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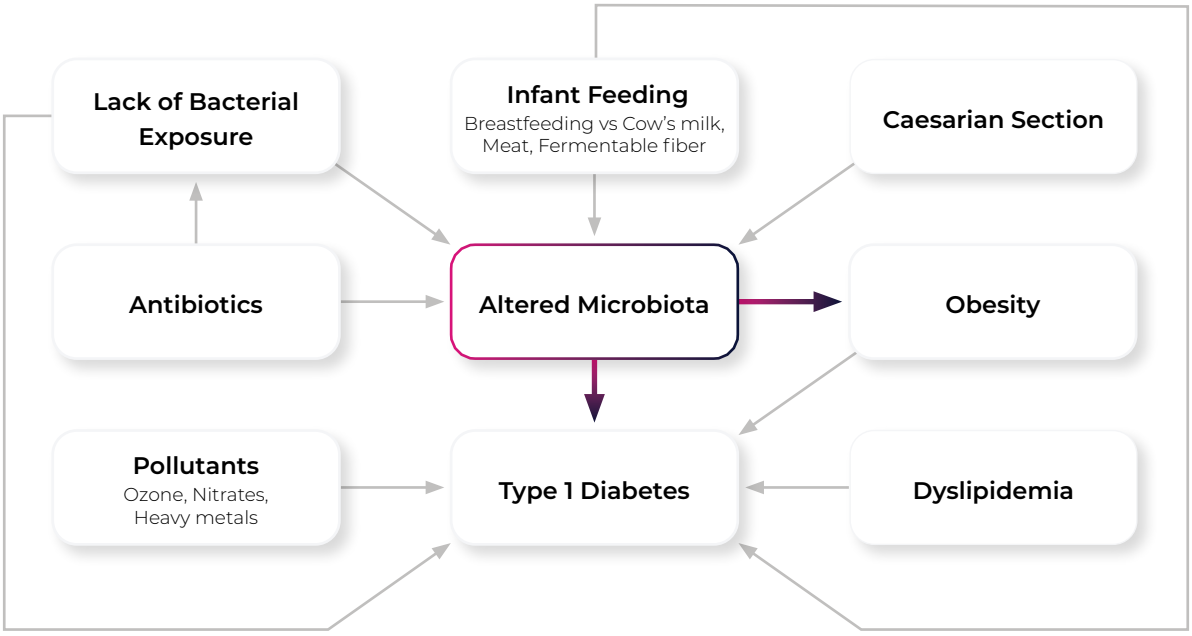
TYPE 1 DIABETES MOUSE MODELS

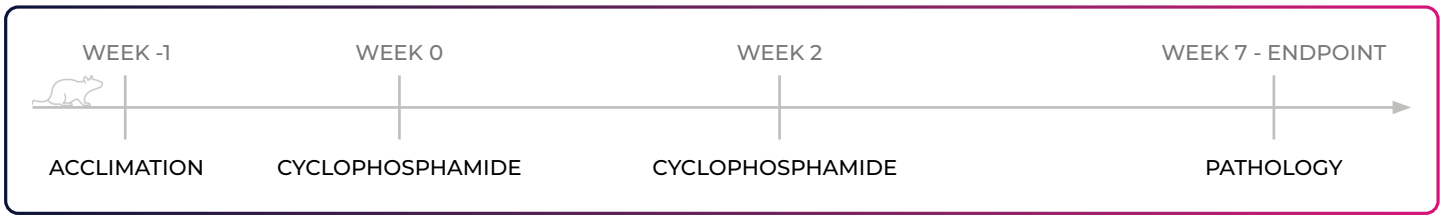
Type 1 diabetes is a chronic autoimmune metabolic disorder that arises as a result of the autoimmune destruction of β cells of the endocrine pancreas.

- The pathogenesis of type 1 diabetes is multifactorial, and the following could all play a role in the genesis of autoimmune diabetes:
  - Genetic factors
  - Environmental factors
  - Prenatal and perinatal factors
  - Immunological factors
- Type 1 diabetes currently has no cure. Treatment involves the careful management of blood sugar levels using insulin. Diet and lifestyle changes are also advised to prevent complications.

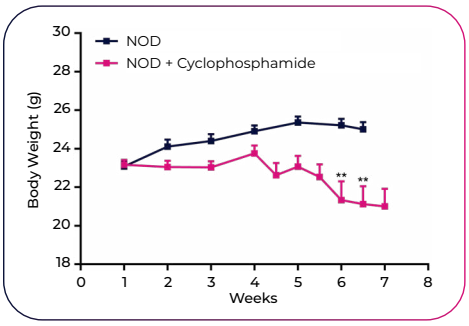


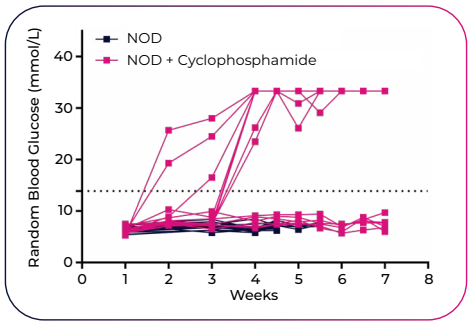
- Non-obese diabetic (NOD) mice can spontaneously develop type 1 diabetes via an autoimmune pathway, but this process can take an extended period of time (around 24 weeks for 50% of mice to develop type 1 diabetes) and can be inhibited by immune tolerance.
- Treatment of NOD mice with cyclophosphamide accelerates destruction of insulin-producing cells in the pancreas (model duration ~7 weeks).
- Streptozotocin (STZ) is a nitrosourea related antibiotic and antineoplastic drug that is produced by Streptomyces achromogenes. Injection of multiple, sub-diabetogenic doses of STZ to mice results in pancreatic insulitis that progresses to near complete destruction of β-cells and a type 1 diabetes (T1D) phenotype.

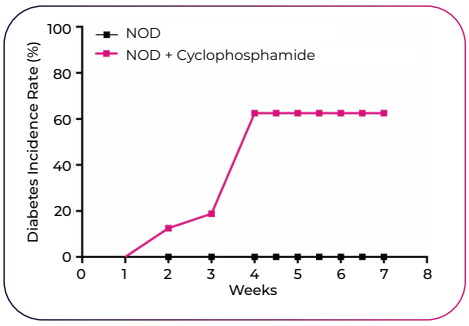
CYCLOPHOSPHAMIDE-INDUCED TYPE 1 DIABETES NOD MOUSE MODEL DATA

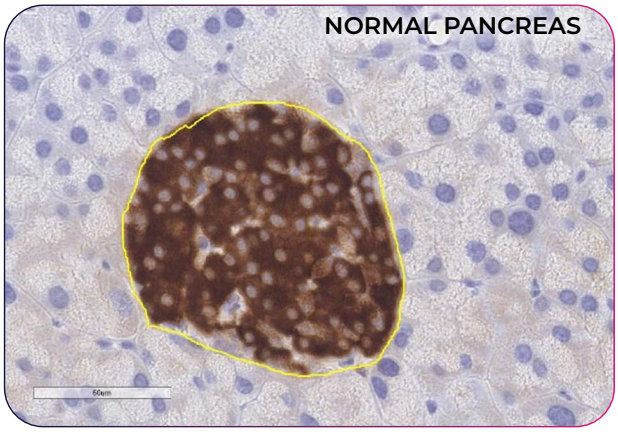


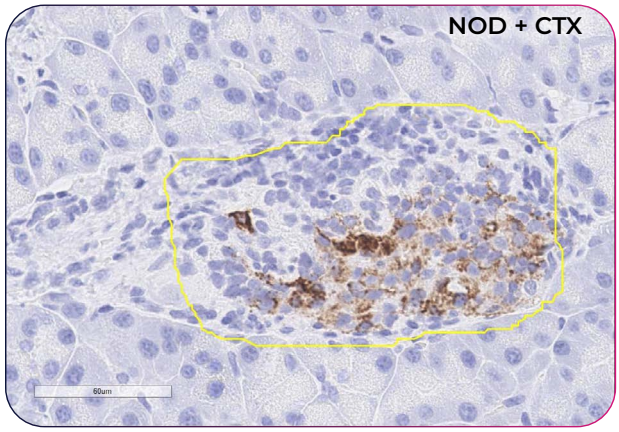
- Mouse
  - SPF female non-obese diabetic (NOD) aged 7 weeks on arrival
- Model
  - Type 1 diabetes onset accelerated by once-a-week intraperitoneal injections of cyclophosphamide in weeks 0 and 2
- Test article administration
  - Oral
  - Intraperitoneal
  - Intravenous
  - Subcutaneous
  - *Other routes available on request*
- 62.5% of animals on study were type 1 diabetic as defined by the diabetes incidence standard: blood glucose ≥ 13.8 mmol/L measured on two separate consecutive occasions within a week
- Staining of mouse pancreas revealed a significant decrease in the number of insulin positive cells









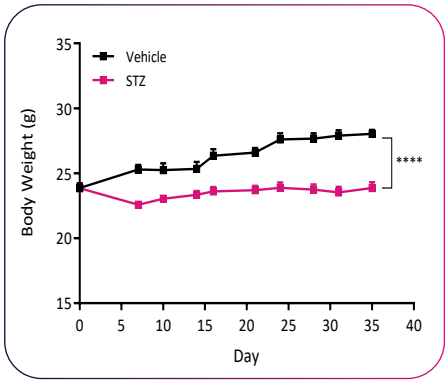


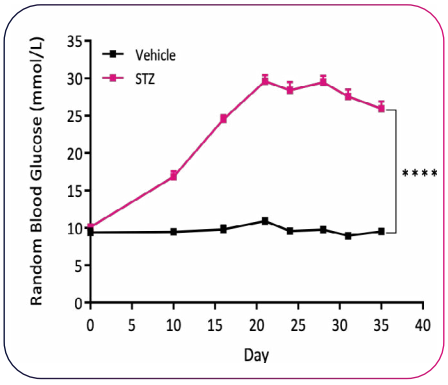
SUMMARY

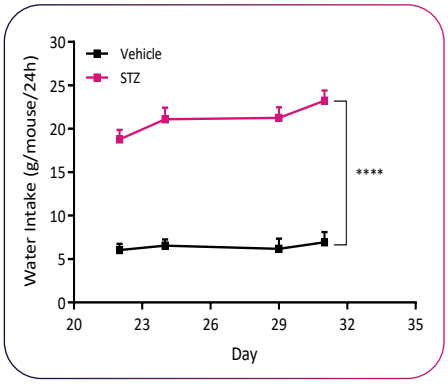
The cyclophosphamide-induced type 1 diabetic mouse model serves as a reliable and clinically relevant platform for assessing drug candidates. With an accelerated onset for disease development, lead times for assessing candidates is significantly reduced.

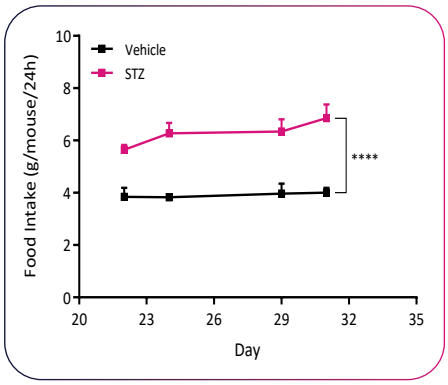
STREPTOZOCIN (STZ)-INDUCED TYPE 1 DIABETES PRECLINICAL *IN VIVO* MODEL

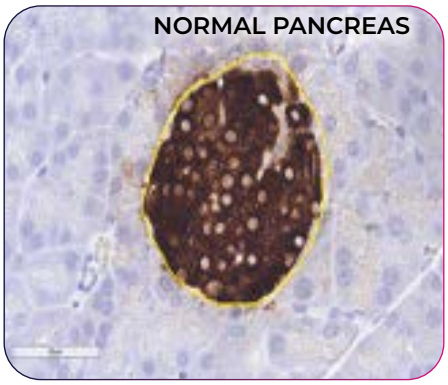
- Mouse
  - SPF male C57BL/6 aged 7 weeks on arrival
- Model
  - Type 1 diabetes induced by intraperitoneal injections of Streptozocin from day 1 to day 5
- Test article administration
  - Oral
  - Intraperitoneal
  - Intravenous
  - Subcutaneous
  - *Other routes available on request*
- 93% of animals on study were type 1 diabetic as defined by the diabetes incidence standard: blood glucose > 16.7mmol/L measured on two separate consecutive occasions within a week.
- Staining of mouse pancreas revealed a significant decrease in the number of insulin positive cells.

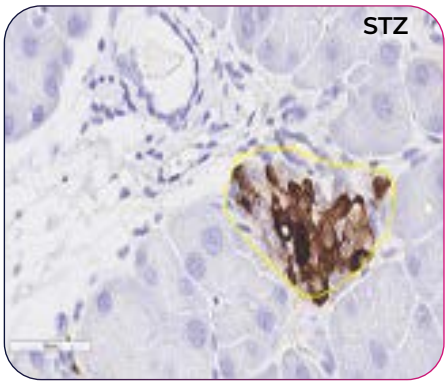












SUMMARY

The streptozotocin-induced mouse model of type 1 diabetes provides an excellent model for the assessment of cell replacement therapy for T1D. Drug candidates can be reliably assessed in accelerated timelines due to its rapid modeling, with the model offering cost effective solutions with high similarity to human disease.

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