Assignment 1: Development of a Joint-on-Chip Platform & First Characterization

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Project background:

Arthritis is a family of diseases affecting millions of patients worldwide, typically characterized by degradation of cartilage, joint inflammation, pain, and joint stiffness. The two most common forms of arthritis are Osteoarthritis (OA) and Rheumatoid Arthritis (RA). Globally, OA affects more than 300 million patients (2017) and RA is estimated to have a global prevalence of up to 1,3%. Furthermore, as obesity and ageing are two major risk factors for OA, and to some extent RA, it is expected that the prevalence of arthritis continues to increase.

Despite the different disease manifestations, there appears to be an overlapping trend in the pathogenesis of both RA and OA: the cartilage destruction resulting from synovitis. Even though synovitis presents differently in both OA and RA, the effects are similar: the release of pro-inflammatory mediators and matrix-degrading enzymes leads to cartilage degradation that can enhance synovitis through the release of matrix products and potentially soluble factors present in the cartilage matrix. Hence, **it can be concluded that both OA and RA involve chondro-synovial crosstalk as part of the disease progression**, which presents as a vicious cycle of cartilage degradation and synovitis, which we call **chondro-synovial crosstalk** (Figure 1).

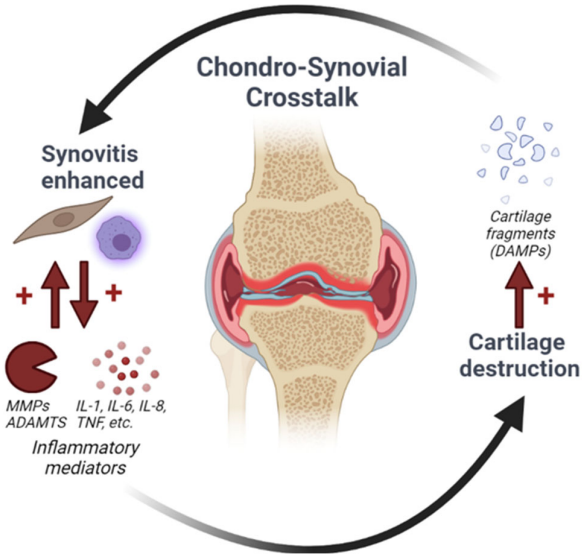
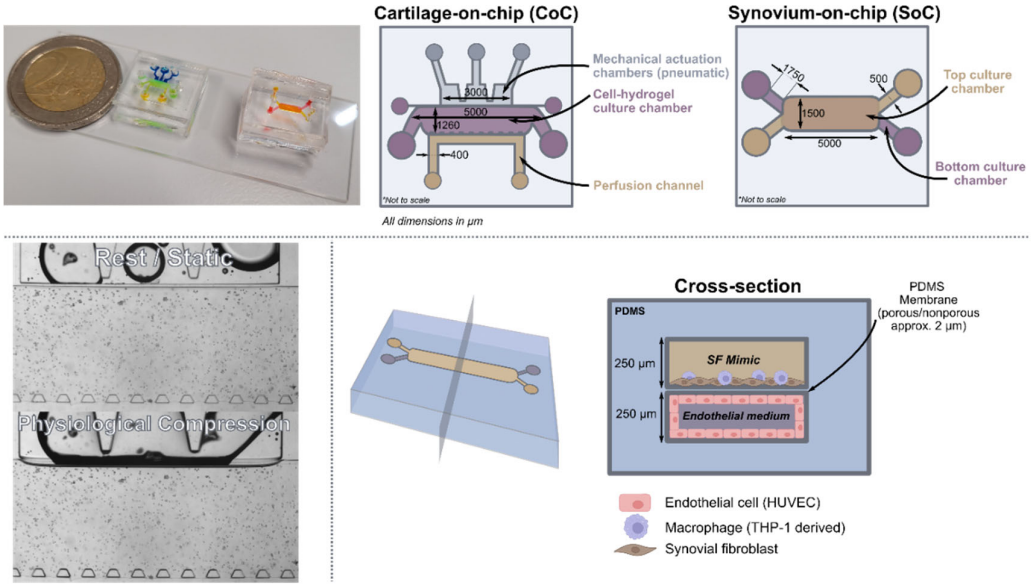


Figure 1: Simplified schematic representation of Chondro-Synovial crosstalk in arthritis.

The need for *in vitro* models for arthritis

To date, no disease-modifying OA drugs (DMOADs) are available and treatment of OA focuses mainly on relieving symptoms and physical therapy. Pharmacological management of OA is mainly based on paracetamol and, alternatively, nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and naproxen. NSAIDs reduce pain and, to some extent, improve joint functionality but not disease severity. For RA, a few disease-modifying anti RA drugs (DMARDs) are available (e.g. methotrexate (MTX) and sulfasalazine (SSZ)) next to the commonly used NSAIDs that are also used for OA. Unfortunately, most DMARDs result in, amongst others, gastrointestinal and cardiovascular side effects.

There is a need for physiologically relevant arthritis models since the lack of such models limits the development and investigation of DMOADs and DMARDs. Current preclinical models consist mainly of monolayer cultures and animal models, which **do not reflect the biological complexity and whole-joint nature of arthritis; amongst which the chondro-synovial crosstalk**. It has been argued in literature repeatedly that novel physiologically relevant models will lead to an increased understanding of arthritis and aid in the development of new drugs. Furthermore, they could enable personalized medicine to address various phenotypes of OA and RA observed in the clinics. So far, we have developed a Cartilage-on-Chip, Synovium-on-Chip, and Ligament-on-Chip (early phase).



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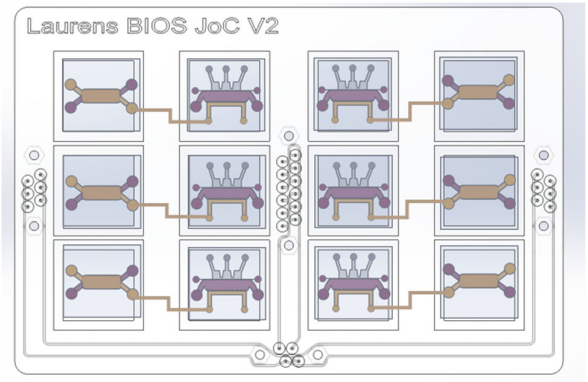

In recent years, the DBE and AMBER groups have developed two OoC models for the key players in Arthritis: the cartilage-on-chip (CoC) and the synovial membrane-on-chip (SoC), see Figure above. So far, these units have not been put together on one platform yet. **In this assignment, you will work on the development of a Joint-on-Chip platform, that combines the currently existing Cartilage and Synovium-on-chip platforms to allow for inter-device crosstalk and mechanical actuation in a highly parallelized manner** (see image below). You will continue working on a pre-existing design for this platform and learn techniques such as PDMS soft lithography, micromilling, 3D printing (potentially), and various microfabrication techniques to assemble the devices.

Key skills/topics the student could learn during this assignment:

- (Advanced) rapid prototyping techniques such as SLA 3D printing and micromilling
- Chip/device design using SolidWorks
- Microfabrication of organ-on-chip devices (PDMS soft lithography)
- Cartilage-on-chip mechanical actuation
- Microfluidics (pressure-driven flow)
- Cell culture of primary cells (human Chondrocytes, human Synovial Fibroblasts, HUVECs) and human cell lines (THP-1)
- Immunofluorescence
- Confocal/fluorescence microscopy
- Biochemical assays such as ELISA, SPR, MMP activity assay
- RT-qPCR

This assignment is in collaboration with the DBE, BIOS/Lab-on-a-chip, and AMBER groups and will be carried out in the Zuidhorst laboraties and the BIOS Laboratories.

Interested? Please contact Laurens Spoelstra (l.r.spoelstra@utwente.nl) for more information.