

# Challenging HIV with antibodies

## HIV prevention & treatment

Manuel E. Sáez Moya; Bachelor's thesis, Degree in Biochemistry

### Introduction & Objectives

- The origin of Human Immunodeficiency Virus (HIV) is unknown, but the most accepted theory is the hunter theory
- HIV is a Retroviridae Lentivirus virus
- This virus has a complex structure & cycle that allow the virus to evade the immune system
- Good antibodies against HIV are not often produced but some infected individuals do and neutralize the virus efficiently forbidding the entrance of the virus to the cell

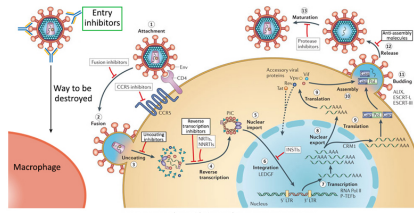


Figure 1: HIV cycle. Modified image from Nature, 2012, 279-290.

- Analyzing the most potent antibodies such as CD4-binding site, understanding where these antibodies are generated (germinal centers (Fig. 5)) and explaining the progress that it has been achieved on this field, are the objective of this review, thanks to the methodology that is based on the understanding of the studies conducted for over more than 20 years

### Beginnings of HIV-1 antibodies

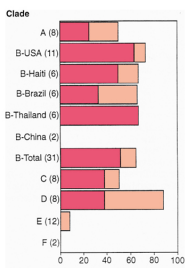


Figure 2: Reactivity of gp120 with broad panels of international isolates of HIV-1. Modified image from Science, 1994, 120-127.

- In the 90s the first group of antibodies against the HIV was found
- b12 was tested against 14 different primary isolated and it showed the capacity to neutralize them at 50% in low titers, in contrast with a pooled human plasma preparation that only neutralized 10 out of these 14 isolates
- 69 international isolates from 6 different clades were tested against b12, showing that b12 has the capacity to neutralize most of them (Fig. 2)
- A model of b12 interacting with gp120 was done to see which aminoacids interact, and the model showed that H3 and Trp100 are important for the antibody binding (Fig. 3)

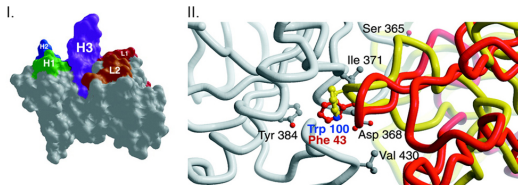


Figure 3: Prominence of H3 (L). Close-up view of a model of b12 interacting with gp120 (H). Modified image from Science, 2001, 1155-58.

### bNabs: progress in the field

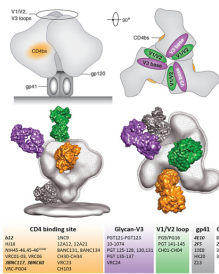


Figure 4: Broad common antibody target sites on the HIV-1 envelope spike. Modified image from Science, 2013, 1199-1204.

- b12 and another antibodies such as 4E10 and 2G12 originate the first generation of broad neutralizing antibodies (bNabs), but second generation have been generated (Fig. 4)
- bNabs have some characteristics in common that confer them special properties:
  - High rate mutation
  - "On" rate and "off" rate, define the affinity of the antibody
  - Framework regions mutated
  - CDRH3 offers the capacity to penetrate the glycan shield
  - Polyreactivity

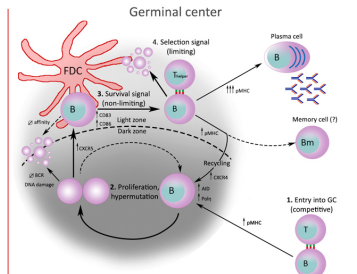


Figure 5: Proposal of germinal center model.

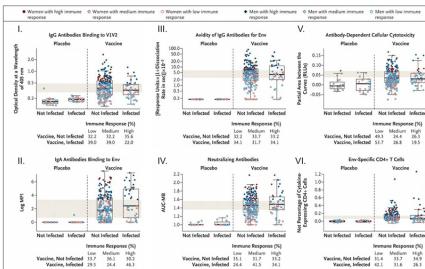


Figure 6: Six primary distribution response variables in infected and uninfected patients, inoculated with vaccine or placebo. The median response of vaccine-injected individuals are indicated by the gray horizontal bar. Modified image from the New England Journal of Medicine, 2012, 1275-1286.

### Alternative methods to attack HIV

#### Gene therapy

- Gene therapy is used to generate an alternative vaccine due to the fact that conventional vaccines are not working
- The antibody consists on a combination of a CD4-Ig and a CCR5mim finally named eCD4-Ig

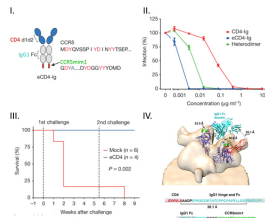


Figure 7: I. & B. Functional characterization of eCD4-Ig response. A: Proposal of a model of eCD4-Ig bound to the HIV-1. B: Low titer. Modified image from Nature, 2013, doi:10.1038/nature12464.

- AAV vector is used to produce the antibody against HIV-1
- *In vivo* trials were done in mice and Rhesus macaques showing great results
- Man-escalation trials should be done to assess the neutralization in human beings

#### Molecular compositions (intra-spike crosslinking)

- bNabs were used to originate a molecular composition to attach one of these molecules to a single spike (Fig. 8)
- This molecular composition consists on a homodimer or heterodimer of bNabs binding regions as b12 or BCN60 which are used in this assay

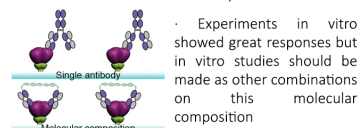


Figure 8: Scheme of differences between common antibodies and the molecular composition. Modified image from Cell, 2015, 433-446.

#### First-in-man dose escalation trial with bNabs

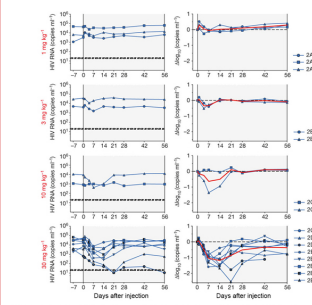


Figure 9: HIV-1 viral load measurements. Modified image from Nature, 2015, doi:10.1038/nature14411.

- 3BNC17 is the antibody chosen to do this assay due to its potency as CD4-binding site bNab
- Infected and uninfected patients were studied and the results proved that 3BNC17 doesn't originate any adverse reaction
- 30 mg kg<sup>-1</sup> was the major dose inoculated and the one which showed a greater descent of HIV
- The average is 28 days but in some infected individuals viral levels didn't reach their baseline after 56 days
- Resistance was shown in some infected patients whereas in others low or no resistance appeared at all
- To sum it up, 3BNC17 could be a good therapy combined with other antibodies or drugs because 3BNC17 is not enough to control viral levels

### Conclusions & future proposals

1. Recent studies have achieved great approximations in the vaccine and cure fields
2. However, no vaccine or cure has been discovered yet
3. High rate mutation is the worst problem to resolve so as to forbid HIV evasion
4. Germinal centers are the most accepted places where bNabs could be generated spontaneously
5. Gene therapy like eCD4-Ig vaccine must be used consciously because immune system is not working by itself
6. New therapies should be tested like combinations of drugs and antibodies that induce the activation of the genome of infected cells helping the virus eradication
7. Customized treatment could be a great approach to treat infected patients because HIV has many different clades and each one evolves differently

#### References

- T. Shors, 2013. Understanding viruses Jones and Bartlett Publisher
- Florian Klein, Hugo Mouquet, Pia Doerflinger, Johannes F. Scheid, Louise Scharf, Michel C. Nussenzweig. Antibodies in HIV-1 Vaccine Development and Therapy. Science, 2013, 1199-1204
- Victoria GD, Nussenzweig MC. Germinal Centers. Annu Rev Immunol. 2012;30(3):429-57
- Gardner ML, Kattenhorn LM, Kondur HB, Van Schueren M, Dorfman T, Chang L, et al. AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges. Nature. Nature Publishing Group; 2015
- Galimidi RP, Klein JS, Polzella MS, Bae S, Seaman MS, Nussenzweig MC, et al. Intra-Spike Crosslinking Overcomes Antibody Evasion by HIV-1. Cell [Internet]. Elsevier Inc.; 2015;160(3):433-46
- Caskey M, Klein F, Lorenz JCC, See-ah M, West AP, Buckley N, et al. Viremia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature. 2015