Working Group III:

Therapeutic Mechanisms to Modify the Cancer Microenvironment and Related Experimental Systems for Validation

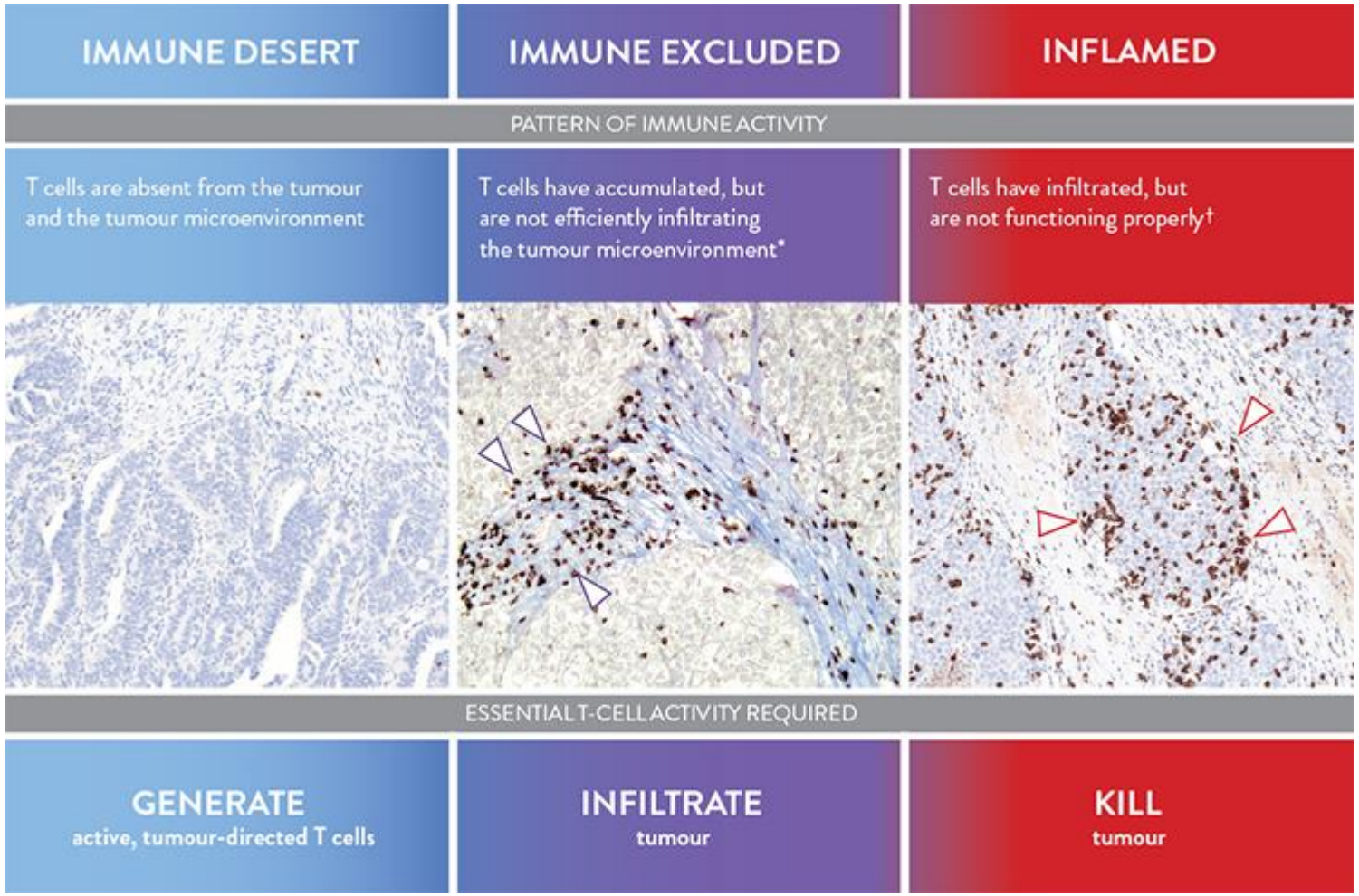
SITC Cancer Immune Response Workshop

September 4-5, 2019

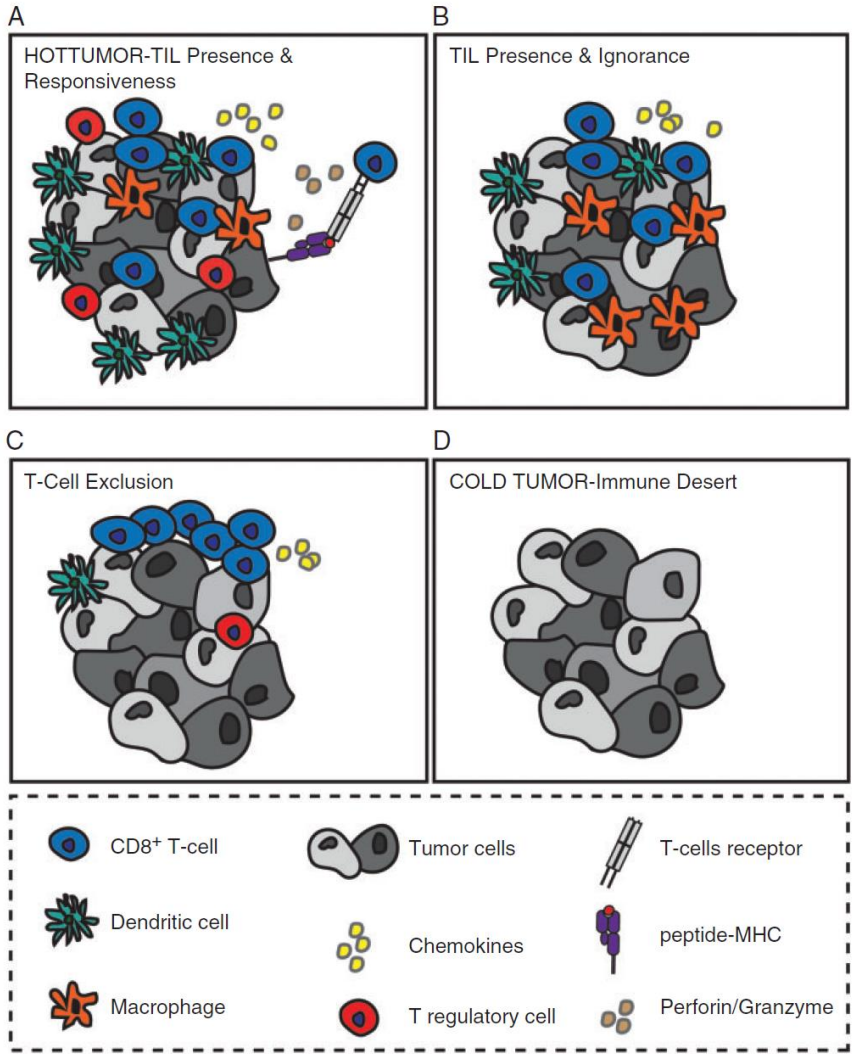
Houston, Texas

Immune Hot, Cold, Excluded Tumors

Cancer Occurs in 3 Immune Phenotypes



Researchcancertherapy.com



Lanitis 2017 *Annals Oncology*

Takeaways

- Honor the complexity of the immune response
  - Time to move beyond the hot/cold/excluded paradigm to describe the spectrum of immune contextures
- Recognize the limitations of the current research approaches and development strategies
- Different therapeutic strategies face will require different development solutions, duh

Sharing Failures to Achieve Success

- Polymaths are few and far between. Most people are only experts in their area of focus.

- Must create opportunities to engage with other experts and exchange knowledge
  - Meetings such as this one are a great start
  - Idea – present your puzzling results along side the positive data
  - Venue for sharing failed experiments
    - Journal of negative results?

Therapeutic Strategies Must Recognize Patient Heterogeneity

- Biomarkers, biomarkers, biomarkers
  - Prognostic when possible to avoid treating unnecessarily
  - Predictive biomarkers for a given therapy
  - Dynamic biomarkers to monitor and mechanisms of action

- Challenge: Access to tissue biopsies to characterize diverse and dynamic immune response
  - Solution: engage with patient population to consent to more participation when possible and appropriate
  - Solution: Develop Liquid Biopsy assays
  - Solution: Leverage imaging based technologies

Privileged Role of PD-1 Pathway as a therapeutic target

- PD-1 has met the most success in the clinic of all the immune checkpoints. Is it due to the central role PD1 plays in regulating immune response and/or good fortune in timing of development and performance of therapeutics?
  - Yes, mouse models suggest unique role of PD-1 (and CTLA4) in priming/regulating immune response
  - PD-1 has also benefitted from focused effort by biopharmas

Durability of Response

- Even in patients that achieve a measure of disease control after immunotherapy, responses are often incomplete or limited in duration. What is preventing patients from achieving longer term response?
  - Immune environment changes over time in response to cell/tissue stress
  - Dynamic regulation of immunomodulatory agents may remove therapeutic target
  - Evolution of immune evasion and/or loss an antigens
    - Solution: develop combination therapies

As always, need better models and better ways to describe human disease

- Mouse models that will capture diversity of human immune variability and tumor progression
- Move beyond TNM Staging to Capture Diversity of Immune Status as better predictor of immune response?
- Clinical trial endpoints that reflect biology of disease
  - E.g. loss of EGFRv3 expression in EGFRv3 targeting therapy

Patients are an untapped resource

- Patients are an untapped resource to advocate for funding, drive research forward, provide samples,
- They may be willing to give more samples or tolerate more side effects than clinicians would think
- Other patient models are being explored too
  - NIH canine oncology research initiatives

Therapeutic Interventions

- Vaccine
- Macrophages
- CART
- Immune Checkpoint Blockade and Radiation Therapy

Therapeutic Interventions

Vaccine:

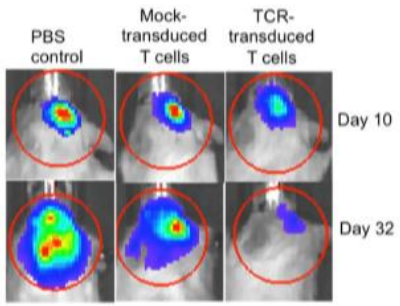
a. How to expand the list of tumor specific antigens: neoantigens and tumor associated antigen exclusive on tumor cells.—Target multiple epitopes

b. What are the reasons of failure of phase III EGFR vIII vaccine trials? What have we learned? What are the advantages of H3.3K27M peptide vaccine and poliovirus vaccine? How to overcome immunosuppressive TME?

JEM

Novel and shared neoantigen derived from histone 3 variant H3.3K27M mutation for glioma T cell therapy

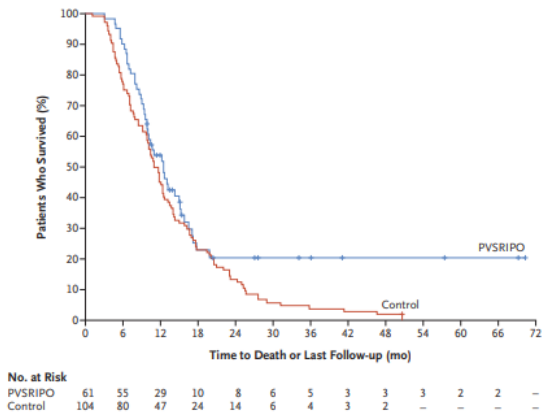
Zinal S. Chheda,[1]* Gary Kohanbash,[1,10]* Kaori Okada,[1] Naznin Jahan,[1] John Sidney,[4] Matteo Pecoraro,[5] Xinbo Yang,[6] Diego A. Carrera,[1] Kira M. Downey,[1] Shruti Shrivastav,[1] Shuming Liu,[1] Yi Lin,[1] Chetana Lagisetti,[9] Pavlina Chuntova,[1] Payal B. Watchmaker,[1] Sabine Mueller,[1] Ian F. Pollack,[10] Raja Rajalingam,[2] Angel M. Carcaboso,[11] Matthias Mann,[5] Alessandro Sette,[4] K. Christopher Garcia,[6,7,8] Yafei Hou,[1] and Hideho Okada[1,3,12]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recurrent Glioblastoma Treated with Recombinant Poliovirus



Experimental Systems for Validation

Vaccine:

What are the experimental systems to validate immunogenicity mediated by vaccination?---Not only elicit tumor-specific T cells but also monitor antigen specific T cells circulation and migration in vivo

JEM

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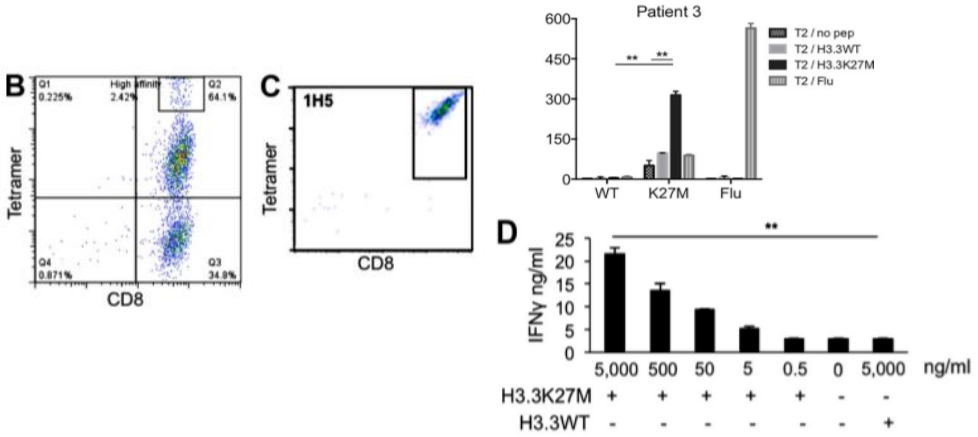
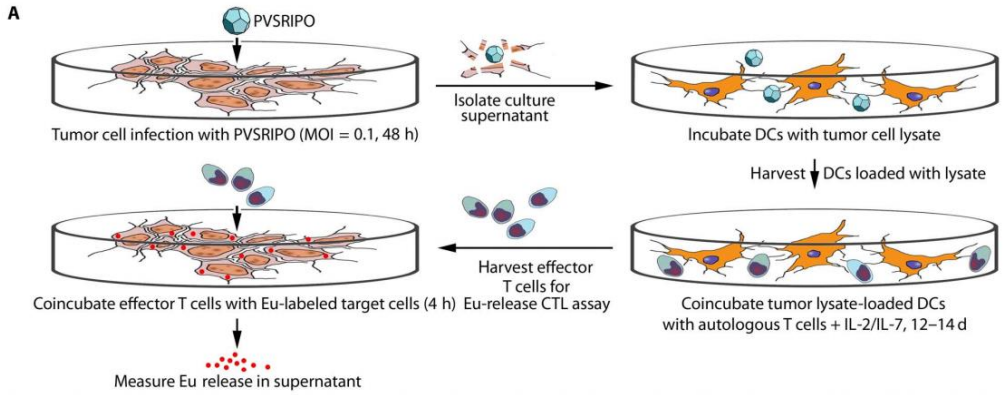




Brown et al., Sci. Transl. Med. 2017

Therapeutic Interventions

Tumor Associated Macrophages and Microglia:

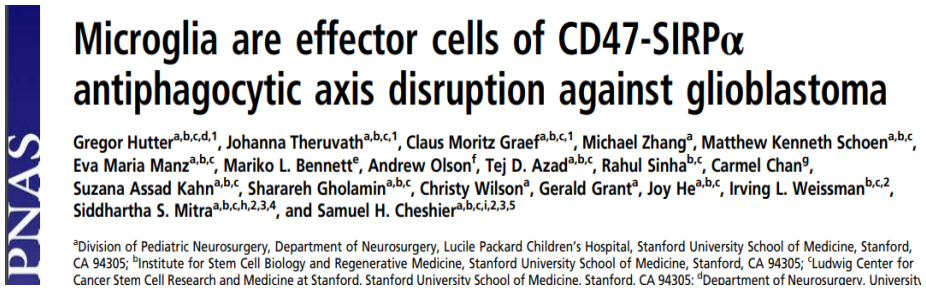
a. Heterogenicity of TAMs:

What are the distinct functions of macrophages vs microglia in TME;

How to identify distinct phenotypes of macrophages in vivo, such as anti-tumor subsets?-scRNAseq

b. CD47 blockade targeting phagocytosis:

Antigen presentation ability of macrophages treated with CD47 blockade.



Microglia are effector cells of CD47-SIRPα antiphagocytic axis disruption against glioblastoma

Gregor Hutter[a,b,c,d,1], Johanna Theruvath[a,b,c,1], Claus Moritz Graef[a,b,c,1], Michael Zhang[a], Matthew Kenneth Schoen[a,b,c], Eva Maria Manz[a,b,c], Mariko L. Bennett[e], Andrew Olson[f], Tej D. Azad[a,b,c], Rahul Sinha[b,c], Carmel Chan[g], Suzana Assad Kahn[a,b,c], Sharareh Gholamin[a,b,c], Christy Wilson[a], Gerald Grant[a], Joy He[a,b,c], Irving L. Weissman[b,c,2], Siddhartha S. Mitra[a,b,c,h,2,3,4], and Samuel H. Cheshier[a,b,c,i,2,3,5]

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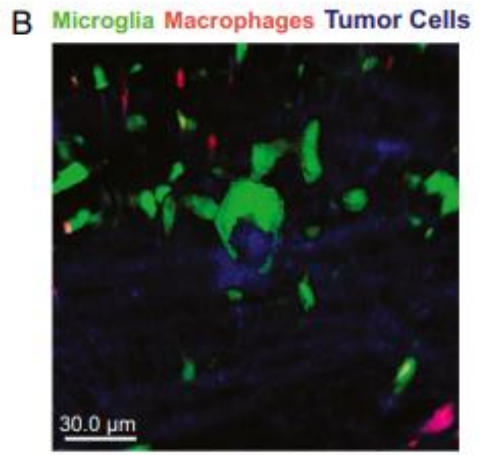
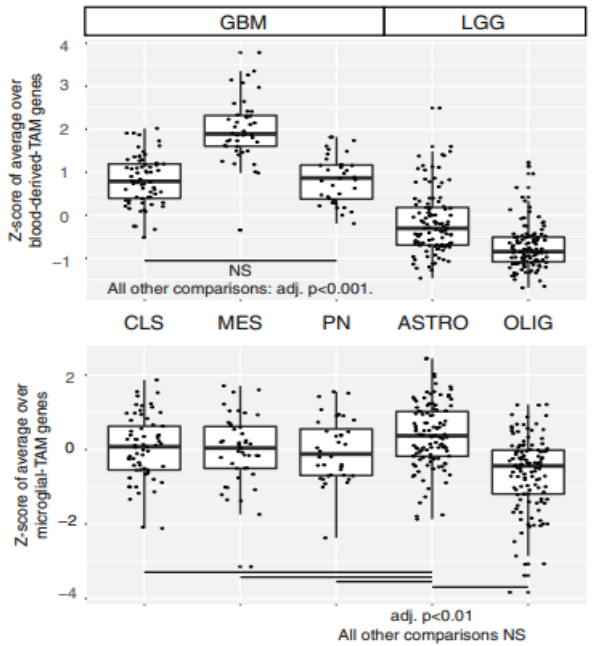


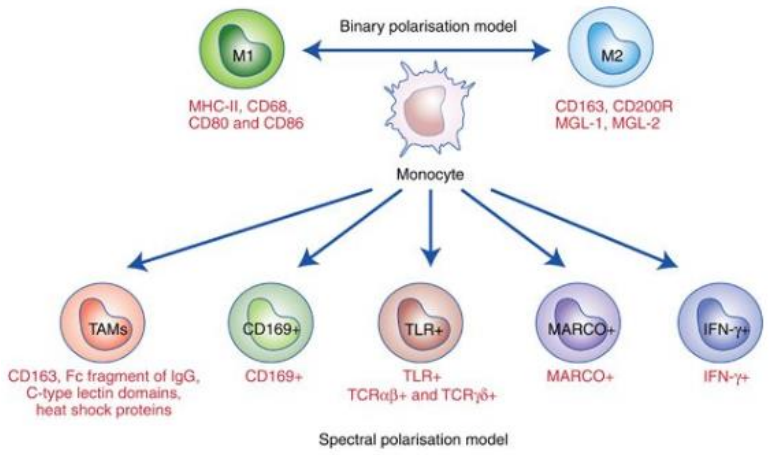


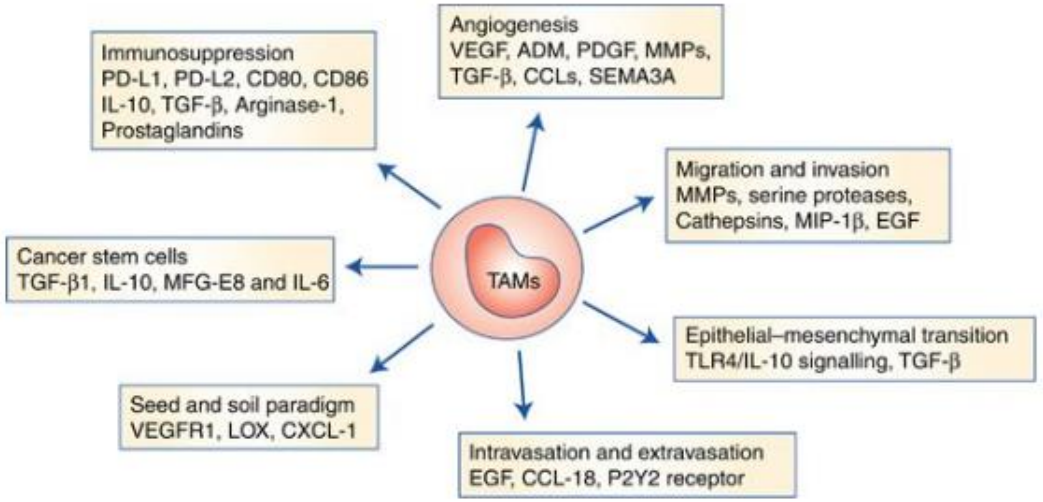
Muller et al Genome Biology 2017

Experimental Systems for Validation

TAMs:

What are the experimental systems to validate the distinct functions of subsets of TAMs? –specific functional assays



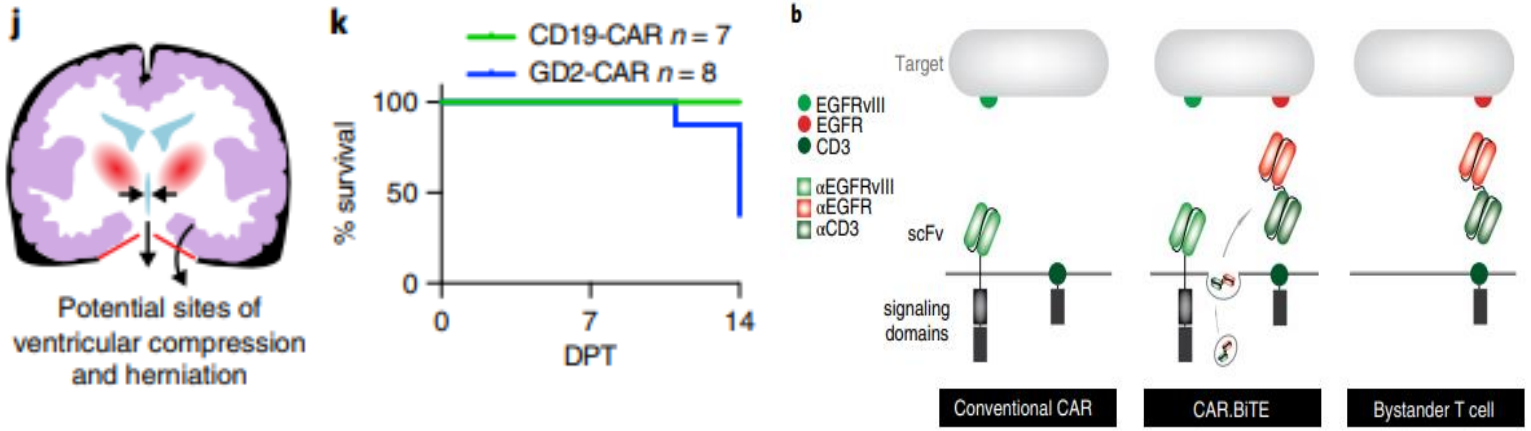


Aras et al British Journal of Cancer 2017

Therapeutic Interventions

CART therapy:

a. How to overcome tumor heterogenicity by CART therapy?-multi-targets CART, CART targeting other cell types
b. How to improve the neuroinflammation toxicity of CART therapy?



LETTERS
https://doi.org/10.1038/s41591-018-0006-x
nature medicine

Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M⁺ diffuse midline gliomas

nature biotechnology
ARTICLES
https://doi.org/10.1038/s41587-019-0192-1

CAR-T cells secreting BiTEs circumvent antigen escape without detectable toxicity

Experimental Systems for Validation

CART therapy:

Most of current models use human xenograft mouse model with adaptive transfer of CAR-T. The immunosuppressive TME mediated by myeloid cells may not be considered. How to improve the current models to validate CART therapy?

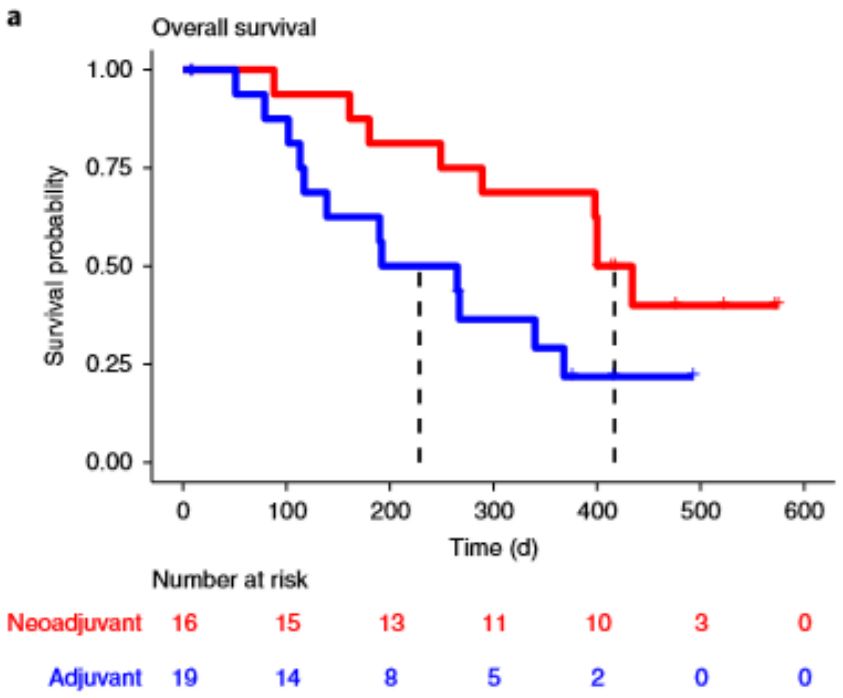
-Certain xenograft cell lines to recapitulate the immunosuppressive phenotypes
-Humanized mouse models

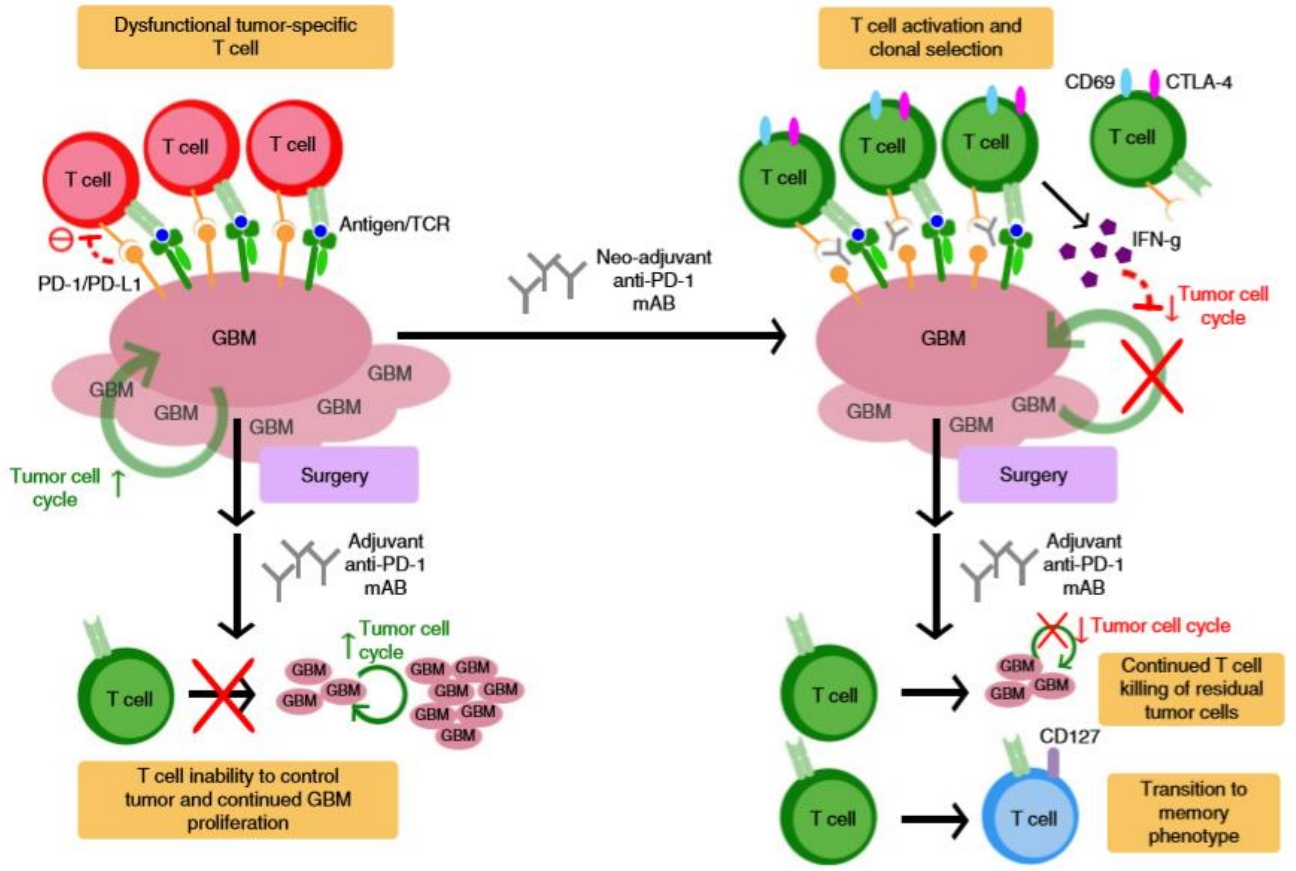
Therapeutic Interventions

Immune Checkpoint Blockade:

nature medicine FOCUS | ARTICLES https://doi.org/10.1038/s41591-018-0337-7

Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma

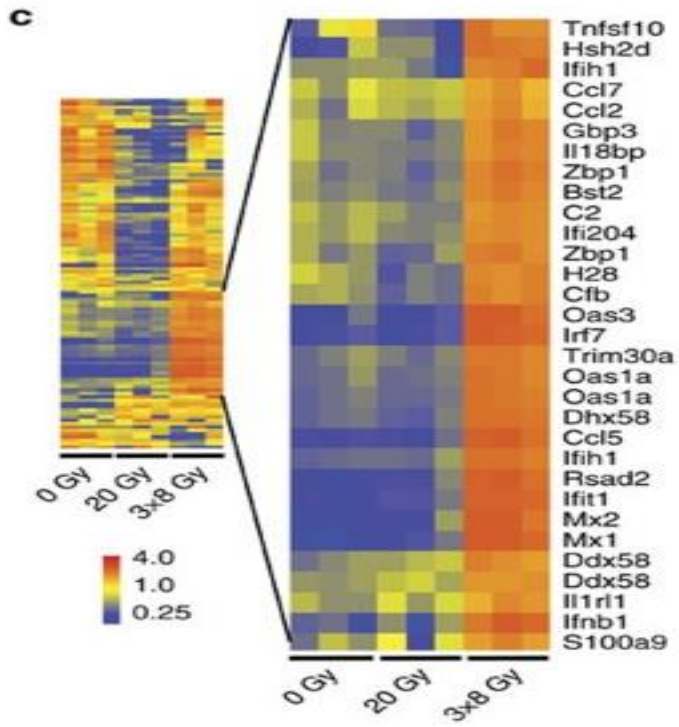


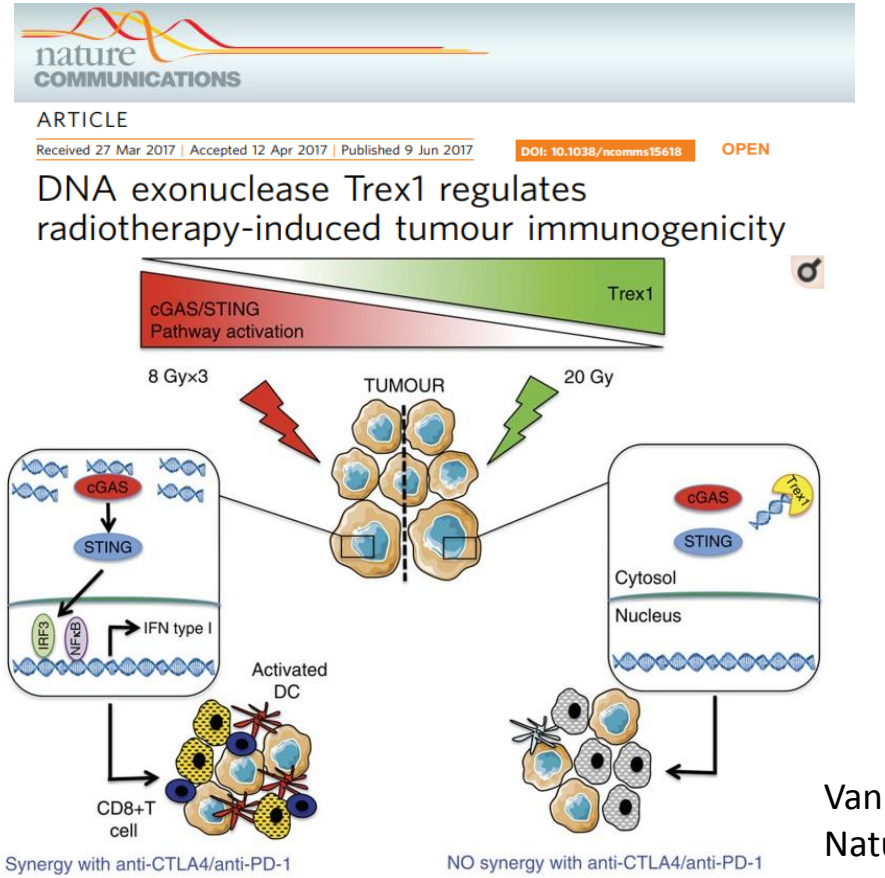


Therapeutic Interventions

Immune Checkpoint Blockade + Radiation Therapy:

Combination of RT and PD-1 blockade failed in newly diagnosed non-MGMT GBM patients. What could we improve from this failure? Would change of the dose regimen of RT improve efficacy? –effect of RT on lymphopenia.





Vanpouille-Box et al
Nature Communications. 2017

Take away messages

1. Expand both neoantigen and tumor associated antigens for cancer vaccine, targeting multiple antigens
2. Better characterization of heterogenicity of TAMs by multiplex platform technologies
3. Multi-targets CART for cancer cells and other type of cells in tumor microenvironments