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FACULTEIT GENEESKUNDE EN FARMACIE

Doctoraat in de Medische Wetenschappen
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UITNODIGING

Voor de openbare verdediging van het doctoraatsproefschrift van

Inge MANNAERTS

donderdag 6 oktober 2011

U wordt vriendelijk uitgenodigd op de openbare verdediging van het proefschrift van

Inge MANNAERTS

'The Role Of Histone Deacetylases During Hepatic Stellate Cell Activation And Fibrogenesis'

Op **donderdag 6 oktober 2011** om **17 uur** in auditorium **R. Vanden Driessche** van de Faculteit Geneeskunde & Farmacie Laarbeeklaan 103, 1090 Brussel

Situering van het proefschrift

Liver fibrosis is caused by prolonged exposure to viruses, toxins, and environmental factors among others. Upon liver injury, hepatic stellate cells transdifferentiate into contractile myofibroblast-like cells that produce matrix proteins eventually leading to scar formation and liver fibrosis. Inhibition of this process is thus an important target for therapeutic intervention in liver fibrogenesis. An important step in developing an efficient anti-fibrotic therapy would be to unravel the underlying molecular mechanism. In this thesis we focused on the transcriptional regulation of the hepatic stellate cell activation process. By using Histone deacetylase inhibitors, valproic acid and MC1568, respectively inhibiting the class I and class II histone deacetylases, we demonstrate that members of both classes play a role in the activation of hepatic stellate cells. During a second part of the study, the effect of valproic acid treatment on gene and microRNA expression was studied. Identification of valproic acid sensitive microRNAs can provide us information about the underlying effect of valproic acid treatment on stellate cell activation. Our data suggest that valproic acid exerts its effect on stellate cells partly by influencing microRNA expression. In a last part, the role of two transcriptional repressors during stellate activation was studied, namely Zfhx1a and Zfhx1b. We showed that over expression of miR-200c mediated a down regulation of Zfhx1a and Zfhx1b, combined with an up regulation of E-cadherin expression levels. Over expression of miR-200c was sufficient to inhibit stellate cell migration and could have potential anti-fibrotic properties. In conclusion, we have shown that HDACs and their associated repressor complexes represent targets to modulate fibrotic disorders.

Curriculum Vitae

Inge Mannaerts was born on May 1st 1983 in the university hospital in Jette. After a one year internship at the CYTO lab, she graduated at the Vrije Universiteit Brussel in 2006 in Biomedical Sciences. Next, she started an I.W.T. funded PhD project in the CYTO lab under supervision of Prof. Leo van Grunsven. Her major work was focused on the role of histone deacetylases in hepatic stellate cells which plays an important role in liver fibrosis and portal hypertension. This work resulted in the publication of 1 first author article in a high ranked journal.