The IL-15 superagonist N-803 enhances antiviral cellular immunity in macaques

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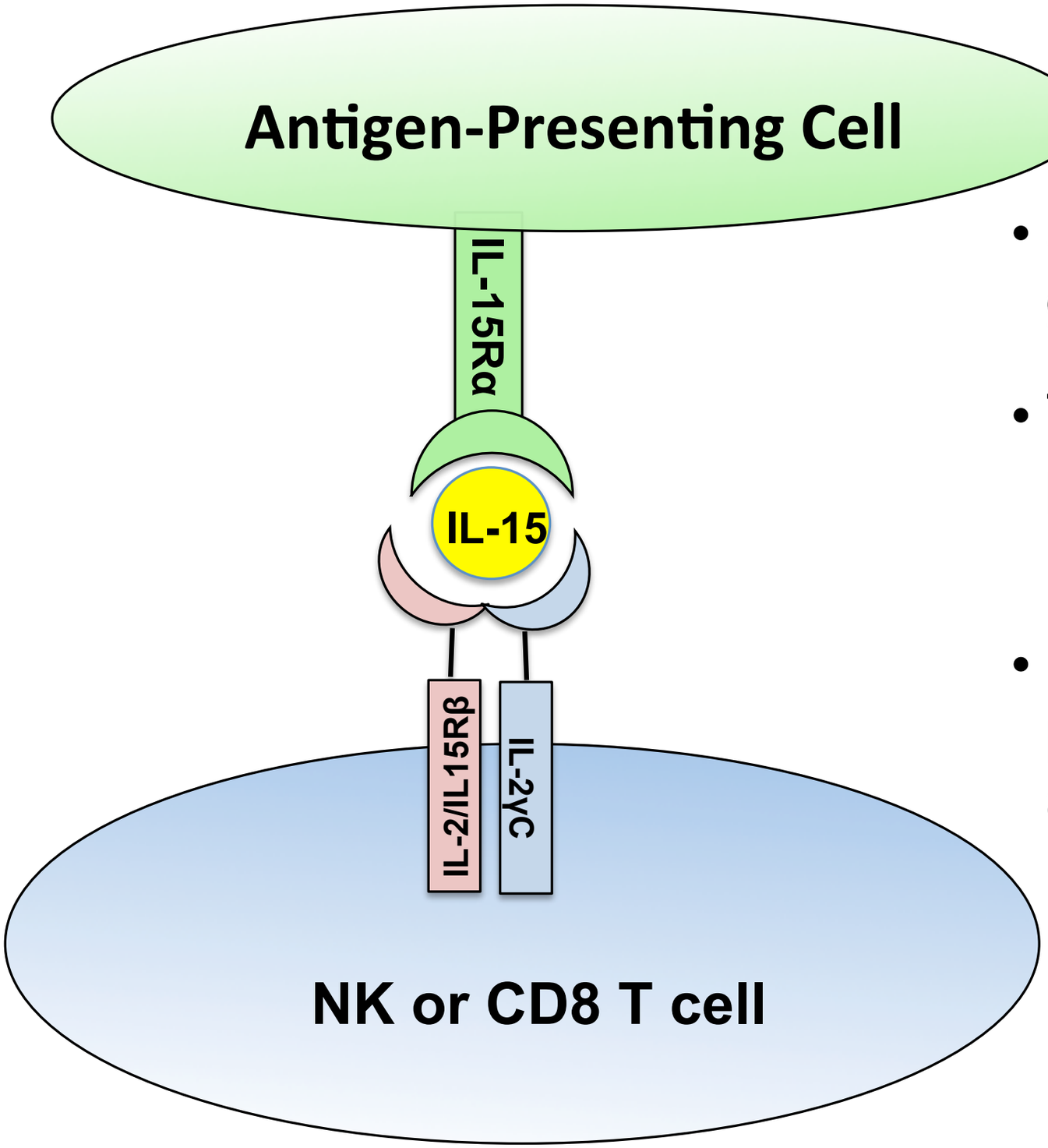
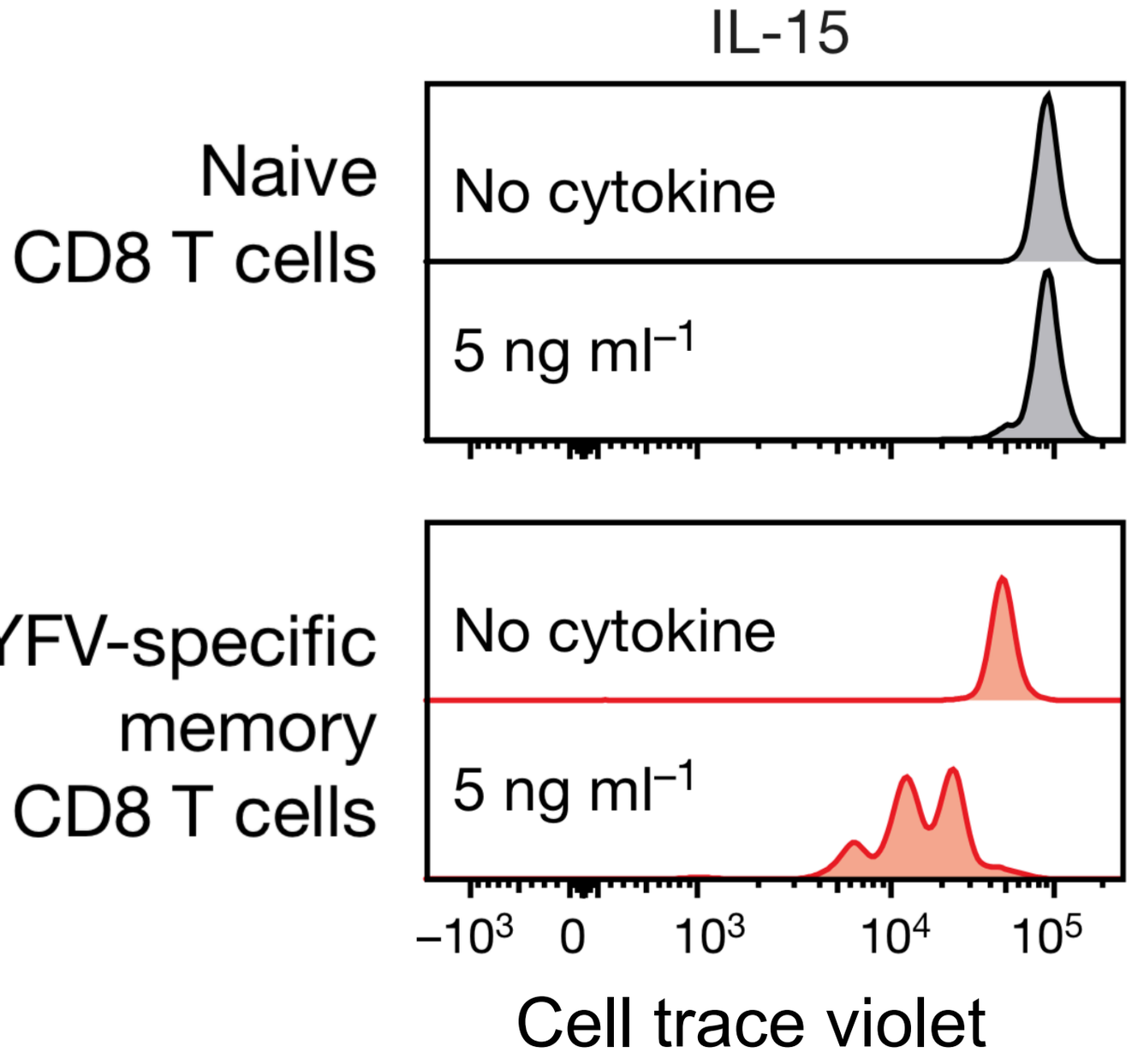
IL-15 is an immunomodulatory agent with the potential to improve HIV control



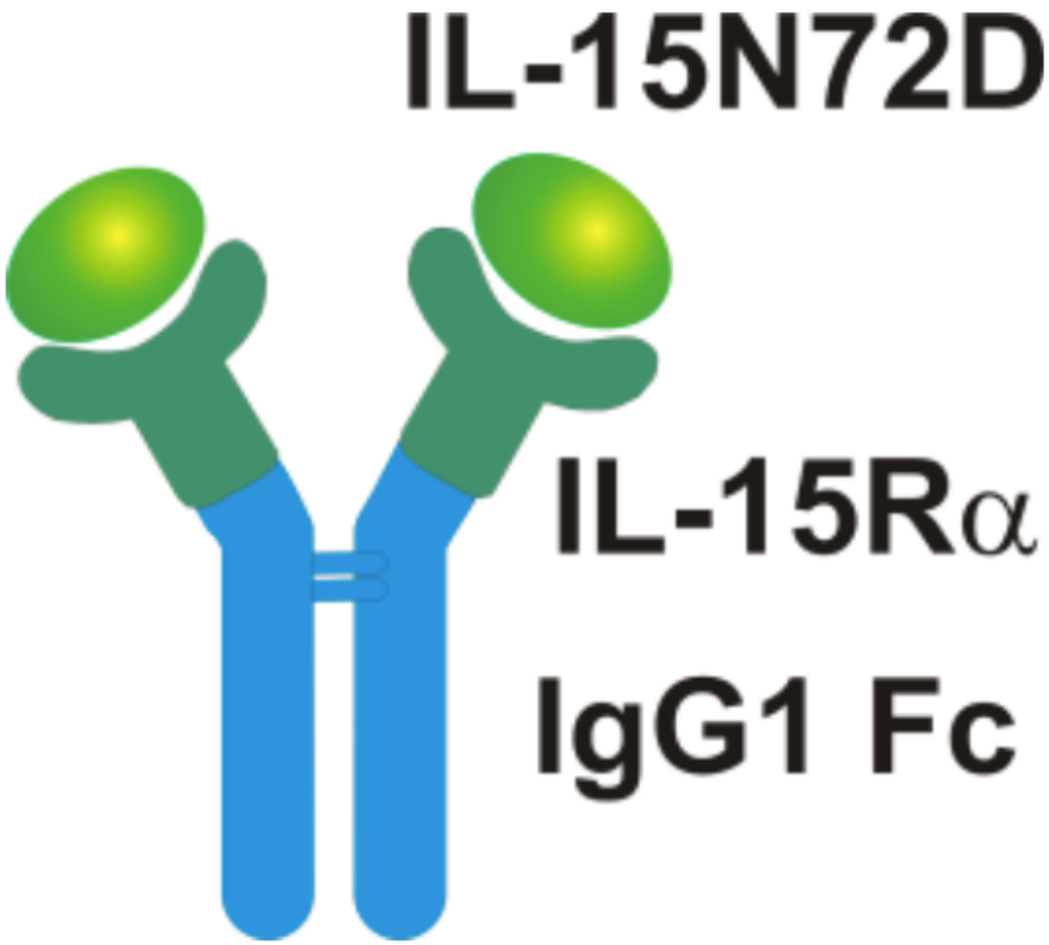
- Signals through the common gamma chain receptor
- The alpha receptor on antigen presenting cells trans-presents it to NK or CD8 T cells
- Promotes development, proliferation, and activation of NK and CD8 T cells

IL-15 treatment can stimulate in vitro proliferation of *memory* CD8 T cells



Modified from Akondy et. al., Nature, 2017

N-803 is a modified IL-15 superagonist with the potential to boost cellular immunity



- Modification enhances binding to receptor molecules
- More activity and longer half life than IL-15
- Is being used for anti-cancer treatments

Zhu X, et al. *J Immunol.* 2009
Han KP, et al. *Cytokine.* 2011
Xu W, et al. *Cancer Res.* 2013
Rhode PR, et al. *Cancer Immunol Res*. 2016

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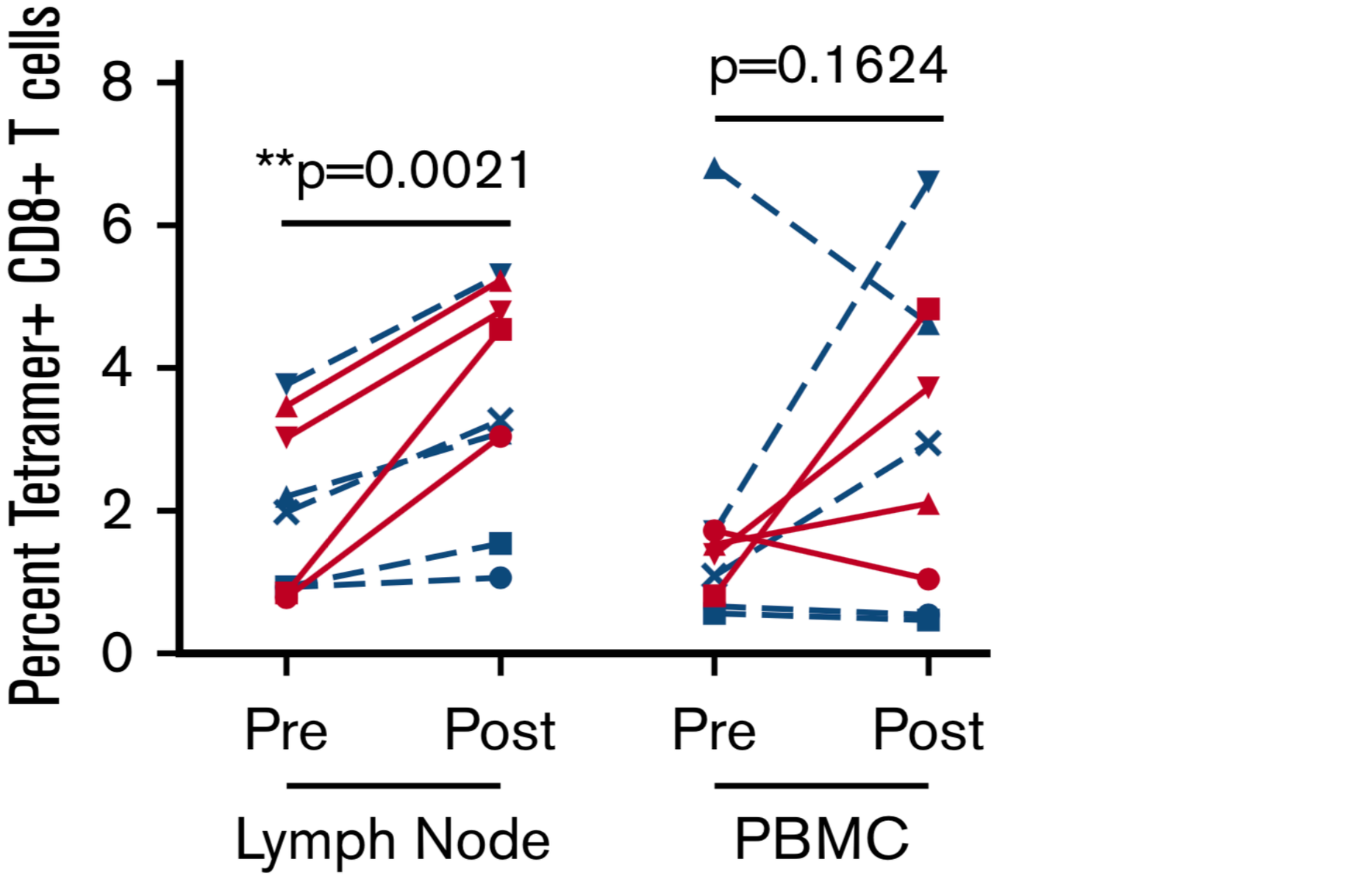
N-803 treatment increases *SIV-specific* CD8 T cells in lymph nodes of SIV+ macaques

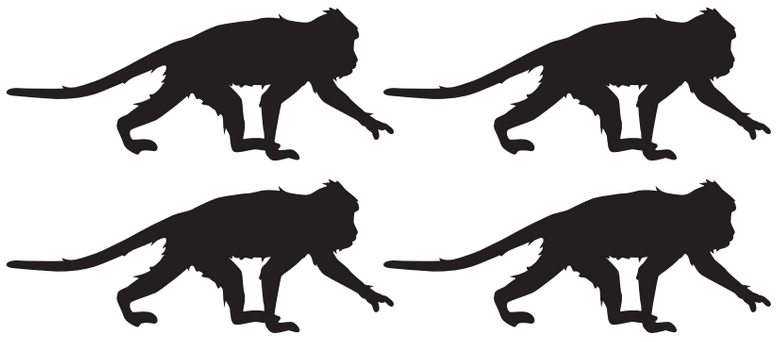


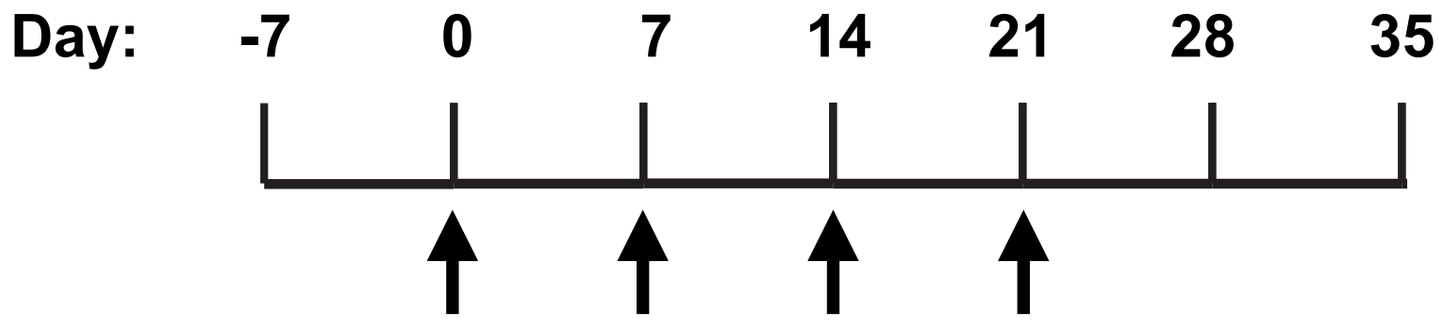
Modified from Webb et. al., Blood Advances, 2018

Can IL-15 agonists enhance the function of vaccine-elicited CD8 T cells?

<u>*Our hypothesis:*</u> Immunomodulation with N-803 suppresses virus replication

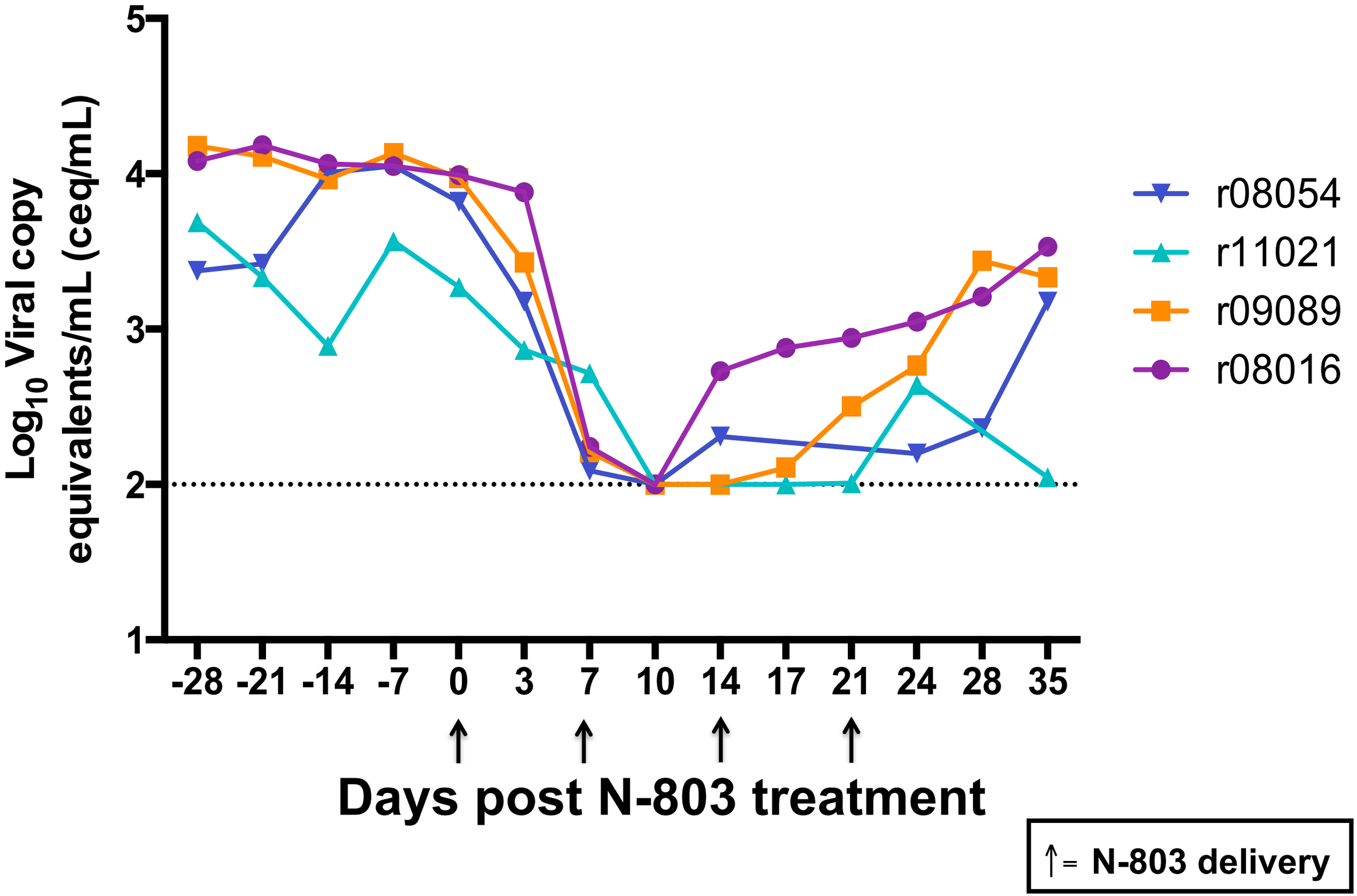
Study #1 outline





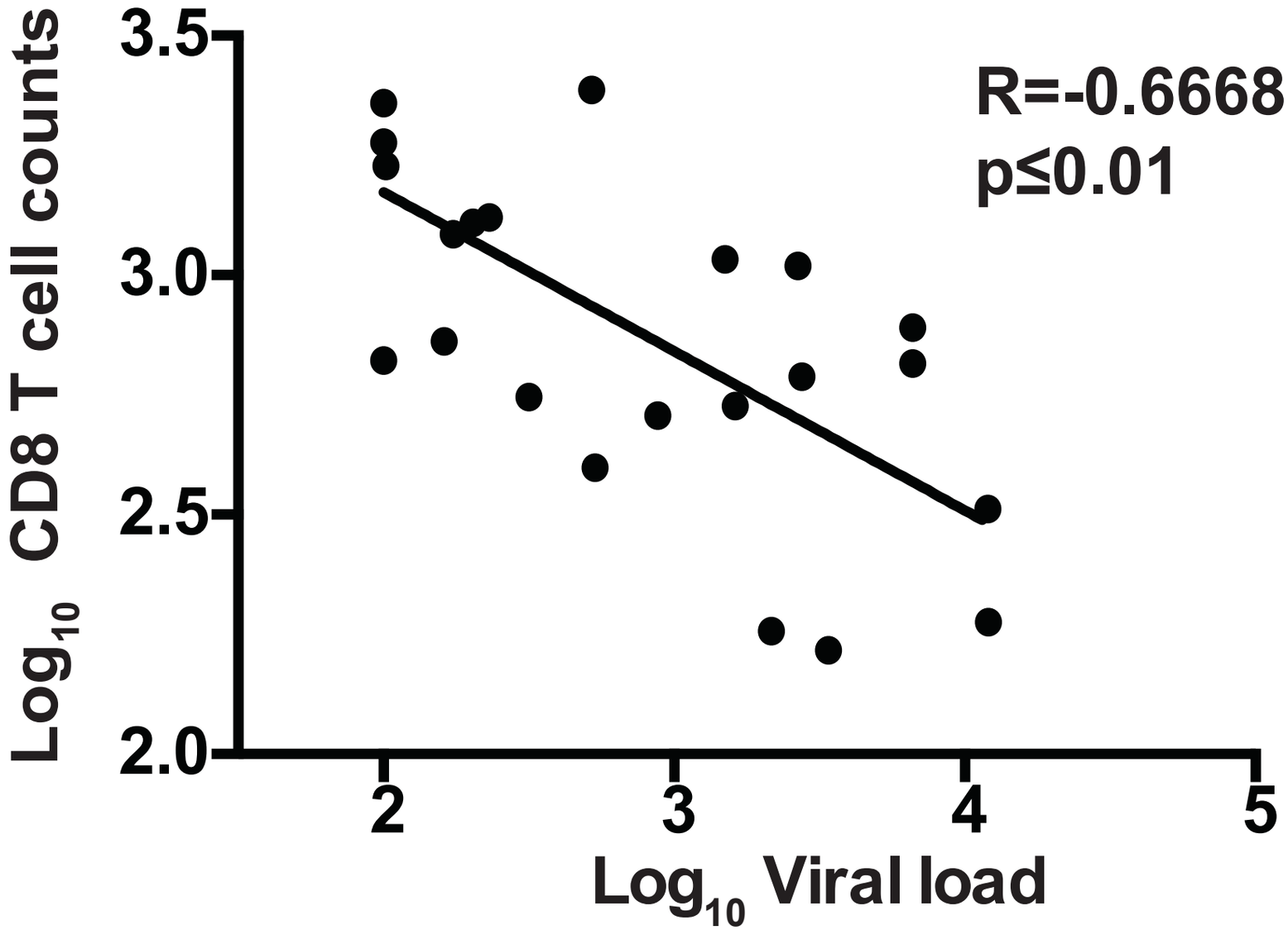
- Three animals were *Mamu-B*08*+ and one was *Mamu-A*01*+
- All 4 animals had received vaccine immunogens prior to SIV infection
- Viremia was ~10^3 or 10^4 copies/ml at time of study
- They received subcutaneous 0.1 mg/kg N-803 weekly
- Note: Unfortunately, we could not obtain lymph nodes

Rapid suppression of plasma viremia with N-803



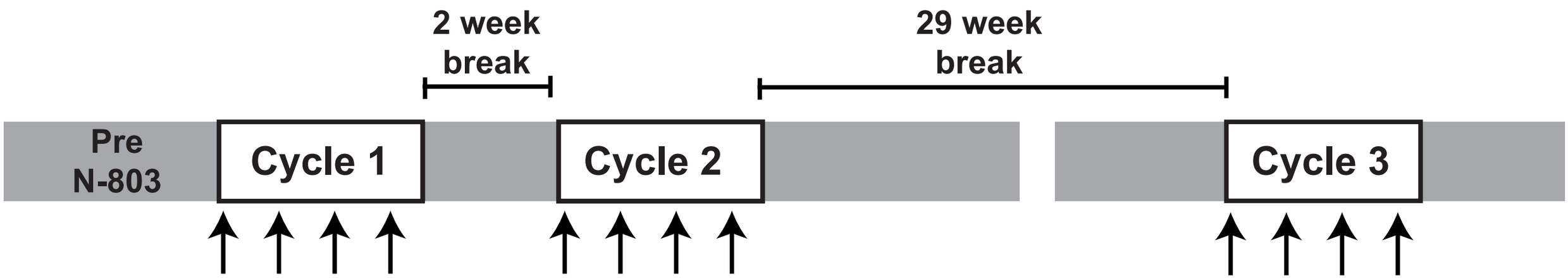
Modified from Ellis-Connell, A. et. al., J Virol, 2018

Peripheral CD8 T cells inversely correlated with SIV viremia

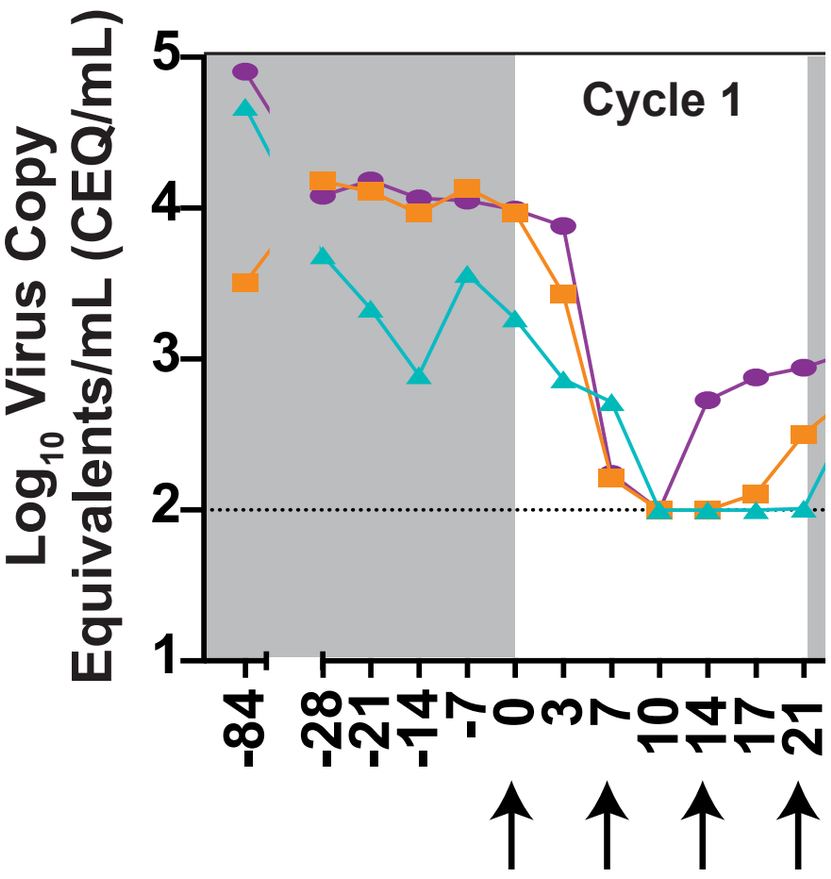


Modified from Ellis-Connell, A. et. al., J Virol, 2018

Could we regain control of viremia if we continued N-803 treatment?

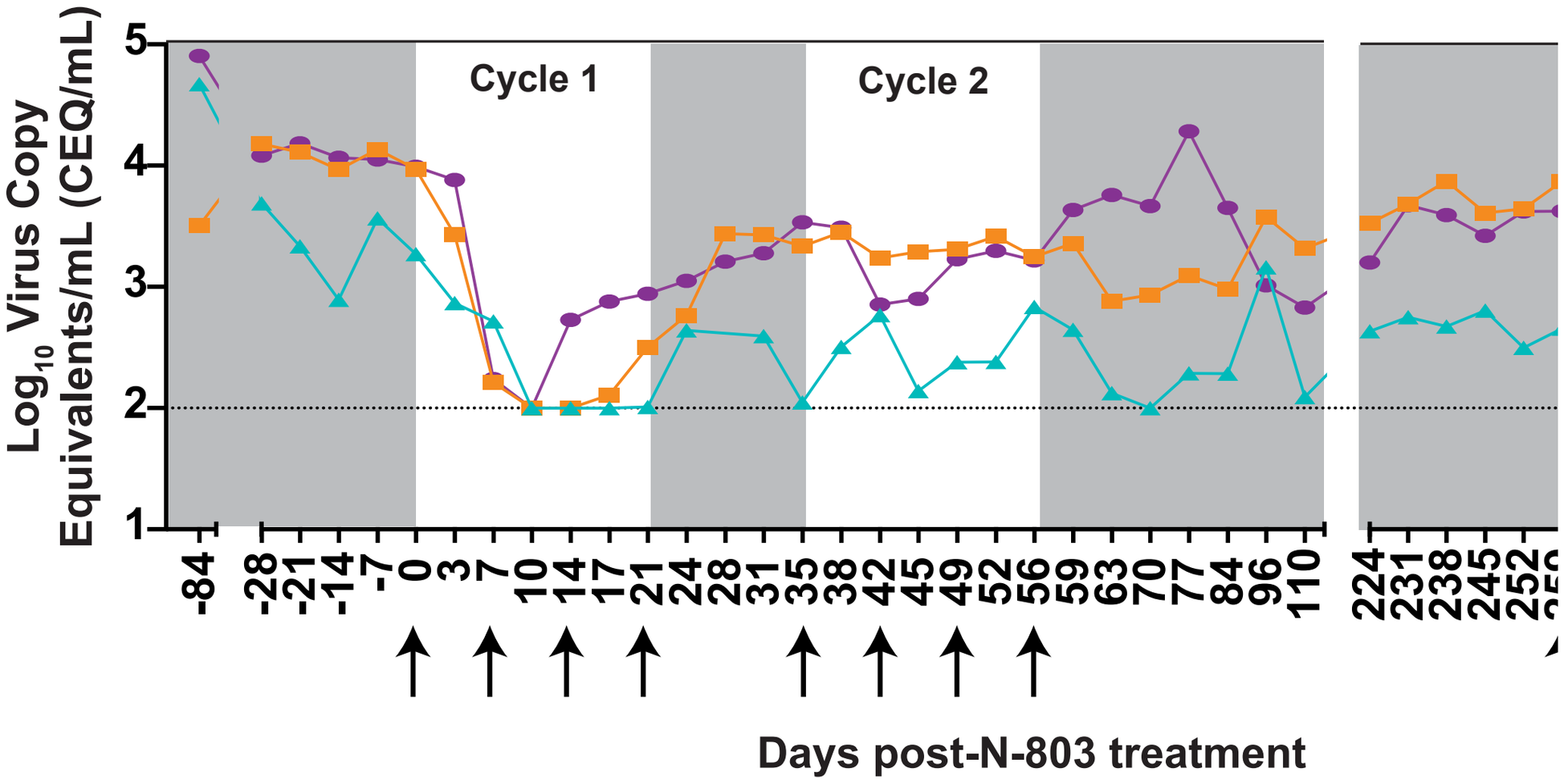


Suppression of SIV viremia during *Cycle #1*



Modified from Ellis-Connell, A. et. al., J Virol, 2018

NO suppression of SIV viremia during *Cycle #2*

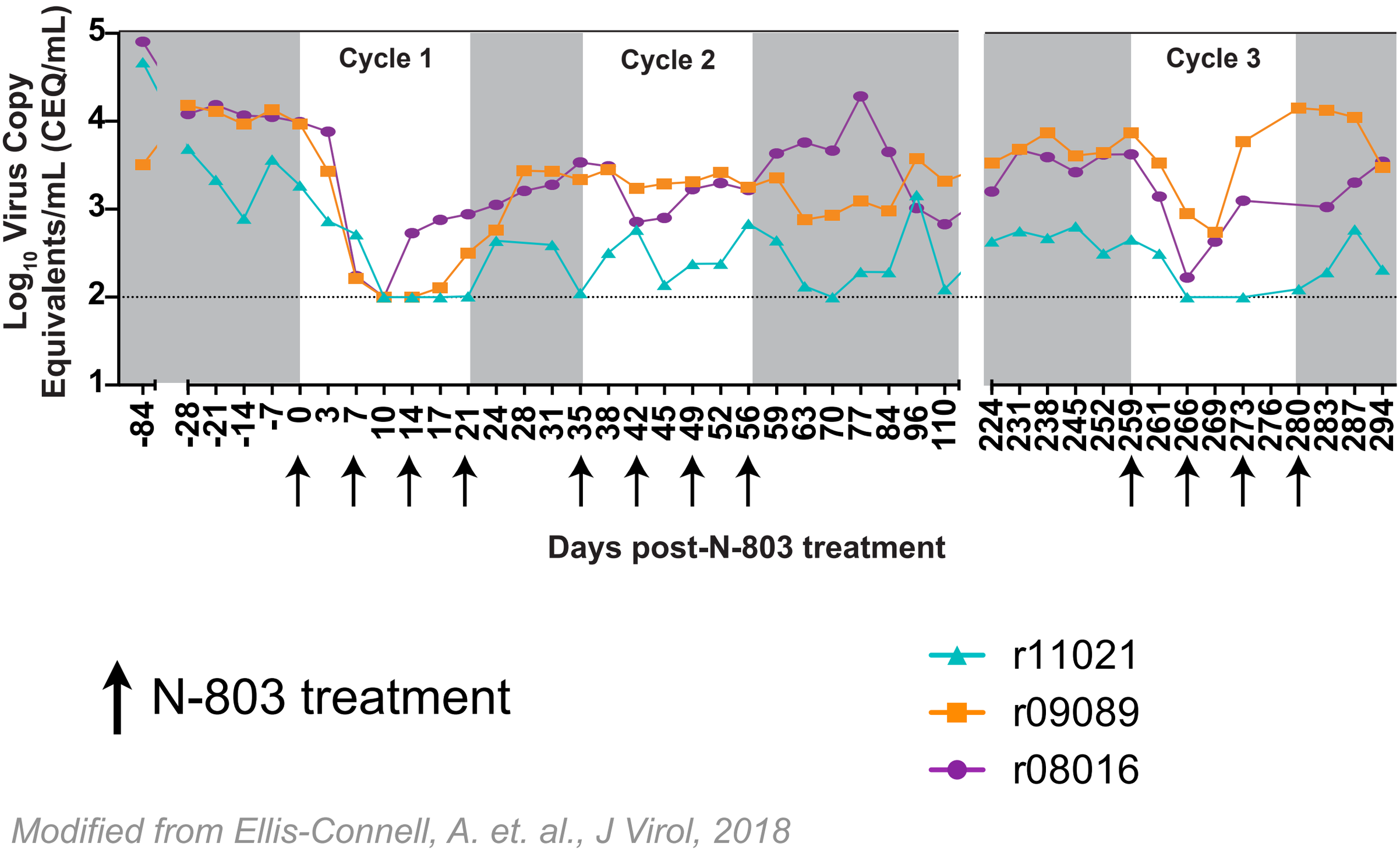


N-803 treatment

r11021
r09089
r08016

Modified from Ellis-Connell, A. et. al., J Virol, 2018

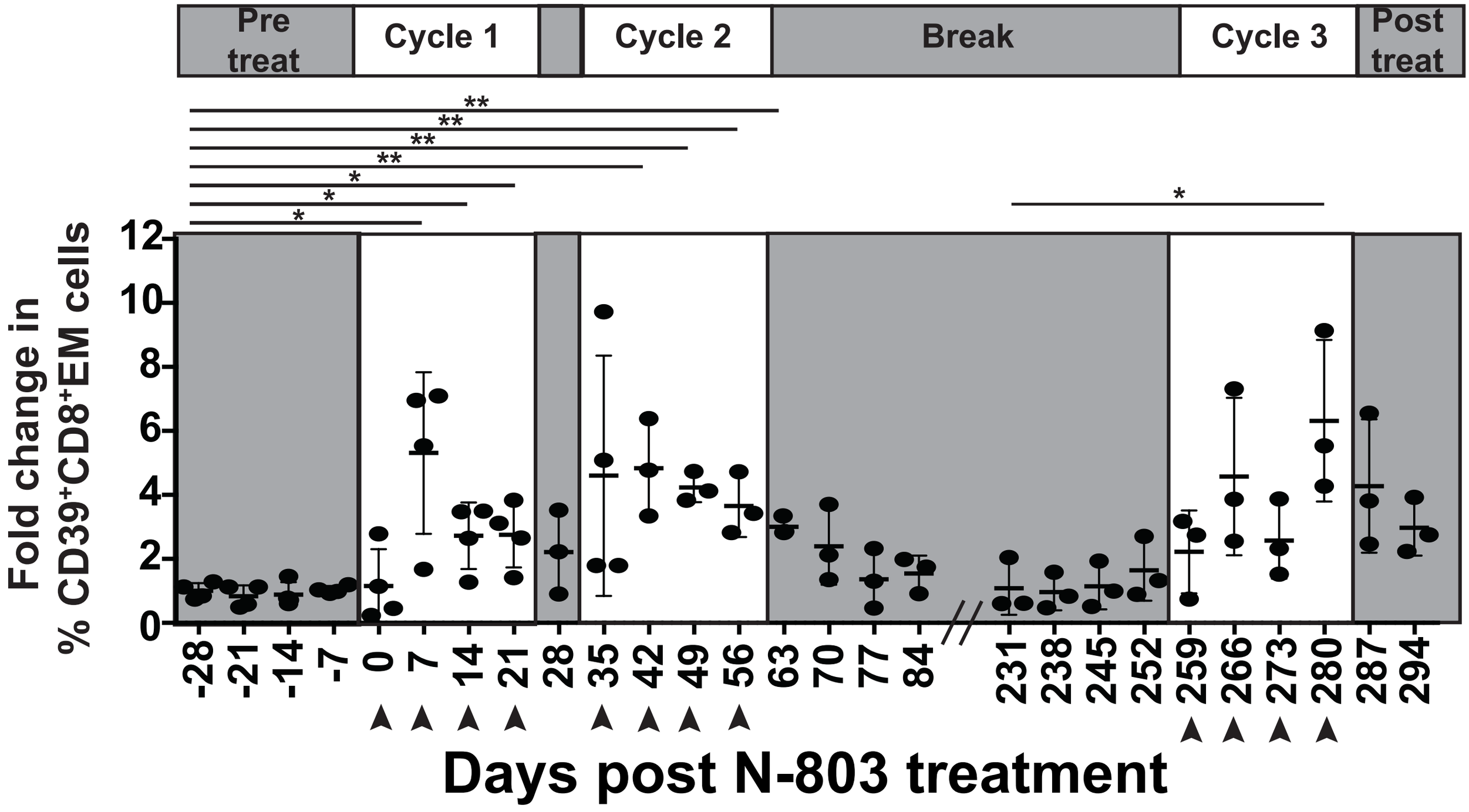
Limited suppression of SIV viremia during *Cycle #3*



Modified from Ellis-Connell, A. et. al., J Virol, 2018

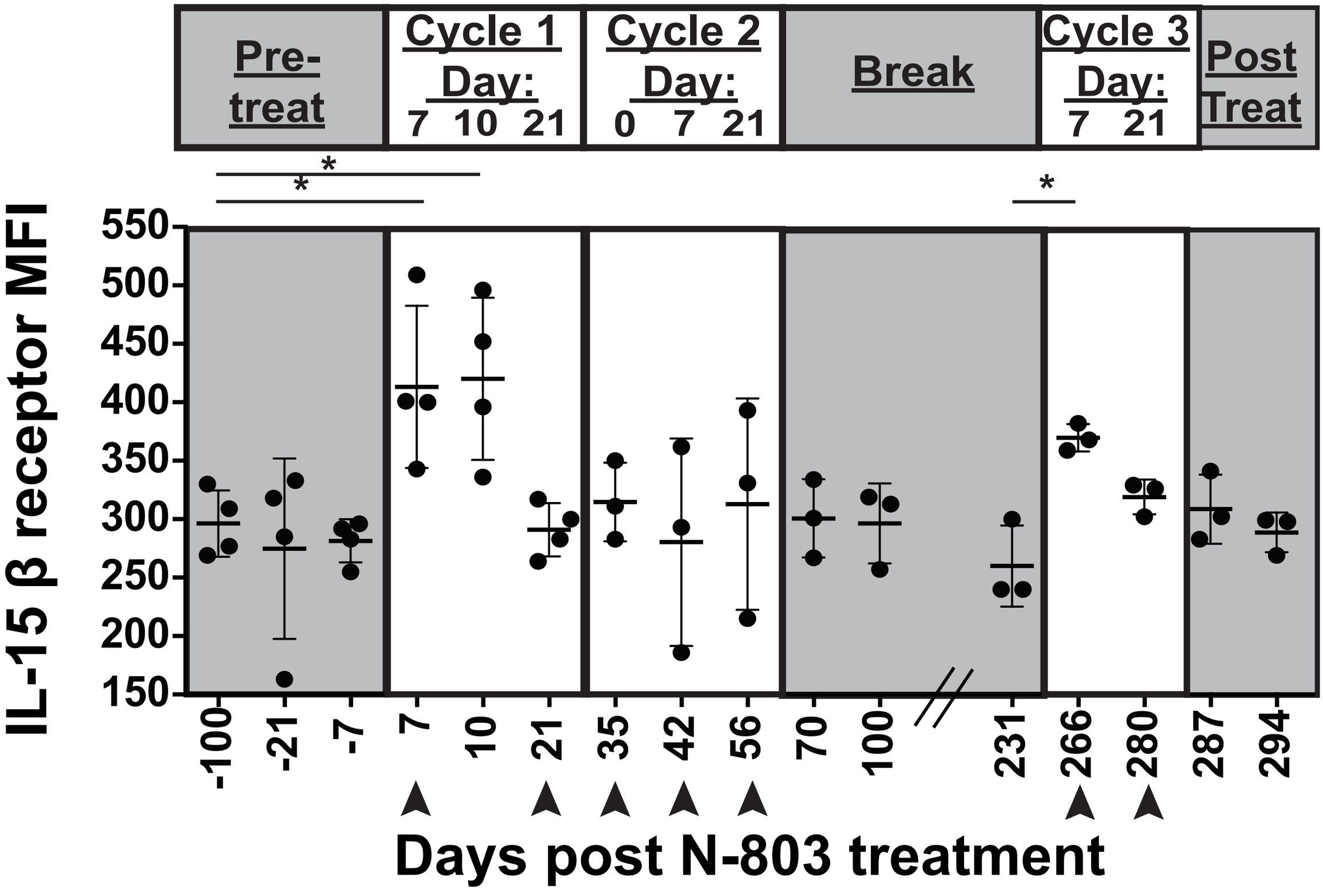
Why is virus suppression transient?

CD8 effector memory T cells start expressing CD39 (a marker of short-lived effector cells)



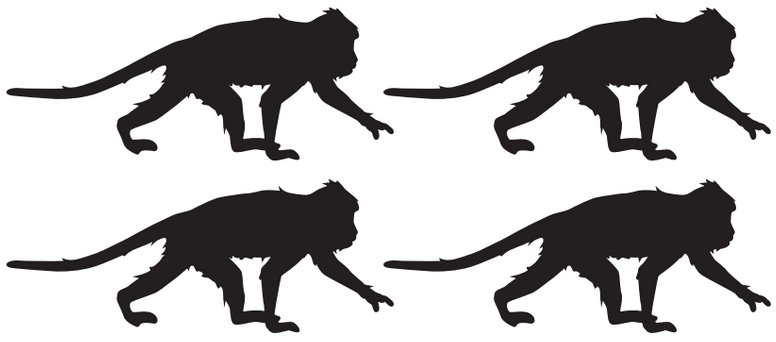
Modified from Ellis-Connell, A. et. al., J Virol, 2018

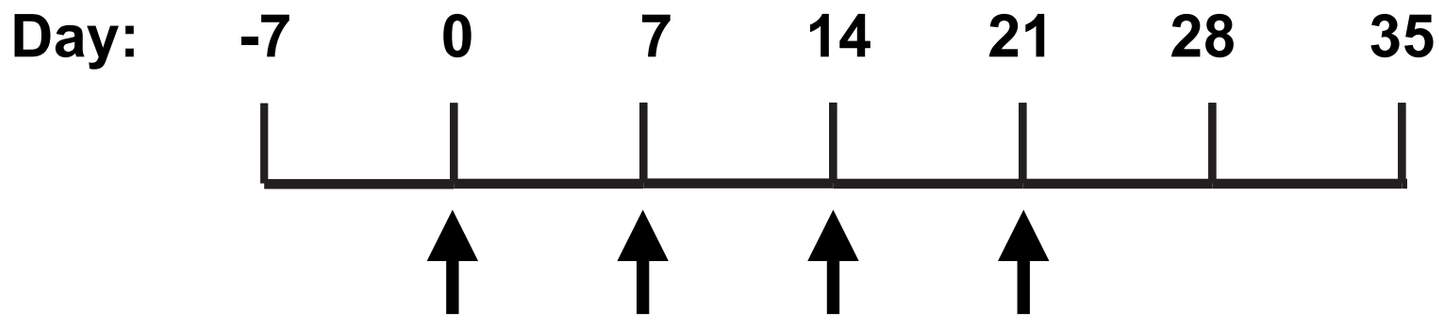
IL-15 receptor expression is not sustainable on CD8 effector memory T cells



Modified from Ellis-Connell, A. et. al., J Virol, 2018

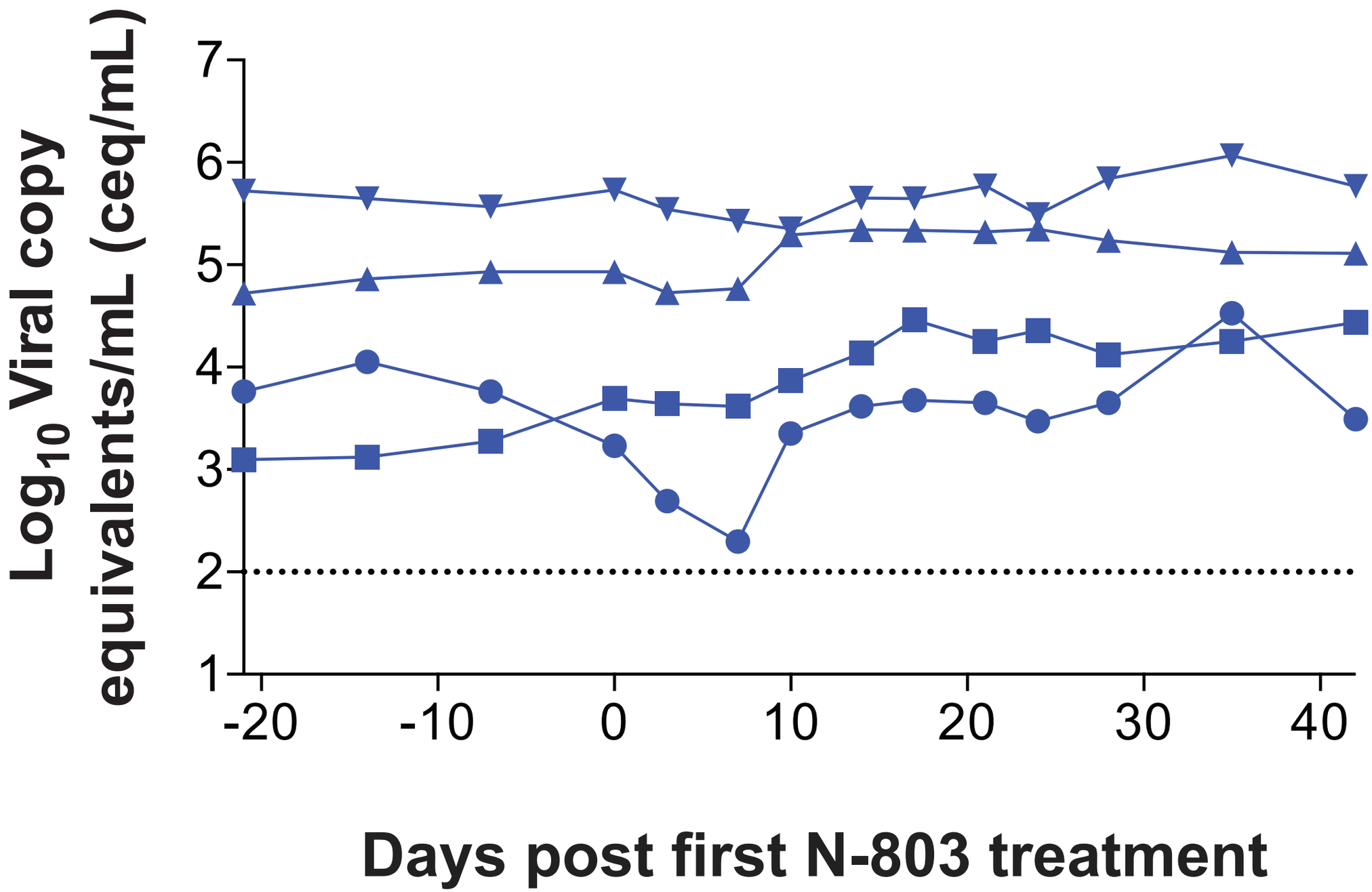
Study #2 outline



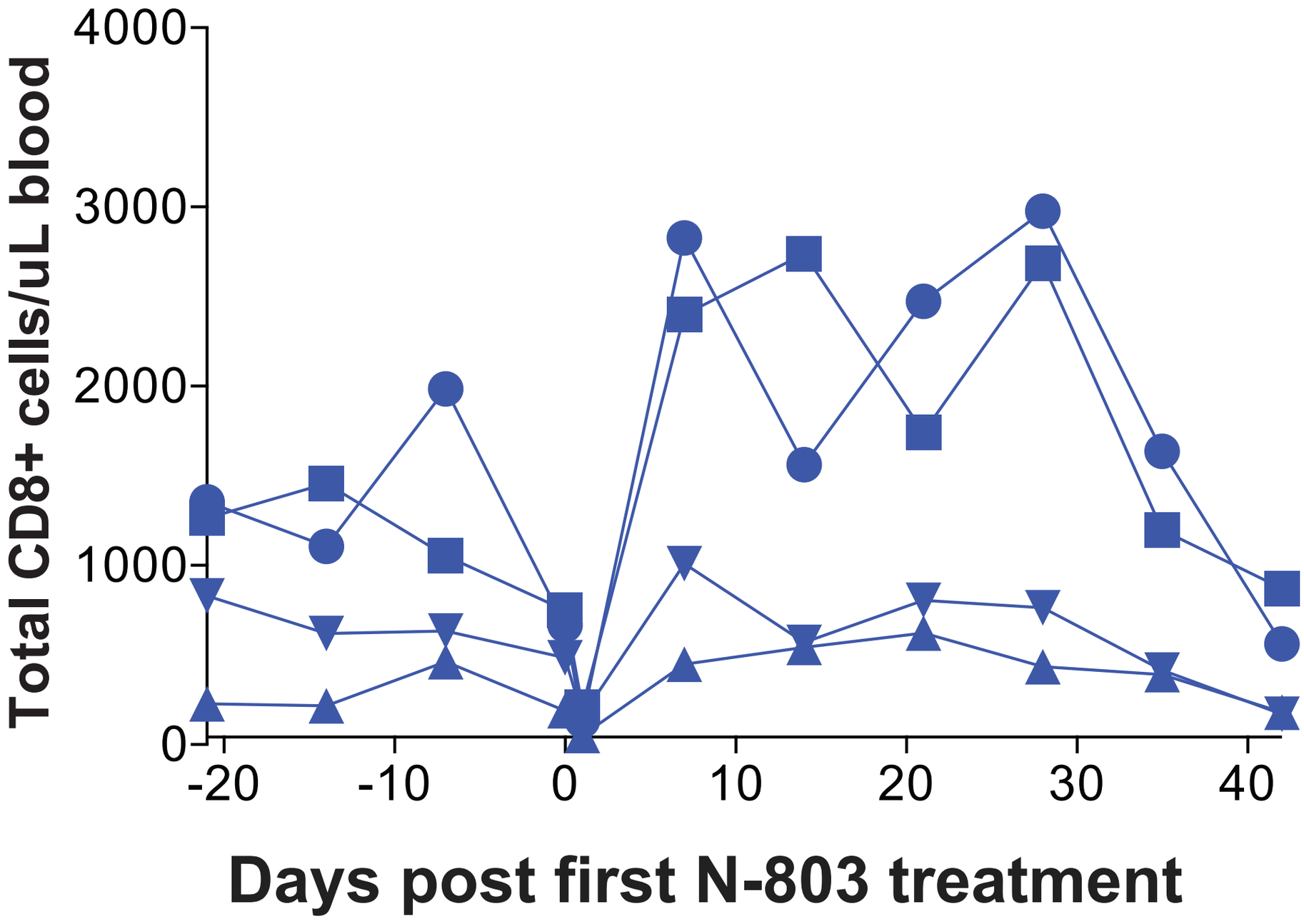


- Four M1/M3 MCMs who were SIV+ for 6 months
- None of the animals had been vaccinated
- 3 were treated with Dextran Sodium Sulfate, while 1 was not
- Animals received subcutaneous 0.1 mg/kg N-803 weekly

N-803 had very little effect on plasma viremia

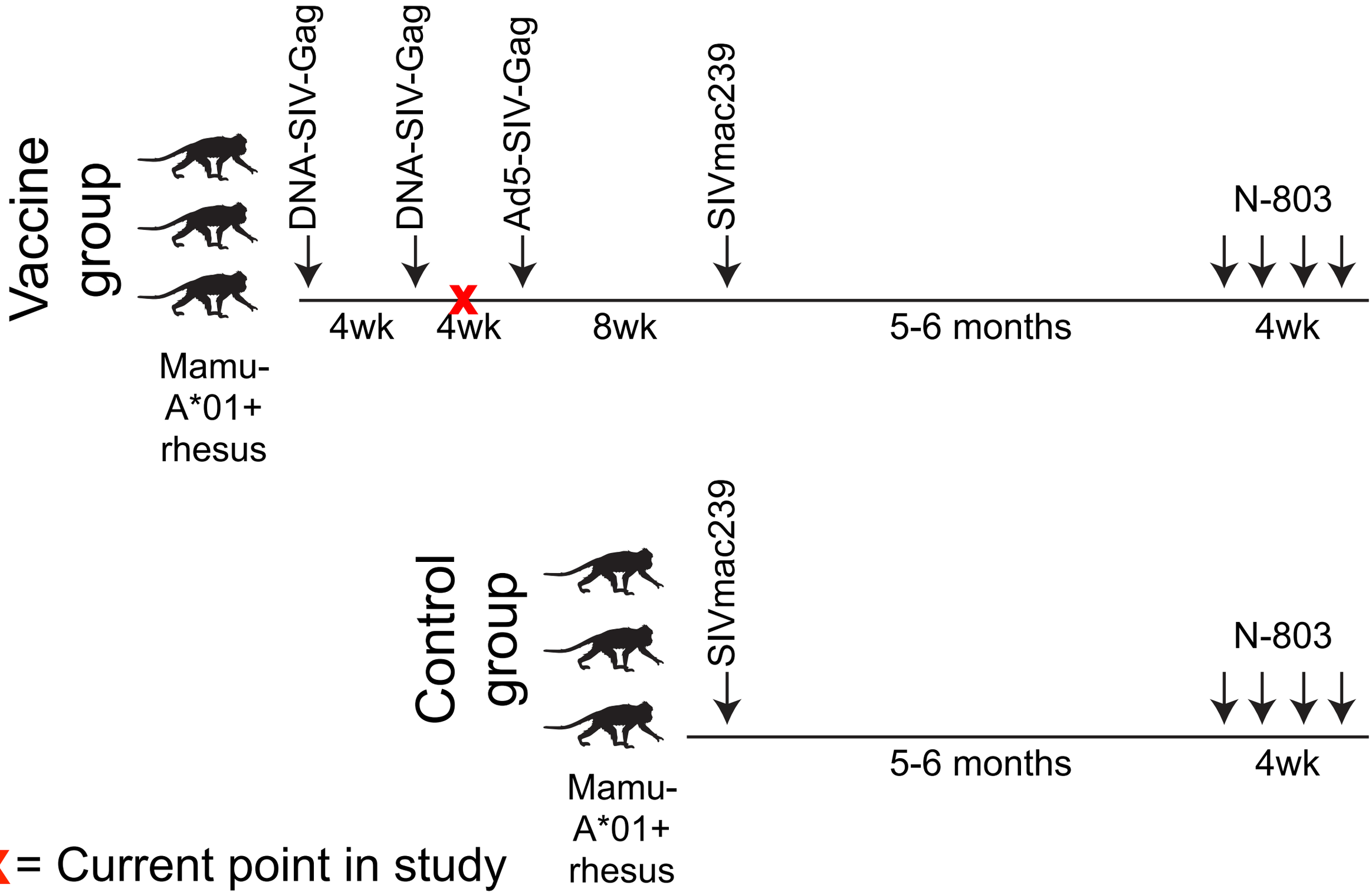


N-803 boosted total numbers of CD8 T cells, but this was insufficient to induce viral control



Hypothesis: N-803 mediated virus suppression requires pre-existing vaccine elicited CD8 T cells

Ongoing study



X = Current point in study

Conclusions and future studies

- Rapid suppression of SIV can occur in previously vaccinated rhesus macaques when treated with N-803

- Moving forward, we will determine the mechanism of N-803 mediated virus suppression:
  - Require vaccination?
  - Require CD8 T cells?
  - Lymph node targeting?
  - Are specific MHC alleles required?
  - Does the species matter?
  - How can we translate the use of N-803 to humans?

Thank you!

<u>UW-Madison</u>
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