Functional genomics nominates **cytarabine** as a **biomarker-guided therapy** for leptomeningeal glioma

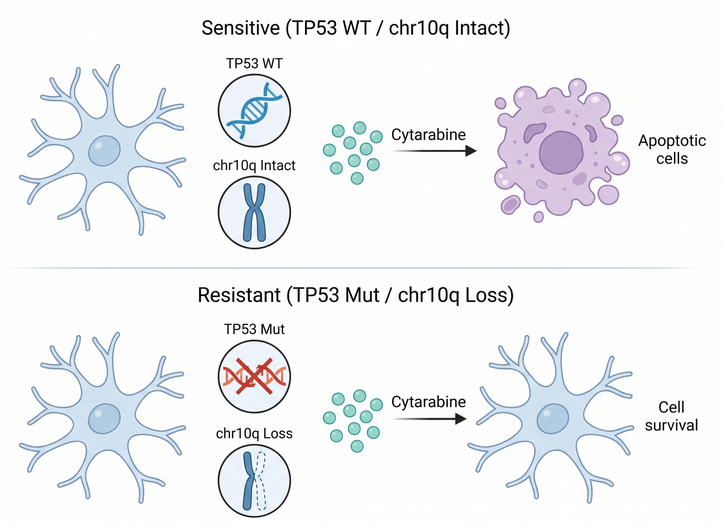
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CoSyne Therapeutics Limited, London, UK

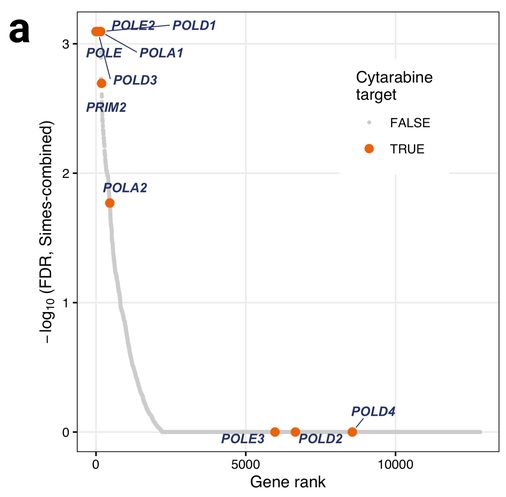
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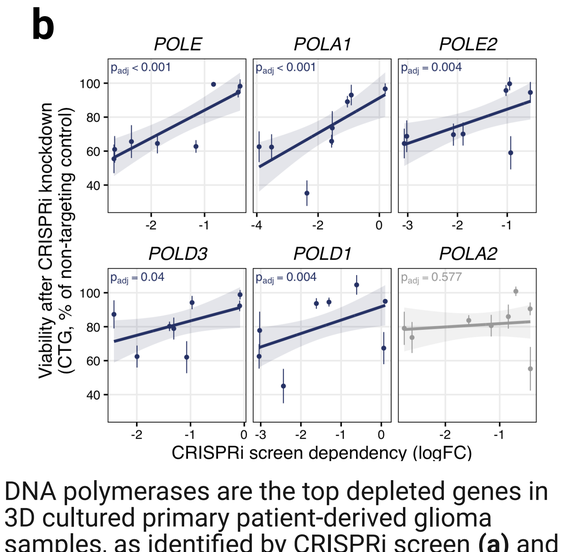
Highlights

- Interventional trials in glioma are commonly conducted **without molecular stratification**, diluting the efficacy signal in genetically heterogeneous populations.
- We used dependency scores from a large **in-house functional genomic screen in primary, patient-derived glioblastoma tumourspheres** to identify selective, genetically-conditioned vulnerabilities.
- This analysis surfaced a **tractable axis** targeted by the clinically available drug **cytarabine**.
- Primary glioma models with **TP53 wild-type and intact chr10q** showed the **greatest sensitivity to cytarabine**.
- **Loss of these tumour suppressors** (i.e. **TP53-mutant and/or chr10q loss**) was associated with **resistance to cytarabine.**



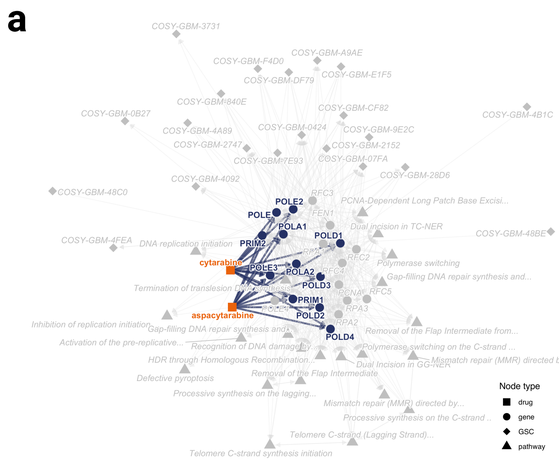
Polymerase-linked dependencies are vulnerabilities suited to pharmacological interception



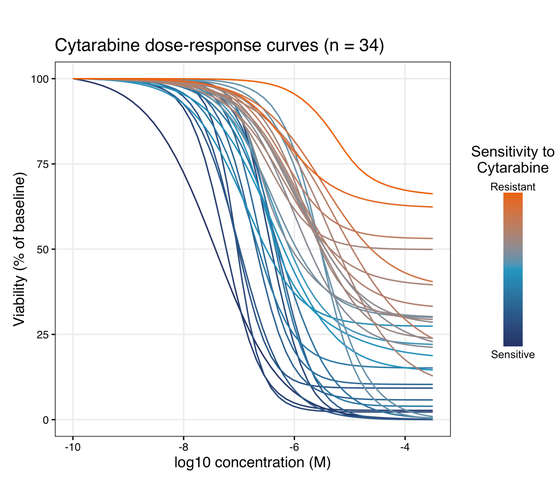


DNA polymerases are the top depleted genes in 3D cultured primary patient-derived glioma samples, as identified by CRISPRi screen **(a)** and validated in a Cell-Titer Glo (CTG) viability assay for 5 of the 6 subunits tested **(b)**

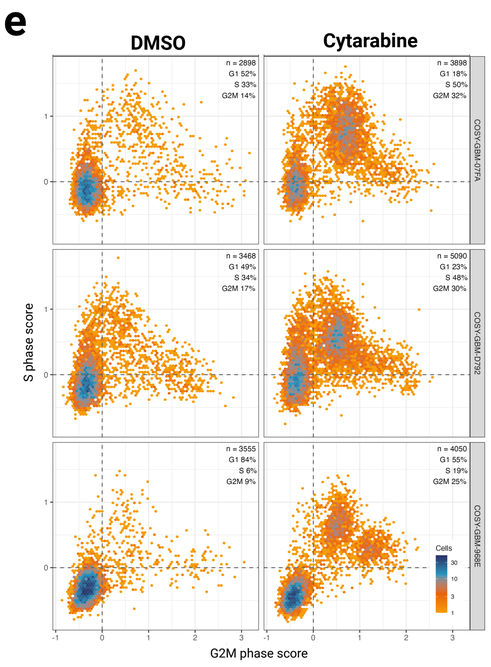
Cytarabine displays biomarker-stratified activity in primary patient-derived glioma models defined by *TP53*/chr10q genotype

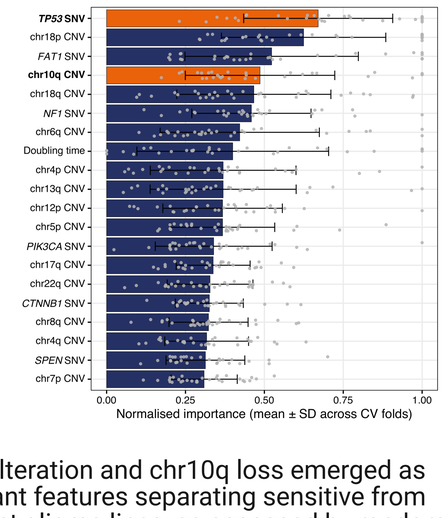


Cytarabine and its pro-drug aspacytarabine (orange squares) were identified as compounds with activity against the DNA polymerase-linked vulnerability cluster (blue nodes) via the CoSyne-internal knowledge graph.

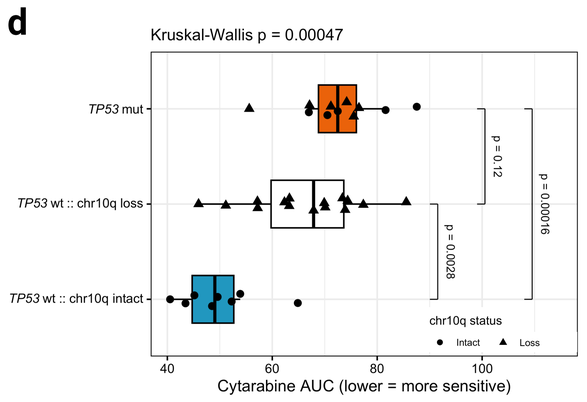


Cytarabine dose-responses across 34 patient-derived glioma cell lines with diverse genetic background. The dynamic range of IC_{50} values indicates intrinsic heterogeneity in susceptibility to cytarabine across glioma models.





TP53 alteration and chr10q loss emerged as dominant features separating sensitive from resistant glioma lines, as assessed by random forest analysis using genetic alterations from whole genome sequencing as the feature space.



Sensitivity to cytarabine treatment for glioma lines (n = 34) grouped by *TP53* and chr10q status. *TP53*-wt/chr10q intact lines (blue) exhibited the greatest sensitivity, while *TP53*-mutant lines (orange) were least sensitive.

Cytarabine induces S/G2M accumulation. Per-cell S vs G2/M module scores (scRNA-seq) for the three glioma lines with the largest S-phase shift, DMSO (left) vs cytarabine (right). The G1 fraction fell in each line (e.g. 07FA 52% to 18%).

These findings have immediate clinical applications as **cytarabine by intrathecal administration is already approved** for leukaemia with leptomeningeal involvement and is **used off-label for leptomeningeal spread of glioma**

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