Brain Tumor Immunotherapy

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Disclosure Information

Conflicts of Interests:

Hideho Okada, MD, PhD is an inventor of the IL-13Rα2 (345-353:1A9V) peptide, for which an exclusive licensing agreement has been executed with Stemline, Inc.

Per COI policies, interpretation of presented data was not performed solely by Hideho Okada, but by the investigator team.

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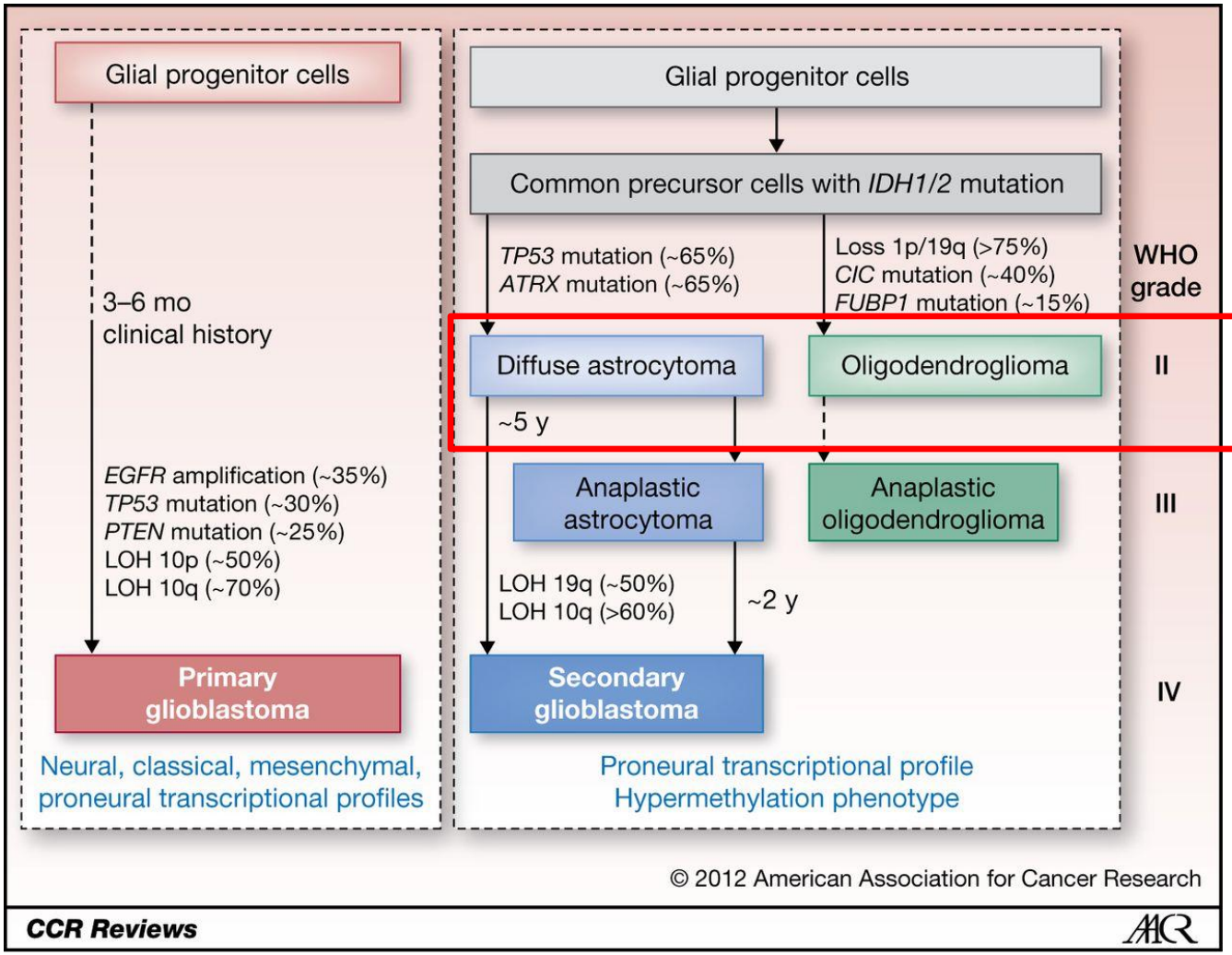
Voices Against Brain Cancer
Participants and their families

Genetic pathways to primary and secondary glioblastomas



Ohgaki H , and Kleihues P Clin Cancer Res 2013;19:764-772

Immunotherapy approaches that are currently evaluated in glioblastoma

- **Vaccine** – dendritic cell (DC)s loaded with lysate, peptides targeting epitopes, such as EGFRviii, cocktail of 10 non-mutated antigens (IMA950), CMV etc.
- **T-cell Adoptive transfer**- CAR targeting EGFRviii, IL-13Ra2, Her2 etc.
- **Immune checkpoint inhibitor**- blockade of TGF-beta, anti-PD-1 plus anti-CLTA4, anti-PD-L1
- **Oncolytic virus**- oncolytic HSV expressing IL-12

Is the brain immune privileged (or not)?

The concept originated in 1921 in Japan, when Shirai observed that rat sarcoma cells grew well when transplanted into the mouse brain parenchyma, but were rejected when implanted subcutaneously or intramuscularly.

Immune privilege is:

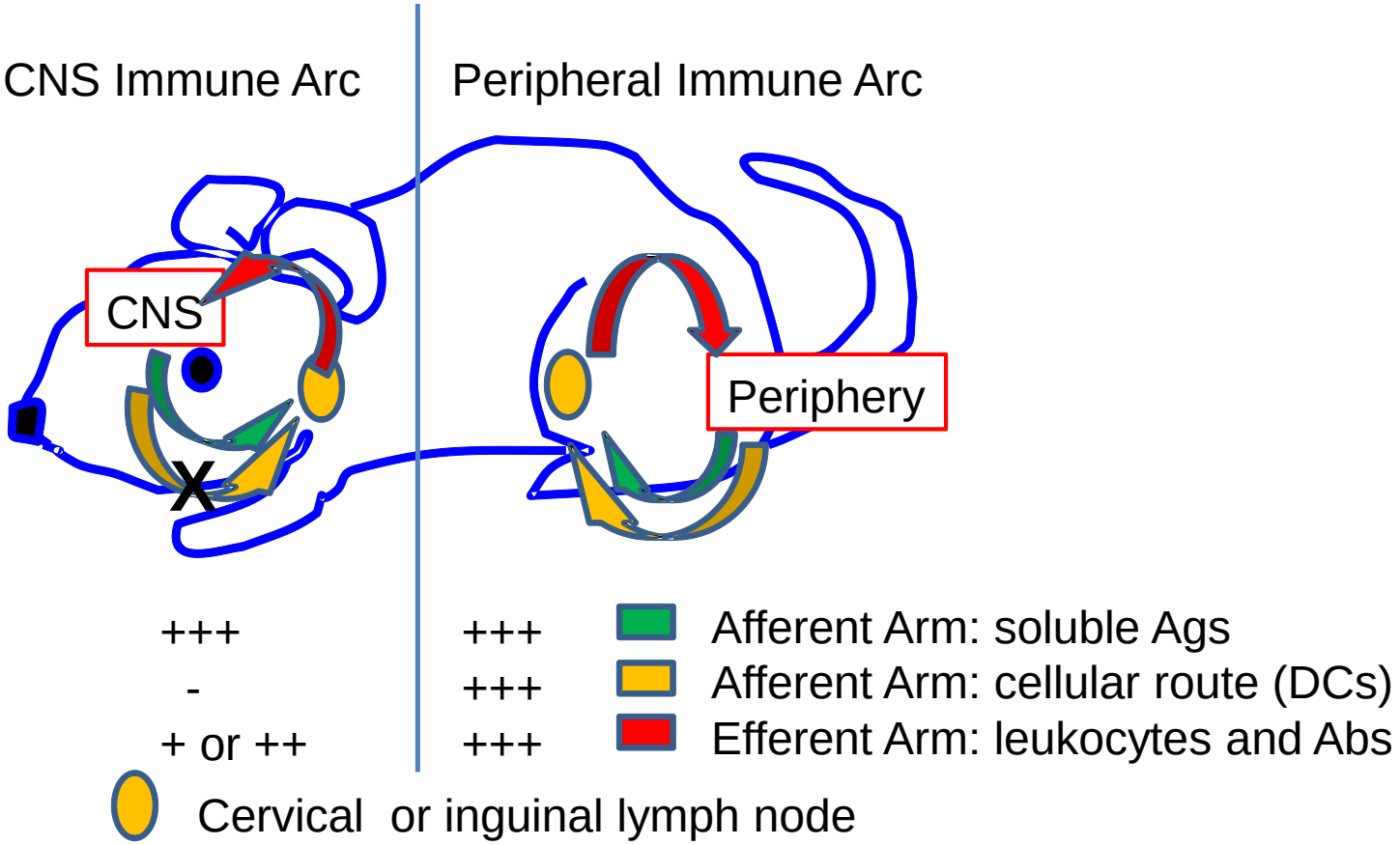
- **Relative**
- **Confined to central nervous system (CNS) parenchyma (see below)**
- **Characterized by lack of the afferent arm in adaptive immunity**

Immune privilege is **not**:

- Absolute
- Solely attributed to the blood–brain barrier (BBB)
- Present in meninges, choroid plexus and ventricles
- Preserved as observed as neurotoxicity in recent cancer immunotherapy studies
- Preserved in the inflamed CNS

Galea I et al. Trends in Immuol 2007
Ransohoff RM and Engelhardt B. Nat. Rev Immuol 2012

What is “Immuno-Privilege”?



Ian Galea et al. Trends in Immuol 2007
with modifications

Central Nervous System (CNS) immunology

- Missing Afferent but somewhat functional Efferent Arms-

- Autoimmune diseases in the CNS

  (Experimental Autoimmune Encephalitis , Multiple Sclerosis, Paraneoplastic Cerebellar Degeneration [PCD] against cdr2)

  - Patients with undiagnosed cancers (e.g. ovarian cancer) visit neurologists' office complaining ataxia (cerebellar signs)

  - Cancer and cerebellar cells express an common antigen cdr2, which trigger systemic CTL response (Albert ML, Darnell JC et al. Nature Med 1998)

Discussion with Dr. Paul Walker (University of Geneva)

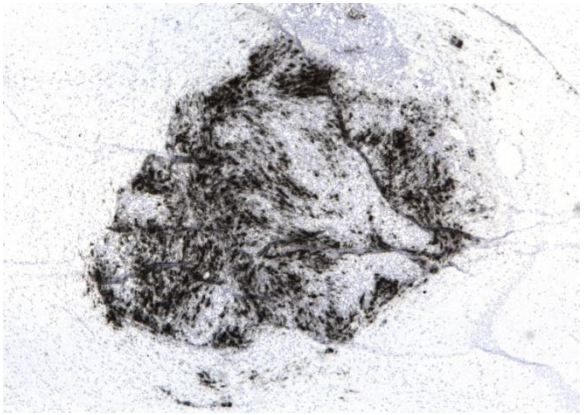
- The lack of afferent arm is relative, too (not absolute).
- Evidence for glioma antigen-specific T cells in TILs of untreated patients (e.g. high frequency of T cells specific for the $BCA_{478–486}$ peptide; Dutoit V et al. Brain 2012).
- Spontaneous anti-glioma immunity is delayed because the threshold for stimulating the afferent arm is high – and we do get a spontaneous immune response when this threshold is reached.

Critical factors mediating efficient CNS-tumor homing of T cells

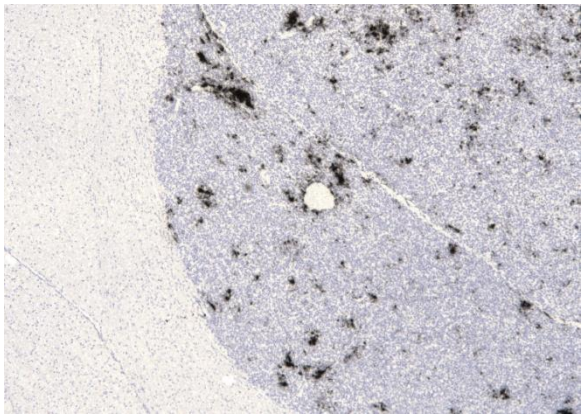
- **Very Late Activation Antigen (VLA)-4** and its ligand Vascular Cell Adhesion Molecule (VCAM)-1 (Calzascia T. et al. Immunity 2005, Sasaki K. *et al.* Cancer Res. 2007, Sasaki K. *et al.* J. Immunol. 2008, Sasaki K. *et al*. 2008)
  - Anti-VLA4 mAb Natalizumab in MS patients caused progressive multifocal leukoencephalopathy (PML) by re-activation of JC virus, suggesting T-cell immunosurveillance
- A chemokine receptor **CXCR3** and its ligands (**CXCL9-11**) including IFN-inducible protein (IP)-10 (Nishimura F. *et al.* Cancer Res. 2006, Fujita M. *et al.* J. Immunol. *2008,* Fujita M. *et al.* Cancer Res. x2 2009 and 2011)

Up-regulated expression of CXCL10 mRNA in murine GL261 glioma treated with glioma-associated antigen (GAA)-vaccines and i.m. poly-ICLC (*In situ* hybridization)

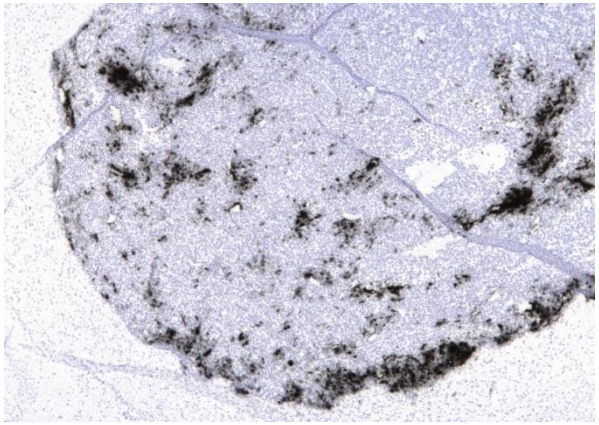
A Vaccine Plus Poly-ICLC



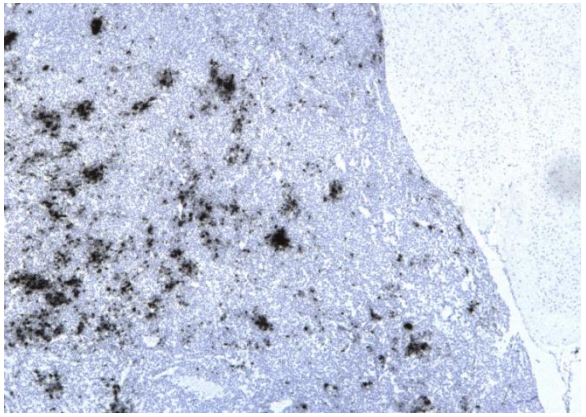
B Vaccine Alone



C Poly-ICLC Alone



D Mock-Treatment



Zhu X. *et al.* Cancer Immunol. Immunother. 2010

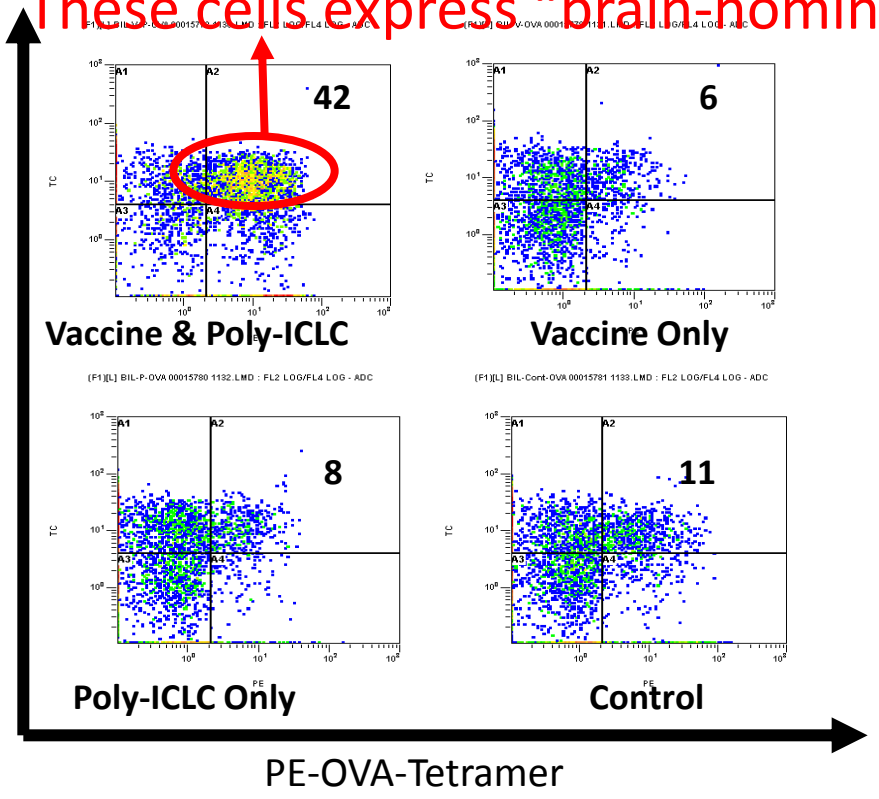
Fujita M. *et al.* Cancer Res. 2011

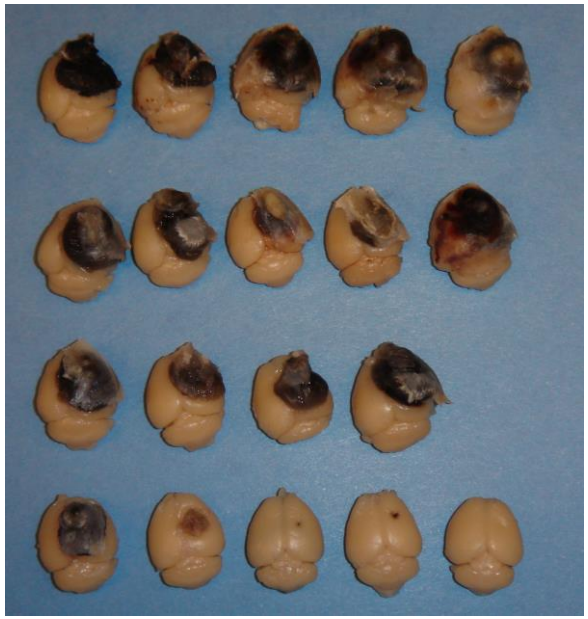
Poly-ICLC administration enhances the infiltration of antigen-specific T cells and therapeutic efficacy

Brain-Infiltrating T-cells

Anti-Tumor Effect

These cells express "brain-homing" receptors VLA-4 and CXCR3





Zhu X. Walker PR. Okada H *et al* 2007.
Zhu X. Okada H *et al.* 2010

Previous and Current Glioma Vaccine Trials in University of Pittsburgh

Study Number	Setting	Patient population	Vaccine Type	Antigens	Status	Funding Sources
UPCI 05-115	Phase I/ Recurrent WHO grade III or IV glioma	Adult	**Dendritic cells**	4 Synthetic GAA peptides	Enrollment completed Booster and follow-up ongoing	NIH **Complete** 1 R21 CA117152 Musella Foundation
UPCI 07-057	Phase I Newly Diagnosed WHO Grade 2 Astrocytoma Oligoastrocytoma	Adult	Peptide	4 Synthetic GAA peptides	Enrollment completed Booster and follow-up ongoing	NIH **Complete** 1R21CA133859 Musella Foundation
UPCI 08-135	Phase I Recurrent WHO Grade 2 Astrocytoma Oligoastrocytoma Oligodendroglioma	Adult	Peptide	4 Synthetic GAA peptides	Enrollment completed Booster and follow-up ongoing	NIH **Complete** 1R21CA133859 Musella Foundation
CHP #PRO 08030085	Phase I Newly diagnosed BSG Incompletely resected Non-brain stem HGG Recurrent LGG	**Pediatric**	Peptide	3 Synthetic GAA peptides	Open for Enrollment and Treatment	NIH **Complete** 1R21 CA149872 The Brain Tumor Society et al.
UPCI 11-136	Phase I WHO Grade 2 Astrocytoma Oligoastrocytoma Oligodendroglioma	Adult	**GBM stem cells cultured in hypoxia**	Whole GBM stem cell lysate (GBM6)	Open for Enrollment and Treatment	VABC NIH **Pending** 1R21CA177787
CHP#PRO	Phase I Pediatric Ependymoma	**Pediatric**	Peptide	3 Synthetic GAA peptides	Open for Enrollment and Treatment	NIH **Active** 1R01CA174858
UPCI 13-093	**Phase I**I Newly Diagnosed WHO Grade IV glioblastoma	Adult	**Dendritic Cells**	4 Synthetic GAA peptides	IRB Pending	NIH **Pending** R01CA183480-01

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"Immuno-Prevention" in WHO Grade II Low-Grade Glioma (LGG) Patients?

- Slow-growing (compared with Grade III or IV), but non-curable
- Tends to occur in young adults and prognosis 3 to 10+ years; More than 50% of LGG transform to High-Grade Gliomas (HGG)
- Radiation (RT) or chemotherapy not curable – Doctors often take "careful follow-up" without any active treatment – Life with a "timed bomb"
- Robust induction of type-1 T-cell response and preliminary clinical response in both adult and pediatric HGG patients in our previous phase I/II studies (Okada H. *et al*. JCO 2011; Pollack IF *et al.* JCO 2014)
- LGG patients may not be as immuno-suppressed as HGG patients and the slow growth rate of LGG should allow sufficient time to repeat multiple vaccinations
- **Can vaccination in these patients prevent progression and recurrence**?- prophylactic brain cancer vaccine?

Synthetic glioma-associated antigen (GAA) peptides and heterologous helper antigens used in the vaccine

Antigen Peptide	Presented By:	Prevalence in HG / GIIA
IL-13Rα2 $_{345\text{-}353:1A9V}$	HLA-A2	>80% / low
EphA2 $_{883\text{-}891}$	HLA-A2	75-80%/ 50%
Survivin $_{96–104:M2}$	HLA-A2	All astrocytoma (GII-IV)
WT1 $_{126\ \text{-}134:Y1}$	HLA-A2	All astrocytoma (GII-IV)
Tetanus Toxoid (Tet_{A830})	Pan-DR	

HG; high grade (grade III-IV) glioma, GIIA; grade II astrocytoma

- The vaccine was formulated as the mixture of these peptides (300 mcg/peptide) in Montanide ISA-51 for subcutaneous administration every 3 weeks x 8 times
- Poly-ICLC (20 mcg/kg) was administered intramuscularly on the day and on day 4 following each vaccine

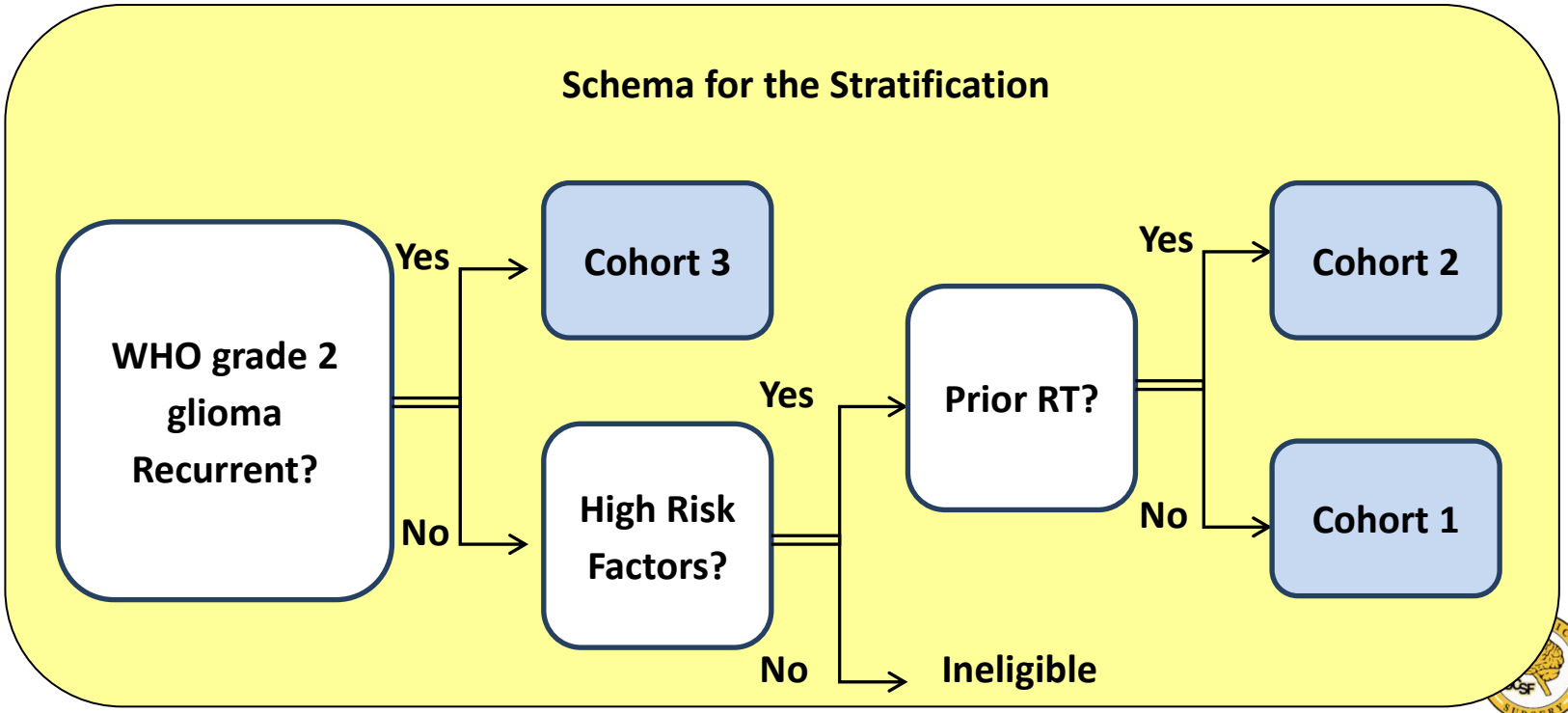
Okada H. *et al.* Clinical Cancer Res. *In Press*

Primary Objectives are to determine safety and glioma-associated antigen (GAA)-specific immune responses of the regimen.

Three Cohorts All cohorts enrolled HLA-A2+ adult WHO G2 LGG

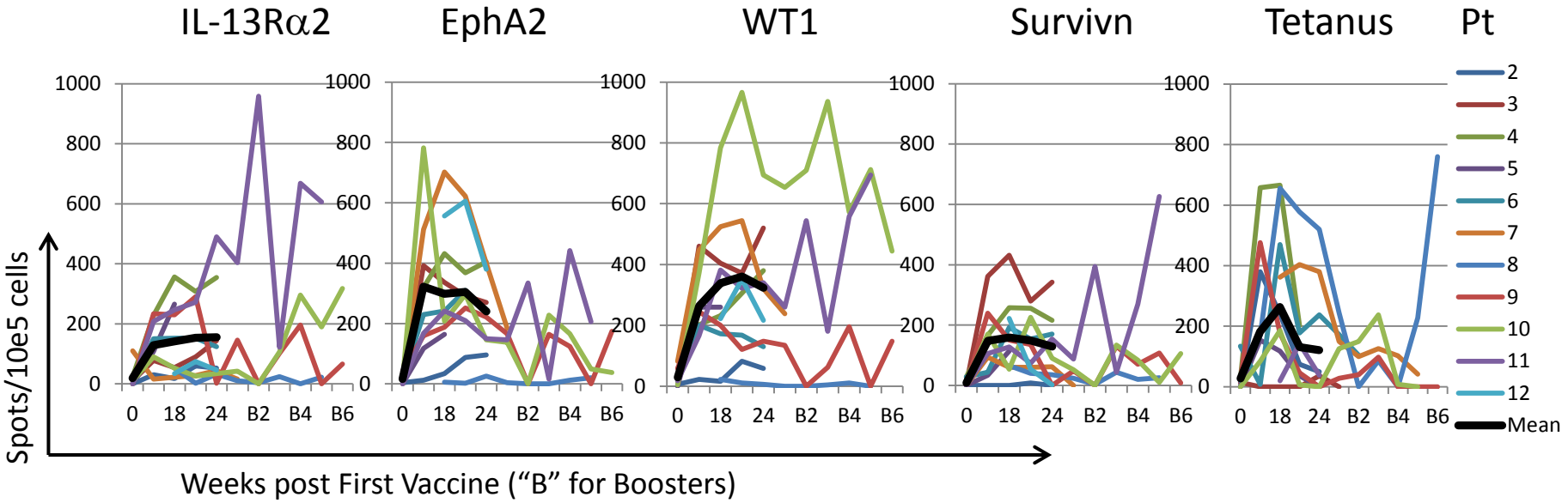
Cohorts 1 and 2- WHO grade II astrocytoma or oligoastrocytoma with "high-risk" factors – at least one of the following conditions: 1) age ≥ 40; 2) incomplete resection or 3) the tumor size is ≥ 4 cm

Cohort 3 – recurrent WHO grade II gliomas

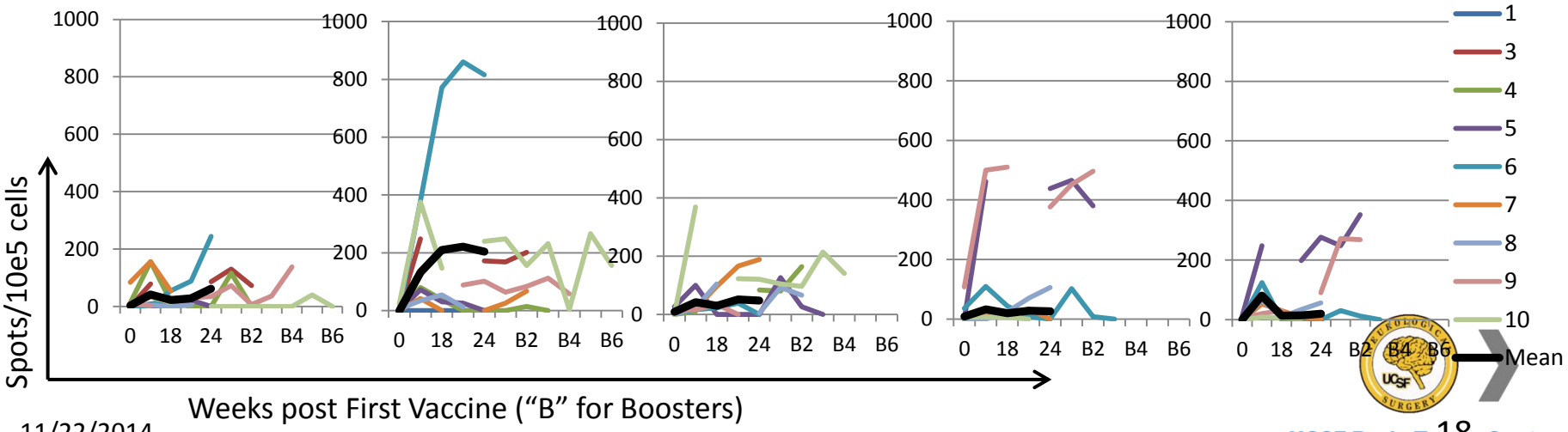


IFN-γ ELISPOT assays on each of vaccine-targeted antigens in Cohorts 1 and 3

Cohort 1 (Newly Dx)



Cohort 3 (Recurrent)



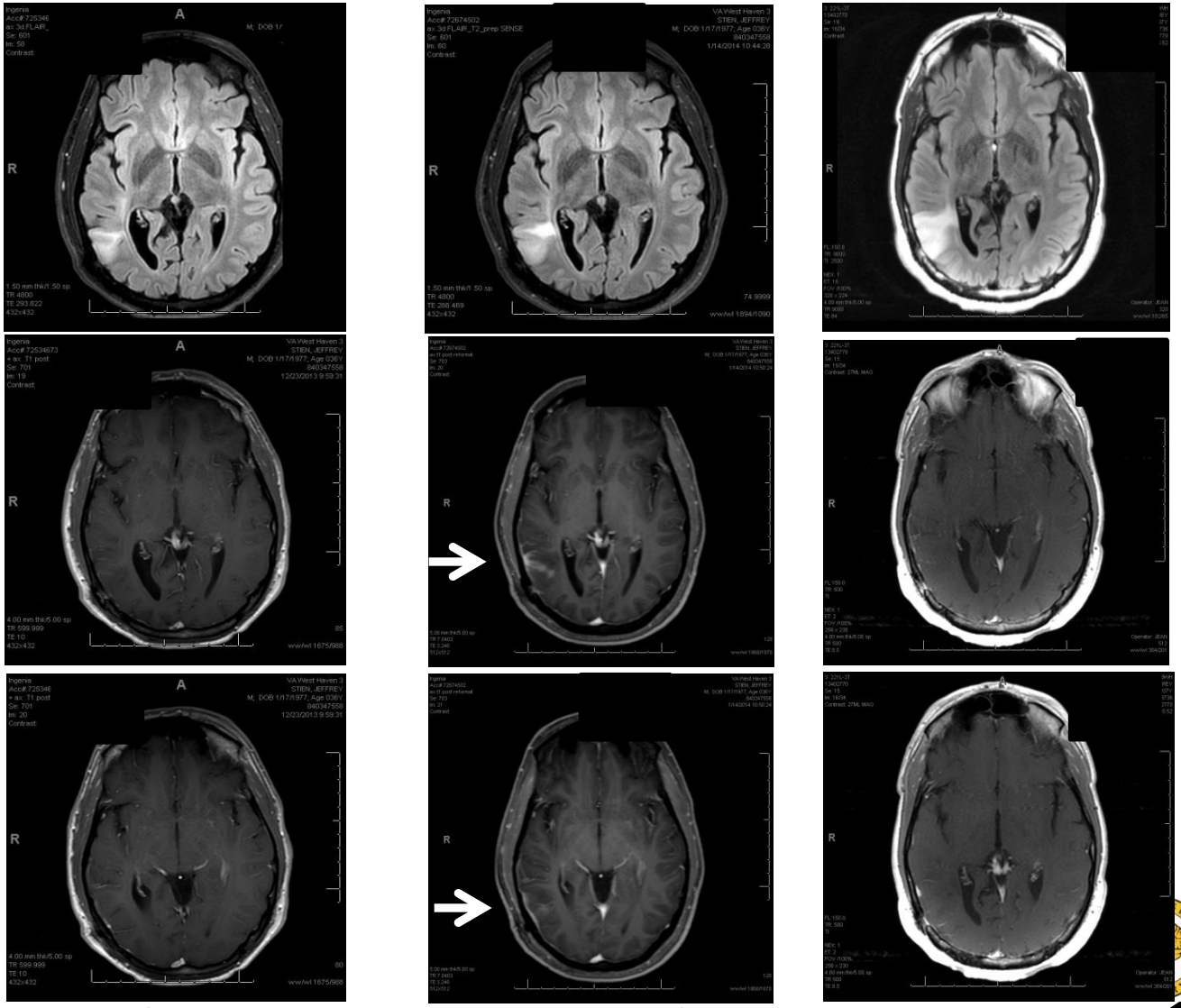
Okada H. *et al.* Clinical Cancer Res. *In Press*

Transient Appearance of Gd Enhancement in a Pt with WHO grade II Oligodendroglioma (IDH1 mut+) Receiving Vaccine

12/23/13 (30d post 2nd Vac) 1/14/14 (11d post 3rd vac) 1/22/14 (19d post 3rd vac)

T2 Flair

T1-Gd (two consecutive slices)



Summary from the pilot LGG vaccine study

- No regimen-limiting toxicity was encountered except for one case with Grade 3 fever and fatigue (Cohort 1).
- **Newly diagnosed** (Cohort 1) patients demonstrated significantly higher IFN-γ responses than **recurrent** (Cohort 3) patients and **pediatric** glioma patients receiving the same vaccine (Pollack IF Okada H et al. J. Clin Onc. 2014)
- For clinical benefit evaluation**, pseudo-progression on MRI may hamper proper PFS evaluation.** We also reported this issue multiple times (Okada H. et al. JCO 2011, Okada and Pollack 2012, Pollack IF *et al.* 2014)
- Nonetheless, these data support further development of the approach with further refinement of target antigens etc.

Overall Summary and Directions

- Understanding of central nervous system (CNS) immunology and CNS tumors is essential for developing novel immunotherapy strategies for CNS tumors

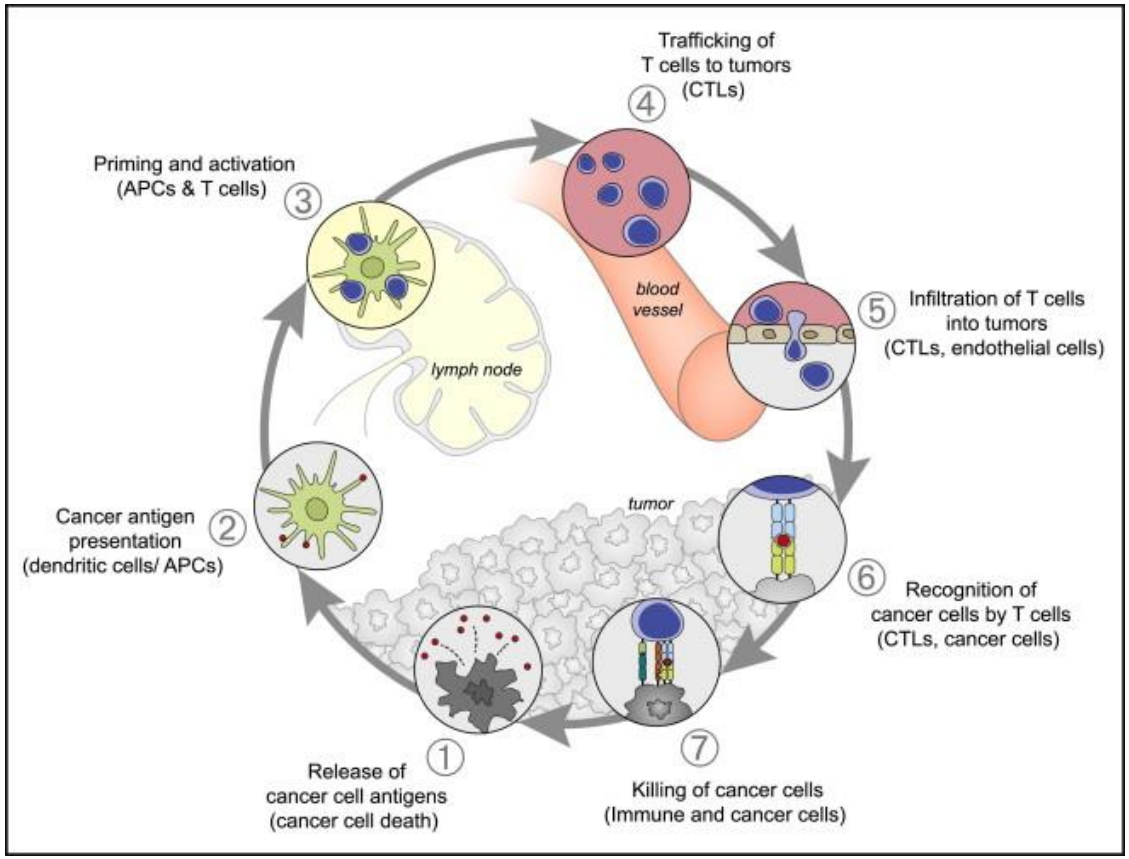
(although I did not present),

- Combination of novel technologies, such as CAR and checkpoint inhibitors, need to be investigated
- Personalized vaccines based on novel technologies, such as NGS, are being developed
- A phase II study for low-grade glioma vaccine is being developed as a concept
- Immunotherapy for pediatric gliomas (Pollack IF, Okada H. *et al.* J. Clin Oncol. 2014)

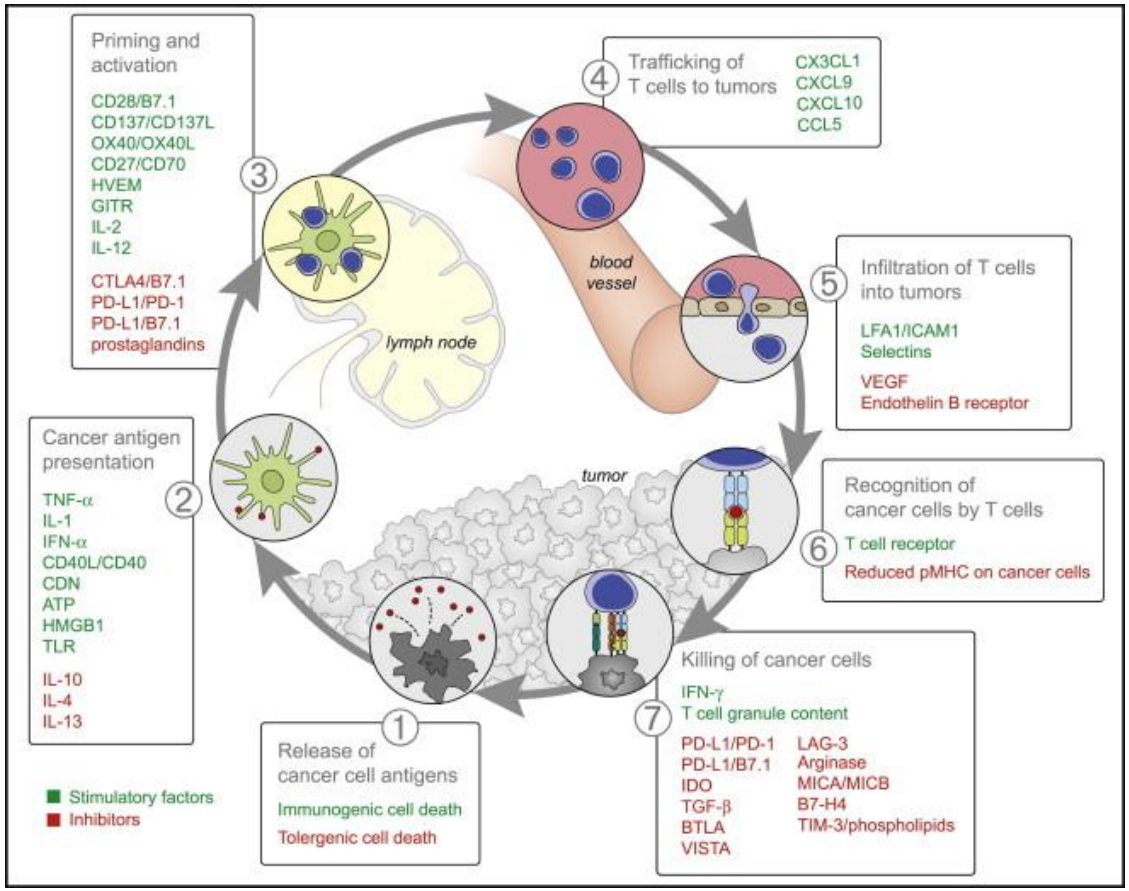
I am stopping my talk

- We will continue our collaboration!

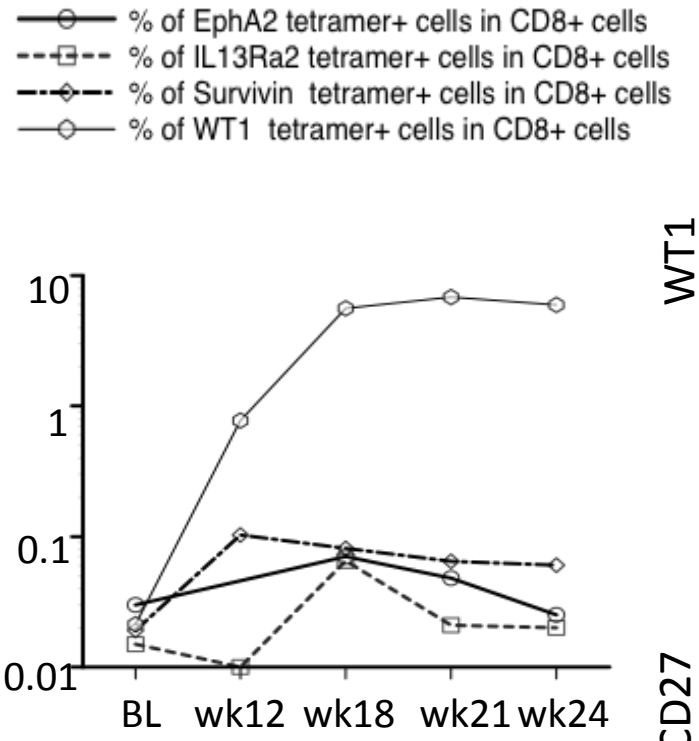
The Cancer-Immunity Cycle (Chen and Mellman, Immuity 2013)

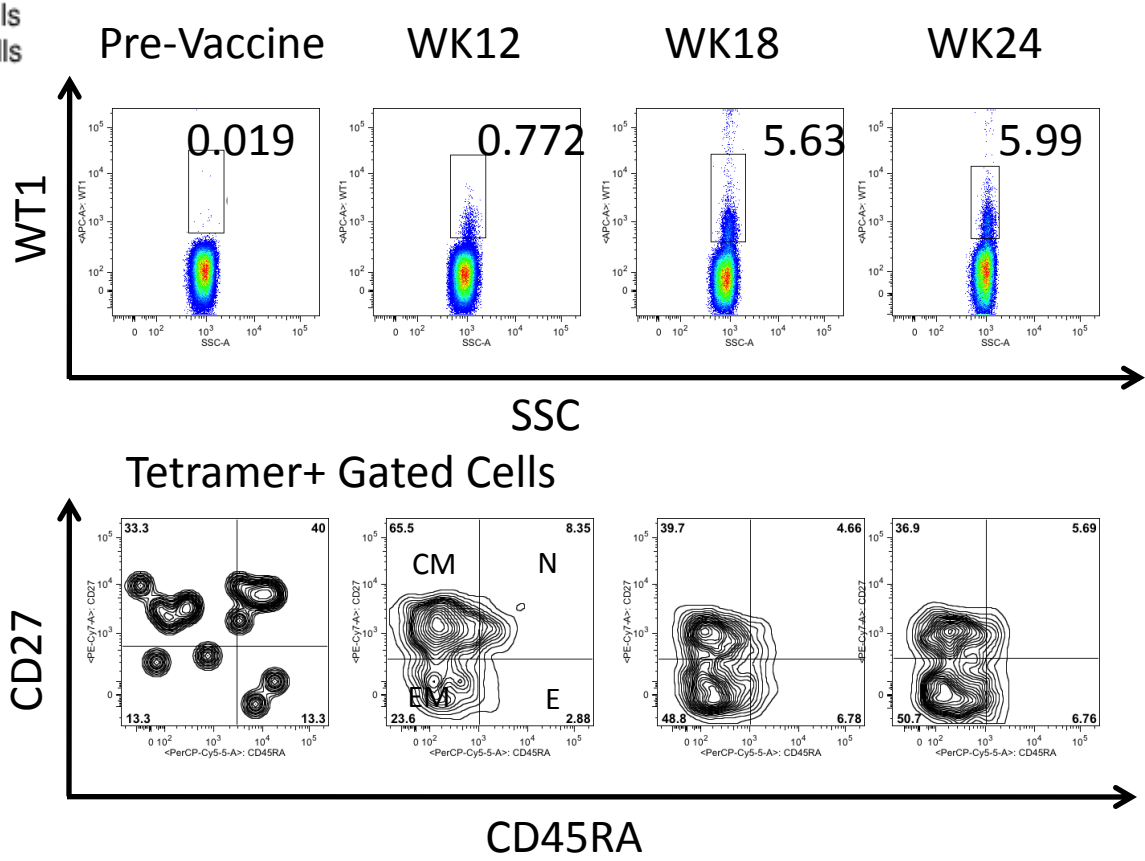


Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle (Chen and Mellman, Immuity 2013)



Robust Induction of GAA–Specific, poly functional CD8+ cell Response in a Subject with WHO Grade 2 Low Grade Glioma



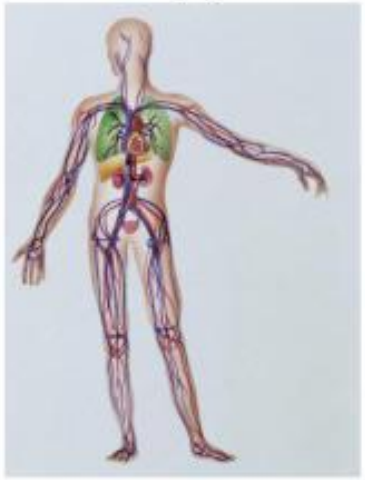


Okada H. *et al.* Clinical Cancer Res. *In Press*

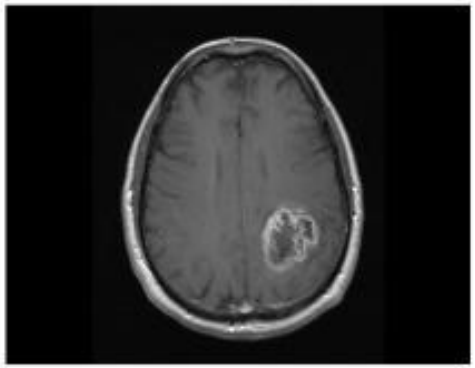
Immunosuppression among glioblastoma patients is mediated by systemic and local (microenvironment) factors

GLIOBLASTOMA

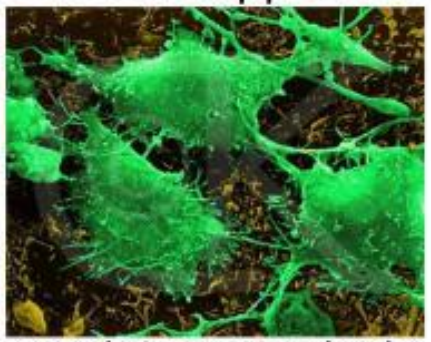
Systemic Immunosuppression



1. Decreased T-cell responsiveness
2. Increased circulating Tregs (CD4+/CD25+/FoxP3+)
3. Diminished IgG production

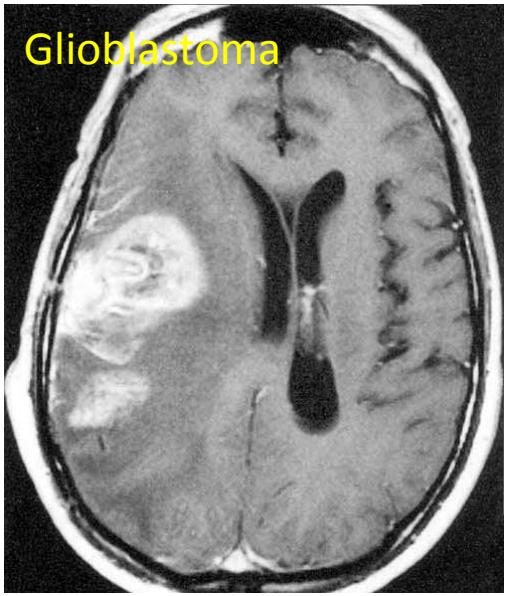


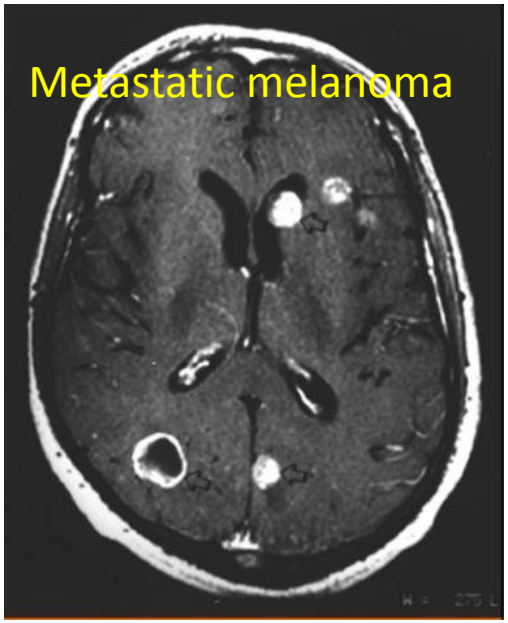
Local (microenvironment) Immunosuppression



1. Downregulation MHC molecules
2. Increased infiltrating Tregs (CD4+/CD25+/FoxP3+)
3. Hypoxia mediated impaired T cell function
4. Secretion of immunoinhibitory cytokines (TGF-β, VEGF, IL-10, prostaglandin E2, LLT-1)
5. Immunosuppressive microglia/TAM (up to 40% GBM mass!)
6. GBM expression of Fas ligand (apoptosis of activated T cells)
7. Increased expression PD-L1

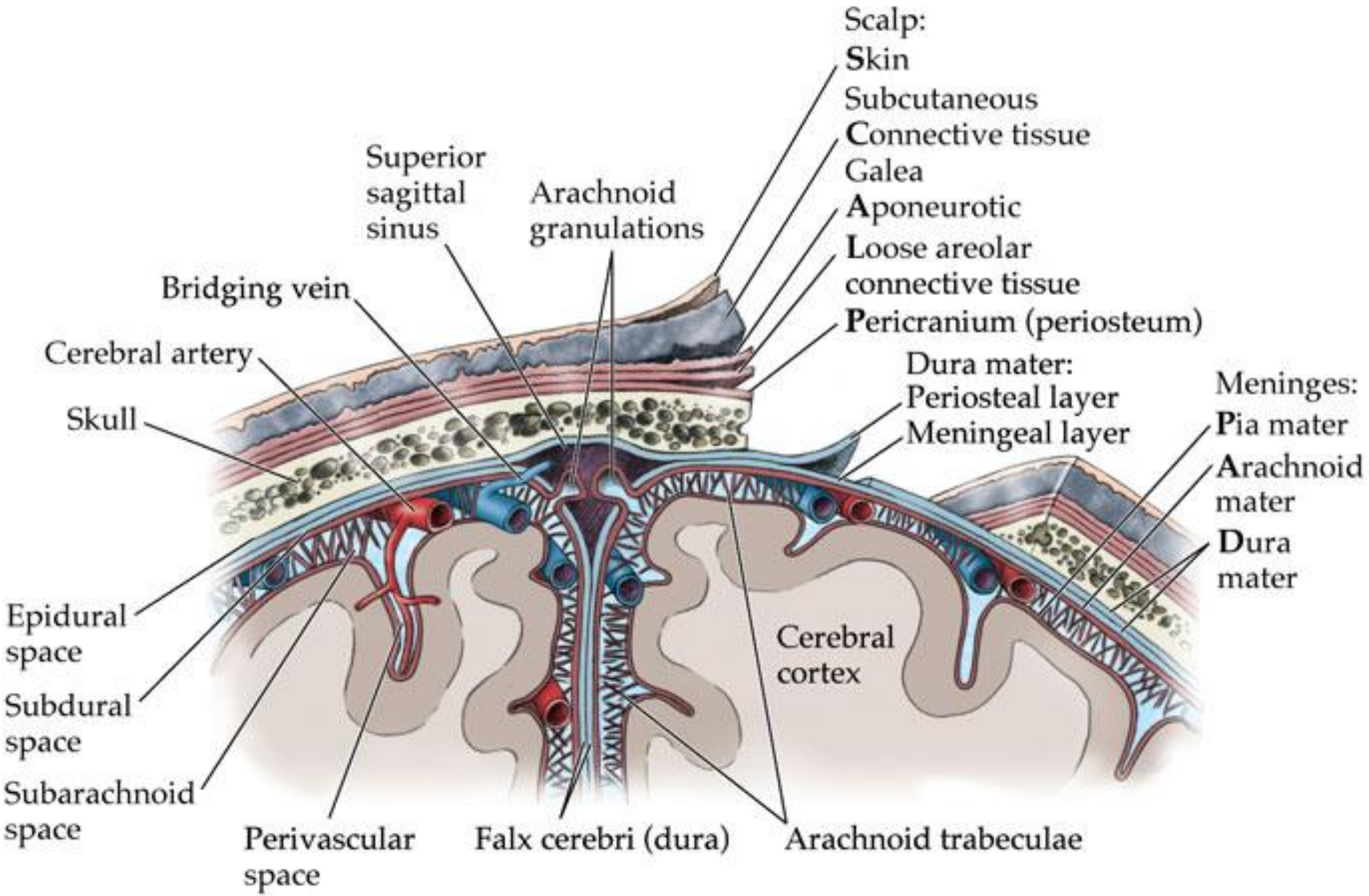
Reardon D et al. 2013



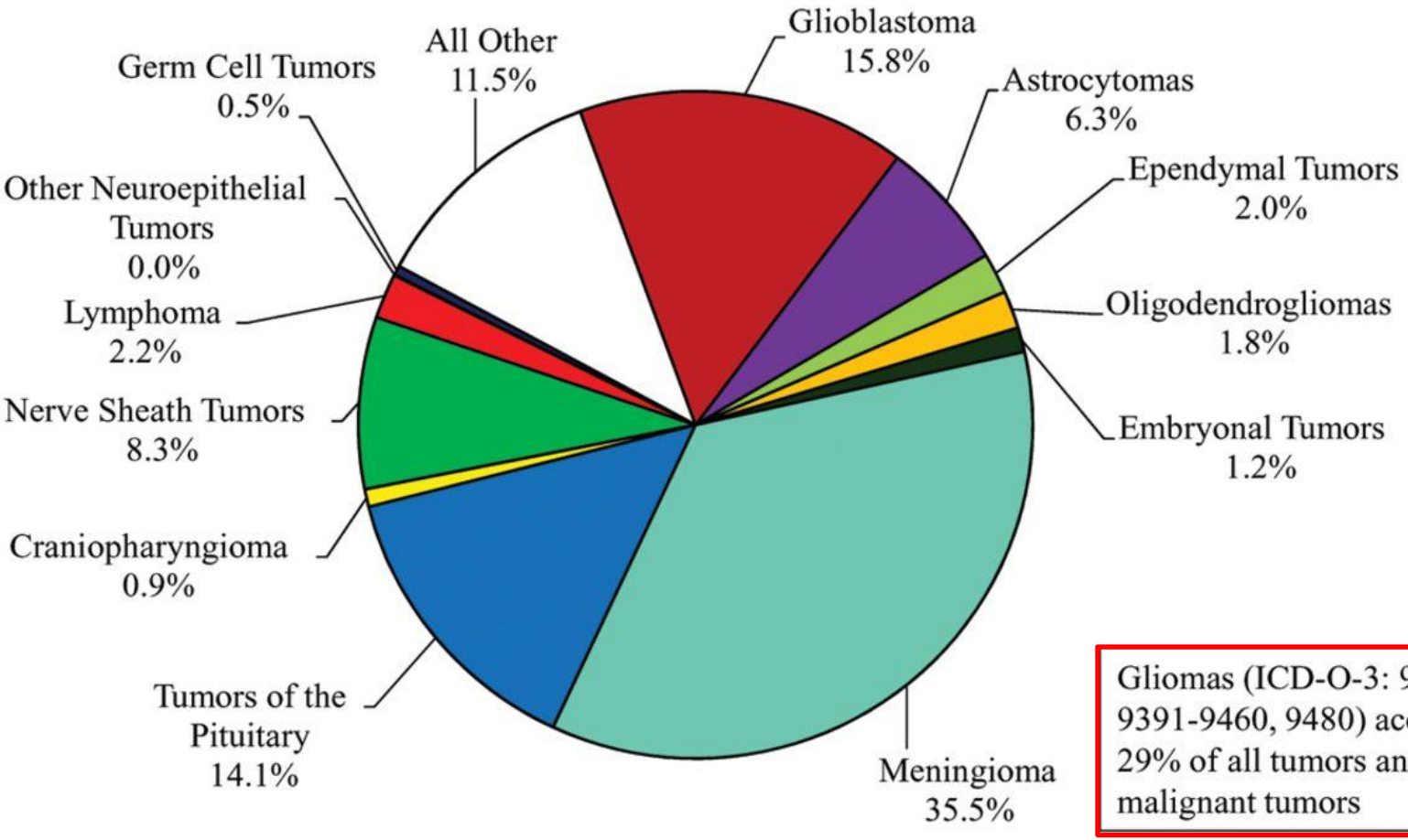


- Primary Brain Tumor
  - Tumors that originate in the CNS
  - Approx. 40,000 pts/year in the USA
  - e.g. gliomas (WHO grade 1-4) and meningiomas
- Metastatic Brain Tumor
  - Most common primary sites are lung, breast, kidney and melanoma
  - Approx. 170,000 pts/year in the USA ↗
  - 20-25% of all cancer
  - **As our ability to diagnose and treat primary tumors improves, a shift in mortality towards metastatic disease has been observed.**

On MRI, contrast agents such as gadolinium can inform us about CNS pathology only when the BBB has been compromised



Distribution of Primary Brain and Central Nervous System (CNS) Tumors by Histology (N = 311,202)



Gliomas (ICD-O-3: 9380-9384, 9391-9460, 9480) account for 29% of all tumors and 80% of malignant tumors

Dolecek T A et al. Neuro Oncol 2012;14:v1-v49