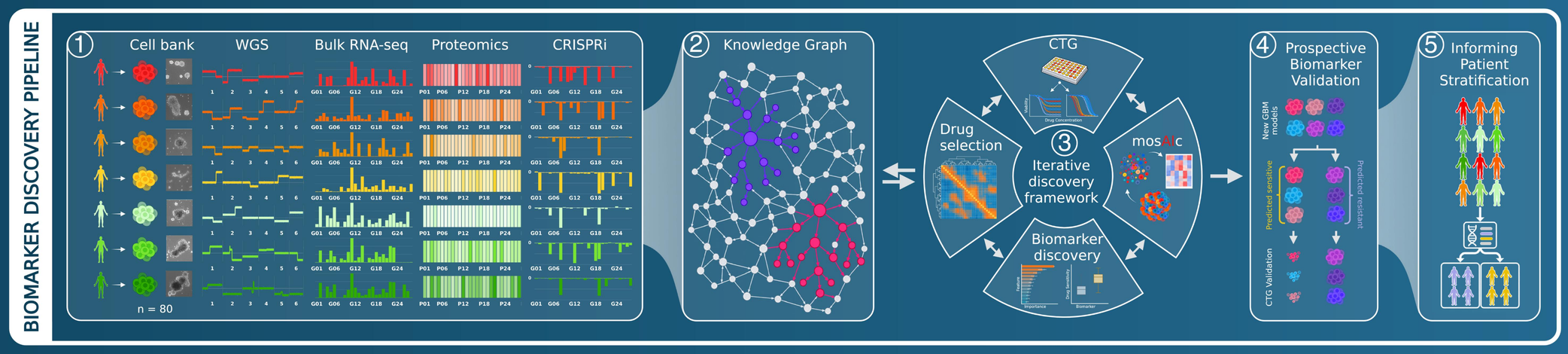
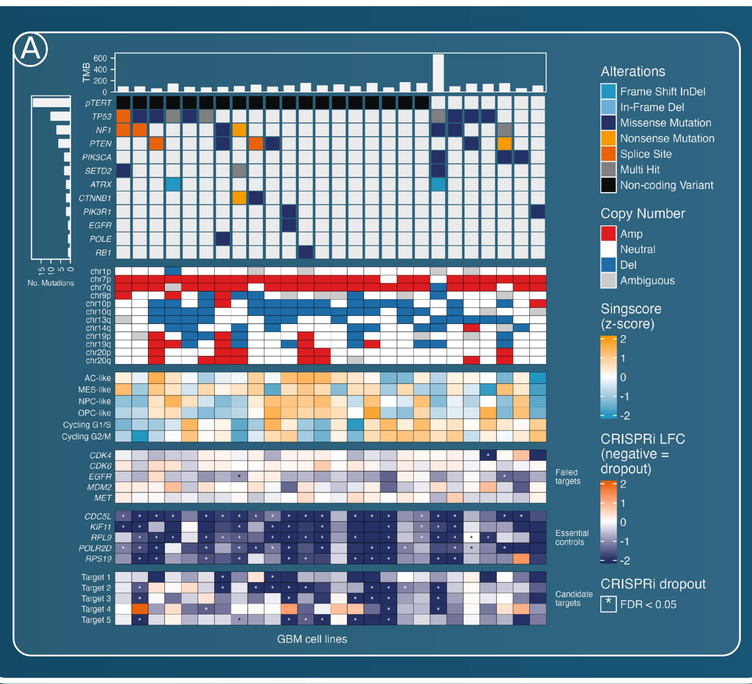
AN INTEGRATED DISCOVERY PIPELINE FOR DRUG PRIORITISATION AND BIOMARKER DISCOVERY IN GLIOBLASTOMA

COSINE THERAPEUTICS

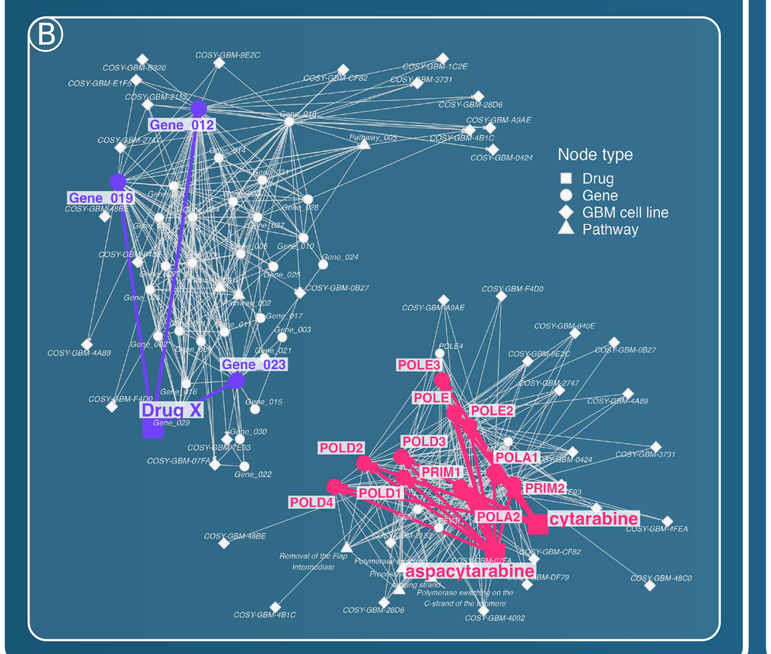


Integrated drug prioritisation and biomarker discovery pipeline. (1) Patient-derived glioblastoma (GBM) models are characterised by whole-genome sequencing, bulk RNA sequencing, proteomics and CRISPRi screens. (2) These data inform a knowledge graph that guides drug selection. (3) Iterative CellTiter-Glo (CTG) viability assays, mosAIc single-cell screens and biomarker analyses refine drug prioritisation and identify candidate predictors of response. (4) Candidate biomarkers undergo prospective validation in new GBM models. (5) Validated drug–biomarker pairs are used to inform patient stratification.

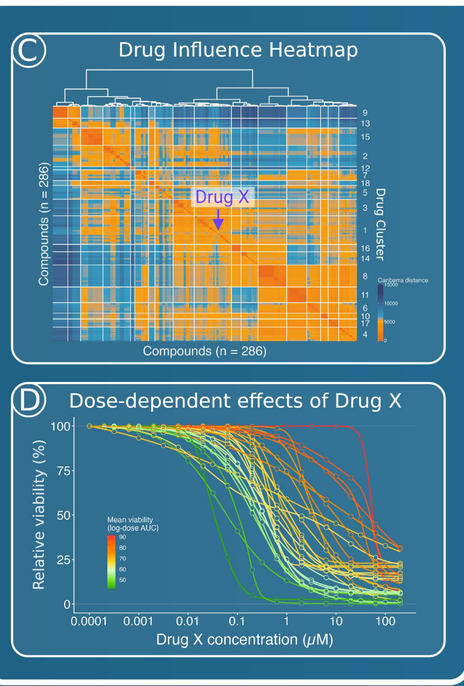
MULTI-OMIC CHARACTERISATION OF GBM MODELS



KNOWLEDGE-GRAPH NEIGHBOURHOOD

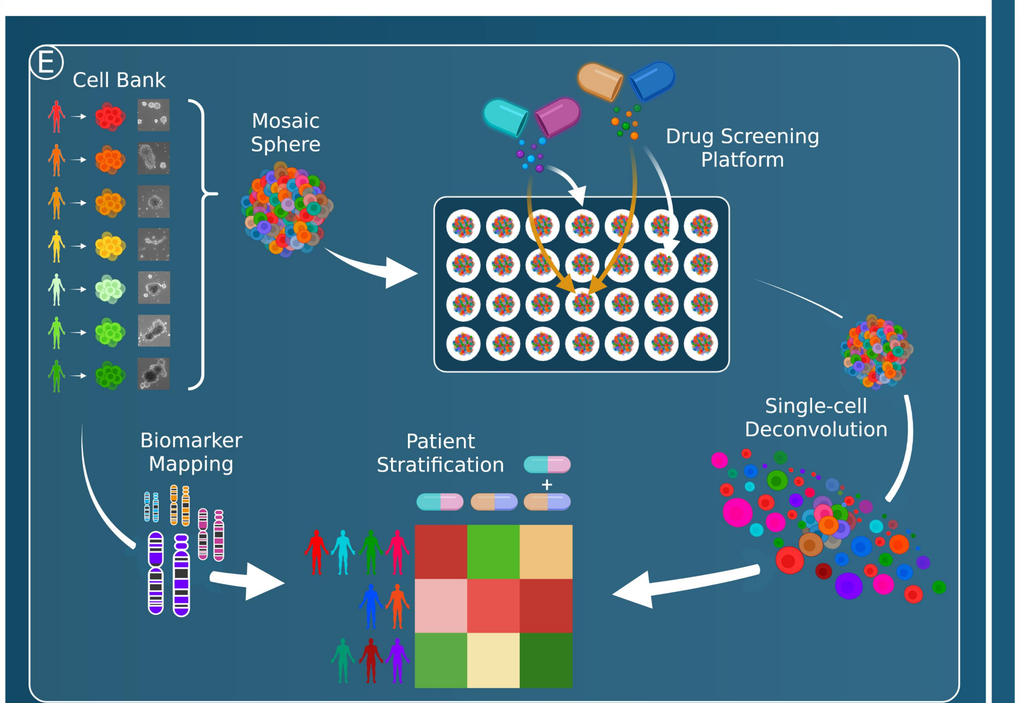


DRUG SELECTION

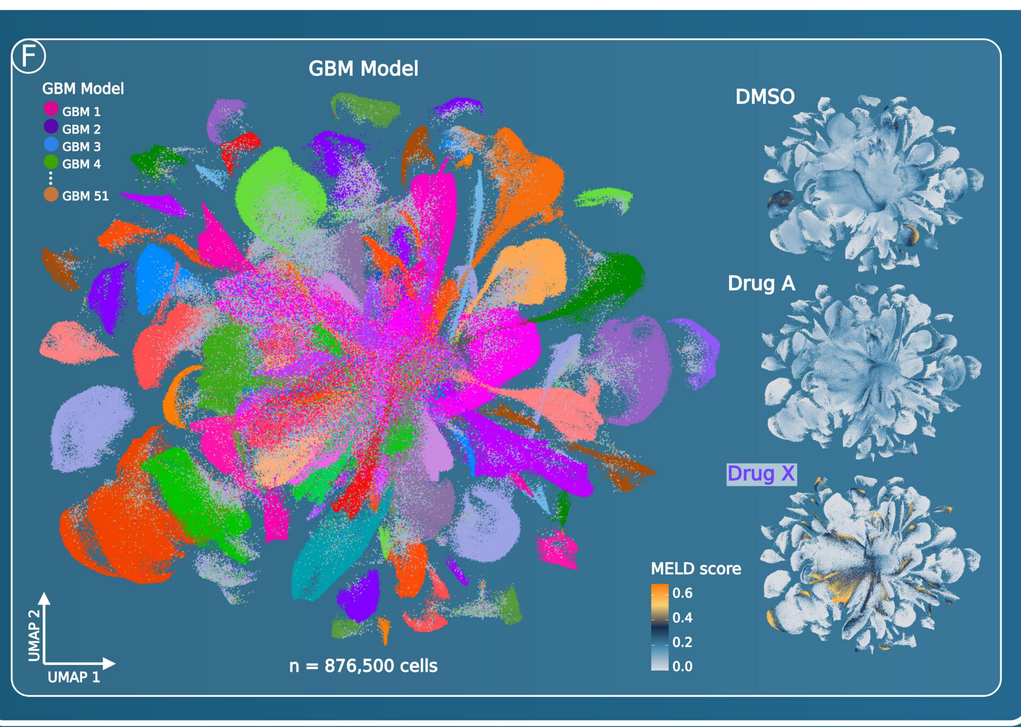


Multi-omic profiling and network-guided drug prioritisation in GBM. (A) Genomic alterations, chromosome-arm copy-number profiles, transcriptional signatures and CRISPRi responses across GBM cell lines. Bars show tumour mutational burden and alteration frequency. Singscores are standardised within signatures; negative CRISPRi log fold changes indicate dropout (*FDR < 0.05). **(B)** Knowledge-graph neighbourhoods linking drugs, genes, pathways and GBM cell lines. Violet highlights Drug X-associated connections; pink highlights cytarabine/aspacytarabine-associated connections. Drug X-associated identities are anonymised; networks are simplified for clarity. **(C)** Hierarchical clustering of 286 compounds into 18 clusters using Canberra distances between predicted network-influence profiles. Orange indicates greater similarity and dark blue greater dissimilarity. **(D)** Six-day CellTiter-Glo dose–response curves for Drug X in 30 randomly selected GBM cell lines. Curves represent mean replicate fits, scaled to 100% at the lowest shared tested concentration. Colours indicate relative sensitivity by normalised log-dose AUC, from green (sensitive) to red (resistant).

THE mosAIc PLATFORM

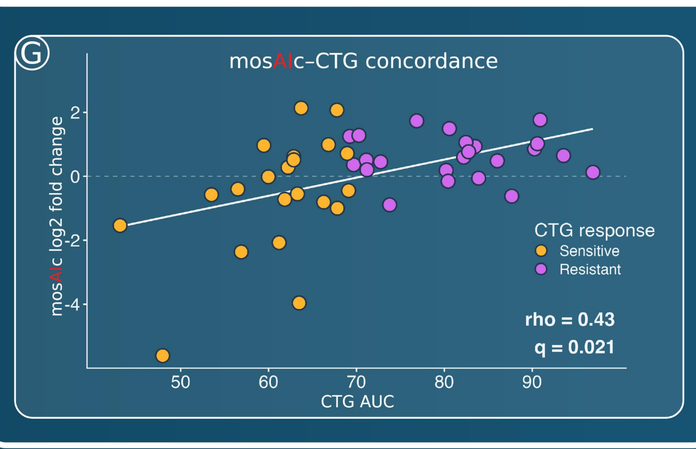


mosAIc-DERIVED DRUG X-ASSOCIATED CELL STATES

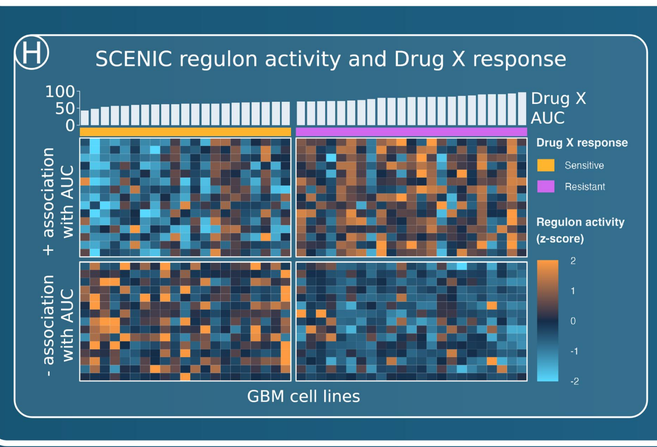


mosAIc screening links GBM model identity to drug-associated cell states. (E) Overview of the mosAIc platform. Patient-derived GBM models are pooled into mosaic spheres for drug screening and subsequent single-cell transcriptomic profiling. Model-specific genetic variants identified by whole-genome sequencing (WGS) enable assignment of individual cells to their originating GBM models. This pooled design allows multiple models to be evaluated within a shared experimental setting while retaining model-resolved readouts. Integration of drug-response profiles with molecular features supports candidate biomarker discovery and model stratification, with the aim of informing patient stratification. **(F)** Shared UMAP embedding of 876,500 cells, coloured by GBM model identity (51 models; left) or MELD scores for DMSO, comparator Drug A and Drug X (right). Each MELD panel displays scores across the full embedding, allowing treatment-associated regions to be compared within the same cellular landscape. Higher scores indicate greater association with the corresponding treatment condition.

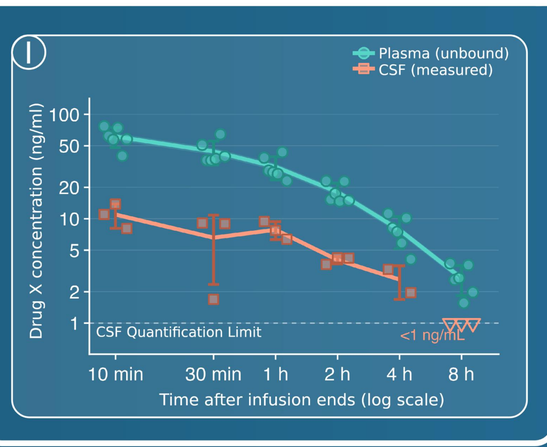
DRUG RESPONSE ACROSS ASSAYS



DRUG X–ASSOCIATED REGULON ACTIVITY



DRUG X EXPOSURE IN PLASMA AND CSF



Drug response concordance, regulon activity and *in vivo* exposure. (G) mosAIc log2 fold change in relative model abundance versus CTG viability AUC across 44 GBM models at 35,000 nM Drug X. Fold change is relative to DMSO; higher AUC indicates lower sensitivity. Colours indicate CTG response groups; q-values are BH-adjusted across six comparisons. **(H)** Mean SCENIC AUCell activity (row z-scores) for 30 regulons across 44 models ordered by Drug X AUC. Rows show the 15 strongest positive and negative associations with AUC. Activity scores pool three Drug X concentrations. **(I)** CSF and unbound plasma exposure following a 30-minute intravenous infusion at nominally 4 mg/kg in minipigs. Points show individual animals; lines and error bars indicate mean ± SD (plasma n = 6; CSF n = 3 per time point). The dashed line marks the CSF quantification limit (1 ng/mL); open triangles represent the three below-limit measurements at 8 hours.

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