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Society for Immunotherapy of Cancer

Rational Design of Tumor-Specific Therapeutic and Biomarker Strategies through Reverse Translational Studies

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Society for Immunotherapy of Cancer (SITC), 2020

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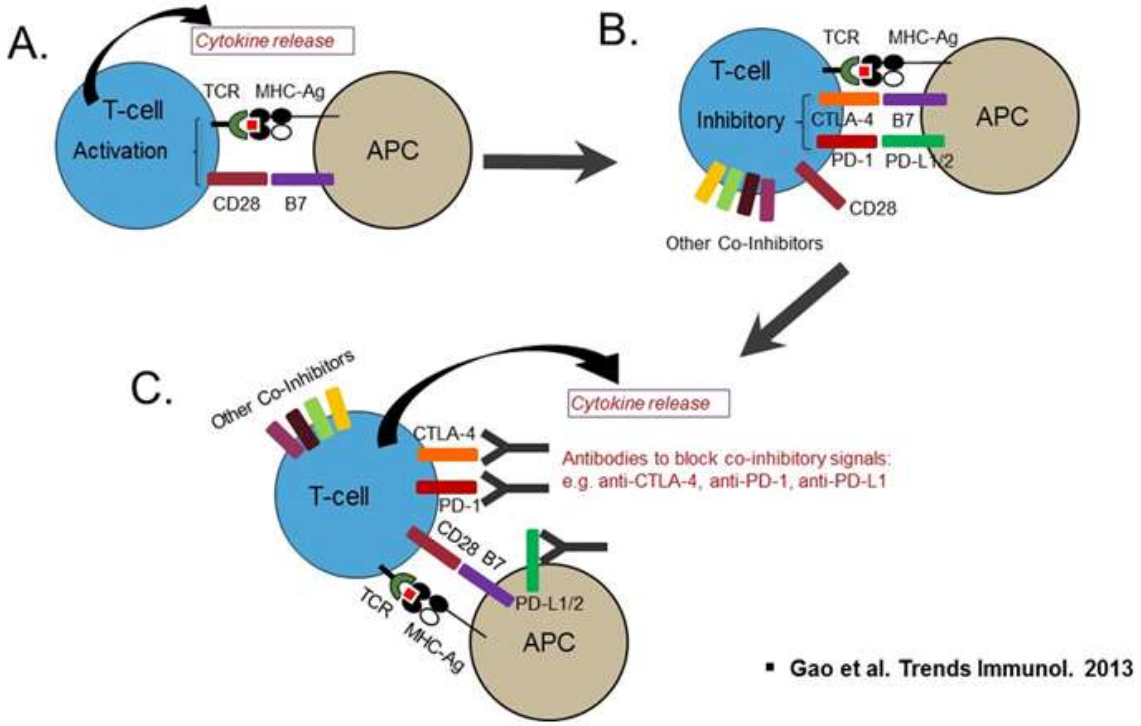
Disclosure

- No Financial Disclosure.

Immune checkpoint therapy provides durable clinical responses in various cancer types



- Gao et al. Trends Immunol. 2013

Challenges with immune checkpoint therapy

- Response rate with monotherapy is 20-30%.

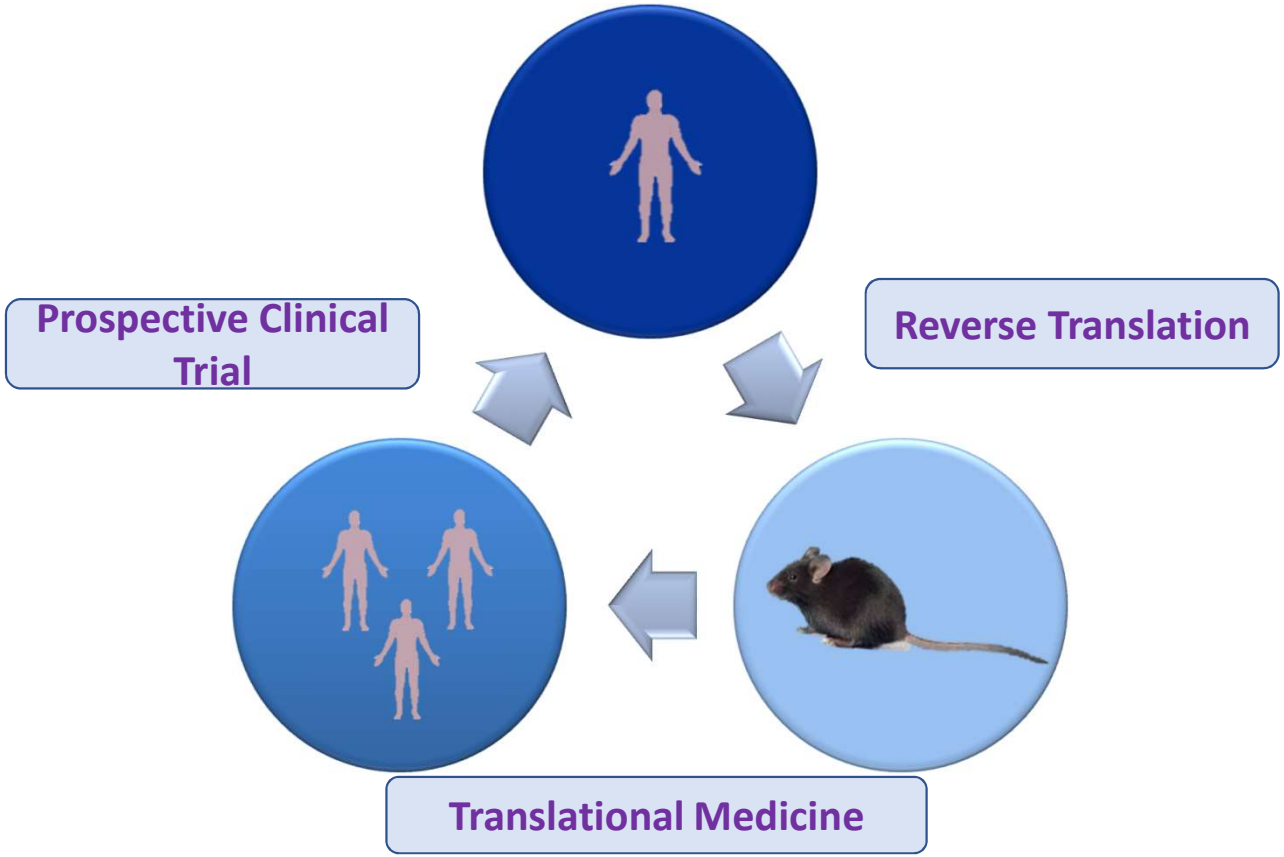
How other modalities could modify the tumor immune microenvironment to improve response to immune checkpoints?

- Multiple immune checkpoint exists.

How to rationally combine different immune checkpoints in a tumor-specific manner?

- No Predictive biomarkers to enable patient selection.

How to identify relevant biomarkers which integrate both tumor and immune microenvironment?


Prospective Clinical Trial
Reverse Translation
Translational Medicine

- Response rate with monotherapy is 20-30%.

How other modalities could modify the tumor immune microenvironment to improve response to immune checkpoint therapy?

- Multiple immune checkpoint exists.

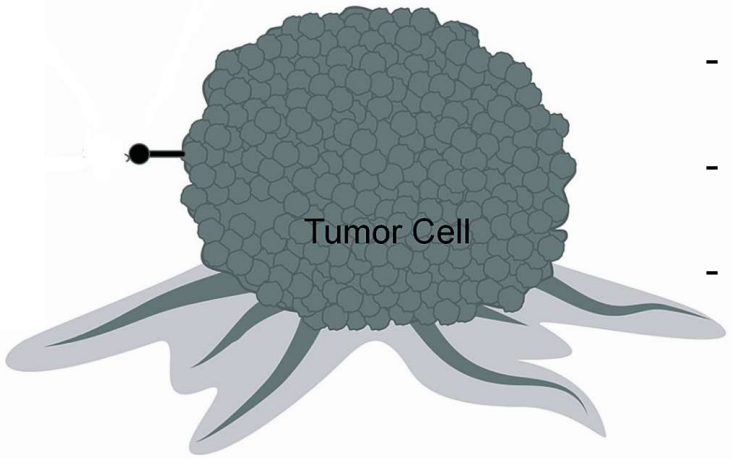
How to rationally combine different immune checkpoints in a tumor specific manner?

- Identification of predictive biomarkers to enable patient selection

How to identify relevant biomarkers which integrates both tumor and immune microenvironment?

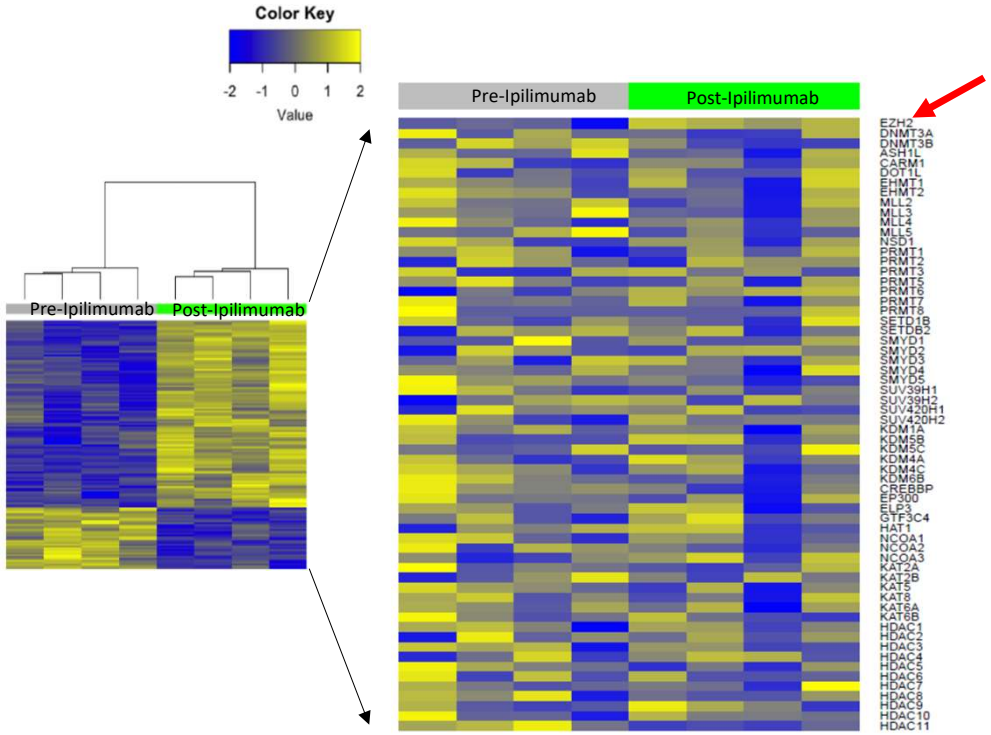
Resistance Mechanisms in Immune Checkpoint Therapy

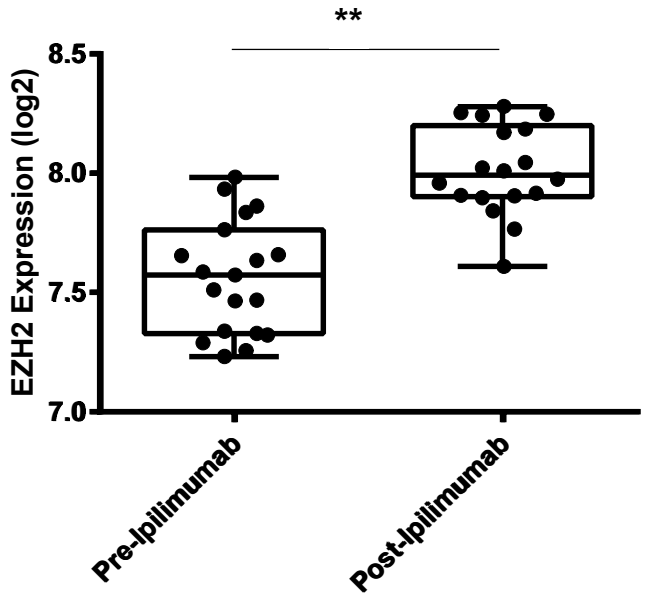
Epigenetic changes in tumor cells



- **Alternation of signaling pathways**
- **Defect in antigen processing machinery**
- **Defective IFN-γ signaling**
- **Immune-suppressive tumor microenvironment**

Anti-CTLA4 (Ipilimumab) treatment increases EZH2 expression in T cells





(Goswami et al., Journal of Clinical Investigation 2018)

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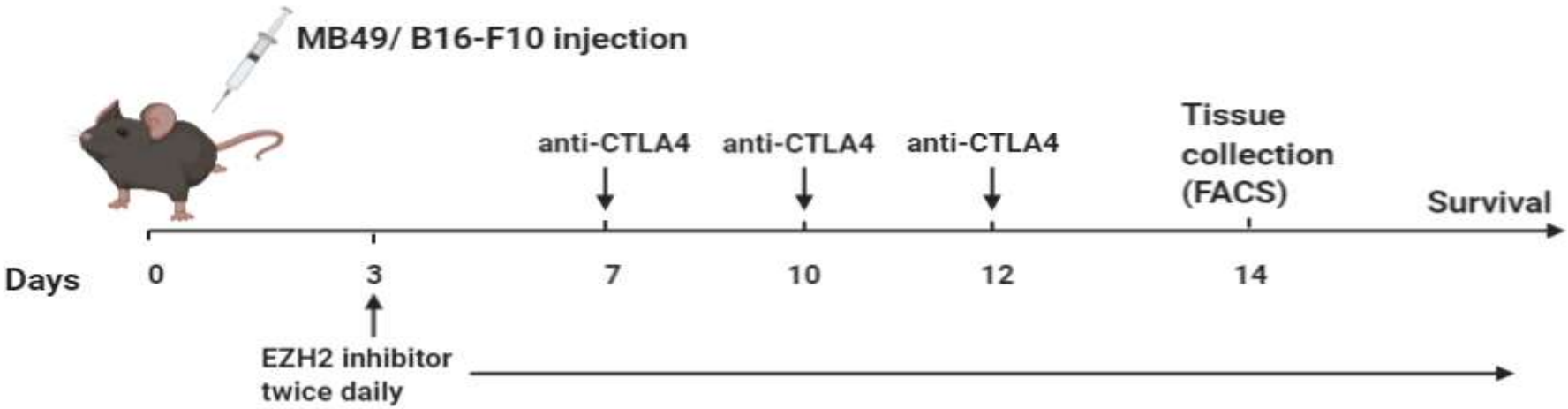
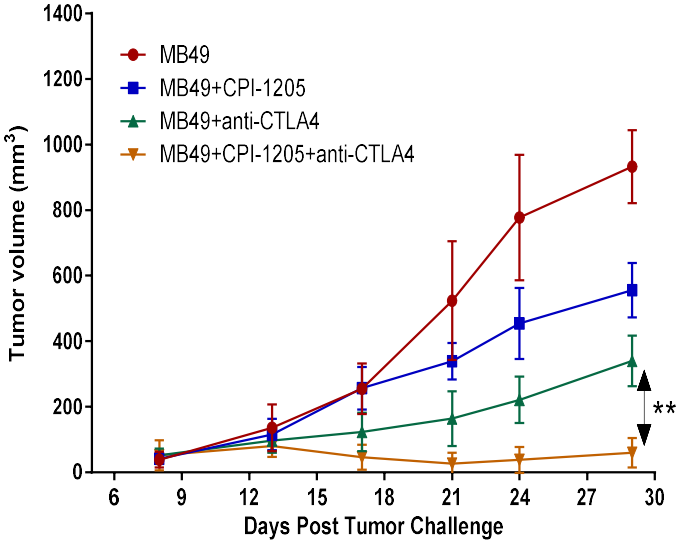
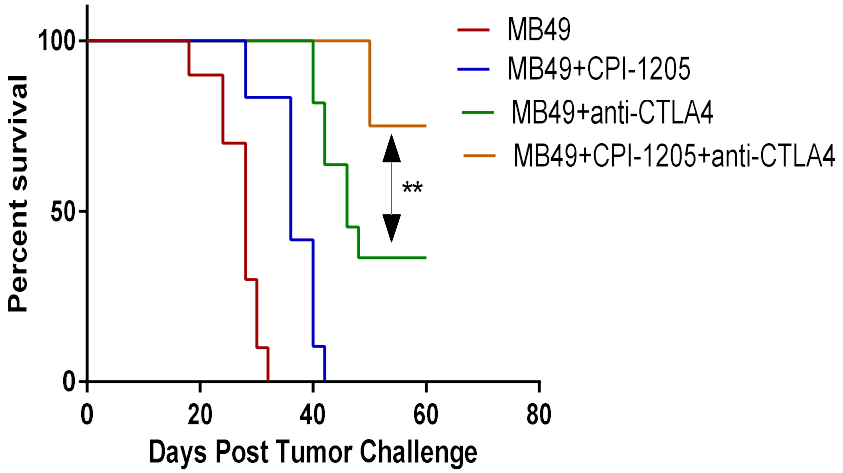
Can immune cells be epigenetically re-programmed to enhance efficacy of immune checkpoint therapy?


MB49/ B16-F10 injection
anti-CTLA4
anti-CTLA4
anti-CTLA4
Tissue collection (FACS)
Survival
Days
0
3
7
10
12
14
EZH2 inhibitor twice daily

Pharmacological inhibition of EZH2 increases the effectiveness of anti-CTLA-4 therapy





(Goswami et al., Journal of Clinical Investigation 2018)

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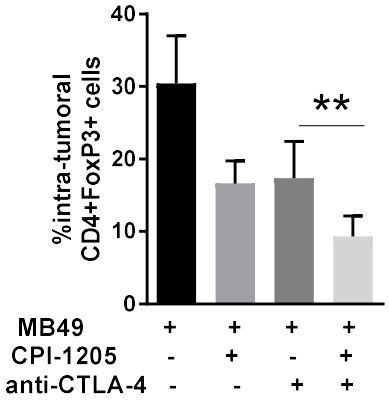
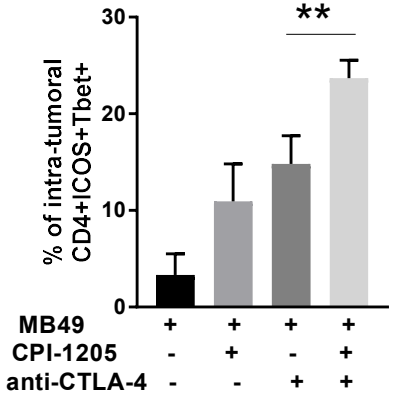
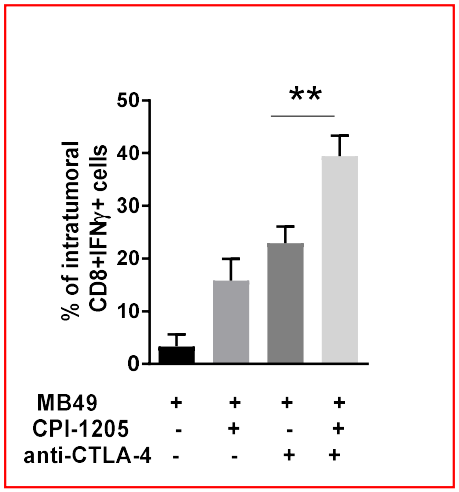
Anti-CTLA-4 mediated expression of EZH2 increases effectiveness of anti-CTLA-4 therapy







(Goswami et al., Journal of Clinical Investigation 2018)

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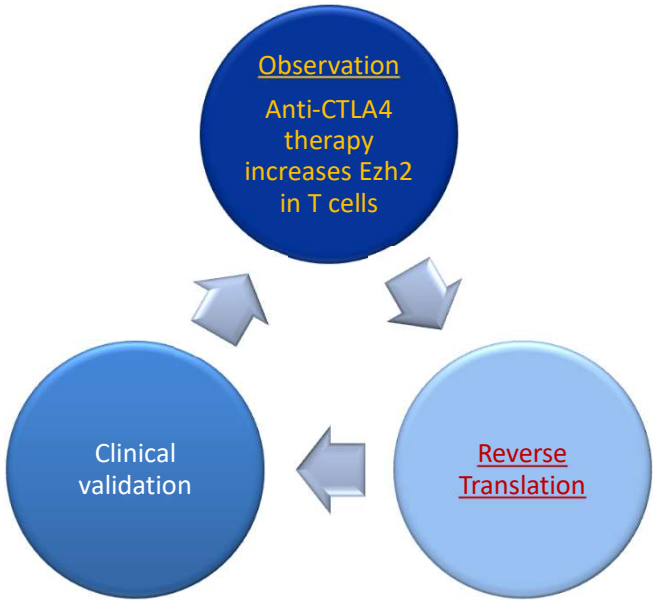
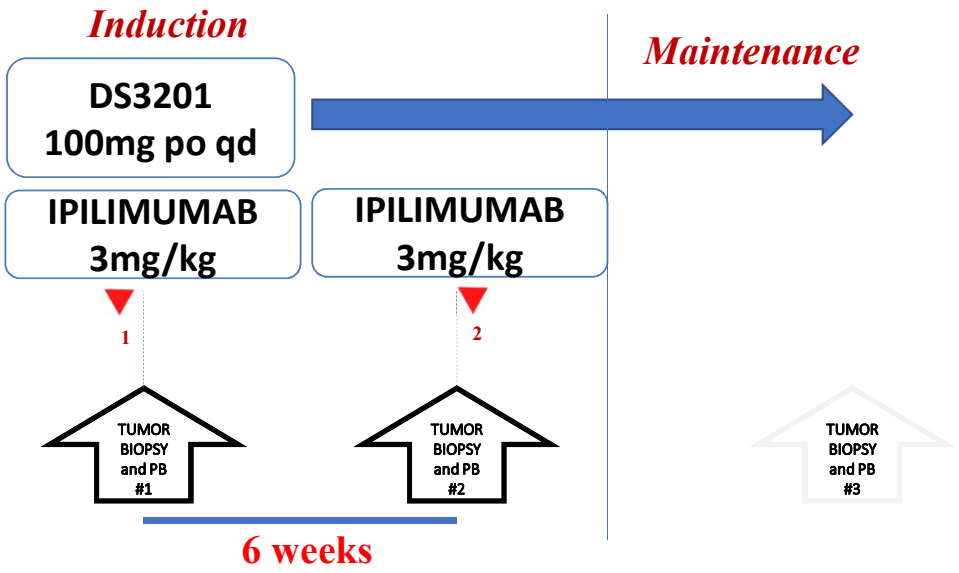
Summary



- Ipilimumab therapy increases EZH2 expression in T cells.

- EZH2 inhibition improves cytotoxic function of effector T cells
- EZH2 inhibition attenuates suppressive function of regulatory T cells.
- EZH2 inhibition changes the phenotype of regulatory T cells to effector like T cells.
- Inhibition of EZH2 increases effectiveness of anti-CTLA-4 therapy.

IRB-approved protocol : DS3201 (EZH1/2-inh) plus Ipilimumab



DS3201-Ipilimumab Clinical Trial Schema.

PI: Aparicio; Co-PI: Goswami

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- Response rate with monotherapy is 20-30%.

How other modalities could modify the tumor immune microenvironment to improve response to immune checkpoints?

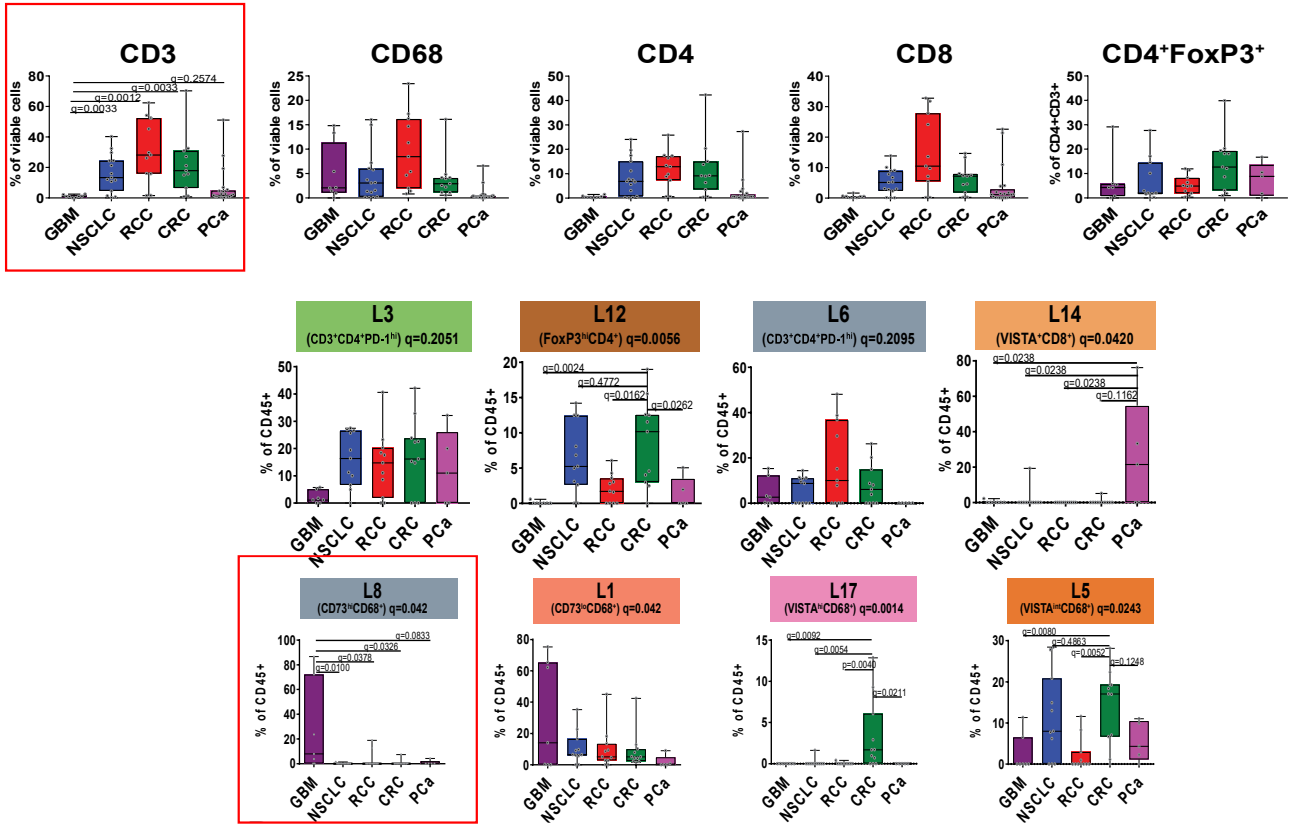
- Multiple immune checkpoint exists.

How to rationally combine different immune checkpoints in a tumor specific manner?

- Identification of predictive biomarkers to enable patient selection

How to identify relevant biomarkers which integrates both tumor and immune microenvironment?

Immune Profiling of 5 Different Human Tumor Types showed distinct tumor immune microenvironments



(Goswami et al., Nature Medicine 2019)

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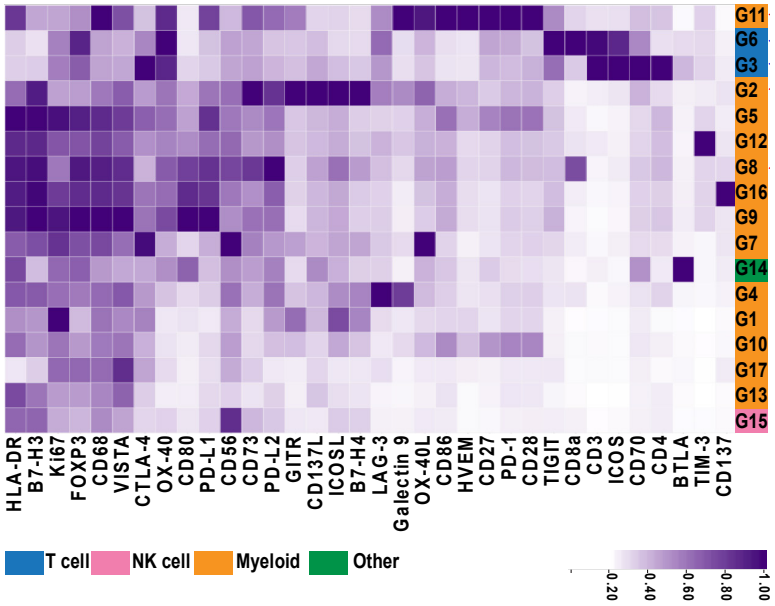
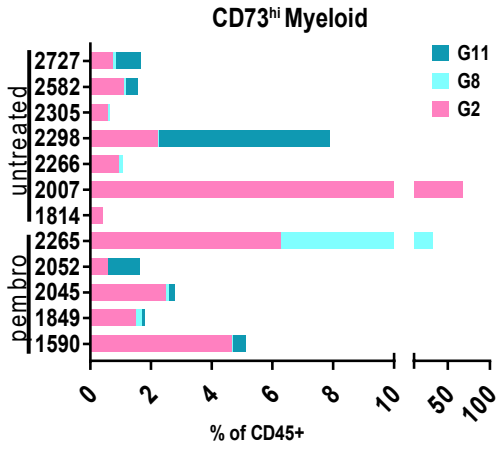
Intra-tumoral immune suppressive myeloid cells persist in GBM after anti-PD-1 therapy





(Goswami et al., Nature Medicine 2019)

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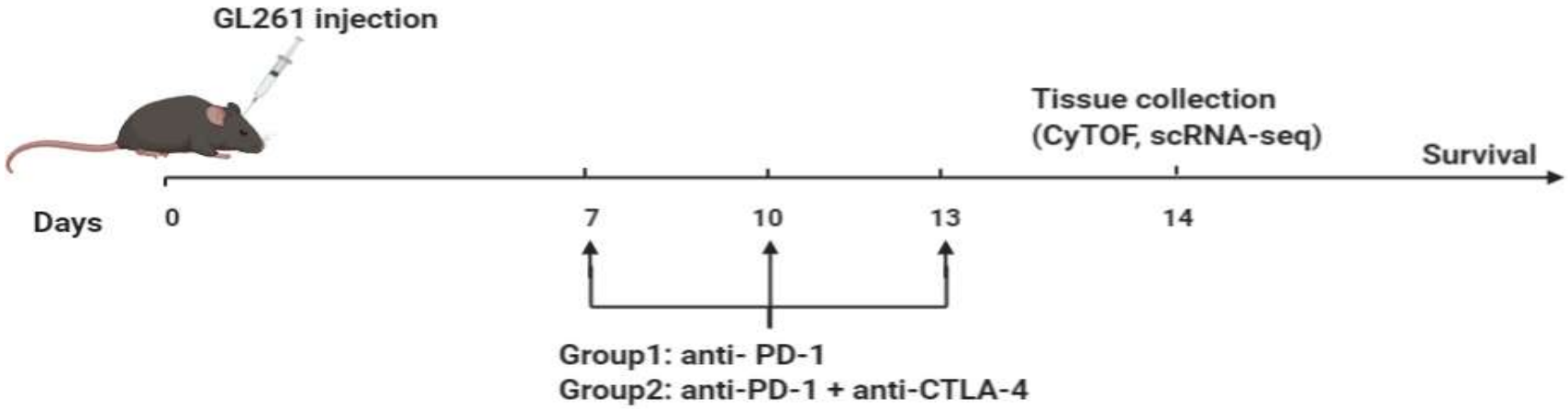
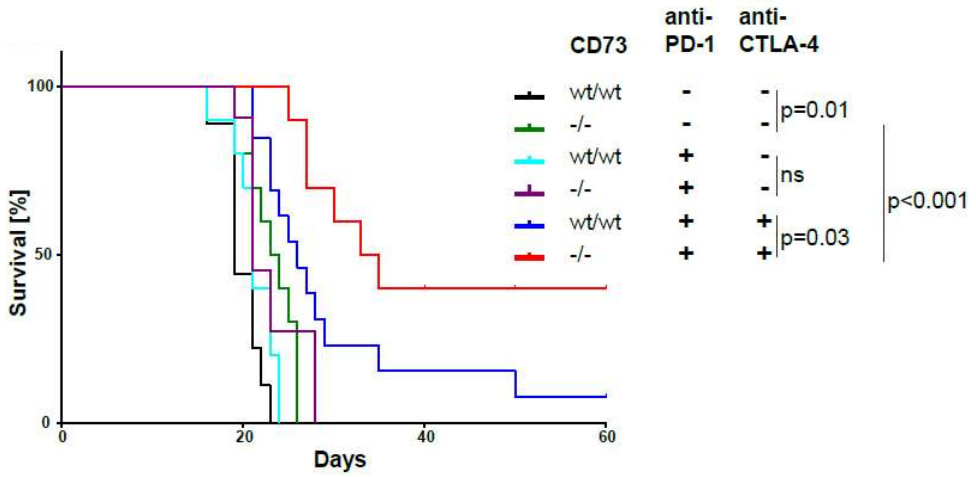
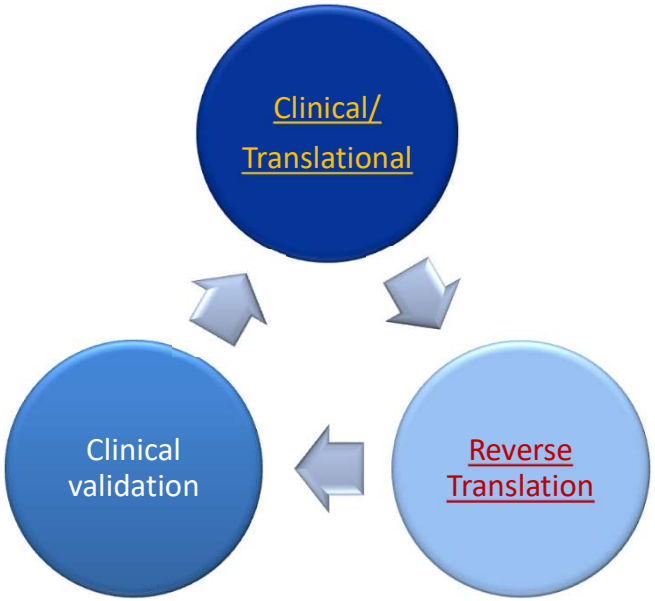

GL261 injection
Tissue collection
(CyTOF, scRNA-seq)
Survival
Days
0
7
10
13
14
Group1: anti- PD-1
Group2: anti-PD-1 + anti-CTLA-4

Improved tumor rejection and survival with ICT in absence of CD73



Goswami et al., *Nature Medicine*, 2020

Summary



- $CD73^{hi}$ myeloid population to be specifically present in GBM that persisted even after treatment with anti-PD-1 therapy.
- Improved survival with ICT in absence of CD73 in a murine model of GBM
- We propose a combination therapy strategy to target CD73 plus dual blockade of PD-1 and CTLA-4.

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- Combination of immune checkpoint agents with other modalities such as chemotherapy or radiation therapy.

How other modalities could modify the tumor immune microenvironment to improve response to immune checkpoints?

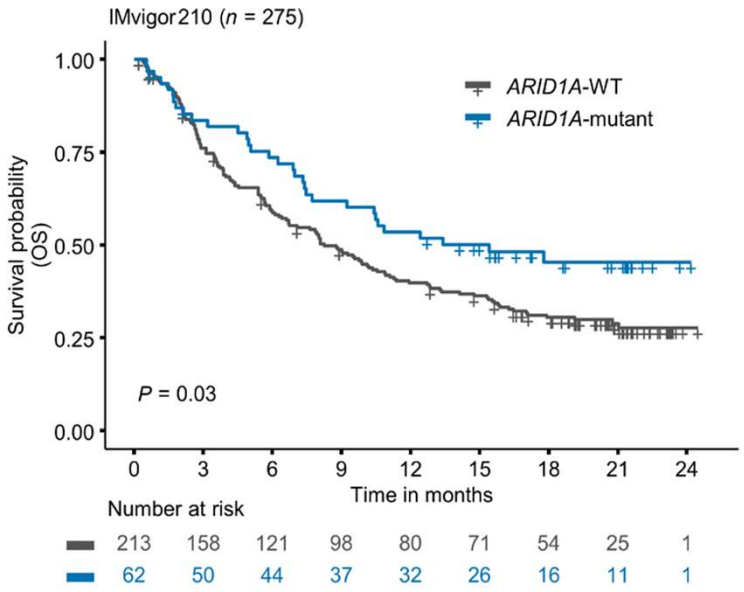
- Multiple immune checkpoint exists.

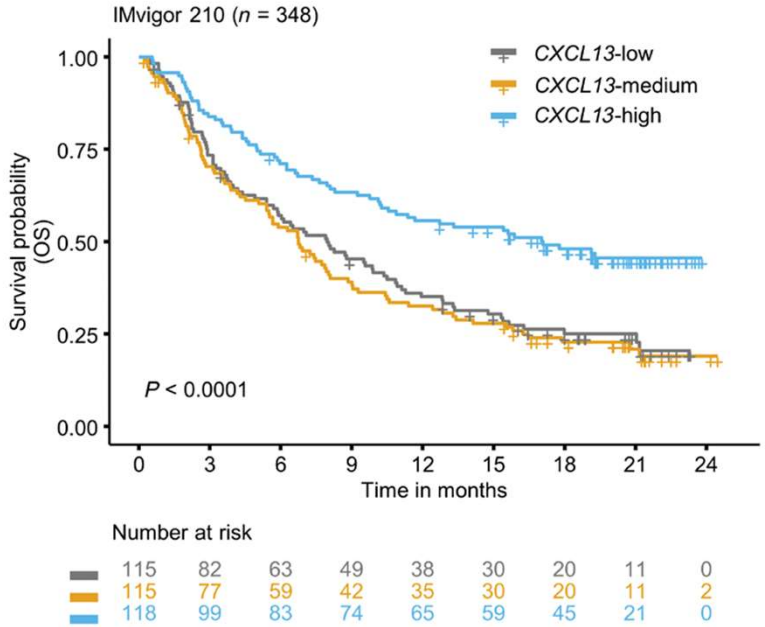
How to rationally combine different immune checkpoints in a tumor specific manner?

- Identification of predictive biomarkers to enable patient selection

How to identify relevant biomarkers which integrates both tumor and immune microenvironment?

ARID1A mutation and high baseline CXCL13 expression correlates with improved overall survival in patients with metastatic urothelial cancer





Goswami et al., *Science Translational Medicine*, 2020

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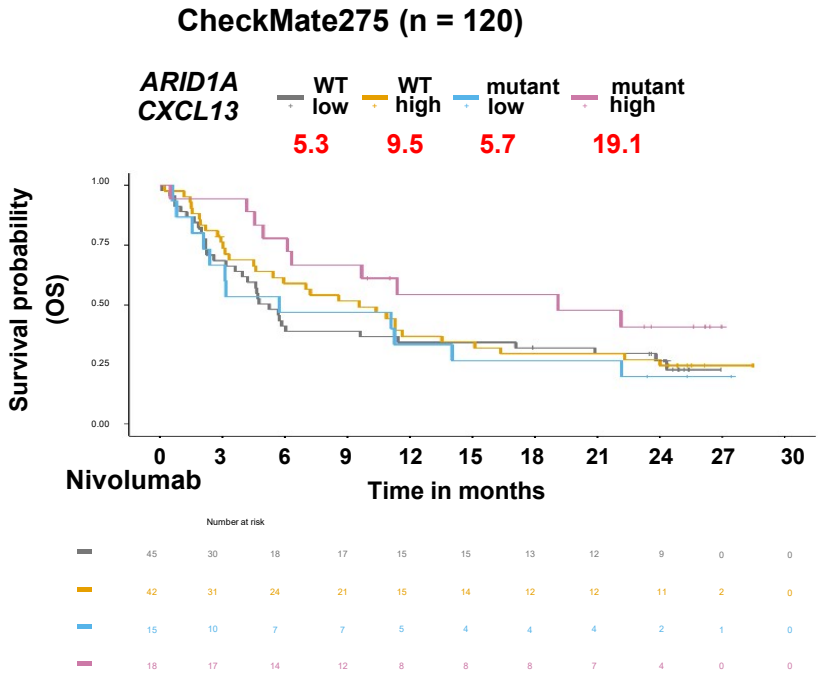
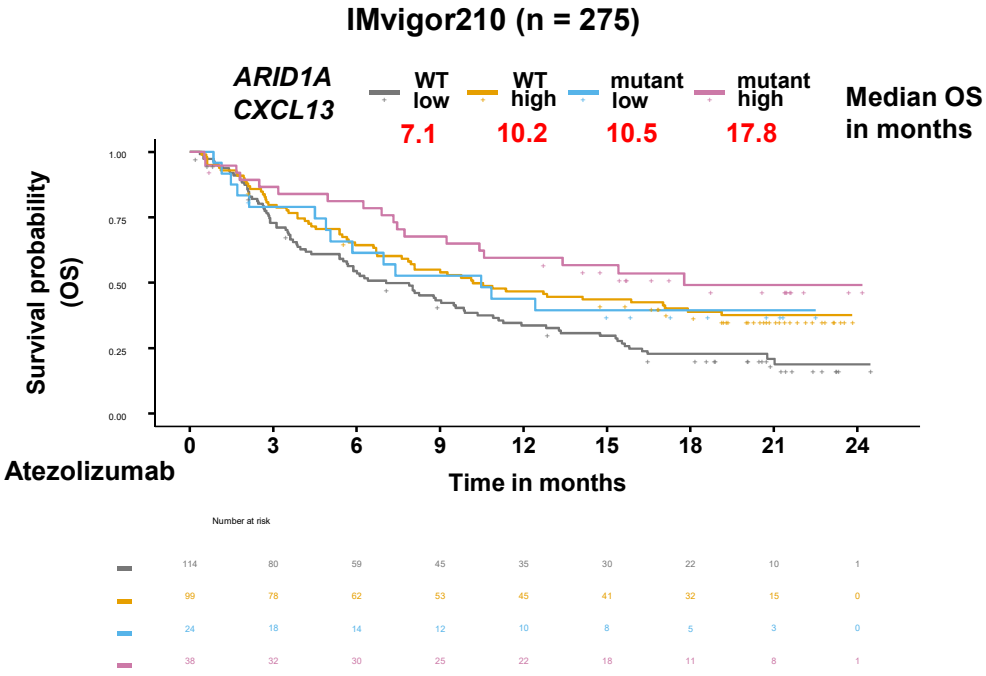
Improved outcomes to anti-PD-1/PD-L1 therapy with combination biomarkers to reflect BOTH tumor mutations and immune response: ARID1A mutation plus CXCL13 expression





Goswami et al., *Science Translational Medicine*, 2020

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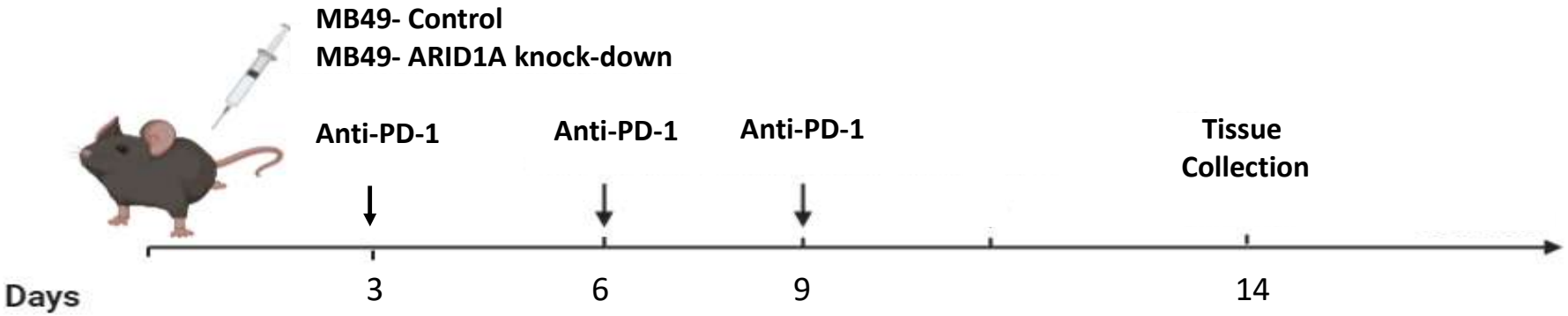

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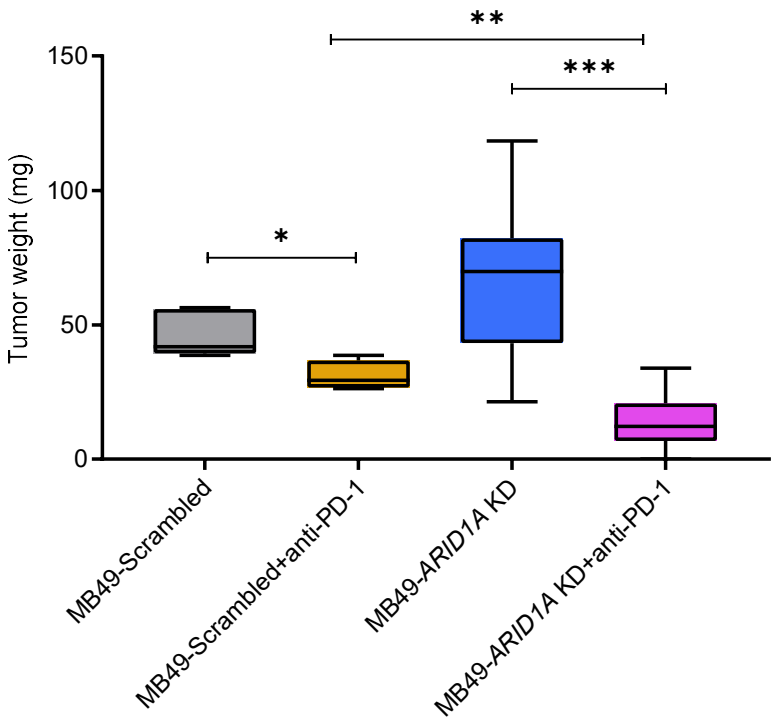
ARID1A knock down confers sensitivity to anti-PD-1 therapy



Goswami et al., *Science Translational Medicine*, 2020

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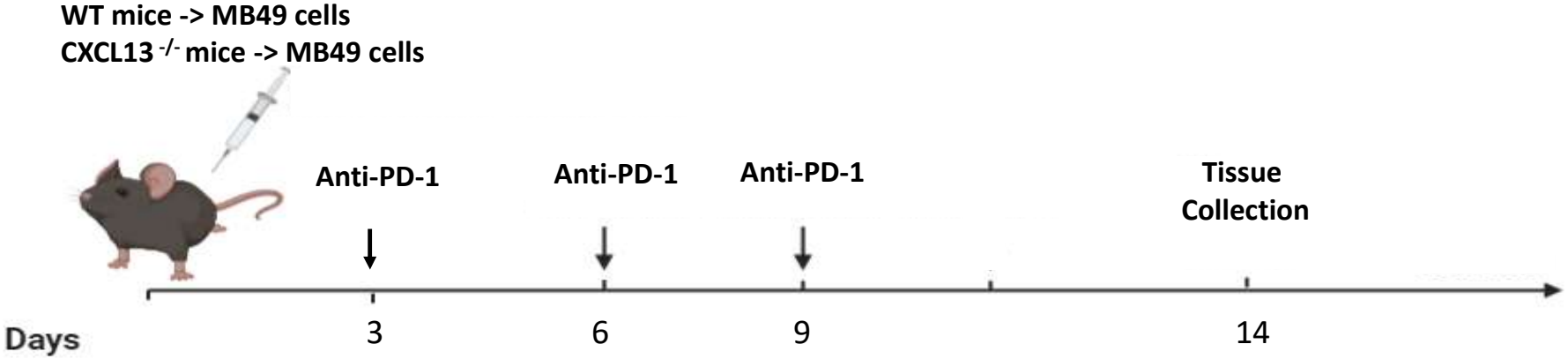
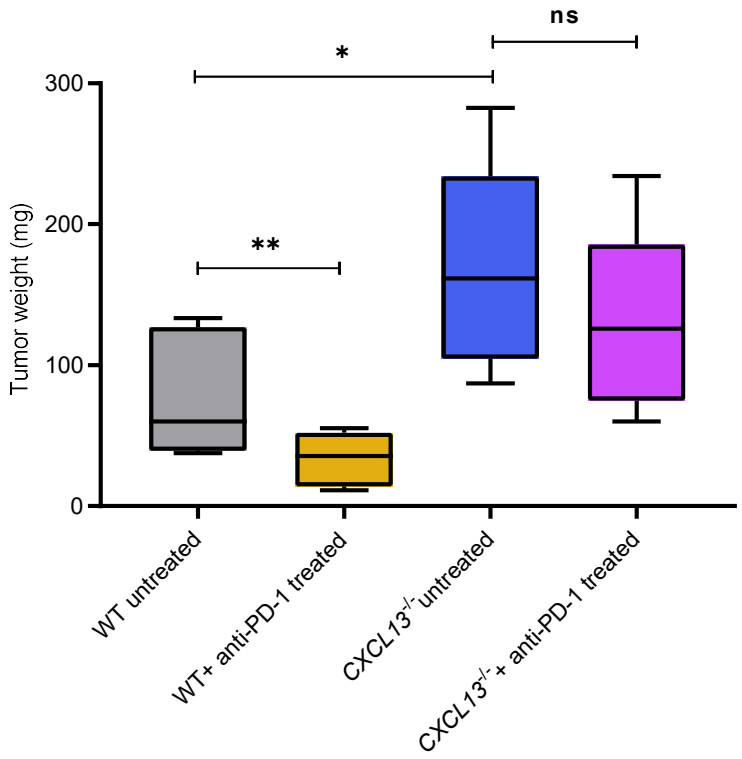

WT mice -> MB49 cells
CXCL13 -/- mice -> MB49 cells
Anti-PD-1
Anti-PD-1
Anti-PD-1
Tissue Collection
Days
3
6
9
14

CXCL13$^{-/-}$ tumor bearing mice are resistant to anti-PD-1 therapy



Goswami et al., *Science Translational Medicine*, 2020

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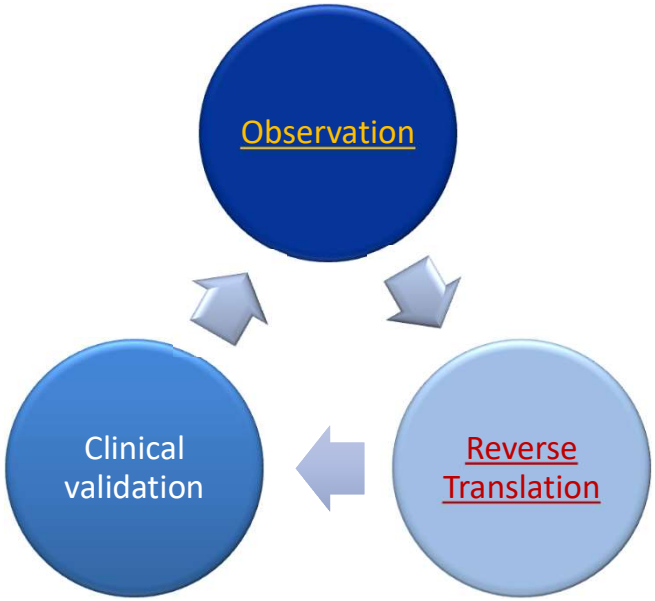
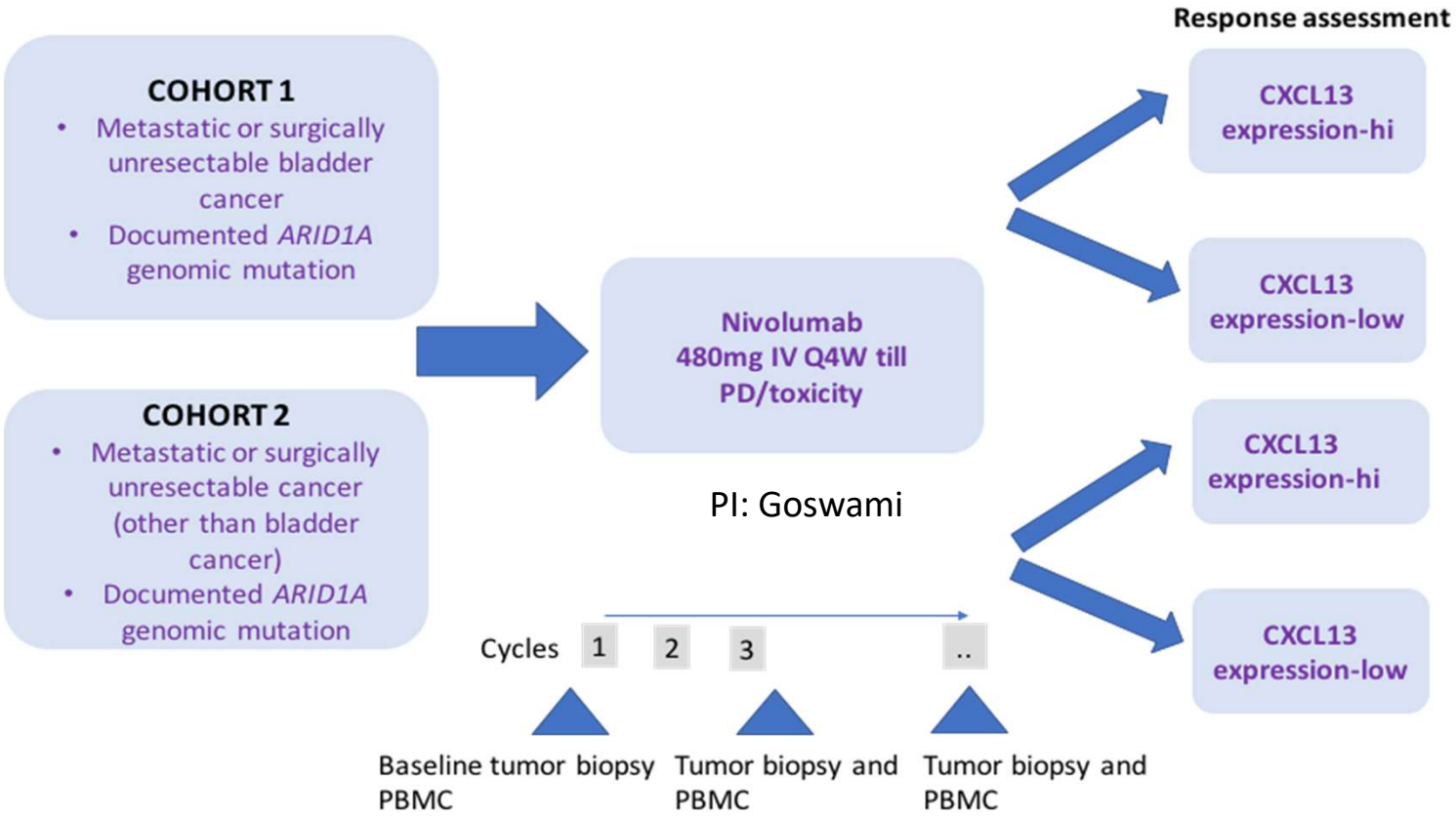
Summary



- *ARID1A* mutation and CXCL13 expression correlates with improved overall survival of patients with metastatic bladder cancer.
- Combinatorial biomarkers have improved predictive power.
- *ARID1A* knockdown in tumor cells enhances sensitivity to anti-PD-1 therapy whereas CXCL13 null tumor bearing mice are resistant to anti-PD-1 therapy.

Prospective Clinical Trial: Under Review



Co-primary endpoints: ORR and OS

Validate CXCL13 gene expression with IHC assay and develop CLIA-certified IHC assay

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Conclusions

- Response rate with monotherapy is 20-30%.

How other modalities could modify the tumor immune microenvironment to improve response to immune checkpoints?

Epigenetic modulator such as EZH2 inhibition enhances anti-CTLA-4 mediated anti-tumor immunity.

- Multiple immune checkpoint exists.

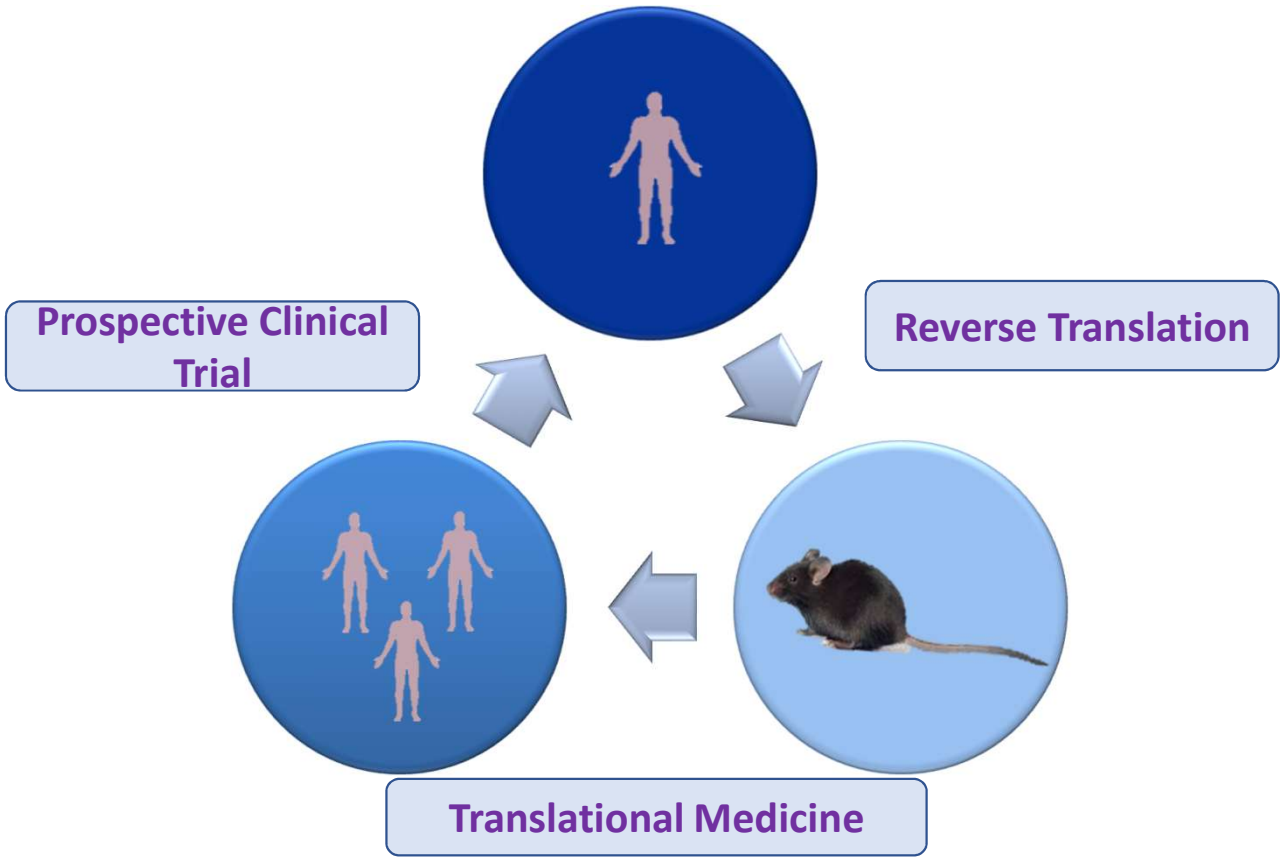
How to rationally combine different immune checkpoints in a tumor specific manner?

CD73 is a rational target to increase efficacy of immune checkpoint therapy in GBM.

- Identification of predictive biomarkers to enable patient selection.

How to identify relevant biomarkers which integrate both tumor and immune microenvironment?

Combination biomarker of ARID1A mutation and CXCL13 expression predicts response to immune checkpoint therapy in metastatic urothelial cancer.


Prospective Clinical Trial
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Acknowledgments

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Dr. Jim Allison

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- K12 Calabresi Scholars Award

PATIENTS

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Thank you!