Human-Relevant Non-Animal Methodologies (NAMs)

Specialised Models Series: ***Cancer & Haematology***

Oncology Models

Reference 1.1 in Full Scope Roadmap

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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 requires that, wherever possible, a scientifically satisfactory method or testing strategy not entailing the use of protected animals must be used instead of a regulated procedure.

Traditional animal models in oncology—particularly patient-derived xenografts (PDX) and genetically engineered mouse models—have well-documented limitations. These include profound species differences in tumour-stroma interactions, immune cell infiltration, drug metabolism, and metastatic tissue homing. These limitations contribute to historically high attrition rates in oncology drug development, rendering animal models non-predictive of human clinical outcomes. At the cellular, microstructural, and microenvironmental levels, human and rodent oncology systems exhibit critical disparities:

- **Tumour Microenvironment (TME) Architecture Mismatch:** Human solid tumours feature a highly complex, heterogeneous stroma consisting of patient-specific cancer-associated fibroblasts (CAFs), extracellular matrix (ECM) cross-linking, and a distinct immune infiltrate. In contrast, rodent subcutaneous xenograft models lack this human-specific stromal architecture, fundamentally altering local cytokine signaling networks, physical drug diffusion barriers, and mechanical fluid pressures.

- **Immune System and Checkpoint Discrepancies:** The molecular machinery governing immuno-oncology interactions differs significantly between species. Human T-cells rely on distinct spatial kinetics and affinity profiles for checkpoint receptors (such as PD-1/PD-L1 and CTLA-4) compared to mice. Consequently, the threshold, therapeutic sensitivity, and downstream toxicity of novel immunotherapies or combination regimes cannot be reliably translated from rodents to humans.

- **Non-Physiological Grafting and Vascularisation:** Traditional in vivo oncology models rely on grafting human tumour fragments into profoundly immunodeficient rodents. This artificial system completely bypasses the complex, adaptive immune-driven pathogenesis of human tumorigenesis. Furthermore, it forces human cancer cells to rely on murine host angiogenesis, creating non-human vascular networks that mask true clinical drug penetration and systemic distribution kinetics.

- **Surgical Implantation and Metastatic Severity:** Simulating metastatic cascades via tail-vein injection or orthotopic surgical implantation inflicts immense, high-severity suffering. Animals experience rapid-onset multi-organ failure, progressive respiratory distress, cachexia, and severe post-operative pain, generating massive systemic physiological stress that acts as a major confounding variable in efficacy data collection.

Transitioning to human-relevant Non-Animal Methodologies (NAMs)—such as microfluidic vascularised tumour-immune microenvironment (vTIME) chips, 3D patient-derived tumour organoids (PDOs), and precisely engineered 3D bioprinted constructs—is a dual scientific and statutory mandate for UK academic research.

Landmark Regulatory & Scientific Momentum

This section details the transition from traditional animal-based oncology assays to high-fidelity, human-relevant NAMs. By leveraging patient-derived organoids and tumour-on-a-chip technologies, institutions can replicate complex human tumour responses with unprecedented accuracy.

- **Patient-derived tumour organoids:** Widely used for high-throughput drug screening and personalised therapy, these models preserve tumour heterogeneity and genetic alterations better than traditional models.
- **Cancer-on-chip and tumour microenvironment (TME) mps:** Platforms that incorporate tumour, stromal, immune, and vascular components under controlled flow to facilitate immunotherapy and metastasis studies.
- **Advanced immuno-oncology models:** Models such as lymph node-on-chip and multi-cellular immune tumour assembloids enable physiologically relevant testing of checkpoint inhibitors and CAR-T therapies.
- **Multi-organ metastasis mps:** Platforms developed to model the full metastatic cascade and systemic effects of cancer therapies.
- **3d bioprinted tumour models:** Precisely engineered constructs featuring controlled architecture and vascular channels.

Landmark Regulatory Milestone

In October 2025, the FDA granted the world's first oncology Investigational New Drug (IND) clearance based solely on human-relevant efficacy data from a vascularised tumour-immune microenvironment (vTIME) platform. By bypassing traditional animal proof-of-concept (POC) efficacy testing, this decision established a historical precedent under the *FDA Modernization Act 2.0*.
core specialised oncology models

Core Specialised Oncology Models & Enabling Platforms

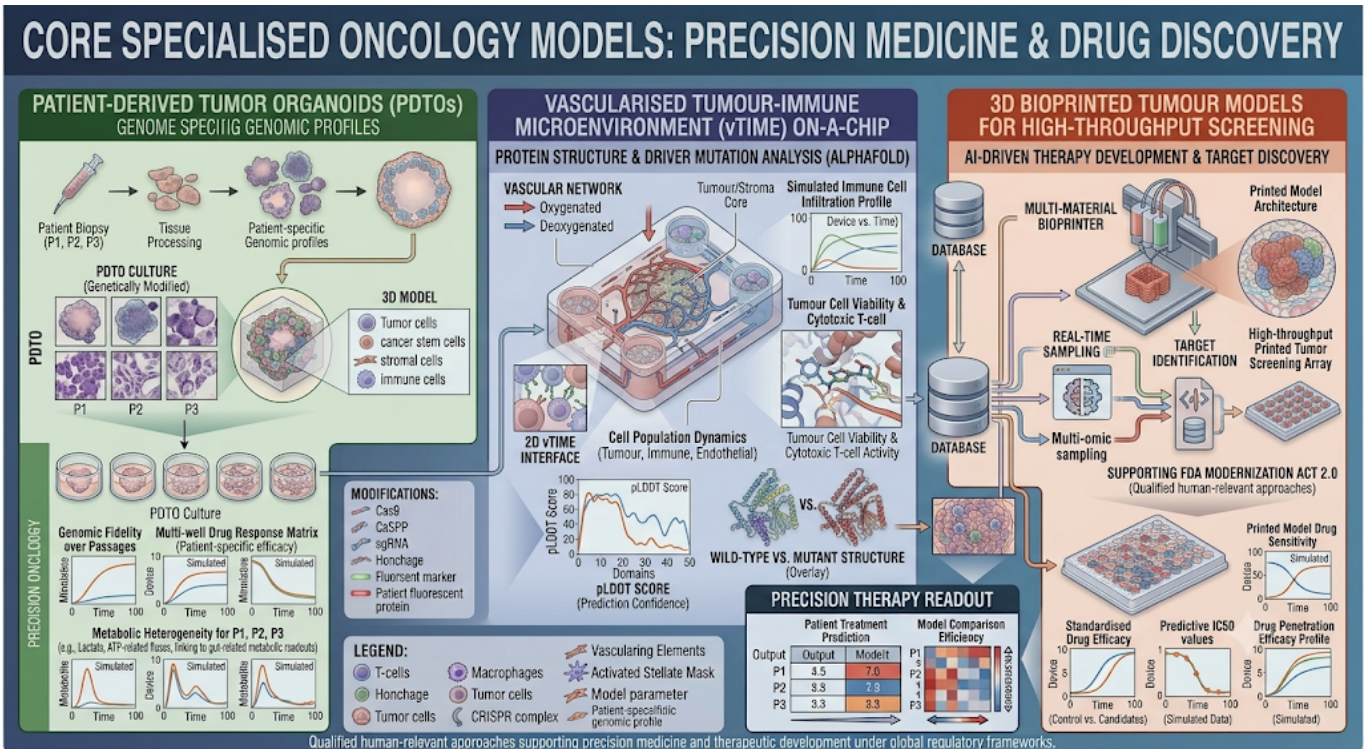

Figure 1: Core Specialised Oncology Models — Patient-derived tumour organoids, vascularised tumour-immune microenvironment (vTIME) on-a-chip, and 3D bioprinted tumour models.

Table 1: Specialised biological & tissue-engineered oncology platforms

Platform	Key Applications	Benefits for Universities & 3Rs
Tumour Organoids	Pharmacotyping & drug screening	Preserves patient-specific tumour heterogeneity
VTIME-on-a-Chip	Immunotherapy & drug delivery	Replaces animal-based POC efficacy testing
3D Bioprinted Models	Microenvironmental replication	High experimental control and reproducibility

Cross-Cutting & Enabling Platforms for Oncology Research

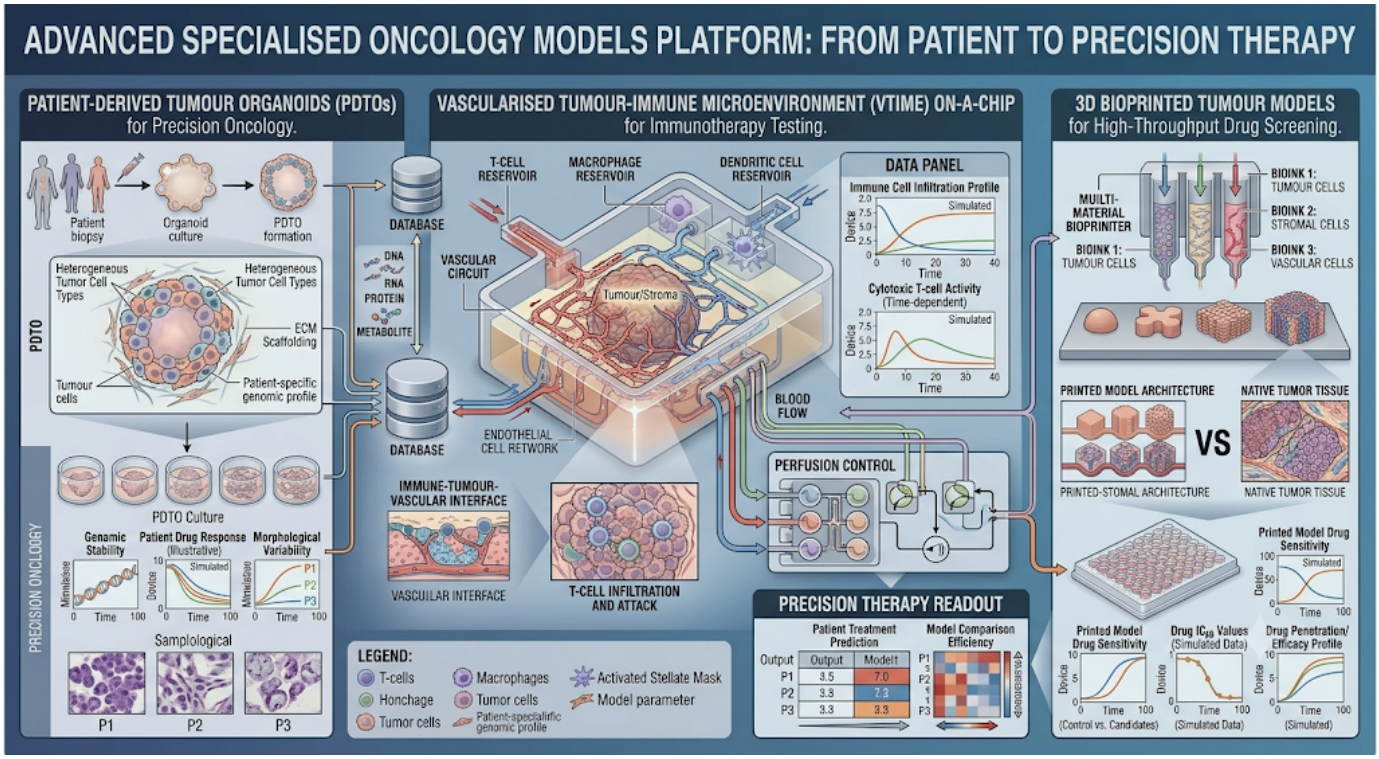

Figure 2: Cross-Cutting & Enabling Platforms for Oncology Research — CRISPR gene editing in tumour organoids (left), AlphaFold (DeepMind) predicting structures of cancer driver proteins (centre), and hybrid AI + organoid workflows for target discovery and personalised therapy development (right). These enabling technologies support qualified human-relevant approaches under the FDA Modernization Act 2.0.

Table 2: Cross Cutting & Enabling Platforms in Oncology Research.

Platform / Model	Description	Key Applications	Benefits for Universities & 3Rs
AlphaFold (DeepMind) for Oncology	AI system that predicts protein structures at experimental-level accuracy. Used for structure-based drug design, mapping cancer driver mutations (e.g. p53, KRAS), and identifying novel therapeutic targets.	Structure-based drug design, mapping oncogenic mutations, accelerating targeted therapy discovery, understanding protein–protein interactions in cancer.	Dramatically accelerates target identification and drug design in oncology; powerful complement to experimental NAMs; ideal for computational oncology training.
Patient-Derived iPSC Cancer Models & CRISPR Engineering	iPSC lines from patients with hereditary cancer syndromes or CRISPR-engineered models of key oncogenic drivers.	Early tumorigenesis, cancer predisposition syndromes, targeted therapy development, genetic screens.	Enables study of early and genetic events in cancer; strong replacement for many transgenic animal models.
Multi-Organ Metastasis MPS & In Silico Oncology Platforms	Interconnected chips modelling metastatic spread combined with computational models for predicting treatment response and resistance.	Metastasis research, virtual clinical trials, resistance mechanism prediction, personalised therapy optimisation.	Holistic systems approach to cancer; ideal for computational oncology and translational training.
High-Throughput & High-Content Oncology Screening Platforms	Automated organoid and MPS-based screening systems for large-scale drug and immunotherapy testing.	Drug repurposing, combination therapy screening, biomarker identification, resistance studies.	Enables rapid, cost-effective, human-relevant screening; excellent for early discovery training.
AOP-Integrated & Regulatory Oncology NAMs	Adverse Outcome Pathway frameworks and qualified platforms for regulatory assessment of oncology drug safety and efficacy.	Regulatory decision support, weight-of-evidence approaches, safety assessment of novel oncology agents.	Supports regulatory science and translational oncology; valuable for students interested in regulatory careers.

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 / Animals** in Science Regulation Unit (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

Successful adoption of high-maturity Non-Animal Methodologies (NAMs) 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 training initiatives to build institutional capacity:

- **Integrated Oncology & Data Science:** Training programmes should bridge the gap between bench-top laboratory biology and computational analysis. Researchers require dual proficiency in 3D culture techniques and the digital pipelines used to interpret complex imaging and high-throughput drug-response data.
- **Regulatory Competency:** Staff should receive formal training on "Fit-for-Purpose" qualification and the specific regulatory expectations of the Home Office / ASRU. This includes understanding how to document evidence for the 3Rs within formal project licence applications to ensure they meet legal standards.
- **Technological Literacy:** Skills in CRISPR-based functional genomics, advanced microscopy, and high-throughput screening are increasingly critical for modern precision oncology research. Universities should facilitate internal workshops or establish external partnerships to provide PhD students and postdoctoral fellows with hands-on experience in these specialised tools.
- **Ethics & Translation:** Education should focus on the scientific imperative of human-relevant research, emphasising why NAMs provide more predictive insights for clinical outcomes than traditional rodent models. This fosters a culture of excellence and ethical research design that is fully aligned with modern international standards.

Table 3: Skills •Training, and Capacity Building

Capability Domain	Focus Area	Impact on 3Rs/Replacement
Technical	3D culture & bioprinting	Direct replacement of PDX models
Bioinformatics	Imaging & drug-response data analysis	Bypasses animal-based tumour measurements
Regulatory	Fit-for-purpose qualification	Facilitates faster ASRU approvals
Computational	Digital twin/AI target discovery	Eliminates invasive animal efficacy studies

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: First FDA IND Clearance Based Solely on Human Organoid Data (October 2025)

- **Background:** Preclinical development of complex oncology drug combinations traditionally requires animal-based proof-of-concept (POC) efficacy data, despite poor rodent-to-human translational fidelity.
- **The Paradigm Shift:** In late 2025, an IND amendment was successfully cleared by the FDA to evaluate the anticancer drug **BAL0891** in combination with the immune checkpoint inhibitor **Tislelizumab**. Crucially, the pivotal efficacy data required for clearance were generated entirely without traditional animal model testing.
- **The Methodology:** Researchers utilised Qureator's proprietary **vascularised tumour-immune microenvironment (vTIME)** platform. Unlike basic 3D cultures, vTIME actively recreates functional human vascular networks and fluid dynamics alongside tumour and immune cells to simulate exact drug penetration, distribution, and immune responses. This biological platform was paired with the **Quricore AI engine** to process and translate high-throughput multi-cellular data into clinical predictability metrics.
- **University & Legal Takeaway:** This precedent serves as definitive, real-world evidence for academic researchers drafting Project Licence applications. It proves to the Home Office / Animals in Science Regulation Unit (ASRU) that complex tumor-immune interactions and combination therapy efficacies can be robustly validated using non-animal microphysiological systems, fully satisfying the legal replacement mandate under Section 2A of ASPA 1986.

Case Study 2: Tumour Organoids in Precision Oncology Clinical Decision-Making

Multiple academic medical centres and pharmaceutical companies are now using patient-derived tumour organoids (PDOs) to guide treatment selection for patients with advanced or rare cancers. In several published studies, organoid drug sensitivity profiles showed strong correlation with clinical outcomes, enabling more personalised and effective treatment choices while reducing exposure to ineffective therapies.

Case Study 3: Multi-Organ Tumour MPS in Metastasis and Drug Metabolism Studies

Pharmaceutical companies are increasingly adopting multi-organ tumour MPS platforms (e.g. tumour–liver, tumour–bone) to study metastasis mechanisms and systemic drug effects. These systems have identified clinically relevant metastatic behaviours and drug metabolism patterns that were not accurately modelled in conventional xenograft studies, improving translational predictions for late-stage clinical trials.

Executive Summary & Compliance Dashboard

Executive Summary

Traditional rodent oncology models often fail to capture the complex, species-specific dynamics of human tumour microenvironments. This roadmap transitions research toward human-relevant NAMs, including patient-derived organoids and vTIME 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
Tumour Microenvironment	PDX / Xenograft Models	Tumour Organoids & VTIME	High

Maturity Matrix

Phase 1 (Exploratory): Audit animal use in oncology efficacy studies.

Phase 2 (Pilot): Integrate patient-derived organoids into drug screening.

Phase 3 (Integration): Implement vascularised tumour-immune MPS.

Phase 4 (Standardisation): Replace 100% of rodent POC efficacy testing.

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 oncology models (1.1) through the systemic complexities explored in later series—demonstrate that replacement is 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.