Human-Relevant Non-Animal Methodologies (NAMs)
Specialised Models Series: Cancer & Haematology
Section 1 – Reference 1.1 - 1.4

Full Scope Roadmap
1.1 Oncology
1.2 Haematological / Blood & Stem Cell Models
1.3 Breast Cancer Models
1.4 Prostate Cancer Models

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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 mandates that whenever 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.

Historically, cancer and haematology research has relied on xenograft mouse models and systemic *in vivo* studies that frequently fail to capture the complexity of human oncogenesis and immune-tumour interactions. These translational failures occur due to:

- **Tumour Microenvironment (TME) Divergence:** Rodent models lack the human-specific stromal, immune, and vascular components of the TME, leading to misleading efficacy results for immunotherapy.

- **Haematopoietic Incompatibility:** Significant biological differences between murine and human bone marrow niches render animal models non-predictive for drug-induced myelosuppression and leukaemia progression.

- **Hormonal & Molecular Mismatch:** Breast and prostate cancer models in rodents often fail to replicate human-specific hormonal signaling pathways and metastatic patterns, contributing to the high attrition rate of oncology therapeutics in clinical trials.

Accelerating the transition to human-relevant Non-Animal Methodologies (NAMs) is an urgent scientific necessity to bridge the translation gap and a statutory mandate for UK academic research programs under *ASPA 1986*.

Executive Summary & Compliance Dashboard

Executive Summary

Oncological and haematological research has historically relied on high-severity animal models that fail to replicate the human TME and complex haematopoietic niches. This roadmap mandates a transition to high-fidelity, human-relevant NAMs—specifically patient-derived organoids (PDOs), microfluidic tumour-on-a-chip systems, and humanised haematopoietic scaffolds—to replace animal-based paradigms. This strategic shift ensures all research is scientifically precise, ethically robust, and fully compliant with the Section 2A statutory duty of the *ASPA 1986*.

Maturity Matrix

Phase 1 (Exploratory): Audit reliance on patient-derived xenograft (PDX) or traditional murine cancer models.

Phase 2 (Pilot): Integrate human patient-derived organoids (PDOs) and tumour-on-a-chip microfluidics.

Phase 3 (Integration): Implement quantitative AI-driven digital pathology for drug-response screening.

Phase 4 (Standardisation): Replace high-severity animal challenge models with qualified, human-specific, predictive NAMs.

Strategic Note: Building institutional expertise in high-maturity human-relevant NAMs is essential for bridging the translational gap in oncology. By training staff in the management of complex cancer-on-a-chip platforms and computational modeming, the institution fulfills its statutory duty under *ASPA 1986*.

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.

Core Specialised Platforms: Scientific & Regulatory Momentum

1.1 Oncology (Solid Tumor) Models: Microenvironment & Metastasis

This section covers platforms designed to model tumour growth, invasion, and vascularisation. Landmark momentum includes **Tumour-on-a-Chip Systems**, which recreate the human vascular-tumour interface, and **Patient-Derived Organoids (PDOs)**, which retain the original tumor's genetic heterogeneity for high-throughput screening.

1.2 Haematological Models: Blood & Stem Cell Niche

This section covers platforms for modelling bone marrow function and leukaemia progression. Landmark momentum includes **Haematopoietic-Niche-on-a-Chip**, which simulates the human bone marrow microenvironment, allowing for the study of stem cell mobilization and drug-induced cytotoxicity.

1.3 Breast Cancer Models: Hormone Sensitivity & Metastasis

This section covers specialised platforms for breast oncology. Landmark momentum includes **3D Bio-printed Mammary Gland Models**, which incorporate human mammary epithelium and stroma to study hormone-dependent cancer progression and targeted therapeutic response.

1.4 Prostate Cancer Models: Androgen Signalling & Tissue Architecture

This section covers platforms for modelling prostate oncogenesis. Landmark momentum includes **Organotypic Prostate Slices** and **Prostate-on-a-Chip**, which replicate human-specific androgen signalling pathways to assess drug efficacy in a clinically relevant context.

Core Specialised Platforms

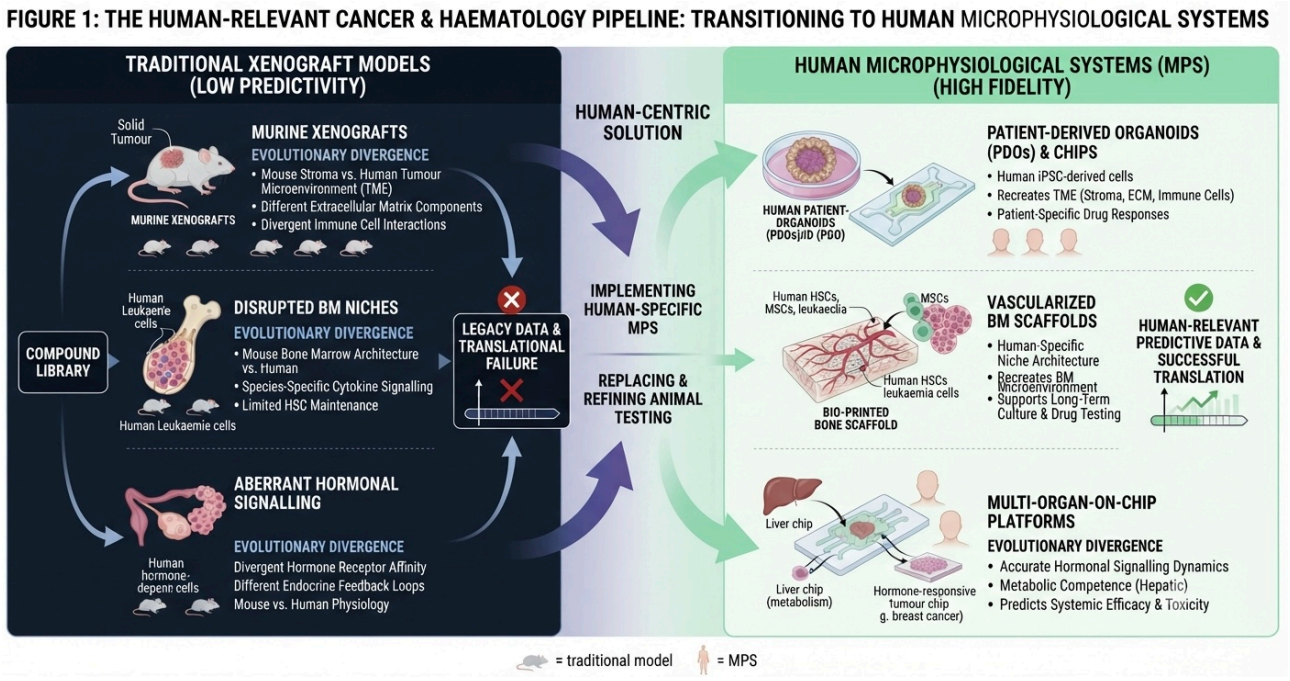

Figure 1: The Human-Relevant Cancer & Haematology Pipeline
Description: A schematic flow diagram illustrating the transition from traditional, low-predictivity xenograft models to high-fidelity human Microphysiological Systems (MPS). The figure contrasts "Evolutionary Divergence" (differences in tumour stroma, bone marrow niches, and hormonal signalling) against the "Human-Centric Solution" (patient-derived organoids, microfluidic chips, and bio-printed scaffolds).

Table1: Core Specialised Platforms

Focus Area	Primary Animal Model	NAM Replacement Technology	ASPA 1986 Status
1.1 Oncology	Murine Xenograft Models	Tumour-on-a-Chip / PDOs	High
1.2 Haematology	Murine Bone Marrow Transplants	Haematopoietic-Niche-on-a-Chip	High
1.3 Breast	Transgenic Mouse Models	3D Bio-printed Mammary Constructs	High
1.4 Prostate	Murine Orthotopic Models	Organotypic Prostate Chips	High

Cross-Cutting & Enabling Platforms

These integrated enabling platforms provide the multi-scale predictive power required for regulatory validation in cancer and haematology research. By combining real-time microphysiological sensing with advanced computational frameworks, these technologies enable robust, "Weight-of-Evidence" (WoE) packages that directly support the replacement of high-severity animal models with human-relevant, predictive data.

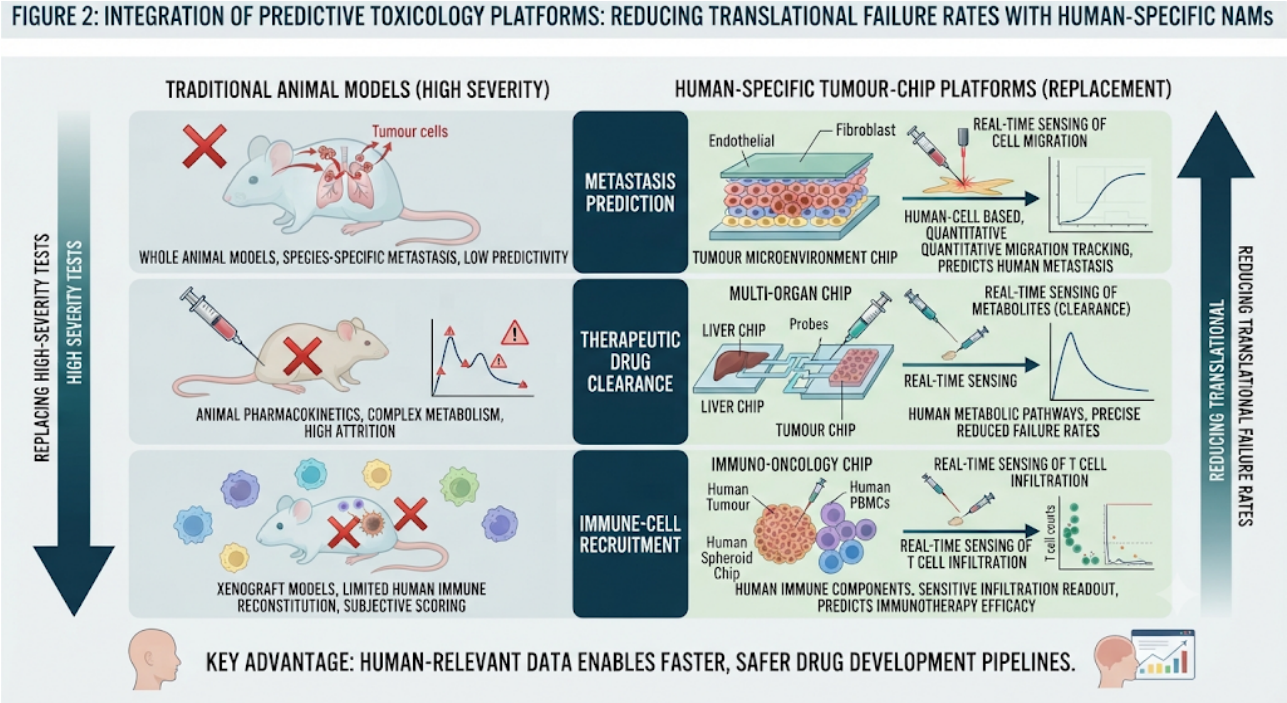

Figure 2: Integration of Predictive Toxicology Platforms

Description: A comparative matrix highlighting the reduction of "Translational Failure Rates" by deploying human-specific NAMs. It visualises how tumour-specific chips provide real-time sensing of metastatic potential, therapeutic drug clearance, and immune-cell recruitment, effectively replacing high-severity animal efficacy and toxicity tests.

Table 2: Genomic & Computational Frameworks

Platform	Key Applications	Benefits for Universities & 3Rs
Digital Pathology AI	Automated tumour-infiltration scoring	Replaces manual animal-tissue histology
Pathway Modelling	Predicting hormone-sensitive drug efficacy	Bypasses murine hormonal screening
Systems Biology Map	Human oncogenic gene signature mapping	Regulatory WoE for Replacement

Integration Context: Roadmap Conclusion

The modules detailed here—from solid tumour microenvironments to haematopoietic niches—demonstrate that replacement is an integrated institutional strategy. Mapping these specialised NAMs into a unified regulatory framework is the essential prerequisite for fulfilling our *ASPA 1986* statutory duty, ensuring all research is sci

Skills • Training, and Capacity Building

Successful adoption of high-maturity Non-Animal Methodologies (NAMs) in oncology and haematology research requires a strategic shift in workforce development. To ensure the long-term success of the platforms outlined in this series, universities should prioritise the following initiatives:

Integrated Oncology & Microfluidics: Training programmes must bridge the gap between human tumour biology, fluidic circuit engineering, and the complex computational mechanics required to simulate the tumour microenvironment (TME).

Regulatory Competency: Staff should receive formal training on "Fit-for-Purpose" qualification and the specific regulatory expectations of the Home Office/ASRU regarding the replacement of high-severity oncological models.

Technological Literacy: Skills in patient-derived organoid (PDO) maintenance, tumour-on-a-chip troubleshooting, and high-throughput digital pathology analysis are critical for modern cancer and haematology research.

Table3: Skills • Training & Capacity Building

Capability Domain	Focus Area	Impact on 3Rs/Replacement
Technical	Patient-derived organoid (PDO) culture	Eliminates murine xenograft models
Computational	AI-driven tumour-infiltration modelling	Bypasses subjective animal-tissue scoring
Regulatory	Weight-of-Evidence (WoE) dossier creation	Streamlines compliance with ASPA 1986
Bioinformatics	Multi-omic analysis of TME integrity	Replaces animal-based efficacy/toxicity studies

Clinical Translation Studies

Oncology: PDOs are currently utilised to develop personalized therapeutic regimens, providing a human-centric alternative for predicting clinical response in solid tumours.

Haematology: MPS platforms that simulate human bone marrow are enabling the study of leukemia progression and stem cell therapies, providing data inaccessible in animal models.

Breast & Prostate: Organotypic tissue models are increasingly used to evaluate the efficacy of targeted inhibitors, bridging the gap between preclinical discovery and clinical trial success.

Summary: Translational researchers are leveraging these systems to improve diagnostic accuracy. Widespread adoption currently depends on standardised manufacturing scalability and regulatory guidance to qualify these systems for clinical dossiers.

Strategic Roadmap Summary

1. Vision & Mandate

This roadmap outlines the institutional transition from traditional *in vivo* animal models to high-fidelity, human-relevant Non-Animal Methodologies (NAMs). Driven by the Section 2A statutory duty of the *Animals (Scientific Procedures) Act 1986*, this strategy prioritises the adoption of human-centric platforms to enhance the scientific validity, reproducibility, and ethical alignment of our research output.

2. Landmark Regulatory & Scientific Momentum

Oncology (Solid Tumor) Models (1.1): Utilising Tumour-on-a-Chip systems to recreate the human vascular-tumour interface and Patient-Derived Organoids (PDOs) to retain genetic heterogeneity for high-throughput screening, replacing murine xenograft models.

Haematological / Blood & Stem Cell Models (1.2): Implementing Haematopoietic-Niche-on-a-Chip platforms to simulate the human bone marrow microenvironment, allowing for the study of stem cell mobilisation and drug-induced cytotoxicity without murine transplants.

Breast Cancer Models (1.3): Adopting 3D bio-printed mammary gland models that incorporate human mammary epithelium and stroma to study hormone-dependent cancer progression and therapeutic response.

Prostate Cancer Models (1.4): Deploying organotypic prostate slices and prostate-on-a-chip architectures to replicate human-specific androgen signalling pathways, superseding traditional orthotopic mouse models.

3. Strategic De-Risking

Financial & Temporal Efficiency: Early-stage identification of off-target toxicities via NAMs prevents the catastrophic costs associated with late-stage clinical trial failures.

Precision Modelling: Moving away from rodent models mitigates the risk of "false positives" driven by species-specific differences in tumour microenvironments (TME) that do not occur in humans.

Data Integrity: Transitioning to human-derived data strengthens "Weight-of-Evidence" submissions, directly increasing the probability of project license (PPL) approval by the Home Office/ASRU.

4. Compliance & Institutional Commitment

Integration Context: Mapping these specialised NAMs into a unified regulatory framework is the essential prerequisite for fulfilling our *ASPA 1986* statutory duty, ensuring all research is scientifically accurate and ethically aligned.

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.