

Does T cell function drive HIV-1 evolution ?

Julia L. Richardt

Helen Horton

FHCRC

Introduction

- IFN- γ secretion alone might not be ideal parameter to assess T cell responses
- CD8 T cells of progressors and non-progressors differed by ability to proliferate, all able to secrete IFN- γ Migueles *et al Nat Immunol* 2002; Horton *et al JI* 2006
- T cells must be able to proliferate in order to be able to upregulate perforin Migueles *et al Nat Immunol* 2002

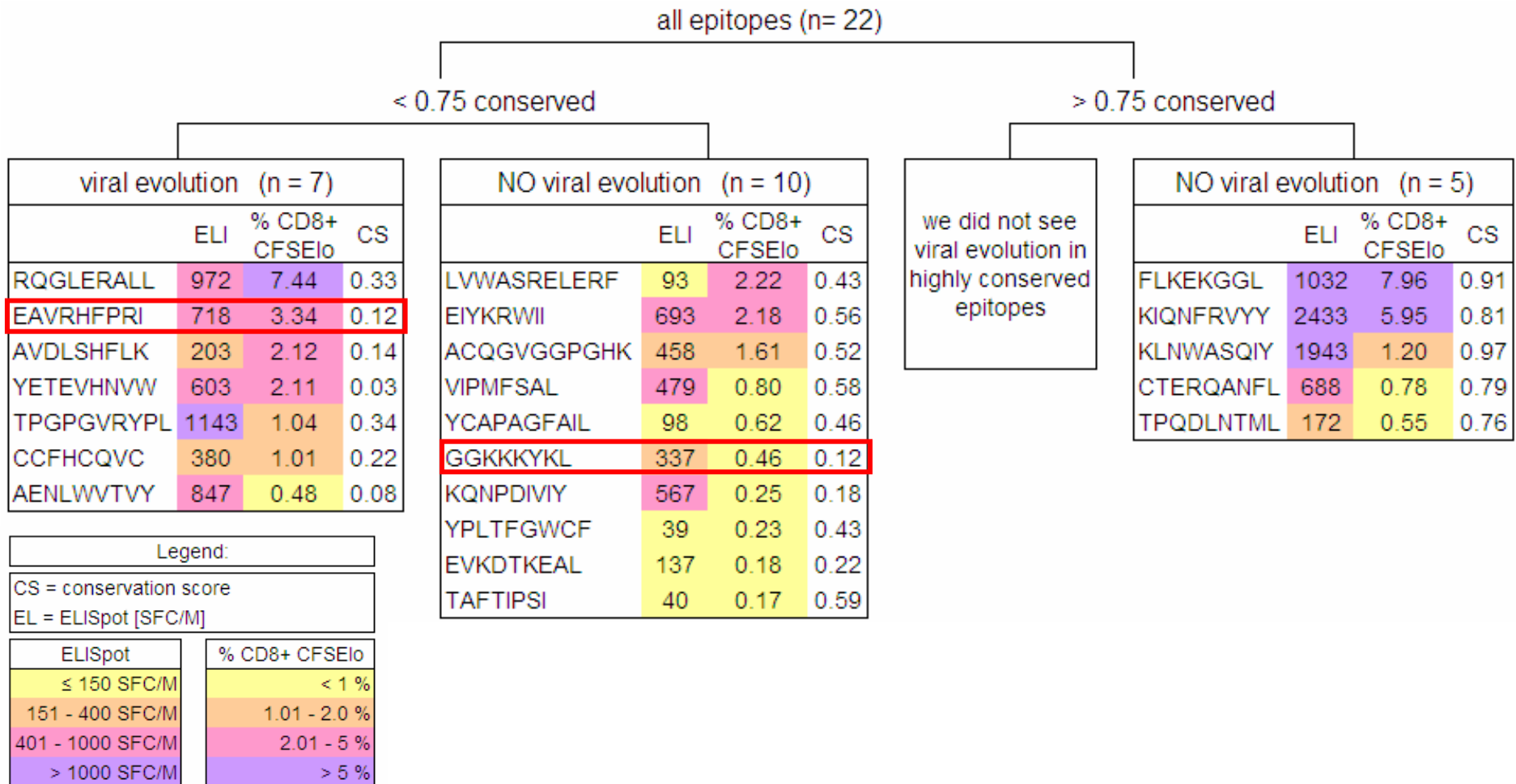
Introduction (cont.)

- Question:
does proliferative capacity impact viral evolution ?
- Hypothesis:
T cells with high proliferative capacity will drive viral evolution unless they target highly conserved epitopes.

Study subjects & epitopes studied

<p>CHPIC 1397 A2; A11; B40; B51 413 - 2643 dpi</p>	<p>ACQGVGGPGHK (p24; A11) CTERQANFL (p2p6p1p6; B40) AVDLSHFLK (Nef; A11)</p>	<p>total number of epitopes: n = 22</p>
<p>CHPIC 1362 A*0201; A*2501 B18; B51 Cw*0102; Cw*1203 34 - 1500 dpi</p>	<p>VIPMFSAL (p24; Cw01) TAFTIPSI (RT; B51) EAVRHFPRI (Vpr; B51) CCFHCQVC (Tat; Cw12)</p>	<p>YCAPAGFAIL (gp160; Cw01) AENLWVTY (gp160; B44) YETEVHNVW (gp160; B18) YPLTFGWCF (Nef; B18)</p>
<p>CHPIC 1692 A23; A30 B8; B42 52 - 954 dpi</p>	<p>LVWASRELERF (p17; A30) EVKDTKEAL (p17; B8) GGKKKYKL (p17; B8) EIYKRWII (p24; B8) TPQDLNTML (p24; B42) KLNWASQIY (RT; A30)</p>	<p>KQNPDIVIIY (RT; A30) KIQNFRVYYY (Int; A30) RQGLERALL (gp160; B8) FLKEKGGL (Nef; B8) TPGPGVRYPL (Nef; B42)</p>

Viral evolution seems to be associated with stronger T cell responses:

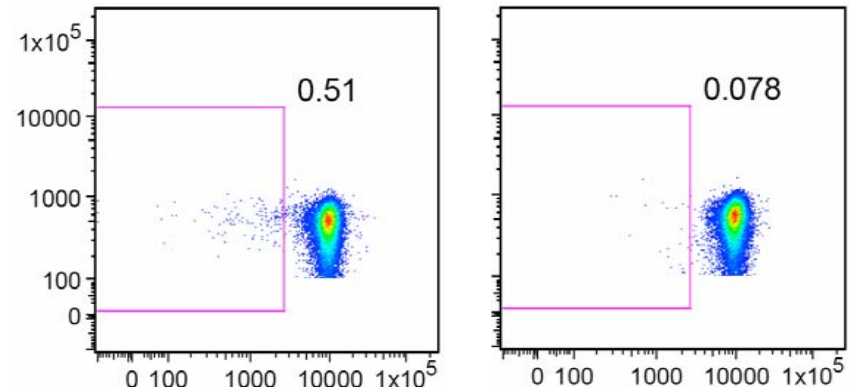
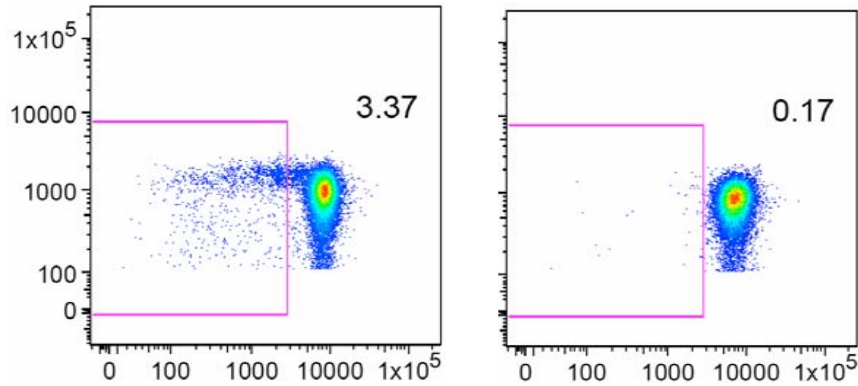
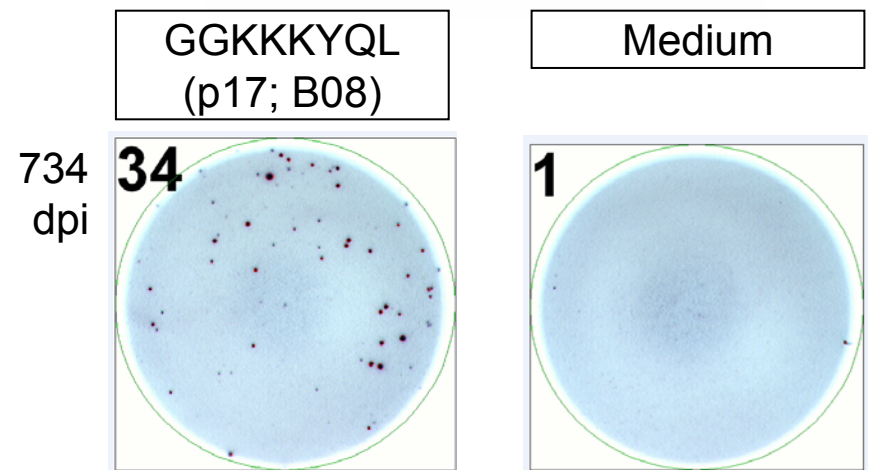
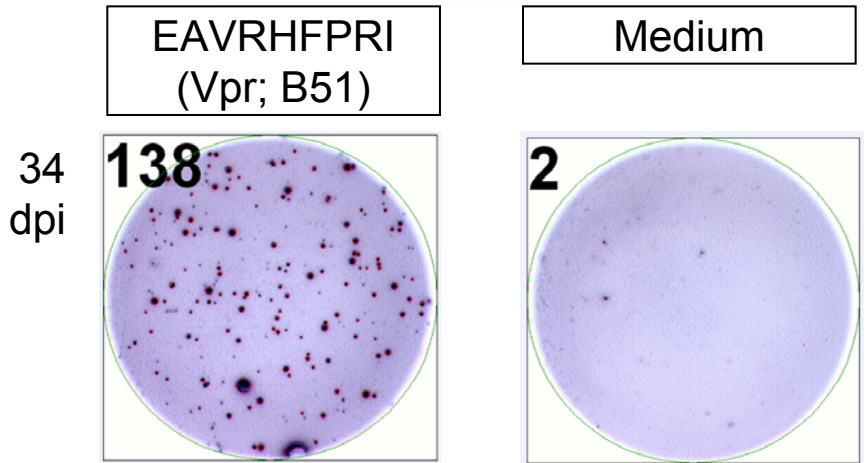


included: 1st positive CFSE_{lo} response & corresponding ELISpot data for which sequence information is available at the time or ≤ 200 days before and within ≤ 400 days of T cell assay

Example of a strong T cell response which is associated with viral evolution, whereas the weak T cell response is not

8 dpi EAVRHFPRI 10/10
 22 dpi ----- 17/17

300 dpi GGKKKYQL 8/8
 734 dpi ----- 8/8

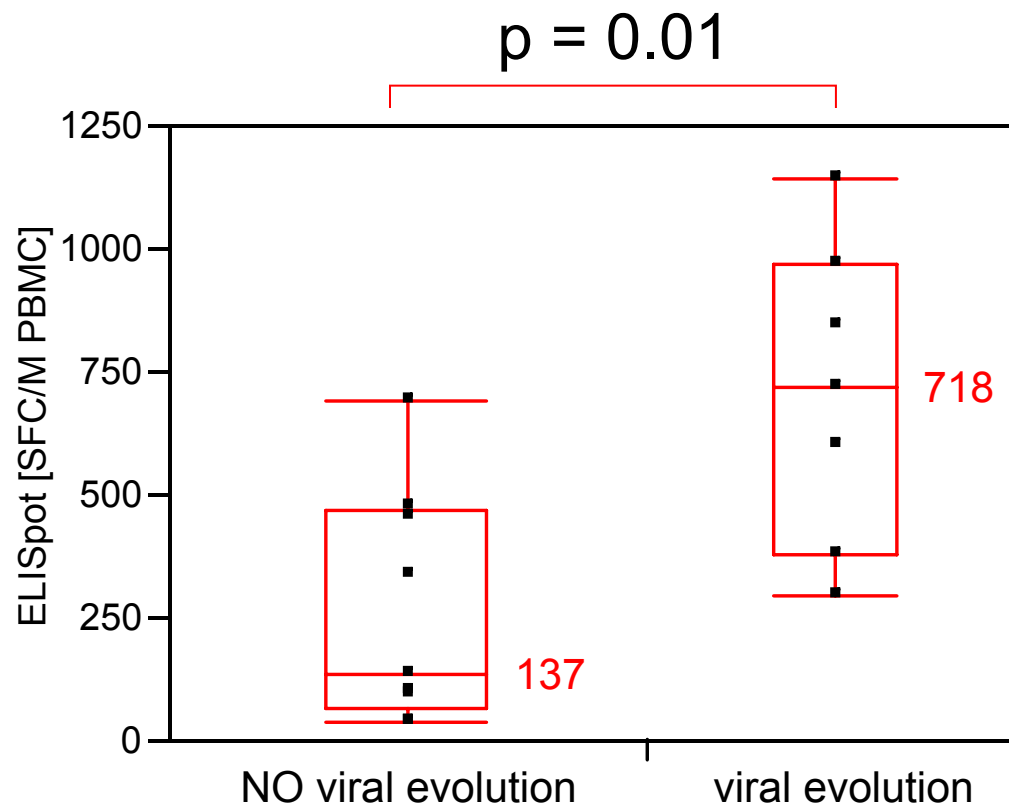


50 dpi ----- 4/9
 -----T 3/9
 76 dpi -----T 7/10
 113 dpi -----T 5/9

954 dpi ----- 8/8

ELISpot: 200k (EI9); 100k (GL8) PBMC/well
 CFSE: % CD8+ CFSElo T cells

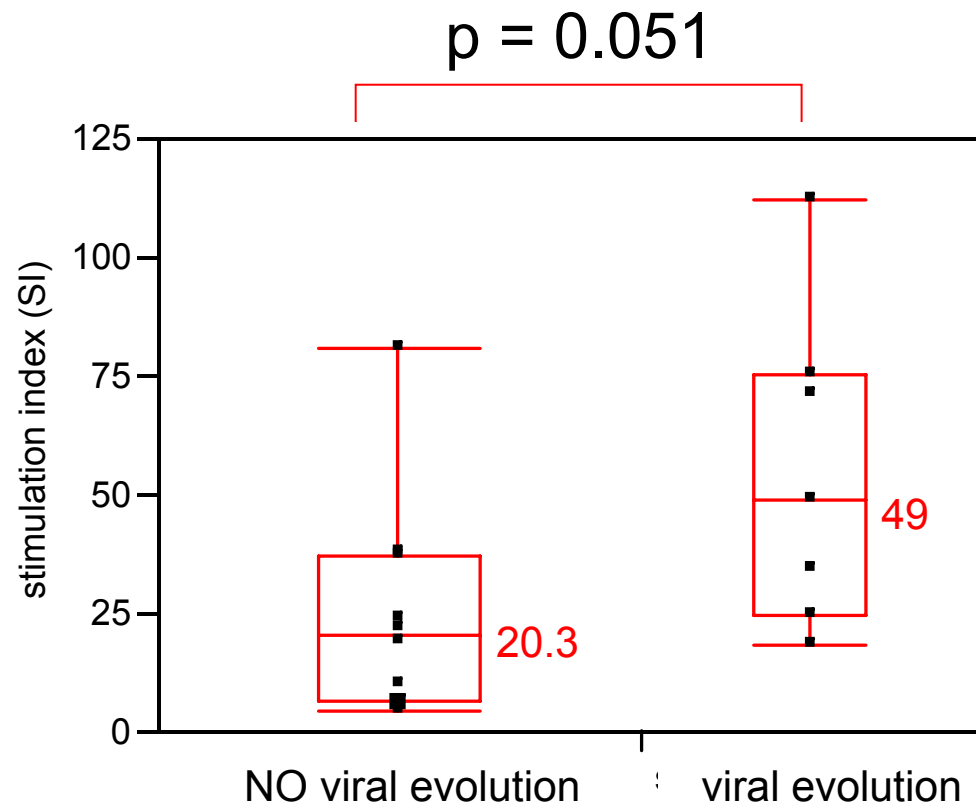
Higher IFN- γ responses are associated with viral evolution:



*Wilcoxon test
n = 17

There is a trend towards T cells recognizing epitopes which changed proliferating stronger than those targeting epitopes which did not change

- Stimulation index:
% CD8⁺ CFSE^{lo} + stimulant
divided by
% CD8⁺ CFSE^{lo} medium control
- SI also used in LPA
- More data should strengthen the association



*Wilcoxon test
n = 17

Conclusions: Does T cell function drive viral escape ?

- Antigen-specific T cell responses associated with viral evolution:
 - have significantly higher IFN- γ responses ($p = 0.01$) &
 - show a trend for greater proliferative capacity ($p = 0.051$).

Conclusions: Does T cell function drive viral escape ? (cont.)

- *Future work:*
 - analyze more epitopes/patients to gain statistical power;
 - collaboration with Yunda Huang at SCHARP to develop statistical methods/model to determine whether high proliferative capacity (SI) drives viral evolution, controlling for initial antigen-specific T cell frequency & conservation score.

Acknowledgements:

FHCRC:

McElrath Lab:

HVTN R & D

John McNevin

Natalie Zheng

SCHARP:

Yunda Huang

University of Washington:

Mullins Lab

Zhu Lab

Patients & Staff at *Seattle PI clinic*

Helen Horton
Julie McElrath

***Thank you for
your attention
and feedback***