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Combinational high-throughput screening of physical niches supporting iPSC-derived hepatocyte maturation

Min Sun, Yang Yu, Ng Chan Way and **Hanry Yu**
Yong Loo Lin School of Medicine - National University of Singapore, Singapore

Statement of the Problem: Induced pluripotent stem cells (iPSC)-derived hepatocytes are viewed as a promising cell source for liver tissue regeneration, disease modeling and drug toxicity testing. However its phenotype mimics still more of fetal hepatocytes rather than mature human primary hepatocytes, a major bottleneck limiting its widespread application. Despite the known roles played by both soluble factors and physical factors (including topographies, stiffness, shear stress, mechanical strain) on stem cell differentiation, the exploration of using physical factors to modulate hepatic maturation is yet very limited. The purpose of this study is to screen suitable physical microenvironment that enhances hepatic maturation, thus generating a more matured cell source for industrial applications.

Methodology & Theoretical Orientation: We hypothesize a systematic non-biased materiomics screening will enable the identification of microenvironments (including optimal cell-cell contact and cell-topography interaction) to preferentially enhance the maturation of iPSC-derived hepatocytes. A materiomics screening approach is proposed here where a holistic study of biomaterial-induced biological response is achieved by machine-learning modeling. Robust statistical and computational tools are applied to build models that can predict maturation responses based on our screened data and chip design parameters.

Findings: We have successfully identified hit microniche where iPSC-derived hepatocytes express up to 5 folds of maturation markers compared to blank ones. Simultaneously we have also built the machine-learnt classification model where an AUC value of 0.76 is obtained, indicating its predicting performance.

Conclusion & Significance: We have demonstrated that the materiomics approach can be used to screen "hits" where the iPSC-derived hepatocytes can be preferentially directed to a more matured state due to the topography and cell spatial organization. With necessary biological validation in the future, this could potentially generate a better cell source useful for drug toxicity testing.

e0001900@u.nus.edu