



**SITC 2019**

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NATIONAL HARBOR, MARYLAND



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

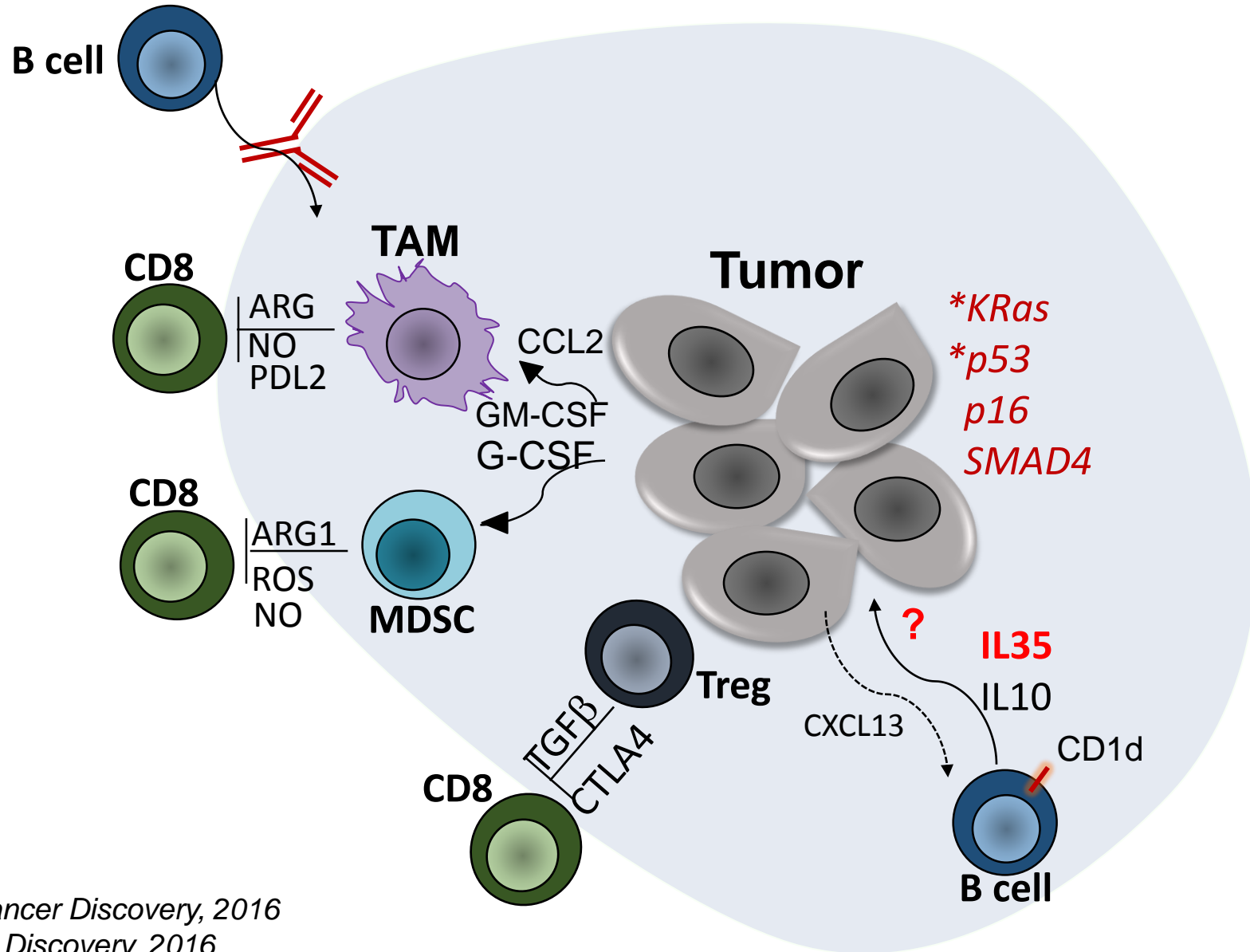
**Rahul Mirlekar, PhD**

**Laboratory of  
Yuliya Pylayeva-Gupta, PhD  
Department of Genetics**

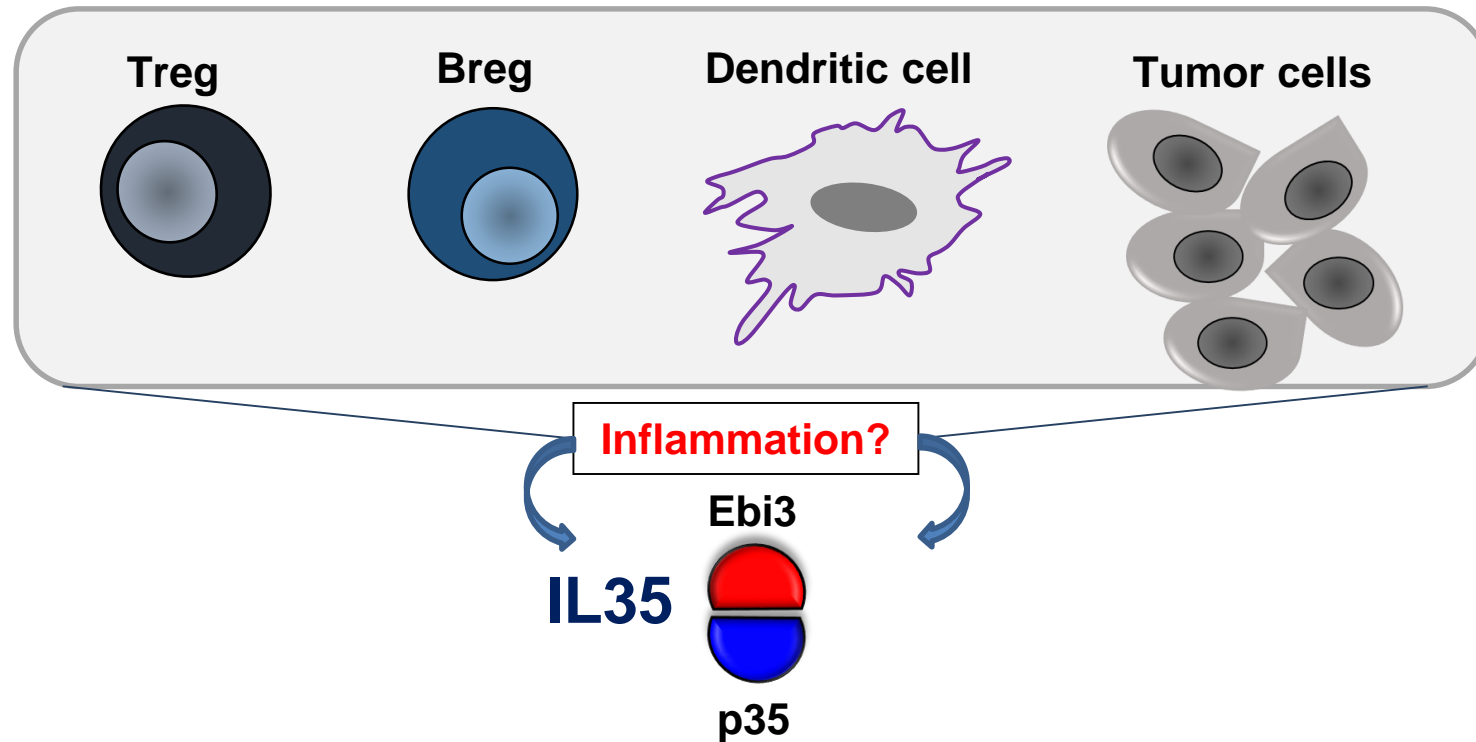
**Lineberger Comprehensive Cancer Center  
University of North Carolina at Chapel Hill**



# Pancreatic ductal adenocarcinoma (PDAC)



# Proposed functional roles of IL35 in disease



## Autoimmunity

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

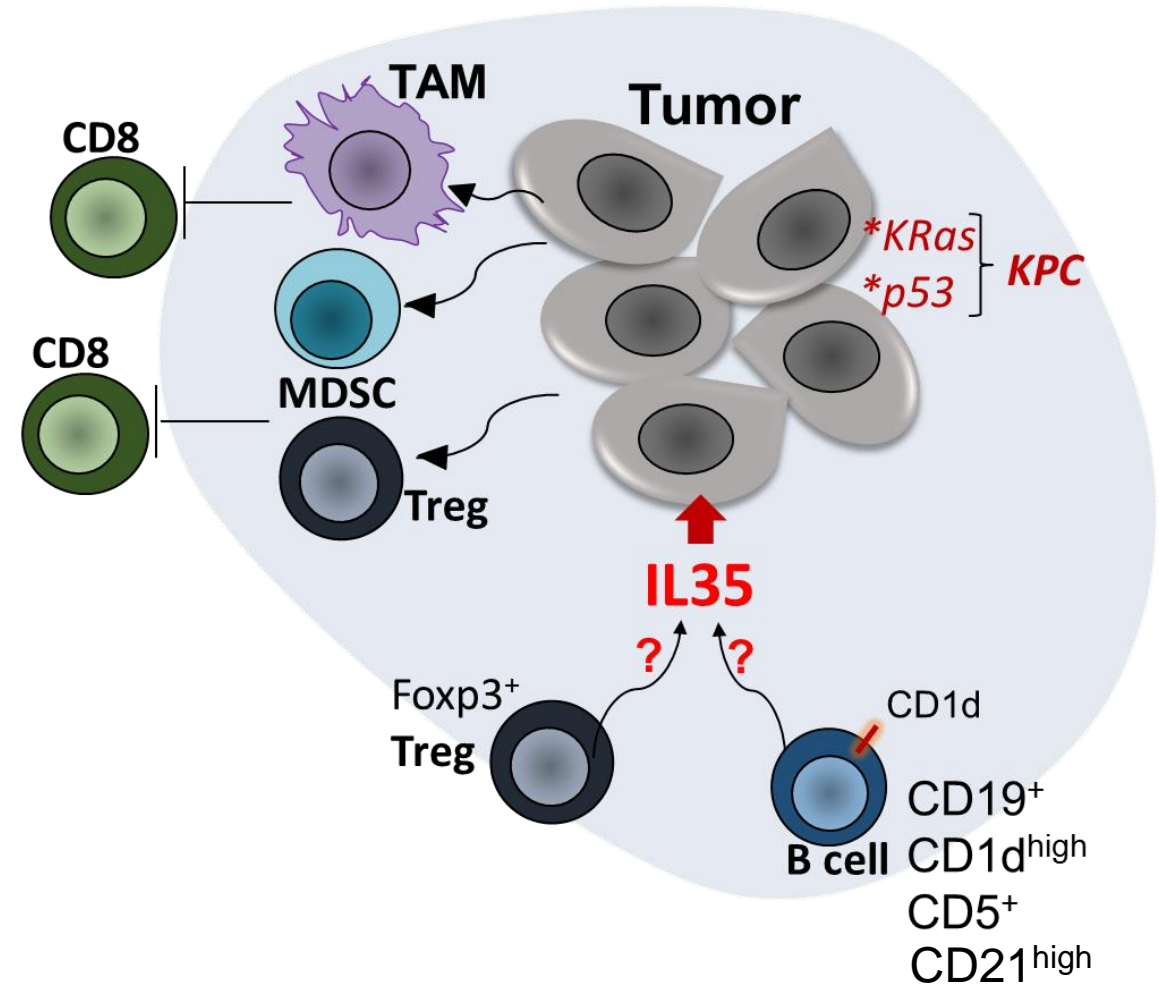
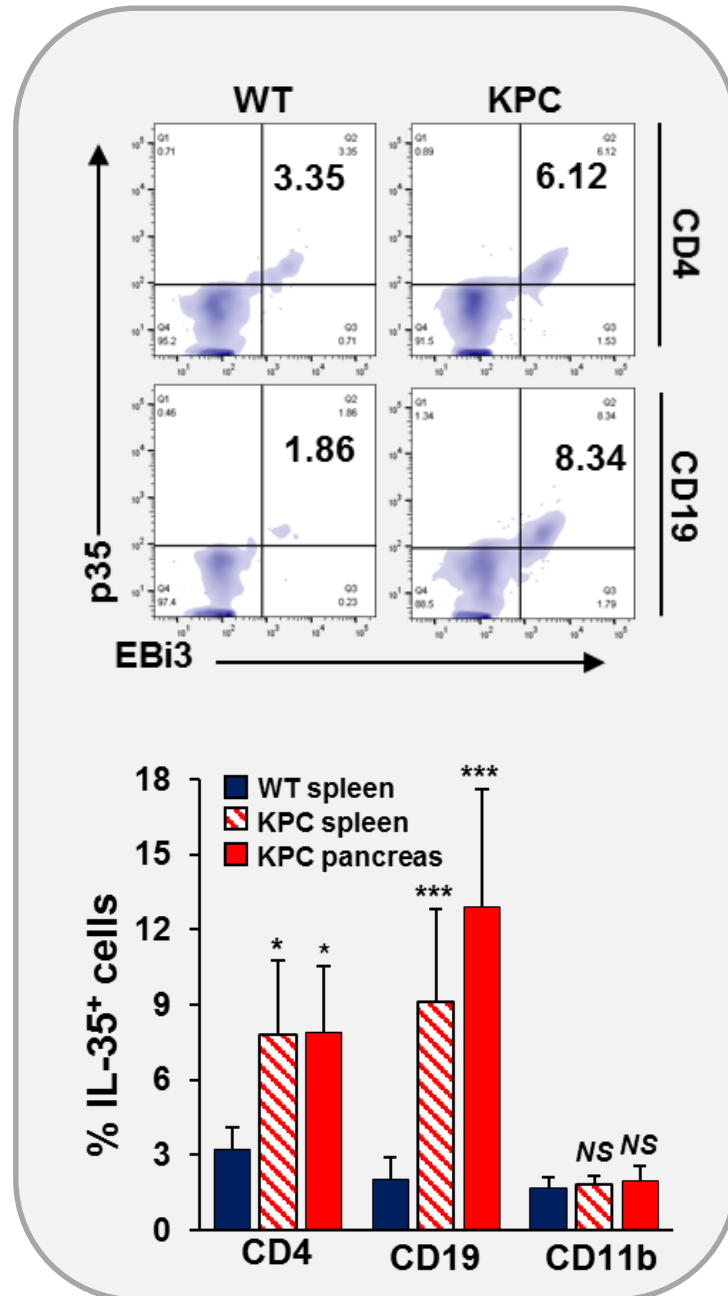
## ?Cancer?

- Exhaustion of T cells in cancer microenvironment
- Angiogenesis/Metastasis

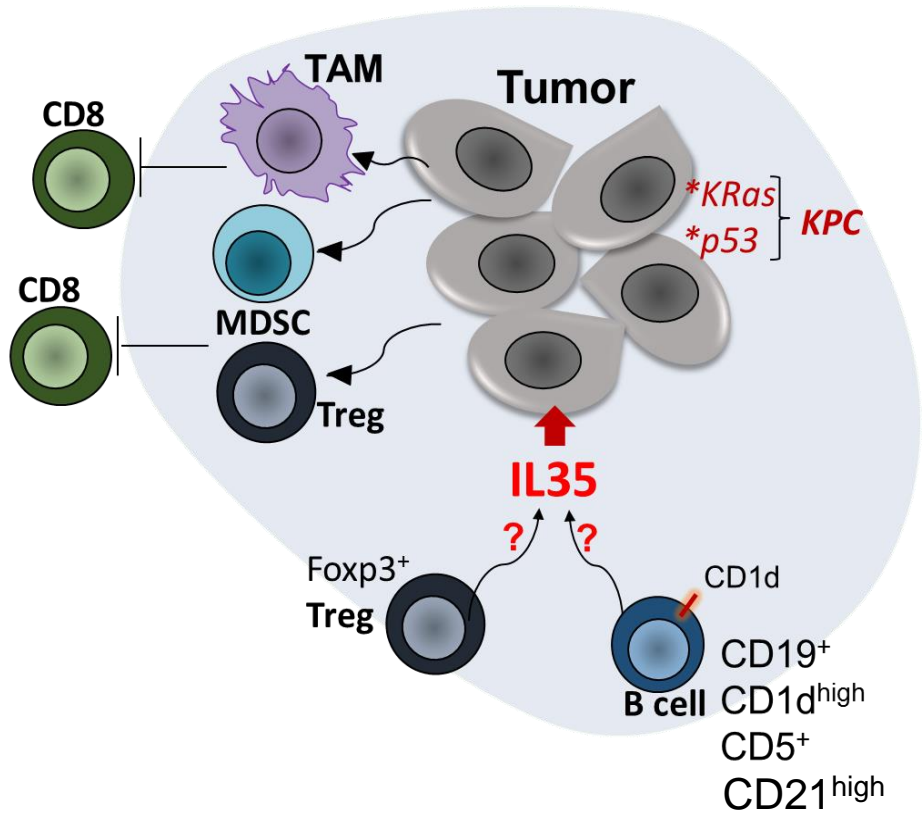
*Collison et al., 2007*  
*Shen et al., Nature 2014*  
*Wang et al., Nature Medicine 2014*  
*Pylayeva-Gupta et al.,*  
*Cancer Discovery, 2016*  
*Huang et al., Nat. Comm. 2017*

**What is the mechanism of IL35 action in PDAC?**

# Increased IL35 expression in tumor-infiltrating B cells and CD4<sup>+</sup> T cells



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



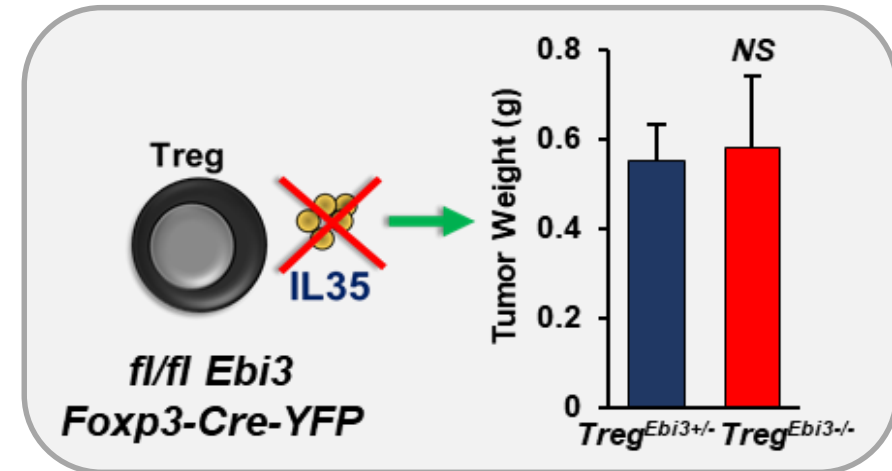
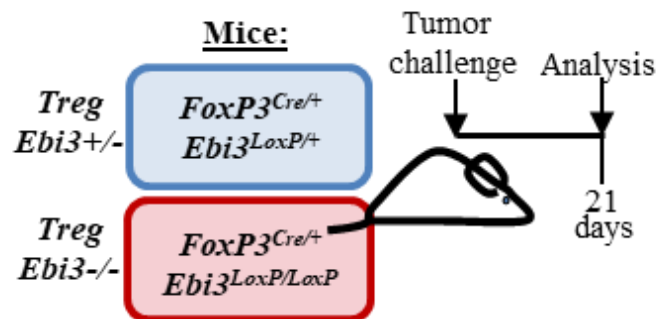
## Immunity

### Interleukin-35 Limits Anti-Tumor Immunity

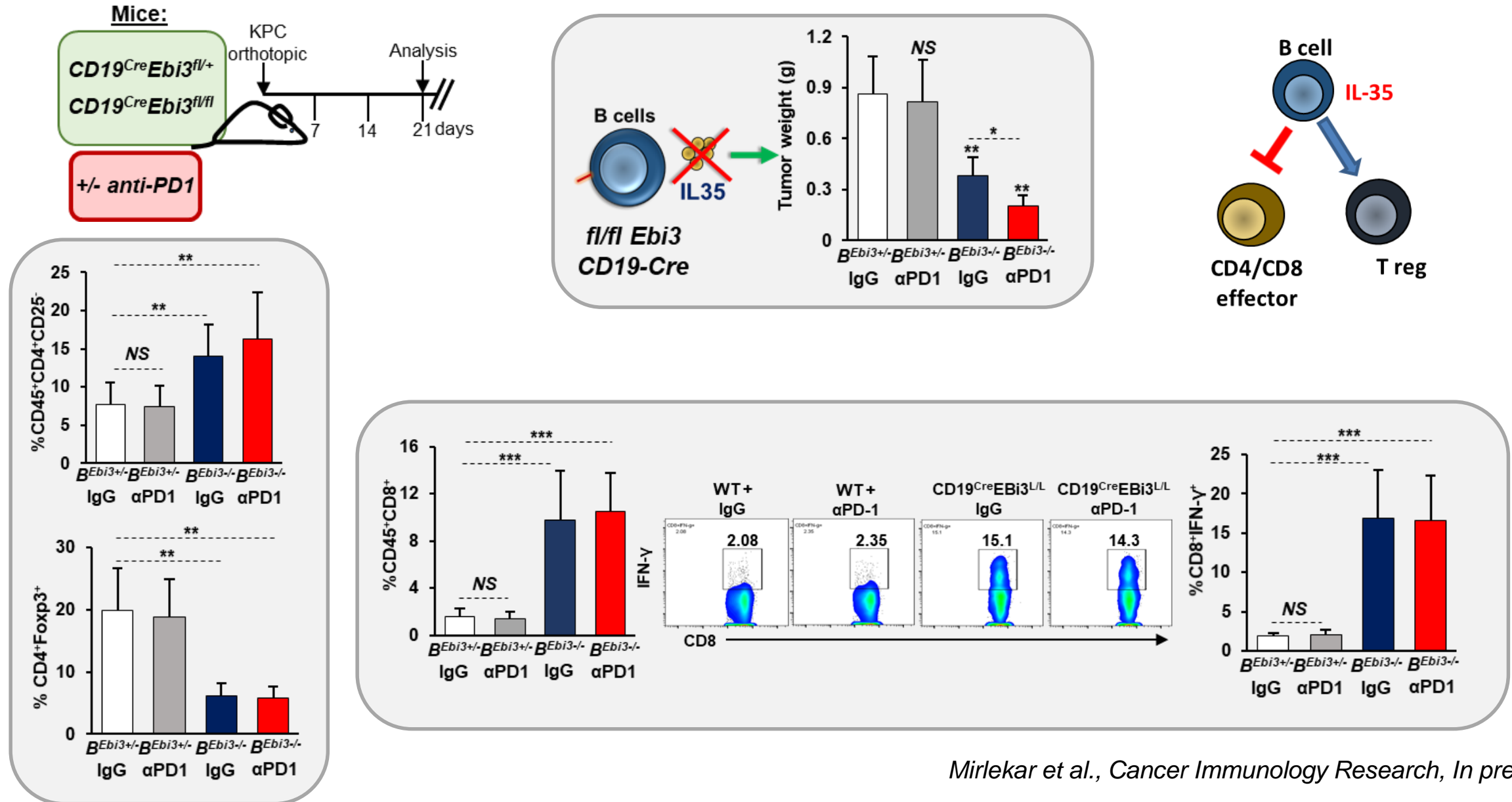
#### Authors

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

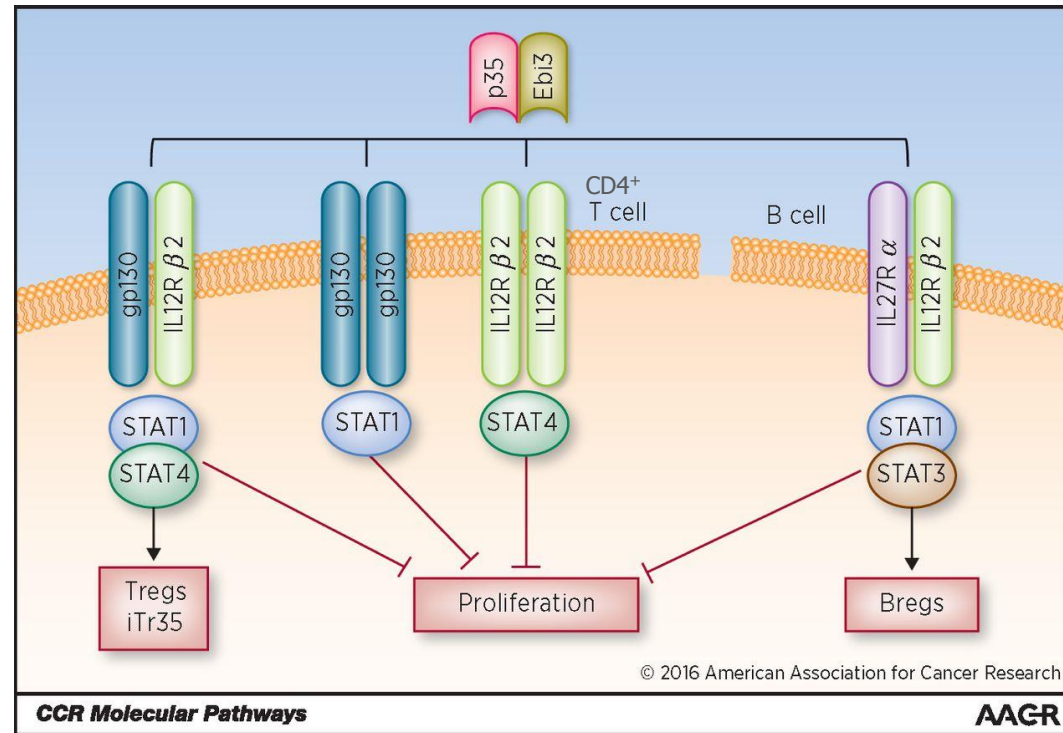
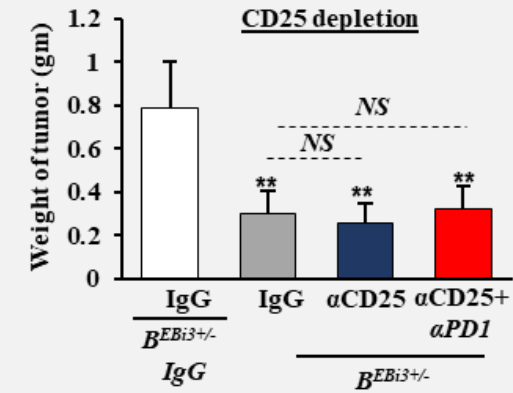
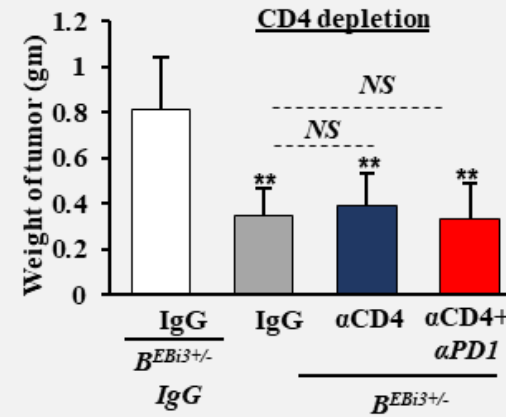
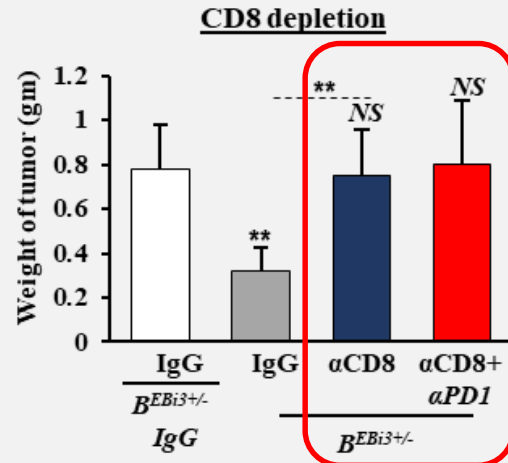
- IL-35<sup>+</sup> Treg cells, which have enhanced suppressive activity, are enriched in tumors



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



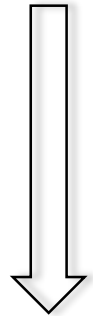
# CD8<sup>+</sup> T cells are required for B cell-IL35-dependent anti-tumor effect.



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

# IL35 mediates activation of STAT3, suppression of IFN $\gamma$ and chemotactic receptors CXCR3 and CCR5 in CD8<sup>+</sup> T cells

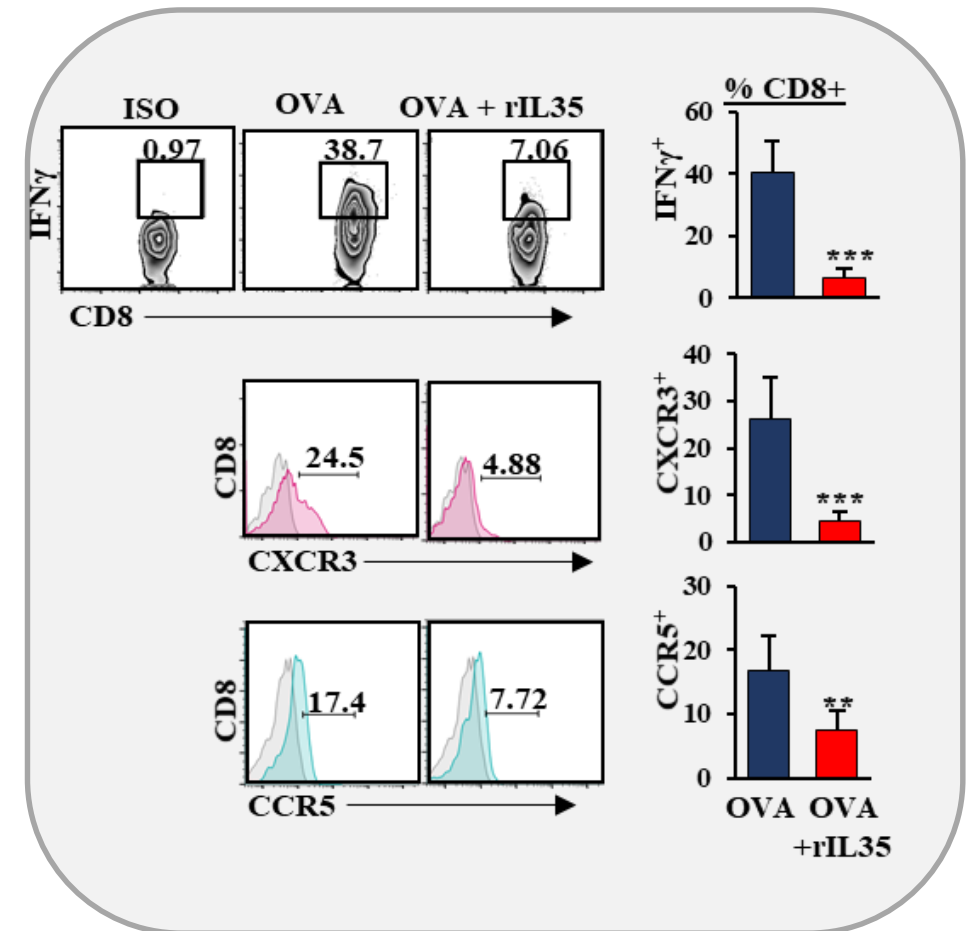
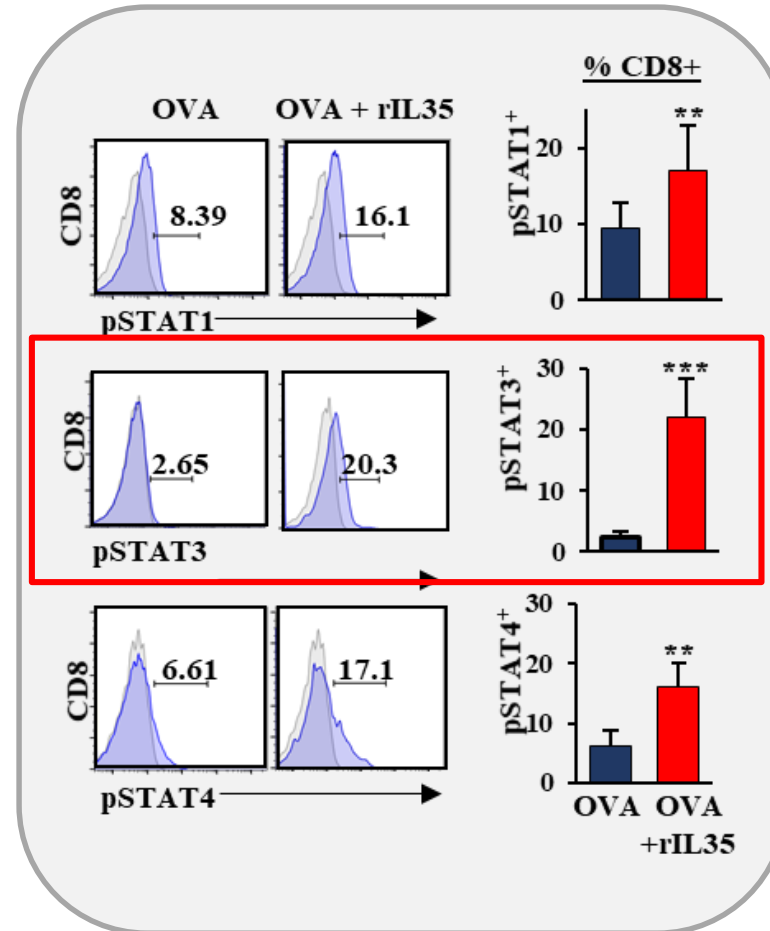
Ex vivo  
Stimulation  
(OVA)



± rIL35

CD8<sup>+</sup> T cells

↑ CXCR3  
CCR5  
IFN $\gamma$



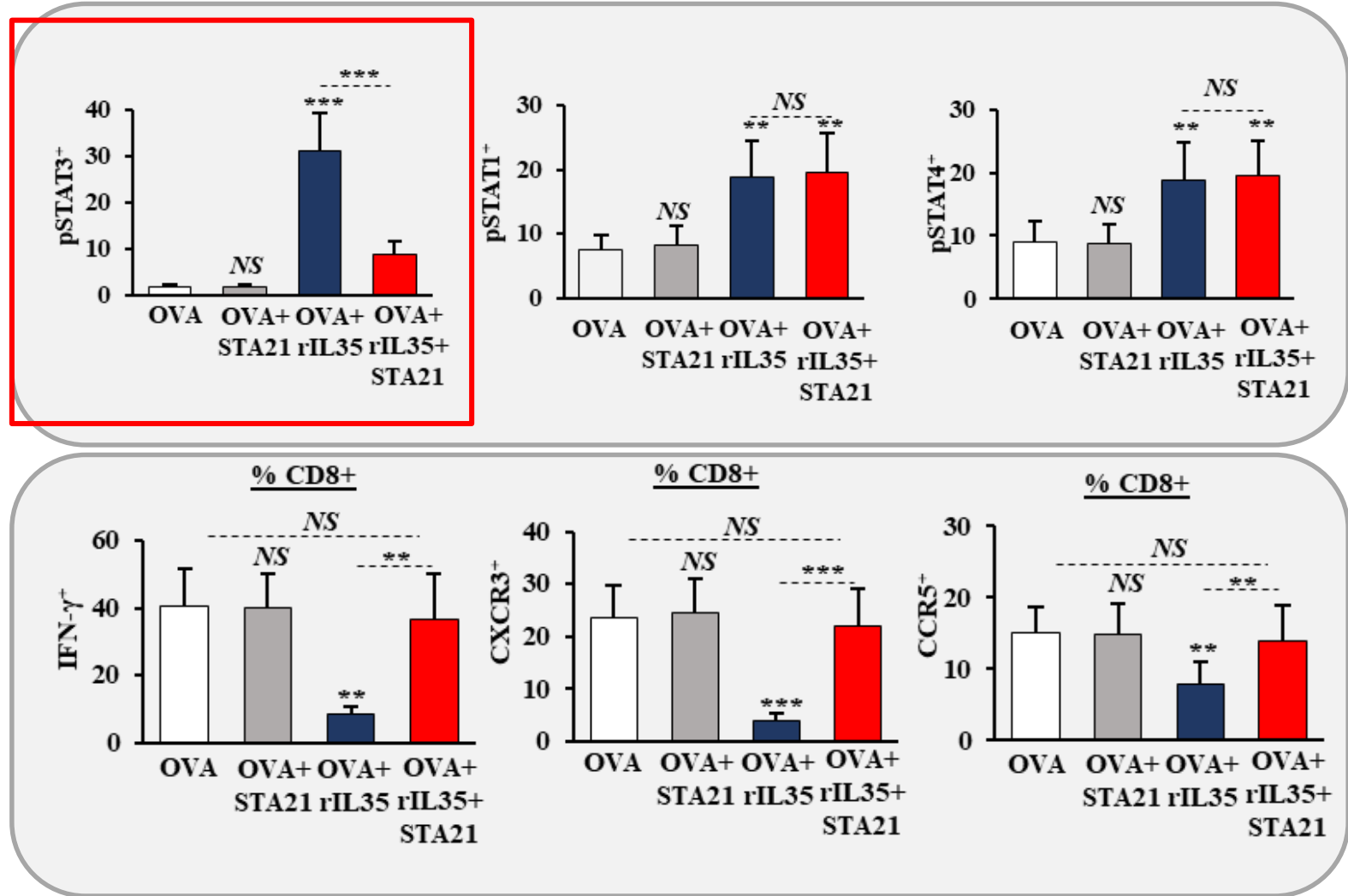
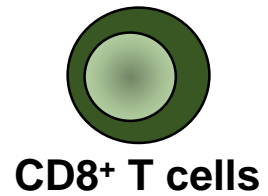


# STAT3 activation in IL35-educated CD8<sup>+</sup> T cells is suppressive *in vitro*

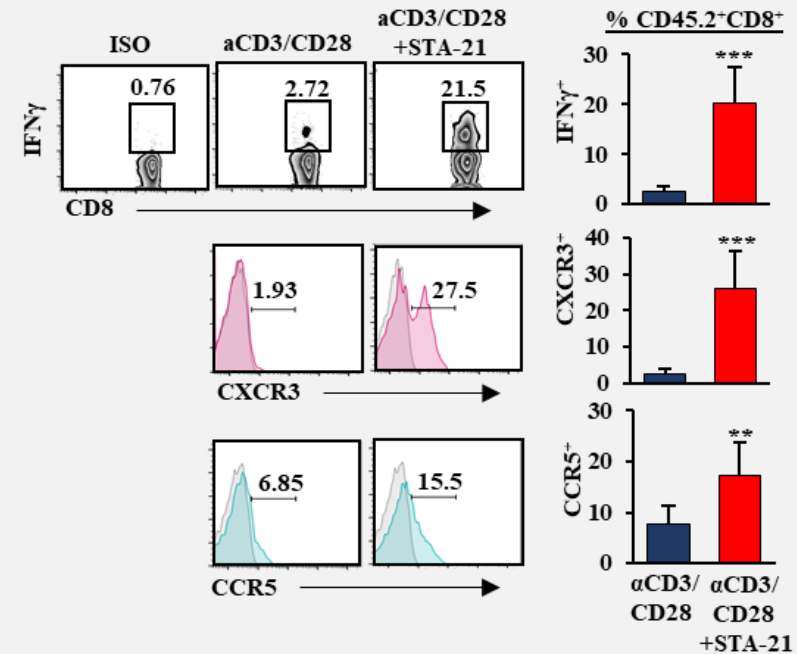
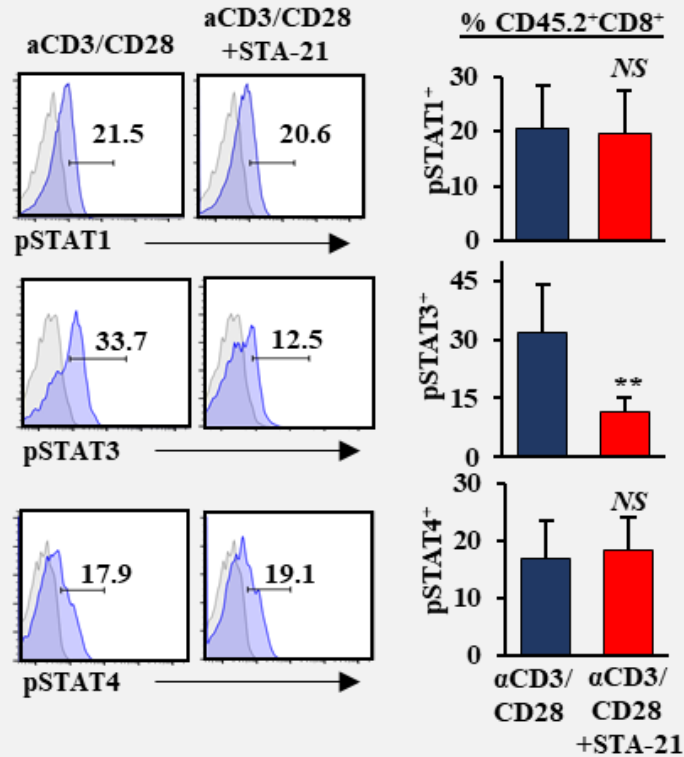
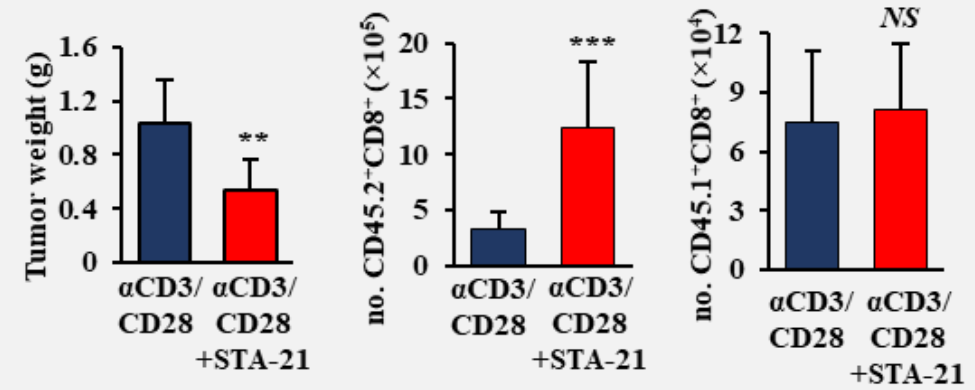
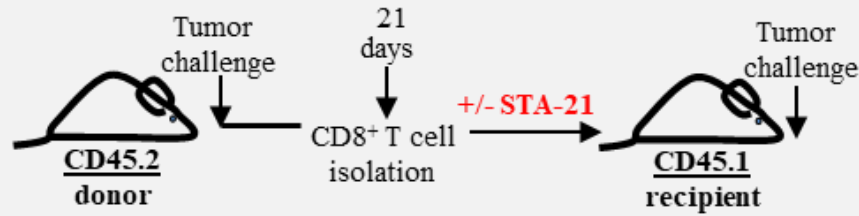
Ex vivo  
Stimulation  
(OVA)

± rIL35

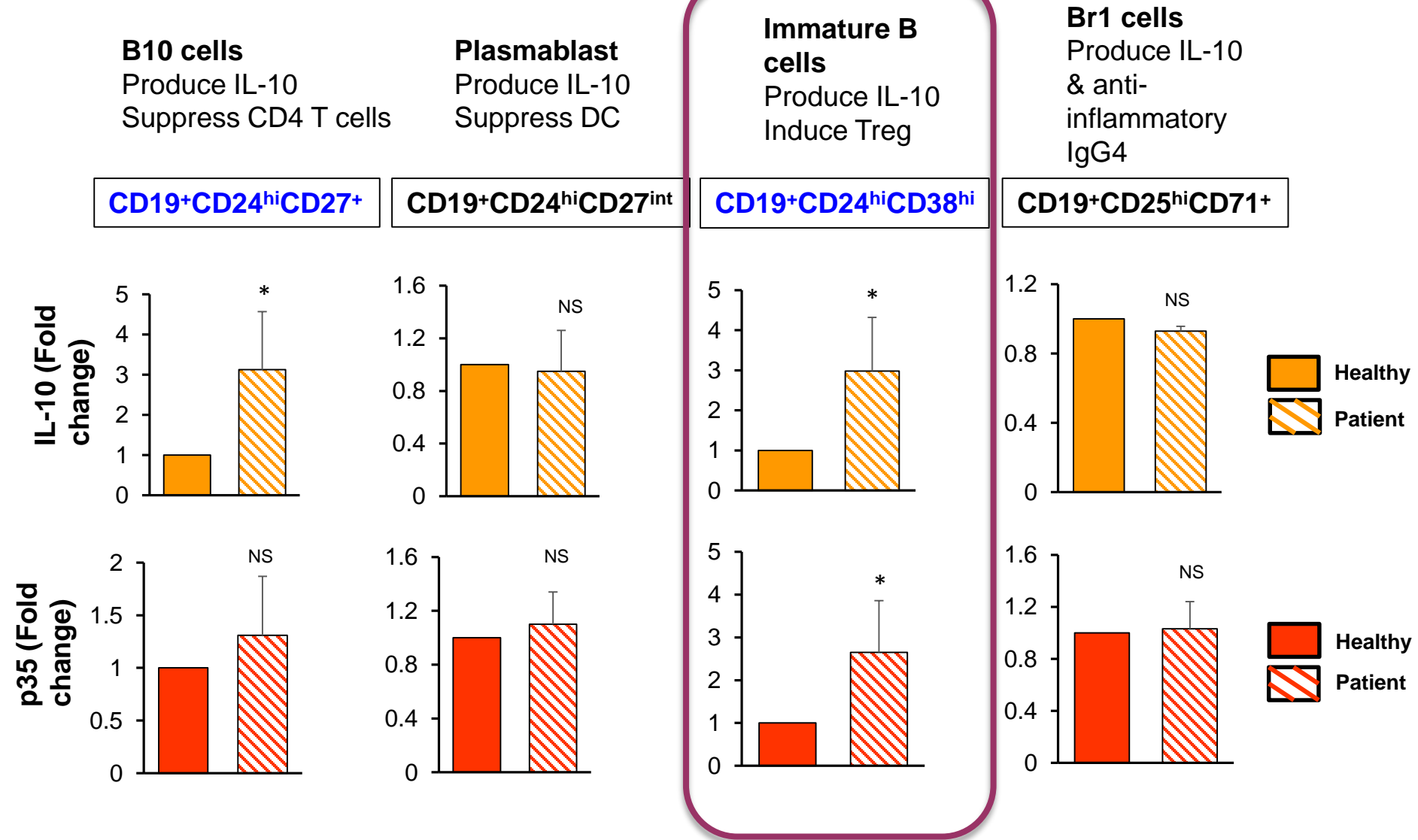
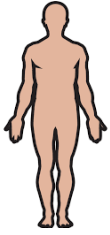
± STA-21



# STAT3 activation in IL35-educated CD8<sup>+</sup> T cells is suppressive *in vivo*

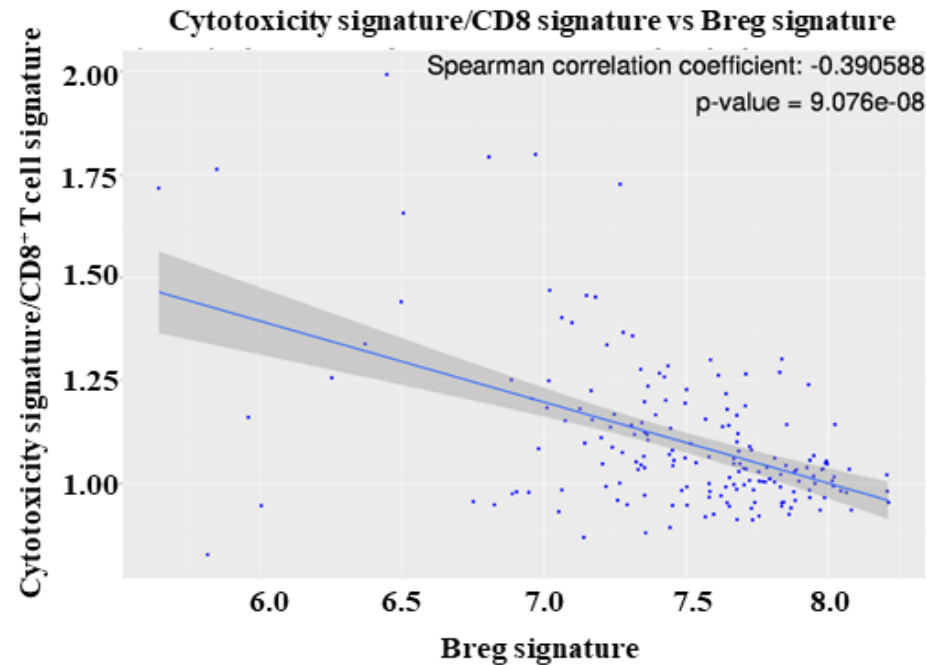
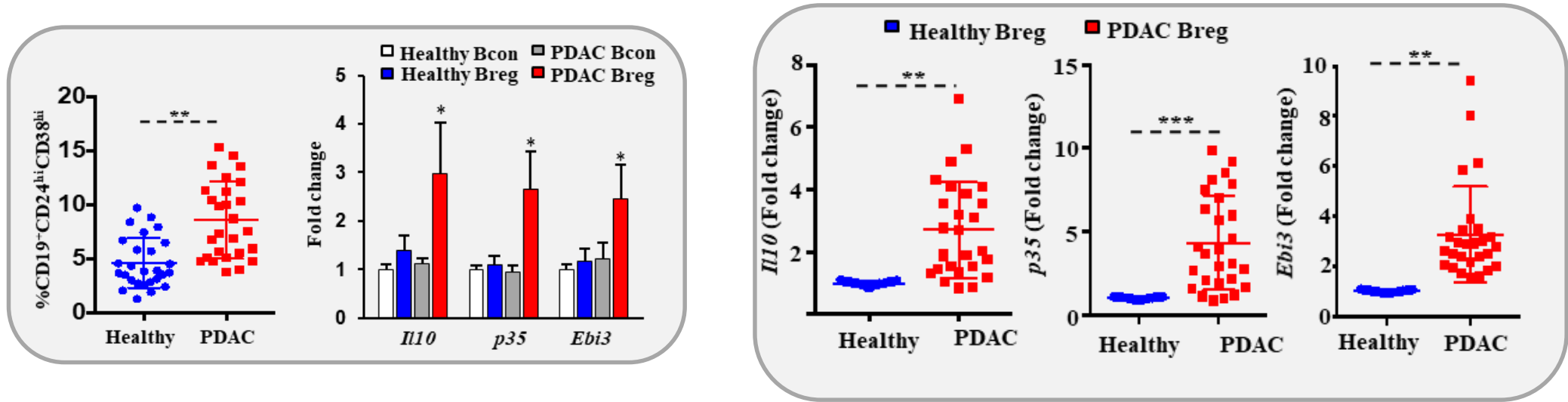
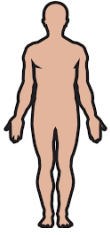


# Characterization of cytokine-producing human B cells.



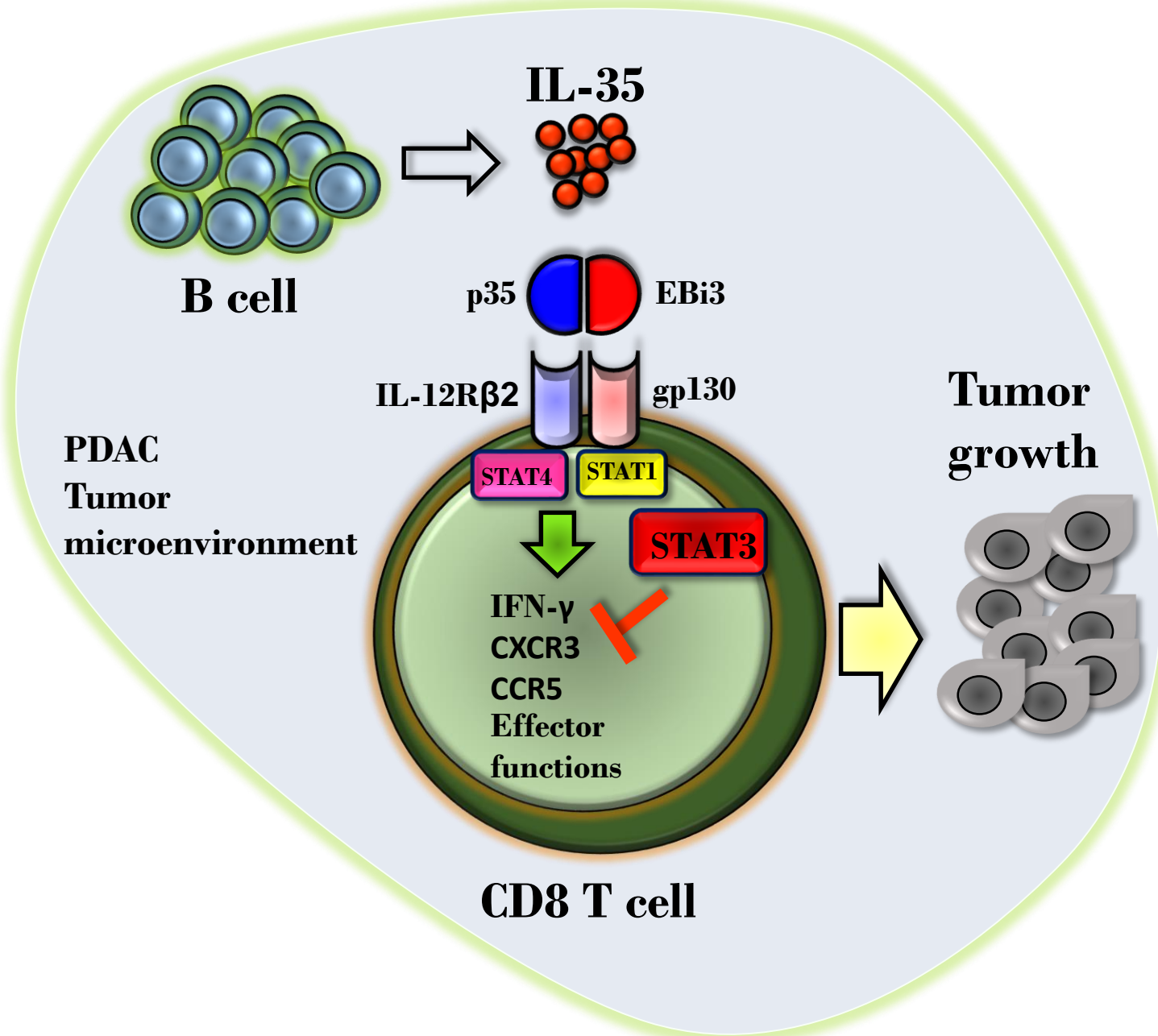


# B cells represent a dominant IL35<sup>+</sup> population in human PDAC (PB)



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

## Pylayeva-Gupta Lab

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*David DeNardo (WashU)*



## Funding

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CANCER  
INSTITUTE**

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