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FROM DISCOVERY THROUGH CLINICAL SUPPORT

Transporters of Emerging Importance in Drug Development: Beyond the Guidance Documents

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Outline

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1. Regulatory view of in vitro transporter studies

2. The ECCS: Prediction of rate-determining step in ADCE

3. Evidence for emerging transporters:
   - OCT1
   - OATP2B1
   - OAT2

4. Unusual routes of administration

Current Regulatory view of in vitro *transporter studies*

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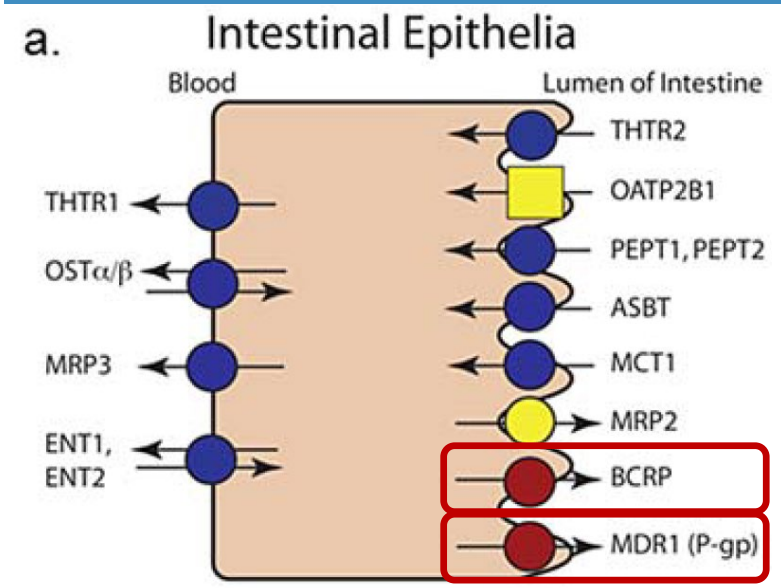

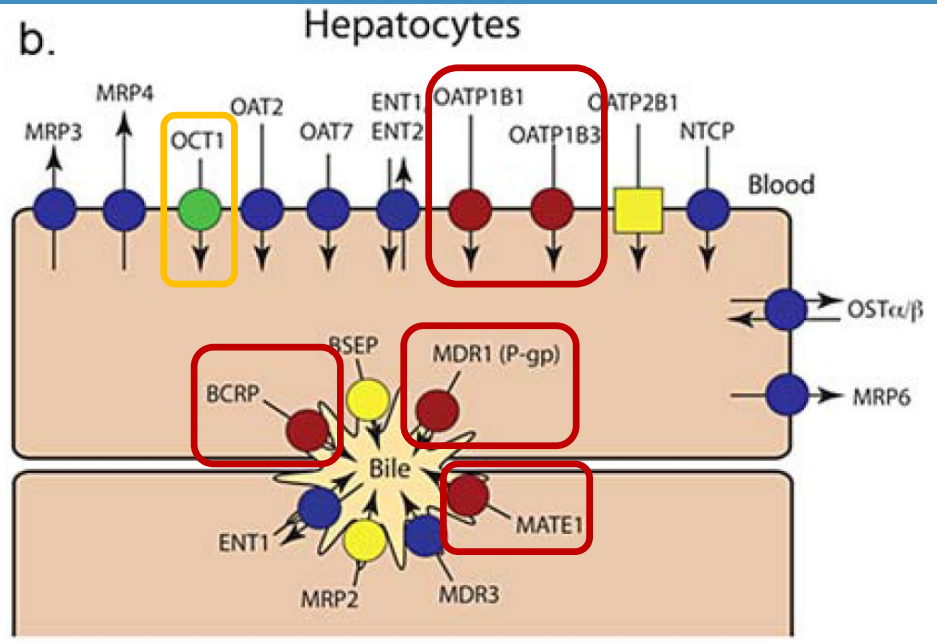

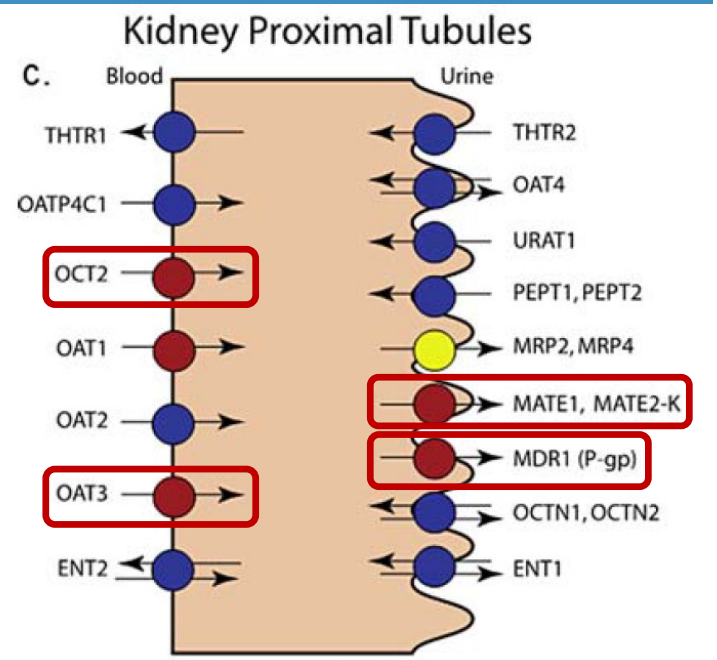

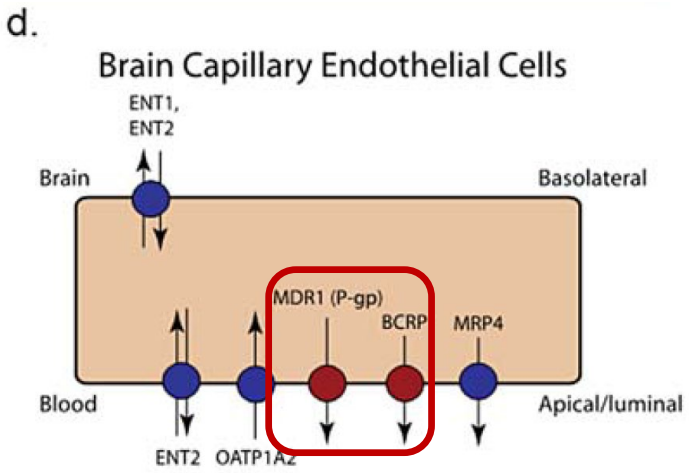

Inhibition for all in red (FDA & PMDA); **orange (EMA)**

Substrate potential:

P-gp and BCRP (all orally administered drugs)

Hepatic uptake: If hepatic metabolism or biliary secretion ≥25%

Renal: If active renal secretion ≥25% of total clearance

"Choice of transporters investigated should be driven by scientific evidence . . ."

Figures from Zamek-Gliszczynski et al. ITC3 (2018) *CPT* **104:**890-899

Timing of in vitro *studies in the FDA guidance*

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- Timing - Work backwards from FDA clinical guidance
  - When are clinical DDI results needed?
  - Before administration to patients:
  - "collect enough DDI information to prevent patients from being unnecessarily excluded"
  - "Inadequate studies of DDIs can hinder the FDA's ability to determine the benefits and risks of [a] . . . drug and . . . result in restrictive labeling, [PMRs or PMCs], and/or delayed approval"

Choice of transporters investigated driven by scientific evidence

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- ITC3 Recommendations based on the evidence (May 2018)
  - Hepatic **OCT1**: Prospective evaluation (inhibition and substrate potential)
  - Intestinal **OATP2B1**: Retrospective evaluation in "specific instances of DDIs or disposition otherwise unexplained by more common mechanisms"
  - MRP2 and 4 and BSEP: "*previously* recommended for retrospective mechanistic explanation of clinical observations"
- Honorable mention: OATP1A2, OATP4C1, OAT2, ASBT, OSTα/β, NTCP, MDR3 "evidence is lacking for specific drug development recommendations"

Zamek-Gliszczynski et al. ITC3 (2018) *CPT* **104:**890-899

Extended Clearance Classification System (ECCS)

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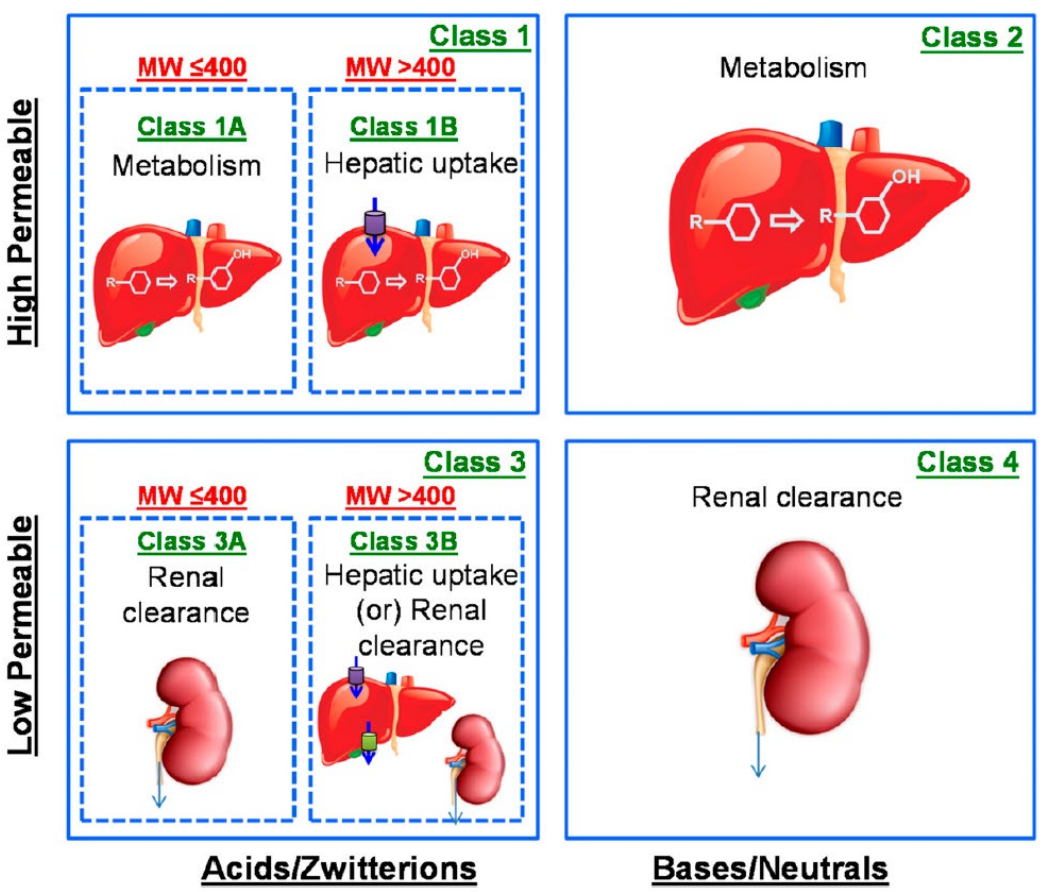
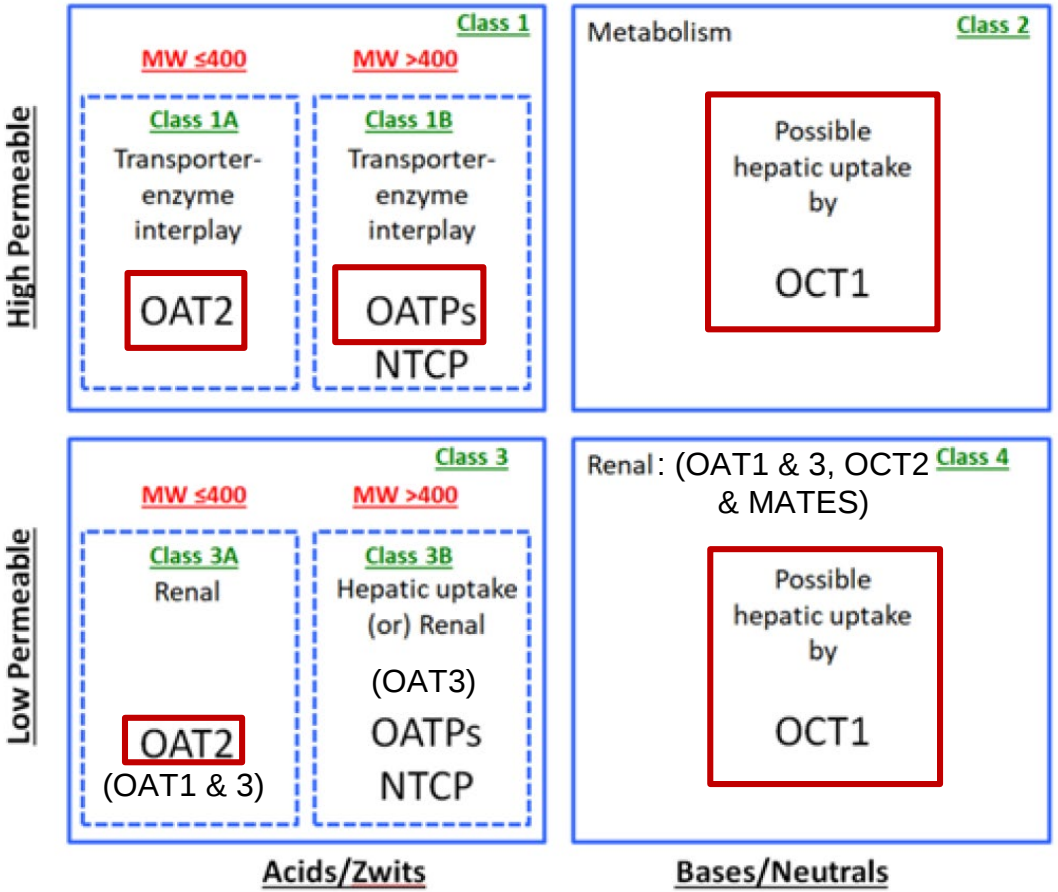
- Goals include earlier prediction of rate-determining step in human absorption, distribution, clearance and elimination (ADCE)

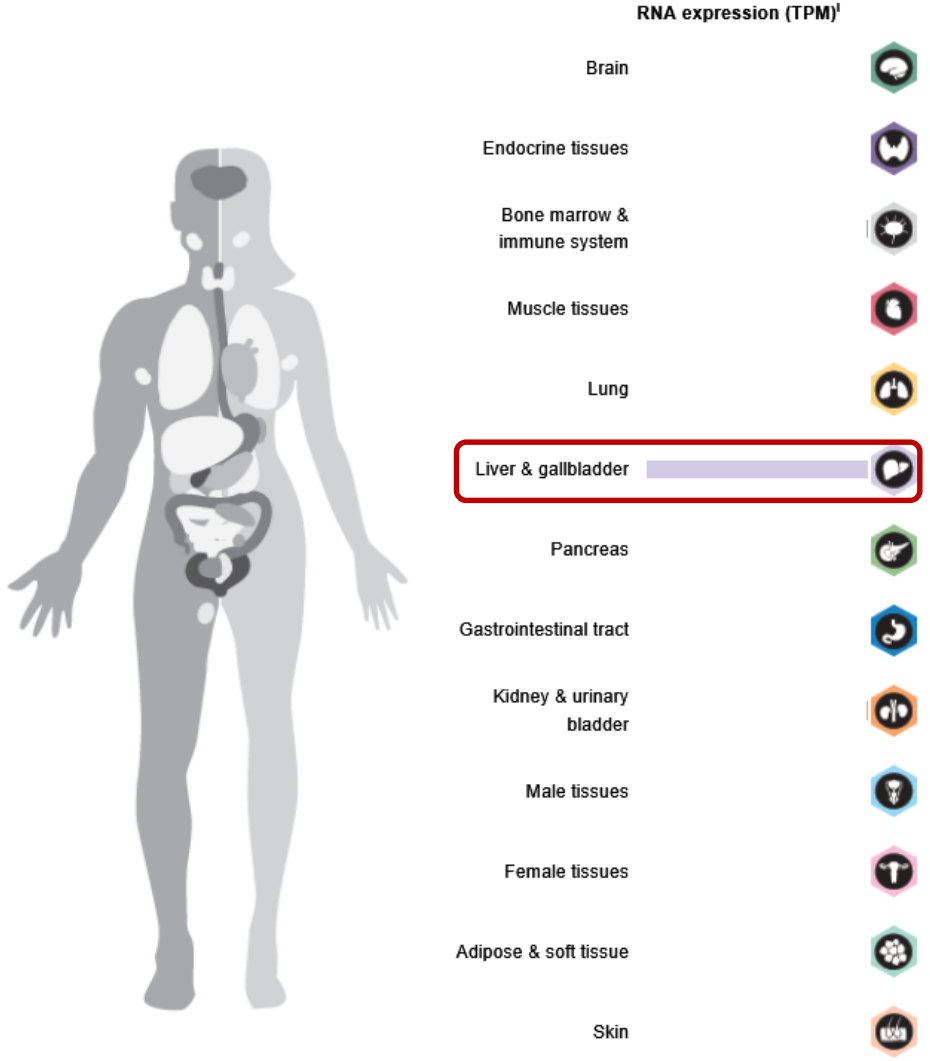




El-Kattan and Varma (2018) *DMD* **46**:729; Varma … El-Kattan (2015) *Pharm Res* **32**:3785; Bi … Rodrigues *JPET* 4/11/19

OCT1 (SLC22A1) basics

- Most highly expressed OCT in human liver
- Sinusoidal
- Facilitative
- Highly polymorphic
- Transports weak bases:
  - Metformin
  - Fenoterol
  - Tropisetron and ondansetron
  - Ranitidine
  - O-Desmethyltramadol
  - Sumatriptan & other triptans



The Human Protein Atlas; Zamek-Gliszczynski et al. ITC3 (2018) *CPT* **104:**890-899

OCT1 (SLC22A1): Impacts of polymorphism on sumatriptan

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OCT1 Mediates Hepatic Uptake of Sumatriptan and Loss-of-Function *OCT1* Polymorphisms Affect Sumatriptan Pharmacokinetics

J Matthaei[1], D Kuron[1], F Faltraco[1], T Knoch[1], JN Dos Santos Pereira[1], M Abu Abed[1], T Prukop[1], J Brockmöller[1] and MV Tzvetkov[1]

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CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 99 NUMBER 6 | JUNE 2016

"OCT1 is a high-capacity transporter of sumatriptan and polymorphisms causing OCT1 deficiency have similar effects on sumatriptan pharmacokinetics as those observed in subjects with liver impairment."

OCT1 (SLC22A1): impacts of polymorphisms

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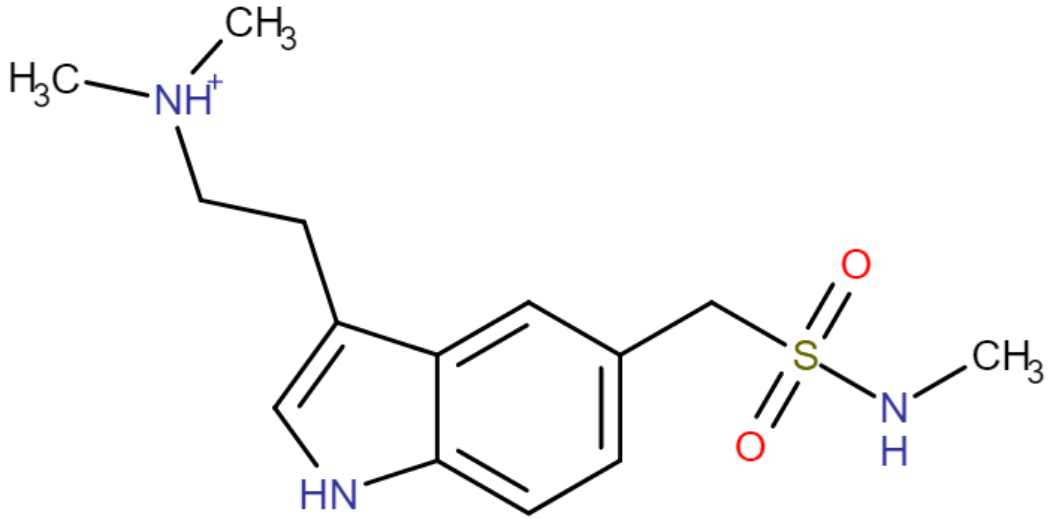
5 common OCT1 polymorphisms in ~9% of Caucasians:

- Strong, or nearly complete decrease in activity (OCT*2, *3, *4, *5 and *6)
- Poor transporters have increased plasma concentrations of:
  - Tropisetron: C_{max} ↑ 377%
  - Sumatriptan: AUC ↑ 215% (similar to hepatic impairment)
  - O-desmethyltramadol: AUC ↑ 74% (from tramadol)
  - Morphine: AUC ↑ 70% (from codeine)
  - Fenoterol: AUC ↑ 92%
  - Others may include imatinib, lamotrigine

Sumatriptan basics

- First triptan on the market, still most prescribed
- Low bioavailability (<15%)
- Predominantly metabolized by MAO-A, mainly in the liver
- $LogD_{7.4}$ = -1.3
- >95% cationic in blood
- $t_{1/2}$ = 2.5 hrs
- Only 3% unchanged
- Excretion of metabolites:
  - 60% urine
  - 40% feces



Matthaei … Tzvetkov (2016) *CPT* **99**:633

OCT1-mediated transport of sumatriptan

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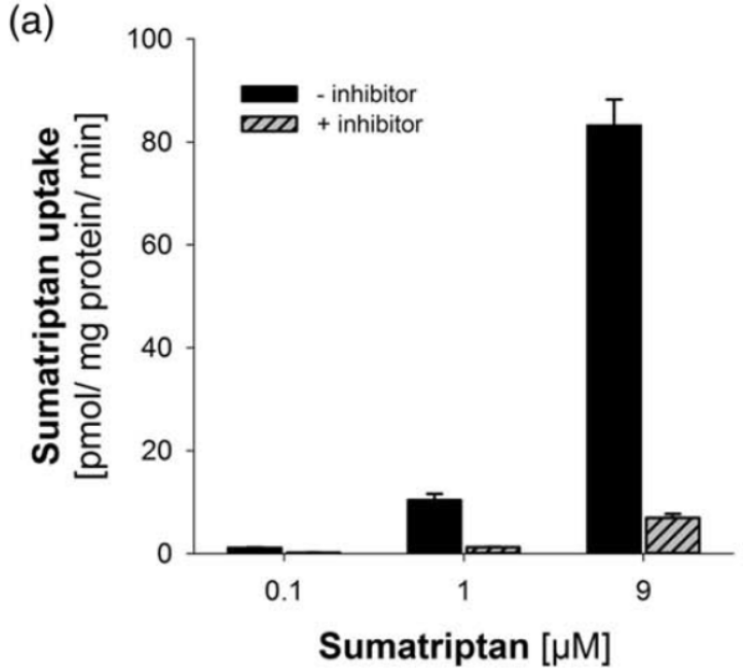
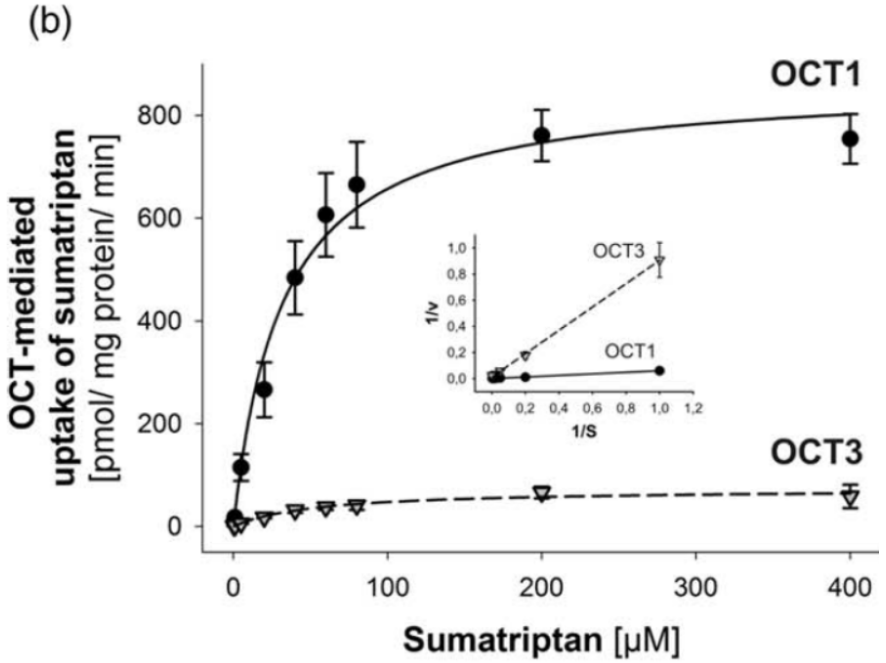
MPP+ inhibition of sumatriptan uptake in human hepatocytes



Sumatriptan uptake by OCT1 vs OCT3 uptake in HEK-293 cells



K_m = 55 µM

V_{max} = 977 pmol/mg protein/min

CL_{int} 6-fold that reported for metformin

Matthaei … Tzvetkov (2016) *CPT* **99**:633

Clinical effect of OCT1 poor transport on sumatriptan

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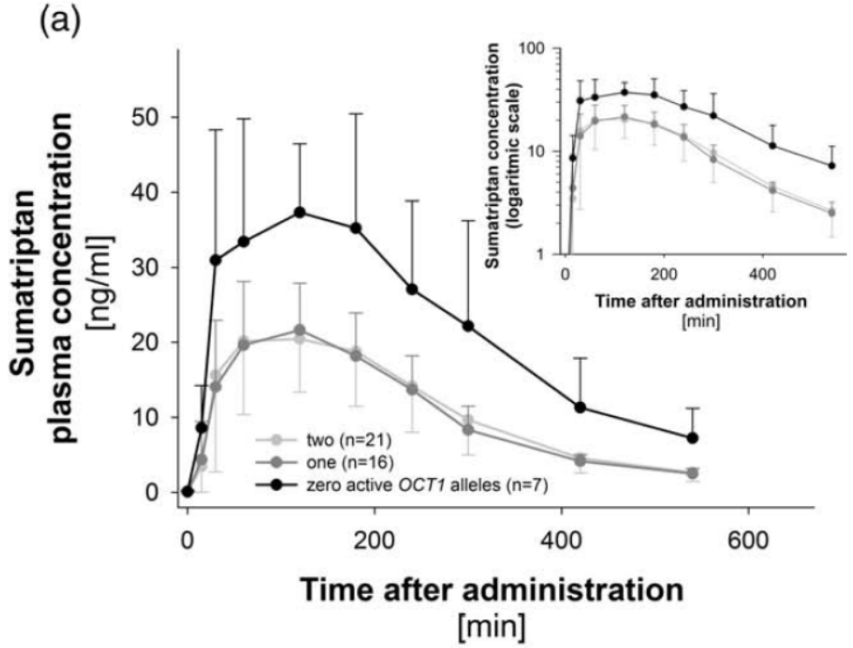
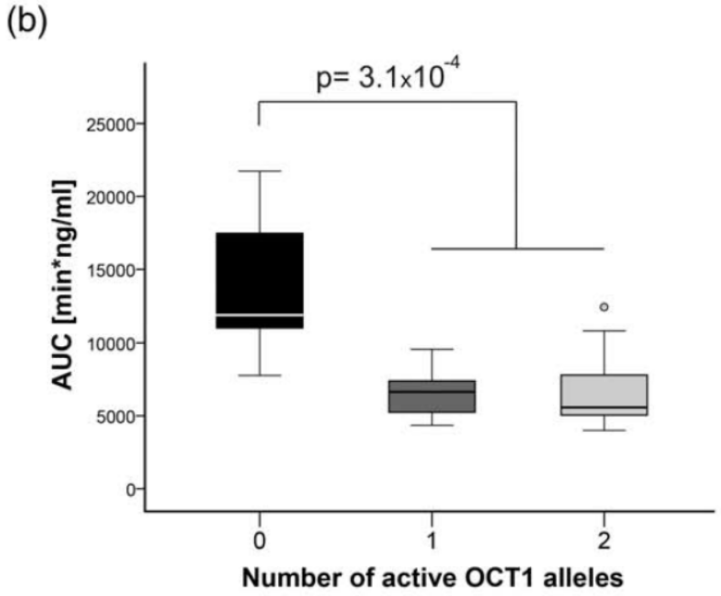
Effects of loss of OCT1 function on human sumatriptan PK



Effects of loss of OCT1 function on human sumatriptan PK



- 53% reduction in total oral clearance – OCT1 “controls” access to hepatic MAO-A
- Similar to 50% reduction of the extrarenal clearance of sumatriptan in Oct1/Oct2 knockout mice

Matthaei … Tzvetkov (2016) *CPT* **99**:633

OCT1-mediated transport of other triptans

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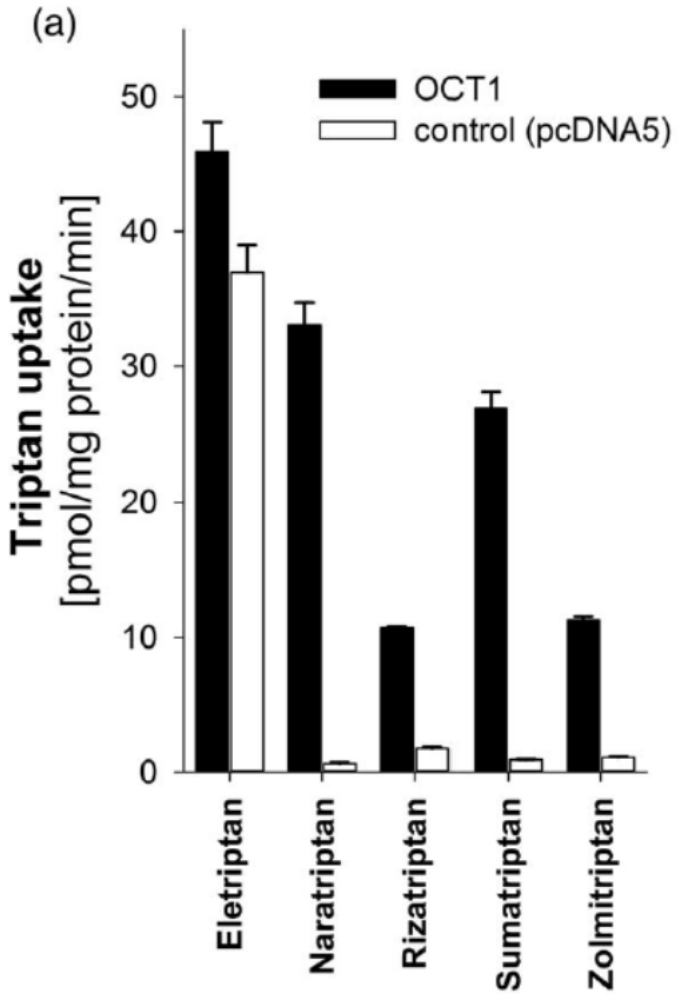
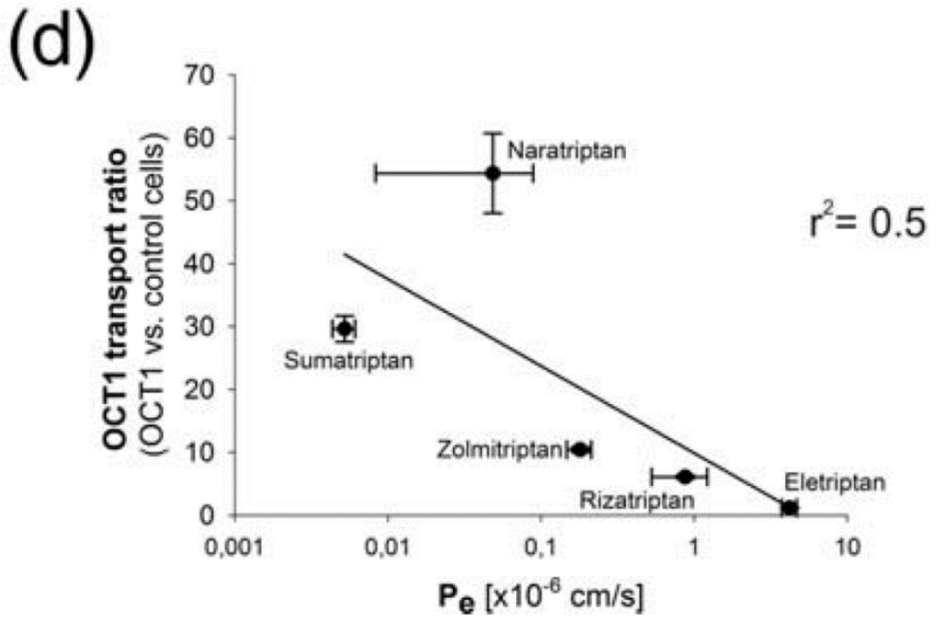
OCT-mediated uptake of triptans



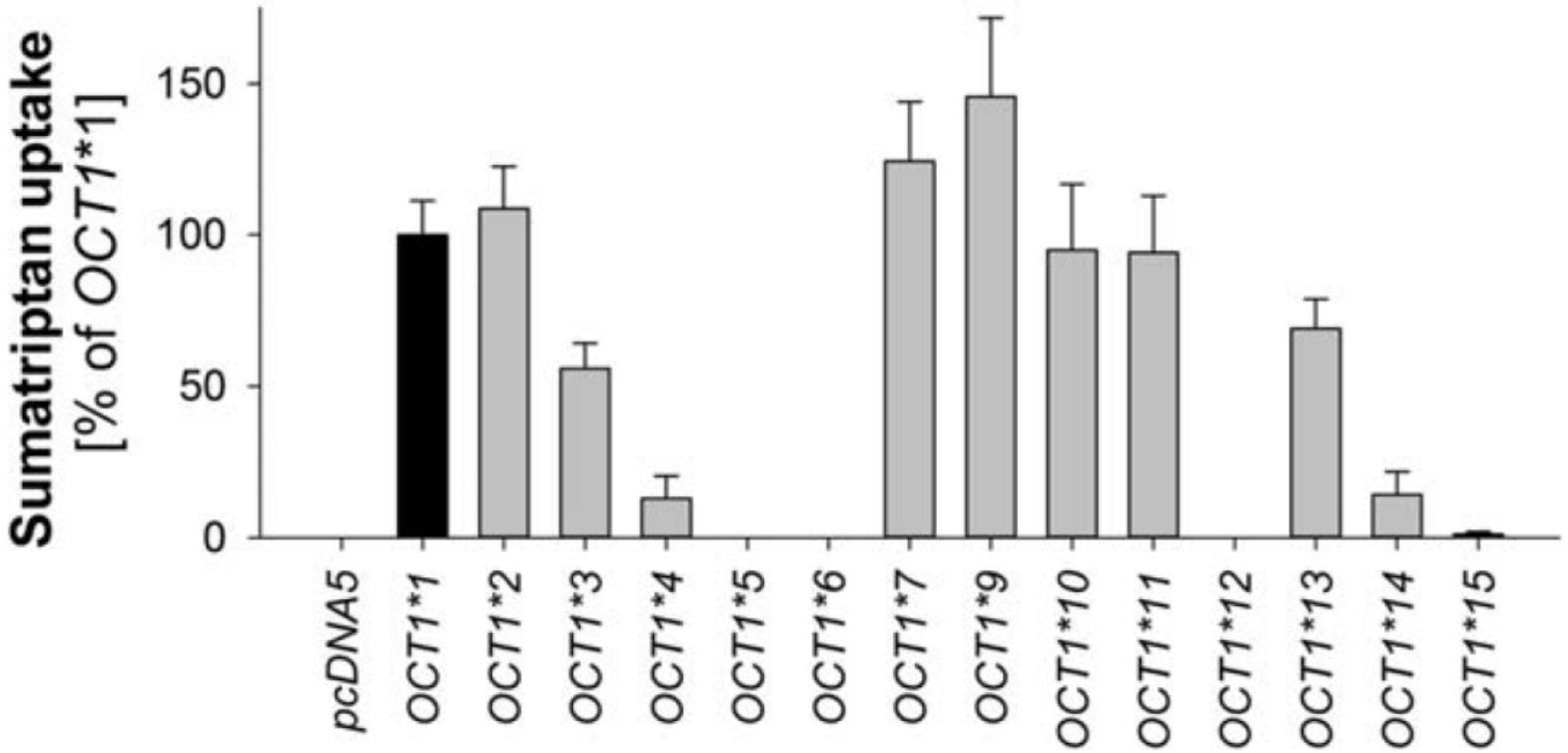
Inverse correlation between uptake and PAMPA permeability



Matthaei … Tzvetkov (2016) *CPT* **99**:633

OCT1 (SLC22A1): impacts of polymorphisms

- 2% of Europeans and white Americans are poor OCT1 transporters **with respect to *sumatriptan***
- Substrate-dependent effects: different polymorphisms affect *O*-desmethyltramadol, morphine and metformin differently



Matthaei … Tzvetkov (2016) *CPT* **99**:633

OCT1 (SLC22A1): Potential DDIs

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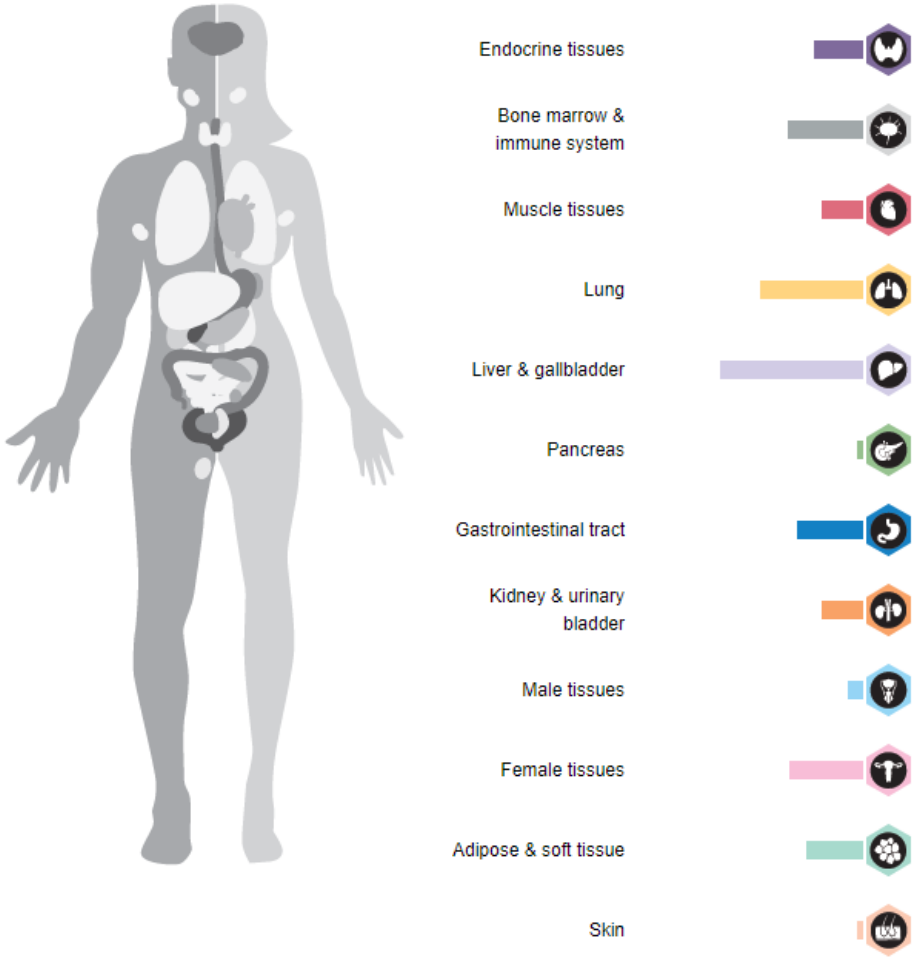
- Main evidence with sumatriptan is with MAO inhibitors, as expected from sumatriptan's metabolism
- Some evidence for increased efficacy of sumatriptan at lower starting doses of 25 – 50 mg with OCT1 poor transporters
- Eletriptan and rizatriptan less likely to have OCT1-mediated interactions because of higher permeability
- Naratriptan?
- It would be interesting to look at the FDA's AERS
- We know that metformin has interactions because PD is (relatively) easy to measure

OATP2B1 (SLC22A1) basics

- Most highly expressed OATP in human intestine
- Apical intestinal and sinusoidal hepatic uptake
- Polymorphic
- Transports several drugs:
  - Rosuvastatin
  - Atorvastatin
  - Pravastatin
  - Celiprolol
  - Fexofenadine
  - Montelukast
  - Aliskiren



UW DIDB; The Human Protein Atlas; Zamek-Gliszczynski et al. ITC3 (2018) *CPT* **104:**890-899

OATP2B1 (SLC22A1): impacts of polymorphisms and DDIs

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Several polymorphisms, not particularly well characterized yet

- Variable, sometimes contradictory, effects:
  - Rosuvastatin: AUC ↑ 112%
  - Celiprolol: AUC ↓ 50%
  - (S)-fexofenadine: AUC ↑ 51%
  - Fexofenadine: AUC ↓ 36%
  - Montelukast: AUC ↓ 46%

If a drug candidate is a strong OATP1B1/3 inhibitor in a definitive study – consider an OATP2B1 inhibition study (promiscuity)

Complex DDIs

- Ronacaleret inhibits intestinal OATP2B1, ↓ rosuvastain AUC 50%
- Asunaprevir inhibits hepatic OATPs, and ↑ rosuvastain AUC ~190%

UW DIDB e-Pkgene; Zamek-Gliszczynski et al. ITC3 (2018) *CPT* **104:**890-899

OAT2 (SLC22A7): Just the beginning?

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Xenobiotica

Xenobiotica, Early Online: 1–13
 DOI: 10.1080/00498254.2017.1384595

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RESEARCH ARTICLE

Check for updates

In vitro studies with two human organic anion transporters: OAT2 and OAT7

Sumathy Mathialagan[1], Chester Costales[1], Laurie Tylaska[1], Emi Kimoto[1], Anna Vildhede[1], Jillian Johnson[1], Nathaniel Johnson[1], Takami Sarashina[2], Kenta Hashizume[2], Caleb D. Isringhausen[3], Lydia M. M. Vermeer[3], Andrea R. Wolff[3], and A. David Rodrigues[1],

[1]*Pharmacokinetics, Dynamics, & Metabolism, Medicine Design, Pfizer Inc, Groton, CT, USA,* [2]*Sekisui Medical Co., Ltd, Tokyo, Japan, and* [3]*Sekisui XenoTech, LLC, Kansas City, KS, USA*

1521-0103/367/2/322–334$35.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

https://doi.org/10.1124/jpet.118.252049
J Pharmacol Exp Ther 367:322–334, November 2018

Organic Anion Transporter 2–Mediated Hepatic Uptake Contributes to the Clearance of High-Permeability–Low-Molecular-Weight Acid and Zwitterion Drugs: Evaluation Using 25 Drugs[S]

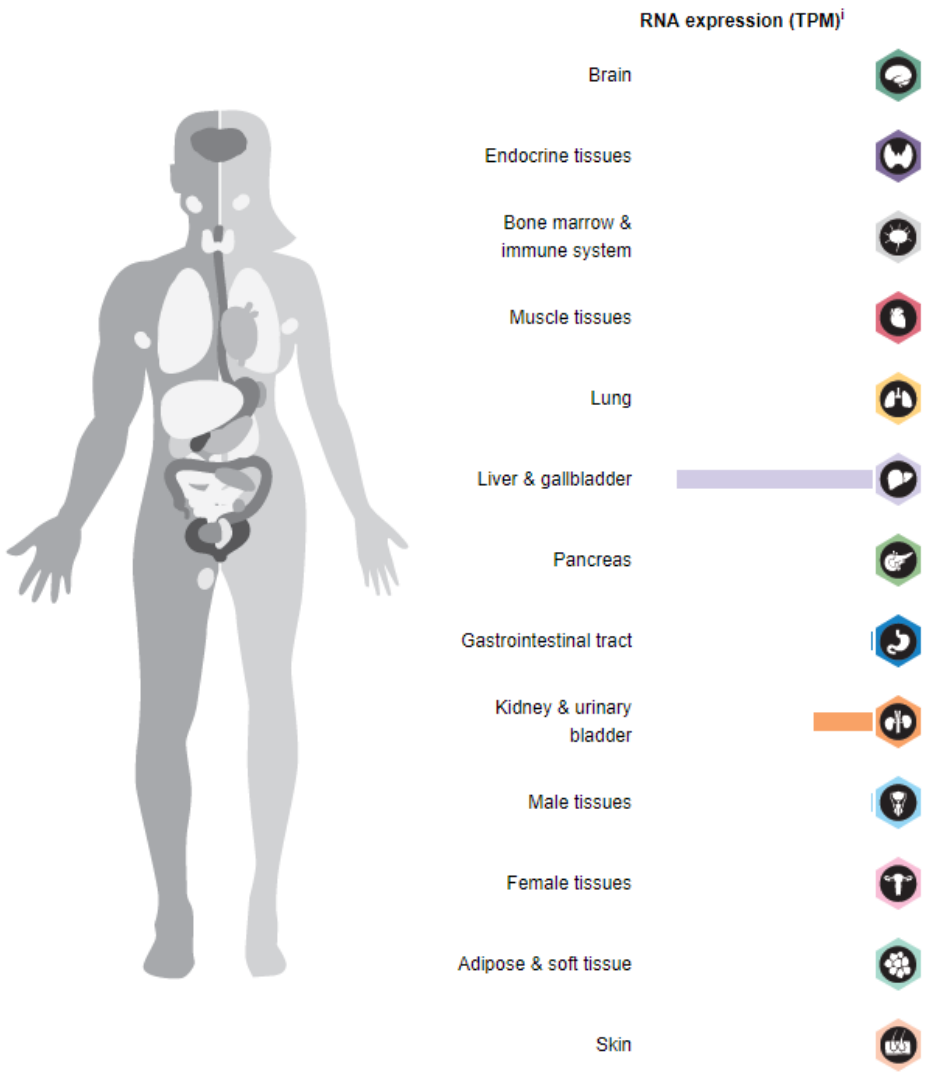
Emi Kimoto, Sumathy Mathialagan, Laurie Tylaska, Mark Niosi, Jian Lin, Anthony A. Carlo, David A. Tess, and Manthena V. S. Varma

Medicine Design, Worldwide Research and Development, Pfizer Inc., Groton, Connecticut

Received July 12, 2018; accepted August 15, 2018

OAT2 (SLC22A7) basics

- Most highly expressed OAT in the liver (sinusoidal)
- Expressed in kidney (basolateral)
- Transports several *high-permeability*–low-molecular-weight acids and zwitterions (permeability-limited ECCS Class 1A drugs):
  - *S*- and *R*-warfarin
  - Tolbutamide
  - Diclofenac
  - Fenoprofen
  - Ibuprofen
  - Ketoprofen
  - Indomethacin
  - Isoxicam
  - Meloxicam
  - Piroxicam
  - Pioglitazone
  - Rosiglitazone
  - Tolcapone
  - Gliclazide



The Human Protein Atlas; Kimoto … Varma (2018) *JPET* **367**:322

OAT2 (SLC22A7): impacts of polymorphisms and DDIs

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Unfortunately not characterized yet

DDIs?

- Many DDIs with OAT2 substrates attributed to CYP2C and UGT inhibition
- However PBPK models that take into account CYP2C/OAT2 interplay provide better prediction: intriguing implications
- One possibility: Some evidence that decreased theophylline CL with erythromycin is due to OAT2 inhibition

UW DIDB e-Pkgene; Kimoto … Varma (2018) *JPET* **367:**322

Unusual routes of administration

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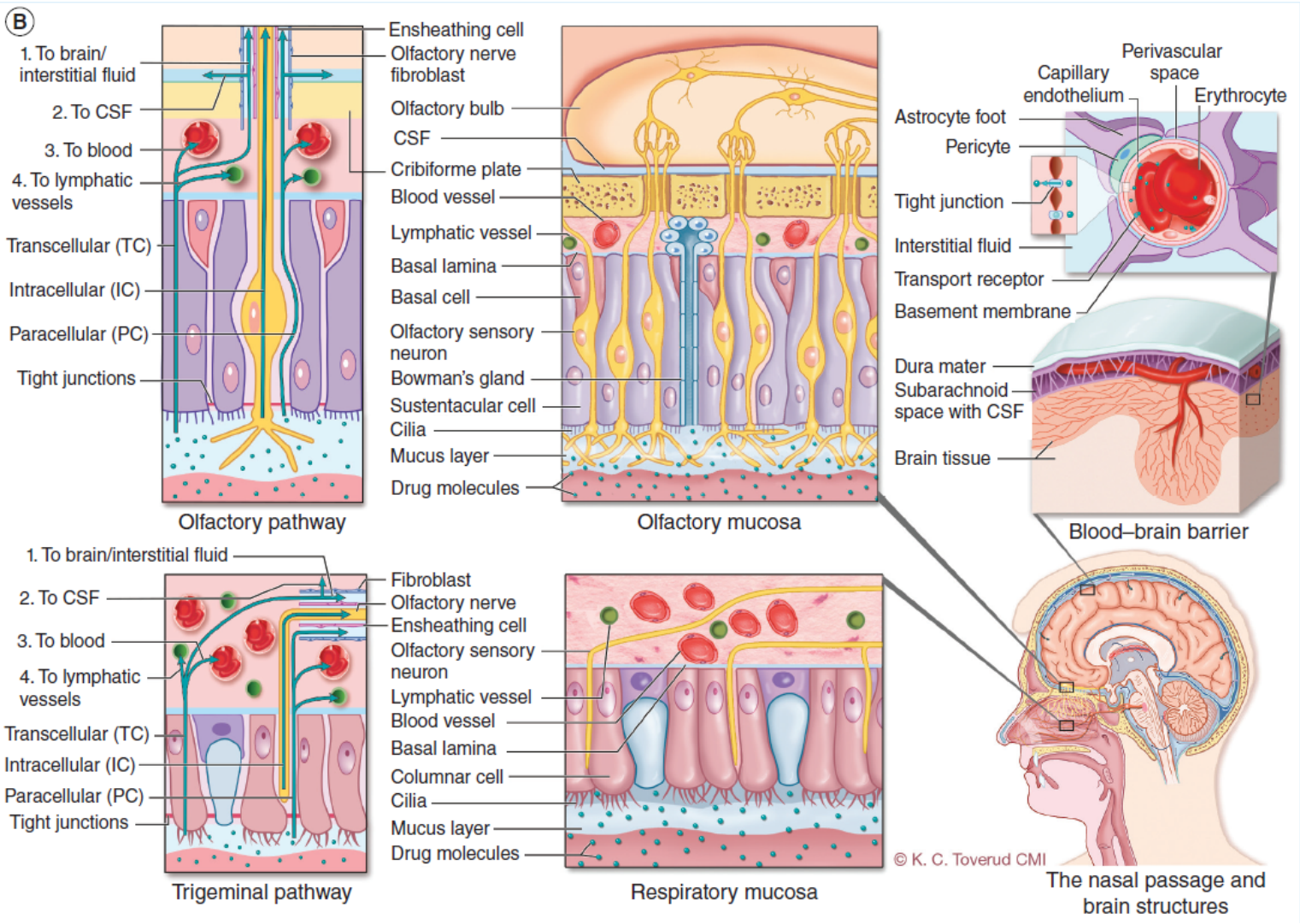
- Nasal
  - OCT1, 2, 3 , OCTNs – possibly several others
  - Also nose-to-brain transport – through olfactory and trigeminal nerves
- Ophthalmic
- Depending on the paper and compartment within the eye:
  - OATP1A2, 1B1, 1B3, 2B1, 1C1, 2A1, 3A1, 4A1, 4C1, 5A1, 6A1
  - OAT1, 2, 3, 4
  - ASBT, NTCP, OCT1, 2, 3, OCTNs, MATEs, PEPTs

Al-Ghabeish, Manar I (2014) Ph.D. Thesis; Lee and Pelis (2016) *DMD* **44:**1675

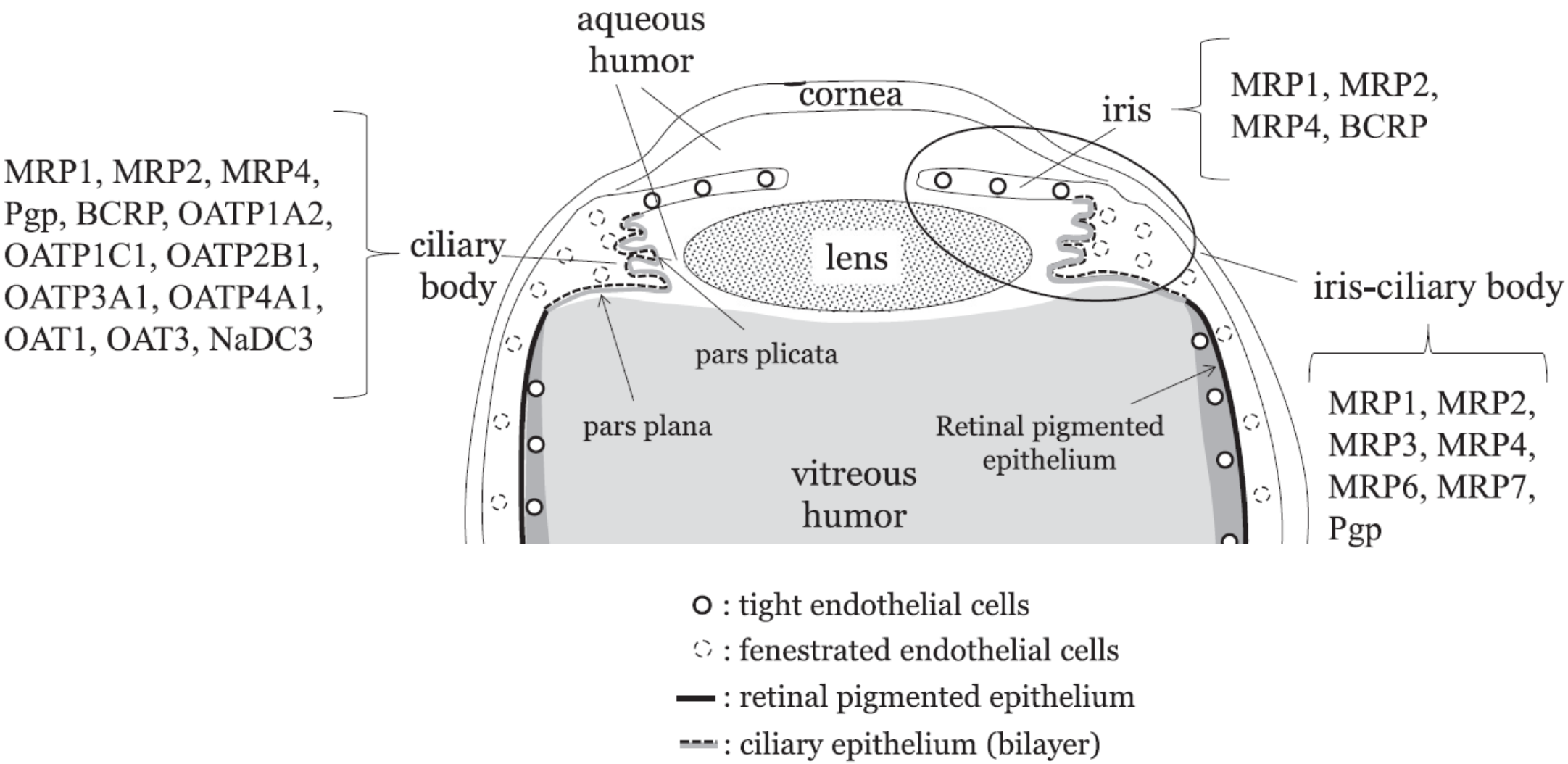
Nasal - overview



- Nasal epithelium: OCTs, OCTNs, others
- Nose to brain transport
- Can cross "leaky" choroid plexus to CSF
- Blood-CSF barrier: OATs, OATPs, OCTs, MRPs, others
- BBB: OCTNs, OATP1A2, P-gp, BCRP, ENT2, others

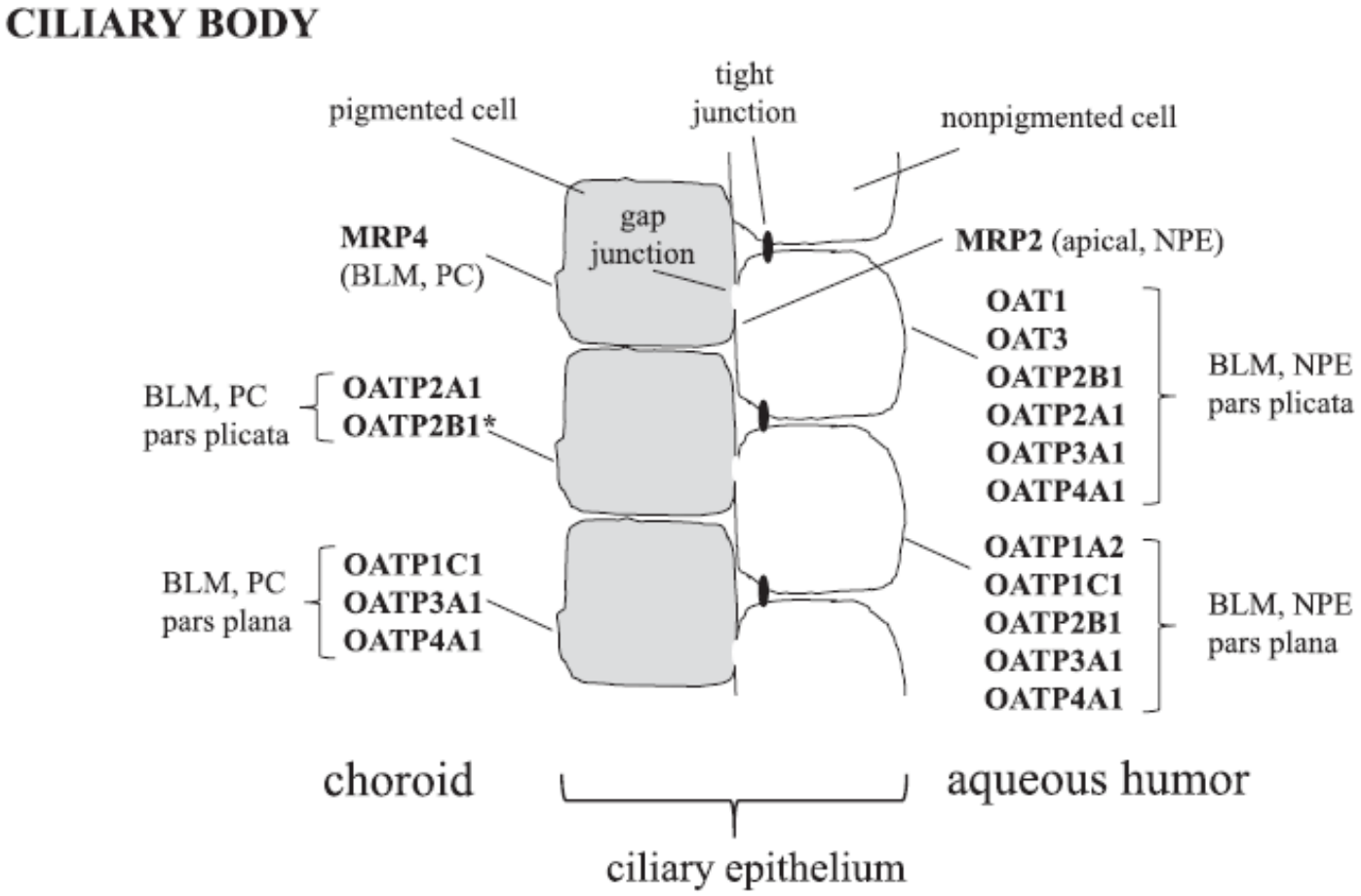
Djupesland et al. (2014) *Ther Deliv* **5**:709

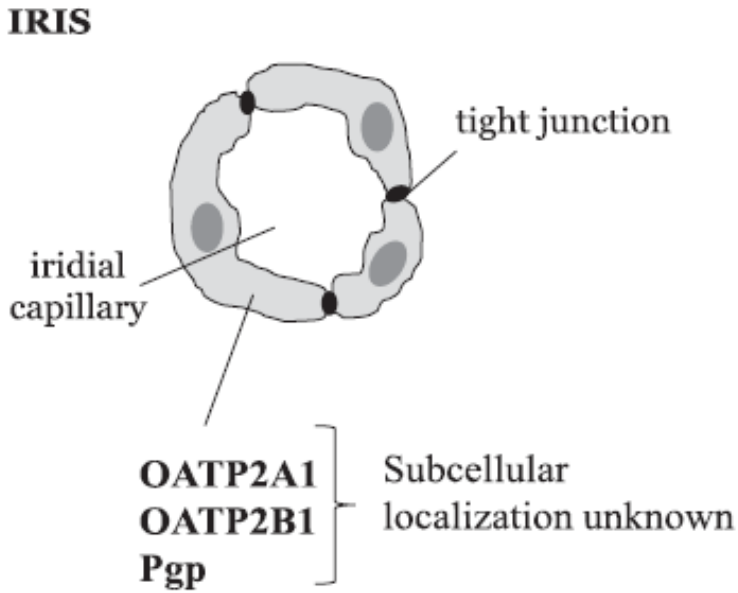
Ophthalmic - overview



Lee and Pelis (2016) *DMD* **44:**1675

Ophthalmic – detailed view





Lee and Pelis (2016) *DMD* **44:**1675

Conclusions

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- Guidance is guidance – may need to go beyond
  - EMA probably had it right in 2013: Routine evaluation of OCT1
- Consider ITC3 recommendations
- Consider ECCS
  - Class 2 and 4: OCT1
  - Could *ALL* ECCS 1A drugs be OAT2 substrates?
- OATP2B1, others as needed
- Special routes of administration?
  - Know the transporters in the tissues

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- Mitochondria
- Extrahepatic Fractions

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