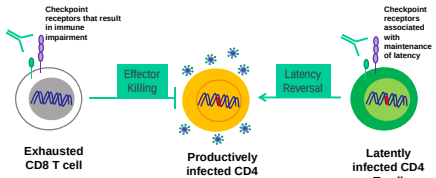
316 - A Bispecific Approach for Targeting Negative Checkpoint Receptors in HIV-1 Latency

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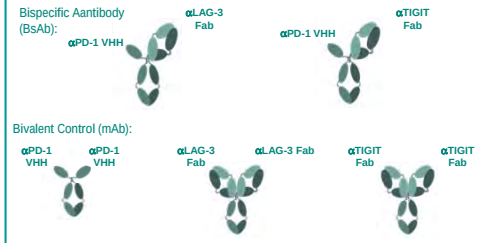
MERCK

Checkpoint Receptors for HIV CURE



Dual blockade of PD-1/Lag3 or PD-1/TIGIT with Bispecifics has therapeutic potential in HIV treatment

Dual-Targeting with Bispecific Antibodies



In addition: One-Armed Abs (OAA) and RSV Isotype Control

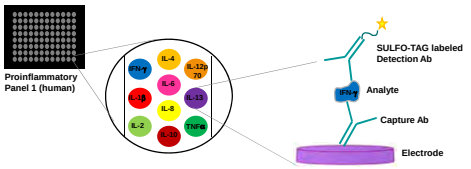
Patient Samples, Antibody Screening

SCOPE Cohort (UCSF): HIV infected donors

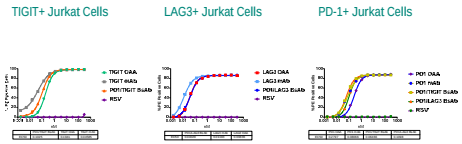
- Clinic based cohort with over 1500 participants
- ART-Suppressed Donors (<50 copies/mL)
- Low CD4 (<350)
- High CD4 (>350)
- Viremic Donors (>50 copies/mL)
- Exclusion criteria: HCV+ co-infection
- Demographic/Clinical data: Age, Gender, CD4 and CD8 count, Viral load, +/-ART, Date of diagnosis
- Field sites: HIV/AIDS clinic of SFGH and SFVAMC
- Whole blood, cryopreserved PBMCs, or leukapheresis

Stanford Blood Bank uninfected donors

Isolate PBMCs from HIV-infected donors, stimulate with Gag-peptide pool and Abs (100nM) for 72h

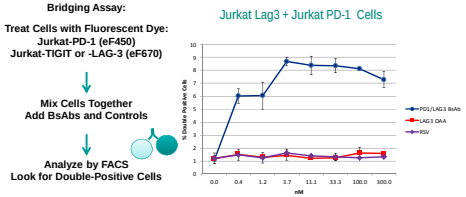


Dose Response Antibody Binding Cells



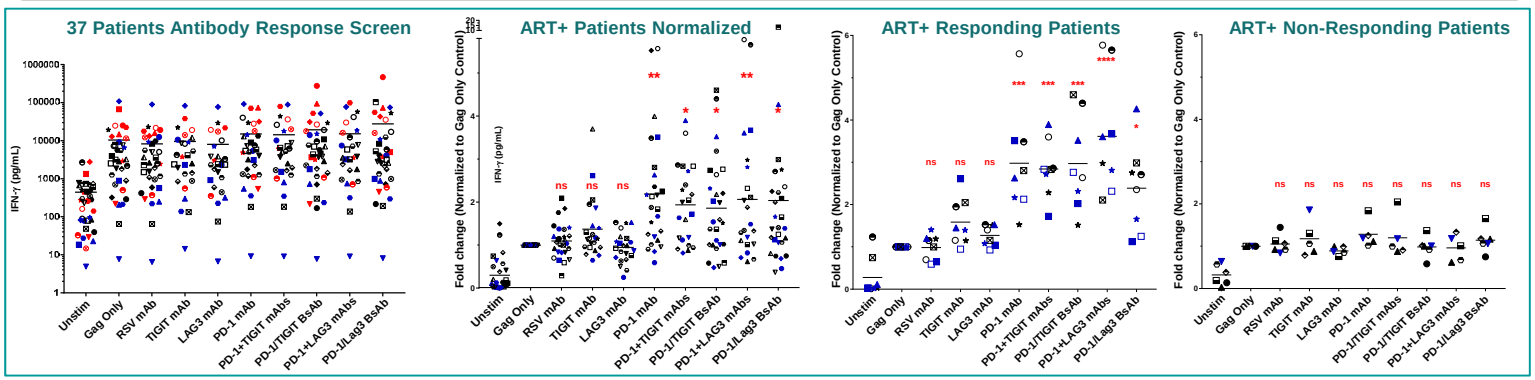
Similar EC50s for Bispecifics Compared to Parental Bivalent

Antibodies Trans-Binding to Cells



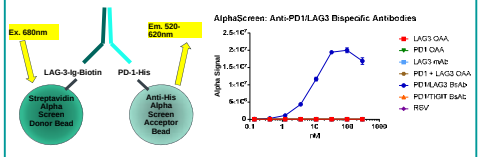
Bispecifics Demonstrates Trans-binding of Target Expressing Cells

IFNγ Production in HIV+ PBMCs Following Treatment With Single, Combo and Bispecific Antibodies



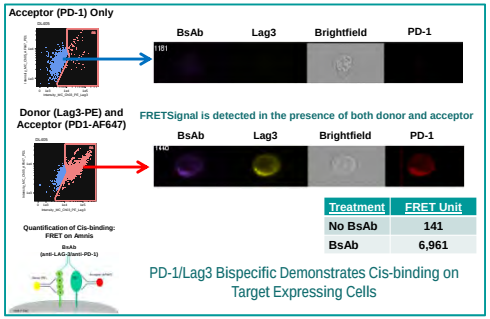
Antibodies Trans-Binding to Antigens

AlphaScreen Assay to Measure Trans-binding



Bispecific Antibodies Demonstrate Simultaneous Engagement of Antigens

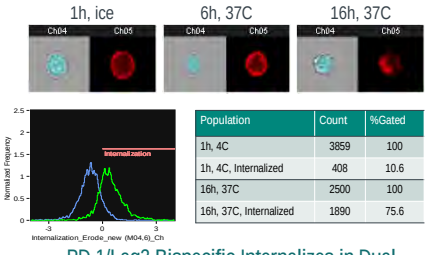
Primary Cells Cis-Binding Assay



Treatment	FRET Unit
No BsAb	141
BsAb	6,961

PD-1/Lag3 Bispecific Demonstrates Cis-binding on Target Expressing Cells

Target(s) Cell Line Internalization Assay



Population	Count	%Gated
1h, 4C	3859	100
1h, 4C, Internalized	408	10.6
16h, 37C	2500	100
16h, 37C, Internalized	1890	75.6

PD-1/Lag3 Bispecific Internalizes in Dual Target Expressing Cell Line

Results, Conclusions, Implications

Results:

Checkpoint inhibitor bispecific antibodies are able to bind targets similar to parental antibodies, additionally they are capable of binding 2 targets simultaneously in cis and trans modes and are capable of internalization.

These antibodies can enhance HIV-antigen stimulated cytokine production in PBMCs isolated from HIV infected patients.

About 1 in 3 of all subjects screened demonstrated increased IFNγ production in response to ex-vivo checkpoint inhibitor antibody treatment versus controls.

Increased IFNγ ex-vivo response was primarily driven by anti-PD-1 and in some patients increased with combination and bispecific antibody treatment compared to controls.

Conclusion:

Checkpoint inhibitor bispecifics can enhance responses to HIV antigens in ex-vivo patient derived PBMC's.

Implications:

This work provides a greater overall understanding of bispecific antibody mechanisms and efficacy for immune checkpoint receptor targeting approaches in HIV infection.

Further studies will probe the phenotypic and molecular signatures of the bispecific antibody treatment in the responding vs non-responding patients.