

Disclosures

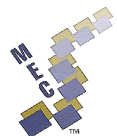
Tim Synold, PharmD

Pharmacokinetics of Anti-Cancer Agents in the CNS

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**14th Annual California Cancer Conference Consortium
August 10-12, 2018**



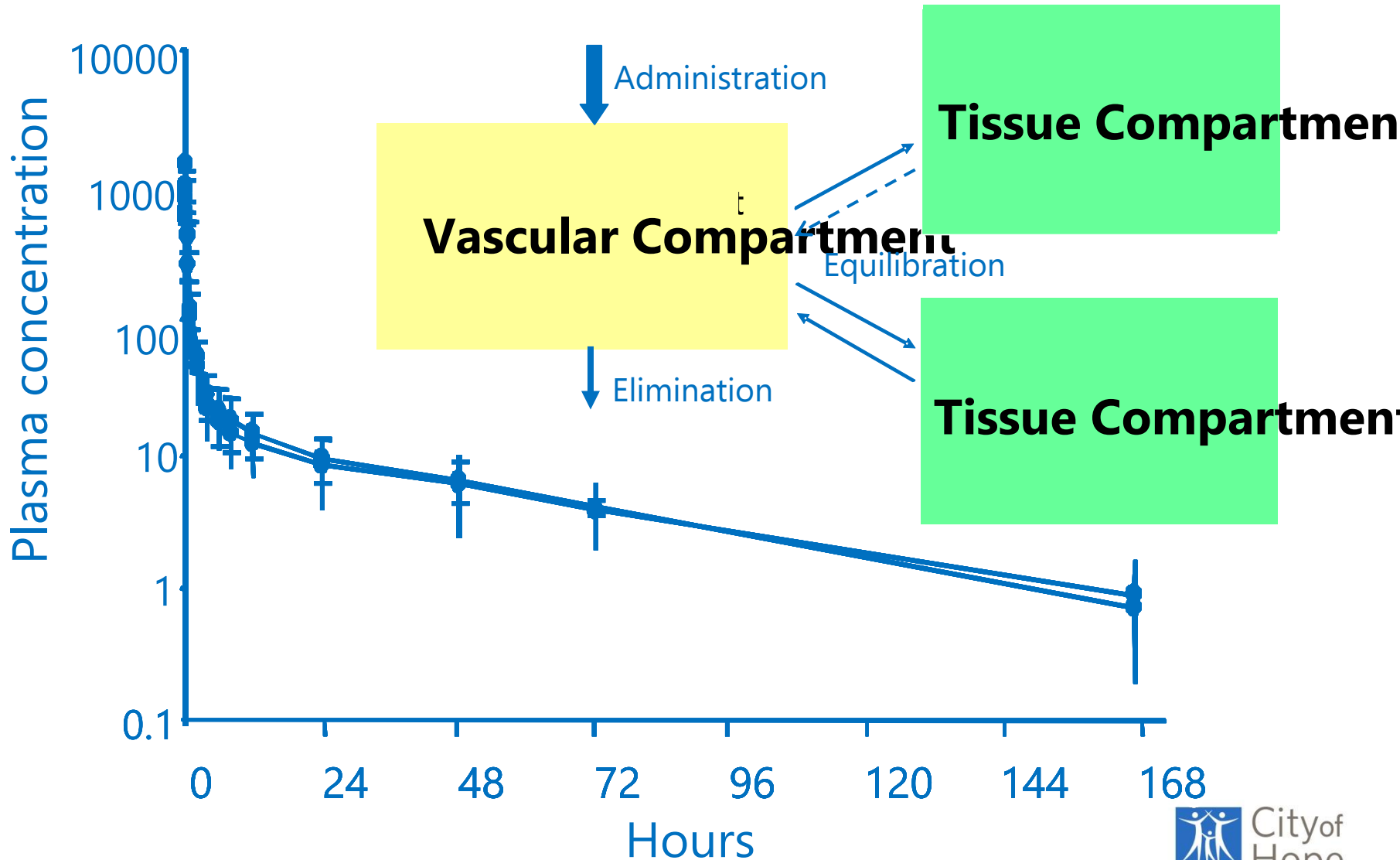
Pharmacokinetics of Anti-Cancer Agents in the CNS

Tim Synold

**Professor, Div. of Molecular Pharmacology
Director, Analytical Pharmacology Core Facility
City of Hope Comprehensive Cancer Center**

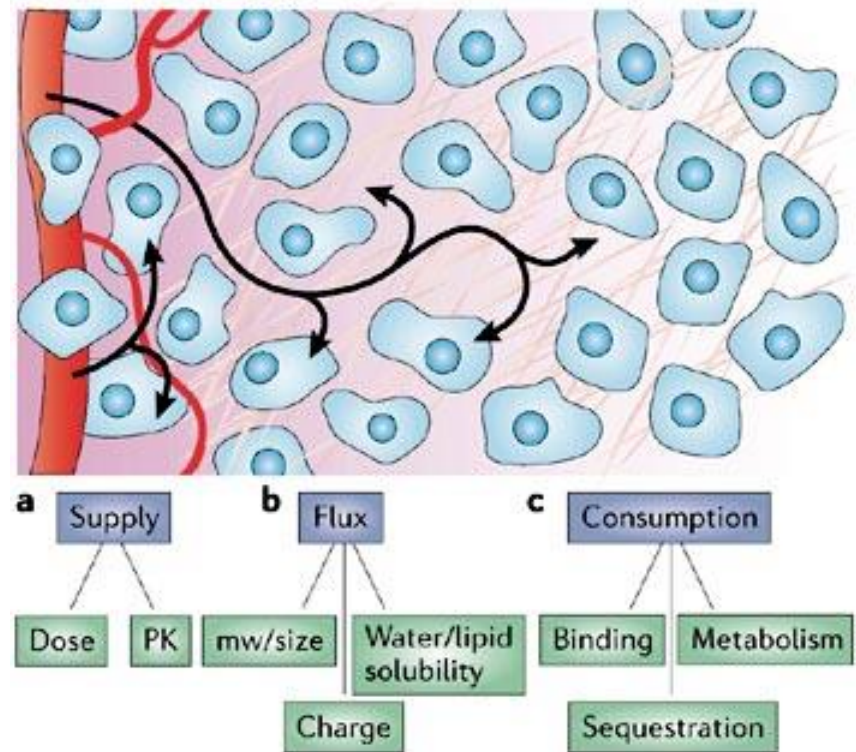


Traditional PK Analyses



Drug Distribution: A Neglected Concern

- Must penetrate tissue
- Must reach all tumor cells in sufficient concentration
- Research focused on molecular mechanisms of resistance
- Evidence suggests distribution in tumor often incomplete



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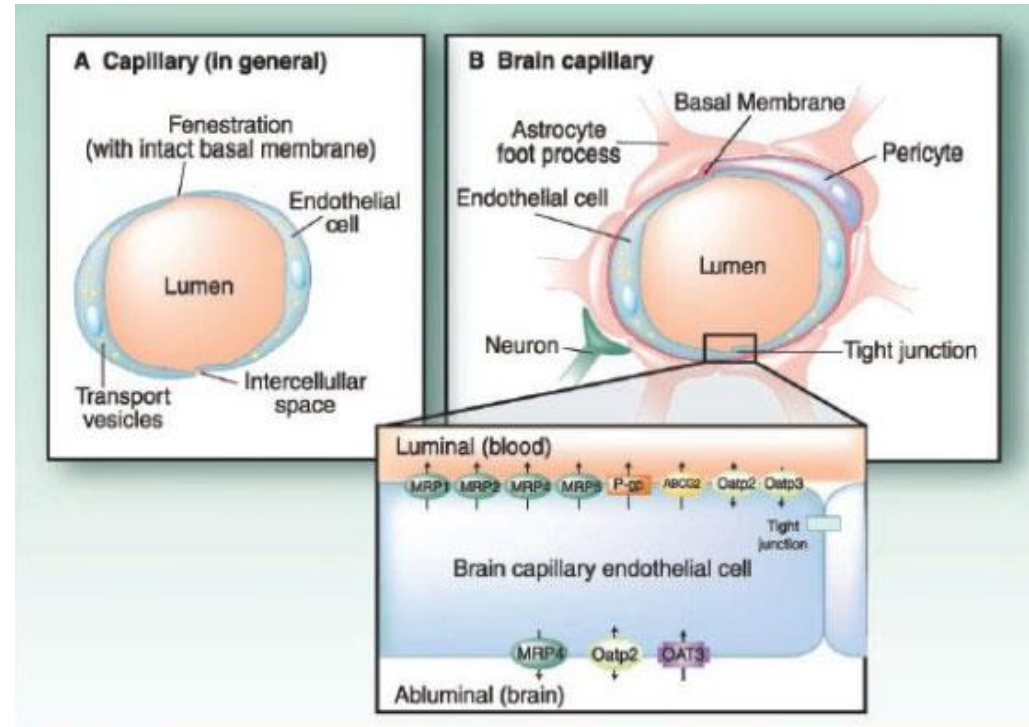
Minchinton et al. Nature Reviews Cancer 2006; 6:583–592

Clinical Significance of the BBB

- ~24,000 primary brain tumors diagnosed per year
- Median survival of unresectable GBM ~14 months
- Number of brain mets are >200,000 (~10x primary brain tumors)
- Untreated, median survival is 2-3 months and 4-12 months with treatment
- A growing problem as systemic therapies improve

Blood-Brain-Barrier

- Network of specialized endothelial cells, other cell types, and basal lamina
- Tight junctions and transporters exclude drugs from brain ECF
- Distinct from blood–CSF barrier
- Few drugs cross BBB, mostly via lipid-mediated diffusion



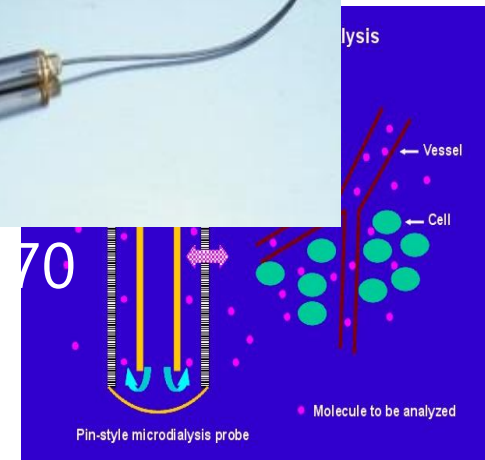
Pardridge WM. J Cereb Blood Flow Metab. 2012; 32:1959-72

COH Intracranial Microdialysis Program

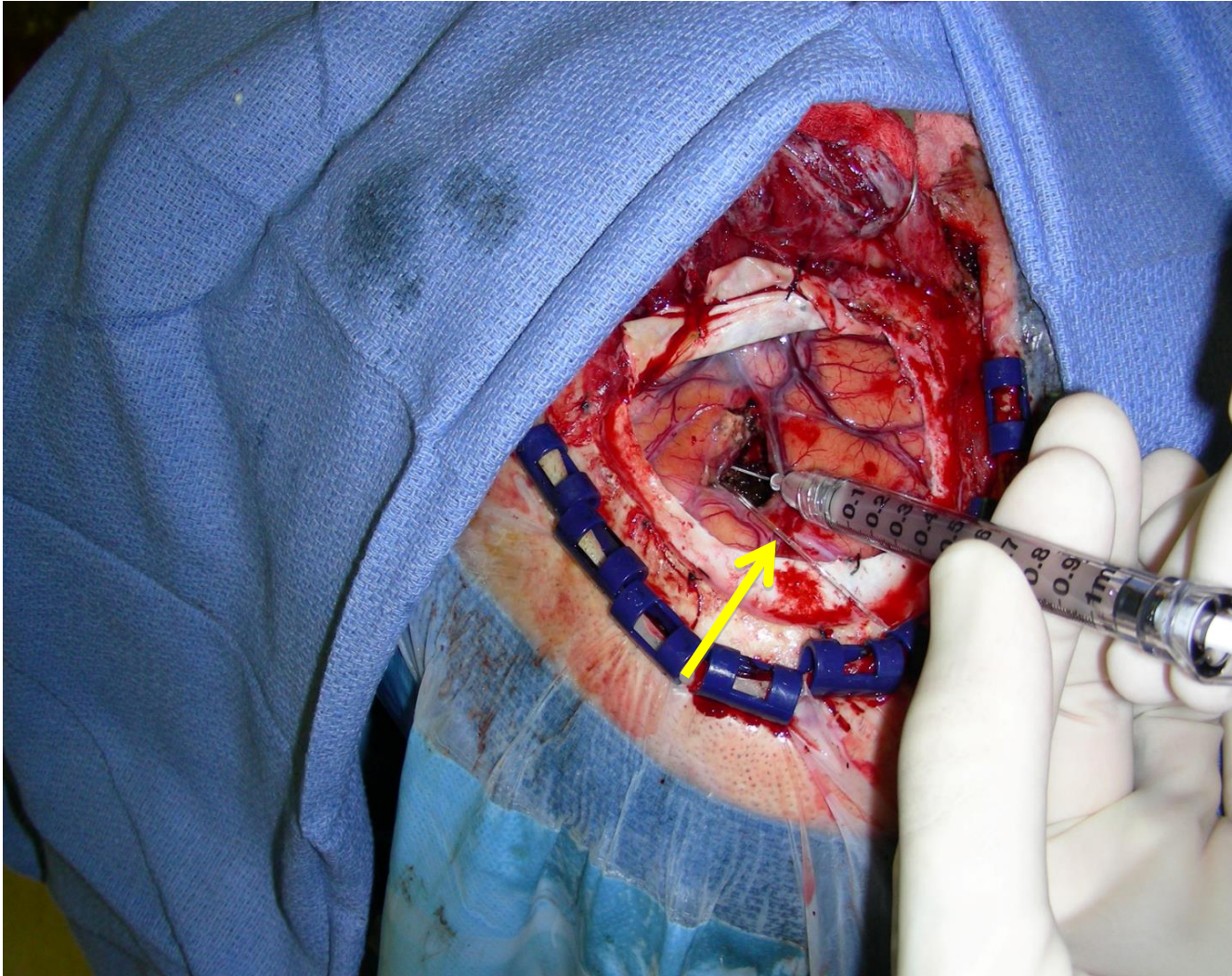
- First clinical trial initiated in 2006
- Addressed need to measure CNS drug penetration
- 6 trials completed to date, one ongoing
- ICMD catheters placed in 56 pts
- Largest single institution experience in U.S.

Interstitial PK Measurement - Microdialysis

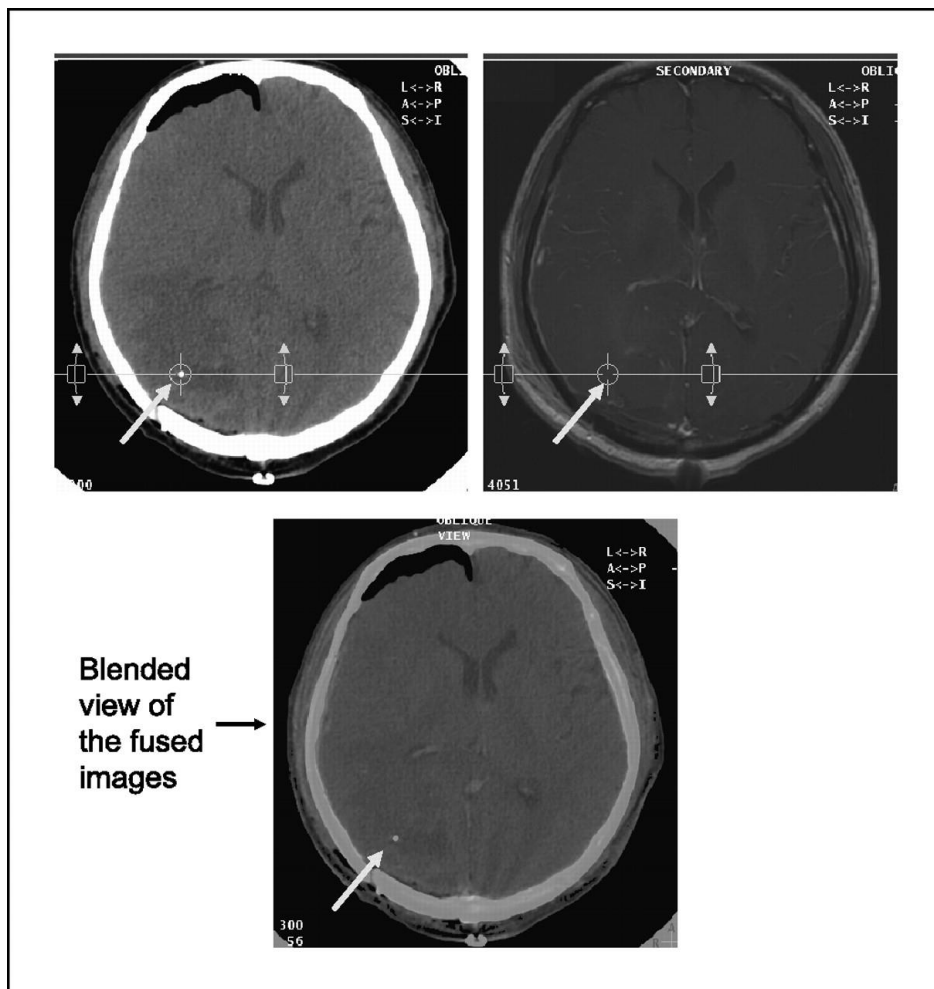
- CMA70 – 20 kDa cut-off
FDA approved for
markers of tissue
damage and repair
- Has also applied to real-
time measurement of
tissue PK



Intracranial Microdialysis (ICMD)

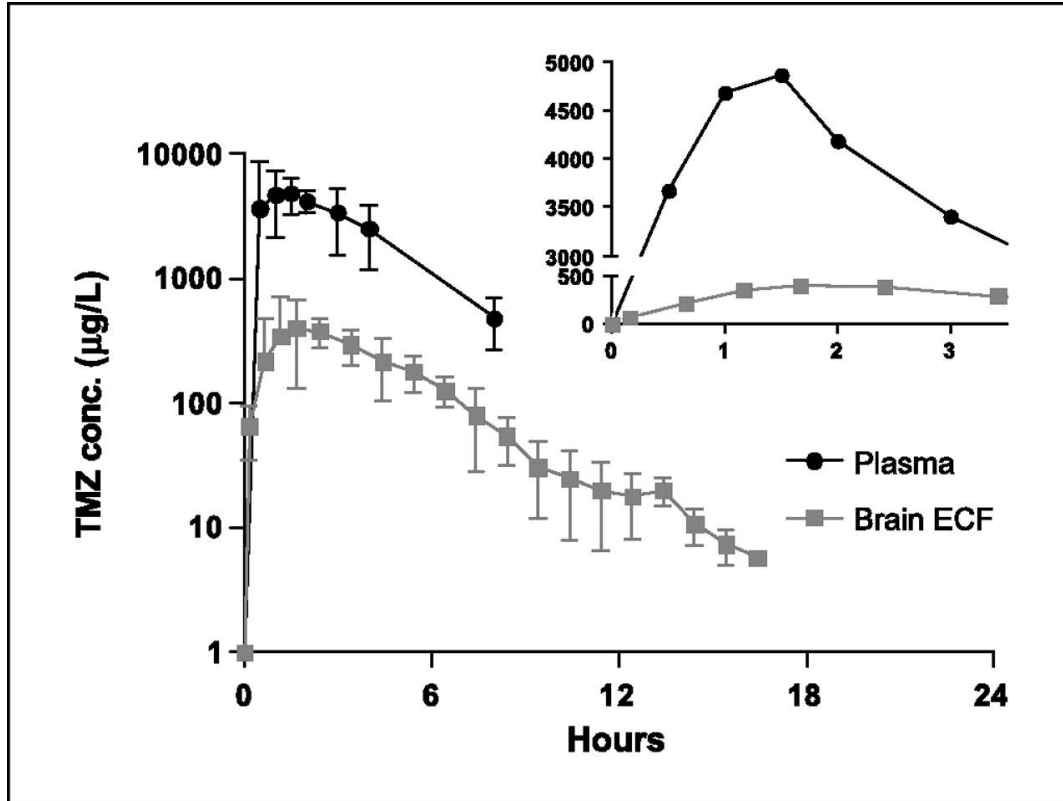


ICMD Catheter Placement

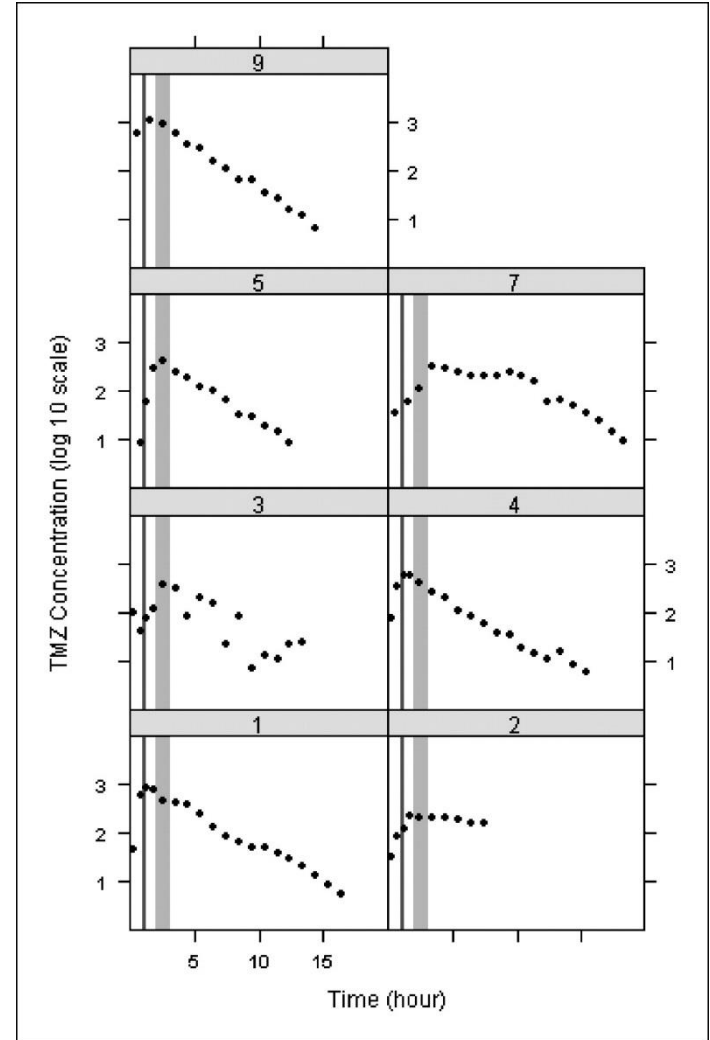


- Gold filament visible on CT.
- Not visible on post-contrast T1 MRI.
- Fused images show tip is in non-enhancing brain.

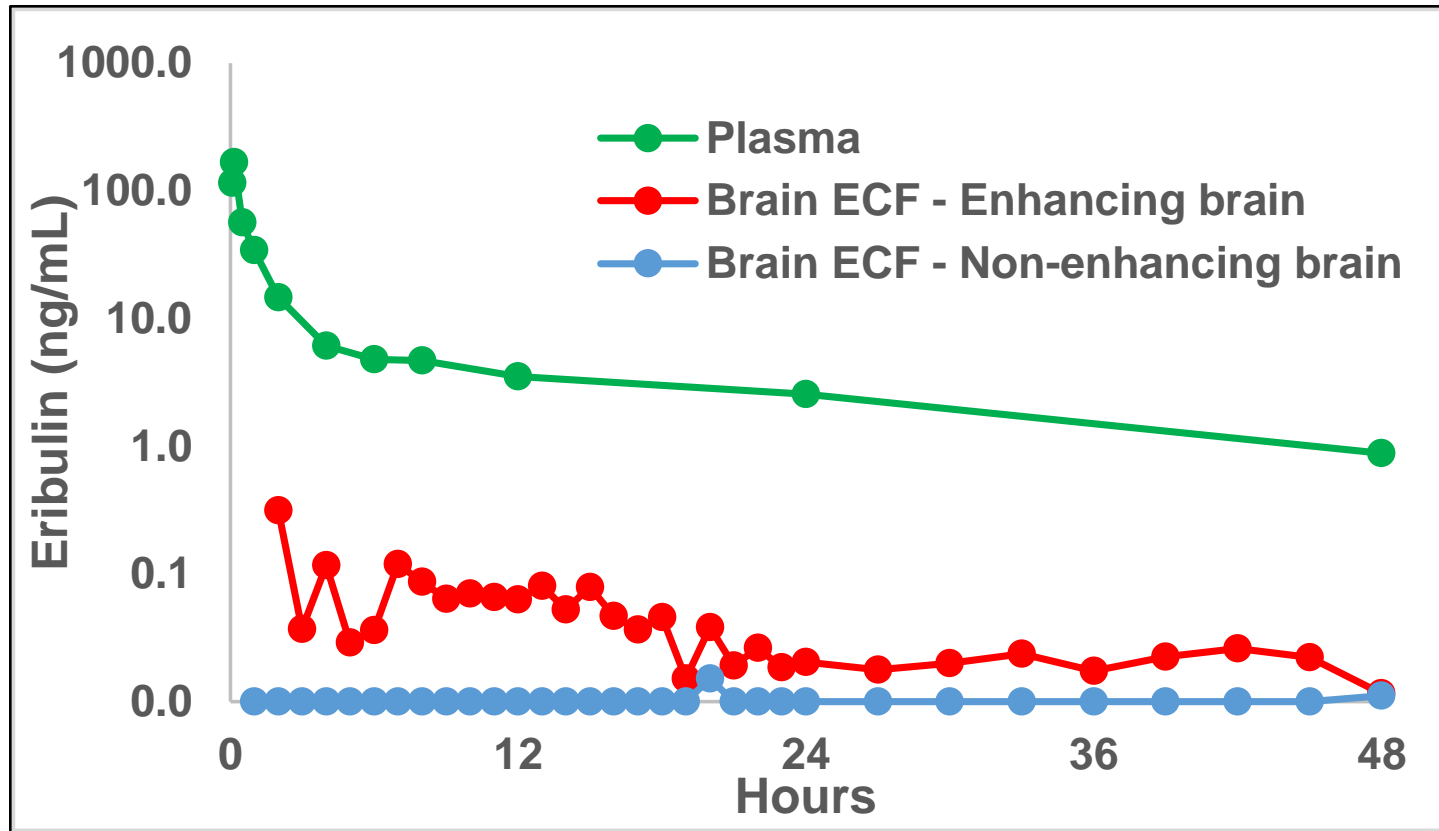
Temozolomide Plasma and Brain PK



- Brain ECF/plasma = $17.8 \pm 13.3\%$
- C_{max} at 2-3 hr in most patients



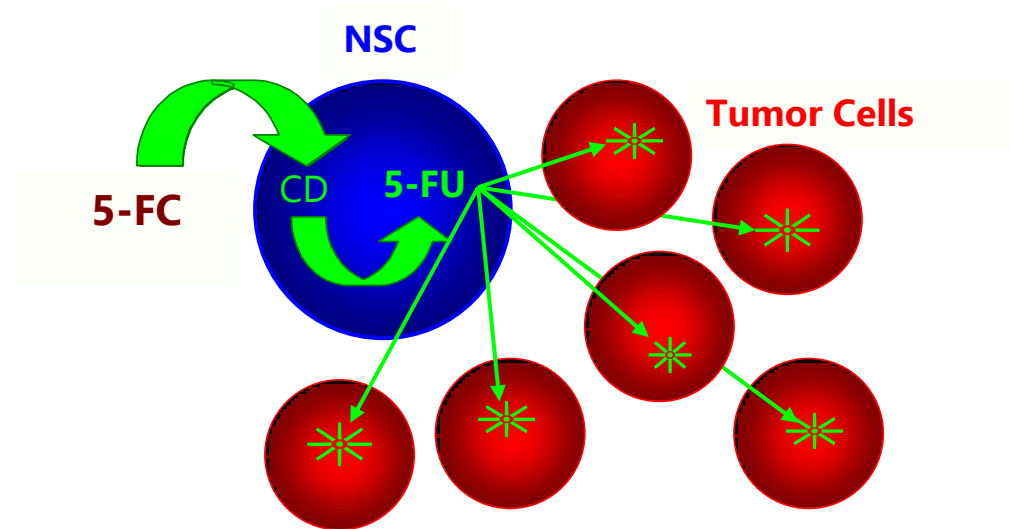
Eribulin Plasma and Brain PK



- Enhancing brain ECF/plasma = 0.8%
- Non-enhancing brain ECF/plasma = 0.02%

Genetically-Modified Neural Stem Cells

Karen Aboody, MD

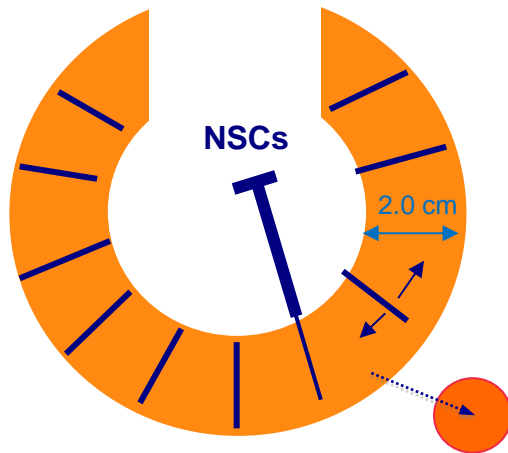


- Takes advantage of the demonstrated tumor tropism of NSCs
- 1st generation cells transduced to expressed a bacterial cytosine deaminase (CD)
- CD converts non-toxic 5-fluorocytosine to 5-fluorouracil
- Goal is brain tumor localized production of chemotherapy and minimal toxicity to normal tissues

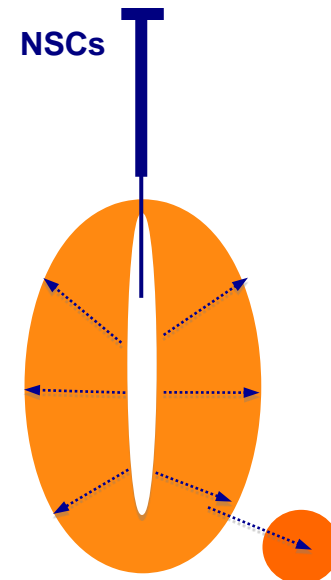
Treatment Schema

Day 0: Intracerebral Administration of HB1.F3.CD NSCs

- Microdialysis catheters placed



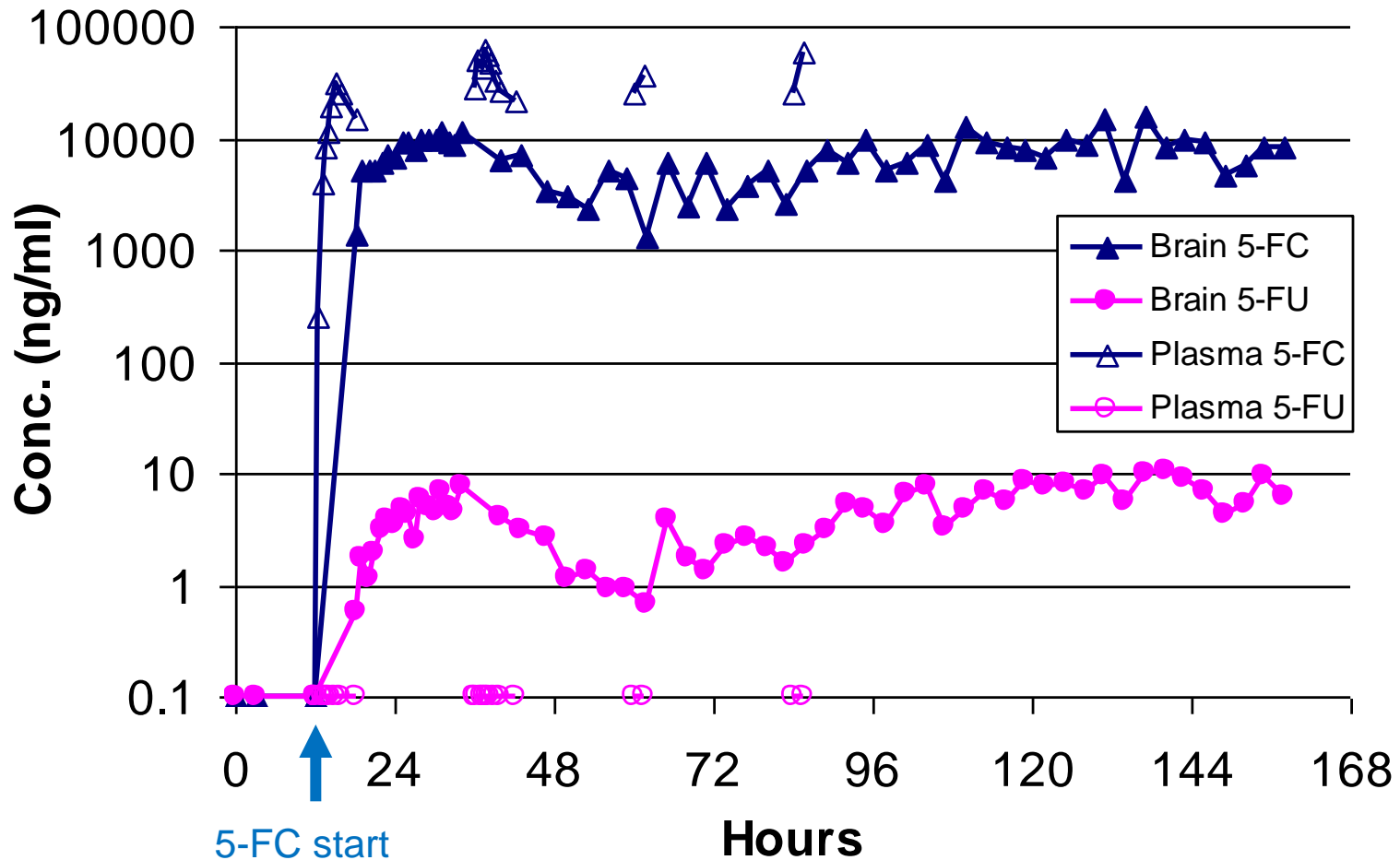
10 NSC INJECTIONS (100-uL each) 2 cm
DEEP INTO RESECTION CAVITY WALL



NSC INJECTION (1 ml) INTO BIOPSY SITE

Day 4-10: 5-FC administered orally, microdialysis studies
Serial dialysate and blood samples drawn for PK

5FC & 5FU in Brain ECF and Plasma



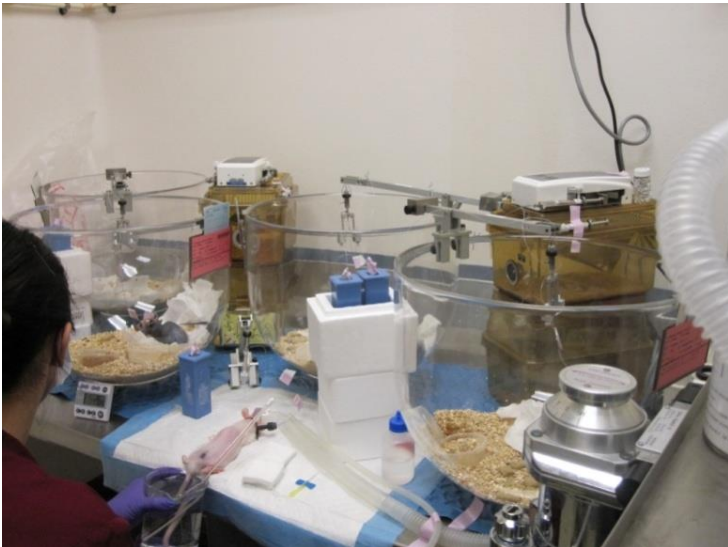
5-FC start
Day 4

*5-FU production in brain consistent during 5-FC
No 5-FU detected in plasma

Microdialysis Studies in Nude Rat Model

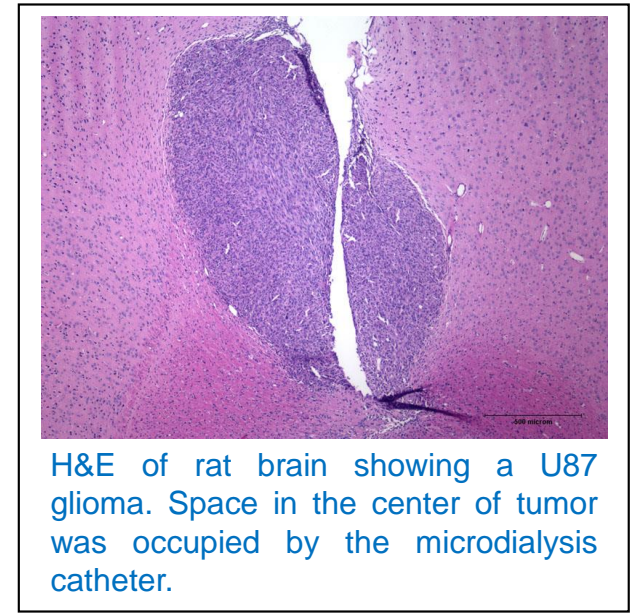
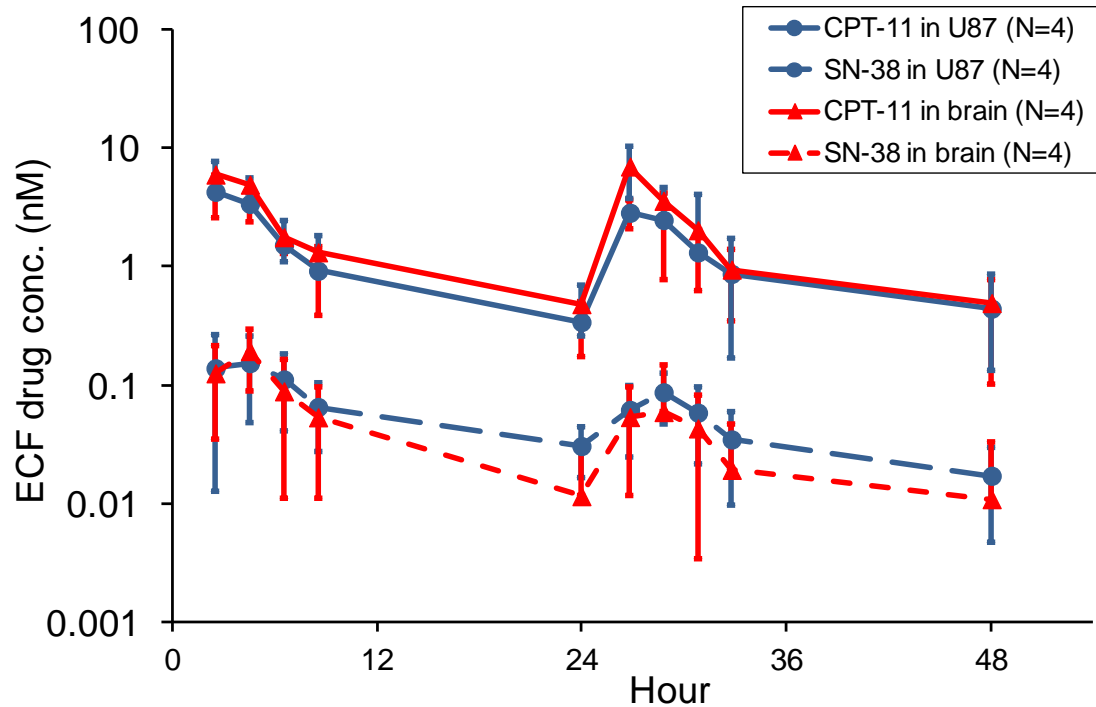


- Guide cannula stereotactically implanted into brain
- Prior to expt, MD probe placed via cannula
- Catheter continuously perfused
- Animals move freely w/catheter



- Drug given iv, ip, or po
- Dialysate and blood collected serially
- Drug and metabolites measured by LC-MS/MS.

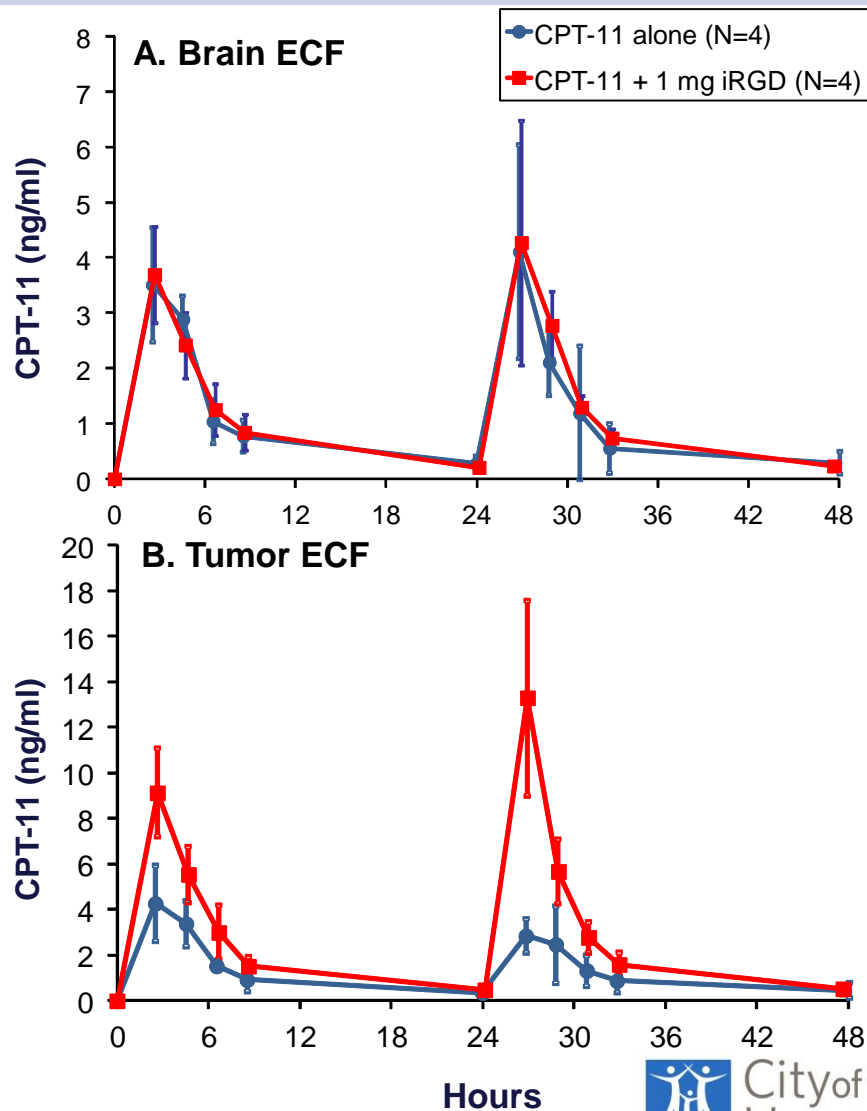
Brain and Tumor ECF Concentrations of CPT-11 and SN-38



- Brain ECF $AUC_{SN-38}/AUC_{CPT-11} \cong 2.5\%$
- Tumor ECF $AUC_{SN-38}/AUC_{CPT-11} \cong 5.0\%$
- AUC_{brain}/AUC_{plasma} of CPT-11 and SN-38 are $< 0.1\%$

iRGD Peptide Enhances Penetration of Irinotecan in CNS Tumor but not Normal Brain

- ICMD nude rat model bearing U87 human glioma
- No effect in normal brain
- 3 to 5-fold increase in irinotecan penetration in tumor
- Optimal dose and schedule of iRGD is TBD



Summary

- Extracellular fluid is key but neglected space
- BBB is a serious impediment to treatment
- As systemic therapies improve, CNS mets have become an increasing clinical concern
- Novel strategies to overcome the BBB are critical
- Clinical and preclinical ICMD will assist development of new approaches

Acknowledgments

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Patients and families

ICMD Animal Model

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