Jewish Congregations of America and the Rabbinical Council of America said, "if cloning technology research advances our ability to heal humans with greater success, it ought to be pursued since it does not require or encourage the destruction of life in the process."

The question is to what extent religion could, or should, influence science and vice versa

The possibility of cloning humans challenges deeply held beliefs about creation and mankind's relationship with God. If God is seen as the only Creator and creation as a completed act, then there would be no right for man to tamper with it. Others, however, regard God as the Power of Creation and creation as a transformative process, and therefore find a role for human participation. Some Jewish scholars advocate the latter view when considering reproductive cloning as a means to accomplish good. "The process or 'mechanical' aspects of human cloning present no major legal obstacles from a Jewish perspective," commented Reichman. "However, the low efficacy and potential adverse outcomes of human cloning are legal concerns that would lead us to reject any human cloning at this time. Prospectively creating people of legally ambiguous lineage, and who may suffer profound social and psychological complications may preclude any future acceptance of cloning despite perfection of the procedure from a medical perspective."

Given the different ethical arguments that revolve around the status of the embryo, the conception of life and the nature of creation, it seems impossible to reach a consensus between different religions with regard to therapeutic and reproductive cloning. What is clear is that religious beliefs exert a strong influence on these debates.

In fact, the relationship between science and religion has often been difficult. Science has repeatedly shaken religious beliefs, at least in the Western tradition. The Copernican and Darwinian revolutions challenged our views of God's agency and forced people to re-examine their understanding of the universe and humanity's place in it. Today, we are in the midst of another scientific revolution that

If it keeps festering, religious hostility might further impede the public acceptance of science...

might change society through the applications of biological research while challenging our beliefs about the value of human life. The question is to what extent religion could, or should, influence science and vice versa. It comes back to the old problem about where to draw the line between the two realms. As Albert Einstein said: "For science can only ascertain what is, but not what should be, and outside of its domain, value judgments of all kinds remain necessary. Religion, on the other hand, deals only with evaluations of human thought and action: it cannot justifiably speak of facts and relationships between facts" (Einstein A (1941) Conference on Science, Philosophy and Religion in Their Relation to the Democratic Way of Life, Inc., New York, USA).

This means that scientists have to take into account the resistance on the part of some religions to resolve this new conflict between science and religion. If it keeps festering, religious hostility might further impede the public acceptance of science and have negative effects on general science education. Nevertheless, some of society's strongest cultural and moral values are deeply embedded in religious contexts. If science and scientists show respect for the moral wisdom emerging from religious traditions, this might help to make use of scientific knowledge in a thoughtful and sensitive way. Conversely, religious leaders need to be open to the knowledge emerging from science so as to advise society about how to apply it in accordance with moral and ethical values. As Einstein put it: "science without religion is lame, religion without science is blind."

Giovanni Franzetto

doi:10.1038/sj.embor.7400175

Like a snake in the grass

As the incidence of type 2 diabetes escalates, new developments offer hope for better treatments

An epidemic of obesity is reaching around the globe (Brower, 2002) and diabetes is sneaking up behind it. Type 2 diabetes, which accounts for 90–95% of all cases of the disease (type 1 is an autoimmune disease), is on a steep rise in both the developing and developed worlds. At its present rate of growth, the first quarter of the twenty-first century will see a doubling of the number of individuals suffering from diabetes to ~300 million worldwide. In the USA alone, diabetes is now the fifth leading cause of death, and cost around US\$132 billion in direct and indirect medical expenditures during 2002 (Hogan *et al*, 2003). There are 16 million diagnosed diabetics in the country, with almost the same number undiagnosed, and ~1 million new cases each year.

This not only has implications for those suffering from diabetes but also puts national healthcare systems under increasing stress. "The economic impact on the global healthcare economy will be overwhelming," said Gerald Bernstein, Associate Professor at Albert Einstein College of Medicine (Bronx, NY, USA) and former president of the American Diabetes Association. The main reason is that diabetes not only affects the pancreas but also slowly destroys the whole body, shortening lifespan by an average of 15 years. "Glucose is toxic to cells, and hyperglycaemia affects every organ of the body," said Bernstein. The increase in diabetes cases is caused by an ageing population, a sedentary Western lifestyle and rising obesity, which is fuelled by poor nutrition. Also, type 2 diabetes, which is

...diabetes not only affects the pancreas but also slowly destroys the whole body, shortening lifespan by an average of 15 years

historically associated with ageing, is now seen in alarmingly high rates in obese children and teenagers. This combined disorder has been dubbed 'diabesity', as ~40% of the obese will develop diabetes, according to Steven Shoelson, Associate Professor of Medicine at Harvard Medical School and Associate Director of Research at the Joslin Diabetes Center (Boston, MA, USA).

At present, there is no cure or treatment to prevent most complications, which include a three- to fivefold higher risk of cardiovascular disease and stroke, lower limb amputations, blindness, neuropathy and end-stage renal disease. In addition, twice as many patients with diabetes are diagnosed with Alzheimer's disease. In February 2004, researchers showed that reduced insulin signalling causes insulin resistance (IR) in the brain, which affects neuronal cells and triggers the biochemical changes that are typically seen in Alzheimer's disease (Schubert *et al*, 2004). Diabetes also causes amyloid plaques to accumulate in major organs, including the pancreas.

As a complex multigenic disease, type 2 diabetes proceeds slowly without apparent symptoms. Insulin-producing β -cells in the pancreas might begin to decline a decade before diabetes is eventually diagnosed, by which time it is thought to be too late to stop further loss of β -cells. "Type 2 diabetes has always been a snake in the grass, sneaking up on both those with the disease and their physicians," observed Roy Taylor, Professor of Metabolic Medicine at the University of Newcastle upon Tyne Medical School in the UK (Taylor, 2004). The disease is usually preceded by years of IR as the muscle gradually fails to respond to insulin. This causes the pancreas to pump out more insulin to lower the glucose levels in the blood, which culminates in the exhaustion and death of pancreatic β -cells and subsequent high blood sugar (hyperglycaemia). "IR in muscle is the earliest detectable defect in persons in whom

type 2 diabetes will later develop, and indeed, the best predictor for the development of type 2 disease," said Gerald Shulman, Professor at the Howard Hughes Medical Institute at Yale University (New Haven, CT, USA). The origins and development of IR, however, have been a tough problem to crack. An individual can be insulin-resistant for years without becoming hyperglycaemic but, alarmingly, younger people are now progressing more rapidly to diabetes, said George Holz, Associate Professor in Physiology and Neuroscience at the New York University School of Medicine (NY, USA).

Most diabetics end up relying on exogenous insulin, but this therapy is inexact at best, and maintaining tight control of blood glucose levels is often difficult, with many experiencing hypoglycaemia from insulin replacement. Although new types of insulin—oral and inhaled—and insulin sensitizers and delivery vehicles have improved, the long-term outlook for diabetic patients remains grim. The UK Prospective Diabetes Study confirmed that the inexorable decline in β -cell function was the same irrespective of treatment with dietary interventions alone, insulin sensitizers or insulin. "The concept of 'cure' in type 2 diabetes has been virtually nil," noted Bernstein. However, the amount of research into diabetes in the USA and elsewhere is pitifully low compared with that for cancer and other diseases. Diabetes research represents 3% of the overall budget of the US National Institutes of Health and has decreased more than 30% since 1981, whereas the death rate owing to diabetes has increased by 30%. Nevertheless, advances being made in the fields of genetics and genomics, epidemiology, inflammation, cell signalling and regulation, and obesity are yielding new drug targets for obesity and type 2 diabetes.

Susan Bonner-Weir, Associate Professor of Medicine at Harvard Medical School (Boston, MA, USA), studies the relationship between β -cell mass and function. Bonner-Weir and her colleague Anna Moore of the Massachusetts General Hospital (Boston, MA, USA) are developing better live-imaging methods to detect the ebb and flow of β -cell mass. Initial results indicate

Although new types of insulin—oral and inhaled—and insulin sensitizers and delivery vehicles have improved, the long-term outlook for diabetic patients remains grim

that type 1 diabetes seems to be caused by abrupt β -cell loss. By contrast, in type 2 diabetes, β -cell mass initially increases with body weight but can subsequently decrease by up to 50% regardless of weight. "Chronic hyperglycaemia results in the reduction of cells and cell mass. Does that mean that apoptosis is more prevalent in type 2? We don't know," Bonner-Weir commented. It might also indicate problems with progenitor-cell differentiation, a lack of compensatory growth or an abrupt loss of β -cells.

Because of its role in β -cell replication and differentiation, and its ability to slow apoptosis, glucagon-like protein 1 (GLP1), which is an incretin hormone produced in the intestine, is attracting much attention. "In type 2 diabetes, there is reduced incretin in the gut; if one restores the incretin effect, will that be useful in treating the disease?" asked Daniel Drucker, Director of the Banting and Best Diabetes Centre (Toronto, Canada).

GLP1 binds to pancreatic β -cells and stimulates insulin gene synthesis and secretion, which makes it an interesting target for pharmaceutical intervention. "The really interesting thing about GLP1 is that it only works when blood sugar levels are high, a potential benefit over [exogenous] insulin, which frequently causes hypoglycaemia," said Holz. Other studies showed that GLP1

also promotes satiety and inhibits food intake, which are useful in treating obese patients.

Amylin Pharmaceuticals (San Diego, CA, USA) is now in phase II testing of a GLP1-like drug, exenatide, which was originally derived from the venom of the South American Gila monster. The injectable 39-amino-acid drug reduced glucose output by the liver, reduced haemoglobin A1c levels—a long-term marker of high glucose levels—and caused an average weight loss of 2.2 kg.

ConjuChem (Montreal, Canada) reported interim results from its phase II trial in mid-April 2004, which showed that its compound DAC™:GLP-1 caused a statistically significant reduction in A1c levels after only one month, an average weight loss of 2.3 kg, and reductions in daily blood glucose and fasting glucose levels. Novo Nordisk (Bagsvaerd, Denmark) and Eli Lilly (Indianapolis, IN, USA) are also developing synthetic GLP1 analogues. Novartis (Basel, Switzerland) has just completed two phase II studies with DPP-4 inhibitors that block the destruction of GLP1. Transition Therapeutics (Toronto, Canada) is developing a therapy based on GLP1 and the hormone gastrin. The company recently reported that the drug normalized blood glucose levels for six weeks after treatment in diabetic

animals. "GLP1 is proliferative [...] and regenerates new insulin-producing cells from islet precursor stem cells," said their Chief Executive Officer, Tony Cruz.

Other evidence connects diabetes, obesity and inflammation. Shoelson found that fat promotes sub-acute levels of inflammation in the liver that produce interleukin-6 (IL-6), TNF- α , plasminogen activator inhibitor 1 (PAI1) and other cytokines, which in turn modify insulin signalling and insulin sensitivity. Shoelson therefore plans to conduct a trial using salicylates, such as aspirin, in diabetes patients, in light of the nineteenth-century discovery and research since then that aspirin acts as an insulin sensitizer in patients with diabetes and arthritis. Research by a Swedish team also found that cyclooxygenase-mediated inflammation is related to diabetes in elderly men, and indicates that chronic inflammation is an early process in disease pathogenesis (Helmersson *et al*, 2004).

Another hallmark of diabetes is the intracellular accumulation of lipids in muscle and liver, known as lipotoxicity. Schulman recently linked these symptoms to functional changes in mitochondria and β -cells (Petersen *et al*, 2004). Using magnetic-resonance spectroscopy, he measured rates of ATP synthesis *in vivo* in the skeletal muscle of lean, healthy children of parents with type 2 diabetes, and found a 60% lower rate of glucose uptake by muscle and a 30% reduction in mitochondrial phosphorylation compared with healthy insulin-sensitive controls. "Our findings suggest that an inherited abnormality in mitochondrial fatty acid metabolism may lead to the accumulation of lipid in muscle and may underlie insulin resistance in that tissue," Shulman said. In 2003, he pinpointed loss of mitochondrial function in muscle in the elderly as a cause of diabetes and showed that physical activity can increase the number of mitochondria by activating AMP kinase (Petersen *et al*, 2003). His most recent research shows how fat causes insulin resistance, which points to glucose-transporter activity as the rate-controlling step for insulin-stimulated muscle glycogen synthesis in type 2 diabetes.

Genetics is making other important contributions to the understanding of diabetes. Gene-expression studies identified groups of genes with reduced activity in patients with both types of diabetes and in individuals with an elevated risk of the disease (Patti *et al*, 2003). This in turn reduces the activity of a larger group of genes that are involved in fat and carbohydrate metabolism in mitochondria. Mary-Elizabeth Patti of the Joslin Diabetes Center therefore believes that reduced expression of genes that regulate oxidative phosphorylation in mitochondria might tip the scales towards insulin resistance.

In April 2004, another group confirmed that four single-nucleotide polymorphism (SNP) variations in the transcription factor hepatocyte nuclear factor 4- α (HNF4- α) correlated with type 2 diabetes in two distinct populations studied: Ashkenazi Jews and Finns (Silander *et al*, 2004). These SNPs are located in the *HNF4A* gene, which acts as a 'master switch' for hundreds of other genes in the liver, pancreas and other organs. Two months earlier, scientists at the Whitehead Institute for Biomedical Research (Cambridge, MA, USA) showed that alterations of the binding sites can cause misregulation of the expression of *HNF4A* and downstream targets, which leads to β -cell malfunction and diabetes (Odom *et al*, 2004).

Since the mid-1990s, when the insulin-sensitizer troglitazone was found to improve insulin sensitivity by interacting with peroxisome-proliferator-activated receptor- γ (PPAR- γ), this molecule has received a lot of attention as a potential drug target. Troglitazone was found to delay the decline in β -cell function and prevent the onset of diabetes in high-risk patients, but not after symptoms had emerged. PPAR- γ also links to PGC1, a transcriptional coactivator of PPAR- γ that is necessary for mitochondrial enzyme synthesis for fatty-acid oxidation. Researchers now recognize the importance of PPARs as lipid-sensing receptors that regulate lipid and glucose homeostasis through a complex neural network, according to Ronald Evans in the Gene Expression Laboratory of the Salk Institute for Biological Studies (La Jolla, CA, USA; Evans *et al*, 2004). Although PPAR- γ induces fat storage and weight gain, PPAR- δ is a key regulator of thermogenesis and

...type 2 diabetes, which is historically associated with ageing, is now seen in alarmingly high rates in obese children and teenagers

might therefore be a more desirable drug target. Evans notes that PPAR- δ activation in transgenic mice produces lean mice that are resistant to obesity, hyperlipidaemia and fat accumulation in tissues. Activation of PPAR- α promotes hepatic fatty-acid oxidation. Agonists of this receptor, such as fibrates, are used to lower triglyceride levels, but the effects on insulin sensitivity have not yet been examined, according to Evans.

Protein tyrosine phosphatase 1b (PTP1b) is another promising drug target. "Work by two groups in 1999 and 2000 showed that when this enzyme's gene was knocked out in mice, they became insulin-sensitive and resistant to obesity," said Zhong-Yin Zhang of the Albert Einstein College of Medicine, who has just started the company Tyr Pharmaceuticals (Cambridge, MA, USA) to develop inhibitors that work directly on the insulin receptor to increase insulin uptake. His team has developed several candidate PTP1b inhibitors that upregulate glucose

in muscle cells. Isis Pharmaceuticals (Carlsbad, CA, USA) is also testing an antisense PTP1b inhibitor, which is now in phase II trials.

Given the exponential increase in the incidence of diabetes worldwide and the enormous stress that the disease puts on healthcare systems, researchers and patients hope that these developments might soon result in new drugs to better handle diabetes and its complications, and might eventually lead to a cure.

REFERENCES

- Brower V (2002) Fighting fat. *EMBO Rep* **3**: 601–603
- Evans RM, Barish GD, Wang YX (2004) PPARs and the complex journey to obesity. *Nat Med* **10**: 355–361
- Helmersson J, Vessby B, Larsson A, Basu S (2004) Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. *Circulation* **109**: 1729–1734
- Hogan P, Dall T, Nikolov P (2003) Economic costs of diabetes in the US in 2002. *Diabetes Care* **26**: 917–932
- Odom DT *et al* (2004) Control of pancreas and liver gene expression by HNF transcription factors. *Science* **303**: 1378–1381
- Patti ME *et al* (2003) Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. *Proc Natl Acad Sci USA* **100**: 8466–8471
- Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI (2003) Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* **300**: 1140–1142
- Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI (2004) Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* **350**: 664–671
- Schubert M *et al* (2004) Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci USA* **101**: 3100–3105
- Silander K *et al* (2004) Genetic variation near the hepatocyte nuclear factor-4 α gene predicts susceptibility to type 2 diabetes. *Diabetes* **53**: 1141–1149
- Taylor R (2004) Causation of type 2 diabetes—the Gordian knot unravels. *N Engl J Med* **350**: 639–641

Vicki Brower

doi:10.1038/sj.embor.7400177