Interactions between Canalicular and Sinusoidal Transporters

Hepatocyte Transporter Network 2019

Les Diablerets, Switzerland, September 02, 2019

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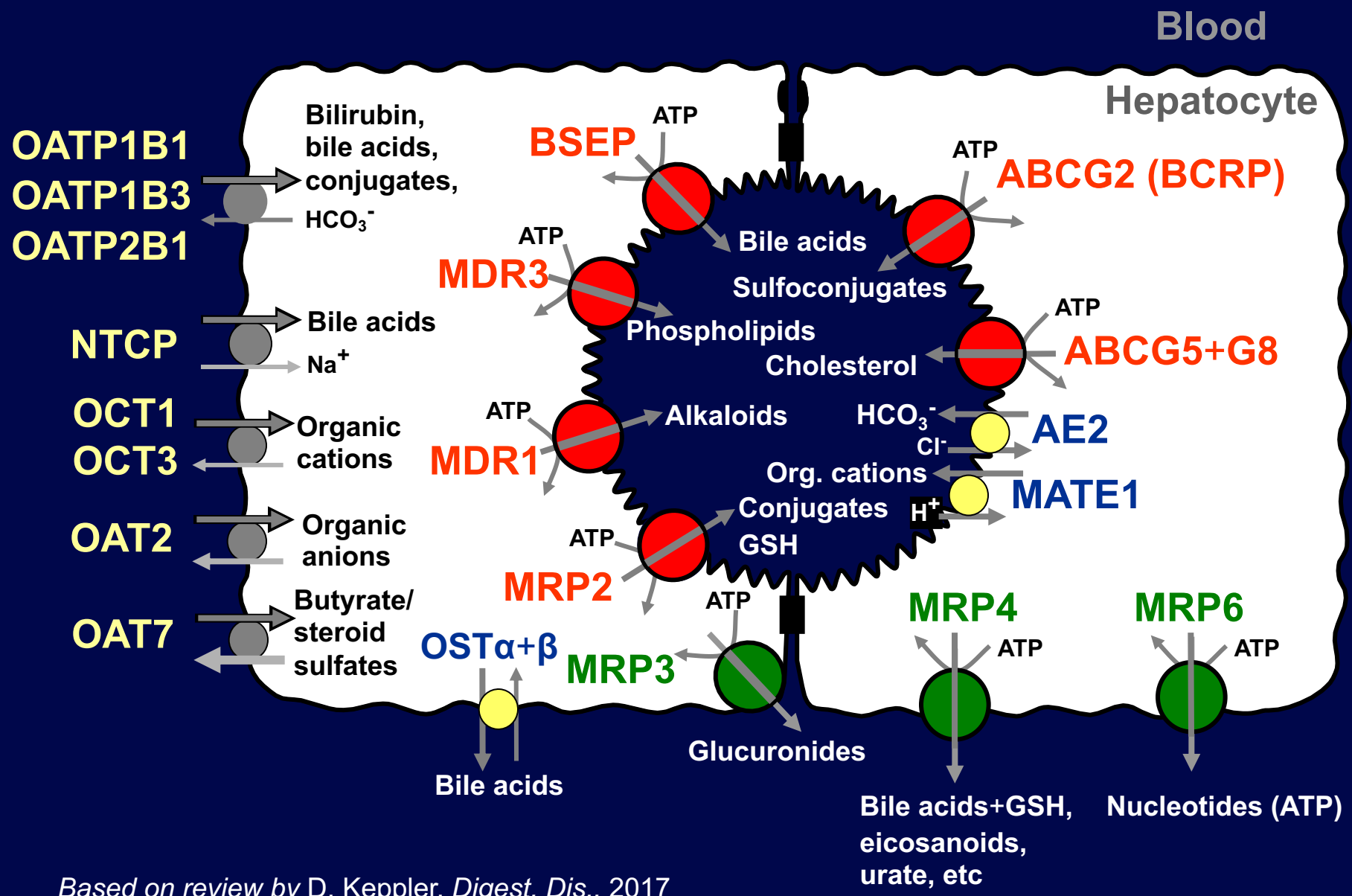
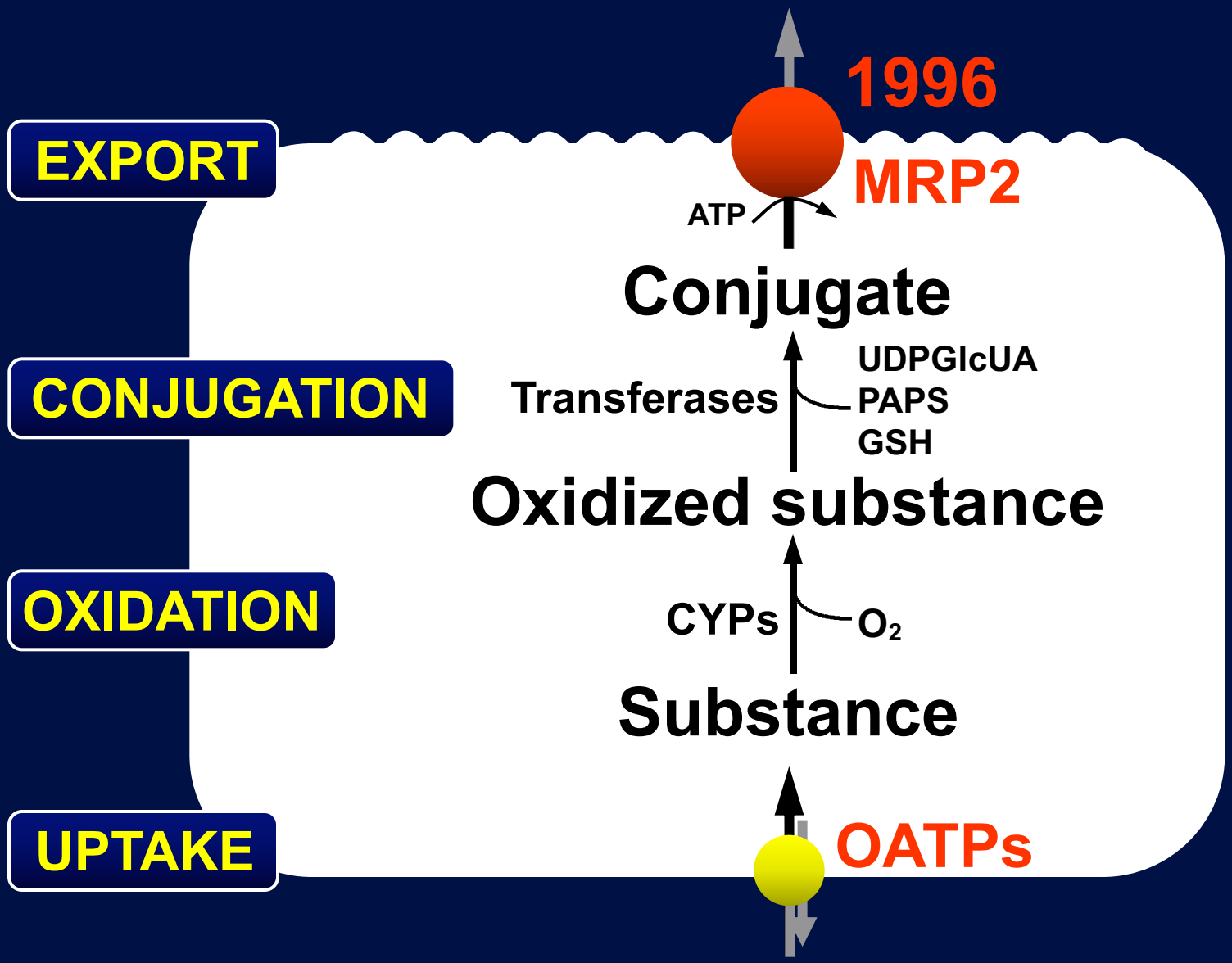
Human Hepatocyte Transporters 2019



Based on review by D. Keppler, *Digest. Dis.*, 2017

Vectorial Transport and Detoxification of Endogenous Substances, Drugs and Drug Conjugates



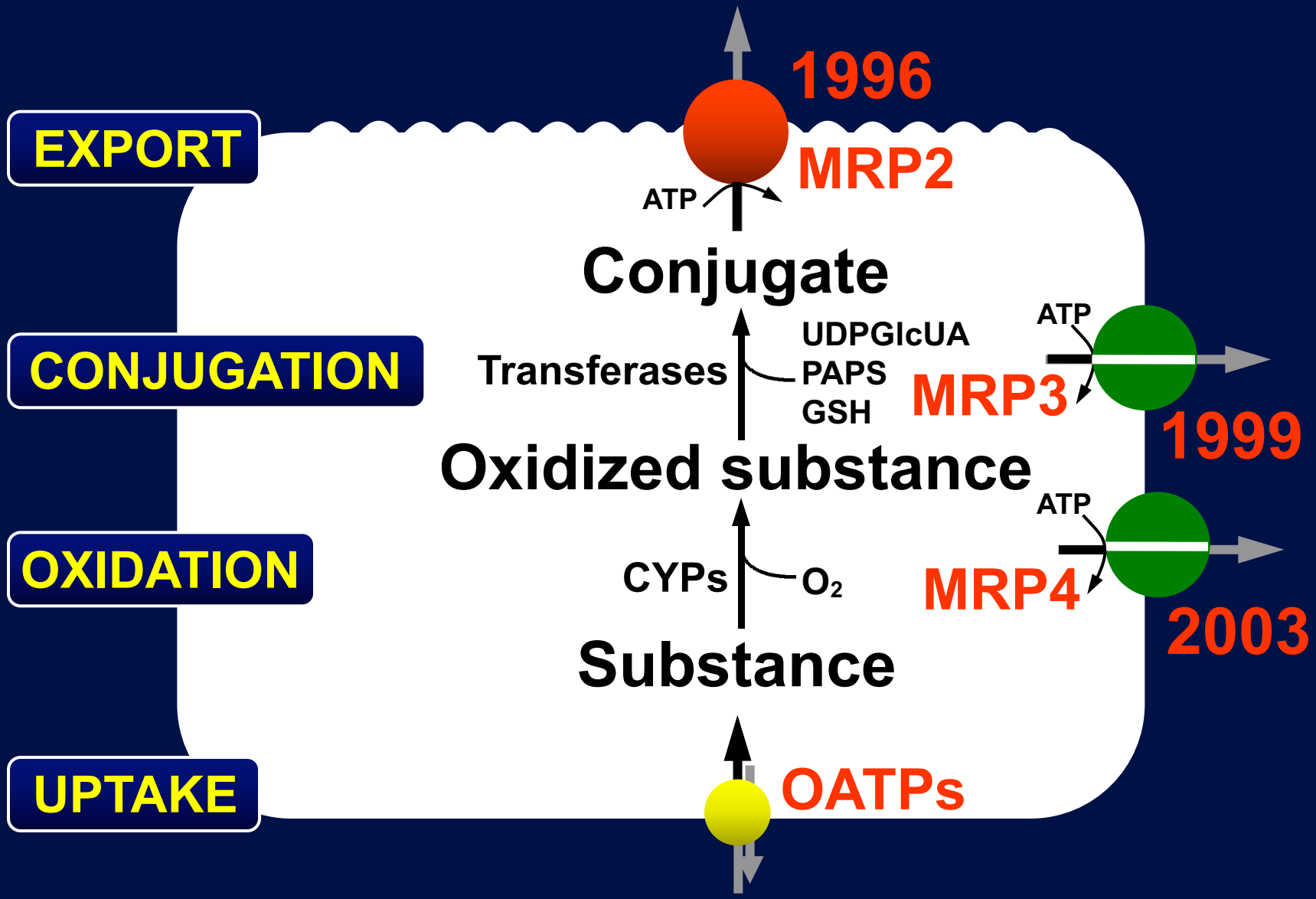
MRP2: Properties

- 190 kDa Glycoprotein in apical membranes:
  - Hepatocyte canalicular membranes
  - Kidney proximal tubules (luminal)
  - Intestinal epithelia (luminal)

- Prototypic, high-affinity substrates:
  - Bilirubin glucuronides
  - Glutathione conjugates (leukotriene C4)

- Genetic variants and impaired function may cause conjugated hyperbilirubinemia and altered pharmacokinetics (⇨ compensation by basolateral efflux)

Vectorial Transport and Basolateral Efflux



MRP3: Some Characteristics

- Widely distributed in polarized cells:
  Hepatocytes, intestinal epithelia, pancreatic epithelia
- Localized to the basolateral plasma membrane
- ATP-dependent transport of anionic conjugates:
  Monoglucuronosyl bilirubin, bisglucuronosyl bilirubin,
  17β-glucuronosyl estradiol, leukotriene C_4
- Compensatory upregulation in hepatocytes
  in MRP2 deficiency and cholestasis

MRP4: Some Characteristics

- Shortest paralog among the 9 human MRP transporters
- Wide tissue distribution:
  Hepatocytes, prostate, vascular endothelia, brain (choroid plexus, capillary endothelia, astrocytes), kidney, platelets, erythrocytes, PMN leukocytes
- Basolateral in hepatocytes, apical in kidney proximal tubules and brain capillary endothelia
- ATP-dependent transport of:
  Bile acids+GSH, LTC_4, LTB_4+GSH, PGE_2, $PGF_{2\alpha}$, TXB_2, cAMP, cGMP, ADP, DHEAS, p-aminohippurate, urate, folate, estradiol 17β-glucuronide

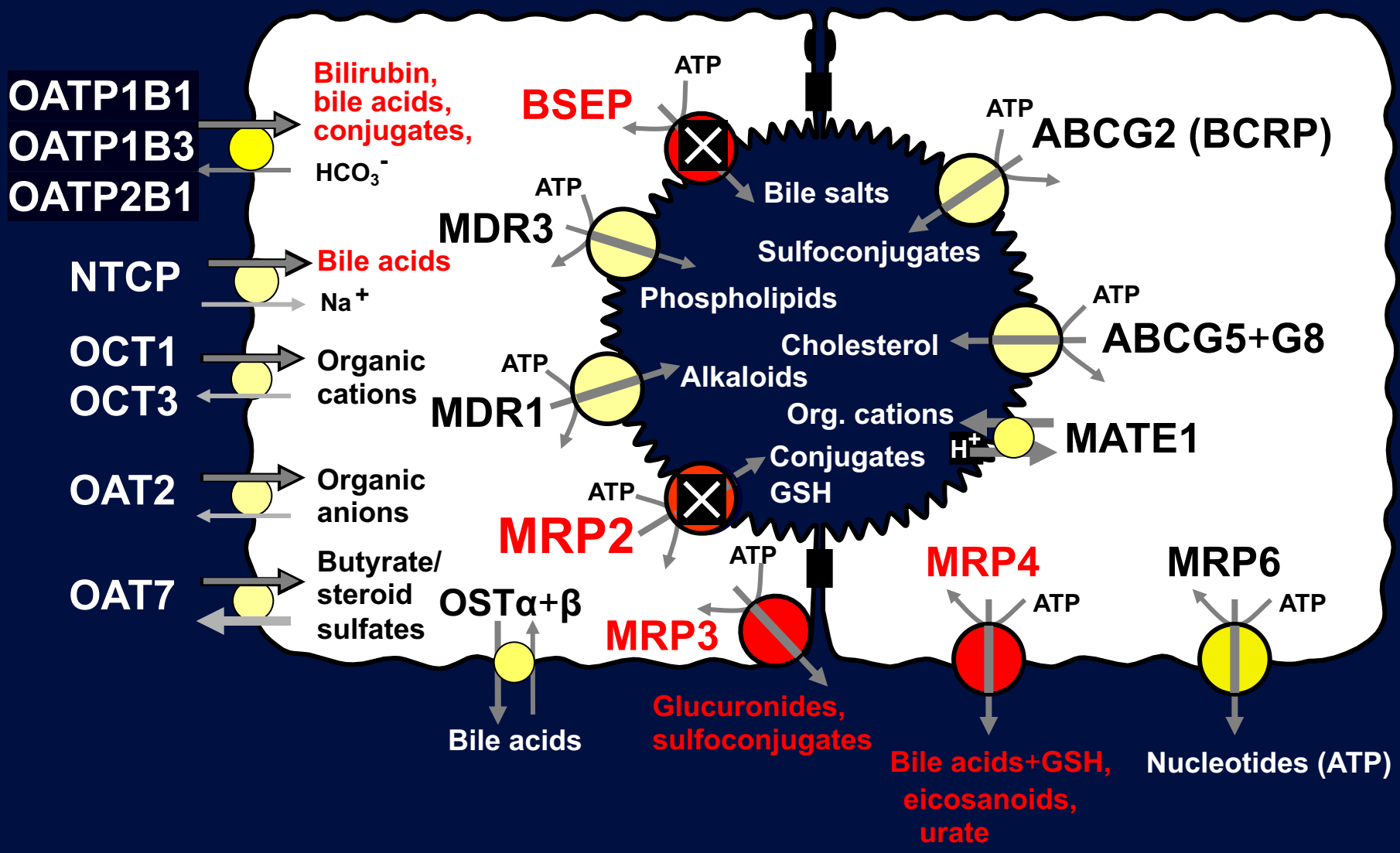
Functions of the Basolateral Efflux Pumps MRP3 and MRP4 of the Human Hepatocyte

- Basolateral efflux pumps serve to maintain the balance when the rate of uptake into hepatocytes exceeds canalicular secretion. This may cause cycling of bile salts and many other conjugates in hepatocytes and along sinusoids
- Basolateral efflux pumps serve as overflow pathways in cholestasis and release sulfoconjugates and glucuronides into blood leading to their renal elimination
- Some basolateral efflux pumps also function in the supply of endogenous substances to extrahepatic tissues, e.g. GSH (together with bile acids) via MRP4

Transport Across Human Hepatocytes

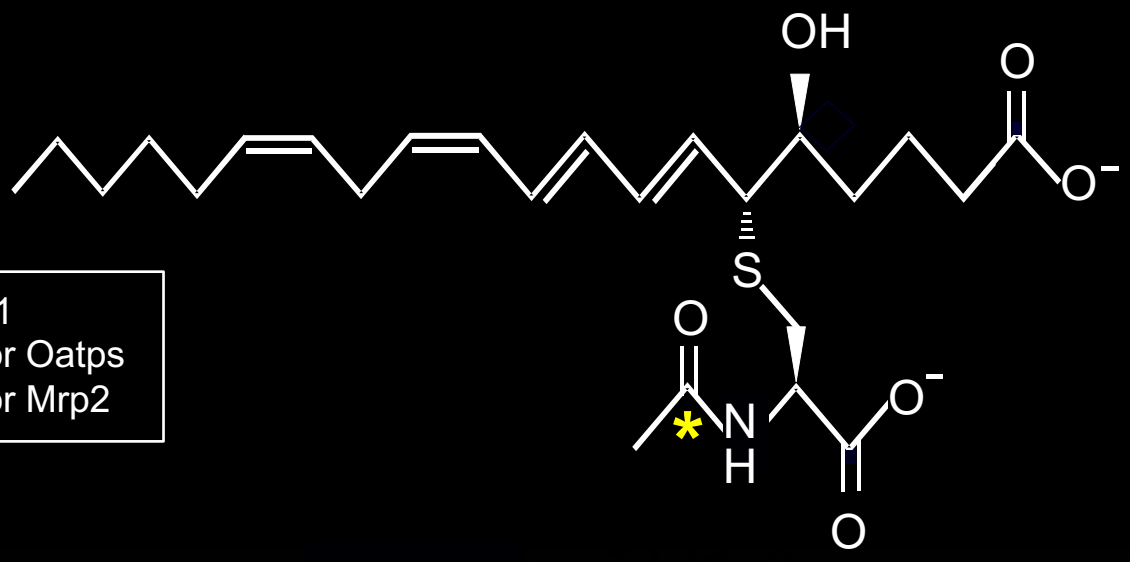
- Deficiency of the export pumps MRP2 and BSEP:

Compensation by basolateral efflux via MRP3 and MRP4

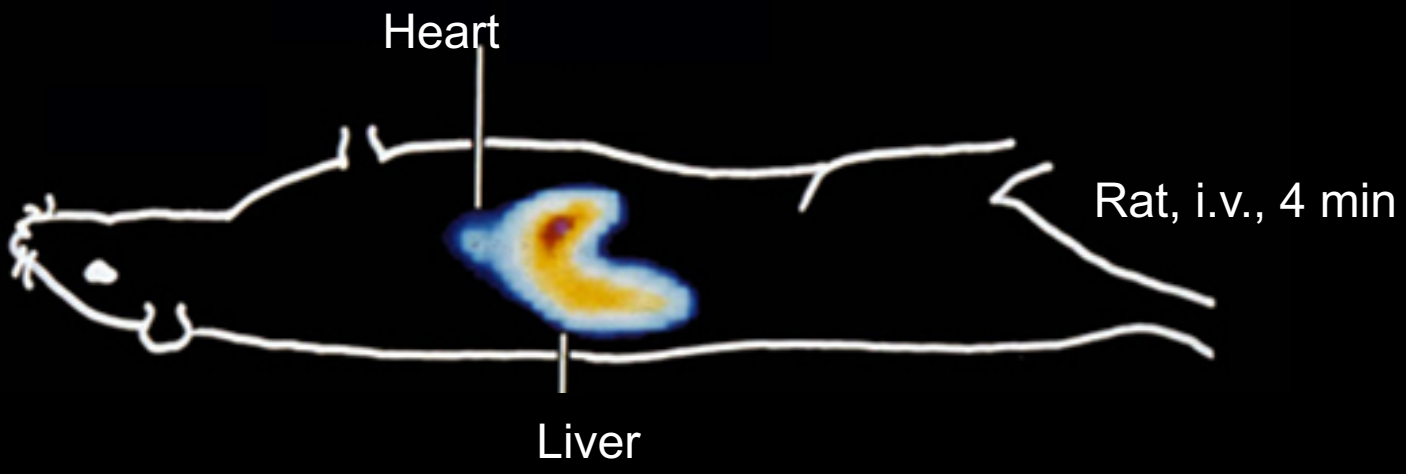


Hepatobiliary Transport Examined by Positron Emission Tomography:

N-[^{11}C]Acetyl-leukotriene E_4

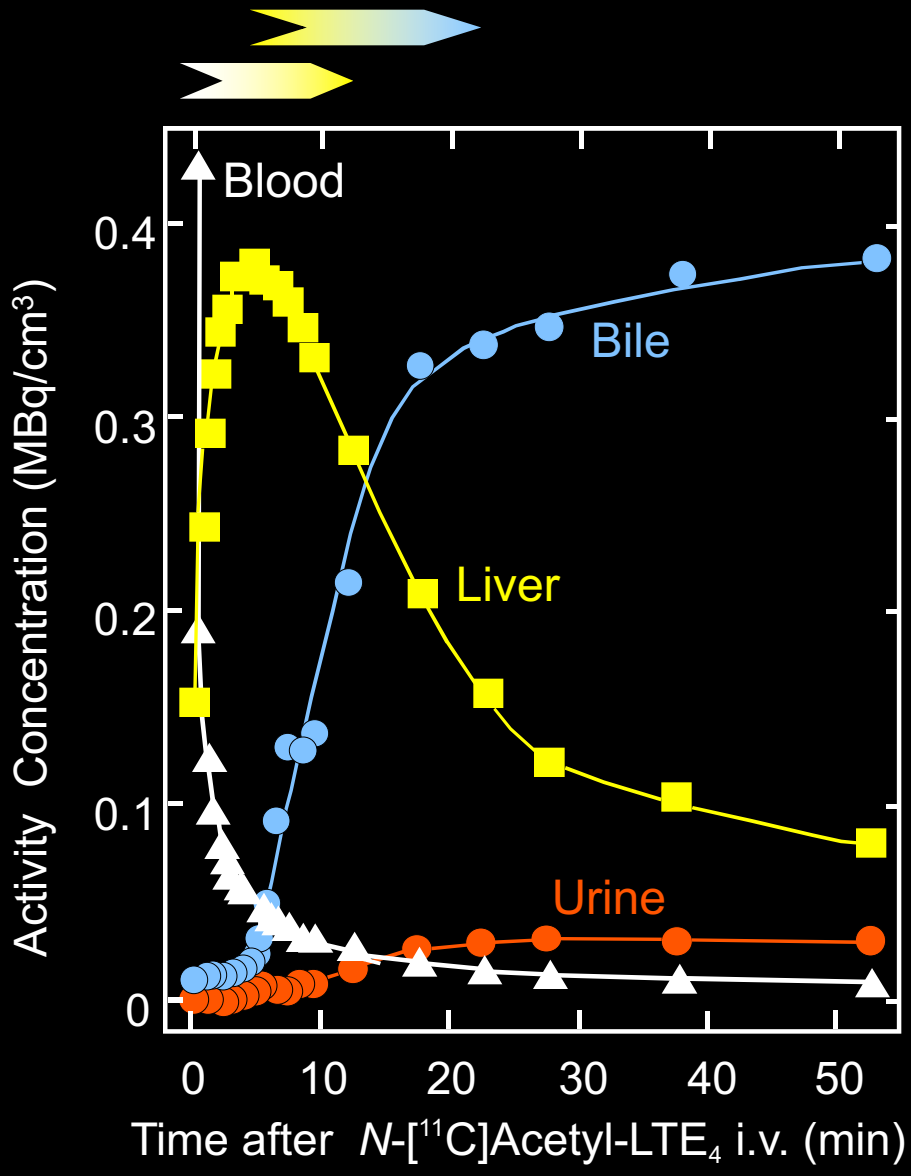


Mol. wt. 481
Substrate for Oatps
Substrate for Mrp2



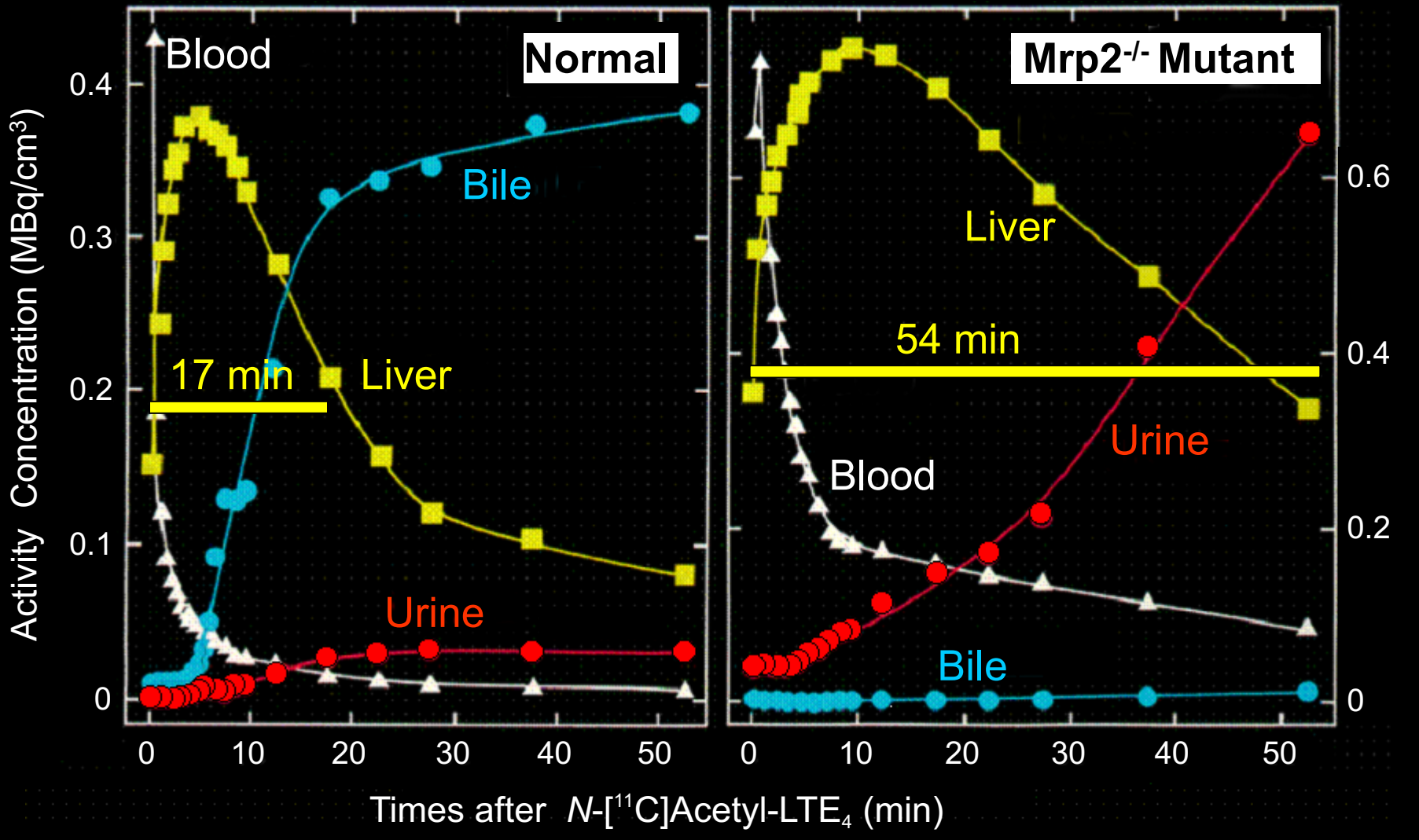
D. Keppler et al., *Ann. N. Y. Acad. Sci.,* 1991

Hepatobiliary Leukotriene Elimination Studied by Positron Emission Tomography in the Rat in Vivo



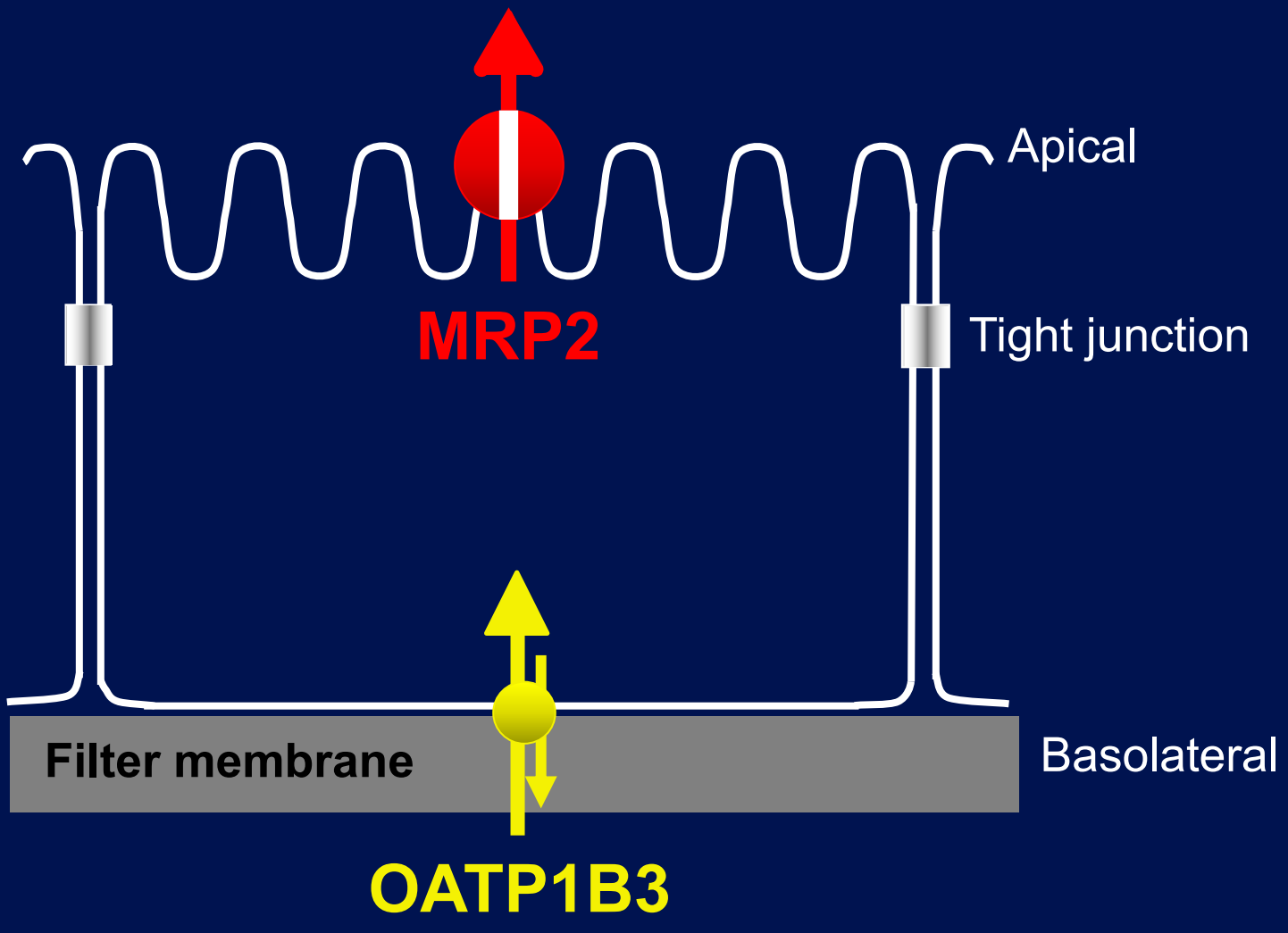
D. Keppler et al., *Ann. N. Y. Acad. Sci.,* 1991

Hepatobiliary and Renal Elimination of Positron-emitting Leukotriene in Normal and Mrp2-deficient Rats



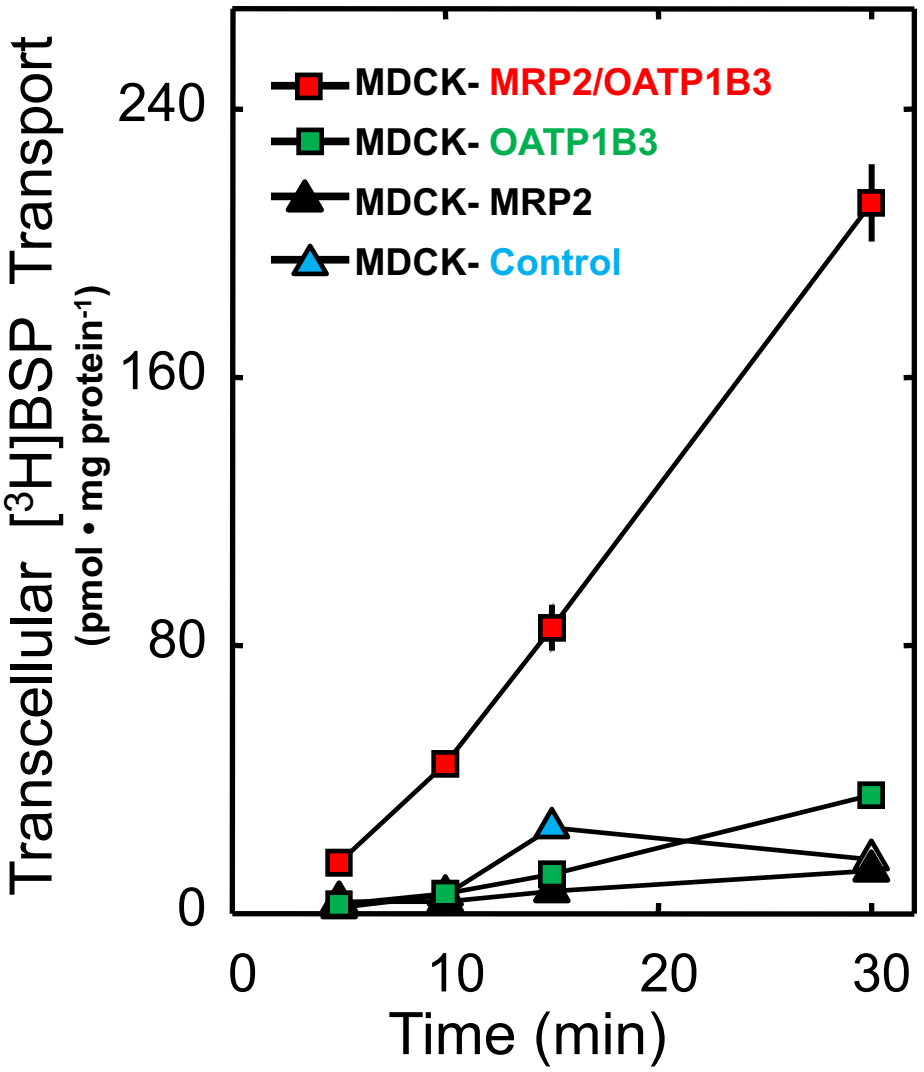
A. Guhlmann,.....D. Keppler, *Hepatology,* 1995

Scheme of Double-transfected MDCKII Cell



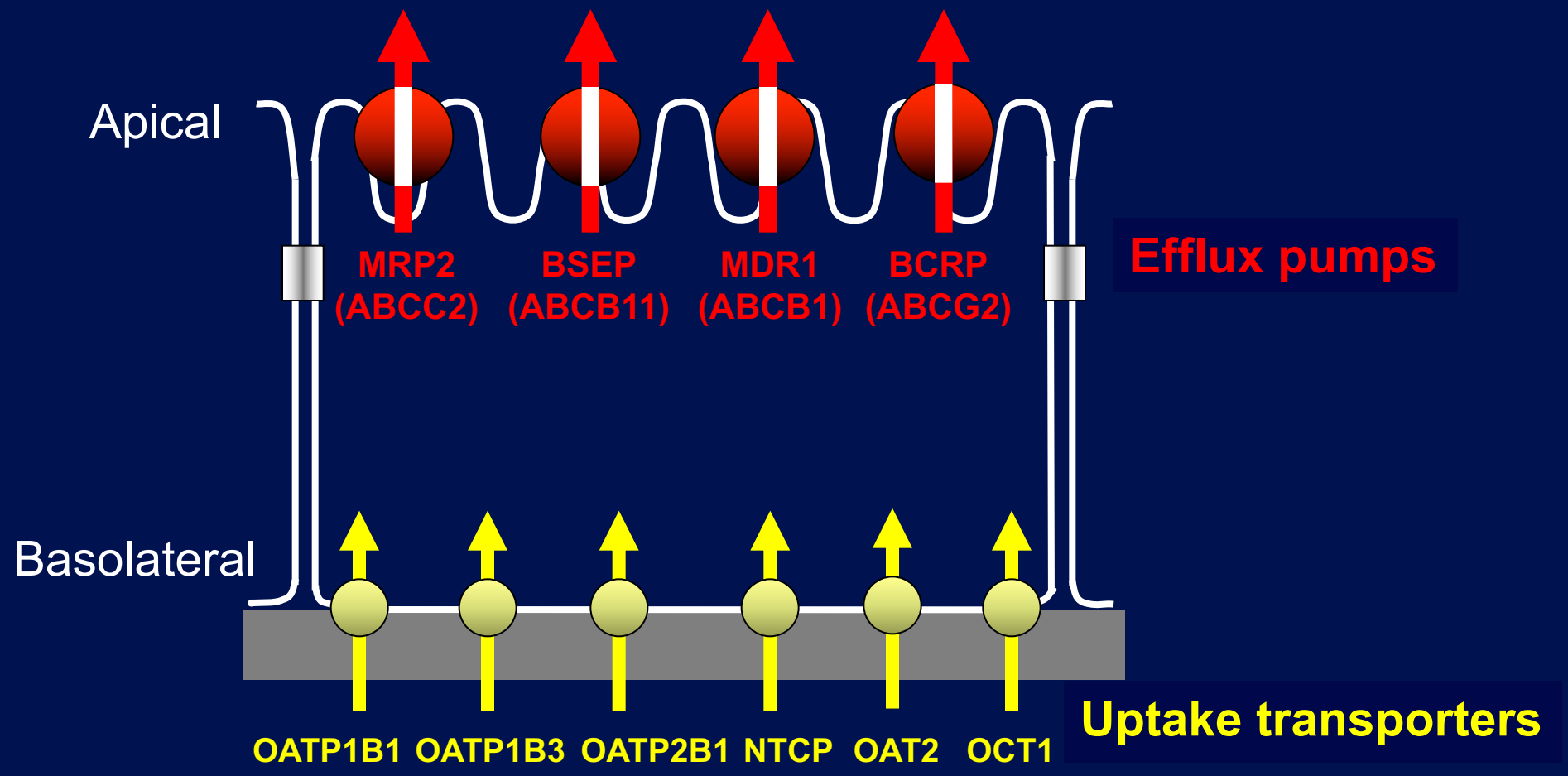
Y. Cui, J. König, D. Keppler, *Mol. Pharmacol*., 2001

Vectorial Basolateral to Apical Transport of Bromosulfophthalein by Double-transfected polarized MDCK Cells



Y. Cui, J. König, D. Keppler, *Mol. Pharmacol*. 2001

Cellular Models for Human Hepatocyte Transporter Combinations Mediating Vectorial Transport



Topics and Co-workers

ATP-dependent transport across canalicular membrane
Toshi Ishikawa, Michael Müller, Inka Leier

MRP2, MRP3, MRP4: Cloning, function, localization
Markus Büchler, Jörg König, Manuela Brom, Anne Nies, Yunhai Cui, Gabi Jedlitschky, Daniel Rost, Maria Rius

Basolateral export by MRP3 and MRP4
Maria Rius, Yunhai Cui, Jörg König, Markus Donner

Hepatobiliary elimination by PET with *N*-[^{11}C]acetyl-LTE$_4$
Albrecht Guhlmann, Franz Oberdorfer

Vectorial transport by double-transfected cells
Yunhai Cui, Jörg König, Katrin Letschert, Anne Nies

Thank you for your attention.

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