# REVIEW

# The use of animal models in diabetes research

Aileen JF King

*Diabetes Research Group, King's College London, London, UK*

**Correspondence**
Aileen King, Diabetes Research Group, Guy's Campus, King's College London, London SE1 1UL, UK. E-mail: aileen.king@kcl.ac.uk

Diabetes is a disease characterized by a relative or absolute lack of insulin, leading to hyperglycaemia. There are two main types of diabetes: type 1 diabetes and type 2 diabetes. Type 1 diabetes is due to an autoimmune destruction of the insulin-producing pancreatic beta cells, and type 2 diabetes is caused by insulin resistance coupled by a failure of the beta cell to compensate. Animal models for type 1 diabetes range from animals with spontaneously developing autoimmune diabetes to chemical ablation of the pancreatic beta cells. Type 2 diabetes is modelled in both obese and non-obese animal models with varying degrees of insulin resistance and beta cell failure. This review outlines some of the models currently used in diabetes research. In addition, the use of transgenic and knock-out mouse models is discussed. Ideally, more than one animal model should be used to represent the diversity seen in human diabetic patients.

## LINKED ARTICLES

Animal Models

This paper is the latest in a series of publications on the use of animal models in pharmacology research. Readers might be interested in the previous papers.

Robinson V (2009). Less is more: reducing the reliance on animal models for nausea and vomiting research.

Holmes AM, Rudd JA, Tattersall FD, Aziz Q, Andrews PLR (2009). Opportunities for the replacement of animals in the study of nausea and vomiting.

Giacomotto J and Ségalat L (2010). High-throughput screening and small animal models, where are we?

McGrath JC, Drummond GB, McLachlan EM, Kilkenny C, Wainwright CL (2010). Guidelines for reporting experiments involving animals: the ARRIVE guidelines.

Kilkenny C, Browne W, Cuthill IC, Emerson M, Altman DG (2010). The ARRIVE guidelines.

Emerson M (2010). Refinement, reduction and replacement approaches to in vivo cardiovascular research.

Berge O-G (2011). Predictive validity of behavioural animal models for chronic pain.

Vickers SP, Jackson HC and Cheetham SC (2011). The utility of animal models to evaluate novel anti-obesity agents.

Percie du Sert N, Holmes AM, Wallis R, Andrews PLR (2012). Predicting the emetic liability of novel chemical entities: a comparative study.

The complete series including future publications, as they occur, can be found at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1476-5381/homepage/animal_models.htm.

## Abbreviations

NOD, non-obese diabetic; SPF, specific pathogen-free; STZ, streptozotocin

## Introduction

Diabetes mellitus is a chronic disease that is characterized by a relative or absolute lack of insulin, resulting in hypergly-caemia. Chronic hyperglycaemia can lead to a variety of complications such as neuropathy, nephropathy and retin-opathy and increased risk of cardiovascular disease. Recent figures suggest the worldwide prevalence of diabetes is

9.2% in women and 9.8% in men, with approximately 347 million people suffering from the disease worldwide in 2008 (Danaei *et al.*, 2011). There are several different classifications of diabetes, the most common being type 1 and type 2 diabetes.

Type 1 diabetes is an autoimmune disease leading to the destruction of the insulin-producing pancreatic beta cells in the islets of Langerhans. Type 1 diabetes is most commonly diagnosed in children and young adults, and by the time of diagnosis, patients have very little endogenous insulin production. Insulin therefore has to be replaced by regular subcutaneous injections, and blood glucose levels must be frequently monitored to manage the risk of hypoglycaemia. Concordance of the disease in identical twins is around 27% (Hyttinen *et al.*, 2003), indicating that although there is a genetic influence, environmental factors play a role in disease development. Indeed, most newly diagnosed patients have no first-degree relatives with the disease. Incidence of type 1 diabetes ranges up to 100-fold, depending on the country and is estimated to be approximately 15–20 per 100 000 in the United Kingdom (Patterson *et al.*, 2009). The incidence in Europe is increasing, with a predicted doubling of children under 5 developing the disease by 2020 (Patterson *et al.*, 2009).

Type 2 diabetes is the most common type of diabetes with prevalence in the United Kingdom of around 4%. It is most commonly diagnosed in middle-aged adults, although more recently the age of onset is decreasing with increasing levels of obesity (Pinhas-Hamiel and Zeitler, 2005). Indeed, although development of the disease shows high hereditability, the risk increases proportionally with body mass index (Lehtovirta *et al.*, 2010). Type 2 diabetes is associated with insulin resistance, and a lack of appropriate compensation by the beta cells leads to a relative insulin deficiency. Insulin resistance can be improved by weight reduction and exercise (Solomon *et al.*, 2008). If lifestyle intervention fails, there are a variety of drugs available to treat type 2 diabetes (Krentz *et al.*, 2008), which can be divided into five main classes: drugs that stimulate insulin production from the beta cells (e.g. sulphonylureas), drugs that reduce hepatic glucose production (e.g. biguanides), drugs that delay carbohydrate uptake in the gut (e.g. α-glucosidase inhibitors), drugs that improve insulin action (e.g. thiazolidinediones) or drugs targeting the GLP-1 axis (e.g. GLP-1 receptor agonists or DPP-4 inhibitors).

As endocrine disorders, type 1 and type 2 diabetes represent quite complex diseases where different bodily systems are involved. Thus, animal models should be chosen carefully, depending on what aspect of the disease is being investigated. In this review, specific models of type 1 and type 2 diabetes are discussed. In addition, models of beta cell regeneration are outlined, and the use of knock-out and transgenic models in diabetes research is considered.

# Animal models of type 1 diabetes

The main characteristic of type 1 diabetes is an autoimmune destruction of the pancreatic beta cells, leading to lack of insulin production. In animal models, this deficiency in insulin production is achieved by a variety of different

mechanisms, ranging from chemical ablation of the beta cells to breeding rodents that spontaneously develop autoimmune diabetes. Some of the most commonly used models of type 1 diabetes are outlined in Table 1.

## *Chemically induced type 1 diabetes*

In chemically induced models of type 1 diabetes, a high percentage of the endogenous beta cells are destroyed, and thus, there is little endogenous insulin production, leading to hyperglycaemia and weight loss. Chemically induced diabetes not only provides a simple and relatively cheap model of diabetes in rodents but can also be used in higher animals (Dufrane *et al.*, 2006). Diabetes is usually induced around 5–7 days prior to the start of the experiment to ensure stable hyperglycaemia. Two main compounds are used to induce diabetes: streptozotocin (STZ) or alloxan. Due to their similarity in structure to glucose (Bansal *et al.*, 1980), glucose can compete with alloxan and STZ, and thus, fasting animals tend to be more susceptible. Both alloxan and STZ are relatively unstable, and the solutions should ideally be made immediately prior to injection.

Chemically induced diabetes is appropriate to use when testing drugs or therapies where the main mechanism of action is lowering blood glucose in a non-beta-cell-dependent manner; for example to test new formulations of insulin (Jederstrom *et al.*, 2005; Sheshala *et al.*, 2009). This is also an appropriate model for testing transplantation therapies where the end point is lowering of blood glucose (Jansson *et al.*, 1995; Makhlouf *et al.*, 2003; Deeds *et al.*, 2011). At the end of the experiment, any 'cured' animal should be nephrectomized of its graft bearing kidney and reversal to hyperglycaemia observed to rule out regeneration of the endogenous beta cells (Baeyens *et al.*, 2005; Rackham *et al.*, 2011). In addition, the endogenous pancreas can be removed for histological examination for insulin-positive cells or for insulin content to be measured (Rackham *et al.*, 2011), although it should be noted that anatomical presence of beta cells is not necessarily correlated to beta cell function (Kargar and Ktorza, 2008).

One disadvantage with chemically inducing diabetes is that the chemicals can be toxic at other organs of the body. It should also be noted that changes in P450 isozymes in the liver, kidney, lung, intestines, testis and brain have been reported after administration of STZ or alloxan, and thus, this should be considered when drugs are being tested in these models (Lee *et al.*, 2010).

*STZ.* STZ [2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose] is synthesized by *Streptomycetes achromogenes*. After i.p. or i.v. administration, it enters the pancreatic beta cell through the Glut-2 transporter and causes alkylation of the DNA (Szkudelski, 2001). Subsequent activation of PARP leads to $NAD^+$ depletion, a reduction in cellular ATP and subsequent inhibition of insulin production (Sandler and Swenne, 1983). In addition, STZ is a source of free radicals that can also contribute to DNA damage and subsequent cell death. STZ tends to be administered as a single high dose or as multiple low doses.

*High-dose STZ.* The dose for a single high dose in mice ranges from 100 to 200 mg·kg$^{-1}$ (Srinivasan and Ramarao,

## Table 1

Summary of rodent models of type 1 diabetes

| Induction mechanism | Model | Main features | Possible uses |
|---|---|---|---|
| Chemical Induction | High dose streptozotocin<br>Alloxan<br>Multiple low dose streptozotocin | Simple model of hyperglycaemia.<br><br>Model of induced insulitis. | New formulations of insulin<br>Transplantation models.<br>Treatments that may prevent beta cell death |
| Spontaneous autoimmune | NOD mice<br>BB rats<br>LEW.1AR1/-iddm rats | Beta cell destruction due to an autoimmune process | Understanding genetics of type 1 diabetes<br>Understanding mechanism of type 1 diabetes<br>Treatments that may prevent beta cell death<br>Treatments that may manipulate autoimmune process |
| Genetically induced | AKITA mice | Beta cell destruction due to ER stress. Insulin dependent. | New formulations of insulin<br>Transplantation models.<br>Treatments to prevent ER stress<br>(could also be used in type 2 diabetes research) |
| Virally-induced | Coxsackie B virus<br>Encephalomyocarditis virus<br>Kilham rat virus<br>LCMV under insulin promoter | Beta cell destruction induced by viral infection of beta cells | Establish potential role of viruses in the development of type 1 diabetes |

2007; Dekel *et al.*, 2009), depending on the mouse strain (Hayashi *et al.*, 2006), and in rats 35–65 mg·kg$^{-1}$ (Srinivasan and Ramarao, 2007). This leads to a rapid ablation of the beta cells and hyperglycaemia. It should be noted, however, that it has been suggested that regeneration of the pancreatic islets can occur after STZ treatment; and thus sufficient controls should be in place to determine that any improvement in glycaemia is not due to spontaneous regeneration of endogenous beta cells (Grossman *et al.*, 2010). High-dose STZ is often used in transplantation models, where islets (Deeds *et al.*, 2011) or putative stem cells (Song *et al.*, 2009) are transplanted under the kidney capsule. It should be noted that STZ has recently been shown to cause lymphopenia and a relative increase in T-regulatory cells (Muller *et al.*, 2011), which could interfere with the interpretation of studies involving immune tolerance to transplants.

*Multiple low-dose STZ.* STZ can be administered as multiple low doses over 5 days to induce insulitis in mice (Like and Rossini, 1976; Wang and Gleichmann, 1998) or rats (Lukic *et al.*, 1998). Doses range from 20 to 40 mg·kg$^{-1}$ per day, depending on the species and strain. A reduction in islet number and volume is apparent with concomitant reduction in insulin secretion capacity (Bonnevie-Nielsen *et al.*, 1981). Macrophages are the first cells to infiltrate the islets, and the development of diabetes is dependent on cytokine production (Lukic *et al.*, 1998). Diabetes develops even in the absence of T and B cells, and therefore, it does not model the human disease as closely as spontaneous models of autoimmunity (Reddy *et al.*, 1995). Therapies targeting cytokines

(Sandberg *et al.*, 1994) and NO (Flodstrom *et al.*, 1999) tend to be successful in reducing diabetes development in this model, indicating their role in the beta cell destruction.

*Alloxan.* The diabetic effect of alloxan (2,4,5,6-tetraoxypyrimidine; 5,6-dioxyuracil) is mainly attributed to rapid uptake by the beta cells and the formation of free radicals, which beta cells have poor defence mechanisms to (Nerup *et al.*, 1994). Alloxan is reduced to dialuric acid and then re-oxidized back to alloxan, creating a redox cycle for the generation of superoxide radicals that undergo dismutation to form hydrogen peroxide and thereafter highly reactive hydroxyl radicals that cause fragmentation of beta cell DNA (Szkudelski, 2001). Alloxan is also taken up by the liver, but it has better protection to reactive oxygen species (Malaisse *et al.*, 1982; Mathews and Leiter, 1999) and therefore is not as susceptible to damage. Other mechanisms of beta cell damage by alloxan include oxidation of essential –SH groups, especially that of glucokinase (im Walde *et al.*, 2002) and disturbances in intracellular calcium homeostasis (Kim *et al.*, 1994). Doses in mice range from 50 to 200 mg·kg$^{-1}$ and in rats from 40 to 200 mg·kg$^{-1}$, depending on the strain and the route of administration with i.p and s.c. administration requiring up to three times as high a dose as the i.v. route (Szkudelski, 2001). A dose of 100 mg·kg$^{-1}$ has been used to create a long-term diabetes models in rabbits (Wang *et al.*, 2010). It should be noted that alloxan has a narrow diabetogenic dose, and even light overdosing can cause general toxicity, especially to the kidney (Szkudelski, 2001).

## Spontaneous autoimmune models of type 1 diabetes

The most commonly used autoimmune models of type 1 diabetes are the non-obese diabetic (NOD) mouse and the Biobreeding (BB) rat (Yang and Santamaria, 2006). In addition, another rat model of autoimmune type 1 the LEW.1AR1/Ztm-iddm rat was described in 2001 (Lenzen et al., 2001). However, the NOD mouse still dominates the literature as the autoimmune model of choice.

*NOD mice.* The NOD mouse was developed at the Shionogi Research Laboratories in Osaka, Japan in 1974 (Hanafusa et al., 1994). NOD mice develop insulitis at around 3–4 weeks of age. In this pre-diabetic stage, the pancreatic islets are infiltrated by predominately $CD4^+$ and $CD8^+$ lymphocytes, although B cells and NK cells are also present (Yoon and Jun, 2001).

The insulitis causes beta cell destruction, but the onset of overt diabetes is usually not until apparent until approximately 90% of pancreatic insulin is lost at around 10–14 weeks, although diabetes can develop up to 30 weeks of age. Diabetes is more prevalent in the females with an incidence in females, ranging from 60% to 90% in most colonies, whereas the incidence in males ranges from 10% to 30% in most colonies (Pozzilli et al., 1993; Hanafusa et al., 1994). When these mice become overtly diabetic, they rapidly lose weight and require insulin treatment. The MHC class 2 in NOD mice share structural similarities to that in humans, which may confer resistance or susceptibility to the disease in both NOD mice and humans (Todd and Wicker, 2001; Wicker et al., 2005). This parallel in type 1 diabetes genes between NOD mice and humans has been extremely useful in dissecting some mechanisms and pathways behind type 1 diabetes (Yang and Santamaria, 2006; Driver et al., 2011). Thus, these mice are potentially suitable for testing therapies in which modulation of the autoimmune response is being targeted. It should however been noted that there are a number of drugs that are effective in NOD mice, which were then shown to be ineffective in humans (von Herrath and Nepom, 2009). One of the major issues is the time point of intervention. Many drugs that have been shown to be successful in NOD mice were administered early on, and it has been suggested that is relatively easy to prevent diabetes in young NOD mouse (Roep, 2007). Another difficulty in the translation of therapies tested in NOD mice is that whereas the pancreas of the NOD can be removed for examination after a study, there is a lack of biomarkers in the peripheral blood in humans that could be used to verify the success of the intervention (von Herrath and Nepom, 2005). There are also problems in translating dosing from the NOD mouse to humans (von Herrath and Nepom, 2005).

Development of diabetes is the NOD mouse is negatively associated with microbial exposure; thus, the mice therefore should be kept in specific pathogen-free (SPF) conditions to maintain diabetes incidence. Due to the gender differences, unpredictability of disease onset and the requirement for SPF conditions, these mice are expensive to maintain as a model of type 1 diabetes compared with chemical induction of diabetes.

A more predictable and accelerated onset can be achieved in NOD mice by injecting the mice with cyclophosphamide (Caquard et al., 2010). In addition, adoptive transfer can prove useful, where T cells from diabetic NOD mice are injected into non-diabetic recipient mice, causing the recipient mouse to develop diabetes (Christianson et al., 1993). Also, NOD mice can be used in a recurrence of autoimmunity model, where syngeneic islets from young non-diabetic NOD mice are transplanted into diabetic NOD mice (Rydgren et al., 2007). The graft is rapidly destroyed by autoimmune mechanisms. All three of these models allow the timing of the autoimmune response to be controlled. The NOD mouse is often used in intervention studies in attempts to prevent or delay the onset of the autoimmune disease (Montane et al., 2011; Tai et al., 2011; Lee et al., 2011b).

Strategies to improve the NOD model include using specific genetic manipulation of NOD mice (Yang and Santamaria, 2003) or the creation of humanized mouse models with components of the human immune system (King et al., 2008; Niens et al., 2011). Despite the limitations of the NOD mouse, it is still used extensively as it does represent many aspects of the human disease and is a model that has helped identify many of the genetic and signalling pathways that can lead to type 1 diabetes.

*BB rats.* BB rats were derived from outbred Wistar rats. Spontaneous autoimmune diabetes in a Canadian colony was first identified in 1974 and lead to the creation of two founder colonies from which all substrains have derived, one inbred (BBDP/Wor) and one outbred (BBdp) (Mordes et al., 2004). Diabetes resistant BB rats have also been bred to act as controls.

BB rats usually develop diabetes just after puberty and have similar incidence in males and females. Around 90% of rats develop diabetes between 8 and 16 weeks of age. The diabetic phenotype is quite severe, and the rats require insulin therapy for survival. Although the animals have insulitis with the presence of T cells, B cells, macrophages and NK cells, the animals are lymphopenic with a severe reduction in $CD4^+$ T cells and a near absence of $CD8^+$ T cells (Mordes et al., 2004). Lymphopenia is not a characteristic of type 1 diabetes in humans or NOD mice (Mordes et al., 2004) and is seen to be a disadvantage in using the BB as a model of type 1 diabetes in humans. Also, in contrast to NOD mice, the insulitis is not preceded by peri-insulitis. However, the model has been valuable in elucidating more about the genetics of type 1 diabetes (Wallis et al., 2009), and it has been suggested that it may be the preferable small animal model for islet transplantation tolerance induction (Mordes et al., 2004). In addition, BB rats have been used in intervention studies (Hartoft-Nielsen et al., 2009; Holmberg et al., 2011) and studies of diabetic neuropathy (Zhang et al., 2007).

*LEW.1AR1/-iddm rats.* This rat model of type 1 diabetes arose spontaneously in a colony of congenic Lewis rats with a defined MHC haplotype (LEW.1AR1), which were being bred at the Institute of Laboratory Animal Science of Hannover Medical School (Ztm). These rats exhibit insulitis, and overt diabetes manifests at around 8–9 weeks. Originally, the incidence of diabetes was approximately 20% (Lenzen et al., 2001); however, with further inbreeding of diabetic rats, the incidence increased to around 60% with equal incidence in both genders (Jorns et al., 2005). The animals exhibit a pre-diabetic period with islet infiltration approximately a week

before animals become hyperglycaemic. This relatively short pre-diabetic period allows for effective analysis of different stages of the immune cell infiltration (Jorns *et al.*, 2005). In contrast to the NOD mouse and BB rat, the LEW-iddm rat does not exhibit other autoimmune diseases. It also survives well after the onset of overt diabetes and thus can be used to study diabetic complications (Mathews, 2005). However, most studies in this rat model so far have been investigating the mechanisms involved in the development of diabetes (Jorns *et al.*, 2004; 2005; Peschke *et al.*, 2011) and intervention studies (Arndt *et al.*, 2009; Jorns *et al.*, 2010).

## Genetically induced insulin-dependent diabetes

*AKITA mice.* The AKITA mouse was derived in Akita, Japan from a C57BL/6NSlc mouse with a spontaneous mutation in the *insulin 2* gene preventing correct processing of pro-insulin. This causes an overload of misfolded proteins and subsequent ER stress. This results in a severe insulin-dependent diabetes starting from 3 to 4 weeks of age, which is characterized by hyperglycaemia, hypoinsulinaemia, polyuria and polydipsia. Untreated homozygotes rarely survive longer than 12 weeks. The lack of beta cell mass in this model makes it an alternative to streptozotocin-treated mice in transplantation studies (Mathews *et al.*, 2002). It has also been used as a model of type 1 diabetic macrovascular disease (Zhou *et al.*, 2011) and neuropathy (Drel *et al.*, 2011). In addition, this model is commonly used to study potential alleviators of ER stress in the islets and in this respect models some of the pathology of type 2 diabetes (Chen *et al.*, 2011).

## Virus-induced models of diabetes

Viruses have been implicated in the pathogenesis of type 1 diabetes (van der Werf *et al.*, 2007). Therefore, several animal models have used viruses to initiate beta cell destruction. The destruction can be either due to direct infection of the beta cell or initiation of an autoimmune response against the beta cell (Jun and Yoon, 2003). Viruses used to induce diabetes in animal models include coxsackie B virus (Yoon *et al.*, 1986; Kang *et al.*, 1994; Jaidane *et al.*, 2009), encephalomyocarditis virus (Craighead and McLane, 1968; Baek and Yoon, 1991; Shimada and Maruyama, 2004) and Kilham rat virus (Guberski *et al.*, 1991; Ellerman *et al.*, 1996).

In addition, a transgenic virus model has been described in which a defined viral antigen (the nucleoprotein or glycoprotein) of lymphocytic choriomeningitis virus (LCMV) is expressed under the rat insulin promoter (von Herrath *et al.*, 1997). These mice do not spontaneously develop any signs of beta cell destruction, but if the mice are then injected with LCMV, the immune response cross-reacts with the antigen expressed in the beta cells, leading to beta cell destruction.

However, the virus-induced model can be complicated as the outcome is dependent on replication levels of the virus as well as timing of the infection. Indeed, it has been shown that viruses can both induce autoimmunity as well as prevent it, depending on the conditions (von Herrath *et al.*, 2011). Although some cases of human type 1 diabetes have been linked to viruses (van der Werf *et al.*, 2007; Richardson *et al.*, 2009), it is unclear to what extent viruses are involved in the pathogenesis of type 1 diabetes.

## Non-rodent models of type 1 diabetes

In addition to the extensively studied rodent models of type 1 diabetes, several large animal models have been developed. In large animal models, spontaneous diabetes is relatively rare and unpredictable in onset, and thus, induced models of type 1 diabetes are required. The most common method of inducing insulin dependence in large models is either by pancreatectomy or STZ.

*Pancreatectomy.* Pancreatectomy has been used to induce hyperglycaemia in pigs (Morel *et al.*, 1991; Mellert *et al.*, 1998), dogs (Fisher *et al.*, 2001) and primates (He *et al.*, 2011). When carried out by a skilled surgeon, this model is a reliable method to induce hyperglycaemia. However, this is very invasive surgery for the animal, increases the chances of hypoglycaemia and also leads to pancreatic exocrine deficiency in the animal (He *et al.*, 2011). However, pancreatectomy in pigs followed by autotransplantation of the isolated islets (Emamaullee *et al.*, 2009) is a reasonably accurate model of autotransplantation of islets in humans (Matsumoto, 2011).

*Chemical ablation of beta cells in large animals.* There is inter-species variation in the beta cell toxicity of alloxan (Tyrberg *et al.*, 2001) and STZ (Eizirik *et al.*, 1994; Dufrane *et al.*, 2006), which may be due to differences in expression in GLUT-2 (Dufrane *et al.*, 2006). It has been reported that while a dose of 50 mg·kg$^{-1}$ can produce irreversible diabetes in the rat and Cynomolgus monkey, pigs require a higher dose (150 mg·kg$^{-1}$) and despite this, a partial correction to hyperglycaemia was seen in pigs 4 weeks after STZ injection (Dufrane *et al.*, 2006). Increasing the dose to 200 mg·kg$^{-1}$ in pigs leads to renal and hepatic toxicity, suggesting a narrow window of efficacy. It should be noted that other studies have successfully used 150 mg·kg$^{-1}$ STZ in pigs (Grussner *et al.*, 1993; Jensen-Waern *et al.*, 2009), thus underlining the difficulties in establishing a STZ-induced model of diabetes in larger animals.

Some models in higher animals combine a partial pancreatectomy with STZ treatment, thus reducing the dose of STZ (Wise *et al.*, 1985; He *et al.*, 2011). In addition, a multiple low-dose STZ model has been described in primates (Wei *et al.*, 2011).

# Animal models of type 2 diabetes

Type 2 diabetes is characterized by insulin resistance and the inability of the beta cell to sufficiently compensate. Therefore, animal models of type 2 diabetes tend to include models of insulin resistance and/or models of beta cell failure. Many animal models of type 2 diabetes are obese, reflecting the human condition where obesity is closely linked to type 2 diabetes development. Some of the most commonly used models for type 2 diabetes are outlined in Table 2.

## Obese models of type 2 diabetes

As type 2 diabetes is closely linked to obesity, most of the current animal models of type 2 diabetes are obese. Obesity

## Table 2

Summary of rodent models of type 2 diabetes

| Induction mechanism | Model | Main features | Possible uses |
|---|---|---|---|
| Obese models (monogenic) | Lep$^{ob/ob}$ mice | Obesity-induced hyperglycaemia | Treatments to improve insulin resistance |
| | Lepr$^{db/db}$ mice | | Treatments to improve beta cell function |
| | ZDF Rats | | |
| Obese models (polygenic) | KK mice | Obesity-induced hyperglycaemia | Treatments to improve insulin resistance |
| | OLETF rat | | Treatments to improve beta cell function |
| | NZO mice | | Some models show diabetic complications |
| | TallyHo/Jng mice | | |
| | NoncNZO10/LtJ mice | | |
| Induced obesity | High fat feeding (mice or rats) | Obesity-induced hyperglycaemia | Treatments to improve insulin resistance |
| | Desert gerbil | | Treatments to improve beta cell function |
| | Nile grass rat | | Treatments to prevent diet-induced obesity |
| Non-obese models | GK rat | Hyperglycaemia induced by insufficient beta cell function/mass | Treatments to improve beta cell function |
| | | | Treatments to improve beta cell survival |
| Genetically induced models of beta cell dysfunction | hIAPP mice | Amyloid deposition in islets | Treatments to prevent amyloid deposition |
| | | | Treatments to improve beta cell survival |
| | AKITA mice | Beta cell destruction due to ER stress. | Treatments to prevent ER stress |
| | | | Treatments to improve beta cell survival |

can be the result of naturally occurring mutations or genetic manipulation. Alternatively, obesity can be induced by high fat feeding.

*Monogenic models of obesity.* Although obesity in humans is rarely caused by a monogenic mutation, monogenic models of obesity are commonly used in type 2 diabetes research. The most widely used monogenic models of obesity are defective in leptin signalling. Leptin induces satiety, and thus, a lack of functional leptin in these animals causes hyperphagia and subsequent obesity. These models include the Lep$^{ob/ob}$ mouse, which is deficient in leptin and the Lepr$^{db/db}$ mouse and Zucker Diabetic Fatty rat, which are deficient in the leptin receptor. These models are often used to test new therapies for type 2 diabetes (Yoshida *et al.*, 2010; Gault *et al.*, 2011; Park *et al.*, 2011).

*Lep$^{ob/ob}$ mouse.* The Lep$^{ob/ob}$ mouse is a model of severe obesity and derives from a spontaneous mutation discovered in an outbred colony at Jackson Laboratory in 1949. The phenotype was bred into C57BL/6 mice, but it was not until 1994 the mutated protein was identified as leptin (Zhang *et al.*, 1994). The weight increase starts at 2 weeks of age, and the mice develop hyperinsulinaemia. By 4 weeks, hyperglycaemia is apparent, with blood glucose concentrations continuing to rise, peaking at 3–5 months, after which they fall as the mouse becomes older (Lindstrom, 2007). Other metabolic aberrations include hyperlipidaemia, a disturbance in temperature regulation and lower physical activity (Lindstrom, 2007). In addition, these mice are infertile (Chehab *et al.*, 1996).

The pancreatic islet volume is dramatically increased in these mice (Bock *et al.*, 2003). Although there are some abnormalities in insulin release (Lavine *et al.*, 1977), islets maintain insulin secretion, and the lack of complete beta cell failure in this model means diabetes is not particular severe and indeed not completely representative of human type 2 diabetes. It should be noted that on the C57Bl/KS background, a much more severe diabetes develops with regression of islets and early mortality (Coleman, 1978).

*Lepr$^{db/db}$ mice.* The Lepr$^{db/db}$ mouse originated from the Jackson Laboratory (Hummel *et al.*, 1966) and is due to an autosomal recessive mutation in the leptin receptor (Chen *et al.*, 1996). These animals are hyperphagic, obese, hyperinsulinaemic and hyperglycaemic. Obesity is evident from 3–4 weeks of age with hyperinsulinaemia becoming apparent at around 2 weeks of age and hyperglycaemia developing at 4–8 weeks. The most commonly used background used is on the C57BLKS/J, and they develop ketosis after a few months of age and have a relative short lifespan (Srinivasan and Ramarao, 2007).

*Zucker fatty rats and Zucker diabetic fatty rats.* The Zucker Fatty rats were discovered in 1961 after a cross of Merck M-strain and Sherman rats. They have a mutated leptin receptor (Phillips *et al.*, 1996) that induces hyperphagia, and the rats become obese at around 4 weeks of age. These rats also are hyperinsulinaemic, hyperlipidaemic and hypertensive. They have impaired glucose tolerance (Srinivasan and Ramarao, 2007).

A mutation in this strain lead to the derivation of a substrain with a diabetogenic phenotype: the inbred Zucker Diabetic Fatty Rats (ZDF). These rats are less obese than the Zucker fatty rats but have more severe insulin resistance, which they are unable to compensate for due to increased apoptosis levels in the beta cells (Pick *et al.*, 1998). This is characterized by initial hyperinsulinaemia at around 8 weeks of age followed by decreased insulin levels (Shibata *et al.*, 2000). Diabetes usually develops at around 8–10 weeks in males, but females do not develop overt diabetes (Srinivasan and Ramarao, 2007). These rats also show signs of diabetic complications (Shibata *et al.*, 2000).

*Polygenic models of obesity.* Polygenic models of obesity may provide a more accurate model of the human condition. A variety of different polygenic mouse models of obesity, glucose intolerance and diabetes exist, allowing a variety of genotypes and susceptibilities to be studied. However, unlike the monogenic models, there are no wild-type controls. In addition, the male sex bias is more extreme in these models (Leiter, 2009). These polygenic models have been used in a wide variety of studies that have aimed to reverse the symptoms of type 2 diabetes (Chen *et al.*, 2009; Fukaya *et al.*, 2009; Guo *et al.*, 2010; Mochizuki *et al.*, 2011; Yoshinari and Igarashi, 2011), understand more about the interplay of obesity and glucose homeostasis (Kluth *et al.*, 2011) (Jurgens *et al.*, 2007) or study diabetic complications (Cheng *et al.*, 2007; Fang *et al.*, 2010; Buck *et al.*, 2011; Lee *et al.*, 2011a).

*KK mice.* KK mice are a mildly obese and hyperleptinaemic strain derived from wild-derived ddY mice in Japan by Kondo in 1957 (Clee and Attie, 2007). They develop severe hyperinsulinaemia and demonstrate insulin resistance in both muscle and adipose tissue. The pancreatic islets are hypertrophic and degranulated. This mouse strain also shows signs of diabetic nephropathy (Ikeda, 1994).

A derivative of this strain is the KK-$A^Y$ mice, which was created by introducing the yellow obese $A^Y$ gene into the KK strain (Chakraborty *et al.*, 2009). This model develops maturity-obesity and has more severe hyperinsulinaemia and more prominent changes in the pancreatic islets. This is due to the ectopic expression of the agouti protein antagonizing the melanocortin receptor 4 (MCR4) in the hypothalamus.

*OLETF rats.* The Otsuka Long-Evans Tokushima Fat rat (OLETF) was derived from a spontaneously diabetic rat discovered in 1984 in an outbred colony of Long Evans Rats. Selective breeding at the Tokushima Research Institute lead to the OLETF strain that has mild obesity and late onset hyperglycaemia (after 18 weeks). Diabetes is inherited by the males. The pancreatic islets undergo three stages of histological change. At an early stage (6–20 weeks old), cellular infiltration and degeneration is seen. This is followed by a stage of hyperplasia between 20 and 40 weeks. The final stage is characterized by islets becoming fibrotic and become replaced by connective tissue (Kawano *et al.*, 1994). These rats also exhibit renal complications (Lee *et al.*, 2011a).

*New Zealand Obese (NZO) mice.* The NZO mouse is a polygenic model of obesity, created by selective breeding. It is hyperphagic and obese, which may be a consequence of leptin resistance as these mice are hyperleptinaemic by 9–12 weeks of age (Leiter and Reifsnyder, 2004). Indeed, they are resistant to peripheral leptin administration but sensitive to centrally administrated leptin (Halaas *et al.*, 1997), indicating a defect in leptin transport across the blood–brain barrier. These mice are also hyperinsulinaemic, which stems from hepatic insulin resistance from an early age, which seems to result from impaired regulation of hepatic fructose-1,6-bisphosphatase (Andrikopoulos *et al.*, 1993). Blood glucose concentrations are elevated, and they show impaired glucose tolerance, which worsens with age and approximately 50% of males develop diabetes (Haskell *et al.*, 2002). Islets are hyperplastic and hypertrophic at 3–6 months of age, but beta cell loss occurs at later time points and there are signs of 'latent autoimmune diabetes of adults' (Junger *et al.*, 2002).

*TallyHo/Jng mice.* The TallyHo mouse is a naturally occurring model of obesity and type 2 diabetes derived from selective breeding of mice that spontaneously developed hyperglycaemia and hyperinsulinaemia in an outbred colony of Theiler Original mice (Kim *et al.*, 2005). In these mice, adiposity is increased, and plasma triglycerides, cholesterol and free fatty acid levels are elevated. Hyperglycaemia is limited to male mice, which develops as early as between 10 and 14 weeks of age. The pancreatic islets are hypertrophied and degranulated, and hyperinsulinaemia is evident. The TallyHo mouse has not yet been completely characterized for diabetic complications (Leiter, 2009), although a recent study has used this model to study diabetic wound healing (Buck *et al.*, 2011).

*NoncNZO10/LtJ mice.* This strain was created by combining independent diabetes risk-conferring quantitative trait loci from two unrelated strains of NZO mice with nonobese nondiabetic mice (NON/Lt) (Cho *et al.*, 2007). These mice develop liver and skeletal muscle insulin resistance at 8 weeks before developing chronic hyperglycaemia from about 12 weeks (Leiter, 2009). Islet mass initially increases before beta cell loss occurs. Diabetic nephropathy has been observed in some males aged about one year (Leiter, 2009), and it has also been suggested that this model is suitable for studies in diabetic wound healing (Fang *et al.*, 2010)

## High fat feeding

The model of high fat feeding to C57BL/6 mice was first described in 1988 (Surwit *et al.*, 1988). High fat feeding can lead to obesity, hyperinsulinaemia and altered glucose homeostasis due to insufficient compensation by the islets (Winzell and Ahren, 2004). Normal chow (on a caloric basis usually around 26% protein, 63% carbohydrate and 11% fat) is exchanged for a diet where the number of calories from fat is increased substantially (around 58% of energy derived from fat). The amount of food eaten should be monitored to ensure that the mice do not compensate by eating less. It has been shown that high-fat-fed mice can weigh more than chow-fed controls within a week of starting the high-fat diet (Winzell and Ahren, 2004), although typically mice are fed the high-fat diet for several weeks to induce a more pronounced weight gain. The weight gain is associated with insulin resistance, and lack of beta cell compensation leads to impaired glucose tolerance.

Since the obesity is induced by environmental manipulation rather than genes, it is thought to model the human situation more accurately than genetic models of obesity-induced diabetes. High fat feeding is often used in transgenic or knock-out models, which may not show an overt diabetic phenotype under normal conditions, but when the beta cells are 'pushed', the gene may be shown to be of importance. It should be noted that the background strain of the mice can determine the susceptibility to diet-induced metabolic changes, and thus, effects could be missed if a more resistant strain is used (Surwit *et al.*, 1995; Bachmanov *et al.*, 2001; Almind and Kahn, 2004). It has also been reported that there is heterogeneity of the response to high fat feeding within the inbred C57BL/6 strain, indicating that differential responses to a high-fat diet are not purely genetic (Burcelin *et al.*, 2002).

*Other diet-induced rodent models of type 2 diabetes.* Although rats and mice are the most commonly used models for studies of type 2 diabetes, other rodents have also been identified as useful models. These include the desert gerbil and the newly described Nile grass rat, both of which tend to develop obesity in captivity.

*Desert gerbil.* The desert gerbil (*Psammomys obesus*) was originally discovered to develop diabetes in captivity in the 1960s. The diabetes ranged from mild hyperglycaemia with hyperinsulinaemia to severe hyperglycaemia with hypoinsulinaemia and ketoacidosis. Indeed, four stages were subsequently identified in the Jerusalem colony: stage A (normal glycaemic normoinsulinaemic), stage B (normoglycaemic hyperinsulinaemic), stage C (hyperglycaemic and hyperinsulinaemic) and stage D (hyperglycaemic insulinopenic). Progression from stage A to stage C can be prevented with food restriction, but there is no recovery from stage D (Shafrir *et al.*, 2006). This animal is not hyperphagic, but when high-energy nutrition is made available in a laboratory setting, obesity, hyperinsulinaemia and subsequently diabetes develop (Ziv *et al.*, 1999). Due to its poor adaption to excess nutrition, it has been suggested that the *Psammomys* represents an ideal model of the 'thrifty gene' effect and could be used for studying populations where insulin resistance and metabolic syndrome is common after a rapid evolution from scarcity to nutritional abundance. Researchers have used these animals in studies that aim to prevent nutritionally induced diabetes (Mack *et al.*, 2008; Bodvarsdottir *et al.*, 2010; Vedtofte *et al.*, 2010).

*Nile grass rat.* The Nile grass rat (*Arvicanthis niloticus*) has recently been suggested as a model for metabolic syndrome (Noda *et al.*, 2010). Most of these animals spontaneously develop obesity, dyslipidaemia and hyperglycaemia by one year of age when kept on a normal chow diet in captivity. They show other signs of diabetes and metabolic syndrome such as reduced beta cell mass, atherosclerosis and liver steatosis.

## Nonobese models of type 2 diabetes

Not all type 2 diabetes patients are obese, and thus, it is important that lean animal models of type 2 diabetes are also studied. These include models that have beta cell inadequacy,

which is what ultimately leads to overt type 2 diabetes in humans (Weir *et al.*, 2009).

*Goto–Kakizaki rats.* Goto–Kakizaki (GK) rats were created by a Japanese group by repetitive breeding of Wistar rats with the poorest glucose tolerance (Goto *et al.*, 1976). This leads to the development of a lean model of type 2 diabetes, which is characterized by glucose intolerance and defective glucose-induced insulin secretion. The development of insulin resistance does not seem to be the main initiator of hyperglycaemia in this model, and the defective glucose metabolism is regarded to be due to aberrant beta cell mass (Portha *et al.*, 2001) and/or function (Ostenson and Efendic, 2007).

However, islet morphology and metabolism seem to differ between differing colonies of these rats. In some colonies (Stockholm and Dallas), the volume and density of beta cells is similar to controls; thus the hyperglycaemia seems to result from insulin secretory defects. However, in the Paris colony of GK rats, it has been reported that there is a reduction in beta cell mass (Ostenson and Efendic, 2007). GK rats have been used in studies ranging from investigations of beta cell dysfunction in type 2 diabetes (Movassat *et al.*, 2007; Ehses *et al.*, 2009; Portha *et al.*, 2009; Dolz *et al.*, 2011; Giroix *et al.*, 2011) to diabetic complications (Liepinsh *et al.*, 2009; Carneiro *et al.*, 2010; Okada *et al.*, 2010).

*hIAPP mice.* A characteristic of type 2 diabetes is the formation of amyloid within the islet tissue, which derives from islet amyloid polypeptide (IAPP). Rodent IAPP is not amyloidogenic, and thus, rodents normally do not model this aspect of the disease (Hoppener *et al.*, 1994). However, transgenic mice have been created to express human IAPP (hIAPP) under the insulin promoter (Matveyenko and Butler, 2006), which can form amyloid within the islets. A variety of hIAPP models have been created, and it has been demonstrated that increasing the expression of hIAPP increases beta cell toxicity (Matveyenko and Butler, 2006). In addition, replicating beta cells are more susceptible to hIAPP toxicity, and thus, beta cell adaption to increased insulin demand in this model is restricted (Matveyenko *et al.*, 2009).

## Non-rodent models of type 2 diabetes

Larger animals have also been utilized in type 2 diabetes research. Type 2 diabetes in cats resembles the human condition in several aspects, including clinical, physiological and pathological aspects. Some characteristics common to humans include that type 2 diabetes in cats develops in middle age, is associated with obesity and insulin resistance, and subsequent beta cell loss occurs (O'Brien, 2002). In addition, cats are one of the few species other than humans and macaques that form amyloid in islets, making them a good model for studying islet amyloidosis (Henson and O'Brien, 2006). Old-world non-human primates can also develop type 2 diabetes, which has similarities to the human condition and thus be useful as a model (Wagner *et al.*, 2006). In addition, several strains of pigs have a phenotype that resembles type 2 diabetes (Bellinger *et al.*, 2006). A novel model of obesity and mild type 2 diabetes has recently been established in the dog (Ionut *et al.*, 2010) by combining a high-fat diet with STZ.

# Models of beta cell function

The beta cell plays a central role in the development of both type 1 and type 2 diabetes as well as playing a key role in less common classifications of diabetes such as maturity onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes and other beta cell syndromes such as hyperinsulinism. Therefore, models of beta cell function are highly relevant in understanding pathways that can lead to the inability of beta cells to secrete appropriate amounts of insulin. Such models are often genetically manipulated, such as mutations of Kir6.2 to study $K_{ATP}$ channel function (Girard *et al.*, 2009) or mutations in glucose kinase to understand the function of the glucose sensor in beta cells (Fenner *et al.*, 2011). A role for serotonin in the expansion of islets in pregnancy has recently been elucidated by studying the islets of mice lacking the serotonin receptor Htr2b (Kim *et al.*, 2010). Studies such as these can increase our knowledge of beta cell function and its role in a variety of conditions. However, it should be pointed out that the same mutation in humans can lead to different symptoms in mice as recently shown by Hugill *et al.*, where a mutation in Kcnj11 (encoding a subunit of the $K_{ATP}$ channel) caused hypersecretion of insulin and hypoglycaemia in their patient, but glucose intolerance and reduced insulin secretion in mice (Hugill *et al.*, 2010). However, this may prove useful in understanding the transition from hyperinsulinism of infancy (HI) to diabetes in some patients (Hugill *et al.*, 2010).

# Models of beta cell regeneration

Both type 1 and type 2 diabetes can be regarded as conditions when beta cell mass is insufficient to cope with demand for insulin. Therefore, a lot of effort has focused on understanding how beta cell mass is regulated. In these models, beta cell mass tends to be partially or nearly completely ablated by a variety of means, and the mechanisms of beta cell mass renewal are investigated.

## Pancreas injury models

Pancreas injury models are often used in studies investigating the regenerative capacity of beta cells or beta cell progenitors. These models of injury include pancreatectomy and duct ligation and due to technical difficulties are more frequently carried out in rats than in mice. Sixty percent pancreatectomy does not lead to an increase in blood glucose concentrations, and there is only a moderate increase in beta cell mass (Leahy *et al.*, 1988). However, a 90% pancreatectomy in the rat leads to moderate hyperglycaemia followed by extensive regeneration of the pancreas (Bonner-Weir *et al.*, 1983). By 60 h after pancreatectomy, duct-enriched areas appear. By 4 weeks, the endocrine portion of the pancreas has increased by eightfold and the exocrine portion by sixfold.

Ligation of the tail portion of the pancreas, which accounts for 50–60% of the pancreas, leads to a significant decrease in mass of this part of the pancreas (Wang *et al.*, 1995). The acinar tissue in the tail portion is replaced by small ductal structures by day 3, which is associated with a fibrotic and inflammatory reaction. By day 5, the tissue predominately consists of ductal tissue and small islets in connective tissue. In the first week after the duct ligation, the beta cell mass in the tail portion nearly doubles, making it an ideal model to study beta cell regeneration. In this model, blood glucose levels in the animal do not rise; indeed, for 2 weeks after the duct ligation, blood glucose levels were significantly lower (Wang *et al.*, 1995). A disadvantage of these models is the invasiveness, which makes them technically difficult and a rather extreme model so any regeneration seen is not physiological. However, they have lead to useful information on the regenerative capacity of the pancreas, at least in rodents.

## Neonatal STZ administration

STZ administration to neonatal rats (2 days old) induces a regeneration and/or type 2 diabetes model in the adults (Portha *et al.*, 1974). In this model, a peak of hyperglycaemia is seen 2 days after STZ administration (100 mg·kg$^{-1}$, i.v. or i.p.), which is followed by regeneration of beta cells and normoglycaemia by day 10. However, hyperglycaemia returns by 6 weeks, which is thought to be due to inadequate beta cells mass and beta cell dysfunction (Bonner-Weir *et al.*, 1981). Therefore, in the later phase, this model can be used to study type 2 diabetes (Tourrel *et al.*, 2001).

## Regeneration after ablation of beta cells using genetic approaches

It has been noted that genetic ablation of beta cells can be followed by extensive beta cell regeneration. However, complete beta cell ablation from birth is not compatible with life as indicated by insulin knock-out mice (Duvillie *et al.*, 1997) and pdx-1 knock-out mice (Jonsson *et al.*, 1994; Duvillie *et al.*, 1997). Therefore, genetically modified mice have been created to allow ablation of beta cells in adult mice.

In these models of beta cell ablation, the gene itself does not induce beta cell death unless a specific compound is injected to activate the gene. This allows temporal control of the beta cell death. Interestingly, these models often show recovery with extensive beta cell replication and thus can be used to study beta cell regeneration (Herrera *et al.*, 1994; Nir *et al.*, 2007; Cano *et al.*, 2008; Wang *et al.*, 2008). Some examples are outlined below.

*Doxycycline-induced expression of diphtheria toxin in beta cells.* In these mice, a reverse tetracycline-dependent transactivator (rtTA) is expressed in beta cells (Insulin-rtTA; in which rtTA expression is driven by 9.5 kb of the 5′ flanking region of the rat insulin II gene). In addition, diphtheria toxin A is expressed under an rtTA responsive promoter. Administration of doxycycline to the mice causes rtTA to induce the expression of diphtheria toxin A, causing beta cell apoptosis (Nir *et al.*, 2007). Approximately 80% of beta cells were lost, and the mice became overtly diabetic. However, on doxycycline withdrawal, beta cell regeneration was evident with beta cell mass increasing and mice reverting to normoglycaemia.

*Diphtheria toxin receptor-RIP mice.* In this model, the beta cells have been genetically modified to express the diphtheria toxin receptor under the rat insulin promoter. Thus, diphtheria toxin can be administered and will selectively ablate the

insulin producing cells as mouse cells do not normally express the DT receptor, and thus, other cells are not susceptible to damage (Buch *et al.*, 2005). Using this method, >99% of the beta cells are ablated. There is extensive beta cell regeneration after ablation, and by 10 months, there is between a 10- and 44-fold increase in beta cells. However, this corresponds to just 4–17% beta cell mass compared with non-treated control mice (Herrera *et al.*, 1994).

*PANIC-ATTAC mice.* The PANIC-ATTAC (pancreatic islet b-cell apoptosis through targeted activation of caspase 8) mouse is a model for inducible and reversible ablation of beta cells. A mutated FK506 binding protein (FKBP) that is fused to caspase 8 is expressed under the insulin promoter. The expression of the FKBP-caspase 8 protein in its monomeric form does not give rise to a phenotype, but dimerization, by administration of a dimerizer compound, leads to apoptosis. Up to a 90% reduction in pancreatic insulin content can be observed with histology, also demonstrating a marked reduction in beta cells. The mice become hyperglycaemic, but there is a recovery, and by 8 weeks, the mice return to normoglycaemia, although still show signs of impaired glucose-stimulated insulin secretion (Wang *et al.*, 2008).

## Knock-out and transgenic mice in diabetes research

Transgenic mice have been used to create specific models of type 1 and type 2 diabetes, including hIAPP mice, humanized mice with aspects of the human immune system and mice allowing conditional ablation of beta cells, as outlined above. Beta cells expressing fluorescent proteins can also provide elegant methods of tracking beta cells for use in diabetes research (Hara *et al.*, 2003).

In addition, knock-out and transgenic mice have become powerful tools in elucidating the influence of specific genes in glucose metabolism and the pathogenesis of diabetes. This includes understanding which transcription factors are involved in pancreas development (Habener *et al.*, 2005) and elucidation of insulin signalling pathways (Kahn, 2003; Wang and Jin, 2009). Tissue-specific knock-outs have proven to be particularly useful in studying insulin signalling (Neubauer and Kulkarni, 2006) as the global insulin receptor knock-out is non-viable (Accili *et al.*, 1996).

As mentioned previously with diet-induced metabolic aberrations, caution should be used when interpreting data as different background strains have differing susceptibilities to obesity and alterations in blood glucose homeostasis. This could potentially lead to the effect of a gene being missed or alternatively the relative importance of a gene being overestimated. An example of the impact of background strain of the mouse has been demonstrated using mice heterozygous for the insulin receptor knockout and heterozygous for the insulin receptor substrate-1 (IRS-1) knockout. When the background is C57BL/6, 85% of the mice are overtly diabetic by 6 months, whereas in 129Sv and DBA mice the incidence of overt diabetes is much lower at 2% and 64% respectively (Kulkarni *et al.*, 2003).

Another consideration with knock-out and transgenic mice in diabetes research is that pancreatic promoters such as the rat insulin promoter (RIP), Ngn3 and Pdx-1 can be expressed at low levels in the hypothalamus (Song *et al.*, 2010). Indeed, it has been suggested that RIP-Cre mice *per se* have disturbed glucose tolerance (Lee *et al.*, 2006), although another study did not see any metabolic aberration in their RIP-Cre mice (Fex *et al.*, 2007). It was suggested this was due to genetic differences as their mice had been rigorously back-crossed onto a C57BL/6 background. Nevertheless, this underlines the importance of including control RIP-Cre mice in experiments.

It is likely that more knock-out models of interest for the study of diabetes will be created due to the efforts of the International Knockout Mouse Consortium (IKMC), which aims to mutate all protein-coding genes in the mouse (http://www.knockoutmouse.org/). In addition, the Mouse Genome Informatics website is a rich source of information that provides an international database resource for the laboratory mouse, providing integrated genetic, genomic and biological data to facilitate the study of human health and disease (http://www.informatics.jax.org/).

## Modelling genome-wide association studies genes in mice

Recently, genome-wide association studies (GWAS) in humans have led to a number of susceptibility loci in the pathogenesis of diabetes and obesity to be identified. Such studies have been instrumental in identifying susceptibility genes in the disease. but their function has not always been clear. Mouse models have allowed mechanistic studies to be carried out to elucidate the function of genes identified in GWAS such as *FTO* (Church *et al.*, 2009; 2010) and the *SLC30A8* gene that encodes the zinc transporter (ZnT8) (Wijesekara *et al.*, 2010). The use of mouse models in the interpretation of human GWAS in type 2 diabetes and obesity has recently been elegantly reviewed by Cox and Church (2011).

## End-points to study in animal models of diabetes

When testing therapies in animal models of diabetes, the most common end-point of measurement is blood glucose concentrations. It should be pointed out that different species tend to have different blood glucose concentrations than humans, and thus, definitions for diabetes in humans should not necessarily be applied to animals. For example, mice tend to have higher blood glucose concentrations than humans, and it has been suggested that a non-fasting blood glucose concentration over 250 mg·dL$^{-1}$ (13.8 mM) or preferably a chronic elevation over 300 mg·dL$^{-1}$ (16.7 mM) is appropriate to consider a mouse diabetic (Leiter, 2009). Normal mice fasted for 16 h during the entire dark period when they usually feed and usually have blood glucose of between 50 and 100 mg·dL$^{-1}$ (2.8–5.6 mM), whereas mice with type 2 diabetes will have fasting blood glucose levels of around 150–300 mg·dL$^{-1}$ (8.3–16.7 mM).

Detection of glucose in the urine can also be measured as a sign of diabetes. However, in a complex disease such as diabetes, other end-points should be investigated. Other end-points will depend on the putative mechanism of the drug and the model being used. In models of type 1 diabetes, it is critical that the animals are also weighed to ensure that decreased blood glucose concentrations are not associated with weight loss. This indicates that decreases in blood glucose concentrations are not due to toxic effects of the therapy and possible cessation of eating. However, it should be noted that in models of type 2 diabetes, the mechanism of the drug lowering blood glucose levels may include weight loss (Knudsen, 2010). Glucose tolerance tests are often used to investigate beta cell function. This can allow impaired glucose tolerance to be identified, which is generally regarded as a pre-diabetic state. This is often done after an overnight fast, although it should be noted that it has been suggested that such a prolonged fast may be inappropriate in mice as it induces a metabolic stress and enhances insulin action (McGuinness et al., 2009), and thus, a 6 h fast may be preferable. There are no clear definitions of impaired glucose tolerance for rodents, but in normal nondiabetic mice, an IPGTT reaches a peak at 15–30 min; and by 120 min, the blood glucose should be close to the baseline value (Leiter, 2009). Serum insulin or c-peptide levels can be measured to indicate beta cell function, although high insulin levels can indirectly indicate insulin resistance. An insulin tolerance test can be carried out as an approximate measure of insulin resistance, or a more elegant hyperinsulinaemic–euglycaemic clamp can be carried out (Declercq et al., 2010). It should be noted that surrogate measures of insulin sensitivity such as the homeostasis model index of insulin resistance (HOMA-IR) can be used in rodents, although species specific adjustments may need to be made (Mather, 2009).

Pancreas histology can be used to study the effects of a therapy on the islets, which may be particularly relevant to study in interventions on insulitis (Tian et al., 2010). Whole pancreas insulin content can also be measured to indicate beta cell mass, although ideally morphometric analysis is preferable (Montanya and Tellez, 2009). Islets can also be isolated and insulin secretion experiments carried out ex vivo (Szollosi et al., 2010).

The time course of the disease should also be carefully considered when considering end-points of a study. Some models of type 2 diabetes show beta cell expansion and hyperinsulinaemia prior to subsequent beta cell failure, and the stage of disease may affect the parameters that are being measured. It should also be noted that in humans, type 2 diabetes tends to present later in life, and thus, the use of older mice when studying this condition should be considered.

## Choosing an appropriate animal model for diabetes research

A variety of animal models of type 1 and type 2 diabetes are described above, each with their own characteristics. There are several different purposes that these models of diabetes could be used for including pharmacological testing, studies of genetics and understanding disease mechanisms. The choice of model will depend on the purpose of the study. For example, in the case of pharmacological testing, the putative mechanism of the drug being tested will be instrumental in choosing an appropriate animal model.

In type 1 diabetes, the main determinant in choosing an animal model is whether a model of autoimmunity is required. The timing and predictability of onset is also variable in different models of type 1 diabetes.

In type 2 diabetes, it is important to consider the mechanisms underlying the hyperglycaemia and whether this is relevant to your study. These mechanisms can include insulin resistance and/or beta cell failure. Indeed, to determine whether a drug intervention can improve symptoms in any given model may depend on whether beta cells have failed. Animal models of type 2 diabetes can be divided into those that are obese and those that are nonobese. The majority of type 2 diabetes models are obese, by either genetic or dietary means. However, this usually comes with a variety of associated pathologies such as dyslipidaemia and artherosclerosis. Although these co-morbidities are common in some humans with type 2 diabetes, it only represents a portion of the diabetic population. Also, it should be noted that not all animal models of diabetes and strains develop diabetic complications (e.g. the C57BL/6 strain is relatively resistant to nephropathy)(Brosius III et al., 2009a), so care should be taken in choosing an appropriate model if the end-point of the study is to investigate diabetic complications such as nephropathy or neuropathy (Breyer et al., 2005; Sullivan et al., 2007; 2008; Brosius III et al., 2009b).

Strain and species differences should also be carefully considered when choosing a model as different species and background strains have different susceptibilities to diabetes and treatments. Ideally, more than one species or strain should be investigated. Gender should also be taken into account (Franconi et al., 2008), with many models described above having a gender bias (e.g. NOD, NZO and TallyHo mice; OLETF, Zucker Diabetic rats), which does not exist in humans. In addition, many knock-out and transgenic models of diabetes show a gender bias (Franconi et al., 2008). It has been suggested that in some cases this is due to the effects of sex hormones (Inada et al., 2007), although the exact mechanism of gender bias has not been elucidated. Indeed, sex hormone effects can be contradictory in different mouse models with, for example, male gonadectomy protecting against diabetes in some models while being ineffective or increasing incidence in other models (Franconi et al., 2008). Indeed, gender bias could also involve mitochondria and stress responses (Franconi et al., 2008). Care should also be taken when using knock-out and transgenic mice to ensure that potential hypothalamic expression is not affecting the phenotype, and relevant controls should be included.

Models also differ in their physiological relevance. with some models more closely resembling disease development than others. Some models such as those of pancreas regeneration are rather extreme, and it remains to be elucidated whether the mechanisms of beta cell expansion in these models can play a role in humans. Indeed, when choosing a model for either type 1 or type 2 diabetes, it is highly desirable that a variety of different models are used to represent the diversity seen in human diabetic patients.

## Conflict of interest

None.

## References

Accili D, Drago J, Lee EJ, Johnson MD, Cool MH, Salvatore P *et al.* (1996). Early neonatal death in mice homozygous for a null allele of the insulin receptor gene. Nat Genet 12: 106–109.

Almind K, Kahn CR (2004). Genetic determinants of energy expenditure and insulin resistance in diet-induced obesity in mice. Diabetes 53: 3274–3285.

Andrikopoulos S, Rosella G, Gaskin E, Thorburn A, Kaczmarczyk S, Zajac JD *et al.* (1993). Impaired regulation of hepatic fructose-1,6-bisphosphatase in the New Zealand obese mouse model of NIDDM. Diabetes 42: 1731–1736.

Arndt T, Wedekind D, Weiss H, Tiedge M, Lenzen S, Hedrich HJ *et al.* (2009). Prevention of spontaneous immune-mediated diabetes development in the LEW.1AR1-iddm rat by selective CD8+ T cell transfer is associated with a cytokine shift in the pancreas-draining lymph nodes. Diabetologia 52: 1381–1390.

Bachmanov AA, Reed DR, Tordoff MG, Price RA, Beauchamp GK (2001). Nutrient preference and diet-induced adiposity in C57BL/6ByJ and 129P3/J mice. Physiol Behav 72: 603–613.

Baek HS, Yoon JW (1991). Direct involvement of macrophages in destruction of beta-cells leading to development of diabetes in virus-infected mice. Diabetes 40: 1586–1597.

Baeyens L, De BS, Lardon J, Mfopou JK, Rooman I, Bouwens L (2005). In vitro generation of insulin-producing beta cells from adult exocrine pancreatic cells. Diabetologia 48: 49–57.

Bansal R, Ahmad N, Kidwai JR (1980). Alloxan-glucose interaction: effect on incorporation of 14C-leucine into pancreatic islets of rat. Acta Diabetol Lat 17: 135–143.

Bellinger DA, Merricks EP, Nichols TC (2006). Swine models of type 2 diabetes mellitus: insulin resistance, glucose tolerance, and cardiovascular complications. ILAR J 47: 243–258.

Bock T, Pakkenberg B, Buschard K (2003). Increased islet volume but unchanged islet number in ob/ob mice. Diabetes 52: 1716–1722.

Bodvarsdottir TB, Hove KD, Gotfredsen CF, Pridal L, Vaag A, Karlsen AE *et al.* (2010). Treatment with a proton pump inhibitor improves glycaemic control in Psammomys obesus, a model of type 2 diabetes. Diabetologia 53: 2220–2223.

Bonner-Weir S, Trent DF, Honey RN, Weir GC (1981). Responses of neonatal rat islets to streptozotocin: limited B-cell regeneration and hyperglycemia. Diabetes 30: 64–69.

Bonner-Weir S, Trent DF, Weir GC (1983). Partial pancreatectomy in the rat and subsequent defect in glucose-induced insulin release. J Clin Invest 71: 1544–1553.

Bonnevie-Nielsen V, Steffes MW, Lernmark A (1981). A major loss in islet mass and B-cell function precedes hyperglycemia in mice given multiple low doses of streptozotocin. Diabetes 30: 424–429.

Breyer MD, Bottinger E, Brosius FC, Coffman TM, Fogo A, Harris RC *et al.* (2005). Diabetic nephropathy: of mice and men. Adv Chronic Kidney Dis 12: 128–145.

Brosius FC III, Alpers CE, Bottinger EP, Breyer MD, Coffman TM, Gurley SB *et al.* (2009a). Mouse models of diabetic nephropathy. J Am Soc Nephrol 20: 2503–2512.

Brosius FC III, Alpers CE, Bottinger EP, Breyer MD, Coffman TM, Gurley SB *et al.* (2009b). Mouse models of diabetic nephropathy. J Am Soc Nephrol 20: 2503–2512.

Buch T, Heppner FL, Tertilt C, Heinen TJAJ, Kremer M, Wunderlich FT *et al.* (2005). A Cre-inducible diphtheria toxin receptor mediates cell lineage ablation after toxin administration. Nat Methods 2: 419–426.

Buck DW, Jin DP, Geringer M, Jong HS, Galiano RD, Mustoe TA (2011). The TallyHo polygenic mouse model of diabetes: implications in wound healing. Plast Reconstr Surg 128: 427e–437e.

Burcelin R, Crivelli V, Dacosta A, Roy-Tirelli A, Thorens B (2002). Heterogeneous metabolic adaptation of C57BL/6J mice to high-fat diet. Am J Physiol Endocrinol Metab 282: E834–E842.

Cano DA, Rulifson IC, Heiser PW, Swigart LB, Pelengaris S, German M *et al.* (2008). Regulated beta-cell regeneration in the adult mouse pancreas. Diabetes 57: 958–966.

Caquard M, Ferret-Bernard S, Haurogne K, Ouary M, Allard M, Jegou D *et al.* (2010). Diabetes acceleration by cyclophosphamide in the non-obese diabetic mouse is associated with differentiation of immunosuppressive monocytes into immunostimulatory cells. Immunol Lett 129: 85–93.

Carneiro FS, Giachini FR, Carneiro ZN, Lima VV, Ergul A, Webb RC *et al.* (2010). Erectile dysfunction in young non-obese type II diabetic Goto-Kakizaki rats is associated with decreased eNOS phosphorylation at Ser1177. J Sex Med 7: 3620–3634.

Chakraborty G, Thumpayil S, Lafontant DE, Woubneh W, Toney JH (2009). Age dependence of glucose tolerance in adult KK-Ay mice, a model of non-insulin dependent diabetes mellitus. Lab Anim (NY) 38: 364–368.

Chehab FF, Lim ME, Lu R (1996). Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. Nat Genet 12: 318–320.

Chen H, Charlat O, Tartaglia LA, Woolf EA, Weng X, Ellis SJ *et al.* (1996). Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. Cell 84: 491–495.

Chen H, Zheng C, Zhang X, Li J, Li J, Zheng L *et al.* (2011). Apelin alleviates diabetes-associated endoplasmic reticulum stress in the pancreas of Akita mice. Peptides 32: 1634–1639.

Chen W, Zhou XB, Liu HY, Xu C, Wang LL, Li S (2009). P633H, a novel dual agonist at peroxisome proliferator-activated receptors alpha and gamma, with different anti-diabetic effects in db/db and KK-Ay mice. Br J Pharmacol 157: 724–735.

Cheng ZJ, Jiang YF, Ding H, Severson D, Triggle CR (2007). Vascular dysfunction in type 2 diabetic TallyHo mice: role for an increase in the contribution of PGH2/TxA2 receptor activation and cytochrome p450 products. Can J Physiol Pharmacol 85: 404–412.

Cho YR, Kim HJ, Park SY, Ko HJ, Hong EG, Higashimori T *et al.* (2007). Hyperglycemia, maturity-onset obesity, and insulin resistance in NONcNZO10/LtJ males, a new mouse model of type 2 diabetes. Am J Physiol Endocrinol Metab 293: E327–E336.

Christianson SW, Shultz LD, Leiter EH (1993). Adoptive transfer of diabetes into immunodeficient NOD-scid/scid mice. Relative contributions of CD4+ and CD8+ T-cells from diabetic versus prediabetic NOD.NON-Thy-1a donors. Diabetes 42: 44–55.

Church C, Lee S, Bagg EA, McTaggart JS, Deacon R, Gerken T *et al.* (2009). A mouse model for the metabolic effects of the human fat mass and obesity associated FTO gene. PLoS Genet 5: e1000599.

Church C, Moir L, McMurray F, Girard C, Banks GT, Teboul L *et al.* (2010). Overexpression of Fto leads to increased food intake and results in obesity. Nat Genet 42: 1086–1092.

Clee SM, Attie AD (2007). The genetic landscape of type 2 diabetes in mice. Endocr Rev 28: 48–83.

Coleman DL (1978). Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia 14: 141–148.

Cox RD, Church CD (2011). Mouse models and the interpretation of human GWAS in type 2 diabetes and obesity. Dis Model Mech 4: 155–164.

Craighead JE, McLane MF (1968). Diabetes mellitus: induction in mice by encephalomyocarditis virus. Science 162: 913–914.

Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ *et al.* (2011). National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 378: 31–40.

Declercq J, Kumar A, Van Diepen JA, Vroegrijk IOCM, Gysemans C, Di Pietro C *et al.* (2010). Increased +¦− cell mass by islet transplantation and PLAG1 overexpression causes hyperinsulinemic normoglycemia and hepatic insulin resistance in mice. Diabetes 59: 1957–1965.

Deeds MC, Anderson JM, Armstrong AS, Gastineau DA, Hiddinga HJ, Jahangir A *et al.* (2011). Single dose streptozotocin-induced diabetes: considerations for study design in islet transplantation models. Lab Anim 45: 131–140.

Dekel Y, Glucksam Y, Elron-Gross I, Margalit R (2009). Insights into modeling streptozotocin-induced diabetes in ICR mice. Lab Anim (NY) 38: 55–60.

Dolz M, Movassat J, Bailbe D, Le SH, Giroix MH, Fradet M *et al.* (2011). cAMP-secretion coupling is impaired in diabetic GK/Par rat beta-cells. A defect counteracted by GLP-1. Am J Physiol Endocrinol Metab 301: E797–E806.

Drel VR, Pacher P, Stavniichuk R, Xu W, Zhang J, Kuchmerovska TM *et al.* (2011). Poly(ADP-ribose)polymerase inhibition counteracts renal hypertrophy and multiple manifestations of peripheral neuropathy in diabetic Akita mice. Int J Mol Med 28: 629–635.

Driver JP, Serreze DV, Chen YG (2011). Mouse models for the study of autoimmune type 1 diabetes: a NOD to similarities and differences to human disease. Semin Immunopathol 33: 67–87.

Dufrane D, van Steenberghe M, Guiot Y, Goebbels RM, Saliez A, Gianello P (2006). Streptozotocin-induced diabetes in large animals (pigs/primates): role of GLUT2 transporter and beta-cell plasticity. Transplantation 81: 36–45.

Duvillie B, Cordonnier N, Deltour L, ndoy-Dron F, Itier JM, Monthioux E *et al.* (1997). Phenotypic alterations in insulin-deficient mutant mice. Proc Natl Acad Sci U S A 94: 5137–5140.

Ehses JA, Lacraz G, Giroix MH, Schmidlin F, Coulaud J, Kassis N *et al.* (2009). IL-1 antagonism reduces hyperglycemia and tissue inflammation in the type 2 diabetic GK rat. Proc Natl Acad Sci U S A 106: 13998–14003.

Eizirik DL, Pipeleers DG, Ling Z, Welsh N, Hellerstrom C, Andersson A (1994). Major species differences between humans and rodents in the susceptibility to pancreatic beta-cell injury. Proc Natl Acad Sci U S A 91: 9253–9256.

Ellerman KE, Richards CA, Guberski DL, Shek WR, Like AA (1996). Kilham rat triggers T-cell-dependent autoimmune diabetes in multiple strains of rat. Diabetes 45: 557–562.

Emamaullee JA, Merani S, Toso C, Kin T, Al-Saif F, Truong W *et al.* (2009). Porcine marginal mass islet autografts resist metabolic failure over time and are enhanced by early treatment with liraglutide. Endocrinology 150: 2145–2152.

Fang RC, Kryger ZB, Buck DW, De la Garza M, Galiano RD, Mustoe TA (2010). Limitations of the db/db mouse in translational wound healing research: is the NONcNZO10 polygenic mouse model superior? Wound Repair Regen 18: 605–613.

Fenner D, Odili S, Hong HK, Kobayashi Y, Kohsaka A, Siepka SM *et al.* (2011). Generation of N-ethyl-N-nitrosourea (ENU) diabetes models in mice demonstrates genotype-specific action of glucokinase activators. J Biol Chem 286: 39560–39572.

Fex M, Wierup N, Nitert MD, Ristow M, Mulder H (2007). Rat insulin promoter 2-Cre recombinase mice bred onto a pure C57BL/6J background exhibit unaltered glucose tolerance. J Endocrinol 194: 551–555.

Fisher SJ, Shi ZQ, Lickley HL, Efendic S, Vranic M, Giacca A (2001). Low-dose IGF-I has no selective advantage over insulin in regulating glucose metabolism in hyperglycemic depancreatized dogs. J Endocrinol 168: 49–58.

Flodstrom M, Tyrberg B, Eizirik DL, Sandler S (1999). Reduced sensitivity of inducible nitric oxide synthase-deficient mice to multiple low-dose streptozotocin-induced diabetes. Diabetes 48: 706–713.

Franconi F, Seghieri G, Canu S, Straface E, Campesi I, Malorni W (2008). Are the available experimental models of type 2 diabetes appropriate for a gender perspective? Pharmacol Res 57: 6–18.

Fukaya N, Mochizuki K, Tanaka Y, Kumazawa T, Jiuxin Z, Fuchigami M *et al.* (2009). The alpha-glucosidase inhibitor miglitol delays the development of diabetes and dysfunctional insulin secretion in pancreatic beta-cells in OLETF rats. Eur J Pharmacol 624: 51–57.

Gault VA, Kerr BD, Harriott P, Flatt PR (2011). Administration of an acylated GLP-1 and GIP preparation provides added beneficial glucose-lowering and insulinotropic actions over single incretins in mice with Type 2 diabetes and obesity. Clin Sci (Lond) 121: 107–117.

Girard CA, Wunderlich FT, Shimomura K, Collins S, Kaizik S, Proks P *et al.* (2009). Expression of an activating mutation in the gene encoding the KATP channel subunit Kir6.2 in mouse pancreatic beta cells recapitulates neonatal diabetes. J Clin Invest 119: 80–90.

Giroix MH, Irminger JC, Lacraz G, Noll C, Calderari S, Ehses J *et al.* (2011). Hypercholesterolaemia, signs of islet microangiopathy and altered angiogenesis precede onset of type 2 diabetes in the GotoΓÇôKakizaki (GK) rat. Diabetologia 54: 2451–2462.

Goto Y, Kakizaki M, Masaki N (1976). Production of spontaneous diabetic rats by repetition of selective breeding. Tohoku J Exp Med 119: 85–90.

Grossman EJ, Lee DD, Tao J, Wilson RA, Park SY, Bell GI *et al.* (2010). Glycemic control promotes pancreatic beta-cell regeneration in streptozotocin-induced diabetic mice. PLoS ONE 5: e8749.

Grussner R, Nakhleh R, Grussner A, Tomadze G, Diem P, Sutherland D (1993). Streptozotocin-induced diabetes mellitus in pigs. Horm Metab Res 25: 199–203.

Guberski DL, Thomas VA, Shek WR, Like AA, Handler ES, Rossini AA *et al.* (1991). Induction of type I diabetes by Kilham's rat virus in diabetes-resistant BB/Wor rats. Science 254: 1010–1013.

Guo K, Yu YH, Hou J, Zhang Y (2010). Chronic leucine supplementation improves glycemic control in etiologically distinct mouse models of obesity and diabetes mellitus. Nutr Metab (Lond) 7: 57.

Habener JF, Kemp DM, Thomas MK (2005). Minireview: transcriptional regulation in pancreatic development. Endocrinology 146: 1025–1034.

Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM (1997). Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc Natl Acad Sci U S A 94: 8878–8883.

Hanafusa T, Miyagawa J, Nakajima H, Tomita K, Kuwajima M, Matsuzawa Y *et al.* (1994). The NOD mouse. Diabetes Res Clin Pract 24 (Suppl.): S307–S311.

Hara M, Wang X, Kawamura T, Bindokas VP, Dizon RF, Alcoser SY *et al.* (2003). Transgenic mice with green fluorescent protein-labeled pancreatic beta -cells. Am J Physiol Endocrinol Metab 284: E177–E183.

Hartoft-Nielsen ML, Rasmussen AK, Bock T, Feldt-Rasmussen U, Kaas A, Buschard K (2009). Iodine and tri-iodo-thyronine reduce the incidence of type 1 diabetes mellitus in the autoimmune prone BB rats. Autoimmunity 42: 131–138.

Haskell BD, Flurkey K, Duffy TM, Sargent EE, Leiter EH (2002). The diabetes-prone NZO/HlLt strain. I. Immunophenotypic comparison to the related NZB/BlNJ and NZW/LacJ strains. Lab Invest 82: 833–842.

Hayashi K, Kojima R, Ito M (2006). Strain differences in the diabetogenic activity of streptozotocin in mice. Biol Pharm Bull 29: 1110–1119.

He S, Chen Y, Wei L, Jin X, Zeng L, Ren Y *et al.* (2011). Treatment and risk factor analysis of hypoglycemia in diabetic rhesus monkeys. Exp Biol Med (Maywood) 236: 212–218.

Henson MS, O'Brien TD (2006). Feline models of type 2 diabetes mellitus. ILAR J 47: 234–242.

von Herrath MG, Nepom GT (2005). Lost in translation: barriers to implementing clinical immunotherapeutics for autoimmunity. J Exp Med 202: 1159–1162.

von Herrath MG, Nepom GT (2009). Animal models of human type 1 diabetes. Nat Immunol 10: 129–132.

von Herrath MG, Homann D, Gairin JE, Oldstone MBA (1997). Pathogenesis and treatment of virus-induced autoimmune diabetes: novel insights gained from the RIP-LCMV transgenic mouse model. Biochem Soc Trans 25: 630–635.

von Herrath MG, Filippi C, Coppieters K (2011). How viral infections enhance or prevent type 1 diabetes-from mouse to man. J Med Virol 83: 1672.

Herrera PL, Huarte J, Zufferey R, Nichols A, Mermillod B, Philippe J *et al.* (1994). Ablation of islet endocrine cells by targeted expression of hormone-promoter-driven toxigenes. Proc Natl Acad Sci U S A 91: 12999–13003.

Holmberg R, Refai E, Hoog A, Crooke RM, Graham M, Olivecrona G *et al.* (2011). Lowering apolipoprotein CIII delays onset of type 1 diabetes. Proc Natl Acad Sci U S A 108: 10685–10689.

Hoppener JW, Oosterwijk C, van Hulst KL, Verbeek JS, Capel PJ, de Koning EJ *et al.* (1994). Molecular physiology of the islet amyloid polypeptide (IAPP)/amylin gene in man, rat, and transgenic mice. J Cell Biochem 55 (Suppl.): 39–53.

Hugill A, Shimomura K, Ashcroft FM, Cox RD (2010). A mutation in KCNJ11 causing human hyperinsulinism (Y12X) results in a glucose-intolerant phenotype in the mouse. Diabetologia 53: 2352–2356.

Hummel KP, Dickie MM, Coleman DL (1966). Diabetes, a new mutation in the mouse. Science 153: 1127–1128.

Hyttinen V, Kaprio J, Kinnunen L, Koskenvuo M, Tuomilehto J (2003). Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study. Diabetes 52: 1052–1055.

Ikeda H (1994). KK mouse. Diabetes Res Clin Pract 24 (Suppl.): S313–S316.

Inada A, Arai H, Nagai K, Miyazaki J, Yamada Y, Seino Y *et al.* (2007). Gender difference in ICER Igamma transgenic diabetic mouse. Biosci Biotechnol Biochem 71: 1920–1926.

Ionut V, Liu H, Mooradian V, Castro AV, Kabir M, Stefanovski D *et al.* (2010). Novel canine models of obese prediabetes and mild type 2 diabetes. Am J Physiol Endocrinol Metab 298: E38–E48.

Jaidane H, Sane F, Gharbi J, Aouni M, Romond MB, Hober D (2009). Coxsackievirus B4 and type 1 diabetes pathogenesis: contribution of animal models. Diabetes Metab Res Rev 25: 591–603.

Jansson L, Eizirik DL, Pipeleers DG, Borg LA, Hellerstrom C, Andersson A (1995). Impairment of glucose-induced insulin secretion in human pancreatic islets transplanted to diabetic nude mice. J Clin Invest 96: 721–726.

Jederstrom G, Grasjo J, Nordin A, Sjoholm I, Andersson A (2005). Blood glucose-lowering activity of a hyaluronan-insulin complex after oral administration to rats with diabetes. Diabetes Technol Ther 7: 948–957.

Jensen-Waern M, Andersson M, Kruse R, Nilsson B, Larsson R, Korsgren O *et al.* (2009). Effects of streptozotocin-induced diabetes in domestic pigs with focus on the amino acid metabolism. Lab Anim 43: 249–254.

Jonsson J, Carlsson L, Edlund T, Edlund H (1994). Insulin-promoter-factor 1 is required for pancreas development in mice. Nature 371: 606–609.

Jorns A, Kubat B, Tiedge M, Wedekind D, Hedrich HJ, Kloppel G *et al.* (2004). Pathology of the pancreas and other organs in the diabetic LEW.1AR1/Ztm- iddm rat, a new model of spontaneous insulin-dependent diabetes mellitus. Virchows Arch 444: 183–189.

Jorns A, Gunther A, Hedrich HJ, Wedekind D, Tiedge M, Lenzen S (2005). Immune cell infiltration, cytokine expression, and beta-cell apoptosis during the development of type 1 diabetes in the spontaneously diabetic LEW.1AR1/Ztm-iddm rat. Diabetes 54: 2041–2052.

Jorns A, Rath KJ, Terbish T, Arndt T, Meyer ZV, Wedekind D *et al.* (2010). Diabetes prevention by immunomodulatory FTY720 treatment in the LEW.1AR1-iddm rat despite immune cell activation. Endocrinology 151: 3555–3565.

Jun HS, Yoon JW (2003). A new look at viruses in type 1 diabetes. Diabetes Metab Res Rev 19: 8–31.

Junger E, Herberg L, Jeruschke K, Leiter EH (2002). The diabetes-prone NZO/Hl strain. II. Pancreatic immunopathology. Lab Invest 82: 843–853.

Jurgens HS, Neschen S, Ortmann S, Scherneck S, Schmolz K, Schuler G et al. (2007). Development of diabetes in obese, insulin-resistant mice: essential role of dietary carbohydrate in beta cell destruction. Diabetologia 50: 1481–1489.

Kahn CR (2003). Knockout mice challenge our concepts of glucose homeostasis and the pathogenesis of diabetes. Exp Diabesity Res 4: 169–182.

Kang Y, Chatterjee NK, Nodwell MJ, Yoon JW (1994). Complete nucleotide sequence of a strain of coxsackie B4 virus of human origin that induces diabetes in mice and its comparison with nondiabetogenic coxsackie B4 JBV strain. J Med Virol 44: 353–361.

Kargar C, Ktorza A (2008). Anatomical versus functional beta-cell mass in experimental diabetes. Diabetes Obes Metab 10 (Suppl. 4): 43–53.

Kawano K, Hirashima T, Mori S, Natori T (1994). OLETF (Otsuka Long-Evans Tokushima Fatty) rat: a new NIDDM rat strain. Diabetes Res Clin Pract 24 (Suppl.): S317–S320.

Kim H, Toyofuku Y, Lynn FC, Chak E, Uchida T, Mizukami H et al. (2010). Serotonin regulates pancreatic beta cell mass during pregnancy. Nat Med 16: 804–808.

Kim HR, Rho HW, Park BH, Park JW, Kim JS, Kim UH et al. (1994). Role of Ca2+ in alloxan-induced pancreatic beta-cell damage. Biochim Biophys Acta 1227: 87–91.

Kim JH, Stewart TP, Zhang W, Kim HY, Nishina PM, Naggert JK (2005). Type 2 diabetes mouse model TallyHo carries an obesity gene on chromosome 6 that exaggerates dietary obesity. Physiol Genomics 22: 171–181.

King M, Pearson T, Rossini AA, Shultz LD, Greiner DL (2008). Humanized mice for the study of type 1 diabetes and beta cell function. Ann N Y Acad Sci 1150: 46–53.

Kluth O, Mirhashemi F, Scherneck S, Kaiser D, Kluge R, Neschen S et al. (2011). Dissociation of lipotoxicity and glucotoxicity in a mouse model of obesity associated diabetes: role of forkhead box O1 (FOXO1) in glucose-induced beta cell failure. Diabetologia 54: 605–616.

Knudsen LB (2010). Liraglutide: the therapeutic promise from animal models. Int J Clin Pract Suppl. 64: 4–11.

Krentz AJ, Patel MB, Bailey CJ (2008). New drugs for type 2 diabetes mellitus: what is their place in therapy? Drugs 68: 2131–2162.

Kulkarni RN, Almind K, Goren HJ, Winnay JN, Ueki K, Okada T et al. (2003). Impact of genetic background on development of hyperinsulinemia and diabetes in insulin receptor/insulin receptor substrate-1 double heterozygous mice. Diabetes 52: 1528–1534.

Lavine RL, Voyles N, Perrino PV, Recant L (1977). Functional abnormalities of islets of Langerhans of obese hyperglycemic mouse. Am J Physiol 233: E86–E90.

Leahy JL, Bonner-Weir S, Weir GC (1988). Minimal chronic hyperglycemia is a critical determinant of impaired insulin secretion after an incomplete pancreatectomy. J Clin Invest 81: 1407–1414.

Lee JH, Yang SH, Oh JM, Lee MG (2010). Pharmacokinetics of drugs in rats with diabetes mellitus induced by alloxan or streptozocin: comparison with those in patients with type I diabetes mellitus. J Pharm Pharmacol 62: 1–23.

Lee JY, Ristow M, Lin X, White MF, Magnuson MA, Hennighausen L (2006). RIP-Cre revisited, evidence for impairments of pancreatic beta-cell function. J Biol Chem 281: 2649–2653.

Lee MY, Shim MS, Kim BH, Hong SW, Choi R, Lee EY et al. (2011a). Effects of spironolactone and losartan on diabetic nephropathy in a type 2 diabetic rat model. Diabetes Metab J 35: 130–137.

Lee SM, Yang H, Tartar DM, Gao B, Luo X, Ye SQ et al. (2011b). Prevention and treatment of diabetes with resveratrol in a non-obese mouse model of type 1 diabetes. Diabetologia 54: 1136–1146.

Lehtovirta M, Pietilainen KH, Levalahti E, Heikkila K, Groop L, Silventoinen K et al. (2010). Evidence that BMI and type 2 diabetes share only a minor fraction of genetic variance: a follow-up study of 23,585 monozygotic and dizygotic twins from the Finnish Twin Cohort Study. Diabetologia 53: 1314–1321.

Leiter EH (2009). Selecting the 'right' mouse model for metabolic syndrome and type 2 diabetes research. Methods Mol Biol 560: 1–17.

Leiter EH, Reifsnyder PC (2004). Differential levels of diabetogenic stress in two new mouse models of obesity and type 2 diabetes. Diabetes 53 (Suppl. 1): S4–11.

Lenzen S, Tiedge M, Elsner M, Lortz S, Weiss H, Jorns A et al. (2001). The LEW.1AR1/Ztm-iddm rat: a new model of spontaneous insulin-dependent diabetes mellitus. Diabetologia 44: 1189–1196.

Liepinsh E, Vilskersts R, Zvejniece L, Svalbe B, Skapare E, Kuka J et al. (2009). Protective effects of mildronate in an experimental model of type 2 diabetes in Goto-Kakizaki rats. Br J Pharmacol 157: 1549–1556.

Like AA, Rossini AA (1976). Streptozotocin-induced pancreatic insulitis: new model of diabetes mellitus. Science 193: 415–417.

Lindstrom P (2007). The physiology of obese-hyperglycemic mice [ob/ob mice]. Scientificworldjournal 7: 666–685.

Lukic ML, Stosic-Grujicic S, Shahin A (1998). Effector mechanisms in low-dose streptozotocin-induced diabetes. Dev Immunol 6: 119–128.

Mack E, Ziv E, Reuveni H, Kalman R, Niv MY, Jorns A et al. (2008). Prevention of insulin resistance and beta-cell loss by abrogating PKCepsilon-induced serine phosphorylation of muscle IRS-1 in Psammomys obesus. Diabetes Metab Res Rev 24: 577–584.

Makhlouf L, Duvivier-Kali VF, Bonner-Weir S, Dieperink H, Weir GC, Sayegh MH (2003). Importance of hyperglycemia on the primary function of allogeneic islet transplants. Transplantation 76: 657–664.

Malaisse WJ, Malaisse-Lagae F, Sener A, Pipeleers DG (1982). Determinants of the selective toxicity of alloxan to the pancreatic B cell. Proc Natl Acad Sci U S A 79: 927–930.

Mather K (2009). Surrogate measures of insulin resistance: of rats, mice, and men. Am J Physiol Endocrinol Metab 296: E398–E399.

Mathews CE (2005). Utility of murine models for the study of spontaneous autoimmune type 1 diabetes. Pediatr Diabetes 6: 165–177.

Mathews CE, Leiter EH (1999). Constitutive differences in antioxidant defense status distinguish alloxan-resistant and alloxan-susceptible mice. Free Radic Biol Med 27: 449–455.

Mathews CE, Langley SH, Leiter EH (2002). New mouse model to study islet transplantation in insulin-dependent diabetes mellitus. Transplantation 73: 1333–1336.

Matsumoto S (2011). Autologous islet cell transplantation to prevent surgical diabetes. J Diabetes 3: 328–336.

Matveyenko AV, Butler PC (2006). Islet amyloid polypeptide (IAPP) transgenic rodents as models for type 2 diabetes. ILAR J 47: 225–233.

Matveyenko AV, Gurlo T, Daval M, Butler AE, Butler PC (2009). Successful versus failed adaptation to high-fat diet-induced insulin resistance: the role of IAPP-induced beta-cell endoplasmic reticulum stress. Diabetes 58: 906–916.

McGuinness OP, Ayala JE, Laughlin MR, Wasserman DH (2009). NIH experiment in centralized mouse phenotyping: the Vanderbilt experience and recommendations for evaluating glucose homeostasis in the mouse. Am J Physiol Endocrinol Metab 297: E849–E855.

Mellert J, Hering BJ, Liu X, Brandhorst D, Brandhorst H, Brendel M et al. (1998). Successful islet auto- and allotransplantation in diabetic pigs. Transplantation 66: 200–204.

Mochizuki K, Fukaya N, Tanaka Y, Fuchigami M, Goda T (2011). Treatment with the alpha-glucosidase inhibitor miglitol from the preonset stage in Otsuka Long-Evans Tokushima Fatty rats improves glycemic control and reduces the expression of inflammatory cytokine genes in peripheral leukocytes. Metabolism 60: 1560–1565.

Montane J, Bischoff L, Soukhatcheva G, Dai DL, Hardenberg G, Levings MK et al. (2011). Prevention of murine autoimmune diabetes by CCL22-mediated Treg recruitment to the pancreatic islets. J Clin Invest 121: 3024–3028.

Montanya E, Tellez N (2009). Pancreatic remodeling: beta-cell apoptosis, proliferation and neogenesis, and the measurement of beta-cell mass and of individual beta-cell size. Methods Mol Biol 560: 137–158.

Mordes JP, Bortell R, Blankenhorn EP, Rossini AA, Greiner DL (2004). Rat models of type 1 diabetes: genetics, environment, and autoimmunity. ILAR J 45: 278–291.

Morel P, Kaufmann DB, Matas AJ, Tzardis P, Field MJ, Lloveras JK et al. (1991). Total pancreatectomy in the pig for islet transplantation. Technical alternatives. Transplantation 52: 11–15.

Movassat J, Calderari S, Fernandez E, Martin MA, Escriva F, Plachot C et al. (2007). Type 2 diabetes – a matter of failing beta-cell neogenesis? Clues from the GK rat model. Diabetes Obes Metab 9 (Suppl. 2): 187–195.

Muller YD, Golshayan D, Ehirchiou D, Wyss JC, Giovannoni L, Meier R et al. (2011). Immunosuppressive effects of streptozotocin-induced diabetes result in absolute lymphopenia and a relative increase of T-regulatory cells. Diabetes 60: 2331–2340.

Nerup J, Mandrup-Poulsen T, Helqvist S, Andersen HU, Pociot F, Reimers JI et al. (1994). On the pathogenesis of IDDM. Diabetologia 37 (Suppl. 2): S82–S89.

Neubauer N, Kulkarni RN (2006). Molecular approaches to study control of glucose homeostasis. ILAR J 47: 199–211.

Niens M, Grier AE, Marron M, Kay TW, Greiner DL, Serreze DV (2011). Prevention of 'Humanized' diabetogenic CD8 T-cell responses in HLA-transgenic NOD mice by a multipeptide coupled-cell approach. Diabetes 60: 1229–1236.

Nir T, Melton DA, Dor Y (2007). Recovery from diabetes in mice by beta cell regeneration. J Clin Invest 117: 2553–2561.

Noda K, Melhorn MI, Zandi S, Frimmel S, Tayyari F, Hisatomi T et al. (2010). An animal model of spontaneous metabolic syndrome: Nile grass rat. FASEB J 24: 2443–2453.

O'Brien TD (2002). Pathogenesis of feline diabetes mellitus. Mol Cell Endocrinol 197: 213–219.

Okada S, Saito M, Kinoshita Y, Satoh I, Kawaba Y, Hayashi A et al. (2010). Effects of cyclohexenonic long-chain fatty alcohol in type 2 diabetic rat nephropathy. Biomed Res 31: 219–230.

Ostenson CG, Efendic S (2007). Islet gene expression and function in type 2 diabetes; studies in the Goto-Kakizaki rat and humans. Diabetes Obes Metab 9 (Suppl. 2): 180–186.

Park JS, Rhee SD, Kang NS, Jung WH, Kim HY, Kim JH et al. (2011). Anti-diabetic and anti-adipogenic effects of a novel selective 11beta-hydroxysteroid dehydrogenase type 1 inhibitor, 2-(3-benzoyl)-4-hydroxy-1,1-dioxo-2H-1,2-benzothiazine-2-yl-1-phenylethano ne (KR-66344). Biochem Pharmacol 81: 1028–1035.

Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G (2009). Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 373: 2027–2033.

Peschke E, Hofmann K, Bahr I, Streck S, Albrecht E, Wedekind D et al. (2011). The insulin-melatonin antagonism: studies in the LEW.1AR1-iddm rat (an animal model of human type 1 diabetes mellitus). Diabetologia 54: 1831–1840.

Phillips MS, Liu Q, Hammond HA, Dugan V, Hey PJ, Caskey CJ et al. (1996). Leptin receptor missense mutation in the fatty Zucker rat. Nat Genet 13: 18–19.

Pick A, Clark J, Kubstrup C, Levisetti M, Pugh W, Bonner-Weir S et al. (1998). Role of apoptosis in failure of beta-cell mass compensation for insulin resistance and beta-cell defects in the male Zucker diabetic fatty rat. Diabetes 47: 358–364.

Pinhas-Hamiel O, Zeitler P (2005). The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 146: 693–700.

Portha B, Levacher C, Picon L, Rosselin G (1974). Diabetogenic effect of streptozotocin in the rat during the perinatal period. Diabetes 23: 889–895.

Portha B, Giroix MH, Serradas P, Gangnerau MN, Movassat J, Rajas F et al. (2001). beta-cell function and viability in the spontaneously diabetic GK rat: information from the GK/Par colony. Diabetes 50 (Suppl. 1): S89–S93.

Portha B, Lacraz G, Kergoat M, Homo-Delarche F, Giroix MH, Bailbe D et al. (2009). The GK rat beta-cell: a prototype for the diseased human beta-cell in type 2 diabetes? Mol Cell Endocrinol 297: 73–85.

Pozzilli P, Signore A, Williams AJ, Beales PE (1993). NOD mouse colonies around the world – recent facts and figures. Immunol Today 14: 193–196.

Rackham CL, Chagastelles PC, Nardi NB, Hauge-Evans AC, Jones PM, King AJ (2011). Co-transplantation of mesenchymal stem cells maintains islet organisation and morphology in mice. Diabetologia 54: 1127–1135.

Reddy S, Wu D, Elliott RB (1995). Low dose streptozotocin causes diabetes in severe combined immunodeficient (SCID) mice without immune cell infiltration of the pancreatic islets. Autoimmunity 20: 83–92.

Richardson SJ, Willcox A, Bone AJ, Foulis AK, Morgan NG (2009). The prevalence of enteroviral capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. Diabetologia 52: 1143–1151.

Roep BO (2007). Are insights gained from NOD mice sufficient to guide clinical translation? Another inconvenient truth. Ann N Y Acad Sci 1103: 1–10.

Rydgren T, Vaarala O, Sandler S (2007). Simvastatin protects against multiple low-dose streptozotocin-induced type 1 diabetes in CD-1 mice and recurrence of disease in nonobese diabetic mice. J Pharmacol Exp Ther 323: 180–185.

Sandberg JO, Andersson A, Eizirik DL, Sandler S (1994). Interleukin-1 receptor antagonist prevents low dose streptozotocin induced diabetes in mice. Biochem Biophys Res Commun 202: 543–548.

Sandler S, Swenne I (1983). Streptozotocin, but not alloxan, induces DNA repair synthesis in mouse pancreatic islets in vitro. Diabetologia 25: 444–447.

Shafrir E, Ziv E, Kalman R (2006). Nutritionally induced diabetes in desert rodents as models of type 2 diabetes: acomys cahirinus (spiny mice) and Psammomys obesus (desert gerbil). ILAR J 47: 212–224.

Sheshala R, Peh KK, Darwis Y (2009). Preparation, characterization, and in vivo evaluation of insulin-loaded PLA-PEG microspheres for controlled parenteral drug delivery. Drug Dev Ind Pharm 35: 1364–1374.

Shibata T, Takeuchi S, Yokota S, Kakimoto K, Yonemori F, Wakitani K (2000). Effects of peroxisome proliferator-activated receptor-alpha and -gamma agonist, JTT-501, on diabetic complications in Zucker diabetic fatty rats. Br J Pharmacol 130: 495–504.

Shimada A, Maruyama T (2004). Encephalomyocarditis-virus-induced diabetes model resembles 'fulminant' type 1 diabetes in humans. Diabetologia 47: 1854–1855.

Solomon TP, Sistrun SN, Krishnan RK, Del Aguila LF, Marchetti CM, O'Carroll SM et al. (2008). Exercise and diet enhance fat oxidation and reduce insulin resistance in older obese adults. J Appl Physiol 104: 1313–1319.

Song J, Xu Y, Hu X, Choi B, Tong Q (2010). Brain expression of Cre recombinase driven by pancreas-specific promoters. Genesis 48: 628–634.

Song WJ, Shah R, Hussain MA (2009). The use of animal models to study stem cell therapies for diabetes mellitus. ILAR J 51: 74–81.

Srinivasan K, Ramarao P (2007). Animal models in type 2 diabetes research: an overview. Indian J Med Res 125: 451–472.

Sullivan KA, Hayes JM, Wiggin TD, Backus C, Su OS, Lentz SI et al. (2007). Mouse models of diabetic neuropathy. Neurobiol Dis 28: 276–285.

Sullivan KA, Lentz SI, Roberts JL, Jr, Feldman EL (2008). Criteria for creating and assessing mouse models of diabetic neuropathy. Curr Drug Targets 9: 3–13.

Surwit RS, Kuhn CM, Cochrane C, McCubbin JA, Feinglos MN (1988). Diet-induced type II diabetes in C57BL/6J mice. Diabetes 37: 1163–1167.

Surwit RS, Feinglos MN, Rodin J, Sutherland A, Petro AE, Opara EC et al. (1995). Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. Metabolism 44: 645–651.

Szkudelski T (2001). The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. Physiol Res 50: 537–546.

Szollosi A, Nenquin M, Henquin JC (2010). Pharmacological stimulation and inhibition of insulin secretion in mouse islets lacking ATP-sensitive K+ channels. Br J Pharmacol 159: 669–677.

Tai N, Yasuda H, Xiang Y, Zhang L, Rodriguez-Pinto D, Yokono K et al. (2011). IL-10-conditioned dendritic cells prevent autoimmune diabetes in NOD and humanized HLA-DQ8/RIP-B7.1 mice. Clin Immunol 139: 336–349.

Tian L, Gao J, Hao J, Zhang Y, Yi H, O'Brien TD et al. (2010). Reversal of new-onset diabetes through modulating inflammation and stimulating +¦– cell replication in nonobese diabetic mice by a dipeptidyl peptidase iv inhibitor. Endocrinology 151: 3049–3060.

Todd JA, Wicker LS (2001). Genetic protection from the inflammatory disease type 1 diabetes in humans and animal models. Immunity 15: 387–395.

Tourrel C, Bailbe D, Meile MJ, Kergoat M, Portha B (2001). Glucagon-like peptide-1 and exendin-4 stimulate beta-cell neogenesis in streptozotocin-treated newborn rats resulting in persistently improved glucose homeostasis at adult age. Diabetes 50: 1562–1570.

Tyrberg B, Andersson A, Borg LA (2001). Species differences in susceptibility of transplanted and cultured pancreatic islets to the beta-cell toxin alloxan. Gen Comp Endocrinol 122: 238–251.

Vedtofte L, Bodvarsdottir TB, Gotfredsen CF, Karlsen AE, Knudsen LB, Heller RS (2010). Liraglutide, but not vildagliptin, restores normoglycaemia and insulin content in the animal model of type 2 diabetes, Psammomys obesus. Regul Pept 160: 106–114.

van der Werf N, Kroese FG, Rozing J, Hillebrands JL (2007). Viral infections as potential triggers of type 1 diabetes. Diabetes Metab Res Rev 23: 169–183.

Wagner JE, Kavanagh K, Ward GM, Auerbach BJ, Harwood HJ, Jr, Kaplan JR (2006). Old world nonhuman primate models of type 2 diabetes mellitus. ILAR J 47: 259–271.

im Walde SS, Dohle C, Schott-Ohly P, Gleichmann H (2002). Molecular target structures in alloxan-induced diabetes in mice. Life Sci 71: 1681–1694.

Wallis RH, Wang K, Marandi L, Hsieh E, Ning T, Chao GY et al. (2009). Type 1 diabetes in the BB rat: a polygenic disease. Diabetes 58: 1007–1017.

Wang J, Wan R, Mo Y, Zhang Q, Sherwood LC, Chien S (2010). Creating a long-term diabetic rabbit model. Exp Diabetes Res 2010: 289614.

Wang Q, Jin T (2009). The role of insulin signaling in the development of beta-cell dysfunction and diabetes. Islets 1: 95–101.

Wang RN, Kloppel G, Bouwens L (1995). Duct- to islet-cell differentiation and islet growth in the pancreas of duct-ligated adult rats. Diabetologia 38: 1405–1411.

Wang Z, Gleichmann H (1998). GLUT2 in pancreatic islets: crucial target molecule in diabetes induced with multiple low doses of streptozotocin in mice. Diabetes 47: 50–56.

Wang ZV, Mu J, Schraw TD, Gautron L, Elmquist JK, Zhang BB et al. (2008). PANIC-ATTAC: a mouse model for inducible and reversible beta-cell ablation. Diabetes 57: 2137–2148.

Wei L, Lu Y, He S, Jin X, Zeng L, Zhang S et al. (2011). Induction of diabetes with signs of autoimmunity in primates by the injection of multiple-low-dose streptozotocin. Biochem Biophys Res Commun 412: 373–378.

Weir GC, Marselli L, Marchetti P, Katsuta H, Jung MH, Bonner-Weir S (2009). Towards better understanding of the contributions of overwork and glucotoxicity to the beta-cell inadequacy of type 2 diabetes. Diabetes Obes Metab 11 (Suppl. 4): 82–90.

Wicker LS, Clark J, Fraser HI, Garner VE, Gonzalez-Munoz A, Healy B et al. (2005). Type 1 diabetes genes and pathways shared by humans and NOD mice. J Autoimmun 25 (Suppl.): 29–33.

Wijesekara N, Dai FF, Hardy AB, Giglou PR, Bhattacharjee A, Koshkin V et al. (2010). Beta cell-specific Znt8 deletion in mice causes marked defects in insulin processing, crystallisation and secretion. Diabetologia 53: 1656–1668.

Winzell MS, Ahren B (2004). The high-fat diet-fed mouse: a model for studying mechanisms and treatment of impaired glucose tolerance and type 2 diabetes. Diabetes 53 (Suppl. 3): S215–S219.

Wise MH, Gordon C, Johnson RW (1985). Intraportal autotransplantation of cryopreserved porcine islets of Langerhans. Cryobiology 22: 359–366.

Yang Y, Santamaria P (2003). Dissecting autoimmune diabetes through genetic manipulation of non-obese diabetic mice. Diabetologia 46: 1447–1464.

Yang Y, Santamaria P (2006). Lessons on autoimmune diabetes from animal models. Clin Sci (Lond) 110: 627–639.

Yoon JW, Jun HS (2001). Cellular and molecular pathogenic mechanisms of insulin-dependent diabetes mellitus. Ann N Y Acad Sci 928: 200–211.

Yoon JW, London WT, Curfman BL, Brown RL, Notkins AL (1986). Coxsackie virus B4 produces transient diabetes in nonhuman primates. Diabetes 35: 712–716.

Yoshida S, Tanaka H, Oshima H, Yamazaki T, Yonetoku Y, Ohishi T et al. (2010). AS1907417, a novel GPR119 agonist, as an insulinotropic and beta-cell preservative agent for the treatment of type 2 diabetes. Biochem Biophys Res Commun 400: 745–751.

Yoshinari O, Igarashi K (2011). Anti-diabetic effect of pyroglutamic acid in type 2 diabetic Goto-Kakizaki rats and KK- A y mice. Br J Nutr 106: 995–1004.

Zhang W, Kamiya H, Ekberg K, Wahren J, Sima AA (2007). C-peptide improves neuropathy in type 1 diabetic BB/Wor-rats. Diabetes Metab Res Rev 23: 63–70.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM (1994). Positional cloning of the mouse obese gene and its human homologue. Nature 372: 425–432.

Zhou C, Pridgen B, King N, Xu J, Breslow JL (2011). Hyperglycemic Ins2AkitaLdlr-/- mice show severely elevated lipid levels and increased atherosclerosis: a model of type 1 diabetic macrovascular disease. J Lipid Res 52: 1483–1493.

Ziv E, Shafrir E, Kalman R, Galer S, Bar-On H (1999). Changing pattern of prevalence of insulin resistance in Psammomys obesus, a model of nutritionally induced type 2 diabetes. Metabolism 48: 1549–1554.