Dr Lucy Dorrell
University of Oxford
The antiviral inhibitory capacity of CD8+ T cells predicts the rate of CD4+ cell decline in HIV-1 infection

Hongbing Yang, Hao Wu, Gemma Hancock, Genevieve Clutton, Nellia Sande, Xiaoning Xu, Huiping Yan, Xiaojie Huang, Brian Angus, Kristin Kuldane, Sarah Fidler, Thomas N. Denny, Jacqueline Birks, Andrew McMichael, Lucy Dorrell

University of Oxford
**Background**

- HIV-specific CD8+ T cell responses control acute viraemia but fail to clear or control infection.
- Superior functional capacity of HIV-specific CD8+ T cells from HIV controllers / long-term nonprogressors.
- Cause or consequence of long-term virus control?
- Laboratory assays do not adequately reflect immune recognition of HIV in vivo.
CD8+ T cell antiviral inhibitory activity: an immune correlate of HIV control?

- Potent inhibition of HIV replication by ex vivo CD8+ T cells
  
  (Saez-Cirion et al., 2007, Freel et al., 2010)

- Unique to HIV controllers?
- A determinant of the rate of disease progression in viraemic individuals?
To investigate the relationship between CD8+ T cell antiviral activity and HIV progression in chronic infection

To determine whether CD8+ T cell antiviral activity in early HIV infection can predict HIV progression
Activate CD4+ T cells then super-infected with HIV

Blood separated into CD4+ and CD8+ fractions

Autologous unstimulated CD8+ T cells added on day 3

Culture for 5-7 days

CD4

HIV p24 antigen

5.1%

0.38%

Reduction in viral growth by CD8+ T cell is expressed as % inhibition

(% infected CD4+ cells (p24+) in CD4/CD8 co-culture) / % infected cells in CD4+ cells alone
CD8+ T cell antiviral activity is expressed on a continuum in chronic HIV infection

- 30 patients with chronic HIV infection, ART-naïve, asymptomatic
- CD4 counts > 350 cells/μl
- 20 males, 10 females
- Median age - 34 yrs
- Median diagnosed infection: 3 years
- Protective HLA class I allele - 20%

\[ \text{CD8+}/\text{CD4+ cell ratio} = 2:1 \] (in assay)
CD8+ T cell antiviral suppressive activity in chronic HIV infection is strongly associated with the rate of CD4+ cell decline

CD4 slopes derived from median 4.5 years’ follow-up
Linear mixed models to investigate interaction between CD4 slope and CD8+ T cell antiviral activity (% inhibition)
Is potent CD8+ T cell antiviral activity the cause or consequence of HIV disease control?

- Prospective study in recently infected patients with known date of HIV-1 acquisition – Beijing PRIMO cohort

- CD8+ T cell antiviral activity measured at a single time-point in early infection

- Examined predictive value of % inhibition for the rate of CD4 decline over first 3 years of infection
Prospective analysis of 20 patients with recent HIV infection

- 20 MSM, ART-naïve, asymptomatic
- CD4 counts > 350 cells/μl
- Median age - 28 yrs

- CD8+ T cell antiviral activity measured at single time-point at 3 CD8+/CD4+ cell ratios
- Duration of infection: median 198 days
- Follow-up: median 895 days

- Protective HLA class I allele*: n = 6 (30%)
CD8+ T cell antiviral activity was a strong predictor of the rate of CD4+ cell decline at all CD8+/CD4+ cell ratios tested ($p < 0.0001$)

Explained up to 73% of inter-individual variation in CD4 slope
Potent CD8+ T cell antiviral activity is associated with longer survival with CD4 > 350 cells/μl

Patients stratified by % inhibition value above ▲ or below ◆ median

**CD8/CD4 = 2:1**

p = 0.06

**CD8/CD4 = 1:10**

p = 0.0002

**CD8/CD4 = 1:100**

p = 0.003
Assay enables measurement of ‘total’ HIV-specific CD8+ T cell response

The capacity of CD8+ T cells to inhibit HIV replication in vitro is:
- highly predictive of the rate of CD4+ cell decline in the first 3 years of infection
- explains majority of inter-individual variation in CD4 slope
- inversely correlated with viral load set-point
Assessment of CD8+ T cell function could have prognostic value in patients with CD4 counts above current thresholds for ART-initiation

Potential as a benchmark of effective immunity in the clinical evaluation of HIV vaccine candidates
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