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## **American Liver Foundation Research Award: Alternative Cell Sources for the Treatment of Metabolic Liver Diseases**

by Holger F. Willenbring, MD

Metabolic liver diseases caused by rare genetic aberrations often manifest early in life, progressively impairing liver function and requiring liver transplantation in childhood.

The majority of these diseases affect hepatocytes, which are the cells of the liver that provide its characteristic functions including production of proteins, detoxification and energy storage. Remarkably, pioneering studies suggest that exclusively replacing a patient's hepatocytes by transplantation of cells isolated from a healthy donor liver may be sufficient to correct most metabolic liver diseases. Donor livers are sparse however, and thousands of patients die each year while waiting for a suitable donor organ.

Hepatocyte transplantation and whole organ transplantation currently compete for the same donor organs. Although hepatocyte transplantation might represent an efficient and well tolerated alternative strategy for the treatment of metabolic liver diseases, it is not routinely performed due to the established effectiveness of whole organ transplantation.

In order to develop hepatocyte replacement strategies and limit the number of patients in need of a donor organ, alternative cell sources must be established. Surprisingly, cells as readily available as bone marrow cells might be suited for this purpose. Experiments in mice have shown that bone marrow transplantation can correct metabolic liver disease. How does this work? First nothing out of the ordinary happens: the transplanted bone marrow cells do what they are expected to do which is produce blood cells. These blood cells circulate through the body and, as in every mouse and human, some cells end up in the liver. There, a previously unknown process occurs: a subset of the donor-derived blood cells melds with the recipient's hepatocytes. This phenomenon is called cell fusion and the resulting fusion product contains the genetic material of both the blood cell and the hepatocyte. Importantly, the genetic programming and thus function of the blood cells and hepatocytes differ so that the genes that are defective in metabolic liver diseases are normally not active in blood cells. This means that although a transplanted blood cell contributes a healthy copy of the defective gene to the fusion product, this gene is not expected to be turned on and therefore cannot correct the disease. Remarkably however, hepatocytes represent the dominant partner in fusion products and appear to be capable of reprogramming the blood cells. The blood cell abandons its old function and acquires a completely new genetic program, that of a hepatocyte. Since the blood cell copy of the gene defective in the hepatocyte is activated as part of the reprogramming, the metabolic defect is corrected in the fusion product.

Cell fusion between transplanted blood cells and hepatocytes is a rare event and currently not therapeutically effective for most metabolic liver diseases. Fortunately, much knowledge already exists on fusion processes in other organs and organisms which can be exploited to increase the frequency of cell fusion in the liver. If this can be achieved and proves to be safe for application in humans, readily available bone marrow or blood cells could be used to correct genetic liver diseases by cell fusion.

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