Hepatocyte Transporter Network 2019
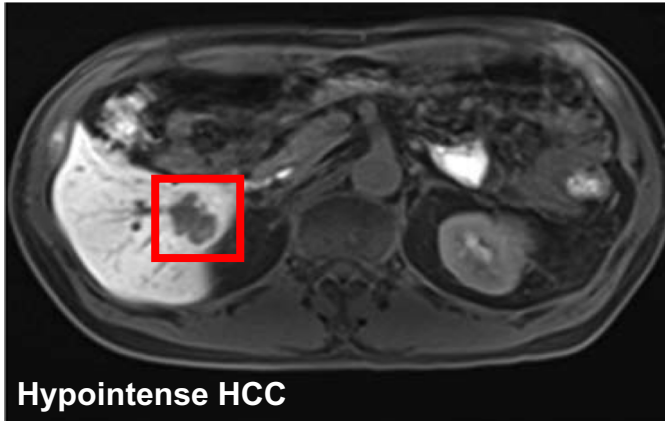Les Diablerets, Switzerland
1-4 September, 2019

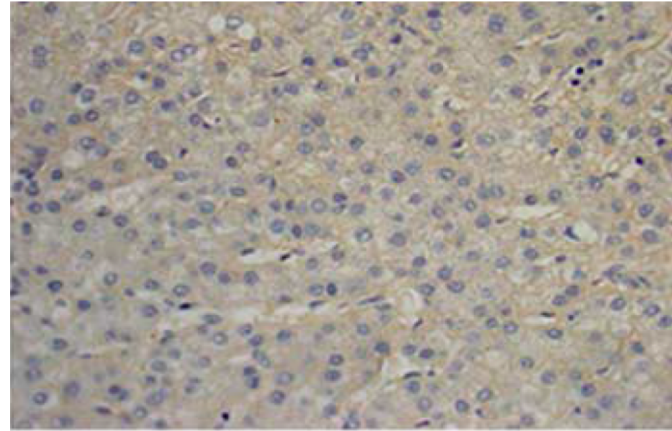# Gd-EOB-DTPA transport across hepatocyte membranes and transporter scores in chronic liver disease

Catherine M PASTOR, MD, PhD

catherine.pastor@unige.ch

Université de Paris

HUG Hôpitaux Universitaires Genève

EOB-DTPA in hepatocellular carcinomas

No EOB-DTPA uptake into tumour cells

No OATP1B3 expression in the lesion

Hypointense HCC

➡ **Drugs similar to EOB-DTPA are unlikely to enter into tumour cells**

M Narita, J Gastroenterol, 2009, 44, 793

Expression of OATP1B3 and MRP2 in surrounding parenchyma?
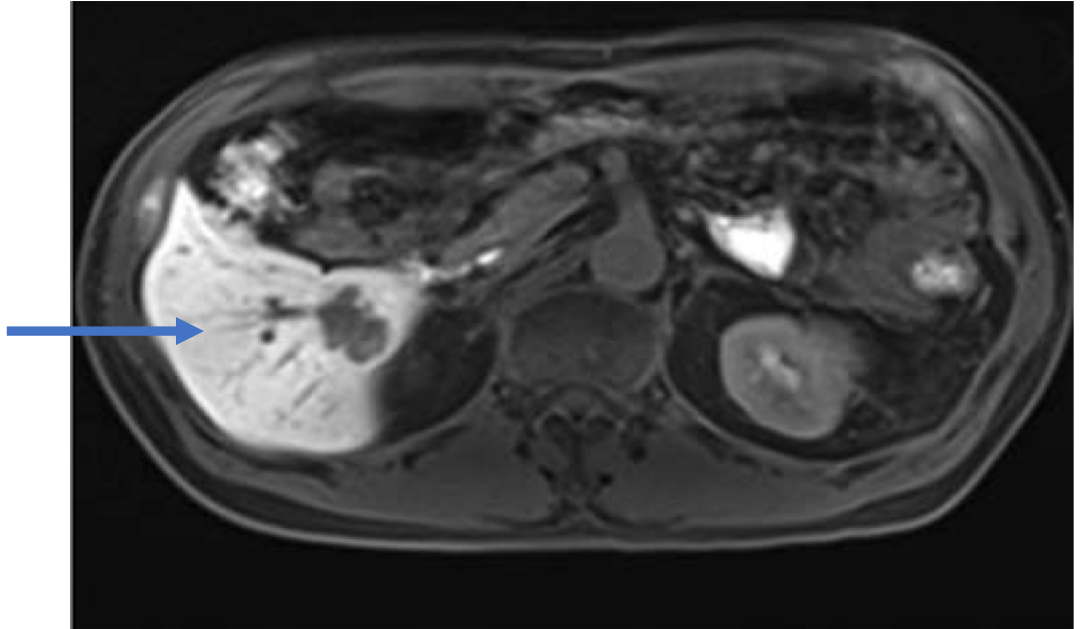
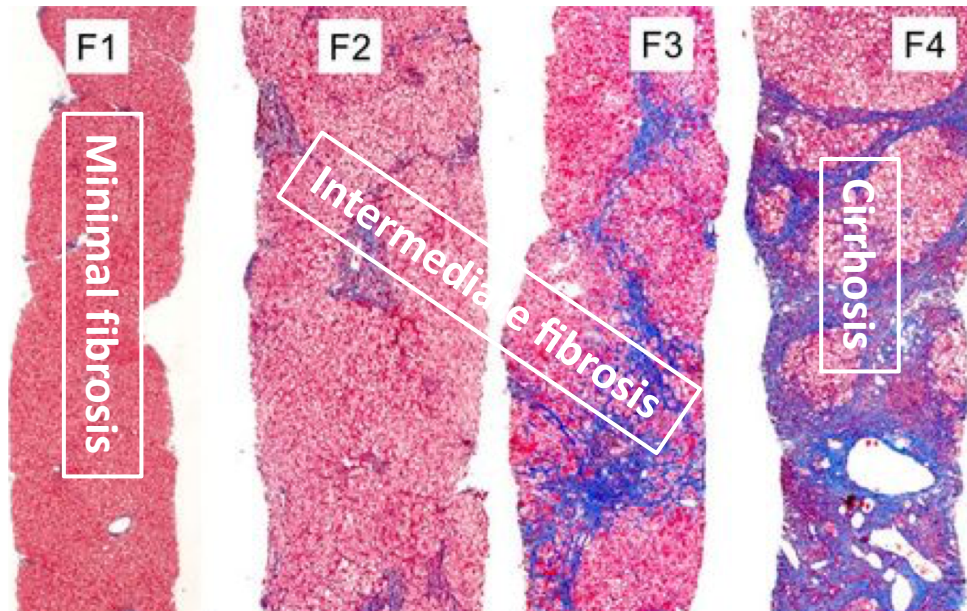# EOB-DTPA distribution in livers with chronic liver disease

- 42 patients had MRI with EOB-DTPA and liver biopsies
- We used a dual-input three-compartment model to quantify EOB-DTPA clearances across OATPs, MRP2, and MRP3
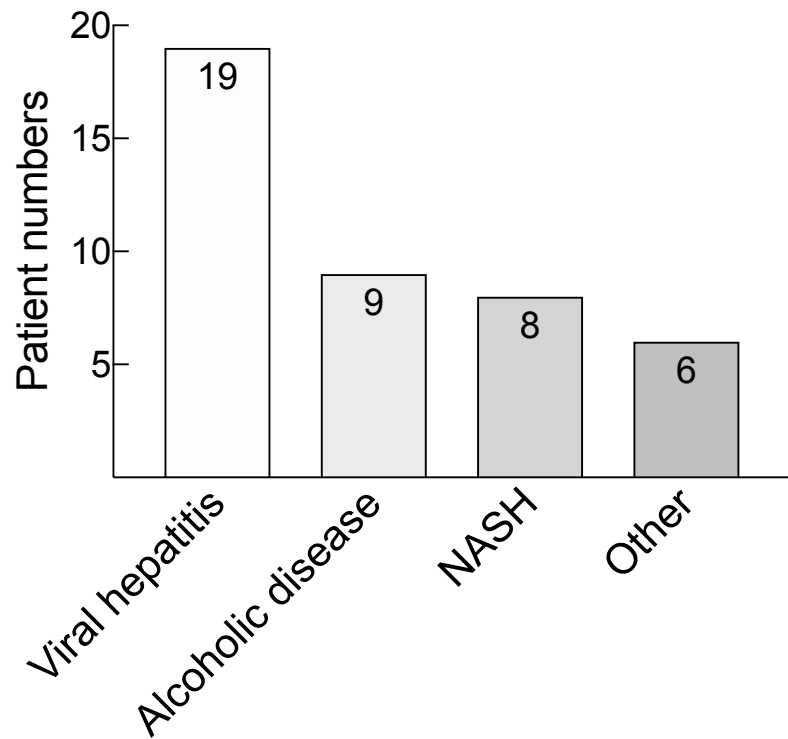- First, patients were grouped according to liver fibrosis
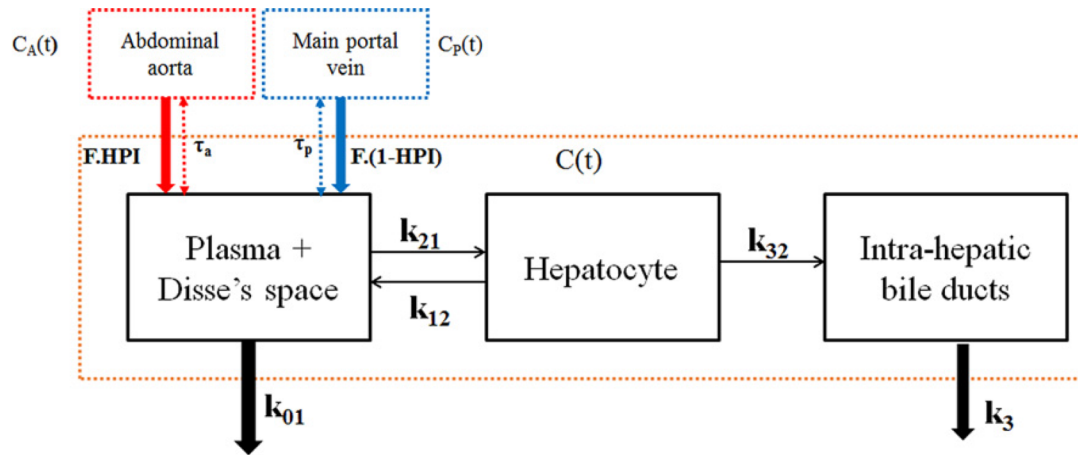
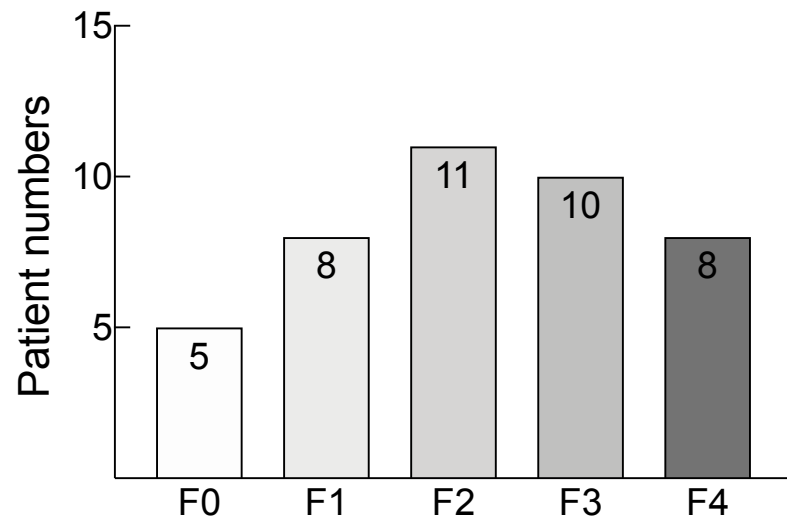# EOB-DTPA clearances and fibrosis expansion
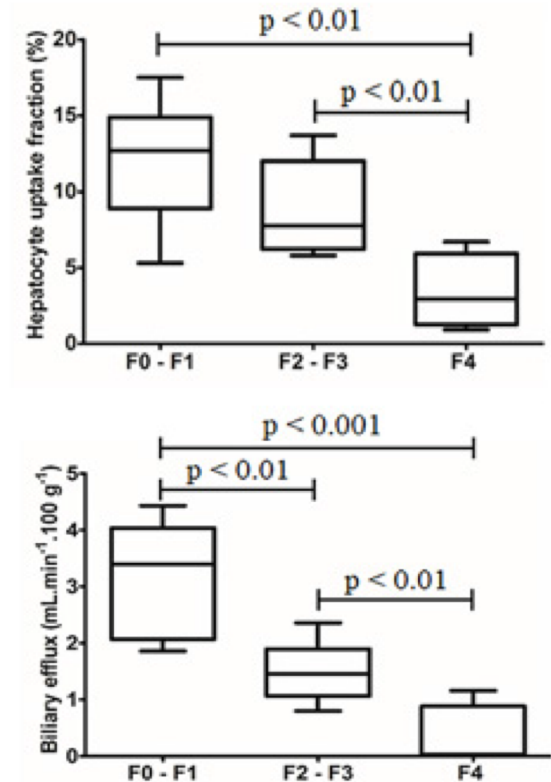
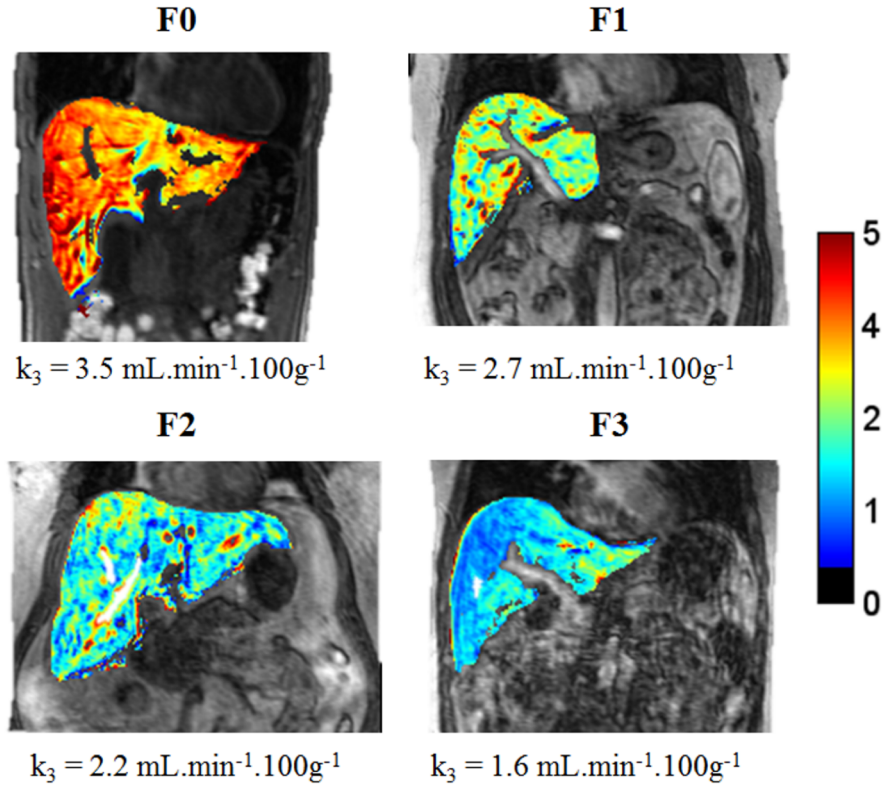- Liver fibrosis estimated by the METAVIR score

Aetiology

Patient numbers
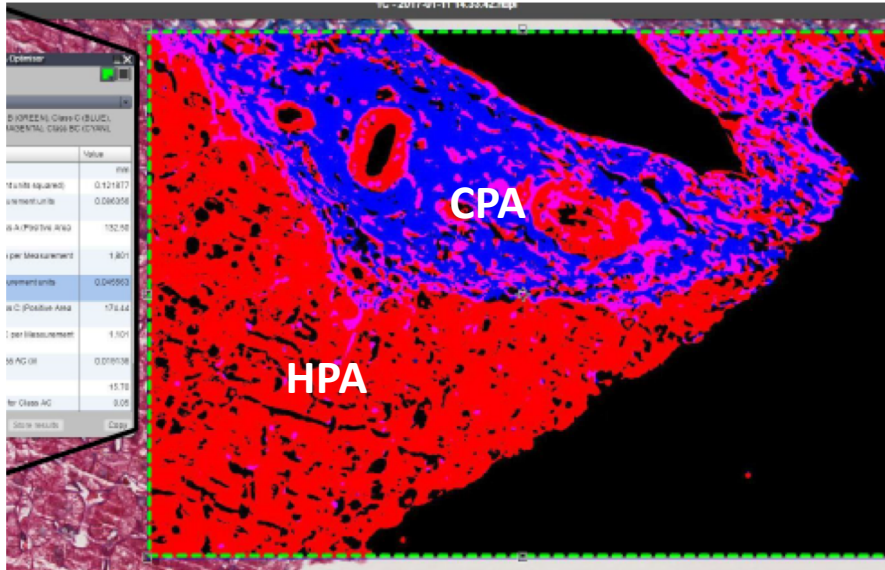
- Viral hepatitis: 19
- Alcoholic disease: 9
- NASH: 8
- Other: 6

METAVIR score

Patient numbers

- F0: 5
- F1: 8
- F2: 11
- F3: 10
- F4: 8

EOB-DTPA biliary clearances (mL.min^{-1}.100 g^{-1})

F0

$k_3 = 3.5$ mL.min^{-1}.100g^{-1}

F1

$k_3 = 2.7$ mL.min^{-1}.100g^{-1}

F2

$k_3 = 2.2$ mL.min^{-1}.100g^{-1}
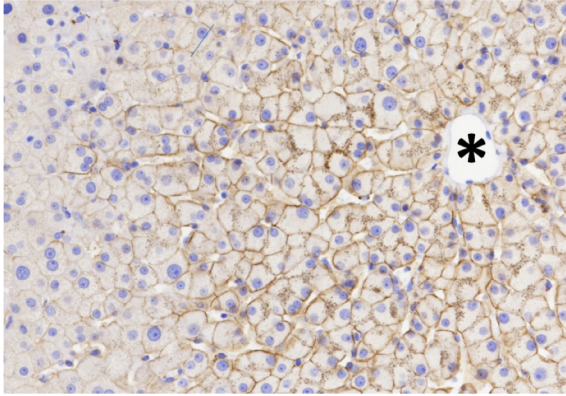
F3

$k_3 = 1.6$ mL.min^{-1}.100g^{-1}

Correlation between EOB-DTPA clearances and new transporter scores
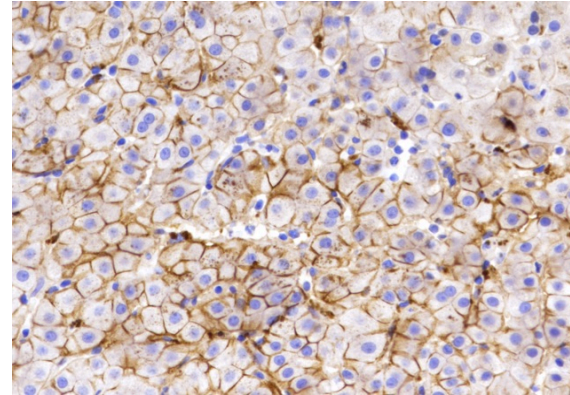
Estimation of residual hepatocytes

- Morphometric analysis
- Mean collagen area (CPA, %)
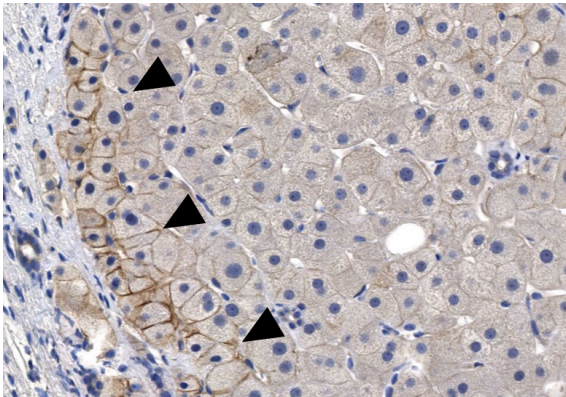- Mean hepatocyte area (HPA, %) = 100 - CPA

Score 3
Low centrolobular

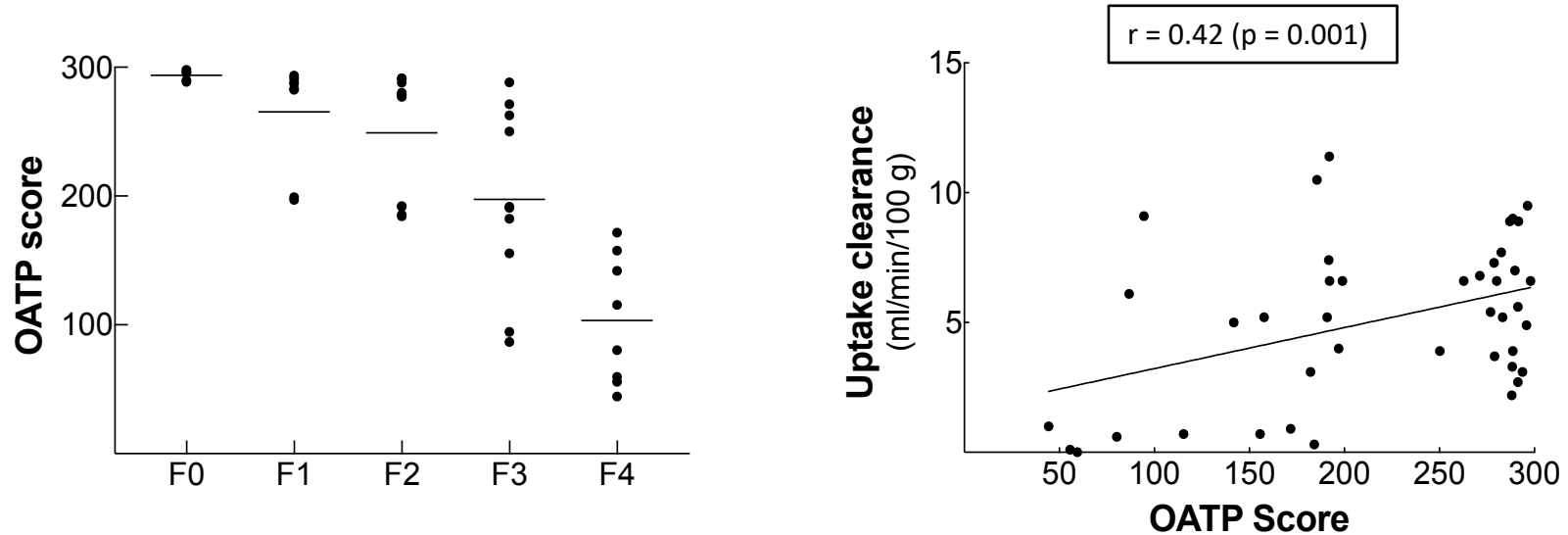OATP1B1/B3 expression

Score 1
Lobular expansion

Score 2
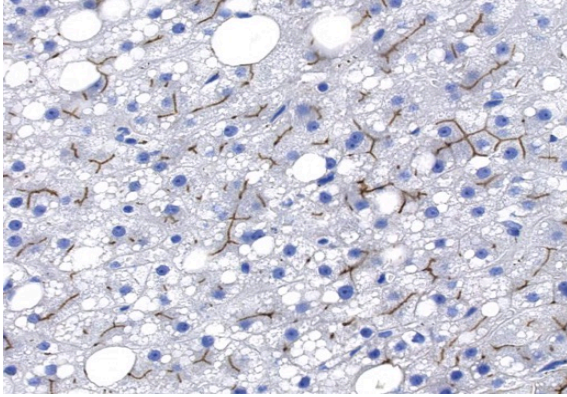Progressive expansion

Transport score: (1,2, or 3) x HPA

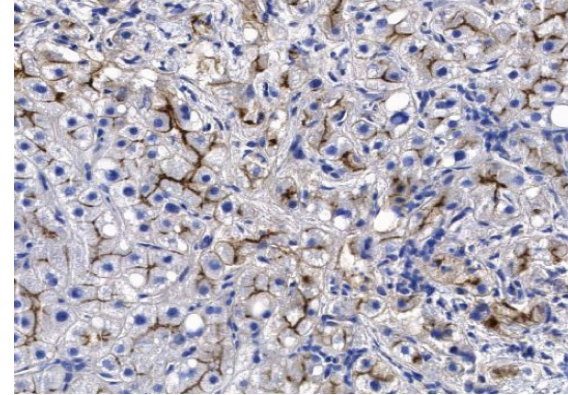# OATP1B1/B3 transport score correlates to uptake clearance

For drugs similar to EOB-DTPA, uptake clearance should be related to residual hepatocytes and OATP1B1/B3 expression
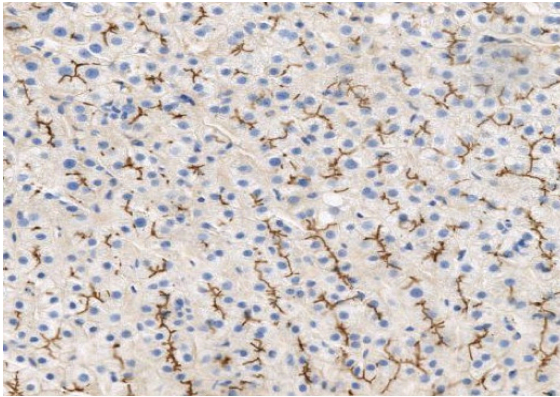
Score 3
Thin
Regular,
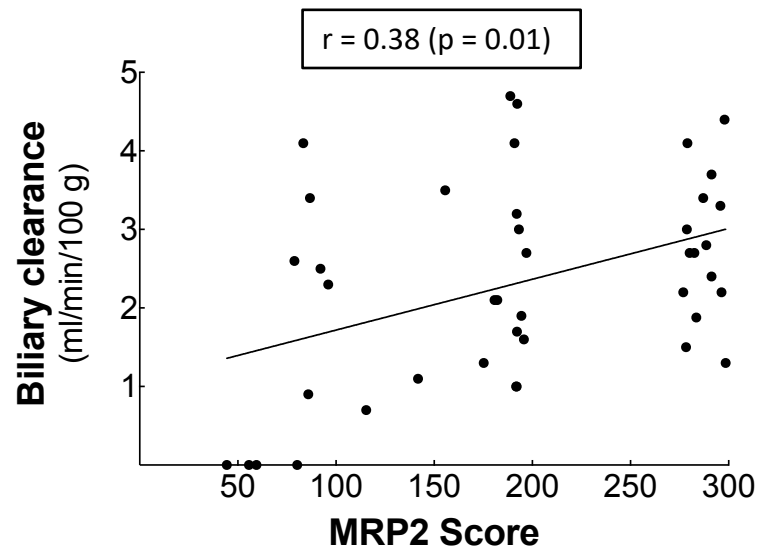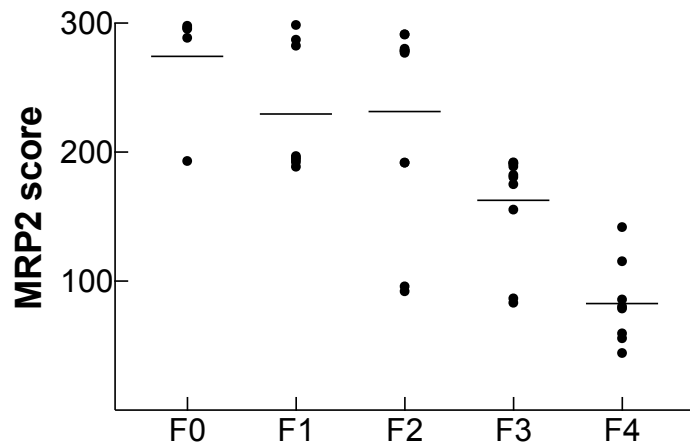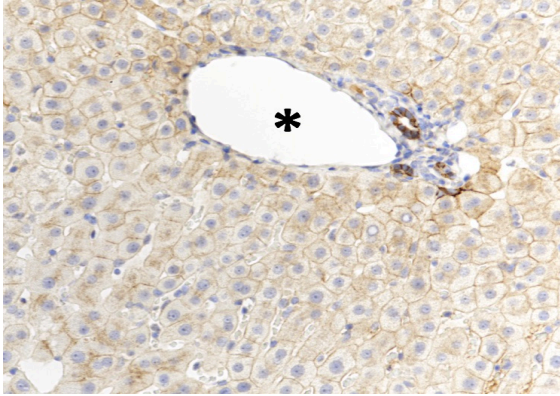Panlobular

MRP2 expression

Score 1
Thick
Irregular
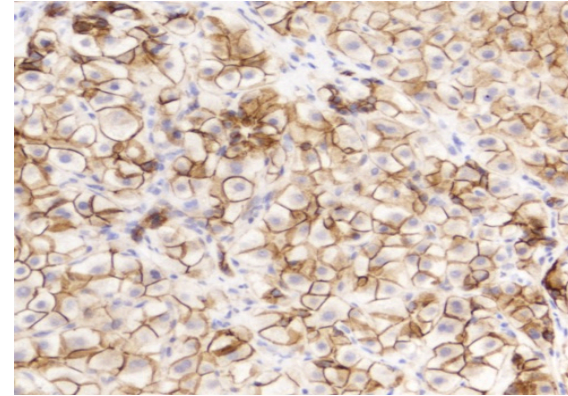
Score 2
Thick

Transport score: (1,2, or 3) x HPA
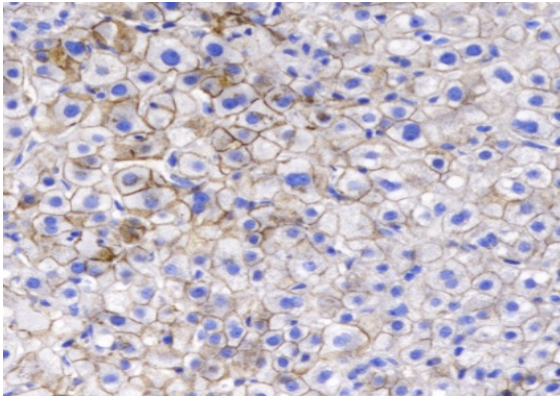
MRP2 transport score correlates to biliary clearance

r = 0.38 (p = 0.01)

Score 3
Minor
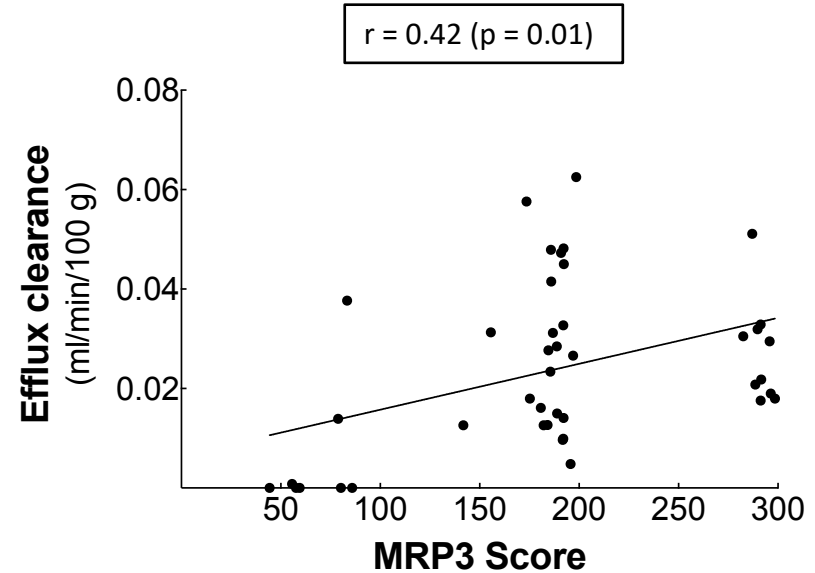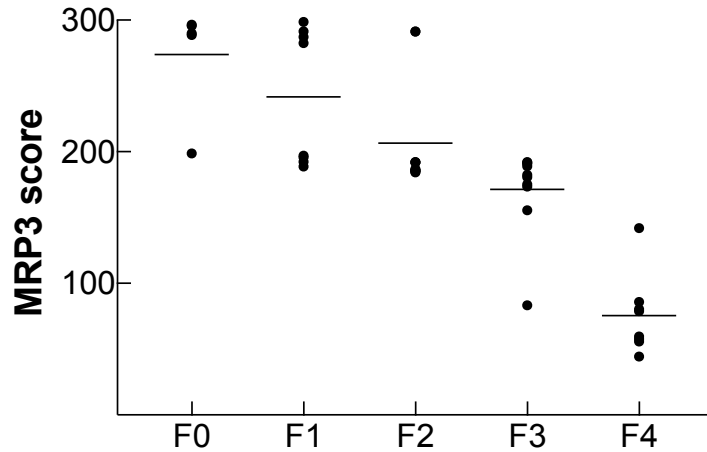Periportal

MRP3 expression

Score 1
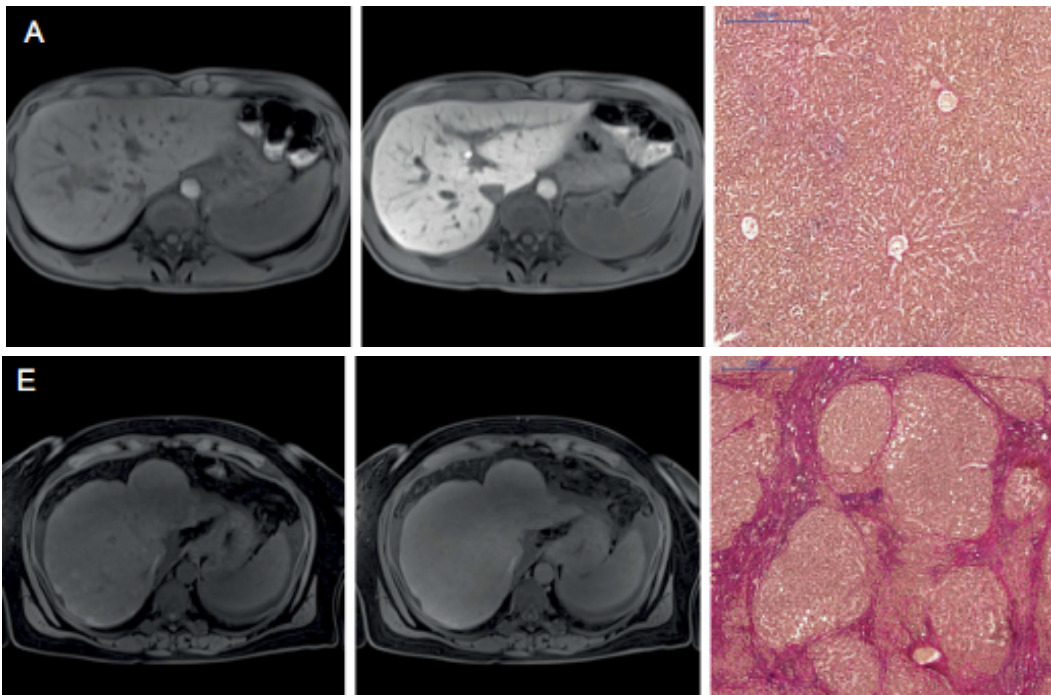Panlobular
Expansion

Score 2
Focal
Lobular
Expansion

Transport score: (1,2, or 3) x HPA

MRP3 score correlates to efflux clearance back to sinusoids
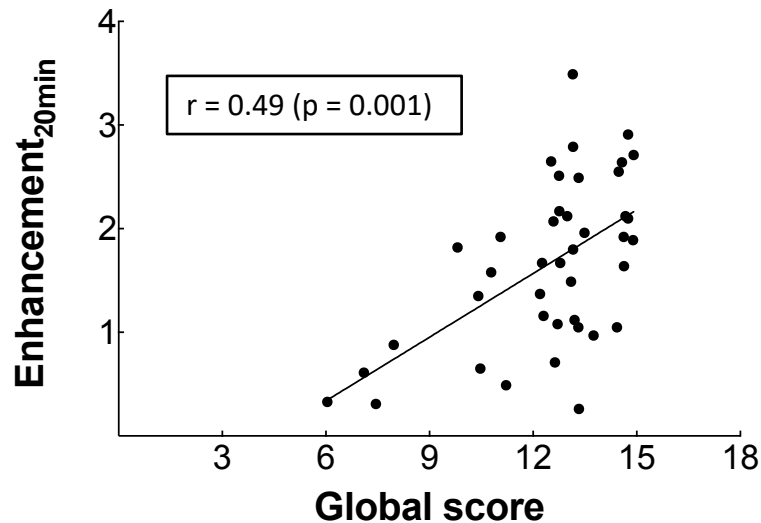
Pre-injection

20 min after
EOB-DTPA injection

A

E

r = 0.49 (p = 0.001)

Enhancement$_{20min}$

Global score

N Verloh, Sci Reports, 2015, 5, 15408

Global score of biopsy

0.093 HPA + 0.55 OATP$_s$ + 0.13 MRP2$_s$ + 1.21 MRP3$_s$

Important points

- Quantification of residual hepatocytes

- With increasing liver fibrosis, OATP1B1/B3 expression extends from zones 3 to the entire lobule, while high MRP3 expression appears progressively in the entire lobule

- Pathological expression of MRP2 corresponds to a progressive thickening and irregular expression that remains visible in the entire lobule

Important points

- OATP1B1/B3, MRP2, and MRP3 expression in residual hepatocytes determine EOB-DTPA clearances and decreased concentrations observed in patients with liver disease

- Similar changes might be anticipated with drugs close to EOB-DTPA