Stellingen bij het proefschrift

Lentiviral Hematopoietic Stem Cell Gene Therapy for MNGIE

1- Due to the relatively high risks associated with allogeneic hematopoietic stem cell transplantation for the treatment of MNGIE and its limited therapeutic outcomes, promising alternative treatments such as gene therapy should be pursued.
This thesis

2- To achieve long-lasting gene correction in MNGIE patients, ex vivo culture and lentiviral vector transduction conditions should not impede the repopulation and self-renewal capacities of gene-modified hematopoietic stem and progenitor cells.
This thesis

3- Lentiviral vectors have a preference to integrate in highly expressed genes, and do not selectively integrate near proto-oncogenes, a pattern that is conserved between species, and is not affected by the promoters or transgenes used in this thesis.
This thesis

4- In addition to neuro- or myo-genic changes, alterations to the interstitial cells of Cajal (the gut's pacemakers) are observed in the intestines of MNGIE patients.
This thesis

5- The preclinical results reported here and elsewhere support the efficacy of LV-mediated hematopoietic stem cell gene therapy as a treatment for MNGIE without evident signs of genotoxicity. However, assessment of the treatment's impact on additional clinical phenotypes and the in-depth evaluation of its safety, are required prior to the initiation of clinical trials.
This thesis

6- Gene therapy returns to centre stage.
Naldini, L. Nature 2015; 526 (7573):351-60

7- Autologous LV-mediated HSCGT does not necessarily require myeloablative conditioning, and bears a low genotoxicity risk while offering long-lasting therapeutic outcomes.
Aiuti, A. et al., Science 2013; 341 (6148): 1233151-1-12

8- Targeted genome editing holds great promise to cure hereditary and acquired diseases. Optimizati on of in vivo targeting, and adequate evaluation of the specificity and off-targeting of the engineered nucleases are major challenges.
Cornu, T.I. et al., Nature Medicine 2017; 23 (4): 415-423

9- The clinical translational value of animal models could be improved by: appropriate design and execution of experiments, inclusion of safety and quality of life parameters, validation and humanization of the model, introducing clinical trial endpoints, and back translation from clinical trials to animal models.
Denayer, T. et al., New Horizons in Translational Medicine 2014; 2 (1): 5-11

10- The four fundamental needs to keep employees productive and devoted to their job are trust, opportunity to advance, sense of worth, and competence.
Branham, L. 2005; ISBN: 0-8144-0851-6

11- Be strong enough to stand alone, smart enough to know when you need help, and brave enough to ask for it.
(Author unknown)

Rana Yadak, 2017