



**HKU
Med**

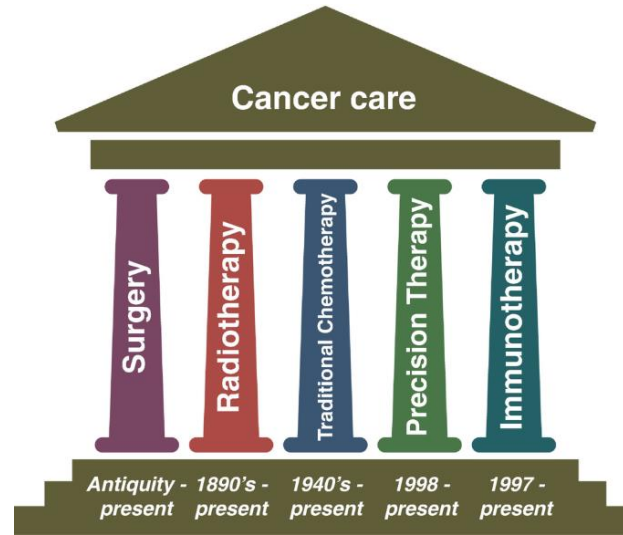
LKS Faculty of Medicine
The University of Hong Kong
香港大學李嘉誠醫學院

Decoding the immune paradox in the tumors

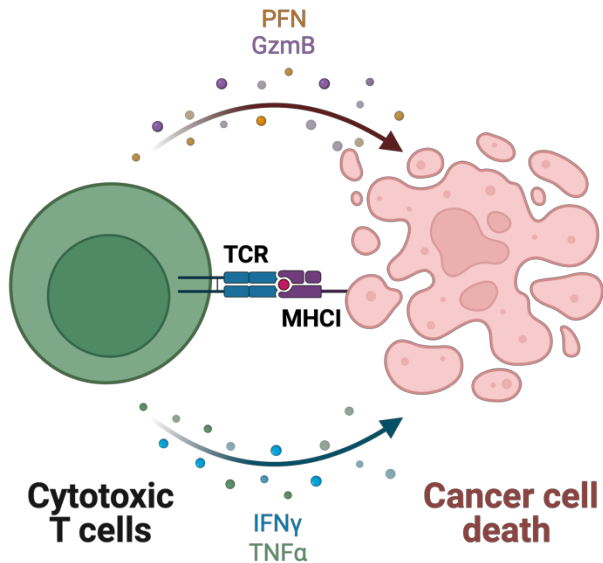
Heidi Ling



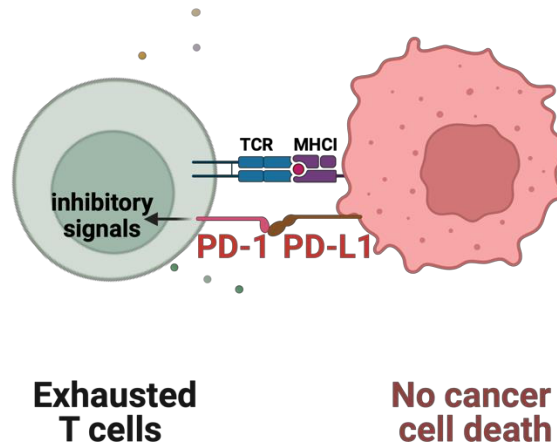
Immune checkpoint blockade (ICB) therapy



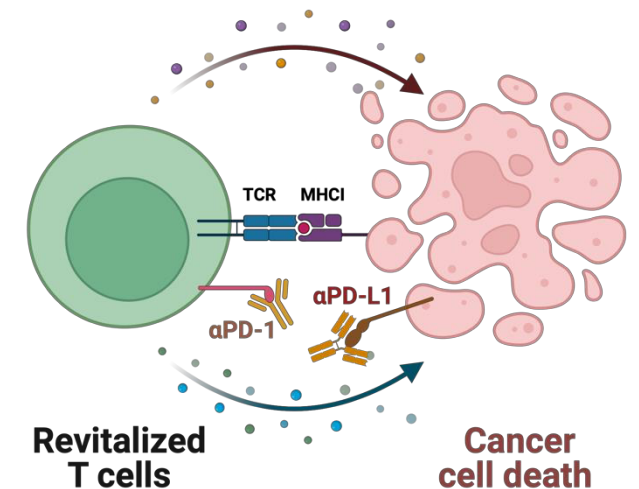
Immune surveillance



Immune evasion

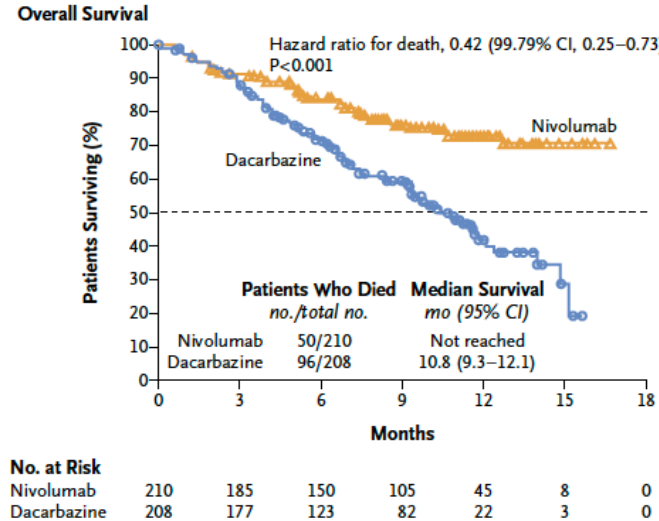


Immune Checkpoint Blockade Therapy



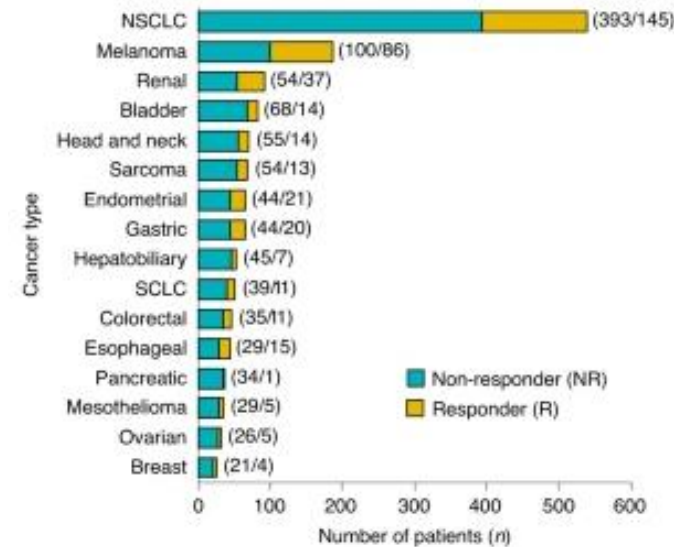
Immune checkpoint blockade (ICB) therapy

Melanoma patients



Postow et al NEJM 372;21 (2015)

MSK-IMPACT Cohort



Chowell et al Nat. Biotech 40;499 (2022)

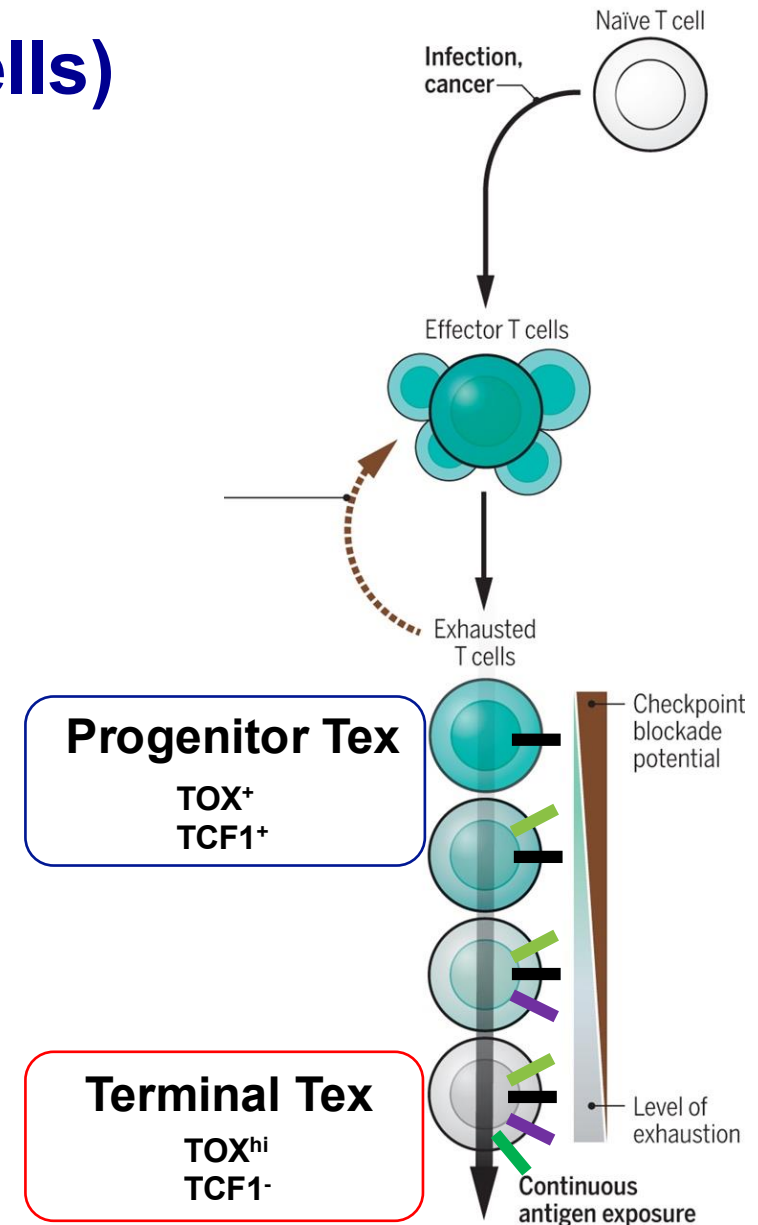
Our group's research focuses

What are the mechanisms underlying ICB therapy resistance ?

- focus on how the tumor microenvironment (TME) forms barriers that hinder ICB-mediated T cell reactivation

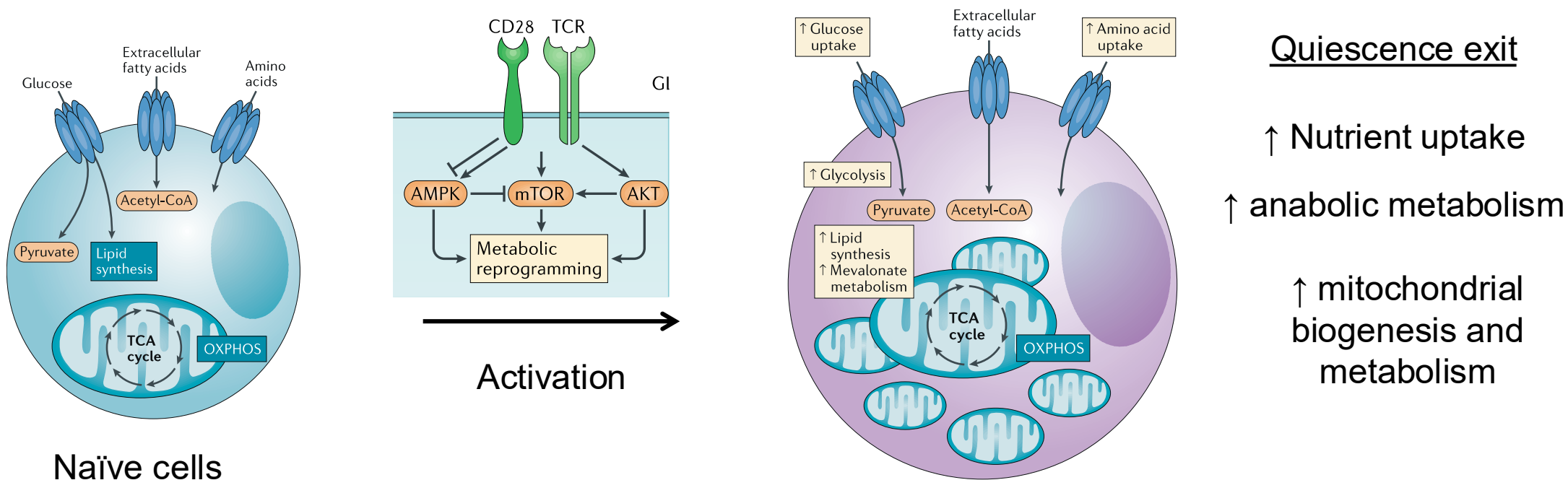
Exhausted CD8⁺T cells (Tex cells)

- TOX-mediated transcriptional program
- Progressive loss of effector functions and poor self-renewal capacity
- Co-expression of co-inhibitory receptors : e.g.
 - PD-1
 - LAG3
 - CTLA4
 - Tim-3
- Metabolic defects (suppressed glycolysis and damaged mitochondria)

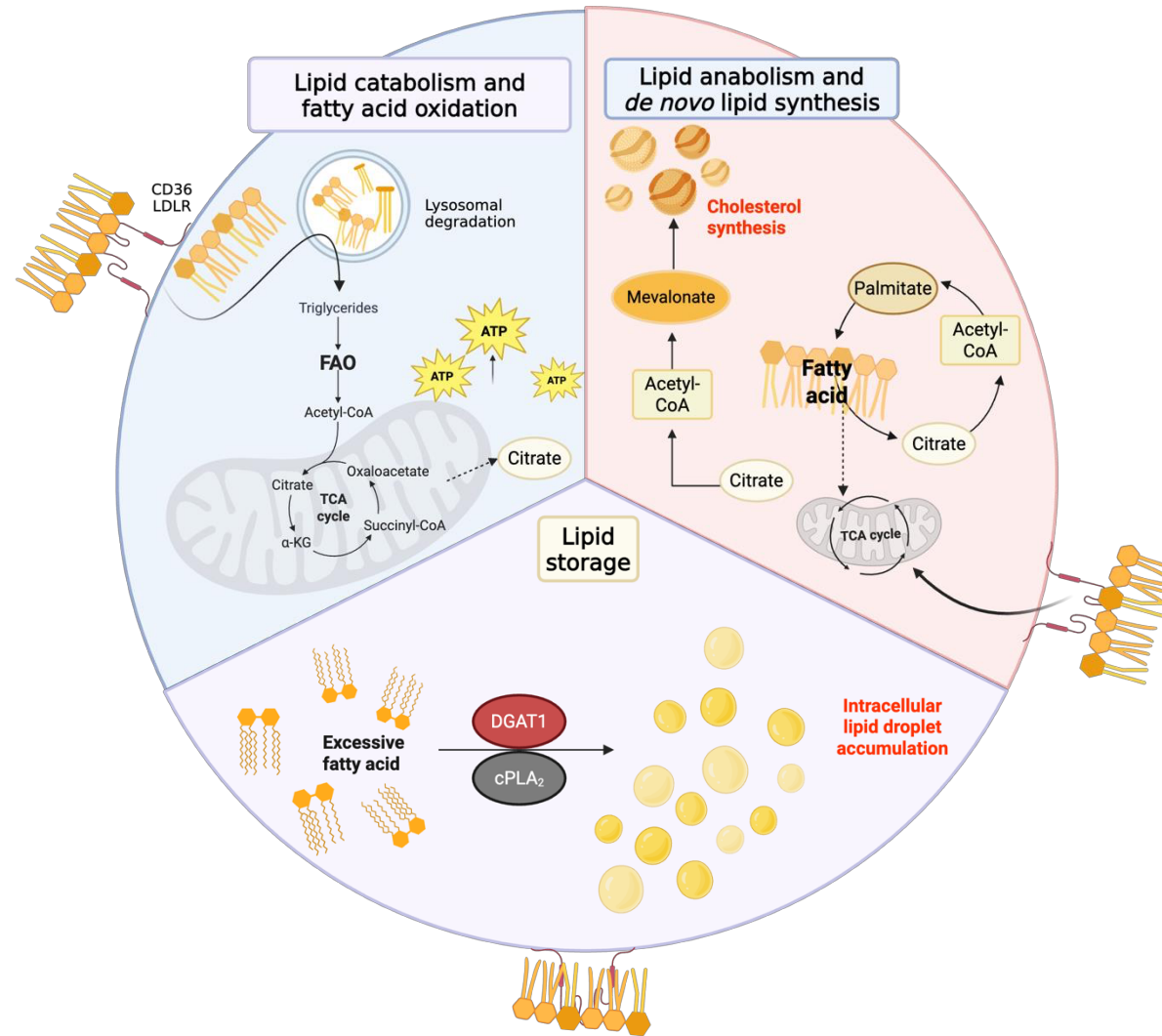


Metabolic reprogramming during T cell activation

- Cells undergo an alteration in their mode of energy metabolism in order to fulfill the bioenergetic and biosynthetic needs for proliferation, function and differentiation after activation

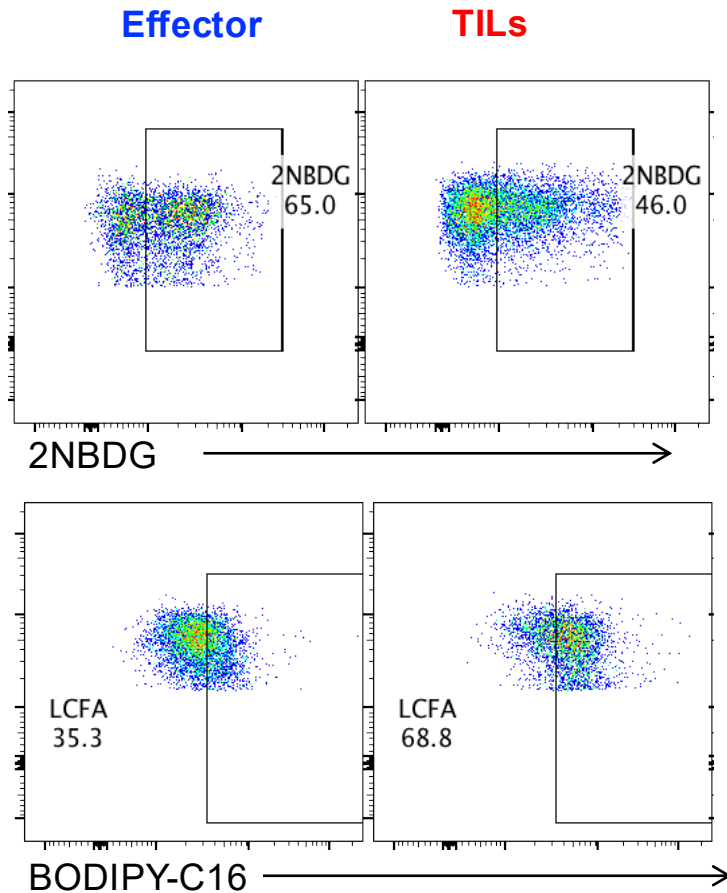


Coordinated lipid metabolism for T cell function

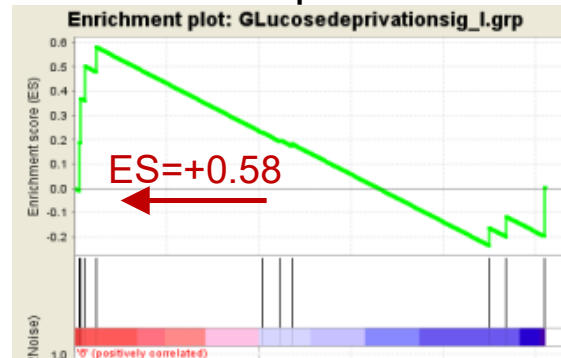


Metabolic features of tumor-infiltrating T cells (TILs)

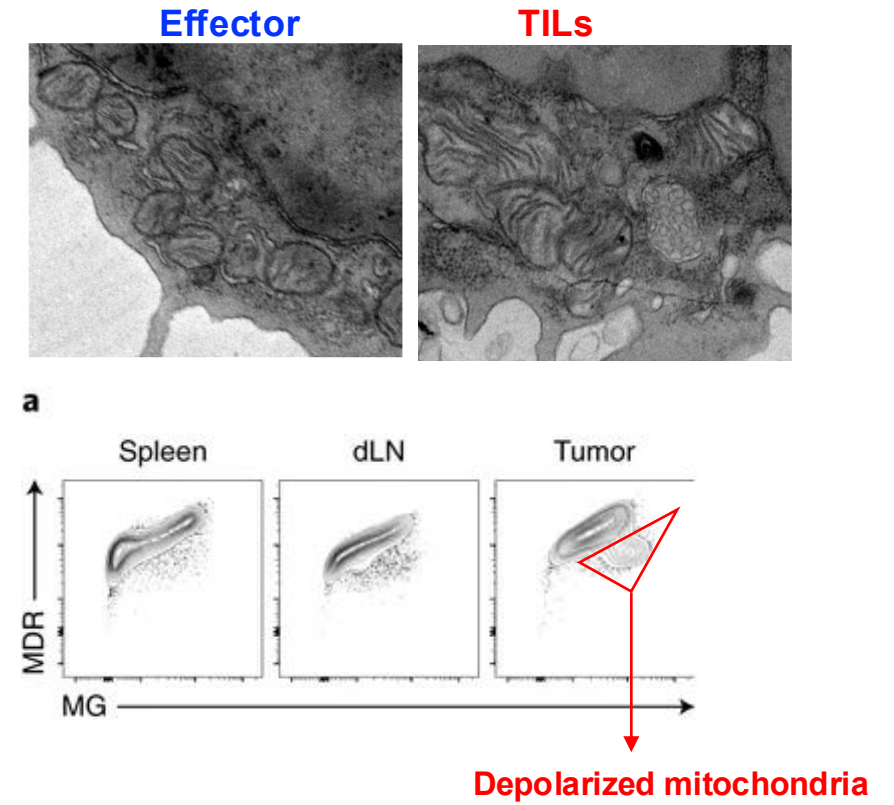
1. Increase in LCFA uptake



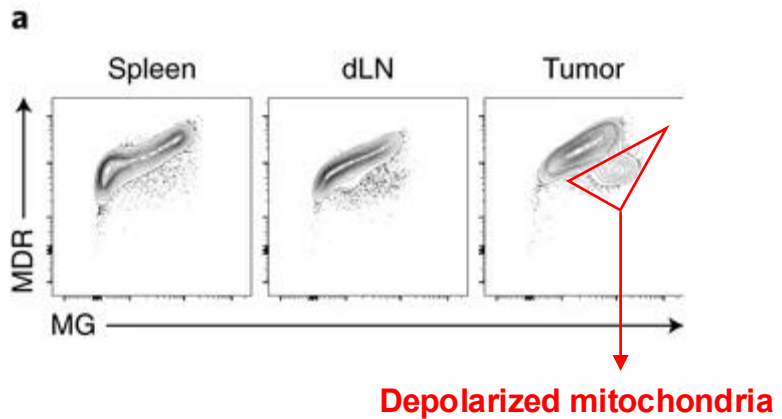
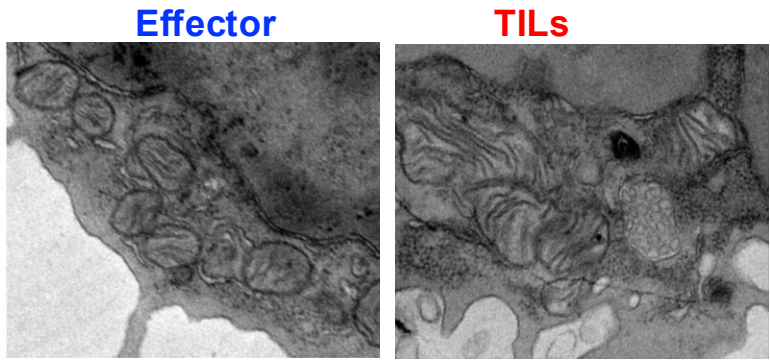
2. Reduced glycolysis



3. Dysfunctional mitochondria



How dysfunctional mitochondria contribute to T cell exhaustion ?

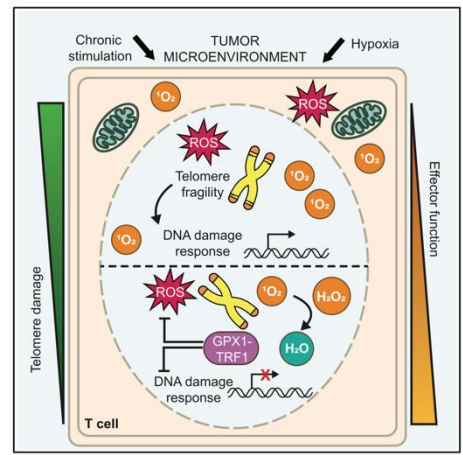


Immunity

Oxidative-stress-induced telomere instability drives T cell dysfunction in cancer

Rivadeneira et al., 2025, Immunity 58, 2524–2540
October 14, 2025 © 2025 The Author(s). Published by Elsevier Inc.
<https://doi.org/10.1016/j.immuni.2025.08.008>

Graphical abstract



Authors

Dayana B. Rivadeneira,
Sanjana Thosar, Kevin Quann, ...,
Marcel P. Bruchez, Patricia L. Opresko,
Greg M. Delgoffe

Correspondence

dar177@pitt.edu (D.B.R.),
gdelgoffe@pitt.edu (G.M.D.)

In brief

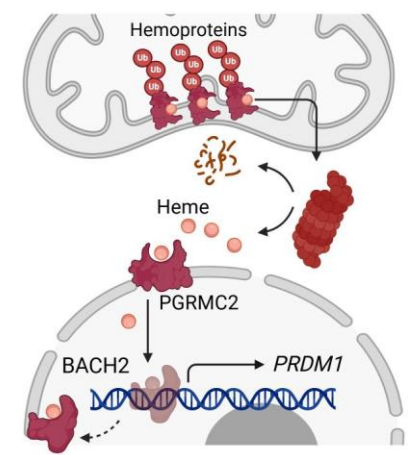
The functional state of tumor-infiltrating lymphocytes is a critical determinant of antitumor immunity and response to immunotherapy. Rivadeneira et al. demonstrate that mitochondrial ROS accumulation induces oxidative damage at telomeres, which is sufficient to drive T cell dysfunction. Neutralizing ROS at telomeres mitigates T cell dysfunction and improves cellular therapies.

Article

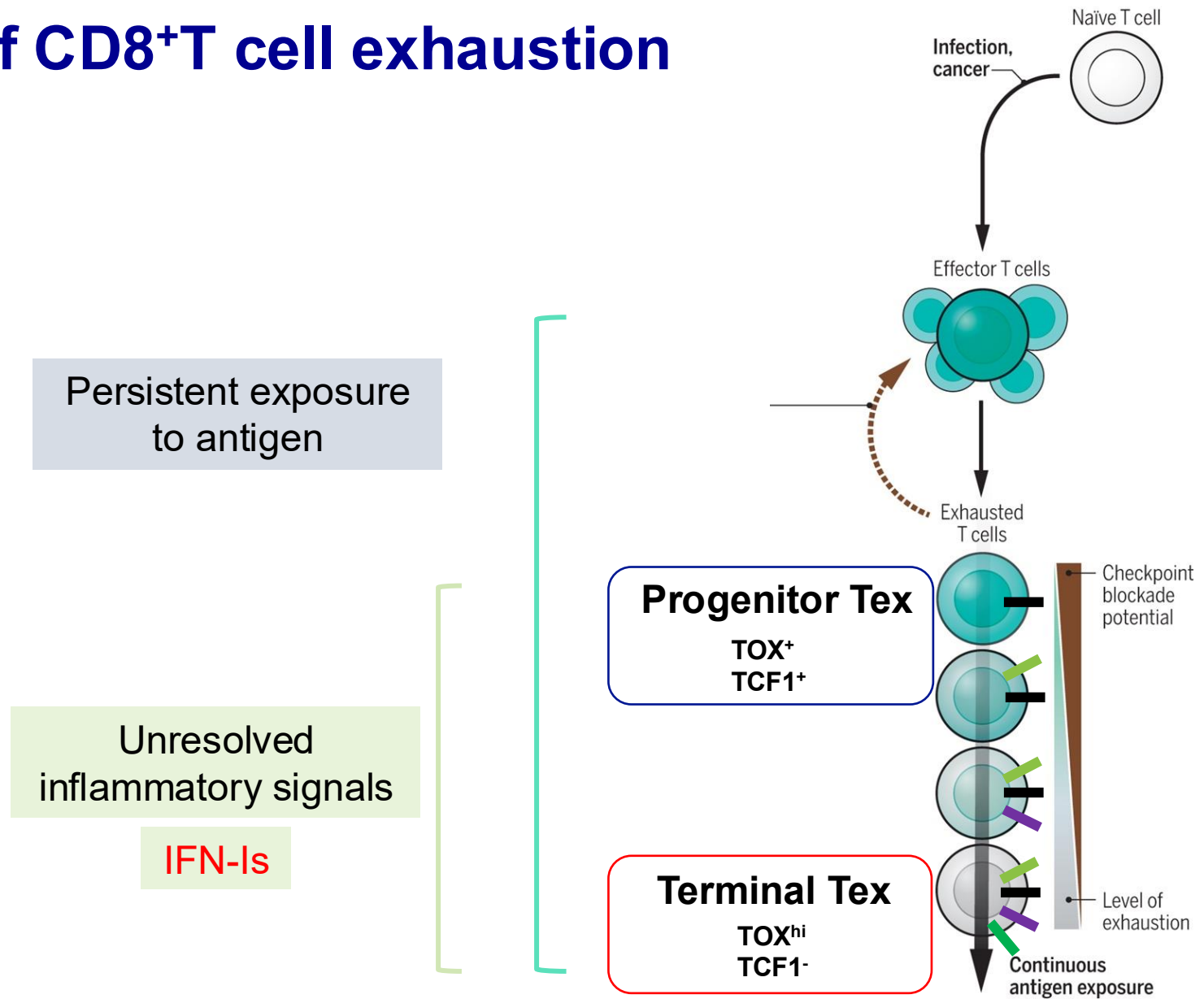
Proteasome-guided haem signalling axis contributes to T cell exhaustion

<https://doi.org/10.1038/s41586-026-10250-y>
Received: 24 June 2024
Accepted: 6 February 2026
Published online: 18 March 2026
 Check for updates

Yingxi Xu^{1,2,3,4,5}, Yangtao Shangguan^{3,4}, Yu-Ming Chuang^{1,2}, Tzu-Hsuan Chang^{1,2}, Wenbing Liu^{3,4}, Jhan-Jie Peng^{1,2,5,6}, Josep Garnica^{1,2,7}, Leling Xie^{3,4}, Pei-Chun Hsueh^{1,2}, Mei-Chun Lin^{1,2,8}, Yi-Hao Wang^{1,2}, Karina Lobo Hajdu^{1,2}, Yibo Wu^{9,10}, Maryam Akrami¹¹, Chen Wang^{12,13,14}, Anna Kohl^{1,2}, Alfred Zippelius^{11,15}, Wei Qi¹⁶, Min Wang^{3,4}, Bugi Ratno Budiarto^{17,18}, Shih-Yu Chen¹⁷, Zhengtao Xiao¹⁹, Panagiota Vardaka^{20,21}, Rahul Roychoudhuri^{20,21}, Zhiliang Bai²², Rong Fan²², Santiago Carmona^{1,2,7}, Yi-Ru Yu^{1,2}, Christoph Scheiermann^{12,13}, Jianxiang Wang^{3,4,5} & Ping-Chih Ho^{1,2,23}

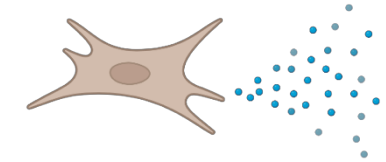
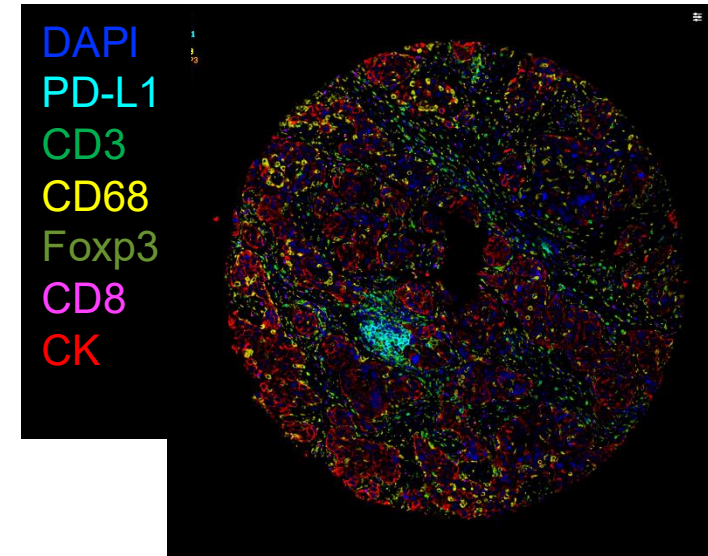


Drivers of CD8⁺T cell exhaustion

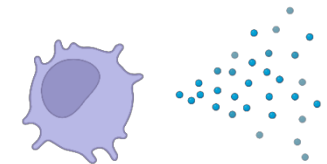


Type I interferon (IFN-Is) in the tumor microenvironment

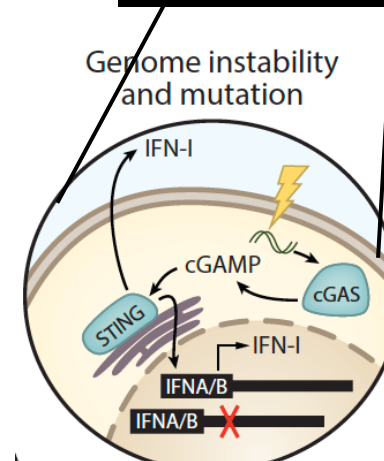
- IFN- α and IFN- β
- Potent anti-viral properties
- Key immuno-modulatory cytokines
- Signal through the IFNAR
- Canonical signaling : STAT1/2



Tumor-associated fibroblasts



Tumor-infiltrated myeloid cells

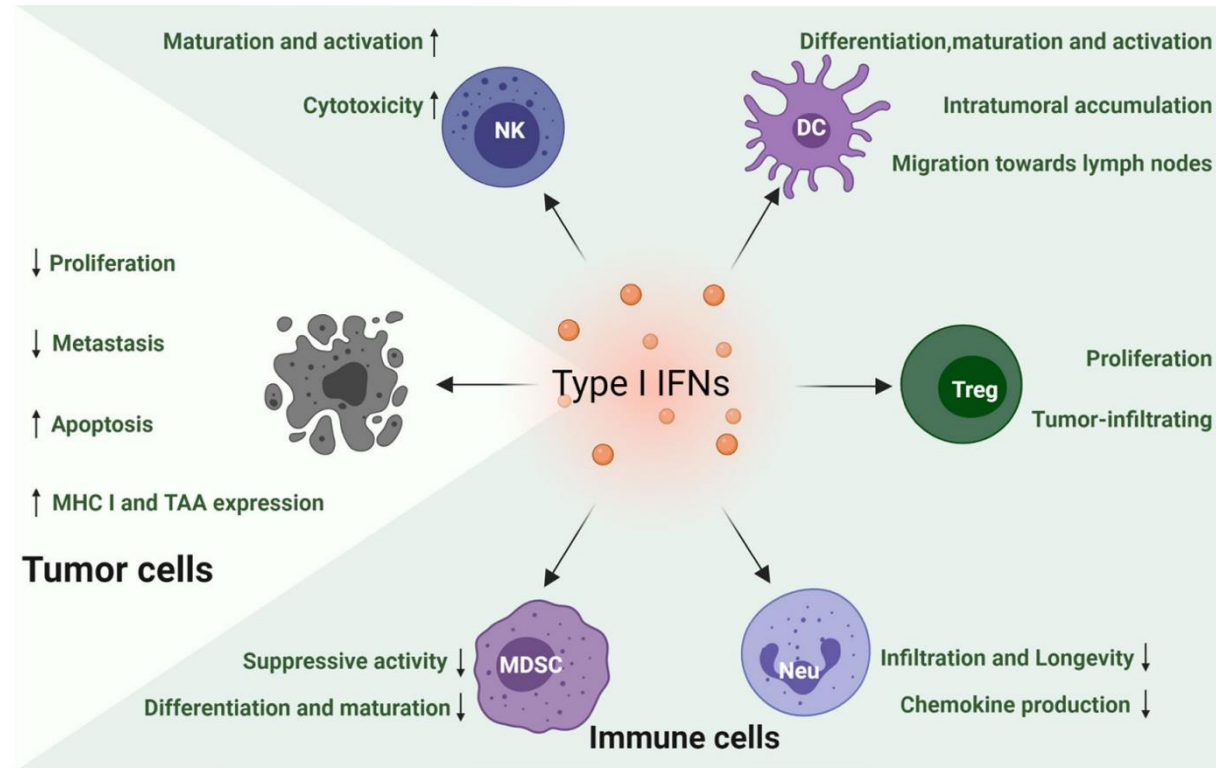


Tumor cells

Type I Interferon (IFN-Is)



Anti-tumorigenic



Chronic IFN-Is signaling



Pro-tumorigenic ?!

Cell Research (2019) 29:846–861; <https://doi.org/10.1038/s41422-019-0224-x>

Sustained Type I interferon signaling as a mechanism of resistance to PD-1 blockade

Nicolas Jacquelot^{1,2,3,4,26}, Takahiro Yamazaki^{1,3}, Maria P. Roberti^{1,3,5}, Connie P. M. Duong^{1,3}, Miles C. Andrews^{6,7,8}, Loïc Verlingue^{3,9}, Gladys Ferrere^{1,3,5}, Sonia Becharef^{1,3}, Marie Vétizou^{1,3}, Romain Daillère^{1,3}, Meriem Messaoudene^{1,3}, David P. Enot^{3,10}, Gautier Stoll^{10,11,12,13,14}, Stefano Ugel¹⁵, Ilaria Marigo¹⁶, Shin Foong Ngiew^{17,18}, Aurélien Marabelle^{1,2,3}, Armelle Prevost-Blondel^{14,19,20}, Pierre-Olivier Gaudreau⁶, Vancheswaran Gopalakrishnan⁶, Alexander M. Eggermont³, Paule Opolon³, Christophe Klein¹¹, Gabriele Madonna²¹, Paolo A. Ascierto¹⁵, Antje Sucker²², Dirk Schadendorf¹⁵, Mark J. Smyth^{17,18}, Jean-Charles Soria^{2,3,4,9}, Guido Kroemer¹⁵, Vincenzo Bronte¹⁵, Jennifer Wargo^{6,25} and Laurence Zitvogel^{1,2,3,4,5}

NATURE COMMUNICATIONS | (2021)12:1980 | <https://doi.org/10.1038/s41467-021-22312-y> | www.nature.com/naturecommunications

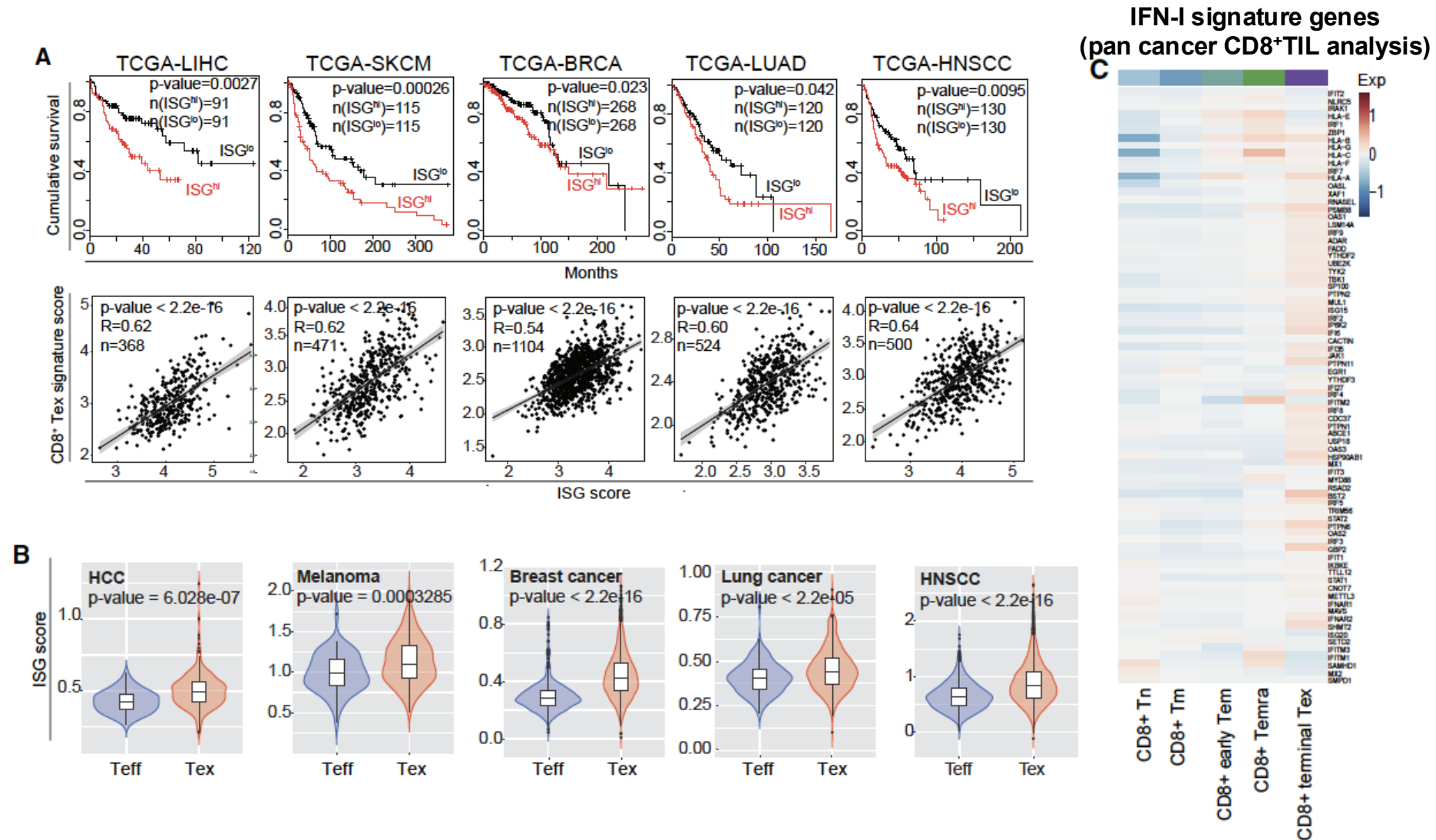
Type I interferons affect the metabolic fitness of CD8⁺ T cells from patients with systemic lupus erythematosus

Norzawani Buang¹, Lunnathaya Tapeng¹, Victor Gray¹, Alessandro Sardini², Chad Whilding², Liz Lightstone^{1,3}, Thomas D. Cairns³, Matthew C. Pickering^{1,3}, Jacques Behmoaras¹, Guang Sheng Ling^{1,4,5} & Marina Botto^{1,3,5}

Question :

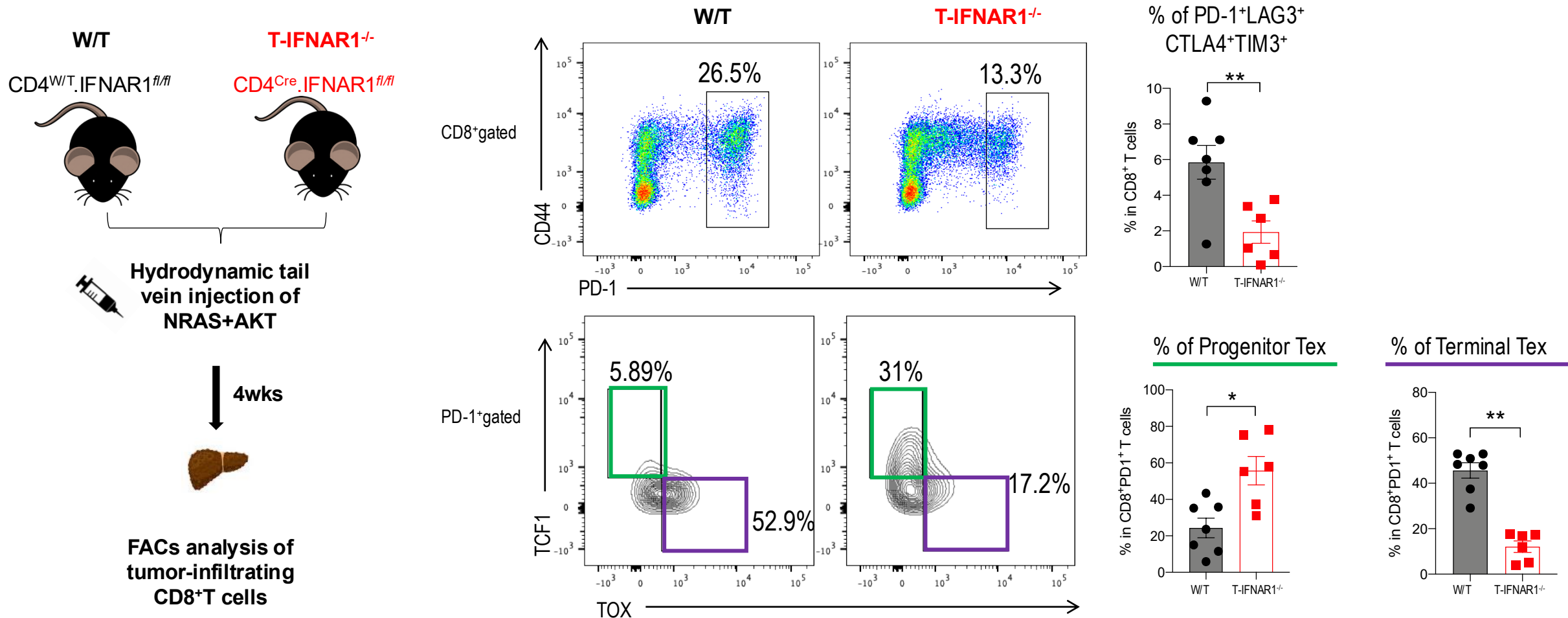
Dose chronic IFN-Is signaling in the tumor microenvironment trigger metabolic defects that promote terminal Tex differentiation ?

Intratumoral Tex cells in cancer patients are enriched in IFN-I signature genes (ISGs)

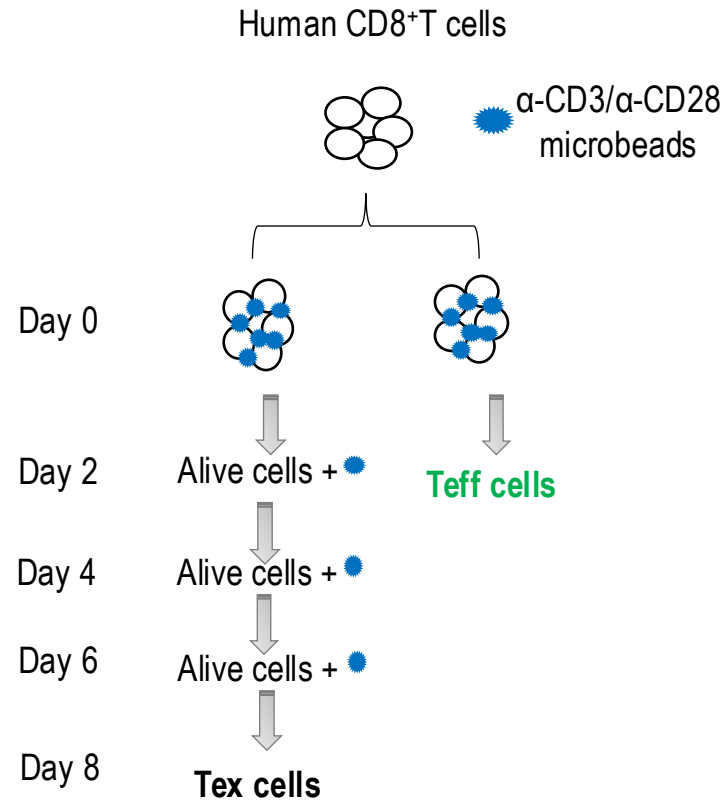


→ IFN-I_s are linked to T cell exhaustion in cancer

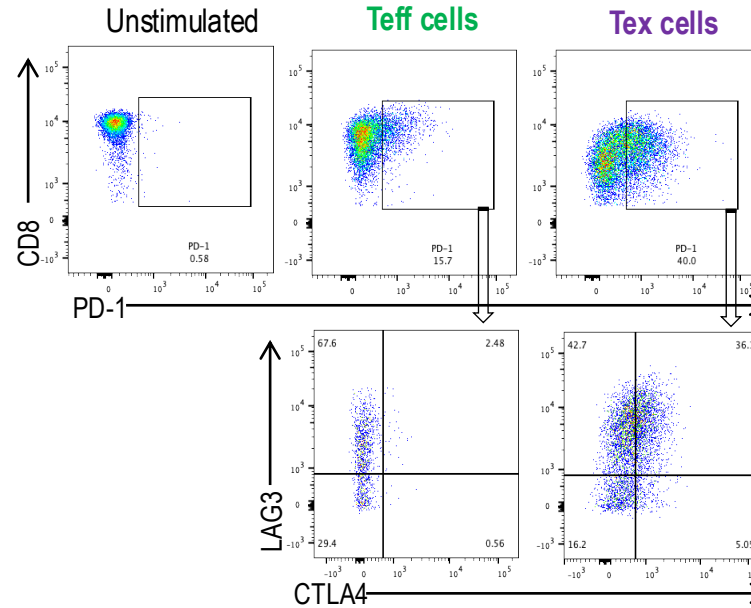
IFN-Is promote terminal Tex differentiation in murine HCC



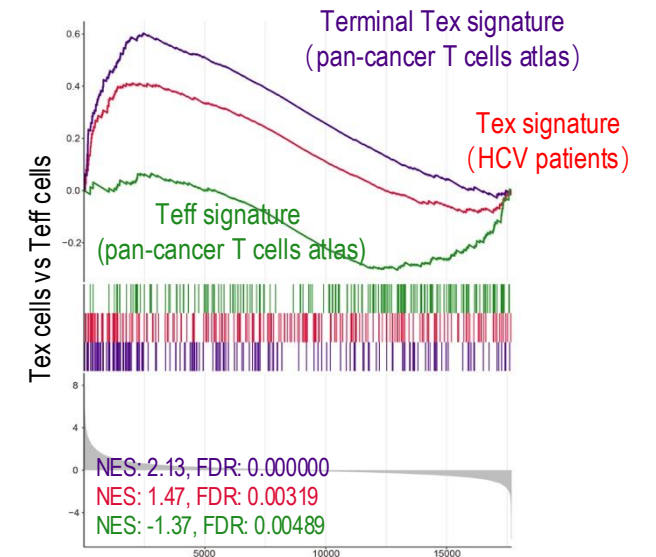
In vitro Tex differentiation assay with human CD8⁺T cells



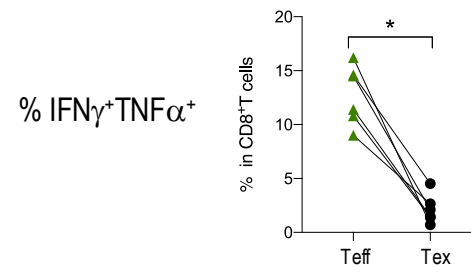
(i) Phenotypical



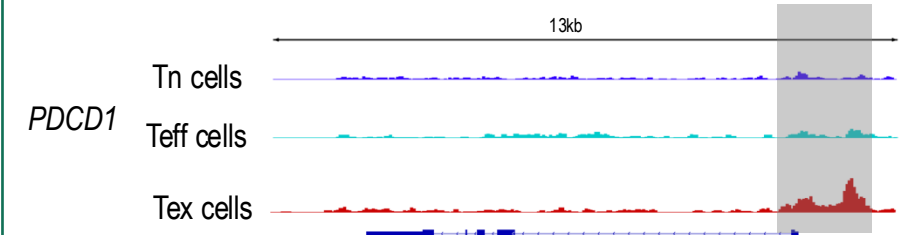
(iii) Transcriptional



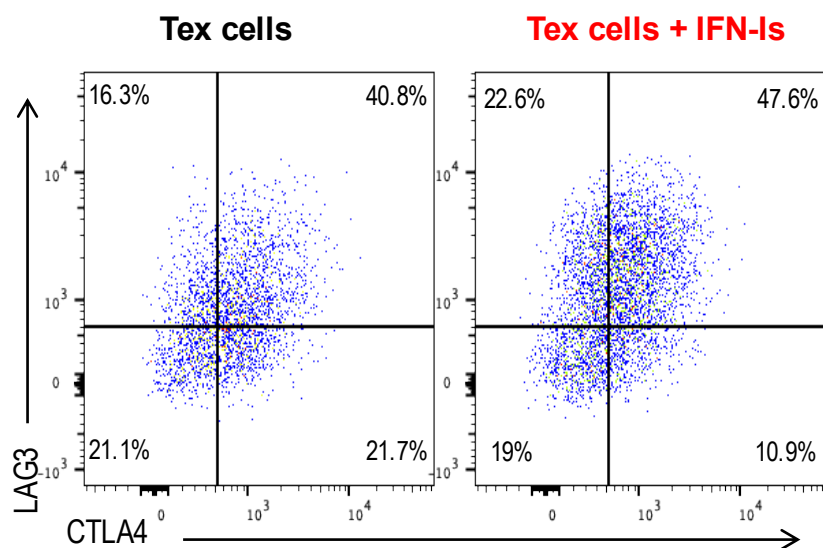
(ii) Functional



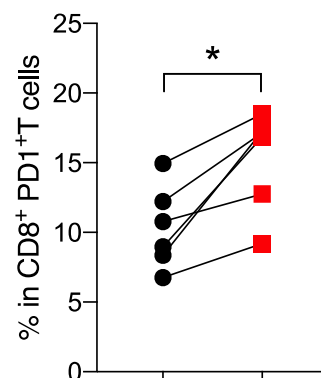
(iv) Epigenetic



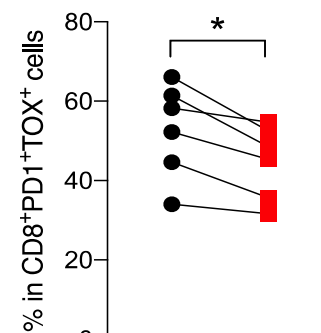
IFN-Is stimulation accelerates Tex differentiation *in vitro*



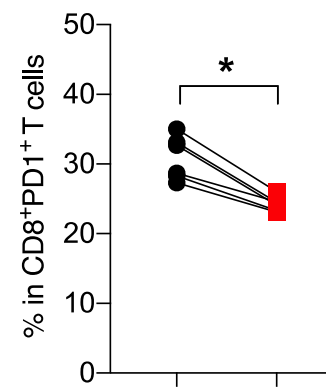
% of PD-1⁺LAG3⁺
CTLA4⁺TIM3⁺TIGIT⁺



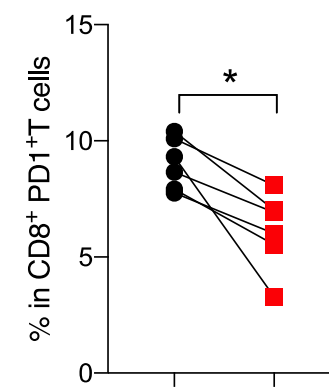
% of progenitor Tex



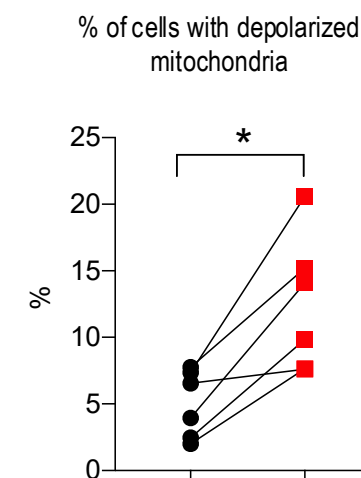
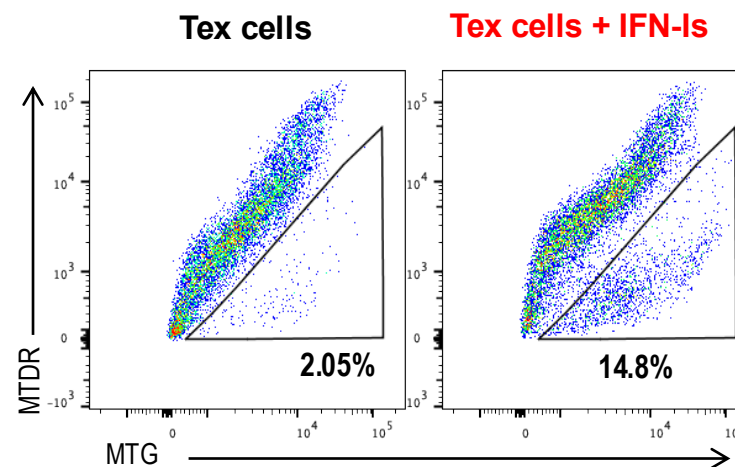
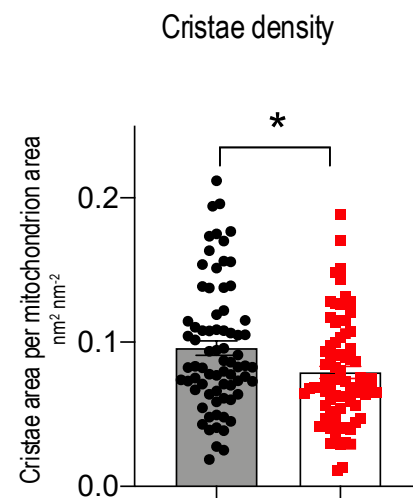
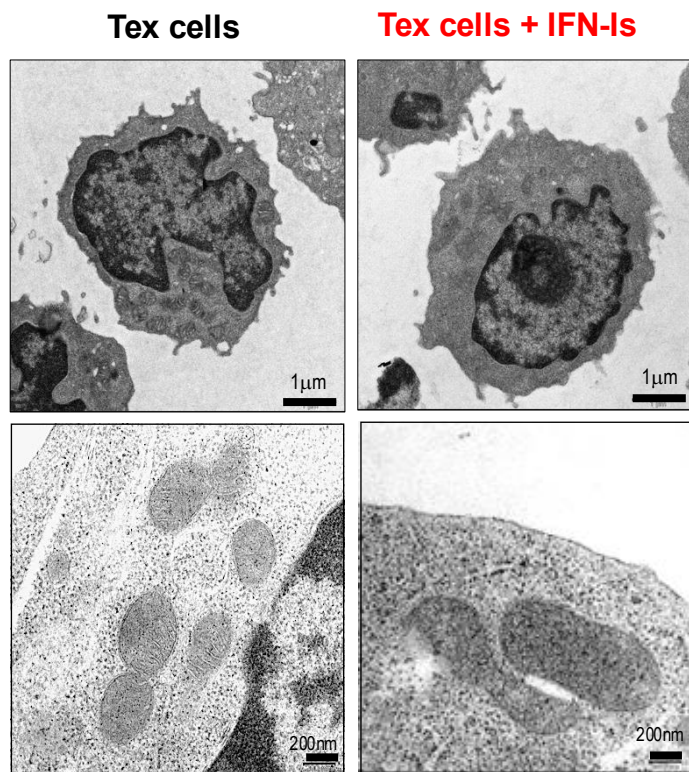
% of proliferating cells



% of IFN γ ⁺TNF α ⁺



IFN-Is trigger mitochondrial defects that associate with terminal Tex differentiation

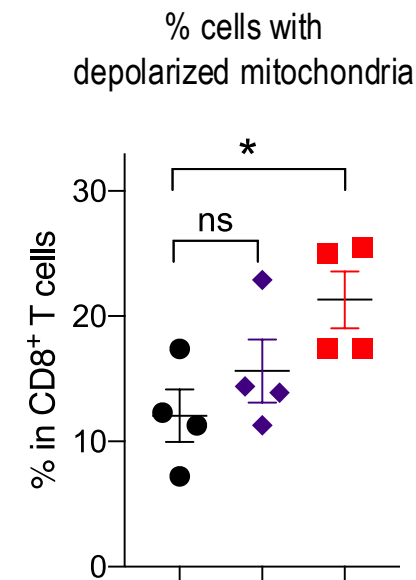
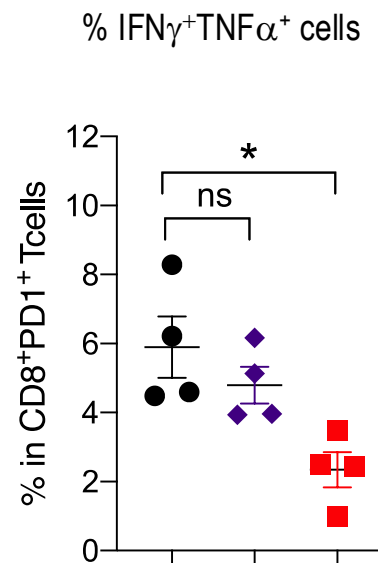
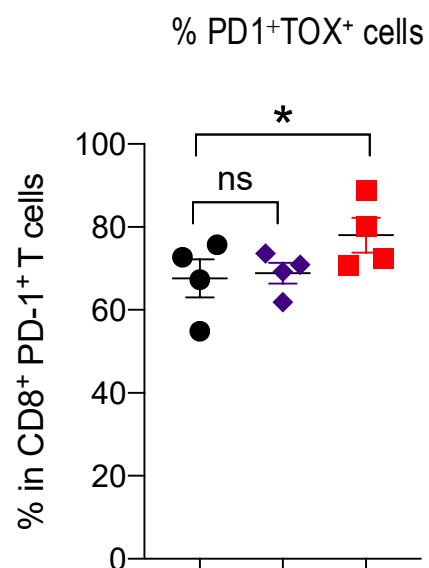
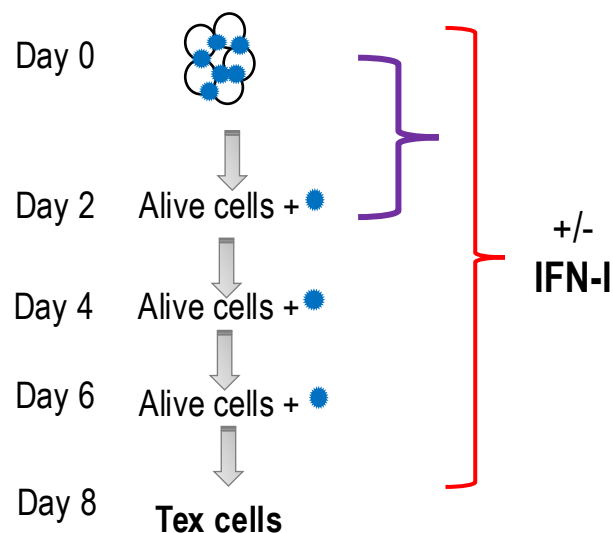


Chronic, not acute, IFN-Is stimulation promote terminal Tex differentiation

α -CD3/ α -CD28
microbeads



Human CD8⁺T cells



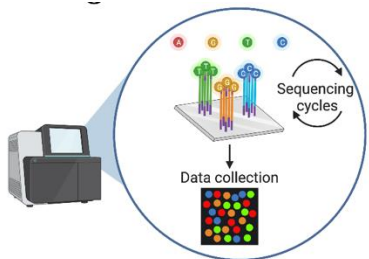
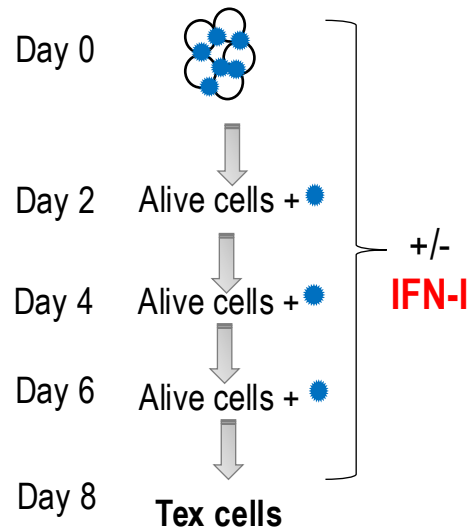
- Tex cells
- ◆ Tex cells + IFN-Is (d2)
- Tex cells + IFN-Is (d8)

How dose chronic IFN-Is stimulation promote T cell exhaustion?

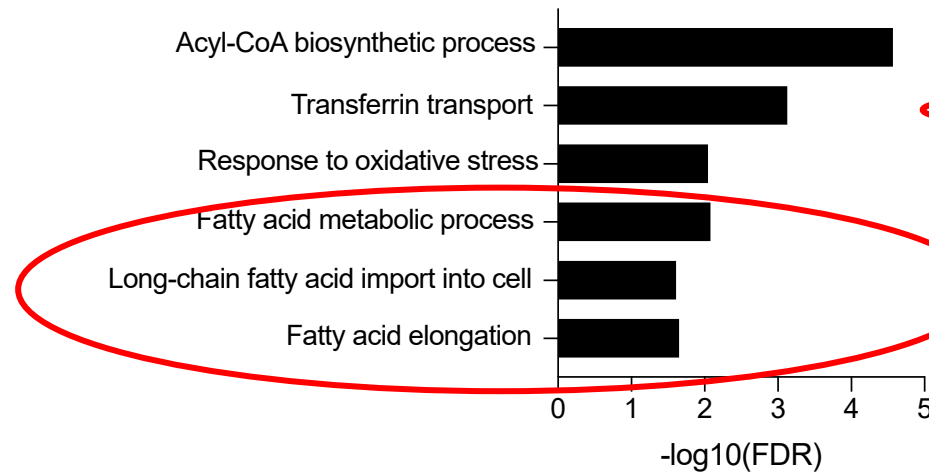
α -CD3/ α -CD28
microbeads



Human CD8⁺T cells

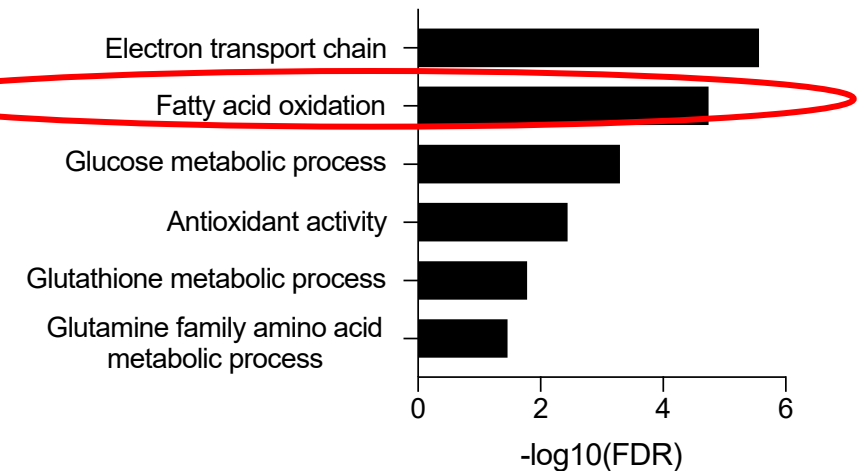


Upregulated pathways



↑ Fatty acid intake

Downregulated pathways

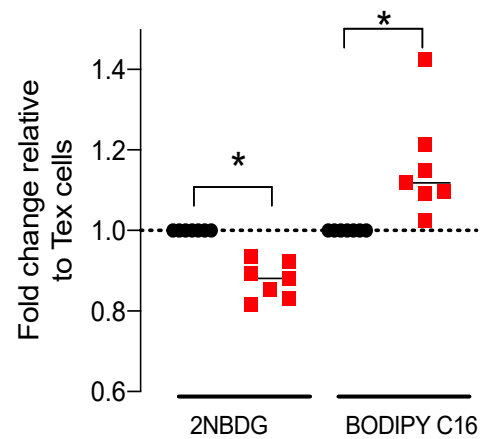


↓ Fatty acid consumption

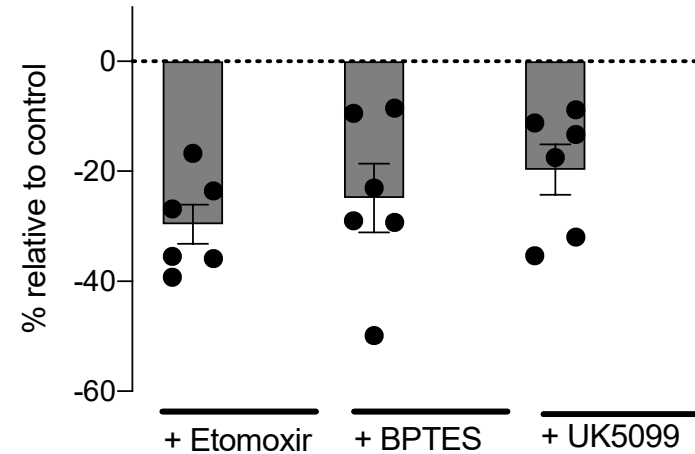
Chronic IFN-Is stimulation perturbs lipid metabolism

● Tex cells
■ Tex cells + IFN-Is

Nutrients uptake



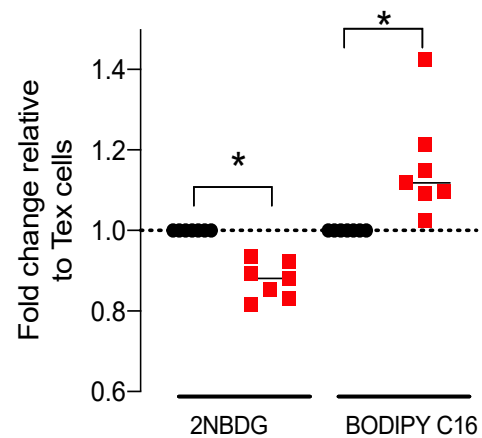
Mito Fuel Flex test



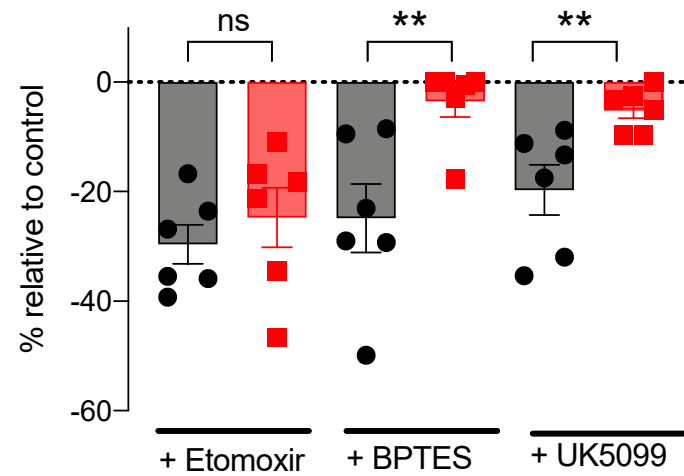
Chronic IFN-Is stimulation perturbs lipid metabolism

● Tex cells
■ Tex cells + IFN-Is

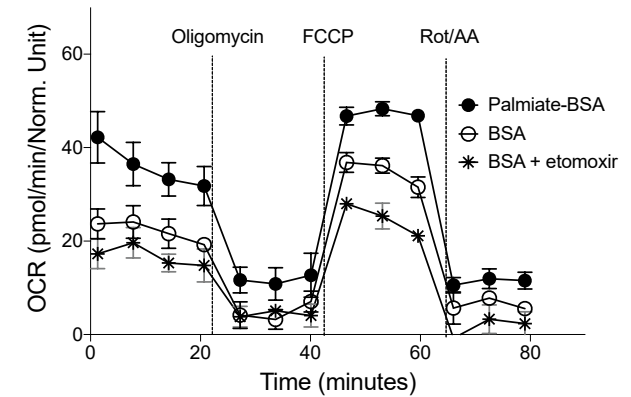
Nutrients uptake



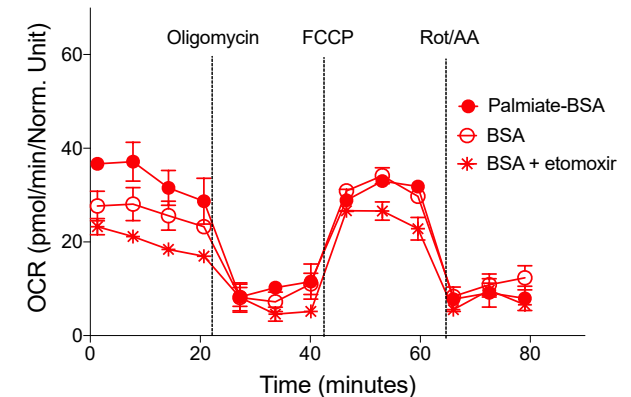
Mito Fuel Flex test



Palmitate Oxidation stress Test

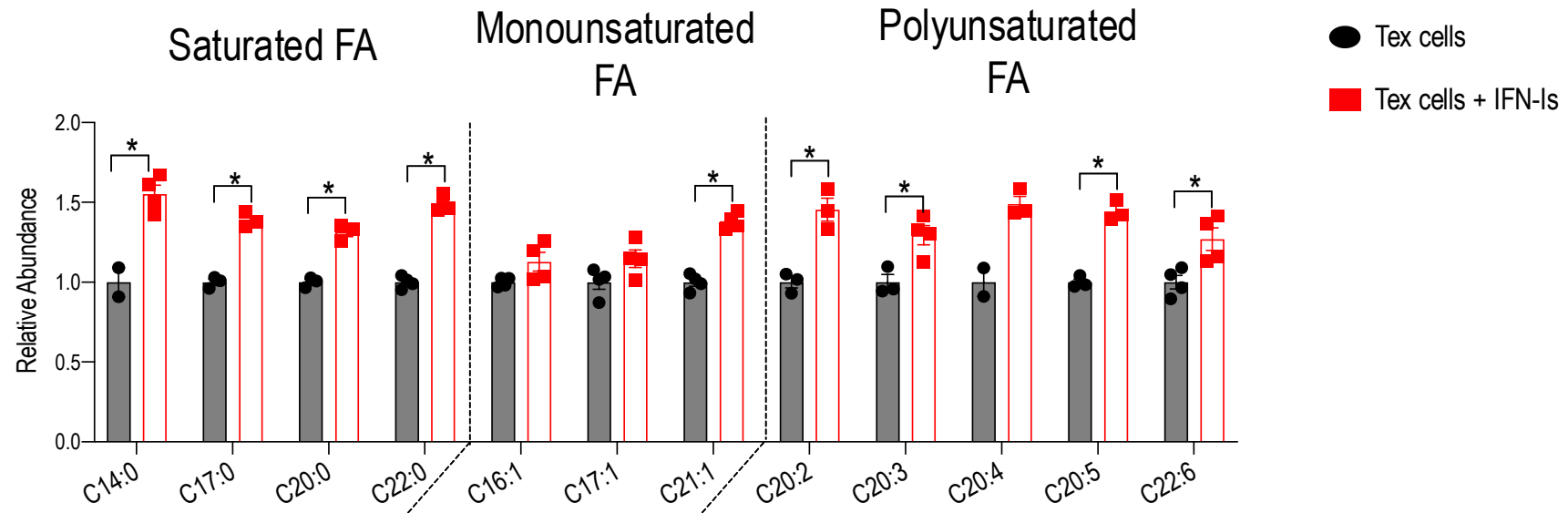


Tex cells



Tex cells
+ IFN-Is

Chronic IFN-Is stimulation perturbs lipid metabolism

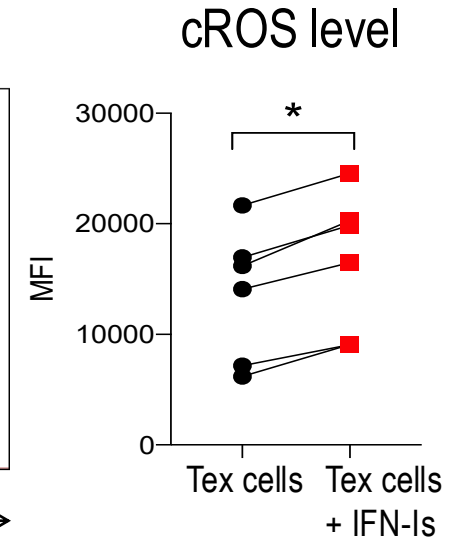
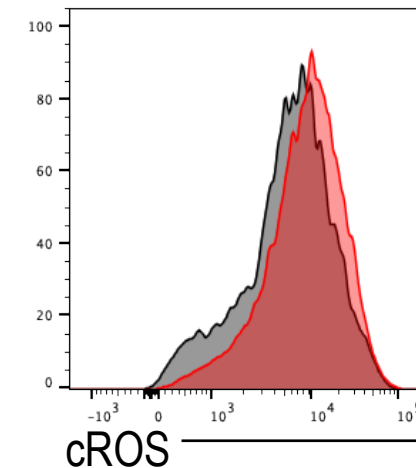
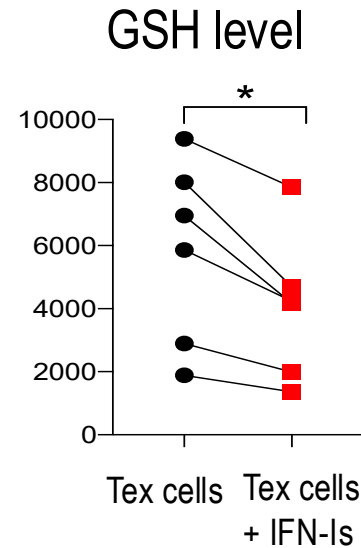
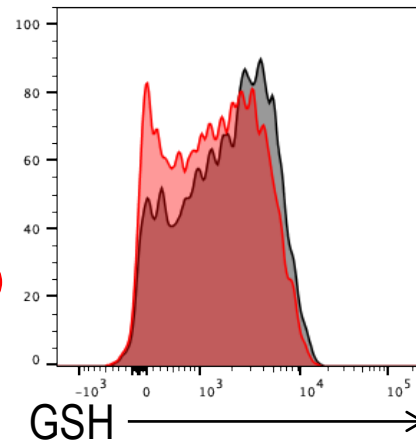
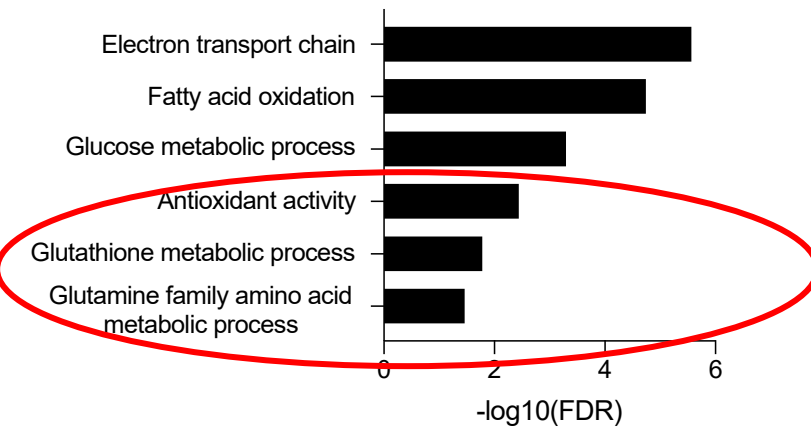


→ IFN-Is increases intracellular FA contents in Tex cells

Chronic IFN-Is stimulation dysregulate redox homeostasis

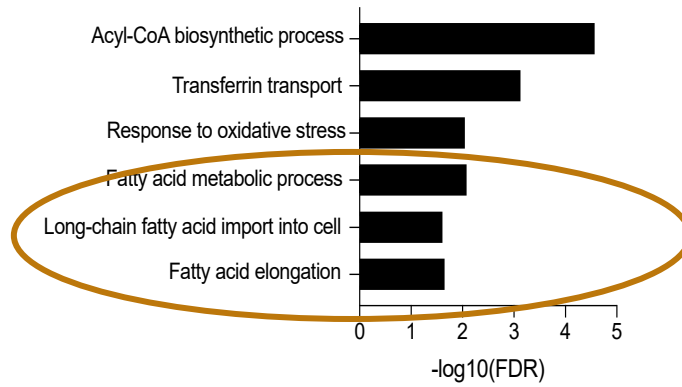
■ Tex cells
□ Tex cells + IFN-Is

Downregulated pathways

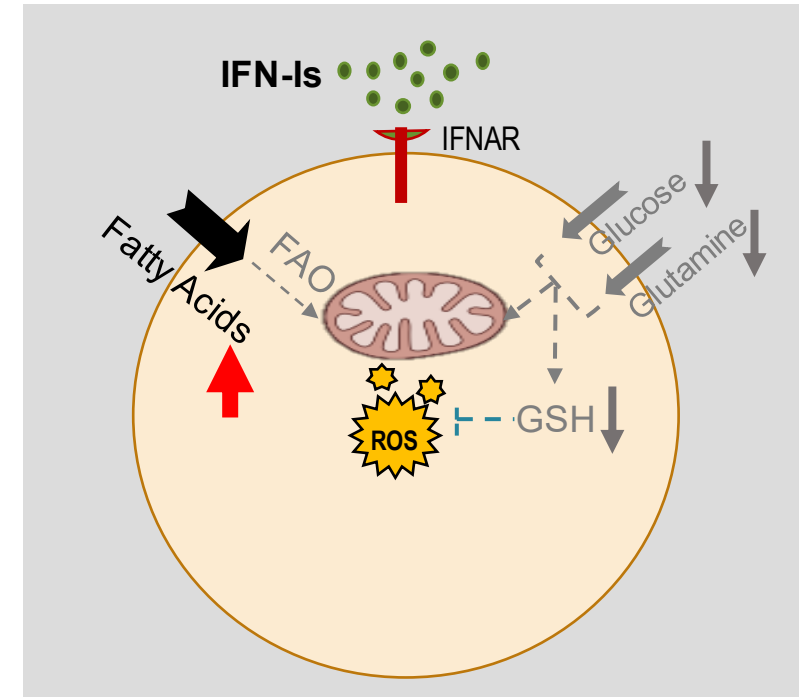


Chronic IFN-Is stimulation derails T cell metabolism

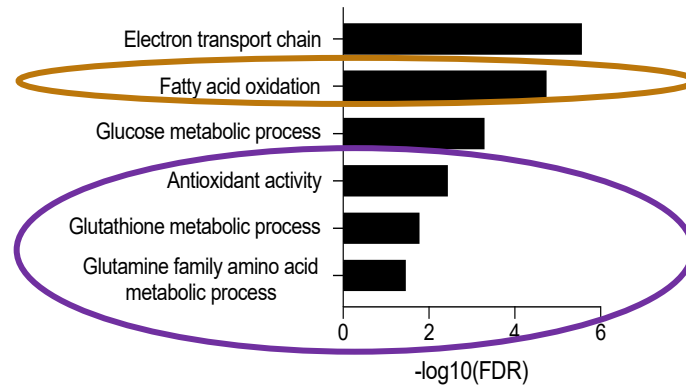
Upregulated pathways



↑ Polyunsaturated Fatty acids (PUFAs)

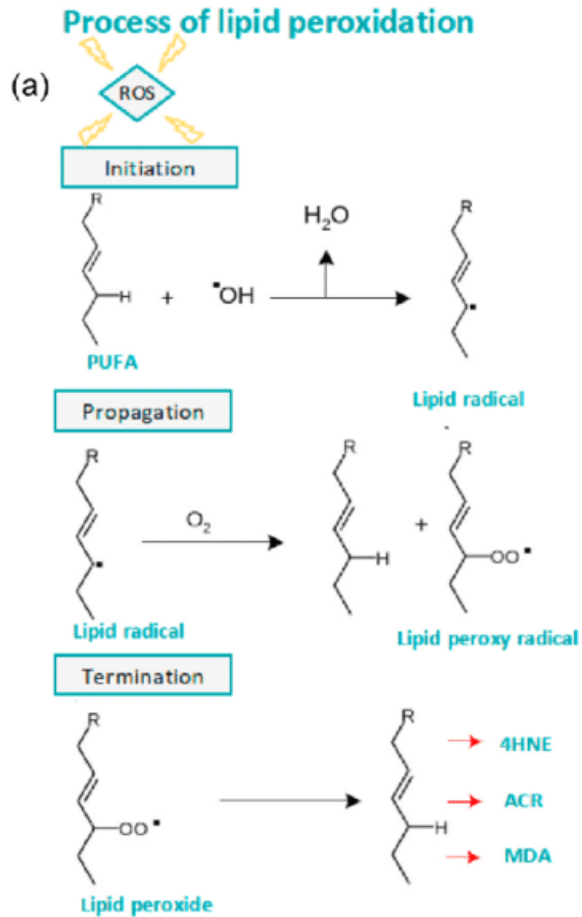


Downregulated pathways

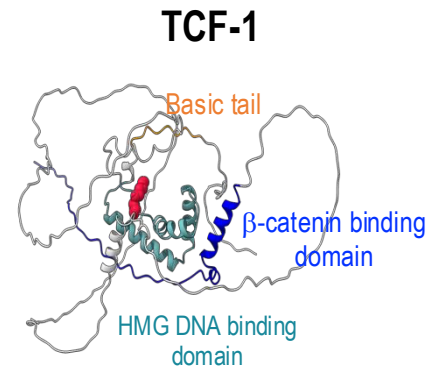
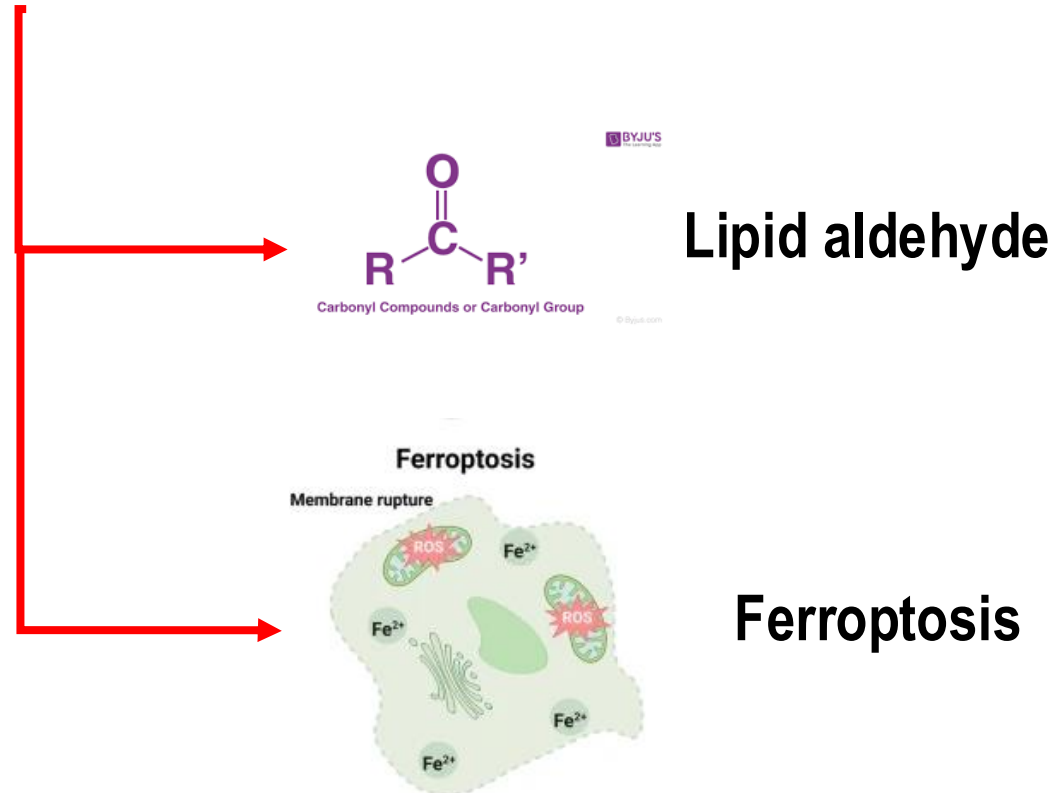


↑ Reactive oxygen species (ROS)

Lipid peroxidation (LPO)



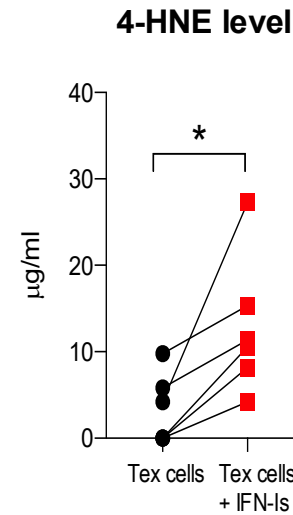
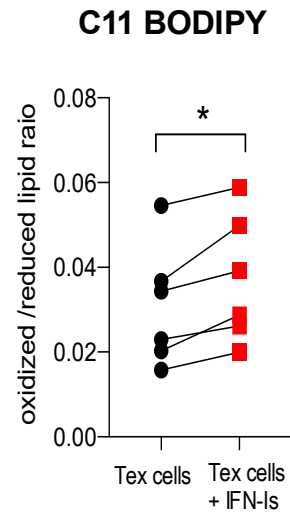
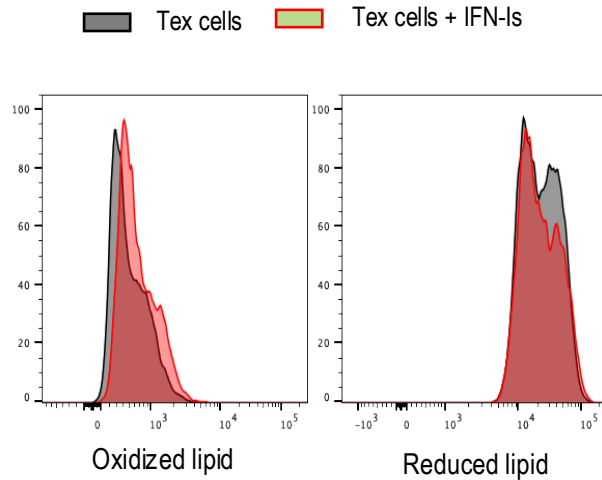
- Chain reaction that a free radical extracts an electron from a lipid $\rightarrow$ oxidative degradation of lipid



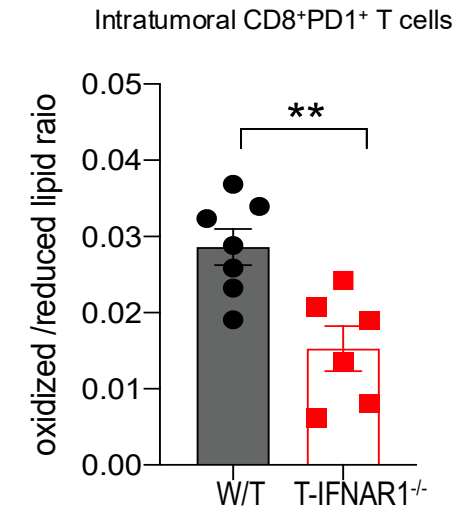
Carbonylation sites:
K271, P272

Chronic IFN-Is stimulation promotes lipid peroxidation (LPO) in Tex cells

In vitro assay

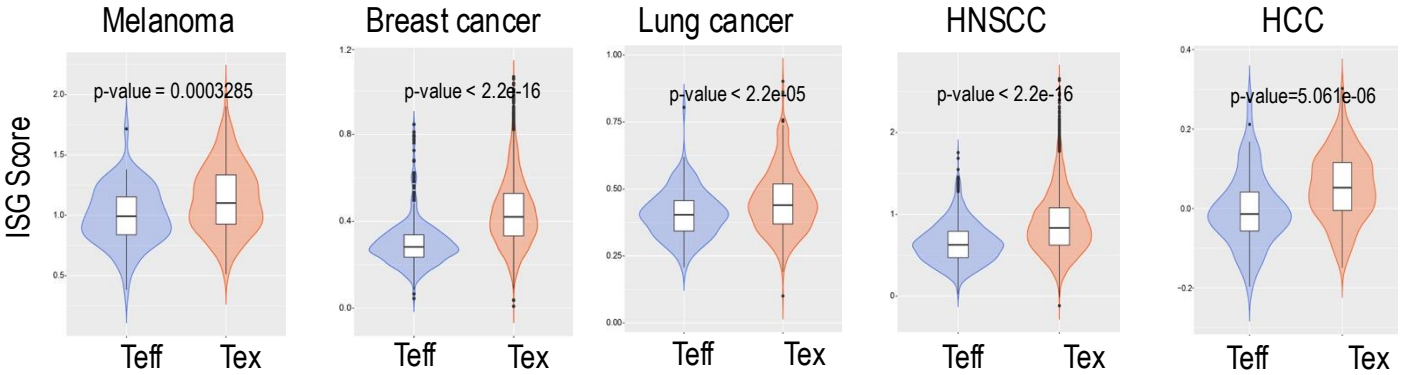


NRAS/Akt HCC model

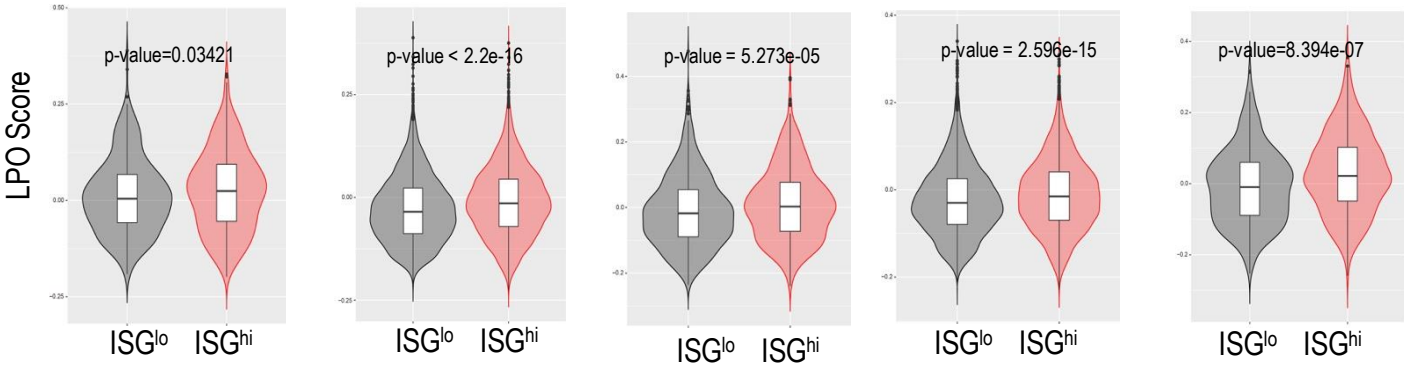


Chronic IFN-Is stimulation promotes LPO in Tex cells

Within intratumoral
CD8+T cells

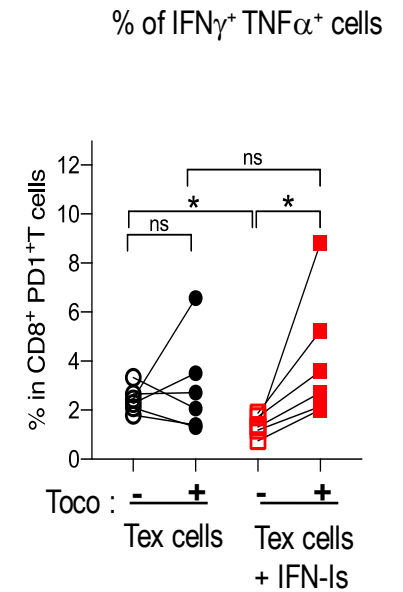
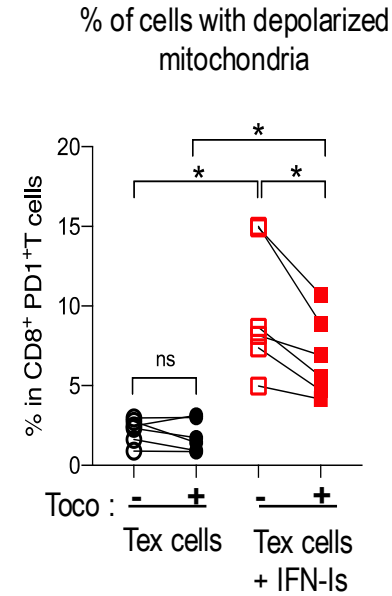
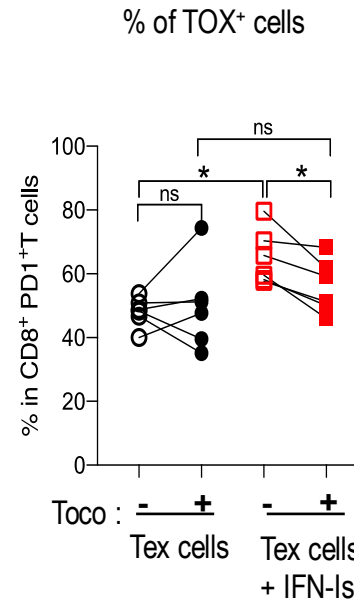
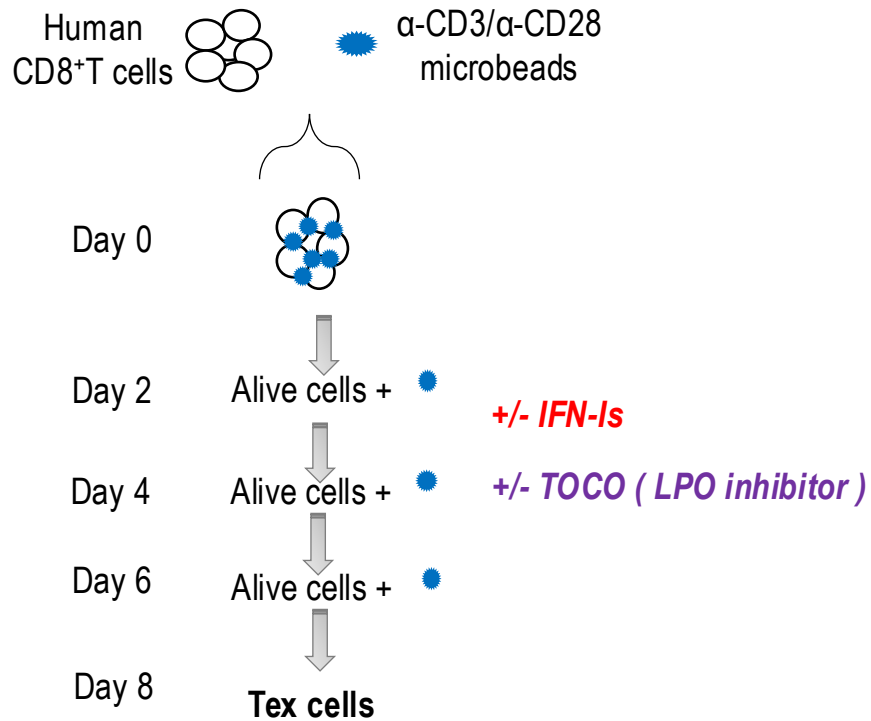


Within intratumoral
Tex cells

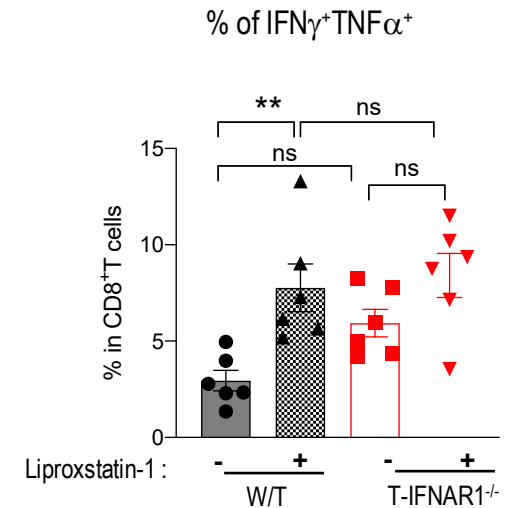
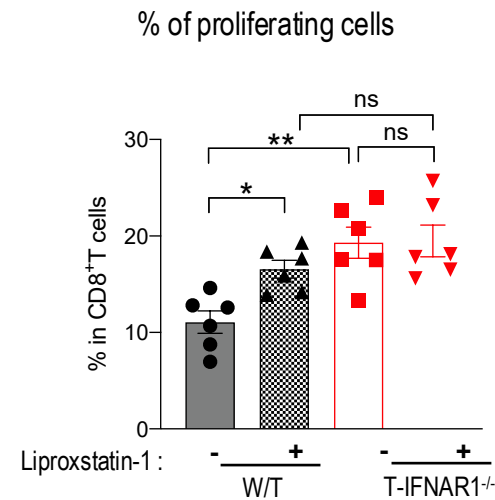
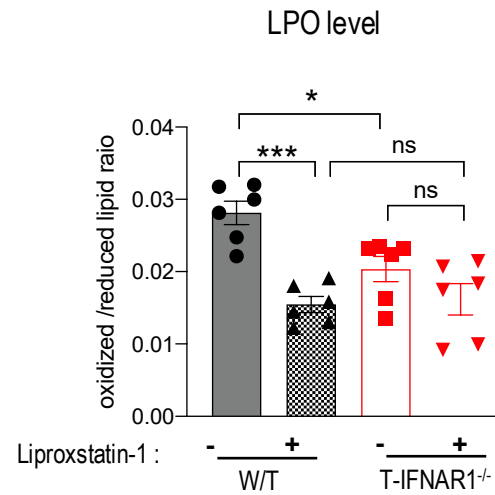
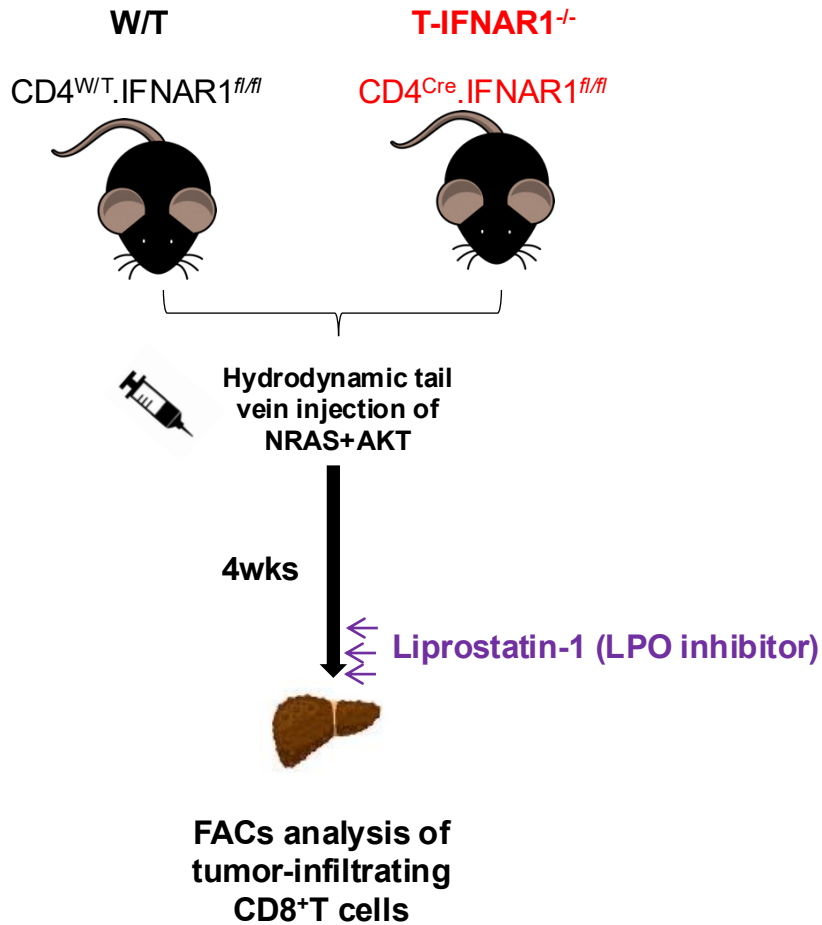


Pan-cancer dataset
(Zheng et al, Science, 2021)

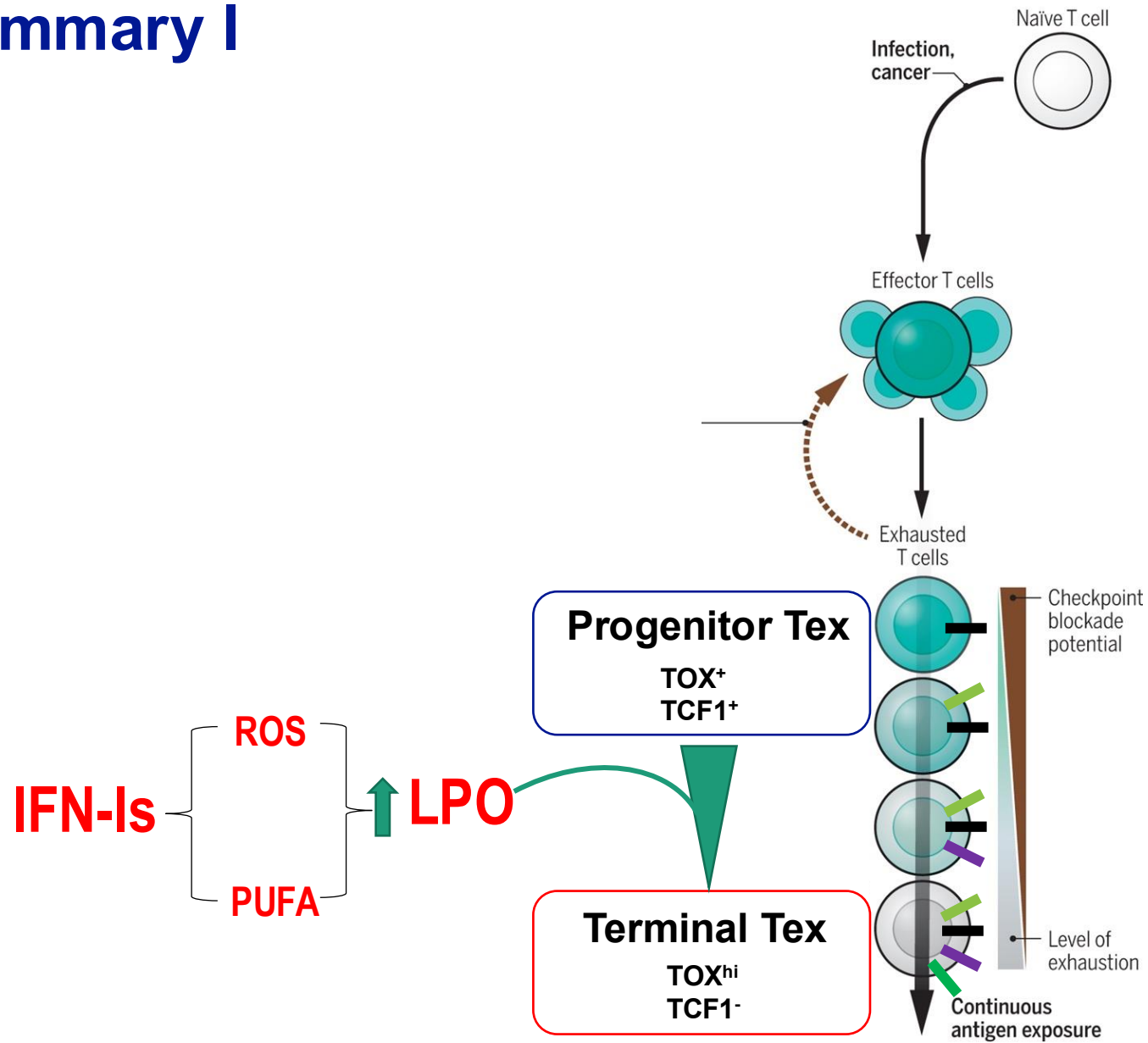
IFN-Is facilitates Tex differentiation via LPO induction



IFN-Is facilitates Tex differentiation via LPO induction

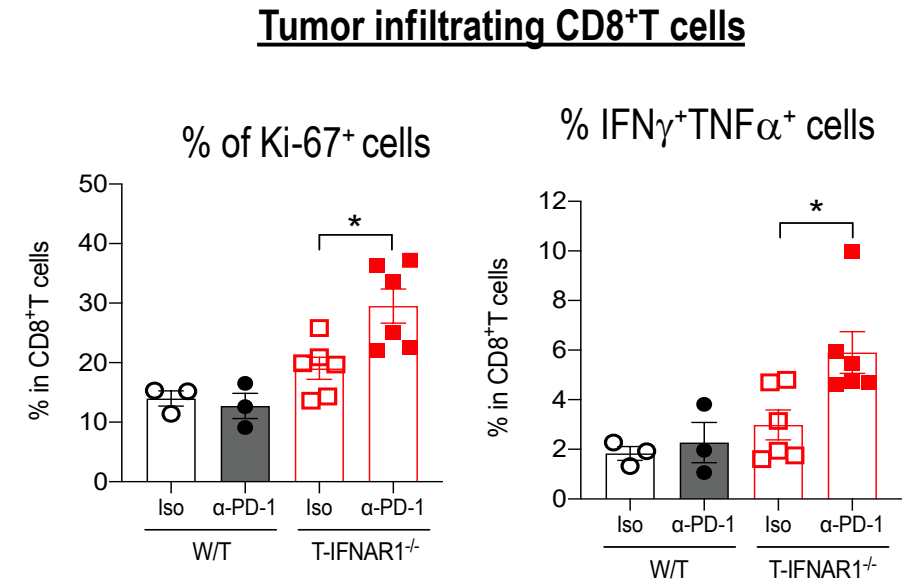
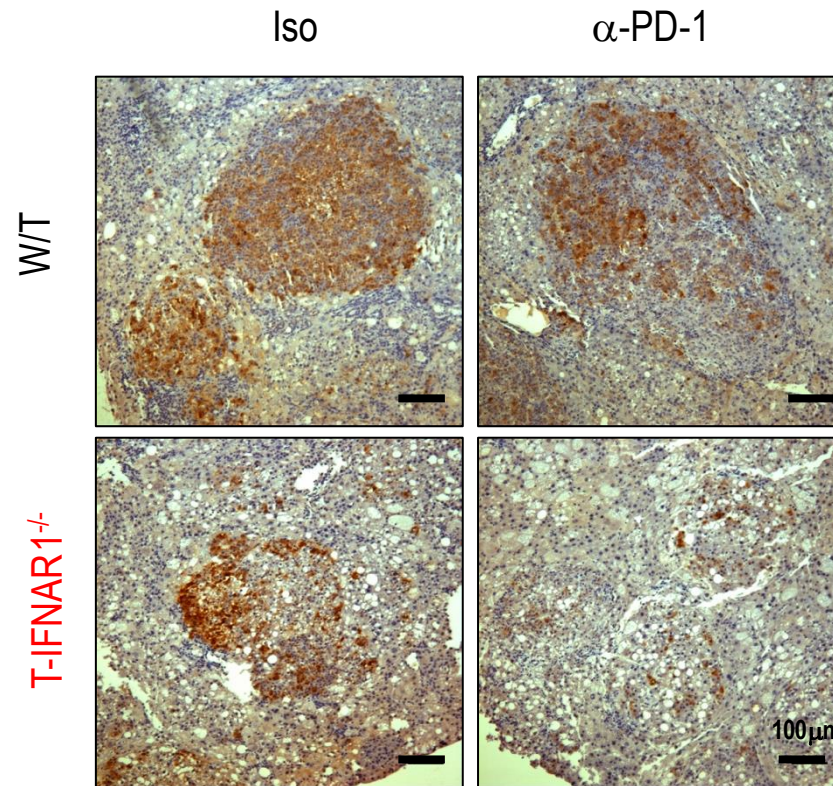
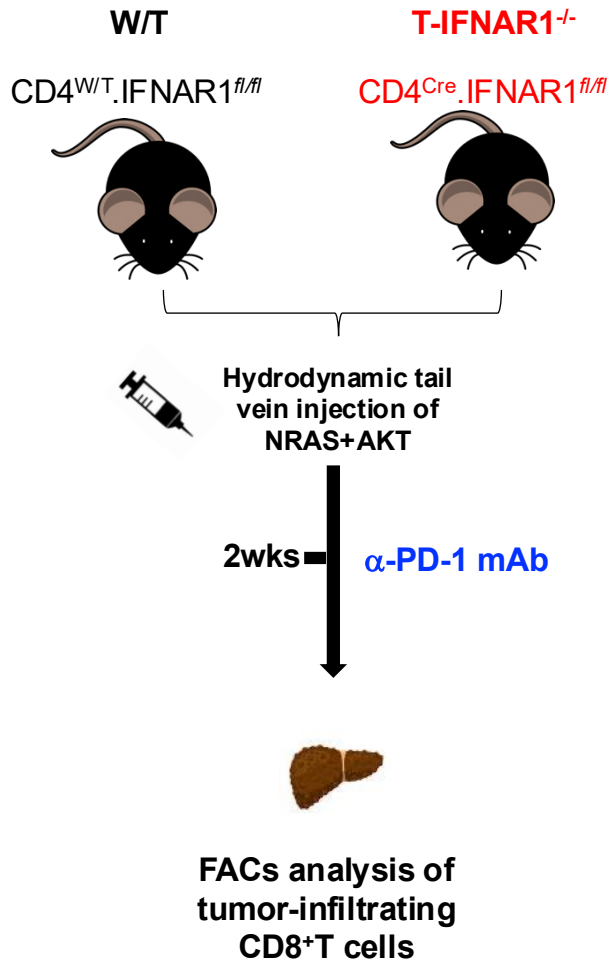


Summary I

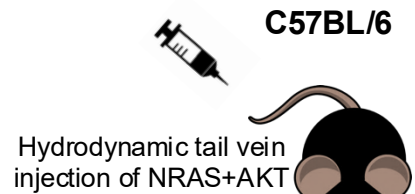


Question :
*Can blocking IFN-Is signaling
enhances the efficacy of α -PD1
therapy?*

Blocking IFN-Is signaling improves the efficacy of anti-PD-1 therapy



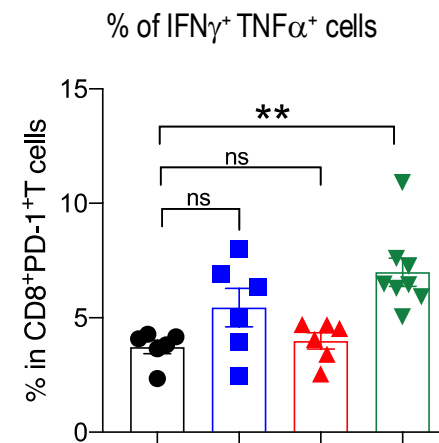
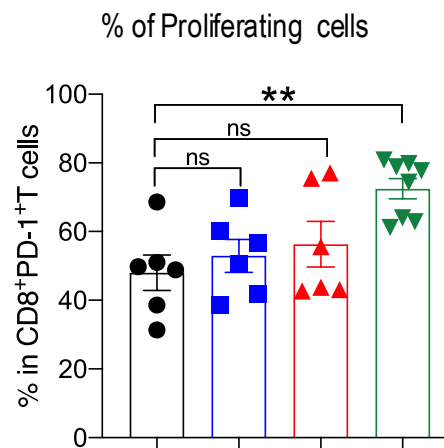
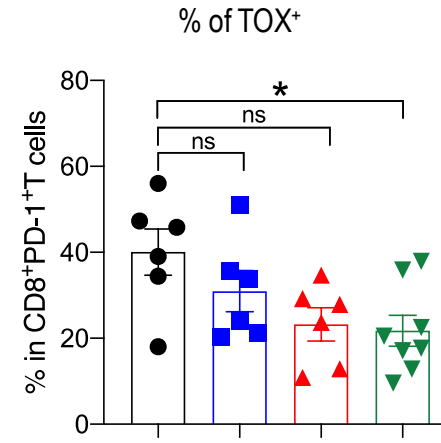
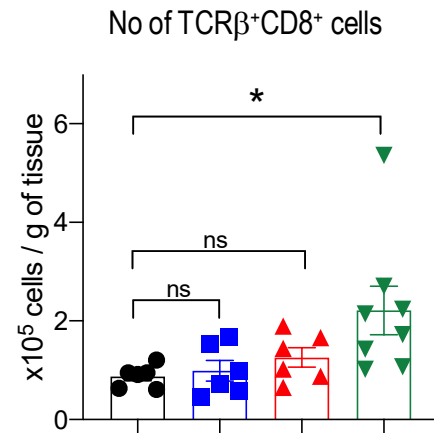
Blocking IFN-Is signaling improves the efficacy of anti-PD-1 therapy



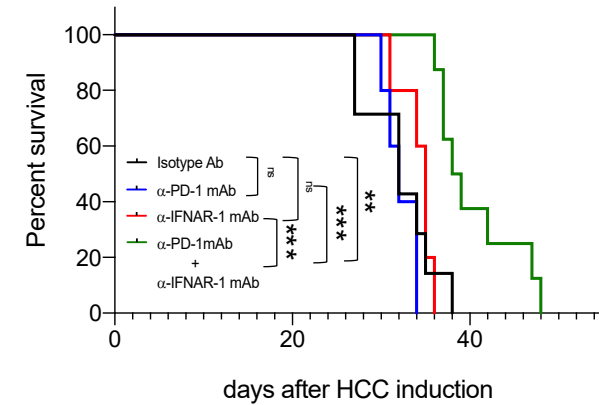
2wks

α -PD-1 mAb
+/-
 α -IFNAR-1 mAb

1st set : FACs analysis on
intratumoral CD8⁺ T cells at Wk4
2nd set : Survival rate



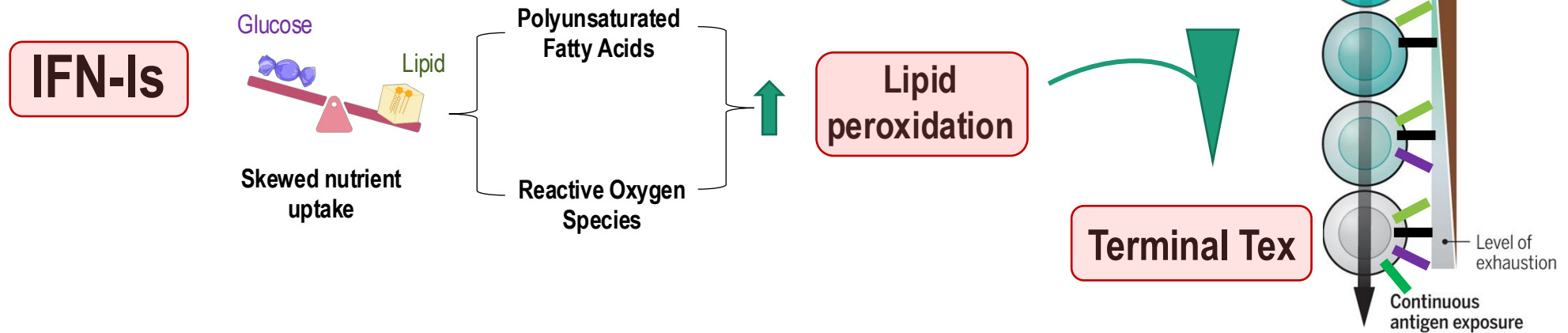
- Isotype Ab
- α -PD-1 mAb
- ▲ α -IFNAR-1 mAb
- ▼ α -PD-1mAb + α -IFNAR-1 mAb



Article

Chronic type I interferon signaling promotes lipid-peroxidation-driven terminal CD8⁺ T cell exhaustion and curtails anti-PD-1 efficacy

Chen et al. (22) 41(7):111647



→ Poor anti-tumor activities
→ Resistance to ICB therapy

The janus face of IFN-Is in cancer

Anti-tumorigenic effects (acute exposure)

Tumor cells : apoptosis

DCs : activation

CD8⁺T cells : priming/activation



Pro-tumorigenic effects (chronic exposure)

Tumor cells : DNA-damage resistance genes

DCs : upregulate PD-L1

CD8⁺T cells : terminal exhaustion

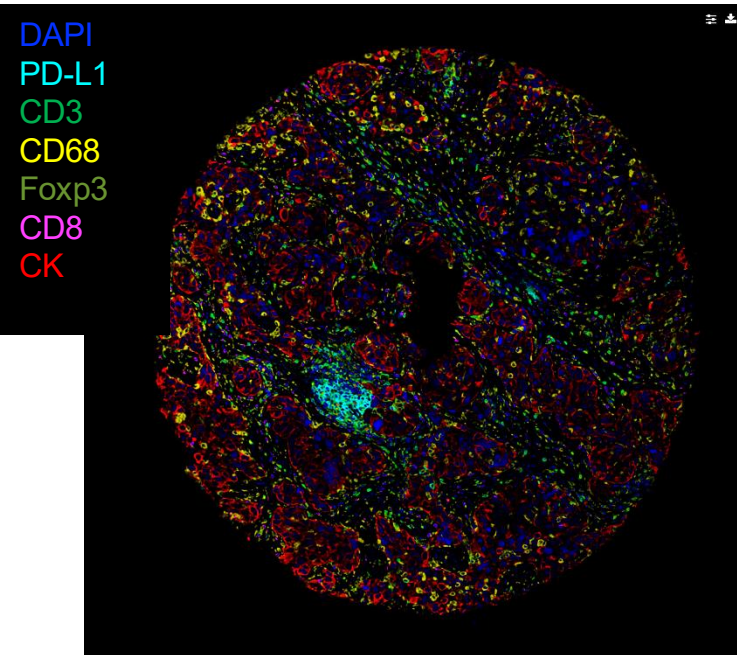
Duration ?

Dose ?

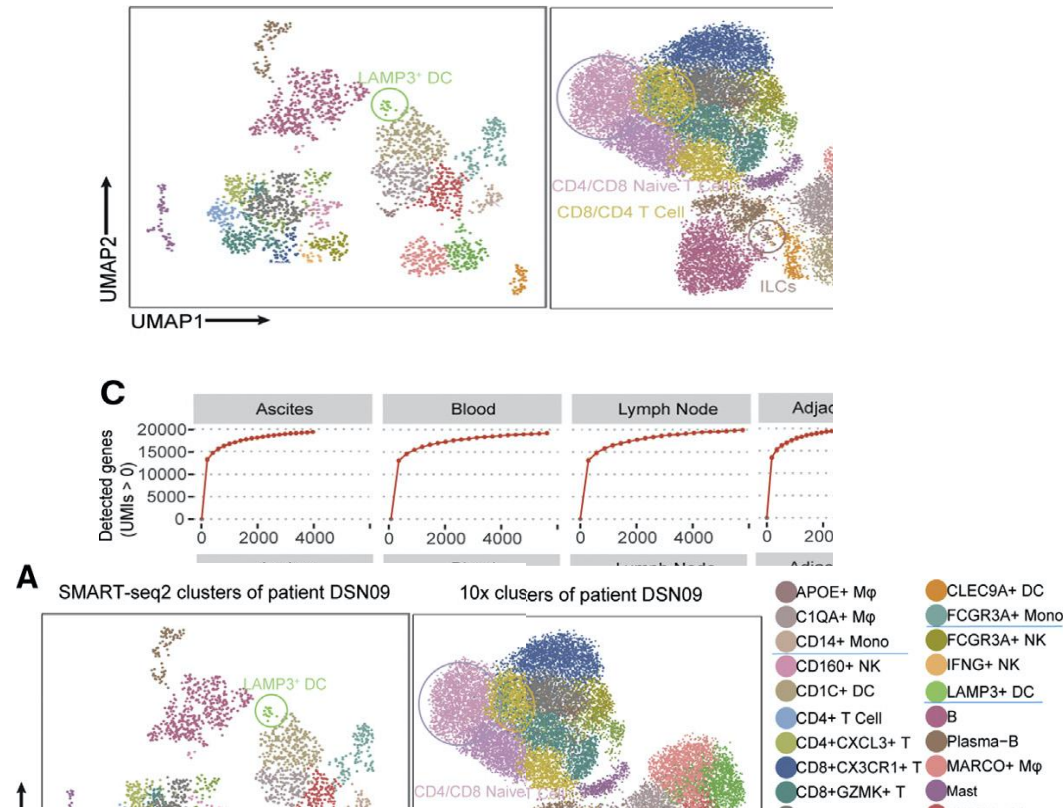
Stage of cancer development ?

State of intratumoral T cells ?

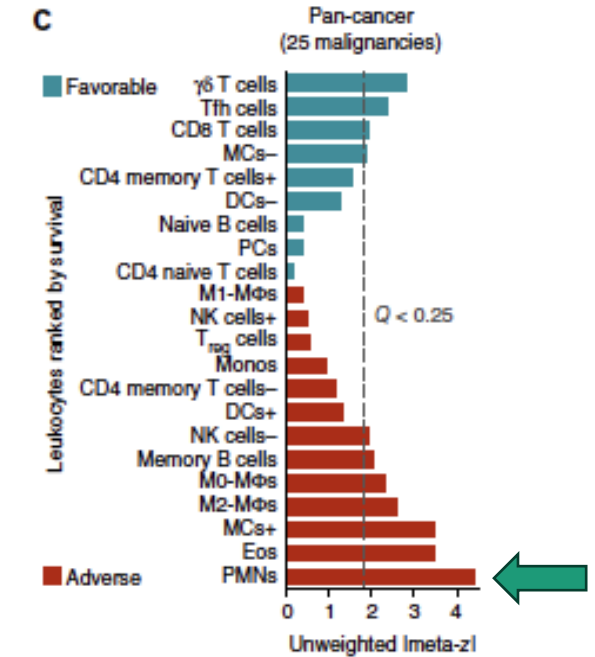
Immune contexture in the tumor microenvironment (TME)



Human lung cancer tissue
ImmunoAtlas: JEDI-21012

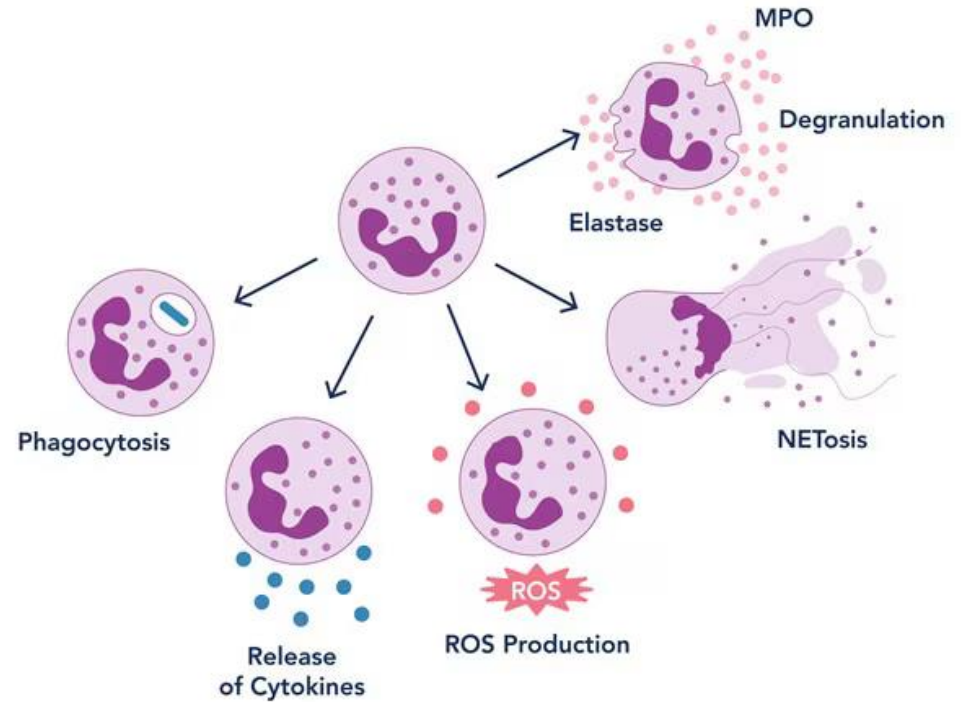
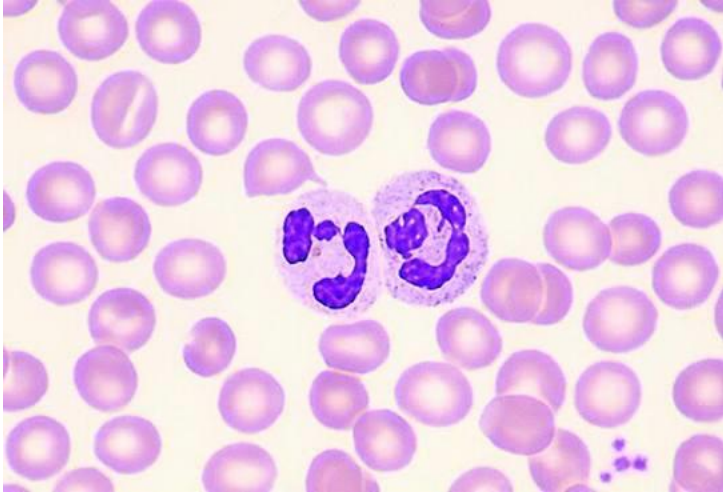


Tumor infiltrating CD45⁺ cells in human HCC
Cell (2019) Vol 179: 829



Gentles et al .
Nat. Medicine (15) 21:(8) 938-945

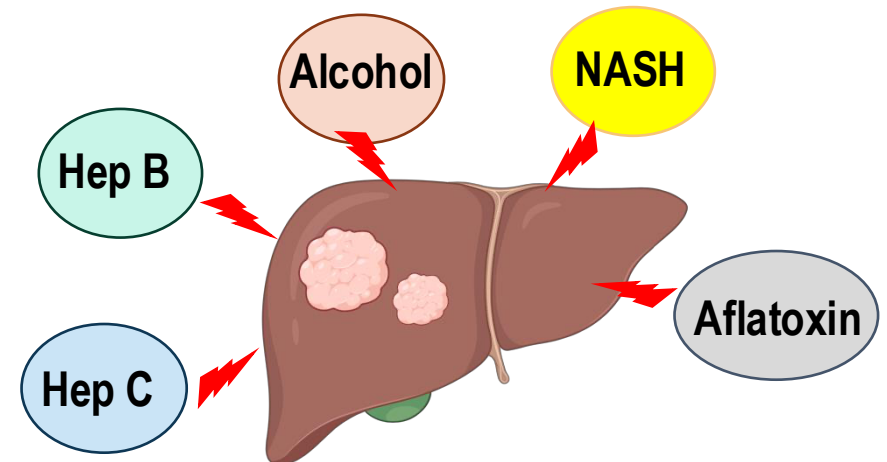
Neutrophils



- Most abundant innate immune cells
- Rapid first responders to invading pathogens
- Short half-life (6-8 hours)

Hepatocellular carcinoma (HCC)

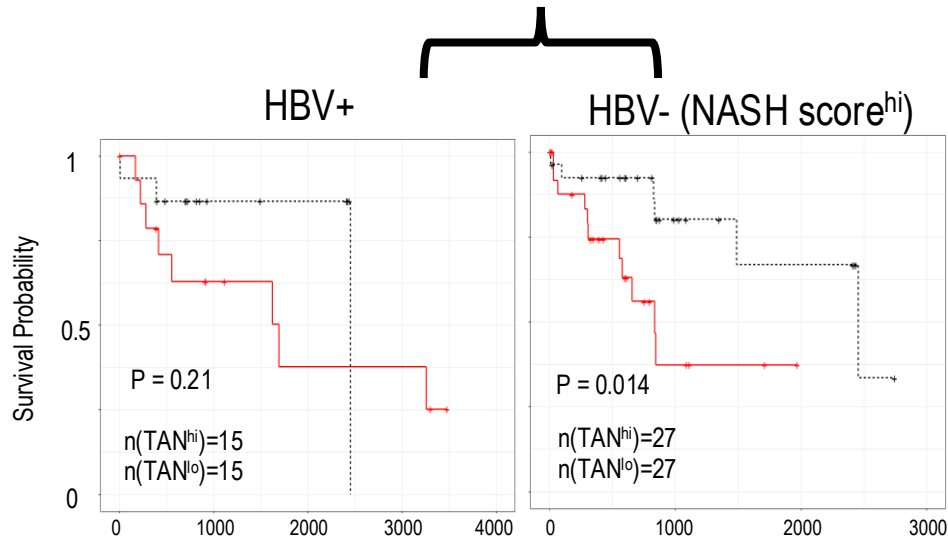
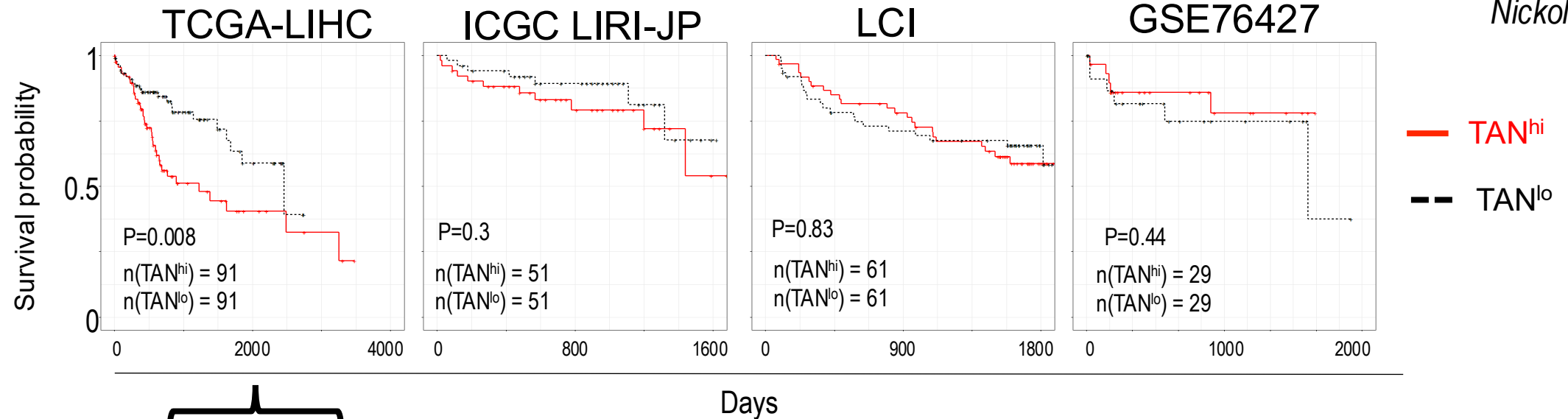
- Third leading cause of cancer-related deaths worldwide
- Diverse etiologies
- Prototypical inflammation-associated cancer
- ~30% of HCC patients respond to immune-checkpoint blockade (ICB) therapy
- NASH-HCC patients are most resistant to ICB therapy



High neutrophil infiltration predicts poor prognosis in HCC, but not for all etiologies!



Nickolas Teo

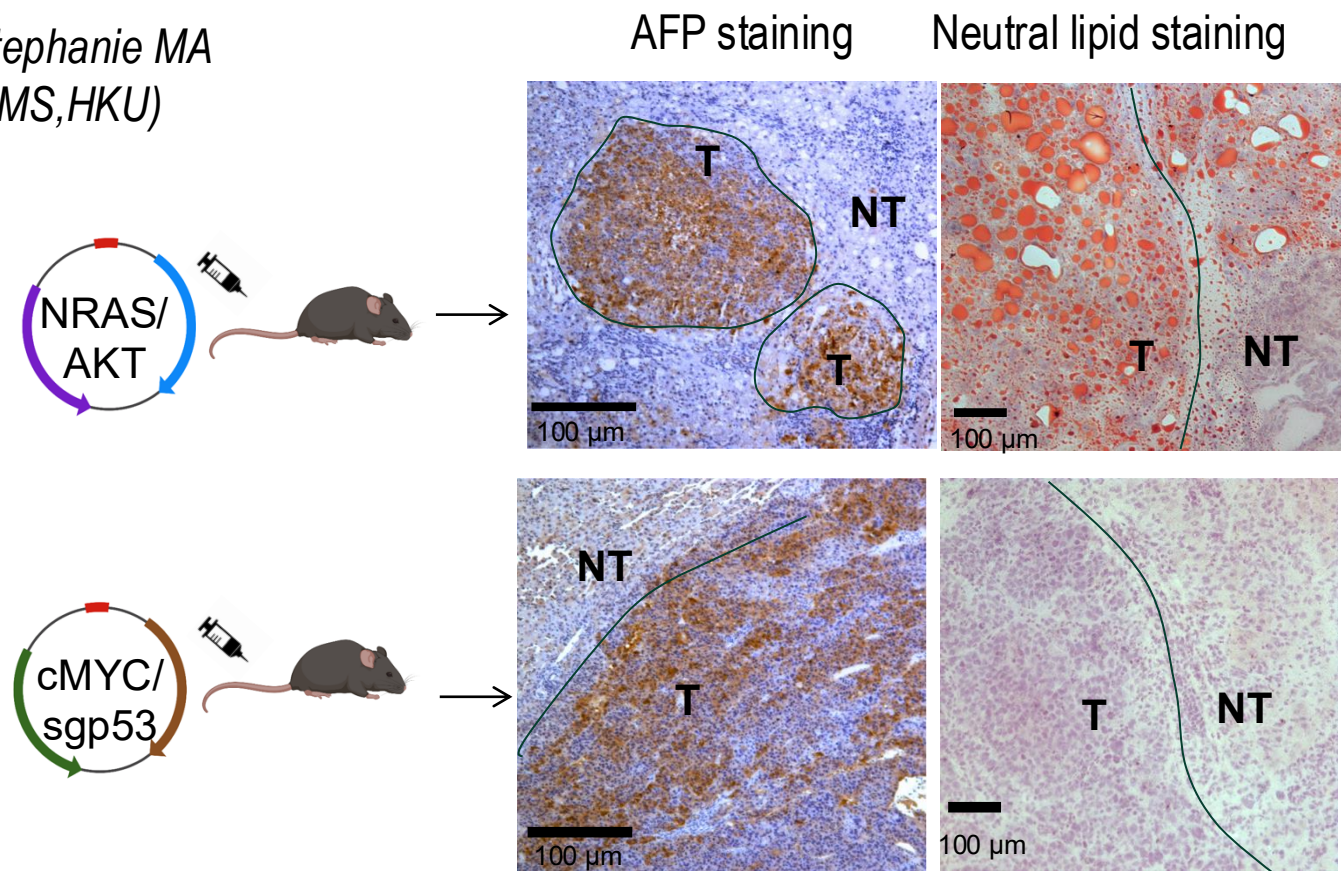


→ TANs are more pathogenic in NASH-HCC

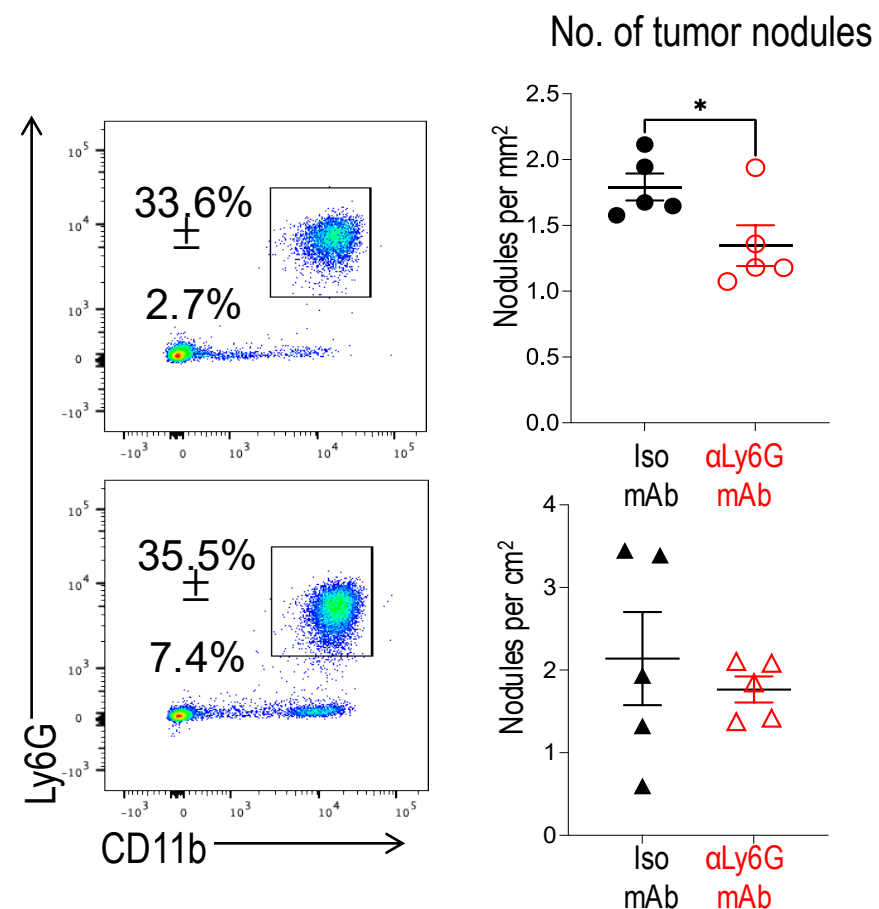
TANs are pathogenic in NASH-HCC model



Prof Stephanie MA
(SBMS, HKU)



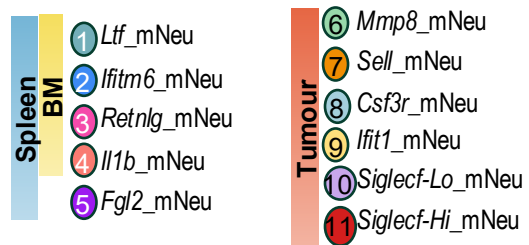
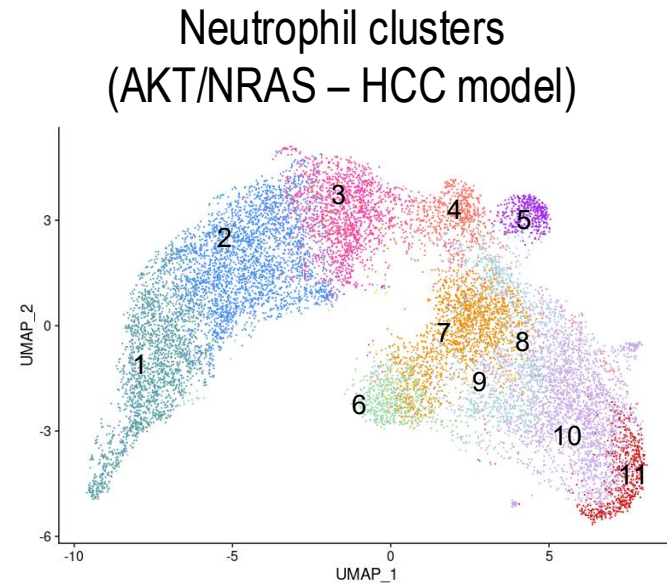
T = Tumor
NT = Non-Tumor



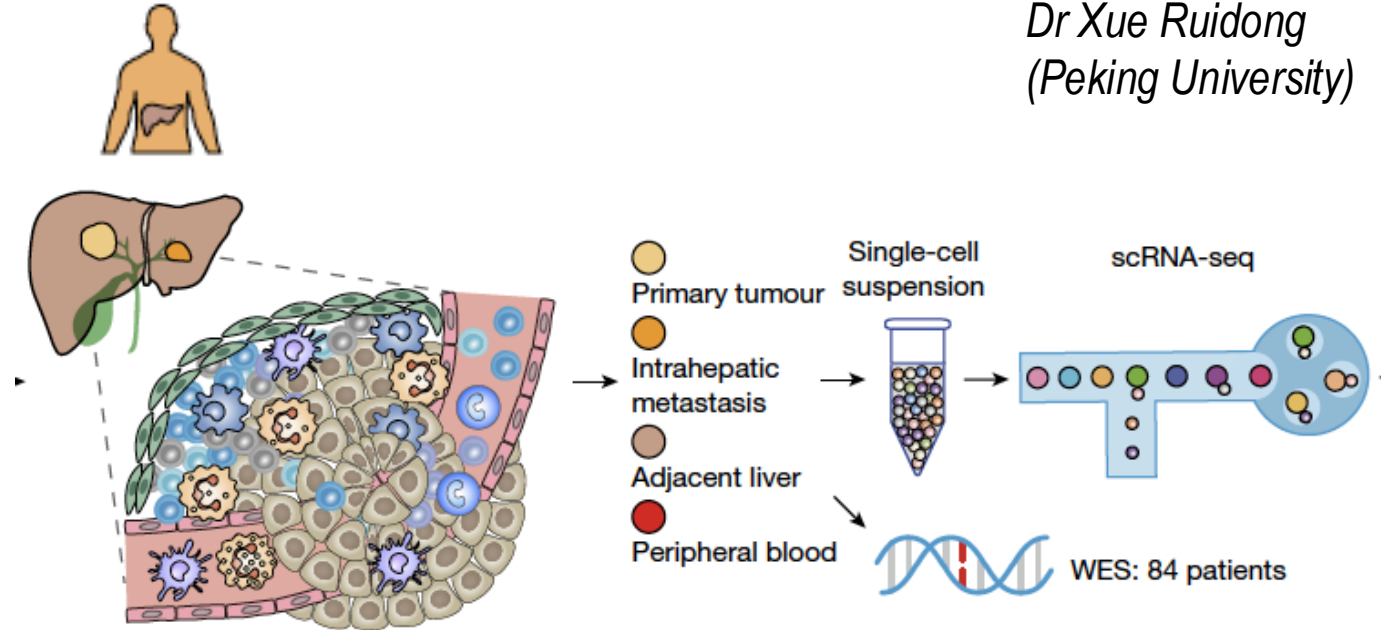
TANs heterogeneity in HCC



Dr Xue Ruidong
(Peking University)



79 HCC patients

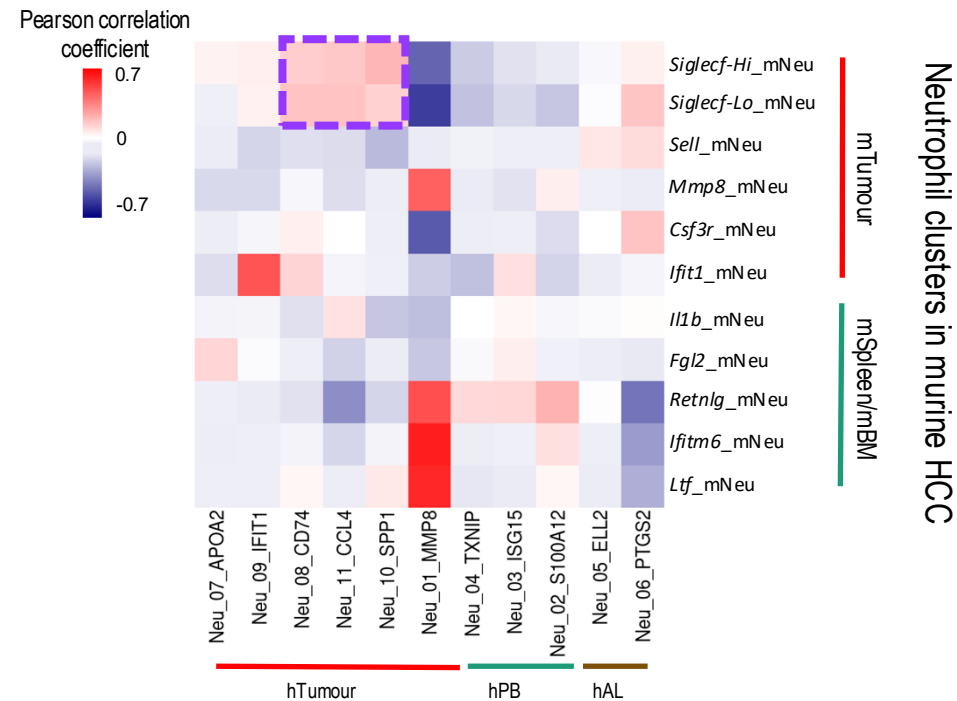
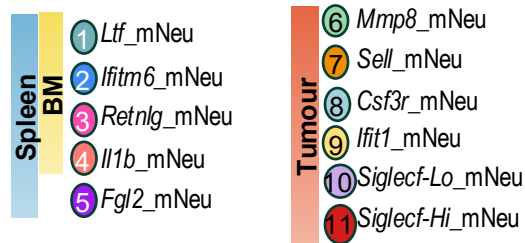
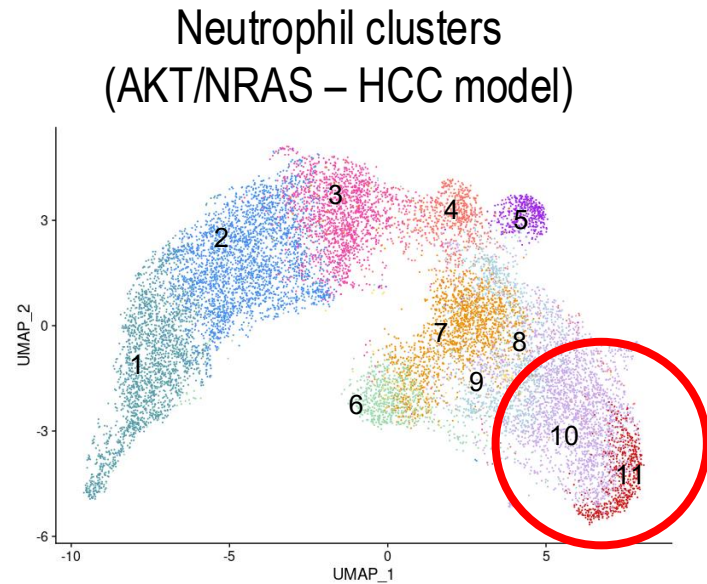


HCC TME Atlas : Xue et al. (22)Nature Vol 612: 141-147

TANs heterogeneity in HCC



Dr Xue Ruidong
(Peking University)

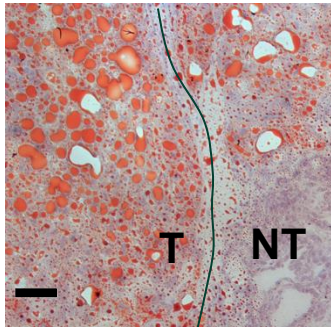


Neutrophil clusters in HCC patients
(HRA001748; Xue et al. 2022)

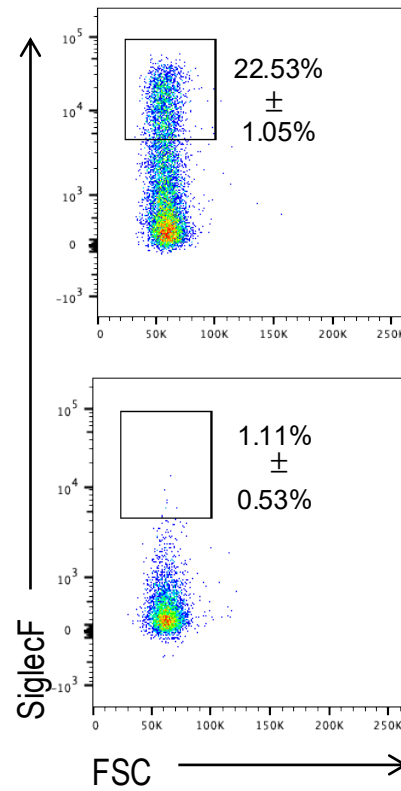
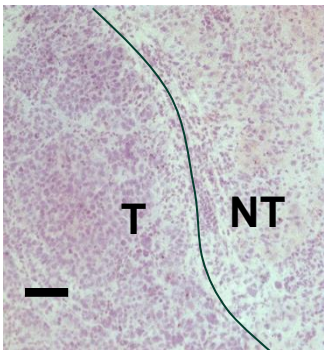
Pro-tumorigenic SiglecF^{Hi}TANs are enriched in NASH-HCC

AKT/
NRAS

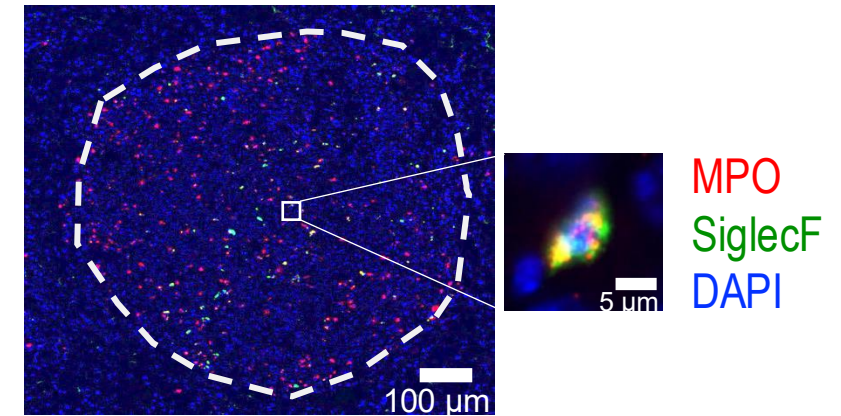
Neutral lipid staining



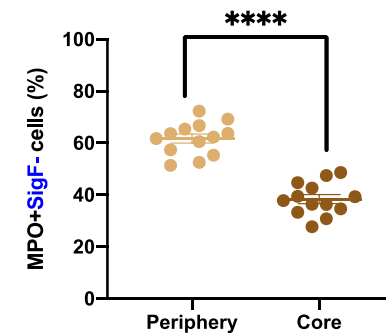
cMYC/
sgTP53



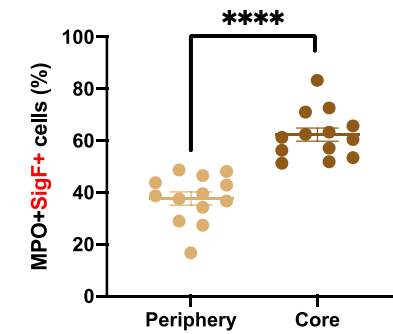
AKT/NRAS Tumor



MPO+SigF- across nodule



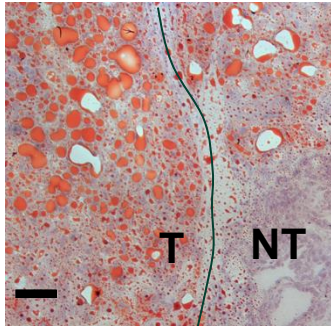
MPO+SigF+ across nodule



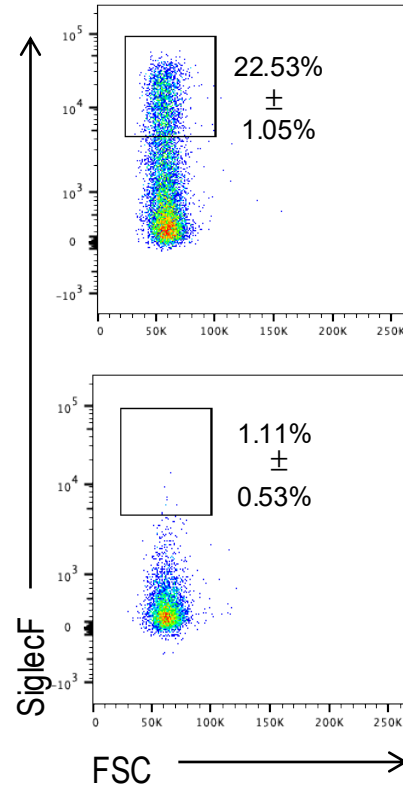
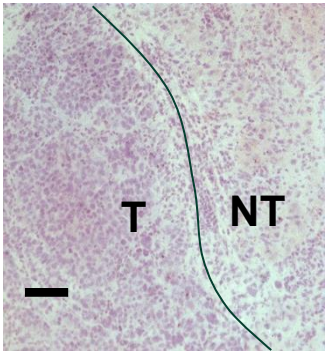
Pro-tumorigenic SiglecF^{Hi}TANs are enriched in NASH-HCC

Neutral lipid staining

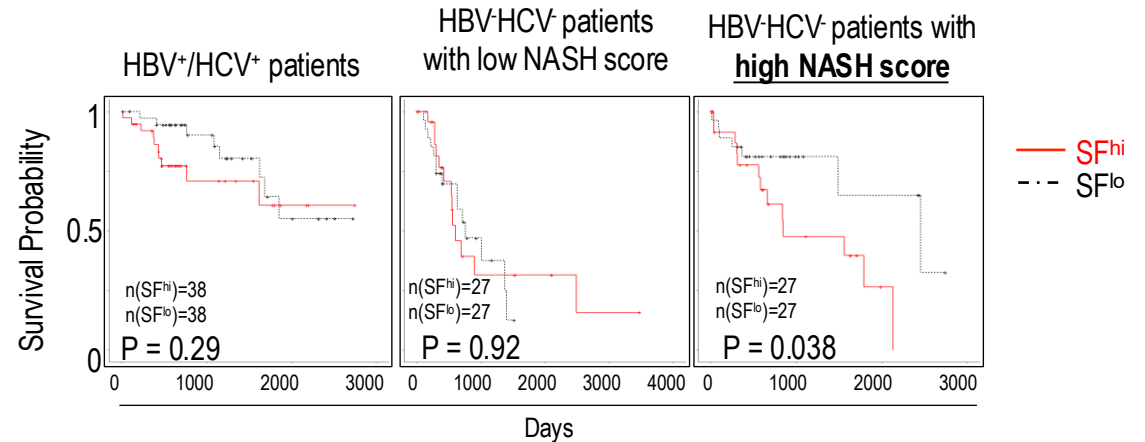
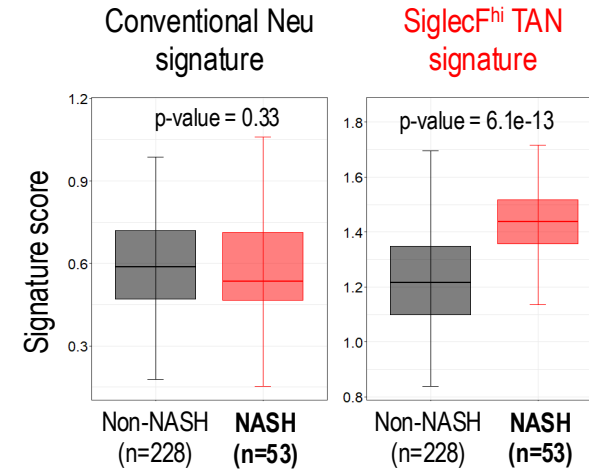
AKT/
NRAS



cMYC/
sgTP53



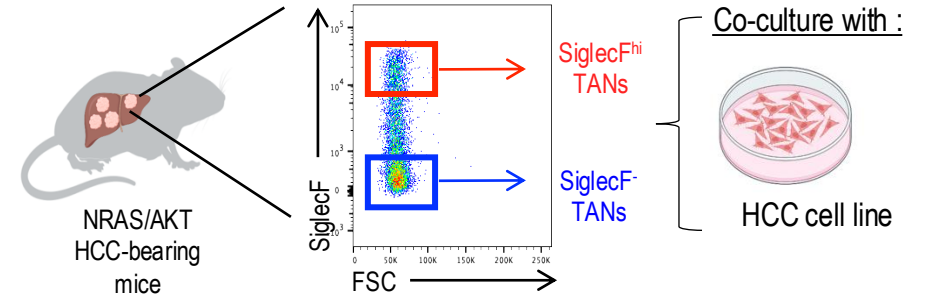
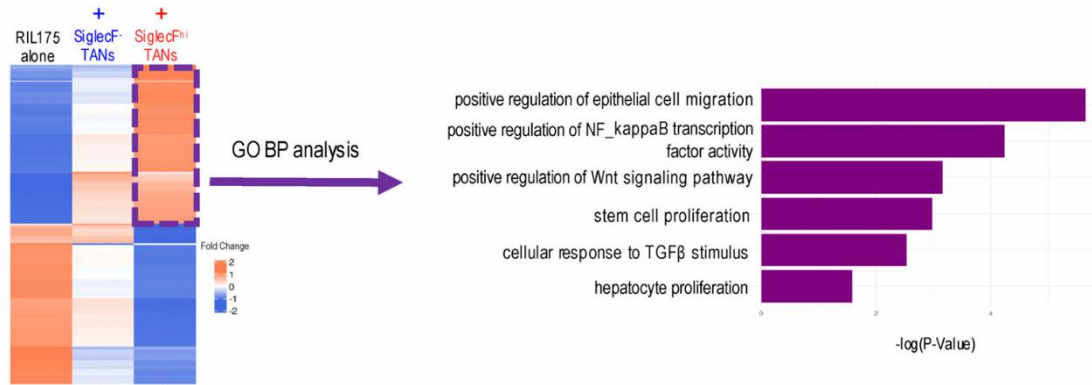
Murine HCC



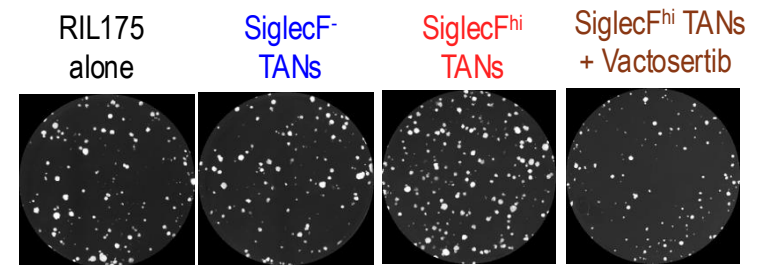
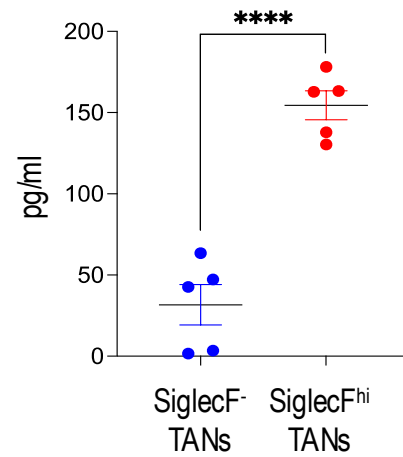
HCC patients

SiglecF^{Hi}TANs directly promote tumorigenesis via TGF- β

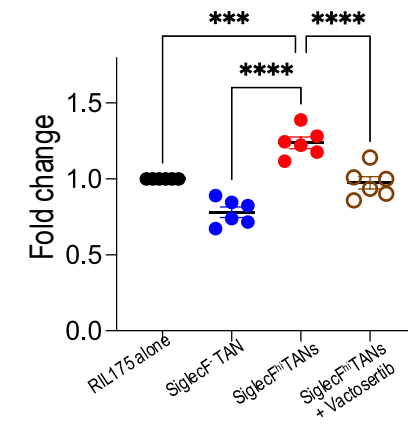
A



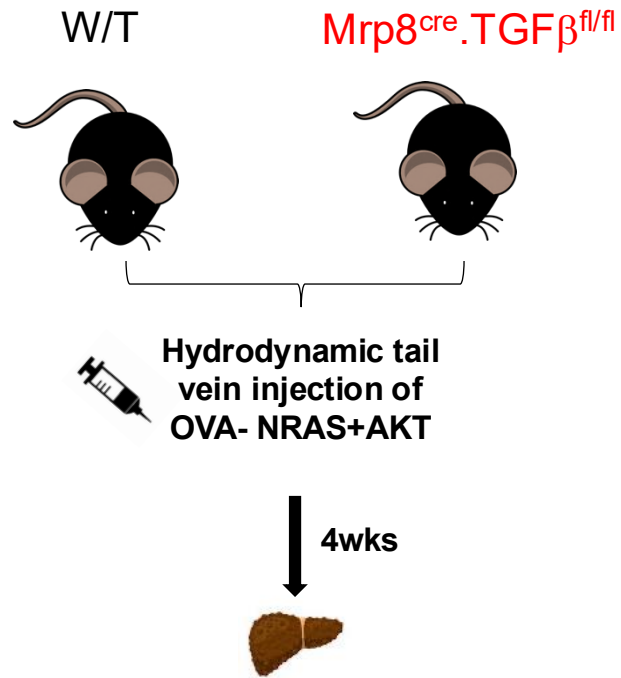
TGFβ1



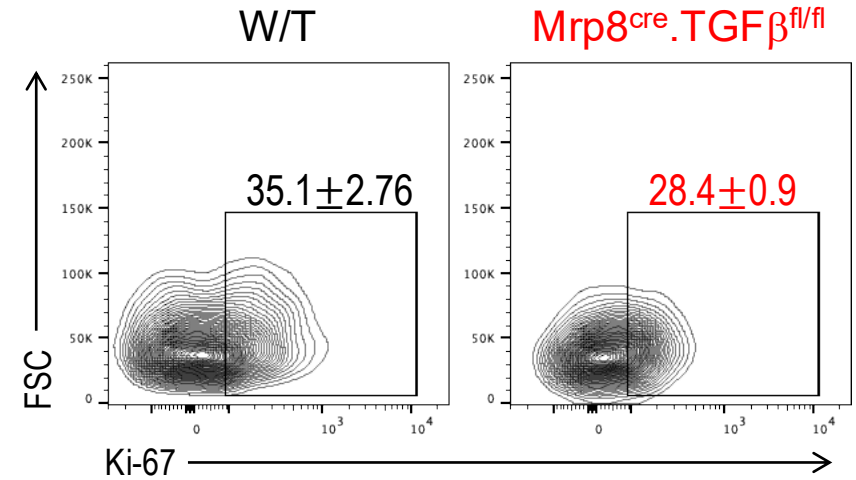
Colony Formation



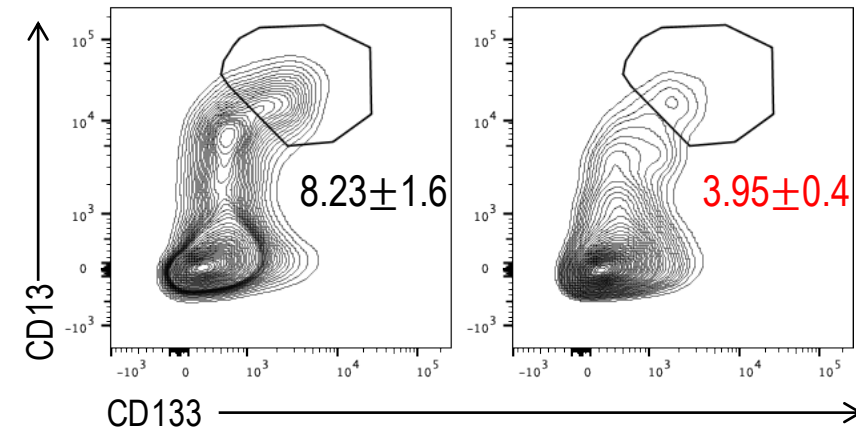
TANs mediate their pro-tumor roles via TGF- β *in vivo*



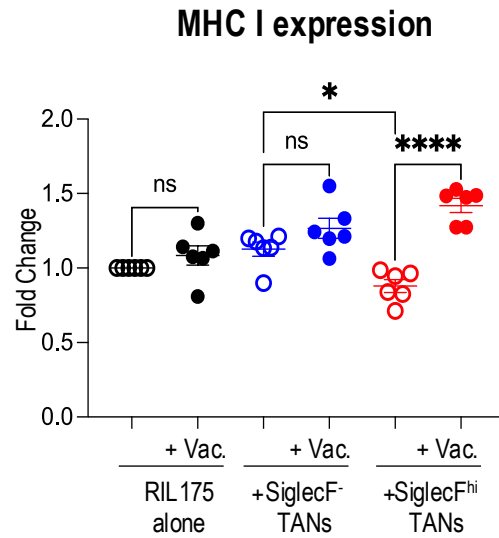
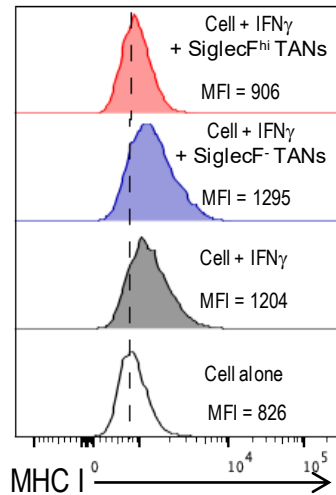
Tumor cell proliferation



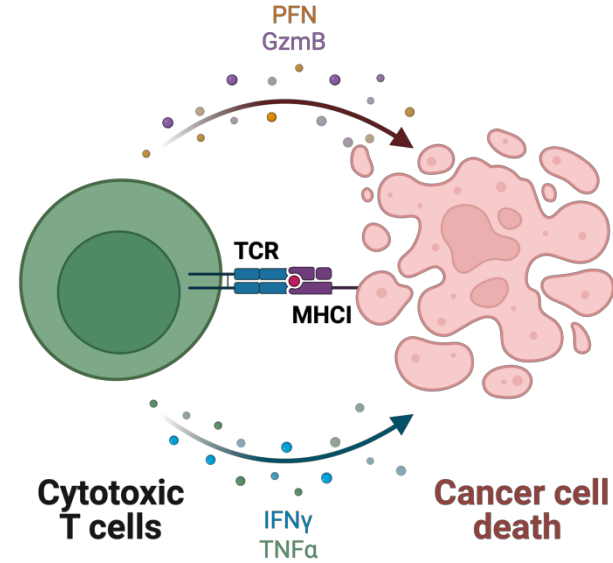
% of cancer stem cells



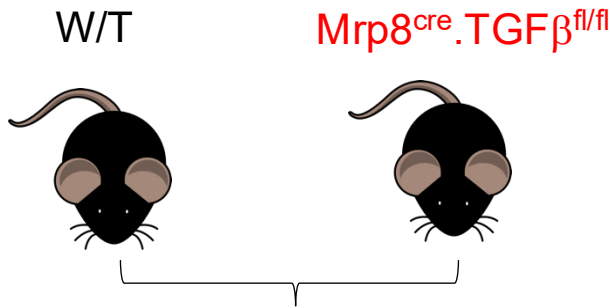
SiglecF^{hi}TANs downregulate tumor antigenicity via TGF- β



Immune surveillance



TANs regulate tumor antigenicity via TGF- β

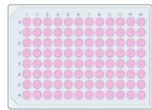


Hydrodynamic tail vein injection of OVA- NRAS+AKT

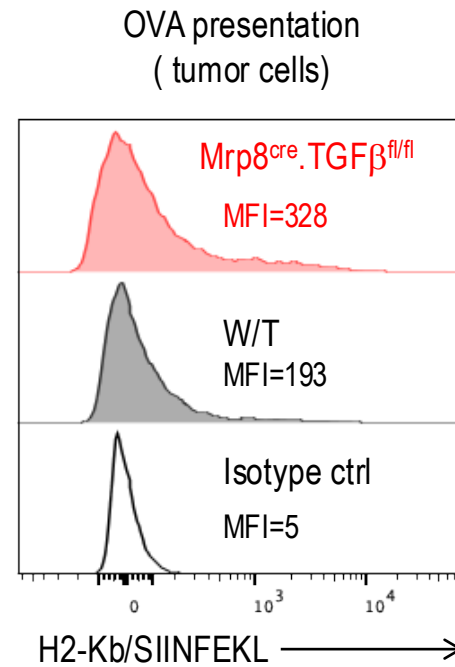
4wks

Harvest tumor cells :

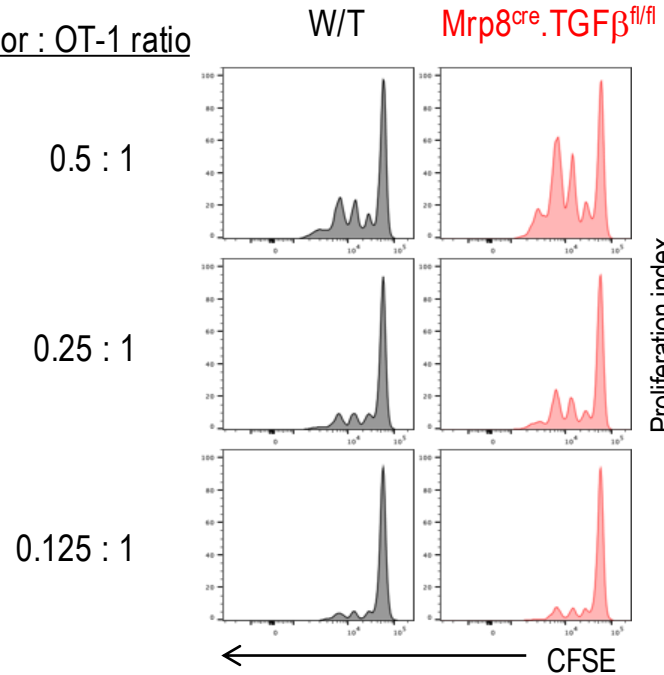
- FACs analysis



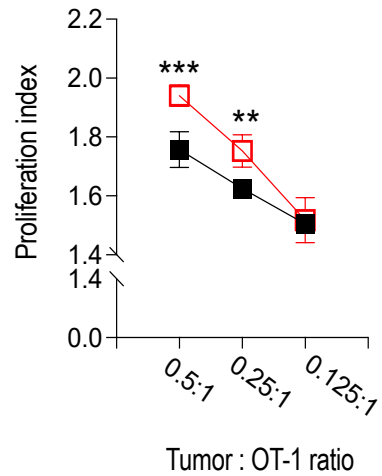
- OVA presentation
- OT-1 recognition



Tumor : OT-1 ratio



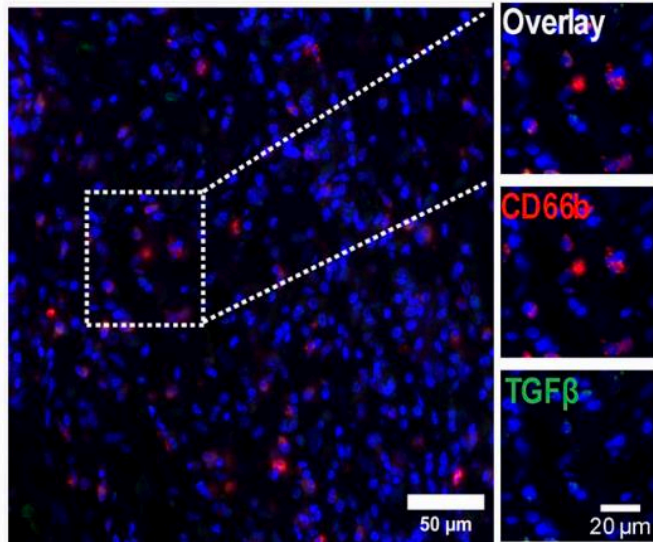
OT-1 cell proliferation



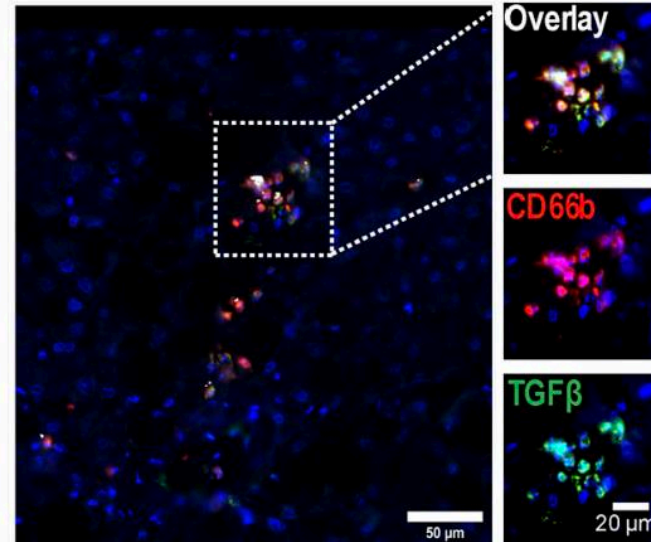
SigleF^{Hi} –like TANs regulate tumor antigenicity in HCC patients via TGF- β

C

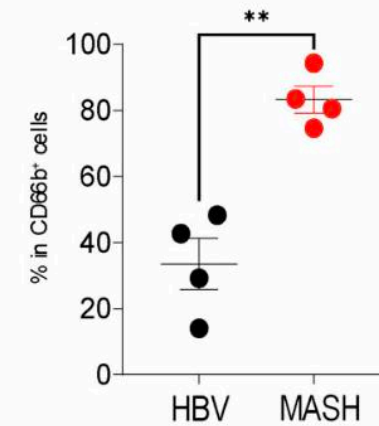
HBV-related HCC



MASH-related HCC



Frequency of TGF β ⁺CD66b⁺ neutrophils

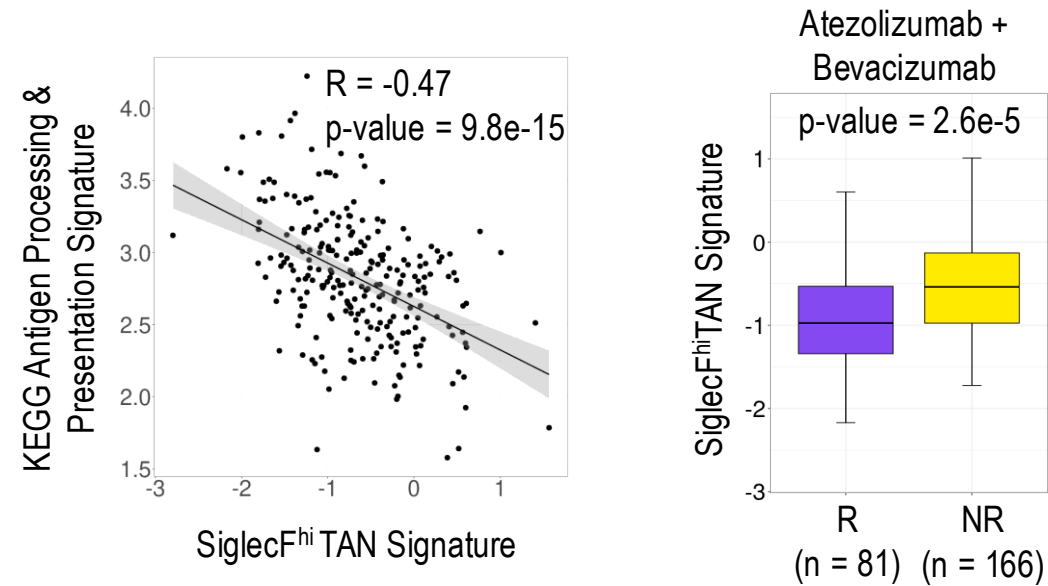


SiglecF^{Hi} –like TANs regulate tumor antigenicity in HCC patients via TGF-β

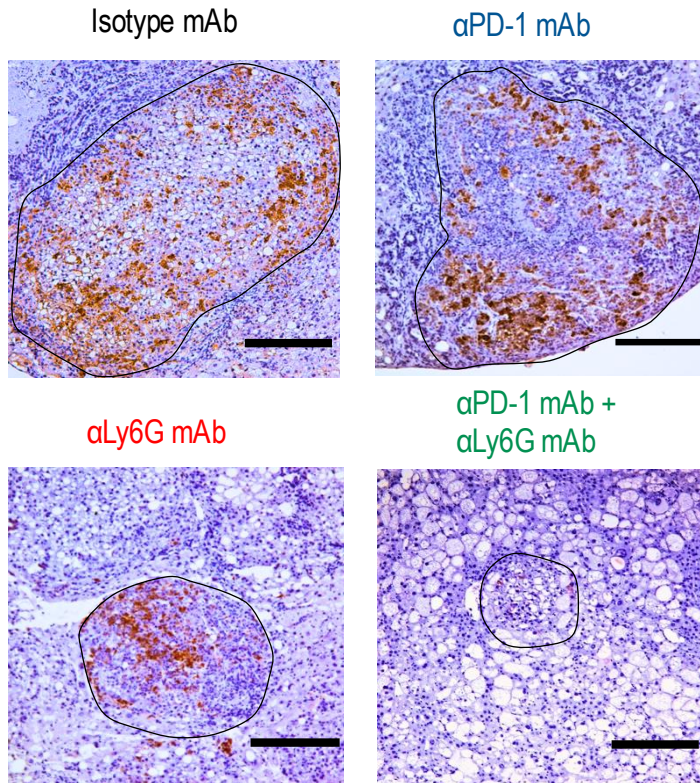
[HRA001748; Xue et al. 2022](#)



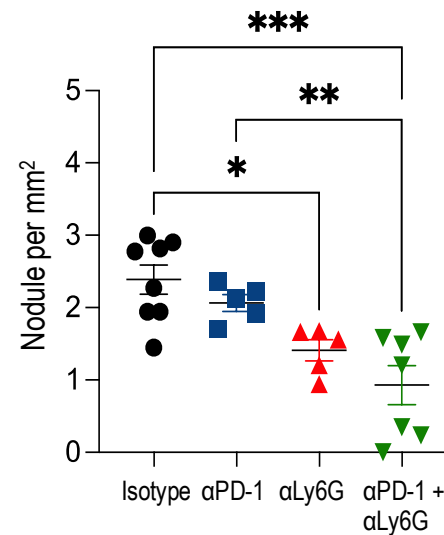
[IMbrave150 + GO30140 trials](#)



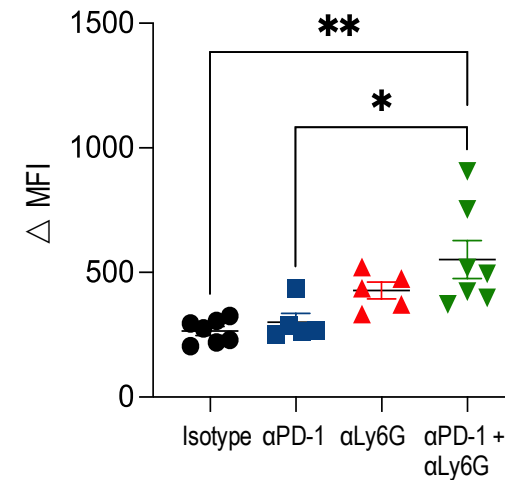
TANs removal sensitizes NASH-HCC mice to α PD-1 therapy



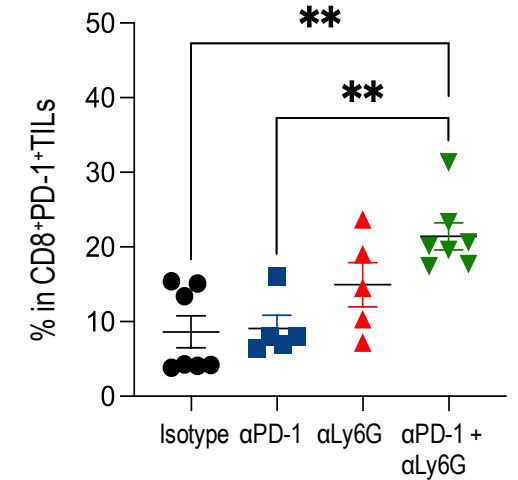
No. of tumor nodules



MHC I expression

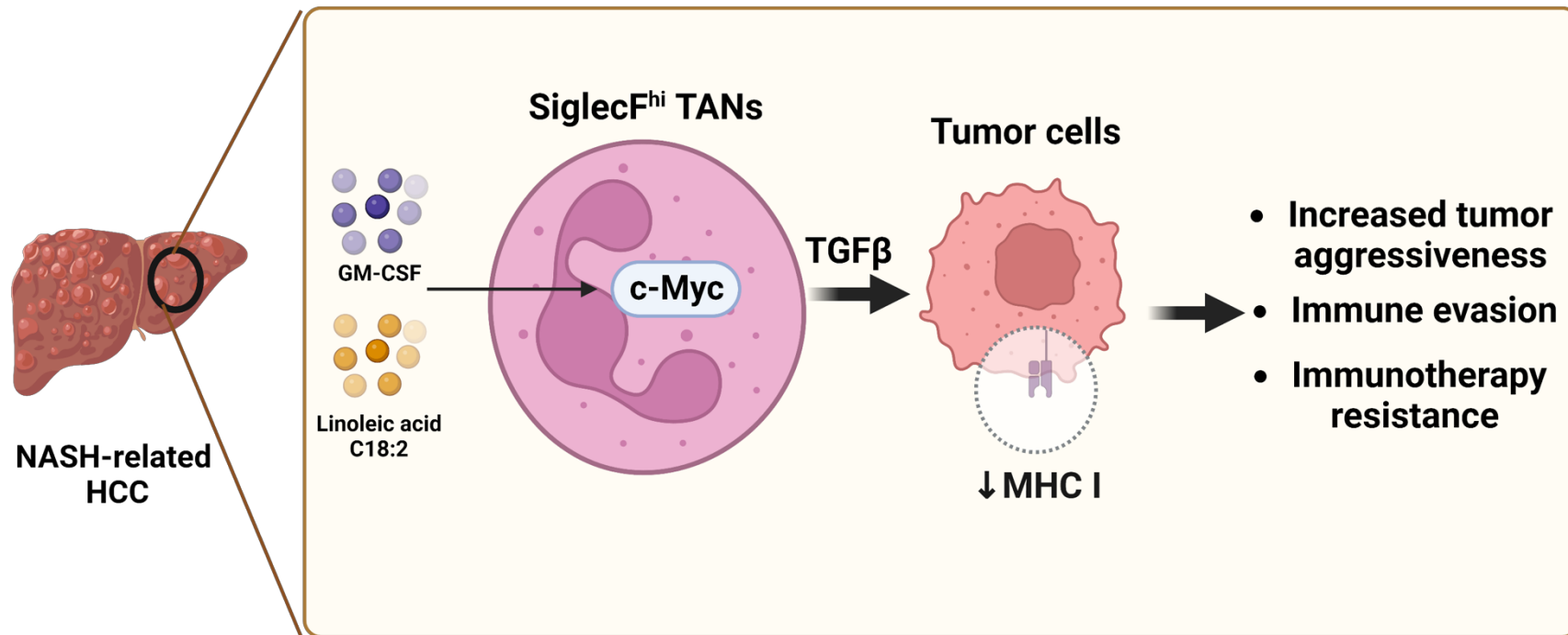


% of IFN γ ⁺TNF α ⁺ cells



Proposed new role of TANs in tumor development

SiglecF^{hi} TANs directly suppress the antigen presentation machinery of tumor cells



Acknowledgements

HL team:

Rachael Tan
Qier Gao
David Zhang
PakLam Hui

Collaborators:

Prof Stephanie Ma (HKU)
Prof Terence Lee (PolyU, HK)
Prof Ruidong Xue (Peking University)
Prof Burkhard Becher (University of Zurich)



Nickolas Teo
Victor Gray
Weixin Chen

Funding body:

UGC 大學教育資助委員會
University Grants Committee



Health Bureau

The Government of the Hong Kong Special Administrative Region
of the People's Republic of China

