Cleveland Clinic Innovations

PRODUCT
A method to generate and culture qHSCs; study HSC activation to develop therapeutic agents.

INDICATION
Drug development

VALUE PROPOSITION
- Method to generate and culture qHSCs from iPSCs
- Study activation of HSCs
- Development of therapeutic agents in liver disease

DEVELOPMENT STAGE
Currently developed and validated protocol to develop qHSCs and aHSCs from iPSCs.

INTELLECTUAL PROPERTY
Patent Application Submitted

RELATED PUBLICATIONS
Park, J. *et. al.* (2023). IL-6/STAT3 axis dictates the PNPLA3-mediated susceptibility to non-alcoholic fatty liver disease. Journal of hepatology, 78(1), 45–56

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Method to generate qHSCs from iPSCs

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PROBLEM/OPPORTUNITY
Hepatic Stellate Cells (HSCs) are liver-specific pericytes that are located in the perisinusoidal space of the liver, are the main matrix-producing cells in the liver and are essential to a healthy liver function. Under normal conditions HSCs are present in quiescent state (qHSCs) but become activated (aHSCs) upon liver injury or under stress. Commercially available HSC cell lines are usually in the activated state. Moreover, primary HSCs, either quiescent or active from human healthy human livers are limited and difficult to obtain in a pure state. Moreover, HSC activation over a continuous period result in producing growth factors and extracellular matrices which can result in cirrhosis and hepatocellular carcinoma. Therefore, quiescent to HSC activation can be an effective way to study chronic liver diseases. There is a need to develop novel protocols/media compositions that can generate qHSCs in order to perform basic and drug discovery research in the field of chronic liver disease. Moreover, understanding the transformation of aHSCs from qHSCs can provide insights into mechanisms and help develop potential therapeutic targets.

SOLUTION/PRODUCT
Researchers at Cleveland Clinic have developed a culture system (protocol and media composition) to generate qHSCs from iPSCs. The differentiation protocol developed here was using fibroblast growth factor 1 (FGF1) and FGF2, epidermal growth factor (EGF), retinol and lipids which are required for HSC quiescence. After 13 days, differentiated iPSCs expressed qHSC markers. More importantly, Vitamin A storage in lipid droplets – a key feature of qHSCs was observed in these differentiated cells. The cells displayed remarkably high levels of qHSCs and low levels of aHSCs. Lastly, the qHSCs upon replating were successfully transformed to aHSCs that could be maintained for up to three passages. The derived cell lines were further characterized and validated by gene expression profile of molecular markers.