

Platelets and fibrin in liver injury and repair

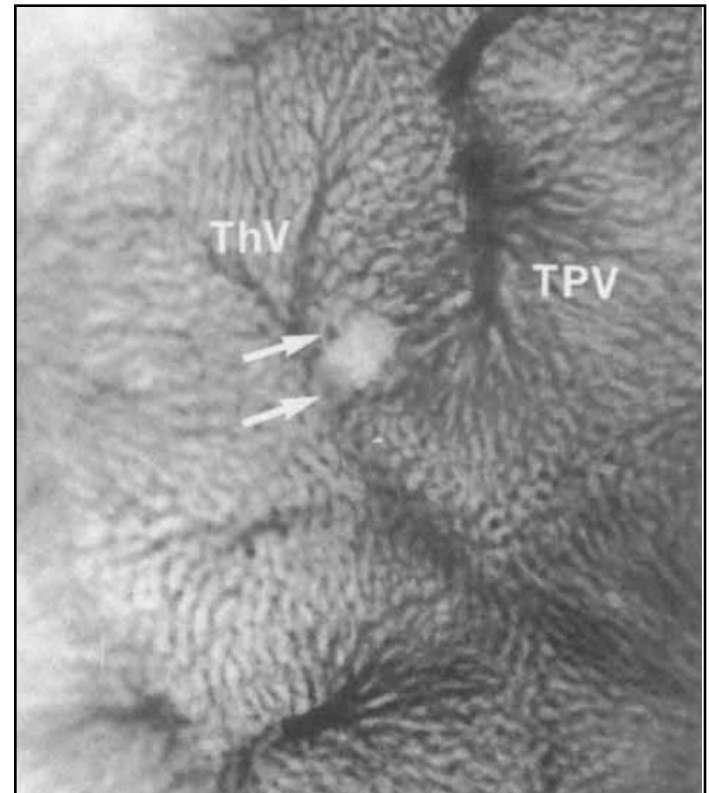
Ton Lisman, Dept Surgery, UMC Groningen, The Netherlands



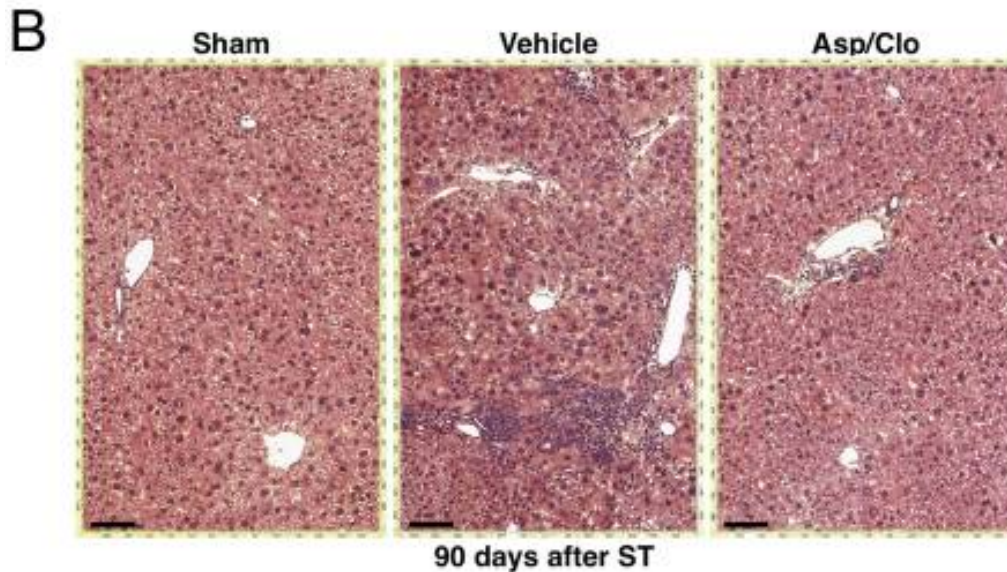
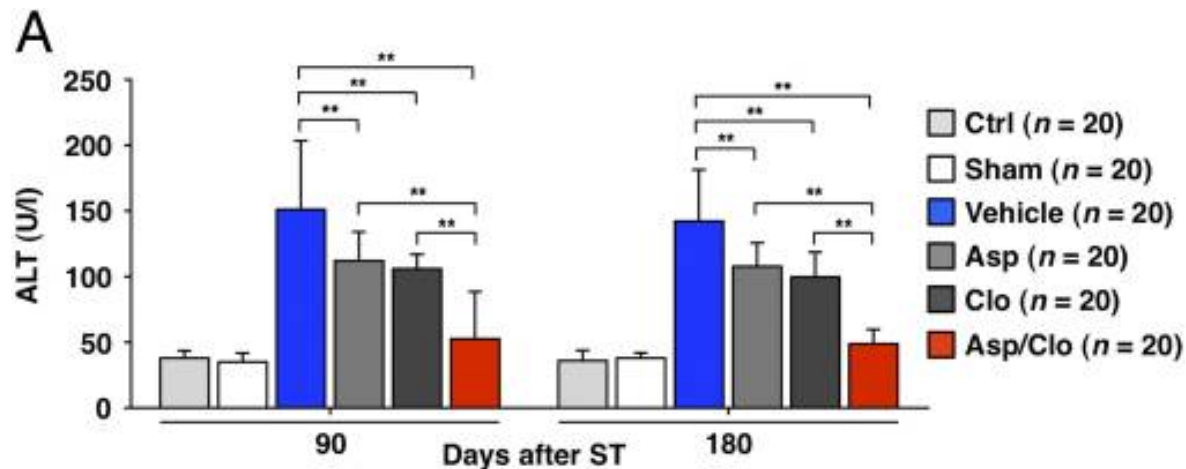
Acute and Chronic Changes in the Microcirculation of the Liver in Inbred Strains of Mice Following Infection with Mouse Hepatitis Virus Type 3

PEGGY J. MACPHEE, VINCENT J. DINDZANS, LAI-SUM FUNG AND GARY A. LEVY

- The first evidence for a role for the coagulation system in the pathogenesis of hepatitis came from studies examining the effects of MHV infection in inbred strains of mice.
- These reports demonstrated the presence of microthrombi within the hepatic microvasculature in areas of inflammation and subsequent tissue necrosis.



Platelets and liver disease progression



Coagulation and liver disease progression

Coagulation status influences fibrogenesis 1341

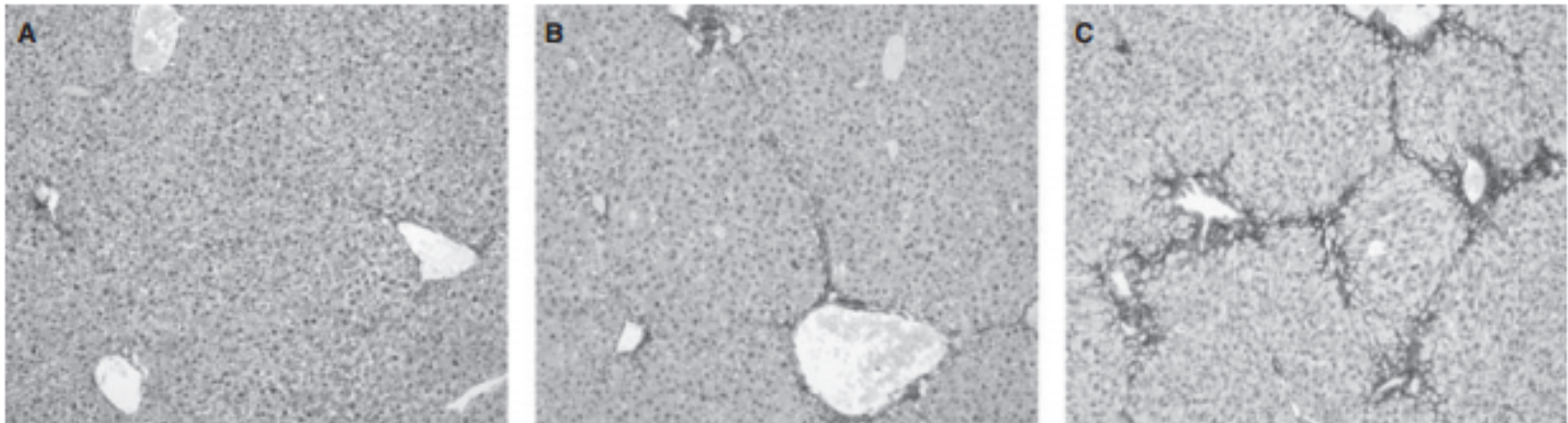
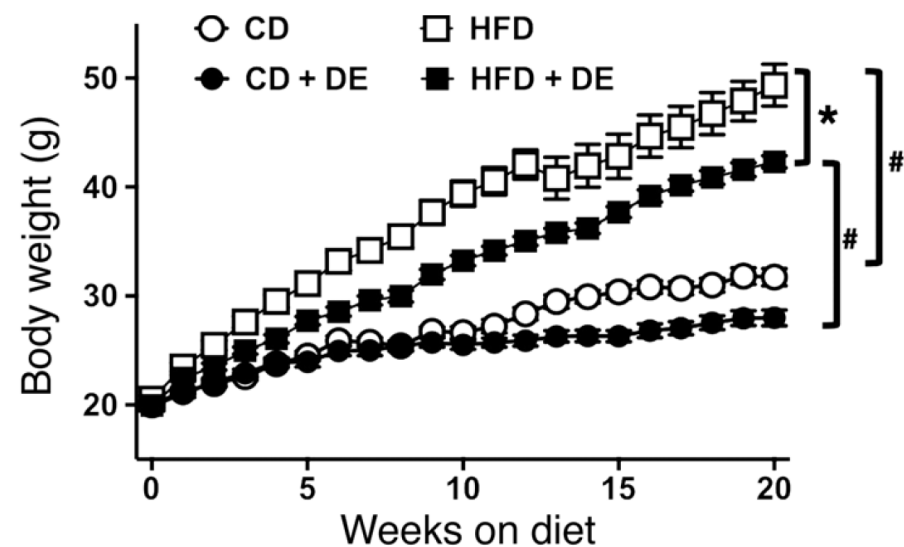
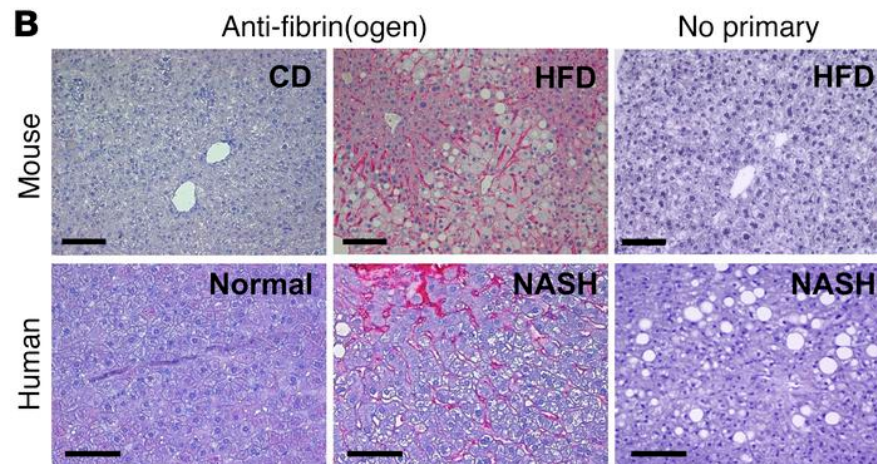
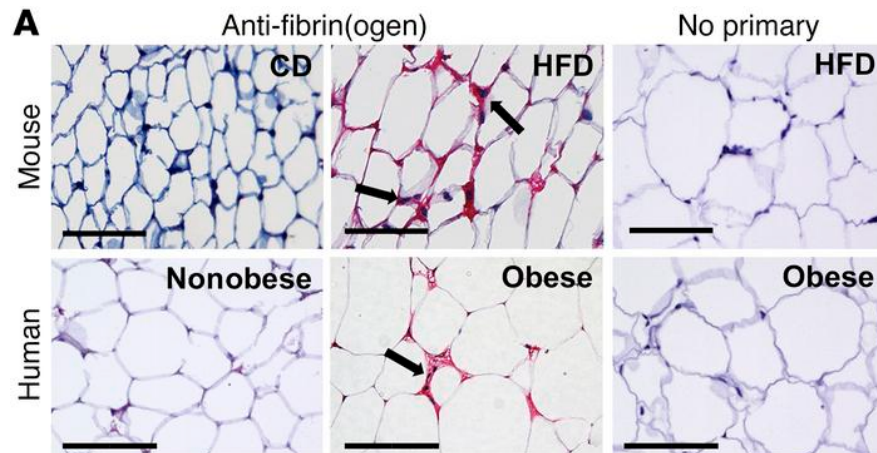


Fig. 4. Immunohistochemical staining of liver tissue for alpha-smooth muscle actin. Tissue samples from some male animals culled at 4 weeks were stained for α SMA. Relative to C57BL/6 control mice (B), these demonstrated reduced numbers of α SMA positive cells in warfarin-treated C57BL/6 mice (A) and increased numbers of α SMA positive cells in factor (F)V Leiden mutant animals (C).

Thrombin promotes diet-induced obesity through fibrin-driven inflammation

Anna K. Kopec,¹ Sara R. Abrahams,² Sherry Thornton,³ Joseph S. Palumbo,⁴ Eric S. Mullins,⁴ Senad Divanovic,⁵ Hartmut Weiler,⁶ A. Phillip Owens III,⁷ Nigel Mackman,⁸ Ashley Goss,⁹ Joanne van Ryn,¹⁰ James P. Luyendyk,¹ and Matthew J. Flick²



Aspirin use, VWF levels, blood group and FVleiden carriership in general population are associated with risk of fibrosis development

Platelets as Modulators of Liver Diseases

Ton Lisman, PhD¹ James P. Luyendyk, PhD²

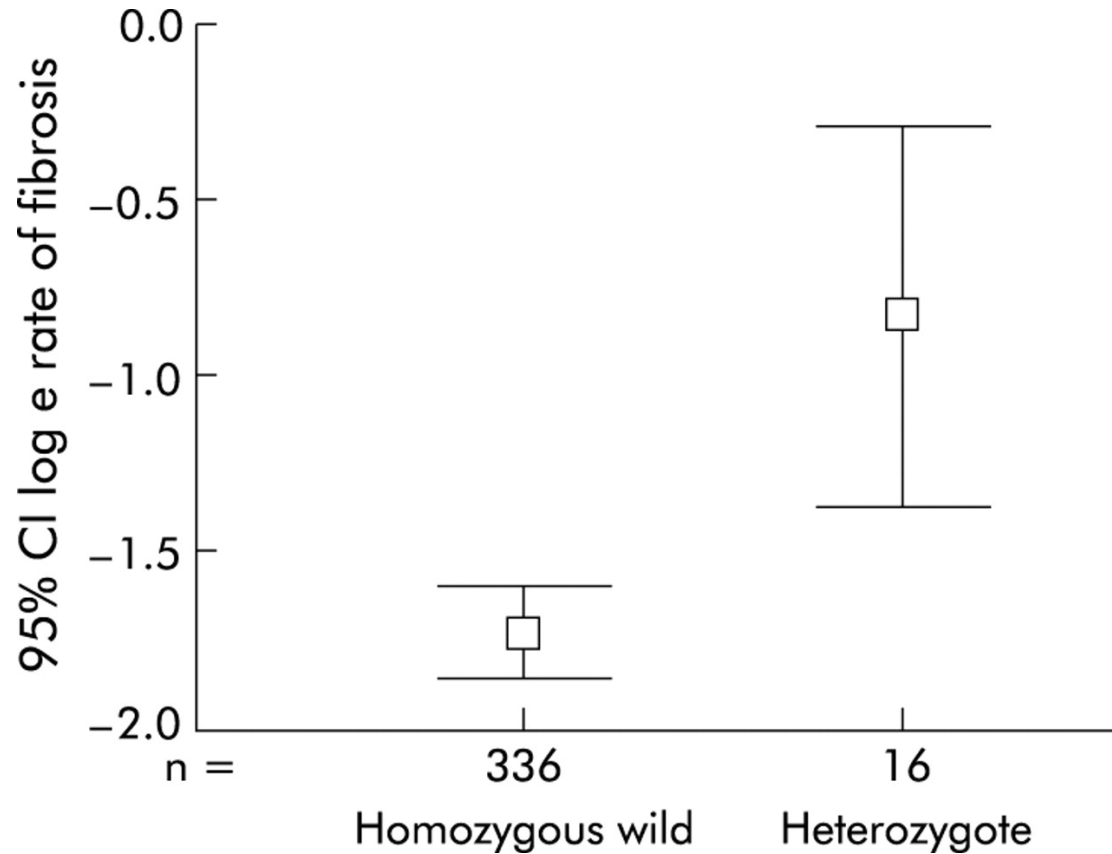
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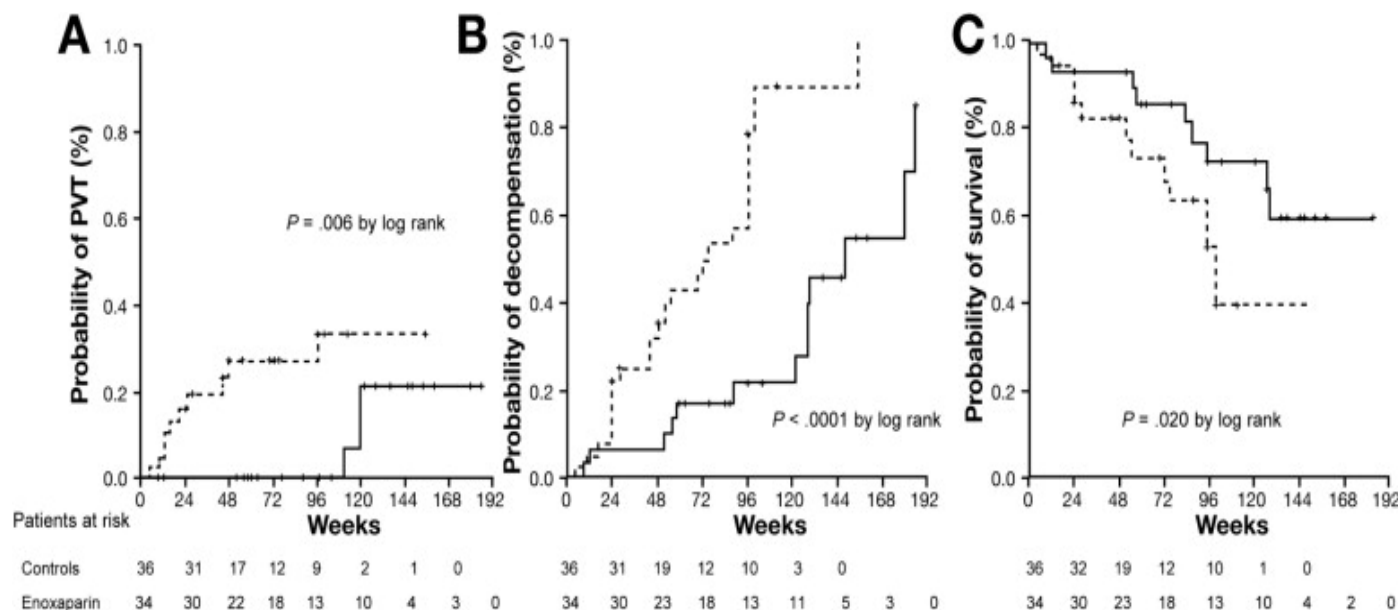
Faster progression of fibrosis in patients with thrombophilia



Enoxaparin Prevents Portal Vein Thrombosis and Liver Decompensation in Patients With Advanced Cirrhosis

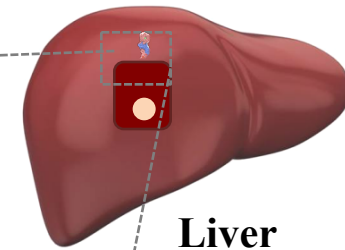
ERICA VILLA,* CALOGERO CAMMÀ,† MARCO MARIETTA,§ MONICA LUONGO,* ROSINA CRITELLI,* STEFANO COLOPI,|| CRISTINA TATA,|| RAMONA ZECCHINI,* STEFANO GITTO,* SALVATORE PETTA,‡ BARBARA LEI,* VERONICA BERNABUCCI,* RANKA VUKOTIC,* NICOLA DE MARIA,* FILIPPO SCHEPIS,* AIMILIA KARAMPATOU,* CRISTIAN CAPOREALI,|| LUISA SIMONI,¶ MARIAGRAZIA DEL BUONO,* BEATRICE ZAMBOTTO,* ELENA TUROLA,* GIOVANNI FORNACIARI,# SUSANNA SCHIANCHI,# ANNA FERRARI,* and DOMINIQUE VALLA**,††,§§

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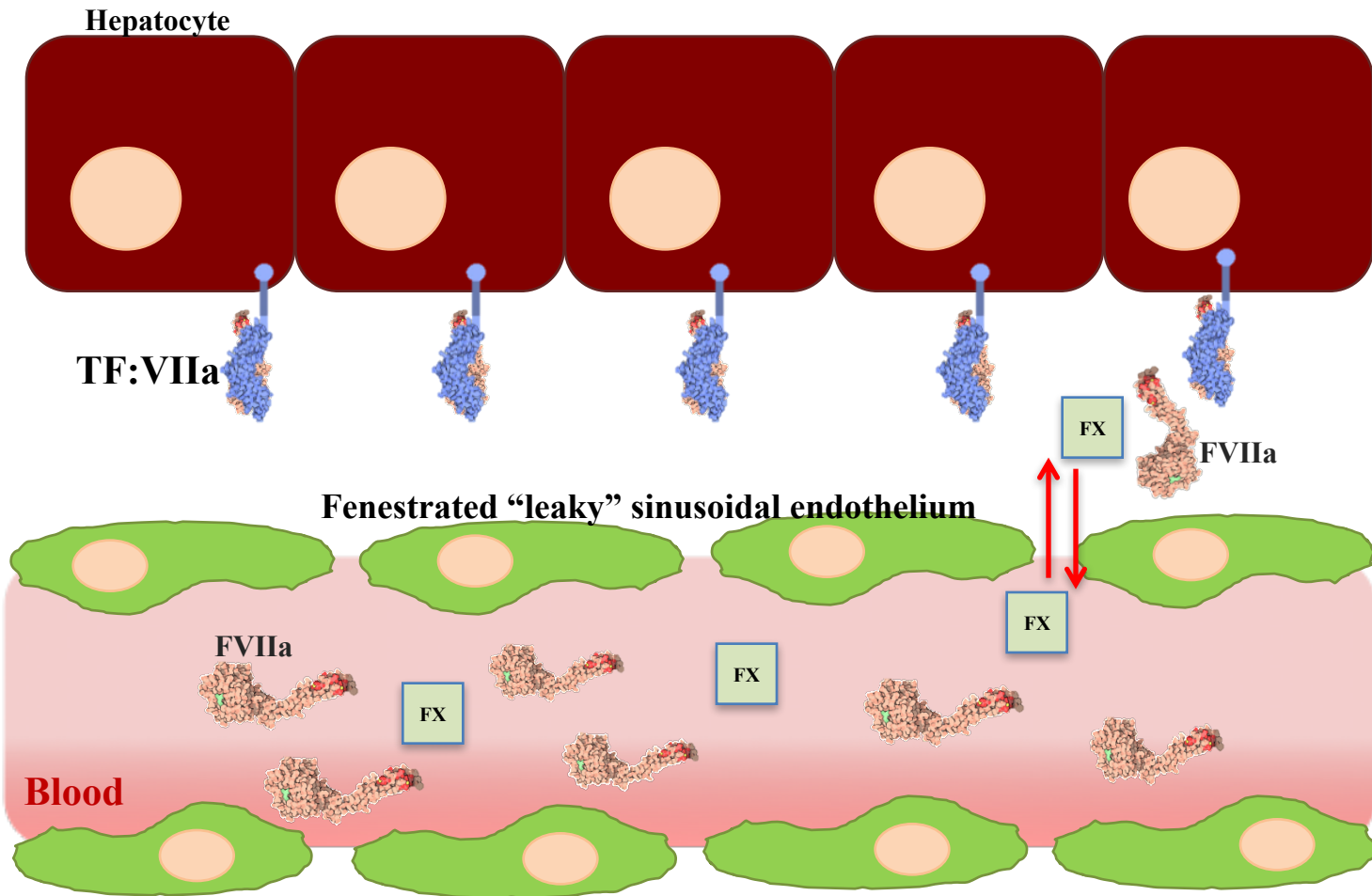


Why do platelets and fibrin accumulate in the injured liver?

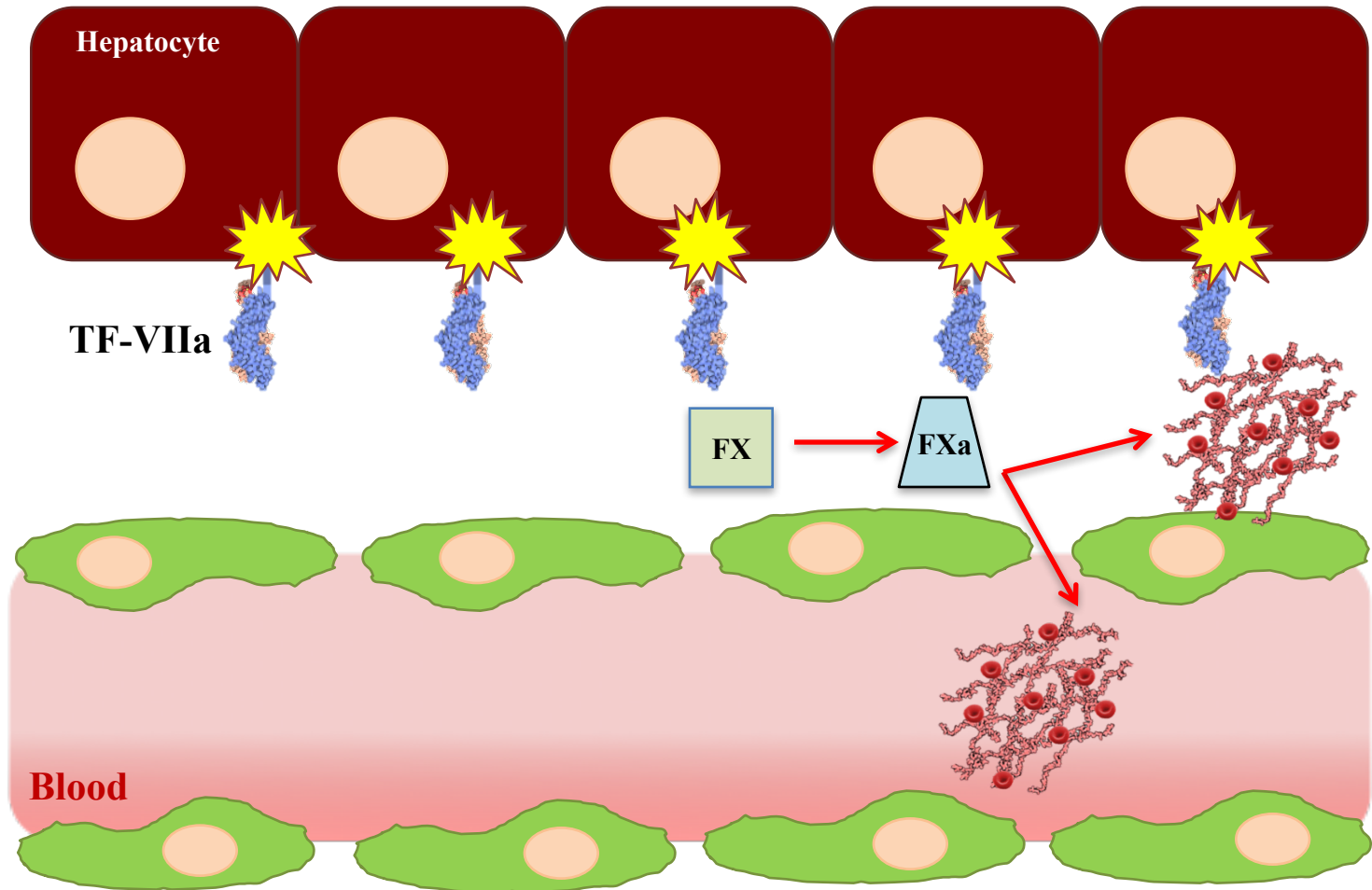
Hepatocytes express cryptic tissue factor



Liver



Liver injury leads to TF decryption and intrahepatic fibrin deposition



Some studies suggest beneficial effects of intrahepatic activation of coagulation:

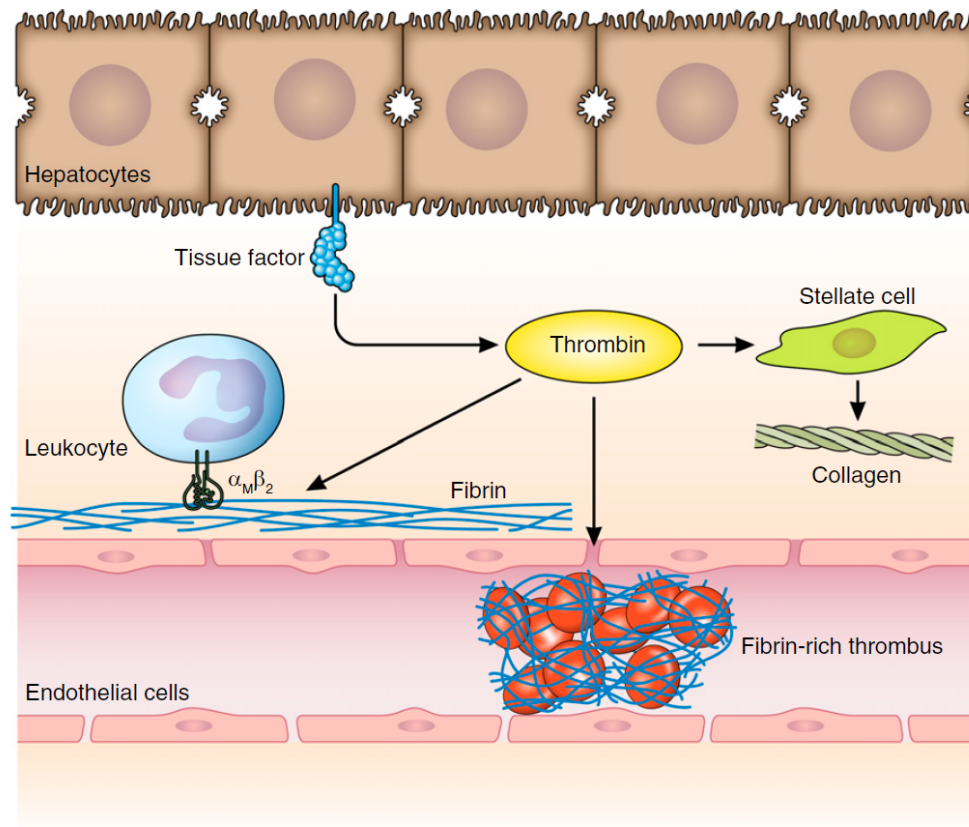
- FASTER disease progression in fibrinogen deficiency under some conditions
- Fibrin is required for recovery from profibrotic insults

Comment on Joshi et al, page 2751

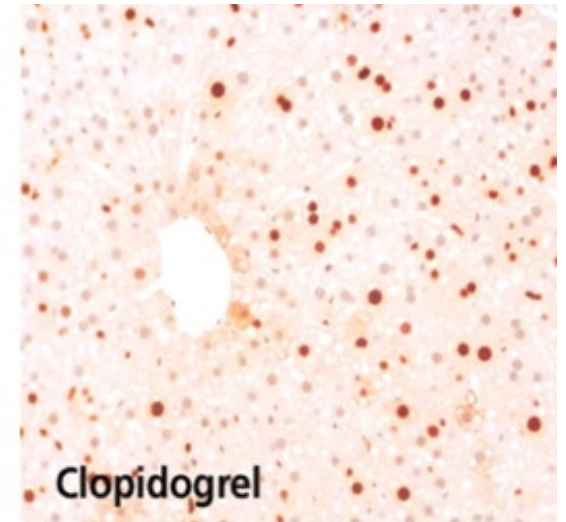
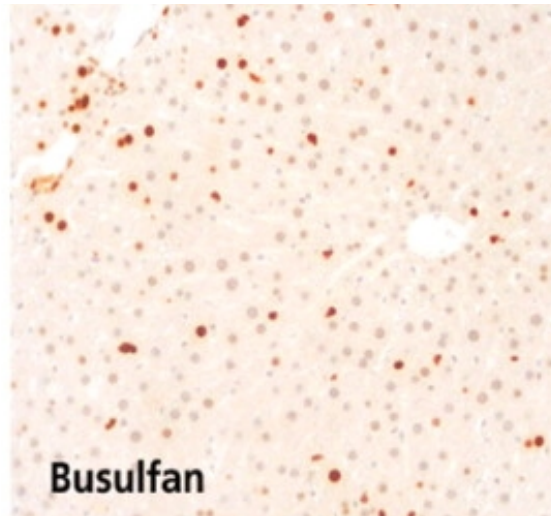
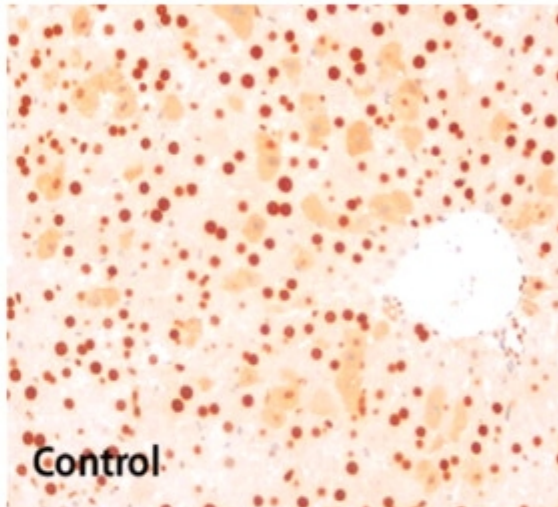
Fibrin fixes fibrosis

Ton Lisman UNIVERSITY OF GRONINGEN

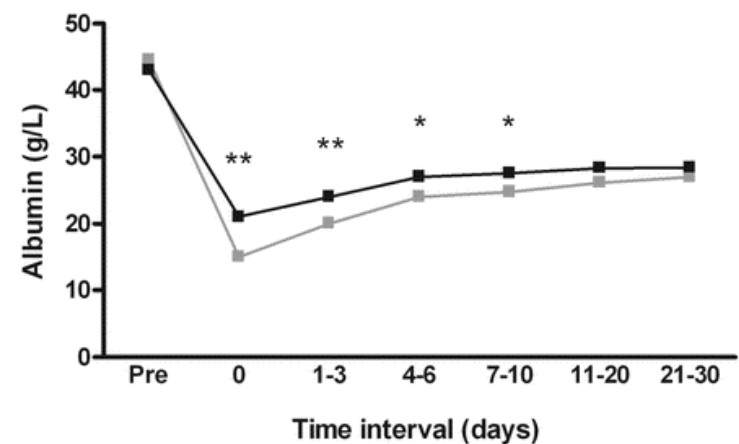
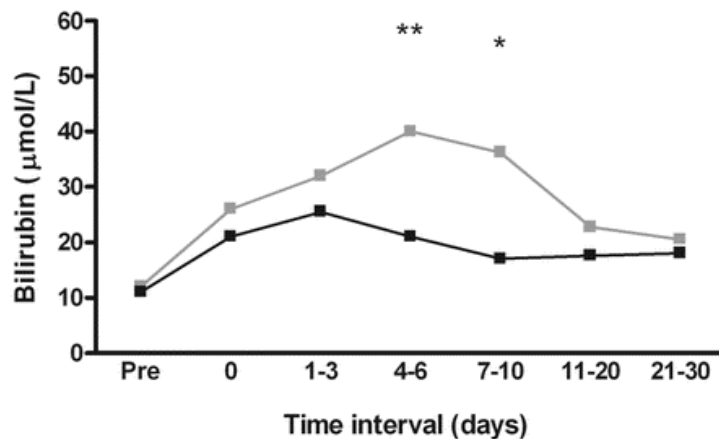
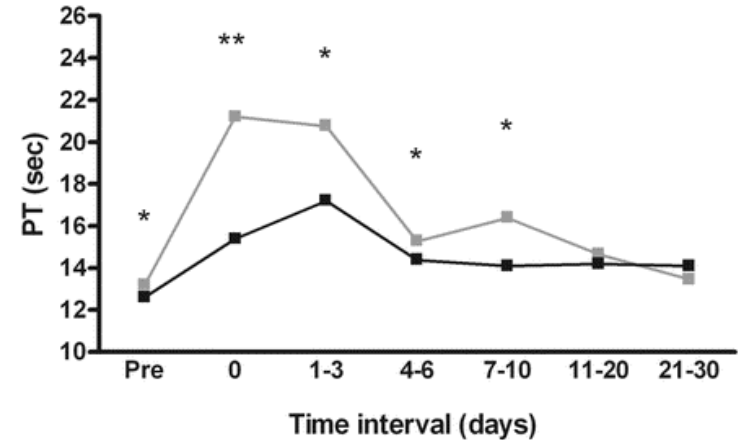
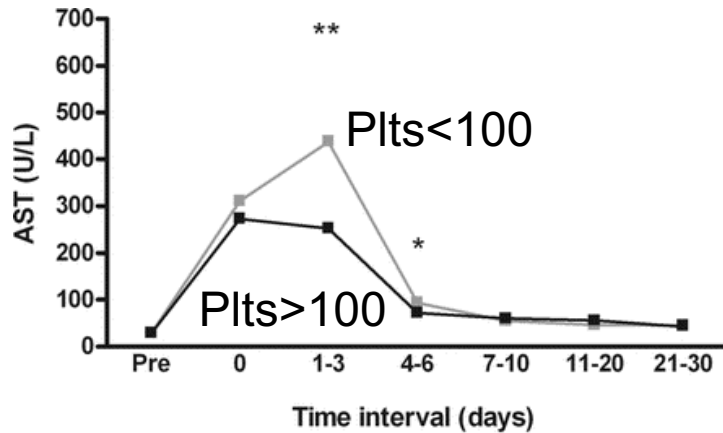
In this issue of *Blood*, Joshi et al demonstrate that the interaction between fibrin and $\alpha_M\beta_2$ on leukocytes reduces the development of liver fibrosis in a mouse model of cholestatic injury.¹



Platelets contribute to liver regeneration in mice



Post-operative platelet count is associated with delayed function recovery and mortality after partial hepatectomy in humans



Post-operative platelet count is associated with delayed function recovery and mortality in humans

TABLE 3. Multivariate Analysis of Independent Risk Factor for Delayed Postoperative Recovery of Liver Function

Variables	OR (95% CI)	<i>P</i>
Age	1.00 (0.95–1.06)	0.99
RBC transfusion, (yes vs. no)	6.62 (2.24–19.58)	<0.01
Liver volume removed	2.40 (1.21–4.79)	0.01
Platelet count (<100 × 10 ⁹ /L vs. ≥100 × 10 ⁹ /L)	11.49 (1.08–122.41)	0.04
Preoperative serum bilirubin (μmol/L)*	1.19 (1.06–1.33)	<0.01
Preoperative serum GGT (mg/dL)*	1.01 (1.00–1.03)	0.03
Preoperative PT (s)*	1.15 (0.74–1.79)	0.52
Preoperative AT (%)*	0.99 (0.97–1.02)	0.58
Preoperative ALT (U/L)*	1.01 (0.99–1.03)	0.27

*Preoperative laboratory values were entered as continuous variables in the model.
Abbreviations as in Table 2.

Post-operative platelet count is associated with speed of liver regeneration in humans

Table 2. Volumetric assessment and short-term outcomes stratified by platelet count

	Low platelet count (<i>n</i> = 25)	Normal–high platelet count (<i>n</i> = 74)	<i>P</i> [†]
Volume outcomes [*]			
TLV (cm ³)	1787 (1484–2410)	1710 (1397–2240)	0.276 [‡]
TLV adjusted to bodyweight (%)	2.23 (1.87–3.74)	2.28 (1.90–2.68)	0.393 [‡]
RLV _p (cm ³)	1267 (831–1610)	1090 (787–1520)	0.256 [‡]
RLV _p /TLV (%)	69.0 (52.8–80.9)	70.1 (46.9–81.9)	0.903 [‡]
RLV _p adjusted to bodyweight (%)	1.39 (1.23–2.04)	1.44 (1.04–1.90)	0.473 [‡]
Regeneration index within 2 months	3.9 (–17.4 to 18.9)	16.5 (–3.0 to 44.6)	0.043 [‡]
Postoperative outcomes			
Morbidity			
Overall	18 (72)	28 (38)	0.003
Major complication	6 (24)	10 (14)	0.218
Liver failure	6 of 24 (25)	7 of 72 (10)	0.058
Length of hospital stay (days) [*]	8 (6–12)	6 (4–8)	0.004 [‡]
Median survival (months)	24.5	67.3	0.005

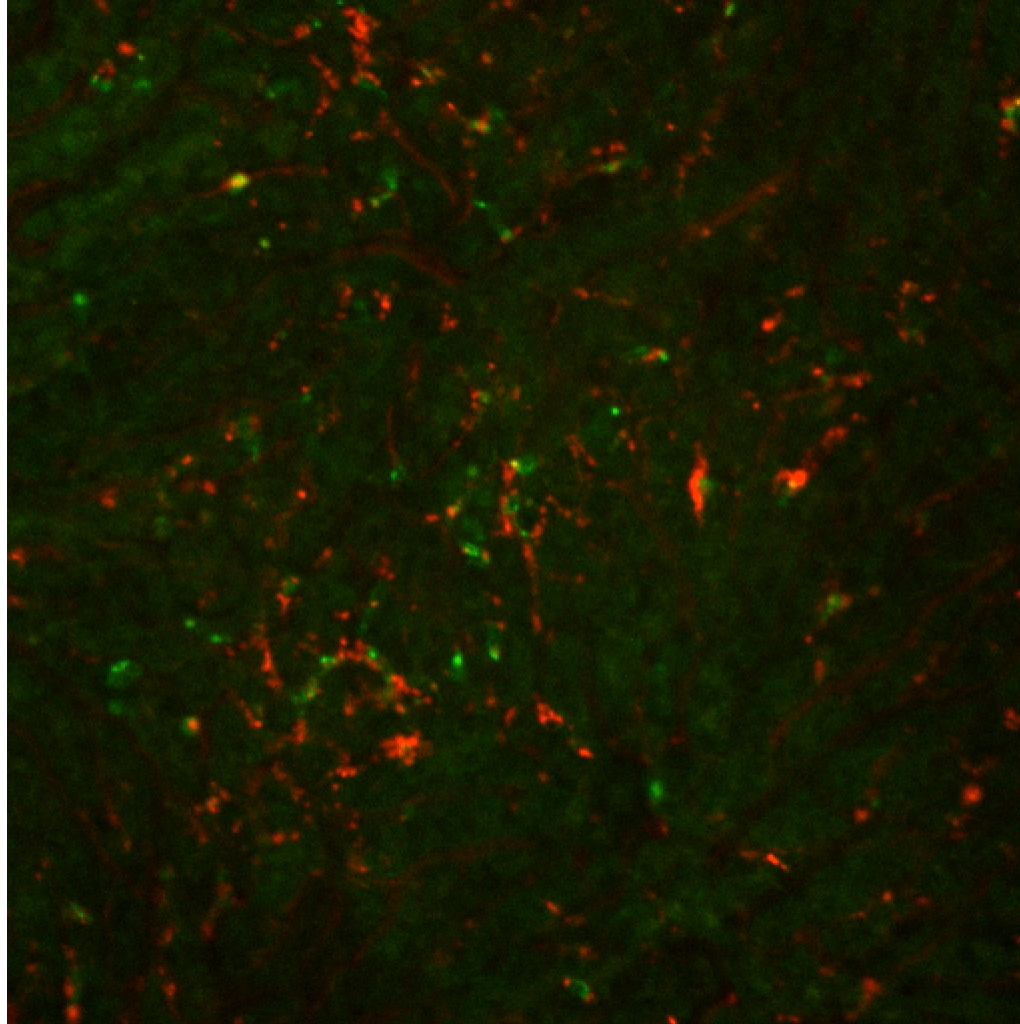
Values in parentheses are percentages unless indicated otherwise;

* values are median (i.q.r.). TLV, total liver volume; RLV_p, postoperative remnant liver volume.

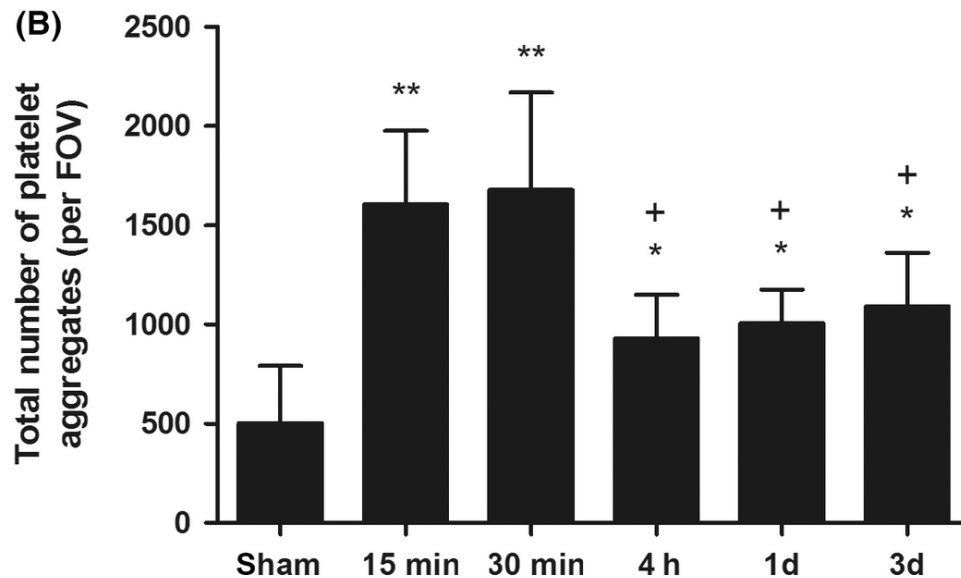
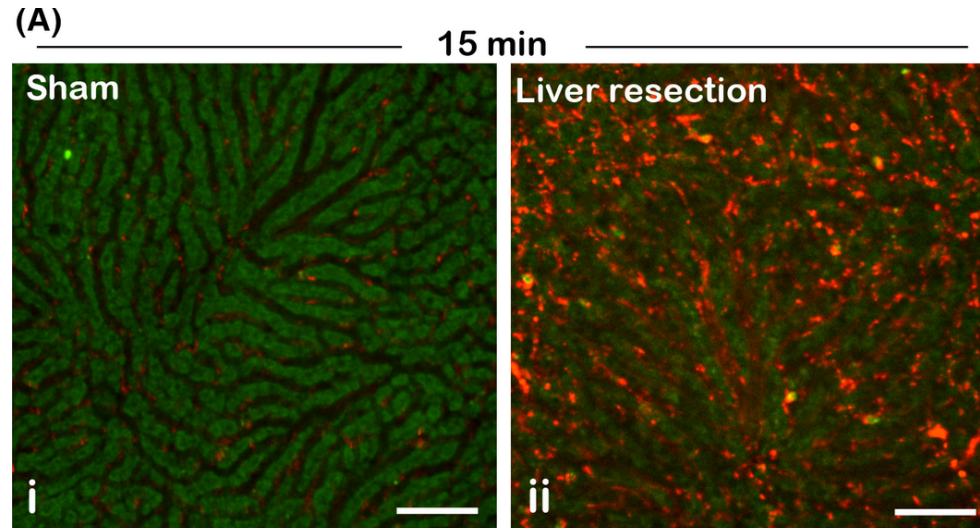
† χ^2 test, except

‡ Mann–Whitney *U* test.

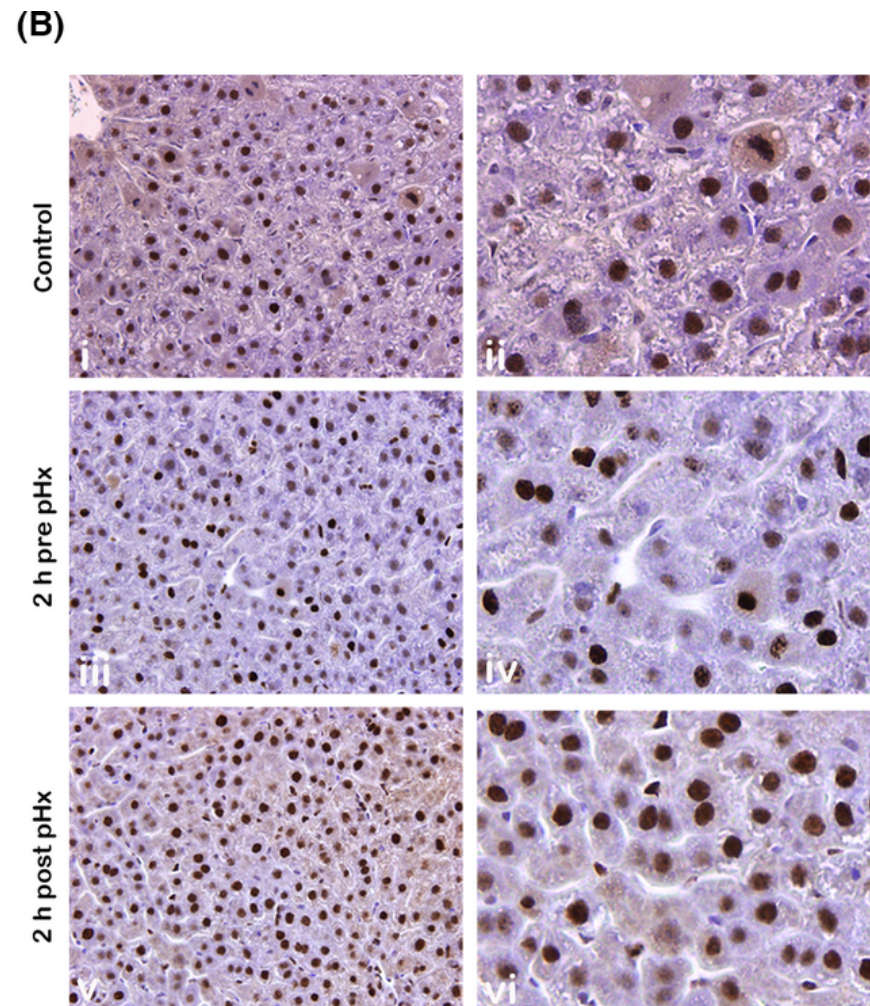
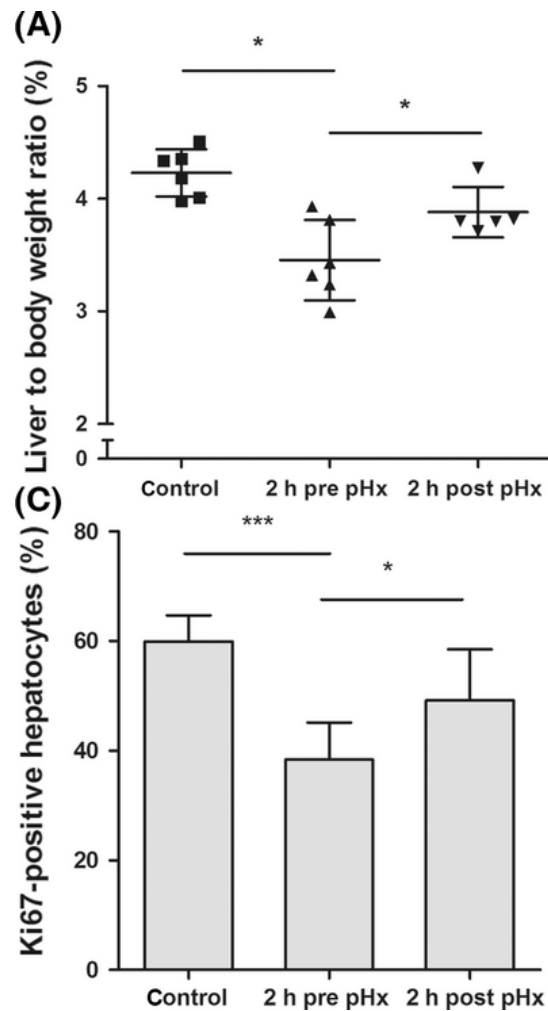
Platelet influx in the regenerating liver



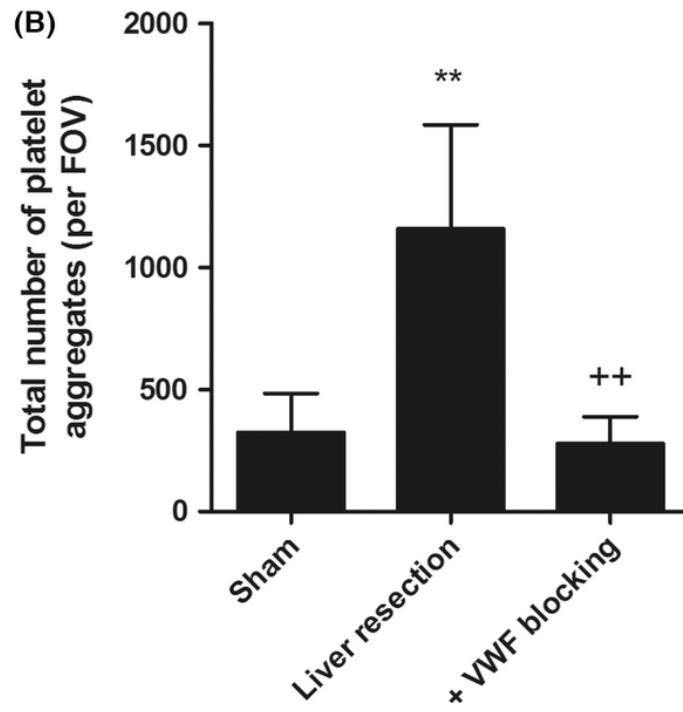
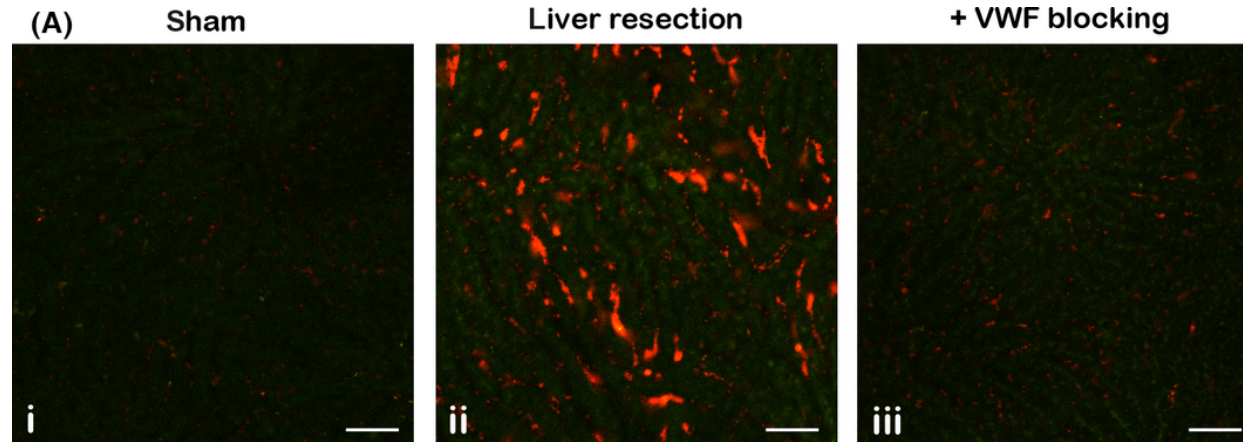
Platelet influx in the regenerating liver is transient



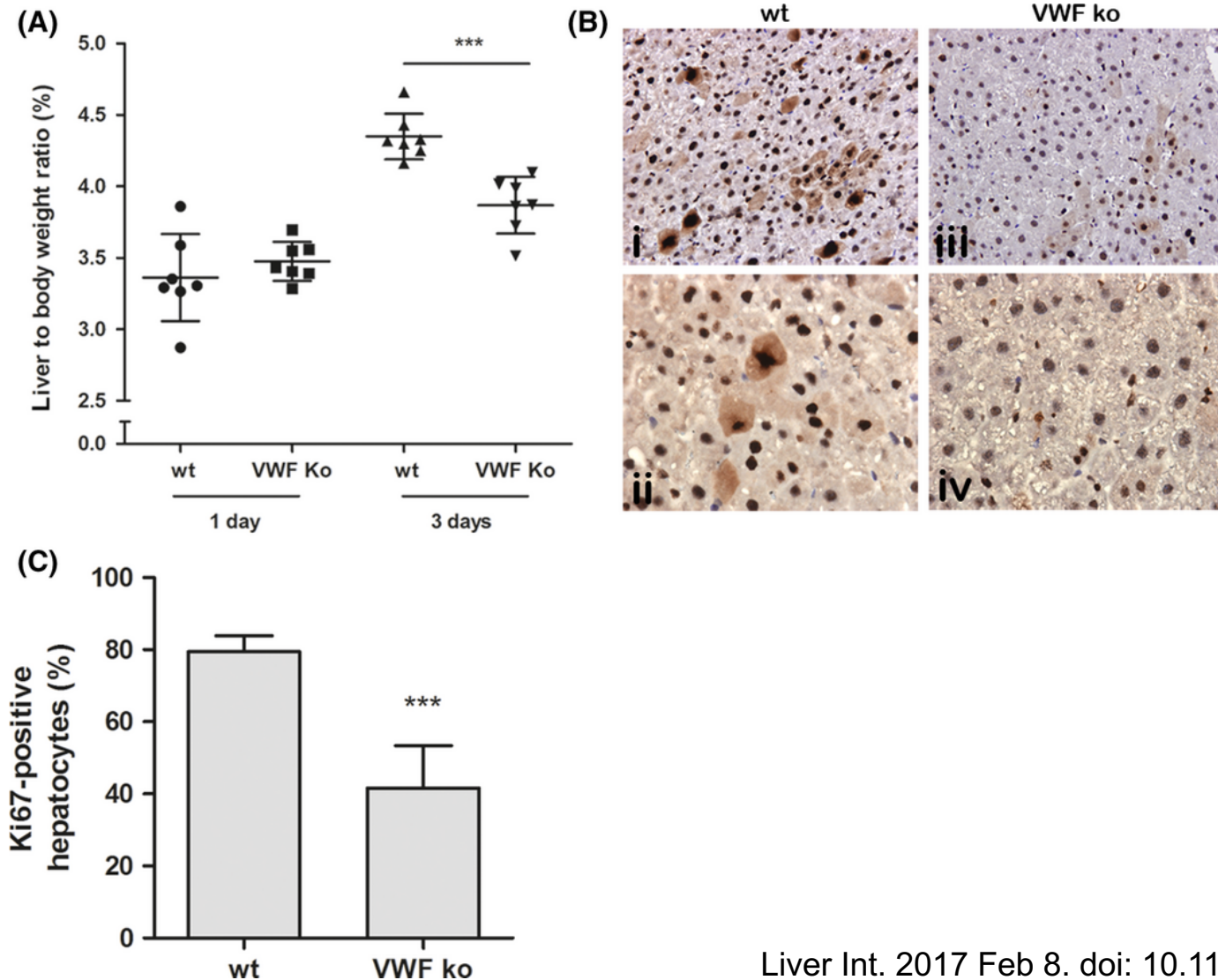
Transient platelet influx stimulates liver regeneration



Transient platelet influx is VWF-dependent



VWF deficiency delays liver regeneration



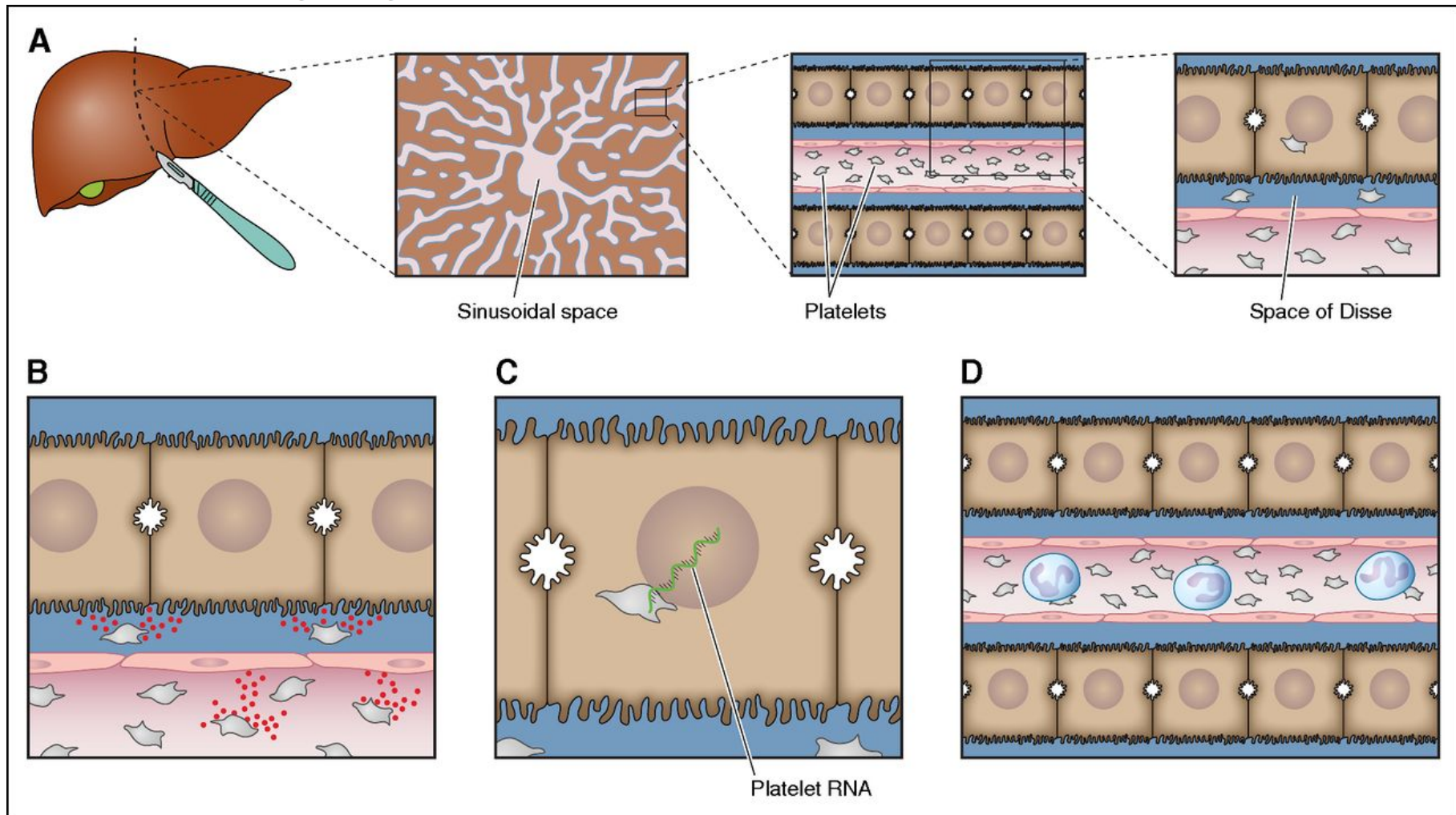
Platelet influx is rapid and transient: delivery of cargo?



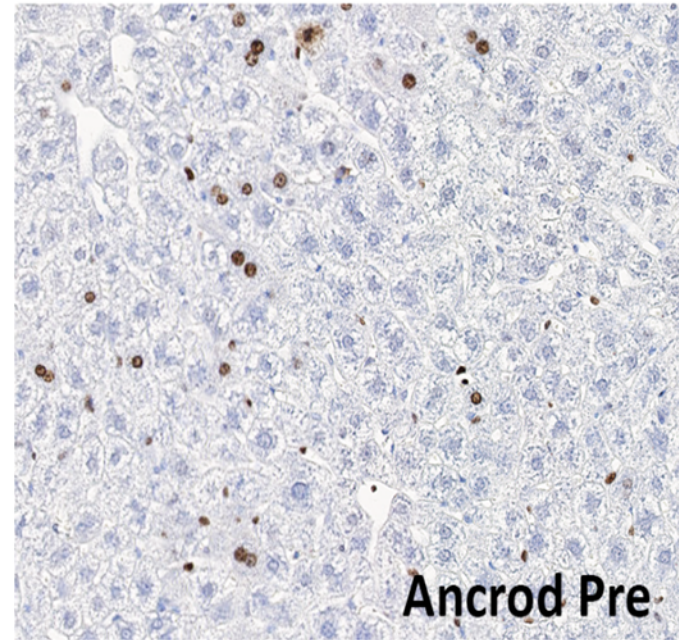
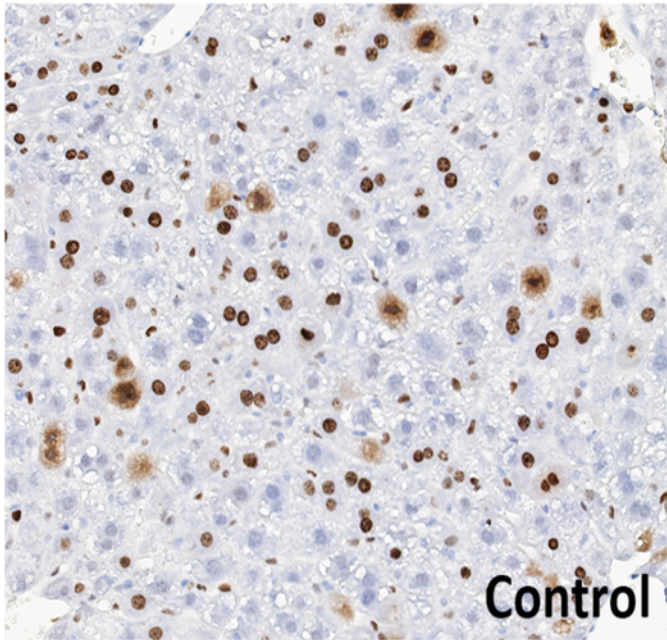
Mechanisms of platelet-mediated liver regeneration

Ton Lisman and Robert J. Porte

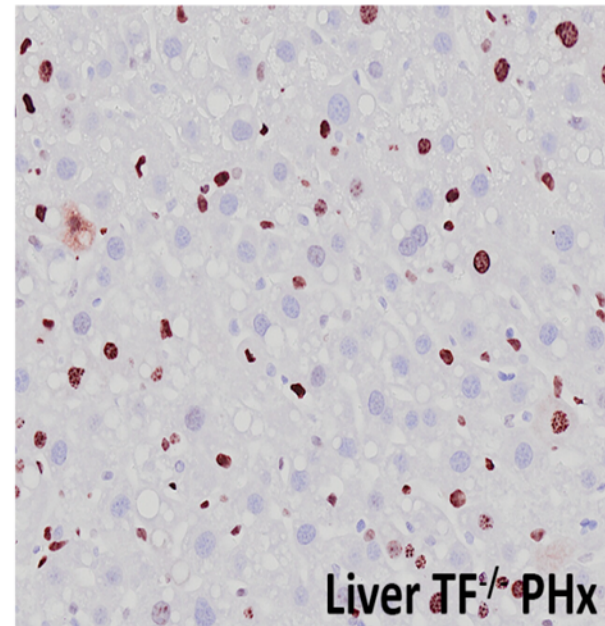
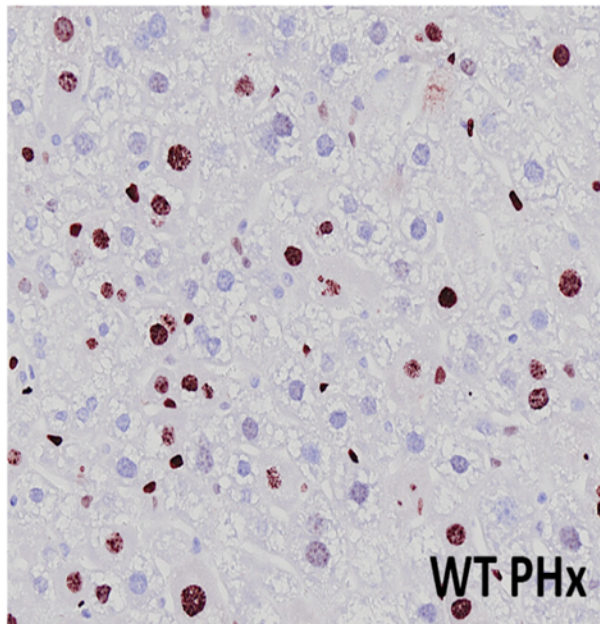
Surgical Research Laboratory and Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands



Fibrinogen depletion impairs liver regeneration after partial hepatectomy



Deficiency in liver TF impairs liver regeneration after partial hepatectomy



In summary:

- Platelets and fibrin accelerate acute and chronic liver injury
- Antithrombotic therapy may be beneficial
- Platelets and fibrin aid repair of the injured liver
- Prothrombotic therapy may be beneficial
- Better understanding of mechanisms involved may result in targeted therapies