T Cell Response Signatures in Breast Cancer vs Chronic Infection

Holden T. Maecker, Ph.D.

Stanford University

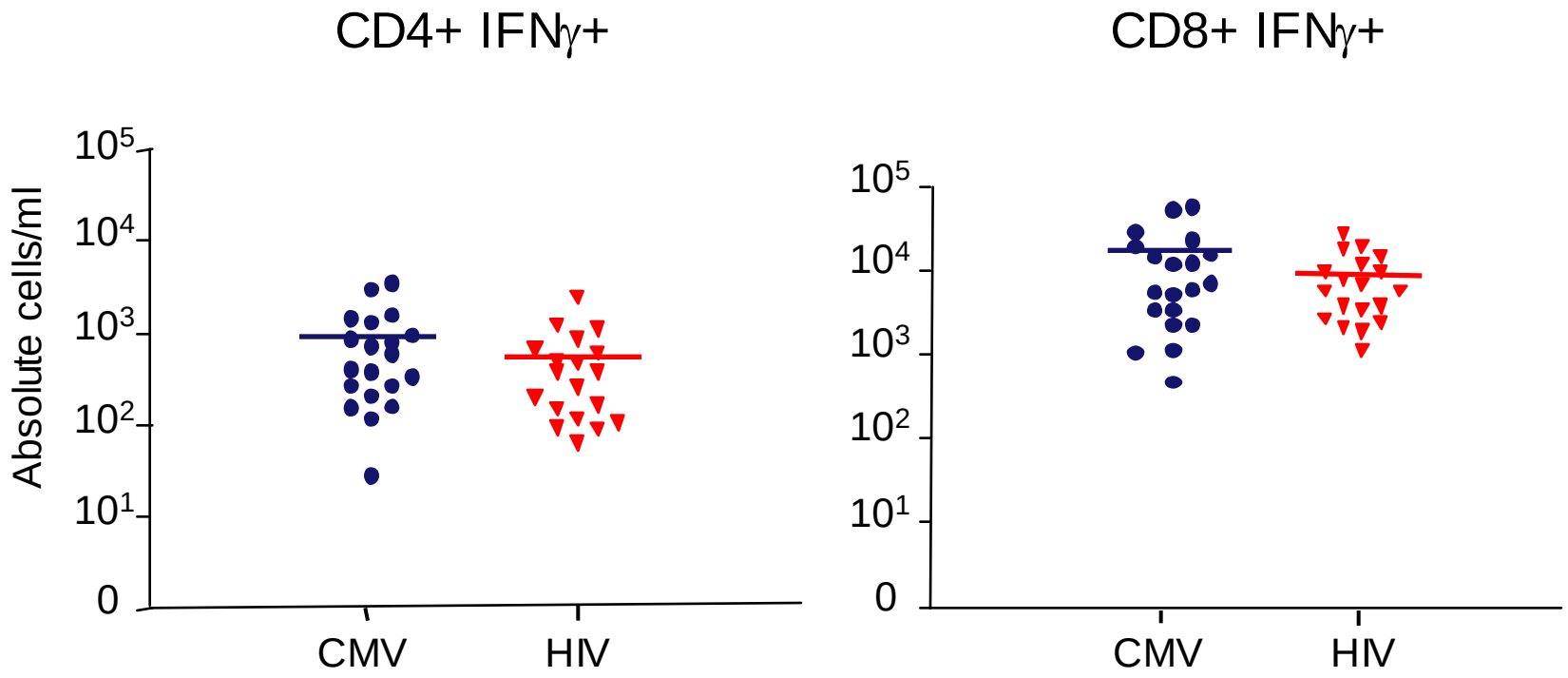
Features of a T cell response signature

- Magnitude and Breadth
  - Total frequency of Ag-specific T cells
  - Breadth of epitope responses
- Functional properties
  - Cytokine production
  - Degranulation or lytic capacity
  - Fraction of Ag-specific cells that are functional
- Phenotypes
  - Markers of memory and effector differentiation
  - Markers of exhaustion (PD-1, etc.)
  - Perforin, granzymes, etc.

Cancer vs. chronic infections (HIV, CMV)

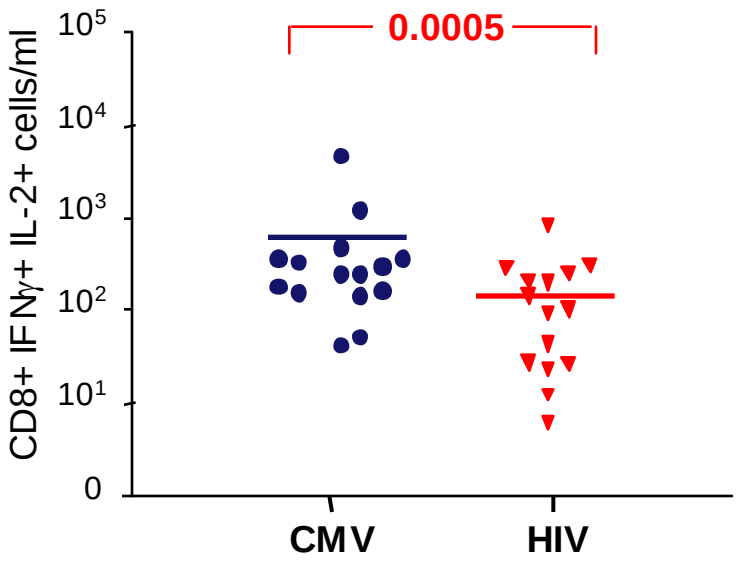
- All require cellular immunity for protection
  - Virus-infected and cancer cells are both altered host cells, targets for CTL killing
- All result in chronic antigen exposure
  - Antigen usually not cleared from host
- CMV does not cause pathology in immunocompetent hosts
  - What is unique about the CMV signature?

Magnitude of CMV & HIV responses

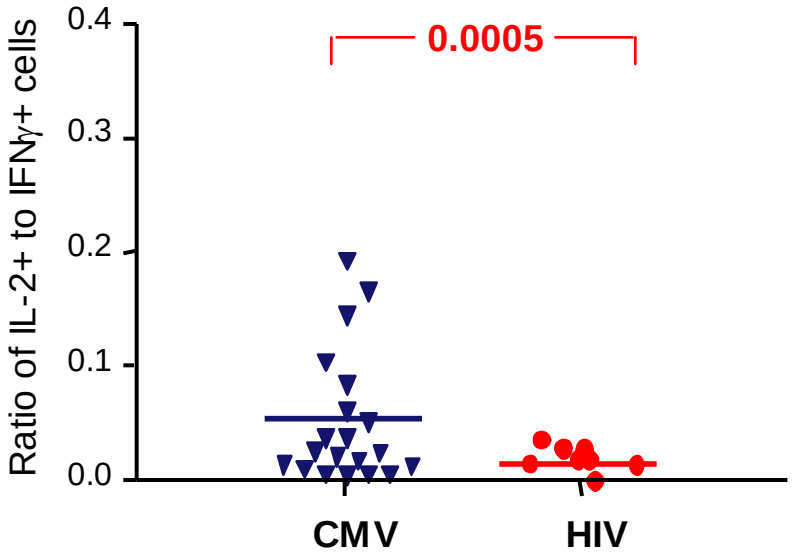


Function of CMV & HIV responses

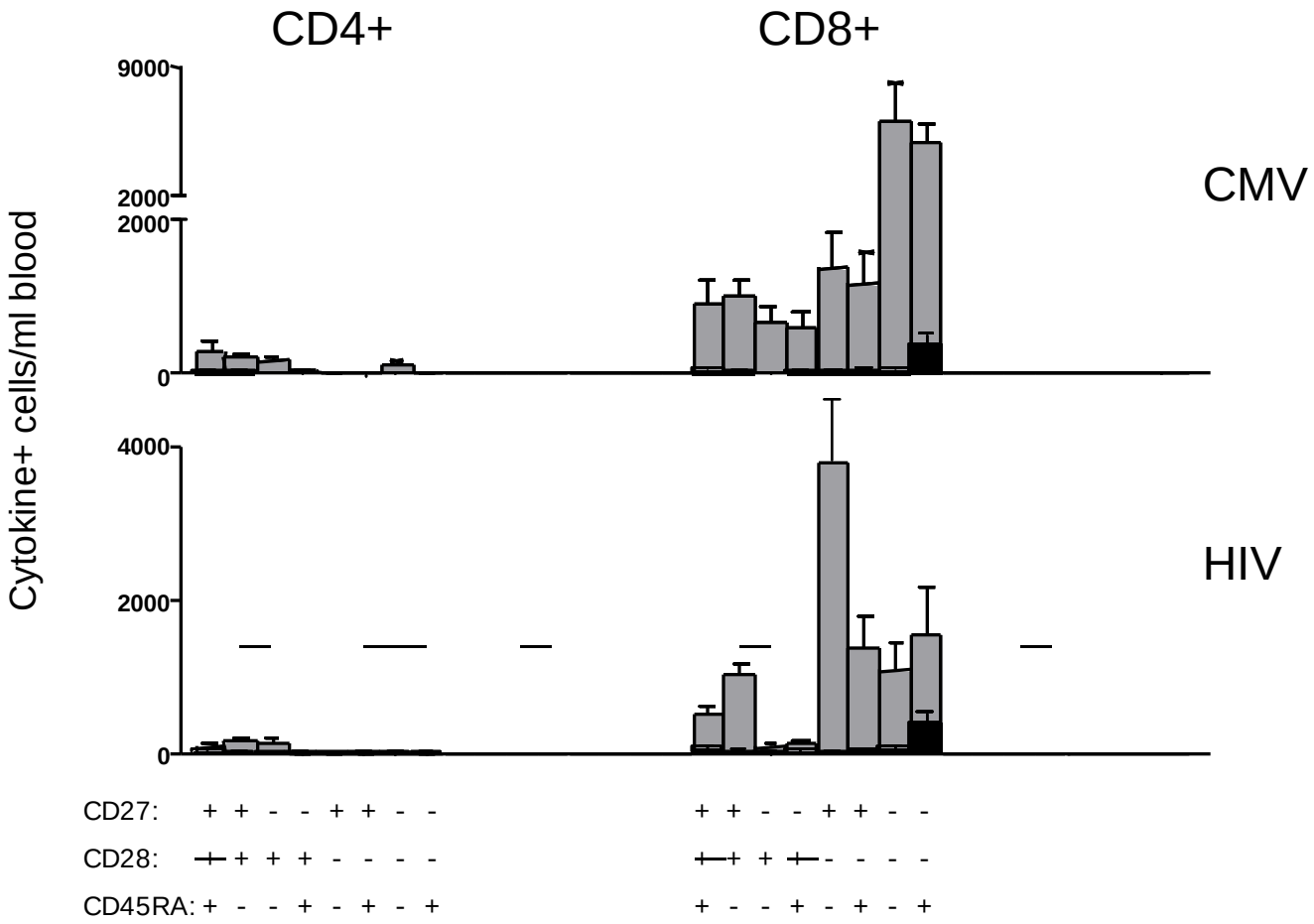
Absolute counts of IL-2+ cells:



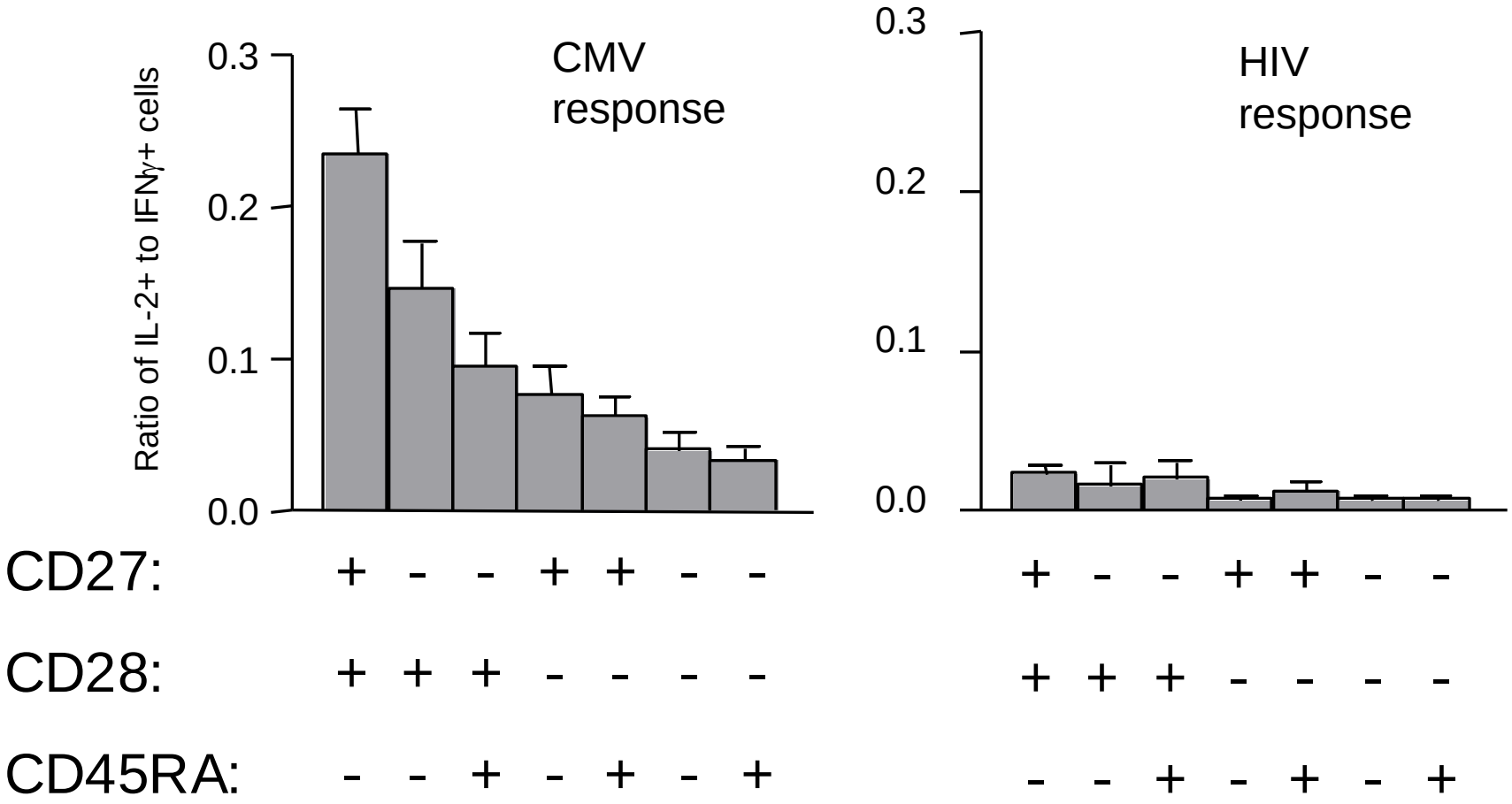
Ratio IL-2+/IFNγ+ cells:



Phenotype of CMV & HIV responses



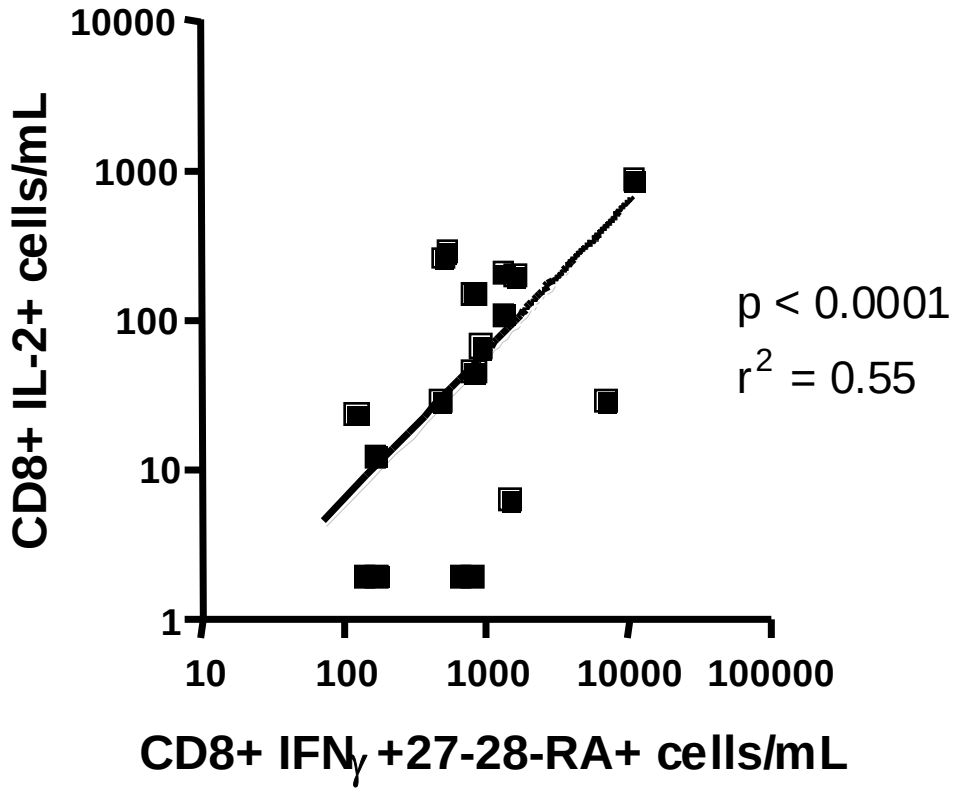
HIV-responsive CD8+ T cells lack IL-2 production regardless of phenotype



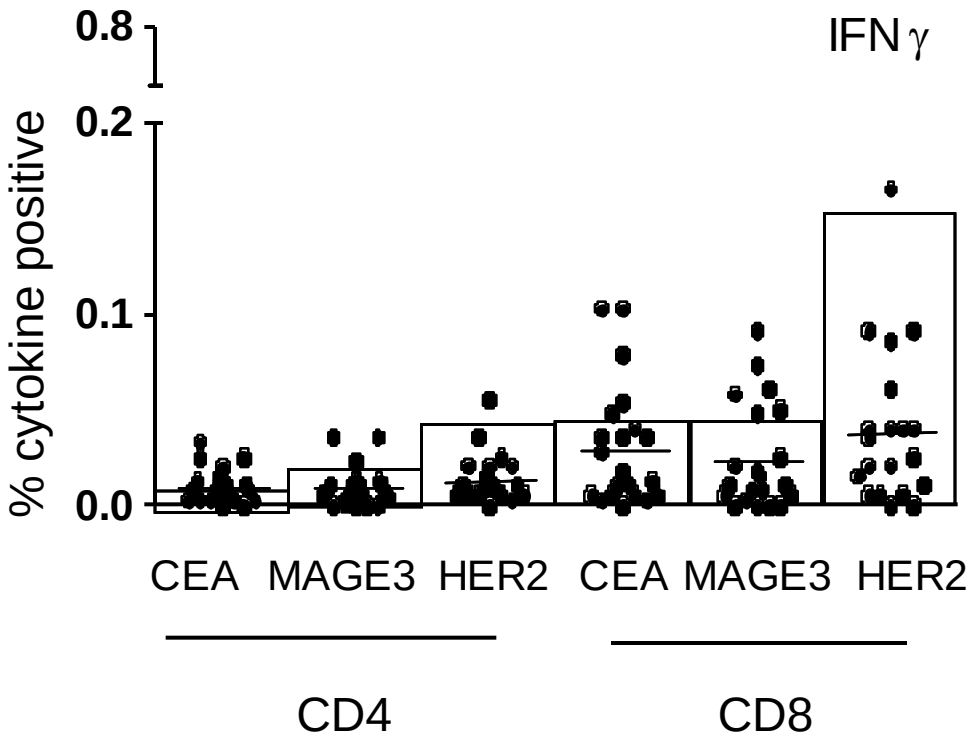
Hypothesis

- IL-2 producing CD8+ T cells may be required to drive terminal effector differentiation

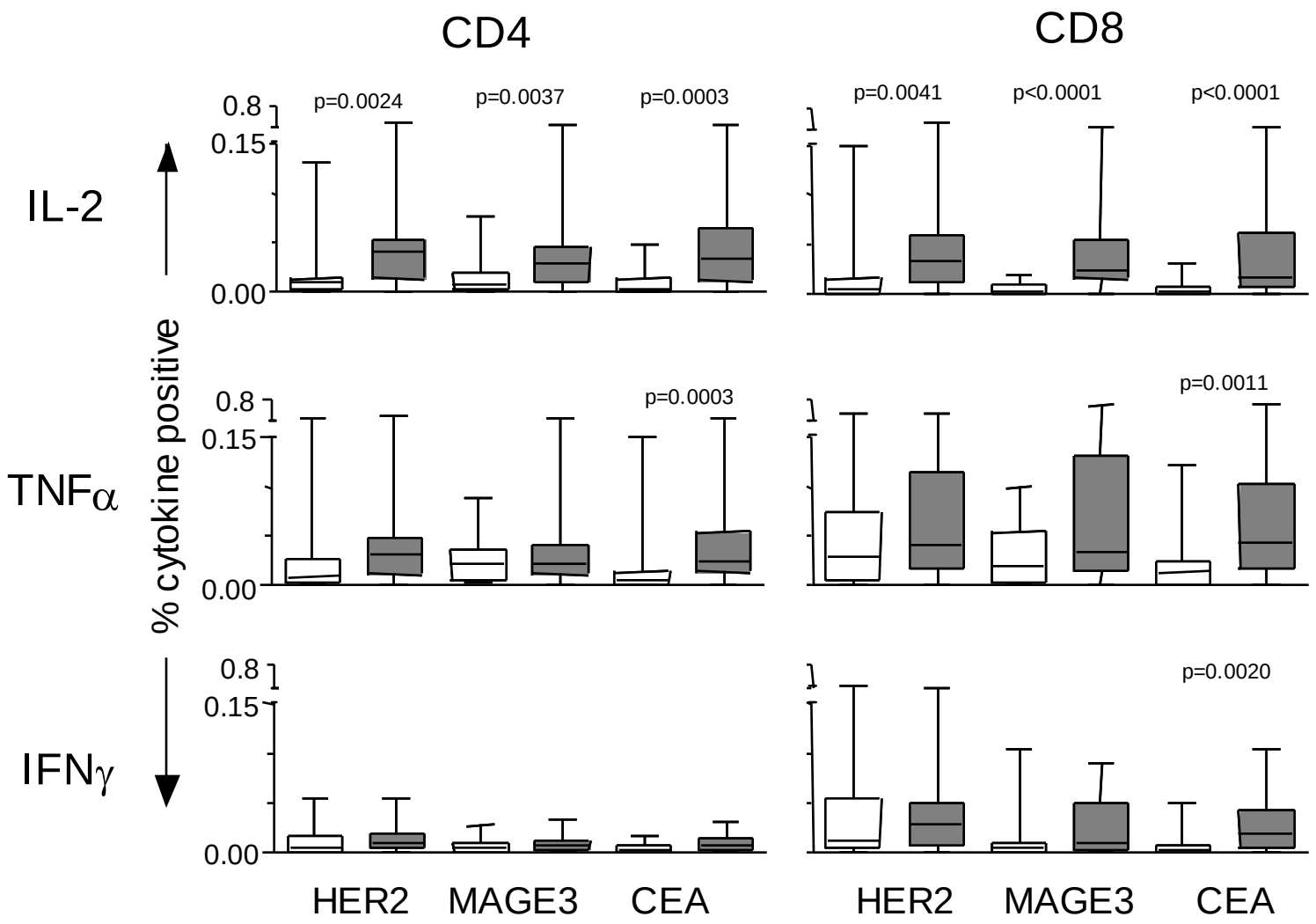
Correlation of CD8+ IL-2 production and presence of effector cells (HIV)



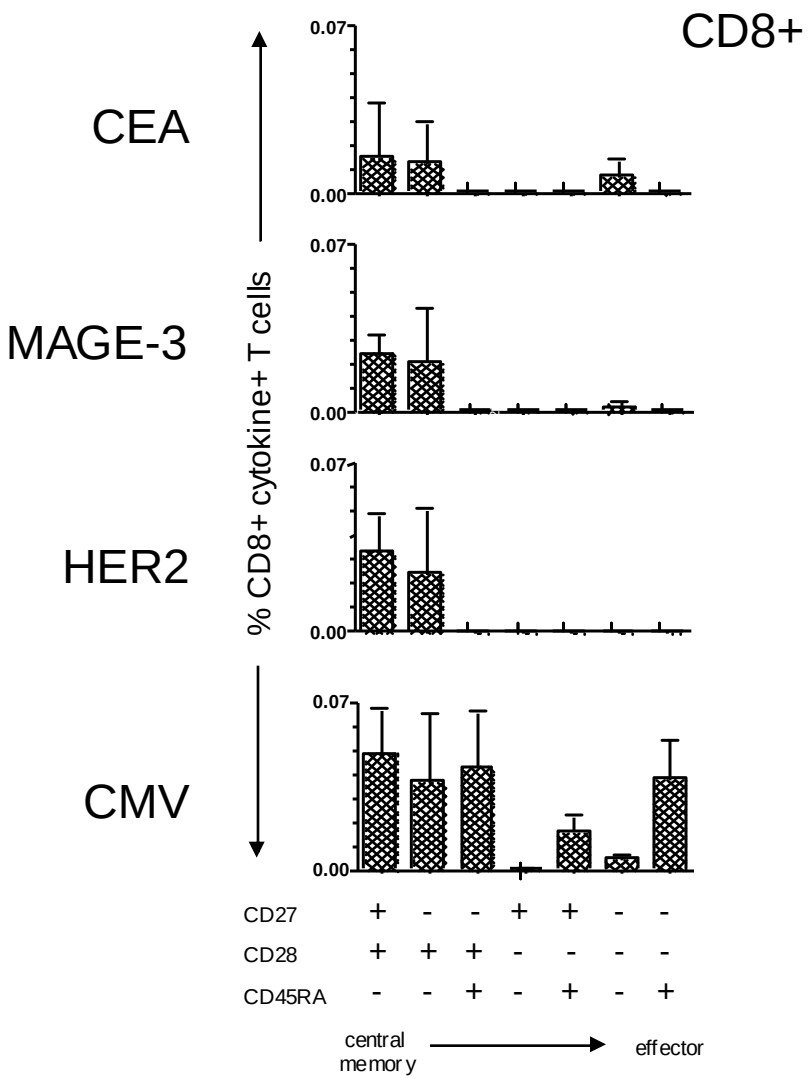
Magnitude of breast cancer responses



Functions of breast cancer responses



Phenotype of breast cancer responses



Conclusions

- CMV, HIV, and cancer can all induce endogenous T cell responses of varying magnitudes
- Only CMV responses tend to be protective
- The T cell response signatures for CMV, HIV, and cancer are very different
  - CMV: relatively high proportion of IFNγ+IL-2+ cells, heterogenous phenotypes with lot of effectors
  - HIV: few CD8+IL-2+ T cells, intermediate phenotype
  - Cancer: low magnitude, IL-2+ but not IFNγ+ T cells, central memory phenotype
- The mechanisms leading to these signatures need to be further elucidated

Implications

- T cell response signatures may be prognostic of disease progression
- Alteration of the endogenous signature may be necessary for vaccines to be effective

Acknowledgements

- BD Biosciences:
  - Laurel Nomura
  - Margaret Inokuma
  - Holli Dunn
  - Joyce Ruitenberg
  - Sonny Bhatia
  - Smita Ghanekar
  - Maria Jaimes
  - Daiva Gladding
  - Christine Dawson
  - Jack Dunne
  - Maria Suni
  - Skip Maino

  - Doug Petry
  - Meng-Xiang Tang
  - Perry Haaland
  - Charles Schmitt

- UCSF:
  - Brinda Emu
  - Rebecca Hoh
  - Steve Deeks
  - Jeff Martin
  - Mike McCune
  - Doug Nixon

- University of Washington:
  - Corazon delaRosa
  - Nora Disis

- Other:
  - Janet Siebert, Cytoanalytics
  - Eugene Veteska, consultant