Propositions:

Molecular and Cellular Defects Driving the Leukemic Progression of Severe Congenital Neutropenia

1. PML plays a key role in SCN with *ELANE*-mutations predicted to result in NE-protein misfolding by inhibiting CSF3-responsiveness, increasing metabolism, and inducing mutant *ELANE* transcription. *This thesis*

2. Activation of the truncated *CSF3R*-d715 in SCN-derived HPCs results in increased interferon-signaling, but not in increased proliferation as is observed in *CSF3R*-d715 control HPCs, indicating that the SCN-causative mutation affects CSF3R signaling. *This thesis*

3. The combination of mutations in *Csf3r* and *RUNX1,* and CSF3-treatment results in selective expansion of myeloblasts, but is not enough to cause overt AML, in a murine leukemic progression model of SCN. *This thesis*

4. Increased inflammatory signaling plays a critical step in the leukemic transformation of SCN. *This thesis*

5. An internal-tandem-duplication in *CXXC4*, extending the glycine-repeat, results in increased CXXC4 protein stability and decreased TET2 protein levels. *This thesis*

6. Looking at post-translational modifications of proteins is more informative than total protein abundance.

7. Artificial intelligence is a keystone in modern science.

8. Gene expression changes can be modest at single gene level, but combined with expression changes in other genes, result in significant activation or repression of signaling pathways.

9. Taking an open-minded, unbiased, approach might produce a lot of un-useful data clouding the main, important, alterations, but also provide an opportunity to make new, unexpected, observations and create new hypotheses.

10. Journal impact factors are not always a good reflection of the quality of science and should therefore not be a measure of a scientist's capabilities.

11. "Everyone experiences tough times; it is a measure of your determination and dedication how you deal with them and how you can come through them". *Lakshmi Mittal*

Patricia Anita Olofsen-Dieleman
Rotterdam 2021