# The power of help: mechanistic insights into CD4$^+$ T cell differentiation in vaccination and cancer

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Stellingen behorend bij het proefschrift getiteld:

# The power of Help:

## Mechanistic insights into CD4⁺ T cell differentiation in vaccination and cancer

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1. CD4⁺ T cells in infection, cancer and vaccination pass through a non-committed Th1/Tfh precursor state prior to bifurcation into the mature Th1 or Tfh cell state *(Lönnberg et al. Sci. Immunol., 2017; Cardenas et al. Nature 2024; this thesis).*
2. Polyclonal CD4⁺ T Th1/Tfh precursor cells are clonally related to Th1 and Tfh cells and undergo a multistep differentiation program that depends on sequential interactions with distinct APCs and multiple costimulatory molecules *(this thesis).*
3. MoDC optimize both CD4⁺ and CD8⁺ T cell effector differentiation *(Leal et al. Sci Immunol., 2021; de Koker et al Sci. Rep., 2017; this thesis).* Activated CD4⁺ T cells promote MoDC generation via CD40L and IFNγ, creating a feedforward loop that enhances MoDC induction and T cell effector function *(this thesis).*
4. CD4⁺ T cell help to cDC1 is critical to promote anti-tumor immunity *(Lei et al. Nat Commun 2023)*, but antigenicity or immunogenicity does not equal CD4⁺ T cell help delivery in tumor contexts *(Hos et al. Cell Rep, 2022; this thesis)*.
5. Understanding how the immune cell composition in tumors affects activation of conventional and regulatory T cells in response to treatment is essential for rational design of combination therapy *(this thesis).*
6. A detailed molecular understanding of how different immune-checkpoint therapies such as PD-1 and PD-L1 blockade work is required to optimize treatment outcome and to develop improved combination strategies *(Borst et al. Eur. J. Immunol., 2021*; *Zhao et al. Immunity, 2019)*.
7. While murine *in vivo* model systems remain indispensable, it should not be neglected that specific pathogen free mice have an immune system composition similar to newborn rather than adult humans *(Beura et al. Nature, 2016)*.
8. CD4⁺ T cell differentiation states should be defined by functional characteristics rather than transcriptomic markers alone, to better distinguish Tfh differentiation from CD4⁺ T cell exhaustion in cancer and infection *(This thesis).*
9. *"Facta non verba"*; Scientific conclusions should be confirmed with experimental evidence rather than assumptions or prevailing dogmas. Too often, cellular functions are inferred from limited molecular data instead of being rigorously tested, or results are dismissed because they challenge existing models.
10. *"Als de bami niet te eten is, kan je beter de pan uit het raam gooien" (saying from Rotterdam)*. If something is not working, it is better to stop and rethink or to optimize the process than to keep repeating the same experiment and expecting different results.