

Human-Relevant Non-Animal Methodologies (NAMs)
Specialised Models Series: Metabolic, Digestive & Endocrine
Pancreatic/Islet/Diabetic Models
Reference 5.3 in Full Scope Roadmap

Version 1.0 | June 2026 Edition

Compiled for the Alliance for Cruelty Free Science by Georgina Rednall
Prepared for Academic Leadership, Animal Welfare & Ethical Review Bodies (AWERB), and
Principal Investigators

Legal & Scientific Imperative for Universities

Section 2A of the Animals (Scientific Procedures) Act 1986 imposes a statutory duty on the Secretary of State to ensure compliance with the principles of replacement, reduction, and refinement. The principle of replacement requires that, wherever a specialised, scientifically satisfactory method or testing strategy not entailing the use of protected animals is available, it must be used to replace the use of a regulated procedure.

The endocrine pancreas, specifically the islets of Langerhans, is the master regulator of systemic glucose homeostasis through the tightly coordinated secretion of insulin, glucagon, and somatostatin. Pancreatic disorders—including Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), pancreatitis, and pancreatic ductal adenocarcinoma—constitute severe global healthcare challenges. Historically, preclinical diabetes research and drug safety pipelines have relied extensively on in vivo animal models. However, the cellular architecture, glucose-sensing machinery, and immunological profiles of rodent pancreas diverge fundamentally from those of human patients, rendering animal models non-predictive of clinical outcomes.

At the cellular, molecular, and micro-structural levels, human and rodent pancreatic systems exhibit critical disparities:

- **Islet Micro-Architecture Mismatch:** Human islets feature a highly integrated, dispersed cellular arrangement where insulin-secreting β -cells, glucagon-secreting α -cells, and somatostatin-secreting δ -cells are interspersed throughout the entire islet core and mantle. This architecture permits immediate, bidirectional paracrine and autocrine communication. In contrast, rodent islets are strictly segregated in a "core-shell" structure, with β -cells tightly clustered in the core and α - and δ -cells restricted to the outer mantle. This spatial mismatch fundamentally alters local hormonal feedback loops and insulin-secretion kinetics.
- **Glucose Transporter and Sensing Discrepancies:** The molecular machinery for glucose sensing differs significantly between species. Human β -cells rely on the low-affinity glucose transporters GLUT1 and GLUT3, as well as glucokinase, to regulate glucose-stimulated insulin secretion (GSIS). Rodent β -cells, conversely, rely almost exclusively on the high-capacity transporter GLUT2. Consequently, the threshold, sensitivity, and dynamics of insulin release in response to glucose or novel insulin-sensitising therapeutics (such as GLP-1 receptor agonists) cannot be translated from rodents to humans.
- **Non-Physiological Diabetes Induction:** Traditional in vivo diabetes models rely on injecting high doses of streptozotocin (STZ), a toxic chemical that selectively targets and ablates β -cells via GLUT2 transporters. While this chemical ablation forces acute hyperglycaemia, it does not mimic the complex, autoimmune-driven pathogenesis of human Type 1 Diabetes, nor does it capture the progressive, lipid-induced insulin resistance and low-grade systemic inflammation characteristic of human Type 2 Diabetes.
- **Surgical Pancreatectomy and STZ Severity:** Achieving diabetic phenotypes via surgical pancreatectomy or high-dose STZ administration inflicts immense, high-severity suffering. Animals experience rapid-onset diabetic ketoacidosis, chronic dehydration, severe polyuria, weight loss, and progressive multi-organ damage, while surgical pancreatectomy causes severe post-operative pain and exocrine pancreatic insufficiency, generating massive physiological stress that acts as a major confounding variable.

Transitioning to human-relevant Non-Animal Methodologies (NAMs)—such as microfluidic Islet-on-Chips, 3D primary human islet spheroids, and ex vivo human precision-cut pancreatic slices (PCLS)—is a dual scientific and statutory mandate for UK academic research.

Introduction & Regulatory Momentum

This section details the transition from traditional animal-based pancreatic assays to high-fidelity, human-relevant NAMs. By leveraging iPSC-derived organoids and pancreas-on-a-chip technologies, research institutions can replicate complex human pancreatic responses to metabolic stressors and secretory demands with unprecedented accuracy.

The shift toward these human-centric models is driven by the urgent need to address the limitations of rodent-based islet research. These advanced NAMs provide a superior platform for studying the interplay between beta-cell function, systemic nutrient levels, and the early-stage endocrine dysregulation that precedes full-scale metabolic pathology.

Landmark Regulatory & Scientific Momentum

3D Islet Organoids: Human iPSC-derived beta-cells co-cultured to model glucose-stimulated insulin secretion (GSIS) and endocrine cross-talk, providing a stable human-relevant model of islet function.

Pancreas-on-a-Chip: Microfluidic platforms that simulate physiological nutrient gradients and vascular supply, critical for replicating human-specific pancreatic responses under varied metabolic loads.

In Silico Metabolic Modelling: Computational frameworks that integrate human-derived kinetic data to predict secretagogue response, facilitating safer and more predictive drug screening without animal use.

Core Specialised Pancreatic Platforms

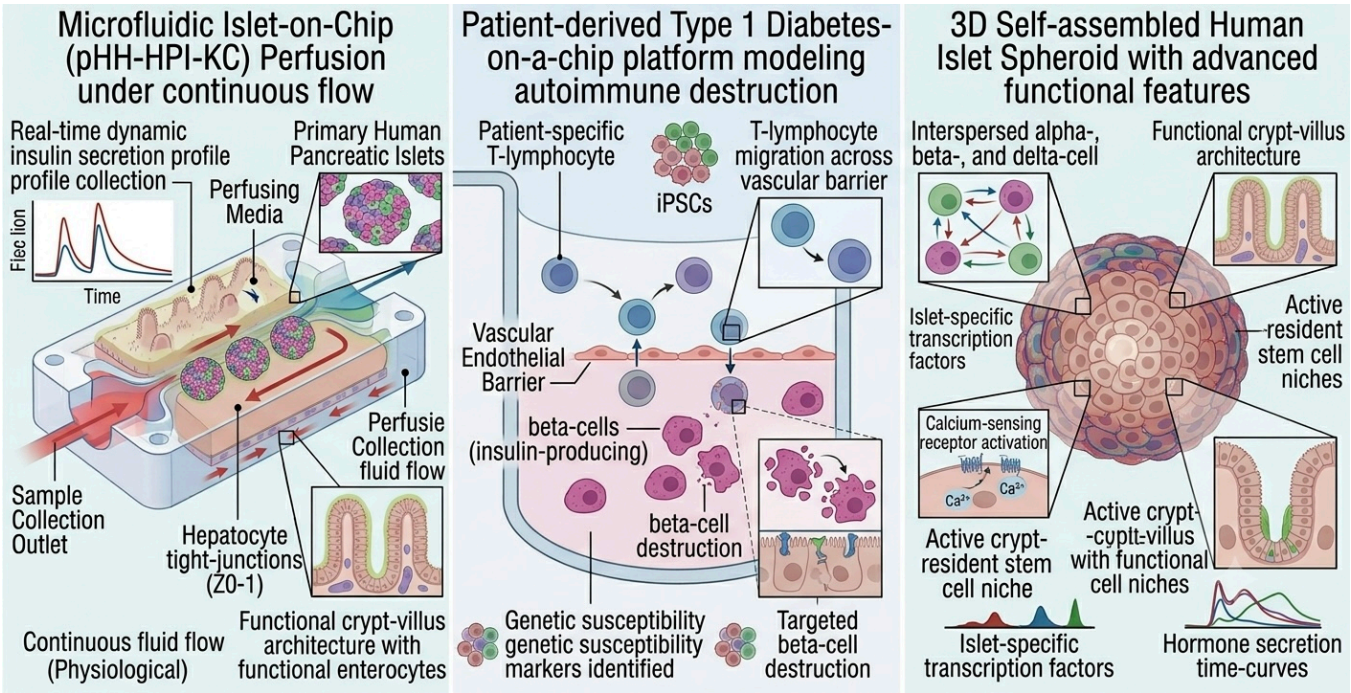


Figure 1: Core Specialised Pancreatic Platforms — Microfluidic Islet-on-Chip showing primary human pancreatic islets perfused under a continuous fluid flow, enabling real-time collection of dynamic insulin secretion profiles (left); co-cultured autoimmune Type 1 Diabetes-on-a-chip platform showing patient-specific T-lymphocytes migrating across a vascular endothelial barrier to selectively target and destroy human β -cells (centre); and a 3D self-assembled human islet spheroid showcasing interspersed α -, β -, and δ -cell paracrine networks with functional calcium-sensing receptors (right).

Table 1: Specialised Biological & Tissue-Engineered (In Vitro) Pancreatic Platform

Platform / Model	Description	Key Applications	Benefits for Universities & 3Rs
Dynamic Islet-on-Chip	Microfluidic channels lining human islets or iPSC-derived β -cells subjected to continuous flow and automated glucose stimulations.	Measuring real-time insulin secretion kinetics, dynamic glucose-stimulated insulin secretion (GSIS), and rapid compound profiling.	Directly replaces the highly distressing rodent in vivo glucose tolerance tests (GTT) and insulin tolerance tests (ITT).
Autoimmune T1D-on-Chip	Co-culture of human pancreatic β -cells and autologous immune cells across a microfluidic membrane under flow.	Modelling T-cell infiltration, antigen presentation, cytotoxic β -cell lysis, and evaluating immune-checkpoint inhibitors.	Eliminates the need for long-term breeding and spontaneous disease monitoring in transgenic Non-Obese Diabetic (NOD) mice.
3D Human Islet Spheroids	Scaffold-free 3D micro-tissues constructed by self-assembling primary human α -, β -, and δ -cells.	High-throughput drug screening, evaluating long-term paracrine islet feedback loops, and investigating anti-diabetic drug candidates.	Replaces the routine, highly stressful isolation of primary rodent islets via invasive collagenase perfusion of the common bile duct.
Ex Vivo Pancreatic Slices (PCLS)	Thin, viable slices of human donor pancreatic tissue containing intact exocrine acini, endocrine islets, and native muscular tone.	Tracking local islet-acinar cellular crosstalk, dynamic calcium signaling waves, and drug-induced acute pancreatitis toxicities.	Bypasses highly invasive large-animal surgical pancreatectomies and ductal ligation procedures used to model pancreatic insufficiency.

Cross-Cutting & Enabling Platforms for Pancreatic/Islet/Diabetic Research

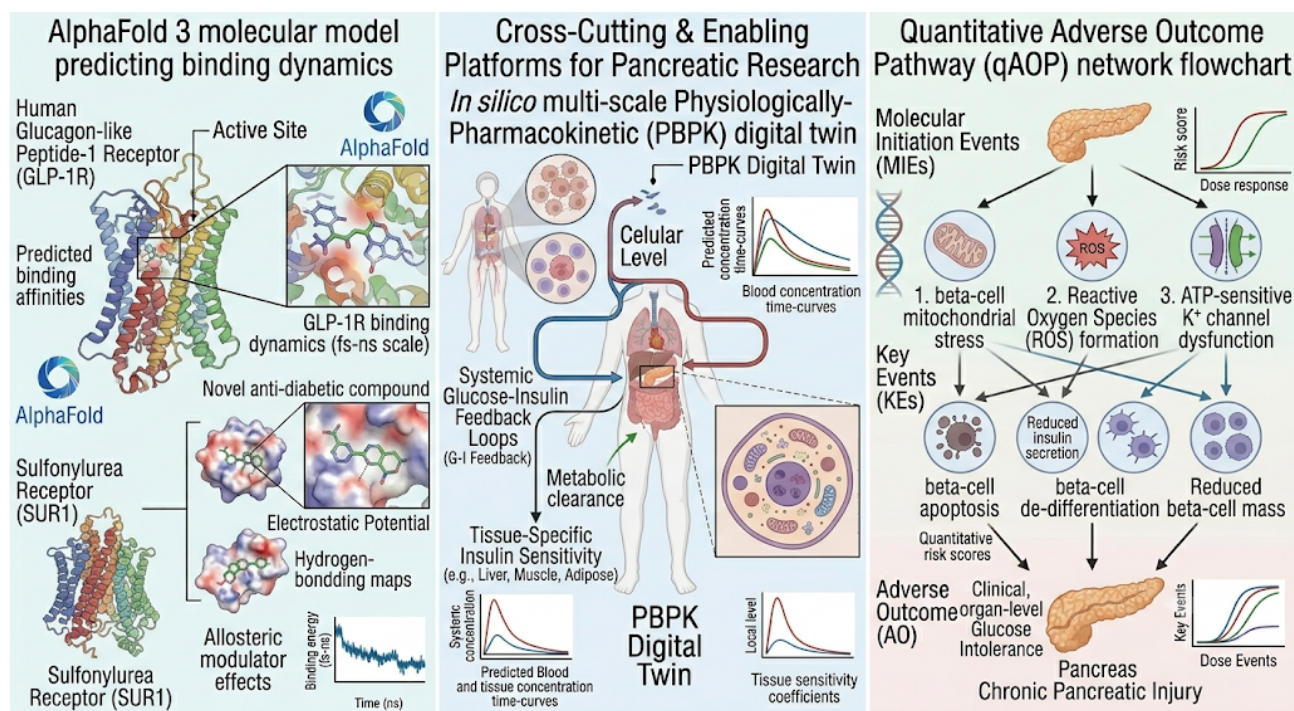


Figure 2: Core Specialised Pancreatic Platforms — Microfluidic Islet-on-Chip showing primary human pancreatic islets perfused under a continuous fluid flow, enabling real-time collection of dynamic insulin secretion profiles (left); co-cultured autoimmune Type 1 Diabetes-on-a-chip platform showing patient-specific T-lymphocytes migrating across a vascular endothelial barrier to selectively target and destroy human β -cells (centre); and a 3D self-assembled human islet spheroid showcasing interspersed α -, β -, and δ -cell paracrine networks with functional calcium-sensing receptors (right).

Table 2: Specialised Biological & Tissue-Engineered (In Vitro) Pancreatic Platforms

Platform / Model	Description	Key Applications	Benefits for Universities & 3Rs
In silico Endocrine PBPK Simulators	Multi-scale mathematical models simulating systemic human glucose-insulin feedback loops, hepatic glucose output, and muscle insulin sensitivity.	Predicting human-specific pharmacokinetic profiles, optimizing clinical dosage, and simulating virtual patient populations with T2D.	Bypasses highly invasive rodent and canine hyperinsulinaemic-euglycaemic clamp studies and chronic blood-sampling.
Molecular Dynamics & GPCR Docking	AI-driven structural predictions mapping the interactions of small molecules with human GPCRs (GLP-1R, GIPR, glucagon receptor).	Screening compound libraries for receptor agonists/antagonists, predicting drug binding affinity, and lead candidate optimisation.	Replaces animal-tissue-derived cell membrane preparation protocols and radioactive ligand-binding assays using animal membranes.
Patient-Derived iPSC Pancreas Models	Reprogrammed patient-specific iPSCs differentiated into functional β -cells and assembled into diseased, multi-cellular pancreatic organoids.	Precision modelling of genetic neonatal diabetes and maturity-onset diabetes of the young (MODY), and testing gene therapies.	Bypasses the need for breeding and maintaining specialised transgenic rodent strains with human-restricted genetic pancreatic mutations.
qAOP-Integrated Endocrine Screeners	Quantitative Adverse Outcome Pathways linking molecular initiation events (e.g., glucokinase inhibition) to clinical hyperglycemia.	Regulatory safety assessment of environmental chemicals, food additives, and high-throughput endocrine-disruptor target prioritisation.	Integrates multiple in vitro data points into a legally defensible weight-of-evidence Replacement package for Project Licence applications.

Strategy • Skills & Capacity

Regulatory Software & Strategy Frameworks

Regulatory acceptance of NAMs—referred to as "fit-for-purpose qualification"—is not a one-size-fits-all process. Researchers should utilise the following frameworks to ensure their computational and biological strategies align with the *Animals (Scientific Procedures) Act 1986* and industry best practices:

- **Context of Use (COU) Documentation:** Before deploying models, clearly define the specific scientific question the model is intended to address. This is critical for demonstrating that the NAM is reliable and suitable for its intended regulatory purpose.
- **Technical Characterisation:** Maintain comprehensive Standard Operating Procedures (SOPs) and study plans for both the biological NAM and any software used to analyse its output. This transparency is vital for successful project licence applications.
- **Early Regulatory Engagement:** Leverage institutional or external regulatory support to track "fit-for-purpose" milestones. Early engagement with the Home Office/ASRU is strongly encouraged to test the acceptability of a computational or NAM-based approach before full project submission.
- **Weight-of-Evidence (WoE) Frameworks:** Use integrated digital dashboards to aggregate data from both *in vitro* (NAM) and *in silico* (computational) sources. Building a strong "weight-of-evidence" argument is the most effective way to strengthen Replacement justifications when moving away from traditional animal models.

Skills, Training, and Capacity Building

The transition from legacy murine diabetic models to human-relevant islet-on-a-chip and organoid systems necessitates a targeted expansion of institutional expertise. Success in this domain requires mastery of the delicate requirements for culturing insulin-producing beta-cells and the engineering of microfluidic devices that mimic pancreatic vascularisation. Furthermore, training must emphasise the interpretation of real-time secretory dynamics, moving away from static end-point measurements toward kinetic data analysis. By institutionalising these competencies, the university builds a self-sustaining research pipeline that supports both basic metabolic discovery and pharmaceutical drug screening, all while maintaining strict adherence to the Replacement mandates of ASPA 1986.

Table 3: Skills •Training, and Capacity Building

Capability Domain	Focus Area	Impact on 3Rs/Replacement
Technical	3D Islet-Organoid Culture	Direct Replacement of animal models
Bioinformatics	Secretory Kinetic Data Analysis	Bypasses murine islet isolation studies
Regulatory	ASPA 1986 Compliance & AWERB	Facilitates faster ASRU approvals
Computational	Secretagogue Response Prediction	Eliminates invasive animal testing

Strategic Note: This investment in human expertise is a key component of a robust, future-proof institutional roadmap, demonstrating to regulators that the institution is committed to the safe and effective operation of high-maturity NAMs.

Clinical Translation Case Studies

Case Study 1: Human Islet-on-Chip Correcting Rodent GLP-1/GIP Receptor Agonist False Positives

- **Background:** A novel dual GLP-1/GIP receptor agonist candidate designed for Type 2 Diabetes demonstrated exceptional insulinotropic efficacy and excellent safety across extensive preclinical rodent screens. However, during early human clinical trials, the compound failed to show significant insulin secretion or glucose-lowering effects in patients, forcing the immediate termination of the program.
- **The Paradigm Shift:** An academic research laboratory re-evaluated the failed candidate using a human-relevant Islet-on-Chip platform. The human system correctly predicted the clinical failure, demonstrating that rodent GPCR expression levels and core-shell islet structures fail to reflect human-specific co-receptor interaction kinetics.
- **The Methodology:** Researchers cultured primary human pancreatic islets inside a microfluidic device, applying continuous flow and automated glucose steps. Upon introducing the drug candidate, the chip recorded a lack of enhanced insulin secretion due to human-specific differences in GIP receptor density on interspersed α - and β -cells. This mismatch was completely masked in rodent islets due to their segregated, core-shell architectures, directly explaining the clinical trial failure.
- **University & Legal Takeaway:** This study highlights how human-relevant Islet-on-Chip platforms can successfully replace animal insulinotropic efficacy screening, proving to the Home Office under ASPA 1986 that the rodent preclinical efficacy data had been actively misleading.

Case Study 2: Autoimmune Diabetes-on-Chip Replacing High-Severity STZ Rodent Models of Islet Ablation

- **Background:** Traditional preclinical research into Type 1 Diabetes (T1D) pathogenesis and drug screening relies heavily on injecting rodents with high, toxic doses of streptozotocin (STZ). This high-severity procedure induces rapid necrotic islet ablation and severe diabetic ketoacidosis. The animals suffer from extreme dehydration, dramatic weight loss, chronic inflammatory pain, and require daily exogenous insulin injections to survive before tissue harvesting.
- **The Paradigm Shift:** A university research department implemented a co-cultured human autoimmune Diabetes-on-Chip, completely replacing the need for high-severity rodent STZ ablation models for target validation.
- **The Methodology:** The team co-cultured human primary pancreatic β -cells with autologous, patient-derived T-lymphocytes across a porous membrane in a microfluidic device. By presenting specific islet auto-antigens, they successfully induced a human-relevant autoimmune reaction, recording real-time T-cell activation, homing, and selective β -cell destruction. They measured the efficacy of novel immunomodulatory therapeutics in preventing cell death using non-invasive fluorescent imaging and dynamic insulin collection, validating key targets in human tissue without animal suffering.

University & Legal Takeaway: This study showcases a highly predictive human alternative that completely replaces high-severity animal protocols, aligning perfectly with Home Office and ASRU expectations for the application of high-maturity Replacement models.

Executive Summary & Compliance Dashboard

Executive Summary

Traditional rodent models of diabetes and pancreatic disease often fail to capture the complex, species-specific dynamics of human glucose-stimulated insulin secretion (GSIS) and autoimmune beta-cell destruction. This roadmap transitions research toward human-relevant NAMs, including 3D islet organoids and pancreas-on-a-chip platforms. By adopting these high-fidelity systems, the institution enhances scientific reproducibility, reduces dependency on unreliable cross-species extrapolation, and fulfills the statutory ASPA 1986 mandate to replace regulated procedures with scientifically superior, human-centric methodologies.

Compliance Dashboard

Focus Area	Primary Animal Model	NAM Replacement Technology	ASPA 1986 Status
Endocrine Function	Murine Islet/Diabetes Models	Islet-on-a-Chip & Organoids	High

Maturity Matrix

- Phase 1 (Exploratory):** Audit animal use in pancreatic islet and diabetes research.
- Phase 2 (Pilot):** Integrate human-derived 3D islet organoids into metabolic protocols.
- Phase 3 (Integration):** Implement pancreas-on-a-chip multi-organ circuits.
- Phase 4 (Standardisation):** Replace 100% of high-severity pancreatic disease protocols.

Final Compliance Statement

All proposed models satisfy the Section 2A statutory duty of ASPA 1986. By adopting these methodologies, the institution positions itself at the forefront of the global transition toward human-centric, cruelty-free medical science.

Integration Context: Roadmap Conclusion

The modules detailed in this roadmap—from fundamental pancreatic islet models (5.3) through the systemic metabolic complexities explored in the later series—demonstrate that Replacement is not a siloed scientific exercise but an integrated institutional strategy. By mapping these specialised NAMs into a unified framework, the institution moves toward a standardised, human-centric research paradigm. This systemic integration is the essential prerequisite for fulfilling the ASPA 1986 statutory duty, ensuring all research is scientifically accurate, ethically aligned, and regulatory compliant.