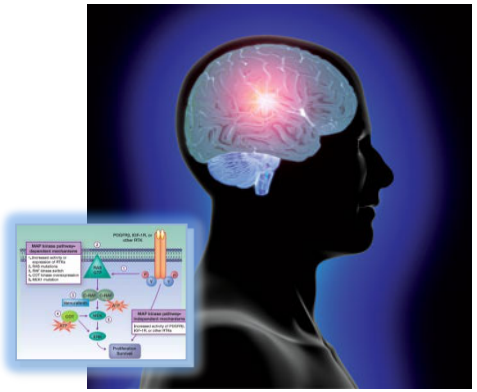
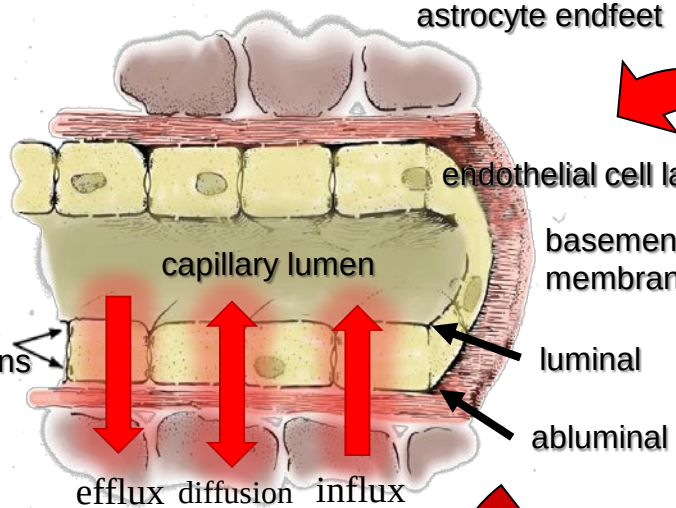
Drug Delivery to the CNS: Barriers that May Influence Efficacy in Treating Tuberculosis in the Brain

TB-Meningitis

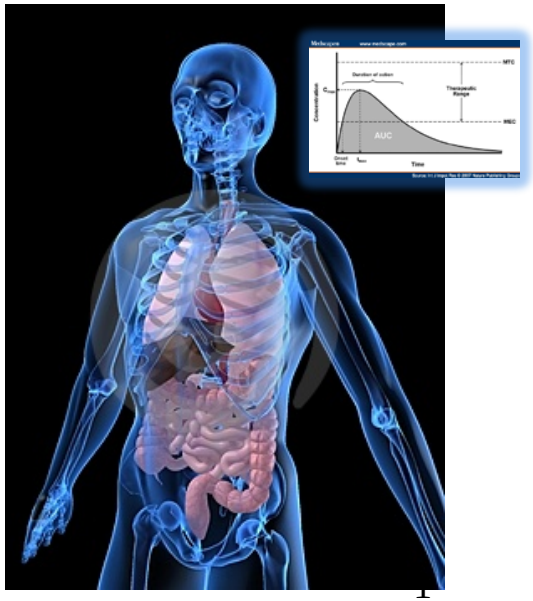


Blood Brain Barrier



TB-Meningitis
Rockville MD
22-23 May 2017

Systemic Pharmacokinetics



University of Minnesota Brain Barriers Research Center

William F. Elmquist
Pharmaceutics
UNIVERSITY OF MINNESOTA

Translational research in CNS Drug Delivery
- Must keep in mind the big questions !

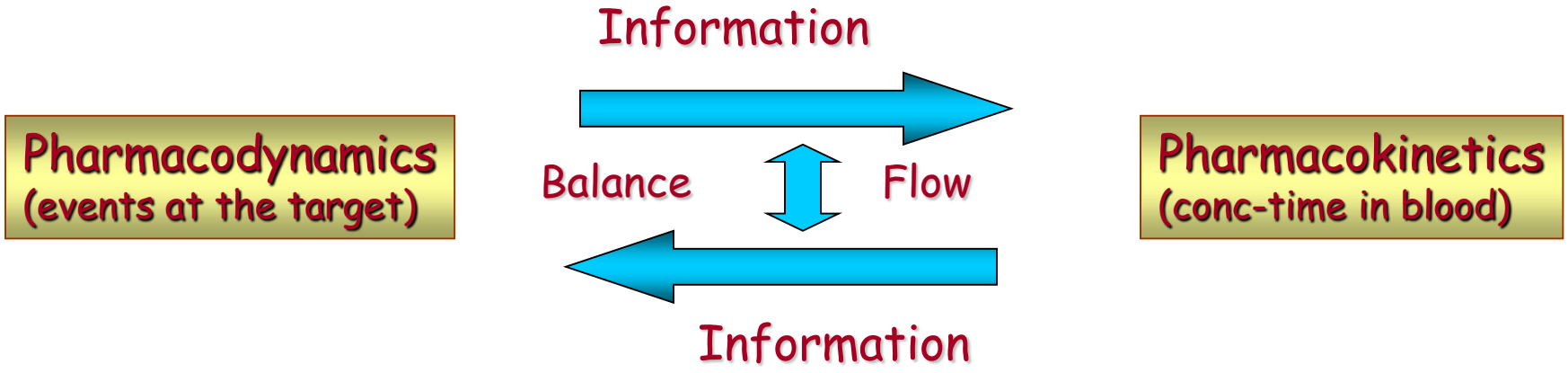
Why

Why Does a Drug Work ??

Why Doesn't a Drug Work ??

Why does this one work, and that one doesn't ??

Connect - Disconnect of the PK-PD Relationship



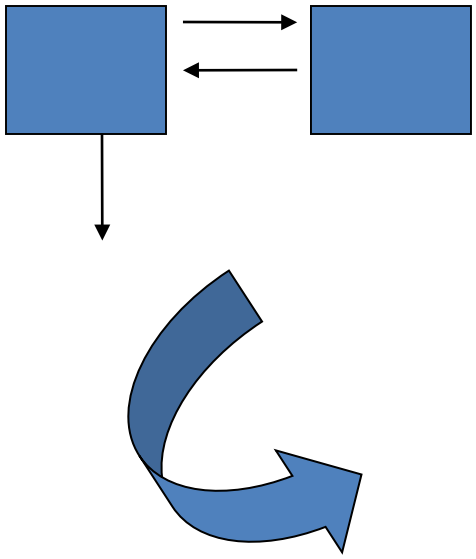
Overview

CNS Drug Delivery in the Era of Systems Biology

Dose and dosing regimen

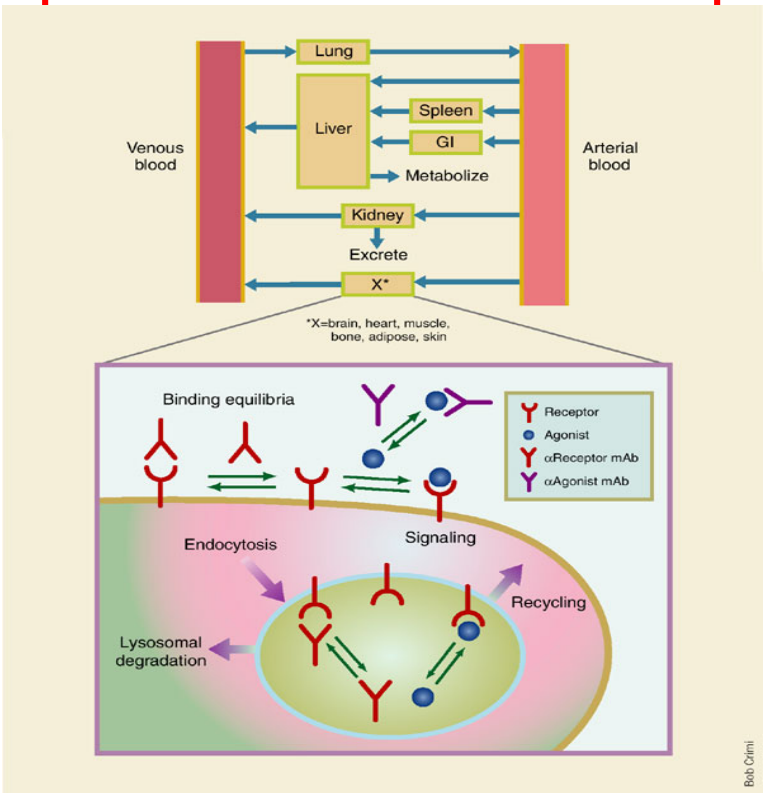
"Traditional PK/PD"

Black box models



"the Big Picture"

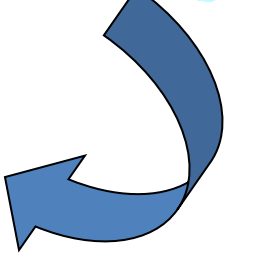
Systems model

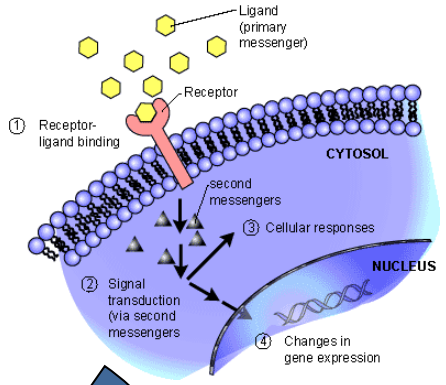


Mechanisms of delivery and action

"Molecular pharmacokinetics"

System – structure function

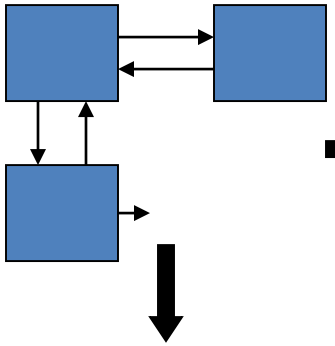


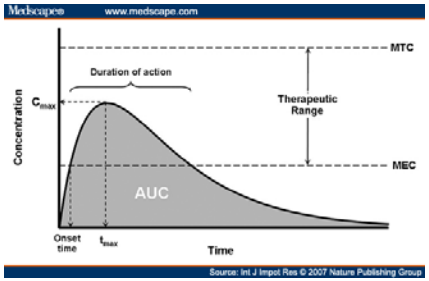


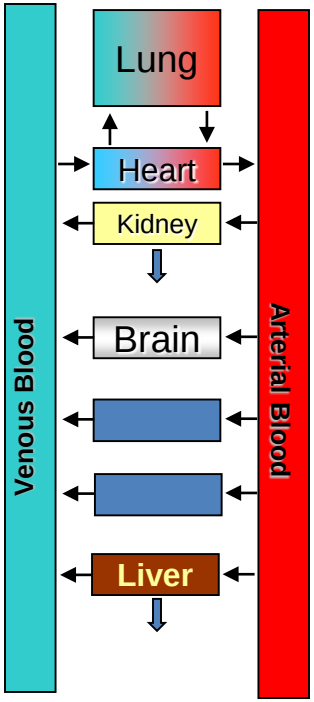
Nature Biotechnology **23, 191 - 194 (2005)**

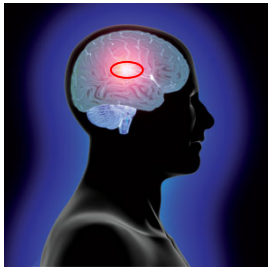
Examine drug pharmacokinetics / delivery to CNS sites across several scales

macro

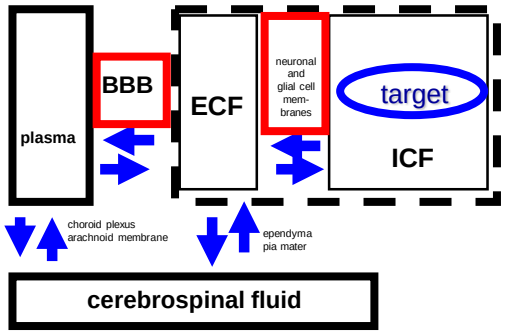






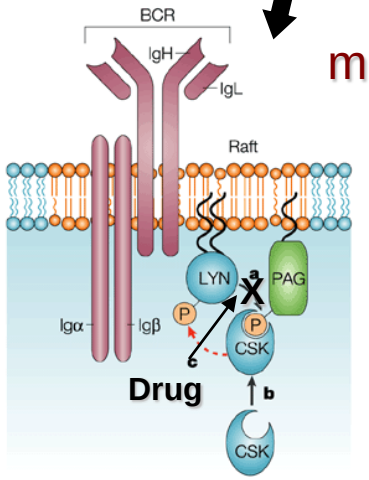


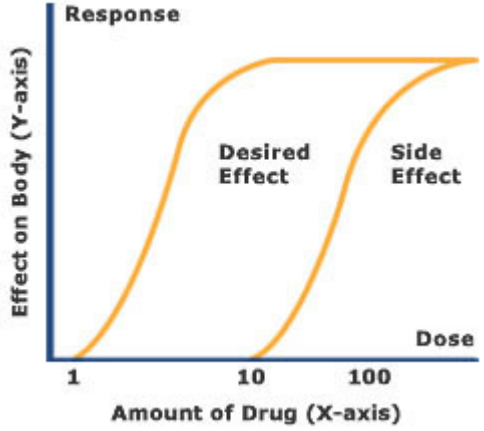
meso

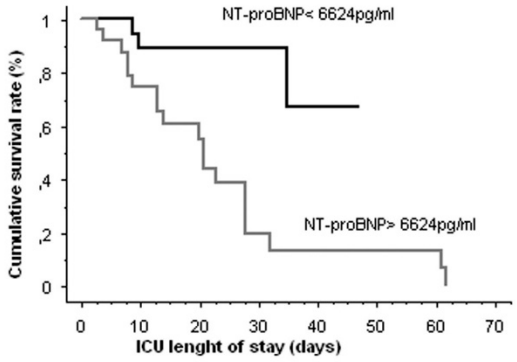


Quantitative – Qualitative Oscillations in the Thought Cycle

micro



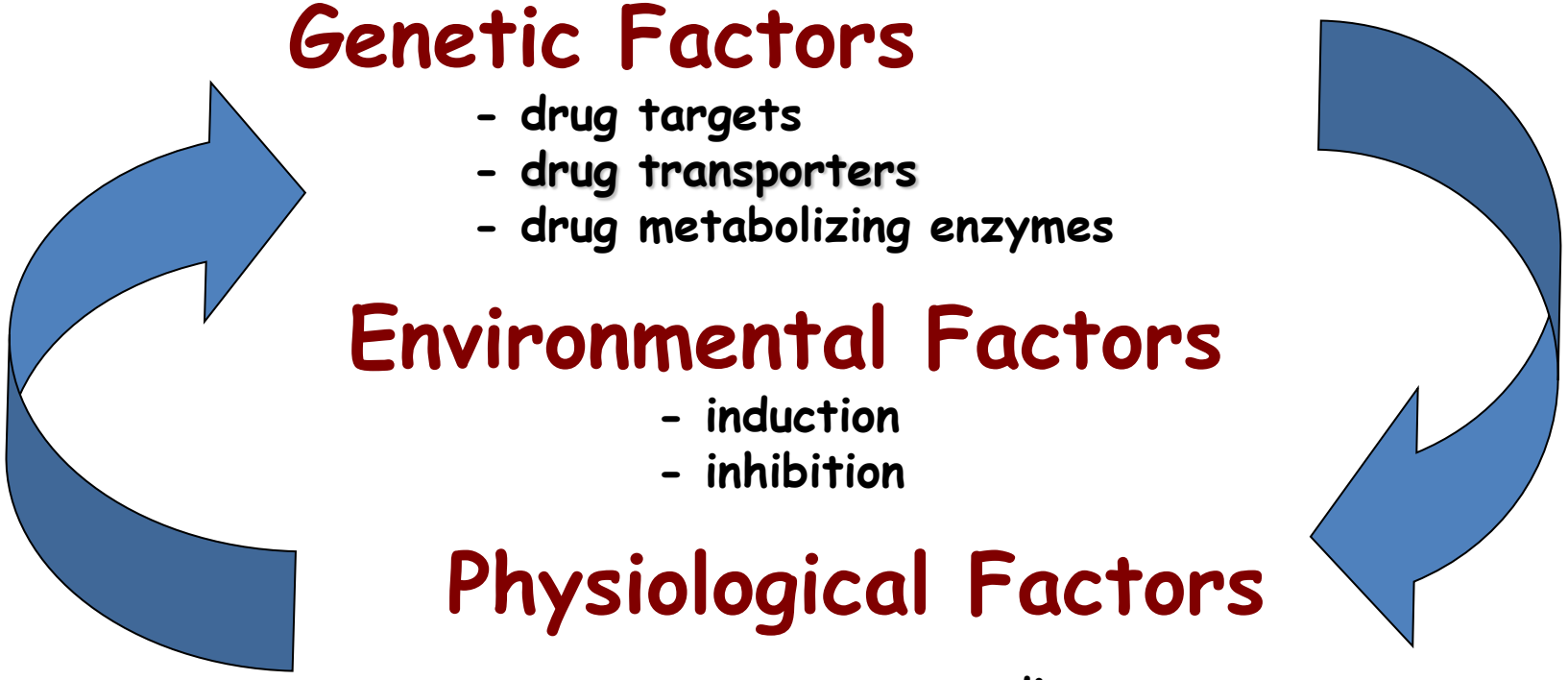




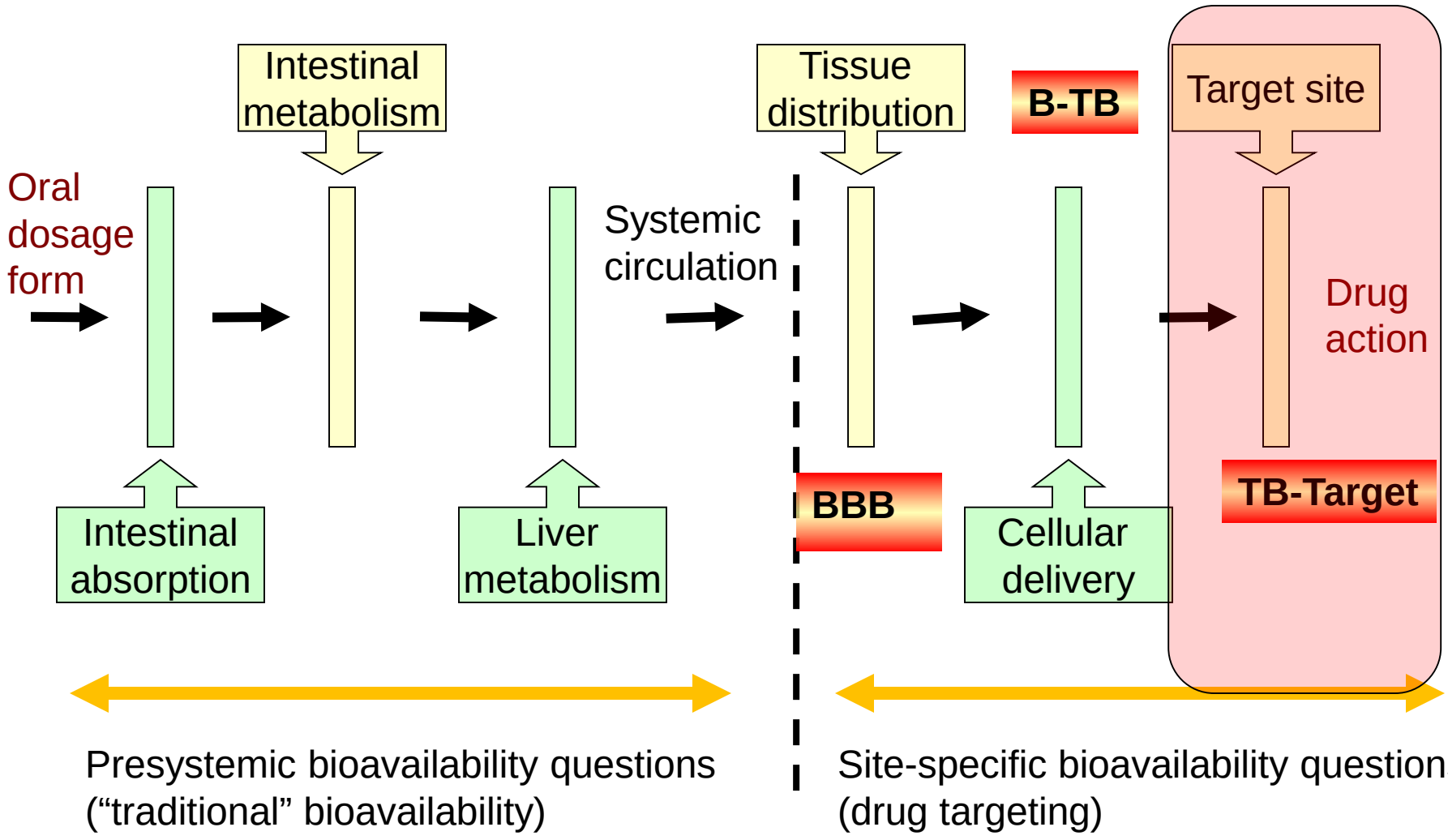
Connect - Disconnect of the PK-PD Relationship

Understanding Sources of Variability in Drug Response

Variability Cycle



"Locations" of Variability in Drug Efficacy In CNS Tuberculosis

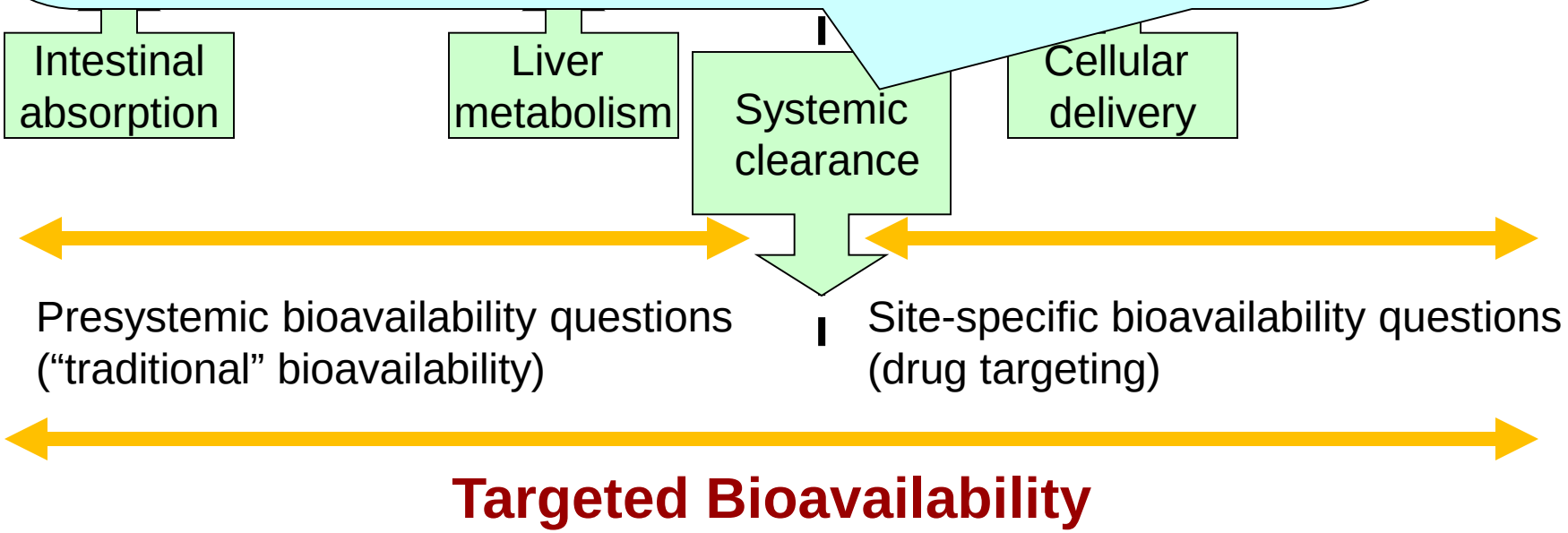


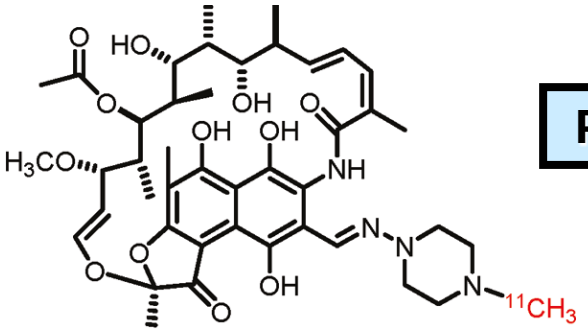
Mechanisms that influence the fraction of the drug in the systemic circulation that is available for distribution to target tissue and the exposure of the tissue to the drug

- distribution of blood flow
- ratio of total clearance to a distributional clearance

Distributional clearance - membrane permeability, competing carrier-mediated transport (influx or efflux), protein-binding, intracellular metabolism, tissue transit time, capillary structure

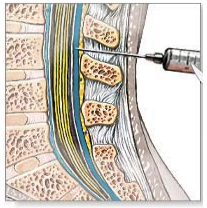
Total clearance – will affect the availability of the drug in the blood to distribute to the tissue

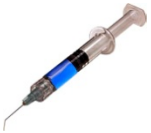




[^{11}C]RIF

Physicochemical Properties





Physiology / Pathology

Drug Metabolism

Protein Binding

Gene Regulation

Protein Expression

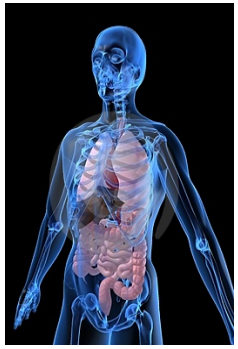
Receptor Affinity

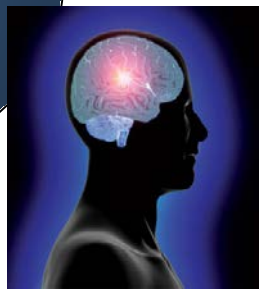
Membrane Permeability

Drug Transport

Targeted Bioavailability

Dosage Regimen

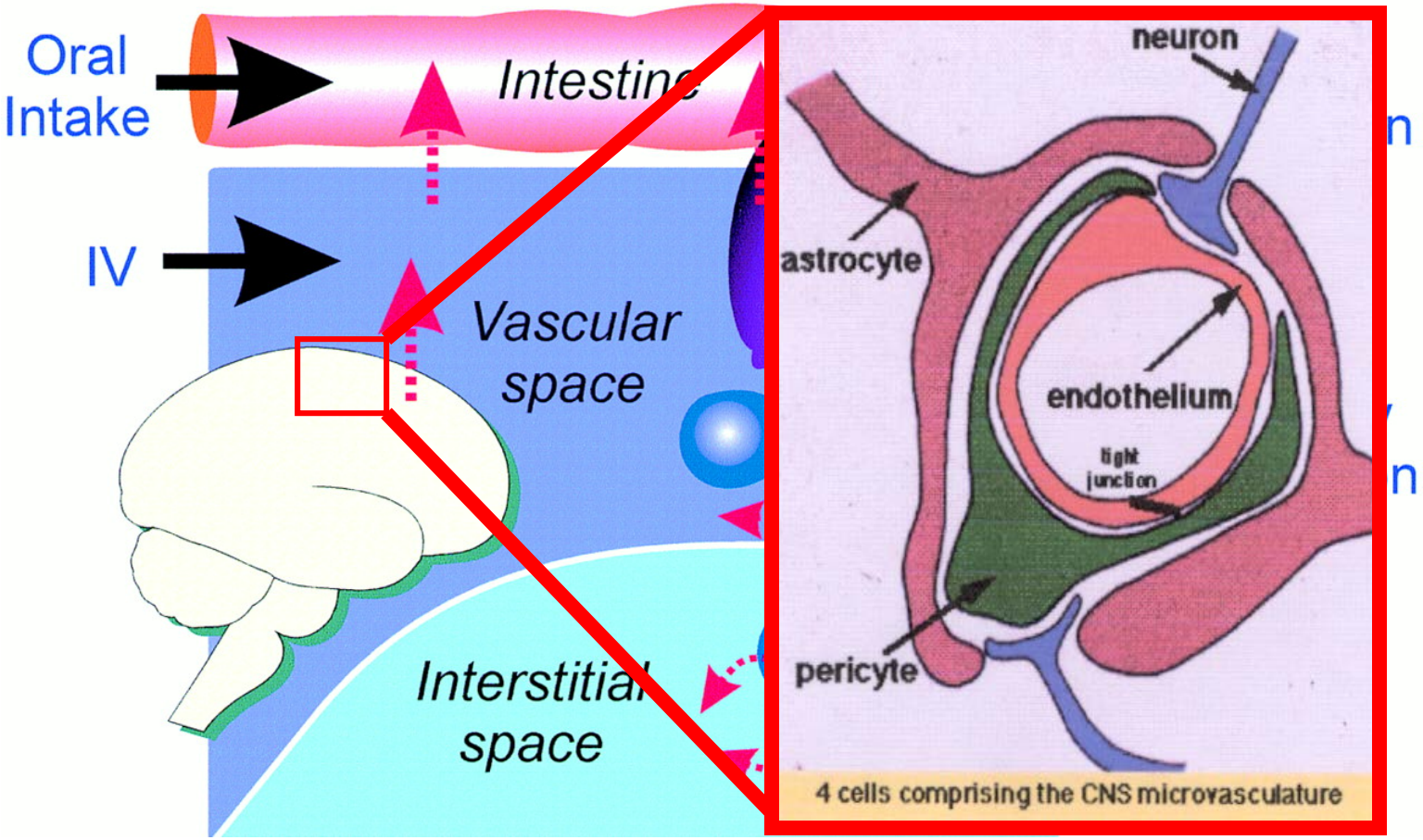




Pharmacological / Toxicological Response

One "Location" : Blood-brain Barrier

Importance of Transporters in the CNS Disposition of Drugs

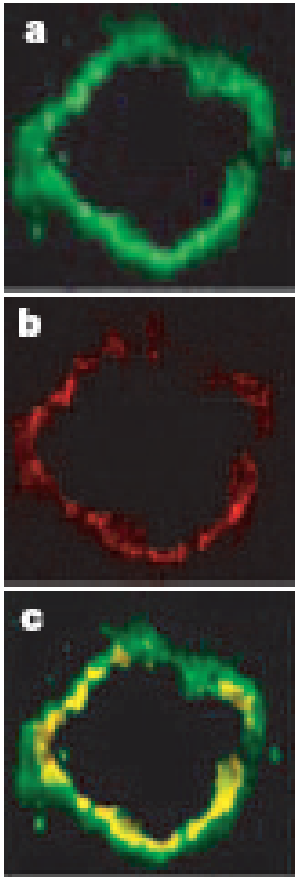


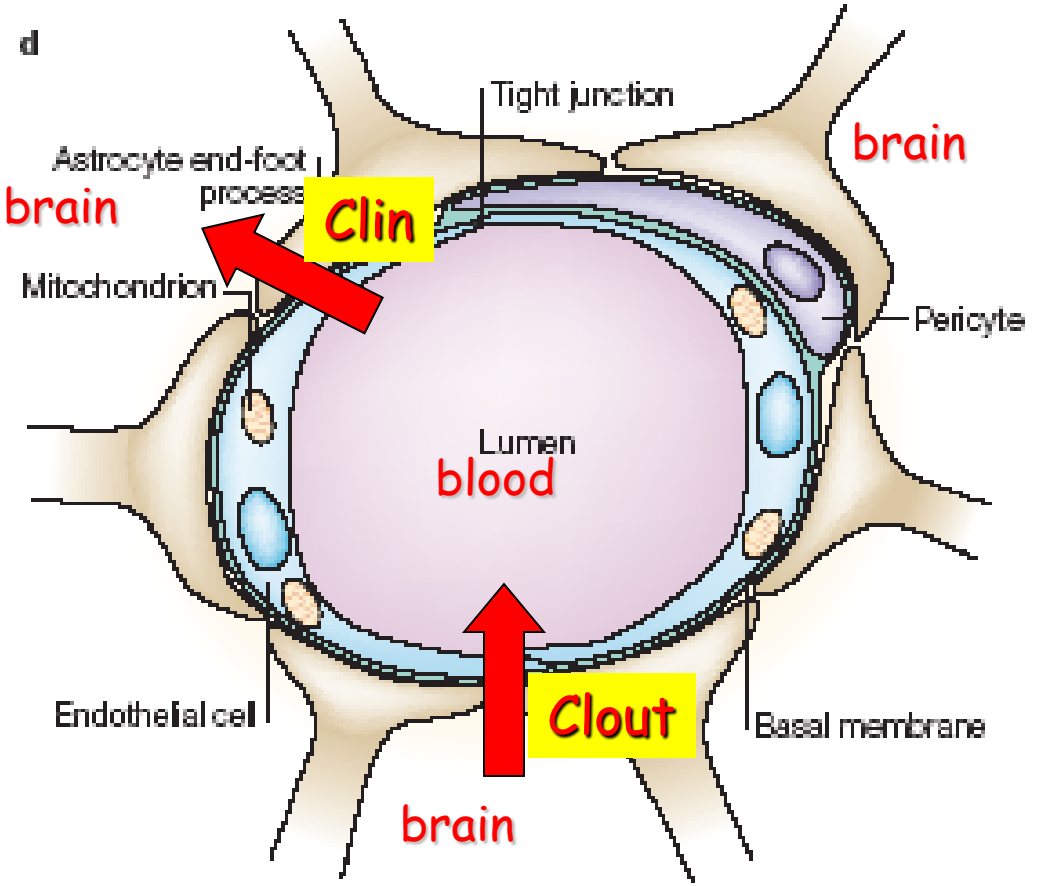
From Lee and Gottesmann. Journal of Clinical Investigation, 1998
illustration by Naba Bora, Medical College of Georgia.

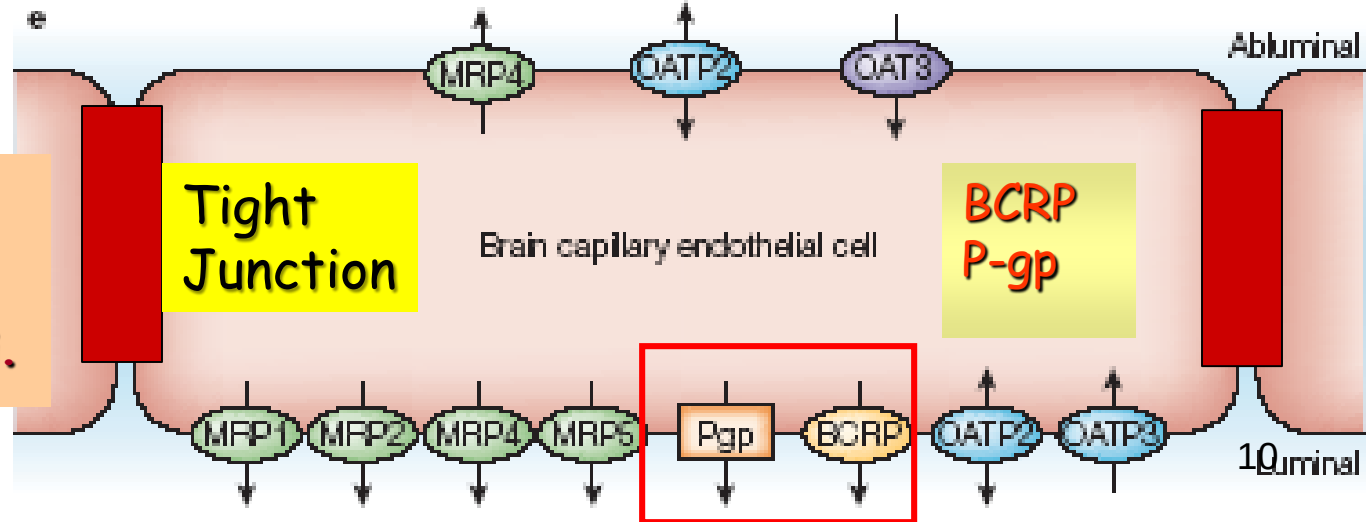
GLUT1

P-gp
(p-glycoprotein)

Co-localization
GLUT1 - P-gp



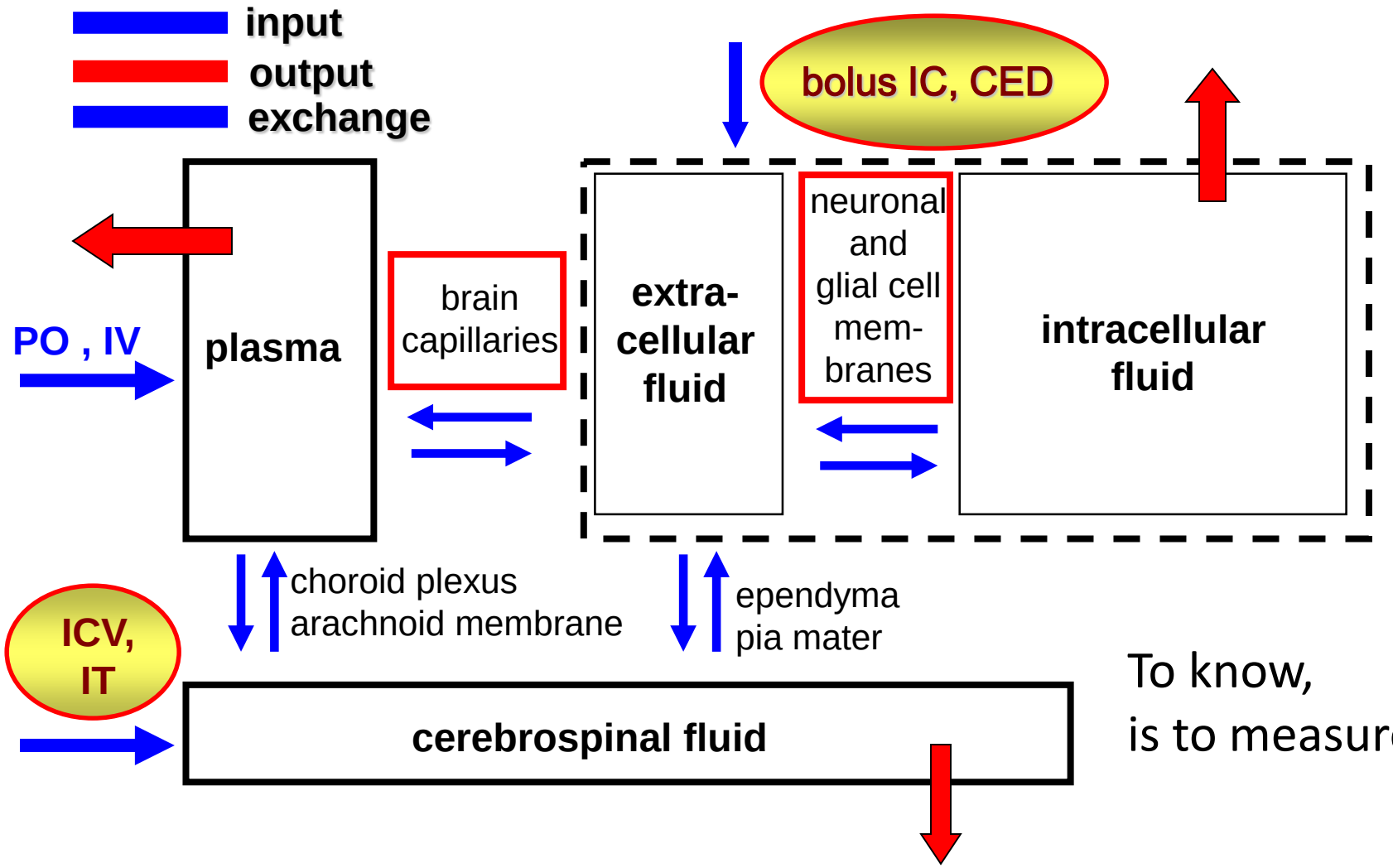




Modifed from:

Loscher, Aug. 2005
Nature Rev. Neurosci.

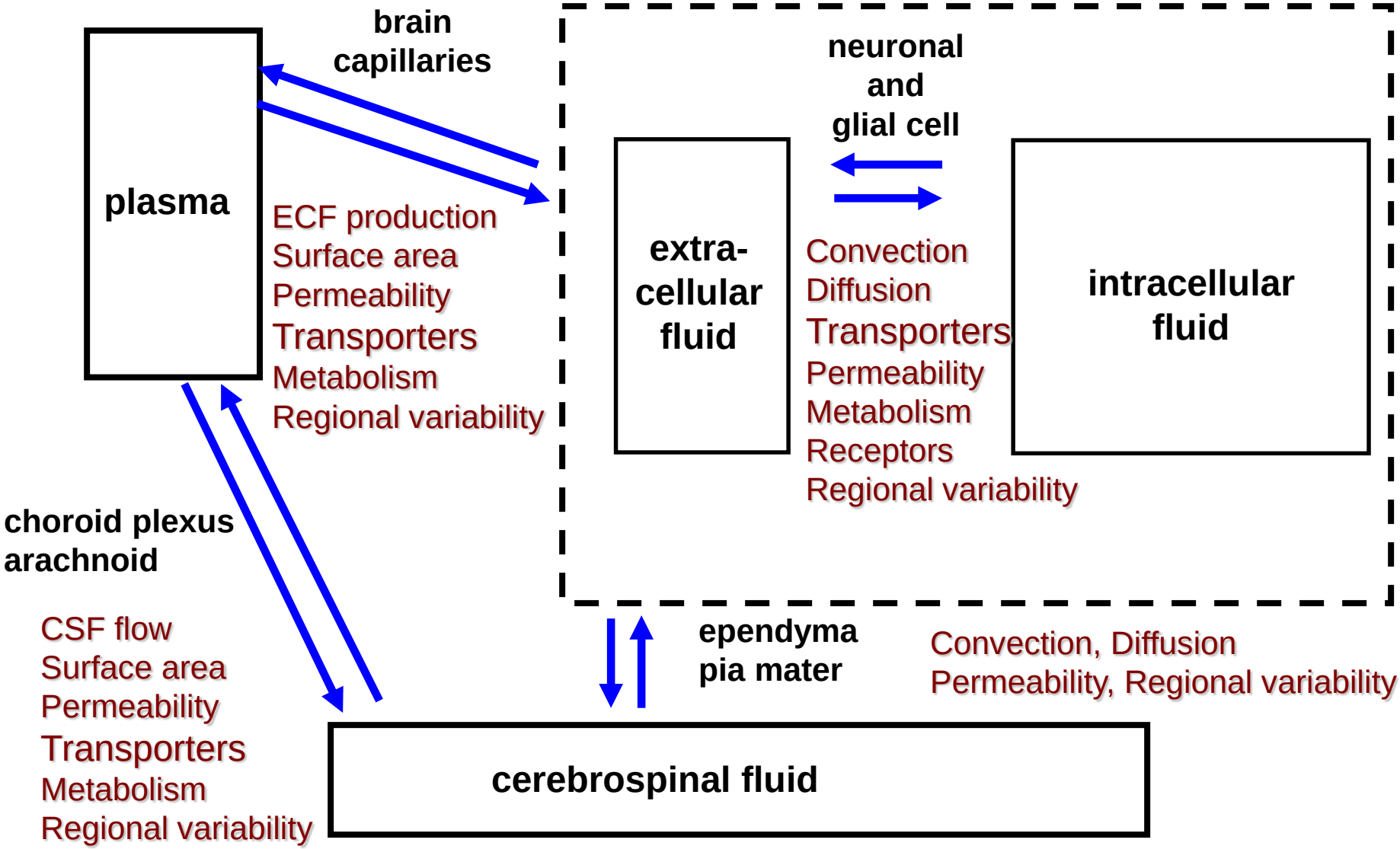
Therapeutic decisions limited by available data at specific sites



To know,
is to measure.

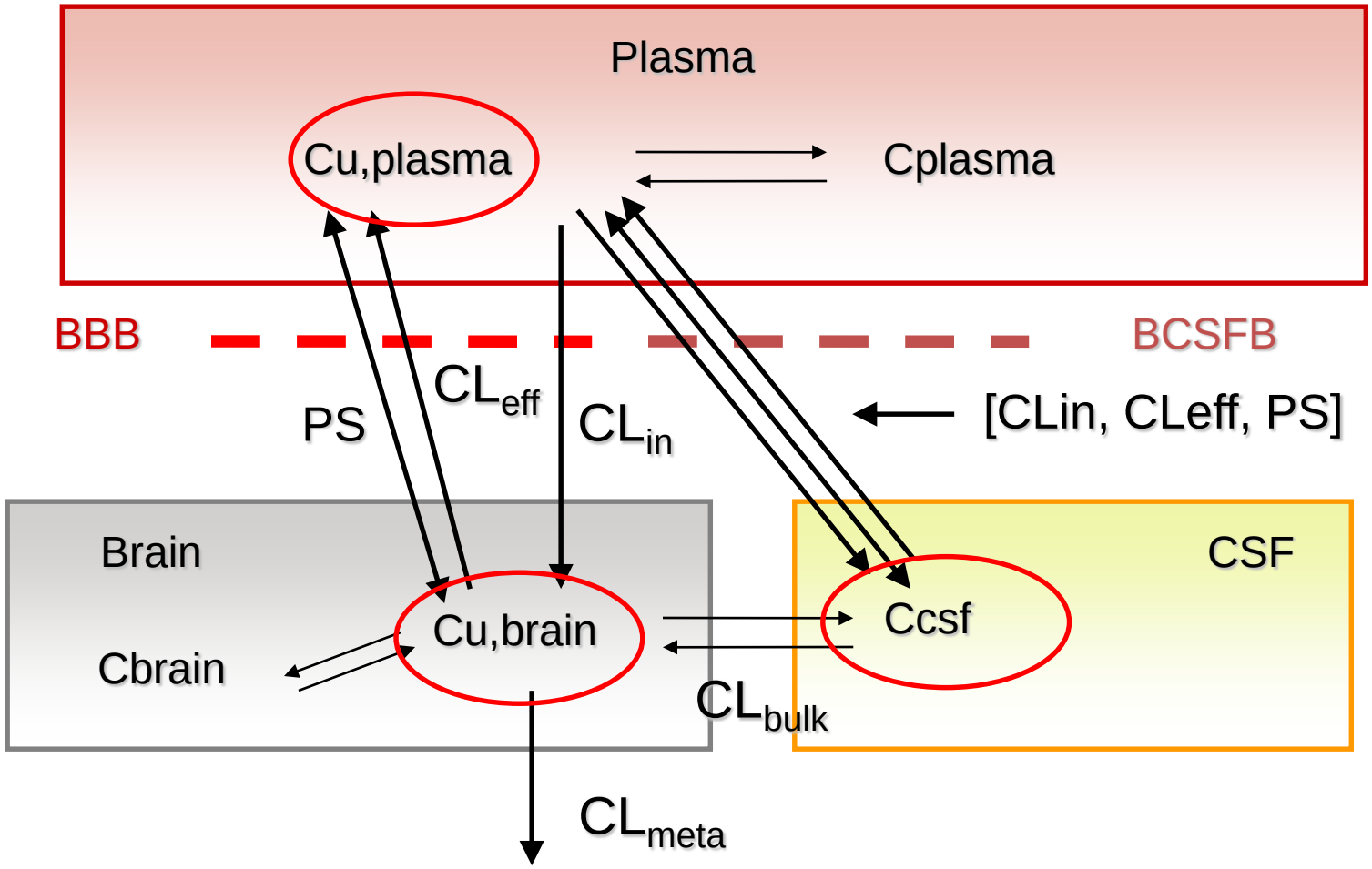
Compartmental model for solute exchange in the brain

Modeling limited by available mechanistic data at specific sites



Simplified Quantitative Analysis of Drug Transfer In CNS

Drug “Binding” – Plasma and Brain



Simplified Quantitative Analysis of Drug Transfer In CNS

Kinetics of distribution - Rate and Extent

Rate (onset) - described by maximum concentration (Cmax)

Extent (exposure) - described by area under the curve (AUC)

Ratio of areas gives tissue partition coefficient

$$Kp = \frac{AUC_{brain}}{AUC_{plasma}}$$

Total concs

$$Kp,uu = \frac{AUC_{brain-unbound}}{AUC_{plasma-unbound}}$$

Unbound concs

Simplified Quantitative Analysis of Drug Transfer In CNS

Extent - partitioning of free concentration

$$K_{p,free} = \frac{CL_{in}}{CL_{out}}$$

Sum of clearances in each direction

$$K_{p,free} = \frac{PS + CL_{uptake}}{PS + CL_{efflux} + CL_{metabolism} + CL_{bulk}}$$

Simplified Quantitative Analysis of Drug Transfer In CNS

Extent - partitioning into a specific brain region

Tight-junction opening

Substrate for Influx Transporter

$$K_{p,free} = \frac{PS + CL_{uptake}}{PS + CL_{efflux} + CL_{metabolism} + CL_{bulk}}$$

Tight-junction opening

Substrate for Efflux Transporter

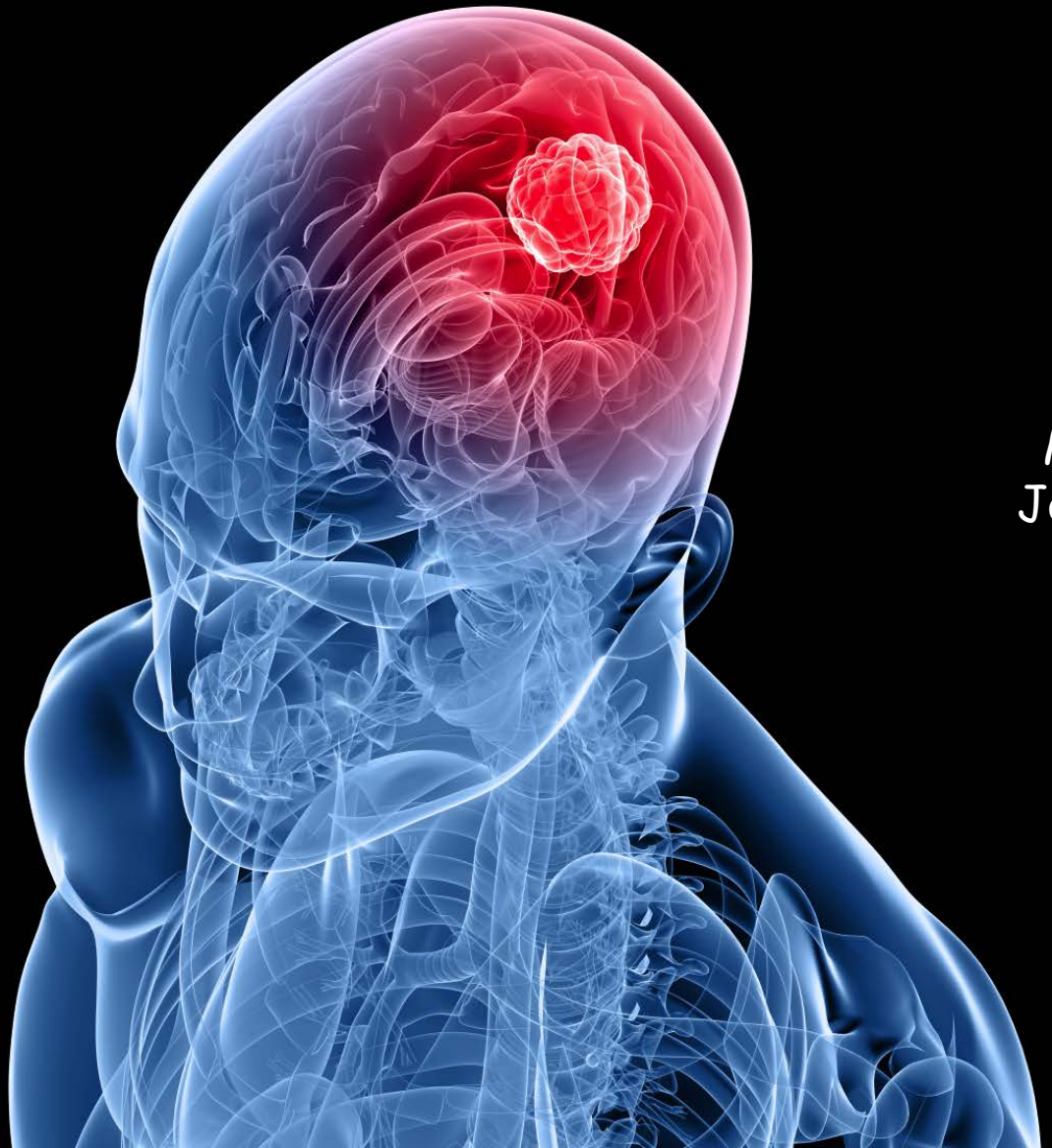
Brain Metabolism

Fluid flow

Active transport CL depends on both capacity and affinity

$$CL_{act} = \frac{T_{max}}{Km + C}$$

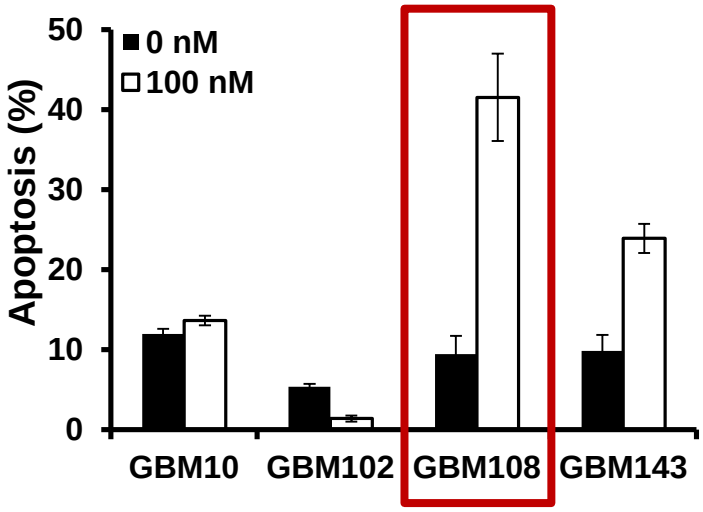
Representative Case Study: The Treatment of Glioblastoma with Inhibition of P53 Degradation – MDM2 Inhibitor

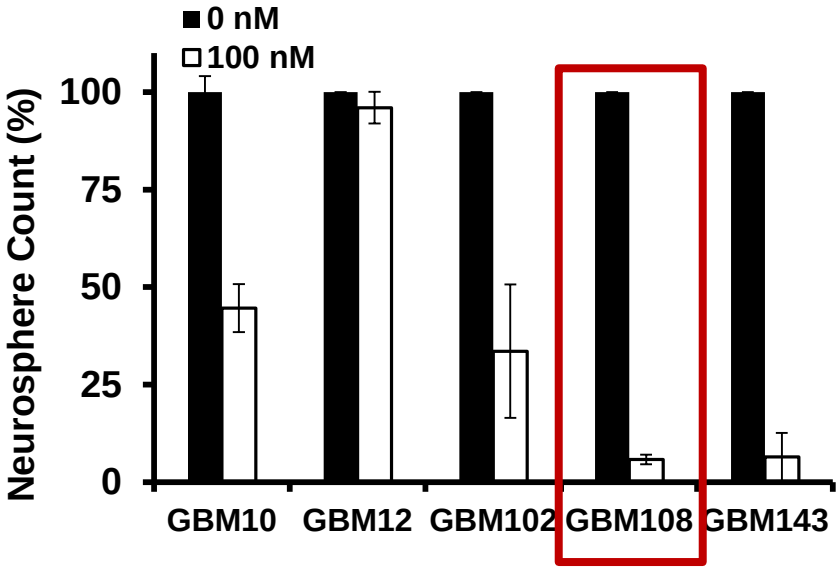


Minjee Kim,
Jann Sarkaria

Choice of PDX Glioma Model

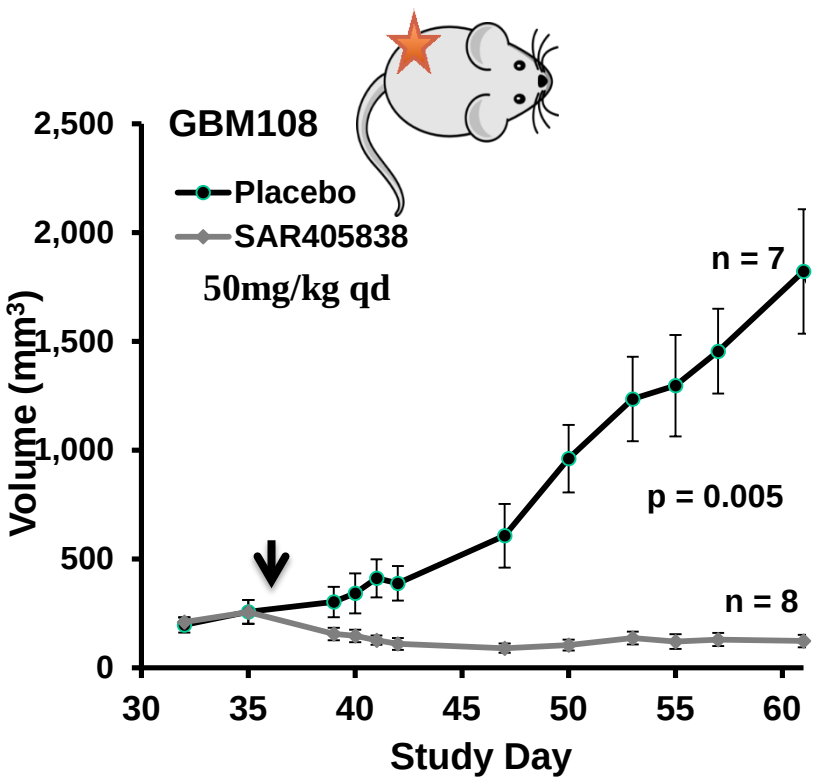
GBM Line	MDM2 amplification	MDM2 expression	p53 status
10	no	low	wildtype
12	no	low	mutant
102	yes	low	wildtype
108	yes	high	wildtype
143	yes	high	wildtype



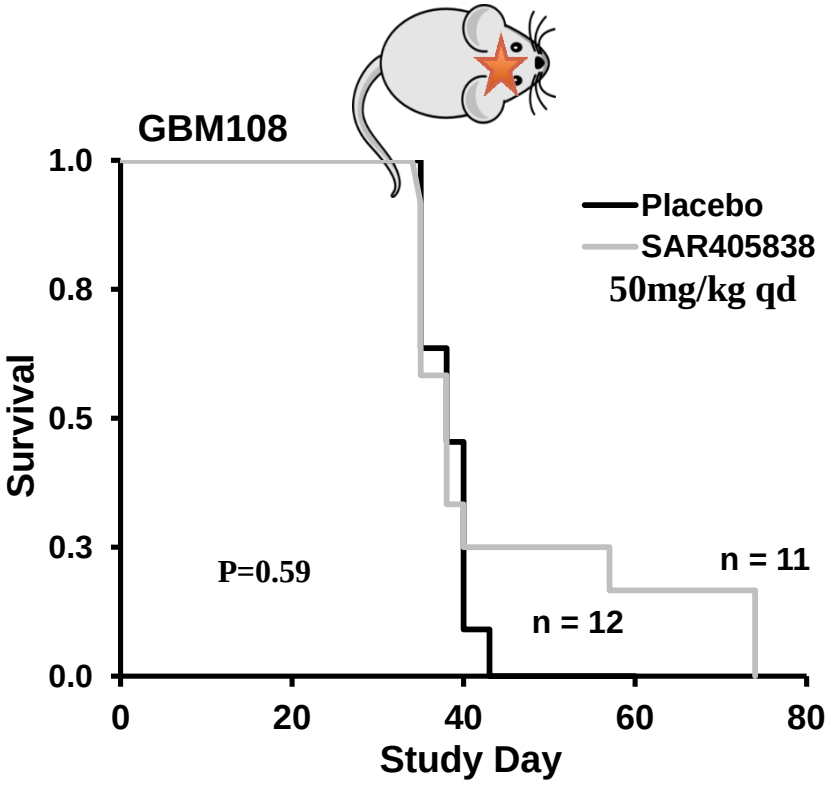


Efficacy of SAR405838 depends on tumor location

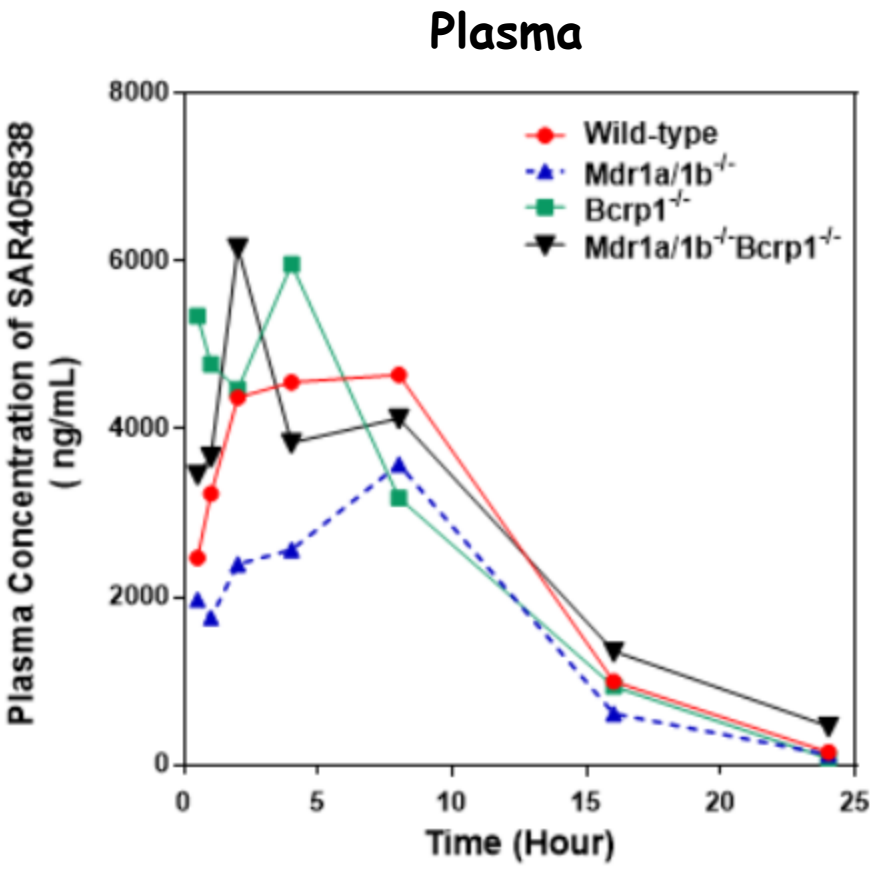
Heterotopic Xenograft

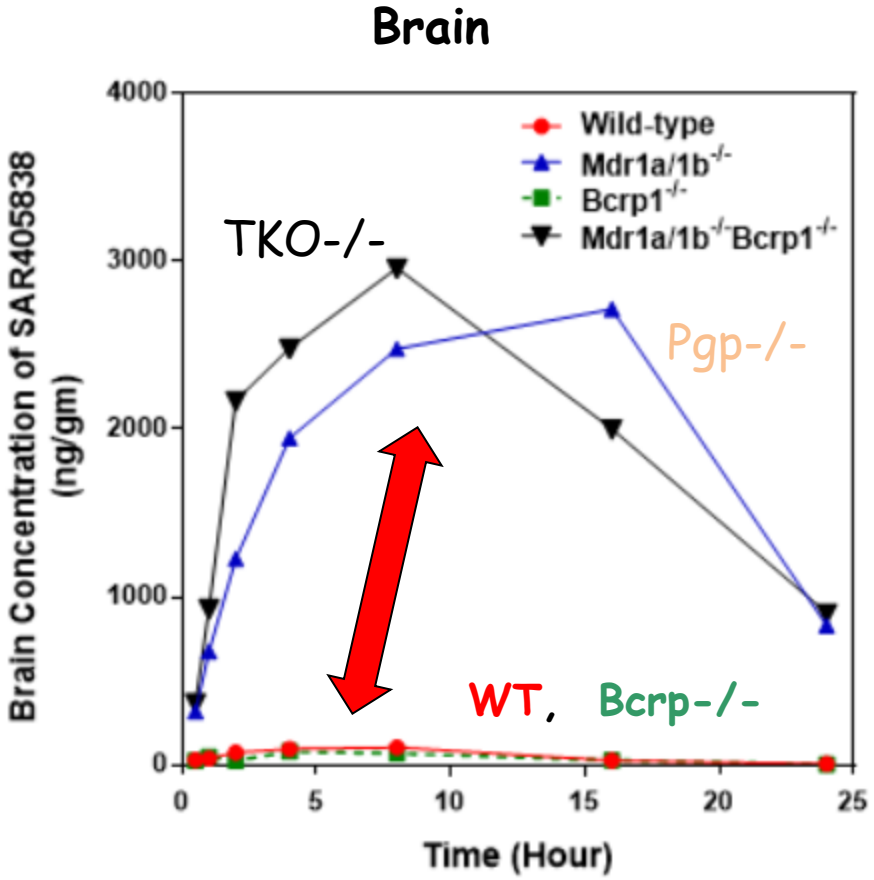


Orthotopic Xenograft



SAR405838 Concentration vs. Time Profiles in Plasma and Brain





Influence of Efflux Transporters at the BBB On Brain Penetration of SAR405838

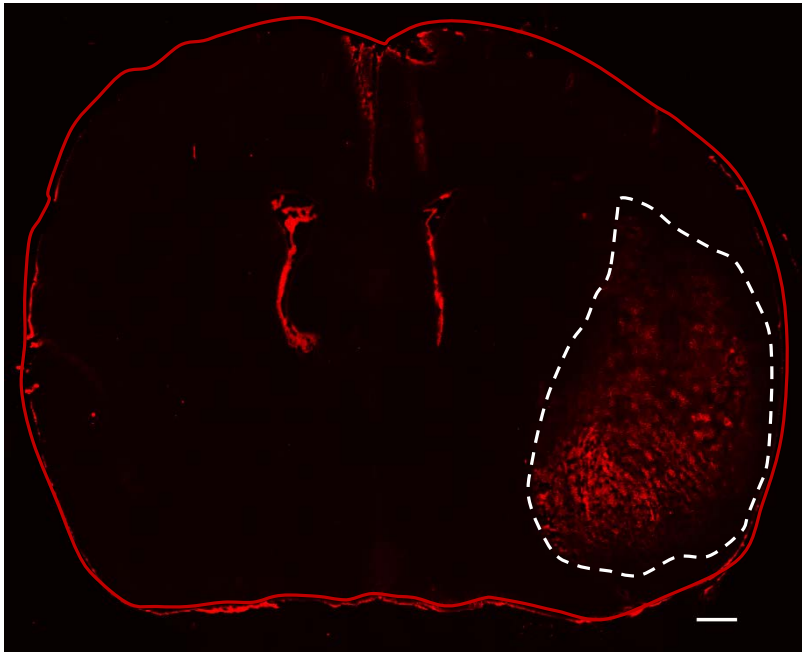
SAR405838 - Plasma and Brain Distribution Kinetics

		Wild-type	Mdr1a/1b$^{-/-}$	Bcrp1$^{-/-}$	Mdr1a/1b$^{-/-}$ Bcrp1$^{-/-}$
$T_{1/2}$	Hr	3.26	4.18	3.02	5.08
T_{max}	Hr	8	8	4	2
C_{max}	ng/ml	4651	3582	3976	6164
AUC_{inf_pred}	hr*ng/ml	61195	41382	47804	65867
Vz/F	ml/kg	1922	3642	2281	2779
CL/F	ml/hr/kg	409	604	523	380
AUC_{brain}	hr*ng/ml	1335	**63234**	1956	**65442**
$K_{p,brain}$ $(\frac{AUC_{brain}}{AUC_{plasma}})$		0.022	**1.53**	0.041	**0.994**
Distribution Advantage		1.00	**70.0**	1.88	**45.5**

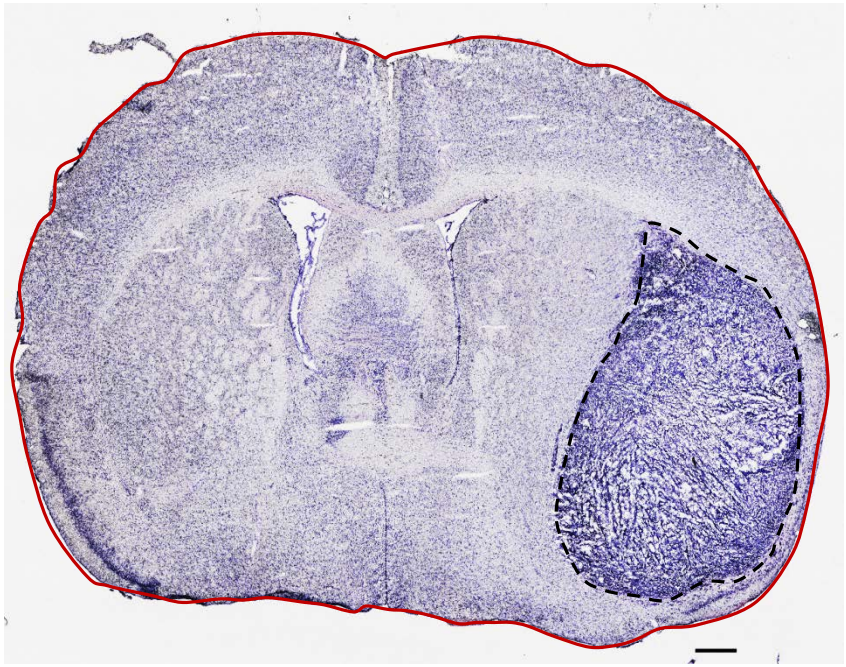
$$\text{Distribution Advantage} = \frac{Kp\ knockout\ mice}{Kp\ wild-type\ mice}$$

orthotopic GBM108 parental line

TexasRed

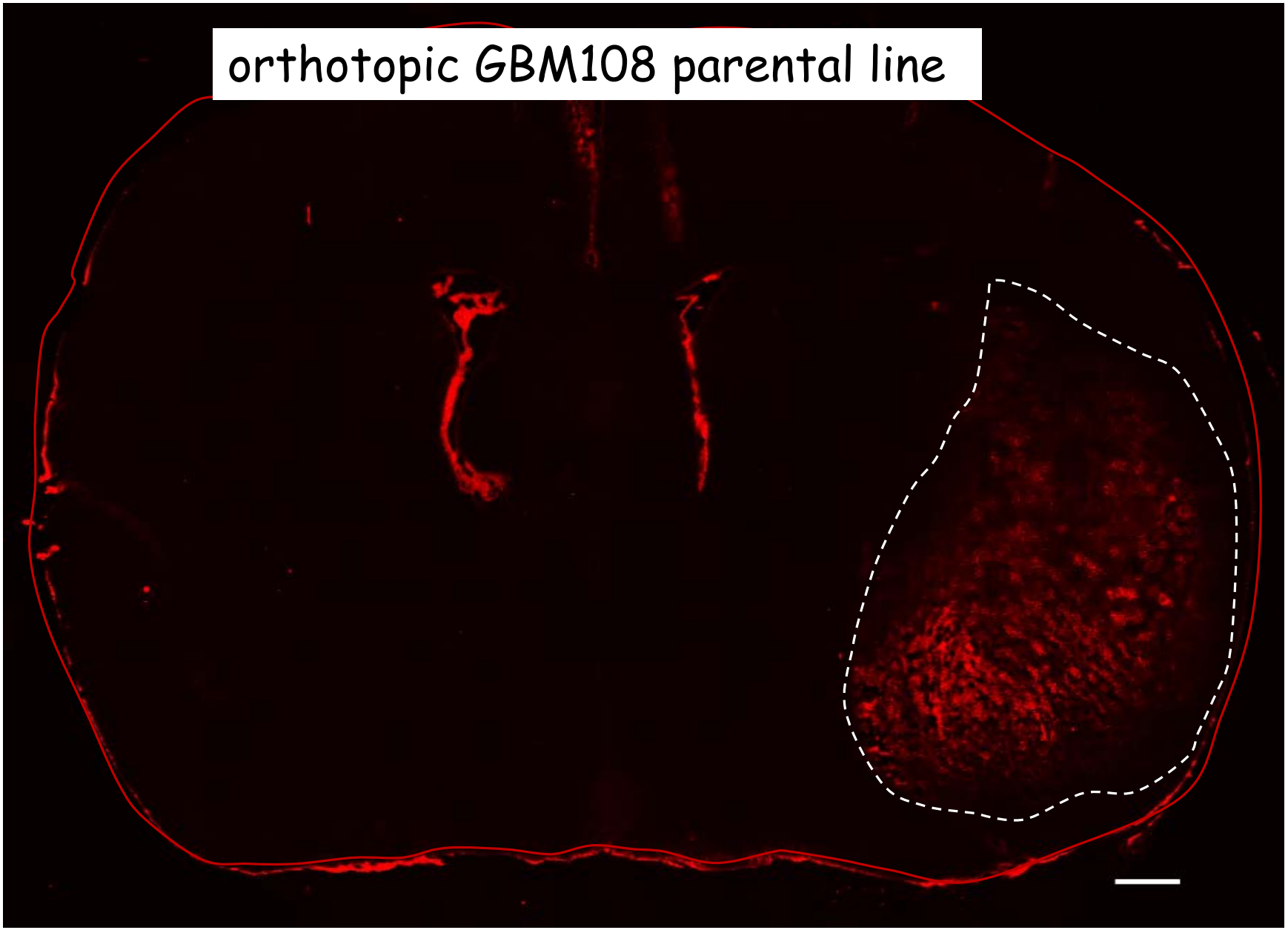


Cresyl Violet

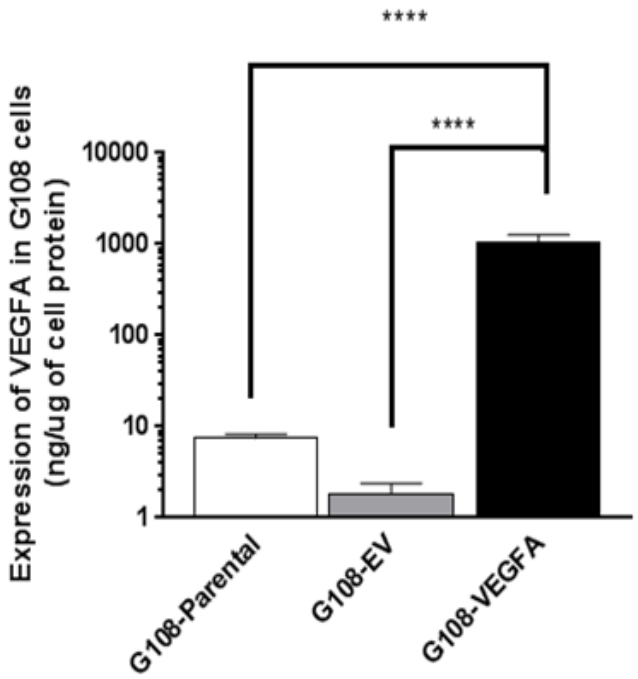


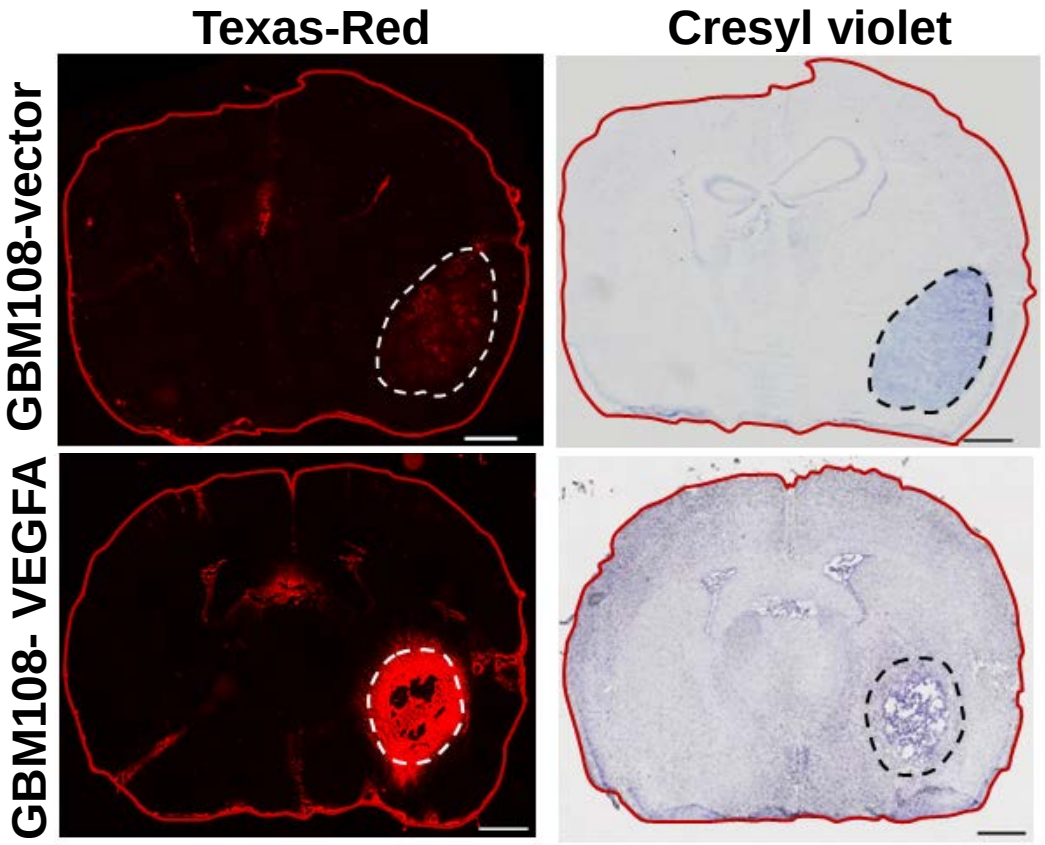
Blood brain barrier integrity in orthotopic tumors. Near-moribund mice with orthotopic GBM108 tumors were injected with TexasRed-3 kDa dextran conjugate 10 min before euthanasia and processed for cresyl violet and fluorescent microscopy on serial histology sections. Accumulation of TR-dextran within the tumor reflects disruption of the BBB. Results presented are representative of five mice analyzed. Scale bar = 500 μm.

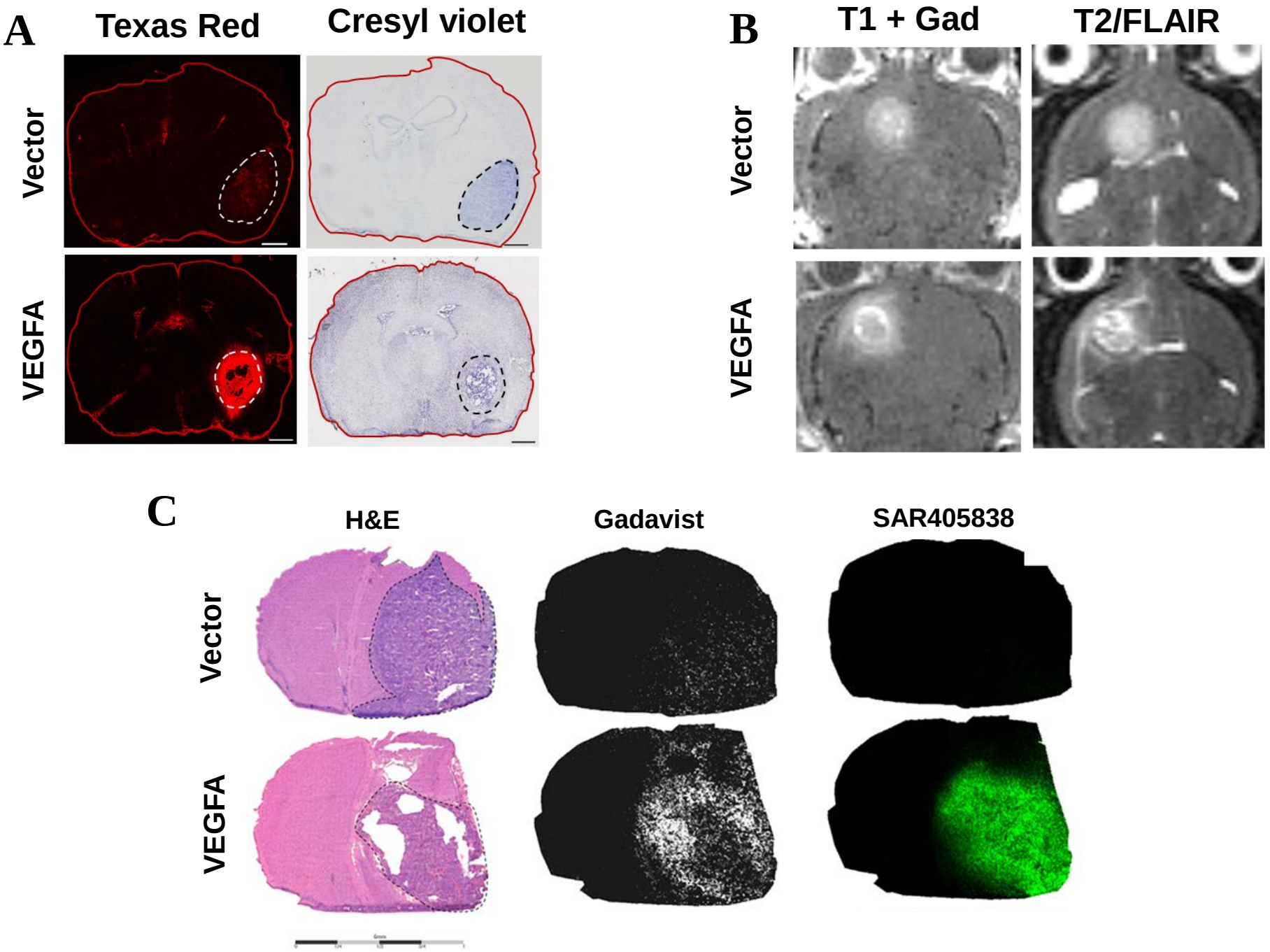
Heterogeneous Breakdown of Tumor BBB



G108-VEGFA Cell Line Generation

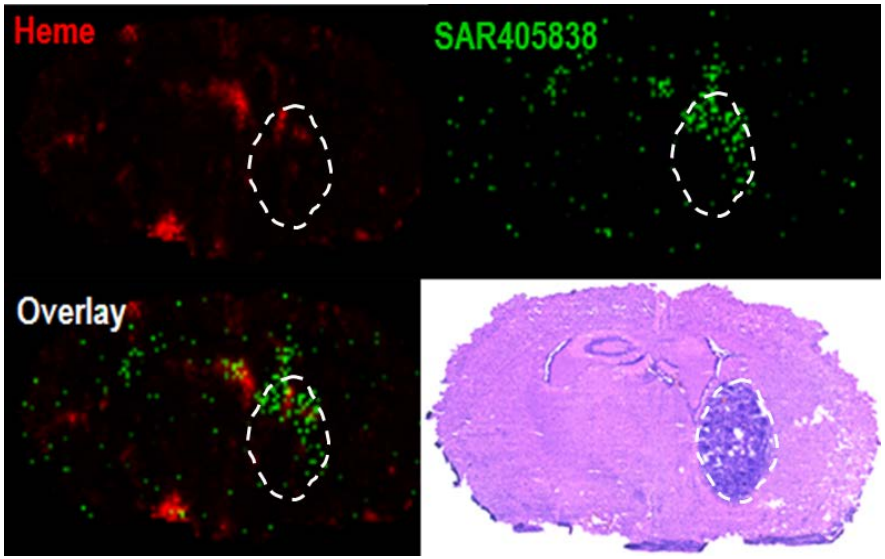




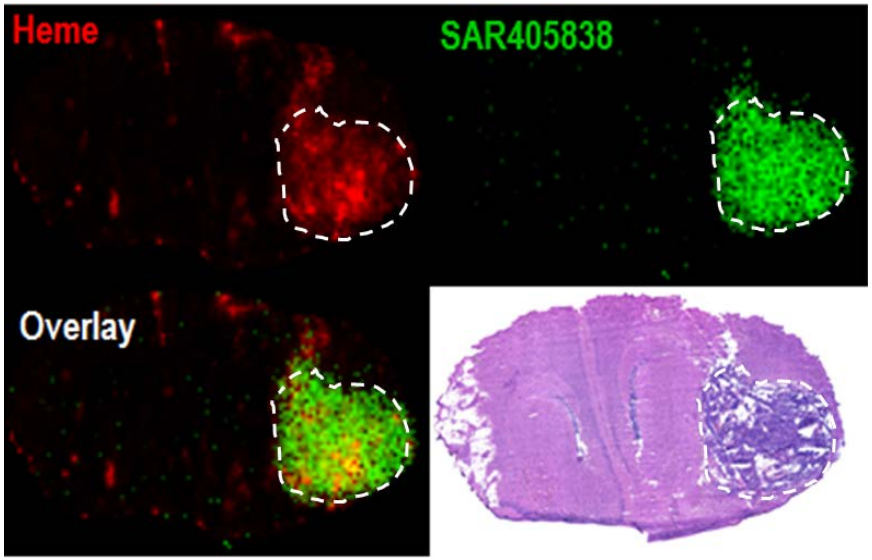

A
Texas Red
Cresyl violet
Vector
VEGFA
B
T1 + Gad
T2/FLAIR
Vector
VEGFA
C
H&E
Gadavist
SAR405838
Vector
VEGFA

Spatial Distribution of SAR405838 (MALDI-MSI)

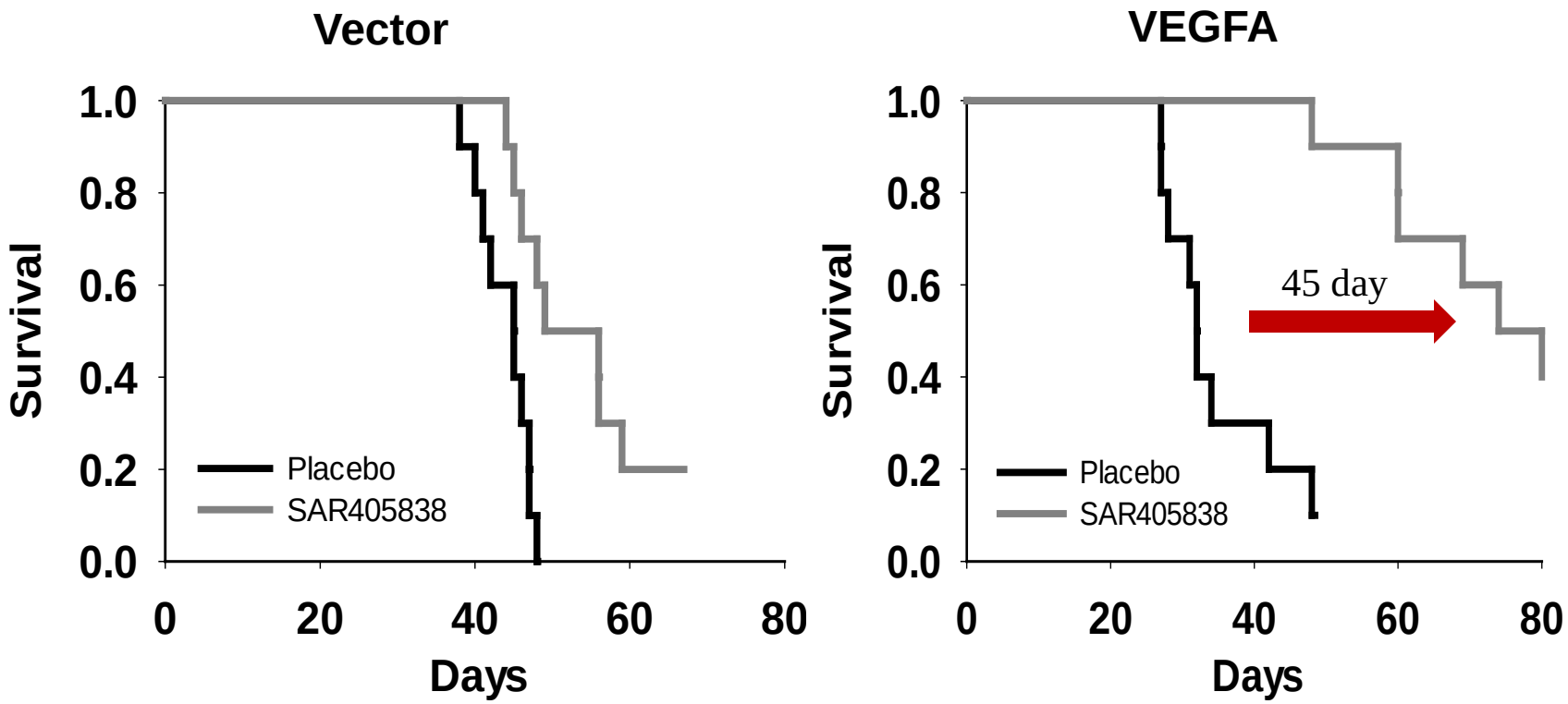
GBM108-Empty vector



GBM108-VEGFA



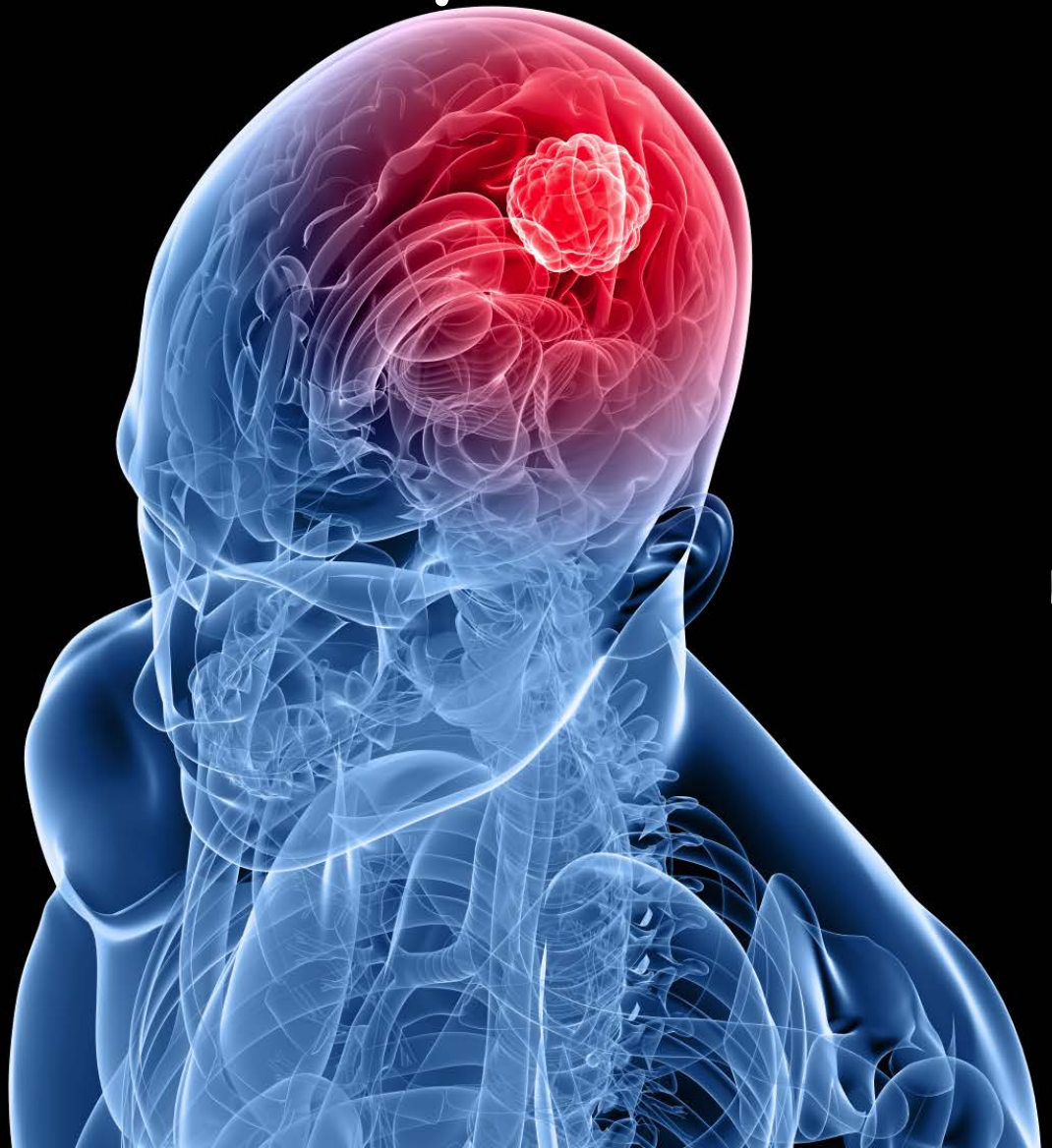
Orthotopic Survival



Conclusions for SAR405838 Study

- SAR405838, a potent MDM2 inhibitor, is subject to BBB efflux
- This preclinical study indicates enhanced delivery of SAR405838 will improve its efficacy
- Strategies to overcome limited delivery of drug across BBB will result in better treatment for brain tumors

Translation in the Clinic - Delivery and the BBB



Deb Brinkmann,
Jann Sarkaria
(Mayo Clinic)

J Neurooncol (2013) 111:11–18
DOI 10.1007/s11060-012-0986-1

Use of Uptake Transporters in BBB

LABORATORY INVESTIGATION

The role of LAT1 in ^{18}F-DOPA uptake in malignant gliomas

Ryan S. Youland · Gaspar J. Kitange · Timothy E. Peterson · Deanna H. Pafundi · Judi A. Ramiscal · Jenny L. Pokorny · Caterina Giannini · Nadia N. Laack · Ian F. Parney · Val J. Lowe · Debra H. Brinkmann · Jann N. Sarkaria

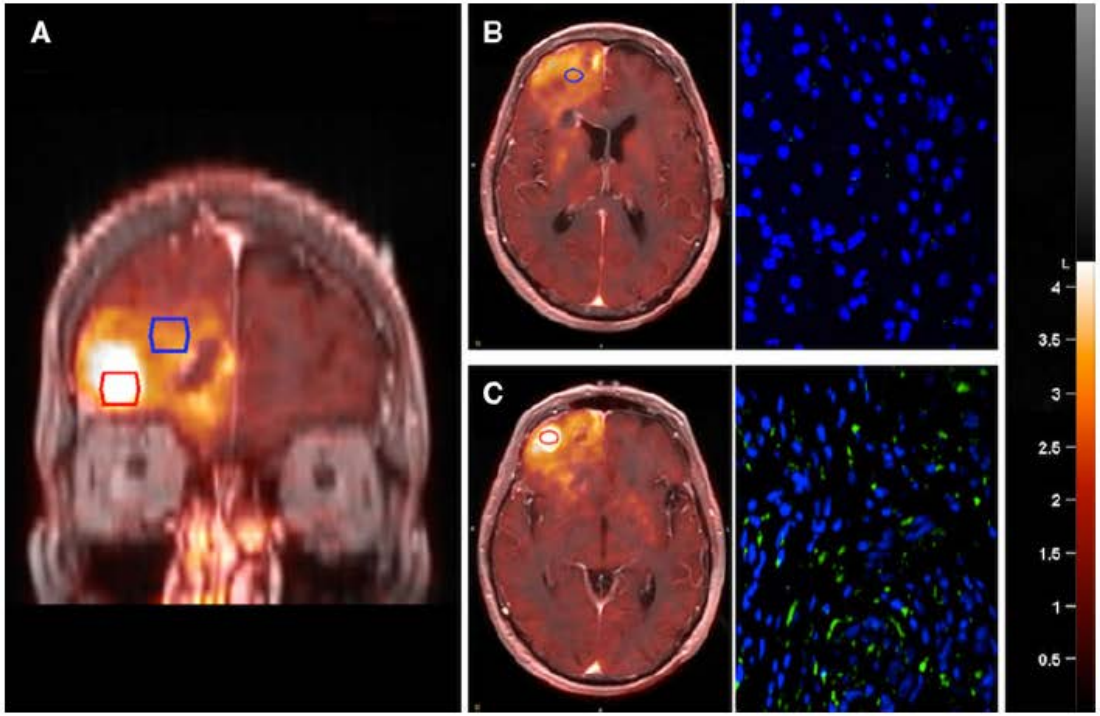
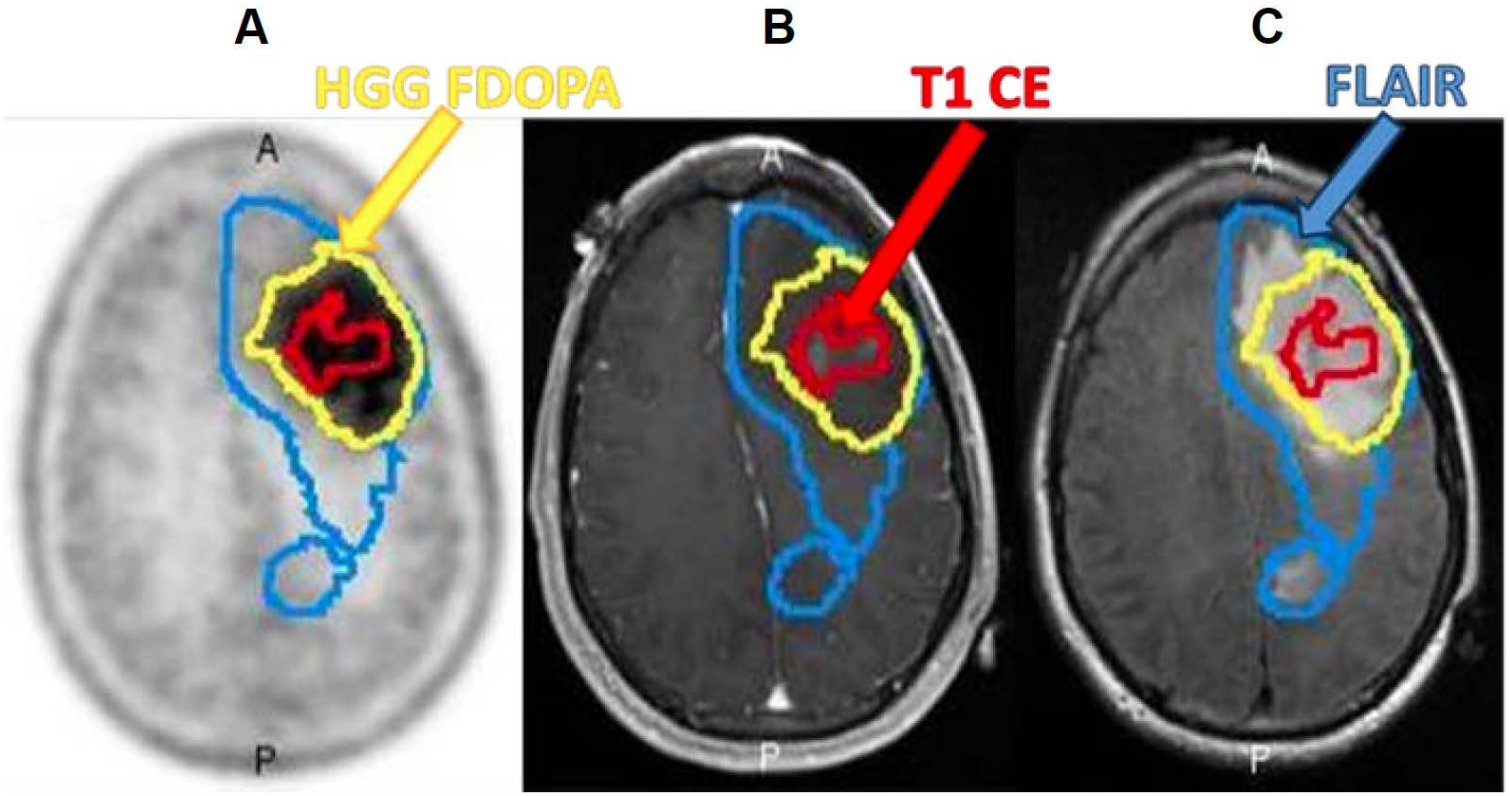


Fig. 4 LAT1 expression correlates with ^{18}F-DOPA SUVmedian in newly diagnosed human astrocytoma. Biopsy samples were taken from regions of high (*red outlined region*) and low (*blue outlined region*) ^{18}F-DOPA uptake (**a**). Samples were then stained for LAT1 using immunofluorescence (*green*, Cy5-Lat1; *blue*, DAPI-nuclei). Regions of low (**b**) or high (**c**) ^{18}F-DOPA uptake demonstrated corresponding low and high LAT1 expression, respectively

Deb Brinkmann, Jann Sarkaria - Mayo Clinic , Rochester

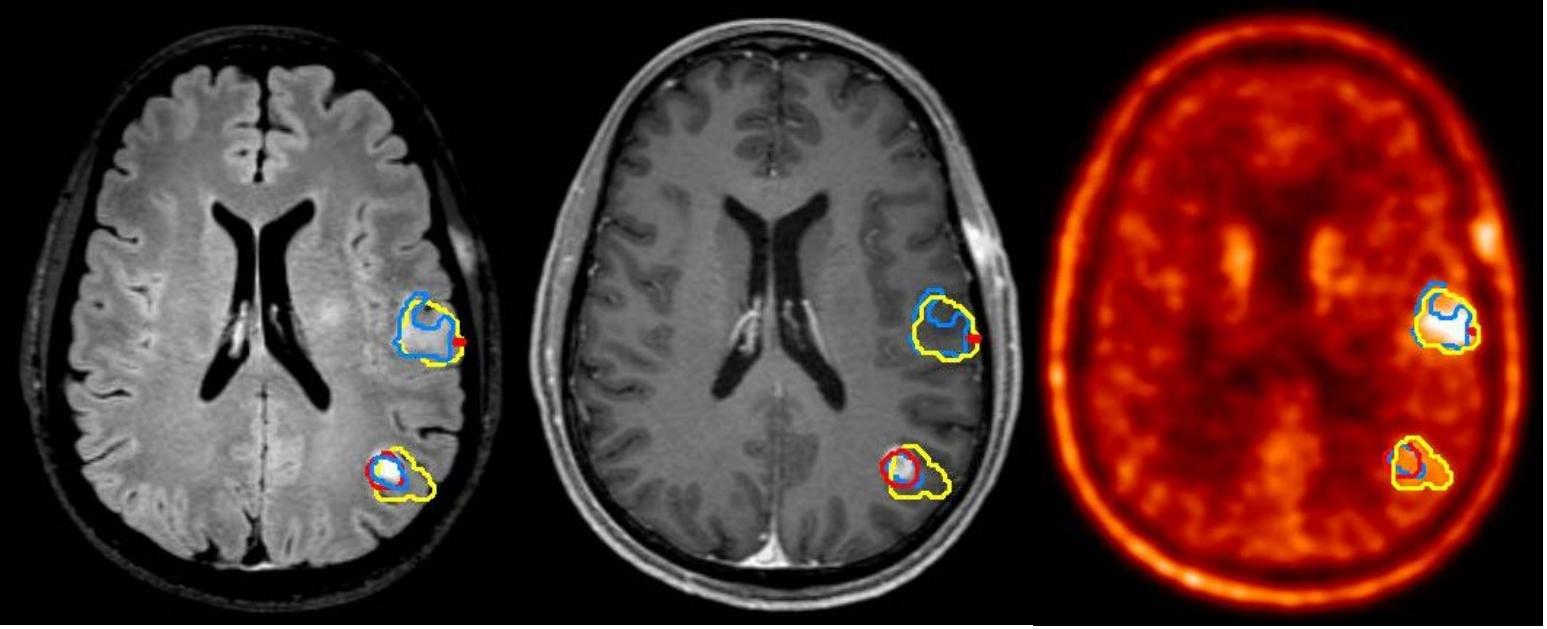


Discordance in tumor delineation by 18F-FDOPA PET and MRI.

Volumes defined for :

A) FDOPA positivity (yellow) by PET
B) T1 contrast enhancement (red) on T1 contrast enhanced images
C) FLAIR positive (blue)

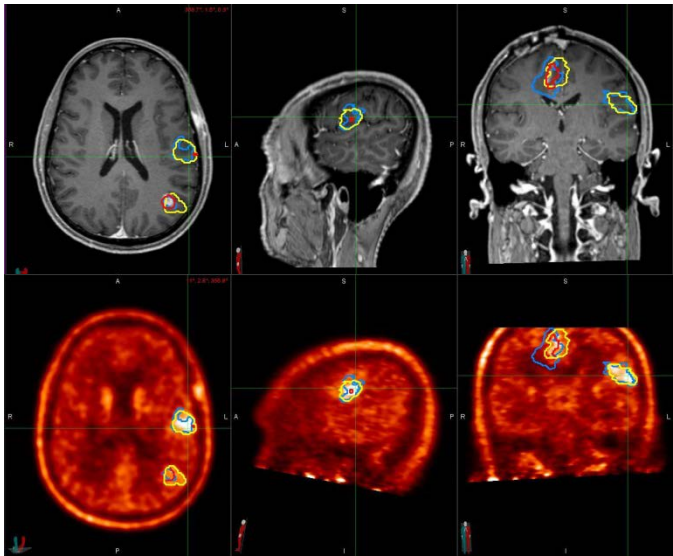
outlined for a single patient



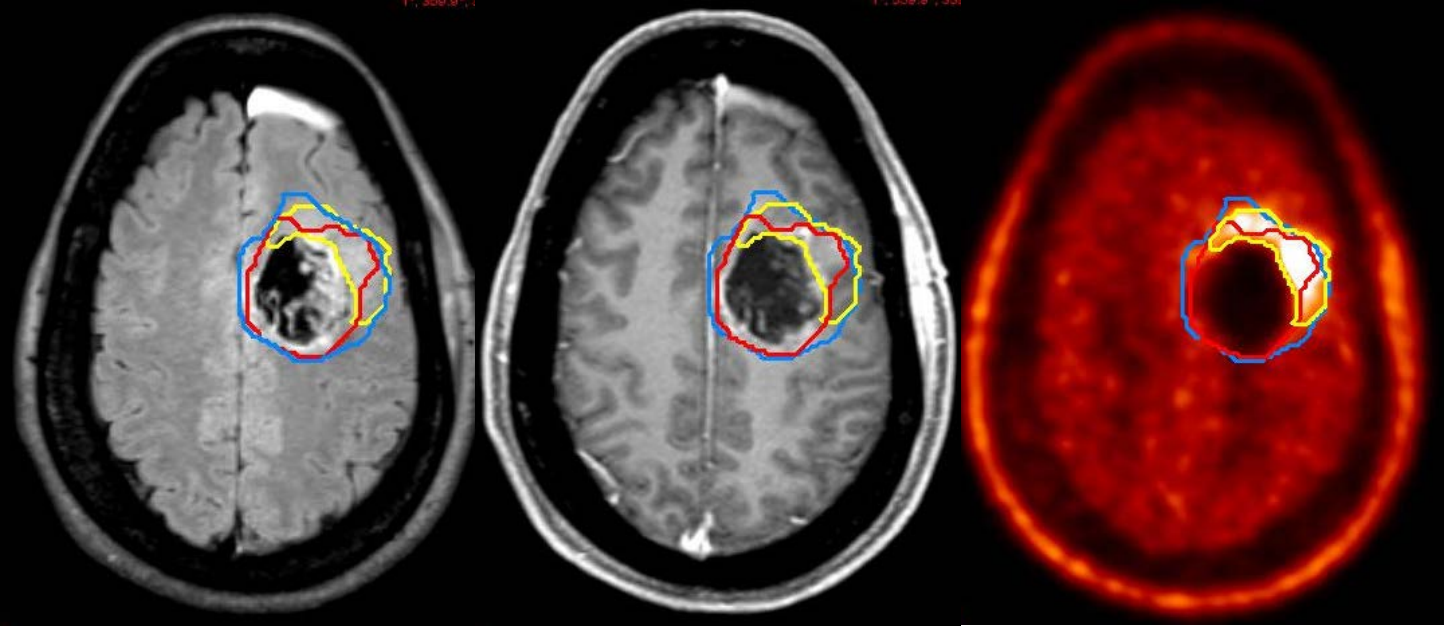
Structure	Structure Volume (cc) *from Eclipse*	PET Volume outside of T1-GAD (cc) *from Eclipse*	PET Volume outside of FLAIR (cc) *from Eclipse*	MR Volume outside of PET (cc) *from Eclipse*
T1-GAD	10.4	N/A	N/A	4.9
FLAIR	32.0	N/A	N/A	21.7
PET	19.5	13.8	9.1	N/A

Regions of tumor with intact BBB protected from treatment by efflux transporters and TJ

RT_FDOPA02
Grade IV
Total Multi-focal
FLAIR contour in blue
T1-GAD contour in red
PET contour in yellow



Orthogonal views with crosshairs turned on, for reference



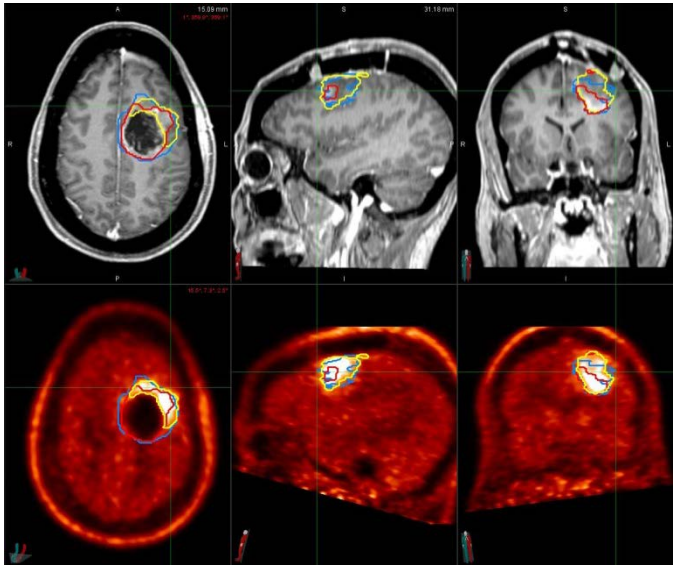
Structure	Structure Volume (cc) *from Eclipse*	PET Volume outside of T1-GAD (cc) *from Eclipse*	PET Volume outside of FLAIR (cc) *from Eclipse*	MR Volume outside of PET (cc) *from Eclipse*
T1-GAD	47.7	N/A	N/A	33.2**
FLAIR	54.3	N/A	N/A	36.4
PET	21.7	7.1	3.8	N/A

Regions of tumor with intact BBB protected from treatment by efflux transporters and TJ

RT_FDOPA05
Grade IV Total Single

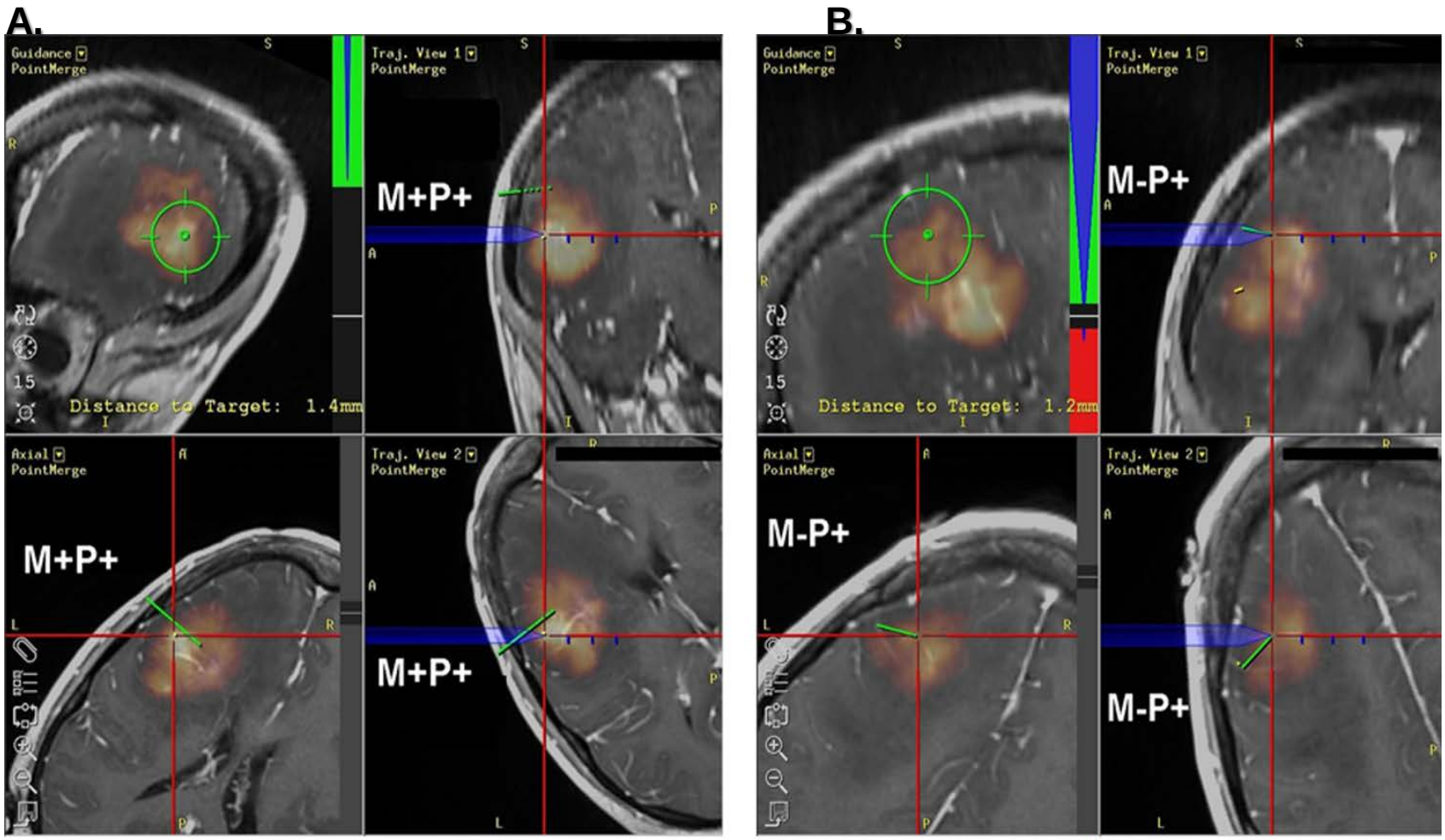
FLAIR contour in blue
T1-Gad contour in red
PET contour in yellow

***T1-GAD contour includes post-op cavity (not just enhancement)*



Orthogonal views with crosshairs turned on, for reference

Jann Sarkaria – Mayo Clinic Rochester



Screen capture of biopsy planning using the registered ^{18}F-DOPA PET and T1-CE MRI in the Stealth™ Neuronavigation System for blue needle locations at:
A) a T1 contrast enhancing, PET positive (M+P+) location
B) a non-contrast enhancing but PET positive (M-P+) location.

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Central Nervous System Tuberculosis

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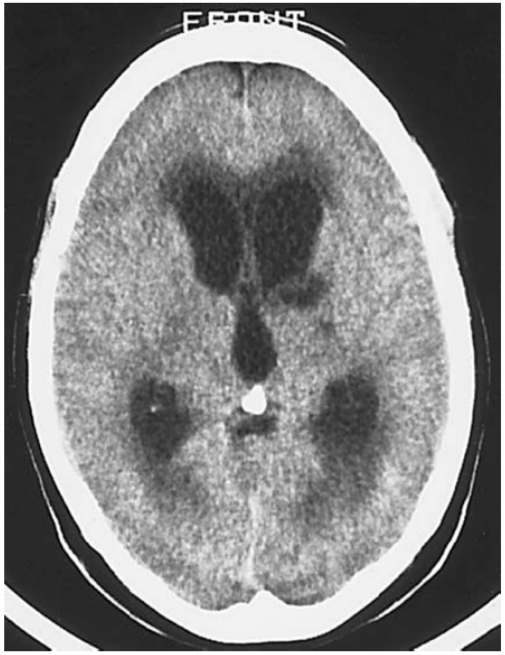
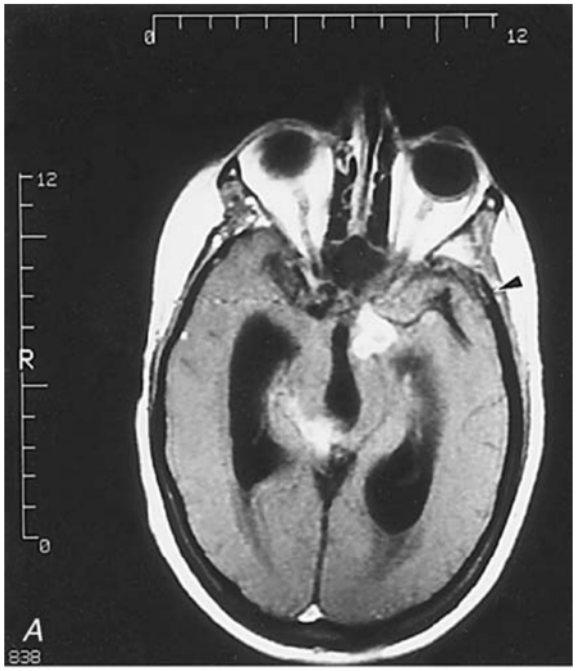
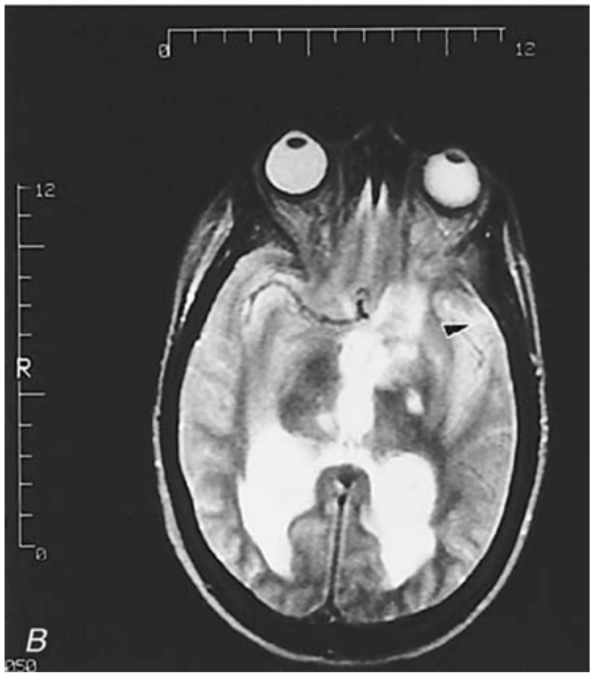
[1]Department of Medicine—Infectious Disease, Vanderbilt University Medical Center, Nashville, TN 37232



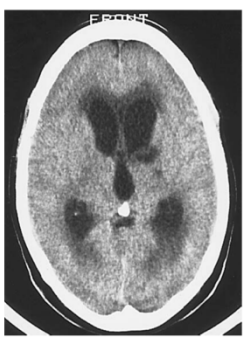




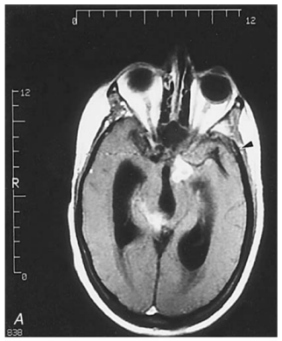
CT scan **T1 – CE - MRI** **T2 - MRI**

Region specific disease, requires region specific consideration of drug delivery

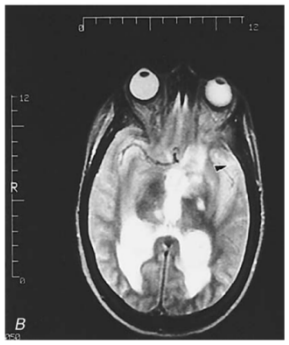
Spatial and Temporal Changes in Delivery of Drugs as Disease Progresses



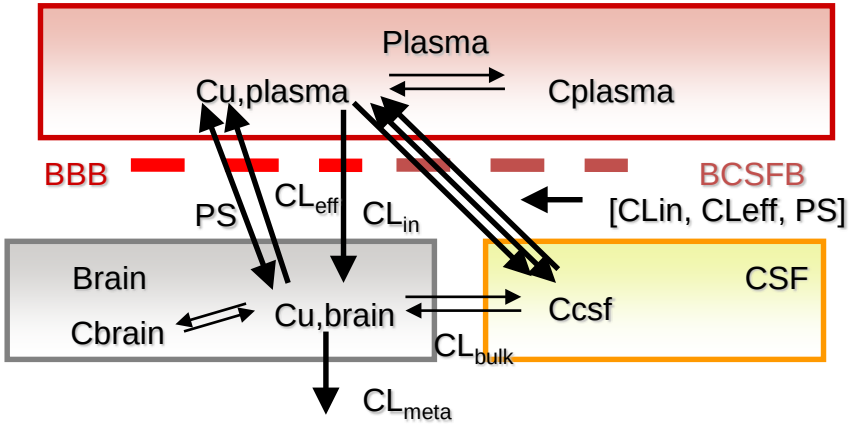
CT scan



T1 – CE - MRI



T2 - MRI



Questions:

1) In the tuberculomas, is there a change in drug penetration as they encapsulate?

2) Is there active disease in the peripheral regions that show edema?

3) What is the integrity of the BBB at different sites within an infected brain?

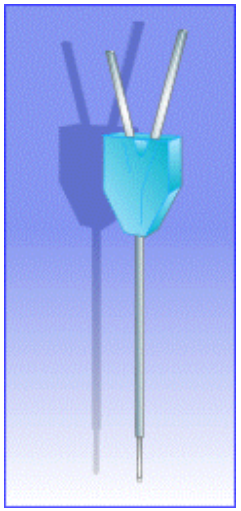
4) Are drug concentrations in each region adequate to treat disease?

5) Are there significant differences in delivery limitations amongst drugs used in the necessary combinations in different regions of disease?

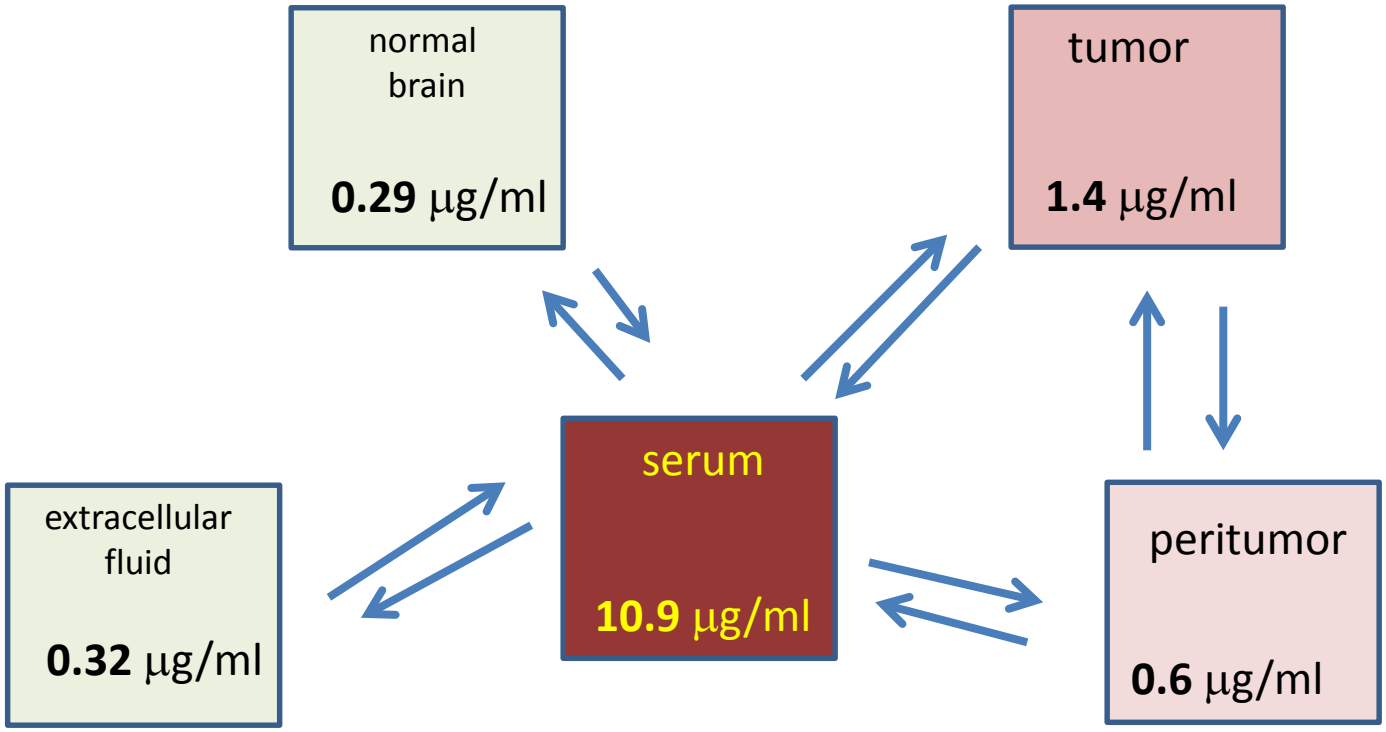
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1998, p. 2626–2629 Vol. 42, No. 10
0066-4804/98/$04.00+0

Rifampin Concentrations in Various Compartments of the Human Brain: A Novel Method for Determining Drug Levels in the Cerebral Extracellular Space

THOMAS MINDERMANN,[1]* WERNER ZIMMERLI,[2] AND OTMAR GRATZL[1]
Neurological Surgery[1] and Infectious Diseases,[2] University Hospitals Basel, 4031 Basel, Switzerland



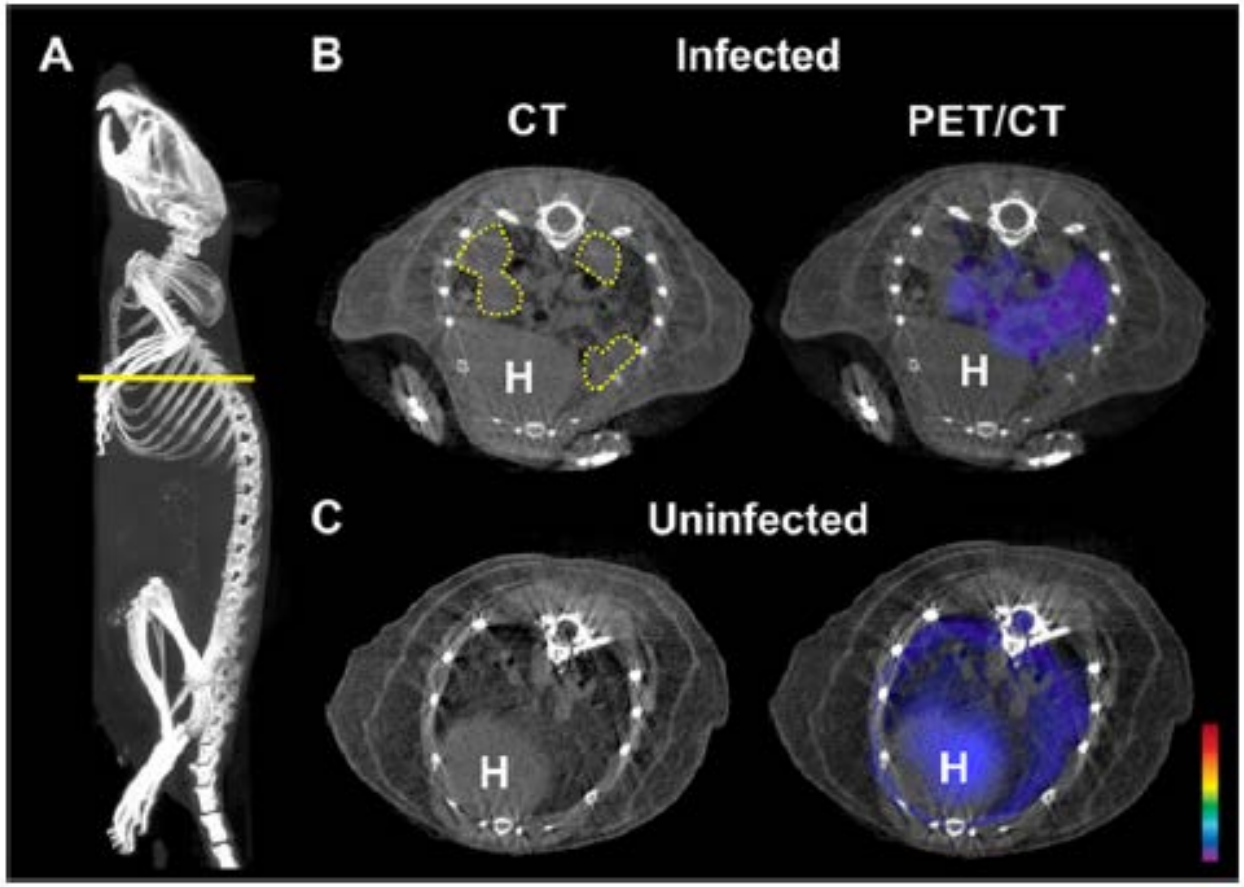
microdialysis



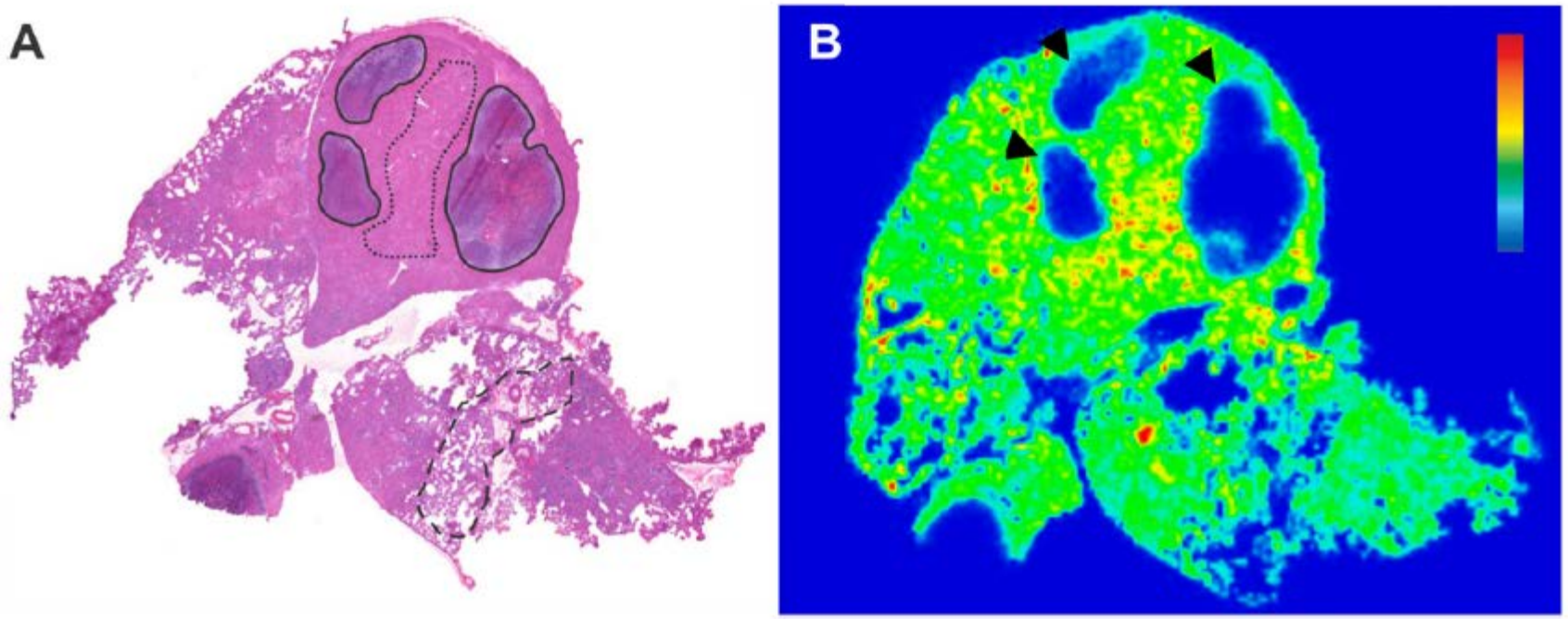
Rifampicin Spatial Differences in Distribution within the Human Brain

Determination of [^{11}C]Rifampin Pharmacokinetics within *Mycobacterium tuberculosis*-Infected Mice by Using Dynamic Positron Emission Tomography Bioimaging

Vincent P. DeMarco,[a,b,c] Alvaro A. Ordonez,[a,b,c] Mariah Klunk,[a,b,c] Brendan Prideaux,[d] Hui Wang,[e] Zhang Zhuo,[e] Peter J. Tonge,[e] Robert F. Dannals,[f] Daniel P. Holt,[f] Carlton K. K. Lee,[c] Edward A. Weinstein,[a,b,g] Véronique Dartois,[d] Kelly E. Dooley,[b,g] Sanjay K. Jain[a,b,c]



MALDI-MSI for Rifampicin Distribution in the Lung



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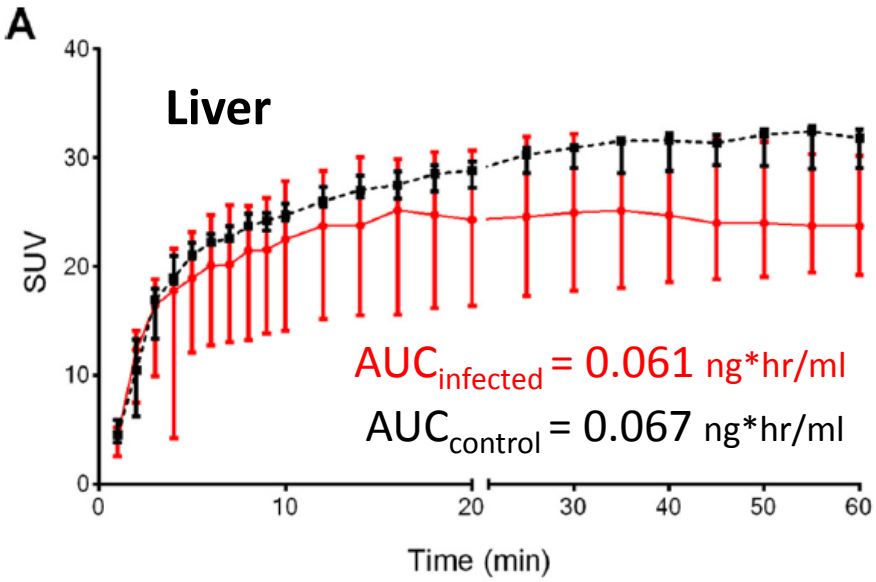
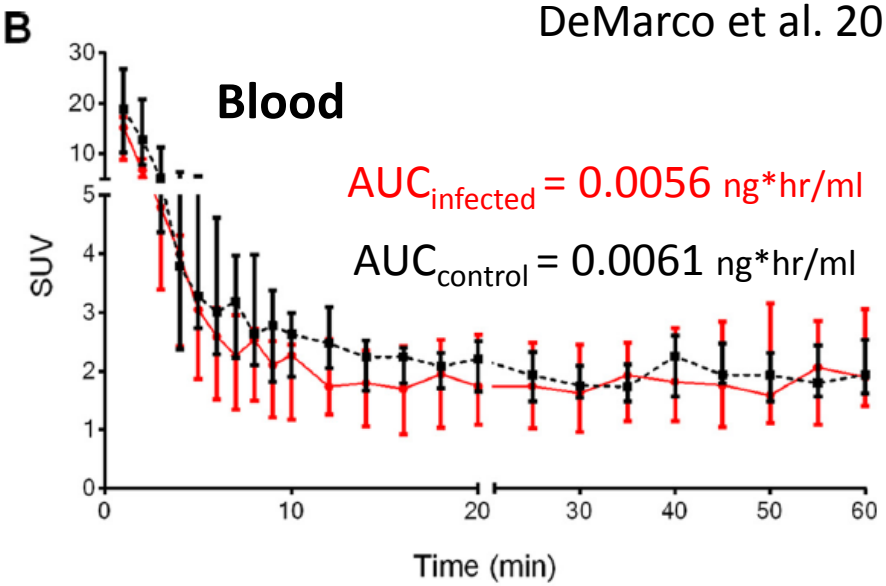
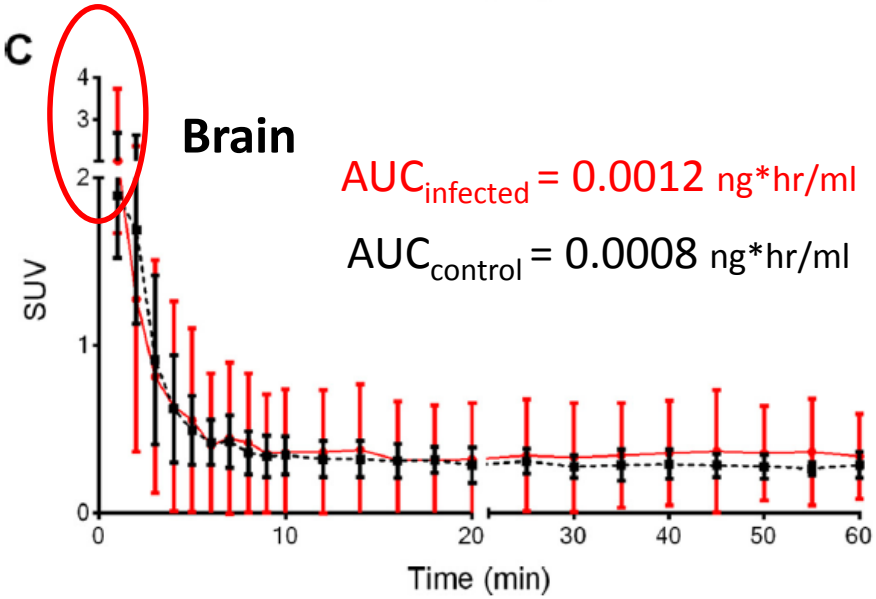
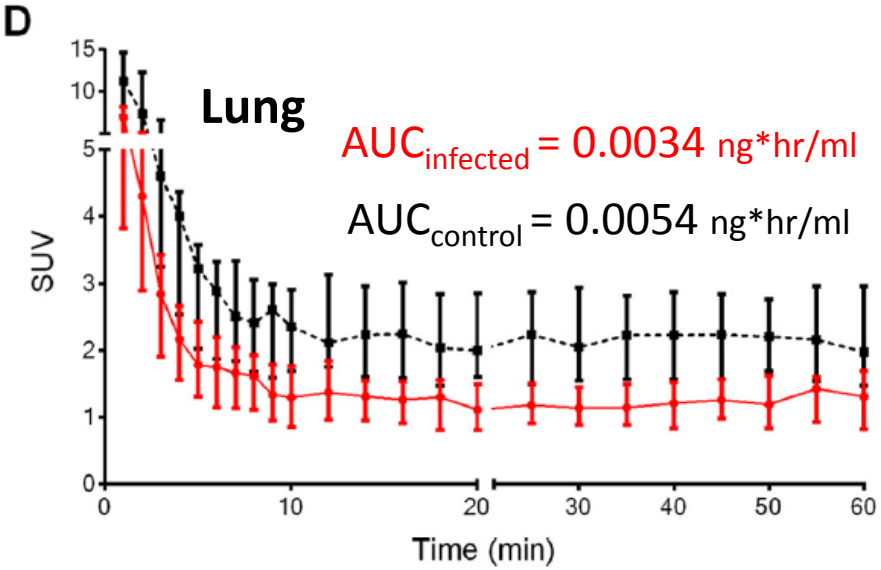
PET scan for distribution of 11C-Rifampicin in *M. tuberculosis* Infected Mouse Model

DeMarco et al. 2015









Radiosynthesis and Bioimaging of the Tuberculosis Chemotherapeutics Isoniazid, Rifampicin and Pyrazinamide in Baboons

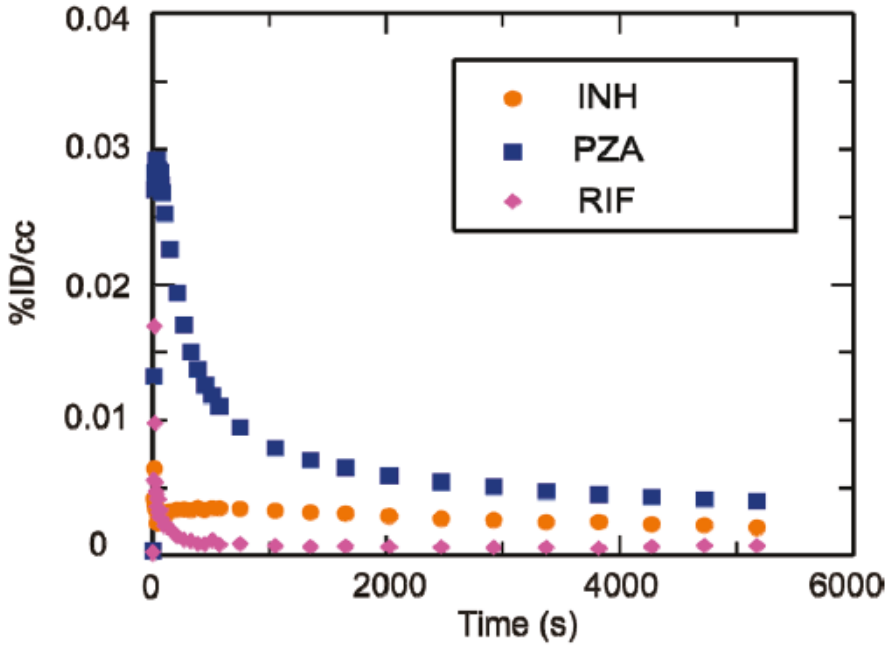
Li Liu,[†] Youwen Xu,[‡] Colleen Shea,[‡] Joanna S. Fowler,[‡] Jacob M. Hooker,*[,‡,∥] and Peter J. Tonge*[,†]

J. Med. Chem. **2010,** *53,* 2882–2891
DOI: 10.1021/jm901858n

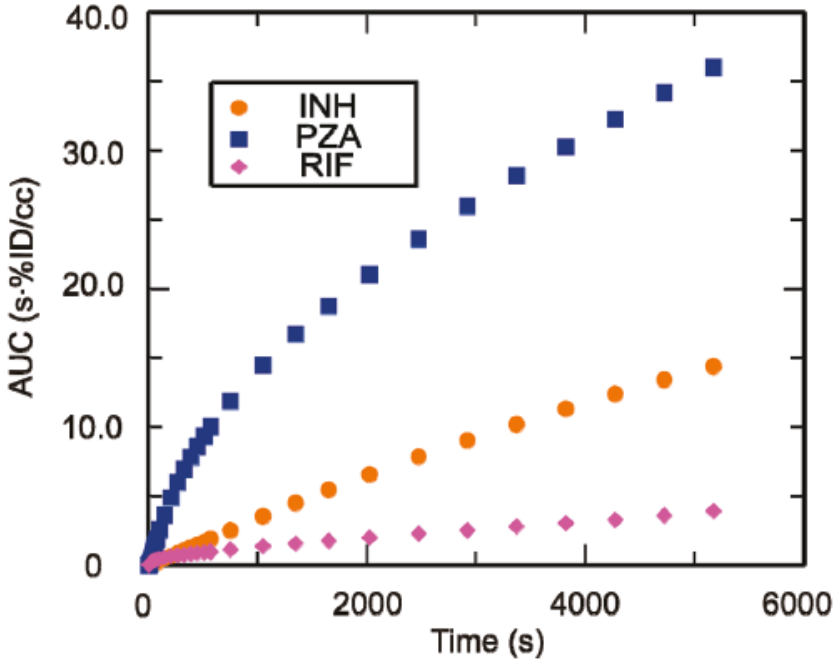
Journal of Medicinal Chemistry Article

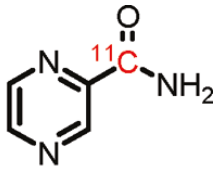
^{11}C PET

(a)

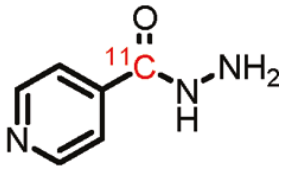


(b)

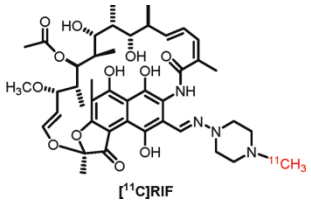




[^{11}C]PZA



[^{11}C]INH



RIF

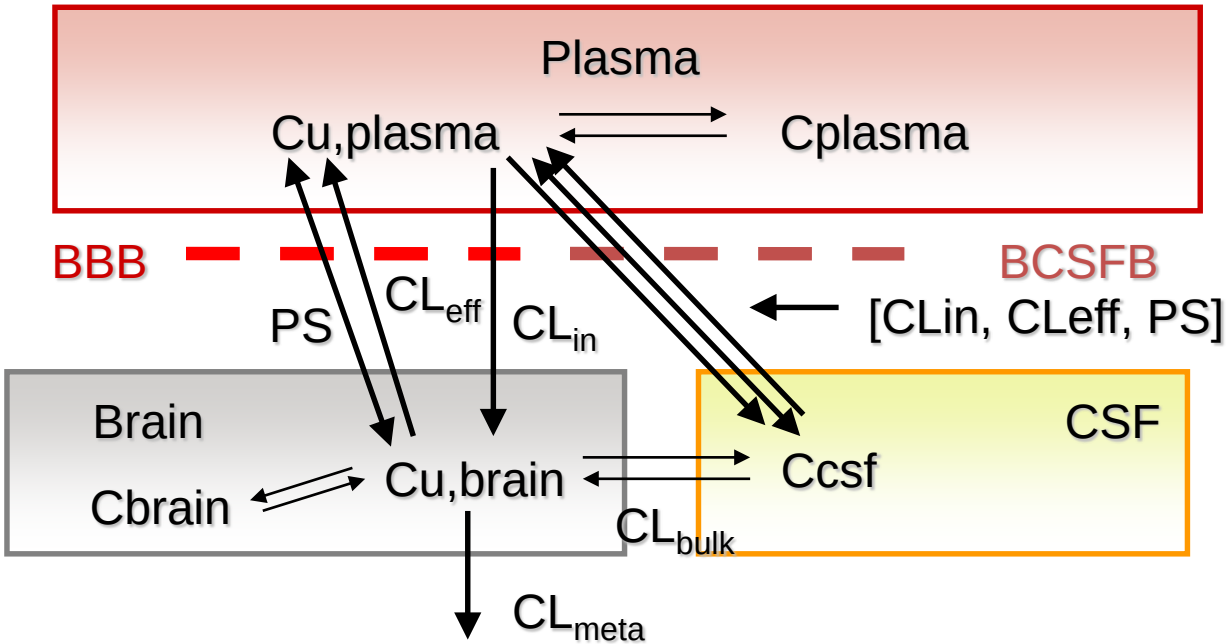
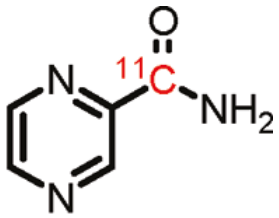


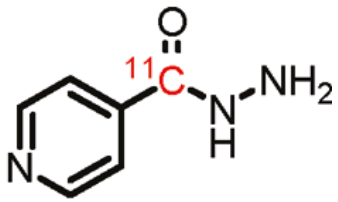
Table 1. LogD and PPB Determination

	LogD	PPB,[a] %
RIF	1.67	27.32
INH	nd[b]	94.63
PZA	−0.41	91.32

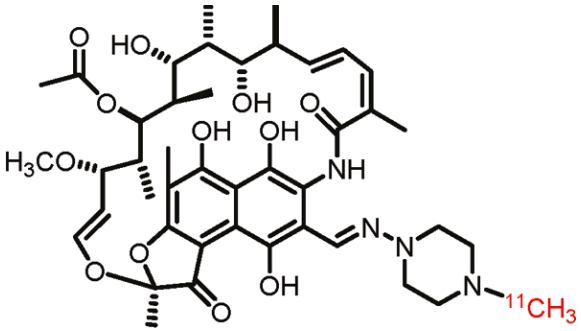
[a] Value expressed as % of free fraction in plasma. [b] Octanol−water partitioning was highly variable.



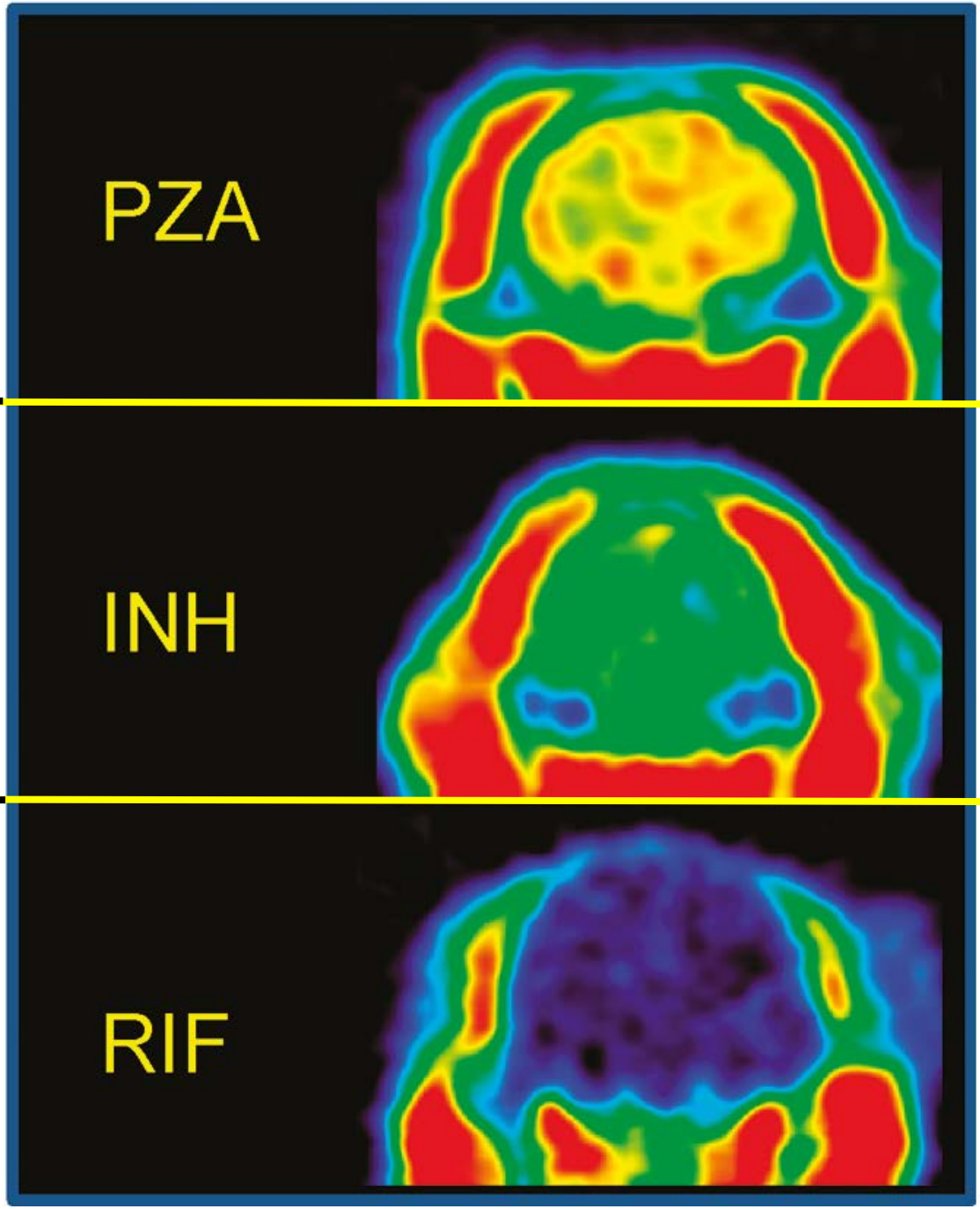
[11C]PZA



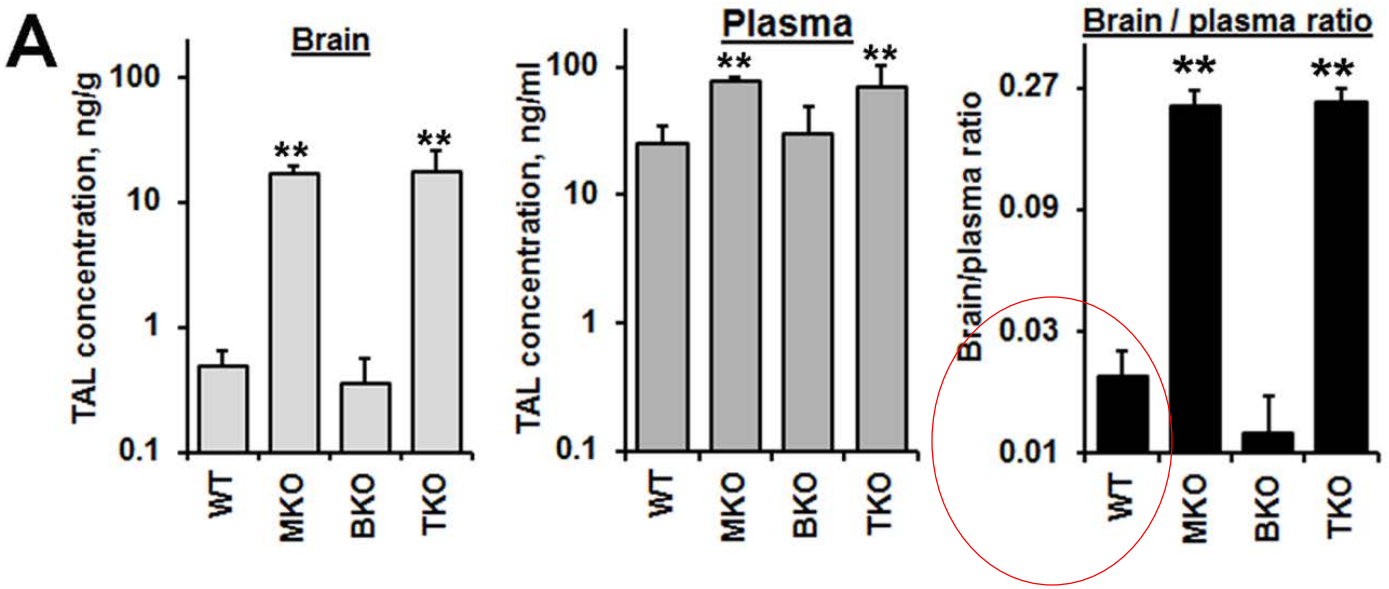
[11C]INH



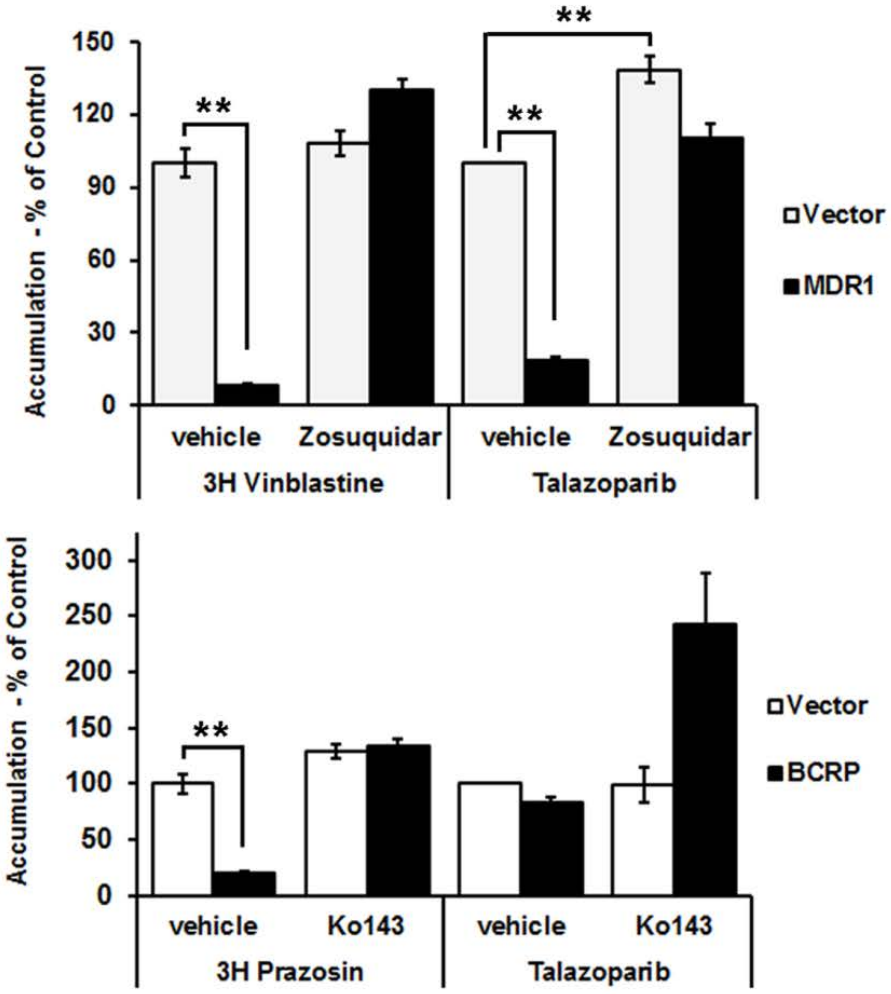
[11C]RIF

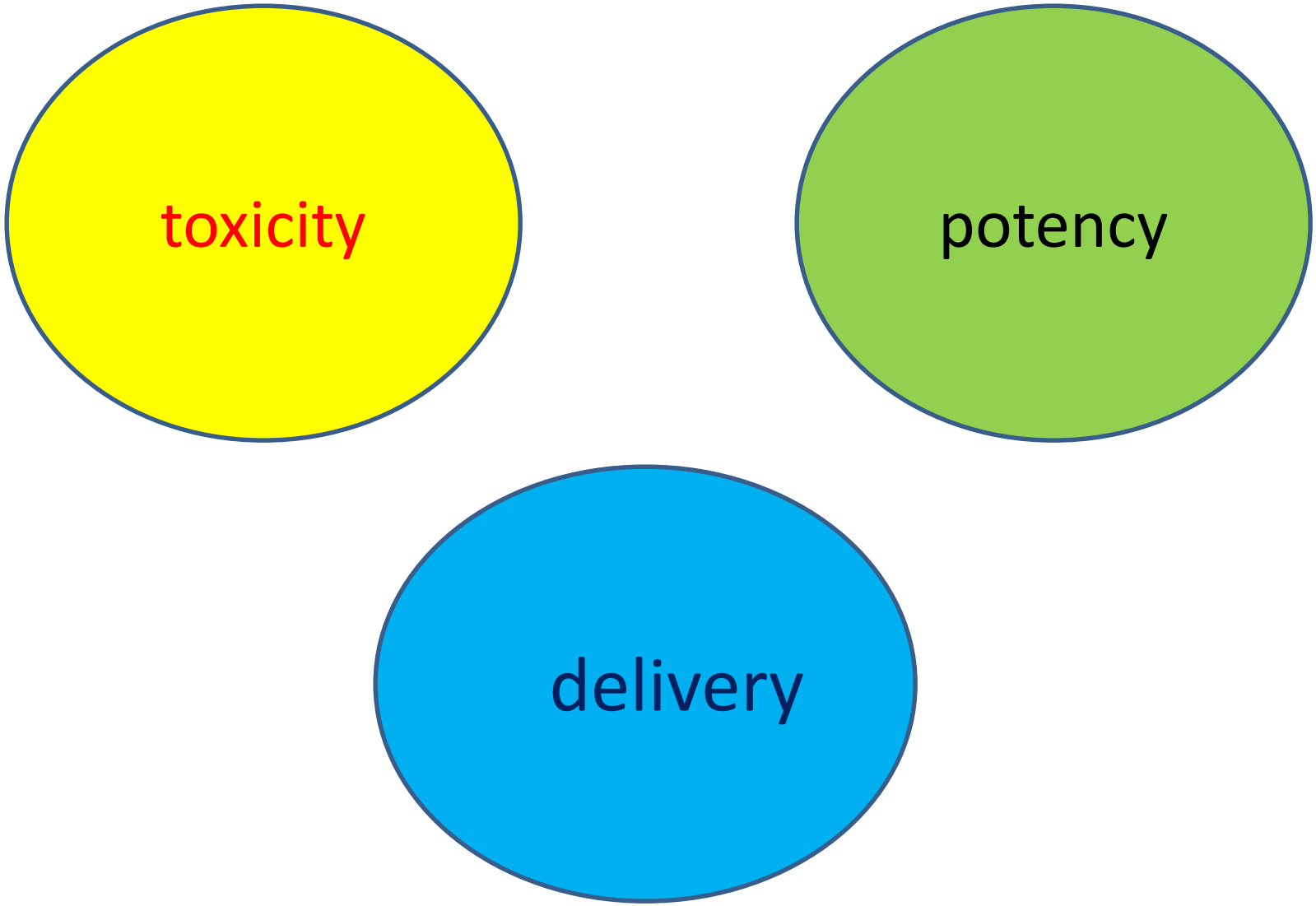


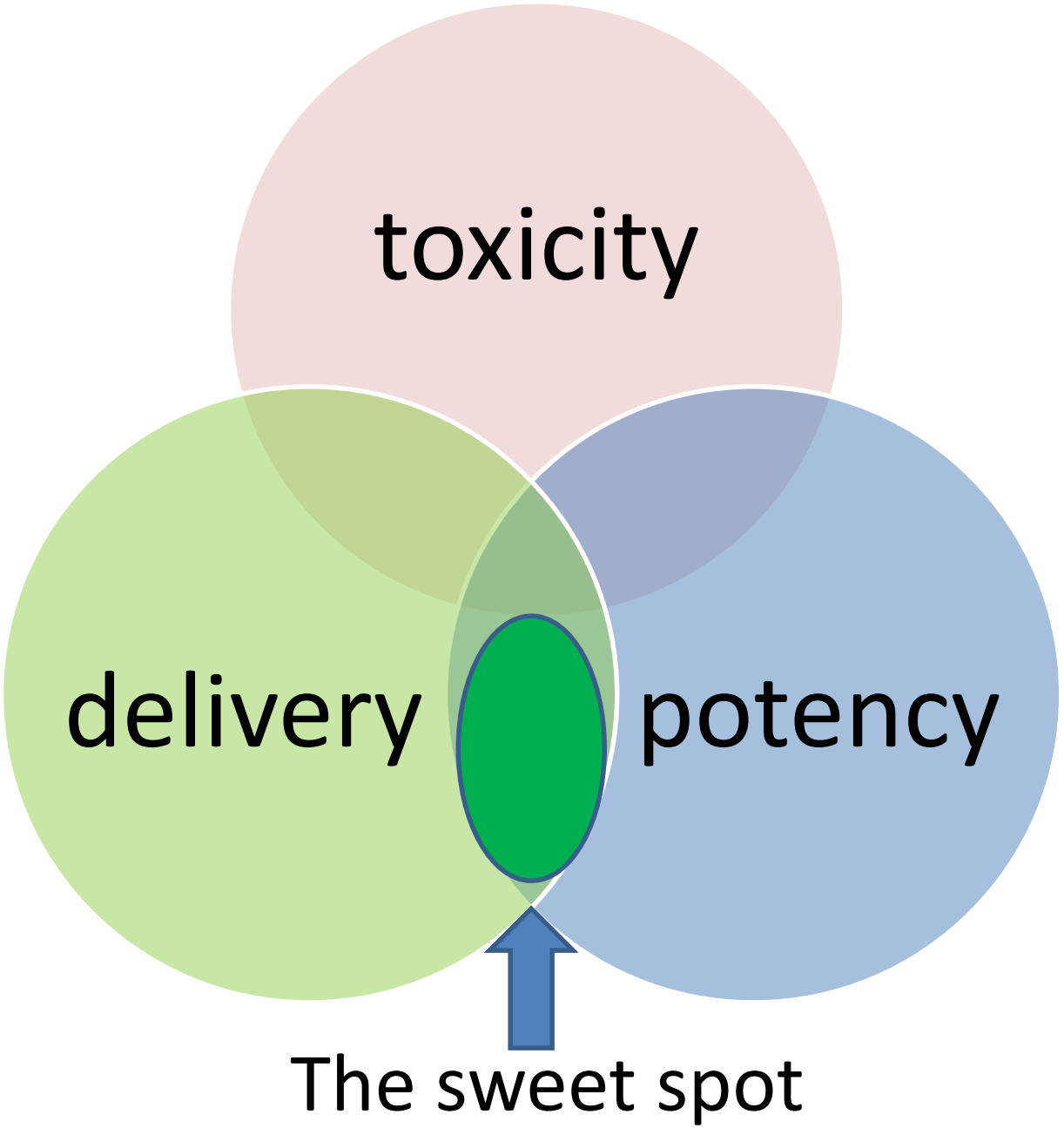
Parp1 inhibitor - Talazoparib



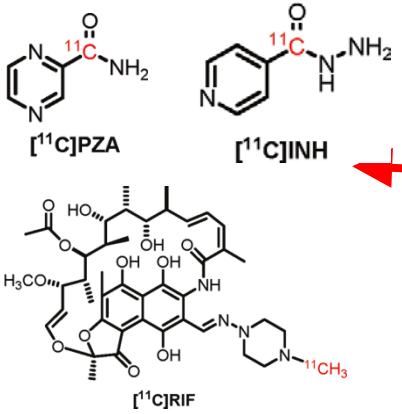
Talazoparib – Pgp substrate - poor penetration into the brain


Accumulation - % of Control
150
120
90
60
30
0
**
**
**
Vector
MDR1
vehicle
Zosuquidar
vehicle
Zosuquidar
3H Vinblastine
Talazoparib
Accumulation - % of Control
300
250
200
150
100
50
0
**
Vector
BCRP
vehicle
Ko143
vehicle
Ko143
3H Prazosin
Talazoparib

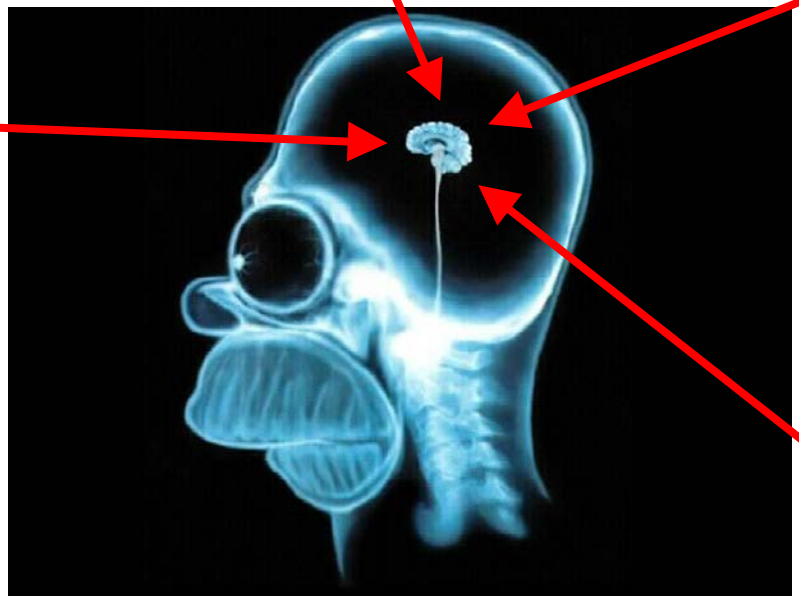

toxicity
potency
delivery


toxicity
delivery
potency
The sweet spot

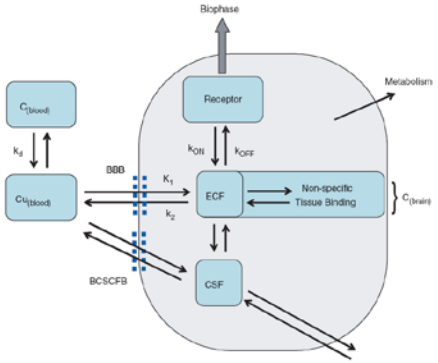
Delivery across the BBB: Beware of the simplest explanation.



"Sweet Spot" for CNS Rx

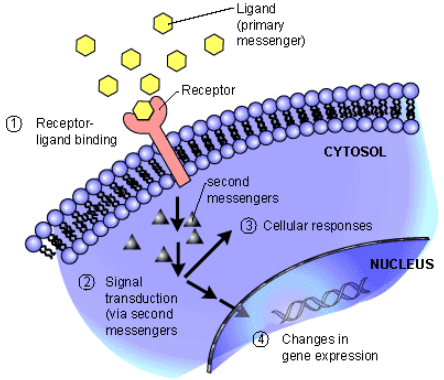


"Intelligent Drug Design"



Empiric "Black-Box" Pharmacokinetics

Systems Pharmacology



Mechanistic "Molecular" Pharmacokinetics

Make things as simple as possible, but not simpler.

Albert Einstein