DIABETES RESEARCH & WELLNESS FOUNDATION

RESEARCH STRATEGY

The Diabetes Research & Wellness Foundation (DRWF) was established in 1998 to support people living with diabetes and fund research into the causes, complications, treatments and cure for diabetes by supporting projects of original scientific or clinical merit and researchers with a commitment to diabetes

DIABETES RESEARCH WELLNESS FOUNDATION

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PURPOSE

The aim of DRWF's Research Strategy is to clearly set out the charity's objectives and priorities for research funding and outline a plan for achieving them.

The strategy will demonstrate a knowledge and understanding of the role the charity plays in consideration of the needs and requirements of its members and the wider community. It will provide a clear focus for stakeholders, illustrating the charity's commitment to its aims and plans for achieving its goals. In turn, this will build a clear picture and understanding of the role of research within the charity's wider objectives.

The provision of a clear research strategy will allow researchers to determine whether their research falls within the charity's funding remit. Furthermore, it will enable DRWF's Research Advisory Board to make recommendations for funding in-line with the charity's aims and objectives, whilst assisting the Trustees to assess the effectiveness and impact of the charity's activities.

Although DRWF will set the basis of the Research Strategy in place for a period of 5 years, it will be reviewed on an annual basis, when aspects of which may need to be amended or updated. This could be for a number of reasons, not least when the need to rethink mechanisms of funding, arise. Likewise, as the needs of the charity's members and the wider community change, the charity's research funding programmes will adapt and evolve in consideration of those requirements.

ROLE OF THE CHARITY

Since becoming fully operational in 1999, thanks to an extremely successful fundraising programme, DRWF have been able to commit nearly £3.5 million to diabetes research.

Analysis of the 2004 DRWF Network Member Survey (sent to over 10,000 members, healthcare professionals and other interested parties) revealed that in order to maximise the benefit to people with diabetes our research should concentrate on:

- improving the treatment of diabetes
- preclude it from developing in those at risk
- ultimately find a cure

DRWF's aim, through its research strategy, is to fund research projects focused on the

- prevention, complications and treatment of diabetes
- causes
- cure

Each year our goal becomes more important as the number of people diagnosed continues to rise. Today more than 200 million people worldwide are living with diabetes and, by 2025, this total is expected to increase to around 333 million people. Currently, about 6 million people develop diabetes each year.

Research with a strong relevance to diabetes and patient benefit is paramount. This reflects the views and wishes of our network members and donors, with whom we have a close connection, and reinforces DRWF's charitable objectives.

Our ultimate goal is to discover a cure for diabetes. We know that this is a long road but are intent on maximising the potential by funding the highest quality clinical and scientific research at the very best research institutions and supporting innovative projects.

Through fundraising, donations and legacies and in line with the charity's mission of relieving the suffering of people with diabetes, each year DRWF offers financial support for a selected number of proposals and projects connected with diabetes research.

As a patient focused charity with a close relationship with our network members, in addition to the responsibility we have to our donors, DRWF are committed to investing in research projects with tangibly beneficial/practical outcomes. Our research funding programme and successes are proof of this.

RESEARCH FUNDING PROGRAMME

The DRWF research programme is designed to support bright young researchers, as well as established institutions, as they strive to make the kind of life-changing break-through our members and supporters are hoping for.

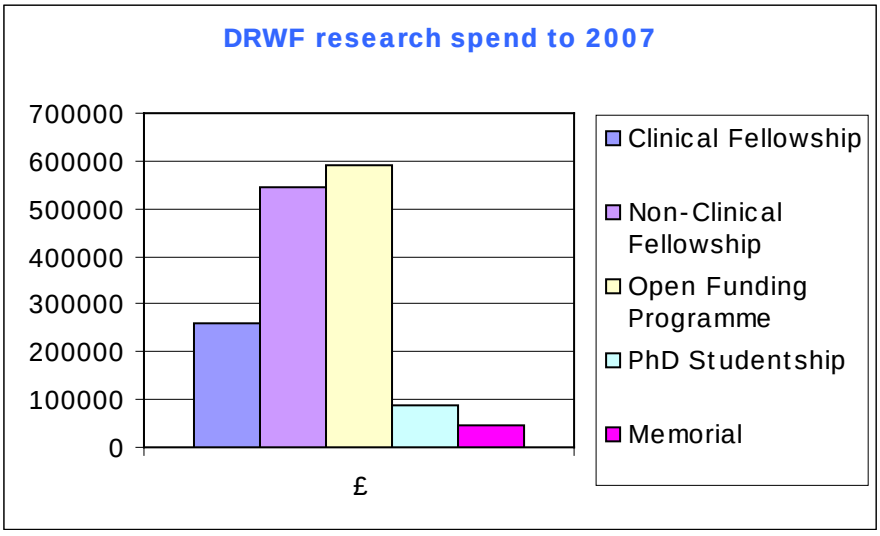
Since inception, the Diabetes Research and Wellness Foundation, through its Clinical and Non-Clinical Fellowships, Open Funding Programme and PhD Studentship awards, has funded numerous innovative research projects (focused on diabetes; its causes, treatment and cure) based at recognised institutions or within creditable research groups.

We continue to develop an ever-expanding grants award programme (on the whole based within institutions in the UK but exchanges and collaborative projects are also considered).

DRWF Research Fellowships are given for research related to causes, cures or complications of diabetes. Clinical applications are invited from medically qualified doctors working towards a higher degree (up to 3 years) and non-clinical from post-doctoral scientists at fellowship level (3 years) and are alternated between clinical and non-clinical, year-by-year. When we are awarding a DRWF Fellowship, we are also intent on rewarding determined and committed individuals who have a proven track record in diabetes research and can display an intention to continue working in the field. It is our hope that a DRWF Fellowship can serve as a significant and fruitful step in the career of a bright, young and ambitious researcher.

The DRWF Open Funding programme supports smaller projects offering hope of improving and enhancing the lives of those living and coping with diabetes on a daily basis. Most likely they will be centred on advancement or exploration of treatments, services or products. The charity favours original clinical or scientific projects and selects on original clinical or scientific merit. Exchange fellowships will also be considered, especially between the UK and the USA. These grants may also be used to top-up a shortfall in funding of a larger, more ambitious project. Duration 1 year (although extensions may be considered).

When funds allow, the DRWF calls for PhD Studentship applications – these awards are intended for a PhD clinical or non-clinical student researcher working in the field of diabetes (duration 3 years).



It is considered central to the ethos of the DRWF that our researchers show a commitment to a future in diabetes research and consequently improving the lives of people with diabetes. Some examples of research supported by DRWF are outlined on pages 6 - 9.

Diabetic Nephropathy **Open Funding Programme**

Recipient: Dr Andrew Advani
Institution: University of Newcastle
Project: Does Urotensin II receptor blockade prevent progression of experimental diabetic nephropathy?

Summary: Diabetic nephropathy is the commonest single cause of end-stage renal disease in the western world, continuing to rise in both incidence and prevalence with further major increases expected as part of the world-wide epidemic of the disease. Despite their importance, blood pressure management and current treatments are only partially effective in diabetic nephropathy with only a 20% reduction in the number of patients progressing to endstage renal failure. Supported by a research grant awarded by DRWF in 2005 and the Samuel Leonard Simpson Fellowship in Endocrinology from the Royal College of Physicians, Dr Andrew Advani and was able to study at one of the leading research centres in diabetic nephropathy worldwide (based in Melbourne, Australia and lead by Professor Gilbert). The preliminary research looked into the use of Urotensin II receptor blockers which could potentially be used in conjunction with conventional therapies to halt the progression of diabetic kidney disease. Dr Advani's research produced extremely interesting findings as to the role of growth factors in the pathogenesis of angiotensin II dependent hypertension and renal disease and he is continuing this research on the back of his success due to the award from DRWF in Newcastle and Toronto in order to extrapolate his previous findings to the diabetic setting in the anticipation that this will lead to new therapies that may slow the progression of diabetic kidney disease.

Hypoglycaemia **Studentship**

Recipient: Mr Mayowa Osundiji
Institution: Department of Medicine, University of Cambridge
Project: Glucokinase in specialised glucose-sensing neurones in Brain plays a key role in controlling blood glucose

Summary: Glucokinase (GK) is a specialised protein used in the pancreas to sense changes in blood glucose. It acts as a "gate" controlling the amount of glucose flowing into glucose-sensing pathways. It is also found in brain areas which sense low blood glucose (hypoglycaemia).
Some patients with type 1 diabetes lose these protective responses putting them at an increased risk of suffering episodes of severe hypoglycaemia. Mr Osundiji will also examine whether blocking brain GK might help restore protective responses to hypoglycaemia.
Finally, he will examine whether brain GK plays a wider role in controlling blood glucose and the sensitivity of tissues outside the brain such as fat and muscle to the glucose lowering effects of insulin. If this is true, brain GK might also represent a pharmacological target for reducing insulin resistance in type 2 diabetes, although probably in this case by increasing the activity of GK.
Due to excellent progress in this research the DRWF Trustees have approved continued support on the recommendation of the Chairman of the charity's Research Advisory Board.

Insulin resistance and cardiovascular disease — **Open Funding Programme**

Recipient: Dr Antonio Vidal-Puig
Institution: University of Cambridge
Project: Insulin resistance and cardiovascular disease in PGC1b-/-mice

Summary: This project is relevant to diabetes because it addresses how metabolic defects typically associated with diabetes promote cardiovascular problems. The objective is to investigate why diabetes is a cardiovascular risk factor and how it makes us more susceptible to myocardial infarction. Cardiovascular mortality and morbidity are rapidly increasing worldwide in parallel with metabolic disorders like insulin resistance, type 2 diabetes (DM2) and obesity, all well known cardiovascular risk factors. Molecular mechanisms linking insulin resistance or any other metabolic disorder to cardiovascular disease remain largely unknown. Dr A Vidal-Puig was awarded research funding by DRWF in 2005 in order to explore energy homeostatis processes and the effect they have on metabolic, mechanical and electrophysiological alterations. The results of this research have been published (see page 12) and identified a general defect in the expression of genes involved in mitochondrial function, and specifically, the electron transport chain.

Cardiovascular disease — **Clinical Research Fellowship**

Recipient: Dr Balasubramanian Ravikumar
Institute: University of Newcastle
Project: Is the abnormal postprandial suppression of hepatic glucose production (HGP) in type 2 diabetes reversible by decreasing intrahepatic triglyceride (TG) stores?

Summary: Type 2 diabetes (T2DM) is characterised by both fasting and postprandial hyperglycaemia. T2DM carries a markedly increased risk of cardiovascular disease and this excess risk is not explained by the increase of conventional cardiovascular risk factors. Recently, increasing evidence indicates that postprandial hyperglycaemia is an independent risk factor for both macrovascular and microvascular complications of diabetes. A DRWF Clinical Research Fellowship was awarded to Dr Ravikumar in 2004 to study the effect of normalising insulin and glucagon on the rate of suppression of HGP and the effect of decrease in hepatic TG stores on postprandial suppression of HGP in T2DM and impaired glucose tolerance (IGT) subjects.

Genes **Non-Clinical Research Fellowship**

Recipient: Dr Sergey Nezhentsev
Institution: Cambridge Institute for Medical Research, University of Cambridge
Project: Mapping novel type 1 diabetes genes in the major histocompatibility complex

Summary: Type 1 diabetes (T1D) is a complex immune-mediated disease with strong genetic susceptibility. Genes located in the Major Histocompatibility Complex (MHC) on human chromosome 6 are its major genetic determinants. Previous research has shown that MHC contains an uncharacterised type 1 diabetes gene. The present study will localise this gene and analyse a new type 1 diabetes-associated molecule. It will improve our understanding of the disease pathogenesis and open new possibilities for genetic prediction of type 1 diabetes. In his first year, Dr Nezhentsev has achieved significant success. The results make a valuable contribution to our understanding of the role of the HLA region in type 1 diabetes and providing new insights into how this chromosome region may be conferring susceptibility to disease. The prospects for the second year look exciting.

Diabetic retinopathy **Open Funding Programme**

Recipient: Dr Stephen Aldington
Institution: Imperial College London
Project: Does the location of hard exudates affect the likelihood of subsequent visual loss, or the likelihood of laser treatment to the macula?

Summary: Diabetic retinopathy remains the most common cause of blindness in the UK in the working age population. The most common reason for loss of sight as a result of diabetic retinopathy is the development of macular oedema. In this small study the researchers used photographs of the retina from a completed study called the UKPDS to investigate whether patients who had these hard exudates located physically above the centre of the macula (a point called the fovea) were more likely to eventually suffer from loss of sight than those in whom the hard exudates were located only below or to the side of the fovea. Although the original hypothesis has proved to be rejected by the study, it has nonetheless generated some good quality useful data on retinopathy.

Insulin Resistance **Open Funding Programme**

Recipient: Professor Peter Arner
Institution: Karolinska Institutet
Project: Finding the genes in human adipose tissue that cause insulin resistance

Summary: Insulin Resistance is a major pathogenic factor behind the development of type 2 diabetes. It is still unknown what factors are causing insulin resistance but it is likely that adipose tissue plays a key role. DRWF funded a collaborative project between Lipid Laboratory at Huddinge University Hospital, Karolinska Institutet, Stockholm, Sweden (head Professor Arner) and Integrative Physiology Group, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford (head Keith Frayn) which aimed to find the genes causing low lipolytic capacity in subcutaneous fat cells. The project was judged to be highly relevant to the understanding of the role of insulin resistance for type 2 diabetes and the results of the research demonstrated a human specific gene in adipose tissue which could be of importance for insulin resistance. The results of this research have been published (see page 12).

Funding recipients are required to provide interim, annual and final reports as a condition of the research grant awarded

INSTITUTIONAL GRANTS

Our research portfolio also demonstrates a commitment to support institutions whose aim is to relieve the symptoms of diabetes whilst aiming for a cure.

DRWF Human Islet Isolation Facility, OCDEM — Institutional grant

Islet Cell Transplantation

Islets are clusters of cells within the pancreas that produce insulin, a hormone that controls blood glucose levels. In type 1 (insulin-dependent) diabetes these islets have stopped functioning and therefore insulin injections are required. Preliminary trials demonstrated that it is possible to reverse type 1 diabetes by transplanting healthy islets from organ donors. This relatively minor, minimally invasive procedure can potentially reverse some of the long-term complications of the disease such as blindness, kidney failure and heart disease.

In 2004 DRWF made a 6 year institutional grant commitment to the Nuffield Department of Surgery, Oxford in order to provide a state-of-the-art facility for isolating human pancreatic islets. This unprecedented £1.2 million award not only enabled the Oxford Programme to advance, but facilitates a range of research projects that require isolated human islets, aimed at finding a cure for diabetes.

The new facility is based within the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) at the Churchill Hospital and the generosity of DRWF supporters was recognised on a plaque naming the 'DRWF Human Islet Facility' at OCDEM on 19th January 2006.

As part of DRWF's ongoing collaboration with and commitment to the Oxford islet programme additional funding has been awarded to: purchase essential equipment within the islet isolation facility, support salary of Transplant Co-ordinator and fund a post-doctoral scientist within the human islet isolation facility.

It is expected that the facility will become regarded as one of the best in Europe and hoped that the minimally invasive treatment of islet transplantation could be offered as a treatment to children within 5 to 10 years.

The DRWF are proud to be associated with the Oxford Islet Transplant Programme and believes investing in this programme validates the Diabetes Research & Wellness commitment to fund, and continue to fund, world-leading scientific research.

Spring Point Project **Institutional grant**

As promising as human islet cell transplantation is, the limited number of donors remains a stubborn obstacle. Researchers argue that animal-to-human transplants may be necessary to make islet transplantation a viable solution for the tens of thousands of people who suffer from diabetes.

Following the success of relevant pre-clinical trials, in which primates with diabetes were cured by porcine islet transplants, Dr Bernhard Hering and the team at the University of Minnesota's Diabetes Institute for Immunology and Transplantation hypothesised that islet cells from pigs could be developed into a widely available islet cell replacement therapy.

The DRWF network of charities worldwide has raised funds to support the Spring Point Project (headed by lead investigator Dr Hering) which aims to: establish facilities to raise pigs with high islet yields, incapable of transmitting porcine endogenous retroviruses; genetically modify porcine islet cells to minimise recipients' need for immunosuppressive drugs; produce animals with sufficient islet supplies for clinical trials and develop high-capacity production facilities for widespread distribution of porcine islet cells, following successful clinical trials.

The results of research conducted by the University of Minnesota mark a turning point in developing islet replacement therapies into a viable and widely available solution for type 1 and potentially type 2 diabetes. The research team also identified critical pathways involved in immune recognition and rejection of pig islet transplants.

It is anticipated that with all relevant ethical approval, human trials could commence by 2009 and may have huge future potential in the treatment of people with diabetes.

Institutions are required to provide annual reports as a condition of the award.

ACKNOWLEDGEMENTS

The DRWF require researchers to make every effort to inform them of any potential publication or dissemination of research findings and to acknowledge the charity in any publication or publicity.

The Diabetes Research & Wellness Foundation is acknowledged in the following publications:

Professor Peter Arner **DRWF Open Funding 2004**

American Journal of Clinical Nutrition 2005
Changes in adipose tissue gene expression with energy-restricted diets in obese women

Diabetes 2005
A human specific role of cell death-inducing DFFA (DNA fragmentation factor-alpha)-like effector A (CIDEA) in adipocyte lipolysis and obesity

Diabetes - Accepted for publication June 25, 2005
The CIDEA gene V115F polymorphism is associated with obesity in Swedish subjects

Journal of Clinical Endocrinology and Metabolism - Accepted for publication July 13, 2005
A unique role of monocyte chemoattractant protein 1 among chemokines in adipose tissue of obese subjects

Dr Chris Burns **DRWF Non-Clinical Fellowship 2003**

Diabetes 2004
The role of cytosolic phospholipase A_2 in insulin secretion

Diabetes 2004
Glucose-induced regulation of COX-2 expression in human islets of Langerhans

Drug Discovery Today 2004
Beta-cell replacement technologies: the potential of stem cells

Journal of Endocrinology 2004
Stem cell therapy for diabetes: do we need to make beta cells?

Reproductive BioMedicine Online 2005
Generation of a human embryonic stem cell line encoding the cystic fibrosis mutation ΔF508, using preimplantation genetic diagnosis

Diabetes 2005
Uncoupling of nutrient metabolism from insulin secretion by overexpression of cytosolic phospholipase A_2

BBRC 2005
Generation of insulin-expressing cells from mouse embryonic stem cells

BBRC 2005
The in vitro differentiation of rat neural stem cells into an insulin-expressing phenotype

Diabetes Mellitus – Current Stem Cell Research & Therapy 2006
Diabetes Mellitus: A Potential Target for Stem Cell Therapy

Diabetes 2007
The Role of Arachidonic Acid and its Metabolites in Insulin Secretion from Human Islets of Langerhans

Dr Hari Hundal **DRWF Open Funding 2003**

Eur. J. Biochem. 2003
Use of lithium and SB-415286 to explore the role of flycogen synthase kinase-3 in the regulation of glucose transport and glycogen synthase

FEBS Letters 2003
Insulin regulates the expression of the GLUT5 transporter in L6 skeletal muscle cells

Molecular and Cellular Biology 2003
Ceramide Disables 3-Phosphoinositide Binding to the Pleckstrin Homology Domain of Protein Kinase B (PKB)/Akt by a PKCζ-Dependent Mechanism

Molecular and Cellular Biochemistry 2004
Fructose transport and metabolism in adipose tissue of Zucker rats: Diminished GLUT5 activity during obesity and insulin resistance
Biochem. J. 2004
Intracellular ceramide synthesis and protein kinase Cζ activation play an essential role in palmitate-induced insulin resistance in rat L6 skeletal muscle cells

Dr Antonio Vidal-Puig **DRWF Open Funding 2005**
PloS Biology - Open Access November 2006
Ablation of PGC-1β Results in Defective Mitochondrial Activity, Thermogenesis, Hepatic Function, and Cardiac Performance

Professor Peter Jones **DRWF Open Funding 2005**
Diabetologia 2006
A role for kisspeptin in islet function

Dr Sergey Nejentsev **DRWF Non-Clinical Fellowship 2005**
Nature Genetics 2007
Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes
BMC Genetics May 2007-07-18
Sequencing and association analysis of the type 1 diabetes – linked region on chromosome 10p12-q11

DRWF STRUCTURE

BOARD OF TRUSTEES

A Board of Trustees governs the Diabetes Research & Wellness Foundation – the trustees' role is to guide, advise and support the Chief Executive as she and her team implement the vision of the charity.

It is imperative that the Diabetes Research & Wellness Foundation's research portfolio facilitates first class research into the cause, care and advances in the treatment of diabetes. With the guidance and recommendation of our Research Advisory Board, the charity Trustees make funding decisions with these priorities in mind.

DRWF RESEARCH ADVISORY BOARD

The DRWF Research Advisory Board comprises experts in a wide variety of research disciplines to ensure that all applications are assessed knowledgeably and fairly.

The Advisory Board oversees our Open Funding Programme and biennial Clinical and Non-Clinical Fellowships (alternating) and currently meet once a year. While there is no set upward limit on tenure, board members are not expected to remain on the board for longer than three years.

We endeavour to minimise as far as possible the workload generated by these applications but, as a charity, we consider it vital that we operate a rigorous assessment procedure and we are greatly indebted to our board members for their commitment to our work. We do not pay an honorarium, but all expenses are reimbursed.

AMRC

As a member of the Association of Medical Research Charities we are committed to maintaining a rigorous peer review process for the assessment of research applications, for which our Research Advisory Board are responsible. This process ensures that only the highest quality research at the best institutions receives DRWF funding.

EVIDENCE OF TRANSPARENCY

DRWF Website:

- Details of members of the DRWF Research Advisory Board
- Board of Trustees
- Annual Report
- DRWF research funding available
- DRWF funded research (lay summaries, researchers and institutions)

Diabetes Wellness News: (10,000+ DRWF network members):

- DRWF funded research (lay summaries, researchers and institutions)

DRWF Annual Report: (distributed to large donors and available on request)

- Contains details of grants awarded within the financial year with total commitment to-date.

AN EFFECTIVE RESEARCH STRATEGY

Research is key to the aims of the Diabetes Research & Wellness Foundation.

Investing in the most committed diabetes researchers is fundamental to the DRWF strategy. Groundbreaking research has been funded by the DRWF and has produced significant results. These results will, we hope, assist in the prevention and treatment of people with diabetes and improve their lives - enabling them to stay well until a cure is found.

Through the monthly Diabetes Wellness News (sent to our members and supporters) we are able to communicate effectively what research has been funded and the anticipated (and actual) result. At the same time, we report on and publicise this information through our website www.drwf.org.uk so reaching a wider audience.

The Diabetes Research & Wellness Foundation, the DRWF Board of Trustees and Research Advisory Board will endeavour to apply AMRC principles and operate best practice in all areas of its Research Strategy. For information on Peer Review and Application Procedure, please see separate document.

STRATEGIC AIMS AND PRIORITIES

The Diabetes Research & Wellness Foundation will endeavour to adhere to its Research Strategy whilst continuing to look at ways in which it can improve as outlined below:

Transparency

- Publish DRWF research strategy and processes on website
- Lay summaries of **outcomes** of research completed to be made available in the public domain via DRWF website and Wellness News (DRWF newsletter)

Peer Review processes

- Evaluate and implement revisions where required to comply with AMRC best practice

Measuring research outcomes

- Evaluation
- Review
- Methodology

Research Priorities

- Continue to identify priorities with DRWF aims in mind
- Adjust when necessary
- Define methodology

Funding research

- Review fundraising schemes
- Assess effectiveness and ongoing achievement levels
- Review values and terms of awards at the recommendation of the Research Advisory Board

Collaboration

- Explore prospect of partnerships to further enhance the strength and financial viability of the charity

Review

- The DRWF are conscious of the need to review its research objectives and priorities on a regular basis thereby meeting the needs and objectives of the charity, its members and supporters in an ever-changing environment. With this in mind a survey involving over 10,000 people with diabetes has been undertaken in 2007 and will be repeated every 2 years
- Assess DRWF effectiveness
- Define and implement improvement as, when and where required
- Assess whether DRWF's ongoing fundraising programme will meet its research funding commitments

February 2007