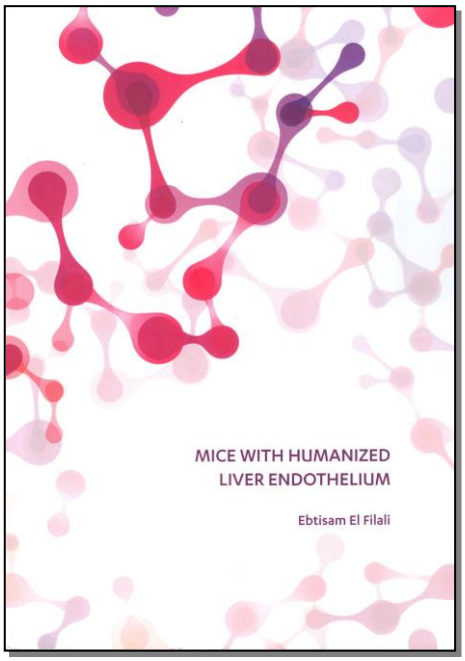

Samenvatting proefschrift Ebtisam El Filali

'Mice with humanized liver endothelium'

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The only curative treatment option for a large proportion of patients suffering from a liver disorder is liver transplantation. This is however a very invasive procedure and, due to shortage of healthy donor livers, only limited numbers of patients can benefit from this procedure. The use of ex vivo genetically modified autologous liver cells instead of whole liver transplantation could overcome the problem of donor scarcity. Even though clinical trials have shown that transplantation of liver cells is feasible, long-term outcome is disappointing.
Poor translation of animal studies to humans is one of the reasons for the disappointing outcome of clinical studies on cell transplantation. In the present thesis, we sought out to solve this problem by developing a mouse with a "humanized liver", which would serve as an excellent in vivo model for studies on liver-directed cell and gene therapy.
The aim of the present thesis was to identify cells that are suitable for liver engraftment and use these mice with a humanized liver in gene therapy.

In the first set of experiments, we found that human fetal liver sinusoidal endothelial cells have the unique ability to engraft and repopulate the mouse liver niche, while macrovascular and microvascular endothelial cells fail to do so. In addition, we also were unable to generate liver endothelium from human hematopoietic progenitor cells, either by direct transplantation of hematopoietic progenitor cells or by inducing endothelial regeneration in mice with human immune systems.
Human liver sinusoidal endothelial cells had a much higher liver engraftment and repopulation potential than human adult hepatocytes. Transplantation of fetal liver hepatocytes (hepatoblastst) failed to generate mature functional liver cells in vivo following transplantation further emphasizing the utility of endothelial cells for liver cell therapy.
We subsequently used our model of mice with human liver endothelium for ex vivo regulated erythropoietin gene therapy and to study in vivo gene therapy specifically targeted to human endothelium.

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