

Stellingen behorende bij het proefschrift

## Normal and malignant B-cells in acute lymphoblastic leukemia

Insight into clonal distribution, minimal residual disease and normal B-cell recovery

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1. In children with acute lymphoblastic leukemia (ALL), leukemic clones disseminate homogenously throughout the bone marrow compartment via the blood stream. *This thesis*
2. After ALL therapy, B-cell reconstitution in bone marrow and blood follows a pattern which is very similar to B-cell development in healthy infants. *This thesis*
3. During and after ALL therapy, the B-cell system recovers by means of de novo generation of the earliest B-cell precursors rather than compensatory proliferation of (immature) B-cells, thereby enabling the reestablishment of a highly diverse B-cell receptor repertoire. *This thesis*
4. Previously unknown CD34-/dim pre-B-I cells, which are abundantly present in regenerating bone marrow, should be carefully discriminated from ALL cells during flow cytometric detection of minimal residual disease (MRD) for monitoring of treatment effectiveness. *This thesis*
5. Due to an optimal 8-color antibody panel and the acquisition of sufficient cells (preferably  $>4 \times 10^6$ ), flow cytometric MRD detection is currently capable of reaching a sensitivity level that is at least comparable to that of PCR-based MRD measurements ( $\leq 10^{-5}$ ). *This thesis*
6. It may be expected that in the very near future all antibody repertoire studies will be based on single cell analyses, which will provide new insights into subclone formation in hematological malignancies and clonal expansions during immune responses. *Based on Georgiou et al., Nat. biotechnol., 2014*
7. Exact timing and sequential order of all choices in each cell underlie normal hematopoiesis, both in steady-state and injury situations. Disruptions of normal cell fate decisions can cause both malignant and benign hematological disorders. *Based on Rieger and Schroeder, Cold Spring Harb. Perspect. Biol., 2012*
8. Therapeutic intervention may destroy cancer clones and erode their habitats, but it can also inadvertently provide a potent selective pressure for the expansion of resistant variants. *Greaves and Maley, Nature, 2012*
9. Strengths of flow cytometry-based assays include accurate quantification of MRD and the capacity to examine the status of normal hematopoietic cell maturation simultaneously. *Campana, Semin. Hematol., 2009*
10. It is impressive how much genetic and cellular waste is generated during B-lymphocyte development. Making a well-fitting antibody molecule with unique CDRs to recognize the wide world of antigens appears to be a rare event. *Melchers et al. Immunol. Rev., 2000*
11. Whether or not it is clear to you, no doubt the universe is unfolding as it should. *Max Ehrmann, Desiderata: A Poem for a Way of Life, 1927*