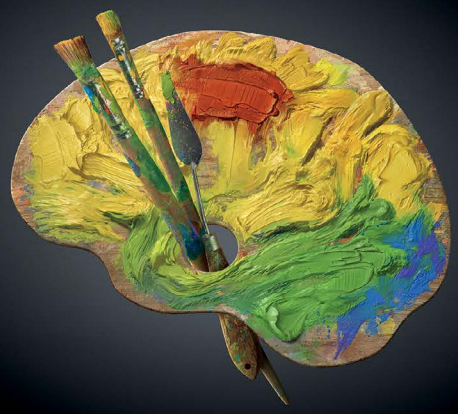
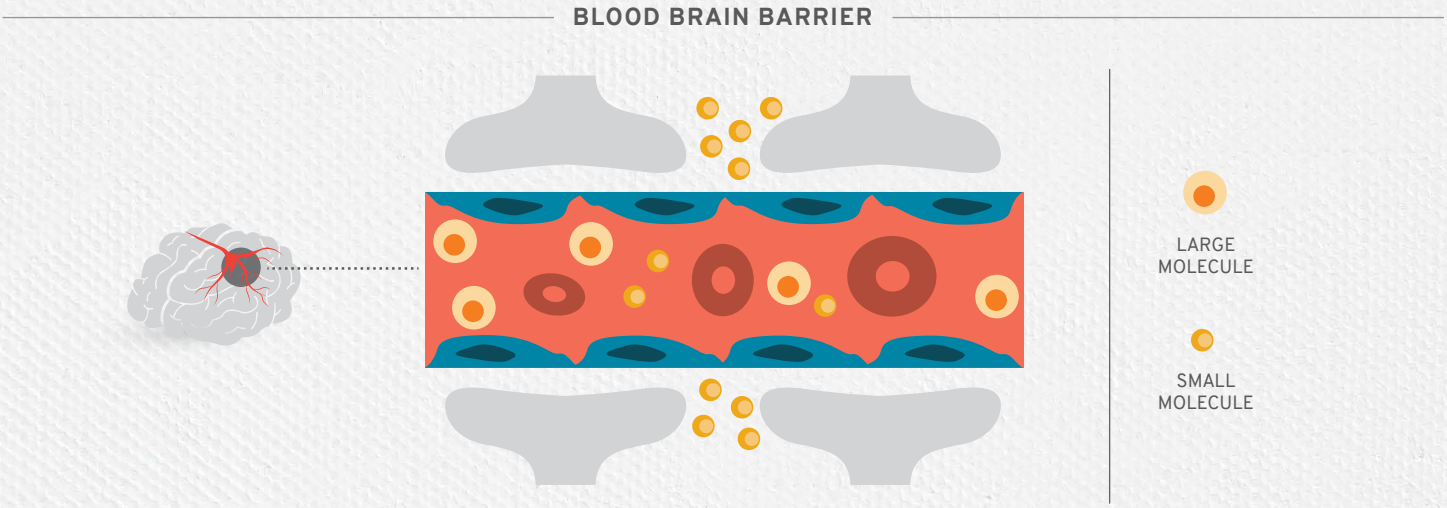
IT'S TIME TO PAINT A BETTER PICTURE OF HIGH GRADE GLIOMA[a]

IMMUNE SUPPRESSION AND THE TUMOR MICROENVIRONMENT IN HIGH GRADE GLIOMA



The blood brain barrier provides the first line of defense

The uniquely structured and highly selective blood brain barrier protects the central nervous system. This results in many pharmacologic agents failing to achieve clinically effective levels in the brain.[1-3]



High grade glioma is capable of inhibiting the immune system by remodeling the tumor microenvironment

Even some treatments that have been successful in overcoming the challenges of the blood-brain barrier have failed to provide durable benefits. In part, this is because the tumor microenvironment poses challenges to effective treatment due to tumor mechanisms that aid in immune evasion.[3]

[a]High grade glioma includes grade 3 (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic ependymoma) and grade 4 (glioblastoma) gliomas, as defined by World Health Organization criteria.

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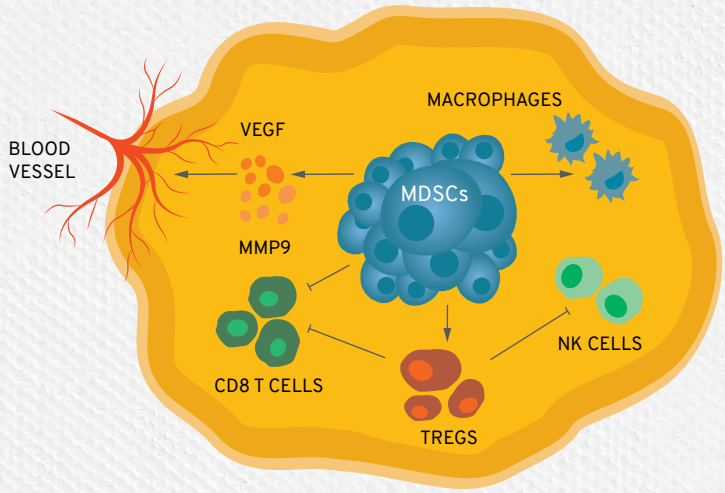
T-cell dysfunction is a key mechanism for immune suppression

A functional T-cell repertoire is necessary for adequate immune surveillance and the initiation and maintenance of productive antitumor immune responses.[4] High grade glioma can inhibit the immune system by causing T-cell dysfunction through multiple processes, including tolerance.[4] Specifically, high grade glioma can take control of mechanisms of immune tolerance, which normally prevent aberrant autoimmunity, to promote T-cell unresponsiveness thereby reducing or avoiding antitumor immune responses.[4]

Multiple cell types are involved in immune suppression/dysfunction in high grade glioma, including myeloid-derived suppressor cells (MDSCs)

MDSCs, and other immunosuppressive myeloid cells such as tumor associated macrophages (TAMs), help the tumor evade detection via immune-mediated killing protection (eg, cluster of differentiation 8 [CD8] cells, natural killer [NK] cells), tumor microenvironment remodeling, premetastatic niche creation, and facilitation of epithelial-to-mesenchymal transitions.[5]

MDSCs



MDSCs have been shown to produce essential mediators of neoangiogenesis such as vascular endothelial growth factor (VEGF) and matrix metallopeptidase 9 (MMP9) at the tumor site.[5] They also support recruitment and expansion of other immunosuppressive cells in addition to directly supporting tumor growth and metastasis.[6-8]

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Overcoming the challenges posed by the blood brain barrier, reducing immune system suppression, and enhancing immune activation within the microenvironment may play key roles in addressing unmet needs in the treatment of high grade glioma. Go to **FUTUREofGLIOMA.com** for informative videos featuring prominent experts in neuro-oncology discussing the challenges of high grade glioma.

Tregs = regulatory T cells.

References: **1.** Gao Z, Chen Y, Cai X, et al. *Bioinformatics*. 2017;33(6):901-908. **2.** Omidi Y, Barar J. *Bioimpacts*. 2012;2(1):5-22. **3.** Tomaszewski W, Sanchez-Perez L, Gajewski TF, et al. *Clin Cancer Res*. 2019. doi:10.1158/1078-0432.CCR-18-1627. [Epub ahead of print]. **4.** Woroniecka KI, Rhodin KE, Chongsathidkiet P, et al. *Clin Cancer Res*. 2018;24(16):3792-3802. **5.** Marvel D, Gabrilovich DI. *J Clin Invest*. 2015;125(9):3356-3364. **6.** Gieryng A, Kaminska B. *Contemp Oncol (Pozn)*. 2016;20(5):345-351. **7.** Schiffer D, Annovazzi L, Casalone C, et al. *Cancers (Basel)*. 2018;11(1). pii: E5. **8.** Ho IAW, Shim WSN. *Biomed Res Int*. 2017;2017:9634172. doi:10.1155/2017/9634172.

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