Patient-Derived Pediatric Glioblastoma Models Provide Key Insights into IDH1-driven Drug Resistance

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Poster 6171

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Introduction

Pediatric glioblastoma (GBM) is a rare and highly aggressive brain cancer with molecular features that are distinct from those of adult GBM. Isocitrate dehydrogenase (IDH) enzymes play central roles in cellular metabolism, including the Krebs cycle, glutamine metabolism, lipogenesis, and redox regulation. Mutations in IDH1, which occur more frequently in pediatric gliomas, are associated with distinct clinical outcomes and therapy resistance mechanisms. IDH mutations are prevalent in gliomas and are detected in >80% of World Health Organization (WHO) grade II/III tumors. Among grade IV gliomas, IDH-mutant cases account for approximately 73% of reported clinical GBM cases. Despite its severity, GBM remains incurable, with limited effective treatment options. This challenge is particularly pronounced in pediatric populations, where patient scarcity limits clinical trial enrollment and underscores the need for clinically relevant in vitro models for preclinical research and therapeutic development. The Human Cancer Models Initiative (HCMI) has established patient-derived brain tumor models, including organoids and spheroids, that are annotated with comprehensive clinical and molecular data. These models provide a robust platform for investigating tumor biology and therapeutic response in IDH1-mutant GBM.

As part of the HCMI program, ATCC® is the sole distributor of these models providing more than 300 fully characterized 2-D and 3-D cancer models derived from over 28 tissue types including colorectal, pancreatic, brain, and esophageal cancers as well as rare cancers like Wilms tumor and Ewing's sarcoma. These models reflect diverse clinical backgrounds and retain high genomic fidelity, preserving over 80% of oncogenic drivers and maintaining transcriptional and epigenetic landscapes comparable to patient tumors. By offering clinically relevant models with available sequencing data and patient metadata through the HCMI portal, this work supports improved preclinical testing, biomarker discovery, precision oncology research, and studies of tumor heterogeneity and health disparities.

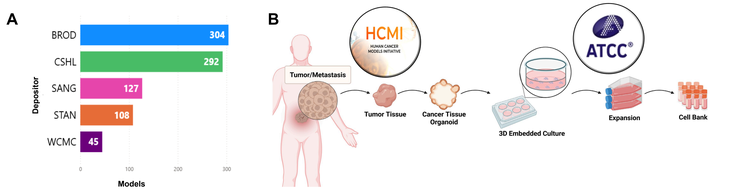

Figure 1: The Human Cancer Models Initiative (HCMI). (A) Model distribution by depositor within the HCMI portfolio. (B) ATCC® initiates the production pipeline and generates cell banks from this material. Figure created with BioRender.com.

Materials & Methods

Patient-derived glioblastoma models from the HCMI biobank—representing primary and recurrent tumors—were genomically profiled for key pediatric GBM mutations. Genomic data were compared to patient records and The Cancer Genome Atlas (TCGA) to validate model fidelity. A subset of models, including commonly used GBM cell lines, was exposed to a panel of six compounds, including standard and experimental drugs. Drug sensitivity was assessed via 8-point dose curves, with IC50 values calculated. Cytotoxicity was measured using live/dead staining and ATP-based viability assays. This integrated approach links genomic alterations to drug resistance, supporting the development of targeted therapies for high-risk pediatric GBM.

Culture conditions: Spheroids were sourced from ATCC and cultured in standard suspension conditions using NeuroCult NS-A Proliferation Kit (Human; STEMCELL Technologies 05751), Rock Inhibitor Y27632 (ATCC® ACS-3030™), and Ultra-Low Attachment (ULA) vessels via Corning.

Drug sensitivity testing: Models were passaged as single cells and seeded at the equivalent of 2.5x10^3 cells/well in 100 µL NeuroCult media, then left undisturbed for 72 hours to develop into uniform small spheroids prior to dosing within 96-well ULA plates (Corning 4515). For the single cells assay condition, the 72-hour spheroid formation step was skipped and flat bottom plates were used (Corning 3610). The spheroids were tested for sensitivity to a custom panel of 6 chemotherapeutic compounds with varying mechanisms of action and molecular targets reconstituted in either D-PBS (ATCC® 30-2200™) or DMSO (ATCC® 4-X™) and treated with an 8-point, half-log curve in triplicate. After 5 days exposure the spheroids were stained using Hoechst 33342 (Thermo Fisher Scientific 62249), Calcein AM (Thermo Fisher Scientific C1430), and Ethidium Homodimer-1 (Thermo Fisher Scientific E1169) then imaged in Brightfield and using fluorescence for visualization. Lastly viability was measured using a luminescent ATP viability assay, CellTiter-Glo 3D (Promega G9681).

Data analysis: Responses were normalized to vehicle treatment condition and expressed as percent viability. Figures were plotted, non-linear curves were generated, and IC50s were calculated in GraphPad Prism.

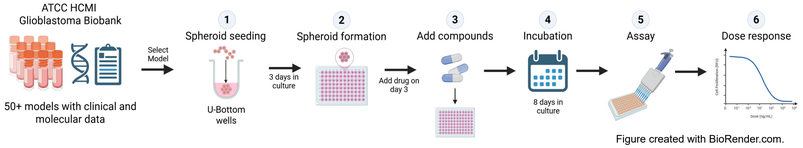

Figure created with BioRender.com.

Results

Table 1: Clinical characteristics of a subset of glioblastoma. Glioblastoma models derived from a variety of acquisition sites, gender, races, age, and clinical stage. 2-D model type (●), 3-D model type (●)

ATCC® No.	Cancer Type	Disease Status	Type	Acquisition Site	Gender	Race	Age	Tissue Status	Key Mutations
PDM-121™	Glioblastoma	Progressive	3-D Spheroid	Brain	Female	White	11	Primary	IDH1, TTN, TP53
PDM-668™	Glioblastoma	Progressive	3-D Spheroid	Brain	Male	White	50	Recurrent	TP53, TTN, EGFR
PDM-22™	Glioblastoma	Progressive	3-D Spheroid	Brain	Male	White	58	Recurrent	PIK3CA, MUC1, PARP15
PDM-16™	Glioblastoma	Progressive	2-D Adherent	Brain	Male	White	66	Primary	TP53, PTEN, EGFR
PDM-21™	Glioblastoma	Progressive	2-D Adherent	Brain	Female	White	60	Recurrent	PTEN, EGFR, IGF1R
PDM-23™	Glioblastoma	Progressive	2-D Adherent	Brain	Male	Asian	62	Recurrent	PTEN, TP53, MUC16

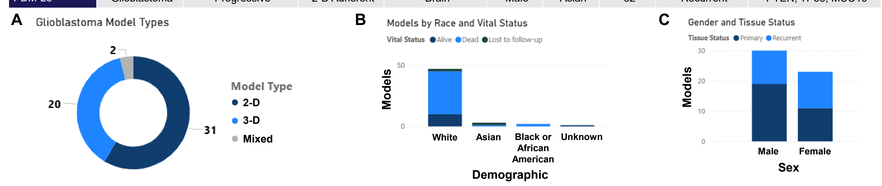

Figure 1: Clinical characteristics of glioblastoma models. The HCMI portfolio comprises a diverse collection of patient-derived GBM models. The graphs illustrate the distribution of models across key clinical attributes— including (A) Morphology or model type, (B) race, and (C) Gender and tissue status—summarized in Table 1.

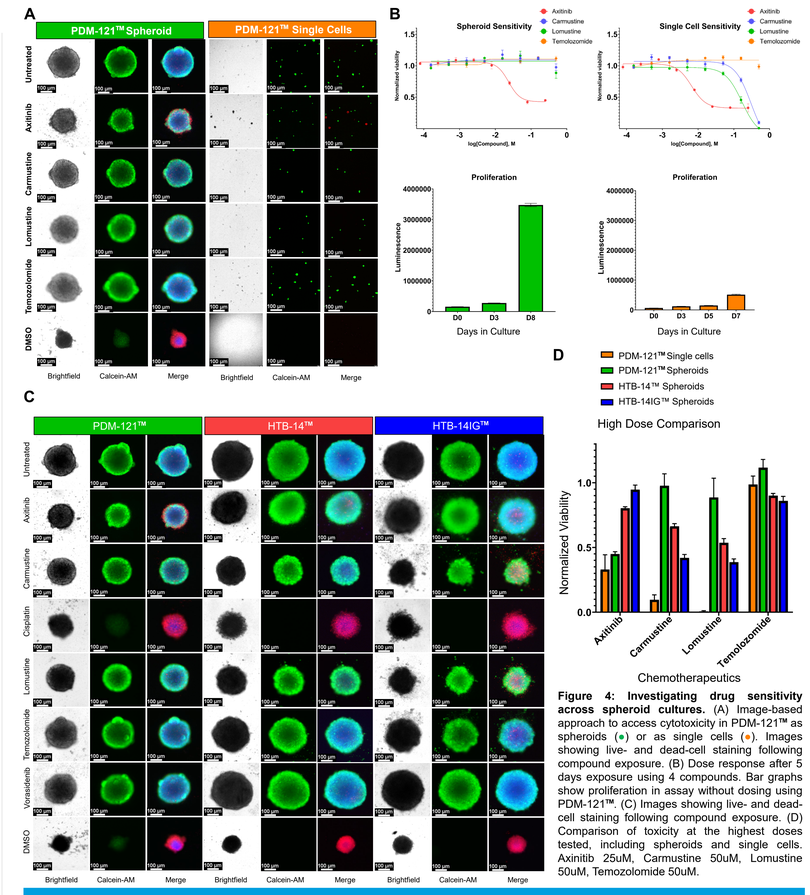

Figure 4: Investigating drug sensitivity across spheroid cultures. (A) Image-based approach to access cytotoxicity in PDM-121™ as spheroids (●) or as single cells (●). Images showing live- and dead-cell staining following compound exposure. (B) Dose response after 5 days exposure using 4 compounds. Bar graphs show proliferation in assay without dosing using PDM-121™. (C) Images showing live- and dead-cell staining following compound exposure. (D) Comparison of toxicity at the highest doses tested, including spheroids and single cells. Axinitib 25uM, Carmustine 50uM, Lomustine 50uM, Temozolomide 50uM.

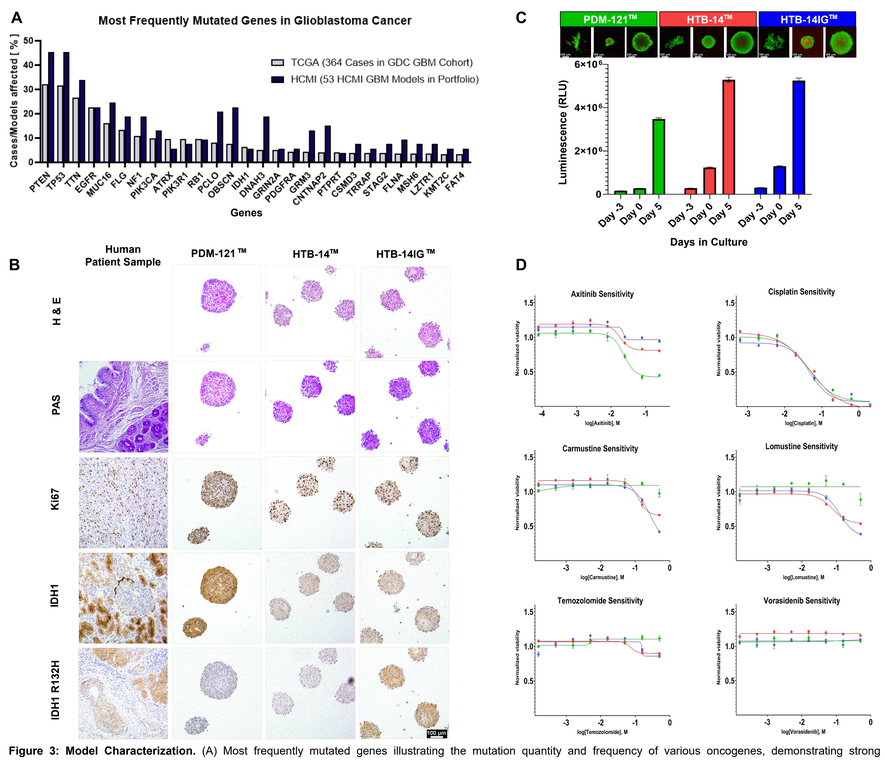

Figure 3: Model Characterization. (A) Most frequently mutated genes illustrating the mutation quantity and frequency of various oncogenes, demonstrating strong concordance between HCMI GBM models and clinical tumor profiles. The x-axis denotes individual oncogenes, and the y-axis represents mutation frequency (%). (B) H&E staining, PAS staining, and IHC panel for a HCMI model and glioblastoma cell lines, highlighting morphological diversity and molecular heterogeneity. IHC markers include Ki-67, IDH1, and IDH1 R132H. (C) Proliferation in assay demonstrating initial seeding, spheroid formation, and final spheroid size without dosing. (D) Dose response using targeted and non-specific therapeutics in a HCMI patient-derived model and glioblastoma cell lines. PDM-121™ (●), HTB-14™ (●), HTB-14IG™ (●)

Conclusions

- Patient-derived pediatric GBM models recapitulate key disease-defining genomic alterations, including IDH1, PTEN, TP53, etc., and demonstrate strong concordance with patient tumors.
- Models retain clinically relevant molecular features and tumor-specific phenotypes across both 2-D and 3-D formats.
- Drug response profiling revealed heterogeneous sensitivities across models, with ATP-based viability assays enabling robust, reproducible comparisons.
- Differential responses to standard-of-care and targeted agents highlight the influence of underlying genotype on therapeutic sensitivity.
- Together, these data support the use of HCMI-derived spheroids as high-fidelity, clinically relevant platforms for drug discovery, biomarker development, and precision oncology research.

Explore HCMI Models

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