Directional 3D nanofiber network to mimic *in-vivo* myocardial syncytium towards guiding contraction patterns in *in-vitro* heart models

First advisor: Dr. Maurizio Gullo, 3D bioprinting and biohybrid microsystems, University of Applied Science FHNW Muttenz, BL, CH
Shared first advisor: PD Dr. Anna Marsano, Cardiac Surgery and Engineering, Department of Biomedicine, University Hospital Basel, BS, CH
Second advisor: Prof. Dr. Martino Poggio, Nanomechanics and Nanomagnetism, Department of Physics, University of Basel, BS, CH

PhD Project Outline

Cardiac diseases, like cardiac ischemia/infarction, are the major cause of death in Switzerland (31.4% in 2017)[1] and the world combined (16.6% in 2016).[2] Since myocardial tissue lacks intrinsic regenerative capabilities,[3] ways to come up or improve already existing medical applications have gathered growing interest in biomedical research. The evolvement of shifting from general towards patient-specific approaches lead to the development of patient-specific *in-vitro* cardiac tissues. Despite recent advances in functional cardiac tissue engineering, current *in-vitro* models are not yet able to closely mimic *in-vivo* myocardial tissue.[4] Especially the functional unit of the heart, the so-called syncytium, which consists of highly conductive Purkinje fibers enabling the electrocoupling of cardiomyocytes, is a very sophisticated piece of biological engineering.[5] The Purkinje fibers enable the transmission of electrical signals and therefore the synchronized contraction patterns of cardiomyocytes which ultimately leads to the synchronized beating of the heart.

In this interdisciplinary PhD project, we focus on mimicking the cellular composition, i.e. the interplay of cells with its extracellular matrix, of the heart using 3-dimensional bioprinting. By using a hydrogel with incoorporated cells, bioprinting permits the construction of complex 3D living tissues,[6] mimicking the interplay of cells with one another as well as with the extracellular matrix. By dotting the used cell-laden bioink with specific and organized nanocomposites, a functioning Purkinje fiber network is mimicked, promoting a biofabricated, functional and synchronized mature cardiac tissue, which can be applied in regenerative medical applications.

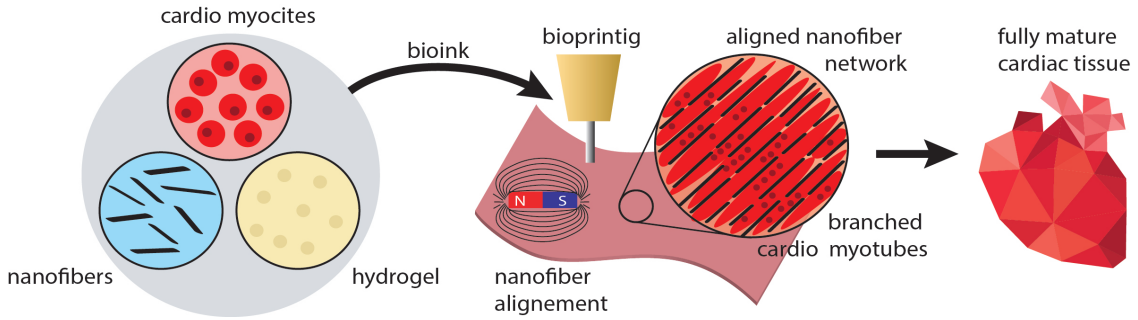

Figure 1: A specific cell-laden bioink, consisting of cardiomyocytes, nanofibers and hydrogel, is used in a 3-dimensional bioprinting process, producing a nanostructured construct. The alignment of the fibers and therefore the cells can be achieved through external stimuli, inducing proper cardiac maturation. The branched cardiomyocytes along with the Purkinje fiber network mimicking nanofibers form a functional syncytium, i.e. a functional cardiac tissue which can ultimately be used for regenerative medical purposes.

References

[1] B. für Statistik, 'Herz-Kreislauf-Erkrankungen und Krebs sind weiterhin die häufigsten Todesursachen in der Schweiz - Todesursachenstatistik 2017 -', Bundesamt für Statistik, Dec. 16, 2019. /content/bfs/de/home/aktuell/medienmitteilungen.assetdetail.11227248.html (accessed Jun. 30, 2020)

[2] 'The top 10 causes of death'. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death (accessed Jun. 30, 2020)

[3] P. Zammaretti and M. Jaconi, 'Cardiac tissue engineering: regeneration of the wounded heart', Curr. Opin. Biotechnol., vol. 15, no. 5, pp. 430–434, Oct. 2004, doi: 10.1016/j.copbio.2004.08.007

[4] A. Mathur, Z. Ma, P. Loskill, S. Jeeawoody, and K. E. Healy, 'In vitro cardiac tissue models: Current status and future prospects', Adv. Drug Deliv. Rev., vol. 96, pp. 203–213, Jan. 2016, doi: 10.1016/j.addr.2015.09.011

[5] R. E. Ideker, W. Kong, and S. Pogwizd, 'Purkinje Fibers and Arrhythmias', Pacing Clin. Electrophysiol. PACE, vol. 32, no. 3, pp. 283–285, Mar. 2009, doi: 10.1111/j.1540-8159.2008.02232.x

[6] S. V. Murphy and A. Atala, '3D bioprinting of tissues and organs', Nat. Biotechnol., vol. 32, no. 8, Art. no. 8, Aug. 2014, doi: 10.1038/nbt.2958