LAG-3 and PD-1 blocking synergizes to restore invariant Natural Killer T Cell Functionality: Implications for HIV treatment

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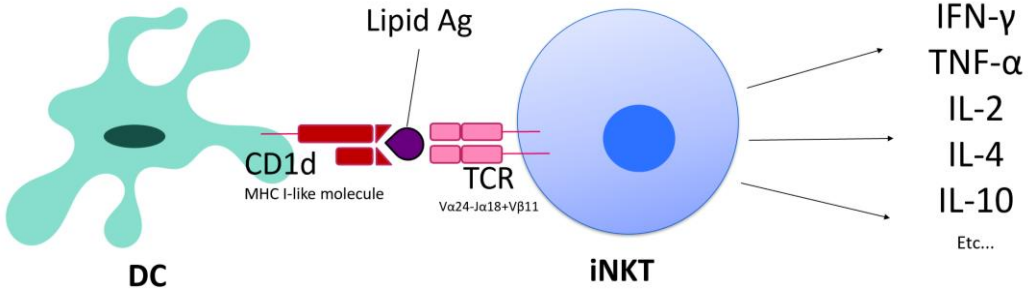
Background

A) One hallmark of chronic HIV infection is immune system exhaustion

- ❑ *Loss of immune system effectiveness*
- ❑ Cellular Immune Exhaustion Markers = **LAG-3, PD-1, etc…**

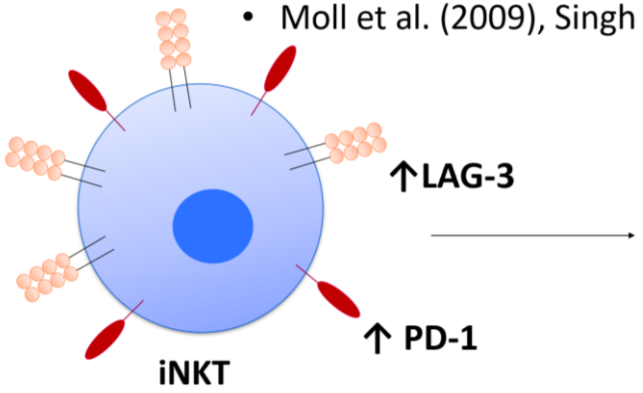
B) Innate Natural Killer T (iNKT) cells are powerful immune cells



- ❑ iNKT cells are quick + critical responders: link innate & adaptive immunity

C) iNKT immune cells are exhausted and dysfunctional in chronic HIV infection

- ❑ **↑ PD-1 in chronic HIV infection, correlated with ↓ iNKT cell functionality**
  - Moll et al. (2009), Singh et al. (2018)



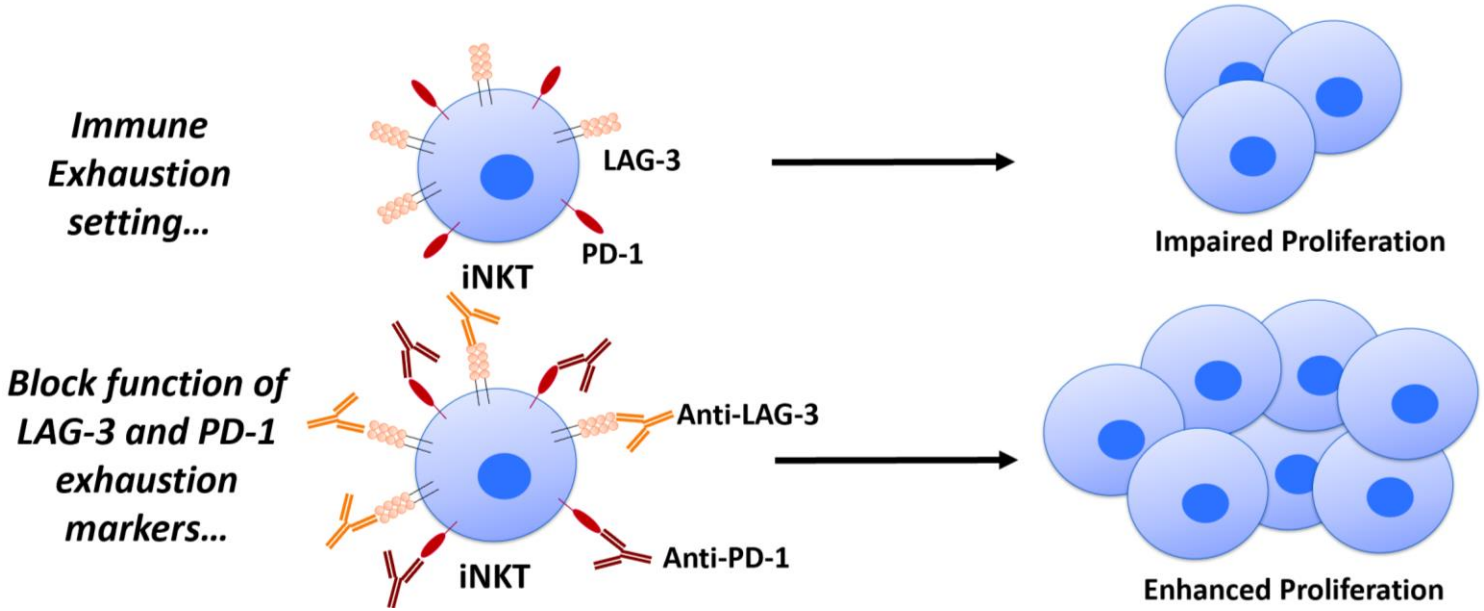
In chronic HIV infection, iNKT cell dysfunction has been correlated with dysfunctional T and NK cell responses

- ❑ **Our lab has shown: ↑LAG-3 correlates with ↓ iNKT cell functionality**

Q: Can we reverse iNKT cell immune exhaustion to restore cellular functionality in chronic HIV infection?

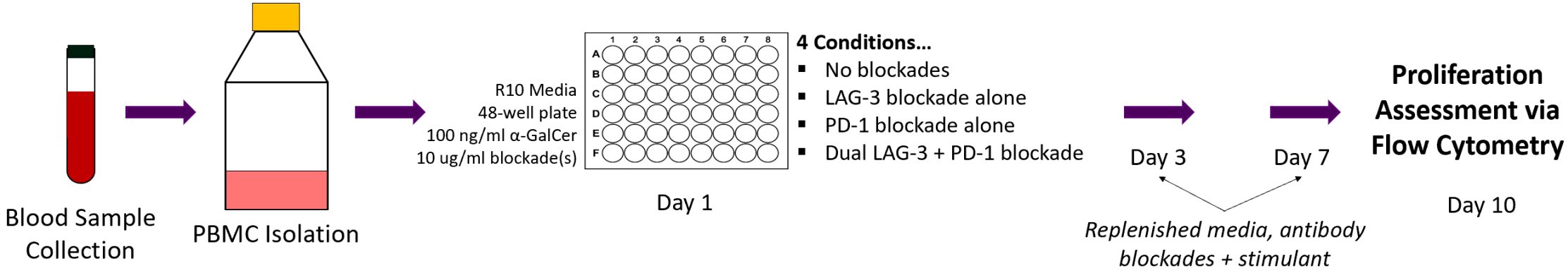
Hypothesis

We hypothesize that blocking LAG-3 and/or PD-1 exhaustion markers via an antibody blockade system will enhance cell function* in vitro *by measure of proliferative ability



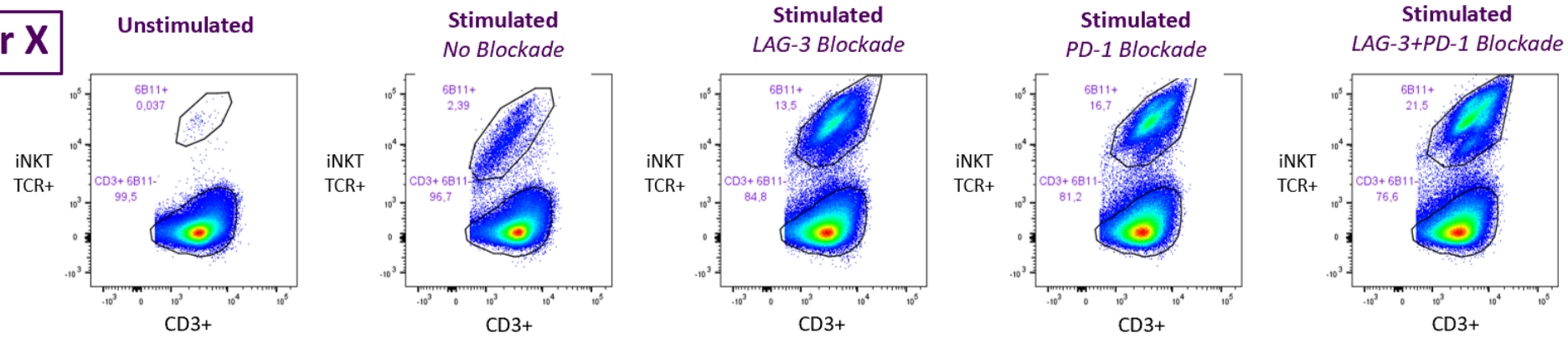
Methods

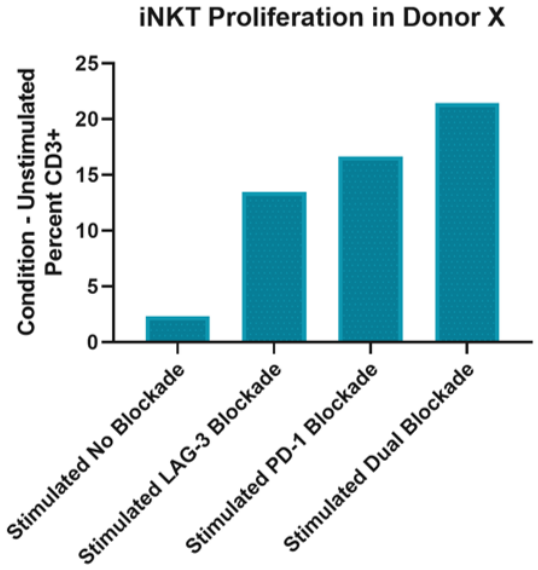
10-day iNKT Cell Stimulation - *Using lipid antigen α-GalCer*



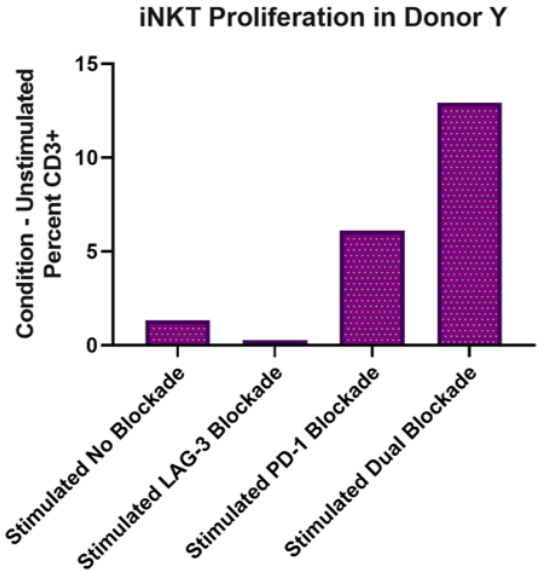
Results

Donor X

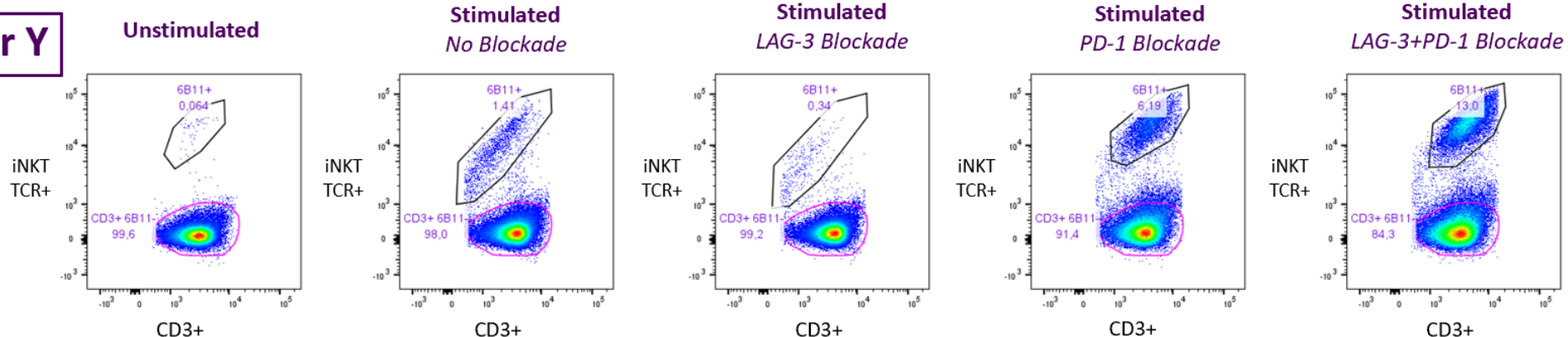




***The LAG-3, PD-1 and Dual blockade conditions enhance proliferative ability of iNKT cells* in vitro**



Donor Y



Implications in HIV

- ❑ **In chronic HIV infection, iNKT cells are exhausted with upregulated LAG-3 and/or PD-1**
- ❑ **We believe that by blocking LAG-3 and/or PD-1 via an antibody blockade immunotherapy, will can reverse iNKT cell exhaustion and enhance cellular function**
- ❑ **This proliferation model works as proof that the iNKT cell population in HIV-positive individuals has potential to be restored**

<u>Overall Goal</u>: Decrease HIV-associated immune dysfunction to improve immune recovery in treated HIV infection