

University of Groningen

## The design of a liver-selective form of interleukin-10

Rachmawati, Heni

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2005

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Rachmawati, H. (2005). *The design of a liver-selective form of interleukin-10: a new strategy for the treatment of liver fibrosis*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

# Chapter - 1

## **Aim of the thesis**

## Aim of the thesis

In 1989, Mosmann and coworkers first described a cytokine that was produced by T helper 2 (Th2) cell clones and inhibited interferon- $\gamma$  synthesis in Th1 cell clones. This cytokine synthesis inhibiting factor is nowadays known as interleukin-10 (IL-10). IL-10 is produced by different cell types, such as T cells, monocytes, and B cells, after activation of these cell types by various stimuli. Endogenous IL-10 has potent anti-inflammatory activities. This endogenous IL-10 attenuates inflammatory disease processes amongst other via downregulation of proinflammatory cytokines released by activated immune competent cells. In recent years, IL-10 has attracted much attention since several studies also demonstrated direct antifibrotic properties of endogenous IL-10. The potential effects of this endogenous cytokine to limit fibrosis have encouraged clinical trials with recombinant IL-10 to treat chronic diseases in various tissues including the kidney and the liver. However, the exogenous administration of IL-10 into the systemic circulation yielded inconsistent and even controversial results from one model to the other. A possible reason for these different effects may be due to a short plasma half-life when IL-10 was given intravenously as a daily single dose. This plasma half-life is only 2 minutes due to renal clearance of this low molecular weight protein. This creates problems to therapeutic use of this cytokine for chronic diseases because its activity on cells is usually most optimal after long exposure times. In addition, IL-10, just like many other cytokines, affects many cells leading to multiple actions in various tissues *in vivo*. These side effects often limit the use of cytokines as therapeutic agents. This is also true for IL-10 whose therapeutic application during liver fibrosis is limited by the systemic immunosuppressive effect, next to the low efficacy due to low uptake in target tissues.

The aim of the thesis is therefore to modify IL-10 in such a way that an enhanced delivery to the site of action is achieved. The final aim is to test whether it is possible to use modified IL-10 as a therapeutic agent to treat liver fibrosis.

First, we reviewed the therapeutic effects that have been described for IL-10 *in vivo*. All current clinical applications of IL-10 and the clinical trials that are ongoing with this cytokine are outlined in **chapter 2**.

Secondly we assessed the pharmacokinetic profile of recombinant IL-10 and the expression of IL-10 receptor in several organs including kidney and liver,

in normal rats and in rats with extensive liver fibrosis. Results show a short plasma half-life and a rapid clearance of this cytokine by the kidney within minutes (**chapter 3**). Although receptor expression is increased during liver fibrosis, receptor expression remains low and uptake of native IL-10 in this organ is low (**chapter 3**).

Since the initial studies revealed high uptake of IL-10 in the kidney, we tested the anti-inflammatory and antifibrotic effects of this cytokine in the kidney during glomerulonephritis. Acute as well as more chronic effects of IL-10 in anti-Thy 1-induced glomerulonephritis in rats were examined (**chapter 4** respectively **chapter 5**).

In order to enhance the effectivity of this cytokine for the treatment of liver fibrosis, this cytokine has to be actively delivered to this organ to overcome the normal low uptake. We designed a modified form of IL-10 that rapidly accumulates in the liver in particular on hepatic stellate cells (**chapter 6**). These hepatic stellate cells are the most important target cells for antifibrotic therapies because this cell type is a major matrix-producing cell during liver injury and enhanced extracellular matrix deposition is the hallmark of liver fibrosis. The challenge is to modify IL-10 without destroying the biological activity of this bioactive compound.

We designed mannose 6-phosphate IL-10 and tested its pharmacokinetic profile, its receptor binding activity *in vivo* and biological effects *in vitro* (**chapter 6**). Subsequently, we tested the therapeutic effects of this modified cytokine during liver fibrosis induced by bile duct ligation in rats (**chapter 7**).

The studies presented in this thesis describe the development of a liver-selective form of a therapeutic cytokine, IL-10, from its synthesis and its characterization *in vitro* and *in vivo* to the testing of its biological activities *in vitro* and in an animal model of liver fibrosis. Since up till now, no antifibrotic drugs are approved due to safety problems, a potent antifibrotic effect of a liver-selective form of IL-10 during liver fibrosis may offer novel ways for the treatment of this chronic liver disease.

