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PhD in Medical Sciences  
2014-2015

INVITATION to the Public defence of

**Lien THOEN**

To obtain the academic degree of '**DOCTOR IN MEDICAL SCIENCES**'

**The Role Of Stress Pathways During Hepatic Stellate Cell Activation****Wednesday 1 July 2015**

Auditorium **Brouwer**, **16:00**

Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

How to reach the campus Jette:

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Vrije Universiteit Brussel

## Summary of the dissertation

Liver fibrosis is characterized by chronic injury caused by a wide array of insults such as viruses, toxins, diabetes and alcohol abuse. Upon liver injury, lipocytic quiescent hepatic stellate cells (HSCs) activate towards contractile, proliferative myofibroblast-like cells. These activated HSCs show a decreased content of the characteristic lipid droplets and produce matrix proteins leading to scar formation and liver fibrosis. Unravelling the underlying mechanisms of this HSC activation process is therefore essential to develop novel liver fibrosis treatments. In this thesis, we focused on the role of stress pathways, more specifically autophagy and the unfolded protein response, during HSC activation. We demonstrated an increased autophagic flux during the activation process and showed that inhibition of autophagy hinders HSC activation. Moreover LC3B, an autophagy related protein, colocalizes with lipid droplets in quiescent HSCs after PDGF-BB stimulation suggesting a role for autophagy during lipid droplet metabolism. During both *in vitro* and *in vivo* HSC activation we observed a strong up-regulation of unfolded protein response markers already after several hours. This early UPR seems to be JNK1-dependent and contributes to HSC activation, but does not drive the activation process. In conclusion, we identified autophagy as a novel process important for HSC activation and a possible target for the development of new anti-fibrotic therapies. The unfolded protein response on the other hand is associated with HSC activation but is not necessary to drive this process.

## Curriculum Vitae

Lien Thoen was born on December 14<sup>th</sup> 1987 in the hospital in Asse. After a one year internship at the Liver Cell Biology lab (LIVR), she graduated at the Vrije Universiteit Brussel in 2010 in Biomedical Sciences. Lien started her doctoral studies in January 2011 in the LIVR lab under supervision of Prof. Leo A. van Grunsven and was funded by the Flanders agency for Innovation by Science and Technology (IWT). Her work focused on the role of stress pathways during hepatic stellate cell activation which plays an important role in liver fibrosis and portal hypertension. The results obtained during her PhD were presented at several national and international scientific meetings and were the subject of one first author paper in the Journal of Hepatology, one Punctum in Autophagy and a second submission to the Journal of Hepatology.