

Propositions (Stellingen)

Role of genetic haploinsufficiency in the biology and targeted therapy of del(5q) myelodysplastic syndrome

1. *Rps14* haploinsufficiency induces a p53-dependent erythroid differentiation defect, megakaryocyte dysplasia, and loss of hematopoietic stem cell quiescence in myelodysplastic syndrome (MDS) with del(5q) (this thesis).
2. *Rps14* haploinsufficiency and genetic abnormalities in MDS link activation of the innate immune system via induction of S100A8/S100A9 to the p53-dependent erythroid differentiation defect (this thesis).
3. *Casein kinase 1a1* (*Csnk1a1*) haploinsufficiency increases hematopoietic stem cell function and number in del(5q) MDS (this thesis).
4. The sensitivity of hematopoietic cells to *Csnk1a1* gene dosage provides a therapeutic window for targeting CK1 α in haploinsufficient cells in del(5q) MDS (this thesis).
5. *CSNK1A1* is recurrently mutated in del(5q) MDS and is the genetic driver of clonal dominance in this disease (this thesis and Heuser et al. *Leukemia* 2015; Bello et al. *British Journal of Hematology* 2015 and Smith et al. *Lancet Hematology* 2015).
6. Mice with heterozygous loss of tumor suppressor genes may appear normal but exhibit a phenotypic crisis under stress conditions.
7. When it comes to recapitulating genetic complexity of disorders, the potential of genome engineering using CRISPR-Cas9 technology surpasses that of classical genetic murine models.
8. Modest changes in expression of individual genes can synergize and exponentially activate a pathway that drives malignant transformation
9. Inflammation can act synergistically with DNA damage to induce cancer.
10. Impact factors should not be a surrogate measure of the quality of individual research articles, to assess an individual scientist's contributions, or in hiring, promotion, or funding decisions.
11. The most beautiful experience we can have is the mysterious. It is the fundamental emotion that stands at the cradle of true art and true science (adapted from Albert Einstein, *The World as I see it*, 1931).