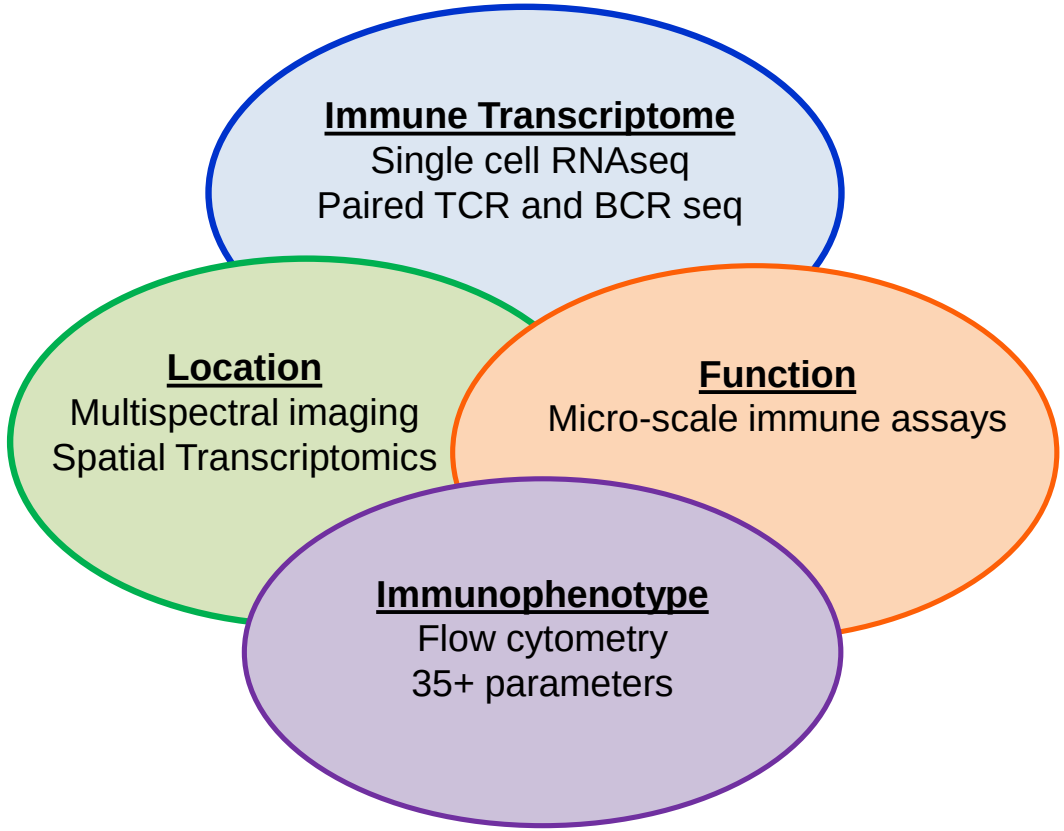
University of Pittsburgh

UPMC | HILLMAN CANCER CENTER

Targeting LAG3 in the human TME for improved anti-tumor immunity



Tullia C. Bruno, PhD

SITC Deep Dive Webinar

University of Pittsburgh

UPMC Hillman Cancer Center

Department of Immunology

June 13, 2021

tbruno@pitt.edu


The Hopkins/Medarex (+ Dario) PD-1/LAG-3 team
in 2009 just before Medarex took over BMS

The Complete Team!

Bruno-Vignali Team

Anthony Cillo

Carly Cardello

Ashwin Somasundaram

Sheryl Kunning

Caleb Lampenfeld

Center for Research Computing

University of Pittsburgh Genomics Core

Melanoma and Skin Cancer SPORE

John Kirkwood

Hassane Zarour

Lilit Karapetyan

Ryan Massa

Anjali Rohatgi

Yana Najjar

Diwakar Davar

Cindy Sander

Amy Rose

HNSCC SPORE

Robert Ferris

Heath Skinner

Cardiothoracic Surgery

Jim Luketich

Arjun Pennathur

Julie Ward

Funding

Melanoma and Skin Cancer SPORE

HNSCC SPORE

BMS

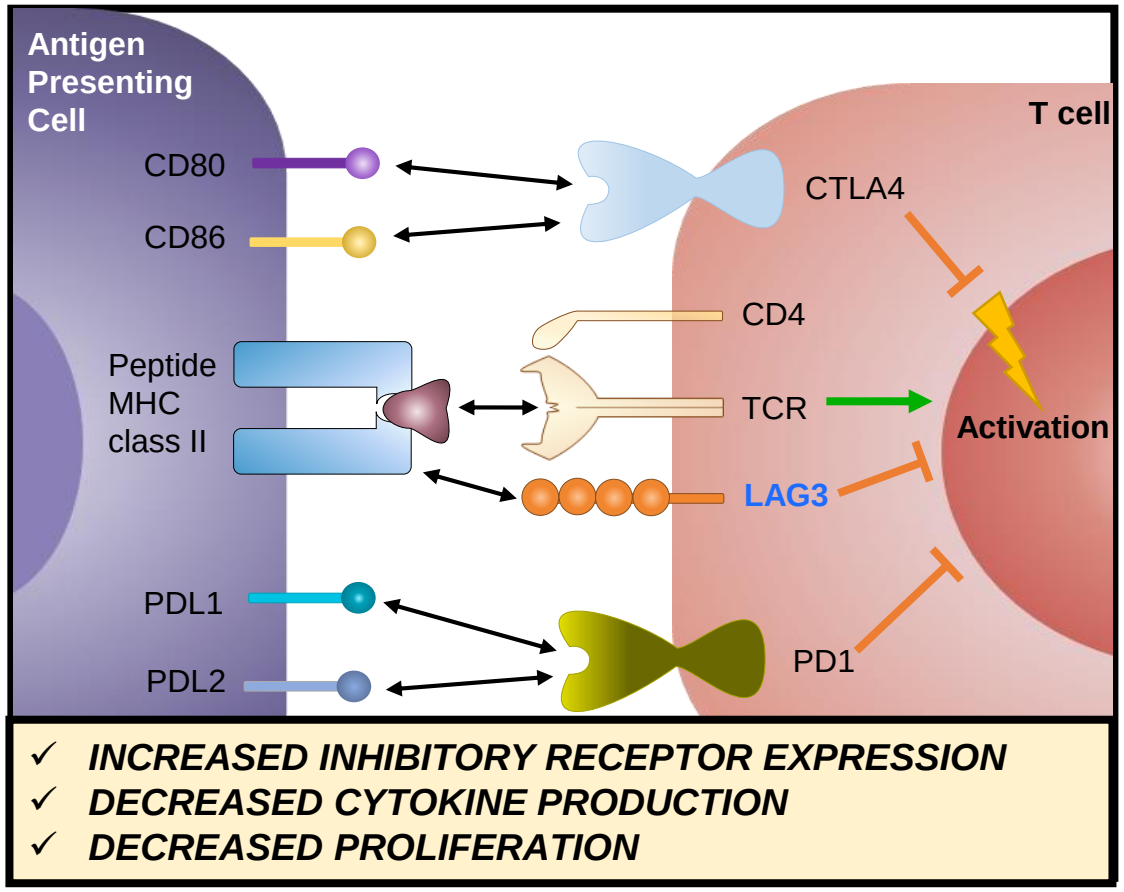
Patients and their families!

Ashwin Somasundaram

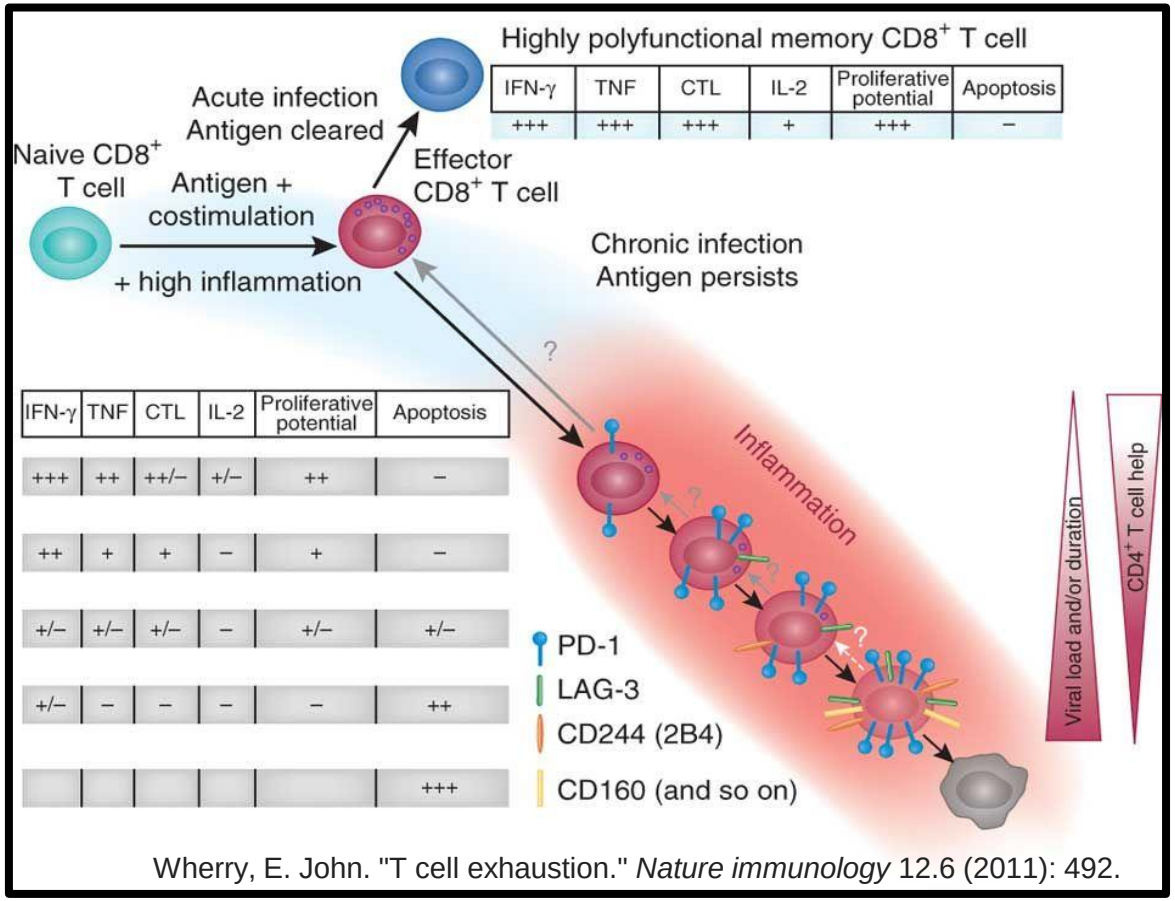
Carly Cardello

Tony Cillo

There is clear evidence to move beyond the PD1:PDL1 axis in solid tumors



- ✓ *INCREASED INHIBITORY RECEPTOR EXPRESSION*
- ✓ *DECREASED CYTOKINE PRODUCTION*
- ✓ *DECREASED PROLIFERATION*



Wherry, E. John. "T cell exhaustion." *Nature immunology* 12.6 (2011): 492.

Does LAG3 only affect local, tumor infiltrating CD8+ T cells?
Does LAG3 have a differential biological effect on CD8+ T cells in the TME?
Why is the combination of anti-LAG3 and anti-PD1 important?

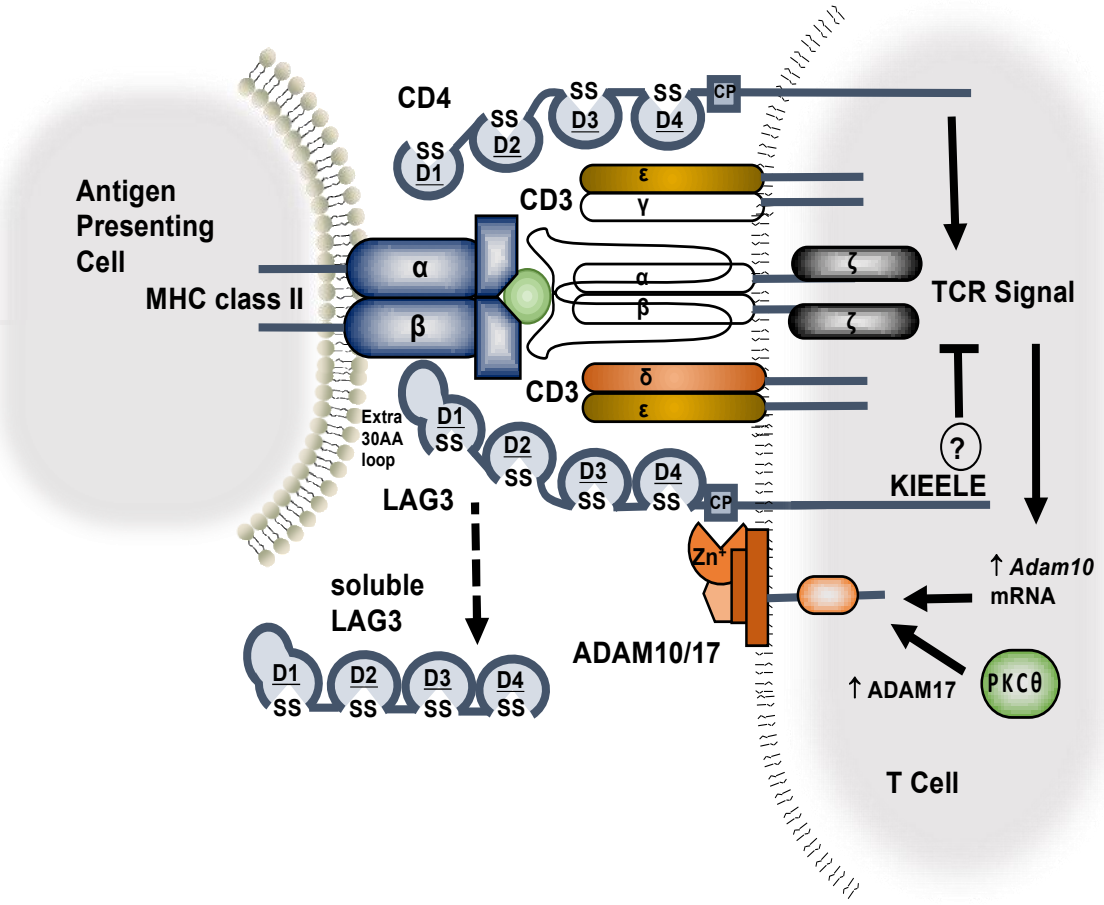
LAG3: A third generation checkpoint molecule

- **Preclinical evidence has led to successful clinical trials**
  - Rela + Nivo in IO-unresponsive MEL patients – OOR 13% (20% LAG3 >1%; *Ascierto, 2017, ASCO*)
  - REALTIVITY-047: Rela + Nivo phase 3 trial in treatment-naive patients with metastatic melanoma met primary endpoint of progression-free survival (*Lipson*, 2021, ASCO)

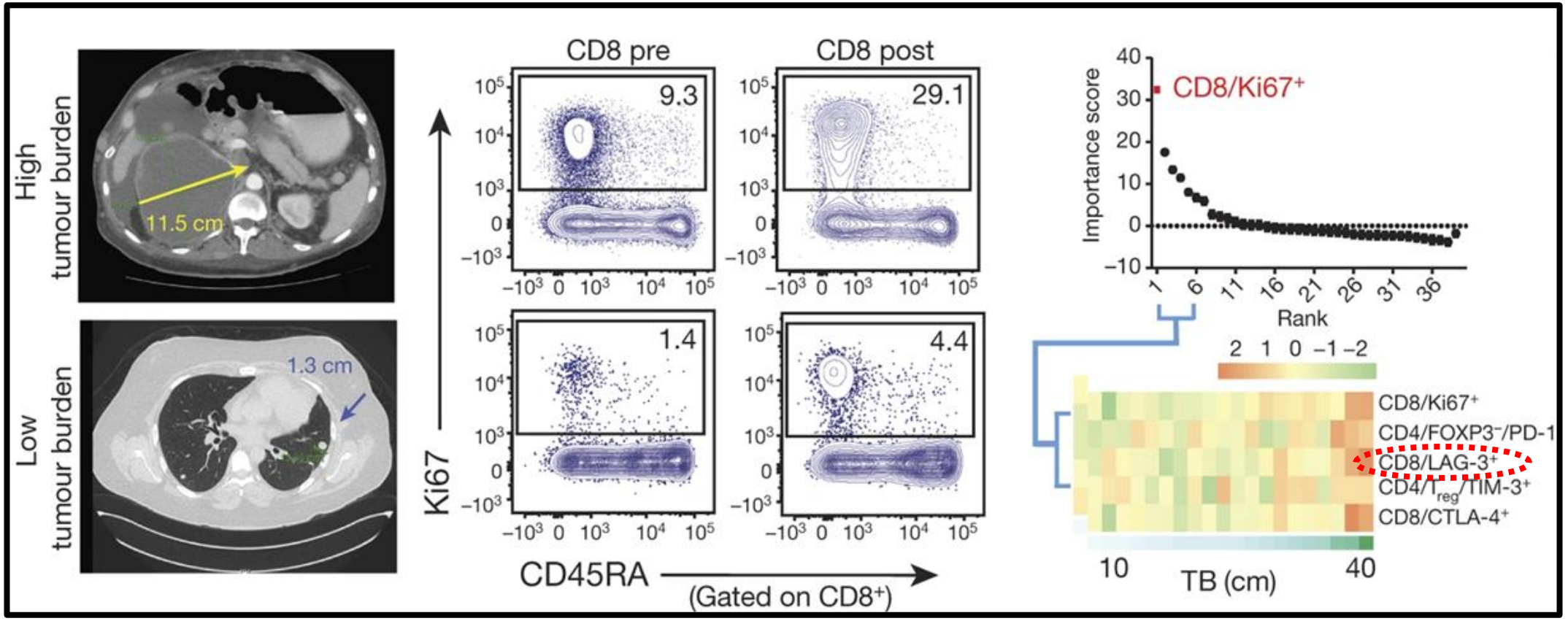
Biological considerations for this complex molecule

- LAG3 binds to MHC class II but may have other ligands
- LAG3 can be expressed on other immune cell types
- Reports of low LAG3 expression in cancer patients
- LAG3 can be stored intracellularly
- LAG3 is rapidly shed by ADAM10/17; high sLAG3 in plasma
- **There could be local and systemic effects of this molecule**

LAG3 signaling and regulation



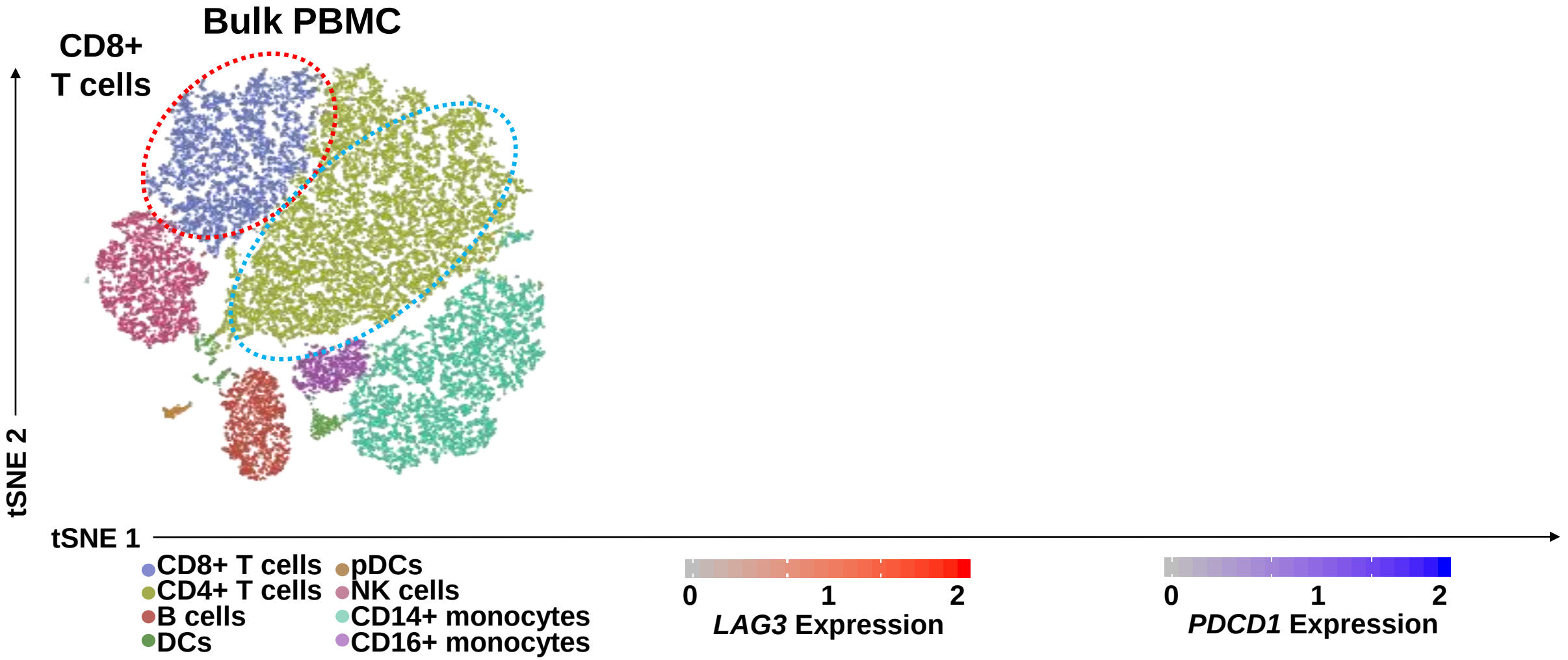
Peripheral T cell signatures are associated with differences in tumor burden and ICB response



Huang, AC et al. T-cell invigoration to tumor burden ratio associated with anti-PD-1 response, Nature 2017.

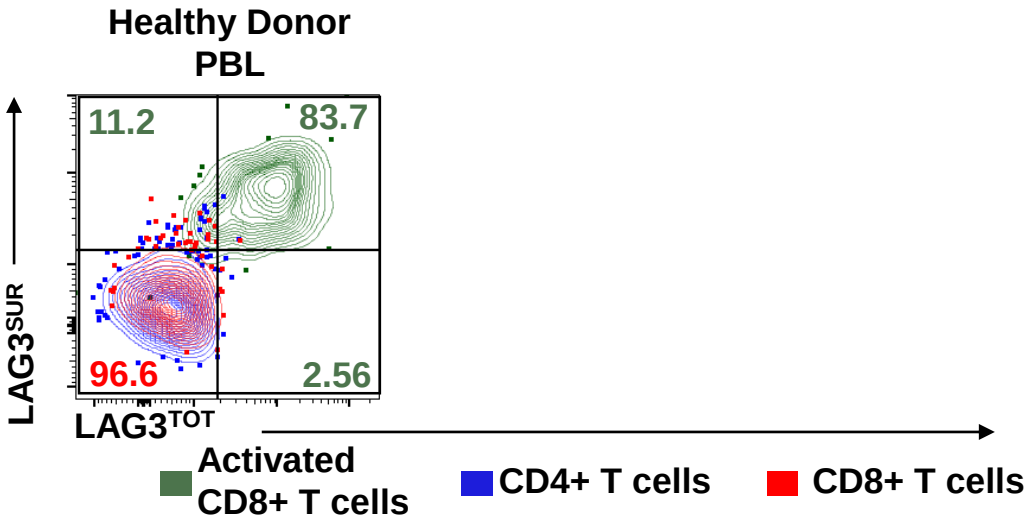
LAG3 is predominantly expressed in peripheral CD8+ T cells from head and neck cancer patients

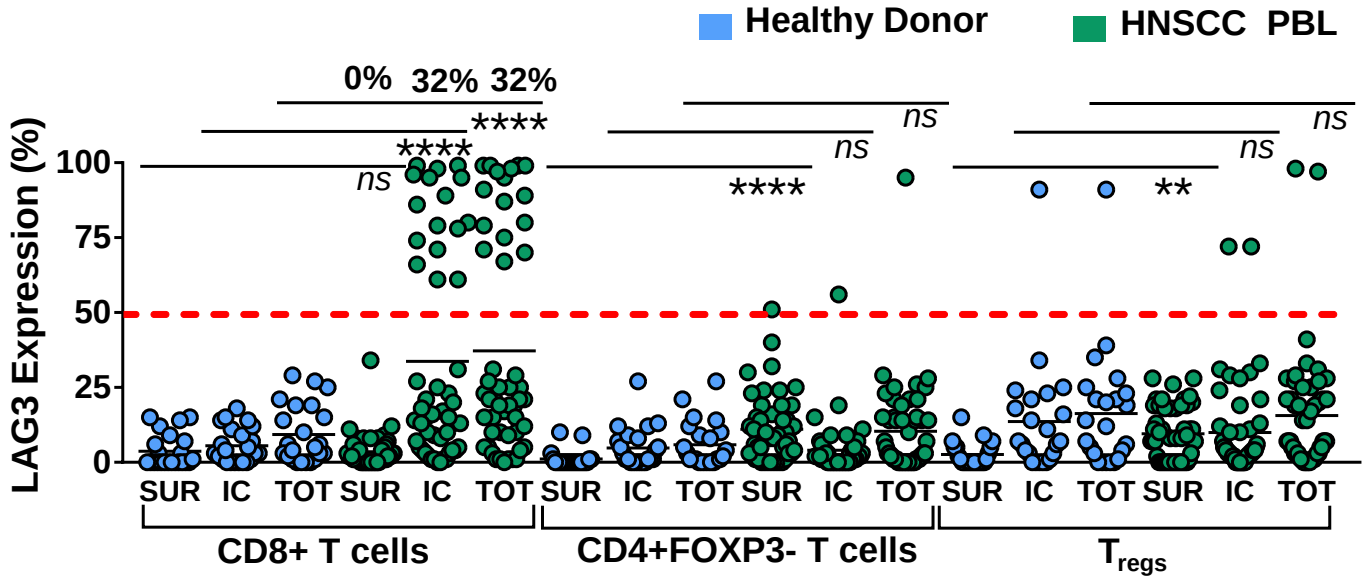
HNSCC PBL (n=11) & HD PBL (n4) – single cell RNAseq

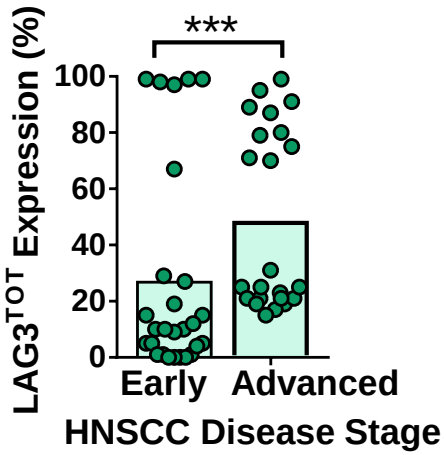


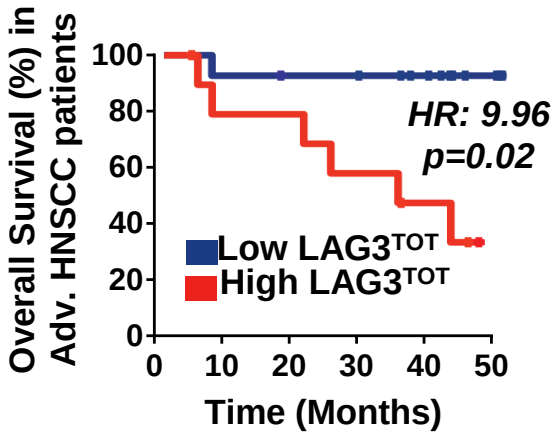
Tony Cillo (Immunity, 2020), Ashwin Somasundaram (CIR, 2022)

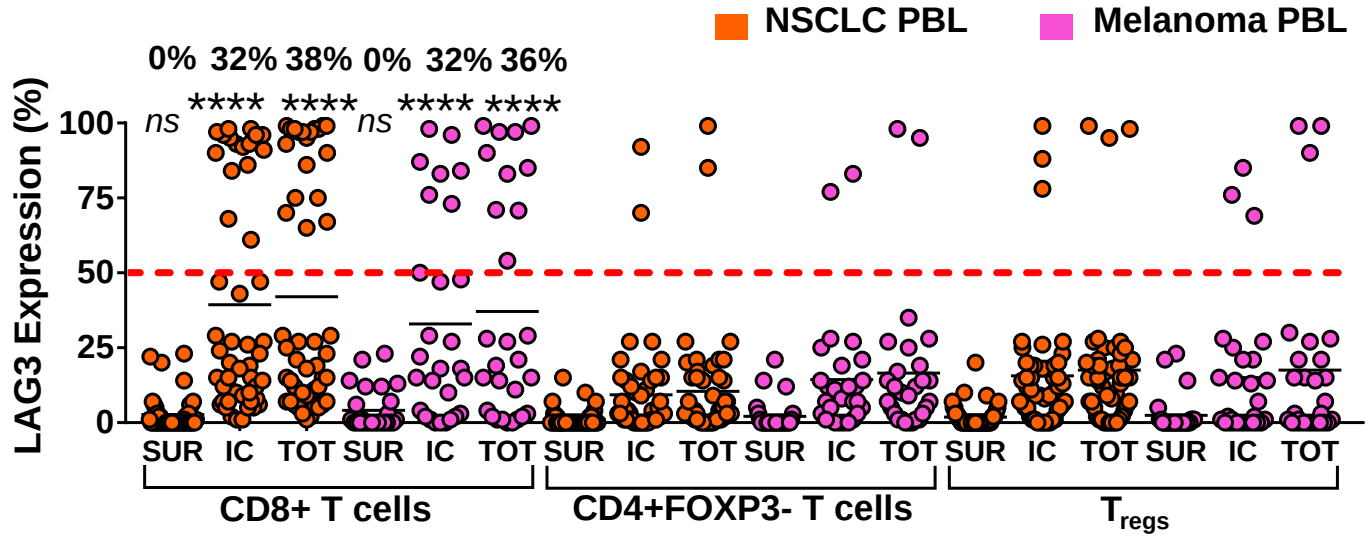
Protein validation of scRNAseq demonstrates that LAG3 is intracellularly expressed in peripheral CD8+ T cells





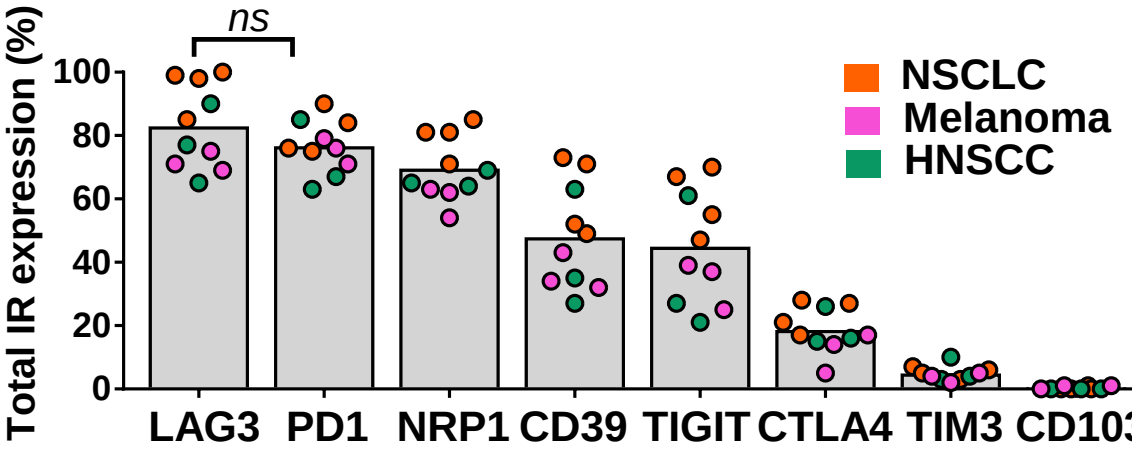


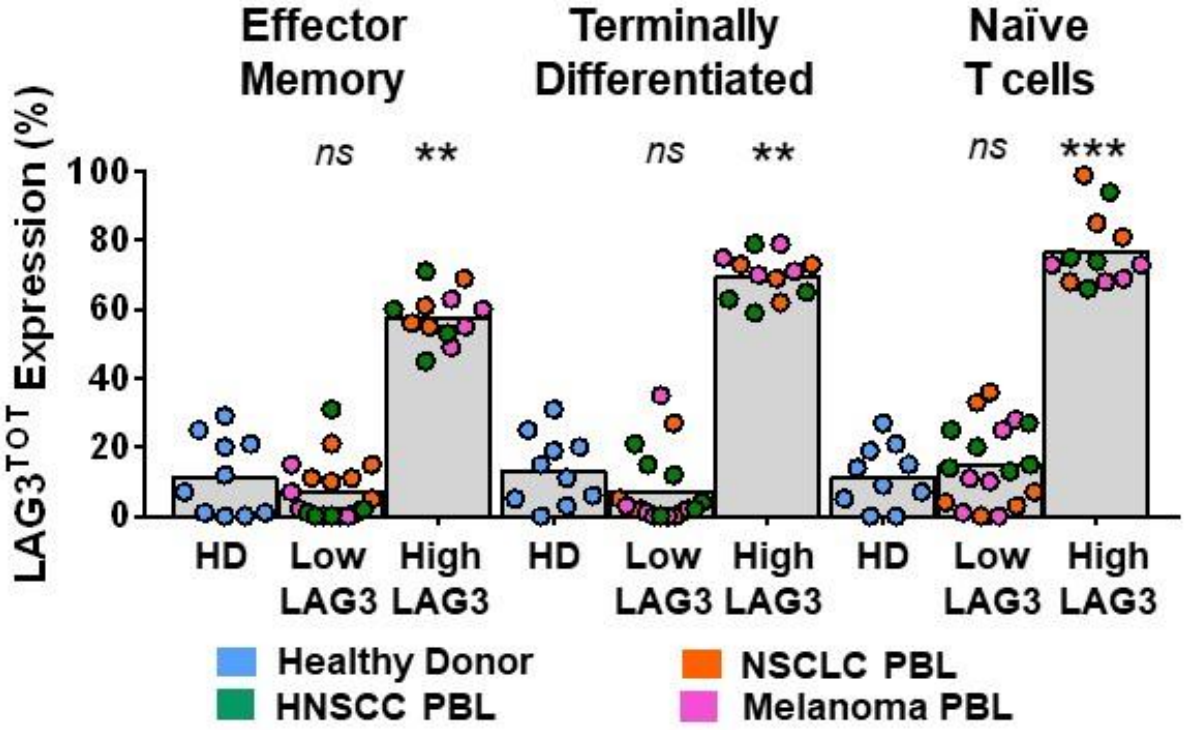




Ashwin Somasundaram (CIR, 2022)

LAG3 is the dominant inhibitory receptor on all peripheral CD8+ T cell subsets

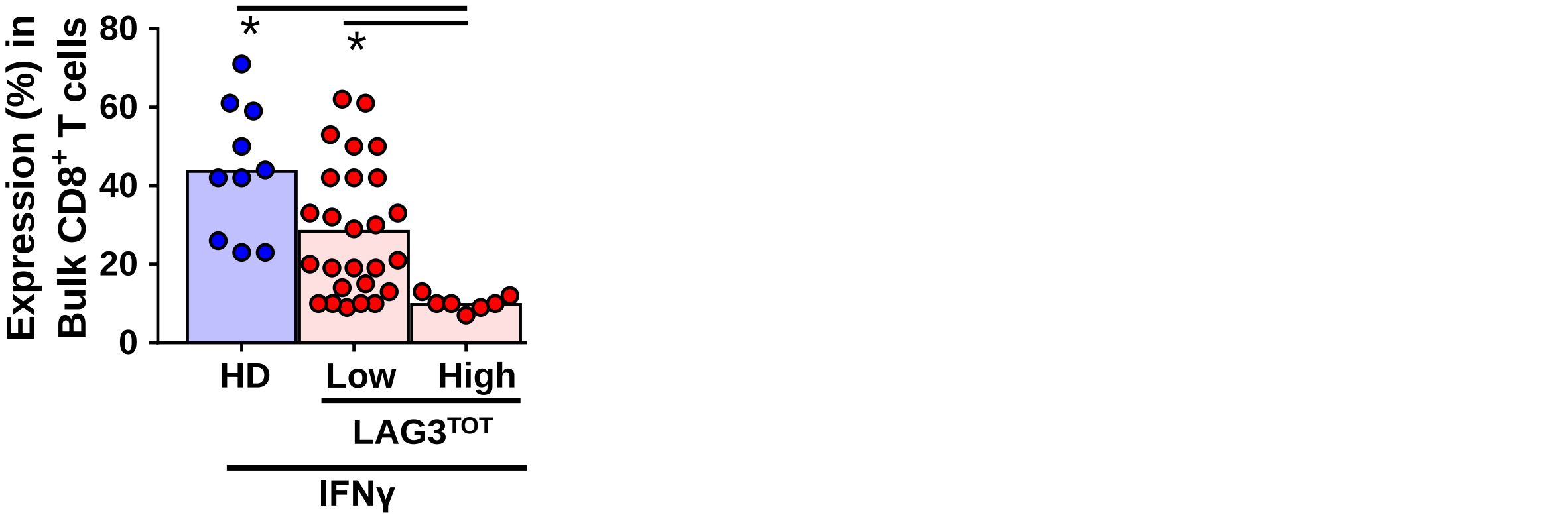




What is the functional consequence of LAG3^{TOT}?
How is LAG3^{TOT} regulated?

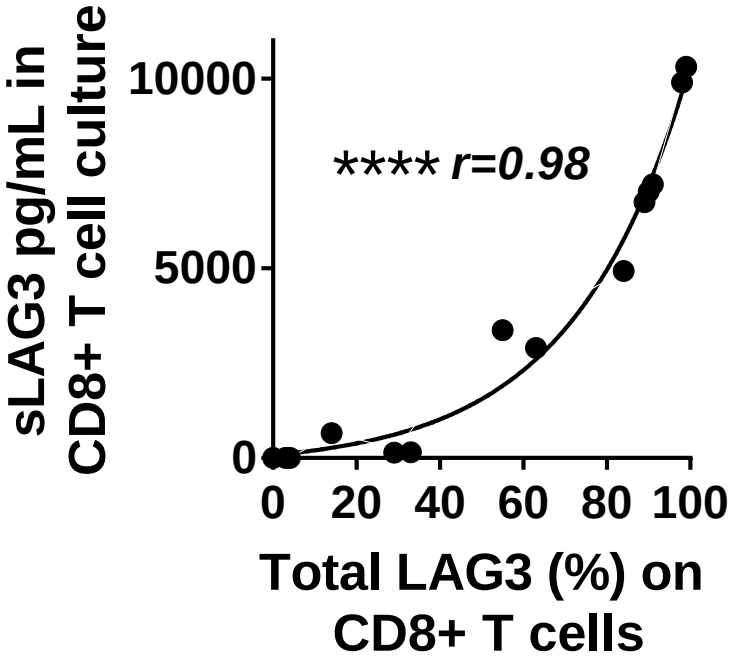
Ashwin Somasundaram (CIR, 2022)

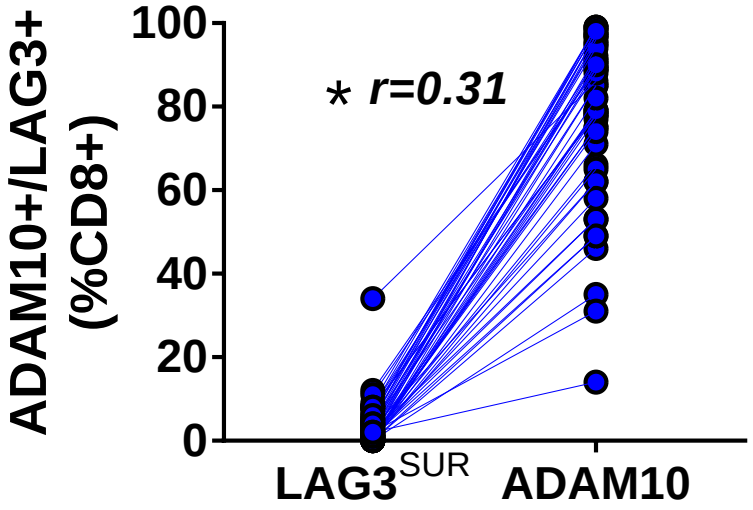
Peripheral CD8+ T cells with high LAG3^{TOT} have reduced function

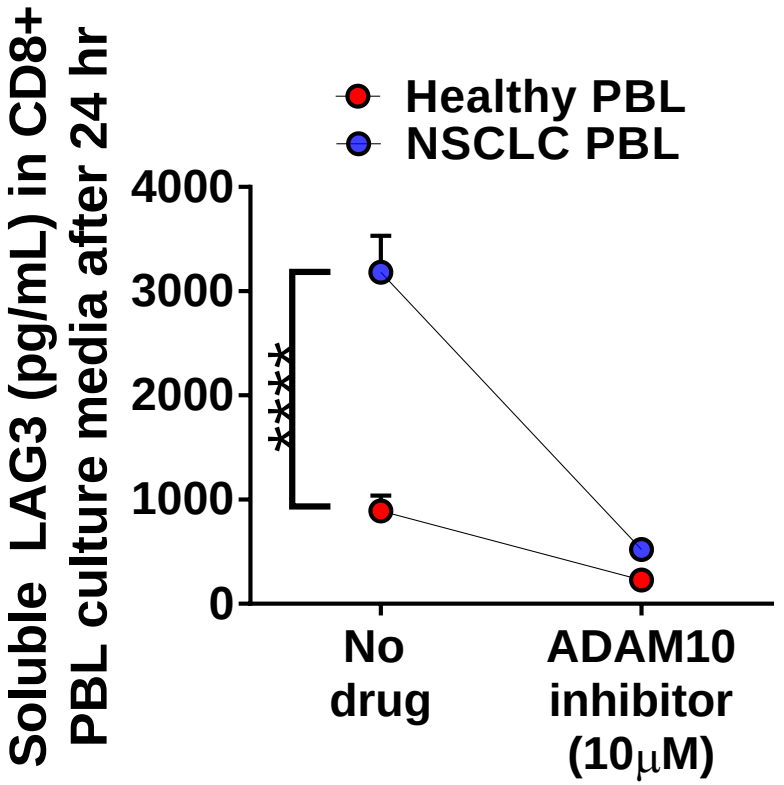


Ashwin Somasundaram (CIR, 2022)

Surface expression of LAG3 is limited by ADAM10-mediated shedding

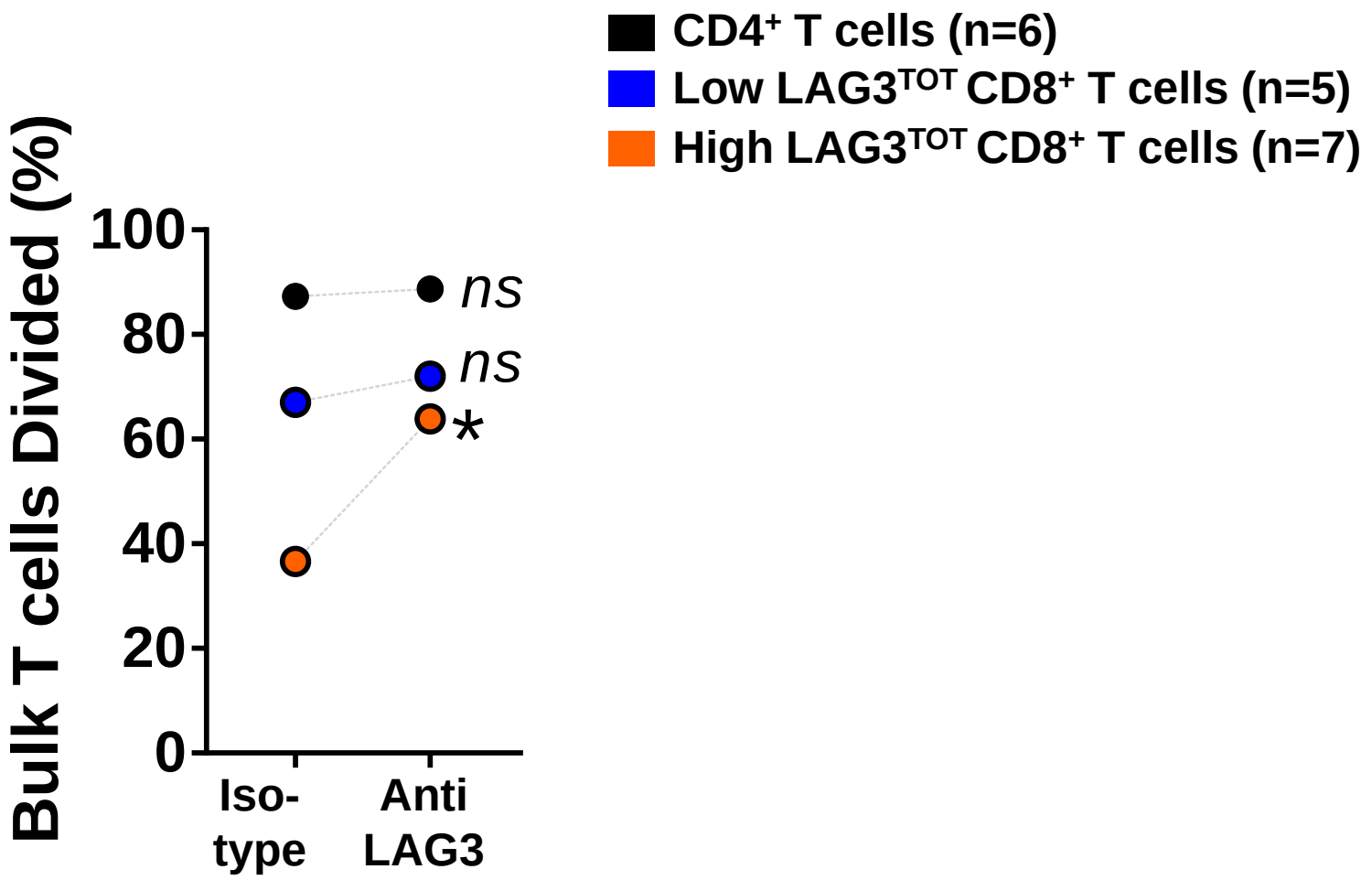






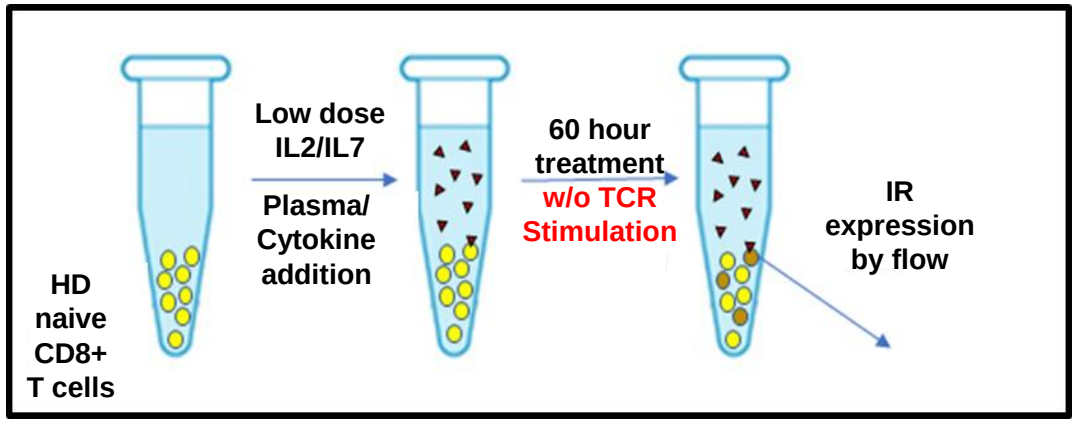
Ashwin Somasundaram (CIR, 2022)

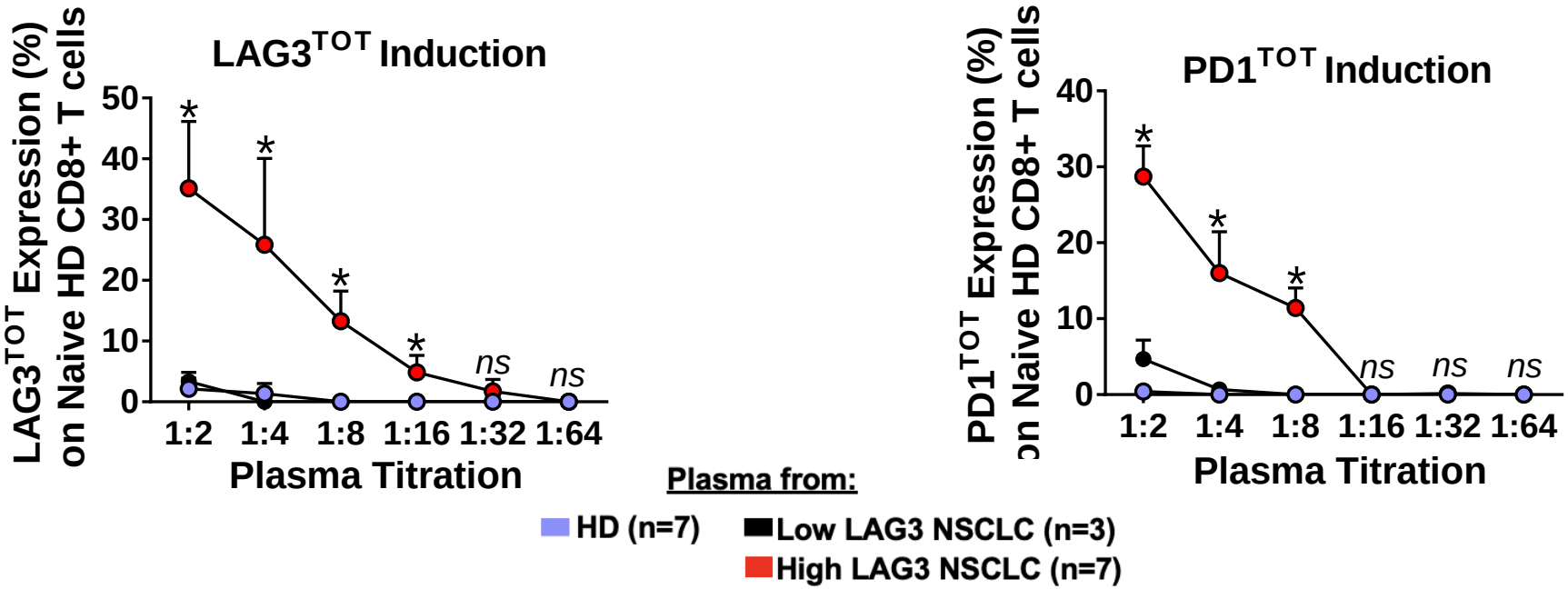
Peripheral CD8+ T cells with high LAG3^{TOT} expression have reduced proliferation



Ashwin Somasundaram (CIR, 2022)

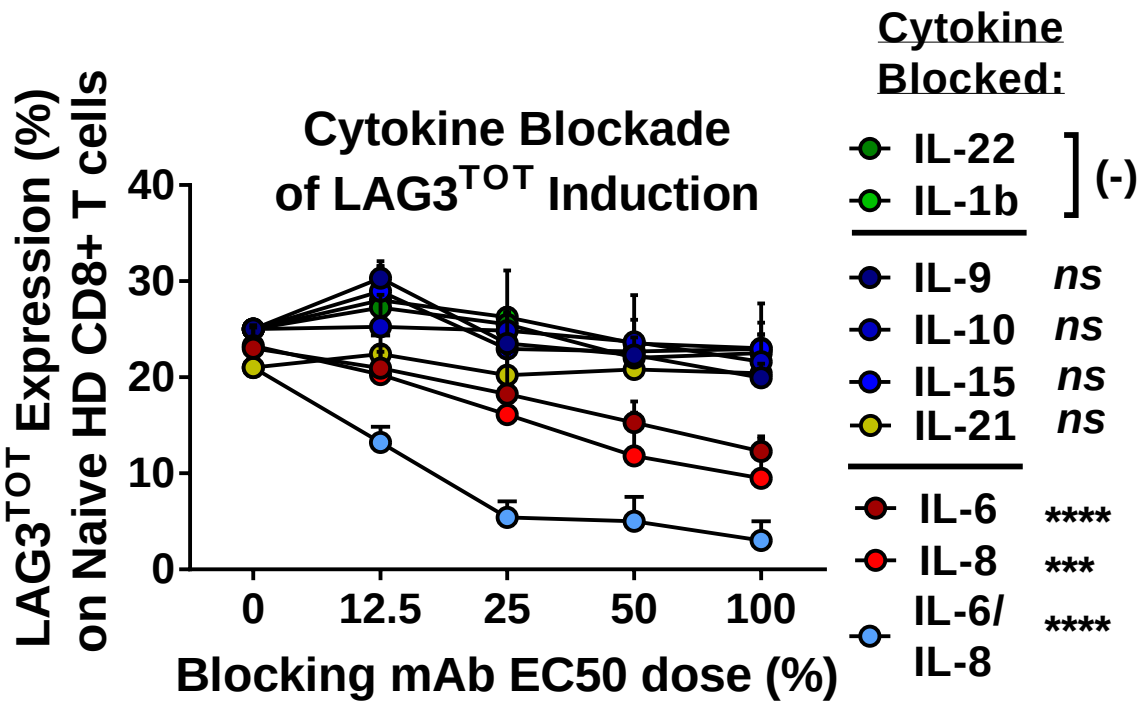
Understanding the induction of LAG3^{TOT} on peripheral CD8+ T cells

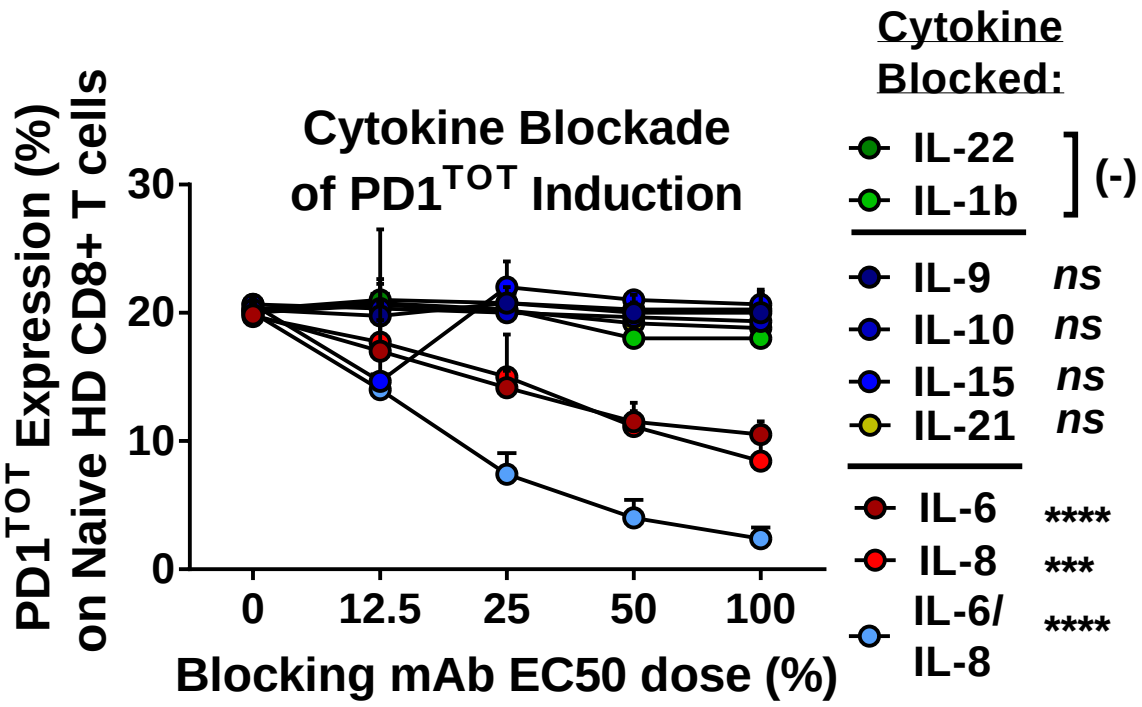




Ashwin Somasundaram (CIR, 2022)

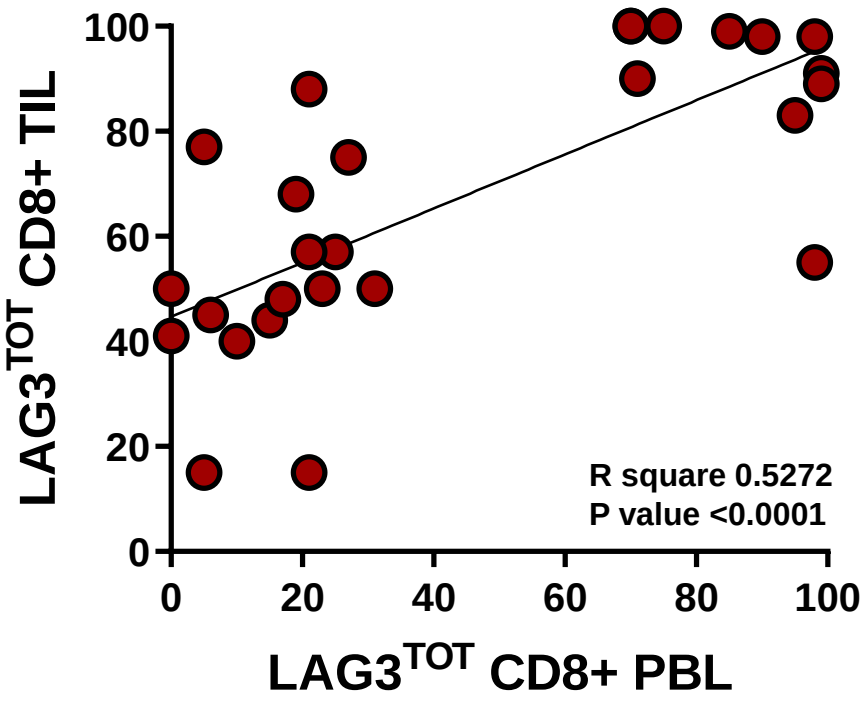
IL6 and IL8 drive LAG3^{TOT} in peripheral CD8+ T cells





Systemic immune dysfunction in cancer patients is driven by IL-6 and IL-8 induction of an inhibitory receptor module

LAG3 expression in the periphery is linked to the tumor microenvironment



Can we design a clinical trial that assesses:

- What immunological and transcriptional pathways are uniquely modified by initial lead in treatment with Rela?
- If the initial Rela, Nivo or the Rela/Nivo combination lead-in impact subsequently immunological and transcriptional parameters that might predict the most responsive patients?
- Identifies valid biomarkers to predict responsiveness to Rela, Nivo or the Rela/Nivo combination?
- Comprehensive impact on the periphery AND tumor microenvironment?

Ashwin Somasundaram (CIR, 2022)

Our Team

Tullia C. Bruno, PhD
Basic Co-Leader

Expertise:
Translational research
Human tumor immunology
Cellular and spatial analysis of the TME
10+ years in tumor immunology

Dario AA. Vignali, PhD
Basic Co-Leader

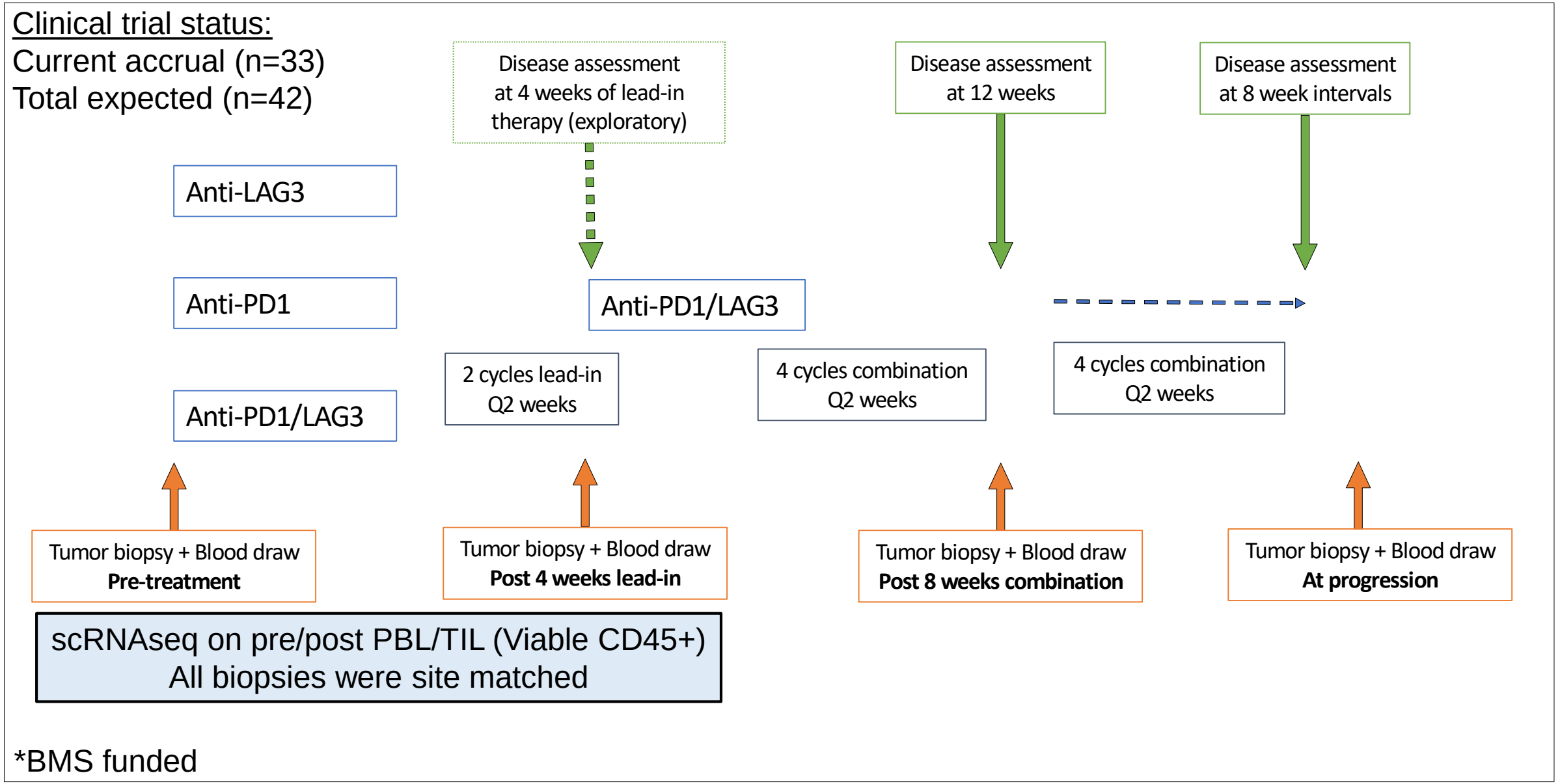
Expertise:
Basic and translational research
LAG3 biology - 20+ years experience
Transcriptional evaluation of the human TME
15+ years in tumor immunology

John Kirkwood, MD
Clinical Leader

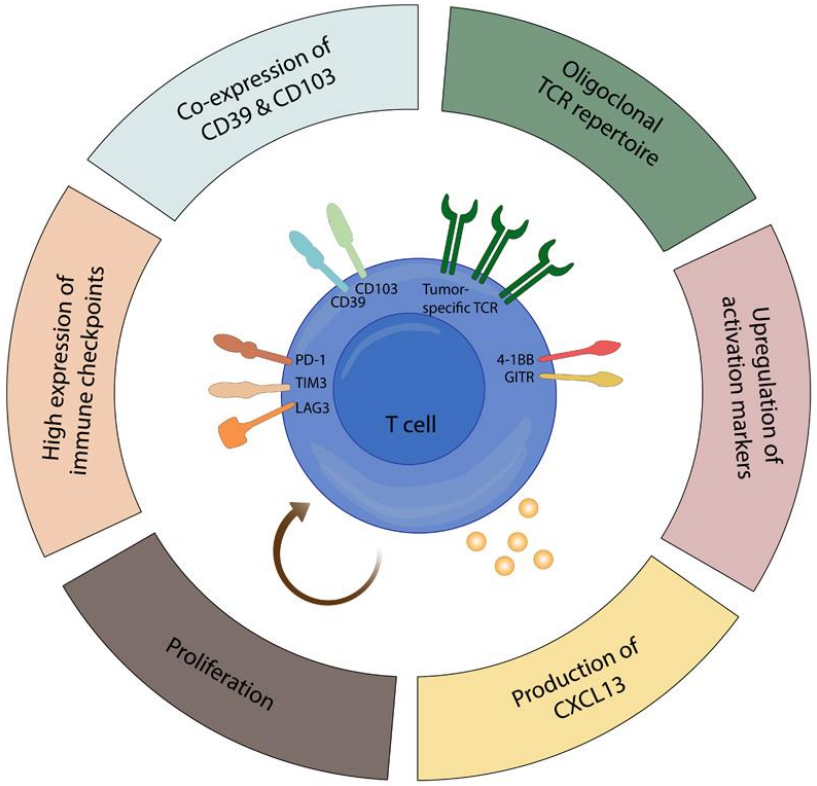
Expertise:
Clinical and translational research
Melanoma biology
IO clinical trial design and execution
40+ years in melanoma

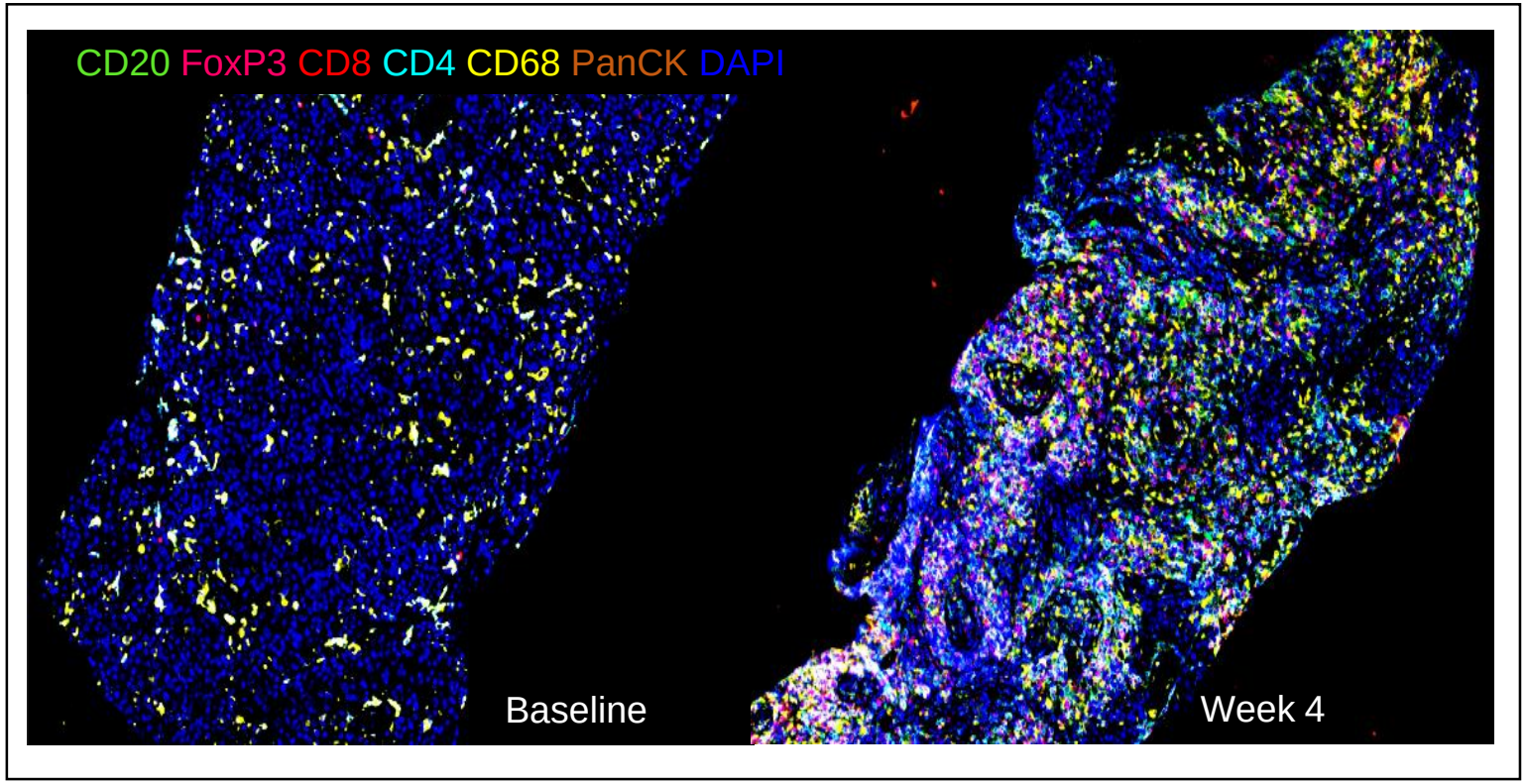
A HUGE THANKS TO THE NEWLY FUNDED MELANOMA AND SKIN CANCER SPORE

HCC 18-071: A phase II clinical trial to assess biological impact of LAG3 alone



Spatial validation of these transcriptomic signatures is necessary





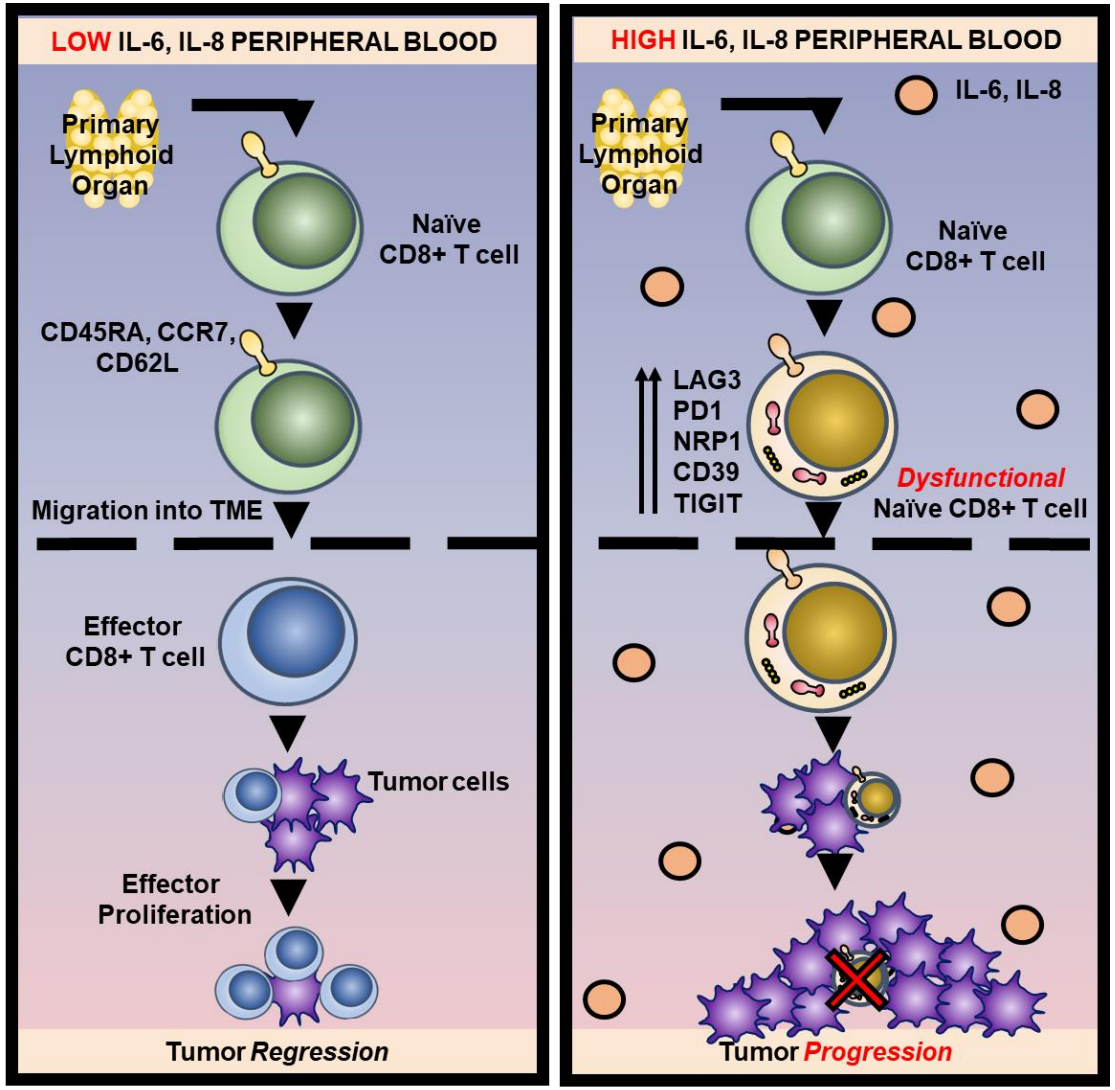
Immune cell influx in a melanoma patient treated with rela/nivo combination at baseline and 4 weeks post tx. Patient had stable disease at week 4.

CD8 + T cell states in human cancer: insights from single-cell analysis

Anne M van der Leun [1], Daniela S Thommen [1], Ton N

Conclusions and Future Directions

INTRACELLULAR STORES OF LAG3 HAVE FUNCTIONAL CONSEQUENCE



18-071 Trial

- Trial offers a robust platform for transcriptomic interrogation of systemic and local responses
- Bioinformatic analyses that enrich conditions by distinct cellular neighborhoods are important for a granular view of immune cells via scRNAseq
- Targeting LAG3 and PD1 lead to distinct gene signatures that correlate with improved survival
- TCR and IFNγ signaling are increased in peripheral and local CD8+ T cells with combination therapy
- Relate immune signatures to clinical outcomes
- Link transcriptional profiles to spatial patterning in the tumor microenvironment
- Interrogation of other immune subsets that could be affected differentially by LAG3 and PD1 targeting

The Complete Team!

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