Lead R&D at the Alberta Diabetes Institute (ADI)

(last updated November 2, 2020)

Investigator(s)	Title	Description	Stage of Development/Needs
Greg Korbutt, Andrew Pepper	Biodegradable scaffolds for improving cellular transplantation	- Transform the subcutaneous site into a friendly environment to engraft islets (human and neonatal pig). Functionalize this site with matrix that elutes drugs and growth factors to keep back the immune system and improve vascularization. - Dr. James Shapiro has patented device-less islet transplant technology; we are improving this approach by 'functionalizing' this site with drugs/growth factors	- *In vitro* and *in vivo* (small and large animal) proof of concept has been completed - Need additional funding for: more preclinical, safety testing, patents and clinical trials, hiring a consultant to prepare a pre-CTA to submit to Health Canada
	Localized immuno-suppression for islet transplantation optimization	- Provide localized immunosuppression to the islet graft (whether human, porcine or stem cell derived) using mesenchymal stem cells and drug eluting microparticles (micelles)	
Doug Zochodne	Reversing diabetic neuropathy – retinoblastoma 1	Manipulation of Rb1 (retinoblastoma 1) protein pathways in enhancing regrowth of nerves damaged by trauma or neuropathy (particularly experimental diabetic polyneuropathy). We are identifying novel ways to influence expression focusing on nonviral siRNA delivery approaches. Permanent deficits in nerve regeneration are a very large cause of disability in Canadians	- Current focus is on adult neuron models *in vitro* translated into preclinical models of diabetes and nerve regeneration in mouse and rat models - Zochodne is also involved in clinical trials which may be a focus of promising candidates

For more information contact:

Vince Rogers, Director of Operations, ADI
T: 1 780 492 0799
E: vince.rogers@ualberta.ca

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Doug Zochodne (cont.)	Reversing diabetic neuropathy – beyond retinoblastoma 1	Expanding a repertoire of intrinsic growth pathways in peripheral neurons beyond Rb1 that might be in addition to or supplement Rb1 knockdown. Largely but not exclusively focusing on siRNAs. We have now about 4-5 of these including PTEN manipulation, APC knockdown and others.	- Personnel is their largest challenge: funding and supporting the high quality postdoctoral fellows who can accelerate our timetable. Later needs could include safety testing and clinical trial support
	Reversing diabetic neuropathy - protection of axons	Protection of axons from damage in neuropathies by inhibiting intrinsic axonal degeneration pathways- relevant to toxic, including chemotherapeutic neuropathic axon damage and diabetes mellitus. Caspase-6 is an example	
John Ussher	Novel drug/ target for T2D and obesity	First to show that inhibition of rate-limiting enzyme for ketone oxidation SCOT (succinyl-CoA: 3ketoacid CoA transferase) leads to marked protection against obesity-induced glucose intolerance. Using pimozide as SCOT antagonist	- Have recently filed the provisional patent with TEC Edmonton on pimozide (J&J) being repurposed for T2D. Have also synthesized customized drugs that will be compared for efficacy/safety - Need additional funding to finish preclinical, regulatory safety testing and pursue clinical research
James Shapiro	Metallo-porphyrin improves islet engraftment via antioxidant protection	Administration of redox active metalloporphyrin BMX-001 greatly enhances performance of transplanted islets	- Mouse proof of concept completed showing excellent glucose control Need additional funding for additional preclinical research
	Polyclonal Treg clinical trial for immuno-modulation	Using autologous *ex vivo* expanded human Tregs (regulatory T cells) to facilitate immunological tolerance (collaboration with UCSF)	-Phase 1 clinical trial ongoing in Edmonton - Additional funding needed for Phase 2 clinical research

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James Shapiro (cont.)	Stem cell mobilization and immunologic reset without myeloablative treatment or chronic immuno-suppression	T-depletion therapy (alemtuzumab), anti-inflammatory treatment (anakinra, etanercept) promotes self-tolerance; autologous, peripheral-blood mobilized CD34+ enriched stem cells (using plerixafor) and a long-lasting GLP-1 analogue promotes islet regeneration/repair	- Phase 1 clinical trial currently ongoing in Edmonton - Additional funding needed for Phase 2 clinical research
	Autologous human iPSC-derived islet generation and scale-up	- Developing methods to scale-up and produce inducible pluripotent stem cells (iPSCs) that can be used for islet transplantation without the need for immunosuppressant drugs	- Early in method development, but have developed iPSC line using Sendai virus and scale-up procedure - Have assessed cells for functionality *in vitro* and *in vivo* (SCID mice) with positive results - Funding needed to support further method development and preclinical testing of islets for functionality and immuno-tolerance
Pat MacDonald	Islet beta cell signaling controlling insulin synthesis and secretion	Role of SENP1 (sentrin/SUMO-specific protease-1) in the amplification of insulin exocytosis ("dimmer switch")	*In vitro* proof of concept completed - Funding needed to pursue proof of concept in animal models
		Mechanism of ZMIZ1 gene upregulation and impaired insulin secretion	- Mouse proof of concept in KO models completed - Funding needed to pursue additional *in vivo* proof of concept

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Pat MacDonald (cont.)		Influence of Kv2.1 calcium channel clustering on improving insulin secretion	- Mouse proof of concept, early mechanistic studies completed - Funding needed to pursue additional *in vivo* proof of concept
		Demonstrated down regulation of epithelial antigen (STEAP4 – six-transmembrane epithelial antigen of the prostate 4) in islets was correlated with chronic obesity and inflammation, suggesting a mechanism for reduced islet protection against cellular damage	- *In vitro* proof of concept in human islets - Funding needed to pursue *in vivo* proof of concept
	Islet alpha cell signaling controlling cell mass and glucagon synthesis and secretion	Role of mTOR complex 1 in α cell mass and glucagon secretion	- Mouse proof of concept in KO models completed - Funding needed to pursue additional *in vivo* proof of concept testing
Peter Light	Non-invasive monitoring of glucose/lactate/ dehydration	Using low energy microwave technology for external sensing of plasma concentrations	- Early stage *ex vivo* testing completed - Funding required to do *in vivo* proof of concept testing
	Novel drug target for heart failure	Have identified the cardio-protective target for SGLT2 inhibitor (empagliflozin) and are modifying the drug to remove anti-diabetic properties	- *In vitro* and *ex vivo* testing completed - Additional funding needed to do proof of concept testing in animal models

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Peter Light (cont.)	Immunomodulation via designer regulatory T cells (Tregs) [in conjunction with Lori West]	Will use lentiviral transduction to produce islet specific Tregs that express tissue homing and antigen-recognition molecules for targeted immune tolerance	- Early method development completed that demonstrated successful lentiviral transduction to Tregs (murine & human) using reporter molecule eGFP. Sorting and expansion protocol also completed - Funding needed to pursue *in vivo* proof of concept testing
	Bio-engineering fat cells to produce insulin in controllable manner	Using gene transfer technology to allow activation of insulin production in adipose cells. Would transplant cells under skin then activate with blue light	- Proof-of-concept experiments in insulin-deficient animal models are currently ongoing - Patent pending - Need funding to pursue additional preclinical research
	Novel drug target for T2D	Have identified small molecule drug that can increase GLP-1 from the intestine when taken orally. Also enhances insulin secretion from islets	- Mouse proof of concept in diabetic mouse model completed; good glucose lowering ability in OGTT - Funding needed for additional preclinical testing, regulatory safety testing
Cathy Chan	Bioactive peptides (i.e., nutraceuticals) derived from egg protein protect against CV disease and diabetes	Egg derived tripeptide IRW (Ile-Arg-Trp) has proven to: - reduce high blood pressure in hypertensive rats via ACE inhibition - reduce blood glucose level and improve insulin sensitivity in high-fat diet induced mice - improve insulin sensitivity in skeletal muscle via enhanced GLUT4 translocation to plasma membrane	- *in vitro* and *in vivo* proof of concept completed - Matching funding needed to pursue clinical trials (2 x $200K)

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Jessica Yue	Targeting the CNS to improve glucose, lipid metabolism and body weight gain in diabetes	Pharmacological and genetic inhibition of glucocorticoid action within targeted brain regions can improve metabolic health (e.g., IR, obesity). Testing/proof of this involved stereotaxic "brain" placement of cannulas to allow for consequent direct and specific delivery/inhibition	- Have proof of concept data from animal models - Funding for future studies could involve preclinical testing of alternative means to target glucocorticoid action within the brain (e.g. brain-targeted intranasal delivery, or nanoparticle delivery to cross the blood-brain-barrier), which could provide additional efficacy and safety testing prior to consideration for clinical testing.
Colin Anderson	Reversal of new onset and established type-1 diabetes by an immune system reset	Technology: multiple subthreshold antibodies combined with donor cells and regulation of blood vessels and elimination of pathogenic antibodies with enzymes.	- The enzyme approach has a patent pending (Anderson et al. are listed as inventors but rights are with a company in Sweden; see our 2020 AJT publication - Funding needed to continue animal proof of concept research for 2-3 years, followed by clinical trials

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Jean Buteau	Lyn activation as a strategy to protect and expand functional beta-cell mass	- Have identified the tyrosine kinase Lyn as an important genetic regulator of beta-cell “life and death". *In vivo*, beta-cell-specific deletion of Lyn reduces beta-cell mass and precipitates diabetes -Importantly, small molecule activators of Lyn (e.g., MLR1023) stimulate beta-cell mass expansion and protects beta-cells in animal models of both type 1 and type 2 diabetes. Thus, Lyn activation translates into increased beta-cell mass and enhanced insulin secretory capacity. Lyn activation represents a novel and unique strategy to prevent/cure type 1 diabetes.	- Have established proof-of-concept in animal models - Funding needed for lead optimization studies for identifying best drug candidates - Hope to enter clinical trials thereafter
Gary Lopaschuk	Novel compounds that inhibit pyruvate dehydrogenase kinase (PDK)	- Have developed novel compounds to increase PDK and glucose oxidation in heart and skeletal muscle - These compounds can be used to treat heart failure, ischemic heart disease, and diabetes	- Six of the novel compounds are patent-protected and proof-of-concept established in mouse models of heart failure, ischemic heart disease, and diabetes. - Compounds have also undergone PK and toxicology testing with good results - Need additional preclinical testing to achieve Investigational New Drug status prior to Phase I and Phase 2 clinical testing. Funding is required to achieve this

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Spencer Proctor	Novel antibody that protects against CVD	- Antibody (e.g, IgG. IgM) titers are known to be correlated with CVD risk - Proctor working in collaboration with a group in Cuba to develop a novel antibody that has vaccine-like properties and protects against CVD	- Efficacy has been validated in mice models, rats and rabbits - Positive immuno-genicity has been tested in pigs (UofA) and Monkeys (Cuba) - Need funding to do further proof-of-concept to demonstrate extended lifespan (rabbit FH model), large scale-up in Canada, pilot phase 1 clinical trials (likely in very high risk FH subjects).
Jason Dyck	Empagliflozin suppresses inflammation and protects against acute septic renal injury	- Studies have suggested that empagliflozin may assist in treatment of inflammatory diseases - Dyck demonstrated for the first time the beneficial effect of empagliflozin on acute sepsis-induced renal injury using lipopolysaccharides (LPS) - mouse model	- Efficacy has been demonstrated in mice models, and MOA partially established (i.e., LPS induced acute renal injury) - Would like to move towards a small-scale RCT involving repurposing empa-gliflozin in septic patients - Want to do further preclinical testing of empagliflozin for other indications (e.g., IBD)

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Richard Lehner	CES1 activity modulates lipid metabolism	- Lehner and his research team are world leaders in studying the role of carboxylesterases (CES) in lipid metabolism, and the first to show that CES1 action promotes secretion of bad lipids from hepatocytes - Advantage; we have access to unique tools, reagents, novel target, unique insight into mechanism of action, unpublished data: We have developed necessary tools and reagents such as CES mutants, cells stably expressing CES family members (wt and mutant), CES ko mice, CES activity assays, anti-CES antibodies, etc.	- Developed CES1 inhibitors with GSK, have tested *in vivo* and *in vitro*, proof-of-concept for disease progression established, but need to improve specificity (i.e., not inhibit other members of CES family) - Further testing needed to establish importance of CES1 in drug metabolism (although this could be an attribute)

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