



Antibody-mediated clearance of soluble MIC significantly enhances response to CTLA4 blockade and reduces therapy-induced colitis

Jennifer Wu, PhD

Professor

Feinberg School of Medicine

Robert Lurie Comprehensive Cancer Center

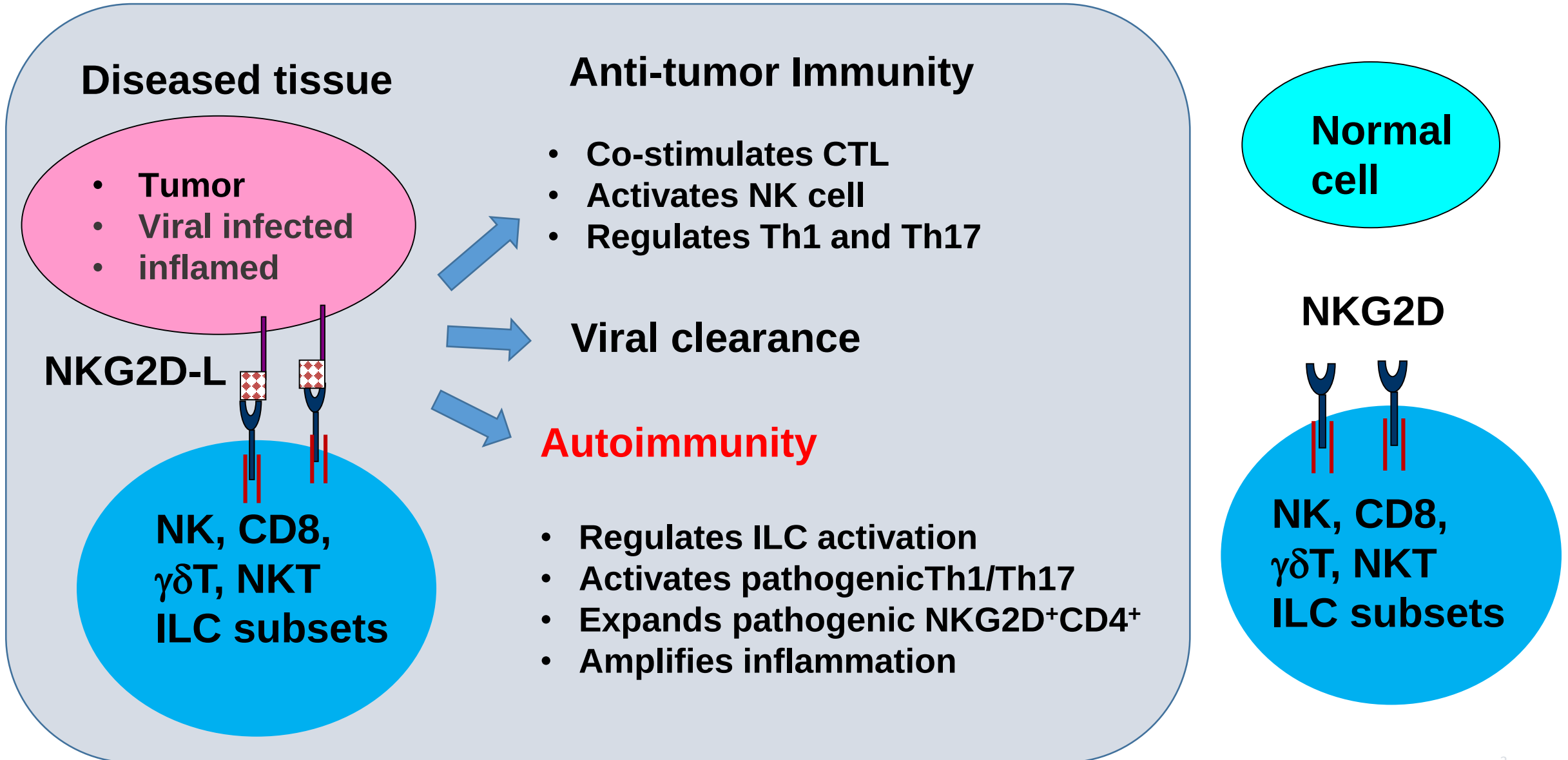
Northwestern University

Disclosure

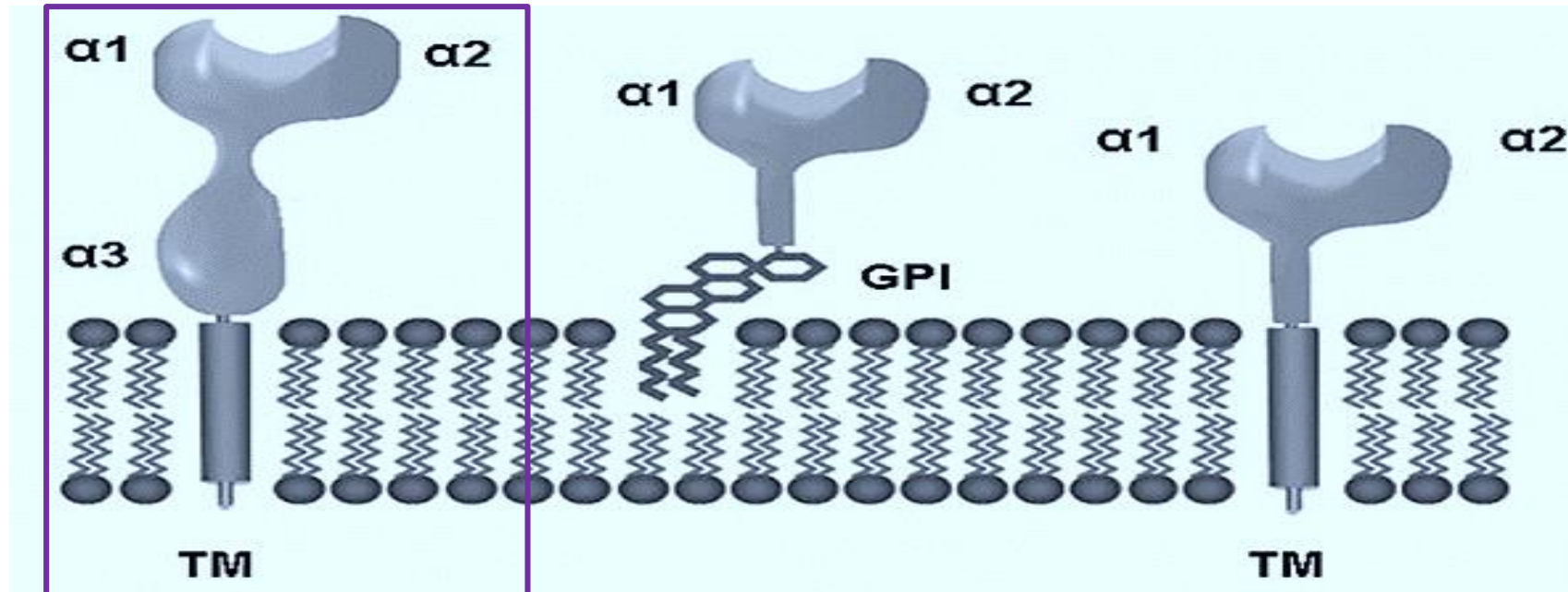
I have no disclosure related to this presentation

“No alternative facts”

Versatile Signaling of NKG2D receptor



Distinct NKG2D-L in Human and Mouse



Human:

MICA, MICB

ULBP1,2,3,6

ULBP4,5

Mice:

NONE

RAE-1 α - ϵ

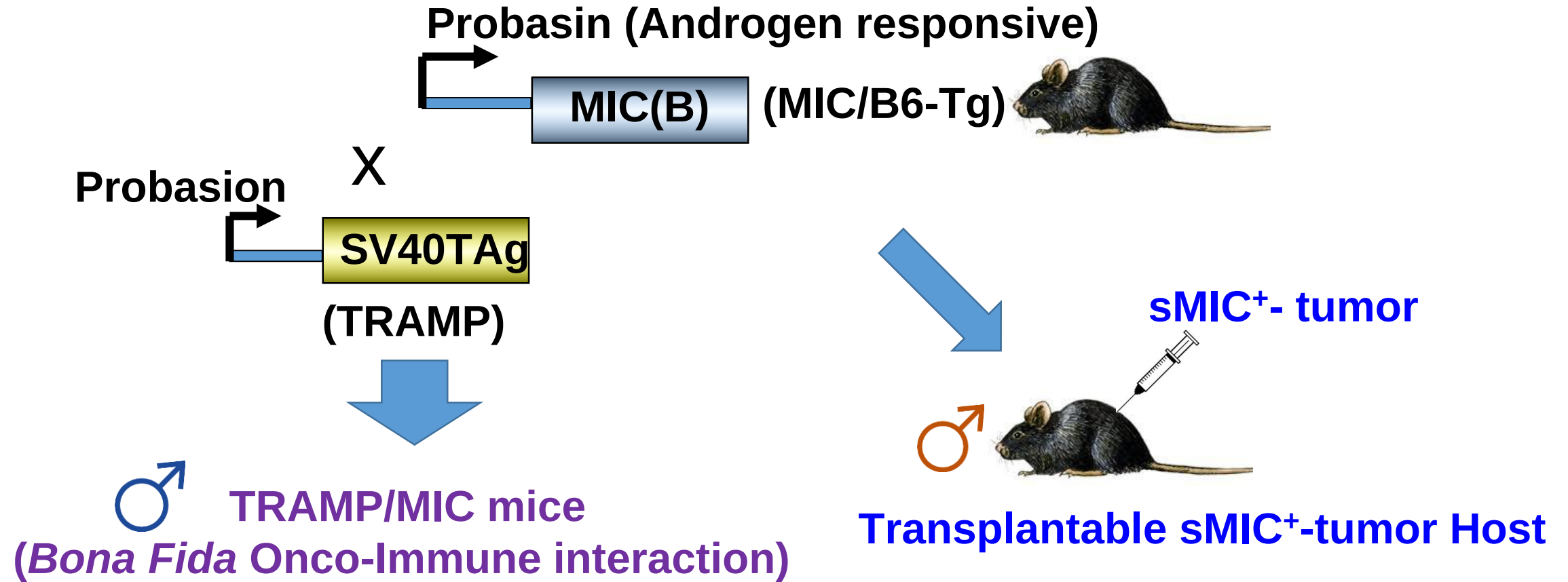
MULT1, H60a,b

MIC = MHC I chain related molecule

ULBP = UL16 binding protein

(Modified From Huergo-Zapico et al.)

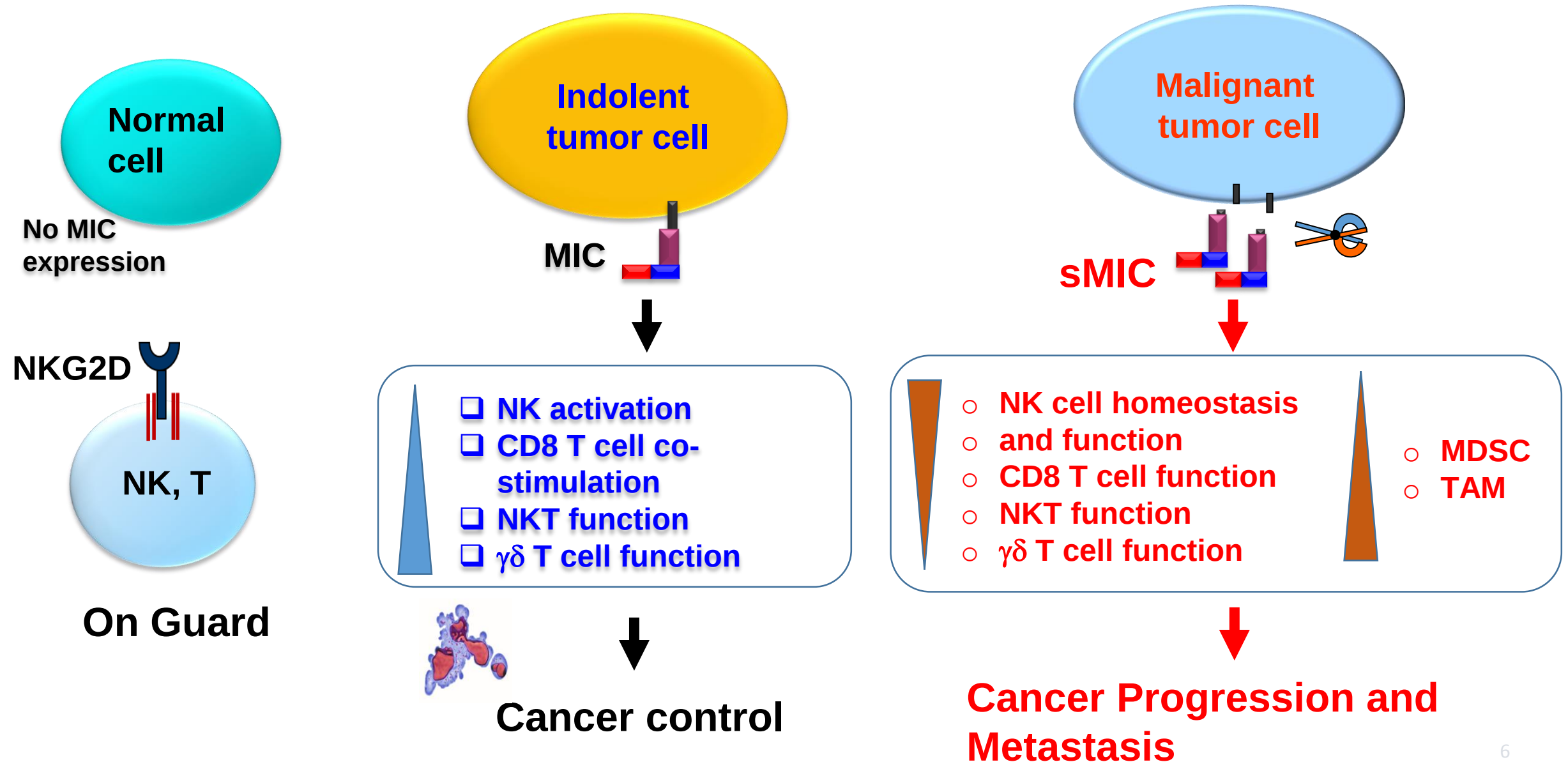
Animal models recapitulate onco-immune dynamics in human



(Liu et al, JCI 2013, Zhang, Sci. Adv., 2017)

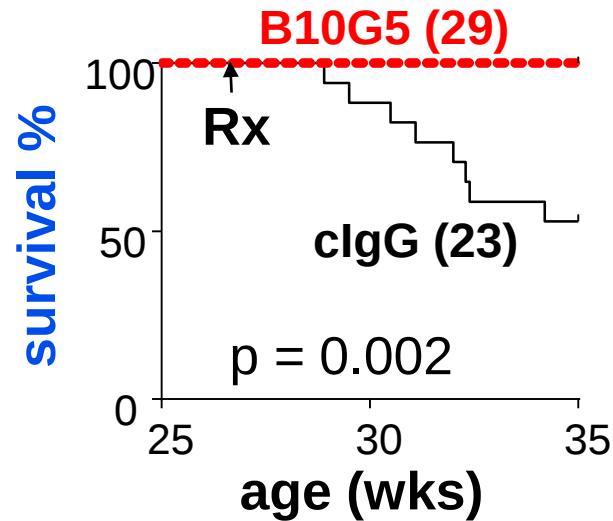
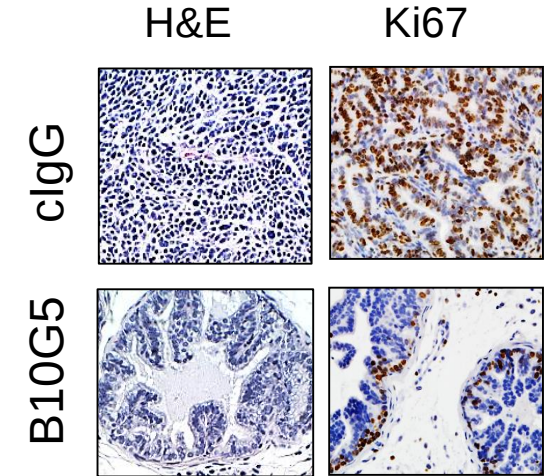
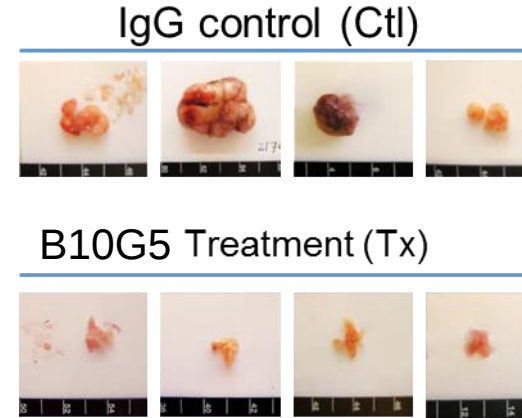
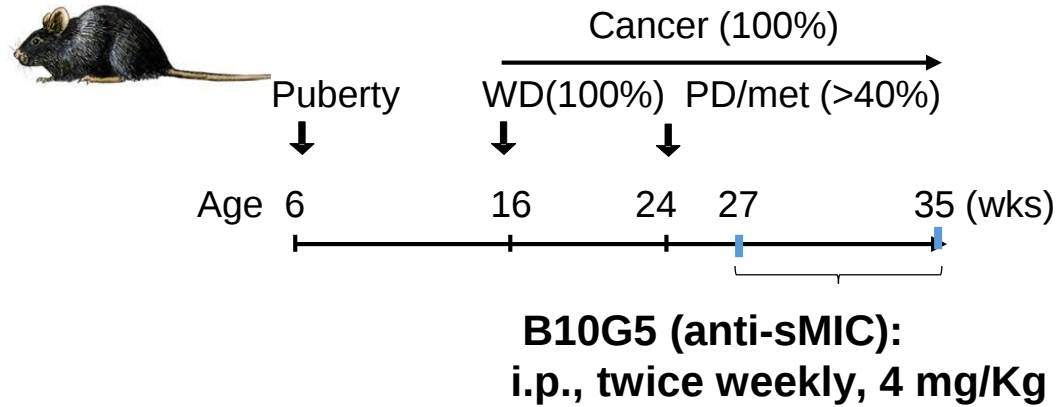
(Liu, et al, JCI, 2013; Lu et al., CCR, 2015; Basher, Oncotarget, 2015)

Opposite role of Human NKG2D-L MIC in tumor immunity

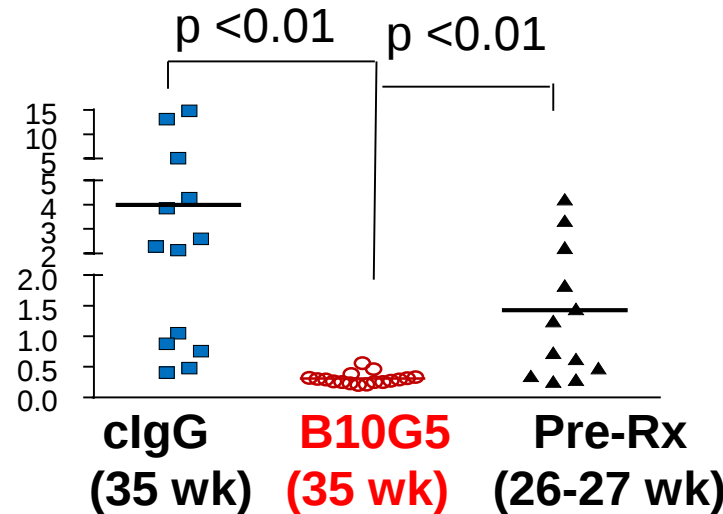


Targeting sMIC Induces Primary Tumor Regression and Eliminates Metastasis

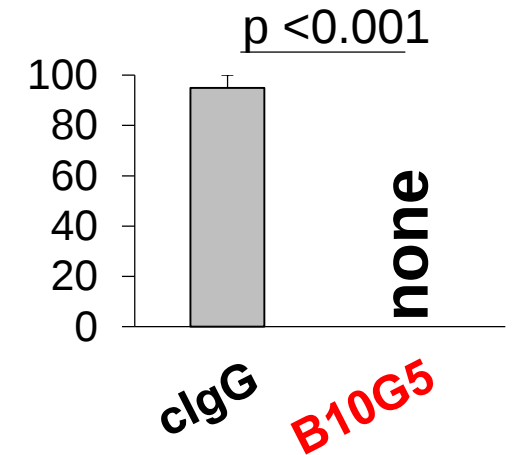
TRAMP/MIC mice



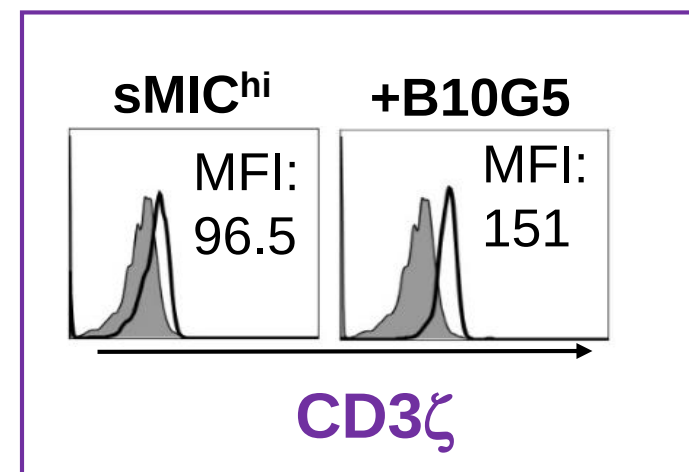
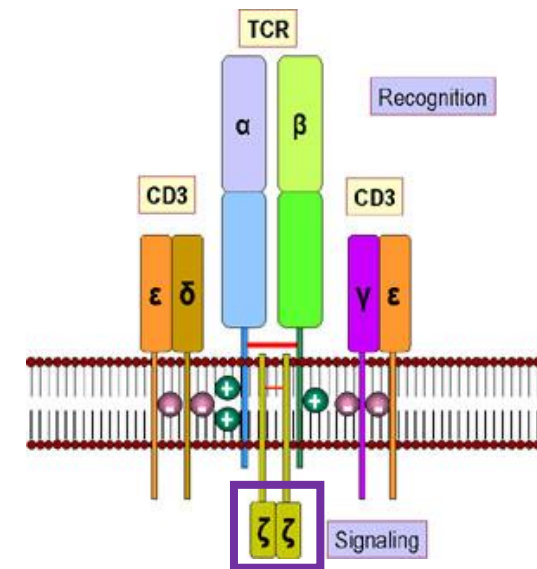
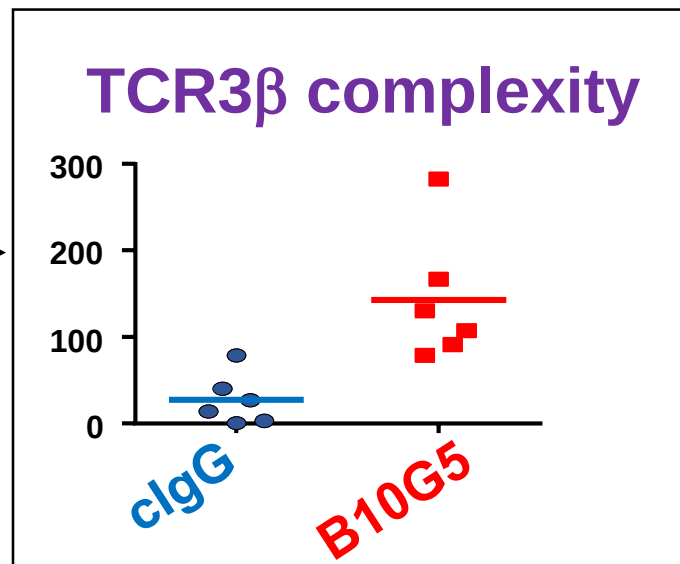
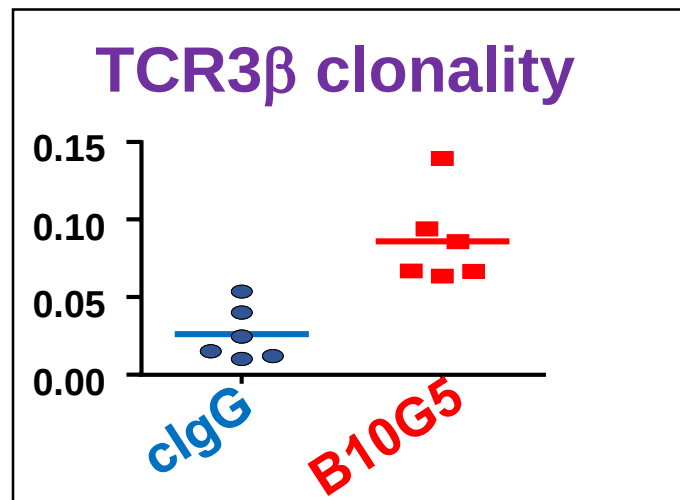
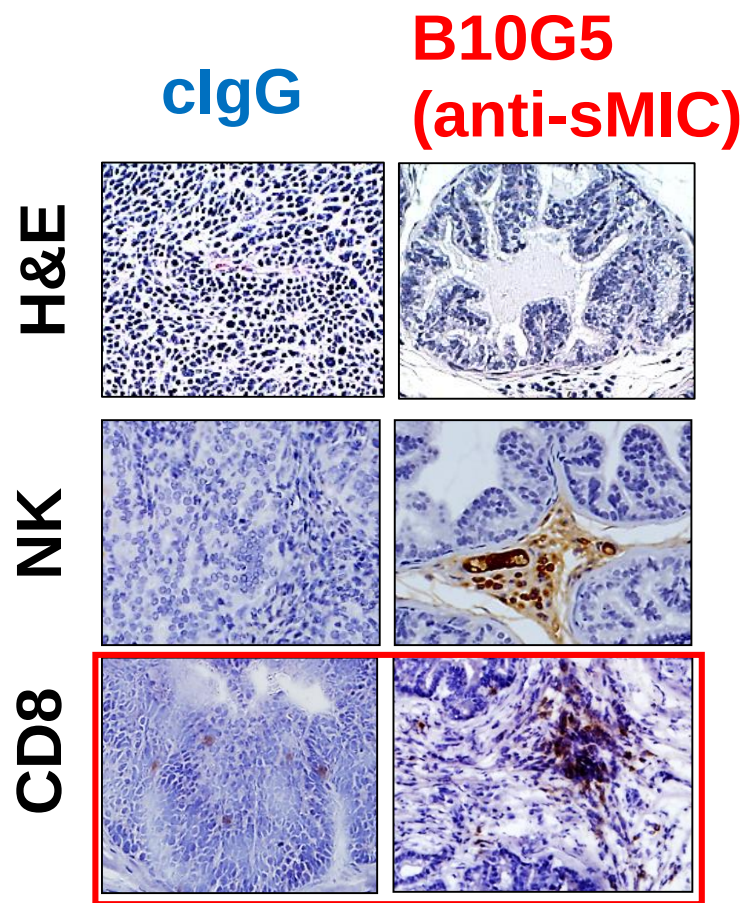
Prostate Weight (g)



Mice% with Metastasis



Clearing sMIC flares up a "cold" tumor



How does it work?



Revive NK cell
homeostasis and function



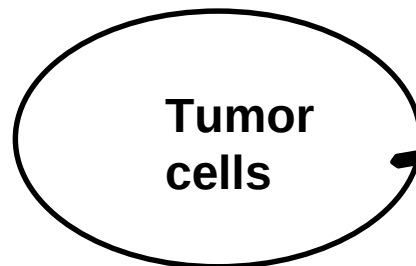
Killing

Cytokines (IFN γ)
Neoantigens

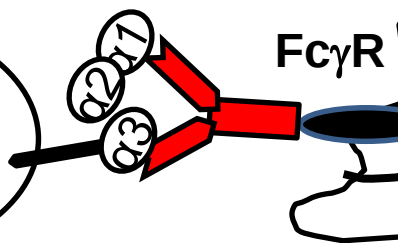
Alleviate global
immune
suppression

Stabilize **CD3 ζ**
(TCR/CD3 complex,
NK-R)

Optimal TCR
stimulation



DC opsonization
cross-presentation



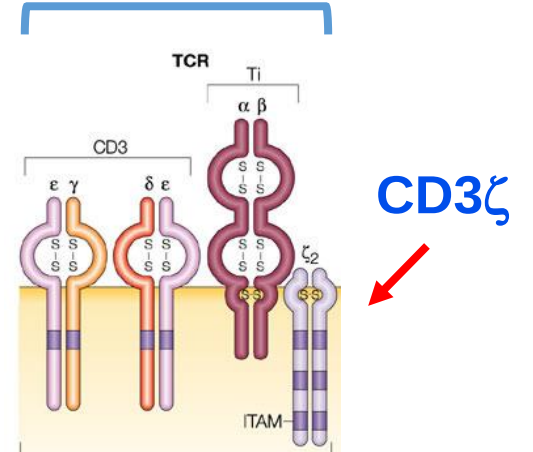
Fc γ R

DC

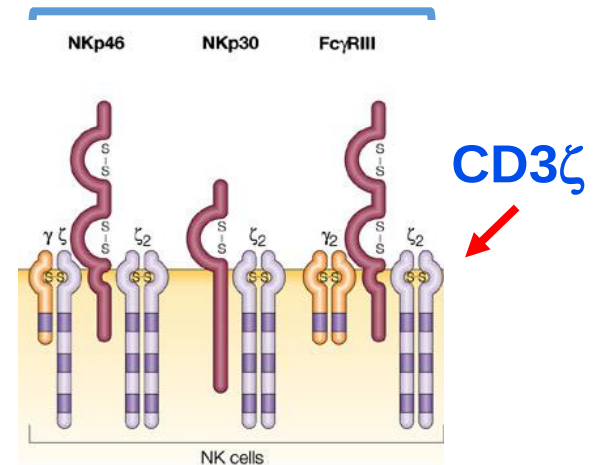
MHC I

CTL

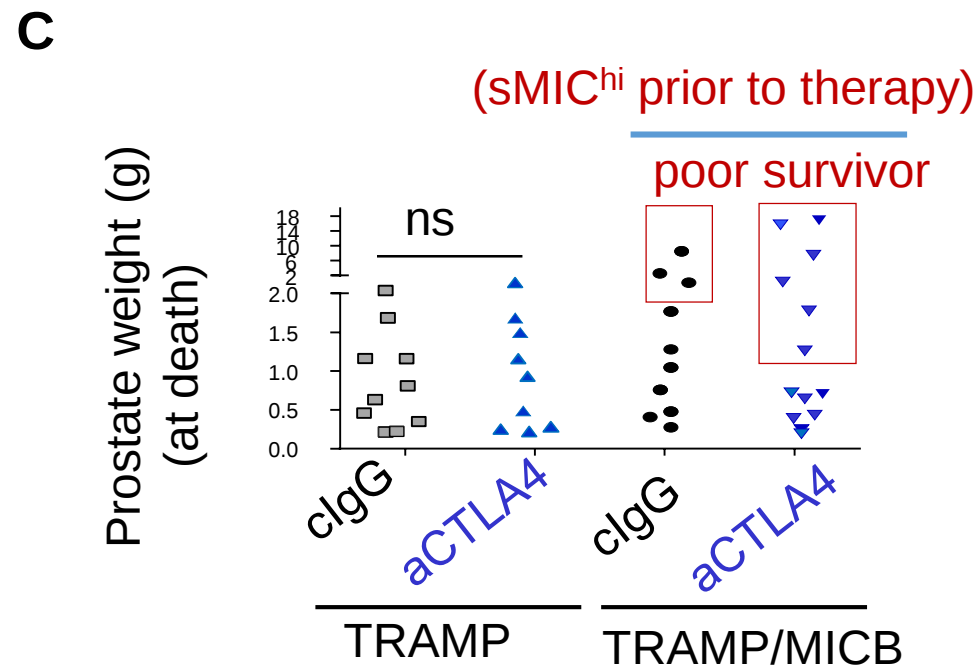
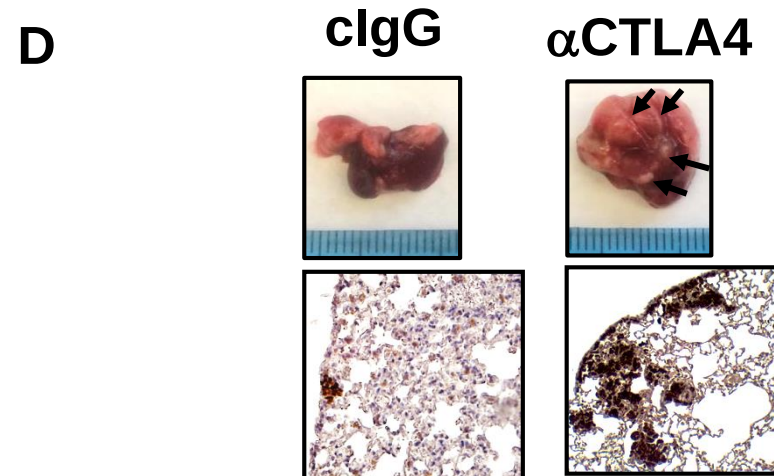
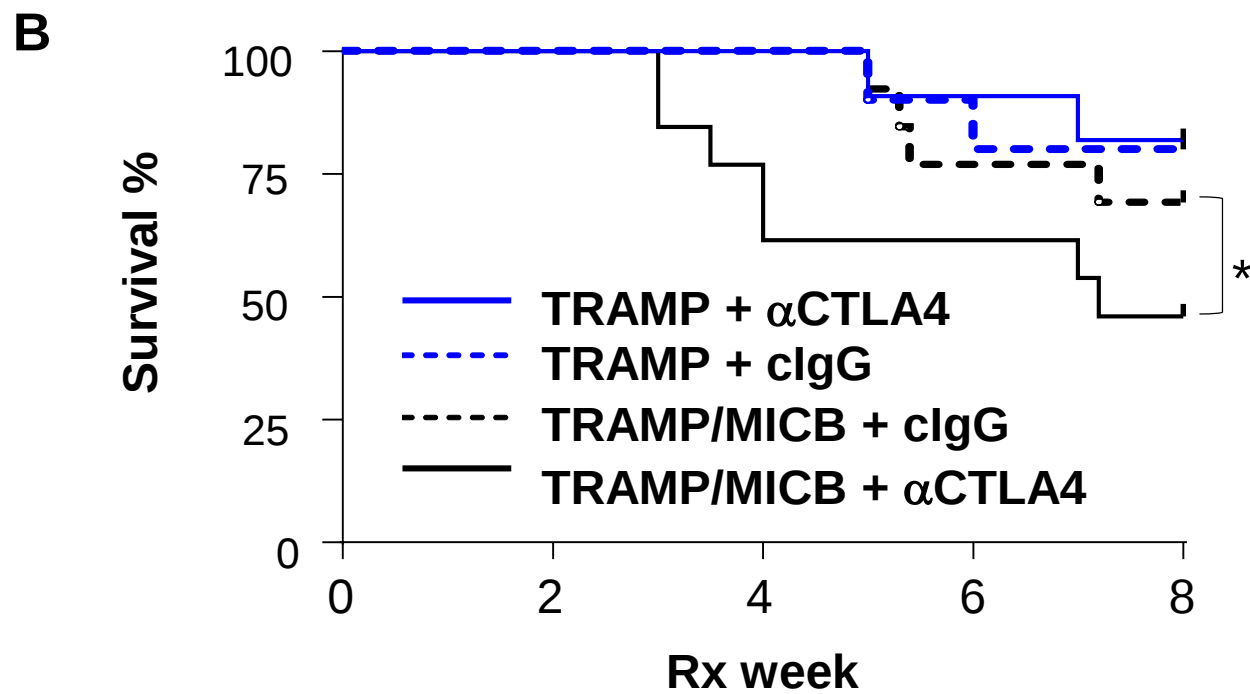
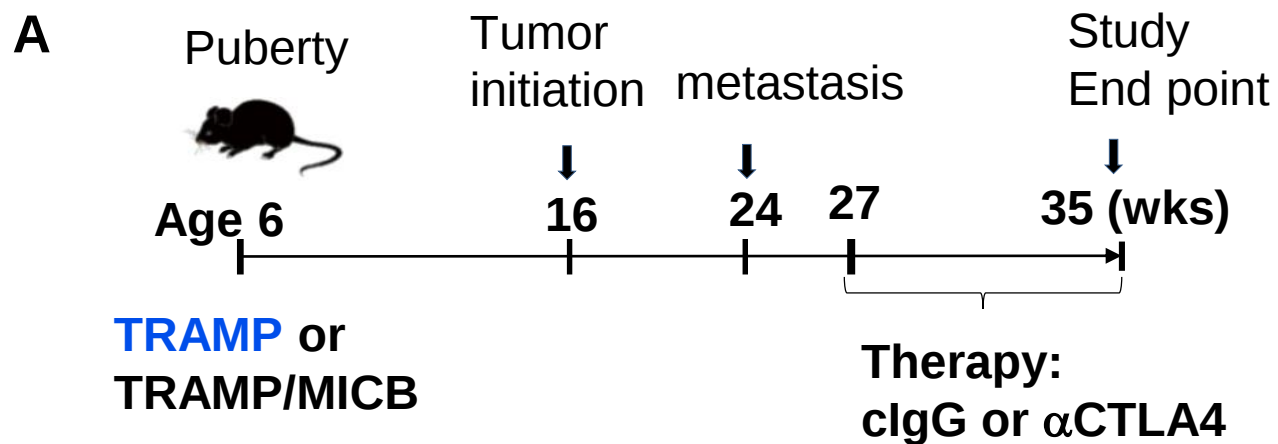
CD3/TCR



NK-R

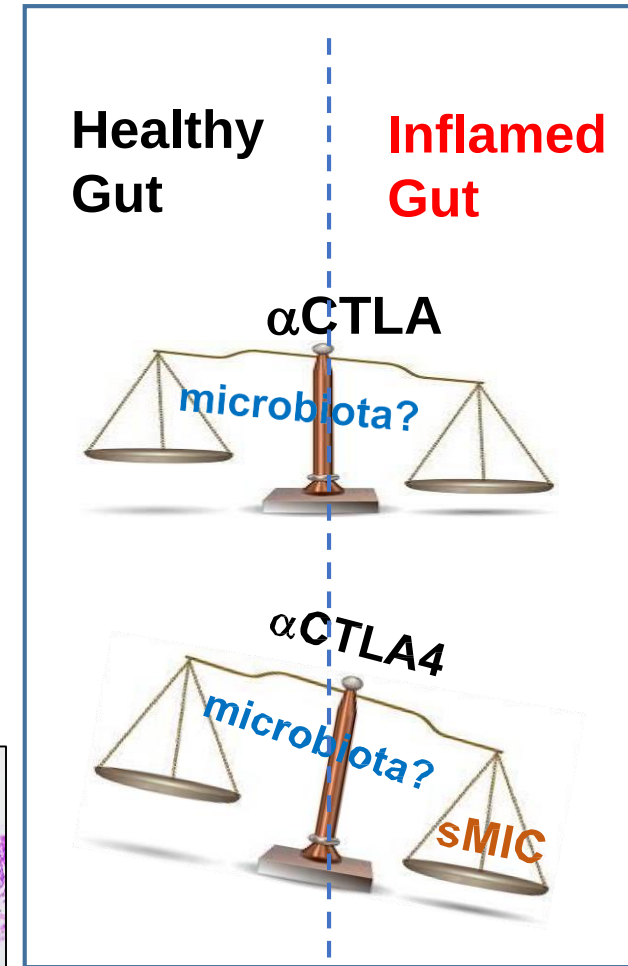
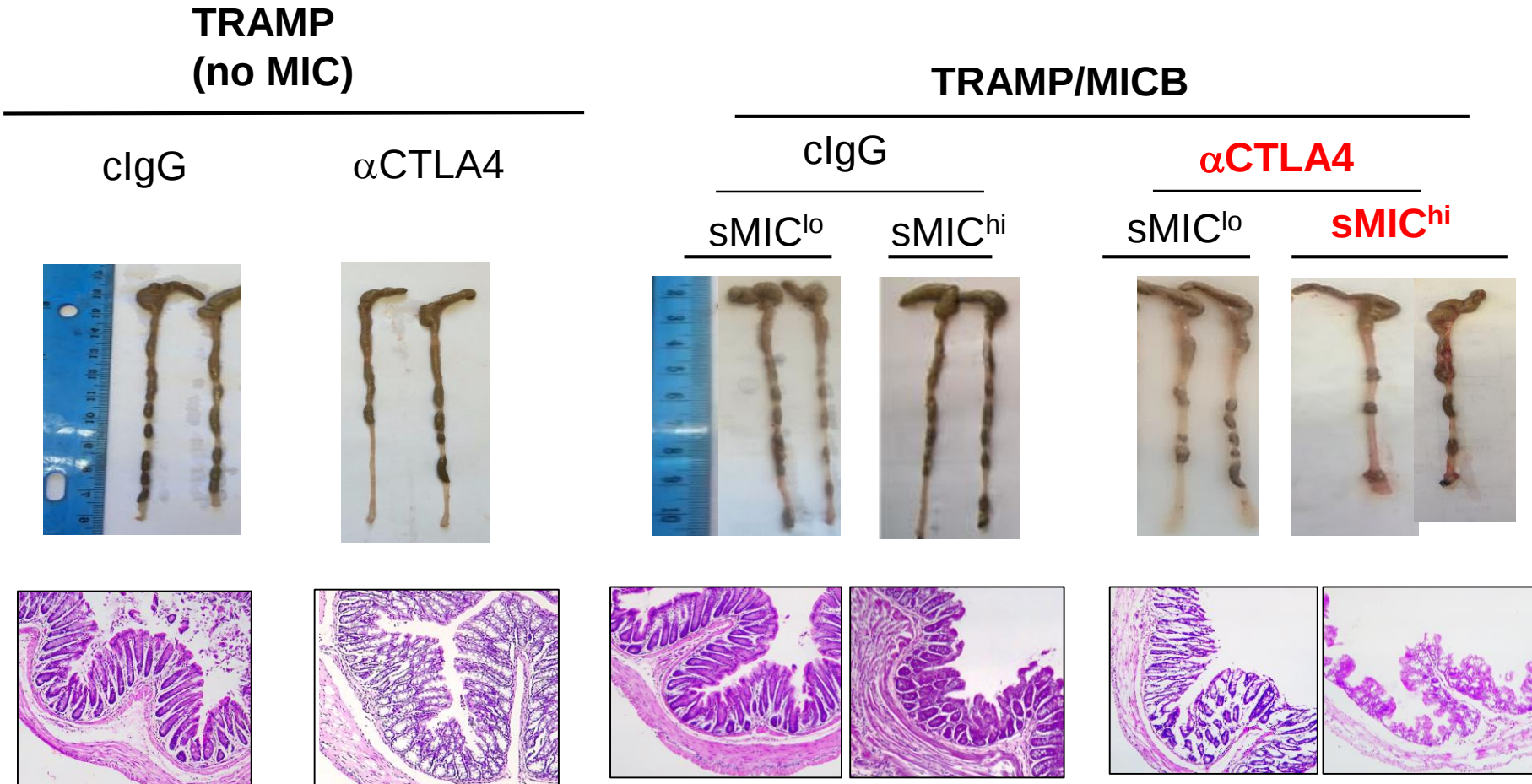


Poor response to anti-CTLA4 therapy in sMIC^{hi} mice

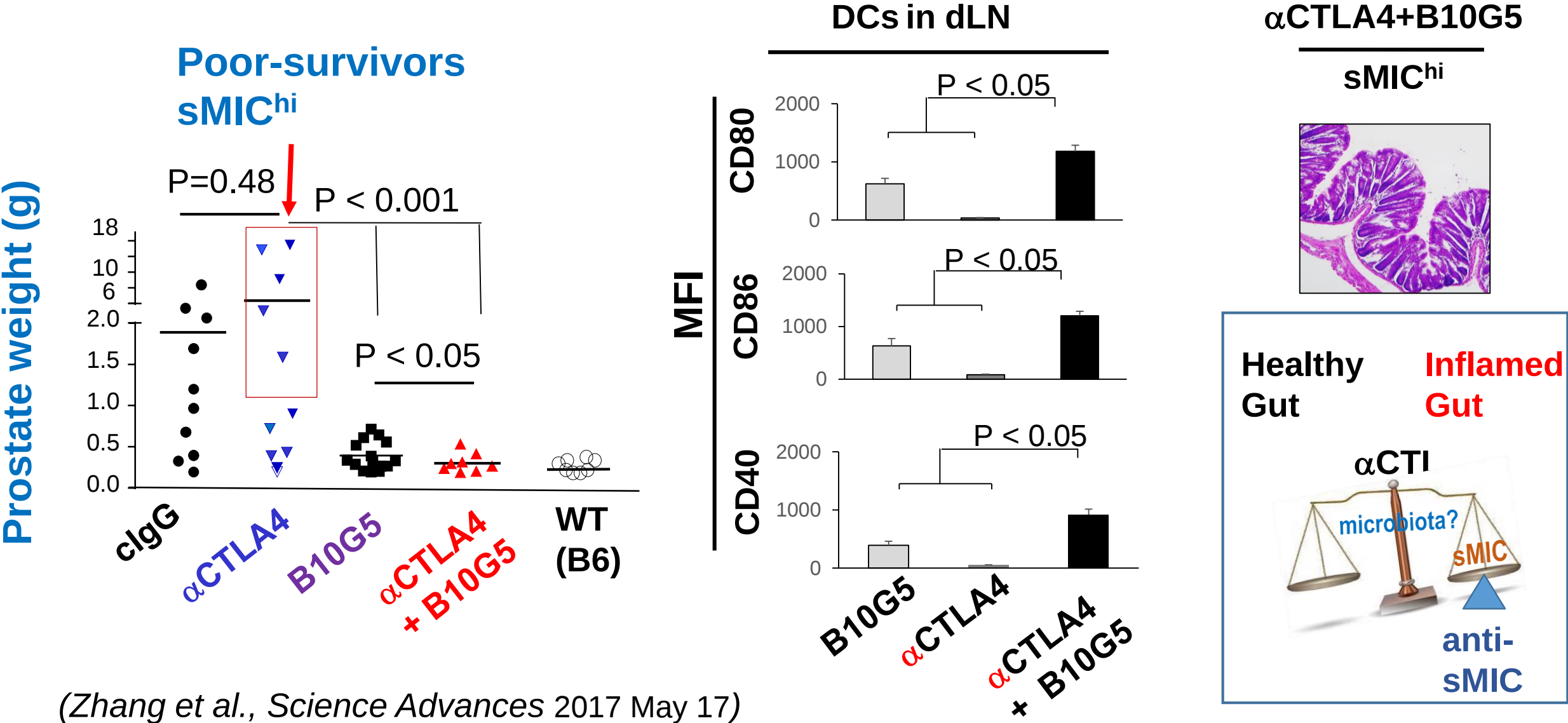


(Zhang et al., Science Advances May 17th 2017)

High circulating sMIC exacerbated anti-CTLA4-induced colon inflammation

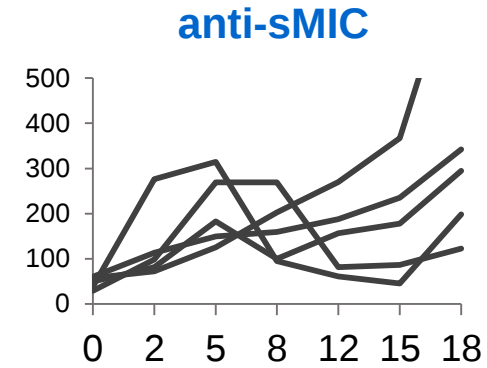
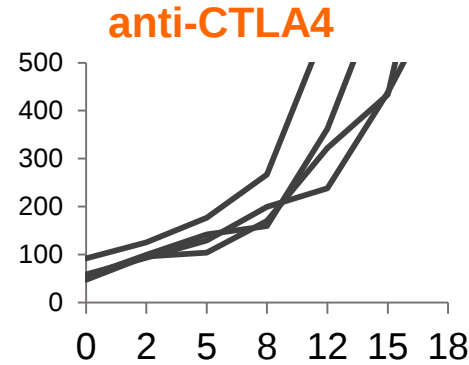
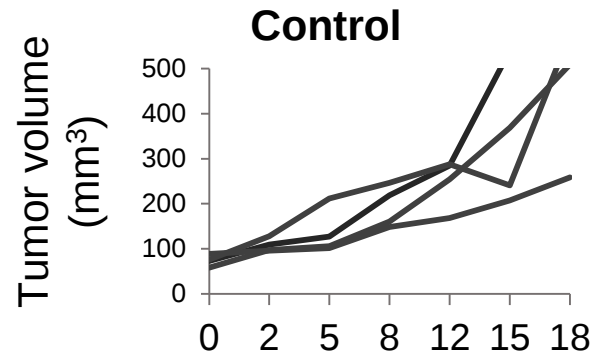


Clearing sMIC enhanced anti-CTLA4 response and alleviates colitis



(Zhang et al., Science Advances 2017 May 17)

Optimal dosing of combination therapy induces CR of established tumors with no colitis

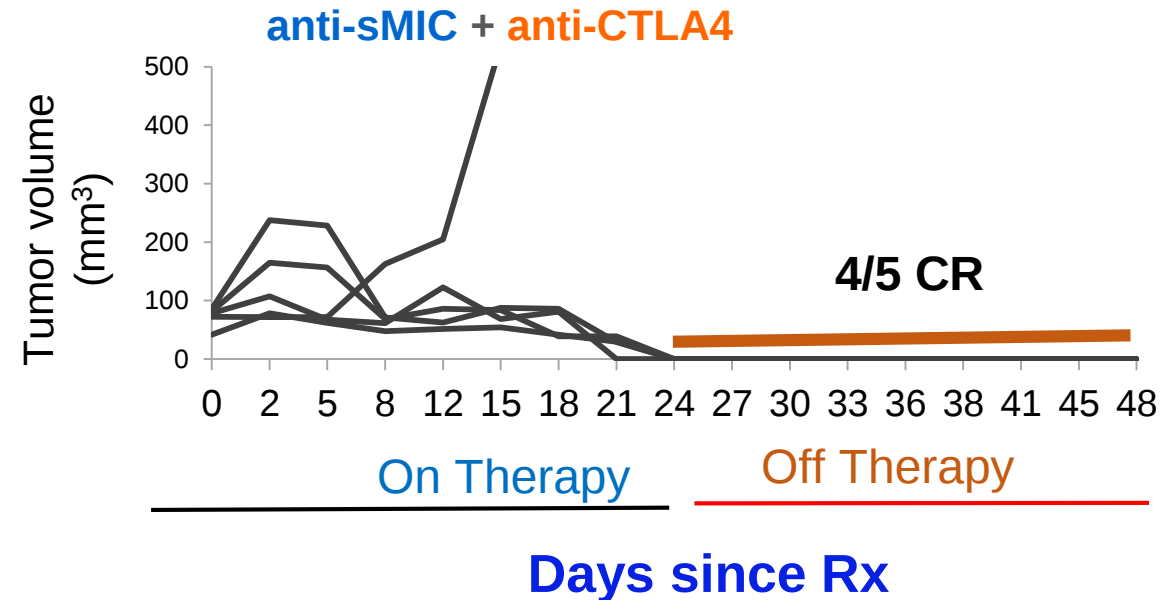


Transplant Syngeneic

sMIC⁺-TRAMP-C2



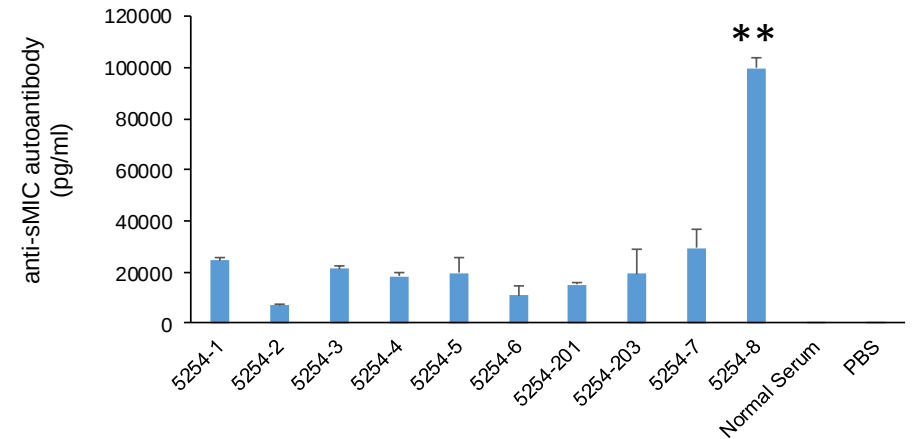
MIC/B6 Tg host



Development of anti-sMIC autoantibody associates with better clinical response to anti-CTLA4 or vaccine

Prostate Cancer

- A man with mCRPC developed anti-sMIC autoantibody at early cycle of **Ipilimumab** elicited durable response in combination with ADT, PSA 191 ng/ml → 4.6 ng/ml after 8 cycle. No colitis was developed in this patient.
(*Zhang et al., Science Advances May 17, 2017*)



Melanoma and Multiple Myeloma

- Patients who developed anti-MIC autoantibodies during anti-CTLA4 or vaccine therapy elicited better clinical response (Jinushi M, Hodi FS, Dranoff G. PNAS 2006)

Take Home Message

- NKG2DL, sMIC can skew response anti-CTLA4 therapy
- Patients may be screened for serum sMIC to improve clinical outcome with anti-CLA4 therapy
- Antibody clearing sMIC could potentiate anti-CTLA4 therapy and alleviate therapy-induced colon toxicity

Acknowledgements

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