Poster #469LB

Efficacy of an Engineered Bispecific Anti-HIV Antibody in Humanized Mice

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INTRODUCTION

While the search for an efficacious HIV vaccine remains elusive, the emergence of a new generation of virus-neutralizing monoclonal antibodies (Abs) has re-ignited the field of passive immunization as an alternative strategy for HIV prevention. However, the plasticity of HIV demands additional improvements to these Abs in order to better ensure their clinical utility. Here, we report the impressive *in vitro* and *in vivo* activity of an engineered bispecific Ab.

METHODS

The CrossMab technology was used to construct a library of bispecific Abs. One potent and broad Ab, 10E8$_{V2.0}$/iMab, was identified, with one arm targeting the human CD4 receptor using ibalizumab (iMab) and the other arm targeting gp41 using a modified 10E8 (10E8$_{V2.0}$). We then evaluated its *in vivo* efficacy in NSG mice reconstituted with human hematopoietic cells. First, mice infected with HIV JR-CSF received weekly injections of 0.5 mg 10E8$_{V2.0}$/iMab for 7 weeks, alone or in combination with 0.5 mg of an anti-gp120 engineered trispecific Ab. Second, uninfected mice receiving weekly injections of 0.2 mg 10E8$_{V2.0}$/iMab were challenged 3 times intraperitoneally with JR-CSF to assess its protective efficacy. In both experiments, viral RNA in plasma was assessed weekly.

RESULTS

Impressive breath and potency of the engineered HIV CrossMAbs 10E8$_{V2.0}$/iMab and 10E8$_{V1.1}$/P140

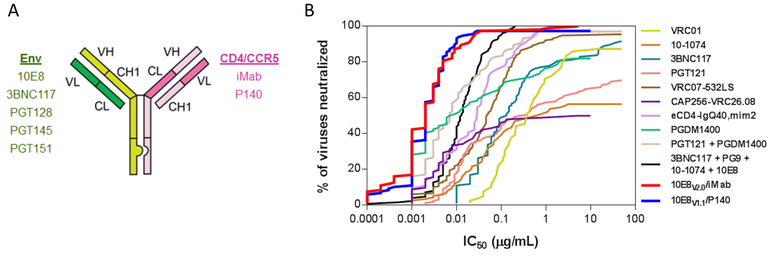

Figure 1. A. Schematic of an HIV CrossMAb and list of examples of parental antibodies from which each CrossMAb was derived. **B.** Percent of large panels of multi-clade HIV-1 Env pseudoviruses neutralized by antibodies currently in development for HIV prevention.

Therapeutic efficacy of 10E8$_{V2.0}$/iMab in humanized NSG mice

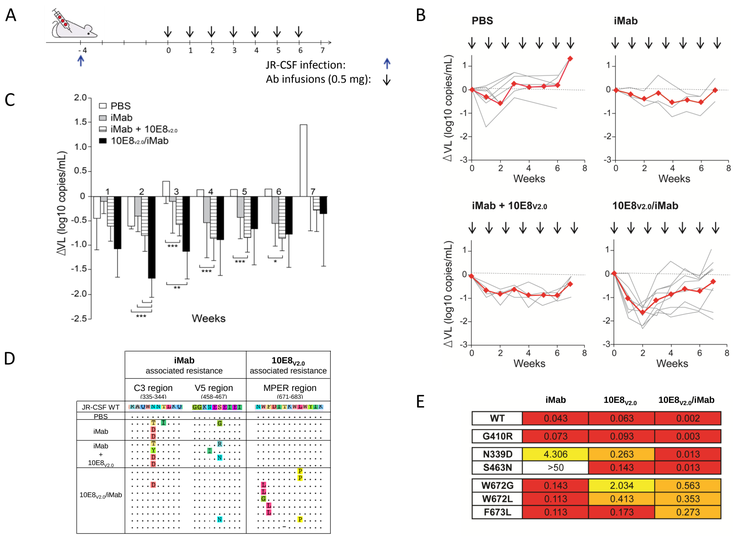

Figure 2. A. Schematic timeline for the treatment study. **B.** Changes in plasma viral RNA from baseline at week 0. **C.** Comparison of the therapeutic efficacy of 10E8$_{V2.0}$/iMab with the comparator groups. Columns represent changes in viral load. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ as determined by the Mann-Whitney test. **D.** Mutations in HIV Env associated with resistance after viral rebound. All mutations are aligned to the JR-CSF sequence and numbered according to the HXB2 sequence. **E.** IC_{50} concentrations (μg/mL) of the antibodies listed in the top row against the wild-type HIV$_{JR-CSF}$ or mutants containing the indicated mutations in the envelope shown in the left column.

10E8$_{V2.0}$/iMab protects humanized mice against repeated systemic HIV challenges

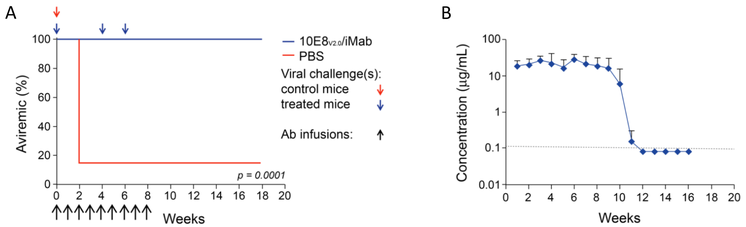

Figure 3. A. Kaplan-Meier plot depicting the percentage of aviremic mice in 10E8$_{V2.0}$/iMab-treated versus non-treated challenged mice. Mice received 200 μg of 10E8$_{V2.0}$/iMab every week from week 0 to week 8 (black arrows) and were challenged at day 1 and weeks 4 and 6 (blue arrows). PBS control mice were challenged once at day 1 (red arrow). Statistics were calculated by log-rank test. **B.** Quantification of 10E8$_{V2.0}$/iMab plasma concentration by ELISA.

Combining 10E8$_{V2.0}$/iMab with an anti-HIV engineered trispecific Ab leads to sustained viral reduction

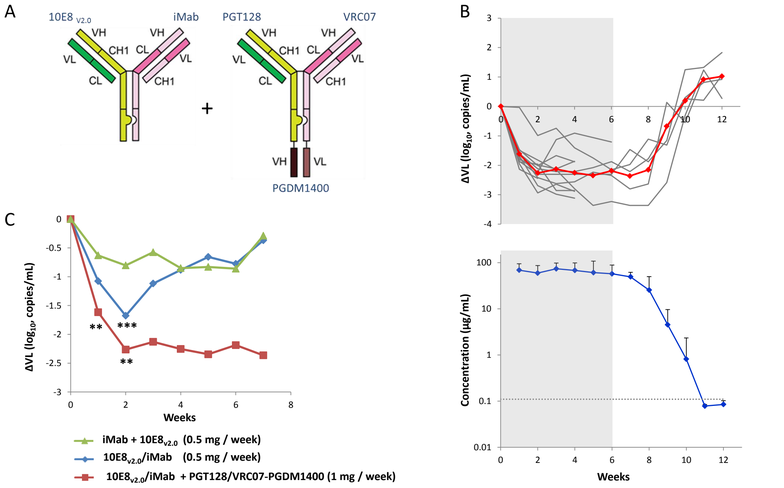

Figure 4. A. Schematic of the HIV bispecific and trispecific Abs combination. **B top.** Changes in plasma viral RNA from baseline at week 0. Mice received the combination (10E8$_{V2.0}$/iMab + PGT128/VRC07-PGDM1400) at 0.5 + 0.5 mg every week from week 0 to week 6 (grey shaded area). **B bottom.** Quantification of 10E8$_{V2.0}$/iMab plasma concentration by ELISA. **C.** Comparison of the therapeutic efficacy of the combination treatment vs 10E8$_{V2.0}$/iMab alone or the associated parental Abs alone. ** $p < 0.01$, *** $p < 0.001$ as determined by the Mann-Whitney test.

CONCLUSION

10E8$_{V2.0}$/iMab and 10E8$_{V1.1}$/P140 appear to be the broadest and most potent HIV-1-neutralizing biologic agents described to date. 10E8$_{V2.0}$/iMab has shown unprecedented activity for an Ab in both treating and preventing HIV in a humanized mouse model. In combination with an anti-HIV engineered Ab, sustained viral reduction was achieved using a low dose of 1 mg total Ab per week. 10E8$_{V2.0}$/iMab thus holds promise as a novel prophylactic and therapeutic agent in the fight against HIV and is currently under clinical development. 10E8$_{V2.0}$/iMab could potentially serve as an anchor for a combination of antibodies to treat HIV on a monthly basis.