10E8.4/iMab Bispecific Antibody for Immunoprophylaxis Against High-Dose Intravenous SHIV Exposure

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Background

- 10E8.4/iMab is a novel bispecific antibody that neutralizes HIV. It is an engineered antibody with two distinct antigen-binding arms (Fig 1):
  - ➢Ibalizumab targets CD4
  - ➢10E8.4 targets the HIV-1 envelope membrane-proximal external region (MPER)
- This combination of targets places 10E8.4 near the primary entry receptor utilized by HIV, facilitating the binding and neutralization of incoming viral particles (Fig 2).
- 10E8.4/iMab has high potency against multiple HIV subtypes (Fig 3).
- 10E8.4/iMab has been manufactured for use in humans and has been safe to date.

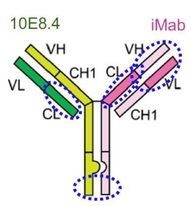


Fig 1. Bispecific 10E8.4/iMab antibody

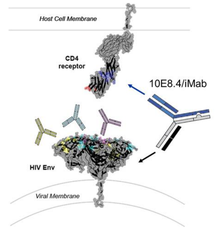


Fig 2. Schematic of bispecific antibody binding to cell and virus

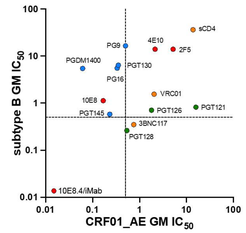


Fig 3. 10E8.4/iMab Neutralization Potency

Methods

SHIV.BG505[1] intravenous challenge

- Model blood transfusion risk from donor with untreated HIV
  - ➢ Viral load ~10^4 copies/ml of blood
  - ➢ 4-unit trauma blood transfusion
- Target: 40 million copies of viral RNA
  - ➢ 50,000 $TCID_{50}$ (~50-500X typical i.v. dose)

10E8.4/iMab (IgG1)

- 30 mg/kg dose to maximize CD4 receptor occupancy
- Fc L234F, L235E and P331S triple mutation minimizes effector functions

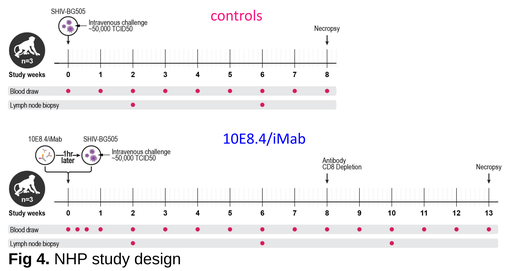


Fig 4. NHP study design

We developed a nonhuman primate model of immunoprophylaxis in the context of high-dose intravenous HIV exposure. We assessed the 10E8.4/iMab bispecific antibody as a preventative agent. Control animals developed plasma viremia one week after high-dose intravenous viral challenge (peak: 8.7E6–1.1E7 copies/ml). Animals given 10E8.4/iMab exhibited no evidence of viral infection, even during a five-week interval following systemic depletion of CD8α+ lymphocytes. **Passive intravenous provision of potent anti-HIV bispecific bNAbs is a highly promising prophylaxis strategy for high-dose intravenous HIV exposure.**

Results

Fig 5. 10E8.4/iMab Neutralization of Candidate SHIVs

	SHIV SF162P3	SHIV BG505	SHIV AD8EO
10E8.4/iMab	0.002	0.002	ND
VRC07	0.02	0.10	1.66
PGT121	0.09	ND	0.156
10E8	0.05	0.95	ND
PGDM1400	>8.3	0.01	>50
3BNC117	0.01	0.05	0.52

mAb Potency (IC50)

<0.01
0.01-0.1
0.1-5.0
>5.0

Fig 6. 10E8.4/iMab pharmacokinetics in blood

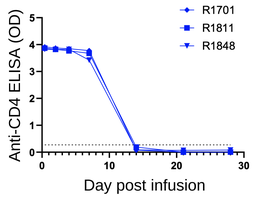


Fig 7. Immunoprophylactic efficacy

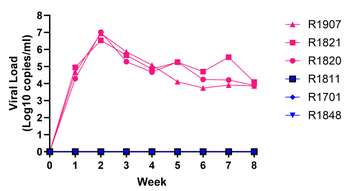


Fig 8a. CD8α depletion

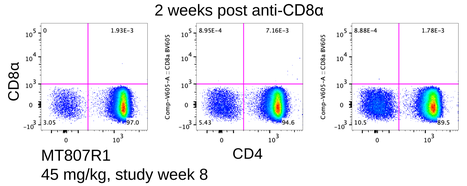
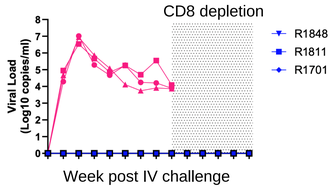


Fig 8b. Viral loads post-CD8α depletion



Summary

- Intravenous SHIV-BG505 is a rigorous infection model.
- 10E8.4/iMab shows promising efficacy against high-dose intravenous SHIV challenge, with no evidence of viremia post-challenge, including following CD8α depletion
- Corroborates prior work using PGT121 in intravenous SHIV-SF162P3 challenge model[2]

Ongoing and future steps

- CD4 receptor occupancy, plasma neutralization activity, and anti-SHIV immune responses
- A more extensive study to explore this immunoprophylaxis strategy, including defining the window of opportunity (Fig 9) and efficacy against cell-associated virus

Conclusion

10E8.4/iMab:

- Demonstrates distinguishing potency and breadth in neutralization assays
- Shows initial promise of mitigating risk to the emergency whole blood supply in a pilot NHP study

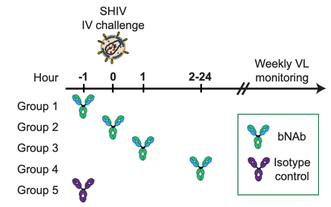


Fig 9. Follow-up study

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References

1. New SHIVs and Improved Design Strategy for Modeling HIV-1 Transmission, Immunopathogenesis, Prevention and Cure. Li H, Wang S, Lee FH, Roark RS, Murphy AI, Smith J, Zhao C, Rando J, Chohan N, Ding Y, Kim E, Lindemuth E, Bar KJ, Pandrea I, Apetrei C, Keele BF, Lifson JD, Lewis MG, Denny TN, Haynes BF, Hahn BH, Shaw GM. J Virol. 2021 May 10;95(11):e00071-21. doi: 10.1128/JVI.00071-21. Epub 2021 Mar 3.PMID: 33658341

2. Partial efficacy of a broadly neutralizing antibody against cell-associated SHIV infection. Parsons MS, Lloyd SB, Lee WS, Kristensen AB, Amarasena T, Center RJ, Keele BF, Lifson JD, LaBranche CC, Montefiori D, Wines BD, Hogarth PM, Swiderek KM, Venturi V, Davenport MP, Kent SJ. Sci Transl Med. 2017 Aug 9;9(402):eaaf1483. doi: 10.1126/scitranslmed.aaf1483.PMID: 28794282