What to learn from deep immunological monitoring in phase I/II vaccine trials?

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INSERM U897, INRIA SISTM, Bordeaux University

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Systems biology

Systems Biology Has its Backers and Attackers

D.F. Dowd Though coined 40 years ago, a lot of people still ask, "What's that?" when the term systems biology comes up. The Scientist - October 6, 2003

Systems Vaccinology

Bali Pulendran,[1,2,*] Shuzhao Li,[1] and Helder I. Nakaya[1]
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Objectives

- To address the mechanisms that control immune responses to vaccination
- To identify predictors of vaccine efficacy

Methods

- Using all available information
- Potentially leading to specific experimentations

Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans

Troy D Querec[1,8], Rama S Akondy[1,8], Eva K Lee[2], Weiping Cao[1], Helder I Nakaya[1], Dirk Teuwen[3], Ali Pirani[4], Kim Gernert[4], Jiusheng Deng[1], Bruz Marzolf[5], Kathleen Kennedy[5], Haiyan Wu[5], Soumaya Bennouna[1], Herold Oluoch[1], Joseph Miller[1], Ricardo Z Vencio[5], Mark Mulligan[1,6], Alan Aderem[5], Rafi Ahmed[1] & Bali Pulendran[1,7]

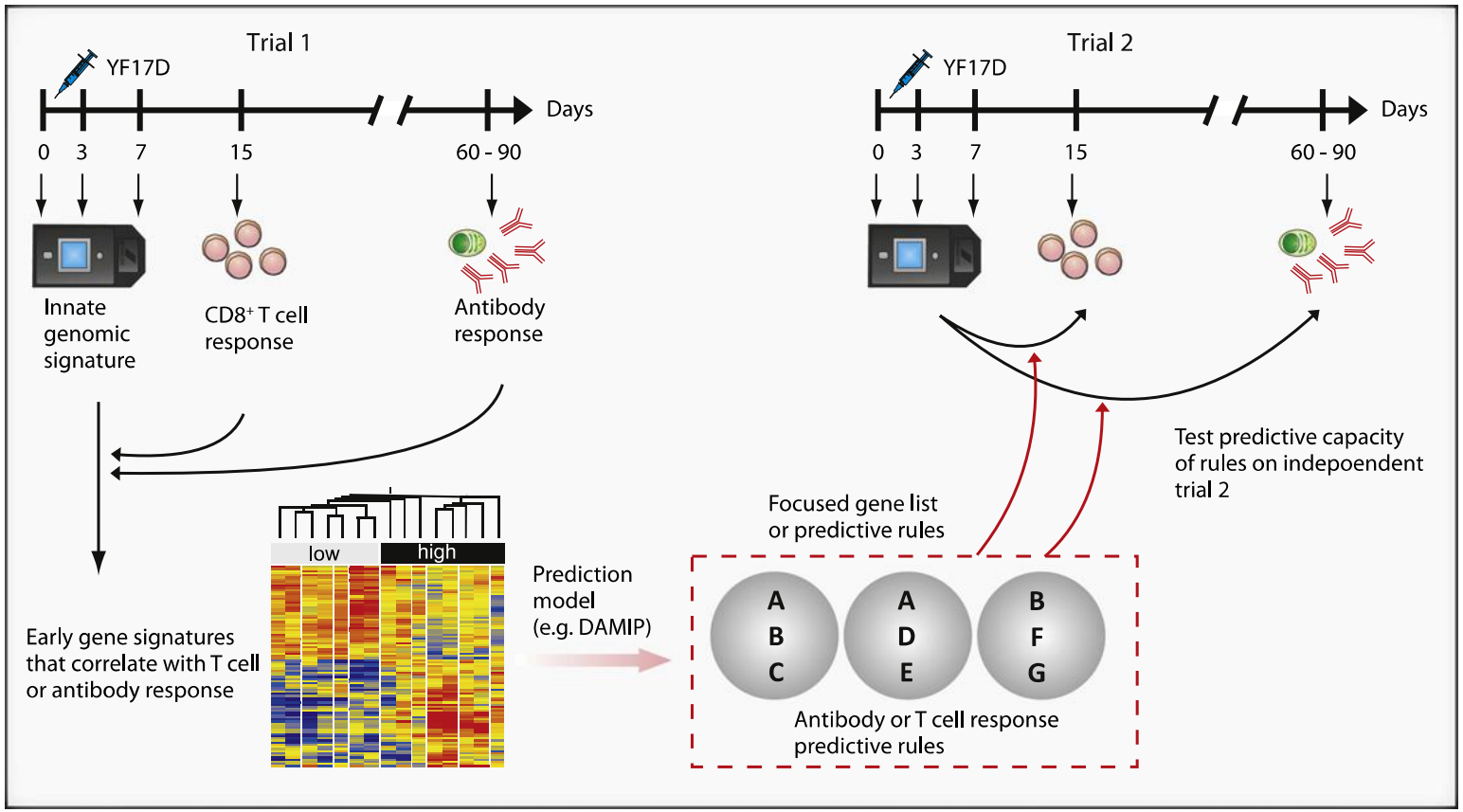
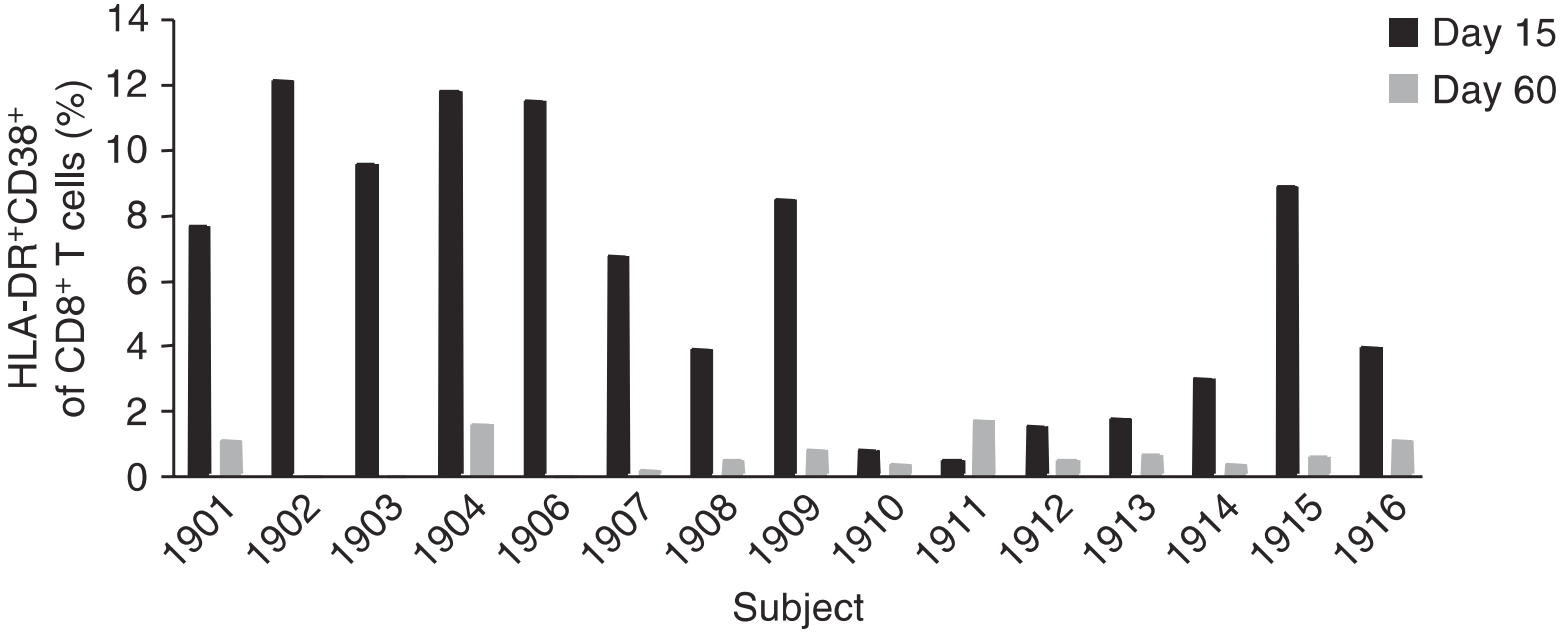


Figure 1. Using Systems Biology to Predict the Immunogenicity of the YF-17D Vaccine

Schematic representation of the systems biology approach used to predict the T and B cell responses of YF-17D vaccinees (Querec et al., 2009). Healthy humans vaccinated with YF-17D are bled at the indicated time points and the innate and adaptive responses studied. Innate signatures obtained with microarrays are found to correlate with the later adaptive immune responses. The predictive power of such signatures is tested in an independent trial (trial 2).


HLA-DR+CD38+ of CD8+ T cells (%)
14
12
10
8
6
4
2
0
Day 15
Day 60
1901
1902
1903
1904
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1907
1908
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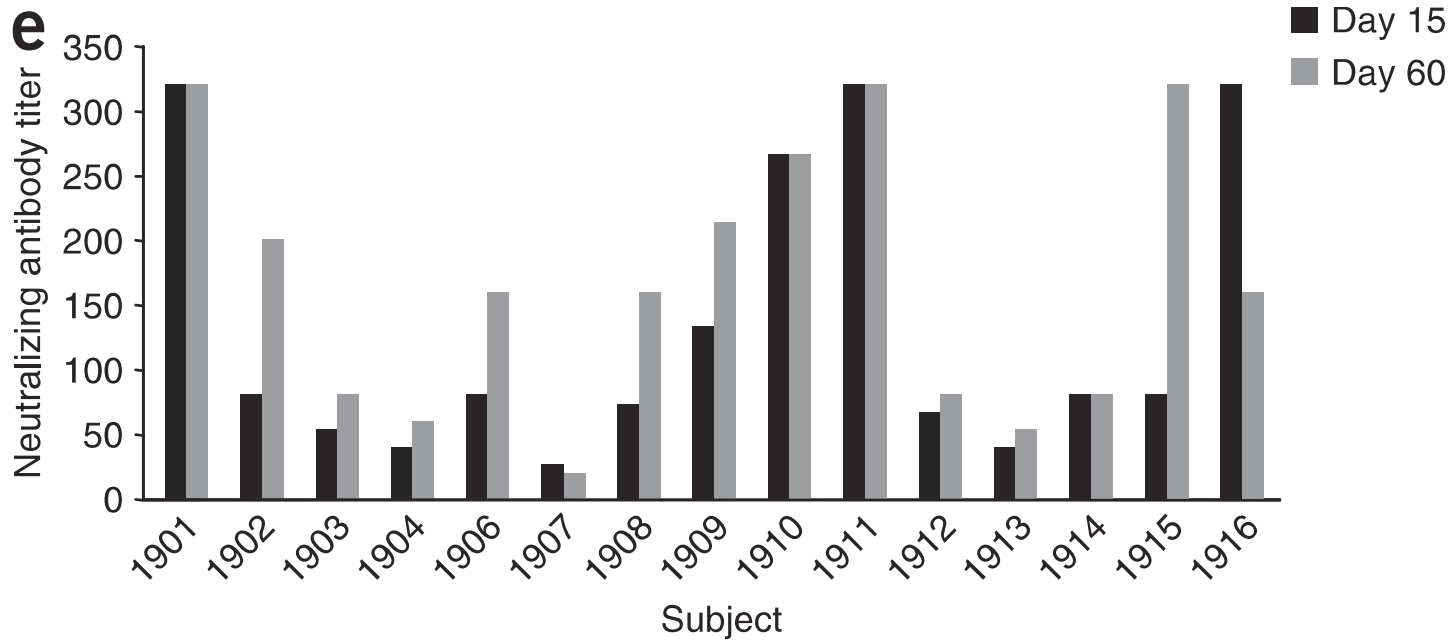
1910
1911
1912
1913
1914
1915
1916
Subject


e
Neutralizing antibody titer
350
300
250
200
150
100
50
0
Day 15
Day 60
1901
1902
1903
1904
1906
1907
1908
1909
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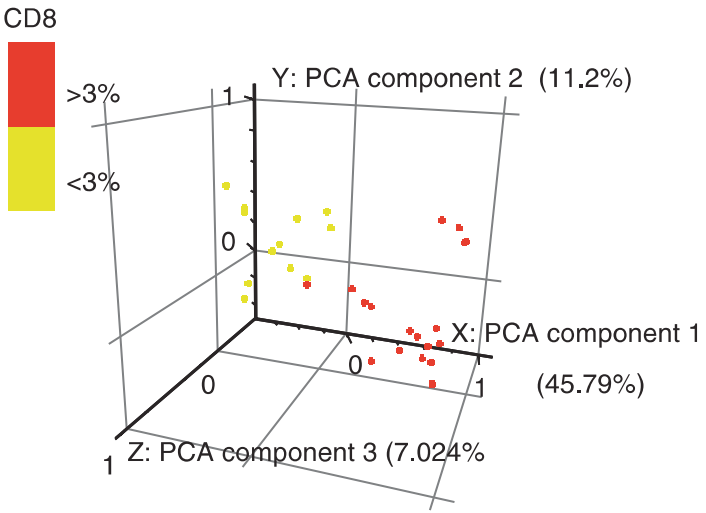
1912
1913
1914
1915
1916
Subject

Gene signatures

CD8 T cell response



Complement protein C1qB and eukaryotic translation initiation factor 2 alpha kinase 4

Neutralizing antibody response

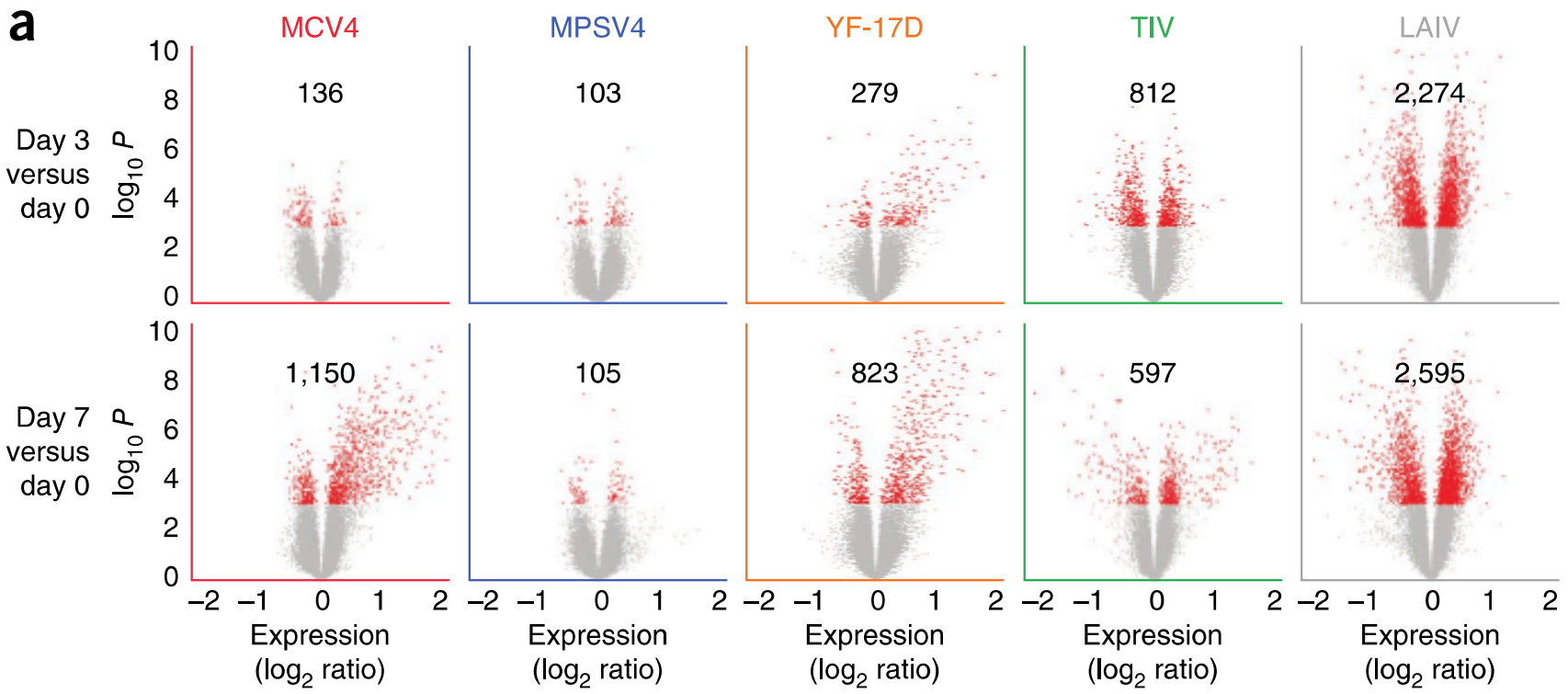
Table 5 RT-PCR validation of genes in the DAMIP models for signatures that predict neutralizing antibody titers

Symbol	UniGene	Day	Pearson *r*	*P*-value
BEND4	Hs.120591	7	0.764	0.00002
KBTBD7	Hs.63841	7	0.543	0.02510
TNFRSF17	Hs.2556	7	0.784	0.000001
TPD52	Hs.368433	7	0.530	0.00667

TNFRSF17 (which encodes the receptor for the B cell growth factor BAFF) is highly predictive of the later antibody response

Molecular signatures of antibody responses derived from a systems biology study of five human vaccines

Shuzhao Li[1,2,10], Nadine Rouphael[1,3,10], Sai Duraisingham[1,2,10], Sandra Romero-Steiner[4], Scott Presnell[5,6], Carl Davis[1,7], Daniel S Schmidt[4], Scott E Johnson[4], Andrea Milton[4], Gowrisankar Rajam[4], Sudhir Kasturi[1,2], George M Carlone[4], Charlie Quinn[5,6], Damien Chaussabel[5,6], A Karolina Palucka[6], Mark J Mulligan[1,3,7], Rafi Ahmed[1,8], David S Stephens[1,7], Helder I Nakaya[1,2,9] & Bali Pulendran[1,2,9]



Geneset approach

- Geneset analysis*: analysing change of gene expression of functionnal groups of genes defined with prior biological knowledge
  - Single-gene analysis may miss important effects on pathways
- Chaussabel's modules** : 260 groups of genes defined
- Blood transcription modules (BTM)

* Subramanian et al. PNAS 102:15545 (2005)

** Chaussabel et al. Immunity 29:150 (2008)

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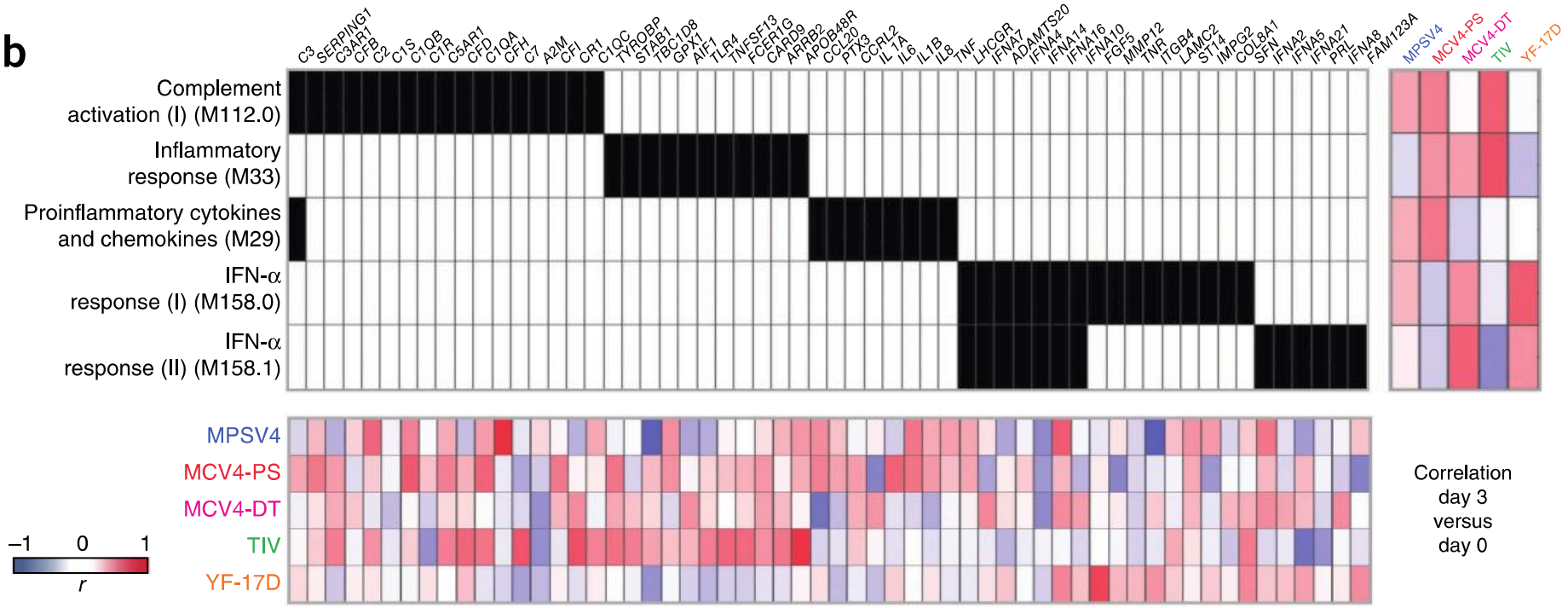

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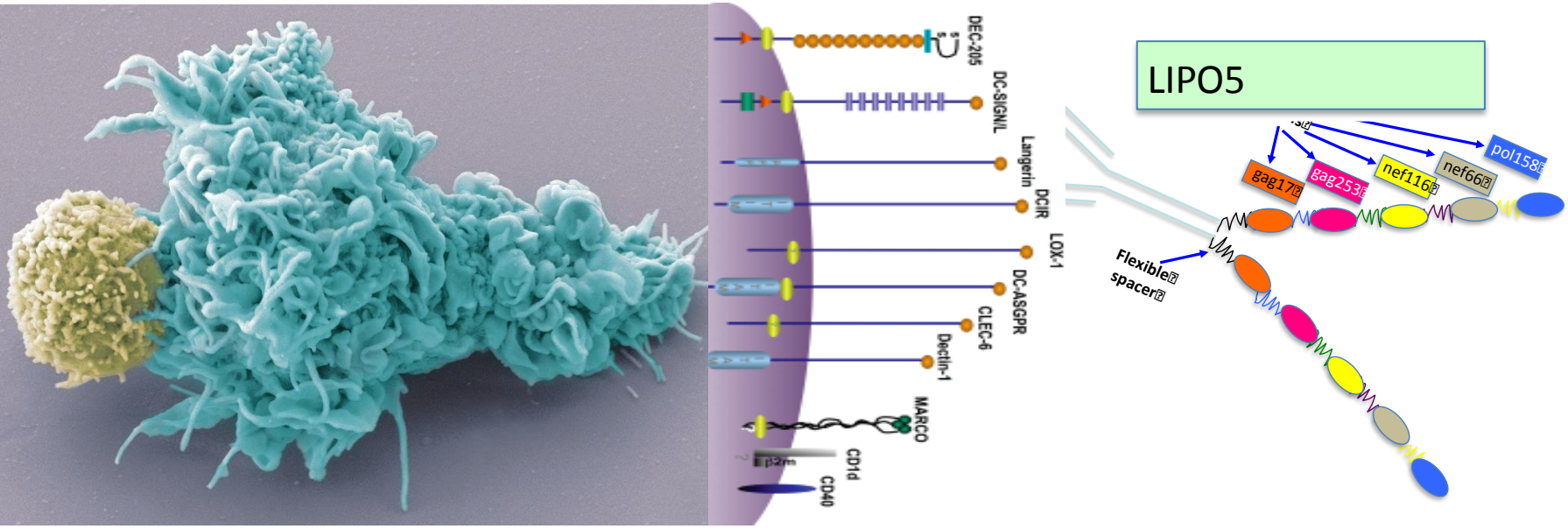
Dendritic cell based vaccine

- Therapeutic vaccine in HIV-infected patients
- Dendritic Cells are loaded with 5 HIV peptides



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BAYLOR Institute for Immunology Research
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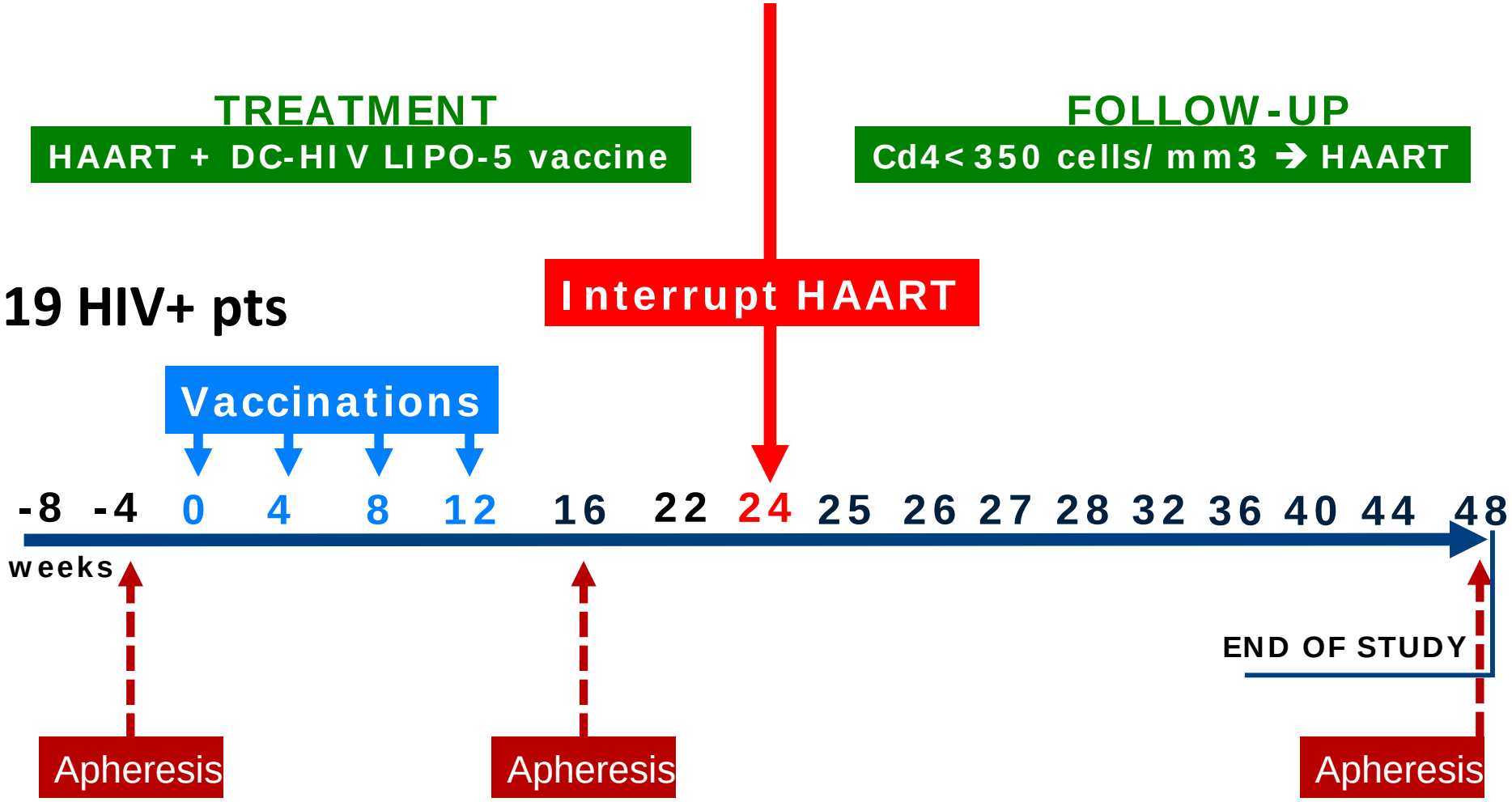
DALIA-1 trial design



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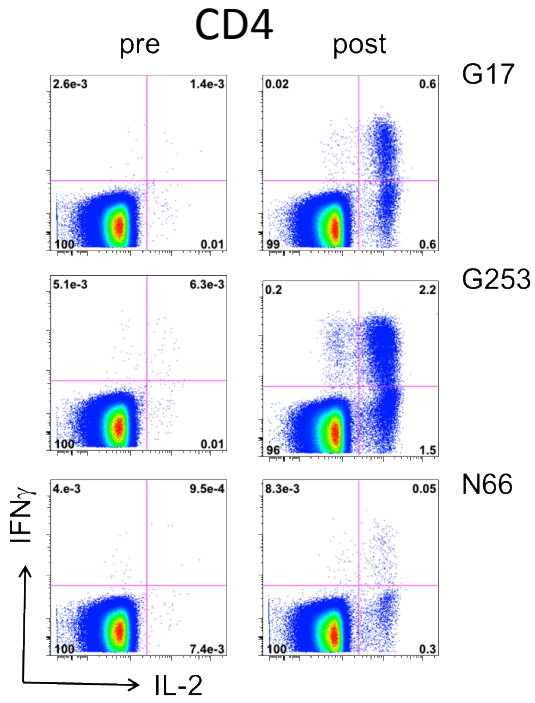
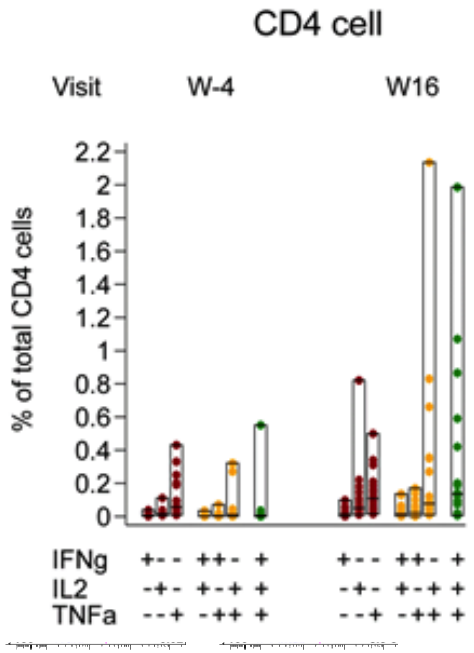
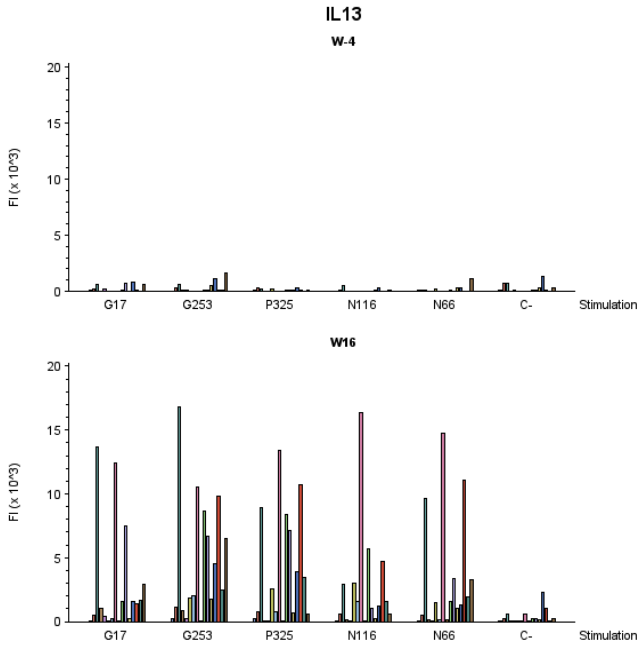
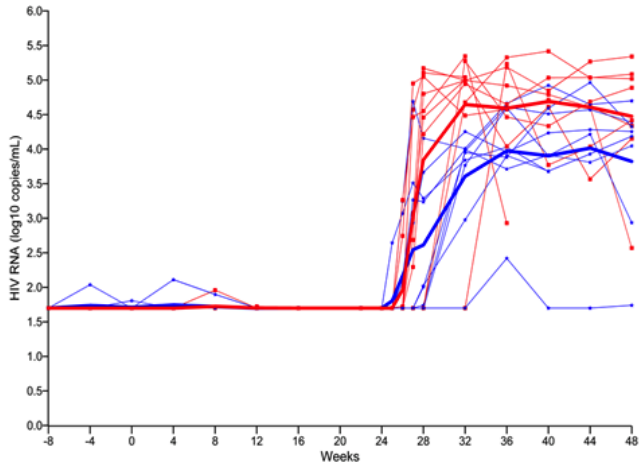
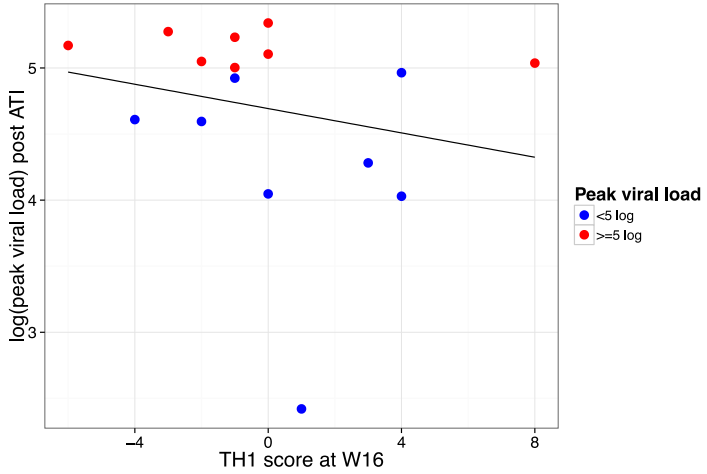
DALIA-1 trial results











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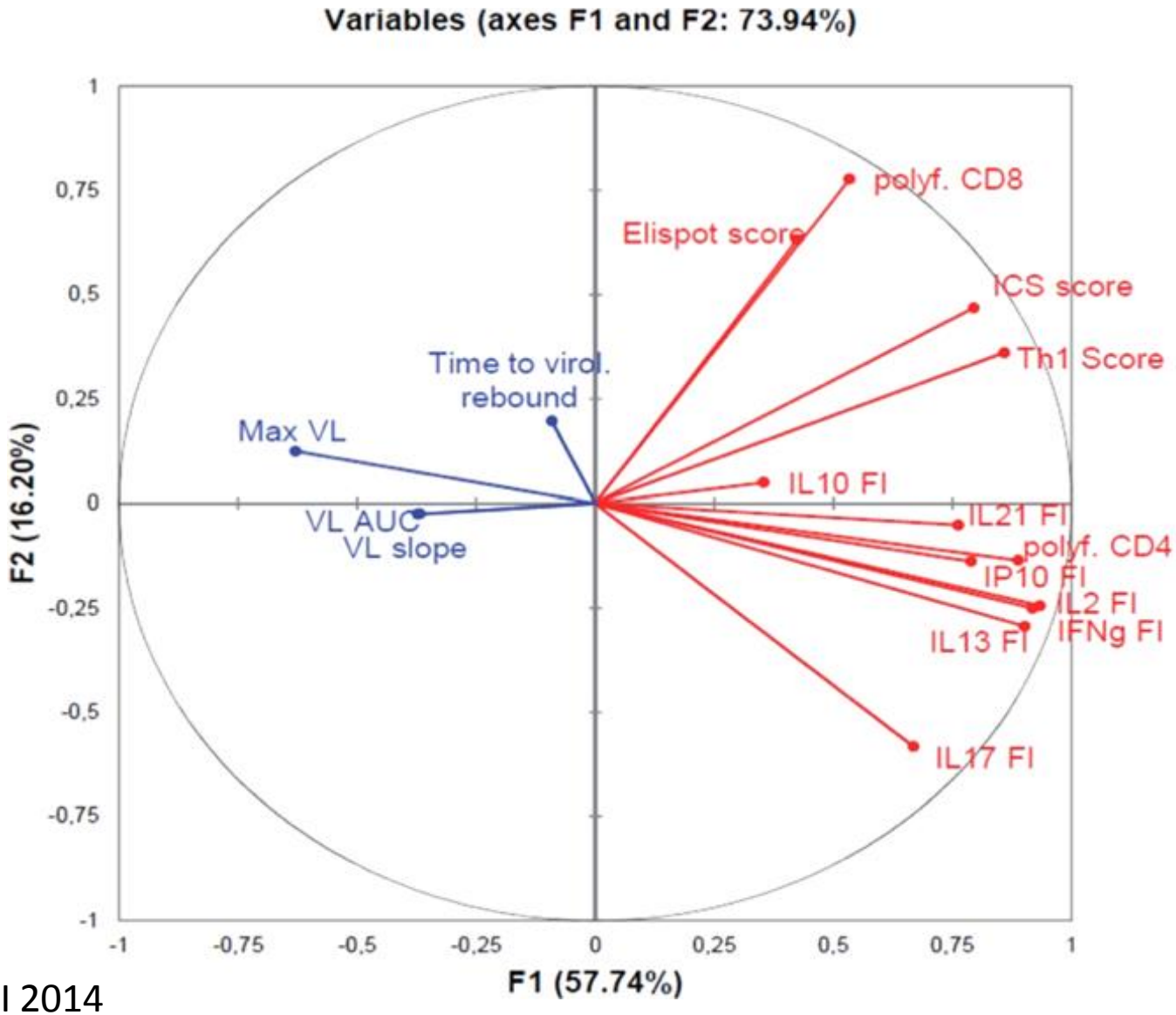
DALIA-1 trial results



Levy, Thiebaut EJI 2014

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Objectives

- Signature: to look at changes in gene expression* in peripheral blood induced by the vaccination

- Correlates: to look at any association between gene expression and vaccine elicited immunological responses (by Elispot, ICS, Luminex) and viral dynamics after ATI

* Illumina HT-12 V4 beadchips

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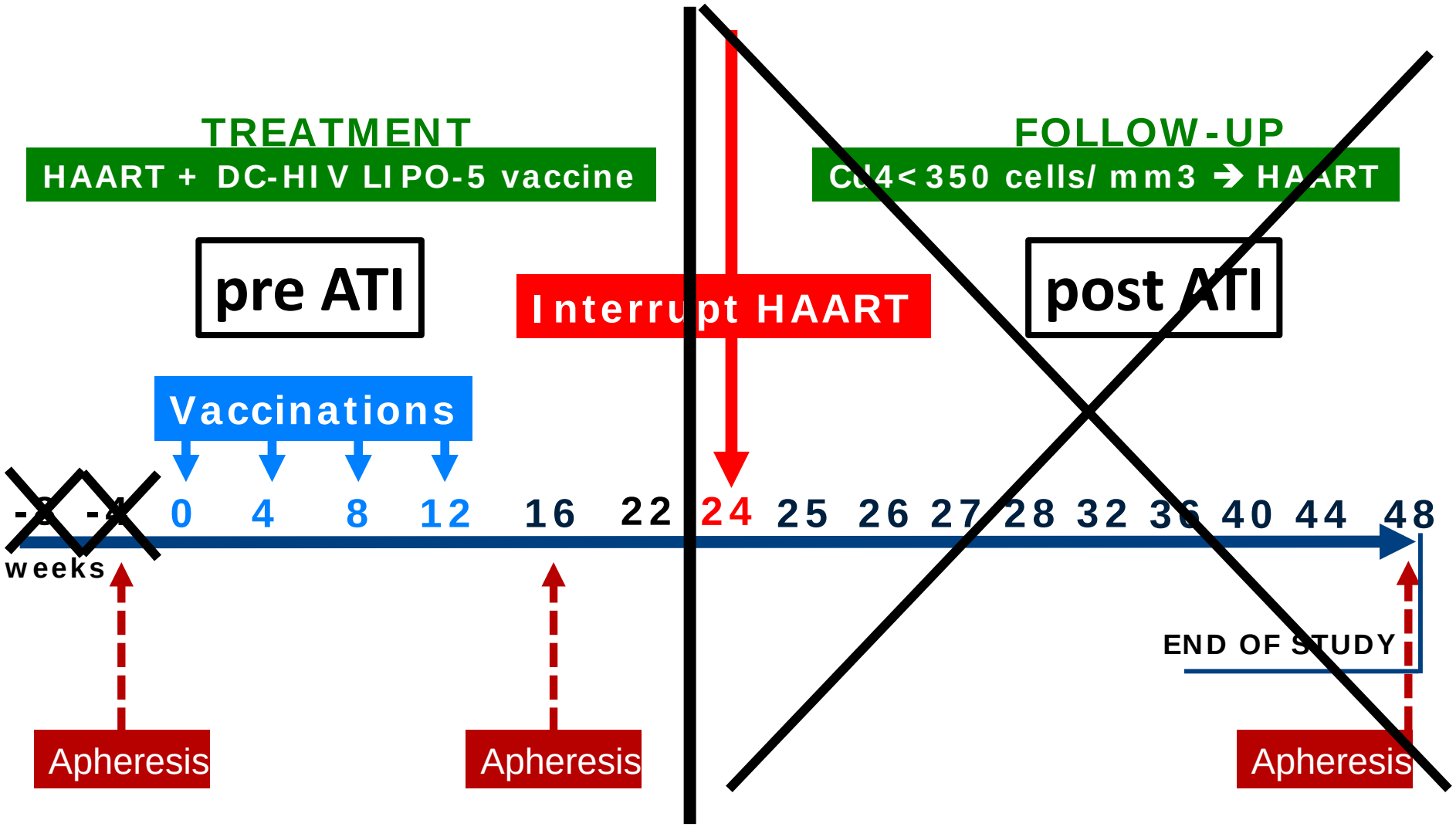
DALIA-1 trial design
Longitudinal transcriptomic analysis



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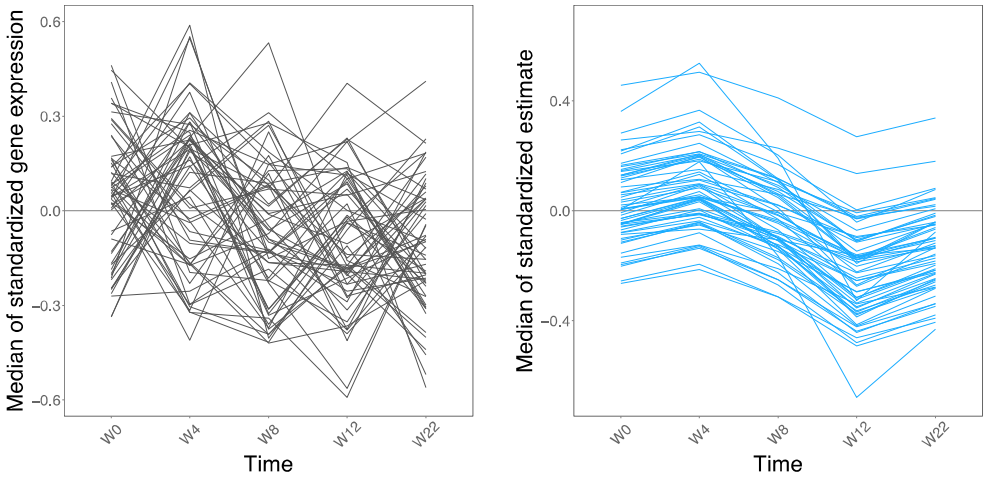
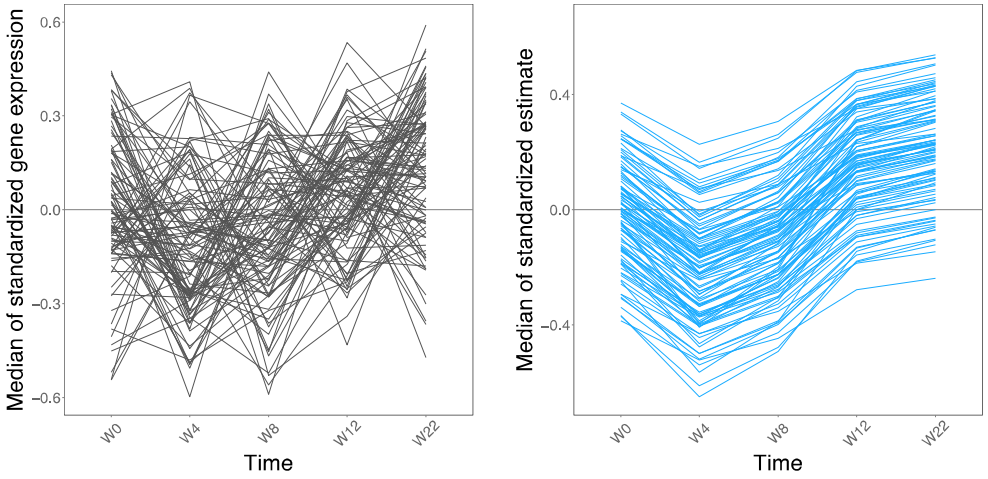
Time course geneset analysis



M 4.1: T cell – 86th percentile



M 4.6: Inflammation – 96th percentile

M3.2[99th pctile]: Inflammation 1/1
M1.1[99th pctile]: Platelets 1/1
M4.13[98th pctile]: Inflammation 1/1
M5.10[97th pctile]: Mitochondrial Respiration 1/1
M4.6[96th pctile]: Inflammation 1/1
M5.6[96th pctile]: Mitochondrial Stress / Proteasome 1/1
M3.5[95th pctile]: Cell Cycle 1/1
M5.7[94th pctile]: Inflammation 1/1
M3.1[94th pctile]: Erythrocytes 1/1
M2.3[94th pctile]: Erythrocytes 1/1
M7.1[93th pctile]: Inflammation 1/1
M6.2[93th pctile]: Mitochondrial Respiration 1/1
M4.3[91th pctile]: Protein Synthesis 1/1
M4.11[91th pctile]: Plasma Cells 1/3
M4.11[91th pctile]: Plasma Cells 2/3
M4.11[91th pctile]: Plasma Cells 3/3
M6.13[90th pctile]: Cell Death 1/1
M4.5[89th pctile]: Protein Synthesis 1/1
M4.14[88th pctile]: Monocytes 1/1
M4.2[88th pctile]: Inflammation 1/1
M4.7[87th pctile]: Cell Cycle 1/1
M4.1[86th pctile]: T cell 1/1
M3.6[85th pctile]: Cytotoxic/NK Cell 1/1
M5.9[84th pctile]: Protein Synthesis 1/1
M5.15[82th pctile]: Neutrophils 1/1
M4.15[81th pctile]: T cells 1/1
M6.6[80th pctile]: Apoptosis / Survival 1/1
M5.1[74th pctile]: Inflammation 1/1

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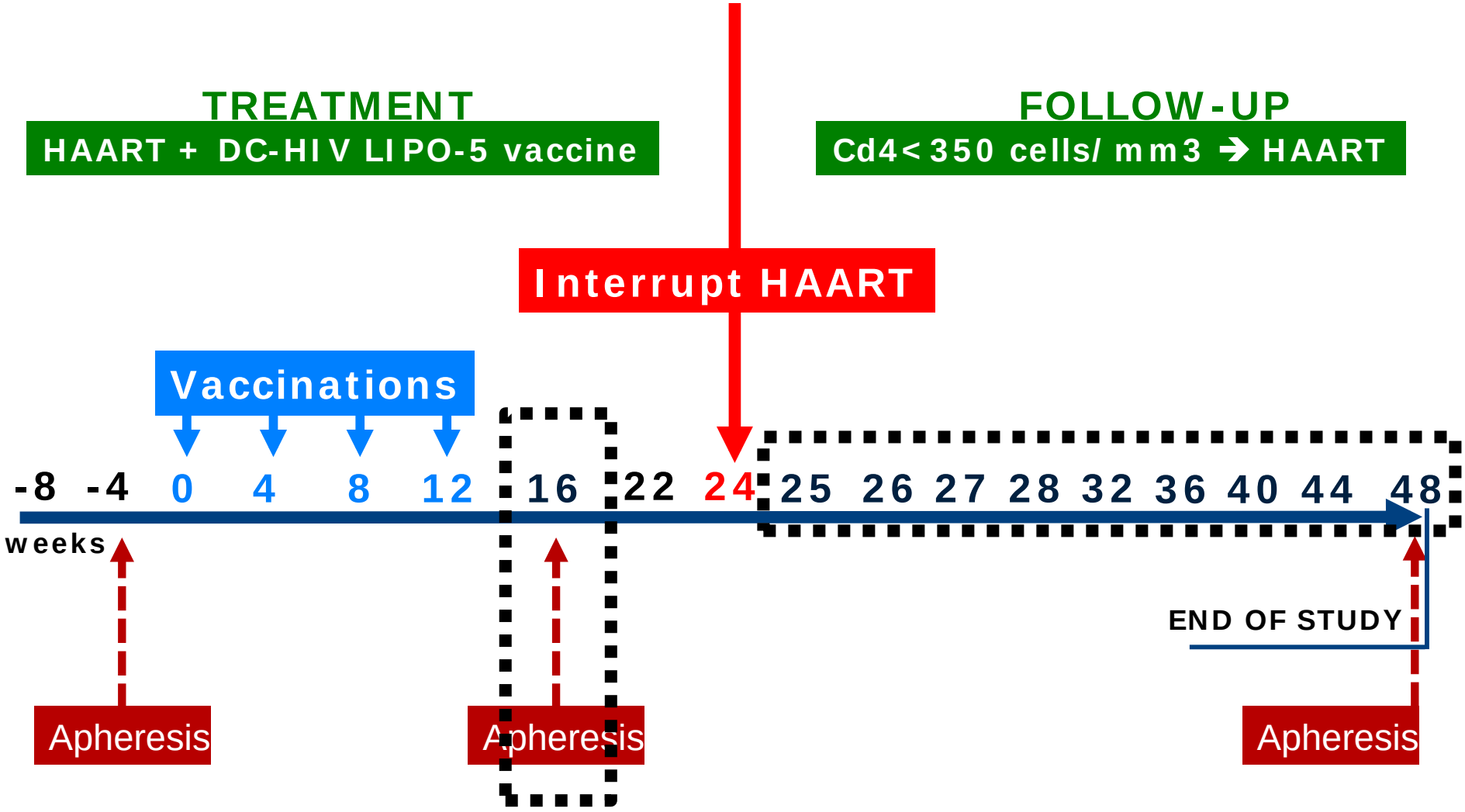
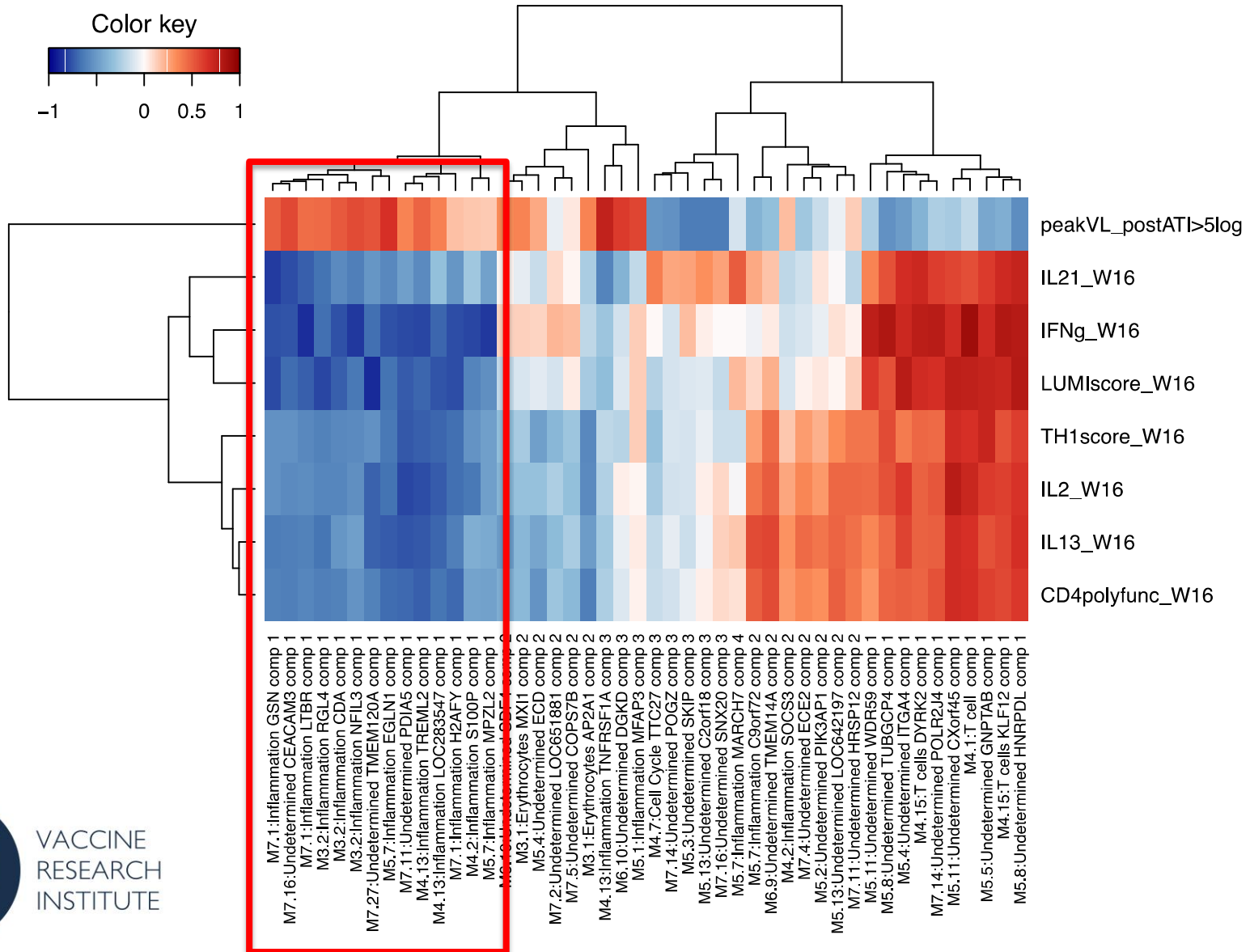
DALIA-1 trial design
Integrative Analysis



Correlations with immune response (W16) and peak of viral load (post ATI)



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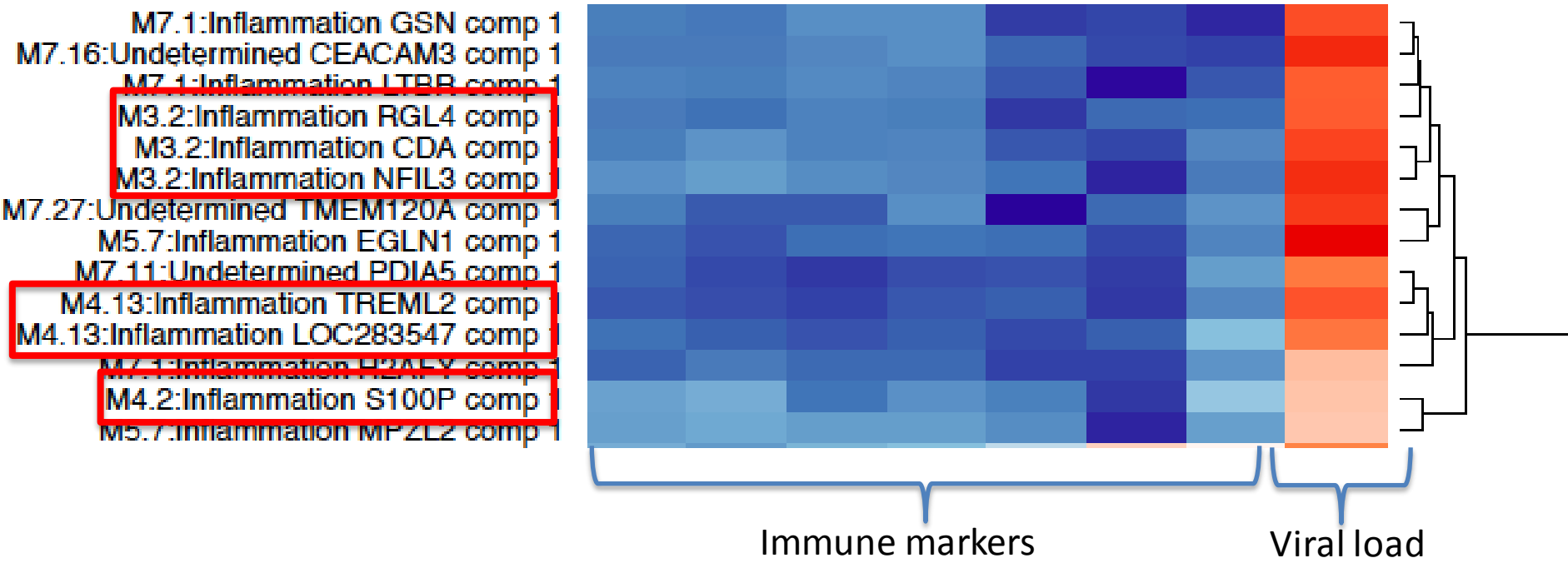

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Modules also negatively associated with Pneumococcal vaccine response (Obermoser et al., Immunity 2013)

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Conclusion

- The goals of the systems vaccinology approach: understanding and predicting the response to vaccine
- The requirements:
  - Early harvest times (innate response)
  - Whole blood (signature) vs. selected cell populations (mechanism)
  - Several assays at the same time (flow cyto, ICS…)
- Opportunity to learn more about the Ebola vaccine (substudies)

Acknowledgments

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