Cholestatic liver dysfunction during critical illness

Yoo-Mee Vanwijngaerden
Lies Langouche
Dieter Mesotten
Greet Van den Berghe

Department of Cellular and Molecular Medicine
Laboratory of Intensive Care Medicine – KU Leuven
University Hospitals Leuven

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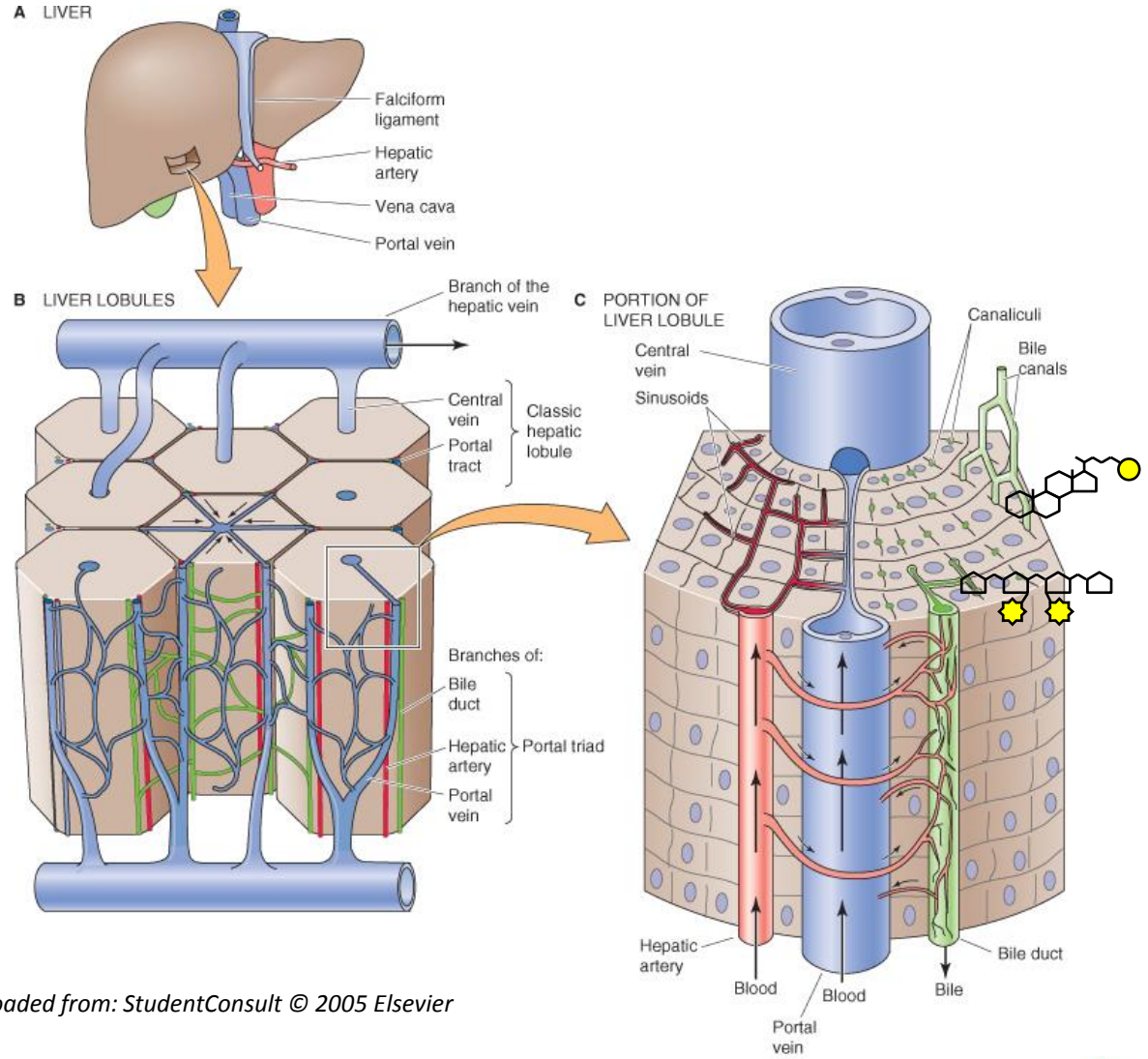
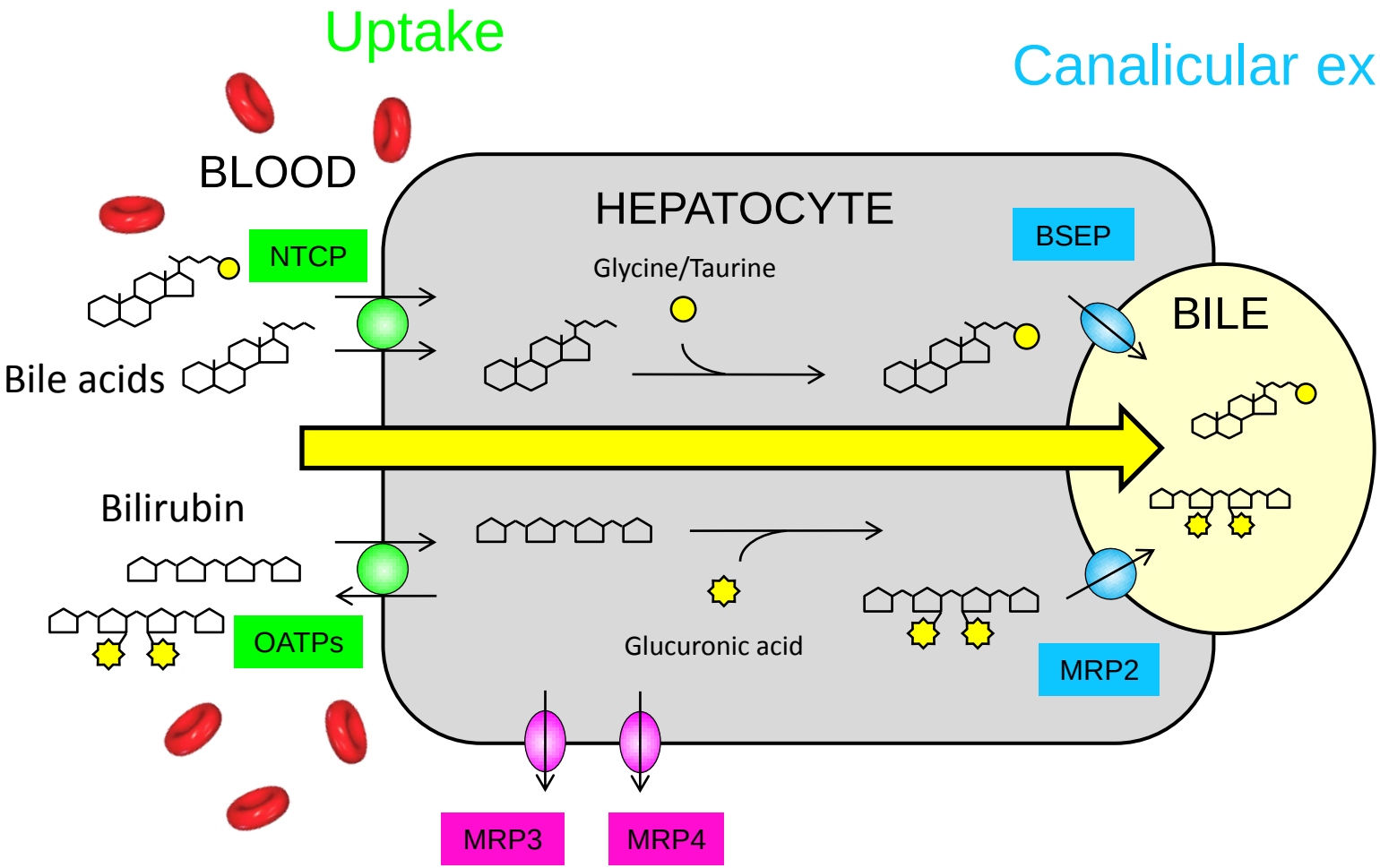
"Cholate stasis"



"Cholate stasis"

Simplified scheme of hepatobiliary transporters



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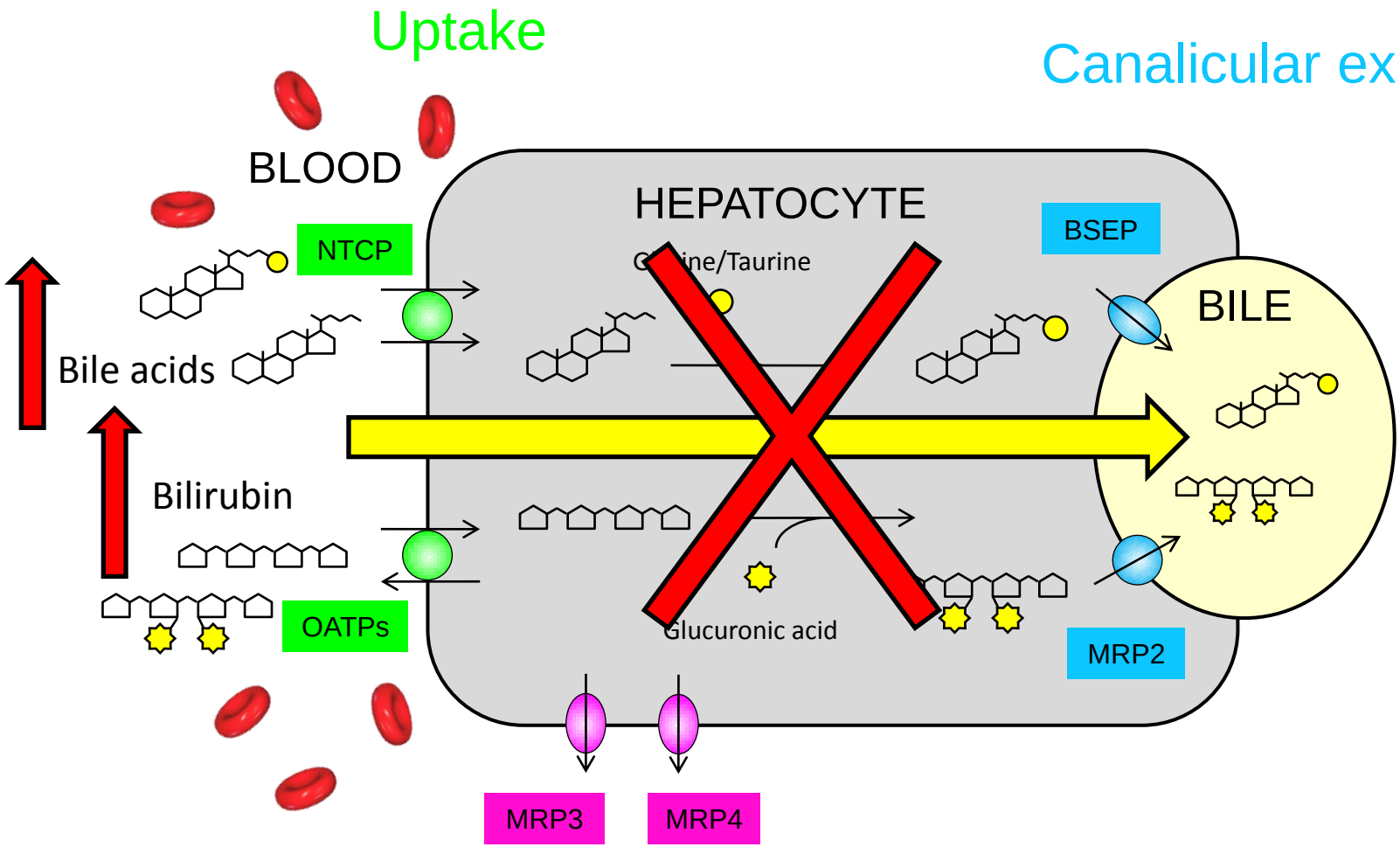
Simplified scheme of hepatobiliary transporters



ICU cholestasis

- No consensus
- Criteria:
  - Bilirubin total > 3 mg/dL
  - ALP > 400 U/L and gammaGT > 80 U/L
- Incidence: 20% after 10d
- ↑mortality, ↑LOS

Kramer L. Crit Care Med 2007. *Incidence and prognosis of early hepatic dysfunction in critically ill patients: a prospective multicenter study.*

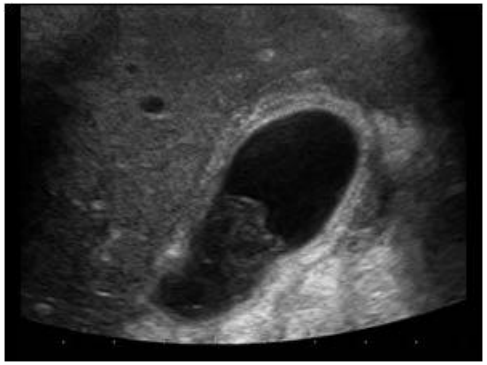
Mesotten D. J Clin Endocrinol Metab 2009. *The effect of strict blood glucose control on biliary sludge and cholestasis in critically ill patients.*

Patel JJ. J Intens Care Med 2013. *The Association of Serum Bilirubin Levels on the Outcomes of Severe Sepsis.*

Biliary sludge on ICU

- Presence of sediment in the gallbladder
- Diagnosed by ultrasonography
- Prevalence: ± 50% after 5d
- Acute complications:

  biliary colic, necrotizing cholecystitis, cholangitis and acute pancreatitis



Ko CW. Best Pract Res Clin Gastroenterol 2003. *Gastrointestinal disorders of the critically ill. Biliary sludge and cholecystitis*

Shaffer EA. Curr Gastroenterol Rep 2001. *Gallbladder sludge: what is its clinical significance?*

Pazzi P. Dig Liver Dis 2003. *Biliary sludge- the sluggish gallbladder*

Role of parenteral nutrition

- Parenteral nutrition is assumed to aggravate both cholestatic liver dysfunction and biliary sludge formation

Central hypothesis

"Cholestasis" in the early phase of critical illness is brought about by changes in synthesis and transport of bile acids and is a protective response of the liver. Parenteral nutrition can modify this protective cholestatic response.

Hyperbilirubinemia

Cholestasis

Part 1

Unravel the mechanisms behind cholestasis during critical illness

Data published as:
Vanwijngaerden YM, Wauters J, Langouche L, Vander Perre S, Liddle C, Coulter S, Vanderborght S, Roskams T, Wilmer A, Van den Berghe G, Mesotten D. Critical illness evokes elevated circulating bile acids related to altered expression of hepatic transporters, synthesis enzymes and nuclear receptors. *Hepatology. 2011 Nov;54(5):1741-52.*

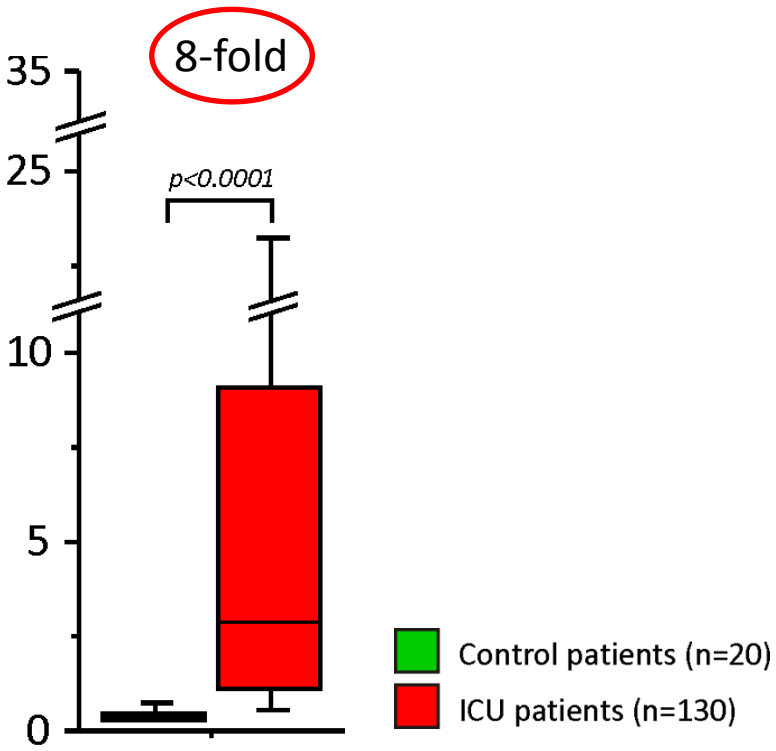
Study outline

- 130/40 prolonged critically ill vs 20/10 control patients
- Serum levels of **bile acids**, **bilirubin**

  (HPLC-MS)
- mRNA expression, protein expression of

  (real time-PCR, western blotting, immunohistochemistry)
  - **Hepatobiliary transporters**
  - **Synthesis enzymes**
  - **Nuclear receptors**

Serum bilirubin (mg/dL)



Serum levels are expressed in mg/dL, and represented as median with IQR (25th – 75th percentiles) - p-values are calculated with unpaired Mann-Whitney U test

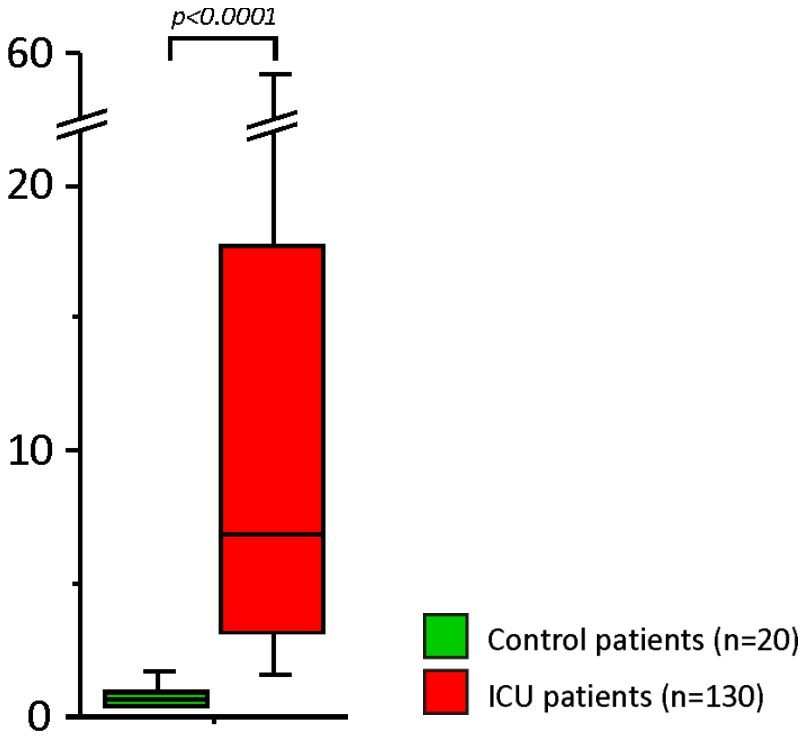
Serum bile acids (µM)

Bile acids – HPLC-MS

Total bile acids = Free bile acids + Conjugated bile acids

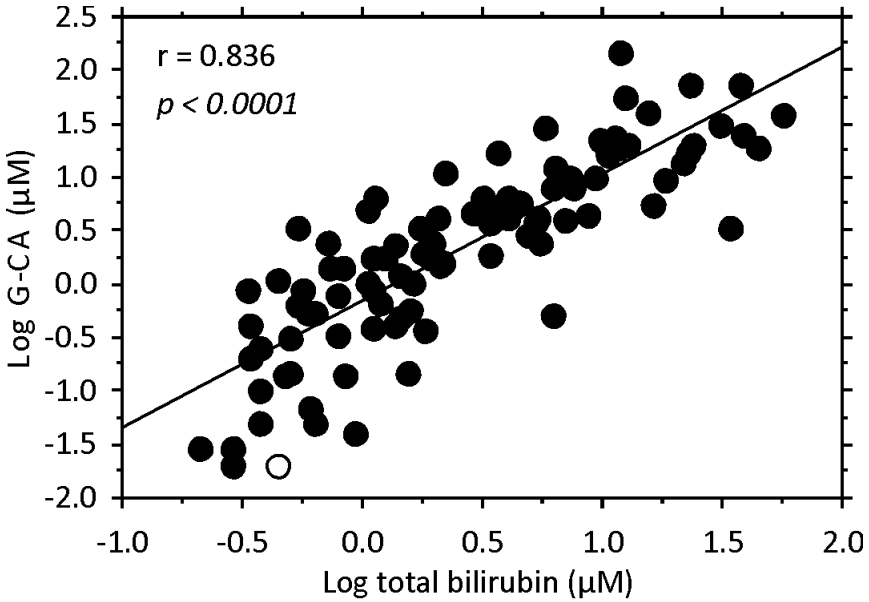
11-fold

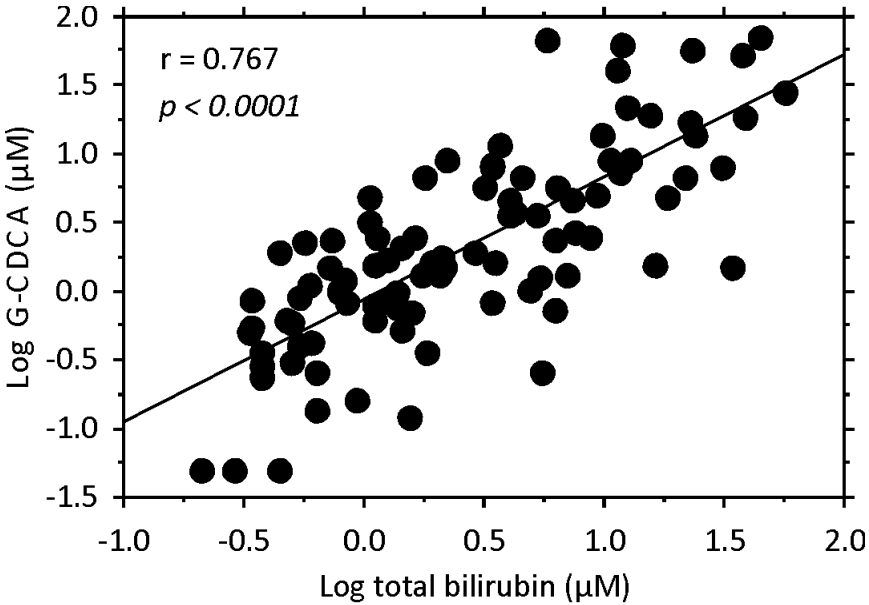
> 90%



Serum levels are expressed in µM and represented as median with IQR (25th – 75th percentiles) – p-values are calculated with unpaired Mann-Whitney

Correlation bilirubin – bile acids



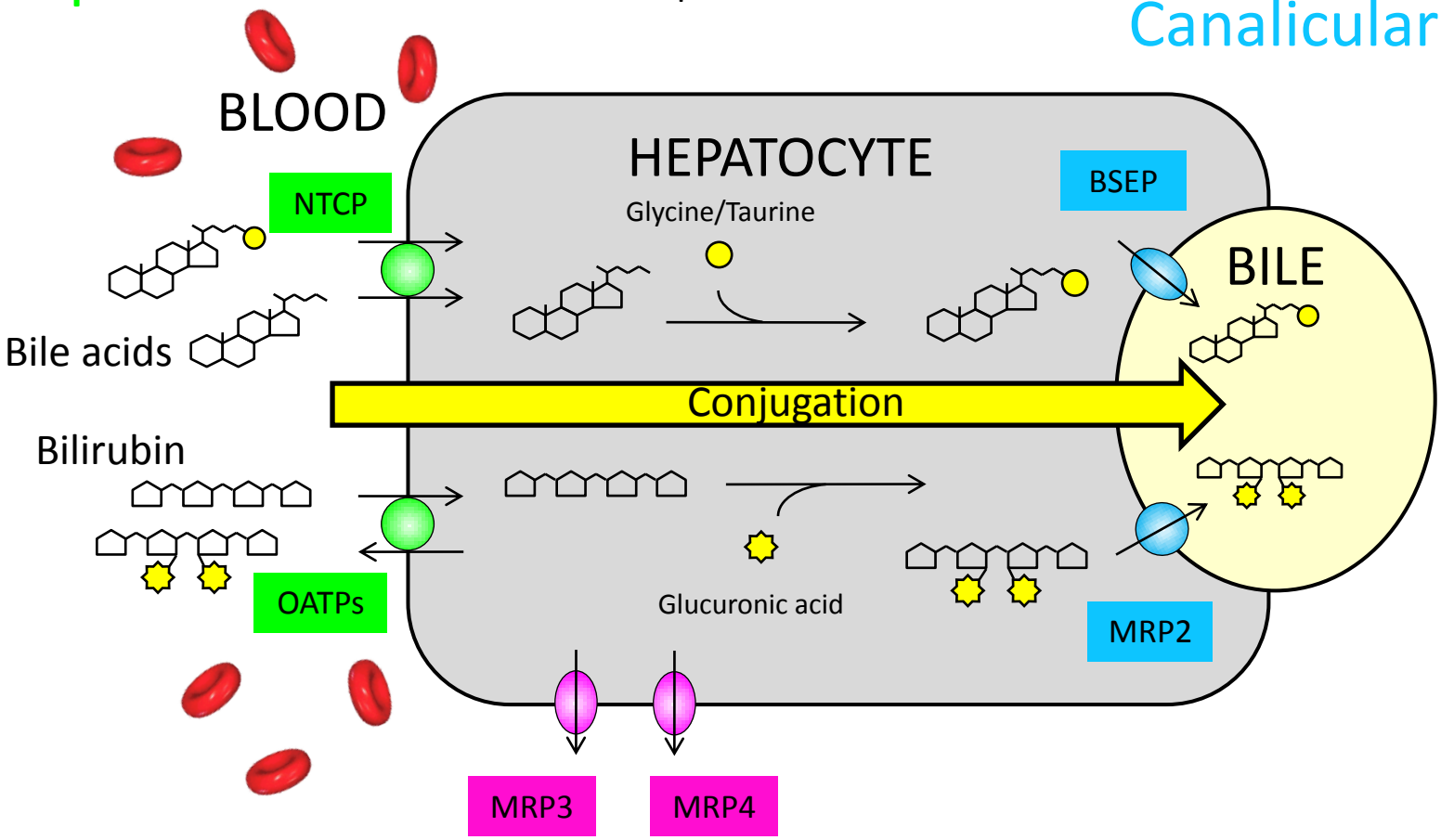


All patients (n=150)

Correlations were calculated using Pearson's correlation test

Bilirubin and bile acid transporters

Protein expression – semi-quantitative via immunohistochemistry
mRNA expression – real-time PCR



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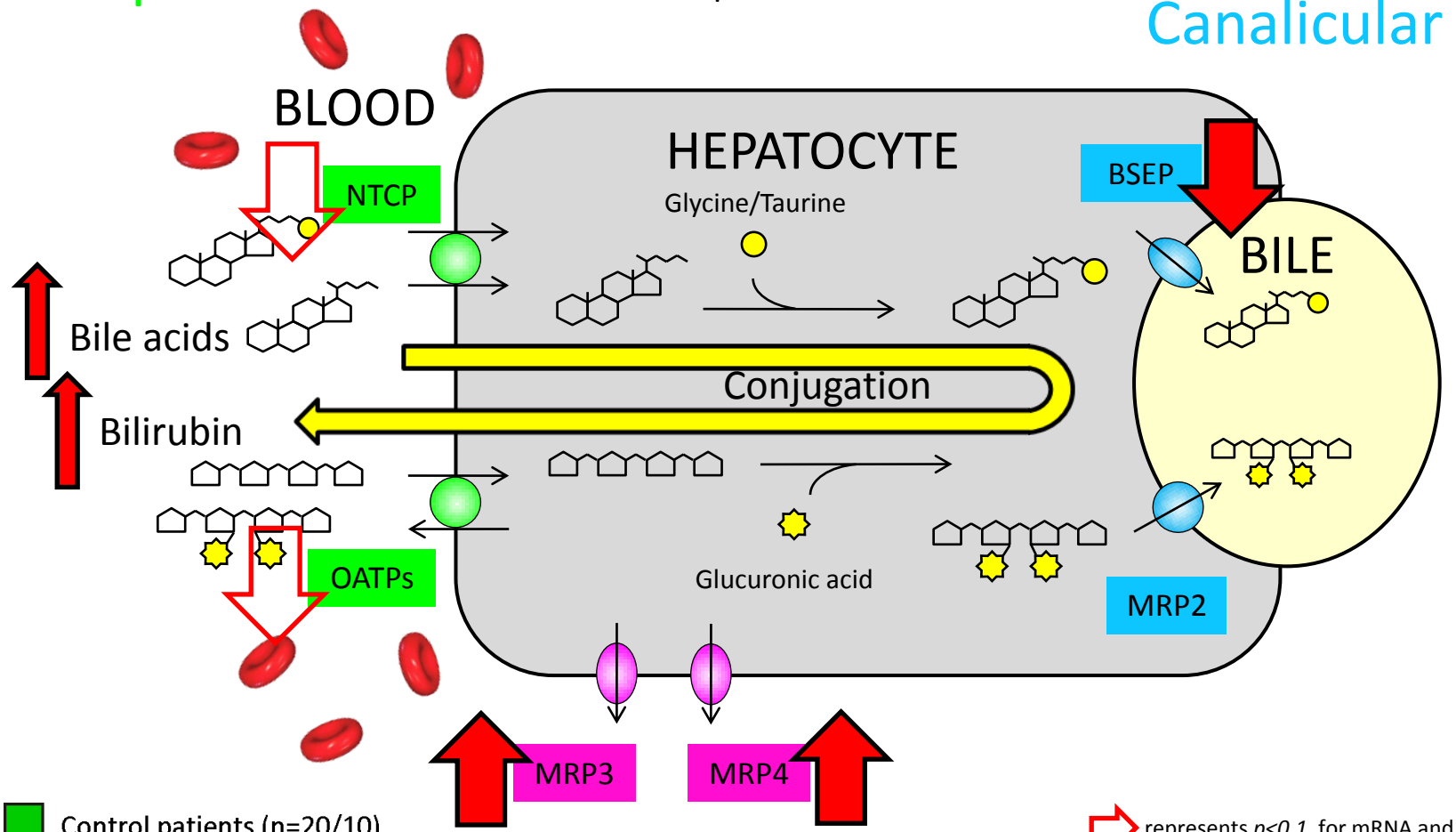
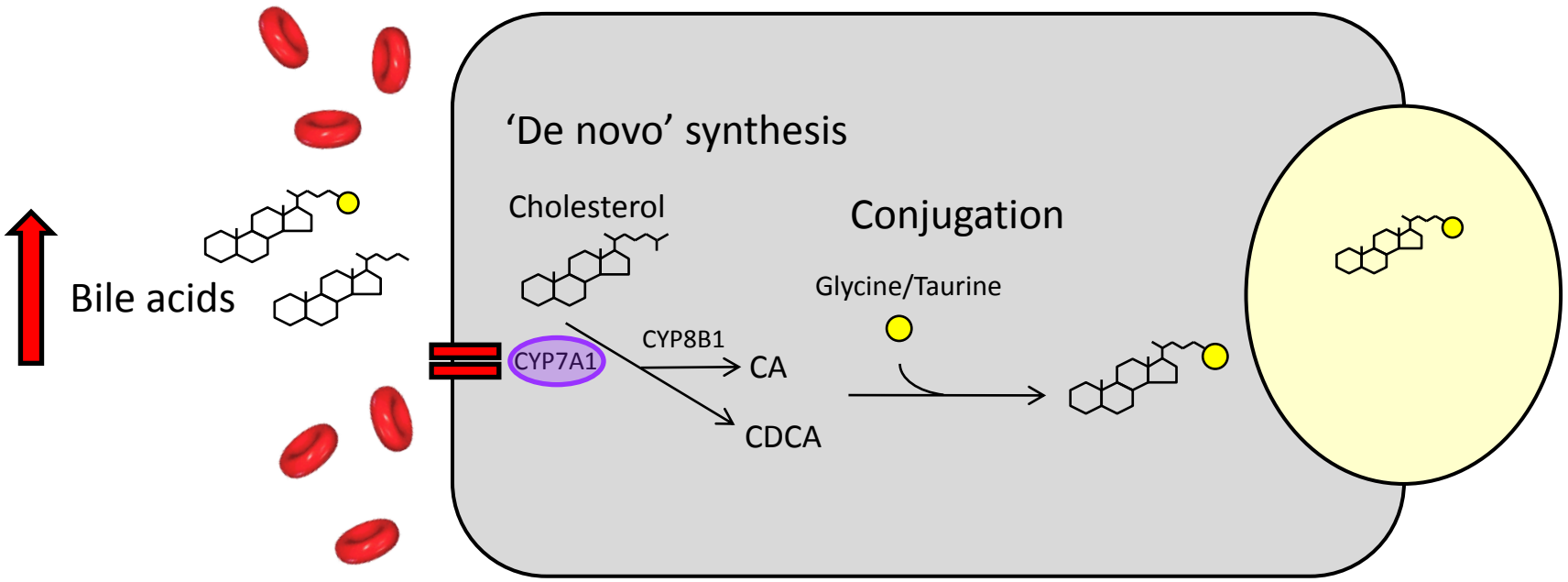


Control patients (n=20/10)
ICU patients (n=130/40)

represents $p<0.1$ for mRNA and/or protein expression
represents $p<0.05$ for mRNA and/or protein expression
p-values are calculated with either unpaired Mann-Whitney or Fisher's exact test

Bile acid synthesis enzymes

Protein expression – quantitative via western blotting
mRNA expression – real-time PCR



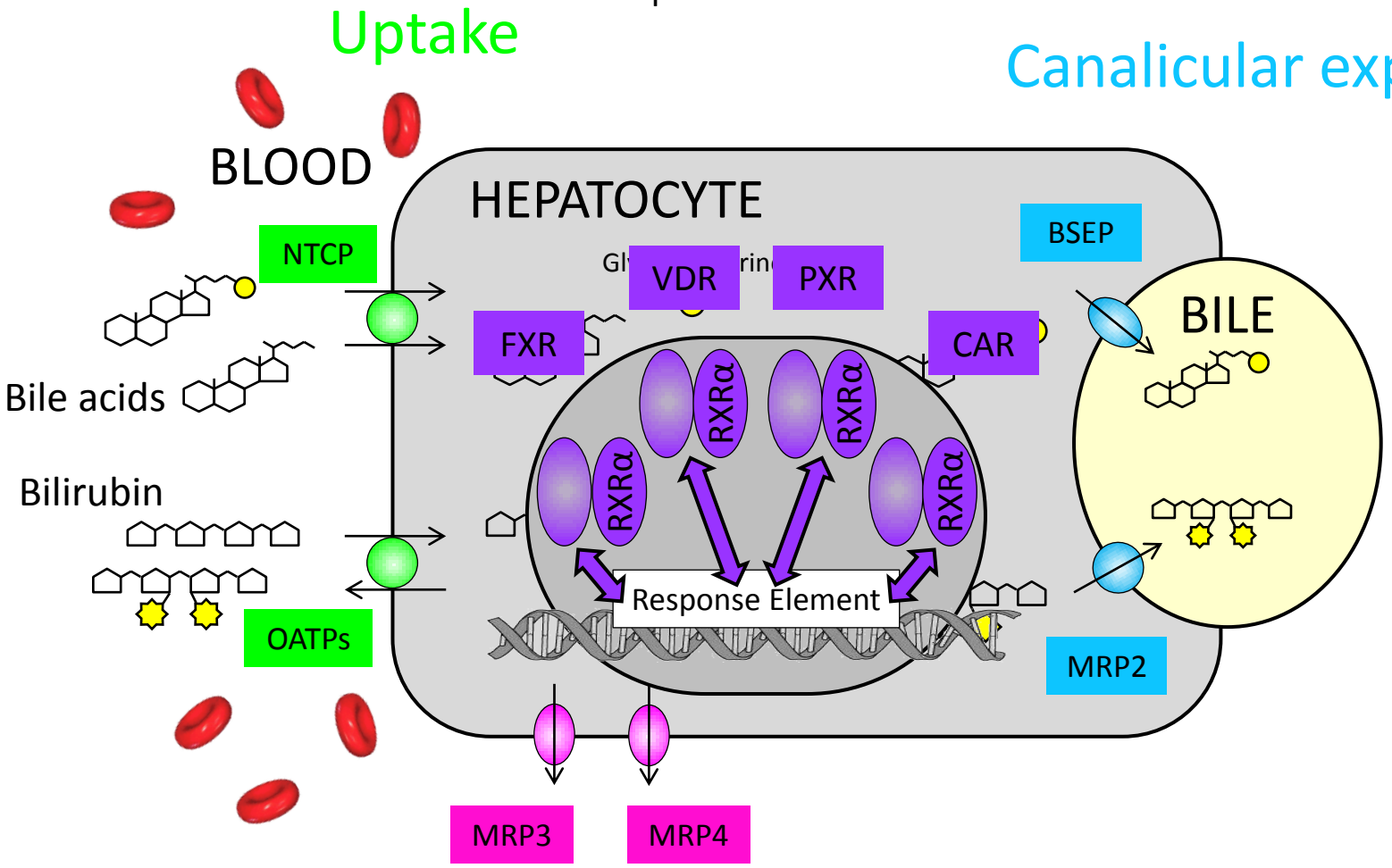
Control patients (n=20)
ICU patients (n=130)

represents p<0.05 for mRNA and/or protein expression

p-values are calculated with unpaired Mann-Whitney test

Nuclear receptors

Protein expression – semi-quantitative via immunohistochemistry
mRNA expression – real-time PCR



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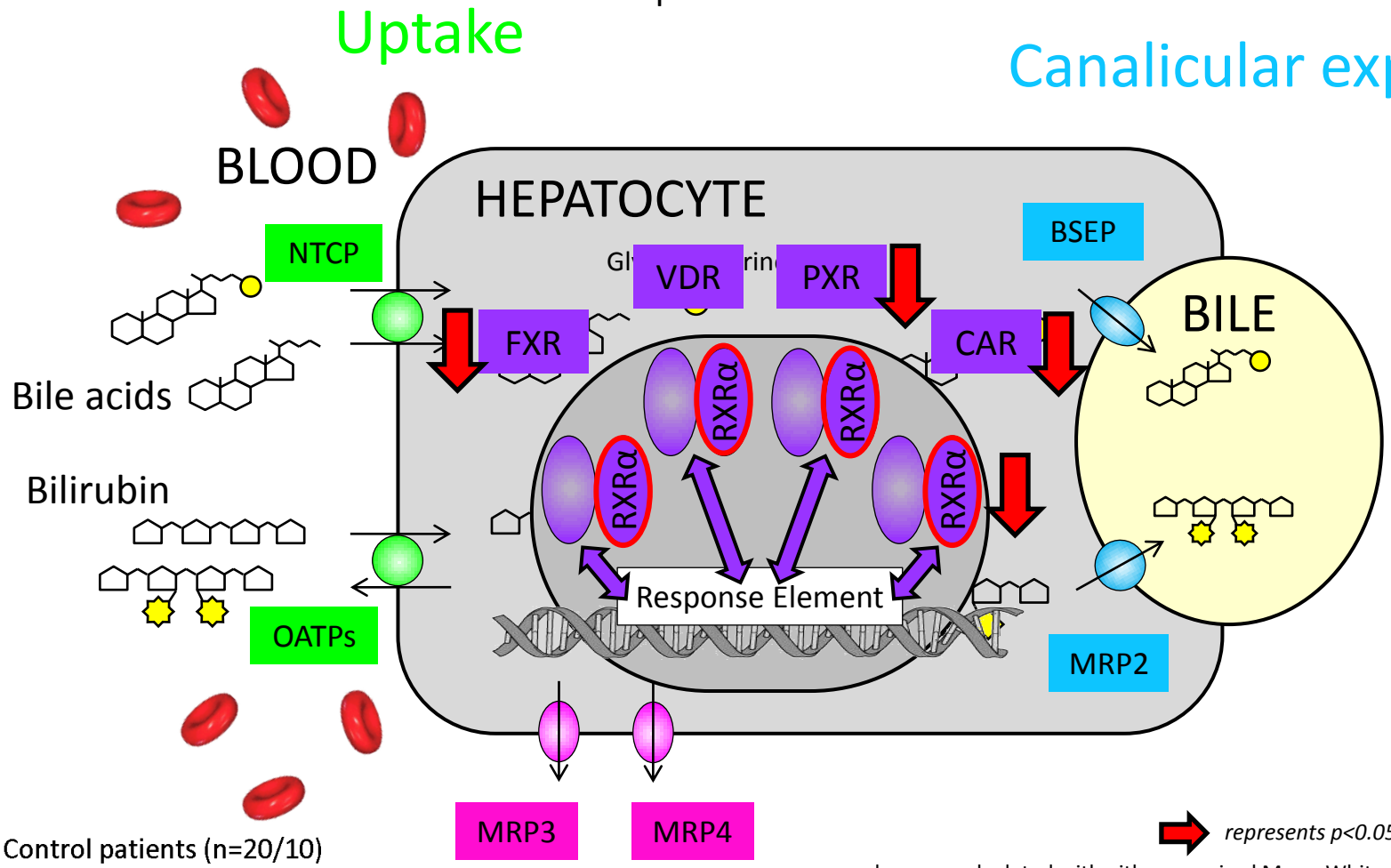
mRNA expression – real-time PCR



Conclusion

- Failing hepatobiliary system during critical illness

  Failure to inhibit bile acid synthesis, upregulate canalicular bile acid export and localize pivotal nuclear receptors in the hepatocytic nuclei may indicate dysfunctional feedback regulation by increased circulating bile acid levels

- Beneficial response to critical illness

  Critical illness may result in maintained bile acid synthesis (CYP7A1), reversal of normal bile acid transport (BSEP/MRP3) and suppression of nuclear receptors (FXR/RXRα) to increase serum bile acid levels

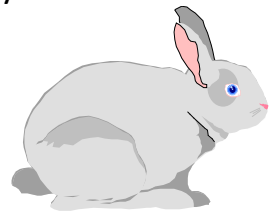
Part 2

Compare the impact of caloric restriction or nutritional support with parenteral nutrition on "cholestasis" during critical illness

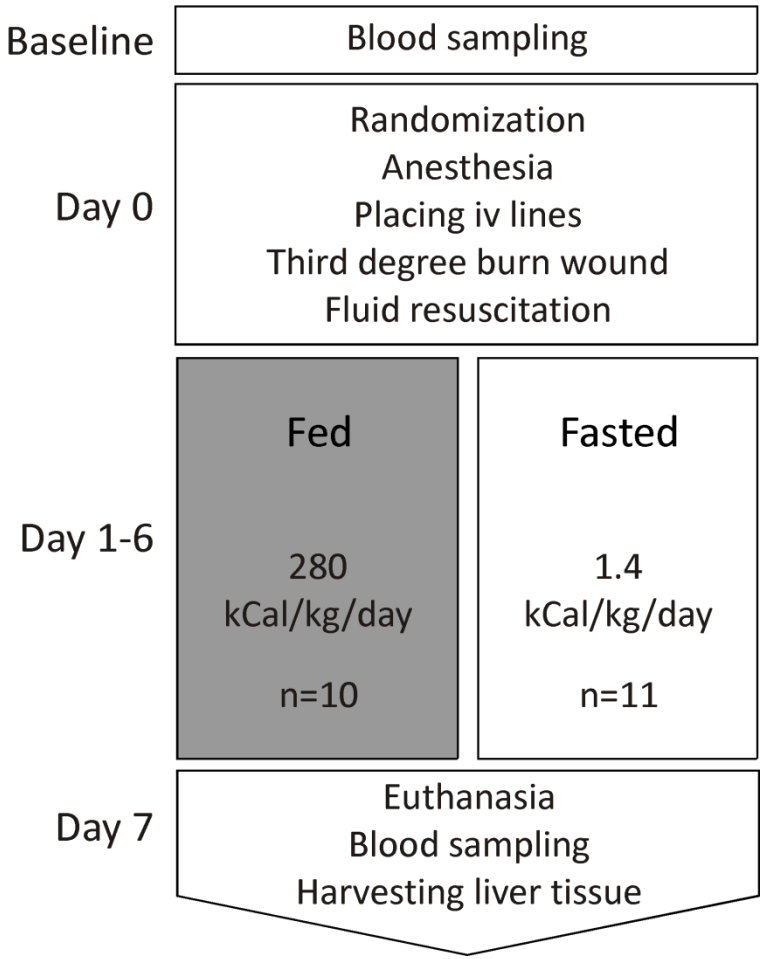
Data published as:

Vanwijngaerden YM, Langouche L, Derde S, Liddle C, Coulter S, Van den Berghe G, Mesotten D. Impact of parenteral nutrition versus fasting on hepatic bile acid production and transport in a rabbit model of prolonged critical illness. *Shock. 2014 Jan;41(1):48-54*

Vanwijngaerden YM, Langouche L, Brunner R, Debaveye Y, Gielen M, Casaer M, Liddle C, Coulter S, Wouters P, Wilmer A, Van den Berghe G, Mesotten D. Withholding parenteral nutrition during critical illness increases plasma bilirubin but lowers the incidence of biliary sludge. *Hepatology. 2013 Nov 9. [Epub ahead of print]*



Study outline



- Serum levels of **liver enzymes, bile acids**

  (enzymatic colorimetric assays, HPLC-MS)

- Protein expression, mRNA expression of

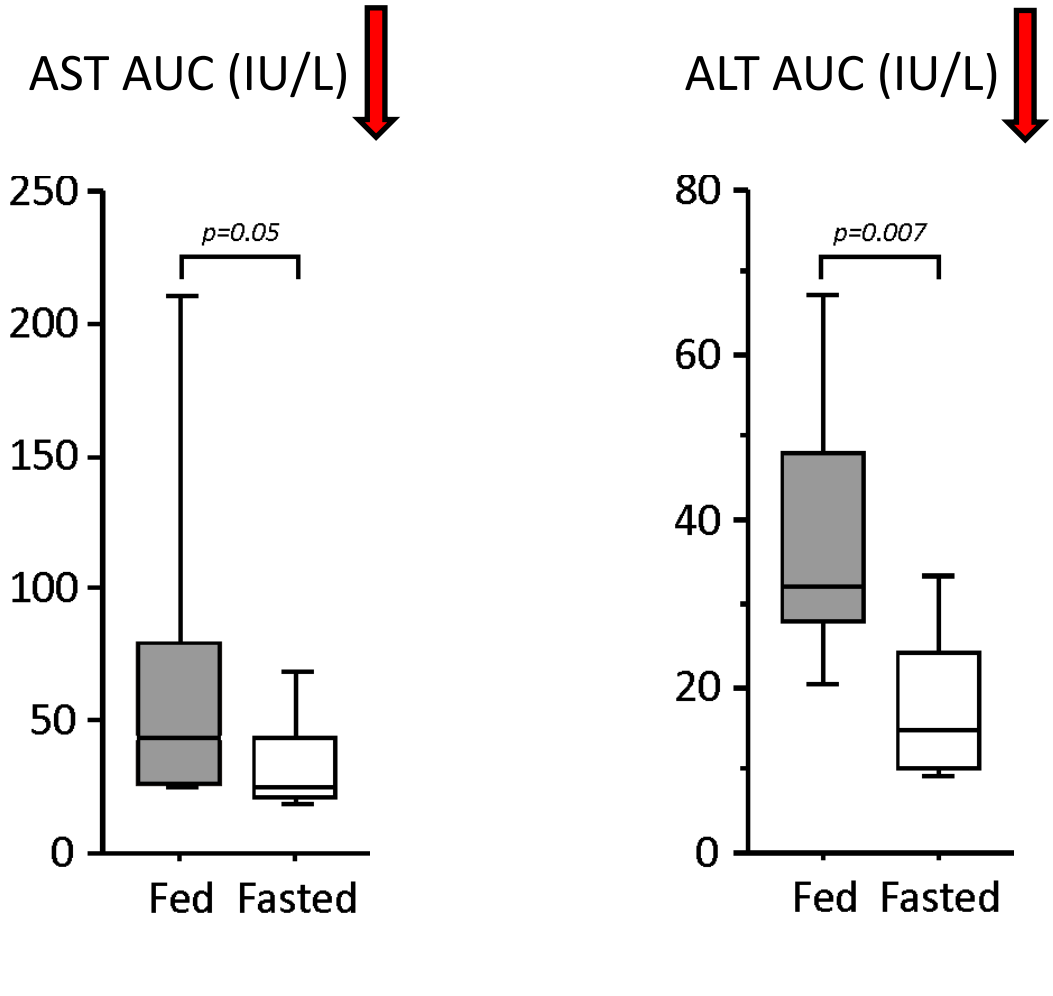
  (western blotting, real time-PCR)

  – **Synthesis enzymes**

  – **Hepatobiliary transporters**

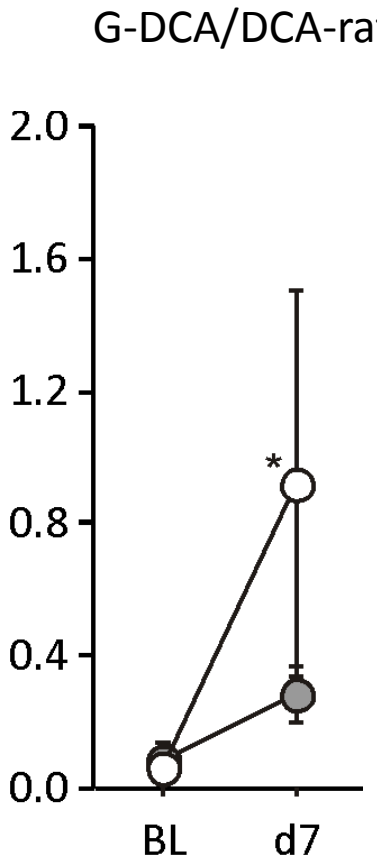
  – **Nuclear receptors**

Serum liver enzymes



AUC is area under de curve using dialy measurements. Levels are expressed as median with IQR. p-values are calculated with unpaired Mann-Whitney U test

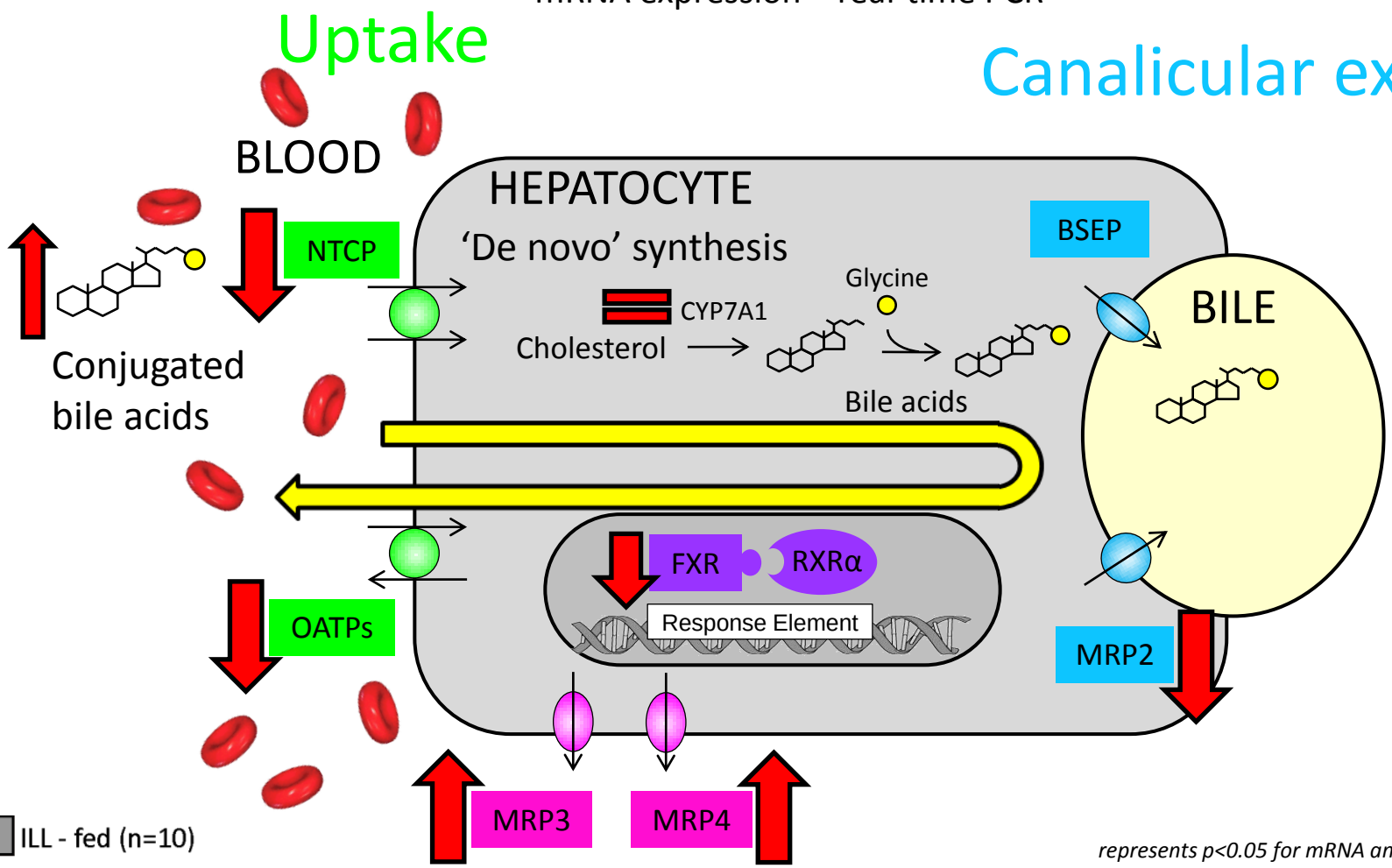
Profile serum bile acids



* represents p≤0.05 for comparison of changes over time (baseline vs day 7 levels) using Wilcoxon Signed Rank test

Hepatobiliary transport system

Protein expression – quantitative via western blotting
mRNA expression – real-time PCR



represents p<0.05 for mRNA and/or protein expression

Unpaired Mann-Whitney U test was used for comparison of mRNA/protein expression between fed and fasted critically ill rabbits

Background

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early versus Late Parenteral Nutrition in Critically Ill Adults

Michael P. Casaer, M.D., Dieter Mesotten, M.D., Ph.D., Greet Hermans, M.D., Ph.D., Pieter J. Wouters, R.N., M.Sc., Miet Schetz, M.D., Ph.D., Geert Meyfroidt, M.D., Ph.D., Sophie Van Cromphaut, M.D., Ph.D., Catherine Ingels, M.D., Philippe Meersseman, M.D., Jan Muller, M.D., Dirk Vlasselaers, M.D., Ph.D., Yves Debaveye, M.D., Ph.D., Lars Desmet, M.D., Jasperina Dubois, M.D., Aime Van Assche, M.D., Simon Vanderheyden, B.Sc., Alexander Wilmer, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.*

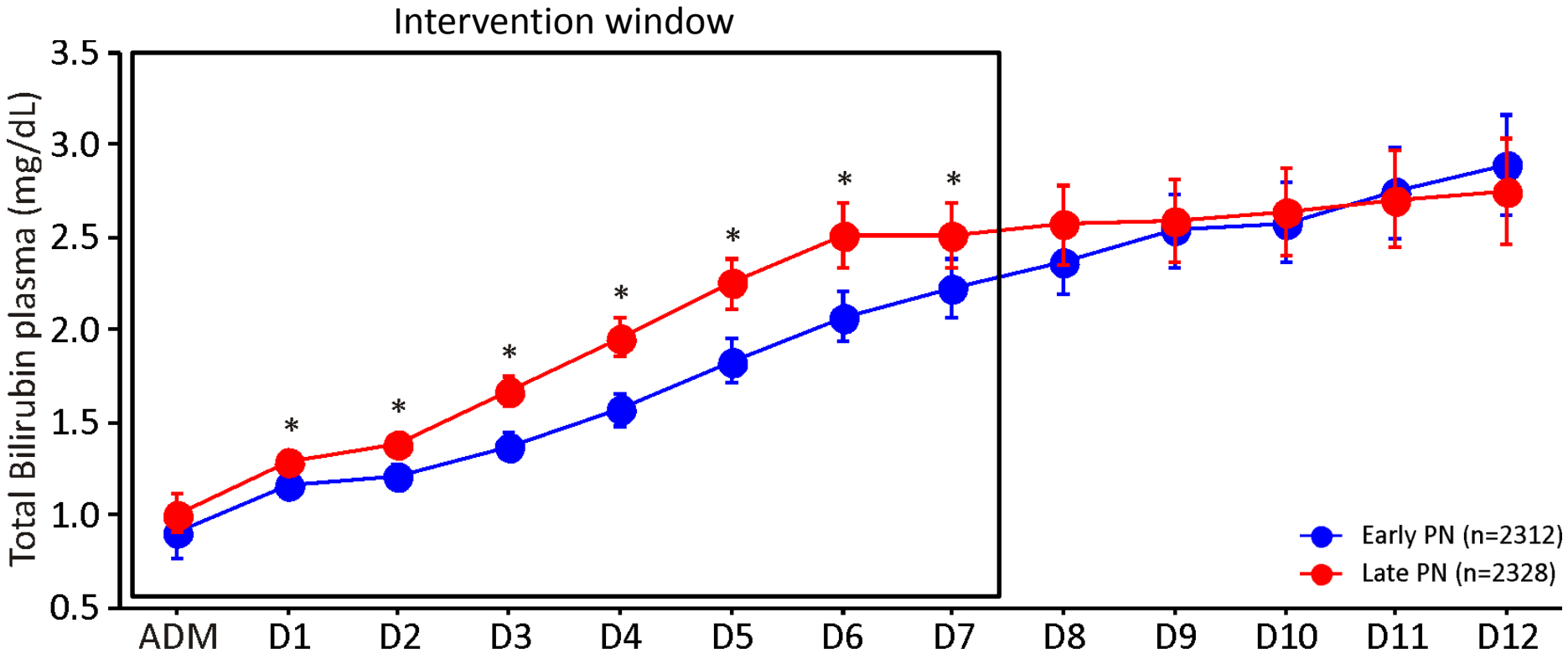
Casaer MP. NEJM 2011. *Early versus Late Parenteral Nutrition in Critically Ill Adults.*

Study outline

Preplanned subanalysis of EPaNIC

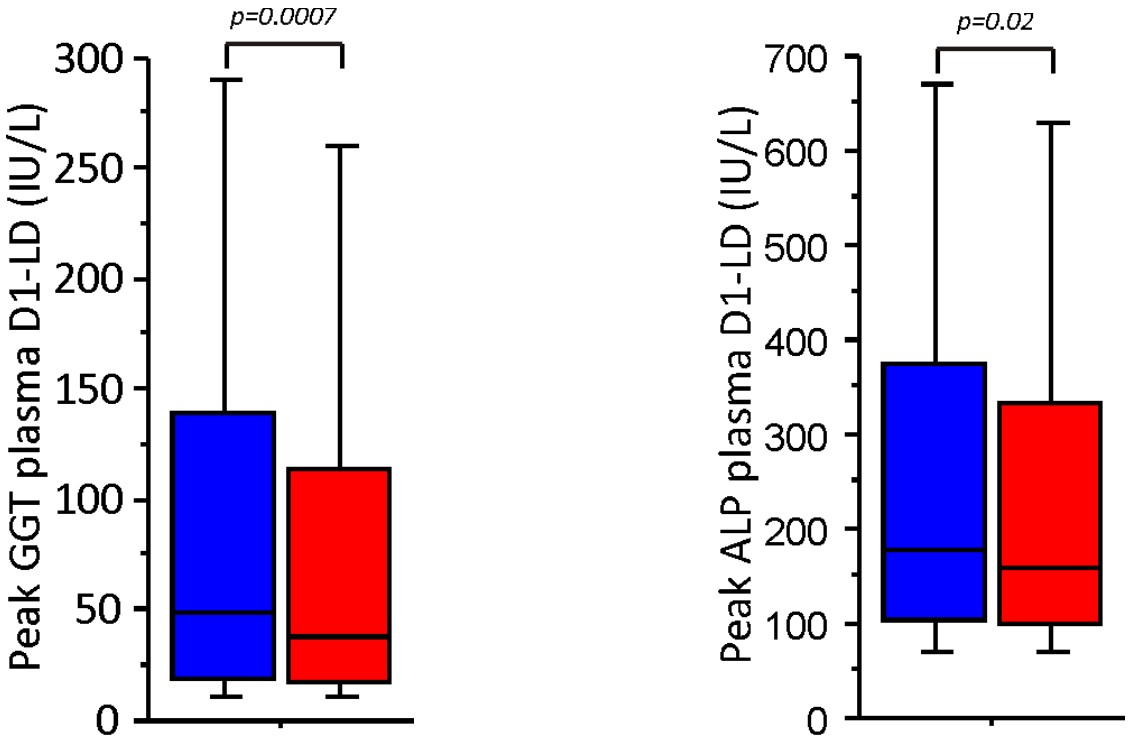
- Total bilirubin, daily, n=4640; Conjugated bilirubin n=3216; (standard routine automated laboratory assays)
- Liver enzymes (GGT, ALP, ALT and AST), twice weekly, n=3216; (standard routine automated laboratory assays)
- Bile acids, BL-D3-D5, n=280; (HPLC-MS)
- Ultrasonography gallbladder, D5, n=776

Daily total bilirubin (mg/dL)



Plasma total bilirubin levels of all patients in ICU are presented as mean ± standard error of the mean
* represents p≤0.05 after comparison using the unpaired Student's t-test after logarithmic transformation

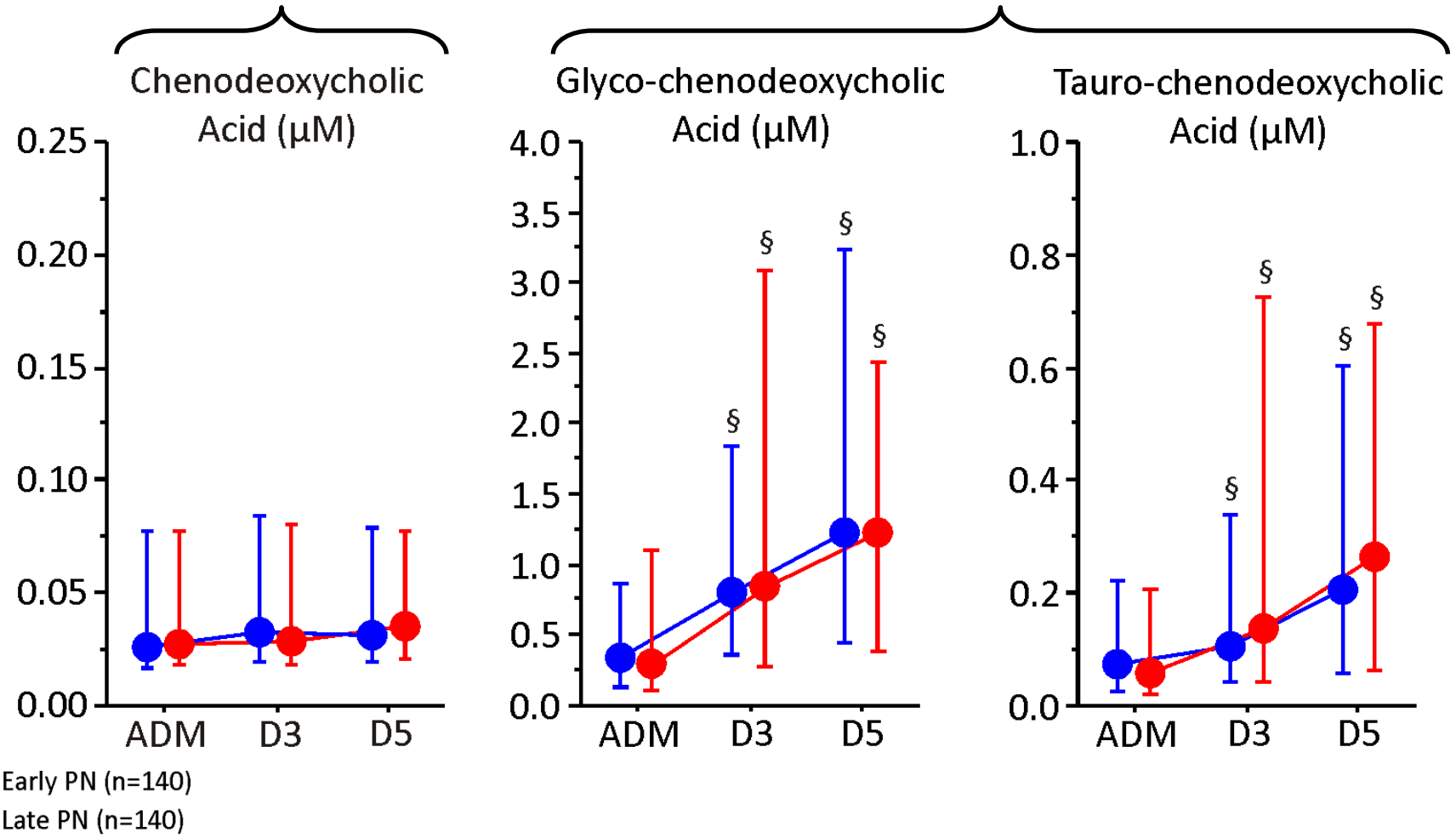
Peak levels GGT/ALP (IU/L)



Early PN (n=1755)
Late PN (n=1787)

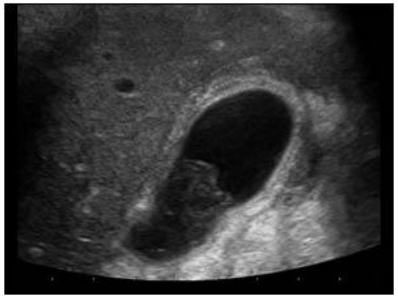
Peak levels of plasma liver enzymes GGT, ALP are presented as boxplots (median with IQR)
P-values are calculated after comparison using the Mann-Whitney U test

Free bile acids Conjugated bile acids

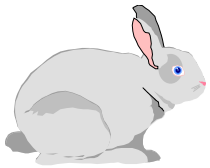


Plasma levels of bile acids on admission, on day 3 and day 5 of ICU stay are presented as median with IQR
§ represents p≤0.05 using Wilcoxon signed rank test for comparison with admission vallues

Ultrasonography gallbladder D5



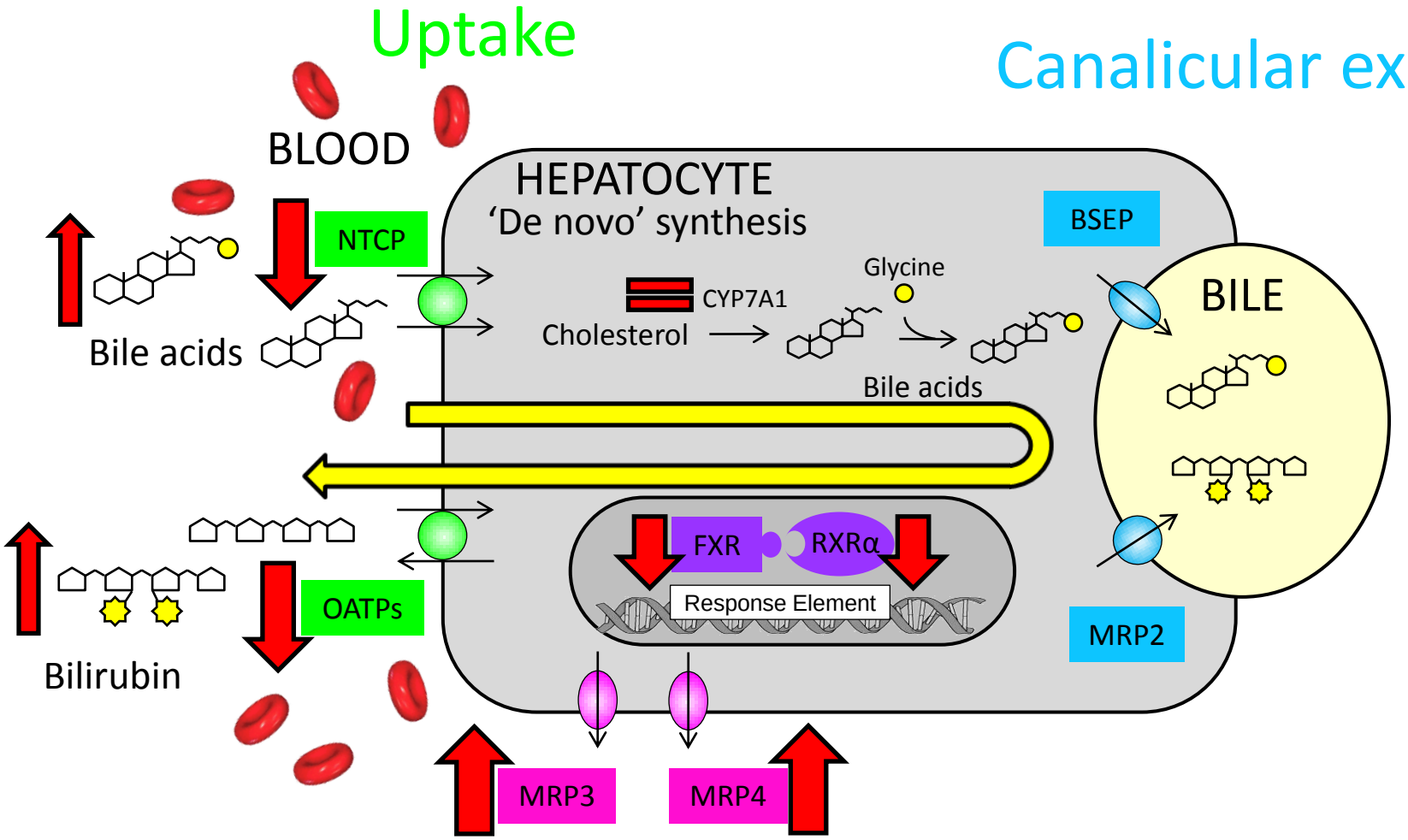
	Early PN n=420	Late PN n=356	p-value
Sludge - n(%)	175 (44.8)	124 (37.3)	0.04
Wall thickening - n(%)	24 (6.2)	19 (5.7)	0.8
Double wall - n(%)	24 (6.1)	11 (3.3)	0.08



Conclusion

- Withholding parenteral nutrition improved markers of hepatocellular injury in association with the reversal of normal bile acid trafficking and increased bile acid detoxification through conjugation
- Patients in the late PN group revealed higher biliribin levels, but lower levels of “cholestatic” liver enzymes (ALP/GGT) in the first week intervention window, coinciding with better outcome.
- Withholding parenteral nutrition and accepting a large caloric deficit during the first week of critical illness reduced the incidence of gallbladder sludge and thus appears to be in part a preventable complication of critical illness

General conclusion



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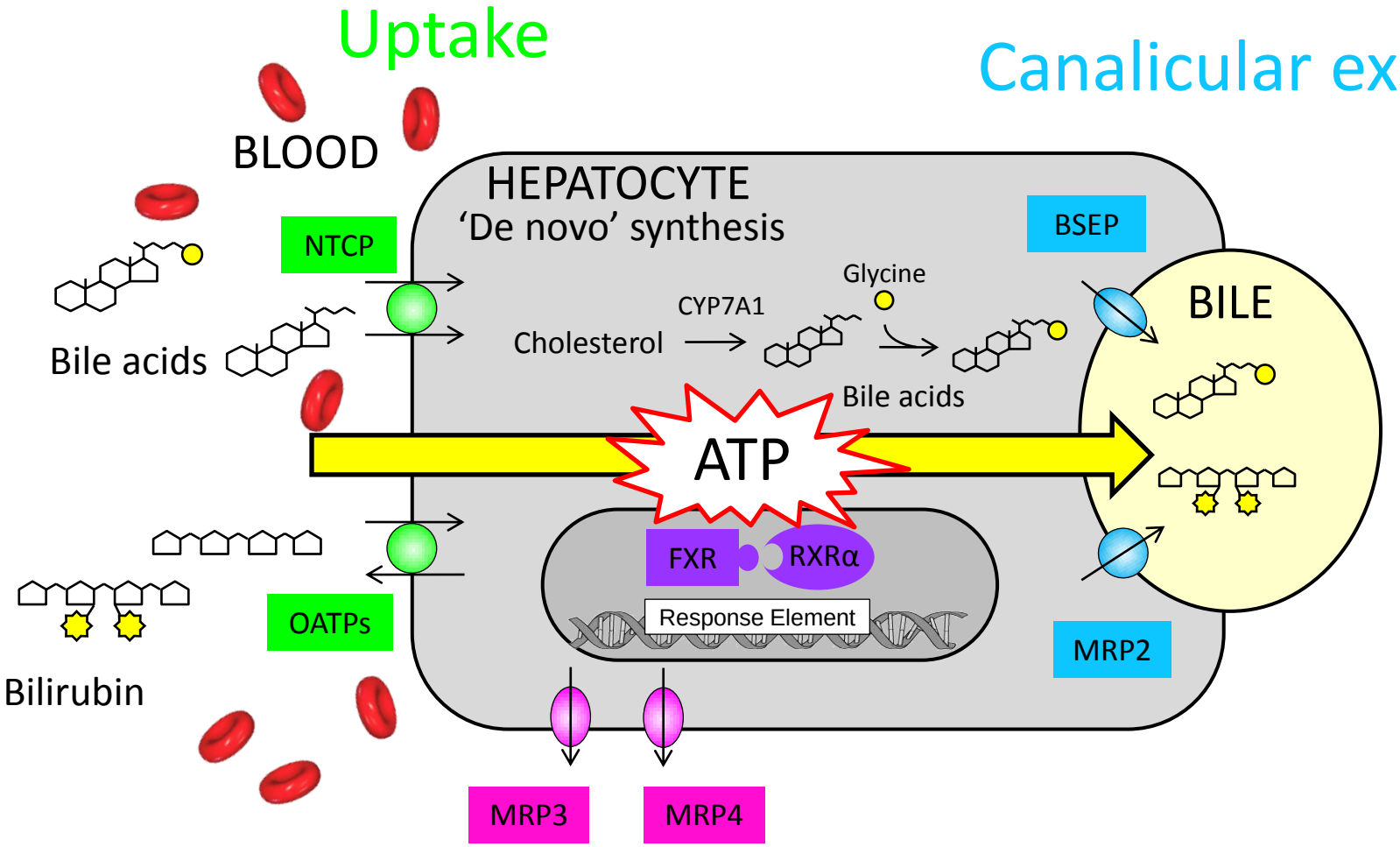

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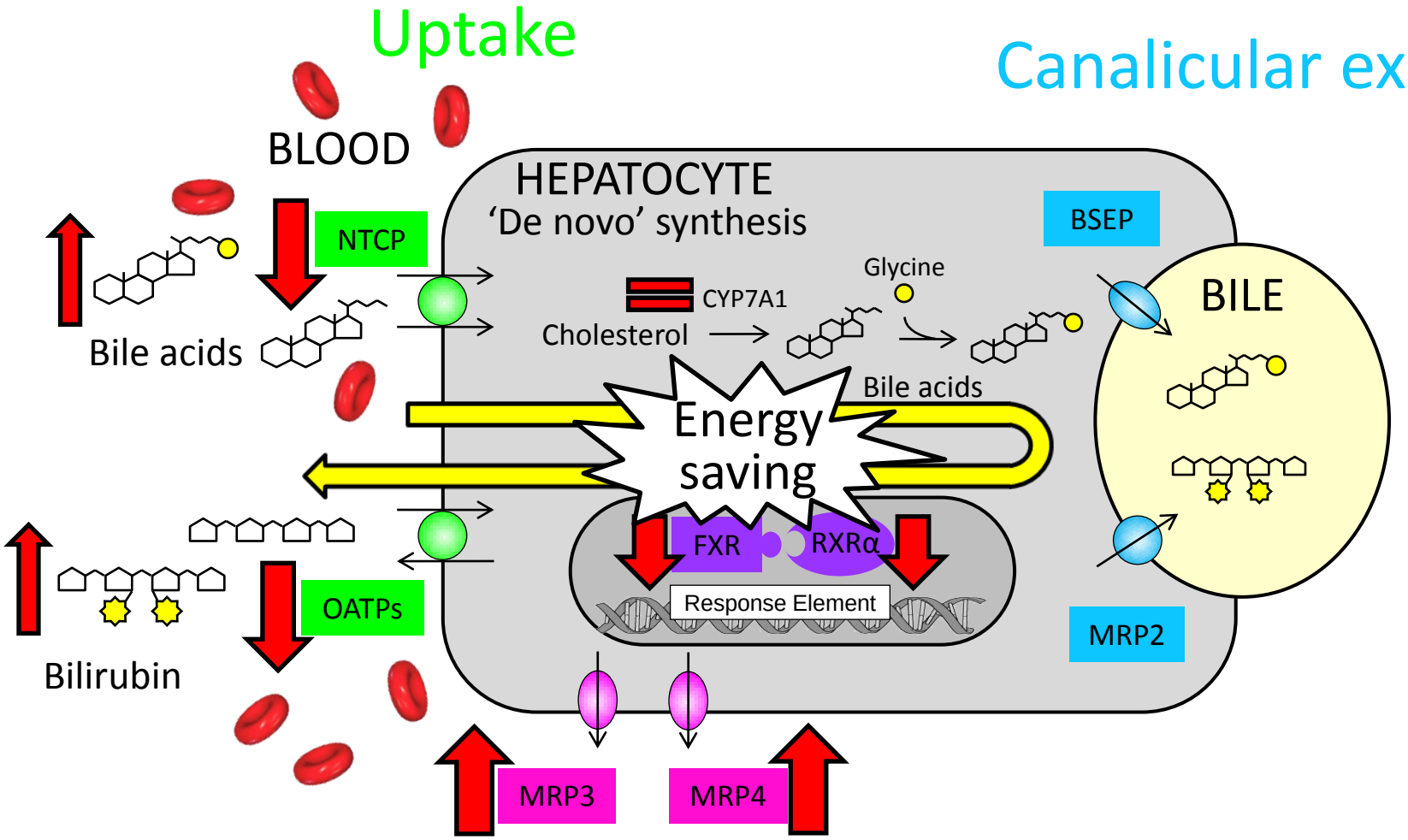
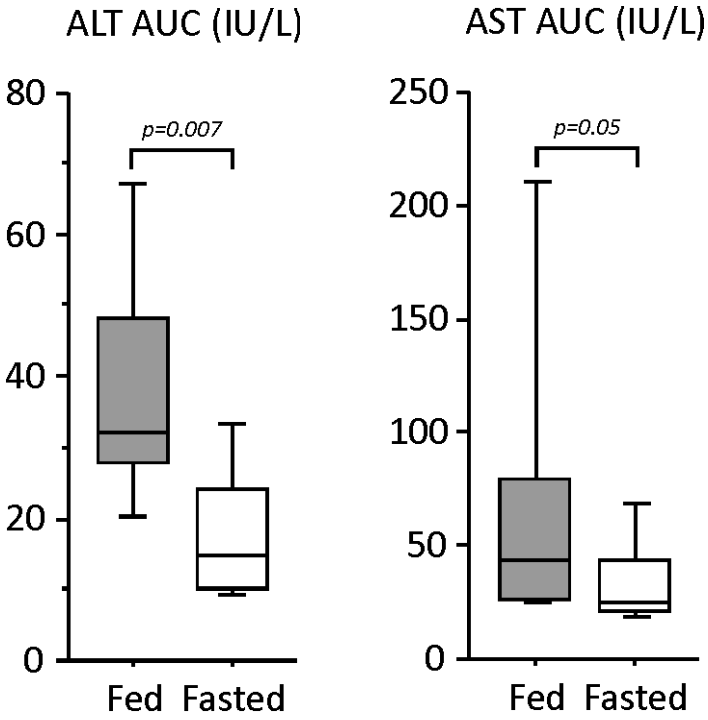
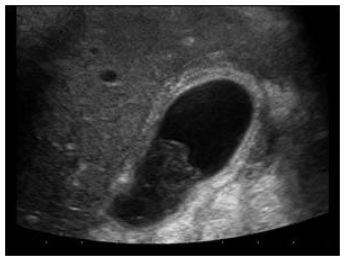


General conclusion

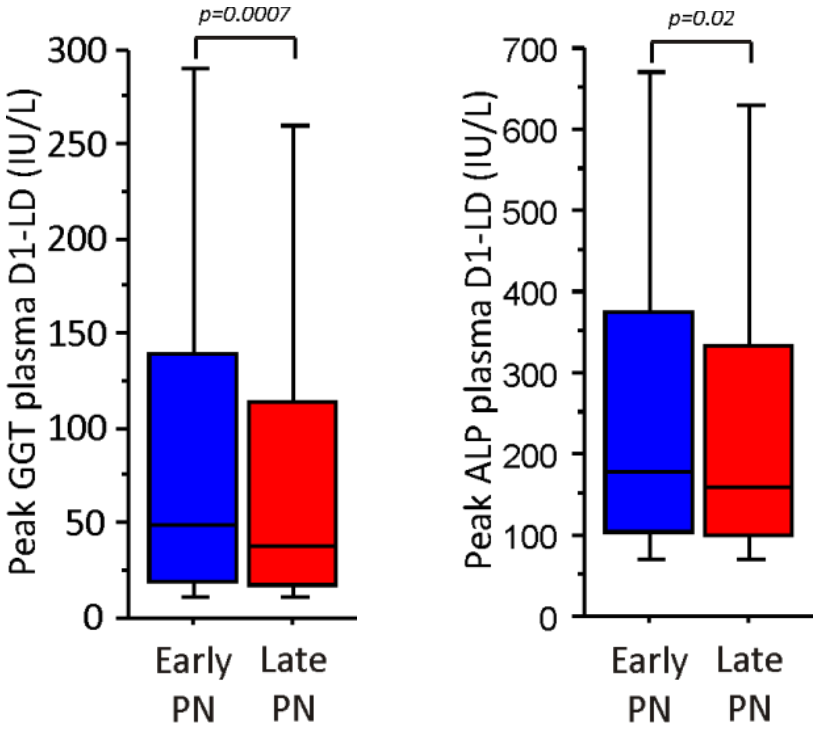
Rabbit study



EPaNIC trial



Early PN	45%
Late PN	37%



General conclusion

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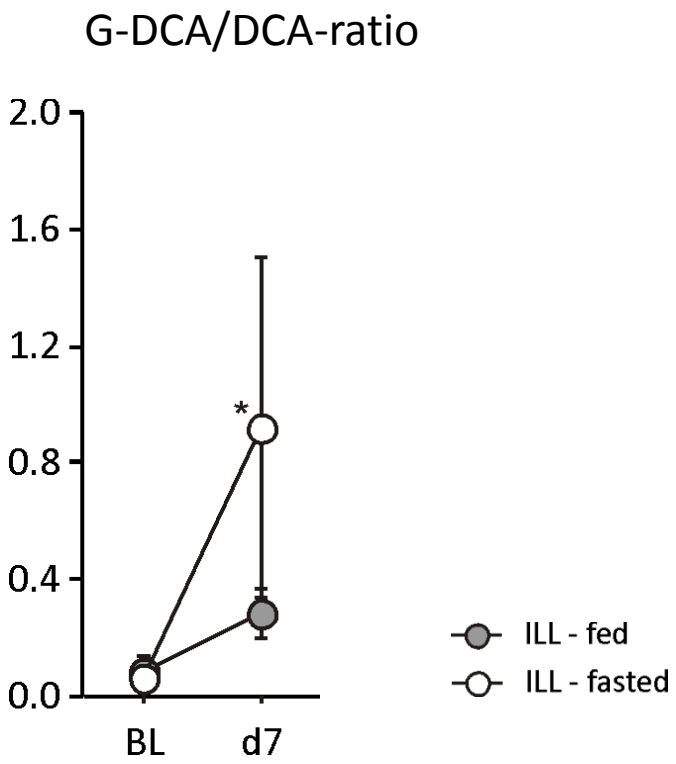
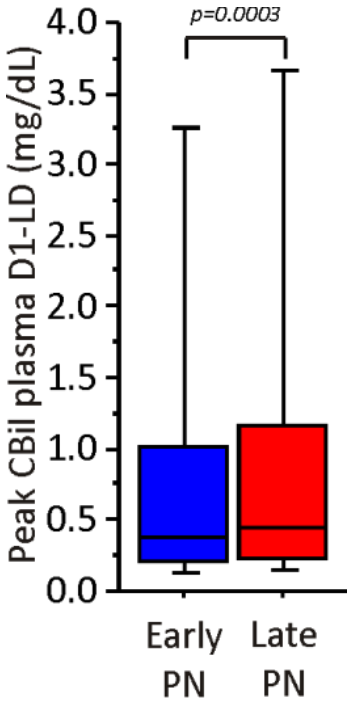


EPaNIC trial



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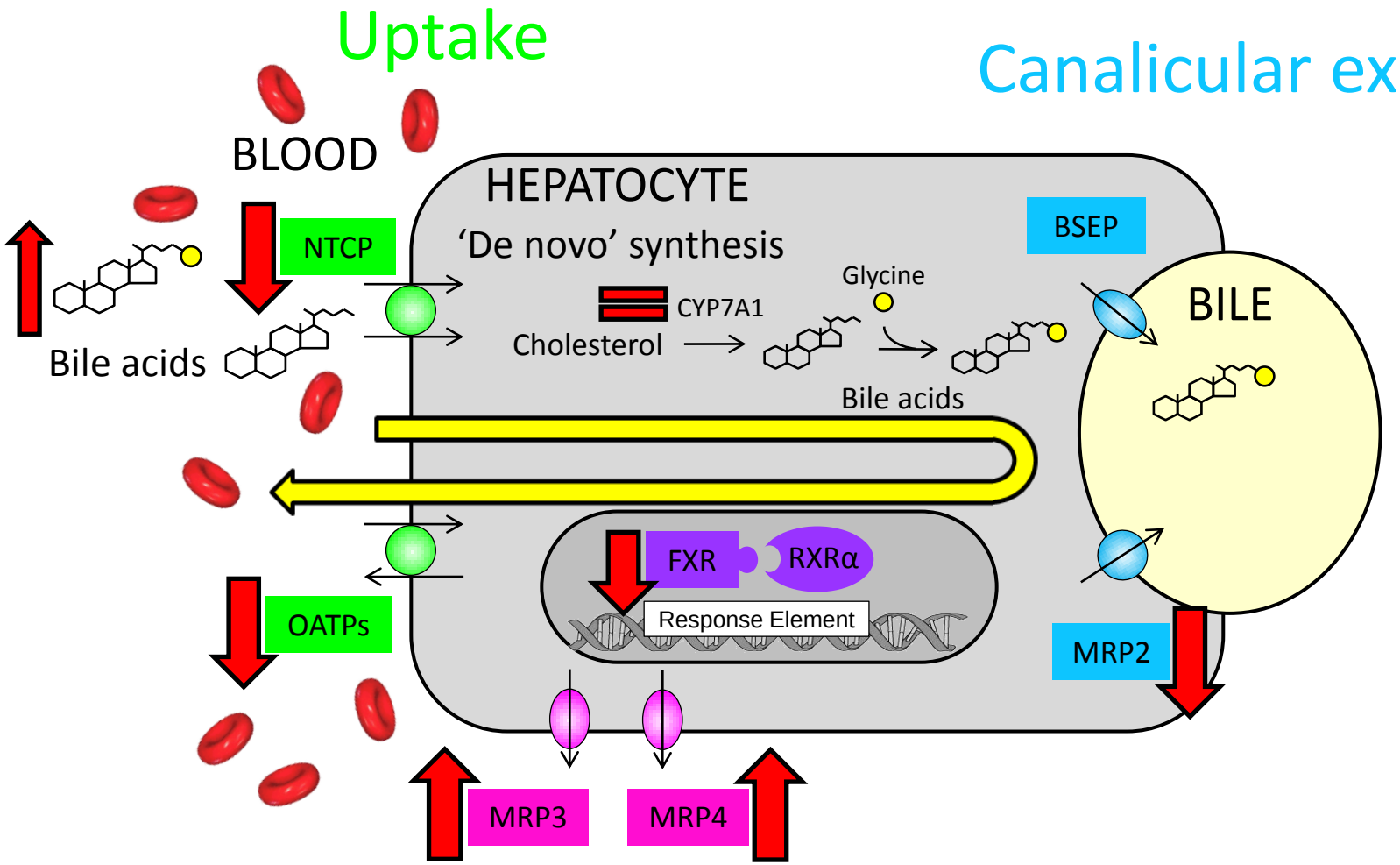

General conclusion

Hyperbilirubinemia = Protective

Hyperbilirubinemia ≠ Cholestasis

Acknowledgements

Lies Langouche

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