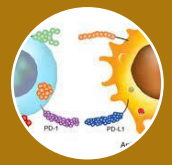
EFFECT OF ACIDOSIS ON TUMOR PHENOTYPE

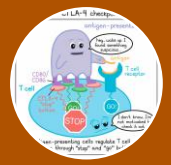
1. Increases Radiotherapy Resistance

2. Increases Chemotherapy Resistance



3. Increases Immuno-Oncology Therapy Resistance

4. Promotes Metastasis



5. Hinders Immune Cell Function

6. Higher Mutation Rate

7. Promotes Cancer Stem Cell Phenotype / Angiogenesis

Acidic Tumor Microenvironment

Under hypoxic conditions, there may be insufficient O_2 for radiosensitisation[1]

Doxorubicin becomes highly ionized, inhibiting uptake across cell membranes in low pH[2]

Acidic pH can lead to increased expression of immune checkpoint proteins including PD1/PDL1, CTLA4, TIGIT, TIM3, LAG3 CD226[3]

Varied mechanisms, e.g., increased proteinase expression and matrix metalloprotease activity thereby degrading extracellular matrix aiding cancer cell invasion and migration[4-10]

Inhibits effector T and NK cells, while enhancing protumor macrophage polarization immunosuppression *via* MDSCs[11-13]

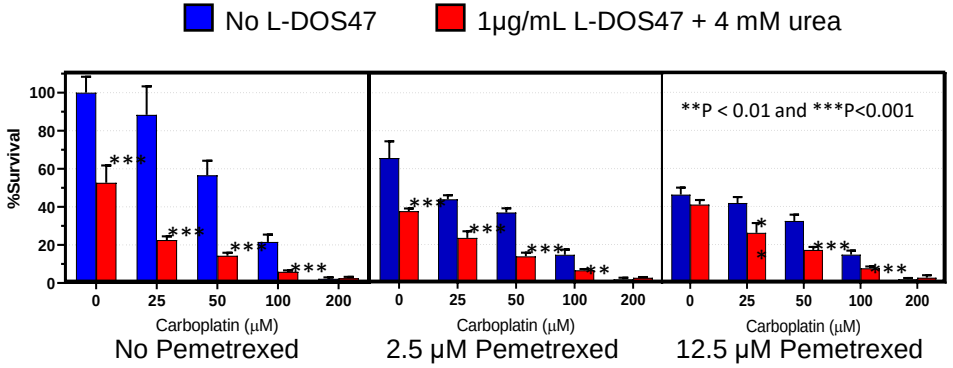
Reversed gradient of acidic extracellular pH and alkaline pH inside cells inhibits apoptosis as caspase activation requires acidic pH. Basic intracellular pH also promotes DNA synthesis and cell proliferation, leading to tumor growth and higher rates of mutation in cancer cells, favoring cellular survival resulting in rapid disease progression[1,14-16]

Acidic pH enhances glioma cell malignancy, promoting expression of stem cell markers and promoting angiogenesis by increasing VEGF *via* an acidic pH-driven increase in HIF-2α. Increases expression of IL-6, IL-8 and VEGF, supporting tumor progression and angiogenesis[17-20]

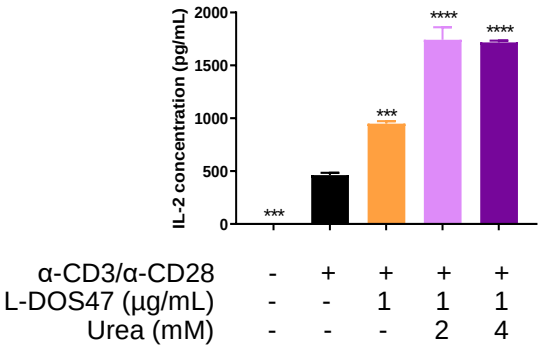
Sources: [1]Webb BA *et al. Nat Rev Cancer* 2011; [2]Gerweck LE *et al. Mol Cancer Ther* 2006; [3]Hyung-seung J *et al. Journal of Controlled Release* 2019; [4]Parks SK *et al. Nat Rev Cancer* 2013; [5]Gatenby RA et al. *Br J Cancer* 2007; [6]Rofstad EK *et al. Cancer Res* 2006; [7]Walenta S et al. *Cancer Res* 2000; [8]Gatenby RA et al. *Cancer Res* 2006; [9]Bourguignon LY *et al. J Biol Chem* 2004; [10]Estrella V *et al. Cancer Res.* 2013; [11]Nakagawa Y *et al. Immunol Lett* 2015; [12]Chanmee T *et al. Cancers* 2014; [13]Nasi A *et al. J Immunol* 2013; [14]Matsuyama S *et al. Nat Cell Biol* 2000; [15]Schreiber R *et al. J Membr Biol* 2005; [16]Ward C *et al. Cancer Treat Rev* 2013; [17]Pillai SR *et al. Cancer Metastasis Rev.* 2019; [18]Kareva I *et al. Cancer Res*. 2013; [19]Xu L *et al. J Biol Chem* 2002; [20]Rafiee P *et al. Am J Physiol Gastrointest Liver Physiol* 2009.

NEUTRALIZING ACIDOSIS IMPROVES OUTCOME (Numbered per categories on previous slide)

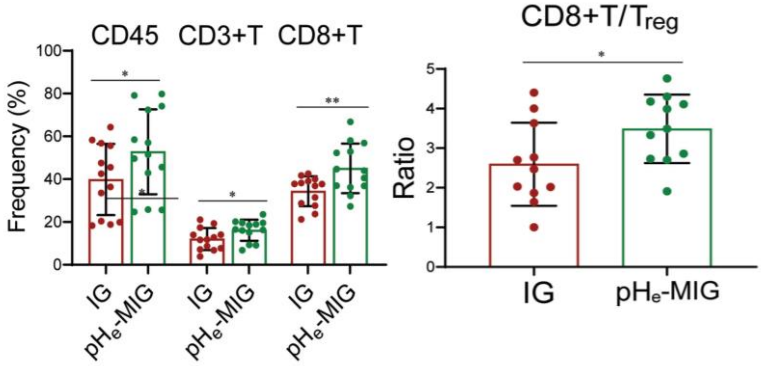
2. Enhanced chemotherapeutic efficacy



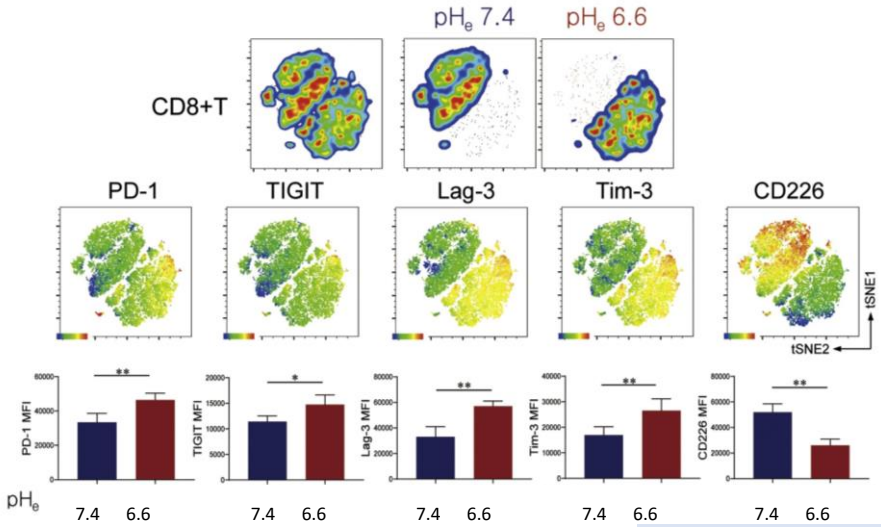
5. Increased IL-2 supporting T cell function



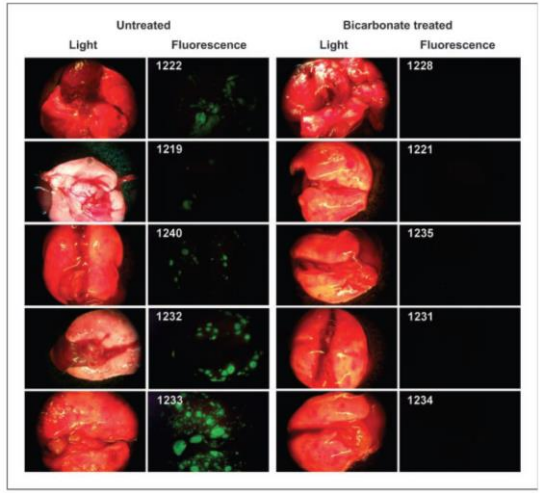
Increased TIL Migration[1]



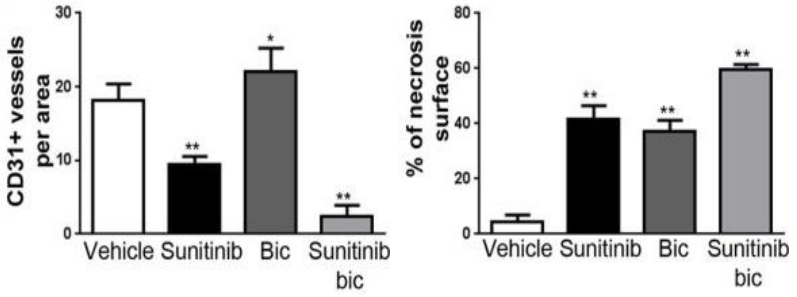
3. Reduced Immune Checkpoint Protein Expression[1]



4. Decreased metastasis[2]



7. Reduced angiogenesis & increased necrosis[3]



Sources:
[1]Jin H-S *et al Journal of Controlled Release*, 2019
[2]Robey IF *et al Cancer Res* 2009
[3]Faes S *et al. Oncotarget* 2016

Additional data with LDOS-47 being currently generated