

JDRF REQUESTS LETTERS OF INTENT FOR: USE OF HUMAN SAMPLES FROM THE T1D EXCHANGE BIOBANK

BACKGROUND AND PURPOSE

The T1D (Type 1 Diabetes) Exchange Biobank, or “Biobank”, is a collection of thousands of stored samples from participants in various T1D Exchange (T1DX) clinical studies. The Biobank was created to aid investigators doing T1D research by distributing biosamples collected from people with T1D to the research community. In 2020, the Biobank was transferred from the T1D Exchange to the University of Florida (UF) Diabetes Institute through funding from JDRF with the original mission of the Biobank—to aid T1D research— unchanged. The purpose of this RFA is to solicit letters of intent (LOIs) from the T1D research community to obtain Biobank samples for use in research.

THE BIOBANK

The Biobank is a collection of samples and clinical, demographic and study-derived data on individuals with T1D. The Biobank has stored samples from ~2,200 unique participants with T1D who participated in T1D Exchange clinical studies. Types of samples collected from each study include: plasma, serum, peripheral blood mononuclear cells (PBMCs), DNA, and Tempus tubes for downstream RNA extraction. With the exception of DNA, serial samples were collected for each sample type. Per study protocol, the dataset also includes sample-derived lab values (e.g. diabetes related autoantibodies, HbA1c, glucose, insulin, C-peptide, proinsulin, and lipids). For ~2,000 participants, there are associated data from the T1D Exchange Clinic Registry, which includes data extracted from medical records (80 chart elements) and questionnaire data. Details about available biosamples and associated data are contained in an appendix to this RFA.

OBJECTIVES

LOIs are sought from academic or industry applicants with innovative projects that may require large and varied sample sets to use Biobank samples to answer important open questions in T1D research.

Examples of research topics appropriate for this RFA include:

- Identification or validation of biomarkers and assays
- Analysis of pathways affected by T1D therapies
- Understanding T1D progression and heterogeneity
- Understanding treatment response and heterogeneity
- Other hypothesis-driven or hypothesis-generating approaches to understand T1D and its complications

CRITICAL CONSIDERATIONS

- Successful applicants will receive biosamples and associated data. No funds will be provided by JDRF.
- All costs to ship biosamples will be paid by the applicant.
- Applications from collaborative groups to conduct multi-parameter, integrated studies will be prioritized.
- JDRF will prioritize LOIs where the applicant has funding for the proposed work or a feasible plan to obtain funding.
- Successful applicants should acknowledge JDRF, UF, and T1DX in publications resulting from research with these samples.

ELIGIBILITY

LOIs may be submitted by domestic and foreign non-profit organizations, public and private institutions, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. Applicants must hold a faculty position or equivalent at a college, university, medical school,

industry setting or other research facility. Please note that LOIs from for-profit entities or industry collaborations with academia may be submitted to this RFA; however, additional information may be requested.

There are no citizenship requirements for this program. To assure continued excellence and diversity among applicants and awardees, JDRF welcomes LOIs from all qualified individuals and encourages LOIs from persons with disabilities, women, and members of minority groups underrepresented in the sciences.

LOI

Prospective applicants should submit a brief LOI (1 page maximum excluding references) online via RMS360 (<http://jdrf.smartsimple.us>). The LOI template provided on the RMS360 website must be used to complete the LOI. Applicants will be notified if they have been approved to obtain biosamples according to the timeline below. Note there will be no additional proposal requested after the LOI. The dollar amount requested should be \$0.01.

Please see below for complete instructions. LOIs must use the template provided and include the following information:

- Biosamples requested
- Specific research question(s) being investigated
- Background
- Research plan
- Statement of whether the applicant has funding to complete the study, and if not, the plan to obtain funding
- Intellectual property or commercial efforts associated with the LOI
- References cited

DEADLINES

- | | |
|--|---------------------------|
| • RFA release date | September 15, 2020 |
| • LOI deadline | October 30, 2020 |
| • Response to applicants | December 2020 |
| • Earliest anticipated receipt of samples | February 2021 |

SUBMISSION INSTRUCTIONS

Applicants should register and submit their completed LOI in RMS360 (<http://jdrf.smartsimple.us>).

REVIEW CRITERIA

LOIs will be evaluated by JDRF, The University of Florida, and the T1D Exchange based on JDRF's standard confidential award policy and according to the following criteria:

- Significance
- Approach
- Innovation
- Investigator experience
- Environment

CONTACTS

Please contact JDRF for questions related to RFA process, including grant-specific questions about RMS360:

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Please contact UF for questions related to biosamples:

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For any **non-grant-specific** inquiries or issues, please contact SmartSimple Support Services via email support@smartsimple.com or phone (866) 239-0991. Support hours are Monday through Friday between 5:00am and 9:00pm US Eastern Standard Time.

APPENDIX: DESCRIPTIONS OF AVAILABLE BIOSAMPLES

Prevalence of detectable C-Peptide according to age at diagnosis and duration of type 1 diabetes

Diabetes Care. 2015;38(3):476-481. doi:10.2337/dc14-1952

Davis AK, DuBose SN, Haller MJ, et al.

<https://www.ncbi.nlm.nih.gov/pubmed/25519448>

Abstract

OBJECTIVE:

It is generally accepted that complete β -cell destruction eventually occurs in individuals with type 1 diabetes, which has implications for treatment approaches and insurance coverage. The frequency of residual insulin secretion in a large cohort of individuals at varying ages of diagnosis and type 1 diabetes duration is unknown.

RESEARCH DESIGN AND METHODS:

The frequency of residual insulin secretion was determined by measurement of nonfasting serum C-peptide concentration in 919 individuals with type 1 diabetes according to prespecified groups based on age at diagnosis and duration of disease (from 3 to 81 years' duration). Stimulated C-peptide was measured in those with detectable nonfasting values and a group of those with undetectable values as control.

RESULTS:

The overall frequency of detectable nonfasting C-peptide was 29%, decreasing with time from diagnosis regardless of age at diagnosis. In all duration groups, the frequency of C-peptide was higher with diagnosis age >18 years compared with \leq 18 years. Nineteen percent of those with undetectable nonfasting C-peptide were C-peptide positive upon stimulation testing.

CONCLUSIONS:

The American Diabetes Association's definition of type 1 diabetes as "usually leading to absolute insulin deficiency" results in clinicians often considering the presence of residual insulin secretion as unexpected in this population. However, our data suggest that residual secretion is present in almost one out of three individuals 3 or more years from type 1 diabetes diagnosis. The frequency of residual C-peptide decreases with time from diagnosis regardless of age at diagnosis, yet at all durations of disease, diagnosis during adulthood is associated with greater frequency and higher values of C-peptide.

Biological samples collected

- Serum
- Plasma
- PBMCs
- DNA
- RNA

Analytic tests performed on biological samples:

- C-peptide
- Autoantibodies (GAD, IA2, Znt8)
- Glucose
- HbA1c
- Serum creatinine
- MMTT

Risk Factors Associated With Severe Hypoglycemia in Older Adults With Type 1 Diabetes

Diabetes Care. 2016;39(4):603-610. doi:10.2337/dc15-1426

Weinstock RS, DuBose SN, Bergenstal RM, et al.

<https://www.ncbi.nlm.nih.gov/pubmed/26681721>

Abstract

OBJECTIVE:

Severe hypoglycemia is common in older adults with long-standing type 1 diabetes, but little is known about factors associated with its occurrence.

RESEARCH DESIGN AND METHODS:

A case-control study was conducted at 18 diabetes centers in the T1D Exchange Clinic Network. Participants were 60 years old with type 1 diabetes for 20 years. Case subjects (n = 101) had at least one severe hypoglycemic event in the prior 12 months. Control subjects (n = 100), frequency-matched to case subjects by age, had no severe hypoglycemia in the prior 3 years. Data were analyzed for cognitive and functional abilities, social support, depression, hypoglycemia unawareness, various aspects of diabetes management, C-peptide level, glycated hemoglobin level, and blinded continuous glucose monitoring (CGM) metrics.

RESULTS:

Glycated hemoglobin (mean 7.8% vs. 7.7%) and CGM-measured mean glucose (175 vs. 175 mg/dL) were similar between case and control subjects. More case than control subjects had hypoglycemia unawareness: only 11% of case subjects compared with 43% of control subjects reported always having symptoms associated with low blood glucose levels (P < 0.001). Case subjects had greater glucose variability than control subjects (P = 0.008) and experienced CGM glucose levels <60 mg/dL for ≥20 min on 46% of days compared with 33% of days in control subjects (P = 0.10). On certain cognitive tests, case subjects scored worse than control subjects.

CONCLUSIONS:

In older adults with long-standing type 1 diabetes, greater hypoglycemia unawareness and glucose variability are associated with an increased risk of severe hypoglycemia. A study to assess interventions to prevent severe hypoglycemia in high-risk individuals is needed.

Biological samples collected

- Serum
- Plasma
- PBMCs
- DNA
- RNA

Analytic tests performed on biological samples:

- C-peptide
- Glomerular Filtration Rate
- Glucose
- HbA1c
- Serum creatinine

Additional data:

- CGM data

Effect of Metformin Added to Insulin on Glycemic Control Among Overweight/Obese Adolescents With Type 1 Diabetes: A Randomized Clinical Trial

JAMA. 2015;314(21):2241-2250. doi:10.1001/jama.2015.16174

Libman IM, Miller KM, DiMeglio LA, et al.

<https://www.ncbi.nlm.nih.gov/pubmed/26624824>

Abstract

OBJECTIVE:

To assess the efficacy and safety of metformin as an adjunct to insulin in treating overweight adolescents with type 1 diabetes.

DESIGN, SETTING, AND PARTICIPANTS:

Multicenter (26 pediatric endocrinology clinics), double-blind, placebo-controlled randomized clinical trial involving 140 adolescents aged 12.1 to 19.6 years (mean [SD] 15.3 [1.7] years) with mean type 1 diabetes duration 7.0 (3.3) years, mean body mass index (BMI) 94th (4) percentile, mean total daily insulin 1.1 (0.2) U/kg, and mean HbA1c 8.8% (0.7%).

RESULTS:

Between October 2013 and February 2014, 140 participants were enrolled. Baseline HbA1c was 8.8% in each group. At 13-week follow-up, reduction in HbA1c was greater with metformin (-0.2%) than placebo (0.1%; mean difference, -0.3% [95% CI, -0.6% to 0.0%]; P = .02). However, this differential effect was not sustained at 26-week follow up when mean change in HbA1c from baseline was 0.2% in each group (mean difference, 0% [95% CI, -0.3% to 0.3%]; P = .92). At 26-week follow-up, total daily insulin per kg of body weight was reduced by at least 25% from baseline among 23% (16) of participants in the metformin group vs 1% (1) of participants in the placebo group (mean difference, 21% [95% CI, 11% to 32%]; P = .003), and 24% (17) of participants in the metformin

group and 7% (5) of participants in the placebo group had a reduction in BMI z score of 10% or greater from baseline to 26 weeks (mean difference, 17% [95% CI, 5% to 29%]; P = .01). Gastrointestinal adverse events were reported by more participants in the metformin group than in the placebo group (mean difference, 36% [95% CI, 19% to 51%]; P < .001).

CONCLUSIONS AND RELEVANCE:

Among overweight adolescents with type 1 diabetes, the addition of metformin to insulin did not improve glycemic control after 6 months. Of multiple secondary end points, findings favored metformin only for insulin dose and measures of adiposity; conversely, use of metformin resulted in an increased risk for gastrointestinal adverse events. These results do not support prescribing metformin to overweight adolescents with type 1 diabetes to improve glycemic control.

Biological samples collected

- Serum
- DNA
- RNA
- PBMC
- Heparin Plasma
- Urine (Clamp Participants only)

Analytic tests performed on biological samples:

- C-peptide
- Proinsulin
- Liver enzymes (ALT & AST)
- Creatinine
- Autoantibodies (GAD, IA2, ZnT8)
- HbA1c
- Adipocytokine panel
- MMTT

Additional data:

- CGM data

Insulin Clamp Ancillary Study for Assessment of Insulin Resistance

An ancillary study involving a 2-stage hyperinsulinemic euglycemic clamp procedure was conducted to assess if metformin would improve tissue-specific insulin resistance. 44 participants with normal hemoglobin and hematocrit levels were randomly selected from the Metformin study described above to participate in this study addition. Clamps were performed at baseline and after 13-weeks of treatment with metformin versus placebo. Ancillary clamp participants ended follow-up at 13-weeks when the primary outcome for the ancillary study was completed and were not included in the primary analysis for the main study.

The 2-stage hyperinsulinemic euglycemic clamp is performed to determine adipose, hepatic and muscle insulin resistance (16 and 80mU/m²/min insulin, 90 min first stage, 120 min second stage).

Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A1c Levels

Ann Intern Med. 2017;167(2):95-102. doi:10.7326/M16-2596

Bergental RM, Gal RL, Connor CG, et al.

<https://www.ncbi.nlm.nih.gov/pubmed/28605777>

Abstract

BACKGROUND:

Debate exists as to whether the higher hemoglobin A1c (HbA1c) levels observed in black persons than in white persons are due to worse glycemic control or racial differences in the glycation of hemoglobin.

OBJECTIVE:

To determine whether a racial difference exists in the relationship of mean glucose and HbA1c.

DESIGN:

Prospective, 12-week observational study.

SETTING:

10 diabetes centers in the United States.

PARTICIPANTS:

104 black persons and 104 white persons aged 8 years or older who had had type 1 diabetes for at least 2 years and had an HbA1c level of 6.0% to 12.0%.

MEASUREMENTS:

Mean glucose concentration, measured by using continuous glucose monitoring and compared by race with HbA1c, glycated albumin, and fructosamine values.

RESULTS:

The mean HbA1c level was 9.1% in black persons and 8.3% in white persons. For a given HbA1c level, the mean glucose concentration was significantly lower in black persons than in white persons ($P = 0.013$), which was reflected in mean HbA1c values in black persons being 0.4 percentage points (95% CI, 0.2 to 0.6 percentage points) higher than those in white persons for a given mean glucose concentration. In contrast, no significant racial differences were found in the relationship of glycated albumin and fructosamine levels with the mean glucose concentration ($P > 0.20$ for both comparisons).

CONCLUSION:

On average, HbA1c levels overestimate the mean glucose concentration in black persons compared with white persons, possibly owing to racial differences in the glycation of hemoglobin. However, because race only partially explains the observed HbA1c differences between black persons and white persons, future research should focus on identifying and modifying barriers impeding improved glycemic control in black persons with diabetes.

Biological samples collected

- Serum
- DNA
- RNA
- PBMC
- Heparin Plasma

Analytic tests performed on biological samples:

- Serum creatinine
- Glycated albumin
- Fructosamine
- HbA1c

Additional data:

- Accelerometer
- CGM data
- Insulin pump data

REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Well-Controlled Type 1 Diabetes

Diabetes Care. 2017;40(4):538-545. doi:10.2337/dc16-2482

Aleppo G, Ruedy KJ, Riddlesworth TD, et al.

<https://www.ncbi.nlm.nih.gov/pubmed/28209654>

Abstract

OBJECTIVE:

To determine whether the use of continuous glucose monitoring (CGM) without confirmatory blood glucose monitoring (BGM) measurements is as safe and effective as using CGM adjunctive to BGM in adults with well-controlled type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS:

A randomized noninferiority clinical trial was conducted at 14 sites in the T1D Exchange Clinic Network. Participants were ≥ 18 years of age (mean 44 ± 14 years), had T1D for ≥ 1 year (mean duration 24 ± 12 years), used an insulin pump, and had an HbA1c $\leq 9.0\%$ (≤ 75 mmol/mol) (mean $7.0 \pm 0.7\%$ [53 ± 7.7 mmol/mol]); prestudy, 47% were CGM users. Participants were randomly assigned 2:1 to the CGM-only ($n = 149$) or CGM+BGM ($n =$

77) group. The primary outcome was time in range (70-180 mg/dL) over the 26-week trial, with a prespecified noninferiority limit of 7.5%.

RESULTS:

CGM use averaged 6.7 ± 0.5 and 6.8 ± 0.4 days/week in the CGM-only and CGM+BGM groups, respectively, over the 26-week trial. BGM tests per day (including the two required daily for CGM calibration) averaged 2.8 ± 0.9 and 5.4 ± 1.4 in the two groups, respectively ($P < 0.001$). Mean time in 70-180 mg/dL was $63 \pm 13\%$ at both baseline and 26 weeks in the CGM-only group and $65 \pm 13\%$ and $65 \pm 11\%$ in the CGM+BGM group (adjusted difference 0%; one-sided 95% CI -2%). No severe hypoglycemic events occurred in the CGM-only group, and one occurred in the CGM+BGM group.

CONCLUSIONS:

Use of CGM without regular use of confirmatory BGM is as safe and effective as using CGM with BGM in adults with well-controlled T1D at low risk for severe hypoglycemia.

Biological samples collected

- Serum
- DNA
- RNA
- PBMC
- Heparin Plasma

Analytic tests performed on biological samples:

- HbA1c

Additional data:

- CGM data

Intranasal Glucagon for Treatment of Insulin-Induced Hypoglycemia in Adults With Type 1 Diabetes: A Randomized Crossover Noninferiority Study

Diabetes Care. 2016;39(2):264-270. doi:10.2337/dc15-1498

Rickels MR, Ruedy KJ, Foster NC, et al.

<https://pubmed.ncbi.nlm.nih.gov/26681725/>

Abstract

OBJECTIVE:

Treatment of severe hypoglycemia with loss of consciousness or seizure outside of the hospital setting is presently limited to intramuscular glucagon requiring reconstitution immediately prior to injection, a process prone to error or omission. A needle-free intranasal glucagon preparation was compared with intramuscular glucagon for treatment of insulin-induced hypoglycemia.

RESEARCH DESIGN AND METHODS:

At eight clinical centers, a randomized crossover noninferiority trial was conducted involving 75 adults with type 1 diabetes (mean age, 33 ± 12 years; median diabetes duration, 18 years) to compare intranasal (3 mg) versus intramuscular (1 mg) glucagon for treatment of hypoglycemia induced by intravenous insulin. Success was defined as an increase in plasma glucose to ≥ 70 mg/dL or ≥ 20 mg/dL from the glucose nadir within 30 min after receiving glucagon.

RESULTS:

Mean plasma glucose at time of glucagon administration was 48 ± 8 and 49 ± 8 mg/dL at the intranasal and intramuscular visits, respectively. Success criteria were met at all but one intranasal visit and at all intramuscular visits (98.7% vs. 100%; difference 1.3%, upper end of 1-sided 97.5% CI 4.0%). Mean time to success was 16 min for intranasal and 13 min for intramuscular ($P < 0.001$). Head/facial discomfort was reported during 25% of intranasal and 9% of intramuscular dosing visits; nausea (with or without vomiting) occurred with 35% and 38% of visits, respectively.

CONCLUSIONS:

Intranasal glucagon was highly effective in treating insulin-induced hypoglycemia in adults with type 1 diabetes. Although the trial was conducted in a controlled setting, the results are applicable to real-world management of severe hypoglycemia, which occurs owing to excessive therapeutic insulin relative to the impaired or absent endogenous glucagon response.

Biological samples collected

- Serum
- DNA
- RNA

Analytic tests performed on biological samples:

- HbA1c
- Glucose
- C-peptide
- Autoantibodies (GAD, IA2, ZnT8)
- Glucose & Glucagon

Glucagon Nasal Powder: A Promising Alternative to Intramuscular Glucagon in Youth With Type 1 Diabetes

Diabetes Care. 2016;39(4):555-562. doi:10.2337/dc15-1606

Sherr JL, Ruedy KJ, Foster NC, et al.

<https://pubmed.ncbi.nlm.nih.gov/26884472/>

Abstract

OBJECTIVE:

Treatment of severe hypoglycemia outside of the hospital setting is limited to intramuscular glucagon requiring reconstitution prior to injection. The current study examined the safety and dose-response relationships of a needle-free intranasal glucagon preparation in youth aged 4 to <17 years.

RESEARCH DESIGN AND METHODS:

A total of 48 youth with type 1 diabetes completed the study at seven clinical centers. Participants in the two youngest cohorts (4 to <8 and 8 to <12 years old) were randomly assigned to receive either 2 or 3 mg intranasal glucagon in two separate sessions or to receive a single, weight-based dose of intramuscular glucagon. Participants aged 12 to <17 years received 1 mg intramuscular glucagon in one session and 3 mg intranasal glucagon in the other session. Glucagon was given after glucose was lowered to <80 mg/dL (mean nadir ranged between 67 and 75 mg/dL).

RESULTS:

All 24 intramuscular and 58 of the 59 intranasal doses produced a ≥ 25 mg/dL rise in glucose from nadir within 20 min of dosing. Times to peak plasma glucose and glucagon levels were similar under both intramuscular and intranasal conditions. Transient nausea occurred in 67% of intramuscular sessions versus 42% of intranasal sessions ($P = 0.05$); the efficacy and safety of the 2- and 3-mg intranasal doses were similar in the youngest cohorts.

CONCLUSIONS:

Results of this phase 1, pharmacokinetic, and pharmacodynamic study support the potential efficacy of a needle-free glucagon nasal powder delivery system for treatment of hypoglycemia in youth with type 1 diabetes. Given the similar frequency and transient nature of adverse effects of the 2- and 3-mg intranasal doses in the two youngest cohorts, a single 3-mg intranasal dose appears to be appropriate for use across the entire 4- to <17-year age range.

Biological samples collected

- DNA
- RNA

Analytic tests performed on biological samples:

- Urine Pregnancy
- HbA1c
- Glucose
- C-peptide
- Autoantibodies (GAD, IA2, ZnT8)
- Glucose & Glucagon

High residual C-peptide likely contributes to glycemic control in type 1 diabetes

J Clin Invest. 2020;130(4):1850-1862. doi:10.1172/JCI134057

Abstract

BACKGROUND:

Residual C-peptide is detected in many people for years following the diagnosis of type 1 diabetes; however, the physiologic significance of low levels of detectable C-peptide is not known.

METHODS:

We studied 63 adults with type 1 diabetes classified by peak mixed-meal tolerance test (MMTT) C-peptide as negative (<0.007 pmol/mL; n = 15), low (0.017-0.200; n = 16), intermediate (>0.200-0.400; n = 15), or high (>0.400; n = 17). We compared the groups' glycemia from continuous glucose monitoring (CGM), β cell secretory responses from a glucose-potentiated arginine (GPA) test, insulin sensitivity from a hyperinsulinemic-euglycemic (EU) clamp, and glucose counterregulatory responses from a subsequent hypoglycemic (HYPO) clamp.

RESULTS:

Low and intermediate MMTT C-peptide groups did not exhibit β cell secretory responses to hyperglycemia, whereas the high C-peptide group showed increases in both C-peptide and proinsulin ($P \leq 0.01$). All groups with detectable MMTT C-peptide demonstrated acute C-peptide and proinsulin responses to arginine that were positively correlated with peak MMTT C-peptide ($P < 0.0001$ for both analytes). During the EU-HYPO clamp, C-peptide levels were proportionately suppressed in the low, intermediate, and high C-peptide compared with the negative group ($P \leq 0.0001$), whereas glucagon increased from EU to HYPO only in the high C-peptide group compared with negative ($P = 0.01$). CGM demonstrated lower mean glucose and more time in range for the high C-peptide group.

CONCLUSION:

These results indicate that in adults with type 1 diabetes, β cell responsiveness to hyperglycemia and α cell responsiveness to hypoglycemia are observed only at high levels of residual C-peptide that likely contribute to glycemic control.

Biological samples collected

- Serum
- Plasma
- PBMCs
- DNA
- RNA

Analytic tests performed on biological samples:

- C-peptide
- Glucagon-like peptide-1 (GLP-1)
- Glucose
- Glucose-dependent insulinotropic polypeptide (GIP)
- Glucose-potentiated arginine (GPA) test
- HbA1c
- MMTT

Additional data:

- CGM