HIV

Predicting the effects of combining broadly neutralizing antibodies (bNAbs) binding to different HIV viral epitopes

III-38

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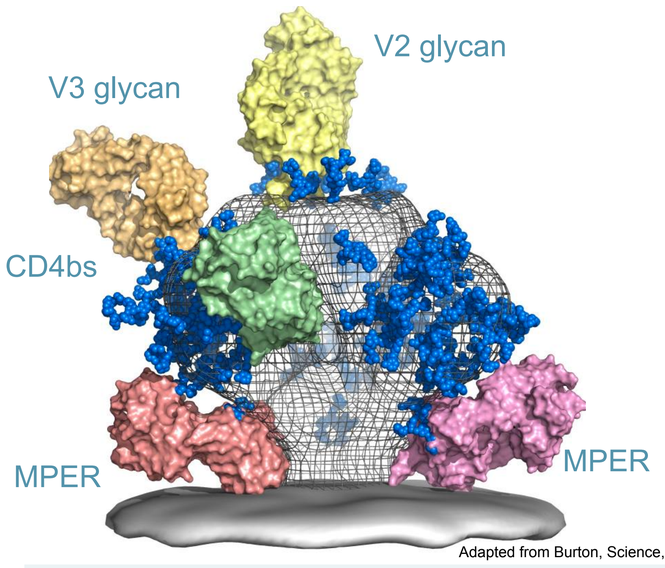

Adapted from Burton, Science, 2012

Objectives

Promising findings demonstrate that broadly neutralizing antibodies (bNAbs) significantly reduce viral loads in people living with HIV—giving hope for its eventual use in treatment and cure strategies. Numerous highly potent broadly reactive HIV-1-neutralizing antibodies continue to be isolated by different teams. The potency of these antibodies in neutralizing a wide variety of HIV-1 strains is initially explored in-vitro before deciding which molecules progress into optimization and drug development. The objective here was to model the inhibition caused by a range of bNAbs across a panel of 199 clade-C HIV-1 virus strains, using nonlinear mixed effects modelling, and to predict the effects of combining bNAbs binding to different viral epitopes in order to support programmatic decision-making, and selection of suitable combinations and dosage regimens.

Methods

A panel of bNAbs targeting different epitopes were tested in a highly quantitative pseudovirus neutralization assay using TZM-bl target cells [1] on a panel of 199 viral clones. Neutralization curves of 9 different bNAbs (Table 1) in the 0.000128 to 50 ug/mL concentration range were available for analysis. Sigmoidal Emax models were fitted to the data from each bNAb, including between-strain variability (BSV) on E0, IC50, and the Hill factor ɣ. The maximal neutralization was fixed to 1. For combinations of bNAbs, the effects were predicted using the principles of Loewe additivity or Bliss independence [2] and were compared to the observed inhibition in assays using these combinations. From the model, the concentration giving at least 80% inhibition in 80% of viruses types, the IC80(80), was estimated. NONMEM 7.2 with FOCE was used to fit the data.

$$Neutralization_i = N0_i + \frac{C^{\gamma_i}}{C^{\gamma_i} + IC50_i^{\gamma_i}} \bullet (1 - N0_i)$$

Loewe additivity

Loewe additivity assumes that with no synergism or antagonism, one drug can be replaced by an equipotent dose of another. If there is no additional "synergistic" effect when two drugs are combined, the effects of the combination can be predicted by adjusting dose or concentration for potency using Loewe additivity.

$$\frac{C_A}{IC_{50,A}} + \frac{C_B}{IC_{50,B}} = 1$$

If $Emax_A = Emax_B$ and $\gamma_A = \gamma_B$ (the Hill factor), the effect of the combination can be predicted by:

$$E_{A,B} = \frac{E\max}{1 + \left(\frac{C_A}{EC_{50,A}} + \frac{C_B}{EC_{50,B}}\right)^{\gamma}}$$

e.g. if drug A is twice as potent as drug B, 1mg of A will give the same effect as 2mg of B, or as 0.5mg of A + 1 mg of B.

Bliss independence

Bliss independence predicts effects to be sequential, i.e., the effects are "probabilistically independent". Using the Emax model, the effect can be calculated from:

$$E_{A,B} = 1 - \left(1 - \frac{E\max \cdot C_A^{\gamma}}{\varphi \cdot EC50_A^{\gamma} \cdot C_A^{\gamma}}\right)\left(1 - \frac{E\max \cdot C_B^{\gamma}}{\varphi \cdot EC50_B^{\gamma} \cdot C_B^{\gamma}}\right)$$

where φ is a parameter describing any synergism (if φ<1) or antagonism (φ>1).

Loewe additivity and Bliss independence give similar but different predictions of the combined effects.

Table 1. bNAbs in the modeled dataset.

Binding location	Binding site	bNAb
Envelope protein	V2 glycan	PGDM1400
		CAP256-VRC26.25
	V3 glycan	PGT121
		PGT145
		10-1074
Top of the trimer	MPER	10E8
CD4 binding site	CD4bs	VRC07-523-LS
		3BNC117
		VRC13

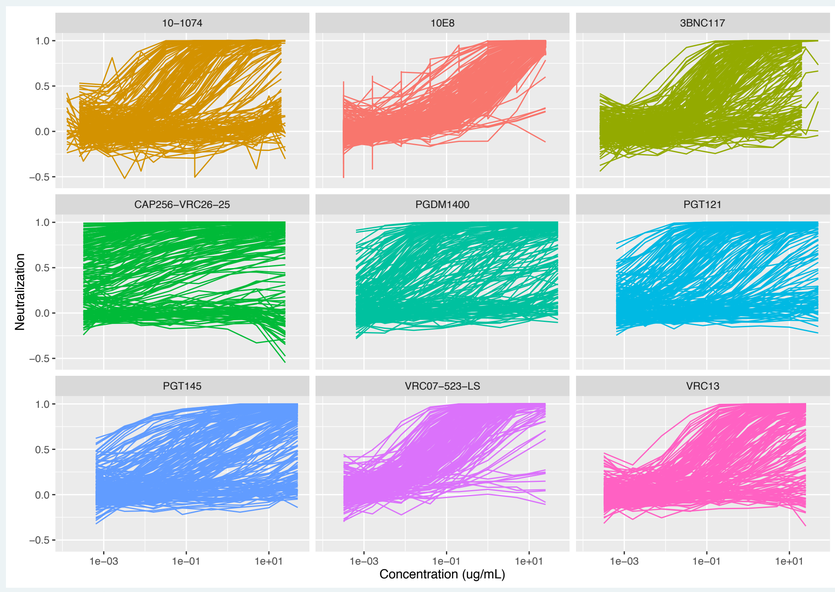

Figure 1. Observed neutralization vs bNAb concentration, by bNAb type. Each line represents one viral clone.

Results

For each bNAb, the inhibition curves varied widely between the virus strains. Notably, some bNabs do not always achieve 100% neutralization even at high concentrations. To fit this wide variability, a mixture model was introduced for IC50, which lead to reasonable fits to the data (Figure 3). Even so, the BSV of IC50 within each mixture subset remained large. Standard errors were generally below 30%, but were usually higher for IC50.2, the IC50 value for the less sensitive subpopulation. For two bNAbs this value had to be fixed to a high value. The values for selected parameters are presented in Table 2.

BSV was found to be additive for N0, and exponential for IC50 and ɣ. Residual variability was higher at low neutralization, and was modeled as

$$\sigma^2 = \sigma_{add}^2 + \sigma_{prop}^2 \cdot (1 - Neutralization)$$

IC50s generally correlated across strains for bNAbs binding to the same epitope (Figure 2). Predictions using the Bliss independence method agreed better with the observed effect of combinations, than effects predicted using Loewe additivity (Figures 4 and 5). φ was estimated at 0.96 and was not significantly different from 1, indicating that there was no significant synergism or antagonism, but that the bNAbs interacted as described by Bliss independence. Predicted IC80(80) values of selected combinations are shown in Table 3.

Table 2. Selected parameters from the final models.

bNAb	IC50.1 (µg/mL)	IC50.2 (µg/mL)	Fr	ɣ	BSV IC50 (%)	IC80(80) (µg/mL)
VRC07-523-LS	0.233	25000 (fixed)	5%	1.65	158	3.12
10E8	0.652	69.3	3%	0.96	112	7.21
3BNC117	0.306	75.6	24%	1.09	151	74.8
PGT121	0.118	329	32%	0.98	222	733
10-1074	0.164	468	34%	1.35	213	768
VRC13	0.483	858	24%	0.80	207	788
PGDM1400	0.00725	207	33%	0.63	254	1240
PGT145	0.136	670	34%	0.50	288	7350
CAP256-VRC26.25	0.000151	20000 (fixed)	26%	0.35	389	15800

IC50.1: low IC50, IC50.2: high IC50, Fr: proportion of virus strains with high IC50, ɣ: Hill factor, IC80(80): concentration needed to reach 80% neutralization in 80% of viruses.

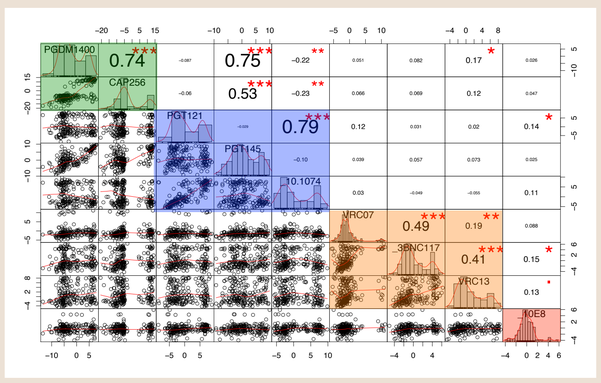

Figure 2. log IC50.1 values by virus strain, correlation across bNAbs. V-2 glycans (green), V-3 glycans (blue), CD4bs (orange) and MPER (red)

*p<0.05, **p<0.01, ***p<0.001

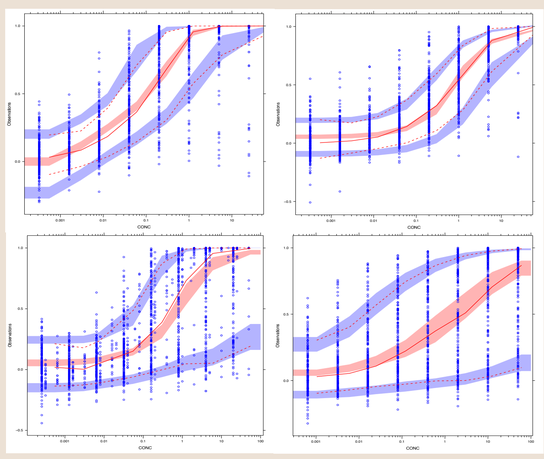

Figure 3. VPCs of selected models. VRC07 (top left), 10E8 (top right), 3BNC117 (bottom left) and PGT145 (bottom right)

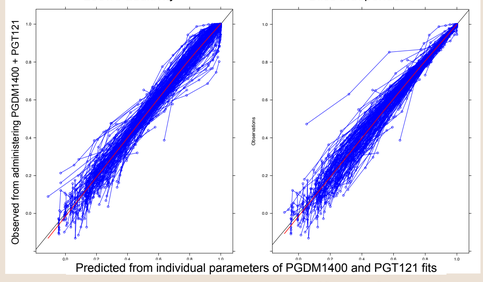

Figure 4. Predicted vs observed effect of combining PGDM1400 and PGT121

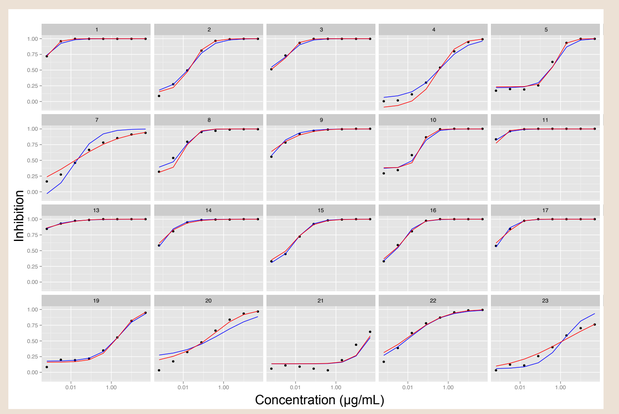

Figure 5. Predictions of the combined effects of PGDM1400 and PGT141 on different viral clones, based on individual parameter estimates, compared to the observed effects of the combination. Bliss independence (red) and Loewe additivity (blue).

Table 3. Predicted IC80(80) for selected two and three bNAb combinations

Two bNAb combinations			Three bNAb combinations			
bNAb 1	bNAb 2	IC80(80) (µg/mL)	bNAb 1	bNAb 2	bNAb 3	IC80(80) (µg/mL)
VRC07-523-LS	CAP256-VRC26-25	0.856	VRC07-523-LS	CAP256-VRC26-25	PGT121	0.483
VRC07-523-LS	PGDM1400	1.25	VRC07-523-LS	CAP256-VRC26-25	10-1074	0.537
VRC07-523-LS	PGT121	1.81	3BNC117	CAP256-VRC26-25	PGT121	0.654
VRC07-523-LS	10-1074	1.96	3BNC117	CAP256-VRC26-25	10-1074	0.726
VRC07-523-LS	10E8	2.02	VRC07-523-LS	PGDM1400	PGT121	0.726
PGT121	CAP256-VRC26-25	2.10	VRC07-523-LS	10E8	CAP256-VRC26-25	0.738
3BNC117	CAP256-VRC26-25	2.20	VRC07-523-LS	PGDM1400	10-1074	0.807
VRC07-523-LS	PGT145	2.28	3BNC117	PGDM1400	PGT121	1.03
10-1074	CAP256-VRC26-25	2.48	VRC07-523-LS	10E8	PGDM1400	1.04

References

1. Kong, R., Louder, M. K., Wagh, K., Bailer, R. T., deCamp, A., Greene, K., … Mascola, J. R. (2015). Improving Neutralization Potency and Breadth by Combining Broadly Reactive HIV-1 Antibodies Targeting Major Neutralization Epitopes. Journal of Virology, 89(5), 2659–2671.
2. Berenbaum, M. C. (1989). What is synergy? Pharmacol Rev, 41, 93–141

Conclusions

- In vitro data of bNAb effects in neutralizing HIV-1 virus showed a highly variable potency between viral strains.
- Data could be well fitted using sigmoidal Emax models with a mixture model on IC50.
- When assuming Bliss independence, the model proved predictive for the effects of combinations of bNAbs binding to different viral epitopes.
- The bNAb combinatorics predictive platform is firmly at the core of data-driven decision-making for the bNAb program, helping to select efficient combinations and dosage regimens.