Propositions (Stellingen)

The mesenchymal niche in leukemia predisposition syndromes

1. Purified bone-marrow mesenchymal cells from low risk Myelodysplastic Syndromes (LR-MDS) patients are molecularly and functionally distinct from both normal and *ex vivo* expanded cells, characterized by cellular stress and inflammatory signaling. (this thesis)

2. Deletion of *Sbds* from mesenchymal progenitor cells in mice recapitulates the osteoporotic bone phenotype in human Shwachman-Diamond Syndrome (SDS). (this thesis)

3. *Sbds* deficient mesenchymal progenitor cells induce genotoxic stress in heterotypic hematopoietic stem/progenitor cells (HSPCs). (this thesis)

4. The inflammatory molecules S100A8 and S100A9 are candidate niche factors driving genotoxic stress in a mouse model of SDS and the human leukemia predisposition syndromes SDS and MDS. (this thesis)

5. Overexpression of mesenchymal S100A8 and S100A9 at the transcript level identifies a subset of LR-MDS patients and predicts poor disease outcome. (this thesis)

6. The *in vitro* definition of mesenchymal stem cells (MSCs) with trilineage differentiation capacity in culture does not necessarily reflect multipotency of the same mesenchymal cells *in vivo*

7. Genetic mouse models have helped us better understand the cellular architecture and hierarchy within the hematopoietic niche; however, translation of these findings to humans remains an important challenge to the field.

8. Impact factors are over-rated, when judging the quality of a paper, it is the quality of the science that matters, not the journal's brand. (Modified from Randy Schekman, 2013 Nobel Prize Laureate)

9. Using immunophenotypic markers or candidate genes to define cells has inherent biases and limitations.

10. Alterations in the tumor stroma are not only secondary to changes in the parenchymal tumor cells, they may play a primary role as well.

11. A journey of a thousand miles begins with a single step. (Chinese proverb)

Si Chen, Rotterdam, 13 June 2017