

Mechanism and management of pruritus in chronic cholestatic disorders

Malaga, 24 May, 2019

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Amsterdam University Medical Centers
Location: Academic Medical Center
Amsterdam
The Netherlands

Disclosures

2014-2019

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Netherlands Foundation of Gastroenterology and Hepatology (MLDS)
EU project LIVERHOPE

Support for investigator-initiated studies

Dr. Falk, Intercept

Consulting fees / Consulting without fees

Intercept, Novartis, Shire / NGM

Lecture fees

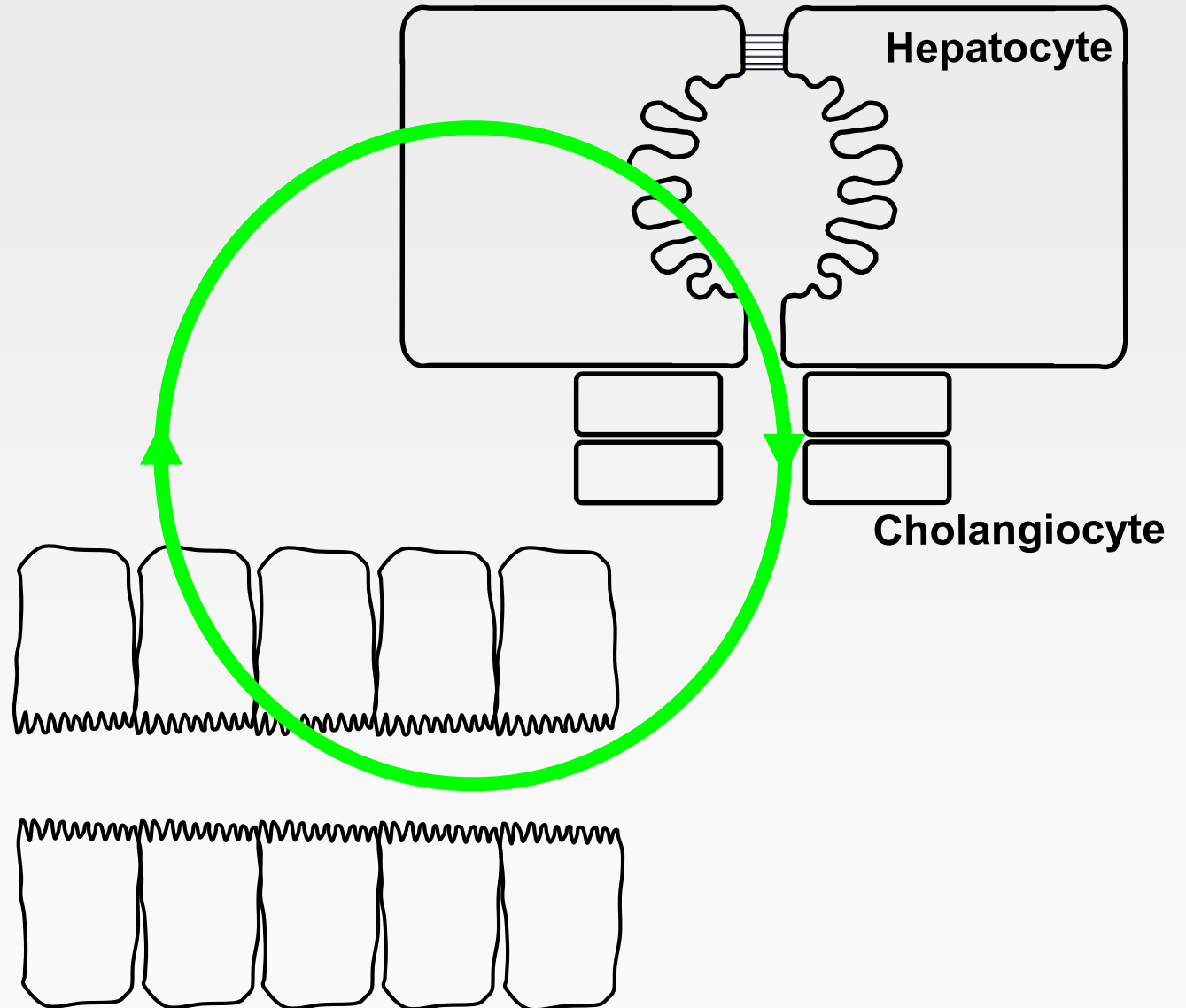
Abbvie, Falk Foundation, Gilead, Intercept, MSD, Novartis, Roche, Shire, Zambon

Motus Circularis Bilis

Mauritius Reverhorst
1690



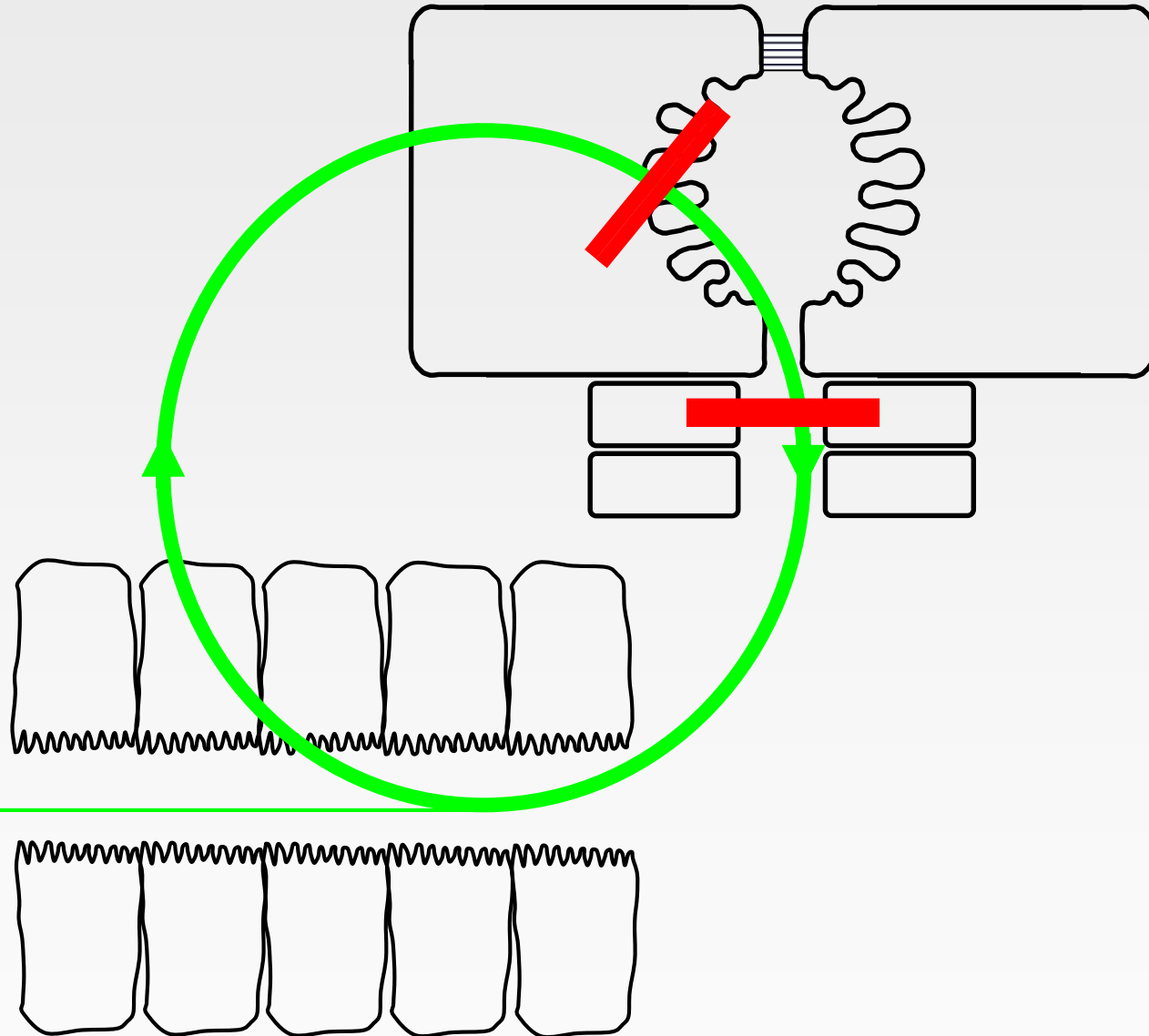
Giovanni Alfonso Borelli
1710



Impairment of Bile Secretion may Induce Pruritus



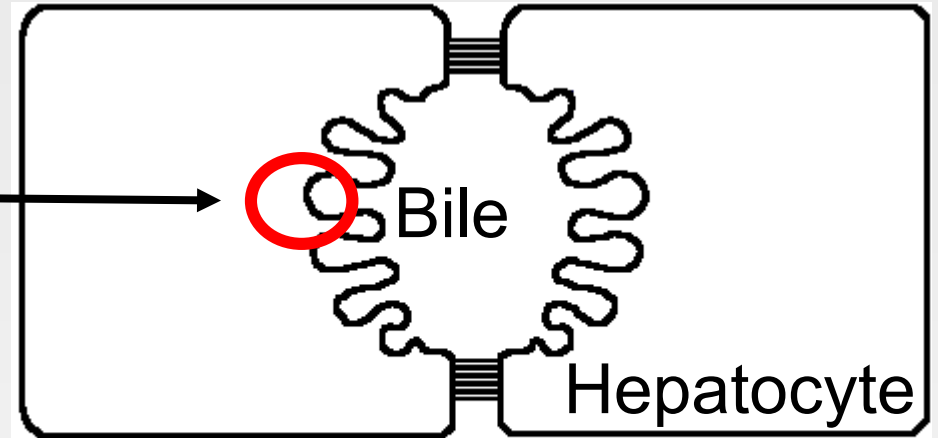
Sherlock and Summerfield, 1979



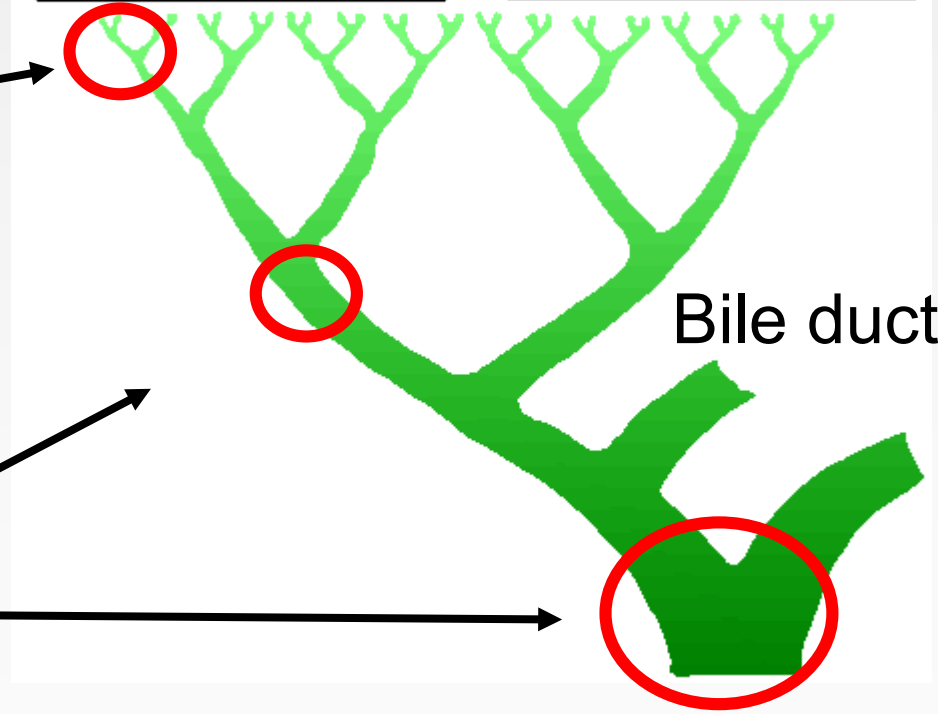
Causes of Pruritus in Cholestasis

Intrahepatic cholestasis of pregnancy

Hormones
Drugs
BRIC / PFIC
Alcohol
HCV



Primary biliary cholangitis (PBC)

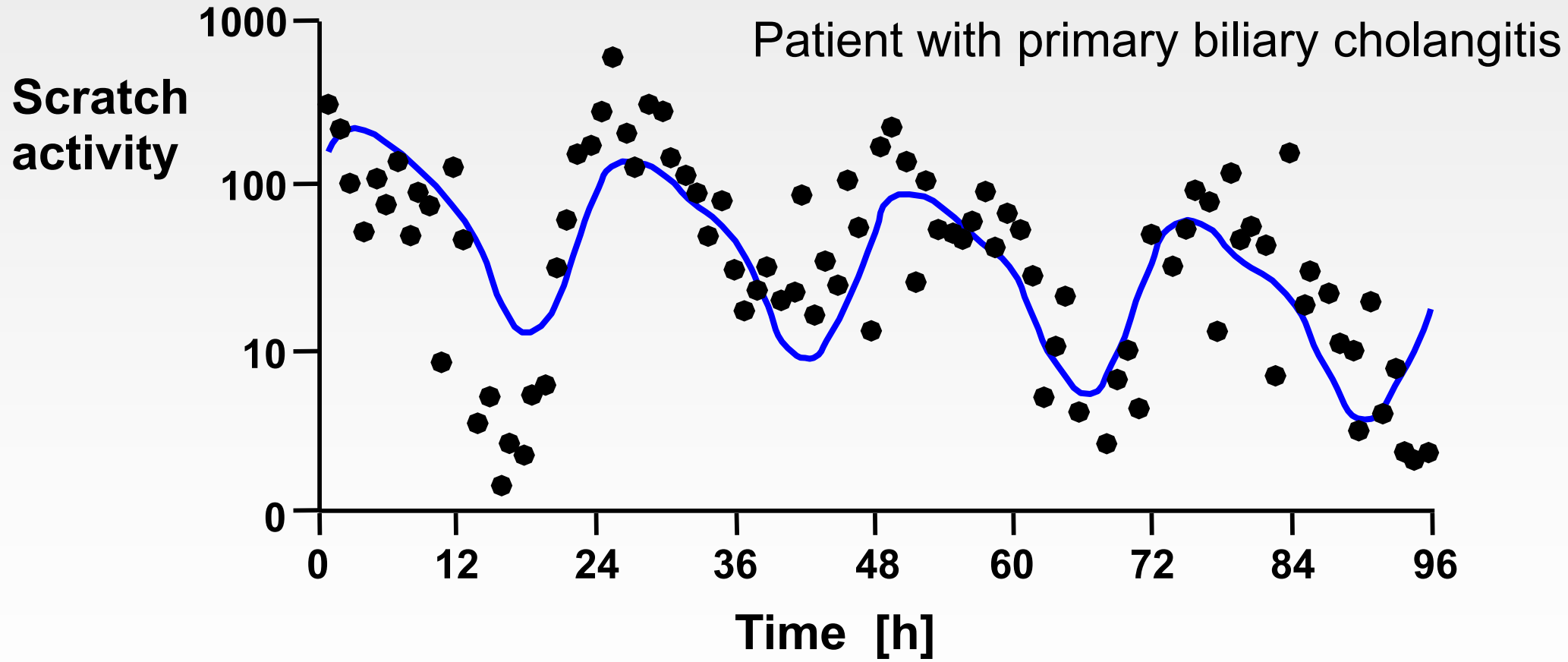


Primary sclerosing cholangitis (PSC)

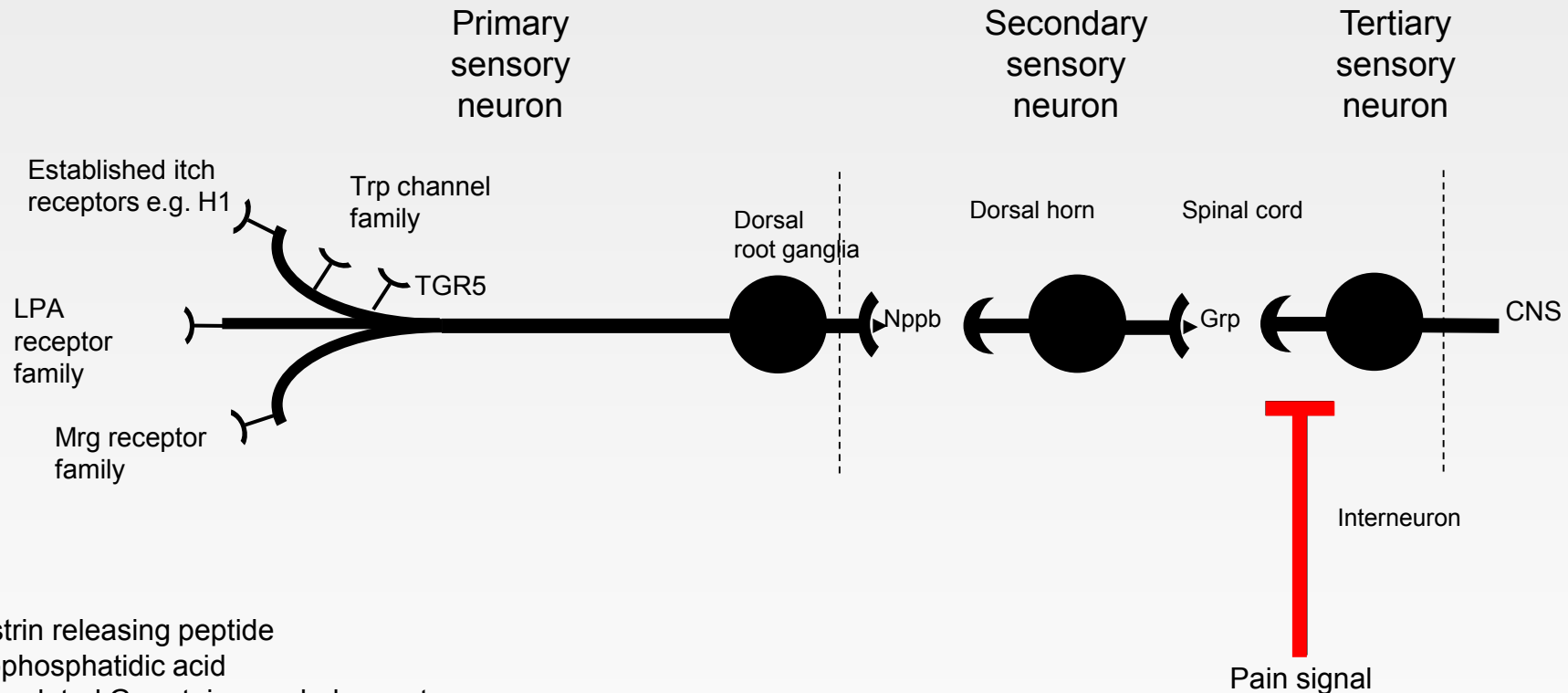
Secondary sclerosing cholangitis
IgG4-associated cholangitis
Cholangiocarcinoma
Hilar lymphadenopathy
Metastases
Biliary atresia, Alagille syndrome, others

Pruritus in Primary Biliary Cholangitis

- Diurnal variation -

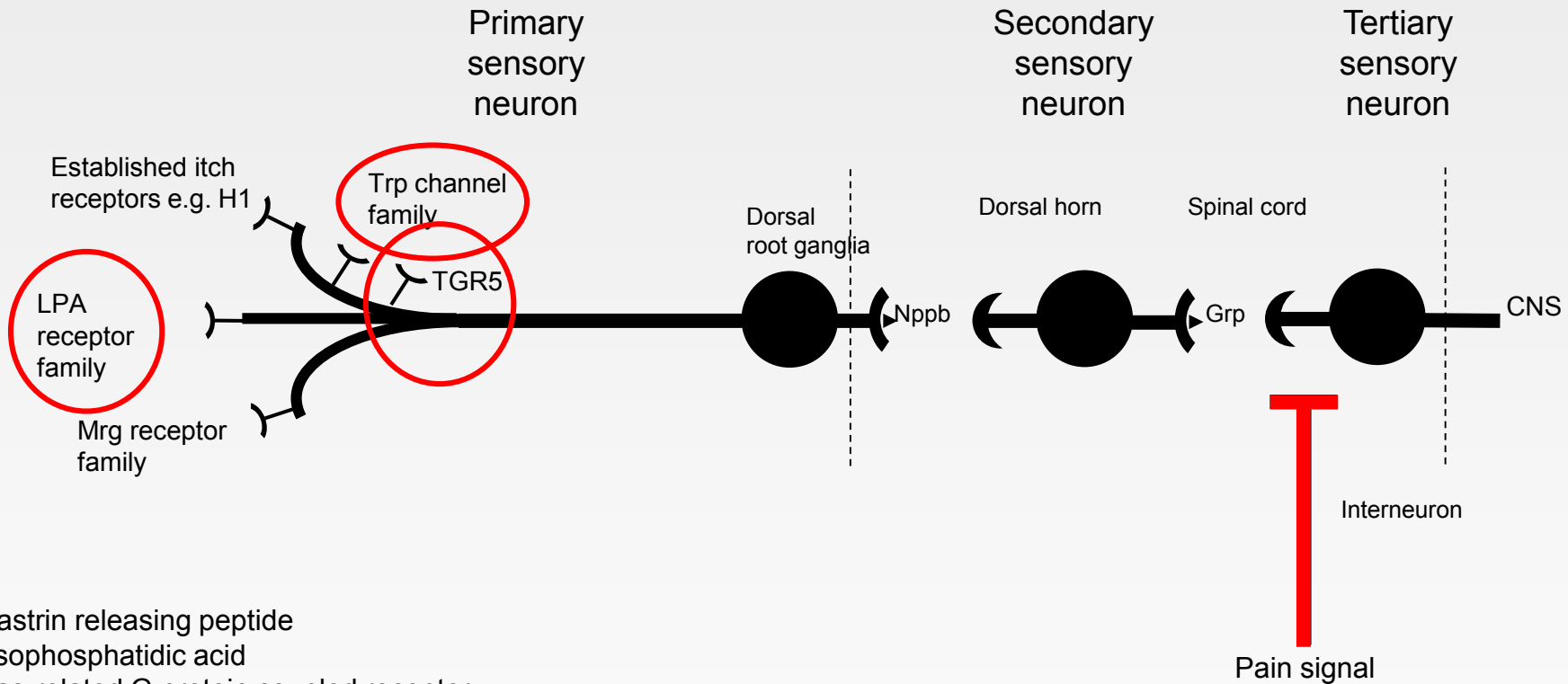


The Itch Neuron



GRP, gastrin releasing peptide
LPA, lysophosphatidic acid
Mrg, Mas-related G protein coupled receptor
Nppb, natriuretic polypeptide b
TGR5, G protein coupled bile acid receptor
Trp, transient receptor potential

The Itch Neuron

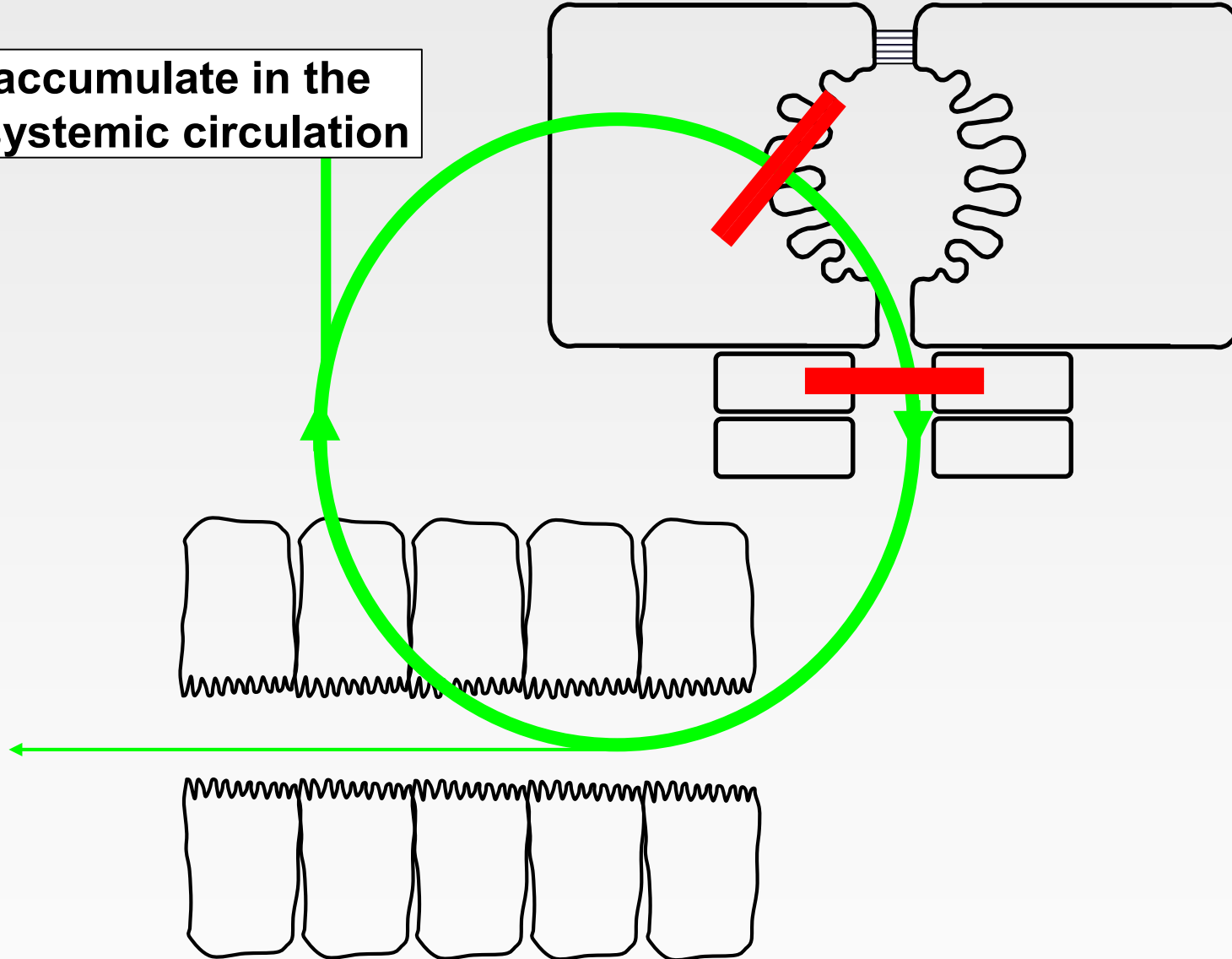


GRP, gastrin releasing peptide
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Potential Pruritogens in Cholestasis

Pruritogens...

accumulate in the systemic circulation



Pruritus in Cholestasis

- Therapy 2019 -

Evidence

1st line :	● Cholestyramine (1-2 x 4 g/d, max. 16 g/d)	II-2 / B1
2nd line :	● Rifampicin (2 x 150 – 300 mg/d)	I / A1
3rd line :	● Naltrexone (25 - 50 mg/d)	I / B1
4th line :	● Sertraline (75 - 100 mg/d)	II-2 / C2

- Experimental**
- Cannabinoids
 - UV light therapy
 - Albumin dialysis
 - Nasobiliary drainage
 - Liver transplantation

Categories of evidence:

- I Randomized controlled trial
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Evidence grading:

A: High quality; B: Moderate quality; C: Low quality

Recommendation:

1: Strong; 2: Weak

Pruritus in Cholestasis

- Therapy 2019 -

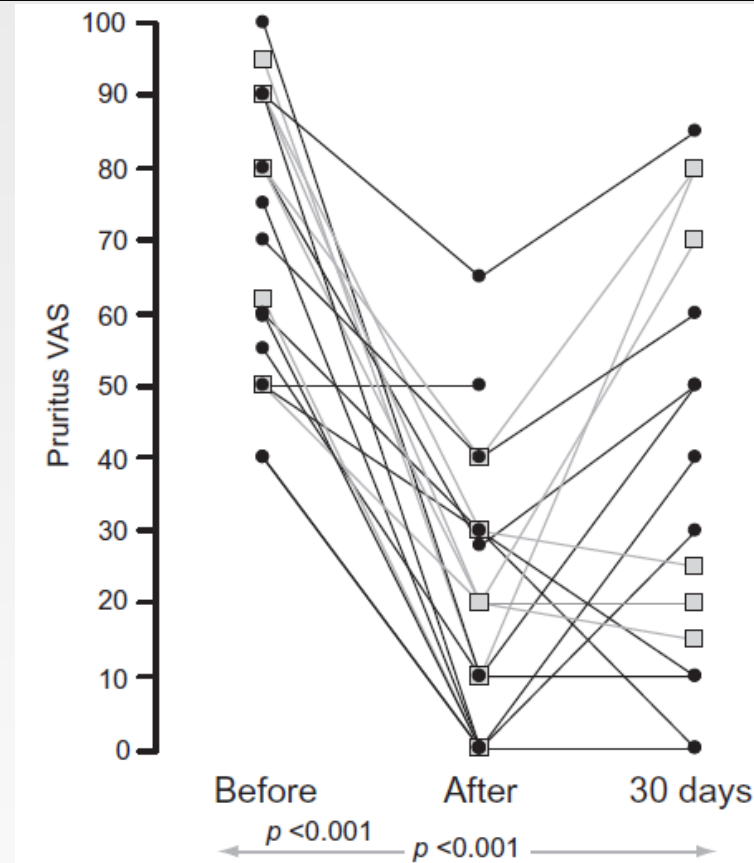
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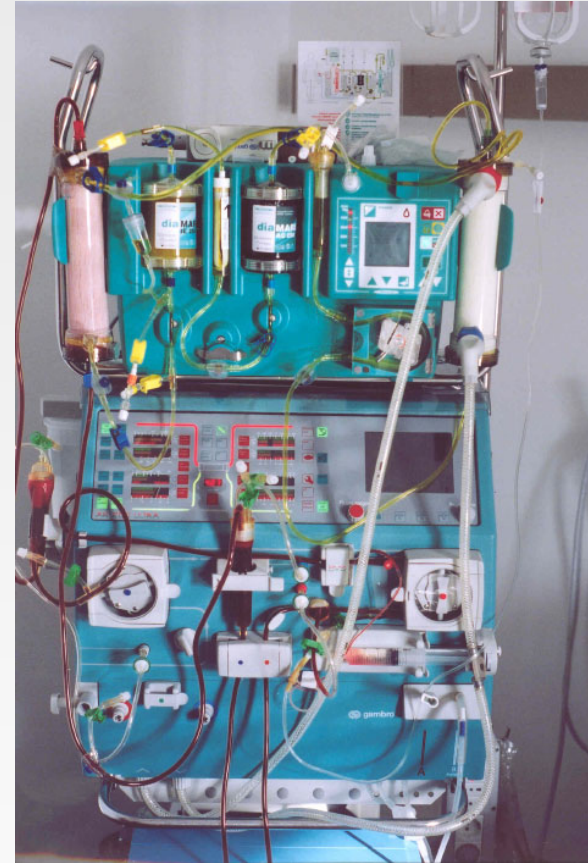
- Experimental**
- Cannabinoids, Ondansetron
 - UV light therapy
 - **Albumin dialysis (e.g. MARS^R); plasma separation/anion absorption**
 - Nasobiliary drainage
 - Liver transplantation

Severe Refractory Pruritus in Cholestasis

- Experimental Therapeutic Approaches -



Pares et al., J Hepatol 2010;53:307



Plasmapheresis ¹

Albumin dialysis (MARS^R, Prometheus^R) ²

Plasma separation / anion absorption ³

1. Cohen et al., Gut 1985; 26 (3); 291

2. Pares et al., Am J Gastroenterol 2004;99:1105, J Hepatol 2010;53:307

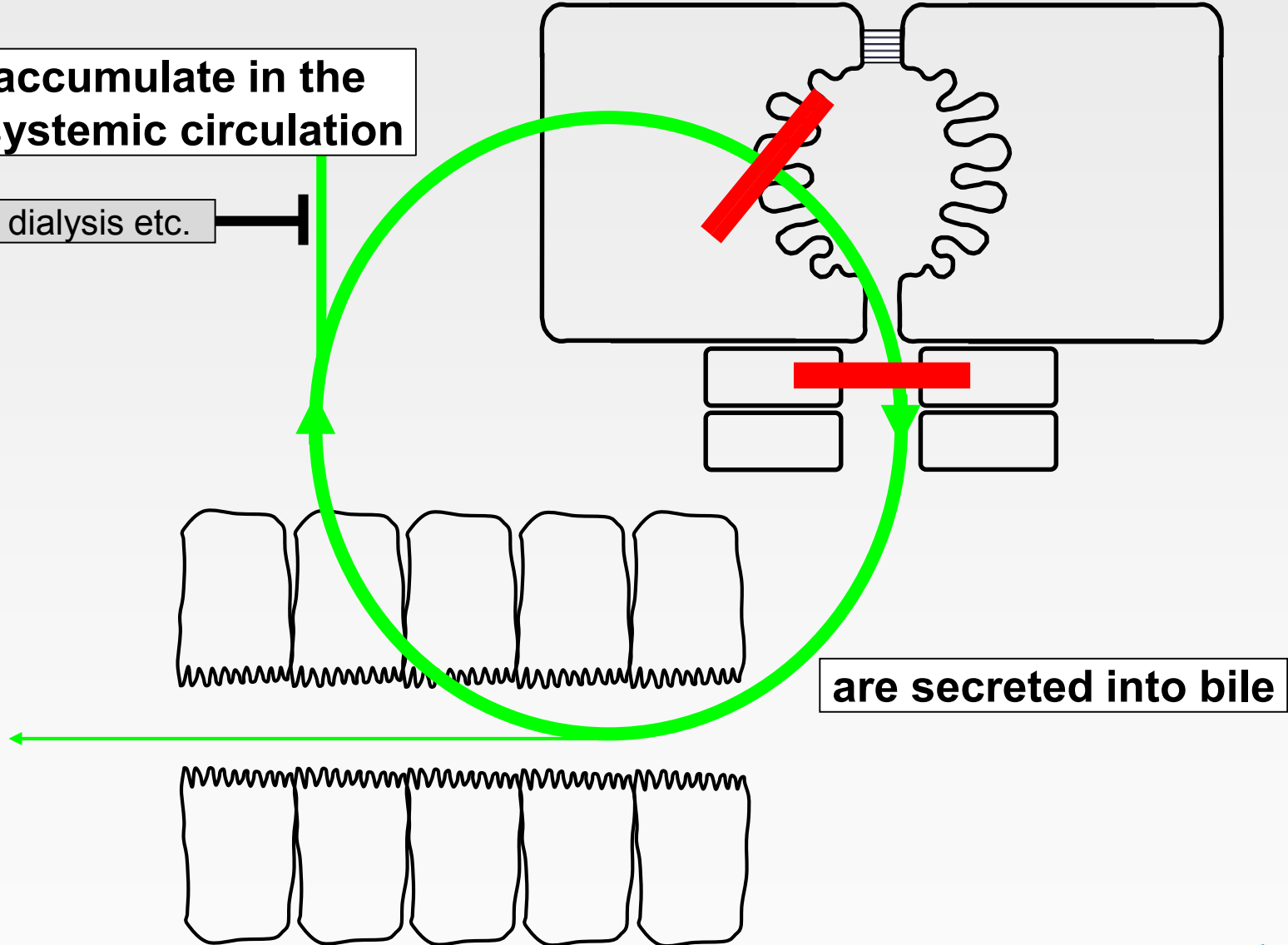
3. Pusi et al., J Hepatol 2006;45:887

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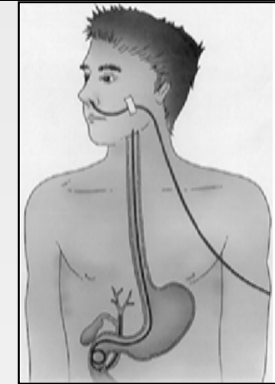
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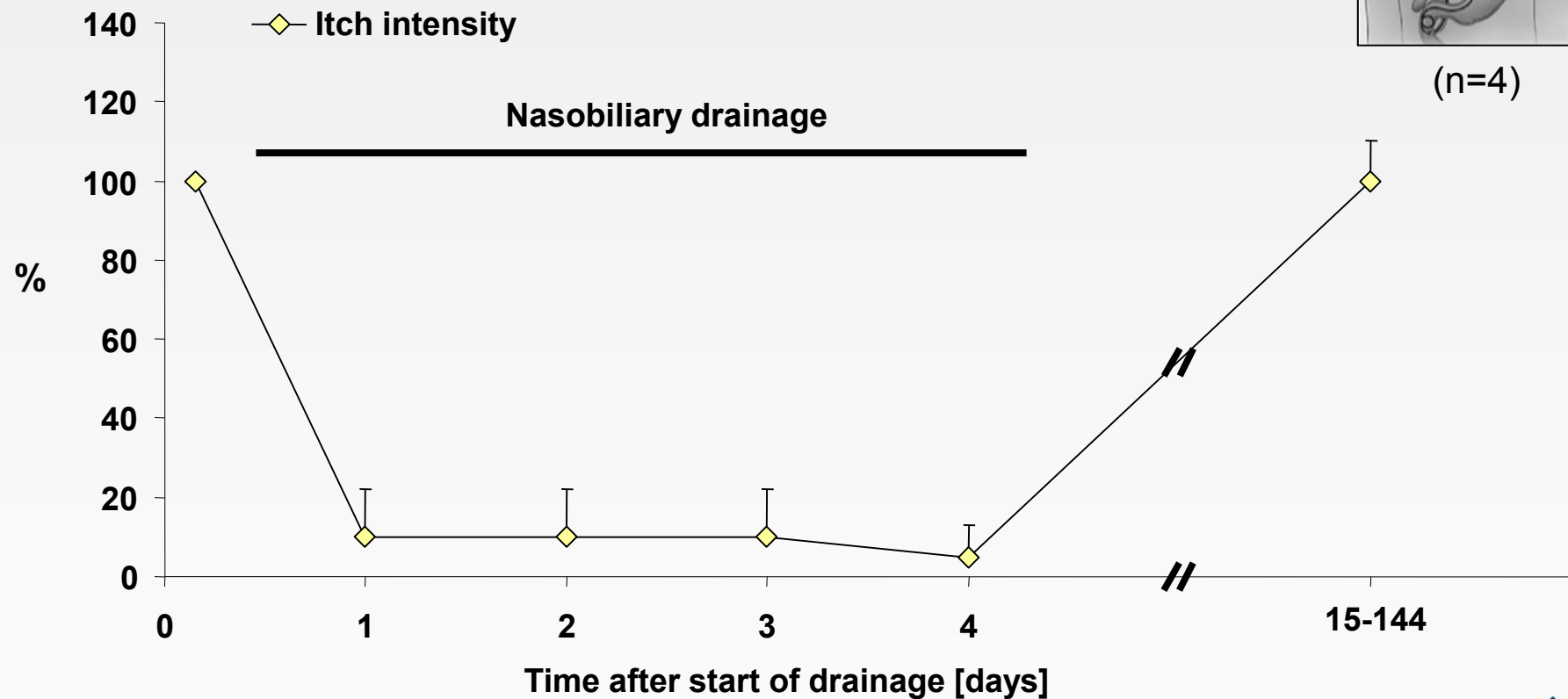
Severe Refractory Pruritus in Cholestasis

- *Experimental Therapeutic Approaches* -

Nasobiliary drainage in PBC



(n=4)



Potential Pruritogens in Cholestasis

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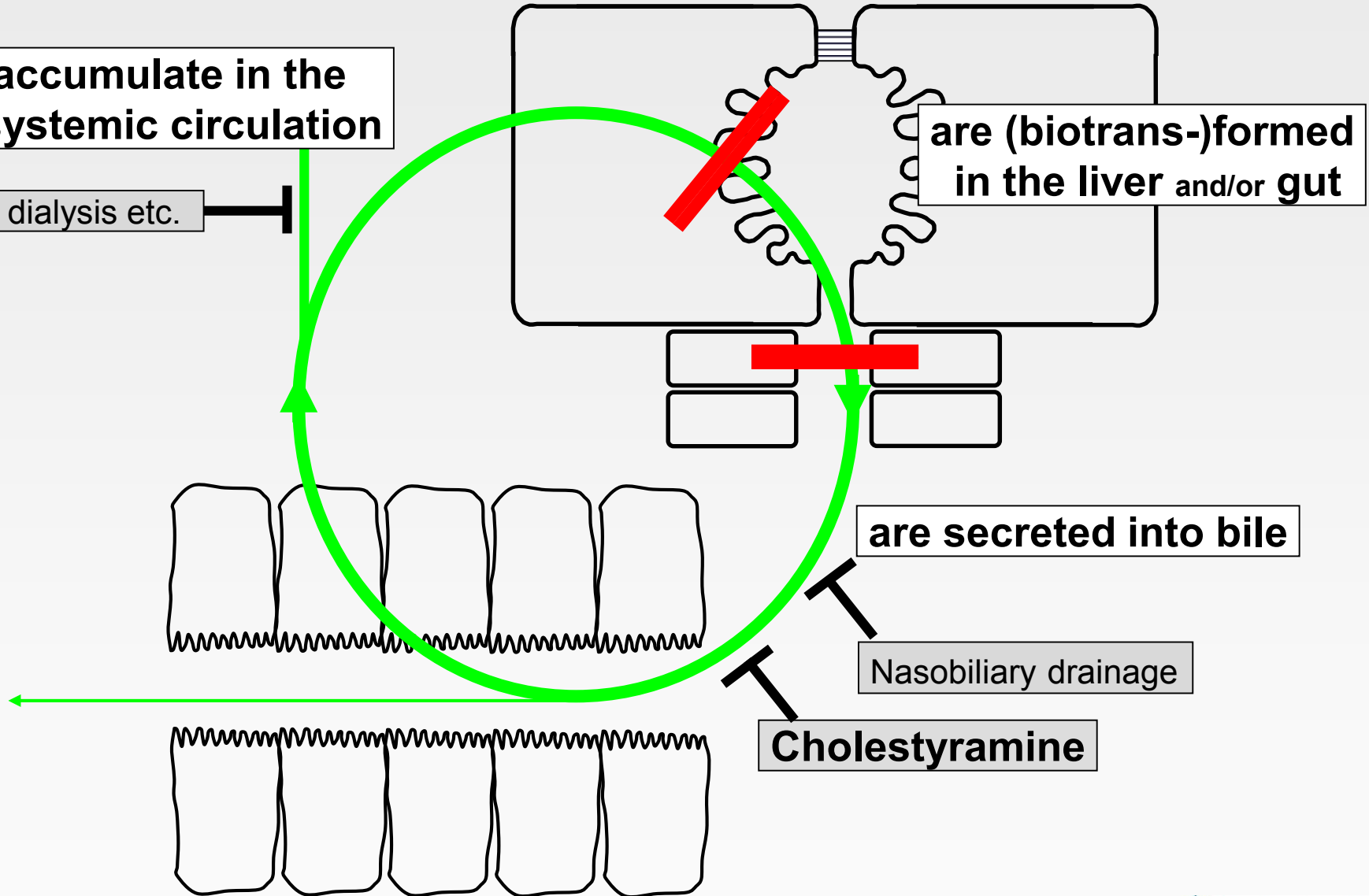
Albumin dialysis etc.

are (biotrans-)formed in the liver and/or gut

are secreted into bile

Nasobiliary drainage

Cholestyramine



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- Therapy 2019 -

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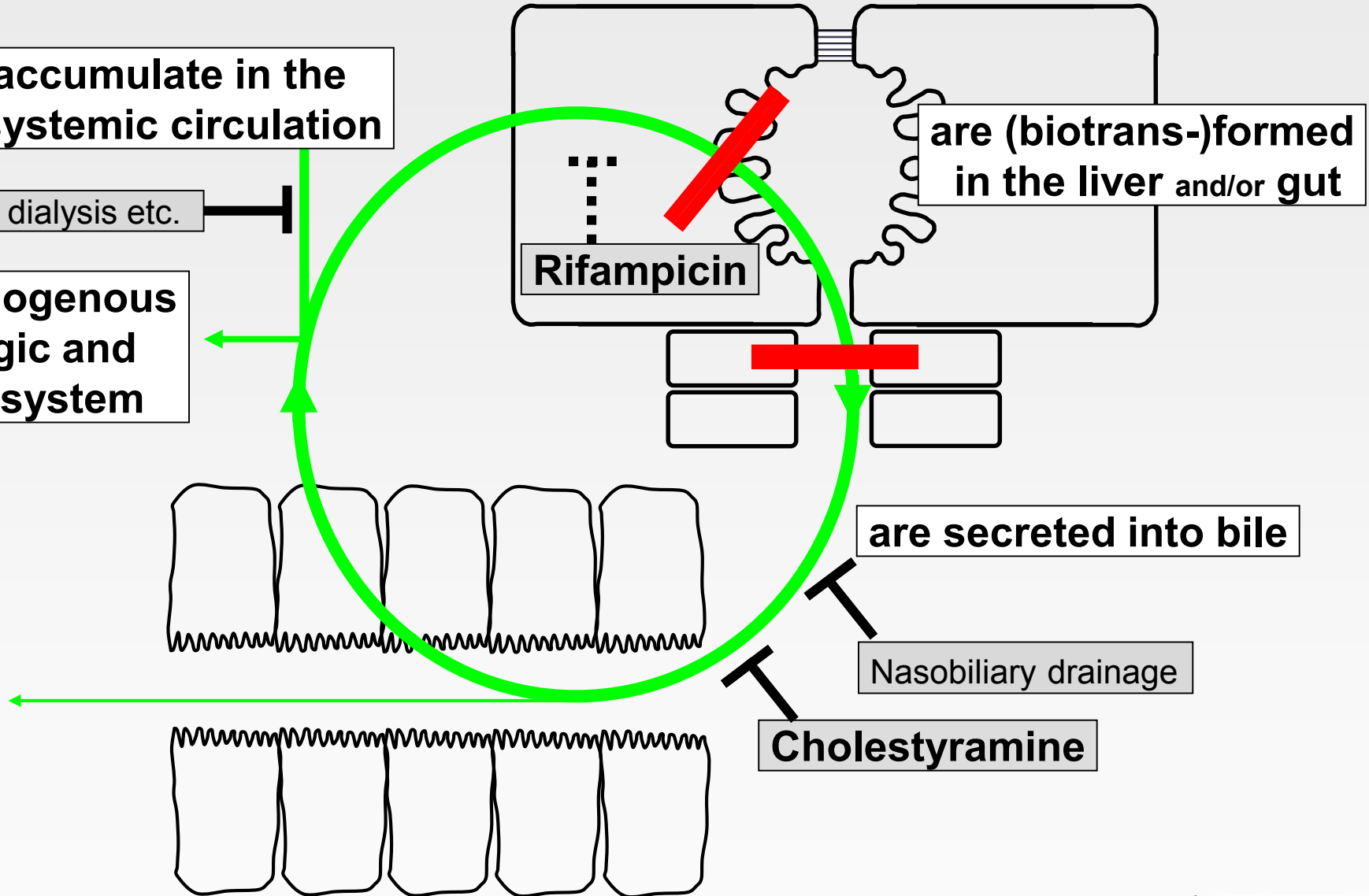
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Therapeutic Targets in Pruritus of Cholestasis

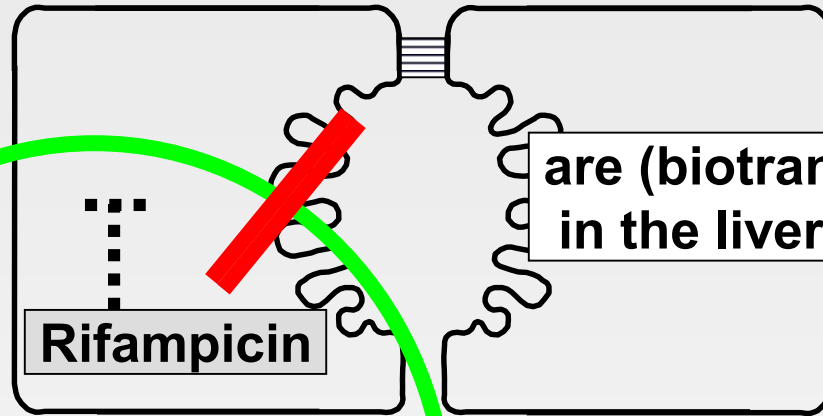
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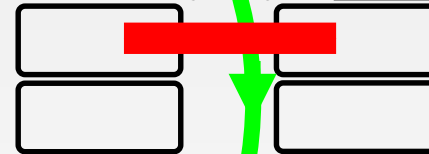
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Sertraline



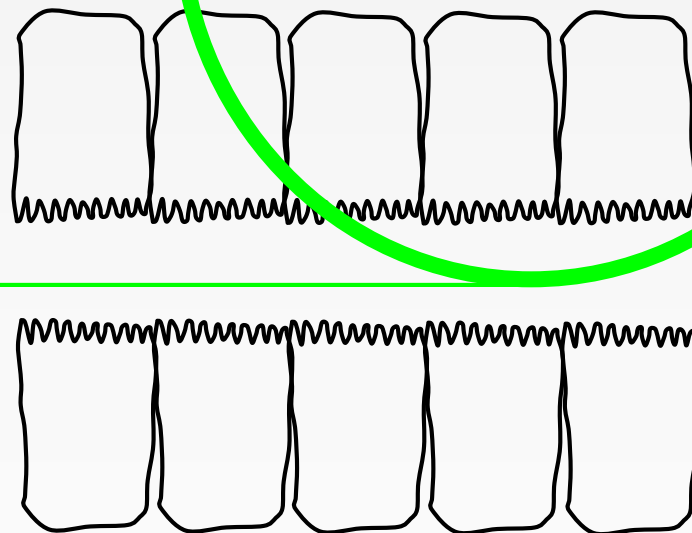
are (biotrans-)formed in the liver and/or gut



are secreted into bile

Nasobiliary drainage

Cholestyramine



What causes Pruritus in Cholestasis?



www.drug-rehab-headquarters.com

Aretaeus the Cappadocian

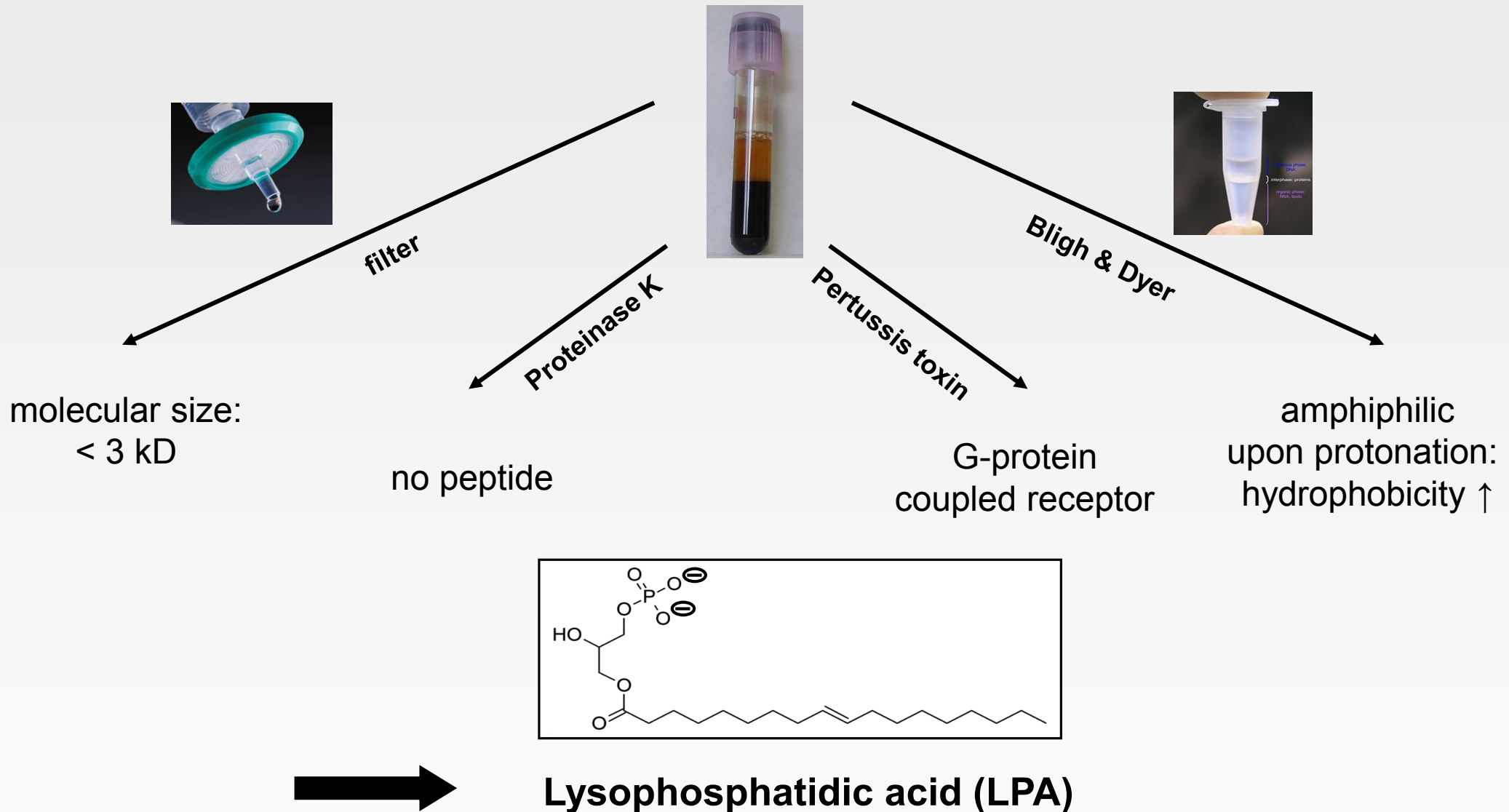
(1st century A.C.)

‘Pruritus in jaundiced patients is caused by prickly bilious particles’

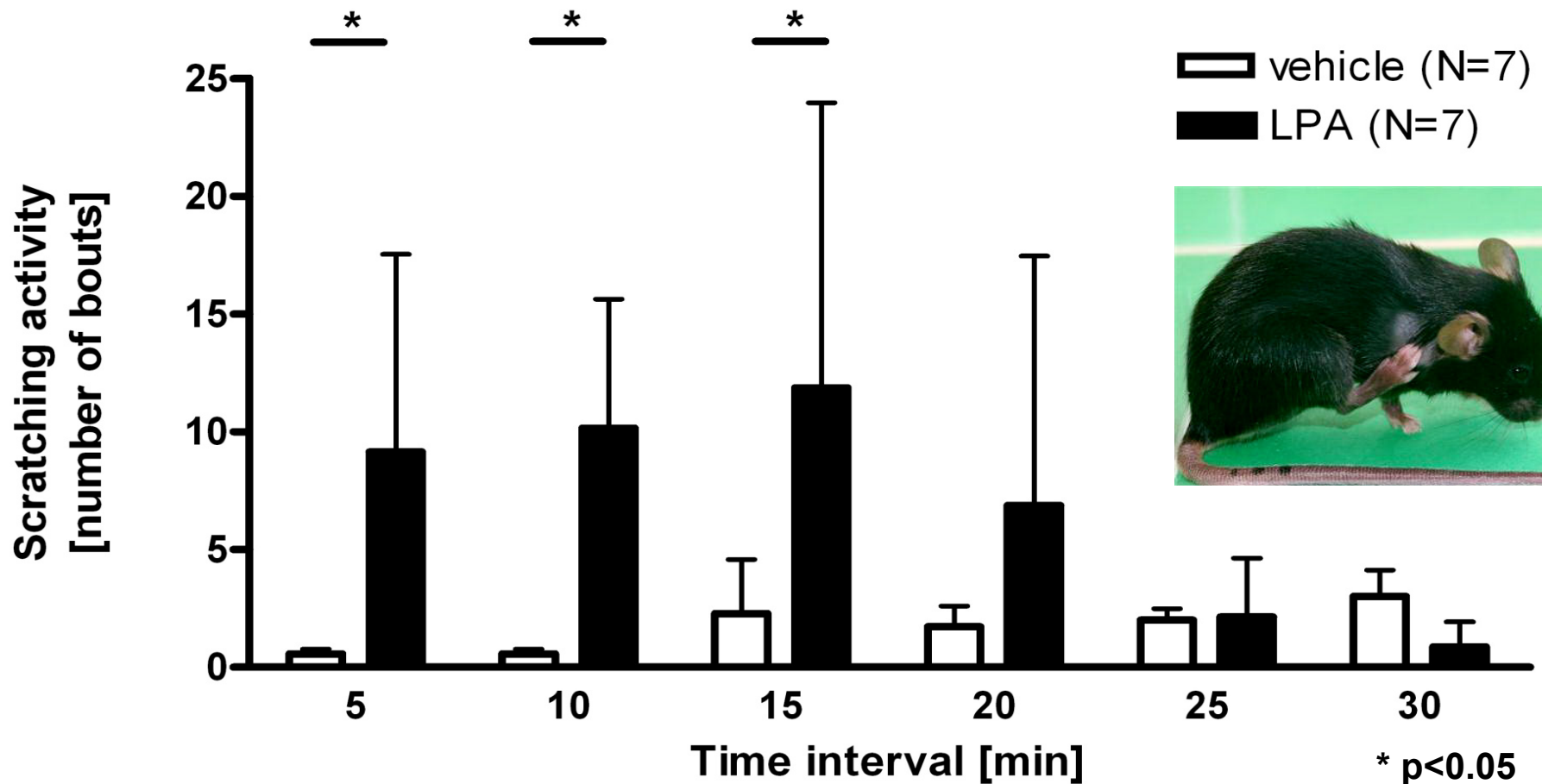
Which substance classifies as pruritogen in cholestasis?

- **Bile salt**
- **Bilirubin**
- **Endogenous μ -opioid**
- **Fatty acid**
- **Histamin**
- **Lysophosphatidic acid (LPA) / autotaxin (ATX)**
- **Neuropeptides (substance P, calcitonin gene-RP)**
- **Serotonin**
- **Steroid metabolite**

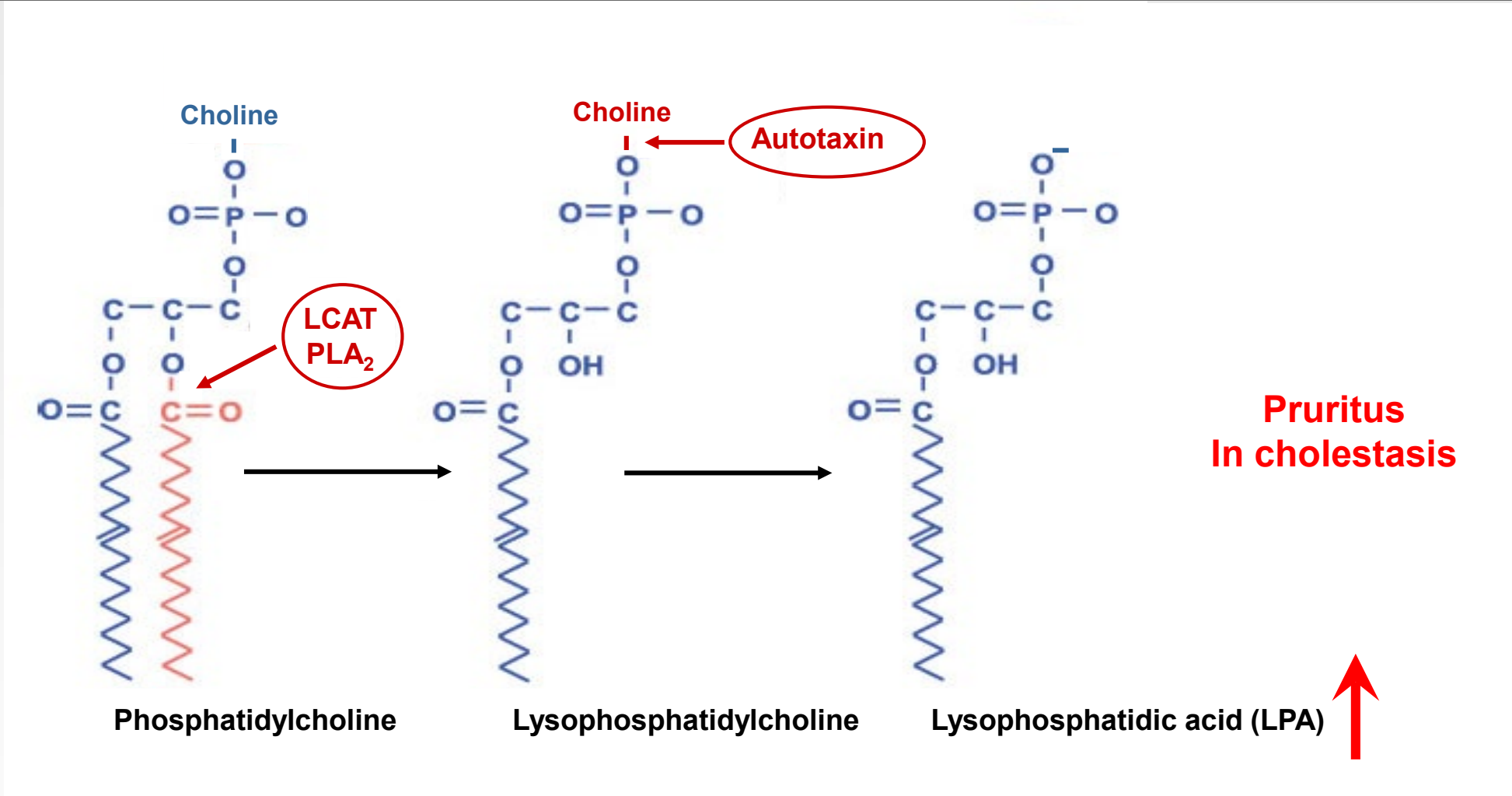
Identification of a Neuronal Activator in **Serum** of Pruritic Patients



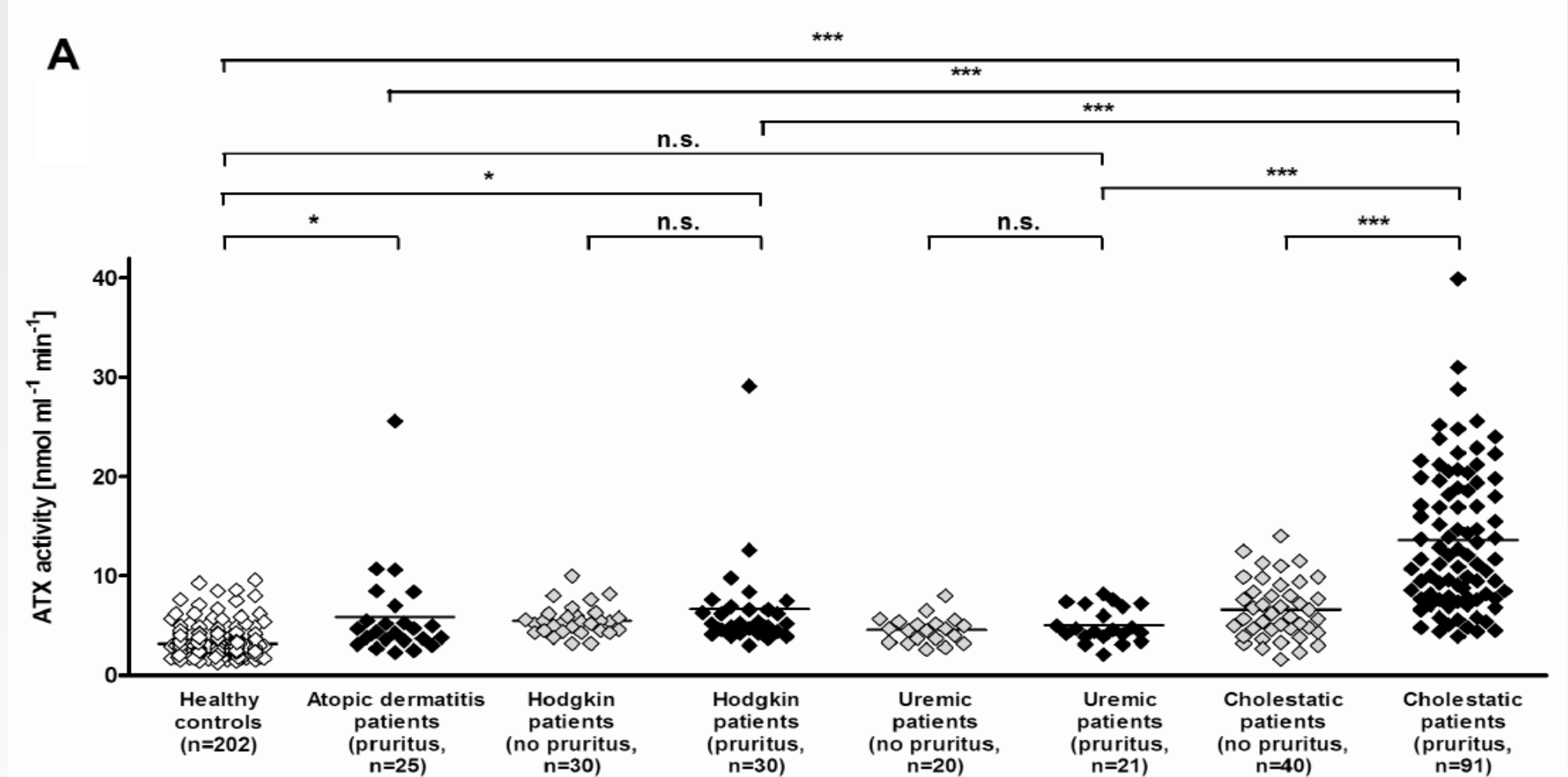
Intradermal LPA Increases Scratching Behaviour in Mice



Lysophosphatidic Acid (LPA) is Elevated in Serum of Pruritic Patients

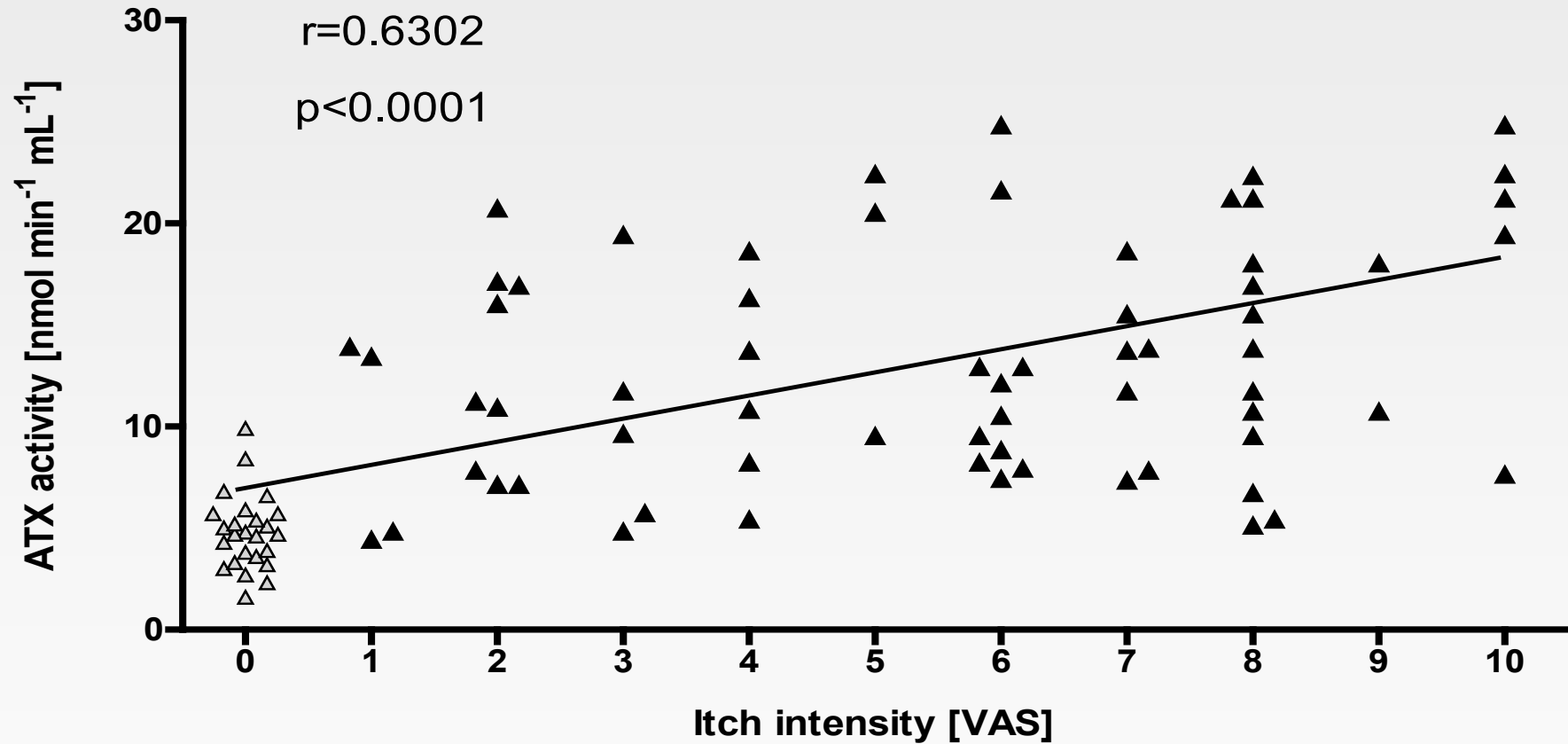


Increased Autotaxin Activity is rather specific for Pruritus of Cholestasis



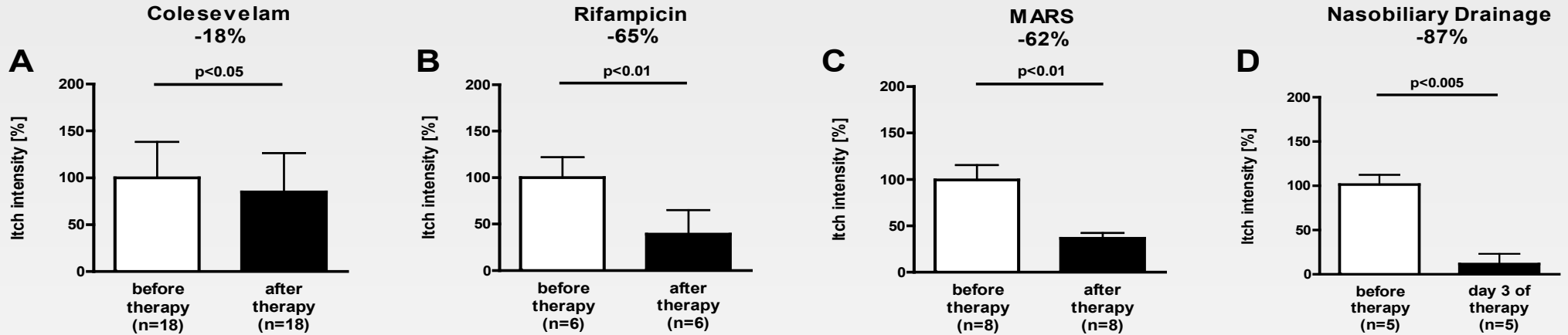
* $p < 0.05$, *** $p < 0.001$ (ANOVA)

Linear Correlation between Autotaxin Activity and Itch Intensity



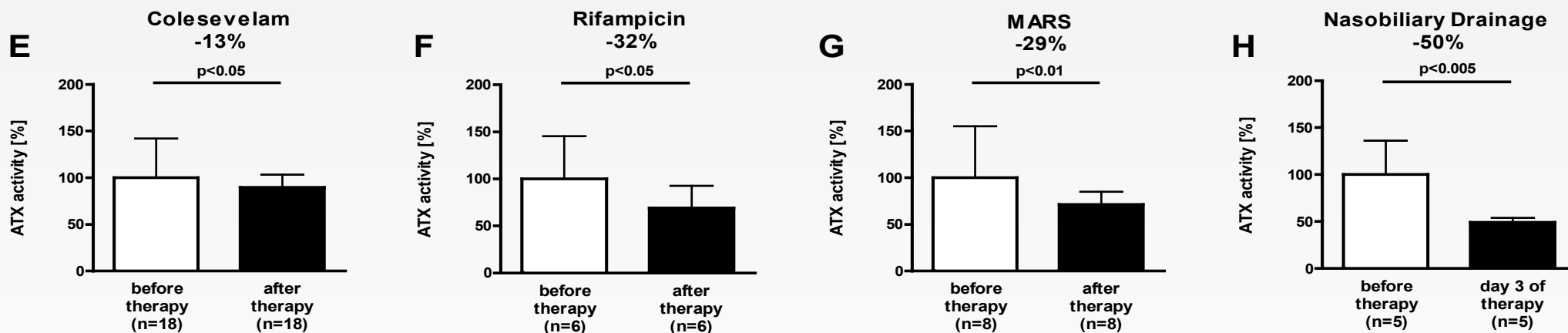
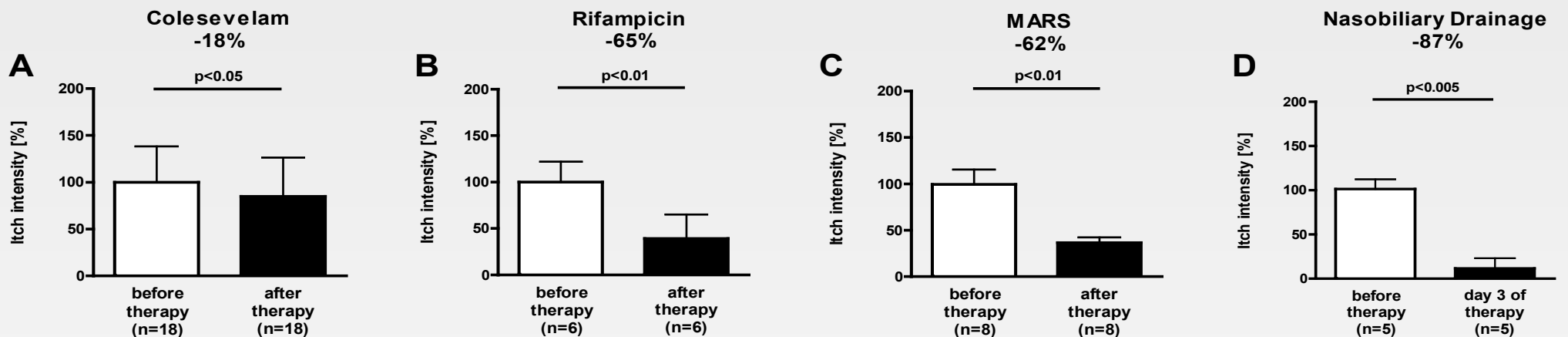
Autotaxin Activity Mirrors Therapeutic Efficacy in Pruritus of Cholestasis

Itch



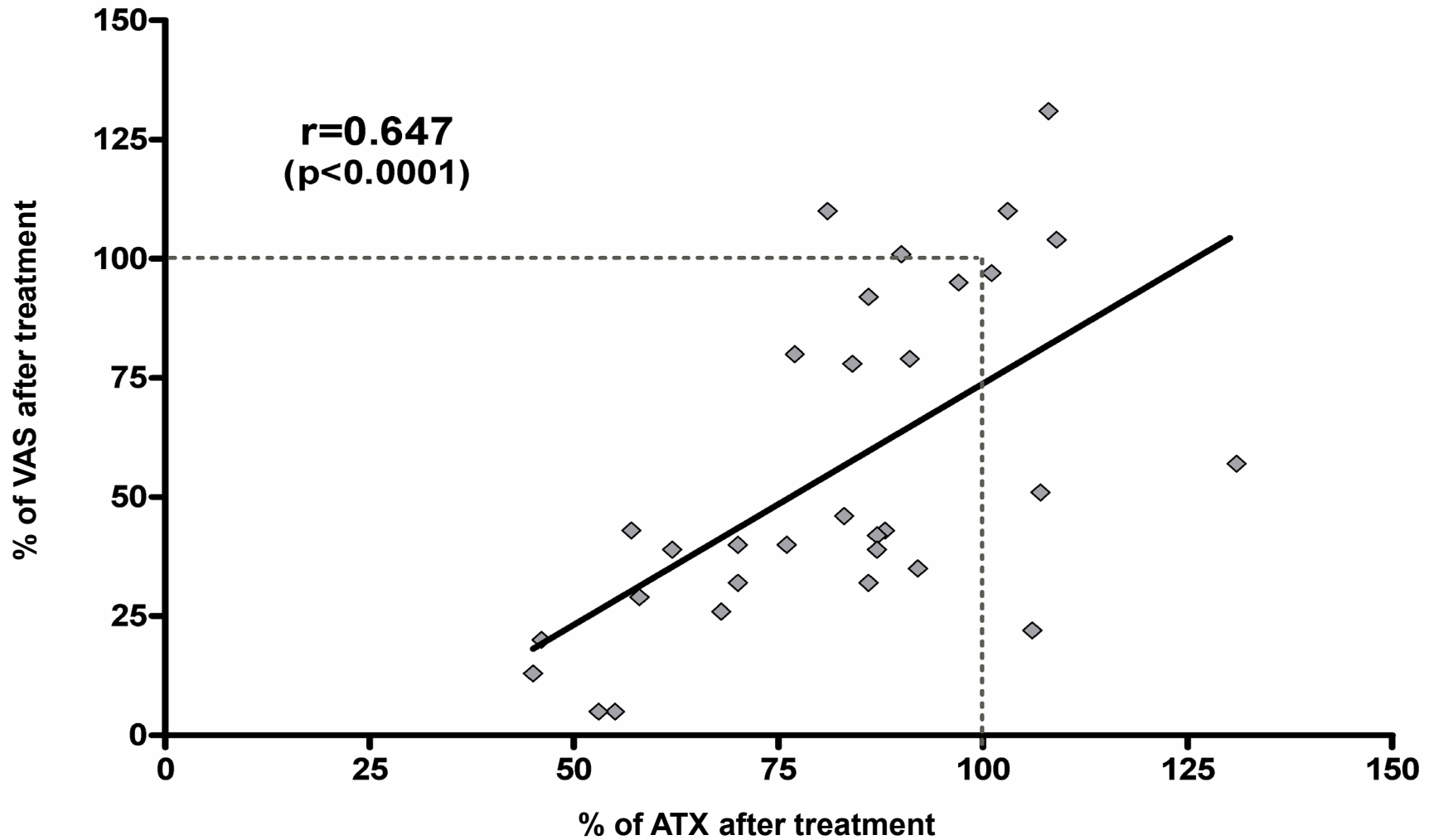
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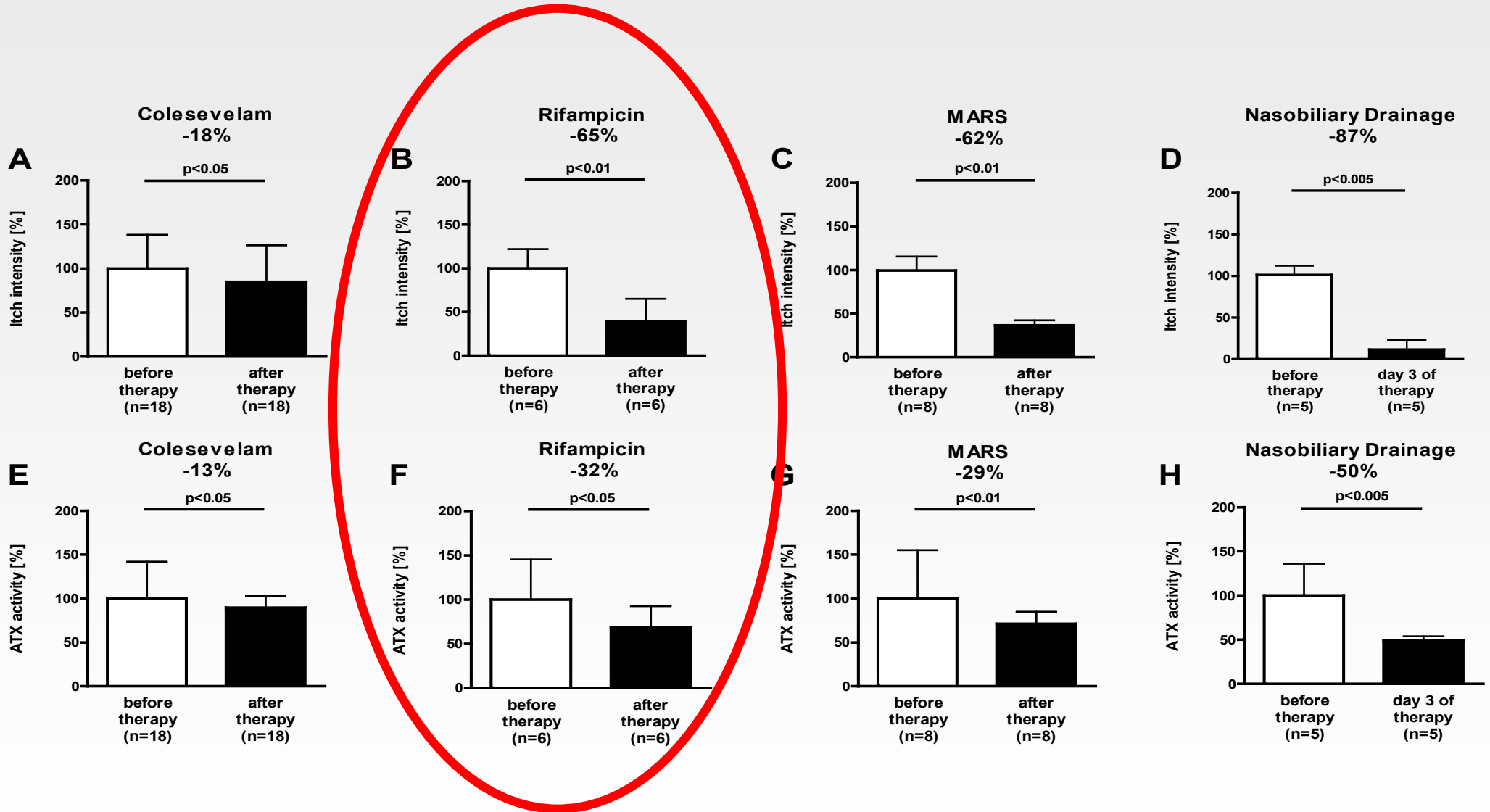


ATX

Correlation between Change in Autotaxin Activity and Itch Intensity

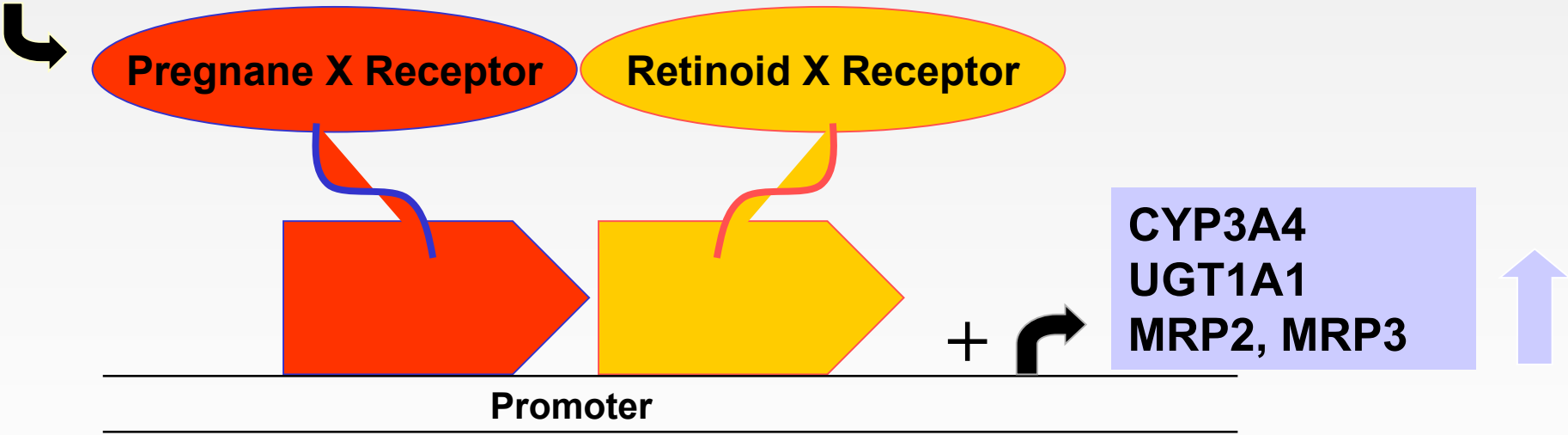


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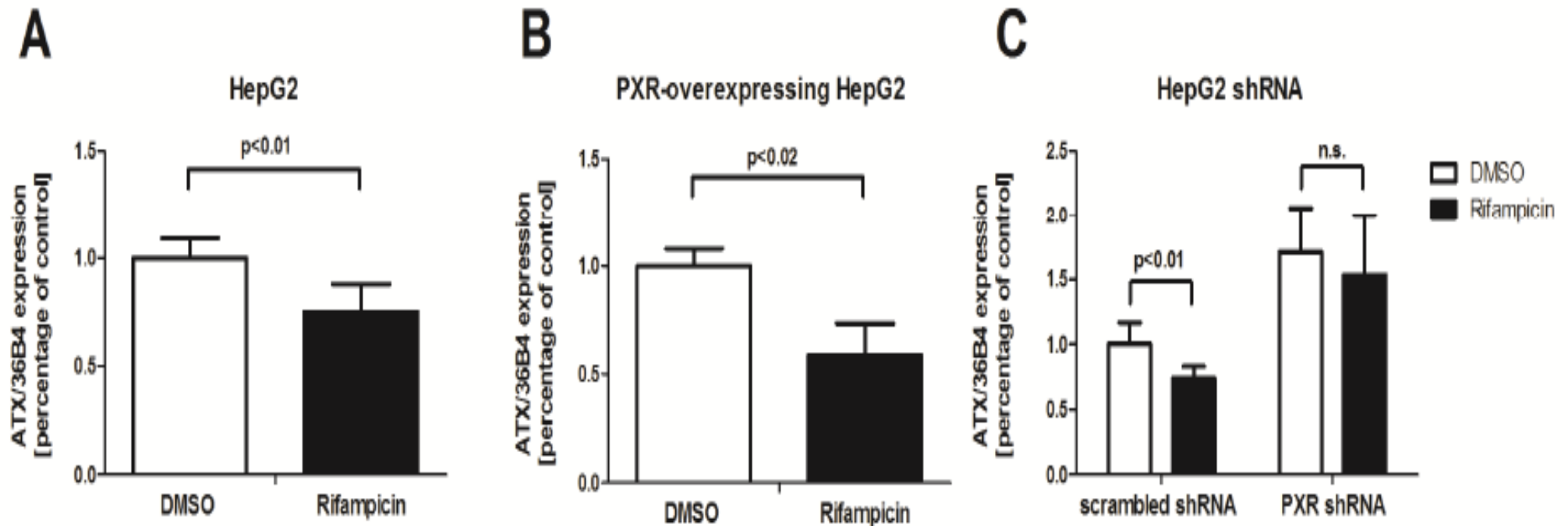


Rifampicin stimulates detoxification capacity in liver and intestine via the pregnane X receptor (PXR)

Rifampicin

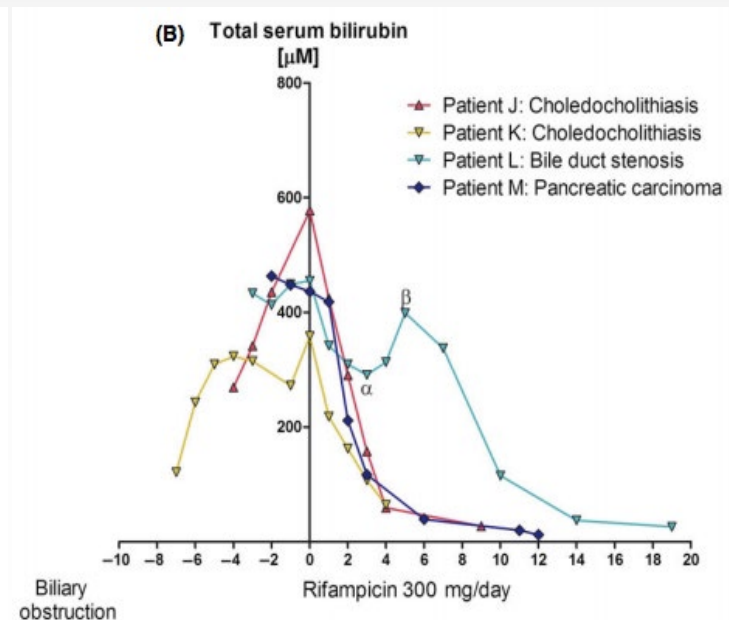
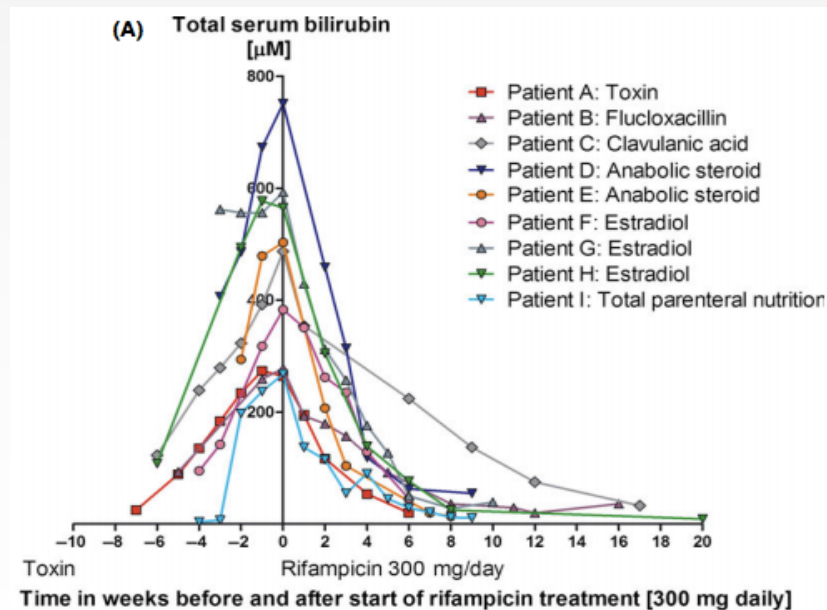


Autotaxin mRNA Expression *in vitro* is downregulated by Rifampicin via Pregnane X Receptor (PXR)-dependent Mechanisms

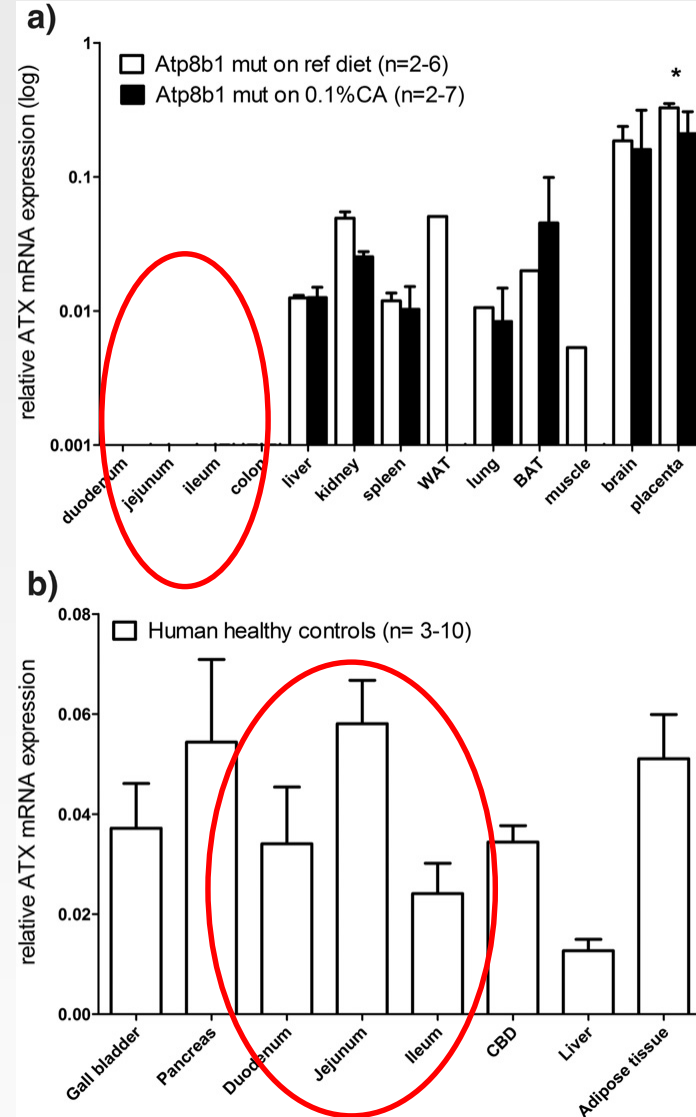
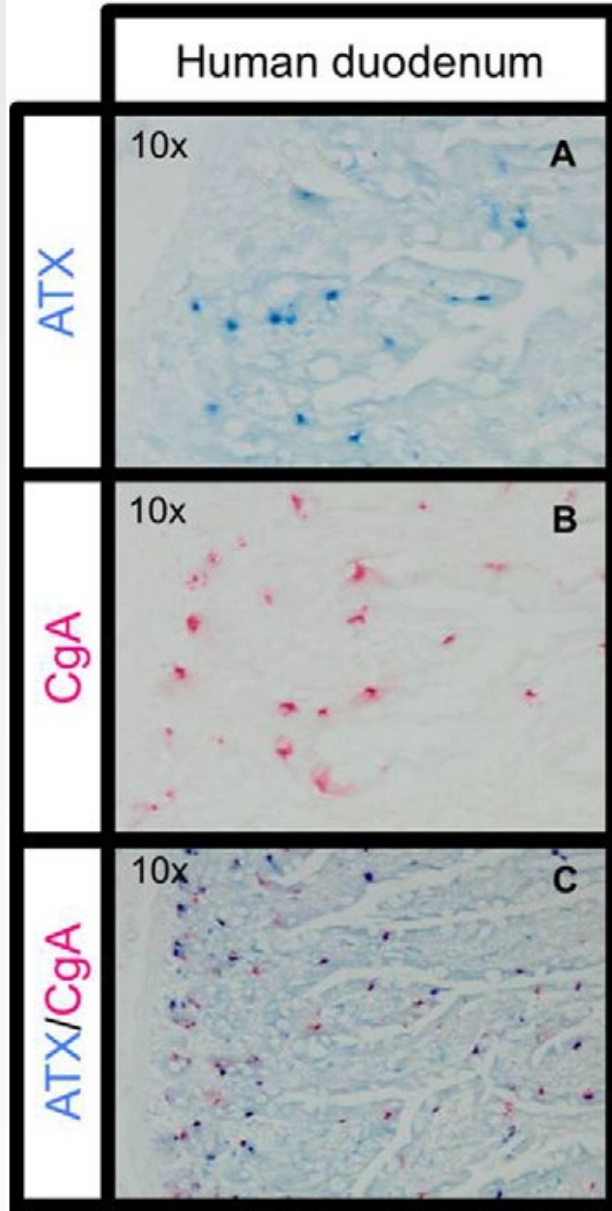


Persistent hepatocellular secretory failure (PHSF)

- Serum bilirubin $>255 \mu\text{mol/L}$ ($>15 \text{ mg/dL}$)
- Persistently elevated bilirubin (>1 week) after removal of the underlying cause (medication, toxin, transient mechanical obstruction)
- Exclusion of bile duct obstruction by imaging
- No underlying liver disease
- Rapid response to rifampicine



Enteroendocrine Cells are a Potential Source of Autotaxin in Man



Mouse

Man

Therapeutic Targets in Pruritus of Cholestasis

“Actual treatment“

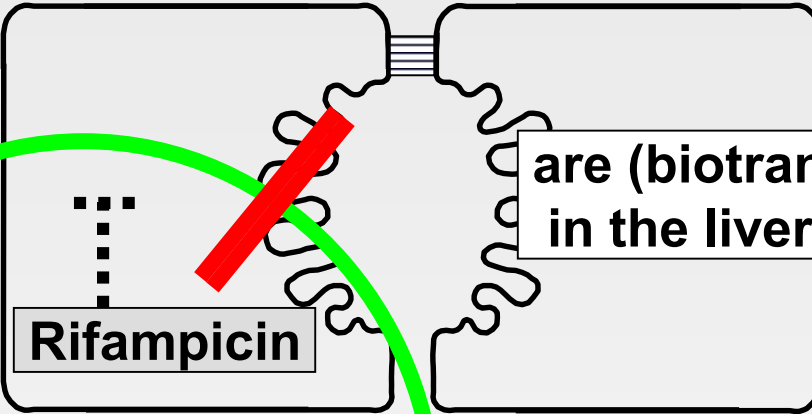
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accumulate in the systemic circulation

Albumin dialysis etc.

affect the endogenous serotonergic and opioidergic system

Naltrexone
Sertraline



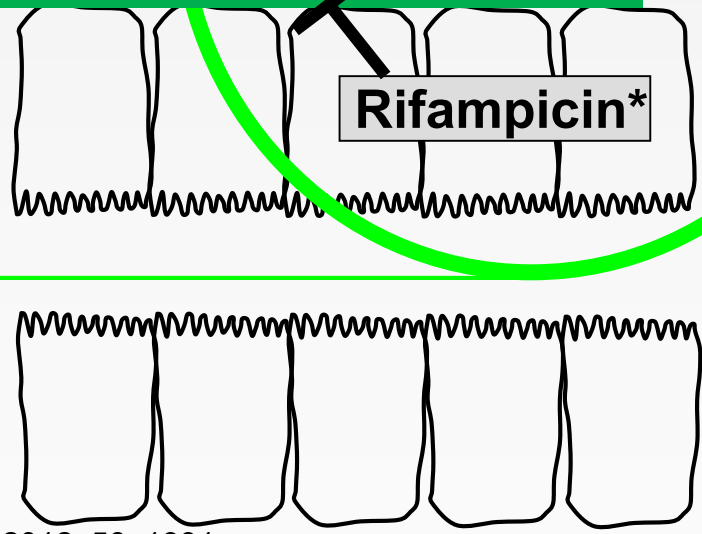
Autotaxin → LPA

Rifampicin*

are secreted into bile

Nasobiliary drainage

Cholestyramine



* Kremer, van Dijk et al., Hepatology 2012; 56: 1391

Pruritus of Cholestasis

Actual and **potential future** treatment

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ATX inhibitors?
LPA receptor blockers?

Autotaxin → LPA

Rifampicin

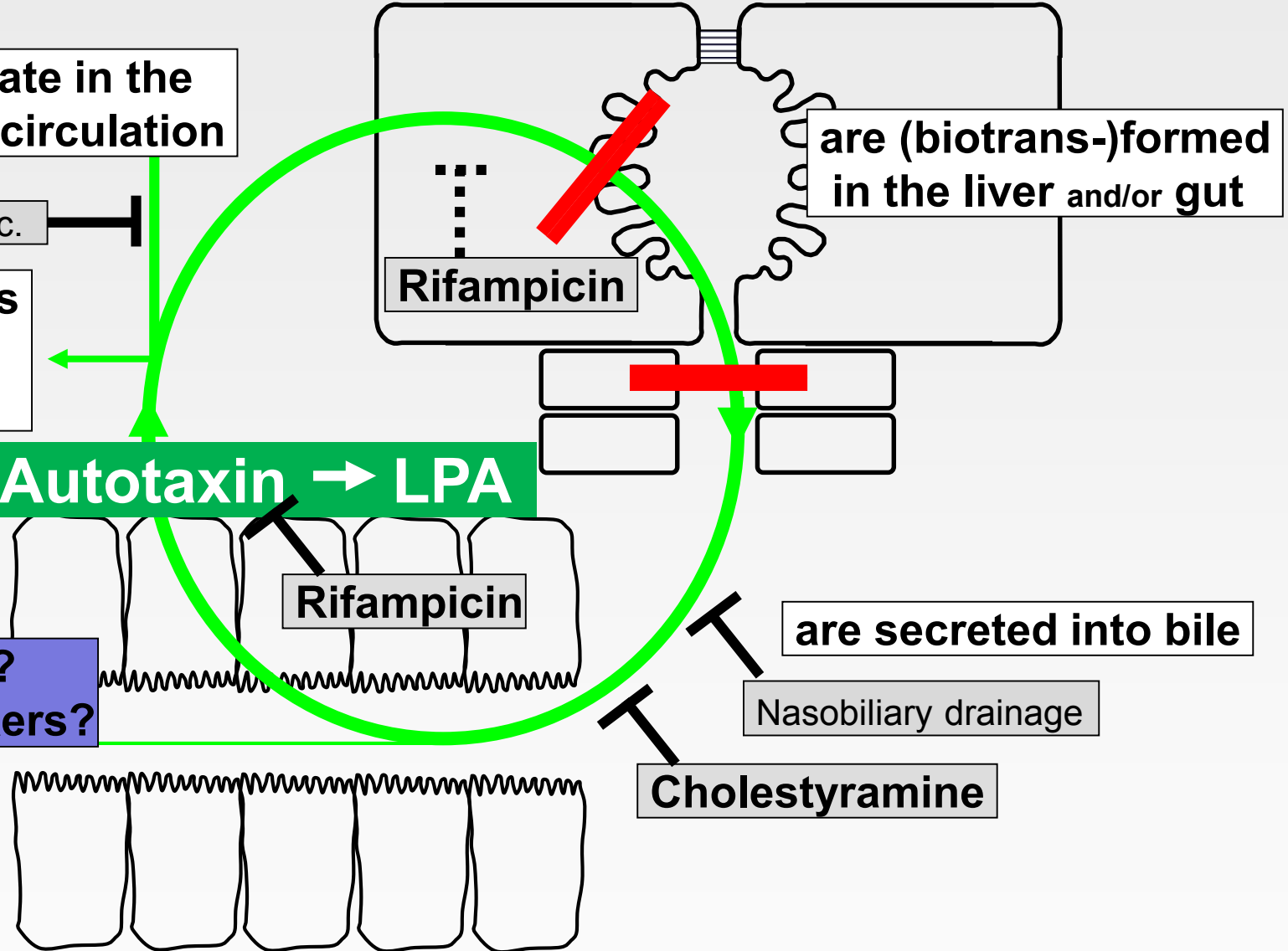
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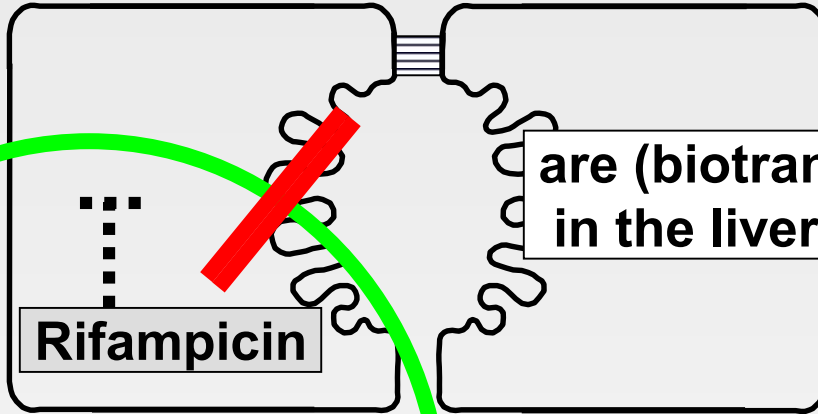
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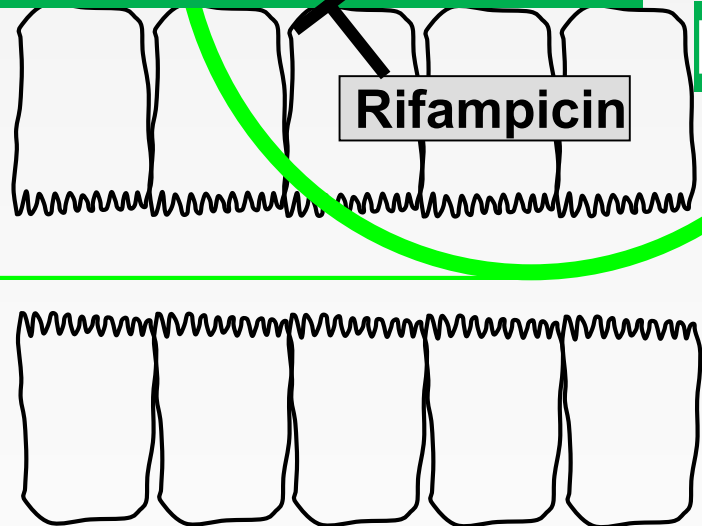
Factor X

Rifampicin

are secreted into bile

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Cholestyramine



Identification of a Neuronal Activator in **Bile** of Pruritic Patients



Pruritus of Cholestasis

Actual and **potential future** treatment

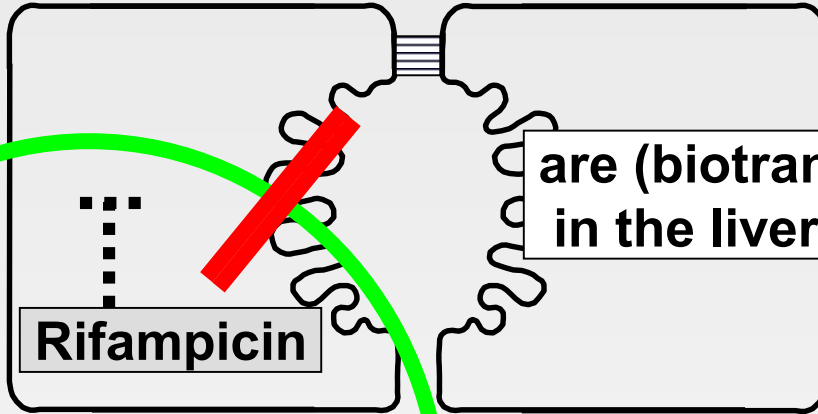
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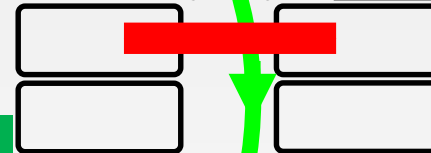
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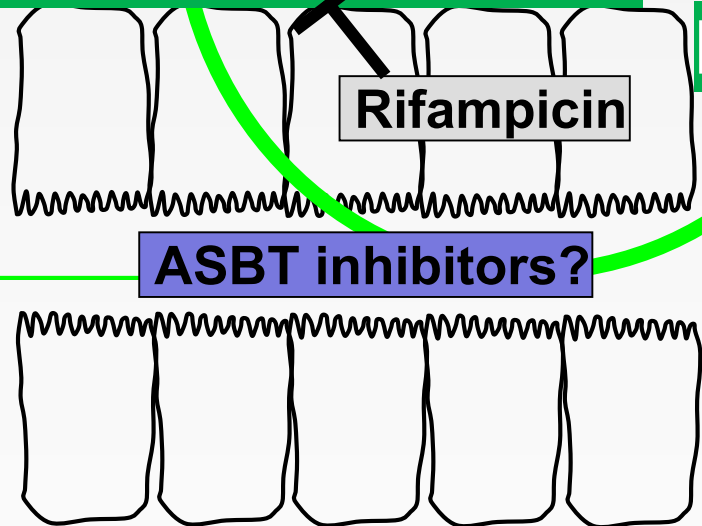
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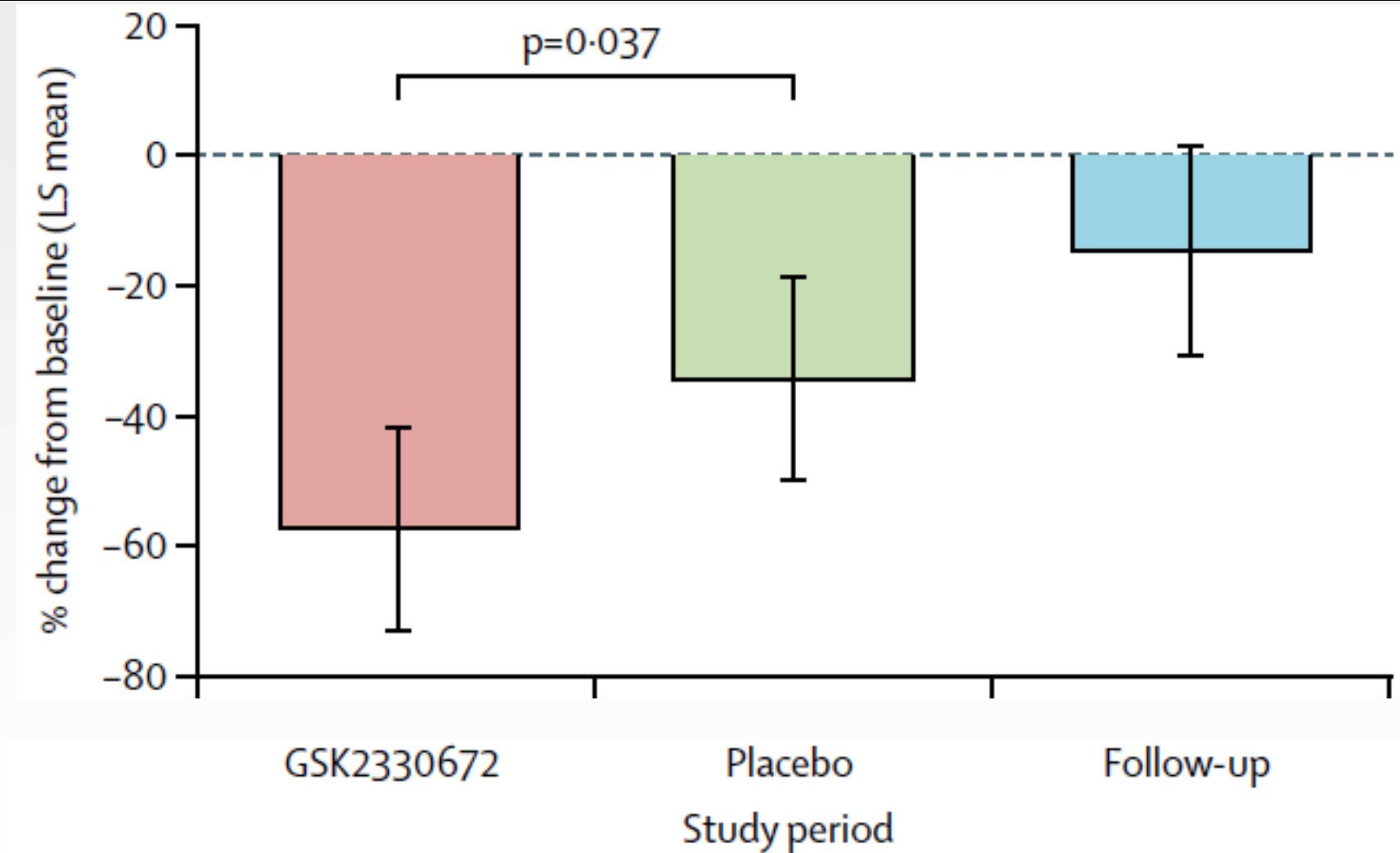
Nasobiliary drainage

ASBT inhibitors?

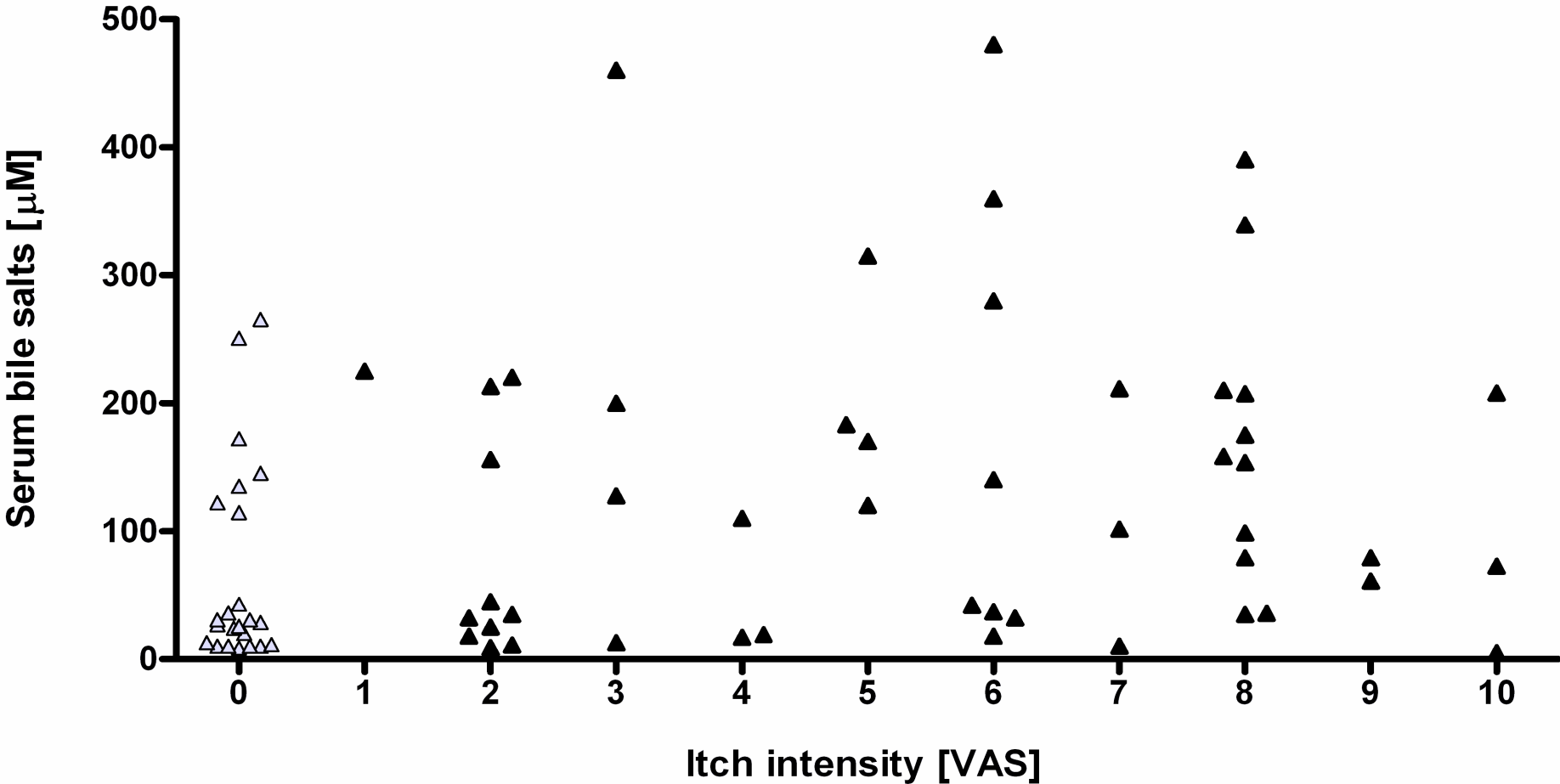
Cholestyramine



The ASBT inhibitor GSK2330672 improves pruritus in primary biliary cholangitis



No Correlation between Serum Bile Salts and Itch Intensity



Pruritus of Cholestasis

Actual and **potential future** treatment

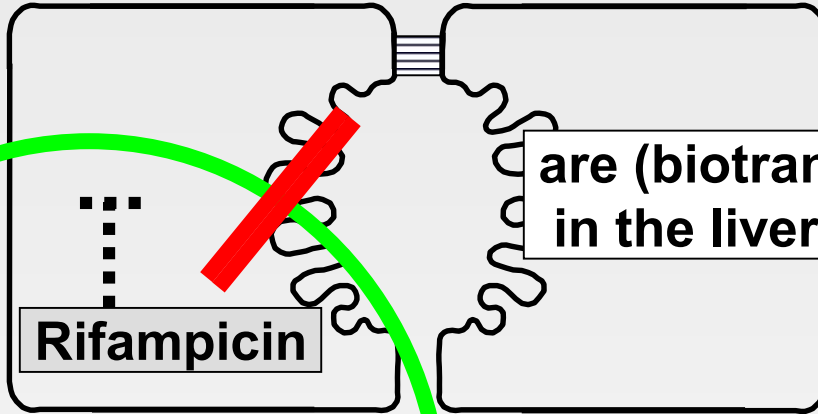
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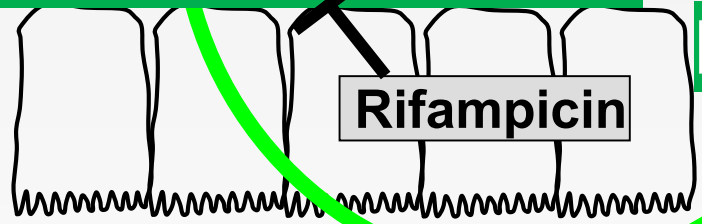
Rifampicin

Red bar

Fibrates?
(FITCH trial)

Autotaxin → LPA

Factor X



Rifampicin

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Nasobiliary drainage

ASBT inhibitors

Cholestyramine

Pruritus of Cholestasis

Actual and **potential future** treatment

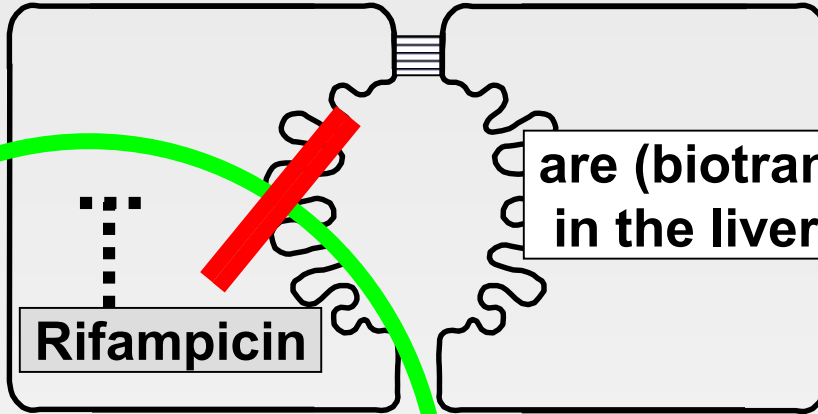
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Red bar indicating inhibition

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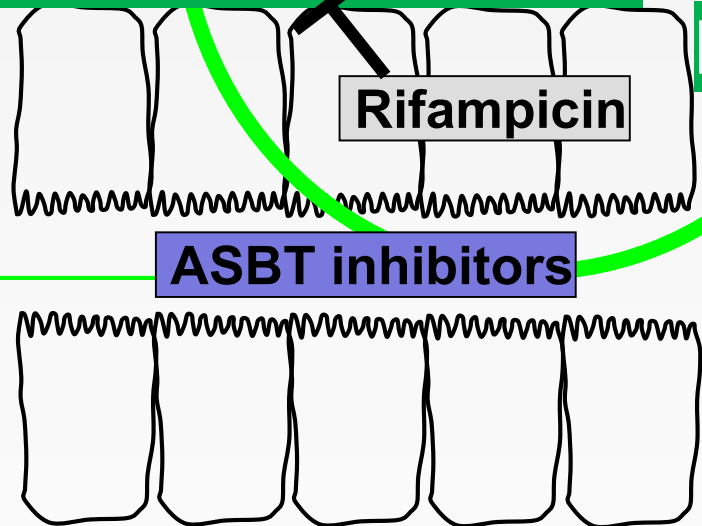
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Pruritus of Cholestasis

Mechanisms and management

Three of many open questions:

- **What is the role of the hepatocyte, cholangiocyte and ileocyte in pruritus of cholestasis ?**
- **What is the biliary factor X in pruritus of cholestasis ?**
- **How do ASBT inhibitors and PPAR agonists ameliorate pruritus in cholestasis ?**

Thank you

Tytgat Institute for Liver and Intestinal Research & AMC, Amsterdam

Germany

Andreas Kremer, Ruth Bolier, Dagmar Tolenaar, Remco van Dijk, Jacqueline Langedijk
Ronald Oude Elferink

Christian Rust

United Kingdom

Catherine Williamson
Rajiv Jalan

Lithuania

Jurate Kondrackiene

Spain

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Belgium

Tania Roskams
Mina Komura

NKI, Amsterdam

Wouter Moolenaar

UMC, Utrecht

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Erasmus MC, Rotterdam

Edith M. Kuiper
Maren Harms
Henk R. van Buuren

