

HIV-Specific CD8⁺ T Cells of Vaccinees Exhibit Proliferative and Cytotoxic Capacities Comparable to Those of Progressors



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Introduction

- Encouragement for the development of effective HIV vaccines can be derived from rare patients, termed long-term nonprogressors (LTNP), elite controllers, HIV controllers, or elite suppressors, who have naturally occurring immune-mediated control of HIV
- Qualitative features of HIV-specific CD8⁺ T cells distinguishing LTNP from Progressors:
 - Greater proliferation and perforin upregulation (*Migueles et al., 2002; Lichterfeld et al., 2004; Arrode et al., 2005; Horton et al., 2006*)
 - Increased “polyfunctionality” (*Migueles et al., 2009; Betts et al., 2006; Zimmerli et al., 2005*)
 - Enhanced suppression of HIV replication (*Saez-Cirion et al., 2007; de Quiros et al., 2000*)
 - **Higher per-cell cytotoxic capacity** (*Migueles et al., 2008*)

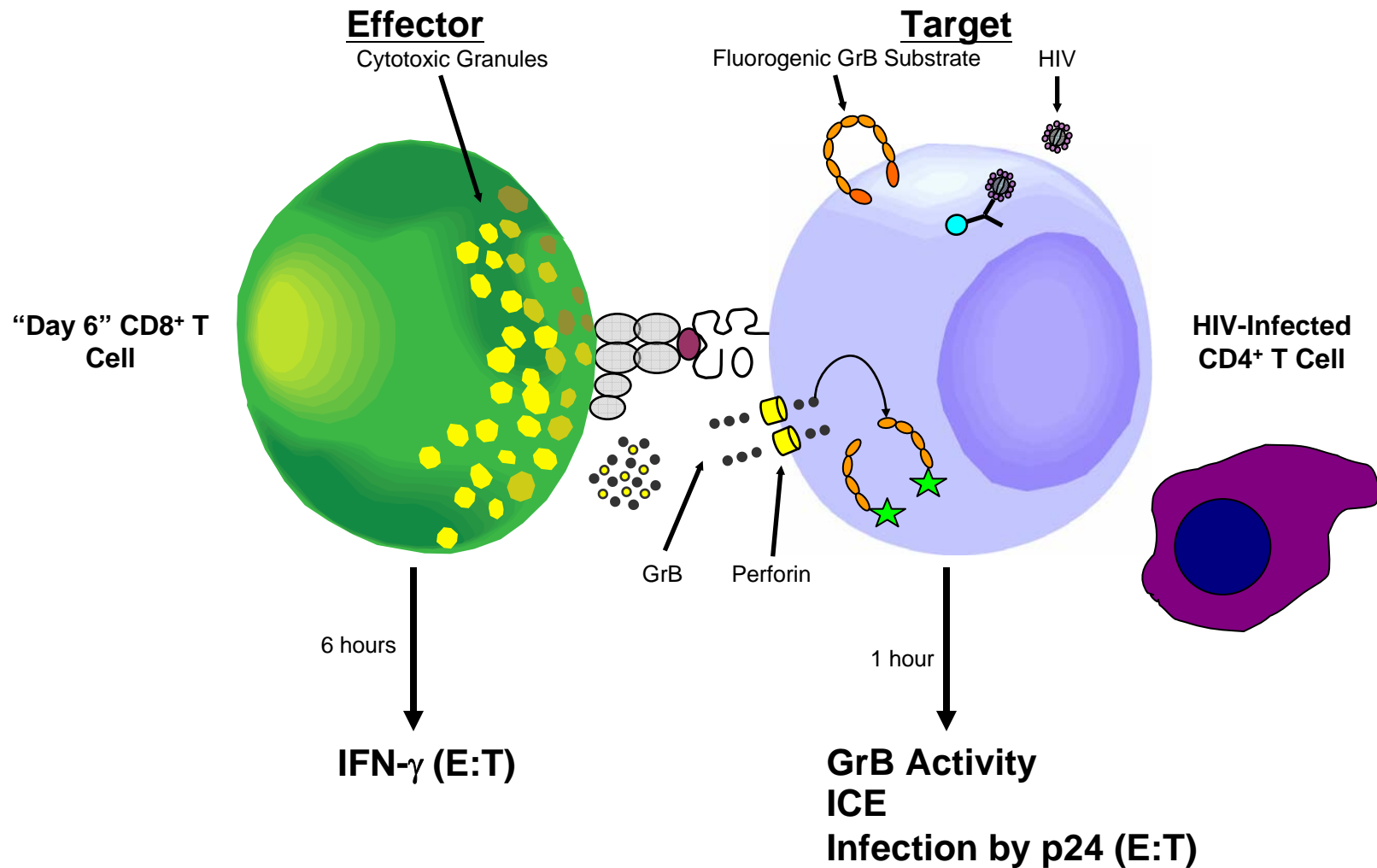
Purpose

- Cytotoxic capacity is a clear correlate of protective immunity in chronic infection but has not yet been applied to recipients of HIV vaccines
- **Primary goal:**
 - **To determine per-cell cytotoxic capacity of vaccine recipients relative to other patient cohorts**
- **Secondary goal:**
 - To develop higher throughput cytotoxicity assays that can be applied to larger vaccine trials

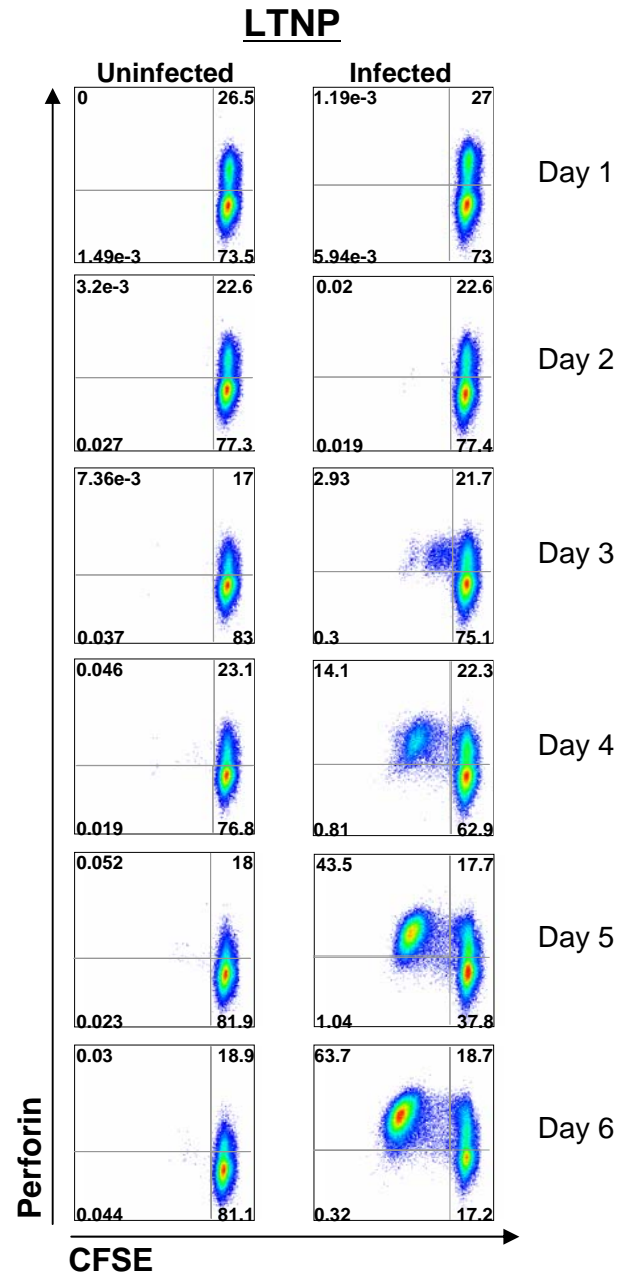
Methods

- Patient groups:
 - HVTN 071 Vaccinees
 - 19 HIV-seronegative individuals
 - Received 2 immunizations of the Merck Ad5-HIV trivalent vaccine at months 0 and 1
 - Leukapheresed a median of 56 (8, 318) days post-vaccination
 - LTNP
 - Healthy with no opportunistic diseases
 - Set point HIV RNA levels <50 copies/mL
 - No antiretroviral or immune-based treatment
 - Stable, non-declining CD4⁺ T Cell counts
 - Progressors: treated (Rx<50) and untreated
 - HIV-negative individuals
- Parameters:
 - Delivery of Granzyme B (GrB) to target cells
 - Infected CD4⁺ T Cell Elimination (ICE)
 - HIV-specific CD8⁺ T Cell proliferation
 - HIV-specific CD8⁺ T Cell perforin upregulation

In Vitro Cytotoxicity Assay for Measuring Granzyme B Activity in Live Cells and Infected Cell Elimination (ICE)



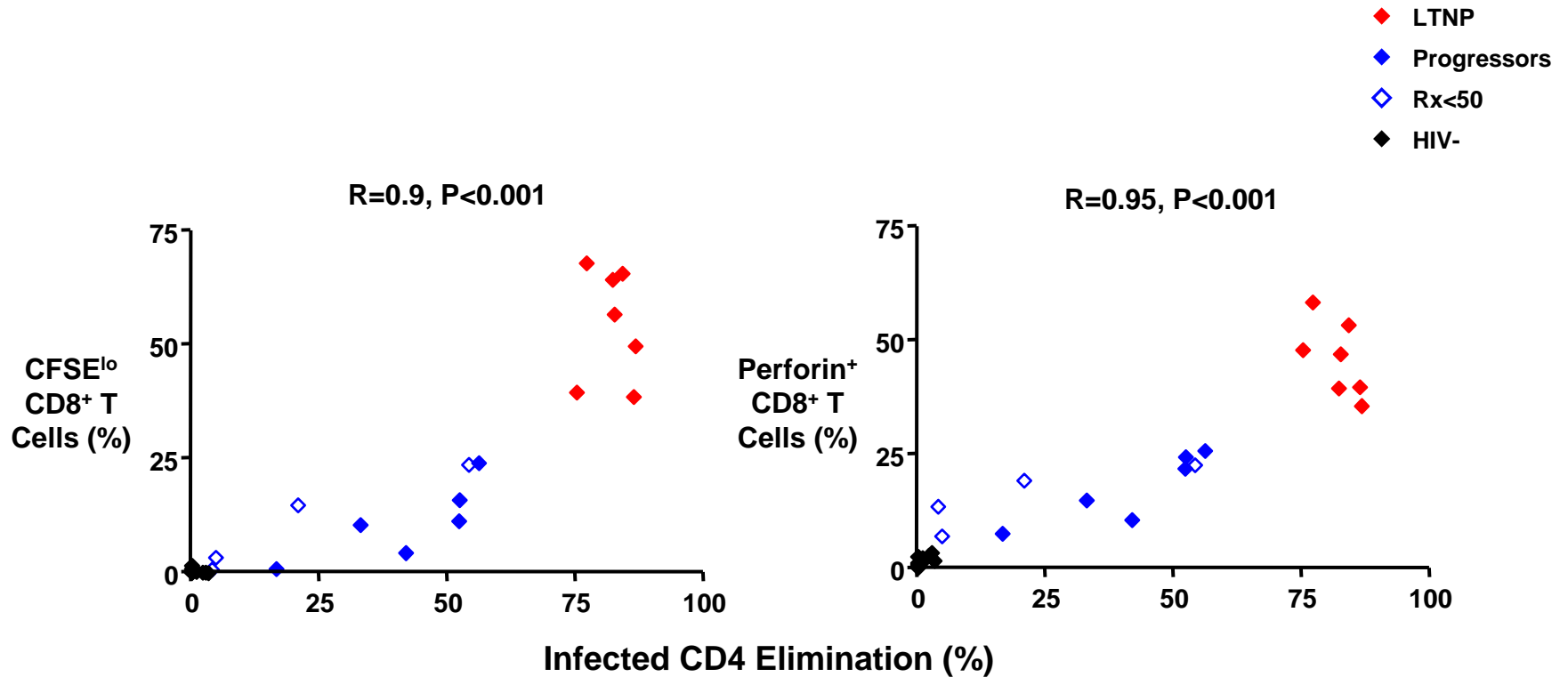
Perforin Expression of Stimulated CD8⁺ T Cells Peaks on Day 6



2 Proxy Measurements

1. CFSE^{lo} CD8⁺ T Cells
2. Perforin⁺ CD8⁺ T Cells

Day 6 HIV-Specific CD8⁺ T Cell Proliferation and Perforin Expression Predict Cytotoxic Capacity



Acknowledgments

HIV-Specific Immunity Section (NIH)

Stephen Migueles

Amy Berkley

Daniel Mendoza

Tiffany Guo

Christine Osborne

Alex Compton

Rohan Joshi

Kristin Weeks

Andy Patamawenu

Claire W. Hallahan

Mark Connors

H. Clifford Lane

Anthony S. Fauci

HVTN

Julianna McElrath

Nicole Frahm

Ann Duerr

Clinics

Nancy Cogliano-Shutta

Margaret Lloyd

Mary McLaughlin

Richard Kwan

Gregg Roby

Julia A. Metcalf

Sara Stallings

Catherine Rehm

***The Patients & Vaccinees**

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Beverly Z. Packard

Akira Komoriya