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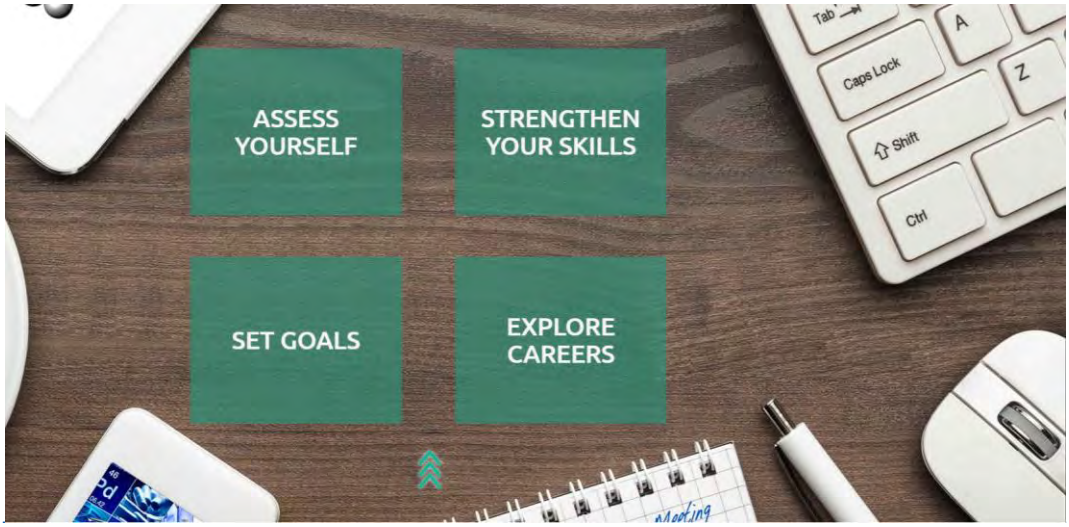

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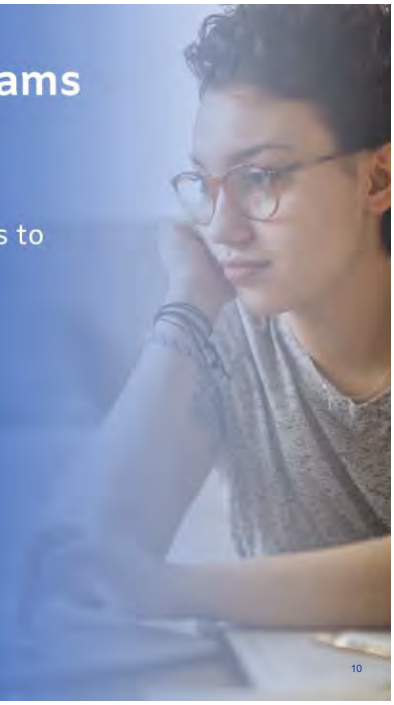

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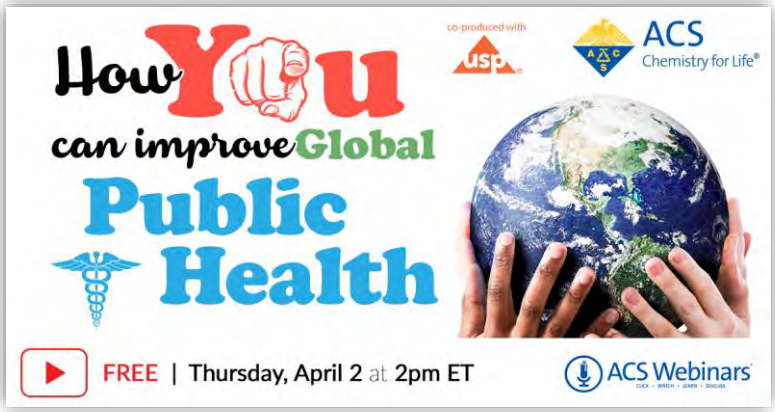

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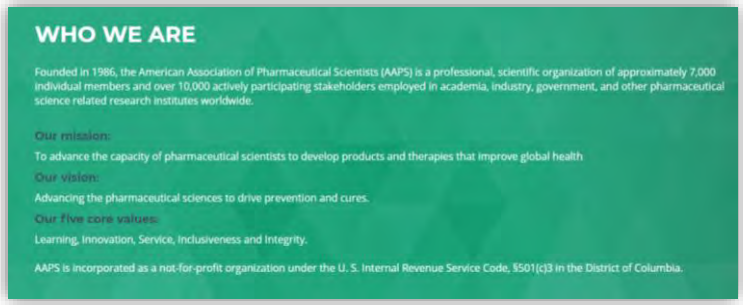

Members of the American Association of Pharmaceutical Scientists (AAPS) gathered during the 2013 AAPS Annual Meeting and Exposition to discuss why they chose a career in pharmaceutical sciences and how AAPS has helped foster their journey. The I Am AAPS video series displays the diversity of AAPS membership while exhibiting one common goal: to impact global health.

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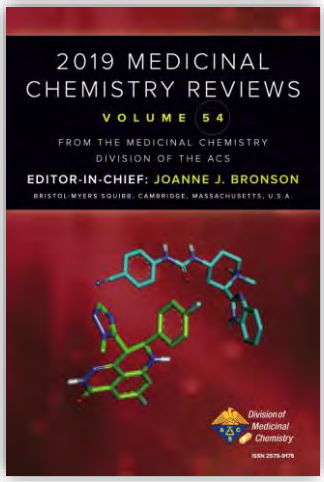

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PASSIVE PERMEABILITY

An Important Mechanism for Drug Absorption

THIS ACS WEBINAR WILL BEGIN SHORTLY...

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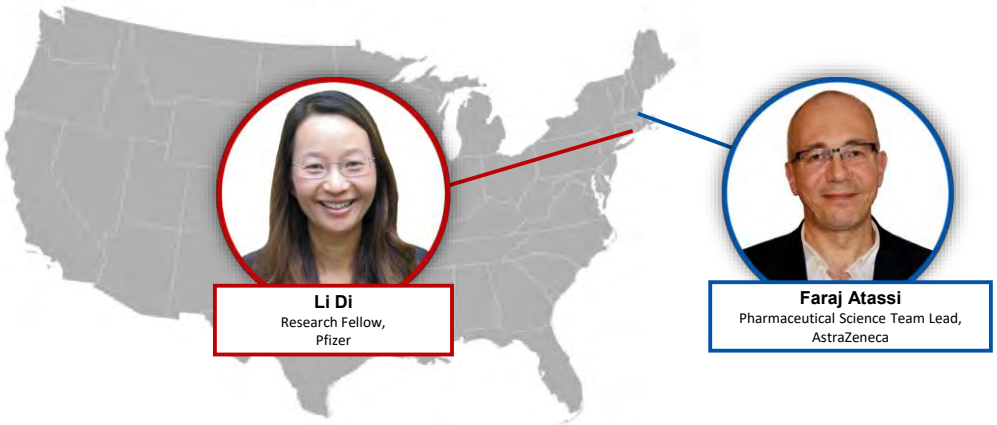
Passive Permeability: An Important Mechanism for Drug Absorption



Li Di
Research Fellow,
Pfizer

Faraj Atassi
Pharmaceutical Science Team Lead,
AstraZeneca

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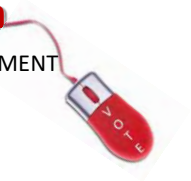
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



How are drugs absorbed?

- By transporters only
- By passive diffusion only
- By both transporters and passive diffusion
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

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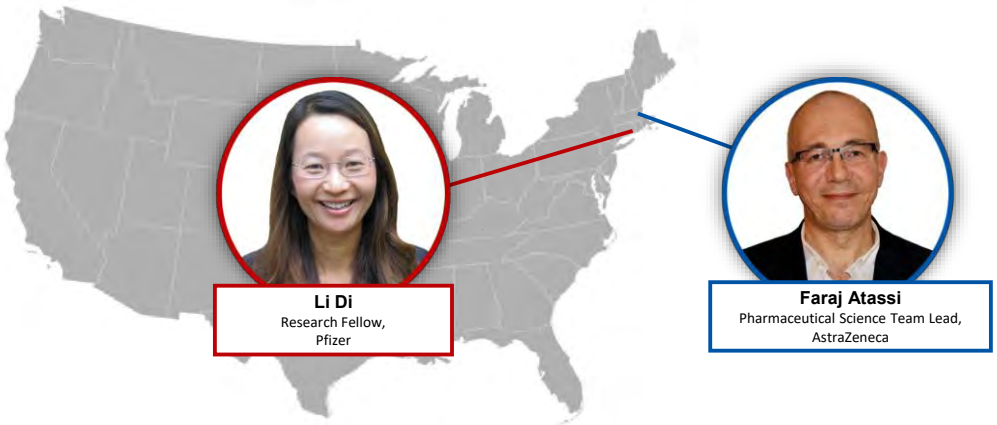
Passive Permeability: An Important Mechanism for Drug Absorption



Li Di
Research Fellow,
Pfizer

Faraj Atassi
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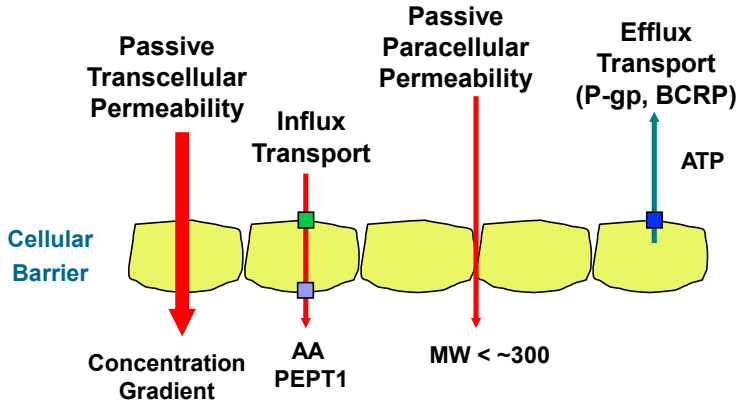
Mechanisms of Drug Absorption



Passive permeability and transporter-mediated mechanisms coexist to impact drug absorption and disposition

"Transporter-Only" Claim

- All transmembrane transport of drugs requires the use of transporters
- No passive diffusion through the bilayer occurs

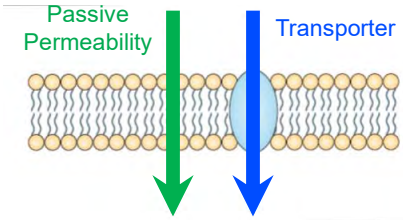
Dobson, P.D. and Kell, D.B. (2008) Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? Nat. Rev. Drug Discov. 7, 205–220. Dobson, P. et al. (2009) Implications of the dominant role of transporters in drug uptake by cells. Curr. Top. Med. Chem. 9, 163–181. Kell, D.B. et al. (2011) Pharmaceutical drug transport: the issues and the implications that it is essentially carrier-mediated only. Drug Discov. Today 16,704–714

- **"Transporter-only" claim ignores the basic scientific facts and is fundamentally flawed**
  - **Experienced scientists in DMPK, Med Chem, Pharm Sci: minimal impact**
  - **Can be misleading for students and less experienced scientists**

Sugano, K.; et al., Coexistence of passive and carrier-mediated processes in drug transport. Nat. Rev. Drug Discovery 2010, 9, 597−614. Di, L.; et al., Evidence-based approach to assess passive diffusion and carrier-mediated drug transport. Drug Discov.Today 2012, 17, 905−912. Smith, D. et al., Passive lipoidal diffusion and carrier-mediated cell uptake are both important mechanisms of membrane permeation in drug disposition. Mol. Pharm. 2014, 11, 1727–1738. Balaz, S., Does transbilayer diffusion have a role in membrane transport of drugs? Drug Disc. Today, 2012, 17, 1079-1087.

Successful examples of applying the principles of passive permeability and transporter-mediated mechanisms in real-world drug discovery

Passive Permeability & Transporter-Mediated Mechanisms



Passive Diffusion

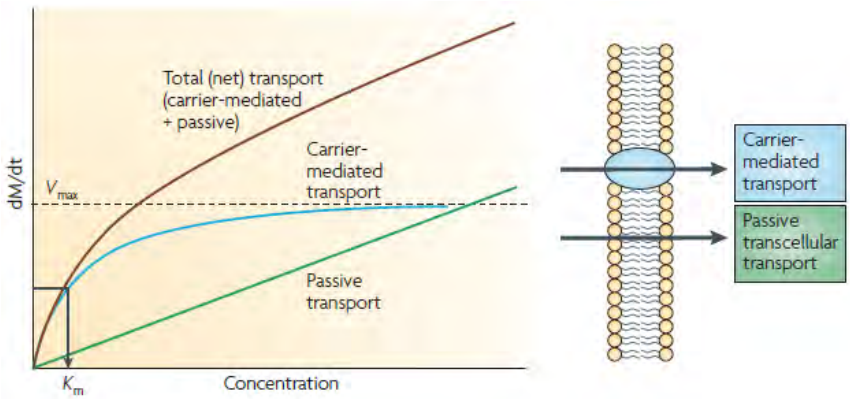
- Not dependent on substrate concentration, non-saturable, linear
- Not subject to inhibition / induction / drug-drug interactions
- Less structure specific: Log D, PSA, H-bonds, MW, rotatable bonds
- Less specific to tissue, cell-type, species

Transporter

- Dependent on substrate concentration, saturable, nonlinear
- Subject to inhibition / induction / drug-drug interactions
- More structure specific interactions between substrates and transporters
- Specific to tissue, cell-type, species

K. Sugano, et al., Nat. Rev. Drug Disc. 2010, 9, 597–614.

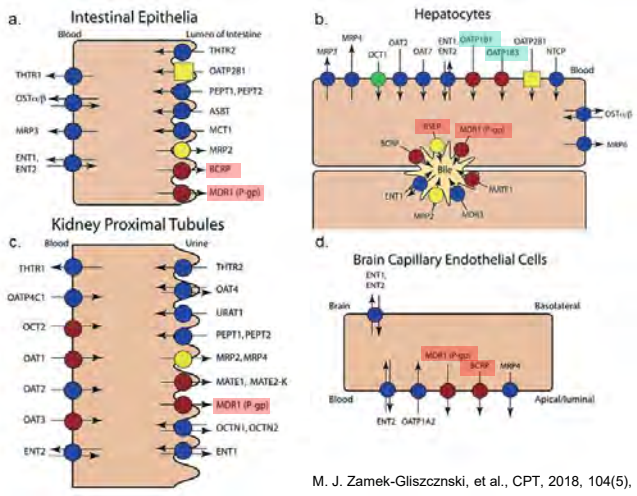
Saturable vs. Non-Saturable Mechanisms



- Transporter-mediated mechanisms are saturable at high concentrations and nonlinear with increasing concentrations
- Passive permeability is not saturable and linear with increasing concentrations
- Total (net) transport = passive + transporter

K. Sugano, et al., Nat. Rev. Drug Disc. 2010, 9, 597–614.

ADME Transporters in the Major Organs

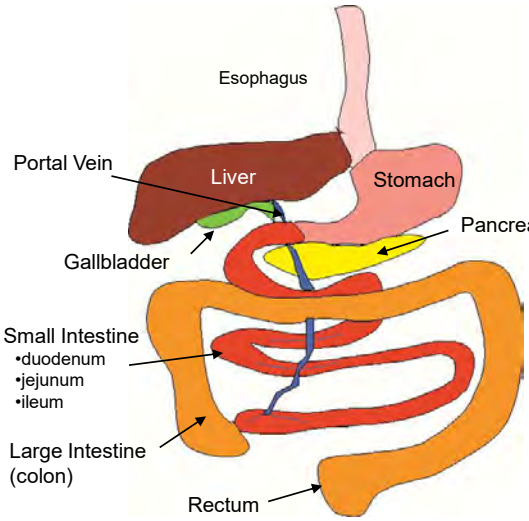


- Transporters are tissue / membrane /directional specific
- P-gp/BCRP: apical membrane for most tissues
- OATP1B1/1B3: liver specific
- Expressions and activities of transporters can be species dependent
- An "universal transporter" doesn't exist

M. J. Zamek-Gliszczynski, et al., CPT, 2018, 104(5), 890-899.

If "transporter-only", an oral CNS drug would need specific transporters for each of the membranes in the gut, the liver and the brain. Expect high incidences of DDIs.

The Role of Passive Permeability in ADME



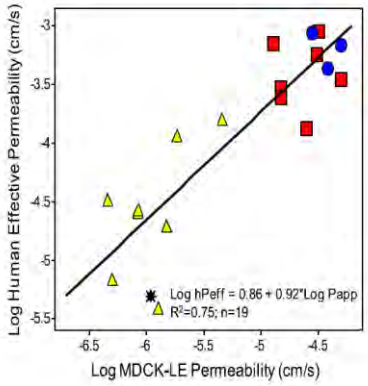
- Absorption
  - Oral absorption
- Distribution
  - Tissue exposure
  - Brain penetration
  - Target exposure
- Metabolism
  - Entry to hepatocytes
- Excretion
  - Hepatobiliary clearance
  - Renal clearance / reabsorption

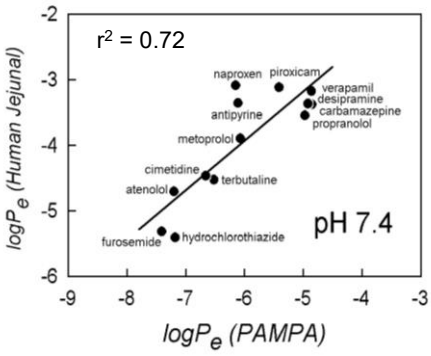
ADME = Absorption, Distribution, Metabolism, Excretion

In Vitro Methods to Predict Human Intestine Passive Permeability

BCS: I II III IV

Rate





DMD, 2013, 41: 1975-1993

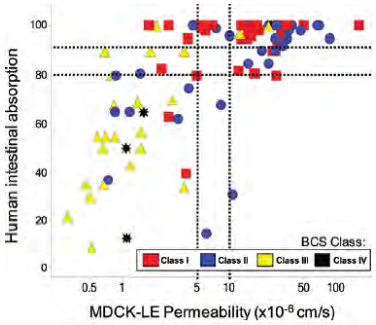
A. Avdeef

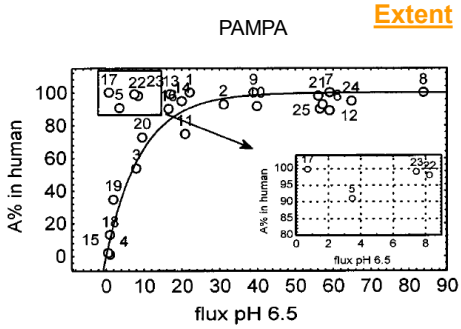
Passive permeability plays a major role in oral absorption

PAMPA = parallel artificial membrane permeability assay

Impact of Passive Permeability in Oral Absorption

Extent

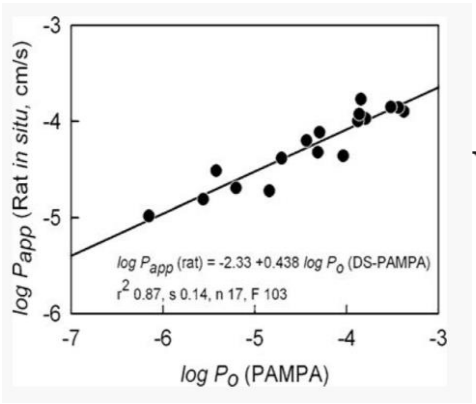


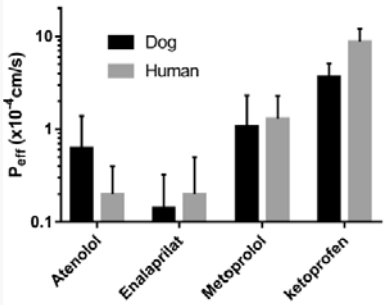


High passive permeability leads high human intestinal absorption (F_a) when no solubility/dissolution restriction

Varma, et al., Mol Pharm, 2012, 9, 1199-1212. Kansy, et al., JMC, 1998, 41(7), 1007-1010.

Correlation between PAMPA and Rat Intestine Permeability

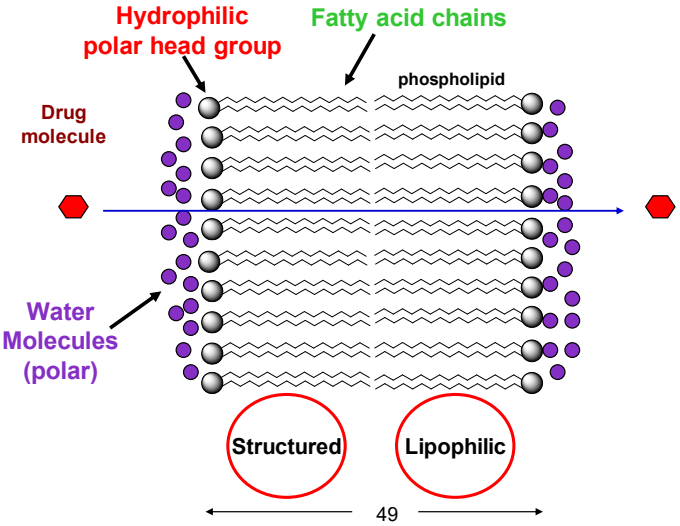




Passive permeability is insensitive to species. Enable direct translation of *in vitro* or animal data to humans with different physiology

M. Bermejo, et al., Eur J Pharm Sci, 2004, 21, 429–441. D. Dahlgren, et al., Mol Pharm, 2016, 13, 3022-3033

Cell Membrane Lipid Bilayer: Self-assembling Phospholipids



Molecular Properties Govern Absorption by Passive Permeability

Oral Absorption

- Lipinski's Rule of 5 (Ro5)

  Poor absorption
  - HBD >5 (OH and NH)
  - MW > 500
  - cLog P > 5
  - HBA > 10 (O and N)

- Veber's Rules:

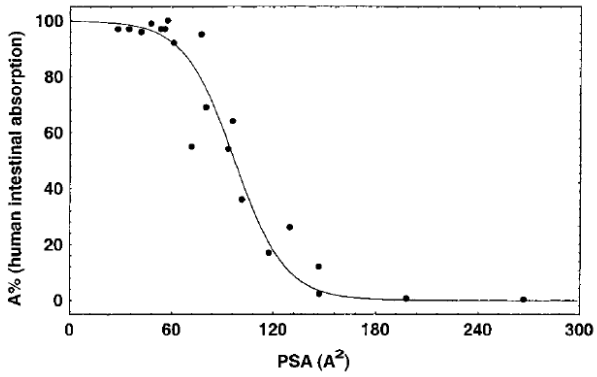
  Good Bioavailability
  - Rotatable bonds < 10
  - PSA < 140 Å^2 or HB <12

Brain Penetration

- CNS MPO > 4
  - cLogP
  - MW
  - TPSA
  - pKa
- CNS Rules
  - N+O < 5
  - ClogP-(N+O) > 0
  - PSA < 60-70
  - MW < 450
  - Log D 1-3
- Pardridge's Rules
  - HB < 8 -10
  - MW < 400-500
  - Non-acids

C. Lipinski, *et al. Adv. Drug Deliv Rev* 23:3-25 (1997). D. Veber, *et al., JMC* (2002), 45, 2615-2623. Wager, et. al., ACS Chem Neurosci, 2010, 1, 435-449. *D. E. Clark, DDT, 2003, 8, 927-933; M. Lobell et al, J. Pharm. Sci., 2003, 92, 360-370. W. Pardrigde, NeuroRx, 2005, 2, 3-14.*

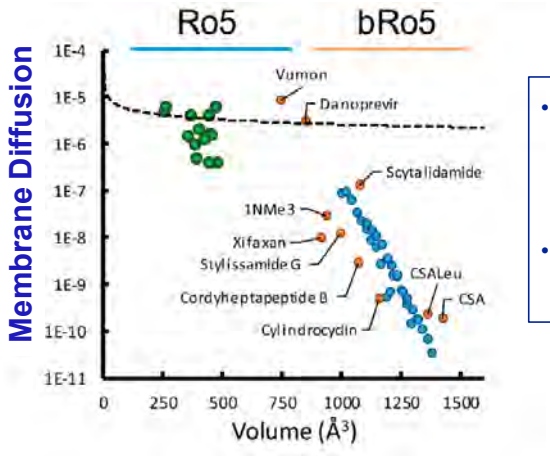
Effect of PSA on Oral Absorption



High fraction absorbed with low PSA (Polar Surface Area)

β-Blocker: Van de Waterbeemd *et al.,* (2001) *J. Med. Chem*, **44**, p1313

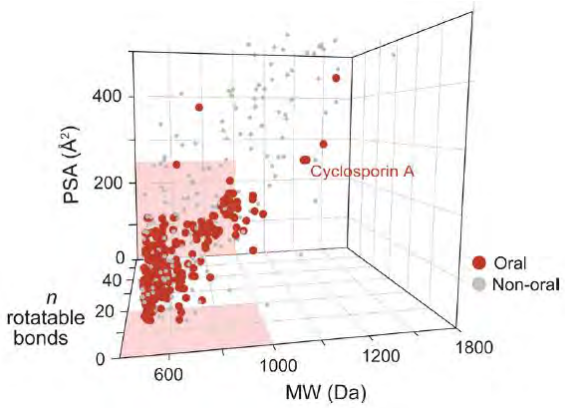
Size Penalty on Passive Permeability in bRO5 Space



- **Macrocyclic per-N-methylated peptides (no IMHB). AlogP 0-8, MW 800-1200**
- **Steep drop off of passive permeability with increasing size**

C. R. Pye, et al., JMC, 2017, 60, 1665-1672

Impact of Molecular Properties on Oral Absorption

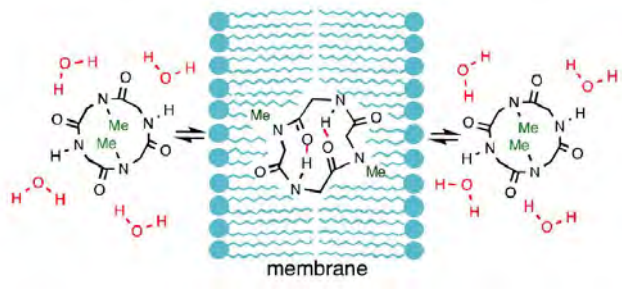


Compounds with high MW, rotatable bonds and PSA are rare as oral drugs

P. Matsson, J. Kihlberg, JMC, 2017, 60, 1662-1664. B. C. Doak, et al., Chem Bio, 21 (18), 2014, 1115-1142.

Cyclic Peptides to Increase Passive Permeability

- **Peptides: poor membrane permeability, instability, injectables**
  - H-bonds, charges, polar, low Log D
- **Cyclic peptide: improved membrane permeability & stability, oral (CsA)**
  - no charged termini, intramolecular H-bonds
  - Cyclosporin A: 4 intramolecular H-bonds, lipophilic side chains shield polarity, MW 1202, F 28%



T. Rezai, et al., JACS, 2006, 218, 2510-2511. T. White, et al., Nat Chem Biol, 2012, 7(11), 810-817.

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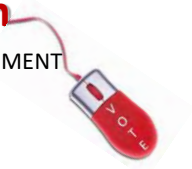
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



What are some effective strategies to INCREASE Passive Permeability?(select all that apply)

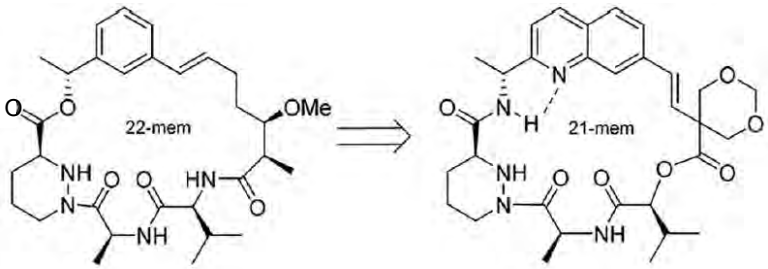
- Introduce intra-molecular hydrogen bonds
- Reduce polarity
- Reduce molecular weight
- Add carboxylic acid for brain penetration
- Reduce rotatable bonds

** If your answer differs greatly from the choices above tell us in the chat!*

Strategies to Increase Passive Permeability

- Optimize lipophilicity
- Reduce hydrogen bonds
  - ✓ Introduce intra-molecular hydrogen bonds
- Reduce polarity
- Reduce molecular weight
- Reduce rotatable bonds
- Remove carboxylic acid for brain penetration
- Prodrug approach

HCV: Orally Bioavailable Cyclophilin Inhibitor Derived from the Sanglifehrin Macrocycle

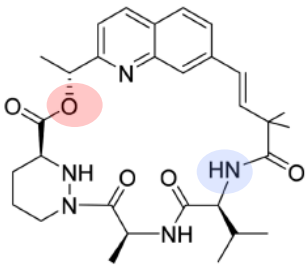


2
CyP A TR-FRET K_d = 24 nM
Human pred. Cl = 1.1 L/h/kg

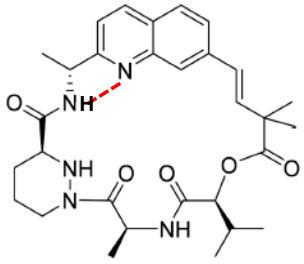
3
CyP A TR-FRET K_d = 5 nM
Human pred. Cl = 0.4 L/h/kg
F% (Rat, Dog) = 100, 55

R. M. Mackman, et al., JMC, 2018, 61, 9473-9399

Introduce Intramolecular Hydrogen Bonds to Increase Passive Permeability



Caco-2 P_{app}= 2.2 x 10^{-6} cm/s

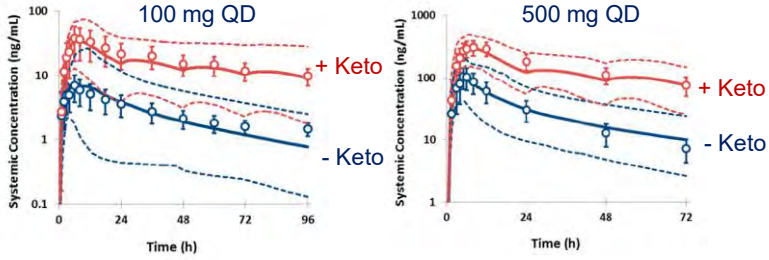


Caco-2 P_{app}= 17 x 10^{-6} cm/s

R. M. Mackman, et al., JMC, 2018, 61, 9473-9399

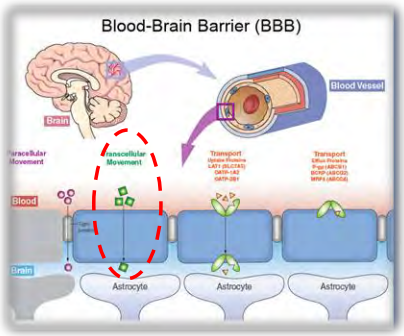
Saturation of Transporters in the Intestine: Nonlinear PK

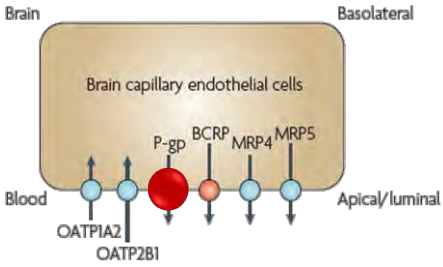
- Bosutinib: orally available TKI for leukemia, CYP3A & P-gp substrate
- Low doses (50-200 mg): super-proportional oral exposure - **saturation of intestinal P-gp efflux**
- High doses (200-600 mg): dose-proportional linear PK - **passive absorption**
- PBPK (SIMCYP-ADAM) modeling incorporates passive permeability, CYP3A metabolism and P-gp intestine efflux nicely captures PK and DDI
- If "transporter-only", expect to have much high frequencies of nonlinear PK – not reality



Shinji Yamazaki, et al., DMD, 2018, 46:1200-1211.

Passive Permeability in Brain Penetration

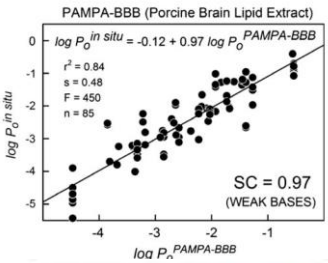


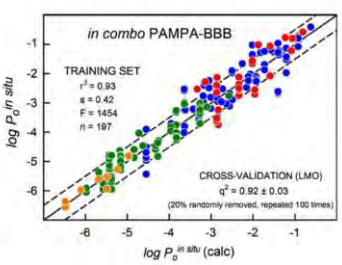


Nature Reviews Drug Discovery ***Discovery*** 9: 2010, 215–236

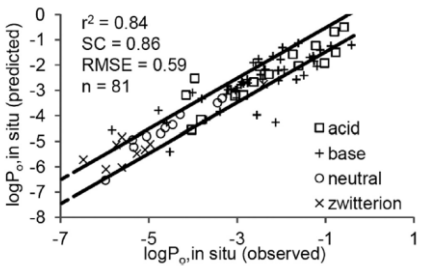
- **Blood-brain barrier at the microvascular endothelial cells is a dynamic barrier made up of tight junctions, efflux transporters and drug metabolizing enzymes**
- **Most small molecule drugs cross the BBB by passive diffusion**

Passive Permeability Through Blood Brain Barrier





O. Tsinman, et al., Pharm Res. 2011, 28: 337-363



Brain Passive Permeability

- In silico
- In vitro (e.g., PAMPA-BBB)
- Combo (in silico + in vitro)

P. Trapa, et al., J Pharm Sci. 105(2): 2016, 965-971

PBPK Model: Passive Permeability and Efflux

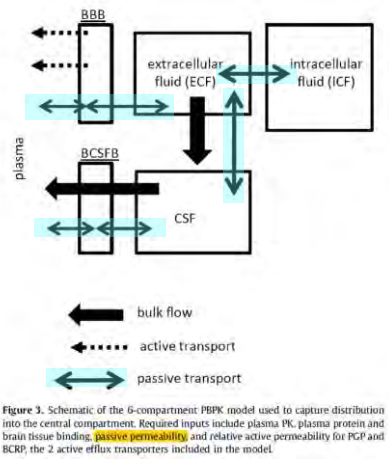
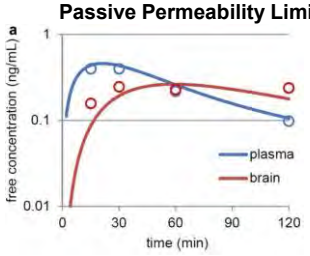


Figure 3. Schematic of the 6-compartment PBPK model used to capture distribution into the central compartment. Required inputs include plasma PK, plasma protein and brain tissue binding, passive permeability and relative active permeability for PGP and BCRP, the 2 active efflux transporters included in the model.

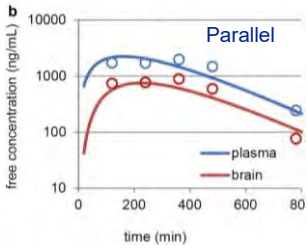
P. Trapa, et al., J Pharm Sci. 105(2): 2016, 965-971

Passive Permeability Limited



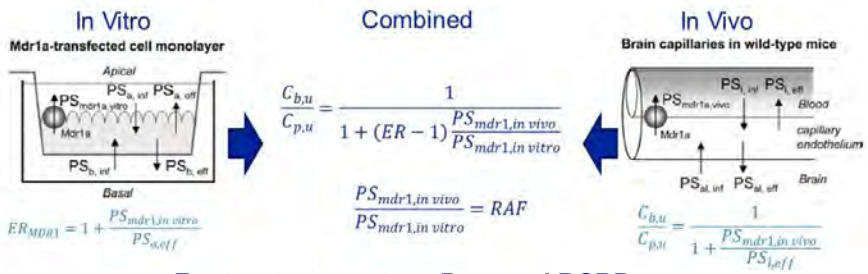
K_{puu} ~ 1
Slow in
Slow out

Efflux Limited Brain Exposure



K_{puu} < 1
Fast in
Fast Out
~Steady-State

Steady State Brain-to-Plasma K_{puu} ($C_{b,u}/C_{p,u}$)



$$\frac{C_{b,u}}{C_{p,u}} = \frac{1}{1 + (ER - 1)\frac{PS_{mdr1,in\ vivo}}{PS_{mdr1,in\ vitro}}}$$

$$ER_{MDR1} = 1 + \frac{PS_{mdr1,in\ vitro}}{PS_{a,eff}}$$

$$\frac{PS_{mdr1,in\ vivo}}{PS_{mdr1,in\ vitro}} = RAF$$

$$\frac{C_{b,u}}{C_{p,u}} = \frac{1}{1 + \frac{PS_{mdr1,in\ vivo}}{PS_{i,eff}}}$$

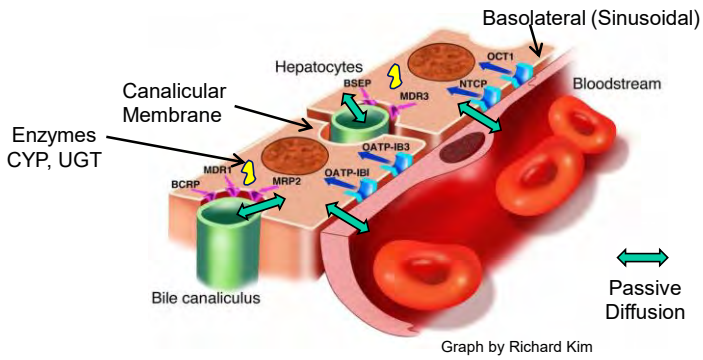
For two transporters, P-gp and BCRP

$$\frac{C_{b,u}}{C_{p,u}} = \frac{1}{RAF_1 \times (ER_1 - 1) + RAF_2 \times (ER_2 - 1) + 1}$$

Models have been widely applied in drug discovery programs to identify successful CNS drug candidates

Uchida, JPET 2011, 339 (2) 579-588. *Trapa, J Pharm Sci, 2011, 105(2): 2016, 965-971.*

Passive Permeability in Hepatobiliary Clearance

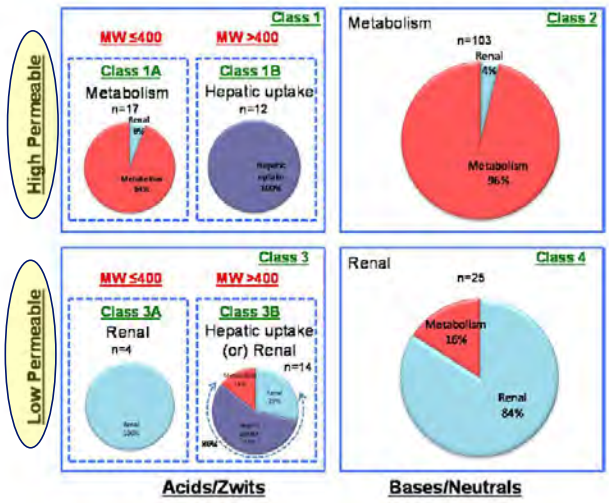


Graph by Richard Kim

Extended Clearance

$$CL = (CL_{met} + CL_{bile}) \times \frac{(CL_{pass} + CL_{uptake})}{(CL_{pass} + CL_{met} + CL_{bile})}$$

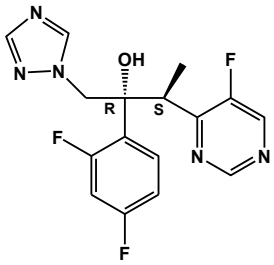
Impact of Passive Permeability, Ionization and MW on Major Clearance Pathways - ECCS

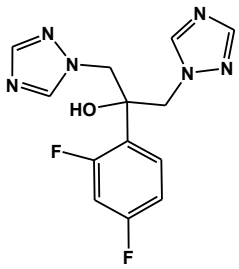


Passive permeability plays an important role in defining major clearance mechanisms

M. Varma, et al, Pharm Res, 2015, 32, 3785-3802

Effects of Passive Permeability on Clearance and PK

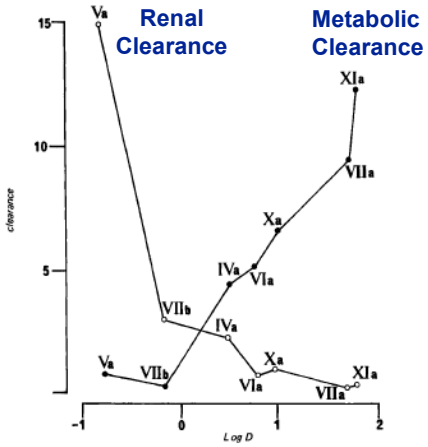


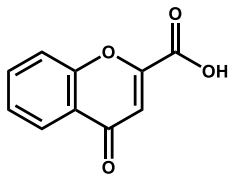


Log D $_{7.4}$ = 1.8	Log D $_{7.4}$ = 0.5
Hepatic clearance	Renal clearance of unchanged drug
Capacity-limited nonlinear PK	Linear PK

S. J. Roffey, et al, Drug Met. Disp., 2003, 31, 731-741

Effects of Passive Permeability on Clearance Mechanisms

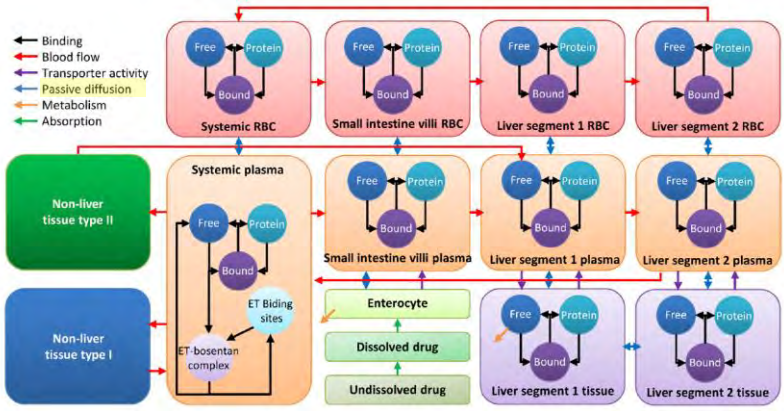




chromone-2-carboxylic acid

Smith et al., (1985) Drug Metabolism Reviews, 16, p365

PBPK Modeling of Enzyme- and Transporter-Mediated Clearance and Drug-Drug Interactions for Bosentan



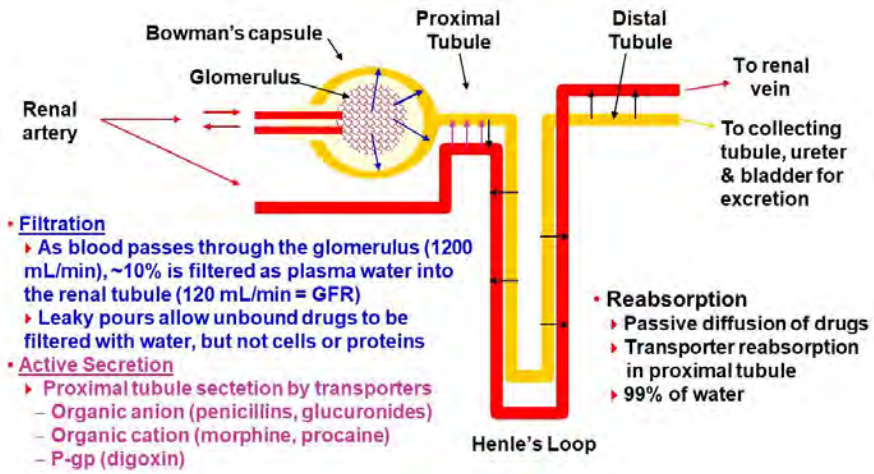
Successfully model bosentan nonlinear PK, liver concentration and DDI

Rui Li, et al., DMD, 2018, 46:346–356 and 357-366.

Renal Clearance

$CL_r = GFR * f_{ub} + CL_{sec} - CL_{reabs}$

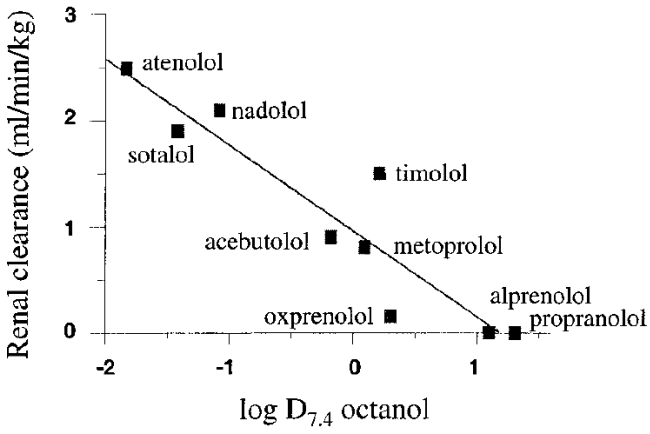
Reabsorption: $CL_r < GFR * f_{ub}$



- Filtration
  - As blood passes through the glomerulus (1200 mL/min), ~10% is filtered as plasma water into the renal tubule (120 mL/min = GFR)
  - Leaky pours allow unbound drugs to be filtered with water, but not cells or proteins
- Active Secretion
  - Proximal tubule sectetion by transporters
    - Organic anion (penicillins, glucuronides)
    - Organic cation (morphine, procaine)
    - P-gp (digoxin)

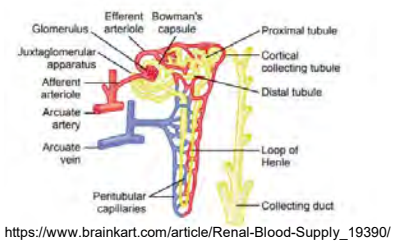
- Reabsorption
  - Passive diffusion of drugs
  - Transporter reabsorption in proximal tubule
  - 99% of water

Passive Permeability in Renal Clearance / Reabsorption

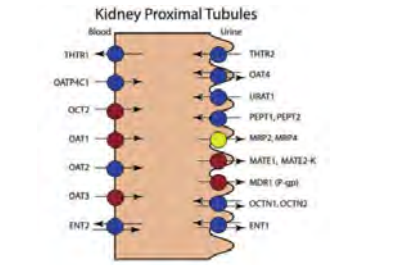


β-Blocker: Van de Waterbeemd *et al.,* (2001) *J. Med. Chem*, **44**, p1313

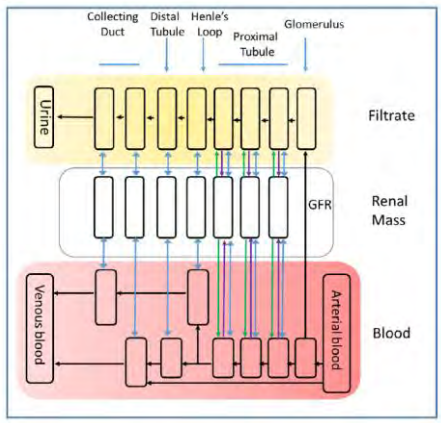
Passive Permeability in Renal Clearance



https://www.brainkart.com/article/Renal-Blood-Supply_19390/



M. J. Zamek-Gliszczynski, et al., CPT, 2018, 104(5), 890-899.

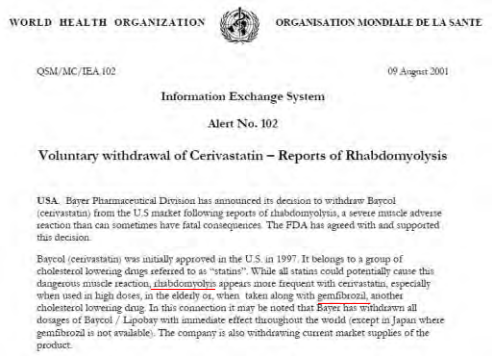


Prediction of renal clearance
Prediction of crystal nephropathy

Zhenhong Li, et al., Seminars in Nephrology, 2019, 39(2), 176-189
Zhenhong Li, et al., JMC, 2020, online

DDI between Cerivastatin and Gemfibrozil

- Cerivastatin (Baycol): approved 1997, withdrawn 2001, muscle weakness, 51 death, ~40% co-administrated with gemfibrozil (another cholesterol lowering drug)
- Cerivastatin: CYP2C8 and OATP1B substrate
- Gemfibrozil and glucuronide metabolite: potent CYP2C8 and OATP1B inhibitors



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QSM/MC/IEA/102 09 August 2001

Information Exchange System

Alert No. 102

Voluntary withdrawal of Cerivastatin – Reports of Rhabdomyolysis

USA. Bayer Pharmaceutical Division has announced its decision to withdraw Baycol (cerivastatin) from the U.S market following reports of rhabdomyolysis, a severe muscle adverse reaction than can sometimes have fatal consequences. The FDA has agreed with and supported this decision.

Baycol (cerivastatin) was initially approved in the U.S. in 1997. It belongs to a group of cholesterol lowering drugs referred to as "statins". While all statins could potentially cause this dangerous muscle reaction, rhabdomyolysis appears more frequent with cerivastatin, especially when used in high doses, in the elderly or, when taken along with gemfibrozil, another cholesterol lowering drug. In this connection it may be noted that Bayer has withdrawn all dosages of Baycol / Lipobay with immediate effect throughout the world (except in Japan where gemfibrozil is not available). The company is also withdrawing current market supplies of the product.

- **Inhibition / induction of enzymes and transporters can lead to DDI**
- **Enzyme-transporter interplay can lead to increased magnitude of DDI**

DDI Due to Enzyme and Transporter Inhibition

Extended Clearance

$$CL = (CL_{met} + CL_{bile}) \times \frac{(CL_{pass} + CL_{uptake})}{(CL_{pass} + CL_{met} + CL_{bile})}$$

With Inhibitor

$$CL_{inh} = \left(\frac{CL_{met}}{R_1} + \frac{CL_{bile}}{R_2}\right) \times \frac{\left(CL_{pass} + \frac{CL_{uptake}}{R_3}\right)}{\left(CL_{pass} + \frac{CL_{met}}{R_1} + \frac{CL_{bile}}{R_2}\right)}$$

Reversible inhibition in liver only

$R = 1 + [I]/K_i$

[I] inhibitor concentration
K_i inhibition constant

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

2018 was a record year for new drugs approved by the FDA with 59 total, how many of these were New Chemical Entries?

- About a quarter
- About half
- About three quarters
- All of them
- None of them

** If your answer differs greatly from the choices above tell us in the chat!*

DDI of 2018 FDA Approved Drugs

- 42 New Chemical Entries (small molecules) approved in 2018 (59 total; 71%)
- 22 (52%) have label recommendations based on DDI evaluations
- CYP3A involved in the majority (72%) of all interactions
- Only three drug interactions with label recommendations were mediated mainly by transporters
- If "transporter-only" and no passive permeability, one would expect much higher incidences of transporter-mediated DDIs

Substrate	Precipitant	AUCR	Transporter	Label Impact
elagolix	rifampin	5.58	OATP1B1	Contraindicated with strong OATP1B1 inhibitors.
baricitinib	probenecid	2.03	OAT3	Not recommended with strong OAT3 inhibitors.
talazoparib	P-gp inhibitors[1]	1.45 (popPK)	P-gp	Reduce the dose of talazoparib with any of these P-gp inhibitors.

J. Yu, et al., 2019 ISSX poster

Conclusions

- Passive permeability: an important mechanism for drug absorption and disposition
  - ✓ Oral absorption
  - ✓ Brain penetration
  - ✓ Renal reabsorption
  - ✓ Defining major clearance pathways
  - ✓ Enzyme / transporter interplay – extended clearance, DDI
- "Transporter-only" claim is fundamentally flawed and misleading
- Passive permeability and transporters coexist to impact drug absorption and disposition
- Many successful drugs have been developed by using the design principles of passive permeability and transporters

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- Brian Houston (Manchester Univ.)
- Manfred Kansy (Roche, retired)
- Edward Kerns (NIH, retired)
- Stephanie Krämer (ETH)
- Hans Lennernäs (Uppsala Univ.)
- Kiyohiko Sugano (Ritsumeikan Univ.)

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- Amit Kalgutkar
- Chris Keefer
- Cindy Li
- Rui Li
- Jian Lin
- Jenny Liras
- Tristan Maurer
- Scott Obach
- David Rodrigues
- Dennis Scott
- Dennis Smith (retired)
- David Tess
- Matt Troutman
- Susanna Tse
- Manthena Varma
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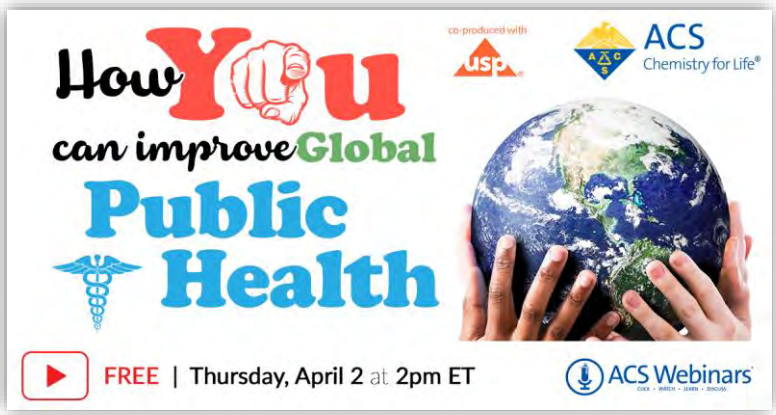

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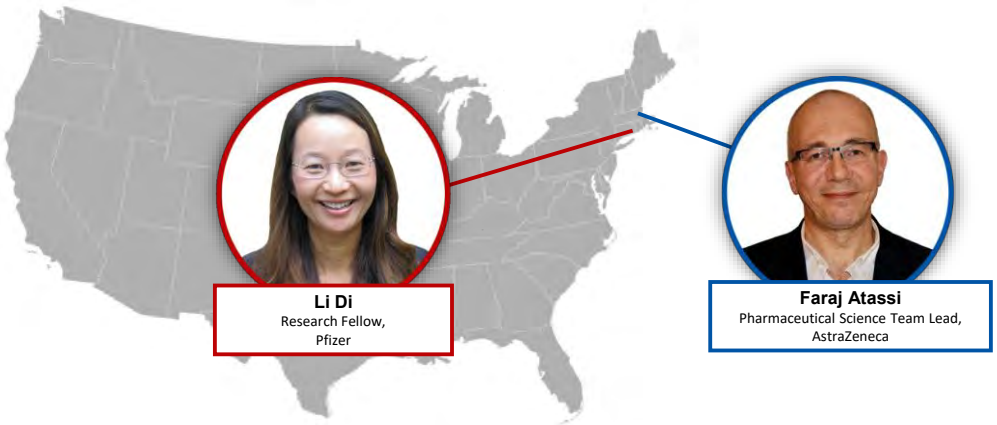
Passive Permeability: An Important Mechanism for Drug Absorption



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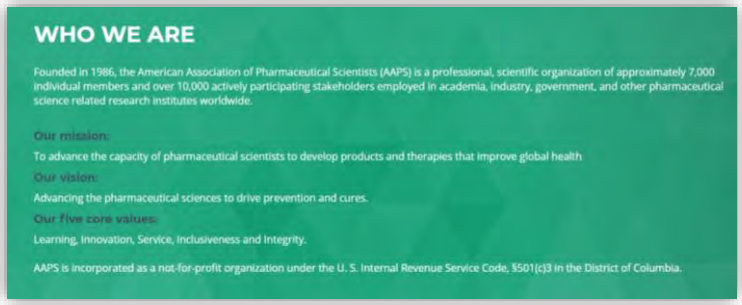

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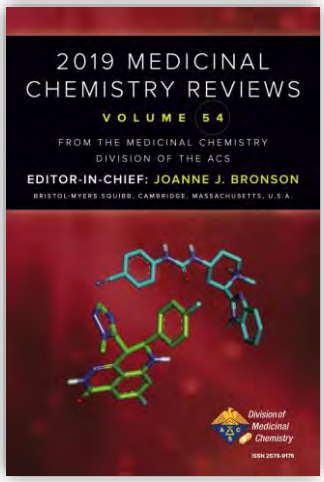

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