Title	Engineering micro-alignments of 2- and 3-D hESC-derived ventricular tissues to reproduce anisotropic properties of the native heart: an accurate arrhythmias model for cardiotoxicity screening
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26] Engineering micro-alignments of 2- and 3-D hESC-derived ventricular tissues to reproduce anisotropic properties of the native heart: An accurate arrhythmias model for cardiotoxicity screening.

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In the native heart, ventricular CMs are aligned in a highly organized structured manner such that the conduction of electrical signals is anisotropic for directional and coordinated contractions to effectively pump blood. In other words, *electrical conduction is asymmetrical* (i.e. anisotropy) with distinct transverse and longitudinal velocities. Unlike the native ventricle, clusters of hESC-CMs differentiated using either the EB formation or directed differentiation are *random* structures with NO obvious organization and anisotropy as we previously published. Using a microgroove technology, here we engineered organized 2- and 3-D hESC-derived ventricular strips, followed by high-resolution optical mapping recordings to examine in details their action potential and conduction properties. Compared with randomly distributed unaligned controls, hESC-CMs seeded on micro-fabricated polydimethylsiloxane (PDMF) consisting of nanometer-microgrooves induced cell alignment with more organized sarcomeric structures. Functionally, an anisotropic ratio (i.e. transverse/longitudinal velocities) of 2.3 (vs. 1.0 of controls) was uniquely observed. Furthermore, the occurrence of reentrant arrhythmias (in the form of sustained spiral waves) was significantly reduced (to 0 in five vs. 5 in 5) when the vulnerability/inducibility of arrhythmias was probed using programmed electrical stimulations. As for 3D trabeculae-muscle strip, point stimulation led to electrical propagation in a classical cable fashion. In conclusion, our micro-nanofabrication strategy has successfully functionally reproduced anisotropic properties. These results will be crucial for future development of viable cardiac patches for myocardial repair with improved efficacy and safety, and for rendering cardiotoxity screening, prediction assays and heart disease model more accurate and indicative of the native heart.