**TITLE:** Development of Autonomous Glycemic Control Mechanism for Patients Suffering Glycemic Abnormalities as a Result of Critical Illnesses

**TECHNOLOGY AREA(S):** Biomedical, Human Systems

**OBJECTIVE:** Develop mechanical or biologically engineered solutions to revolutionize reliable, autonomous, multi-hormonal glycemic control to improve patient outcomes stemming from traumatic organ injury and loss, critical illness, and long-term therapeutic maintenance.

**DESCRIPTION:** Traumatic pancreatic injury or loss (about 7% of battle injuries) [1], and various pancreatic pathologies can cause glucose abnormalities that significantly affect patient morbidity and mortality. In addition, traumatic injuries of other organs, infection and other non-pancreatic illnesses also disturb normal blood glucose levels, which likewise negatively impact patient outcomes [2-9]. There is thus a compelling DoD need to improve automated blood glucose control in such cases in order to reduce mortality, duration of illness and ameliorate long-term outcomes [10].

Blood glucose levels are tightly controlled by the pancreas’ multi-hormonal regulatory system; dysregulation can cause coma, death, organ injury and failure, and a reduction in the body’s ability to heal itself. It is well established that outcomes for patients suffering emergent or pathological loss of pancreas function are associated with an increase in patient morbidity, mortality, duration of hospital stay, as well as long-term health outcomes. It is also well known that stress-induced glycemic abnormalities, general glucose intolerance, and insulin resistance are common among critically ill patients, including those without a diagnosis of diabetes. Data suggests that a restoration of euglycemia in critically ill patients significantly lowers morbidity and mortality in the surgical ICU and morbidity in the medical ICU. Glycemic regulation is also impacted by burns and other trauma incurred by the warfighter, thus an automated means to control glycemic levels is especially critical for far forward medical operations, as well as to treat pathologic hyperinsulinism, diabetes and all varieties of secondary insulin dysfunction. While recent developments in blood glucose monitoring have led to improved patient diagnosis and care, treatment has continued to be hampered by the lack of accurate interpretation, constant continuous treatment, and the inability to imitate pancreatic function through multi-hormonal therapy. At present no technology exists to autonomously regulate abnormal glycemia in these patients.

This project seeks the creation of autonomous, multi-hormonal systems, either mechanical - utilizing machine learning techniques, or biological engineering solutions capable of reestablishing glycemic balance in both the critical care environment, and in patients with long-term pathologies. Solutions should seek to avoid the use of immune-suppressants as a part of their solution. A combined mechanical biological solution with embedded machine learning techniques is acceptable as well.

The program manager has identified this topic as research involving Human and/or Animal use. In accordance with DoD policy, human and/or animal subjects in research conducted or supported by DARPA shall be protected. Although these protocols may not apply to Phase I research activities, proposers should be aware that significant lead time is required to prepare the documentation and obtain approval. Please visit http://www.darpa.mil/work-with-us/for-small-businesses/participate-sbir-sttr-program and click on the Human Research Guidelines link or the Animal Research Guidelines link to understand what is required to comply with human protocols and animal protocols in order to avoid delays in awards. Further, proposers are encouraged to separate research tasks and tasks involving human and/or animal use in the Technical Volume and Cost Volume in order to avoid delay of contract award.

**PHASE I: Mechanical / computational approaches must demonstrate the ability to continuously adapt delivery of hormones or drugs based on a patient's rapidly changing blood sugar levels. Approaches must include an autonomous, closed loop system capable of sensing blood glucose levels and delivering appropriate hormones or drugs to assert proper glycemic control. Biologically engineered approaches must demonstrate the ability to produce an autologous, multi-hormonal pancreatic organoid consisting (at a minimum) of pancreatic alpha and beta cells, for use as the solution to, or as the basis for improving long-term management and outcomes.**

**Mechanical / Computational Phase I Deliverables:**
1. Generation of biocompatible device specifications, including Machine Learning (ML) / adaptive control algorithms.
3. Prototype should be tested against and meet design specifications. Device should demonstrate capability of injecting the correct hormone / drug based on glycemic environment.

Biologically Engineered Phase I Deliverables:
1. Generation of viable, human autologous pancreatic organoids consisting (at a minimum) of pancreatic alpha and beta cells from IPSC’s or Stem cells.
2. Provide evidence (morphological, histological, biochemical) that organoids produce appropriate hormones based on glycemic environment.

Both mechanical and biological projects should provide a plan for testing; biological projects must specify plans for improving Phase II yield to achieve sufficient organoids for testing.

PHASE II: Biologically engineered approaches will continue refinement of autologous, multi-cell type organoid production, viability, and function, while the mechanical/computational approaches will refine the algorithms based on studies. Both approaches will conduct preclinical or clinical feasibility studies as appropriate.

Mechanical / computational Phase II Deliverables
1. Prepare regulatory documentation related to FDA (IND) submission as appropriate.
2. Pre-clinical or clinical feasibility studies as appropriate (safety, efficacy).
3. Refine reliable, multi-hormonal (or multi-drug) autonomous glycemic control system based on results of preclinical and/or clinical feasibility studies. In particular, improve ML/adaptive control algorithms as indicated.
4. Documentation and/or publication of results from preclinical or clinical feasibility studies.

Biologically Engineered Phase II Deliverables:
1. Improved production of Organoids to levels that enable preclinical studies
2. Verification of hormonal response to glycemic environment
3. Estimate size and number of organoids required for efficacious preclinical studies.
4. Method of biocompatible delivery in test subject (e.g., encapsulated subcutaneous implantation, direct in vivo implantation, or via scaffold implantation).
5. Prepare regulatory documentation related to FDA (IND) submission as appropriate.
6. Pre-clinical or clinical feasibility studies as appropriate (safety, efficacy).
7. Documentation and/or publication of results, if relevant preparation for FDA approval.

PHASE III DUAL USE APPLICATIONS: If successful, the glycemic control method developed in this STTR is equally applicable for far-forward medical operations treating the wounded soldier in battle as well as in the treatment of civilian illness and emergency situations. Targeted DoD programs and missions, identified in Phase II, will be given the opportunity to apply the device.

REFERENCES:
1. Surgical Management of Modern Combat-Related Pancreatic Injuries: Traditional Management and Unique Strategies,” MAJ Amy Vertrees, MC USA; CAPT Eric Elster, MC USN; Rahul Jindal, MD, PhD, MBA; Camillo Ricordi, MD; COL Craig Shriver, MC USA, MILITARY MEDICINE, 179, 3:315, 2014


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