

# Licensing Opportunity



## Serum autotaxin: tool and target for the diagnosis and treatment of disease-related pruritus (itch)

- First diagnostic tool for specific types of pruritus
- First target for development of therapeutic agents to treat cholestatic itch

Metabolic diseases, cancer, pregnancy

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## Background

Chronic pruritus is a disabling symptom accompanying a broad range of systemic disorders such as chronic liver diseases, chronic renal failure, malignancies, infections, and endocrine and hematologic diseases. Despite the recent discovery of itch-specific neuronal pathways, including novel itch mediators and their receptors, the pathogenesis of pruritus remains enigmatic. In many patients pruritus is a major burden, can dramatically reduce quality of life and even lead to suicidal ideas. Treatment options are limited in most diseases associated with pruritus due to the lack of knowledge about the pathological molecular mechanisms and there is an urgent need for novel therapeutic options.



## The Technology

Prof. Ronald Oude Elferink and Dr. Andreas Kremer at AMC have discovered in patients with different forms of cholestasis (such as intrahepatic cholestasis of pregnancy (ICP) and primary biliary cirrhosis (PBC)) that there is a highly significant correlation between the cholestasis-associated pruritus and serum autotaxin levels. Autotaxin is the enzyme that converts lysophosphatidylcholine (LPC) into lysosphosphatidic acid (LPA). When LPA is injected into mice intradermally the animals display scratching behaviour.

ICP is associated with premature birth and complications, and gives rise to severe itching. There are however many other conditions in pregnant women that give rise to itch. Serum autotaxin could therefore become an important diagnostic tool for ICP and patients with pruritus due to liver diseases. This invention is most likely not limited to cholestasis-associated pruritus. Other forms of local and systemic itch exist which may very well have the same background. Furthermore, autotaxin may be an important target for lymphoma and itch after wound healing.

There is no satisfactory drug against various forms of pruritus. Now, administration of an inhibitor of autotaxin could provide a better alternative to reduce itch perception.

## Applications

- Systemic diagnostic test to distinguish pregnancy-related cholestasis and primary biliary cirrhosis from other forms of itch.
- Diagnostic test to identify patients with pruritus due to liver diseases
- Autotaxin and LPA receptors as a target for an inhibitor to reduce itch.
- Autotaxin and LPA receptors as a target for lymphoma and itch after wound healing.

## R&D Status

The relationship between cholestasis-associated pruritus and serum autotaxin level has been established. The mechanism of this relationship is now further being unraveled. We are now also working on applications in cancer (lymphoma) and itch after wound healing. Animal models will be used to test candidate autotaxin inhibitors and LPA receptor antagonists.

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## Intellectual Property

Patent:

Priority application filed in October 2009 (PCT/NL2009/050642), PCT in October 2010.

## Inventors

Prof. Dr. Ronald P.J. Oude Elferink is Professor of Experimental Hepatology, Academic Medical Center Amsterdam and Department head of the Tytgat Institute for Liver and Intestinal Research. Prof. Oude Elferink did his PhD in biochemistry and has a long lasting interest in the physiological function of various ABC transporters and P-type ATPases. He published several high ranked papers about the role these transporters play in bile formation and could unravel the mechanisms of various cholestatic liver diseases. Prof. Oude Elferink is Executive Editor *Biochimica Biophysica Acta* (section Molecular Basis of Disease) and member of several scientific and editorial boards. His outstanding publishing quality is best represented by his Hirsch factor of 53 and the acquisition of various large research grants.

Dr. Andreas E. Kremer is Medical Doctor, worked in the University Hospital of Munich as a fellow in the Department of Gastroenterology and Hepatology. He is author of a German Biochemistry book for Medical and Biochemistry students published by Elsevier. Since 2007 Dr. Andreas Kremer works as a research fellow on a basic research project about the molecular mechanisms of cholestatic pruritus at the Academic Medical Center, University of Amsterdam. For the discovery of lysophosphatidic acid and autotaxin in cholestatic patients suffering from pruritus he won several prizes among which were the best presentation on the International Forum for the Study of Itch (IFSI) in 2009 and the best abstract of the European Liver Congress (EASL) in 2010.

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## Key publications

1. Kremer AE, Martens JJ, Kulik W, Ruëff F, Kuiper EM, Buuren HR, van Erpecum KJ, Kondrackiene J, Prieto J, Rust C, Geenes VL, Williamson C, Moolenaar WH, Beuers U, Oude Elferink RP. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. *Gastroenterology* 2010; 139(3):1008-18.
2. Folmer DE, van der Mark VA, Ho-Mok KS, Oude Elferink RPJ, Paulusma CC. Differential effects of progressive familial intrahepatic cholestasis type 1 and benign recurrent intrahepatic cholestasis type 1 mutations on canalicular localization of ATP8B1. *Hepatology* 2009; 50(5):1597-1605.
3. Paulusma,C.; Folmer,D.; Mok,K.; de Waart,D.R.; Hilarius,P.; Verhoeven,A.J.; Oude Elferink,R.P.J. (2008) ATP8B1 requires an accessory protein for endoplasmic reticulum exit and plasma membrane lipid flippase activity. *Hepatology* 47: 268-278.
4. Groen A, Kunne C, Jongasma G, van den Oever K, Petruzzelli M, Vrins CLJ, Bull LN, Paulusma CC, Oude Elferink RP. Abcg5/8 independent biliary cholesterol excretion in Atp8b1 deficient mice. *Gastroenterology* 2008; 134:2091-2100.
5. Kremer AE, Beuers U, Oude Elferink RP, Pustl T. Pathogenesis and treatment of cholestatic pruritus. *Drugs*. 2008; 68(15):2163-82.