Injectable functional tissue-adhesives for controlled gene delivery to be used in cartilage repair

Osteoarthritis (OA) is one of the major causes of disabilities worldwide, affecting hundreds of millions of people and leading to a high socioeconomic burden. OA is a progressive disease characterized by degeneration of articular cartilage and mild to moderate inflammation, resulting in pain and loss of joint function. Currently, there are no approved therapeutics that can reverse, halt, or even just decelerate the disease progression. Therefore, the development of novel approaches and therapies to tackle this complex disease is needed.

One tissue engineering approach that has been developed to treat OA is based on the use of injectable cell-free hydrogels for cartilage repair. [1] In particular, it has been recently demonstrated that the application of injectable supramolecular hydrogels that combine gene delivery (SOX9 or IGF-I) with the recombinant adeno-associated viral vector (rAAV), improved cartilage repair after microfracture in minipig model and protected against perifocal OA. [2,3] Despite this encouraging progress, two important challenges are still faced by these therapies: a) the so far limited duration of the gene release from the hydrogel, and b) the lack of tissue adhesion of the hydrogel to the damaged tissue after microfracture. It is hypothesized that a hydrogel design that improves these key properties will show longer therapeutic effects and better tissue integration, ultimately improving the processes of cartilage repair/OA protection.

Building up on previous work, in this project we will develop an injectable hydrogel for sustained gene delivery that presents tissue adhesion properties. The workplan includes the chemical modification of biopolymers to introduce functional groups that can be used for hydrogelation under mild oxidative conditions and that confer tissue adhesion. Next, the functional hydrogels will be formulated, their physical chemical, rheological, swelling properties will be assessed, and their capability to release rAAV and their biocompatibility will be tested in vitro. Finally, the tissue adhesion strength to animal tissue will be tested as a proof of concept. If successful, in collaboration with local and international partners, this new biomaterial design could be adjusted and further expanded toward animal studies.

References:

[1] Zoetebier, B.; Schmitz, T.; Ito, K.; Karperien, M.; Tryfonidou, M.; Paez, J.I. *Tissue Engineering Part A*, **2022**, 28 (11-12), 478-499.
[2] Madry, H., Gao, L., Rey-Rico, A., Venkatesan, J. K., Müller-Brandt, K., Cai, X., Goebel, L., Schmitt, G., Speicher-Mentges, S., Zurakowski, D., Menger, M. D., Laschke, M. W., Cucchiarini, M., *Adv. Mater.* **2020**, 32, 1906508.
[3] Maihöfer, J., Madry, H., Rey-Rico, A., Venkatesan, J. K., Goebel, L., Schmitt, G., Speicher-Mentges, S., Cai, X., Meng, W., Zurakowski, D., Menger, M. D., Laschke, M. W., Cucchiarini, M. *Adv. Mater.* **2021**, 33, 2008451.