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## **Modeling the genetic and mechanical interplay in osteoarthritis: from in vitro systems to mechanistic insights**

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Stellingen behorend bij het proefschrift getiteld

## **Modeling the Genetic and Mechanical Interplay in Osteoarthritis: from in vitro systems to mechanistic insights**

Niek Gerardus Carolus Bloks

1. Studies on the role of COL6A3 in osteoarthritis are incomplete without the addition of mechanical perturbations. **(Scientific field, Chapter 5)**
2. Injurious mechanical loading as a risk factor of osteoarthritis is marked by long-term persistent changes in methylation and associated gene expression levels. **(Chapter 4)**
3. Although chronic inflammation is generally considered deleterious, the COL6A3 R1504W damaging variant demonstrates that pericellular matrix dysfunction can abolish necessary beneficial inflammatory responses to mechanical loading, highlighting that inflammation can serve a dual role in cartilage homeostasis. **(Chapter 5)**
4. Multi-omics analysis is invaluable to identify factors that could further improve hiPSC differentiation protocols. **(Chapter 3)**
5. Genetic studies should form the basis of disease modifying osteoarthritis drugs development. **(Chapter 2 and 5, Razuvayevskaya O., Nature Genetics 2024)**
6. Exercise therapy modality, frequency, intensity and duration for osteoarthritis patients in physical therapy practice should be informed by relevant tissue state biomarkers and associated load-bearing capacity. **(Scientific field and Chapter 4)**
7. Pre-clinical studies should carefully consider their perturbations based on the gene of interest. **(Scientific field and Chapter 2 and 5)**
8. Not all PhD theses are created equally – data collection in genetically modified hiPSC driven experimental research requires diving into the unknown, troubleshooting and thus a variable amount of time. This should be accounted for in the length of a PhD contract.
9. “One sees clearly only with the heart. What is essential is invisible to the eye.”- The Little Prince by Antoine De Saint-Exupéry  
*Not everything that has value can be measured.*