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## **The bone and cartilage interplay in osteoarthritis: key to effective treatment strategy**

Tuerlings, M.

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Stellingen behorend bij het proefschrift getiteld  
**THE BONE AND CARTILAGE INTERPLAY IN OSTEOARTHRITIS:  
KEY TO EFFECTIVE TREATMENT STRATEGY**

1. Development disease modifying OA drugs (DMOADs) should focus on druggable targets in articular cartilage and subchondral bone simultaneously to have efficient therapeutic effects on OA **(this thesis)**.
2. Molecular scientists should be aware that RNA expression patterns in OA pathophysiology are not necessarily causal to the disease. Allelic imbalanced expression or expression quantitative trait loci, however, do represent causation **(this thesis)**.
3. Upregulation of OA risk gene *WWP2* has detrimental effects on cartilage matrix deposition, acting via hypoxia associated chondrocyte dedifferentiation **(this thesis)**.
4. Treatment of lesioned OA osteochondral explants with hrIL11, as previously proposed OA treatment strategy, unlikely has a beneficial outcome on articular cartilage and subchondral bone **(this thesis)**.
5. Microfluidic chip technology offers an advanced multi-tissue *in vitro* model system of OA and could eventually be an alternative for pre-clinical animal testing **(this thesis; Ingber, D.E. (2022), Nat Rev Genet 23, 467-491)**
6. OA heterogeneity between patients and joint sites should be considered in the development and clinical trials of DMOADs and should replace the one-drug-fit-all-patients strategy **(this thesis, den Hollander, W., et al. (2014), Ann Rheum Dis 73(12): 2208-2212, Hall, M., et al. (2022) Osteoarthritis Cartilage 30(1): 32-41, Coutinho de Almeida, R., et al. (2020), Rheumatology 60(3): 1166-1175.)**

7. Circulating miRNAs could serve as non-invasive biomarkers reflecting ongoing processes in the joint and could further advance the development of personalized medicine of OA and lead to a higher clinical trial success rate (**this thesis; Ramos, Y. F. M., et al. (2021), Biomolecules 11(9); Ntounou, E., et al. (2017), Clin Epigenetics 9: 127**).
8. Genetic studies should be the basis for development of DMOADs, as drug targets founded by genetic evidence have at least two times higher success rates (**Nelson, M. R., et al. (2015), Nat Genet 47(8): 856-860; King, E. A., et al. (2019), PLOS Genetics 15(12): e1008489**).
9. The DMOAD development should focus much more on repurposing strategies. (**Pushpakom, S., et al. (2019), Nature Reviews Drug Discovery 18(1): 41-58; Oo, W. M. and D. J. Hunter (2022), Ther Adv Musculoskelet Dis 14: 1759720x221090297**.)
10. “Intellectuals solve problems, geniuses prevent them” – Albert Einstein  
*Prevent or cure osteoarthritis should be preferred over symptom relief treatment.*
11. “Sometimes we can only find our true direction when we let the wind of change carry us” – Mimi Novic  
*The focus of your education does not always determines your future direction*