Australian Type 1 Diabetes Research Agenda

Partnering science, government and the community

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Mr Mike Wilson
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Dear Mike

The National Health and Medical Research Council (NHMRC) is Australia's peak body for supporting health and medical research; for developing health advice for the Australian community, health professionals and governments; and for providing advice on ethical behaviour in health care and in the conduct of health and medical research.

One of NHMRC's strategic objectives is to support the best and most relevant research in Australia. Internationally, health and medical research delivers new insights into the human condition and the processes that lead to ill health. Australia has contributed strongly to this international effort, and this has benefited both individual and community health here at home.

Australia's research in the pursuit of a cure for type 1 diabetes has enhanced international progress. NHMRC funds many project and program grants in this area, and supports some of Australia's emerging as well as most experienced researchers.

Type 1 diabetes is a complex disease, requiring input and insight from diverse disciplines such as immunology, cell biology, and genetics. Researchers in Australia are well placed to play an increasing role in preventing, treating, and curing type 1 diabetes, building on the best of Australia's research capabilities and infrastructure. The Type 1 Diabetes Research Agenda will assist their contribution, highlighting global developments, profiling Australia's type 1 diabetes research strengths, and outlining potential future directions for type 1 diabetes research in Australia.

I congratulate the researchers and other stakeholders involved in the production of this Agenda.

Yours sincerely

Professor Warwick Anderson
Chief Executive Officer
26 February 2010

Executive summary

Type 1 diabetes in Australia – a growing health concern

Type 1 diabetes is a lifelong autoimmune disease with complex origin, dramatic onset and a strong association with serious long term health complications. The disease imposes a considerable medical, financial and emotional burden on individuals and families in Australia. It also incurs substantial costs to the Australian health system. A large proportion of the costs can be attributed to the cost of medication and hospitalisation for ongoing health complications, although indirect costs such as loss of productivity and carer support are also significant.

The last two decades have seen extraordinary advances made in type 1 diabetes research but there is as yet no cure and no proven method of disease prevention. Despite significant progress, over 2000 new cases are diagnosed each year in Australia. With incidence rising, particularly in children, Australia is estimated to have the sixth highest incidence rate in the world. There is an urgent need to support research efforts by consolidating existing knowledge, defining priorities and supporting the most promising research avenues available.

The Australian Type 1 Diabetes Research Agenda – a clear vision for the future

The Australian Type 1 Diabetes Research Agenda was developed in partnership with researchers, clinicians, funders, and patient representatives across Australia. This unique document provides a comprehensive snapshot of the current Australian research landscape in type 1 diabetes, as well as a selected review of global research directions to which Australia's contributions are most significant with the strongest predictions of future growth. The Agenda facilitates the establishment of a shared vision for type 1 diabetes research in Australia and encourages increased and coordinated support research activities. To this end, it:

- Identifies existing Australian research strengths and capabilities relevant to type 1 diabetes
- Describes internationally relevant type 1 diabetes research priorities for Australia
- Encourages collaboration and communication between academia, clinicians, governments, commercial organisations, funding bodies and the type 1 diabetes community
- Recommends further support to accelerate the advancement of Australian research and enable the translation of research into real clinical outcomes

The summary table on the following two pages outlines initiatives in four research areas to prevent, treat and cure diabetes; namely immune therapies, beta-cell therapies, complication therapies and glucose control. In each research area the shared key research directions for Australia that are most likely to lead to eventual patient benefit are outlined. The overall research strategy ensures that research needs to assist individuals at different stages of the type 1 diabetes spectrum – those at risk, newly diagnosed and living with established disease – are addressed.

Accelerators and research enablers – supporting the implementation of research directions

The further growth of Australian research in type 1 diabetes depends on ongoing co-ordination of local and international research efforts, and initiatives that will accelerate and enable research from the level of individual researchers to large research organisations. These initiatives include elements such as the infrastructure, knowledge, and tools that can impact positively across a number of research programs. The summary table outlines the key initiatives that would be valuable in Australia to hasten the implementation of the agreed research directions.

GOAL 1 - Immune therapies

Prevent and arrest autoimmunity, and restore immune-regulation

At risk
- Unravel the physiological function of the newly identified 'susceptibility' gene loci
- Clarify the key functional differences between the healthy and diabetic immune system
- Confirm or disprove the effects of environmental triggers in high risk individuals
- Finalise current prevention and vaccine development studies for those in the highest risk group
- Develop therapies aimed at the specific immune cells that attack beta-cells

Newly diagnosed
- Build on the current advances in therapies aimed to prolong beta-cell function
- Leverage the understanding of inflammatory processes and autoimmunity recognition from other disorders

Established diabetes
- Increase basic understanding of autoimmunity in established disease compared to the earlier stages of immune attack
- Explore the potential of immune-protection of islets after replacement
- Engage investigators to explore immune tolerance during pregnancy in animal models of type 1 diabetes

GOAL 2 - Beta-cell therapies

Prevent loss and restore beta-cell function

At risk and newly diagnosed
- Increase our understanding of factors involved in the regeneration of insulin-producing cells from endogenous islet precursors
- Initiate local or introduce international clinical trials that target individuals shortly after diagnosis

Established diabetes
- Establish allogeneic islet transplantation as part of the Australian health system
- Identify the key targets to minimise side-effects of current systemic immunosuppressive regimens
- Identify the key steps to move research in pig islets for human transplantation into clinical trials in Australia
- Increase the understanding of late-stage beta-cell differentiation and maturation from human pluripotent stem cells
- Identify new beta-cell imaging techniques and further develop existing approaches

Accelerators and

- Establish a type 1 diabetes clinical platform and patient registry network
- Establish a map of available databases and resources
- Engage Australian biotechnology to support technology transfer and intellectual property capture
- Establish co-ordinated and easily accessible DNA, tissue and data-banks

- Support development of a 3D imaging centre
- Establish comprehensive, cross-functional and multidisciplinary centres of excellence
- Maintain and expand international linkage of data and information sharing
- Support researchers in all stages in their career, with particular focus on early and middle stage

research directions

GOAL 3 - Complications therapies

Prevent, arrest and reverse diabetes complications

At risk

- Develop novel approaches to understand how hyperglycaemia interferes with the function of key genetic and cellular pathways
- Understand how epigenetic imprinting and hyperglycaemic memory occurs
- Identify therapeutic targets in the oxidative stress, inflammatory and glycation pathways
- Develop non-invasive techniques to identify and characterise early markers of complications
- Determine if early pharmaceutical interventions will delay the onset or reduce the impact of complications
- Develop clinical trials that combine validated drug targets with the use of novel detection technology

Established diabetes

- Neuropathy: Focus on early diagnosis of peripheral and autonomic neuropathy
- Retinopathy: Build on the progress of VEGF blockade in combination therapies
- Nephropathy: Target fibrotic pathways to treat kidney disease while it is still silent, and prevent end-stage renal disease
- Determine whether targeting psychological aspects will reduce worsening of diabetes complications
- Increase our understanding on cardiovascular disease processes in type 1 diabetes

GOAL 4 - Glucose control

Improve or restore glucose control

Newly diagnosed and established diabetes

- Design and implement clinical trials in the outpatient setting to test artificial pancreas systems capable of eliminating extremes in blood glucose levels
- Develop novel algorithms for safe incorporation into automated insulin delivery systems
- Incorporate novel dietary paradigms to enhance glucose control
- Optimise approaches to physical activity in type 1 diabetes to help minimise fluctuations in blood glucose

research enablers

- Support clinician researchers by increasing research presence in the large teaching hospitals
- Provide funding for travel awards to increase opportunities for scientific visits/exchanges
- Support multidisciplinary workshops to engage the research community in finding novel solutions

- Increase and reward collaborative grant initiatives
- Engage funders to provide a clear and transparent national research priority map
- Increase the level of interaction between funding agencies and increase co-funding opportunities
- Assess the Australian prevalence and total health cost impact of type 1 diabetes

Document structure

The first part of the document, Sections 1 and 2, provides an introduction to the impact of type 1 diabetes on individuals, Governments and the Australian community.

Section 1. Type 1 diabetes overview:
Includes information on type 1 diabetes as well as the burden of the disease.

Section 2. Type 1 diabetes research in Australia:
Details the history of global achievements in type 1 diabetes research and the impact of Australian research in an international setting.

Section 3 provides an in-depth analysis of current type 1 diabetes research in Australia, highlighting Australian strengths in the type 1 diabetes research and outlining the future research directions for the Australian research community.

Section 3. Australian Type 1 Diabetes Research Agenda – A clear vision for the future:
A description of the global research context in which Australian advances are made, and an in-depth analysis of selected high-impact Australian research.

The final part of the document, Sections 4 and 5, highlights the importance of the engagement of multiple stakeholders, including Governments, communities and funding bodies, to support the ongoing development and implementation of the Agenda to facilitate and realise research goals.

Section 4. Accelerators and research enablers - Supporting the implementation of research:
Outlines the necessary support to achieve the goals of the research directions described in the previous section of the document.

Section 5. Future development and implementation of the Australian Type 1 Diabetes Research Agenda:
Initiates discussion of the development and enhancement of the Agenda as a tool to consolidate research efforts and achieve research goals to ultimately prevent, treat and cure type 1 diabetes.

Introduction & objectives

Type 1 diabetes imposes a considerable personal, medical, financial and emotional burden on individuals and families. Type 1 diabetes also represents a substantial cost to the Australian health system due to the lifelong nature, the intensity of management required, and the associated co-morbidities of the disease.

The last two decades have seen extraordinary advances made in type 1 diabetes research and management, but there is as yet no cure and no proven method of disease prevention.

Australia has made a significant contribution to the advancement of type 1 diabetes research. Our researchers and clinical services are globally respected and well placed to make an increasing contribution over time.

Despite significant progress, the incidence and impact of type 1 diabetes is still escalating in Australia and around the world. There is an urgent need to better promote promising research efforts by consolidating existing knowledge, defining priorities and supporting the most promising research avenues available.

The Australian Type 1 Diabetes Research Agenda has been compiled to help continually increase Australia's contribution to this progress. Developed in partnership with researchers, clinicians, funders, and patient representatives across Australia, this unique document provides a valuable snapshot of the current Australian situation, as well as a broad ranging review of global research directions to which Australia can valuably contribute.

The Agenda aims to facilitate an increased contribution by Australian researchers and encourage targeted and ongoing support for their research activities. More specifically, it aims to:

- Provide a snapshot of type 1 diabetes

- Identify existing Australian research strengths and potential capabilities relevant to type 1 diabetes

- Outline internationally relevant type 1 diabetes research goals and priorities for Australia to maximise future research contributions

- Encourage collaboration and communication between academia, clinicians, governments, commercial organisations, funding bodies and the type 1 diabetes community, in the pursuit of research progress

- Recommend appropriate developments for existing research programs to nourish and support the advancement of Australian research and enable the translation of research into real clinical outcomes

A cure for type 1 diabetes will only be realised through the advancement of scientific and clinical research, and ongoing strong support for the research community by governments, business and community partners. This document represents a strong first step towards achieving this important goal.

|1.| An overview of type 1 diabetes

|*1.1*| What is type 1 diabetes?

Type 1 diabetes is a serious autoimmune disease affecting millions of people worldwide. It occurs when the body's immune system mistakenly destroys the insulin-secreting beta-cells of the pancreas, removing the body's ability to regulate blood glucose levels. Regardless of the age at diagnosis, children and adults with type 1 diabetes are absolutely dependent on external insulin delivery for survival.

Causes

Clinical symptoms of type 1 diabetes manifest as the body fails to produce a sufficient amount of insulin needed to regulate blood glucose levels, resulting in elevated and eventually extreme high blood glucose levels. The disease process, however, begins with much earlier metabolic changes leading to the onset of beta-cell destruction.

Genetic component: Type 1 diabetes is a polygenic disease, meaning many different genes work together and individually to contribute to its development. Over 40 genes have been associated with type 1 diabetes risk, including IDDM1, which is located in the MHC Class II region on chromosome six and is believed to be responsible for encoding one of the Human Leukocyte Antigens (HLA).

Environmental component: Environmental factors can strongly influence the development of type 1 diabetes, evidenced by identical twins studies showing that, given type 1 diabetes in one twin, the second will develop the disease in only 30-50 percent of cases. The exact environmental triggers involved are yet to be conclusively confirmed. Current evidence suggests that a variety of factors including microbial infection, dietary components, vitamin D levels and common environmental toxins may be involved.

Classical symptoms

The classic symptoms involved with the initial diagnosis of type 1 diabetes result from high blood glucose levels and include frequent urination (polyuria), increased thirst (polydipsia), increased hunger (polyphagia), blurry vision, fatigue, and often serious and rapid weight loss if not addressed quickly. In some cases, diagnosis of the disease is associated with diabetic ketoacidosis, a situation where the body is completely starved of insulin and begins to burn fatty acids resulting in the build-up of ketones in the blood. This requires immediate hospitalisation and can be life-threatening. A slower onset form of type 1 diabetes, known as Late-onset Autoimmune Diabetes of Adulthood (LADA) generally presents with milder symptoms of hyperglycaemia, and insulin therapy may not be immediately required at the time of diagnosis.

|1.2| Management of type 1 diabetes and medical prognosis

Treatment options

Only thirty years ago, standard type 1 diabetes management involved multiple daily injections of animal-derived insulin using a reusable glass syringe. Glucose testing involved boiling a urine sample with Benedict's solution, monitoring dietary intake and a lot of guesswork. Today the most common insulins are biosynthetic products produced using genetic recombination. More recently long acting insulin analogues have been made widely available, generally reducing the number of injections required and enhancing glucose control.

Insulin is now more commonly administered using a pre-loaded insulin pen or through continuous subcutanteous insulin infusion using an insulin pump, both of which allow finer dose adjustment, portability and ease of use. Insulin pumps are proven to be an effective method of managing blood glucose and minimising health complications for many people with type 1 diabetes. Despite this, only around four percent of Australians with type 1 diabetes are "connected" to a pump – a lower number than in many other developed countries with a similar disease burden.

Blood glucose testing using readily available test strips is significantly more convenient and accurate, however, it is recognised that this technique only provides a snapshot of blood glucose levels at a given point in time. While most Australians with type 1 diabetes still use this method, continuous glucose monitoring using sensor technology is available and can be helpful in improving long term glucose control.

The impact of diabetes in Australia

- More than 60 percent of people with diabetes have cardiovascular disease, three to five times as high as in the general population.

- There were 11,732 deaths of people with diabetes in 2004, which represents nine percent of all adult deaths.

- Diabetes was recorded as a principal or additional diagnosis in seven percent of all hospital admissions in 2003–04.

- Expenditure on diabetes included $289 million (36.9 percent) on hospital services, $183 million (23.3 percent) on out-of-hospital medical services, and $204 million (26.0 percent) on diabetes-related pharmaceuticals.

- Nearly one-third of new cases of end stage renal disease in 2004 were attributed to diabetic nephropathy.

- The treatment for end-stage renal disease incurs public hospital costs of around $67,000 per person per year.

- In 2003 more than 86,000 Australians had a disability caused mainly by diabetes.

Information taken from Australian Institute of Health and Welfare and ABS publications.

Diabetes complications

Despite recent medical advances, type 1 diabetes is difficult to control and patients can suffer devastating health complications and premature death. The most common long term health complications are diabetic eye disease, kidney disease including renal failure, cardiovascular disease and peripheral nerve damage leading to amputations.

The severity of complications is increased by the duration of the disease, thus type 1 diabetes tends to have a greater health impact in comparison to type 2 diabetes. For example, while type 2 diabetes increases the risk of heart disease by two- to four-fold, heart disease is increased by up to 10-fold in patients with type 1 diabetes.

Results from the landmark Diabetes Control and Complications Trial (DCCT) demonstrated that individuals who follow a more intensive diabetes management regimen aimed at maintaining very tight glucose control have significantly lower incidences of complications. The DCCT, a prospective, randomised, controlled trial of intensive versus standard glycaemic control in patients with recently diagnosed type 1 diabetes showed definitively that improved glycaemic control is associated with significantly decreased rates of microvascular complications (retinopathy and nephropathy), macrovascular complications such as heart attacks and strokes, and neuropathic complications. The epidemiological follow-up of the DCCT showed reductions in cardiovascular complications at approximately 18 years after DCCT commencement. This was found to be due to intensive blood glucose control over the median 6.5 years of the DCCT.

Normalisation of blood glucose by intensive insulin treatment, dietary management and regular blood glucose testing is therefore fundamental to optimal management of diabetes.

The downside of intensive insulin therapy is an increase in the daily risk of life-threatening episodes of low blood glucose (hypoglycaemia) that can lead to loss of consciousness, coma and occasionally death.

Severe hypoglycaemia can regularly occur in individuals who have lost the ability to recognise the symptoms of decreasing blood glucose and therefore do not treat appropriately. In Australia it is estimated that 30 percent of children with type 1 diabetes under the age of 19 experience moderate to severe hypoglycaemic unawareness. This impaired awareness of hypoglycaemia is particularly common in children and its prevalence increases with longer diabetes duration over the years and decades into adulthood.

End-organ complications of type 1 diabetes are associated with greater psychological dysfunction and reduced quality of life, further emphasising the importance of preventing the chronic complications.

|1.3| Type 1 diabetes in Australia: Prevalence and incidence

Prevalence

Using data from 2006 the Australian Institute of Health and Welfare (AIHW) estimated that there were 122,300 Australians living with type 1 diabetes, with over 2,000 new cases diagnosed every year. Prevalence estimates from the past 15 years, tied with rising incidence rates suggests a trend of increasing prevalence of the disease in Australia.

While the disease is most commonly diagnosed in childhood, type 1 diabetes is a chronic disease and as such is prevalent through all age groups. The disease is slightly more prevalent in males, accounting for 58 percent of diagnoses, compared to 42 percent women (AIHW 2008 – Incidence of type 1 diabetes in Australia).

One of the hurdles to accurately determining the burden of type 1 diabetes in Australia is a lack of accurate and comprehensive prevalence data. There are several factors which detract from estimates of prevalence, such as ambiguity from self-reporting and a lack of sufficient resources to accurately assess the national population of people with type 1 diabetes.

Incidence

Australia has one of the highest numbers of new cases annually per capita in the world: Australia is in the top-ten countries worldwide for incidence of type 1 diabetes in children under 15, and is projected to have the sixth highest incidence rate in 2010 (IDF 2006, IDF 2009). Between 2000 and 2007, records show that 7,278 Australian children aged between 0–14 years with type 1 diabetes began using insulin. There were a further estimated 10,219 new cases of type 1 diabetes in people aged 15 years and over. The total number of new cases over the eight year period equates to about 2,187 annually, or six new cases per day (AIHW, 2009).

Type 1 diabetes is one of the most common chronic diseases in children: The incidence of type 1 diabetes is highest in children and adolescents, resulting in half of the people with type 1 diabetes being diagnosed by the age of 18 (AIHW, 2006). The incidence rates are highest in the lowest age brackets (see Figure 1.1), then decrease significantly among people aged 15 years and over and continue to decrease with age, plateauing at around 45 years of age (AIHW 2008, Incidence of type 1 diabetes in Australia).
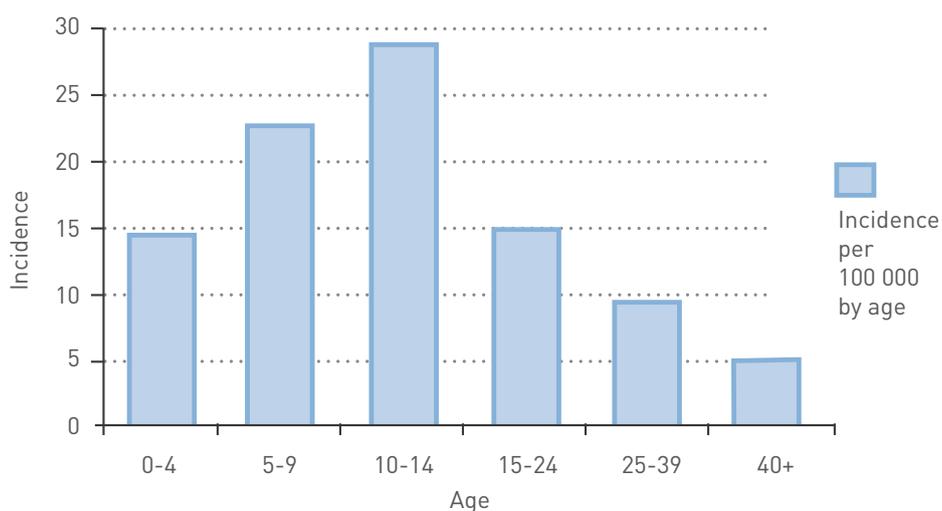
Figure 1.1 The average annual rate of incidence of type 1 diabetes in Australia by age from 2000-2006 (AIHW 2008, Incidence of type 1 diabetes)

The number of new diagnoses is increasing and is occurring at a younger age: The incidence rates of type 1 diabetes are increasing every year, particularly in the 0-14 year old age bracket. An average three percent increase per year in the incidence of type 1 diabetes overall has been seen since 1999 (AIHW 2008, Incidence of type 1 diabetes in Australia), with incidence rates for type 1 diabetes among children aged 0–14 years, experiencing the strongest growth, increasing significantly from 19.1 to 24.2 cases annually per 100,000 of population in the period from 2000-2007 (AIHW, 2009).

The rate of diagnosis of new cases in Australia varies between states: The incidence rates of type 1 diabetes in Australia vary geographically. Tasmania has typically shown the highest annual rate of incidence and the Northern Territory the lowest as seen in Table 1.1. The rate of diagnosis of new cases of type 1 diabetes in children appears to be highest in people living in major cities and lowest in people living in remote areas.

State	TAS	SA	VIC	QLD	ACT	WA	NSW	NT	AUS
Rate	28.9	25.4	23.5	23.0	22.9	21.9	20.6	10.3	**22.4**

Table 1.1 Average rate of incidence per 100 000 of type 1 diabetes in Australia from 2000-2006, by state (AIHW 2008 – Incidence of type 1 diabetes)

Type 1 diabetes accounts for about 13% of all diabetes in Australia, but more than 90% of diabetes in children aged 15 years and younger.

(AIHW, 2009)

|1.4| Social and economic impacts of type 1 diabetes

Type 1 diabetes is a disease that creates tremendous personal and financial burden. The burden extends beyond the individual to primary caregivers, family, friends, teachers, employers, health care providers and the health system. This burden is particularly heavy on parents of children with type 1 diabetes and the partners of patients living with serious associated health complications.

The limitations of current insulin treatment regimes, means that patients are susceptible to potentially dangerous blood glucose fluctuations – both high and low. Both of these situations can have immediate and long term health repercussions, and also long term physiological and psychological effects. Type 1 diabetes can create challenges in work settings and requires particular vigilance during driving. In women, type 1 diabetes places major demands in preparation for and during pregnancy.

Costs of diabetes

In 2002 diabetes was estimated to cost the Australian community in excess of $6 billion a year (AusDiab). Rising prevalence and incidence rates suggest that the current cost is now well in excess of this figure. Although people with type 1 diabetes comprise 13-15 percent of the diabetic population in Australia (AIHW, 2009), they consistently account for a relatively higher percentage of the cost incurred by diabetes each year (AIHW, 2002, AIHW, 2005, AIHW 2008, Diabetes facts).

A comprehensive and systematic estimate of all costs of type 1 diabetes in Australia has not been completed to date, however several different reports illustrate the far-reaching personal and economic cost impacts of the disease.

The direct costs of type 1 diabetes to the health system are substantial: The health care expenditure for type 1 diabetes in Australia was estimated at over $180 million in 2004/05 (AIHW 2008, Incidence of type 1 diabetes in Australia). However, this is probably only a fraction of the economic cost of the disease. Direct non-health costs such as home support, special dietary requirements and transport, indirect costs such as loss of wages due to inability to work and the costs associated with type 1 diabetes carers, both direct and indirect, make up a more complete picture of the economic cost of this disease.

The high use of hospital care by people with type 1 diabetes is a major contributor to cost burden, with hospitalisation accounting for nearly half the direct health care costs incurred by people with the disease. In a recent survey of people with type 1 diabetes, more than a third of respondents indicated they had been admitted to hospital emergency departments in the year prior to survey.

There are also significant indirect costs associated with the disease: There are several additional factors that contribute to the high health care burden of type 1 diabetes in Australia. The chronic nature of the disease and daily reliance on insulin injections and glucose monitoring for survival create a substantial economic burden

Quality of life

One in four people with type 1 diabetes experience anxiety and depression.

One in five report problems with pain and discomfort.

Almost one in six are unable to undertake their usual activities.

(DiabCo$t Australia Type 1, 2009)

on individuals and their carers. The cost of medications for a person with type 1 diabetes is 12 times that of someone of the same age and sex without the disease. Less than half that cost is for insulin (DiabCo$t Australia Type 1, 2009).

In a recent report, 29 percent of people with type 1 diabetes indicated they had a diabetes carer. Costs associated with the role of a diabetes carer also contribute to the overall economic burden of the disease in particular through wages lost due to the reduced ability to sustain paid employment. It has been estimated that, on average, diabetes carers face an average annual wage loss of $7,413. For type 1 diabetes patients the associated carer costs are greatest at childhood, due mainly to parents of children with type 1 diabetes taking time off work, and carer costs again increase for people over 65 years of age (DiabCo$t Australia Type 1, 2009).

The cost of type 1 diabetes triples with the development of complications: Much of the financial burden of the disease is taken on by the individual sufferers. The personal cost to people with type 1 diabetes escalates rapidly with age due to both increased general health care costs associated with ageing seen also in the general population and to the appearance of diabetes complications.

Reports have shown that complications are present in a large proportion of people with type 1 diabetes 30 years after diagnosis. The current average for the prevalence of retinopathy for those who have had diabetes for 30 years is 47 percent, nephropathy is 17 percent and cardiovascular disease is 14 percent. Even with the intensive management, which also increases the risk of life-threatening hypoglycaemia, 21 percent of people with type 1 diabetes develop retinopathy, nine percent develop neuropathy and another nine percent develop cardiovascular complications (Archives of Internal Medicine, DCCT, 2009). The association of health complications with type 1 diabetes accounts for a large amount of the health care costs incurred by people with the disease (Figure 1.2).

Type 1 diabetes reduces quality of life:
The quality of life for people with type 1 diabetes is significantly lower than that of the general population, and lower than that of people with type 2 diabetes. Daily injections and the onset of complications play a large role in this reduced quality of life. Self-reported quality of life is dramatically reduced even further upon the presentation of diabetes complications.
In addition, the quality of life for people with type 1 diabetes shows a decreasing trend with increasing age (DiabCo$t Australia Type 1, 2009).
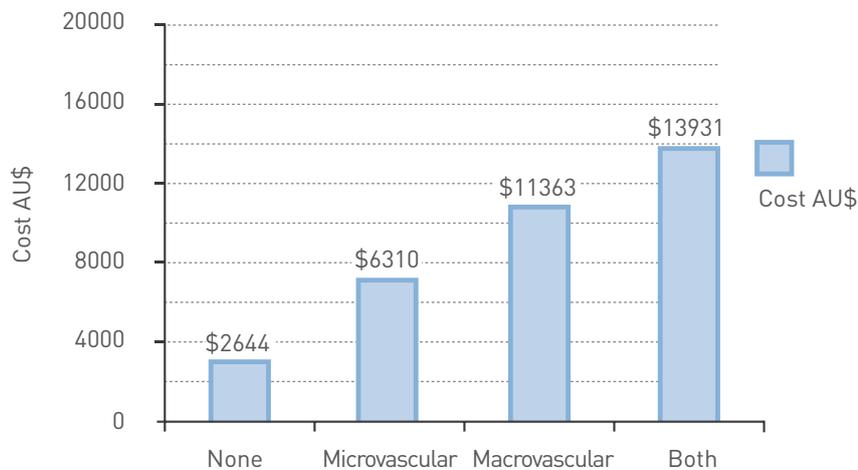
Figure 1.2 Personal cost associated with type 1 diabetes and the presence of complications
(DiabCo$t Australia Type 1, 2009)

|2.| Type 1 diabetes research

|2.1| Timeline of discovery – The history of research into type 1 diabetes

Diabetes mellitus is a disease known to human kind since ancient times. Current and future research opportunities in the field of type 1 diabetes, both in Australia and around the world, are only possible due to prior research progress.

The disease was first mentioned in 1552 BC by an Egyptian physician, Hesy-Ra. Found in the Ebers Papyrus, early medical writings, it included a list of remedies to combat the passing of too much urine.

Aretaeus of Cappadocia, a Greek physician from the time of 200 AD, initially called the disease diabetes mellitus. Commonly known as diabetes, meaning 'to flow', referring to the excess flow of urine, with the Latin word mellitus, meaning 'honey', to indicate the existence of sugar in the urine. Indeed, the sweet taste of urine from people with the disease was noticed by the Greeks, Chinese, Egyptians, Indians and Persians, and was commonly used as a diagnostic tool.

The connection between the pancreas and diabetes was first made by an 18th century physician, Thomas Cawley. During an autopsy of a patient with diabetes, he noticed that the pancreas appeared unhealthy. Around 1869, a German medical student, Paul Langerhans discovered that the pancreas consisted of many different types of cells, including clustered cells later termed "islets of Langerhans". He was unable to explain their function at the time.

In 1889, two scientists, Oskar Minkowski and Joseph von Mering demonstrated in a dog that removing the pancreas produced diabetes. In 1921, Canadian doctors Frederic Banting and Charles Best delivered a report describing the discovery and characterisation of insulin.

For centuries, a child diagnosed with diabetes died quickly, often within days of onset. The average life expectancy for a 10 year old child diagnosed with diabetes was a little over a year. In 1922, the treatment of a 14 year old boy, Leonard Thompson, a patient with diabetes at the Toronto General Hospital, heralded a change to this unforgiving prognosis. He became the first person to receive an injection of an extract containing insulin to treat diabetes. Leonard lived another 13 years before dying of pneumonia at age 27.

Subsequently, the last century and in particular the last decade was marked by significant research breakthroughs made possible by an increased investment in medical research.

Timeline of discovery

1901 • Diabetes mellitus was defined as the destruction of the Islets of Langerhans in the pancreas • "Rainbow test" glucose monitoring with Benedict's Solution provided an inexpensive way to roughly measure glucose levels in urine • Frederick Banting and Charles Best discovered insulin and successfully treated a diabetic dog • The first diabetes patient was successfully treated with insulin • Doctors recognised a distinction between type 1 and type 2 diabetes based on insulin sensitivity • The development of delayed action insulin reduced the number of insulin injections required daily • The standard insulin syringe was developed, helping to make type 1 diabetes management more uniform • Scientists discovered that insulin promotes glucose transport • The amino acid sequence of the insulin protein was determined • The first "dip and read" urine tests allowed instant monitoring of glucose levels • The development of immunoassays allowed researchers to measure insulin in blood, showing for the first time that people with type 1 diabetes produced no insulin • Self-monitoring of blood glucose with the "wet" method using glucose oxidase strips was developed • The first kidney transplant undertaken in person with diabetes • The first pancreas transplant performed on a patient with type 1 diabetes • Laser treatment was used to revolutionise the care of diabetic retinopathy • Scientists determined the 3D protein structure of insulin • Scientists discovered the insulin receptor, a protein on the cell surface that mediates the effects of insulin in cells • Type 1 diabetes was shown to be an autoimmune disease by the discovery of antibodies to insulin producing cells in newly diagnosed patients • Glucagon was purified and synthesised and becomes an important treatment for hypoglycaemia • The first insulin pump was introduced • The HbA1c test was developed, allowing the monitoring of longer-term blood glucose levels • Insulin became the first human protein to be made by cloning the insulin gene and genetic engineering • The first animal model of type 1 diabetes was developed – the non-obese diabetic mouse • The first biosynthetic human insulin was made publicly available **1984**

1985

• Researchers showed that blood glucose control was paramount to fetal development, leading to new treatment standards that dramatically increased the delivery of healthy babies to mothers with diabetes • Researchers identified an early kidney disease marker – called microalbuminuria – that allowed medical intervention to prevent kidney failure • The first insulin pen delivery system was introduced • The hormone gastrin was shown to have potential in beta-cell regeneration therapy • The first successful transplantation of human islet cells was conducted, reversing insulin dependency and removing hypoglycaemia • The Diabetes Control and Complications Trial was concluded, showing conclusively that tight glucose control could delay or prevent diabetes complications• The Edmonton Protocol improved the success rate of islet transplantation from less than five percent to 90 percent • The Type 1 Diabetes Prevention Trial established the first genetic risk assessment test for type 1 diabetes • Research showed that treating newly diagnosed type 1 diabetes patients with a monoclonal antibody preserved residual beta-cell function • The international TRIGR study was launched to examine the relationship between duration of breastfeeding and the development of type 1 diabetes • Research showed that insulin itself was a key target in the autoimmune attack on pancreatic beta-cells • Long term follow-up of Diabetes Control and Complications Trial participants showed that intensive glucose therapy reduced cardiovascular complications • First generation continuous glucose monitors paired with insulin pumps pave the way towards an artificial pancreas • The international TEDDY study was launched to identify the environmental triggers of type 1 diabetes in the young • Skin cells were "reprogrammed" to form pluripotent stem cells • A small study showed that the immune system could be "reset" to overcome autoimmunity using a procedure similar to a bone marrow transplant • Research into dietary factors showed that omega 3 and vitamin D supplements may help to prevent or delay type 1 diabetes onset in people who are genetically at risk • Pancreatic progenitor cells were identified and shown to develop into beta-cells • Type 1 diabetes was cured in mice by transplanting insulin-producing cells grown from embryonic stem cells • Clinical trials began into the efficacy of Smart Insulin - a once-a-day therapy that combined insulin with glucose sensing molecules to dramatically reduce the risk of hypoglycaemia • A new drug was shown to be more effective than laser treatment in treating diabetic macular oedema • Continuous glucose monitors were proven to significantly improve blood glucose control • Australian researchers demonstrated that cells could "remember" the metabolic effects of high blood glucose • Studies showed that minute metabolic and immune changes could be used to identify a risk of type 1 diabetes at an early age • The Type 1 Diabetes Genetic Consortium identified a number of genes responsible for type 1 diabetes, as well as a number of genes linked with other autoimmune diseases • Australian researchers showed that, in animals, the immune system could be modified to allow the acceptance of transplanted islet tissue without immune-suppression • Pancreatic cells were converted into insulin-producing beta-cells • Common gut bacteria were shown to be important in the prevention of autoimmunity •

2010

|2.2| Type 1 diabetes research in Australia

Australian type 1 diabetes research is internationally recognised and contributes to the global search for a cure in several research areas, most notably in transplantation, immunity and type 1 diabetes prevention, and treatment and prevention of complications.

A systematic bibliometric assessment of Australian research output in the areas relevant to type 1 diabetes since 2003 has revealed a significant level of contribution across major Australian research institutions. In particular:

- Australia's share of global publication output in type 1 diabetes research grew by over 50 percent between 2003 and 2008 – the only country among the eleven countries analysed to show growth in share over this time.

- Australia has a very high relative citation impact (RCI) of 1.6 for the period reported. (RCI measures the rate of citations of Australian publications).

- Australia has relatively few low-cited publications – the lowest proportion for any of the countries in the analysis, and almost half the world average.

Australia makes an internationally significant contribution to research in type 1 diabetes: Australia's global share of medical and health sciences publications for the period 2002-2006 was 3.08 percent, among the ten top nations contributing to two-thirds of world input. For clinical sciences (the sub-field to which diabetes research is classified), Australia's share of world output for the same period was 3.14 percent. Australia's share of type 1 diabetes related research was 3.16 percent, and again was in the top ten contributing countries (Table 2.1). Australia's share of output in the discipline has grown by over 50 percent in five years – the only country among those included in this analysis to show a significant increase over the period. In terms of output, it has moved up from ninth to sixth position among these countries.

Published research by Australian researchers in the area of type 1 diabetes is internationally respected: Calculating the RCI of type 1 diabetes research output for each country provides an indication of the esteem in which other researchers hold these publications. To put Australia's RCI for type 1 diabetes research into context, the country's RCI for medical and health sciences for the period 2002-2006 was 1.11, and for clinical sciences was 1.18. Australia's relative citation performance in type 1 diabetes research is above that for medical and clinical sciences. While Australia has a relatively smaller share of global output of the countries analysed, it holds the second highest RCI of countries included in this analysis.

Australia has several institutions leading research in type 1 diabetes: The expertise in type 1 diabetes is spread across several major research institutes in the country. Australian institutions with the highest impact of published, type 1 diabetes research are listed below alphabetically.

- Australian National University
- Baker IDI Heart and Diabetes Institute
- Garvan Institute of Medical Research
- Monash University
- Murdoch Children's Research Institute
- Royal Children's Hospital Melbourne
- St Vincent's Institute of Medical Research
- University of Melbourne
- University of New South Wales
- University of Sydney
- University of Western Australia
- Walter and Eliza Hall Institute of Medical Research
- Westmead Children's Hospital

Country	Citations per publication	Relative citation impact	% share of world output
Norway	26.57	1.90	0.89
Australia	**22.41**	**1.61**	**3.16**
Denmark	16.71	1.56	3.03
Canada	21.25	1.52	5.3
USA	20.82	1.49	32.49
UK	19.63	1.41	10.02
Netherlands	18.93	1.36	2.59
France	16.95	1.21	4.24
Finland	16.71	1.20	1.98
Sweden	15.33	1.10	4.64
Germany	14.91	1.07	6.68
New Zealand	10.84	0.78	0.55
World	**13.96**	**1.00**	**100.00**

Table 2.1 Relative citation impact and percentage share of world output by country, 2003-2007 and national shares of type 1 diabetes publications, 2003-2008

Type 1 diabetes research in Australia is supported by several major funding bodies: Research in Australia in the area of type 1 diabetes is supported by several government and not-for-profit organisations – both Australian and international. Selected major funders contributing to type 1 diabetes research in Australia, as reported by researchers contributing to the Agenda, are listed below alphabetically. Pharmaceutical and biotechnology funding sources are not included.

- Australian Research Council
- Department of Health and Ageing
- Diabetes Australia Research Trust
- Diabetes Research Foundation of Western Australia
- Financial Markets Foundation for Children
- The Juvenile Diabetes Research Foundation (JDRF)
- Macquarie Group Foundation
- National Health and Medical Research Council
- National Institutes of Health (USA)
- Ramaciotti Foundation
- Rebecca L. Cooper Medical Research Foundation
- Royal Australian College of Physicians

Australian research secures a significant proportion of global funding: JDRF is an international funding body and is the largest non-governmental funder of type 1 diabetes research worldwide. Figure 2.1 shows the distribution of funding money for the year 2009. Australia holds the second largest share of JDRF funding globally. Funding is competitively reviewed by international scientific and lay review panels, underscoring the global success of Australian researchers.

Australia
6.4%

Belgium
2.5%

Canada
2.0%

Germany
1.0%

Israel
3.4%

Italy
1.5%

Denmark
1.2%

Switzerland
1.2%

United States
73%

United Kingdom
6.1%

Others
3.3%
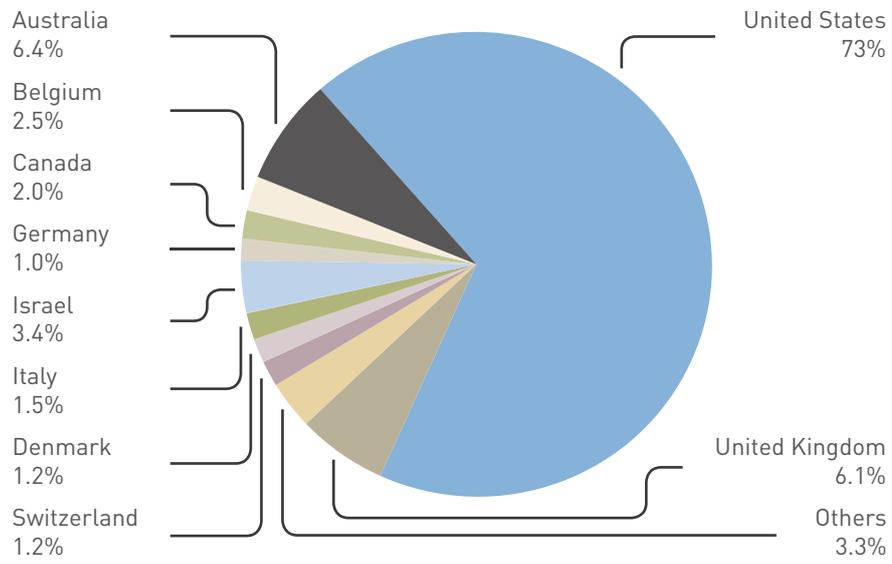
Figure 2.1 Global share, by country, of JDRF International funding for 2009

|3.| Australian Type 1 Diabetes Research Agenda
A clear vision for the future

|*3.1*| Development of the Australian
Type 1 Diabetes Research Agenda

|*3.2*| Four goals to prevent, treat and cure
type 1 diabetes

|*3.3*| Goal 1. Prevent and arrest autoimmunity
and restore immune-regulation:
Immune therapies

|*3.4*| Goal 2. Prevent loss and restore
beta-cell function: *Beta-cell therapies*

|*3.5*| Goal 3. Prevent, arrest and
reverse diabetes complications:
Complications therapies

|*3.6*| Goal 4. Improve and restore
glucose control: *Glucose control*

|3.1| Development of the Australian Type 1 Diabetes Research Agenda

Developed with the support of the Australian diabetes research community, the Australian Type 1 Diabetes Research Agenda represents a single, shared and globally relevant research blueprint for Australia's role in the search for a cure for type 1 diabetes. This broad-based national strategy will outline key projects and programs as well as the optimal policy framework to support its realisation.

Specifically, the Australian Type 1 Diabetes Research Agenda will propose shared goals, identify and support new avenues for cross-disciplinary research collaboration, and provide the basis for increased investment into Australian type 1 diabetes research.

Collaborative and inclusive process

This Agenda was developed collaboratively with researchers, clinicians, patient groups and funding bodies with support from JDRF in Australia.

As the first step in the process, the inaugural Australian Type 1 Diabetes Research Directions Workshop was held in March 2009 with support from the Macquarie Group Foundation. Over 100 of Australia's best diabetes researchers gathered together to discuss and evaluate the Australian type 1 diabetes research landscape in order to consolidate expertise, enhance collaboration and accelerate research progress.

The Workshop, held over three consecutive days, brought together a range of scientific and clinical disciplines to consolidate existing expertise and identify the strategies discussed in this document. The first day focused on beta-cell therapies, the second on immune therapies, and the third on complications therapies and glucose control. During the Workshop presentations were also received from the National Health and Medical Research Council (NHMRC), the Diabetes Vaccine Development Centre (DVDC), and Research Australia. International strategy and global research directions in type 1 diabetes were presented by Scientific Directors from JDRF International.

In preparation for the Workshop all participants were invited to take part in an anonymous questionnaire focused on identification of research strengths and emerging research focus areas, impediments to research progress, and suggestions for solutions. Independent facilitators analysed the data from the survey, presented outcomes during the Workshop and guided the discussion. Subsequent to the Workshop the facilitators summarised the key points in each of the research areas. The results and discussions of the Workshop are reflected in this document.

Scientific Contributors: Further to the process, several leading researchers in Australia were invited to provide a written contribution to the Australian Type 1 Diabetes Research Agenda, giving their perspective on future research direction in their specific area of expertise and potential progress towards clinical benefits in individuals with type 1 diabetes. All contributions were included in the document.

Consultations and revision process: To ensure scientific accuracy and relevance to the global and Australian scientific community, the Agenda was circulated in draft form to international experts in the area of research strategy development and representatives of other funding and patient-focused organisations. A volunteer Editorial Board was convened to guide the overall development of the Agenda.

Organisation of the Agenda

The Australian Type 1 Diabetes Research Agenda aims to support and hasten the progress of the most promising research to cure, better treat and prevent type 1 diabetes. The ultimate beneficiaries will be those affected by diabetes across the stages of disease progression (shown in Figure 3.1).

Stages in the progression of type 1 diabetes

At risk	Newly diagnosed	Esablished diabetes
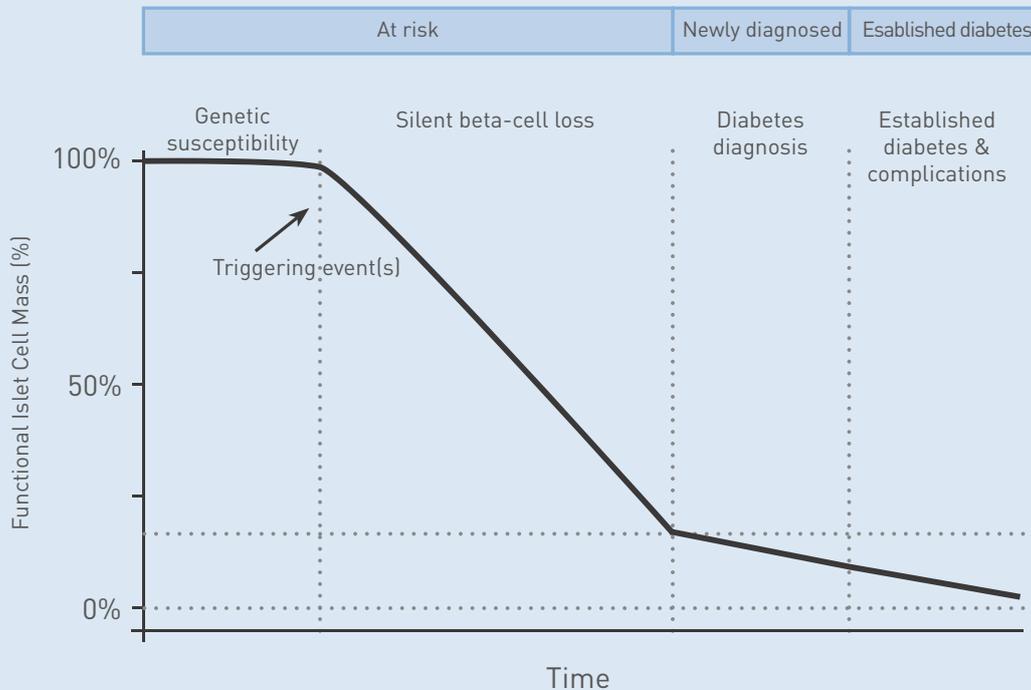
Figure 3.1 Stages in the progression of type 1 diabetes

This Agenda describes research interventions three stages in the pathogenesis of type 1 diabetes:

- **At risk:** This includes those who are genetically predisposed to varying extents to type 1 diabetes and in particular those who have one or more beta-cell antibodies but in whom clinical symptoms are not yet visible.

- **Newly diagnosed:** This includes individuals typically within the first year of diagnosis with varying degrees of residual beta-cell activity. At this stage the functional beta-cell mass is not sufficient for effective glucose control but a transient "honeymoon period" can occur when the toxic effects of hyperglycaemia are still relieved by endogenous insulin production.

- **Established diabetes:** This includes individuals with established type 1 diabetes who are fully dependent on insulin and are typically a year or more post diagnosis. A proportion of these individuals will develop complications depending on the duration of diabetes, glucose control and genetic predispositions.

|*3.2*| Four research goals to prevent, treat and cure type 1 diabetes

This Agenda identifies specific objectives and research directions around four research goals underpinned by recommendations for ongoing research support. These areas are interdependent and research in one area will impact on research in others – hence a co-ordinated approach is required.

These goals are as follows:

Goal 1. Prevent and arrest autoimmunity and restore immune-regulation: *Immune therapies*
Developing safe and effective therapies to induce immunoregulation and to prevent and halt immune-mediated destruction of beta-cells.

Goal 2. Prevent loss and restore beta-cell function: *Beta-cell therapies*
Understanding the process of beta-cell genesis, destruction and function with the ultimate aim of restoring insulin production by either replacing or regenerating insulin-producing cells in people with type 1 diabetes.

Goal 3. Prevent, arrest and reverse diabetes complications: *Complications therapies*
Discovering and developing treatments for the range of long term complications that can strike people with diabetes, including diseases of the eyes, nerves, kidneys, and blood vessels.

Goal 4. Improve and restore glucose control: *Glucose control*
Developing therapies, medical devices and novel drugs that will improve and eventually normalise glucose control.

Accelerate and enable research progress
Creating a supportive research environment that will facilitate the implementation of the research directions described in the goals above by providing infrastructure, co-ordinating multidisciplinary approaches, supporting people, and creating partnerships.

The information in each goal is provided in the following sections:

Background and aims: A description of the nature of each of the goals and the research focus, also identifying potential long term benefits to individuals with type 1 diabetes.

Key recent advances and clinical benefits: A discussion of a selection of major advances in type 1 diabetes, with particular focus on examples of global achievement in the last three to five years.

Overview of Australian research landscape: An outline of major strengths in Australian research in type 1 diabetes in relation to the specific objectives identified as critically important in accelerating research progress.

Future research directions: An overview of key areas of future research focus and potential to be nurtured in Australia based on relative local strengths and research expertise.

Research Focus

Research programs		Clinical goals	At risk
GOAL 1	Immune therapies	Prevent and arrest autoimmunity and restore immune-regulation	► **Objective 1.1:** Prevent onset of autoimmunity in genetically predisposed individuals
GOAL 2	Beta-cell therapies	Prevent loss and restore beta-cell function	► **Objective 2.1:** Prevent loss of beta-cells i
GOAL 3	Complications therapies	Prevent, arrest and reverse diabetes complications	
GOAL 4	Glucose control	Improve and restore glucose control	
	Accelerators & enablers	Supporting the implementation of research directions	**Aim:** Encourage translational research **Aim:** Support collaboration, networking **Aim:** Nurture the current and attract n

Patient Focus

Newly diagnosed	Established diabetes

► Objective 1.2: Arrest the autoimmune attack in newly diagnosed and those with established disease

► Objective 1.3: Protect restored islets from immune attack

n individuals at high risk and newly diagnosed

► Objective 2.2: Promote growth of beta-cells through regeneration

► Objective 2.3: Replace beta-cells or islets in individuals with established diabetes

► Objective 3.1: Prevent or protect against complications

► Objective 3.2: Treat early to prevent progression and reduce impact of complications

► Objective 4.1: Improve and normalise glucose control

► Objective 4.2: Eliminate or reduce hypoglycaemia

to deliver novel treatments and medical devices

g and resource sharing.

ew researchers into the field of type 1 diabetes

Immune therapies

Prevent and arrest autoimmunity and restore immune-regulation:
Developing safe and effective therapies to induce immunoregulation and to prevent and halt immune-mediated destruction of beta-cells.

Objective 1.1: Prevent onset of autoimmunity in genetically predisposed individuals

Objective 1.2: Arrest the autoimmune attack in newly diagnosed and those with established disease

Objective 1.3: Protect restored islets from immune attack

|*3.3.1*| Immune therapies: Background and aims

Research in immune therapies aims to unravel the immune-pathogenesis of type 1 diabetes at each stage of disease progression, from genetic predisposition to long term established disease. By understanding this process we will be able to develop screening regimens to identify and protect those at risk, preserve residual beta-cell function in early disease and protect replaced or regenerated islets from ongoing immune attack.

Understanding and arresting the autoimmune attack relies as much on a comprehensive understanding of healthy immune physiology as it does on identifying type 1 diabetes specific immune pathologies. Many recent breakthroughs in understanding the pathogenesis of type 1 diabetes have come from researchers working in fundamental areas of immunology.

Whilst a detailed characterisation of autoimmunity in animal models has been achieved to date, there are a number of important questions that remain to be answered in human disease before research can be fully translated into therapeutics. These include the identification of key functional and cellular differences between the immune systems of healthy subjects and subjects with type 1 diabetes, elucidation of the trigger and relative importance of the inflammatory response in pre-diabetes, and assessing the potential and efficacy of different immunotherapy avenues under different situations.

Research into these questions is underway with promising results. One key area of focus is the development of antigen-specific immunotherapies (i.e. therapies that target specific subsets of immune cells) to prevent the onset of type 1 diabetes and antigen non-specific immunotherapies to dampen down cytotoxic T cell attack and/or increase regulatory T cells. It is hoped that this promising research avenue will prevent beta-cell destruction in those predisposed to type 1 diabetes with an acceptable safety profile. For patients with established disease, the development of treatments to induce tolerance to beta-cells may be used in combination with beta-cell regeneration and replacement therapies to reverse effects of the disease and prevent the recurrence of an immune attack.

Potential clinical applications

- Molecular identification of those at risk through screening programs and early diagnostics (for both type 1 diabetes and linked autoimmune disorders)

- Development of safe and effective 'vaccines' to prevent disease onset in those at risk

- Identification of environmental triggers and development of preventative health strategies

- Protection of residual islet cells and reduction in insulin requirements

- Successful long term transplantation of insulin producing cells without recurrence of autoimmune attack

|3.3.2| Immune therapies: Key research and clinical advances

Better identification of disease-relevant genetic loci: Major efforts are underway to identify genes conferring susceptibility or resistance to human type 1 diabetes aided by a deeper understanding of molecular and cellular pathways in mice and the development of precise tools to measure genetic variation in humans. Over the last decade more than 40 genetic loci have been identified and validated, including 16 new regions recently identified by the International Type 1 Diabetes Genetics Consortium and the Wellcome Trust Diabetes and Inflammation Laboratory. Common genetic links have also been identified between type 1 diabetes and other autoimmune conditions such as coeliac disease, Crohn's disease and multiple sclerosis (the latter by an Australia/New Zealand research group). Whilst the underlying mechanisms of action of these gene products have not been fully elucidated, they are potential targets to be used as genetic markers of risk.

Identification of novel antigens and biomarkers: Non-genetic markers and diagnostic agents have been discovered and are currently undergoing trials. These include the now well established use of beta-cell autoantibodies that indicate if the body is mounting an attack on the beta-cells. In addition to well established autoantibodies, a fourth such marker, called ZnT8 was recently identified. Monitoring the presence of these autoantibodies can now be used to estimate the level of risk for the development of the onset of type 1 diabetes.

The quest for early biomarkers is driven by the desire to diagnose the autoimmune process years before disease onset. Researchers from the University of Wisconsin used a novel genomic technique to show that people with type 1 diabetes have a specific "proinflammatory signature" that appears well before diagnosis. Ground-breaking research from Finland has discovered that children who develop type 1 diabetes have distinct metabolic abnormalities that can be seen years before disease onset.

Characterisation of environmental triggers: Research is also directed into the identification of environmental triggers that interact with the immune system in type 1 diabetes. In 2003 an international study, The Environmental Determinants of Diabetes in the Young (TEDDY) study was launched to tie all of this knowledge together in the human situation. The study screens newborn babies from the general population as well as newborns with first-degree relatives with type 1 diabetes. Over the course of the 15 year follow-up, researchers will constantly monitor selected environmental and lifestyle aspects including cows milk, cereal products and vitamin D, the development of viral infections, exposure to pesticides, vaccinations, and pets, and psychological issues such as stress.

Use of animal models: The value of animal models to type 1 diabetes research is significant – from the development of islet transplantation techniques, to the determination of efficacy and safety of potential treatments for type 1 diabetes and its complications - the reliance on animal models for research is critical. Research recently published in the journal Diabetes looked at the efficacy of combining two immunotherapies to treat type 1 diabetes in non-obese diabetic (NOD) mice. Both immunotherapies are currently undergoing separate clinical trials for the treatment of type 1 diabetes in humans, and the study found that combining the two agents was more efficacious than either therapy alone in reversing new onset diabetes in NOD mice. Animal models are being used to trigger and facilitate human based research. A recent publication in Nature Immunology identified a key regulator of antigen expression in NOD mice, a variant of the Deaf1 transcriptional regulator. The researchers were then able to recognise the variant Deaf1 in human tissue samples from people with type 1 diabetes.

However, there are difficulties in translating animal research into clinical treatments for human disease, often due to the dissimilarity between rodent and human immune systems. Furthermore, the process of inbreeding used to develop strains such as the NOD mouse can result in genes that are unrelated to type 1 diabetes being enriched, hampering genetic studies.

Clinical advances: A number of key discoveries have recently expanded our understanding of the immune process in type 1 diabetes and has opened up new therapeutic avenues. In the USA, a not-for-profit consortium of researchers, the Immune Tolerance Network (ITN) was established to test new treatments for diseases of the immune system. The ITN's most recent type 1 diabetes study tested the efficacy and safety of vaccination with an insulin-B chain peptide to extend the "honeymoon period" in newly diagnosed individuals. The vaccine was well-tolerated with evidence to support its prevention potential and a second, Phase II study was initiated. The ITN is also leading the way with clinical studies of a promising therapeutic agent (anti-CD3 monoclonal antibody hOKT3γ1 (Ala-Ala)), which has been shown to prolong the insulin "honeymoon period" for up to two years in people recently diagnosed with type 1 diabetes.

International clinical networks have been established to facilitate testing of the most promising target molecules. TrialNet is one such network, focusing on prevention studies in at risk populations such as an oral insulin vaccine and studies in newly diagnosed individuals that focus on factors that may prolong beta-cell function directly after the diagnosis. An example of a current study is a trial looking at the effects of the drug CTLA-4Ig (Abatacept) which is already being used to treat rheumatoid arthritis, to try to protect remaining insulin production.

While these breakthroughs are significant as proof-of-concept approaches the development and delivery of a safe therapy is crucial to its success. Newer approaches to immune regulation are looking for less toxic forms of treatment.

Australian research case study

Blocking B cell function – Research targeting B cells leads to cure for type 1 diabetes in mice

In an attempt to understand the autoimmune mechanism behind type 1 diabetes, recent Australian research targeting B cell development and activation demonstrated a technique that stopped the development of type 1 diabetes in mice. By blocking the BAFF and APRIL proteins responsible for the development of B cells, researchers were able to completely protect type 1 diabetes-prone mice from the disease.

The research showed that during treatment, B cell numbers were decreased as were T cell numbers and inflammatory mediators. The protective mechanism identified was an increased population of a subset of cells called regulatory T cells, which moderate the autoimmune process and may protect mice from the development of type 1 diabetes.

This research reveals an exciting avenue by which a preventative therapy against the development of type 1 diabetes can be attained. The translation of this data into human research is an important step in the development of this therapy and an advantage of the BAFF blocker used in this study is that it has previously been shown to be safe in humans with other autoimmune conditions. This research is currently being developed for preclinical trials with the Diabetes Vaccine Development Centre.

Mariño E et al, Diabetes. 2009;58(7):1568-77.

|3.3.3| Immune therapies: Overview of Australian research landscape

Australia has an impressive track record in the field of immunological research with two Nobel prize winners and a history of research that has often resulted in paradigm shifts in global thinking. With this as a foundation, research into the autoimmune aspects of type 1 diabetes is both well established and well advanced in Australia.

Australia also plays a key role in the Type 1 Diabetes Genetics Consortium, an international research group searching for the genetic causes of type 1 diabetes. Spread across four regions (North America, the UK, Europe, and Asia-Pacific), the key objective of the Consortium is to generate the statistical power needed to identify all genetic risk factors, including those which may occur infrequently in the population or have a lesser impact. The Western Australian Institute of Medical Research leads the Asia-Pacific section of this group and is joined by over 30 researchers from research institutes and hospitals around the country.

The international TrialNet consortium is conducting clinical trials with researchers from 18 centres and over 150 medical centres in eight countries, including sites in Australia and New Zealand. There is considerable potential to boost Australian participation in TrialNet trials in the future, as the recent Australian participation in TrialNet has been declining.

National clinical activities in immune therapies are supported by the DVDC, established in 2003 as a partnership between the NHMRC and JDRF. The primary aims of the DVDC are to accelerate the development of treatments to prevent the onset, or delay the progression of type 1 diabetes; provide support for research and clinical trials, and facilitate the commercialisation of outcomes through industry linkages. The DVDC is currently supporting three promising research programs, two of which are in human clinical trial stage and one in pre-clinical development. The largest and most established of these is the multi-centre Intranasal Insulin Trial (INIT II).

Objective 1.1: Prevent the onset of autoimmunity in genetically predisposed individuals

Increasing the understanding of genetic predisposition: The quest for genetic insight on type 1 diabetes is motivated by the desire to predict disease at a very early stage and act to prevent it. The Type 1 Diabetes Genetics Consortium conducts research in samples taken from thousands of affected siblings and their families. The consortium has defined over 40 genes that affect susceptibility to type 1 diabetes, as well as supporting detailed analysis of links between the HLA complex and type 1 diabetes.

Intensive study of the HLA complex has indicated that what a person inherits in the way of HLA genes determines up to 50 percent of his or her genetic risk of having type 1 diabetes. Most of the risk is attributable to HLA class II genes, at chromosomal regions labelled DR, DQ, and DP. The HLA region is also involved in other autoimmune diseases; indeed, associations observed between HLA and autoimmunity in general are among the most valuable findings in human genetics. There is still much to be learned about the HLA complex, however. The exact manner in which it affects type 1 diabetes susceptibility is not clear, nor is the nature of its interactions with other risk genes.

Decoding the function of susceptibility genes: Research could lead to "small-molecule" therapies that could be designed based on identification of novel susceptibility genes or the biological pathways in which they are involved. Consortium findings should also significantly fertilise research efforts in other autoimmune diseases, such as thyroid disorders, rheumatoid arthritis, multiple sclerosis, and scleroderma. HLA-related risk applies with all of these diseases; though some genes in the region may turn out to be type 1 diabetes-specific, others may apply across a number of autoimmune diseases.

Advances in molecular genetics have bridged the translation gap between clinical studies of type 1 diabetes in humans and experimental studies in mice. This is best exemplified by the discovery and analysis of mutations in the AIRE and FOXP3 genes. Human studies provided evidence of the importance of these genes in self-tolerance, but it was the examination of these mutations in mice that revealed the cell types and biological pathways involved.

With further research in mice and the implementation of more precise genomic tools in humans, research is now able to analyse the effect of more subtle genetic variations on the autoimmune process. Understanding these pathways will enable the development of more pharmacologically defined targets for therapeutic intervention, identify the levels of risk associated with different genotypes, and yield the necessary biomarkers for identifying different clinical subsets of type 1 diabetes and measuring individual responses to intervention.

Road to simple prevention strategies: The recent discovery that certain aspects of diet, and particularly gut bacteria, are intrinsically linked to the autoimmune process has opened up a number of new research avenues. A number of trials have hinted that dietary factors such as cows milk protein, gluten and essential fatty acids may contribute to type 1 diabetes risk and a recent paper published in Nature has provided the first steps towards understanding the role of nutrition in immune responses. Whilst still in initial stages, researchers at the Garvan Institute in Sydney have identified a mechanism that links diet, gut bacteria and autoimmunity. The link between gut bacteria and autoimmunity was previously established in 2008, with the discovery that mice which were exposed to common intestinal gut bacteria from birth were significantly less likely to develop type 1 diabetes when compared to those bred in a germ-free environment.

We may be able to apply innovative and inexpensive treatments - both dietary and pharmacological - to the management and prevention of type 1 diabetes. In the longer term, we may be able to use targeted therapies to mimic the action of gut bacteria to alter the incidence and severity of type 1 diabetes.

Focusing on antigen-specific therapies: Of particular interest is the growing recognition that insulin occupies a special place among the antigenic targets in type 1 diabetes. Asymptomatic individuals in the pre-clinical stage of type 1 diabetes can be identified by the presence of circulating antibodies to the islet autoantigens including (pro) insulin autoantigen that is specific for beta-cell and appears to play a key role in driving autoimmune beta-cell destruction. Australian research published in 2006 pinpointed that the insulin molecule rather than the beta-cell is what draws the first autoimmune attack and drives a more widespread assault on other beta-cell proteins. Further to this, researchers have identified that the impairment of thymic tolerance to insulin induces early onset autoimmune diabetes.

In Australia, a Phase II clinical trial is investigating whether the intranasal administration of insulin to children and young adults at risk for type 1 diabetes will reduce the rate of development of the disease. Another study, funded by DVDC, currently in late Phase I stage (safety assessment) aims to assess the potential of pro-insulin peptide injections to slow down the progression of beta-cell destruction in newly diagnosed individuals.

Objective 1.2: Arrest the autoimmune attack in newly diagnosed and those with established diabetes

Inhibiting the autoimmune attack: Generally, at the time of diagnosis, from 60-85 percent of a type 1 diabetes patient's pancreatic beta-cells have already been destroyed by the ongoing autoimmune attack. Protecting the remaining 15-40 percent of these cells to preserve what insulin production remains is paramount, as even small amounts of natural insulin production can lead to greatly improved control of blood glucose. Researchers have discovered new molecular and cellular mechanisms for deleting islet-reactive T cells that destroy beta-cells and inducing differentiation of islet-specific regulatory T cells

that normally inhibit T cell destruction of beta-cells. They also demonstrated that maternally transmitted anti-islet antibody is an important environmental factor in type 1 diabetes. The discovery of these mechanisms, and the genes that co-ordinate these mechanisms, will provide critical information to guide the analysis of human genetic susceptibility to type 1 diabetes, and to design new therapeutic agents and early preventive strategies.

Investigating the potential of B cells in the aetiology of type 1 diabetes: Researchers are now looking at the possibility that a subset of immune cells called B cells, involved principally in antigen formation, may play the role in the aetiology of type 1 diabetes. Autoantibodies generated against beta-cell proteins may be important for type 1 diabetes initiation, or facilitate antibody dependent cytotoxic processes that lead to beta-cell destruction. Additionally, B cells may activate pathogenic T cells that go on to destroy beta-cells directly. As a proof-of-principle, a recent study showed that a rheumatoid arthritis drug rituximab (an antibody against the protein CD20

which is primarily found on the surface of B cells), was found to partially preserve beta-cell function and lower insulin needs in patients with new-onset type 1 diabetes over the course of months.

Leveraging therapies for other indications as a means to accelerate treatments for type 1 diabetes: The genetic susceptibility and basic molecular mechanisms of the autoimmune process are often shared by a number of autoimmune conditions including type 1 diabetes. Thus it is critically important that trials of potential therapies be applied that were beneficial in other immune conditions and at an appropriate disease stage. Aforementioned rituximub is a good example of this approach as it is a drug approved initially for inflammatory arthritis and in a subgroup analyses it showed a greater response in children and adolescents than in adults. A number of existing treatments are now being considered for use in type 1 diabetes with recent research showing that the antibody cancer drugs imatinib and sunitinib can induce remission of type 1 diabetes in newly diagnosed patients.

Australian research case study

Understanding the mechanisms behind autoimmunity

Recent Australian research provides insight into the mechanism of the development of autoantibodies which are capable of triggering autoimmune attacks such as type 1 diabetes. Published findings demonstrate that formations of immune cells called germinal centres play a pivotal role in the development of high-affinity autoantibodies and autoimmunity.

The research found that key immune cells, called follicular helper T cells played a part in allowing the development of these self-reactive antibodies within germinal centres. The team was able to reduce the number of these cells by altering a single gene. Identifying key players in the development of autoimmunity is an important step in understanding how diseases such as type 1 diabetes can arise.

Unravelling the complexity of the immune system and the disregulations that cause autoimmunity are central to understanding diseases such as type 1 diabetes and research such as this has the possibility to lead to new diagnostic tools as well as a cure for type 1 diabetes.

Linterman MA et al, The Journal of Experimental Medicine. 2009; 206(3): 561-76.

Objective 1.3: Protect restored islets from immune attack

Inducing immunotolerance: For established type 1 diabetes to be successfully treated, the process of autoimmunity has to be arrested and beta-cell mass has to be replaced. The ultimate goal of immunotherapeutic strategies is to remove or inactivate the killer cells that attack beta-cells, while leaving other killer cells, e.g. those required for protection from infectious diseases and tumours, unaffected. Removal or inactivation of these killer cells would prevent further beta-cell damage and preserve blood glucose control in individuals with established type 1 diabetes, allow regrowth of beta-cells or prevent their destruction after islet transplantation. Inactivation of killer cells remains a major hurdle for immunotherapeutic approaches to type 1 diabetes. Some of the novel approaches to inactivating killer cells involve antigen-presenting cells to re-educate beta-cell-attacking killer cells. Queensland based researchers are investigating if antigen-expressing cells can induce peripheral tolerance in antigen-experienced diabetogenic T cells and prevent these cells from mediating autoimmune beta-cell destruction. If successful this would provide a new approach to immunotherapy of type 1 diabetes.

Australian research case study

Potential type 1 diabetes biomarker – Researchers identify a pathogenic marker of type 1 diabetes with hope for diagnostic value

Recent research has identified a likely pathogenetic biomarker for type 1 diabetes. This Australian research has reported that dendritic cells in people with type 1 diabetes responded differently to stimulation, in particular with low levels of activation of a protein called RelB, which is a component of the transcription factor, NF-κB.

The identification of a biomarker that can predict the risk of developing type 1 diabetes is a valuable asset in the management of people who are at high risk of developing the disease, in particular family members of people with type 1 diabetes. There is potential that this research will confirm the identity of a new biomarker that can reliably assess the risk of type 1 diabetes in any individual.

Research is currently continuing into the value of developing an assay to predict the susceptibility of a person to developing type 1 diabetes, by assessing the RelB response in dendritic cells. A long term study to understand the exact relationship between this RelB response and the development of type 1 diabetes is currently being run.

The development of an easy diagnostic test will be a valuable tool in recognising those at risk, developing and implementing preventative measures, and catching type 1 diabetes before it causes potentially dangerous pathology. Ultimately it is hoped that a vaccination strategy can be developed for people at high risk, retraining the immune system before the symptoms of type 1 diabetes develop.

Mollah ZU et al., Journal of Immunology, 2008; 180(5): 3166-75.

|3.3.4| Immune therapies: Future research directions for Australia

The state of current research in autoimmunity globally combined with Australia's current activities and strengths in this field indicates areas of future research progress to which Australia is well placed to contribute. These are outlined below around the stages of the progression of type 1 diabetes.

At risk

- Unravel the physiological function of the newly identified 'susceptibility' gene loci

- Clarify the key functional differences between the healthy and diabetic immune system

- Confirm or disprove the effects of environmental triggers in high risk individuals; in particular the role of vitamin D in immune regulations, the process of innate or mucosal immunity and the role of intestinal gut barrier and flora in immune regulations

- Finalise the current prevention and vaccine development studies for those in the highest risk group with antigen specific approaches such as trial of intranasal insulin

- Support development of therapies aimed at the specific immune cells that attack beta-cells

Newly diagnosed

- Build on the current advances in the antigen non-specific therapies to prolong beta-cell function and find safer option with less side-effects

- Leverage the understanding of inflammatory processes and autoimmunity recognition from other disorders to prevent beta-cell apoptosis

Established diabetes

- Increase basic understanding of autoimmunity in established disease compared to the earlier stages of immune attack prior to diagnosis

- Explore the potential of immune-protection of islets after replacement from both the auto- and alloimmune attack

- Engage investigators to explore the immune tolerance during pregnancy in animal models of type 1 diabetes

Beta-cell therapies

Prevent loss and restore beta-cell function:
Understanding the process of beta-cell genesis, destruction and function with
the ultimate aim of restoring insulin production by either replacing or regenerating
insulin-producing cells in people with type 1 diabetes.

Objective 2.1: Prevent loss of
beta-cells in individuals at high risk
and newly diagnosed

Objective 2.2: Promote growth
of beta-cells through regeneration

Objective 2.3: Replace beta-cells
or islets in individuals with
established diabetes

|3.4.1| Beta-cell therapies: Background and aims

Research in this area focuses on the understanding of the process of beta-cell genesis, destruction and function with the ultimate aim of preventing loss in people at risk of type 1 diabetes and restoring euglycaemia and insulin independence in people with existing type 1 diabetes.

One of the fastest growing research areas in the field, three key research avenues have emerged as the most promising. These include:
(i) transplantation of functional beta-cells into people with type 1 diabetes, (ii) the potential of stem or progenitor cells to generate glucose-responsive, insulin producing cells that offer an unlimited source of cells for transplantation, and (iii) the discovery that beta-cells can be regenerated from endogenous precursors.

Currently, the only procedure shown to reverse type 1 diabetes is islet or whole pancreas transplantation. Islet cell transplantation using cadaveric human donor cells is being carried out in over 30 countries, primarily as a clinical option for people living with type 1 diabetes complicated by severe hypoglycaemia unawareness. In order for islet cell replacement to be a widely available option in the long term, alloimmune and autoimmune rejection of transplanted beta-cells must be prevented. Whilst immune-suppression regimens can achieve this with some success,

it is associated with side effects and precludes transplanting islets into a wider population. To counter this, physical approaches to thwart immune rejection or immunologically targeted approaches to create stable immune tolerance are desirable alternatives.

An additional limitation to the wide use of human islet transplantation is the restricted number of donated pancreata available in Australia. Potential solutions to this limited cell source include use of animal sources of islets or beta-cells (xenotransplantation) and the generation of glucose-responsive, insulin-secreting cells or their precursors from other human sources. These include human embryonic, fetal or adult stem cells, progenitor cells, or reprogrammed non-beta-cells taken from alternative tissues.

To expand this approach from simply supplying a cell source for transplantation, research is focused on identifying and developing existing and novel therapeutic strategies to regenerate endogenous beta-cells in the body, promote survival of existing beta-cells, and re-program other cells types to become beta-cell like. Such regeneration therapeutics would have the potential to prevent type 1 diabetes, improve glucose control and to prevent complications, and ultimately to lead to a cure for type 1 diabetes.

Potential clinical applications

- Increased availability of glucose-responsive functional islets for transplantation from human pluripotent cells or animal sources

- Removal or significant reduction of the immune-suppression requirement that may allow expansion of islet transplantation to a wider population of individuals with type 1 diabetes

- Development of therapies to that will allow an increase of beta-cell mass from endogenous sources, either by replication of mature beta-cells or differentiation of precursor cells

|3.4.2| Beta-cell therapies: Key research and clinical advances

Improving islet transplantation outcomes:
The development of the Edmonton Protocol for islet transplantation at the University of Alberta in Canada in 1999 transformed this technique into a clinically viable procedure. Independence from insulin injections was initially achieved in about 80 percent of patients at one year post-transplant and significant reduction in hypoglycaemia unawareness. Five years after islet transplantation (under the original Edmonton protocol), the majority of patients (around 80 percent) have c-peptide present, indicating insulin production, but only a minority (around 10 percent) maintain insulin independence. Those who resumed insulin therapy required half of their pre-transplant insulin dose. Hypoglycaemic score improved significantly post-transplant, and was maintained over five years. Fifty percent of patients demonstrated stabilisation or improvement of their diabetic neuropathy. A recent long term follow up has confirmed that transplant recipients also report a significantly increased quality of life.

While initial patients experienced a loss of islet function after several years, ongoing improvements of the original protocol (including islet isolation, transplantation and immune-protection) have resulted in prolonged insulin independence. While transplantation of donor cadaver islets is a cure in the short term, it will ultimately serve as the clinical platform for other forms of beta-cell replacement.

Developing alternative sources of insulin-producing cells: With donor human cells being in short supply and of variable quality, researchers are looking to other animal species to provide a readily available source of cells. Researchers at two islet transplant centres have reversed diabetes in monkeys by transplanting islet cells from pigs. The milestone studies, reported in the journal Nature Medicine, showed that with a combination of immune-suppressing drugs, the transplanted pig islets were not rejected by the monkeys and functioned for several months. Another way of protecting transplanted islets and reducing rejection is by encapsulating the transplant tissue in a non-reactive material.

Recent developments in stem cell science, alongside government policy changes, have resulted in a number of highly significant discoveries occurring during 2008-2009. These discoveries, concerning the use of stem cells and cells reprogrammed to act like stem cells, have provided real hope that a replenishable supply of glucose-responsive, insulin-producing cells can be commercially developed.

In 2008 scientists successfully developed a protocol to derive pancreatic cell precursors from human embryonic stem cells (hESC) that, when implanted into mice and allowed to mature into glucose-responsive endocrine cells, were able to reverse chemically induced diabetes. The study provided conclusive proof that hESC can be differentiated down the path to eventually becoming insulin-secreting beta-cells under the right conditions.

Two teams of scientists successfully reprogrammed human skin cells into cells that look and act like pluripotent embryonic stem cells. Called human induced pluripotent stem cells (iPS), they are theoretically able to be turned into insulin-producing cells for autograft transplantation. The cells were transformed using a relatively simple technique involving the manipulation of only four genes.

Research into the use of non-insulin producing pancreatic tissue is also gaining momentum. In a significant proof of concept study, researchers from Harvard University successfully converted pancreatic exocrine tissue into functional insulin-producing tissue by using adenoviruses to ferry three key regulatory genes into the cells. These genes, all transcription factors, turned off the normal digestive function of the exocrine cell and turned on the genes that enable production of insulin, this represents one of the first examples of "direct reprogramming" - changing the functional identity of adult cells without using hESC or complex genetic manipulation. A European research group subsequently demonstrated that it is possible to transform pancreatic alpha cells into insulin-producing cells by forcing them to express a single gene called Pax4.

Regeneration of beta-cells from endogenous sources: Researchers demonstrated that average total insulin secretion of newly diagnosed patients was approximately 52 percent of that in a person without diabetes, much higher than previously thought. The conclusions from the study were important. If significant insulin producing capability exists at the time of diagnosis, researchers have a much better chance at restoring glucose regulation by expanding existing mass of beta-cells. With this in mind, a strong research focus is being placed on ways to coax existing beta-cells to regenerate and replenish as well as ways to promote survival of beta-cells.

Previous studies have shown that adult beta-cells maintain a capacity to replicate in the body by self-duplication. Recent research has taken this a step further by showing that adult human beta-cells "de-differentiate" in vitro and can be significantly expanded in culture—a key property if these cells are to be developed for use as an islet replacement treatment.

Interest has also grown in the specific mechanisms or components mediating beta-cell growth with a number of new therapeutic targets and pathways recently identified. For example, researchers from Stanford University demonstrated that impairment of either N-FAT or calcineurin proteins resulted in diabetes and boosting their activity could restore blood glucose control in early stage diabetes.

Further research also identified another potential therapeutic for regulating beta-cell replication. The protein, called menin, is known to reduce the growth of new cells and is naturally reduced by hormones during pregnancy to allow for expansion of insulin production in response to body mass. Scientific insights into beta-cell regeneration, reprogramming and survival are accelerating and provide a new strategy to treat and cure type 1 diabetes.

Australian research case study

Eliminating the need for immunosuppression for islet graft recipients – Research exploits regulatory immune cells to teach the body to accept the graft as 'self'

Recently published findings demonstrate a new technique that could potentially eliminate the need for immunosuppressive drugs for recipients of islet transplantations.

By injecting mice with immune complexes made up of two immune proteins that bind together, researchers were able to rapidly expand a population of cells known as regulatory T cells which have a role in suppressing other immune cells. By expanding the regulatory T cell population more than ten fold during an islet transplantation, the immune system is taught to accept the graft as 'self' and does not mount an immune response against it.

This work has potential application for recipients of islet transplantations. Currently used immunosuppressive drugs can hamper islet survival and cause long term toxicity to patients, as well as leaving them susceptible to other infection. This process requires no immunosuppressants, either at the time of transplantation or afterwards as the immune system has been educated to accept the graft. It was found that islet grafts survived indefinitely in most cases without any further manipulation or treatment required.

Webster KE et al,. The Journal of Experimental Medicine. 2009; 206(4): 751-60

|3.4.3| Beta-cell therapies: Overview of Australian research landscape

Australia is a recognised leader in the area of beta-cell replacement, specifically in the clinical development and application of islet transplantation protocols.

The Australian Islet Transplantation Program (ITP), funded by the Commonwealth Department of Health and Ageing and managed by JDRF, is recognised as being at the forefront of the international effort to take islet transplantation from an experimental protocol to a mainstream therapy for people with type 1 diabetes. Consisting of three linked clinical sites at Westmead Hospital (NSW), St Vincent's Hospital (VIC) and Royal Adelaide Hospital (SA), fourteen patients have already received successful transplantation. In addition to clinical application and research, the ITP supports a number of laboratory research programs investigating beta-cell biology, alternative beta-cell sources and manipulation of transplanted cells to prevent immune attack, in order to improve the efficacy of islet transplantations.

In addition to supporting islet transplantation, the Australian Government has implemented a number of progressive policy decisions to allow research into xenotransplantation and embryonic stem cell lines. They also provide financial support to the Australian Stem Cell Centre, an organisation that fosters stem cell research around the country. These enabling factors provide a valuable level of support to Australian researchers working in the field and a leading edge compared to researchers working under more restrictive research conditions.

Objective 2.1: Prevent loss of beta-cells in individuals at high risk and newly diagnosed

Unraveling the process of beta-cell death: Beta-cell survival is critical for the maintenance of endogenous beta-cell mass as well as that of newly replaced or regenerated beta-cells. Mechanisms to promote the survival of beta-cells and prevent cell death could be exploited clinically to preserve or maintain beta-cell mass in individuals at early stages of type 1 diabetes or individuals undergoing beta-cell replacement or regenerative therapies.

Research in past decades has illuminated the complexities of intracellular signalling pathways leading to cell death in various cell types and has increased our understanding of the mechanisms underlying beta-cell destruction during the type 1 diabetes disease process. Type 1 diabetes pathology is caused by selective destruction of beta-cells, a process that is mediated by killer T cells. A number of cell death mechanisms in animal models of type 1 diabetes have been identified. However, experiments that have targeted single molecules believed to regulate the cell-death pathways have so far produced inconclusive results. Concurrent blocking of multiple effectors of beta-cell destruction and upregulation of protective molecules may be necessary and is currently being extensively investigated.

Objective 2.2: Promote growth of beta-cells through regeneration

Expanding regenerative therapies in a clinical setting: Researchers are investigating a gene therapy technique using a combination of the hormone glucagon-like peptide and gastrin to strengthen transplanted cells and encourage beta-cell regeneration. A Phase II clinical trial is currently underway to test the monoclonal antibody rituximab as a means to prolonging islet survival even further.

Supporting bio-imaging research: One of the key areas underpinning the success of islet regeneration and replacement interventions is the ability to visualise islet mass and function at high temporal and spatial resolution. Having this ability in a clinical setting will enhance understanding of the events leading to beta-cell destruction and allow the assessment and monitoring of beta-cell mass and function over time. This has potential to be developed as a tool to assess cellular function and survival in response to protective or regenerative treatments as they are developed.

Technological advances have provided researchers with an unprecedented capacity to map pancreatic tissue in 3D, at a cellular process level. In small animals, a variety of different targets are currently under development utilising different probes and imaging modalities towards the goal of imaging pancreatic islet mass and function in patients. The opportunity exists to take advantage of the existing strengths in Australian biomedical imaging and focus efforts on a multi-disciplinary program to develop the tools and technology for clinical imaging for diabetes.

Objective 2.3: Replace beta-cells or islets in individuals with established diabetes

Preservation of graft islet function prior to and after transplantation will involve inhibition of mechanical damage induced by isolation, transient hypoxia and instant blood-mediated inflammatory reaction (IBMIR) at the time of portal infusion. Following a successful transplant, the two key reasons for failure of long term grafts are chronic toxicity by immunosuppressive drugs and chronic graft rejection. One of the major breakthroughs in islet transplantation in recent years has been the use of a novel, less toxic immunosuppressive regimen (sirolimus and tacrolimus) that replaced glucocorticoid-based immunosuppression.

Improving outcomes of islet transplantation by local immunosuppresion: The new regimen is less toxic to islets but side effects caused by a systemic delivery of immunosuppressive drugs are one of the barriers preventing islet transplantation being widely available to sufferers of type 1 diabetes. Studies are being conducted that will use a combination of immunomodulatory molecules that can effectively protect islets from immunological attack whilst maintaining systemic immunity. Local immunosuppression can be generated using adenoviruses to deliver immunomodulatory molecules to islets prior to transplantation. A comprehensive understanding of the mode of action of local immunosuppressants and their interplay with other agents will maximise the potential for the translation of these studies into clinical practice.

Genetic enhancement of islets to induce transplant resilience: Adenoviral delivery of a set of regulatory genes to the outer cell layers of the islet may afford protection from IBMIR while ensuring maintenance of metabolic function from the non-transduced islet core. The products of these genes will target genes that are known to be activated during trauma of isolation and have contact with the donor blood. This strategy has the potential to reduce both the number of islets required to reverse type 1 diabetes, and the level of immunosuppression required to prevent islet graft rejection.

Islets can also be engineered to express anti-cell death and anti-inflammatory genes, to create a "death-defying" islet, which would reduce beta-cell death and improve islet transplant outcomes. Genes that form a part of the natural physiological stress response of beta-cells and/or are deficient in diabetes prone beta-cells potentially may be the best candidates for gene therapy such as the zinc-finger protein A20. Indeed, by over-expressing A20 in islet grafts in mice, long term allograft acceptance can be achieved in around 20 percent of cases. Using this technique removed the requirement for systemic immunosuppression, and was consistent with the induction of long term allograft tolerance in recipient mice.

Another approach is pre-treating islets prior to transplantation with well known non-toxic drugs such as DFO that increase expression of proteins enhancing islet survival. Several other pro-survival candidates are under close investigation such as CD39 (a clotting enzyme that is expressed on blood vessels) and the potential of immunoregulatory molecules originating from parasites that induce the proliferation of regulatory T cells to prevent their expulsion from the host. Thus, a focus on novel cellular targets, may present attractive candidates as adjunctive therapies, which when used in combination with current therapies, may enable the induction of allograft tolerance for successful, immunosuppression free islet transplantation.

Addressing the key issues in stem cell research: Successful and safe differentiation of pancreatic beta-cells from human pluripotent

stem cells is an important step to increasing the supply of beta-cells for replacement. Further progress depends on discovery of small molecules and generation of antibodies that are critical to the process. In Australia, researchers are taking advantage of existing reagents and methodologies for the culture and differentiation of hESC and combining them with new capabilities in high throughput screening for bioactive small molecules and in automated antibody production. Researchers hope to identify small molecules that can substitute for and/or improve upon existing factors used for the in vitro differentiation of hESCs and iPS to pancreatic lineages. Furthermore, they hope to generate antibodies which recognise the specific stages of differentiation of these cells, including pancreatic progenitors and insulin expressing cells.

Identifying alternative sources of islets for xenotransplantation: Xenotransplantation is a fast moving field with a number of promising directions. While the initial work demonstrated proof of principle, the original form of immunosuppression is not currently available for human use. To counter this, research efforts have been focused on identifying alternative immunosuppression regimens and establishing a quarantined pig colony suitable for clinical use. In addition to this, work with CD46 transgenic pig islets showed interesting initial results. Encapsulation of pig islets may solve the problem of immunosuppression but as yet this technology has not been sufficiently developed to fully manage type 1 diabetes.

By genetically engineering pig islets to present fewer targets to the human immune system and produce molecules to prevent blood clotting and inflammation, researchers plan to dramatically improve the process and reduce the number of pig islets required. Studies in mice have shown that it is possible, but achieving this goal in practice will be time consuming and costly as current techniques require animal cross-breeding strategies. Researchers are now working on a way of using porcine embryonic cells to circumvent this need and facilitate the production of pigs containing up to six genetic modifications in one generation. As research in primates shows that porcine islet transplants are possible, there is an increased impetus for xenografts to undergo clinical trials.

|3.4.4| Beta-cell therapies: Future research directions for Australia

The state of current research in beta-cell therapies globally combined with Australia's current activities and strengths in this field indicates areas of future research progress to which Australia is well placed to contribute. These are outlined below around the stages of the progression of type 1 diabetes.

At risk and newly diagnosed

• Increase the number of basic and clinical projects to increase our understanding of factors involved in the regeneration of insulin-producing cells from endogenous islet precursors

• Initiate local or introduce international clinical trials that target individuals shortly after diagnosis, who can benefit from agents that can expand the number of mature beta-cells by replication

Established diabetes

• Establish allogeneic islet transplantation as part of the Australian health system for a selected population with difficult-to-control diabetes

• Identify the key targets involved in protecting newly transplanted cells in order to minimise side effects of the systemic immunosuppressive regimen

• Identify the key steps needed to move research in pig islets for human transplantation into clinical trials in for human transplantation in Australia

• Increase the focus on identification of signals and structural components required for late-stage beta-cell differentiation and maturation from human pluripotent stem cells and improve the methods to purify differentiated cells to minimise the risk of tumor formation

• Identify new beta-cell imaging techniques and further develop existing approaches

Complications therapies

Prevent, arrest and reverse diabetes complications:
Discovering and developing treatments for the range of long term complications that can strike people with diabetes, including diseases of the eyes, nerves, kidneys, and blood vessels.

Objective 3.1: Prevent or protect against complications

Objective 3.2: Treat early to prevent progression and reduce impact of complications

|*3.5.1*| Complications therapies: Background and aims

Research in this therapeutic area aims to accelerate discovery and development of strategies to prevent and treat complications of type 1 diabetes through the support of research. These include diseases of the eyes, nerves, kidneys, heart and blood vessels. These complications place an enormous burden on the individual and their carer, as well as imposing significant costs and pressures on the health care system.

The complications associated with type 1 diabetes can be severe. Peripheral neuropathy can lead to disability from chronic pain, chronic ulcers and amputations. Autonomic neuropathies have devastating effects on vital organs such as the heart, bladder and gastric system. Diabetic retinopathy can lead to loss of vision and blindness. Diabetic kidney disease can lead to renal failure, dialysis, kidney transplantation, and in some cases, death. People with type 1 diabetes are also at markedly increased risk of developing cardiovascular disease with its associated morbidity and premature mortality.

The aim of research in this area is to develop early diagnostic agents, protect against progression of complications, arrest underlying processes leading to disease, and facilitate the body's repair processes. With appropriate biological disease markers, it may be possible to interrupt the complications disease process in people with type 1 diabetes.

Clinical benefits

- Development of a single therapeutic treatment to reduce the risk of long term diabetes complications across all body systems

- Molecular identification of those at risk of specific health complications with associated preventative strategies

- Higher quality of life for people with diabetes and their carers

- Reduction in health care costs, both economic and social

- Increased availability of new and more efficient treatments

|*3.5.2*| Complications therapies: Key research and clinical advances

The ongoing results of the ground-breaking DCCT have demonstrated that intensive glycaemic control reduces the risk of complications in individuals with type 1 diabetes. They also clearly show that ongoing poor glucose control is certainly not the only risk factor. In the last decade, researchers have delved further into the genetic and environmental factors involved with development of diabetes complications with significant results.

The epidemiological follow up of the DCCT indicated that intensive blood glucose control during the trial lead to more than a halving of major cardiovascular events up to 18 years from the beginning of the trial.

Common mechanisms of complications: Recent research has pointed to regulation of diabetes complications by common biochemical and inflammatory mechanisms, supporting the theory that neutralising these common mechanisms may be a key to the early prevention of complications. Cellular mitochondria produce energy from glucose but this process also makes toxic by-products called reactive oxygen species which leads to inflammation. By interrupting this process at a key point, researchers are hoping to prevent long term complications.

In another significant leap in understanding, researchers have pinpointed an epigenetic mechanism that could explain the link between changes in blood glucose levels and the increased risk for cardiovascular complications in diabetes patients. Novel research shows that normal cells cultured intermittently in high blood glucose can acquire epigenetic changes that survive even after culture glucose is adjusted to normal culture levels. The changes affect a specific gene, leading to increased expression. This event launches a cascade of events, ending with the activation of several inflammatory genes and contributing to the development of diabetes complications. These changes persisted even during and after subsequent periods of normal glycaemia in the culture system.

This ground-breaking work does engender a number of new questions – specifically is hyperglycaemia causing all complications and will these complications continue even after the diabetes is cured?

Can genetic profile modulate predisposition to complications? While these research breakthroughs offer hope of a single therapeutic for diabetes complications, research is also continuing into ways to prevent, alleviate and reverse individual complications.

While it has been long known that there are a number of genes associated with development of type 1 diabetes, researchers suspected that there were additional genes associated with the risk of developing diabetes complications, in particular, diabetic nephropathy. To investigate this theory, the US-based Genetics of Kidneys in Diabetes (GoKinD) study was established in 2004. The purpose of the GoKinD study was to establish a repository of DNA and clinical information from adults with long term type 1 diabetes, with or without kidney disease. Maintained by JDRF, the National Institutes of Health, the Joslin Diabetes Center and the Centers for Disease Control, this accessible database has served as the basis for the recent discovery of four genomic loci strongly associated with nephropathy.

In addition to therapeutics in the pipeline, such as advanced glycation end-product cross-link breakers and inhibitors, researchers are placing focus on the identification of suitable diagnostics and biomarkers to predict the onset of diabetes complications. One such early diagnostic is the use of specialised, yet widely available, optical equipment to non-invasively examine the corneal nerve to predict, classify and monitor peripheral neuropathy in other parts of the body.

|3.5.3| Complications therapies: Overview of Australian research landscape

Australian researchers have been instrumental in understanding the process of diabetes complications and in the development of new therapies. Many of these are now considered standard clinical treatment, including the involvement in the early stages of research into the Angiotensin-Converting Enzyme (ACE) inhibitors and description of microalbuminuria as a predictor of diabetes complications. Australian researchers continue to work at the forefront of international research into the treatment and prevention of diabetes complications.

Support from the NHMRC has facilitated the establishment of the first Australian Centre for Clinical Research Excellence (CCRE) focused on diabetes, a national collaboration of leading research institutions from around Australia. The CCRE represents a significant step in establishing a network of diabetes experts involving clinicians and scientists in hospital and community settings. Researchers at the CCRE are leaders in translational research and focused on a multi-disciplinary approach to pioneer treatments for diabetes complications as well as a broader focus on technologies to improve the management of type 1 diabetes.

Objective 3.1: Prevent or protect against complications

Examining molecular pathways leading to multi-organ complications: Chemical modification of proteins and lipids by excess glucose is mediated by a process called glycation that leads to the production of harmful molecules that form as a result of high blood glucose called advanced glycation endproducts (AGEs). AGEs are known to activate inflammatory responses through interaction with a well-characterised cell surface receptor called the Receptor for Advanced Glycation Endproducts (RAGE).

First identified in 1990, the RAGE molecule sits on the surface of cells and acts as a binding site for AGEs. When these bind to RAGE, they disrupt critical cell functions and cause damage, especially in blood vessel walls. In the last few years, research on RAGE has found it is involved in the pathogenesis of many complications of diabetes. The administration of RAGE antagonists to diabetic rats or mice attenuates many diabetes complications, including kidney, eye and vascular injury, and greatly attenuates the initiation and acceleration of atherosclerosis. A RAGE antagonist is now moving into clinical trials.

Recent research has directly challenged the existing dogma that damage caused by hyperglycaemia accumulates throughout the lifespan of a person living with diabetes. Promising new research suggests that the risk of complications increase with periods of high blood glucose and remains high after glucose levels are returned to normal. Called "metabolic memory", this theory is being used to understand why some people with good glucose control suffer progressive diabetes complications.

The underlying molecular mechanisms for this are being investigated and epigenetic pathways seem to particularly play a role. The rapid progress in this field is partly a result of major technological advances such as New Generation Sequencing and the development of inhibitors to certain key enzymes involved in histone and DNA methylation. Whilst these techniques were initially developed for cancer research, they are increasingly being translated to diabetes research and will be used in the development of early-stage therapeutics targeting cellular memory.

Objective 3.2: Treat early to prevent progression and reduce impact of complications

Searching for early, non-invasive diagnosis of diabetes complications: Novel diagnostic systems will allow the prediction of onset and detection of early changes whilst monitoring the progress of interventions and therapies. Technology in this area is advancing considerably,

evolving along multiple pathways according to specific complication areas.

One example of this is retinal imaging. The eye is the only part of the body where blood vessels can be non-invasively visualised. To this end, retinal photography is being used to analyse characteristics of the blood vessel width and length, branching angle and tortousity. Changes in these factors can be important markers of future retinopathy and micro- and macrovascular disease.

Ophthalmic markers are also being investigated as a means to detect the presence and severity diabetic neuropathy. A four-year clinical study is currently underway to assess the viability of two non-invasive tests of corneal nerve morphology and function. The first test involves using the corneal confocal microscope to observe fine nerves in the cornea to investigate whether degenerative changes in these nerves mirror neuropathic changes occurring in the arms and legs of diabetes patients. The second test uses a non-contact corneal aesthesiometer to detect corneal sensitivity, thus providing a direct measure of the health of the corneal nerves which correlates to the health of peripheral nerve.

Australian researchers are also investigating the use of plantar fascia thickness and skin autofluorescence as a measure of metabolic tissue burden. This research will provide important new information about tissue damage and the potential for early predictors of micro- and macrovascular damage.

Researchers at the NHMRC-funded Diabetes Clinical Centre for Research Excellence are undertaking cross-sectional studies into the markers and mediators of atherosclerosis, retinopathy and nephropathy in cohorts of type 1 and type 2 diabetes patients. Biochemical and tissue-based assays of glycation, inflammation and oxidation, and assessments of insulin resistance and beta-cell function will be related to measures of macrovascular function and retinal vascular structure, with the goal of establishing early markers for complications. These markers can also act as surrogate measures for the effectiveness of potential interventions.

Improving cardio-renal prevention: Clinical trials are also underway to investigate effectiveness of existing therapeutics early in the disease process. One such study is the Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT). AdDIT is a large multi-centre, multi-national intervention study looking at the protective effects of ACE inhibitors and statins in adolescents aged 11-15 years with type 1 diabetes and high albumin excretion. Results of this trial will have major implications for management of type 1 diabetes in young people, with follow-up studies providing much-needed direct evidence of long term disease outcomes.

Australian researchers have also identified a potential therapeutic pathway by showing that the antioxidant enzyme glutathione peroxidise-1 plays a protective role in diabetes-associated artherosclerosis.

Diabetic kidney disease is the leading cause of end-stage renal disease in Australia. Although today's interventions can slow the progression, no therapies have been shown to effectively halt progression until recently. Three anti-fibrotic approaches are now in development. These are combination therapy of anti-TGFbeta and anti-connective tissue growth factor (CTGF) – injected antibodies against growth factors heavily linked to fibrosis – and Pirfenidone and FT-011, which are delivered orally. Australian researchers have contributed to preclinical and clinical studies that substantiate CTGF as a marker and, in blood and urine, mediator of diabetic nephropathy in type 1 diabetes. Specific studies are now underway into the therapeutic and safety potential of these drugs.

Improving retinopathy prevention: Diabetic retinopathy is one of the significant causes of vision impairment, particularly in the older population. A number of therapies have now undergone initial trials and proven successful in slowing the progression of the disease. One of these is vascular endothelial growth factor blocker, ranibizumab. Somewhat controversial is the role of angiotensin system blood pressure medications, losartan and enalapril, based on results from the Renin Angiotensin System Study and Diabetic Retinopathy Candesartan Trials. A promising new approach has also recently been discovered by researchers at

the Joslin Diabetes Centre. In a study in rats, the scientists were able to prevent retinal blood vessels from leaking—associated with retinopathy—using an enzyme called kallikrein. An inhibitor to this enzyme is now in commercial development.

Improving neuropathy prevention: Painful neuropathy is a less common form of nerve damage in the feet but it is persistent and is difficult to treat. Australian researchers are investigating its pathogenesis using functional brain MRI imaging and nerve fibre counting at skin biopsy, and are undertaking clinical trials in optimising therapy in painful neuropathy including use of transdermal patch therapy.

People with type 1 diabetes are at increased risk of amputation if they develop foot ulceration. Those with 'insensate neuropathy' where dense peripheral neuropathy develops are especially prone to experience these complications. The diabetic foot ulcer wound 'microenvironment' is characterised by a persistent inflammatory phase with lack of induction of healing granulation tissue. Researchers in Sydney are studying methods to accelerate diabetic wound healing using complimentary anti-inflammatory therapies such as the bee extract propolis and have developed new translational models of wound healing in type 1 diabetes.

Preventing autonomic neuropathy: This condition can contribute to complications such as diabetic gastroparesis, diabetic cardiomyopathy, "dead in bed" syndrome and hypoglycaemia unawareness with increased risk of severe hypoglycaemia and silent myocardial ischaemia. Australian researchers are world leaders in diabetic gastroparesis pathogenesis and therapy.

Australian research case study

Understanding metabolic memory – Research uncovers the role of epigenetics in the development of diabetes complications

Epigenetics is the study of changes in gene function caused by environmental factors, that do not change the genetic coding. Epigenetic changes to genes are mediated through mechanisms such as chromatin remodelling, histone modifications and DNA methylation. Interestingly, these epigenetic marks can be inherited, suggesting that genes can be affected by factors such as diet.

In 2009, research published in Diabetes delineated the effect of transient hyperglycaemic episodes on methylation patterns in the promoter region of the NF-κB gene, a gene encoding for a transcription factor involved in a range of cellular processes.

This publication described the striking revelation that epigenetic marks due to transient hyperglycaemia persist even after the restoration of good glucose control, explaining the mechanism behind metabolic memory. Metabolic memory is a phenomenon by which diabetes complications can persist and even further develop, even after the restoration of good glucose control. The methylation marks that transient episodes of high blood glucose make on this gene affect the way it is expressed, even after blood glucose levels are reduced.

This breakthrough introduces the concept that, for people with type 1 diabetes, transient glucose spikes cause an accumulation of risk for developing complications. This has profound implications for metabolic management, the way in which we monitor glucose control, and for prevention strategies against diabetes complications.

Brasacchio D. et al, Diabetes. 2009; 58(5): 1229-36.

|3.5.4| Complications therapies: Future research directions for Australia

The state of current research in diabetes complications globally combined with Australia's current activities and strengths in this field indicates areas of future research progress to which Australia is well placed to contribute. These are outlined below around the stages of the progression of type 1 diabetes.

At risk

- Develop novel approaches to understand how hyperglycaemia interferes with the functioning of key genetic and cellular pathways that ultimately leads to an impaired function of critical organs

- Understand how epigenetic imprinting and hyperglycaemic memory occurs, and identify molecular treatment targets

- Identify critical therapeutic targets in the oxidative stress, inflammatory, glycation and growth factor pathways

- Develop non-invasive techniques to identify and characterise markers of early signs of complications and to evaluate the efficacy of novel treatments in a shorter time frame

- Determine if pharmaceutical interventions in young adults and early adolescents will reduce the onset or the impact of complications

- Develop clinical trials that combine validated drug targets with the use of novel detection technology to provide proof-of-concept for protective drugs

Established diabetes

- Neuropathy: Focus on early diagnosis of peripheral and autonomic neuropathy to allow for the development of therapies for painful neuropathy

- Retinopathy: Build on the progress of VEGF blockade in combination therapies

- Nephropathy: Develop treatments that target fibrotic pathways to treat kidney disease while it is still silent, and prevent end-stage renal disease

- Determine whether targeting psychological aspects such as depression in type 1 diabetes, may lead to improved adherence to therapy and reduce worsening of diabetes complications

- Increase our understanding of cardiovascular disease processes in type 1 diabetes

Glucose control

Improve and restore glucose control:

Developing therapies, medical devices and novel drugs that will improve and eventually normalise glucose control.

Objective 4.1: Improve and normalise glucose control

Objective 4.2: Eliminate or reduce hypoglycaemia

|3.6.1| Glucose control: Background and aims

Research in this area encourages the development of new therapies and technologies to help type 1 diabetes patients maintain optimal glucose regulation, minimise the risk of diabetes complications, reduce the scope for human error and dramatically increase quality of life.

Research has shown that glycaemic control directly impacts the risks associated with diabetes, including hypoglycaemia, heart disease, kidney disease, eye disease, and peripheral nerve disease. It also affects the viability of either regenerated or transplanted beta-cells, preserves beta-cell mass in newly diagnosed patients, and possibly also impacts the rate of disease progression in pre-diabetes.

Despite progress in treatments and technology, glycaemic control goals, as measured by time spent in target glucose ranges vs. elevated mean blood glucose and hypoglycaemic exposure, for many people with type 1 diabetes remain out of reach.

Potential clinical applications

- Prevention of life-threatening hypoglycaemia and reduction in fear of hypoglycaemia attack

- Improvement of glucose control and decreased risk of chronic health complications

- Simplified diabetes management that reduces the risk of human error

|3.6.2| Glucose control: Key research and clinical advances

Research has focused on the development of new technologies to improve diabetes management, including the measurement of blood glucose and dispensing of appropriate amounts of insulin. This area of research has led to the development, production and clinical recommendation of insulin pumps, as well as the recent development, and increasing availability, of continuous glucose monitors (CGM) to give long term but real time measurements of blood glucose levels.

The first portable insulin pump was developed in 1979 and carried as a large backpack. In the last five years, pumps have evolved to be today lightweight and user-friendly with valuable additions including reminders, alarms and automatic shut-off mechanisms. A number of versions released onto the market in 2008/09 have been designed to interact directly with CGM technology to allow substantial automation of the management process, with patients still needing to check blood glucose levels intermittently and actively trigger bolus insulin injections when required, for example at meal times.

The next step for researchers is to reduce the need for human intervention and develop a "closed loop" device that will automatically monitor and predict fluctuations, and treat appropriately. This involves the development and implementation of complex mathematical models that work as a human pancreas does – predicting when blood glucose levels will peak and trough, then calculating the appropriate amount of insulin, and possibly the amount of counter-acting glucagon, required.

In 2005, JDRF initiated the Artificial Pancreas Program and the international Artificial Pancreas Consortium to directly address the development, testing and production of such a device.

This group have achieved significant success including the design and positive testing of different computer algorithms in partnership with linked insulin delivery and monitoring systems. Two versions of this system have undergone initial human testing in a hospital environment with apparent success and testing is expected to extend further over the next year. A large scale trial of CGM users found that people using CGM spent an average of two more hours per day within the desired glycaemic range, reducing hypoglycaemia attacks and the long term risk of health complications.

Recent research has also developed new insulin delivery mechanisms. This includes the creation of novel insulins such as long-lasting insulin analogues and a new form of "intelligent" insulin, taken once a day and triggered to work when a certain amount of glucose is in the blood. The former is currently available and subsidised for use in Australia and the latter is undergoing testing in US-based trials. This also includes "pain-free" needles, insulin patches and inhaled and orally administered insulin that are all currently in development and undergoing trials.

While technology advances, other research groups are looking to improve glycaemic control using day-to-day lifestyle changes including diet and exercise.

|3.6.3| Glucose control: Overview of Australian research landscape

Australian researchers have a strong history in this area, particularly investigating the causes and effects of hypoglycaemia in children.

Australian researchers are also leaders in the dietary management of glucose control. Research has demonstrated that different forms of carbohydrates are metabolised in different ways. This finding has major applications for people with type 1 diabetes.

Objective 4.1: Improve and normalise glucose control

Improving insulin delivery and glucose monitoring: Research has shown that an effective way to improve glucose control is to use a CGM. These systems take continuous measures of glucose levels in interstitial fluid, providing both a short and long term view of glucose fluctuations. Further improvements are seen when CGMs are combined with an insulin pump, particularly newer versions with insulin suspend systems during times of recognised low blood glucose. The ultimate goal of this research is to develop an artificial pancreas for people with type 1 diabetes.

Dietary adjustments can improve glucose control: Matching the dose of insulin more closely to the expected insulin demand generated by a meal would reduce some of the unpredictability of blood glucose control and reduce the risk of hypoglycaemia. One relatively simple and non-invasive method to do this is to count carbohydrate intake. The Dose Adjustment for Normal Eating (DAFNE) study demonstrated that carbohydrate counting improved glucose control and quality of life. The challenge is that not all carbohydrates are created equal. Australian researchers are one of the international leaders in research investigating the health impact of different types of carbohydrates.

Objective 4.2: Eliminate or reduce hypoglycaemia

One of the most serious acute complications of type 1 diabetes is hypoglycaemia, particularly affecting children and people with unpredictable or "brittle" diabetes where patients are not capable of perceiving the onset of low blood glucose. A study from Western Australia, demonstrated impaired awareness of hypoglycaemia in 29 percent of their paediatric clinic population of type 1 diabetes patients. Among patients aged less than six years, 59 percent of care providers reported impaired awareness of hypoglycaemia and the rate of severe hypoglycaemia was six-fold greater in those reporting impaired awareness. People with impaired hypoglycaemia awareness were almost twice as likely to suffer severe hypoglycaemic episodes resulting in seizures or coma.

The immediate effects of hypoglycaemia can include impaired cognitive, cardiovascular and nervous system function with a serious risk of coma and occasionally death. Up until recently, the ongoing effect of fluctuating blood glucose levels under different life situations was acknowledged, but not understood. Recent advances have shown that extreme highs and lows can have ongoing effects on the cognitive, psychological and behavioural health of children and young people. These changes are associated with neurometabolic changes and morphological changes in the brain.

Hormonal control of glucose counter-regulation fails in diabetes, the result of combined deficiencies of glucagon and epinephrine responses to falling glucose levels. Research is needed to delineate the mechanisms of glucose sensing, counter-regulation, and brain function during hypoglycaemia and to develop therapeutic approaches to prevent hypoglycaemia and its potential effects on brain function.

Australian research case study

Developing strategies for improving the dietary management of type 1 diabetes

The glycaemic index (GI) is a ranking of carbohydrates on a scale from 0 to 100 according to the extent to which they raise blood glucose levels after eating. Low-GI foods, by virtue of their slow digestion and absorption, produce gradual rises in blood glucose and insulin levels, reducing the marked fluctuations in blood glucose levels associated with high GI foods.

The GI may be an important tool for the everyday management of type 1 diabetes. The progress made in this area has enhanced our understanding of the role which GI plays in the daily blood glucose fluctuations and hypoglycaemia that are part of the management of type 1 diabetes.

A further extension to the concept of GI is the food insulin index (FII). This is an index ranking food based on the insulin demand in response to consumption of that food. The study found that the observed insulin responses in healthy individuals were highly correlated with the predicted insulin demand using the FII. Using either GI or FII to calculate insulin demand proved highly superior to the simple method of 'carbohydrate counting'.

Both hypoglycaemia and hyperglycaemia pose acute and long term risks to people with type 1 diabetes. In the short term, use of GI and FII principles can help to minimise fluctuations to reduce the risk of hypoglycaemia and has the potential to minimise long term health complications.

Bao J, et al. The American Journal of Clinical Nutrition. 2009;90(4):986-92

|3.6.4| Glucose control: Future research directions for Australia

The state of current research in glucose control globally combined with Australia's current activities and strengths in this field indicates areas of future research progress to which Australia is well placed to contribute. These are outlined below around the stages of the progression of type 1 diabetes.

Newly diagnosed and established diabetes

- Increase understanding of the mechanisms involved in prevention and reversal of hypoglycaemia unawareness

- Design and implement clinical trials in the outpatient setting to test the first generation of artificial pancreas systems capable of eliminating extremes in blood glucose levels

- Develop novel algorithms that will allow for effective and safe incorporation into the automated, integrated blood glucose measurement and insulin delivery systems

- Incorporate novel dietary paradigms to work in parallel and enhance novel medical devices for insulin delivery and glucose control

- Better define optimal approaches to the management of physical activity in type 1 diabetes to help minimise fluctuations in blood glucose control

Accelerators and research enablers

Creating a supportive research environment that will facilitate the implementation of the research directions described in the goals above by providing infrastructure, co-ordinating multidisciplinary approaches, supporting people, and creating partnerships.

Aim 1: Encourage translational research to deliver novel treatments and medical devices

Aim 2: Support collaboration, networking and resource sharing

Aim 3: Nurture the current and attract new researchers into the field of type 1 diabetes

|4.1| Accelerators and Research Enablers: Background and aims

Type 1 diabetes is a complex condition affecting multiple systems in the body. Solving the type 1 diabetes puzzle will require a novel, well-supported multidisciplinary research strategy. Approaches beyond the traditional research structures may be needed to reduce the impact of type 1 diabetes on the individuals and health care systems and translate research findings to improved patient outcomes.

The last decade has seen the pace of scientific discovery accelerate significantly due in part to advances in molecular science and research technology. The next step is to ensure that what we learn from basic research discoveries is being incorporated into contemporary medical therapies. This calls for large investments in infrastructure and a skilled workforce, with longer funding timelines and increased collaboration between basic and translational research and clinical practice sectors. Due to the escalating cost of bringing even a single new medical treatment to market, novel collaborations and partnerships between academia, governments and industry will be required.

As research advances, so must the established systems of medical research management and resource provision and allocation. New technologies have increased the costs of health research and resulted in the convergence of some traditionally distinct disciplines and the divergence of others. A focus on chronic health conditions has seen an increase in multidisciplinary research, often conducted across different institutions and sometimes across different countries.

The increasing size and skill of the medical research community is increasing the pace of research, but also placing strong competitive pressure on scientists for research funds at different levels of their careers. This section summarises the current situation and provides recommendations for supporting and enhancing the activities of the type 1 diabetes research sector in Australia.

|4.2| Accelerators and research enablers: The Australian situation

Diabetes health and research organisations and support: The NHMRC is Australia's peak funding body for medical research, with total grant payments exceeding $589 million in 2007. The NHMRC commitment towards type 1 diabetes research involves funding for single projects, some specific partnerships, and also larger programs such as the Centre for Clinical Research Excellence in Clinical Science in Diabetes based at the University of Melbourne.

In recognition of the impact that diabetes has on the Australian community, it is recognised as a National Health Priority Area. Key to this was the establishment of the National Diabetes Strategy and the National Diabetes Services Scheme (NDSS). Administered by Diabetes Australia and accessed via a nationwide network of pharmacies, the NDSS provides subsidised health products and support services to people with all types of diabetes. An estimated 97 percent of Australians diagnosed with diabetes are signed up to this service.

Statistics and information: The AIHW, Australia's national agency for health and welfare statistics and information, systematically collects diabetes-related health statistics. The AIHW utilises information from the NDSS, the Australian Paediatric Endocrine Group register, and the self-reporting National Health Survey to synthesise information about incidence, prevalence and the impact of diabetes on the Australian health system. Despite the national network and enormous epidemiological potential for valuable longitudinal studies, these initiatives remain largely administrative and under-utilised from a type 1 diabetes research perspective.

Health system structure and guidelines:
From a research and medical perspective, the national and universal structure of the Australian health system is also a valuable asset. Whilst "coalface" medical services are provided by State authorities, they are underpinned by federally funded initiatives that regulate and administer medical treatments and subsidies via Medicare, the Therapeutic Goods Administration and the Pharmaceutical Benefits Scheme.

Research is also underway into the development of evidence based approaches to clinical care of type 1 diabetes. The Australasian Paediatric Endocrine Group and the Australian Diabetes Society, with support from patient advocacy groups, are developing the first ever NHMRC-approved Clinical Care Guidelines for type 1 diabetes across the lifespan of the person with type 1 diabetes. Once completed these guidelines should support standards of clinical care and health care delivery in type 1 diabetes in Australia.

Changes in funding and support: While funding for Australian medical research has increased significantly over the last few years, these funds have been directed in general more towards established individual researchers rather than novel research avenues, cross-disciplinary programs or new technology.

This expansion of available funds has been accompanied by increased expectations of accountability and results from the governments and the funding community, and the requirement for new ways of co-ordinating and supporting research progress. This fact was emphasised in the recent reviews commissioned by the NHMRC to assess research funding and peer review processes and to consider the broader future vision of health and medical research in Australia. The first review, chaired by Professor Alan Bernstein, then President of the Canadian Institutes of Health Research, and the second, chaired by Dr Elias Zerhouni, Director of the United States National Institutes of Health, identified that greater co-ordination and integration between discovery research, innovation and translational research are central to scientific success, particularly where increasing scope and complexity requires "unconventional" interdisciplinary efforts.

According to both Reviews, and the subsequent NHMRC response, health systems should seek to be integrated on some level with higher education facilities, research institutes, research funding bodies and disease advocacy groups to ensure effective information transfer and collaboration.

Existing research resources: Australia has no official national resource, nor central data storage database, for type 1 diabetes research. There are a number of local resources such as DNA/tissue banks and specialised imaging and genomic equipment but these are geographically fragmented within individual research centres and are often not available for wider use.

Scientific perspective: The above strengths and limitations were also reinforced by Australian type 1 diabetes researchers and clinicians at the Australian Type 1 Diabetes Research Directions Workshop in March 2009. Participants worked together to develop a list of the key challenges they saw as being faced by scientists working across the research spectrum.

They included:

- The inadequate and short-term nature of research funding, meaning that large scale programs can run out of funding before protocols and ongoing skills are fully established.

- Insufficient funding for cross-disciplinary collaborations, hampering potentially successful networking opportunities.

- Physical, bureaucratic and funding segregation between basic and clinical research, slowing down the translation of scientific breakthroughs into clinical trials and approved medical therapies.

- Insufficient research leadership from funding organisations, leading to a simplistic focus on funding for the individual and limited projects, rather than long term programs.

- The often geographically isolated, fragmented, under-funded and under-utilised nature of vital research resources such as databases and registries, cutting edge research technology and clinical networks.

- .The "brain drain" caused by uncertainty of career structure, leading to a where both highly qualified and experienced research personnel and early career researchers are lured overseas with the promise of stable and ongoing funding.

Given these challenges and the existing Australian research landscape, the following objectives are proposed to better accelerate and enable type 1 diabetes research progress in Australia.

Aim 1: Encourage translational research to deliver novel treatments and medical devices

The ultimate aim of any medical research process is to deliver successful breakthroughs to the clinic and to people who can benefit. For this to occur, stable and ongoing support for translational research and human clinical trials is required.

As illustrated in Figure 4.1, the translation pipeline from basic research to patient access moves through a series of important stages involving engagement from research partners – starting at the academic community, to the inclusion of the commercial sector, then finally approval of new therapeutics by regulatory and government bodies. Movement between these stages can be difficult, particularly if individual research programs are left responsible and with limited support for managing the transition.

The translational gap is not well supported for type 1 diabetes research in Australia, despite a strong base of successful basic research and provision of funding or support from the NHMRC, JDRF, the Diabetes Australia Research Trust, the Diabetes Research Foundation, individual medical research institutes, and others. One of the major challenges that has been identified by researchers is the lack of support for movement into human clinical trial activity, particularly the co-ordination of large scale trial support activities, services, patient recruitment and sites.
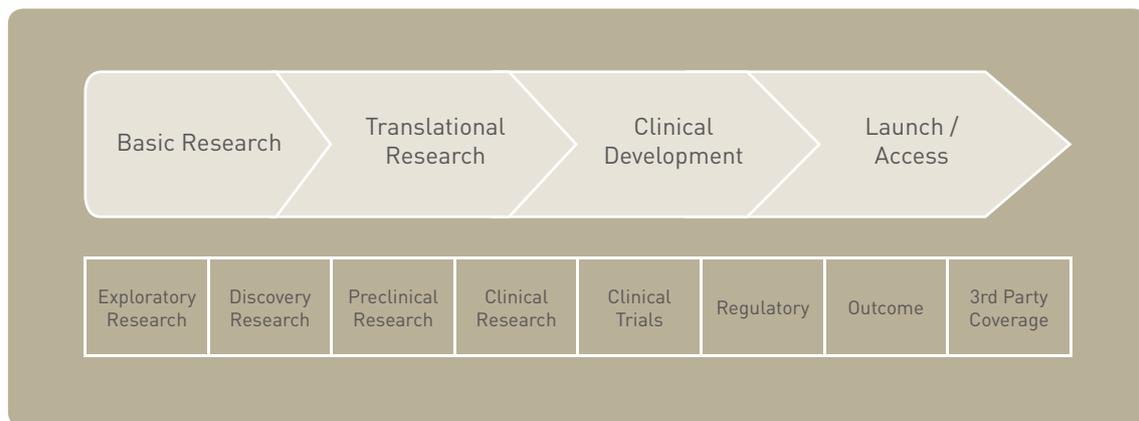
Figure 4.1 Translational pipeline of research progress

Establish a national clinical trial platform in type 1 diabetes: Globally, the number of type 1 diabetes clinical trials is growing significantly. In 2009, JDRF alone funded 41 clinical trials, up from only five in 2000.

Close collaborations between multiple funders would leverage resources and influence. In Australia, the NHRMC and JDRF have a long-established partnership including the DVDC that manages a portfolio of projects with a focus on disease prevention at various stages of the translational pipeline, including providing assistance with study design to move a basic research outcome towards preclinical and safety studies.

In addition, there are no co-ordinated national patient referral networks for type 1 diabetes in Australia at present. Each trial is generally required to conduct its own recruitment, generally from scratch and in conjunction with individual centres. This is not a cost effective or efficient use of the time of clinicians and trial development experts.

The establishment of a type 1 diabetes clinical trial network in Australia would provide clinical experience and early access for Australian patients to new medicines and therapies, and ultimately assist in the delivery of improved clinical practice and long term health outcomes.

Australian research case study

The Diabetes Vaccine Development Centre

The Diabetes Vaccine Development Centre Ltd (DVDC) is a joint initiative of the Australian Government, through the NHMRC, and JDRF. Both organisations initially contributed $5 million each to establish the DVDC, with a second round of funding underway.

The DVDC was initially established to accelerate the development of one or more vaccines that would prevent or delay the progress of early onset diabetes, aiming to have clinical proof of concept in three to five years, with studies conducted to a standard acceptable to regulatory agencies and to an eventual industrial partner.

The DVDC currently manages a portfolio of preclinical and clinical research projects, and co-ordinates a network of eight sites across Australia involved in these projects as well as providing trial co-ordination, data management and other support services.

Build early partnerships across sectors, agencies and patient groups: The progression of any basic research breakthrough towards medical therapy will necessarily involve multiple commercial parties offering specialised services. Strategic partnerships and alliances between traditional research hubs, pharmaceutical and biotechnology companies may accelerate the projects through the pipeline and open access to capabilities and broader financing structures.

Partnerships with patient groups are also essential on a number of levels. In addition to representing a disease-specific community and therefore facilitating access to potential trial participants, they are able to add the 'patient perspective' to the consideration by regulators of the potential benefit of any class of products or therapies. Many patient groups and specialist foundations are also a source of research funding, particularly for clinical and early career research.

Aim 2: Support innovative technologies, networking and resource sharing

The access and availability of modern biotechnology has already transformed the face of type 1 diabetes research. For Australia to maintain a high international standing, it is imperative researchers have access to cutting-edge technology as it emerges.

Novel technologies are costly, advanced and often require skilled technical staff to operate. This can make it difficult and cost prohibitive for individual research laboratories and even institutes to acquire. Hence, centres of excellence or consortia for sharing of equipment and expertise would enable broad access. Highlighted below are some of the more promising directions being taken to address this issue.

Non-invasive technologies foster novel research avenues: Technological breakthroughs achieved over the last five years using bioimaging approaches such as cellular electron tomography and magnetic resonance imagery (MRI) are providing diabetes researchers with the unprecedented capacity to map pancreatic cells with greater reliability and detail than ever before, both in vivo and in vitro.

This field of '3D imaging' has a common goal of imaging key events and structures related to islet and beta-cell biology and the pathophysiology of type 1 diabetes as reliably as possible in a native tissue setting, as opposed to using isolated primary cells or immortalised cell lines. This holds great promise for a number of key research avenues, particularly beta-cell regeneration and replacement.

Despite the fact that a number of these technical advances have essentially been developed in parallel, there has been little if any co-ordinated and considered overlap between the groups pioneering use of this technology. There is therefore a unique opportunity to develop integrated multi-modal imaging approaches that incorporate the shared development of molecular tags to allow a given process or structure to be visualised across a range of scales/resolutions.

Emerging technologies support functional genomics, proteomics and developmental biology: Thousands of genes and gene clusters are involved in the development, growth and function of the beta-cell in type 1 diabetes. The expression of these genes changes with shifts in their environment and understanding this requires complex technologies including bioinformatics to identify the patterns of activity and key regulatory molecules.

Furthermore the translation of gene products to proteins provides further opportunities to identify drug targets and disease biomarkers. Working with clinicians, researchers will be able to identify easy to measure surrogate markers of the immune attack and progression of the disease to complications. Appropriately validated markers would increase the ability of researchers to conduct clinical trials as well as reduce the cost and shorten the duration of trials.

Aim 3: Nurture current and attract new researchers into the field of type 1 diabetes

Research in type 1 diabetes spans across a broad range of scientific disciplines and research focus is shifting to incorporate and combine these into multidisciplinary research programs. Research progress is therefore reliant on, and requires investment in, an appropriately trained and diverse group of medical researchers, scientists and clinical researchers who at present may have a more limited presence in the area of type 1 diabetes.

Enhance support for current researchers in all stages of their career: In recent years the amount of general funding for medical and health research in Australia has increased steadily. Nevertheless a survey of the medical research workforce by the Australian Society for Medical Research indicated that 73 percent of respondents were considering leaving active research. The reasons given for this high number were varied and included lack of employment security, shortage of long term funding, lack of adequate infrastructure for research, the large administrative burden (including grant applications) and a lack of

career development opportunities. Although the number of postgraduate students being trained has increased, the number of tenured academic positions had fallen.

As discussed in section 2.2, Australia's contributions towards international efforts to cure, treat and prevent type 1 diabetes are of high quality and have increased substantially in the last five years, but the type 1 diabetes research community is affected in the same manner as other disciplines by the changes in the biomedical career paths. A structured plan to support researcher career paths is critical to maintain the international performance, reputation and excellence of type 1 diabetes research in Australia and ensure the timely incorporation of modern therapies into medical practice.

A strong clinical trial platform is the cornerstone of translational research: Most Australian clinician researchers have significant clinical loads (compared to their North American and European colleagues) and hence limited research time. Some areas of medicine such as endocrinology (particularly paediatric) are attracting less than desired numbers of young trainees and this poses a significant risk to the sustainability of high quality clinical treatment and research. Future progress and improvement in medical treatments depend on the research training and mentoring of researchers who are interested in pursuing a career in the clinical area and vice versa.

Partnerships across sectors accelerate research translation: The advancement of research in type 1 diabetes into new territories, such as epigenetic research, insulin bioengineering or algorithm development, requires novel expertise. Often collaborations of this nature are not easily supported as novel ideas can be perceived as high risk by funders, and investigators may be unequally recognised for their involvement. A realistic support system should be established where a wide range of high-risk, high-impact research is funded and investigators from diverse fields receive awards that are supportive of their career pathways and also recognised by their home institutions.

Australian research case study

The Australian Islet Transplantation Program – An example of translational research and increasing research infrastructure and capacity in Australia.

Australian researchers are pioneers in the field of islet transplantation, spearheading the international effort to move islet transplantation from an experimental procedure to a more widely available clinical option for people with type 1 diabetes. The Australian Islet Transplantation Program was established in 2005 as a collaboration between JDRF and the Commonwealth Department of Health and Ageing - the first partnership of its kind in Australia.

To date, fourteen Australians with particularly difficult to manage diabetes have benefited from this procedure with many more on waiting lists at the three clinical centres in Sydney, Melbourne and Adelaide. To enhance the success of the process, 17 laboratory based projects have also been funded to encourage innovative approaches to the remaining challenges including immune rejection, tolerance and islet cell availability.

|4.3| Accelerators and research enablers: Recommendations

Undertake a systematic assessment of Australian research resources and diabetes landscape

a. **Establish a working group to map available resources:** Identify and describe available databases and resources in Australia with consideration of how to merge, combine and manage access to the information. This will support the future establishment of tissue and DNA repositories and clinical trials resources.

b. **Engage Australian and international biotechnology companies:** Support technology transfer and intellectual property capture, including identifying Australian biotechnology and pharmaceutical opportunities.

c. **Support collection of comprehensive statistical data regarding the key diabetes facts in Australia:** Assess Australian prevalence of type 1 diabetes and estimate the total impact of type 1 diabetes on the health system.

Establish large scale, co-ordinated infrastructure

d. **Establish a type 1 diabetes clinical platform and patient referral network:** A clinical platform providing the services, sites, and support for trials will improve Australian capacity to conduct clinical trials including linking with large multicentre international trials. Access to clinical trials also means more timely access to new therapies for Australians with type 1 diabetes.

e. **Establish co-ordinated and easily accessible DNA, tissue and data-banks:** Research would be enhanced by access to human tissue banks such as islets, whole pancreata, and DNA samples co-ordinated with patient sample cohorts. This would help promote novel research directions such as testing biomarkers. In addition, a web based database of patient information can be used as a centralised forum for information sharing.

f. **Development of 3D Imaging Centre:** A virtual 'global 3D imaging centre' aimed at co-ordinating expertise, reagent design and data sharing among experts in each of these areas would foster more collaborative research.

g. **Establish comprehensive, cross-functional and multidisciplinary centres of excellence:** Centres in the type 1 diabetes area, well fitted with high class equipment to promote cost sharing and achieve critical mass for research, mentoring and career opportunities. Provide targeted funds for infrastructure to run consolidated animal breeding/housing facilities that increase efficiency and quality of research models.

h. **Maintain and expand international linkage of data and information sharing:** Establish formal and co-ordinated partnerships with large international, open resources such as the existing type 1 diabetes human genetics database that will allow data sharing and downloading in the Australian setting. Foster an opportunistic mindset that will leverage international resources with the national data.

Facilitate researcher career paths

i. **Support should be improved for researchers in all stages in their career:** With particular focus on the early and middle stages that often corresponds to time of increased grant competition and conflicting personal priorities. This would benefit from a co-ordinated support network leveraging funding opportunities with multiple organisations and partners.

j. **Support clinician researchers:** Increase research presence in the large teaching hospitals through clinical research programs that offer research nursing support, allied health, research labs, and statistical support that are well connected to a clinical trial platform. Support would also be improved through the creation of career packages for clinicians that include and reward research time.

k. **Provide funding for travel awards:** Increasing opportunities for scientific visits or exchanges aimed at early to mid-career scientists with the purpose of increasing collaboration and funding opportunities.

Support and reward information exchange and collaborative efforts

l. **Conduct specialised type 1 diabetes workshops:** Convene multidisciplinary workshops that engage diverse experts in the research community in finding novel solutions to scientific questions in the area of type 1 diabetes.

m. **Increase grants for collaborative research:** Researchers applying for collaborative grants, including those outside of the existing type 1 diabetes medical field (such as bioengineers), should be recognised and awarded with equal capacity for budgetary independence.

Increase collaboration and communication between funding agencies

n. **Provide a clear and transparent research priority map:** Type 1 diabetes research in Australia is funded by several organisations. The focus and funding priorities may differ between the organisations as priorities are influenced by available budget, increasing cost of research, basic versus translational research focus and differing stakeholders. A clear and transparent map of research priorities may assist researchers and research progress.

o. **Increase the level of interaction between the agencies and co-funding opportunities:** Although individual agencies may differ in their funding priorities, increased partnership between them is desirable for research progress. It would increase the potential for building capacity and infrastructure, for example, as the cost of the resources can be shared.

|5.| Future development and implementation of the Australian Type 1 Diabetes Research Agenda

This Australian Type 1 Diabetes Research Agenda is the product of input from, and collaboration across, a diverse range of stakeholders. The content is relevant to the researchers, Governments, funding bodies, and the type 1 diabetes community.

It is hoped that this Agenda will spark further discussions within and between these groups that will ultimately increase the pace at which progress is made in Australia in the field of type 1 diabetes research. Such discussions will ideally lead to the further refinement of the Agenda over time, and hopefully also be a catalyst for increased collaboration in future planning and implementation of its directions.

Within the research community, broad-based input that was critical to the development of the Agenda will also be critical for its refinement. Structures for this will need to be created, including potentially the establishment of Scientific Advisory Committees to support refinement, evaluation, and implementation of the recommendations presented in the Agenda. This will required ongoing collaboration and intellectual exchange across institutions, geographies, and scientific disciplines, for which appropriate forums or workshops will be required building on the initial Australian Type 1 Diabetes Research Workshop.

The effective and efficient implementation of the Agenda also provides both opportunity and a responsibility for funders, with the potential for significant and beneficial collaboration around their response to these recommendations and the directions outlined in the Agenda.

The content of the Agenda should also be of interest to Governments, as they are influencers of research progress through direct and infrastructure funding and the administration of the legislative environment in which research is conducted.

The further development of the Agenda will also require the establishment of more formal connections with existing and planned international activities that are targeted towards the global development of research strategies for type 1 diabetes. This Agenda also creates for Australia the opportunity to play a more direct role with a greater contribution to these activities.

Importantly, the content and ongoing development of the Agenda will be of enduring interest to people with type 1 diabetes, as evidence of research planning and progress nurtures and sustains their deeply held hope for a cure.

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|6.3| Acknowledgements

|6.4| Abbreviations

ACE	Angiotensin-converting Enzyme
AdDIT	Adolescent type 1 Diabetes cardio-renal Intervention Trial
AGEs	Advanced Glycation Endproducts
AIHW	Australian Institute of Health and Welfare
BGLs	Blood glucose levels
CCRE	Centre for Clinical Research Excellence
CGM	Continuous glucose monitor
CTGF	Connective tissue growth factor
DAFNE	Dose adjustment for normal eating
DCCT	Diabetes Control and Complications Trial
DNA	Deoxyribonucleic acid
DVDC	Diabetes Vaccine Development Centre
GI	Glycaemic index
GoKinD	Genetics Of Kidneys in Diabetes
hESC	Human embryonic stem cells
HLA	Human Leukocyte antigen
INIT II	Intranasal Insulin Trial
iPS	Induced pluripotent stem cells
ITN	Immune Tolerance Network
ITP	Islet Transplantation Program
JDRF	The Juvenile Diabetes Research Foundation
MHC	Major Histocompatibility Complex
NDSS	National Diabetes Services Scheme
NHMRC	National Health and Medical Research Council
NOD	Non-Obese Diabetic
RAGE	Receptor for Advanced Glycation Endproducts
RCI	Relative citation impact
VEGF	Vascular endothelial growth factor

|6.5| Glossary

ACE inhibitor (angiotensin-converting enzyme) - a type of medication used to lower blood pressure and help treat kidney problems related to diabetes.

Adult stem cell - A cell found in the different tissues of the body such as blood, skin or muscle – that can renew itself and produce the specialised cells needed by that tissue (known as multipotency).

Alloimmune attack - The sort of immune response that occurs to material from another member of the same species, this is a common issue in transplantation.

Antibodies - Proteins made by the immune system to protect itself from foreign substances such as bacteria and viruses. In type 1 diabetes the antibodies are self-reactive.

Apoptosis - Programmed cell death that is triggered by physiological processes.

Autoantibodies - Antibodies that react to self, causing autoimmune disease.

Autoimmune disease - A disorder of the body's immune system in which the immune system mistakenly attacks and destroys body tissue.

Autoimmunity - An immune response where the body's immune system mistakenly reacts to self.

B cell - A type of immune cell that produces antibodies.

Beta-cells - Cells that produce insulin. They are located within the islets of Langerhans in the pancreas.

Blood glucose - The main sugar that the body makes from the food we eat. Glucose is carried through the bloodstream to provide energy to all of the body's living cells. The cells cannot use glucose without the help of insulin.

DiabCo$t Type 1 - A survey assessing the burden of type 1 diabetes and its complications, in Australia.

Diabetic ketoacidosis - An acute complication of type 1 diabetes that results from a lack of sufficient insulin in the body. This triggers the body to breakdown fatty acids instead of glucose, leading to ketone formation and dangerously high acidity of the blood. It is an extremely serious and life-threatening condition that may lead to coma and death. The symptoms of ketoacidosis are nausea, stomach pain, vomiting, chest pain, rapid shallow breathing, and difficulty staying awake.

Diabetic macular edema - A condition that can occur in either stage of diabetic retinopathy in which fluid collects in the central part of the retina resulting in blurred vision. Macular edema can be treated with laser surgery when central vision is threatened.

Embryonic stem cell - An unspecialised cell in an embryo that can divide indefinitely (self renew) and produce any cell in the body needed after birth (known as pluripotency).

Epigenetics - Changes in gene expression without changes in the DNA coding, that can be inherited and lead to long term complications.

Genetic loci - Locations on chromosomes where genes or groups of related genes can be found.

Glucagon - A hormone that raises the blood glucose level.

Glucose - A simple form of sugar that is created when the body's digestive processes break down the food we eat. Glucose is the body's main source of energy.

Glycaemic index (GI) - A system of ranking foods according to how much they raise blood glucose levels. For instance, the carbohydrate in a low glycaemic index food may have less impact on blood glucose than a high glyacemic index food.

Hemoglobin A1c (HbA1c) test - A blood test that measures average blood glucose over the past two to three months and is the best way to measure overall glucose control. For people with type 1 diabetes the goal is less than seven percent.

Honeymoon period - A period, in people with recently diagnosed type 1 diabetes, after the initiation of insulin treatment when the toxic effects of hyperglycaemia are relived by treatment and insulin production can increase.

Hyperglycaemia - High blood glucose, a condition that occurs in people with diabetes when their blood glucose levels are too high. Symptoms include having to urinate often, being very thirsty, and losing weight.

Hypoglycaemia - Low blood glucose, a condition that occurs in people with diabetes when their blood glucose levels are too low. Symptoms include feeling anxious or confused, feeling numb in the arms and hands, and shaking or feeling dizzy. Hypoglycaemia can lead to coma and death.

Hypoglycaemia unawareness - A condition in which one no longer recognises the symptoms of low blood glucose.

Insulin - A hormone produced by the beta-cells in the pancreas that regulates the production of glucose by the liver and the utilisation of glucose by cells to create energy for the body. Insulin is a medication necessary for people with type 1 diabetes.

Insulin pump - An insulin delivery system; a small mechanical device, that delivers a continuous flow of insulin (plus additional amounts before meals) through a needle inserted under the skin.

Islet cell transplantation - A surgical procedure involving transplanting islet beta-cells that produce insulin from a donor pancreas into a person whose pancreas no longer produces insulin.

Islet cells - Cells that make insulin and are found within the pancreas; also called pancreatic beta-cells.

Macrovascular complications - Pathology of the larger blood vessels due to high blood glucose associated with type 1 diabetes such as coronary heart disease, stroke and peripheral vascular disease.

Microvascular complications - Pathology of the smaller, peripheral blood vessels due to high blood glucose associated with type 1 diabetes such as retinopathy, neuropathy and nephropathy.

Nephropathy - Kidney disease caused by damage to kidney cells or blood vessels, Naphropathy can occur in people who have had diabetes for a long time, particularly if their diabetes has been poorly controlled.

Neuropathy - Damage to the nerves that can be very debilitating and painful. There are two main types of neuropathy, depending on which nerve cells are damaged. One type is called sensory neuropathy, which affects feelings in the legs or hands and is referred to as peripheral neuropathy. The other type is autonomic neuropathy, which affects nerves that control various organs, such as the stomach or urinary tract.

Pancreas - An organ in the body that produces insulin so that the body can use glucose for energy. The pancreas also makes enzymes that help the body digest food.

Retinopathy - A disease of the small blood vessels of the retina of the eye. In this disease, the vessels swell and leak liquid into the retina, blurring the vision and sometimes leading to blindness.

T cell - Cells of the immune system that can different roles either activating immune responses or killing targeted cells.

TEDDY - The Environmental Determinants of Diabetes in the Young trial looking at genetic and environmental causes of type 1 diabetes.

TrialNet - TrialNet is a network of 18 Clinical Centres working in cooperation with screening sites throughout the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia, and New Zealand. This network is dedicated to the study, prevention, and early treatment of type 1 diabetes.

TRIGR - Trial to Reduce Insulin dependent diabetes mellitus in the Genetically at Risk. This trial looks at the relationship between cows milk formula and the development of type 1 diabetes in children.

Type 1 diabetes - An autoimmune disease in which the immune system mistakenly destroys the insulin-secreting beta-cells of the pancreas, removing the body's ability to regulate blood glucose levels. Daily insulin injections are necessary to stay alive.

Type 2 diabetes - A condition in which the body either makes too little insulin or cannot properly use the insulin it makes to convert blood glucose to energy. Type 2 diabetes may be controlled with diet, exercise, and weight loss, or may require oral medications and/or insulin injections.

Xenotransplantation - A surgical procedure in which tissue or whole organs are transferred from one species to another species.

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