Glioma Associated Immune Cells: Potential Targets for Novel Theranostics Molecules

Ac225 User-group
8/30/22

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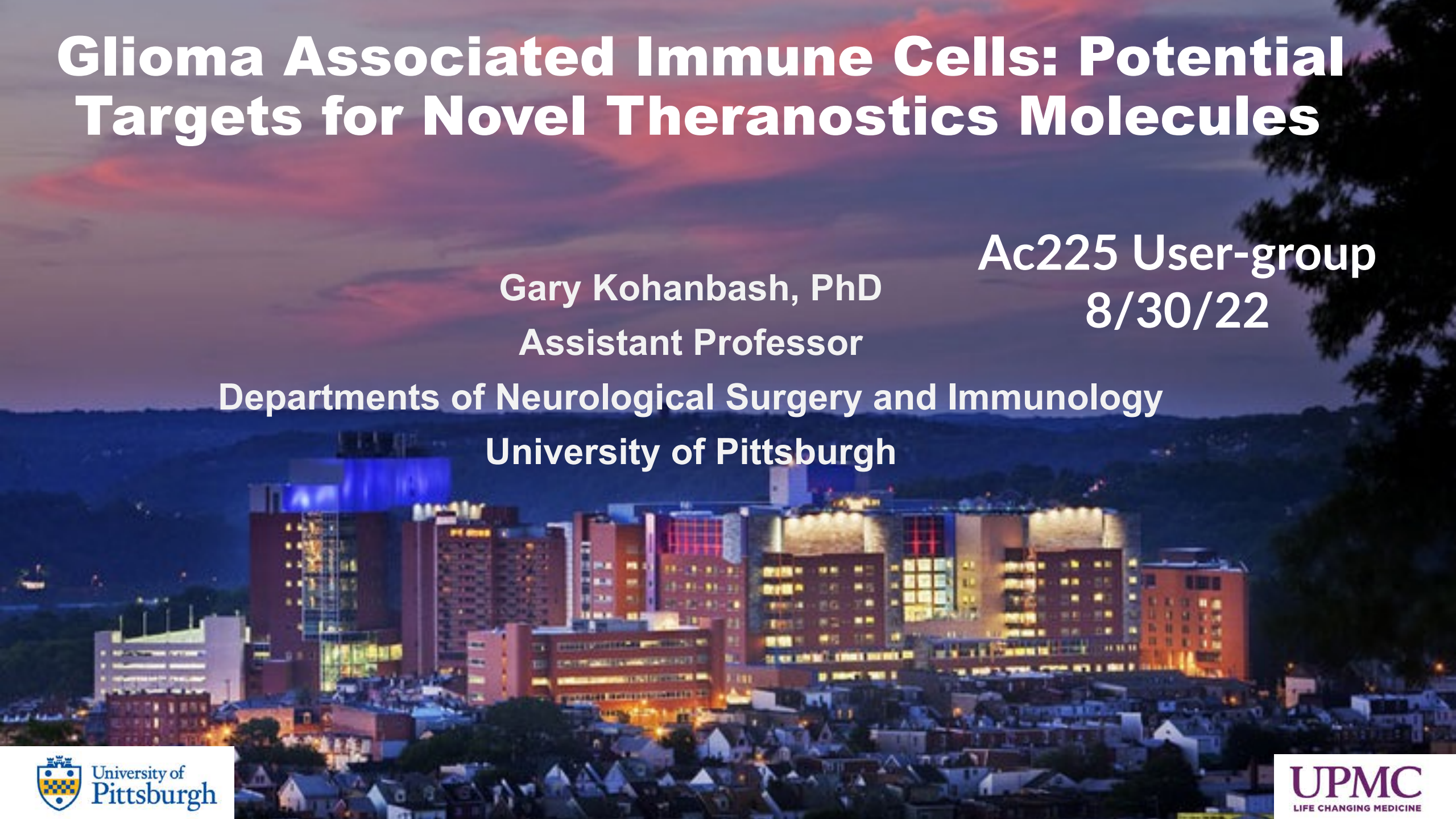

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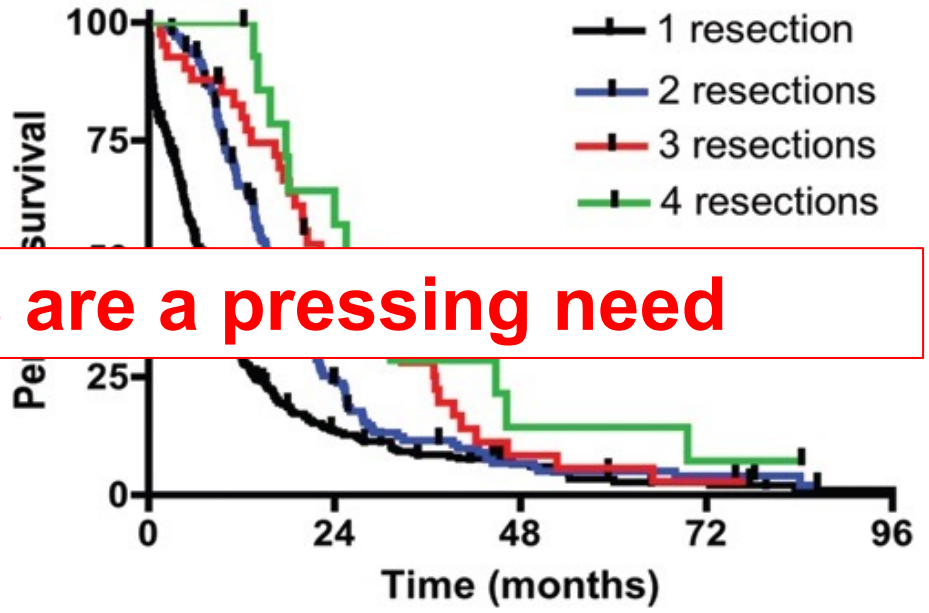
Brain tumors – an overview

- 700,000 Americans are living with a primary CNS tumor
- Gliomas are the most common
- Glioblastoma (GBM-IDHwt) is the deadliest and most

Better treatments for brain cancers are a pressing need

- GBM median survival is 12-14 months
- Brain tumors are the leading cause of cancer-related deaths in children



J Neurosurg 118:812–820, 2013

Despite decades of research outcome for brain tumors patients have only improved marginally

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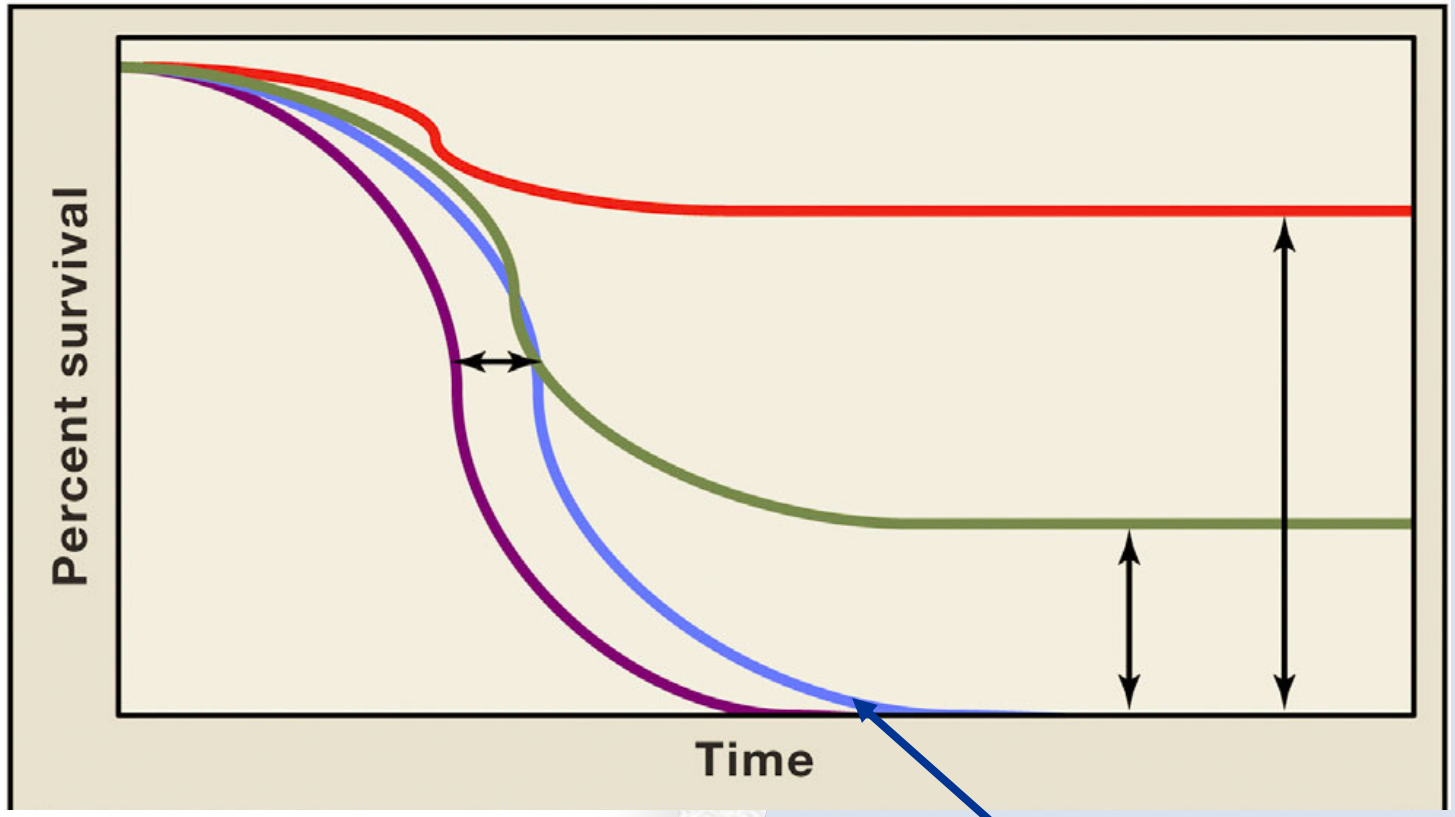
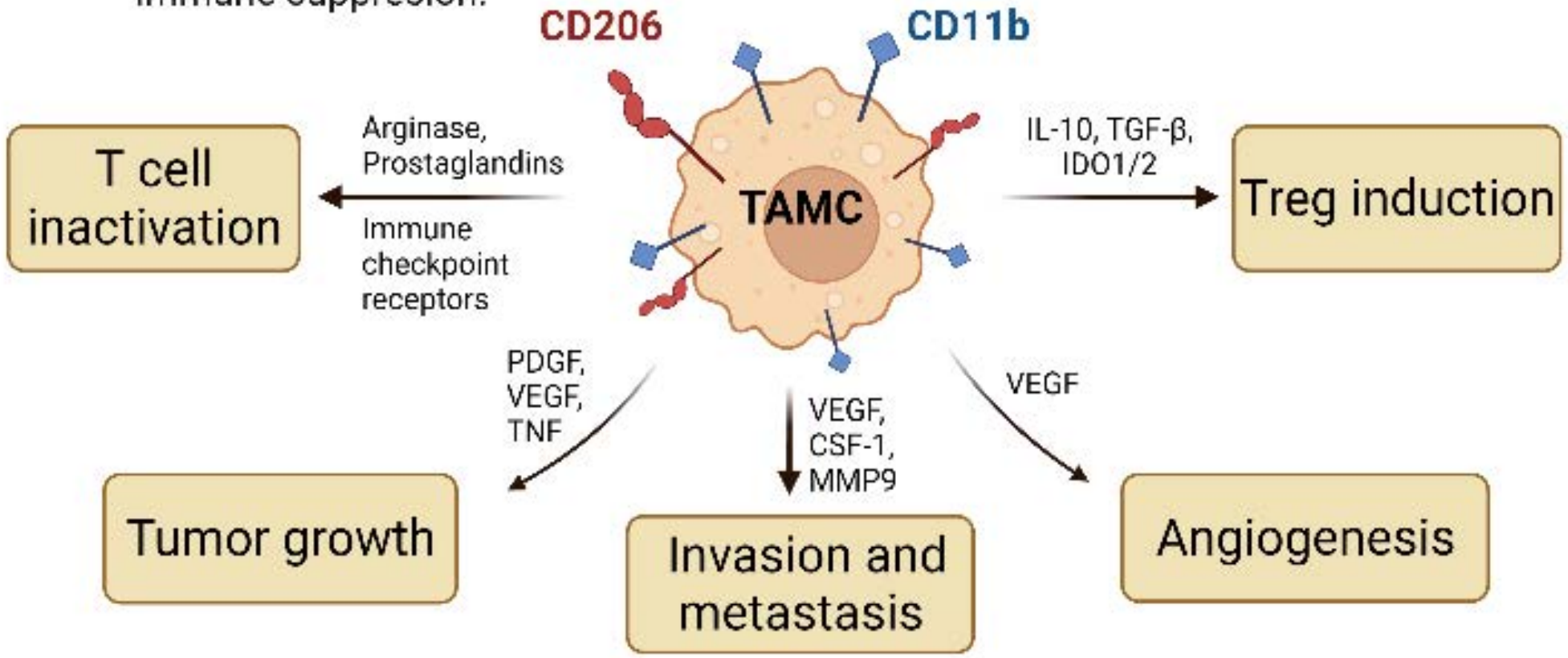
Why Immunotherapy (hope)?



Adapted from: https://medicalxpress.com/news/2015-04-highlights-potential-cancer-immunotherapy-therapy.html

Tumor associated myeloid cells (TAMCs) are a heterogeneous populations of immunosuppressive tumor-infiltrating myeloid cells that poses an impediment to efficacious immunotherapy by facilitating tumor progression and immune suppresion.



- ***CD11b+ Tumor Associated Myeloid cells (TAMs) can account for >30% of a glioma's mass***
- ***Multiple trials targeting TAMCs in glioma***

We keep developing immunotherapies for BT patients, but still we must overcome the very clear issue of TAMCs

Can we non-invasively image immunosuppressive TAMs in gliomas?

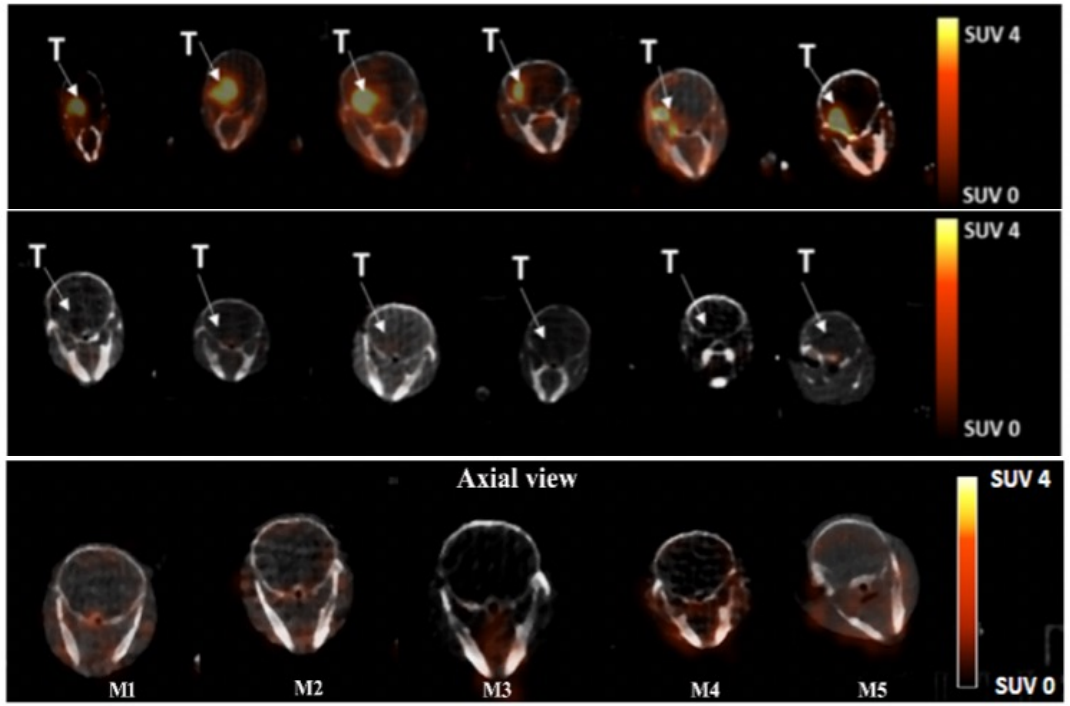
PET/CT of ^{89}Zr-DFO-anti-CD11b (clone M1/70) in GL261 gliomas

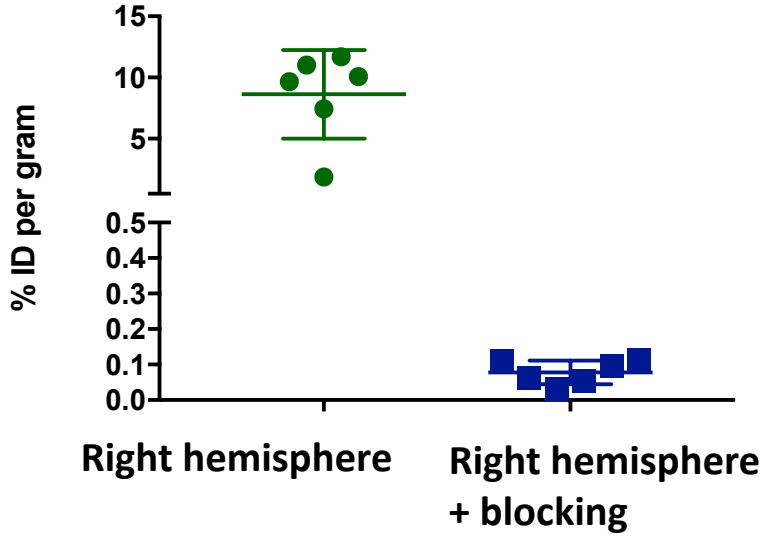
Comparison of tumor without and with a blocking dose of Mab and normal brain

^{89}Zr-anti-CD11b (tumor implant)

^{89}Zr-anti-CD11b+ blocking Mab (tumor implant)

^{89}Zr-anti-CD11b (normal brain)





Nigam S...Kohanbash G, Edwards WB, *MIB* (2019)

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What about an RPT approach to deplete TAMCs?

1. Will radioimmunotherapy targeting CD11b^{+} TAMCs contribute to greater survival through TAMC depletion?
2. Will TAMC depletion enhance checkpoint immunotherapy?

The chelator DOTA (used for Lu177) does not readily complex Zr-89. So, we tested a new chelator that could label both Lu-177 and Zr-89 at room temperature.

Zr89-Lumi804-anti-CD11b can be used to visualize TAMs in gliomas by immunoPET

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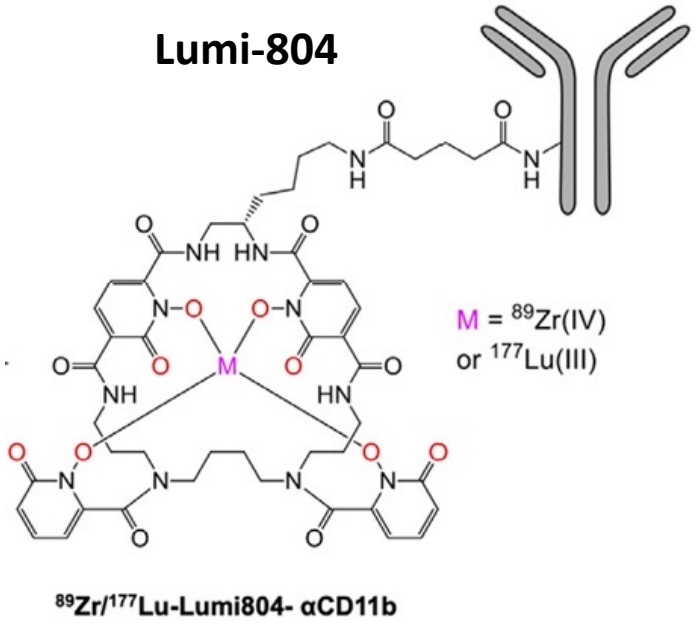
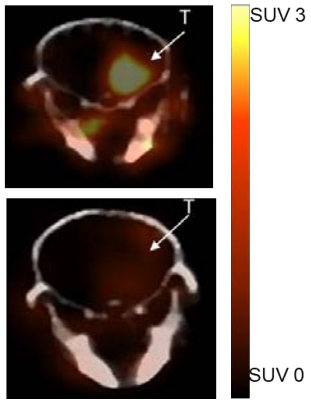
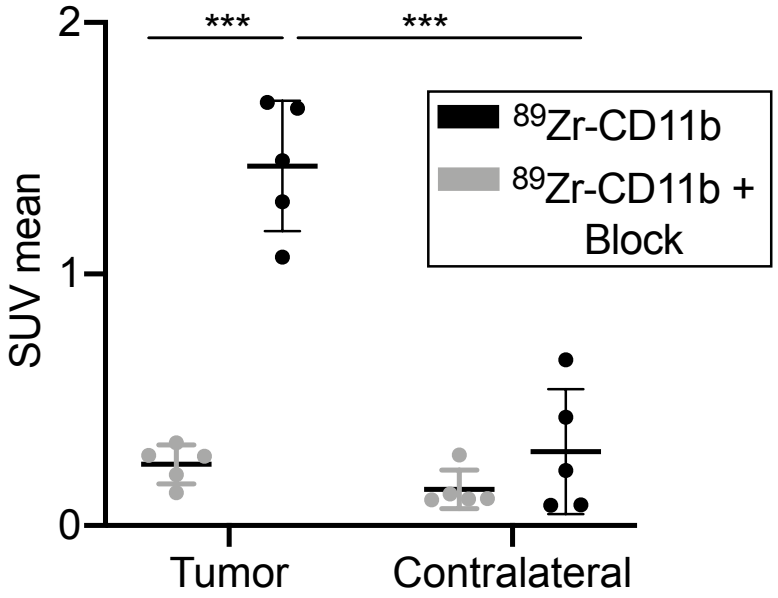


Provided by Lumiphore





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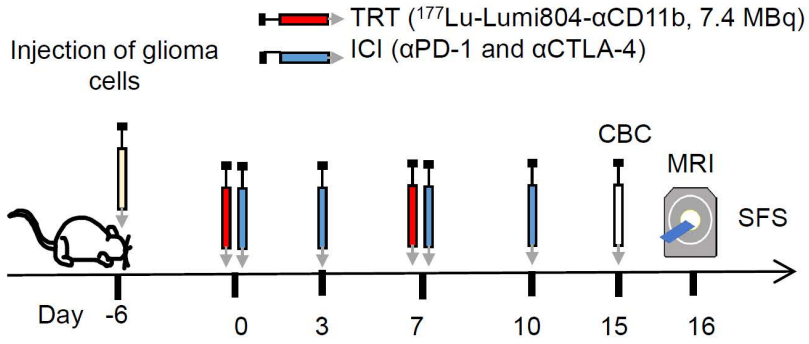
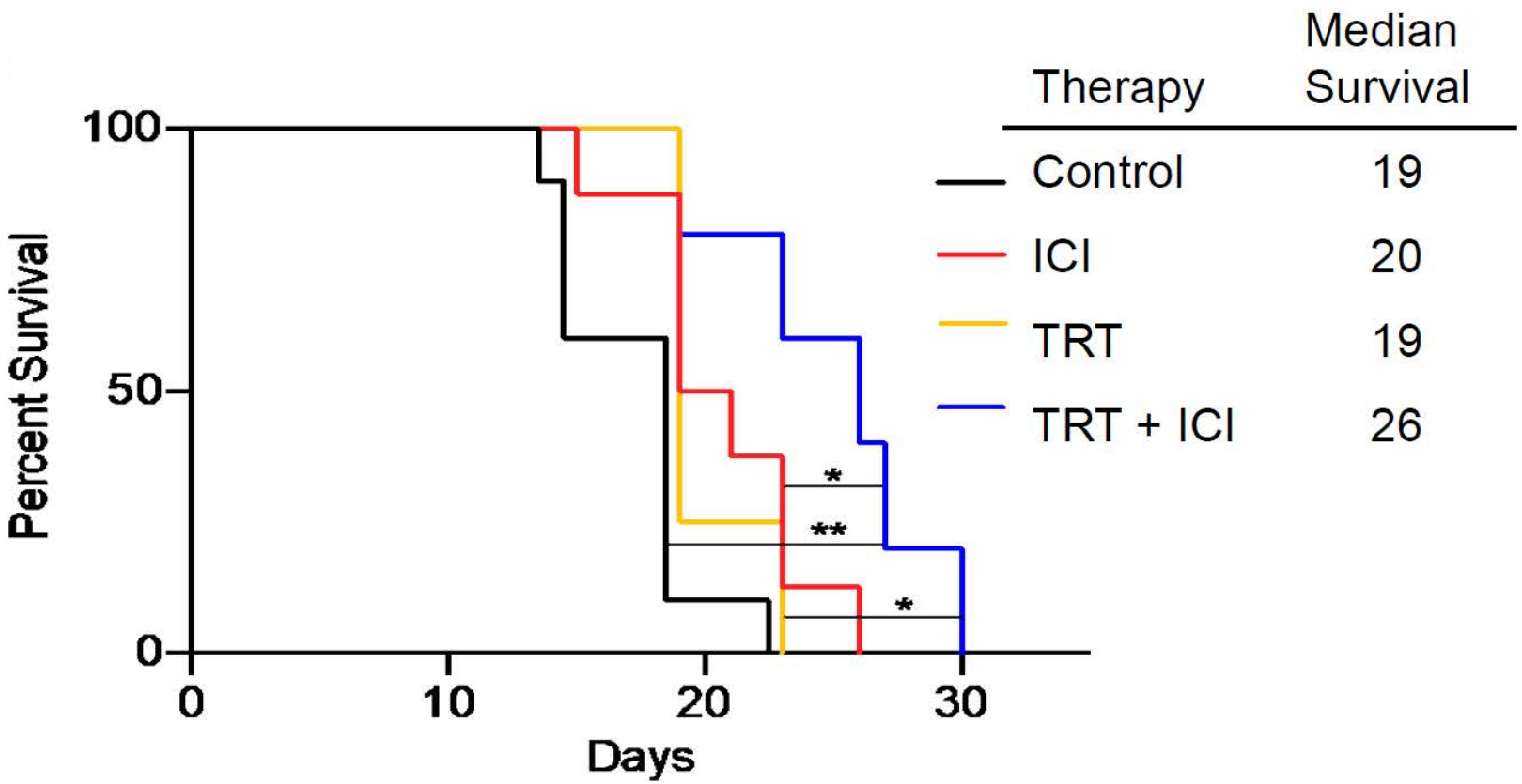
TRT-treatment sensitizes murine gliomas to immunotherapy





Therapy	Median Survival
Control	19
ICI	20
TRT	19
TRT + ICI	26

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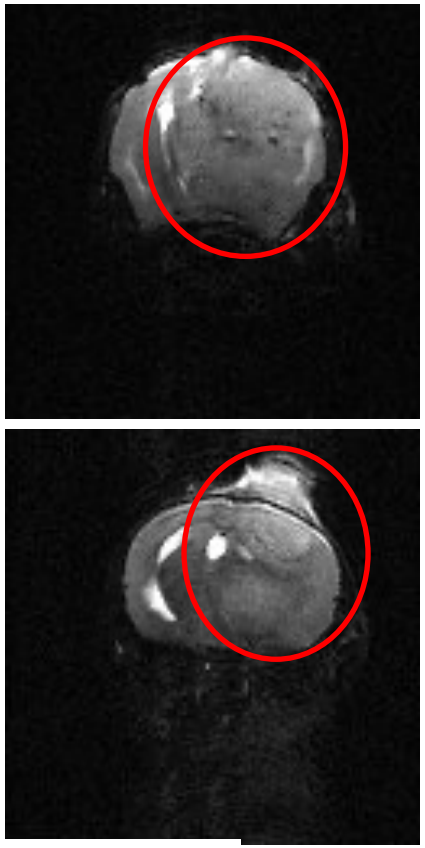
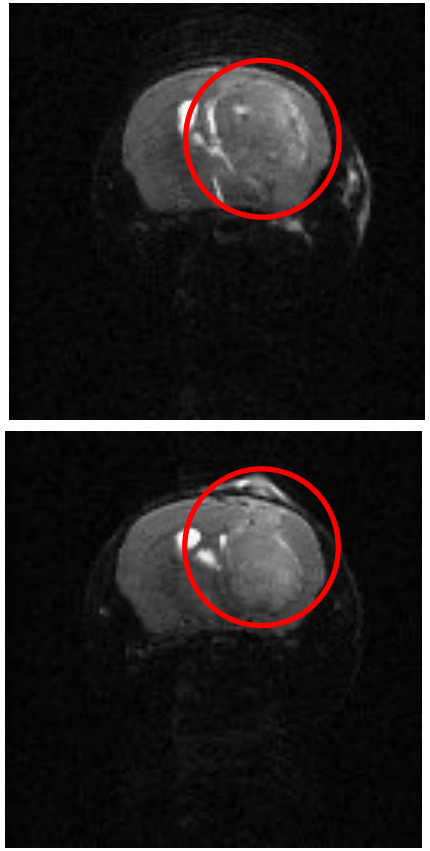
Day 21 TRT-treated tumors are smaller than control or checkpoint treated tumors

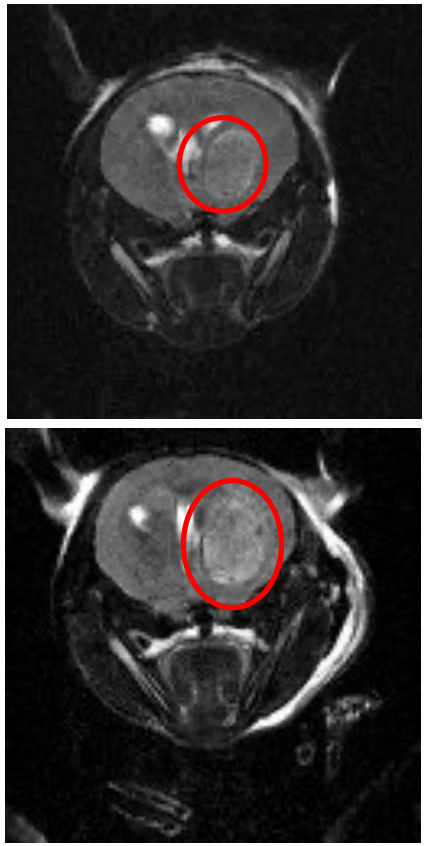
Control



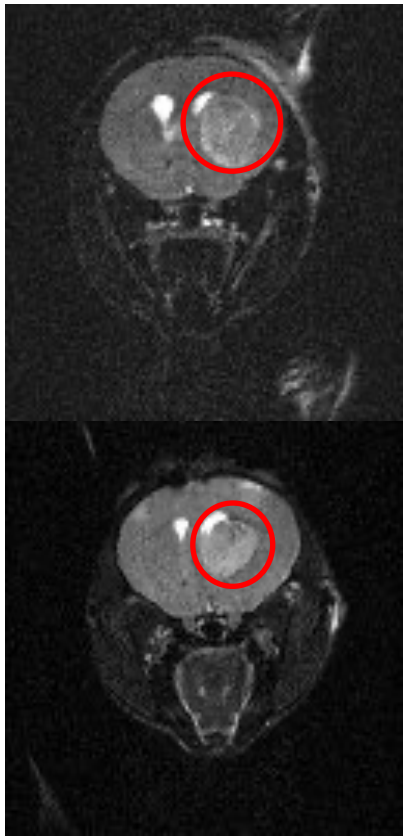
Checkpoint Inhibitors



TRT



TRT + Checkpoint Inhibitors



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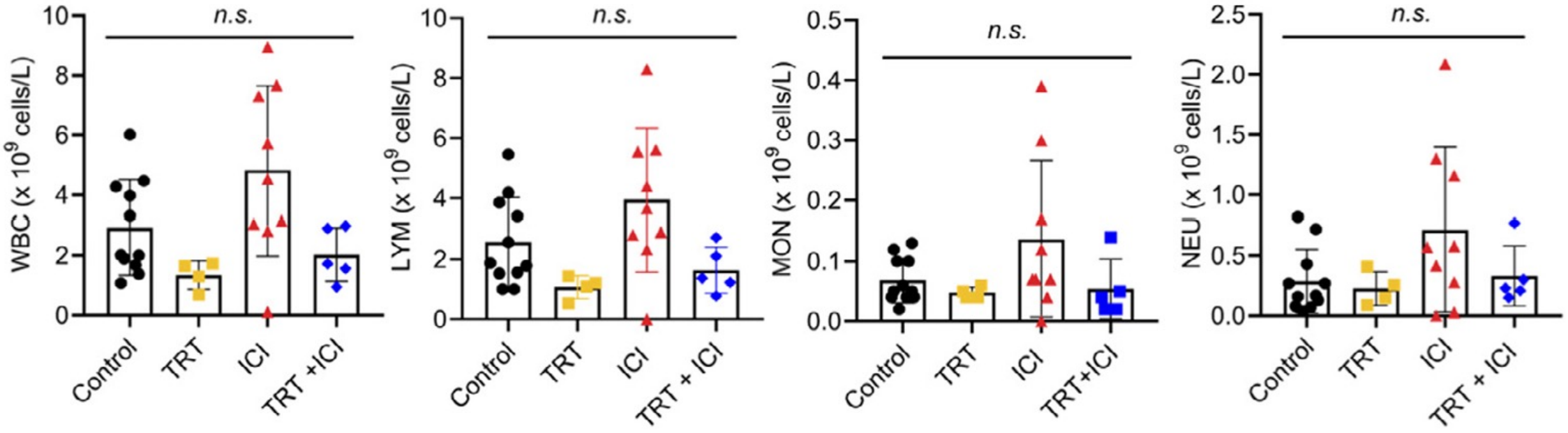
No signs of BM toxicity by CBC (at this dose)



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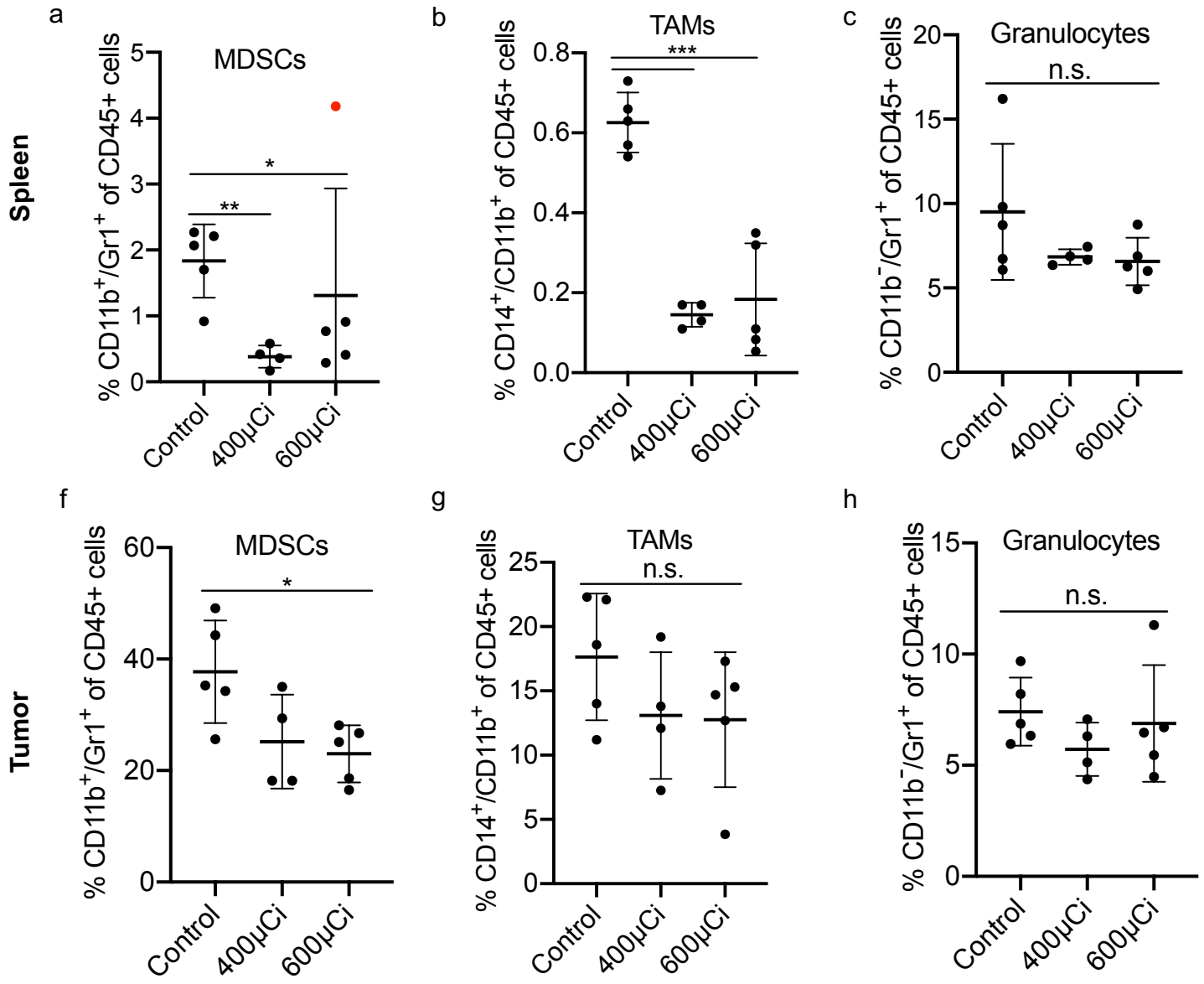
^{177}Lu-Lumi804-anti-CD11b reduces intratumoral and splenic CD11b+ cells



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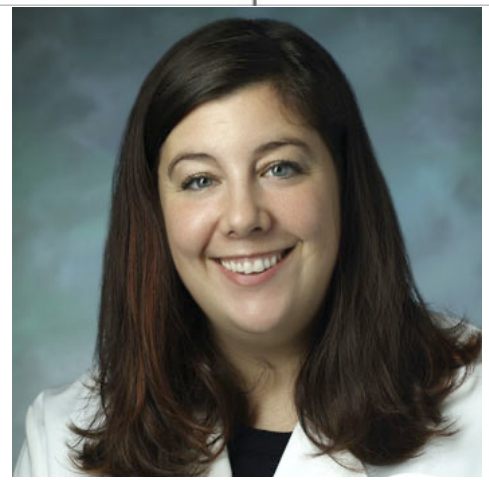
Alpha vs beta emitting radionuclide

	α	β
Particle	He	β -electron
Num. Of tracks to kill cell	2-3	10^3-10^4
Energy/distance	80 Kev/μm	0.2 Kev/μm
DNA damage	Irreversible	Reversible
Average distance	50-80 μM	1-10 mm
Potent single cell cluster kill	Yes	No



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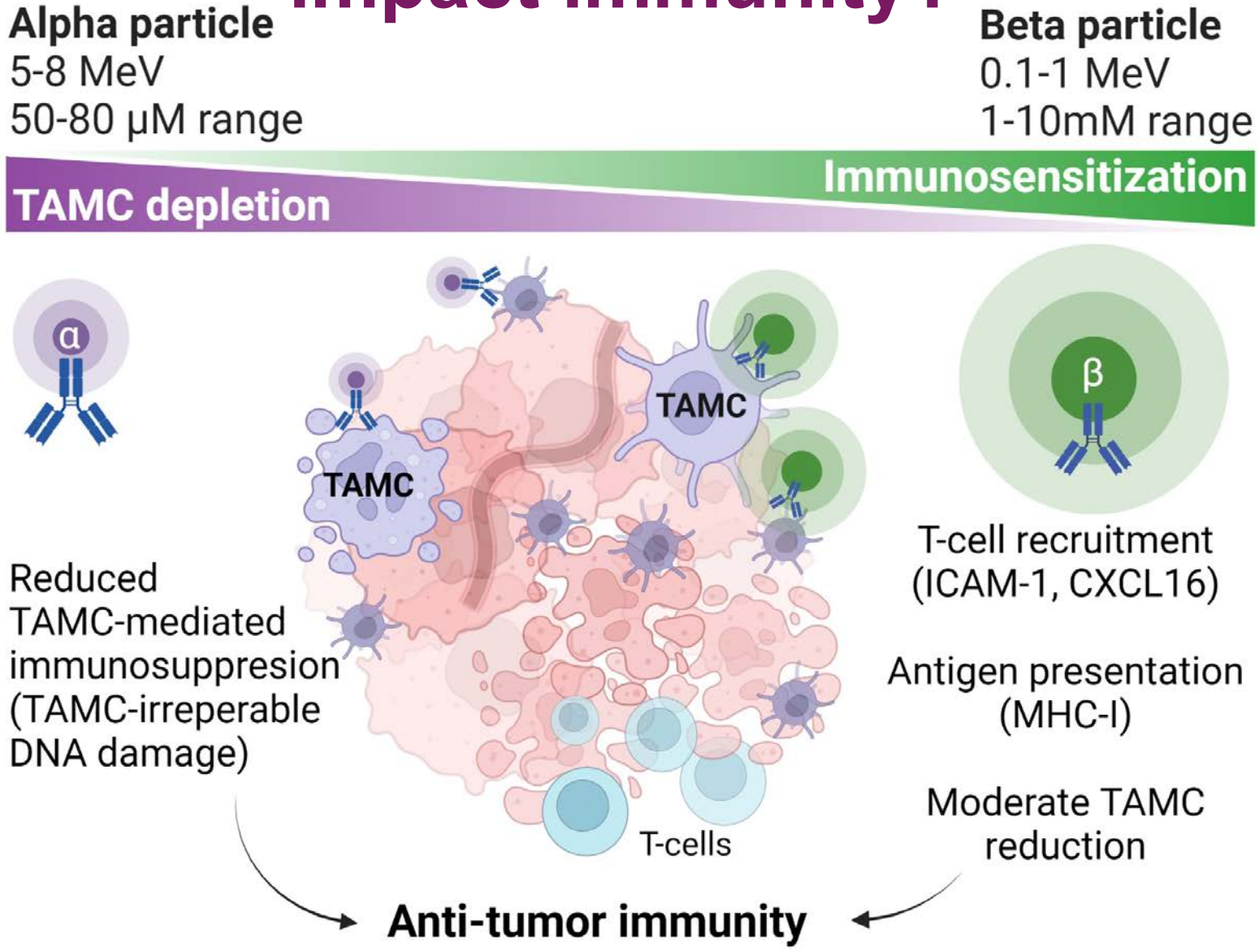
Our theory on how the different radionuclides may impact immunity?



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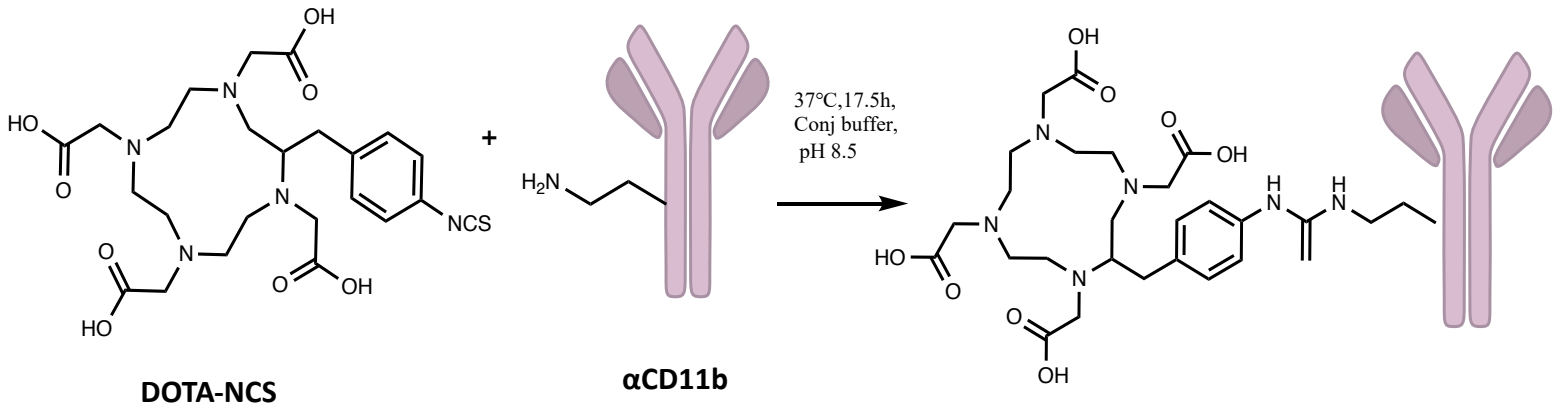
^{225}Ac-DOTA-anti-CD11b

Immunoprobe conjugation Strategy



Radiolabeling

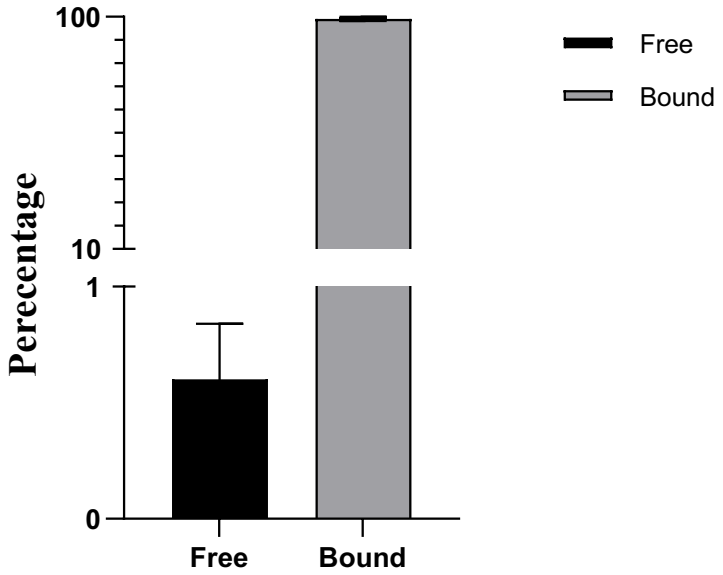


Fig: Bar graph representing percent radiolabelling yield calculated by ITLC method.
*Data represented as Mean±SD (N=4) Optimized Radiolabelling conditions found were
60 min incubation at 37C with Sodium Acetate buffer.

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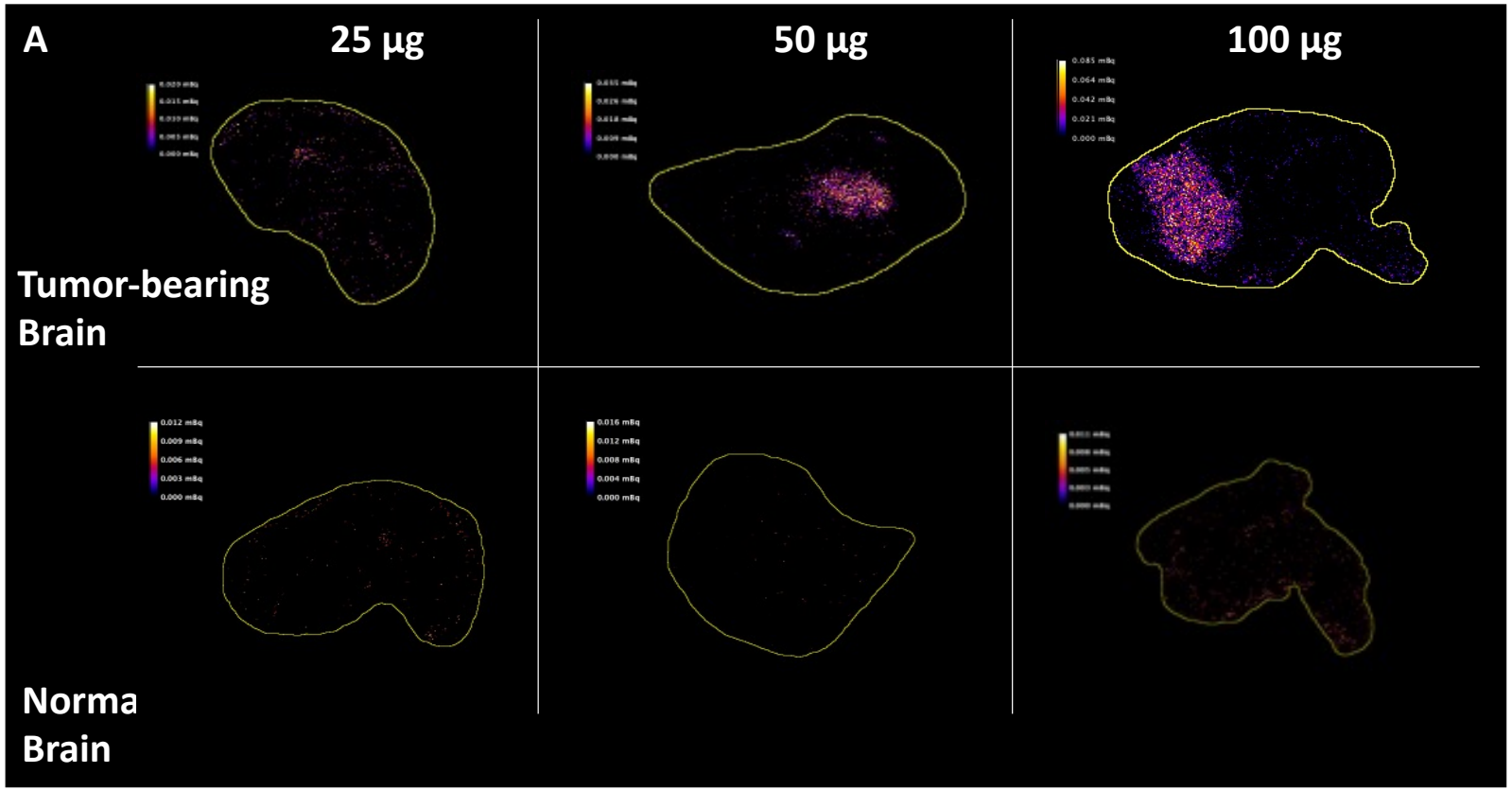
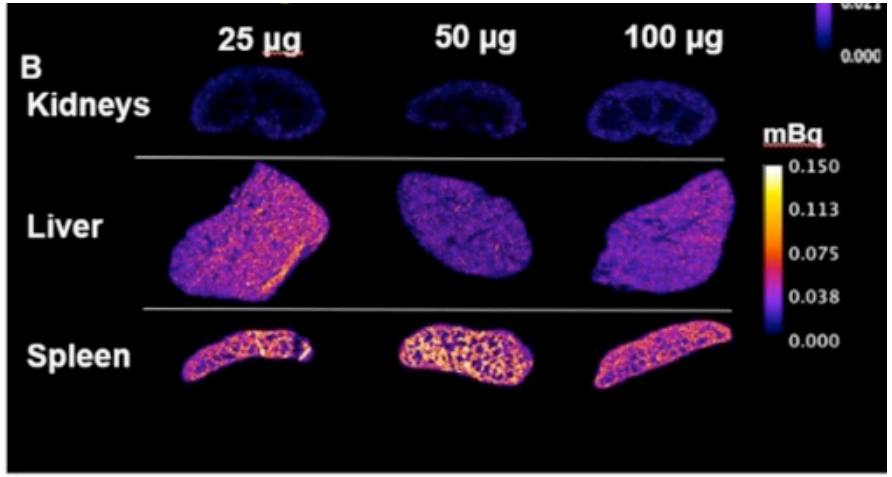
Can cold antibody co-injection increase tumor uptake?

Alpha camera imaging of ^{225}Ac-anti-CD11b following cold antibody coinjection (25-100ug)





200 nCi 225Ac on 6ug antibody

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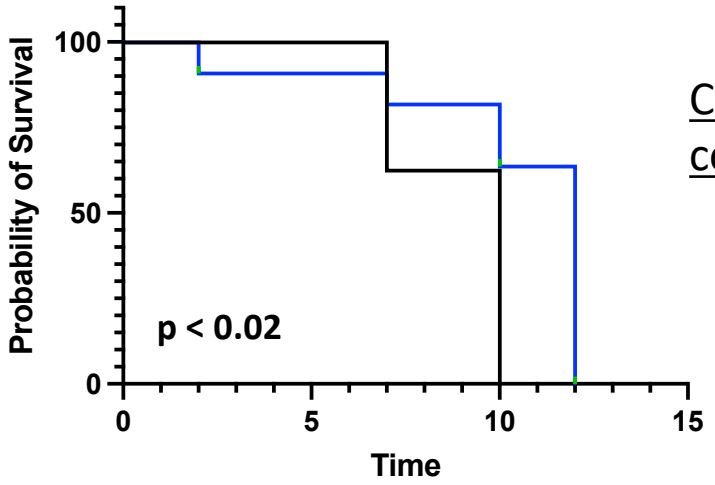
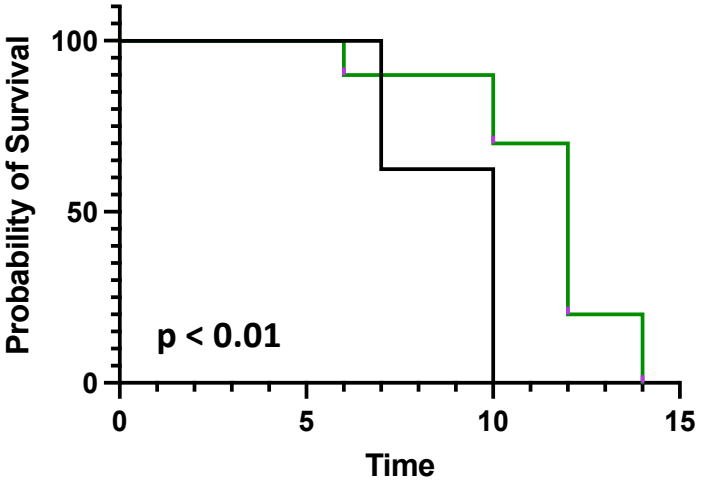
Survival of glioma-bearing mice following TAT with cold antibody pretreatment

Black line- Control
Colored lines- 225Ac-DOTA-CD11b (~200 nCi on 6ug antibody)

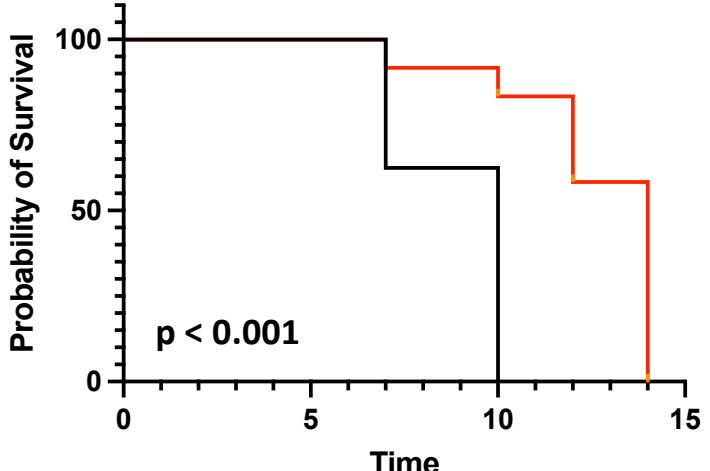


Cold Antibody co-injection

25 ug



50 ug



100 ug

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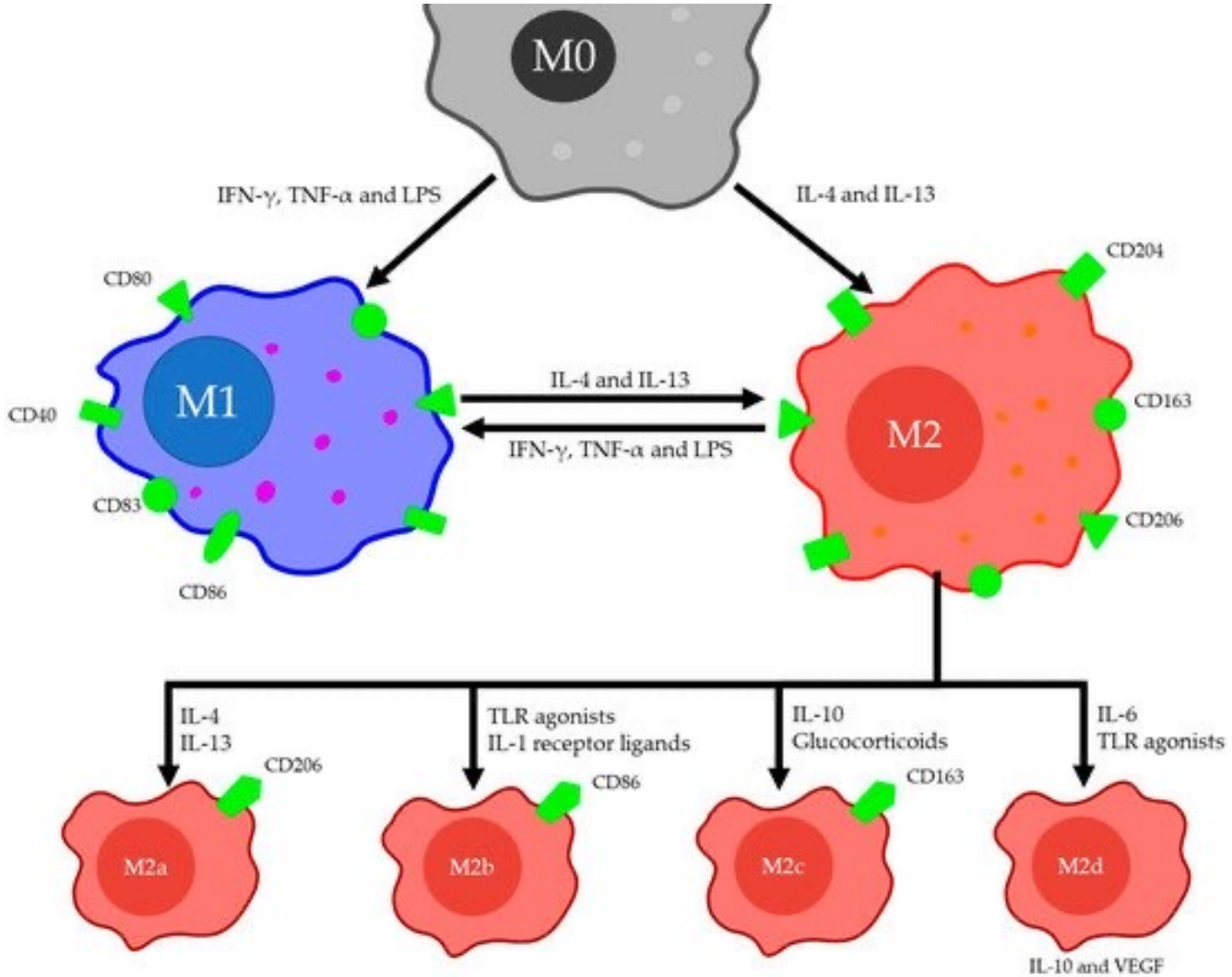
Can we better target the immunosuppressive TAMCs?



Kim, Y.; Nurakhayev, S.; Nurkesh, A.; Zharkinbekov, Z.; Saparov, A. Macrophage Polarization in Cardiac Tissue Repair Following Myocardial Infarction. *Int. J. Mol. Sci.* **2021**, *22*, 2715. https://doi.org/10.3390/ijms22052715

<u>Good target</u>

- High expression level
- Restriction to the cell type of interest
- Higher expression in the tumor than normal tissues

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Yet another consideration: Radio-sensitization

Macrophages, especially M2 type TAMs, are one of the most radioresistant cells. Anti-oxidative molecules are produced by TAMs during radiotherapy, such as manganese superoxide dismutase (MnSOD), a scavenger of superoxide (O_{-2}) ions, which confer cellular resistance against damaging effects of radiotherapy.

Yumin Zhang, Zujian Feng, Jinjian Liu, Hui Li, Qi Su, Jiamin Zhang, Pingsheng Huang, Weiwei Wang, Jianfeng Liu, Polarization of tumor-associated macrophages by TLR7/8 conjugated radiosensitive peptide hydrogel for overcoming tumor radioresistance, Bioactive Materials, Volume 16, 2022, Pages 359-371,

Genard, Géraldine, Stéphane Lucas, and Carine Michiels. "Reprogramming of tumor-associated macrophages with anticancer therapies: radiotherapy versus chemo-and immunotherapies." *Frontiers in immunology* 8 (2017): 828.

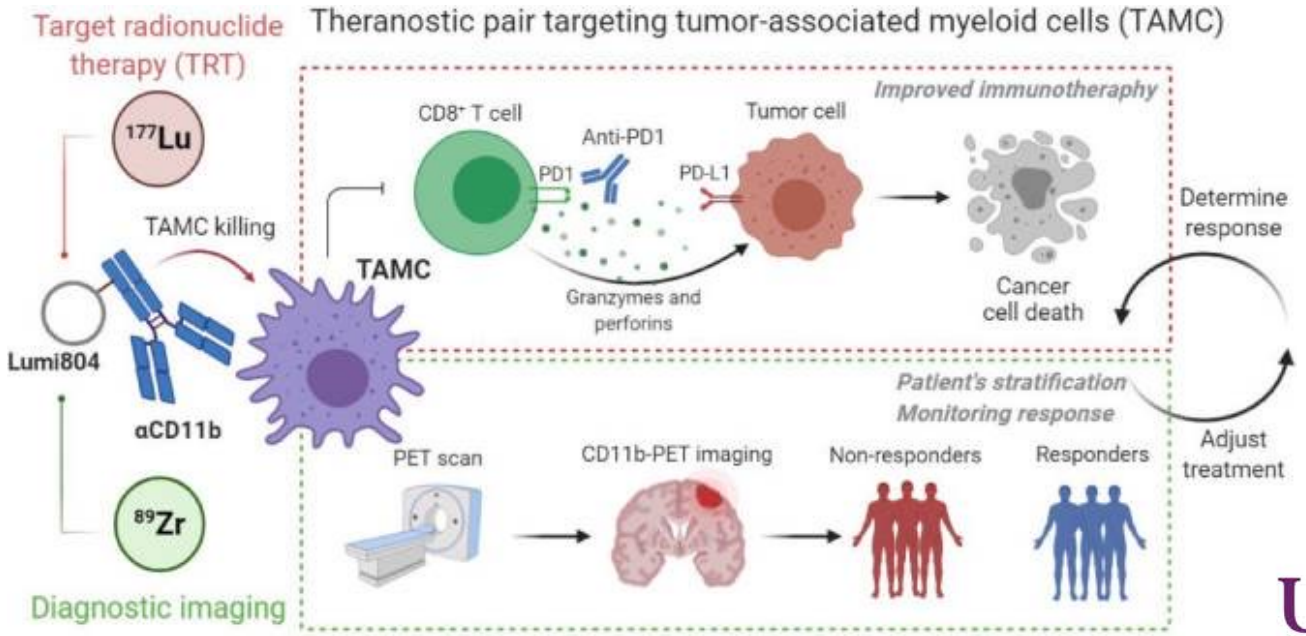
Leblond MM, Pérès EA, Helaine C, Gérault AN, Moulin D, Anfray C, Divoux D, Petit E, Bernaudin M, Valable S. M2 macrophages are more resistant than M1 macrophages following radiation therapy in the context of glioblastoma. Oncotarget. 2017 Aug 7;8(42):72597-72612. doi: 10.18632/oncotarget.19994. PMID: 29069812; PMCID: PMC5641155.

So many questions remain?

1) High dose vs low dose for immunotherapy-sensitization?
2) Differences of alpha and beta emitters on the TME?
3) Other therapeutic radionuclides?
3) How will specific activity impact tumor uptake?
4) What is the best target to deplete immunosuppressive TAMCs?
5) How many times should we give the TRT?
6) Timing (unique for targeting TAMC vs tumors antigens)?
7) Should we target other immunosuppressive cells (Tregs)?
8) Ultimately, can we deplete TAMCs safety in patients to improve immunotherapy responses?

Summary

1) TAMCs in brain tumors promote tumor growth and are a barrier to effective immunotherapy
2) TAMCs can be visualized in preclinical gliomas using Zr-89-DFO-anti-CD11b
3) anti-CD11b RPT can allow for both imaging (with Zr-89) of TAMs and targeting (with Lu-177 or Ac-225) of TAMs within our glioma model
4) Targeting of TAMCs can improve immunotherapy responses in murine gliomas.



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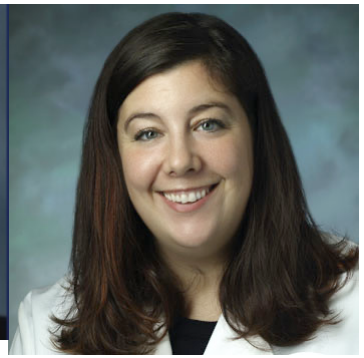
Credits

Funding: DIPG ALL-IN (PI), St. Badrick's Foundation (PI), Brain Tumor Funders' Collaborative (PI),American Brain Tumor Association, UPMC CMRF (PI), Pittsburgh Foundation Copeland Fund (PI), CHP Scientific Program, NIBIB R21 EB02667501 (Co-PI), NCI R01 CA187219 (Co-I), NCI R01CA222804 (Co-I), NCI P01 CA163205 (Co-I).

Collaborations

Dr. Jessie Nedrow

Dr. W. Barry Edwards



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