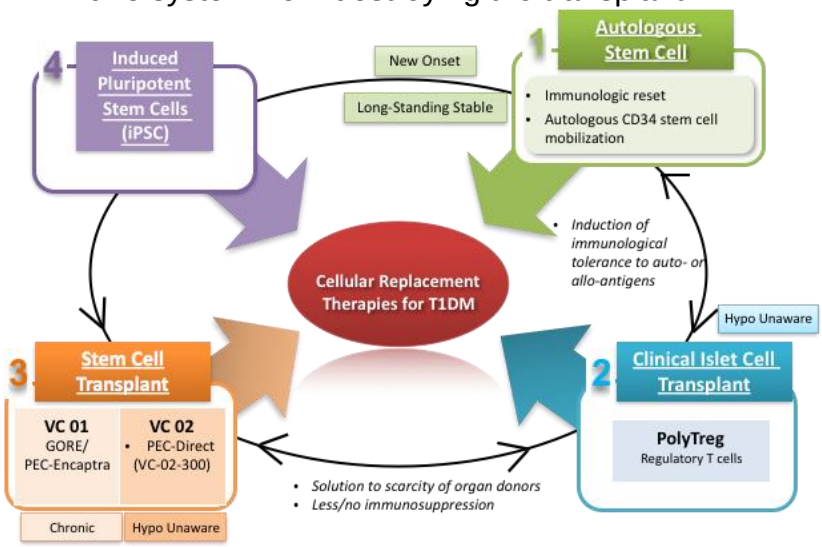
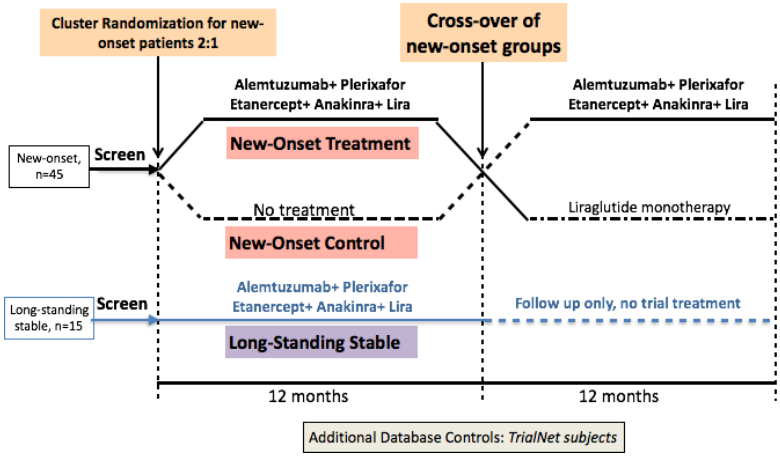
The Edmonton Protocol is named for the islet transplantation group (Dr. James Shapiro, Lead Investigator) at the University of Alberta in Edmonton, Alberta, Canada, where it was first devised in the late 1990s and published in The New England Journal of Medicine in July 27, 2000. It involves transplanting islet cells from a donated pancreas, which can then produce the needed insulin in the recipient's body.

Although used to successfully treat type 1 diabetes mellitus (T1DM) patients around the globe, the Edmonton Protocol is not without its limitations. Human islets, derived from scarce organ donors, are in short supply. In T1DM, the body's immune system attacks and destroys insulin-producing beta cells in the pancreas. For this reason, islet recipients must take immunosuppressive drugs to keep their immune system from destroying the transplant.

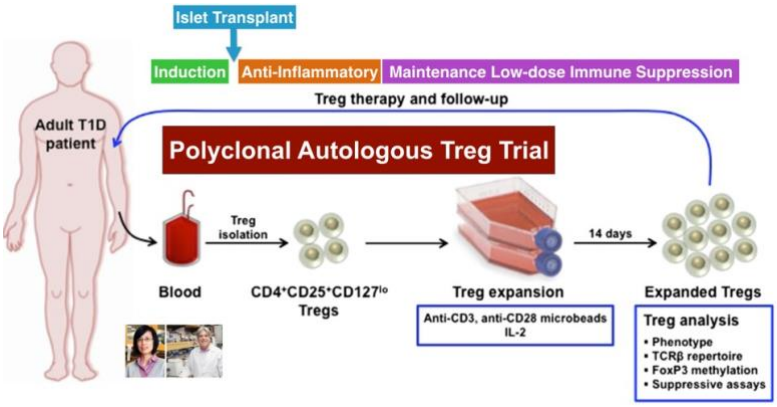


The Clinical Islet Transplant Program / CITP (Director: Dr. James Shapiro) is developing **FOUR BOLD PLATFORMS** that will take us from today to a robust future cure for type 1 diabetes. The platforms are developed to address the spectrum of T1DM from diagnosis to chronicity: 1) **Immune intervention trials** in patients with newly diagnosed type 1 diabetes; 2) **Promoting safer islet** and future cell transplant treatments with less or no need for the anti-rejection drugs (**immune tolerance**) by using patients' own expanded polyclonal regulatory T cells (**Tregs**); 3) Moving forward with our **first-in-human insulin producing PEC-01 human embryonic-derived stem cell trials** from ViaCyte; and 4) Ultimately using patients' own cells – **Induced Pluripotent Stem Cells (iPSCs)** to turn them into self-insulin producing cells that will not be rejected by their immune system.

1) **<u>NEW-ONSET DIABETES IMMUNE INTERVENTION RCT</u>.** This trial mobilizes patient's own CD34+ bone marrow stem cells (plerixafor), combined with immune reset (anti-CD52 alemtuzumab), anti-inflammatory (anakinra + etanercept) and regenerative (long-acting GLP-1 analogue) to 'turn off' and repair T1DM. A second trial arm (longstanding T1DM) has recently been approved by Health Canada and HREB. Early results demonstrate good tolerability and safety, and promising preliminary marked reduction in insulin requirements.

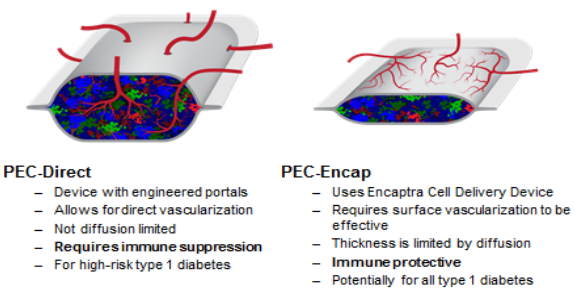


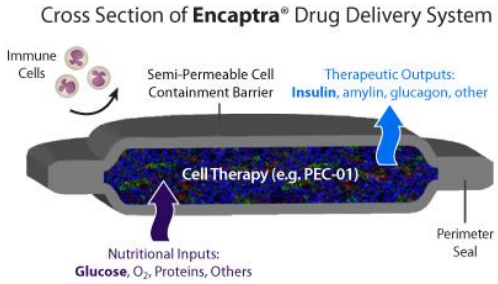
2) **<u>Tregs IN ISLET TRANSPLANT</u> (first-in-human clinical trial)** – autologous *ex vivo* expanded human Treg infusion trial to facilitate tolerance induction in patients receiving intraportal islet transplants in Edmonton. PBMCs are shipped to UCSF San Francisco to Jeff Bluestone and Qizhi Tang for generation of polyclonal alloreactive expansion, then transferred back to Edmonton for clinical infusion. Patients are maintained on minimal immunosuppression (¼ of the standard dose) to look for protective impact of Tregs. Cells are labeled with deuterium for tracking. This is the first time that self-expanded Tregs have ever been used in patients with type 1 diabetes combined with an islet cell transplant to reduce the need for the antirejection drugs. This is a highly exciting and important trial that has the potential to dramatically alter the risk:benefit for all future cell therapies in diabetes, and may also improve the lives of thousands of patients receiving organ transplants.



3) **<u>STEM CELL TRANSPLANT TRIALS</u> (first-in-human) – VC-01 (PEC-Encap) and VC-02 (PEC-Direct)** – Success with the Edmonton Protocol led to a partnership with ViaCyte Inc., a leading regenerative medicine research organization based in San Diego, California, that has pioneered the reproduction of stem cells. Use of these stem cells is key to finding a cure for type 1 diabetes mellitus, or T1D. To date, 17 subjects implanted in Edmonton with iterative dose increase in PEC-01 pancreatic progenitor cells, different Encaptra configurations (immuno-isolating vs perforated devices).

Data presented at American Diabetes Association Meeting 2018, Orlando Florida. To date, we have clearly shown: i. PEC-01 cell implants – no major safety concerns to date; ii. Cells survive up to 2 years within devices, and without immunosuppression; iii. Micro-laser perforations (VC-02) considerably enhance human PEC-01 cell survival and beta cell differentiation, but immunosuppression is needed presently; iv. Current trials (Health Canada and FDA approved) are dose- escalating to determine early therapeutic efficacy in patients. We continue to work with ViaCyte and Gore and Associates to optimize the Encaptra device.





These early results show remarkable promise: it may be possible to transplant a virtually limitless source of appropriate human stem cells. When stem cells—rather than islet cells—are transplanted and end up producing insulin, they can fulfill patients' insulin requirements without risk of rejection or the need for lifetime immunosuppression. This transformative therapy for patients with T1D, if approved, will bring us far closer to a robust cure for diabetes than ever before.

4) **<u>INDUCED PLURIPOTENT STEM CELLS (iPSC)</u> preclinical -** Patient-specific cells converted to iPSC represent potential for generating clinical grade transplantable β-cells. As such, Dr. Shapiro's lab at the Alberta Diabetes Institute is conducting preclinical studies to demonstrate proof-of-concept to manufacture consistent, disease-free and clinical grade (GMP) iPSC lines. Specifically, we will (1) Create iPSCs using blood cells i.e. PBMCs of non-diabetic (ND-iPSC) and T1DM patients (T1D-iPSC), (2) Evaluate ND-iPSC and T1D-iPSC for genomic errors and mutations, (3) Correct genetic defects using CRISPR/Cas9 gene-editing tool for creating T1D-iPSC disease-free. Once proven T1D-iPSC technology could transform the clinical practice for patients with T1DM.

CITP Clinical Trials	
Protocol number	**Trial Title**
Pro00053082	Stem Cell Mobilization (Plerixafor) and Immunologic Reset in T1DM
Pro00052228	VC01-101: A Prospective, Multicenter, Open-Label, First-in-Human Phase 1/2 Study with Two Cohorts to Evaluate the Safety, Tolerability, and Efficacy of Various Doses of VC-01 Combination Product (PEC-Encap) in Subjects with Type 1 Diabetes Mellitus
Pro00070143	VC02-101: An Open-Label, First-In-Human, Study Evaluating The Safety, Tolerability, And Efficacy Of VC-02 Combination Product In Subjects With Type 1 Diabetes Mellitus And Hypoglycemia Unawareness
Pro00071320	Polyclonal Regulatory T cell (PolyTreg) Immunotherapy in Islet Transplantation
Pro00067564	Clinical Study using Antiaging Glycopeptide (PKX-001) in Islet Transplantation
Pro00001120	On-going review of islet and progenitor cell transplant patients at the University of Alberta
Pro00041528	A prospective study of health related quality of life, employment, driving and ethical issues among candidates for islet cell transplantation and recipients of islet cell transplantation

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