Stellingen/Propositions behorende bij het proefschrift

Development and Safety Assessment of Lentiviral Vector Gene Therapy for SCID-X1

1. Clinical trials have demonstrated the potential of *ex vivo* hematopoietic stem cell gene therapy to treat severe combined immunodeficiencies (SCID-X1 and ADA-SCID) using gammaretroviral vectors.
   Cavazzana-Calvo et al., *Science* 2000;288(5466):669-72
   Gaspar et al., *Lancet* 2004;364(9452):2181-7
   Aiuti et al., *NEJM*, 2009;360(5):447-58

2. The clinical benefit of gene therapy using gammaretoriviral vectors has been tempered by the occurrence of leukemia in 5 SCID-X1 patients in the SCID-X1 trials.
   Hacein-Bey-Abina et al., *J Clinical Investigation* 2008;118(9):3132-42
   Howe, et al., *J Clinical Investigation* 2008;118(9):3143-5

3. Integration of retroviral vectors took place preferentially in gene coding regions and was skewed towards the transcriptional start site of highly expressed genes.
   Deichmann et al., *J Clinical Investigation* 2007;117(8):2225-32

4. Integration analysis in pre-clinical evaluation in animal models reveals the relative safety potential of new gene therapy vectors under investigation, allowing those vectors with potentially dangerous integration patterns to be excluded before use in human patients and adding a further argument in favor of vectors with a low risk of triggering insertional mutagenesis.
   This thesis

5. The importance of pre-transplant conditioning for consistent successful correction by stem cell gene therapy should have an impact on current clinical protocol development.
   This thesis

6. X-linked agammaglobulinaemia patients sometimes have significant levels of serum immunoglobulins, but nevertheless suffer from recurrent infections.
   Timmers et al., *Clinical Immunology and Immunopathology* 1991;61(2):S83-93

7. Reprogramming of primary human fibroblasts into pluripotent stem cells is possible using only factors *OCT4* and *SOX2* in the presence of histone deacetylase inhibitor valproic acid.
   Huangfu et al., *Nature Biotechnology* 2008;26:1269-75

8. The human thymus contains multipotent $CD34^{+}$ progenitor cells that are able to develop into lymphoid, myeloid and erythroid lineages, but lack sufficient self-renewal capacity to be considered true hematopoietic stem cells.
   Weerkamp et al, *Blood* 2006;107(8):3131-3137

9. Since 2008, the costs of DNA sequencing have been decreasing at a rate far faster than the corresponding increase in the number of transistors per integrated circuit over the same time period.
   National Human Genome Research Institute

10. Due to time dilation, a 33-year old human travelling at 0.9*c* could celebrate his $40th^{th}$ birthday orbiting Barnard's Star while back on Earth his mother simultaneously celebrates his 48^{th}.

11. Never turn your back on a drug.
    Hunter S. Thompson, *Fear and Loathing in Las Vegas*, 1971