

Induction of Innate Immune Responses in HVTN 071: a Trial using the MRKAd5 *gag/pol/nef* Vaccine from the Step Study

Erica Andersen-Nissen
Vaccine and Infectious Disease Institute
Fred Hutchinson Cancer Research Center
Seattle, Washington, USA

FRED HUTCHINSON
CANCER RESEARCH CENTER
VACCINE AND INFECTIOUS DISEASE INSTITUTE



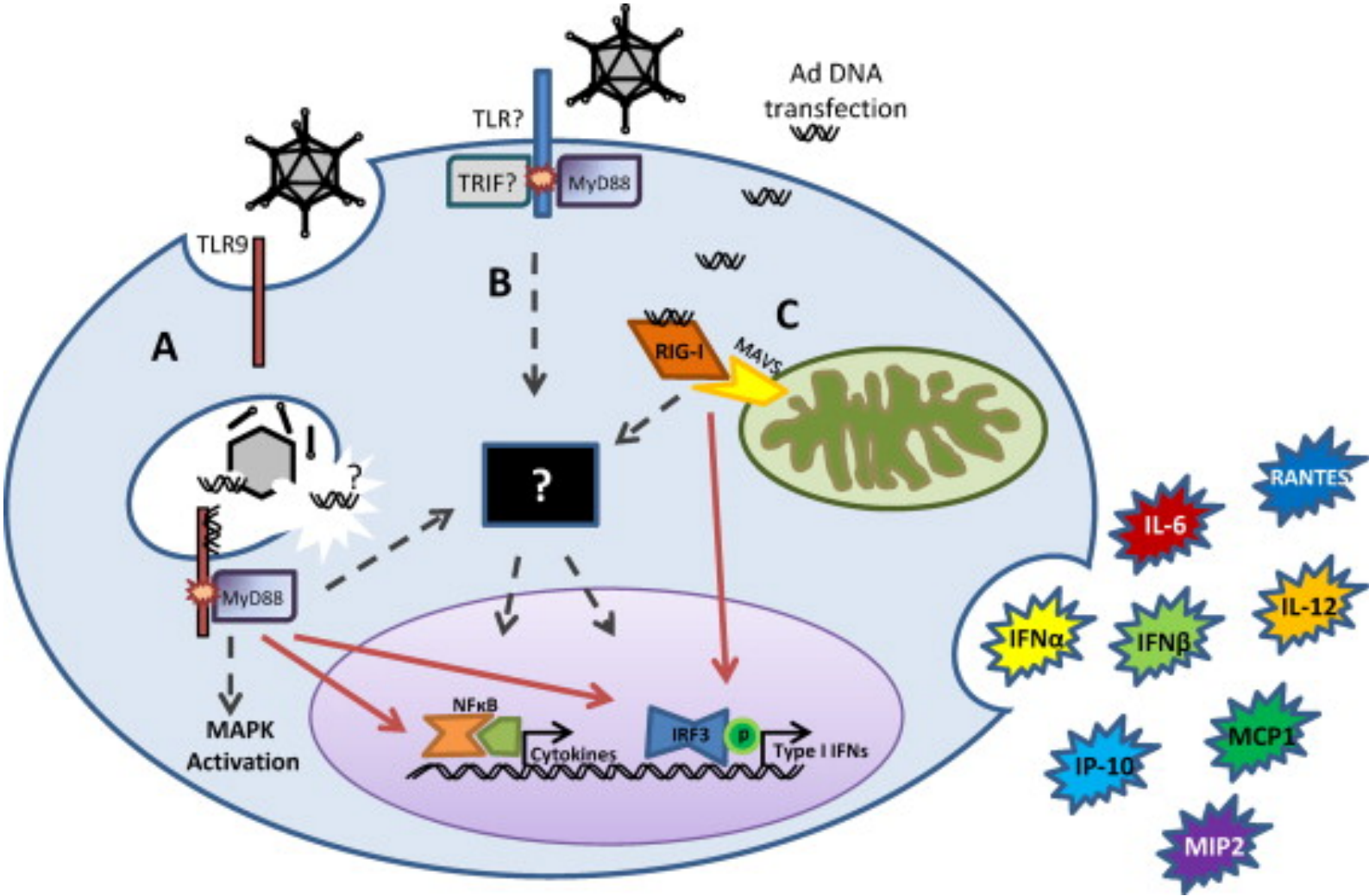
HIV VACCINE
TRIALS NETWORK



Innate Immune Responses to Vaccination

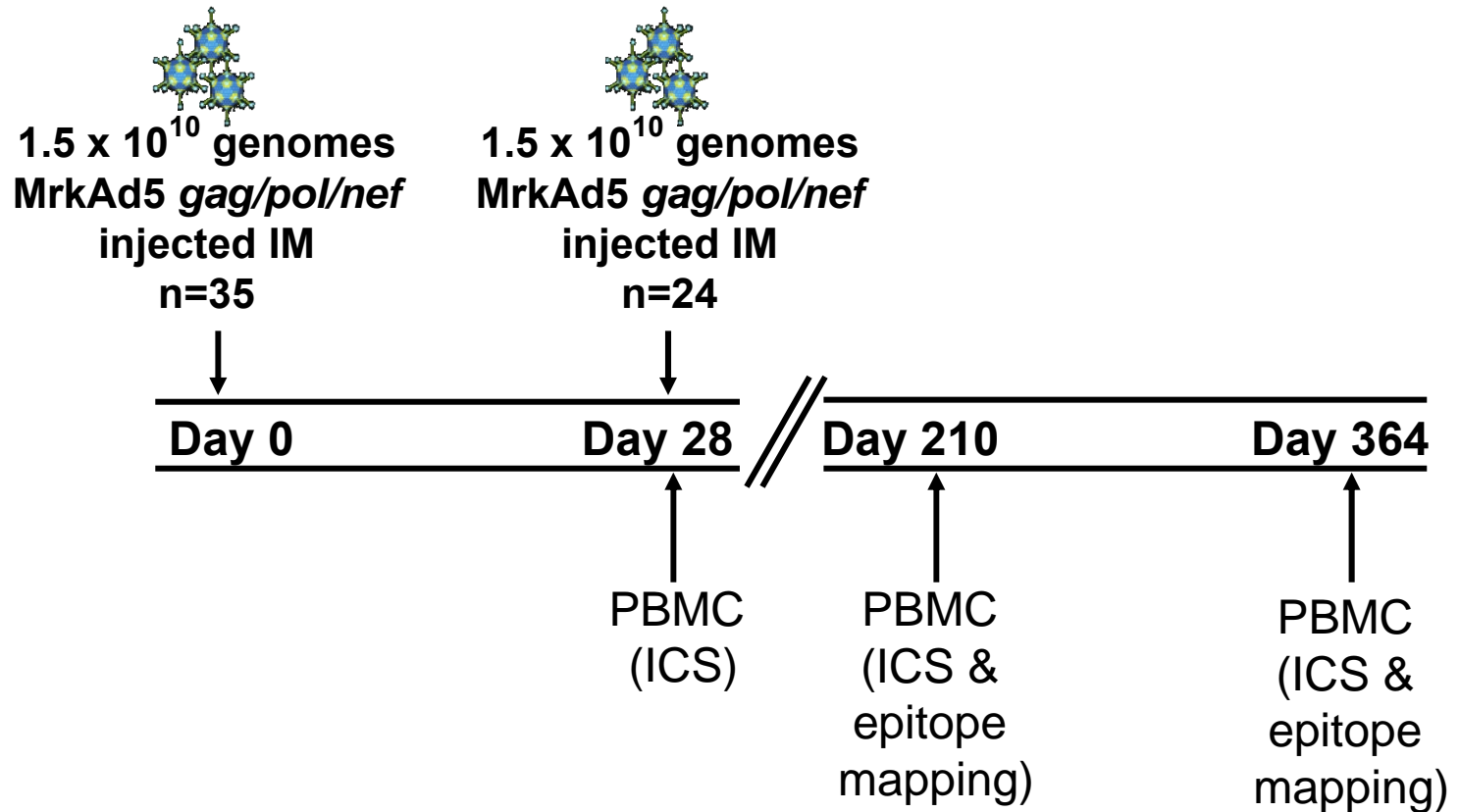
- **Innate immune responses shape the quantity, quality and longevity of the adaptive immune response, yet few studies have examined innate responses in humans after vaccination.**
- **We implemented HVTN 071, a trial administering MRKAd5 *gag/pol/nef* vaccine to ask:**
 - **Which systemic innate immune responses can be measured in blood after vaccination by intramuscular injection?**
 - **What are the optimal time points to identify these innate responses in humans?**
- **When the Step trial was halted, we also asked:**
 - **Do the innate immune responses induced by the MRKAd5 *gag/pol/nef* vaccine offer any explanations for its lack of efficacy?**

Innate Immune Recognition of Adenovirus

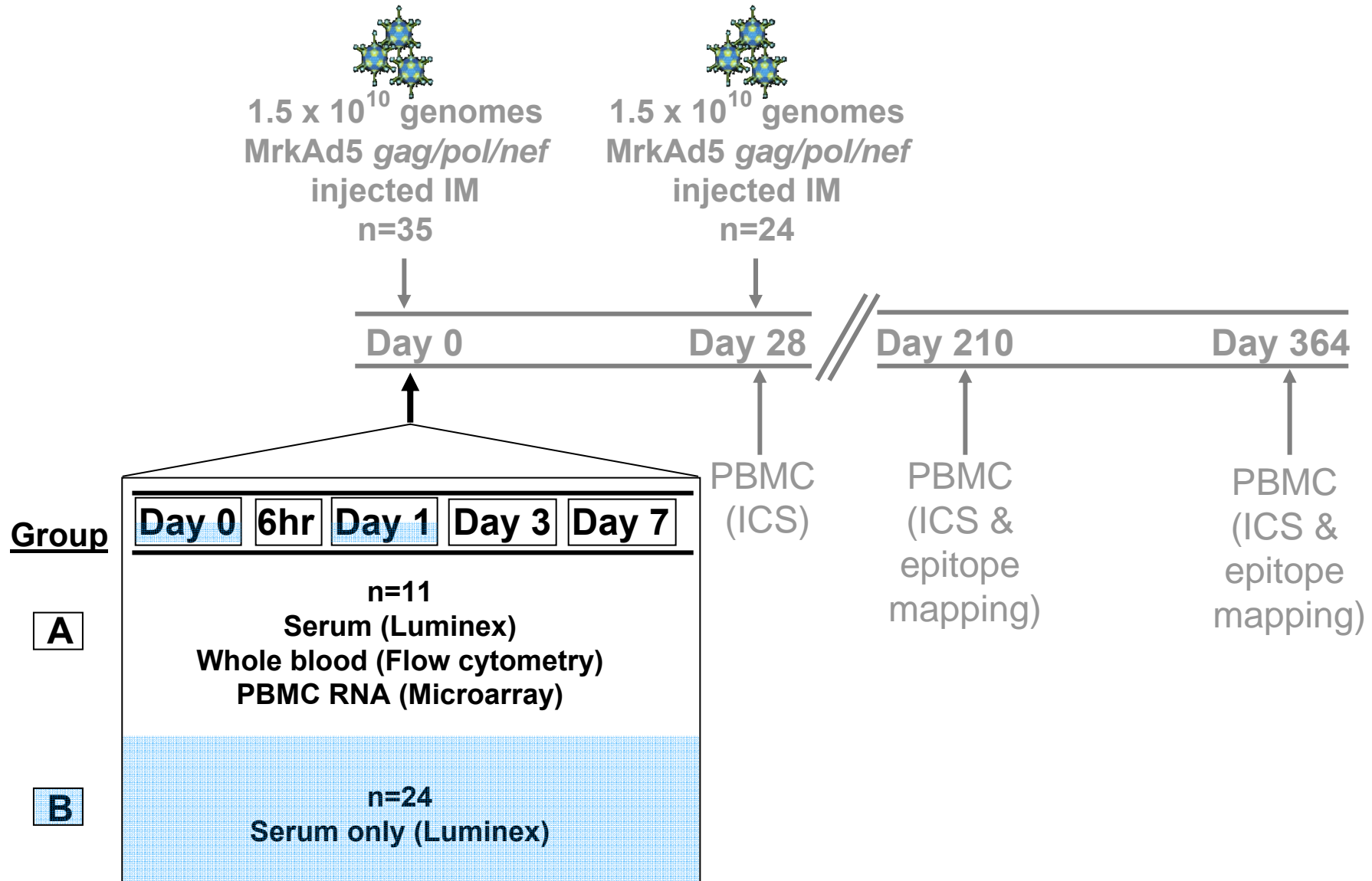


(Hartman et al., *Virus Research* 2008)

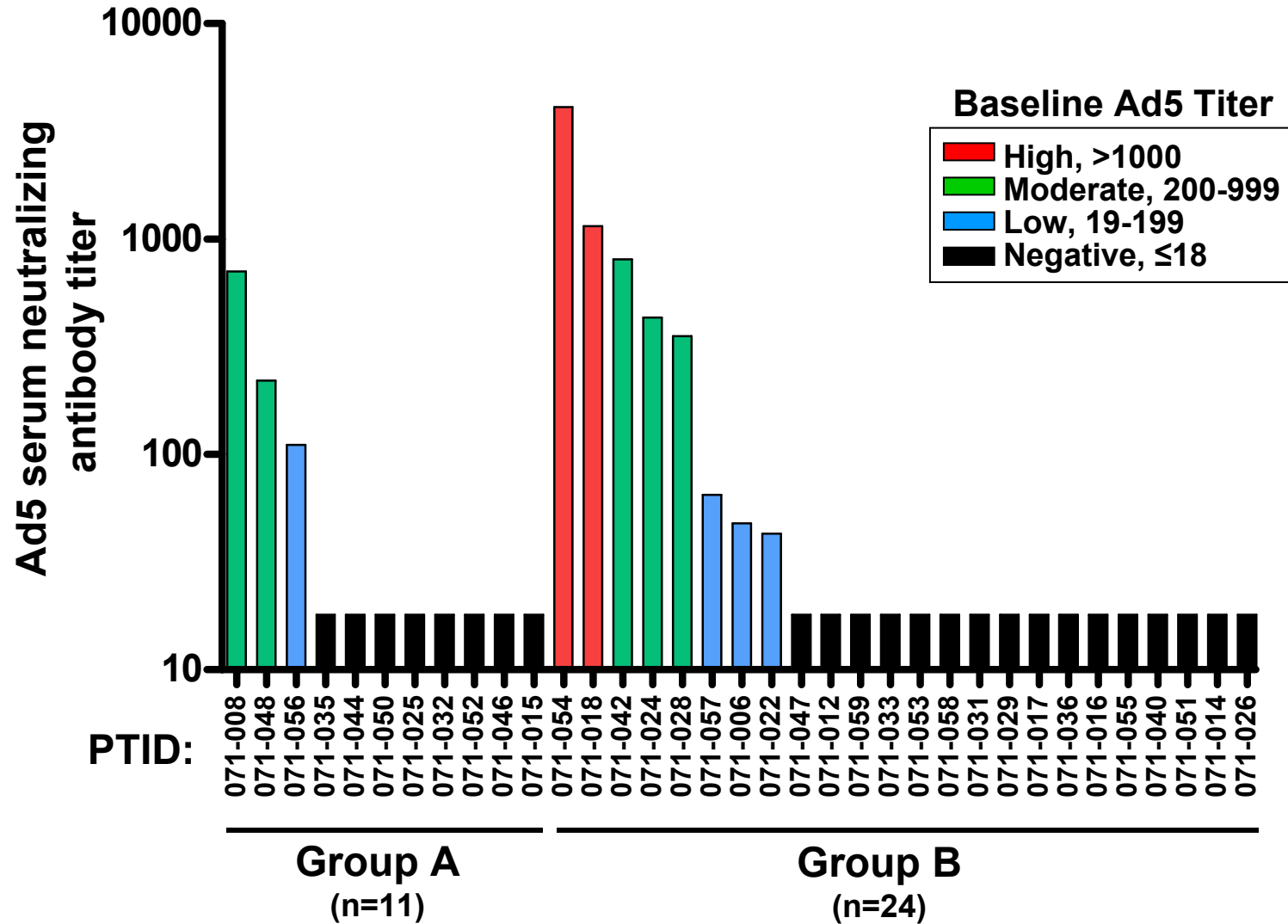
HVTN 071 Study Schedule



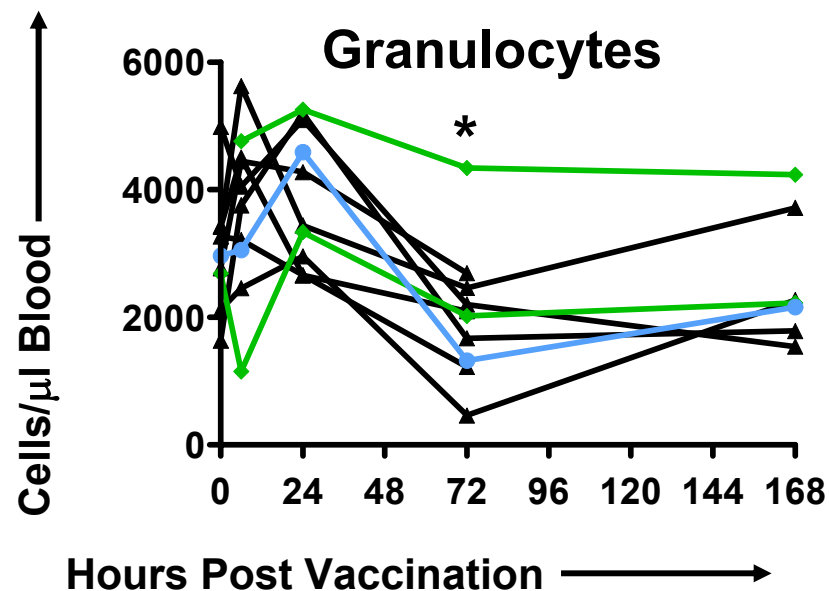
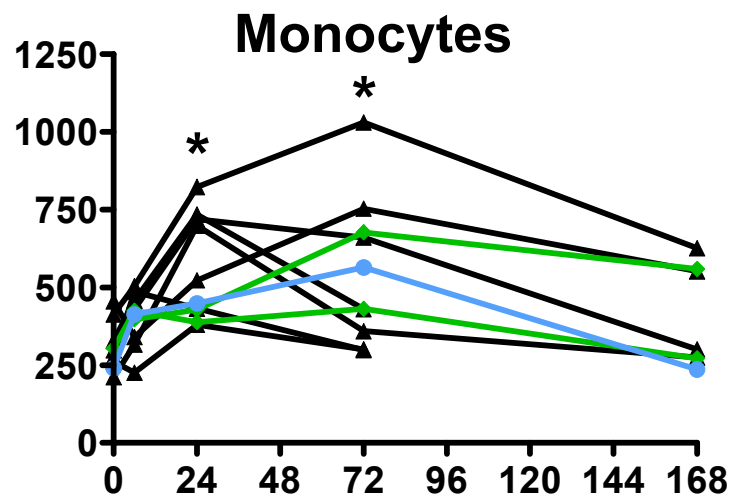
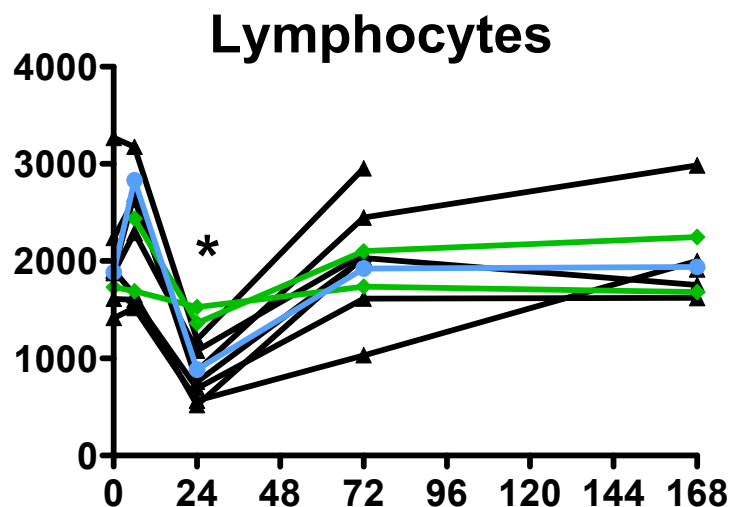
HVTN 071 Study Schedule



Baseline Serum Ad5 Neutralizing Antibody Titers



Rapid Changes in Peripheral Blood Cell Populations after MRKAd5 *gag/pol/nef* Vaccination

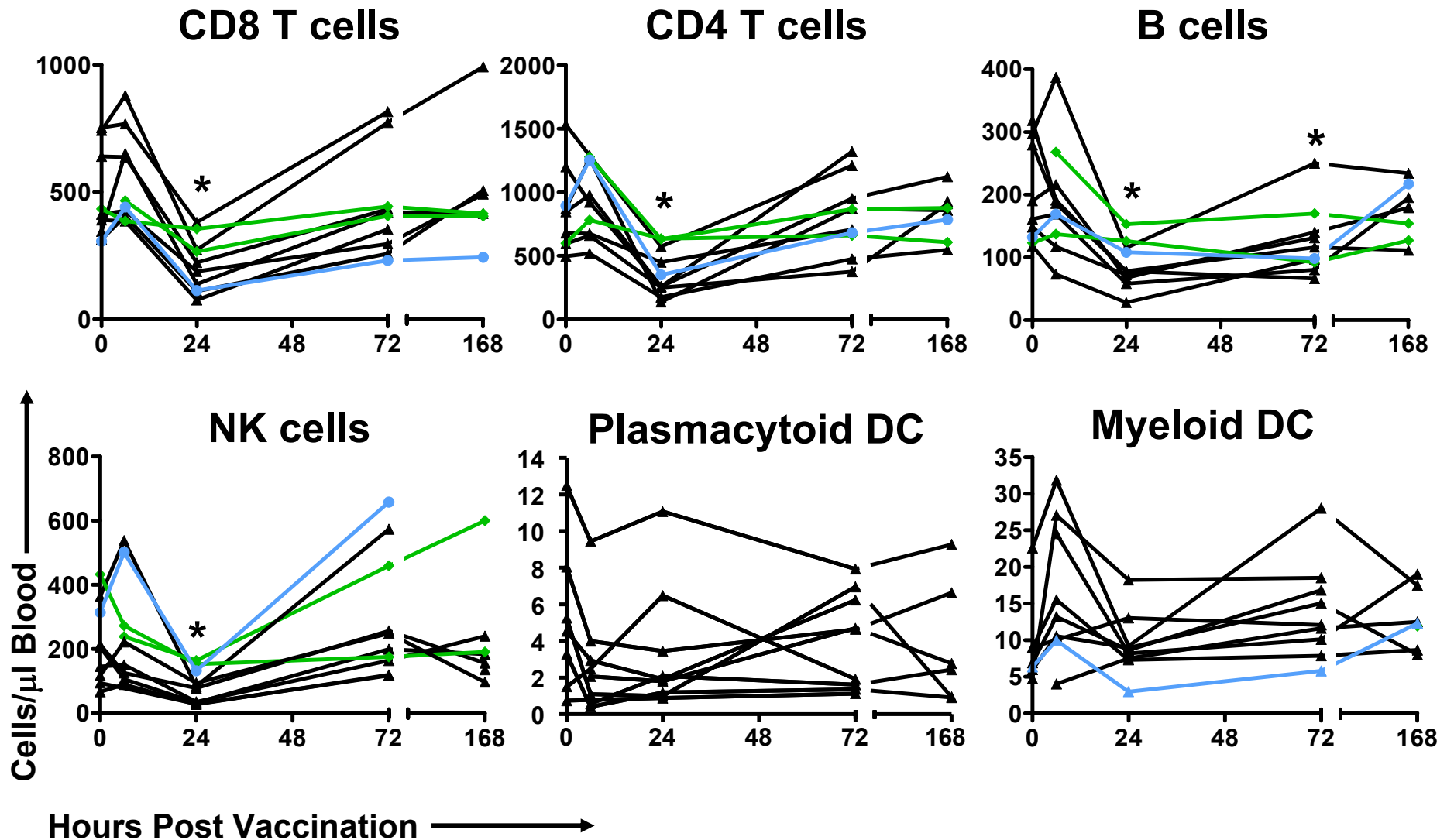


Baseline Ad5 Titer

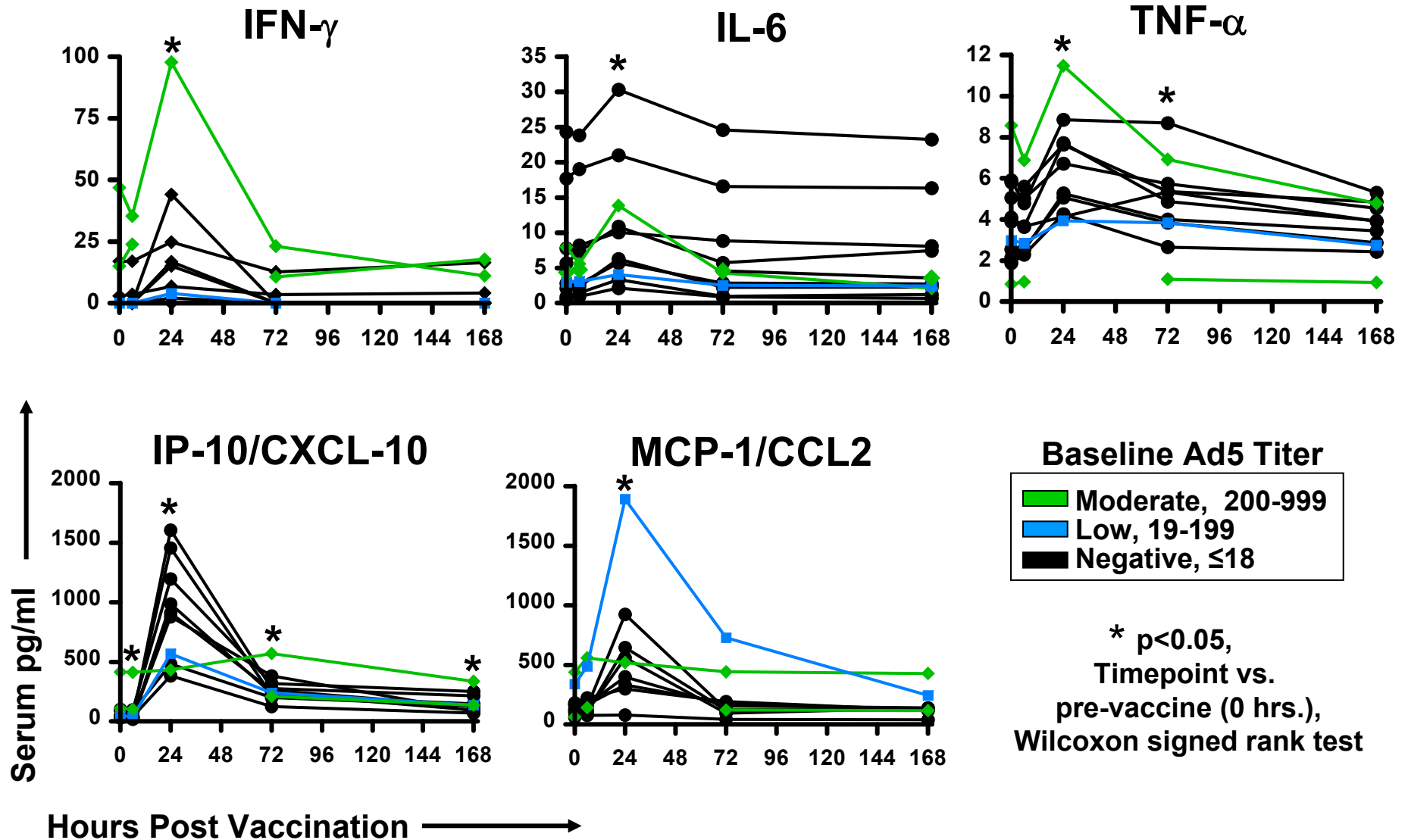
- Moderate, 200-999
- Low, 19-199
- Negative, ≤18

* $p < 0.05$,
Timepoint vs.
pre-vaccine (0 hrs.),
Wilcoxon signed rank test

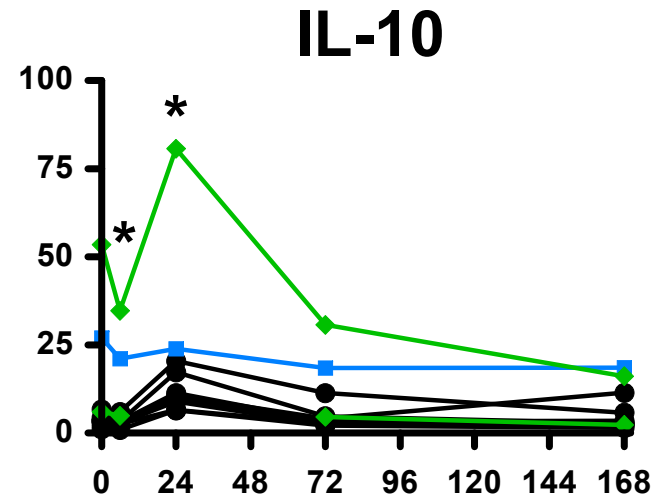
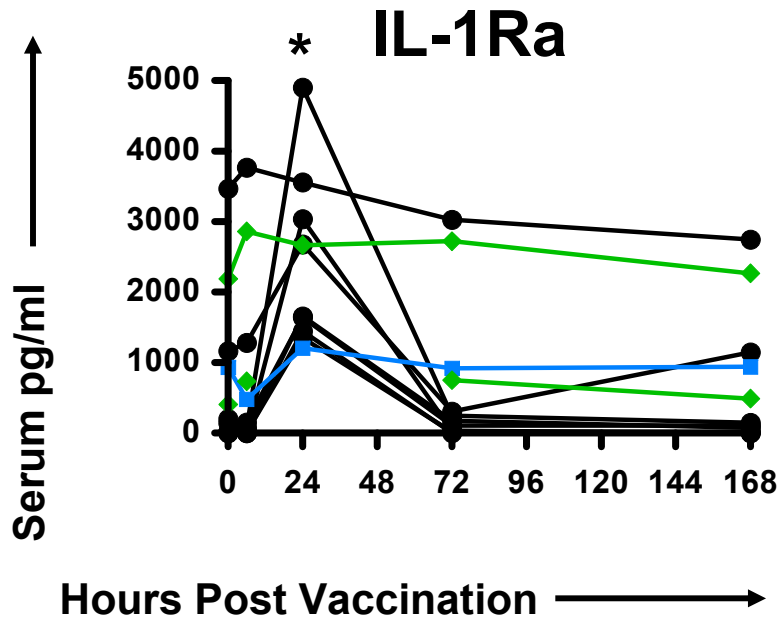
Multiple Cell Types Exit the Blood



Serum Proinflammatory Cytokines & Chemokines Increase Rapidly after Vaccination



Serum Anti-inflammatory Cytokines Also Increase after MRKAd5 *gag/pol/nef* Vaccination



Baseline Ad5 Titer

- Moderate, 200-999
- Low, 19-199
- Negative, ≤ 18

* $p < 0.05$,
Timepoint vs.
pre-vaccine (0 hrs.),
Wilcoxon signed rank test

Summary of Significant Changes in Serum Cytokines/Chemokines at 24 Hours

Cytokine/ Chemokine	Median Serum Cytokine Levels (pg/ml) n=35		Median Fold Change n=35
	Pre-vaccine	24 hours	
IP-10/CXCL10	70	630	11
IL-1Ra	350	1700	4.7
IL-10	5.4	12	2.4
IFN- γ	0.1	4.4	2.4
MCP-1/CCL2	180	380	2.0
IL-6	4.3	6.7	1.7
IL-7	7.1	8.0	1.4
TNF α	5.1	7.1	1.3
MIP-1 β	120	160	1.2

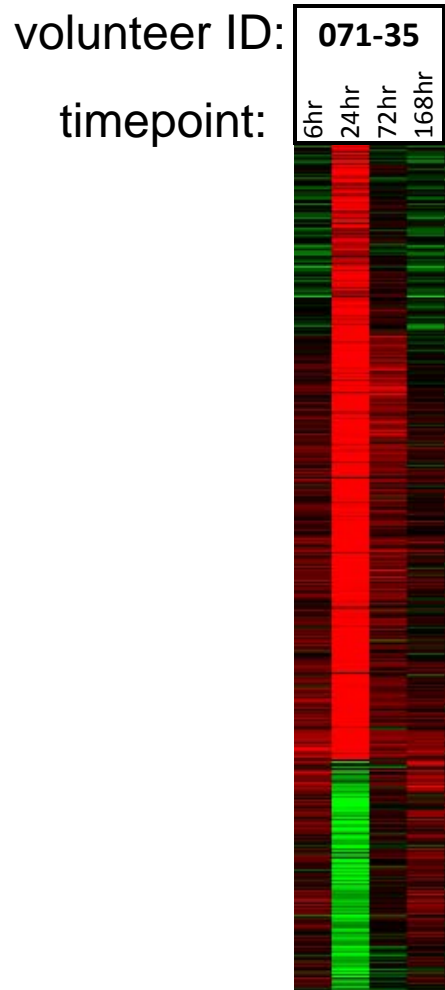
Other serum analytes that were measured, but did not change at 24 hours:

EGF, Eotaxin, Fractalkine, G-CSF, GM-CSF, IFN- α , IL-1 α , IL-1 β , IL-2, IL-4, IL-5, IL-8, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, MIP-1 α , sCD40L, TGF- α , VEGF

Ad5 Negative/Low Titer Individuals Show Significantly Greater Changes in Serum Cytokines/Chemokines at 24 Hours

Cytokine/ Chemokine	Median Serum Cytokine Levels (pg/ml) At 24 Hours Post Vaccination		p-value (Wilcoxon Rank Sum Test on log fold change relative to pre- vaccine)
	Ad5 negative/low n=27	Ad5 medium/high n=6	
MCP-1	420	260	0.002
IP-10	720	180	0.02
IL-1Ra	2100	870	0.02

PBMC Microarrays Show 490 Genes with Significant* Temporal Expression Responses

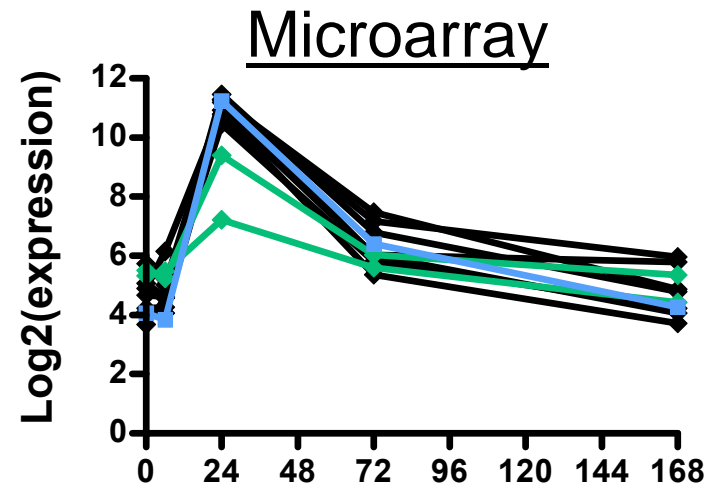
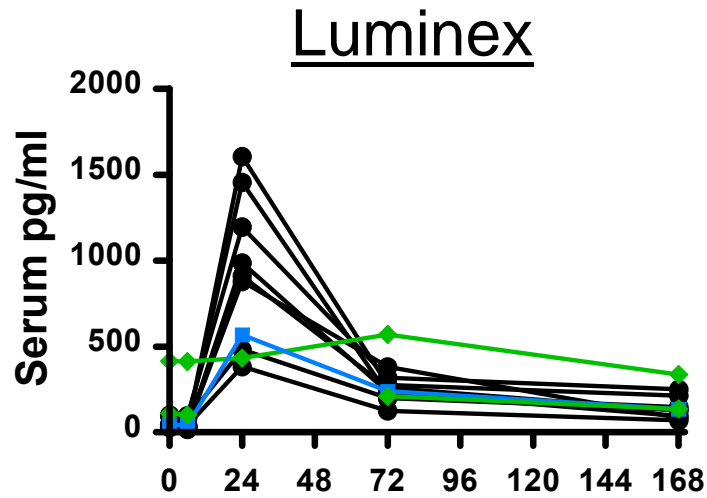


■ Up-regulated

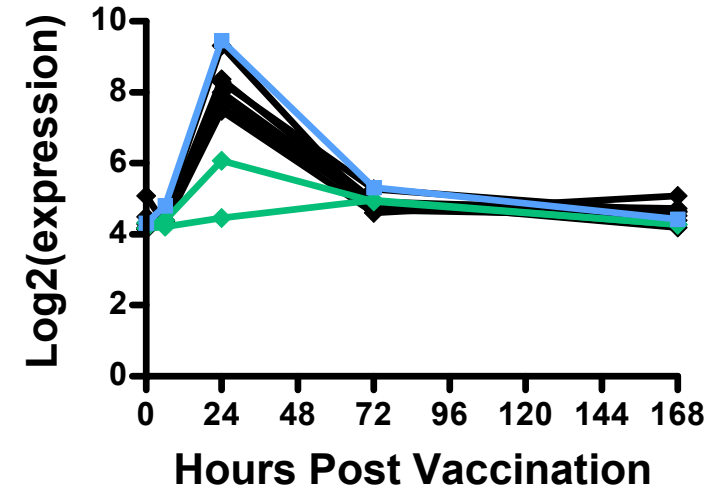
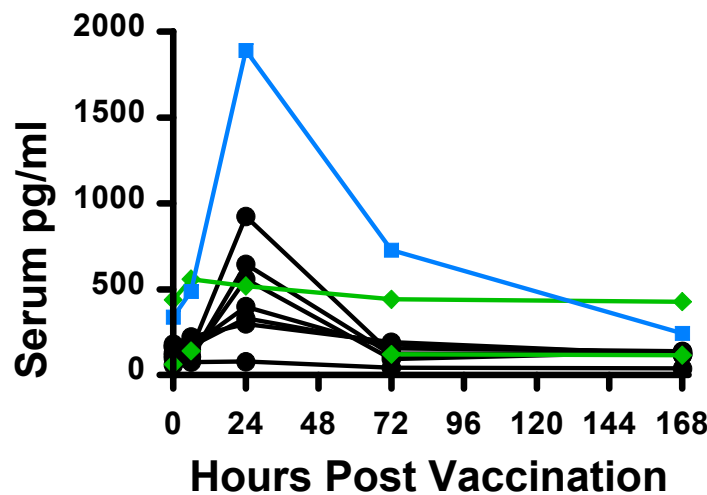
■ Down-regulated

Serum Cytokine Changes Reflected in PBMC RNA Expression Data

IP-10:



MCP-1:



Summary of Early Changes in the Blood Post MRK Ad5-gag/pol/nef Vaccine

	6 hr	Day 1	Day 3	Day 7
Serum Cytokines & Chemokines				
Lymphocytes				
CD4+ T cells				
CD8+ T cells				
B cells				
NK cells				
Monocytes				
Dendritic Cells				
Plasmacytoid				
Myeloid				
PBMC Gene Expression				

Summary and Conclusions

- **Intramuscular vaccination induced a rapid influx of monocytes and mDC into the blood and an efflux of lymphocytes and pDC from the blood, suggesting trafficking to and from the site of vaccination and draining lymph nodes**
- **As detected by the microarrays, PBMC appear to produce some of the cytokines and chemokines present in the serum after vaccination**
- **PBMC responses occurred up to 1 week post-vaccination, but general sustained inflammatory activation was not observed**
- **Pre-existing Ad5 immunity reduced serum IP-10, MCP-1 and IL-1Ra responses to the vaccine**

Future Directions

- **Comprehensively analyze the PBMC gene expression data for changes that may explain the increased HIV acquisition in Ad5-immune subjects from the Step trial**
- **Determine the innate responses that correlate with the magnitude and quality of the T cell response to MRK Ad5 *gag/pol/nef***
- **Compare innate responses to MrkAd5 *gag/pol/nef* with responses to other vaccines to better understand the roles of specific vectors in driving HIV-specific responses**
- **Evaluate innate immune responses to vaccines at mucosal sites to determine effects at the site of HIV acquisition**

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