# Temsavir protects bystander cells from ADCC and blocks cytokine burst by monocytes

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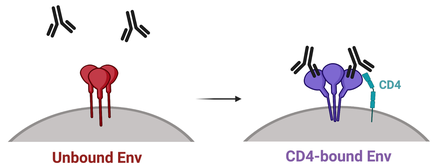
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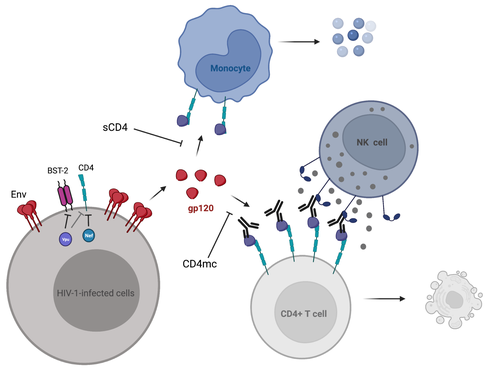
## BACKGROUND

**ADCC-mediating nnAbs present in HIV+ plasma target the Env CD4-bound conformation**




Veillette *et al.*, 2014 ; Veillette *et al.*, 2015

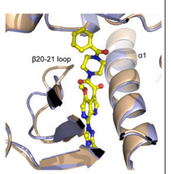
**Shed gp120 sensitizes uninfected bystander cells to ADCC responses and induces a cytokine burst by monocytes**




Veillette *et al.*, 2014 ; Veillette *et al.*, 2015 ; Richard et al, 2016 ; Levast *et* al., 2017; Richard *et al.*, 2018

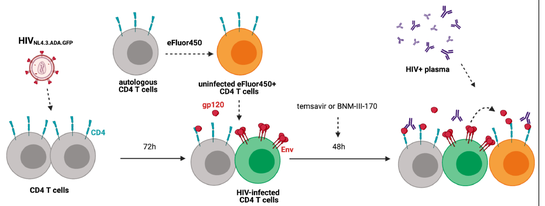
### Temsavir (BMS-626529)

- The FDA-approved small molecule **temsavir** (BMS-626529) acts as an HIV-1 attachment inhibitor by preventing Env-CD4.
- Temsavir binds under the Env β20-β21 loop and in the Phe43 cavity, creating a channel orthogonal to the Phe43 cavity opening. (Pancera *et al.*, 2017)
- Upon temsavir binding, the Env trimer is kept «closed» and allosterically prevents CD4 binding by separating the bridging sheet and the inner domain of gp120. (Pancera *et al.*, 2017)



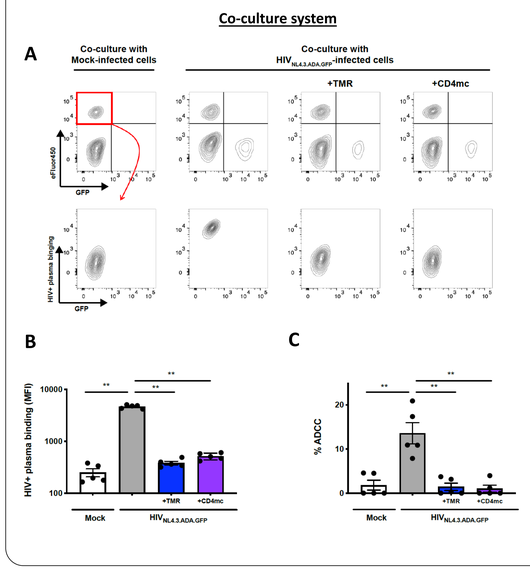

Pancera *et al.*, 2017

### Co-culture system

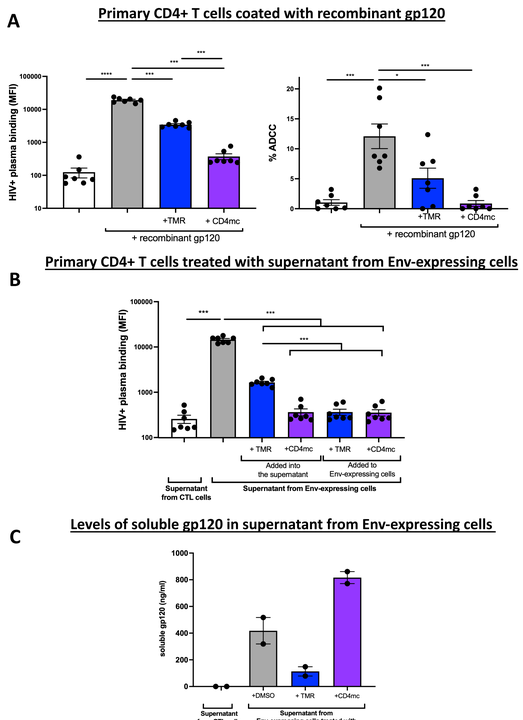



## RESULTS

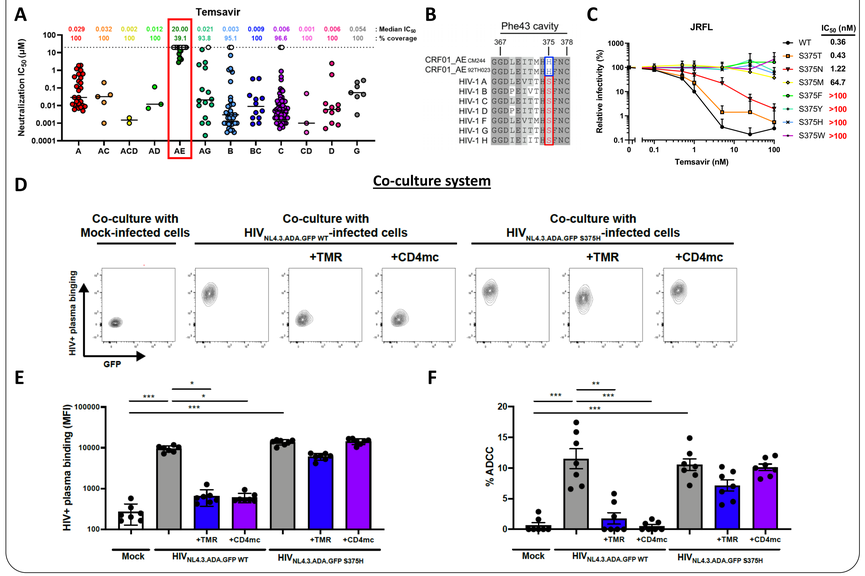
### Figure 1.Temsavir protects uninfected bystander cells from ADCC mediated by HIV+ plasma




### Figure 2 . Temsavir controls the level of soluble gp120 and prevents its interaction with uninfected cells

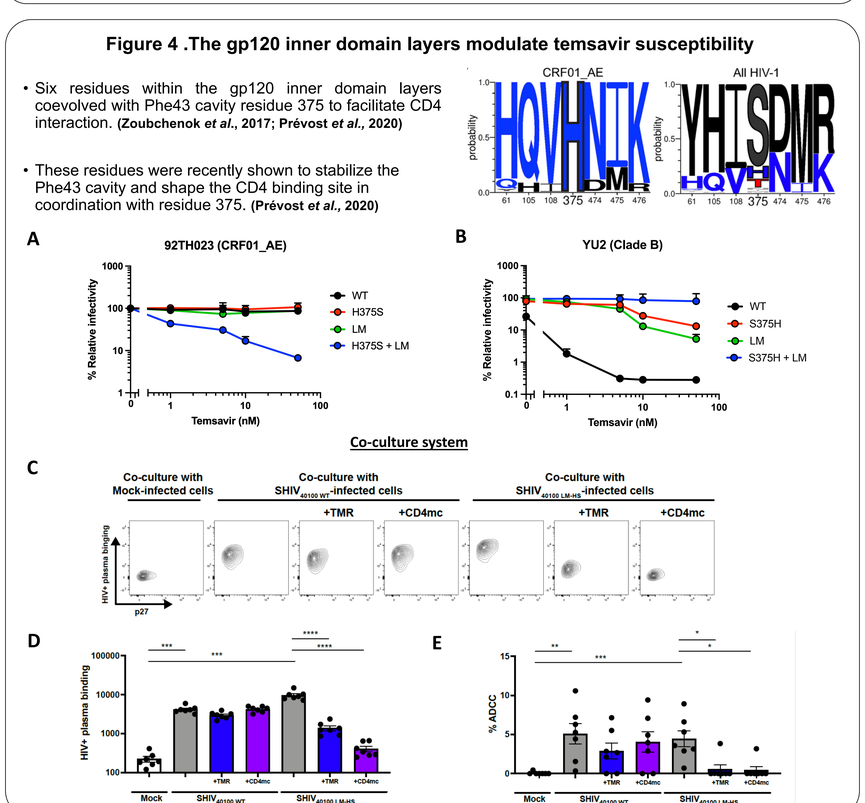



### Figure 3.Residue 375 modulates the capacity of temsavir to protect uninfected bystander cells from ADCC



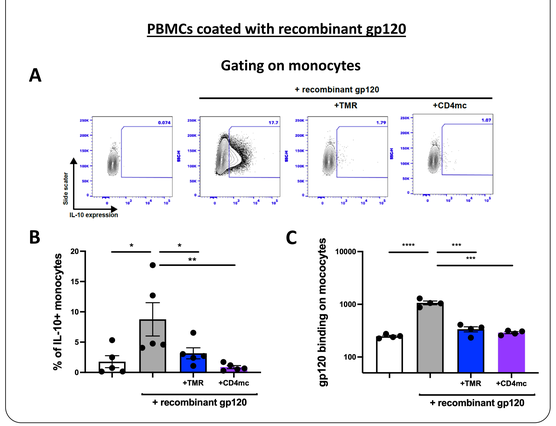

### Figure 4 .The gp120 inner domain layers modulate temsavir susceptibility

- Six residues within the gp120 inner domain layers coevolved with Phe43 cavity residue 375 to facilitate CD4 interaction. **(Zoubchenok *et al.*, 2017; Prévost *et al.*, 2020)**
- These residues were recently shown to stabilize the Phe43 cavity and shape the CD4 binding site in coordination with residue 375. **(Prévost *et al.*, 2020)**

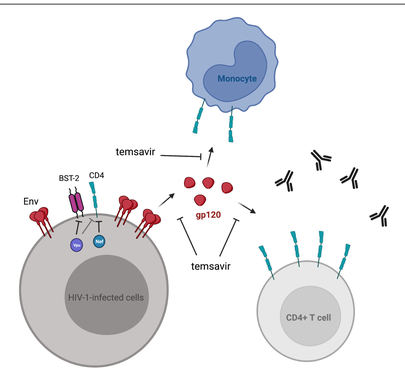



### Figure 5. Temsavir prevents gp120-induced IL-10 secretion by monocytes

PBMCs coated with recombinant gp120




## CONCLUSIONS




- Temsavir prevents gp120 shed from productively-infected cells to interact with uninfected CD4+ T cells and monocytes.
  - ➢ By controlling the level of soluble gp120 and its interaction with CD4.
- This protects uninfected bystander CD4+ T cells from ADCC responses and prevent IL-10 secretion by monocytes.
- The Phe43 cavity and the gp120 inner domain layers are critical in determining the susceptibility of HIV-1 to temsavir.

➢ **This suggests that the clinical benefits provided by temsavir treatment could extend beyond blocking viral entry.**

## ACKNOWLEDGMENTS

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Canada
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NIH National Institutes of Health
Mitacs
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