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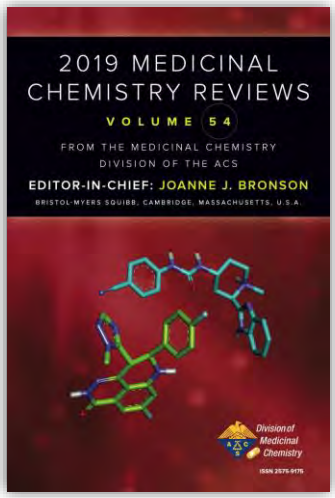

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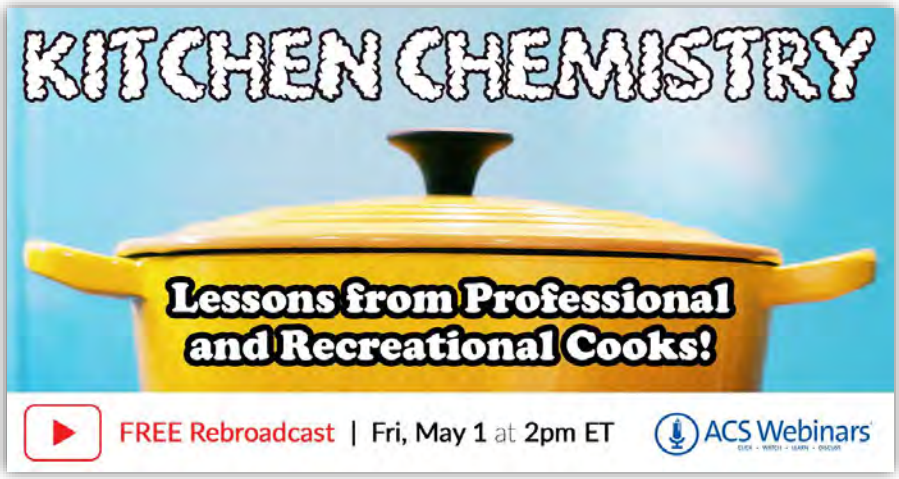

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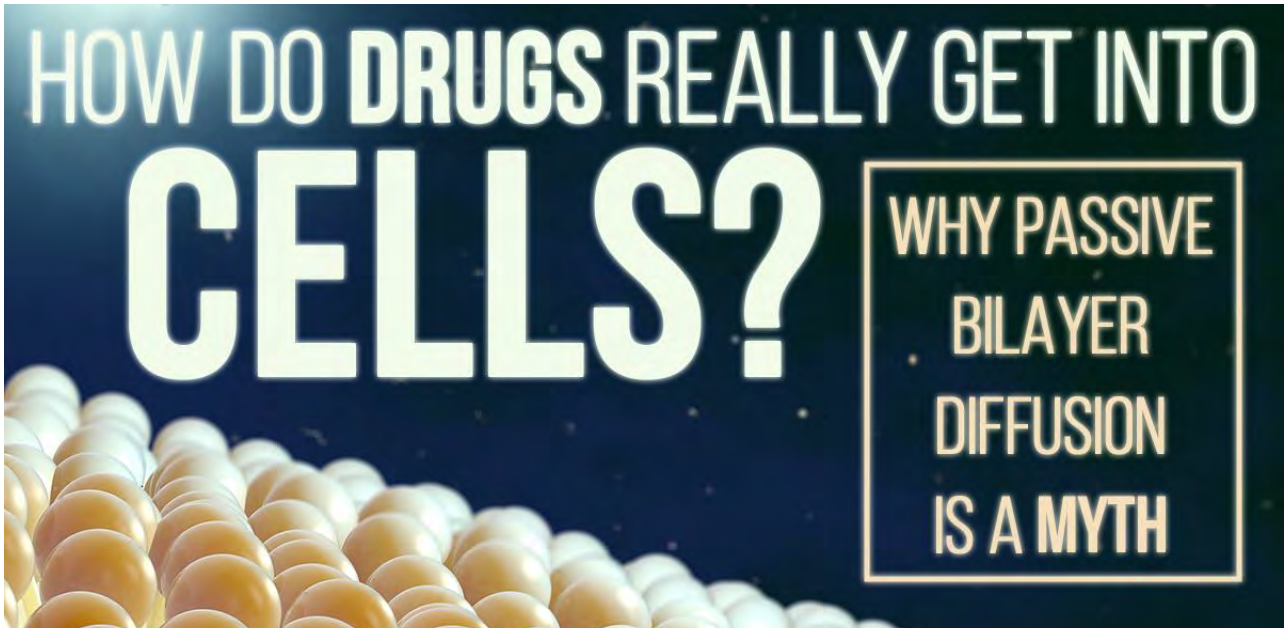

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How Drugs Really Get Into Cells: Why Passive Bilayer Diffusion is a Myth

Douglas Kell
Professor of Systems Biology, Department of Biochemistry, University of Liverpool

Michael Sinz
Senior Research Fellow, Bristol-Myers Squibb

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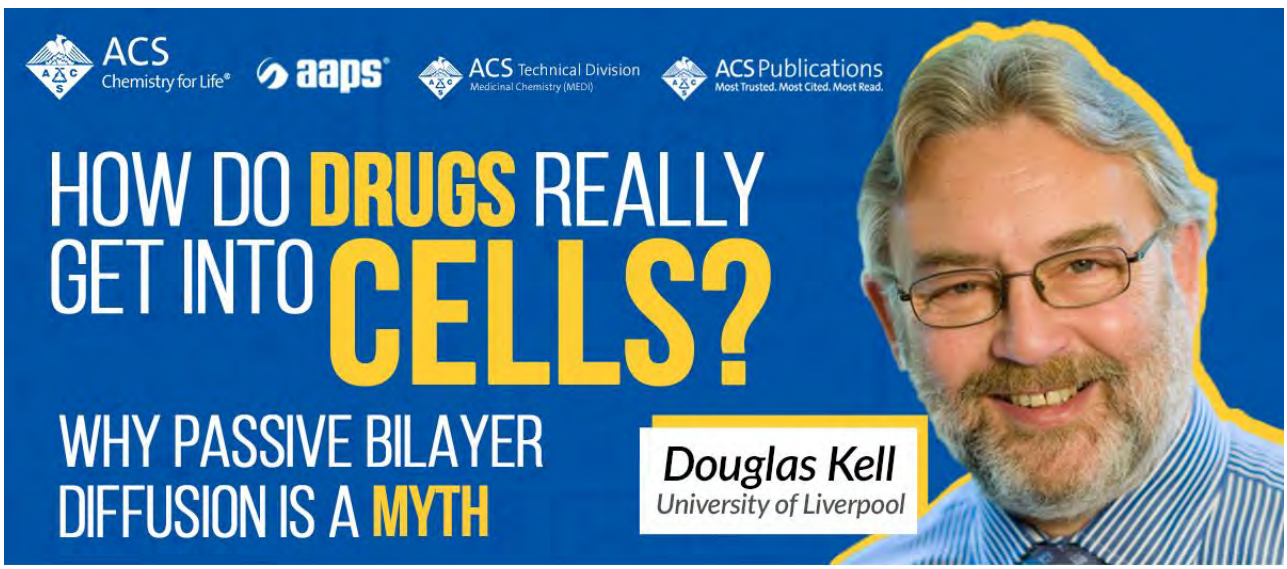

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Take-Home Messages

- **There is not much phospholipid bilayer in real cell membranes, and most diffusion through it is negligible**
- **Uptake is mainly determined by biology, not physical chemistry**
- **Transporters** (SoLute Carriers, SLCs) **easily explain heterogeneity of cell/tissue uptake, including via blood brain barrier**
- **Systems biology approaches are required**

Background – Drug Discovery

Forward and reverse (chemical) genomics in drug discovery

Classical

Function-first

Screen tissue or Organism

Find mechanisms (plural) later

PHENOTYPIC ASSAY

IDENTIFY/ FORWARD

VALIDATE/ REVERSE

MOLECULAR TARGET(S)

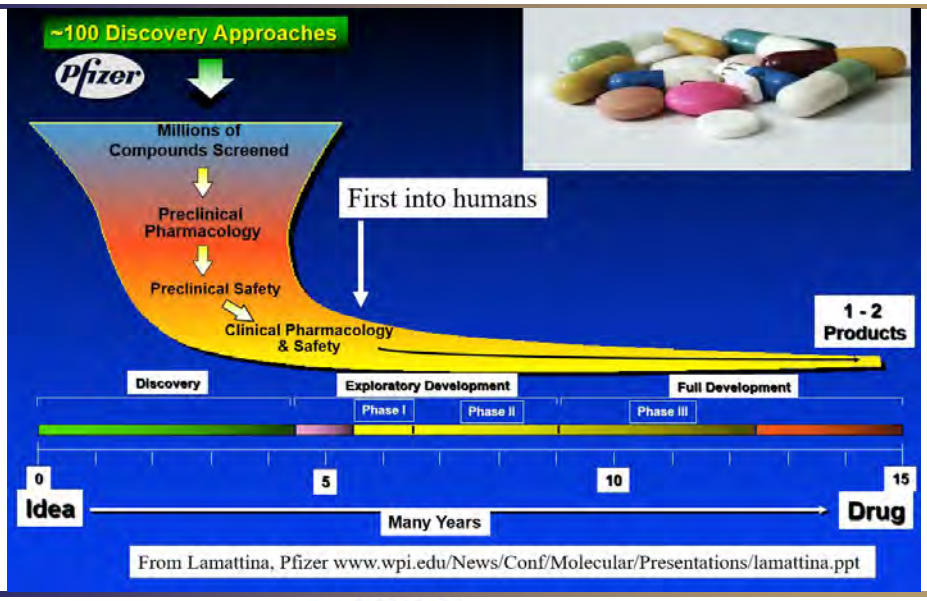
Modern

Gene/target /mechanism -first

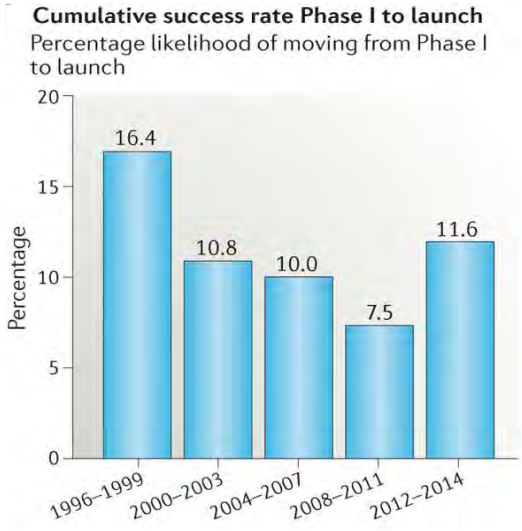
Screen target

Test in organism later

High Attrition



Attrition: ~90% of new molecules fail to make it to the clinic, even from phase I



Smietana, et al. (2016). Nat Rev Drug Disc 15: 379-380

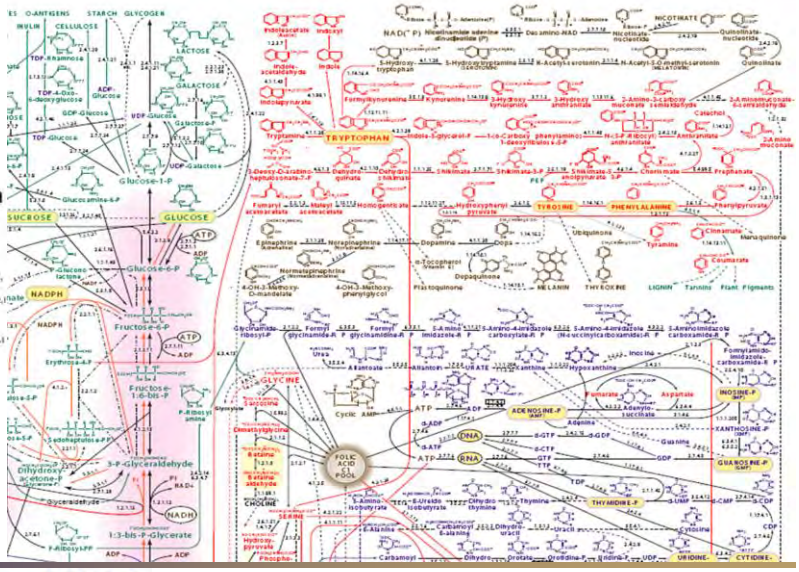
Issues of Attrition

- **Gross** PK/PD seen as less of an issue in last decade
- Now mostly due to (i) **lack of efficacy**, (ii) **toxicity**
- Both problems are underpinned by the fact that drugs are typically first developed on the basis of isolated molecular assays before being tested in the intact system
- These failures turn drug discovery – if it was not already – into a problem of systems biology

Herrgård et al., Nat Biotechnol 26, 1155-60 (2008)

A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology

Markus J Herrgård[1,19,20], Neil Swainston[2,3,20], Paul Dobson[3,4], Warwick B Dunn[3,4], K Yalçin Arga[5], Mikko Arvas[6], Nils Blüthgen[5,7], Simon Borger[8], Roeland Costenoble[9], Matthias Heinemann[9], Michael Hucka[10], Nicolas Le Novère[11], Peter Li[2,3], Wolfram Liebermeister[12], Monica L Mo[1], Ana Paula Oliveira[12], Dina Petranovic[12,13], Stephen Pettifer[2,3], Evangelos Simeonidis[3,7], Kieran Smallbone[3,14], Irena Spasić[2,3], Dieter Weichart[3,4], Roger Brent[15], David S Broomhead[3,13], Hans V Westerhoff[5,7,13], Betül Kirdar[5], Merja Penttilä[6], Edda Klipp[8], Bernhard Ø Palsson[1], Uwe Sauer[9], Stephen G Oliver[3,16], Pedro Mendes[2,3,17], Jens Nielsen[12,18] & Douglas B Kell[3,4]



Human network, Nature Biotechnol 31, 419-425 (2013)

A community-driven global reconstruction of human metabolism

Ines Thiele[1,2,36], Neil Swainston[3,4,36], Ronan M T Fleming[1,5], Andreas Hoppe[6], Swagatika Sahoo[1], Maike K Aurich[1], Hulda Haraldsdottir[1], Monica L Mo[7], Ottar Rolfsson[1], Miranda D Stobbe[8,9], Stefan G Thorleifsson[1], Rasmus Agren[10], Christian Bölling[6], Sergio Bordel[10], Arvind K Chavali[11], Paul Dobson[12], Warwick B Dunn[2,13], Lukas Endler[14], David Hala[15], Michael Hucka[16], Duncan Hull[4], Daniel Jameson[3,4], Neema Jamshidi[7], Jon J Jonsson[5], Nick Juty[17], Sarah Keating[17], Intawat Nookaew[10], Nicolas Le Novère[17,18], Naglis Malys[3,19,20], Alexander Mazein[21], Jason A Papin[11], Nathan D Price[22], Evgeni Selkov, Sr[23], Martin I Sigurdsson[1], Evangelos Simeonidis[22,24], Nikolaus Sonnenschein[25], Kieran Smallbone[3,26], Anatoly Sorokin[21,27], Johannes H G M van Beek[28–30], Dieter Weichart[3,31], Igor Goryanin[21,32], Jens Nielsen[10], Hans V Westerhoff[5,28,33], Douglas B Kell[3,34], Pedro Mendes[3,4,35] & Bernhard Ø Palsson[1,7]

7440 reactions **(~1/3 transport)**, 5,063 metabolites, 2,626 unique metabolites

Freely available at http://humanmetabolism.org/

Predicts e.g. Inborn errors of metabolism, exometabolites, drug actions, cellular differences

Crossing Membranes

Nat Rev Drug Disc 7, 205-220 (2008)

PERSPECTIVES

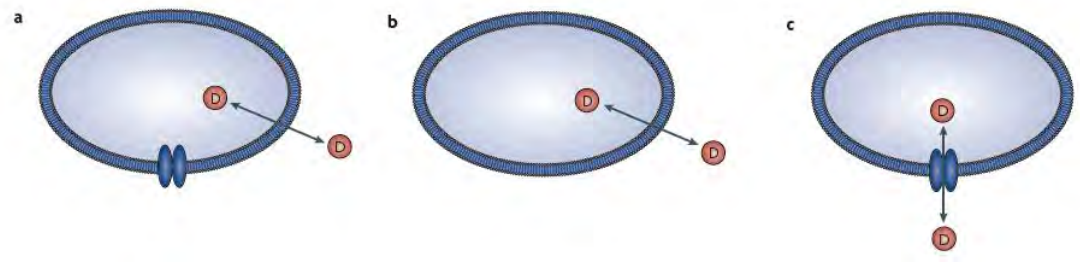
OPINION

Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule?

Paul D. Dobson and Douglas B. Kell

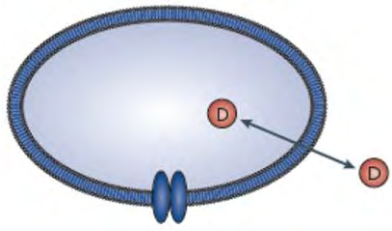
The types of biophysical forces that determine the interaction of drugs with lipids (especially hydrophobic and hydrogen-bonding interactions) are no different from those involved in their interaction with proteins, especially hydrophobic transport proteins. Therefore, biophysical arguments alone cannot make a mechanistic distinction between the two modes of transport that are outlined in FIG. 1. Indeed, four lines of reasoning together suggest that carrier-mediated

How drugs can cross cellular membranes



By free diffusion or carrier-mediated?

Regular misuse of the word 'passive'



1. **A thermodynamic usage, to mean equilibrative rather than concentrative**

   Purely thermodynamic; no mechanism is implied, **nor could be**

2. A mechanistic usage, typically implying 'through or across the bilayer'

Usually does not admit to this intended meaning, or simply assumes it. **Often conflated with 1**.

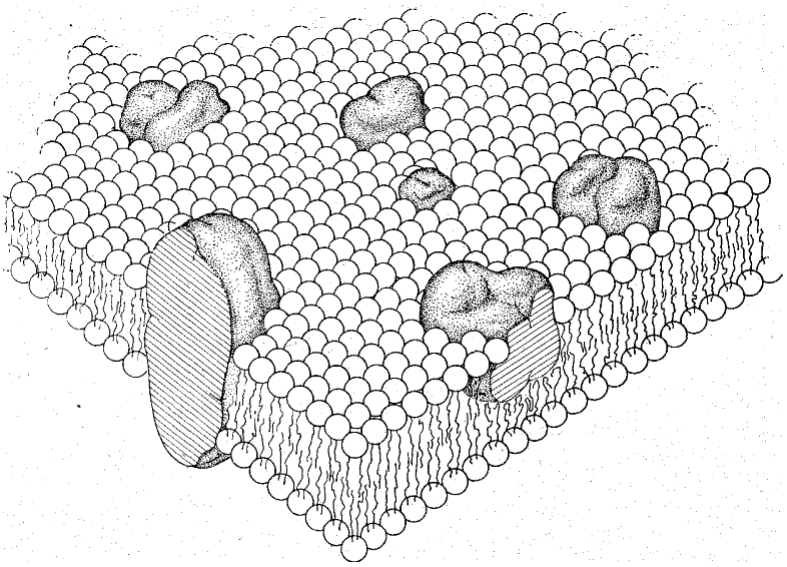
The terminology of transport reactions

Avoid ***the use of "passive" – it has too much baggage***

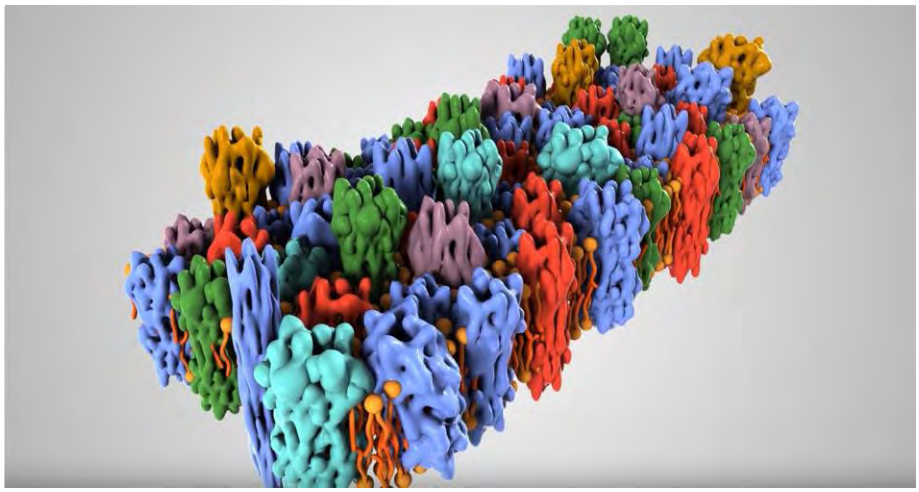
Means of Transport

Thermodynamics	Purely lipoidal	Transporter-mediated
Equilibrative Concentrative	Concentrative bilayer diffusion (may be driven by e.g. a pH gradient or membrane potential)	**Active transport**
	Simple or equilibrative bilayer diffusion	**Facilitated diffusion**

Singer & Nicolson, Science 1972



Protein:lipid ~1:10

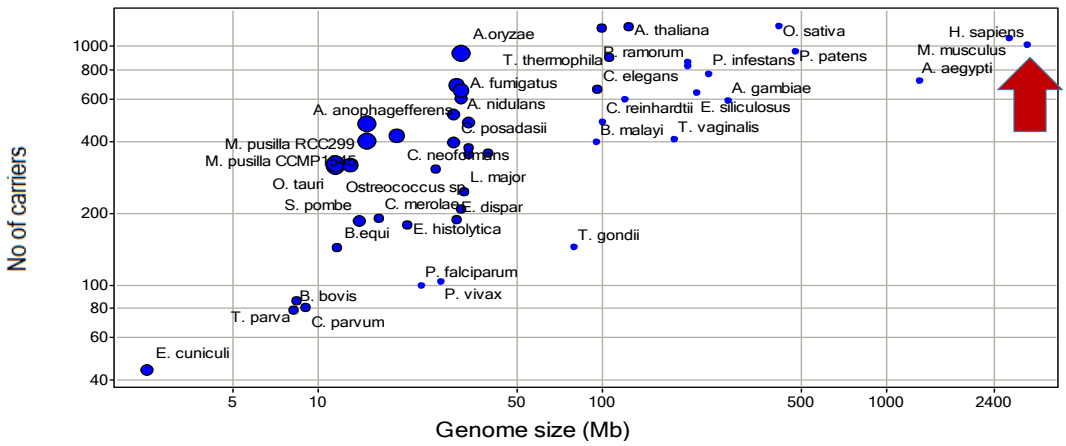


In real biological membranes there is little or no **unperturbed** bilayer: Dupuy AD, Engelman DM: Protein area occupancy at the center of the red blood cell membrane. PNAS (2008) 105, 2848-2852.

Drug Disc Today 16, 704-714 (2011)

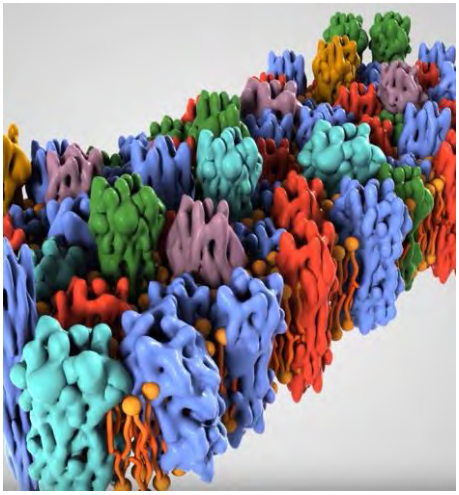
Pharmaceutical drug transport: The issues and the implications that it is essentially carrier-mediated only

Nu Douglas B. Kell[1,2], Paul D. Dobson[1,2,3] and Stephen G. Oliver[4,5]



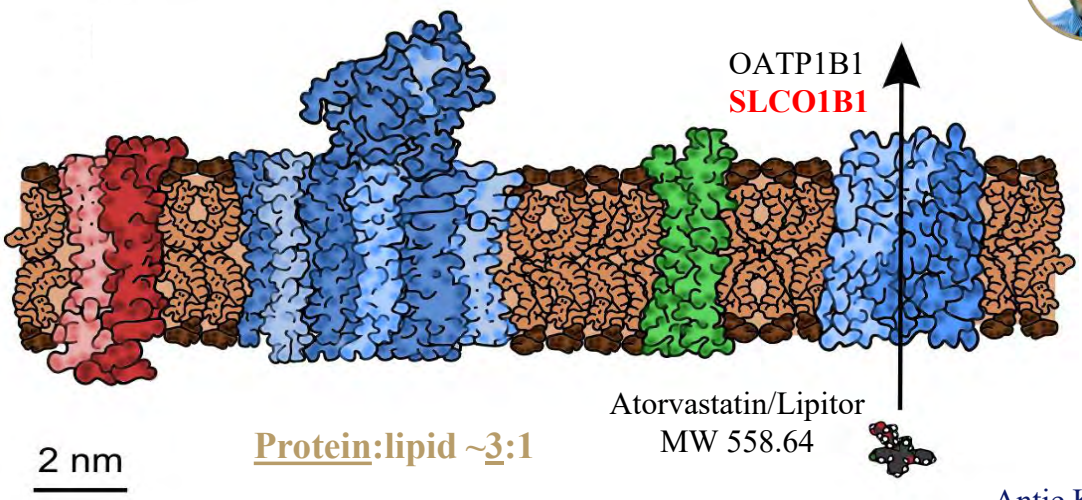
Symbol size proportional to carriers per Mbase

SoLuteCarriers (SLCs) & ATP-Binding Cassette (ABC) transporters



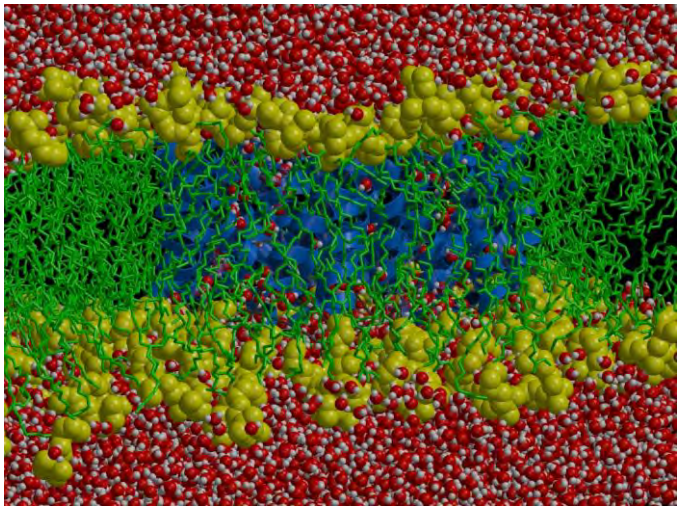
- **~500 SLCs** (mainly influxers/ antiporters)
- **~50 ABCs** (mainly effluxers)
- **Up to 4% of genes involved in transport**
- **Bioparadigms.org**

A typical biomembrane drawn to scale



Antje Kell

Membrane with aquaporin



http://www3.mpibpc.mpg.de/groups/de_groot/gallery/aqp1_snapshot.jpg

No water is crossing via phospholipids

Two Views

molecular pharmaceutics 11, 1727-1738 (2014) Review pubs.acs.org/molecularpharmaceutics

Passive Lipoidal Diffusion and Carrier-Mediated Cell Uptake Are Both Important Mechanisms of Membrane Permeation in Drug Disposition

Dennis Smith,*[,†] Per Artursson,[‡] Alex Avdeef,[§] Li Di,[∥] Gerhard F. Ecker,[⊥] Bernard Faller,[#] J. Brian Houston,[¶] Manfred Kansy,[□] Edward H. Kerns,[■,▽] Stefanie D. Krämer,[○] Hans Lennernäs,[‡] Han van de Waterbeemd,[●] Kiyohiko Sugano,[△] and Bernard Testa[▲]

frontiers in PHARMACOLOGY 5, 231 (2014) (32pp) REVIEW ARTICLE published: 31 October 2014 doi: 10.3389/fphar.2014.00231

How drugs get into cells: tested and testable predictions to help discriminate between transporter-mediated uptake and lipoidal bilayer diffusion

Douglas B. Kell[1,2] and Stephen G. Oliver[3,4]*

Phospholipid Bilayer diffusion Is Negligible (PBIN)

Placating the corn God

Hypothesis: The corn God must be placated to get good yields of corn;

Add **fish** when planting corn → Good yield this is done by sacrificing a fish

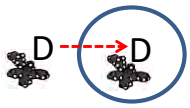
Inference: the data show that the corn God (although she is never measured directly) is important for (i.e. involved mechanistically in determining) the measured output (maize yield)

No fish at planting time gives poor yields

Placating the bilayer lipoidal diffusion God

Hypothesis: Lipoidal bilayer diffusion is important in cellular drug uptake

Add drug external to cells and make a **wish** that it enters → Drug measured inside cells



Inference: the data show that the lipoidal bilayer diffusion God (although it is never measured directly) is important for (i.e. involved mechanistically in determining) the measured output (drugs in cells)

(No) drug added external to cells
→ (No) drug measured inside cells

Measuring <u>outcomes</u> is not the same as measuring mechanisms

Position statement (≡ hypothesis)

- There is in fact **<u>no actual evidence</u>** (**evidence = data plus correct theory and interpretation**) that <u>any</u> significant drug permeability goes via undisturbed lipid bilayers in real (undamaged) biomembranes
- In the presence of potentially 100s of carriers that might serve to transport drugs it is very hard to obtain it
- Think if your own data <u>are consistent with</u> this

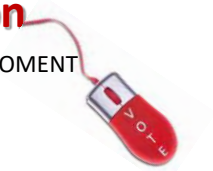
Counterfactuals that lipid-only theories need (and fail) to explain

1. **Why most drugs do not diffuse across the blood-brain barrier** (and others) **where the lipids are not significantly different**

2. **The substantially varying tissue and species distributions in cellular drug uptake**

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



Do you think CO_2 crosses intact cellular membranes by using a transporter?

- No. 100% via bilayer, for sure
- Probably through the bilayer
- Probably needs a protein transporter
- Yes, 100% - definitely needs a transporter
- Other (Tell us more in the chat)

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

It needs a transporter, of course

BBA 1840, 1592-5 (2014) Biochimica et Biophysica Acta 1840 (2014) 1592–1595

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Review

Aquaporins and membrane diffusion of CO_2 in living organisms ☆

Ralf Kaldenhoff *, Lei Kai, Norbert Uehlein

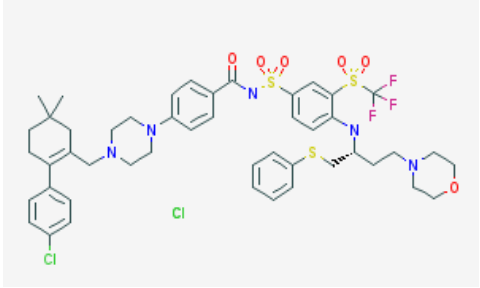
Department of Biology, Applied Plant Sciences, Technische Universität Darmstadt, Schnittspahnstrasse 10, D-64287 Darmstadt, Germany

Drug Transport – Lipinski's 'Rule of 5'

- **Poor absorption or permeation is more likely when**
- **H-bond donors > 5**
- **H-bond acceptors > 10**
- **MW > 500, and**
- **calculated Log P (CLogP) > 5**

Lipinski *et al*., Adv Drug Delivery Rev 46, 3-26 (2001) (reprint of 1997 version)

Lipinski Ro5

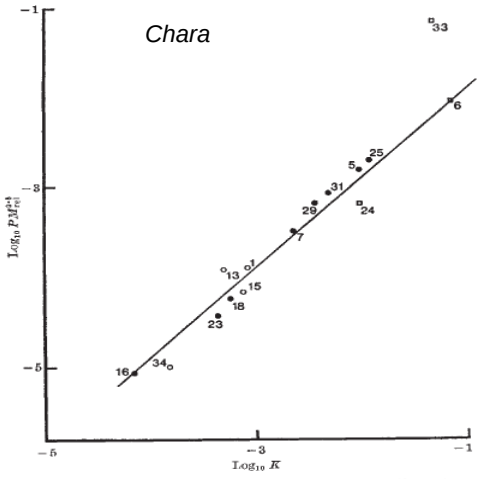


- While empirical, it effectively imputes a trade-off between lipophilicity to cross membranes and hydrophilicity to ensure aqueous solubility

- Lipinski's Rule-of-5 for determining the likely bioavailability of a compound does **implicitly** assume the pre-eminence of the lipid diffusion route as it **explicitly** classes carrier-mediated transport as an exception

- Navitoclax.2HCl – $C_{47}H_{57}Cl_3F_3N_5O_6S_3$, MW**1047.53**, 7 ring systems!

"Overton's Rule" (1899)



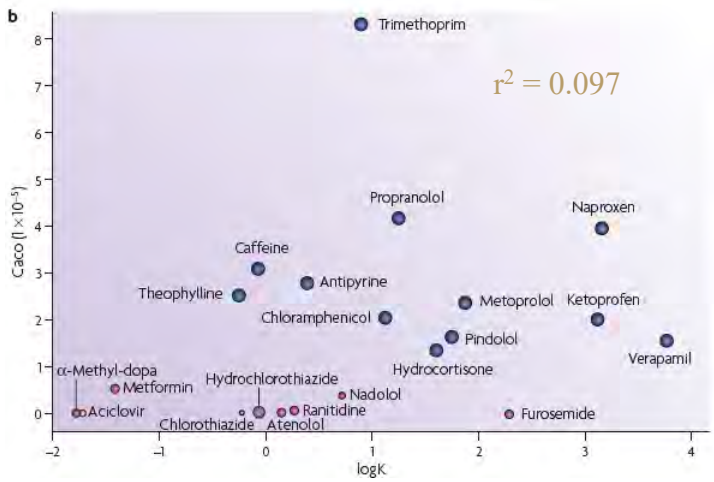
Lieb & Stein, Nature 224, 220-3 (1969)

- **Permeability coefficients of nonelectrolytes across biomembranes correlate well with olive oil/water partition coefficients.**

- (nowadays octanol is more typically used)

- **Log $K_{o/w}$ ≡ log D or sometimes log P**

Poor relationship between Caco-2 permeability and log $K_{o/w}$ (log P)



THESE log P THEORIES OF DRUG UPTAKE ARE BIOPHYSICAL, 'LIPID-ONLY' THEORIES

Corti *et al.* Eur J Pharm Sci 7, 354-362 (2006)

Narcotics ('general anaesthetics')

- **Potency also correlates with log P** (up to a cut-off) (Meyer & Overton)
- **Was assumed that they also act by a 'biophysical' mechanism by partitioning 'nonspecifically' into membrane and e.g. 'squeezing' nerve channels**

Anaesthetic potency does largely correlate with partitioning into membrane

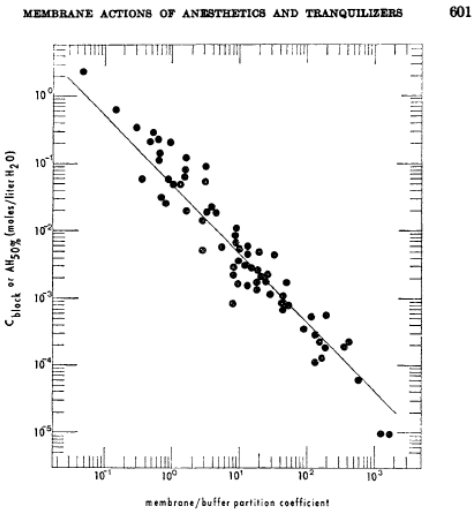
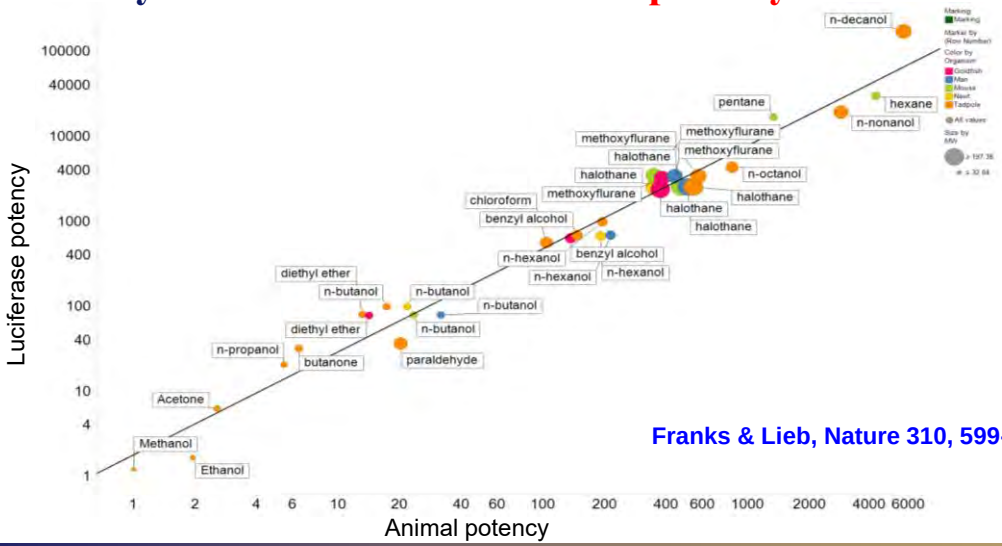


FIG. 9. Showing that the nerve-blocking (or antihemolytic) concentration of an anesthetic directly correlates with the membrane/buffer partition coefficient. See table 5 for code to anesthetics.

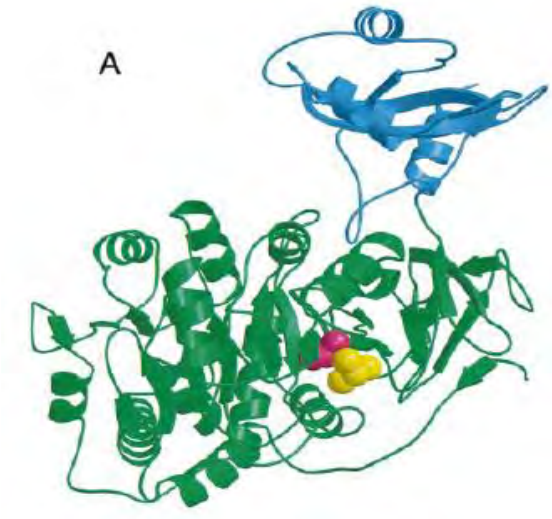
P. Seeman, Pharmacol Rev 24, 583-655 (1972) (>2800 citations!)

Relationship between ability to inhibit the soluble enzyme luciferase and narcotic potency in animals



Franks & Lieb, Nature 310, 599-601 (1984)

The structural basis is known



Binding of bromoform to luciferase

Franks *et al.*, Biophys J 75, 2205-11 (1998)

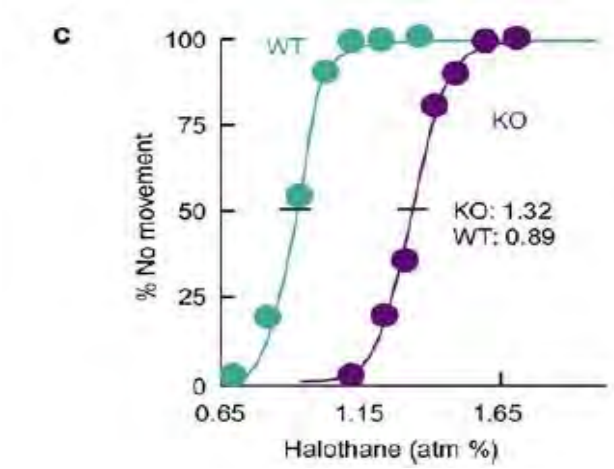
The biophysical forces

The biophysical forces required to enter (and cross) **a low dielectric are no different from those required to bind to a hydrophobic pocket of a protein**

- **Making and breaking H-bonds**
- **'hydrophobic' interactions**
- **Polarisation/ polarisability**

Biophysical arguments alone cannot realistically discriminate mechanisms

Halothane affects narcosis in part via a TREK-1 K^+ channel



Heurteaux et al. EMBO J 23, 2684-95 (2004)

Huge differences in uptake in different cell and tissue types

In Support of the Pre-eminence of Transporter-mediated Uptake

1) The existence of many proteins involved in drug efflux, which illustrates the widespread existence of the ability of natural proteins to transport xenobiotic drugs.

2) **The demonstration of the requirement of carriers for molecules (such as lipophilic cations) that had been assumed on biophysical grounds to cross biological membranes without them.**

3) **The fact that drugs do concentrate in specific tissues and do not, in fact, leak out as they would if transmembrane diffusion on the basis of log P alone was the whole (or even most of) the story.**

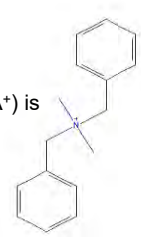
4) The increasing and by now abundant evidence from specific cases that particular drugs do in fact enter cells via identified carrier molecules for which they are not the 'natural' ligand.

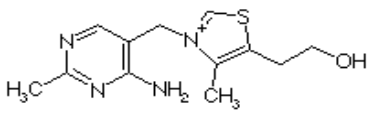
5) The ability to enhance permeability substantially by modifying the drug chemically to form a prodrug that can act as a substrate for drug carriers and thereby enter cells.

"Lipophilic cations"

"Lipophilic cations" had been assumed on biophysical grounds to cross biological membranes without the need of transporters

Uptake of the lipophilic cation dibenzyldimethyl ammonium (DDA^+) is mediated via the xxx transport system.





C00378

Thiamine (clog P ~ 2)

It is not *a priori* easy to guess from structures which xenobiotics use which carriers, though these can be rationalised post hoc via QSAR!

Barts, P. W. J. A., Hoeberichts, J. A., Klaassen, A. & Borst-Pauwels, G. W. F. H. (1980). Uptake of the lipophilic cation dibenzyldimethylammonium into *Saccharomyces cerevisiae*. Interaction with the thiamine transport system. *Biochim Biophys Acta* **597,** 125-36.

Multiple influx and efflux transporters

Jindal *et al. BMC Microbiology* (2019) 19:195
https://doi.org/10.1186/s12866-019-1561-0

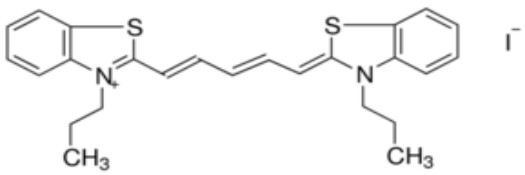
BMC Microbiology

RESEARCH ARTICLE Open Access

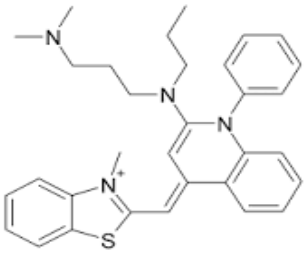
Involvement of multiple influx and efflux transporters in the accumulation of cationic fluorescent dyes by *Escherichia coli*

Srijan Jindal[1,2,3], Lei Yang[4], Philip J. Day[2,3] and Douglas B. Kell[1,2,4,5*]

Two membrane-permeant cationic dyes

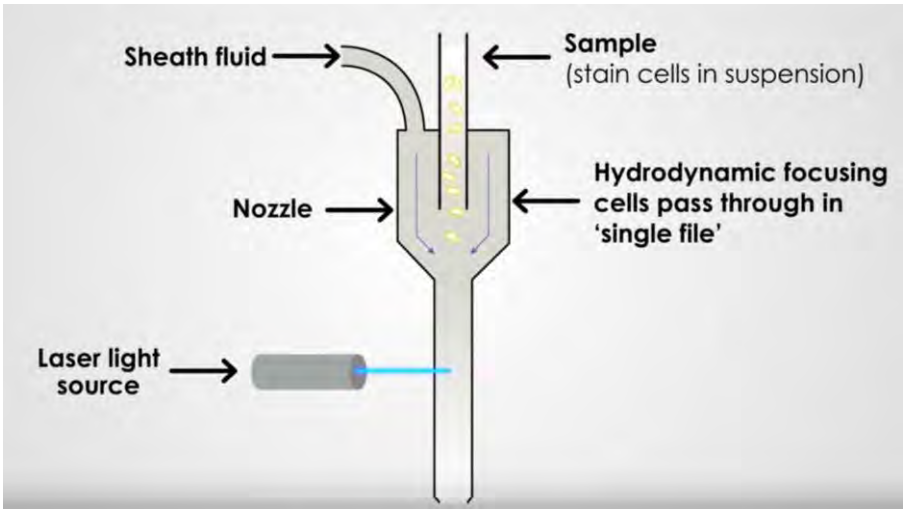


3,3′-Dipropylthiadicarbocyanine iodide
('carbocyanine' or diS-C3(5))

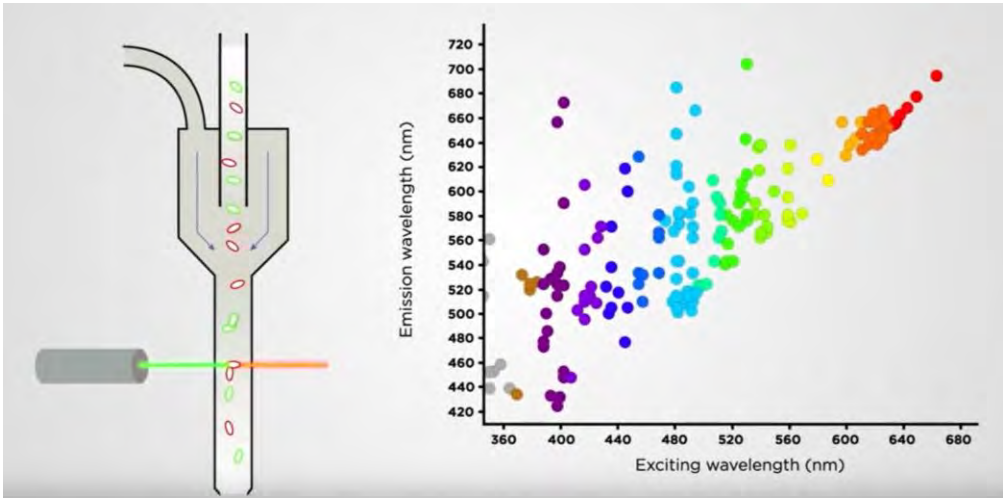


Sybr Green

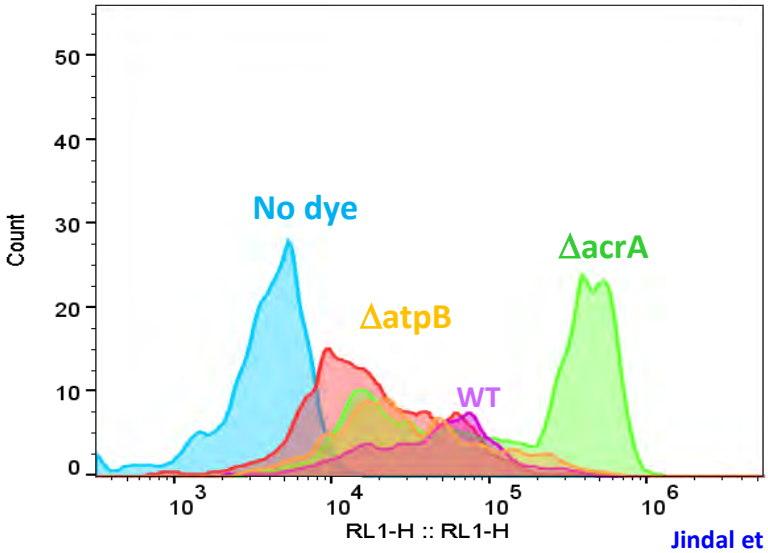
Flow Cytometry



Flow Cytometry and Fluorescence – many dyes

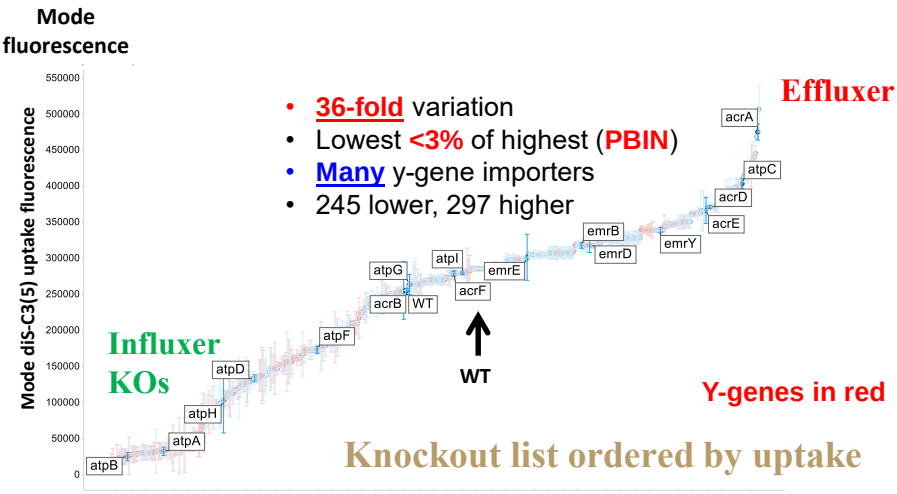


Carbocyanine uptake into *E. coli* as assessed by flow cytometry



Jindal et al. (2019) BMC Microbiol 19, 195

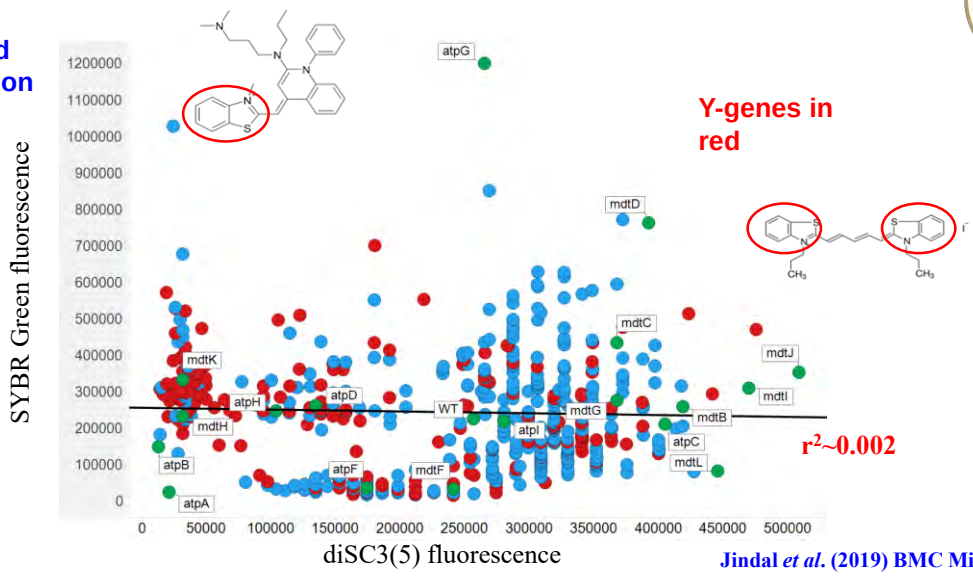
Carbocyanine uptake in *E. coli* with single-gene knockouts



Jindal *et al*. (2019) BMC Microbiol 19, 195

SYBR Green vs diSC3(5) uptake in different *E. coli* knockouts

70-fold variation



Y-genes in red

r^2~0.002

Jindal *et al.* (2019) BMC Microbiol 19, 195

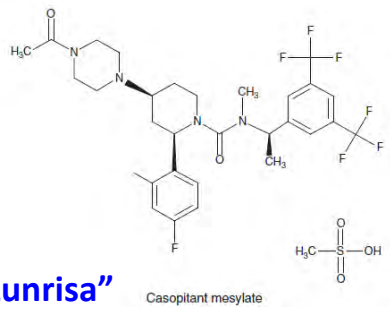
Exp Op Drug Metab Toxicol (2011) 7:137-146

Expert Opinion

1. Introduction
2. Casopitant: case study
3. Accumulation of drug related material in tissues and its effects

Drug and metabolite concentrations in tissues in relationship to tissue adverse findings: a review

Mario Pellegatti[†] & Sabrina Pagliarusco
[†]GlaxoSmithKline, Via Fleming 2, Verona, Italy



"Zunrisa"

Casopitant mesylate

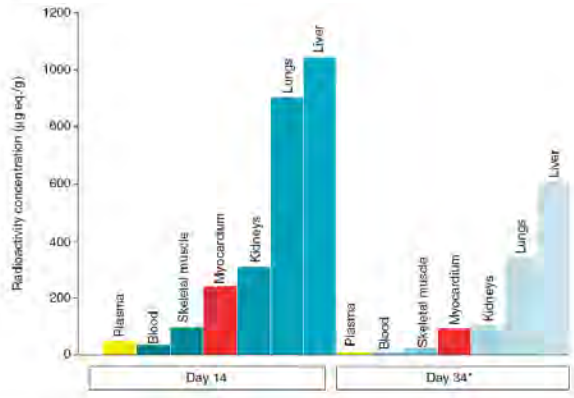
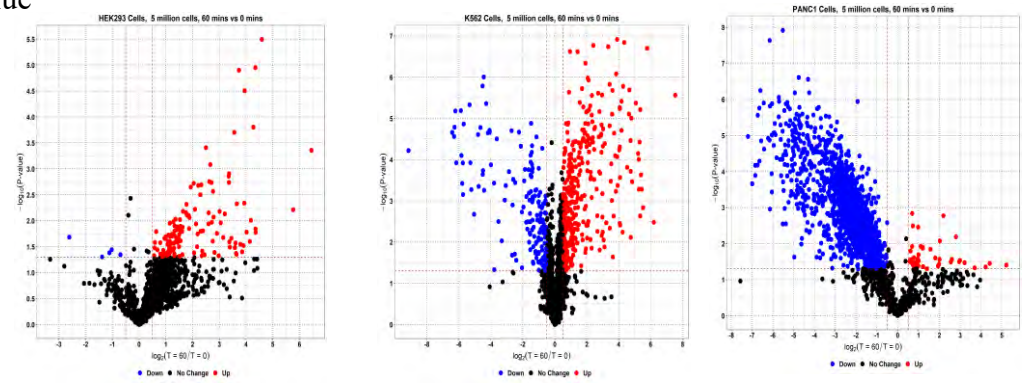


Figure 3. Concentration of drug related material in dog tissues after repeated oral doses of casopitant at 40 mg/kg.
*After a recovery period of 20 days.

Differences in serum metabolite uptake and secretion across human cell lines

-$\log_{10}$ P-value

HEK 293 **K562** **PANC1**



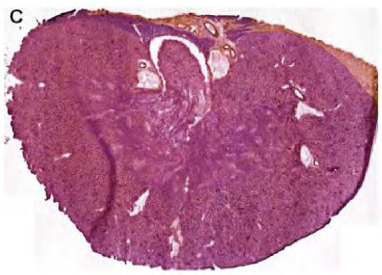
Influx

Efflux

Log_2(accumulation ratio)

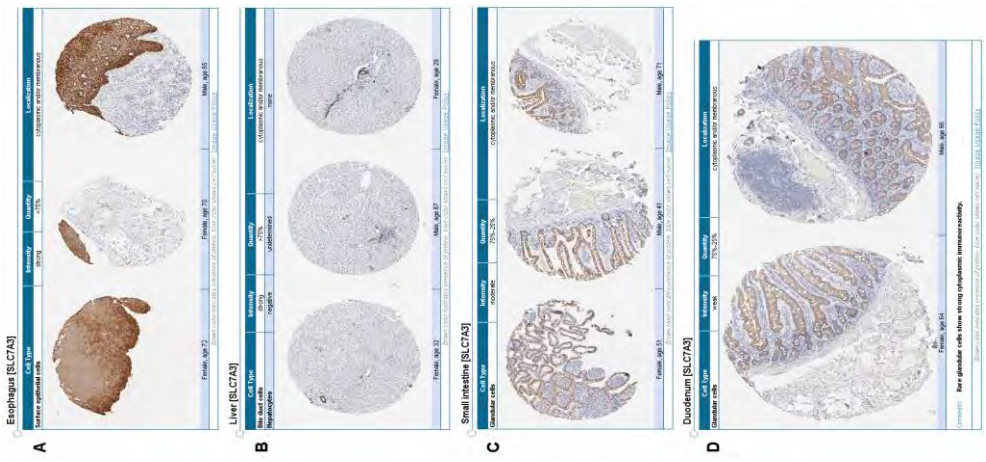
Unpublished mass spectrometric analysis, Marina Wright Muelas (Liverpool)

Imatinib distribution in mouse kidney



Römpp, A. et al. (2011) Anal Bioanal Chem 401, 65-73

Tissue-selective expression of SLC7A3

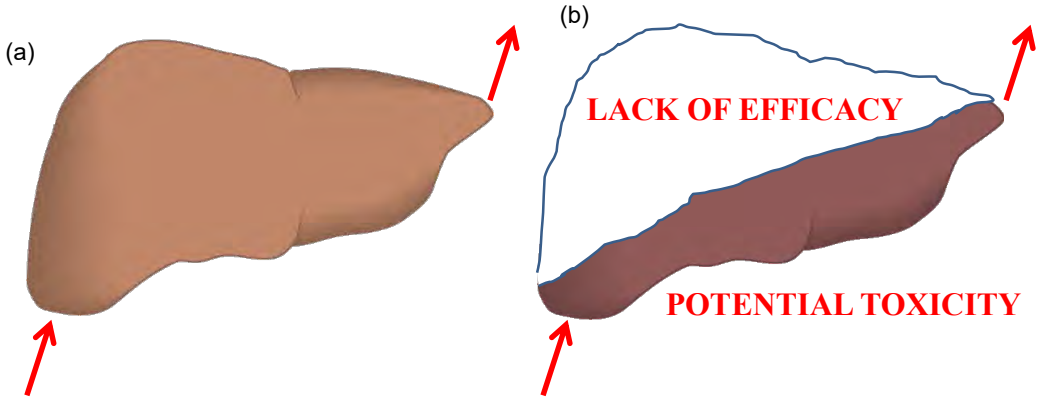


cationic amino acid transporter, y+ system

http://www.proteinatlas.org/tissue_profile.php?antibody_id=3629

Two livers with the same gross PK/PD

Heterogeneous distributions of a drug in an organ can lead to a toxicity or a lack of efficacy **while retaining the same gross PK/PD**



Total amount of drug in organ is the same, but in (b) it has **no efficacy** in most of the cells (as it does not enter them all) and **may exhibit toxicity** (as it is more highly concentrated in some)

Two ramifications of the view that drug transport is largely carrier-mediated

- **Successful** (marketed) **drugs may be more like endogenous** (intermediary) **metabolites**

- **But how do we tell which transporters are used by particular drugs?**

Carriers involved in the cellular uptake of drugs

Lanthaler *et al. BMC Biology* 2011, **9**:70
http://www.biomedcentral.com/1741-7007/9/70

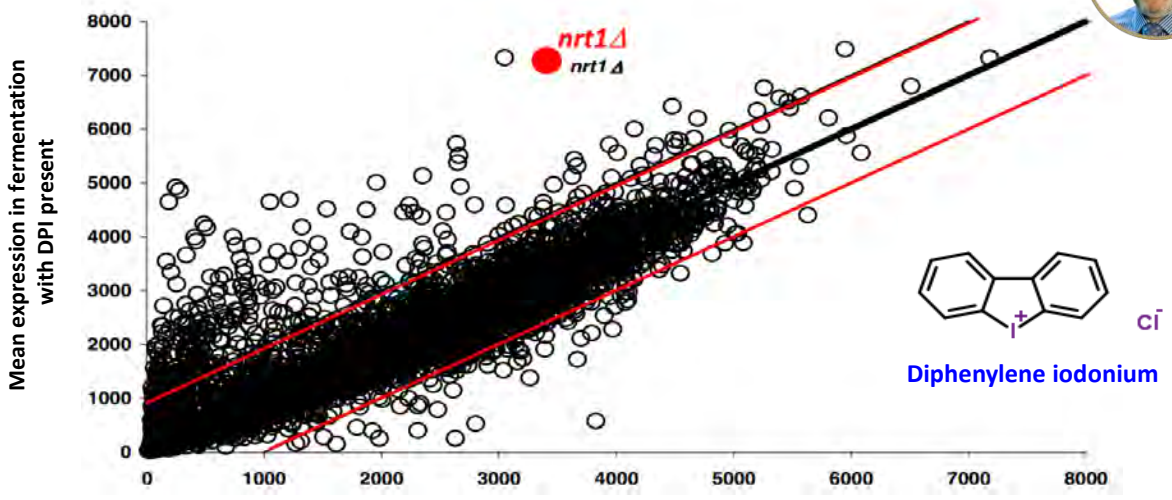
BMC Biology
incorporating Journal of Biology

RESEARCH ARTICLE Open Access

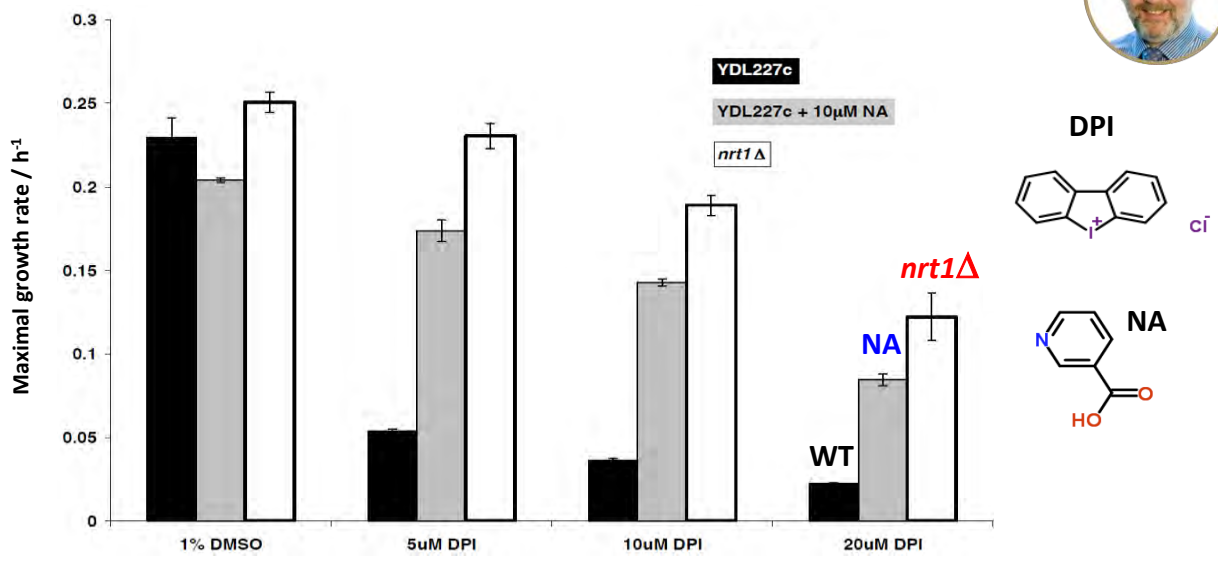
Genome-wide assessment of the carriers involved in the cellular uptake of drugs: a model system in yeast

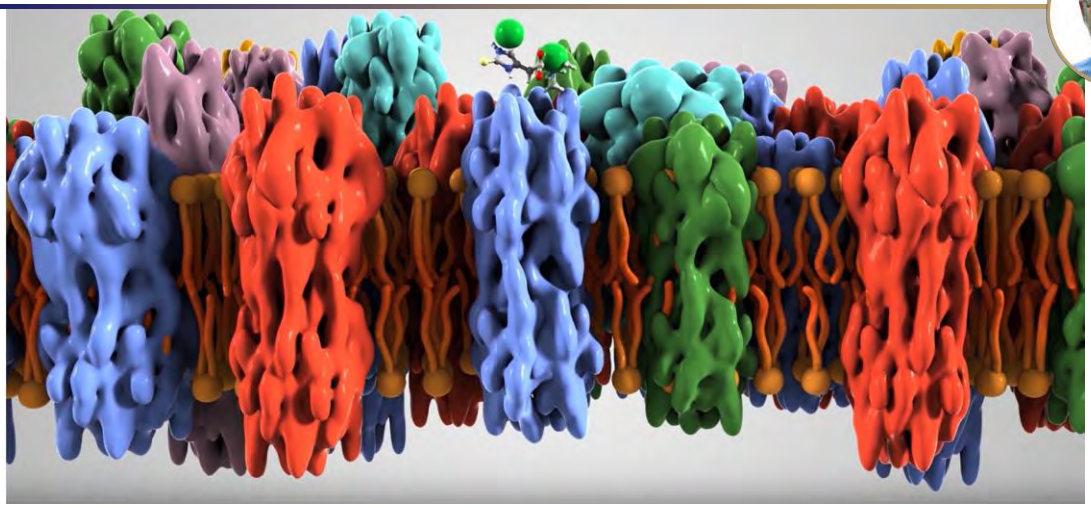
Karin Lanthaler[1,2,3†], Elizabeth Bilsland[4†], Paul D Dobson[1,2], Harry J Moss[4], Pınar Pir[3,4], Douglas B Kell[1,2] and Stephen G Oliver[3,4*]

A) Effect of yeast gene deletions on DPI toxicity



B) Effect of *nrt1* deletion on DPI toxicity and its rescue by nicotinic acid





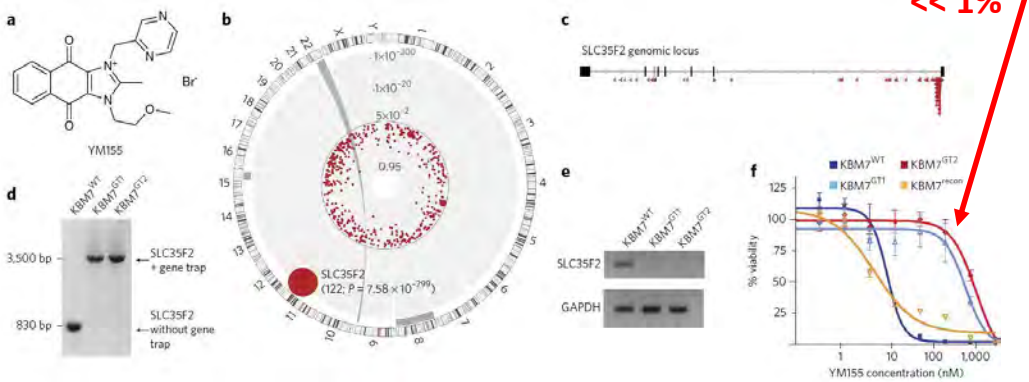
NB – even this approach will miss cases in which there are very many transporters – as is probably often true for marketed drugs

The solute carrier SLC35F2 enables YM155-mediated DNA damaged toxicity

ARTICLE
PUBLISHED ONLINE: 27 JULY 2014 | DOI: 10.1038/NCHEMBIO.1590
nature chemical biology
10, 768-773 (2014)

The solute carrier SLC35F2 enables YM155-mediated DNA damage toxicity

Georg E Winter[1], Branka Radic[1,4], Cristina Mayor-Ruiz[2,4], Vincent A Blomen[3], Claudia Trefzer[1], Richard K Kandasamy[1], Kilian V M Huber[1], Manuela Gridling[1], Doris Chen[1], Thorsten Klampfl[1], Robert Kralovics[1], Stefan Kubicek[1], Oscar Fernandez-Capetillo[2], Thijn R Brummelkamp[1,3] & Giulio Superti-Furga[1]*



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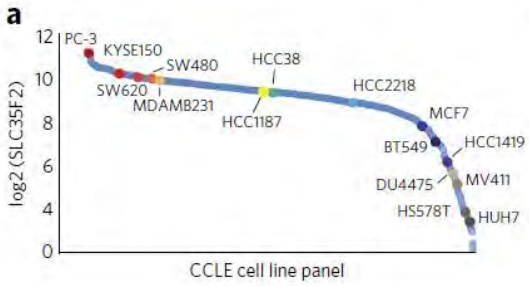


Note the negligible background activity

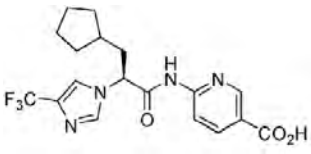
Of course the converse is also true

drugs with transporters only in one tissue can be targeted there

Journal of Medicinal Chemistry
JMC 55, 1318−1333 (2012)
Article
pubs.acs.org/jmc

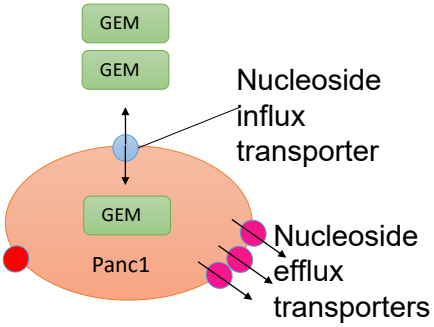
Discovery of (*S*)-6-(3-Cyclopentyl-2-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)propanamido)nicotinic Acid as a Hepatoselective Glucokinase Activator Clinical Candidate for Treating Type 2 Diabetes Mellitus

Jeffrey A. Pfefferkorn,*[,†] Angel Guzman-Perez,[‡] John Litchfield,[‡] Robert Aiello,[‡] Judith L. Treadway,[‡]



- Inhibiting gluokinase non-selectively is toxic
- Isozymes essentially identical in liver and pancreas
- Substrate for OATPs in liver
- Hepatocyte: pancreas ratio ~50:1….

Proposed partial mode of action of fragments in enhancing gemcitabine toxicity in Panc1 cells



Influx/efflux transporter expression ratio insufficient for full toxicity


frontiers in Pharmacology 8, 155 (2017)

ORIGINAL RESEARCH

Enhancing Drug Efficacy and Therapeutic Index through Cheminformatics-Based Selection of Small Molecule Binary Weapons That Improve Transporter-Mediated Targeting: A Cytotoxicity System Based on Gemcitabine

Justine M. Grixti, Steve O'Hagan, Philip J. Day and Douglas B. Kell

Drug varies transporter expression → increased toxicity

74

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What are mainly the 'real' substrates of these drug transporters?

- Pharmaceutical drugs
- Endogenous metabolites
- Exogenous natural products
- Fluorescent compounds
- Other (Tell us more in the chat)

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

Drug-metabolite likenesses

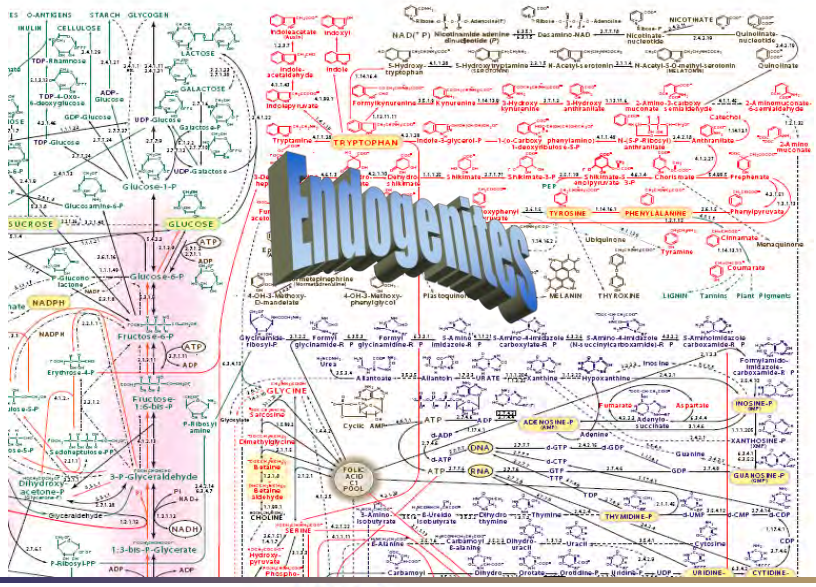
Metabolomics
DOI 10.1007/s11306-014-0733-z

11, 323-339 (2015)

ORIGINAL ARTICLE

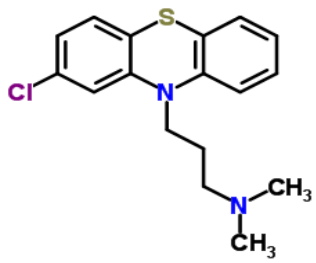
A 'rule of 0.5' for the metabolite-likeness of approved pharmaceutical drugs

Steve O'Hagan · Neil Swainston · Julia Handl · Douglas B. Kell

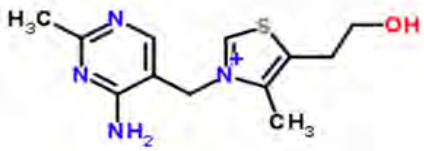


Drug-metabolite similarities

Chlorpromazine



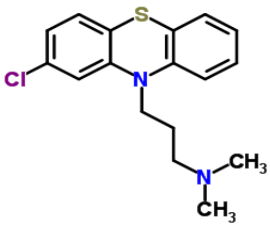
Thiamine



- **Encode as a string of 1s and 0s** (various encodings exist)
- **Compare strings, commonly as Jaccard/Tanimoto distance of shared bits/ total bits**

Drug-metabolite similarities

Chlorpromazine

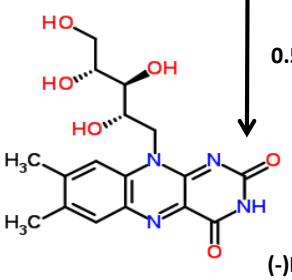


0.485

Thiamine

0.33

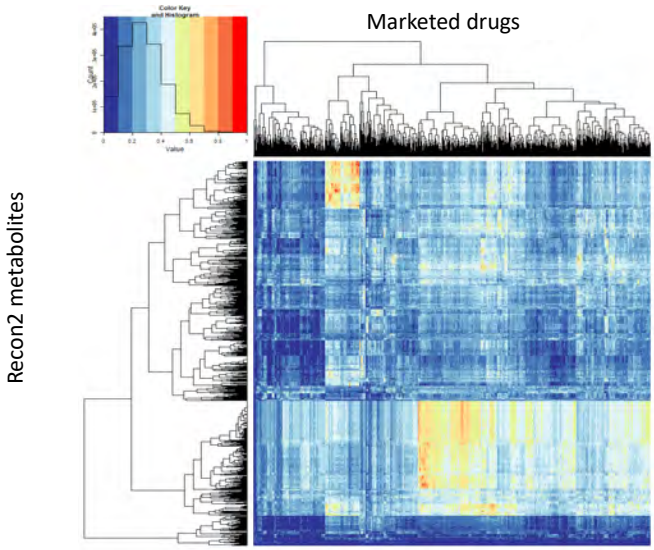
0.50



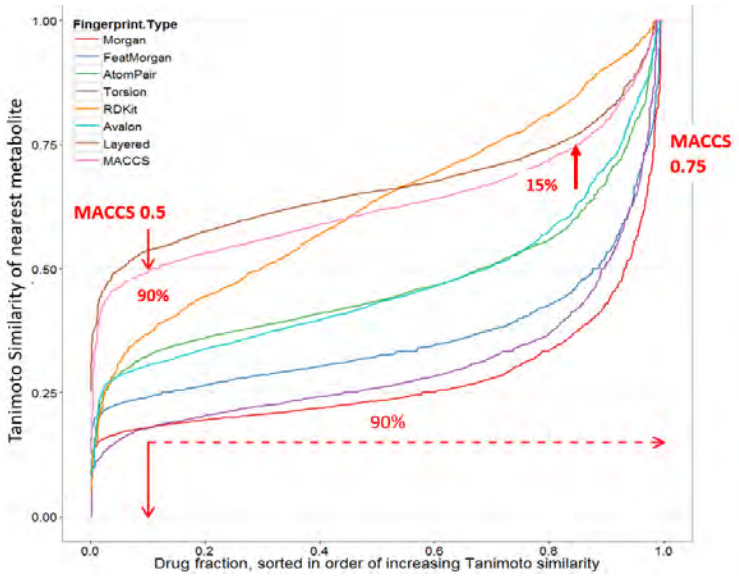
(-)Riboflavin

MACCS 166 ENCODING

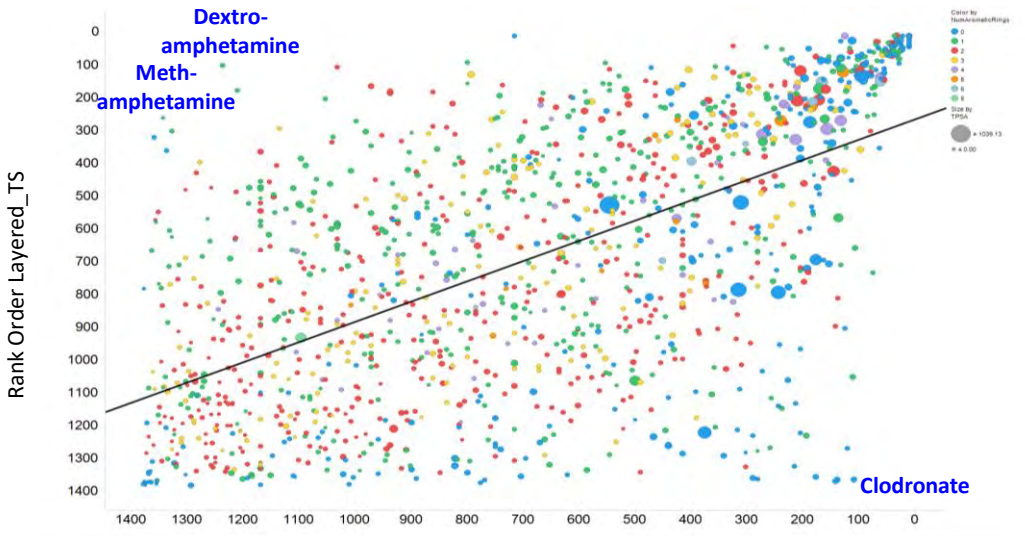
O'Hagan & Kell, (2015) Metabolomics 11, 323-329



Cumulative Closest Tanimoto distance for different fingerprints

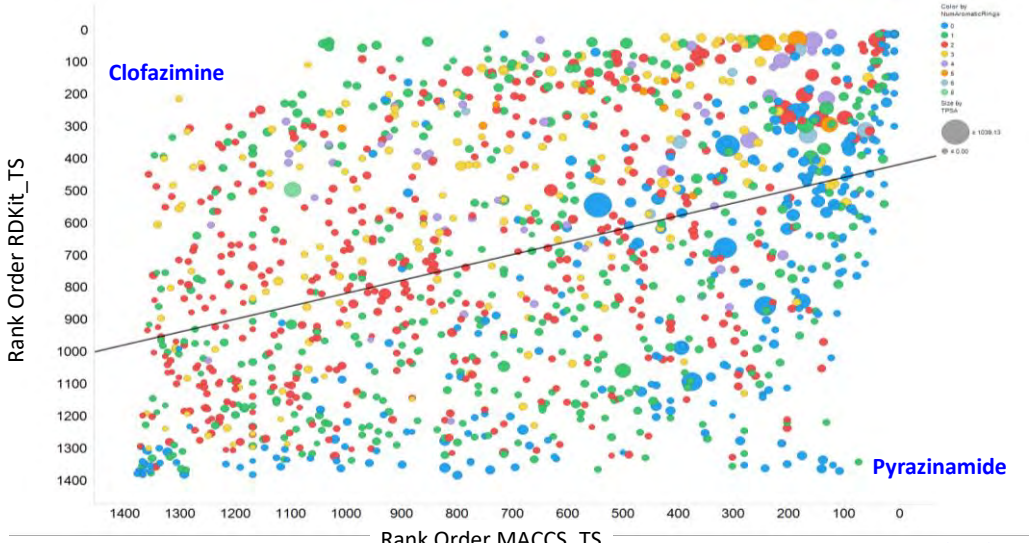


Rank Order of Layered_TS vs MACCS_TS



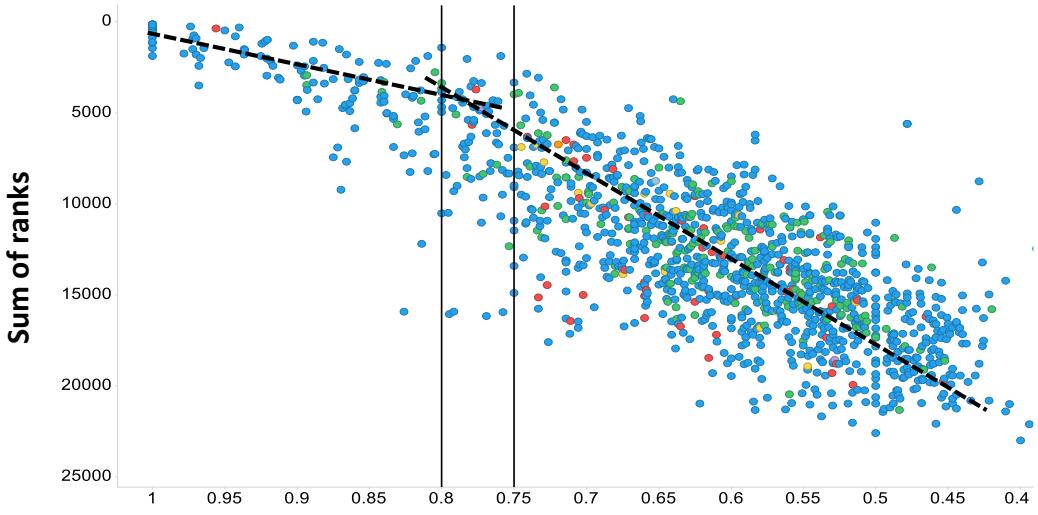
O'Hagan & Kell, (2017) ADME & DMPK 5, 85-125

Rank Order of RDKit_TS vs MACCS_TS



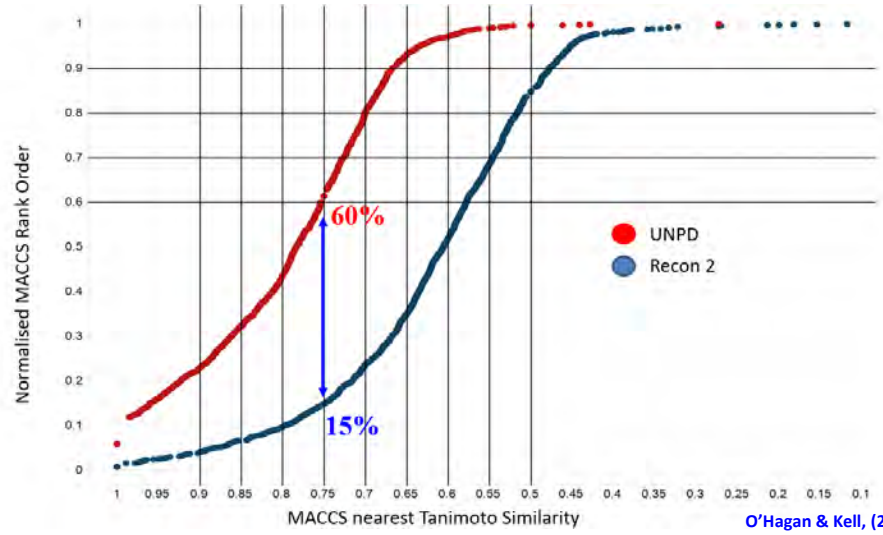
O'Hagan & Kell, (2017) ADME & DMPK 5, 85-125

Sum of ranks vs MACCS max_TS implies 0.75-0.8 cutoff



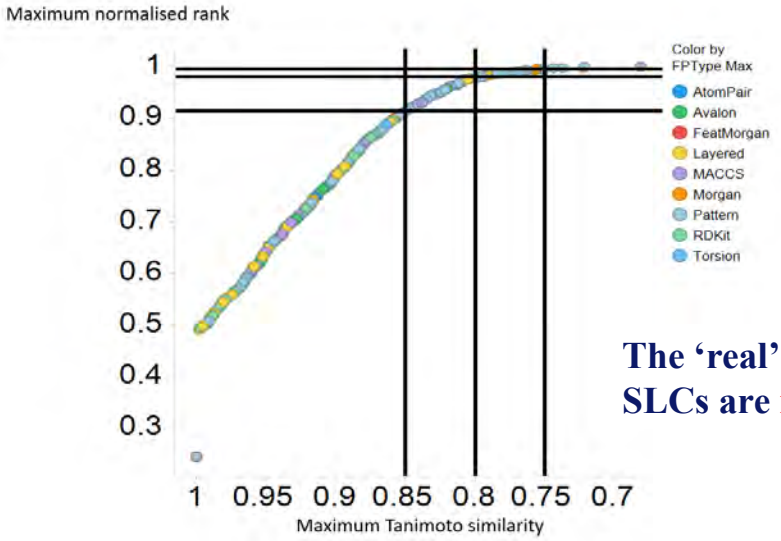
O'Hagan & Kell, (2017) ADME & DMPK 5, 85-125

Normalised MACCS rank order vs MACCS_TS full for pharmaceutical drugs vs endogenites or natural products



O'Hagan & Kell, (2017) ADME & DMPK 5, 85-125

Maximum rank with TYPICAL encoding, 196k NPs



The 'real' substrates of most SLCs are natural products

O'Hagan & Kell, (2017) ADME & DMPK 5, 85-125

Unlocking SLC Transporters

https://re-solute.eu/

nature reviews drug discovery

COMMENT · 07 APRIL 2020

The RESOLUTE consortium: unlocking SLC transporters for drug discovery

The Innovative Medicines Initiative Consortium RESOLUTE has started to develop tools and produce data sets to de-orphanize transporters in the solute carrier protein (SLC) superfamily, thereby lowering the barrier for the scientific community to explore SLCs as an attractive drug target class.

Giulio Superti-Furga, Daniel Lackner, Tabea Wiedmer, Alvaro Ingles-Prieto, Barbara Barbosa, Enrico Girardi, Ulrich Goldmann, Bettina Gürtl, Kristaps Klavins, Christoph Klimek, Sabrina Lindinger, Eva Liñeiro-Retes, André C. Müller, Svenja Onstein, Gregor Redinger, Daniela Reil, Vitaly Sedlyarov, Gernot Wolf, Matthew Crawford, Robert Everley, David Hepworth, Shenping Liu, Stephen Noell, Mary Piotrowski, Robert Stanton, Hui Zhang, Salvatore Corallino, Andrea Faedo, Maria Insidioso, Giovanna Maresca, Loredana Redaelli, Francesca Sassone, Lia Scarabottolo, Michela Stucchi, Paola Tarroni, Sara Tremolada, Helena Batoulis, Andreas Becker, Eckhard Bender, Yung-Ning Chang, Alexander Ehrmann, Anke Müller-Fahrnow, Vera Pütter, Diana Zindel, Bradford Hamilton, Martin Lenter, Diana Santacruz, Coralie Viollet, Charles Whitehurst, Kai Johnsson, Philipp Leippe, Birgit Baumgarten, Lena Chang, Yvonne Ibig, Martin Pfeifer, Jürgen Reinhardt, Julian Schönbett, Paul Selzer, Klaus Seuwen, Charles Bettembourg, Bruno Biton, Jörg Czech, Hélène de Foucauld, Michel Didier, Thomas Licher, Vincent Mikol, Antje Pommereau, Frédéric Puech, Veeranagouda Yaligara, Aled Edwards, Brandon J. Bongers, Laura H. Heitman, Ad P. IJzerman, Huub J. Sijben, Gerard J.P. van Westen, Justine Grixti, Douglas B. Kell, Farah Mughal, Neil Swainston, Marina Wright-Muelas, Tina Bohstedt, Nicola Burgess-Brown, Liz Carpenter, Katharina Dürr, Jesper Hansen, Andreea Scacioc, Giulia Banci, Claire Coles, Daniela Digles, Gerhard Ecker, Barbara Füzi, Viktoria Gamsjäger, Melanie Grandits, Riccardo Martini, Florentina Troger, Patrick Altermatt, Cédric Doucerain, Franz Dürrenberger, Vania Manolova, Anna-Lena Steck, Hanna Sundström, Maria Wilhelm & Claire M. Steppan

Conclusions

- The human metabolic network contains many transporters of unknown specificity, and often not for endogenites
- **Much** evidence shows that specific drugs do enter cells by known carriers, and probably do so **only** via this route – "bilayer diffusion" is **negligible** and **a myth**
- Carrier-mediated uptake is thus almost certainly the rule and not the exception, and **makes drug and xenobiotic transport a problem of systems biology**
- This has **considerable** implications for the design of safe and efficacious drugs that behave at a SYSTEMS level
- We thus need to develop systems pharmacology, **especially including expression proteomics of transporters……**

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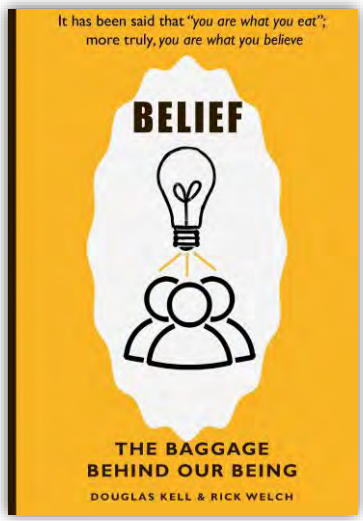

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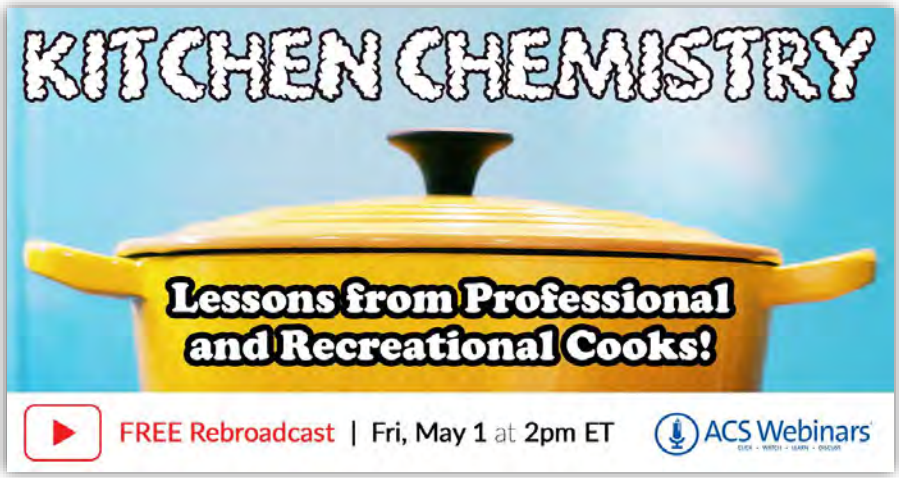

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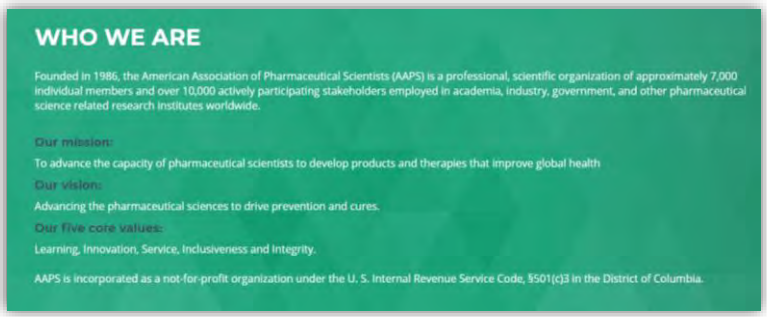

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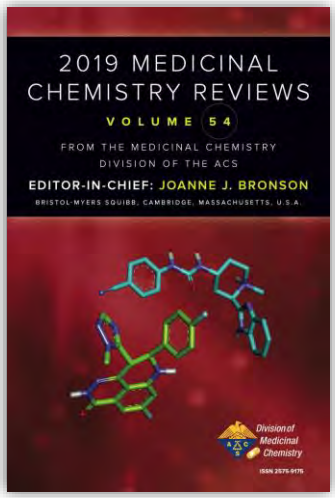

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