On Thursday the 3rd of September 2021 we hosted prof. Mark Mercola from Stanford University, USA, for the third special seminar of the DCVA iPSC-CM Journal Club. Prof. Mercola has played a pivotal role in elucidating the factors that contribute to heart induction and formation and has applied that knowledge to iPSC technology, building and using high-throughput assays for patient-specific drug screening. Prof. Mercola shared his work during his talk entitled 'Using patient iPSCs in high-throughput physiological cardiovascular drug development' where he highlighted three projects.

In the first project, iPSC-CMs were used to optimize the efficacy and remove the proarrhythmic potential of mexiletine[1]. Mexiletine is a modestly selective late sodium (I_{NaL}) inhibitor used in the treatment of Long QT Syndrome 3 (LQT3), but I_{NaL} inhibition could also be of therapeutic interest for other cardiac disorders. Mexiletine analogues were developed and tested in LQT3 iPSC-CMs, which recapitulated the disease phenotype and drug response. Iterative experiments were performed to improve the potency and selectivity of the mexiletine analogues. The optimized analogues were tested in rats, where the anti-arrhythmic potential was demonstrated without proarrhythmic side effects. Further experiments in dogs will be performed to provide a proof of concept for these mexiletine analogues. In the second project, iPSC-CMs were employed for the repurposing of the highly cardiotoxic tyrosine kinase inhibitor ponatinib. Ponatinib analogues were developed and tested in iPSC-CM, tumor and microvessel high-throughput assays to assess the potency and off-target effects. Iterative experiments allowed optimization of the analogues, revealing two analogues that strike the right balance between efficacy and safety. *In vivo* experiments in mice with the analogues showed a decrease in tumor size without the cardiotoxicity as signified by a lack of mortality. In the third project, iPSC-CMs were used to discover new therapeutic targets for cardiomyopathy patients harboring a mutation in phospholamban (PLN; R14del)[2]. PLN R14 del iPSC-CMs recapitulated the decreased contractility that was similar to the patient phenotype. Single-cell RNA sequencing revealed the presence of the unfolded protein response (UPR) in iPSC-CMs, which was also observed in hearts from R14del patients. Blocking the UPR in PLN R14del iPSC-CMs aggravated the contractile deficit, while activating the UPR with a small molecule improved cardiomyocyte contraction. Currently the small molecule activator is explored for off-target effects, after which it will be further optimized for *in vivo* testing.

The three projects discussed in this talk demonstrate the potential of iPSC-CMs in disease-specific drug discovery and repurposing. The studies highlight the power of iPSC-CMs as a tool that ''can be used to drive a medicinal chemistry campaign'', as advocated by prof. Mercola. During the discussion following the talk, prof. Mercola dives into future goals for his lab and his personal interest: defining therapeutic targets for cardiomyopathies, specifically dilated cardiomyopathy (DCM). Since DCM is caused by different mutations, prof. Mercola is interested to examine whether those mutations also translate to different etiologies or if they lead to a common disease mechanism for which targeted therapies can be developed. Regarding future goals for our young researchers, prof. Mercola advises to always keep a 'where do I want to be in 20 years' trajectory in mind when making choices for next steps in their research career.

References:

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