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Universiteit Leiden



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**Title:** Chemical biology of glucosylceramide metabolism : fundamental studies and applications for Gaucher disease

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# Propositions (Stellingen)

Accompanying the thesis

## **Chemical Biology of Glucosylceramide metabolism** *Fundamental studies and applications for Gaucher Disease*

Saskia Oussoren, Leiden, 28 september 2017

1. Inhibiting one specific lysosomal protease seemed like an attractive way to prolong the lysosomal life of glucocerebrosidase, but turned out to be fairly unfeasible and unappealing. This thesis, *Chapter 1*.
2. Stabilization of glucocerebrosidase by active-site occupancy provides basal evidence and additional motivation for the clinical development of chaperones to supplement ERT and treat (neuronopathic) Gaucher disease. This thesis, *Chapter 2*.
3. Combined with activity based protein profiling, photo activatable and clickable lipids offer a novel way to study glucocerebrosidase, despite their low crosslinking efficacy. This thesis, *Chapter 3*.
4. Deficiency of LIMP-2 shows that this protein is needed for efficient enzyme replacement therapy (ERT) and it has to be considered that LIMP-2 levels might have to be taken into account in treatment of Gaucher patients with ERT. This thesis, *Chapter 4*.
5. Lipid buildup in lysosomal storage disorders seems to level with age, which implies the existence of metabolic adaptations, as revealed by deacetylation of accumulating glycosphingolipids and their (extra)lysosomal transglucosylation. This thesis, *Chapter 5 & 6*.
6. LIMP-2 deficiency shows that it is not always the primary substrate or storage lipid which is most important to monitor, but rather the secondary storage material originating from deacetylation or transglucosylation. This thesis, *Chapter 5 & 6*.
7. The ability of glucocerebrosidase to transxylosidate and hydrolyse xylose substrates once again shows its catalytic versatility and merits further examination. This thesis, *Chapter 7*.
8. The ability to simultaneously quantitate sphingoid bases can provide a broad view of lipid levels in both health and disease conditions, even beyond lysosomal storage disorders. This thesis, *Addendum*.
9. "Everything will be okay in the end. If it's not okay, it's not the end". John Lennon
10. "One cannot think well, love well, sleep well, if one has not dined well". Virginia Woolf
11. "Sometimes the most ordinary things could be made extraordinary, simply by doing them with the right people". Elizabeth Green