Childhood Cancer Data Initiative Webinar Series

Molecular Targeted Therapies Reveal Glioma Cell Plasticity Linked to Immune Evasion in BRAF-Mutant Brain Tumors

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NIH NATIONAL CANCER INSTITUTE

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Today's Speaker

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Stanford School of Medicine

- Sr. Scientist, Department of Neurology
- Associate Professor in Research, Department of Neurosurgery
- Director, Pediatric Cancer Model Development Center

Agenda

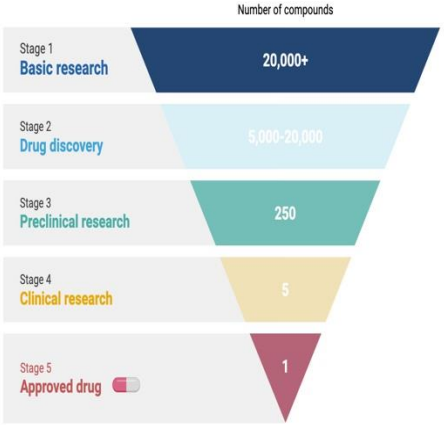
1. *The Human Cancer Model Initiative (HCMI)*
2. *High-Grade Glioma Challenges and Treatment*
3. *Unraveling Molecular Therapy Resistance in Novel BRAF V600E HGG Models*
4. *The HCMI for Pediatric Cancer*

The Human Cancer Model Initiative

Objectives and Achievements in a Nutshell

Barriers for Drug Development in Oncology

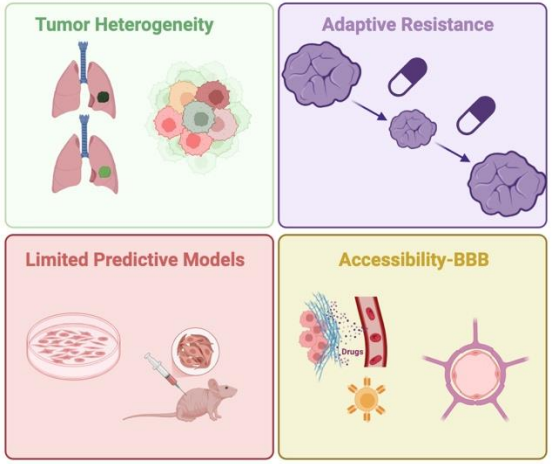
Oncology drug development attrition rate



Phase Success	2016		2021	
	Phase I to Phase II	N	Phase I to Phase II	N
Ophthalmology	84.8%	66	71.6%	88
Hematology	73.3%	86	69.6%	92
Others	66.7%	96	63.6%	154
Metabolic	61.1%	95	61.8%	136
Infectious disease	69.5%	347	57.8%	403
Allergy	67.6%	37	56.4%	55
Respiratory	65.3%	150	55.9%	179
Autoimmune	65.7%	297	55.2%	413
Psychiatry	53.9%	154	52.7%	150
All indications	**63.2%**	**3582**	**52.0%**	**4414**
Cardiovascular	58.9%	209	50.0%	214
Oncology	62.8%	1222	48.8%	1628
Neurology	59.1%	462	47.7%	516
Gastroenterology	75.6%	41	46.7%	45
Endocrine	58.9%	299	43.3%	319
Urology	57.1%	21	40.9%	22

Bio, February 2021

Causes for lack of efficacy for oncology drugs



~50-60% of drugs fail in the clinic due to lack of efficacy_ up to 85% in oncology)
FDA Approval can take up to 13 years and cost up to $2.5b

Conventional vs. Next-Generation Cancer Models

Conventional Models

(*monolayer, 2-dimensional (2D) cultures on plastic*)
•Cells plated on flat **plastic surfaces**

•Cells grown in high levels of animal **serum**

•Poorly recapitulate **tumor heterogeneity and plasticity**

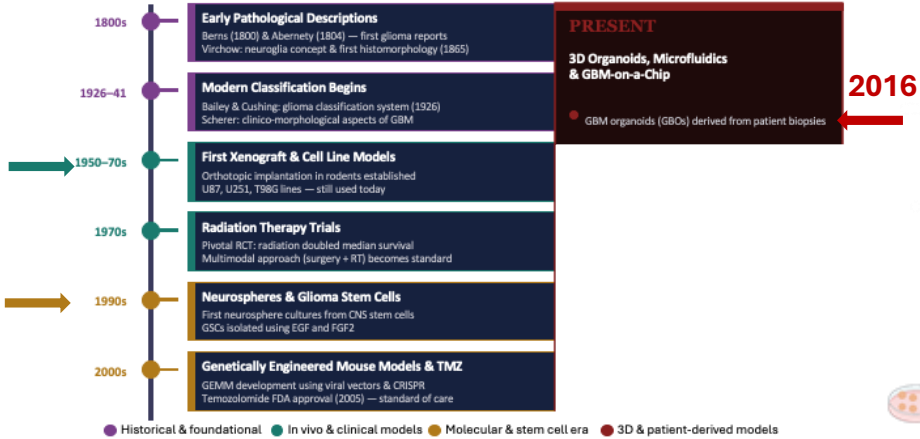
•Often **overpredict drug efficacy**

•Often lacking clinical information of **parental tumor origin**

→ Simple, scalable, but **low physiological relevance**

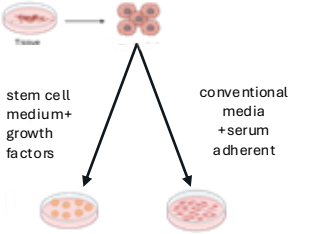
Timeline of Glioblastoma Model Development

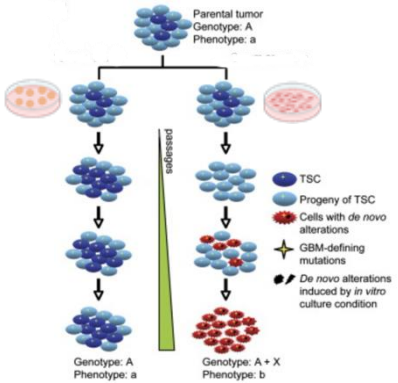
1 Timeline of glioblastoma research and models

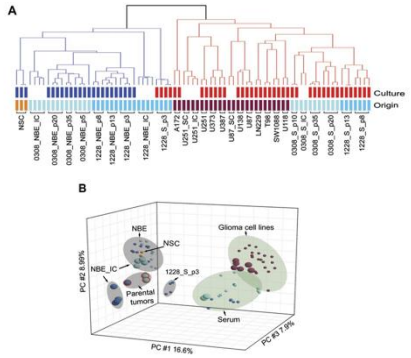


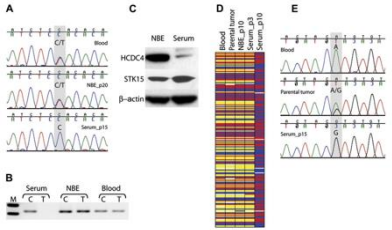
Features	3D/Spheroids w/oSerum	2D/Adherent w/Serum
Proliferation	+++	Limited at early passages
Tumorigenicity	+++	Limited at early passages
Differentiation potential	+++	+
Telomerase activity	+++	Limited at early passages
Infiltrative growth	+++	-
Concordance/transcriptome	+++	+
Concordance/genome	+++	+

2 Conventional serum vs 3D cell culture models





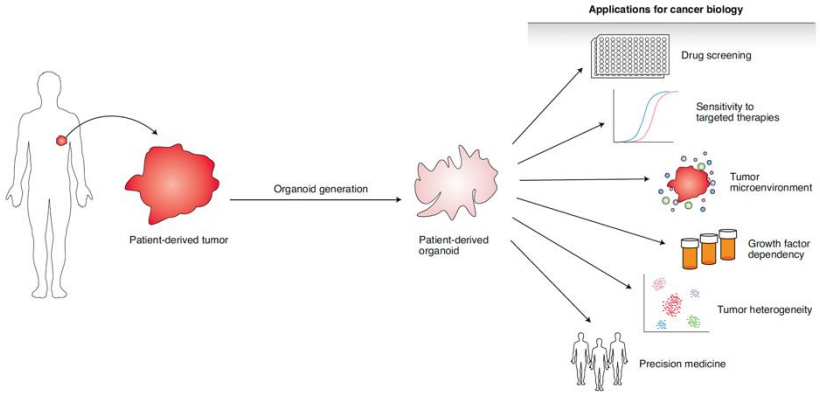




Lee *et al*, Cancer Cell 2006, PMID:16697959

Opportunities and Challenges for Next-Gen Cancer Model Development

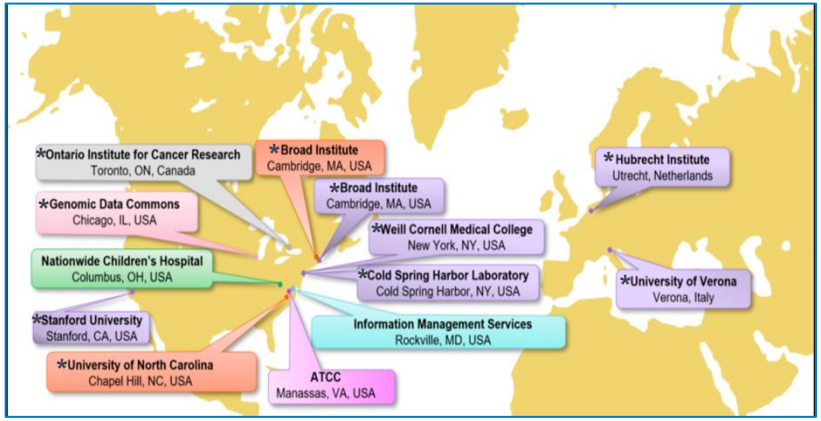
Applications in Oncology
Cancer Modeling, Cancer Biology
Drug Discovery and Tox Studies
Precision Medicine



Lo et al, Nature Cancer 2020, PMCID:PMC8208643

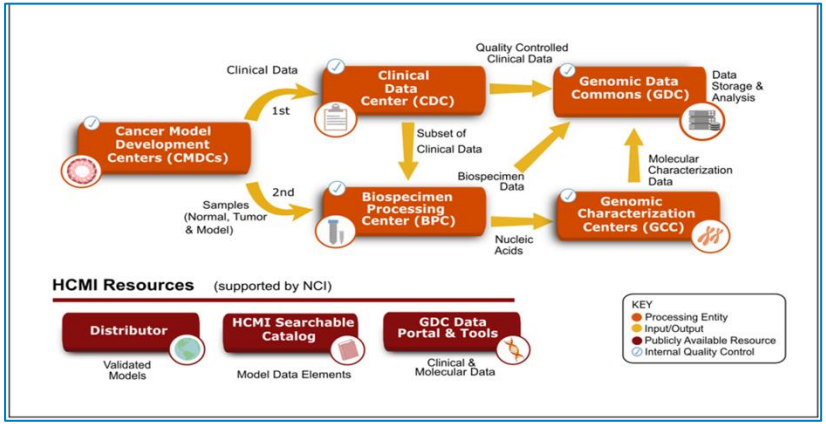
The Human Cancer Model Initiative (HCMI)

The HCMI is an international consortium founded by the **National Cancer Institute** and dedicated to generating **next-generation, patient-derived cancer models as a community resource** to facilitate cancer research



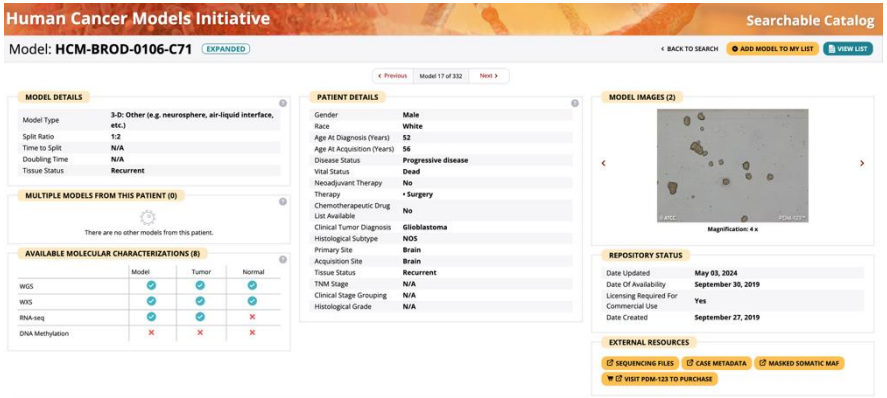
Source: https://www.cancer.gov/ccg/research/functional-genomics/hcmi/about/cancer-model-development

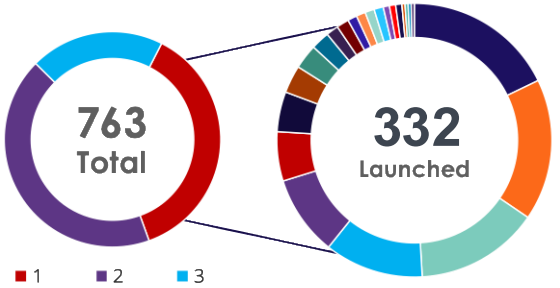
*Managed by the Frederick National Laboratory for Cancer Research (FNLCR), Leidos Biomedical Research, Inc.



Source: https://ocg.cancer.gov/programs/hcmi/nci-cancer-model-development

HCMI Models in the ATCC Catalogue - Adult



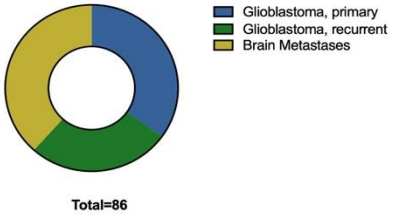


Collection includes models derived from rare adult and pediatric cancers such as rhabdomyosarcoma, leiomyosarcoma, Ewing sarcoma, and Wilms tumor.

TOP 10 (90% of total)

Colon	55
Pancreas	52
Brain	50
Esophagus	36
Skin	29
Rectum	21
Stomach	18
Lung	7
Breast	7
Connective tissue	5

Courtesy of Carolina Lucchesi @ ATCC

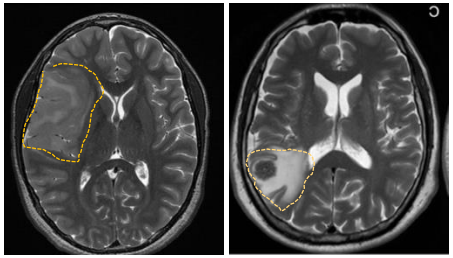


High-Grade Glioma Treatment and Challenges

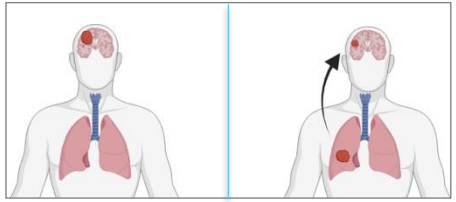
Therapeutic Challenges and Opportunities

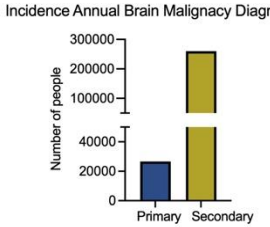
Primary High-Grade Gliomas: Distinction, Frequency, and Mortality

1 Primary vs. Secondary Brain Malignancies



Glioblastoma | Brain Metastasis





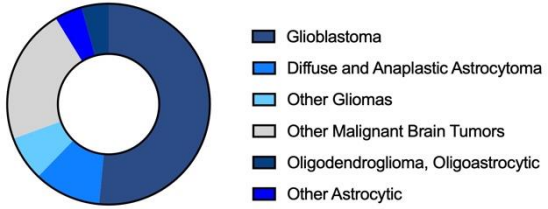
2 Primary Malignant Brain Tumor Incidence, Mortality

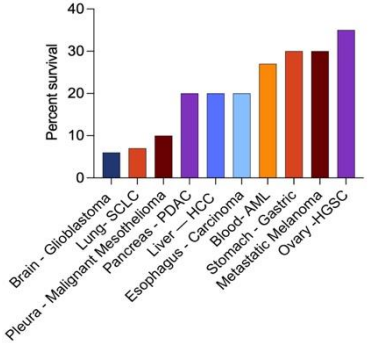
People in the U.S. living with primary, malignant brain tumor: Est. 338,000+

70-80% are glioma

Glioblastoma most common malignant glioma

Tumor Types with Highest Mortality (5-year Survival)



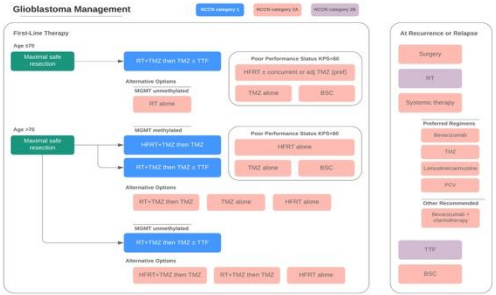


Sources: NCI SEER CSR 1975–2021; SEER Stat Facts; CBTRUS (Ostrom et al., Neuro-Oncology); ACS Cancer Facts & Figures.

High-grade gliomas and in particular glioblastoma <5% 5-year survival rate

Glioblastoma: Standard-of-Care (SoC) and Experimental Therapeutics

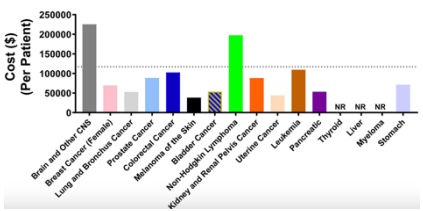
1 Standard-of-Care - Surgery plus Chemoradiotherapy+TTF

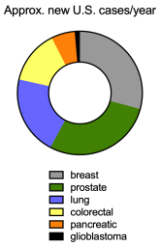


CA A Cancer J Clinicians, 2020, DOI: (10.3322/caac.21613)

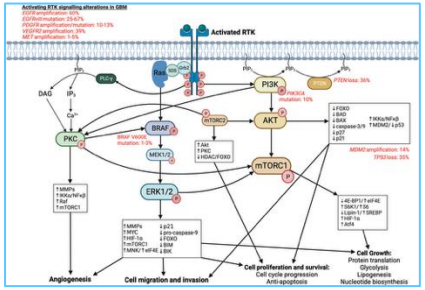
Mehta, M et al, Critical review in Onc, 2017, PMID:28259296

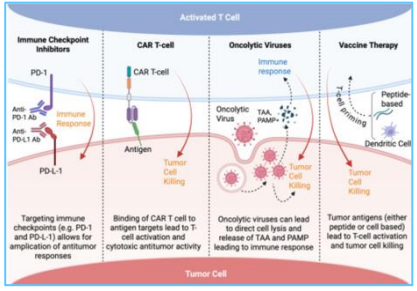
2 Treatment Costs





2 Targeted and Immunotherapy for glioblastoma in clinical trials





Dewdney *et al*, Signal Transduct Target Ther 2023 PMCID:PMC10587102

Song *et al*, Immunity 2025, PMIC:40324379

Standard-of-Care is multi-modal

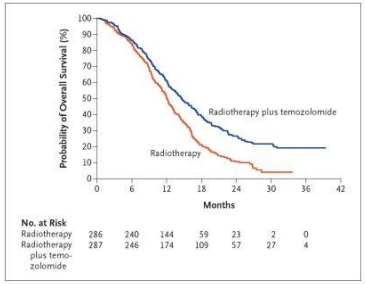
Promising therapies in clinical trials (~2000 clinical trials)

Costs up to $250K/patient

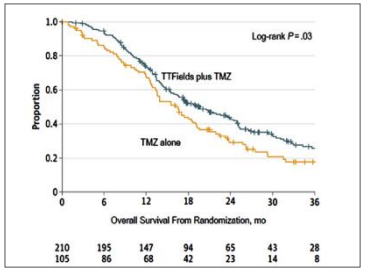
Clinical trials for glioblastoma are expensive (tens of millions of $)

Survival with SoC and Brain Tumor Drug Approvals

1 Survival rates with SoC

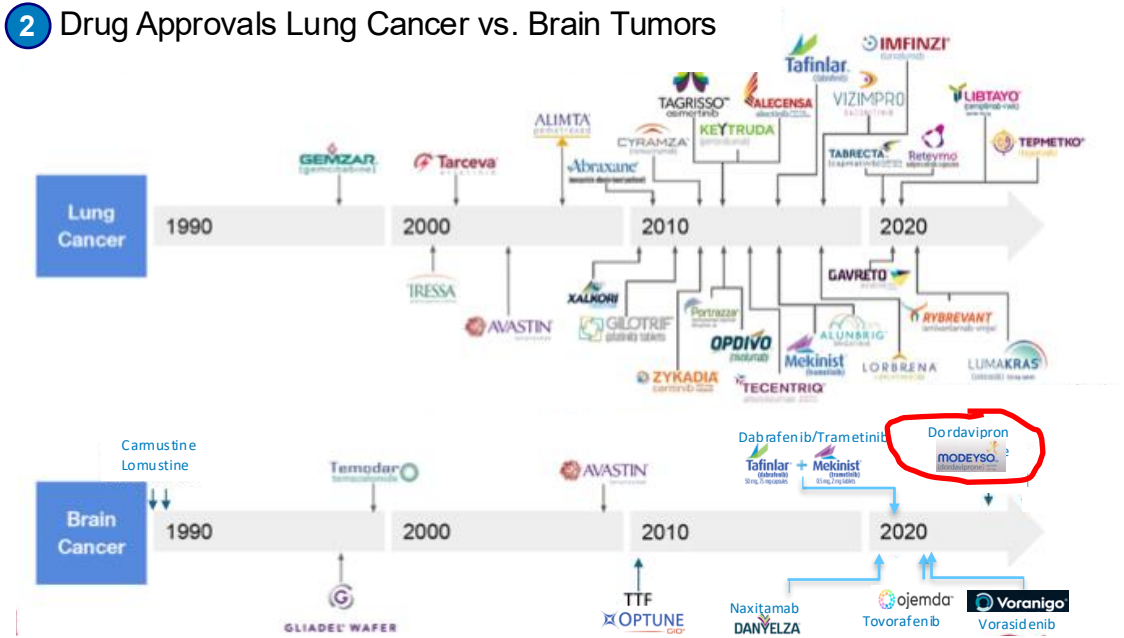


Stupp *et al*, Lancet 2005, PMID15758009



Mehta *et al*, Critical review in Onc 2017, PMID:28259296

2 Drug Approvals Lung Cancer vs. Brain Tumors



Challenges for Development of Malignant Brain Tumor Therapeutics

Tumor Heterogeneity
HGG contains multiple genetically distinct clones. Targeting one subpopulation allows resistant clones to repopulate.

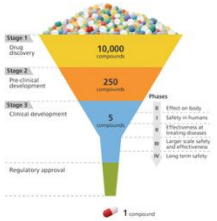
Therapy Resistance, Plasticity, Glioma Stem Cells
A subpopulation of cells is resistant to radiation and chemotherapy, showing plasticity, driving tumor re-initiation after treatment.

Diffuse Infiltration
Tumor cells invade surrounding brain tissue far beyond the visible mass, making complete surgical resection impossible.

Near-Universal Recurrence
Nearly all HGGs recur, often with acquired resistance to TMZ and altered molecular profiles after treatment.

Blood-Brain Barrier
Tight junctions prevent most systemic drugs from reaching the tumor, severely limiting chemotherapy options.

Immunosuppressive TME
The tumor microenvironment is deeply immunosuppressive, blunting CAR-T and checkpoint inhibitor efficacy.



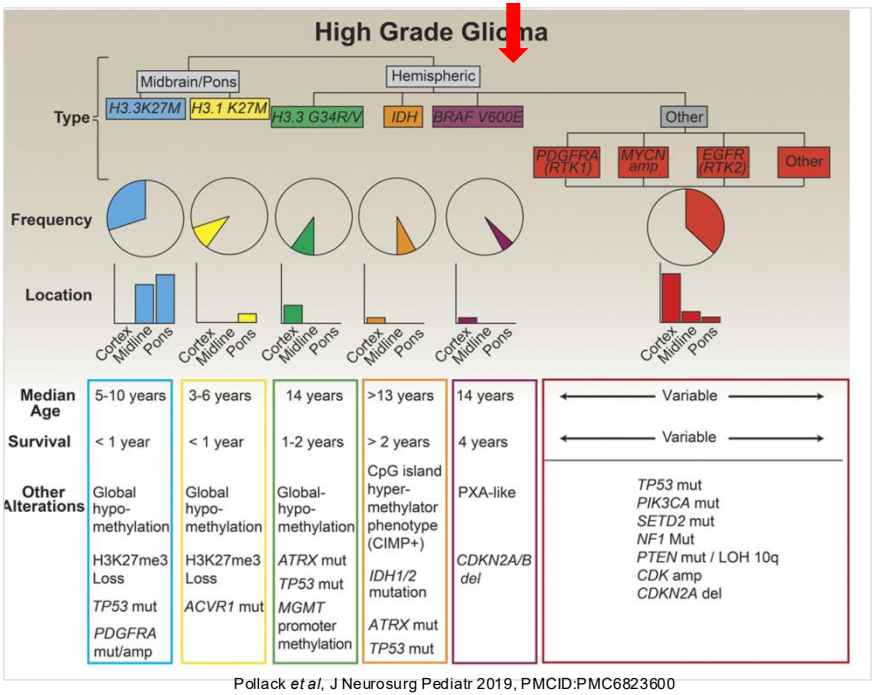
Several key features of malignant brain tumors contribute to difficulties in developing new treatments

Next-generation models recapitulating these key features will facilitate impactful research & pave the way for developing new therapies with high clinical efficacy

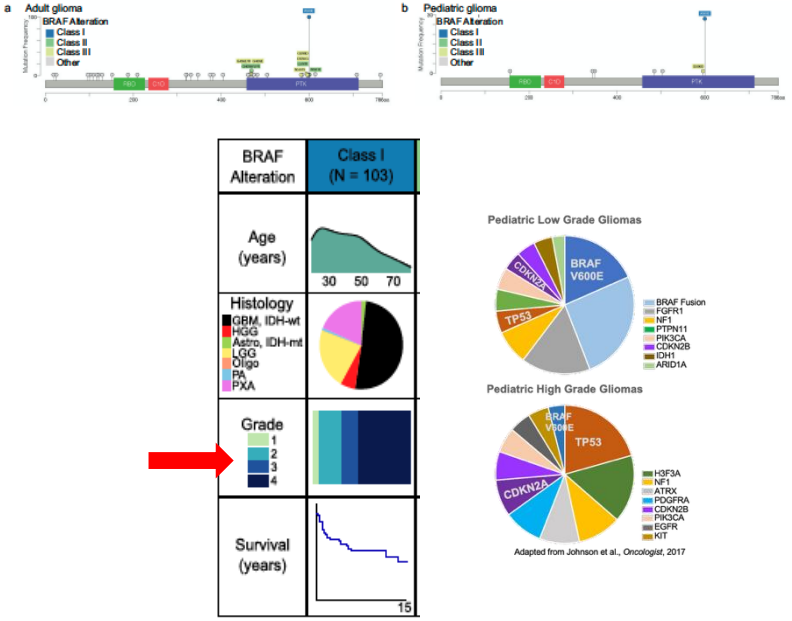
Malignant brain tumors are very diverse and have many subtypes

BRAF V600E-Mutant Glioblastoma as a Paradigm for Precision Medicine in Brain Tumors

1 BRAF V600E-altered glioma occur in pediatric + adult patients but in different types



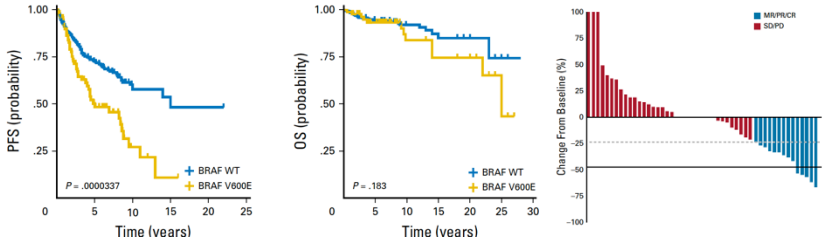
Pollack *et al*, J Neurosurg Pediatr 2019, PMCID:PMC6823600



Schreck *et al*, NPJ Precis Oncol 2023, PMCID:PMC9975216

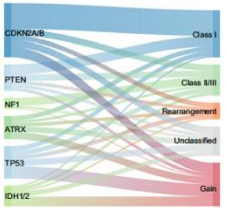
The BRAF V600E-mutant glioma frequency, types, and prognosis

1 BRAF V600E-altered glioma are chemotherapy-resistant

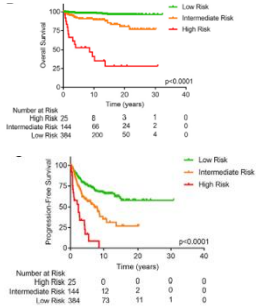


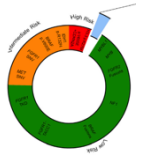
Lassaletta *et al*., JCO 2017, PMCID:PMC5791837

2 BRAF V600E co-mutations affect risk for progression



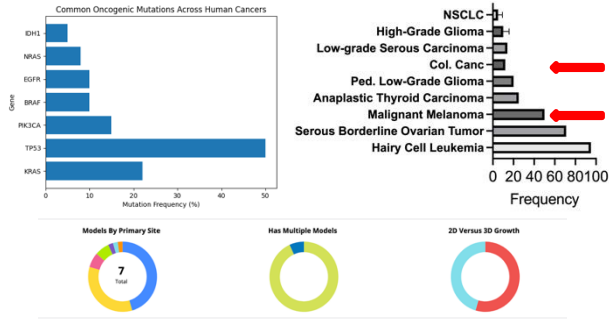
Schreck *et al*, NPJ Precis Oncol
2023, PMCID:PMC9975216





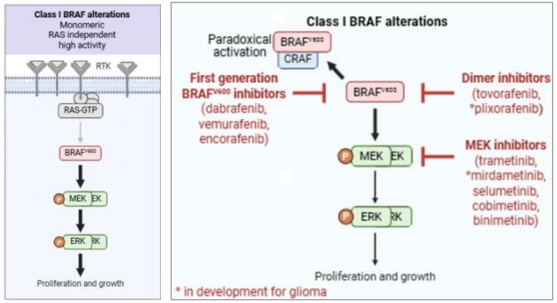
Ryall *et al.* Cancer Cell
2020, PMCID:PMC7169997

3 BRAF V600E mutations found in various cancer



BRAF V600E models in HCMI catalogue

4 BRAF/MEK inhibitors in the clinical arena

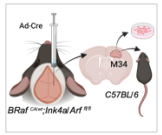


Courtesy of Karisa Schreck

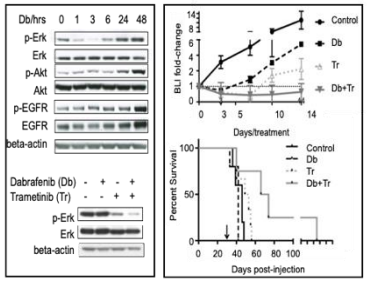
Research Objectives Based on Low-Response Rates

1 MAPK pathway reactivation after BRAF inhibition

Syngeneic Mouse Models For BRAF V600E-mutant High-Grade Glioma:



Grossauer *et al.* Oncotarget, 2016, PMCID:PMC5342782



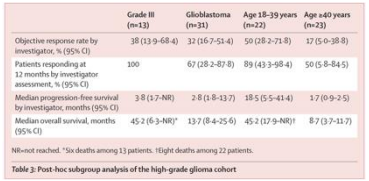
Dabrafenib (DB)=BRAF inhibitor
Trametinib (Tr)=MEK inhibitor

Understand how BRAF V600E mutated high-grade gliomas respond to clinically relevant, molecular-targeted inhibition (BRAF V600E and MEK inhibition)

Identified potential mechanisms of therapy escape

Find novel therapeutic opportunities to combine with BRAF V600E- targeted therapy to overcome resistance

2 Combined BRAF and MAPK inhibition response rates

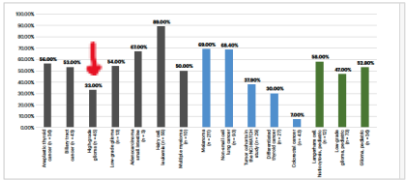


	Grade III (n=13)	Glioblastoma (n=31)	Age 18–39 years (n=22)	Age ≥40 years (n=23)
Objective response rate by investigator, % (95% CI)	38 (13·9–68·4)	32 (16·7–51·4)	50 (28·2–71·8)	17 (5·0–38·8)
Patients responding at 12 months by investigator assessment, % (95% CI)	100	67 (28·2–87·8)	89 (43·3–98·4)	50 (5·8–84·5)
Median progression-free survival by investigator, months (95% CI)	3·8 (1·7–NR)	2·8 (1·8–13·7)	18·5 (5·5–41·4)	1·7 (0·9–2·5)
Median overall survival, months (95% CI)	45·2 (6·3–NR)*	13·7 (8·4–25·6)	45·2 (17·9–NR)†	8·7 (3·7–11·7)

NR=not reached. *Six deaths among 13 patients. †Eight deaths among 22 patients.

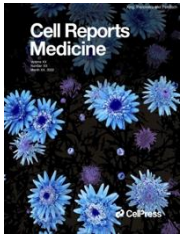
Table 3: Post-hoc subgroup analysis of the high-grade glioma cohort

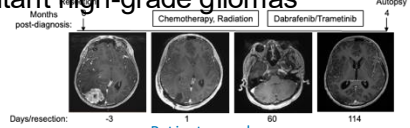
Wen *et al*, The Lancet Oncology 2022, PMID:34838156



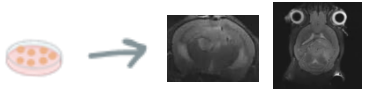
Subbiah *et al*, Nat Med 2023, PMCID:PMC10202803

3 Model Development for BRAF V600E-mutant high-grade gliomas



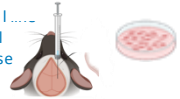


Patient samples

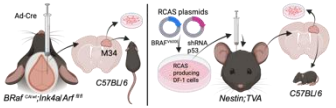


3 patient-derived spheroid lines
+ matched patient-derived xenografts

Patient samples
1 conventional cell ……
1 xenograft model
1 orthotopic mouse model



Lerner *et al.* Cancer Res 2015, PMCID:PMC4698003



2 syngeneic mouse models-
fully immunocompetent

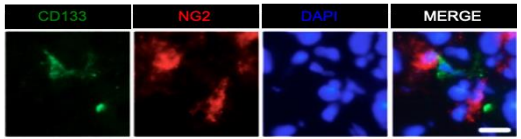
Xing, Panovska et al, Cell Reports Med 2025, PMCID:PMC12208339

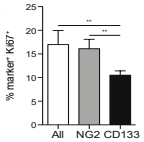
Unraveling Molecular Therapy Resistance in Novel BRAF V600E HGG Models

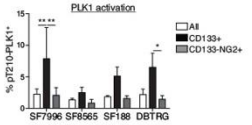
Identifying novel therapeutic combinations to overcome resistance

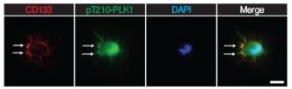
Targetable Therapy Escape Mechanisms in BRAF V600E-mutant Glioblastoma

1 Intratumoral heterogeneity of BRAF V600E-mut glioblastoma

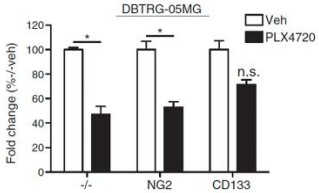


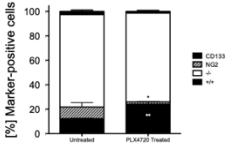




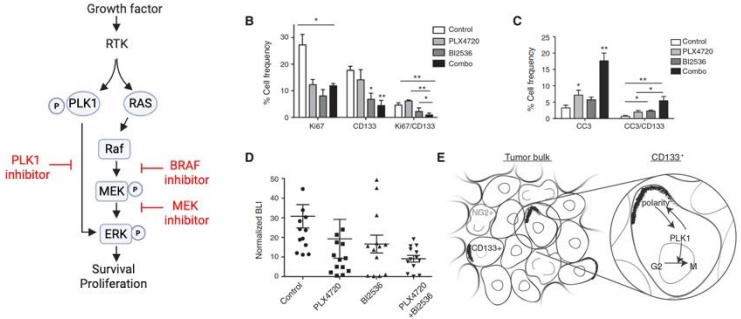


2 BRAF inhibitor treatment does not eliminate CD133+ stem-like cells

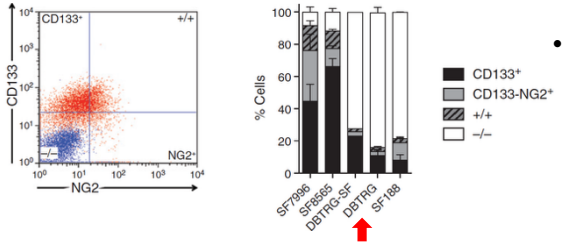




3 Combination therapy eliminates CD133+ cells = cancer stem cells and increases survival in xenografts



4 BRAF V600E-mutant glioblastoma cell line (serum) is homogeneous

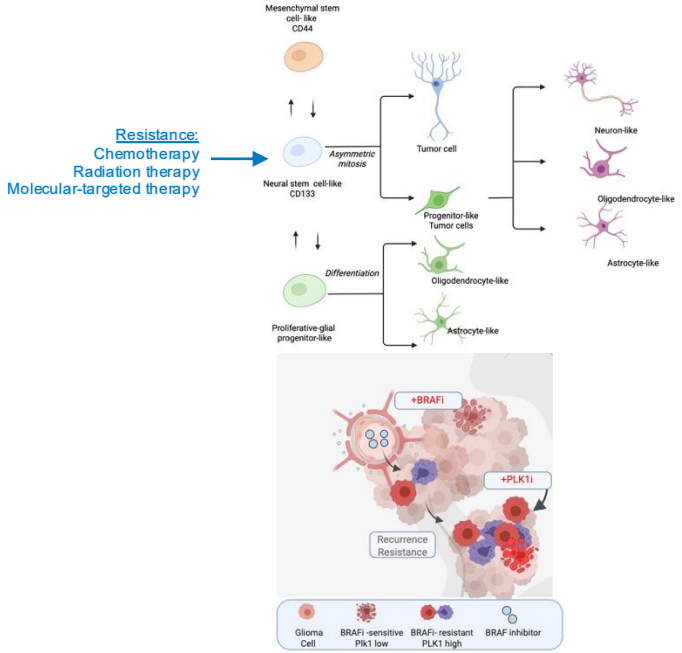


- **Low plasticity and heterogeneity (few CD133+ and NG2+ cells)**

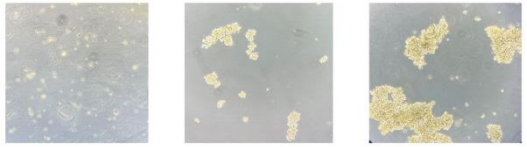
Lerner *et al.* Cancer Res 2015, PMCID:PMC4698003

Next-gen BRAF V600E-mutant Glioblastoma Models are Sensitive to PLK1 inhibition

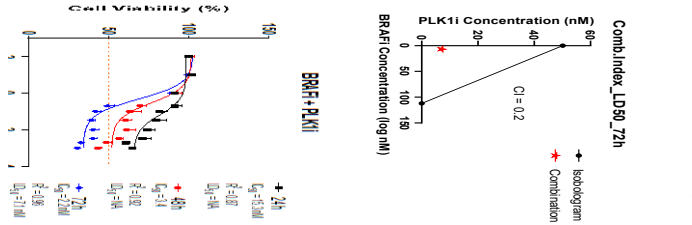
1. High-grade glioma exhibit plasticity, intra-tumoral heterogeneity, differentiation



2. BRAF V600E-mutant 3D/spheroid glioblastoma models sensitive to PLK1i



Morphology of an epithelioid glioblastoma tumor 3D spheroid cell line HCM-STAN-1297-C71. Morphology. **left**. 2 h after thawing; **center**. at low density; **right**. at high density.



Cell line	Type	IC50 BRAFi (nM)	IC50 PLK1i (nM)	IC50 Combo
Patient-derived cell line 2- BRAF V600E	Human adult glioblastoma	71.13	172.8	43.83
HCM-STAN-1297-C71_A- BRAF V600E	Human pediatric glioblastoma	1.73	~2469	3.55
2341-luc-BRAF V600E	Murine high-grade glioma	0.63	NR	0.44

Petritsch Lab, Unpublished Data, Do not post

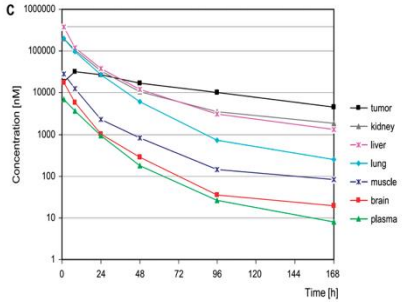
PLK1 inhibition in the clinical arena

1. PLK1 inhibitors FDA-approved for non-brain cancers

TABLE 1 | Clinical trials based on PLK1 inhibitors.

NCT number	Phase	Disease	PLK1i	Ref
NCT02211859	I	Advanced solid tumors	BI2536	(127)
NCT02211872	I	Advanced solid tumors	BI2536	(128)
NCT00412880	II	Small cell lung cancer	BI2536	(129)
NCT01662505	I	Acute myeloid leukaemia	BI6727 (Volasertib)	(130)
NCT00804856	I/IIa	Acute myeloid leukaemia	BI6727 (Volasertib)	(131)
NCT01023958	II	Urothelial cancer	BI6727 (Volasertib)	(132)
NCT00824408	II	NSCLC	BI6727 (Volasertib)	(133)
NCT01014429	I	Advanced solid tumors	NMS-1286937 (Onvansertib)	(134)
NCT00539835	I	Advanced solid tumors	GSK461364	(135)
NCT01179399	I	Advanced solid tumors	TAK960	Not yet published
NCT01538537	I	Advanced solid tumors	ON01910 (Rigosertib)	(136, 137)
NCT00854646	I/II	Myelodysplastic syndrome Acute myeloid leukemia	ON01910 (Rigosertib)	(138)
NCT01168011	I	Advanced solid tumors	ON01910 (Rigosertib)	(139)

2. PLK1 inhibitor Volasertib is stable in the brain



Rudolph et al, Clin Can Res 2009, PMC19383823

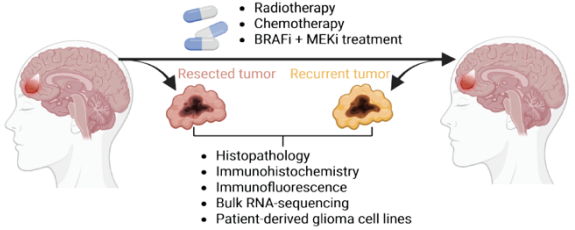
Plk1 inhibitors are in clinical trials against several cancer types

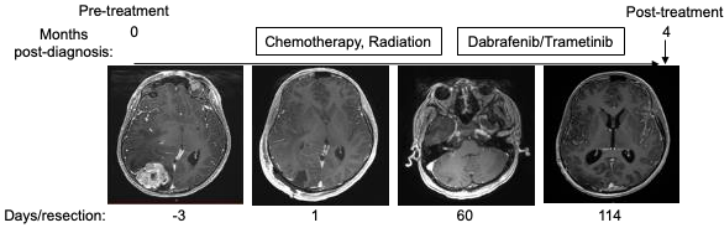
Volasertib: FDA rare disease breakthrough and orphan drug designation
-stable in brain
-high systemic toxicity

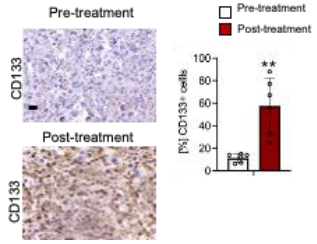
New inhibitors in early stages of development for brain tumors (e.g., onvasertib) showing promising results in pediatric patients

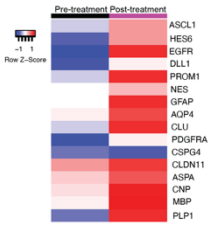
Combination with BRAF/MEK inhibitors to be determined

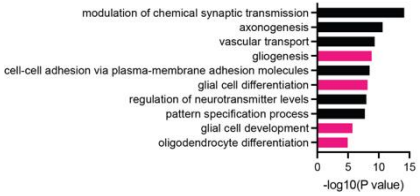
Analyses of Pre- and Post-treatment BRAF V600E-mutant Glioblastoma Samples

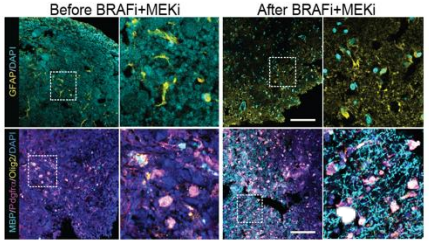


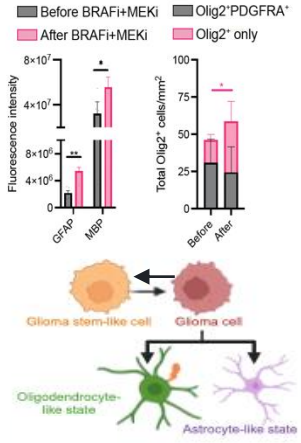








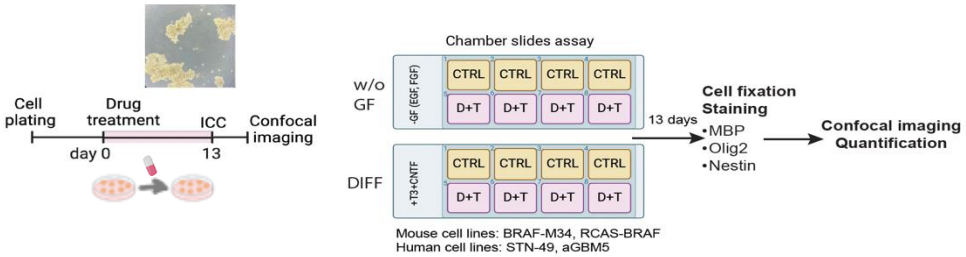




BRAF/MEK inhibition in patients upregulated not only stem-cell markers but also glial differentiation, indicative of therapy-induced increases in cell plasticity and differentiation

Xing, Panovska et al, Cell Reports Med 2025, PMCID:PMC12208339

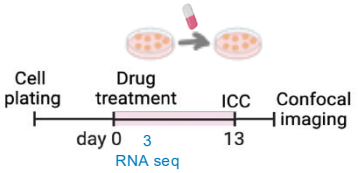
BRAF/MEK Inhibition Direct Effects on Cell States and Differentiation in Patient-Derived 3D Tumor Models



BRAF/MEK inhibition upregulated not only stem-cell markers but also glial differentiation, in cell culture-based assays, indicative of direct effects on tumor cell plasticity and differentiation

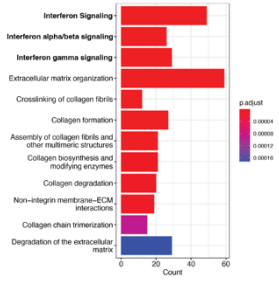
Xing, Panovska et al, Cell Reports Med 2025, PMCID:PMC12208339

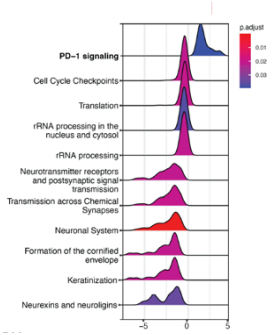
Immune-modulatory Effects of BRAF/MEK inhibitors?

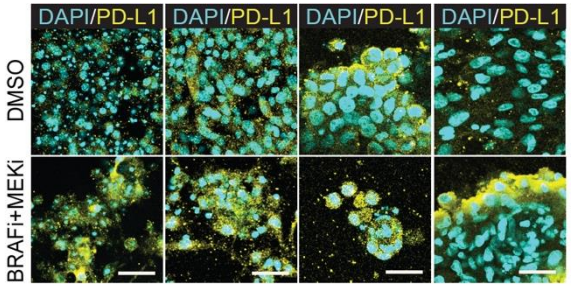


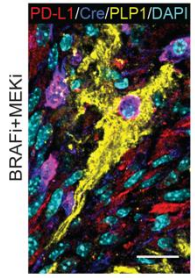
Dabrafenib (DB)=BRAF inhibitor
Trametinib (Tr)=MEK inhibitor

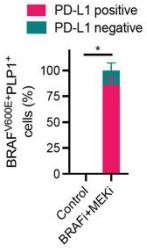
Xing, Panovska et al, Cell Reports Med 2025, PMCID:PMC12208339

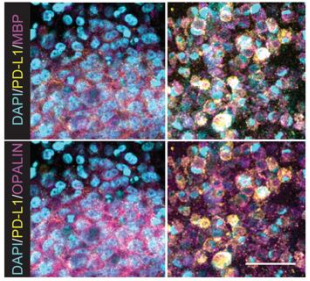


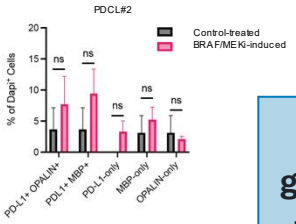




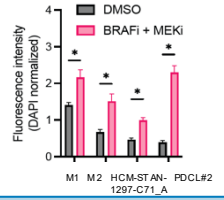






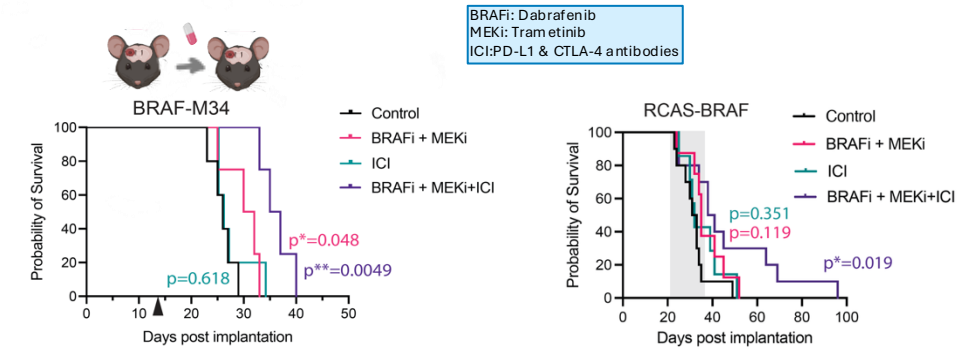


Petritsch Lab, Unpublished , Do not post



BRAF+MEK inhibitors induced **glioma cell differentiation** along with upregulated **antigen presentation** & up-expression of **immune checkpoint inhibitors**

Immune Checkpoint Inhibition Enhancing BRAF/MEK inhibition Anti-Tumor Effects?

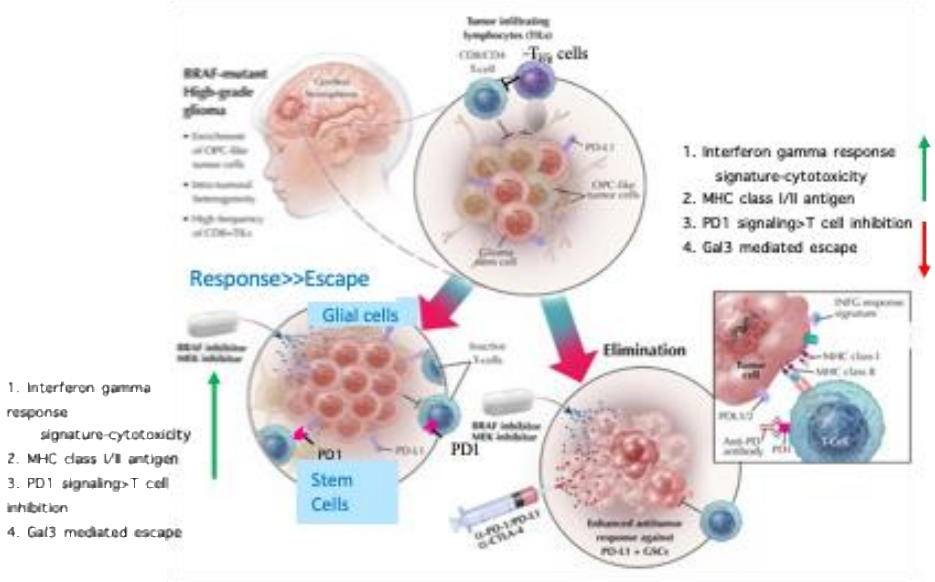


BRAF/MEK inhibitor treatment **inactivates T cells** mediating immune escape

BRAF/MEK inhibition Synergizes with **Immune Checkpoint Inhibition** to Reactivate **T cells** and Overcome Therapy Resistance.

Xing, Panovska et al, Cell Reports Med 2025, PMCID:PMC12208339

Summary



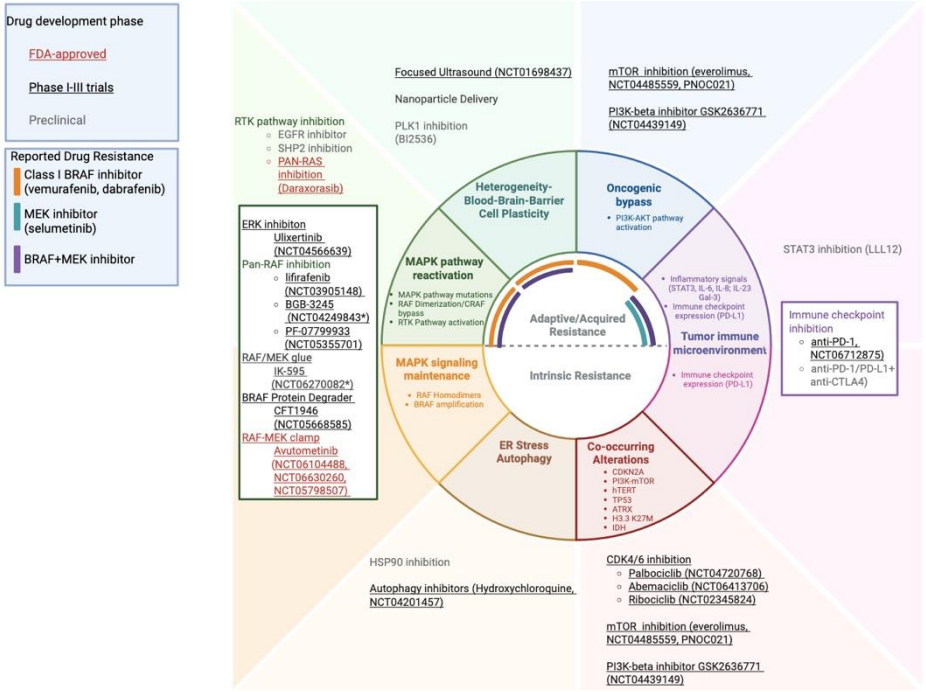
MAIN FINDINGS

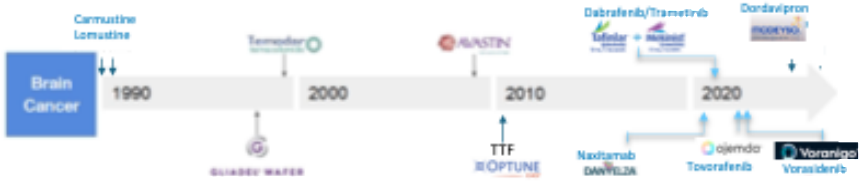
- BRAF/MEK inhibition induces **glioma cell state transitions** that triggers increases in stem cells, and immune evasion
- BRAFi+MEKi activates the interferon response and anti-tumor immunity, while simultaneously **suppressing T cells via PD-L1 upregulation in glial cells**
- Glial differentiation and immune evasion could be mediated by therapy-induced **secretion of immune modulatory factors**
- High PD-L1 expression in BRAF-mutant GBM provides a criterion for anti-PD-1 therapy
- **Concurrent BRAF/MEK and checkpoint inhibition** enhances anti-tumor immunity and survival

CLINICAL IMPLICATION

Our preclinical findings highlight the potential of integrating BRAFi+MEKi treatment with PLK1 inhibition and with ICI, with emphasis on concurrent treatment

Clinical implications of BRAF/MEK inhibitor resistance studies





Challenges

Toxicity (75 % of long-term survivors have chronic health conditions)

These are especially devastating for pediatric patients

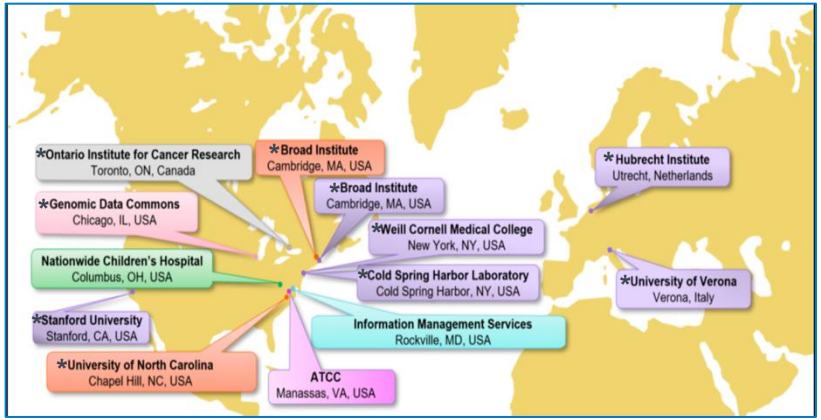
Include neurosensory impairments, cognitive and visual deficits, memory and attention deficits, slower processing speed.

The HCMI Pediatric Cancer Models

Introducing the developing collection of models

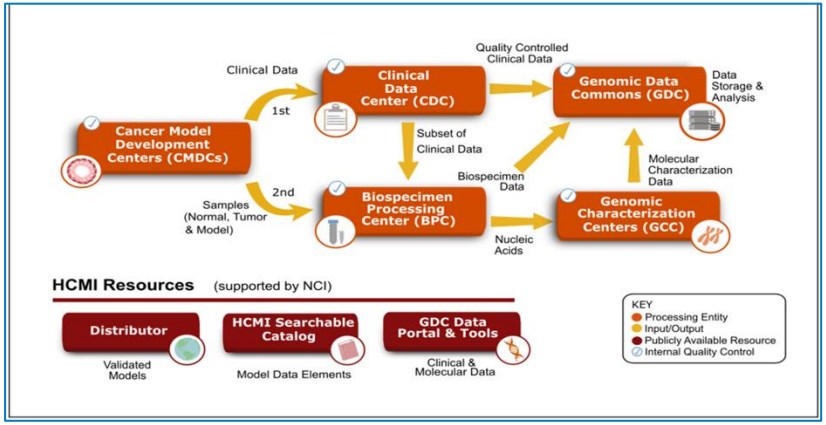
The Human Cancer Model Initiative (HCMI)

The HCMI is an international consortium founded by the **National Cancer Institute** and dedicated to generating **next-generation, patient-derived cancer models as a community resource** to facilitate cancer research



(Source: https://www.cancer.gov/ccg/research/functional-genomics/hcmi/about/cancer-model-development)

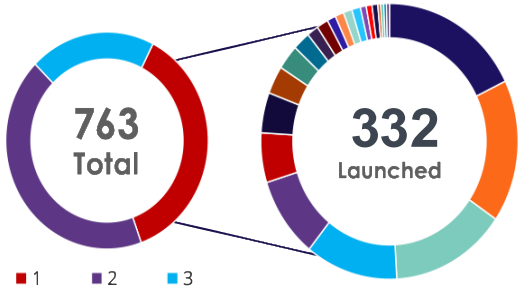
(* Managed by the Frederick National Laboratory for Cancer Research (FNLCR), Leidos Biomedical Research, Inc.)



(Source: https://ocg.cancer.gov/programs/hcmi/nci-cancer-model-development)

HCMI Has Focused on Adult Cancer

- Current HCMI models are mainly from adult tumors

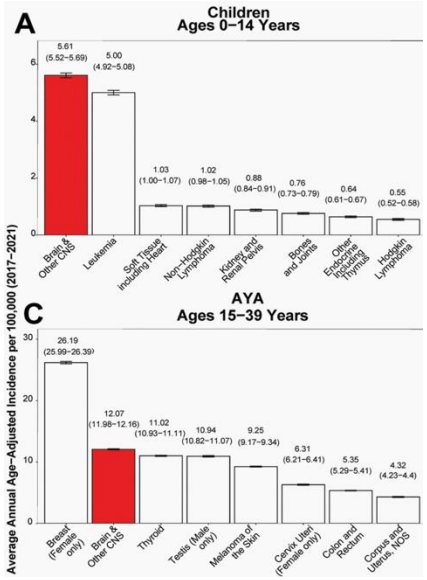


Collection includes models derived from rare adult and pediatric cancers such as rhabdomyosarcoma, leiomyosarcoma, Ewing sarcoma, and Wilms tumor.

TOP 10 (90% of total)

Colon	55
Pancreas	52
Brain	50
Esophagus	36
Skin	29
Rectum	21
Stomach	18
Lung	7
Breast	7
Connective tissue	5

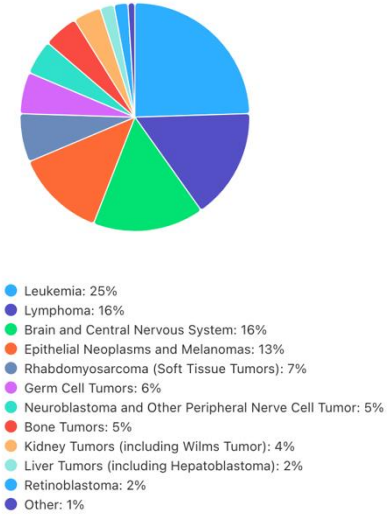
12 models are from pediatric patients



Neuro Oncol, Volume 26, Issue Supplement_6, October 2024, Pages vi1–vi85, https://doi.org/10.1093/neuonc/noae145.

Rationale for Developing Next-Generation Pediatric Solid Tumor Models

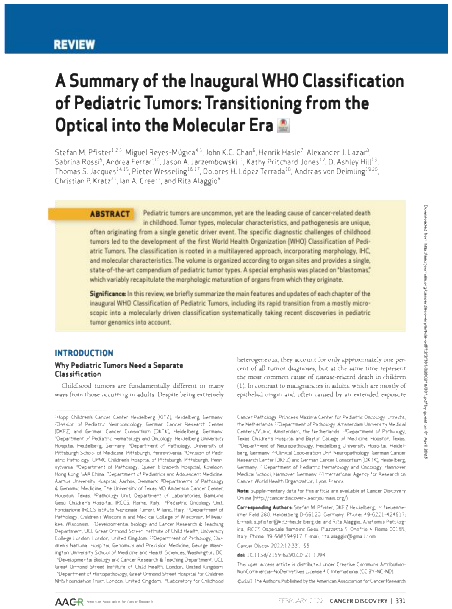
Childhood Cancer Incidence, Age 0-19, 2017-2021



Characteristics

- Rare (4-5 x lower incidences than in adults)
- *Different* treatment strategies (minimize long-term sequelae)
- Different pathogenetic mechanisms (developmental, MAPK pathway vs. RTK, onco-fusions, epigenetic regulation)

>100 subtypes of pediatric solid tumors


REVIEW

A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era

ABSTRACT

INTRODUCTION

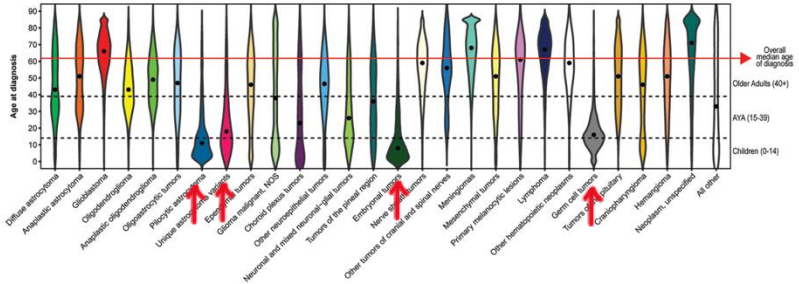
Why Pediatric Tumors Need a Separate Classification

Pfister, SM et al; Cancer Discov. 2022; PMCID:PMC9401511

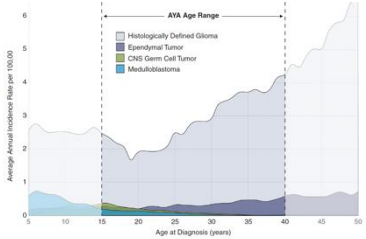
Adult versus Pediatric Brain Tumors Incidence & Subtypes

1 Distribution of age at diagnosis by selected primary brain tumors

Price *et al*; Neuro-oncology 2024; https://doi.org/10.1093/neuonc/noae145



2 Overview of the relative incidence of brain tumors with age

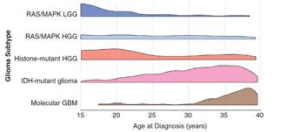


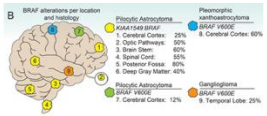
Lim-Fat *et al*; Neuro-oncology 2025, PMCID:PMC11726256

3 Incidence of different subtypes of glioma, medulloblastoma, and ependymma

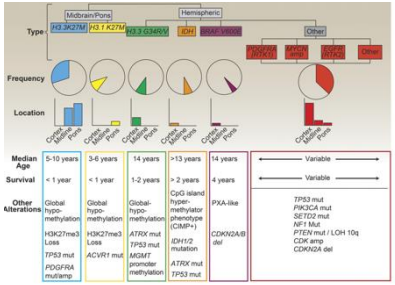
Glioma

Low-grade glioma are the most common

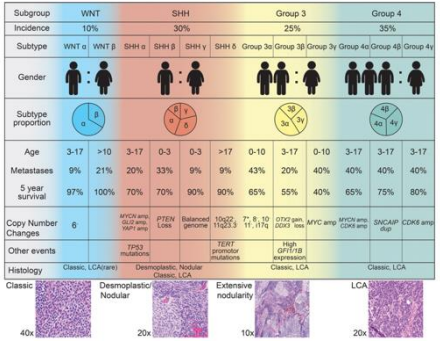




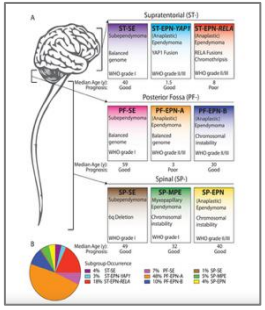
Pediatric high-grade glioma are rare but devastating and carry unique genetic alterations



Medulloblastoma

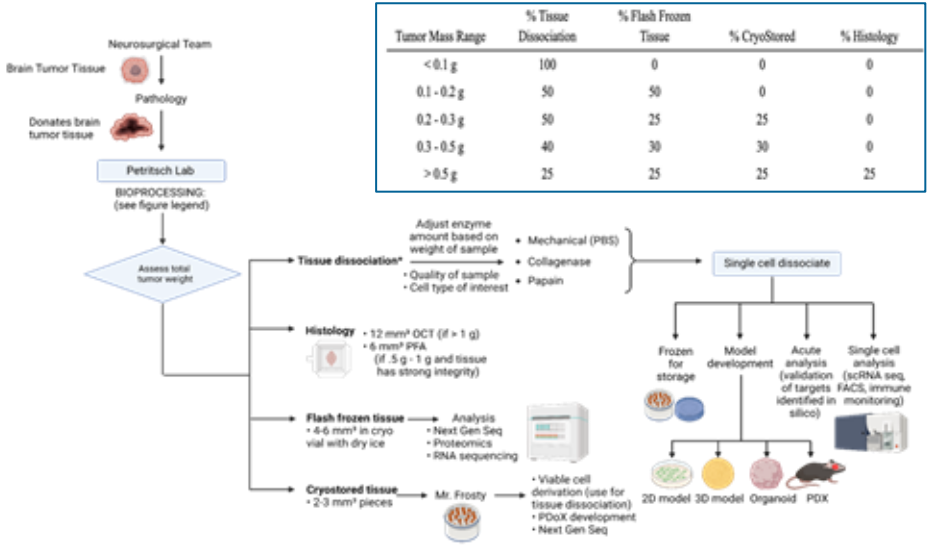


Ependymoma



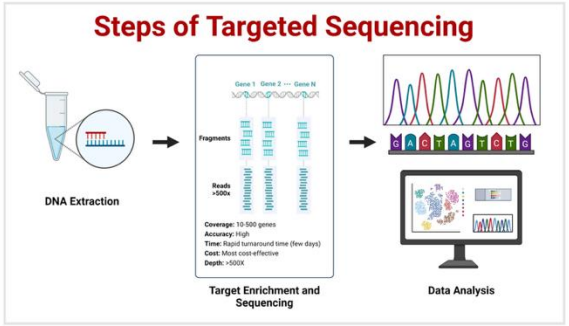
Pediatric Cancer Model Development - Workflow

Established Bioprocessing Workflow in our laboratory



Tumor Mass Range	% Tissue Dissociation	% Flash Frozen Tissue	% CryoStored	% Histology
< 0.1 g	100	0	0	0
0.1 - 0.2 g	50	50	0	0
0.2 - 0.3 g	50	25	25	0
0.3 - 0.5 g	40	30	30	0
> 0.5 g	25	25	25	25

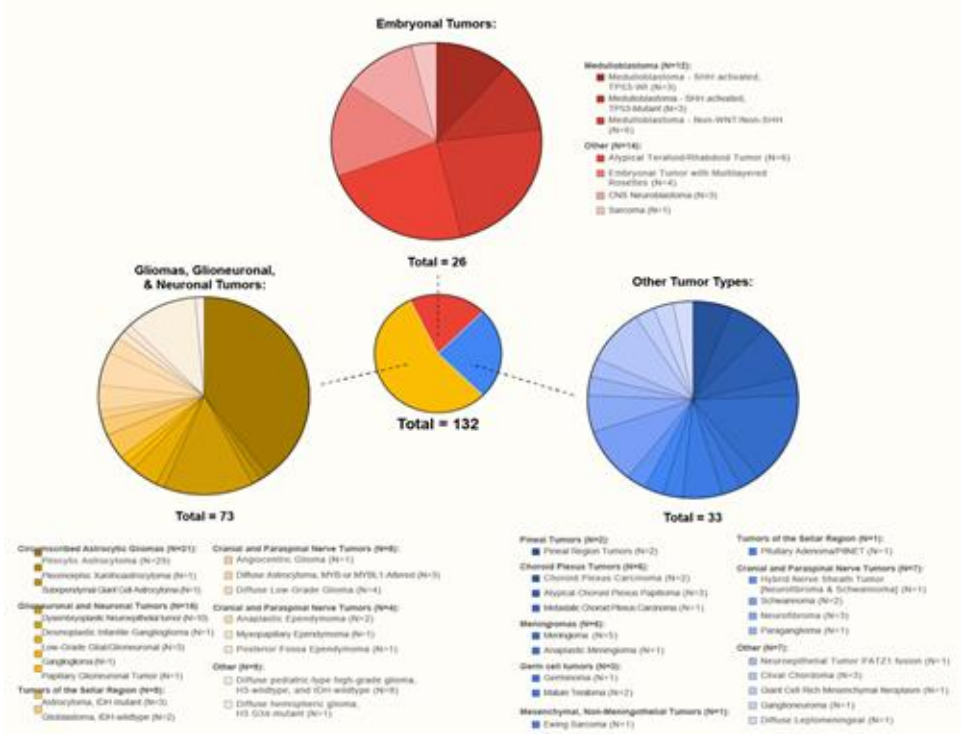
Established Mutation Identification



Stanford Actionable Mutation Panel ~250 genes, UCSF 500 Caris (WES)

An established biobanking workflow with standardized targeted sequencing of patient Tumors to identify recurrent mutations, including oncofusions

Representative Cohort of Pediatric Brain Cancer Types at Stanford Pediatrics CMDC

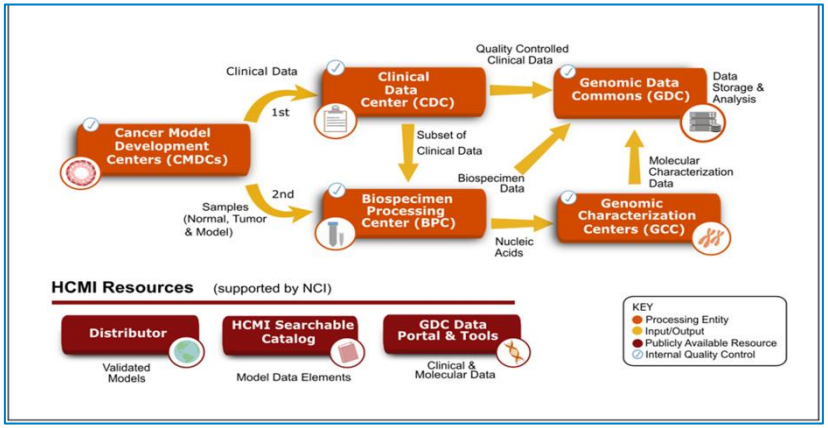


No. of Ranked Cases	Tumor Type	Genes/Molecular Profiles Characteristically Altered
3	Astrocytoma, IDH-mutant	IDH1, IDH2, ATRX, TP53, CDKN2A/B
2	Glioblastoma, IDH-wildtype	IDH-wildtype, TERT promoter, chromosomes 7/10, EGFR
2	Diffuse astrocytoma, MYB- or MYBL1-altered	MYB, MYBL1
1	Angiocentric glioma	MYB
4	Diffuse low-grade glioma, MAPK pathway-altered	FGFR1, BRAF
1	Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, TP53, ATRX
9	Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	IDH-wildtype, H3-wildtype, PDGFRA, MYCN, EGFR (methylome)
30	Pilocytic astrocytoma	KIAA1549-BRAF, BRAF, NF1
1	Pleomorphic xanthoastrocytoma	BRAF, CDKN2A/B
1	Subependymal giant cell astrocytoma	TSC1, TSC2
2	Chordoid glioma	PRKCA
1	Ganglion cell tumors	BRAF
10	Dysembryoplastic neuroepithelial tumor	FGFR1
1	Papillary glioneuronal tumor	PRKCA
1	Diffuse leptomeningeal glioneuronal tumor	KIAA1549-BRAF fusion, 1p (methylome)
3	Supratentorial ependymomas	ZFTA, RELA, YAP1, MAML2
1	Posterior fossa ependymomas	H3 K27me3, EZHIP (methylome)
6	Medulloblastoma, SHH-activated	TP53, PTCH1, SUFU, SMO, MYCN, GLI2 (methylome)
6	Medulloblastoma, non-WNT/non-SHH	MYC, MYCN, PRDM6, KDM6A (methylome)
6	Atypical teratoid/rhabdoid tumor	SMARCB1, SMARCA4
5	Embryonal tumor with multilayered rosettes	C19MC, DICER1
3	CNS neuroblastoma, FOXR2-activated	FOXR2
6	Meningiomas	NF2, AKT1, TRAF7, SMO, PIK3CA, KLF4, SMARCE1, BAP1 in subtypes; H3K27me3; TERT promoter, CDKN2A/B in CNS WHO grade 3

- ~90% of cases yield tissue for research
- 45 subtypes of brain cancer and 12 subtypes of non-CNS cancers captured over a 4-year period
- Longitudinal collection is crucial to capture diverse, rare cancers

Pediatric Cancer Types for HCMI

- Pediatric central nervous system (CNS) solid tumors
  - Diffuse Midline Glioma (DMG), H3-K27-mutant
  - Diffuse High-Grade Glioma (HGG), MAPK activated, H3 and IDH wildtype & IDH-mutant
  - Recurrent Lower Grade Glioma
  - Medulloblastoma
  - Ependymoma
- Non-CNS pediatric solid tumors
  - Malignant Rare Soft Tissue and Bone sarcoma
  - Wilms' Tumor
  - Neuroblastoma
  - Hepatoblastoma
- Other rare cancer types and subtypes as feasible.



(Source: https://ocg.cancer.gov/programs/hcmi/nci-cancer-model-development)

60-70% success rate for model development
27 subtypes of brain cancer and 4 of non-CNS cancer were captured in models
Challenges: small tumor size

Planning and management oversight by the team at Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc.
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Stanford Cancer Institute
NCI Designated Comprehensive Cancer Center

Q&A

Join Us at Our Next Webinar

CCDI Pediatric, Adolescent, and Young Adult Rare Cancer Study

Monday, April 27, 2026
12:00–1:00 p.m. ET

Come learn about the newly launched study from Mary Frances Wedekind, D.O., Associate Research Physician at NCI!

Learn more and register at **events.cancer.gov/ccdi/webinar**

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NCIChildhoodCancerDataInitiative@mail.nih.gov

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