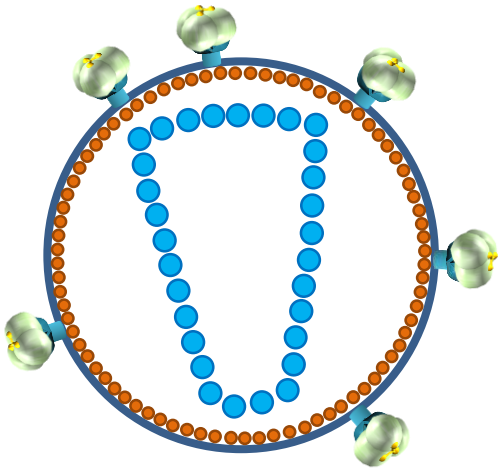
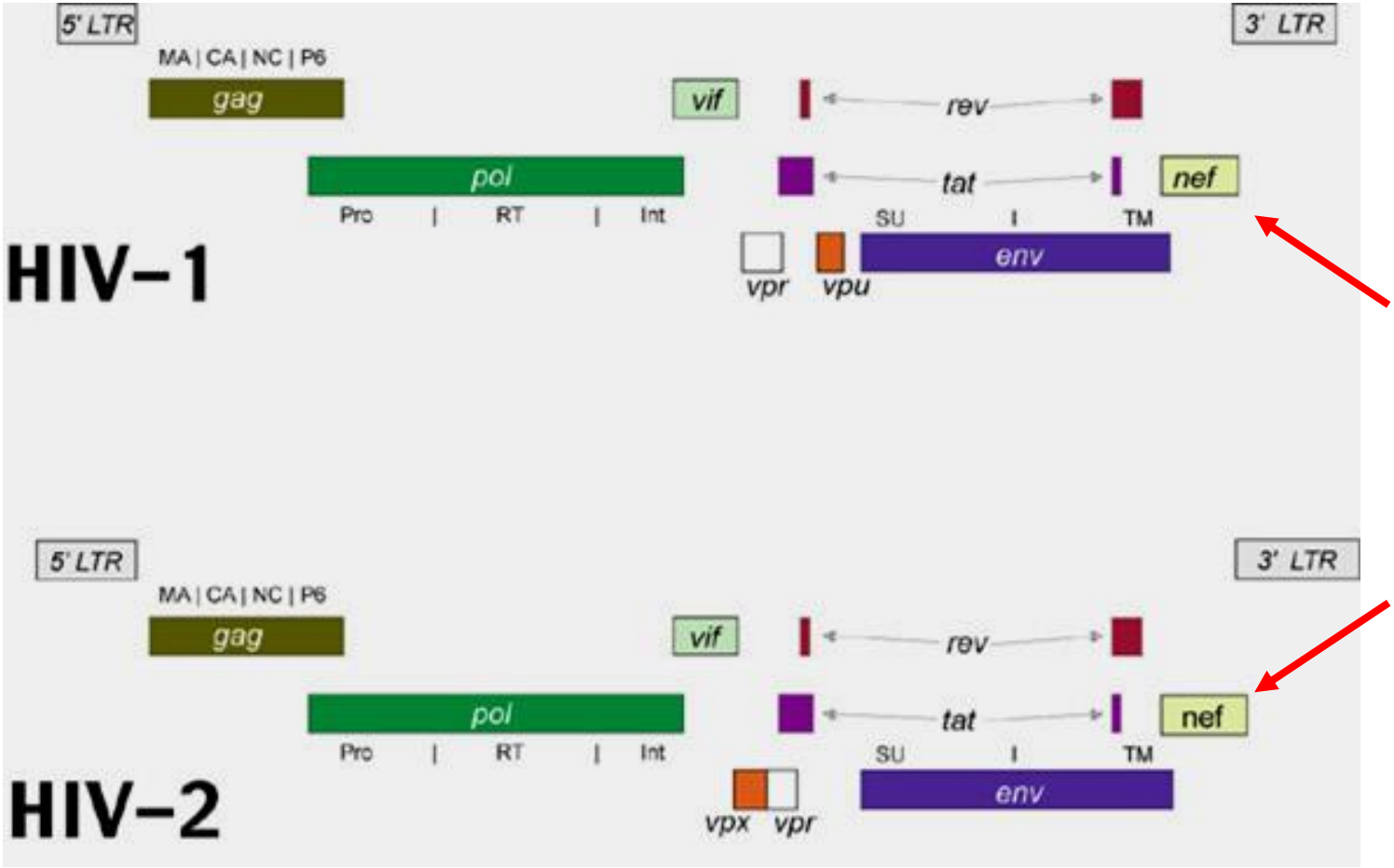
SERINCs: novel restriction factors counteracted by HIV Nef

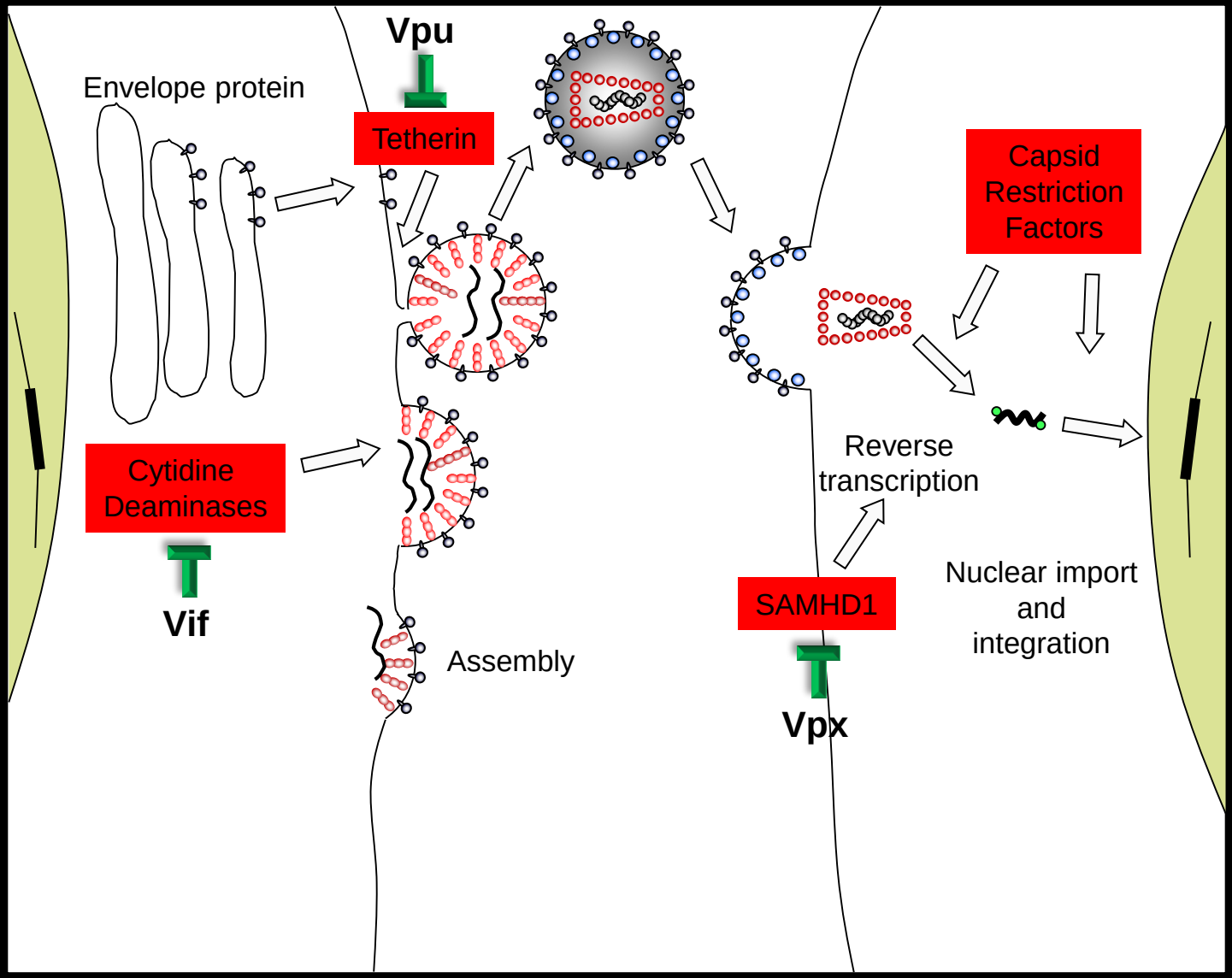


Heinrich Göttlinger, MD
Molecular, Cell and Cancer Biology
UMass Medical School

HIV-1 Genes and Proteins



Intrinsic cellular-defense against retroviruses



Role of HIV-1 Nef

- Crucial for high viral loads and disease progression
- In cell culture:
  - Robustly down-regulates CD4
  - Down-regulates MHC-I
  - **Enhances infectivity**
    - CD4-independent
    - No obvious effect on virion
    - Producer cell-dependent
    - Effect depends on **dynamin, clathrin, AP2**
    - Effect mimicked by **MLV glycoGag**
    - Effect determined by **Env**

ARTICLE

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HIV-1 Nef promotes infection by excluding SERINC5 from virion incorporation

Annachiara Rosa[1]*, Ajit Chande[1]*, Serena Ziglio[1]*, Veronica De Sanctis[2], Roberto Bertorelli[2], Shih Lin Goh[3], Sean M. McCauley[3], Anetta Nowosielska[3], Stylianos E. Antonarakis[4,5], Jeremy Luban[3], Federico Andrea Santoni[4] & Massimo Pizzato[1]

ARTICLE

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SERINC3 and SERINC5 restrict HIV-1 infectivity and are counteracted by Nef

Yoshiko Usami[1]*, Yuanfei Wu[1]* & Heinrich G. Göttlinger[1]


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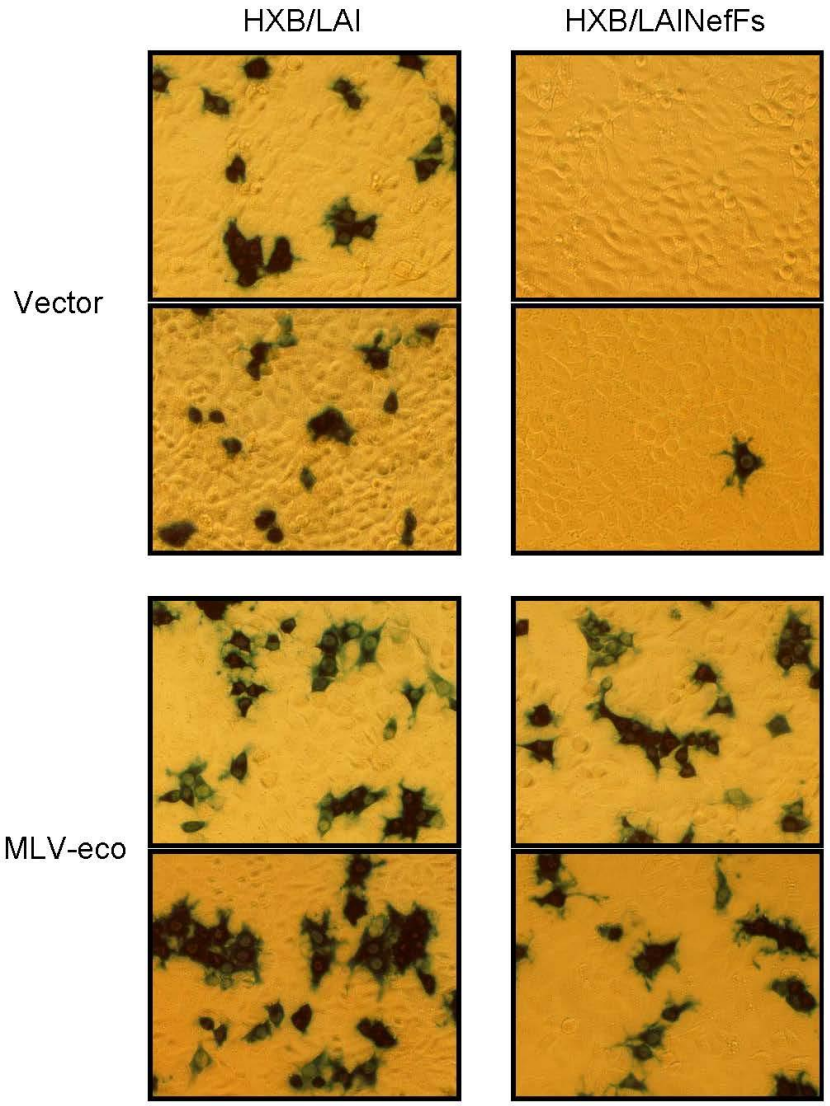
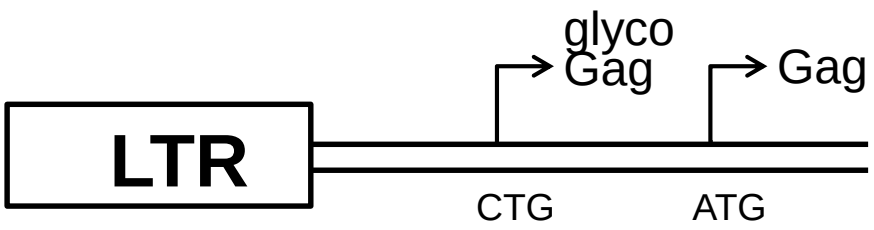
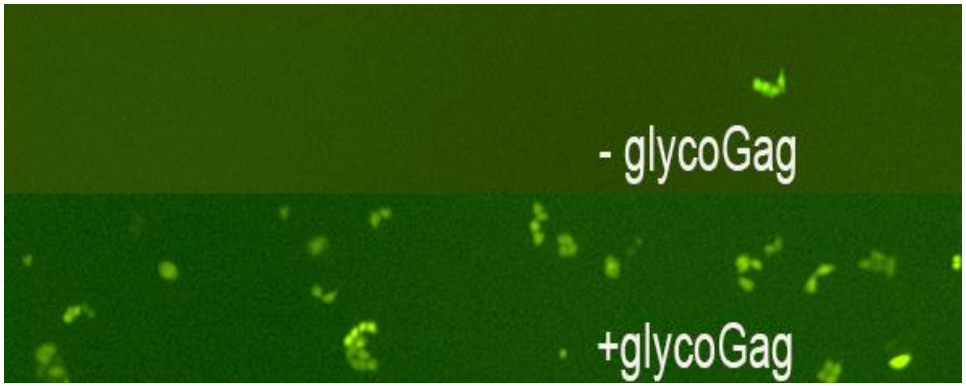


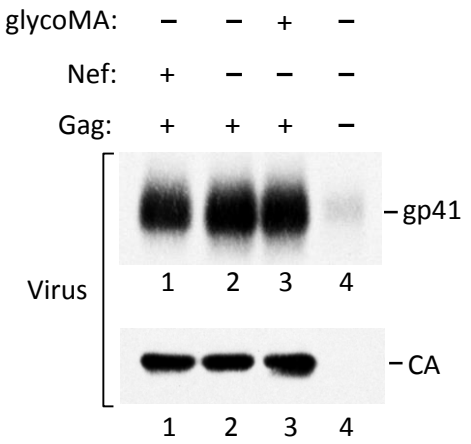
provided by Massimo Pizzato

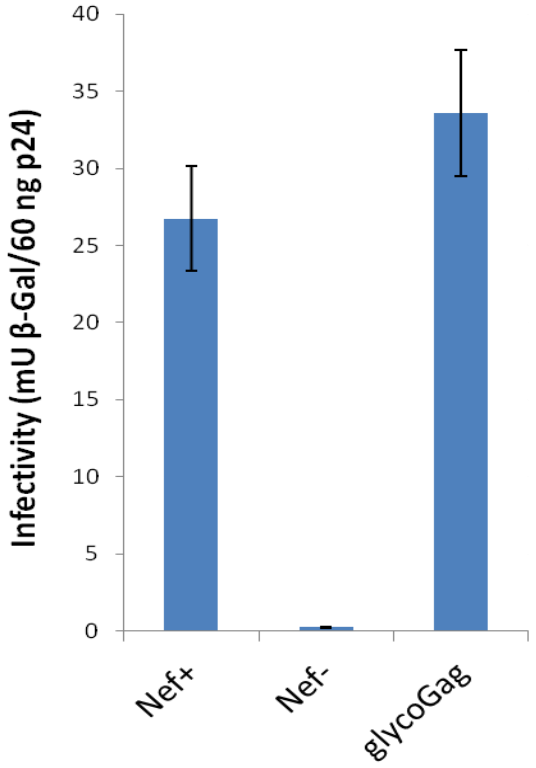
MLV glycoGag has Nef-like effect on HIV infectivity

5’ end of murine leukemia virus:



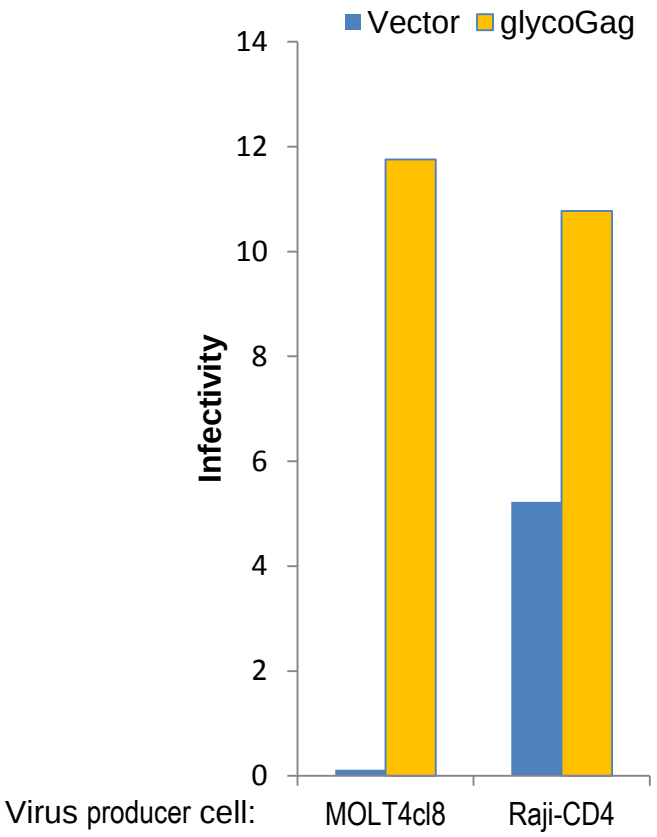




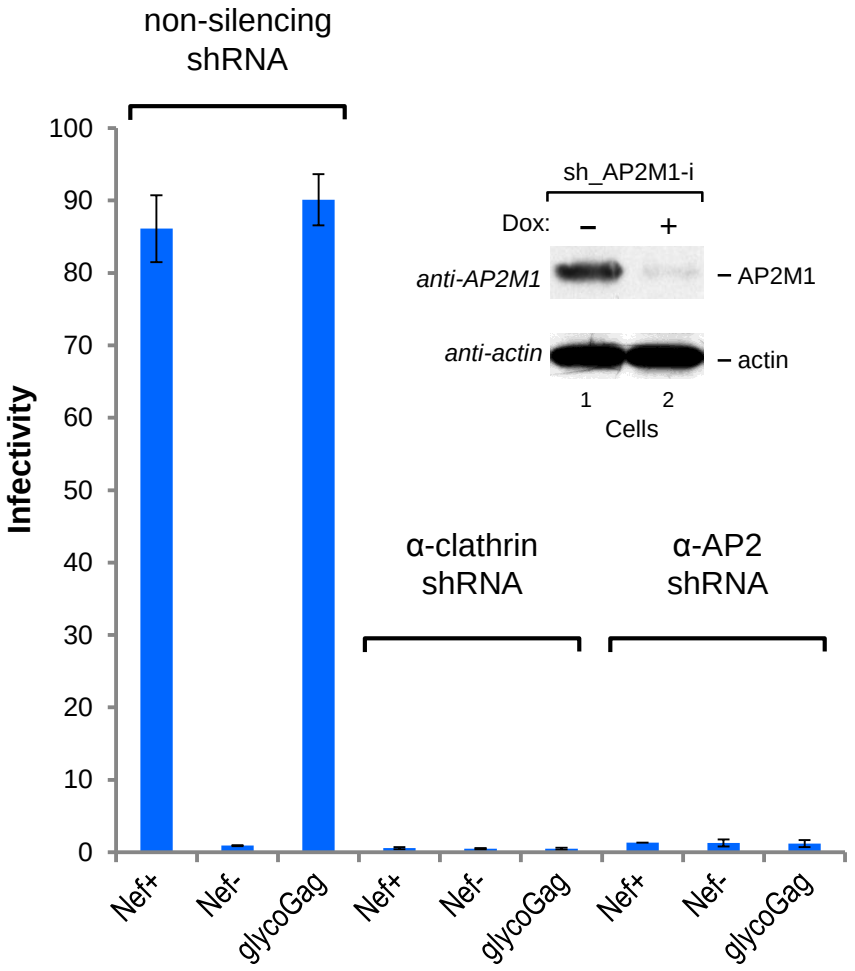


HIV-1 infectivity enhancement by Nef and glycoGag

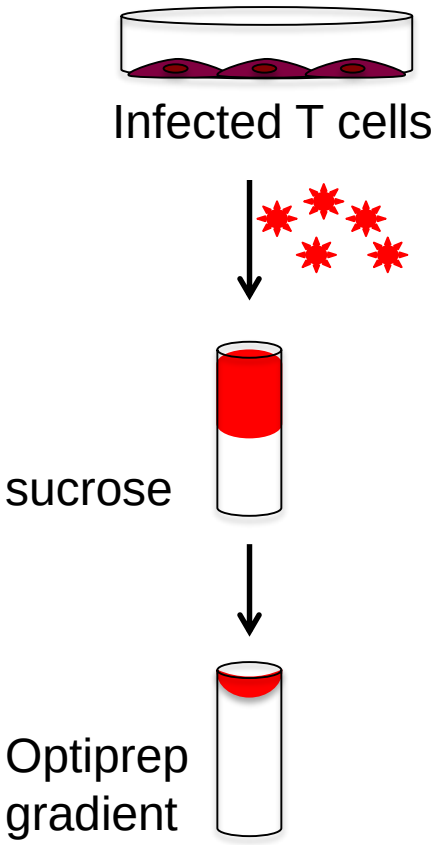
Dependence on producer cell type:



Dependence on clathrin-mediated endocytosis:



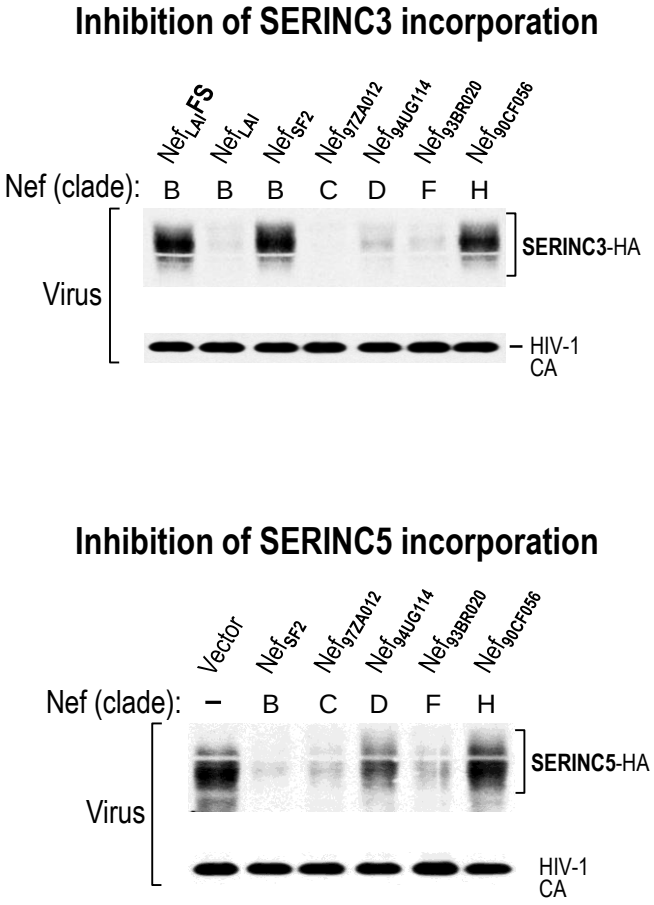
- HIV Nef and MLV glycoGag similarly enhance HIV-1 infectivity
- Effects are similarly dependent on producer cell type
- Effects exhibit a similar reliance on clathrin-mediated endocytosis

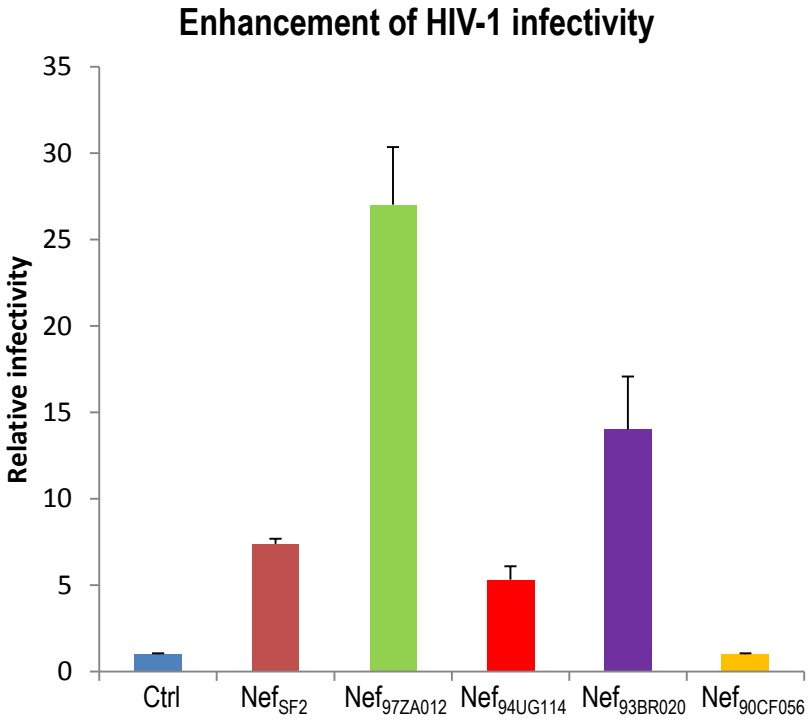


Proteins identified only in Nef⁻ virions

	Protein Symbol	Gradient Fraction	Total Spectrum Count	% Coverage
Experiment 1	**SERINC3**	8	7	15
		9	11	16
	STOM	8	2	7
		9	6	16
	PFKP	8	5	5
		9	10	8
Experiment 2	**SERINC3**	8	5	9
		9	9	9

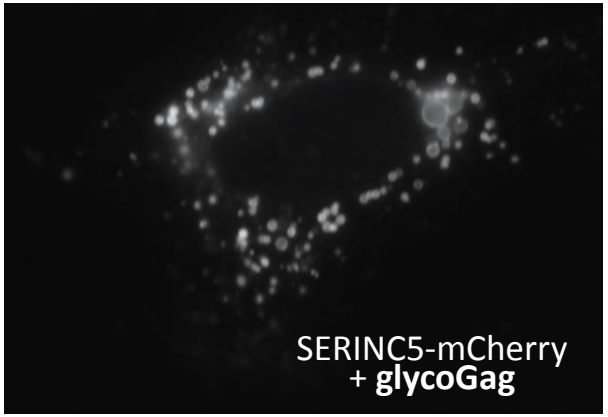
Inhibition of SERINC incorporation by Nef correlates with infectivity enhancement



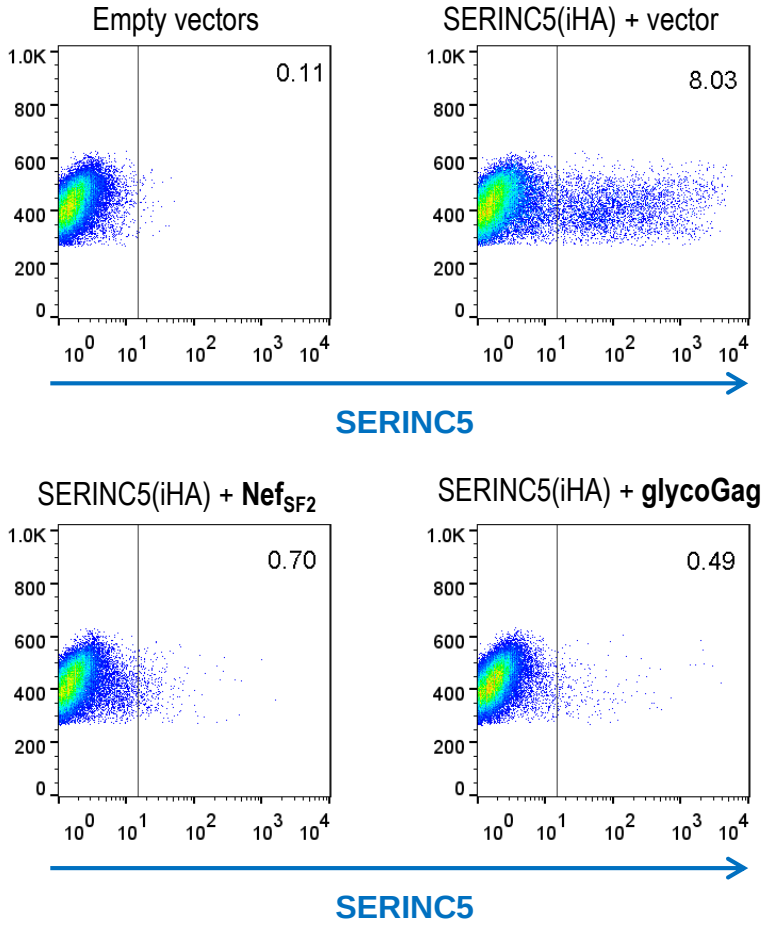


Nef and glycoGag remove SERINC5 from the cell surface

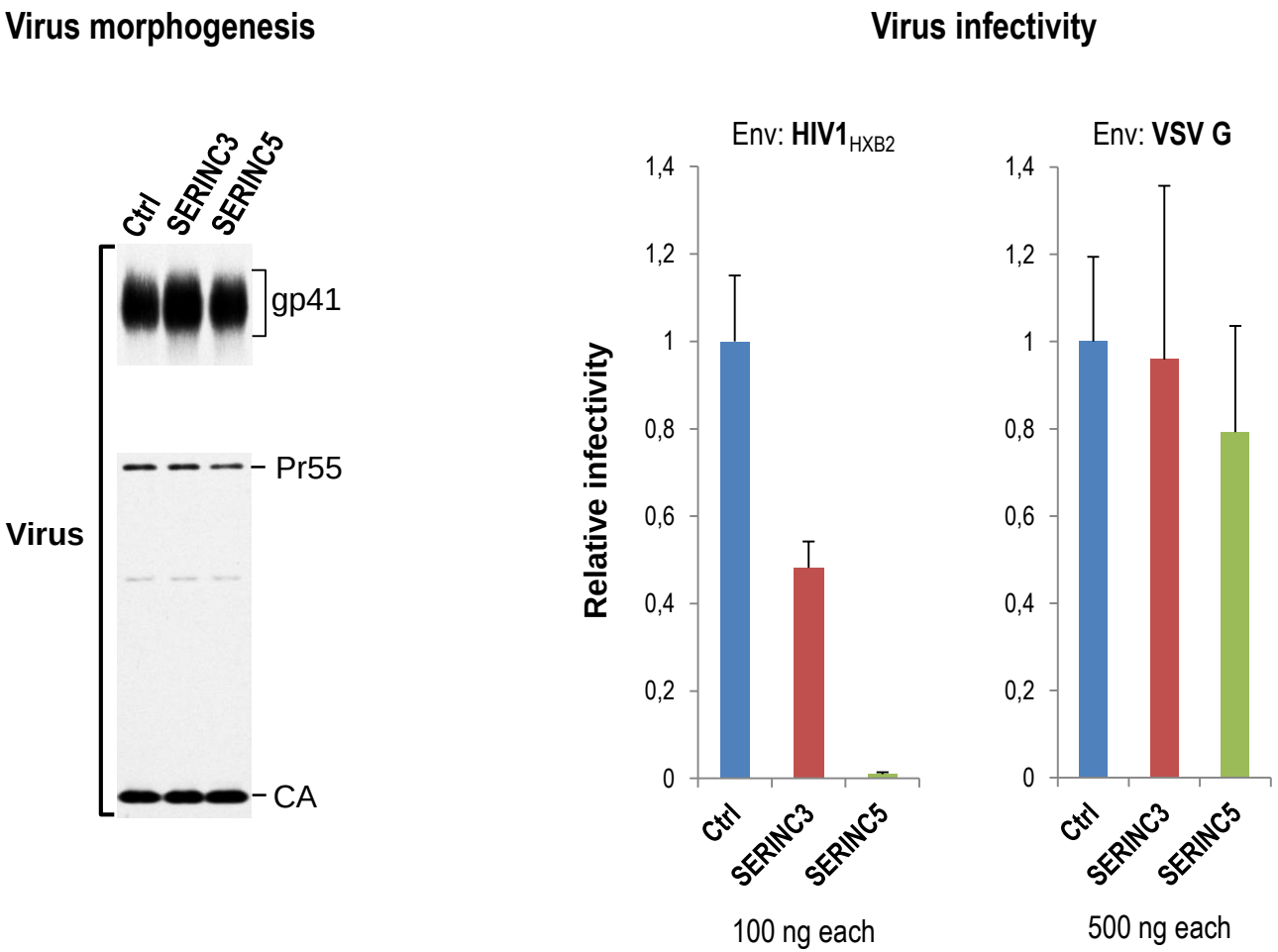
Effect on subcellular localization



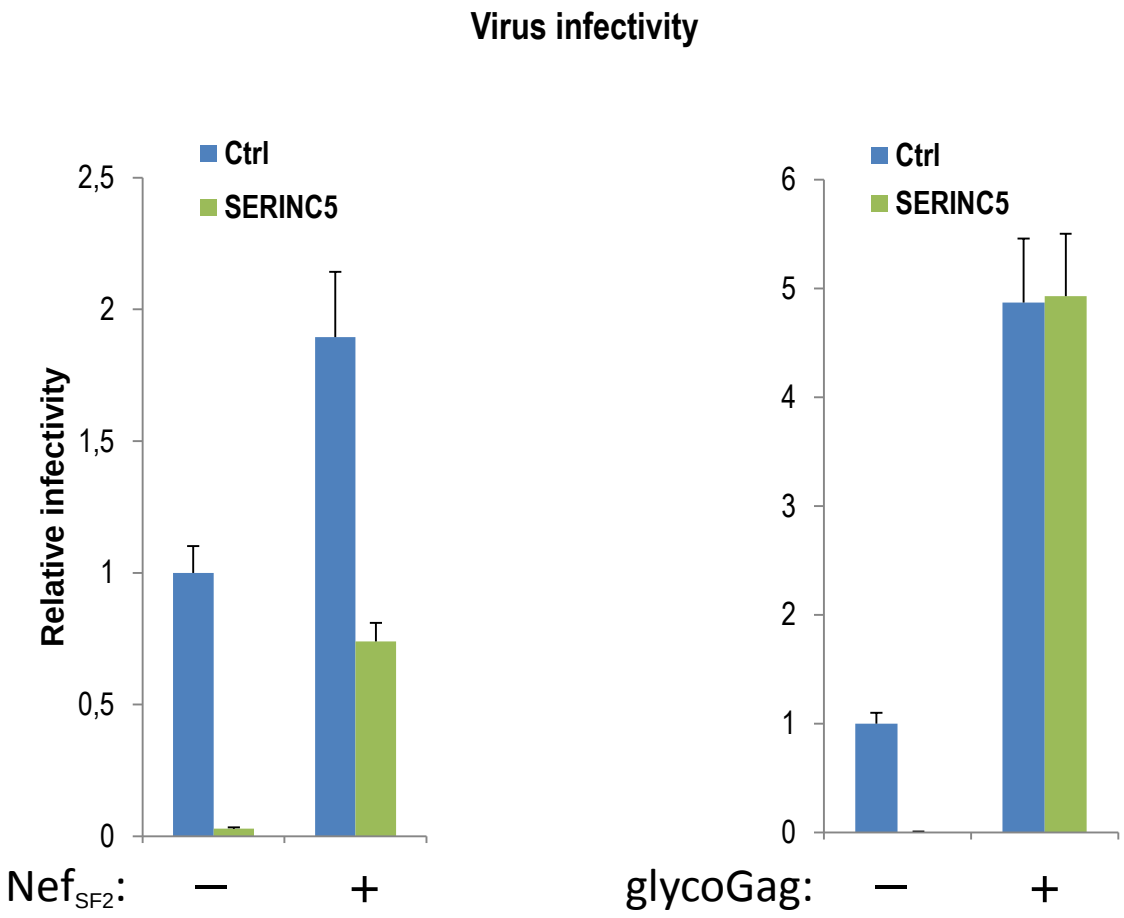
Effect on cell surface expression



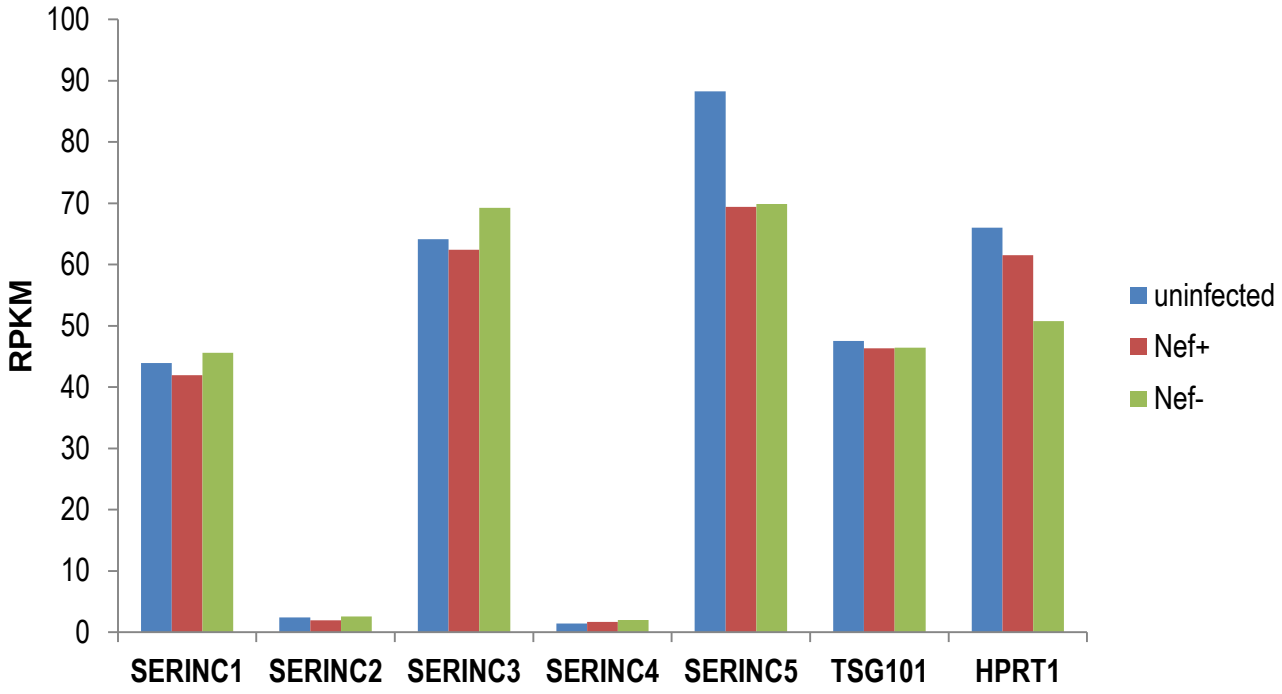
Exogenous SERINC5 specifically blocks HIV-1 Env-mediated infectivity



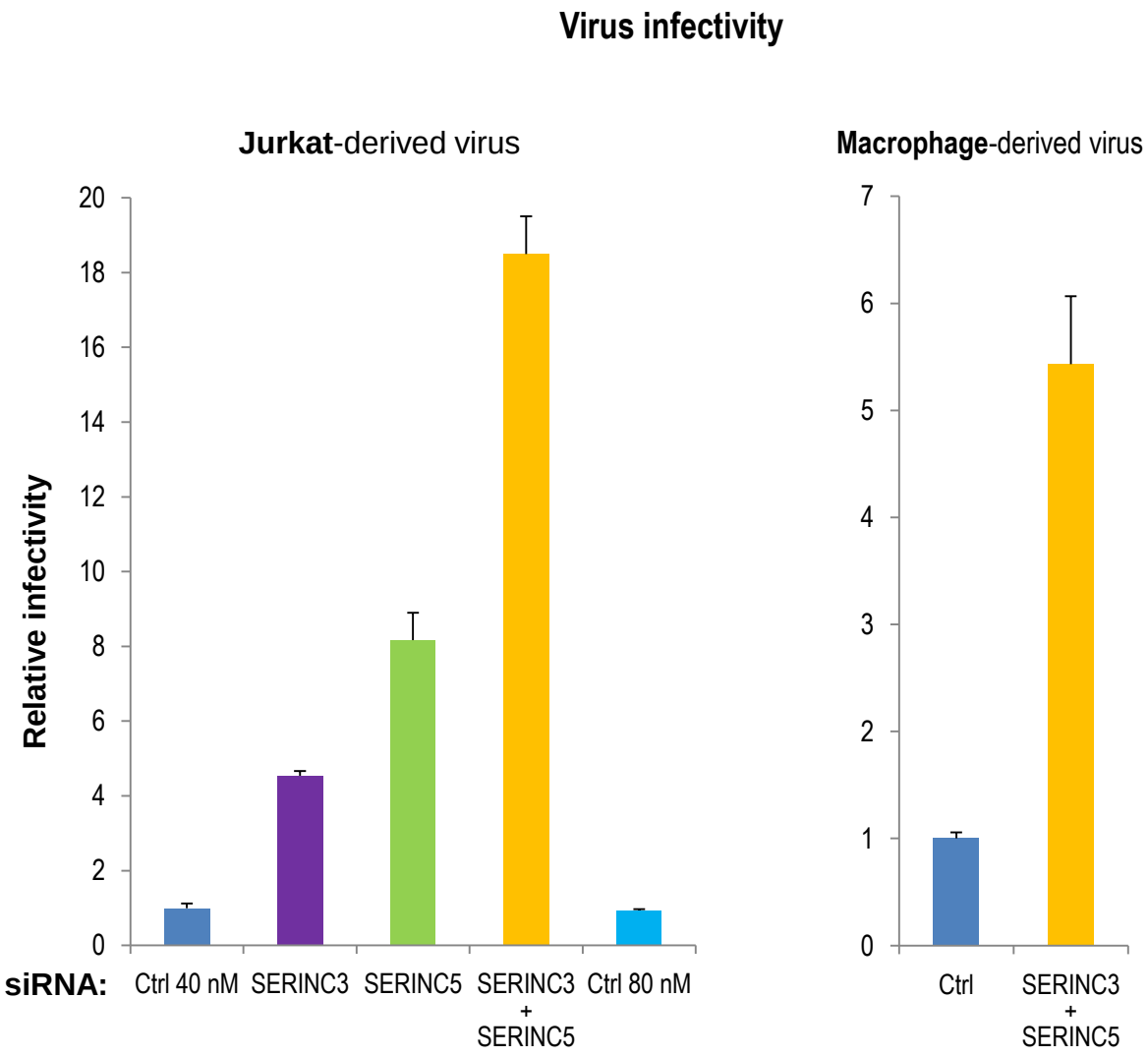
Exogenous SERINC5 is counteracted by Nef and glycoGag



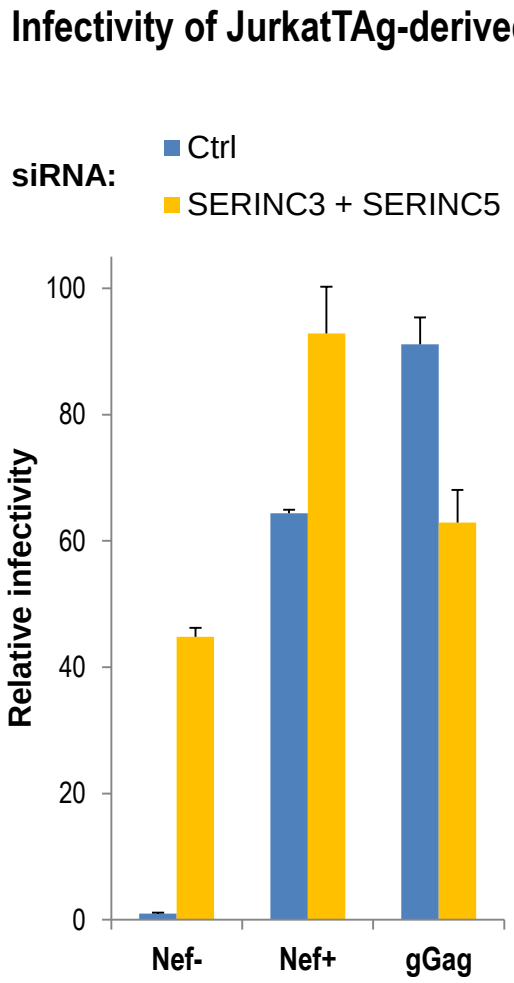
Expression of SERINCs in Jurkat cells



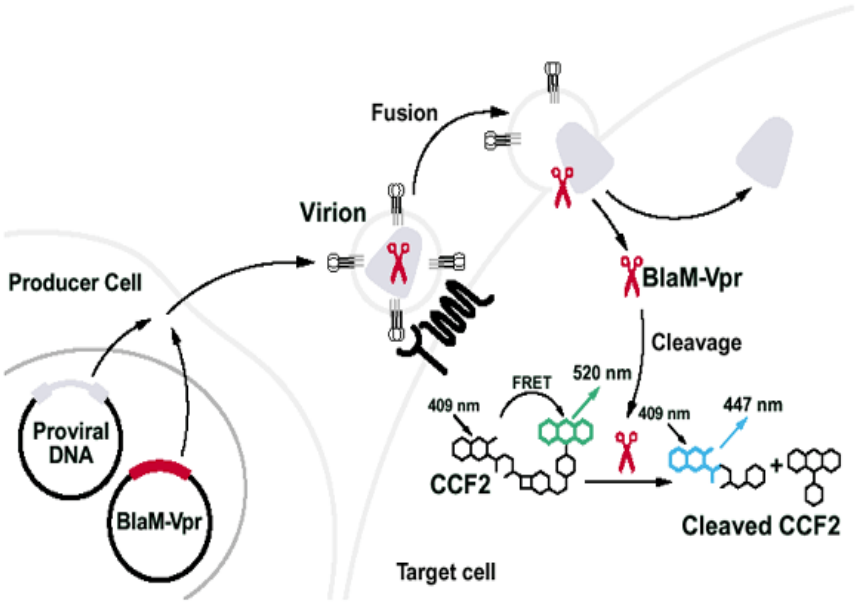
Endogenous SERINC3 and SERINC5 synergistically restrict Nef^{-} HIV-1 infectivity

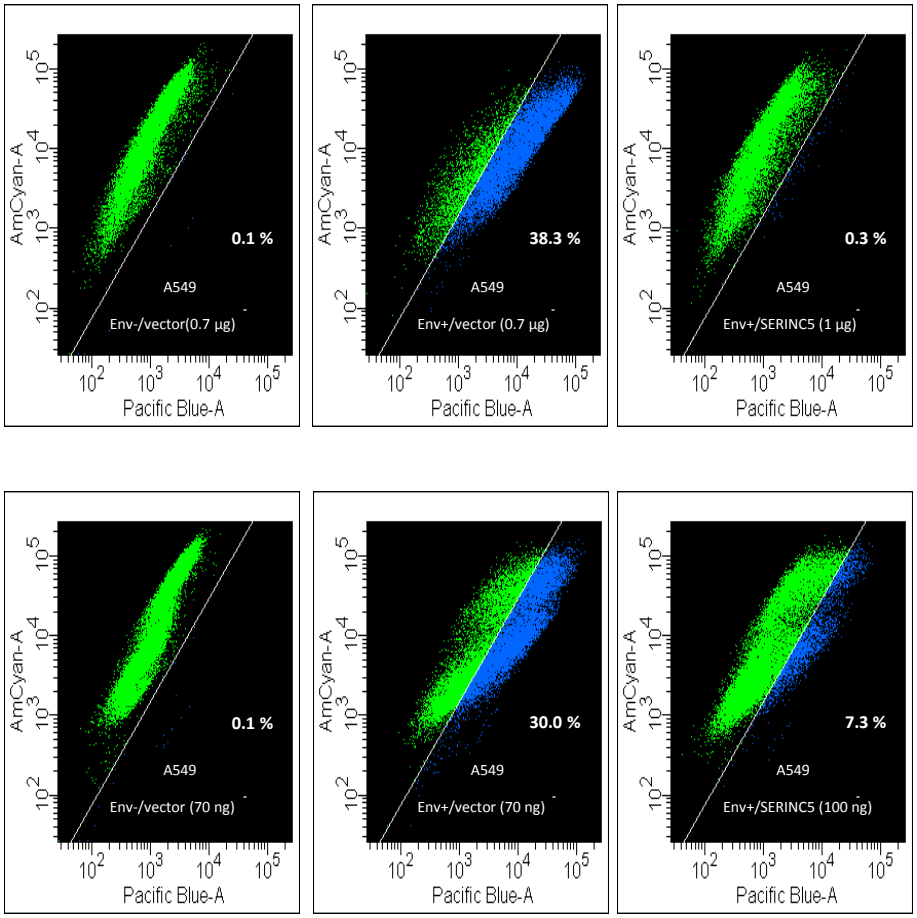


SERINC depletion has negligible effects on HIV infectivity in the presence of Nef or glycoGag

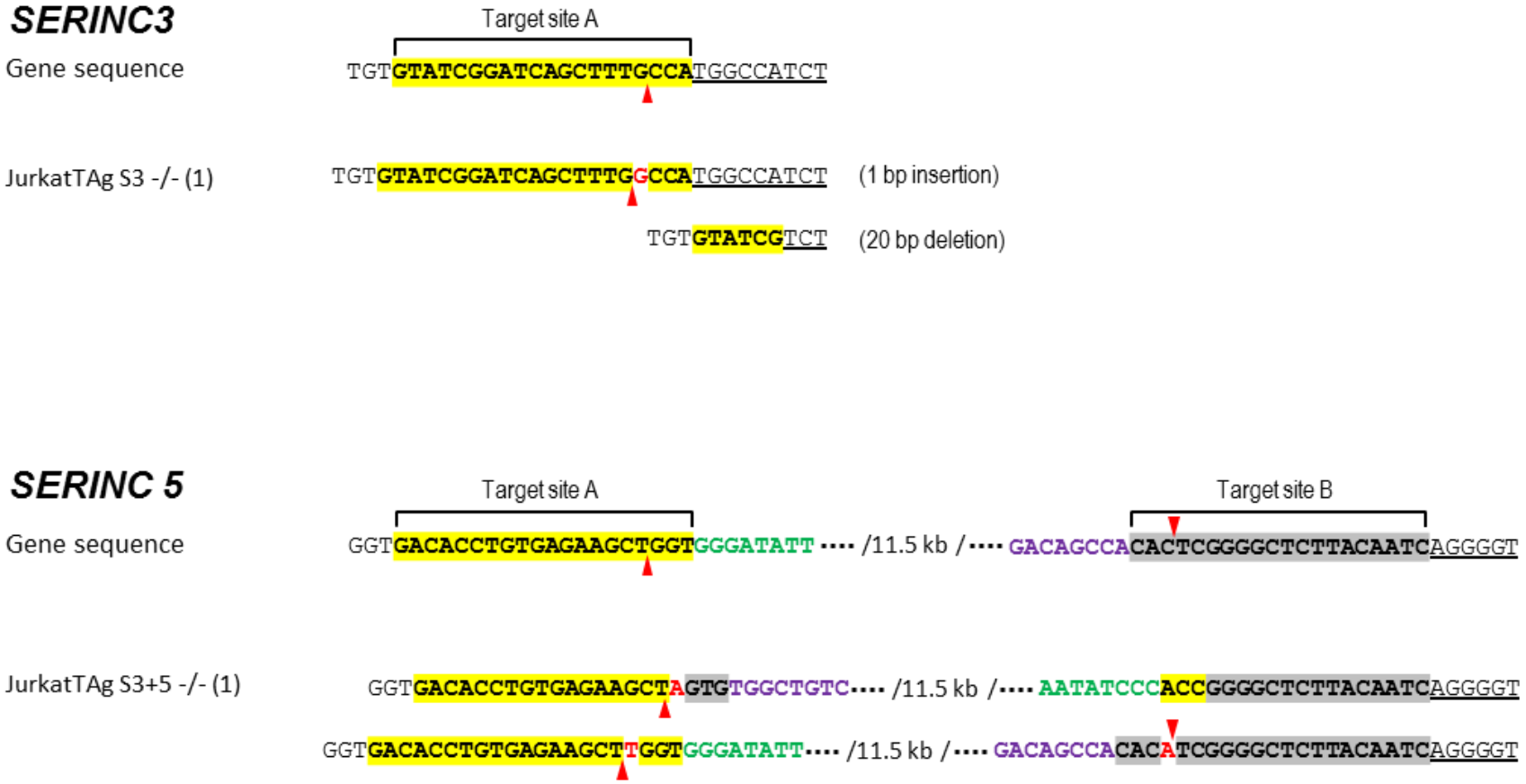


Exogenous SERINC5 blocks HIV-1 entry

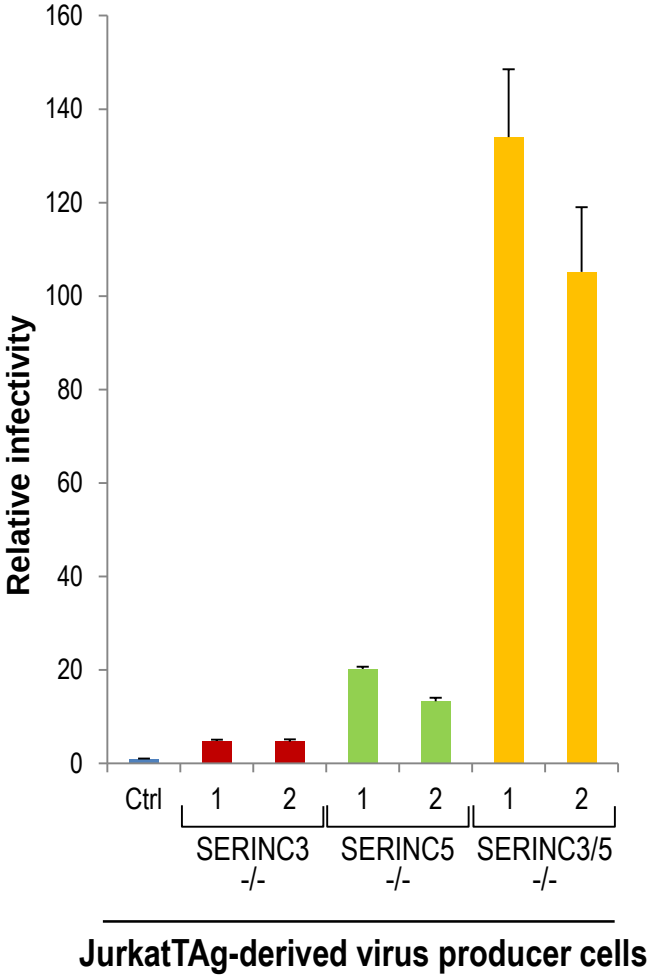




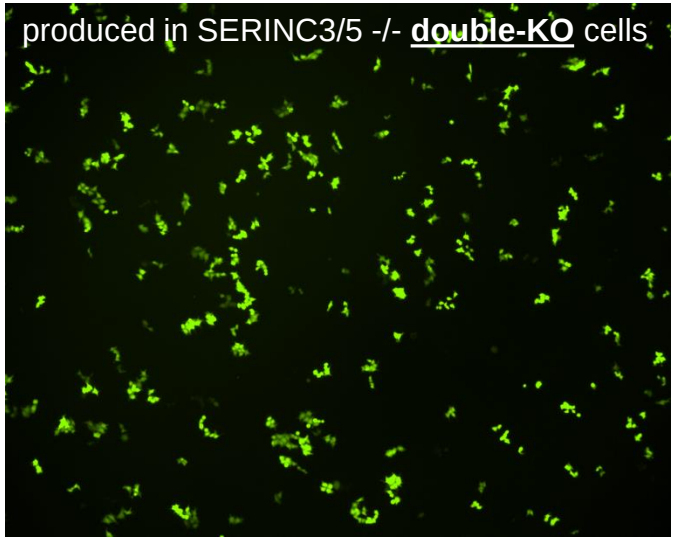
CRISPR/Cas9-mediated knockout of SERINC3 and SERINC5 in Jurkat-TAg cells



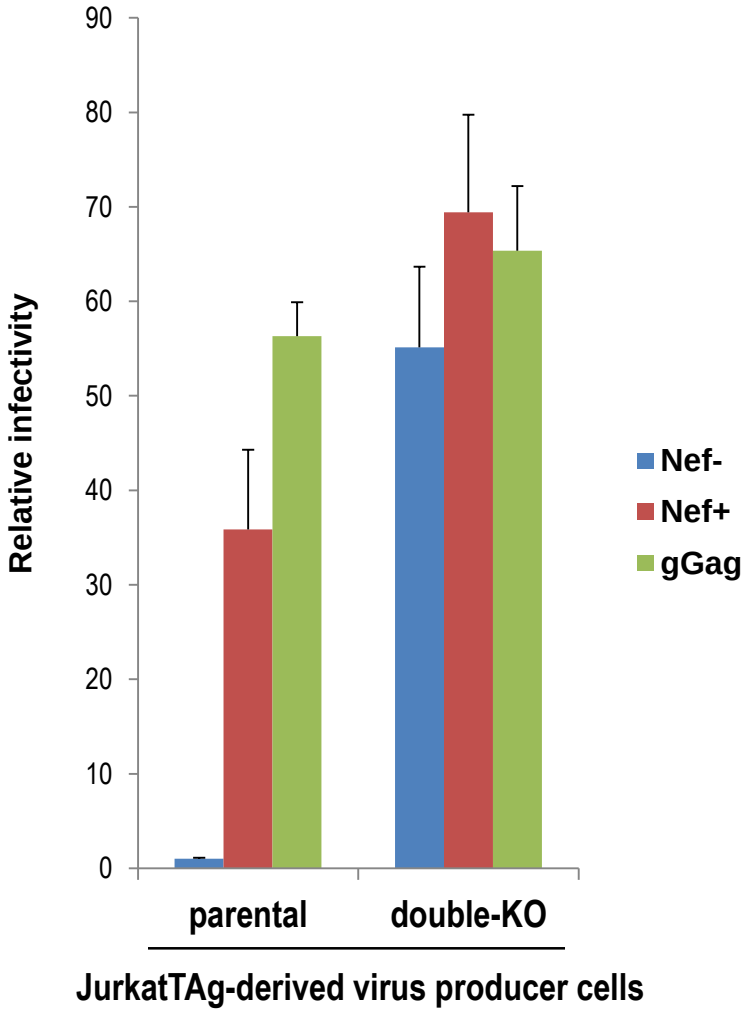
Infectivity of Nef⁻ HIV-1 produced in SERINC knockout JurkatTAg cells



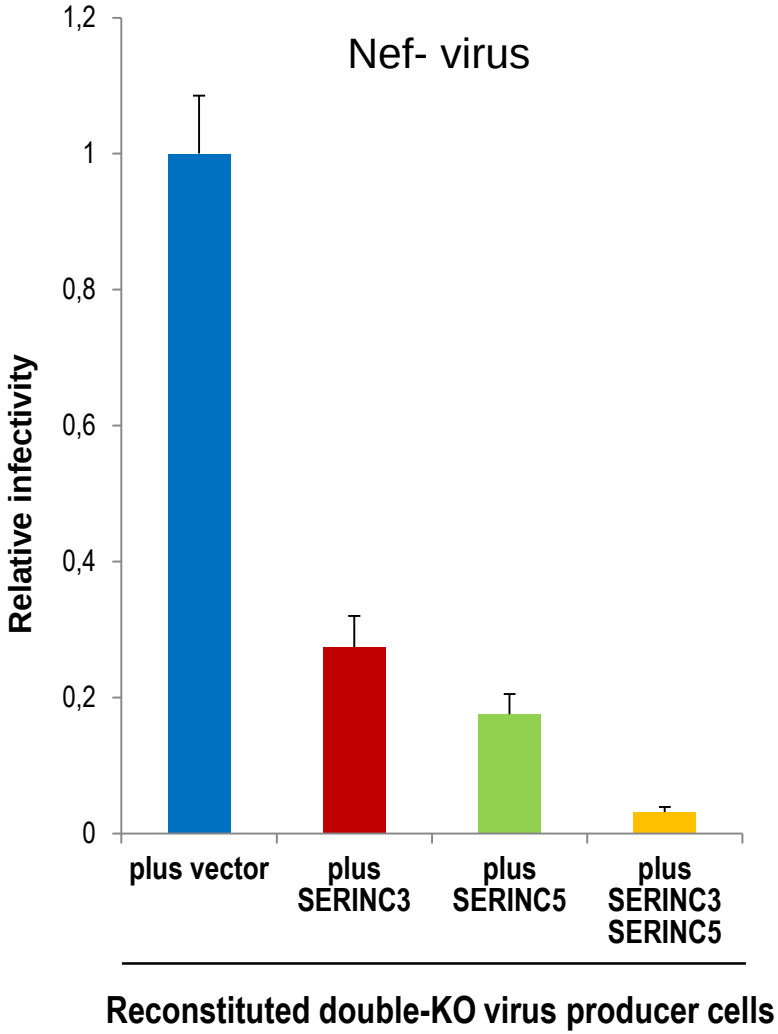
HIV-1-GFP (Nef-)



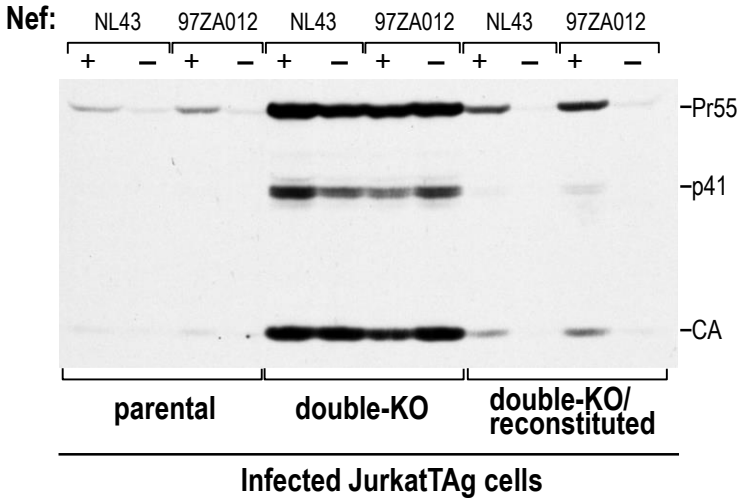
Nef and glycoGag have negligible effects on HIV infectivity in double-KO cells lacking SERINC3 and SERINC5

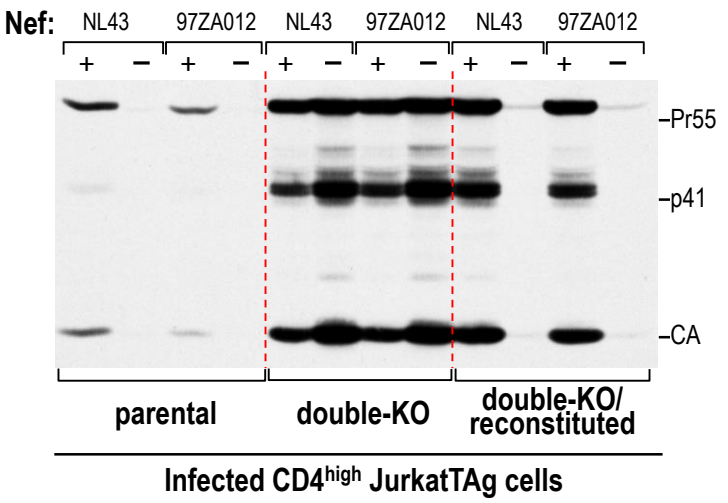


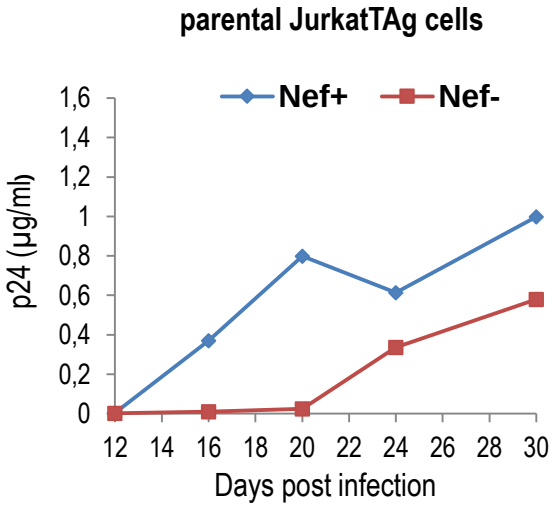
Re-expressed SERINCs restrict HIV-1 infectivity

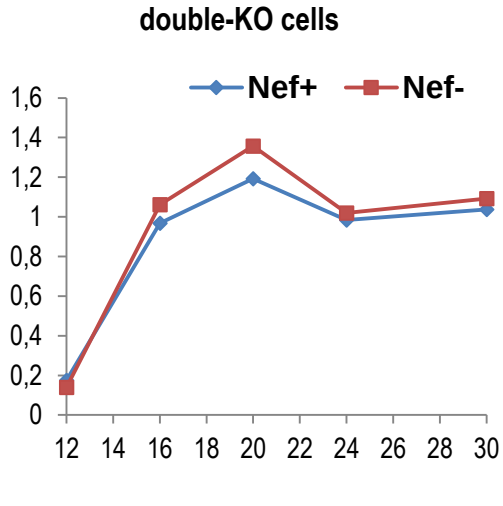


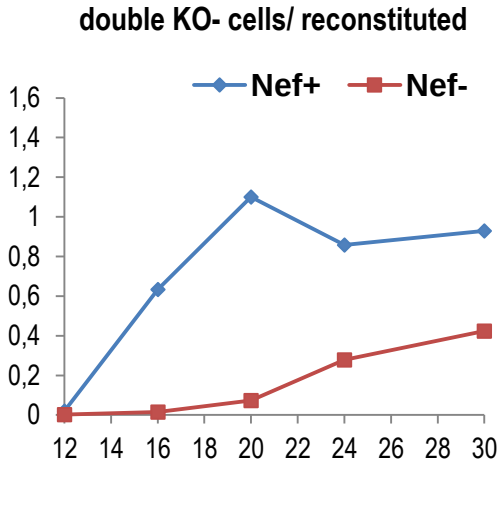
Nef counteracts inhibition of HIV-1 replication by SERINC3 and SERINC5

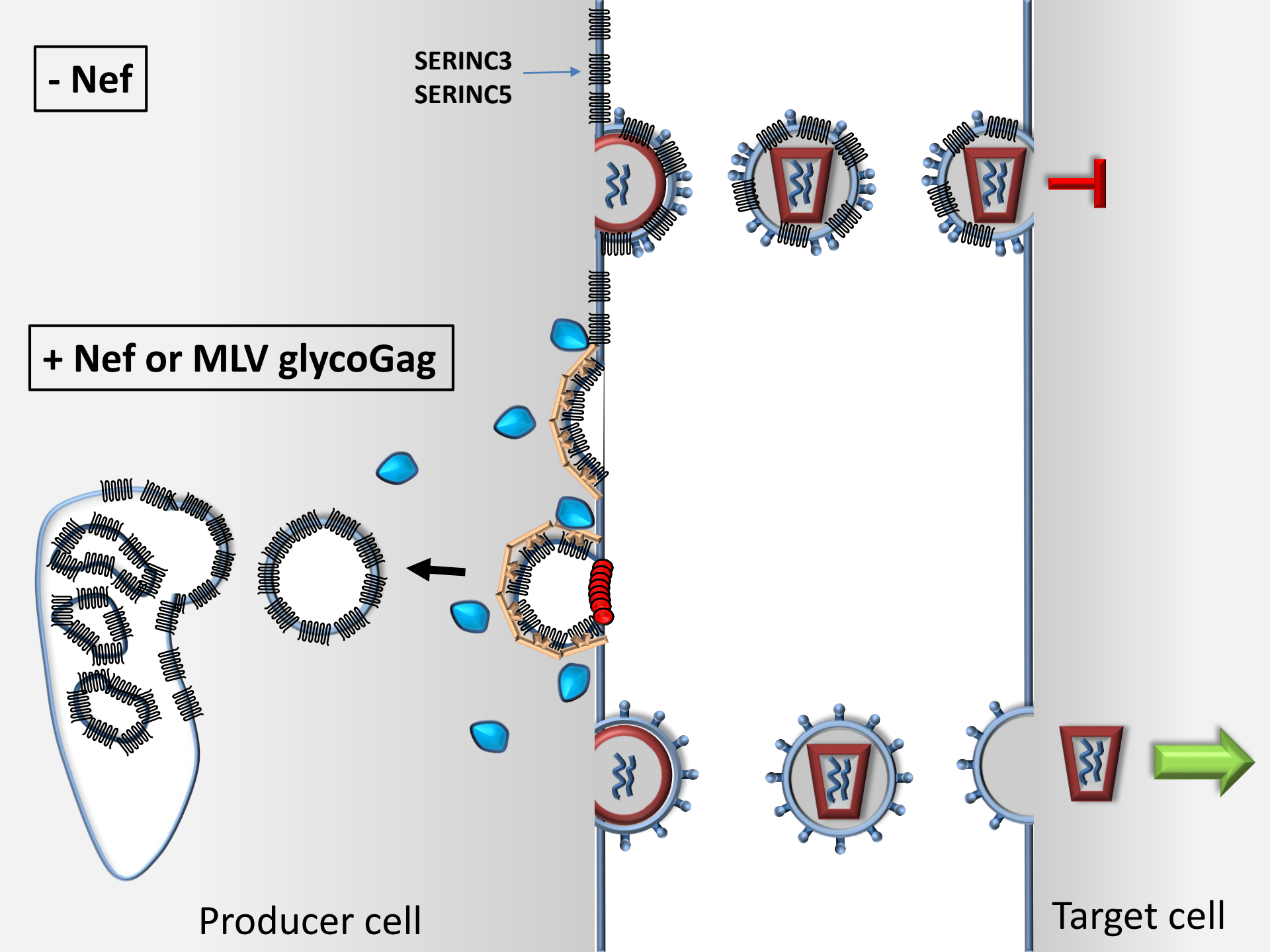











- Nef
SERINC3
SERINC5
+ Nef or MLV glycoGag
Producer cell
Target cell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ON DRUG ABUSE