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CD47 Targeting in Peripheral T-cell Lymphomas

Salvia Jain, MD
Assistant Professor of Medicine, Harvard Medical School
Jon and Jo Ann Hagler Center for Lymphoma

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Conflicts

Company	Nature
Abcuro, Inc	SRA, SAB, Consultancy
Acrotech Biopharma, Inc	SRA
SIRPant Immunotherapeutics	SRA, SAB, Consultancy
Daiichi Sankyo	SRA, SAB, Consultancy
Myeloid Therapeutics	SRA, SAB, Consultancy
Mersana Therapeutics	SRA, Consultancy
CRISPR Therapeutics	SAB

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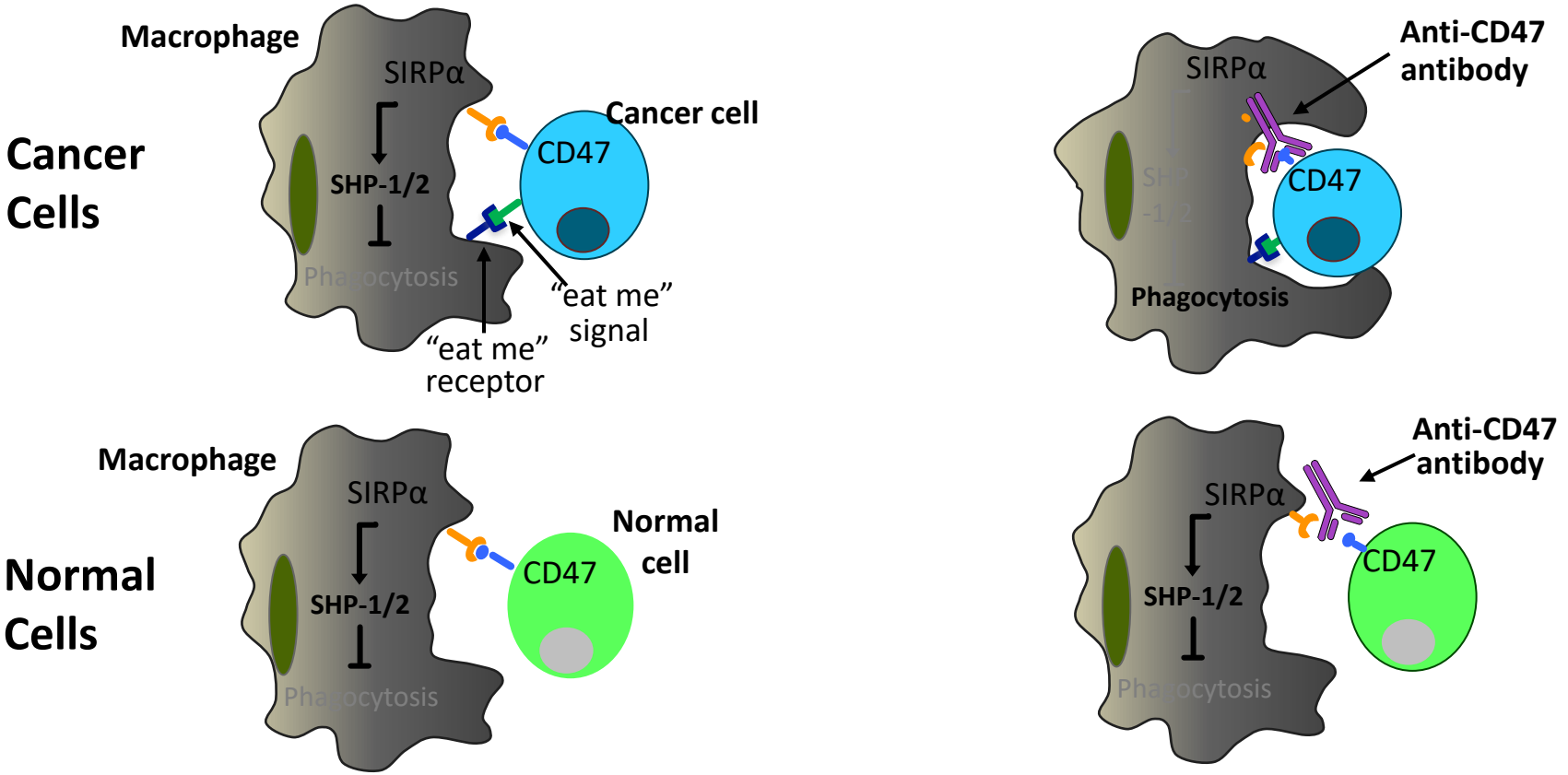
CD47-SIRPα: MYELOID IMMUNE CHECKPOINT



- Antibodies that block the CD47:SIRPα interaction potently stimulate macrophage phagocytosis of cancer cells
- Collaboration with Surface Oncology: SRF231: human IgG4 anti-CD47 antibody

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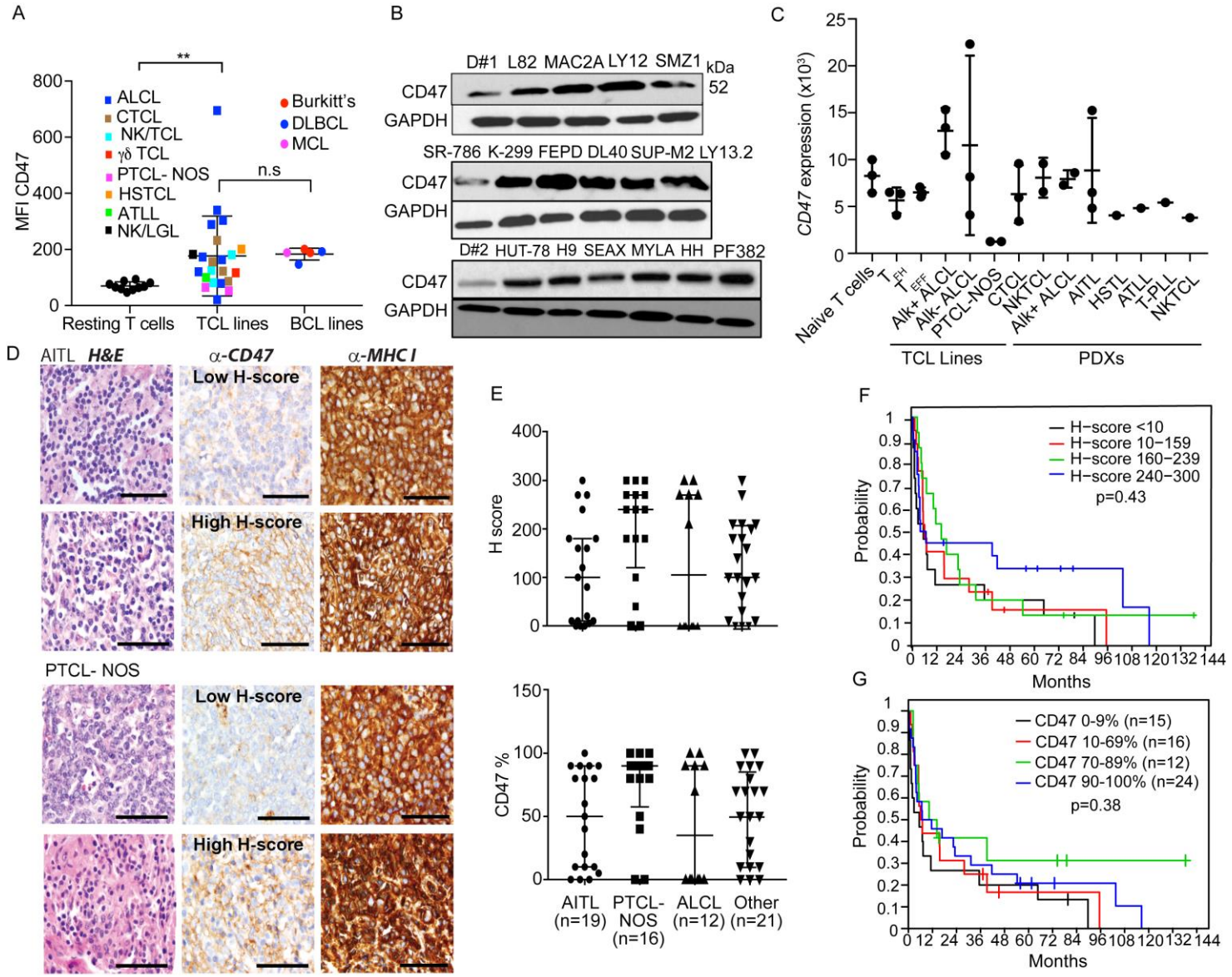
CD47 Expression Is Heterogeneous In TCL & Not Associated with With Poor Outcome



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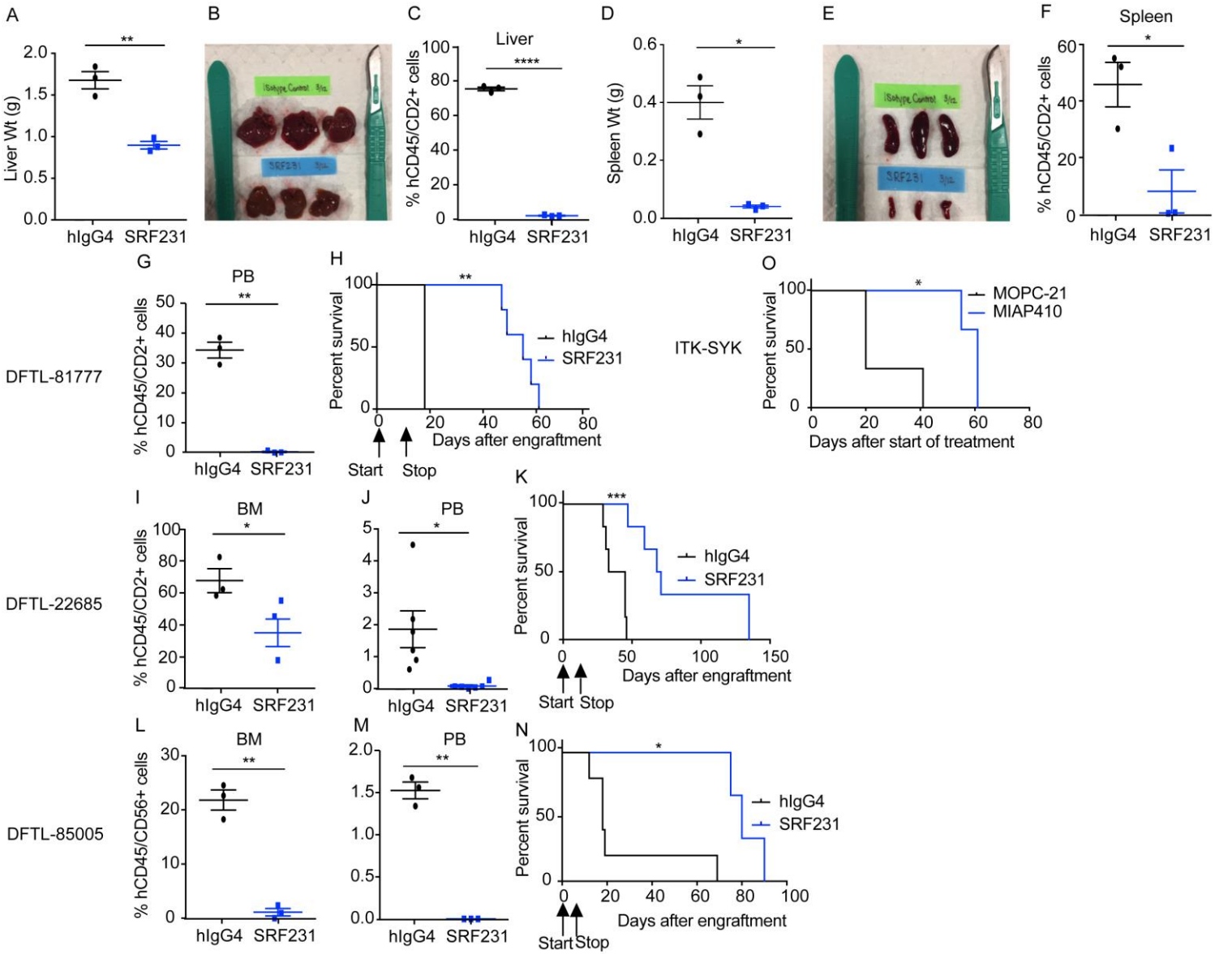
Jain S, et al. *Blood*. 2019; 134(17): 1430–1440

CD47 ANTAGONISTS PROLONG SURVIVAL IN DIVERSE MODELS OF TCL



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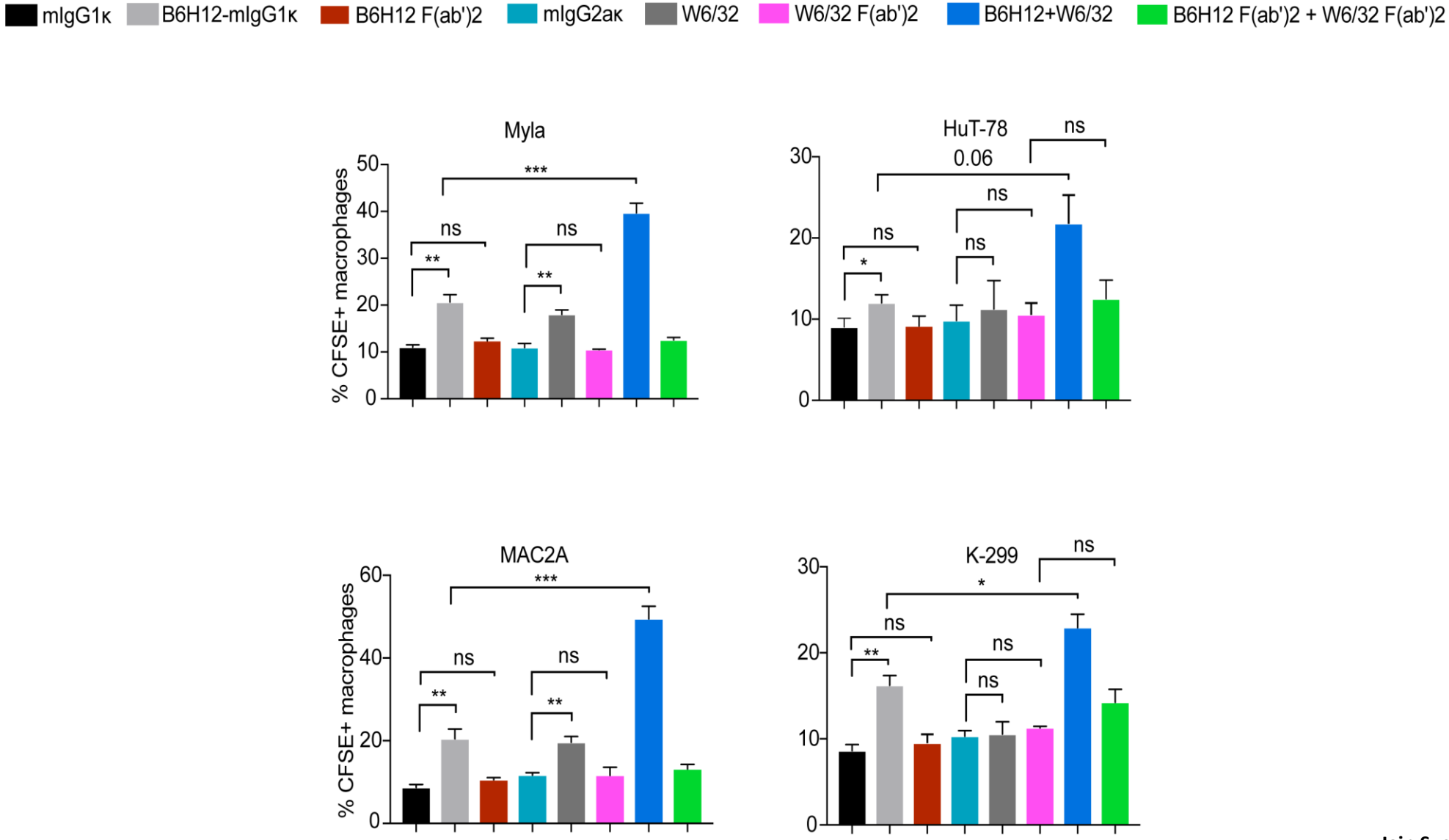
Jain S, et al. *Blood*. 2019; 134(17): 1430–1440

Fc-FcγR Interactions Are Critical To CD47 Antagonists



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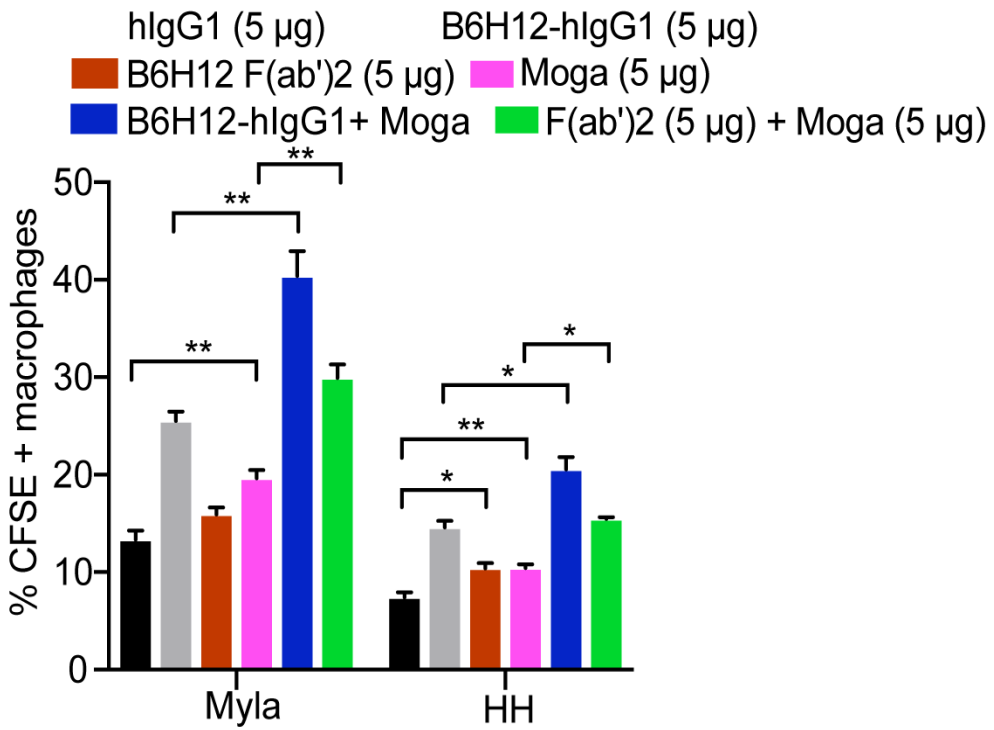
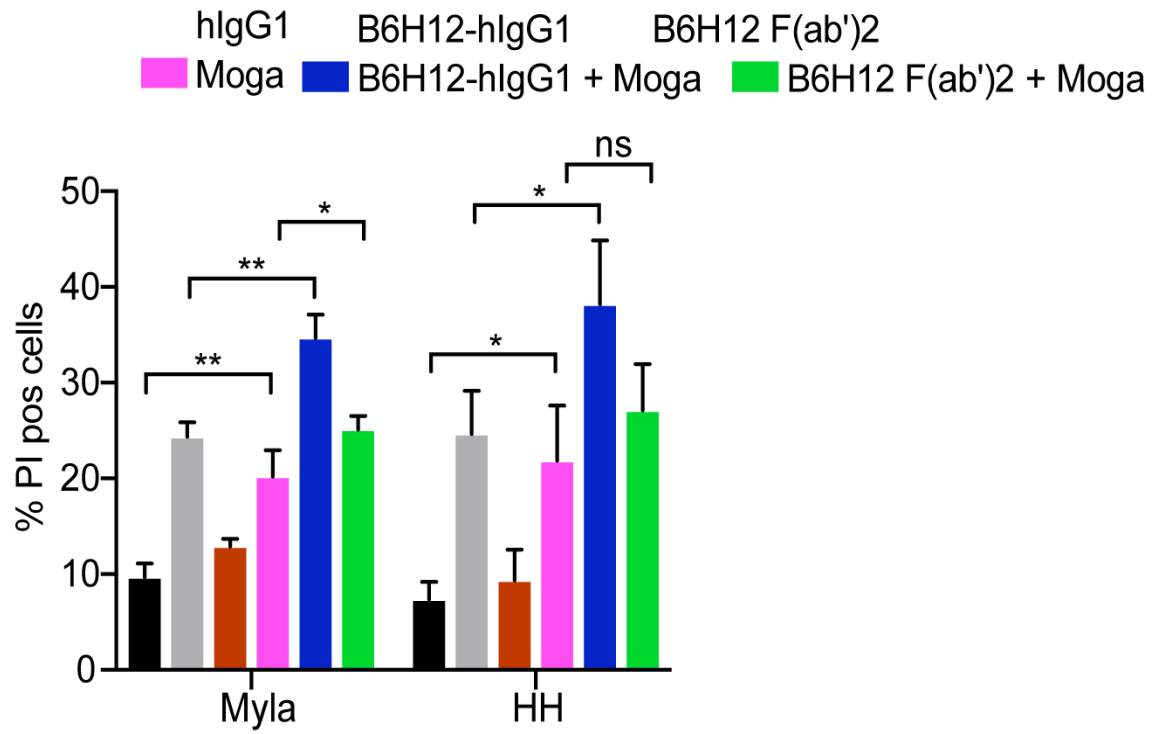
Jain S, et al. *Blood*. 2019; 134(17): 1430–1440

Mogamulizumab enhances efficacy of CD47 antagonists in CTCL

Antibody-dependent cellular phagocytosis



Antibody-dependent cellular cytotoxicity



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Jain S, et al. *Blood*. 2019; 134(17): 1430–1440

A Phase 1b/2 Study of Hu5F9-G4 (Magrolimab) in Combination with Mogamulizumab in Relapsed/Refractory Treated T-Cell Lymphoma
NCI Protocol # 10384

Michael Khodadoust, MD PhD
mkhodado@stanford.edu

NIH NATIONAL CANCER INSTITUTE

Slide Courtesy: M. Khodadoust

Clinical Data In T-cell Lymphomas

	TTI-621 (hIgG1-Fc)	TTI-622 (hIgG4-Fc)
Enrollment	Phase I (Completed)	Phase I
Route of Administration	IV weekly	IV weekly
Stage of Phase I	MTD: 0.2 mg/kg	Doses up to 12 mg/kg well tolerated and ongoing at 12 mg/kg
CTCL	29 (MF=24 & SS=5)	3
PTCL	12	3
Median no of prior therapies	4 (1-18)	3 (1-9)
Total Responses Evaluable (75) CTCL (29) PTCL (11)	 1 CR (SS), 5 PR (MF) 0 CR, 2 PR, 3 SD	 2 PR 1 PR
≥ Grade 3 Frequent AEs Thrombocytopenia Anemia Neutropenia	 20% 8% 8%	 1% 4%

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Ansell SM, et al. *Clin Cancer Res.* 2021

NEXT QUESTIONS

1. Dissect immune responses in TCL upon CD47 blockade

2. Define signatures that mediate resistance

3. Develop strategies to overcome resistance

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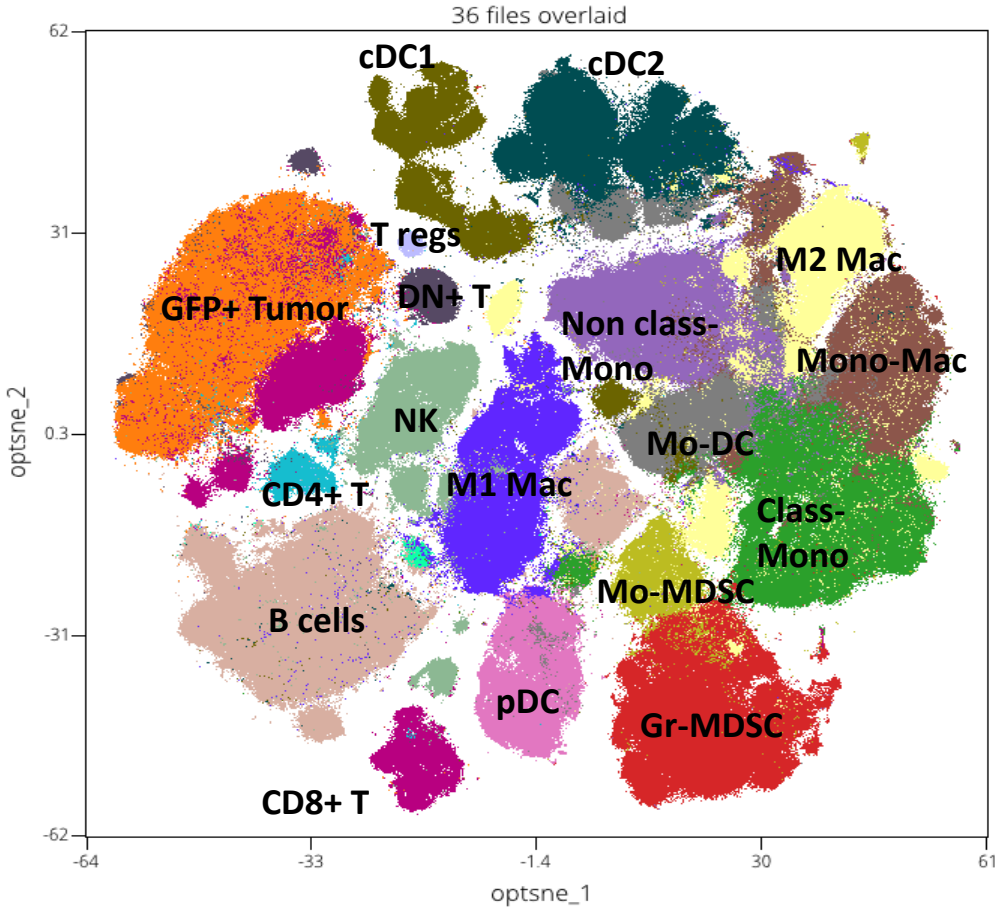
Dissecting Cd47-mediated Immune Responses In Transgenic Model Of Tcl At Single Cell Level

Model: ITK-SYK transgenic murine model of T-cell lymphoma (Courtesy, Jurgen Ruland)

CyTOF Panel, scRNA-seq and TCR-seq: 43 marker lineage-defining, myeloid centric activation and exhaustion murine panel



Mice randomized to treatment in one of the 3 groups:

1) Unengrafted C57BL/6 treated with anti-CD47 mAb

2) ITK-SYK TCL mice treated with anti-CD47 mAb

3) ITK-SYK TCL mice treated with isotype control

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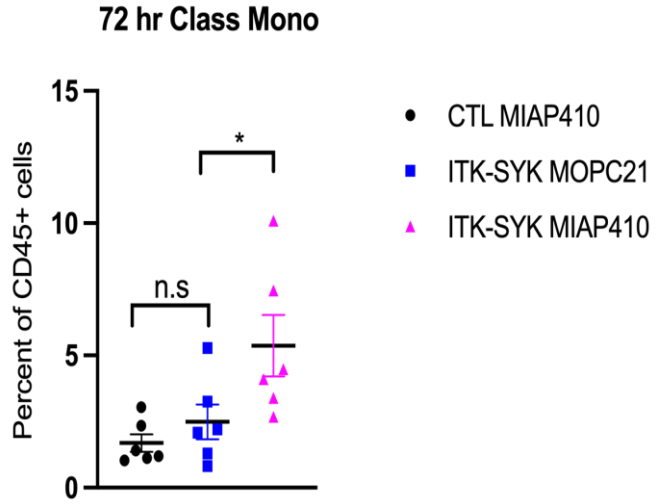
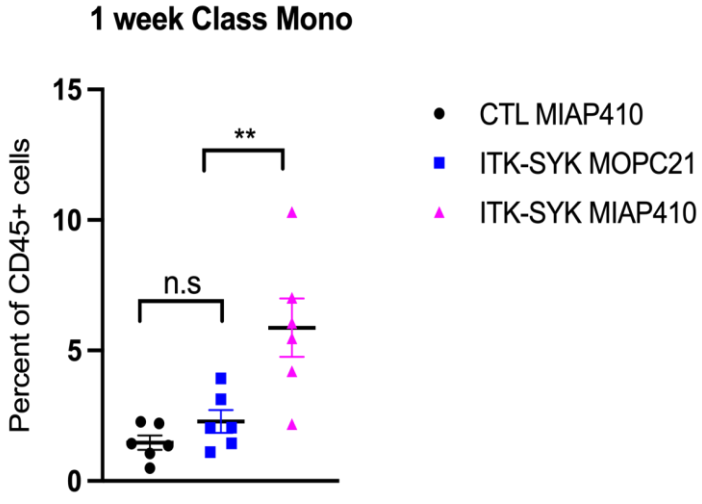
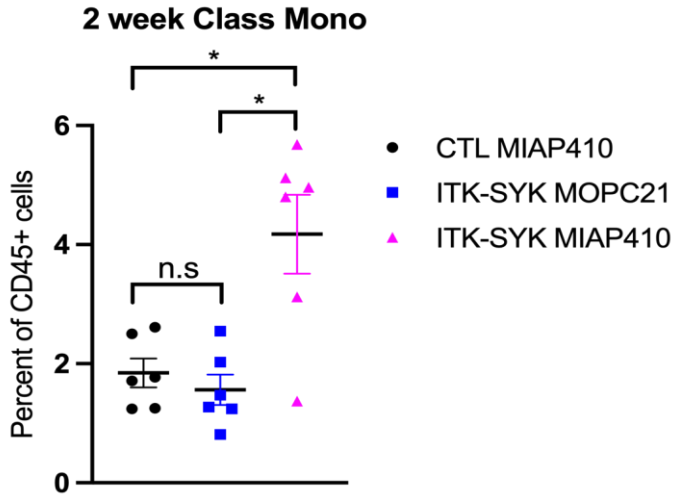
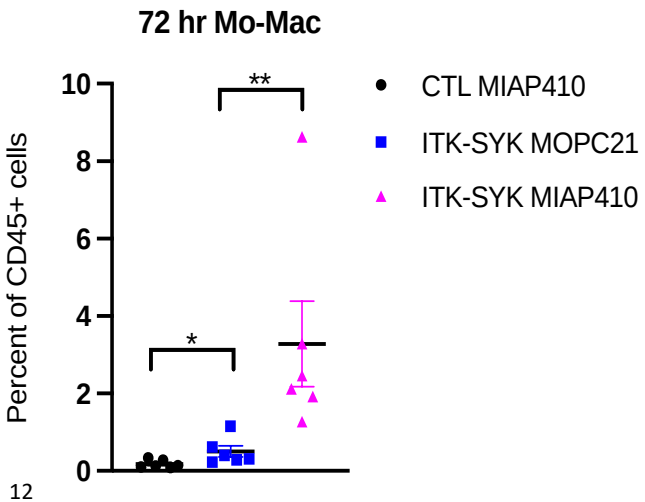
Unpublished Data

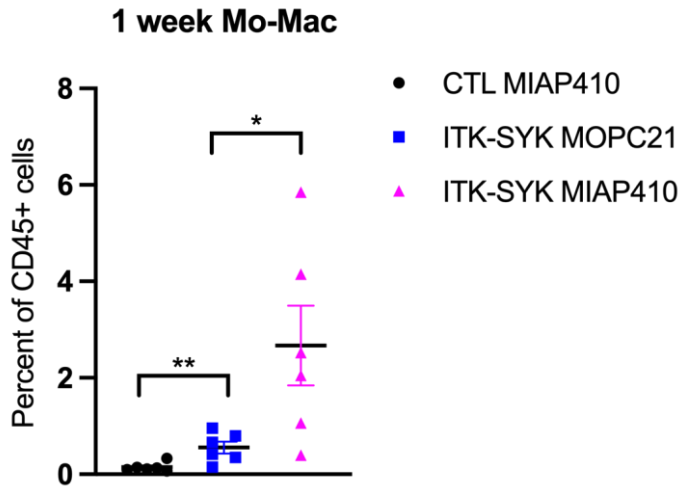
Anti-CD47 mAbs Increase Classical Monocytes (Mo) and Monocyte-derived Macrophages (Mo-Mac) in TME

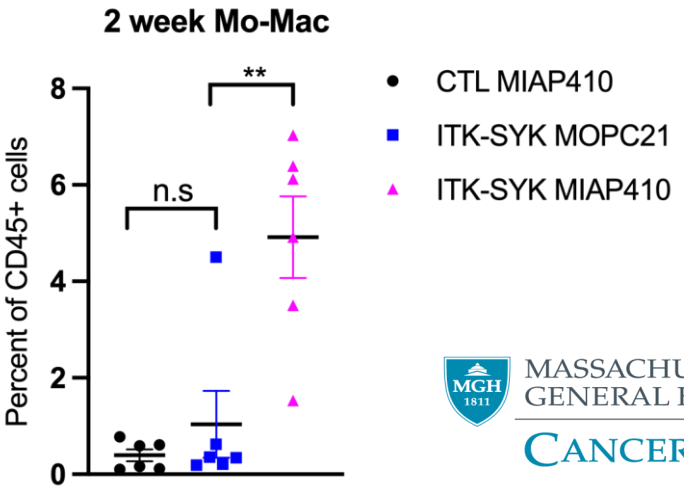












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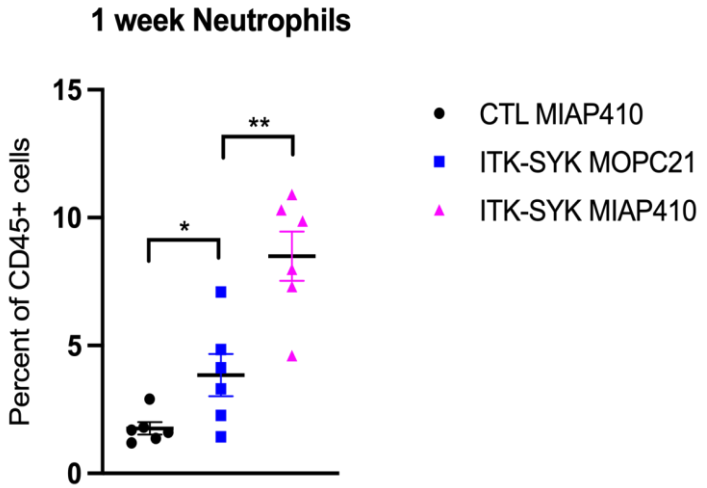
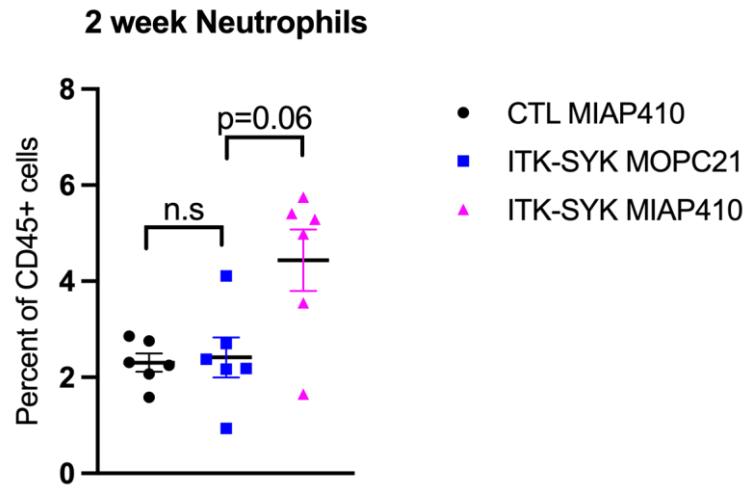
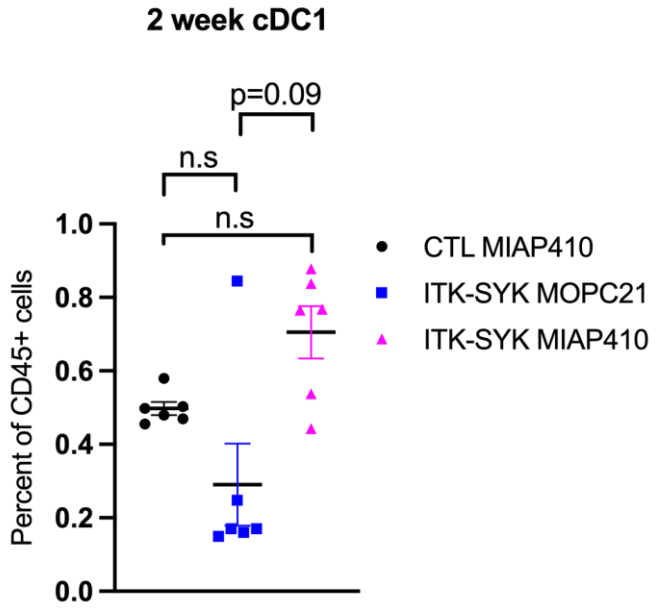
Anti-CD47 Antibodies Increase Neutrophils and Dendritic Cells in TME







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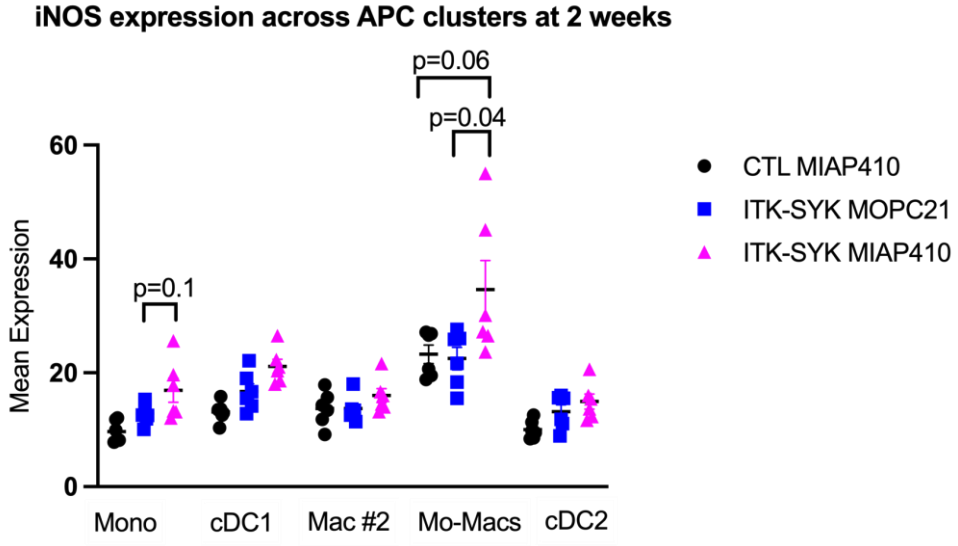
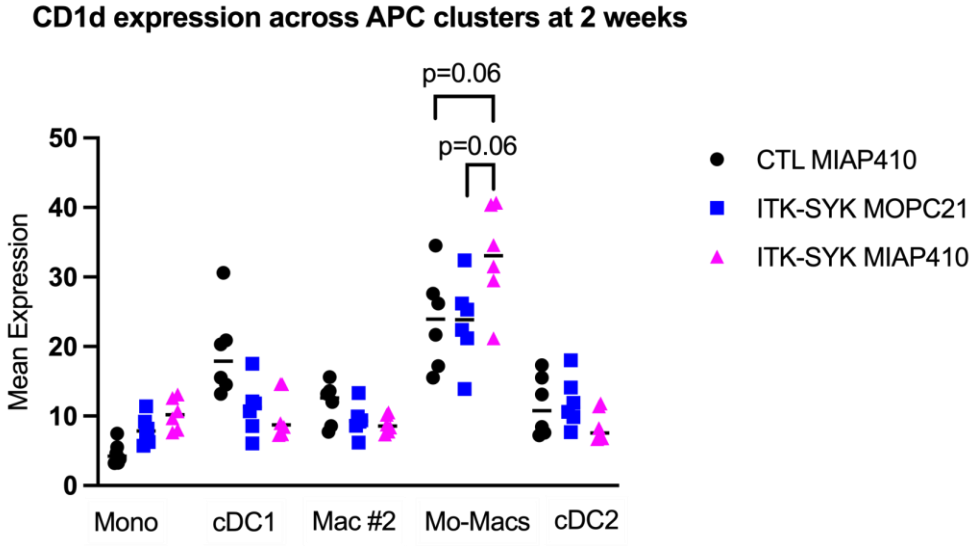
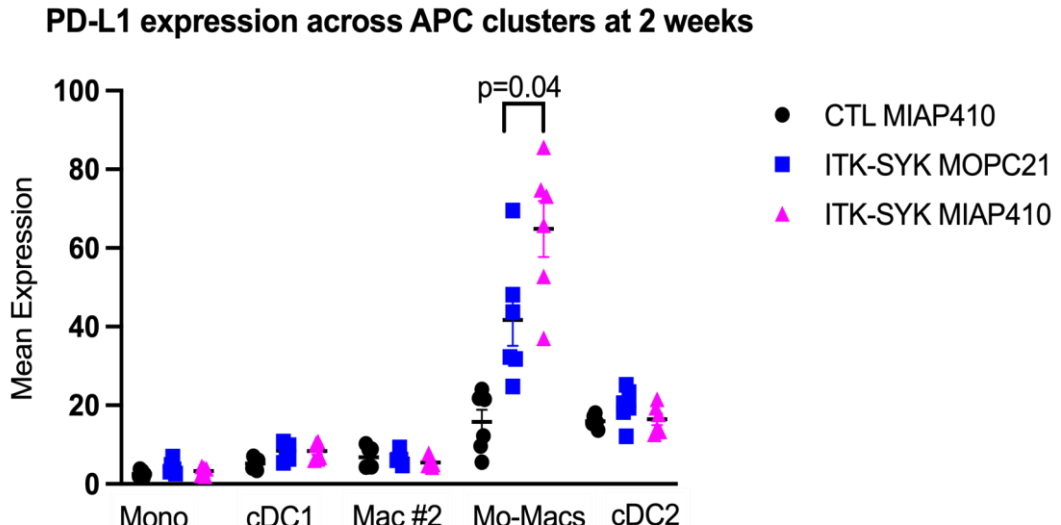
Anti-CD47 mAbs Increase iNOS, CD1d and PD-L1 Expression in Monocytes and Monocyte-derived Macrophages in TME







scRNA-seq and TCR-seq analysis is being completed

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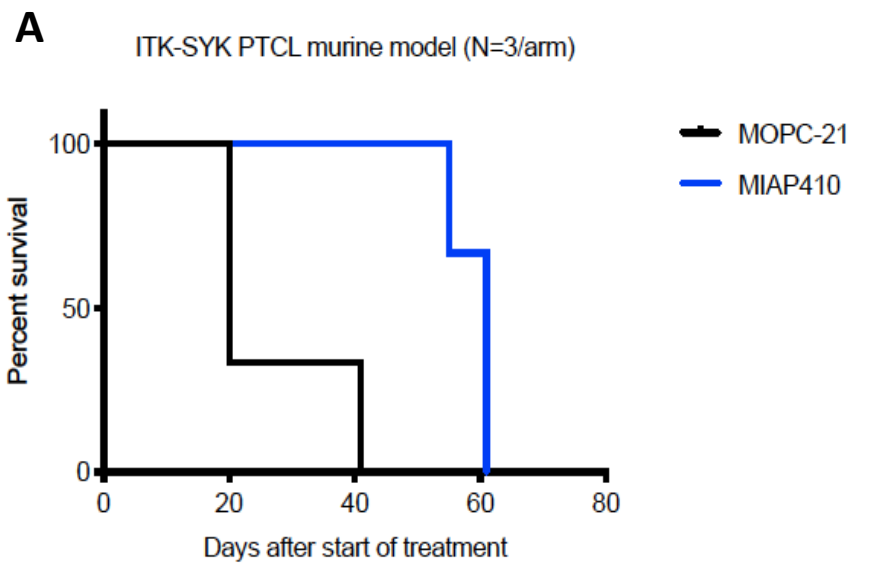
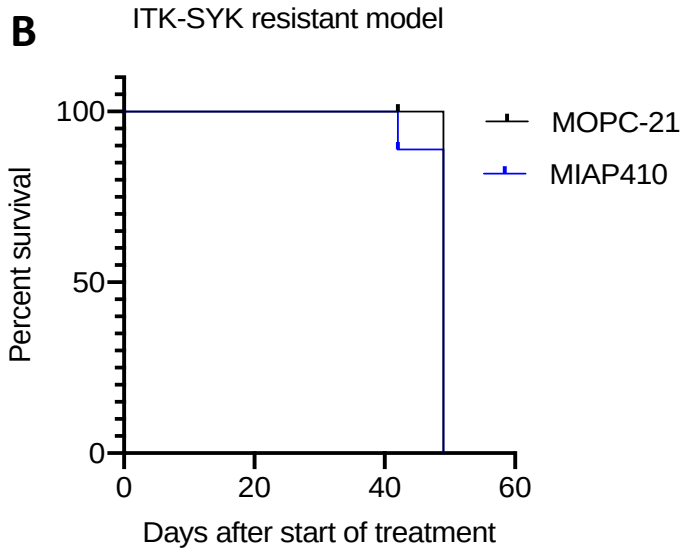
Generation Of Itk-syk Transgenic Tumors Resistant To Cd47 Antagonists

Tx initiated after 10 weeks of injection

Tx initiated after 4 weeks of injection





WES, ATAC-seq and Bulk RNA-seq analysis of resistant tumors underway

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Unpublished Data

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Preclinical and Clinical Role of SIRPant-M™ Macrophages in PTCL

(SIRPant Immunotherapeutics, Inc)

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KLRG1 is a novel target in patients with mature T and NK/T-cell lymphomas

- There is a desperate need to develop novel immunotherapy for TCLs
- **KLRG1**
  - Co-inhibitory, immune checkpoint, expressed on differentiated T and NK cells
  - KLRG1 KO mice alone demonstrated a significant decrease in tumor growth in melanoma and breast cancer models
  - Abcuro, Inc has generated first-in-class afucosylated anti-human KLRG1 mAbs

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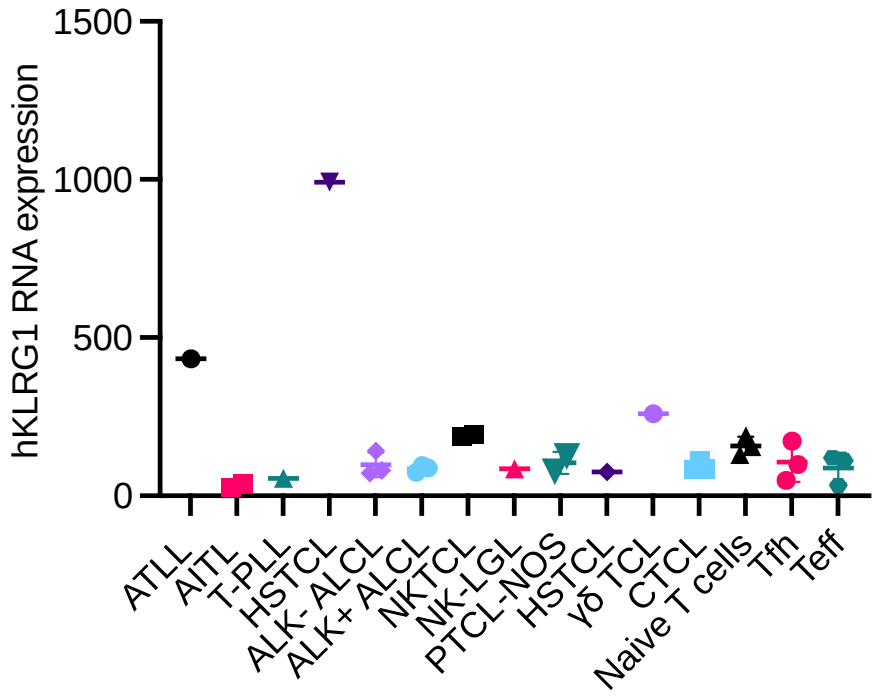
Greenberg et al., *Oncotarget,* 2019, Tata et al., *OncoImmunology*, 2021

Molecular Epidemiology of KLRG1 Across T-cell Lymphomas

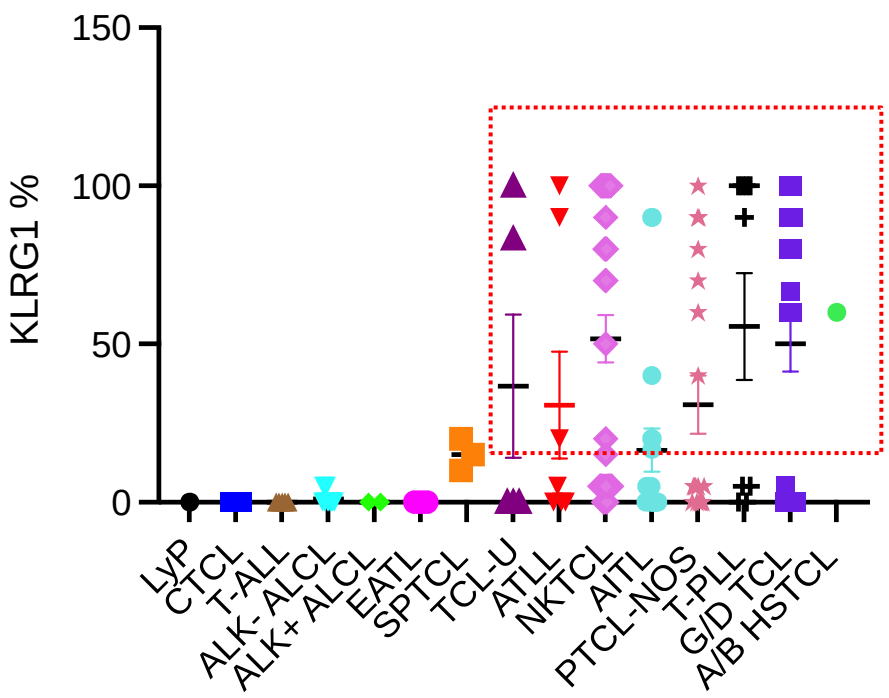
Differential hKLRG1 RNA expression among TCL cell lines, PDXs, and T cells

A.



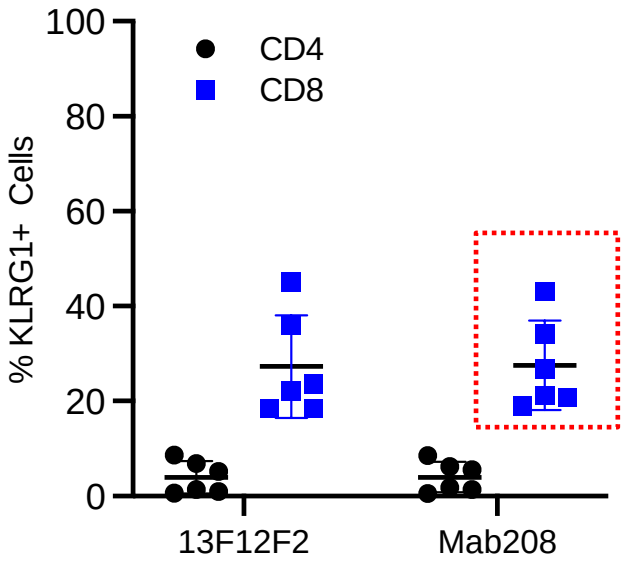
Differential surface KLRG1 by IHC in TCLs

B.



Comparable binding b.w Abcuro mAb and off-the-shelf clone

C.



Certain subtypes express greater percentage of KLRG1+ tumor cells than others

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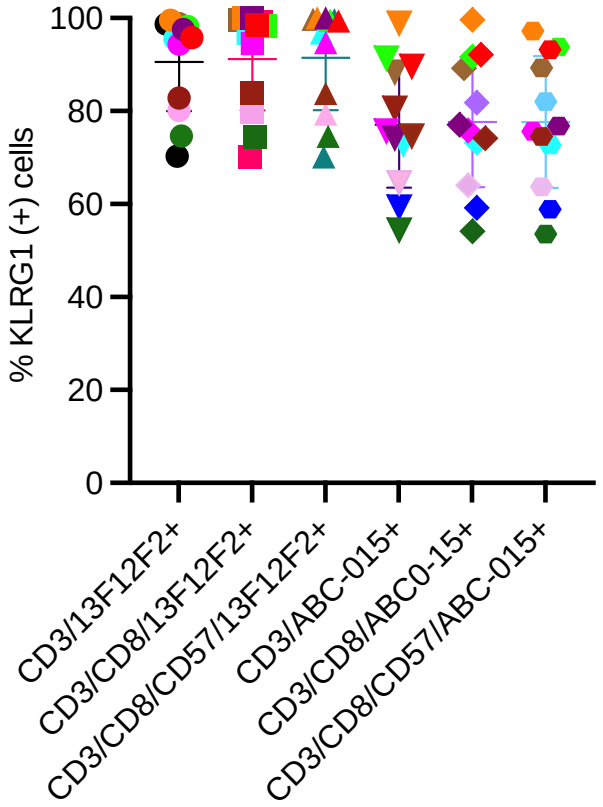
Ubiquitous expression of KLRG1 in T-LGLL and CLPD-NK

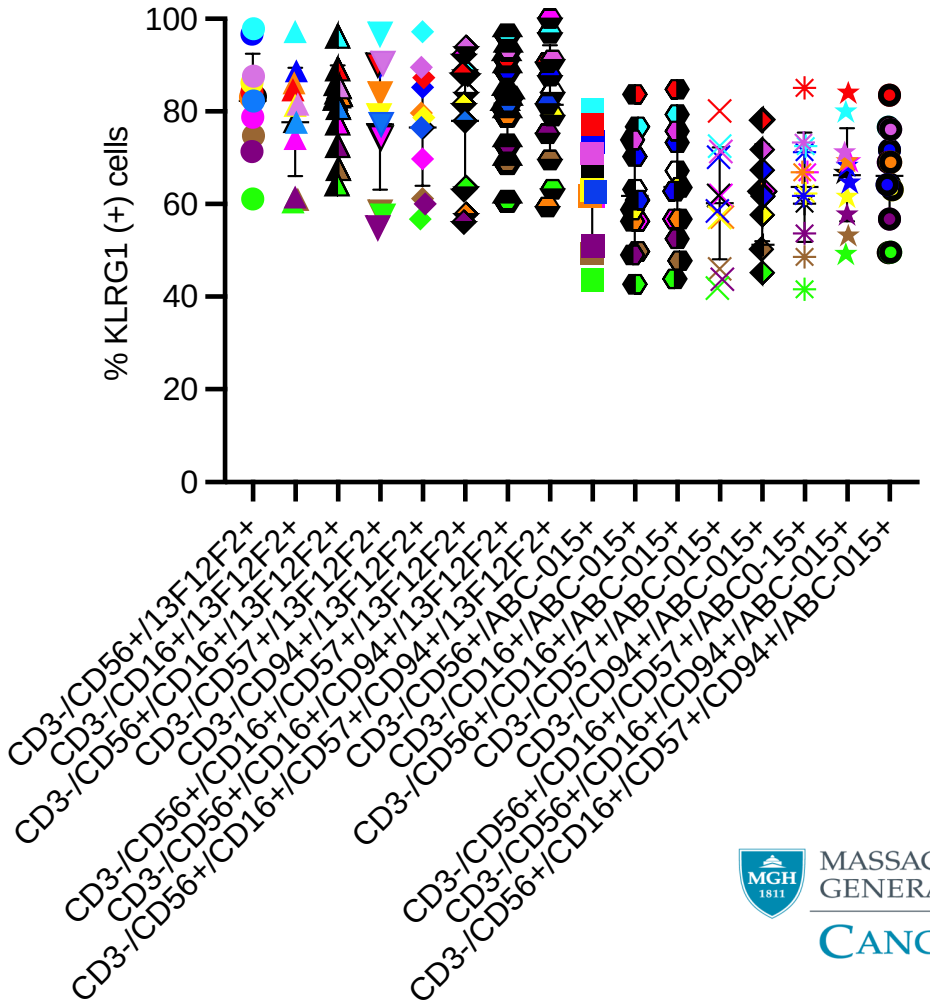
KLRG1 expression in T-LGLL cells

A



KLRG1 expression in CLPD-NK cells

B



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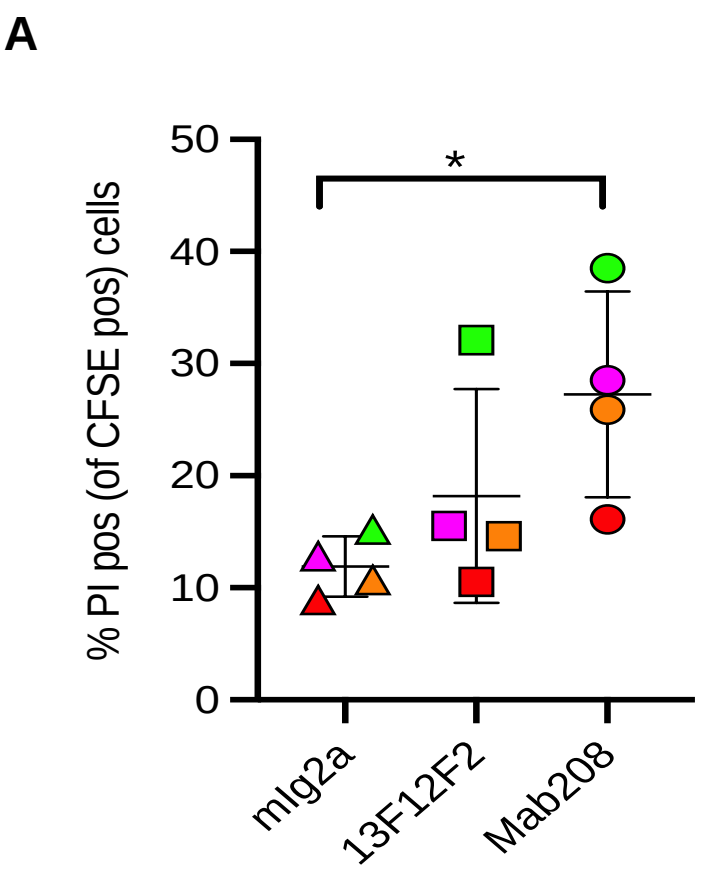
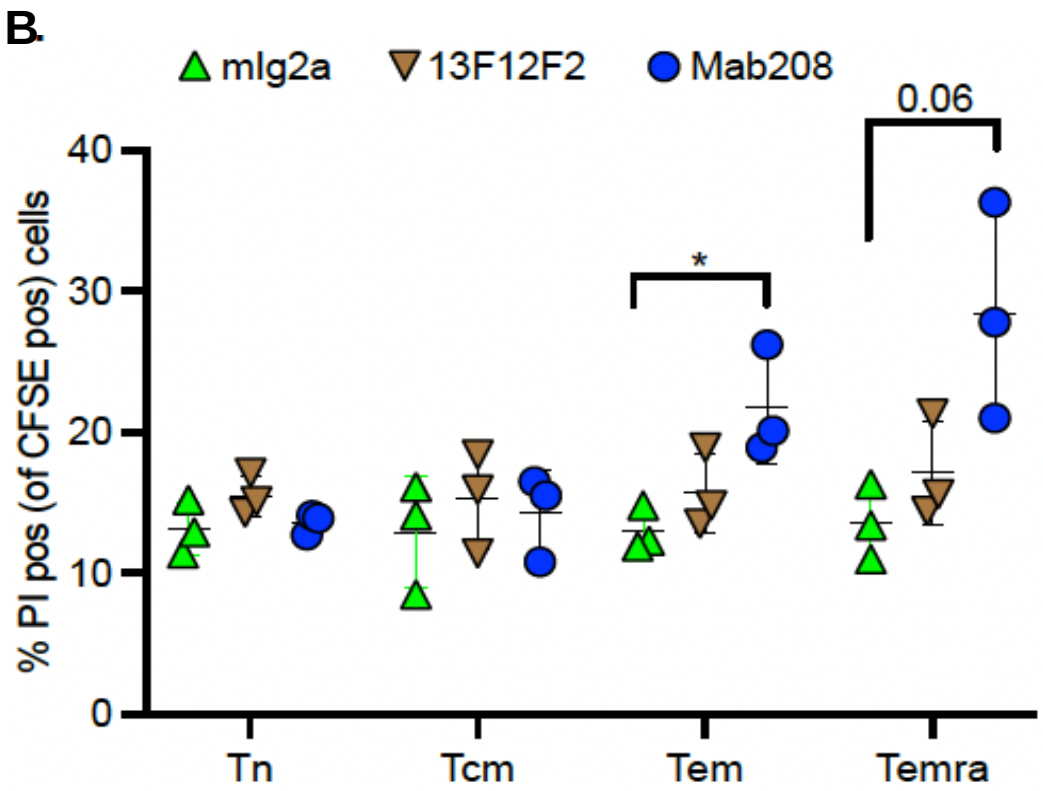
KLRG1 depleting mAbs selectively deplete KLRG1^{+} TCL cells and spare KLRG1^{-} naive and memory T cells

ADCC of KLRG1+ T-LGLL cells



ADCC of KLRG1+ TEM and TEMRA cells



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Multicenter Phase I/II trial of ABC008 (anti-human KLRG1 mAb) in Subjects with T-LGLL launched

ABC008-LGL-101

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ASH oral presentation Abstract #937: Monday 4.30-6

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Incorporation of machine learning tools to predict survival & treatment outcomes for patients with R/R PTCL and NK/TCL: International Study

Leora S Boussi, MD , Min Jung Koh, MS , Xinyi Han, BS , Luke Peng , Min Ji Koh, BA , Ijeoma Eche, PhD , Josie Germain Ford, BS , Shambhavi Singh, MD, PhD , Eliana Miranda, MEd, PhD , Carlos S. Chiattone, MD, PhD , Carrie Van Der Weyden, MBBS (Hons), FRACP, FRCPA , Henry Miles Prince, MBBS (Hons), MD, FRACP, FRCPA, AFRCMA, MACD, FAHMS , Francine M. Foss, MD , Sang Eun Yoon, MD , Won-Seog Kim, MD, PhD , Girisha Panchoo, MBBS , Estelle Verburgh, MBChB, M Med Int, FCPSA, PhD , Jackielyn Cuenca Alturas, BA , Mubarak Al-mansour, MD , Martina Manni, PhD , Massimo Federico, MD , Maria Elena Cabrera, MD , Beatrice Casadei, MD, PhD , Pier Luigi Zinzani, MD, PhD , Noriaki Yoshida, MD, PhD , Takeshi Okatani, MD , Mwanasha H. Merrill, MD , Eric D Jacobsen, MD , Owen A. O'Connor, MD, PhD , Enrica Marchi, MD, PhD and Salvia Jain, MD

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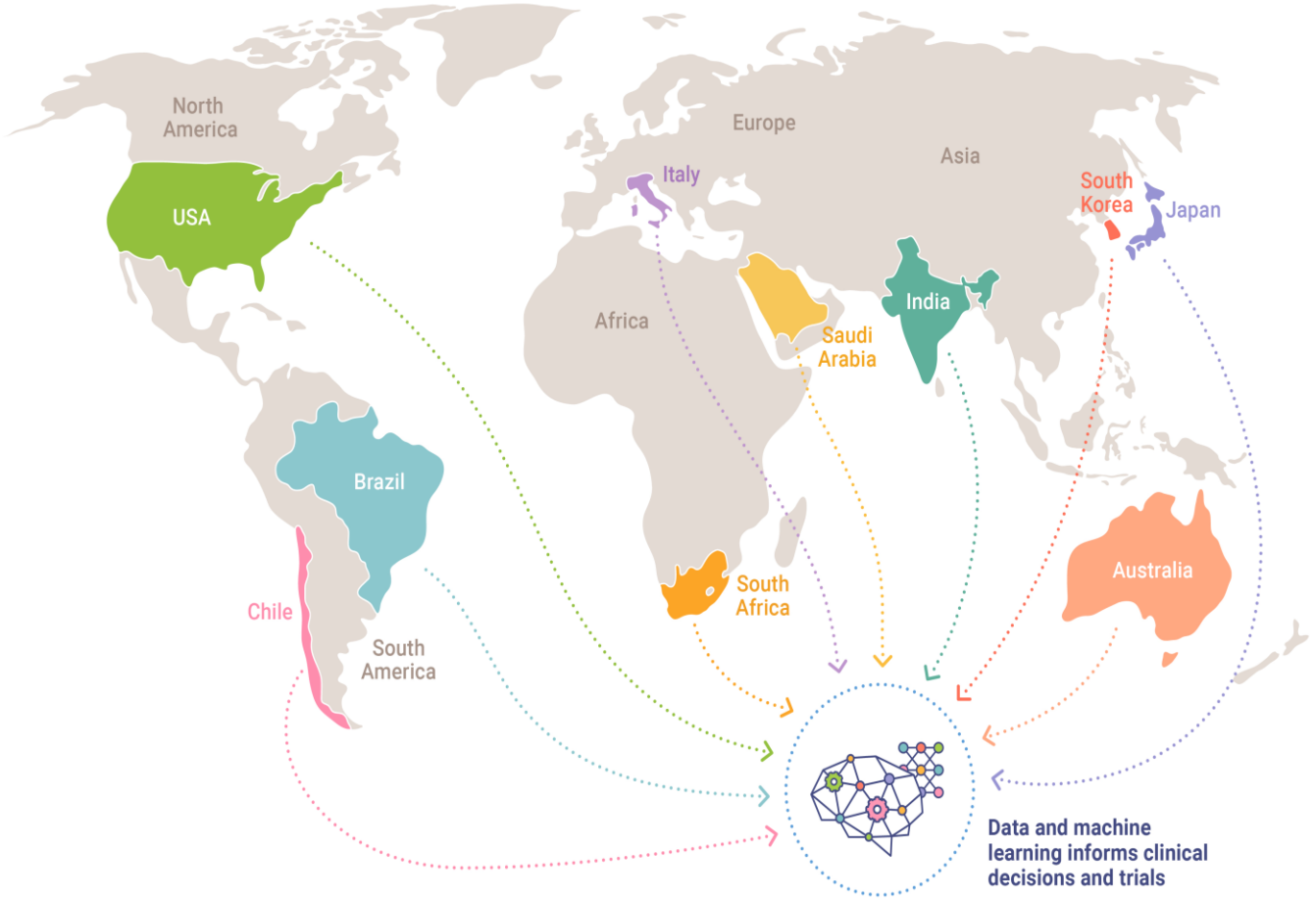
ASH presentation Abstract #4931: Monday 6-8 pm

Global Retrospective Cohort of R/R PTCL

- Retrospective cohort study with exhaustive treatment details for 1200 patients with R/R PTCL (650 enrolled)
- Participating countries: USA, Brazil, South Africa, Italy, Saudi Arabia, India, Australia, South Korea, and Japan
- Primary objective:
  - Compare single novel agents to chemotherapy
  - Utilize machine learning tools like synthetic intervention to estimate RR and survival



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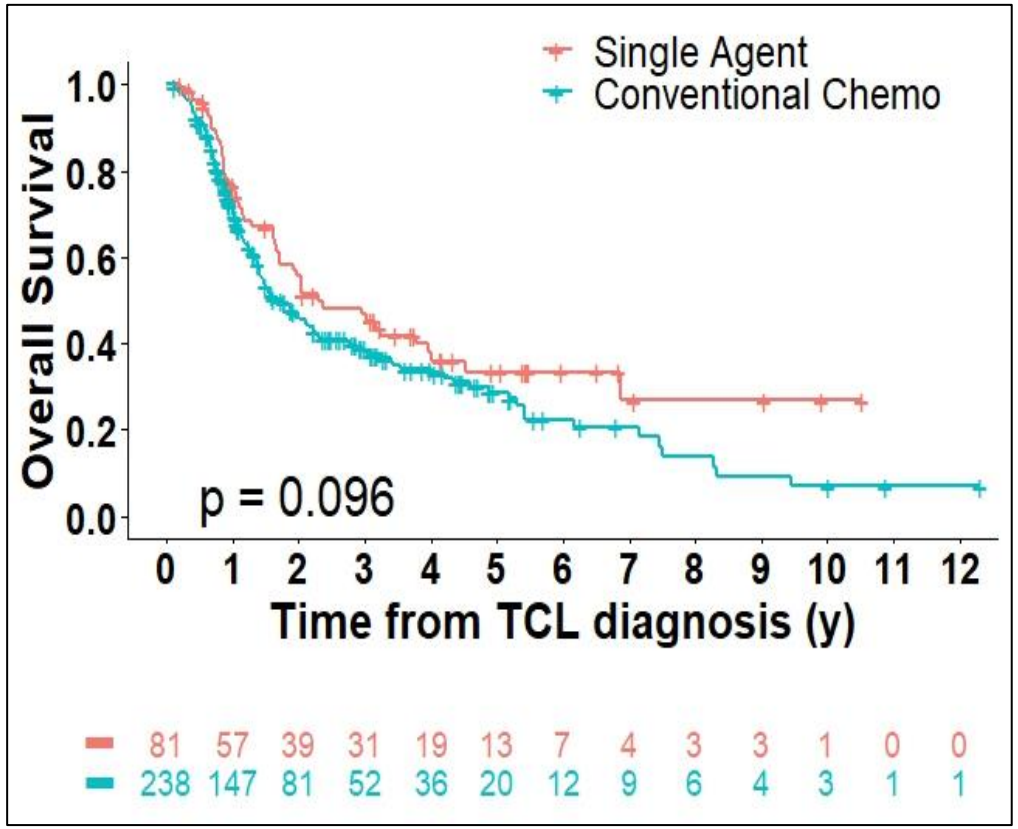
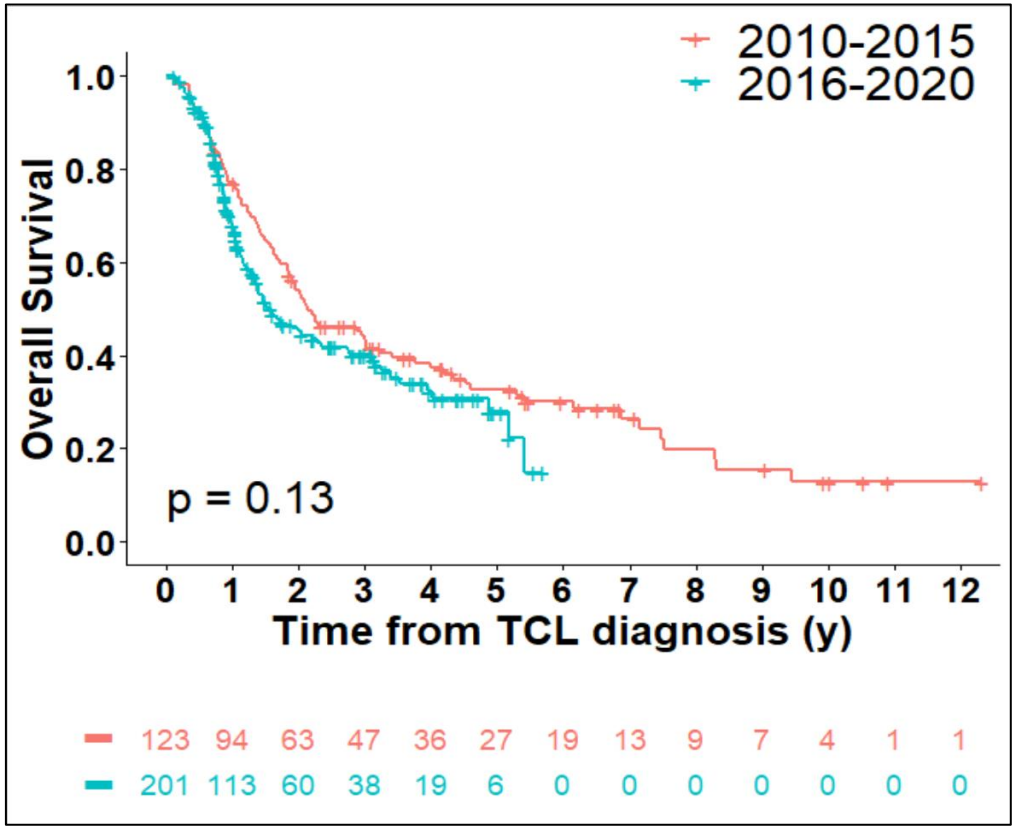
Survival analysis – Kaplan-Meier

Conventional chemo *vs* single agents



Per Calendar Period



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Survival analysis: Cox regression, Random forest, Synthetic Intervention

COX REGRESSION SURVIVAL ANALYSIS						
HR (P value)	Univariate	Multivariate				
Treatment type (ref: single agent) Conventional chemotherapy Conventional chemotherapy plus single agent	 1.20 (0.35) 0.55 (0.55)		 1.18 (0.39) 0.51 (0.51)	 1.04 (0.85) 0.62 (0.64)	 1.02 (0.94) 0.57 (0.58)	 1.12 (0.63) 0.71 (0.74)
Histological subtype (Ord: ALCL, ENKTL, AITL, PTCL-NOS, EATL, HSTCL, ATLL)#	1.16 (<0.005)	1.11 (0.03)	1.14 (0.01)		1.12 (0.03)	1.11 (0.04)
PIT score at diagnosis (Ord: 0, 1,2, ≥3)#	1.47 (<0.005)	1.49 (<0.005)	1.48 (<0.005)	1.50 (<0.005)	1.48 (<0.005)	1.48 (<0.005)
Country (ref: Australia) USA (Complete) Brazil South Korea South Africa Saudi Arabia	 1.15 (0.64) 1.32 (0.33) 0.58 (0.12) 3.46 (0.23) 0.59 (0.48)					 2.26 (0.03) 1.54 (0.17) 0.95 (0.89) 4.92 (0.13) 0.62 (0.53)
Diagnosed period (ref: 2010-2015) 2016-2020	 1.00 (0.99)				 0.94 (0.74)	 1.35 (0.31)
Response to 1st treatment (Ord: Complete response, partial response, stable disease, progressive disease)#	1.26 (<0.005)	1.25 (<0.005)		1.27 (<0.005)	1.25 (<0.005)	1.26 (<0.005)
AIC		1317.28	1328.99	1323.73	1322.80	1321.87
Concordance index		0.69	0.62	0.68	0.68	0.69
RANDOM SURVIVAL FOREST ANALYSIS						
Concordance index		0.70	0.64	0.68	0.70	0.70

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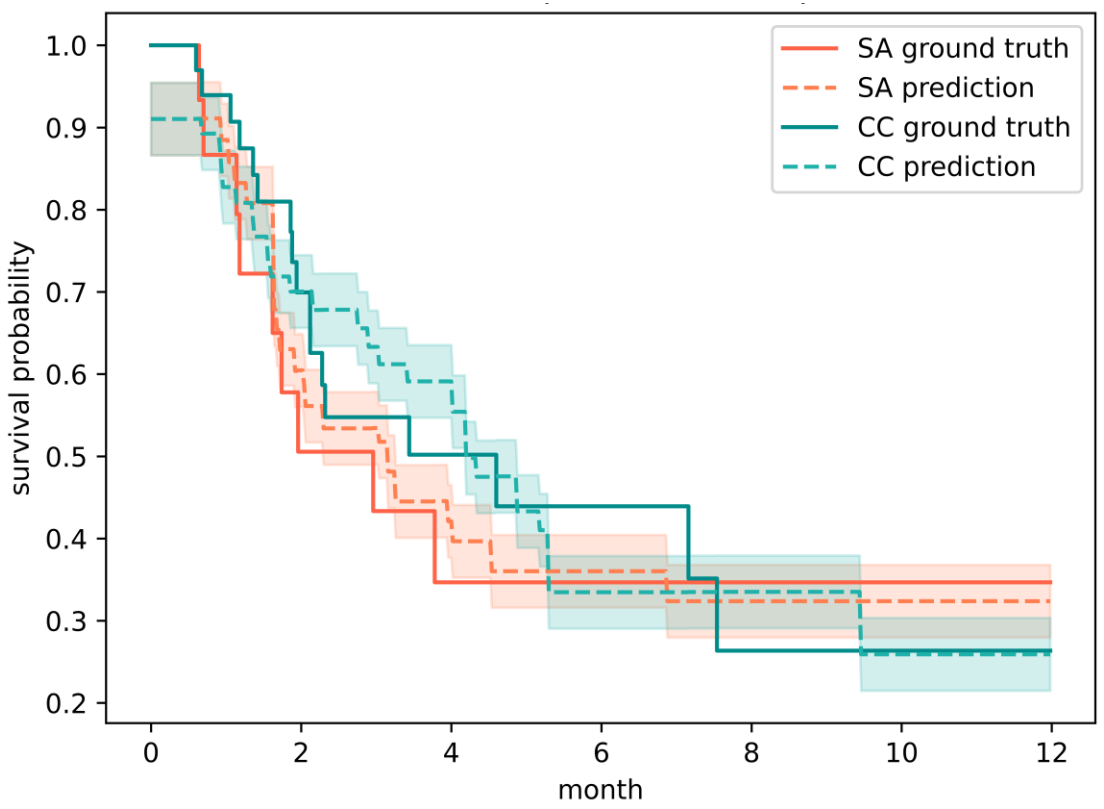
Synthetic Intervention predicts survival probability to various treatments with > 90% accuracy with as little as 20 patients

PTCL-NOS (15 SA and 33 CC)

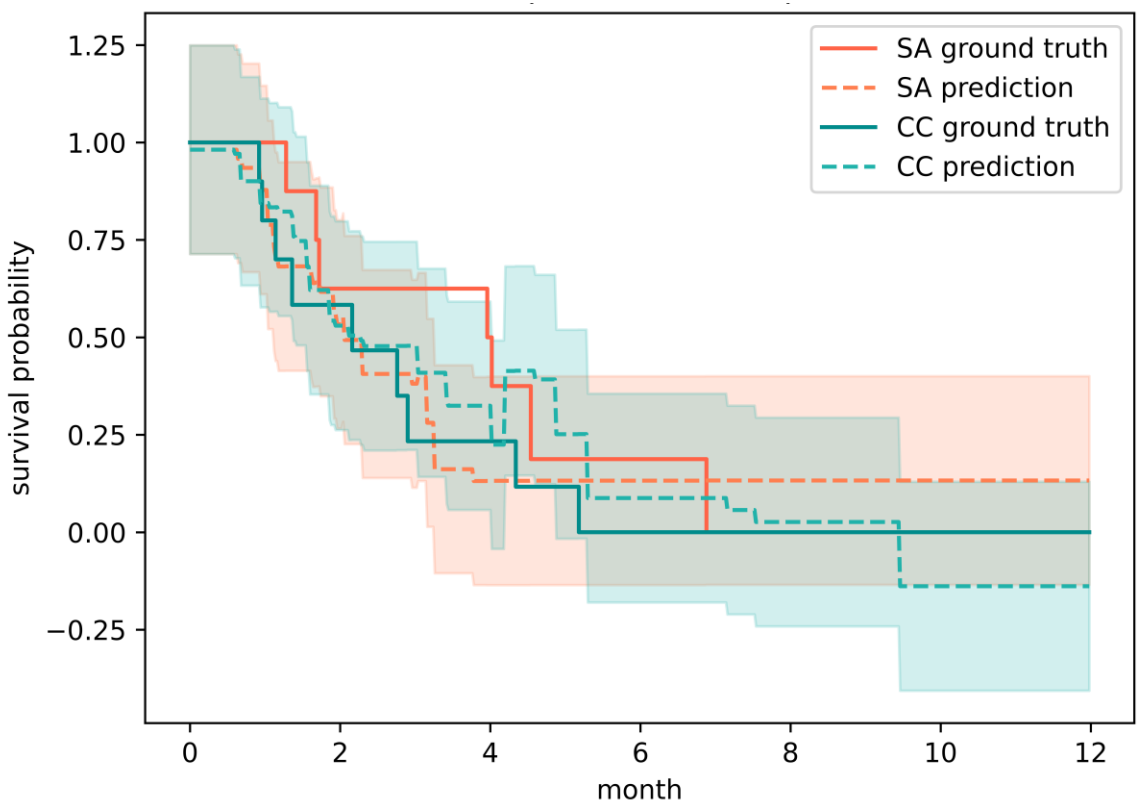
A



R^2 = 0.949 (SA)
0.900 (CC)

AITL (9 SA and 11 CC)

B



R^2 = 0.75 (SA)
0.85 (CC)

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Francine Foss
Steven Horwitz
Min Jung Koh
Luke Peng
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Miles Prince
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Abcuro, Inc
Acrotech Biopharma, Inc
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MGH Lymphoma Research

Thank you team!!!!!

We are looking for graduate students and postdoctoral fellows and no one is left behind!

salvia.jain@mgh.harvard.edu

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