

## Stellingen behorende bij het Proefschrift

# “Normal and aberrant TCR $\gamma\delta$ + T cells and T cell large granular lymphocyte leukemia”

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1. Ageing and CMV persistence collectively cause maturation of the TCR $\gamma\delta$ + T cell population to late differentiated effector cells with increased V $\delta$ 1 and exhaustion marker expression. *This thesis.*
2. Immunosenescence does not influence the TCR repertoire of naive TCR $\gamma\delta$ + T cells, but narrows TCR diversity of the antigen-selected memory TCR $\gamma\delta$ + T cell population. *This thesis.*
3. Contrary to CD8+TCR $\alpha\beta$ + T-LGL leukemia, the higher TCR homology in TCR $\gamma\delta$ + T-LGL leukemia would be suggestive of a common underlying (auto)antigen. *This thesis.*
4. TCR $\gamma\delta$ + T-LGL leukemia cells originate from antigen-experienced normal circulating TCR $\gamma\delta$ + T cells, which – upon a persistent immune response – have undergone a shift towards increased proliferation and survival. *This thesis.*
5. STAT3 plays a central role in LGL leukemogenesis, but this is not explained by exonic mutations only. *This thesis.*
6. A “grey zone” or TCUS where the diagnosis of LGL leukemia is not certain, should be considered in cases of low-LGL count combined with lymphopenia and unexplained cytopenia. *Adapted from T. Lamy et al. Blood* **129**, 1082-1094 (2017) & A.W. Langerak et al. *Br. J. Haematol.* **123(3)**, 561-562 (2003).
7. NGS technology has evolved such that limitations are addressed in complex algorithms, upon which quality has increased exponentially for application with high reproducibility in multicenter diagnostic settings. *Adapted from S. Yohe & B. Thyagarajan, Arch. Pathol. Lab. Med.* **141(11)**, 1544-1557 (2017).
8. Uptake of recombinant glucocerebrosidase in Gaucher’s disease is presumably mediated by the mannose-receptor on macrophages. *Adapted from the thesis of dr. W.W. Kallemeijn (2014).*
9. The ancestral New-Antigen Receptor V-gene forms the basis for Igs and TCRs and is hypothesized to have recombined with the TRDV in sharks >200 million years ago, indicating that TCR $\gamma\delta$  molecules have a long evolutionary history of recognizing free antigen. *Adapted from M.F. Criscitiello et al. PNAS* **103(13)**, 5036-5041 (2006).
10. It is completely unjustified that immunology teaching still pays little attention to  $\gamma\delta$  T cells. *Adapted from P. Vantourout & A. Hayday, Nat. Rev. Immunol.* **13**, 88-100 (2013).
11. Als iedereen hetzelfde doet, denkt men niet na. *Adapted from papa & “If everyone is thinking alike, then somebody isn’t thinking” from General George S. Patton (1885 – 1945).*