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Stellingen behorend bij het proefschrift

**Regulatory, pro-inflammatory and inhibitory human T-cell responses to *M. bovis* BCG**

**Opposing T-cell forces in TB-vaccination**

1. The predominant induction of CD8\(^+\) instead of CD4\(^+\) regulatory T-cells by live *M. bovis* BCG, both in cells from *in vitro* PPD-responsive donors, as well as BCG-vaccinated adults, has been overlooked thus far, and may represent an important negative modulator of BCG vaccine-induced immunity against TB [this thesis].

2. The ectoenzyme CD39 is an essential constituent of the suppressive machinery of BCG-induced CD8\(^+\) regulatory T-cells, since only CD8\(^+\)CD39\(^+\) T-cells, but not CD8\(^+\)CD39\(^-\) T-cells, suppress T-helper 1 cell activity [this thesis].

3. BCG-vaccination of BCG-naive, TST-negative, QuantiFERON-negative healthy adults induces unexpectedly dichotomous responses, being either pro-inflammatory or CD8\(^+\) regulatory T-cell dominated [this thesis].

4. The inhibitory marker KLRG1, but not PD-1, marks non-proliferating T-cells following BCG-vaccination, and could – analogous to murine TB-vaccine studies – imply poor immunity against TB [this thesis].

5. Skin inflammation of the BCG-vaccine lesion, as quantified by classical clinical symptoms of inflammation, as well as serum CRP early after vaccination, is associated with the induction of pro-inflammatory cytokines and polyfunctional CD4\(^+\) T-cells by BCG-vaccination; these inflammation markers that are ‘classical’ in clinical medicine may be used as ‘non-classical’ indicators of vaccine-induced immunity [this thesis].


7. Next to measuring effector responses such as T-helper 1 immunity, it is important to measure other types of responses such as regulatory responses induced by vaccination, since the outcome of vaccination will be dictated by the balance of all these responses rather than a single response [Griffiths et al. *PLoS One* 6: e23463, 2011].

8. The expression of inhibitory receptors by T-cells, and pathogen-driven expansion of regulatory T-cells, are distinct mechanisms that both lead to reduced T-cell activity: targeting both inhibitory receptors and regulatory T-cells in new combination therapies is a promising strategy to treat chronic infectious diseases [Dietze et al. *PLoS Pathog.* 9: e1003798, 2013].

9. ‘It is at the interface of different disciplines, such as the intersection of Medicine and Immunology, that scientists should co-operate and discoveries with impact can be made’ [Prof. Tom H.M. Ottenhoff, *CID seminar Vaccines and Vaccination*, LUMC, 2012].

10. ‘The only thing greater than the power of the mind is the courage of the heart’ [A Beautiful Mind, Universal Studios, 2001; *(tribute to)* John Nash].

- Mardi C. Boer-