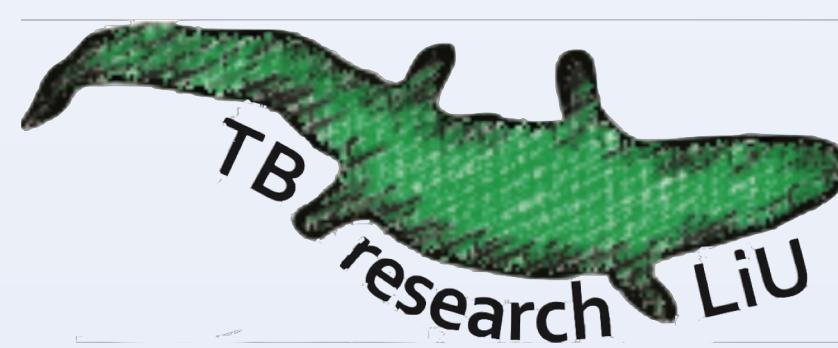


Identification of DNA methylation patterns predisposing for a trained immunity response to BCG vaccination in healthy BCG-naïve subjects



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AIM: *In-silico* identification of differentially methylated patterns in response to BCG vaccination in BCG pre-exposed healthy subjects.

Purpose: To understand the cellular defense mechanism against the mycobacterial infection at the epigenetic level (i.e., DNA methylation) and to recognize the possible bio-signatures.

In a previous study¹, we observed that macrophages from a subset of subjects vaccinated with the TB vaccine, Bacille Calmette-Guérin (BCG), displayed an enhanced anti-mycobacterial response. In response to the vaccine, the immune cells isolated from these “responders” concomitantly showed an altered DNA methylation pattern enriched in immune pathways, suggesting the induction of trained immunity. In responders, we also observed the effective production of IL-1 β in response to mycobacterial stimuli of macrophages at the time point before BCG vaccination, suggesting that the cells were pre-conditioned to mount a proper response towards mycobacteria.

Methods

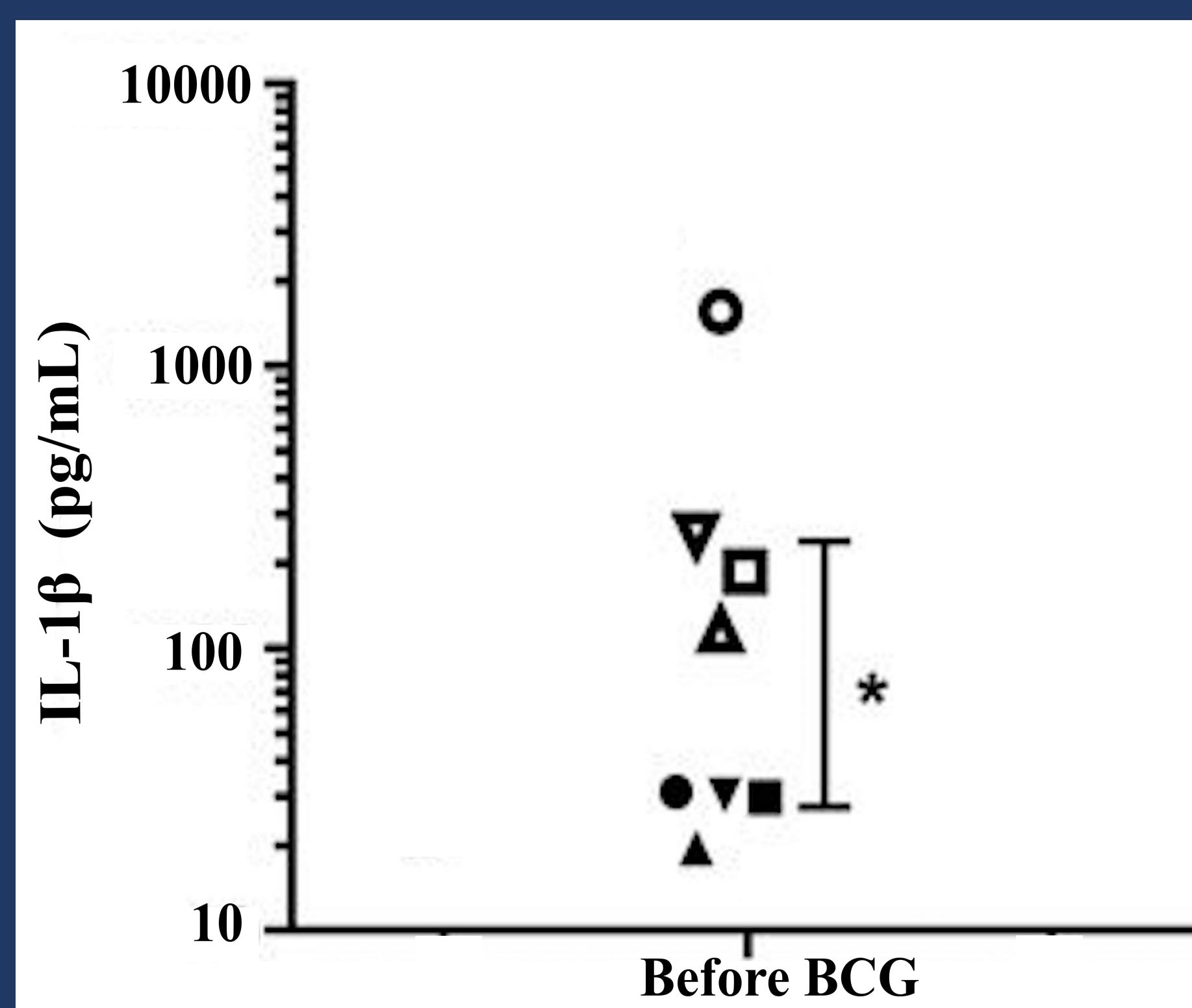
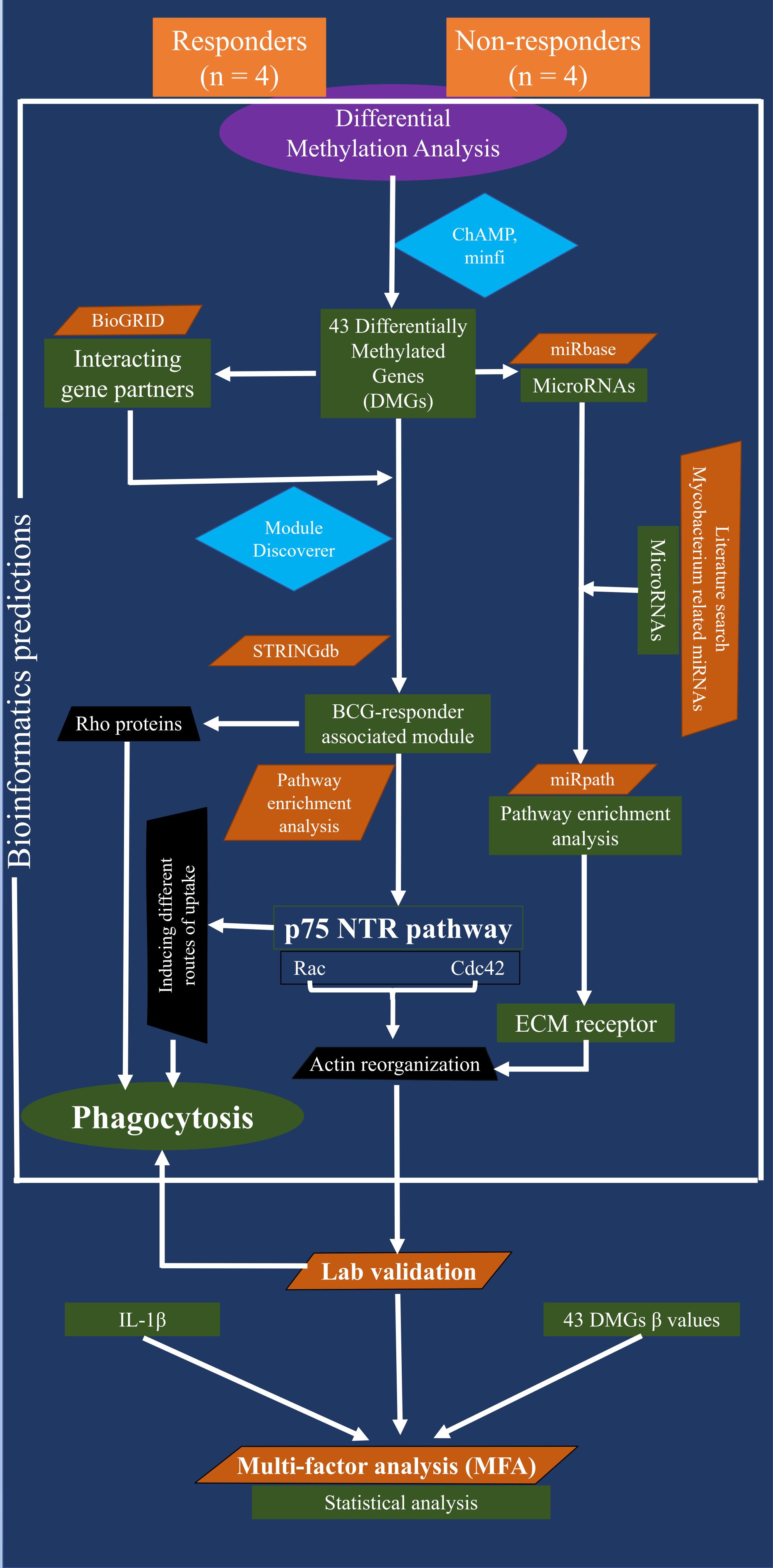


Figure 1: The amount of IL-1 β production before the BCG vaccination in 8 healthy samples. P -value < 0,05

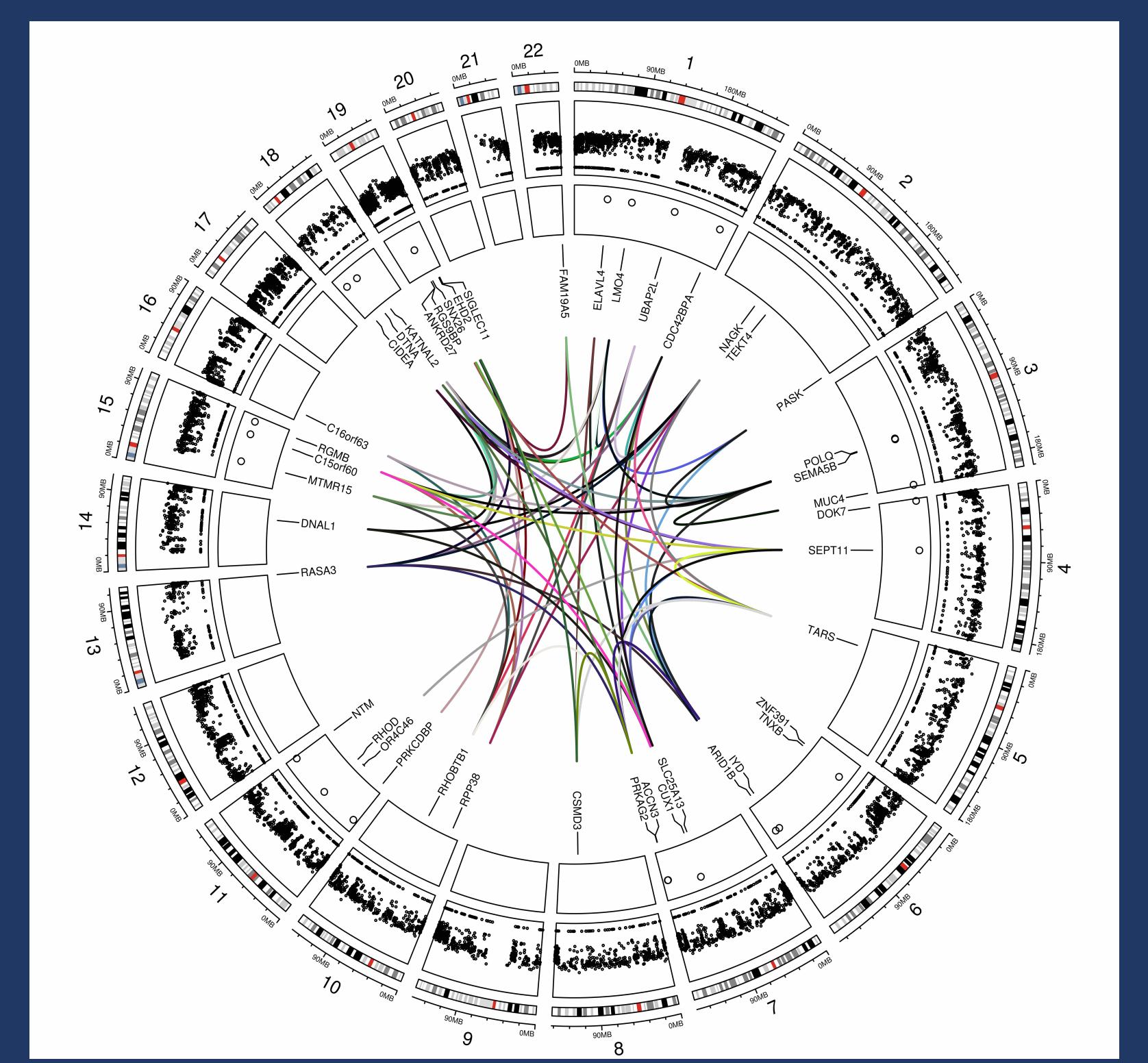


Figure 2: Chromosomal positions² and interconnections among 43 DMGs.

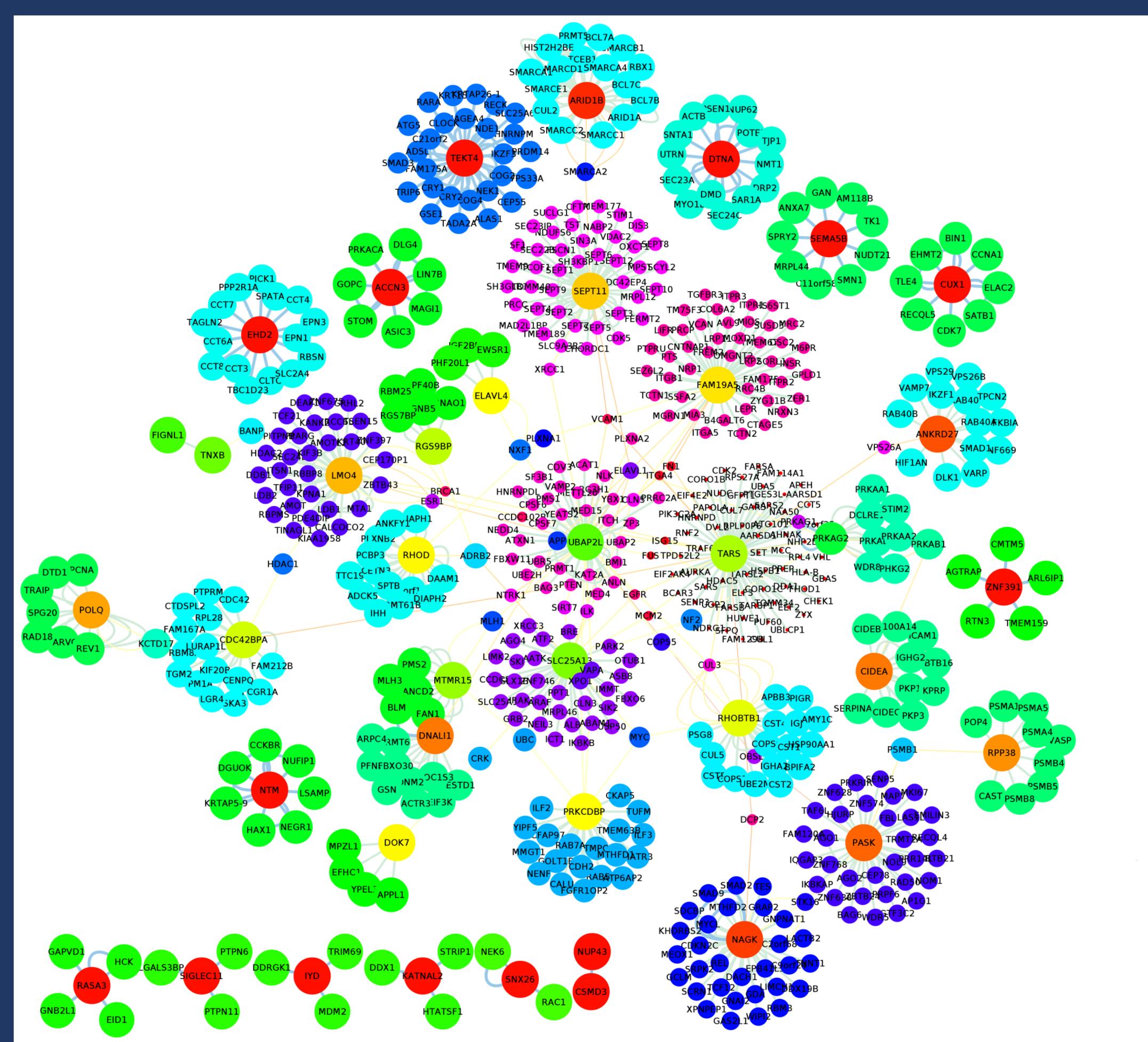


Figure 3: The Gene-Gene interaction network (GGIN) between 43 DMGs and their first interacting partners, painted in Cytoscape.

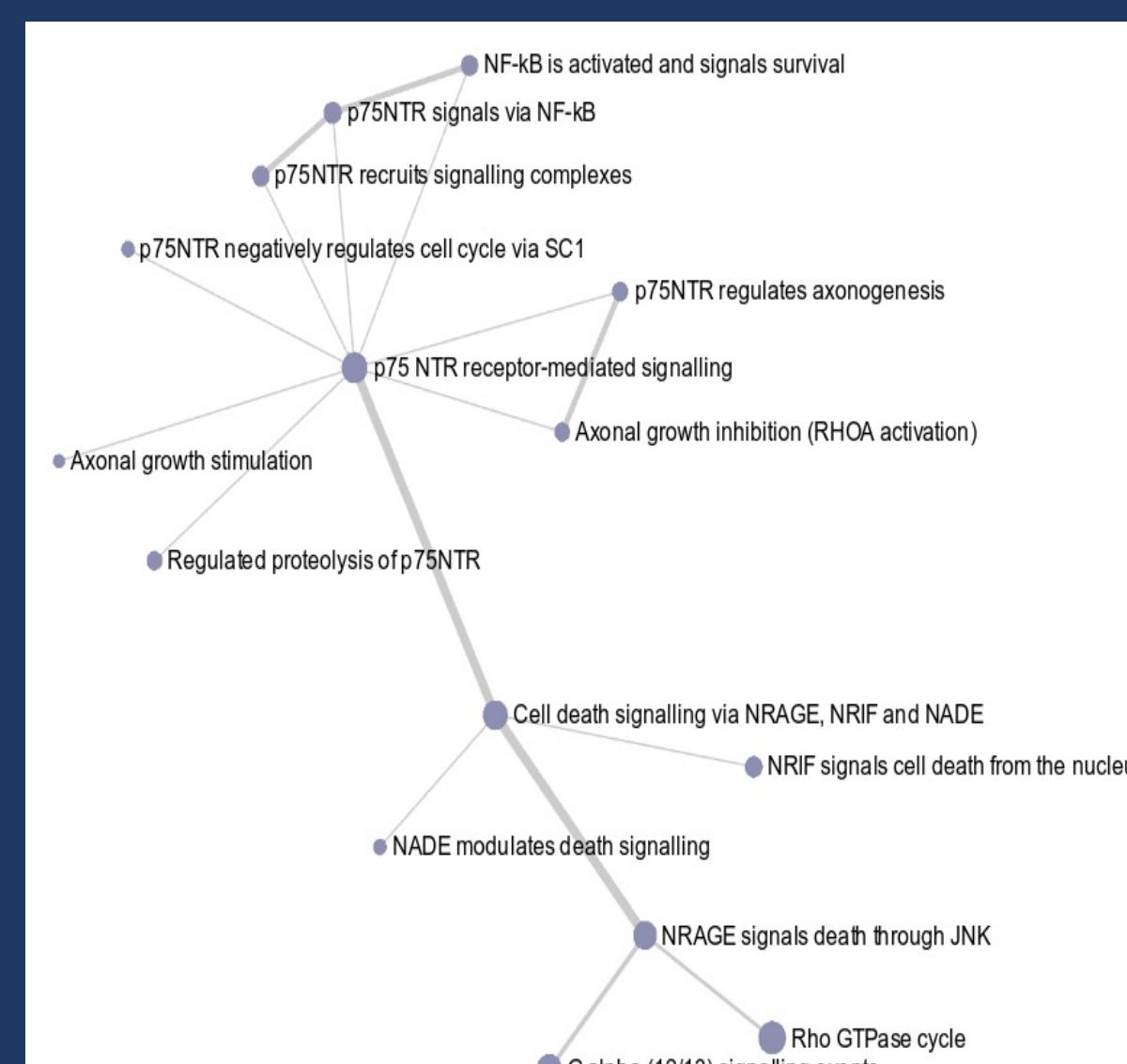


Figure 4: Pathways related to BCG-responder module

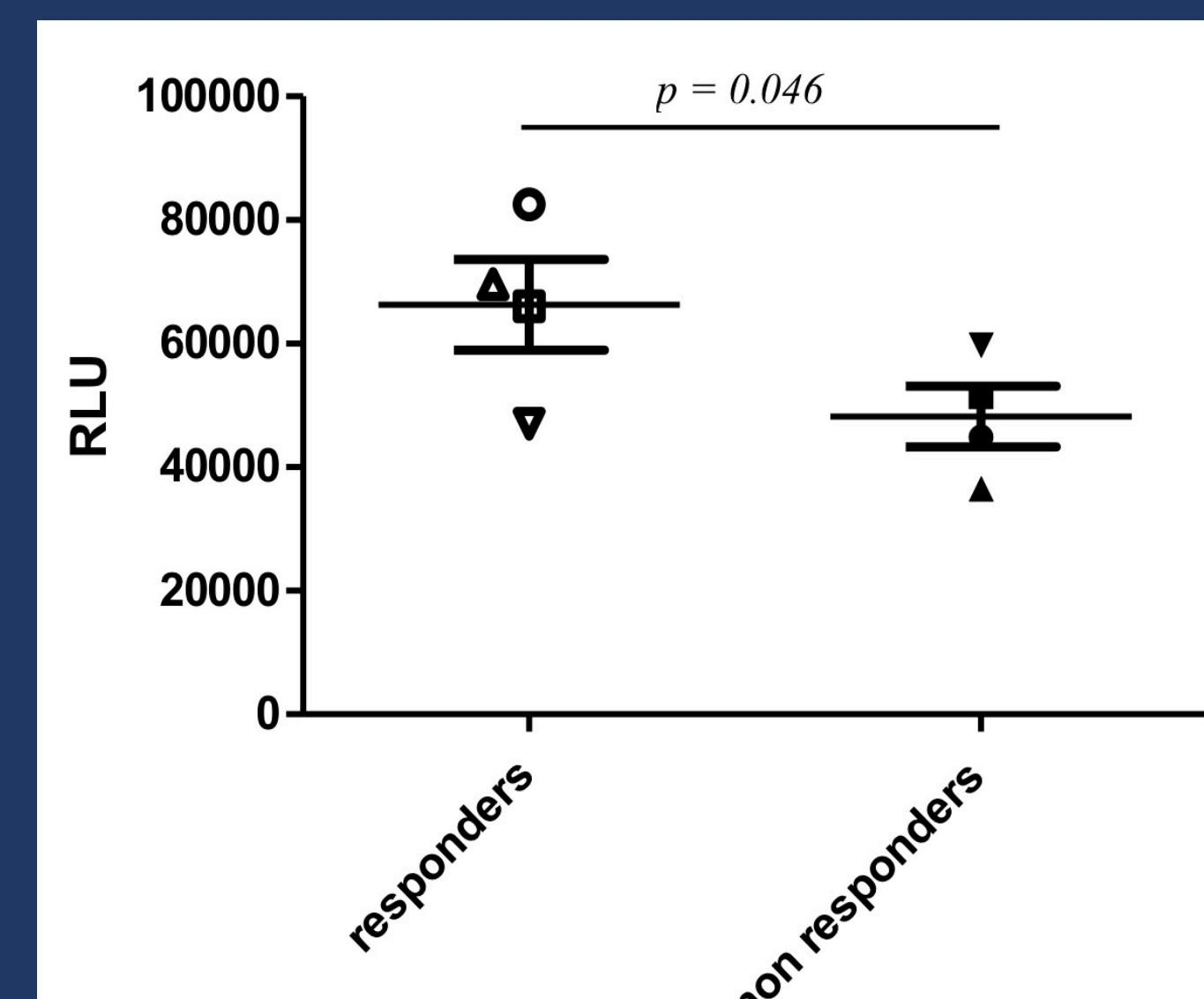


Figure 5: Laboratory data showed significant difference in phagocytosis between responders and non-responders

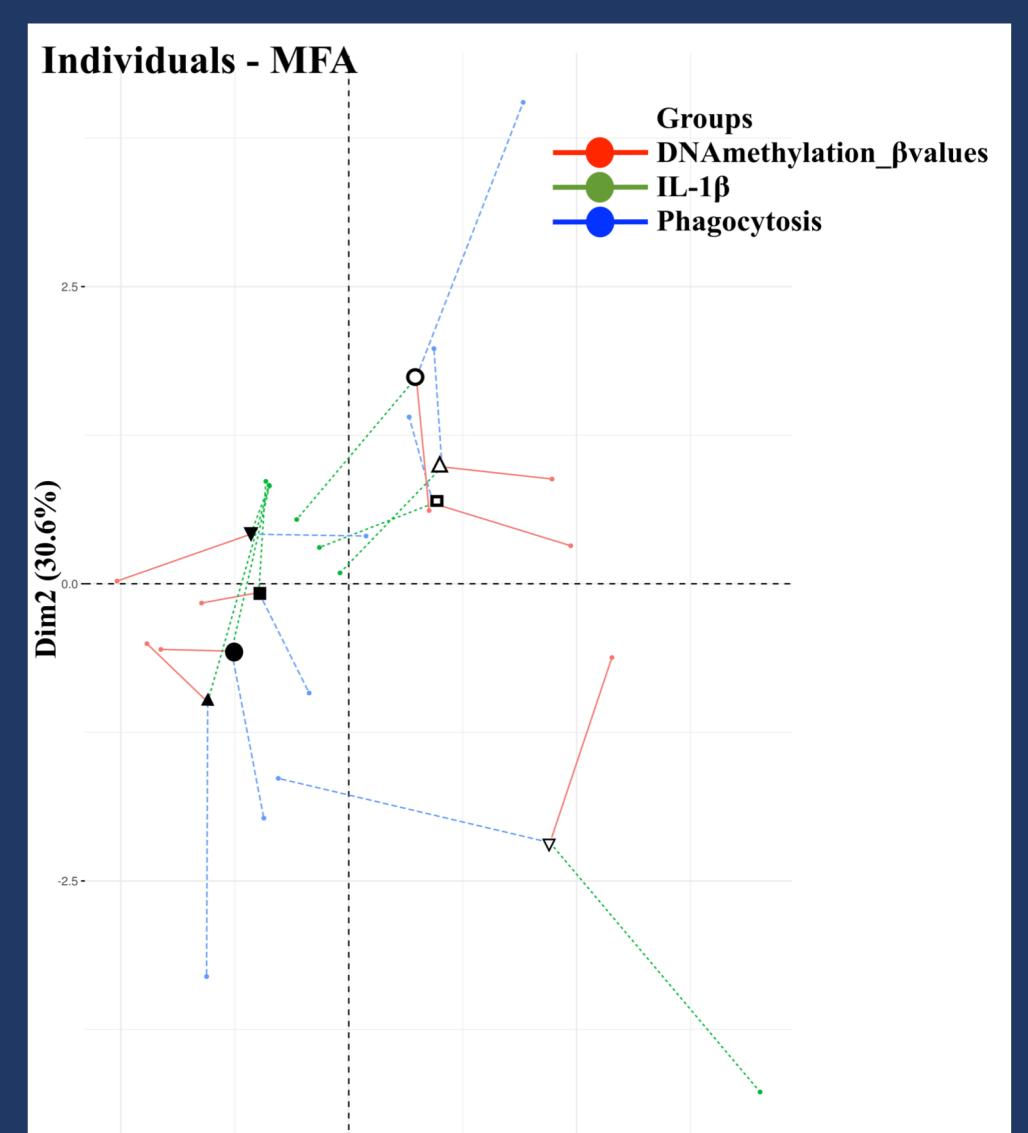


Figure 6: MFA using three determinants, IL-1 β , DMG β values, and phagocytosis

Conclusions

- We were able to identify 43 DMGs that discriminate those who are later responding to BCG vaccine from those who are non-responding.
- A search for a BCG-responder specific module enriched in these DMGs pointed towards phagocytosis as a potential mechanism of macrophages derived from responders and non-responders.
- Assessment of phagocytic capacity showed that responders macrophages are superior in mycobacterial uptake.
- Statistical analysis of all DMGs, IL-1 β release and phagocytosis showed that phagocytosis is more strongly correlated with DMGs than with the IL-1 β , suggesting that IL-1 β is secondary to phagocytosis responses.