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**An iPSC-derived drug screening platform to identify therapeutic compounds for marfan syndrome**

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We have designed and validated a phenotypic assay for high-throughput drug screening using human induced pluripotent stem cells (iPSCs) generated from patients with Marfan syndrome (MFS). MFS is a connective tissue disorder with pleiotropic manifestations including severe cardiovascular complications, such as aortic aneurysms and aortic dissection. The aortic problems are caused by mutations in FBN1, which codes for the extracellular matrix structural component, fibrillin-1. Currently, MFS treatments focus on minimising aortic wall stress by controlling blood pressure and haemodynamics. Although TGF-β signalling blockade has successfully prevented aortic dilatation in a MFS mouse model (Habashi 2006), similar attempts have been unsuccessful in clinical trials (Lacro 2014). Our recent work shows that p38 and KLF4 are novel disease drivers in our human iPSC model (Granata 2017). However, the signalling pathways are complex and varied hence our decision to focus on the downstream pathogenic phenotypes. One of these features includes excessive matrix degradation coupled with increased expression of proteolytic enzymes. Here, we show that MFS smooth muscle cells cultured in a 24-well format and treated with a phenotypic compound library (AstraZeneca) provide a robust assay for high-throughput screening conditions to identify MMP activity reducing compounds. Putative hits will also be assayed for cell-death and proliferation for further validation. These techniques will enable the identification of novel drugs to treat MFS.