Establishing humanized mouse models of HIV and HIV/TB co-infection

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Humanized mouse models are essential for studying HIV and HIV/TB co-infection

- Currently, 38 million people are living with HIV globally (WHO, 2019)
- HIV-infected individuals are 20x more susceptible to TB, which accounts for ~25% of AIDS-related deaths (WHO, 2019)
- Since human CD4+ T cells are required for HIV infection, humanized mouse models (traditionally NRG/NSG based) are essential to study HIV *in vivo* as they possess human immune cells
- With matched CD34+ HSCs, HLA-transgenic (class I A2 & class II DR4 – DRAG-A2) humanized mice show enhanced T cell reconstitution and functionality, resulting in improved cytokine secretion and B cell antibody isotype switching (Danner et al., 2011)

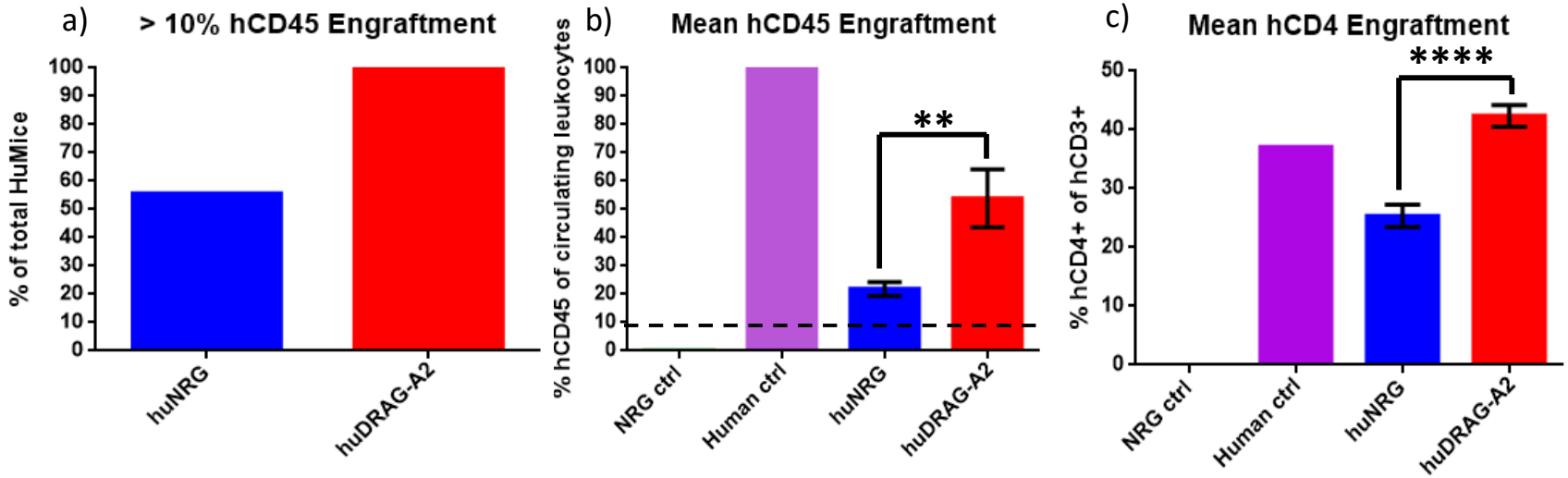


Fig. 1. a) Percentage of mice that are successfully engrafted to greater than 10% hCD45; b) Mean percentage hCD45+ of total circulating leukocytes (p value = 0.0034); c) Mean percentage hCD4+ T cells of hCD3+ T cells (p value = <0.0001), in huNRG (N=61) and huDRAG-A2 (N=6) mice at 12 weeks post-engraftment. Data are expressed as mean ± SEM. Statistical analysis was performed using unpaired t test.

Intravaginal HIV infection results in reduced human CD4+ T cell frequency in the blood of huDRAG-A2 mice and high viral load in the vaginal wash and blood plasma of huNRG and huDRAG-A2 mice

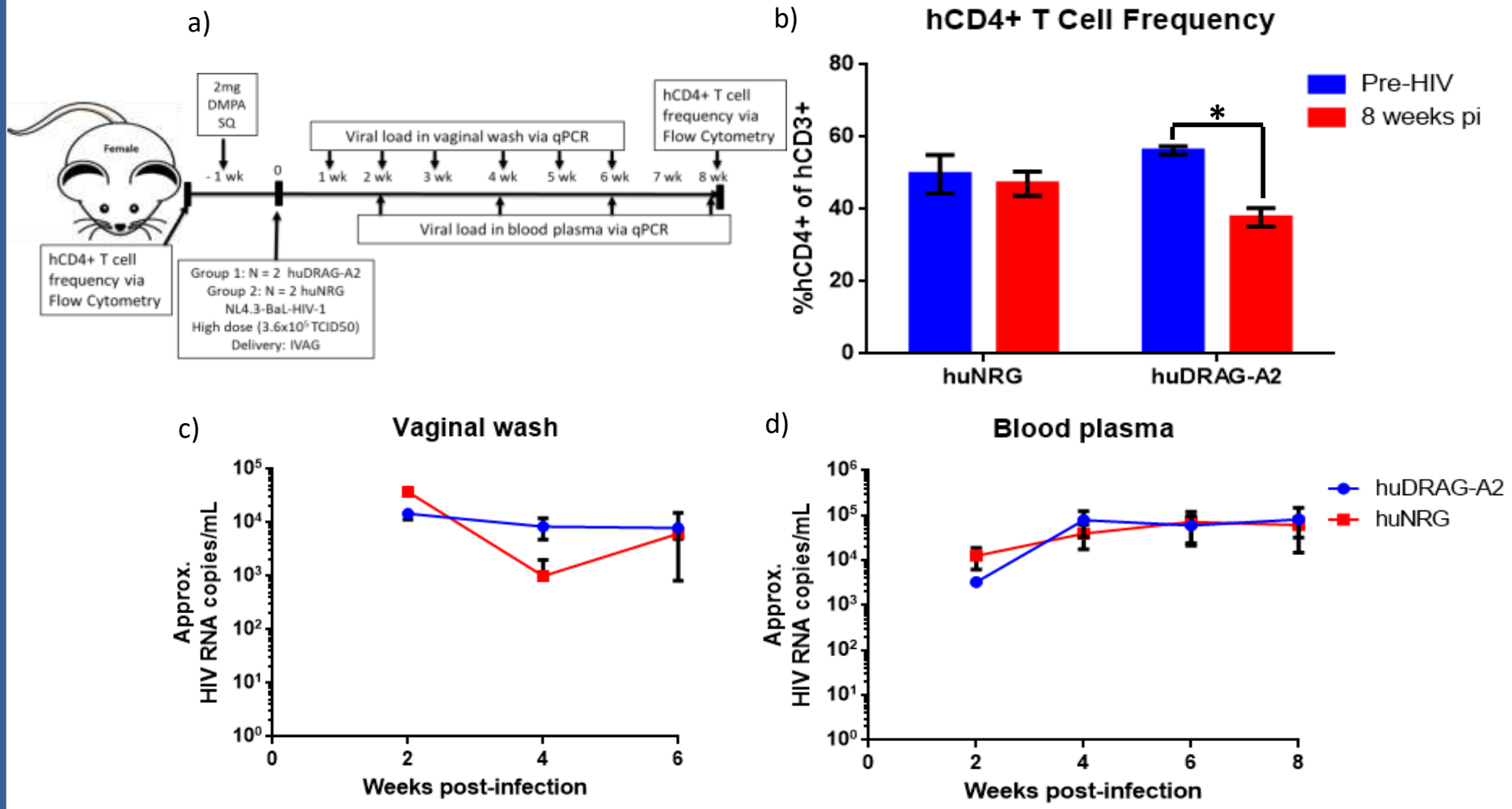


Fig. 2. a) Experimental timeline for intravaginal HIV infection in huNRG (N=2) and huDRAG-A2 (N=2) mice; b) Human CD4+ T cell frequency pre-infection and at 8 weeks post-infection (p value = 0.0368); Mean HIV viral load in c) vaginal wash and d) blood plasma at 2, 4, 6 & 8 weeks post-infection. Data are expressed as mean ± SEM. Statistical analysis was performed using two-way ANOVA test.

Intranasal TB infection results in both pulmonary and disseminated TB in huNRG mice. Caseating granulomas and a high frequency of TB-infected human alveolar macrophages in the lungs indicate homology with human disease

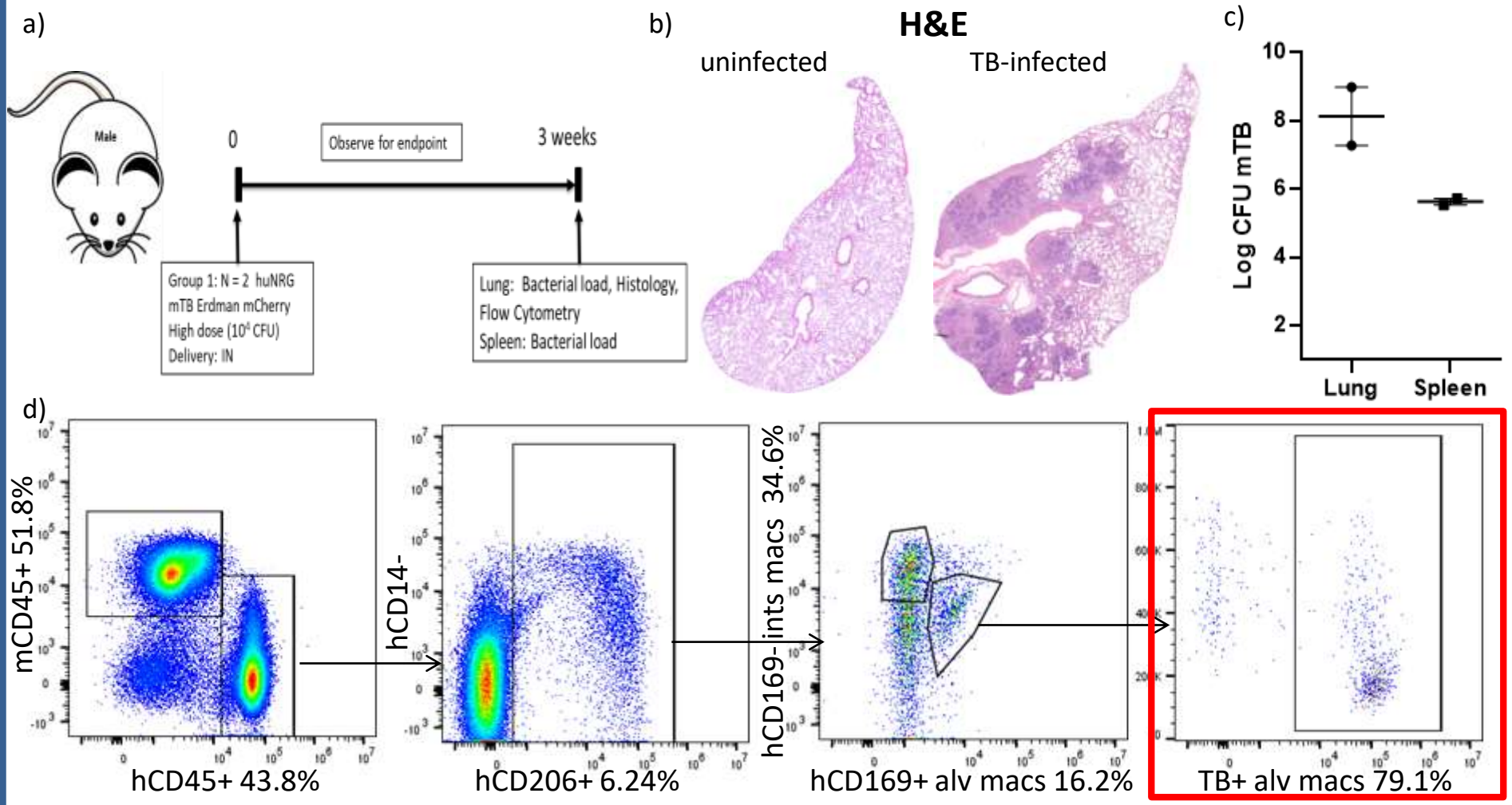
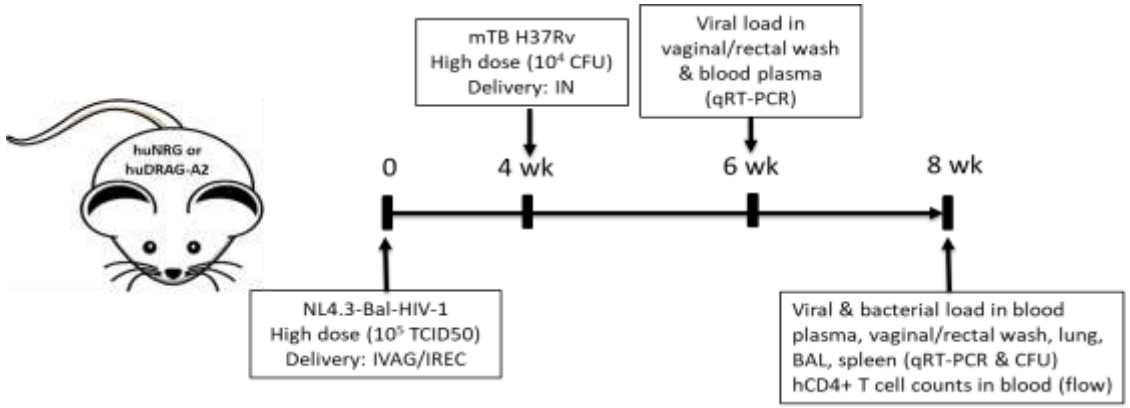


Fig. 3. a) Experimental timeline for intranasal TB infection in huNRG mice (N = 2); b) H&E staining of whole lung sections from uninfected and TB-infected huNRG mice; c) Bacterial load in the lung and spleen at 3 weeks post-infection; d) Flow cytometric analysis of the lung of huNRG mice at 3 weeks post-infection. hCD206+hCD169+ alveolar macrophages in the lungs of huNRG mice were found to be infected with TB (mCherry positive - red panel).

Future Directions & Clinical Significance

- Preliminary TB infection in huDRAG-A2 mice is ongoing
- Our next aim is to establish HIV/TB co-infection in huNRG and huDRAG-A2 mice



- Due to the increased T cell functionality and the ability to develop full B cell responses, the huDRAG-A2 model will be particularly useful for:
  - Vaccine development and testing for both HIV and TB separately, as well as in the context of co-infection
  - Investigating the complex immune interactions that occur during co-infection (ie. the role of macrophages in co-infection, granuloma formation)
- In addition, the ability to perform mucosal HIV infections (intrarectal infection is also being developed) will allow the investigation of prophylactic therapeutics at mucosal sites