

Stellingen behorend bij het proefschrift:

Connecting B Cell Differentiation Pathways And Antibody Deficiencies

1. B cell precursor differentiation is not a single linear route of differentiation, but rather a complex process of V(D)Jrecombination-driven checkpoints, divergence, parallel pathways and convergence to form a unique and functional B cell receptor. Understanding this process requires an integrated approach of single-cell DNA, RNA and protein analysis. *(this thesis)*

2. Concerning B-cell receptor repertoire in primary antibody deficiencies: diversity of the naive IGH repertoire is normal in almost all CVID patients, but in patients with CD19-complex deficiencies and in some patients with PTEN or PI3K δ mutations the antigen experienced repertoire is reduced. *(this thesis)*

3. In CD21 deficiency hypogammaglobulinemia and impaired memory formation result from a defect in signaling threshold rather than from an intrinsic inability to form memory cells, whereas in CD19 and CD81 deficiency the clinical syndrome can be attributed to a defect in the early phases of B-cell memory formation. *(this thesis)*

4. Mutations in PI3K δ lead to disturbed B-cell memory formation and effector function, which contribute to the hypogammaglobulinemia and related infections in these patients *(this thesis)*

5. CD8+ T cells in patients with activated PI3K δ syndrome show characteristics of exhaustion, which contributes to the inability to control chronic viral infections like EBV and CMV. *(this thesis)*

6. In light of emerging human genetic and molecular knowledge, molecular diagnosis of Tuberous Sclerosis Complex and determination of genotype-phenotype correlations might help in the establishment of personalized treatment for Tuberous Sclerosis Complex patients and improve quality of life among these patients.

(Rosset et al, Genet Mol Biol. 2017 Jan-Mar; 40(1): 69–79)

7. It is not the responsiveness of the immune system, but its lack of stability that predisposes for tolerance failure. An increased risk for auto-immunity may be the price we have to pay to preserve some immune function into older age.

(Goronzy, Li, Yang and Weyand, Frontiers in Immunology, 2013)

8. Concerning PI3K δ at a broader level, it is remarkable that this one enzyme is a potential B-cell drug target for indications as diverse as leukemia, immunodeficiency, and inflammation, thereby underlining its broad and critical role in B-cell development.

(Conley and Fruman, Science 15 Nov 2013: Vol. 342, Issue 6160, pp. 814-815)

9. Supporting scientific research should be a top priority of any society that aims to make progress and thrive.

(John Ioannidis JAMA. 2017;317(24):2483-2484.)

10. The art of healing comes from nature, not from the physician. Therefore, the physician must start from nature with an open mind

(Paracelsus, 1493-1541)

11. And above all, watch with glittering eyes the whole world around you because the greatest secrets are always hidden in the most unlikely places. Those who don't believe in magic, will never find it.

(Roald Dahl, The Minpins 1991)