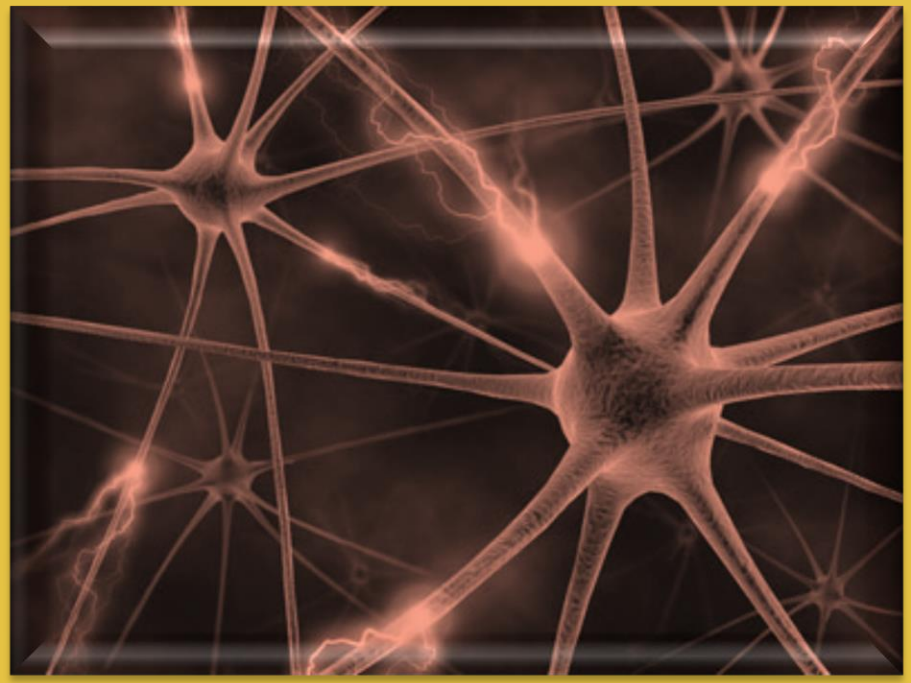
In The Name of God

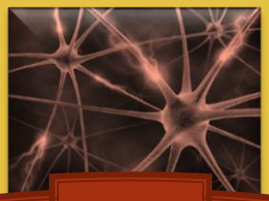
New Approaches To Brain Tumor Therapy

Tehran University of Medical Sciences
School of Advanced Technologies in Medicine

By:
Saereh Hosseindoost
PhD Candidate in Neuroscience



WHO Classification of Brain Tumor



Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion-positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (742A). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.
Italics: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*.

David.N., et al., 2016

Current Treatments For GBM

Surgical Resection

Aggressive & invasive phenotype

Radiation

Resistant to radiation

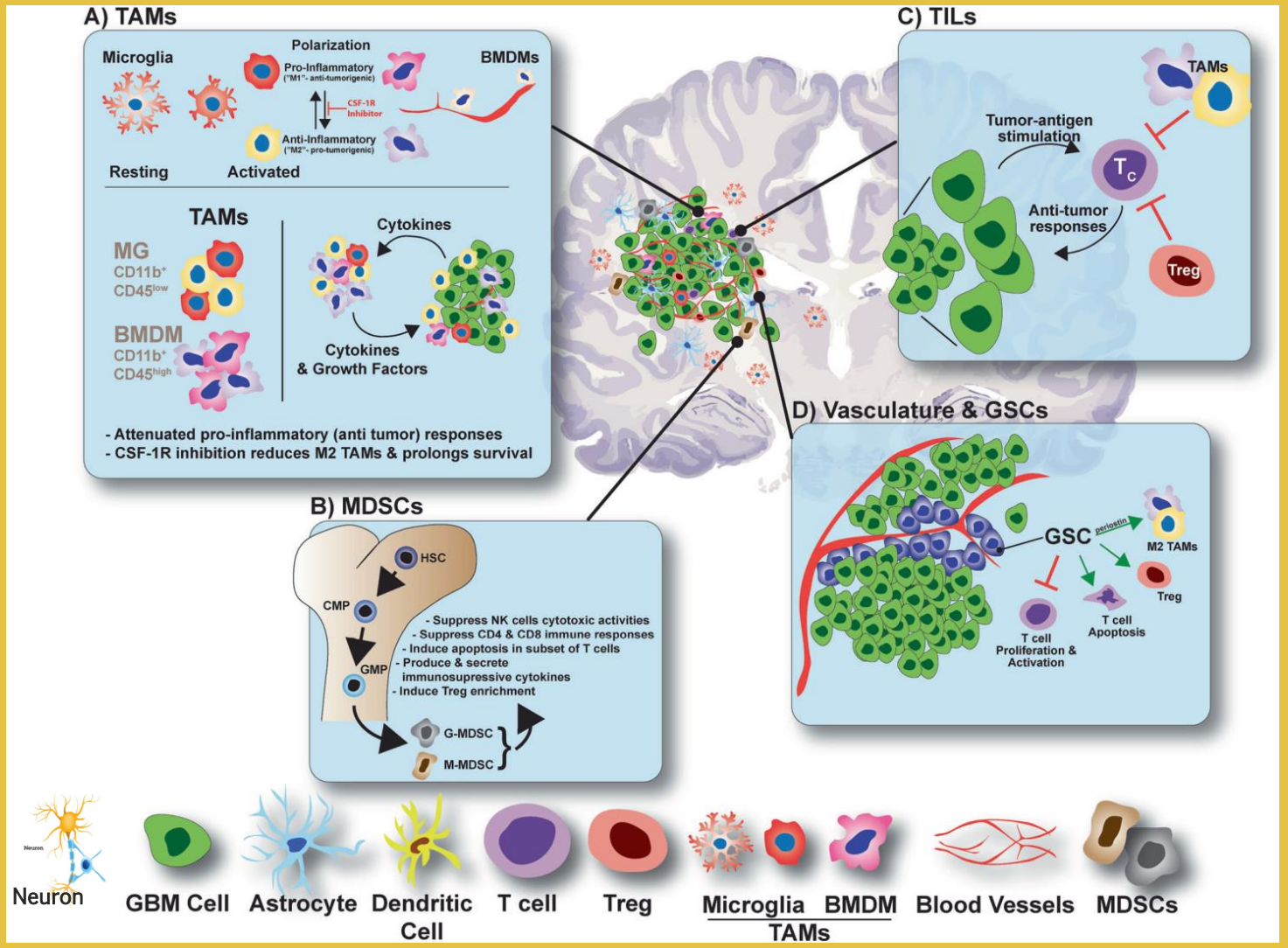
Temozolomide (TMZ) chemotherapy

Resistant to chemotherapy

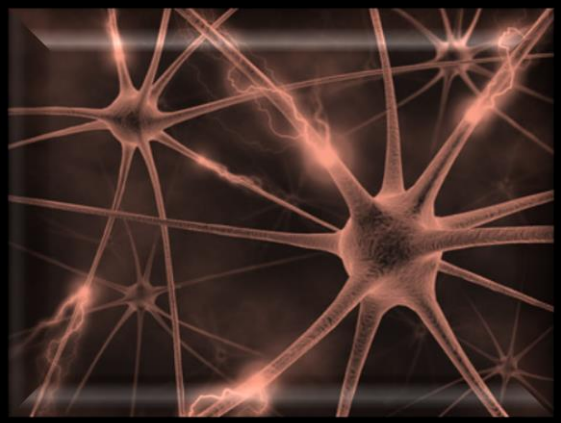
15 months

Stupp et al; 2005

Immune landscape of Glioma

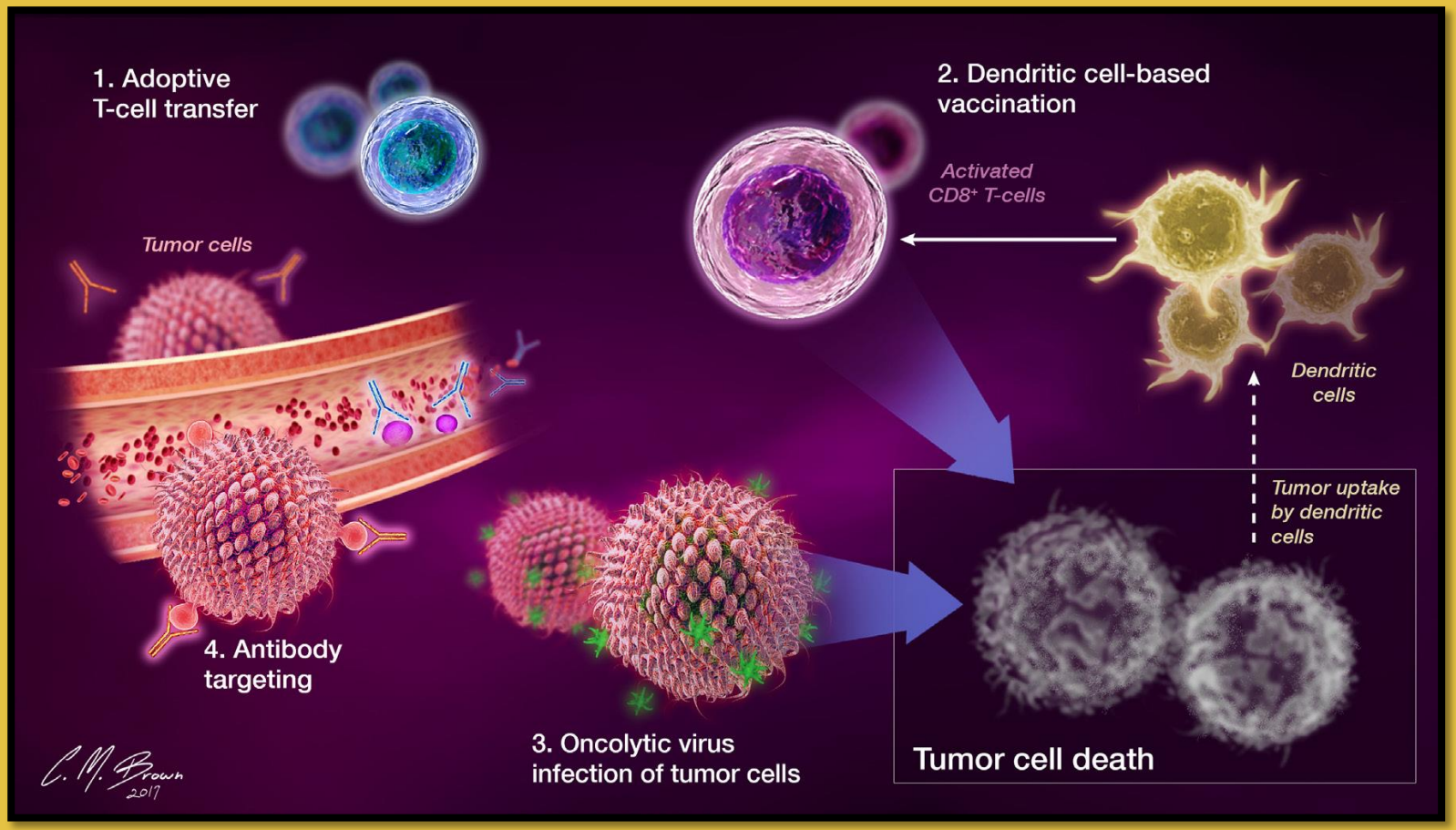


Vassiliki A ., et al., 2017



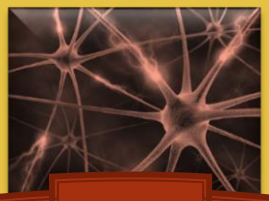
Immunotherapy

GBM & Immunotherapy



Filley. A ., et al., 2017

Approaches to Glioma Immunotherapy



Therapeutic Vaccines

- Peptide vaccines
- Heat-shock proteins (HSP) vaccines
- Dendritic cell-based (DC) vaccines

Oncolytic virotherapy

Chimeric Antigen Receptors (CAR) T cell therapy

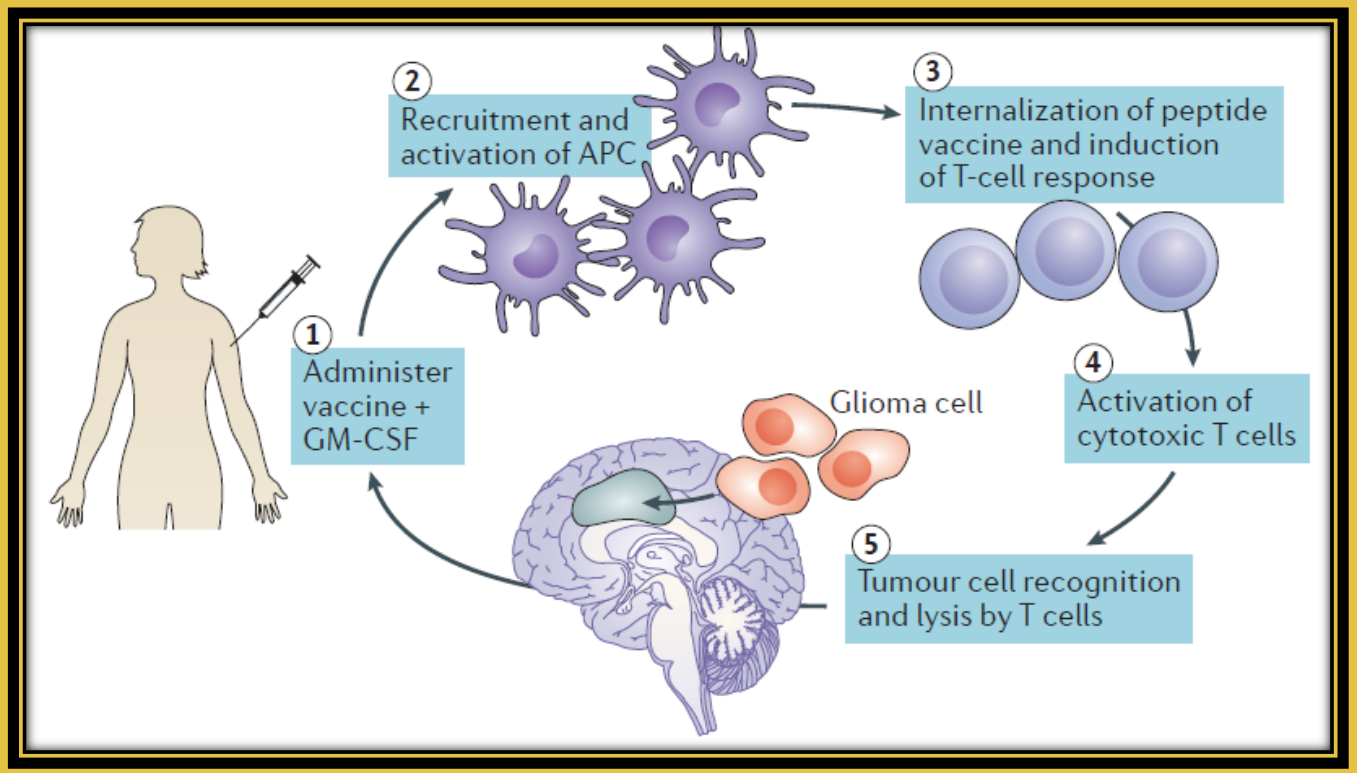
Immune Checkpoint Inhibitors

Anastasie M., et al., 2017

Therapeutic Vaccines

Peptide vaccines:

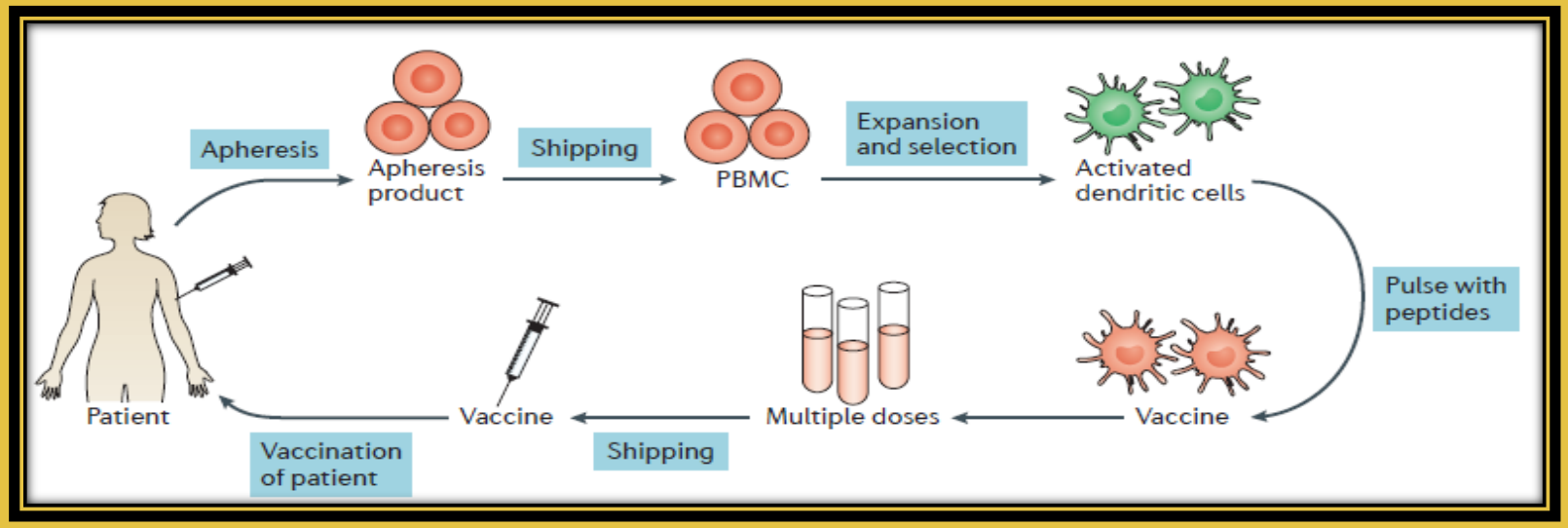
- EGFRvIII - specific vaccines
- IDHR132H - specific vaccines



Michael .W ., et al., 2017

Therapeutic Vaccines

DC vaccines

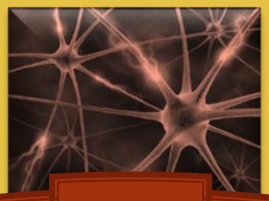


HSP vaccines

HSP-antigen complexes → contact with CD91 → endocytosed into APC → CD8 + T cells stimulation → Driven immune reactions

Michael .W ., et al., 2017

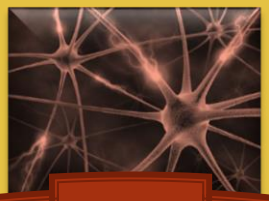
Completed Clinical Trials of Vaccination Therapy for Glioblastoma



Trial name and ClinicalTrials.gov identifier	Active treatment	Control	Sample size	Primary end point	Result
Phase III					
ACT-IV[135] NCT01480479	Rindopepimut plus GM-CSF	KLH plus GM-CSF	700	Overall survival	Negative
Phase II					
ReACT[136] NCT01498328	Rindopepimut plus bevacizumab	KLH and GM-CSF plus bevacizumab	70	Progression-free survival	Positive (trend)
HeatShock[137] NCT00905060	HSPPC-96 plus temozolomide	None	46	Safety and survival	Results pending
HSPPC-96 (REF. 138) NCT00293423	HSPPC-96	None	41	Safety, toxicity	Safe vaccine
GBM-Vax[139] NCT01213407	Trivax (a DC-based vaccine) plus temozolomide plus radiotherapy, followed by maintenance temozolomide	Temozolomide plus radiotherapy, followed by maintenance temozolomide	87	Progression-free survival	Results pending
Phase I					
IMA-950 (REF. 140) NCT01222221	IMA-950 plus GM-CSF	None	45	Safety and T cell responses	Positive for primary end point

Anastasie M., et al., 2017

Ongoing Clinical Trials of Vaccination Therapy for Glioma

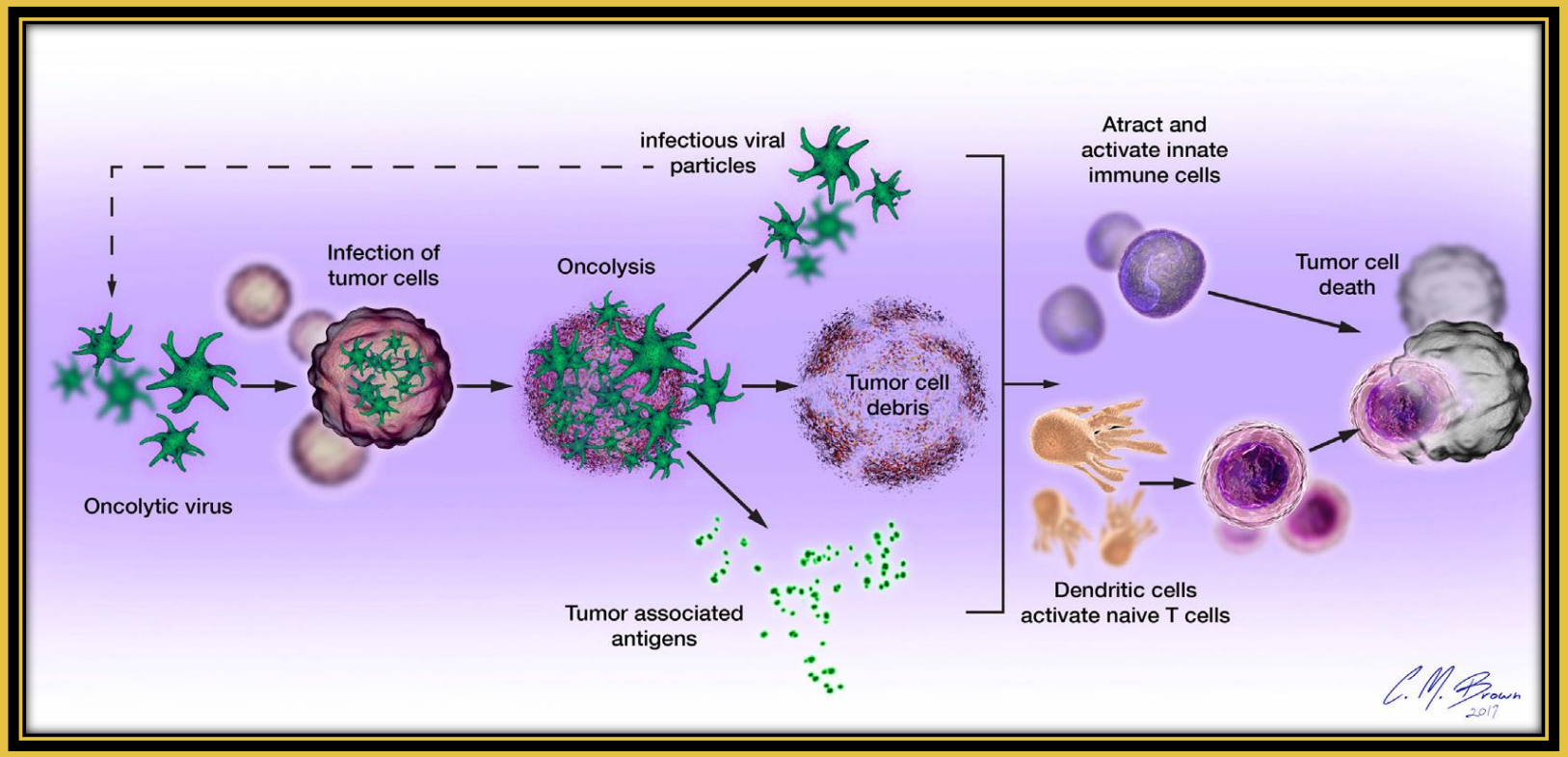


Trial name and ClinicalTrials.gov identifier	Active treatment arms	Control	Sample size	Primary end point
Phase III				
DCVax[64] NCT00045968	DCVax	Autologous PBMC	348	Progression-free survival
STING[67] NCT02546102	ICT-107	Autologous monocyte-enriched PBMC	414	Overall survival
Phase II				
ATTAC-II[141] NCT02465268	Cytomegalovirus RNA-pulsed DCs plus tetanus–diphtheria toxoid	Unpulsed PBMC and saline	150	Overall survival
ALLIANCE IND#15380 (REF. 142) NCT01814813	HSPPC-96 and concomitant bevacizumab versus HSPPC-96 followed by bevacizumab at progression	Bevacizumab	165	Overall survival
HSPPC-96 (REF. 82) NCT03018288	TMZ–RT→TMZ plus pembrolizumab and HSPPC-96	• TMZ–RT→TMZ plus pembrolizumab and placebo • A separate group of patients whose tumours did not fulfil all inclusion criteria also received TMZ–RT→TMZ plus pembrolizumab and placebo	108	Overall survival at 1 year
SurVaxM[143] NCT02455557	SurVaxM	None	50	Progression-free survival
Phase I				
NOA-16 (REF. 76) NCT02454634	IDH^{R132H} peptide vaccine	None	39	Safety and tolerability
GAPVAC[34] NCT02149225	APVAC1 and APVAC2 vaccine plus poly-ICLC and GM-CSF	None	16	Safety and biological activity
NCT02287428 (REF. 59)	Personalized neoantigen vaccine	None	15	Feasibility and safety

Anastasie M., et al., 2017

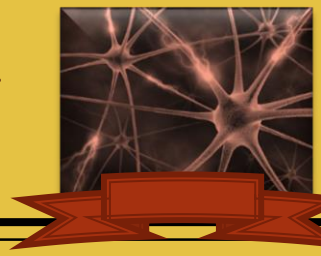
Oncolytic Virotherapy

Oncolytic viral vector that will selectively target, infect, and destroy tumor cells.



Filley. A and Dey.M., 2017

Clinical Trials of Oncolytic Virotherapy for Cancers

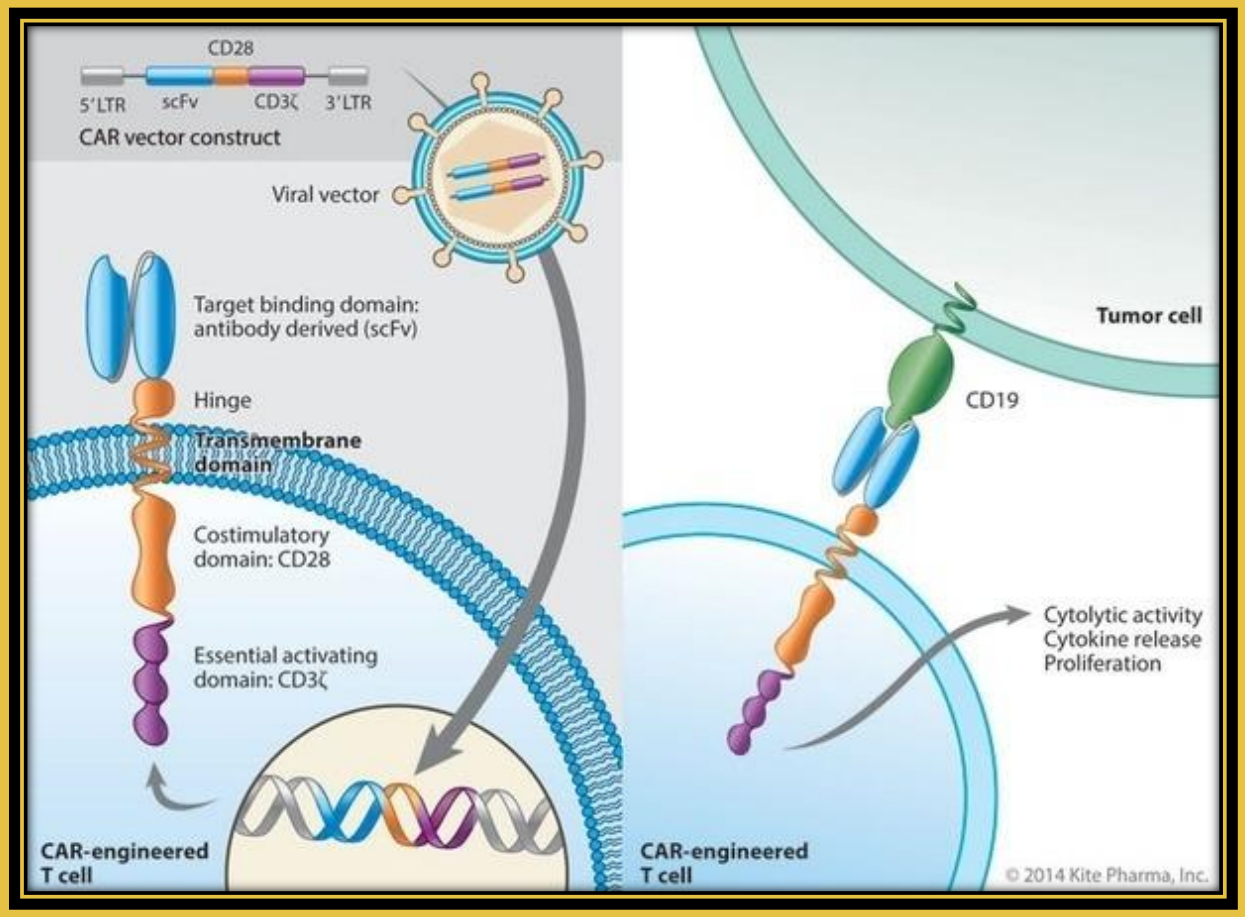


Virus	Name	Phase	Tumor	Combination	Reference
Adenovirus	ONYX-015	III	Squamous cell carcinoma head and neck (SCCHN)	Cisplatin	Khuri et al. (4)
		I/II	Pancreatic cancer	Gemcitabine	Hecht et al. (5)
		Pilot	Advancer cancers	Irinotecan + 5-FU or IL-2	Nemunaitis et al. (6)
		I/II	Advanced sarcoma	Mitomycin-C, doxorubicin, cisplatin	Galanis et al. (7)
	Oncorine (H101)	III	SCCHN or esophageal cancer	5-fluorouracil + cisplatin or adriamycin	Xia et al. (8)
	Ad5-CD/Tkrep	I	Prostate cancer	5-fluorocytosine, valganciclovir, radiation	Freytag et al. (9)
	ONCOS-201	I	Solid tumors	Cyclophosphamide	Ranki et al. (10)
Herpes simplex virus	Talimogene laherparepvec	I/II Ib	SCCHN Melanoma	Radiation, cisplatin Ipilimumab (CTLA-4 inhibitor)	Harrington et al. (11) Puzanov et al. (12)
	G207	I	Glioma	Radiation	Markert et al. (13)
Reovirus	RT3D	I/II	Advanced cancers	Carboplatin/paclitaxel	Karapangiotou et al. (14)
Vaccinia	GL-ONC1	I	Head and neck carcinoma	Cisplatin, radiotherapy	NCT01584284
	JX-594 (Pexa-Vec)	I/IIa	Colorectal cancer	Irinotecan	NCT01394939

Filley. A and Dey.M., 2017

Adoptive T Cell Transfer

Chimeric Antigen Receptors (CAR) T cell therapy



Fousek K., et al., 2015

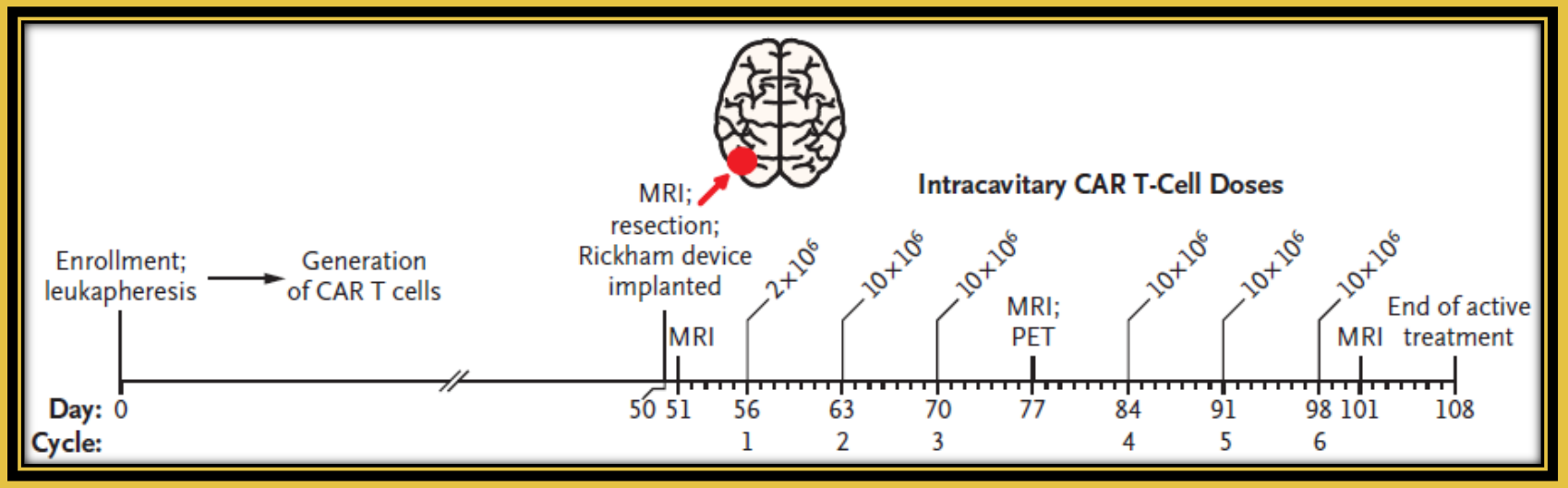
CAR T Cell Therapy

Pilot study

- 1 patients with recurrent GBM

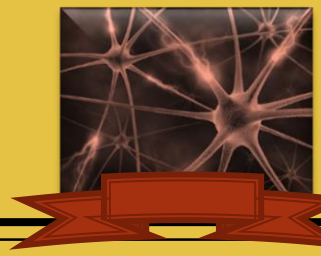
Intracavitary infusions of CAR T cells targeting IL13Rα2

Tumor regression



Christine E., et al., 2016

CAR T Cell Therapy



Phase I/II study

Treatment	Target
NCT01454596	EGFRvIII
NCT02664363	EGFRvIII
NCT02209376	EGFRvIII
NCT02208362	IL-13Rα2
NCT02442297	HER2
NCT01109095	HER2
NCT02575261	EPHA2

EGFRvIII : Epidermal growth factor receptor variant III
IL-13Rα2 : Interleukin receptor 13Rα2
HER2 : Epidermal growth factor receptor 2
EPHA2 : Ephrin type-A receptor 2

Vassiliki A ., et al., 2017

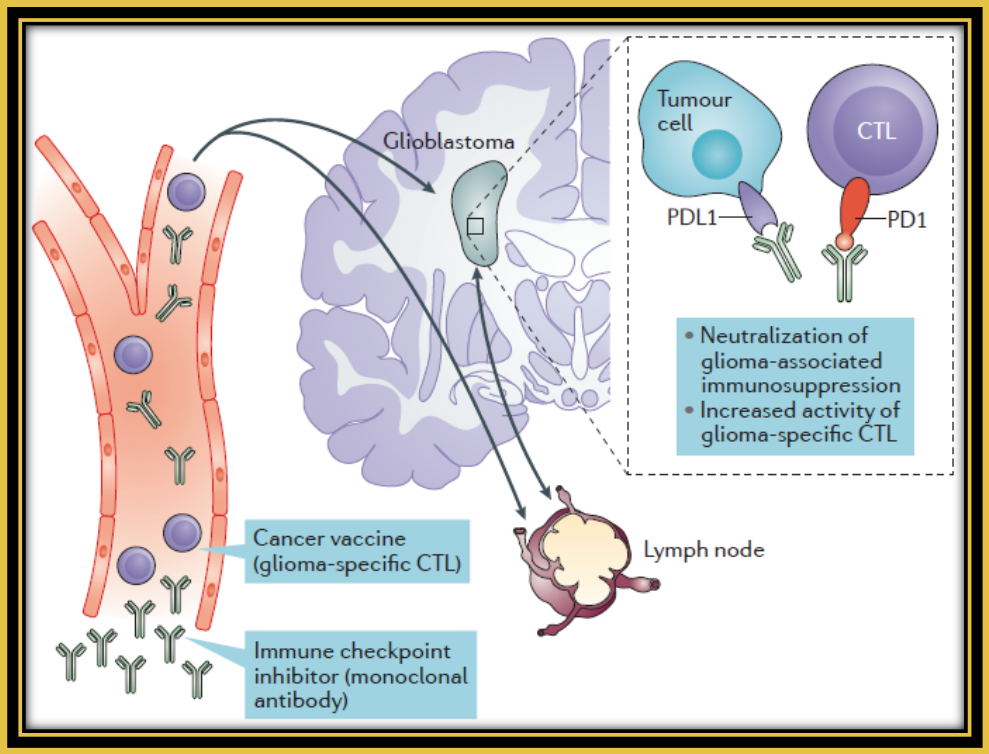
Immune Checkpoint Inhibitors

Therapeutic monoclonal antibodies that intercept receptor–ligand interactions involved in regulating immune cell activity

Cytotoxic T lymphocytes associated protein 4 (CTLA-4)

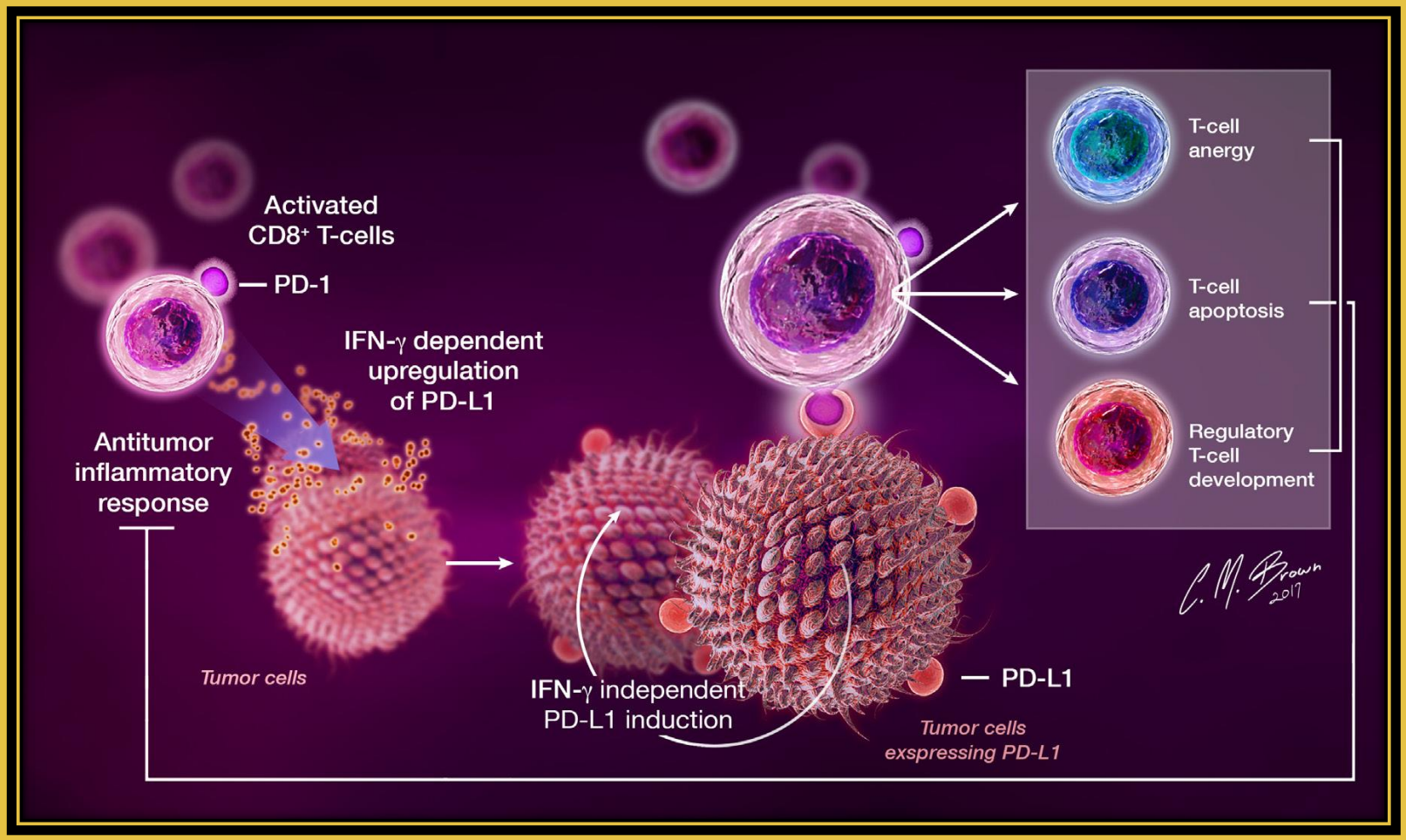
Programmed cell death protein 1 (PD1)

Programmed cell death 1 ligand 1 (PDL1)



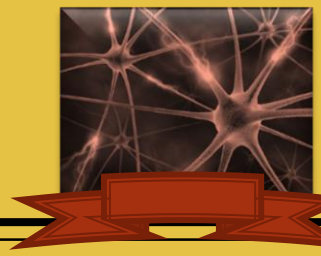
Michael .W ., et al., 2017

Immune Checkpoint Inhibitors



Filley. A ., et al., 2017

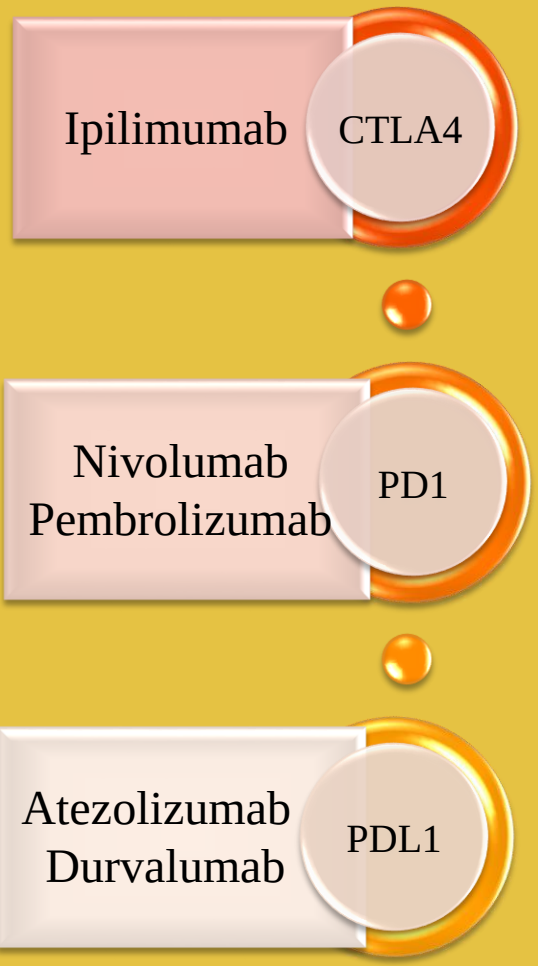
Immune Checkpoint Inhibitors



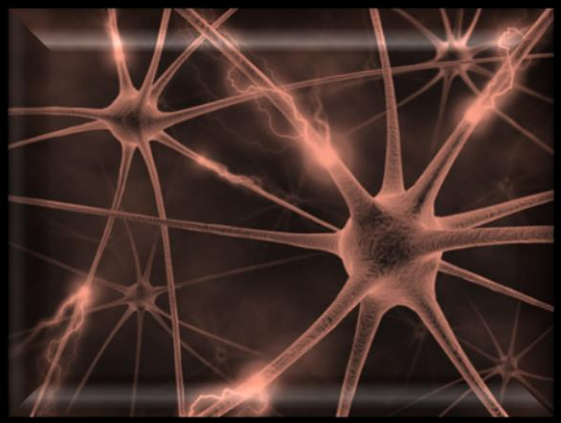
Nivolumab alone versus Nivolumab plus Ipilimumab for recurrent GBM

Nivolumab was well tolerated, but 80% of patients who received combination therapy had adverse events

The 10 patients who received Nivolumab alone had a 75% 6-month OS rate, and the 10 patients who received dual therapy had an 80% 6-month OS rate, and both rates were superior to the rate reported in historic controls



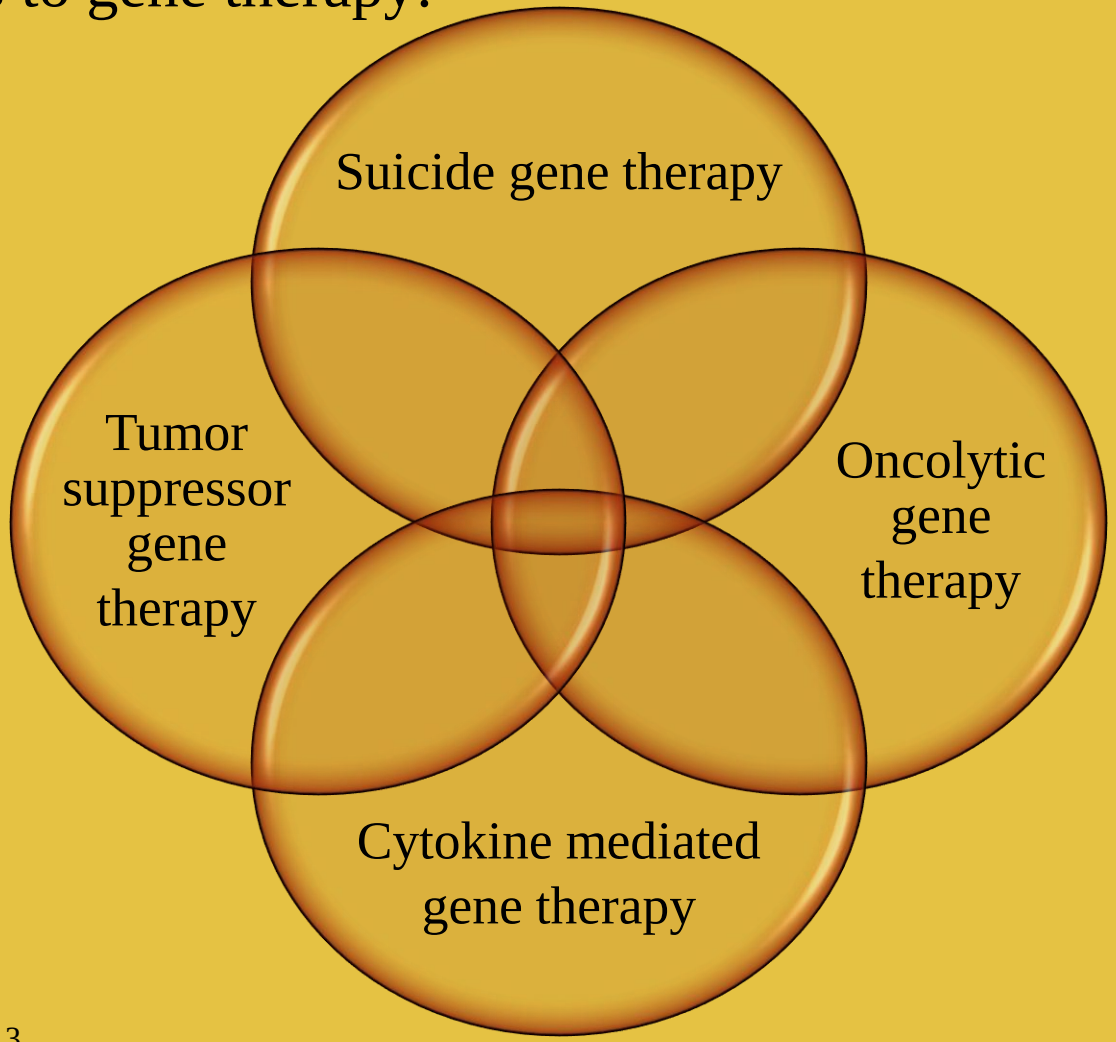
Sampson JH .,et al., 2015



Gene Therapy

Gene Therapy For Malignant Glioma

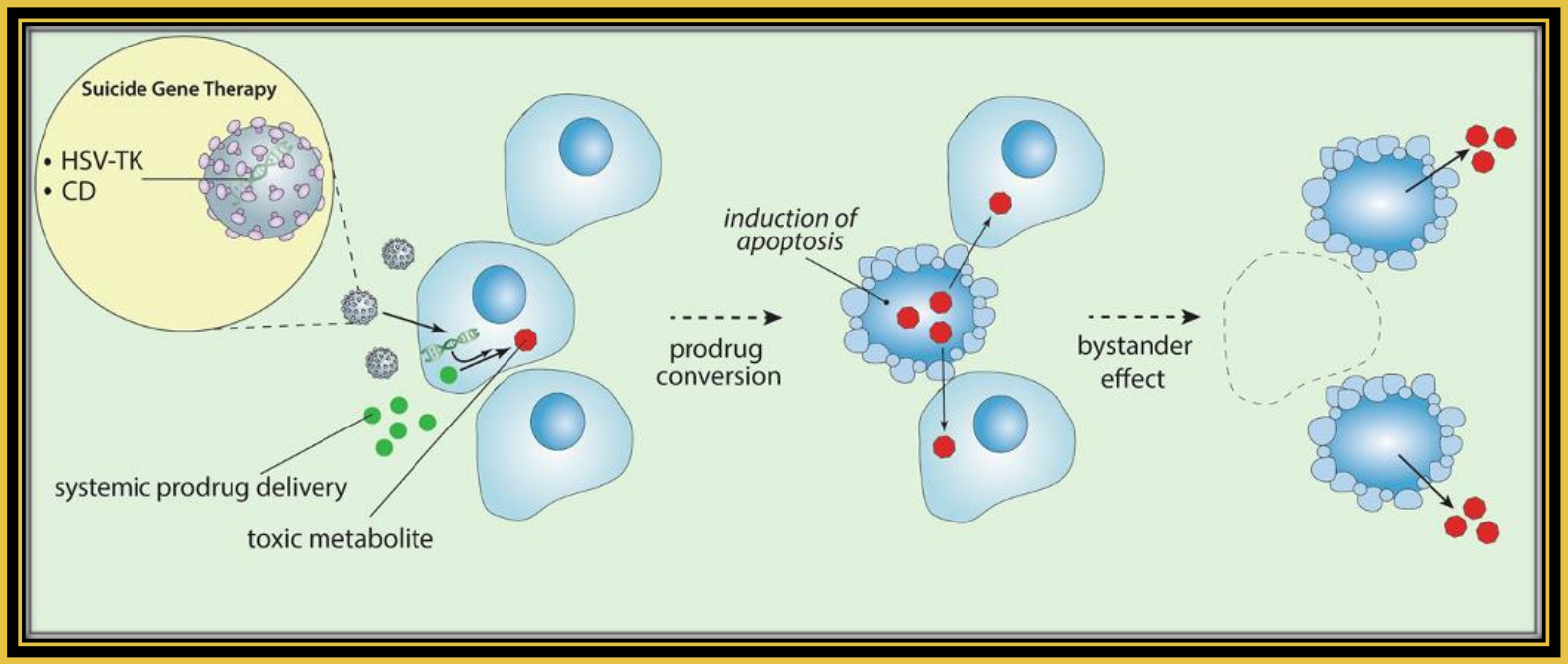
Approaches to gene therapy:



Kwiatkowska A., et al., 2013

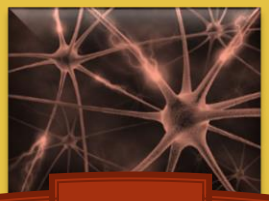
Suicide Gene Therapy

- Cytosine Deaminase / 5-fluorocytosine (CD/5-FC)
- HSV- Thymidine Kinase / Ganciclovir (HSV-TK/GCV)



Duarte. S., et al., 2012

Ongoing Clinical Trials For Gene Therapy Of GBM



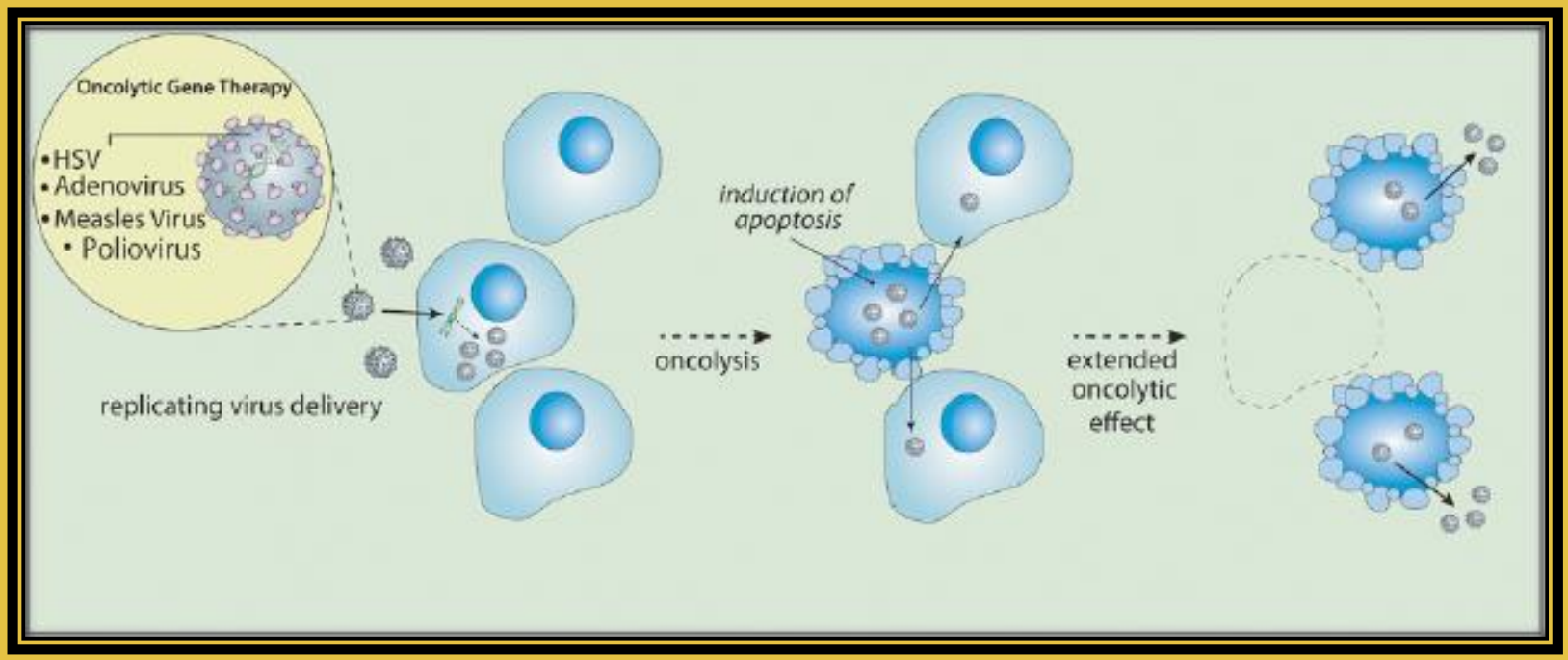
Type of gene therapy	Phase	Vector	Gene	Prodrug	Nation	ID	Title
Suicide	Pilot	NSC	CD	5-FC	USA	NCT01172964	A Pilot Feasibility Study of Oral 5-Fluorocytosine and Genetically-Modified Neural Stem Cells Expressing E. Coli Cytosine Deaminase for Treatment of Recurrent High Grade Gliomas
Suicide	I	AV	HSV-TK	Valacyclovir	USA	NCT00751270	Phase 1b Study of AdV-tk + Valacyclovir Combined With Radiation Therapy for Malignant Gliomas
Suicide/ immune-mediated	I	AV	HSV-TK	Valacyclovir	USA	NCT01811992	Combined Cytotoxic and Immune-Stimulatory Therapy for Glioma
		AV	Flt3L	-			
Suicide	I	RV (Toca 511)	CD	5-FC	USA	NCT01470794	Study of a Retroviral Replicating Vector to Treat Patients Undergoing Surgery for a Recurrent Malignant Brain Tumor
Suicide	I	RV (Toca 511)	CD	5-FC	USA	NCT01985256	Study of a Retroviral Replicating Vector Given Intravenously to Patients Undergoing Surgery for Recurrent Brain Tumor
Suicide	I	AV	HSV-TK	Valacyclovir	USA	NCT00634231	A Phase I Study of AdV-tk + Prodrug Therapy in Combination With Radiation Therapy for Pediatric Brain Tumors
Suicide	I/II	RV (Toca 511)	CD	5-FC	USA	NCT01156584	A Study of a Retroviral Replicating Vector Administered to Subjects With Recurrent Malignant Glioma

Hidehiro.O., et al., 2014

Oncolytic Gene Therapy

Oncolytic gene therapy employs replication competent viral vectors in order to increase the toxicity and efficiency against the tumor

G207: conditionally replicating HSV mutant vector

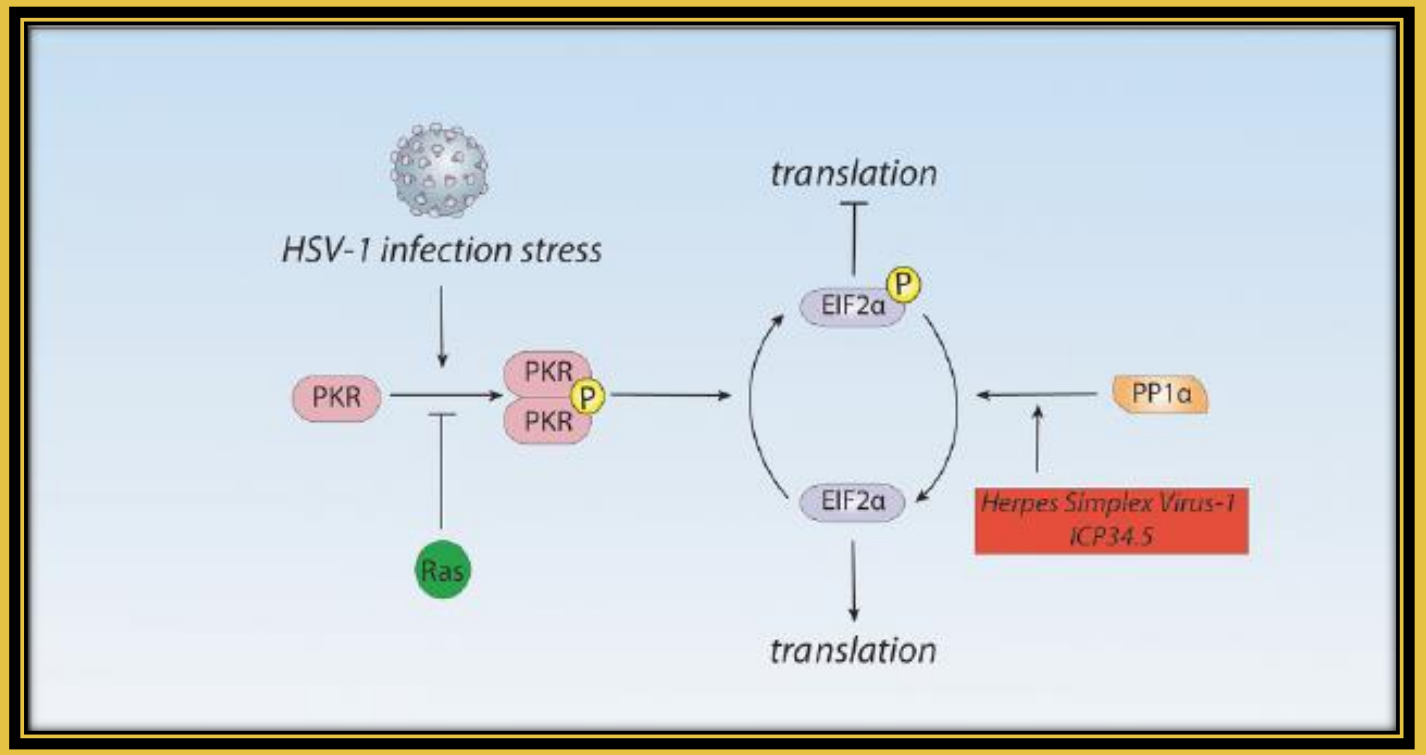


Russell SJ.,et al.,2012

Oncolytic Gene Therapy

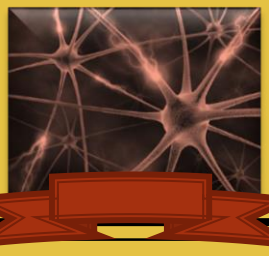
G207

- Mutant γ34.5 gene → Inactive ICP 34.5
- Mutant UL39 gene → Inactive ICP6 → Disrupting the enzyme RR



Aghi M.,et al.,2008

Oncolytic Gene Therapy



Phase I clinical trial using G207:

- 21 patients with malignant glioma
- No treatment related toxicity or serious adverse events
- A positive therapeutic response was identified in eight patients, and one patient survived 5.5 years after the treatment

Phase Ib study using G207:

- 6 patients with malignant glioma
- No evidence of virus-related toxicities and G207 gene therapy
- Three of the patients showed subsequent improvement and the overall survival was greater than 6 months

Markert JM.,et al.,2000 ,2009

Ongoing Clinical Trials For Gene Therapy Of GBM

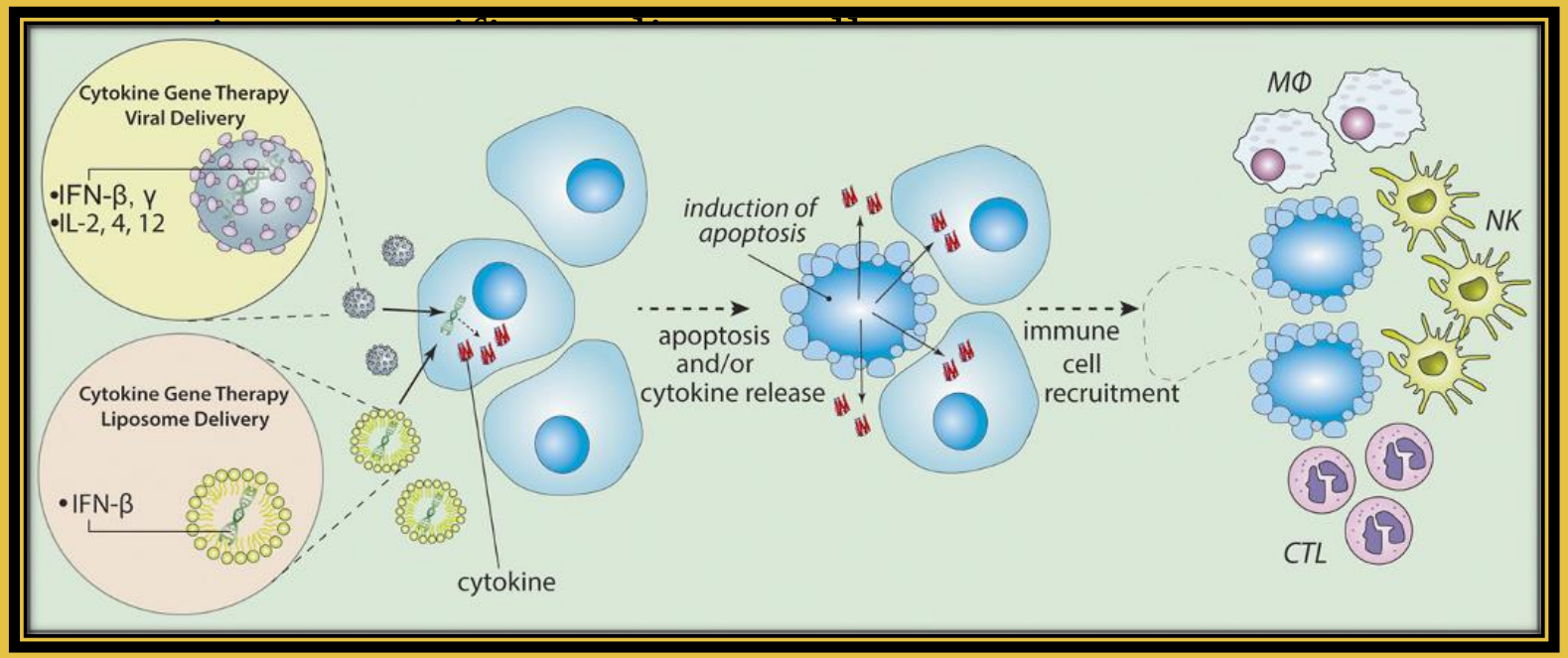
Type of gene therapy	Phase	Vector	Gene	Prodrug	Nation	ID	Title
Oncolytic	I	HSV (HSV1716)	-	-	USA	NCT02031965	Oncolytic HSV-1716 in Treating Younger Patients With Refractory or Recurrent High Grade Glioma That Can Be Removed By Surgery
Oncolytic	I	MV	CEA	-	USA	NCT00390299	Viral Therapy in Treating Patients With Recurrent Glioblastoma Multiforme
Oncolytic	I	AV (DNX-2401)	-	-	Spain	NCT01956734	Virus DNX2401 and Temozolomide in Recurrent Glioblastoma
Oncolytic	I	PoV (PVS-RIPO)	-	-	USA	NCT01491893	Poliovirus Vaccine for Recurrent Glioblastoma Multiforme (GBM)
Oncolytic	I	AV (DNX-2401)	-	-	USA	NCT00805376	DNX-2401 (Formerly Known as Delta-24-RGD-4C) for Recurrent Malignant Gliomas
Oncolytic	I/II	HSV (G47Delta)	LacZ	-	Japan	JPRN-UMIN000002661	A Clinical Study of a Replication-Competent, Recombinant Herpes Simplex Virus Type 1 (G47delta) in Patients With Progressive Glioblastoma
Oncolytic	I/II	PaV (H-1 PV)	-	-	Germany	NCT01301430	Parvovirus H-1 (ParvOryx) in Patients With Progressive Primary or Recurrent Glioblastoma Multiforme
Oncolytic	I/II	AV (Delta24-RGD)	-	-	Netherlands	NCT01582516	Safety Study of Replication-competent Adenovirus (Delta-24-rgd) in Patients With Recurrent Glioblastoma

Hiedehiro.O.,et al.,2014

Cytokine Mediated Gene Therapy

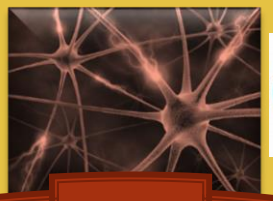
The principle of cytokine mediated gene therapy involves:

- Tumor selective gene transfer
- In situ expression of various cytokine genes such as IL-2, IL-4, IL-12 IFN-β,IFN-γ which can induce robust immune responses restricted



Tobias A.,et al.,2013

Cytokine Mediated Gene Therapy



Pilot clinical trial

- Transfer of IFN-β gene via cationic liposomes
- The 5 patients with malignant glioma
- 2 patients experienced more than 50% tumor reduction for at least 16 months

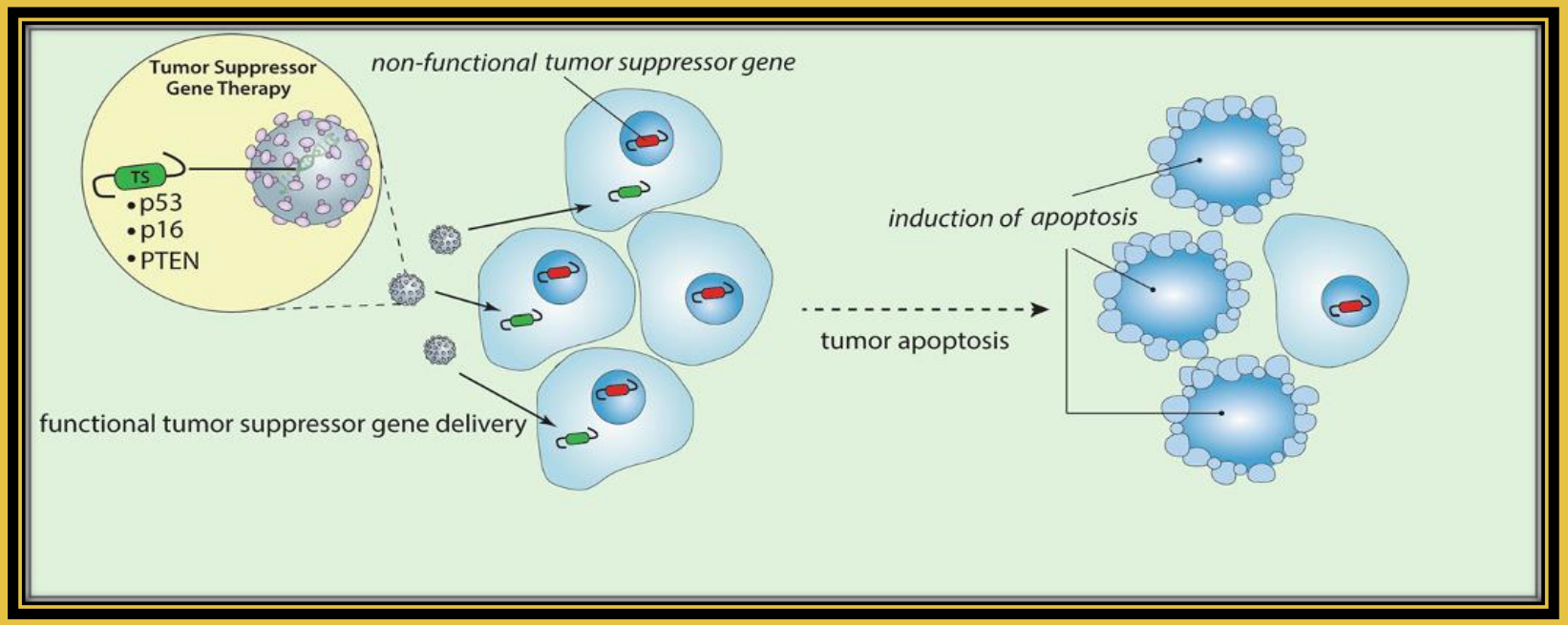
Combined delivery of IL-2 with HSV-TK , intravenous GCV

- 12 patients with recurrent malignant glioma
- The 12-month PFS rate were 14% and OS rates were 25%
- Although there was a marked increase of circulating IFN-γ, TNF-α, IL-2, and IL-10, only minor adverse events were noted.

Yoshida J.,et al.,2004

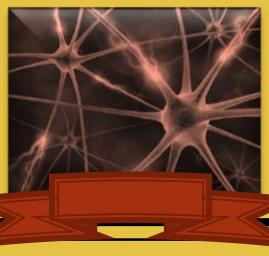
Tumor Suppressor Gene Therapy

Restoring the function of a tumor suppressor gene lost or functionally inactivated in cancer cells



Hiedehiro.O.,et al.,2014

Tumor Suppressor Gene Therapy

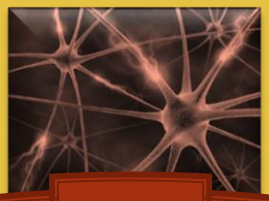


Ad5CMV-p53:

- Phase I clinical trial of Ad5CMV-p53 gene therapy in recurrent malignant glioma.
- Patients underwent stereotactic injection of the virus pre- and post-resection through an implanted catheter.
- Median PFS were 13 and OS were 43 weeks
- 1 patient was alive more than 3years after treatment without evidence of recurrence
- Limitations : insufficient gene transfer, lack of bystander effect

Lang FF.,et al.,2003

Comparison Of Gene Therapy Strategies For GBM



Suicide gene therapy	Oncolytic gene therapy	Cytokine mediated gene therapy	Tumor suppressor gene therapy
• Synergistic therapeutic efficiency of conventional treatment	• Additional therapeutic transgenes available	• Local augmentation of the immune response inside the brain	• Anti-angiogenesis effect
• Bystander effect	• Selective toxicity	• Combination therapy with other types of gene therapy available	• Synergistic therapeutic efficiency of conventional or other of gene therapy
• Selective cytotoxicity	• Higher transduction efficiency	• Reduce tumor vascularization and invasion	
▲ Transduced cells may become resistant to the prodrug	▲ Suppression of virus by host immune response	▲ Lack of antigen presenting cells inside the brain	▲ Resistance from the inherent genetic heterogeneity
▲ Low efficiency for distribution	▲ Cerebral inflammation and edema	▲ CNS toxicity	▲ Lack of bystander effect
▲ Low delivery to target cells		▲ Poor delivery of a gene to the tumor	▲ Poor gene transfer
▲ Limited prolonged efficacy			

•, Advantages; ▲, Disadvantages.

Hiedehiro.O.,et al.,2014

Carriers For Gene Therapy

Synthetic vectors (Nanoparticle , Cationic Liposome)

Disadvantage

Limited gene transfer efficiency

Advantage

Is safe

Viral vectors (Adenovirus, Lentivirus, Retrovirus, HSV)

Disadvantage

Recombination with wild type strain
Stimulation of immune system
Mutation
Limited migration

Advantage

Good gene transfer efficiency

Cellular carriers (NSC, MSC,ESC)

Disadvantage

Tumorigenicity
unwanted differentiation
Angiogenesis (MSC)
Ethical problems (NSC,ESC)

Advantage

Tropism potency

Kwiatkowska.A., et al.,2013

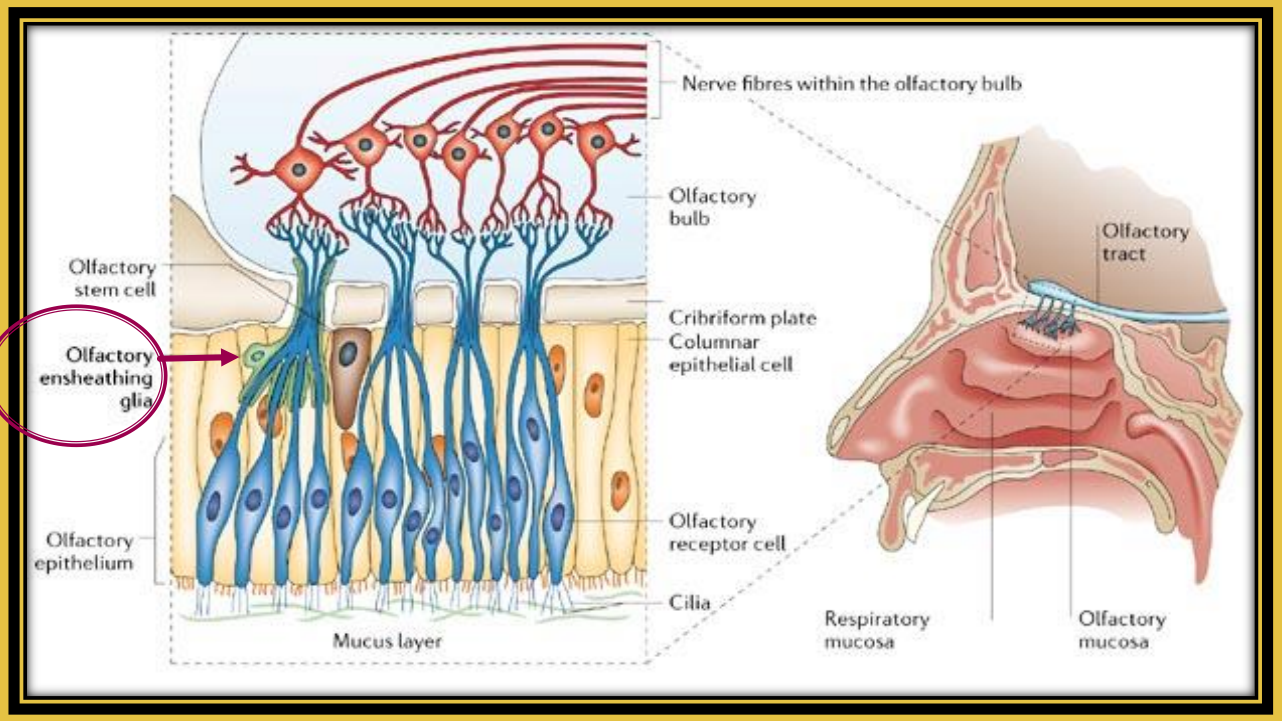
Olfactory Ensheathing Cell

Olfactory Ensheathing Cell (OEC)

✓High migratory capacity

✓Differentiation from stem cells

✓Non-tumorigenicity behaviour



Lankford et al; 2014

Mol Neurobiol
DOI 10.1007/s12035-015-9412-y

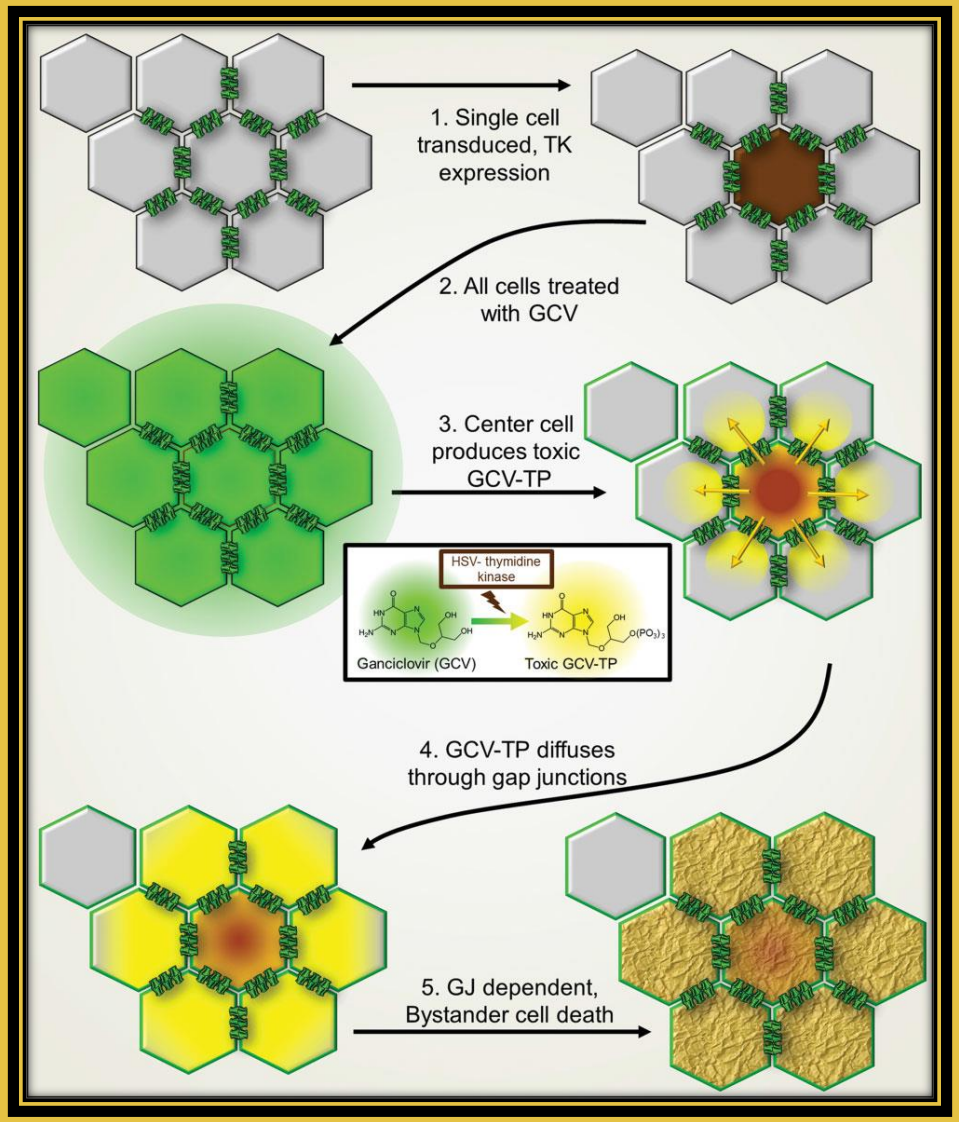
A New Approach in Gene Therapy of Glioblastoma Multiforme: Human Olfactory Ensheathing Cells as a Novel Carrier for Suicide Gene Delivery

Mansoureh Hashemi[1] · Ali Fallah[2] · Hamid Reza Aghayan[3,4] · Babak Arjmand[3,4] · Nasrin Yazdani[5] · Javad Verdi[6,7] · Seyed Mohammad Ghodsi[8] · Seyed Mojtaba Miri[8,9] · Mahmoudreza Hadjighassem[1,8]

Received: 25 March 2015 / Accepted: 27 August 2015

Abstract Olfactory ensheathing cells (OECs) of human olfactory mucosa are a type of glial-like cells that possess good migratory and tropism properties. We believe that neuronal-derived vehicle may have better capability to receive to the site of injury. In addition to, obtaining of such vehicle from the patient reduces risk of unwanted complications. So, in this study, we investigate whether human olfactory ensheathing cells can be used as a cell source for the first time in gene delivery to assay the tumoricidal effect of herpes simplex virus thymidine kinase gene (HSV-tk) on glioblastoma for transient and stable expression of the herpes simplex virus thymidine kinase gene (OEC-tk). The migratory capacity of OEC-tk, their potency to convert prodrug ganciclovir to toxic form, and cytotoxic effect on astrocyte cells were assayed in vitro. The OECs showed fibroblast-like morphology and expressed specific antigens such as p75 neurotrophin receptor, S100-beta, and MAP2. Our results indicated that OECs-tk were able to migrate toward primary cultured human glioblastoma multiforme and affected survival rate of tumor cells according to exposure time and concentration of ganciclo-

Bystander Effect



Spray,D., et al.,2013


Thank you