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► To cite this version:

Aude Remot, Guillaume Sallé, Cécile Ferret, Mégane Fernandez, Florence Carreras, et al.. Immunostimulation of bovine neonate immune cells : metabolomic and transcriptomic responses. Journées d'animation scientifique du département Santé Animale (JAS SA), Oct 2022, Anglet, France. hal-04172281

HAL Id: hal-04172281

<https://hal.science/hal-04172281>

Submitted on 27 Jul 2023

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Immunostimulation of bovine neonate immune cells : metabolomic and transcriptomic responses



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Immunometabolism is an emerging research field that explores the dynamic interactions between bioenergetic metabolic pathways and cells of the immune system. This approach brings a new dimension in our understanding of host defenses against infection. Although being a rapidly expanding field in human health, immunometabolism remains very little explored in cattle.

The **Metabov project** ("SA Incitatif" grant) combines immunology and bioinformatic expertises in order to investigate this new field of research in livestock and at young age, a critical period to develop immunostimulation strategies and increase resistance to infections.

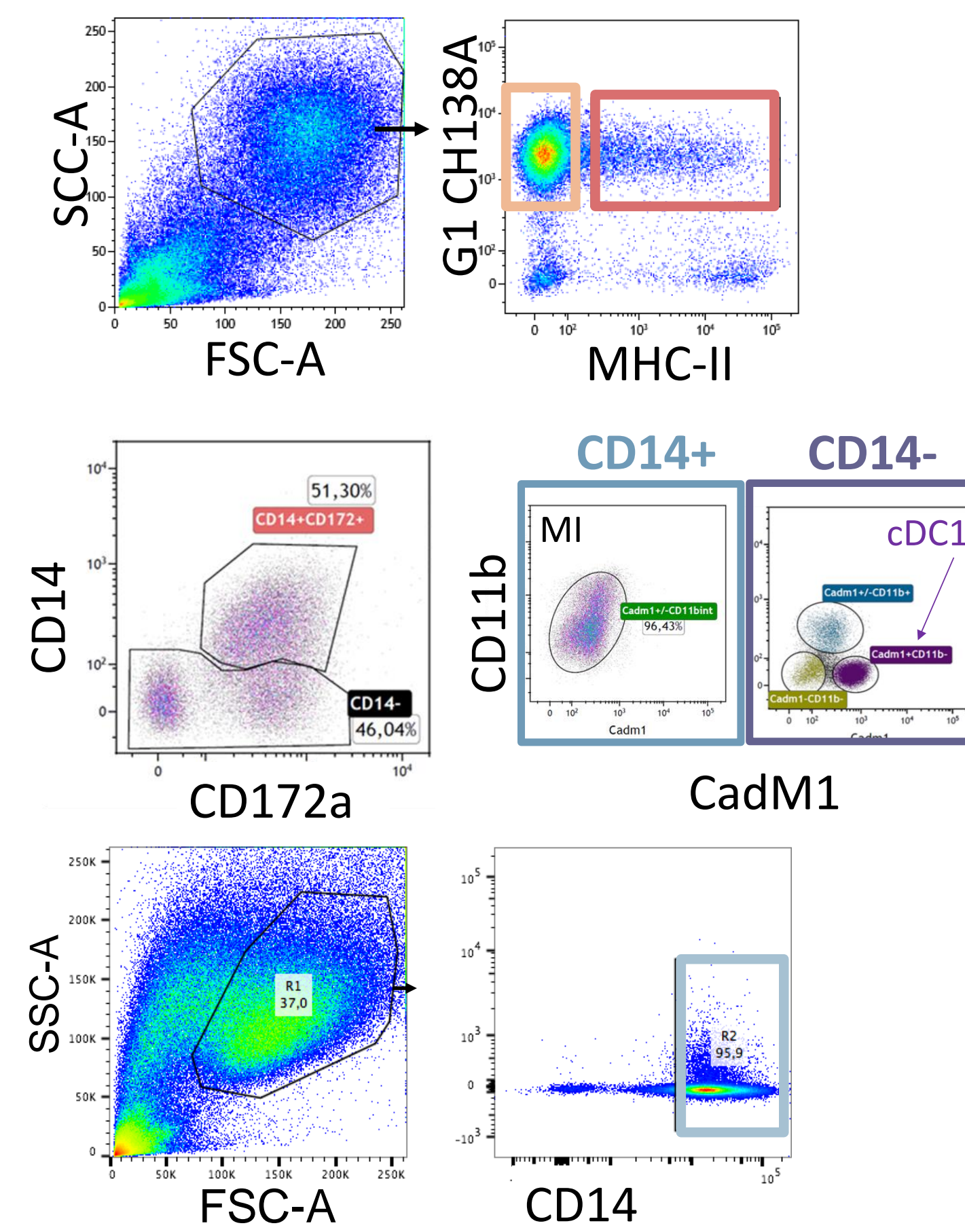
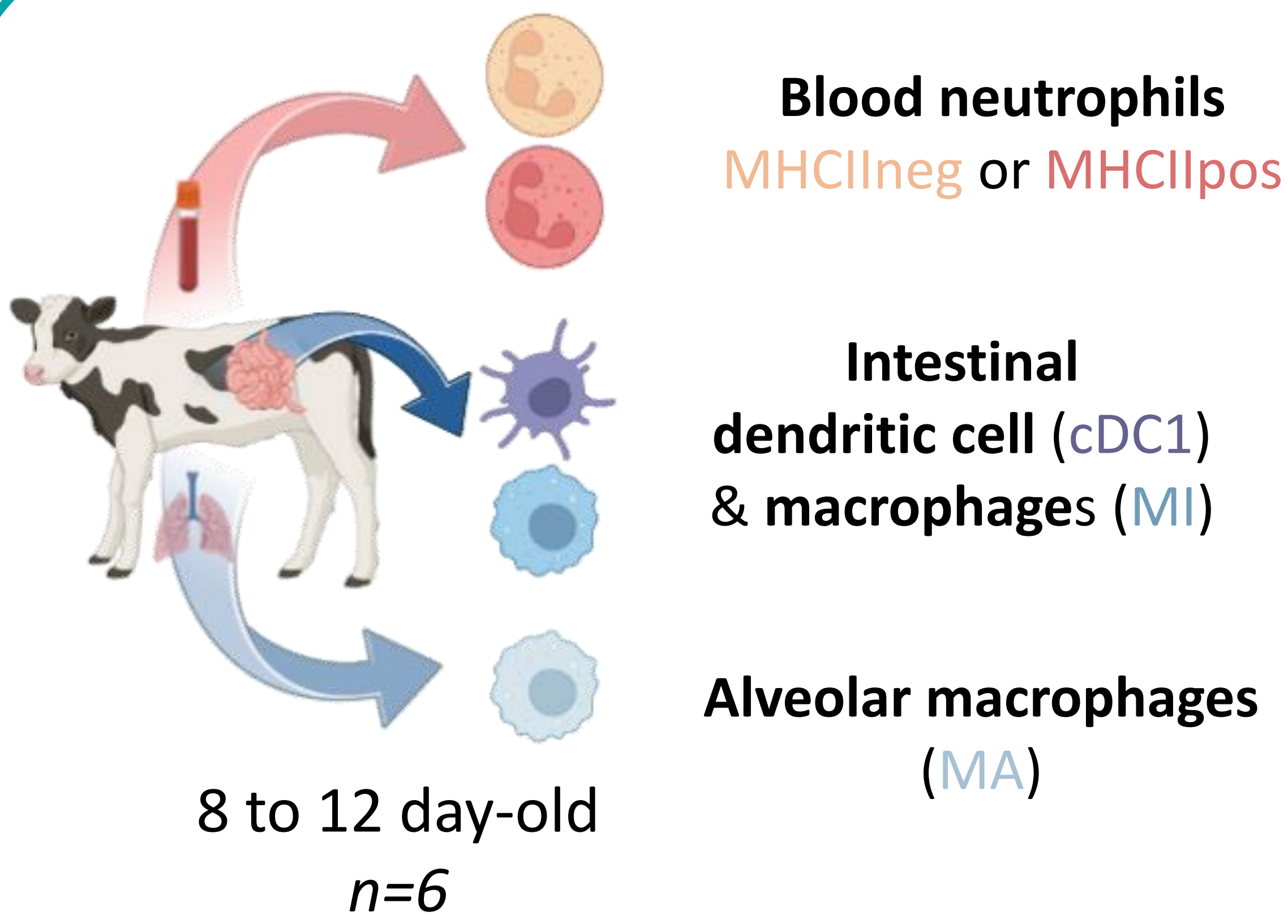
Objectives

Improve knowledge of innate immune cells of calves

Deeper characterization at steady state

Identification of metabolic pathway(s) involved in reprogramming

Define biomarkers of inflammatory or regulatory cells



Methods

10⁵ cells / condition

2 hours of stimulation in the same culture medium

- **BCG** Bacille de Calmette et Guérin
- **bRSV** bovine Respiratory Syncytial Virus
- **CL429** TLR2-NOD2 ligand

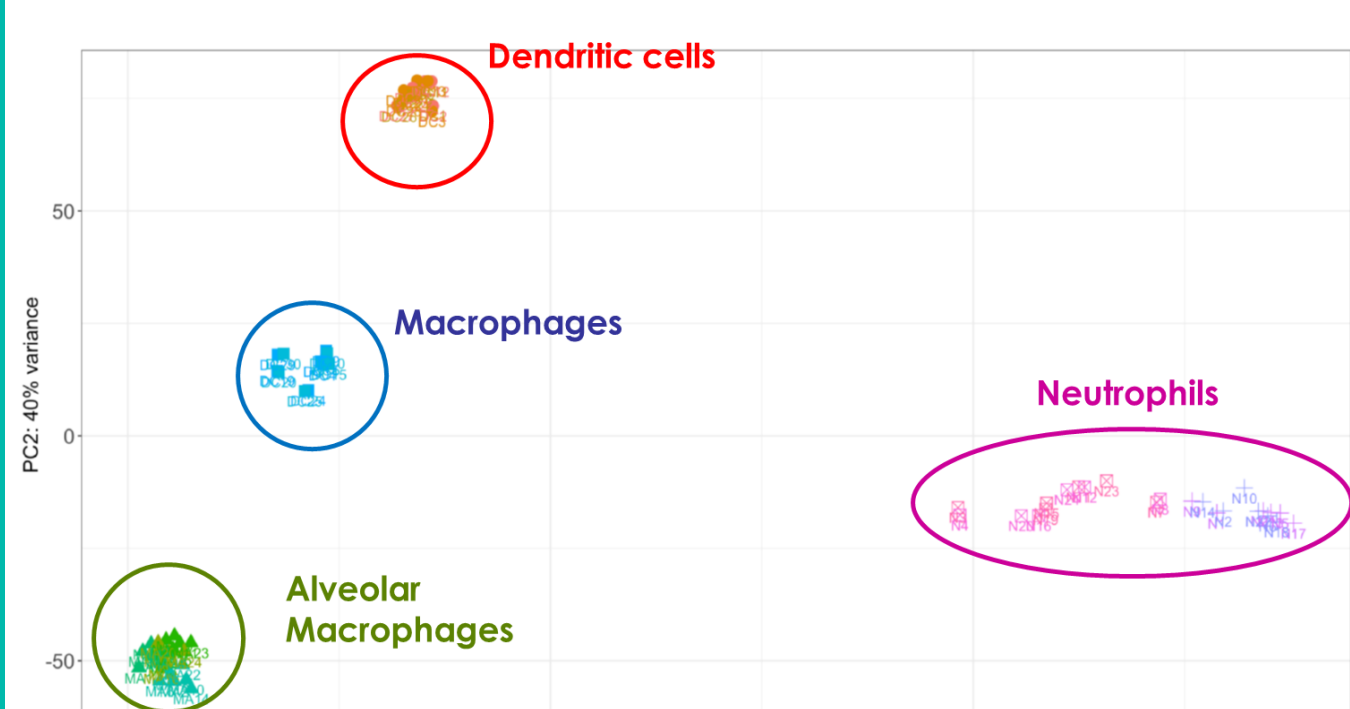
Mix-omics

- **RNAseq** (cells)
- **Metabolomic** (supernatant)

Results

RNAseq : unique signatures for each cell populations

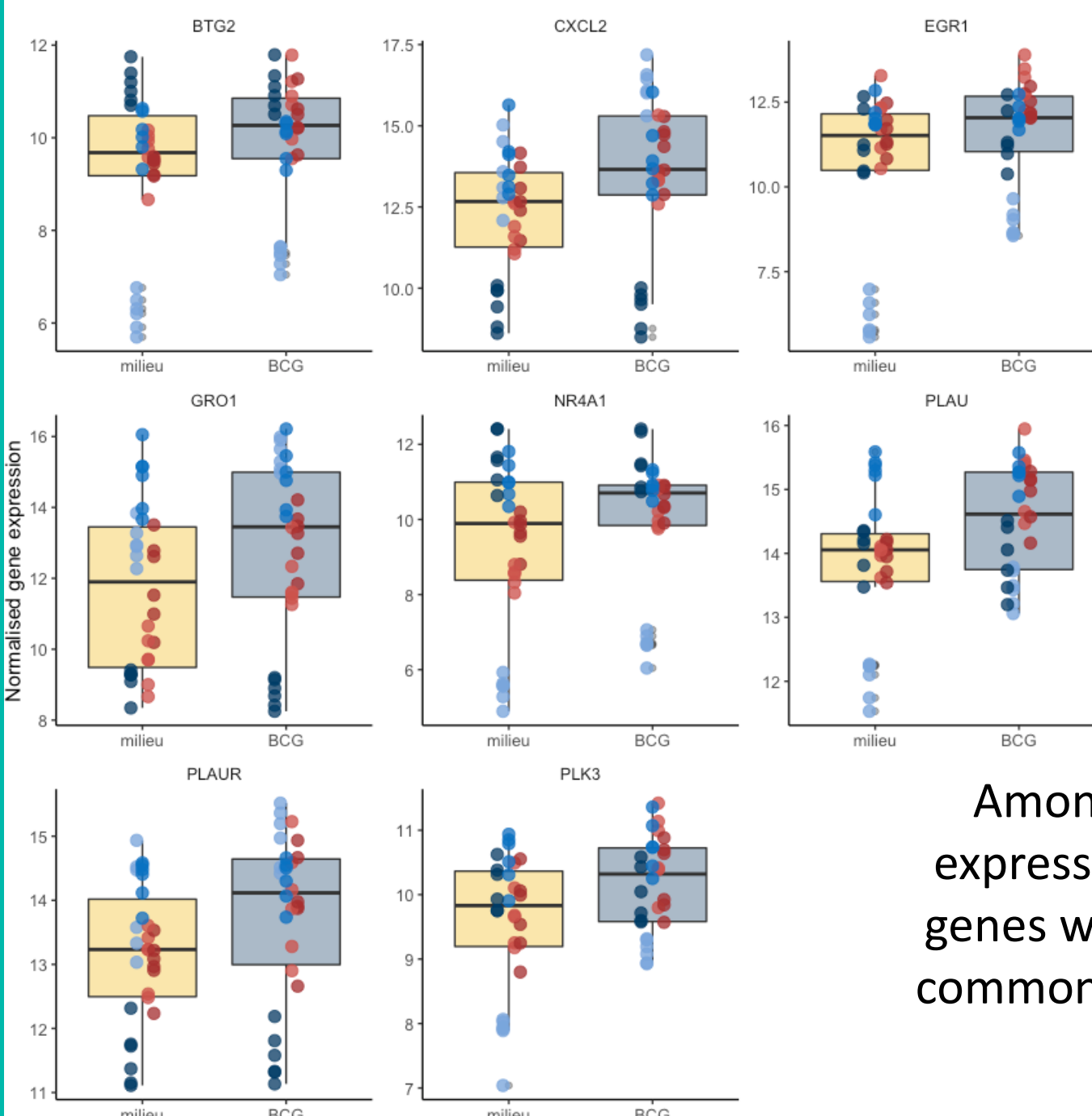
1- Principal Component Analysis



Transcriptomic data illustrated as ACP graph (1) and heat-map (2) reveals :
- a unique signature of each cell population
- The close relationship between the populations that can illustrate shared functions.

3- Common response to BCG

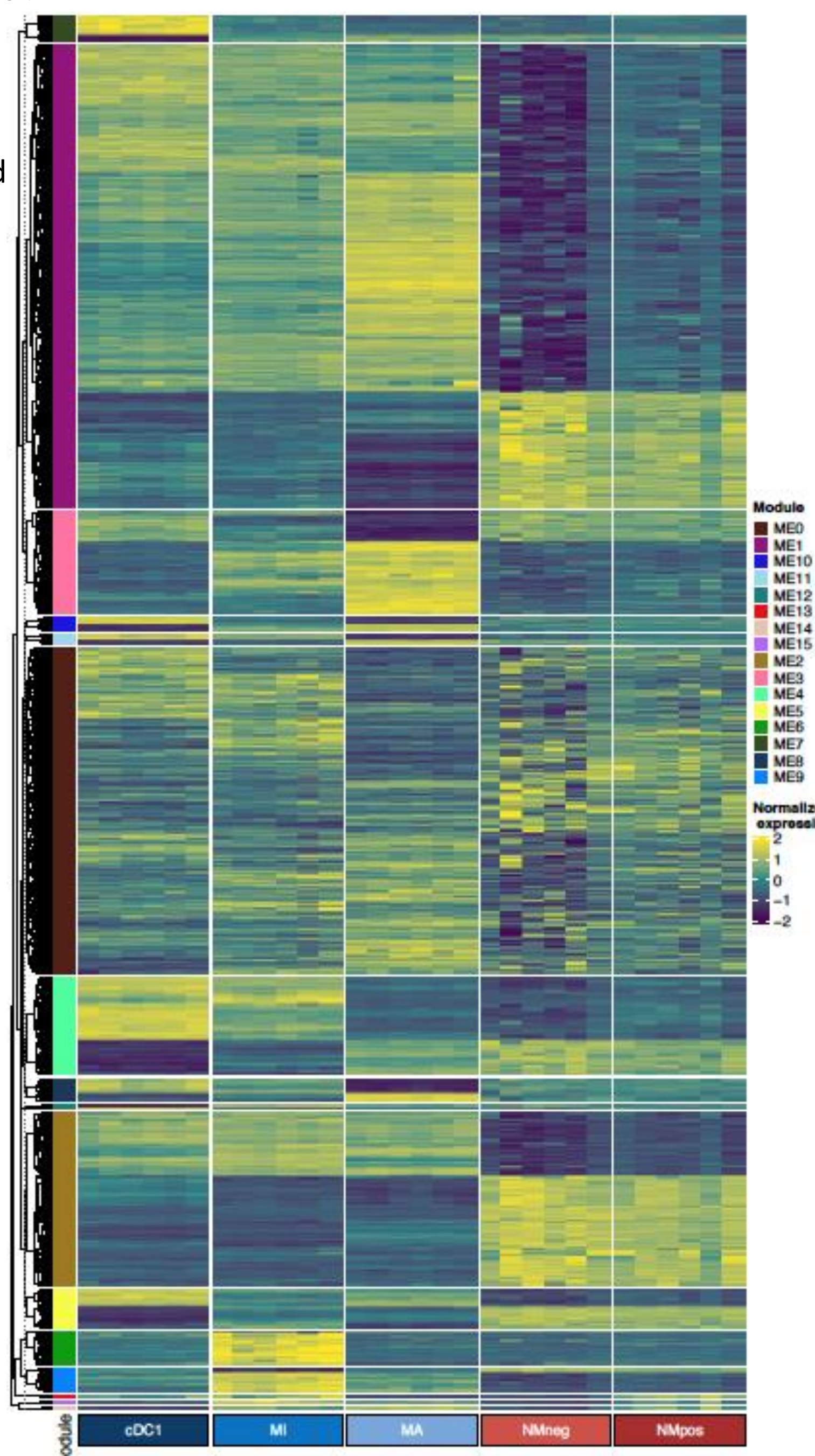
BCG was used as a common stimulant to compare transcriptomic responses of the different calf innate immune cells.



Among the genes differentially expressed after BCG stimulation, 8 genes were differentially expressed commonly by the 5 cell populations.

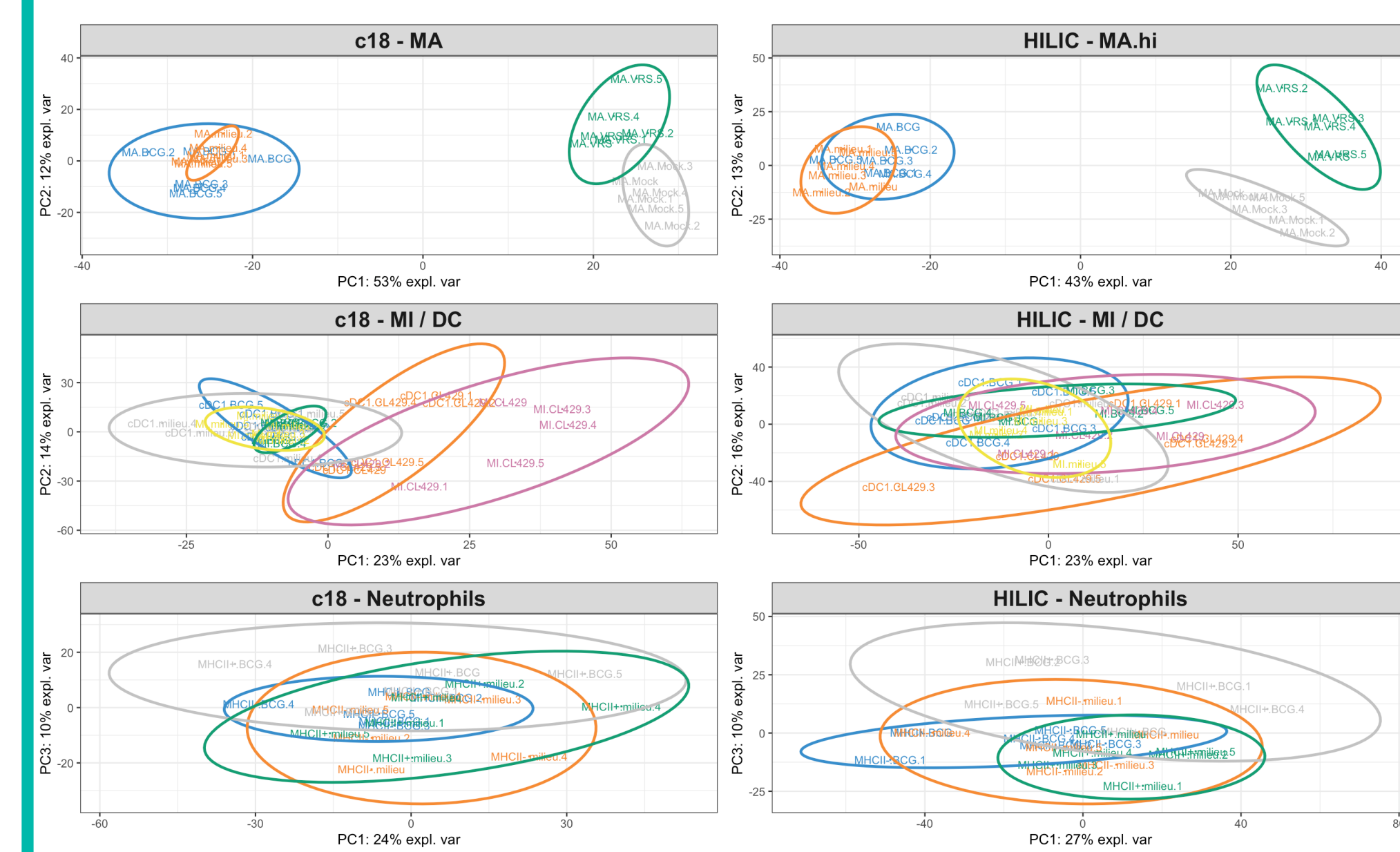
- These genes are involved in inflammation (PLK3, GRO1, CXCL2), in the cell cycle (BTG2, PLK3) and are known to be rapidly induced after stimulation (NR4A1, EGR1).
- Deeper analysis of transcriptomic data are ongoing.

2- Modules of differentially expressed genes



Metabolomic (LC-MS)

From culture supernatants, hydrophobic metabolites were measured with C18 column and hydrophilic metabolites with HILIC column.



- The stimulation of innate immune cells to modify the metabolites' production is more efficient in alveolar macrophages (MA), whatever the stimulant used.
- In intestinal cells (MI, DC), the stimulation of NOD2 and TLR2 is modifying metabolites' production but in a lesser extent compared to AM.
- Neutrophils poorly respond to stimulant at the level of metabolites' production.
- No common response to BCG is observed between the different cell types.

Perspectives:

- Deeper analysis of transcriptomic and metabolomic responses
 - by each cell type
 - by similar cells (MA/MI and DC/MI)
- Analyse of Mix-Omics data will be performed to identify pathways (specific to subsets or ligands).