Closer Look

FDA/JDRF/NIH Workshop on Innovation Towards an Artificial Pancreas

April 9-10, 2013; Bethesda, MD Day #1 Highlights

Executive Highlights

Greetings from Bethesda, MD and the first day of the FDA/JDRF/NIH Workshop on Innovation Towards an Artificial Pancreas. This is the fourth such workshop (2005, 2008, and 2010) and the sense of progress since the 2010 workshop felt really tangible to us today – multiple outpatient studies, mobile phone-based systems, emerging data on other hormones, big strides in CGM accuracy, and impressively robust algorithms. We were impressed to see so many involved people in the room: top academic researchers, regulatory officials, funders, and industry representatives.

Some exciting new data of the day came from Dr. Edward Damiano, who shared preliminary results from five patients in his ambitious five-day, ongoing outpatient Beacon Hill closed-loop study: overall average blood glucose (CGM) has been a stellar ~123 mg/dl, with less than 1% of blood glucose values <60 mg/dl. Dr. Damiano was brimming with confidence in his system, which he is targeting to be on the market in four years. Another highlight was the morning's standout panel discussion, which addressed a variety of fascinating issues: small incremental device approaches vs. striving for a big win out of the gate; safety requirements in a pivotal trial; whether one patient death would kill everything; liability issues; how to incentivize industry; if commercialized systems should ultimately run on a smartphone or the pump itself; and much more.

A plethora of the biggest AP researchers took the stage today, with most providing additional nuance and color on presentations first shared at ATTD 2013 in late February (see our full report and themes at https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2). Today certainly brought a real flavor of the wide variety of approaches in development – there's no question that groups seem to be hyper-focused on their particular areas (e.g., mobile platform development, speeding insulin, improving sensor algorithms, etc.), though there is also immense collaboration going on. Kudos to JDRF and the Helmsley Charitable Trust for making so much of this happen through funding and insights.

We recall that talk of the AP used to center on limitations in algorithms, sensor inaccuracy, and the speed of insulin. As we noted at ATTD 2013, research is now more about fine-tuning systems that are already achieving strong results. Algorithms have made massive improvements, and there was nearly universal consensus today that sensors are accurate enough at this point. We were glad to hear significant discussion of infusion sets today – this has been an under-researched area in our view, though is getting more and more attention. The desperate need for device communication standards was also frequently discussed. Indeed, both Drs. Boris Kovatchev and Roman Hovorka characterized this area as the biggest barrier in AP development. We agree that this is a huge problem and think that progress is most likely to come if the Helmsley Charitable Trust or JDRF start things moving.

Despite being in the room, industry was notably very quiet all day – we would have appreciated hearing more about what would motivate companies to move faster and invest more heartily in AP development. We found most of FDA's questions and commentary to be either in the weeds (e.g., insulin antibodies, heart rate variability) or frustratingly broad (e.g., a general review of device labeling and benefit-risk). There's no question that the final FDA guidance on the AP was a win, though our key question is how this will be implemented in practice since the Agency is not required to abide by it. Last but not least, it was great to hear so many say today that "Perfect shouldn't be the enemy of the good." It has been said a million times on both the drugs and devices side, and we hope FDA takes it to heart.

Table of Contents

Executive Highlights 1

Detailed Discussion and Commentary 3

Welcome 3

Introductory Remarks 3

State of the Art: Design, Results, and Challenges from the Latest Clinical Studies 4

Predictive Pump Shut-off Approaches 4

Preliminary Results of a Bihormonal Bionic Pancreas in an Outpatient Setting: The Beacon Hill Study 5

Time to Go Home 8

Human Factors That May Influence Clinical Efficacy of Closed-loop Technologies 9

AP@home: Lessons Learned From Clinical Studies on the Way to Daily Life Usage 11

Multivariable Adaptive Closed-loop Control of an Artificial Pancreas Without Meal and Activity Announcement 12

The Diabetes Assistant Mobile Artificial Pancreas Platform 12

The DREAM Way to Control Overnight Glucose Using the MD-Logic Artificial Pancreas System 13

FDA Challenges and the Artificial Pancreas 14

Panel Discussion 14

New Developments in Modeling, Algorithms, and Technology 19

Personalized Model-based Algorithms for Controlling the Artificial Pancreas 19

Algorithms to Detect Glucose Sensor and Infusion Pump Anomalies 19

m-Health 19

Improving Insulin and Non-insulin Hormone Replacement 20

Ultra-rapid Insulin Use in Closed-loop Artificial Pancreas: Preliminary Clinical Results 20

Microneedle Intradermal Delivery Enables Rapid Insulin Uptake and Effect 20

Next Generation Insulin Delivery CSII Catheters: Optimized Insulin Delivery Using a Continuous Subcutaneous Insulin Infusion (CSII) Catheter 21

Novel Glucagon Formulations 21

Panel Discussion (Excerpts) 22

Detailed Discussion and Commentary

Welcome

INTRODUCTORY REMARKS

Griffin Rodgers, MD (Director, NIDDK, Washington, DC); Alberto Gutierrez, PhD (Director, Office of In Vitro Diagnostic Device Evaluation and Safety, FDA, Silver Spring, MD); Aaron Kowalski, PhD (Vice President, Treat Therapies, JDRF, New York, NY)

Representatives from each meeting sponsor – FDA, NIH, and JDRF – provided opening remarks to begin the conference. All were optimistic and encouraging ("we've become like a family"), though there was a clear emphasis on past and future challenges as well.

- **Dr. Alberto Gutierrez provided a historical perspective on the FDA/NIH/JDRF meetings, which began in 2005, had a rocky bump in 2010, and is now on an upward trend.** The three groups began working on CGM and "had a good working relationship back then." Dr. Gutierrez called the 2008 workshop "a very good meeting" with " a lot of excitement." Unfortunately, communication between the FDA and investigators subsequently "became more difficult" at the 2010 meeting. According to Dr. Gutierrez, that workshop's disappointing tone led to the Agency and investigators "at each other's heads." This rocky relationship culminated in November 2011 when JDRF took out a full-page ad in the New York Times and Washington Post. Dr. Gutierrez was frank in saying that the Agency "had some issues to work out," and now "we have turned the corner in many ways." The main change has been putting the AP group into one office, a move that has allowed the Agency to work hard at improving overall response time and interaction with researchers. He also closed optimistically, echoing CDRH Director Dr. Jeffrey Shuren's goal to make the US first in the world in terms of medical devices coming to market first. In our view, this is a highly ambitious goal given the Agency's history.
- **Dr. Aaron Kowalski emphasized the "incredible progress" that's been made since the first AP innovation workshop in 2005.** He reminisced that at that initial meeting, there were few AP studies even going on and the transition was just beginning to the age of portable CGM. We also recall so much discussion at that meeting about accuracy and reliability and the state of the state was so much less advanced that that seems like it was a different age. Fast forward to today, where there is "tremendous data" from outpatient studies and many devices that are approved and in use. Yet, Dr. Kowalski also underscored the "huge unmet medical need today," referencing the high A1cs seen in the T1D Exchange and the significant burden posed by hypoglycemia. He thanked the FDA for working tremendously hard on the final AP guidance, and also acknowledged JDRF's partnership with NIH. Promisingly, the latter allows the organizations to pursue co-funding initiatives and leverage each other's strengths to accelerate research. He did not address major problems in regularly timing, e.g., there are devices that have been approved in other countries since 2009, such as the Veo, and are not yet approved in the US.
- **Dr. Griffin Rodgers discussed the efforts at several government agencies to prioritize development of an artificial pancreas.** The FDA has established the critical path initiative, Health and Human Services has developed the Interagency AP Working Group (helped in the development of the final FDA AP guidance), while NIDDK and its partners have supported a variety of cutting edge research. Dr. Rodgers highlighted that it "takes a village," giving a particular shout-out to JDRF's important efforts to get the Special Diabetes Funding renewed. He also highlighted the Helmsley Charitable Trust's important efforts to coordinate (to say nothing of funding) research. Dr. Rodgers closed with optimism that the meeting's focus on innovation

would result in a valuable exchange of ideas and strategies for future developments. We hope very much that the rare coming together of government, industry, non-profit organizations, academics, etc will culminate in some very candid and frank conversation that is actionable on the regulatory and commercial landscapes.

State of the Art: Design, Results, and Challenges from the Latest Clinical Studies

PREDICTIVE PUMP SHUT-OFF APPROACHES

Bruce Buckingham, MD (Stanford University, Stanford, CA)

Dr. Bruce Buckingham reviewed pilot study results assessing a predictive low glucose suspend (PLGS) system and presented initial safety data from the team's ongoing randomized outpatient study. The system was designed with the intention of eliminating prolonged episodes of nocturnal hypoglycemia, while working "in the background" with a reduced number of alarms. The system only alarms if blood glucose is less than 60 mg/dl or greater than 250 mg/dl and does not alarm for system failure (instead, it reverts back to usual basal rate). For the ongoing randomized trial, Dr. Buckingham is targeting 42 subjects each completing 42 nights. Each night is randomized, such that 21 nights use active PLGS and 21 nights serve as the control. The study will assess the primary outcome of nights with sensor glucose <60 mg/dl; secondary outcomes include mean overnight glucose, percentage of time in range (71-180 mg/dl), area under the curve >180 mg/dl, percentage of nights with sensor glucose >250 mg/dl, and number of mornings with ketones >0.6 mmol/l. To date, 49 subjects have enrolled (five of whom did not complete the study run-in period) and 21 individuals have completed the study for a total of 1,354 randomized nights and 1,266 valid nights (i.e., at least four hours of CGM data was available for the night). Given that the study is blinded, Dr. Buckingham could not share efficacy data; however, pooled safety data from the 1,354 nights showed no episodes of diabetic ketoacidosis and no seizures. Morning ketone levels above 0.6 mmol/l occurred in less than 1% of nights and there were no morning ketone levels above 1.5 mmol/l. The study is slated to complete in May and we look forward to learning whether its findings will corroborate the promising reductions in hypoglycemia seen in the initial pilot study.

- **The pilot study included 19 patients (375 nights total) and tested three iterations of the algorithm**; data was first presented at the Diabetes Technology Meeting (see our discussion on page 19 of our DTM full report at https://closeconcerns.box.com/s/3b1bj4dx1e7wu8kgrixa). The first algorithm had a prediction horizon of 70 minutes, the second used a prediction horizon of 50 minutes, and the third iteration used a prediction horizon of 30 minutes. The third algorithm conferred the best overall nighttime management; as such, a 30-minute horizon algorithm was used for the larger outpatient study.
- **Notably, final visit data from the 19 patients indicated that 100% of patients would opt to use a similar system if it was commercially available**, despite 47% of patients (n=9) saying the system "occasionally" disrupted their sleep and 11% of patients (n=2) saying the system "often" disrupted their sleep. Fifty-eight percent of patients felt that the hypoglycemia alarms were not appropriate, which they mainly attributed to sensor inaccuracies. We think the 100% positive response towards continued use of such a system is an impressive testament to the system's benefits and exemplifies the sentiment that "perfect should not be the enemy to good."

Subjects that felt system disruptive of sleep	n (%)

Never	8 (42%)
Occasionally	9 (47%)
Often	2 (11%)
Subjects that felt hypoglycemia alarms were not appropriate	11 (58%)
Because wanted to change thresholds	1
Because of sensor inaccuracies	10

Questions and Answers:

Dr. William Tamborlane (Yale University, New Haven, CT): What percent of patients wore the sensor six to seven days per week of the 19 that finished?

A: Most were using it almost continuously.

Q: The Agency's concerns with low glucose suspend is that it would increase A1c over time and our contention is if you are using it for the prevention of nighttime hypoglycemia, patients will wear the sensor during the day too and they will actually lower A1c.

A: That is a good point. Our trial cannot address A1c because we randomized each night.

Q: How did you deal with exercise?

A: Our algorithm does not incorporate exercise. It was an information item. We are also doing work using an accelerometer with the system to tell when the person is sleeping, which is a good way to tell if they are sleeping on the sensor.

Dr. Robert Vigersky (Walter Reed National Military Medical Center, Washington, DC): What is the relationship you've seen between ketones and snacks? Could there be starvation ketosis?

A: That's a good question – final data cuts will come later.

PRELIMINARY RESULTS OF A BIHORMONAL BIONIC PANCREAS IN AN OUTPATIENT SETTING: THE BEACON HILL STUDY

Edward Damiano, PhD (Boston University, Boston, MA)

Dr. Ed Damiano – interrupted mid-slide three by an NIH fire alarm test – shared exciting results from his ambitious five-day, ongoing outpatient Beacon Hill closed-loop study. In the five patients completed thus far, overall average blood glucose (CGM) has been a stellar 124 mg/dl on days two and three and 121 mg/dl on days four and five, with less than 1% of blood glucose values <60 mg/dl. Notably, the FDA approved the IDE for Dr. Damiano's 32-patient, five-day-long camp study today, which will take place this summer at Camp Joslin and the Clara Barton Camp. He noted that the team's new mobile device "has increased our productivity by eight or nine fold," enabling the team to perform more closed-loop experiments in the first eight months of 2013 than in the previous four years combined! In Q&A, Dr. Damiano also shared his two key wish list items: stabilized glucagon and calibration-free CGM. Dr. Damiano had a very visible role throughout the meeting and later in the day said that his goal is to get his artificial pancreas approved in four years because that is when his son with type 1 diabetes will be going to college. Many things have to go right for that to happen, but we think it's valuable for the field to have someone who is so openly ambitious.

- **The ongoing Beacon Hill outpatient closed-loop study involves five-day experiments in 20 adults with type 1 diabetes (≥21 years).** The randomized crossover design compares five days of closed-loop therapy to five days of usual care. Patients have free run of a three-square-mile area of downtown Boston. Patients have blinded point-of-care capillary blood glucose tests during the day (Hemocue) under 1:1 nursing conditions. Patients are allowed to eat and exercise as they please, with a maximum of two alcoholic drinks per day. At night, participants sleep in a hotel with venous blood glucose monitoring (GlucoScout) under 1:2 nursing. The study began in February 2013 and Dr. Damiano expects to collect over 3,000 hours of data.
- **The Beacon Hill Study is using an iPhone 4S to run their controller, a Dexcom G4 Platinum CGM/receiver, and two Tandem t:slim pumps (insulin and glucagon).** With help from SweetSpot Diabetes Care and Egret Technologies, the G4 Platinum CGM receiver is attached to the iPhone via custom hardwire through the 30-pin connector – we had only previously seen the Navigator version of the iPhone controller, which was far more brick-like than the sleeker Dexcom version. The Tandem pumps are controlled wireless (Bluetooth) from the iPhone controller. Glucagon reservoirs are changed every day, while insulin is changed every other day. The researchers elected to go with the Dexcom G4 Platinum based on the results of their head-to-head-to-head comparison studies: Dexcom G4 Platinum had a MARD of 10.8%, compared to 12.3% for the Navigator and 17.9% for the Enlite.
- **The study is essentially fully closed-loop control, with the control algorithm initialized only with a participant's weight.** The controller does allow for an optional manual pre-meal priming bolus component, which allows patients to select if this is more than, less than, or about equal to the number of carbs they typically eat (i.e., no carb counting). The algorithm learns over time from its meal-priming bolus performance and improves its dosing by automatically adapting the size of the meal-priming bolus based on the historical data it collects online. In the study, patients are told about the meal-priming bolus, but are not required to use it. In fact, if a subject forgets to take the priming bolus before the meal, he or she is advised to allow the controller to take care of the meal by itself. To date, most subjects use the priming-bolus feature intermittently, but few have used the feature routinely at every meal, which makes the results much more real world. We also like the no carb-counting and learning algorithm approach to meals, since highly accurate carb counting is quite difficult in practice.
- **Dr. Damiano showed preliminary, very impressive results from five Beacon Hill patients tested to date ("we're nearly normalizing blood glucose").** The average is certainly one of the best we've seen in a daytime closed-loop study, especially with the low prevalence of hypoglycemia. Dr. Damiano emphasized that these averages predict an A1c in adults around 6.1%, handily beating the standard of care. He also noted that patients in the study are probably more active than they otherwise might be, perhaps because the presence of glucagon gives patients more confidence in avoiding lows.

	CGM Average		BG Average		% BG Values <60 mg/dl	
	Days 2 & 3	Days 4 & 5	Days 2 & 3	Days 4 & 5	Days 2 & 3	Days 4 & 5
Average	124 mg/dl	121 mg/dl	128 mg/dl	128 mg/dl	0.9%	0.1%

- **The FDA just approved the IDE for a Beacon-Hill-like 2013 summer camp closed-loop study.** Thirty-two patients will be studied over four weeks in a randomized, crossover

design comparing five days of closed loop therapy to five days of open loop therapy. The study will occur in an integrated camp experience at Camp Joslin (boys) and the Clara Barton Camp (girls). There will be point-of-care blood glucose checks and study staff providing 24-hour coverage via telemetry. Like Beacon Hill, the camp study will be transitional and real world in nature, with no restrictions on eating, activity, etc.

Questions and Answers

Dr. Ken Ward (Oregon Health and Science University, Portland, OR): You initialize the system with just weight. But wouldn't total daily dose as an index of insulin sensitivity allow you to come in with tighter control sooner?

A: What happens during inter-current illness? Why would I do this if my system works this well with just weight? Why pour all that information into the device. And what about someone with an A1c of 9% vs. 12%? (Dr. Damiano later asked the question "What about a newly diagnosed patient who doesn't know their total daily dose?")

Dr. Ward: You can adjust A1c for total daily dose.

A: Let's let the device find that out. I do not need that information. I've got two subjects at 70 kilos. One is a 15 year old with raging hormones vs. a 70-year old. We're controlling these people and beating standard of care. And there's still the issue of inter-current illness. Any system that requires that kind of insulin information is going to have a hard time.

Dr. Ward: I meant you could use it just to start out.

A: It's transient. People go through changes over months. You can see a two or three fold change in insulin sensitivity. Or worse, say you have a vomiting illness. You need to be able to dial that insulin dosing down. I'm getting good results on day one. We're testing a time course that is relevant to inter-current illness. That is key. You've got to be able to adapt to that in a six to 12-hour window. The system initializes at the same weight, but within about 12 hours could be dosing at 1.5 units per kilo per day vs. 0.3 units per kilo per day. That's what we want to be able to show. I don't want a system that is so rigid and inflexible that it requires initialization with total daily dose. (Editor's note: Dr. Damiano pointed out in a later conversation with us that such a system would not likely be able to handle the dramatic changes in insulin demand people with diabetes experience over periods of weeks, months, and years.)

Q: Have any subjects had inter-current illness during the study?

A: We do not allow subjects with inter-current illness in the trials. We have studied a system that knows nothing more than weight. You could say adolescence is a chronic state of inter-current illness [laughter]. What we haven't tested are adolescents with inter-current illness. The highest total daily dose we have seen is 1.5 units per kilo per day, and the lowest is 0.3 units per kilo. That's a five-fold difference. Our one system, initialized only with subject weight, handles this five-fold variability in total daily dose very well.

Q: How does the glucagon release in this outpatient study compare to your previous study?

A: We're using more. The last study was 0.5-0.7 mg per day. Now we're dosing 0.8-0.9 mg per day. We attribute the higher glucagon usage in our Beacon Hill Study to the greater

level of activity are subjects engaging in in the outpatient setting as compared with their relatively sedentary state in our previous CRC-based studies.

Q: In terms of Hemocue fingersticks every two hours, are those blinded?

A: Yes, they are blinded. One of the highest things on my propriety list besides stable glucagon is calibration free CGM systems. We do the fingersticks calibrations before dinner and before breakfast in this study. We do have rules – if you are rising or falling too rapidly, we will delay the calibration. We generally do two calibrations per day with the Dexcom G4 Platinum.

Dr. Vigersky: What's the inclusion/exclusion criteria for subjects? Are we studying the cream of the crop and the best-controlled and most reliable patients? What about those with hypoglycemia unawareness?

A: We used to only allow strictly C-peptide negative participants, but we are relaxing that in the camp study going forward. We used to only allow A1cs of 9% or below, now we're opening the doors to that. The averages in our subjects during their usual care experiments are coming in lower than what you'd expect from the national average A1c of 8 to 8.5% in adults with type 1. However, only four of our subjects have completed their usual care experiments, so these results are still very preliminary. It's also possible that our subjects really do manage their diabetes better than average, and we have a bit of a self-selected group.

TIME TO GO HOME

Roman Hovorka, PhD (University of Cambridge, United Kingdom)

Complimenting his recent ATTD presentation, Dr. Roman Hovorka gave an overview of the Cambridge team's three ongoing home studies using the FlorenceD closed-loop system. The ongoing studies consist of an adolescent overnight trial (APCam06; n=16), adult overnight trial (Angela03; n=24), and adult day-and-night trial (AP@home02; n=18). To date, 14 patients have completed APCam06 (for over 250 closed-loop nights), three have completed Angela03 (for over 80 closed-loop nights), and three have completed AP@home02 (for 21 closed-loop days). Notably, the studies do not employ remote monitoring. Individual glucose profiles from the outpatient studies suggest positive benefits of FlorenceD and that overnight and day-and-night closed-loop control is feasible. Further, a snap shot of controller effort data over 21 days for one adolescent in APCam06 demonstrated how difficult maintaining glucose control overnight is without such a system given intra-individual variability in insulin needs (for background, controller effort is measured by the percentage of insulin used relative to programmed basal). Dr. Hovorka reserved the last minute of his presentation to engage in broader discussion about closed-loop studies. He raised awareness to the potential for CGM to overestimate treatment effects when it is used to simultaneously control the system and assess the outcome. We don't hear much discussion on this front and wish time had allowed for Dr. Hovorka to delve into how best to address this bias. For greater detail on FlorenceD and study design, see our discussion of Dr. Hovorka's excellent ATTD presentation on page 12 of our full report at https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2.

Questions and Answers

Arleen Pinkos (FDA, Silver Spring, MD): Can you comment on frequency of blood glucose monitoring and how much diversity there was between that frequency?

A: The minimum compliance was at least four blood glucose readings per day. We asked patients to use to use the FreeStyle meter, but some used their own meter. Our requirements were at least four readings and the range was up to seven.

Dr. Aaron Kowalski (JDRF, New York, NY): With respect to the insulin load variation day to day, my interpretation is that it could relate to the infusion set. How much of that variation was due to food consumption versus bad infusion sets?

A: That is an important topic. We are capturing the data, but we haven't really analyzed it yet. My view is that infusion sets cause a major failure, so those are the extremes. My other view is that sometimes people overdose for evening meals and this would mean that not as much insulin was needed for the rest of night. The factors are difficult to assess and there is a lot of underlying variability. We are looking into that.

Q: Can you comment on day-and-night closed-loop control and the use of meal boluses? Where are you with those today?

A: Meal boluses are used based on the bolus wizard.

Q: So patients still have to do what they do in open-loop control?

A: I'd love to be able to run, but I think we need to walk first.

Q: Giving meal boluses in advance creates a huge risk factor in children under seven years old or people who don't count their carbohydrates correctly.

A: We did a study in the CRC where we didn't bolus in meals. Our system can cope, but we don't recommend it to be used as a standard feature.

HUMAN FACTORS THAT MAY INFLUENCE CLINICAL EFFICACY OF CLOSED-LOOP TECHNOLOGIES

Linda Gonder-Frederick, PhD (University of Virginia Health System, Charlottesville, VA)

Dr. Linda Gonder-Frederick gave an excellent behavioral perspective on the artificial pancreas and use of diabetes technology. She presented a number of psychological models and studies that characterize adoption and continued use of diabetes technology. We particularly valued her discussion of a UVa patient focus group on concerns over wearing an artificial pancreas – the two common themes that emerged were 1) patients' loss of perceived control over their own diabetes management ("humans are control freaks") and 2) systems that lack personalization. Dr. Gonder-Frederick concluded that behavioral research "lags far, far behind" technology development research and we need more research to improve the cost-benefit ratio of diabetes technology. We couldn't agree more and hope to see far more emphasis in this area – with only ~30% of US patients on insulin pumps and ~5% on CGM, there is much work to be done on patients' perceived barriers to tech and how to overcome them.

- **Dr. Gonder-Frederick emphasized the importance of *perceived* ease of use and usefulness.** She called these *perceived* factors the primary determinants of technology acceptance. This ultimately leads to intention to use and behavior. We thought this was a very interesting point, since perceived ease of use is much broader than just designing a simple-to-use product – it also has to do with marketing, education, training, etc.
- **UVa focus groups have revealed two main patient concerns with using an artificial pancreas.** The first is a loss of perceived control over diabetes management – said Dr. Gonder-Frederick, "For humans, loss of control is anxiety provoking. Humans are control freaks." She believes we need to incorporate perceived control into technology design (i.e., making us *think* we

are in control). This reminded us of the encouraging potential of hybrid systems that could augment open-loop therapy, though not completely take it over. The second main patient concern was lack of system personalization; in other words, how could an AP take into account all the information a patient takes into account? Dr. Gonder-Frederick encouraged a greater look into personalized technology – ultimately, she believes it will allow systems to maximize individual risk tolerance for high and low blood glucose.

- **Dr. Gonder-Frederick presented a temporal model of patients' adoption of diabetes technology.** First, patients decide whether or not to adopt a device – this is termed "initial use" and is influenced by things like perceptions, distress factors, hassle factors, and ease of use. Then, patients decide whether to continue using a device or not – does it improve glycemic control, quality of life, and reduce diabetes burden? The last step is incorporating technology into the daily diabetes management routine ("long-term adherence").
- **Research has revealed several predictors of discontinued or inadequate CGM use:** high hassle factor/low satisfaction, a mismatch between patient expectations and patient experience, physicians' failure to review CGM data, and patient difficulty interpreting CGM data. Dr. Gonder-Frederick believes there are things providers can do up front to give patients more realistic expectations about CGM. She also covered a study from Dr. William Polonsky of 2,500 Dexcom CGM users. The two major predictors of discontinuing CGM use were physicians' failure to review CGM data with patients and patient difficulties interpreting CGM data.
    - **We hope that better software in the coming years can directly address both of these issues.** In that vein, UVa has developed a Glycemic Risk Feedback output, which reports data in an intuitive red-yellow-green light manner. It provides feedback about glycemic variability, overall glycemic risk, and hourly risk. It is being tested right now with patients.
- **While consistent CGM use is difficult for many patients, some data supports less frequent use:** 40-50% use (Scaramauzza et al., 2011), intermittent use (Vigersky et al., 2012), and a stepped care approach (Riveline et al., 2012). Dr. Gonder-Frederick believes it is important to think in terms of flexibility, tailored therapy, and "different strokes for different folks." We completely agree – certainly, while 24/7 use is optimal, intermittent CGM use is better than none at all.
- **Out of 93 CGM studies listed on ClinicalTrials.gov, only two are focused on behavioral interventions** (Dr. Lori Laffel on family teamwork and Dr. Tim Wysocki on family behavioral therapy).

Questions and Answers

Dr. Yogish Kudva (Mayo Clinic, Rochester, MN): In terms of closed-loop subjects, one of our concerns is that the same patients keep getting enrolled in short duration studies.

A: This is something we need to do something about. We cannot keep studying the same people. We need to expand out subject population and study the less ideal populations. We also need some standardization of how we ask people things. There are opportunities to ask anonymous questionnaires.

Q: What about next gen device studies – it seems like the CGMs used in many of these studies were older generations.

A: The technology is constantly changing and we are running to keep up with it. But there are some fundamental issues that won't change. We should be looking for what they are. One is people's need for

perceived control. That's not going to change. It's definitely a challenge. We already have so many different kinds of technologies. For something like overnight closed loop control, I think parents will adhere. That's not an issue.

Dr. Moshe Phillip: Is there any consensus about which tools to use?

A: Yes, I think I'm going to write a paper on that. We need a paper on that and we need to think about this. I'm part of the fear of hypoglycemia research effort. I think that's a critical factor. We need diabetes specific measures of quality of life, as well as more general measures.

AP@HOME: LESSONS LEARNED FROM CLINICAL STUDIES ON THE WAY TO DAILY LIFE USAGE

Lutz Heinemann, PhD (Profil Institut für Stoffwechselforschung, Germany)

Dr. Lutz Heinemann reviewed the AP@home consortiums' clinical studies as well as gave background on a single-port artificial pancreas (being developed by GRZ/4A). The single port fuses the sensor and infusion cannula to enable a single insertion site: both ex-vivo (where the sensor rests outside the body with glucose drawn up to contact the sensor) and in-vivo (where the sensor is attached to the outside of the infusion cannula) approaches have been considered. Prototypes of the system have been tested in murine models and recently, single-port experiments have been done in healthy humans. As we understand it, the in-vivo approach is being more actively pursued; data on the single-port system is expected to emerge at ADA.

- **The AP@home's CAT Trial showed that closed-loop control gave similar time in target compared to open-loop control with diminished hypoglycemia.** For background and details on the CAT trial, see Dr. J Hans DeVries (Academic Medical Center, Amsterdam, The Netherlands) overview on page 21 of our Diabetes Technology Meeting full report at https://closeconcerns.box.com/s/3b1bj4dx1e7wu8kgrixa.
- **The consortium's CIPHER study suggested improved glucose control on day three of pump use vs. day one of pump use, with no significant inter-pump differences**. The aim of CIPHER was to access the effect of pump time on glucose control and whether the effect was mediated by pump tubing length (Medtronic Paradigm was compared to Insulet OmniPod).

Average Postprandial Glucose (mg/dl)		
Day	**OmniPod**	**Paradigm**
Day 1	168.2	159
Day 3	139.4	139.5
p-value	0.013	0.084

- **Dr. Heinemann reviewed data from a head-to-head comparison of the Abbott FreeStyle Navigator I, the Medtronic Enlite, and the Dexcom G4 Version A** (i.e., the version used with the Animas Vibe in Europe, not the more advanced G4 Platinum available in the US). In addition to assessing accuracy, sensor longevity was assessed. For results details, see our discussion of Dr. Yoeri Luijf's (Academic Medical Center, Amsterdam, The Netherlands) presentation on page 44 of our ATTD Full report at https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2.

MULTIVARIABLE ADAPTIVE CLOSED-LOOP CONTROL OF AN ARTIFICIAL PANCREAS WITHOUT MEAL AND ACTIVITY ANNOUNCEMENT

Ali Cinar, PhD (Illinois Institute of Technology, Chicago, IL)

Patients "don't want to do the work of the beta cells," said Dr. Ali Cinar. As such, his team's closed-loop system does not use meal and activity announcements. The system uses a generalized predictive control algorithm that incorporates energy expenditure and galvanic skin response information gleaned from BodyMedia's Sensewear armband; his presentation was tailored to the engineer in the room as he described algorithm's design and rationale in detail. Dr. Cinar also reviewed results from a small fully closed-loop study in three patients (seven experiments) using the system and spoke to the promise of integrating a hypoglycemia early warning system. These results were shown at ATTD; see our discussion of the closed-loop study on page 29 of our ATTD full report at https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2.

THE DIABETES ASSISTANT MOBILE ARTIFICIAL PANCREAS PLATFORM

Boris Kovatchev, PhD (University of Virginia, Charlottesville, VA)

Dr. Boris Kovatchev reviewed UVa's mobile artificial pancreas platform, Diabetes Assistant (DiAs), emphasizing the system's flexibility through a modular design, unified safety system, user interface, and upcoming studies. Three studies have been completed thus far on the system, with data from two of them to be presented at ADA 2013. Notably, two of the four studies (AP@Home and JDRF) planned for 2013-2014 will use a Dexcom Gen 5 sensor wirelessly sending data directly to the DiAs smartphone (i.e., no translator), which will ultimately dose a Tandem or Roche insulin pump. Dr. Kovatchev called communication between devices the biggest roadblock in AP development and something that "desperately" needs to be changed.

- **Two studies of DiAs will be presented at ADA 2013 this summer in Chicago:** The first was a November 2011-May 2012 42-hour feasibility study of the DiAs platform with a USB connection to the Insulet OmniPod iDex PDM. The second study is a multi-center November 2012-May 2013 trial that included five subjects per site and two 40-hour outpatient sessions. That study had no meal restrictions, mandatory restaurant dinners (alcohol permitted), and 45 minutes of light exercise. The DiAs system was connected via USB to the Dexcom G4 Platinum receiver. DiAs is connected to the Tandem t:slim via low energy Bluetooth.
- **The planned 2013-2014 studies of DiAs will use the Dexcom Gen 5 sensor directly connected wirelessly to DiAs. The investigators will use either Roche or Tandem insulin pumps.** The four slated studies include 1) a multisite trial of advisory control and telemedicine (NIH); 2) a multi-center outpatient trial of closed control (AP@ home); 3) diabetes camp studies of closed loop control (Helmsley Charitable Trust); and 4) a multi-center home trial of closed control (Jaeb Center and JDRF).
- **The Diabetes Assistant is a modular, portable AP platform based on an Android smartphone.** Dr. Linda Gonder-Frederick did extensive focus groups and human factors studies in this field and based on this work, DiAs' user interface was developed in 2011 by Dr. Kovatchev and other colleagues. The system incorporates hypoglycemia and hyperglycemia traffic lights: green means things are okay, yellow means the system is doing something to mitigate hypoglycemia or hyperglycemia, and red means human intervention is needed. DiAs also has a unified safety system (USS Virginia) that gauges the safety of insulin delivery. If the USS Virginia determines delivery is not safe, it will alert the user or attenuate delivery.

- **Dr. Kovatchev emphasized the impressive flexibility of the DiAs platform.** It can run with a CGM alone; a pump alone; open loop control with SMBG, CGM, and a pump; advisory mode with SMBG, CGM, and a pump; and closed-loop control. These modes can run interchangeably and can be used differently as studies require (e.g., Dr. Bruce Buckingham's summer camp study used DiAs in a remote monitoring capacity, while other studies have used it for closed-loop control). The modular design allows researchers to drop their own algorithms into the system. Importantly, DiAs also allows inputs above and beyond glucose readings and insulin delivery – for example, Dr. Marc Breton has studied the addition of heart rate and accelerometry data.

Questions and Answers

Dr. Robert Vigersky: What types of parameters go into the safety system (USS)?

A: It's a one-sided MPC algorithm. It can give less insulin but not more. From the insulin request, it's working down to attenuate it. It has all the characteristics of MPC – looking at insulin delivery, glucose traces, and predicting where glucose is going. It only attenuates and discontinues insulin. It has been used in probably 200 people so far.

Dr. Robert Vigersky: In those 200, how often does it activate?

A: Small attenuation of insulin delivery is common. It happens almost every 24 hours. That's the yellow light of the safety system – it is working and doesn't bother the patient. The red light means human intervention is needed. That's very rare and happens once a day at most. It signifies that with the current insulin on board, even if the pump shut off right now, hypoglycemia would result.

Q: What is the impact of not having a common communication standard? Is that something that needs to be addressed moving forward?

A: I have repeatedly stated that the communication between devices is the weakest link in the closed loop. We desperately need this.

THE DREAM WAY TO CONTROL OVERNIGHT GLUCOSE USING THE MD-LOGIC ARTIFICIAL PANCREAS SYSTEM

Moshe Phillip, MD (Schneider Children's Medical Center of Israel, Petah Tikvah, Israel)

Dr. Phillip reviewed data on the DREAM studies presented at ATTD 2013; ATTD was very successful for this group as some results were published in the New England Journal of Medicine. See pages 13-17 in our ATTD 2013 full report at https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2.

Questions and Answers

Dr. Steven Russell: Do you have thoughts on overnight-only closed-loop control – is that a viable product? What about from a regulatory standpoint? Or do you see it as a step towards 24-hour closed-loop control.

A: I don't know even one parent who sleeps a full night at our clinic. They get up in the middle of the night and check if the child is breathing, sweating, cold… I think that nocturnal hypoglycemia is an unmet need and should be a specific indication for closed-loop control during the night before we reach 24 hours.

Q: How would you keep people from using a nocturnal system during the day? Once they have it, wouldn't they use it all the time?

A: That's a wonderful question. I'm not afraid of them using it during the day. That's why we started doing daytime studies – just to make sure it is safe. We're not trying to show efficacy; we're focusing on safety.

Dr. Ron Pettis (Becton Dickinson): Can you speculate on the decrease in variability?

A: It was the algorithm and the way we developed it. We take into consideration changes in insulin sensitivity and other parameters.

Dr. Gary Steil: I'm wondering about the switch to pre-programmed basal rates from overnight fuzzy logic control. What if the fuzzy logic basal rate was turned down, the patient was hypoglycemic, and then a higher open-loop basal rate was turned back on?

Dr. Eran Atlas: When changing the basal, we're changing it as a temporary basal. It will revert back to the default program. Usually, that's in the morning, so the patient is awake and can control it.

Dr. Atlas: So during the night there is not a pre-programmed basal rate?

A: Right – it's totally on the logic.

FDA CHALLENGES AND THE ARTIFICIAL PANCREAS

Arleen Pinkos (FDA, Silver Spring, MD)

Dr. Arleen Pinkos gave the FDA perspective, with particular emphasis on "truth in labeling." She opened her presentation by building on the positive energy from investigators' presentations that morning – results look promising, she said. The Agency recognizes that "one size does not fit all", she said, and that the first artificial pancreas out of the gate will not be perfect for everyone; ultimately, patients and their HCPs will determine whether the AP is right for them, she said. However, when it comes to weighing benefits and risks during regulatory review, Dr. Pinkos explained that the Agency places great weight on whether users will thoroughly understand the limitations of the system and when they may need to take additional action. Thus, Dr. Pinkos challenged the audience to determine how best to communicate clinical performance (and potential limitations) through labeling. Said Dr. Pinkos, we need to relay the complexity of study design in an easy to understand way that is concise yet comprehensive, and suitable for all audiences – this is no small task. While Dr. Pinkos finished her presentation with time to spare (one of the rare few), disappointingly, no Q&A session was held after her presentation in order to allow adequate time for the round table discussion that followed.

PANEL DISCUSSION

Roy Beck, MD, PhD (Jaeb Center for Health Research, Tampa, FL); Joseph Cafazzo, PhD (University Of Toronto, Canada); Kelly Close (Close Concerns, San Francisco, CA); Barry Ginsberg, MD, PhD (Diabetes Technology Consultants, Wyckoff, NJ); Fouad Kandeel, MD, PhD (City of Hope, Duarte, California) City Of Hope; Aaron Kowalski, PhD (JDRF, New York, NY); Lori Laffel, MD (Joslin Diabetes Center, Boston, MA); Steve Russell, MD, PhD (Harvard University, Boston, MA); Bill Tamborlane, MD (Yale School Of Medicine, New Haven, CT); and Chip Zimliki, PhD (Medtronic Diabetes, Minneapolis, MN)

Dr. Richard Bergenstal: Just to start, is there really a need for this exciting technology?

Dr. Roy Beck: There certainly is a need. You can assess that in different ways. If you look at the percentage of patients with type 1 diabetes that actually meet target and minimize hypoglycemia, it's a minority of

people. There's a need for better ways to manage type 1 diabetes. We need to reduce burden and improve quality of life. Take that together, there's a tremendous need.

Ms. Kelly Close: I don't think that there is any other therapeutic area when patients are commended for being so far from normal. Patients are eager to get back to normal, and if we had something like the AP, we would all be much closer to normal. There is so much anxiety and work and stress that comes on the families and partners of those with diabetes, and all of that is so silent. Something like this would have a profound impact.

Dr. Lori Laffel: One of the challenges Roy articulated is we aren't achieving goals by A1c levels. We haven't really reduced the occurrence of hypoglycemia nor the presence of long-term complications. Despite wonderful tools, we need to talk about the need for adherence. Until we have seamless approaches to care that don't require a lot of input, we're going to be burdened with having behaviors as a focus of any technology. There will be that behavioral component with any technological advancement.

Dr. Tamborlane: In pediatrics, the mean A1c in adolescents is almost 9%. Still. That's as bad as the control group in the DCCT. We have inadequate ways to assess the quality of life of technologies. That might be a problem down the road, especially as we become more cost conscious. We've seen this in the JDRF CGM trial. If you use standard tools, the quality of life perceived by patients with diabetes is pretty good. In a DCCT manuscript in prep, we're using fairly sophisticated methods to measure quality of life. One is a perfect score, and the difference between perfectly healthy diabetes patients and those on dialysis was a tenth of a point. We need better ways to assess quality of life.

Dr. Kowalski: I have a very provocative question. Are we crazy right now? What I'm hearing is that we have this pressing unmet medical need. We want data, perspective from patients, and perspective from clinicians. And what we're seeing from all the investigators who have spoken is that these systems are much safer, giving much better glycemic control, and folks don't want to give these devices up. I worry we are paralyzed by over analysis to some degree. We have a tool that could transform diabetes and we are sitting on it to some degree. What is the hang up in our minds that is preventing us from moving faster?

Dr. Damiano: This perception that we're not moving quickly, I don't understand. We are flying. We have a device that needs to be tested. We just entered into an outpatient study; we just got approval to test the device in children. In eight months, we will have done more closed-loop hours than in 4.5 years combined. I don't feel like we are delaying things, I can't imagine moving faster. I think the technology we have will be transformative, but we need to test it in a sufficient number of people and circumstances. I do not want perfection to be the enemy of the good but I don't want incrementalism to be the enemy of the good either. I think we can do this in four years. I think we are moving at a reasonable pace. I don't want to do it so quickly that we compromise what's out there. If something goes wrong, it will be the device that will be at stake; the entire initiative will be at stake. We have to do the transitional and pivotal studies.

Kelly Close: I think we are flying too. I totally agree with Arleen, there has been so much progress, but for those of us who look at drug side, sometimes things get really stalled as well. We are flying and it's good we are talking about what regulators want to see and, with respect to the commercial landscape, what does liability look like. There are so many patients that are going to want this.

Dr. Phillip: I don't think we need four years. We have to have a safe product. Even if we pay the price of remote monitoring at the beginning until we have enough safety data, I think we can get there faster.

Dr. Barry Ginsberg: One of the problems is that people fail to look at opportunity cost. Patients with type 1 diabetes on intensive therapy have a high rate of severe hypoglycemia – maybe as high as two events per

year. When we talk about safety, we have to take that cost into account. We'll never get a device that absolutely prevents all hypoglycemia from happening.

Dr. Robert Vigersky: FDA has said that they're not going to tell you what those safety parameters should be. What does the pivotal trial look like in terms of safety parameters? Can we inform FDA about safety?

Dr. Moshe Phillip: It's easy. In terms of safety, it's reduction in events of hypoglycemia and time spent in hypoglycemia, without increasing severe events, without DKA, and without increasing A1c. That's enough. We don't have to show the patient is happy and we don't have to show that we improved A1c. The enemy of the good is the best. Closing the loop for 24 hours and having the best solution with a mean blood glucose of 110 mg/dl jeopardizes the progress.

Dr. Bill Tamborlane: There are two aspects of safety. One is the benefit of the closed loop: preventing or reducing the risk of hypos. Despite what we've heard, we still don't have the Veo approved. We should also have a predictive low suspend pump. Then there's what Ed was talking about – the potential injury due to system failure. That's a lot more challenging. There are unusual cases and there should be sufficient mitigation to prevent horrendous events from happening. This is why we don't have everyone climbing on board to start on closed loop right now.

Dr. Sanjoy Dutta (JDRF, New York, NY): Can we hear about the design of pivotal trials with respect to end points? What are we looking for? It can't be A1c. What do we agree the end point should be?

Dr. Bergenstal: Is time in range still a good marker?

Dr. Beck: I think it depends on the patient population. There won't be one-size-fit-all for outcomes. If we take patients who have high A1c, we want to reduce A1c. Whereas if we take a group with A1c less than 7%, I think there we are looking to reduce hypoglycemia, which would be biochemical. It depends on whether you are doing a night study too. I think overnight we can look at time in range and reducing hypoglycemia.

Dr. Tamborlane: I have a controversial point. Look at all the data - the control patients are doing too well. If you have a treat to target vs. open loop and you are looking at A1c differences, it should be non-inferiority. If you do just as well with closed loop and reduce the burden of therapy by 90%, you have a big winner.

Dr. Hovorka: To be approved in the UK, the system has to be cost effective. We should aim for those patients who will benefit most: those with high A1c and those with hypoglycemia. From my viewpoint we need these patients in our trials. If it were an overnight study, implementing A1c would be challenging, so maybe time in target is appropriate.

Dr. Damiano: With respect to the timing of pivotal trials, people are saying four years is a long time. In 2008, I remember people talking about closed loop being available now. In a system that just suspends glucose at night, you have a smaller effect size, but we are going to absolutely crush the control group. Our effect size will be so big that our pivotal trial can be smaller and faster – six months – compared to what can be done with an inferior system that's not as ambitious. I think the pivotal study does drive a lot of the timeline. We are going with a system that can really substantially improve quality of glycemia.

Dr. David Klonoff: In addressing the targets for trials, I was on a JDRF panel that looked at this. We looked at three groups of people. First, are those with too much hypoglycemia. The goal is less hypoglycemia with no sacrifice in A1c. Second is people in poor control – we want a better A1c with no

increase in hypoglycemia. The third group of people are doing fine – we don't want to see A1c or hypoglycemia get worse; we just want to improve quality of life.

Todd Zion (cofounder, SmartCells): Aside from the stability of glucagon, why not use it? Dr. Damiano, you are the only one really adopting it in a clinical manner.

Dr. Damiano: I am not the only one. Ken Ward is using it. There are a lot of groups. I think we will see popularity over time. I think it will shine in outpatient settings. When people are physically active, glucagon is critical. It is dysfunctional in type 1 diabetes. So we have a dual hormone problem in type 1 that we are addressing. The biggest obstacle has been that it is not a stable, pumpable drug. But the fact of the matter is, there has been a lot of attention as a result of what we've done and what Ken has done. I'm seeing small pharmaceutical companies coming up with stable glucagon on a fast regulatory pathway. Tandem is developing a dual chambered pump. We are getting into more sophisticated real-life studies and these other things are coming in parallel. I think there will be fewer barriers.

Dr. Tessa Lebinger (FDA, Silver Spring, MD): I have a scientific question for the panel. Is anybody looking at correlation of either glycemia or insulin requirements dependent on how much insulin has been infused one, two, or three days earlier? Dr. Damiano presented some data previously that patients with antibodies had longer duration of action of insulin. You get patients where no matter what they do they are running low. Other days they are running high without explanation except possibly, low affinity antibodies. Is blood glucose on a given day a function of a couple days ago? Is any one looking at these longer-term associations?

Dr. Kovatchev: Claudio Cobelli and colleagues from the Mayo Clinic looking at inter-day variability will answer that question. The answer is yes, there are people looking at it.

Q: We have Apple systems, Android system, two Linux systems…Is the fact that we are choosing different systems making sharing results more difficult? Can we move towards one system?

Dr. Boris Kovatchev: That's why we're introducing this – for people to use it and move faster. For choice of operating system, there are some reasons to believe that at the first stages, you must have an operating system that is medical grade. The only way to do so is with Android. We would love to do that on an iPhone, but it would require some participation from Apple.

Dr. Roman Hovorka: There are limitations in Europe when it comes to manufacturing responsibility. Someone must take legal responsibility. There are also cost challenges. What is more limiting is connectivity to the pumps and CGMs. That has been holding up the progress.

Dr. Ed Damiano: I have no desire to run this on an iPhone. I don't envision this running on an iPhone. If there is a medical grade system that can run on Android, we should consider that. But I think of it as just a miniature laptop that gets us out of the CRC and into the real-world setting. Android or iPhone is a portable computer. The algorithm is not going to live on this. It's just one step towards the final embodiment.

Q: Will any AP be restricted to a small number of users? Would one death stop this in its tracks?

Dr. Ali Cinar: I've had this question in my mind for a while. At the end of the day, most of the studies are in the proof of concept phase. I don't think that any of the universities will be selling APs to the general public. We haven't heard from industry about additional elements that are necessary to produce a mass scale AP system. It integrates many components, but it also has legal problems. A university can sell 1,000

of these and make a small profit, but if there is one litigation, they would pay 10x more and go bankrupt. It would be good to hear from industry on the things that would motivate them.

Dr. Chip Zimliki (Medtronic, Minneapolis, MN): I will say that our president has devoted a lot of time in moving the AP initiative forward. I do think there are concerns related to the risks. I love the progress we have made, but we have to be concerned about what happens when the sensor is wrong. I think there are really interesting answers to that in the next session.

Anna McCollister-Slipp (Co-founder, Galileo Analytics): The biggest issues we've had as we're trying to think of how to put together a steering committee and a public-private-partnership relates to data silos. As we assess the potential of the AP and where we are going to go in the next three years, whether regulators or patients, what we're going to need is – and we have power to – get better data on device stability, pump data, and device failures. The FDA only has the capability of getting reported device failures. We don't have any context for really judging these devices. The data I've seen is much safer than what I see on the day to day. We need to break down data silos and get data on pump safety and the number of hypoglycemia events, whether severe or non-severe. We need this data to properly judge the safety of the artificial pancreas.

Dr. Tamborlane: I think there are fundamental differences between open-loop and closed-loop CSII. For 30 years or more with CSII, there has been remarkably few if any events where the pump was responsible for the over delivery of insulin that caused injury. Usually it related to patients' interactions with the pump and usually it is under delivery.

Dr. Jeff Joseph: I have experience in the operating room trying to document and do evaluation of rare events. An adverse event happens rarely, and there is usually a series of events that led up to that. What do we have to do make this device in the hands of the end user safe enough, especially so that it is taking the patient out of the loop as much as possible. If the patient does too much, it actually may do harm and increase the risk of an adverse event. When you take a meter and put it in the hands of a lab researcher, the results are better than when you put it in the hands of an end user.

Dr. Aaron Kowalski: I think we're stuck on the trees and not looking at the forest. We need to focus on the comparator. These trials are pretty straightforward. Look at what we're doing today – drawing up insulin in a syringe. There are kids who don't test ever. They are dosing insulin on no information. These systems are going to blow away open loop therapy. Open loop therapy is terrible right now. As these studies ramp up, it's going to be very clear that these systems are much safer than what we're doing right now. We need to capitalize on that. We need to get companies comfortable with a pathway to market. The systems are not going to dump 300 units of insulin into you.

Dr. Alberto Gutierrez: The liability issue is a strange one because there is enough law out there. When things go through a PMA and are approved by FDA, a certain liability gets taken away. FDA is certainly very aware of the problems. We are clearly trying to take a measured approach, but things happen that you make you wonder if we are moving too fast. An example just happened recently on a system that one would have thought was well vetted by now and we wouldn't make stupid mistakes: glucose meters. A company didn't think about values over 1,000 mg/dl. They coded the system so that when it a patient's blood glucose value was 1024 mg/dl or higher, it would give an erroneously low value. What about if you do this in the closed loop? We need to approach this in a way that makes sense. I'm not sure we're quite there yet. I think the timeline of four years to an artificial pancreas is a doable one, though companies will need to vet their systems and do lots of safety studies. [Editor's Note: Dr. Gutierrez was referring to LifeScan's recent recall of the OneTouch Verio IQ, Verio Pro, and Verio Pro+ meters; see our report at https://closeconcerns.box.com/s/g3bh2rzi8aqkr7owcp1b for more information].

New Developments in Modeling, Algorithms, and Technology

PERSONALIZED MODEL-BASED ALGORITHMS FOR CONTROLLING THE ARTIFICIAL PANCREAS

Frank Doyle, PhD (University of California, Santa Barbara, CA)

Dr. Frank Doyle described his team's work to bring personalization into algorithm development. To set the stage for his discussion, Dr. Doyle explored the fundamental tradeoff between controller robustness and performance. Dr. Doyle simplified the demonstrative mathematical formula with a single tenant: the ability of a controller to handle variability (e.g., noise, varying insulin action, uncertainties) is diametrically opposed to performance. As such, he argued that the key to balancing robustness and performance is mitigating uncertainty through better patient descriptions. Algorithms have traditionally been personalized either by 1) adaptive control, which is used when patient characteristics are poorly understood or change unpredictably and the system learns day to day; or 2) initialization, which is used when sufficient a priori information about the patient is available to adjust available settings. However, the adaptive approach generally takes six to seven days to reach optimal performance and the initialization approach requires a sufficiently rich data set, which may often be unavailable. Dr. Doyle and his team are exploring a third approach whereby the algorithm's patient model is personalized a priori with total daily insulin. "Patient customization is crucial for closed-loop AP algorithms," concluded Dr. Doyle. His statement seemed to reflect the permeation of personalized medicine into every level of diabetes care – from the doctor's office to the devices to the algorithms that run the devices.

ALGORITHMS TO DETECT GLUCOSE SENSOR AND INFUSION PUMP ANOMALIES

Wayne Bequette, PhD (Rensselaer Polytechnic Institute, Troy, NY)

Dr. Wayne Bequette discussed fault detection theory relevant to the artificial pancreas, with particular focus on insulin set failure and sensor attenuation. Drawing from lessons learned in aircraft and chemical refinery fault detection, Dr. Bequette explained that closed-loop control can potentially mask problems. As such, he underscored that measured output (e.g., glucose value) doesn't tell the whole story – you really need to understand what's going on with input (e.g., insulin delivery, insulin on board), he said. To date, Dr. Bequette has focused on two fault detection models: infusion set failure and pressure-induced sensor attention (i.e., when a patient rolls onto the sensor during the night causing sensor attenuation; PISA). Dr. Bequette and his team are exploring real-time PISA detection based on CGM rate of change, CGM rate of change increase rate, and the attenuation time window. Further, the PISA model incorporates activity monitoring to account for daytime exercise that could be misconstrued as PISA. Preliminary data was presented at ATTD – see page 45 of our ATTD full report at https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2.

M-HEALTH

David Klonoff, MD (Mills Peninsula Health Services, San Mateo, CA)

Dr. David Klonoff explored the mHealth landscape, with particular focus on current barriers to uptake. Chief among them is that patients, clinicians, regulators, payers and industry all have different concerns and priorities muddying mHealth's path forward. For example, clinicians want mHealth to

save them time, save them or the patients money, or improve outcomes. Meanwhile, patients want improved human factors, regulators are laser-focused on safety, payers want to save money, and industry wants to make money. However despite these hurdles, Dr. Klonoff envisions a future in which the artificial pancreas will provide remote cloud-based mHealth interventions (coined "KlOnStar" to capture the utility of the familiar OnStar car navigation system). The system would funnel sensor data through an enhanced 911 device to deliver alerts to physicians, designated "next of care," or call centers (Dassau, Journal of DST *2009). In addition to improving safety, Dr. Klonoff believes that mHealth research can improve AP efficacy, potentially through new wearable sensors that can provide additional novel input to AP systems and improved human factors (which would increase adherence and therefore the benefit of the AP). To meet this end, Dr. Klonoff outlined four buckets of research that he considered "worthy" of NIH funding: 1) incorporation of data from multiple wearable sensors in addition to CGM to determine insulin dosing; 2) creation of remote safety systems to notify HCPs; 3) validated human factors tools to simplify necessary manual patient overrides; and 4) security for wireless data transmission and pump control. We thought Dr. Klonoff's presentation was one of the more clear and crisp talks we've heard with respect to mHealth in the diabetes arena. We will be curious to learn whether his research buckets will receive the necessary investigator interest and research funding in the short term; certainly, if ever there was an audience to pitch these ideas to, it was the collection of expert thinkers in Lister Hill Auditorium.*

Improving Insulin and Non-insulin Hormone Replacement

ULTRA-RAPID INSULIN USE IN CLOSED-LOOP ARTIFICIAL PANCREAS: PRELIMINARY CLINICAL RESULTS

Howard Zisser, MD (Sansum Diabetes Research Institute, Santa Barbara, CA)

Dr. Howard Zisser discussed two approaches to improving closed loop control: inhalable Technosphere insulin (MannKind's Afrezza) as an adjunct to closed-loop control and intraperitoneal insulin delivery. As to the former, Dr. Zisser explained that without precise insulin dosing, large carbohydrate meals (i.e., ≥50 g) can lead to hyperglycemic excursions and/or rebound hypoglycemia. As such, his team is investigating the use of Technosphere, which has an ultra-rapid on/off profile, to blunt postprandial glucose excursions without elevating the risk of hypoglycemia. In his team's ongoing clinical trial, ~four of 12 patients have completed the study; the first patient's postprandial glucose profile looked promising. Turning to intraperitoneal delivery, Dr. Zisser is collaborating with Dr. Eric Renard to compare closed loop control using Roche's DiaPort 2 vs. a subcutaneous pump. Dr. Zisser expects to show data from the study's 10-patient cohort later this year. For greater detail, see our discussion of Dr. Zisser's Technosphere and DiaPort 2 presentations on page 23 and 25, respectively, of our ATTD full report: https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2.

MICRONEEDLE INTRADERMAL DELIVERY ENABLES RAPID INSULIN UPTAKE AND EFFECT

Ron Pettis, PhD (BD, Franklin Lakes, NJ)

Dr. Ron Pettis reviewed the design, published studies, and upcoming research on BD's microneedles for intradermal insulin delivery (1.5 mm long x 34 gauge). We look forward to seeing results from a 24-hour biomechanical device functionality study, which will be presented at EASD 2013. Meanwhile, the company recently completed a 72-hour basal-bolus insulin infusion study to examine device function and extended PK/PD variability/stability. The company has ongoing, unspecified work to optimize

microneedle device design. Important next steps include defining the regulatory pathway (current analogs are not approved for intradermal delivery) and incorporation of microneedles in closed-loop trials.

NEXT GENERATION INSULIN DELIVERY CSII CATHETERS: OPTIMIZED INSULIN DELIVERY USING A CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) CATHETER

Jeffrey Joseph, DO (Thomas Jefferson University Hospital, Philadelphia, PA)

Dr. Jeffrey Joseph explored how tissue trauma might contribute to CSII failure and variable subcutaneous insulin delivery. To set the stage for his discussion, Dr. Joseph explained that insertion causes initial trauma to the tissue as well as ongoing trauma due to micro- and macro- movements at the interface between the catheter and tissue. Catheter issues start to become clinically significant on day three (after which longer catheter use tends to correlate with worsening glucose control), necessitating insulin set change every two to three days. He proposed two histologically based hypotheses for the altered performance: 1) insulin could be degrading in the wound site around the catheter; and 2) insulin may be leaking out through the entrance wound. In order to optimize CSII catheter insulin performance, Dr. Joseph proposed myriad approaches: standardize catheter depth and location through automated insertion; minimize initial insertion trauma through a non-cutting pencil point needle or lubricious catheter/needle surface; minimize ongoing tissue trauma by using a soft, flexible, rounded catheter; increase capillary blood and lymphatic flow through heat or medication; inhibit blood coagulation and inflammation; inhibit insulin degradation with hyluronidase; and increase fibrinolysis (the break down of the fibrin that builds as a result of bleeding upon needle insertion). Dr. Joseph's presentation and the round table discussion that followed drew attention both to the need for greater focus in this area and the potential to improve insulin absorption through catheter design.

NOVEL GLUCAGON FORMULATIONS

Steve Prestrelski, PhD (CEO, Xeris Pharmaceutics, Austin, TX)

Dr. Steve Prestrelski reviewed Xeris' efforts to develop a stabilized liquid glucagon. The company has three products in in the pipeline: a glucagon rescue pen for the treatment of severe hypoglycemia (G-Pen), a glucagon mini-dosing pen for the treatment of moderate hypoglycemia, and a formulation for use with a bi-hormonal pump. As to the latter, Xeris is targeting a product that is pump agnostic, has a two year expiration date at room temperature, stability at 37°C (98.6°F) for up to four weeks, and is marketed in 1 ml vials (5 mg/ml in vial). According to Xeris' Brett Newswanger's ATTD presentation, the company was expecting IDE approval of the pump solution by 2017-2018. The "key issue" to a bi-hormonal pump agnostic formulation, explained Dr. Prestrelski, was ensuring compatibility between DMSO (the solvent Xeris uses) and pump parts/infusion sets. For example, most infusion sets used in the US use polycarbonate, which is incompatible with DMSO; however, Xeris believes incompatibility is a solvable problem and noted its collaboration with multiple pump companies to make sure all pump parts could be used with a DMSO-based solution. Turning to Xeris' lead G-Pen product timeline, Xeris expects to begin its phase 2 trial in 3Q13 (a slight delay from the company's previous 1Q13 target). Dr. Prestrelski's talk nicely complimented Mr. Newswanger's presentation on the topic at ATTD – for greater detail on Xeris and its ongoing development efforts see our ATTD discussion on page 109 of our full report: https://closeconcerns.box.com/s/tf5n9kn7dgxz7jdxmmn2.

PANEL DISCUSSION (SELECTED EXCERPTS)

Claudio Cobelli, PhD (University of Padova, Italy); Sanjoy Dutta, PhD (JDRF, New York, NY); Bruce Frank, PhD (Thermalin, Cleveland, OH); David Klonoff, MD (Mills Peninsula Health Services, San Mateo, CA); Boris Kovatchev, PhD (University of Virginia, Charlottesville, VA); Allan Krasner, Biodel, Danbury, CT); Sean Saint (Tandem Diabetes Care, San Diego, CA); Bill Tamborlane, MD (Yale University, New Haven, CT)

Dr. Boris Kovatchev: If you had to pick up a second hormone for dual hormone closed loop, would you pick up glucagon or pramlintide?

Dr. Stuart Weinzimer: It's easier to pick a hormone where you can have a co-formulation or co-delivery potential. That's a benefit and part of the attractiveness of pramlintide. You are also mimicking natural physiology a little better. The idea is that it's just like the native beta cell. However, it's a bit reductionistic to pick a hormone like it's a game show.

Dr. Tamborlane: I agree with Stu. I'm not sure it's one or the other. We can achieve the same effects of pramlintide with a GLP-1. Once a day liraglutide is something we're very interested in. We're surprised Novo Nordisk up until now has not been looking into that, but they are now. Or a Bydureon once a month injection, along with glucagon as an adjunctive therapy. We're approaching things from two ways: glucagon to rescue from a low, GLP-1 to prevent highs that may contribute to lows.

Dr. Aaron Kowalski: I have been obsessed with infusion sets over the last few years. It stems from a transition I made from MDI to pumps – I did that on CGM. I posit that the reason we don't see a bigger separation between MDI and CSII is because of pump set failure. I commend what you're doing because there is such a huge problem. JDRF is funding BD on this front. But I would challenge the community that we've got to get insulin into people, and we've got to do it more consistently.

Dr. Jeffrey Joseph: Thank you Aaron. One thing I got out of a thorough review of the literature is that there's never been a systematic study to understand what happens to an infusion set after days three, four, and five. We need systematic studies.

Dr. Bruce Buckingham: We've studied 120 weeks of seven days of insulin infusion with one set – 40% of people can go seven days with no deterioration in glucose control. Some people can only go two or three days. There is a huge biologic factor that is not well understood, whether it's fat cells, cytokines, histology, etc.

-- by Adam Brown, Kira Maker, and Kelly Close

Editor's note: The original review of day #1 at the FDA Workshop on Innovation Towards an Artificial Pancreas noted that four studies in which Dr. Kovatchev is involved would use the Dexcom G5; this has been corrected. It is two of the four studies (AP@Home and JDRF). We apologize for this error.