Organization Name	Contact PI / Project Leader	Project Title	OniX Summary
HARVARD UNIVERSITY	LIU, JIA	Charting human islet maturation via combined soft nanoelectronics and single-cell spatial transcriptomics	**Research Question:** Can we improve the development of human stem cell-derived islet organoids (SC-islets) for type 1 diabetes treatment by understanding the 3D cellular interactions and activity within these organoids? **Stage:** In Vitro (laboratory setting) **Methods:** 1. **Designer SC-islets:** Creating SC-islets with specific alpha and beta cell composition. 2. **Cyborg Islets:** Implanting tiny sensors within SC-islets to track electrical activity of individual alpha and beta cells. 3. **3D Tissue Mapping:** Using a combination of techniques to map hormones, biomarkers, gene expression, and cell types within intact SC-islets at high resolution. 4. **Fluorescent Barcoding:** Labeling sensor positions within SC-islets to connect electrical recordings with other data at the single-cell level. **Drug Development:** This research is not directly developing a drug, but the findings could be used to improve the development of SC-islets as a future therapeutic approach for type 1 diabetes.
UNIVERSITY OF CALIFORNIA, SAN DIEGO	WORTHAM, MATTHEW	Metabolic requirements of pancreatic beta cell proliferation	**Research Question:** Does ATP-citrate lyase (Acly) play a critical role in regulating lipid metabolism and epigenetic changes needed for optimal β-cell proliferation in type 1 diabetes (T1D)? **Stage:** In Vitro (laboratory setting) using primary human islets **Methods:** 1. **Modulating Islet Lipid Metabolism:** Researchers will use genetic or metabolic interventions to manipulate lipid synthesis pathways in human islets.

			2. **Targeted Metabolomics and Genomics Assays:** They will measure how these interventions affect specific metabolites and gene activity related to β-cell proliferation. 3. **ChIP-seq Analysis:** This technique will be used to assess changes in histone modifications associated with β-cell proliferation after treatment with pro-mitotic drugs. **Drug Development:** This study is not directly developing a drug, but the findings could help identify new targets for drugs that stimulate β-cell proliferation for T1D treatment. They could also inform the development of nutritional interventions to support β-cell regeneration therapies.
RENOVA THERAPEUTICS, INC.	HAMMOND, H. KIRK	Urocortin-2 Gene Transfer for Type 1 Diabetes and Associated LV Dysfunction	**Research Question:** Can urocortin 2 (UCn2) gene therapy improve glycemic control and reduce cardiovascular risk in type 1 diabetes (T1DM) patients receiving insulin therapy? **Stage:** Not directly stated in the abstract, but likely in pre-clinical development using animal models (mice). **Methods:** • Researchers will test adeno-associated virus type 8 (AAV8) encoding UCn2 for its effectiveness in a model of T1DM. • They will assess glycemic control, heart function, and mortality in the mice. **Drug Development:** This research is directly developing a gene therapy approach using AAV8 encoding UCn2 as an adjunct therapy for T1DM patients receiving insulin.
LOUIS STOKES CLEVELAND VA MEDICAL CENTER	SAMUELS, IVY S	Glut1 and the microvascular complications of diabetes	**Research Question:** Does systemic reduction of Glut1 (a glucose transporter) prevent microvascular complications (diabetic retinopathy, kidney disease, and neuropathy) in type 1 and type 2 diabetes? Can it also improve the effectiveness of current standard treatments? **Stage:** In vivo with animals (mice) **Methods:** 1. **Glut1 Reduction:** Researchers will use mice with a reduced expression of Glut1 (Glut1+/-) to see if it prevents microvascular

			complications in models of type 1 (STZ-induced) and type 2 (Leprdb/db) diabetes. 2. **Combination Therapy:** They will assess if adding Glut1 reduction to standard diabetic treatment (metformin, ramipril, and empaglifozin) offers further protection. 3. **Mechanism of Action:** Using the type 1 diabetes model, they will investigate how intensive insulin therapy might regulate Glut1 expression (both through gene transcription and protein turnover). **Drug Development:** This research is investigating Glut1 reduction as a potential future therapeutic approach for treating diabetic microvascular complications. It is not directly developing a drug at this stage.
ONEVAX, LLC	MARSHALL, GREGORY PAUL	Therapeutic Administration of Suppressor of Cytokine Signaling Mimetics to Ameliorate Type 1 Diabetes	**Research Question:** Can small peptide SOCS-1 mimetics prevent the onset of type 1 diabetes (T1D) in an animal model? **Stage:** In vivo with animals (likely mice) **Methods:** • Researchers will test different doses of their small peptide SOCS-1 mimetics in an animal model of T1D. **Drug Development:** This research is directly developing a drug in the form of small peptide SOCS-1 mimetics as a potential therapy to prevent T1D. This is a phase I SBIR proposal aiming to establish feasibility for further development.
UNIVERSITY OF CALIFORNIA, SAN DIEGO	ZHU, HAN	Gene regulatory programs drivingmetabolic maturation of human pluripotent stem cell derived β-cells	**Research Question:** • Can researchers manipulate human pluripotent stem cell-derived beta cells (SC-β-cells) to mature in vitro and acquire glucose-dependent mitochondrial function, a hallmark of mature beta cells? • Are SC-β-cells a suitable model for studying human beta cell maturation? **Stage:** In Vitro (laboratory setting) **Methods:** • Researchers will use genetic and functional assays to identify key transcriptional programs regulating mitochondrial function in SC-β-cells.

			• They will manipulate these programs to induce maturation in SC-β-cells in vitro. • They will compare epigenetic changes (modifications to DNA that affect gene expression) that occur during in vitro maturation with those observed during in vivo maturation (when SC-β-cells are transplanted into mice). **Drug Development:** This research is not directly developing a drug. However, improved understanding of human beta cell maturation using SC-β-cells could inform future therapeutic approaches for type 1 diabetes.

VANDERBILT UNIVERSITY MEDICAL CENTER	BONAMI, RACHEL H	The Origins of Human Anti-Insulin B Lymphocytes in Type 1 Diabetes	**Research Question:**
			Can a specific type of B lymphocyte (anti-insulin B cells, AIBCs) be used as a biomarker to identify and understand the progression of type 1 diabetes (T1D)?
			Stage:
			In Vitro (laboratory setting) with samples from human donors
			Methods:
			• Researchers will analyze B lymphocytes from a biobank of pre-symptomatic T1D patients (TrialNet participants).
			• They will measure the presence and characteristics of AIBCs, including:
			  ○ Memory B cell phenotype
			  ○ B cell receptor (immunoglobulin) sequence and clonal expansion
			  ○ B cell receptor affinity/avidity for insulin
			  ○ Insulin epitope mapping
			  ○ V and J immunoglobulin gene usage
			• They will develop a method (LIBRAseq) to identify candidate autoreactive B cell receptors for further testing.
			• They will create a publicly available database of human monoclonal antibodies and anti-insulin B cell receptor sequences.
			Drug Development:
			This research is not directly developing a drug, but the findings could lead to the identification of AIBCs as a biomarker for T1D diagnosis, treatment response prediction, and monitoring disease progression.

BECKMAN RESEARCH INSTITUTE/CITY OF HOPE	THURMOND, DEBBIE C	Targeting an atypical signaling hub to restore and protect whole body glucose homeostasis	**Research Question:**
			• How does the protein PAK1 influence insulin secretion, beta cell health, and skeletal muscle function in type 2 diabetes (T2D)?
			• Can manipulating PAK1 signaling pathways prevent or reverse pre-diabetes and T2D development?
			Stage:
			In Vitro (laboratory setting) with human tissues/cells and In Vivo with animals (inducible tissue-specific mice)
			Methods:
			• Researchers will use genetic tools to manipulate PAK1 signaling in beta cells and skeletal muscle of mice.
			• They will assess the effects on:
			  ○ Insulin secretion
			  ○ Beta cell mass and health
			  ○ Skeletal muscle insulin sensitivity
			• They will investigate the specific PAK1 effector molecules involved in these processes.
			Drug Development:
			This research is not directly developing a drug, but it aims to understand the role of PAK1 signaling in T2D development. This knowledge could be used to develop future therapeutic approaches targeting PAK1 or its effectors to prevent or reverse pre-diabetes and T2D.

JOSLIN DIABETES CENTER	KULKARNI, ROHIT N.	Using ex vivo, in vivo models and patient mutations to interrogate pancreatic exocrine-endocrine cross talk	**Research Question:** How do secretions (extracellular vesicles, EVs) from acinar and duct cells in the pancreas impact the function of human islet and beta cells? Can these interactions contribute to type 1 diabetes pathogenesis? **Stage:** In Vitro (laboratory setting) with human cells derived from induced pluripotent stem cells (hiPSCs) and human pancreas slices. **Methods:** • Researchers will isolate and characterize EVs from hiPSC-derived acinar and duct cells. • They will incubate these EVs with human islet/beta cells and human pancreas slices to assess the effects on islet cell function. • They will specifically analyze the cargo within the EVs, focusing on transfer RNA fragments.

			• Additionally, they will use EVs derived from acinar organoids from patients with MODY8 (a genetic form of diabetes) to see how they influence human islet-beta cell biology. **Drug Development:** This research is not directly developing a drug. However, a better understanding of how acinar and duct cell secretions affect beta cells could inform future therapeutic approaches for type 1 diabetes by potentially targeting these communication pathways.
ASAKE BIOTECHNOLOGY, LLC	WU, SHIYONG	A dual-acting small molecule for the treatment of type 1 diabetes	**Research Question:** • How does the small molecule MSB-3 protect beta cells and stimulate insulin production in type 1 diabetes (T1D)? **Stage:** In Vitro (laboratory setting) with human and rodent pancreatic islets and In Vivo with animals (NOD mice) **Methods:** • Researchers will investigate the mechanism of action of MSB-3 by identifying the protein target(s) it interacts with in beta cells. • They will assess the effects of MSB-3 on insulin secretion and beta cell protection in response to inflammatory signals. • In vivo studies will test the ability of MSB-3 to prevent and reverse T1D in NOD mice. • They will also explore different administration methods for MSB-3, including a long-acting subcutaneous pellet, and determine its pharmacokinetics and pharmacodynamics (how the drug behaves in the body). • Finally, they will investigate the potential of MSB-3 as an additive to improve the efficacy of human islet transplantation procedures. **Drug Development:** This research directly targets drug development for type 1 diabetes. MSB-3 is a small molecule therapeutic candidate that has shown promise in protecting beta cells, stimulating insulin production, and preventing/reversing T1D in animal models. This study aims to understand how MSB-3 works and optimize its delivery method for potential clinical application.

TRANSCHROMIX, LLC.	CHEN, XIAN	Novel therapeutic intervention of early-stage T1D	**Research Question:**
			• Can inhibiting the enzymes G9a and Ezh2 prevent or reverse type 1 diabetes (T1D) by specifically suppressing translation of T1D-causing proteins in immune T cells?
			Stage:
			In Vivo with animals (NOD mice) and potentially In Vitro with human cells from T1D patients
			Methods:
			• Researchers will use inhibitors of G9a and Ezh2 to treat NOD mice at various stages of T1D development.
			• They will assess the effects of these inhibitors on:
			  ○ Specificity for targeting pathogenic T cells (Teff)
			  ○ Toxicity
			  ○ Prevention/treatment of T1D development
			  ○ Suppression of Teff cell infiltration into the pancreas
			  ○ Translation of proteins involved in Teff cell function
			• Additionally, they will investigate the effects of G9a/Ezh2 inhibitors on protein translation in immune cells isolated from T1D patients (potentially).
			Drug Development:
			This research directly targets drug development for type 1 diabetes. G9a and Ezh2 inhibitors are being explored as a new generation of T1D therapeutics based on their ability to specifically suppress translation of T1D-causing proteins in Teff cells. This study aims to validate the effectiveness and safety of these inhibitors in preventing/treating T1D in mice and potentially humans.

UNIVERSITY OF FLORIDA	SAMOJLIK, MAGDALENA M	Engineering a dynamic three-dimensional in vitro platform for the investigation of human Type 1 Diabetes immunopathogenesis	**Research Question:** • Can a new 3D in vitro human islet-immune platform be developed to study type 1 diabetes (T1D) pathophysiology and test potential interventions? **Stage:** In Vitro (laboratory setting) **Methods:** • Researchers will engineer a 3D biomaterial platform for culturing human islet cells and immune cells together.

			• They will validate this platform using a tiered approach, starting with single antigen mouse model cells and progressing to human T1D-antigen cells.
			• The platform will be used to study:
			  ○ T cell activation pathways in T1D
			  ○ Effects of potential therapeutic interventions on human T cells and islets
			Drug Development:
			This research is not directly developing a drug, but it aims to create a new human-based testing platform for type 1 diabetes. This platform could be used to evaluate the efficacy and safety of potential therapeutic drugs in a more human-relevant setting than traditional methods.

UNIVERSITY OF COLORADO DENVER	SUSSEL, LORI	PTPN2 mutations affect islet beta cell susceptibility in T1D	**Research Question:**
			• How do mutations in the PTPN2 gene, a T1D risk factor, affect the function and survival of insulin-producing beta cells?
			• Can understanding these effects inform the development of therapies to prevent T1D progression?
			Stage:
			In Vitro (laboratory setting) with human stem cell-derived beta cells and potentially with tissue samples from T1D patients
			In Vivo with animals (transgenic mice)
			Methods:
			• Researchers will use:
			  ○ Transgenic mice with beta cell-specific PTPN2 knockout (PTPN2-bKO)
			  ○ Human stem cells with PTPN2 deletion
			  ○ Potentially, tissue samples from T1D patients with PTPN2 mutations
			• They will investigate the effects of PTPN2 mutations on beta cell function and survival under:
			  ○ Normal conditions
			  ○ T1D-mimicking stress conditions
			• They will focus on the role of PTPN2 in regulating:
			  ○ Metabolic pathways (e.g., glycolysis)
			  ○ Beta cell survival pathways
			Drug Development:

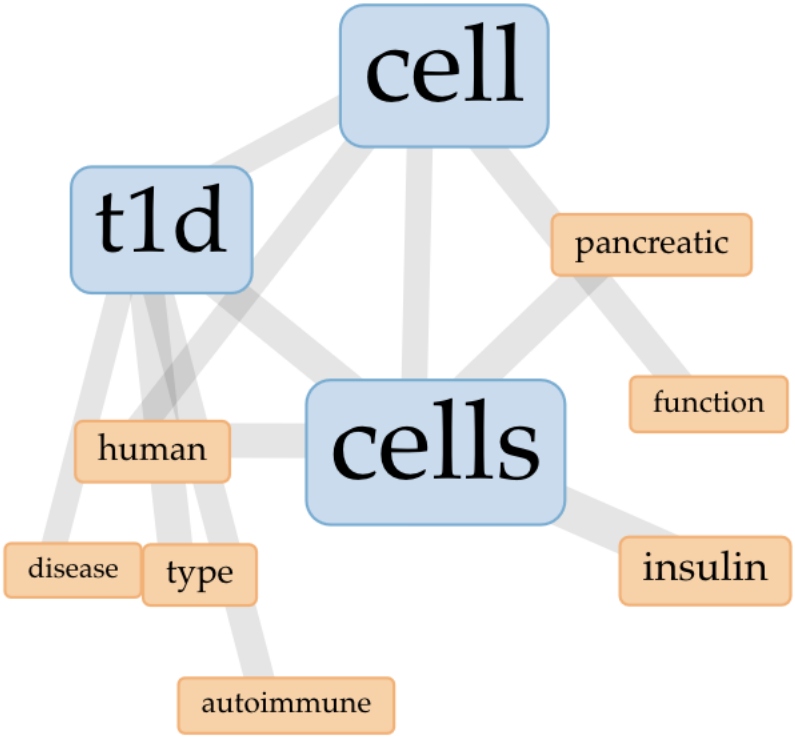
			This research is not directly developing a drug, but it aims to understand how PTPN2 mutations in beta cells contribute to T1D development. This knowledge could be used to develop future therapeutic approaches targeting beta cell function and survival in T1D patients with specific PTPN2 mutations.

UNIVERSITY OF PITTSBURGH AT PITTSBURGH	TAYLOR, D. LANSING	Human Microphysiology Systems Disease Model of Type 2 Diabetes Starting with Liver and pancreatic Islets	**Stage:**
			In Vitro (laboratory setting) with primary human liver and pancreatic islet cells
			Methods:
			• Researchers will develop and validate two microphysiological systems (MPS):
			  ○ Vascularized liver acinus MPS (vLAMPS)
			  ○ Vascularized pancreatic islet MPS (vPANIS)
			• These MPS will be built using primary human liver and pancreatic islet cells.
			• They will assess the ability of these MPS to model:
			  ○ Normal liver and pancreatic islet function
			  ○ T2D-associated pathophysiology in these organs
			• Later stages of the project may utilize induced pluripotent stem cell (iPSC) derived cells instead of primary human cells.
			• Once validated, the vLAMPS and vPANIS will be functionally and physically linked to investigate how:
			  ○ Factors secreted by the liver
			  ○ Hyperglycemia
			  ○ Hyperinsulinemia
			  ○ Contribute to beta cell dysfunction in T2D
			Drug Development:
			This research is not directly developing a drug, but it aims to create a new human-based MPS model of T2D. This model could be used to study the complex interplay between the liver and pancreas in T2D, potentially leading to the identification of new therapeutic targets or strategies.

University of Utah	Helena Safavi	Optimization of fast-acting venom insulins as therapeutic candidates for T1D	**Research Question:** • Can fast-acting insulin derived from cone snail toxins be developed to improve blood sugar control in type 1 diabetes (T1D)? **Stage:**

			Not explicitly mentioned, but likely In Vitro (laboratory setting) with cell studies possible In Vivo studies with animals later **Methods:** • Researchers will develop new insulin candidates based on toxins from cone snails. • These insulin candidates will be engineered to mimic the rapid action and lack of aggregation (clumping) of cone snail toxins. **Drug Development:** This research directly targets drug development for type 1 diabetes. The project aims to create a new fast-acting insulin with potential benefits for blood sugar control in T1D patients, particularly within artificial pancreas systems.
Regents of the University of Colorado		Induction of Antigen-Specific Tolerance in Autoimmune Diabetes with Nanoparticles containing Hybrid Insulin Peptides	**Research Question:** • Can nanoparticles containing hybrid insulin peptides (HIPs) induce antigen-specific tolerance in immune cells and prevent or reverse autoimmune diabetes in NOD mice? **Stage:** In Vivo with animals (NOD mice) **Methods:** • Researchers will develop nanoparticles containing hybrid insulin peptides (HIPs). • These nanoparticles will be delivered to NOD mice, a model of type 1 diabetes (T1D). • The effects of the nanoparticles on the immune system will be investigated, specifically their ability to induce tolerance to insulin-producing cells in the pancreas. • The researchers will assess the efficacy of the nanoparticles in preventing or reversing T1D in NOD mice. **Drug Development:** This research directly targets drug development for type 1 diabetes. The project aims to develop nanoparticles containing HIPs as a potential therapeutic approach for T1D by inducing immune tolerance and preventing the destruction of insulin-producing cells.
Children's Hospital of Philadelphia	TBA	Leveraging HLA protection and humoral immunity to develop	**Research Question:** • Can fast-acting insulin derived from cone snail toxins be developed to improve blood sugar control in type 1 diabetes (T1D)?

		microbial therapeutics that prevent T1D	**Stage:** Not explicitly mentioned, but likely In Vitro (laboratory setting) with cell studies possible In Vivo studies with animals later **Methods:** • Researchers will develop new insulin candidates based on toxins from cone snails. • These insulin candidates will be engineered to mimic the rapid action and lack of aggregation (clumping) of cone snail toxins. **Drug Development:** This research directly targets drug development for type 1 diabetes. The project aims to create a new fast-acting insulin with potential benefits for blood sugar control in T1D patients, particularly within artificial pancreas systems.
Zucara Therapeutics	TBA	Preclinical Development of ZT-01, a First-In-Class Drug to Prevent Hypoglycemia in Type 1 Diabetes	**Research Question:** • Can ZT-01, a novel drug, be developed to prevent hypoglycemia (low blood sugar) in type 1 diabetes (T1D)? **Stage:** Not explicitly mentioned, but likely In Vitro (laboratory setting) with cell studies possible In Vivo studies with animals later **Methods:** • Researchers will investigate the effects of ZT-01 on mechanisms related to blood sugar control. • This likely involves cell-based studies but the specific methods are not mentioned. **Drug Development:** This research directly targets drug development for type 1 diabetes. ZT-01 is a new drug candidate specifically designed to prevent hypoglycemia, a major concern for T1D patients. Successful development of ZT-01 could improve quality of life and treatment outcomes for people with T1D.



T1D 3.0 Preclinical Landscape - DRAFT