



THE UNIVERSITY
OF NORTH CAROLINA
at CHAPEL HILL

SITC 2019

Gaylord National Hotel
& Convention Center Nov. 6-10

NATIONAL HARBOR, MARYLAND



UNC
LINEBERGER

IL-35⁺ B cells regulates anti-tumor immune response in pancreatic cancer

Rahul Mirlekar, PhD

Laboratory of

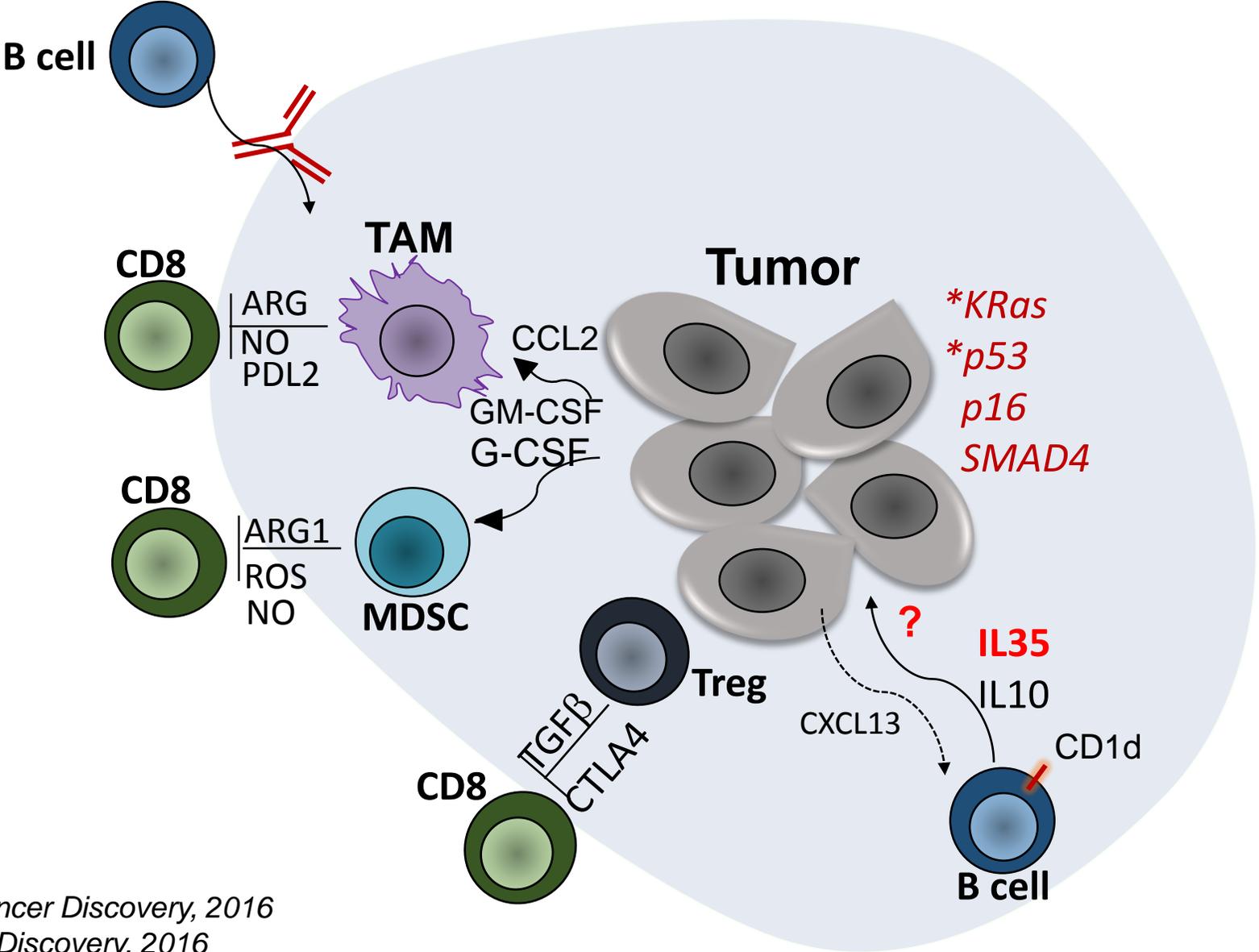
Yuliya Pylayeva-Gupta, PhD

Department of Genetics

Lineberger Comprehensive Cancer Center

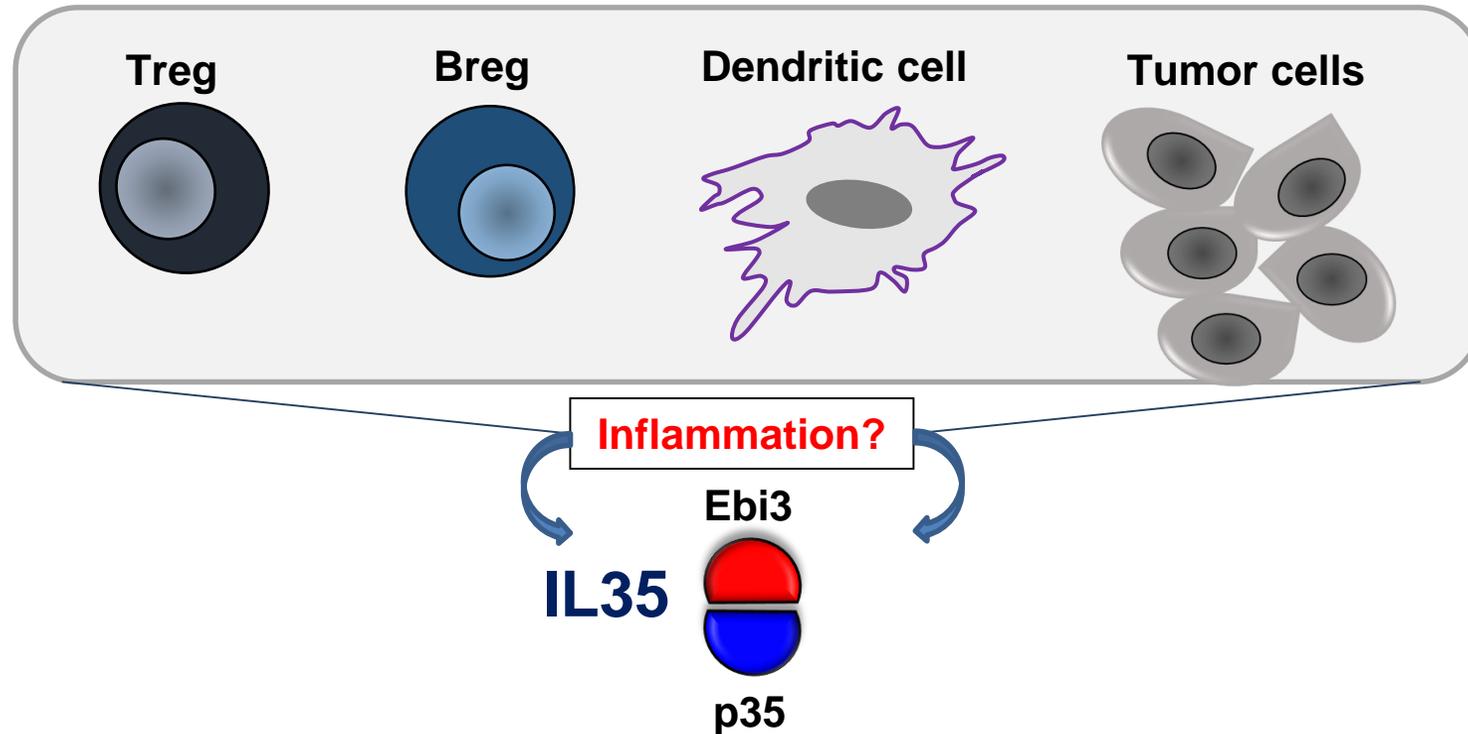
University of North Carolina at Chapel Hill

Pancreatic ductal adenocarcinoma (PDAC)



Pylayeva-Gupta et al., Cancer Discovery, 2016
Gunderson et al., Cancer Discovery, 2016
Lee et al., Cancer Discovery, 2016

Proposed functional roles of IL35 in disease



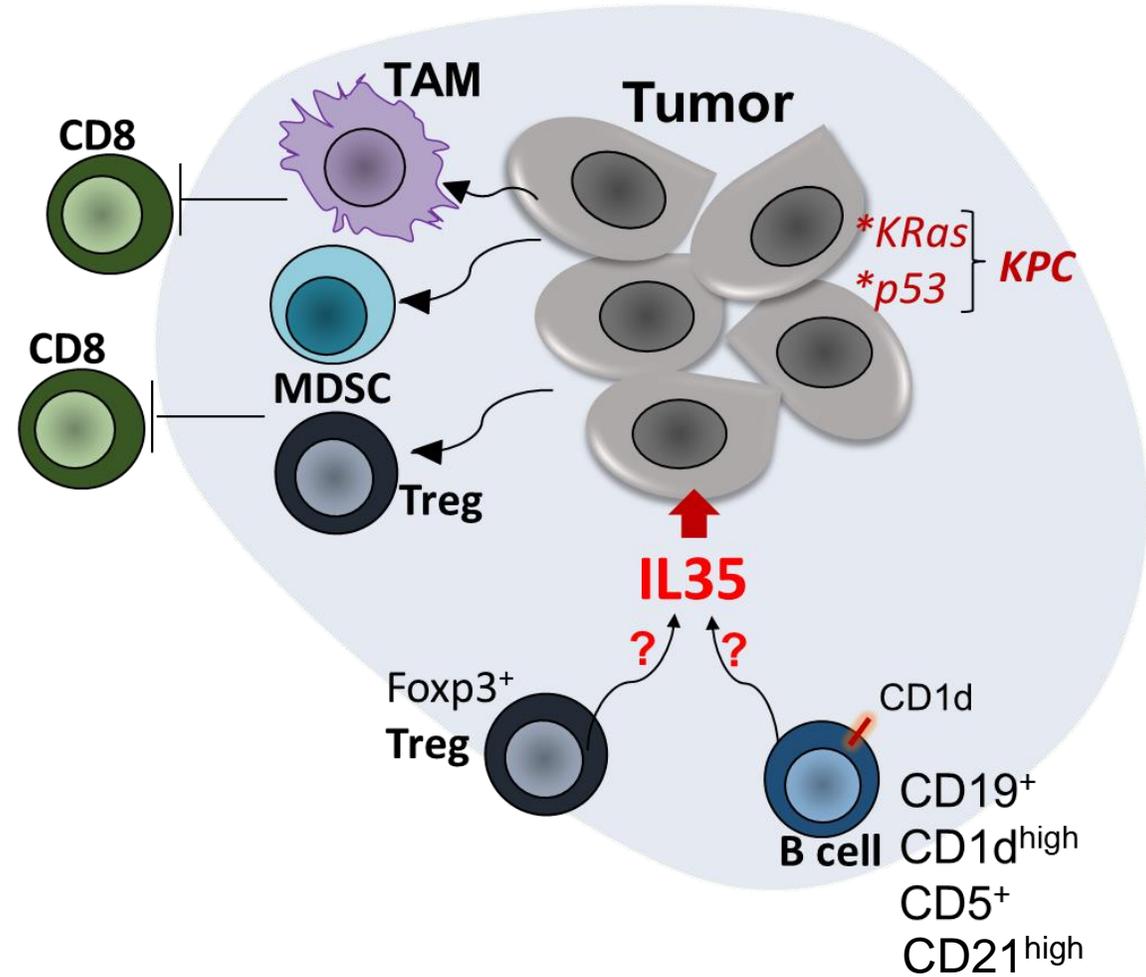
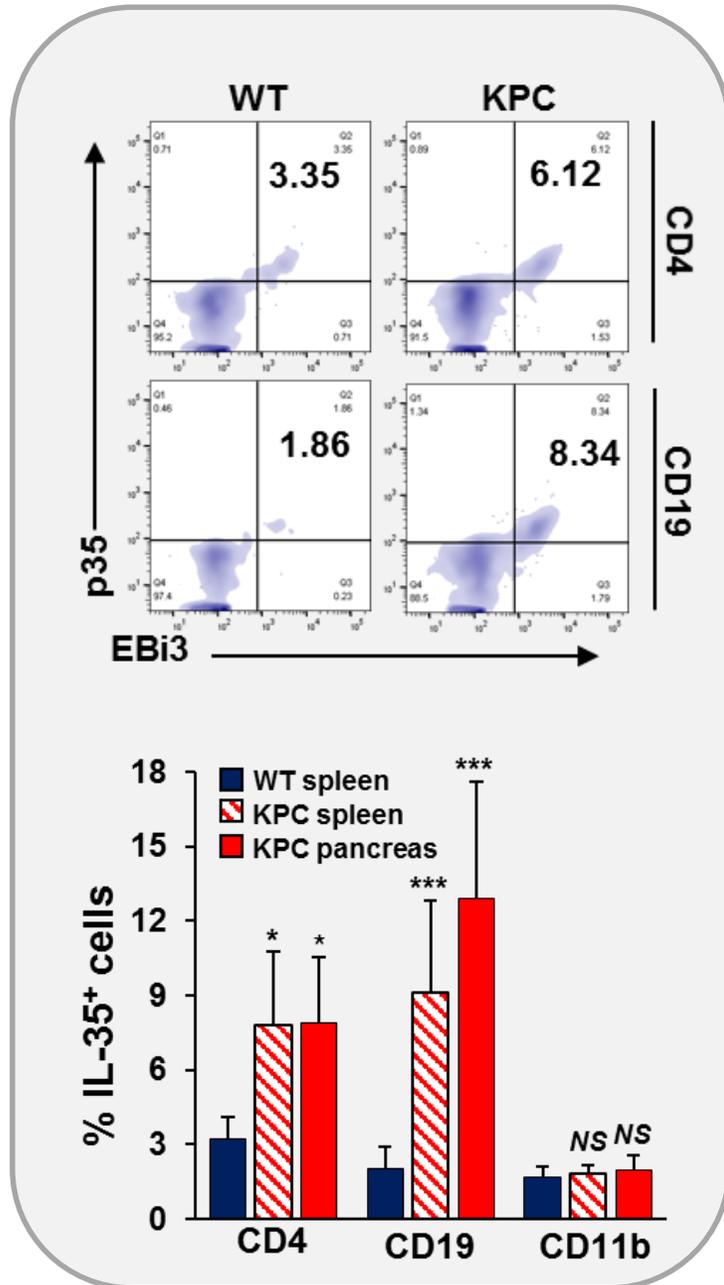
- Autoimmunity**
- Expansion of immunosuppressive cells
 - Suppression of T effector cells and Th17 cells

- ?Cancer?**
- Exhaustion of T cells in cancer microenvironment
 - Angiogenesis/Metastasis

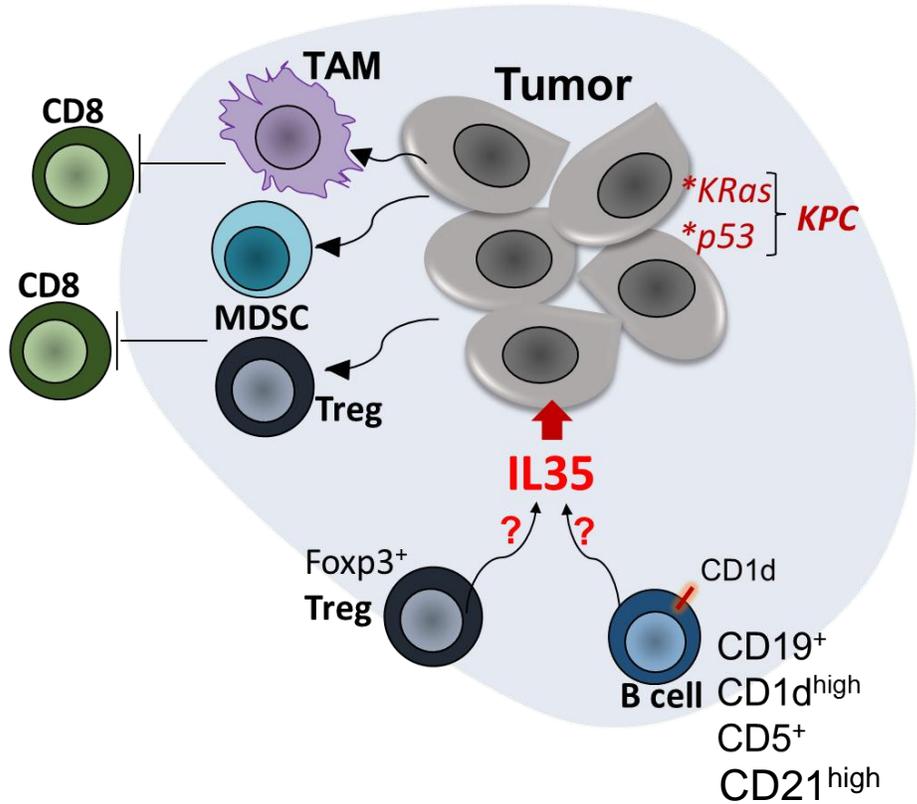
Collison et al., 2007
Shen et al., Nature 2014
Wang et al., Nature Medicine 2014
Pylayeva-Gupta et al., Cancer Discovery, 2016
Huang et al., Nat. Comm. 2017

What is the mechanism of IL35 action in PDAC?

Increased IL35 expression in tumor-infiltrating B cells and CD4⁺ T cells



Treg-specific deletion of IL35 is dispensable for pancreatic tumor growth.



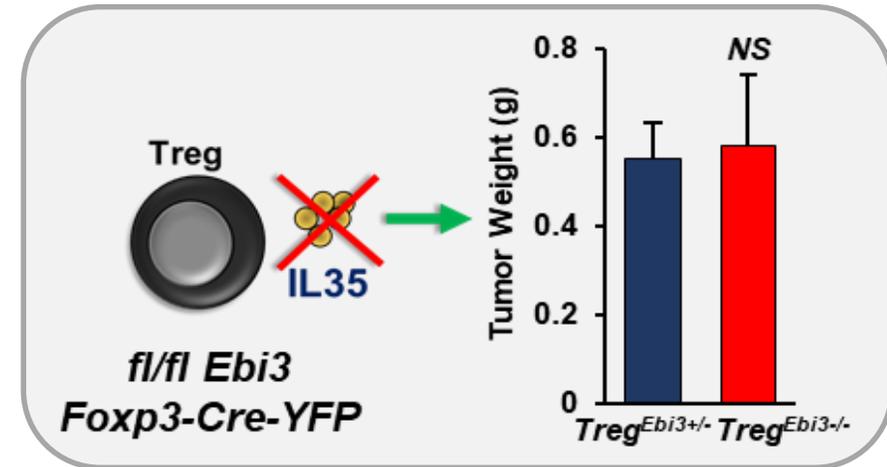
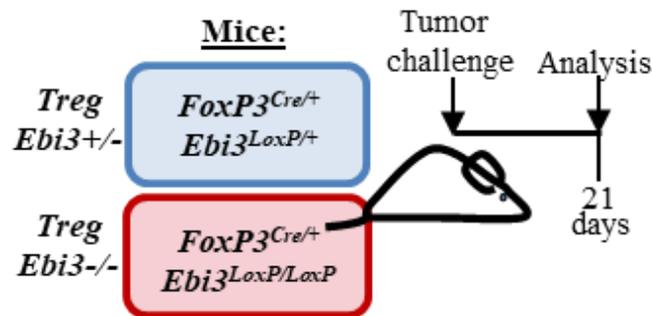
Immunity

Interleukin-35 Limits Anti-Tumor Immunity

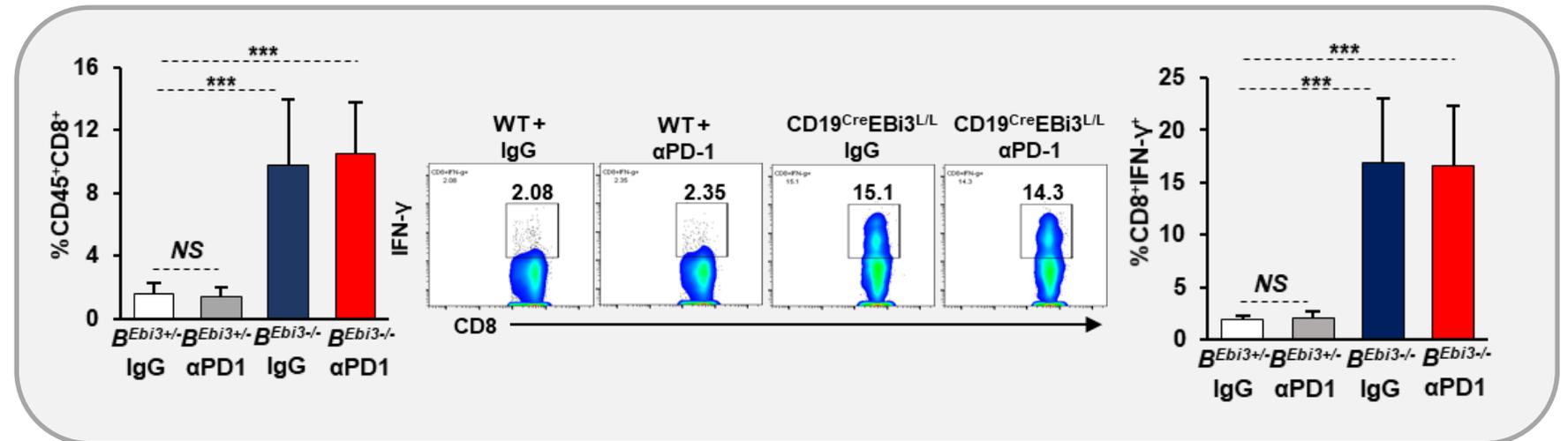
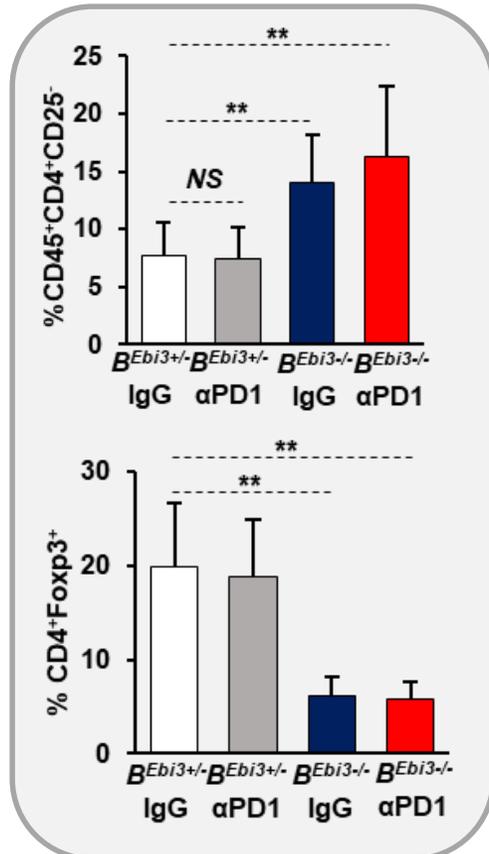
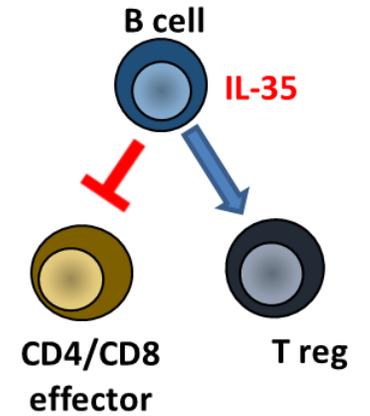
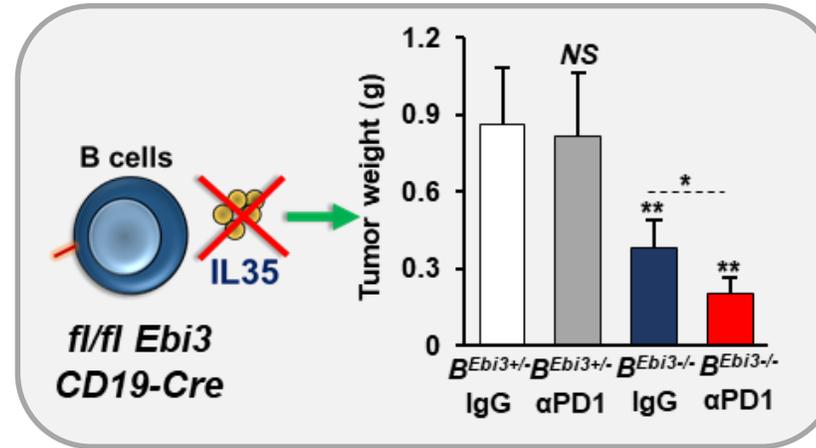
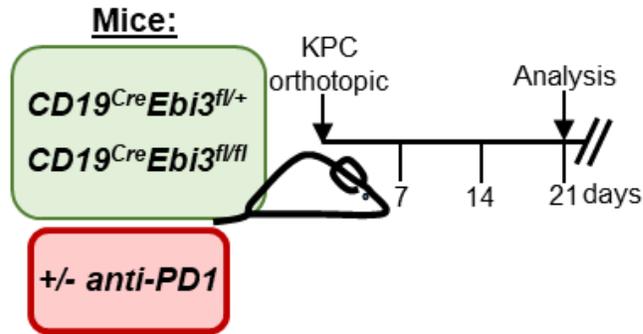
Authors

Meghan E. Turnis, Deepali V. Sawant, Andrea L. Szymczak-Workman, ..., Peter Vogel, Creg J. Workman, Dario A.A. Vignali

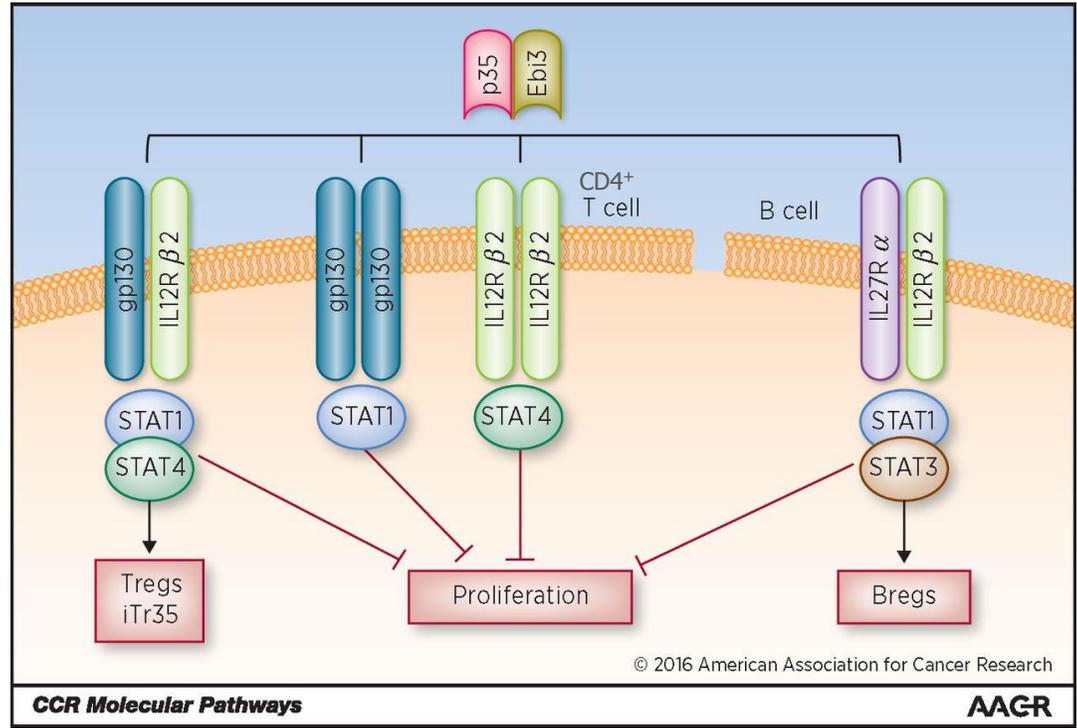
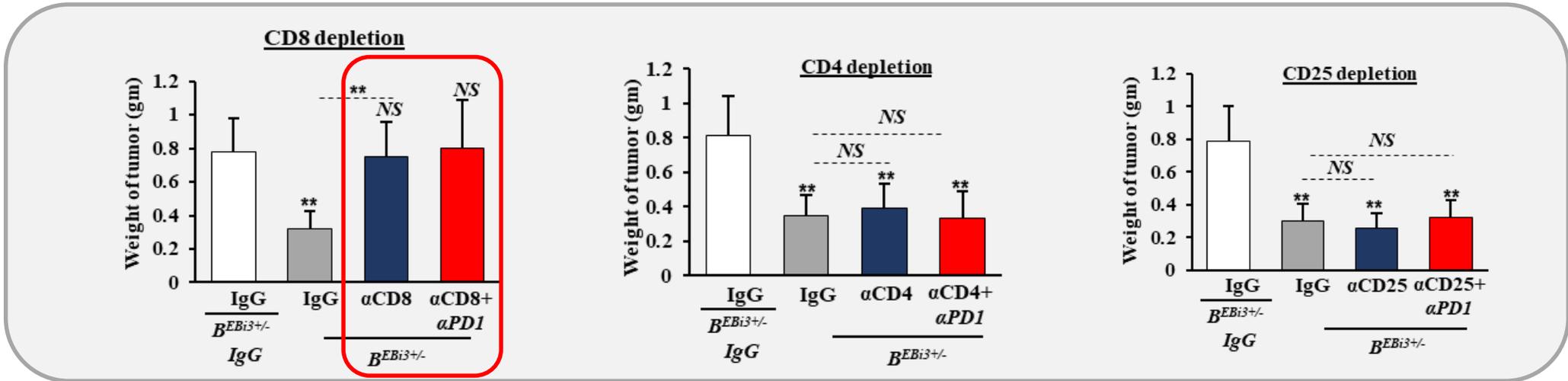
- IL-35⁺ Treg cells, which have enhanced suppressive activity, are enriched in tumors



B cell-specific expression of IL-35 supports PDAC growth



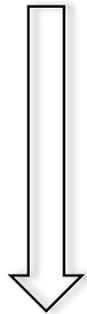
CD8⁺ T cells are required for B cell-IL35-dependent anti-tumor effect.



Pylayeva-Gupta Y., *Clinical Cancer Research*, 2016

IL35 mediates activation of STAT3, suppression of IFN γ and chemotactic receptors CXCR3 and CCR5 in CD8⁺ T cells

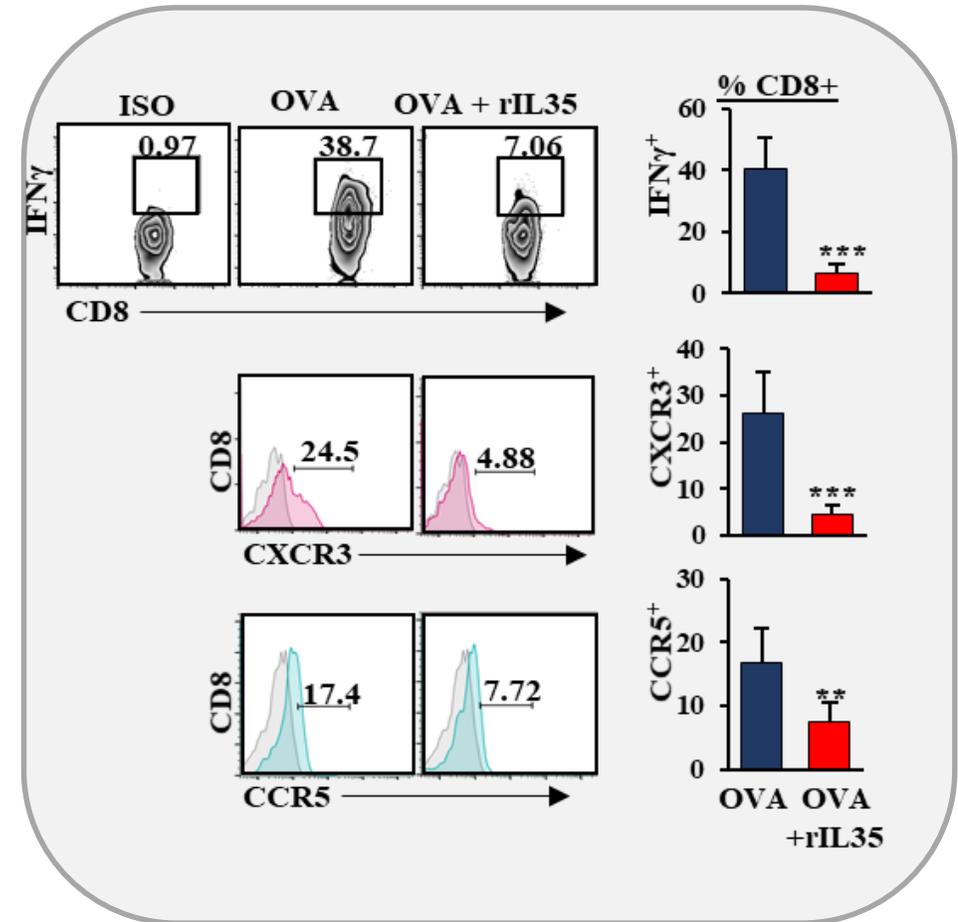
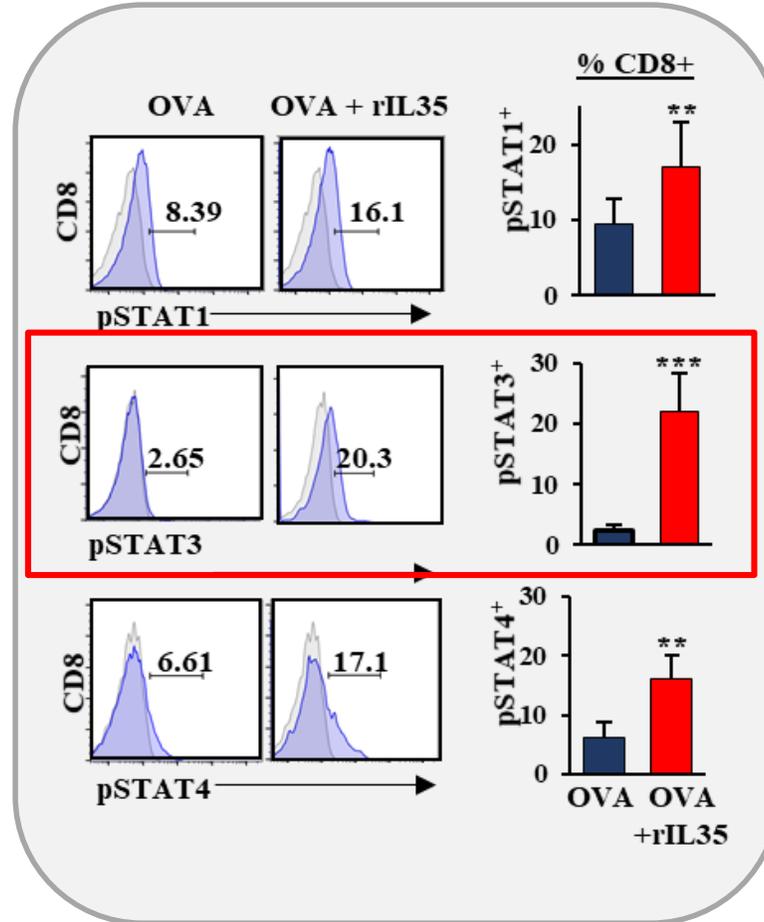
Ex vivo
Stimulation
(OVA)



± rIL35

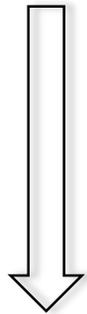
CD8⁺ T cells

CXCR3
CCR5
IFN γ



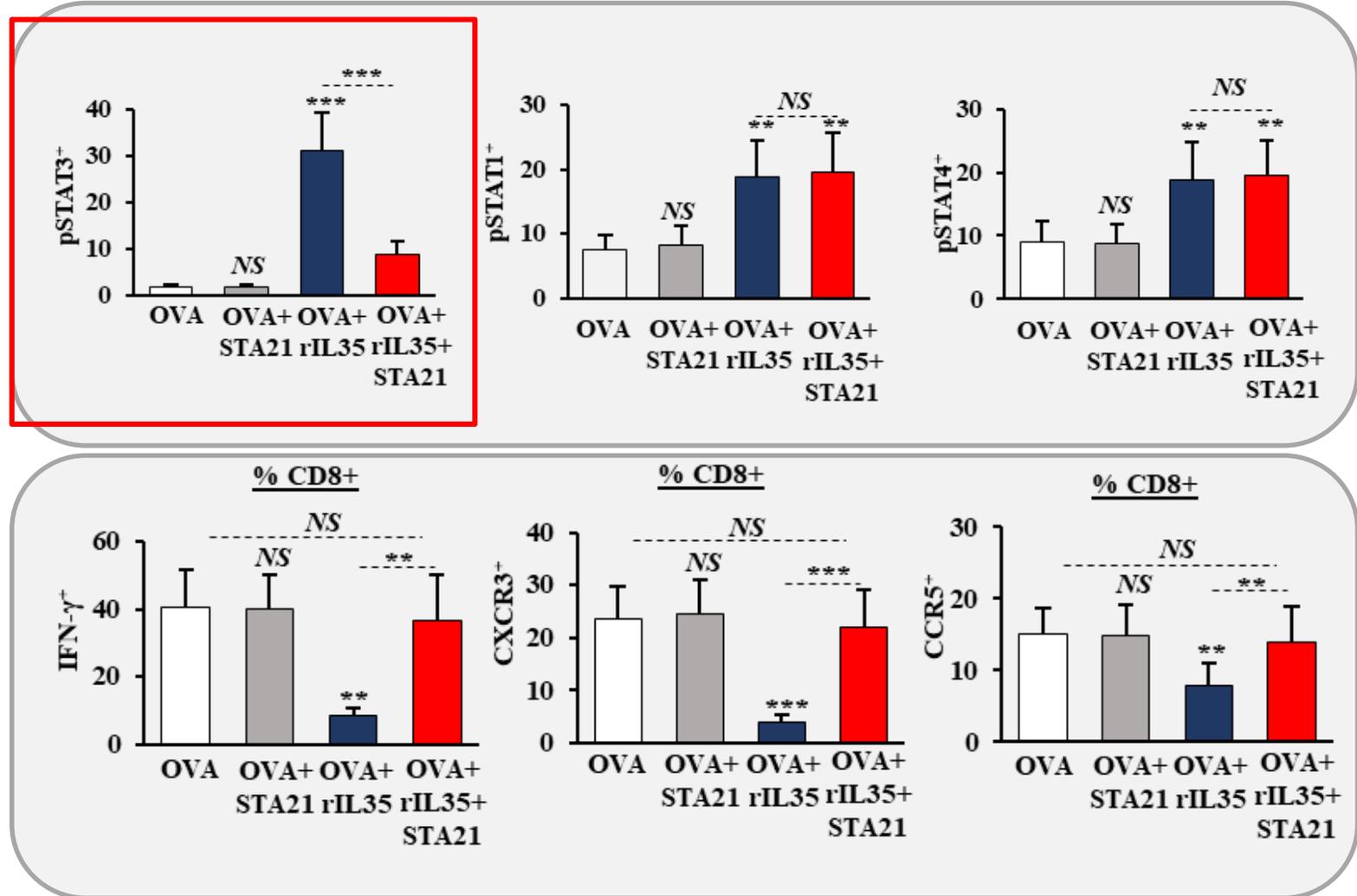
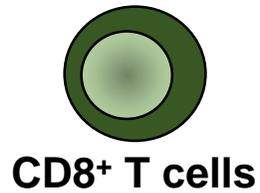
STAT3 activation in IL35-educated CD8⁺ T cells is suppressive *in vitro*

Ex vivo
Stimulation
(OVA)

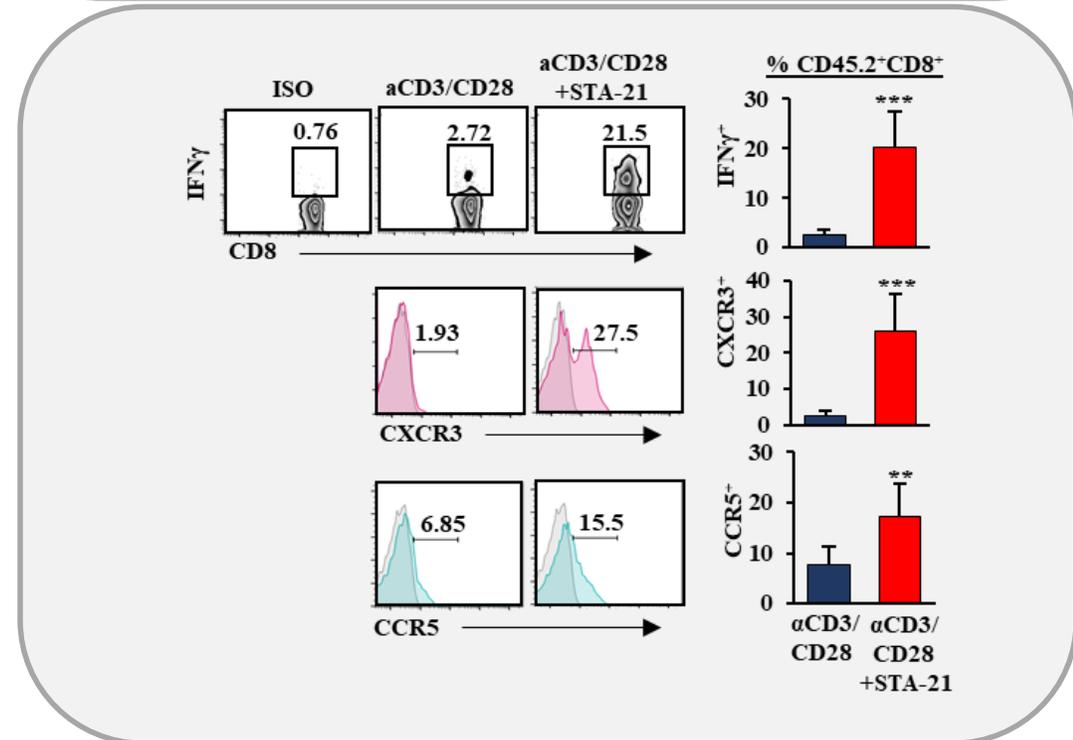
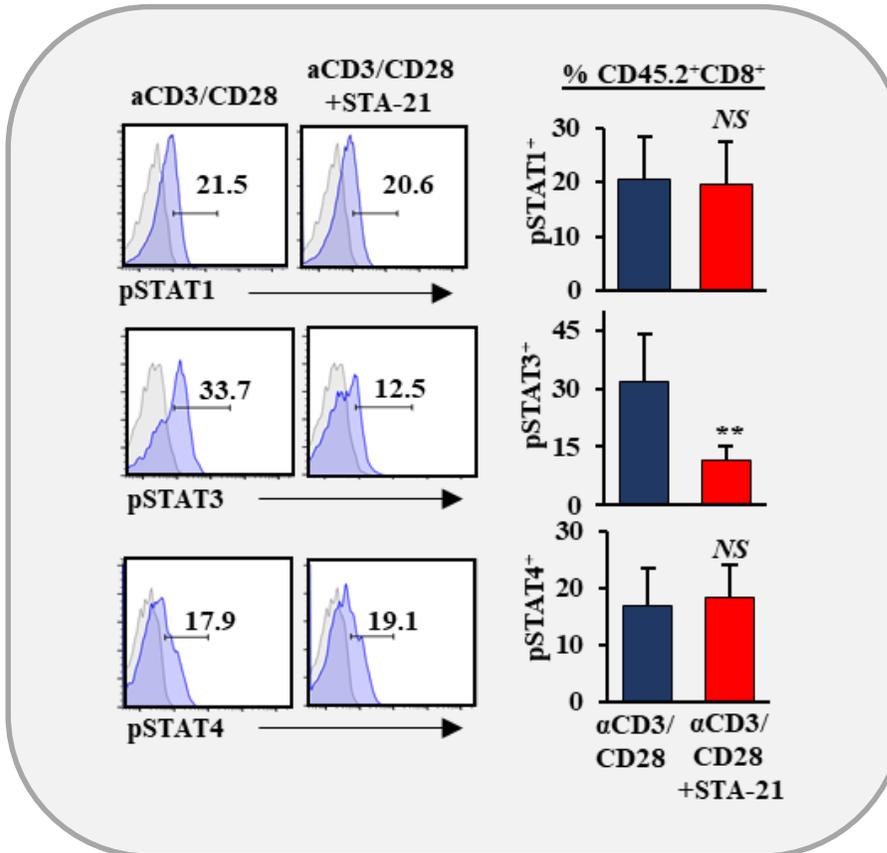
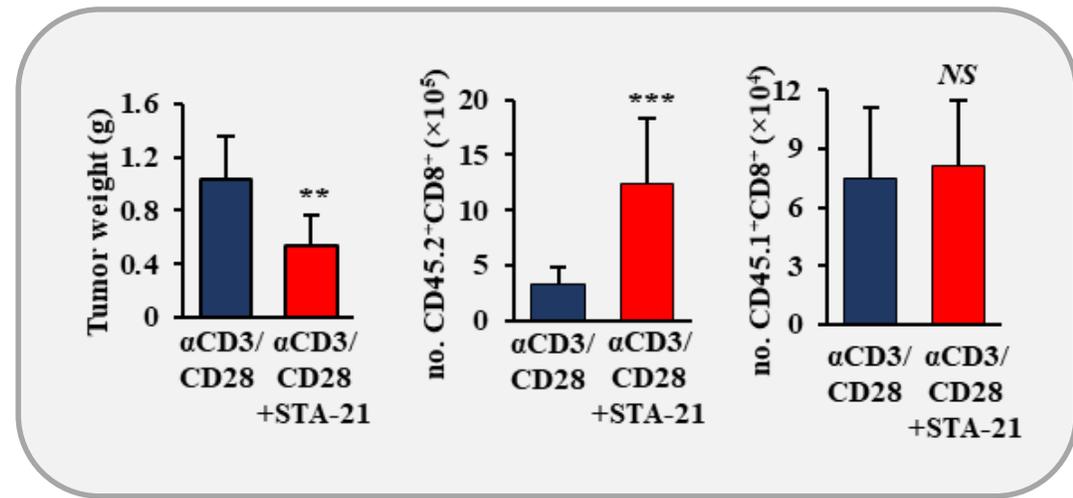
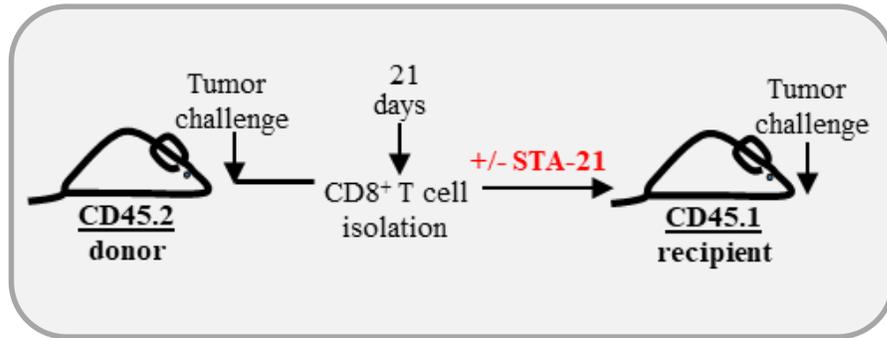


± rIL35

± STA-21



STAT3 activation in IL35-educated CD8⁺ T cells is suppressive *in vivo*



Characterization of cytokine-producing human B cells.



B10 cells
Produce IL-10
Suppress CD4 T cells

Plasmablast
Produce IL-10
Suppress DC

Immature B cells
Produce IL-10
Induce Treg

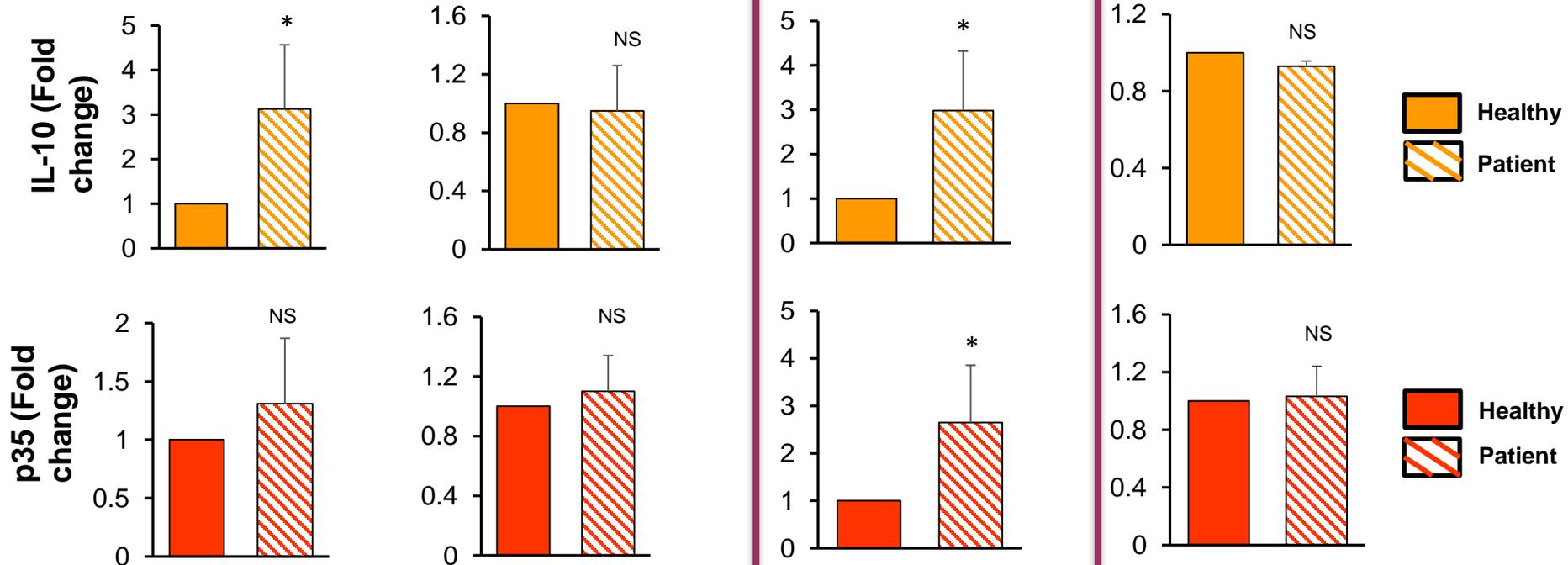
Br1 cells
Produce IL-10
& anti-inflammatory
IgG4

CD19⁺CD24^{hi}CD27⁺

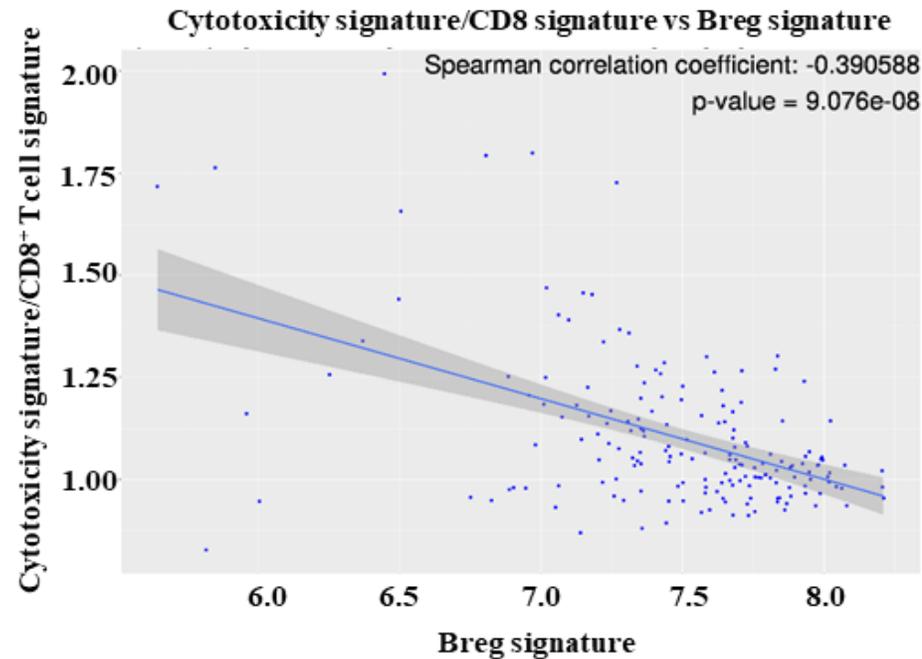
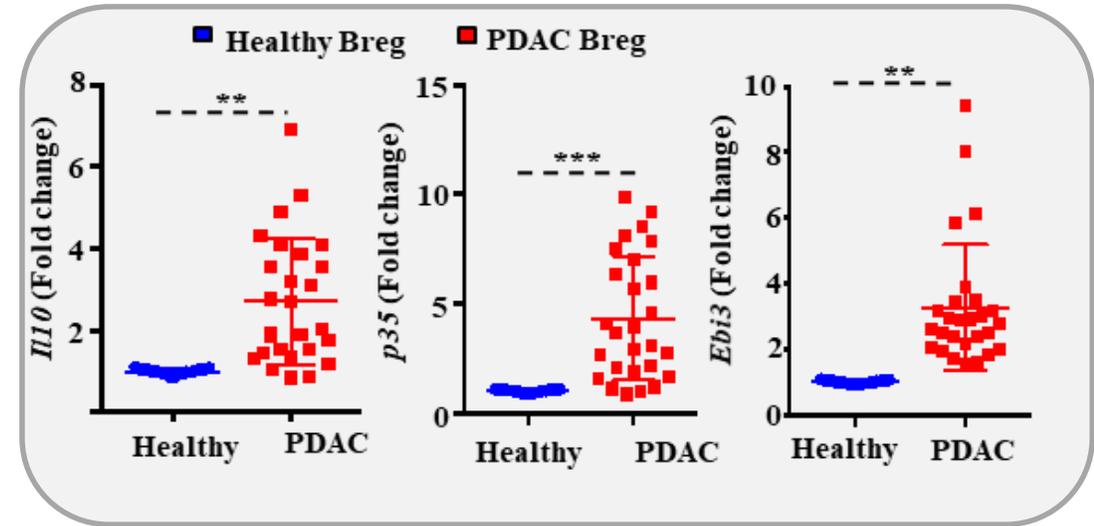
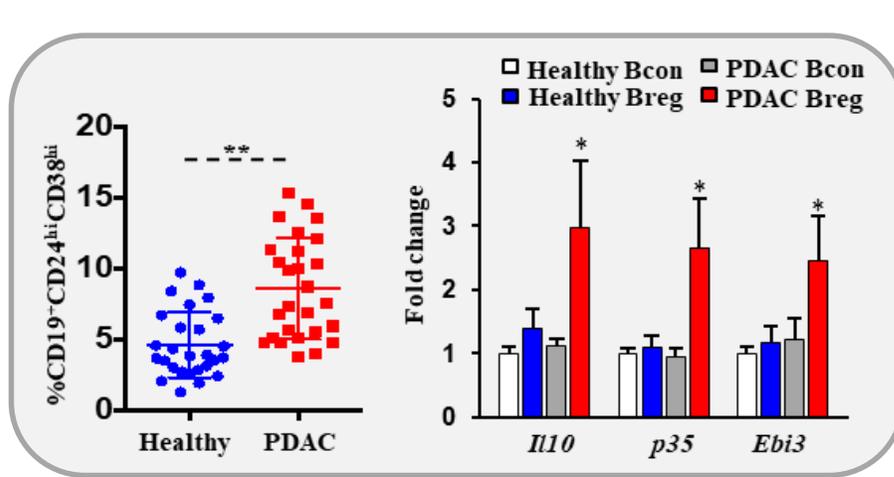
CD19⁺CD24^{hi}CD27^{int}

CD19⁺CD24^{hi}CD38^{hi}

CD19⁺CD25^{hi}CD71⁺

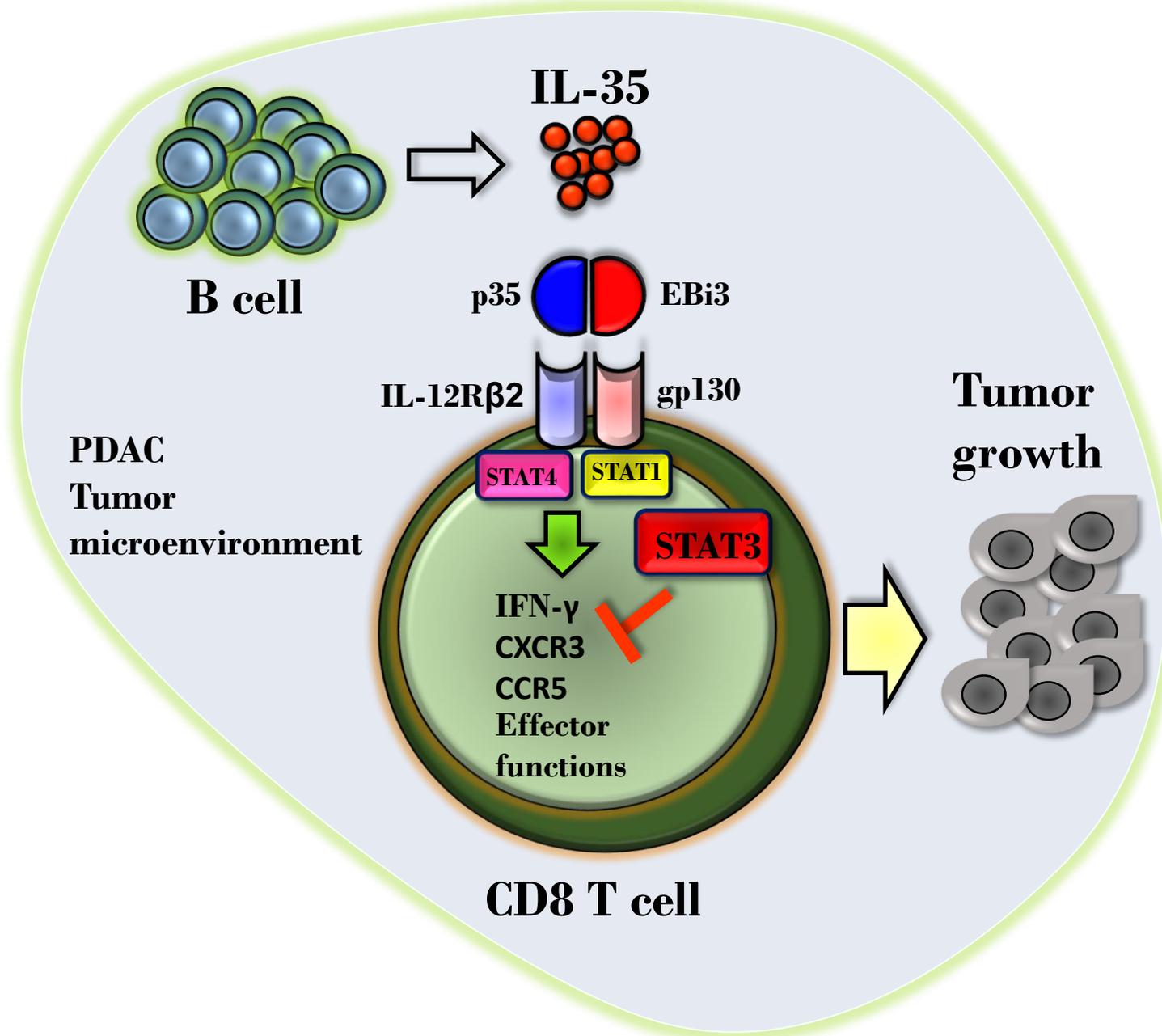


B cells represent a dominant IL35⁺ population in human PDAC (PB)



Expression of IL-35 correlates with poor T cell activity

Schematic of IL-35+ B cell mediated CD8 T cells suppression



- B cell secreted IL-35 controls pancreatic tumorigenesis
- IL-35 drives STAT3 dependent exclusion of CD8 T cells
- Inhibition of STAT3 *in vitro* or *in vivo* enhances CD8 T cells activation and infiltration into tumor

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Funding

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