**Improve the conversion of skin-derived fibroblasts into functional hepatocytes by directed evolution of native hepatic reprogramming factors**

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Large numbers of functional human hepatocytes are required for both biomedical research and pharmaceutical applications. Recent studies have shown that the ectopic expression of hepatic reprogramming factors leads to the direct conversion of human adult skin-derived fibroblasts into induced hepatocyte-like cells (iHeps). Although significant advancements have been made over the years, the reported conversion efficiencies and hepatic functionality of the obtained iHeps remain low. To overcome this problem, Matthias uses directed protein evolution tools to drastically enhance the performance of native hepatic reprogramming factors (HRF). Directed protein engineering is a technology platform that accelerates evolution by more than six orders of magnitude and tailors the functionality of proteins to specific applications. In a Darwinian evolution spirit, he anticipates that applying selection pressure will allow to evolve HRFs (eHRFs) to unprecedented reprogramming performance, capable of generating iHeps with superior hepatic functionality. The performance of the resulting eHRF-iHeps will be challenged in vitro and in an immune deficient murine liver disease model of hereditary tyrosinemia type 1.

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