

MANIFEST: multiomic platform for cancer immunotherapy



MANIFEST

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AI-enabled target/drug discovery

Multimodal ANALysis of Immunotherapy Features Evidencing Success and Toxicity

Personalised cancer treatment can benefit substantially from artificial intelligence-driven models. However, in real-world clinical settings, multimodal patient data are often incomplete, unpaired, or unevenly sampled over time due to challenges in recruitment and longitudinal follow-up, limiting the development of robust predictive models.

To address this, we leverage data from the UK-wide MANIFEST programme, which is building a large-scale, longitudinal, multimodal resource of several thousand patients over five years. MANIFEST integrates digital histopathology, spatial transcriptomics, multiplex immunofluorescence imaging, genomic sequencing, immunophenotyping, and structured clinical and temporal data¹. Here, we present exemplar analytical workflows under development within the consortium to model biological complexity and enable drug discovery.

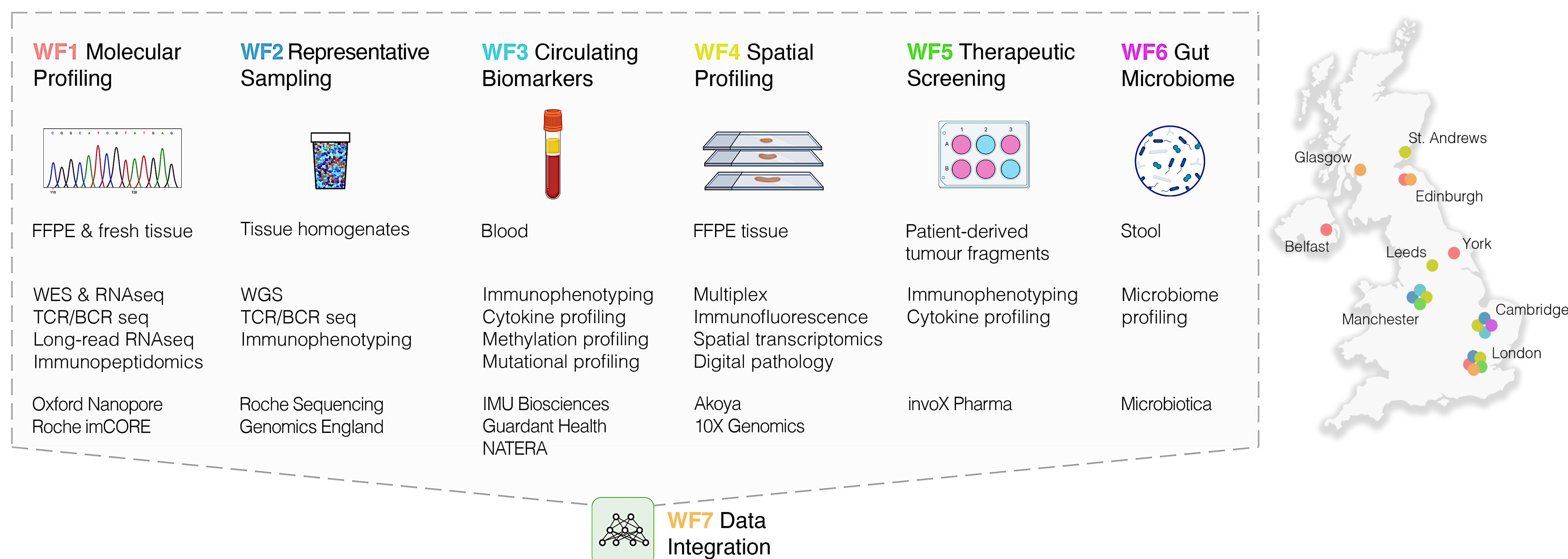


Figure 1. Multiple modalities available through the MANIFEST Project for cancer research

WF3 Circulating Biomarkers

Circulating biomarkers provide a minimally invasive window into tumour biology, enabling dynamic assessment of disease burden, treatment response, tumour evolution, and immune-related adverse events (irAEs). Peripheral immune profiling, cytokine measurements, and circulating cell-free DNA (cfDNA) analyses show promise. However, variability continues to limit clinical translation, highlighting the need for robust standardisation and longitudinal validation.

High dimensional cytometry

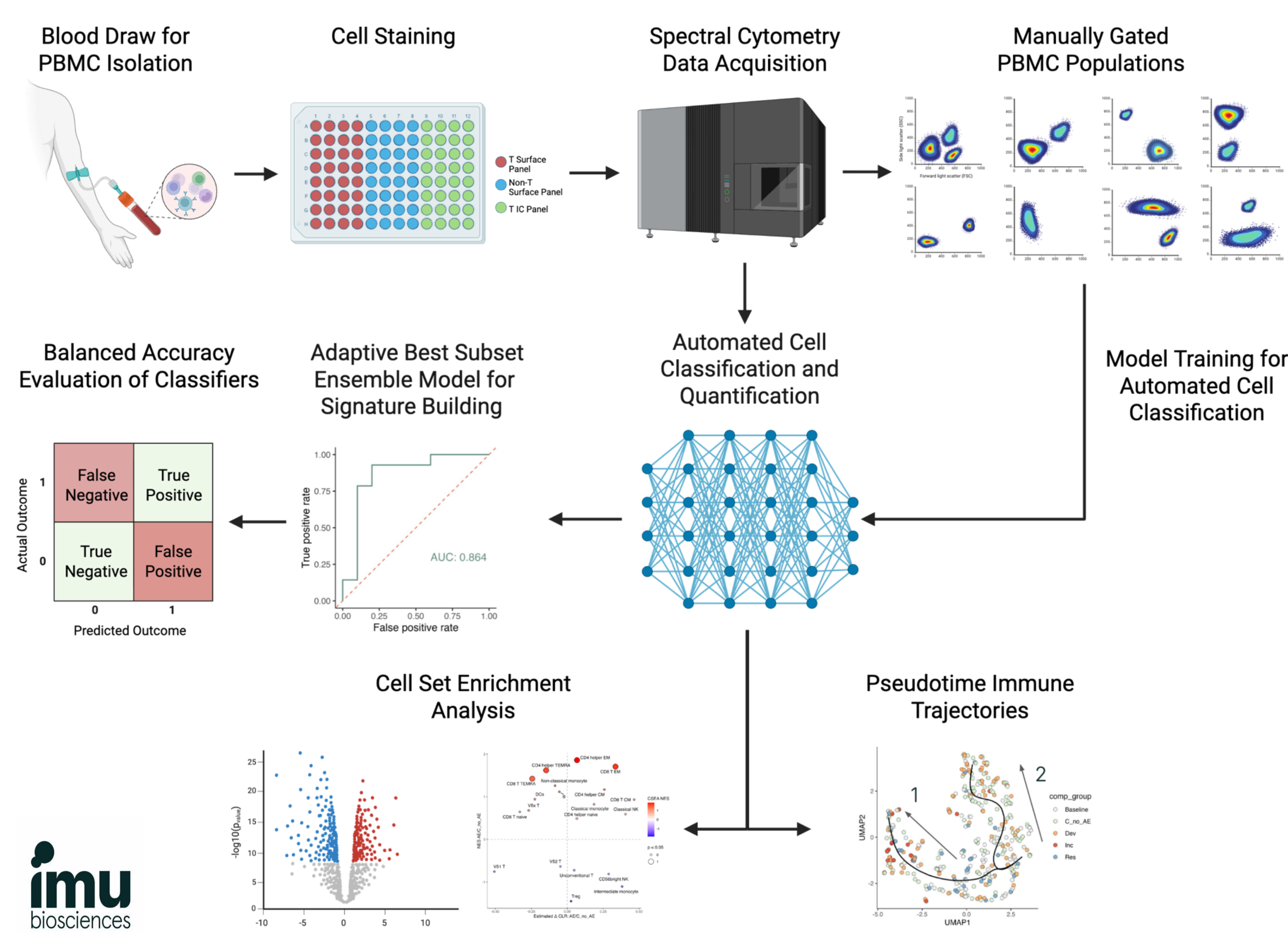


Figure 2. High-dimensional classification of circulating biomarkers

High-resolution spectral cytometry of longitudinal PBMC samples is used to quantify peripheral immune cell states in MANIFEST. Automated classification outputs are integrated into an ensemble modelling framework to derive predictive immune signatures associated with immunotherapy response and irAEs. Model performance, differential analyses, and enrichment approaches identify candidate immune populations.

MANIFEST integrates high-resolution spectral cytometry and cytokine profiling to characterise dynamic peripheral immune responses associated with immunotherapy efficacy and toxicity. Leveraging longitudinal sampling across observational cohorts, we investigate how immunotherapy treatment shapes systemic immune states. Ongoing analyses aim to derive predictive peripheral immune signatures and identify enriched, potentially targetable cell populations linked to irAE development. These peripheral immune features will be cross-validated with single-cell RNA-sequencing and cytokine data to define irAE-associated immunotypes and inform patient stratification.

WF4 Spatial Profiling

The tumour microenvironment (TME) is organised across multiple, interdependent layers of complexity that cannot be captured by a single analytical modality. Histological architecture defines large-scale tissue organisation, while spatial domains reflect intermediate structures shaped by tumour, stromal, and immune interactions. At higher resolution, individual cell phenotypes display substantial heterogeneity in both spatial localisation and molecular state.

Spatial multimodal analysis

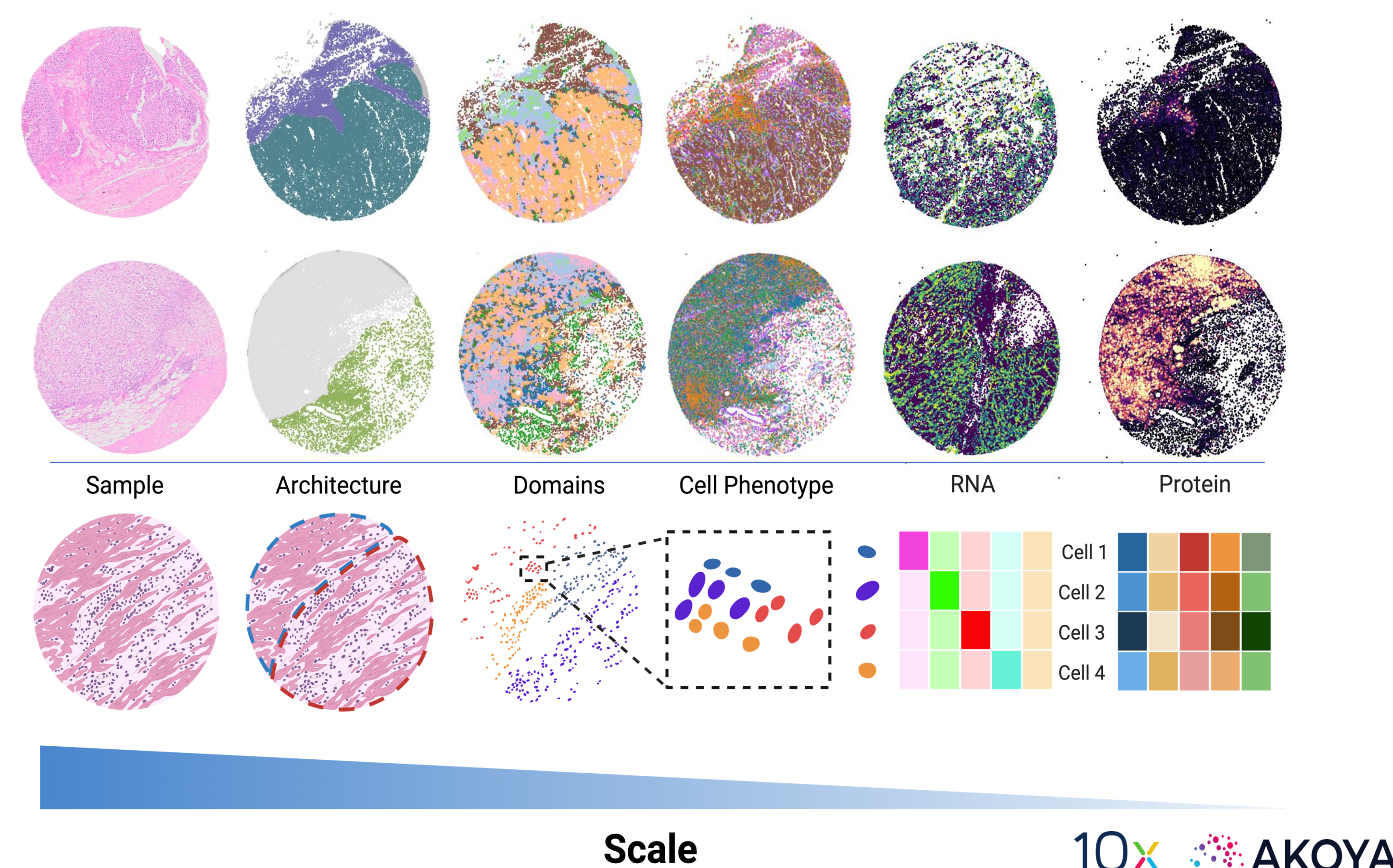


Figure 3. Multi-scale spatial registration

Spatial proteomic data generated using Akoya PhenoCycler and spatial transcriptomic data generated using 10x Genomics Xenium are processed to obtain cell-level measurements mapped to their spatial coordinates. Cross-modality registration enables cell-to-cell correspondence across protein and RNA modalities and across architectural scales, facilitating integrated spatial analyses within and across patients.

These layers are further complicated by discordance between transcriptional and protein-level readouts, with RNA and protein signals capturing overlapping but non-identical aspects of cellular identity and function. As illustrated, the same tissue region can exhibit distinct patterns when viewed through architectural, domain-level, cellular, transcriptomic, or proteomic lenses, underscoring the need for integrated, multimodal analysis.

Together, this multi-scale complexity motivates approaches that jointly model tissue architecture, spatial context, and molecular state. Integrating histopathology, spatial cell phenotyping, RNA expression, and protein abundance enables a more faithful representation of immune and tumour ecosystems, providing a framework to identify biologically meaningful niches and therapeutic vulnerabilities that would be obscured in single-modality analyses.

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<https://www.manifest-io.org.uk/>



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