Estimating and Visualizing HIV-1 Susceptibility to Broadly Neutralizing Antibodies

343

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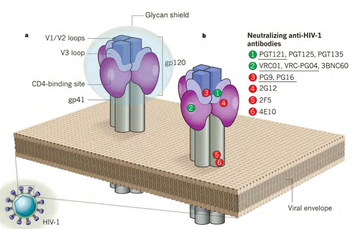
Motivation

In HIV-1 treatment, clinicians still have to face drug-resistant viral strains, while the number of available drugs and drug targets remains limited. Recently, **combination therapy with potent broadly neutralizing antibodies** (bNAbs) was introduced as a viable new option in antiretroviral treatment against HIV-1 that is capable of reducing viral load under detectable levels for up to 60 days in humanized mice[1] and primates[2]. However, similar as with the well established highly active antiretroviral therapy (HAART), the **emergence of neutralization resistant strains** might be a major problem in the selection of an efficient combination therapy of bNAbs for an individual patient. Prior to the administration of an antiretroviral bNAb combination therapy to a patient, it has to be ensured that the patient's viral strains are susceptible to the particular bNAb.

Predict whether a given HIV sequence will be susceptible to a potent broadly neutralizing antibody on the basis of the HIV envelope sequence.

Material

- neutralization assays for seven different bNAbs targeting three major epitopes[3,4]
  - CD4bs: VRC01, VRC-PG04
  - V1/V2 loop: PG9, PG16
  - V3 loop: PGT121, 10-996, 10-1074



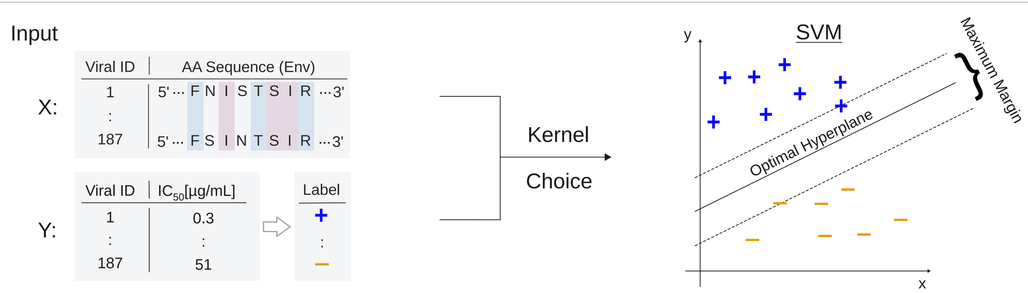
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Fig. 1: The four epitopes of the envelope proteins gp120 and gp41 of HIV-1.

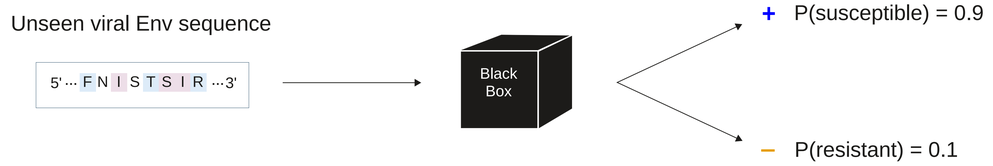
- 115-187 HIV-1 envelope sequences per neutralization assay with corresponding IC_{50} titers
- **Susceptibility** is defined as IC_{50} values below 50 µg/mL. IC_{50} values above indicate **resistance** to the antibody

Methods

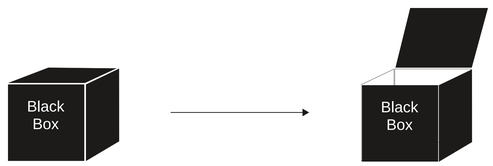
1. Learning



2. Predicting



3. Understanding



3.1 Classifier

bNAb	Discriminant residue x position
PG9	N160/301, N624, S393/613, D187, K168/169/171
PG16	N136/141/160/182, N230, N234/289/356, S393, K169/171, D167, T138
VRC01	N186/276/279/280, G459, K232
VRC-PG04	N186/276/279/280, G459, K232, R456, D368
10-996	N332, N334, S334
10-1074	N332, N334, S334, T388/818
PGT121	QAHCN328, R332

- By definition of the oligo kernel[5], positional information can be retrieved from the classifier
- Identification of most discriminant residues learnt by the classifier is possible

3.2 Classification Result

Additional to the classification result, we can

- Visualize the relationship between the training sequences and the test sequence
- Retrieve contribution of the most discriminative residues to the classification result for a test sequence



Fig. 2: Motif logo for the test sequence HM469973 using the PG9 classifier based on 3% of the strongest discriminant signals. The height of the letter is proportional to the contribution to the classification result. The corresponding amino acid positions of Env in the HIV-1 reference sequence HXB2 are shown on the x-axis.

Results

1. Prediction Performance

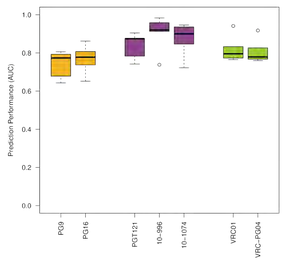


Fig. 3: Prediction performances of the final classifiers for each bNAb using the oligo kernel. The classifiers for the V3 loop-dependent antibodies achieved an AUC performance of up to 84%. In general, classifiers for antibodies targeting similar epitopes yield similar performances.

2. Learnt Parameter Settings

Epitope	bNAb	l-mer	Width
V1/V2 loop	PG9	1	1.0
	PG16	1	0.4
V3 loop	PGT121	6	1.6
	10-996	1	2.6
	10-1074	1	1.6
CD4bs	VRC01	2	3.6
	VRC-PG04	6	20.0

Table 1: Learnt parameter settings for the final classifiers using the oligo kernel for each dataset. The oligo kernel defines the similarity between two sequences by the similarity of their common substrings of a certain size **l**. The width parameter determines the allowed positional variation.

Conclusion

- **Well performing** prediction models (up to 84% AUC)
- Useful in the selection of bNAb combination therapy
- Extendable to new HIV bNAbs or HCV bNAbs
- **Reliable classifiers** identifying potential binding site residues
- Useful for epitope recognition
- **Visualization** of data relationships and **motif logos** improve biological understanding of the classification result

References

[1] Klein et al. 2012, Nature, *HIV therapy by a combination of broadly neutralizing antibodies in humanized mice*

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[4] Mouquet et al. 2012, PNAS, *Complex-type N-glycan recognition by potent broadly neutralizing HIV antibodies*

[5] Meinicke et al. 2004, BMC Bioinformatics, *Oligo kernels for datamining on biological sequences: a case study on prokaryotic translation initiation sites*

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