

# EXPERIMENTAL RHEUMATOLOGY

## Killing the alarm-in osteoarthritis

Validation of novel small molecule inhibitors against S100A8/A9

### Clinical Relevance

Osteoarthritis (OA) is a joint disease that affects millions of people worldwide. Patients suffer from swollen joints, stiffness and pain. The disease is characterized by breakdown of the cartilage and inflammation in a lot of patients. Current treatment consists of pain medication, corticosteroids to reduce the inflammation and eventually joint replacement surgery.

### Background

Inflammation in OA is mainly exerted by innate immune cells, like monocytes, macrophages and neutrophils. One of the pro-inflammatory factors that we have shown to be crucial for this inflammation and OA pathology is S100A8/A9. This protein is a so-called damage-associated molecular pattern (DAMP) that activates immune cells via toll-like receptor 4 (TLR4). Its levels are elevated in OA and predictive for the development of the disease. S100A8/A9 deficient mice show suppressed development of synovial inflammation and less joint destruction after induction of OA compared to wild-type mice.

### Goals

In my PhD project, we are developing small molecule inhibitors against S100A8/A9 to be able to specifically dampen the immune response that occurs in OA. A high-throughput screening has been performed before, and 40 potential compounds were selected for further investigation. In this project, you will validate these potential inhibitors in a cell-based assay. You will develop a cell assay in which S100A8/A9 is overexpressed using lentiviral constructs, after which you will test the effects of the inhibitors on S100 producing cells, using e.g. a TLR4 reporter cell assay for read-out.

### For who?

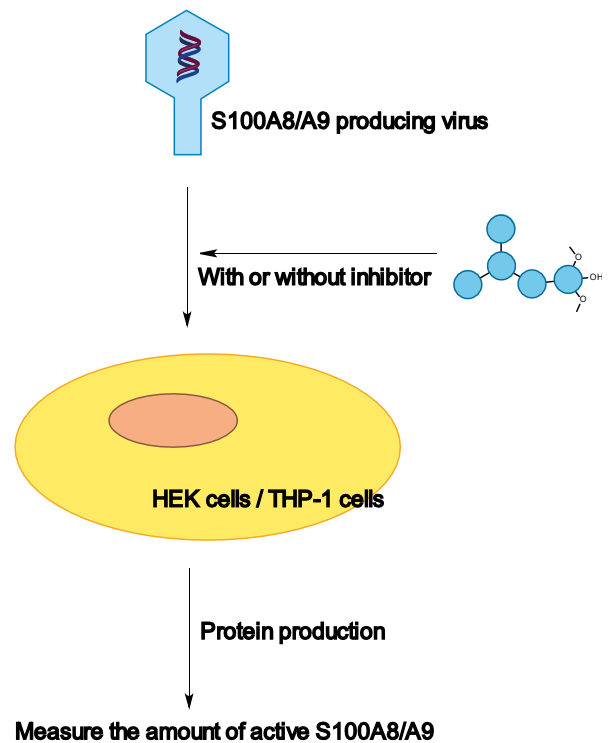
We are looking for a master student that, who is able to work in a relatively independent manner.

### We Offer

In this internship, we offer you the opportunity to develop a cell assay and do the functional tests with promising novel S100A8/A9 inhibitors. The overexpression will be done using an S100A8/A9 lentivirus. Techniques that will be used are cell culture, qPCR, western blotting and cell viability assays. You will be able to improve your laboratory skills and develop your scientific thinking. For practical reasons, the supervision will be done partially by Martijn van den Bosch (post doc) and partially by Yvonne Bartels.

### Contact

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**Figure 1: Goal of the project.** Model cells will be transduced with an S100A8/A9 producing virus and during the protein production inhibitors will be added or not. The amount of active S100A8/A9 complex produced can be measured using a TLR4 reporter cell line.



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