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Towards improved foot-and-mouth disease vaccines by dissecting immune responses using systems immunology approaches

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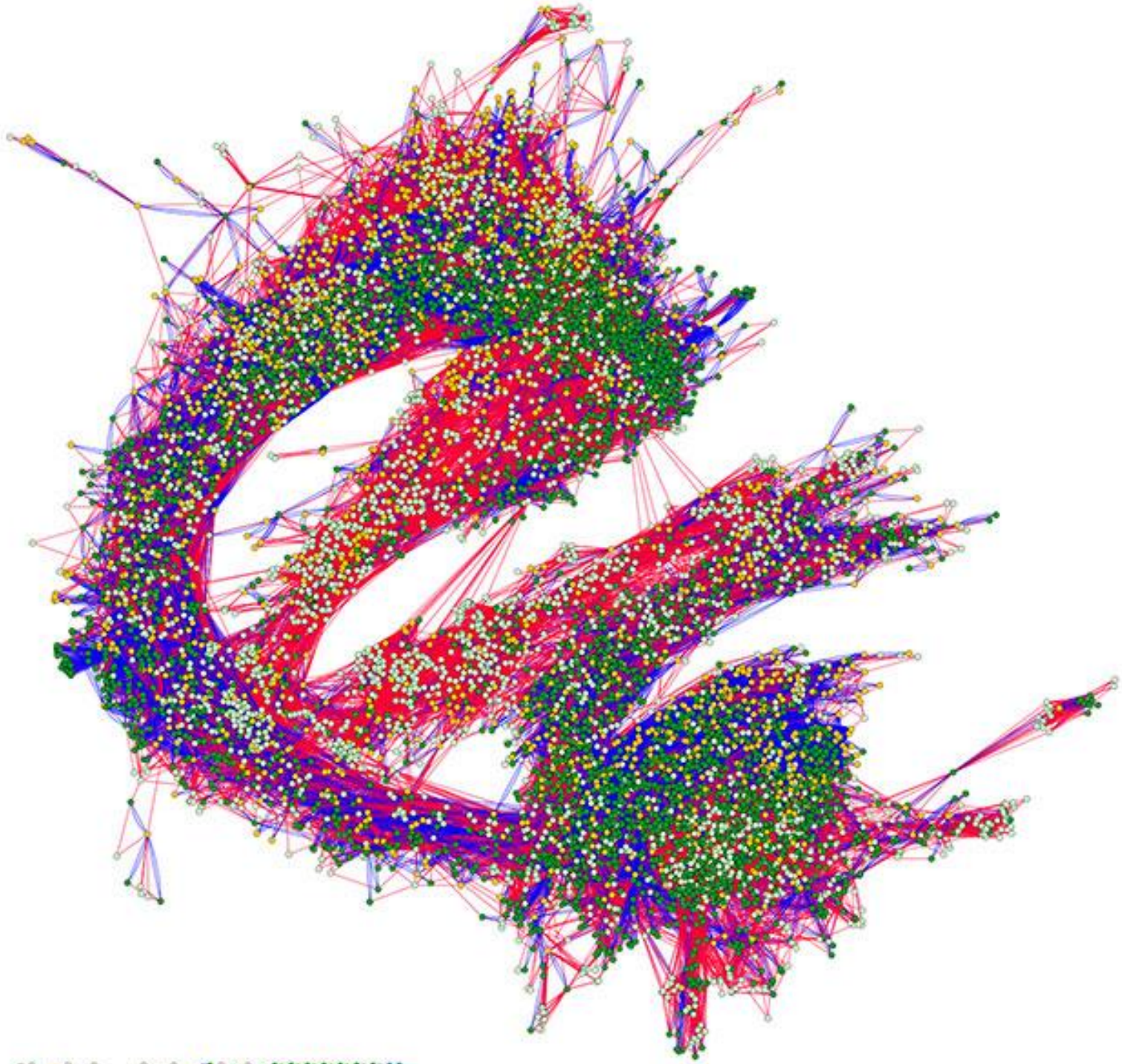
Initial question and overall aim

Improve the neutralizing antibody response with respect to:

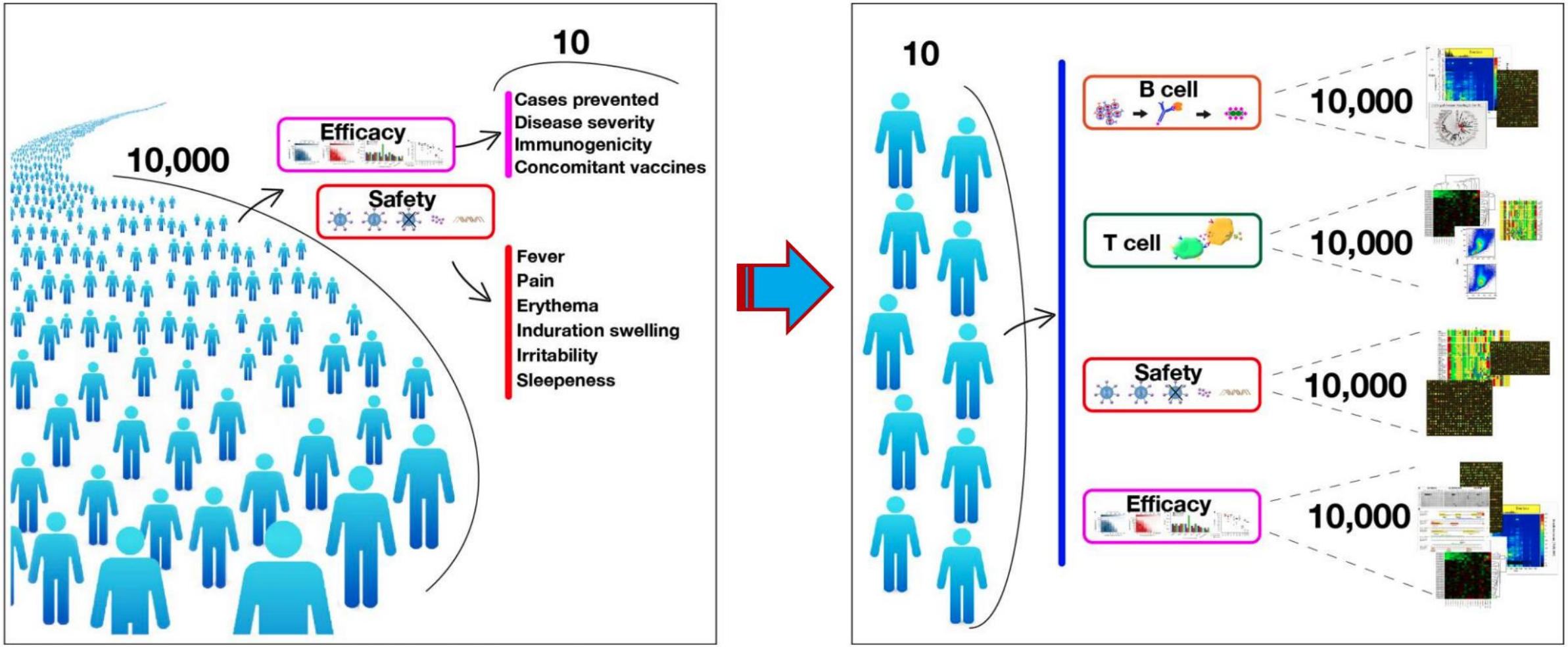
- **Overall levels**
- **Rapidity of development**
- **Longevity**

The immune system functions as network of many cells (hundreds) and molecules (thousends)!



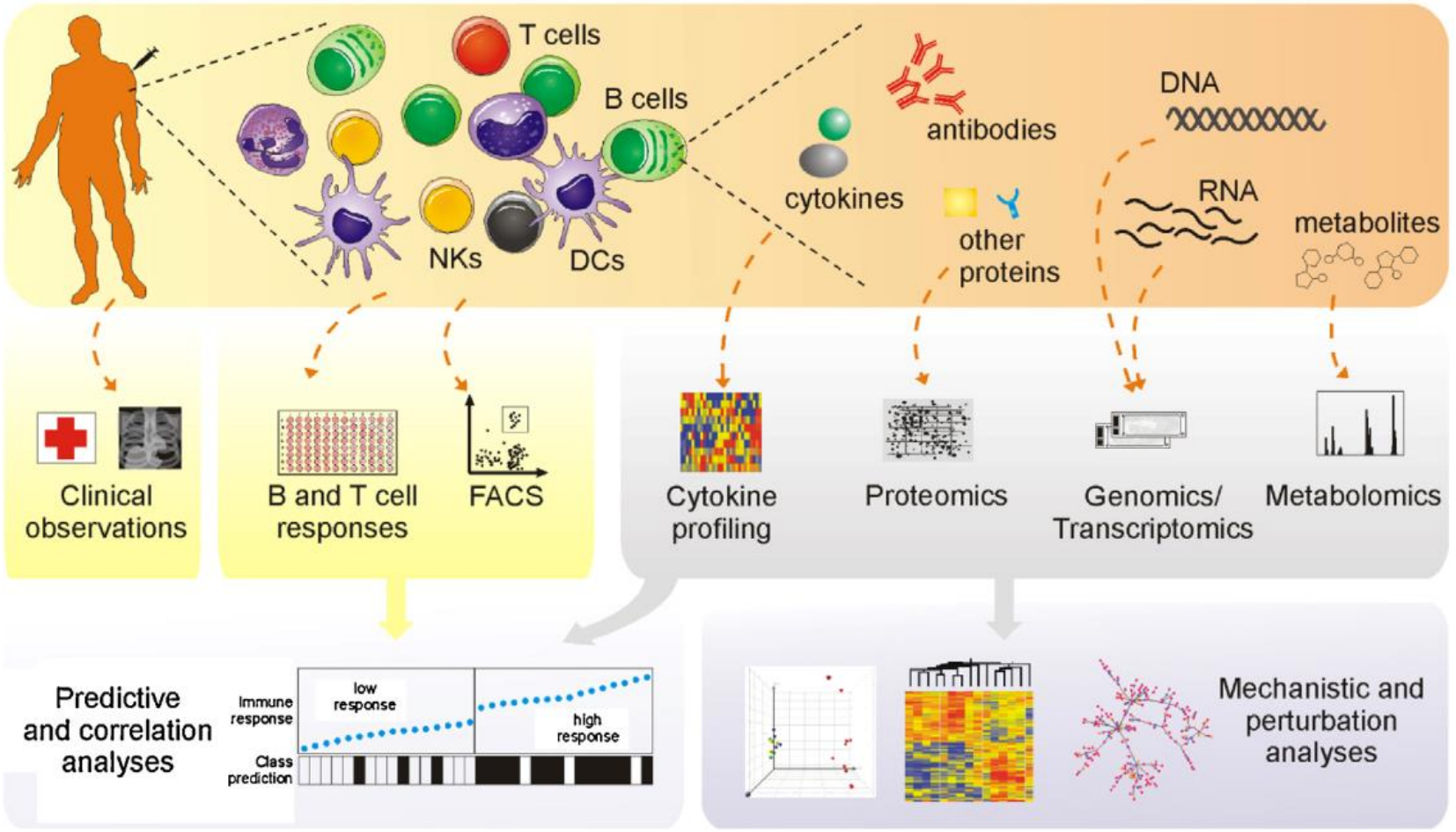
Systems biology

From 10,000 people with 10 data each
to
10 people with 10,000 data each



Systems immunology – the whole is greater than the sum of the parts

Application of computational and mathematical modeling to understand complex biological systems.



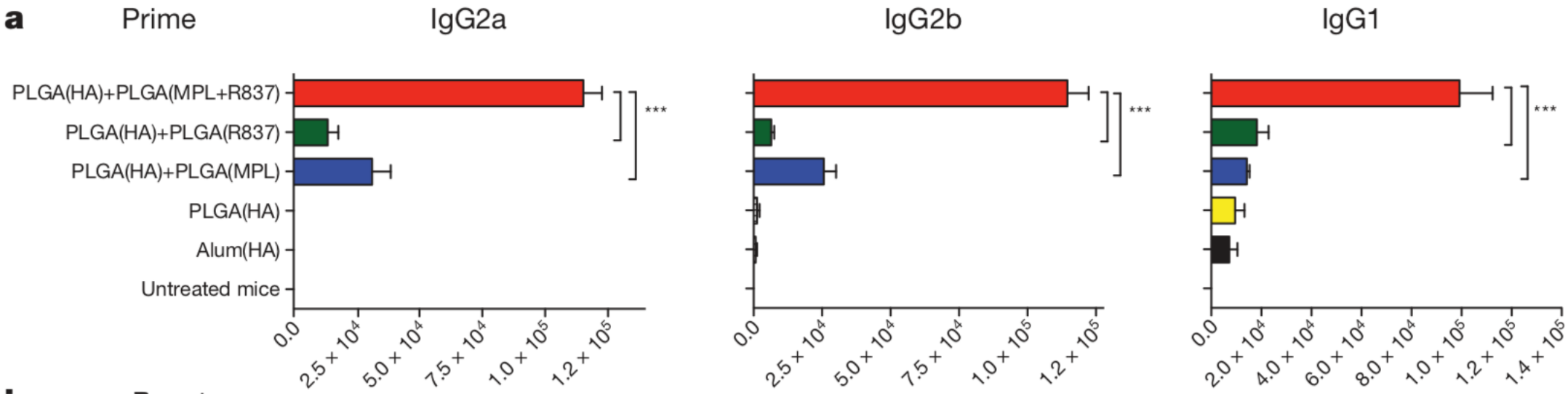
Li et al., Seminars in Immunology, 2013

LETTER

2011 doi:10.1038/nature09737

Programming the magnitude and persistence of antibody responses with innate immunity

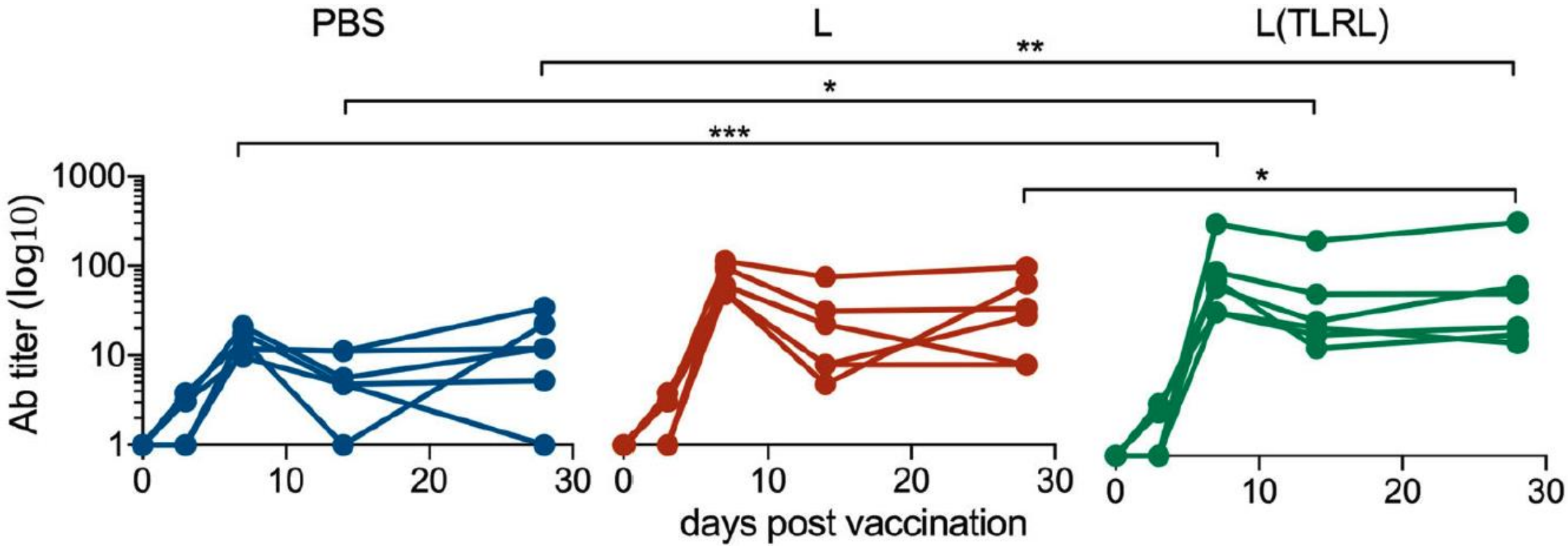
Sudhir Pai Kasturi[1,2], Ioanna Skountzou[1,3], Randy A. Albrecht[4], Dimitrios Koutsonanos[3], Tang Hua[1,2], Helder I. Nakaya[1,2], Rajesh Ravindran[1,2], Shelley Stewart[5], Munir Alam[5], Marcin Kwissa[1,2], Francois Villinger[1,2,6], Niren Murthy[7], John Steel[4], Joshy Jacob[1,2,3], Robert J. Hogan[8], Adolfo García-Sastre[4,9,10], Richard Compans[1,3] & Bali Pulendran[1,2,6]



Sheep trial

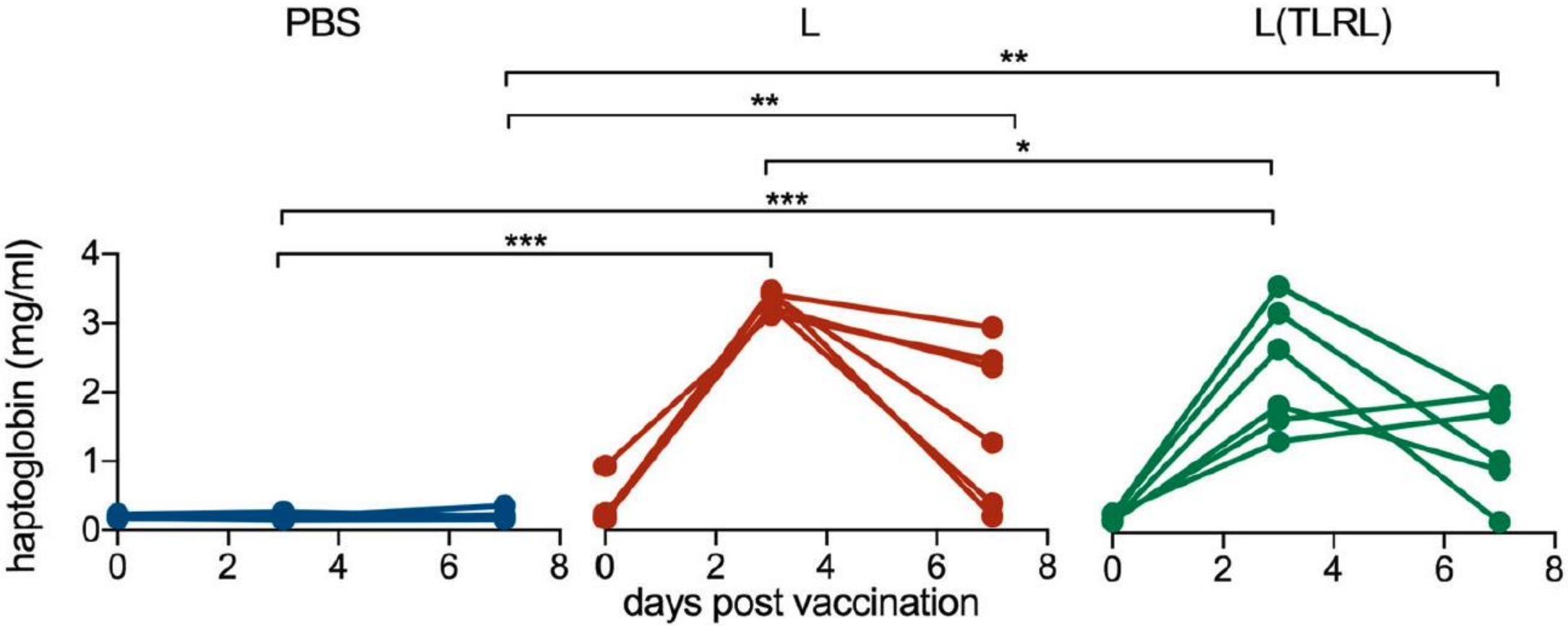
- Vaccination of 6 sheep/group with different FMD vaccines:
  1. FMDV antigen in PBS
  2. FMDV antigen formulated in liposomes
  3. FMDV antigen formulated in liposomes + TLR7/TLR4 ligands (Gardiquimod/MPLA)
- Neutralizing antibody response
- PBMC RNA isolation at 0, 3 and 7 days
  - Illumina RNA sequencing & alignment to the sheep genome

Antibody responses



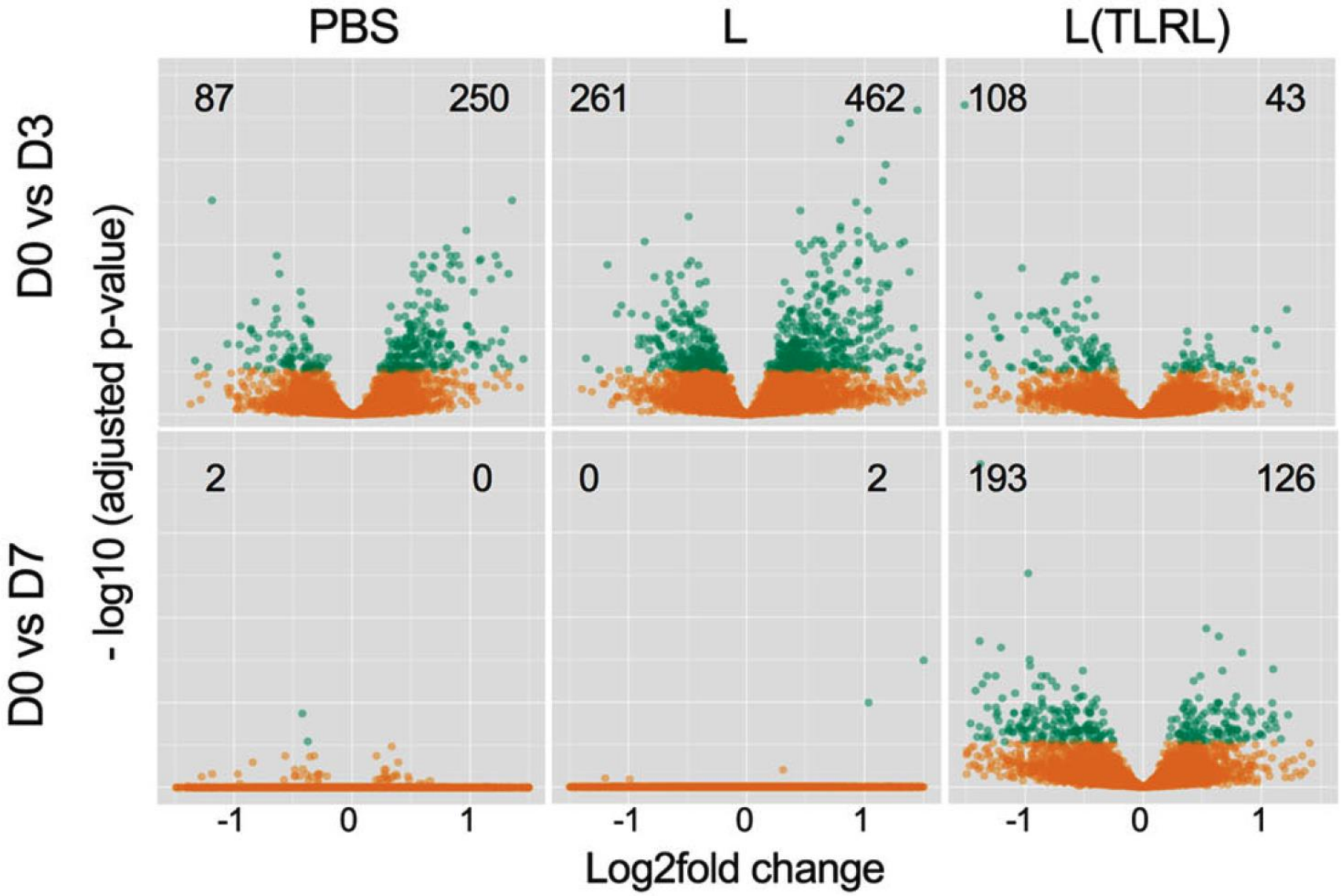
Braun et al., 2018, NPJ Vaccines

Haptoglobin responses



Braun et al., 2018, NPJ Vaccines

Differentially expressed genes



Braun et al., 2018, NPJ Vaccines

Genes correlating to antibody responses - expressed 3 days p.v.

ZNF646, STIM2, C9orf3, NPEPPS, SDR39U1, HEXDC, NUCB2, GHDC, LSR, MYO1E, TRAPPC6A, DCAF12, ABCC2, ZDHHC24, TRIM41, GZMA, NAGK, GMNN, OLFML3, MYO7A, TNFSF13B, GGA3, ASB8, ARNTL, GNG3, PLA2G12A

=B-cell activating factor (BAFF)

Braun et al., 2018, NPJ Vaccines

RESOURCE

nature immunology

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

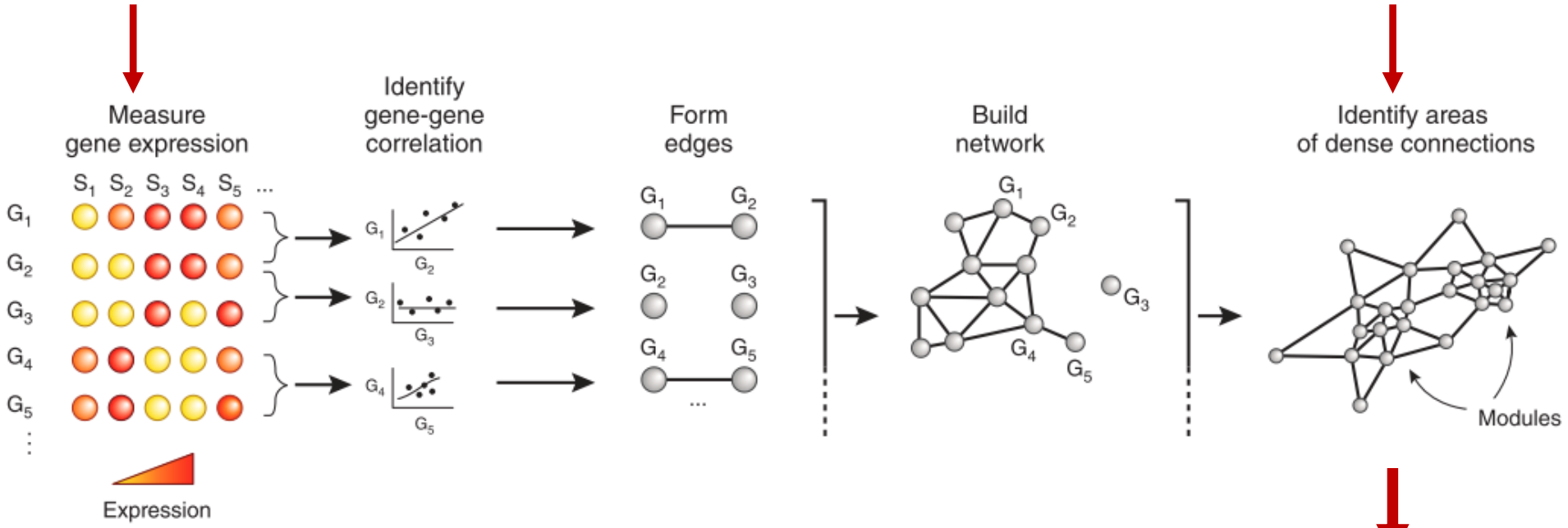
Shuzhao Li[1,2,10], Nadine Rouphael[1,3,10], Sai Duraisingham[1,2,10], Sandra Romero-Steiner[4], Scott Presnell[5,6], Carl Davis[1,7], Daniel S Schmidt[4], Scott E Johnson[4], Andrea Milton[4], Gowrisankar Rajam[4], Sudhir Kasturi[1,2], George M Carlone[4], Charlie Quinn[5,6], Damien Chaussabel[5,6], 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]

2014. Nat Immunol **15**, 195

“Strength in numbers: comparing vaccine signatures the modular way”

Data from 540 studies with a total of 32‘000 samples

Curation with predefined pathways (GO categories, KEGG, Reactome TF targets, Biocarta PID)

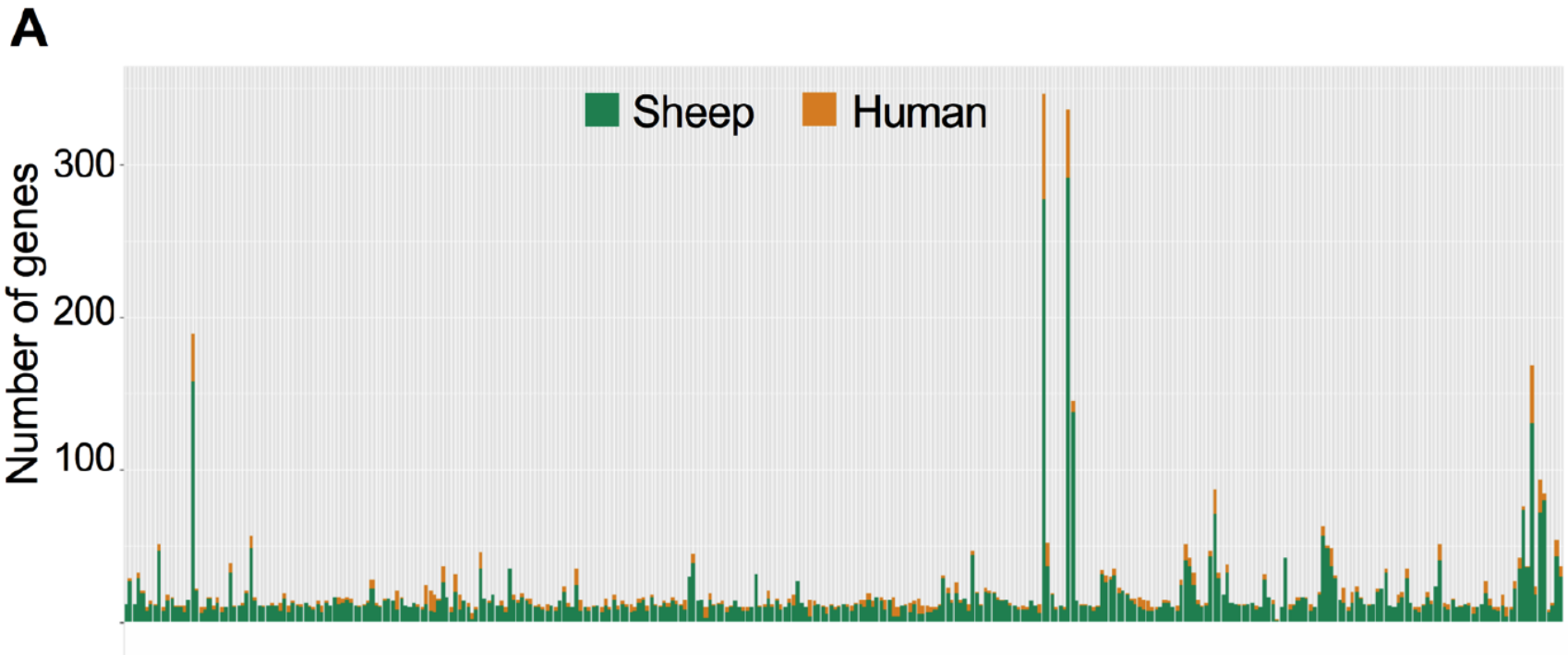


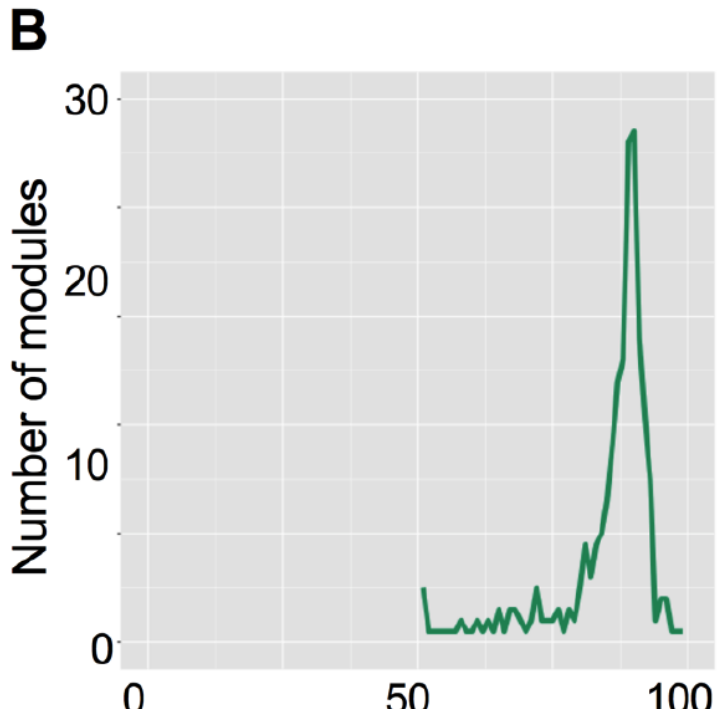
347 BTM‘s

Haining, Nat. Immunol 2014; 15: 139

Adaptation of human BTM to sheep

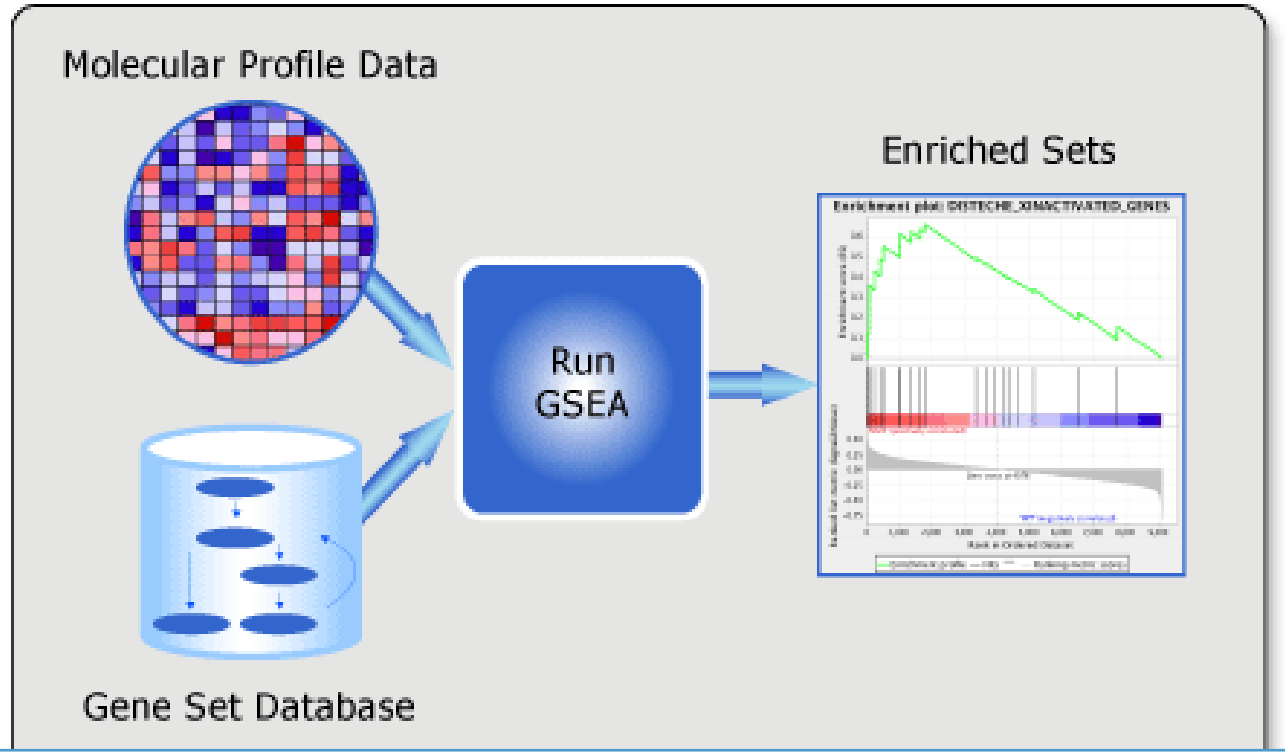
1. Identification of genes in the BTM for which no corresponding sheep gene is annotated or has a different name.
2. Adaptation of gene symbols to sheep names if required (in particular MHC, TCR, Ig, CD1, IFN type 1 genes)
3. Manual annotation of important non-annotated sheep genes





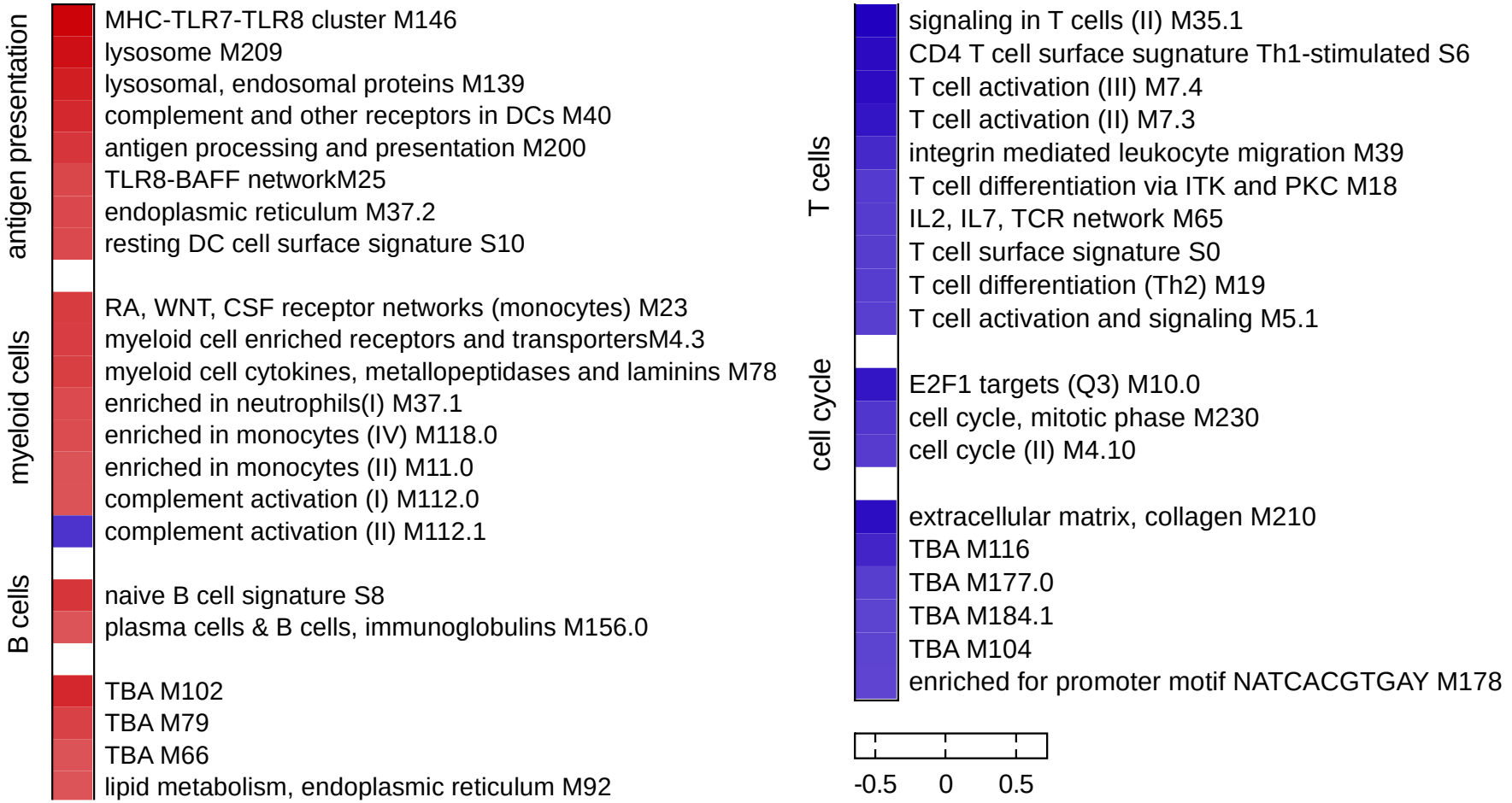
GSEA

Gene Set Enrichment Analysis



Gene Set Enrichment Analysis (GSEA) is a computational method that determines whether a defined set of genes shows statistically significant, concordant differences between two biological states.

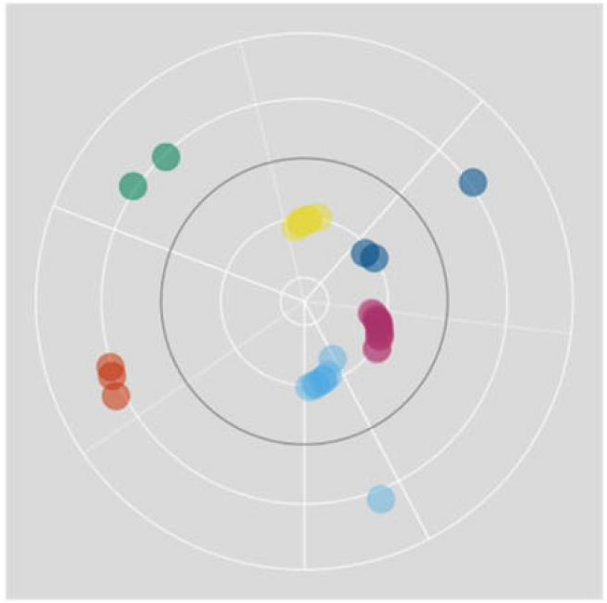
BTM modulation correlating with antibodies in sheep (d3)



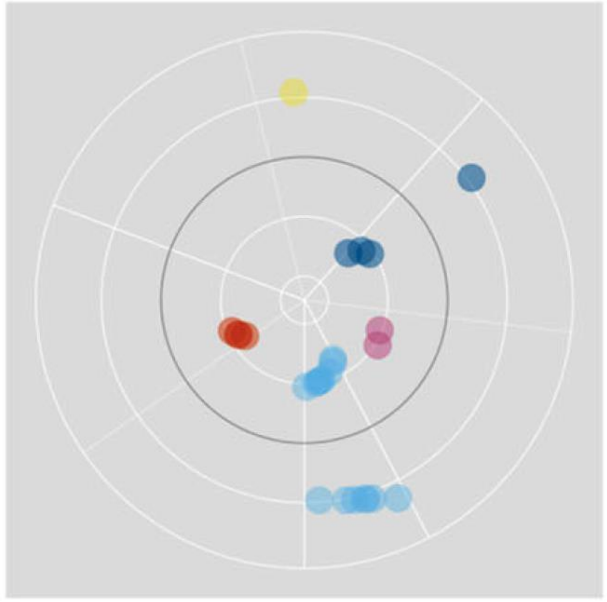
Braun et al., 2018, NPJ Vaccines

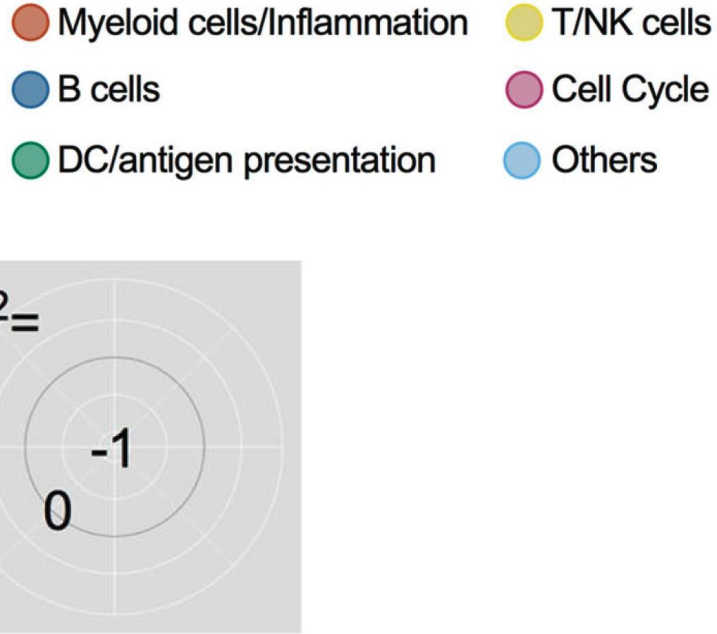
Correlation of BTM families with antibodies

d0 to d3 changes



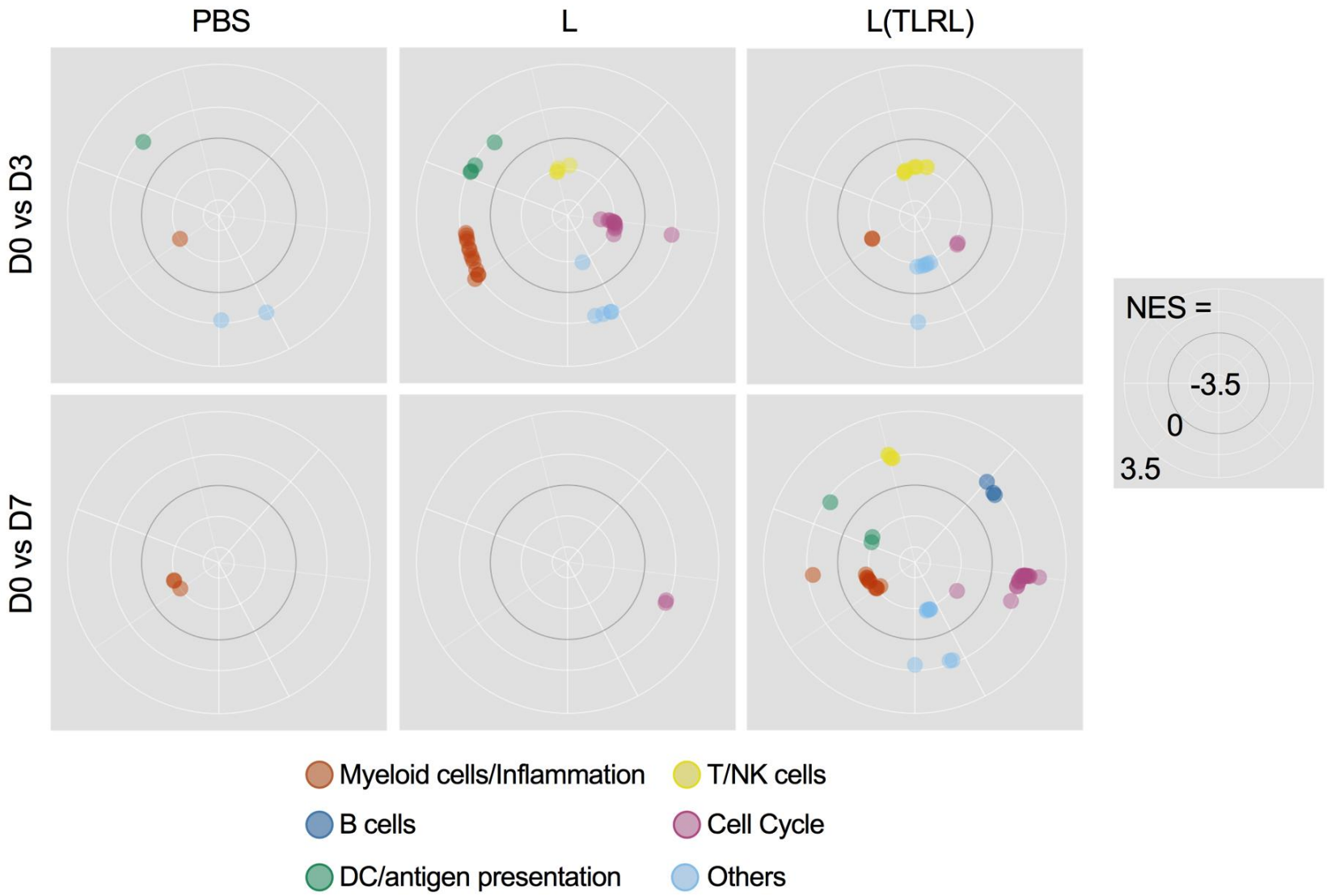
d0 to d7 changes



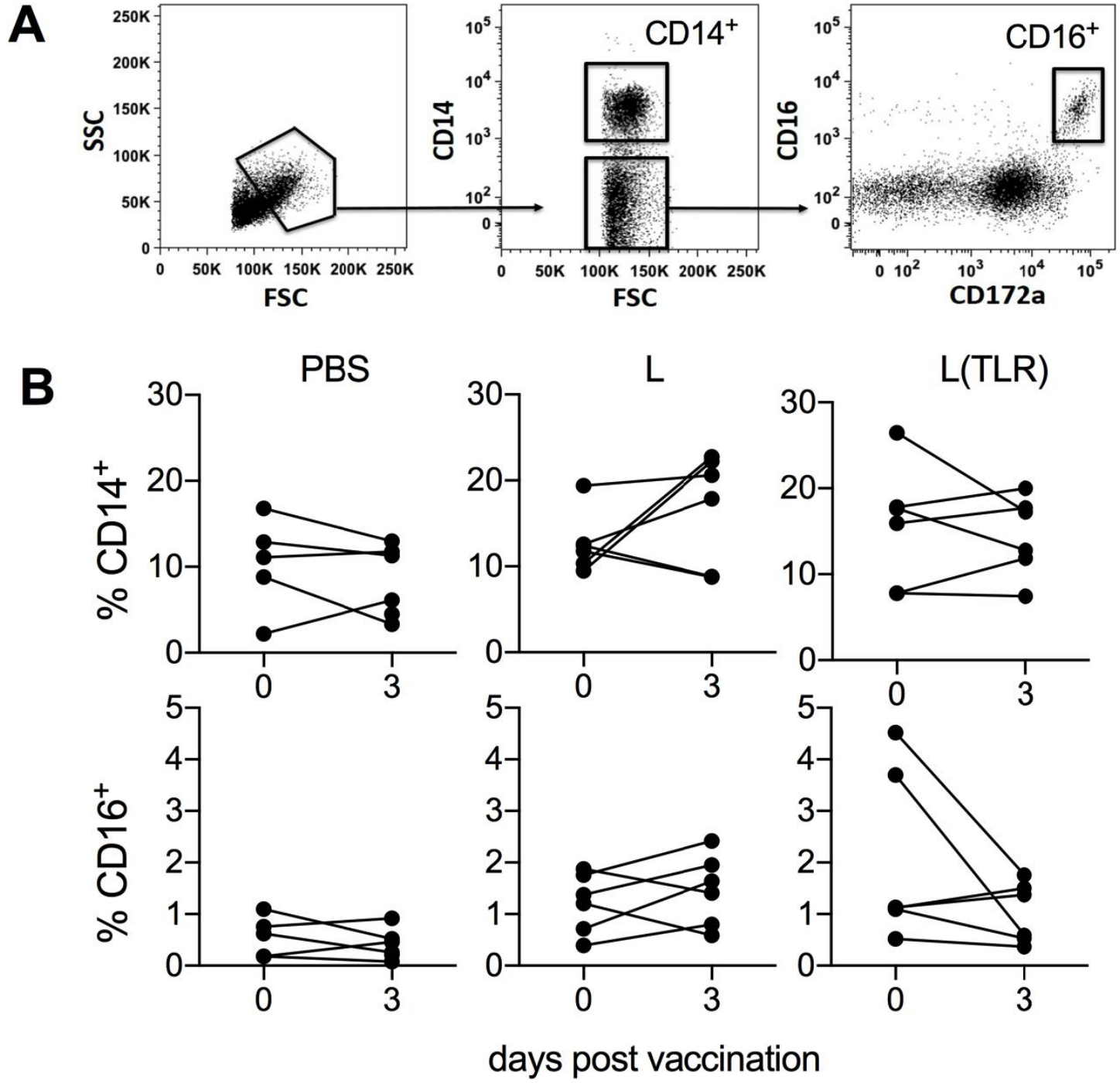


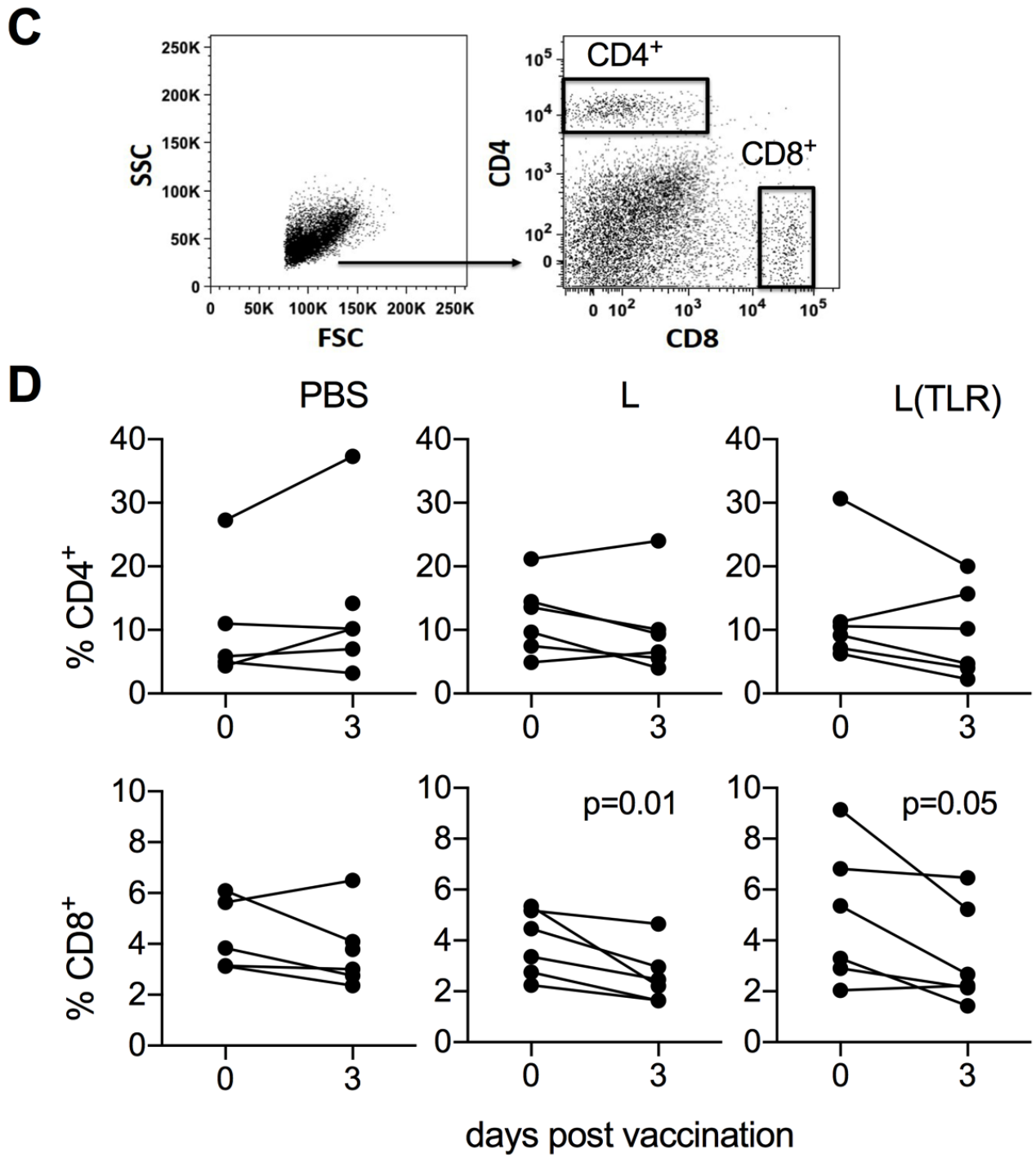
Braun et al., 2018, NPJ Vaccines

Vaccine induced BTM

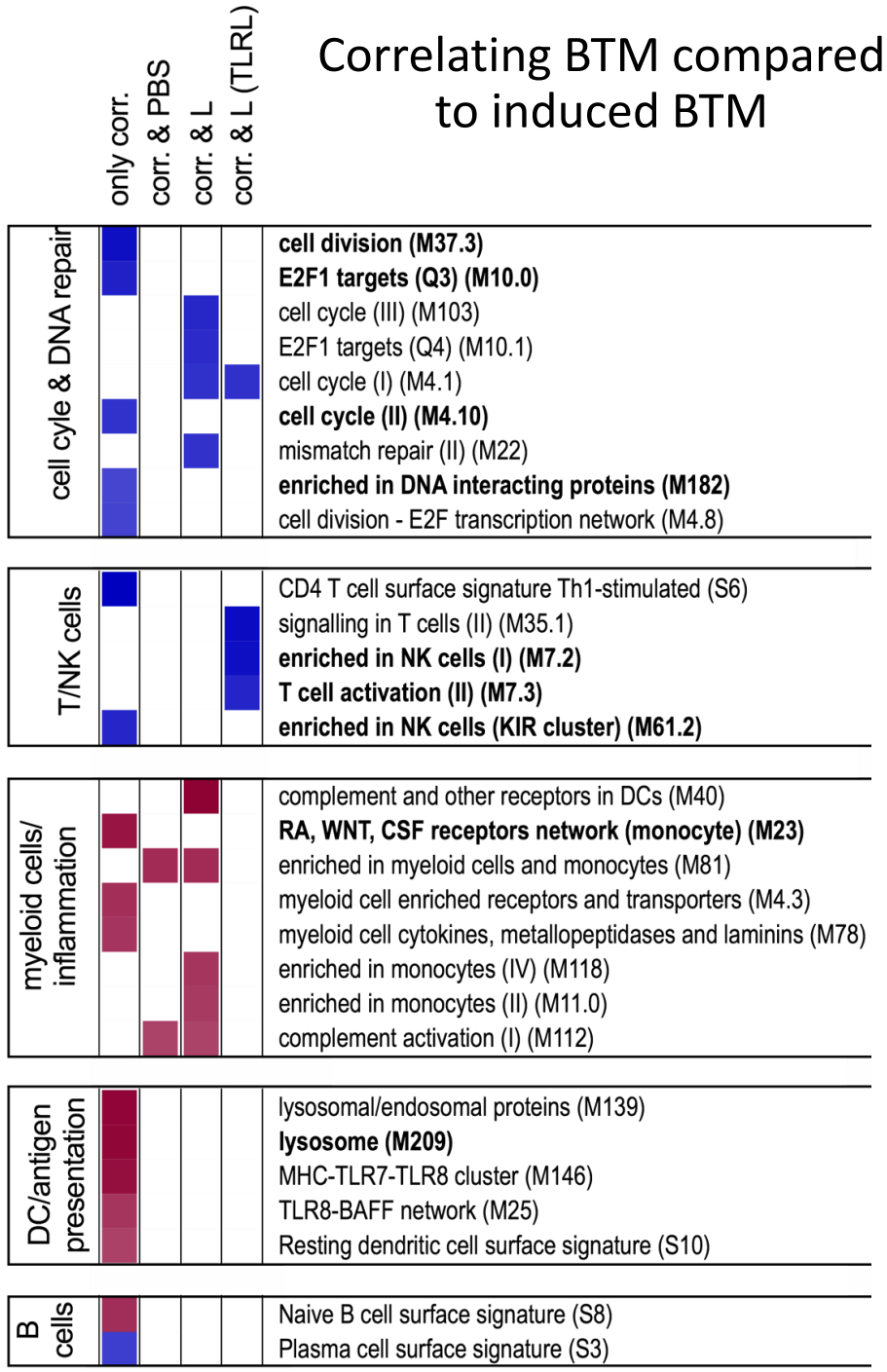


Braun et al., 2018, NPJ Vaccines

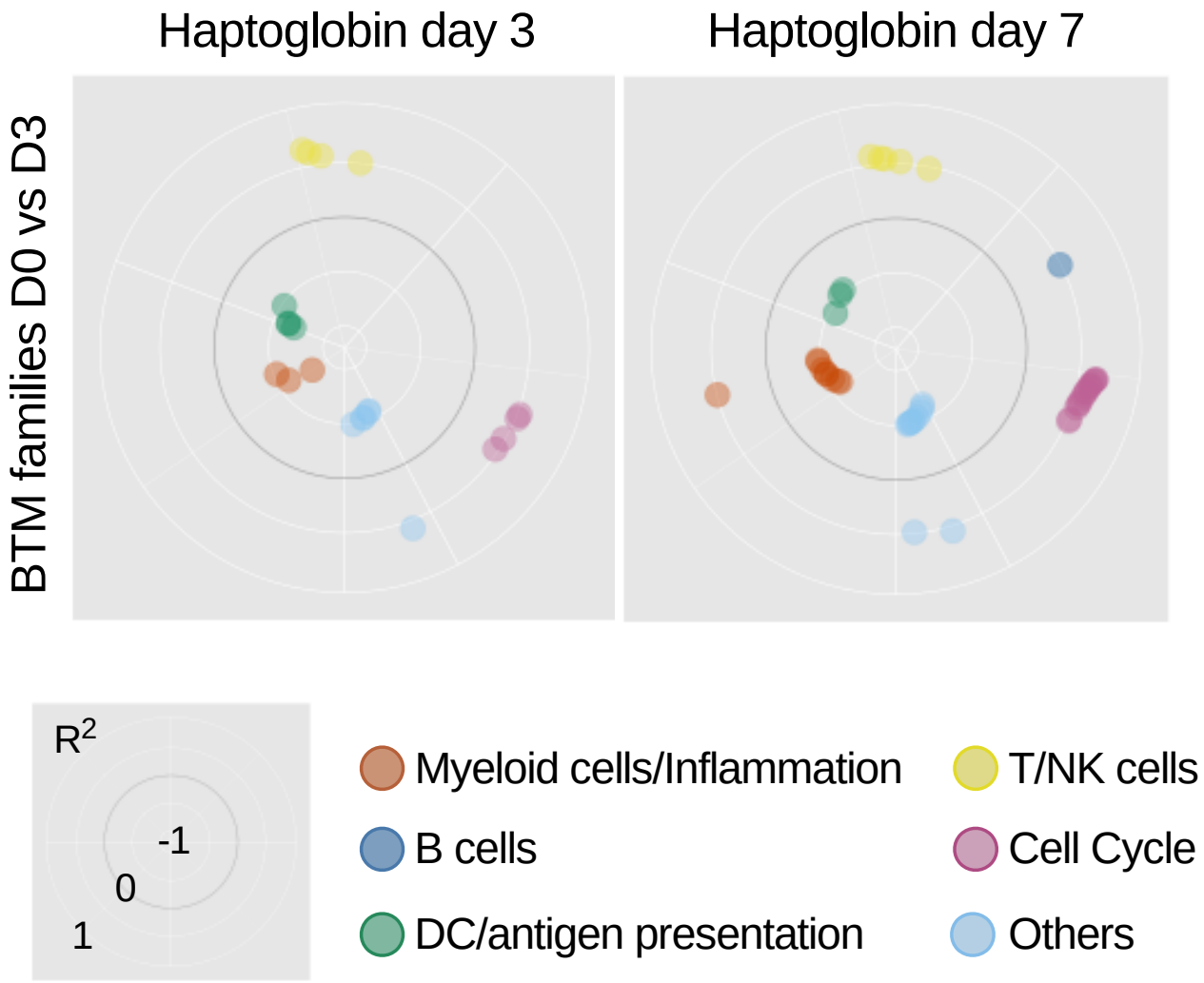

A
SSC
FSC
CD14
CD14+
CD16
CD16+
CD172a
B
PBS
L
L(TLR)
% CD14+
% CD16+
days post vaccination


C
250K
200K
150K
100K
50K
0
SSC
0 50K 100K 150K 200K 250K
FSC
CD4+
CD8+
CD4
CD8
D
PBS
L
L(TLR)
% CD4+
% CD8+
p=0.01
p=0.05
days post vaccination

Correlating BTM compared to induced BTM



BTM correlating with systemic inflammation



Braun et al., 2018, NPJ Vaccines

frontiers in Immunology

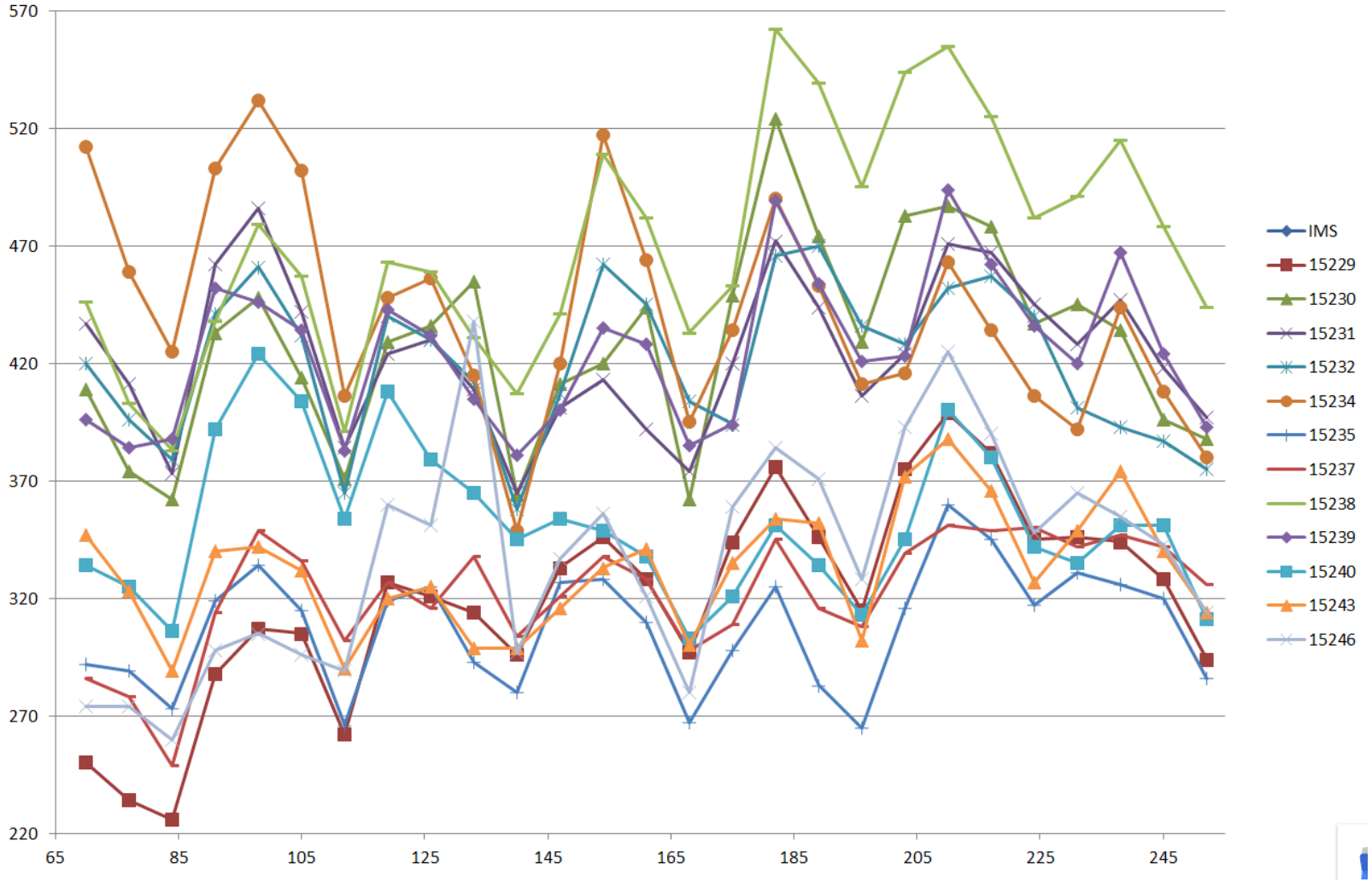
ORIGINAL RESEARCH
published: 24 May 2019
doi: 10.3389/fimmu.2019.01087

Check for updates

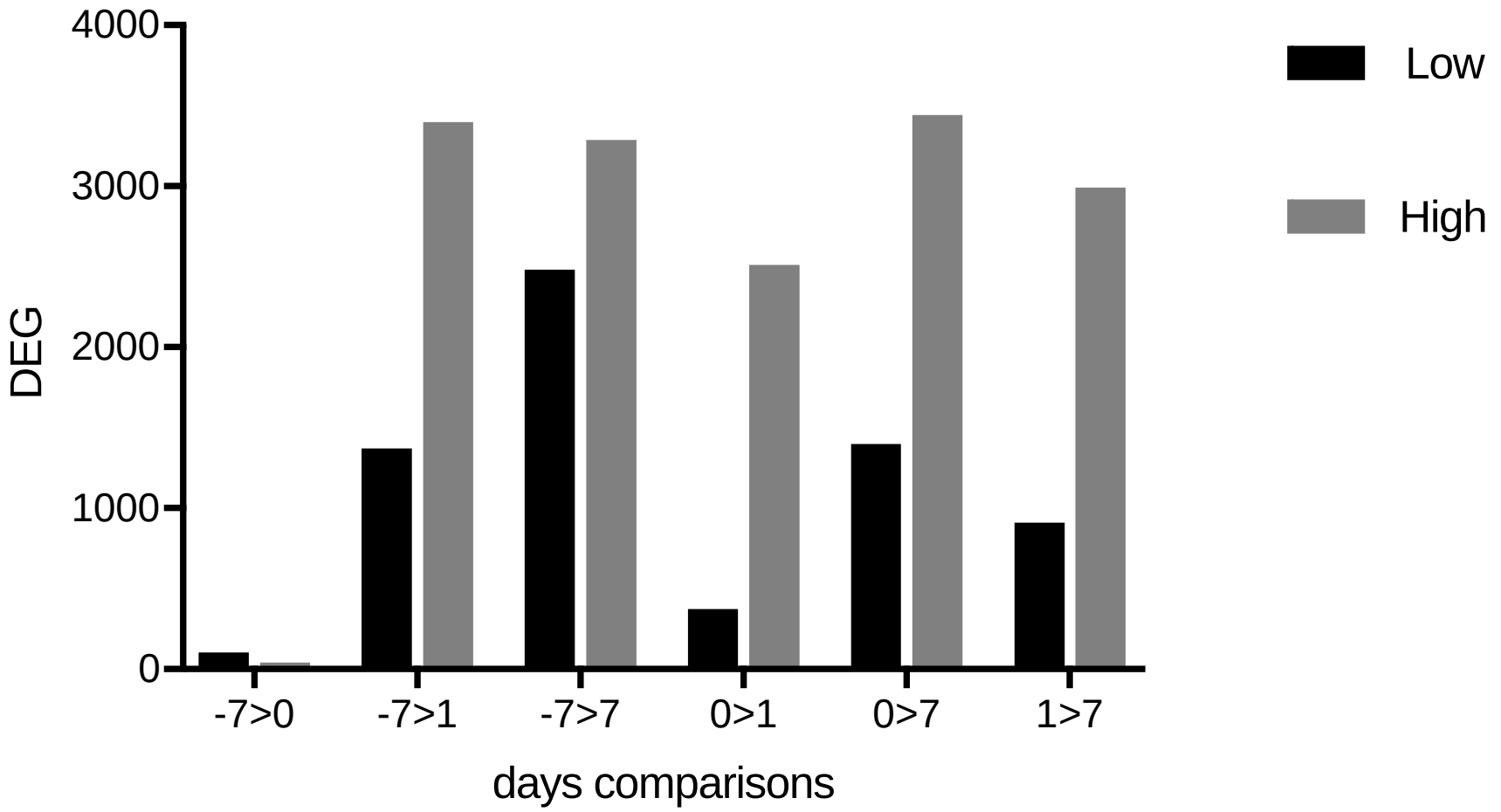
Systems Immunology Characterization of Novel Vaccine Formulations for *Mycoplasma hyopneumoniae* Bacterins

Anneleen M. F. Matthijs[1], Gaël Auray[2,3], Virginie Jakob[4], Obdulio García-Nicolás[2,3], Roman O. Braun[2,3], Irene Keller[5,6], Rémy Bruggman[5], Bert Devriendt[7], Filip Boyen[8], Carlos A. Guzman[9], Annelies Michiels[1], Freddy Haesebrouck[8], Nicolas Collin[4], Christophe Barnier-Quer[4], Dominiek Maes[1†] and Artur Summerfield[2,3†]*

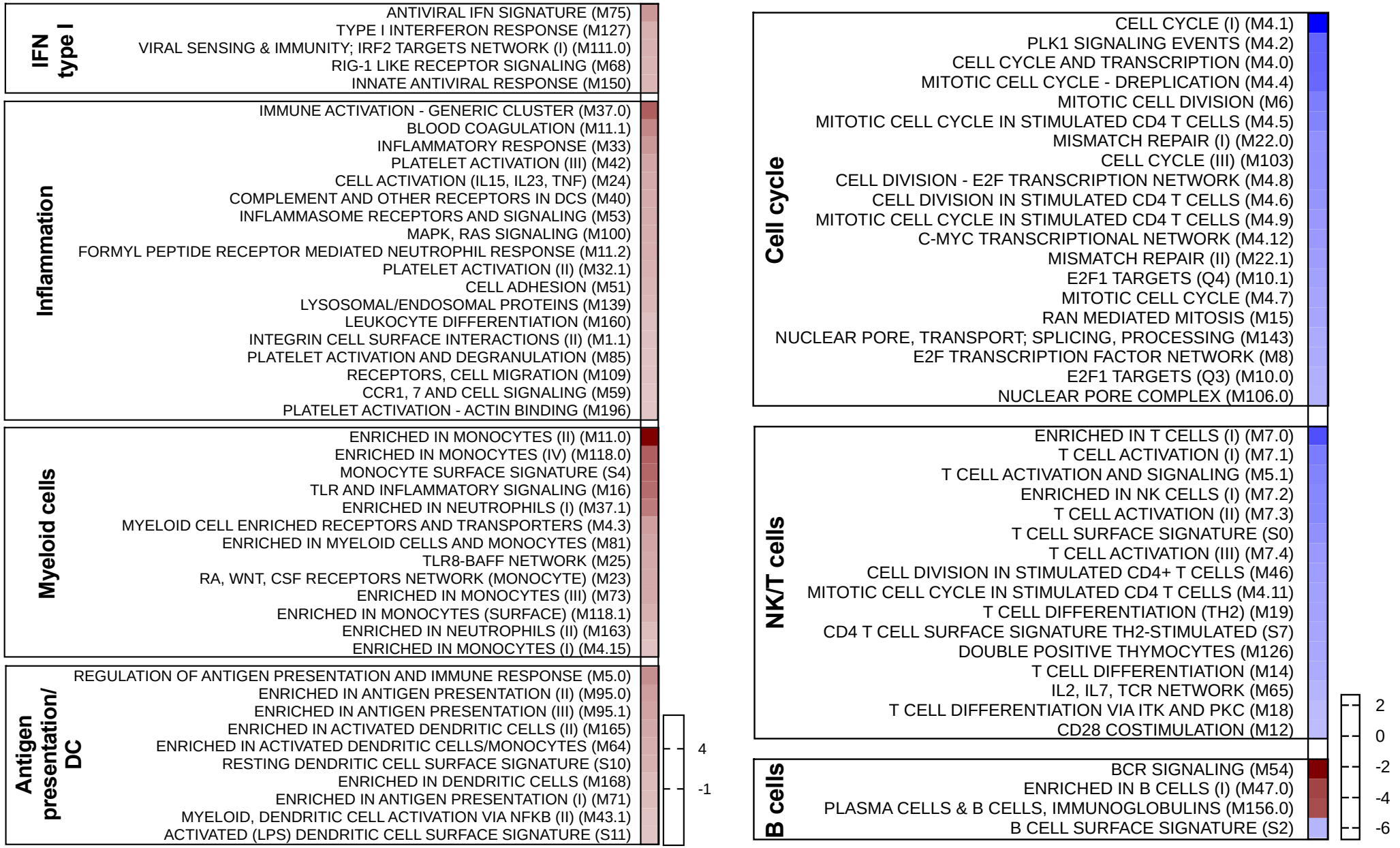
Antibody responses in sheep: high and low responders



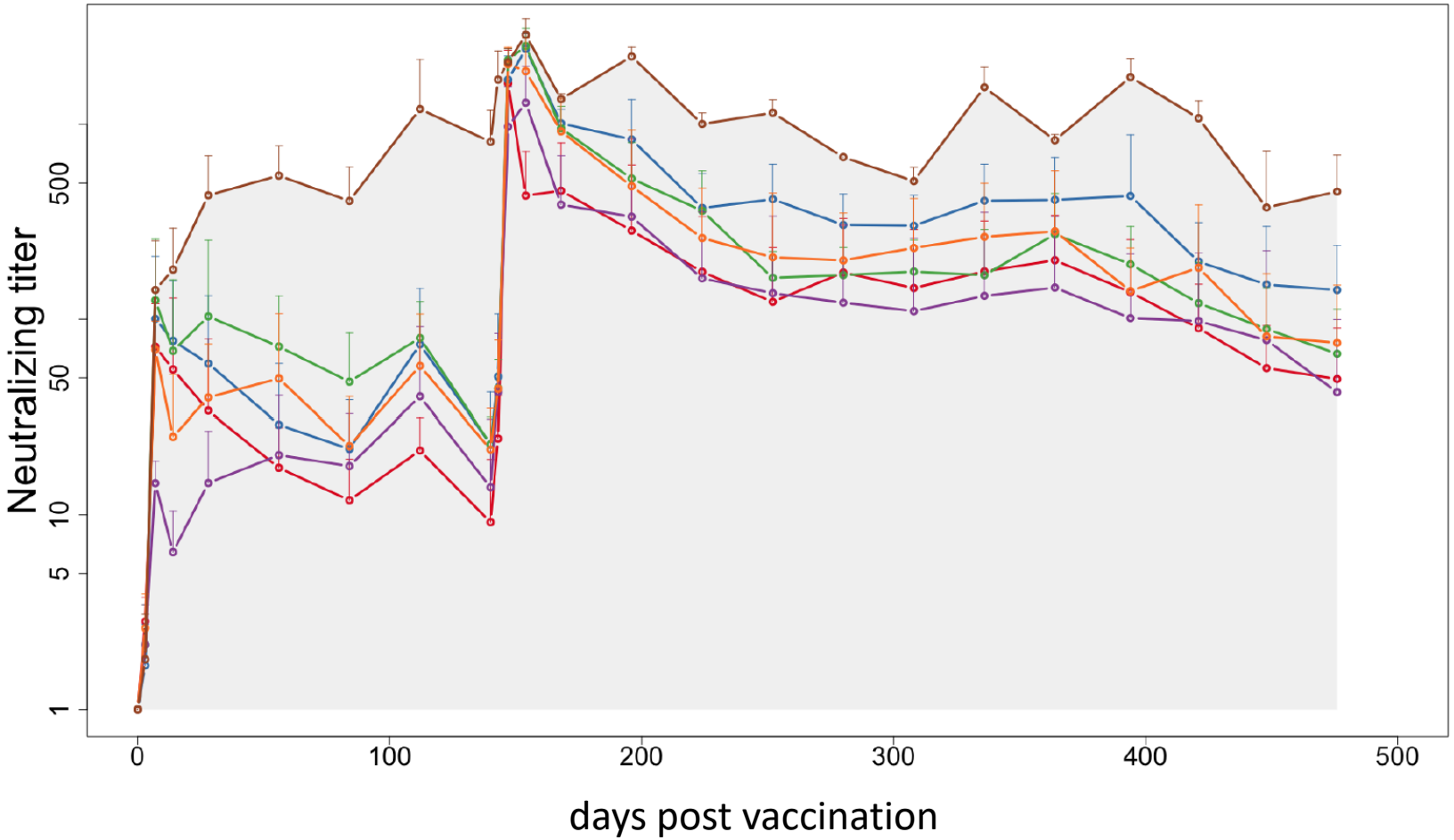
Number of differentially expressed genes of high and low responders

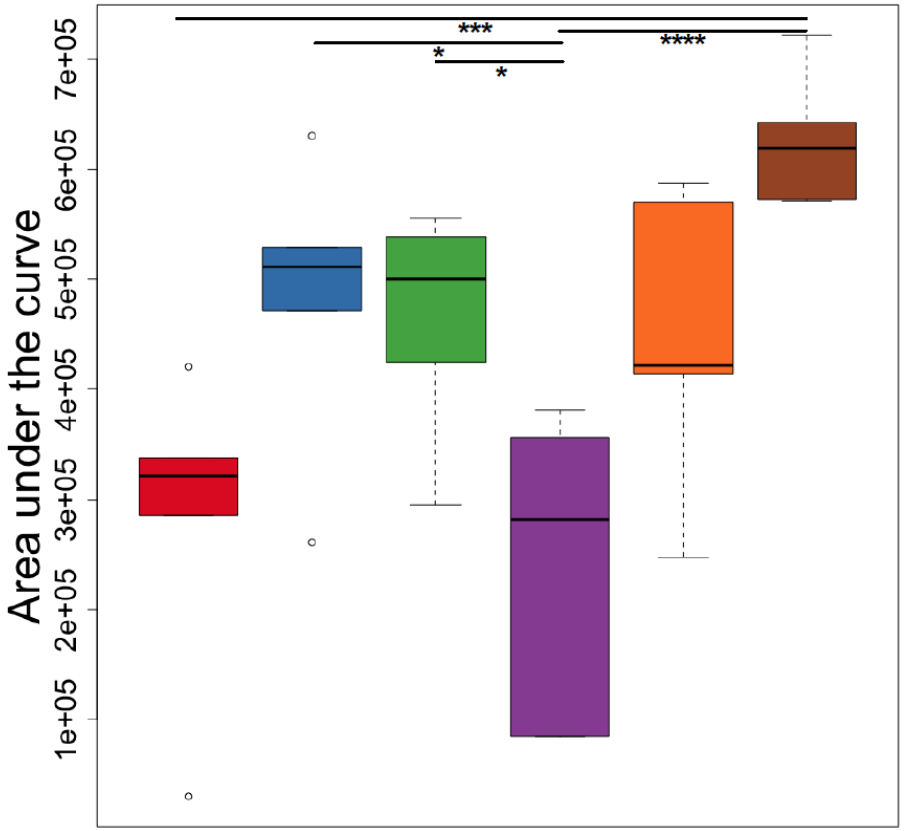


Differences between high and low responders (d1>d0) at the modular level



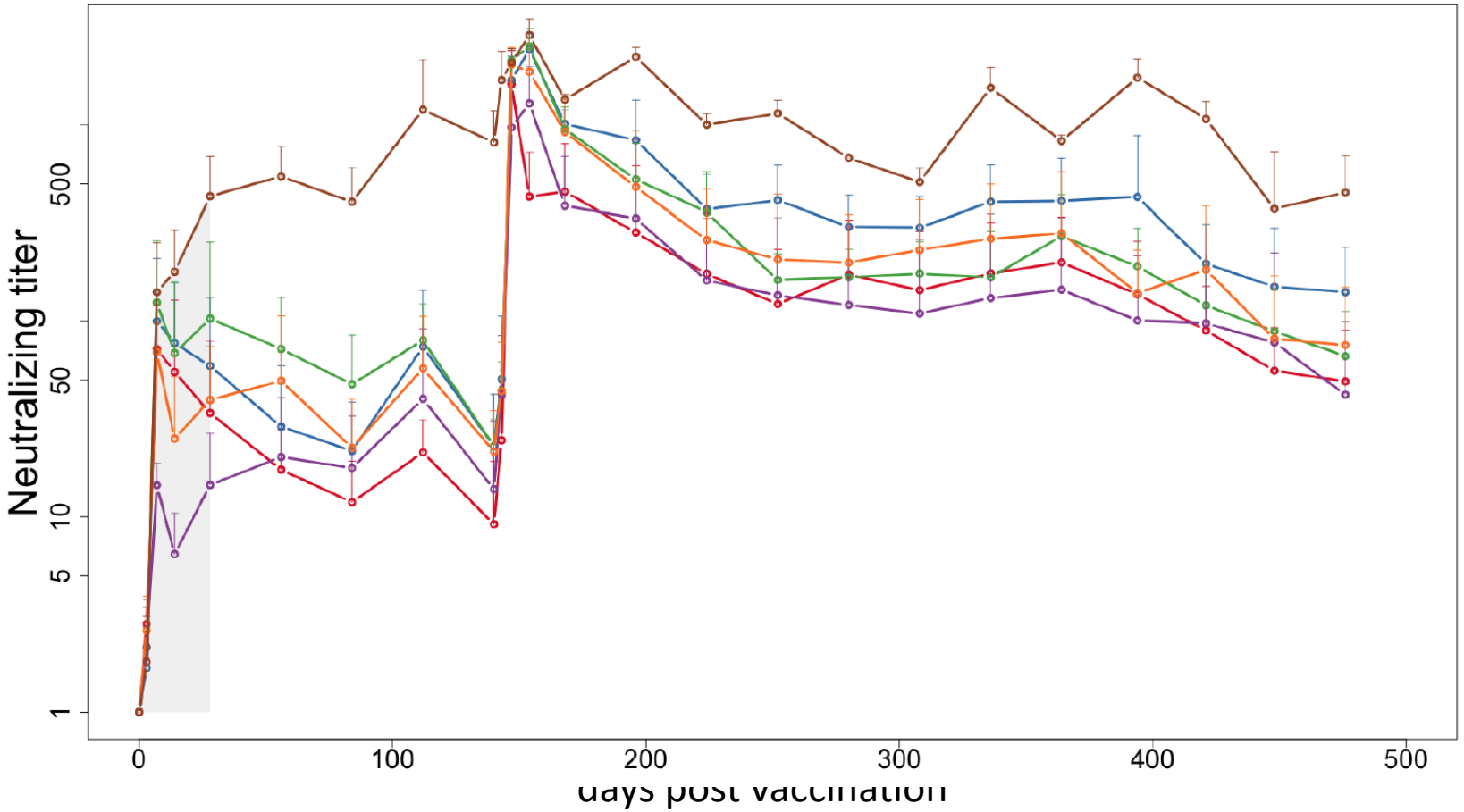
Back to FMDV: DOI

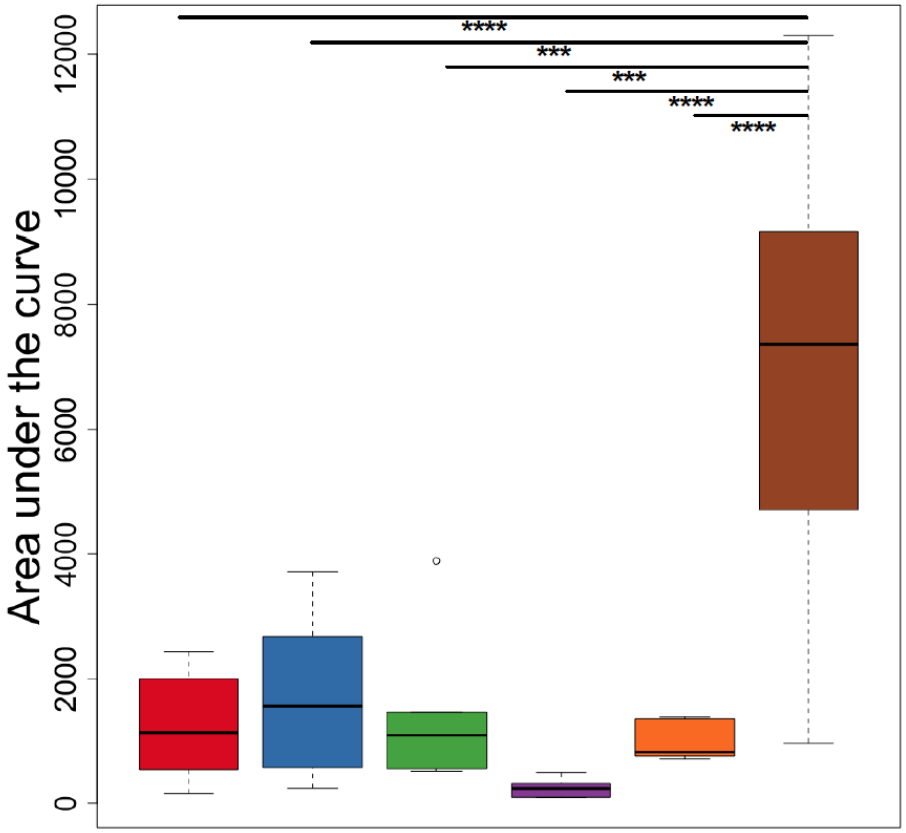




Liposome_MPLA
Liposome_Gard/CpG
Liposome_Gard/MPLA
146S in PBS
Liposome
Montanide ISA 201 VG

Back to FMDV: emergency response





Liposome_MPLA
Liposome_Gard/CpG
Liposome_Gard/MPLA
146S in PBS
Liposome
Montanide ISA 201 VG

Summary

1. Systems vaccinology can help to identify innate correlates and biomarkers of good vaccines and dissect the impact of vaccine components and their formulations on the immune system and thereby help to identify improved delivery systems and immunostimulants
2. We can employ peripheral blood samples collected early after vaccination to better understand immune responses
3. Early innate immune responses indeed dictate late adaptive responses
4. We can identify of pathways responsible for the heterogeneity in vaccine responses (impact of age, nutrition, stress, genetics)
5. Montanide-based vaccines induce rapid, high and long-lasting neutralizing antibodies in sheep
6. Addition of TLR ligands to a liposomal vaccine did not enhance the duration of immunity

Acknowledgments

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„Strengthening Animal Production and Health through the Immune Response“

Topics of Session 4 Pathogenesis and Immunology

Immunology

Innate immunity:

- RIPK3 and its role in the cellular antiviral response (oral)
- Interaction of FMDV with bovine dendritic cells (poster)

Adaptive immunity:

- Neutralizing antibody response: epitopes (poster)
- Antibody response and pathogenesis in goats (poster)
- Difference in antibody response against empty capsids (75S) and 146S FMDV particles (oral)

Topics of Session 4 Pathogenesis and Immunology

Pathogenesis

- Impact of peculiar mutations in the capsid on virulence in a mouse model (oral)
- Pathogenesis in cattle after multiple infections (oral)
- Possible role of CXCL15 and neutrophil recruitement in FMDV carriers (poster)

Topics of Session 4 Pathogenesis and Immunology

Epidemiology

- Seroepidemiology of FMDV in Georgia (poster)
- Decision support system for Australia (poster)
- FMD control and prevention strategies in Thailand (poster)
- FMDV evolution in Thailand (poster)
- FMD in Nigeria (poster)