Understanding Immune Suppression in Pancreas Cancer: A Key Role for Gamma Delta T Cells

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Disclosure of Conflicts of Interest

Johnathan Ebben, MD, PhD, has the following financial relationship to disclose:

- Cofounder, Nano RED

The Challenge of Pancreas Cancer

Metastatic disease at diagnosis

Complicated stroma

- Desmoplasia
  - Limited penetration of therapeutic agents
  - Highly resistant tumors
- Networks with significant crosstalk
  - Tumor-> stroma
  - Tumor-> tumor
  - Stroma->tumor
  - Stroma->stroma

Immunosuppressive environment

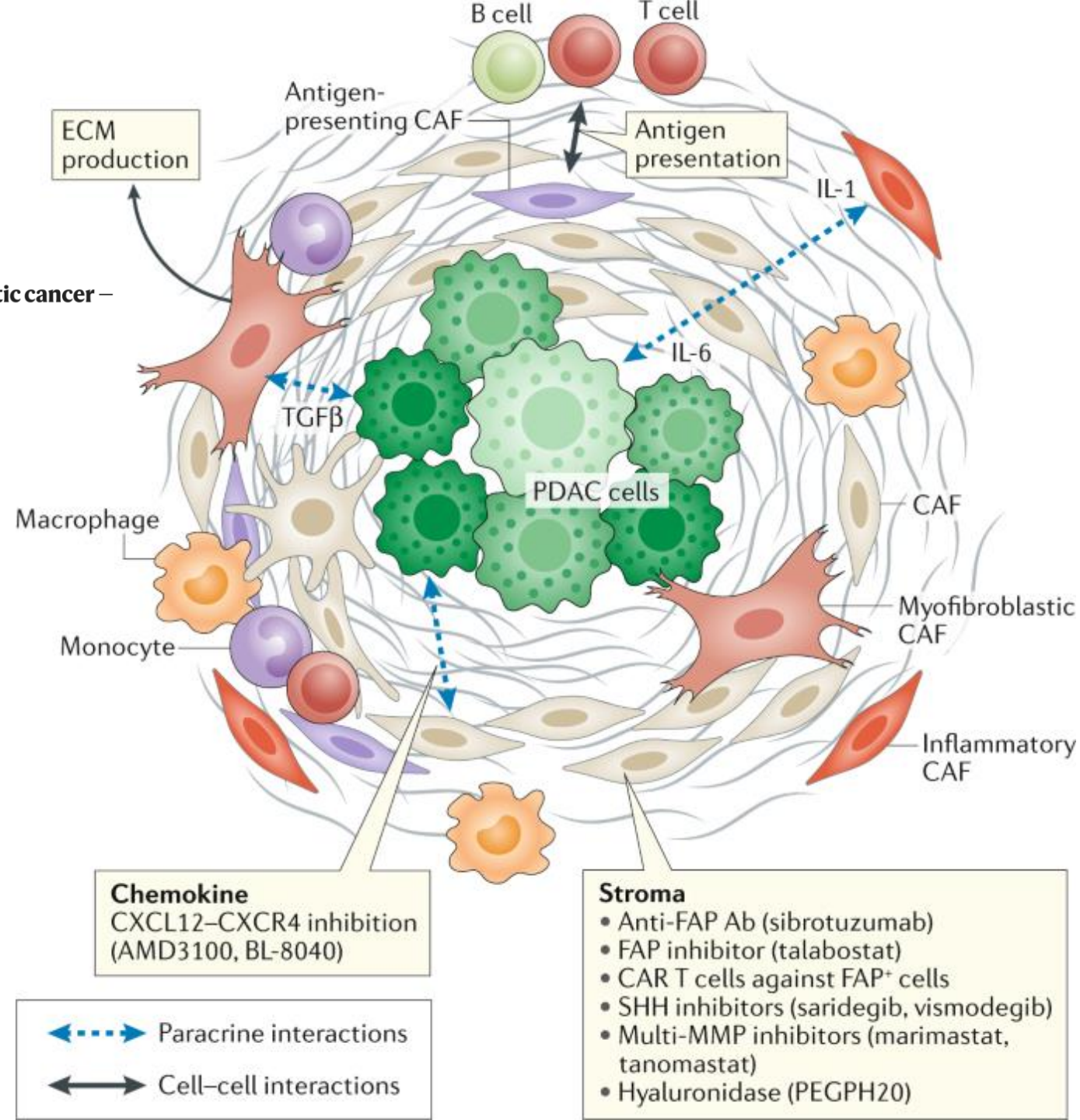
- What drives immunosuppression?

Review Article | Published: 12 May 2020

The tumour microenvironment in pancreatic cancer – clinical challenges and opportunities

Won Jin Ho, Elizabeth M. Jaffee & Lei Zheng ✉

Nature Reviews Clinical Oncology **17**, 527–540 (2020) | Cite this article



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γδ T Cells Support Pancreatic Oncogenesis by Restraining αβ T Cell Activation

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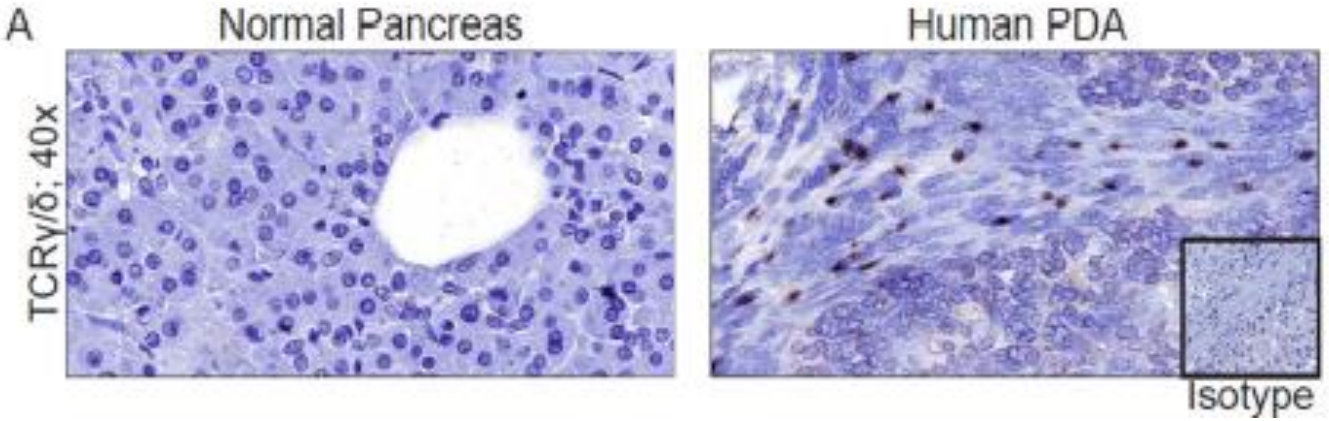
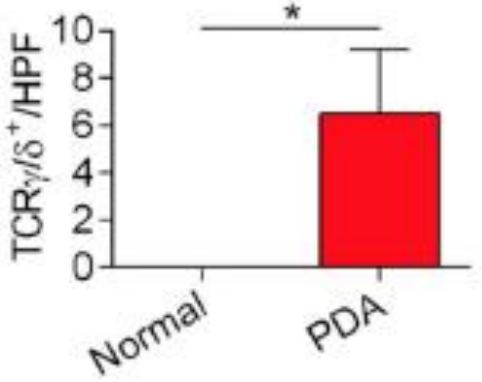
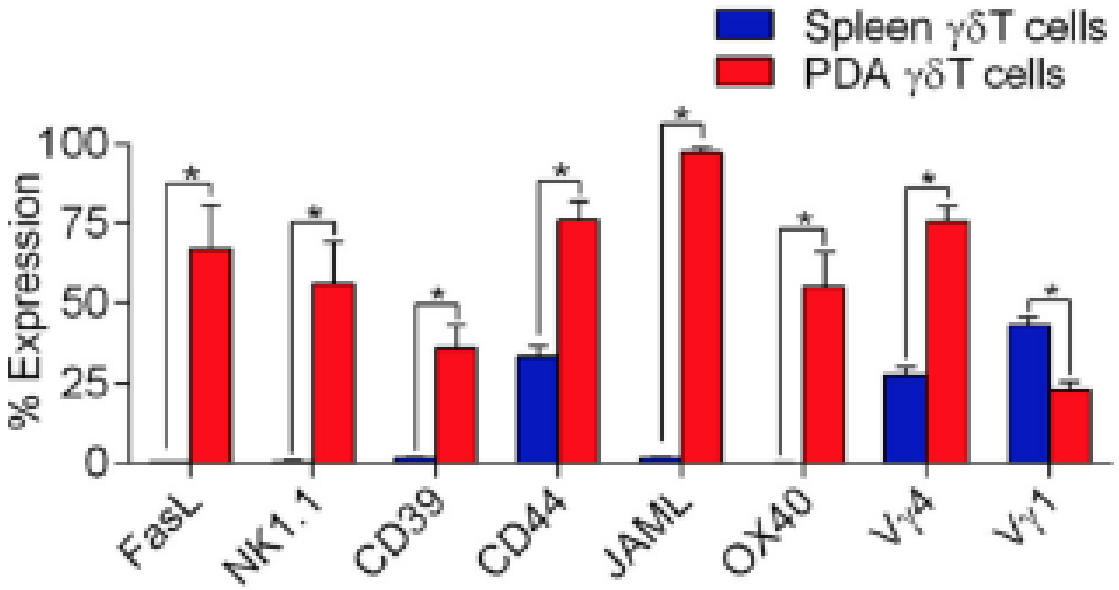
Pancreas cancers are heavily infiltrated by γδ T cells





76% of CD3+ cells

Activated, but with **exhausted** Em phenotype.



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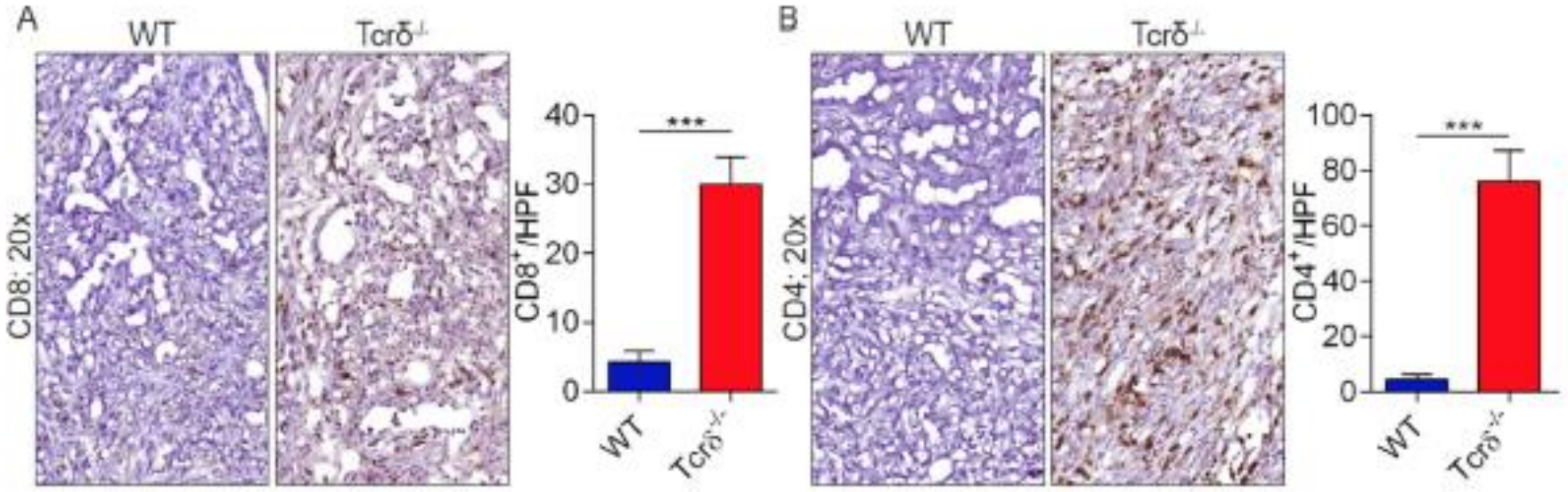
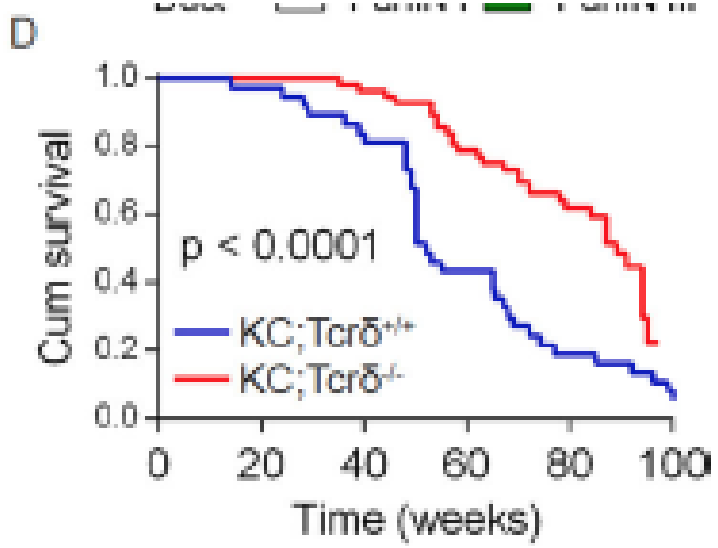
How do they impact tumor/immune phenotype?



TCR gamma depletion leads to increased CD4/CD8 infiltration and improved OS (murine model)



Some Questions

If γδ T cell infiltration is more than a biomarker:

How do γδT acquire a suppressive state?

- Tumor- γδ T interaction: secreted mediator? Cell contact?
- γδ T stroma interaction?

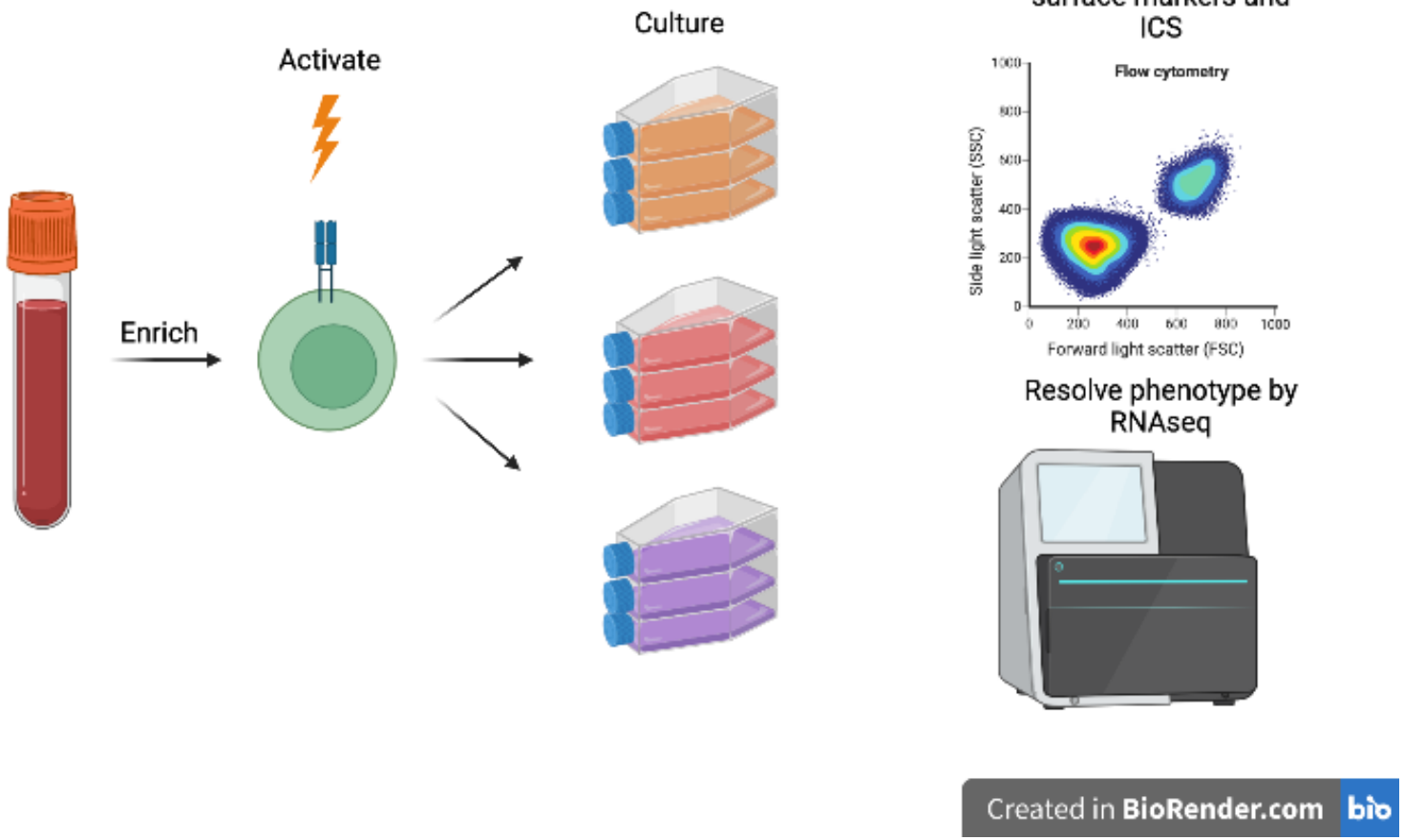
Is γδT mediated suppression reversible and potentially clinically actionable?

First Things First

Global hypothesis

γδ T cells sit at the nexus of immune suppression in PDAC, driving stromal changes and antagonizing αβ T cell infiltration and activation, driven by acquisition of an alternatively activated γδ T phenotype, conferred by soluble mediators produced by PDAC

How do we model this/ask these questions?



Caveats:

Is reprogramming conferred by a soluble mediator (easiest to model), cell-cell interactions (harder) or both + tissue stroma interactions (hardest)?

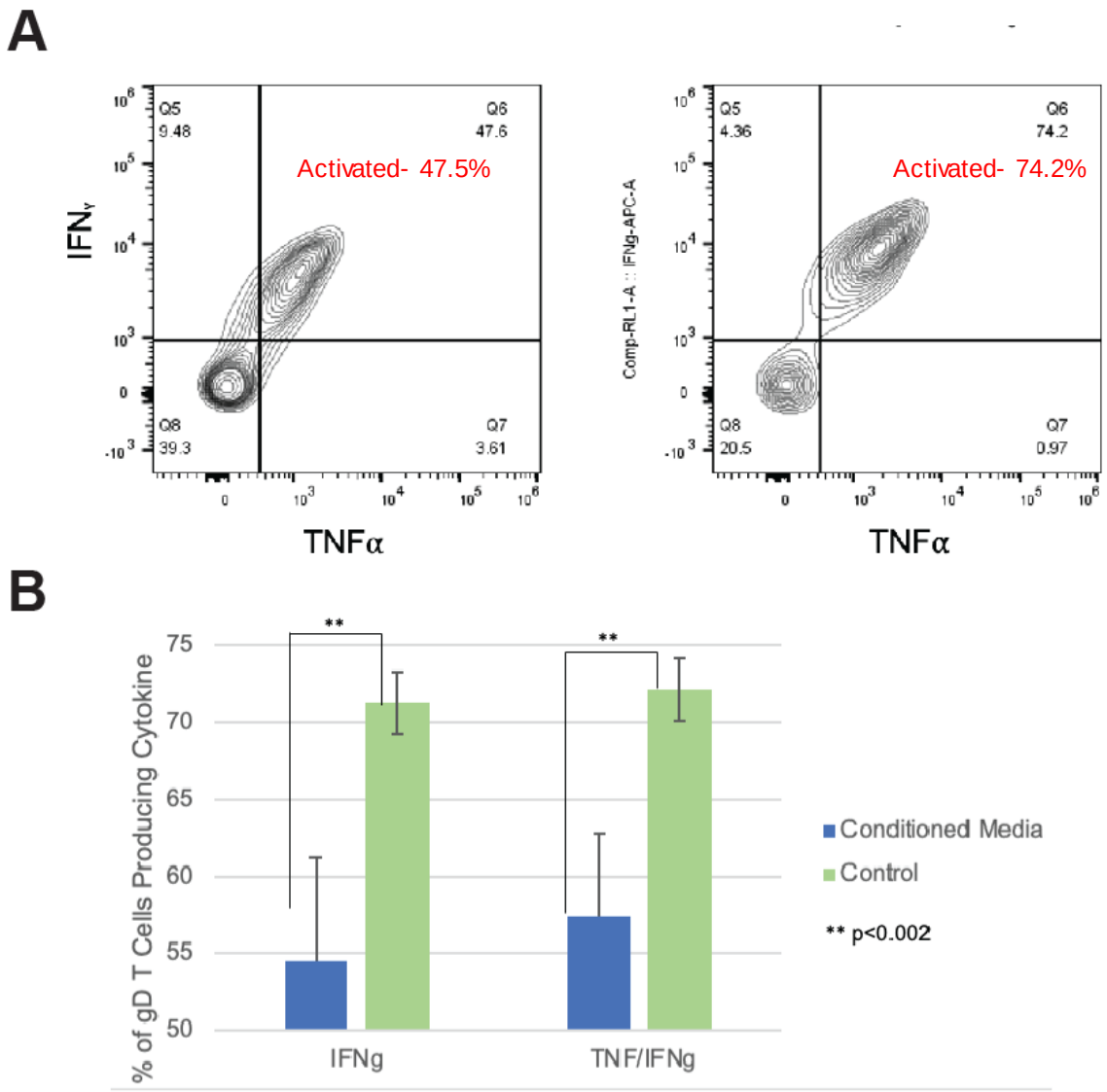
Kinetics of reprogramming?

Predicated on a model where Vd2 circulating γδT home, react, and are subsequently reprogrammed

Alternative approaches:

- Organoid co-culture system
- Source material from metastatic sites

Gamma Delta T Cell Activation is Attenuated by Pancreas Tumor Conditioned Media



Next Steps

- Understand WHAT soluble mediator drives altered γδ T function
  - RNAseq
- Assess γδT interaction with PDAC cell contact
- Assess biomarkers of γδT dysregulation in patient samples
- Apply insights to develop therapies designed to target γδT mediated immunosuppression
- Up-armored γδT cell-based therapies?

Carbone Cancer Center
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