This talk with cover the following objectives:

- Understand the step wise progression of innovations in insulin suspension and hybrid closed loop technology
- Review medical literature and recent studies for closed loop technology
- Clinical applications of hybrid closed loop technology

Despite many advances in type 1 diabetes therapies, most patients are unable to achieve near-normal glycemia (Miller et al, 2015), and remain at risk for severe hypoglycemia, diabetic ketoacidosis, and long-term vascular complications. Closed-loop artificial pancreas technology allows a control algorithm to automatically increase and decrease insulin delivery using data from subcutaneous glucose sensors to improve glucose control and lessen the burden of diabetes management. Due to the absorption profile of rapid-acting insulin analogues, most closed-loop systems under development are hybrid systems, meaning that the patient is required to estimate each meal's carbohydrate content and confirm the recommended bolus dose calculated from the carbohydrate-to-insulin ratio (Weinzimer et al, 2008). Closed loop technology is not specific to diabetes devices. You use it in your everyday life—cruise control on your car, the thermostat in your home.

Step wise iterative approach starting with insulin suspension to the development of hybrid closed loop technology is an approach taken by some. Bergenstal, et al (2013) present data from the ASPIRE in-home study over a three-month period. These data show a reduction in nocturnal hypoglycemia (as measured by sensor glucose values) without affecting A1C values. Danne, et al (2014) present in silico modeling of a predictive low glucose management system and feasibility in youth with type 1 diabetes during exercise. These data demonstrated that predictive low glucose management may further reduce the severity of hypoglycemia beyond what has already been established for algorithms using a threshold-based suspension. Hypoglycemia was prevented in 80% of the experiments.

The real world application of closed loop insulin delivery system in a diabetes practice places safety as the highest priority. Hybrid closed (HCL) systems employ various combinations of control algorithms, glucose sensors, and insulin pumps. The development of a successful algorithm with a closed loop system balances the ability to lower glucose into the target range, but not overshoot insulin delivery so much that it would induce hypoglycemia. What is the best target range for a closed loop algorithm system? Does a closed loop system require administration of meal boluses by user or can it be automatic? How aggressive should the algorithm be at adapting to changes in a patients insulin sensitivity/resistance?

Early studies of artificial pancreas systems, many of which were overnight closed-loop devices, were conducted in silico or under controlled inpatient conditions. Later studies in supervised outpatient settings such as hotels and camps showed that HCL systems increased the time in which sensor glucose (SG) values were in the target range, variously defined as >70 to 145 or 180 mg/dL. More recently, closed-loop systems have been evaluated in the unmonitored home setting in a limited number of studies. Ly, et al (2015) discuss the feasibility and efficacy of a fully integrated hybrid closed loop system in subjects with type 1 diabetes, both in an inpatient setting and during a camp setting.

References:

Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med*. 2013; 369(3):224-32

Conget I, et al. Poster presented at EASD, Sept, 2015, Stockholm, Sweden.

Danne T, et al. *Diabetes Technol Ther*. 2014; 16(6):338:347.

DCCT Research Group. *JAMA*. 1996;276:1409-1415.

Garg S, et al. *Diabetes Technol Ther*. 2012;14:205-209.

Ilany J, et al. Poster presented at the 9th International Conference on Advanced Technologies & Treatments for Diabetes. 2016, February 3-6, Milan, Italy. EP04, A-0428.

Ly TT, Roy A, Grosman B, et al. Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes at diabetes camp. *Diabetes Care*. 2015; 38(7):1205-11.

Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care*. 2015; 38(6):971-8.

O'Grady MJ, Retterath AJ, Keenan DB, et al. The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. *Diabetes Care*. 2012; 35(11):2182-7.

Roy A, et al. Presented at 9th International Conference on Advanced Technologies & Treatments for Diabetes. 2016, February 3-6, Milan, Italy.

Weinzimer SA, et al. Poster presented at 66th Scientific Sessions of American Diabetes Association Scientific Sessions, June 9-13, 2006, Washington, DC.

Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care*. *2008*; 31(5):934-9.