

ALBERTA DIABETES INSTITUTE



BIENNIAL REPORT
2012-2013



DEDICATED TO TRANSLATING DISCOVERY SCIENCE INTO HEALTH SOLUTIONS
FOR THE PREVENTION, TREATMENT AND CURE OF DIABETES.

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ALBERTA DIABETES INSTITUTE



ANSWERING THE DIABETES CALL

The World Health Organization estimates that 347 million people worldwide, about 5% of the global population, have some form of diabetes, and numerous more are in a 'pre-diabetes state.' Worse, the incidence rate of diabetes is rising, and the International Diabetes Foundation anticipates that by 2030 this could reach 10% globally. In Alberta alone, more than 200,000 individuals—about 5.5% of the population—currently suffer from

diabetes. Health care costs for Albertans with diabetes is double that of the non-diabetes population, resulting in direct costs of \$3.6-billion annually, staggering indirect costs and most importantly, a reduction in the quality of life for all affected. An impaired ability to regulate one's blood sugar in itself can be life threatening, but the disease brings with it all kinds of secondary complications that include cardiovascular, neurological and kidney diseases.

The past 100 years have produced life-altering therapies for diabetes

patients, from the discovery and application of insulin to drugs that improve glycemic control in Type 2 diabetes (T2D) patients to pancreatic islet cell replacement therapies in Type 1 diabetes (T1D) patients. Still, the overall risk of premature death for diabetes patients is double that of the non-diabetic population—nearly half of people with diabetes die from cardiovascular disease alone, primarily from heart disease and stroke. Type 2 diabetes is increasing at a particularly alarming rate, with this traditionally 'adult-onset' disease occurring more and more in children.



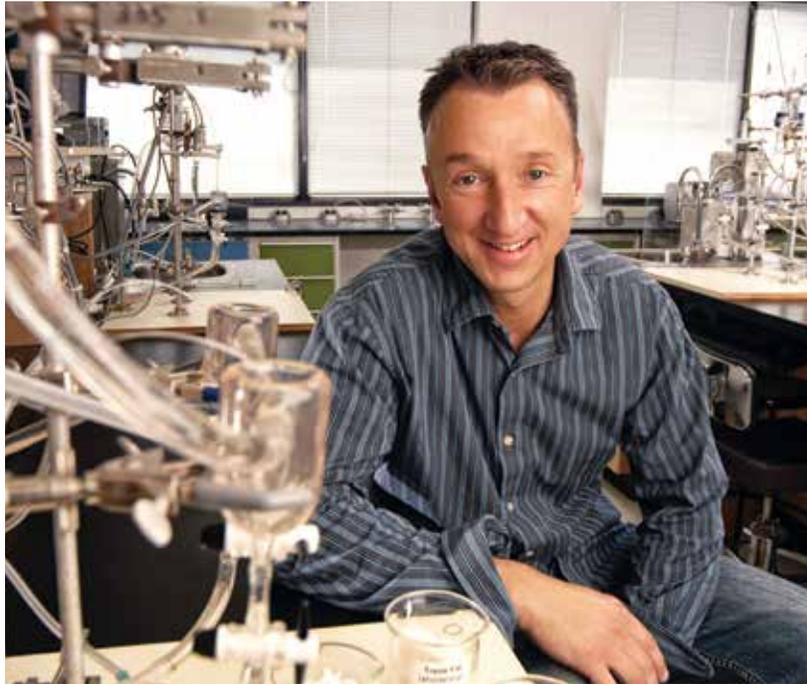
Clearly the battle is not over.

In 2002, plans were put into place to build one of the world's most outstanding and comprehensive research facilities at the University of Alberta dedicated to studying diabetes: the Alberta Diabetes Institute (ADI). This was a logical progression given that the University has been the site of numerous advancements in T1D research and application. These advancements included Dr. James Collip's contributions towards the purification and first clinical use of insulin in 1922, as well as the

internationally acclaimed Edmonton Protocol for transplanting islet cells and relieving patients of daily insulin injections. The first islet transplants using this technique were performed in 1999, and the Edmonton Protocol has since become the world's gold standard for routine clinical islet transplantation programs. Expertise in T2D research has also grown at the University in multiple disciplines, including metabolism, nutrition, and physical activity. In 2007 the Alberta Diabetes Institute opened its doors and is now home to leading researchers that produce an integrated

and collaborative research environment, reflecting the need for a multidisciplinary approach to conquering diabetes. The facility is also dedicated to translating research and includes clinical, health care delivery and health outcomes research. In the near future ADI will partner with Alberta Cell Therapy Manufacturing, a clinical grade manufacturing facility that will translate emerging cellular therapy technologies into patients and help ADI remain at the forefront of innovation for diabetes treatment.

MESSAGE FROM THE DIRECTOR



DR. PETER LIGHT
DIRECTOR
ALBERTA DIABETES INSTITUTE

It's been 25 years since the first islet transplantation took place right here in Alberta. Since then, we have continued to make significant progress in diabetes research. This includes the development of the Edmonton Protocol, a groundbreaking procedure that represents a promising treatment option for diabetes patients worldwide.

We have also established the wonderful research facility that we at the Alberta Diabetes Institute are so proud to call home. As the largest freestanding diabetes research institute in Canada, it brings together over 400 leading

diabetes doctors and researchers, all working toward a cure.

Our research continues to grow more complex with even greater impact, as we remain steadfast in our mission to discover new methods to prevent, treat and cure diabetes. A number of new and existing partners support our efforts, which include the University of Alberta, the Alberta Diabetes Foundation, the University Hospital Foundation, and the Government of Alberta. Without valuable partnerships like these, our work simply wouldn't be possible.

We're also tremendously grateful for the financial contributions we receive from private donors and other supporters. Your generosity enables us to continue providing a world-class research and training environment, with state-of-the-art facilities and funding for students, trainees and research grants.

With your support, I believe the next 25 years will be an even more exciting time for diabetes research—not only for the ADI, but also for Albertans, Canadians, and the rest of the world. Whether you're interested to learn more about diabetes, join our research team or support our work, I hope this report provides you with greater insight into our efforts to provide hope and concrete solutions for all those afflicted with this disease.



OUR RESEARCH CONTINUES TO GROW MORE
COMPLEX WITH EVEN GREATER IMPACT, AS
WE REMAIN STEADFAST IN OUR MISSION TO
DISCOVER NEW METHODS TO PREVENT,
TREAT AND CURE DIABETES.

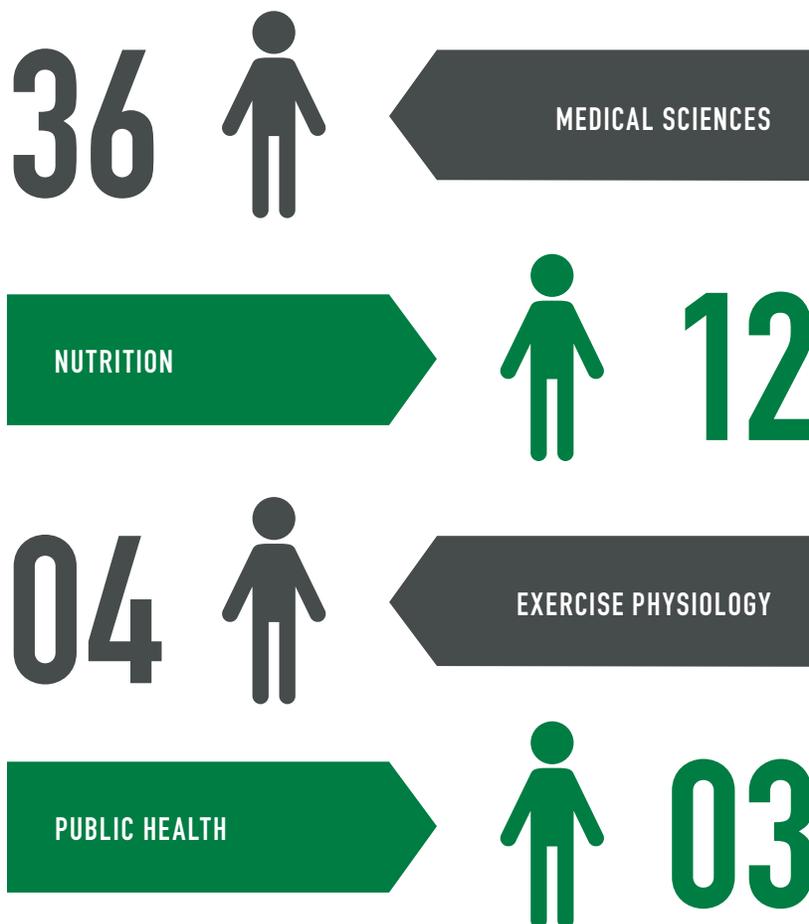
– DR. PETER LIGHT

DIRECTOR, ALBERTA DIABETES INSTITUTE

OUR MEMBERS

The Alberta Diabetes Institute currently has 55 members that are principal investigators from various disciplines. 2013 saw the first member from the University of Calgary join the ADI. Membership is approved based on demonstrated involvement in diabetes research and is reviewed every three years by ADI's Research Coordinating committee. A full list of current members can be found on p. 14.

THE ADI HAS 55 MEMBERS FROM THE FOLLOWING DISCIPLINES:



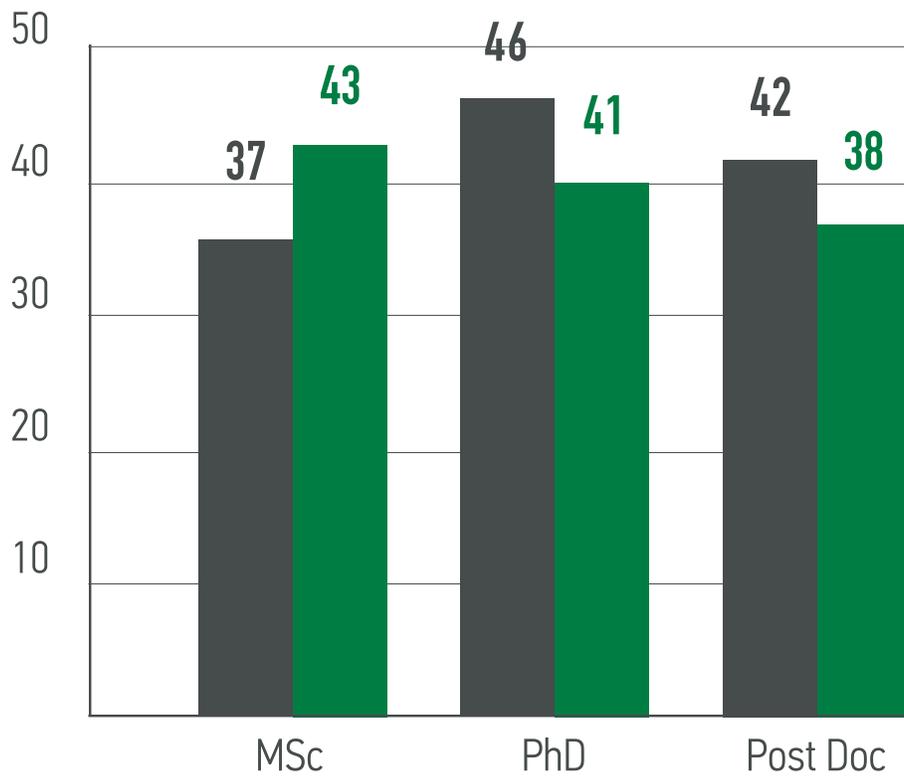


OUR MEMBERS

TRAINEES SUPERVISED

BY ADI MEMBERS

2012 2013



MEMBER MEDIAN

1

1

1

1

1

1

12



THE COOPERATIVE APPROACH TO TREATMENT USED
BY ADI CLINICAL STAFF HAS MADE OUR DIABETES
JOURNEY EASIER. ALSO, SEEING THE DOCTORS AND
RESEARCHERS WORKING TOGETHER TO SUPPORT
DIABETES RESEARCH HAS BROUGHT OUR FAMILY
HOPE THAT A CURE IS COMING.

KNOWING THAT WE ARE NOT ALONE IN OUR DAILY
STRUGGLE TO LIVE WITH DIABETES HELPS US DEAL
WITH THE CHALLENGES WE FACE.

– BILLIE JO KALIEL

MOTHER OF 8 YEAR OLD BRYAN KALIEL WHO IS A DIABETES PATIENT

OUR MEMBERS

OUR MEMBERS INCLUDE

FACULTY OF AGRICULTURAL, LIFE AND ENVIRONMENTAL SCIENCES

Rhonda Bell, Jean Buteau, Cathy Chan, Tom Clandinin, Catherine Field, René Jacobs, Diana Mager, Vera Mazurak, Linda McCargar, Spencer Proctor, Donna Vine, Noreen Willows

FACULTY OF MEDICINE AND DENTISTRY

Babita Agrawal, Colin Anderson, Geoff Ball, Chris Bleackley, Chris Cheeseman, Robert Couch, Jason Dyck, John Elliott, Rose Girgis, Andrea Haqq, Kailish Jindal, Greg Korbitt, Richard Lehner, Peter Light, Gary Lopaschuk, Patrick MacDonald, Sumit Majumdar, Finlay McAlister, Gavin Oudit, Raj Padwal, Ray Rajotte, Gina Rayat, Elizabeth Rosolowsky, Edmond Ryan, Yves Sauvé, Peter Senior, James Shapiro, Arya Sharma, Gita Sharma, Matthew Tennant, Ellen Toth, Amy Tse, Dennis Vance, Lori West, Rachel Wevrick

FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES

Scot Simpson

FACULTY OF PHYSICAL EDUCATION AND RECREATION

Gordon Bell, Normand Boulé, Margie Davenport, Wendy Rodgers

SCHOOL OF PUBLIC HEALTH

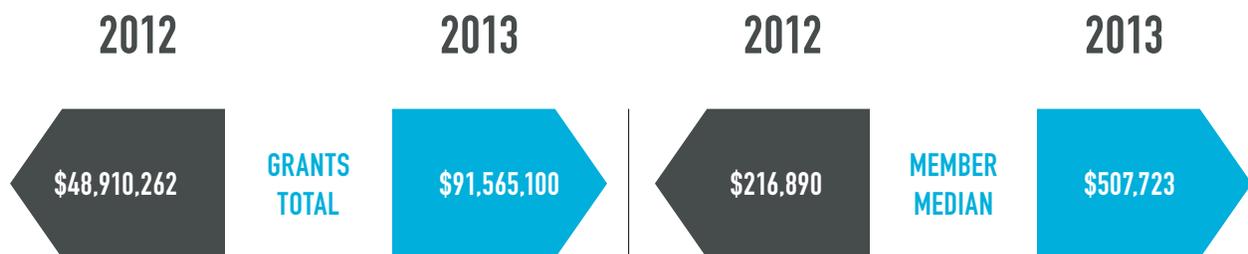
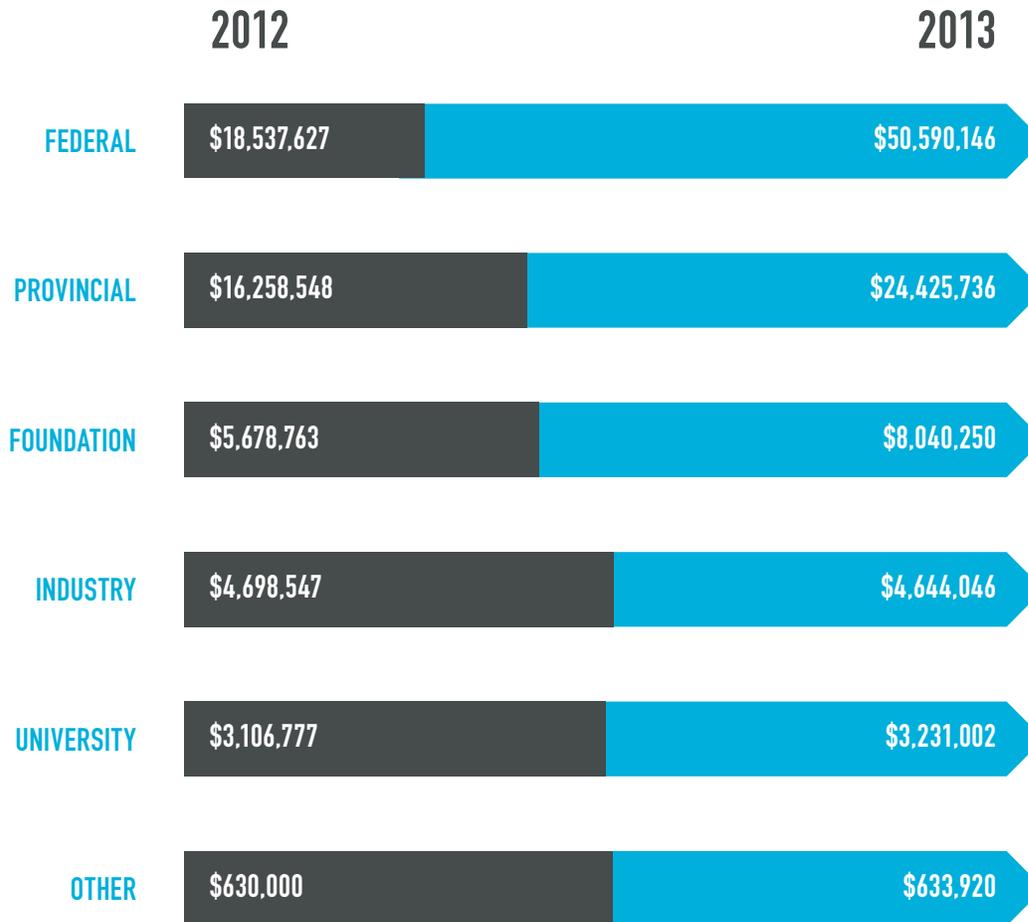
Tim Caulfield, Dean Eurich, Jeff Johnson



GRANTS & PUBLICATIONS

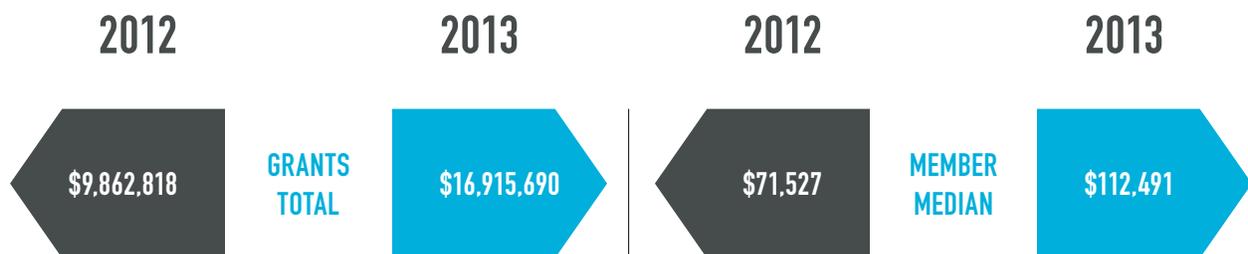
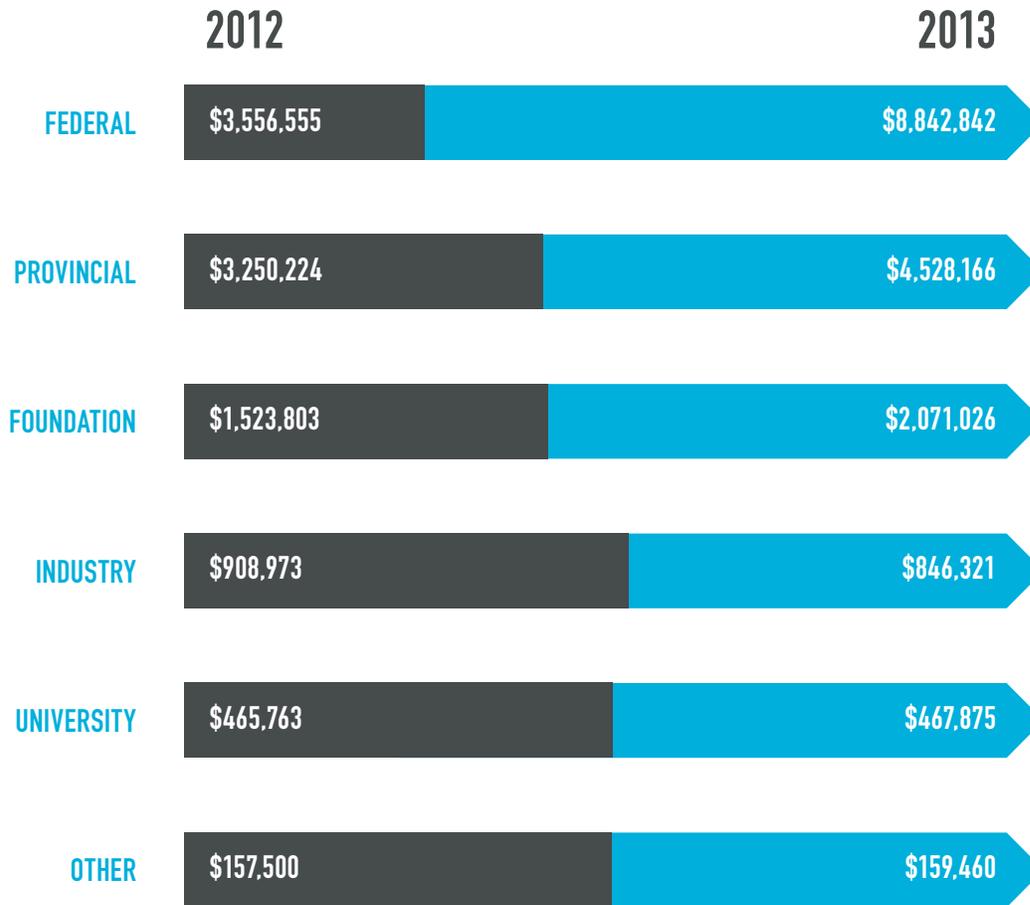
RESEARCH GRANTS

HELD BY ADI MEMBERS (TOTAL VALUE ACROSS FUNDING PERIOD)



RESEARCH GRANTS

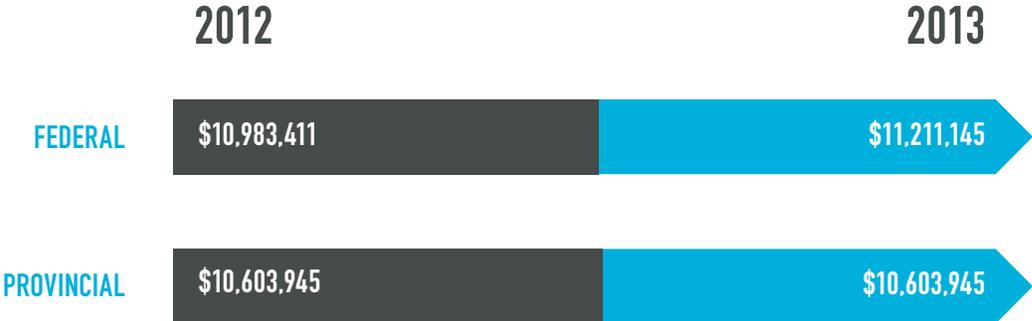
HELD BY ADI MEMBERS (PRORATED BY YEAR)



GRANTS & PUBLICATIONS

INFRASTRUCTURE GRANTS

HELD BY ADI MEMBERS (TOTAL VALUE ACROSS FUNDING PERIOD)



INFRASTRUCTURE GRANTS

HELD BY ADI MEMBERS (PRORATED BY YEAR)

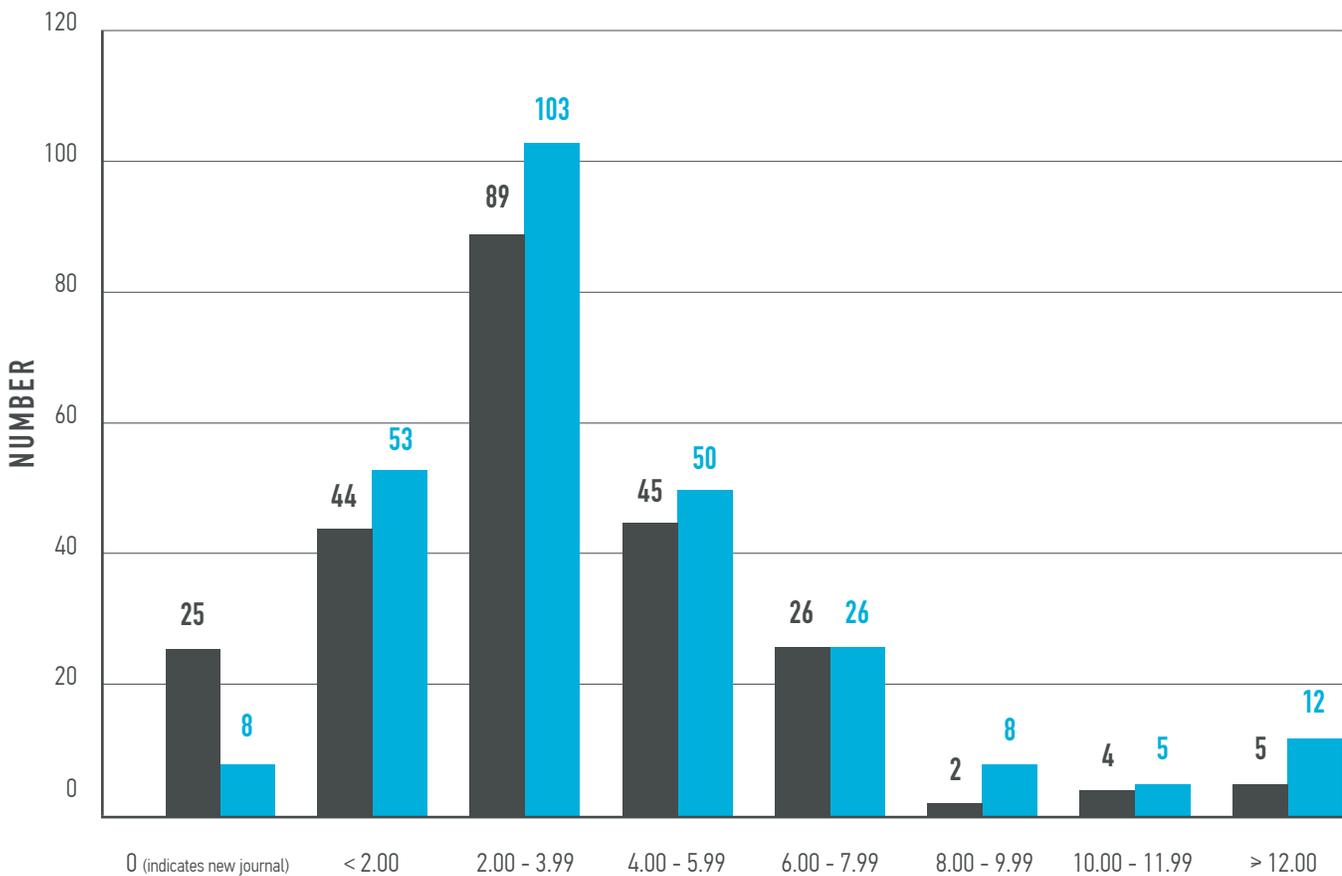


GRANTS & PUBLICATIONS

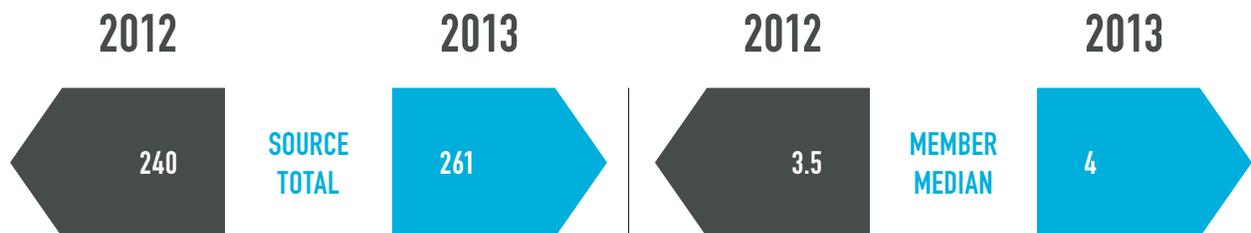
PUBLICATIONS

BY ADI MEMBERS

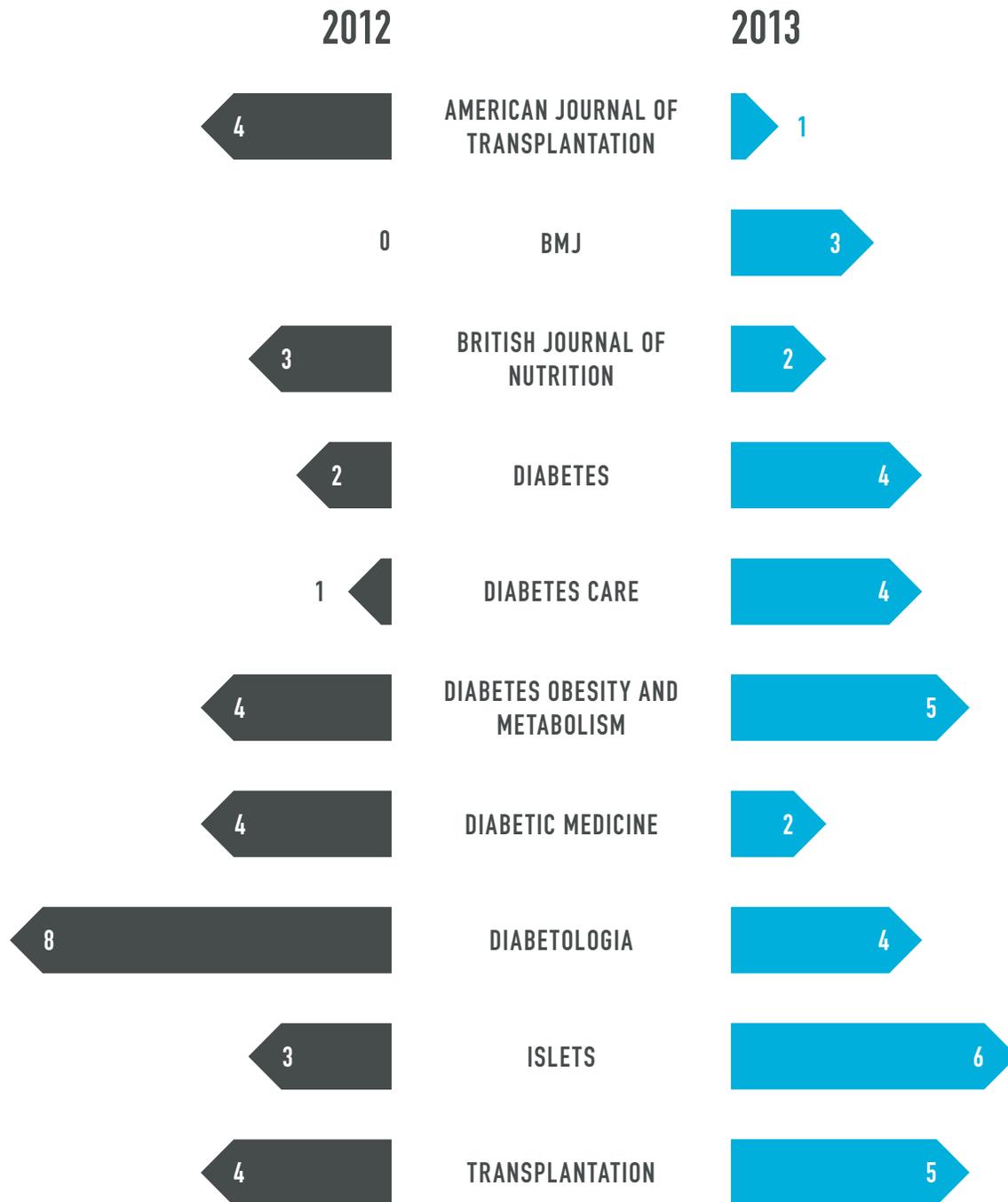
2012 2013



IMPACT FACTOR



PUBLICATIONS IN SELECTED JOURNALS



STRATEGIC FOCUS

STRATEGIC FOCUS

At ADI, we don't just want to be a world leader in diabetes research, we want to set the standard for translating research into meaningful health solutions. This means maintaining a balance of early discovery research, preclinical and clinical research activities, as well as coordinating these efforts with feedback from health delivery and population health research. Our efforts during 2012 and 2013 have demonstrated this focus:

Improving Discovery Research

ADI remains committed to making technical core services available to its researchers in support of their discovery research. The newest service, IsletCore, procures human islets from non-transplantable donor pancreases and redistributes these for valuable research. Since 2012, IsletCore has experienced significant growth, distributing nearly 10-million islets to ADI researchers and to other labs located across Canada, the USA and in the UK. The use of human islets provides a distinct advantage over the use of animal-derived islets for islet biology studies.

Clinical Research

Clinical trials at ADI's Clinical Research Unit resulted in nearly 2,000 outpatient visits during 2012 and 2013, helping advance diabetes treatment and prevention for all forms of diabetes. During that period, our Human Nutrition Research Unit saw 33 clinical studies related to every phase of life, from gestation to senior health. There were also 18 biomedical studies that researched novel anti-diabetic drugs, new indications for existing drugs, combination therapies, Phase IV research, and obesity intervention. In addition, ADI clinical researchers participated in TrialNet, the international effort aimed at improving T1D predictive screening and early intervention, new stem cell beta-cell regeneration and immune-tolerance clinical trials.

In 2012, we officially opened the Physical Activity Diabetes Lab where studies are now assessing the impact of physical activity intervention on glycemic control with or without medications. We also completed validation of our new, whole-body calorimetry unit—an important addition to metabolic research at ADI and the only such facility in Western Canada.

Manufacturing

Construction of the Alberta Cell Therapy Manufacturing (ACTM) facility is nearing completion. This represents an important piece of the future for the translation of new technologies for diabetes treatment into clinical grade products that include engineered islets, islet encapsulation, stem cells and transplantable porcine islets.

Training

Clinical research at ADI provides numerous undergraduates, graduates and post-doctoral fellows with the opportunity to participate in human based studies—part of an intentional strategy to better link discovery scientists with clinical research. ACTM will further expand the trainees' experience to manufacturing cell-based therapies in ultra-clean environments.

Looking Ahead

The University of Alberta, Province of Alberta and Government of Canada have made enormous investments to support knowledge transfer, and ADI wants to integrate with these in order to complete the translational research picture. That means working with the emerging Translational Science Institutes at the University, as well as working with TEC Edmonton and our own in-house regulatory experts to move through



preclinical research. We will also work closely with the Strategy for Patient-Oriented Research (SPOR) and the newly-funded SPOR Support Unit in Alberta, so that we can better align ADI's discovery, clinical research and health care delivery research efforts with clinically relevant problems. In addition, ADI will need to be coordinated with the Diabetes, Obesity and Nutrition (DON) Strategic Clinical Network to help identify improvements in healthcare delivery for diabetes patients in Alberta.

Finally, we are also looking to improve our marketing and communication efforts so that we can better tell the story of what we do and why it's important. Through social media, we plan to increase our community outreach and build relationships with clinics and Primary Care Networks in the Province to increase awareness about clinical research opportunities for diabetes patients. Our ADI website will be redesigned to make it more interactive, so that people can access everything

from virtual tours of our facility to personal experiences of people whose lives or careers have been influenced by the ADI.

*Vince Rogers,
Director of Operations, ADI*

THE FACILITIES

The Alberta Diabetes Institute (ADI) is housed in over 9000 square meters of space found within the Li Ka Shing Centre for Health Research Innovation, located on the North Campus of the University of Alberta. Construction of this impressive seven-floor structure was completed in 2007, and it is now the largest freestanding diabetes research institute in Canada, with leading diabetes clinicians and researchers working together under one roof.

The ADI was designed with a clear vision in mind: a bench-to-bedside-to-community approach to diabetes research. In addition to providing space for core services, the facility offers wet lab space to support discovery research, clinical research facilities, and dry lab space for community health researchers.

Not only does the ADI enable translational research, it also provides young scientists with an optimal training environment. By bringing together peers and mentors from multiple disciplines and providing direct access to equipment and technical expertise, scientists are well supported to conduct cutting edge research. The ADI is one of the world's most comprehensive and integrated research facilities dedicated to translating discovery research into practical health solutions for diabetes patients.

Clinical Research Unit (CRU) –

The Clinical Research Unit (CRU) is connected to the University of Alberta Hospital to ensure easy clinician and patient access and efficient biospecimen delivery. The unit features five private clinical exam rooms, a day-ward and a secure pharmaceutical storage facility. Drawing on 17 years of clinical research experience, LeeAnn Langkaas, LPN, CCRP, manages the CRU and provides efficient coordination between sponsors, clinicians and her clinical team.

Details about ongoing trials at the CRU and the facility can be found on ADI's website: www.adi.ualberta.ca/ClinicalResearchUnit/ClinicalTrials.aspx

Human Nutrition Research Unit (HNRU) –

In keeping with the ADI's multidisciplinary approach, the HNRU subunit within the CRU is equipped to offer controlled dietary studies, body composition analysis and metabolic testing. Featured amenities include spacious food preparation and group dining areas, dual energy x-ray absorptiometry, air displacement plethysmography (BodPod®, PeaPod®) and a state-of-the-art whole body calorimetry unit—the only one of its kind in Western Canada. When combined with PADL (see p.25), clinical research at ADI allows for biomedical, dietary and physical activity intervention and

the study of multiple influences and risk factors pertinent to preventing and managing diabetes. In 2013, the HNRU was pleased to welcome Stephanie Ramage (MSc, RD) as the new HNRU Coordinator. Additional information about clinical trials and the HNRU itself can be found online: www.adi.ualberta.ca/ClinicalResearchUnit/ClinicalTrials.aspx

Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD) –

ACHORD has been recognized at both the national and international levels for its investigation into the economic, health service and humanistic factors related to health outcomes in diabetes care. The goal of this alliance is to shape evidence-based health policies throughout the province that will lead to better management of this disease and improve patients' quality of life. ACHORD Chair, Dr. Jeff Johnson, heads a team comprised of five principal investigators, 19 post-doctoral and graduate trainees, and 13 researchers, who work out of the dry lab located on the second floor of the Li Ka Shing Centre. ACHORD led numerous studies during 2012–13, primarily focusing on post-market drug and medical device safety/efficacy, mental health issues among diabetes patients, and numerous primary health care initiatives that were part of the



Alberta's Caring for Diabetes (ABCD) and Quality Improvement projects. More information about ACHORD can be found online: www.achord.ca.

Physical Activity Diabetes Laboratory (PADL) – Physical activity plays a key role in the prevention and management of diabetes, and ADI's Physical Activity Diabetes Laboratory (PADL) provides the opportunity to study the impact of exercise intervention on glycemic control—with or without medications. This unique facility combines a fully equipped gym with an exercise physiology assessment laboratory. Since opening its doors in 2012, PADL has grown at a rapid pace and, in 2013, PADL Director Dr. Normand Boulé was joined by two exercise physiologists, Drs. Margie Davenport and Craig Steinback. Together with six

post-doctoral and graduate trainees, they form a dynamic team dedicated to optimizing the combination of exercise, meal planning and medication for diabetes patients. Following his recent retirement, the ADI wishes to thank Dr. Gordon Bell for his role in establishing the PADL—his contributions have been immeasurable and he will be dearly missed. Visit the PADL website for additional information: www.physedandrec.ualberta.ca/Research/LaboratoriesandResearchWorksho/PhysicalActivityandDiabetesLaboratory.aspx

Alberta Cell Therapy Manufacturing (ACTM) – As ADI researchers and other groups develop new cell and tissue therapies for diabetes and other diseases, Alberta Cell Therapy Manufacturing (ACTM) will be ready with the facilities needed to

translate these technologies to clinical application. This \$26-million dollar facility will be the first of its kind in Western Canada, and is yet another example of the ADI's commitment to translating science into viable health solutions. Led by ACTM Director, Dr. Greg Korbitt, Project Manager, Gayle Piat, and Quality Assurance Manager, Dr. Janna Kozuska, design and construction of this facility will be completed in 2014. ACTM will provide services and training for non-regulatory and regulatory preclinical product development under Good Laboratory Practices (GLP), as well the production of live, therapeutic cells and tissues in support of clinical trials under Good Manufacturing Practice (GMP) guidelines. The facility design includes segregated clean rooms and equipment that will

THE FACILITIES



allow for simultaneous production of six different products, including the production of transplantable cells and tissues from non-human sources under GMP. Additional information regarding the ACTM and its capabilities can be found online: www.actm.ualberta.ca.

ADI Cores – The ADI maintains a number of core services that provide investigators and trainees with direct access to extensive equipment and expertise for conducting research. These include:

- Histology (HistoCore) – Provides paraffin processing and staining of tissues for histopathology, cryosectioning, as well as protocol development and services for immunohistochemistry and immunofluorescence. Histologist Lynette Elder, who is accredited

with the College of Medical Laboratory Technologists of Alberta, manages HistoCore.

- Molecular Biology (MBioCore) – Enables availability of equipment and training for the synthesis and analysis of nucleic acids, peptides and proteins. Core Manager, Dr. Kuni Suzuki, provides expert technical assistance for plasmid DNA preparation and adenoviral gene delivery.
- Immunology (ImmunoCore) – Services include cell sorting, flow cytometry, and T-lymphocyte killing, as well as maintenance of an antibody biobar.
- Human Research Islets (IsletCore) – Established through a joint investment between the Alberta

Diabetes Foundation and the University of Alberta, IsletCore is a state-of-the-art human islet isolation facility that processes donor pancreases not suited for transplantation, making islets available to researchers across Canada and internationally.

- Cell Imaging (Administered by the Faculty of Medicine and Dentistry) – Offers a comprehensive array of equipment and services related to the imaging and analysis of live or fixed cells and tissues, with technical assistance provided by Dr. Greg Plummer.



I STAND HERE AS A TESTAMENT THAT
DIABETES RESEARCH IN EDMONTON
REALLY DOES WORK,” SAID BOB TESKEY,
MEMBER OF THE BOARD OF THE ALBERTA
DIABETES FOUNDATION AND PATIENT
NUMBER FOUR OF THE EDMONTON
PROTOCOL, THE BREAKTHROUGH ISLET
CELL TRANSPLANTATION TREATMENT
DEVELOPED BY U OF A RESEARCHERS.

– BOB TESKEY

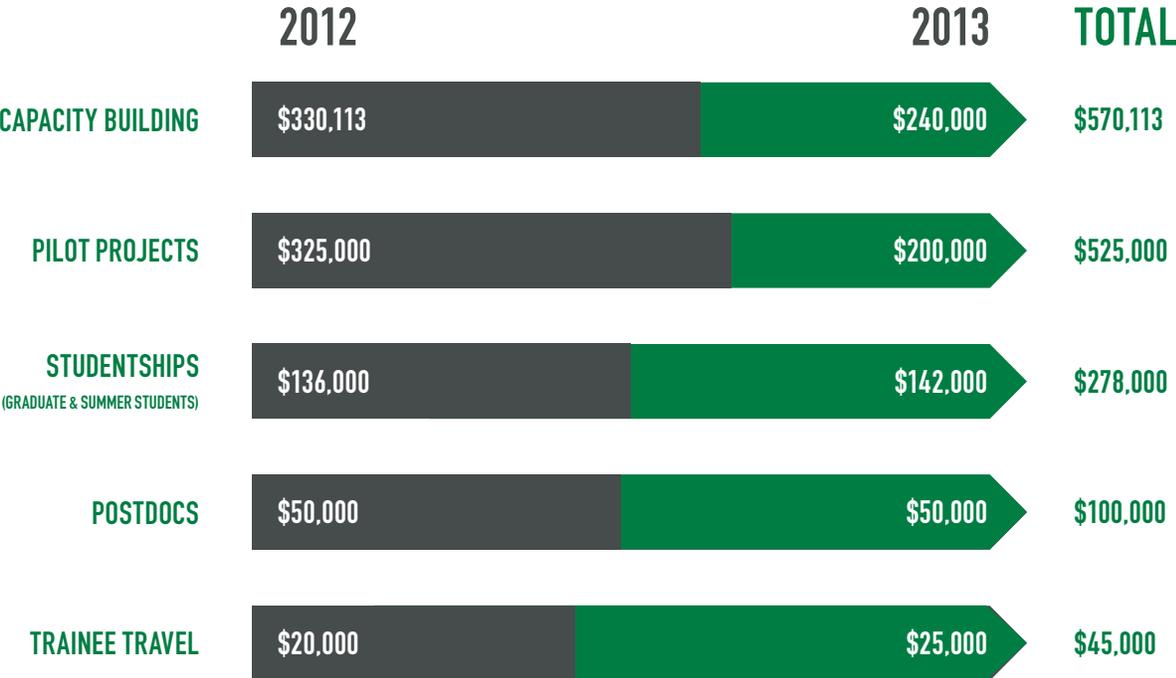
RECIPIENT OF ISLET TRANSPLANTATION BASED ON THE EDMONTON PROTOCOL

DONATIONS

The Alberta Diabetes Foundation works in tandem with the world class Alberta Diabetes Institute to allocate funding where and when it is needed most. This ensures important diabetes research and projects are not stalled. The Alberta Diabetes Foundation is able to fund projects, even at an early stage, and therefore fill the gaps left by traditional granting organizations. In doing this, the Foundation is better able to meet the needs of the diabetes research community.



THESE EFFORTS ALLOW US TO PROVIDE THE FOLLOWING:



Funding also comes directly to the Alberta Diabetes Institute from families and other groups. Because of their outstanding generosity, we are able to provide the following:

1. UNIVERSITY HOSPITAL FOUNDATION

The C.F. "Curly" and Gladys B. MacLachlan Fund for Islet Molecular Biology and Islet Transplantation in Support of Diabetes Mellitus Research and the Paddy and Ken Webb and Family Fund in support of Diabetes Mellitus Research. This is a competition open to scientists in the ADI and will be used for research in islet transplantation / beta cell replacement therapies aimed at finding a cure.

2. THE GLADYS WOODROW WIRTANEN STUDENTSHIPS

Funded through a commitment of \$1,000,000 comprised of \$900,000 to be endowed and \$100,000 to initiate the studentship program.

3. THE EDMONTON CIVIC EMPLOYEES CHARITABLE ASSISTANCE FUND

These funds are to be specifically used to support islet transplantation research in the ADI in the form of pilot operating grant(s) or equipment.

4. BLANCH GRADUATE AWARD

The \$7500 annual award is funded by Morley and Val Blanch and is offered to a graduate student who is studying and researching diabetes in a registered full time master's or doctoral program.

5. TRANSAMERICA

This annual award of \$25,000 is to be used to support islet signaling and biology research.

6. MERCK

Provides approximately \$2,500 in sponsorship for ADI Research Day. They also provide \$7,500 to sponsor the ADI RIP seminar series.

7. BOEHRINGER INGELHEIM / ELI LILLY

Provides funding for the ADI Research Day keynote speaker.

8. MUTTART DIABETES RESEARCH AND TRAINING CENTRE (MDRTC)

MDRTC will fund two studentships for a total amount of \$50,000 per annum.

EVENTS

ADI RESEARCH DAYS

ADI's Annual Research Day is held each fall at the Li Ka Shing Centre and provides trainees the opportunity to present their ongoing research in either speaker symposiums or poster sessions. Research Day is a popular event that showcases the talent, scope and collaboration of the ADI members and trainees and the immense impact research is making in diabetes. The ADI graciously acknowledges Eli Lilly Canada and Merck Canada for their sponsorship of ADI's Annual Research Day in 2012 and 2013.



2012

Keynote Speaker

Dr. Tony K.T. Lam

Associate Director of the University of Toronto Banting and Best Diabetes Centre

Title of talk

"Nutrient sensing in the gut and its relevance in bariatric surgery."

Tony K.T. Lam, Ph.D. holds the John Kitson McIvor (1915-1942) Endowed Chair in Diabetes Research and the Canada Research Chair in Obesity. He is Associate Director of the University of Toronto Banting and Best Diabetes Centre and Associate Professor of Physiology and Medicine at the University of Toronto.

STUDENT AWARD WINNERS 2012

Full Oral Presentation

Nermeen Youssef

"Plasma membrane KATP channels couple cellular stress to metabolism through AMPK signaling."

Mini Oral Presentation

Isabelle Colmers

"Evidence of detection bias and overestimated risk of bladder cancer in Type 2 diabetes."

Senior Poster

Eva Yu

"Activation and sensitization of the vanilloid receptor by ccyl CoAs: potential role in dietary control of glucose metabolism."

Junior Poster

Kaiyuan Yang

"Effects of proanthocyanidins and anthocyanidins on glucose homeostasis."

Trainee Choice Award

Nermeen Youssef

"Plasma membrane KATP channels couple cellular stress to metabolism through AMPK signaling."

EVENTS

32



2013

Keynote Speaker

Dr. André Carpentier

CIHR-GSK Chair in Diabetes, Université de Sherbrooke.

Title of talk

“Dysfunction of white and brown adipose tissues in Type 2 diabetes.”

Dr. Carpentier is the recipient of the CIHR-GSK Chair in Diabetes and professor and clinician-scientist in the departments of Medicine, Faculty of Medicine at the Université de Sherbrooke and the Centre de recherche clinique Étienne-Le Bel. He is also the director of the university’s Diabetes, Obesity and Cardiovascular Complications Research Centre and the director of the new Cardiometabolic Health, Diabetes and Obesity Research Network of the province of Quebec.

STUDENT AWARD WINNERS 2013

Full Oral Presentation

Miranda Sung

"Resveratrol treatment improves survival and whole-body metabolism of mice in heart failure."

Mini Oral Presentation

Anne-Francoise Close

"The nuclear receptor Nor1 / Nr4a3, a novel regulator of beta-cell mass."

Senior Poster

Beshay Zordoky

"Normoglycemia sensitizes MDA-MB-231 breast cancer cells to the anti-proliferative effect of metformin."

Junior Poster

Stuart Astbury

"A high fructose diet during pregnancy significantly affects intestinal development in the offspring."

Trainee Choice Award

Miranda Sung

"Resveratrol treatment improves survival and whole-body metabolism of mice in heart failure."

EVENTS



INAUGURAL A-BC ISLET WORKSHOP

February 11-15, 2012 *Silver Star Resort, BC*

The Alberta Diabetes Foundation provided partial funding to help Alberta Diabetes Institute co-host a joint Alberta-British Columbia retreat in February that brought together top islet researchers in the two provinces. Two world-class diabetes genetics researchers, Drs. Anna Gloyn and Mark McCarthy, from the University of Oxford, were keynote speakers. Research in key areas such as insulin secretion, cellular signaling, stem cell development, genetics

and transplantation/immunology were presented and discussed. This forum allowed for researchers to exchange information and promoted collaborations. Additional sponsorships were secured from Eli Lilly, Merck and CDA, each sponsoring the meeting for \$5,000.

Overall, it was an immense success with more than 60 diabetes researchers from Alberta and British Columbia attending the workshop.



SECOND ANNUAL A-BC ISLET WORKSHOP

February 11-15, 2013 *Silver Star Resort, BC*

The second annual A-BC Islet Workshop was held in Silver Star, British Columbia with the goal of using the scientific, social and chairlift interactions to build new relationships and collaborations between Alberta and British Columbia islet researchers. Several new young investigators joined the program, including the first attendees from Calgary. Two beta cell biologists, Dr. Lydia Aguilar Bryan from Seattle and Dr. Rob Screaton from Ottawa, attended the workshop.

Dr. Bryan's cloning of the beta cell sulfonylurea receptor led to the identification of a number of genetic causes of diabetes and hyperinsulinemic hypoglycemia. She is a world leader in genetic and functional studies of the ion channels in the beta cell who gave an impressive keynote lecture on "ionic regulation of insulin release." Dr. Screaton also gave an exceptional keynote lecture entitled "Can we build a better beta cell?" He brought his signaling, proteomics and screening

expertise to islet biology. His integral work has uncovered important new beta cell signal transduction pathways. Generous and much needed sponsorships were secured from Servier Research, Novo Nordisk, Bio-Rad, Integrated DNA Technologies, Molecular Devices, Alpco, R&D Systems, Child & Family Research Institute, the University of Alberta and the University of British Columbia. Thank you for your support.



DR. MATTHIAS BRAUN

{ 1966 – 2013 }

Dr. Matthias Braun passed away unexpectedly on November 16th, 2013 at the young age of 47. He was an assistant professor in Pharmacology and a valued member of the Alberta Diabetes Institute since 2011.

Dr. Braun completed his medical training (MD) in Bonn, Germany in 1993. Following this was a period of in-hospital military service, during which he interned in neurology. Matthias, who gravitated towards math, physics and engineering, found his particular calling in biomedical research. In 2000, he completed his PhD with Professor Frank Thevenod in the Department of Physiology at Saarland University. His dissertation focused on the molecular regulation of potassium conductance in zymogen granules of the exocrine pancreas. This was awarded the Calogero-Pagliarello prize for best medical thesis at Saarland University.

In 2000, Dr. Braun joined the group of Professor Patrik Rorsman in Lund, Sweden as postdoctoral fellow. His work there established important mechanisms underlying autocrine and paracrine communication between pancreatic islet cells, particularly the control and function of intra-islet GABA signaling. While in Sweden, Matthias held fellowships from the European Union and the Juvenile Diabetes Research Foundation, and was awarded the 'Research Prize for Young Scientists' from Lund University.

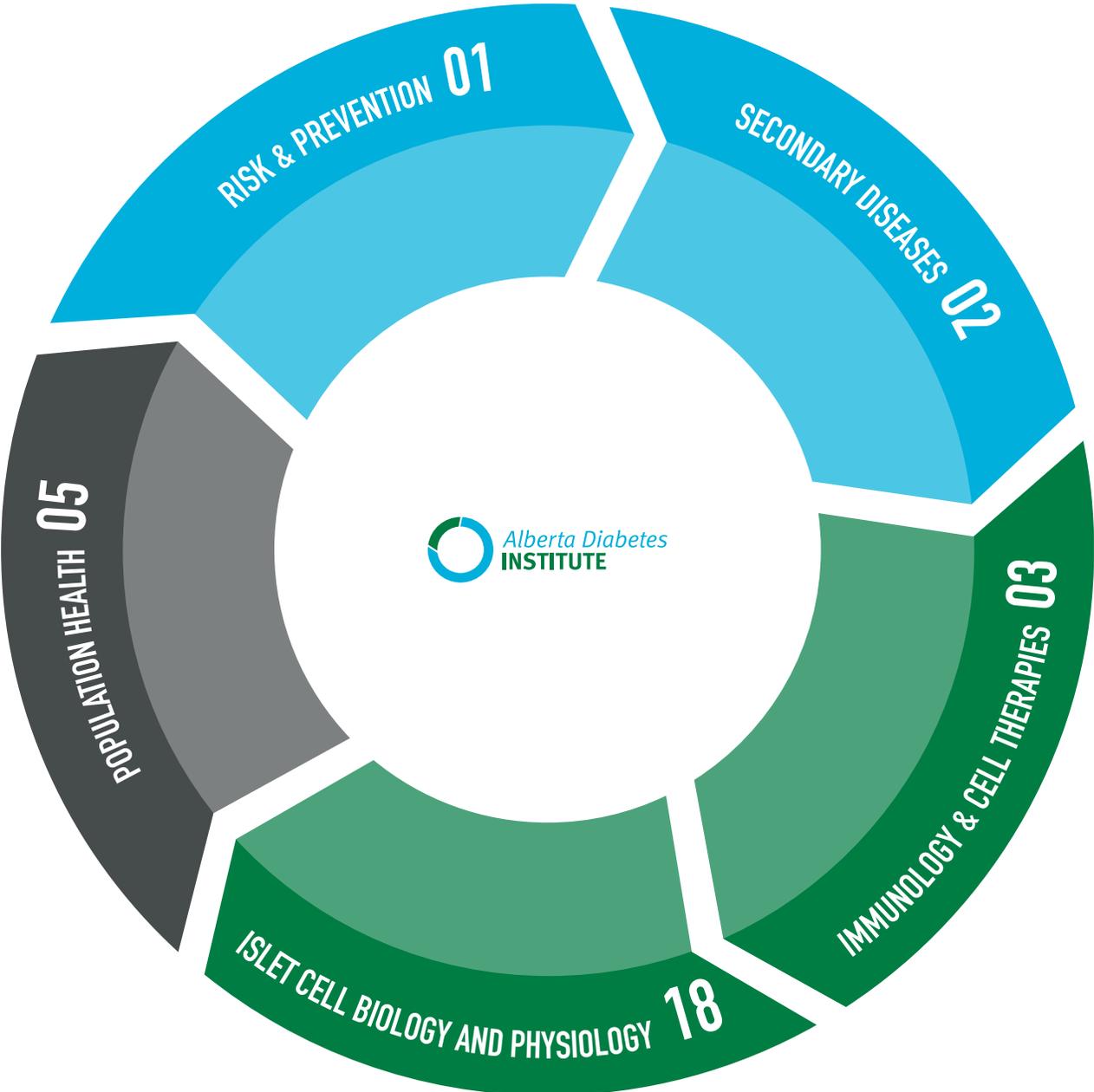
In 2005 several members of the Lund group moved to Oxford, where Dr. Braun held a research associate position at the Oxford Centre for Diabetes, Endocrinology and Metabolism. This was an especially productive time for Matthias' research, where

he developed an interest in understanding the mechanistic differences in islet function between humans and rodents. Several key publications from his work in Oxford established the basic ionic and exocytotic mechanisms of hormone release and cell-to-cell communication in human islets. Dr. Braun had a meticulous approach to science and received an Exceptional Merit award from the University of Oxford for his work there.

Dr. Braun was recruited to the Department of Pharmacology here at the University of Alberta as assistant professor and Alberta Diabetes Institute member. Matthias obtained funding to build his lab from the Canada Foundation for Innovation. His research in the field of diabetes and pancreatic islet biology is well known and highly respected. He had an active research program with Canadian Foundation for Innovation and Canadian Institutes of Health Research funding, and supervised two graduate students, Shara Khan and Richard Yan-Do, as well as research associate, Dr. Xichen Wu. His commitment and the progress of the undergraduate and graduate students who worked in Matthias' lab are a testament to Matthias' outstanding ability as a mentor, his patience, and his unique ability to lead with a quiet confidence and strong principles. He enjoyed playing frisbee, going to football games and particularly appreciated nature in western Canada, making many trips to the mountains and west coast, and running in the North Saskatchewan River valley.

Dr. Matthias Braun is survived by his parents Hans-Gunther and Christa, sister Bettina and her husband Andre Strecker, and twin nieces Anika and Ricarda.

FIVE AREAS OF RESEARCH



RESEARCH HIGHLIGHTS

RISK & PREVENTION

The factors influencing the onset of diabetes vary greatly, from our genetic makeup to body composition to our lifestyle choices. Identifying these factors not only brings to light the risks associated with developing diabetes, it also guides our scientists towards the development of treatment and prevention strategies that can be moved to patient application. This area of research encompasses a broad range of disciplines that are part of the integrated makeup of the ADI and have made significant contributions during 2012-2013:

Obesity – There’s no overlooking the link between excess weight and diabetes: Type 2 diabetes accounts for 90% of all cases of diabetes and of these 90% are obese—technically a Body Mass Index (BMI) greater than 30 kg/m². Obesity is a global problem and is rising at an alarming rate, particularly amongst children. Besides diabetes, there are a myriad of other complications associated with obesity such as cardiovascular disease and a variety of cancers.

Drs. Arya Sharma, Raj Padwal and Sumit Majumdar are hands-down leaders in researching health care delivery in Canada that is aimed at treating and preventing obesity. Along

with collaborating scientists they have made significant inroads during 2012-2013 into the root causes of social, economic and mental health issues that influence behaviours leading to obesity. Dr. Sharma is the founder of the Canadian Obesity Network, the country’s top resource for information exchange and knowledge transfer for weight-related health issues. This includes the *5 A’s of Obesity Management*, a set of practical tools to guide primary care practitioners in obesity counselling and management. The group has led a number of important clinical trials over the past two years that have helped establish evidence-based practices regarding bariatric surgeries and patient prioritization that has been adopted by Alberta Health Services. Included is an advanced scoring system for predicting mortality and surgical urgency that goes beyond a simple BMI calculation: the Edmonton Obesity Staging System. ADI Member **Dr. Geoff Ball** has developed similar findings in a study that looked at 181 obese children aged 8-17 between 2005 and 2010, discovering one third were not at risk of developing insulin resistance, high blood pressure, high cholesterol or other obesity-related symptoms. “Someone with Type 2 diabetes could have less body fat than somebody who has quite a bit more body

fat and doesn’t have Type 2 diabetes. There is considerable variability between individuals.” Analysis of the study data was completed in 2013 (*Diabetes Care*, 2014, 37:1462-8) while Dr. Ball and his research partners have already begun a comprehensive, health outcomes study encompassing 1,600 children nationwide.

Meal Planning – Nutrition-based research in diabetes has always been a pillar of strength at the ADI and 2012-2013 was no exception. In 2013 the *Pure Prairie Eating Plan*, a book inspired by the much-touted Mediterranean diet, was launched by authors **Dr. Rhonda Bell** and **Dr. Cathy Chan**. While the latter emphasises foods such as olive oil and fish that are linked with lower rates of heart disease and other ailments including diabetes, the eating plan relies on foods that provide similar benefits but are more available locally. The eating plan was utilized in a pilot study funded by the ADI and involved diabetes patients who followed the meal guide for three months and experienced significantly better glucose control, lipid profiles and even waist measurements (*Canadian Journal of Diabetes*, 2014, 38:320-5). The authors hope to follow up with prairie meal-planning guides for special groups such as Asian-Albertans and Aboriginals that are prone to Type 2 diabetes.

RESEARCH HIGHLIGHTS

Physical Activity – ADI's Physical Activity Diabetes Laboratory (PADL) has been a highly active facility since officially opening in June of 2013. While past research in this area has established the general benefits of exercise for preventing and managing type 2 diabetes, **Drs. Normand Boulé, Margie Davenport** and other investigators in PADL are expanding the understanding of these benefits. In addition to examining the effects of different types, durations or intensities of exercise, they are also focusing on matching exercise regimes to improved health outcomes. A series of studies have examined the interplay between metformin and exercise, which has provided preliminary information about the effectiveness of exercise on improving metformin monotherapy (*Diabetologia*, 2013, 56:2378-82; *Can J Diabetes*, 2013, 37:375-80). Researchers within PADL are also investigating the impact of pre and postnatal physical (in)activity on women at high risk for developing type 2 diabetes (e.g., gestational diabetes, obesity, preeclampsia) on maternal/fetal health outcomes including metabolic status and cardiovascular function (*Am J Physiol*, 2012, 15:R768-75; *Obstet Gynecol*, 2013, 122:255-61).

Metabolism – The ADI's clinical research unit is now home to one of Canada's only, fully-validated and operational whole-body calorimetry units for studying caloric output and energy metabolism, thanks to the efforts of **Dr. Linda MacCargar** and her research team during the past two years. This state of the art facility houses subjects for 12-48 hours and has been used extensively by their research team to study energy patterns during sleep/wake cycles and in response to meals and exercise. This has led to a greater understanding of respiratory quotients, a ratio of glucose to fatty acid oxidation that is related to diabetes and other complications when too high or low. While Linda will be missed following her retirement in 2014, the ADI is excited to welcome Campus Alberta Innovative Program (CAIP) Chair Dr. Carla Prado, to carry on this exciting research at the Institute.

Intestinal Lipid Absorption – Type 2 diabetes sufferers often have dysfunctional cholesterol, triglyceride, fatty acid and other lipid metabolic profiles that contribute to secondary complications like atherosclerosis. **Dr. Donna Vine** and her research team are contributing to the understanding of the link between intestinal lipid absorption and metabolism in

relationship to cardiovascular disease, metabolic syndrome, polycystic ovarian syndrome (PCOS) and pre-diabetes. Emerging evidence suggests the intestine contributes significantly to whole-body cholesterol and triglyceride metabolism, yet there remains a lack of knowledge regarding the regulation of intestinal lipid absorption and transport of dietary lipids to the circulation via intestinal lipoproteins (chylomicrons). Dr. Vine and her team have been one of the first to contribute to the study of the effect of dietary fats on lipid transport and metabolism pathways in these disease states and they continue to research the basic physiological processes involved. Most recently they have begun to explore dietary improvements and pharmaceutical interventions to understand the etiology of the metabolic complications of PCOS in animal models (*J Am Heart Assoc*, 2012, Oct;1(5):e003434).

Trans Fats – In other lipid research, **Dr. Spencer Proctor** has been changing the way we look at trans-fatty acids, which have traditionally been linked with detrimental health effects. Research in Dr. Spencer's lab during 2012-2013 has demonstrated that a distinction needs to be drawn between naturally-occurring trans-fats and 'industrial' ones produced through hydrogenation.



ONE OF THE MAIN REASONS THAT CATHERINE CHAN AND RHONDA BELL'S WONDERFUL "PURE PRAIRIE EATING PLAN" IS SUCH A REVELATION IS THAT IT IS BUILT AROUND HOW WE ACTUALLY EAT. IT ISN'T A GIMMICK. IT IS REAL, SCIENCE INFORMED, DIET ADVICE THAT IS BOTH EASY AND FUN TO FOLLOW. BEST OF ALL, THE RECIPES ARE TERRIFIC!

DR. TIMOTHY CAULFIELD IS CANADA RESEARCH CHAIR IN HEALTH, LAW AND POLICY AT THE UNIVERSITY OF ALBERTA AND AUTHOR OF *THE CURE FOR EVERYTHING: UNTANGLING THE TWISTED MESSAGES ABOUT HEALTH, FITNESS AND HAPPINESS*. HE IS ALSO AN ADI MEMBER

- DR. TIM CAULFIELD

REGARDING THE PURE PRAIRIE EATING PLAN

RESEARCH HIGHLIGHTS

Research in particular has focussed on vaccenic fatty acids, the most prominent, ruminant-derived trans-fatty acid in our diets. The outcome of this research has major implications to health policy and food labels, attracting the attention of Health Canada and other international stakeholders. Dr. Spencer and his team are leading the generation of knowledge about vaccenic acids (VAs) and how they have health-promoting properties similar to polyunsaturated fatty acids with regards to lowering harmful lipids like triglycerides in the blood. Studies continue to confirm the effects of VA in preclinical models (*British Journal of Nutrition*, 2013, 18:1-15) with the intent of initiating clinical trials in the near future.

Lipases – Elevated plasma concentrations of triacylglycerol (TG), whether during fasting or after meals, are associated with the risk of cardiovascular disease, obesity and insulin resistance. The absorption of dietary TG into the bloodstream is a multi-step process that begins with the action of lipases in the gut and ends with the secretion of TG-rich lipoproteins. During the past several years **Dr. Richard Lehner's** team has studied the role of lipases termed Carboxylesterase 1/Esterase-x (Ces1/Es-x) and Carboxylesterase 3/triacylglycerol hydrolase (Ces3/TGH) in TG metabolism. By generating Ces1/Es-x deficient mice

the team was able to demonstrate that mice lacking this enzyme that were fed high-carbohydrate diet with low fat content exhibited increased TG synthesis and secretion of TG-rich lipoproteins, became obese, hyperlipidemic and insulin resistant. Therefore, the role of Ces1/Es-x is to diminish lipid synthesis and secretion (*Hepatology* 2012; *PLoS One* 2012). On the other hand, mice lacking Ces3/TGH had decreased TG-rich lipoprotein secretion, decreased lipogenesis, improved insulin sensitivity and glucose metabolism on low-fat but high-carbohydrate diet. Therefore Ces3/TGH promotes lipid synthesis and secretion and activation of Ces3/TGH negatively influences glucose metabolism (*Cell Metabolism* 2010; *Hepatology* 2012). Results from this research opens up exciting possibilities for pharmaceutical targeting that either boosts Ces1/Es-x activity or decreases Ces3/TGH activity to alleviate hyperlipidemia and insulin resistance.

Choline – **Dr. Dennis Vance** continues his research in the area of phosphatidylcholine (PC) regulation and biosynthesis in mammalian cells and the function of PC synthesis in diabetes and other diseases. By utilizing phosphatidylethanolamine-N-methyltransferase (PEMT) knockout models that lack this liver enzyme

necessary to produce PC, **Dr. Vance**, fellow ADI Member **Dr. Rene Jacobs** and others are seeking to explain why PEMT knockout mice are protected from diet-induced obesity, insulin resistance, and atherosclerosis. The data from these studies are the first to link de novo choline synthesis to altered whole-body energy metabolism and strongly suggests that PEMT is a potential pharmaceutical target to treat disorders related to the metabolic syndrome (*Diabetes*, 2014, 63:2620-2630; *J Biol Chem*, 2013, 288:837-47).

Pregnancy Outcomes – ADI Member **Dr. Catherine Field** is a co-leader, along with **Drs. Noreen Willows** and **Rhonda Bell**, on *Alberta Pregnancy Outcomes and Nutrition (APrON)*, a study that involves thousands of women from Calgary and Edmonton and is designed to analyze the relationship between maternal nutrient status during pregnancy and maternal mental health and child health and development. The study continues to follow the infants through to 36 months of age. The primary aims of the APrON study are to determine the relationships between maternal nutrient intake and status, before, during and after gestation, and: 1) maternal mood; 2) birth and obstetric outcomes; and 3) infant neurodevelopment. Of obvious



importance to the health outcomes of mom and baby are gestational diabetes and post-partum diabetes in both the mother and offspring. Preliminary results of some parameters were published in *BMC Pediatrics* in 2013 (13:77).

TrialNet – During 2012-2013 ADI Member **Dr. Bob Couch** continued his participation in TrialNet, a global research initiative aimed at screening and monitoring individuals considered high risk for the development of Type 1 diabetes (T1D), or for treating patients that are newly diagnosed with the disease. Screening in patients involves measuring blood-borne auto-antibodies and HbA1c levels that are predictive of developing T1D. High-risk individuals are then closely monitored for evidence of poor blood glucose control through oral glucose tolerance testing, and those

exhibiting early onset diabetes can enroll in experimental treatment studies designed to preserve islet cell function and insulin production/secretion through early intervention. This international collaboration includes 150 clinical research centers in 18 countries, including Canada. The success of the program is documented in numerous publications cited on TrialNet's website (<https://www.diabetestrialnet.org/publications/publications.htm>), reflecting the importance of early intervention and the increasing capacity to slow the progression of T1D. Dr. Couch says, "The only thing limiting greater success of TrialNet is awareness of the program and increased participation."

Vitamin D – There has been a long-standing debate regarding the correlation between vitamin D and a number of

different health benefits that include diabetes. **Dr. Diana Mager's** research during 2012-2013 has focused on vitamin D uptake and its interrelationships with bone health, quality of life, and glycemic control in adults that suffer from both diabetes and chronic kidney disease. Dr. Mager and co-investigators **Dr. Peter Senior** and **Dr. Jindal Kailash** have been following a cohort of adults with diabetes who received vitamin D to study the effects of longitudinal supplementation on these factors, as well as the relative effects of daily versus monthly dosing on vitamin D status and markers of health. Results from these studies will have important implications for developing health guidelines and policies related to vitamin D supplementation in diabetes patients (*BMC Endocr Disord*, 2014, Aug 12;14:66. doi: 10.1186/1472-6823-14-66).

RESEARCH HIGHLIGHTS

Essential Fatty Acids – Studies conducted during the past decade have not produced consistent results regarding the importance of a diet high in essential fatty acids, or the role these components play in preventing and reducing inflammation. This has led to mixed messaging in nutritional guidelines that has been the focus of research by ADI Investigators. **Dr. Tom Clandinin's** research has established the role of dietary fats in the progression and prevention of chronic disease, including obesity, Type 2 diabetes, and cardiovascular disease, through the modulation of hormone and immune function at the synaptosomal level (*Adv Nutr*, 2012 3:60-8). Meanwhile **Dr. Vera Mazurak** has studied aberrations in lipid metabolism in metabolic syndrome, and how inflammatory mediators impact the ability to metabolize essential fatty acids (*Lipids*, 2013, 48:319-32). Together their work is helping to solidify the protective role played by dietary essential fatty acids in both healthy and disease states.

Prader Willi Syndrome (PWS) – PWS is a rare genetic disorder that affects between 1 in 10,000 and 1 in 25,000 newborns. In addition to physical and developmental effects, a hallmark of PWS is a chronic state of hunger that often leads to severe obesity. Unlike in most obese states, the obesity in PWS patients is often associated with a preservation

of insulin sensitivity and increased levels of adiponectin (a hormone linked to insulin sensitivity) and ghrelin (a food stimulating hormone). **Dr. Andrea Haqq** is studying why obese PWS patients seem to be afforded this protection. Preliminary studies suggest that the preservation of insulin sensitivity might be explained by differences in the autonomic nervous system and a differential fat distribution in PWS, characterized by less visceral fat accumulation compared with other obese subjects. Ongoing studies of the developmental changes in hormonal and metabolic regulation and fat distribution in PWS and non-syndromic obesity may shed new light on the pathogenesis of insulin resistance and life-threatening metabolic complications of obesity. Fellow ADI Member **Dr. Rachel Wevrick** has contributed greatly to the co-discovery of many of the genes inactivated in Prader-Willi syndrome, including *Necdin*, *MAGEL2*, and *IPW*. Her research during 2012-13 further clarified the genetic basis for developmental delay and obesity, and helped establish better animal models for studying PWS in humans (*Am. J. Med. Genetics A*, 158A: 966-9668).

Intelligent Diabetes Management – While insulin therapy is a life-saving measure for Type 1 diabetes patients, maintaining blood glucose within normal ranges is a challenge. Decisions about

how much insulin should be administered must take into account food consumption, proposed activity, background glucose and the previous responses to insulin. Continual refinement and personalization of insulin therapy to achieve better glycemic control requires repeated visits between patient and clinic to review all factors involved, but a far better scenario would be for the individual patient to have this decision-making capability at their fingertips. ADI member **Dr. Eddie Ryan** and Dr. Russ Greiner (Dept. of Computing Science) have led the Intelligent Diabetes Management project over the past couple years that began with the collection of nutrition, physical activity, lifestyle and insulin therapy information along with glucose readings from numerous Type 1 diabetes patients. By combining clinicians with computing science experts, Dr. Ryan is aiming to develop a computer-based algorithm accessible through a mobile application that will allow real-time insulin management. The current personalized tool, Edmonton Automated Sugar Intelligence (EASI) — developed in collaboration with Dr. Eleni Stroulia (Dept. of Computing Science) — is one that receives data and offers advice based on the same principles used by diabetes clinicians and in time will facilitate the machine learning application envisaged. Initial clinical trials involving patients accessing the EASI smart phone app will begin in 2014.



SECONDARY DISEASES

While diabetes on its own is a debilitating disease, numerous health complications can arise over time that affect quality of life and longevity. ADI scientists have made exciting contributions during 2012-2013 in a number of related areas, including:

Cardiovascular

(Heart, Blood Vessels) –

Cardiovascular complications such as stroke and heart failure are the largest cause of mortality among diabetes patients, making this a key area of research for ADI scientists studying diabetes-related diseases. During 2012-2013 **Dr. Gary Lopaschuk** led research that is improving our understanding of changes affecting the ‘energetics’ of the heart. Under normal circumstances, both

glucose and fatty acids are used to fuel the basic functions of the heart. But in many forms of heart disease, almost all of the energy required for heart function is obtained through the metabolism of fatty acids. Interestingly, diabetes patients show the same altered energetics, even prior to developing heart complications. These perturbations in cardiac energy metabolism can both decrease cardiac energy supply and decrease cardiac efficiency—both high risk factors.

Dr. Lopaschuk’s laboratory and others have shown that decreasing fatty acid use by the heart will increase the use of glucose as a source of energy, which then decreases the likelihood of the diabetic developing heart problems. By understanding the key enzymes involved in regulating fatty acid use by the heart, the research team has made inroads during the past two years about how

to manipulate these enzymes through pharmacological intervention and decrease heart problems in the diabetic (*Diabetes*, 2013 (62:711-20).

Dr. Gavin Oudit has extensively researched the role of angiotensin II, the main effector of the renin-angiotensin system and its role in cardiac hypertrophy and energy metabolism—in particular, the critical role played by the enzyme pyruvate dehydrogenase kinase 4 (PDK4) in the development of insulin resistance and metabolic flexibility. Results of their rodent study were published in the *American Journal of Physiology* in 2013 (304:H1103-H1113).

Retinopathy (Eye) – Numerous diseases of the eye are linked with diabetes, particularly retinopathy, posing a risk for blindness and placing a serious burden on health care costs and quality of life.

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The cause of diabetic retinopathy is not well understood, and progress has been hampered by a lack of good research models. During the past two years

Dr. Yves Sauvé has led the development of a novel animal model that optimally resembles the visual loss that occurs in human Type 2 diabetes. "Our lab has shown that vision in the Nile rat closely mimics day vision in humans, unlike vision in common lab rodents that have very poor daylight vision." Another advantage is that this novel animal model spontaneously develops diabetes in captivity when fed standard rodent chow, which is contrary to most rodents and again simulates disease development in human patients (*Invest Ophthalmol Vis Sci*, 2012, 53: E-Abstract 565). Dr. Sauvé's work with Nile rats will provide researchers with an improved model for studying interventions aimed at preventing and treating diabetic retinopathy.

Neuropathy (Nervous System)

– The ADI recently welcomed its newest member, **Dr. Doug Zochodne**, who brings with him an enormously successful discovery and clinical research career in diabetic neuropathy. His research work has focused on the neurobiology of axon regeneration, experimental diabetic neuropathy and clinical neuropathies. His research

team at the ADI will investigate molecules and novel approaches that influence regenerative success and the development of neuropathic pain.

Nephropathy (Kidney) – Advanced diabetic nephropathy is the leading cause of end-stage renal disease worldwide. Between 20% - 40% of patients with diabetes ultimately develop nephropathy, although the reason why not all patients with diabetes develop this complication is unknown. Both hemodynamic and hyperglycemic factors are at play in the disease's etiology, and **Dr. Peter Senior** was part of an expert panel that helped develop clinical practice guidelines for detecting and treating diabetic nephropathy. Included in their recommendations were the inclusions of proteinuria screening in patients with chronic kidney disease (CKD), management of associated cardiovascular risks and the use of medications to disrupt the renin-angiotensin-aldosterone system. The panel's recommendations were published in the *Canadian Journal of Diabetes* in 2013 (37:S129-S136) and are part of the Canadian Diabetes Association's practice guidelines. **Dr. Gavin Oudit** has also made significant contributions towards the interplay of diabetes, CKD and the role of the renin-angiotensin system in the development of insulin resistance.

IMMUNOLOGY & CELL THERAPIES

Immunology and transplantation research at the ADI are intimately linked. Immunology strives to better understand the aspects that make up and control the immune system, and to use this knowledge to develop immune response modulation. The goal is twofold: to overcome autoimmunity, (the underlying cause of Type 1 diabetes), and to induce immunosuppression and tolerance of transplantations of insulin-producing islet cells and the introduction of other cellular therapies.

Immune tolerance – Having a mixture of both donor and recipient hematopoietic stem cells in a transplant recipient—a state referred to as "mixed chimerism"—is known to induce immune tolerance to transplants in multiple species, including humans. However, even in the presence of chimerism, it is possible for certain donor grafts to be rejected despite tolerance to donor blood cells, a phenomenon known as 'split tolerance'. Immunologist **Dr. Colin Anderson** has been working towards a more thorough understanding of the mechanisms of tolerance operating in mixed chimerism with the aim of developing a strategy for clinical application that overcomes split tolerance.



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In 2012, Dr. Anderson and his team published the results of an important study in the *American Journal of Transplantation* (12:3235-45) where they achieved mixed chimerism in a challenging pre-clinical model of Type 1 diabetes—the nonobese diabetic (NOD) mouse. Using a combination of busulfan, non-complete myeloablation and T cell antibodies, they were able to avoid split tolerance in a highly relevant preclinical model. Meanwhile

Dr. Lori West and her research team pursued another approach for immune tolerance that exploits the nature of one type of T cell: regulatory T cells, or Tregs for short. These cells are known to be important components of the immune system for suppressing the immune response, especially after an initial threat has subsided. There is even research showing how Treg therapy can induce tolerance in neonatal porcine islet (NPI) xeno-transplantation in preclinical models, setting the stage for application in humans. Results of their research were presented at the 2013 European Society for Organ Transplantation Symposium.

Xenotransplantation – The Edmonton Protocol was one of the most significant medical advancements in diabetes in the past 50 years and has brought new hope to Type 1 diabetes patients, particularly those with a brittle form of the disease. Despite being the world’s gold standard for

pancreatic islet transplantation, an ongoing limitation of the Protocol is that the supply of pancreatic islets is well short of demand. ADI scientists have been at the forefront of research involving the use of non-human islets for human transplantation, or ‘xenotransplantation’. The use of porcine islets as a viable source of transplantable cells has been studied extensively in order to demonstrate the feasibility of achieving normoglycemia in diabetic preclinical models. **Dr. Greg Korbitt** is the Director of Alberta Cell Therapy Manufacturing, a Good Manufacturing Practice (GMP) compliant facility that will generate a wide range of clinical-grade cell-based therapies ranging from gene targeting, monoclonal antibody production to cell and tissue replacement. Construction of this \$26-million facility, jointly funded by the Canada Foundation for Innovation, the Government of Alberta and the University of Alberta, is nearing completion and will begin operations following validation of the infrastructure. Importantly for xenotransplantation, the facility has a dual capacity for accommodating either human or animal-based manufacturing, setting the stage for clinical trials involving porcine islets in the near future. If successful, xenotransplantation represents a near-limitless supply of insulin-producing islet cells for diabetes patients worldwide. In addition **Dr. Gina Rayat**

has worked closely with collaborators from Revivicor Inc. (Blacksburg, VA, USA) and the Transplantation Institute at the University of Pittsburgh Medical Center to develop neonatal pigs that have been genetically altered to promote immunotolerance and reduce clotting that often impairs islet graft survival following transplantation. In the first phase of this work, investigators produced pigs having three gene modifications: alpha 1,3-galactosyltransferase (α-GAL) knockout, aimed at avoiding the hyperimmune preformed antibody response to this surface protein; overexpression of CD39, a regulatory anti-coagulant protein; and overexpression of CD46, a protein that moderates complement activation. Functionality tests for islets isolated from the transgenic pigs are currently being carried out, and future studies will examine additional genetic modifications that target both humoral and cell-mediated immunotolerance. Results of their current work will be presented at the World Transplant Congress in San Francisco in 2014. **Dr. Ray Rajotte**, ADI’s Founding director, retired in 2012 but continues to collaborate on research projects involving xenotransplantation at the ADI as well as the Surgical-Medical Research Institute.

Transplant Network – In 2013 a collaborative team led by ADI Member **Dr. Lori West** was successful in procuring a \$30-million grant from the Canadian Institutes for Health Research (CIHR) to establish the Canadian National Transplant Research Program (CNTRP), centered at the University of Alberta. The team brings together over 100 investigators from 14 research sites across the country, as well as a host of international collaborators. The initiative is designed to increase donations of tissues and organs and improve the survival and quality of life of Canadians. Included in the scope of this program is the procurement and distribution of pancreases for use in islet transplantation therapies. The program includes six research projects, all of which directly impact the supply and success of organ donations and transplantations. For example, one of these projects aims to improve the maintenance of organs during the interval following harvest and prior to recipient transplantation through the use of ex vivo perfusion of organs at normal body temperature. This offers advantages over the standard procedure of chilling organs on ice, improving their transportability over a vast geographical area like Canada.

Regenerative Medicine – ADI Member **Dr. James Shapiro** received a \$5-million team Collaboration Research and Innovation Opportunities (CRIO) grant from

Alberta Innovates Health Solutions in 2013 that will be used to test new stem cell β -cell regeneration strategies in preclinical and clinical trials for treating Type 1 diabetes patients. One study will involve the use of antibodies to remove T cells from the blood, essentially 'switching off' autoimmunity in newly diagnosed T1D patients. Prior to this treatment, the patients' own stem cells will be temporarily removed and, following treatment, re-injected into the pancreas which, along with administration of the drug liraglutide, is anticipated to greatly enhance new islet growth. These new stem cells (called CD34+) have the ability to repair injured tissue and induce regeneration. The second study will clinically test transplantation of new β -stem cell derived islet cells from a company called ViaCyte. The cells will be transplanted within a special immunoisolation device that prevents cell-to-cell contact (Encaptra). These devices will allow easy retrieval for assessing viability and risk, while also offering a highly vascularized matrix for blood-borne oxygenation and nutrient supply. In preclinical efficacy studies completed in 2013, results showed a reversal of diabetes, setting the stage for these exciting, cutting-edge, first-in-human clinical trials.

ISLET CELL BIOLOGY AND PHYSIOLOGY

At the heart of all forms of diabetes are the insulin-producing islet cells themselves. Understanding the intracellular and extracellular mechanisms influencing the production, secretion and action of insulin from β cells as well as whole body physiology helps our scientists work towards targets for treatment and prevention. ADI scientists are leaders in islet cell biology and physiology and have made significant contributions during 2012-2013:

Protein Modifiers – SUMO stands for Small Ubiquitin-like Modifier, and SUMOylation refers to the process of post-translational modification of proteins that influence various intracellular processes. **Dr. Patrick MacDonald** and his research team have done extensive and novel work in the past several years determining how SUMOylation in beta-cells affects signaling pathways and controls islet function and survival. "We've shown that this pathway acts as an important 'brake' on insulin release and conversely as a positive regulator of the other key islet hormone glucagon" (*Diabetes*, 2011, 60:838-47; *J Physiol.*, 2014, 592:3715-26). Those studies suggest that blocking or limiting SUMOylation in islets could lower

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blood sugar by increasing insulin/ decreasing glucagon. The work also shows an important role for the SUMOylation pathway in islet survival during inflammation (*AJP-Endo Metab*, 2014, online ahead of print). MacDonald's lab has also studied proteins called PI3 kinases and recent research has shown that these protein can act as negative as well as positive regulators of insulin release (*Diabetologia* 2013, 56:1339-49; *J. Biol. Chem.*, 2014, online ahead of print). These studies from the MacDonald lab provide valuable insights that set the stage for targeted therapies in the future.

Potassium Channels – Genetic variations in Type 2 diabetes (T2D) patients and their link to altered signaling pathways have been central to some of the work done in **Dr. Peter Light's** lab. Studies by his research team focus on the ionic events that control insulin secretion through cellular channels and how dysfunction can lead to impaired/incorrect insulin secretion contributing to the development of T2D. The Light team has studied the links between common genetic variations in the ATP-sensitive potassium channel in relation to an increased risk for developing T2D, identifying genetic variant K23/A1369 in the process which codes for increased K_{ATP} channel Mg_{ATPase} activity and decreased insulin secretion. This provides a plausible mechanism for increased

T2D susceptibility in humans that are homozygous for this variant (*Diabetes*, 2012, 61:241-9). A follow-up to this study was research demonstrating that the ring-fused pyrrole moiety in several A-site sulfonylurea or glinide drugs likely underlies the observed inhibitory potency of these agents on K_{ATP} channels containing the K23/A1369 risk haplotype. It may therefore be possible to design novel drugs that display an increased efficacy in T2D patients homozygous for these common variants (*Pharmacogenet Genomics*, 2012, 22:206-14).

Calcium Channels – In many nonexcitable cells like pancreatic beta cells, stimulation with low agonist concentrations specifically activates calcium (Ca^{2+}) entry via arachidonic acid-regulated, highly Ca^{2+} -selective (ARC) channels. Research by **Dr. Amy Tse** and her lab found that arachidonic acid triggered a robust Ca^{2+} rise in β cells via two pathways: extracellular Ca^{2+} entry via the activation of the highly selective Ca^{2+} -permeable ARC channels, and intracellular Ca^{2+} release from an IP_3 -sensitive acidic store which was probably the secretory granules (*Cell Calcium*, 2012, 140-8). These findings raise the possibility that ARC channels and secretory granules are potential targets for anti-diabetic drugs.

Cell Mass Proliferation –

Dr. Jean Buteau joined the ADI in 2012 after a successful career at Laval University and has made significant contributions to our understanding of the factors controlling beta cell mass proliferation. Recent studies on the structural protein β -arrestin have shown these scaffolding proteins act not only as binding sites for glucagon like peptide 1 (GLP-1) receptors, but also as docking sites for the recruitment of c-Src, an important signaling protein, and that it is the tandem of structural and signaling proteins that are needed for the proliferative action of GLP-1 to be complete (*Mol Cell Endocrinol*, 2012, 364:65-70). His recent work has also focused on genetic links to beta cell mass growth, with his team identifying a novel gene called CCN3 that is a target of FoxO1, the important transcriptional factor and mediator of insulin signaling in beta cells. Their work demonstrated that CCN3 is increased with insulin resistance and that it contributes to beta-cell deterioration (*PLoS One*, 2013, DOI:10.1371). Dr. Buteau's work opens up exciting new avenues for therapeutic targeting in the future.

New Insight Into Metformin –

The enzymes acetyl CoA carboxylase 1 and 2 (Acc1, Acc2) catalyze the conversion of acetyl-CoA to malonyl-CoA, which is the precursor for fatty acid (FA) synthesis and an allosteric inhibitor of FA transport into



RESEARCH HIGHLIGHTS

mitochondria for oxidation. ACC activity can be regulated via inhibitory phosphorylation by a key metabolic enzyme called AMP—activated protein kinase (AMPK). While regulation of Acc1 and Acc2 is an apparent key step in lipid homeostasis, studies have yielded conflicting results regarding the role these enzymes play with regards to overall lipid metabolism. A collaborative team involving ADI Member **Dr. Jason Dyck** carried out an intricate study aimed at clarifying this role, using ACC double knock-in (DNI) mice that maintained ACC functionality but prevented site-specific AMPK phosphorylation and subsequent inhibition of these two enzymes. What they found was that removing the ability to inhibit these enzymes reduced FA oxidation and increased lipogenesis, contributing to insulin resistance, non-alcoholic fatty liver disease and glucose intolerance. Their data also provided evidence that, similar to AccDNI mice, metformin treatment reduces hepatic lipogenesis and lipid accumulation by activation of AMPK and consequent inhibition of Acc1 and Acc2. This was the first demonstration of a mechanism for metformin-induced insulin sensitivity that parallels the known action of metformin on glucagon-dependent gluconeogenesis. Their work was published in the prestigious journal *Nature Medicine* in 2013 (19:1649-56).

POPULATION HEALTH

Research at the ADI begins with discoveries in the lab surrounding the onset and management of diabetes. But the ultimate goal is to translate these discoveries into practice by developing new therapies and policies for human health application and to overcome obstacles to improving quality of life in the general population. Scientists at ADI study the impacts of new health interventions, including both the effectiveness of therapies themselves and the means by which they are delivered. Researchers are also looking at the choices subpopulations make and how these affect health. Health Outcomes research at the ADI is world-renowned, and contributions made during 2012-2013 were no exception:

Aboriginal Health Screening –

Indigenous Canadians are twice as likely to develop Type 2 diabetes than Caucasians, owing to numerous genetic, lifestyle and social factors.

Dr. Ellen Toth is one of several ADI Members distinguished for research and contributions towards aboriginal community health. Dr. Toth is the lead investigator for *Believing We can Reduce Aboriginal Incidence of Diabetes* (BRAID), a research initiative between

the University of Alberta, Metis and First Nation communities throughout Alberta, focusing on the screening and prevention of diabetes. During 2012-2013 BRAID's largest initiative was the Mobile Diabetes Screening Initiative (MDSi) where staff travelled to Aboriginal communities to provide diabetes screening services. Their research group published important findings of a 12 year longitudinal observational study that revealed diabetes has grown approximately twice as much among Status Aboriginal youth compared with the general population (*J Circumpolar Health*, 2012, 71:18501). Her team has also worked to fill in knowledge gaps about gestational diabetes (GD) in Albertan aboriginal women through epidemiological profiling, identifying in the process that a two-fold higher risk exists for Aboriginal women developing GD compared with non-Aboriginal women (*Can J Diabetes*, 2013, 37:S79). Dr. Toth contributes to the Alberta Diabetes Strategy through its Aboriginal component and co-authored *Chapter 38: Type 2 Diabetes in Aboriginal Peoples* in the Canadian Diabetes Associations' 2013 *Clinical Practice Guidelines*.

Metformin Safety – The popular antiglycemic drug metformin was originally considered contraindicated for diabetes patients that had suffered



heart failure because of concerns about lactic acidosis, but later both Health Canada and the US Food and Drug Administration lifted this strict warning. Clinical experience has suggested the risk of acidosis is similar to other diabetes drugs, and Canadian and American clinical practice guidelines now even recommend metformin as first-line therapy for diabetes patients with heart failure. **Drs. Dean Eurich, Sumit Majumdar, Jeff Johnson and Finlay McAlister** completed a

systematic review of 34,000 diabetes patients with heart failure prescribed metformin, in light of the fact that data had not been reviewed for five years since a loosening of prescription guidelines. Their research led to the conclusion that metformin was associated with reduced mortality compared with controls without increased risk for those with reduced left ventricular ejection fraction, nor in those with both heart failure and chronic kidney disease. The results of this work point

to the conclusion that metformin is at least as safe as other glucose-lowering treatments in patients with diabetes mellitus and heart failure and even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease, and should continue to be considered the treatment of choice for patients with diabetes mellitus and heart failure (*Circ Heart Fail*, 2013, 6:395-402). All the researchers are affiliates of the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD).

Improving Diabetes Health Care Delivery In Alberta –

During 2012-2013, ACHORD Director **Dr. Jeff Johnson** received funding from Alberta Health to lead the Alberta Caring for Diabetes Project (ABCD), an initiative to improve the quality and efficiency of care for diabetes patients in Alberta, with emphasis on supporting primary care outside of the metro Edmonton and Calgary areas. The ABCD project involves a large cohort study that focuses on two main quality improvement interventions: 1) depression screening and collaborative care management for diabetes patients and 2) lifestyle behavioral support intervention that promotes healthy eating and active living with diabetes. Evaluation of these interventions will help ACHORD researchers determine the factors leading to better quality of care and improved health outcomes (*BMJ Open*, 2012, 2:1-10; *BMC Public Health*, 2012, 12:455). This project will help inform Alberta's Primary Care Networks, which are functional units consisting of family doctors and other health professionals that work together with Alberta Health Services to coordinate primary health care delivery for patients. Dr. Johnson says, "We have always aimed our research in ACHORD to be policy relevant, helping to inform decisions at the clinical or governmental level. We are fortunate

to have strong partners with the provincial health ministry, Alberta Health Services, and primary care." **Dr. Scot Simpson** and other members of ACHORD have also investigated the importance of including pharmacists in diabetes patients' care teams. In a randomized trial they found that, compared with usual care, the addition of a pharmacist significantly lowered the predictive 10-year risk of cardiovascular events in Type 2 diabetes patients by reducing factors such as blood pressure, dyslipidemia, and hyperglycemia (*Diabet Med*, 2012, 29:1433-9). A second study investigated T2D patients that were eligible for anti-platelet therapy and found that adding pharmacists to primary care teams significantly and substantially increased the number of such patients actually taking anti-platelet medication after a one-year follow up (*Ann Pharmacother*, 2013, 47:43-8). The results of these studies have demonstrated the need for including pharmacists in diabetic health care planning and will influence future practices.

Aboriginal Youth –

Dr. Sangita Sharma is the Endowed Chair in Aboriginal health and is renowned for her research and knowledge translation in Aboriginal and multi-ethnic community health that

combines nutritional sciences, epidemiology and cultural influences. In 2012 Dr. Sharma received funding from the Public Health Agency of Canada and Alberta Health to lead the development of a screening tool for diabetes risk factors in urban, Aboriginal youth. The result was: Why Act Now?—a project aimed at developing sustainable health intervention for young Aboriginals using a holistic approach that encompasses food access, cultural influences, value systems, and choices. The project builds on insightful data collected in the first phase of research that underlines the specificity of this group in regards to the development of obesity, diabetes and other chronic diseases. For example, why does this group access health care services less frequently than others, and why do youth consume less fruits and vegetables, but more French fries? Dr. Sharma's team is establishing the link between nutrition choices, engagement in school life and overall well-being. With additional support from Alberta Health and Wellness and interaction with Edmonton Public Schools and other organizations, the Why Act Now? program aims to shape policy development that fosters new thinking and lifestyle choices amongst Aboriginal youth.



ALBERTA'S DECADES-LONG
COMMITMENT TO DIABETES RESEARCH
HAS BROUGHT GROUNDBREAKING
DISCOVERIES AND BETTER QUALITY OF
LIFE FOR DIABETES SUFFERERS.

- FRED HORNE

FORMER ALBERTA HEALTH MINISTER

