Mesenchymal stem cell derived hepatocytes (iMHeps): Invaluable tools for predictive hepatotoxicity and immune-compatible surrogates for liver function support

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Scarcity of liver donors and difficulties in obtaining functional primary human hepatocytes in clinically relevant numbers poses immense challenge for liver transplantation. This extrapolates to non-availability of primary hepatocyte culture alternatives for drug induced hepatotoxicity screening and studying hepatotropic infections. Though iPSC-derived hepatocyte cells emerged as alternatives, maturity of the differentiated state, prominence of fetal metabolism, promiscuous differentiation to related endoderm lineages and immune rejection poses a roadblock for preclinical/clinical applications. Owing to ease of expansion and established immune-evasiveness of Mesenchymal stem cells (MSCs), an attempt is made to trans-differentiate human adipose tissue derived MSCs to hepatocytes using a combination of developmentally relevant transcriptional factors and hepatogenic cues. IMHeps so derived manifested robust expression of liver enriched transcription factors, metabolic signatures comparable to human hepatocytes, drug inducible Cytochrome P450 enzyme activities mirroring adult hepatocytes and robust xenobiotic clearance. IMHeps are permissive to hepatotropic viruses certifying junctional maturity, a facet required for viral entry. In-depth analysis of background Mesenchymal memory in iMHeps indicated erasure of connective tissue differentiation potential indicating stability of the hepatic state even upon withdrawal of the initial hepatogenic cues used for trans-differentiation. Though iMHeps have forgone Mesenchymal differentiation abilities an unanticipated conservation of immune-modulatory abilities, a hallmark of native MSCs, was exhibited by iMHeps upon co-culture with activated immune cells. IMHeps could thus emerge as immune-compatible alternatives to primary human hepatocytes and transformed hepatoma lines for studies on drug induced hepatotoxicity, modelling liver infections and as transplantable surrogates for liver failure.

Speaker Biography

S Jyothi Prasanna had completed her Doctoral studies from the prestigious Indian Institute of Science, India. Her Doctoral Research involved studies on IFNγ signaling in hepatocellular carcinomas and the relevance of downstream pathways in antiviral immunity. As a Lead Scientist in Stem Cell Research Center, Manipal Hospital, she was instrumental in developing preclinical models to test the efficacy of allogeneic mesenchymal stem cells and has a patent on clinical scale expansion of human MSCs. Currently, she is heading the Injury, Repair and Regeneration team as a Professor at School of Regenerative Medicine, Manipal Academy of Higher Education..

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