Metabolic Control

OVERALL VISION AND LONG-TERM OBJECTIVES
The JDRF Metabolic Control Program has a vision to support development of non-device based approaches that lead to better outcomes in all individuals with type 1 diabetes (T1D). Outcomes include both improved glycemic control and overall metabolic homeostasis, translating into reduction in long term diabetes-related complications as well as reduced disease burden and stress.

While advances in continuous infusion pumps, continuous glucose monitoring devices and automated closed-loop insulin delivery systems have improved glycemia while reducing burden, it is hoped that further advances in these systems will continue to elicit better outcomes. Furthermore, the goal remains to overcome barriers such as access to, adoption of and psycho-social factors that thwart the widespread usage of these technologies. This is evidenced in many epidemiological and registry studies, most recently from the US-based Type 1 Diabetes Exchange. Drug-based therapies emerging from the Metabolic Control Program may be compatible for adjunctive use with or as part of artificial pancreas (AP) closed-loop systems (please refer to JDRF’s Artificial Pancreas Program’s strategy).

The JDRF Metabolic Control Program focuses on three major areas of research to improve T1D outcomes:

1. Novel insulin therapies: Glucose-responsive insulin (GRI), liver-targeted insulin (LTI) and ultra-rapid insulin (URI).
2. Non-insulin therapies: Non-insulin hormones (amylin, glucagon, GLP-1 receptor agonists, others); novel and repurposed therapies (insulin sensitizers, secretagogues, starch blockers, glucose reabsorption inhibitors, reuptake inhibitors, others); role of alpha (and other islet) cell dysplasia; precision medicine approaches based on responder.
3. Anti-hypoglycemia therapies: Drug and/or behavioral approaches that significantly reduce hypoglycemia risk and imminent hypoglycemia due to incorrect insulin dosage or impaired awareness of hypoglycemia; pathophysiology of autonomic failure and impaired counter-regulatory response.

NOVEL INSULIN THERAPIES
Insulin analogs—the lifeline for individuals with T1D—remain pharmacologically subpar due to kinetic barriers, risks of incorrect dosing, requirement for glucose monitoring and carbohydrate counting, systemic delivery and distribution, and other challenges. A recent report surprisingly showed extreme variability in insulin concentrations when purchased from pharmacies further challenging diabetes treatment (Carter AW, Heinemann L, Insulin concentration in vials randomly purchased in pharmacies in the US: considerable loss in the cold supply chain. J Diab Sci Tech 2017; in press). Current treatments rely on non-physiologic subcutaneous delivery of insulin. With advances in molecular and biomaterial technologies, it is possible to develop “designer” insulins with physiologic action profiles. The Metabolic Control Program has a modest and evolving portfolio of the following novel insulins:
Glucose-Responsive Insulin (GRI)
Sometimes also referred to as “Smart Insulin”, a GRI, by definition, is an insulin that automatically titrates its activity proportional to the ambient circulating glucose levels. Insulin is either modified to incorporate a glucose sensing moiety (non-canonical amino acids, glucose binding protein, etc.) such that its binding to the insulin receptor and subsequent activation is titratable with increasing glucose concentrations (the “on” conformation) and unable to bind efficiently at thresholds under a certain glucose level (the “off” conformation). Alternately, active insulin could also be packaged in glucose-sensing materials (like capsules) wherein the capsule binds to and releases active insulin protein relative to the amount of glucose bound to the capsule, thereby preventing glucose release at lower glucose levels, creating a critical threshold necessary to initiate this sequence. Additional designs are possible and under investigation. It is projected that a true GRI will regulate blood-glucose levels optimally, avoiding hyper- and hypoglycemia, as well as significantly reducing the need to monitor glucose levels. A GRI could be used to treat all forms of insulin-requiring diabetes. GRI holds promise for the individual and has commercial potential and hence is a high-risk, high-reward undertaking. It is possible to envisage that initially GRI may be effective in either the low glucose range (hypoglycemia prevention, GRI_{Gen1}) or high glucose range (hyperglycemia prevention, GRI_{Gen2}) only, and with iterative improvements in effectiveness, lead to the development of a GRI whose activity is titratable at all glucose ranges (GRI_{GenX}).

The Metabolic Control Program is currently supporting early-stage discovery efforts in developing GRI using various, discrete technologies. There is initial preclinical proof-of-concept for a subset of these projects, and it is projected that these will move into preclinical development over the next 2–3 years. It is to be noted that an earlier JDRF-supported GRI project with the Massachusetts-based biotechnology company Smart Cells, Inc. was successful in demonstrating preclinical efficacy and safety. This technology was eventually licensed by Merck and recently completed a clinical Phase 1 program (a recent report indicated that Merck is continuing development of a novel GRI candidate). The GRI portfolio is also supporting computational modeling and model-based designing of GRI candidates for preclinical testing. Such design principles will be shared across the various projects to guide GRI design and accelerate animal testing. Several of the pharmaceutical and smaller biotech companies remain engaged and interested in developing GRI drugs due to its potential promise; however, limited information is available in the public domain.

Gaps and Challenges
1. Technology: No precedence; no known drug that works automatically in response to an endogenous stimulus.
2. Safety: Demonstrate “leak-proof” glucose-dependent regulation to prevent hypoglycemia if excessive insulin released/activated at low glucose levels.
3. Regulatory: Determine path to facilitate clinical development (if unique from other insulins).
5. Market potential: Determine value proposition (benefit vs. cost) compared to other therapeutic options (e.g., artificial pancreas systems, adjunct therapies, cell-based therapies, etc.).
Liver-Targeted Insulin (LTI)
Liver-targeted delivery of insulin using percutaneous infusion pumps with intra-portal catheters has shown remarkable improvements in glycemic control with significantly reduced hypoglycemia, even in individuals with unstable diabetes and recalcitrance to subcutaneous insulin treatment. To realize the dream of non-diabetes like insulin secretion and action profile, the Metabolic Control Program has a small portfolio of discovery and early-stage clinical effort in LTI. The initial goal is to target prandial glucose surges and delayed prandial hypoglycemia, two of the key challenges in glucose management which arise due to the slower action profiles and hepatic hypo-insulinization of subcutaneously delivered insulin analogs. Additional goals of LTI would also be to reduce glycemic variability and increase time in target glucose ranges due to the shorter duration of action of LTI. Some LTIs in development have the added advantage of oral dosing, thus potentially reducing the invasiveness that is inherent to current insulin therapies. Akin to GRI, it is anticipated that LTI will be valuable in the treatment of all forms of insulin-dependent diabetes, thus expanding its market potential. Similar to GRI, LTI remains an attractive drug and several companies have candidates in development (ex: PI406 (NN1406): Type 1 and 2 diabetes; Phase 1: A liver-preferential mealtime insulin analog [https://www.novonordisk.com/rnd/rd-pipeline.html]).

Gaps and Challenges
1. Pharmacology: Demonstrate (oral) bioavailability and dosing flexibility.
2. Clinical: Establish treatment regimen—bolus vs. basal vs. total, and need for peripheral (non-liver) insulinization.

Ultra-Rapid Insulin (URI)
The challenge of subcutaneous, systemic delivery of insulin has been the main roadblock to achieving glucose control for both injection and infusion pump users, and for full automation of closed-loop systems. Several JDRF- and non-JDRF-supported URI projects over the last decade have attempted to overcome the slow speed of insulin action with limited or incremental success. While it is encouraging that there are ongoing efforts, including within the Metabolic Control Program, the most noticeable URI has been Afrezza, developed by Mannkind Corporation. Afrezza, an inhaled insulin using proprietary technology for alveolar delivery of a lyophilized powder approved for adults with diabetes, has a rapid onset and peak, as well as short duration of action—thus reducing prandial glucose and preventing delayed hypoglycemia. An earlier JDRF-supported study demonstrated significant benefits as adjunctive bolus insulin treatment compared to subcutaneously delivered rapid analogs in a small closed-loop artificial pancreas study. This is the targeted profile for a URI, though the magnitude of rapid-on or rapid-off or the duration of action to be clinically meaningful is to be determined.

The lack of URI is a gap that needs to be bridged and the Metabolic Control Program foresees supporting additional programs in the near term.
Gaps and Challenges

1. Pharmacology: Demonstrate rapid-on, rapid-off and reduced duration of action leading to prandial control and reduced delayed hypoglycemia (studies to adjust both clinical dosing advice (both prandial calculation and possibly basal adjustment) and algorithms for automated bolus calculation (dose advisors), i.e. calculation of “insulin on board”, and use of different bolus types need to be investigated in a structured way. This is also important for closed-loop systems).

2. Reimbursement: Demonstrate superiority over standard-of-care insulins (with study designs optimized to deliver outcomes that aid in access and adoption).

3. Market potential: Determine value proposition compared to standard-of-care bolus insulins (and other novel insulins).

NON-INSULIN THERAPIES

Insulin is not the sole hormonal disturbance in those with T1D, yet other aberrant pathways are often overlooked or ignored. Several other molecular entities and mechanistic pathways can be impactful in T1D research and clinical care. Endogenous production and secretion of amylin, the other beta cell hormone which is co-secreted with insulin, dwindles over time in those with T1D who may eventually become entirely deficient in this hormone. Additionally, other hormonal pathways are dysregulated, including glucagon and entero-endocrine hormonal signaling (GLP-1, leptin, others). Insulin resistance, a less well-studied culprit in T1D, is presently not part of the treatment regimen. Further, the epidemic of obesity has not spared the T1D population and it is estimated that two-thirds of individuals living with T1D are overweight or obese (T1D Exchange report), thus exacerbating the pathophysiology of their underlying autoimmune chronic condition. Current T1D treatment is entirely insulin-centric, with limited adoption of the only other approved T1D therapy, Symlin (amylin analog). Taken together, the current statistics showing poor outcomes in T1D even in advanced substrata of the society is not entirely surprising. However, the hope is that some of these metabolic imbalances are not insurmountable.

The Metabolic Control Program has a priority to understand the physiology and heterogeneity of T1D and systematically assess the clinical benefit:risk profiles of potential adjunctive therapies. These can have meaningful impact in restoring the missing metabolic balance while correcting some of the underlying pathology. To that end, this program is supporting preclinical and (primarily) clinical proof-of-concept studies of novel or repositioned hormonal and non-hormonal drugs to complement insulin action and evolve from the current practice and perspective of insulin monotherapy.

The following are key focus areas within the portfolio:

Non-Insulin Hormonal Drugs

Insulin-Amylin Co-Formulation

Initial clinical proof-of-concept using co-infusion of insulin and a synthetic form of the hormone amylin, pramlintide (Symlin), improved glucose management, including increased time in range, reduced prandial glucose, hypoglycemia and glucose variability and other measures. However, the currently approved three-times-daily bolus injection of pramlintide is beset with increased burden, dosing challenges leading to nausea and hypoglycemia, as well as limited benefit profile, thus culminating into...
poor adoption of the drug. Hence, the Metabolic Control Program has prioritized the development of co-formulated insulin-pramlintide in fixed ratios that can be delivered as injection (MDI) or infusion (CSII) to realize the benefits of physiologic beta cell-like secretion and function.

**GLP-1 Receptor Agonists**
Supporting proof-of-concept studies in targeted T1D populations such as overweight/obese, C-peptide positive, open vs. closed-loop automated systems, newly/recently diagnosed individuals with residual beta functional cells and others. It is hoped that these studies and other ongoing and prior clinical data will build a body of evidence that will guide clinical practice. It is noteworthy that these agents have gone from once daily to once weekly formulations, and oral formulations are in development.

**Glucagon, Leptin Receptor Agonists**
Supporting development of stable, soluble glucagon for bihormonal infusion and understand the benefits of leptin treatment to complement insulin action as well as glucagon suppression.

**Non-Hormonal Drugs**
SGLT Inhibitors, Bromocriptine, Metformin, Glucokinase Activators
Supporting several clinical studies to understand the benefits of each of these therapeutic agents to address glycemic and metabolic parameters in general and sub-populations of T1D, including adolescents, overweight/obese, insulin-resistant and others. The SGLT inhibitor class has recently shown promising results in pivotal studies in adults with T1D, including glycemic benefits, and cardio-renal protection (T2D). It will be critical to ensure pediatric studies are completed – an age group particularly prone to high glycemic variability and hypoglycemia.

**Biomarkers**
T1D heterogeneity and lack of stratification are unaddressed research gaps that are impeding clinical use of targeted therapeutics, hence eliciting poor outcomes including in large clinical trials. While personalized medicine approaches will be the way of the future, it is essential to understand the systemic pathology and metabolic milieu in T1D, as well as its variegated clinical presentation. The Metabolic Control Program has a small but significant effort in T1D stratification and hopes to expand the program to test various therapies under development (as discussed above).

**Gaps and Challenges**
1. Clinical: Assess benefit vs. burden profile of each therapy. Stratify responders for each mechanistic class. Evaluate additional benefits vs. potential risks for each class (e.g., weight, insulin resistance, etc.).
2. Regulatory: Identify path to accelerated approval of therapies in pediatric T1D.
4. Market potential: Determine value proposition compared to other therapeutic options (e.g., artificial pancreas systems, novel insulins, cell-based therapies, etc.). Incentivize commercial investment toward label expansion in T1D.
ANTI-HYPOGLYCEMIA THERAPIES

Hypoglycemia and fear of hypoglycemia are the most acute dangers for all individuals living with T1D. Normalizing elevated glucose levels is possible to some extent with intensive insulin treatment; lowering HbA1c prevents microvascular complications, improves cardiovascular health and saves lives, but we need to move beyond HbA1c to additional, impactful outcomes for people with T1D, such as time in range and hypoglycemia minimization (Diabetes Care 2017;40:1611–1613; 1622–1630; 1631–1640). Hypoglycemia is a serious condition associated with cognitive decline, reduced quality of life, cardiovascular events and mortality. It is also established that hypoglycemia begets hypoglycemia, thus intensifying the consequences of all forms of untreated hypoglycemia. Furthermore, in a subset of T1D individuals with autonomic failure that results in hypoglycemia unawareness (HAAF), the counter-regulatory responses and symptomatic awareness of impending hypoglycemia are lost, rendering them vulnerable to catastrophic yet unpredictable consequences of serious hypoglycemia. Hypoglycemia remains the principal barrier to achieving glucose levels necessary to prevent diabetic complications of chronic hyperglycemia. Interestingly, “dead in bed” does not occur in small children for reasons that are currently poorly understood. It is our goal to understand this protective effect in small children, which may enable finding treatment approaches for adolescents and young adults – age groups that are particularly prone to this catastrophic event.

The good news is that most forms of hypoglycemia are treatable and manageable with drug-based and behavioral interventions, in addition to CGM. The advent of automated insulin delivery systems and the promise of beta cell-based therapies, adjunct drugs and novel insulins in development will meaningfully address the clinical issues of hypoglycemia. However, the improved access and adoption of device-based therapies and potential of other drugs in development, or cell replacement therapies (also a JDRF research priority area), will take time to realize, with the lurking possibility of a lingering clinical unmet need. Hence the focus on supporting research toward anti-hyperglycemic treatments.

The Metabolic Control Program has prioritized two major areas of research to prevent hypoglycemia. The near- to mid-term goal is to assess the effectiveness of repurposed or novel drugs, behavioral interventions and better CGM technologies which interact with CSII, in the clinic or in development, as intermittent, adjunct therapies to correct hypoglycemia and hypoglycemia unawareness. The longer-term goal is to support development of promising, novel therapies that address the underlying pathology, as well as gain an understanding of the consequences of loss of pancreatic islet architecture and autocrine and paracrine signaling as sequelae to the autoimmune destruction of beta cells.

Gaps and Challenges

1. Clinical: Demonstrate sustained efficacy. Stratify individuals for specific treatment classes and establish treatment regimen for each class (e.g., daily vs. intermittent dosing, etc.).
2. Regulatory: Determine path to approval of therapies with hypoglycemia as an endpoint (T1D Outcomes Initiative).
3. Reimbursement: Determine payer needs for approval of hypoglycemia preventive therapies.
SHORT-TERM OBJECTIVES AND PRIORITIES
To achieve the goals outlined above, the JDRF Metabolic Control Program has prioritized the following areas for funding in FY2018–2020.

**Novel Insulin Therapies**
1. Preclinical proof-of-concept (efficacy and safety) of GRI candidates.
2. Clinical proof-of-concept of LTI candidates.
3. Clinical proof-of-confidence (differentiation from rapid analogs) of URI candidates.

**Non-Insulin Therapies**
2. Clinical proof-of-confidence (effectiveness) of repositioned adjunct therapies.
3. Preclinical and clinical proof-of-concept of novel adjunct therapies (including alpha cell-based therapies).
4. Validation of biomarkers to guide stratification and/or companion diagnostic.

**Anti-Hypoglycemia Therapies**
3. Clinical proof-of-confidence (effectiveness) of select behavioral therapies.
4. Validation of biomarkers to guide stratification and/or companion diagnostic.