2023 OARSI Travel Scholar Program

Niek Bloks Report

My study trip has focused on determining the functional impact of a mutation in the *COL6A3* gene, likely causal to the severe osteoarthritis phenotype of people carrying the mutation. This *COL6A3* gene encodes collagen type VI, where it forms a major constituent of the pericellular matrix; the matrix directly surrounding chondrocytes (in green, fig 1). This pericellular matrix regulates the transduction of mechanical forces or injurious mechanical stress from the extracellular matrix, towards the chondrocyte, which is the sole cell type in articular cartilage. Any changes to the mechanical properties of this pericellular matrix will affect the transduction of these mechanical forces, and as such impair the responses of chondrocytes. Previous results from our lab have shown that the *COL6A3* mutation alters the response to injurious mechanical stress, impairing the initial repair response directly after damaging mechanical loading. However, we do not yet know exactly if and how the *COL6A3* mutation alters the mechanical properties of the cartilage, and whether this is the driving force behind this lack of repair response.

During my stay I had two main objectives; First, to develop the research methods that would allow us to test changes in mechanical properties of cartilage due to the *COL6A3* mutation. Second, to test potential targets to modulate the response of chondrocytes to injurious mechanical stress. To this end, novel research techniques were employed to determine the effect of the mutation in collagen type VI on the mechanical properties of the pericellular matrix. By having used induced pluripotent stem cell-derived 3D organoid models, i.e. lab-grown cartilage, that were genome-edited to carry the mutation, in combination with novel imaging techniques together with mechanical perturbations, as well as micro-mechanical mapping of the pericellular matrix using atomic force microscopy, a causal link between the mutation and the increased risk of developing severe osteoarthritis has been examined.

The work during my visit has mainly been focused on optimizing the research techniques to allow us to use them in our specific stem cell-derived neo-cartilage organoid model. Towards the end of my stay, we were able to use the system to characterize the mechanical properties of the lab-grown cartilage, and as such created a tool to evaluate the impact of the genetic *COL6A3* mutation on one of the key characteristics of cartilage that are driving the impact of everyday activities such as walking, running, etc. Additionally, in search of druggable targets, we have used the neo-cartilage organoid model to test the effects of a compound that modulates the response to mechanical perturbations, thereby possibly rescuing repair response after mechanical loading. Currently, the data of this study is being analyzed. We hope that the results of this study will add to the quest of finding disease-modifying drugs, that are so urgently needed to treat this ever-growing patient population.

The acquired tools and findings will be highly valuable scientific addition to the completion of my Ph.D. thesis. Additionally, during my stay I enjoyed the opportunity to present the work at a conference, leading to fruitful discussions aiding the development of my thesis. Besides these direct scientific benefits of this study trip, it has enabled me to further develop my international network within the osteoarthritis research community and learn and share knowledge and skills within a cross-cultural research team which has led to a strengthening of the collaborative work. Also, the acquired knowledge and skills have been transferred to the research team within the LUMC, and now will aid the progress of other research lines as well. To conclude, I am grateful to have been awarded the OARSI grant which has allowed for a personal- and professionally enriching experience.