Virus - coreceptor interactions in HIV pathogenesis

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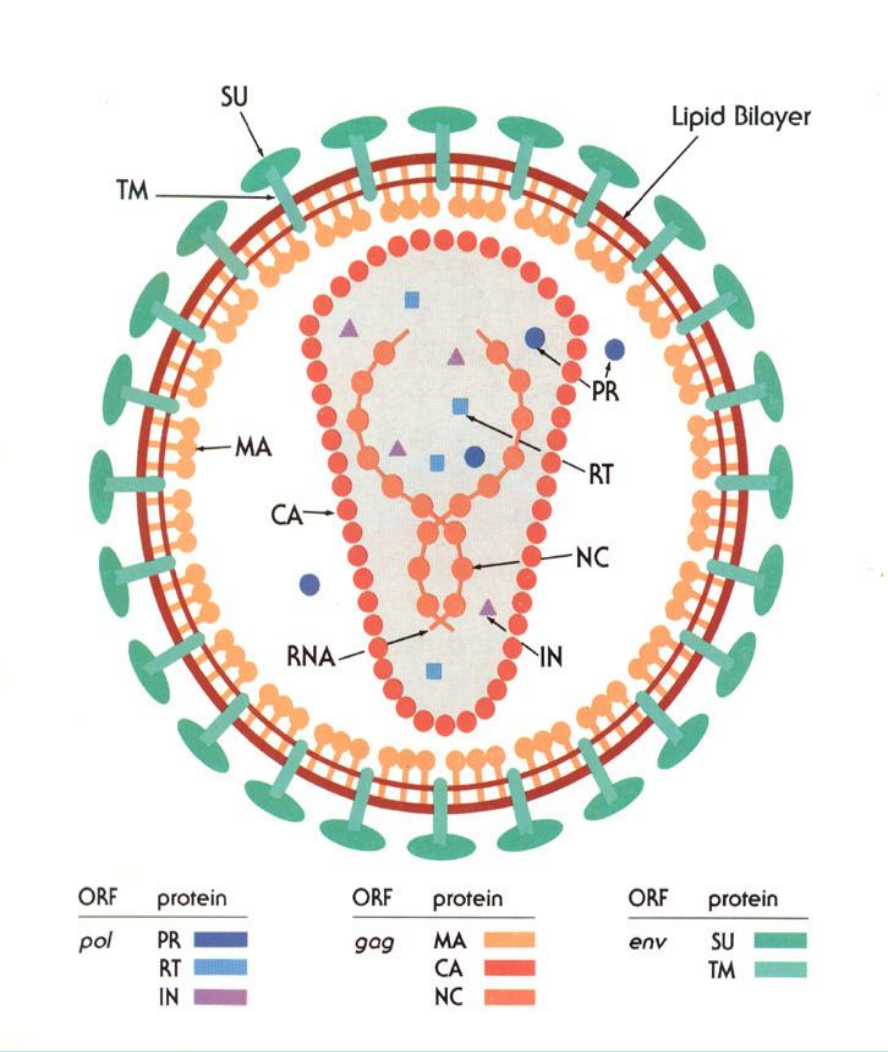
Human retroviruses



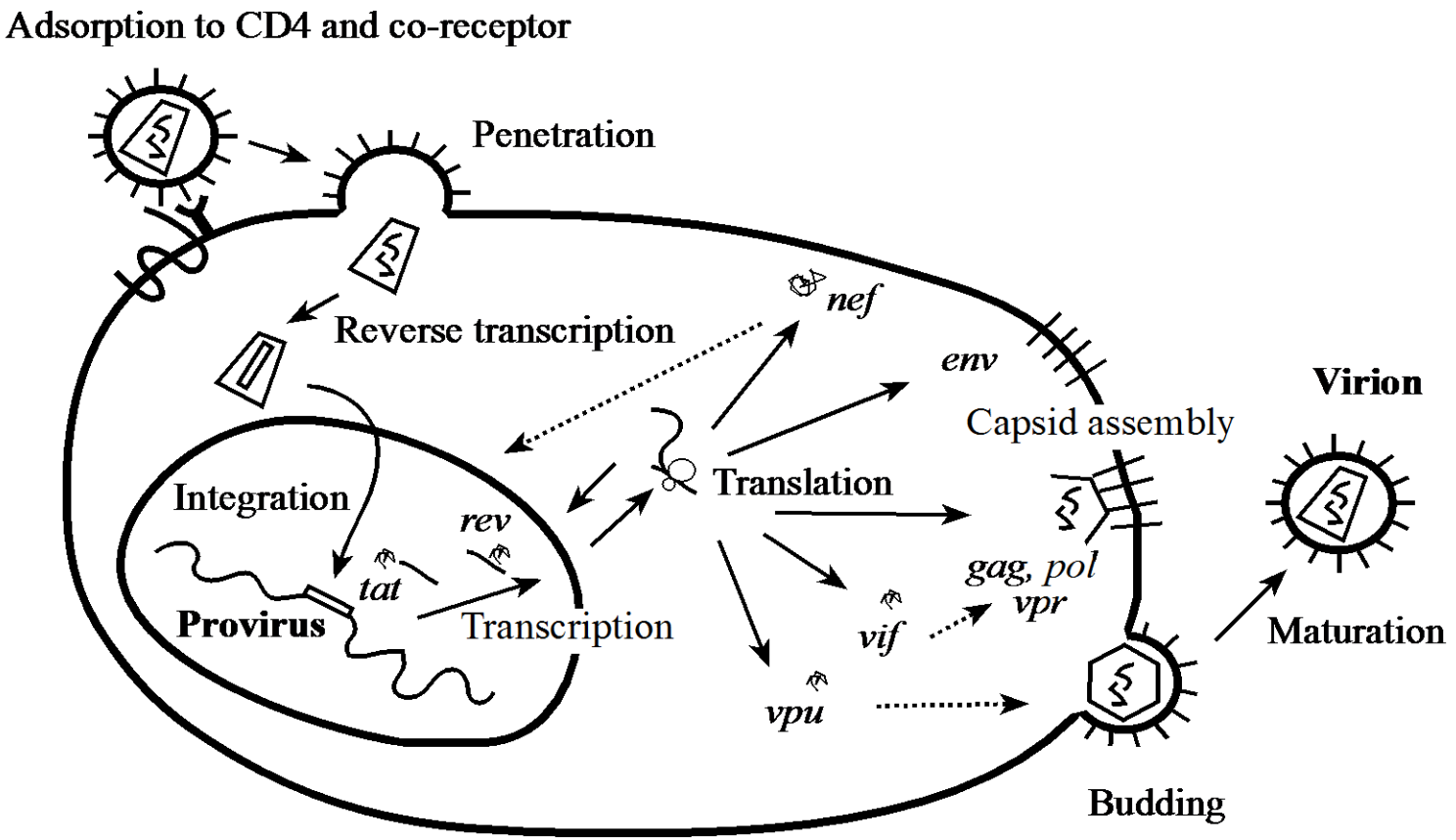
-HIV-1

-HIV-2

-HTLV-I

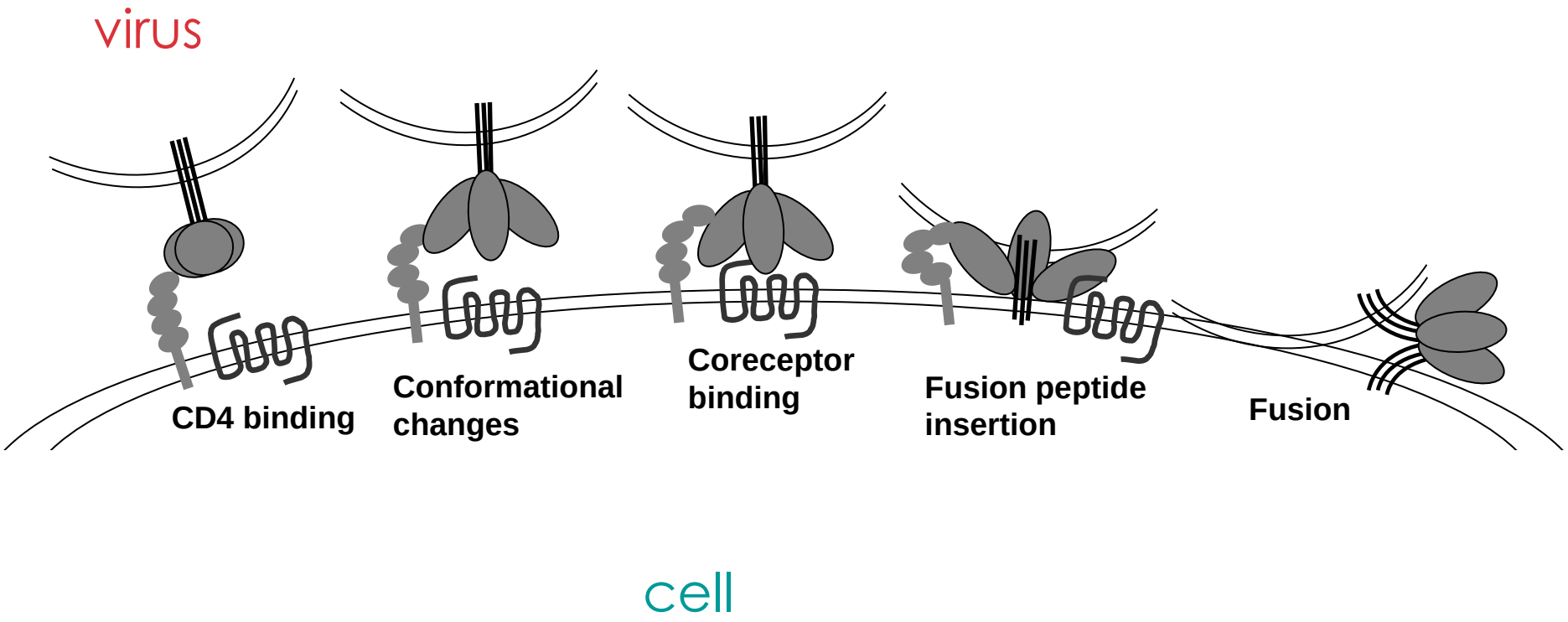
-HTLV-II

HIV life cycle



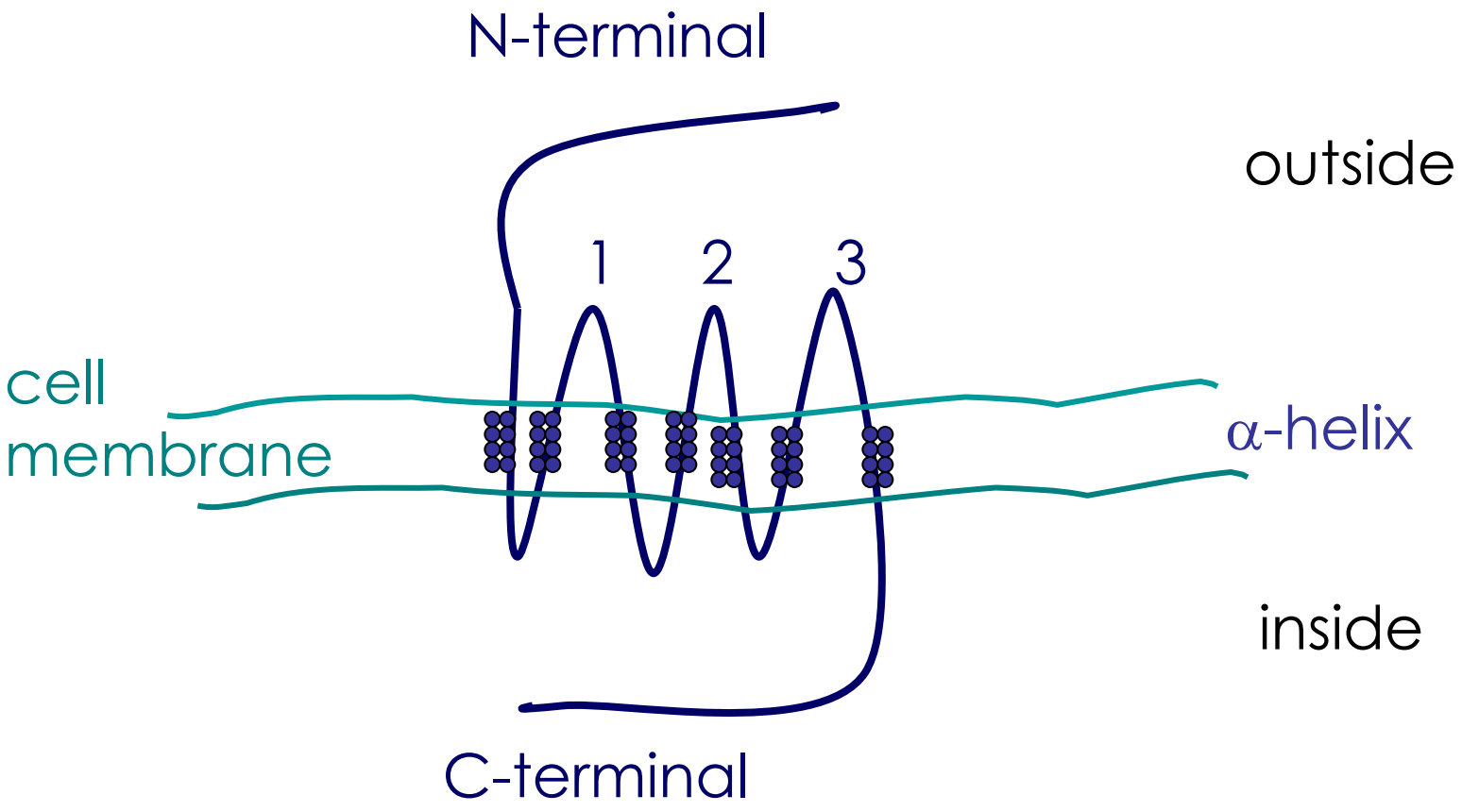
T. Leitner 2000

HIV entry into target cells

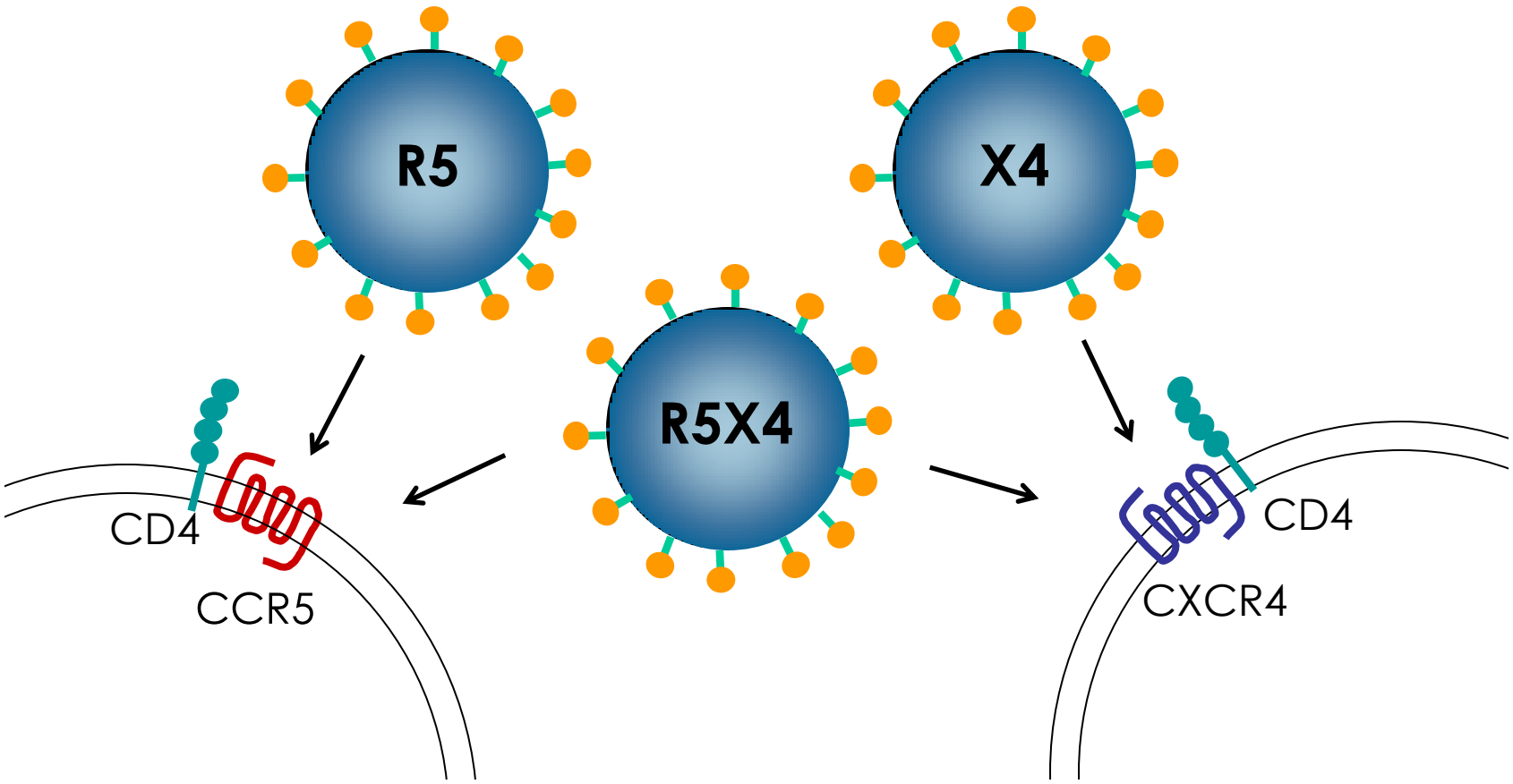


Chemokine receptors

7-transmembrane G-protein coupled



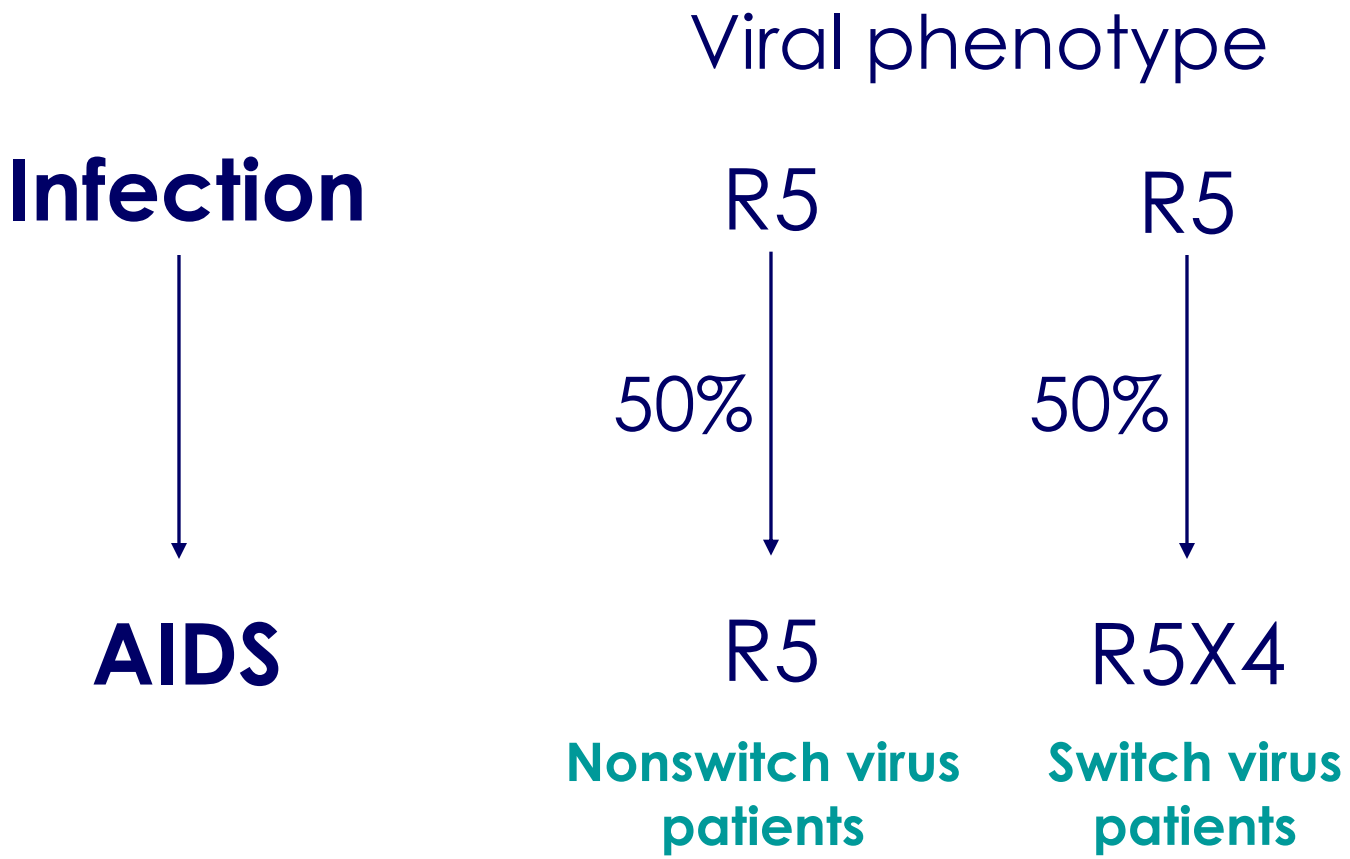
Classification of HIV depends on coreceptor use



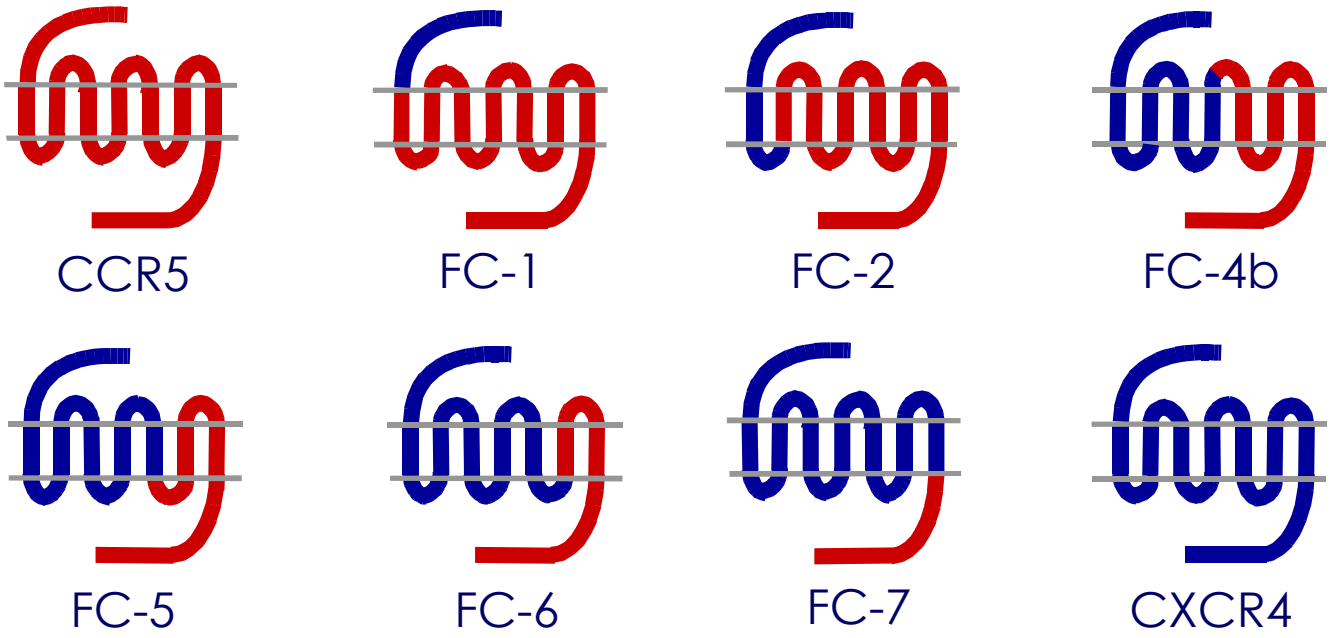
- HIV-1 isolates obtained during the asymptomatic phase generally use the CCR5 coreceptor.

- Disease progression is in the majority of cases accompanied by a shift of co-receptor use, to CXCR4 use. Early acquisition of CXCR4 use is predictive of a poor prognosis.

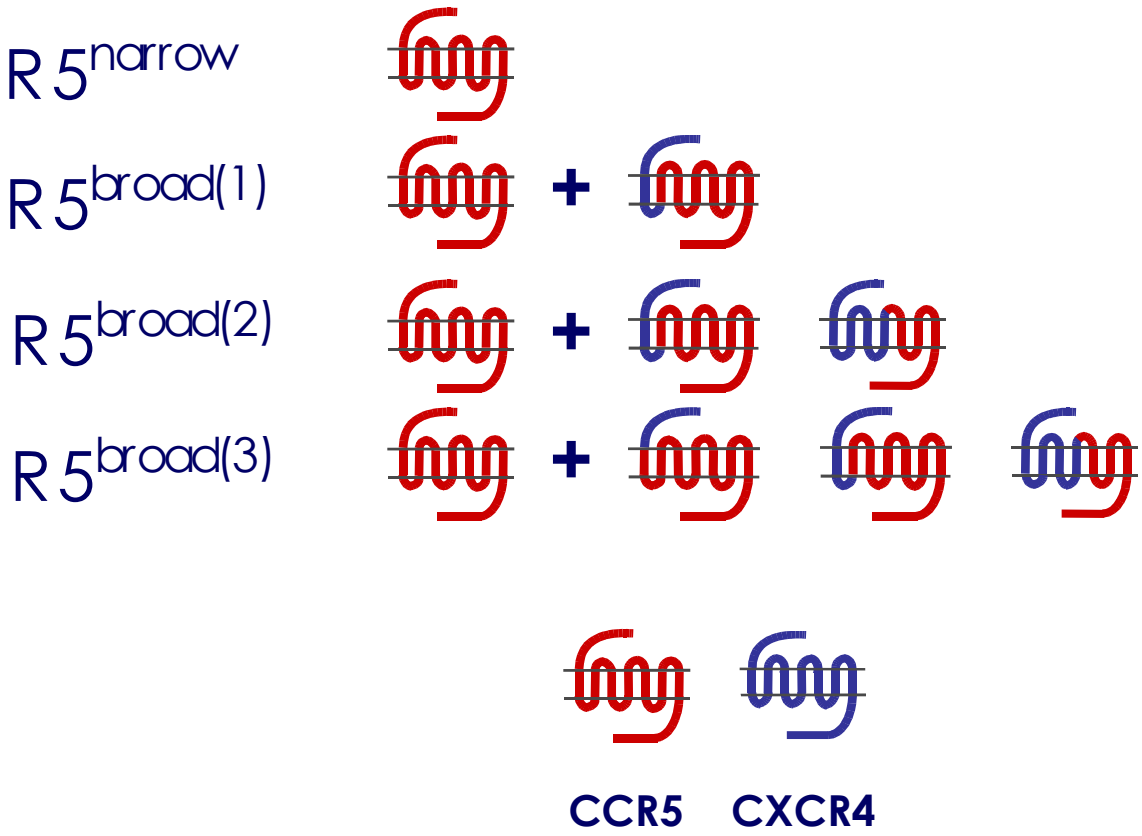
Virus evolution



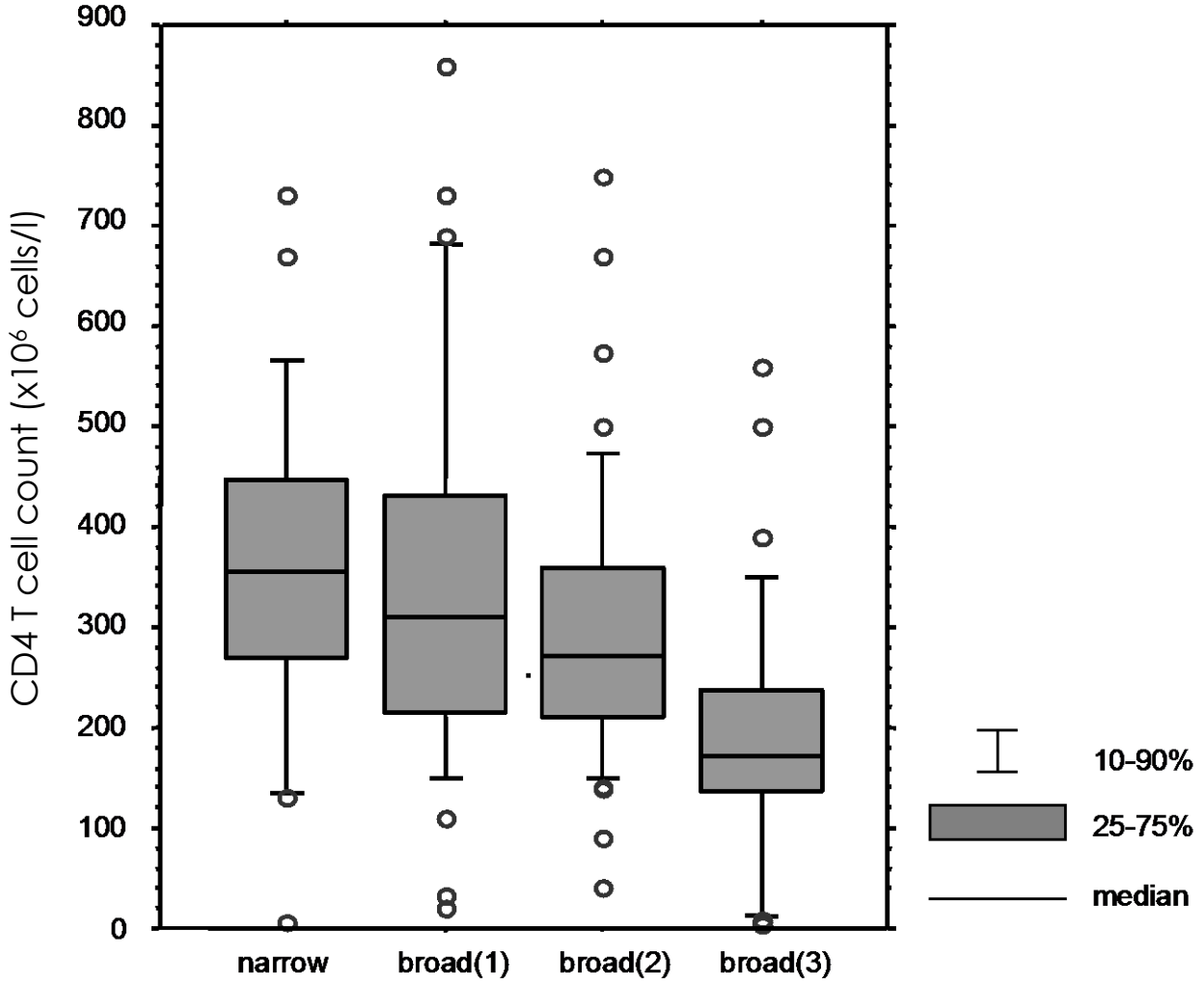
Chimeras between CCR5 and CXCR4



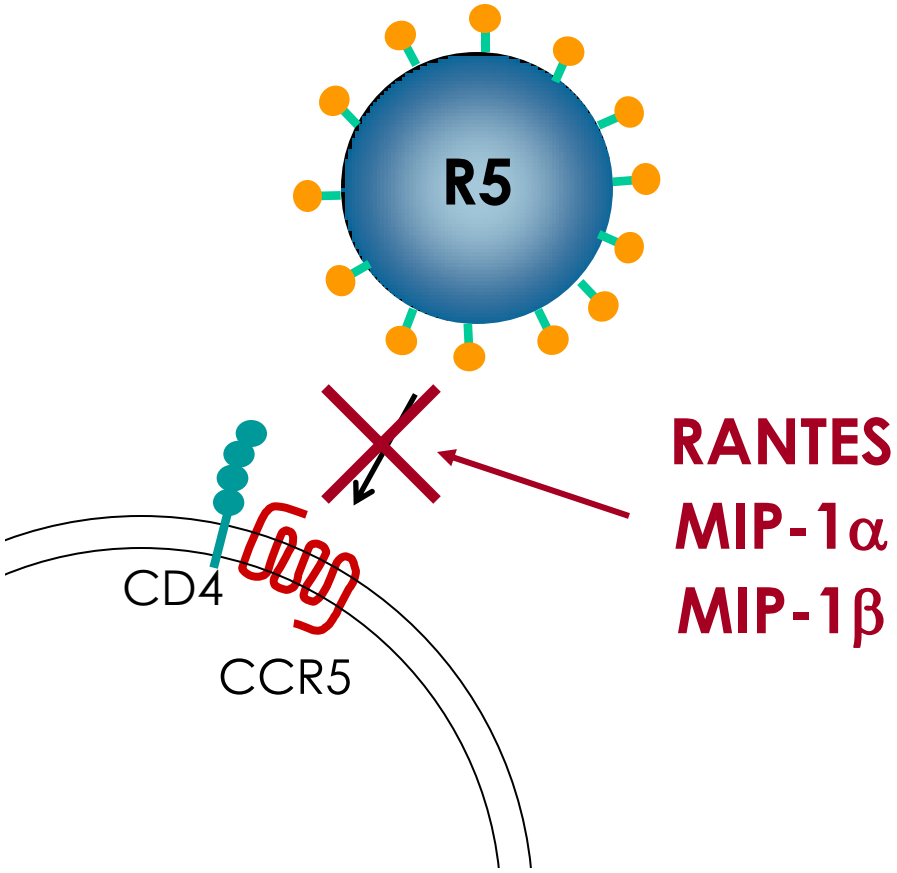
Classification of HIV-1 R5 phenotype according to chimeric receptor use



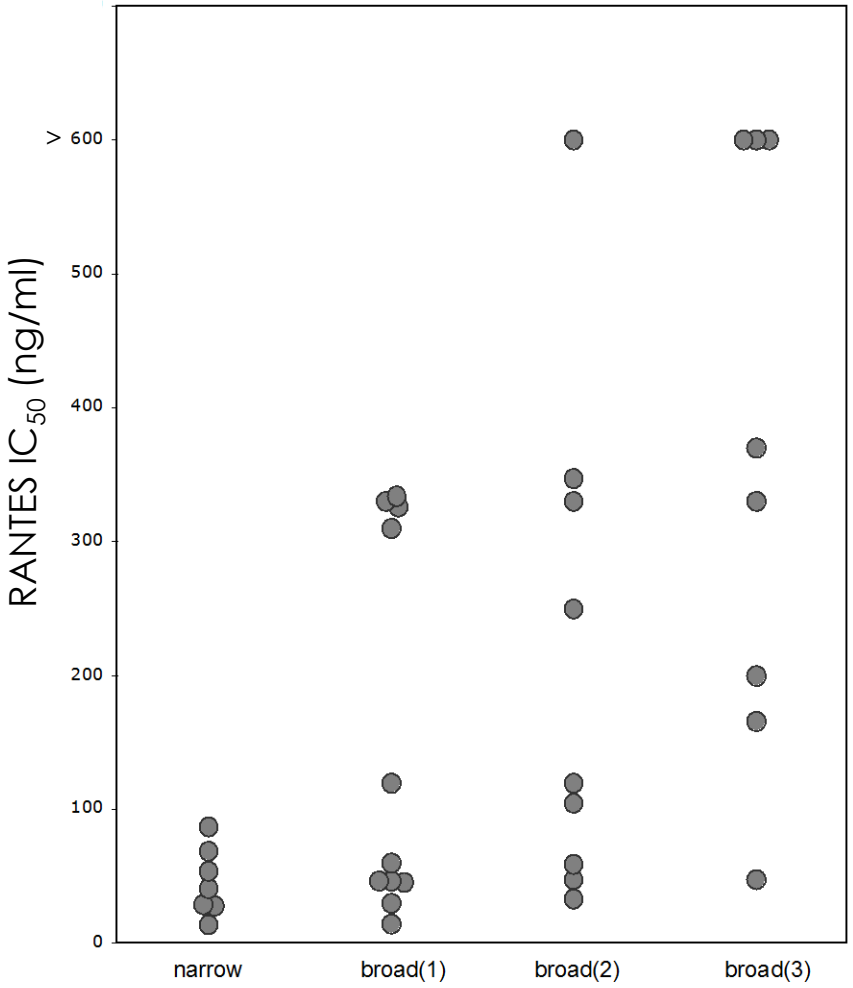
Chimeric receptor use correlates with CD4 T cell count



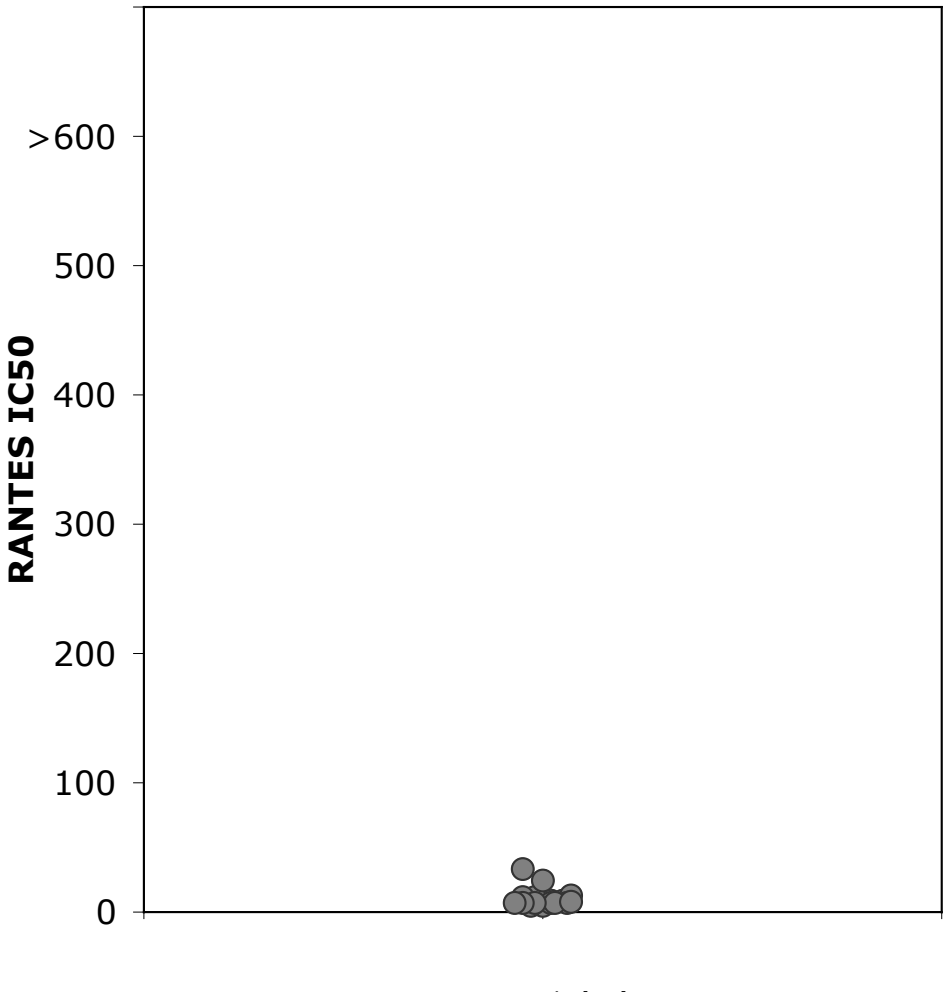
Natural ligands inhibit infection



RANTES resistance in nonswitch virus patients correlates with chimeric receptor use

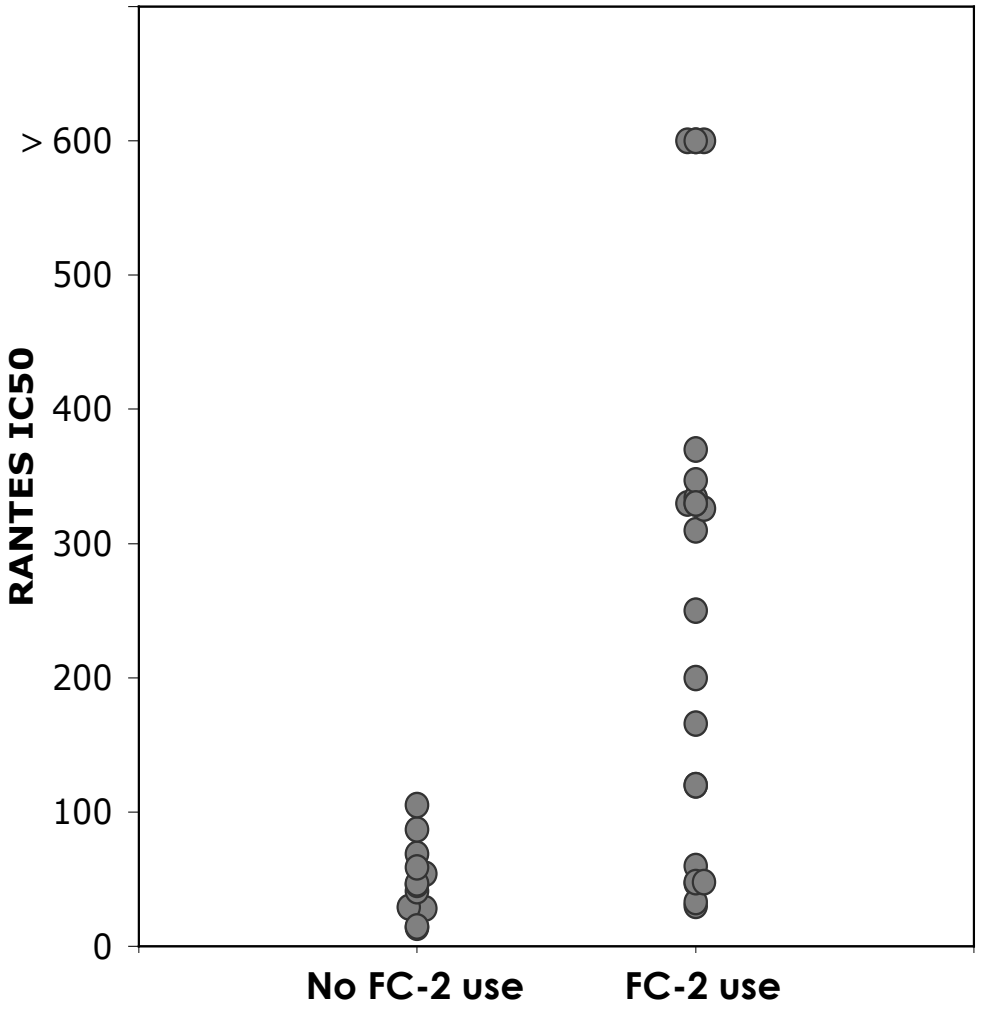


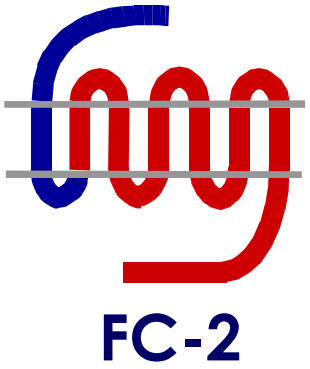
*RANTES sensitivity in **switch** virus patients*



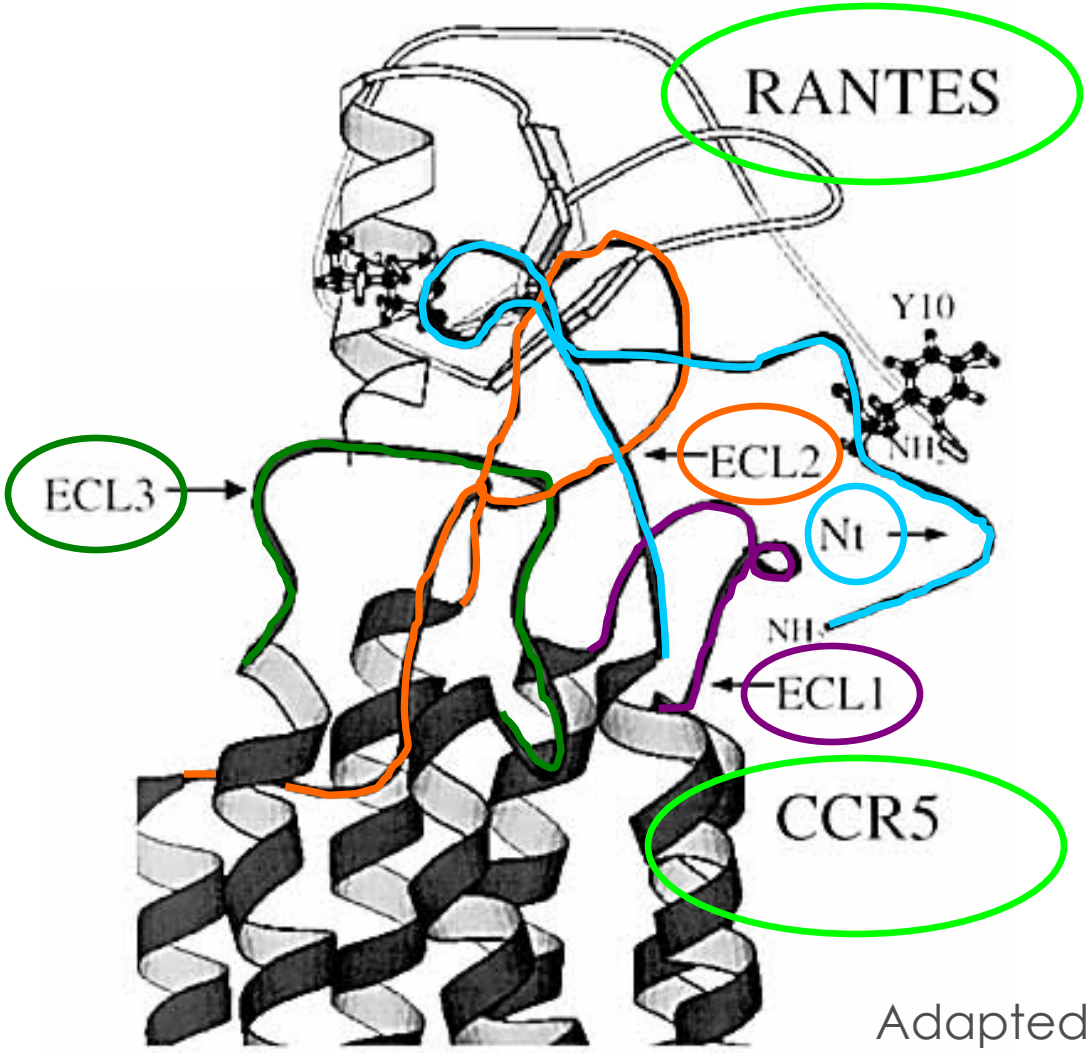
18 isolates
from
10 patients

RANTES resistance in nonswitch virus patients correlates with FC-2 receptor use





CCR5 - RANTES interaction



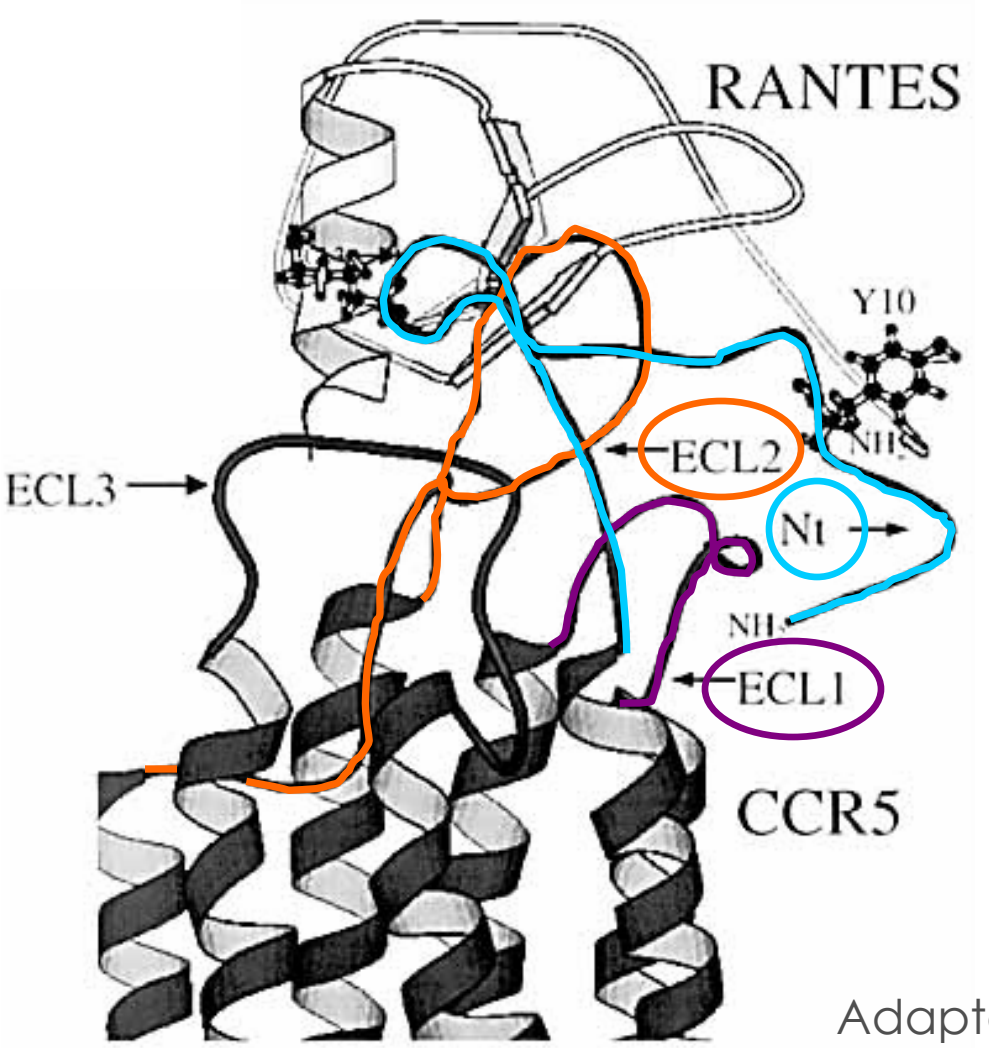
Adapted from Zhou et al.
Eur. J. Immunol. 2000

Important epitopes of chemokine receptors for viral infection

- CCR5 using isolates
  - N-terminal
  - First extracellular loop
- CXCR4 using isolates
  - First extracellular loop
  - Second extracellular loop

- Picard *et al,* Virology -97
- Brelot *et al,* J Virology -97
- Doranz *et al,* J Virology -99
- Alkhatib *et al*, JBC - 97
- Picard *et al,* J Virology -97
- Rucker *et al*, Cell -96
- Doranz *et al,* J Virology -97

CCR5 - RANTES interaction



Adapted from Zhou et al.
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Conclusion

- Evolution of coreceptor use appears to be a general rule and includes HIV-1 of R5 phenotype

We propose:

- *R5 virus evolution is different in nonswitch and switch virus patients*
  - *In nonswitch virus patients evolution towards use of ECL-1* (correlates with RANTES resistance)
  - *In switch virus patients evolution towards use of ECL-2* (*facilitates switch to CXCR4 use?*)

Collaborators

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