

Metabolic Control

Vision

The Metabolic Control (MC) program's vision is a world in which drugs and drug combinations are commercially available to effectively and conveniently restore overall metabolic homeostasis in people with type 1 diabetes (T1D).

Mission

The MC program will continue to support innovations in research and drug development efforts to accelerate progress towards our vision. Taking a holistic view of the opportunities and challenges in driving toward our vision, our efforts will span the gamut of technology translation – from driving earlier-stage discovery and research efforts to accelerating and/or de-risking more mature drug development programs.

Rationale

T1D is a disease characterized by its heterogeneity among those living with it; measures of metabolic control vary widely among individuals based on metabolic characteristics (e.g., duration of T1D, puberty), demographic characteristics (e.g., age, gender), and lifestyle (e.g., as it pertains to eating habits, physical activity, and vigilance with respect to therapy). In fact, metabolic control in T1D entails much more than using insulin to manage glucose levels. While insulin is and will remain the focal point for treating T1D effectively, the MC program's approach to treating T1D is to provide a more holistic solution to effective (and convenient) management, taking into account the various other metabolic imbalances in T1D physiology.

While there are a number of types of insulin formulations indicated to treat T1D with various therapeutic profiles, there remains a large gap between the insulins available today and “ideal” insulins. New insulins are needed by the T1D community with much more favorable therapeutic and usage profiles. In parallel, and importantly, there remains only one other adjunctive drug product approved in the US to further improve glucose control (and to a degree, overall metabolic homeostasis) in people with T1D: pramlintide, an amylin analog, which is under-adopted due to major limitations in its current treatment paradigm. (Recently, the FDA issued a complete response letter around sotagliflozin, an oral dual SGLT1/2 inhibitor, while currently the FDA is reviewing dapagliflozin, an SGLT2 inhibitor, as an adjunctive treatment for T1D. Both drugs were recently approved in Europe and another SGLT2 inhibitor, ipragliflozin, has been approved for T1D in Japan.) In practice, other drug products are being used by people with T1D “off label,” but the fact remains that there is a significant unmet need in the T1D community for safer, more effective, and more convenient drug products studied appropriately in T1D and indicated to treat it. In particular, there is a need for better insulins as well as a wider range of drug products addressing metabolic imbalances in T1D more holistically.

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Drug, other than insulin, is currently indicated to treat type 1 diabetes in the US.

Current Clinical Outcomes are Suboptimal

In a recent study by the T1D Exchange Clinic Network published in early 2019, it was demonstrated that only 17 percent of youth with T1D, and only 21 percent of adults with T1D, are achieving the American Diabetes Association's recommended HbA1c target of <7.5%. Overall, mean HbA1c increased from 7.8% in 2010-2012 to 8.4% in 2016-2018. The study also elucidated disparate results across subgroups based on age and other demographic factors, underscoring the need for a variety of treatment options to address the population's heterogeneity. Clearly, more effective and wider-ranging treatment options are needed for the T1D community. While there are a number of types of insulins available offering different risk/benefit profiles, truly effective T1D treatment will involve much more than just insulin. There is a dearth of adjunctive therapies available to people with T1D to improve glucose control and moreover restore overall metabolic homeostasis, but there are significant opportunities to ensure the future landscape of drug-based T1D treatment includes drugs and drug combinations that will lead to much improved clinical outcomes – HbA1c and beyond.

Available Drugs Involve Inconvenient Dosing Paradigms

The vast majority of drugs currently indicated for the treatment of T1D involve both subcutaneous injections/infusions and vigilance on the part of the user. Subcutaneous delivery of insulin is painful and does not lend itself to discretion. Insulin dosing is generally effective at lowering glucose, but can have very different pharmacokinetic effects on the body (depending on a number of metabolic factors) including lack of efficacy (e.g., in the case of insulin resistance) and hypoglycemia. This variability necessitates frequent glucose monitoring/testing, carbohydrate counting, and onerous decision-making on the part of the user, and even at that, much of the self-management is frustrating “guesswork.” There are opportunities to drive innovations that reduce these burdens, enhancing the quality of life – and increasing the likelihood of successful utilization – of people who choose them.

Strategy

The MC program is focused on two types of novel therapies, and accelerators to bring them to market, to realize our ultimate vision and methods to accelerate these therapies to market:

- Next-generation insulins
- Adjunctive therapies to complement insulin, whether repurposed from other disease states or developed specifically for T1D
- Accelerators, including the establishment and use of core facilities as well as research into pathophysiology and biomarkers

Next-generation insulins

Standard-of-care insulin drugs fail to produce optimal outcomes in people with T1D due to non-physiologic pharmacokinetics and biodistribution, risks of incorrect dosing and hypoglycemia (necessitating burdensome vigilance on the part of the user), and other challenges. With advances in molecular biology, chemistry, and materials science, it is possible to develop “next-gen” insulins that are fundamentally different in design and action profile from the current generation of insulins. Strategically, the MC program's portfolio supports the following classes of next-gen insulins.

Glucose responsive insulins (GRI)

A GRI, by definition, titrates its bioavailability or activity in response to ambient, circulating glucose levels; GRIs are active at higher glucose concentrations but inactive at lower ones. GRIs, as a class of drugs, offer major benefits over existing insulins, including prevention of insulin-induced hypoglycemia, since by design they will not lower blood glucose below a certain threshold. Moreover, GRIs will alleviate the burden of user vigilance since the drug will automatically respond to changes in blood sugar, removing the need to count carbohydrates or frequently monitor blood glucose.

The MC program's strategy in the GRI space is to fund a broad, diverse portfolio of early discovery research in academic labs and the private sector, ultimately selecting the most promising projects for continued investment. There is initial preclinical proof-of-concept for a subset of these projects, and it is projected that these will move into preclinical development in the near future. Key to the MC program's strategy is partnership with the major pharmaceutical insulin makers in supporting promising GRI opportunities. The MC program's GRI portfolio also supports computational modeling and model-based designing of GRI candidates; these design principles will be made available to other researchers to guide GRI design and accelerate preclinical testing.

Liver-targeted insulins (LTI)

The liver is critical for glucose control and a major site of insulin activity, but it is under-insulinized in current treatment paradigms due to the delivery of insulin to the periphery and its systemic distribution. LTIs are insulins modified to target the liver and/or

designed to be delivered directly to the liver, restoring the physiological biodistribution of insulin and reaping clinical benefits including improved control of postprandial hyperglycemia and prevention of subsequent, delayed hypoglycemia. Additional goals of LTI include reducing glycemic variability and increasing time-in-range, due to the shorter duration of action of LTI relative to standard insulin.

The MC program's strategy in the LTI space consists of funding a small number of projects, both clinical and preclinical, academic and industrial, that employ diverse strategies to target insulin to the liver.

Ultra-rapid insulins (URI)

Subcutaneously administered insulin, whether from a syringe, pen, or pump, lowers blood sugar more slowly than endogenous insulin secreted by a non-diabetic pancreas, and remains in the body for longer. As a result, people with T1D often have early postprandial hyperglycemia and are at risk for subsequent, delayed hypoglycemia. A URI, designed to have faster onset of activity followed by faster cessation of activity ("fast on, fast off"), promises to improve these clinical problems.

The MC program's strategy in the URI space consists of funding a small number of preclinical projects that employ innovative strategies to improve the kinetics of insulin activity, either through direct modification of insulin or its excipients, or by exploring non-subcutaneous routes of insulin administration (e.g. oral, alveolar).

Other insulins

In addition to the above highlighted interests in novel insulins, the MC program will be opportunistic in supporting efforts to develop other next-generation insulins such as ultra-concentrated and/or ultra-thermostable insulins, which have applicability in achieving goals in both the MC and Artificial Pancreas programs.

Adjunctive therapies to complement insulin

The absence of insulin secretion from the pancreas 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 (a beta cell hormone co-secreted with insulin) and other hormonal pathways are dysregulated, including glucagon and entero-endocrine hormonal signaling (GLP-1, leptin, others). Insulin resistance, a less understood problem in T1D, is likewise not addressed by current treatments. 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 almost entirely insulin-centric, with limited adoption of the only other T1D therapy approved only in the US market, pramlintide (a synthetic amylin analog). However, these metabolic imbalances are not insurmountable. One of the MC program's priorities is to understand the physiology and heterogeneity of T1D, and systematically assess the clinical risk/benefit profiles of potential adjunctive therapies, which can have meaningful impact in restoring the missing metabolic balance while correcting some of the underlying pathology. To that end, the MC program is supporting preclinical and clinical proof-of-concept studies of novel or repurposed hormonal and non-hormonal drugs to complement insulin action, and evolve from the current practice and perspective of insulin monotherapy. Strategically, the MC program is focused on the following ways to address this objective.

Insulin-amylin co-formulation

Pramlintide, an injectable synthetic amylin analog FDA-approved for T1D, improves glycemic outcomes. However, adoption remains low because it is not currently co-formulated with insulin, meaning that adoption requires additional injections every day. Moreover, the bolus injections of pramlintide can cause nausea and hypoglycemia. To increase adoption and harness more fully the value of adjunctive pramlintide use, the MC program has prioritized the development of co-formulated insulin-pramlintide (or a novel amylin analog) in fixed ratios that can be delivered as multiple daily injections (MDI) or continuous subcutaneous infusion to realize the benefits of physiologic beta cell-like secretion and function. This strategy is supported by clinical proof-of-concept studies previously funded by JDRF showing that co-infusion of insulin and pramlintide from two different pumps, simulating a fixed ratio co-formulation, improved numerous aspects of glycemic control, including time-in-range, prandial glucose levels, and glucose variability.

GLP-1 receptor agonists

GLP-1 receptor agonists have demonstrated efficacy for T2D and are used by some people with T1D off-label. The MC program is supporting proof-of-concept studies in targeted T1D populations such as those who are overweight or obese, C-peptide positive, using

open vs. closed-loop automated systems, newly/recently diagnosed 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.

Glucagon receptor modulators / alpha cell function

The MC program is supporting development of stable, soluble glucagon – a hormone that raises blood glucose concentration – for applications where avoiding hypoglycemia remains a major unmet need, as well as efforts related to suppression of dysregulated glucagon activity (for example, to lower postprandial glucose levels). In addition, as part of the MC program's commitment to facilitate the discovery and translation of promising targets or therapeutics to improve and restore glycemic control in people with T1D, the strategic portfolio includes programs focused on research to evaluate molecular and cellular mechanisms, validate drug targets, or propose novel therapeutic interventions to correct alpha cell dysregulation and improve metabolic control in T1D.

SGLT inhibitors

The MC program supports work on the SGLT inhibitor class, which has shown promising results (including improved glucose control and weight loss) in pivotal studies in adults with T1D. In fact, two SGLT inhibitors [one dual SGLT1/2 inhibitor, sotagliflozin (Zynquista, Lexicon/Sanofi), and one SGLT2 inhibitor, dapagliflozin (Forxiga, AstraZeneca)] have recently been approved in Europe as adjunctive treatments for T1D, and another SGLT2 inhibitor [ipragliflozin (Suglat, Astellas/Kotobuki)] has recently been approved in Japan. Dapagliflozin is currently under review by the FDA for approval for T1D, while recently sotagliflozin was issued a complete response letter by the Agency, but there are reasons to be optimistic about a near-future approval for the latter. Moreover, studies are revealing that SGLT inhibitors are beneficial for cardiovascular and renal outcomes in T2D, raising the possibility they will confer these benefits in T1D as well. It will be critical to ensure SGLT inhibitor studies are also completed in T1D pediatric populations – an age group particularly prone to high glycemic variability and hypoglycemia.

Importantly, clinical studies have shown that the use of SGLT inhibitors as adjunctive therapies in T1D results in elevated risk of DKA. While we believe that these risks are significantly outweighed by the benefits of these drugs (e.g., lowering of A1c, increased time in range, reduced glycemic variability, weight loss, and no increase in hypoglycemia), we also realize that there is a need for mitigation strategies involving increased frequency of ketone monitoring to ensure that people with T1D can safely benefit from this class of drugs.

Repurposed drugs and novel targets for new drugs

The MC program strategy takes advantage of developments in the T2D space by testing select drugs that have shown efficacy in clinical studies in people with T2D, since certain aspects of metabolic dysregulation are similar in T1D and T2D. Such repurposed drugs include bromocriptine, metformin, glucose kinase activators, insulin sensitizers, and GLP-1 receptor agonists (the latter discussed above). While T2D drugs have great promise for T1D, it is also critical to promote the development of novel drugs intended specifically for T1D. Toward that goal, MC program strategy includes support for basic and clinical research to validate novel targets that can be developed into therapies to correct metabolic imbalances specific to T1D that are not adequately addressed by insulin monotherapy. In recognition of the fact that T1D is more than a disease of just glucose control, we are interested in addressing other dangerous metabolic imbalances such as obesity, dyslipidemia, hyperketonemia, counter-regulatory hormonal changes and insulin resistance.

Accelerators: Core facilities, pathophysiology, and biomarkers

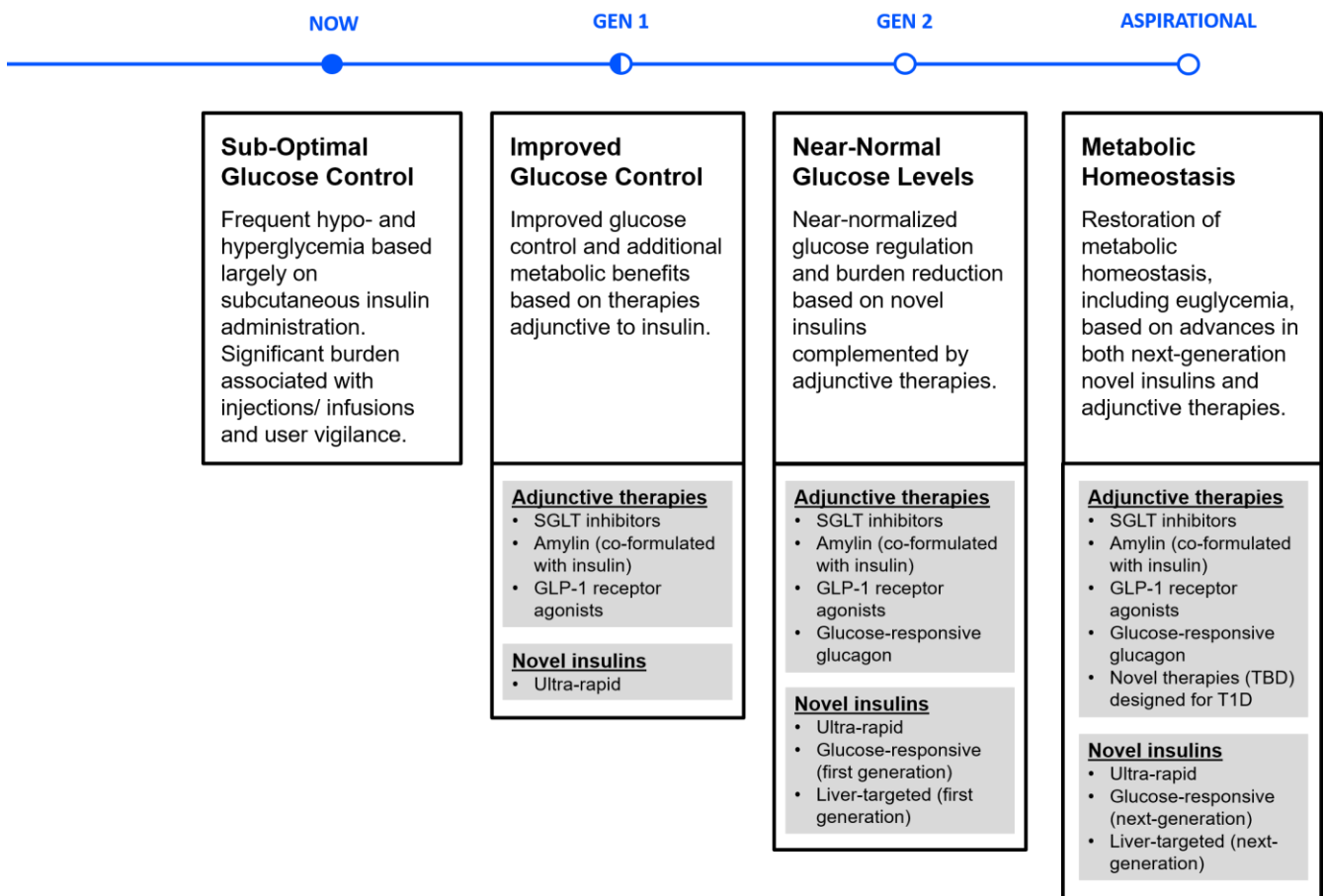
Efficient critical evaluation of drugs in earlier stages of development is complicated by a lack of standardization in experimental protocols and inter-investigator variability. The establishment of strategic core facilities can greatly facilitate scientific evaluation, leading to more informed decision-making and ultimately to accelerated timelines for continued development. To this end, the MC program has established such a core facility that can test candidate drugs (as well as devices and cell-based therapies) using standardized assays and methodologies.

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 MC 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). Moreover, MC program strategy includes clinical research on T1D pathophysiology, since our limited understanding of this topic is a significant hurdle to the development of improved therapies. Efforts in pathophysiology include investigating the effect of obesity on metabolic control in T1D and identifying prognostic biomarkers to support personalized treatments.

The MC program also includes scientific efforts in understanding methods to restore hypoglycemia awareness, including approaches to both elucidate the pathophysiology of autonomic failure and impaired counter-regulatory response, and drive drug and/or behavioral approaches that significantly reduce hypoglycemia risk and imminent hypoglycemia due to incorrect insulin dosage or impaired awareness of hypoglycemia.

Roadmap

While the field of drug-based therapies to treat T1D has existed for almost one century, we are only now on the cusp of meaningful progress beyond insulin-centric approaches. We are confident in the prospects of the emergence of a new generation of drugs labeled for the treatment of T1D, which is likely to include both drugs adjunctive to insulin – improving metabolic balance more holistically – as well as novel, next-generation insulins. It remains to be seen precisely how this generation of potentially disparate treatments evolves, but the outcomes of improved glucose control and metabolic balance will be their unifying feature. Over time, we aspire to drive the development of a holistic pharmaceutical solution, likely consisting of a combination of next-generation insulins and adjunctive drugs, which can restore metabolic homeostasis in T1D.



Current Status

The MC program supports research that spans the gamut from basic discovery to clinical trials, all toward the goal of developing novel drug-based therapies to improve outcomes in people with T1D.

Next-Generation Insulins

The MC program's GRI portfolio consists entirely of projects in the research phase of development. While some represent early, basic discovery research, others are testing novel GRI prototypes in preclinical T1D models and are poised to transition to preclinical development in the near future. The MC program's focus on preclinical GRI research reflects the state of the GRI field as a whole; to date, only one GRI candidate (MK-2640, licensed by Merck from Smart Cells Inc., which was funded by JDRF) has entered clinical studies. Several biotechnology and pharmaceutical companies are currently working on GRI; however, limited information is available in the public domain.

The MC program's small portfolio in LTI includes two projects the preclinical phase and two in clinical development. (One of the latter is supported by the T1D Fund.) LTIs are also being pursued aggressively by the pharmaceutical industry.

The MC program's URI portfolio, like its LTI profile, is modest but impactful. Current and recent work has focused on preclinical development of URI, which includes strategies to directly modify insulin to give it "fast-on, fast-off" properties, as well as strategies to formulate standard insulin in excipients that enhance its speed of action. URI is a major focus of the private sector as well. The most rapid insulin currently available is Afrezza (Mannkind Corporation), which avoids the rate-limiting step of insulin release from the subcutaneous space by utilizing an alternative route of administration (inhalation through the lungs). At the same time, the Artificial Pancreas portfolio includes studies of its application to complement closed-loop therapy.

Adjunctive Therapies

Currently, the only FDA-approved non-insulin drug to treat T1D in the US is pramlintide, and there are no approved insulin-pramlintide co-formulations. The MC program has supported and currently supports work that elucidates the benefits of insulin and pramlintide co-administration in fixed dose ratios, building a body of clinical evidence to justify co-formulation. Additionally, the MC program is currently exploring opportunities to accelerate the development of a co-formulation.

GLP-1 receptor agonists offer similar clinical benefits to pramlintide and are currently approved for T2D. The MC program is investigating their clinical benefits in populations with T1D. It is noteworthy that these agents have gone from once daily to once weekly formulations, and oral formulations are in development.

SGLT inhibitors have the potential to become an integral part of T1D care. The dual SGLT1/2 inhibitor sotagliflozin has received a complete response letter from the FDA, but there is reason for optimism that it will soon be FDA-approved; meanwhile, it has just been approved in Europe by the EMA. JDRF previously supported a phase II clinical trial for sotagliflozin that showed significant benefits to young T1D adults with suboptimal glucose control. The SGLT2 inhibitor dapagliflozin has been approved by the EMA, and is pending at the FDA. The SGLT2 inhibitor ipragliflozin has been approved in Japan. Currently, the MC program is supporting studies in which SGLT inhibitors are being tested in combination with other insulin adjunctive therapies. Relatedly, SGLT inhibitors are being evaluated as drugs adjunctive to closed-loop therapy in the Artificial Pancreas program.

Since T1D and T2D share key clinical features and underlying pathophysiology, there is potential to repurpose T2D drugs for use in people with T1D. Currently, the MC program supports T1D clinical trials for the dopamine agonist bromocriptine (generic, FDA-approved for T2D) and a glucokinase activator (vTv Therapeutics, in clinical development for T2D). The MC program also has interest in insulin sensitizers and other T2D agents in T1D.

In addition to drugs that have shown efficacy in T2D, the MC program is exploring the development of novel targets specifically focused on T1D from the outset that can be exploited to create therapeutics to improve metabolic imbalances (including but not limited to dysglycemia) in T1D. Toward this goal, the MC program will be initiating an effort to drive studies to identify or validate novel targets for T1D metabolic control.

Accelerators

Drugs and other therapies must be tested in large preclinical models before they can be evaluated in clinical trials, but such studies are technically challenging and resource-intensive. Moreover, interpretation of data generated from such studies is complicated by a lack of protocol standardization and inter-user variability. To address these challenges, JDRF is establishing a core facility where studies on preclinical models can be performed in standardized assays, accelerating the path for novel therapies to clinical trials.

The MC program is currently exploring strategic priorities in obesity-related T1D pathophysiology, a topic focused on stratification of patients with obesity in order to define clinically meaningful and relevant subgroups as a premise for driving future prevention and treatment of obesity and its complications as it relates to T1D.

The MC program is currently funding work to identify heterogeneity in people with T1D by establishing existing biomarkers and searching for new ones. This approach will ultimately help drug designers deliver new therapies tailored to specific groups of people with T1D, which is critical since T1D is a heterogeneous disease in both its genetics and clinical progression. The MC program is also exploring opportunities for basic clinical research on T1D pathophysiology, since an improved understanding of the underlying metabolic defects in T1D will lead to novel drug targets and therapeutic approaches.

Gaps

Progress toward Next-Gen and Aspirational Therapies

To accelerate progress towards next-generation therapies, we are focusing efforts on addressing solutions to these critical gaps:

1. Development of Next-Generation Insulins

Next-generation insulins represent a frontier, and thus there are significant gaps that the MC program is focused on addressing.

- Glucose responsive insulins (GRI)
 - There is no precedent for GRI technology, i.e., there is no known drug that works automatically in response to endogenous stimulus. Because there is no clear precedent for this type of drug, JDRF supports a diverse portfolio of early stage scientific projects to determine which approaches have the most promise.
 - Safety in preventing hypoglycemia has not yet been adequately demonstrated. Since prevention of hypoglycemia is the main value proposition of GRI, this is a critical gap to address in GRI development, and testing for hypoglycemia prevention is a major focus of the preclinical work we support.
- Liver-targeted insulins (LTI)
 - (Oral) bioavailability and dosing flexibility must be demonstrated. Since there is no guarantee that (all) LTIs will be administered orally, it is important to understand what additional routes of administration are feasible.
 - Treatment regimen must be established – basal vs. bolus vs. total, and need for peripheral (non-liver) insulin. Insulin regimens for people with T1D consist of both basal and bolus insulins, and it remains to be determined how LTIs should be integrated into that framework. LTIs must be dosed with traditional insulins in a fashion that both optimizes their benefit to the liver yet also ensures that peripheral tissues are adequately insulinized. The ideal liver-periphery distribution of insulin can also be achieved by developing LTIs whose liver-bias is more moderate.
- Ultra-rapid insulins (URI)
 - Pharmacologic properties must be demonstrated, such as rapid-on, rapid-off, with reduced duration of action. The rapid-on characteristic, central to the concept of URI, is essential to reduce postprandial hyperglycemia; the rapid-off characteristic is needed to prevent delayed postprandial hypoglycemia. It is a formidable challenge to engineer rapid-on and rapid-off PK characteristics into insulin, but a next-generation insulin with these physiological-like properties will yield improved glycemic outcomes.

2. Development of Adjunctive Therapies

The field of adjunctive (i.e., non-insulin) therapies labeled for T1D is nascent, but market options are expected to emerge soon. The MC program is focused specifically on addressing the following gaps to accelerate development and approval of these new drug therapies.

- Benefit vs. burden profile of each therapy must be assessed clinically. Like all drugs, adjunctive therapies for T1D have both benefits and potential risks that must be evaluated in order for people with diabetes and their doctors to make treatment decisions. Clinical studies are essential to determine the risk-benefit profile for each therapy.
- Responder stratification must be established for each mechanistic class. Few drugs work for everyone. In order to effectively harness the benefits of emerging adjunctive therapies, it is advantageous to identify which people with T1D are likely to respond to each class of drugs (SGLT inhibitors, GLP-1 receptor agonists, etc.). This information can be used to design efficient clinical trials with increased likelihood of success.
- Early discovery research on T1D adjunctive therapies. Most adjunctive therapies being tested in clinical trials for T1D are repurposed from T2D. While there is some commonality in the metabolic imbalances of T1D and T2D, unique aspects of T1D pathophysiology and disease management demand therapies developed specifically with T1D in mind. Preclinical and clinical research on novel targets for T1D metabolic control is essential to achieve this goal.

3. Accelerators

The MC program is actively funding the development of drugs (and JDRF as a whole is also driving development of devices and cell-based therapies) that will allow people with T1D to achieve superior glycemic control and metabolic health. Critical evaluation of these drugs (and devices and cell-based therapies) requires large preclinical models (e.g. swine and canine), but interpretation of data generated from such studies is complicated by a lack of standardization in experimental protocols and inter-user variability. Additionally, many investigators lack the resources to perform these studies. The MC program is dedicated to addressing this gap by establishing a core facility for testing T1D therapeutics in large preclinical models, ensuring that evaluation of promising therapeutics will be done in a standardized fashion in a facility with the appropriate expertise.

Toward the Aspirational Therapies

There are additional gaps to address before the aspirational therapies are available:

4. Integration of Adjunctive Therapies with Insulins (and/or Next-Generation Insulins)

Insulin regimens must be thoughtfully adjusted when incorporating adjunctive therapies into T1D treatment to ensure safety and the highest level of effectiveness.

5. Understanding T1D Pathophysiology

The aspirational therapies address all meaningful metabolic imbalances – imbalances which are not fully understood yet. A higher degree of basic scientific understanding of T1D pathophysiology, and which imbalances would be most impactful to focus on, is crucial to driving toward the discovery and translation of drugs with the greatest promise.

Regulatory Pathway

Regulatory

Regulatory authorities, namely the Food and Drug Administration (FDA) in the U.S., make decisions about which medical products can be made available to the public. FDA bases its decisions on an assessment of whether the benefits of the product outweigh the risks, as demonstrated in clinical trials. For a novel drug, FDA requires a development program that culminates in at least two adequate and well-controlled phase 3 clinical trials with the expectation of hundreds to thousands of people enrolled in those trials. To expand the indications of an already approved drug to a new patient population or disease, such as is being researched for some adjunct therapies, in general, FDA will also require two adequate and well-controlled phase 3 clinical trials. Some earlier stage clinical and preclinical work from the previous approval can sometimes be relied upon for approval of the new indication, but it will depend on the specific situation. Specifics about the development program including the duration of study, number of subjects enrolled, and efficacy/safety endpoints depend on the exact product, the patient population and the indication for use being sought. FDA and EMA (EU regulatory authority) have each developed a guidance document to provide their current thinking on the development of diabetes therapies including new insulins and adjunct therapies. As specific products are being researched and pursued, JDRF explores the possible development pathway with the developer to identify challenges for that specific product as needed.

And, as mentioned in the Gaps section above, following the consensus reached by the T1D Outcomes Program and other complementary efforts on defining outcomes beyond HbA1c including hypoglycemia, hyperglycemia, time in range, and diabetic ketoacidosis, there is an ongoing effort to ensure that regulators adopt and utilize these outcomes in their decision-making for T1D therapies. Non-severe hypoglycemia and time in range have been prioritized.

Therapeutic Concepts

The below therapeutic concepts are based on limited preliminary clinical data, ongoing pre-clinical research, and input from key opinion leaders on the future-generation systems.

Gen 1 – Improved Glucose Control

| Parameter | Target |
|--------------------|---|
| Primary Indication | Improvement in glycemic control based on faster insulins and therapies adjunctive to insulin |
| Target Population | <ul style="list-style-type: none"> - People with type 1 diabetes, all ages - Possibly people with other forms of insulin-requiring diabetes |
| Features | <p>Novel insulin: Ultra-rapid insulin with faster PK/PD profile than currently available</p> <p>Adjunctive therapy: Oral or injectable treatment adjunctive to insulin regimen; will require education/training around new drug regimen</p> |
| Efficacy | <p>Reduction in HbA1c: 0.5%*</p> <p>Increase in time in range (70-180 mg/dL): 5-10%*</p> <p>No additional risk of hypoglycemia*</p> <p>Improvements in glycemic variability, postprandial glucose, body weight, blood pressure, insulin dose</p> |
| Risk/Side Effect | Class-specific risks requiring mitigation strategies (e.g., increased incidence of DKA for SGLT _i , nausea for amylin analogs) |

*Relative to today's insulin monotherapy

Gen 2 – Near-Normal Glucose Levels

| Parameter | Target |
|--------------------|---|
| Primary Indication | Near-normalization of glucose levels based on novel insulins and adjunctive therapies |
| Target Population | <ul style="list-style-type: none"> - People with type 1 diabetes, all ages - Possibly people with other forms of insulin-requiring diabetes |
| Features | <p>Novel insulin: Oral or injectable treatment with reduced burden related to dosing frequency and/or self-monitoring</p> <p>Adjunctive therapy: Oral or injectable treatment</p> |
| Efficacy | <p>Reduction in HbA1c: 1.0%*</p> <p>Increase in time in range (70-180 mg/dL): 15-20%*</p> <p>Target time < 70 mg/dL: <4%</p> <p>Target time < 54 mg/dL: <1%</p> <p>Improvements in glycemic variability, postprandial glucose, body weight, blood pressure, insulin dose; reduction in burden associated with self-management</p> |
| Risk/Side Effect | No additional significant side effects* |

*Relative to today's insulin monotherapy

Aspirational – Metabolic Homeostasis

| Parameter | Target |
|--------------------|---|
| Primary Indication | Restoration of euglycemia and other metabolic endpoints |
| Target Population | <ul style="list-style-type: none">- People with type 1 diabetes, all ages- Possibly people with other forms of insulin-requiring diabetes |
| Features | Infrequent dosing (maximum 1 dose/day); possibly oral administration; infrequent self-monitoring (1x/day) |
| Efficacy | <p>Target HbA1c: <7.0% Target time in range (70-180 mg/dL): 90% Target time < 70 mg/dL: <1% Target time < 54 mg/dL: ~0%</p> <p>Minimized glycemic variability, postprandial glucose; normalized body weight, blood pressure; minimal burden associated with self-management</p> |
| Risk/Side Effect | No foreseeable significant side effects |

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