ModeX™
THERAPEUTICS
an OPKO Health Company

Multispecific Antibodies for HIV and Infectious Diseases

HIV PERSITENCE DURING THERAPY

Dec 13, 2024

CONFLICTS OF INTEREST

- **Listed as an inventor on NIH patents related to HIV antibodies**

- **Chief Scientific Officer of ModeX Therapeutics, an OPKO Health Company; ModeX/OPKO has filed patent applications on multispecific antibodies**

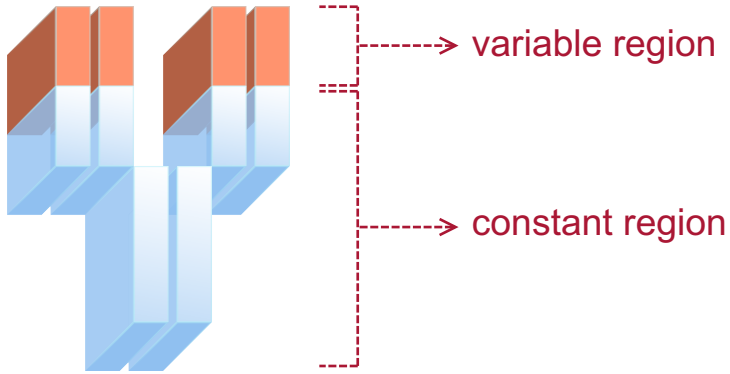
Talk outline

- What are multispecific antibodies and how to we make them?
- Development of a broadly reactive multispecific antibody for COVID-19
- Multispecific antibodies for HIV: Prevention, Treatment and Functional Cure

What are Multispecific Antibodies?

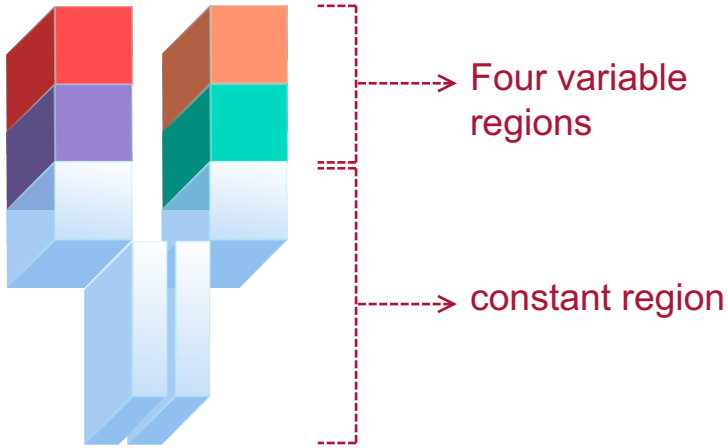
Standard mAb

Bivalent and monospecific
(Binds one antigen)



Multispecific Antibody

Tetravalent and Tetraspecific
(Bind more than one antigen)



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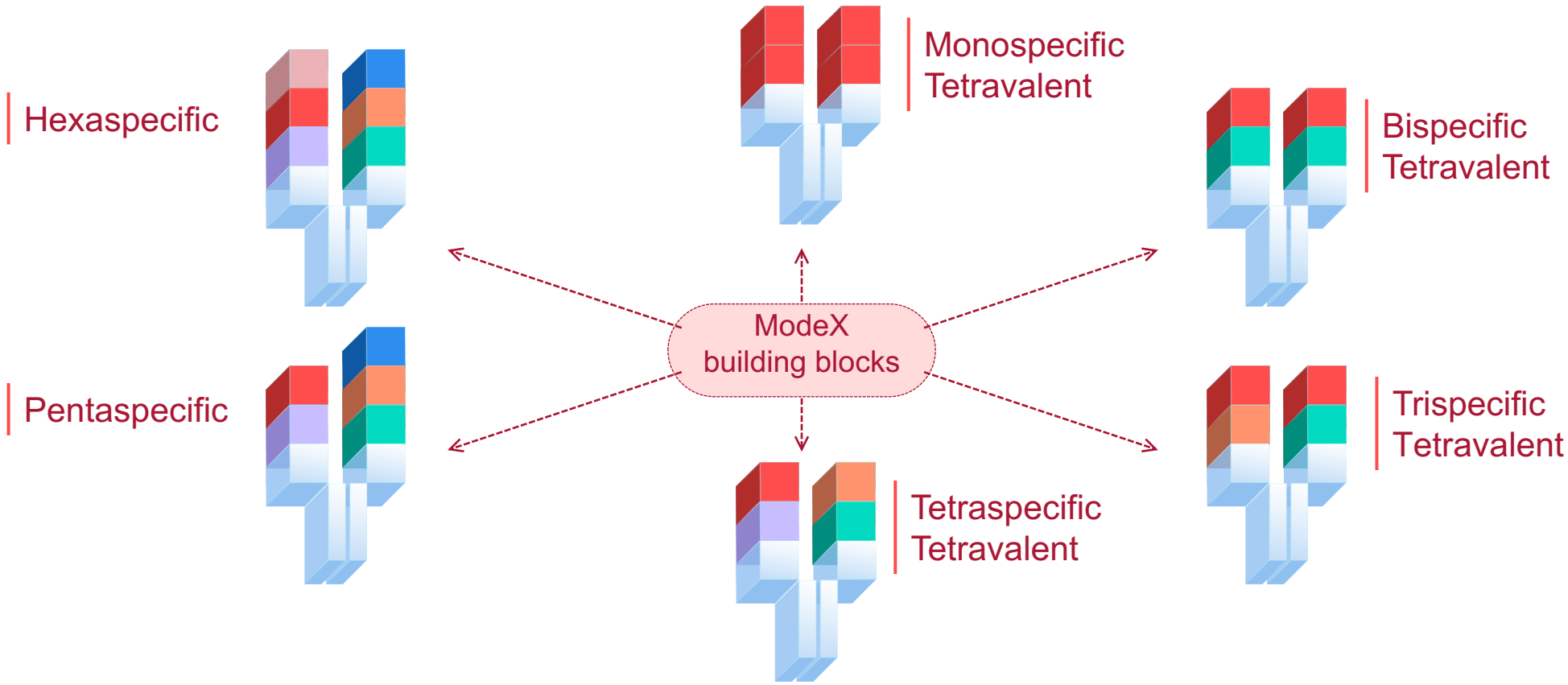
MSTAR Technology Advantages: Modulate Specificity and Valency to Fit Biology



- Modular design enables screening large numbers of diverse candidates in weeks time
- Exploit various specificities, orientations and valencies to optimize function
- Leverage both *in silico* rational design and machine learning to accelerate candidate selection

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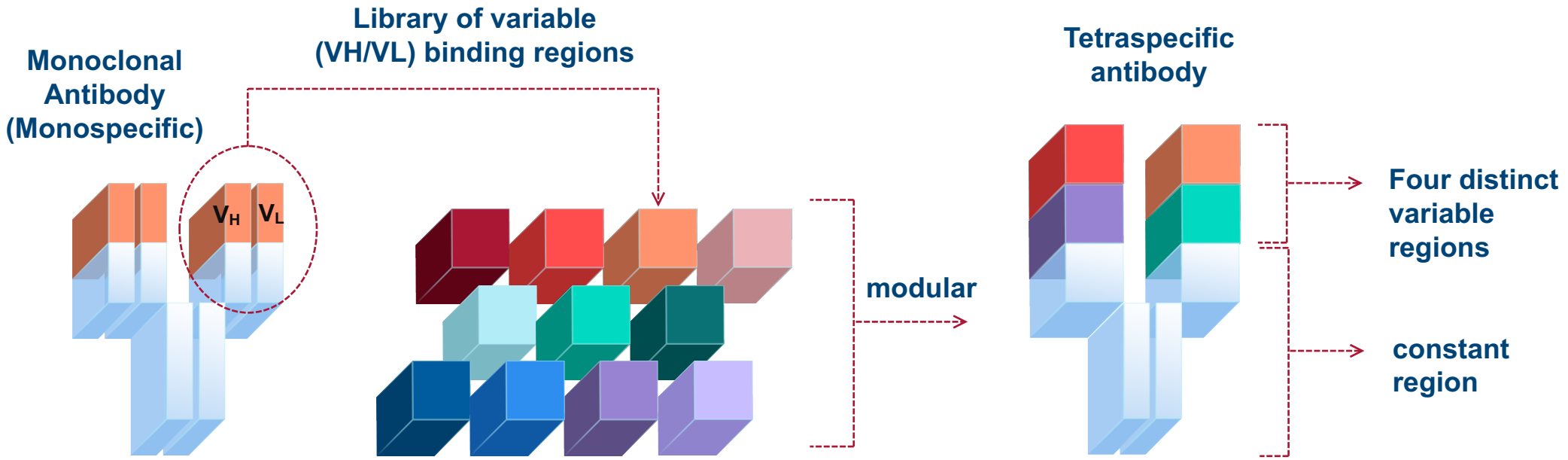
The ModeX Multispecific Antibody Platform



Modular Multispecific Antibody Platform

Antibody library of VH/VL binding regions

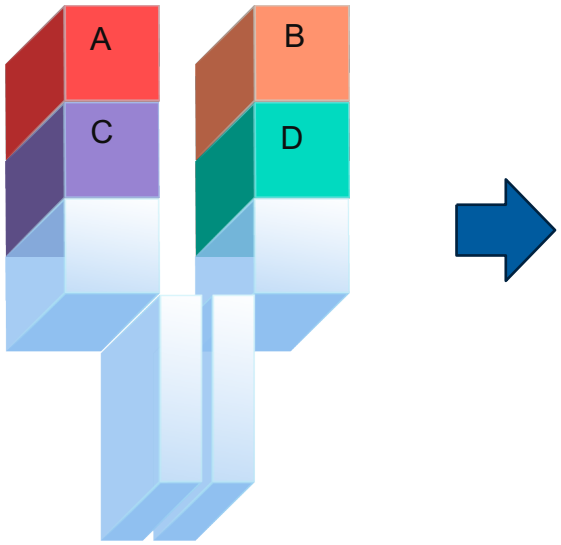
variable region

constant region

multispecific antibody

Multispecifics: Advantages for Infectious Diseases

Multispecific Antibody



- High potency with wider breadth of coverage against multiple strains of a pathogen
- More resilient to pathogen evolution and viral escape
- Single antibody replaces 3-4 antibodies; less complicated therapeutic and decreases cost of goods

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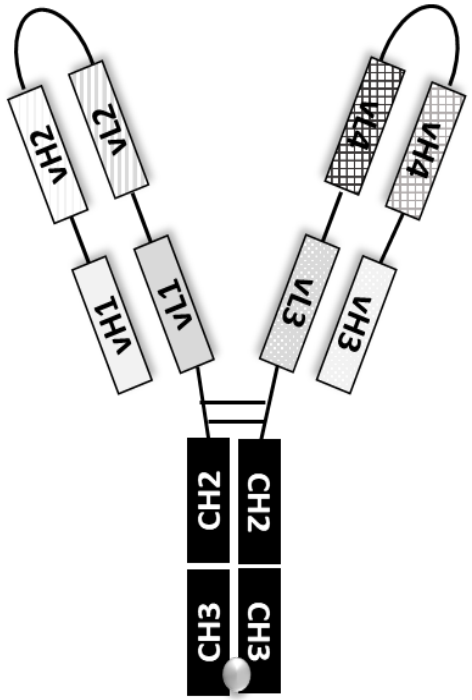
MSTAR Antibodies: Design Advantages

MSTAR Platform



- **Each arm is a single ORF with two binding domains that properly fold**
- **Simplifies gene delivery; i.e. Bispecific tetravalent antibody can be encoded with one mRNA**

Bispecific Tetravalent → **Single DNA or mRNA**

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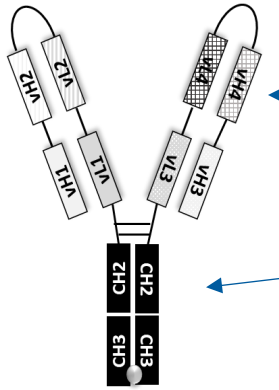
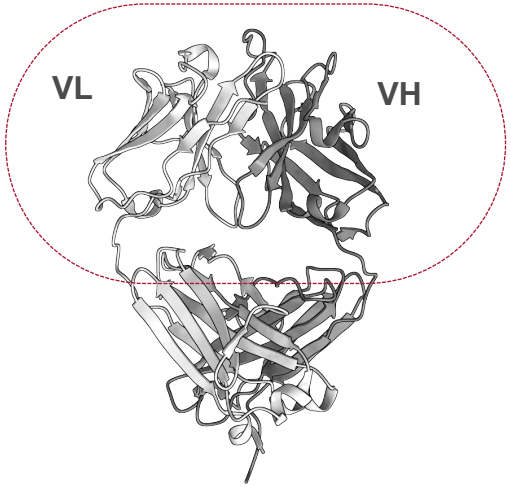
MSTAR Antibodies: Design Advantages

MSTAR Platform





- **Efficient single chain design eliminates heavy/light chain mispairing**
- **Antibody constant (Fc) region to modulate Fc effector functions and to extend antibody half-life**
- **Binding domains are structurally superposable to those of standard IgG Fab**

Zhou *et. al. Vaccine Research Center, NIAID, NIH*

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Talk outline

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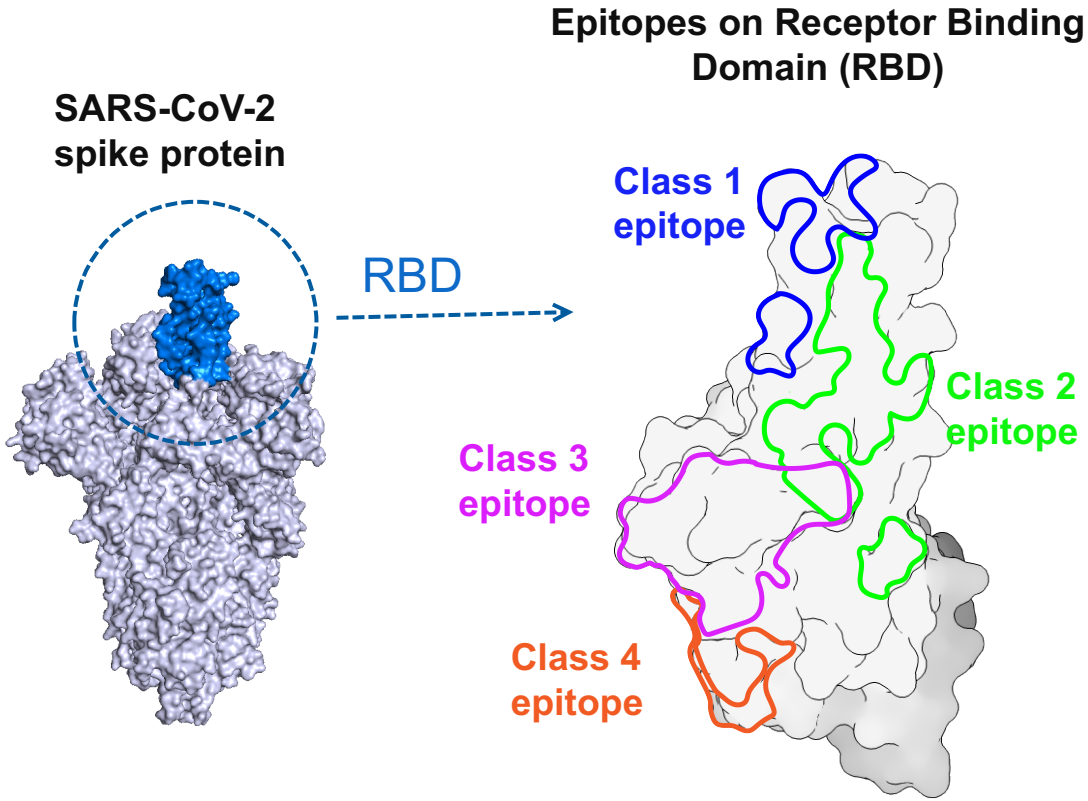
Structural Knowledge to Address SARS-CoV-2 Diversity

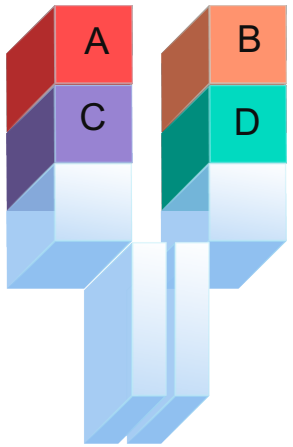


Major neutralizing antibody target epitopes on SARS-CoV-2 Spike RBD
Barnes et al., Nature 2020

RBD is a clinically validated target for effective COVID antibodies

Goal: Develop a multispecific antibody that targets distinct regions of RBD and demonstrates high neutralization potency against all historical and current SARS-CoV-2 variants

Tetravalent Tetraspecific Antibody Potently Neutralizes All SARS-CoV-2 Variants



MDX 2202
Tetravalent
Tetraspecific

		IC_{50} (ng/ml)
Jan 2020	WA-1	52
Alpha	B.1.1.7	26
Beta	B.1.351	19
Gamma	P.1	11
Zeta	P.2	18
	B.1.427	47
	B.1.429	14
	B.1.525	45
	B.1.526	16
	B.1.617.1	10
Delta	B.1.617.2	48

Omicron Nov 2021

	IC_{50} (ng/ml)
B.A.1	5
BA.4/5	8
B.1.621	20
CH.1.1	16
XBB	8
XBB.1.5	12
XBB.2.3.2	17
BA.2.86	6
EG.5.1	8
FL.1.5.1	14
XBB.1.16.6	9
HV.1	6
HK.3	6
JD.1.1	10
JF.1	13
JN.1	15
KP.3	20

Collaboration with VRC/NIAID, NIH

Measured by standardized pseudovirus neutralization assay

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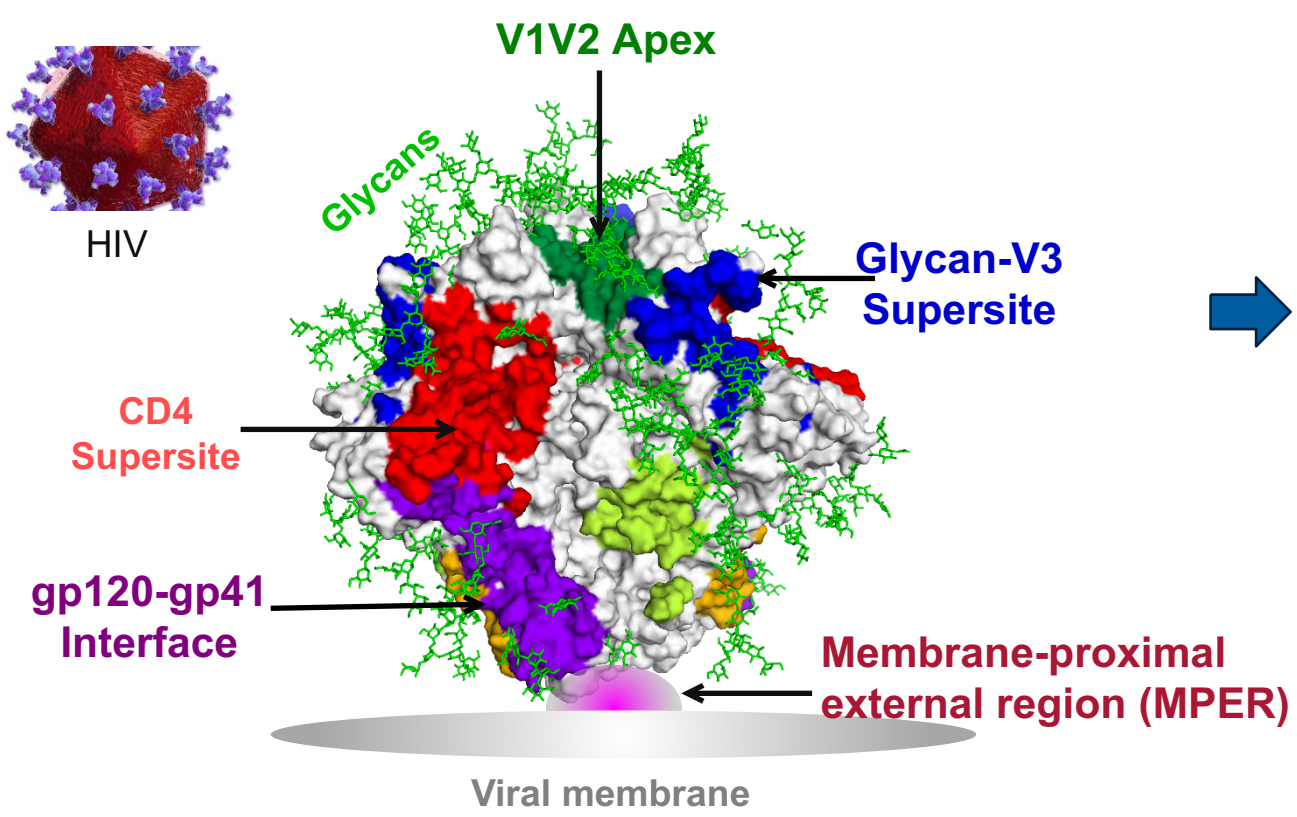
HIV Multispecific Development: Guided by Detailed Structural Knowledge of Vulnerable Regions HIV



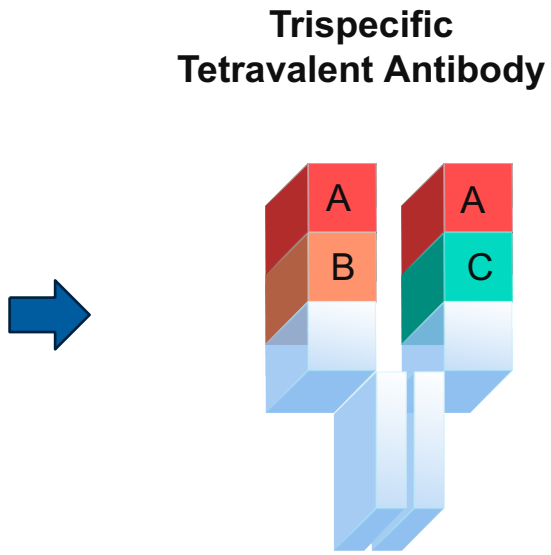


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al.
Cell 2016 and Pancera et al. Nature 2014

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Phase I Study of SAR441236, a Trispecific Broadly Neutralizing Antibody, in Participants with HIV

Athe Tsibris, Pablo Tebas, R Tressler and ACTG investigators; CROI March 2024

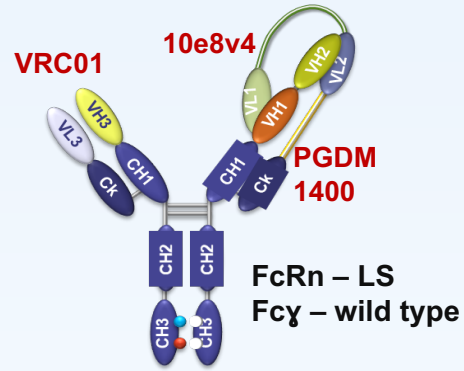
Cohort 4: 30mg/kg IV Q3M x 4 doses

Cohort 3: 10mg/kg IV and SQ; x1 dose

Cohort 2: 3mg/kg IV and SQ; x1 dose

Cohort 1: 1mg/kg IV and SQ: x1 dose

Dose escalation based on 2-wk safety review



CODV Trispecific

Phase 1: Safe and well tolerated by IV and SQ route
Half Life ~ 40 days

ACTG AIDS CLINICAL TRIALS GROUP

NIH National Institute of Allergy and Infectious Diseases

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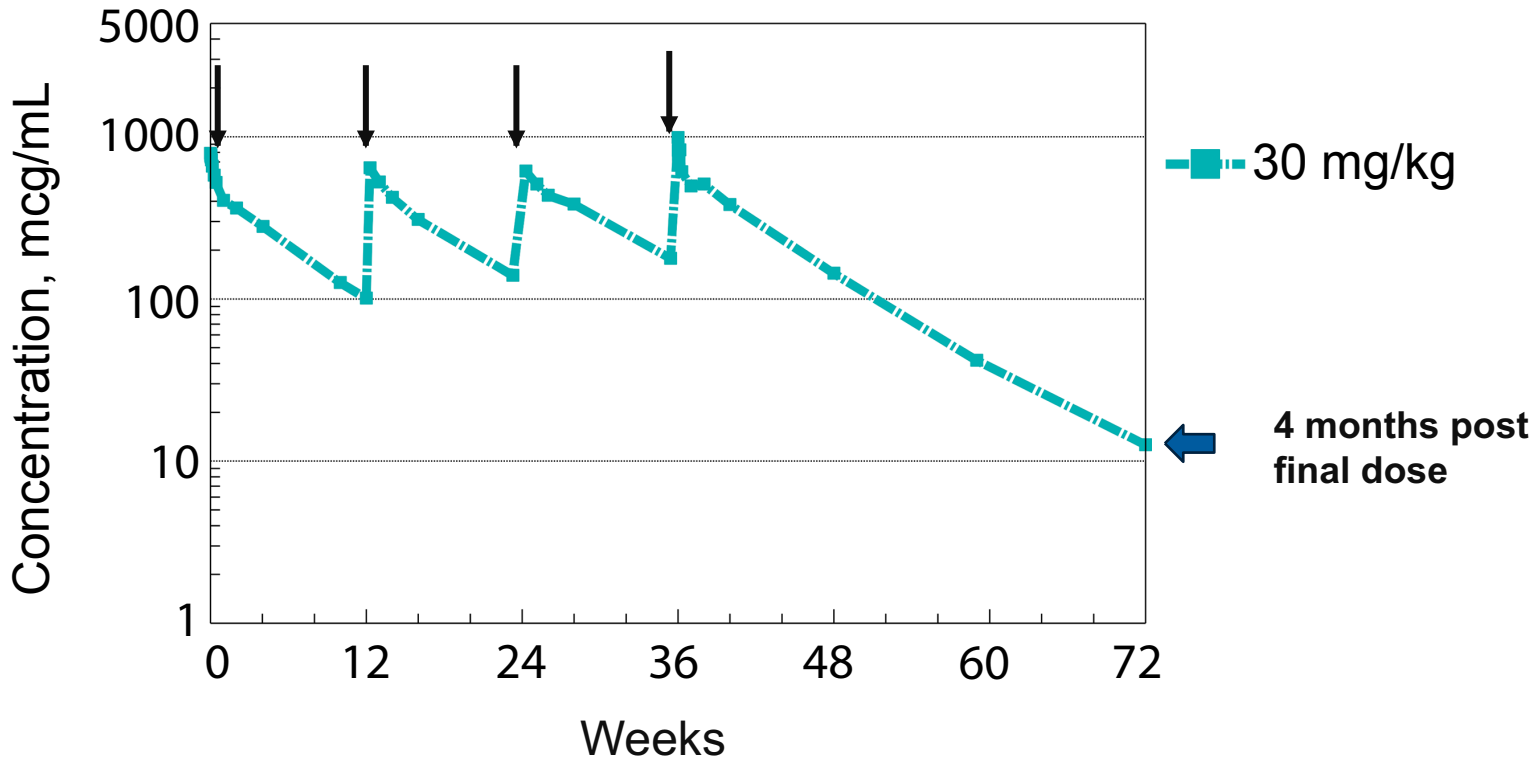
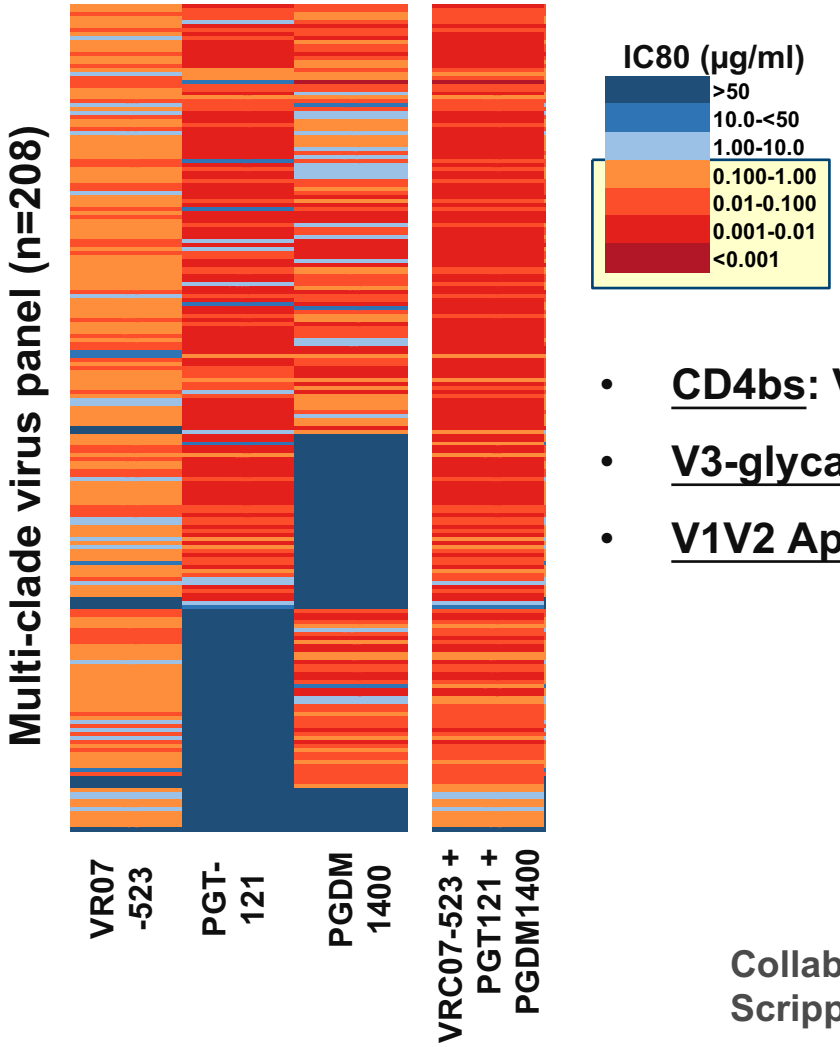
Trispecific: Multiple Administrations

Administered 4 times, 12 weeks apart
Consistent PK without development of ADA



Triple mAb Combination: Complementary Neutralization Profiles; High Potency and Breadth of Coverage



- CD4bs: VRC07-523
- V3-glycan: PGT121
- V1V2 Apex: PGDM1400

Neutralizes 97% of diverse viral strains at IC_{80} < 1.0 ug/ml

Median IC_{80} = 0.010 ug/ml

Collaboration between ModeX, Vaccine Research Center (VRC), NIH; Scripps Research and International AIDS Vaccine Initiative (IAVI)

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HIV Trispecific Antibody: Contains 3 Distinct Specificities

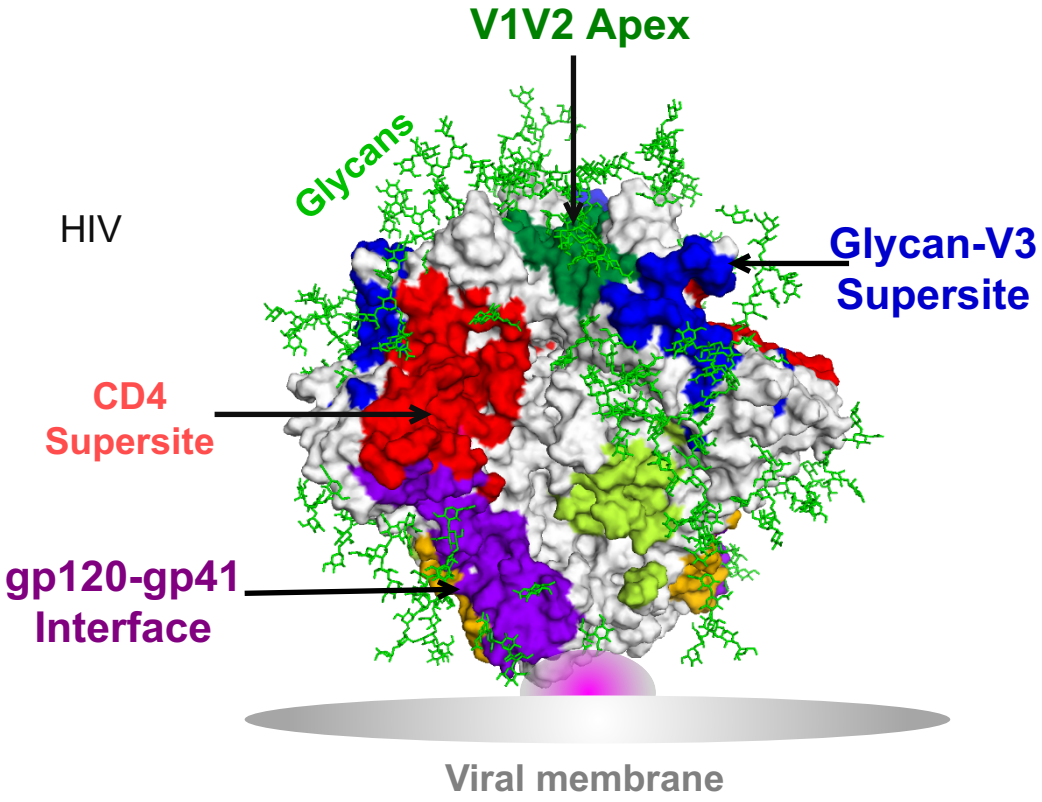

Image by Stewart-Jones, Doria-Rose, Stuckey
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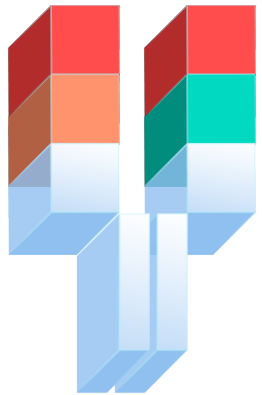

- V3-glycan: New version of PGT121
- CD4bs: VRC07-523
- V1V2 apex: PGDM1400

Trispecific Tetravalent Antibody

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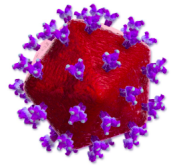
Neutralization Assessment on Contemporary Virus Strains from AMP* Study

The NEW ENGLAND JOURNAL of MEDICINE

March 2021 ORIGINAL ARTICLE

Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

L. Corey, P.B. Gilbert, M. Juraska, D.C. Montefiori, L. Morris, S.T. Karuna, S. Edupuganti, N.M. Mgodi, A.C. deCamp, E. Rudnicki, Y. Huang, P. Gonzales, R. Cabello, C. Orrell, J.R. Lama, F. Laher, E.M. Lazarus, J. Sanchez, I. Frank, J. Hinojosa, M.E. Sobieszczyk, K.E. Marshall, P.G. Mukwekwerere, J. Makhema, L.R. Baden, J.I. Mullins, C. Williamson, J. Hural, M.J. McElrath, C. Bentley, S. Takuva, M.M. Gomez Lorenzo, D.N. Burns, N. Espy, A.K. Randhawa, N. Kochar, E. Piwowar-Manning, D.J. Donnell, N. Sista, P. Andrew, J.G. Kublin, G. Gray, J.E. Ledgerwood, J.R. Mascola, and M.S. Cohen, for the HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams*



Contemporary clade C and clade B viral strains from placebo recipients in Africa and the U.S

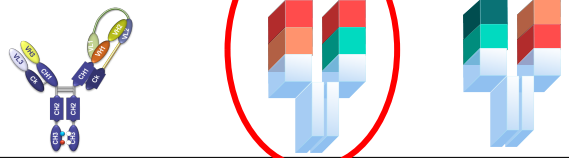
Collaboration with:

- International AIDS Vaccine Initiative (IAVI)
- Duke University/HVTN/HPTN
- VRC/NIAID

*Antibody Mediated Protection (AMP) study conducted by NIAID networks HVTN/HPTN

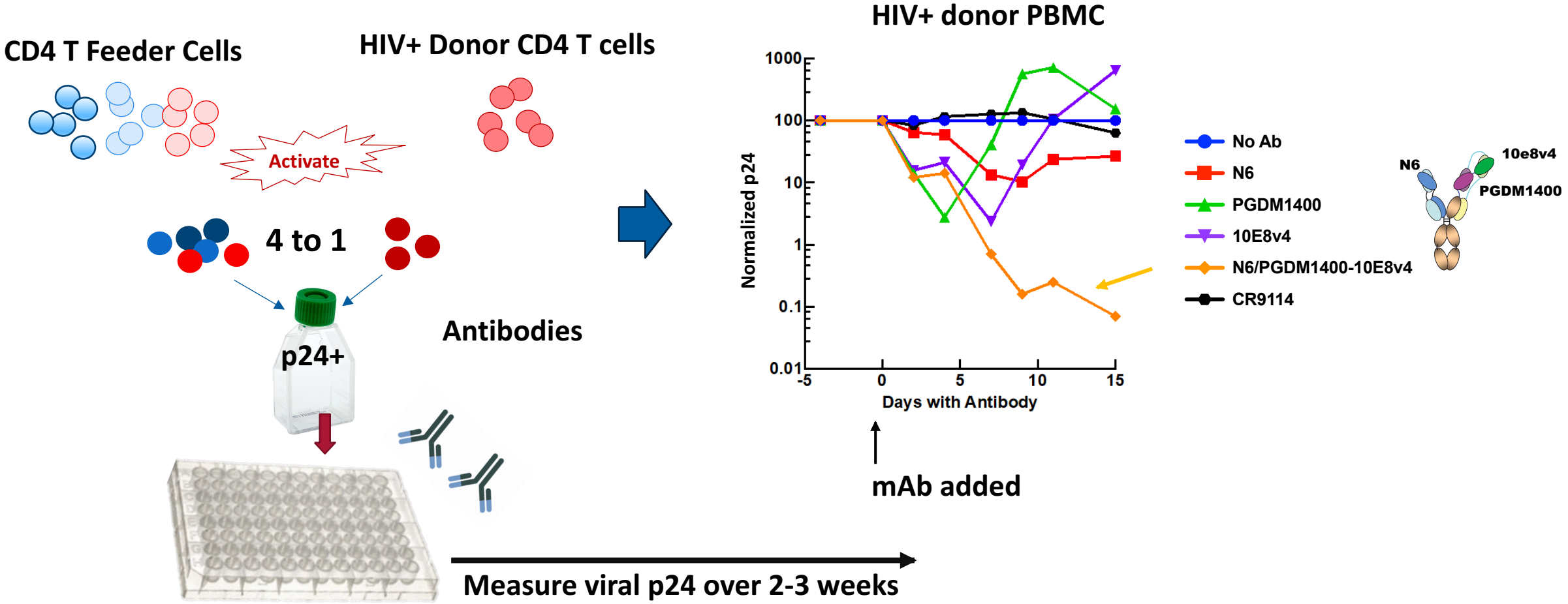
MSTAR Multispecific Abs are Broader and More Potent than First Generation Trispecific Antibody

Panel of 24 viral strains from AMP study



	1st Gen	Version 1	Version 2
# Viruses	24	24	24
Total VS Neutralized			
IC80 <1 μg/ml	15	23	24
IC80 <0.1 μg/ml	9	17	15
% VS Neutralized			
IC80 <1 μg/ml	63	96	96
IC80 <0.1 μg/ml	38	71	63
Median IC80 (ug/ml)	0.177	0.044	0.035
Geometric Mean (ug/ml)	0.227	0.035	0.038

Viral outgrowth assay: Improved suppression of viral replication compared to single antibodies



Pegu et al. Cell Reports (2022)

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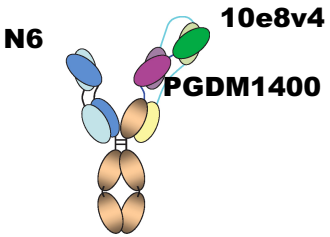
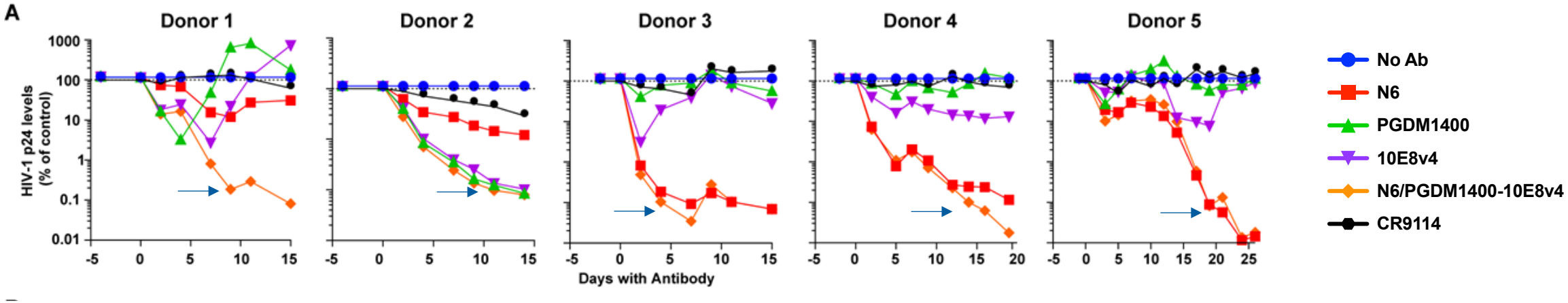
Viral outgrowth assay: Improved suppression of viral replication compared to single antibodies



Outgrowth of virus from five HIV+ donor PBMC samples, incubated with indicated antibody



Trispecific antibody shows potent suppression of viral replication in all five donors compared to parental antibodies

Pegu et al. Cell Host Microbe (2022)

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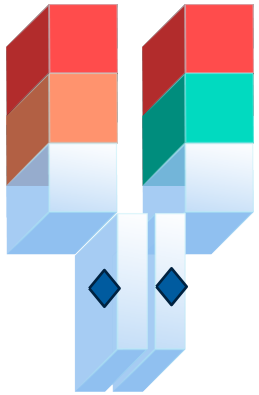
Potential Therapeutic Indications for Long-Acting HIV Antibodies

Trispecific Antibody



modifications to increase affinity for FcRn and improve half-life

*Multispecific Ab can be paired with long-acting small molecule ARV drugs to provide a complementary mechanism of action and improved therapeutic profile

- Prevention: Pre-exposure prophylaxis to prevent HIV-1 infection; e.g., SQ/IM dose once every 6 months; Infants
- Treatment: Long-acting maintenance of viral suppression; e.g., SQ/IM dose once every 6 months, paired with ARV drugs
- Functional Cure: Pair antibody with latency reversal and/or immunomodulatory agents to reduce viral reservoir and augment immunity

Functional Cure

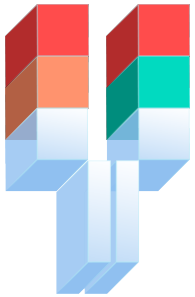
Eradicate or degrade latent viral reservoir to eliminate chronic HIV therapy
~ 1 million individuals in U.S on lifelong ARV treatment

Latency Reversal & Immune Regimens

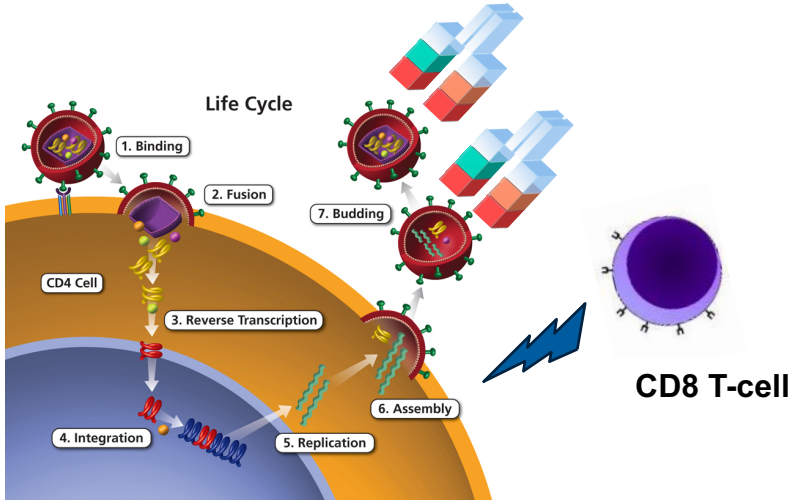
- **Activate latent CD4 T cells to express HIV proteins**
- **Activate CD8 T cells to kill infected cells**

+

Trispecific Ab



- **Bind and neutralize free virus**
- **Kill CD4 T cells expressing HIV**



https://clinicalinfo.hiv.gov/en/glossary/budding

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Unmet Medical Need – Functional Cure

Eradicate or degrade latent viral reservoir to eliminate chronic HIV therapy
~ 1 million individuals in U.S on lifelong ARV treatment

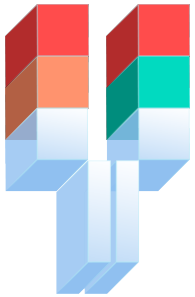
Latency Reversal & Immune Regimens

- Activate latent CD4 T cells to express HIV proteins
- Activate CD8 T cells to kill infected cells

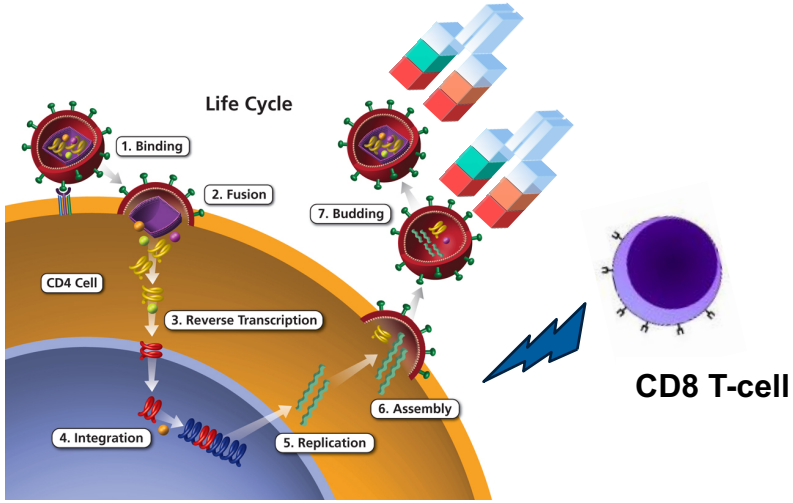
Immuno-modulating antibody
- Activate T cells
- Promote survival and function of memory and effector CD8 T cells

+

Trispecific Ab



- Bind and neutralize free virus
- Kill CD4 T cells expressing HIV



CD8 T-cell

https://clinicalinfo.hiv.gov/en/glossary/budding

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HIV Multispecifics: Summary

- Multispecific antibodies show promise for COVID and potentially other viral diseases
- First generation HIV trispecific was well tolerated, including IV and SQ administration, and had favorable PK with multiple administrations
- Next Gen HIV multispecific antibodies are 5-10 fold more potent and substantially broader, covering > 95% contemporary strains
- Next Steps: Select a lead candidate for manufacturing

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Stella Impano – Scientist
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Zhi-yong Yang- Head, Discovery Research
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