

Discussion for Abstract 10

ROLE OF PDL1 EXPRESSION AND TUMOR INFILTRATING LYMPHOCYTES IN GLIOBLASTOMA AND BRAIN METASTASES

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Disclosure Information

Conflicts of Interests:

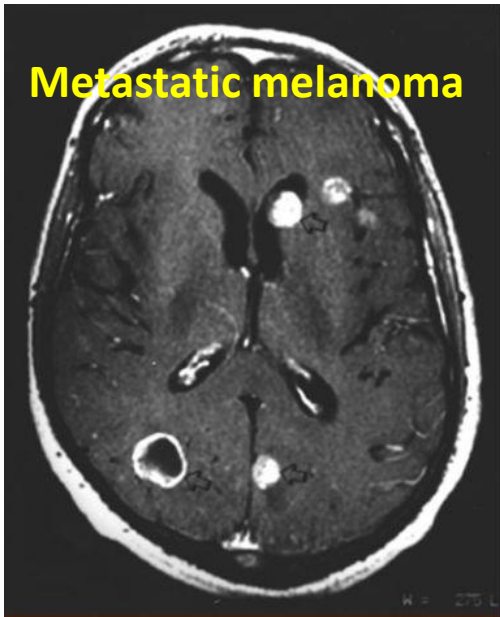
Hideho Okada, MD, PhD is an inventor of the IL-13R α 2 (345-353:1A9V) peptide, for which an exclusive licensing agreement has been executed with Stemline, Inc.

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

Glioblastoma

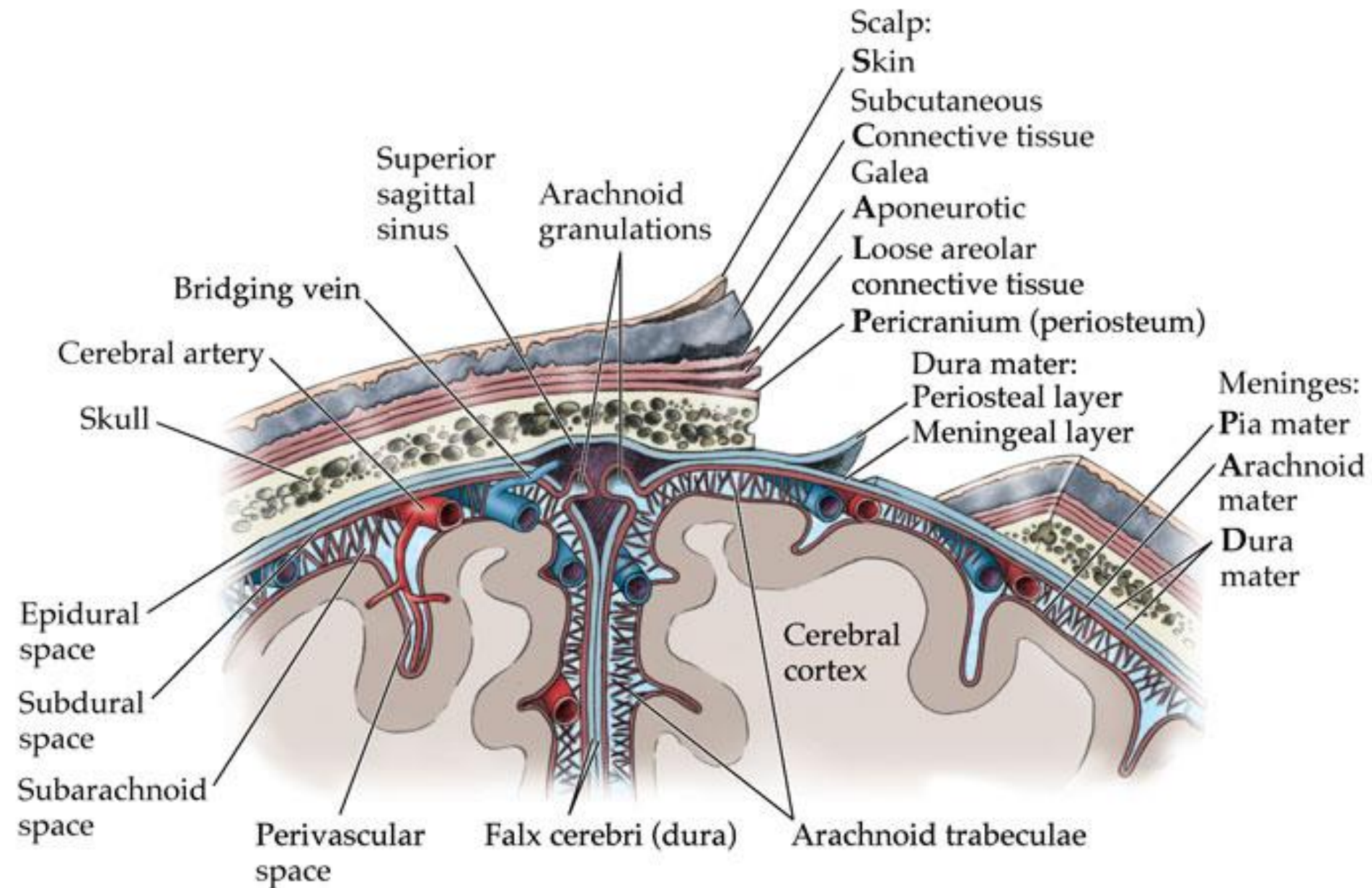


Metastatic melanoma

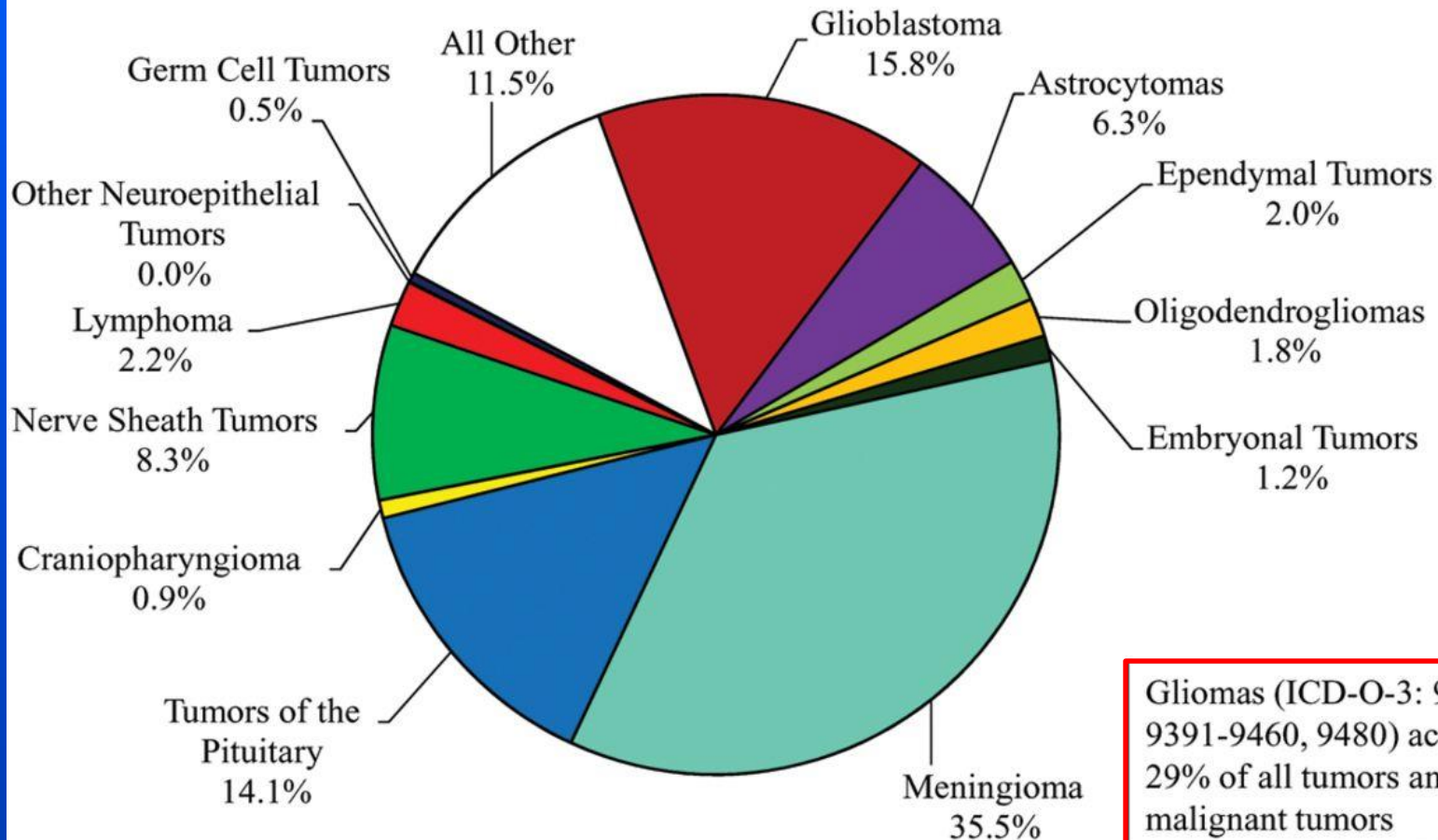


- Primary CNS Tumor
 - Tumors that originate in the CNS
 - Approx. 40,000 pts/year in the USA
 - e.g. gliomas (WHO grade 1-4) and meningiomas
- Metastatic Tumor
 - Most common primary sites are lung, breast, kidney and melanoma
 - Approx. 170,000 pts/year in the USA
 - 20-25% of all cancer
 - **As our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



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

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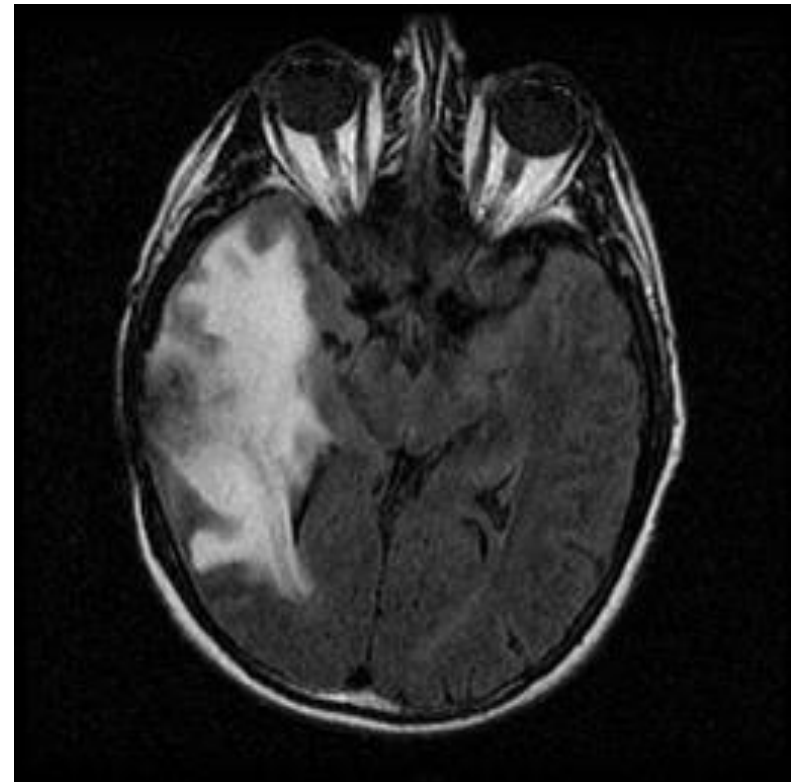
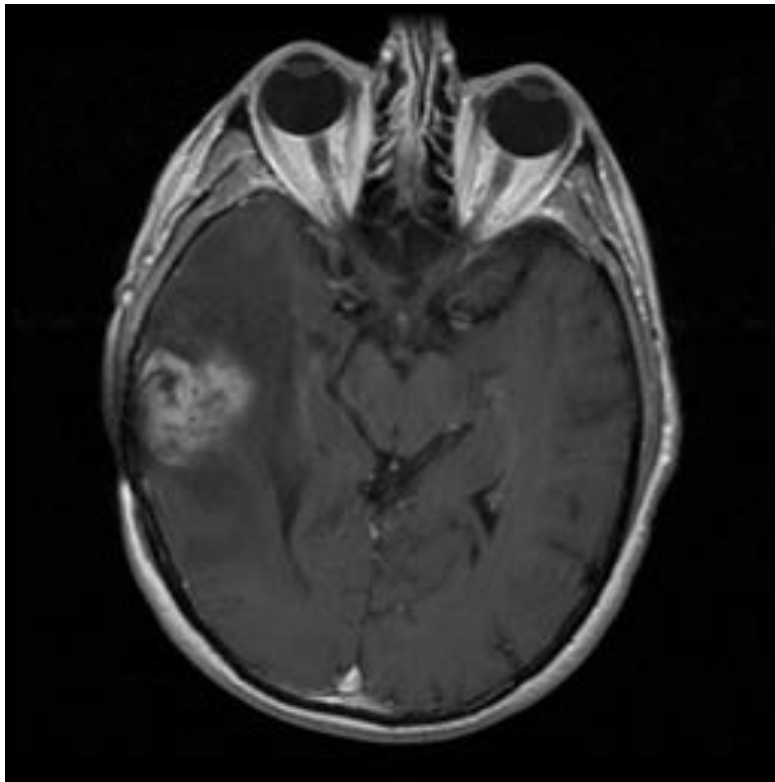
The ESMO Symposium on Immuno-oncology 2014



Neuro-Oncology⁵

A glioblastoma case

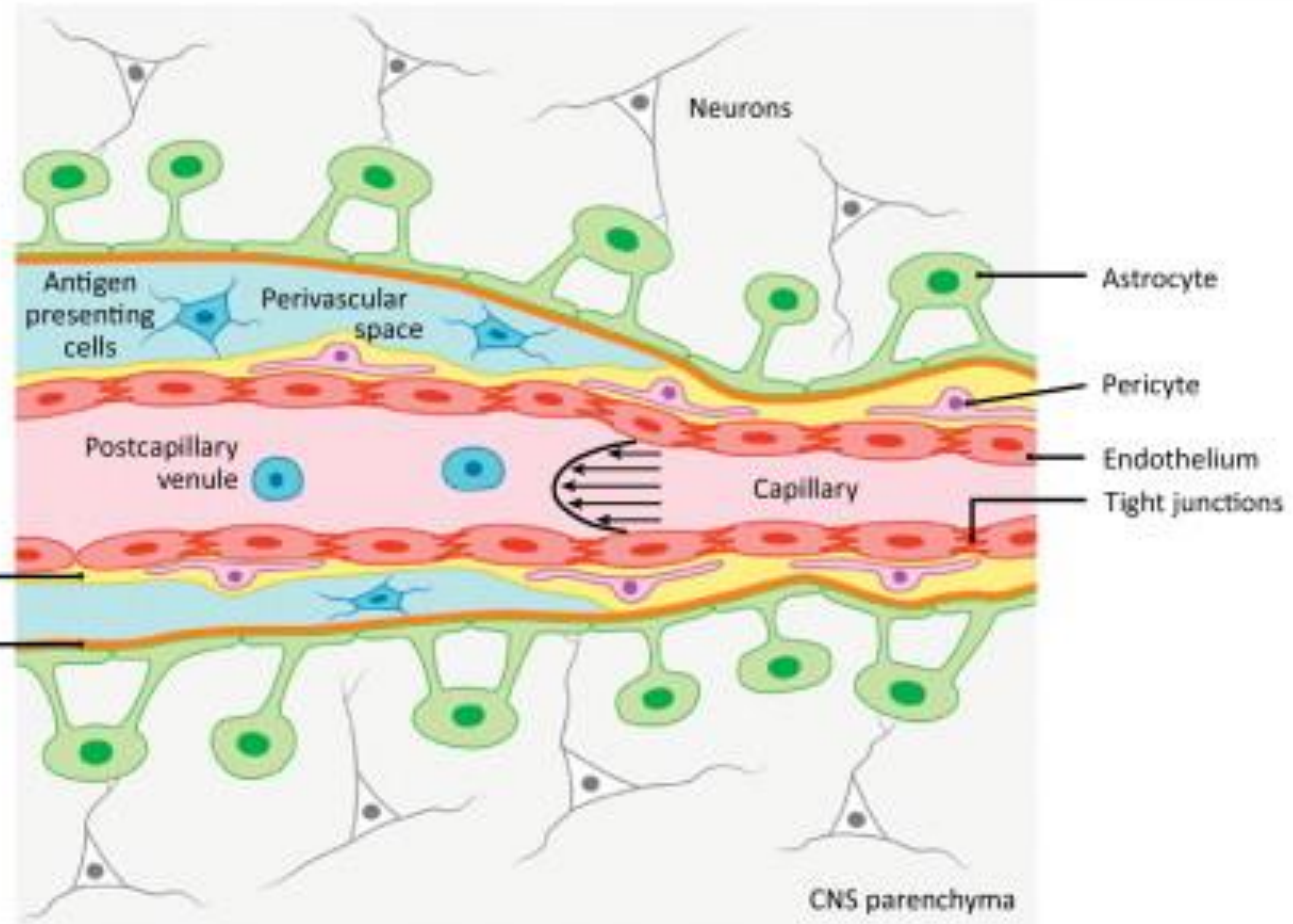
T1 Gadolinium (Gd)-enhanced (Left) vs. T2 Flair (Right) images



- Gd-enhancement in the left panel indicates mechanical disruption of BBB
- Tumor cells disseminate throughout the hemisphere as seen as T2-Flair signals

Neuroanatomy of the vascular blood–brain barrier (BBB)

Perivascular
Space with CSF



TRENDS in Immunology

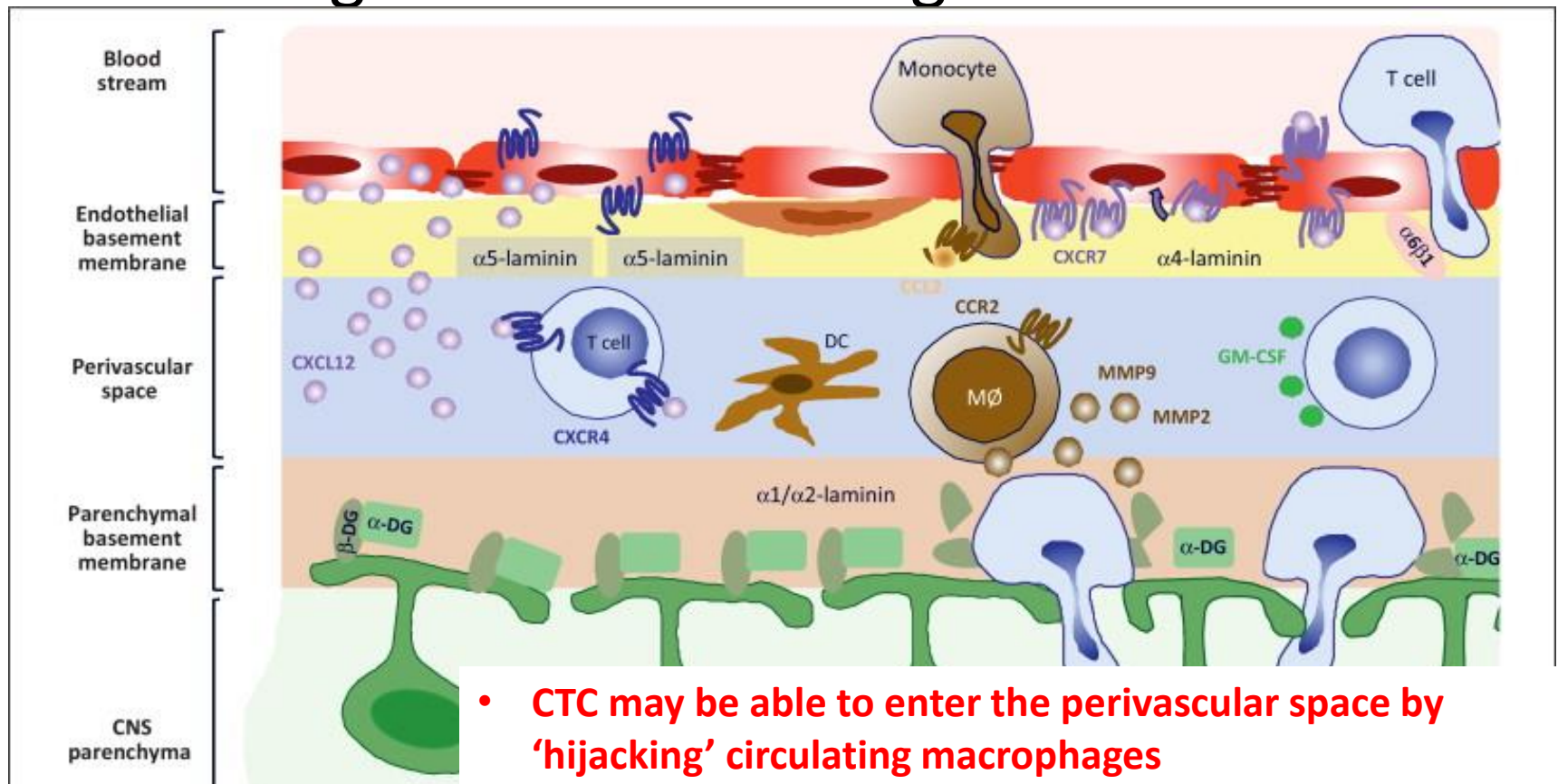
Engelhardt B, Ransohoff RM. Trends Immunol 2012.
The ESMO Symposium on Immuno-oncology 2014

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UCSF Brain Tumor Center

Molecular mechanism involved in T cell migration across the glia limitans



- CTC may be able to enter the perivascular space by 'hijacking' circulating macrophages

- Antigen-specific interaction between APC-T-cells
 - A variety of chemokines, e.g., CXCL10-CXCR3 and CCL20-CCR6, are involved
- DG; dystroglycan from the astrocyte

TRENDS in Immunology

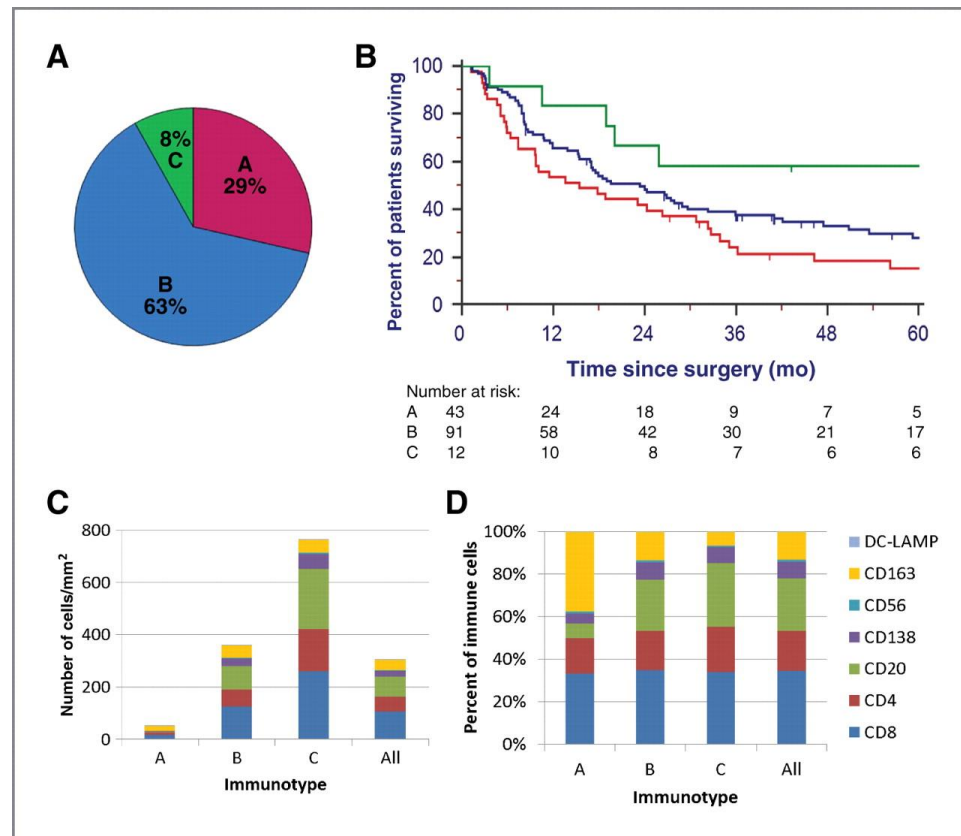
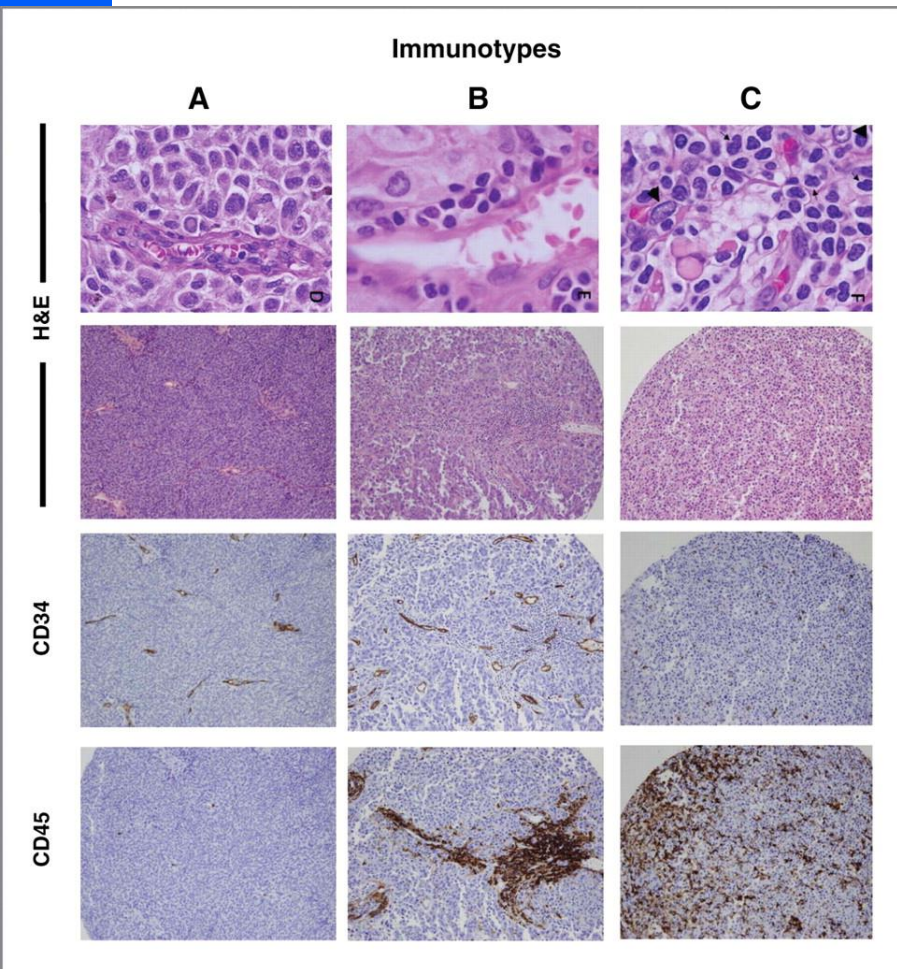
Engelhardt B, Ransohoff RM. Trends Immunol 2012.

Transmigration of systemic immune cells to CNS

-implications for CNS tumor immunotherapy-

- An accumulation of inflammatory cells in the perivascular space, followed by infiltration into the brain parenchyma, is often a characteristic of neuropathologies such as T cell recruitment in MS (Engelhardt, 2008).
- Secondary stages of immune cell invasion from the perivascular space into the brain parenchyma may rely on expression of inducible **MMP-2** and **MMP-9**, which may cause degeneration or retraction of astrocytic end-feet (Bechmann et al., 2007).
- These remind us of implications from a study by Erdag G and Slingluff CL et al. (Cancer Res 2012) Immunotypes A, B and C.

Immunotype frequency, prognosis, and cellular composition.



Erdag G and Slingluff CL et al. Cancer Res
2012;72:1070-1080

Critical factors mediating efficient CNS-tumor homing of T cells and anti-tumor efficacy

- **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)

Recent studies (selected) of immunotherapy approaches in BM and GBMs

- **TIL therapy** for brain melanoma mets- 7 CR (41%) and 6 PR in 17 patients (Hong JJ. Rosenberg SA *et al.* Clin Cancer Res. 2010;16:4892-8)
- Response (10-24%) of melanoma brain mets to **Ipilimumab** alone (Margolin K *et al.* 2012) or combo with fotemustine (Di Giacomo AM *et al.* 2012) or 40% with RT (Silk AW *et al.* 2013).
- **In GBM and gliomas**, a variety of studies have shown preliminary signs of efficacy, including EGFRvIII vaccine (Celldex), DC (DCvax) and our Phase I/II α -type 1 DC vaccine with poly-ICLC (Okada H. *et al.* J Clin Oncol, 2011)

Key Questions and Comments

- Expression of PD-L1 in metastatic brain tumors- did primary or other systemic metastatic tumors in the same individual express similar levels of PD-L1?
- What if the survival assessment was made based on the density of immune cells in the tumor tissue but not in the perivascular space?

I am stopping here



– though our work will
never stop at any time!
THANK YOU!