Propositions

1. Next to dysregulation of TGFβ signaling, altered actin cytoskeleton dynamics, dysfunctional extracellular matrix deposition and reduced mitochondrial respiration are mechanistically involved in aortic aneurysmal disease.
   This thesis

2. Transdifferentiation of fibroblasts to VSMC-like cells by TGFβ stimulation results in upregulation of VSMC-specific genes and can be used for investigation of functional consequences of variants.
   This thesis

3. Mouse models for SLC2A10 do not have to be a clinical phenocopy of patients to be useful for analysis on a cellular level for the molecular mechanisms of SLC2A10 associated disease.
   This thesis

4. New techniques such as single cell RNA sequencing and proteomics analysis are of great importance for the identification of aneurysms genes by studying the unknown underlying molecular mechanisms for aortic aneurysms in contrast to current methods that mainly focus on likely candidates.
   This thesis

5. The Fibulin-$4^{R/R}$ and Fibulin-$4^{f/-}$SM22Cre^{+} mouse models illustrate that different protein levels of fibulin-4 differentially affect specific cellular processes, as patient mutations can result in diverse fibulin-4 levels this should be accounted for in the development of treatment plans of aneurysm patients.
   This thesis

6. In contrast to TAA, identification of genetic causes for AAA is complicated by lifestyle factors such as smoking as well as reduced penetrance in families and late age of onset in patients. (Based on Landenhed et al. J Am Heart Assoc. 2015 and Sakalihasan et al. Nat Rev Dis Primers. 2018)

7. An additional tier for low-penetrant "risk variants" should be added to the current 5-tier system of pathogenicity as the current system only accommodates causative mutations. (Based on *Kwartler et al. Am. J. Hum. Genet. 2018*)

8. The pathogenicity of variants of unknown significance (VUS) can only be identified by analyzing the functional consequences caused by a variant in vitro and in vivo models, otherwise the variant will remain of unknown significance.

9. Strategies aimed at inhibition of TGFβ-dependent signaling are unlikely to provide any benefit to patients with TAAD and may even aggravate their disease. The time has come to abandon the unproven hypothesis of detrimental TGFβ overdrive in TAADs and explore new concepts and horizons. (*Mallat et al. Circ. Res. 2017*)

10. Potential aneurysm genes should not be added to an aneurysm screening panel based solely on limited patient data, but should extensively be tested for function and effects of the mutated gene prior to addition to a screening panel.

11. Opbouwende kritiek is als milde regen, het bevordert de groei, maar tast de wortels niet aan.