Liver Investigation: Testing Marker Utility in Steatohepatitis

Updates from Biomarker Consortia Fibrosis markers

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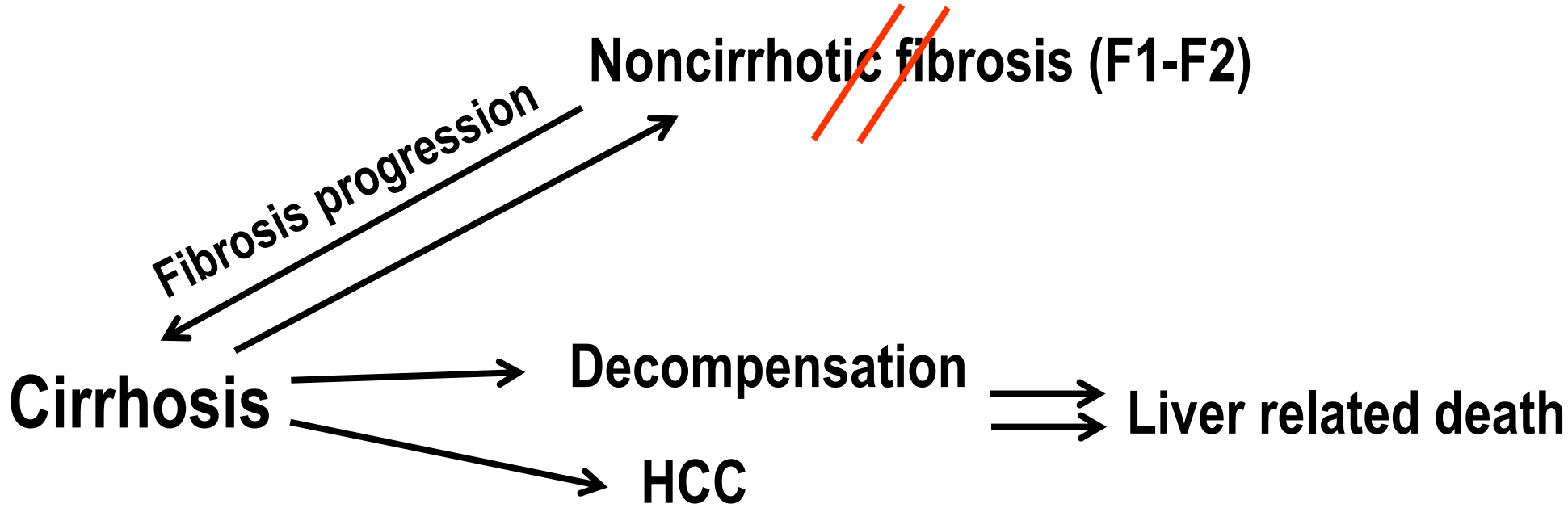
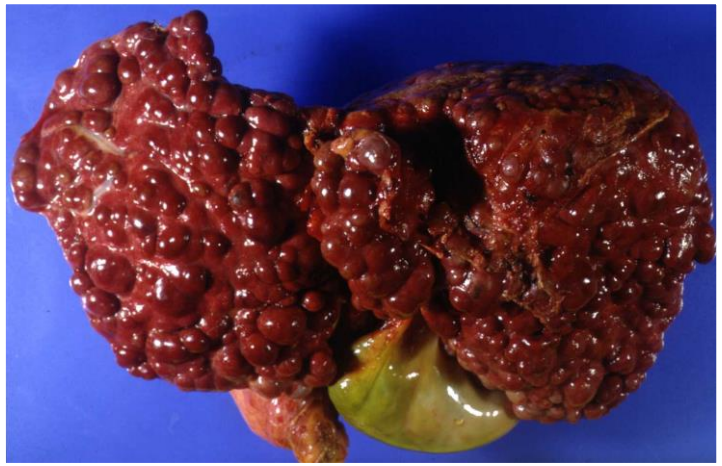
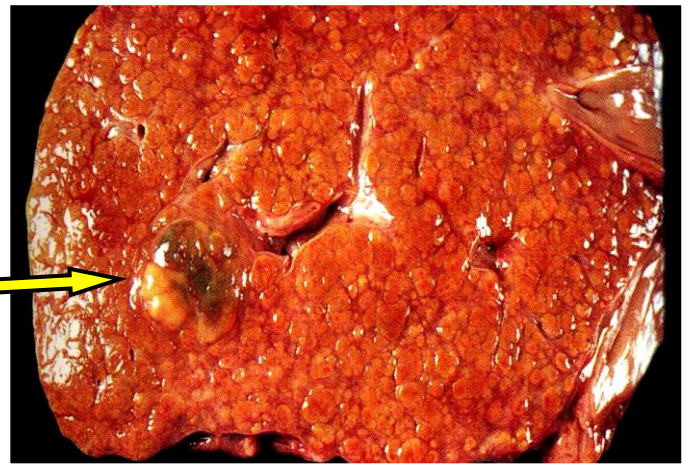

Noncirrhotic fibrosis (F1-F2)
Fibrosis progression
Cirrhosis
Decompensation
Liver related death
HCC

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Collagen and Noncollagen Serum Fibrosis Markers (UMCM, NB, SOMA)

Aim: Development of serum/plasma fibrosis markers to

- Identify patients with advanced fibrosis (>F2; >F1) with highest sensitivity and specificity
- Identify patients with high fibrogenic (fibrolytic) activity (dynamic markers)
- Permit noninvasive selection and stratification of patients in need for treatment
- Permit noninvasive monitoring of treatment efficacy (antifibrotic effect) on a regular basis
- Allow short-term POC studies with novel drugs
- Allow a personalized (antifibrotic) therapy

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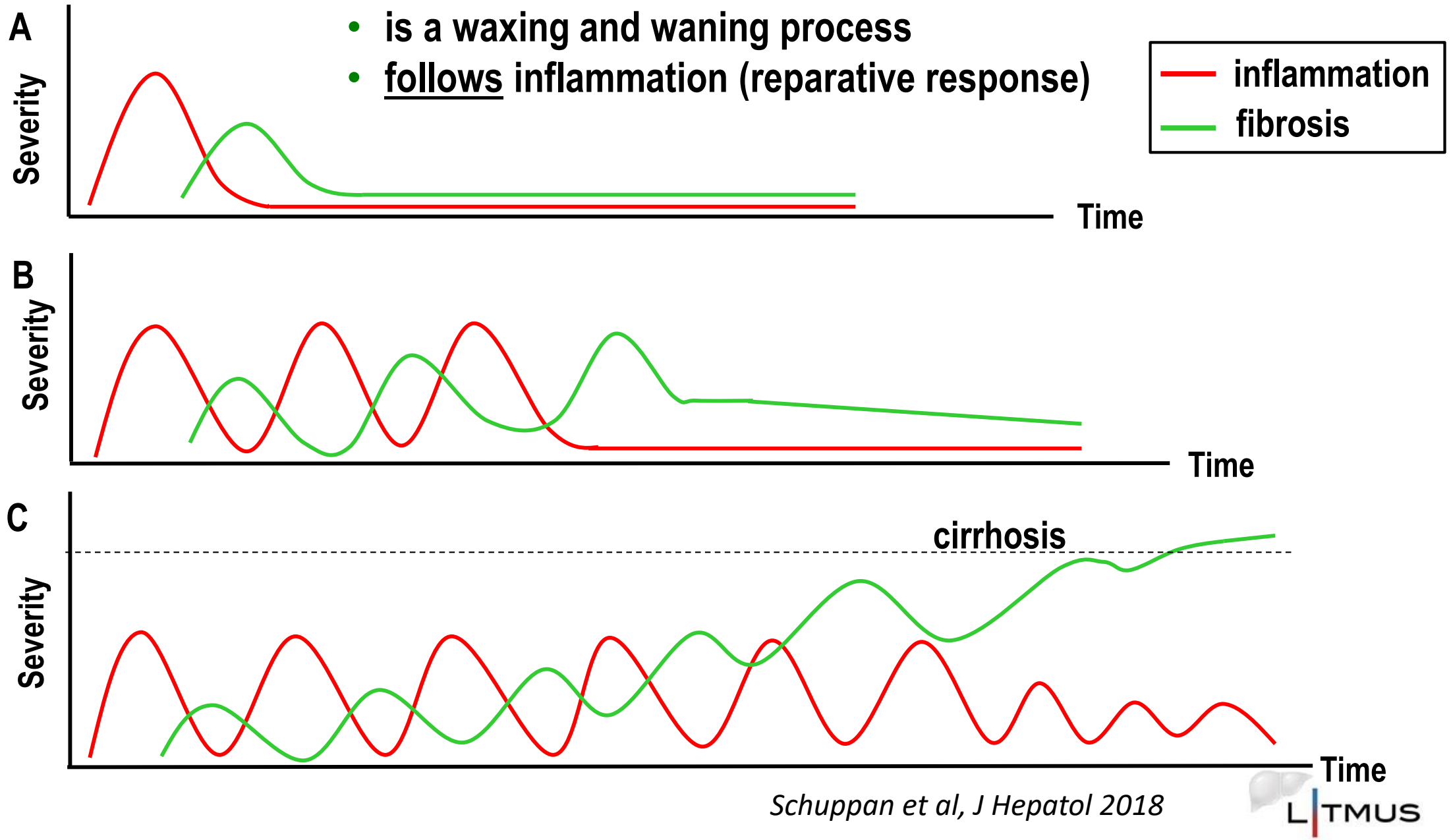
Fibrogenesis

- is a waxing and waning process
- follows inflammation (reparative response)



Schuppan et al, J Hepatol 2018

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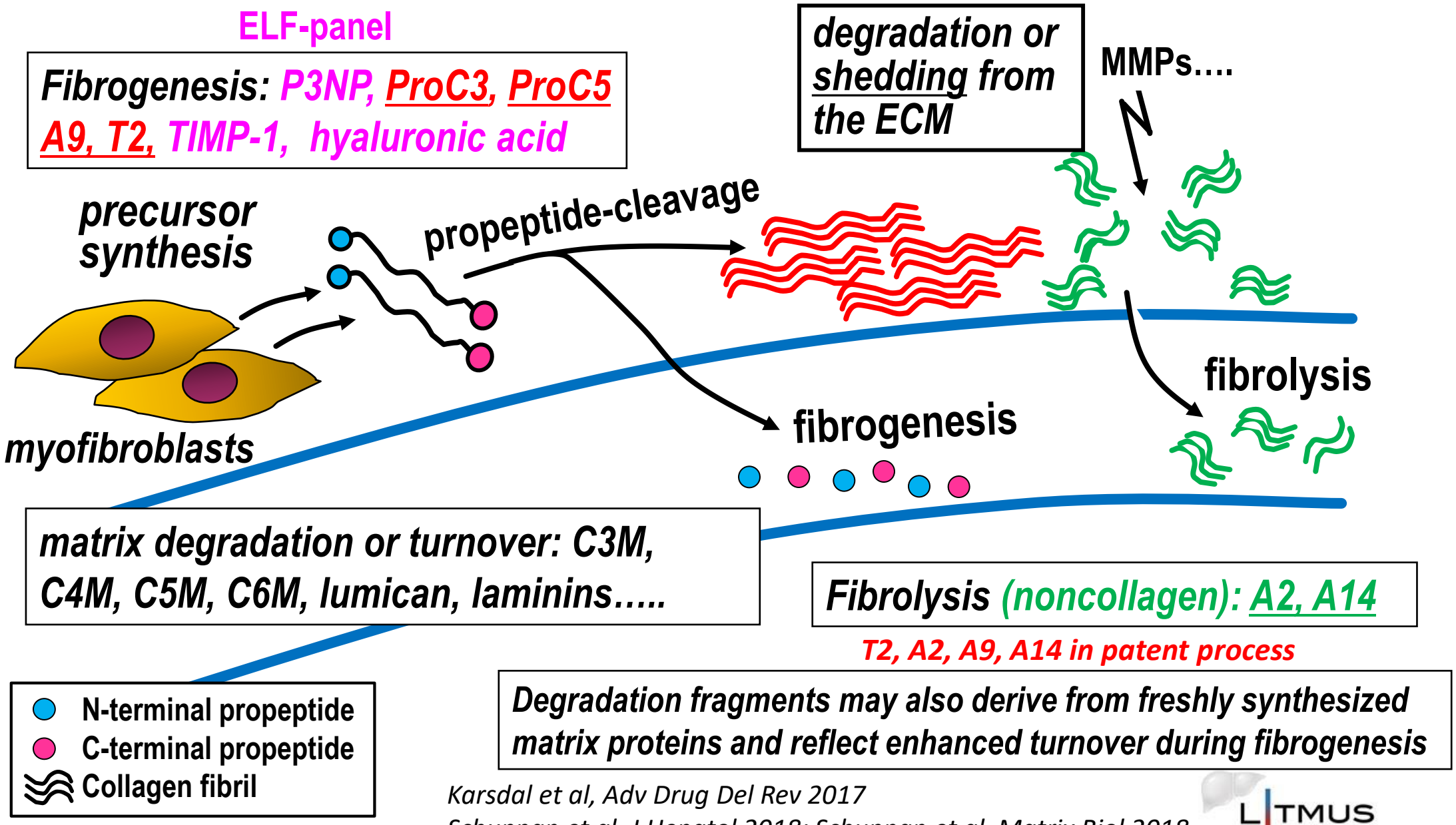
Strategy and current state

Establishment and validation of a panel of (fibrosis) protein biomarkers using cross-sectional and follow-up patient cohorts:

- Noncollagen ECM-markers (via proteomics and rational design, UMCM)
- Collagen ECM-markers (protease ‚fingerprint' epitopes, NB)
- These are largely dynamic markers of the fibrotic ECM in liver
- Establishment of marker panel of disease severity and progression on DNA-aptamer based platform (5000plex, SOMA)
- Discovery of proteomic biomarkers in cases/samples selected from the LITMUS Registry (phase 1a)
- Validation of markers for diagnosis, prognosis and therapy monitoring in independent cohort (especially phase 1b)
- Movement towards regulatory approval

Novel Direct Fibrosis Markers



Karsdal et al, Adv Drug Del Rev 2017
Schuppan et al, J Hepatol 2018; Schuppan et al, Matrix Biol 2018

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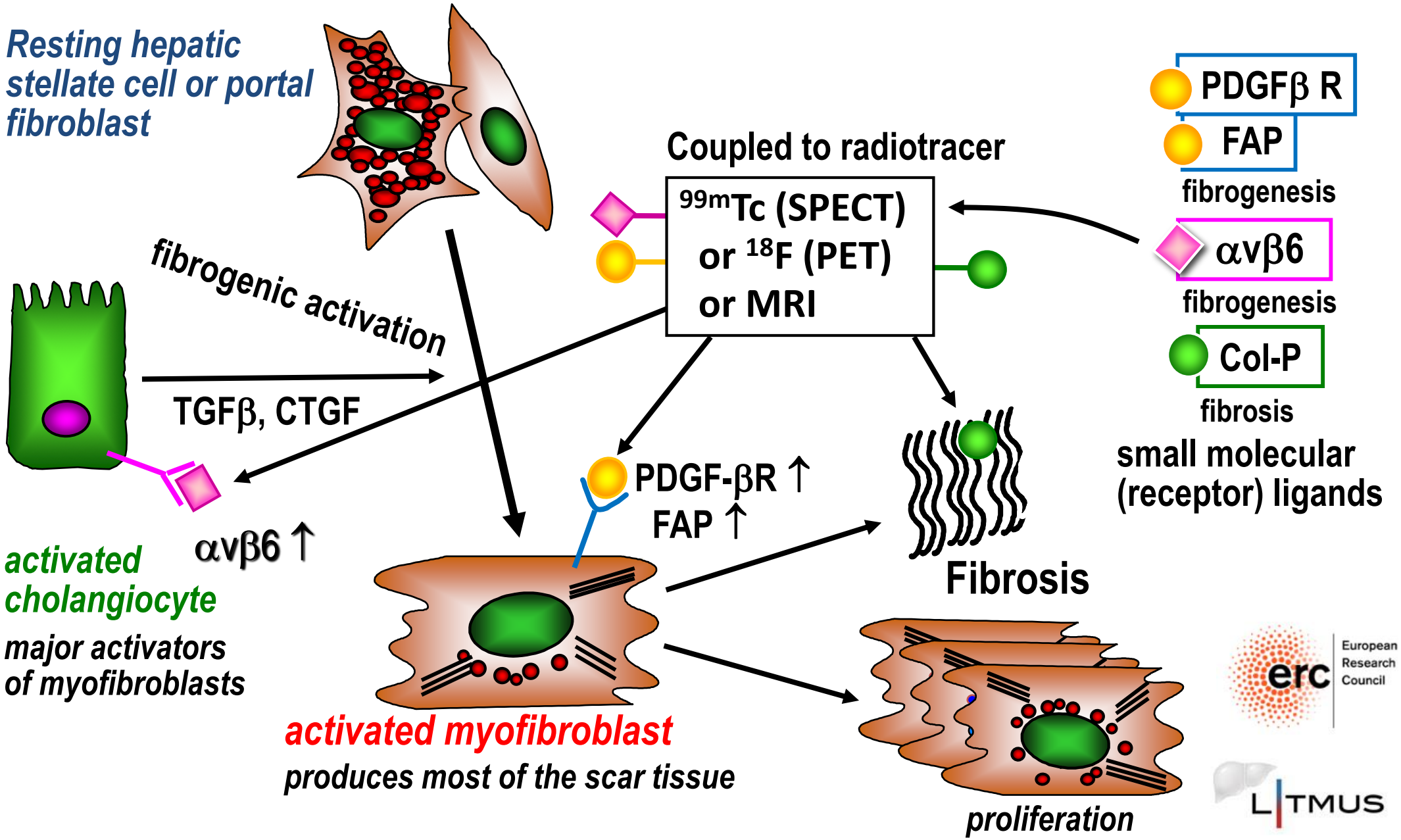
Quantitative imaging of liver fibrosis and fibrogenesis



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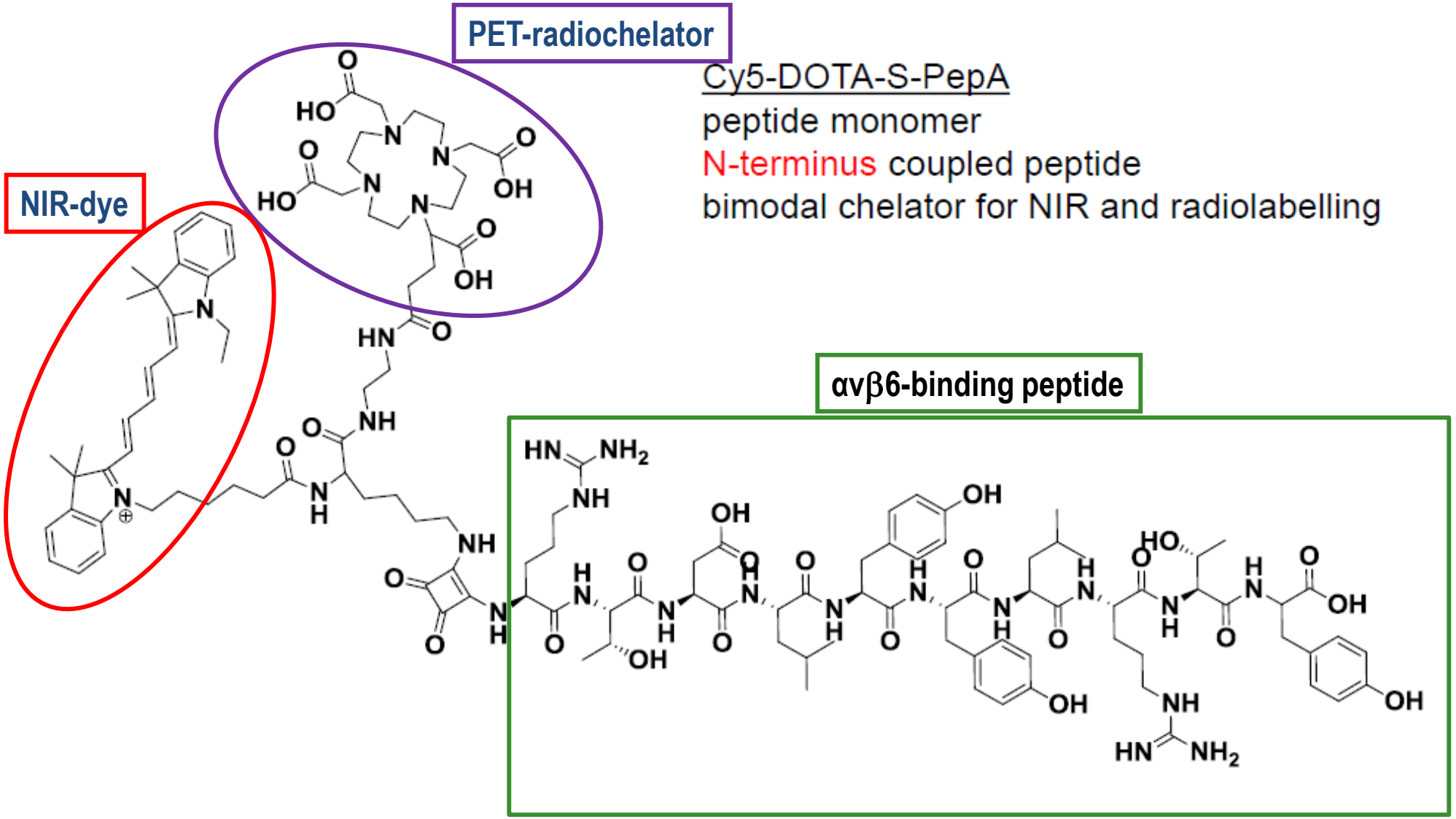
Bifunctional αvβ6-integrin imaging agent



Cy5-DOTA-S-PepA
peptide monomer
N-terminus coupled peptide
bimodal chelator for NIR and radiolabelling

Kim YO et al, EASL 2018 # FRI-108

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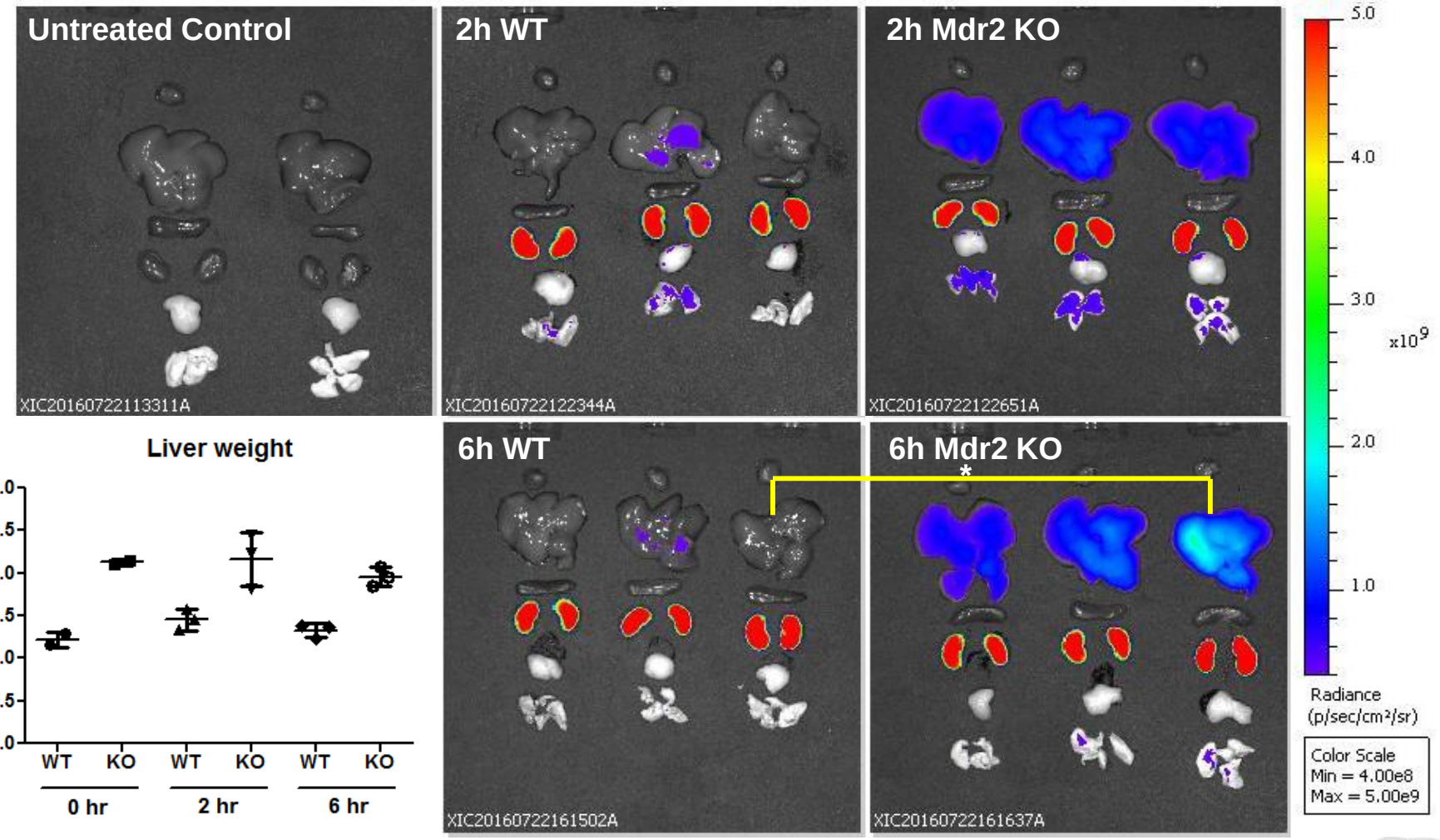
Quantification of αvβ6 integrin binding (ex vivo analysis)

Mdr2KO mice, age 8 weeks, with spontaneous biliary fibrosis (3fold increased liver collagen content) – iv injection of bimodal peptide, 9-mer cyclic αvβ6 integrin-binding peptide-PEG-NODAGA/Sulfo-Cy5.5



Kim YO et al, EASL 2018 # FRI-108

Summary

- Novel serum fibrosis marker development in LITMUS is advancing well
- > 6 markers have been selected as core panel
- Their validation within the EPoS cohort has been initiated
- The LITMUS phase 1a cohort is being established
- Select markers are already moving towards regulatory approval
- Further NAFLD biomarkers (SOMAScan proteomics, phosphoproteomics, metabolomics, genetics/epigenetics/transcrtiptomics, microbial metagenomics) are advancing in parallel
- Apart from refined conventional liver imaging, targeted fibrosis and fibrogenesis imaging is being developed within LITMUS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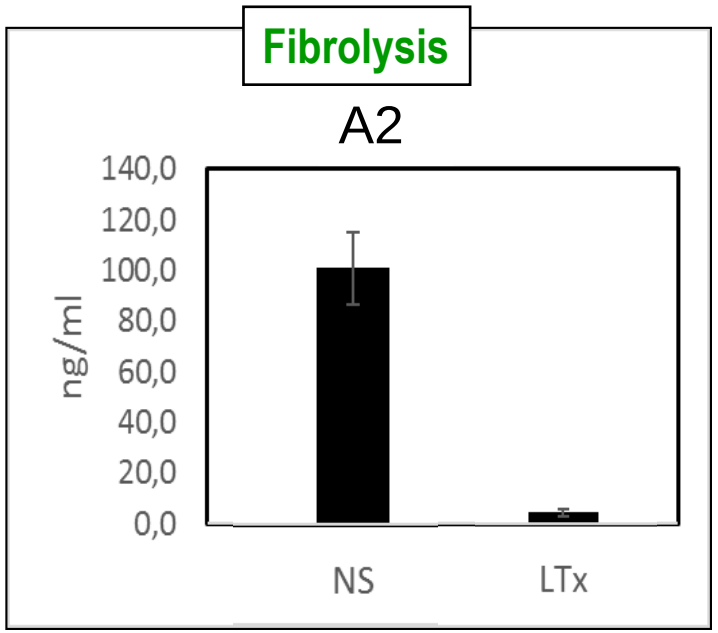
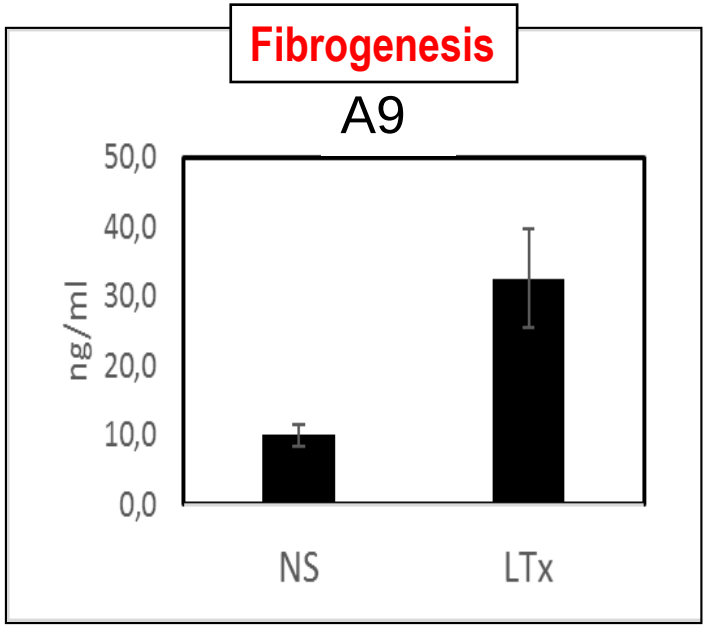
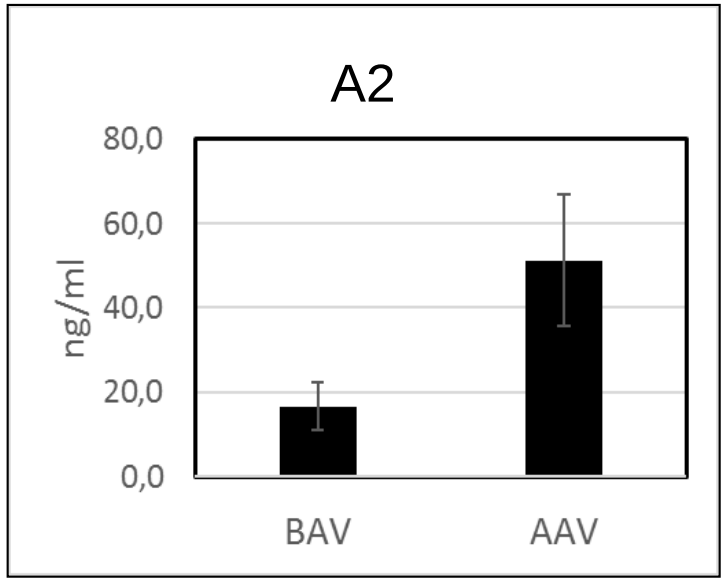
Markers of fibrogenesis and fibrolysis (MOA based markers): A2, A9 and A14: shed cell membrane molecules involved in ECM remodeling

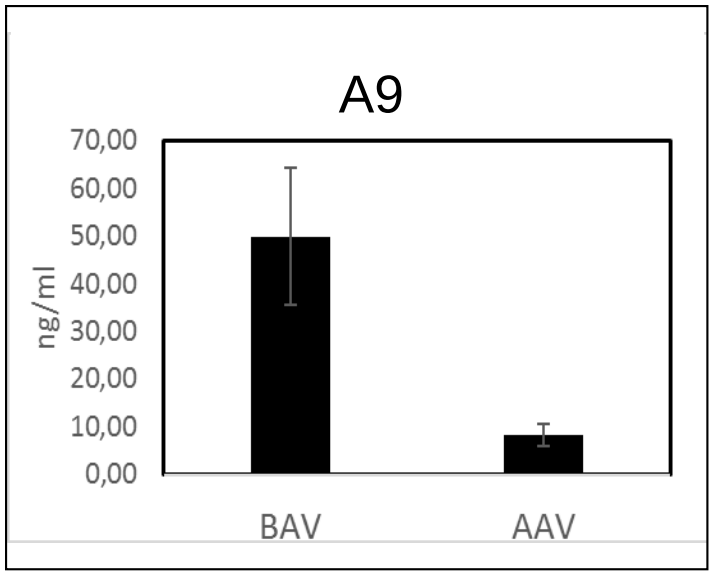




NS, healthy ctr

LTX: post transplant with progression to cirrhosis within 5 yr





BAV: before antiviral Tx for HCV

AAV: 24 w after highly effective antiviral Tx for HCV

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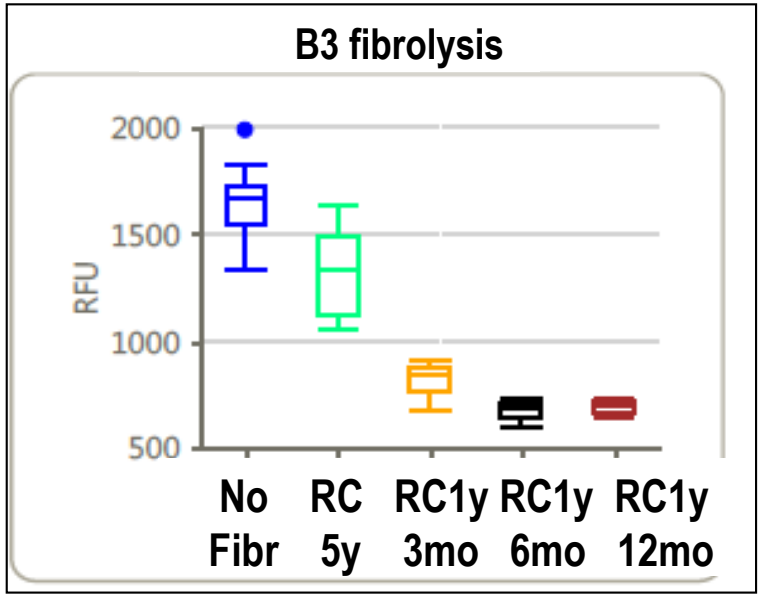
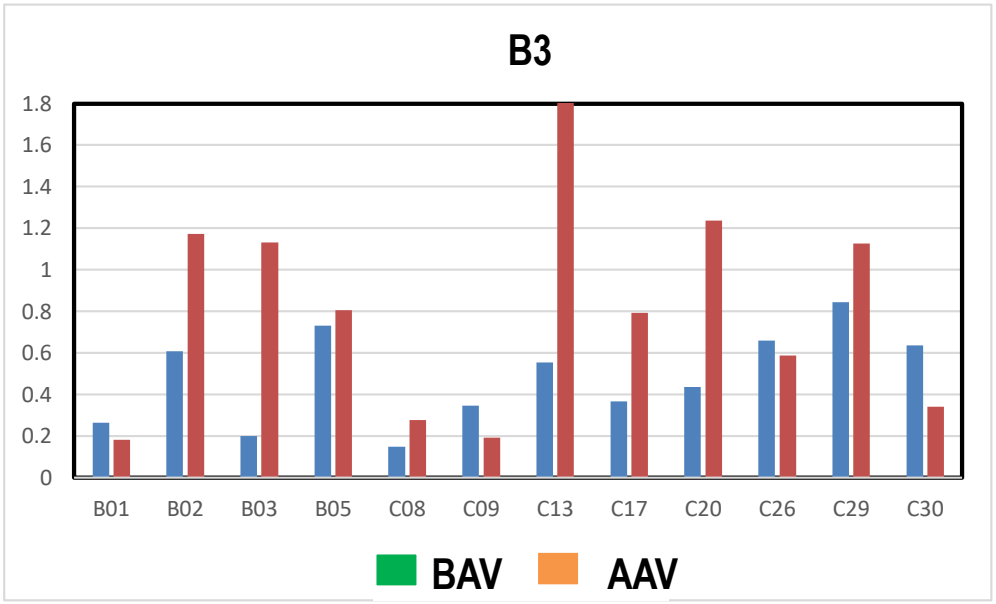
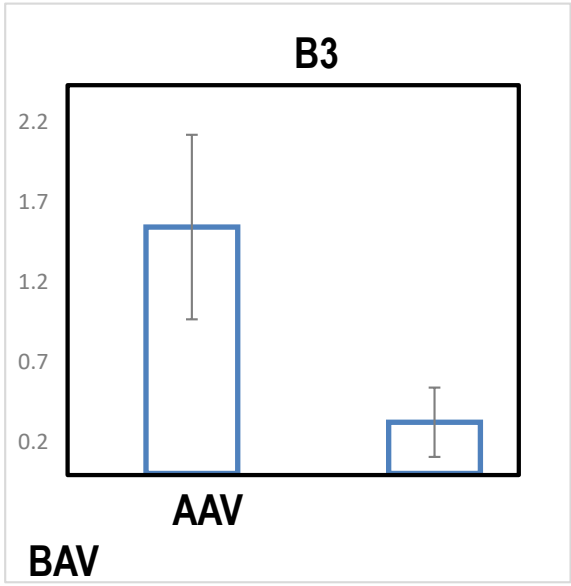
Novel candidates







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Discussion

Panelists:

Roberto Calle, FNIH Biomarkers Consortium
Rohit Loomba, University of California, San Diego
Quentin Anstee, Newcastle University
Detlef Schuppan, Mainz University Medical Center
Sudha Shankar, NGM Biopharmaceuticals

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Afternoon Break

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