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From beta cells to bedsides: A 2018 update on diabetes research in British Columbia

Laboratory and clinical investigators in BC are making notable discoveries as they collaborate to reach a better understanding of diabetes, especially regarding pancreatic beta cell biology, obesity, and autoimmunity.

ABSTRACT: With more than 1.4 million British Columbians impacted by prediabetes or diabetes, the need has never been greater for research into the causes of the disease and new approaches to predict, prevent, and reverse this devastating condition. Fortunately, BC has a rich history of diabetes research dating back to the 1960s and has become a world leader in the area, with research projects underway at three Vancouver sites and more research capacity developing outside Vancouver. Current research strengths lie in pancreatic beta cell biology and replacement, obesity, autoimmunity, and community health. Notable discoveries and plans for future research have resulted from progress made by wet laboratory scientists and diabetologist clinicians based at Vancouver General Hospital, the University of British Columbia, and BC Children's Hospital. The future is bright for the province's strong and collegial community of researchers, especially with the establishment of the BC Diabetes Research Network.

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Worldwide prevalence of both type 1 and type 2 diabetes is on the rise, yet we remain without a cure for this metabolic disease and have limited therapeutic options. With 1.4 million people impacted by prediabetes or diabetes in British Columbia alone,[1] the need has never been greater for research into the causes of the disease and new approaches to predict, prevent, and reverse this devastating condition.

BC has a rich history of diabetes research, discovery, and training that dates back to the 1960s, when experimental studies led to the discovery of the first incretin hormone, gastric inhibitory polypeptide—also called glucose-dependent insulinotropic polypeptide (GIP)—by Drs John Brown and Raymond Pederson in the Department of Physiology at the University of British Columbia (UBC).[2] Subsequent work by this group, including Dr Chris McIntosh, using preclinical models of type 2 diabetes, played a key role in the eventual therapeutic application of dipeptidyl peptidase-4 (DPP-4) inhibitors,[3] today a widely used class of type 2 diabetes drugs that prolong the biological activity of the incretin hormones GIP and glucagon-like peptide-1 (GLP-1). This group of investigators also played a significant part in training many current diabetes researchers in BC and around the world.

Research sites

Diabetes research in BC today takes place primarily at three sites: Vancouver General Hospital (VGH), the UBC Point Grey Campus, and BC Children's Hospital (BCCH). As well, research efforts are underway elsewhere in BC. Close collaboration among the Vancouver research groups is facilitated by complementary expertise, sharing of core infrastructure, and outstanding trainees. In recent years, increasing collaboration among wet laboratory scientists and diabetologist clinicians has benefited the diabetes research community as a whole and enabled innovative clinical trials and translational research that

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has provided cells and blood samples from patients for study at the laboratory bench.

Vancouver General Hospital

At VGH, the world-leading Ike Barber Human Islet Transplant Laboratory was initiated by a donation from Dr Irving K. Barber that enabled the recruitment of Dr Garth Warnock, a pioneer in human islet transplantation in type 1 diabetes. Since 2003, the clinical program at the lab has transplanted islets into 54 individuals with type 1 diabetes. Follow-up of these patients shows that islet transplantation and the resulting improvement in glucose regulation has slowed progression of microvascular complications.[4] Clinical studies of islet transplant recipients in Vancouver have also identified beta cell prohormones as biomarkers of islet graft function that may have value in predicting islet transplant failure.[5]

Importantly, the availability of human islets for research has stimulated collaborative research projects in human islet biology among many BC-based diabetes researchers. For example, using human islets from the Ike Barber lab, local researchers reported that immune-suppressive drugs such as tacrolimus, typically used in islet transplant recipients to prevent allograft rejection, have deleterious effects on human beta cell function and thus may contribute to graft failure.[6] This widely cited finding has led to greater consideration of the impact immunosuppressive protocols have on transplanted islets. Other human islet studies have provided new insight into why toxic islet amyloid plaques form in type 2 diabetes and how they induce inflammation and beta cell loss.[7] Related studies have suggested that the beta cell death and dysfunction in islet transplants resembles the beta cell failure seen in type 2 diabetes,[8] including the part played by amyloid formation.[9]

VGH is also the site of multiple trials in type 2 diabetes and clinical research into the regulation of glucose metabolism in older adults with type 2 diabetes. Given the risk of hypoglycemia in this understudied population, such research has significant implications for clinical practice.[10]

In the area of translational research in diabetes prevention and control, Dr Tricia Tang is leading a program that focuses on high-risk and medically underserved patient populations.[11,12] She is conducting community-based trials investigating the impact of low-cost, sustainable behavioral interventions on glycemic control, diabetes distress, and other health-related outcomes in South Asian Canadians and members of other ethnic communities.

UBC Point Grey campus

In the regulatory peptide group of the UBC Department of Cellular and Physiological Sciences (formerly the Department of Physiology) the retirement of investigators once threatened to leave a void in diabetes research in BC. Fortunately, this was avoided with the recruitment of Dr Tim Kieffer in 2002 and Dr Jim Johnson in 2004. These capable investigators have now developed large and diverse diabetes research programs with strengths in islet biology, and have made significant contributions to our understanding of incretin, leptin, and stem cell biology, as well as hyperinsulinemia and obesity.

Dr Johnson has used novel mouse models of altered insulin production to gain insight into the biology and actions of insulin, pointing to unappreciated roles for hyperinsulinemia in obesity and lifespan. He has shown that genetically decreasing insulin production in mice confers protection from diet-induced obesity[13] and prolongs lifespan.[14]

Dr Kieffer's pioneering work in stem cell derivation of insulin-producing cells[15] has moved us closer to having a source of unlimited, functional beta cells for transplantation in patients with type 1 diabetes. Beta cell replacement—currently by transplantation of pancreatic islets isolated from cadaveric organ donors—has the potential to be a functional cure for persons with type 1 diabetes, but is limited by tissue supply and graft failure. Dr Kieffer's group has also developed protocols for generating human insulin-producing cells from embryonic stem cells completely in the laboratory dish.[15,16] Insulin-producing cells derived from stem cells are now entering clinical trials, including one in Vancouver. This exciting area of research has led to a number of collaborative studies with UBC and BCCH researchers aiming to further improve these protocols and to engineer better beta cells that can evade immune attack, last longer, and function better following transplantation.

Other laboratories in the UBC Life Sciences Institute are studying the genetics of obesity, insulin action, and lipid metabolism, as well as viral pathogenesis of type 1 diabetes. Long-standing research activity at UBC is continuing in the areas of insulin action and diabetes complications, pharmacological modulation of insulin sensitivity, and changes in cardiac metabolism that occur in diabetes. One example is Dr Brian Rodrigues's work, which has led to a better understanding of the metabolic machinery that drives energy metabolism in the cardiomyocyte and endothelial cell and its breakdown in the diabetic state.[17] This information is now being used to devise novel therapeutic strategies to prevent or delay diabetes-related heart disease.

BC Children's Hospital

Laboratory-based diabetes research at BCCH and its associated research institute began in the early 1990s under the leadership of Dr Aubrey Tingle, who partnered with UBC departments to recruit new clinician scientists and wet laboratory investigators to build childhood diabetes research capacity and programs focused on autoimmunity in type 1 diabetes, viral pathology, antigen presentation, and causes of beta cell death and dysfunction in diabetes. In the 2000s, childhood diabetes research in BC received a boost with investments from multiple partners, including the BCCH Foundation, Diabetes Canada (formerly known as the Canadian Diabetes Association), UBC, and the Canucks for Kids Fund (CFKF). With the help of these partners, infrastructure funding from the Canada Foundation for Innovation and BC Knowledge Development Fund, and the construction of the Translational Research Building at BCCH, I was fortunate to be able to recruit four laboratory-based diabetes investigators. These individuals established strong research programs in beta cell development and biology funded by the Canadian Institutes of Health Research.[18-20] Our growing diabetes research group was soon joined by other experienced BCCH investigators looking at the genetics of metabolic disease, the epigenetics of diabetes complications,[21] and the role of nutrition.[22]

Diabetes and transplant immunology research was greatly strengthened by the move from VGH to BCCH of Dr Megan Levings, who has established a leading research program in human T regulatory cell biology.[23,24] Recent studies in diabetes autoimmunity at BCCH by Levings and colleagues have generated a better understanding of the mechanisms that lead to T cell activation and beta cell loss in type 1 diabetes. These studies have also shown the tremendous power of the chimeric antigen receptor (CAR) to generate CAR T regulatory cells with the potential to attenuate allograft responses to islet transplants and enhance graft survival.

The BCCH diabetes research group in the CFKF Childhood Diabetes Laboratories has made a number of impactful discoveries. Pediatric endocrinologists at BCCH teamed with laboratory investigators to demonstrate that children with recent-onset type 1 diabetes have higher circulating levels of a T cell subtype (Th17) that secretes a pro-inflammatory cytokine (IL-17).[25] This work provided the rationale for testing ustekinumab (a drug used in the treatment of psoriasis) in patients with type 1 diabetes in a clinical trial now underway in Vancouver (clinicaltrials .gov: NCT02117765).

Other translational studies at BCCH have led to the recent discovery of circulating biomarkers of potential value in predicting progression to diabetes and prognosis, including a unique gene signature expressed in T regulatory cells in patients with type 1 diabetes[23] and peptides derived from beta cell prohormones.[5] Wet laboratory studies have provided new insight into genes involved in the regulation of pancreatic beta cell development and function,[18-20] and elucidated how beta cell dysfunction occurs in type 2 diabetes, pointing to roles for cholesterol accumulation[26] and islet macrophages.[27]

BCCH also has strengths in clinical pediatric diabetes research. In addition to participating in type 1 diabetes clinical trials through TrialNet, BCCH has strong community-based clinical and population health research programs. Clinical studies have investigated diabetes risk in vulnerable populations, including Indigenous people and youth with mental illness. These studies have shown that youth prescribed certain antipsychotic medications have a twofold to threefold increased risk of being overweight or developing prediabetes,[28] a discovery that has led to changes in clinical practice guidelines regarding the use of such medications in these youth. Other studies have sought a better understanding of cardiovascular complications in obese youth.[29] BCCH is also home to studies aimed at reducing the prevalence of obesity in youth through lifestyle modification approaches such as SCOPE, a program for preventing childhood obesity through community engagement.[30] Finally, BCCH clinicians have played a key role in enabling childhood diabetes translational research to occur, spearheading multiple collaborative clinical studies with laboratory-based investigators.

Research sites outside Vancouver

Outside Vancouver, diabetes research is gaining in strength. At UBC Okanagan, discoveries have been made in the areas of nutrition and exercise. Links have been uncovered between intake of polyunsaturated fats and the risk of developing diabetes,[31] and clinical studies have shown how exercise, in particular high-intensity interval training (HIIT), impacts inflammation and metabolism in humans, providing evidence that HIIT may reduce cardiovascular complications in type 2 diabetes.[32]

At the University of Northern BC, research has been aimed at developing medications to manipulate metabolic signalling pathways in adipose tissue.[33]

Finally, at Simon Fraser University, Dr Scott Lear is investigating obesity and diabetes, and the role of environment, ethnicity, and lifestyle

in chronic disease. This builds on an important international study led by Dr Lear that showed physical activity of any kind can reduce the risk of diabetes and heart disease.[34]

The future

The future is bright for diabetes research in BC. A strong and collegial environment is fostering collaborative studies across the various diabetes research sites in BC, and wet laboratory researchers are increasingly working closely with diabetes clinicians to move research from bench to bedside and back again. Current and future clinical trials show promise in applying laboratory-based discoveries to improving the lives of people with diabetes.

Islet biology is clearly a recognized strength of BC's diabetes researchers, with local investigators making discoveries in how healthy insulin-producing beta cells develop and function, what goes wrong with beta cells in diabetes, and how to create insulin-producing cells in culture and how to regenerate and replace beta cells. Tremendous opportunities exist for training in diabetes research across multiple disciplines, from genetics to cell biology to physiology, allowing BC to attract outstanding diabetes research talent to train here. Fantastic new technologies are available as well. For example, we now have mouse models of disease, and tools that enable deep interrogation of single cells from subjects with diabetes.

The newly formed UBC-funded BC Diabetes Research Network (https://diabetesbc.ca) promises to bring researchers together from different disciplines at regular meetings, including the annual Vancouver Diabetes Research Day held each fall, and UBC Okanagan Diabetes Research Day. These meetings can be expected to create new opportunities through the sharing of data and ideas and the spawning of new partnerships and collaborations. Given the prevalence and burden of diabetes in our province, country, and world, it is timely and exciting that BC is now home to this network and is increasingly taking a leadership role in diabetes research on the international stage.

Summary

The need has never been greater for research into diabetes and new approaches to predict, prevent, and reverse this devastating condition. Fortunately, the rich history of diabetes research in BC that began in the 1960s continues today at Vancouver General Hospital, the UBC Point Grey campus, BC Children's Hospital, and other sites in the province, including UBC Okanagan, the University of Northern British Columbia, and Simon Fraser University. Many notable discoveries have been made by investigators and islet biology has proven to be a particular research strength. With the establishment of the BC Diabetes Research Network, more discoveries and more collaboration can be expected. BCMJ

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Competing interests

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