# Coming of age of human stem cell derived cardiomyocytes : towards functional maturation of human pluripotent stem cell derived cardiomyocytes and their use in understanding inherited arrhythmia syndromes

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Stellingen behorend bij het proefschrift getiteld:

# Coming of age of human stem cell derived cardiomyocytes.

## Towards functional maturation of human pluripotent stem cell derived cardiomyocytes and their use in understanding inherited arrhythmia syndromes.

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1. "Although the expression of key markers of maturation (such as sarcomeric proteins or ion channels) may be considerably upregulated using a particular method, this does not always coincide with functional maturation". ***This thesis***

2. "The maximal diastolic potential values are similar in all hiPSC lines and therefore the (voltage-dependent) availability of sodium channels in mutated hiPSC-CMs and control hiPSC-CMs does not play a role in the reduced $V_{max}$". ***This thesis***

3. "To be classified as a mature ventricular myocyte, stem cell-derived CMs require 100% cTnI (and 0% ssTnI) that is co-localized with MLC2v. MLC2v alone cannot serve as a mature marker in CMs, as we show MLC2V-positive myocytes express primarily ssTnI (the immature marker)". Bedada et al, Stem Cell Reports. 2014 Oct 14;3(4):594-605.

4. "The present literature already demonstrates that a fully mature state might not be strictly necessary for hPSC-CMs to serve as useful human heart disease models". ***This thesis***

5. "our data on the c.1781G>A KCNQ1 mutation, where isogenic heterozygous and homozygous mutated CMs were compared, confirmed that precise gene targeting in hiPSC-CMs is a powerful tool to study the role of such mutations and evaluate dosage effects on disease severity". Zhang et al, Proc Natl Acad Sci. 2014 Dec 16;111(50):E5383-92.

6. "Strategies focusing on one particular aspect of the structural, electrophysiological, or functional phenotype alone may be insufficient to improve overall cardiomyocyte maturity. Combined approaches that impact multiple parameters at different levels simultaneously could be more effective in achieving this goal". ***This thesis***

7. “Upon readthrough Q530X+KCNE1 also produced currents with significantly ($P<0.05$) rightward-shifted $V_{0.5}$ and increased rates of channel deactivation, indicating that readthrough did not produce channels with biophysical properties identical with the wild-type for this mutant either”.
**Harmer et al**, Biochem J. 2012 May 1;443(3):635-42.

8. “The time has come, it may be said, to dream of many things; of genes and life and human cells, of medicine and kings”. **Edward L Tatum** (1909–1975), Perspectives in biology and medicine 1966

9. “Optical APs recorded from human iPSC-CMs loaded with di-4-ANBDQBS closely tracked APs measured by the disrupted patch technique. Values of APD derived from optical APs were nearly identical to directly measured $V_m$.
The tight correlation between optical AP and $V_m$ signals confirm the robust temporal resolution of di-4-ANBDQBS to track rapid changes in membrane potential”. **Lopez-Izquierdo et al**, Am J Physiol Heart Circ Physiol. 2014 Nov 1;307(9):H1370-7.

10. “A scientist in his laboratory is not a mere technician: he is also a child confronting natural phenomena that impress him as though they were fairy tales. **Marie Curie** (1867 –1934)

11. “μὴ μου τοὺς κύκλους τάραττε”. (Do not disturb my circles!). **Archimedes of Syracuse** (c. 287-c. 212 BC)