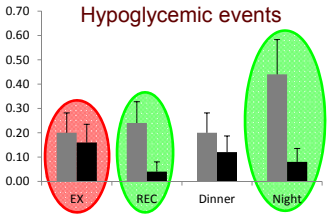
2010-2012 In-Clinic Exercise Feasibility Studies:

Enabling exercise during closed loop control using heart rate.
UVA Center for Diabetes Technology;



Study Design:

- **N= 12 subjects;**
- **Low intensity exercise**
- **Portable AP system + Heart Rate monitor**
- **Randomized cross-over sessions, heart rate enhanced- vs. standard closed-loop control;**
- **Each session continues for 24h;**
- **DiAs runs both open- and closed-loop;**
- **Patient in charge of system communications.**

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2011: Outpatient Artificial Pancreas

User Interface Designed to be Operated by the Patient

Android OS modified to meet medical application requirements (FDA Master File MAF 2109)

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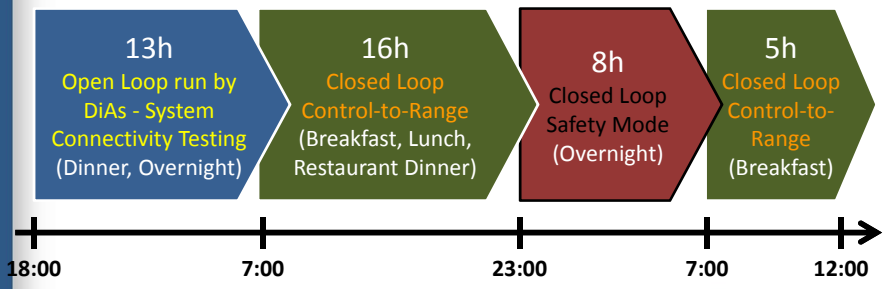
2011-2012: Early Feasibility Studies of Outpatient Closed-Loop Control

- UVA, Padova, Montpellier, Santa Barbara;
- N=5 subjects per site;
- 42-hour outpatient sessions;
- No meal restrictions (e.g. restaurant meals).



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ONLINE LETTERS

OBSERVATIONS

Pilot Studies of Wearable Outpatient Artificial Pancreas in Type 1 Diabetes

Complete Results:
***Diabetes Care*, In Press**

smartphone; sensor and pump communications are handled by the University of California Santa Barbara/Sansum Artificial Pancreas System (APS) running on a communication box connected via Bluetooth to the phone (Fig. 1, *upper panel*). The control algorithm includes safety supervision responsible for the prevention of hypoglycemia and a range correction module delivering insulin corrections as needed (5). The patients interact with the

Day 3—At 8:00, the patients had breakfast at the hotel. At 11:00, they had low intensity exercise (30-min walk in town). Throughout the study, the clinical team remotely observed the system operation and reference blood glucose was measured using HemoCue (HemoCue AB, Ängelholm, Sweden) pre- and post-meals, at bedtime, and upon physician judgment.

The AP, developed at the University of Virginia, is based on the Sony Xperia

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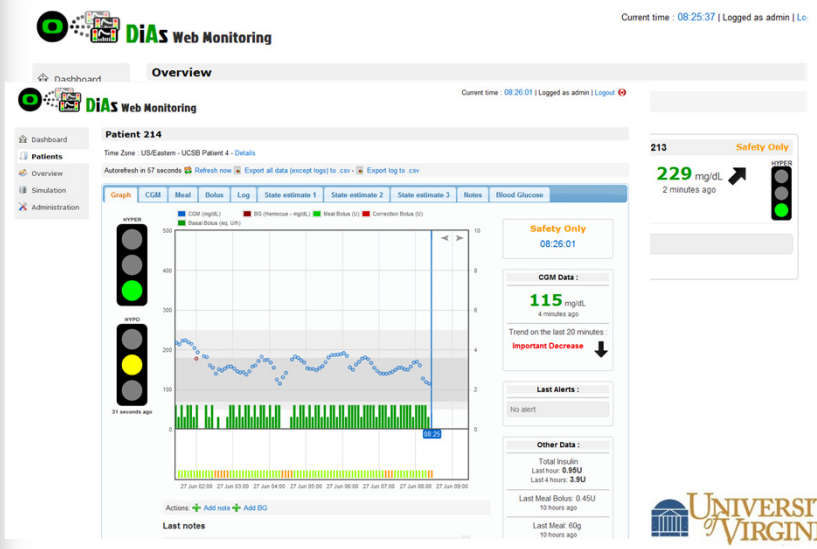
developer of the control algorithm, senior engineer of Montpellier trials; A.F., main study physician of Montpellier trials; D.B., main study physician of Padova trials; E.D., developer of the portable APS; H.Z., consultant on the portable APS; F.J.D., consultant on the portable APS; S.D.P., consultant on safety supervision system; and A.A., principal investigator, senior clinician, Padova. C.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The DiAs Remote Monitoring System

Simultaneous Real-Time Remote Monitoring of Several Patients



LAST SUMMER: Remote Monitoring

Stanford, UVA:
Three camp sessions, N=20 children / camp
N=10 Dexcom G4 + DiAs remote monitoring
N=10 Dexcom G4 only (control group)

- For the control group, hypoglycemia treatment based on standard diabetes camp night-time SMBG;
- For the remote monitoring group, hypoglycemia treatment initiated at 70 mg/dl observed on the remote monitor.

2012-2013: Efficacy of Outpatient Artificial Pancreas

UVA Center for Diabetes Technology;
Sansum Diabetes Research Institute / UC Santa Barbara;
Padova & Pavia (Italy);
Montpellier (France).

Study Design:

- **N= 5 subjects per site;**
- **Randomized cross-over sessions, open- vs. closed-loop control;**
- **Each session continues for 40h;**
- **DiAs runs both open- and closed-loop;**
- **Patient in charge of system communications.**

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System Configuration

3G or WiFi Connection
for remote monitoring

DiAs
Smart
Phone

USB

Dexcom
G4 Receiver

Devices near the subject

Low Power
Bluetooth

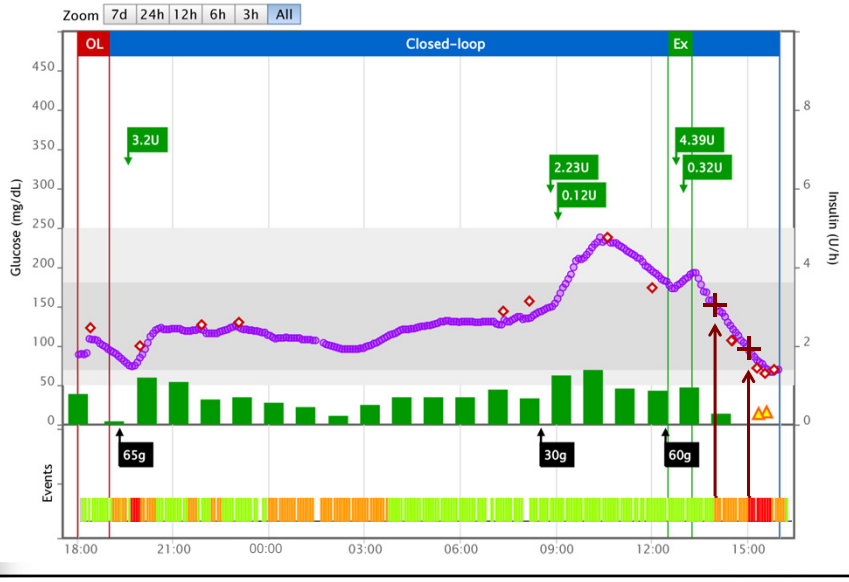
Wireless
connection

Tandem t:slim
insulin pump

Dexcom
G4 Sensor

Devices worn by the subject

Pilot Trial: October 30-31, 2012



Plans for 2013-2014

Multi-Site Home Trials of Control-to-Range
(UVA, Padova, Montpellier, Santa Barbara, Stanford, other)

GOAL:

Design and execute a definitive multi-center trial that will establish the artificial pancreas as viable treatment for type 1 diabetes.

Anticipated System Configuration:

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The Frederick Banting Foundation, Richmond, VA

University of Virginia
Universities of Padova and Pavia, Italy
University of Montpellier, France
Sansum Diabetes research Institute
University of California, Santa Barbara
Stanford University

Insulet Corp,
Dexcom, Inc,
Tandem, Inc.