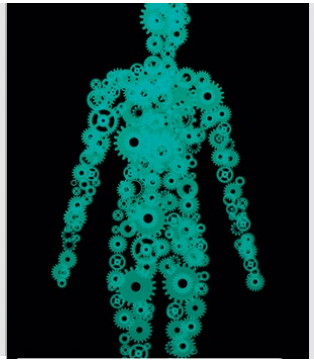
3rd International
Danube Symposium

Enabling Whole Person Research: The
Transformative Impact of Total Body PET,
Complexity Science and Network Medicine



21st – 22nd September 2023
Park Hyatt Vienna
Am Hof 2, 1010 Vienna

The signaling function of bile acids

Michael Trauner

Div. of Gastroenterology & Hepatology

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MEDICAL UNIVERSITY
OF VIENNA

Disclosures

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments, and anything else which could potentially be viewed as a conflict of interest:

Advisor

Abbvie, Albireo, BiomX, Boehringer Ingelheim, Falk, Gilead, Genfit, Hightide, Intercept, Jannsen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens, Shire

Grants / research support

Albireo, Alnylam, Cymabay, Falk Pharma, Gilead, Intercept, MSD, Takeda, UltraGenyx

Speakers bureau

BMS, Falk Foundation, Gilead, Intercept, Madrigal, MSD, Roche

Travel grants

AbbVie, Falk Foundation, Gilead, Intercept, Jannsen, Roche

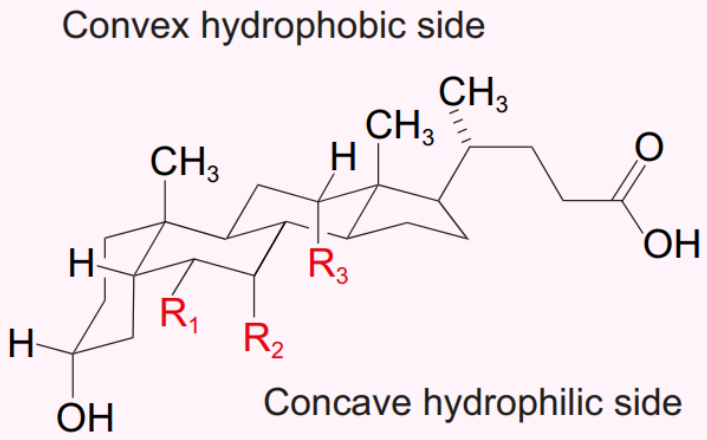
Property rights

The Medical Universities of Graz and Vienna have filed patents on medical use of *nor*UDCA and I am listed as co-inventor

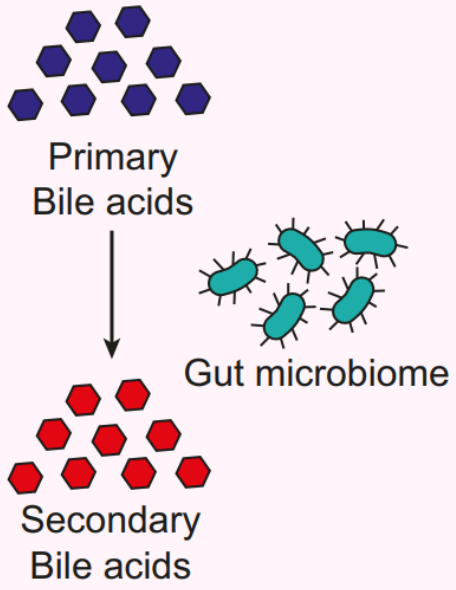
With the exception of UDCA, OCA (PBC), maralixibat (ALGS) and odevixibat (PFIC) all discussed therapeutic approaches are still investigational and not yet approved

Triple action of bile acids

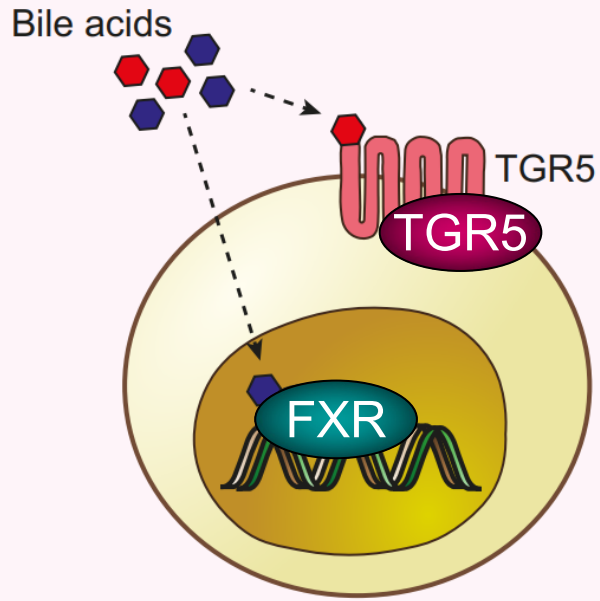
PHYSICOCHEMICAL PROPERTIES



SUBSTRATES



SIGNALING FACTORS



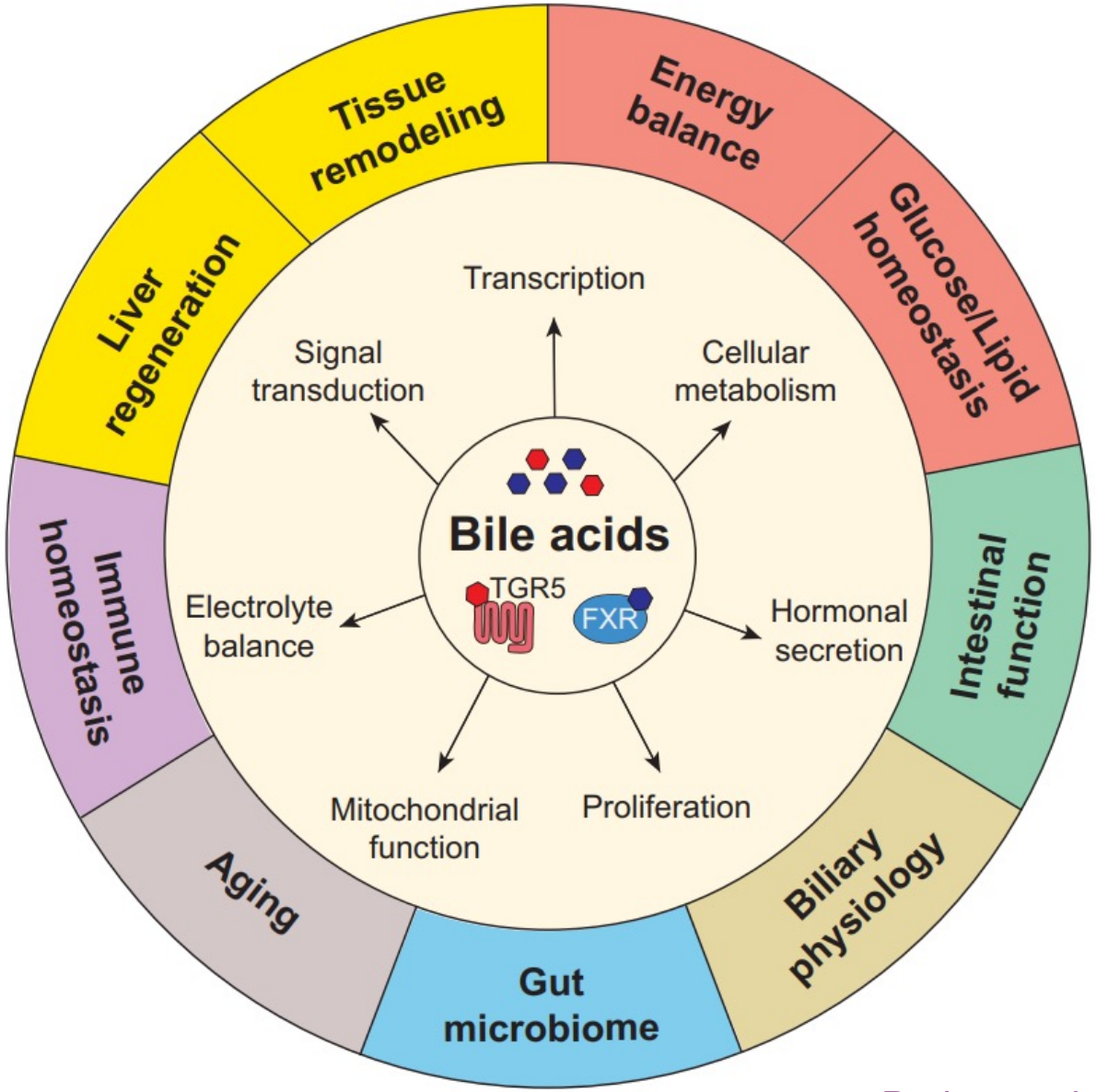
Intestinal lipid absorption

Shaping of microbiome

Regulation of cellular processes

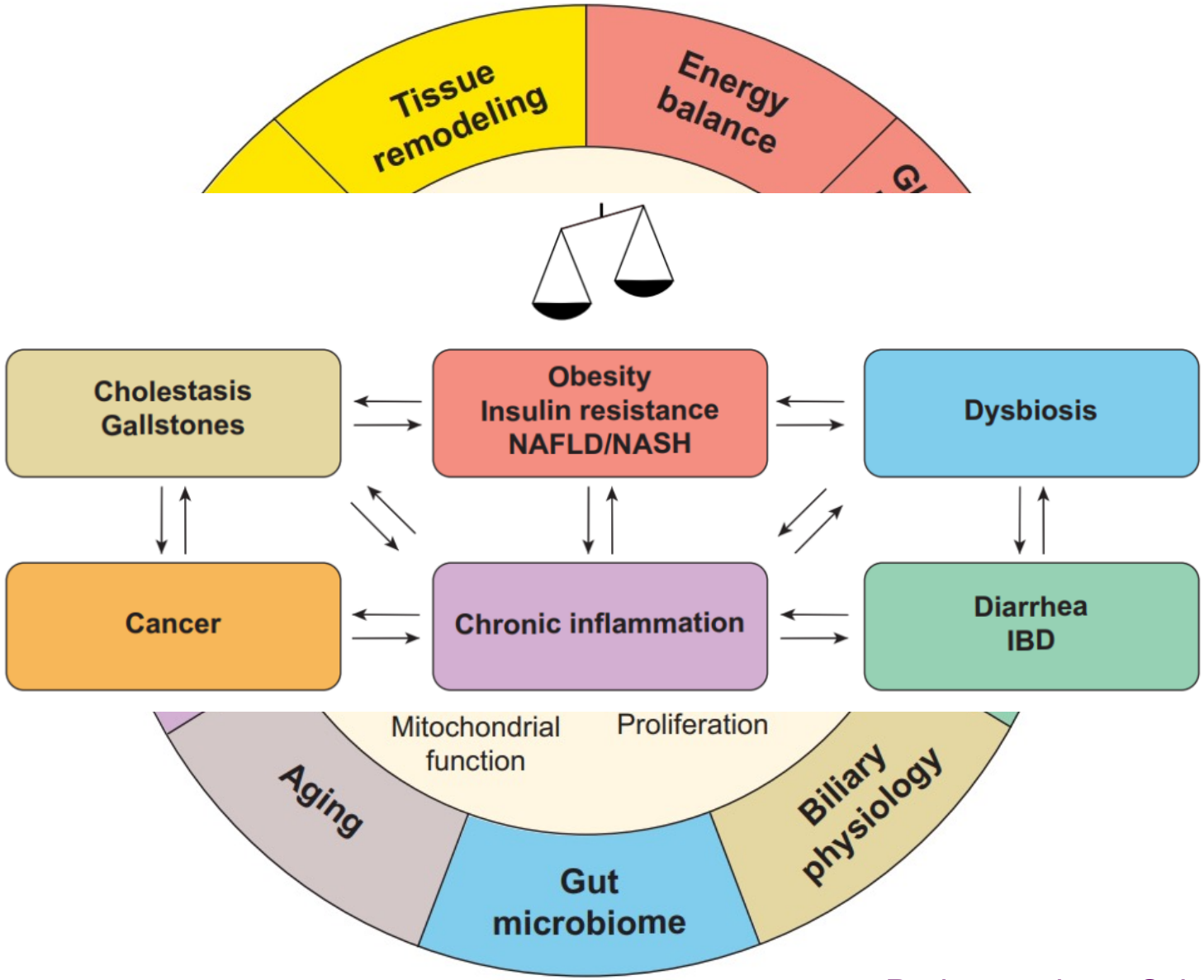
Perino et al., … Schoonjans, *Physiol Rev* 2021

Molecular physiology of BA signaling in health & disease



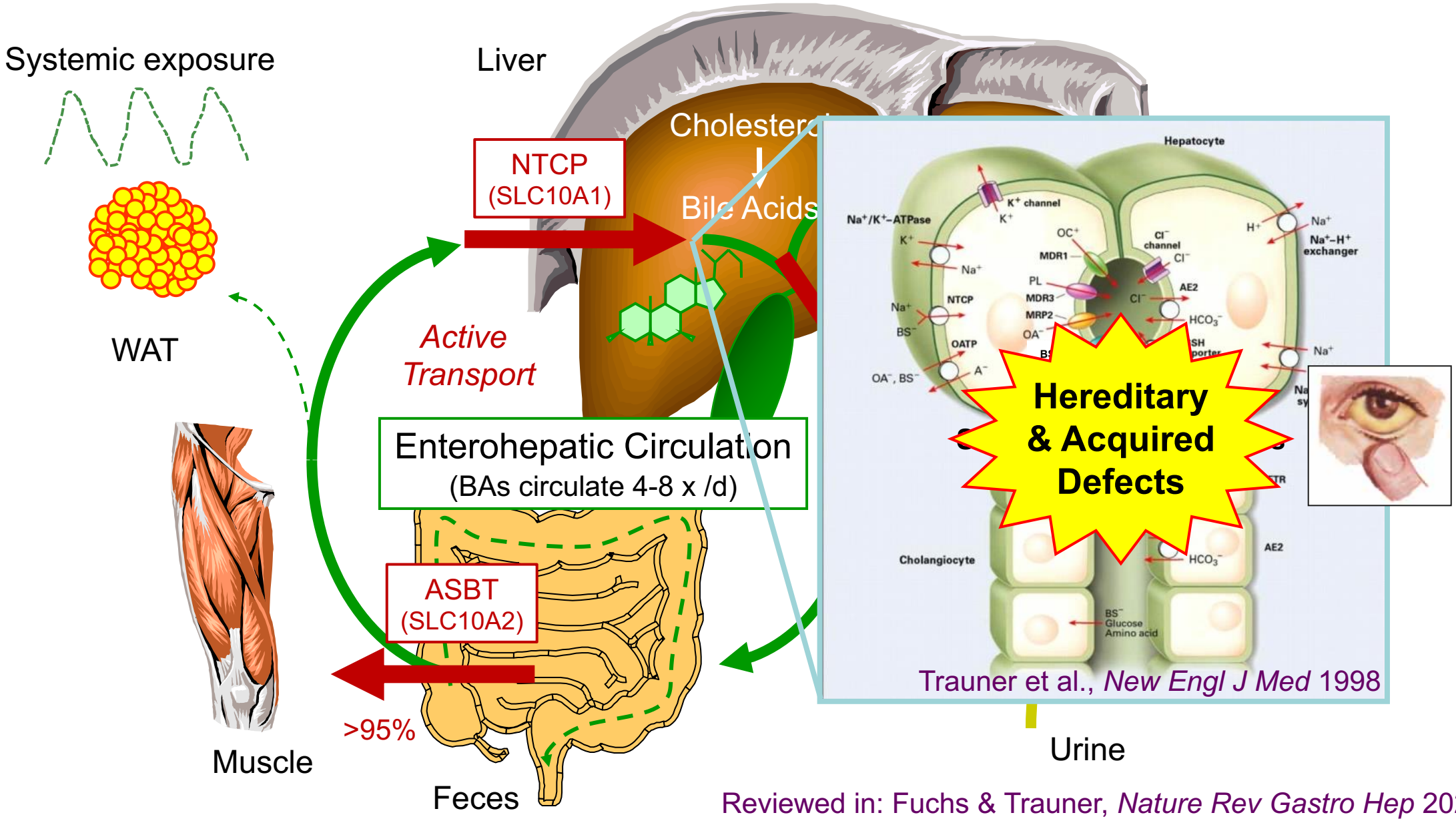
Perino et al., … Schoonjans, *Physiol Rev* 2021

Molecular physiology of BA signaling in health & disease



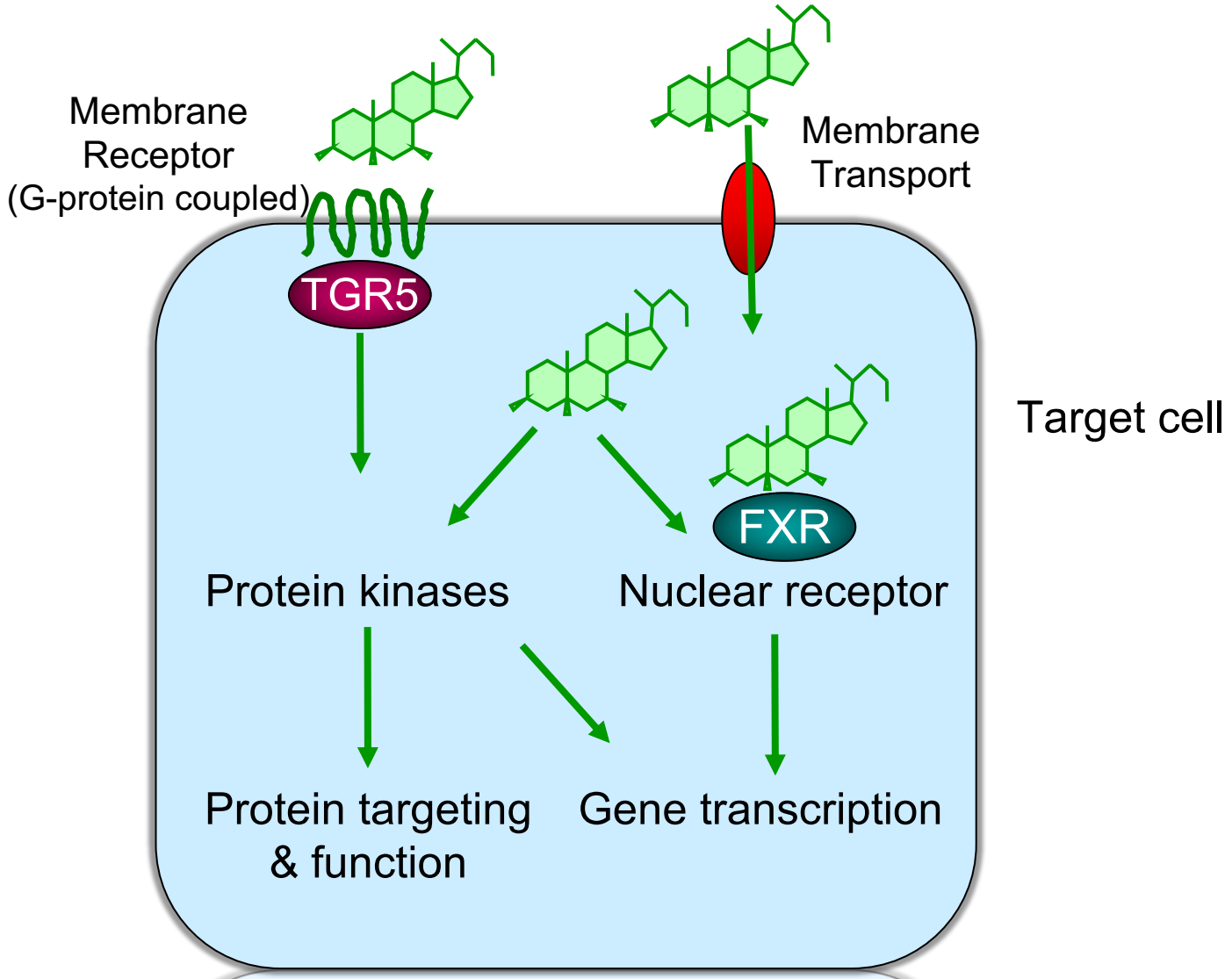
Perino et al., … Schoonjans, *Physiol Rev* 2021

Bile formation as central liver function



Reviewed in: Fuchs & Trauner, *Nature Rev Gastro Hep* 2022

Bile acids signal via dedicated receptors



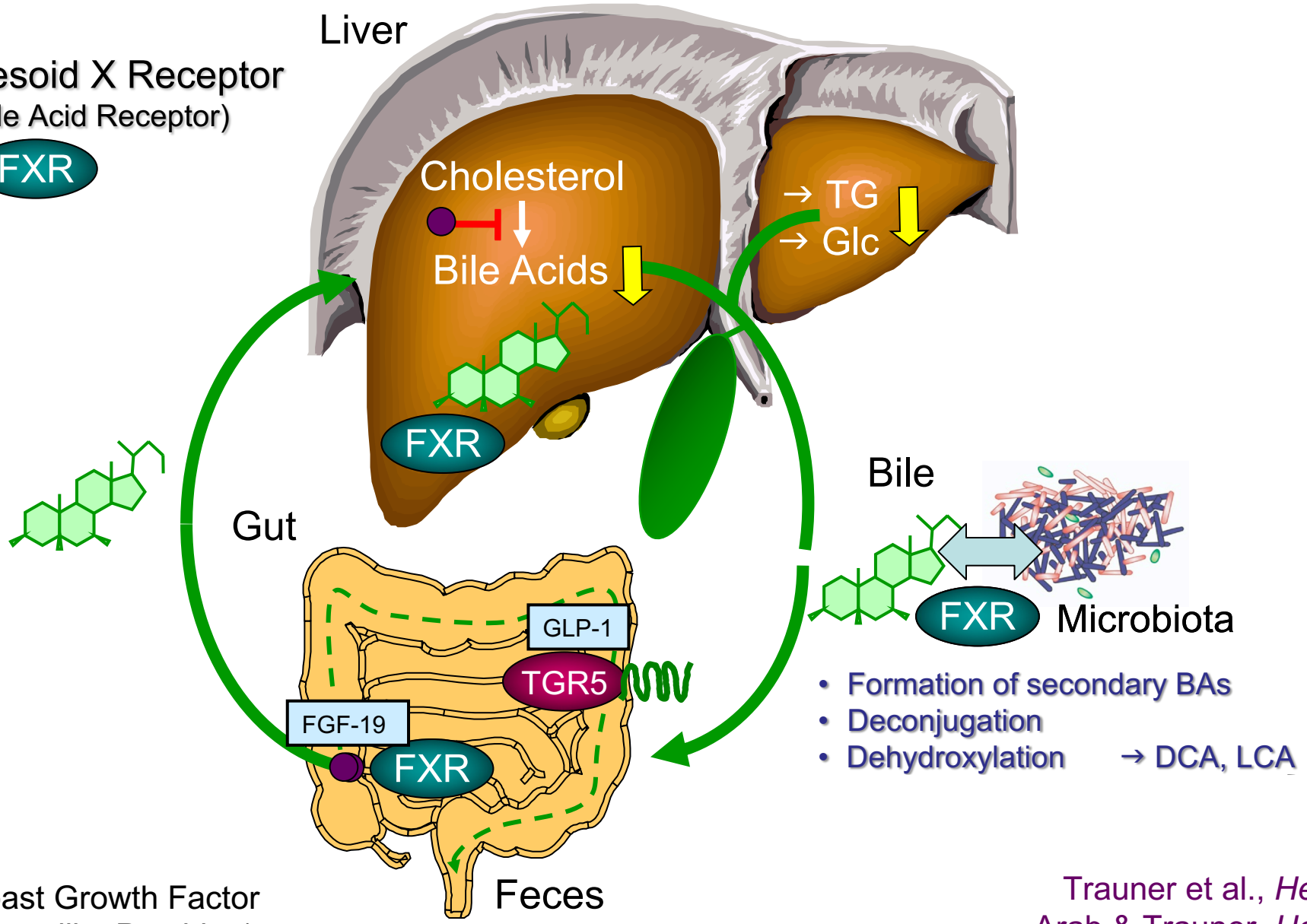
FXR Farnesoid X Receptor
TGR5 Takeda G-protein receptor 5

Reviewed in: Trauner et al., *Hepatology* 2017
Fuchs & Trauner, *Nature Rev Gastro Hep* 2022

Bile acids as enterohepatic hormones

FXR = Farnesoid X Receptor
(Nuclear Bile Acid Receptor)

FXR



- Formation of secondary BAs
- Deconjugation
- Dehydroxylation → DCA, LCA

FGF-19 Fibrobast Growth Factor
GLP-1 Glucagon-like Peptide-1

Trauner et al., *Hepatology* 2017
Arab & Trauner, *Hepatology* 2017

Colonic formation of unconventional 2° BAs by microbiota induces gut RORγ + Tregs → ↓ inflammation

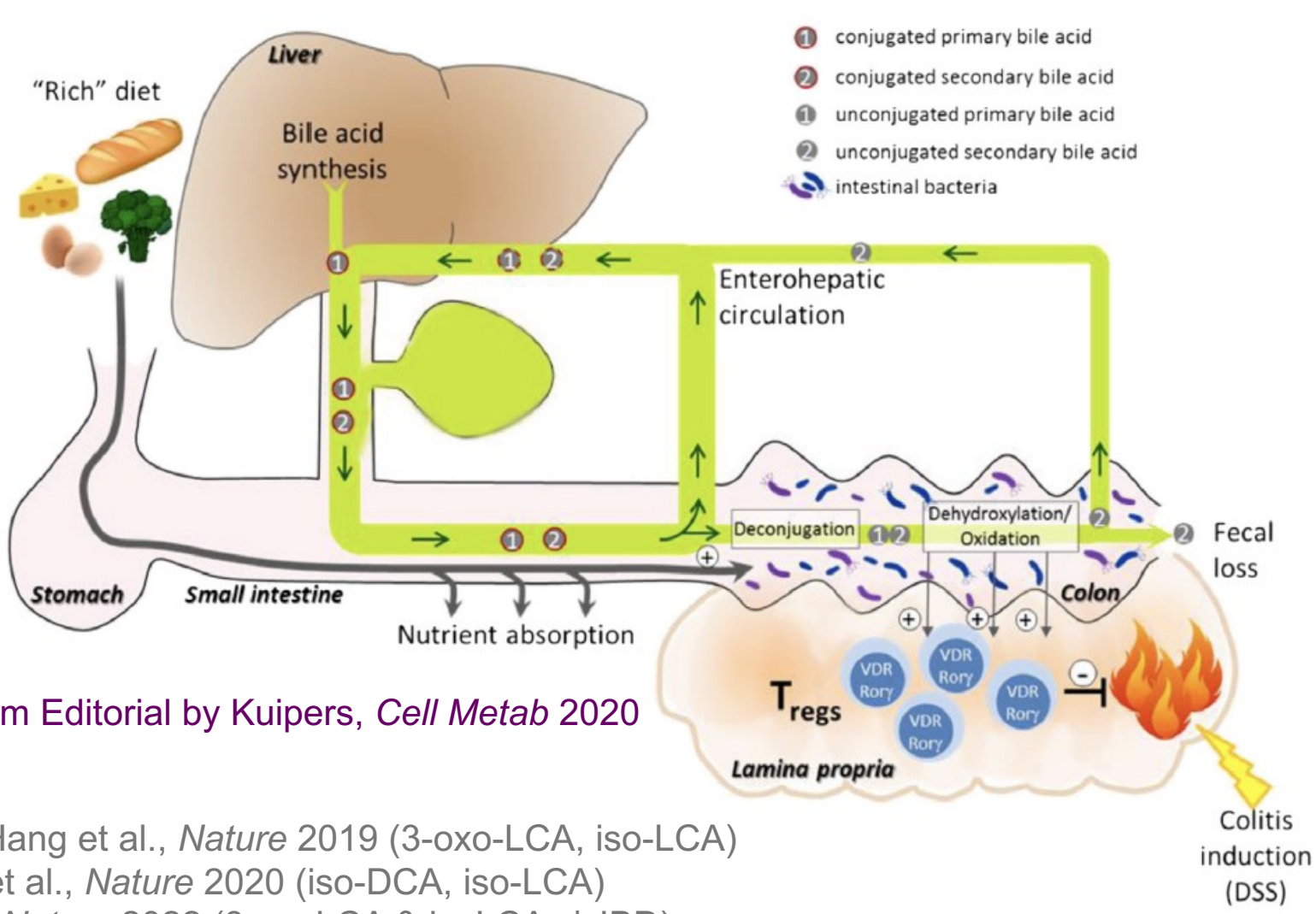
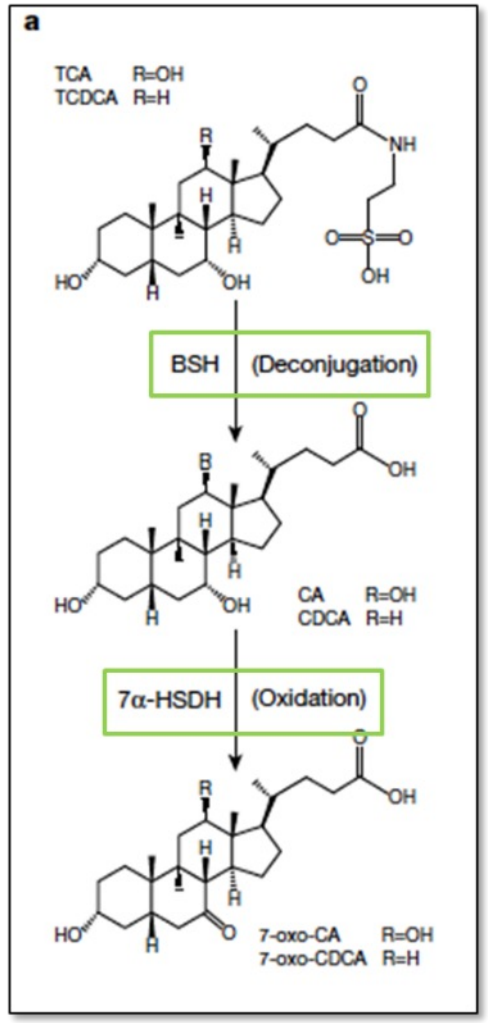


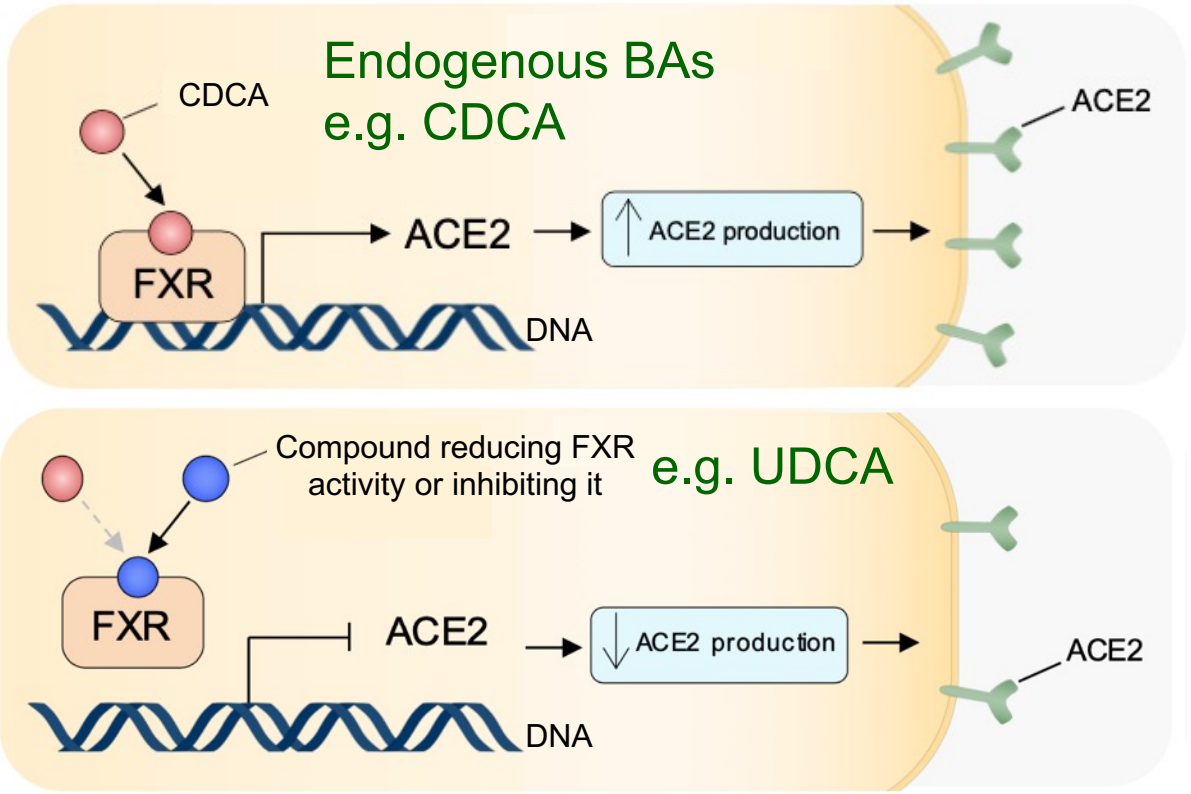
Fig. from Editorial by Kuipers, *Cell Metab* 2020



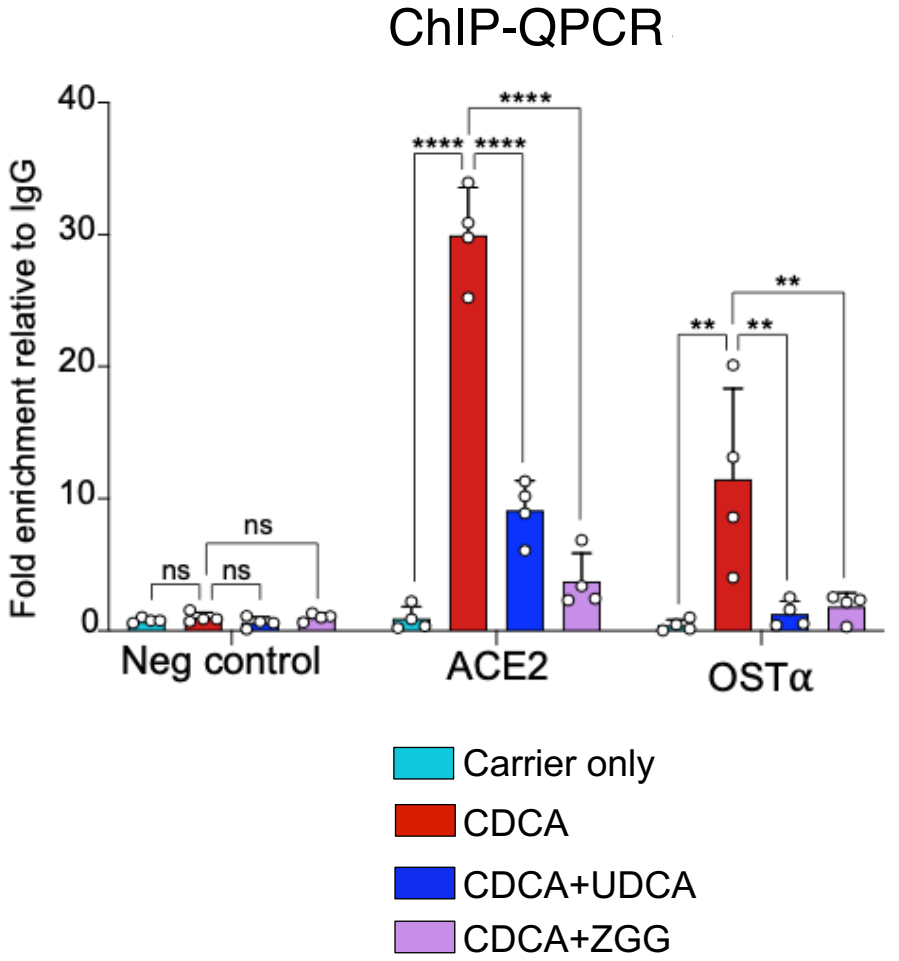
Song et al., *Nature* 2020

Also see: Hang et al., *Nature* 2019 (3-oxo-LCA, iso-LCA)
Campbell et al., *Nature* 2020 (iso-DCA, iso-LCA)
Paik et al., *Nature* 2022 (3-oxoLCA & isoLCA: ↓ IBD)

Bile acid receptor FXR directly controls ACE2 transcription & SARS-CoV-2 infection



FXR = nuclear bile acid receptor



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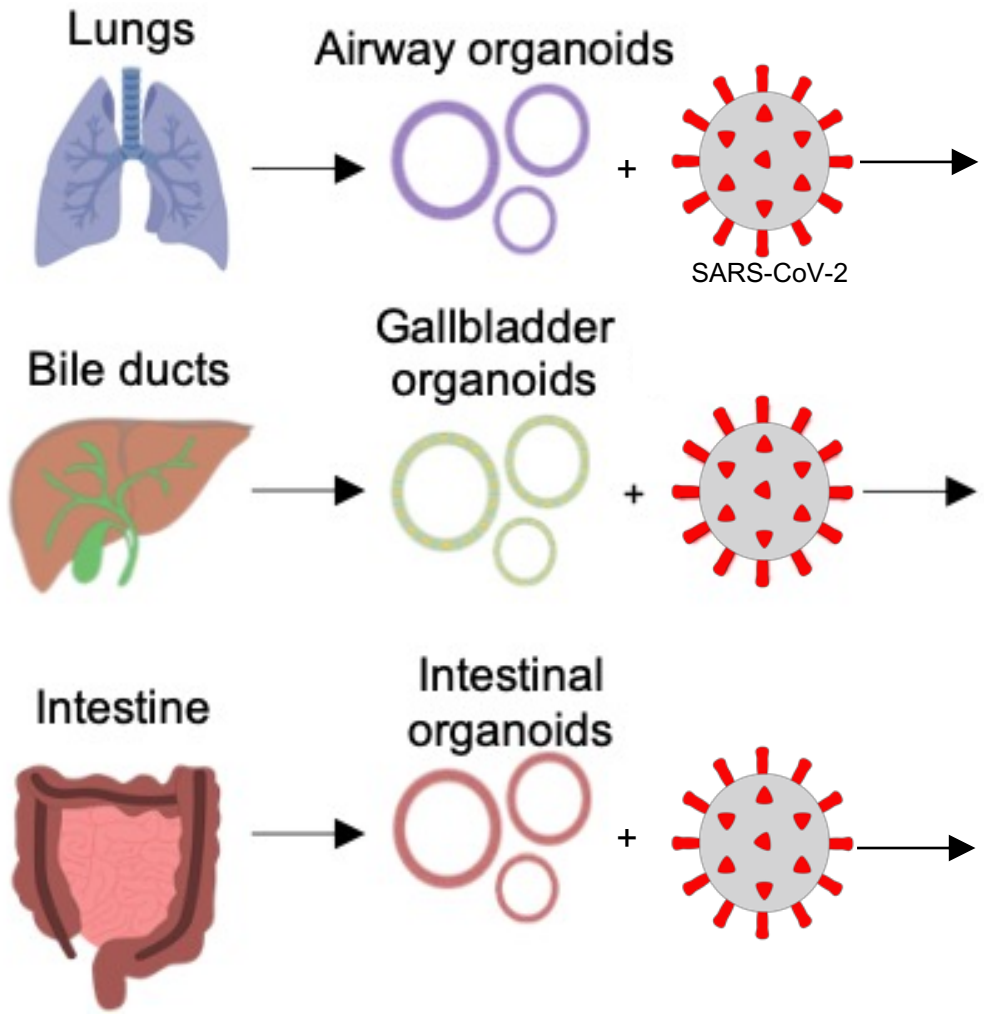
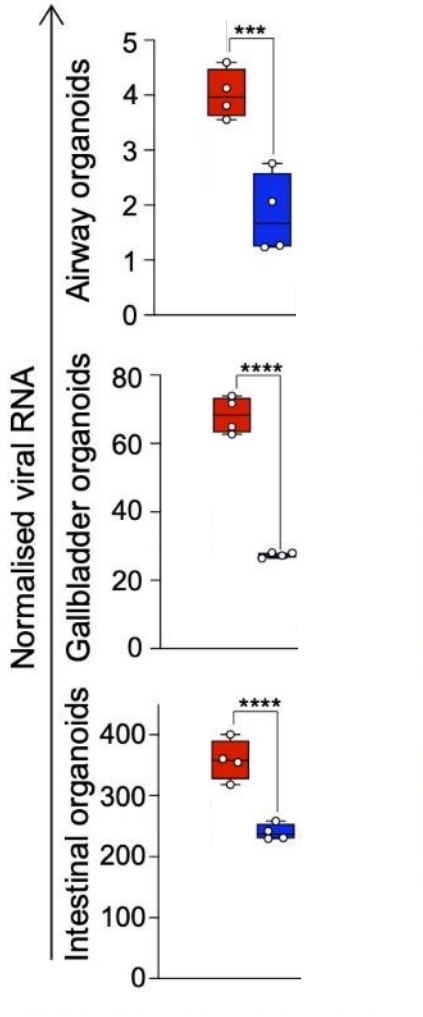
Teresa Brevini
Sampaziotis Lab

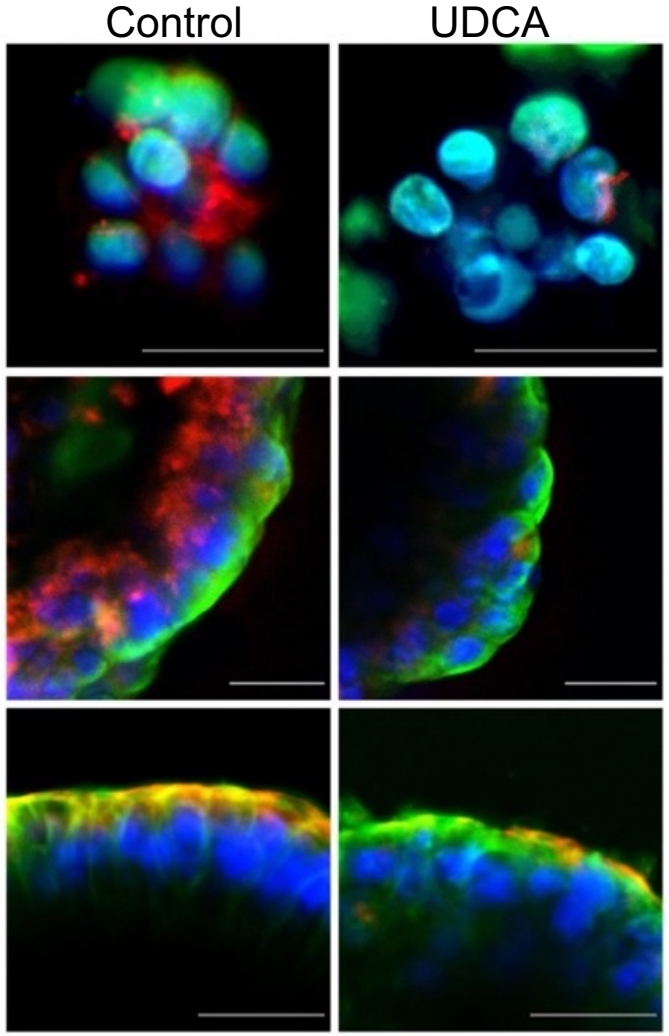
UNIVERSITY OF CAMBRIDGE

Brevini et al., *Nature* 2022

UDCA reduces ACE2 & SARS-CoV-2 infection







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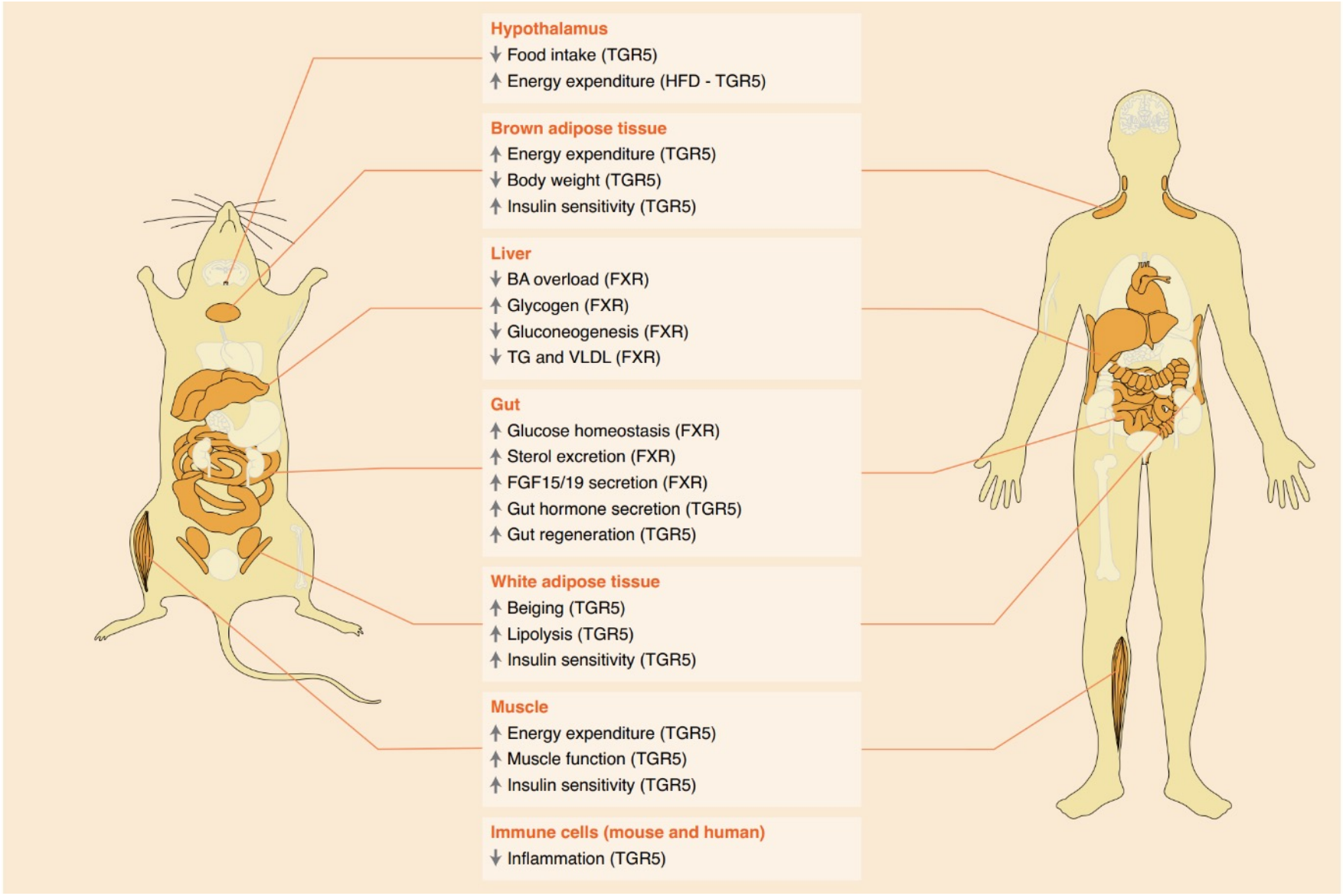
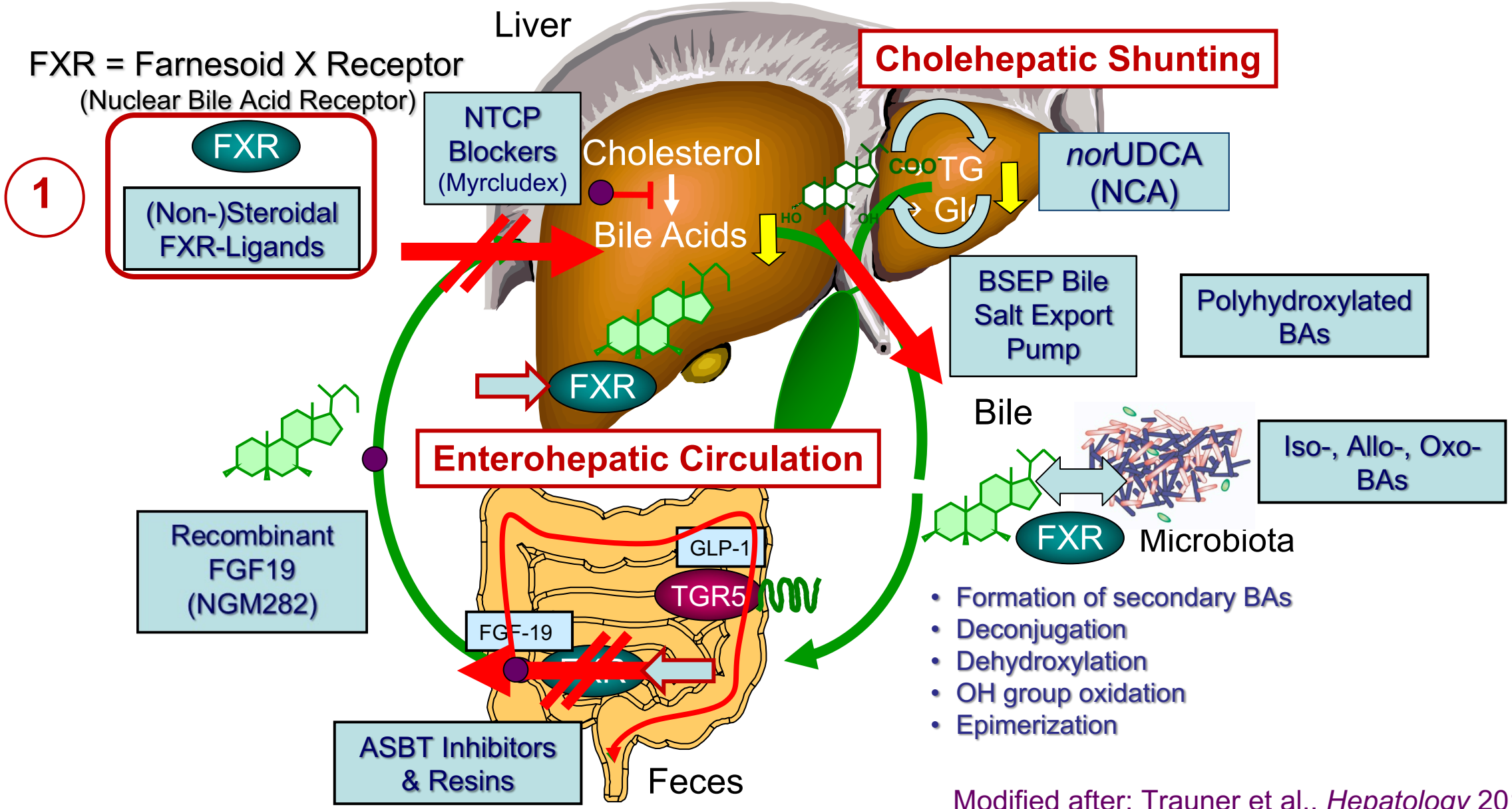
Brevini et al., *Nature* 2022

Broad metabolic activities of BAs in the body



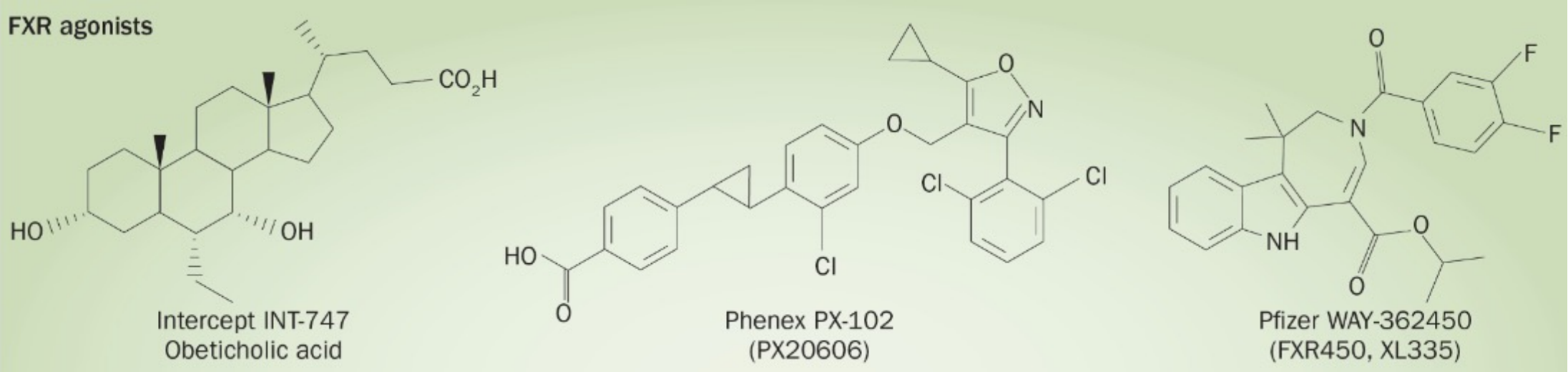
Perino & Schoonjans, *Nature Metab* 2022

Leveraging bile acid signaling for therapeutic purposes



Modified after: Trauner et al., *Hepatology* 2017

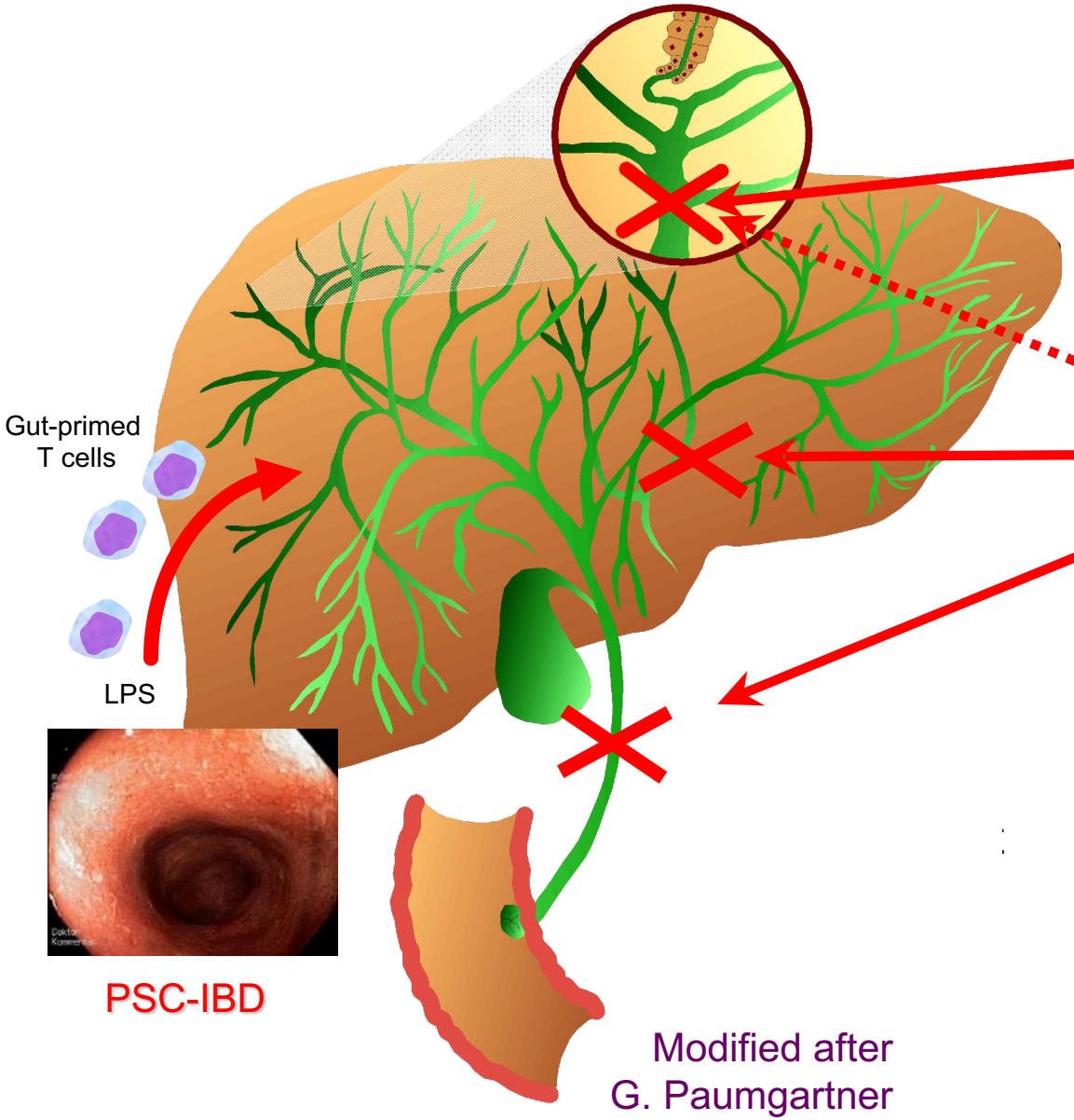
Steroidal and non-steroidal FXR agonists



- **Obeticholic Acid (OCA) - first-in-class steroidal FXR ligand**
  - Approved in PBC; studies in PSC & NASH
- **Non-steroidal FXR ligands - no BA structure**
  - Different pharmacokinetics, efficacy & safety profiles?
  - Cilofexor (PSC, PBC, NASH)
  - Tropifexor (PBC, NASH), LMB763 (NASH)
  - EDP-305 (NASH, PBC), EYP001 (NASH), MET409 (NASH)

Schaap, Trauner & Jansen, *Nature Rev Gastro Hep* 2013
Also see: Trauner et al., *Hepatology* 2017; Trauner & Fuchs, *Gut* 2022, Aldorini & Trauner, *J Hepatol* 2023

Biliary Diseases / Cholangiopathies: Clinical Challenges & Unmet Therapeutic Needs



PSC-IBD

Modified after
G. Paumgartner

Primary Biliary Cholangitis (PBC)

- Effective Rx: UDCA
- 1/3 NR - 2nd line: FXR, PPARs

Primary Sclerosing Cholangitis (PSC)

- No established medical therapy
  - UDCA controversial
- IBD ~ 70%
  - worse prognosis
- Malignancy risk (CCA,CRC, …)
  - 45% of deaths

Reviews: Hirschfield et al., *Lancet* 2013
Karlsen et al., *J Hepatol* 2017

Obeticholic acid improves hepatic bile acid excretion in patients with primary biliary cholangitis

[N-Methyl-^{11}C]Cholylsarcosine

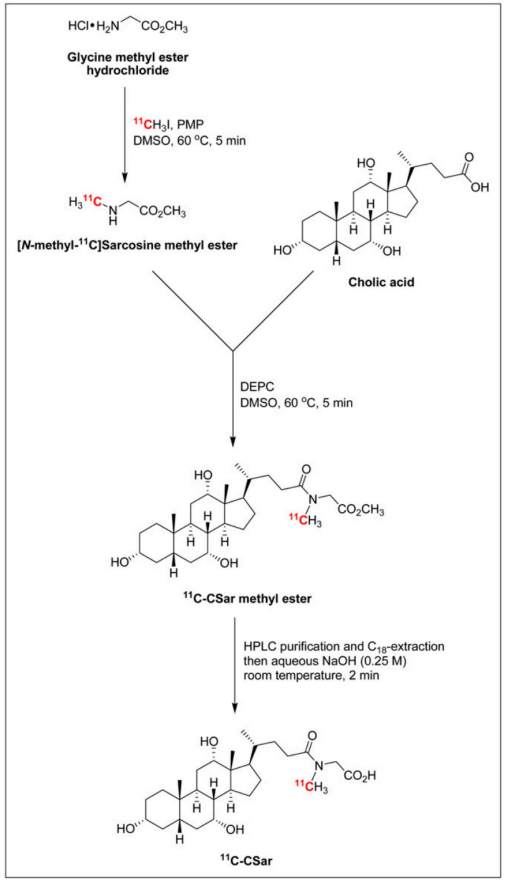
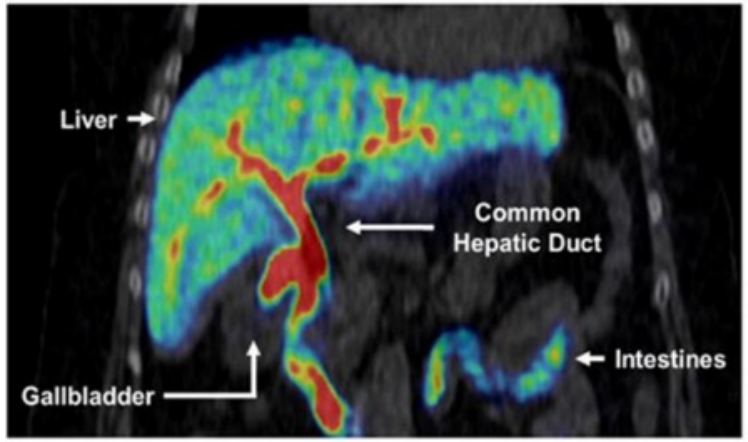
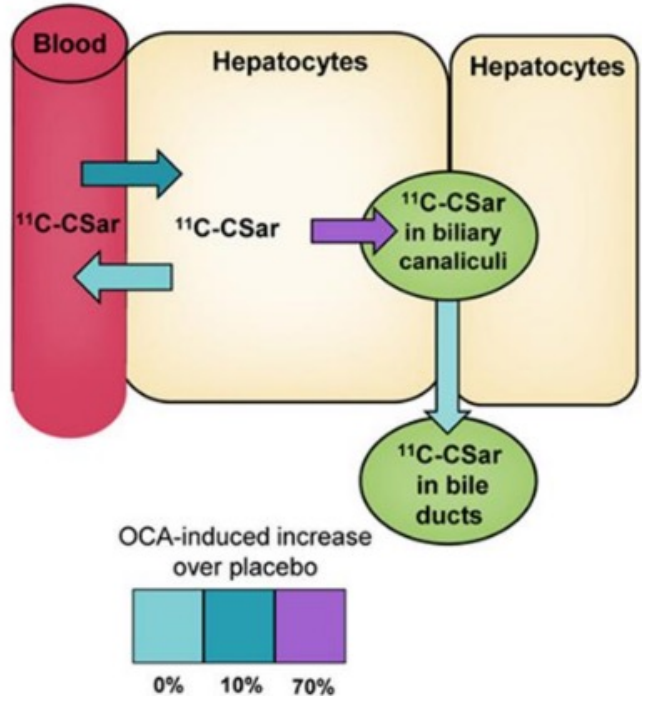


FIGURE 1. Three-step radiosynthesis of ^{11}C-cholylsarcosine.

PET of hepatic ^{11}C-CSar kinetics





Serge Erlinger: Cholestasis = failure of bile secretion to reach the duodenum (in normal/sufficient amounts)

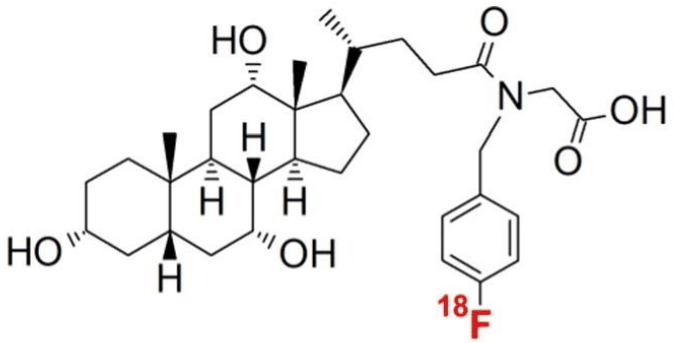
Frisch et al., *J Nucl Med* 2012

Kjærgaard et al., *J Hepatol* 2021

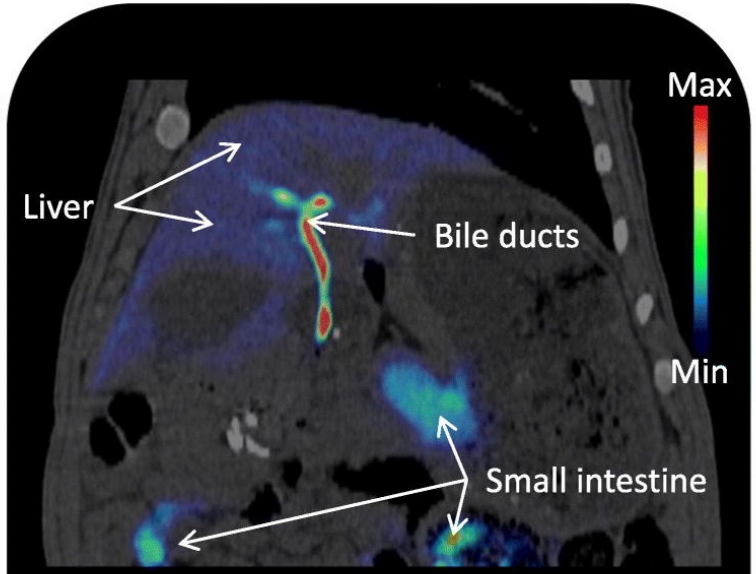
N-(4-[^{18}F]fluorobenzyl)cholylglycine as potential PET tracer for enterohepatic circulation: proof-of-concept study in pigs

***N*-(4-[^{18}F]fluorobenzyl)cholylglycine ([^{18}F]FBCGly), a tracer for PET of enterohepatic circulation of conjugated bile acids**

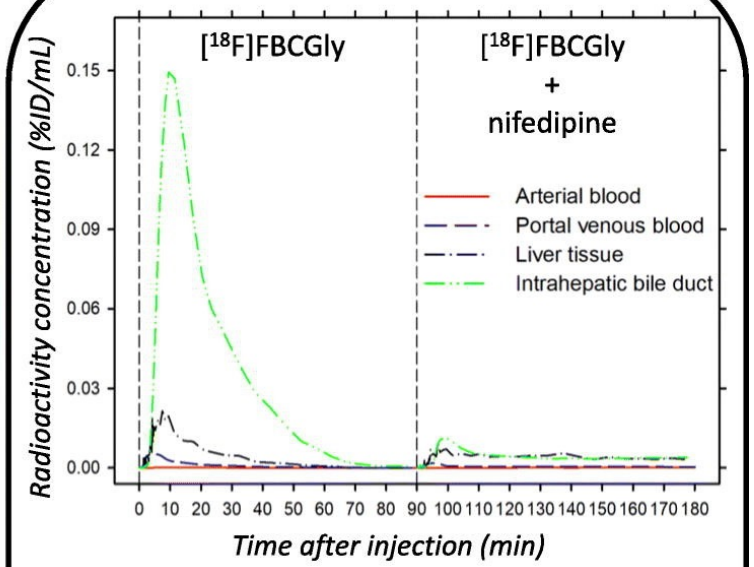
The biodistribution, metabolism, dosimetry and hepatic kinetics of [^{18}F]FBCGly was investigated in pigs



[^{18}F]FBCGly



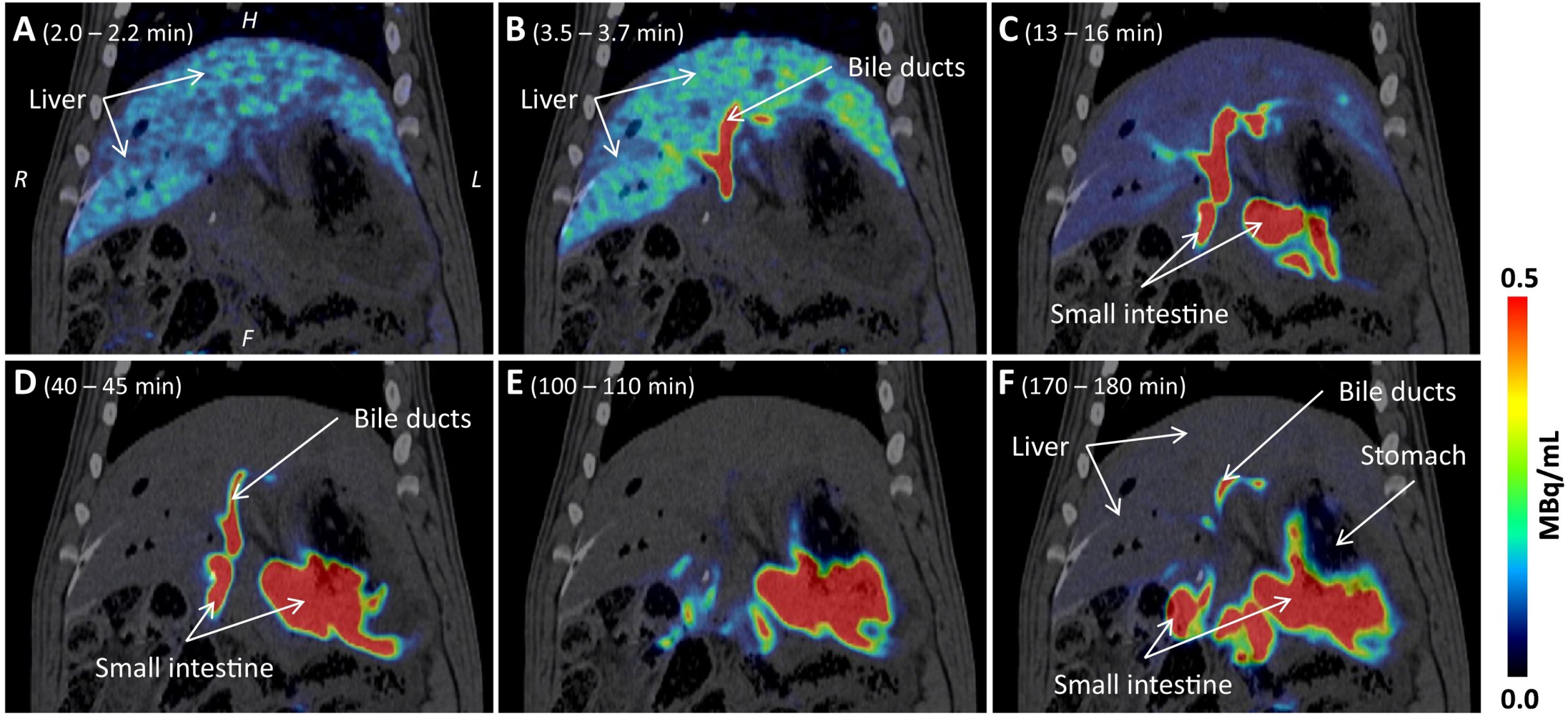
Enterohepatic circulation and no metabolism



Nifedipine and endogenous cholyltaurine inhibit ileal uptake

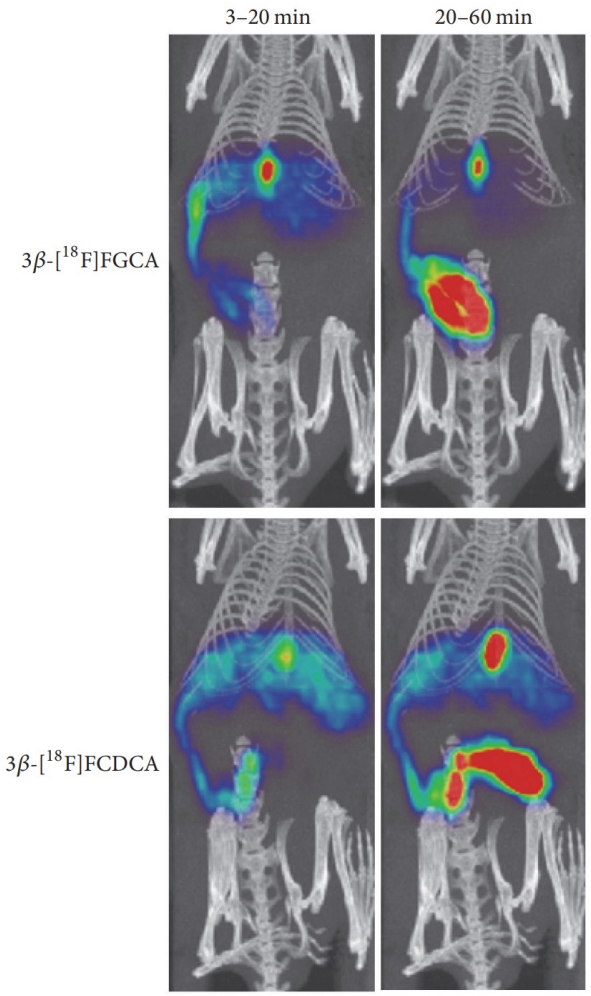
Frisch et al., *Nucl Med Biol* 2022

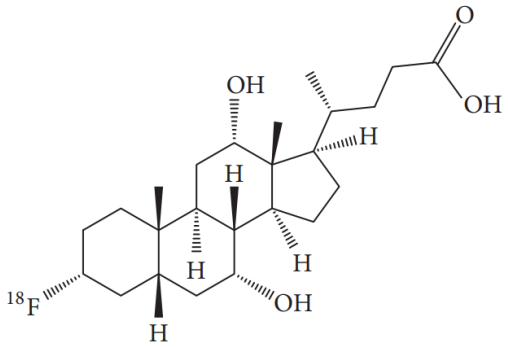
N-(4-[^{18}F]fluorobenzyl)cholylglycine as potential PET tracer for enterohepatic circulation: proof-of-concept study in pigs

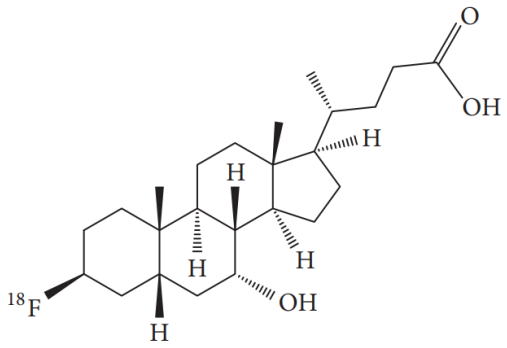


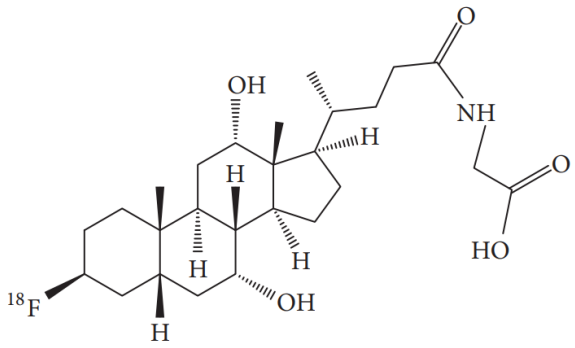
Frisch et al., *Nucl Med Biol* 2022

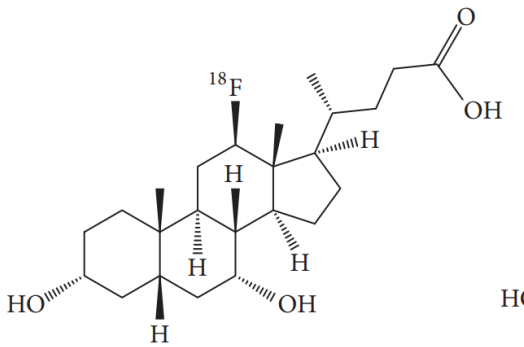
Evaluating Hepatobiliary Transport with ^{18}F-Labeled Bile Acids: The Effect of Radiolabel Position











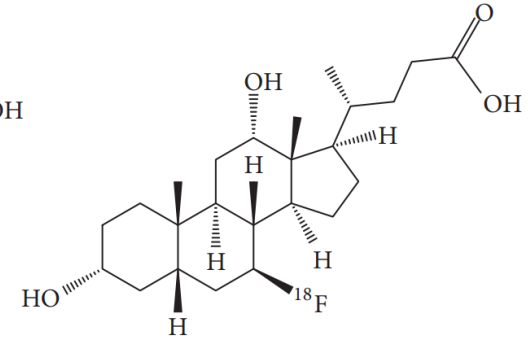
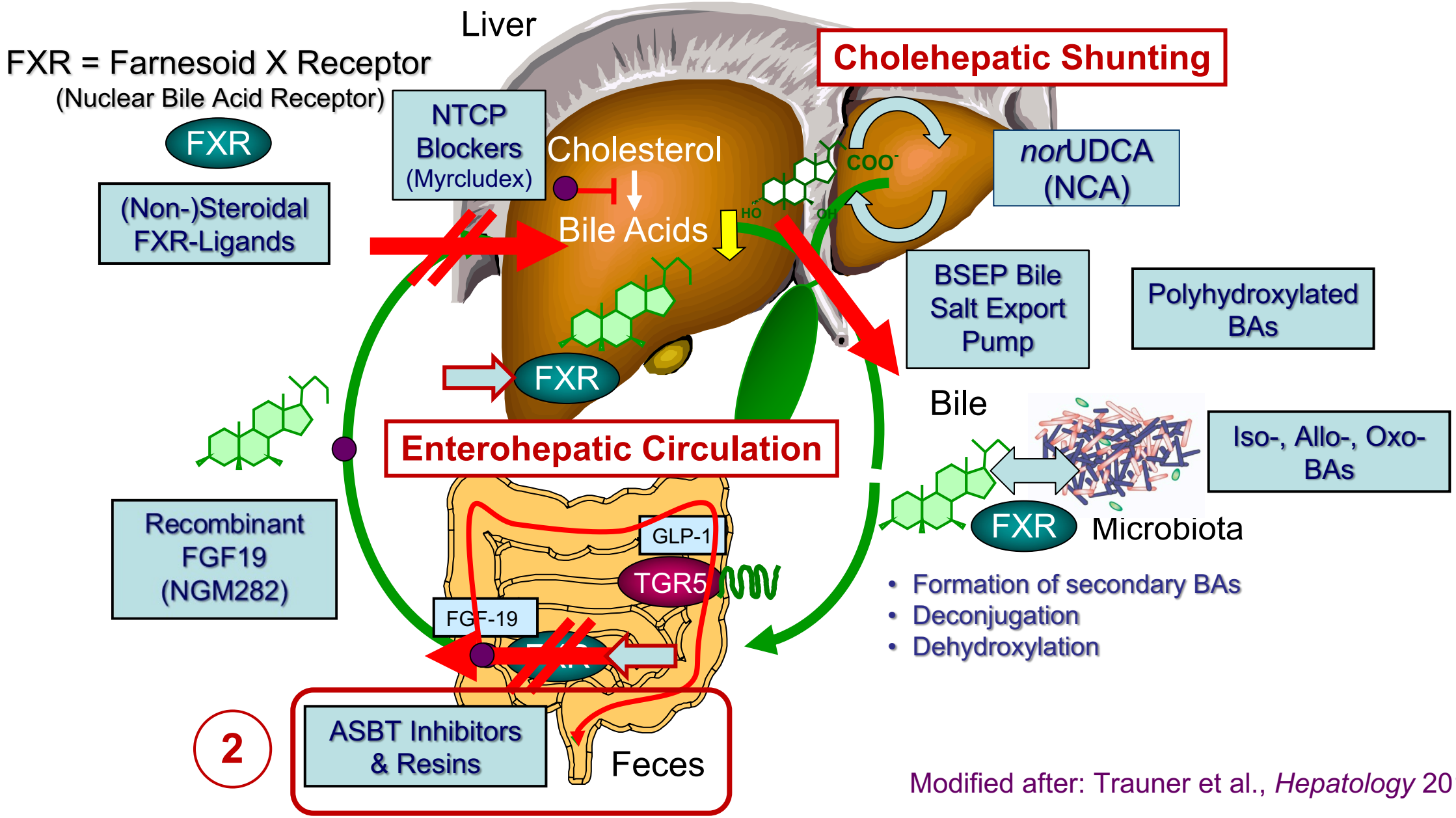


FIGURE 5: Representative Maximum Intensity Projection PET/CT of 9 MBq 3β-[^{18}F]FGCA and 3β-[^{18}F]FCDCA in a wild-type mouse

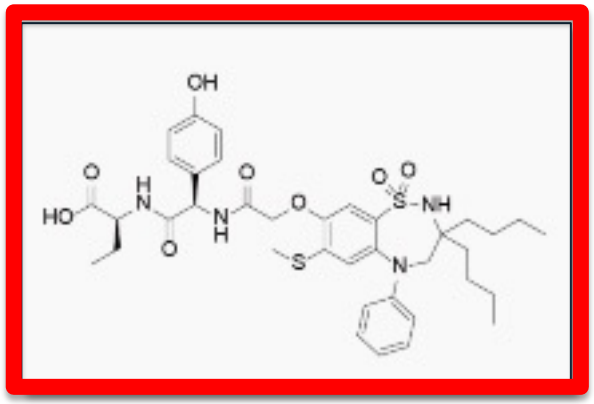
De Lombaerde et al., *Contrast Media Mol Imaging* 2018

Leveraging bile acid signaling for therapeutic purposes

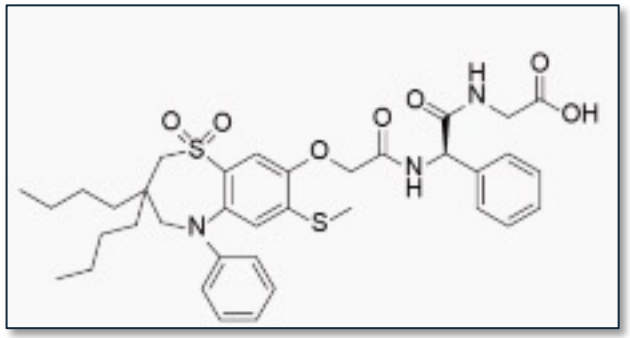


Modified after: Trauner et al., *Hepatology* 2017

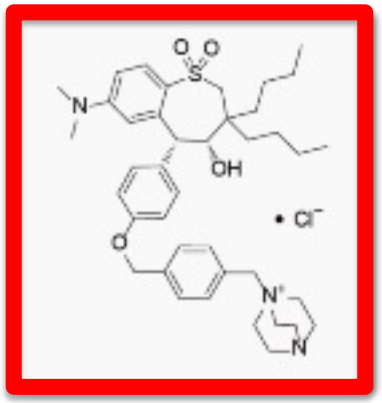
ASBT (IBAT) inhibitors in clinical trials



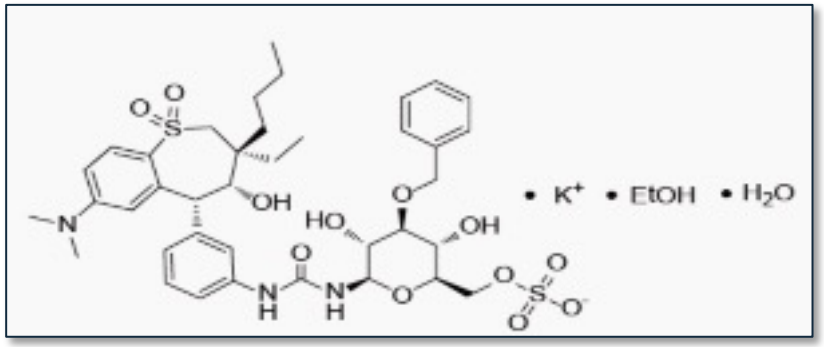
Odevixibat; A4250



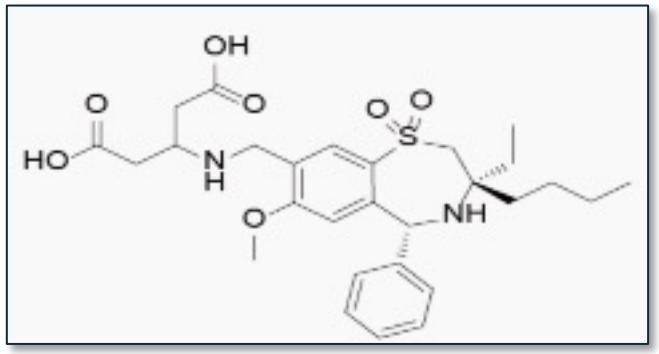
Elobixibat; A3309



Maralixibat; Lum001; SHP625



Volixibat; Lum002; SHP626



Linerixibat; GSK2330672

Diseases:

Alagille Syndrome
PFIC1
PFIC2

Biliary Atresia

PBC
PSC

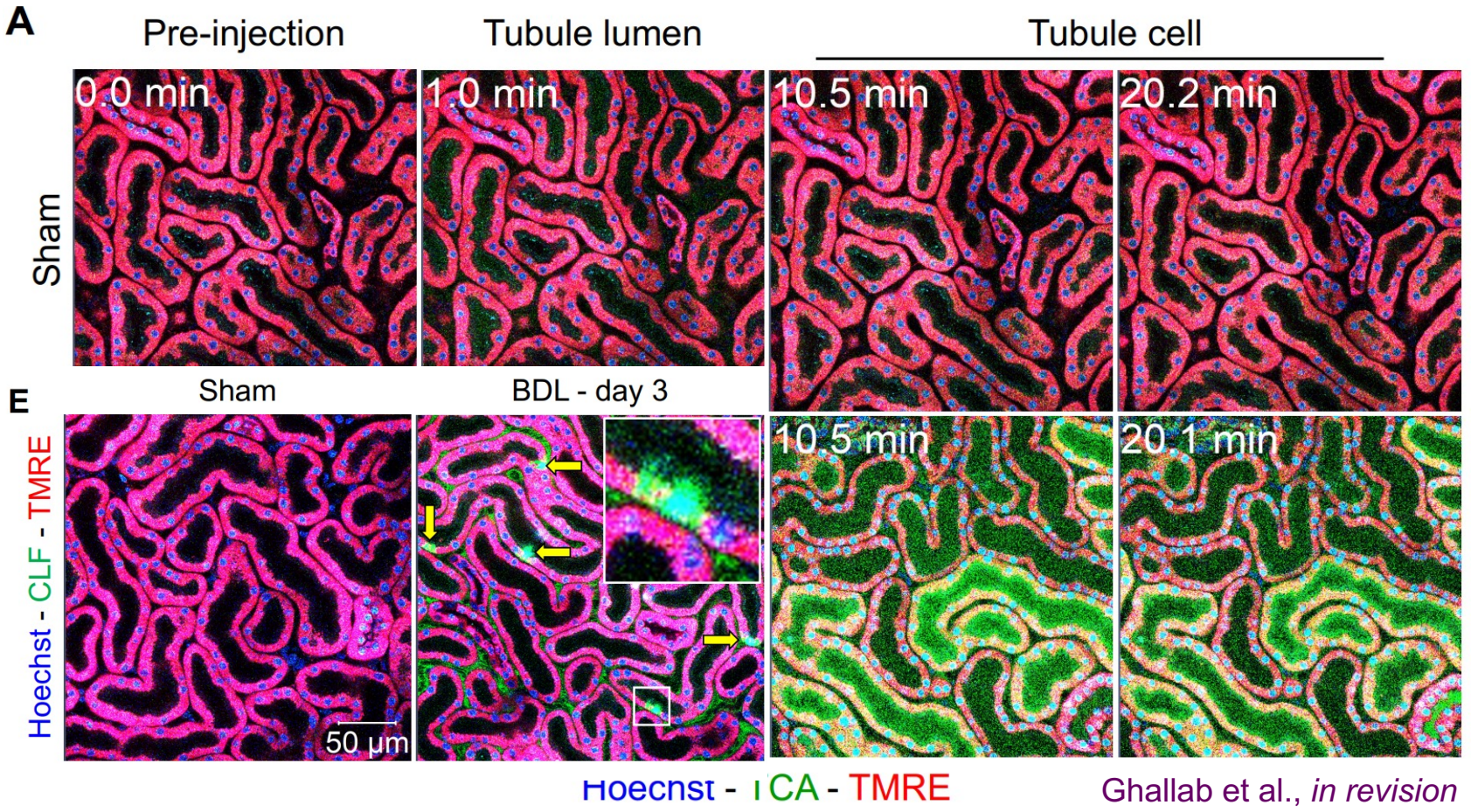
NASH

Constipation

Slide courtesy Saul Karpen

Adaptive hepatic changes result in increased bile acid load to the kidney in cholestasis

Bile acid accumulation in cholemic nephropathy

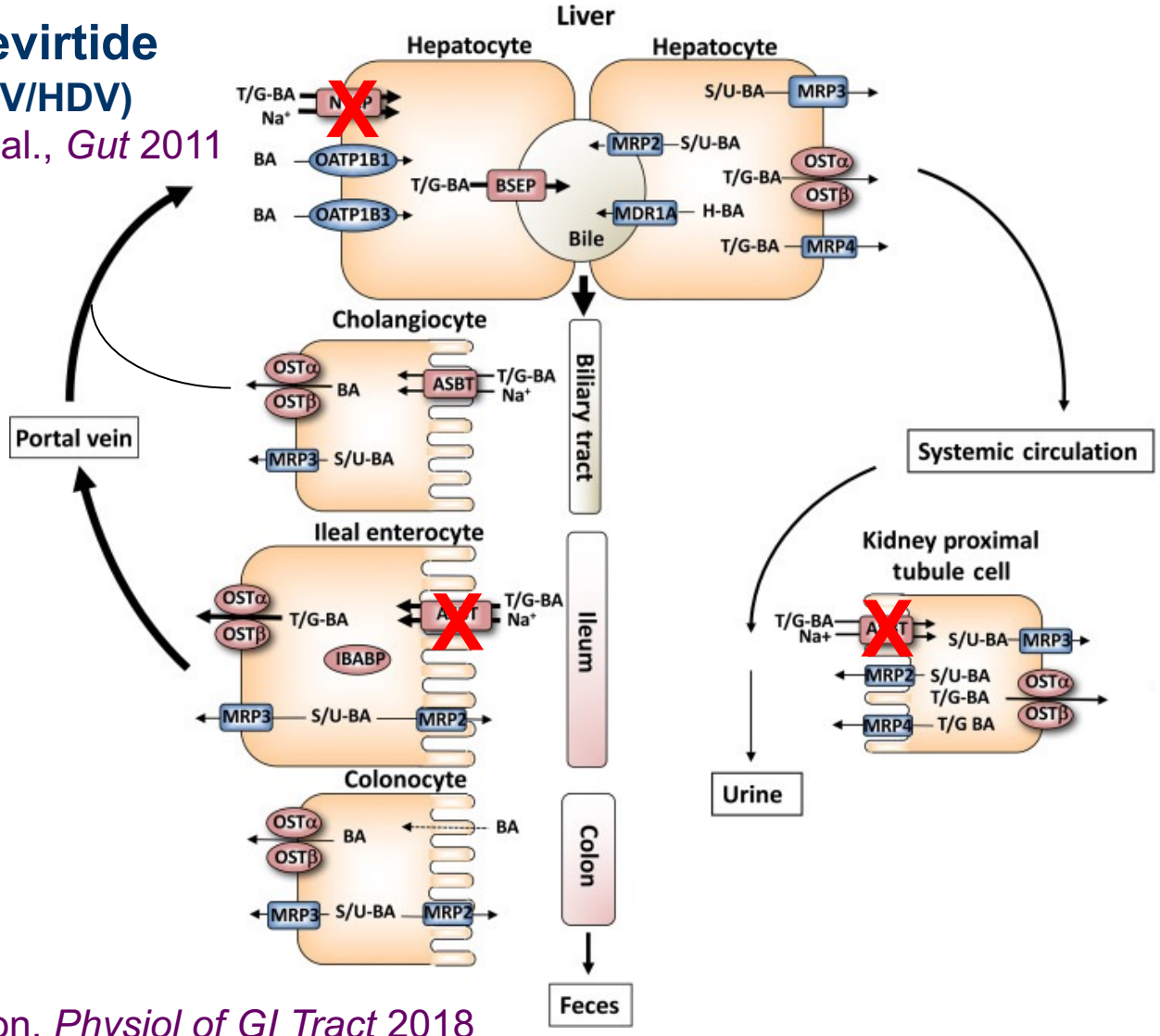


Ghallab et al., *in revision*

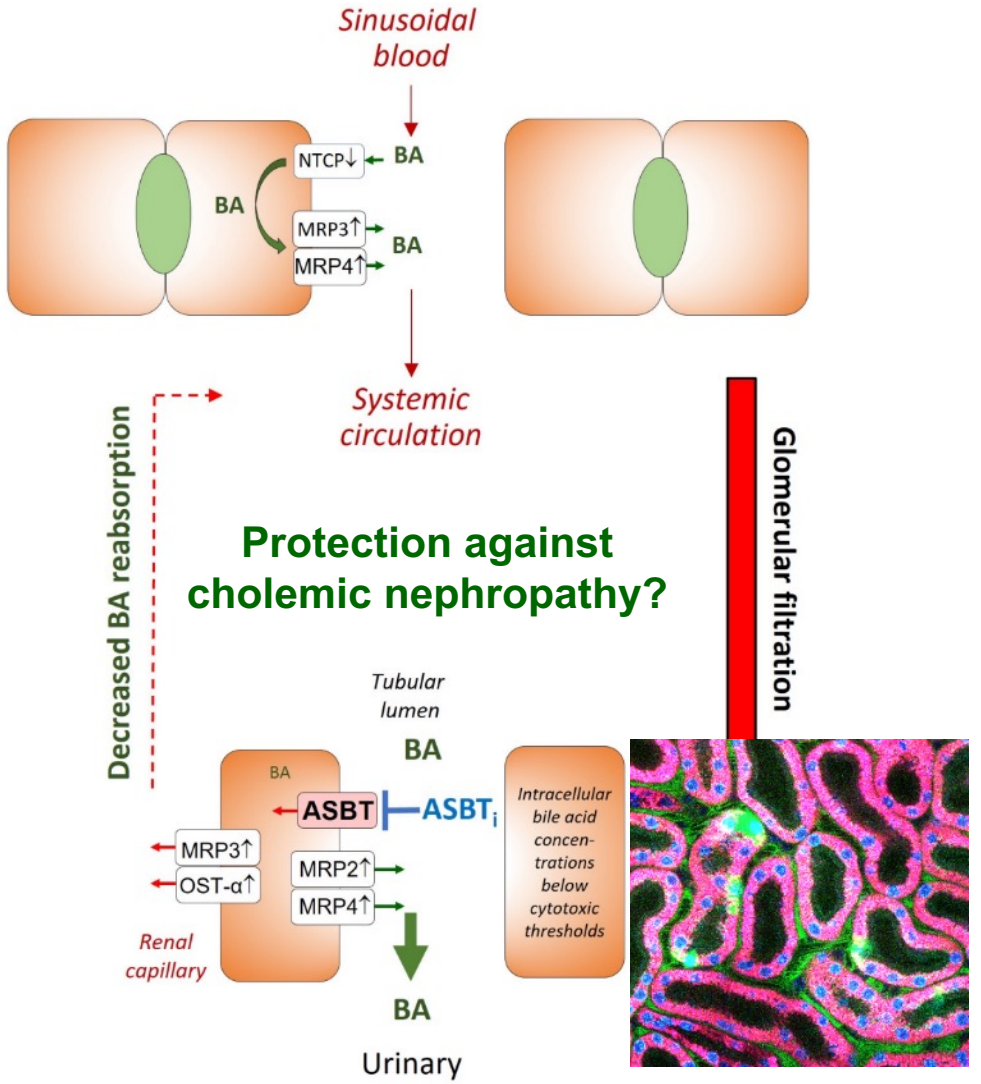
In cooperation with J. Hengstler, & A. Ghallab, IfADo, Dortmund

Therapeutic opportunities for ileal IBAT and systemic ASBT inhibitors (and beyond – NTCP?)

Bulevirtide
(HBV/HDV)
Urban et al., *Gut* 2011

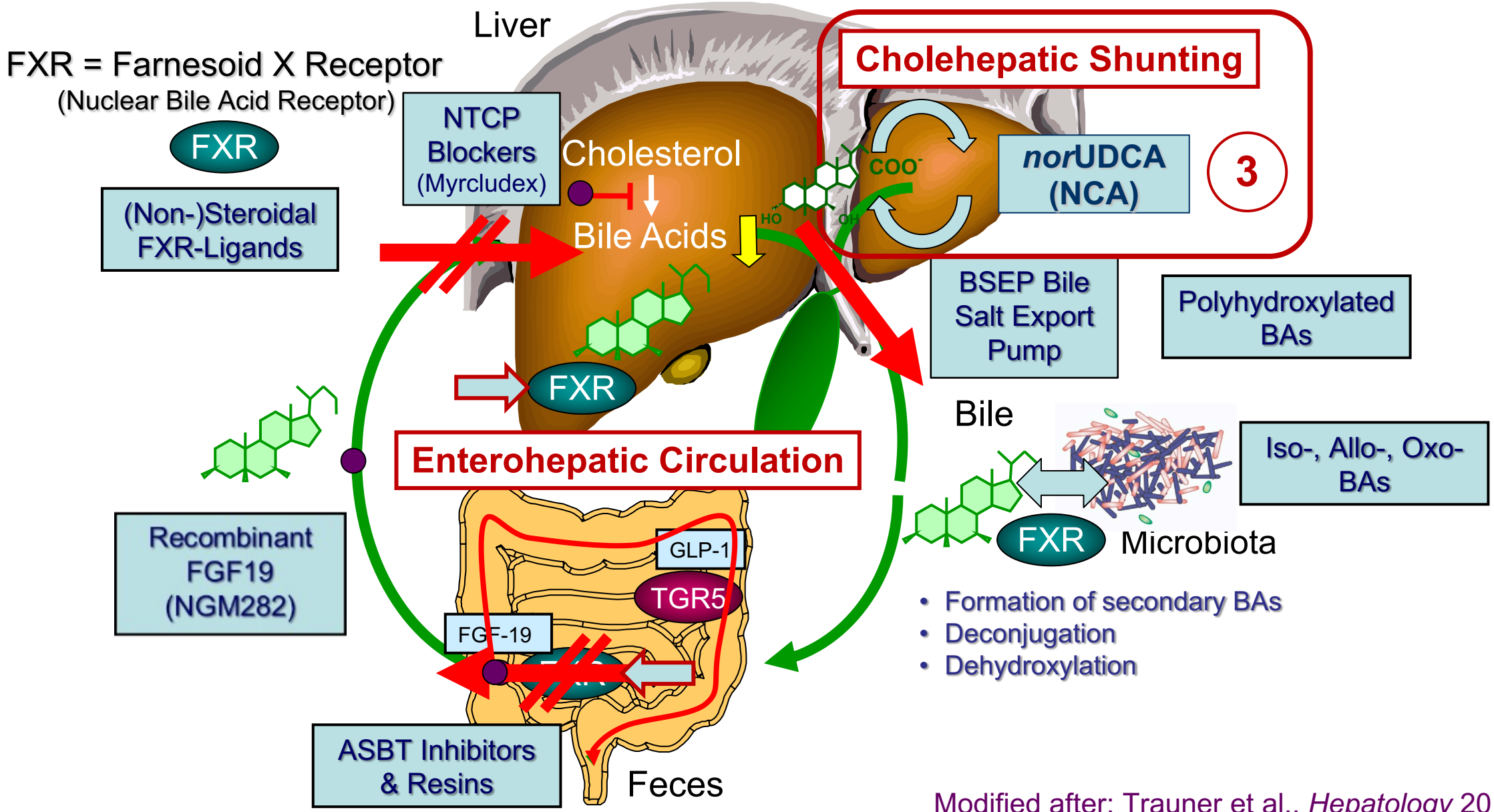


Dawson, *Physiol of GI Tract* 2018



Ghallab et al., *in revision*

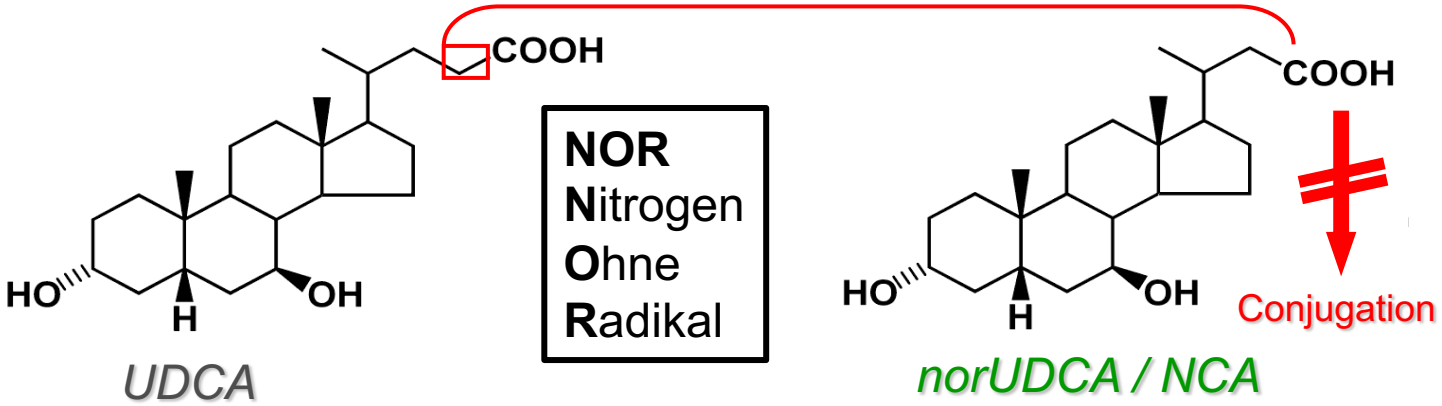
Leveraging bile acid signaling for therapeutic purposes



Modified after: Trauner et al., *Hepatology* 2017

Differential pharmacological profiles of UDCA versus *nor*UDCA / norucholic acid (NCA)

UDCA → *nor*UDCA / NCA: side-chain-shortening alters pharmacological profile

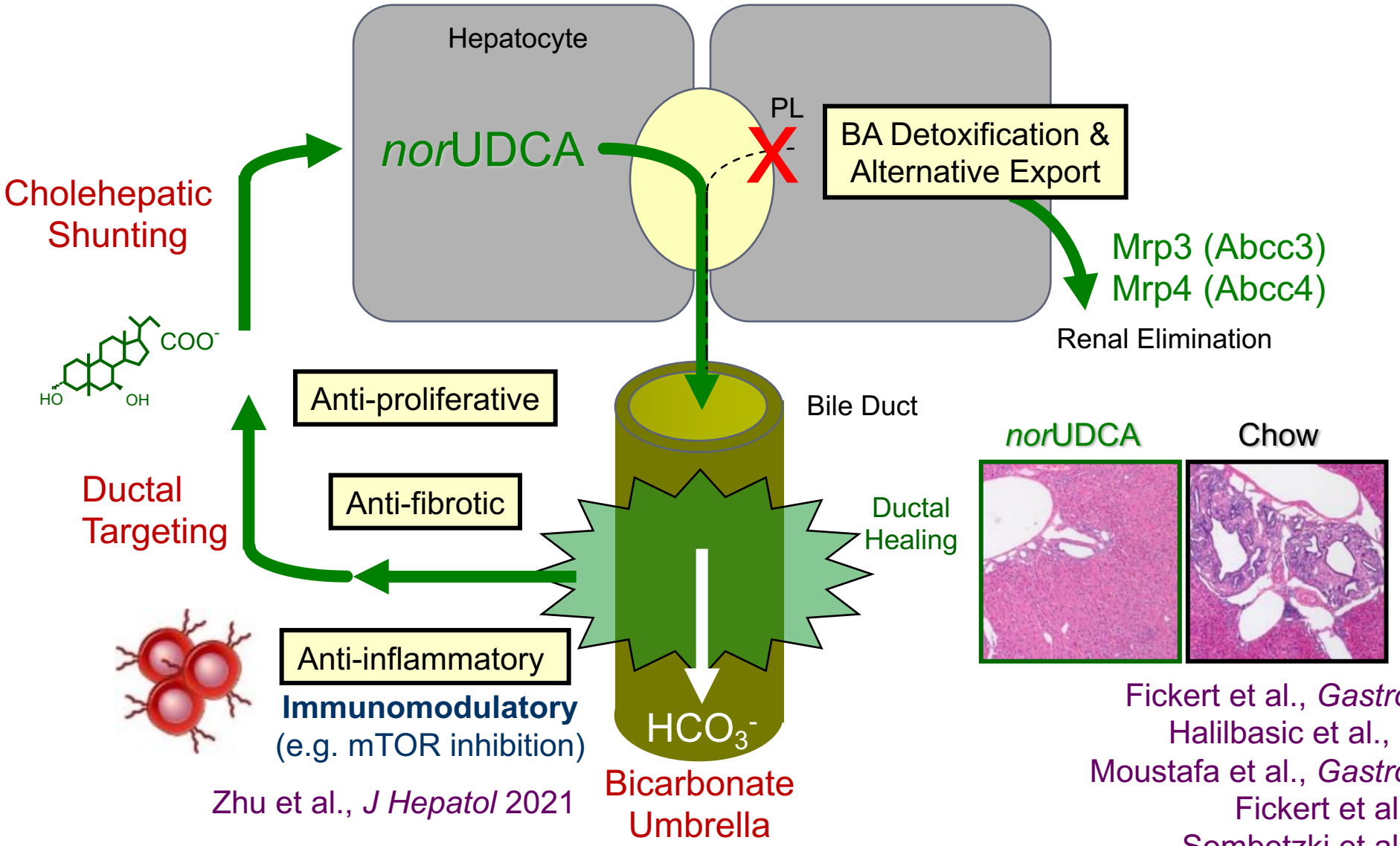


Pharmacokinetics	- Conjugation with taurin/glycin	- Resistant to taurin/glycin conjugation ⇨ glucuronidation
	- Entero-hepatic circulation: **Liver** ⇄ **Gut**	- Cholehepatic shunting: **Hepatocyte** ⇄ **Bile Duct**
Biliary Physiology	- **Bile-acid rich** Choleresis	- **Bi-carbonate rich** Hypercholeresis

***nor*UDCA / NCA is NOT a ligand for FXR or TGR5**

Yoon et al., *Gastro* 1986
Hofmann et al., *Hepatology* 2005
Trauner et al., *Dig Dis* 2015

*nor*UDCA / norucholic acid (NCA): Mechanisms of Action in *Mdr2 (Abcb4)*$^{-/-}$ Model of Sclerosing Cholangitis



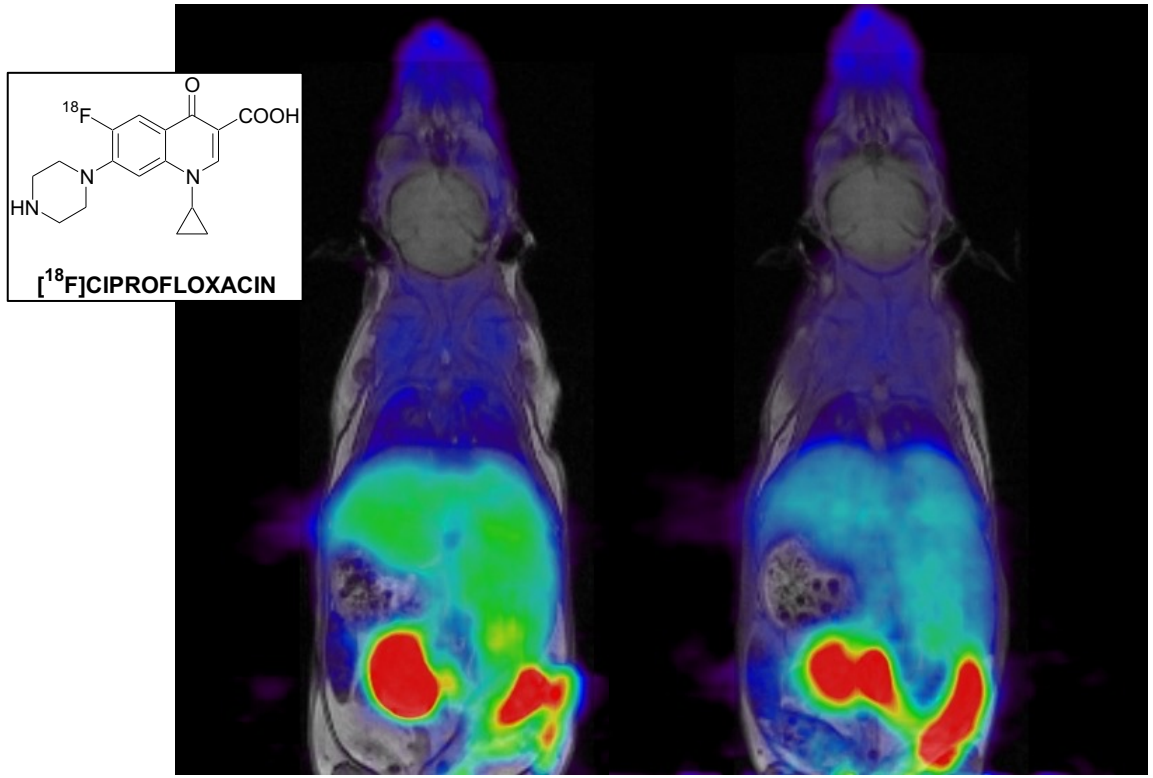
Zhu et al., *J Hepatol* 2021

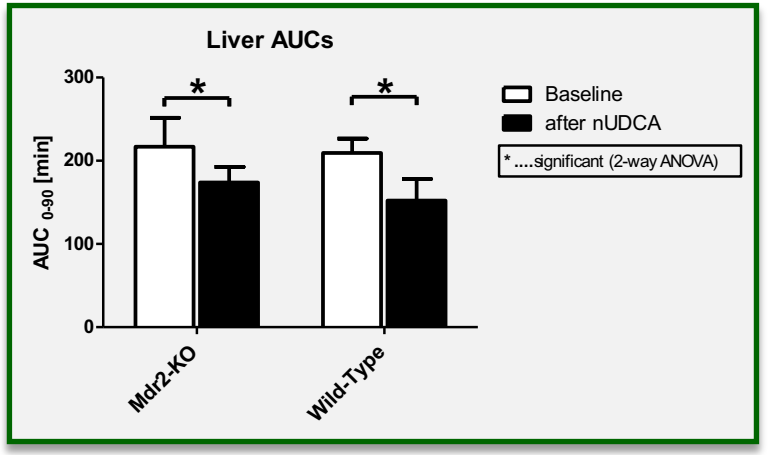
Fickert et al., *Gastroenterology* 2006
Halilbasic et al., *Hepatology* 2009
Moustafa et al., *Gastroenterology* 2012
Fickert et al., *J Hepatol* 2013
Sombetzki et al., *J Hepatol* 2015

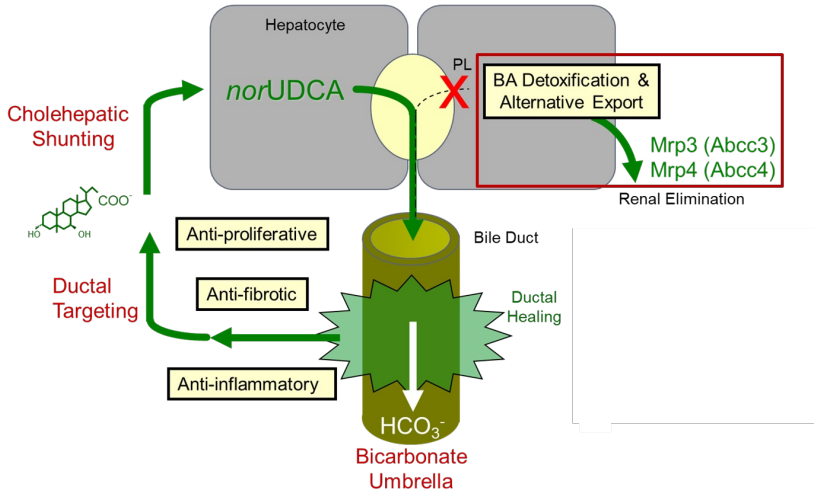
*nor*UDCA and hepatic disposition of [^{18}F] Ciprofloxacin in *Mdr2 (Abcb4)*$^{-/-}$ model of sclerosing cholangitis

Mdr2-KO (M501)

Baseline after nUDCA



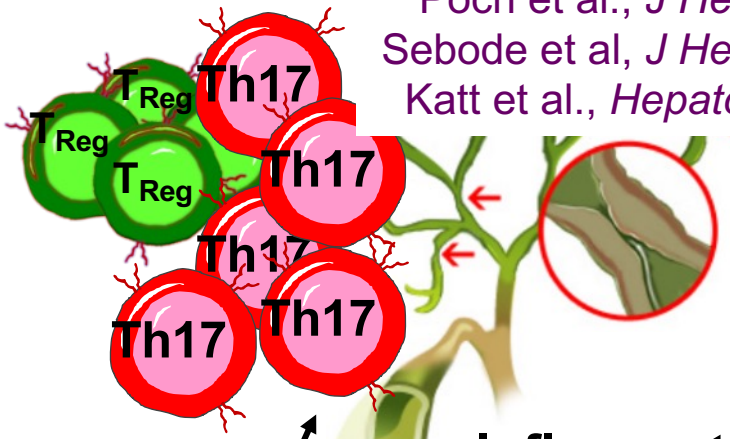


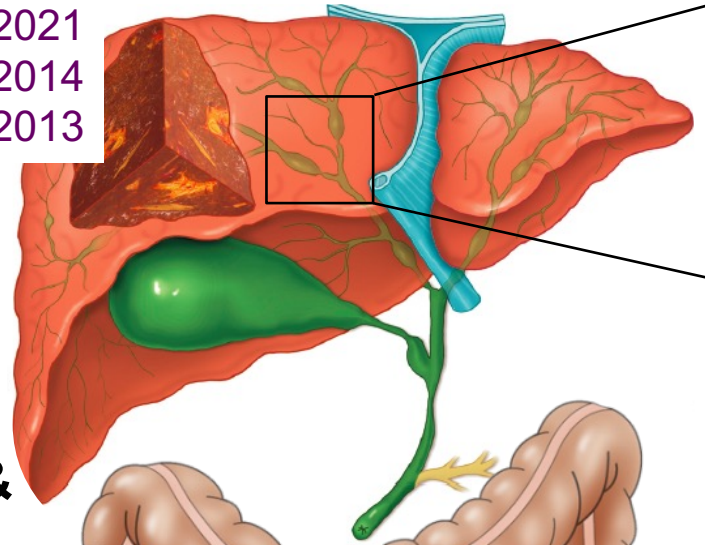


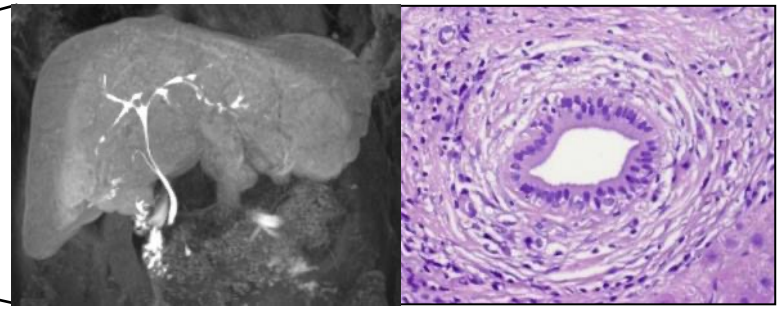
Wanek, Halilbasic, …, Langer, Trauner, *J Pharm Sci* 2016

T_H17/Treg imbalance: Key immunopathological factor driving PSC-IBD

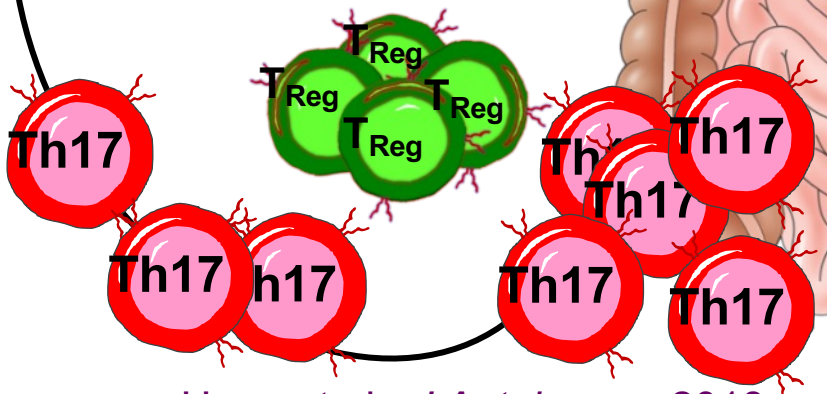
Poch et al., *J Hepatol* 2021
Sebode et al, *J Hepatol* 2014
Katt et al., *Hepatology* 2013

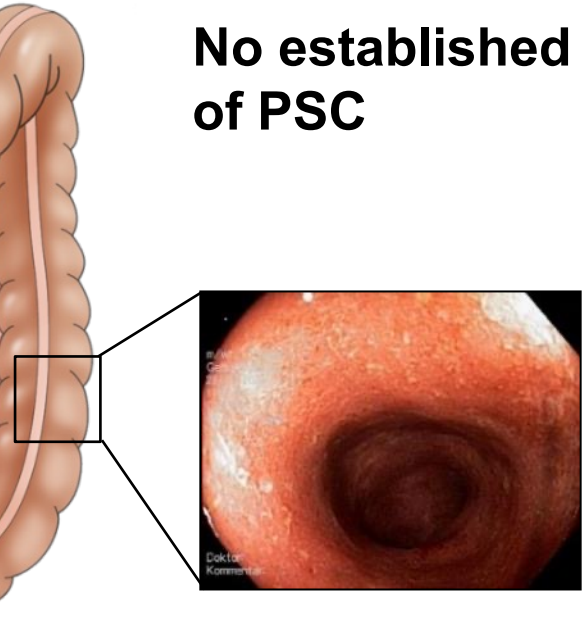






Inflammation & fibrosis of the bile ducts





No established medical therapy of PSC

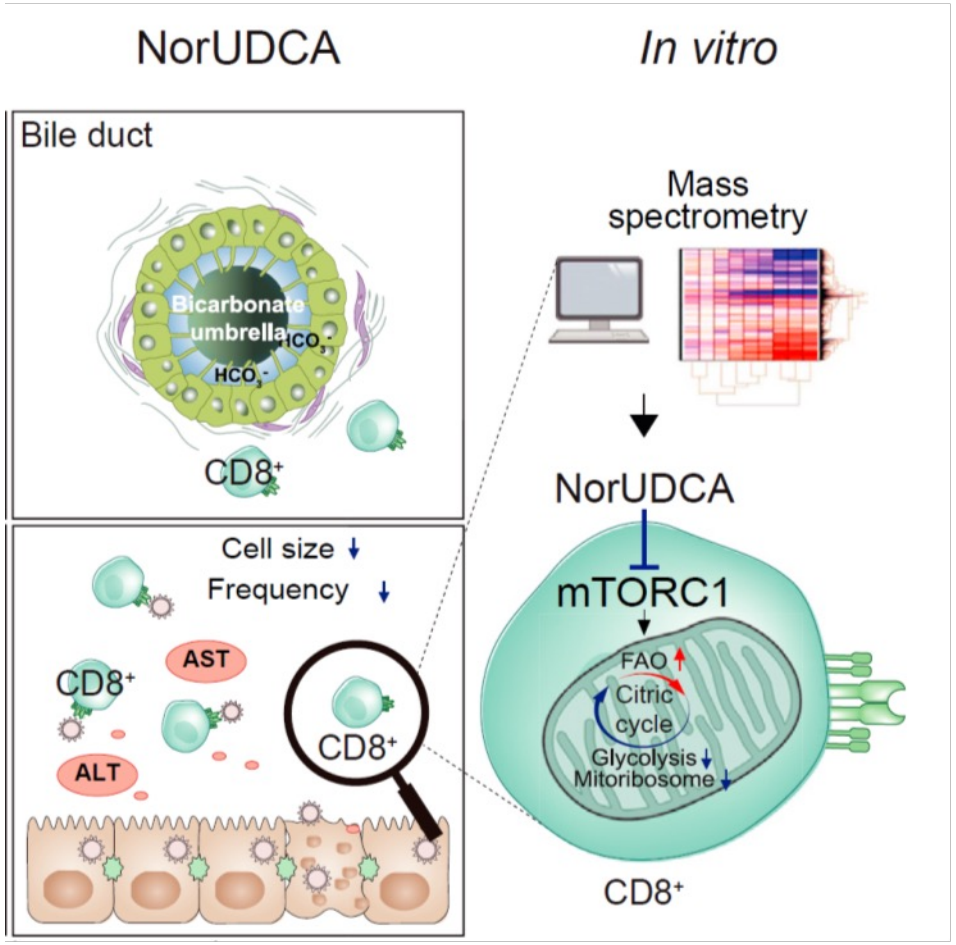
PSC-IBD~70%

Ueno et al., *J Autoimmun* 2018
Fujino et al., *Gut* 2003

Reviewed in Hirschfield et al., *Lancet* 2013
Karlsen et al., *J Hepatol* 2017

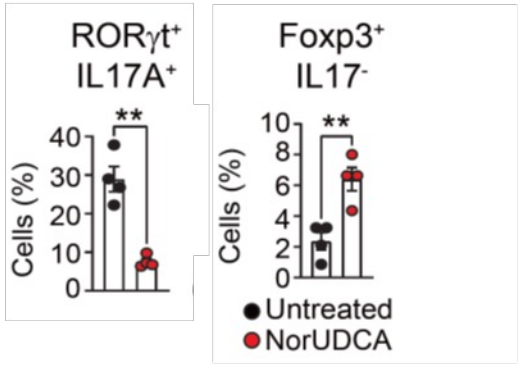
*nor*UDCA ameliorates hepatic & intestinal inflammation by shaping mTOR proteome & metabolism in CD8⁺ & CD4⁺ T cells

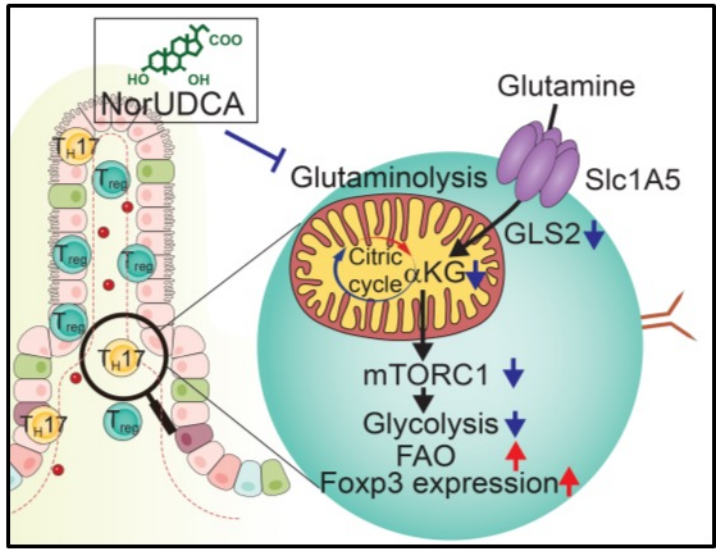
CD8⁺ T cells



Zhu et al., *J Hepatol* 2021

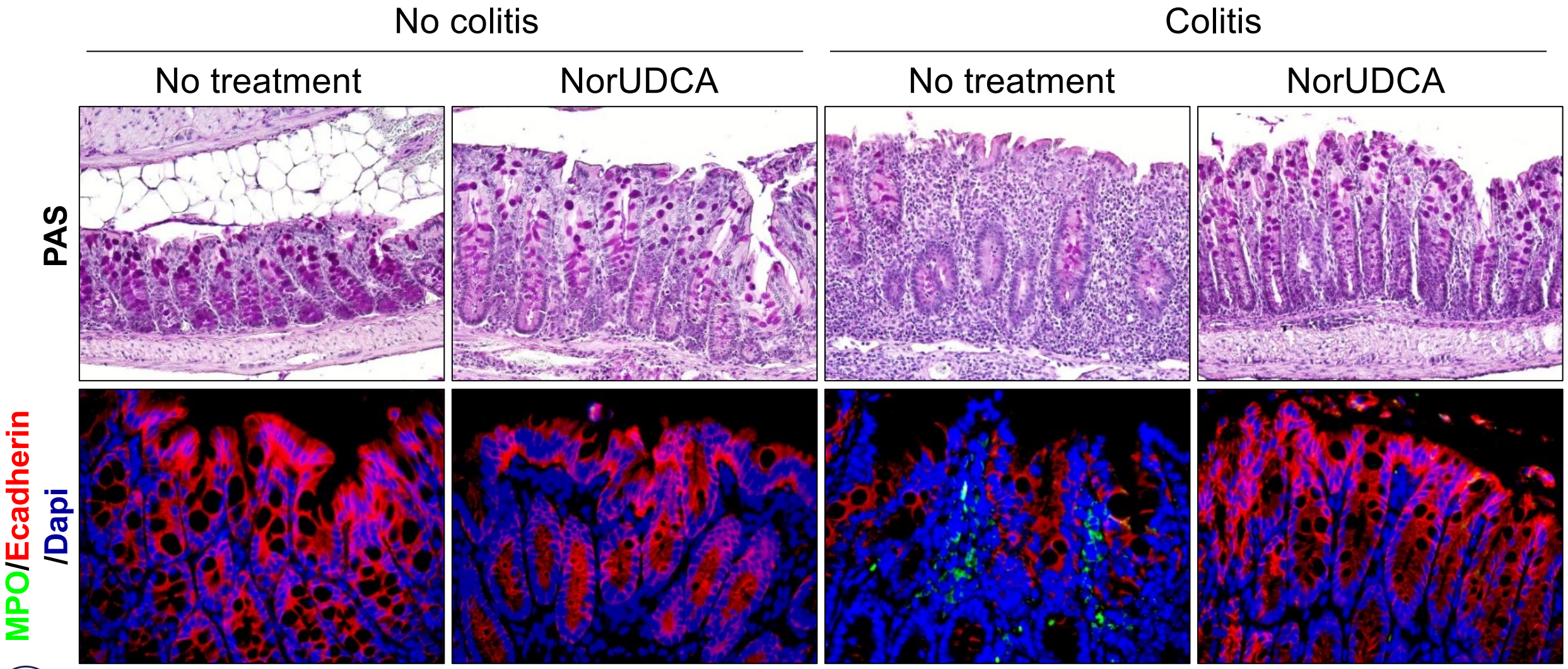
CD4⁺ T cells





Zhu et al., *in preparation*
EASL ILC 2020 AS060

*nor*UDCA protects mucosal goblet cells and barrier integrity against colon inflammation in mice



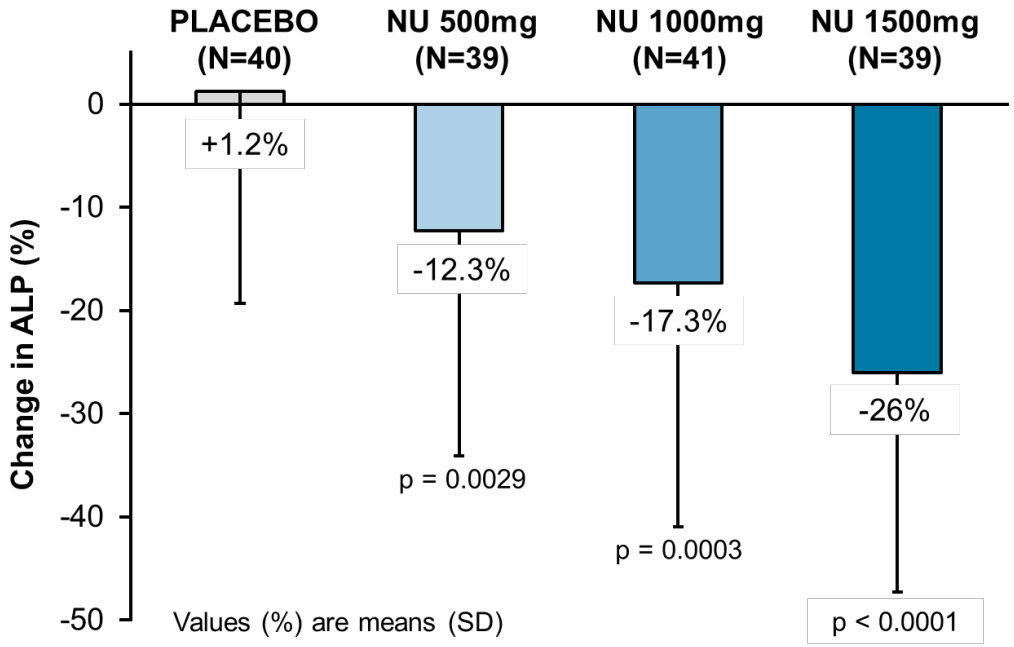
Zhu et al., *unpublished data – do not distribute*

(400x magnification)

Clinical efficacy of *nor*UDCA / norucholic acid (NCA) in PSC and NAFLD Phase 2 trials

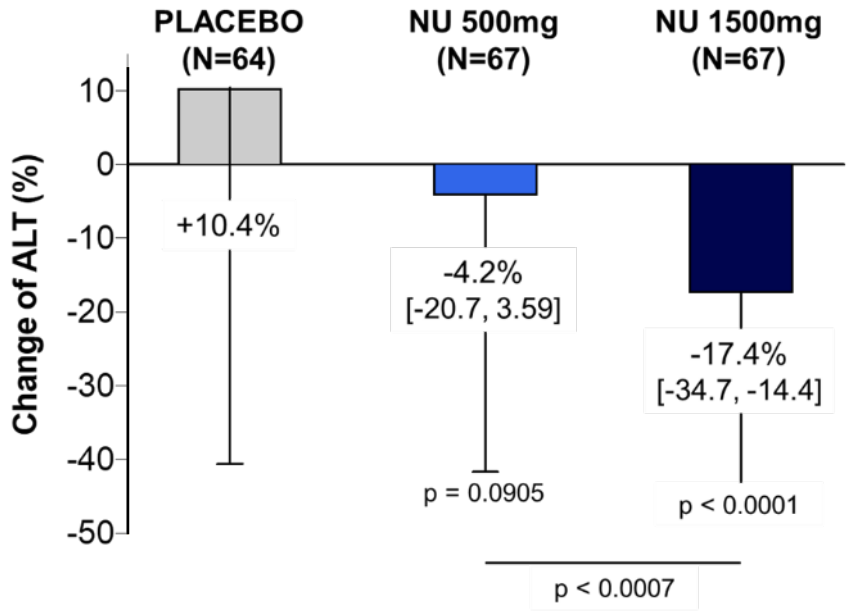
PSC Phase 2 (NUC-3)

Fickert et al. … Trauner, *J Hepatol* 2017



NAFLD Phase 2a (NUC-4)

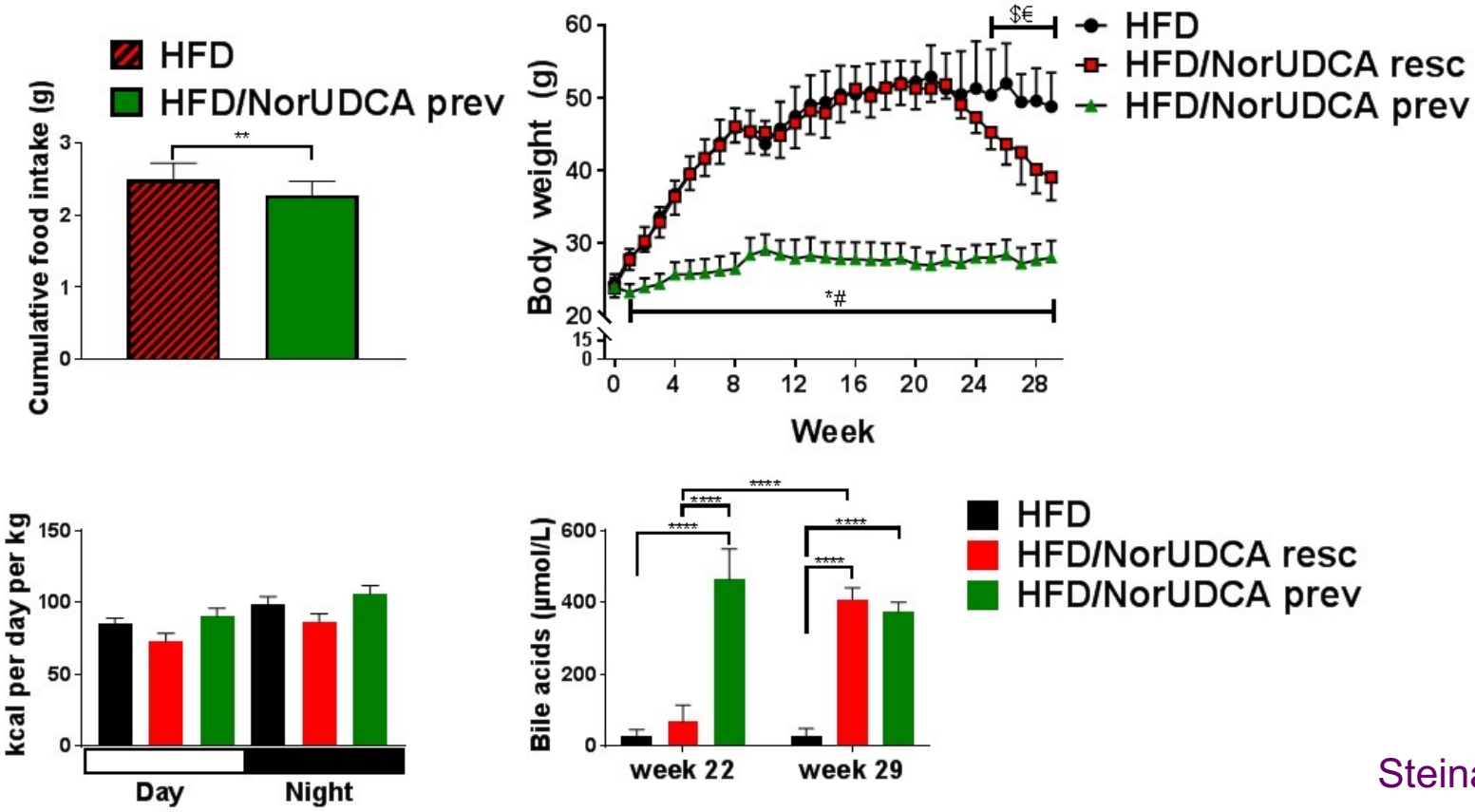
Traussnigg et al. … Trauner, *Lancet Gastro Hep* 2019



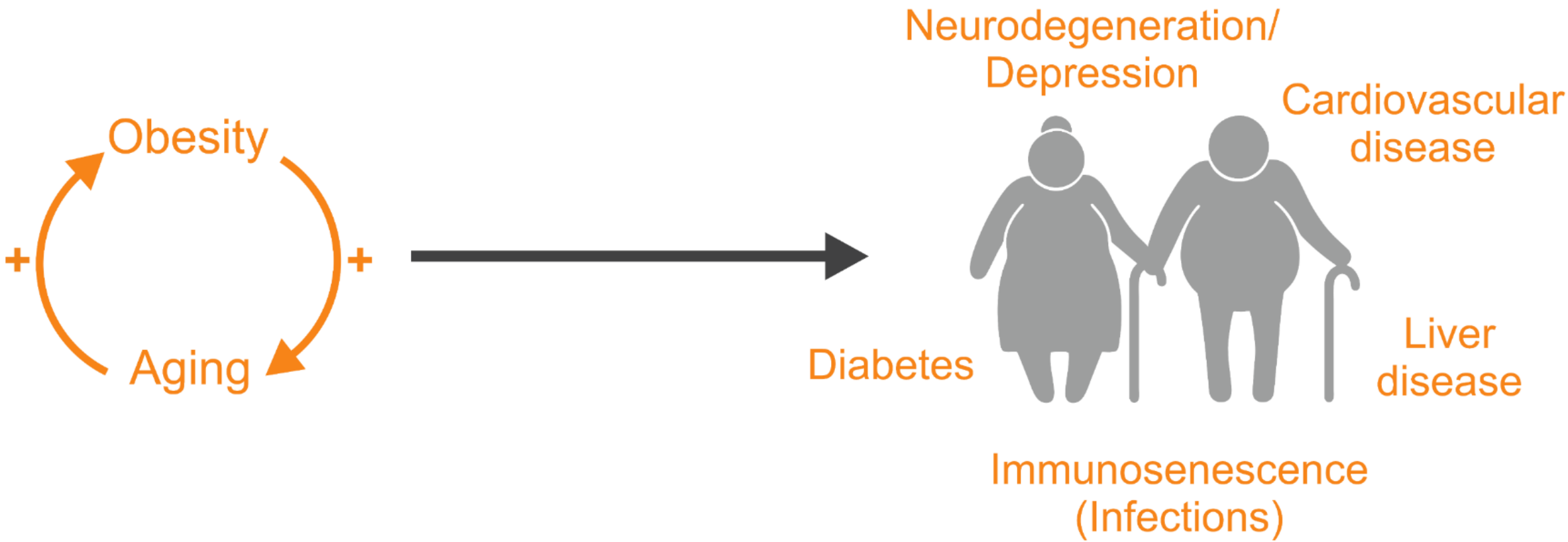
- PSC Phase 3 (NUC-5) fully recruited
- NAFLD Phase 2b (NUT-3 / OASIS) ongoing

*nor*UDCA improves liver injury and metabolic state in mouse models of obesity & hepatic steatosis

HFD : HFD for 29 weeks, since week 22 pair fed to HFD/NorUDCA resc
HFD/NorUDCA resc : HFD for 22 weeks, than HFD + 0.5 % NorUDCA
HFD/NorUDCA prev : HFD + 0.5 % NorUDCA for 29 weeks

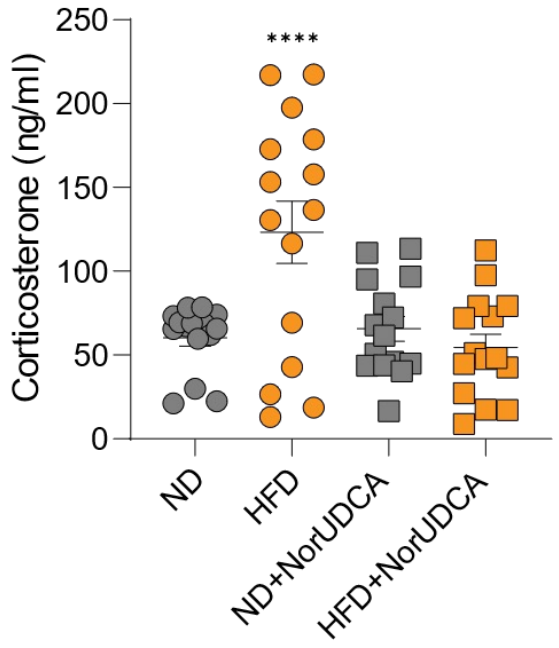


Steinacher et al., *in preparation*

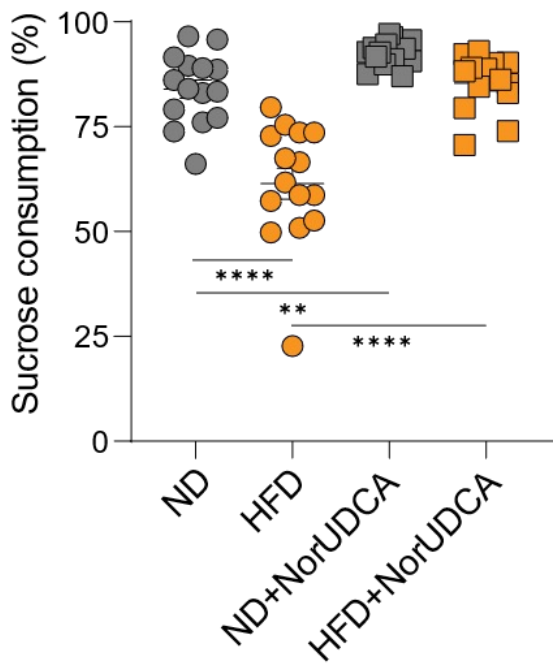

Obesity
+
+
Aging
Neurodegeneration/
Depression
Cardiovascular
disease
Diabetes
Liver
disease
Immunosenescence
(Infections)

*nor*UDCA improves HFD-induced anhedonia and anxiety

Cort Levels

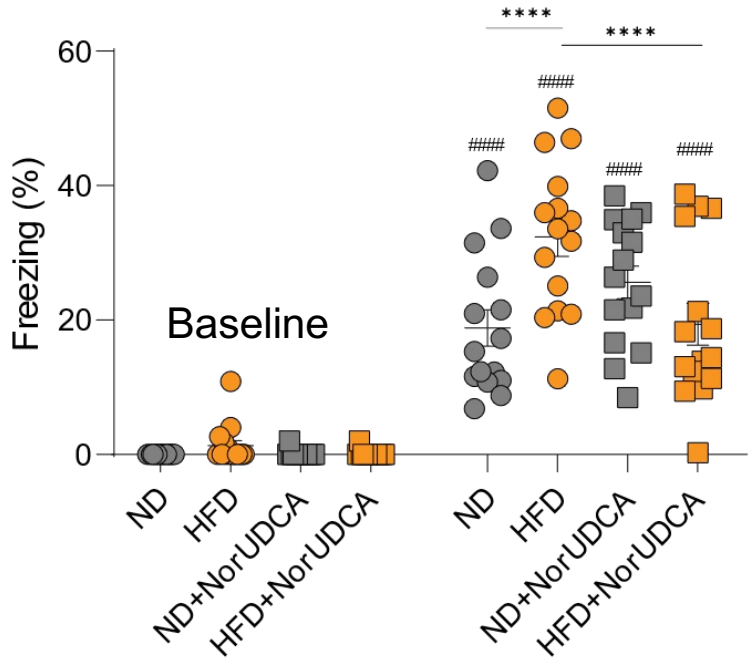


Anhedonia



Anxiety

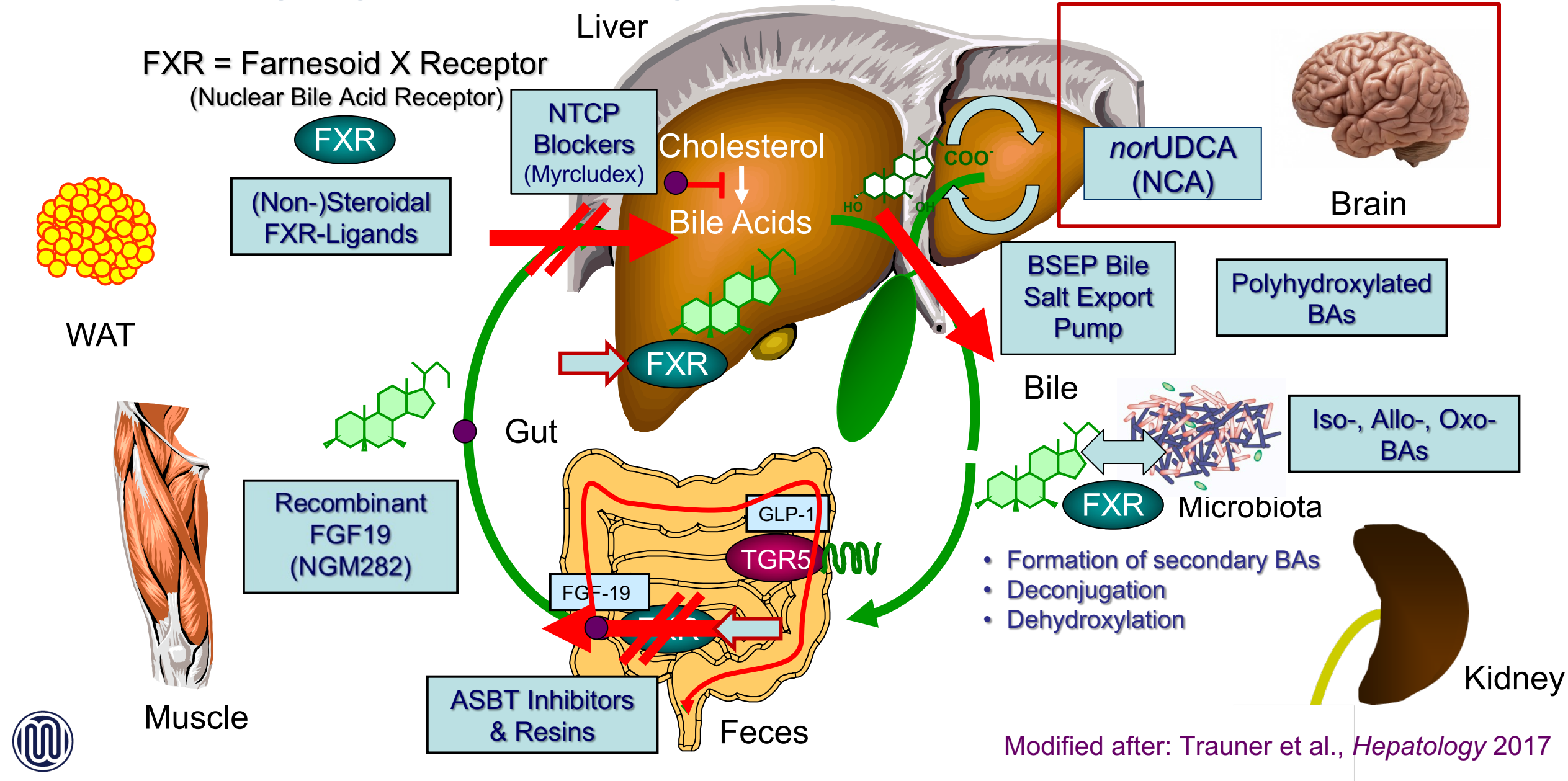
Off-sound freezing as
weight insensitive anxiety marker



Unconjugated BA link gut metabolic states to mood and behavior

Daniel Steinacher and Johannes Griessner
Trauner and Haubensack lab *(submitted)*

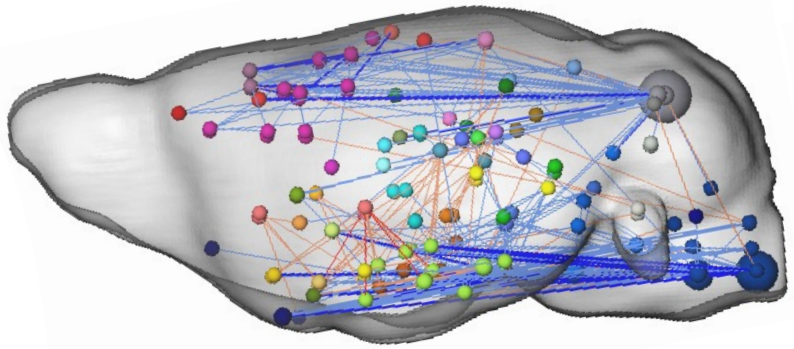
Leveraging bile acid signaling for therapeutic purposes



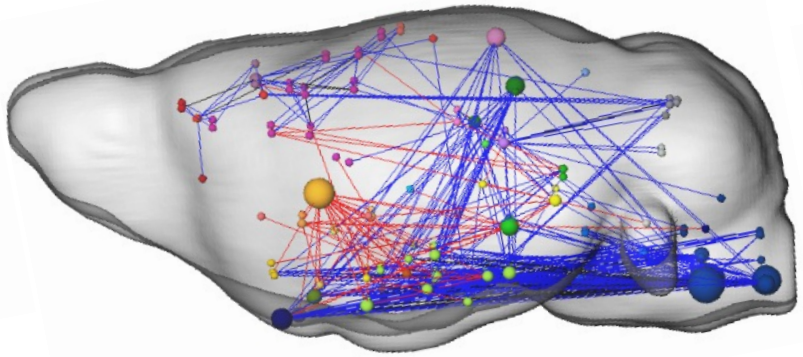
Modified after: Trauner et al., *Hepatology* 2017

HFD and *nor*UDCA modulate affective brain dynamics

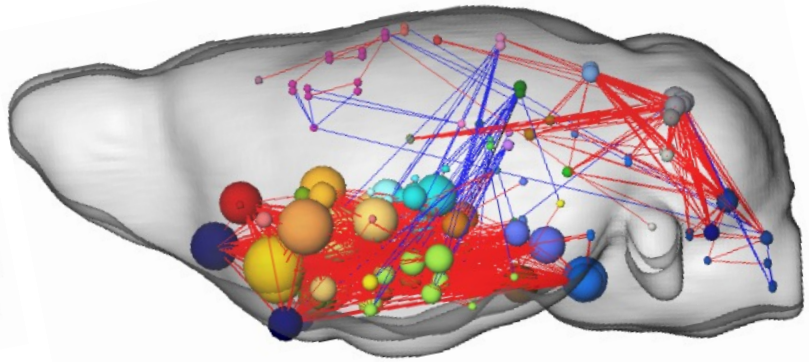
HFD vs. ND

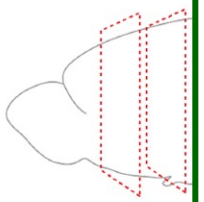


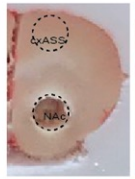
ND+Nor UDCA vs. ND



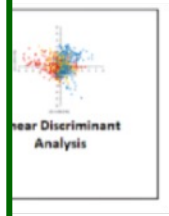
HFD+Nor UDCA vs.HFD





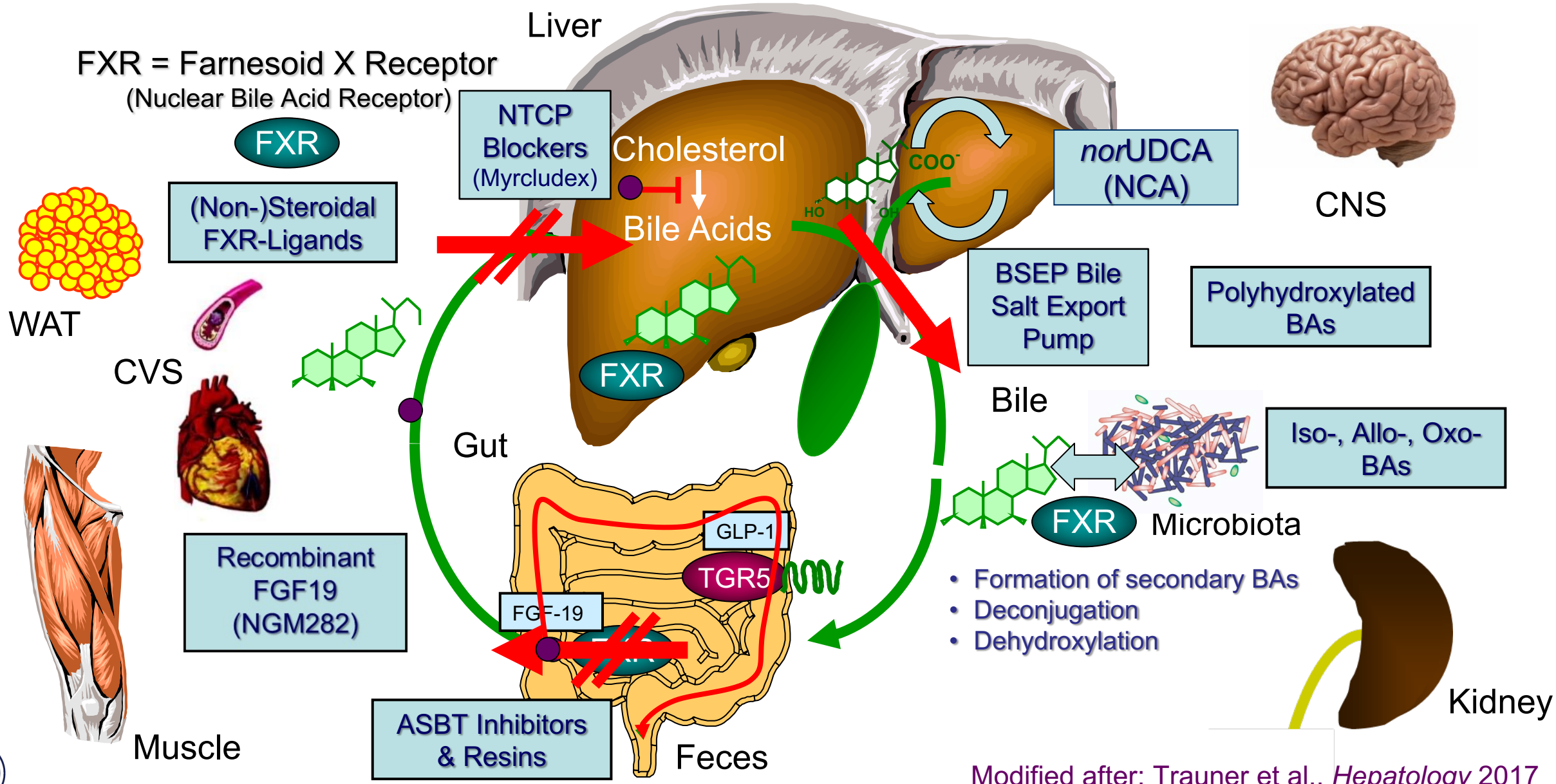


- Focus on sub-network of regions known to be involved in the processing of both **appetitive** and **aversive emotions**
- ND+NorUDCA vs ND suggest positive effects on mood (**reduced** **Hippocampus amygdala interaction**)
- HFD+NorUDCA vs HFD ameliorate negative effects of HFD on mood by reducing Hippocampus amygdala coupling and **increasing** **Amygdala-Tegmantal-basal ganglia** interaction



RsfMRI network analysis in cooperation with Andreas Hess, Erlangen

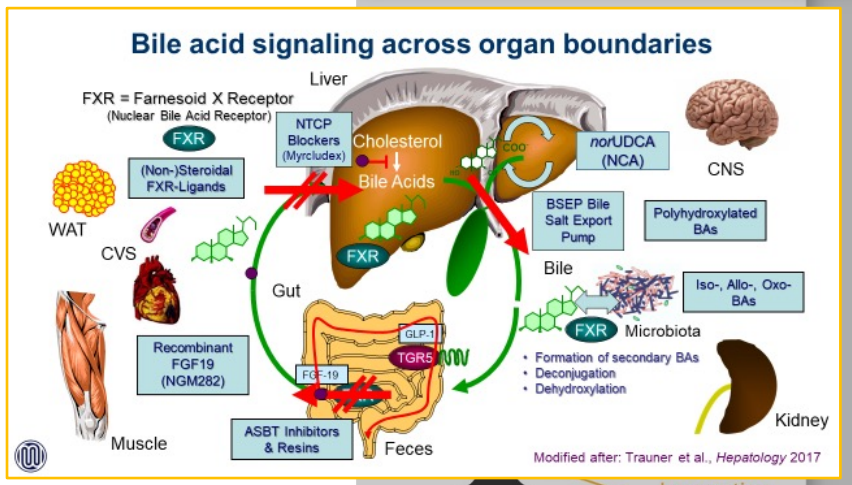
Leveraging bile acid signaling for therapeutic purposes



Modified after: Trauner et al., *Hepatology* 2017

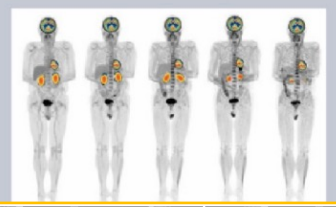
PET imaging of inter-organ communication and networks

Systems signaling | **Reductionism** | **Enablers** | **Systems Medicine**

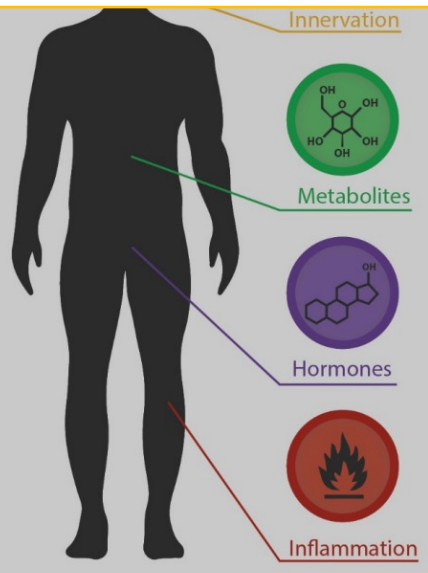


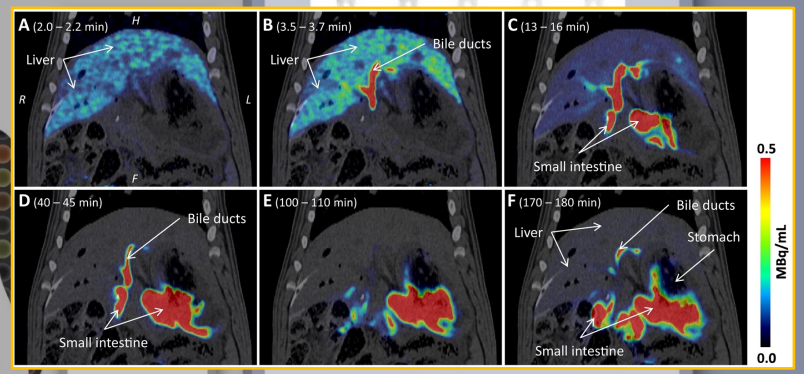
Interpretation of molecular mechanisms at cellular level for cause-effect relationship, including genomics, epigenetics, metabolomics and proteomics.

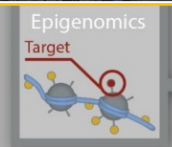
Interrogation of interplay of signaling pathways through dynamic, whole-body PET (DWB-PET).

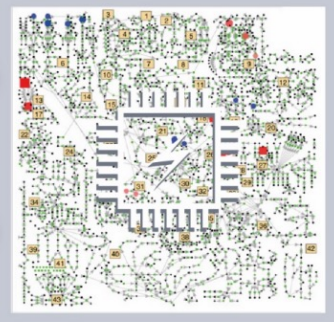


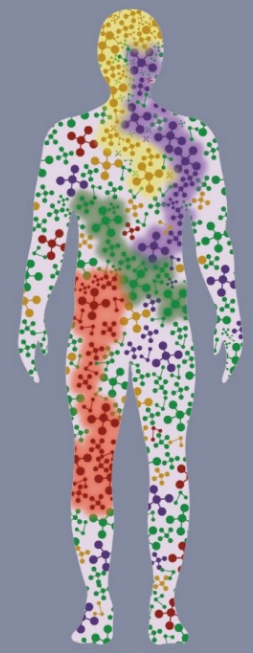
Multi-dimensional integration of systemic signaling pathways enables phenotyping, drug development and advanced patient management
=
Systems Medicine











Hacker, Hicks & Beyer
Eur J Nucl Med Mol Imaging 2020

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MEDICAL UNIVERSITY OF VIENNA

AKH Die menschliche Größe

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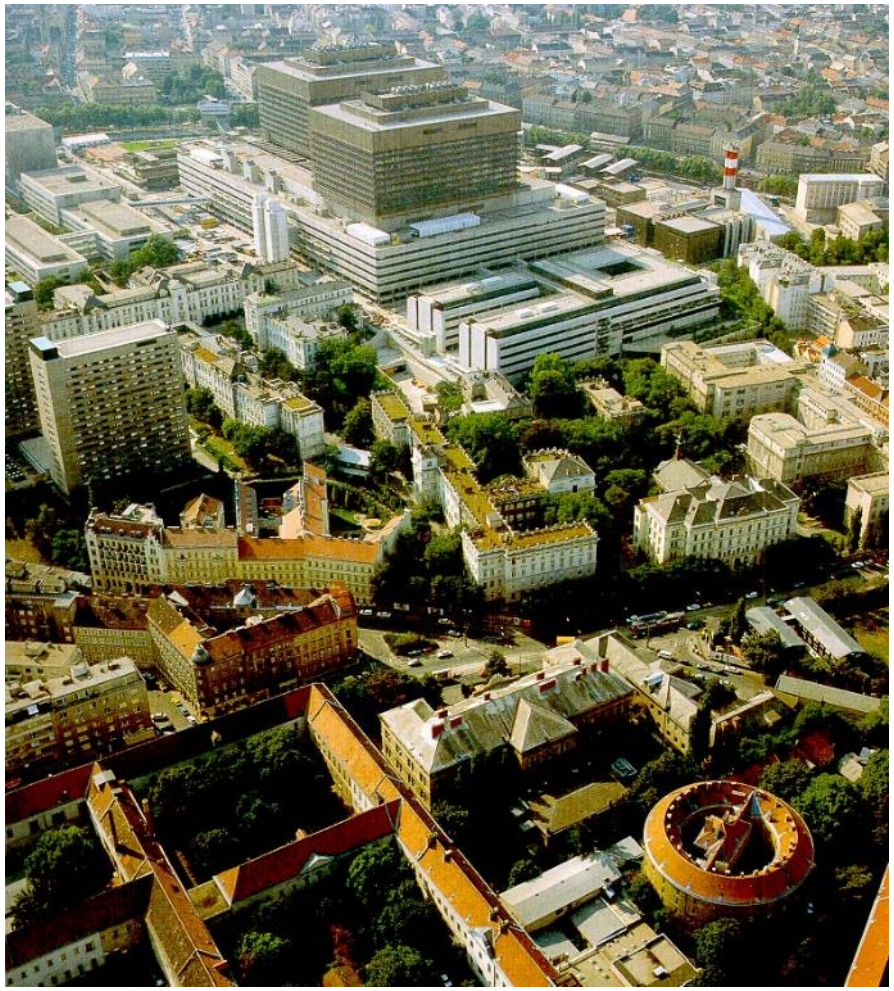

Thank you for your attention!

michael.trauner@meduniwien.ac.at

Funding:

FWF Der Wissenschaftsfonds.

SFB 35

LIPOTOX

SFB Lipid Hydrolysis

WWTF VIENNA SCIENCE AND TECHNOLOGY FUND

flip fatty liver inhibition of progression

SEVENTH FRAMEWORK PROGRAMME