IFITM3 and SERINC5 exert distinct inhibitory pressures on HIV-1 Env over the course of viral infection

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Introduction & Objectives

- **HIV-1 Envelope glycoprotein (Env) is under constant pressure of adaptive immunity and innate immunity (1).**
- **A group of host cellular factors have been reported to inhibit HIV-1 Env mediated virus entry such as serine incorporator 5 (SERINC5) and Interferon inducible transmembrane protein (IFITM3) (2-4).**
- **SERINC5 and IFITM3 inhibit HIV-1 entry by getting into HIV-1 particles and inhibit viral Env-mediated entry (2-5).**
- **We reported that HIV-1 Envelope (Env) can evolve to overcome the inhibition by IFITM3 and SERINC5 (6,7).**
- **It is not entirely known how the susceptibility of HIV-1 Env to SERINC5 inhibition changes over the course of HIV-1 infection.**
- **The aim of this study is to understand if Env sensitivity to either IFITM3 or SERINC5 has any correlation with the progression of HIV-1 infection, and how HIV-1 Env acquires resistance to these restriction factors.**

Methods:

I. HIV-1 Env susceptibility assay to SERINC5 or IFITM3 :

NL4-3 ΔNef ΔEnv
HIV-1 primary Env clones
SERINC5/ IFITM3

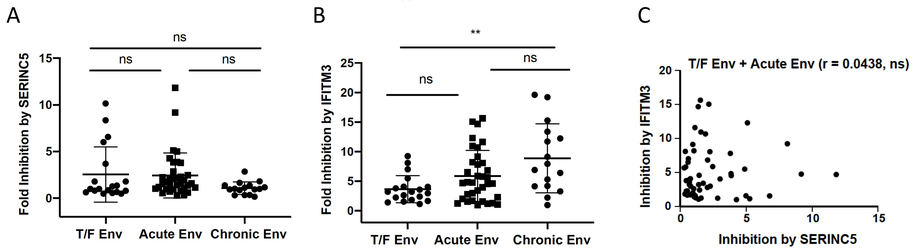
Co-transfection of HEK293T cells

48 hours → Infection of TZM-bl reporter cell → 48 hours → Measure the infectivity of viruses using luciferase assay

II. CD4 mimetic M48U1 neutralization assay:
Viruses were incubated with different concentrations of the CD4 peptide mimetic M48U1 compound

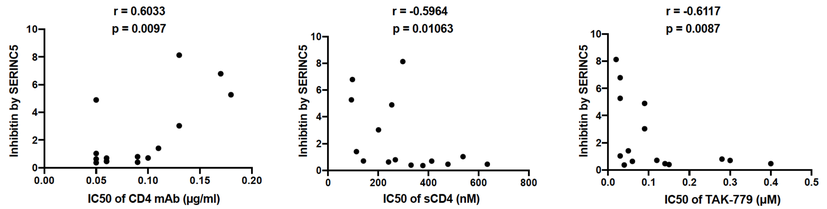
Result (*Click graphs to elaborate and enlarge)*

I.



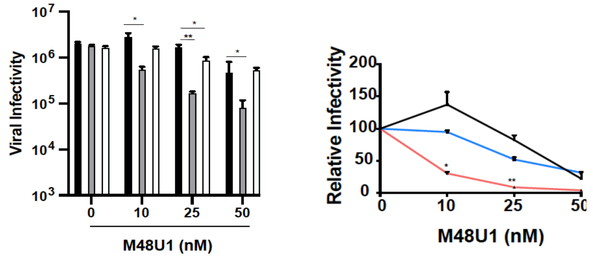
- **HIV-1 Env clones of both acute and chronic infections are resistance to SERINC5 inhibition.**

II.



- **Correlation between the inhibition of HIV-1 Env clones by SERINC5 and IFITM3 with the responses of HIV-1 Env clones to CD4 mAb, sCD4 and CCR5 inhibitor TAK-799**

III.



- **Effect of CD4 mimetic M48U1 on the inhibition of HIV-1 Env by SERINC5 and IFITM3.**

Summary & Significance

- **Resistance to SERINC5 by HIV-1 Env is persisted across different stages of HIV-1 infection, from HIV-1 transmission to acute infection and subsequent chronic infection.**
- **In contrast, while resisting IFITM3 inhibition during transmission, HIV-1 Env gradually loses this resistance property as the infection progresses to the chronic stage**
- **Env clones can have low IC50 values of sCD4, i.e. high affinity to CD4, yet exhibit resistance to SERINC5**

Questions? Contact: saina.beitari@mail.mcgill.ca

References & Acknowledgements

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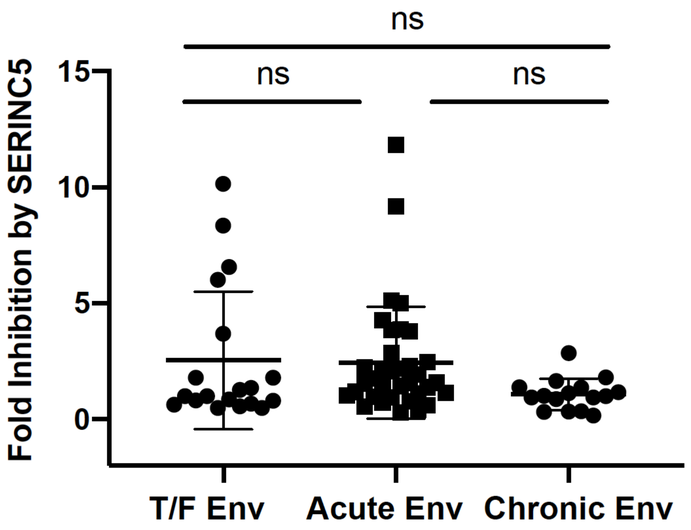
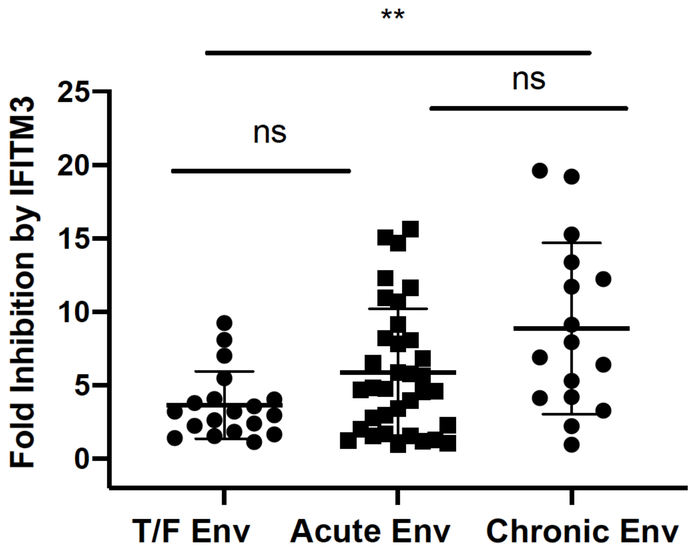
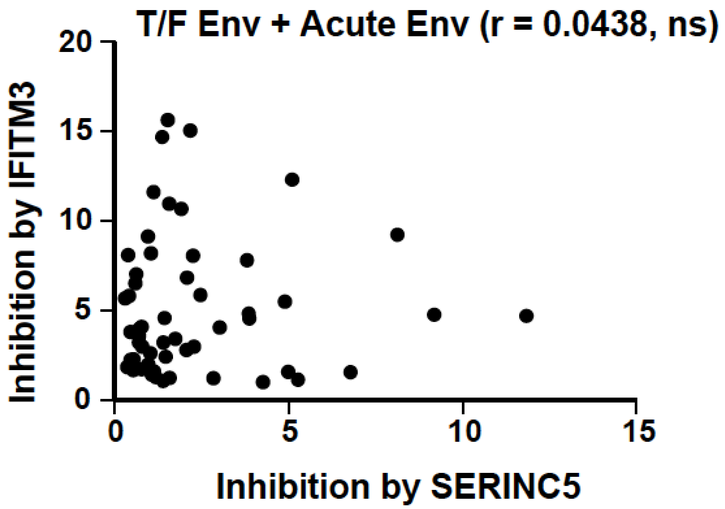
Result I. HIV-1 Env clones present distinct profiles of susceptibility to SERINC5 and IFITM3 restriction.

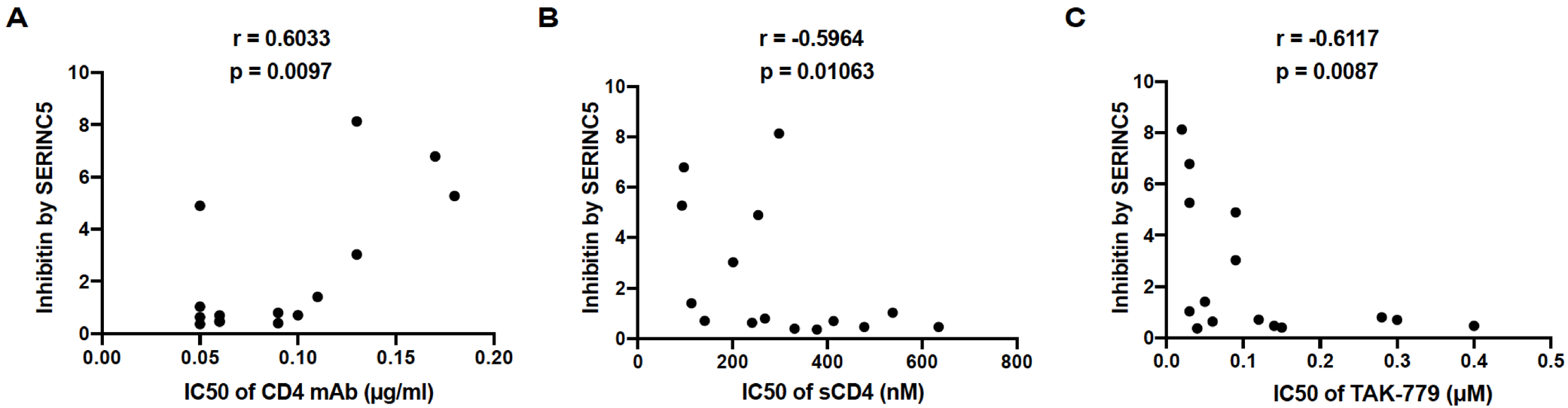






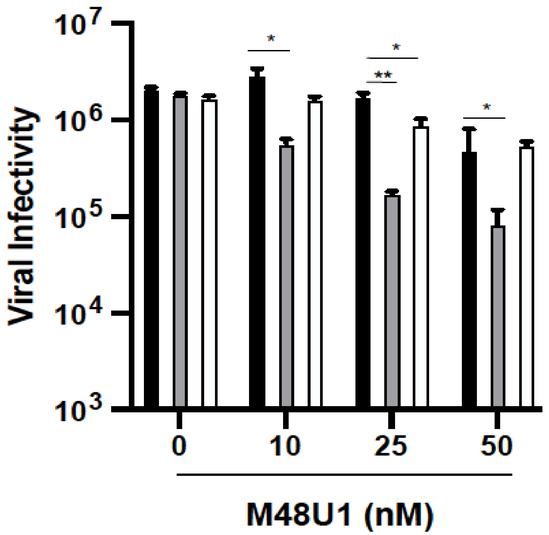
- HIV-1 Env clones of both acute and chronic infections are resistance to SERINC5 inhibition.
- T/F Env clones are relatively resistant to IFITM3 restriction, but this resistance property is lost as the infection advances.
- There is no correlation between the sensitivity of IFITM3 and SERINC5.

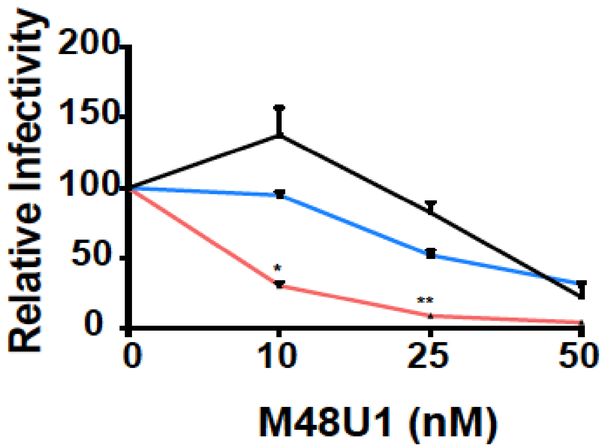
Result II. SERINC5-resistant HIV-1 Envs tends to be refractory to soluble CD4 inhibition.



- A significant positive correlation was detected between the IC50 values of T/F Env against a CD4 monoclonal antibody (mAb) RPA-T4 and the folds of inhibition by SERINC5.
- A significant negative correlation between the folds of inhibition by SERINC5 and the IC50 values for sCD4 against the T/F Env clones.
- A significant negative correlation between the folds of inhibition by SERINC5 and the IC50 values for CCR5 inhibitor (TAK-779) against the T/F Env clones.

Result III: Effect of CD4 mimetic M48U1 on the inhibition of HIV-1 Env by SERINC5 and IFITM3.





- Effect of the miniprotein CD4 mimetic M48U1 on the inhibition of HIV-1 Env by SERINC5 and IFITM3.
- The CD4 mimetic M48U1 sensitizes HIV-1 Env to the inhibition by SERINC5 but not IFITM3