

## Storage solutions

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## Valorisation



## Valorisation

### Societal and clinical relevance

NASH is a disease frequently associated with obesity. In Western countries it is becoming increasingly prevalent and even becomes more common in children. In a general US population of middle-aged adults approximately 12% have NASH. However, the prevalence of NASH strongly increases up to 90% in an obese population. In children, a similar trend is observed, especially when obese. The development of NASH at a young age can have severe consequences later in life, with progression into complicated liver disease and a shorter life expectancy. In line, NASH patients can also progress to other chronic liver diseases such as fibrosis, cirrhosis, liver cancer and eventually liver failure. Unfortunately, in the latter cases, the only solution is a liver transplantation. Recent studies clearly demonstrate that NASH is amongst the leading causes for a liver transplantation and, if left untreated, will progress to become the primary cause in the near future. Thus, NASH is a worldwide health concern and urgently needs adequate diagnosis and therapy. However, so far, accurate methods and treatment options for NASH are nonexistent. The successful results obtained in this thesis show novel methods to diagnose and inhibit NASH and consequently, are extremely promising to society, for example, to alleviate the economic burden related to NASH including healthcare costs. Besides NASH, these findings also hold great potential to affect a wide range of other diseases such as obesity-related diseases (i.e. diabetes and atherosclerosis) and diseases that share disease mechanisms with NASH (i.e. lysosomal cholesterol storage diseases and alcoholic fatty liver disease).

### Scientific relevance

Besides the scientific value, the results found in this thesis have enormous potential clinical relevance and are of interest to foundations, clinicians, patient associations and pharmaceutical companies. To make these clinicians and the pharmaceutical industry aware of these recent discoveries and to gather novel insights from different research perspectives, we organized the European Fatty Liver Conference in Maastricht. In addition, we published these findings in scientific and clinical journals relevant to our research field, such as *The American Journal of Gastroenterology*, *Journal of Hepatology* and *Hepatology* and patented our research data. In order to implement our findings into daily clinical practice, investments must be made into successful valorization procedures upon close collaboration with scientists, clinicians and the pharmaceutical industry. Currently, we are seeking such external collaborations, including the pharmaceutical industry, which can help us with further implementation. The application of a novel biomarker to detect NASH or ways to inhibit NASH development could be of huge benefit to patients with hepatic

inflammation. Eventually, this will result in an improvement of the quality of life of NASH patients but will also dramatically decrease healthcare costs.

Besides NASH, our findings are also relevant to other fields of medicine. In analogy with our observations in the liver, much of the cholesterol is also trapped inside lysosomes of macrophages during atherosclerosis and lysosomal storage diseases. Therefore, the obtained results are also expected to be of high value for future research into the diagnosis and therapy of cardiovascular diseases and lysosomal storage diseases.

## **Novelty**

Many studies in the field of the fatty liver focus on the total amount of lipids within the liver as the trigger for hepatic inflammation. Yet, this point of view does not explain the presence of hepatic inflammation in some healthy lean subjects. Thus, while most studies investigate the total lipid amount, the current thesis focused on the different types of cholesterol and their location within the macrophage. Here, it was shown that it is the oxidized form of LDL as the main trigger NASH, particularly when located inside the lysosomes of the Kupffer cells. Theoretically, this view is innovative and promising as it provides the basis for new prevention, diagnostic and treatment options for NASH. Instead of the prescription of lipid-lowering therapies for NASH patients, methods to prevent or lower lysosomal cholesterol accumulation inside the Kupffer cells should be tested in order to prevent and treat human NASH. From a diagnostic point of view, current non-invasive markers that are used in the clinic to detect NASH lack specificity and sensitivity to distinguish NASH from steatosis. In the current thesis, it was demonstrated that a novel non-invasive marker could help improve the detection of NASH patients before irreversible liver damage has occurred.

## **Potential applications**

The view that lysosomal cholesterol accumulation, particularly the storage of oxLDL, inside Kupffer cells is the central trigger for hepatic inflammation makes it a unique target for the prevention, diagnosis and therapy for NASH. Findings from this thesis suggest that high levels of anti-oxLDL antibody levels are protective for NASH development. In line, a simple immunization procedure with heat-inactivated pneumococci is an easy and inexpensive way in order to give rise to high anti-oxLDL antibody levels and to prevent NASH. Such preventive immunizations are of special interest for patients at high risk for the development of NASH.

Additionally, oxLDL should be considered as a significant risk factor for NASH and to other diseases within the spectrum of the metabolic syndrome. Therefore, circulating oxLDL requires close monitoring as it can add important prognostic information about the progression and regression of NASH and other obesity-related diseases. The view that plasma oxLDL serves as a risk factor for NASH, makes oxLDL an ideal candidate for

NASH therapy. Therefore, reducing the level of LDL oxidation by anti-oxidants is a promising therapeutic strategy to improve NASH.

Lysosomal dysfunction is an aspect subsequent to lysosomal cholesterol accumulation, which is followed by a modified release of lysosomal enzymes into the plasma. The obtained results from this thesis demonstrated that plasma cathepsin D, a lysosomal enzyme, could be used to improve non-invasive diagnosis in both children and adults with NASH. As such, plasma cathepsin D and potentially other lysosomal enzymes have the potential to reduce the amount of liver biopsies, which generally is an invasive procedure that causes a lot of discomfort and stress for the patient.

Additionally, ways to lower lysosomal cholesterol are promising in ameliorating the hepatic inflammatory response. Studies from our group clearly demonstrated that therapies aimed at stimulating lysosomal cholesterol transport into the cytoplasm are successful in reducing NASH. Future research is now ongoing to translate these potential therapies to the human situation.

