

# **Metastasis and the Brain**

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Memorial Sloan Kettering  
Cancer Center

Luke Fildes 1891 *The Doctor*, Tate Gallery London

# Part 1: Clinical Information

*Why do I need to know clinical information?*



Gain access to clinical literature, datasets

View clinical presentations with a mechanistic eye

New territories for bench research

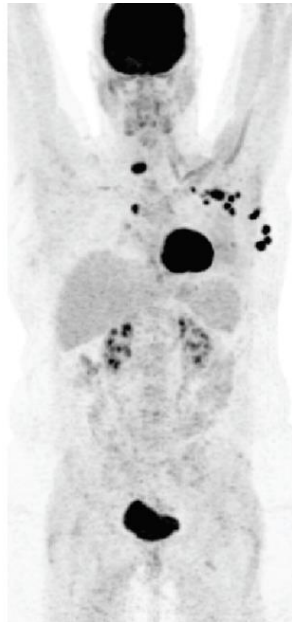
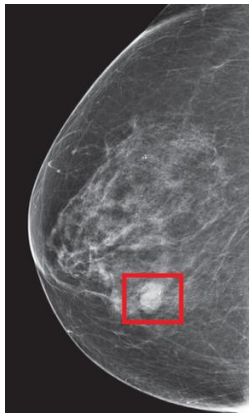
Understand the clinical samples that are (and are NOT) available

Meaningfully interact with clinicians

Write a **Background and Significance** section that is “a heartbreaking work of staggering genius”

# CNS Metastases:

Diagnosis is Late, Treatments are Destructive to Nervous System



Cancer Diagnosis  
Initial Staging



No CNS  
Symptoms



Systemic  
Treatment



CNS  
Symptoms



CNS  
Staging

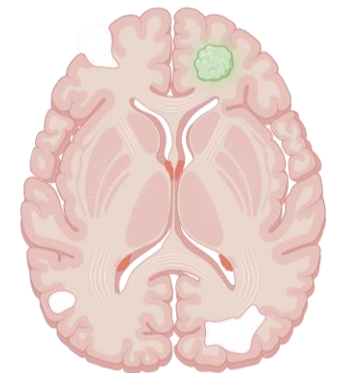
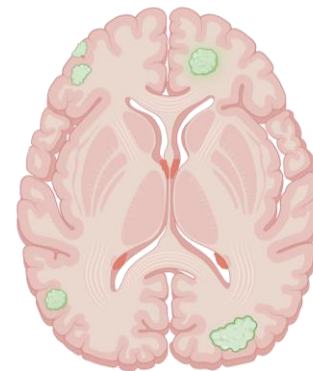
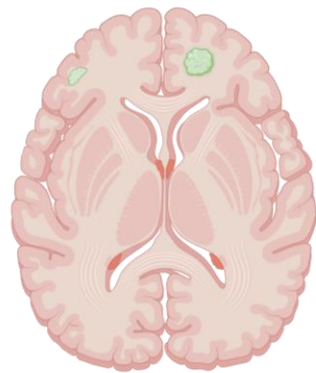
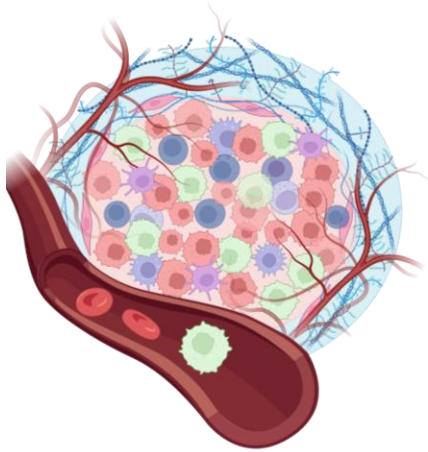
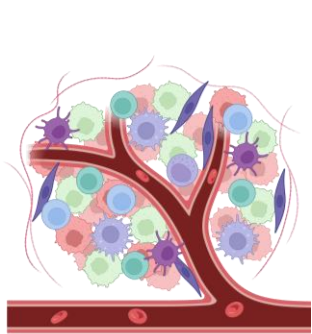


CNS-Directed  
Treatment

# CNS Metastases:

Diagnosis is Late, Treatments are Destructive to Nervous System

Cancer Diagnosis Initial Staging → No CNS Symptoms → Systemic Treatment → CNS Symptoms → CNS Staging → CNS-Directed Treatment



Primary Tumor Growth

Tumor Cell Dissemination

CNS Metastasis Growth

Normal CNS Tissue Damage

CNS Staging

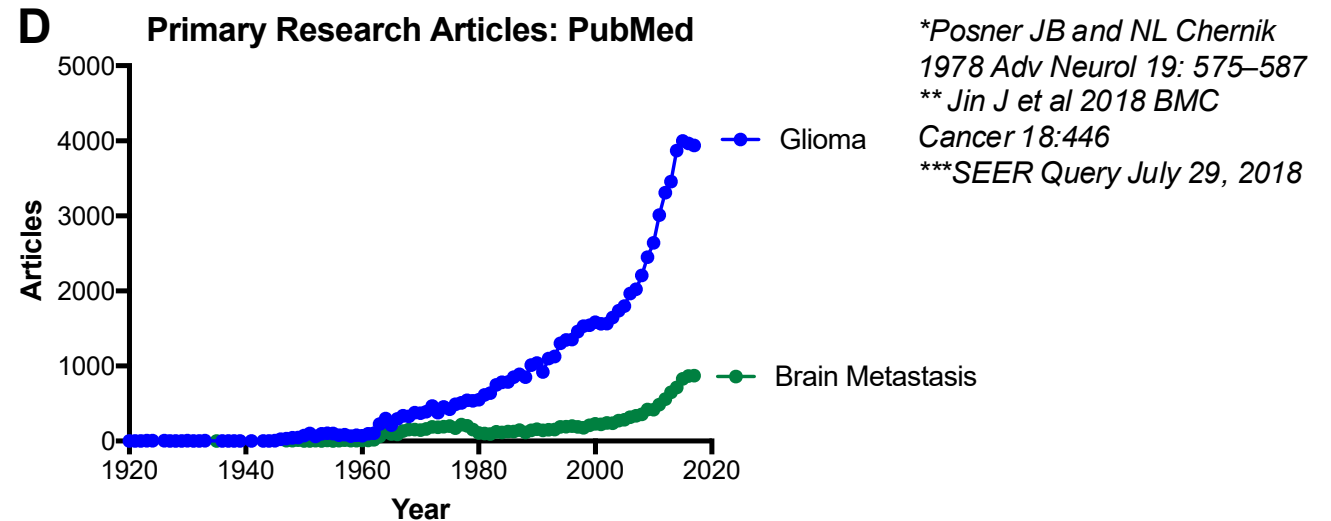
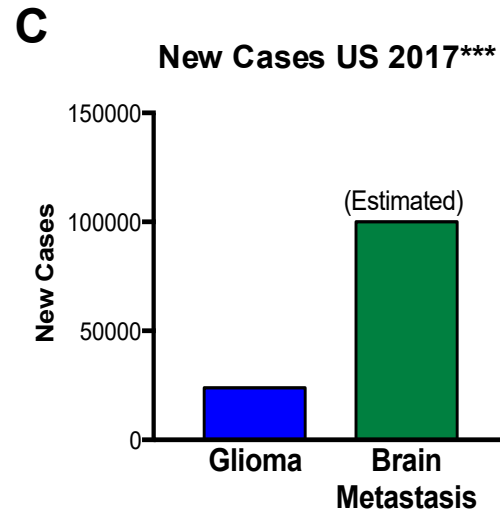
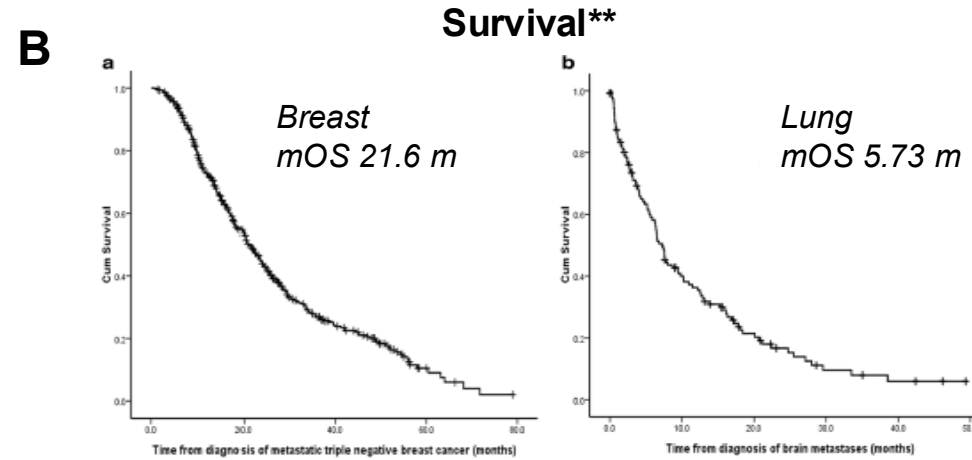
Normal CNS Tissue Damage + Resistant Tumor Growth



# Central Nervous System Metastases: An understudied problem

**A** CNS Metastasis at Autopsy\*

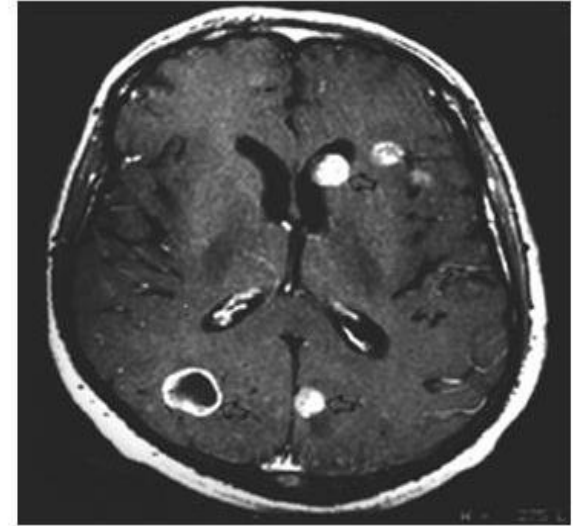
Site	Incidence
Intracranial	24%
Dural	20%
Leptomeningeal	8%
Brain Parenchyma	15%



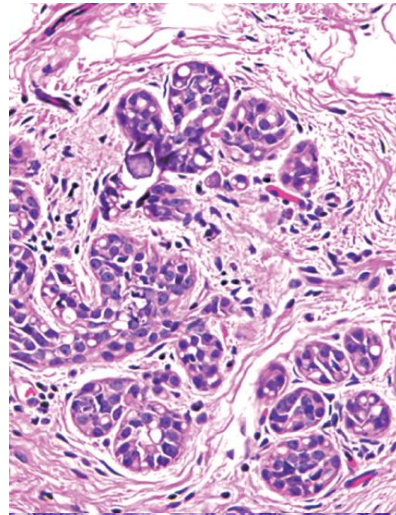
# Incidence of brain metastasis is increasing

Incidence of brain metastasis is increasing:

- Improvements in imaging (e.g. MRI)
- Improvements in systemic cancer control (brain is a sanctuary site)
- Clinical Trial Pre-Screening
- Rates of brain metastasis may be influenced by changing treatments
  - 25% of lung cancer patients have brain metastasis at initial presentation
  - 80% of lung cancer patients surviving >2 years will develop brain metastases



# Primary Tumors Resulting in CNS Metastases:



Non-Small Cell Lung  
Cancer

Small Cell Lung  
Cancer

Breast Cancer

Melanoma

Genito-urinary Cancer

Renal cell carcinoma

Bladder Cancer

Bladder Cancer

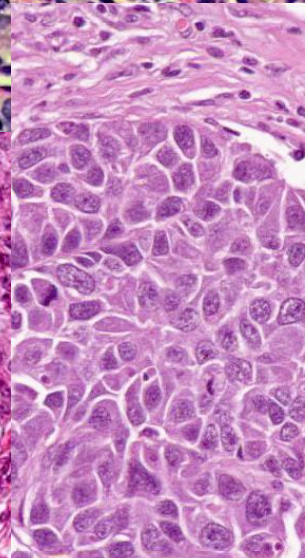
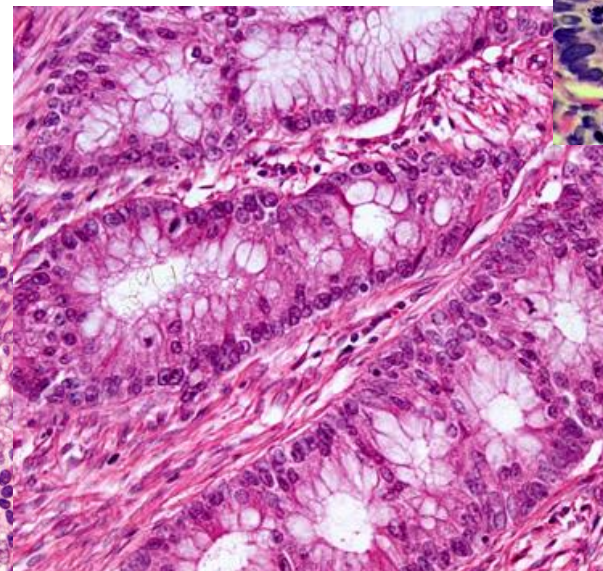
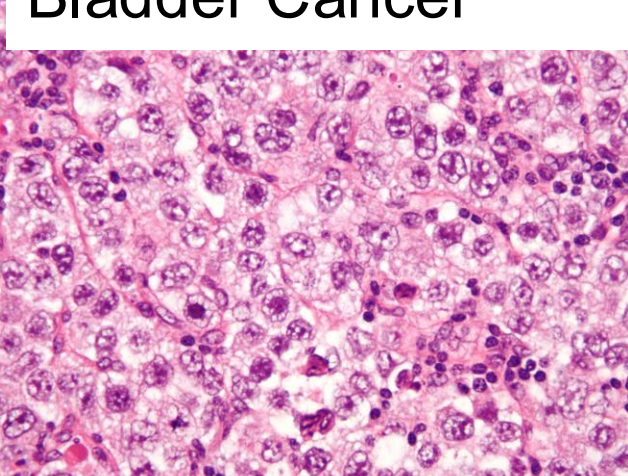
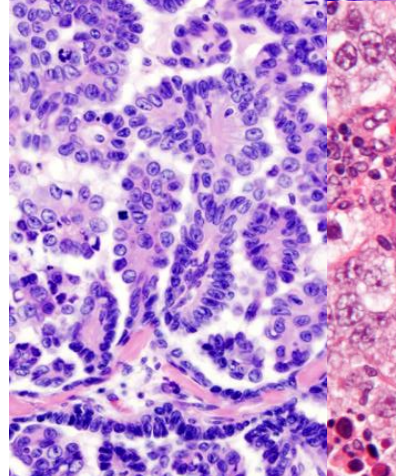
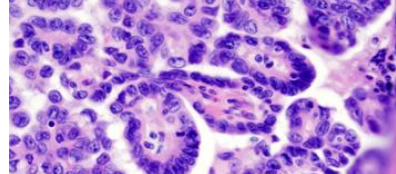
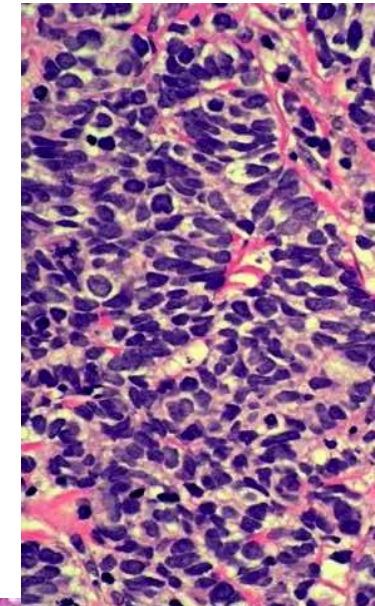
Prostate

Testicular

Uterine

Ovarian

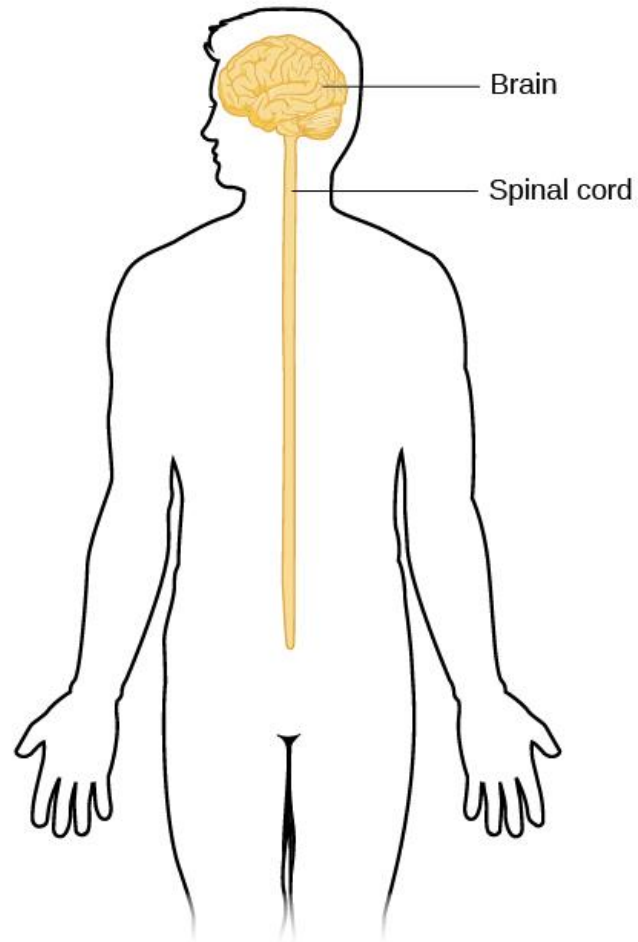
Gastrointestinal



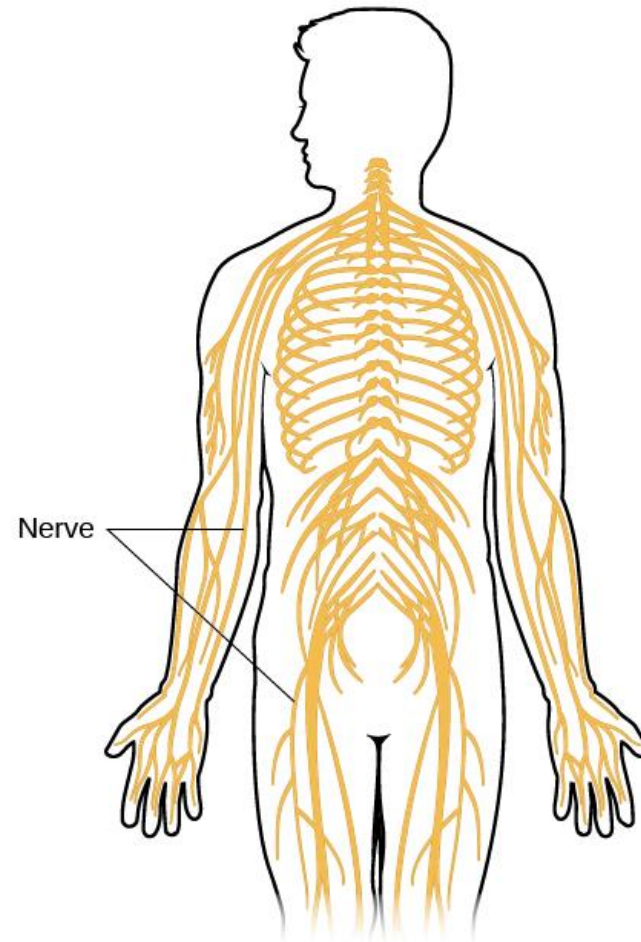
# Anatomy of CNS Metastases:

central nervous system

Central Nervous System

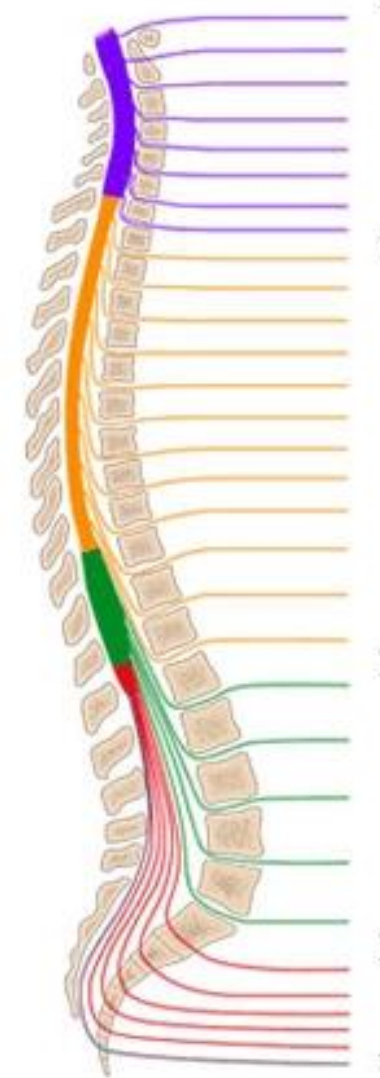
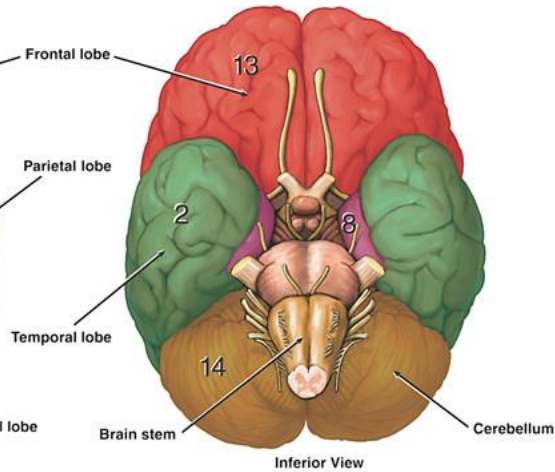
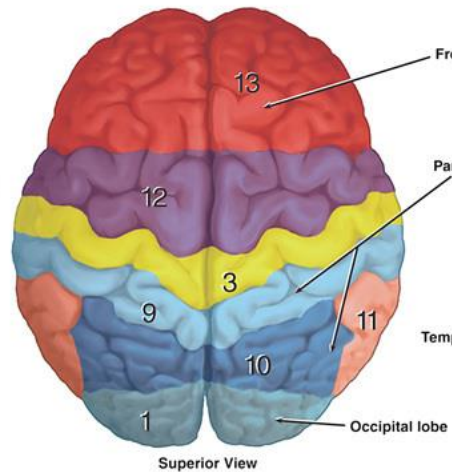
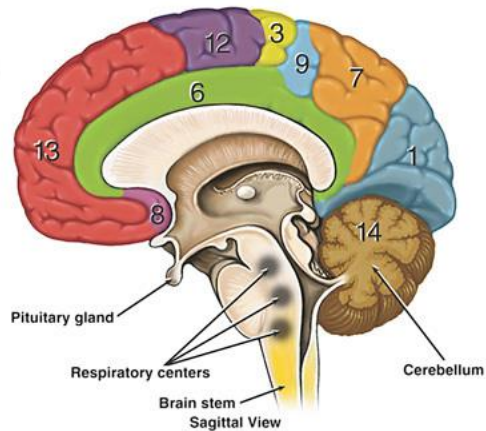
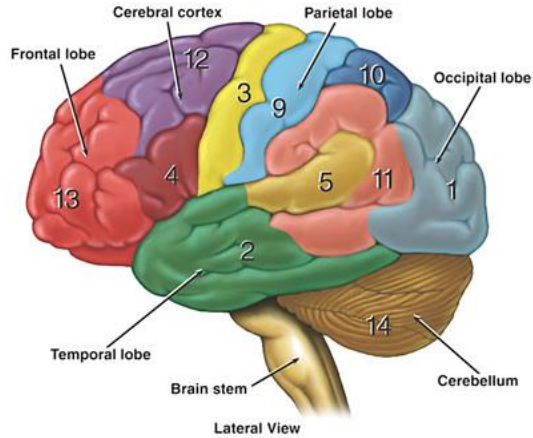


Peripheral Nervous System



# Brain, Spinal Cord

- Functional Areas of the Cerebral Cortex**
- 1 **Visual Area:**  
Sight  
Image recognition  
Image perception
  - 2 **Association Area**  
Short-term memory  
Equilibrium  
Emotion
  - 3 **Motor Function Area**  
Initiation of voluntary muscles
  - 4 **Broca's Area**  
Muscles of speech
  - 5 **Auditory Area**  
Hearing
  - 6 **Emotional Area**  
Pain  
Hunger  
"Fight or flight" response
  - 7 **Sensory Association Area**
  - 8 **Olfactory Area**  
Smelling
  - 9 **Sensory Area**  
Sensation from muscles and skin
  - 10 **Somatosensory Association Area**  
Evaluation of weight, texture,  
temperature, etc. for object recognition
  - 11 **Wernicke's Area**  
Written and spoken language comprehension
  - 12 **Motor Function Area**  
Eye movement and orientation
  - 13 **Higher Mental Functions**  
Concentration  
Planning  
Judgment  
Emotional expression  
Creativity  
Inhibition
- Functional Areas of the Cerebellum**
- 14 **Motor Functions**  
Coordination of movement  
Balance and equilibrium  
Posture



## The Spinal Cord

Cervical  
(8 Cervical Nerve Pairs)

Thoracic  
(12 Thoracic Nerve Pairs)

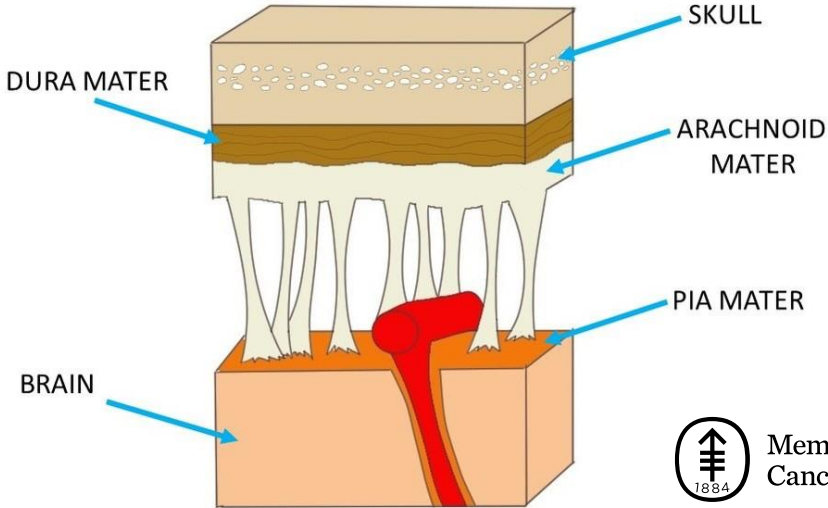
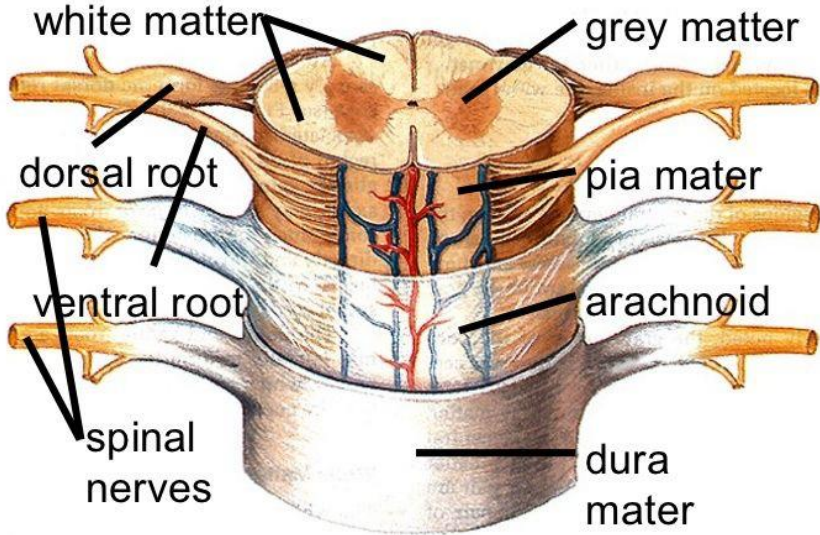
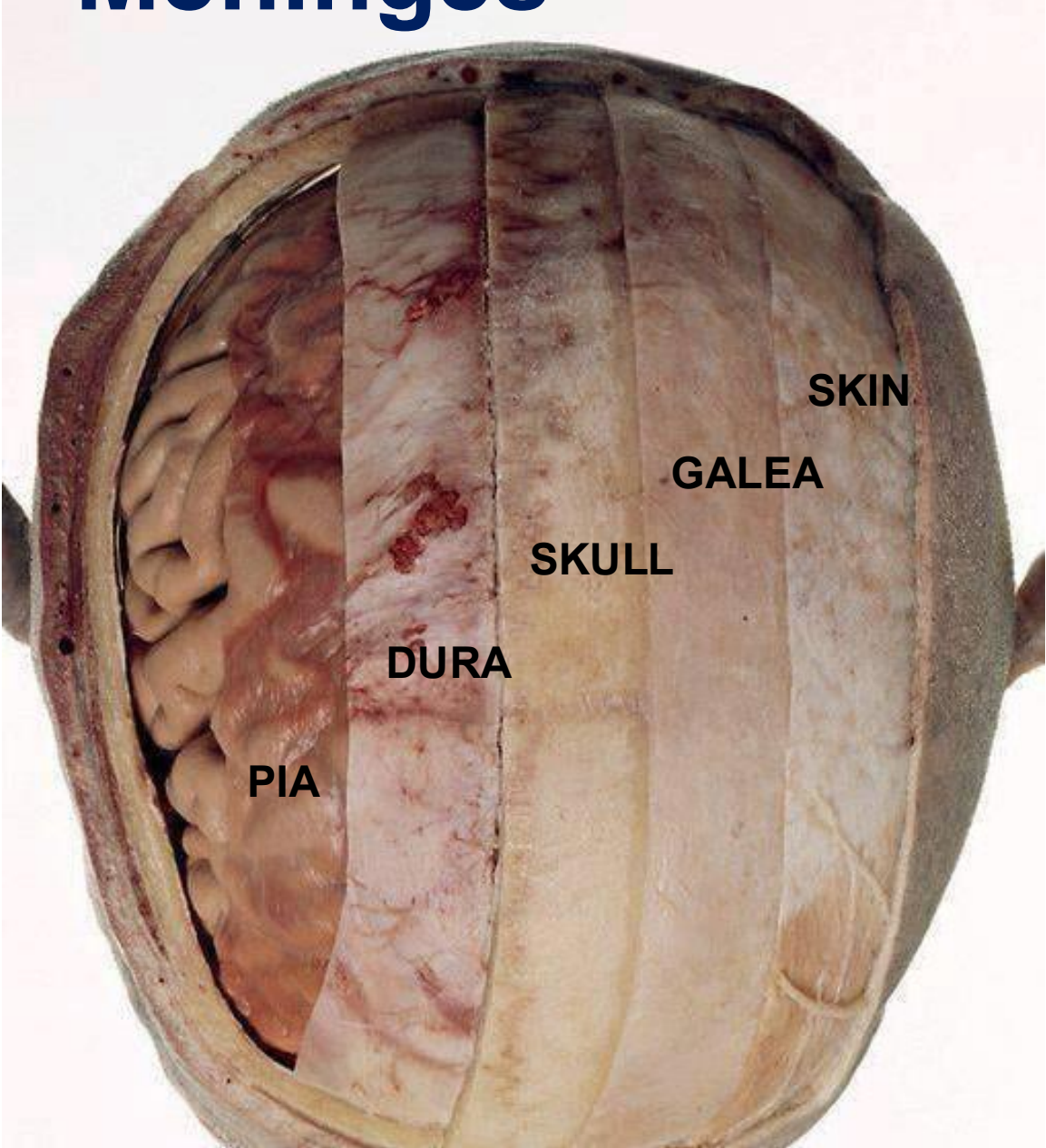
Lumbar  
(5 Lumbar Nerve Pairs)

Sacrum (5 Sacral Nerve Pairs)

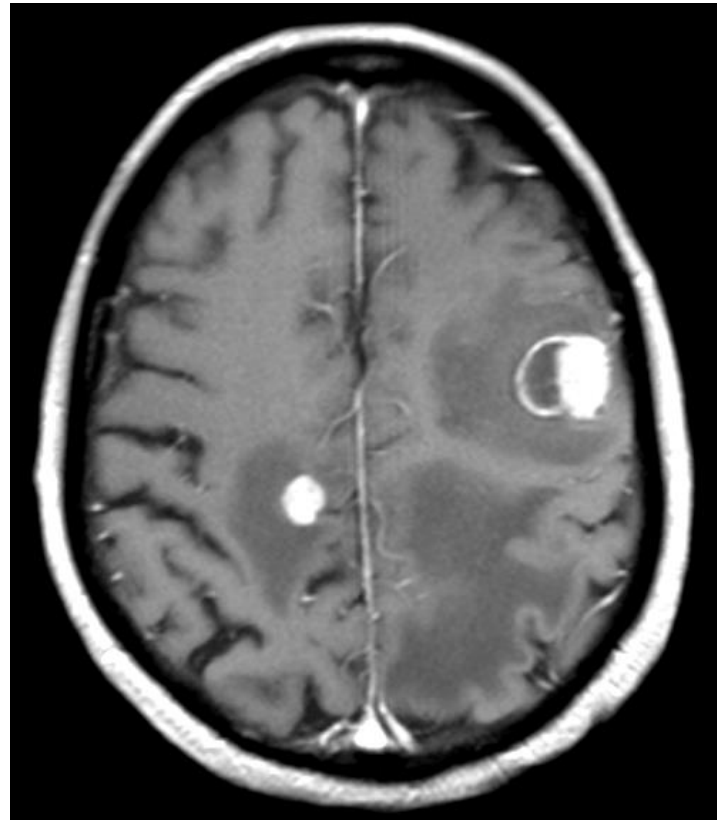
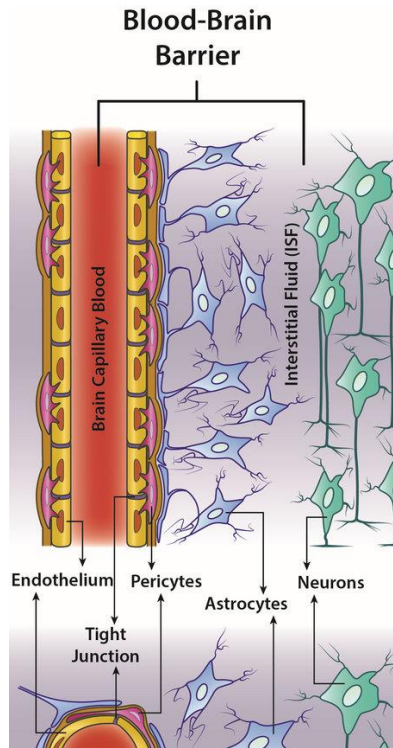
1 Coccygeal Nerve



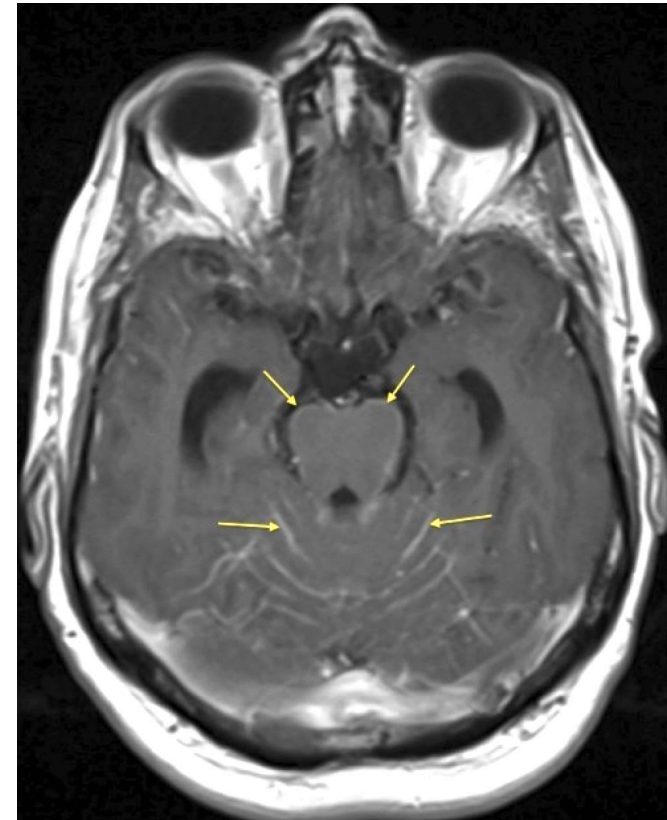
# Meninges



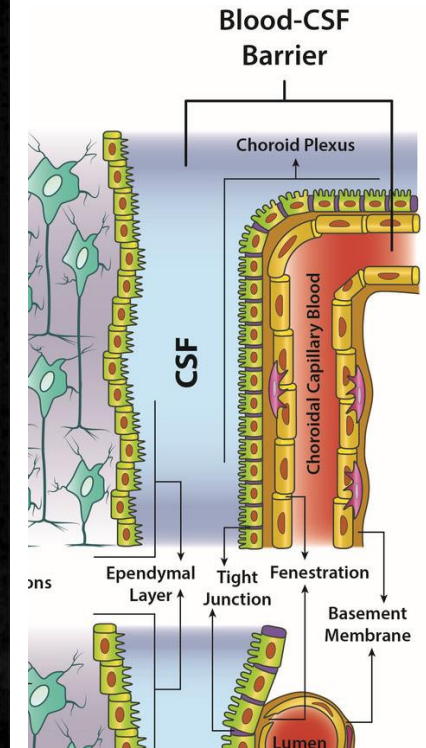
# Metastasis to the CNS reflect microenvironments in the CNS



*Parenchymal*

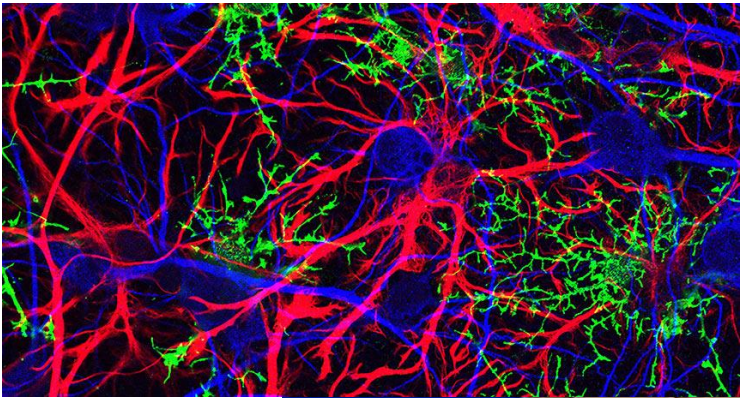


*Leptomeningeal*

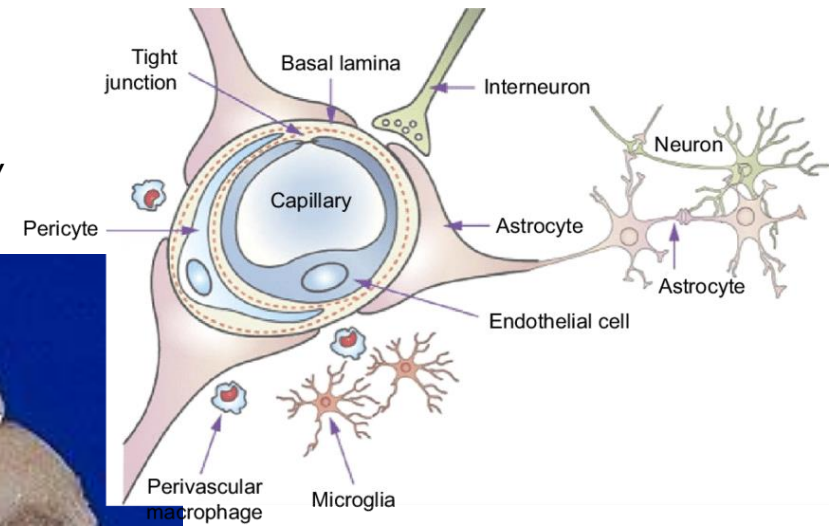


D'Agata F et al 2017 *Molecules* 23:9

# Parenchymal Space

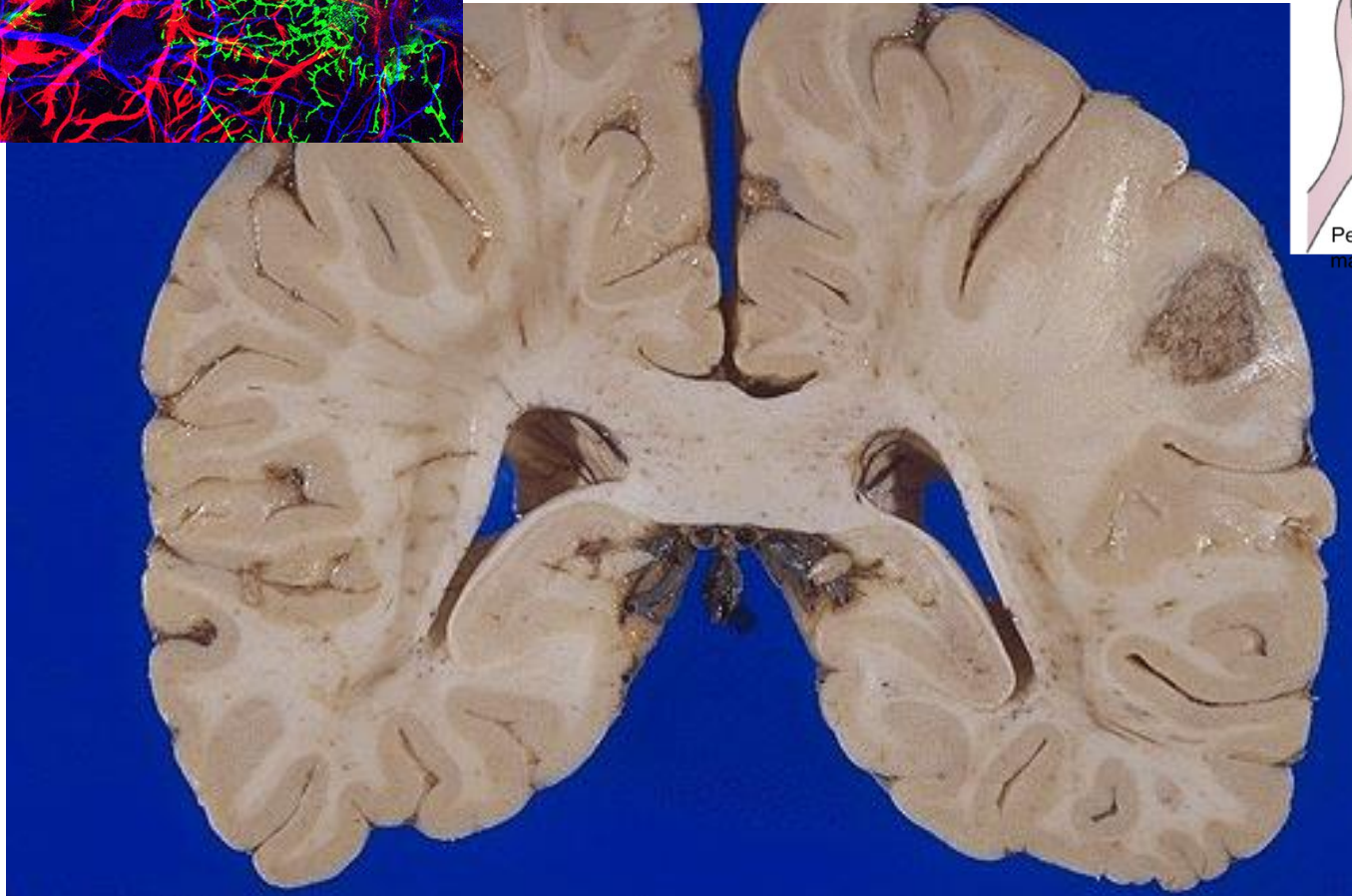


*Electrically active*  
*Tightly regulated blood flow*



Densely cellular:  
Astrocytes  
Oligodendrocytes  
Microglia  
Neurons  
Endothelium  
Pericytes

*Unique players*



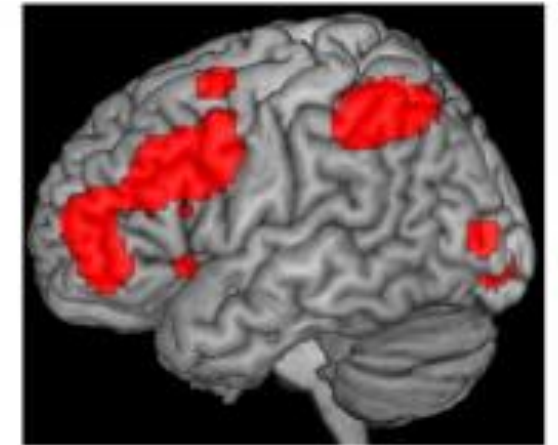
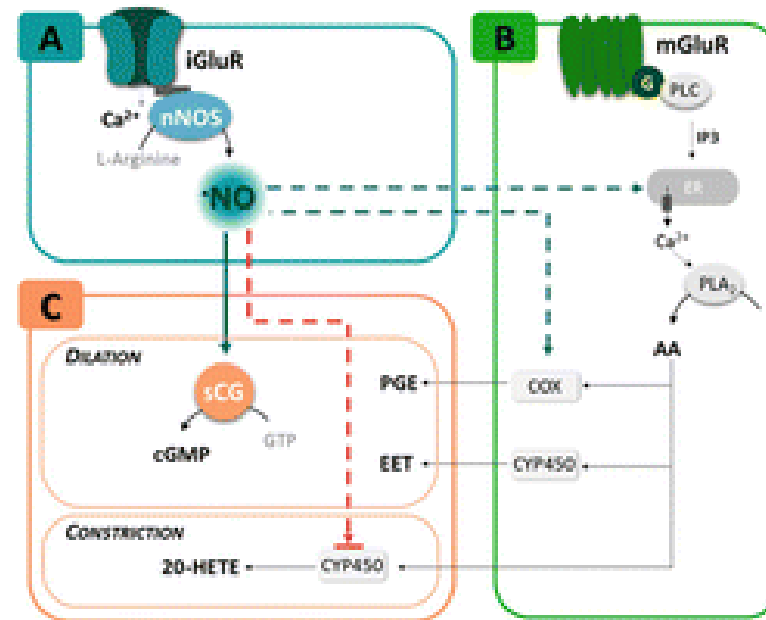
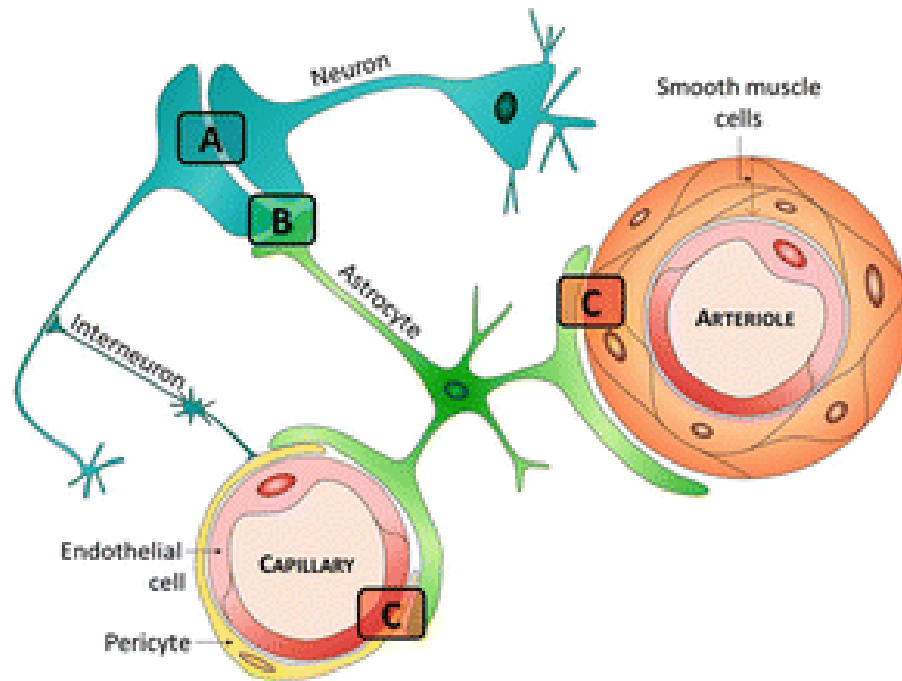
Entry into the space  
is *tightly* regulated:

Immune cells  
Rx  
Metabolites

Blood-Brain-Barrier

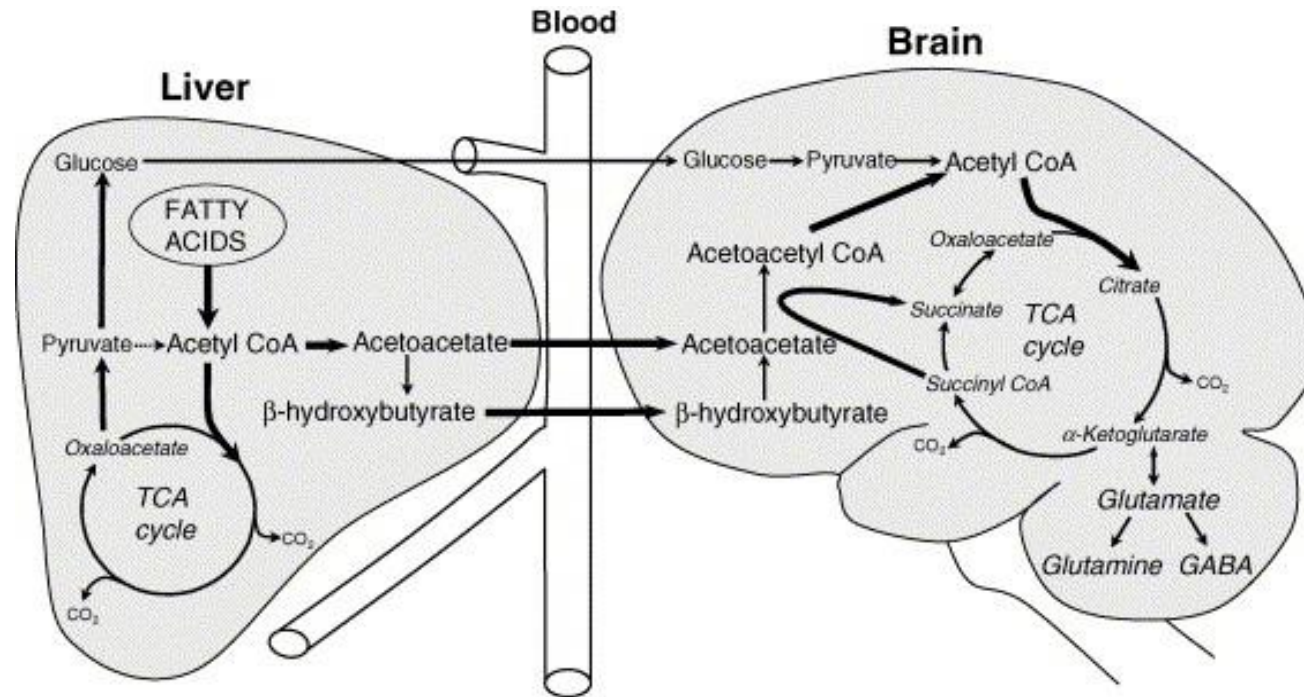


# Neuro-vascular Coupling: Unique to the Brain



- More neural activity, more blood flow needed
- State-dependent blood flow
- Basis for fMRI/BOLD signal

# Energy Metabolism: Unique to the Brain



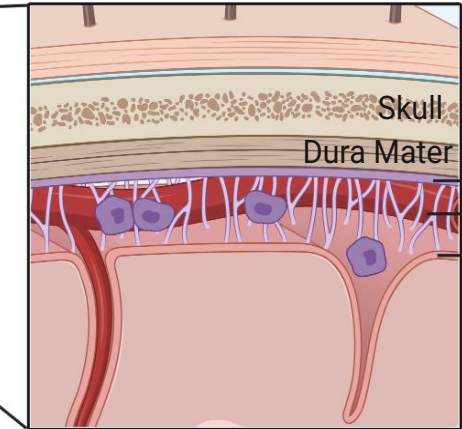
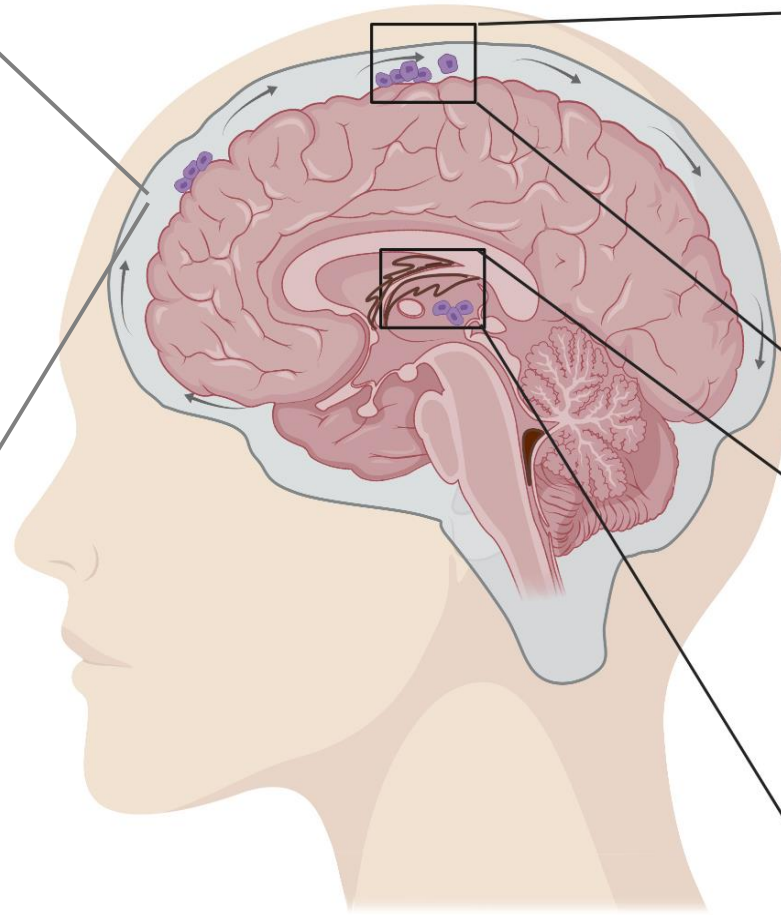
**F-18 FDG PET**

*Recall: Glucose or ketone bodies for fuel; no gluconeogenesis*

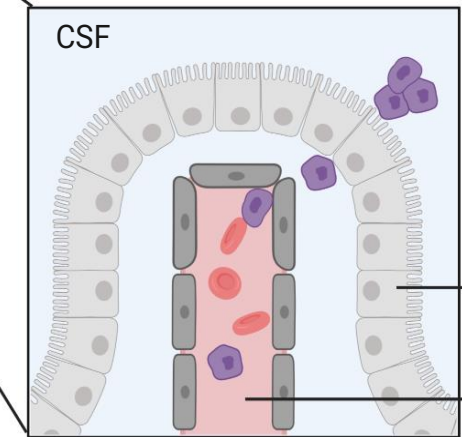
*Recall: Glucose transport is HIGHLY regulated in CNS*

# The Leptomeningeal Space

Analyte	CSF	Serum
Osmolarity (mOsm/mL)	295	295
pH	7.33	7.41
Oxygen (mmHg)	43.0	104.0
Glucose (mg/dL)	60.0	90.0
Lactate:Pyruvate	26.0	17.6
Total Protein (mg/dL)	35.0	7000
Free Amino Acids (mol/dL)	80.9	228.0
Total Lipids (mg/dL)	1.5	750.0
Iron ( $\mu$ g/dL)	1.5	15000



Arachnoid  
Subarachnoid space  
Pia mater



CP epithelial cells  
Blood vessel



# Primaries resulting in Leptomeningeal Metastasis:

*Interpret Retrospective Clinical Data with Caution*

Patients seen at MSKCC ('75-'78)  
with Lepto (n = 140)

Primary Tumor	Number of Patients
Breast	81 (58)
Lung	24 (17)
Melanoma	17 (12)
Lymphoma	14 (10)
Unknown Primary	5 (4)
Renal	3 (2)
Prostate	2 (1)
Pancreas	2 (1)
Sarcoma	2 (1)
Nasopharynx	1 (0.7)
Esthesioneuroblastoma	1 (0.7)

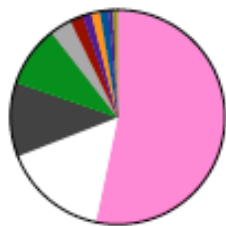
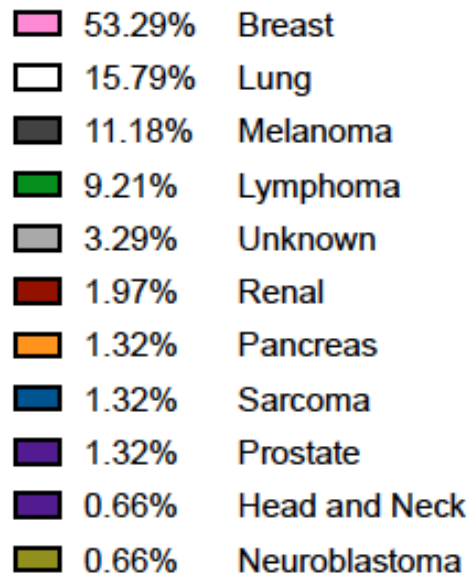
Autopsy series 1978

Primary Tumor	Autopsies	Number with Lepto (%)
Leukemia	287	28 (10)
Lymphoma	309	15 (4)
Breast	324	11 (3)
Melanoma	125	6 (5)
Lung	297	4 (1)
Gastro-intestinal	311	3 (1)
Sarcoma	126	1 (1)

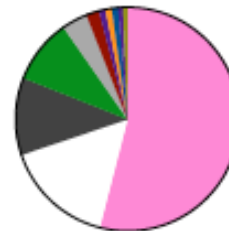
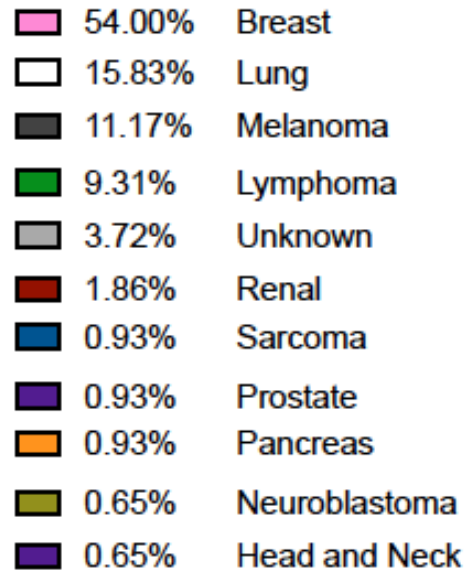
# Any tumor can result in LM:

## *Primaries resulting in Leptomeningeal Metastasis (MSKCC)*

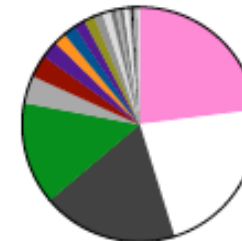
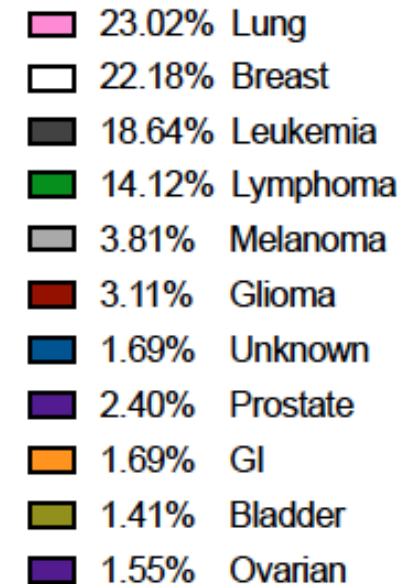
Retrospective Series 1974-78  
n = 140



Retrospective Series 2016  
n = 316



Retrospective Series 2023  
n = 708



# Clinical Presentation of Leptomeningeal Metastasis

Table 1. Percentage of patients presenting with particular features of carcinomatous meningitis or involvement of particular neurological systems.

Site of clinical presentation	Wasserstrom 1982 [3] (n = 90)	Hitchins 1987 [36] (n = 44)	Liaw 1992 [2] (n = 42)	Freilich 1995 [40] (n = 77)	Olson 1974 [2] (n = 50)	Theodore 1981 [31] (n = 33)	Grossmann 1993 [80] (n = 59)	Chamberlain 1994 [41] (n = 61)	Average
Cerebral	50	23	90	43	52	9	29	5	38*
Meningism			43	19		33			29
Headache	33	48	69	12	38	39	62		40*
Mental change	16		62	16	24	55	33		29
Nausea/vomiting	11	16	50	4	12				16
Difficulty walking	13	36	55		10	36			26
Dizziness			24	3	12				11
Fits	6	9	21	5	8	3	4		6
Cranial nerves (any)	39		45	34	78	79	31	34	45*
Cranial nerves II	5			4	8	21	12		8
Cranial nerves V	5		2	4	12				6
Cranial nerves III, IV, VI	20	4	40	9	46	39	15		22
Cranial nerves VII	20			10	42	30			23
Cranial nerves VIII	10	2			30	3			12
Cranial nerves IX, X	4		10	3	16	30			10
Cranial nerves XI					4				4
Cranial nerves XII	4			1	8				4
Spinal nerves	62	32	60	48	24			49	48*
Limb weakness		36		22	22	55	65		38*
Sensory abnormalities				19	10	33	35		23
Cerebellar signs		25				21	25		24
Autonomic dysfunction		4			2				3
Normal examination							10	23	17

\* The most common presenting features of CM.



# Presentation of Parenchymal Brain Metastasis

Solitary or Single Metastasis:

Localize to site of lesion

(UMN motor, aphasia, dysmetria...)

Multiple Metastases:

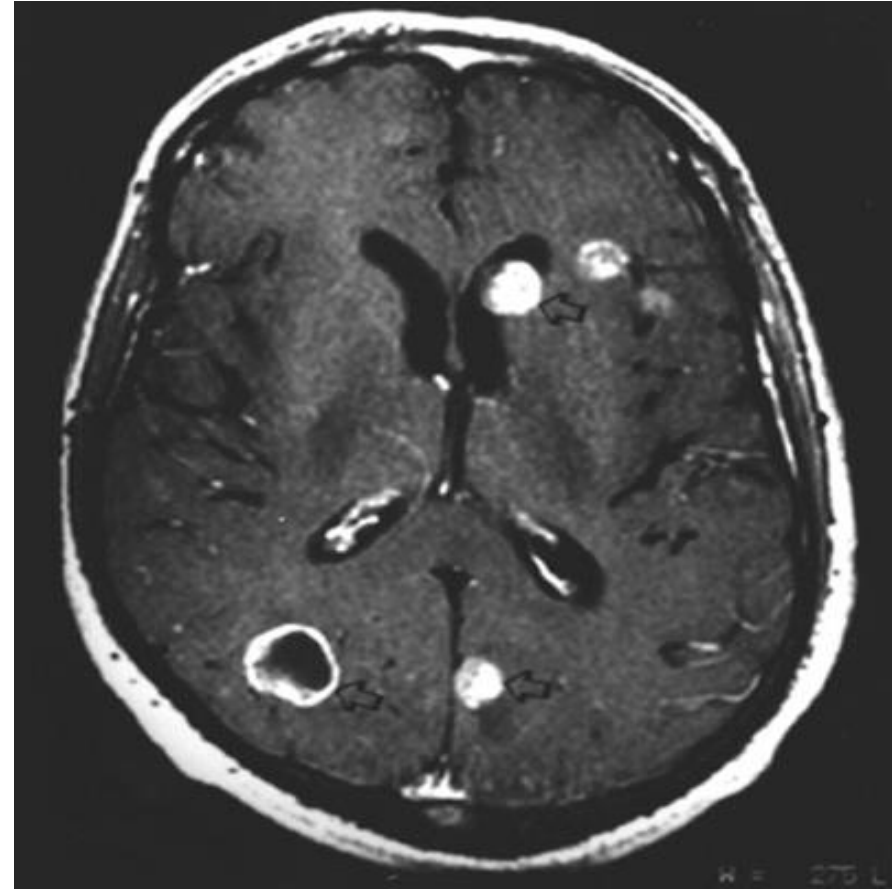
Not all are symptomatic

All lesions:

Headache, Seizure, Intra-cranial

Hypertension, Positional symptoms

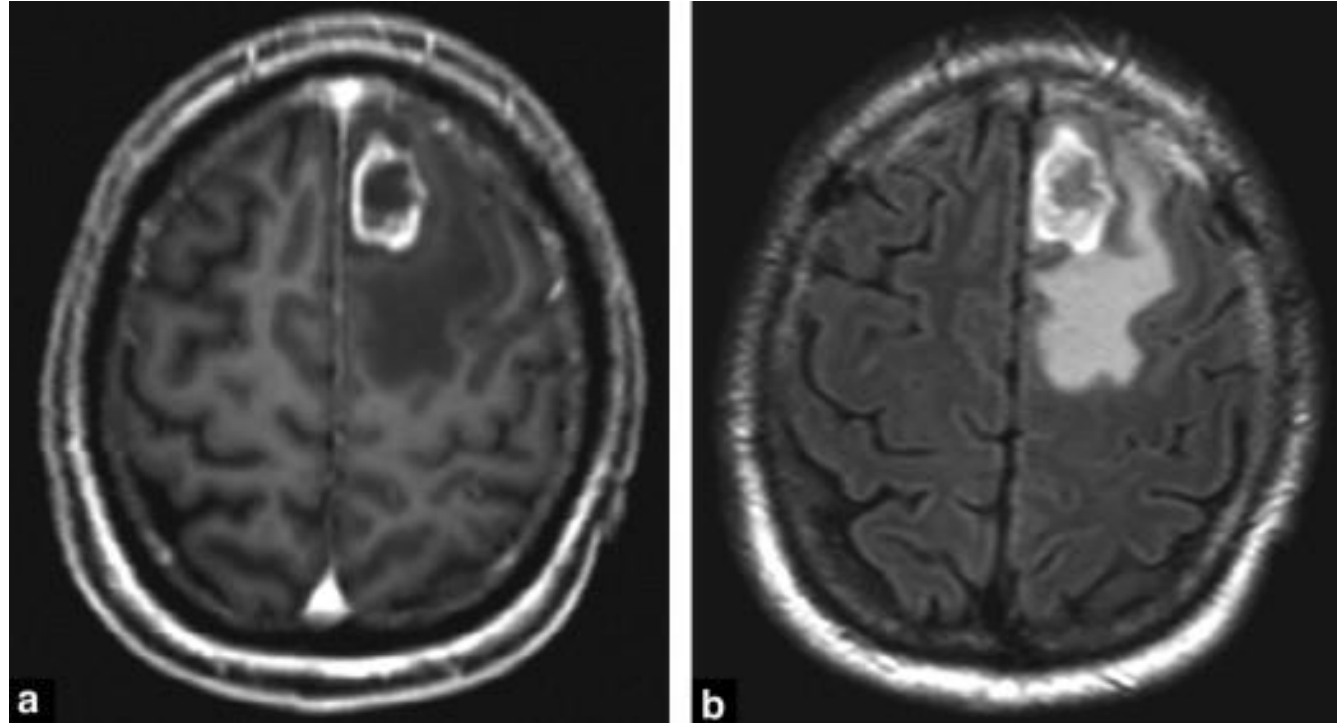
(Pressure Waves),



# Brain Metastasis Diagnosis

T1 Post-Contrast  
Enhancing Lesion

*MRI +/- Tissue*



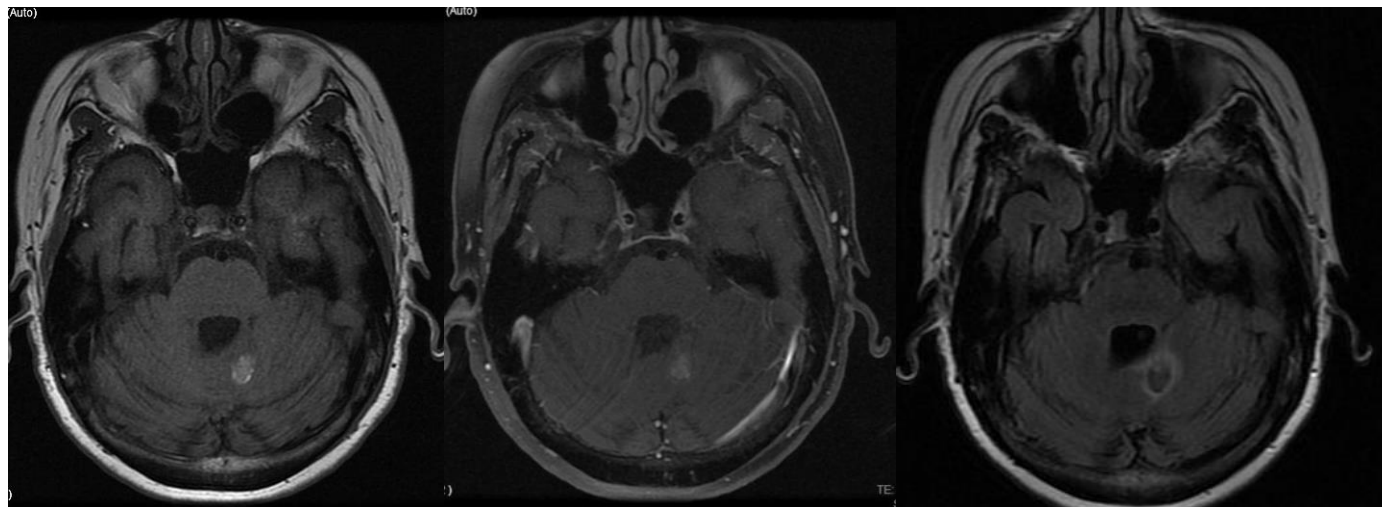
Disproportionate  
Surrounding vasogenic edema

Mass Effect

Solitary mass lesion → Biopsy vs. Resect → Need Tissue Diagnosis  
Single brain metastasis → Resect if possible → Better Outcome!

# Brain Metastasis Diagnosis

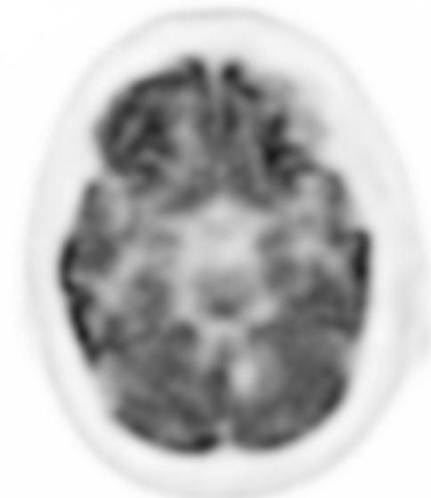
68 yo RH woman with ER/PR +/- breast cancer, NED x 5 y, presents with sudden onset projectile emesis.



T1 Pre

T1 Post

FLAIR



PET

*AVM not Metastasis!*

# LM Diagnosis

Neuroaxis imaging + CSF Examination = Complete LMD staging

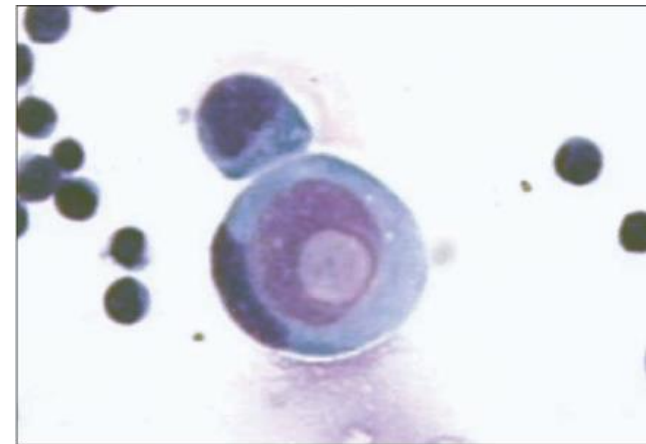
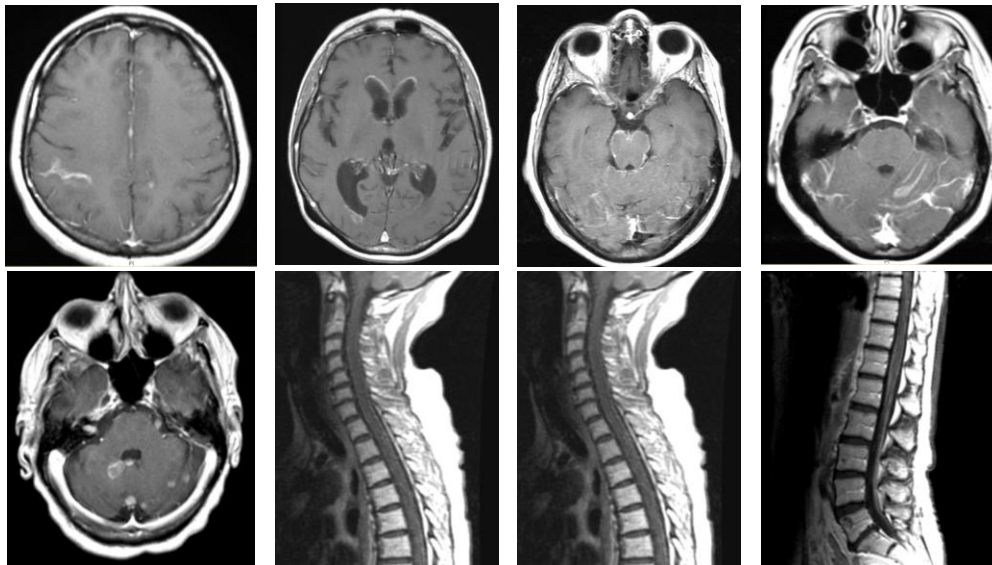


Fig 1. CSF, breast adenocarcinoma cell, Light microscopy (May-Grünwald/Giensa stain, 1,000X). Presence of degenerative vacuoles in the cytoplasm, the nucleus has hyperchromasia. The cell in the center is phagocytosing other cell (cell autophagy). There are normal lymphocytes around the malignant cell (note the difference in size between the cells).

Almeida SM et al 2007 Arq. Neuro-Psiquiatr65(3):1678

# Features of LMD on MR Imaging

Enhancement on T1 post-Gad:

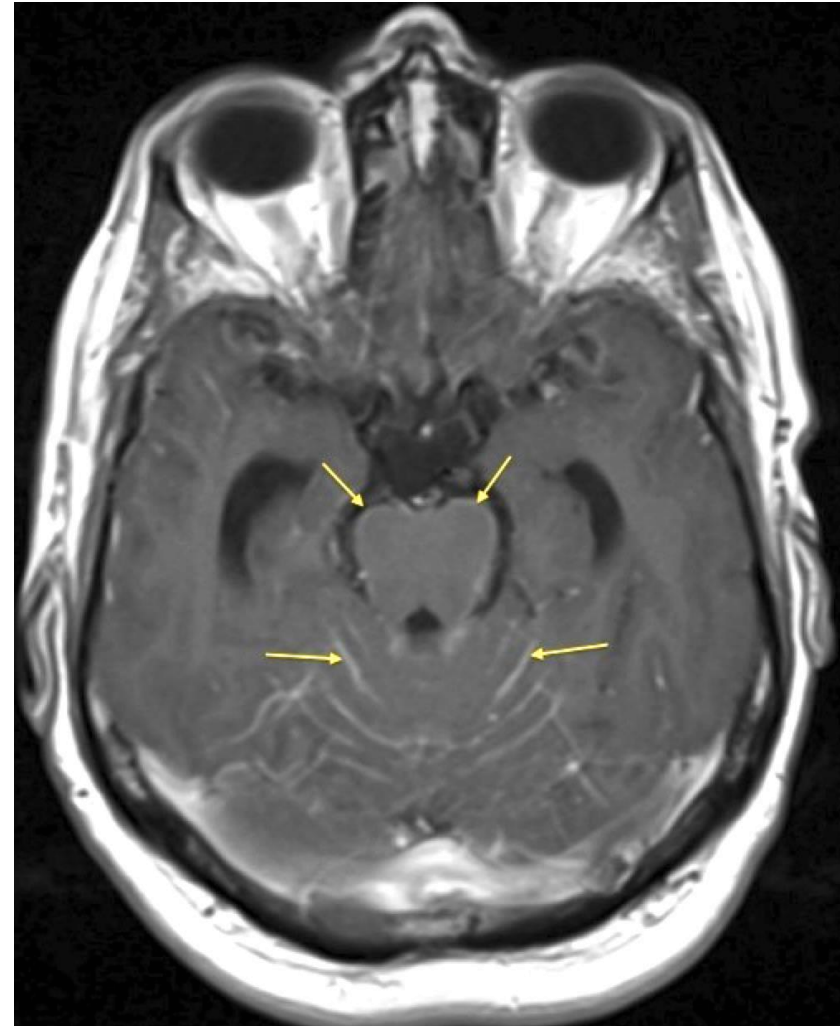
- Sulci
- Cerebellar Folia
- Coating the Pons
- CN and Roots
- Clumping of Cauda

T2 hyperintensity:

- Subcortical Space

Evidence of ICP:

- Enlarged ventricular system
- T2 hyperintense subependyma



# Use of MRI in diagnosis of leptomeningeal metastasis: Sensitivity

- MRI sensitivity ranges from 71-100%, depending on the study
- MRI findings in LMD include enhancement of CN, superficial sulcal or dural enhancement, ependymal enhancement, enhancing nodules in intradural or intraventricular space

**Table 2** Comparison of diagnostic tools

	Diagnostic tool		Overall, count (%)	Hematomatous, count (%)	Solid, count (%)	p Value
	Cytology	MRI				
Cytology and MRI (seg ≥1), n = 93	+	+	45 (48)	12 (36)	33 (55)	0.08
	-	+	14 (15)	4 (12)	10 (17)	
	+	-	34 (37)	17 (52)	17 (28)	
Cytology and full MRI n = 48	+	+	26 (54)	6 (46)	20 (57)	0.42
	-	+	10 (21)	2 (15)	8 (23)	
	+	-	12 (25)	5 (38)	7 (20)	

Clarke JL, Perez HR, Jacks LM, Panageas KS, DeAngelis LM. Leptomeningeal metastases in the MRI era. *Neurology*. 2010; 74(18):1449-1454.

# Use of MRI in diagnosis of leptomeningeal metastasis: Specificity

## Diffuse

### Infectious:

pyogenic meningitis  
viral meningitis  
tuberculous meningitis  
CNS cryptococcal infection  
coccidioidal meningitis  
encephalitis

### Tumors:

diffuse leptomeningeal glioneuronal tumor  
leptomeningeal carcinomatosis  
meningeal melanomatosis

## Diffuse

hemorrhage (e.g. post-subarachnoid)

### Neuroinflammation:

granulomatous conditions  
autoimmune encephalitis  
checkpoint blockade  
neurosarcoidosis (can also be focal)  
post-operative (late finding)  
post-traumatic (late finding)

## Focal

leptomeningeal carcinomatosis  
post-ictal hyperemia

infarction: subjacent acute (leptomeningeal collaterals) or subacute  
lymphoma  
meningitis (e.g. tuberculous)  
encephalitis  
neurosarcoidosis  
postoperative scar  
vasculitis  
neurosyphilis  
Sturge-Weber syndrome

*All that glitters is not gold; All that enhances is not lepto!!*



# CSF Sampling

- Where?
  - Bedside LP is usually fastest, easiest.
  - Fluro does not give accurate OP.
- When?
  - After MRI is best, but not essential.
  - During the week, anytime.
  - On the weekend for symptomatic relief
- Send What?
  - Cytology
  - Circulating tumor markers
  - Circulating tumor cells (rare cell capture technology) cancer centers only
  - Research tests?
- Again?!?
  - If negative, may repeat in two weeks
  - If negative, may repeat in two weeks C-tap.
- Risks?
  - What are you worried about?
  - What is the patient worried about?



# Goals of Treatment

- Control
  - Macroscopic disease
  - Microscopic disease
  - Systemic disease
- Preserve
  - Neurologic function
  - QOL



*Caring for patients with CNS metastases combines palliative care with tumor-directed treatments.*

# Symptomatic lesions drive initial treatment: Neurologic Exam is essential

## 1. Localize symptoms

Diplopia, Urinary retention, Weakness:

*Q. localizable to a radiographic lesion?*

## 2. Establish ICP & Manage

Fundoscopy exam, Direct Measurement by LP for LMD or suspicious exam

## 3. Stop Seizures

Plaques of LMD, cortical parenchymal lesions, bleeding lesions may be epileptogenic,

Loading dose AED followed by maintenance dose (LEV, PHT)

May need cEEG

## 4. Local Treatment

(Treat the tumor you see, the symptomatic sites)

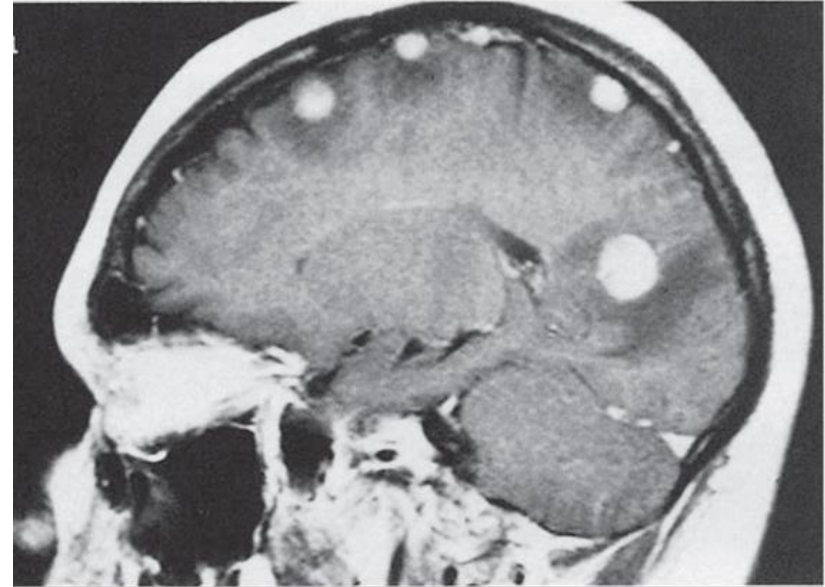
## 5. Systemic Treatment

(Treat the tumor you don't see)



# Surgical Management of Brain Metastasis:

- Symptomatic, accessible:
  - Resect
- 1-3 surgically accessible metastases:
  - Resect.
  - Improves survival by 1-4 mo (depending on study).
- Surgically Accessible, Brain is *only site of active disease*:
  - Biopsy vs. resect



*Neurologic Exam and Localization is Essential.*

# Symptomatic, Inaccessible lesions: RT alone

## 1. RT to symptomatic lesion(s)

SRS or IMRT: Outpatient

If ICP is a concern, in-house, possibly post VPS

If urinary retention +/- or new leg weakness, in-house

## 2. Steroid pulse with RT: Especially if large territory

WBRT, RT to post fossa or C-T spine

Dexamethasone 4 then 2 BID.

## 3. Consider bevacizumab

Steroid-sparing agent

Re-RT

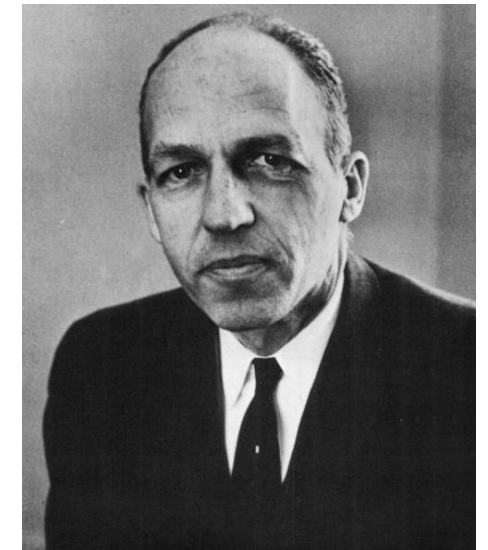
Involved field adjacent to previously treated

Consider possible/probable trips to OR

# KPS: Karnofsky Performance Status

TABLE 1  
PERFORMANCE STATUS

<i>Definition</i>	<i>%</i>	<i>Criteria</i>
Able to carry on normal activity and to work. No special care is needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospitalization is indicated although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.



David A. Karnofsky

# After local, symptomatic treatment, Systemic treatment

*(For patients with “good” KPS )*

## 1. Systemic

Enhancing disease

Treatment with good CSF penetration

## 2. Intrathecal: Leptomeningeal Metastasis only\*

MRI negative (or nearly neg) LM disease. Normal ICP, CSF flow

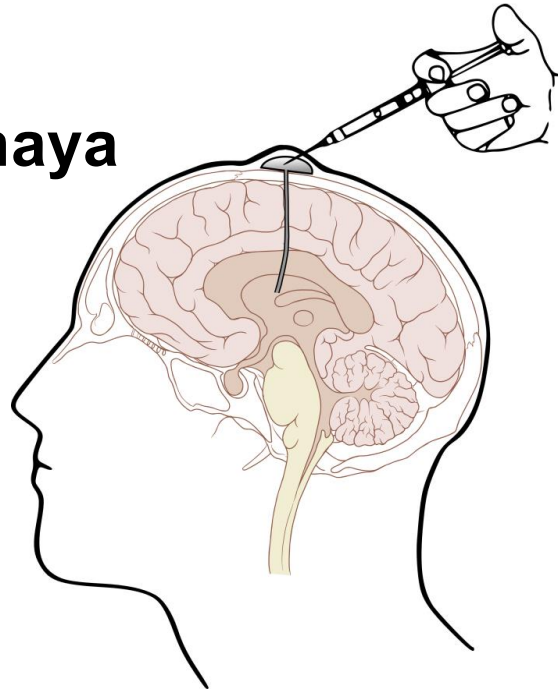
\*IT/IO treatment penetration of bulky disease is poor.

## 3. Trial

These are becoming more common!

# Intrathecal Treatment

## Ommaya



**\*Must have good CSF Flow**

In doubt, establish with dedicated study

### Access:

Ommaya Port:

Access CSF, requires OR trip

Excellent Rx circulation

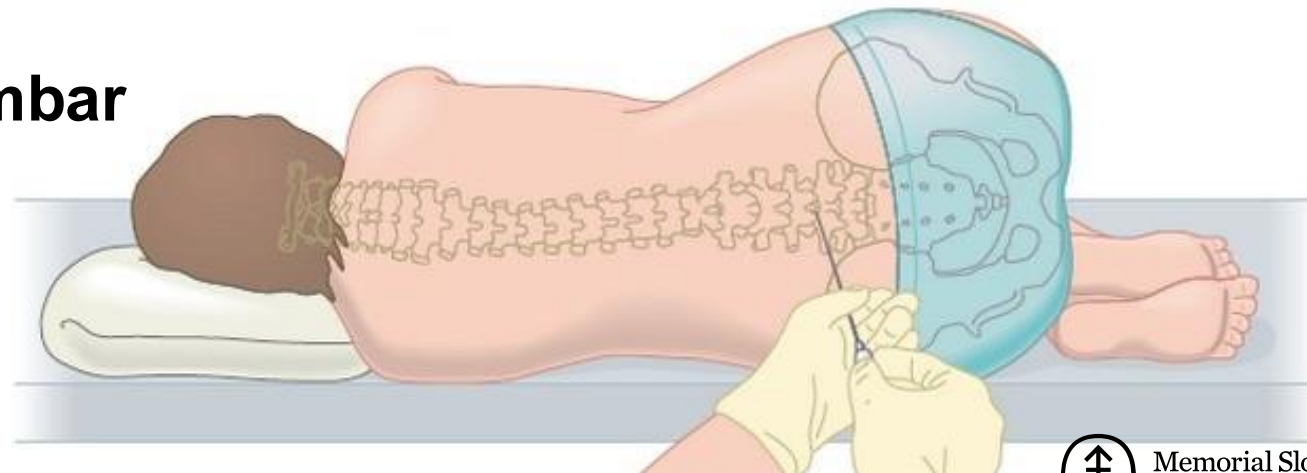
Lumbar Treatment:

No OR required

Imperfect circulation

Rx infiltration outside CSF 10%

## Lumbar



# Intrathecal Treatment: Rx

## **Methotrexate**

12 mg/dose, 2 times weekly x 1 month, then weekly x 1 month (if responsive)

Concurrent oral leucovorin 10 mg PO BID x 3 days

**Cytarabine** (not preferred for solid tumors; liposomal formulation no longer available)

50 mg/dose 2 times weekly x 1 month, then weekly x 1 month

## **Thio-TEPA**

10 mg/dose 2 times weekly x 1 month, then weekly x 1 month

## **Investigational:**

Etoposide, Dacarbazine, Busulfan, Mephelan, Topotecan...

## **All:**

1. Measure pressure after accessing space (LP)
2. Remove equal volume CSF, + rinse
3. Instill Rx slowly, mix
4. Rinse with reserved CSF

## **Risks:**

1. Chemical Meningitis
2. Infection
3. Transient elevated ICP



# Systemic, CNS-penetrant Treatments:

## **EGFR**

Erlotinib

Gefitinib

Osimertinib

## **ALK**

Crizotinib

Ceritinib

Alectinib

Lorlatinib

## **Her2**

Lapatinib

Trametinib

## **VEGF**

Bevacizumab

## **CD20**

Rituxumab

## **PD-1/PDL-1**

Pembrolizumab

Nivolumab

## **MEK**

Trematinib

Cobimetinib

## **CTLA4 MoAb**

Ipilimumab

## **Untargeted:**

HD MTX, with leucovorin rescue

HD Cytarabine

Capecitabine

Carboplatin

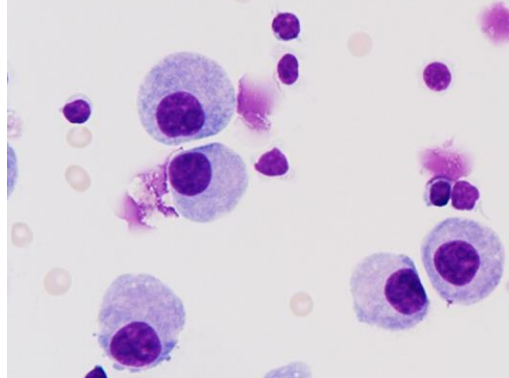
Temozolomide

\*\*This list is not exclusive and is expanding

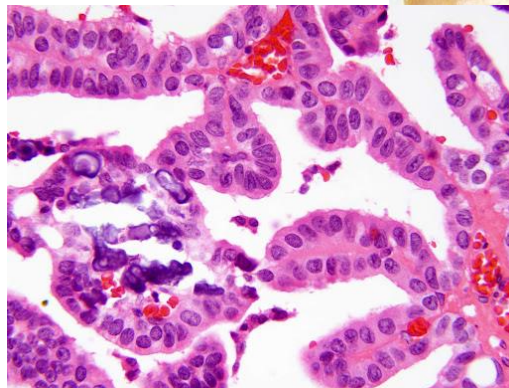


# CNS Metastasis exemplifies cancer as whole-person disease

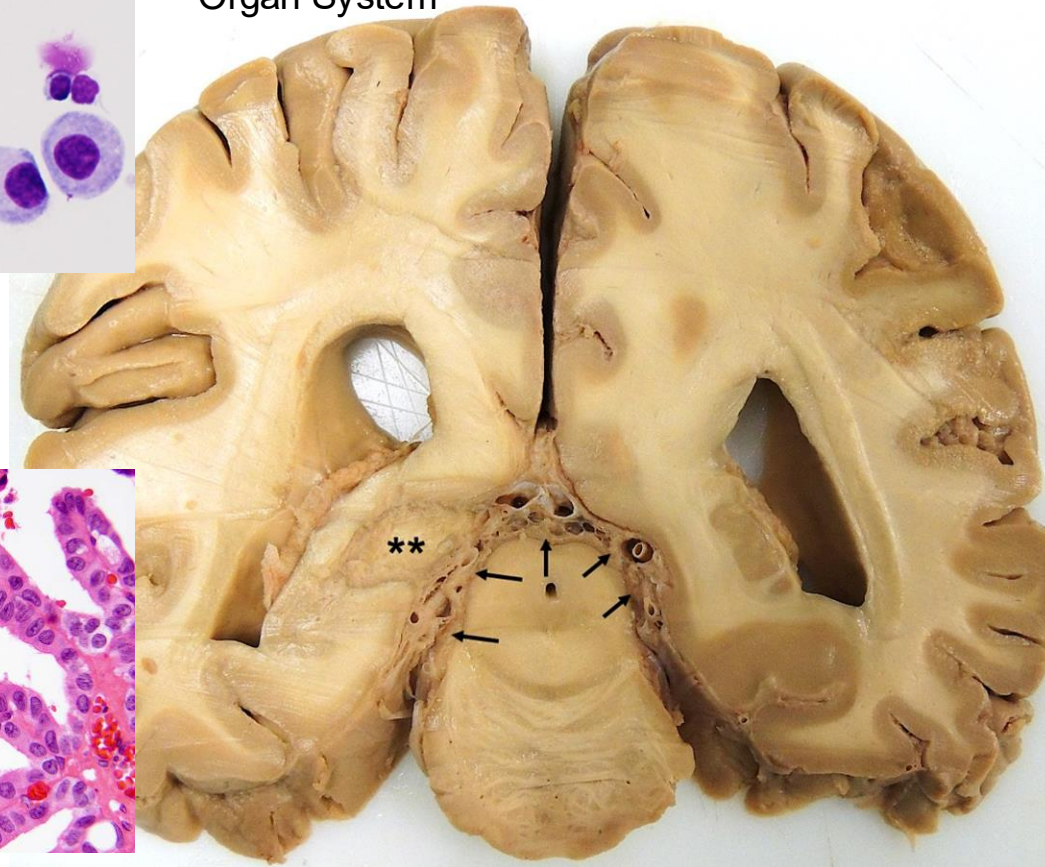
Cancer Cell



Microenvironment



Organ System



Organism



# Metastasis and the Brain

## Part 2: How do we study this?



# The ideal model

Primary tumor

Mets to CNS (+/- other sites)

Intact immune system

Easy to generate large n

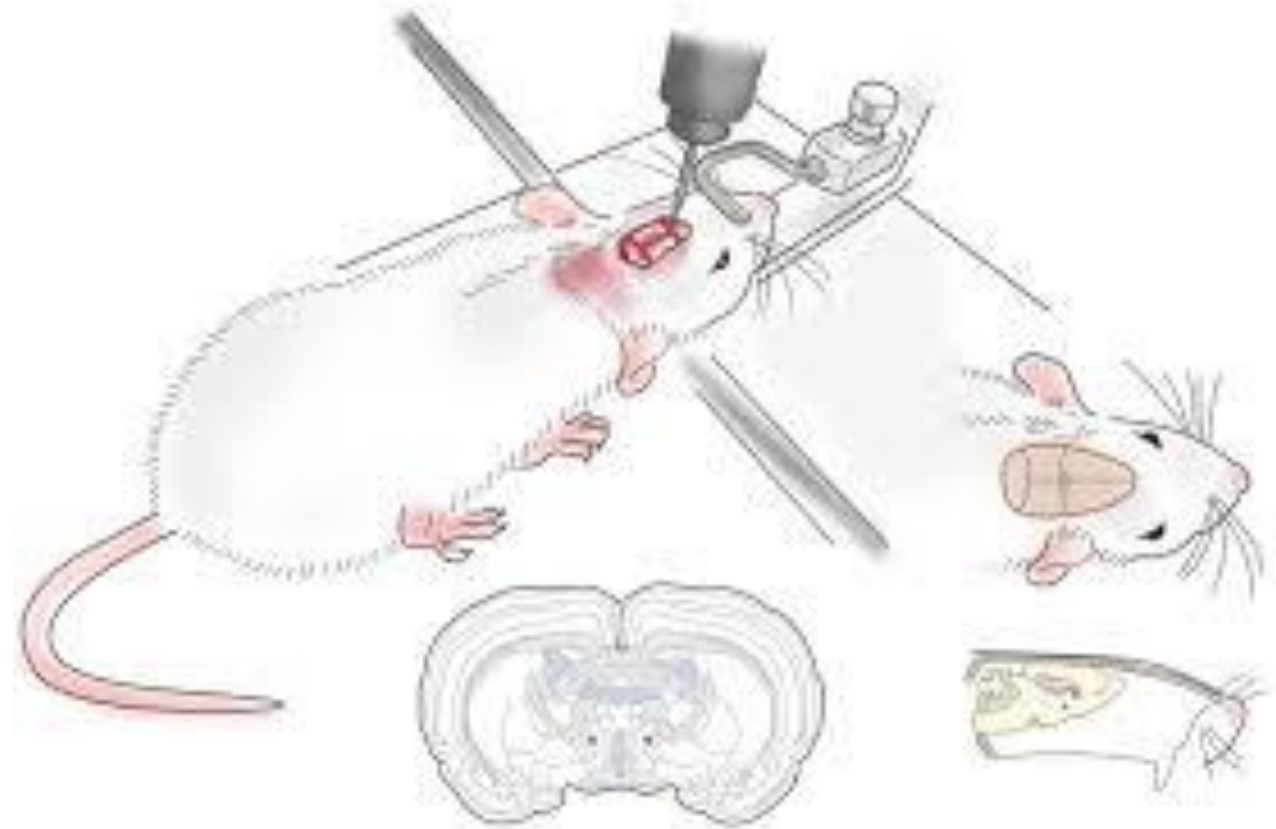
Reproducible

... does not exist



# Intracranial Implant

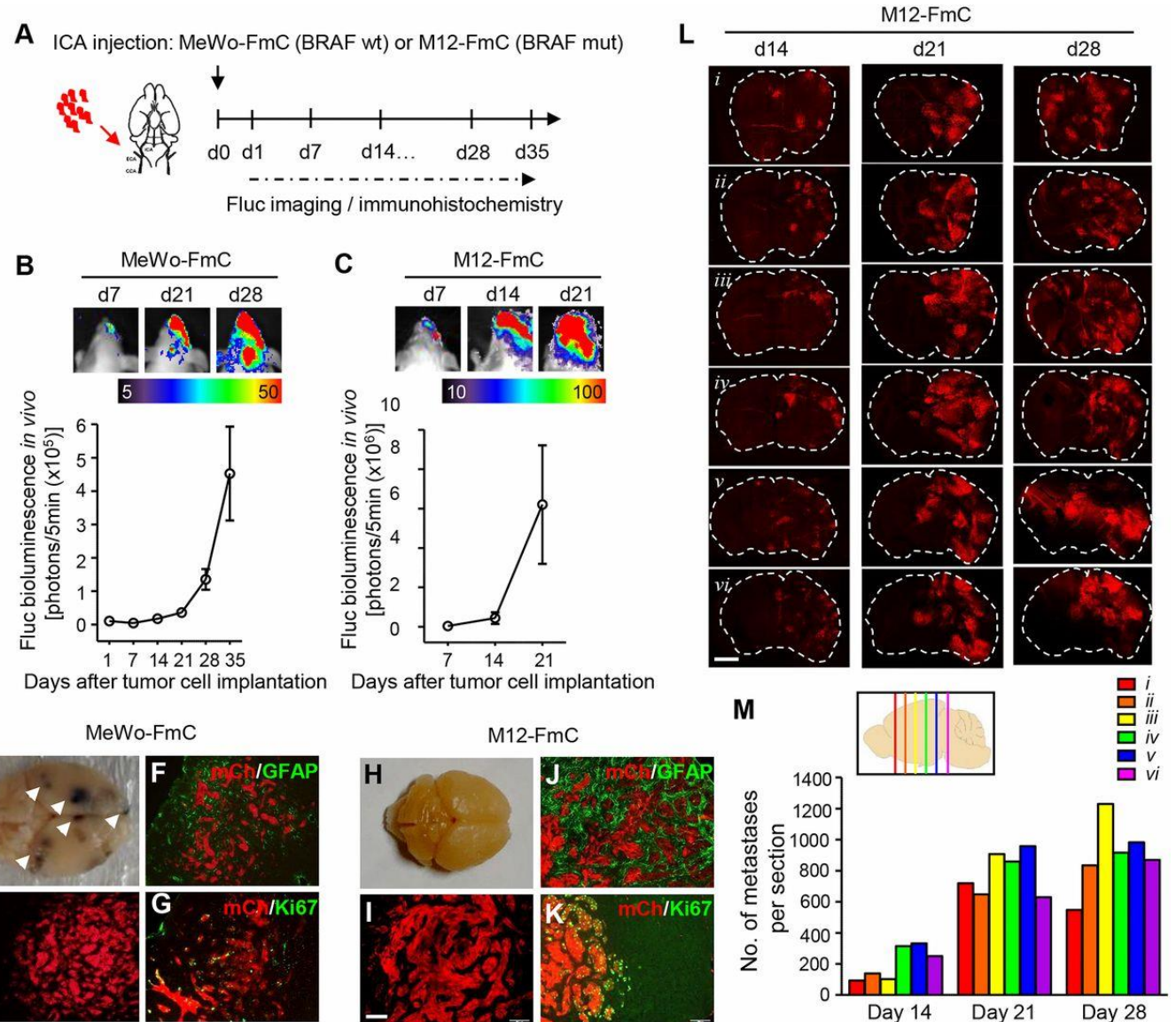
- High take rate
- Large number of cells needed
- Disturbs microenvironment
- No primary tumor
- Typically use nude mice
- Xenografts (PDX) possible



# ICA Injection

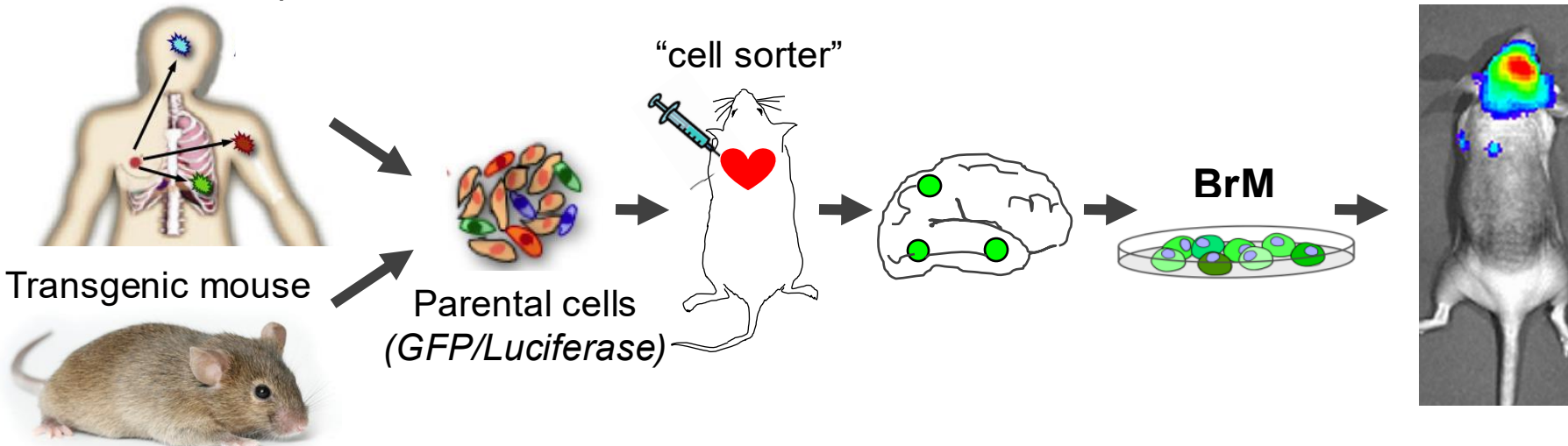
(Fidler & scientific progeny)

- Very likely to generate brain mets
- Nice contralateral control
- Difficult to learn, master
- Does not allow for “below the neck” mets
- No primary tumor

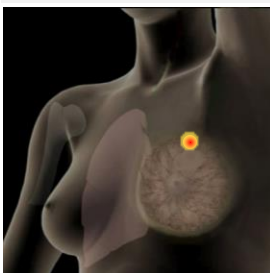


# Iterative in vivo selection

Advanced cancer patient



## Breast Carcinoma



Models:

- MDA231-BrM2 (Triple negative)

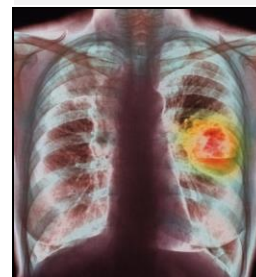
*MMTV-neu*



- ErbB2-BrM2 (ErbB2 hyperactive)

Nguyen et al *Cell* 2009  
 Bos et al *Nature* 2009  
 Valiente et al *Cell* 2014

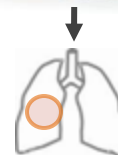
## Lung Adenocarcinoma



Models:

- H2030-BrM3 (*KRAS<sup>G12C</sup>*)
- PC9-BrM (*EGFR<sup>Δexon19</sup>*)

*Kras<sup>G12D</sup>;p53<sup>-/-</sup>*

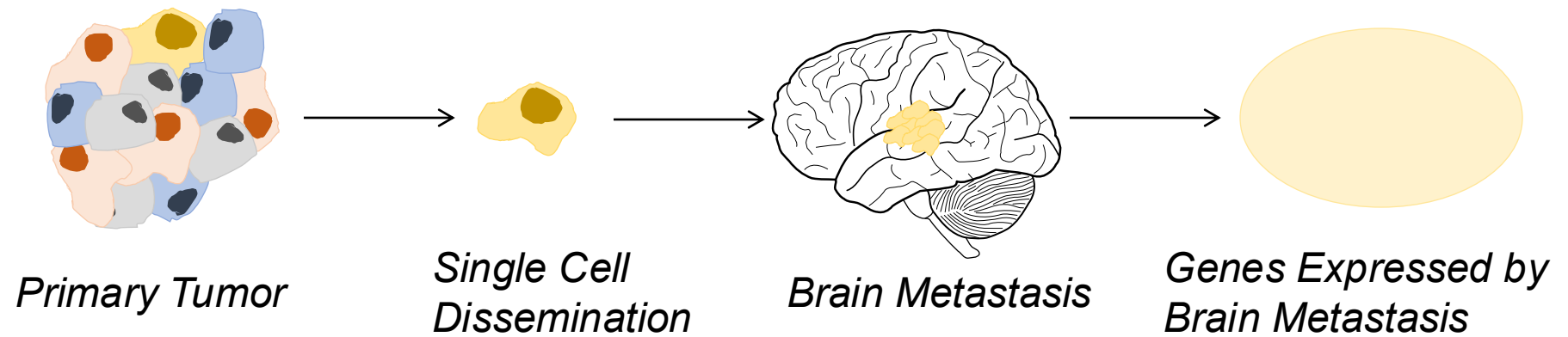


- High brain metastasis:  
*Kras/p53-393N1*  
*Kras/p53-482N1*
- Low brain metastasis:  
*Kras/p53-373N1*  
*Kras/p53-2691N1*

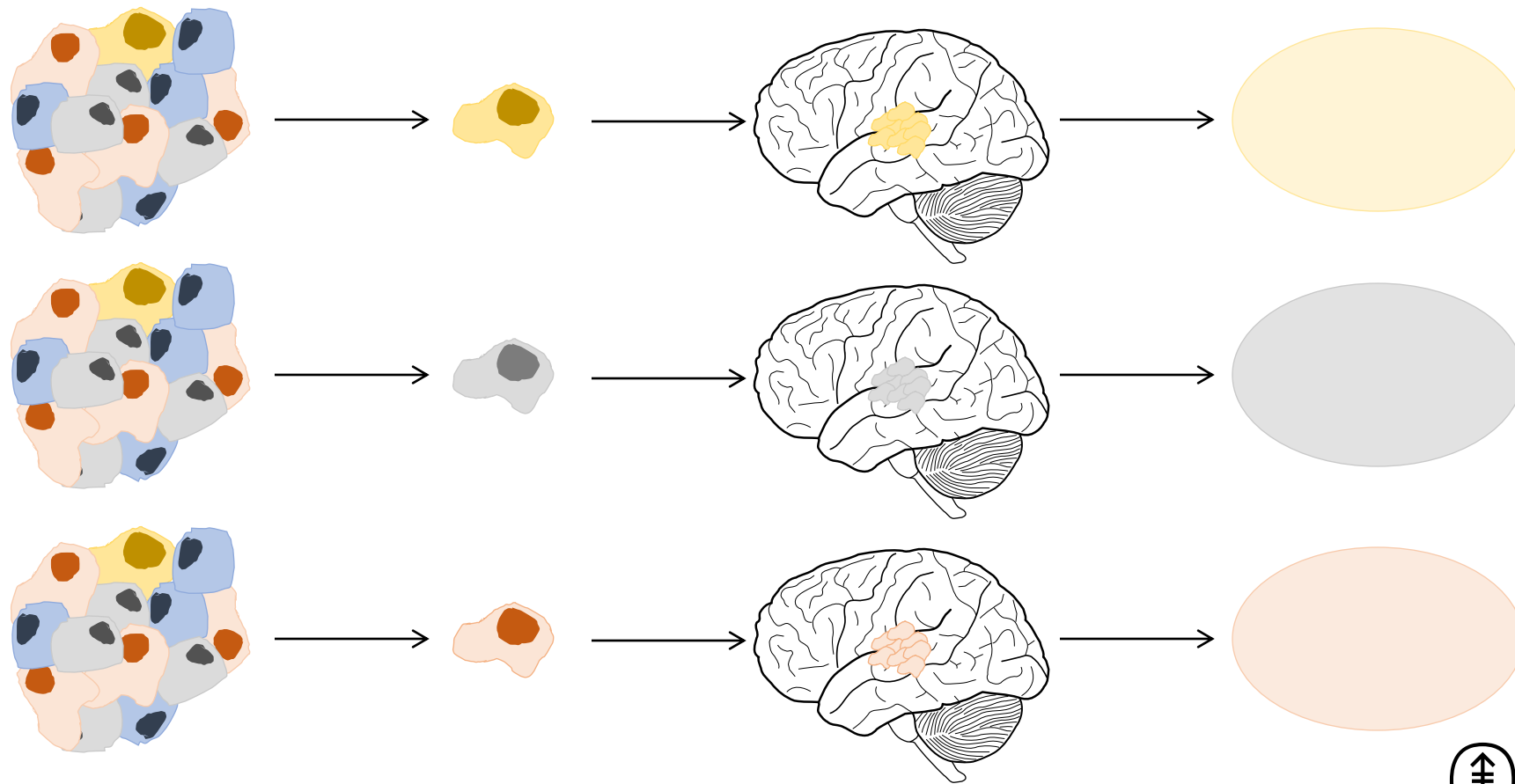


Memorial Sloan Kettering  
 Cancer Center

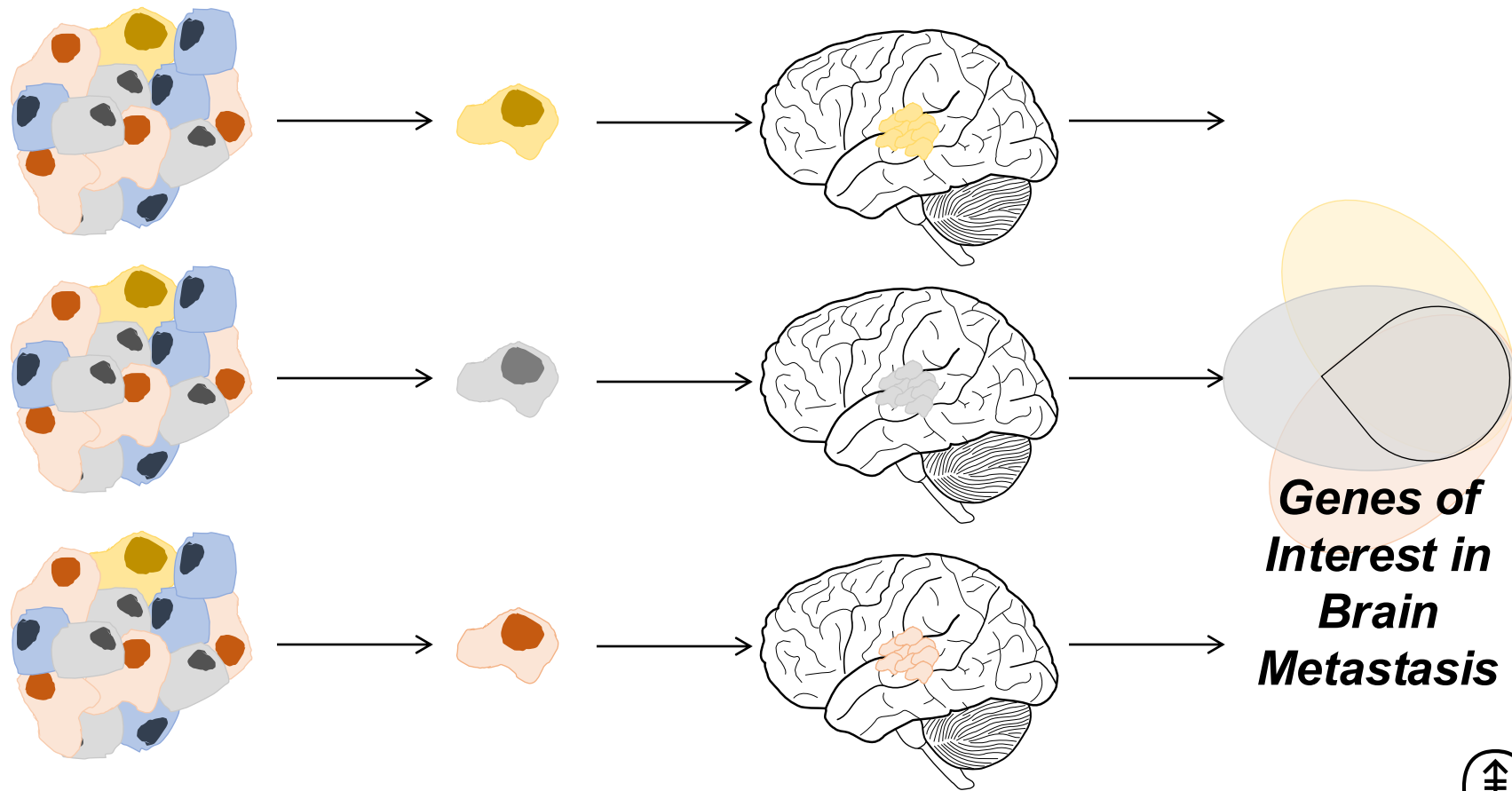
# Exploit Cancer's Diversity and Adaptability



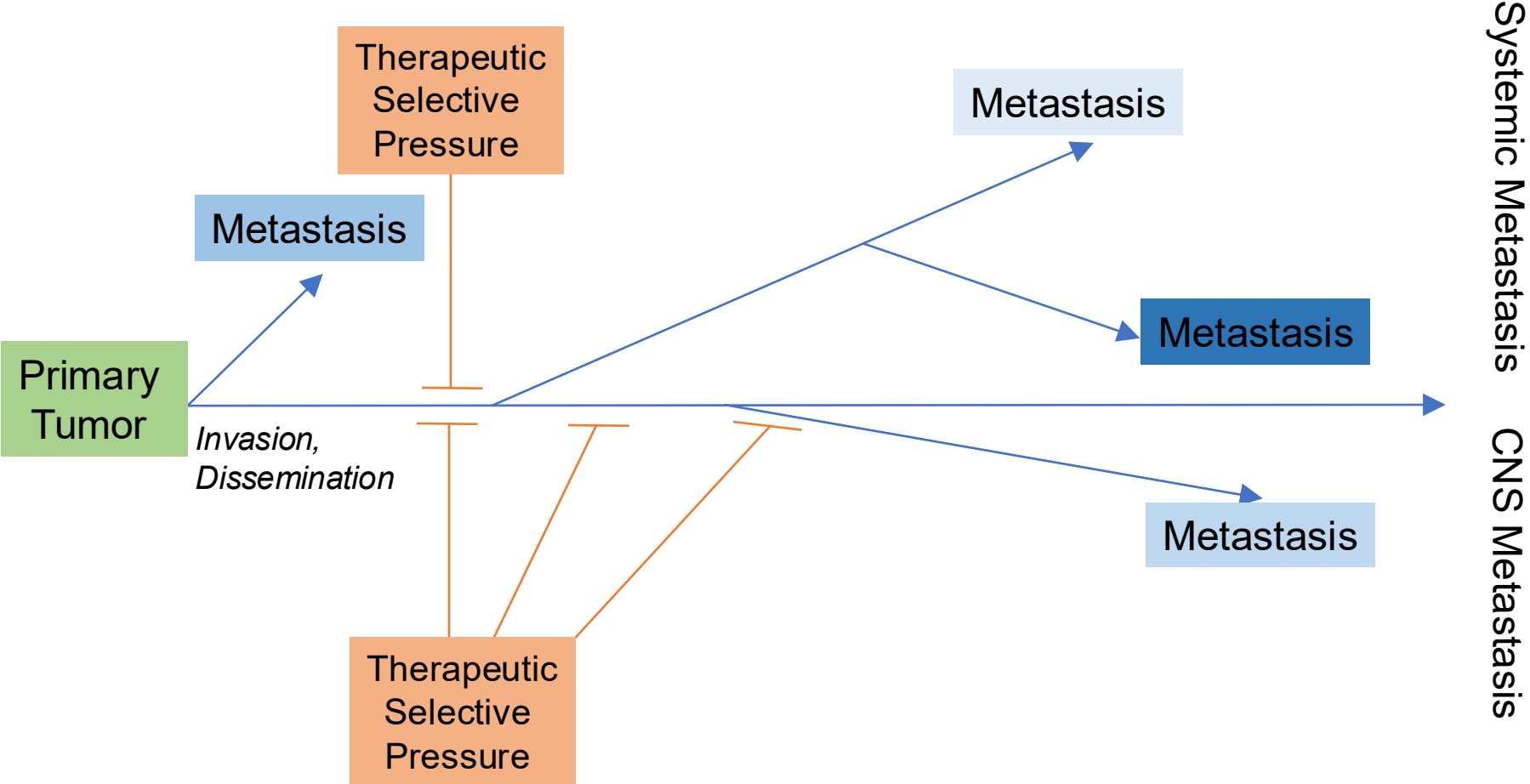
# Exploit Cancer's Diversity and Adaptability



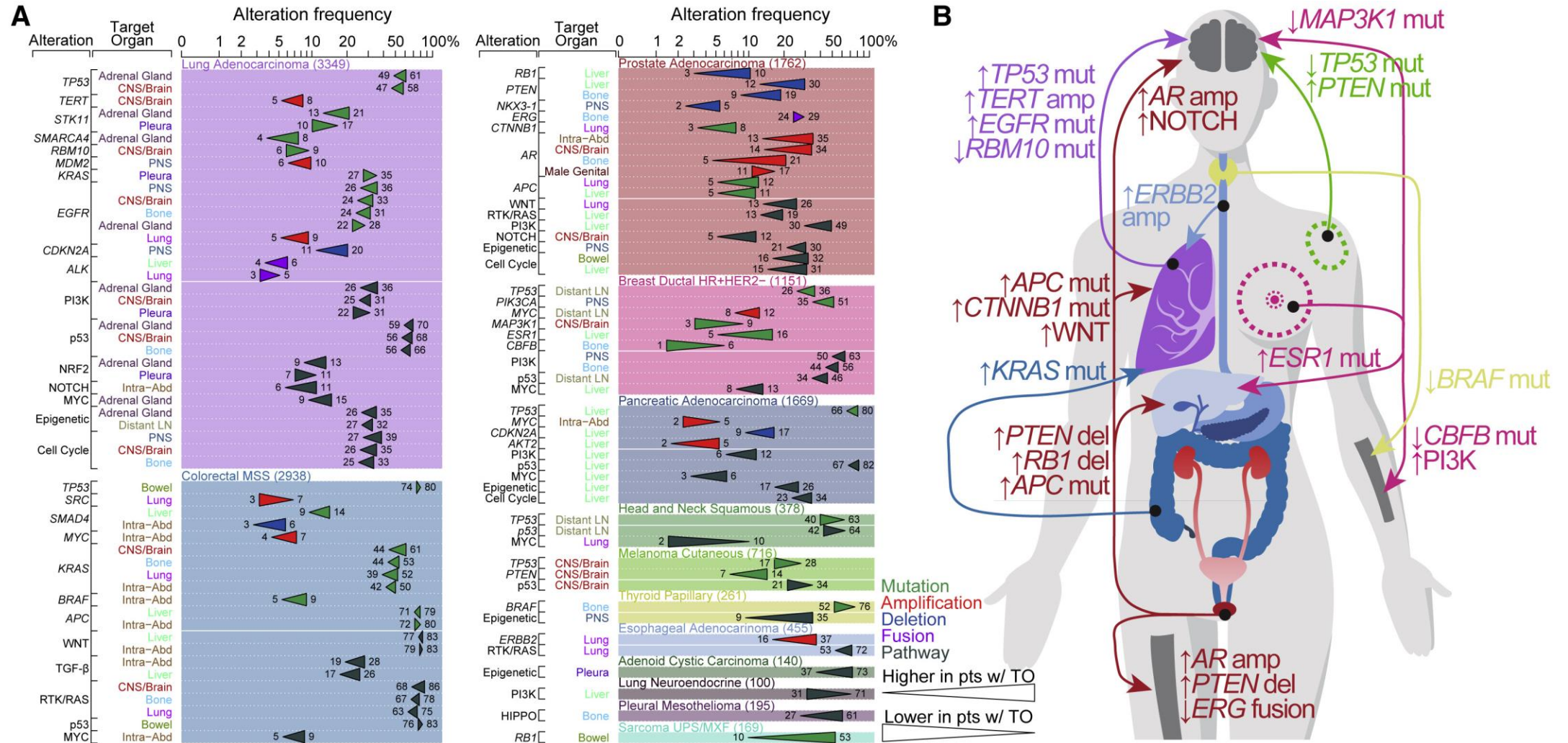
# Exploit Cancer's Diversity and Adaptability



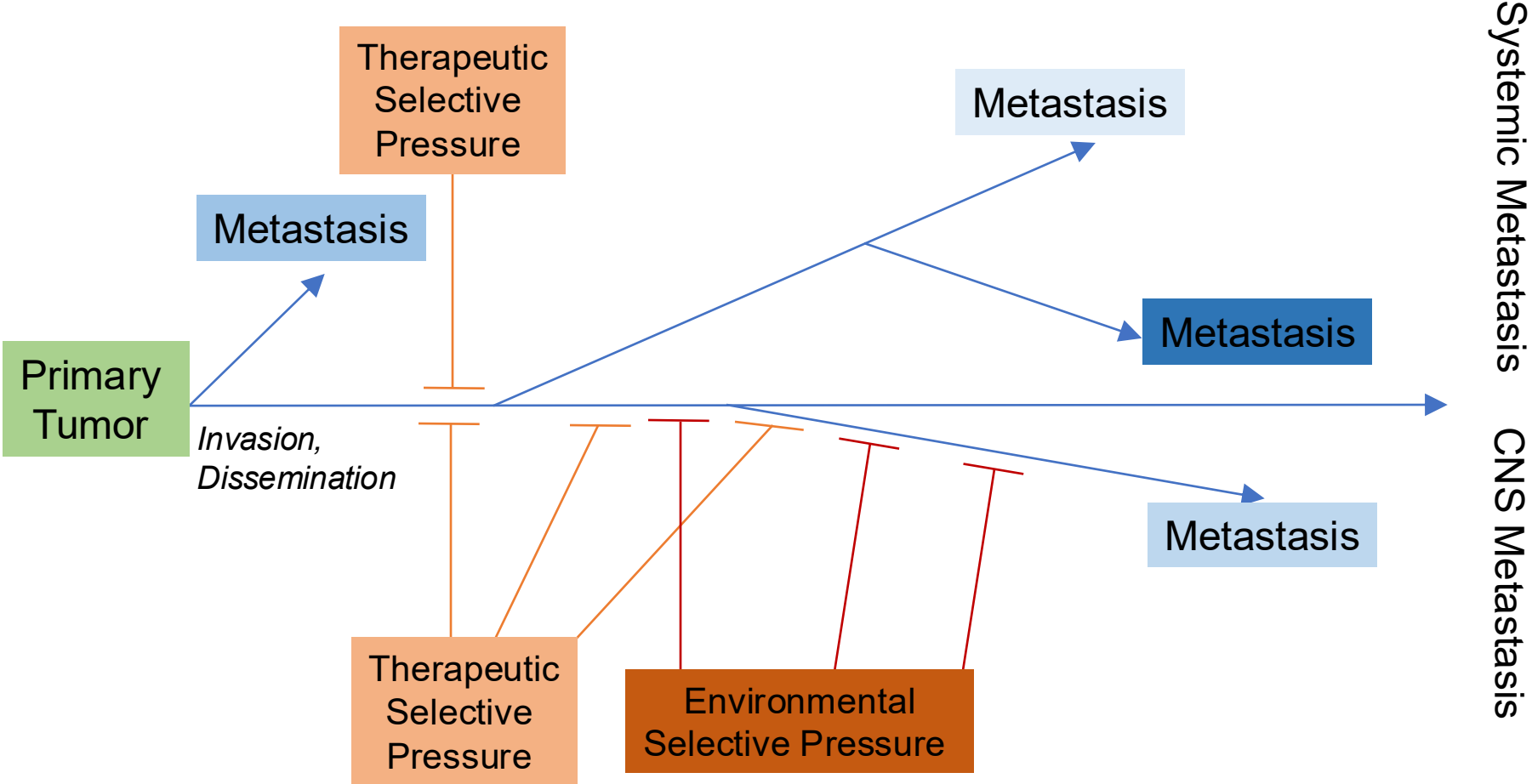
# Metastasis: An Evolutionary Problem



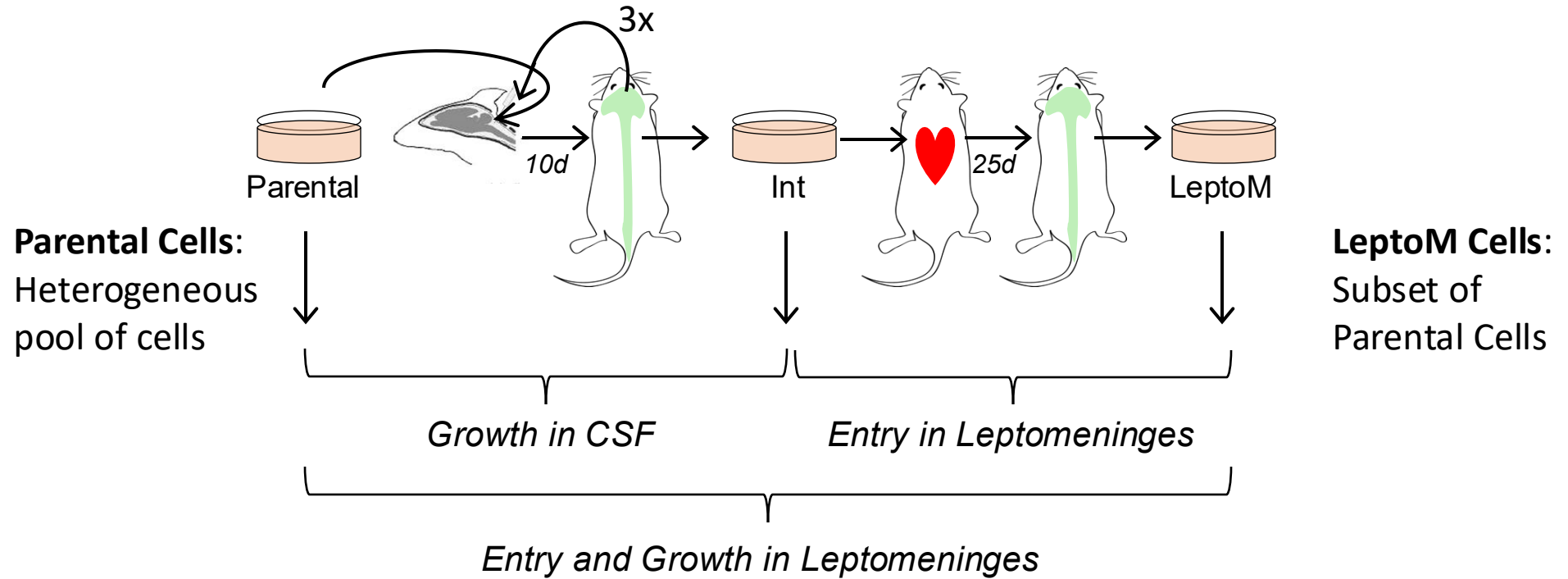
# Metastases Display Evidence of Divergent Evolution



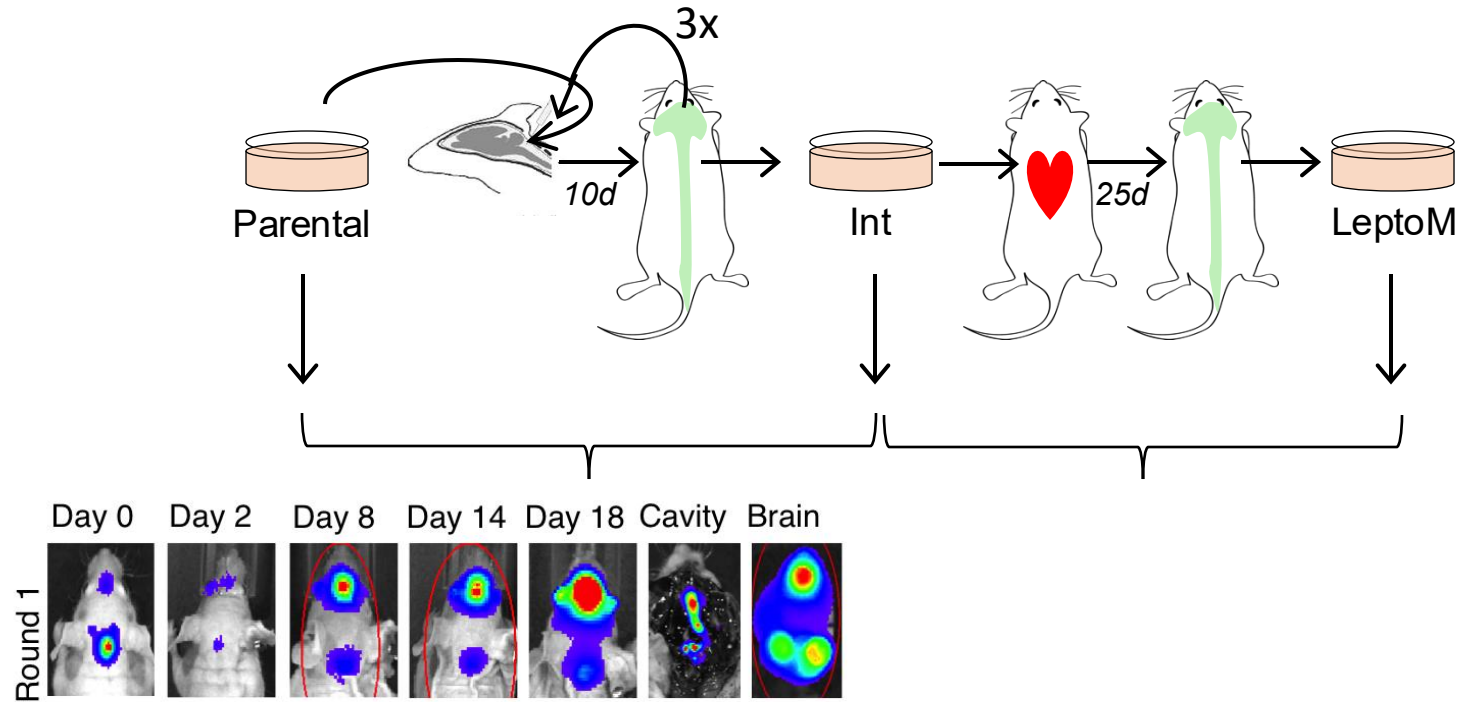
# Metastasis: An Evolutionary Problem



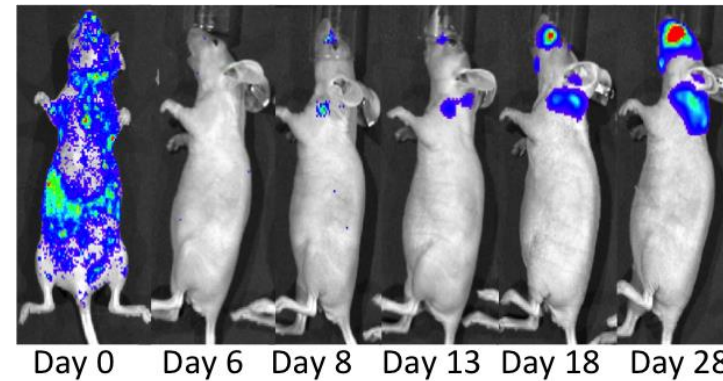
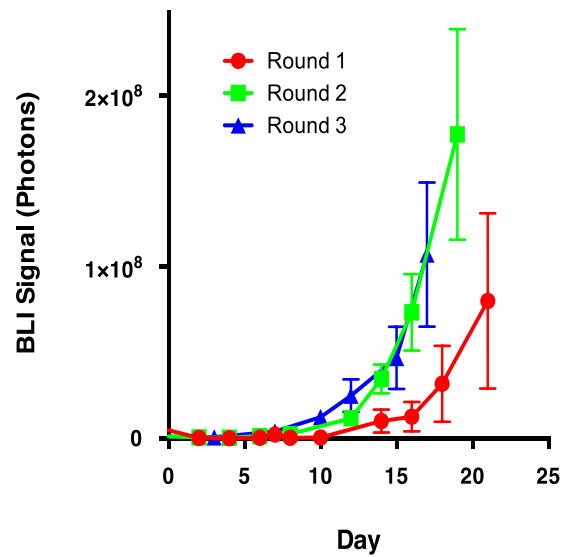
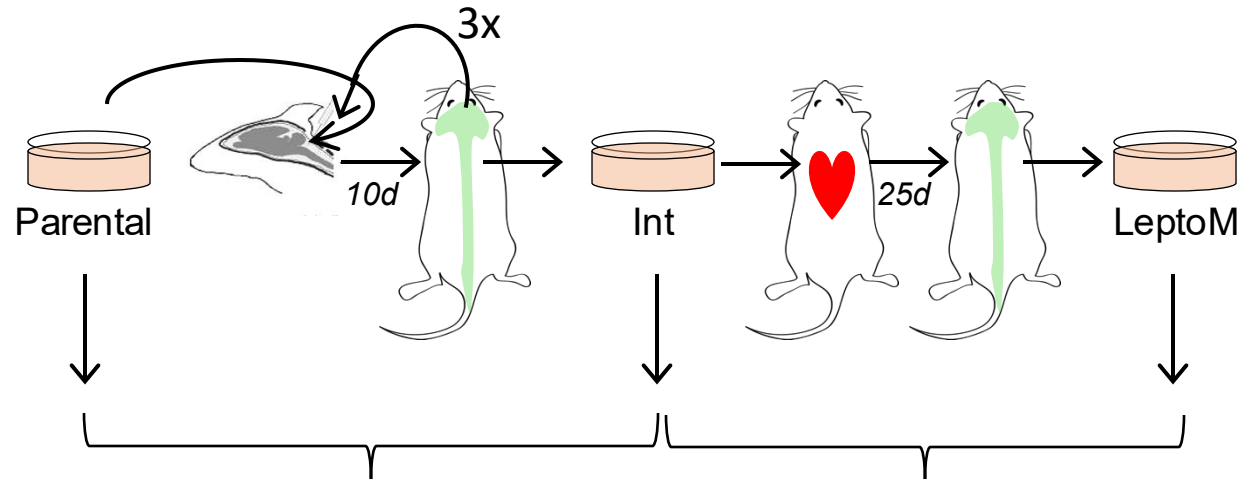
# Mouse Modeling of LM



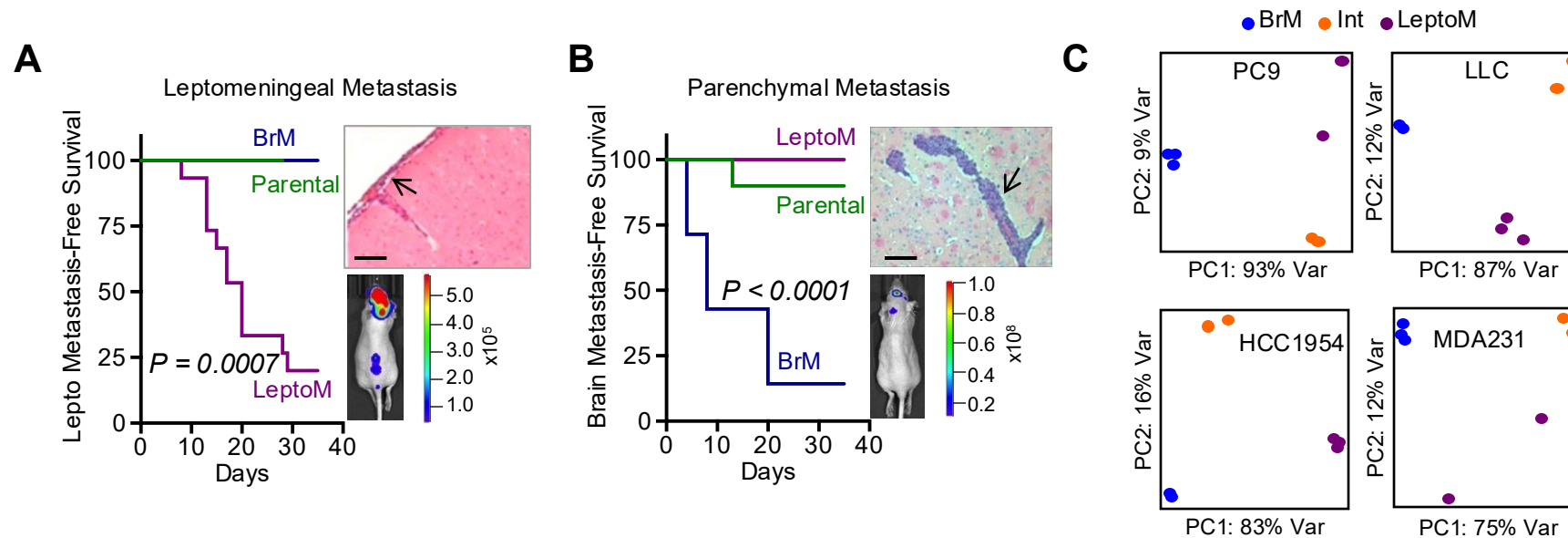
# MDA Leptomeningeal Metastasis Model



# MDA Leptomeningeal Metastasis Model



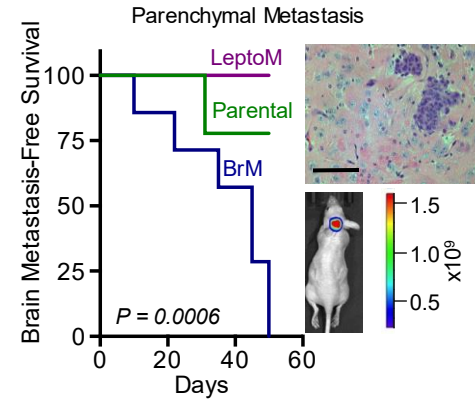
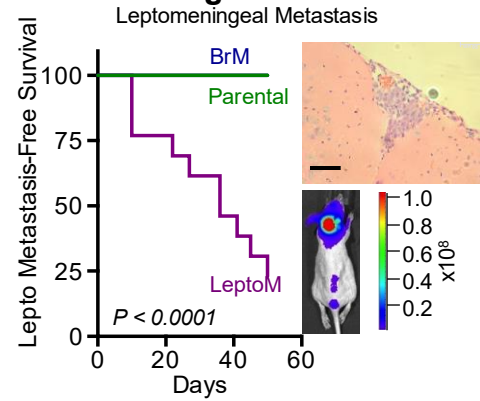
# LeptoM derivatives are phenotypically and transcriptomally distinct from BrM derivatives



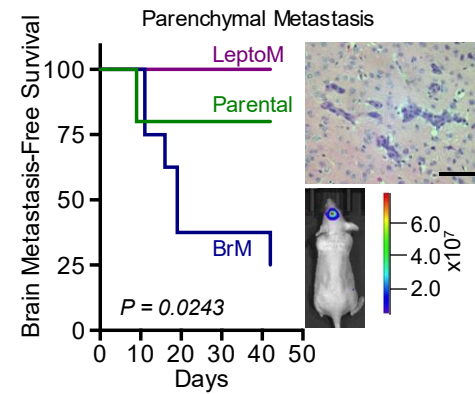
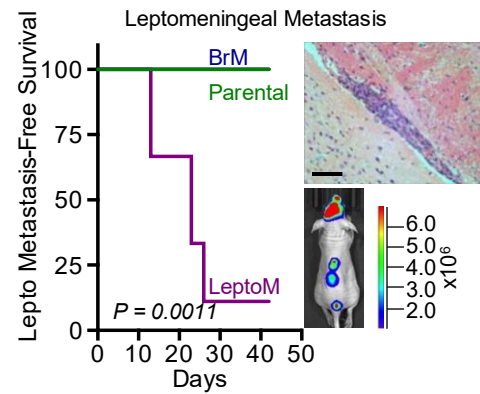
**D**

Cell Line	Primary Cancer	Subtype	Mouse	Ref
MDA231	Human Breast	ER(-)/PR(-)/Her2(-)	Nu/nu	Bos PD et al 2009
HCC1954	Human Breast	ER(-)/PR(-)/Her2(+)	Nu/nu	Malladi S et al 2016
Lewis Lung Carcinoma	Mouse Lung	Non-small cell	C57/Bl6	Chen Q et al 2016
PC9	Human Lung	EGFR	Nu/nu	Nguyen DX et al 2009

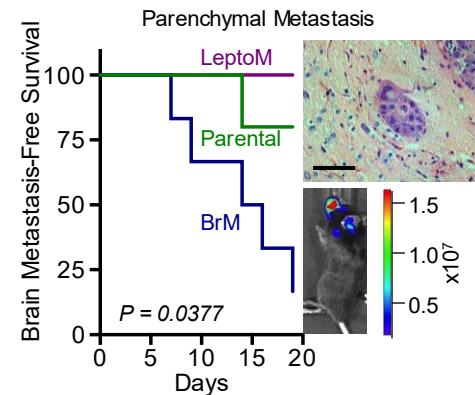
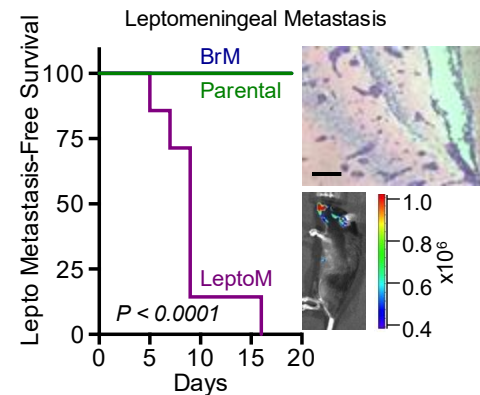
### A PC9 human lung carcinoma



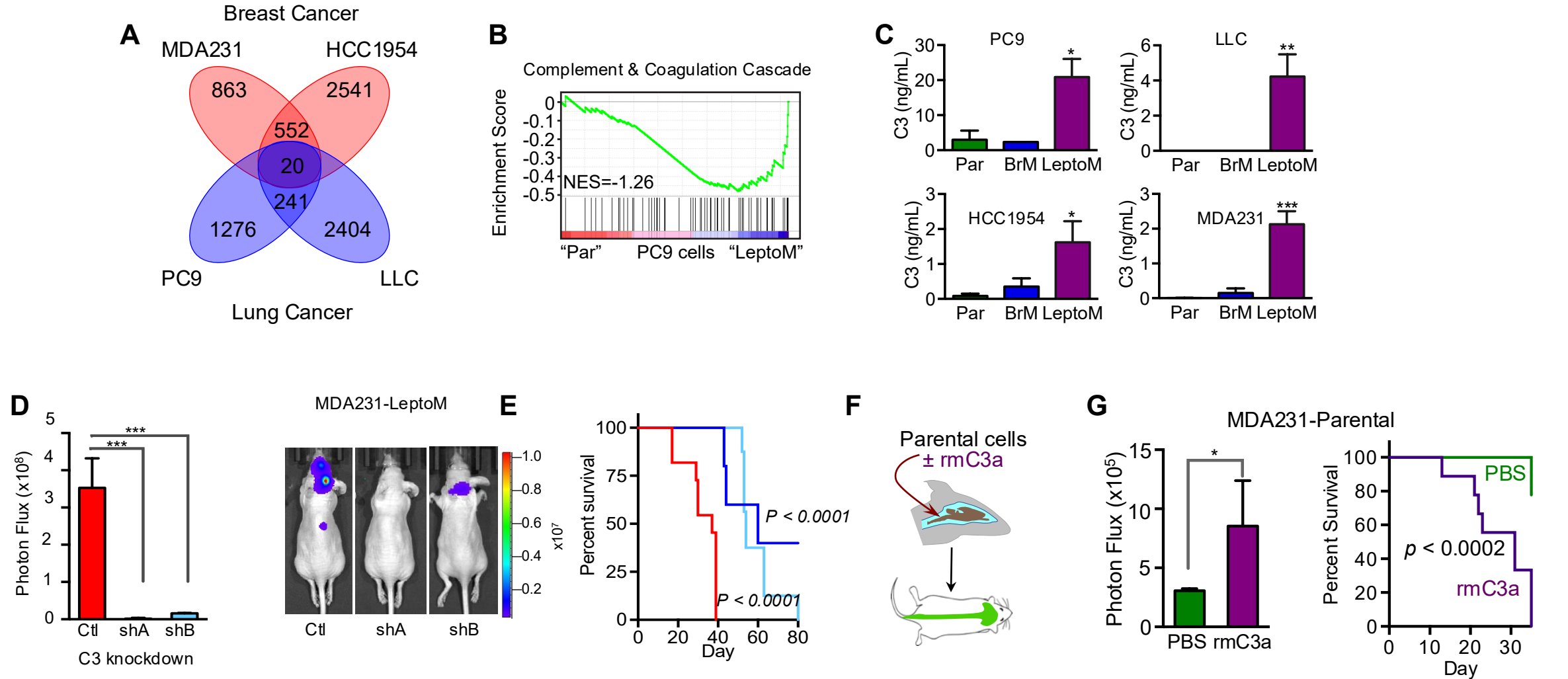
### B HCC1954 human breast carcinoma



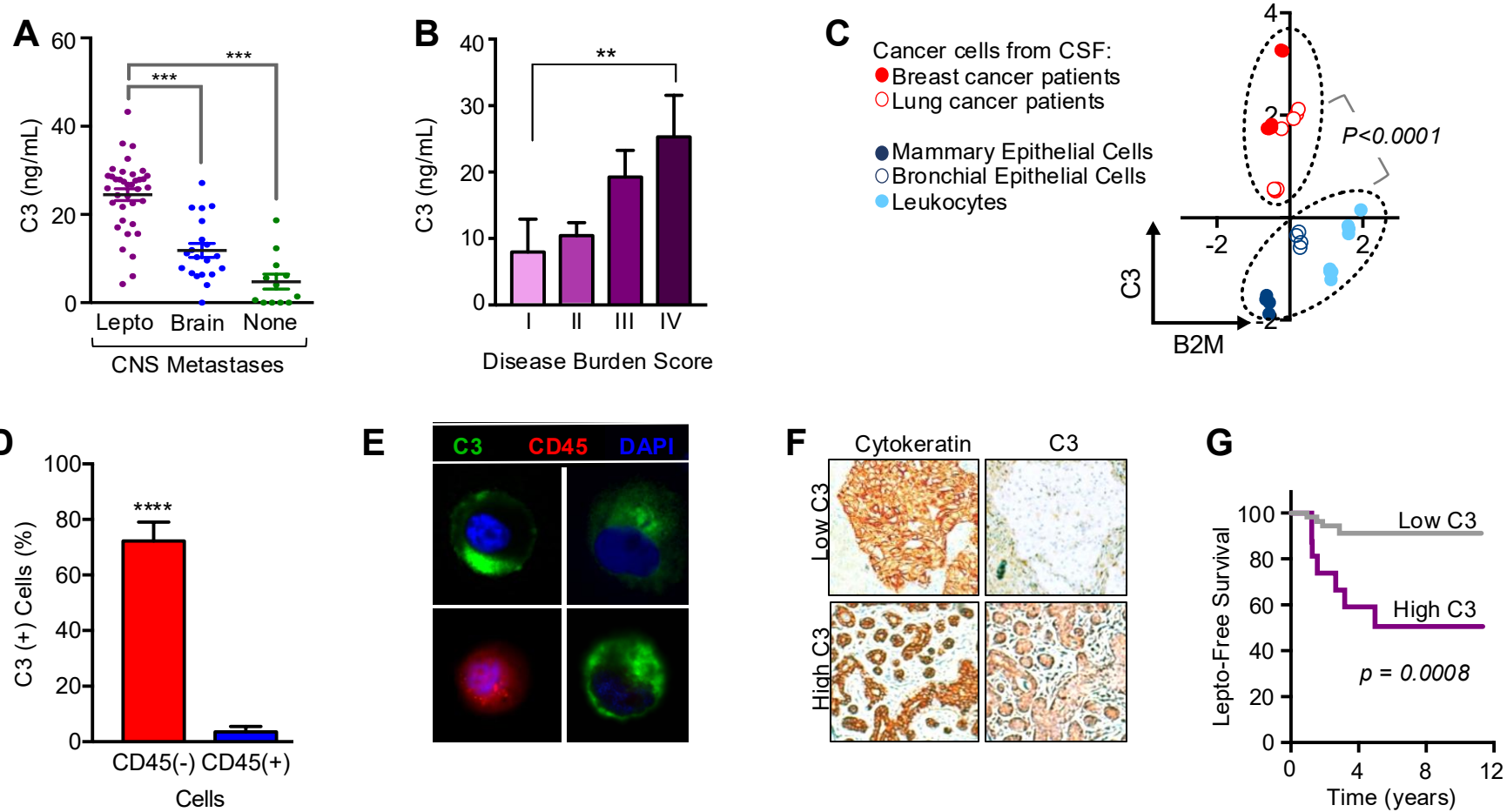
### C LLC murine lung carcinoma



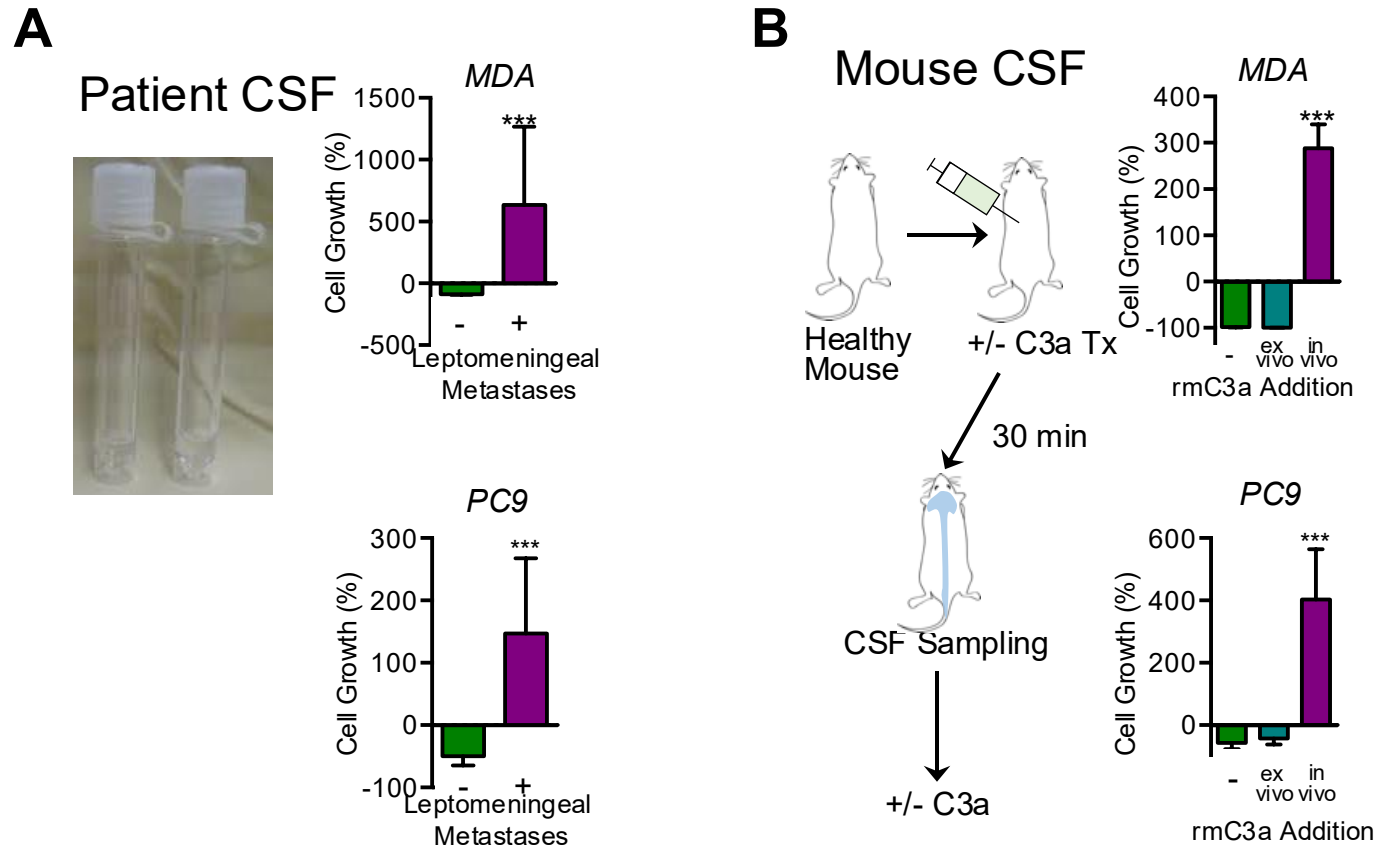
# Complement is C3 associated with cell growth in CSF



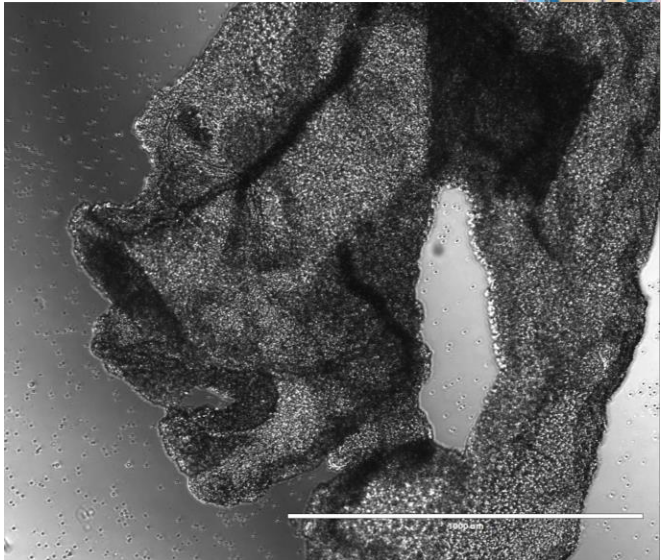
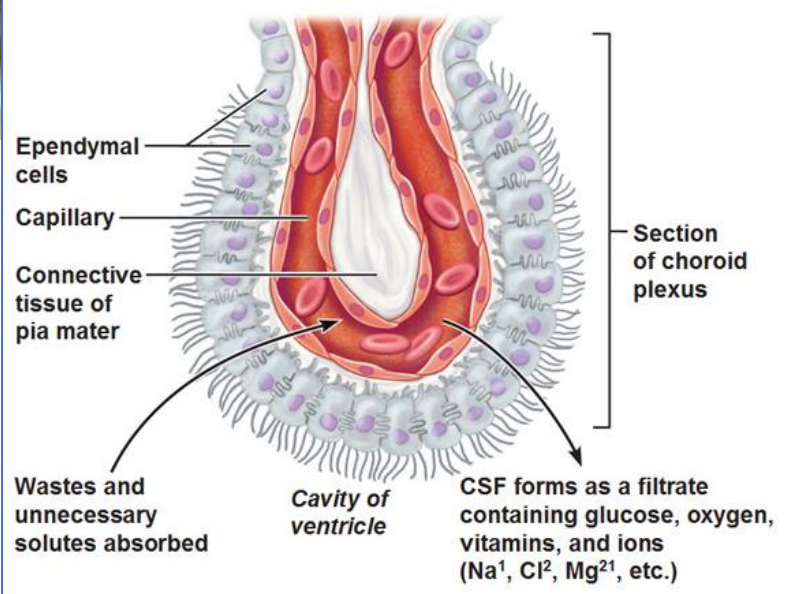
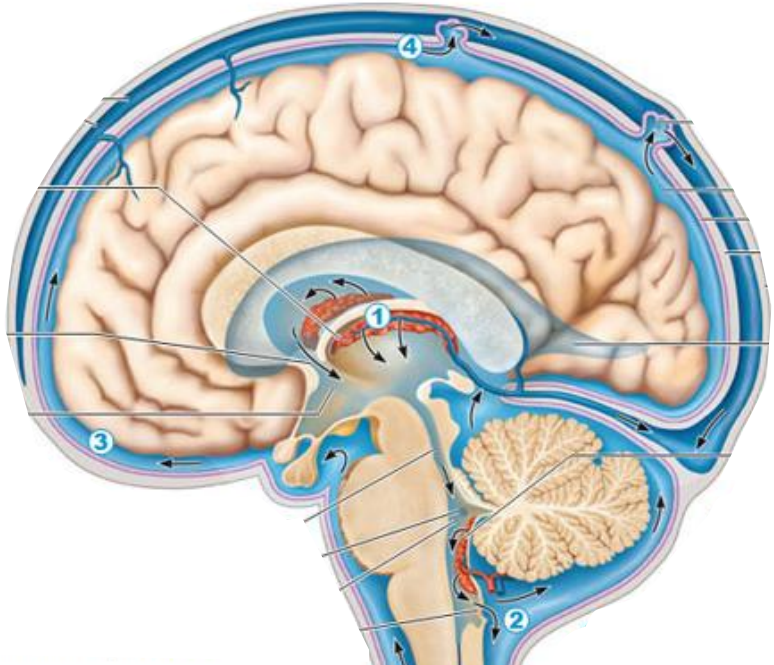
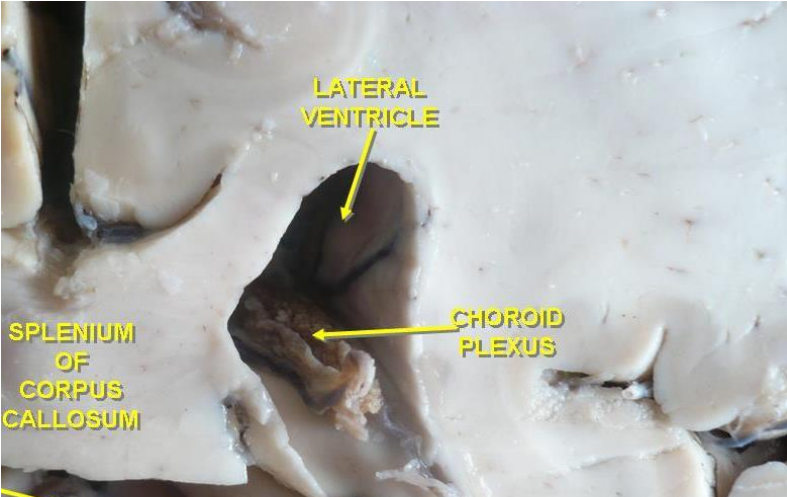
# C3 Implicated in Human LM



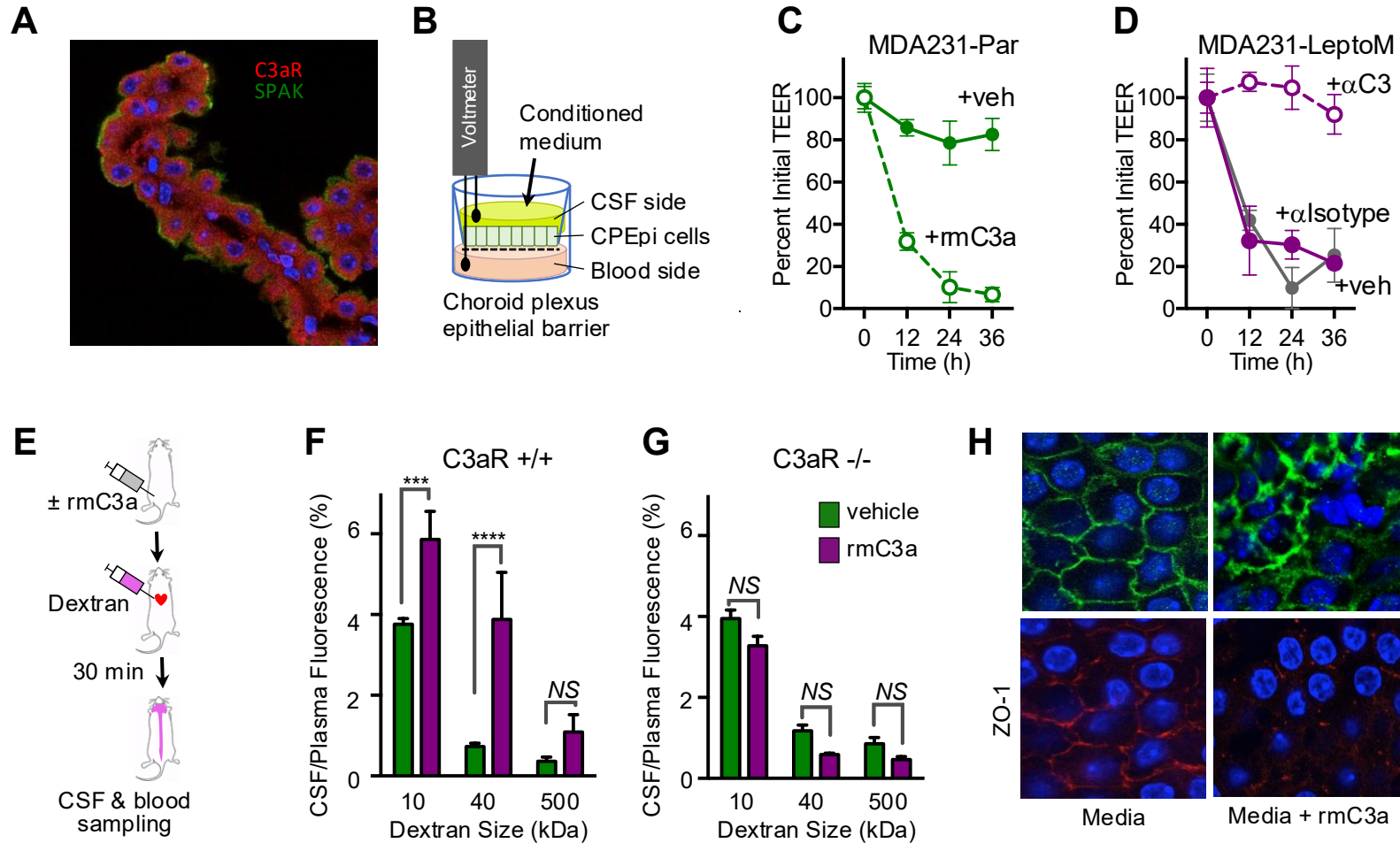
# C3 improves cancer cell growth in CSF



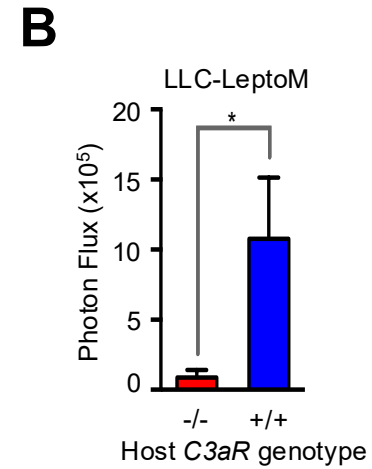
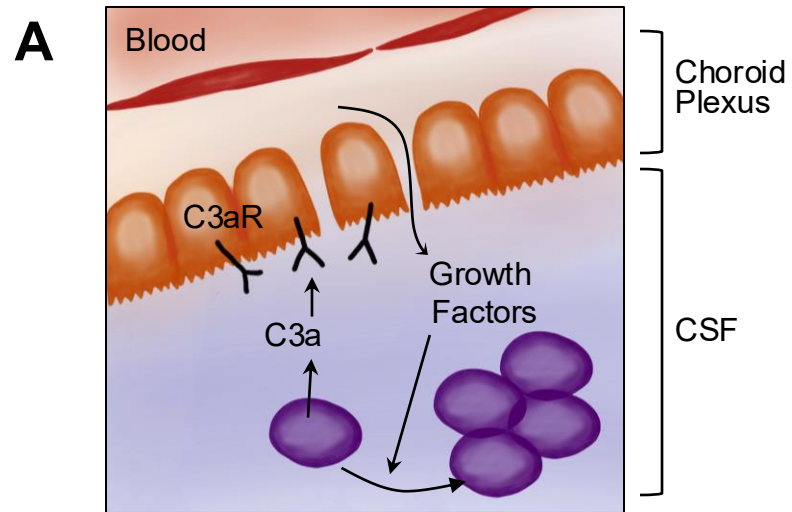
# Choroid Plexus



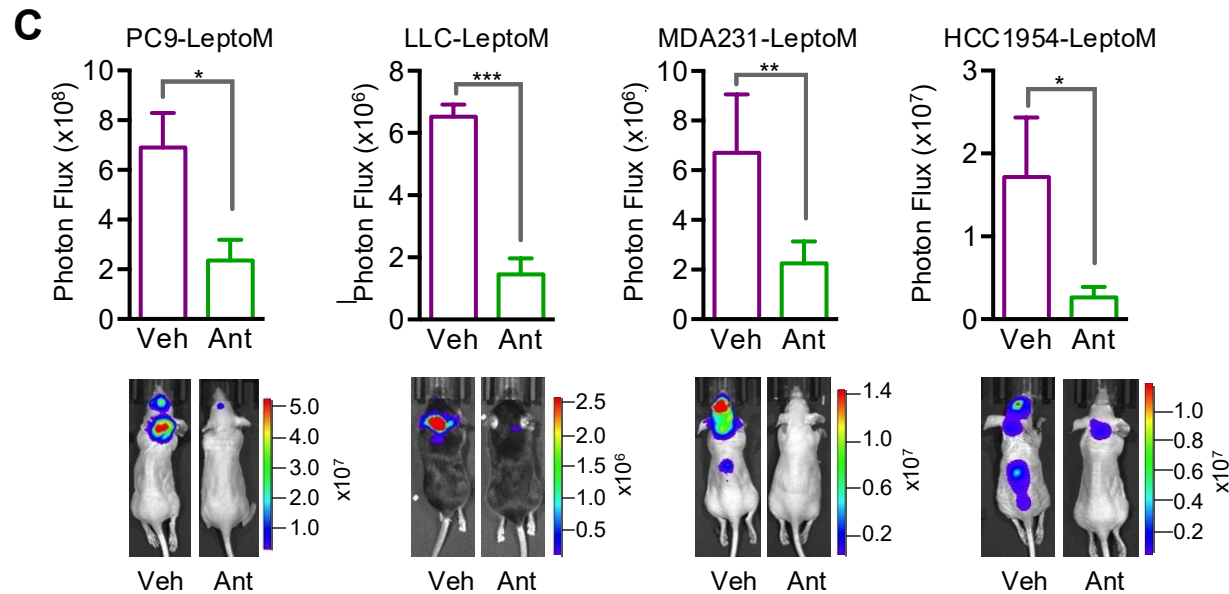
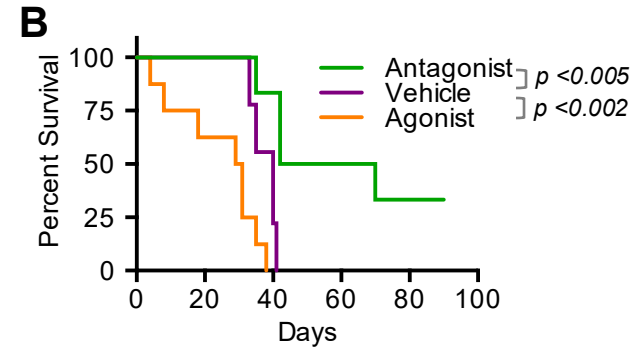
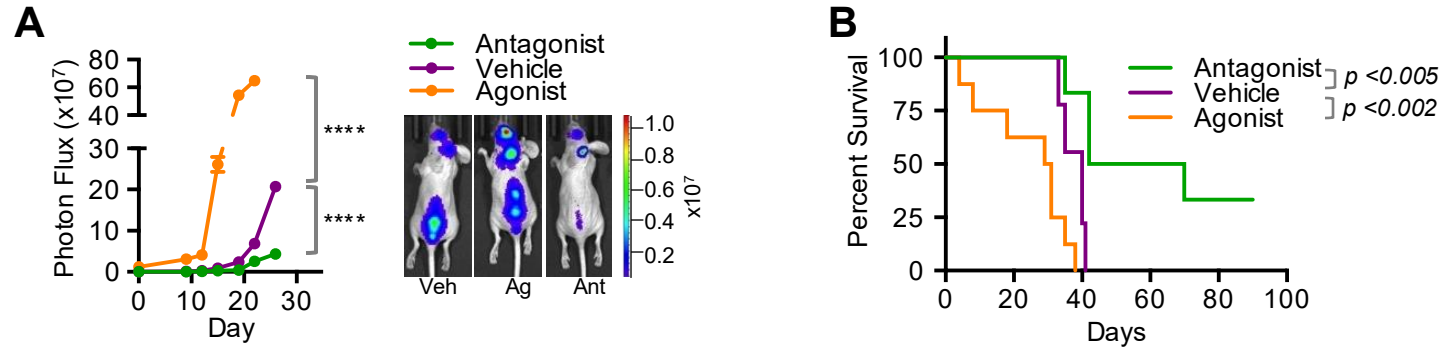
# Complement C3 activates C3aR to loosen choroid plexus tight junctions



# C3aR activation alters composition of CSF



# C3aR antagonism inhibits cancer cell growth in the leptomeninges



# Blood-CSF-Barrier



Castle with Moat  
(BRAIN with CSF)

# Tumors Alter Blood-Brain-Barriers in Unpredictable Ways



Castle with Moat

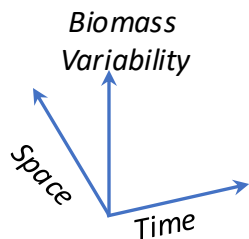
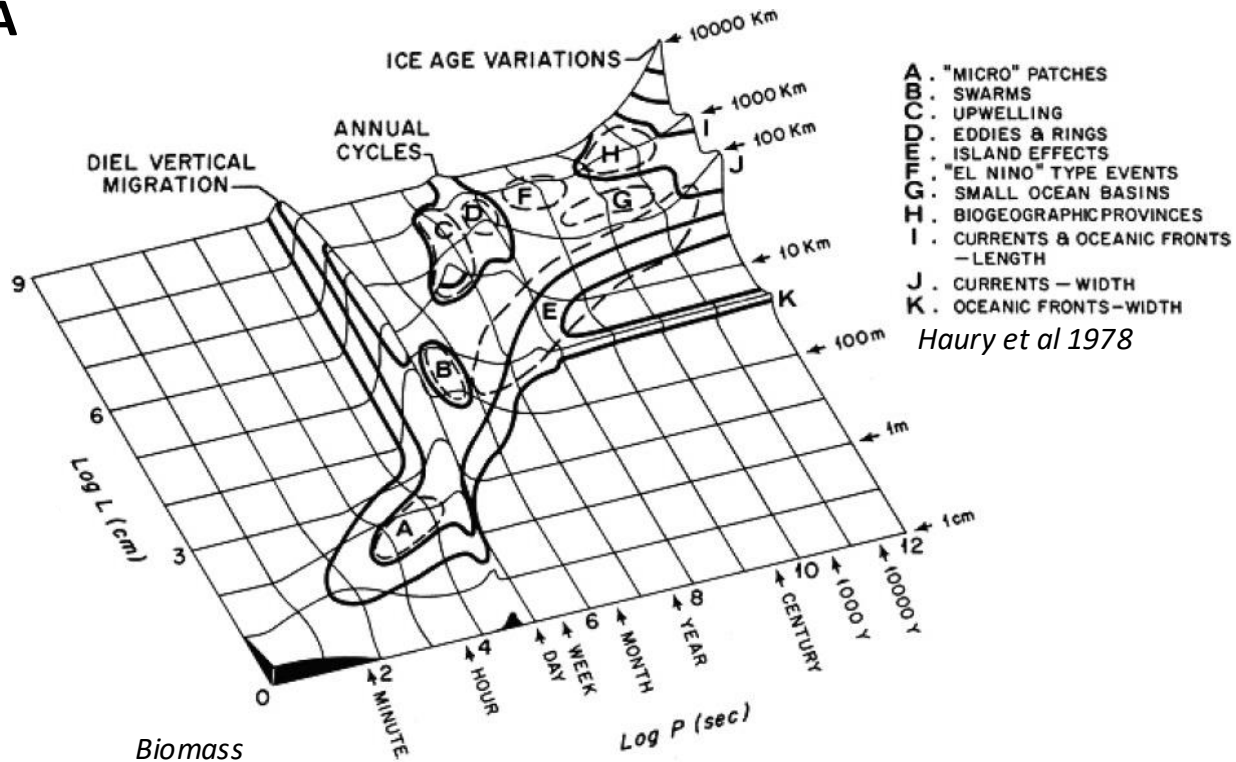


Monty Python: Blood-Tumor-Barrier

*Plan to understand leptomeningeal metastasis: Assume NOTHING, start from basics.*

# Mouse vs. Man: Metastasis as Evolutionary Problem

**A**



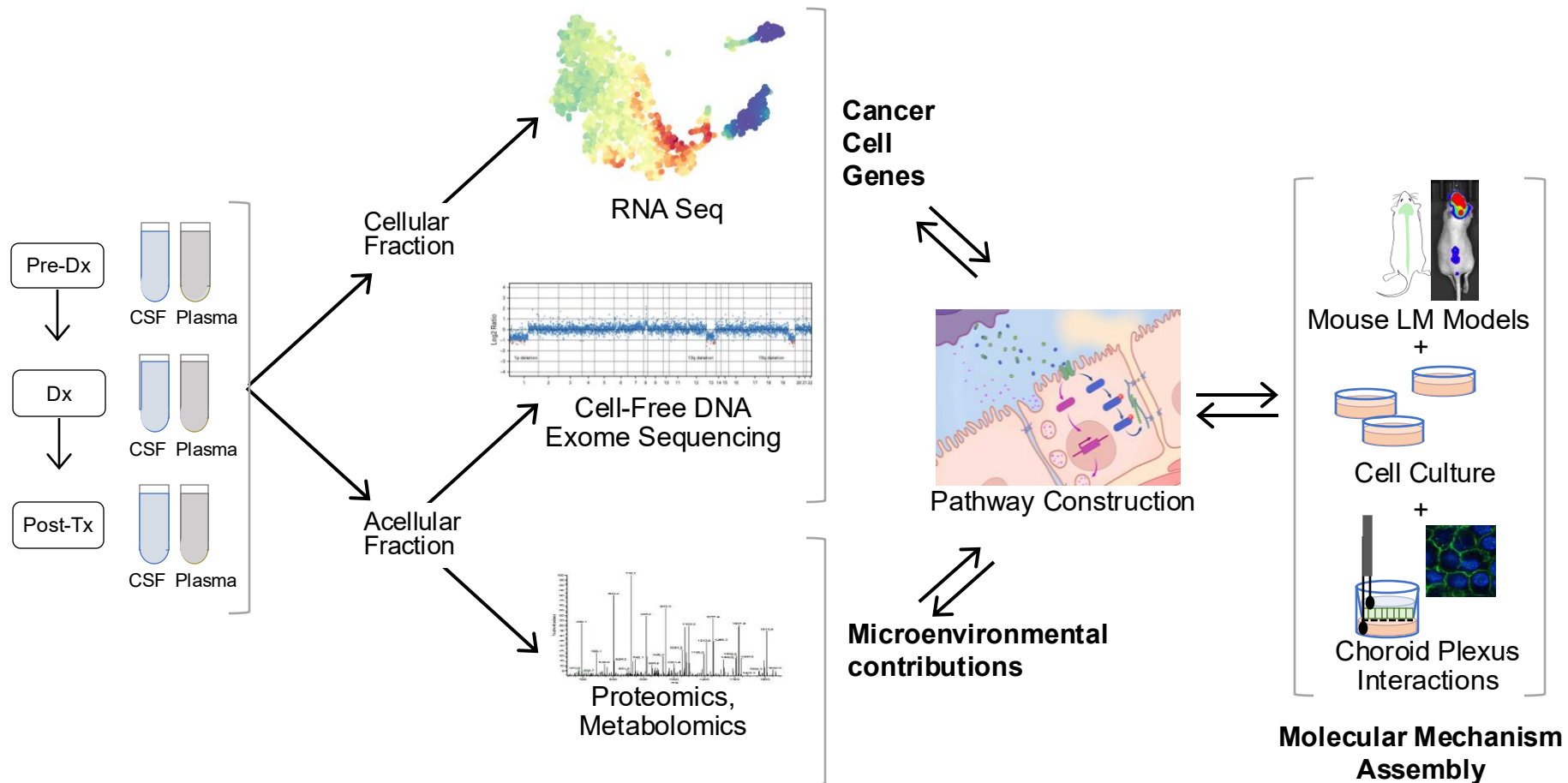
**B**

Human:  
 $3.7 \times 10^{13}$  cells  
 70-80 years  
 Cancer disease course 2-10 years



Mouse:  
 $1.2 \times 10^{10}$  cells  
 2-3 years  
 Cancer disease course: 1-4 months

# Liquid biopsies\* enable use of patient samples as primary discovery tools

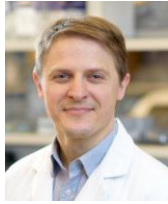


*\*And modern computational biology*

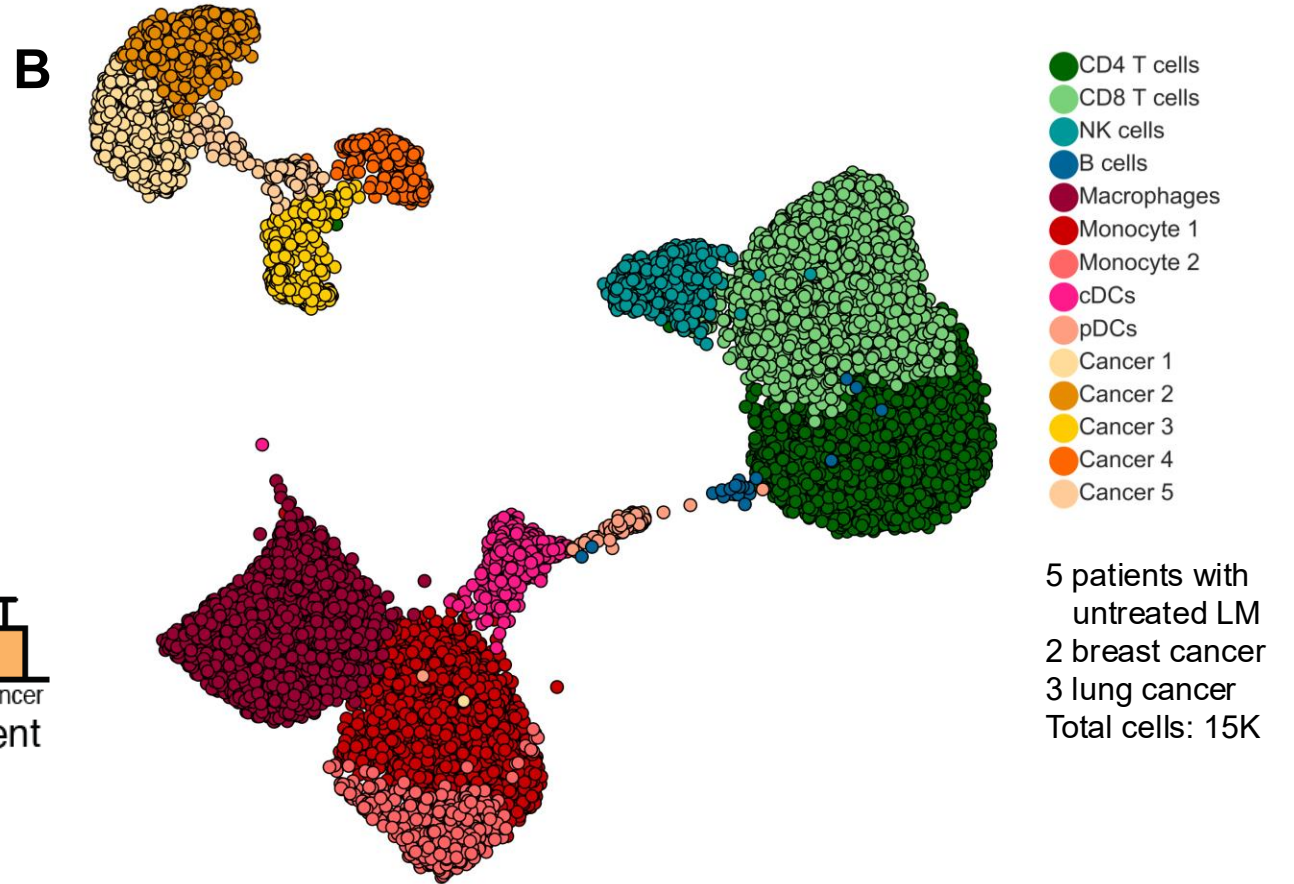
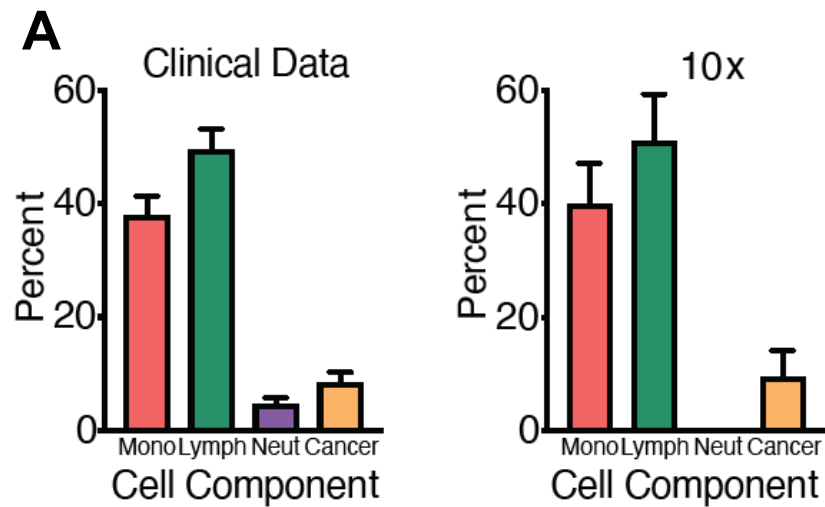
# Capturing Leptomeningeal Metastasis by scRNA Seq



Dana Pe'er



Linas Mazutis





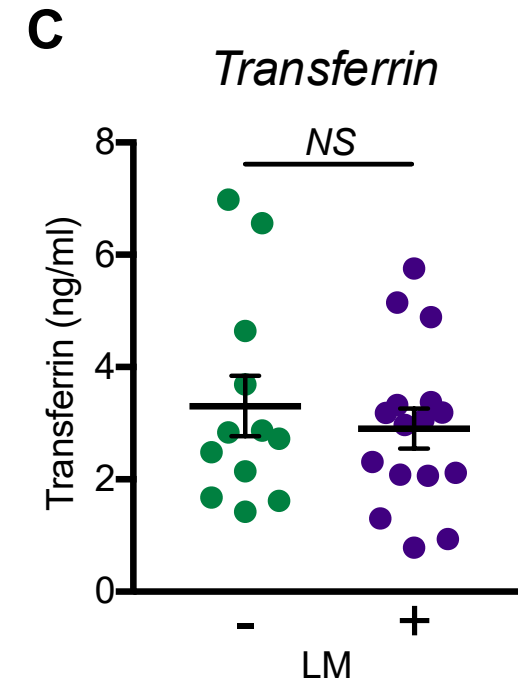
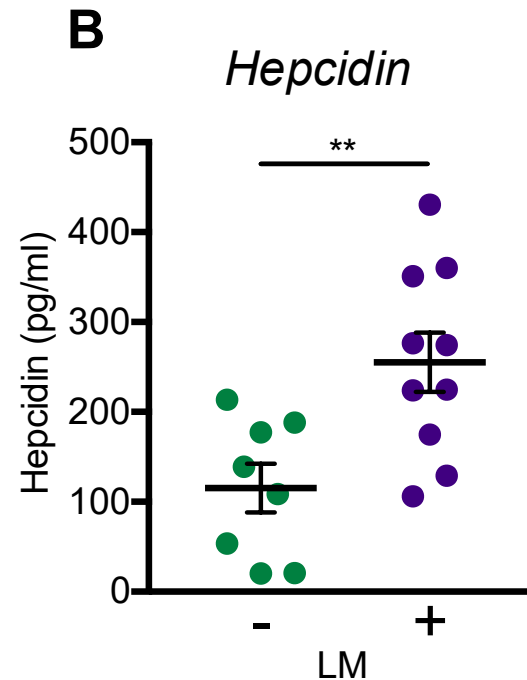
Yudan Chi

# Cancer cells and immune cells inhabit an Fe-deficient environment, and are deficient in iron

**A**

Analyte	CSF	Serum
Osmolarity (mOsm/mL)	295	295
pH	7.33	7.41
Oxygen (mmHg)	43.0	104.0
Glucose (mg/dL)	60.0	90.0
Lactate:Pyruvate	26.0	17.6
Total Protein (mg/dL)	35.0	7000
Free Amino Acids (mol/dL)	80.9	228.0
Total Lipids (mg/dL)	1.5	750.0
Iron ( $\mu\text{g/dL}$ )	1.5	15000

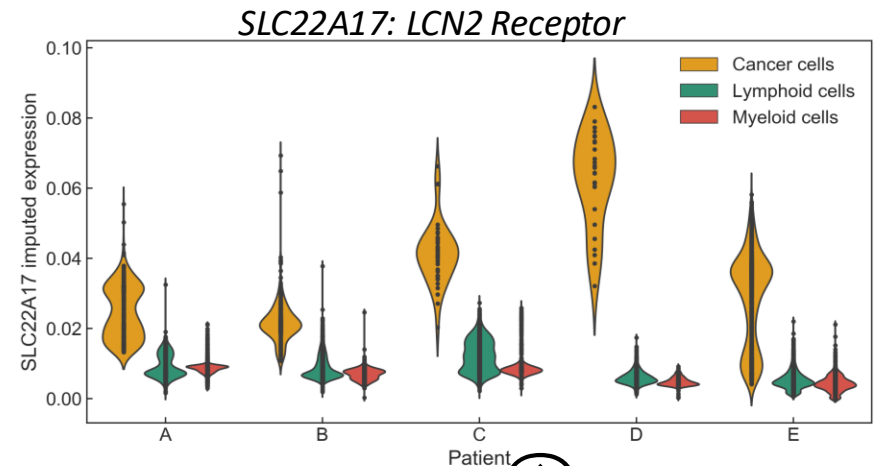
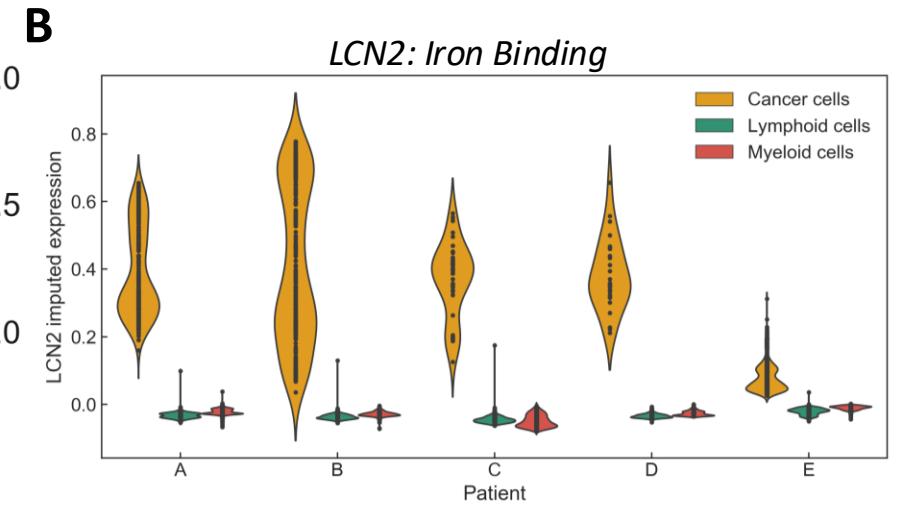
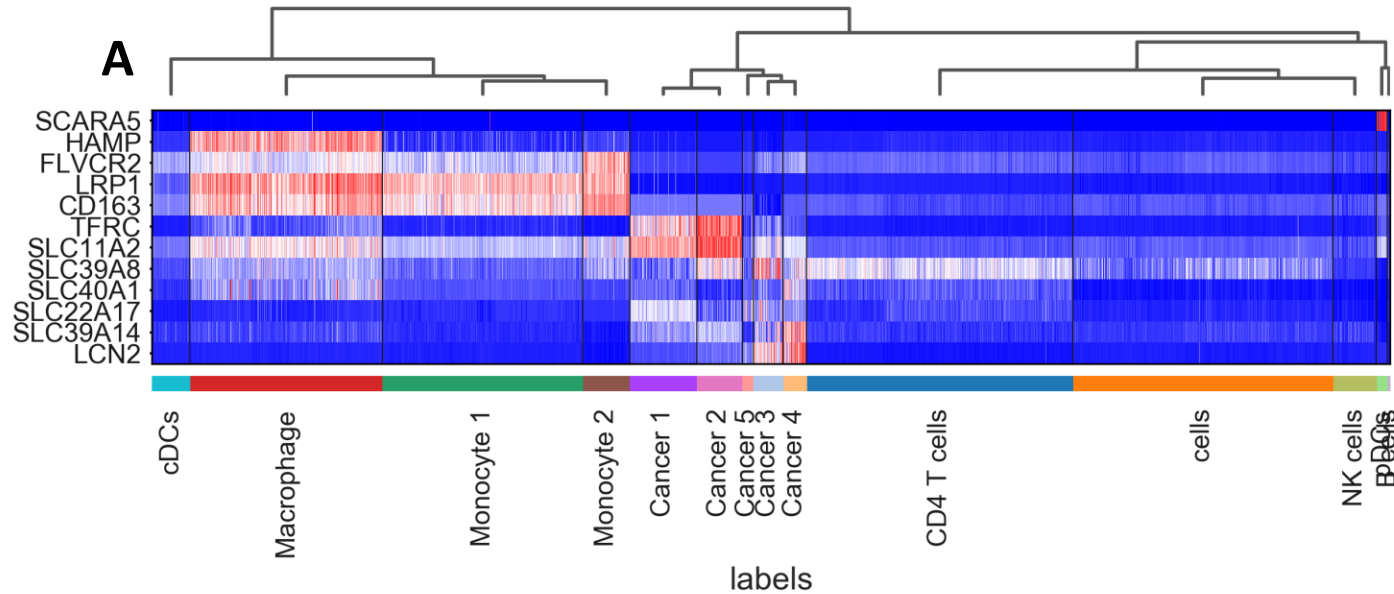
**Composition of CSF and Serum.**  
Adapted from Fishman RA 1992





Vaidotas  
Kiseliovas

# Cancer cells express LCN2 and SLC22A17



# Lipocalin 2 LCN2

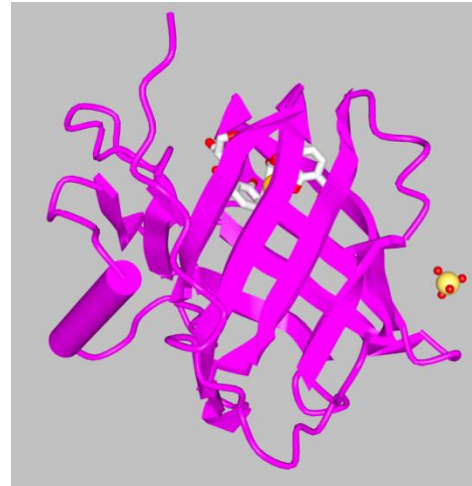
*Neutrophil gelatinase-associated lipocalin, 25kDa alpha-2-microglobulin-related subunit of MMP9, Migration-stimulating factor inhibitor, oncogene 24p3, siderocalin*

Lipocalins are secreted transporters

LCN2 -co-purifying with MMP-9, participates in nutritional immunity through siderophore function (Binds  $\text{Fe}^{3+}$ )

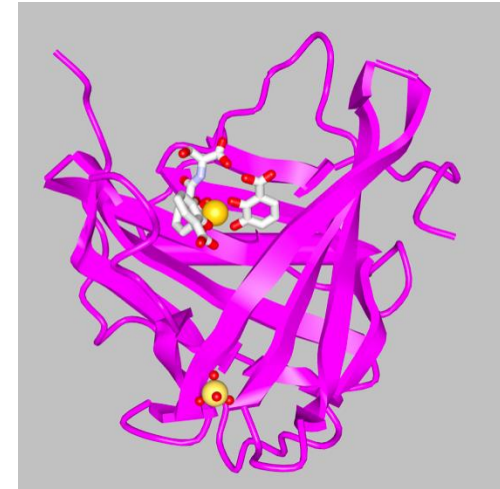
*Yan J et al 2002 Mol Cell*

Generated by Neutrophils and/or Macrophage in inflammatory processes



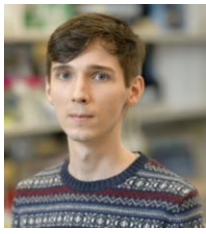
*Goetz DH et al 2002 Mol Cell*

Carrier	Kd (M)
Lcn2 (+catechol)	$10^{-45}$ $10^{-10}$
Transferrin	$10^{-23}$
Lactoferrin	$10^{-20}$
Deferoxamine	$10^{-34}$



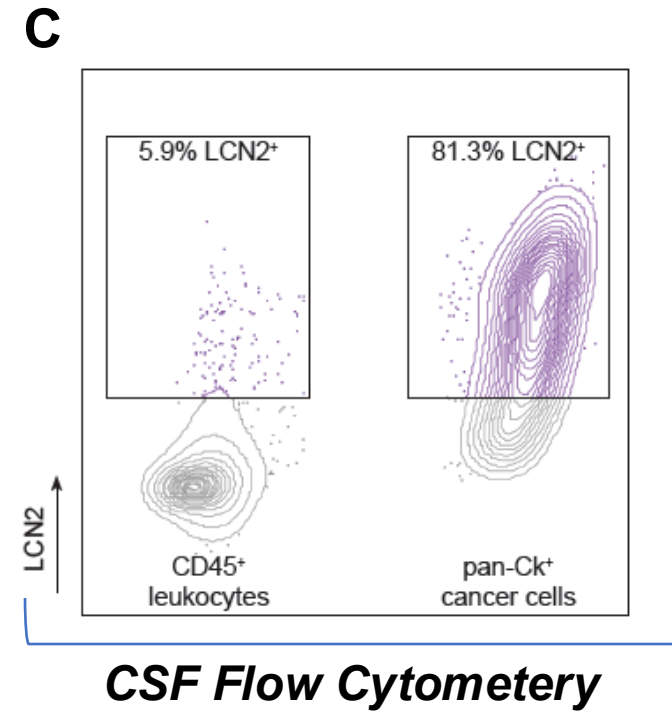
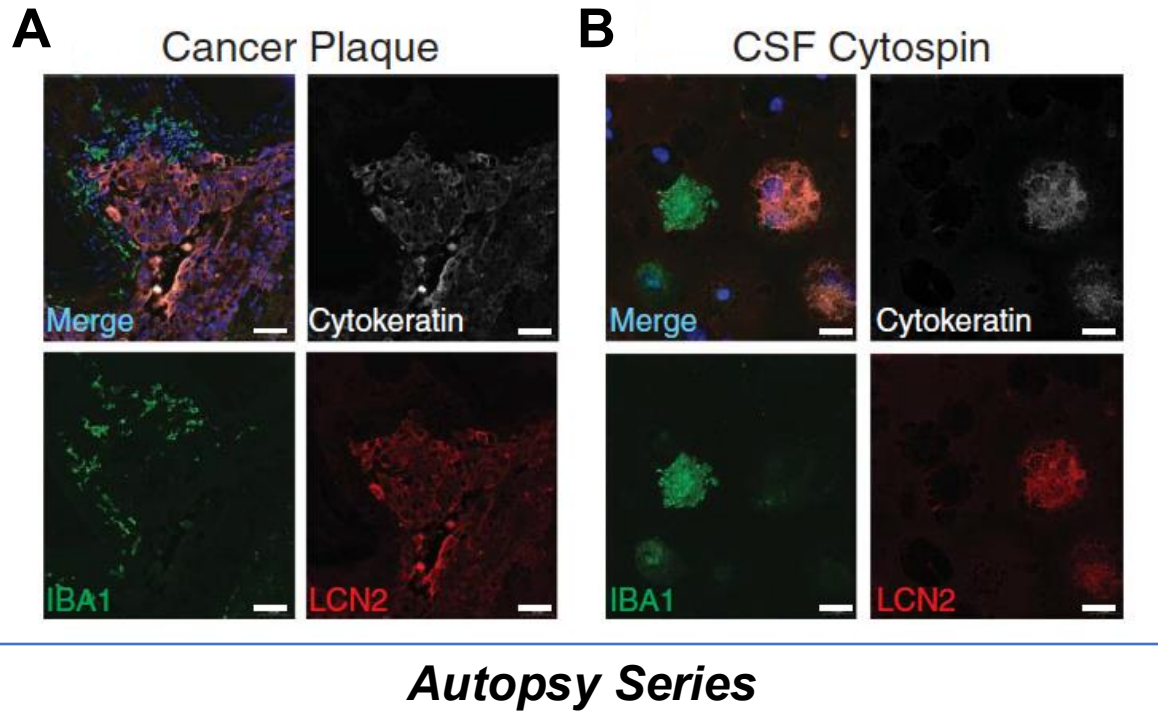


Christine Iacobuzio-Donahue

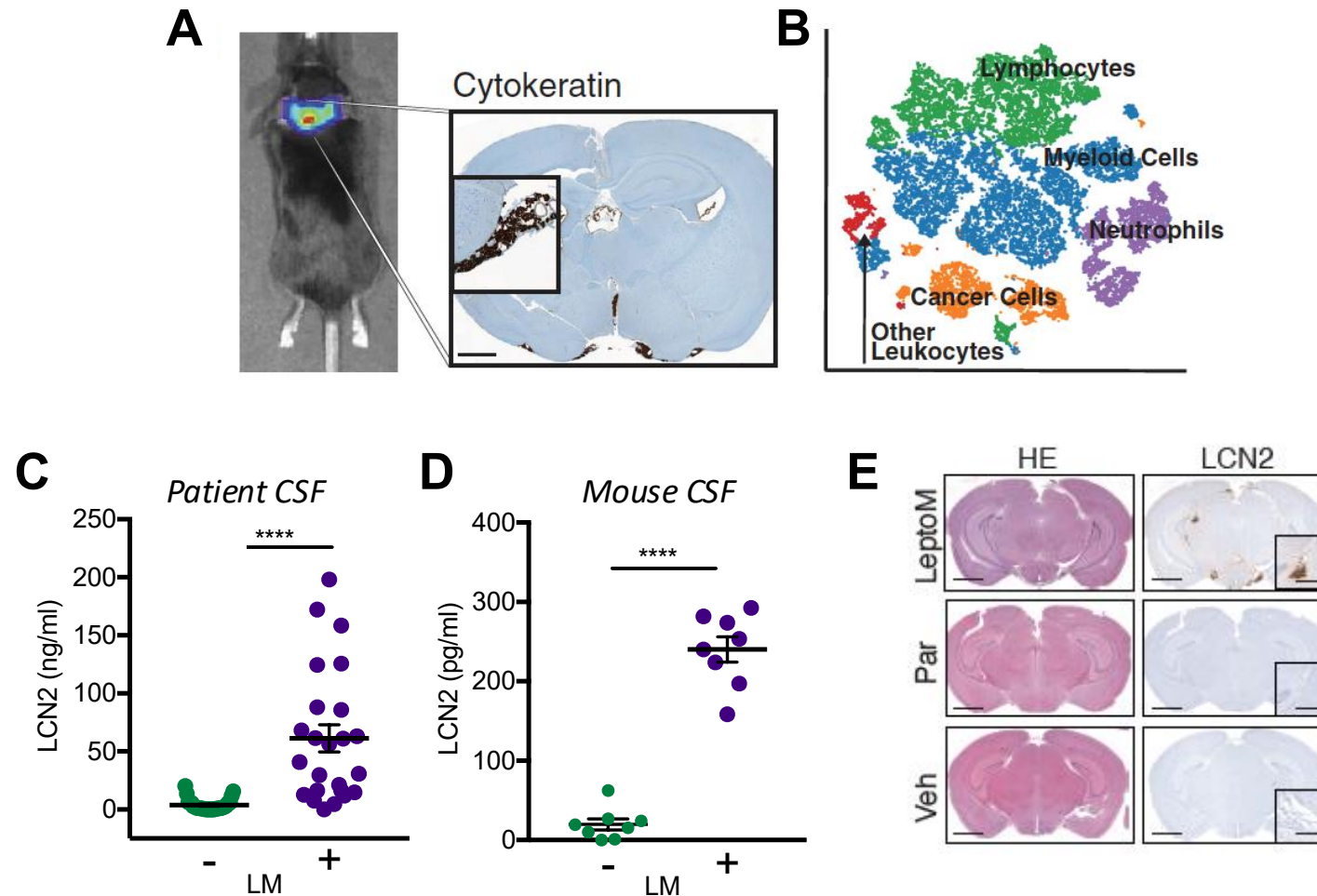


Jan Remsik

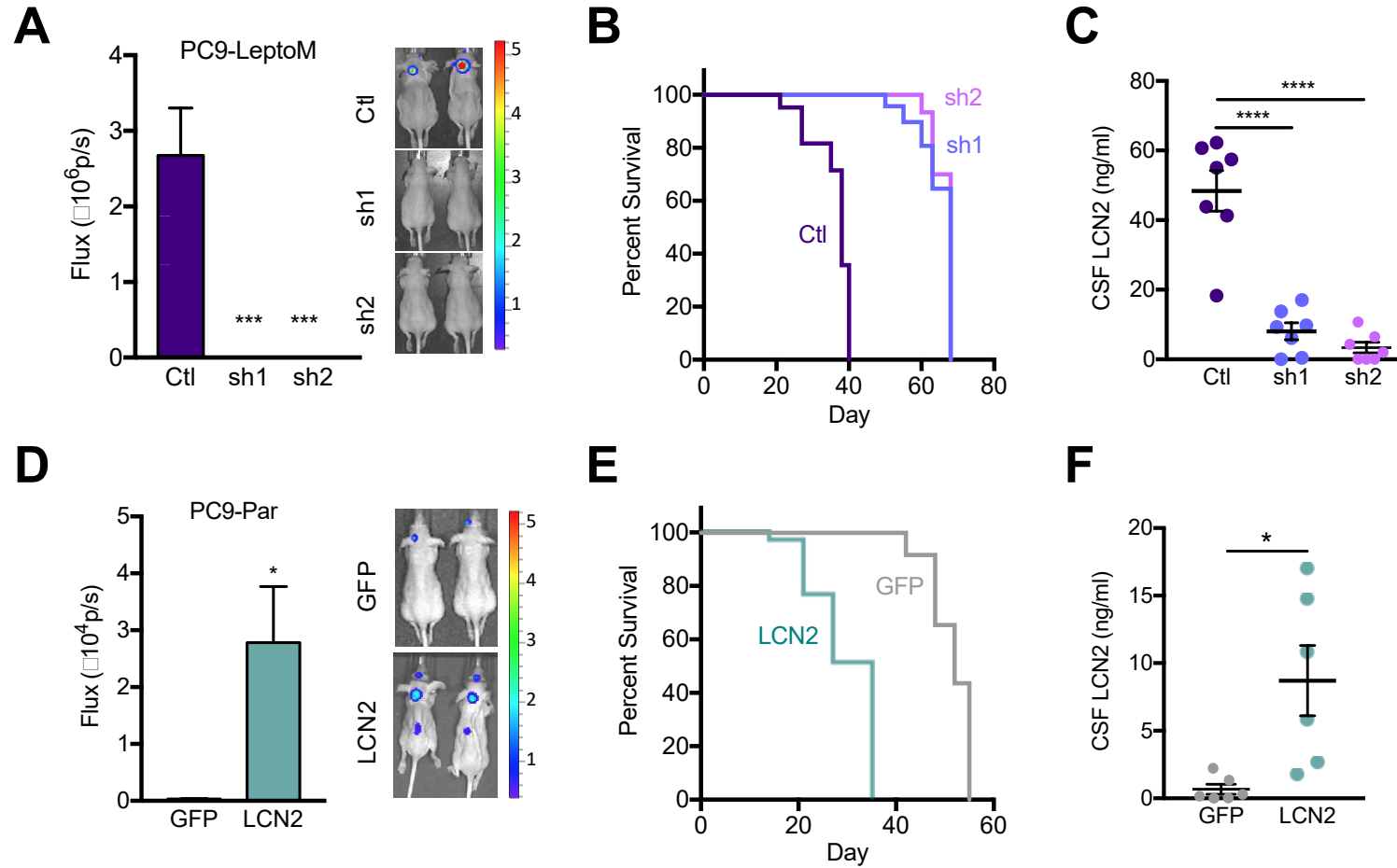
# CSF cancer cells express LCN2; Macrophages do not



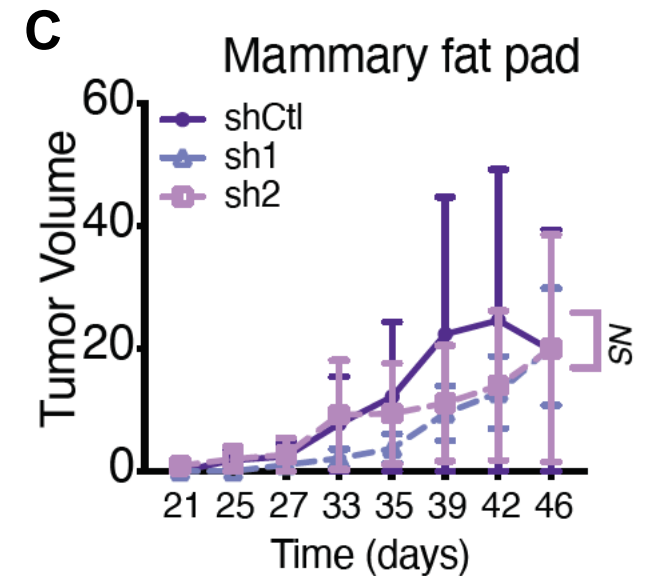
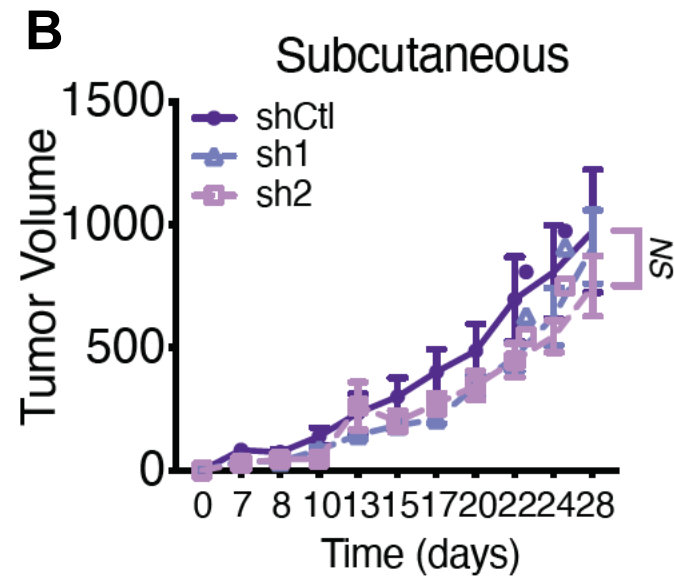
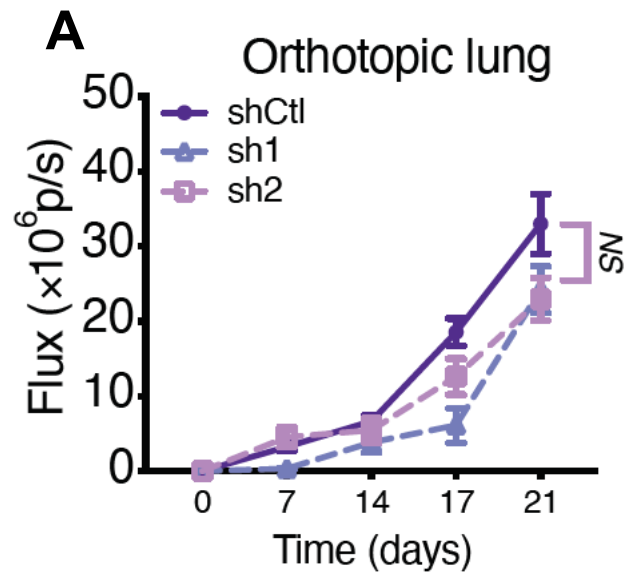
# LCN2 and SLC22A17 is associated with LM in human disease *and* mouse models of LM



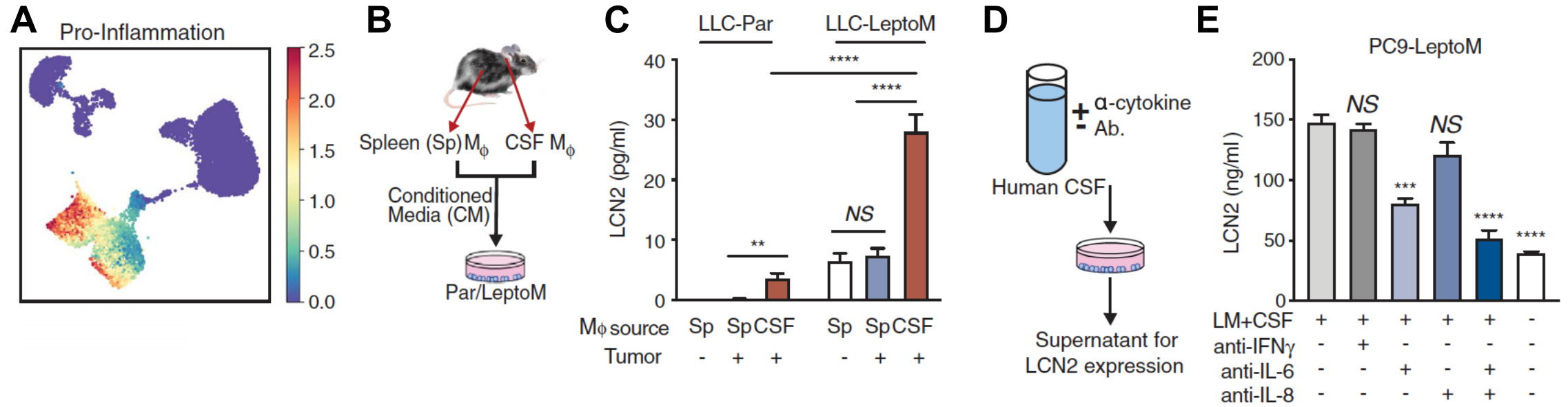
# LCN2 supports cancer cell growth in CSF



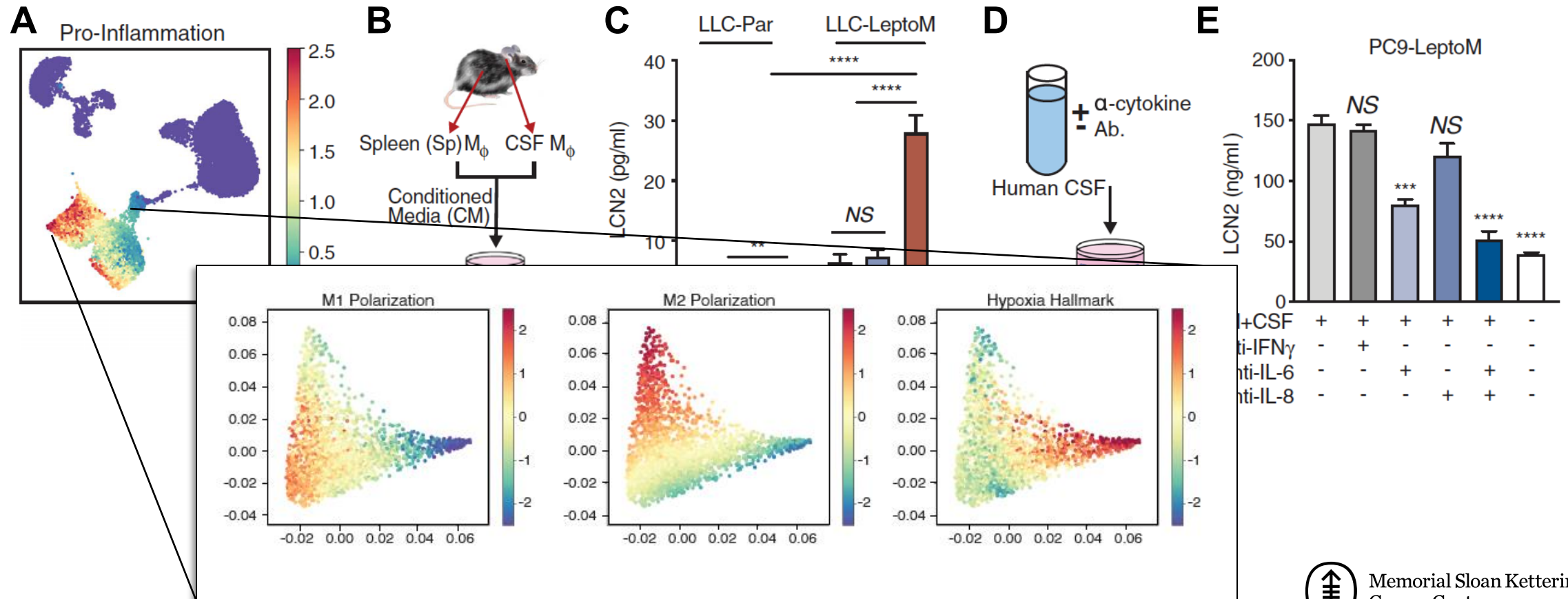
# LCN2 does *not* support cancer cell growth in orthotopic sites



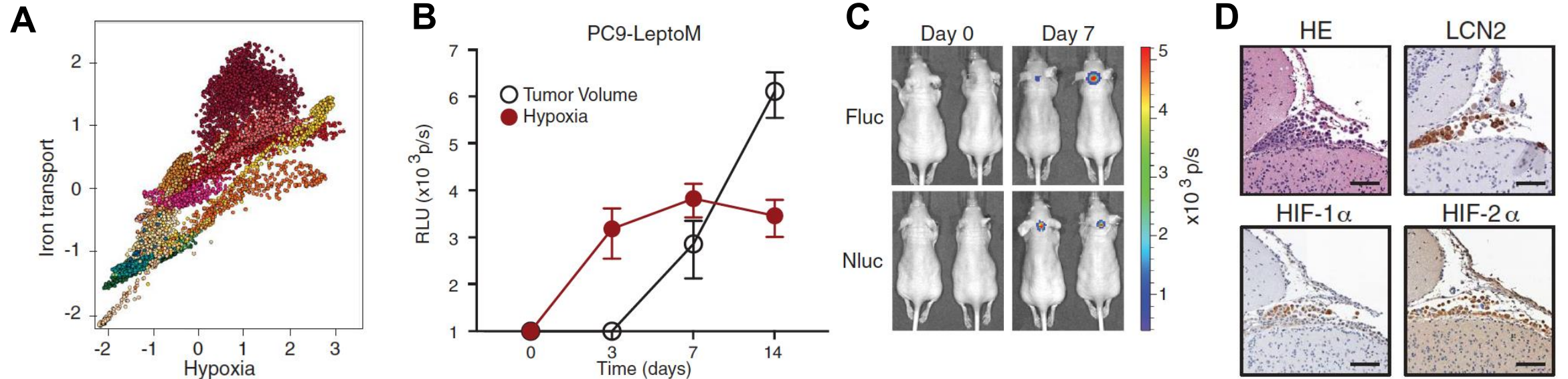
# CSF Macrophage cytokines induce cancer cell LCN2 expression



# CSF Macrophage cytokines induce cancer cell LCN2 expression



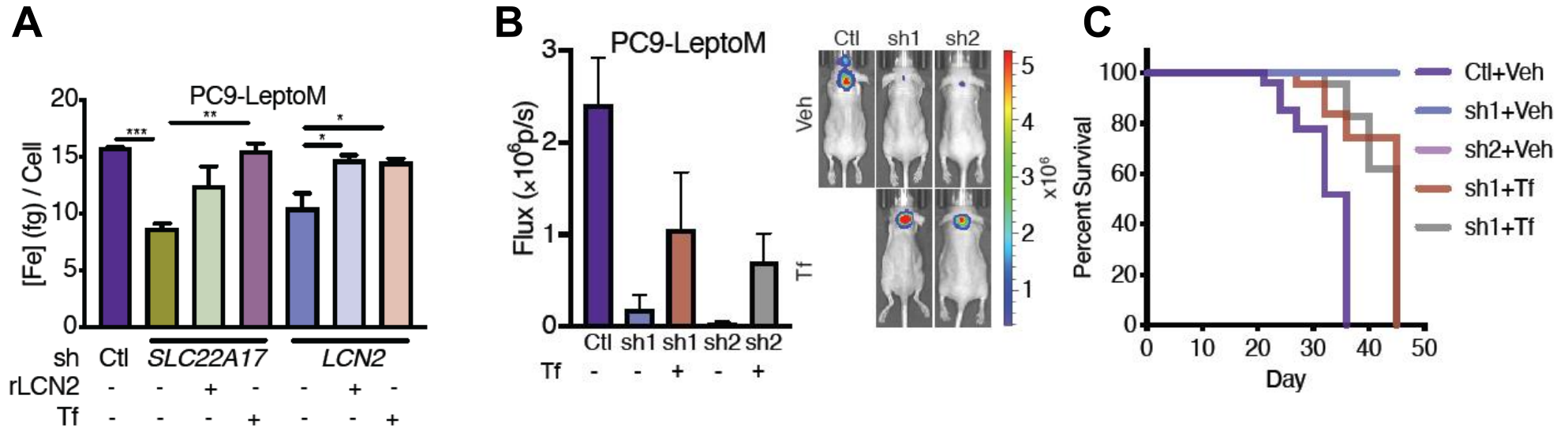
# CSF Macrophage cytokines induce cancer cell LCN2 expression

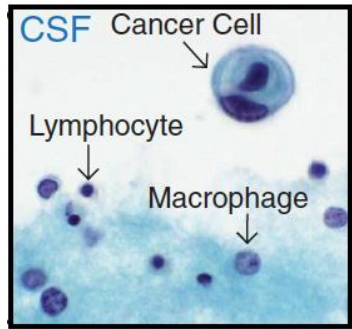




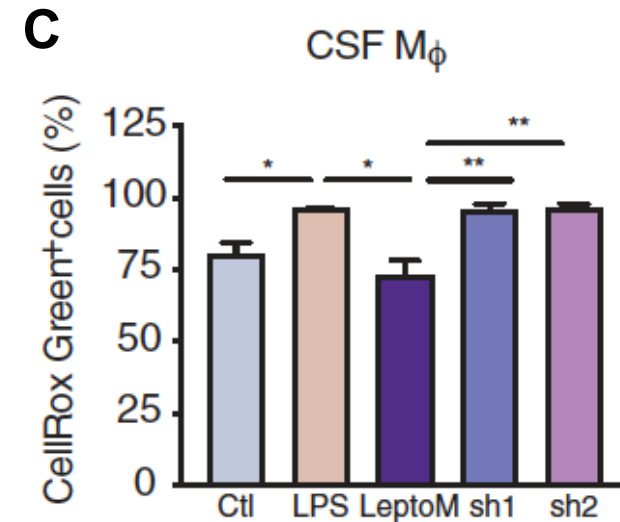
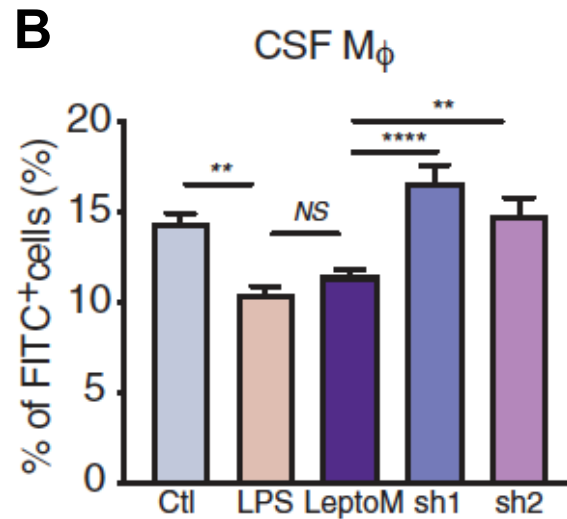
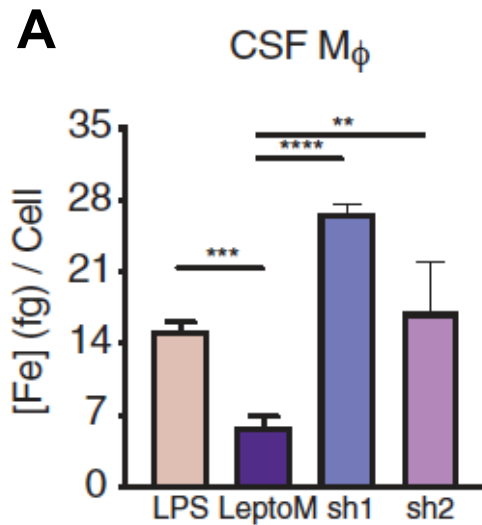
Tiffany Thomas  
(ICP-MS)  
CUMC

# Cancer cells employ Lcn2 to collect extracellular iron

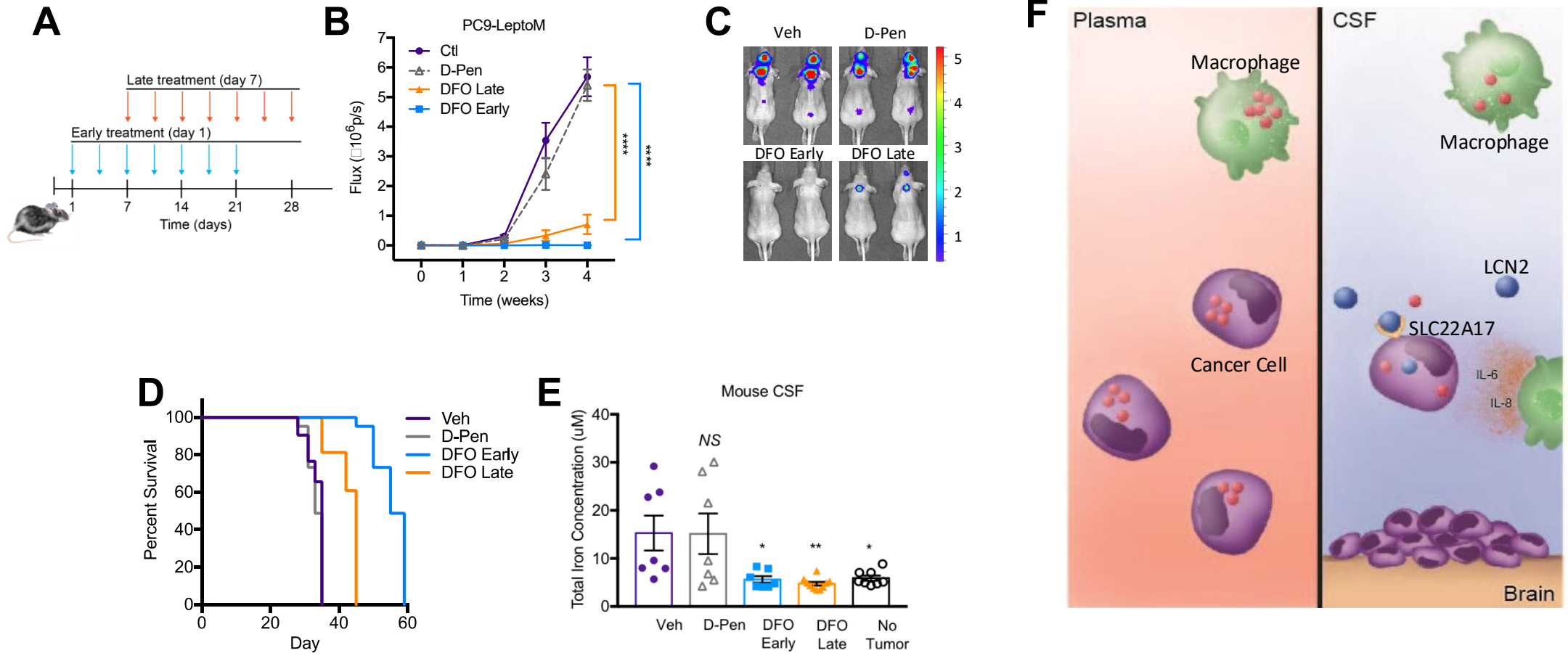




# Cancer cells use LCN2 to outcompete macrophage for extracellular iron



# Iron chelation inhibits cancer cell growth in CSF





Jessica Wilcox

# **NCT05184816:** A Study of Deferoxamine (DFO) in People With Leptomeningeal Metastasis



Open-label, non-randomized, single-center, dose-escalation phase 1a study of IT-DFO in patients with LM from solid tumor malignancies, followed by a phase 1b dose expansion cohort of the RP2D.

# Acknowledgements

## *Our Patients and their Families*



Rachel Estrera  
Francis He  
Lea Doerries

Jenna Snyder  
Xinran Tong  
Morgan Freret

Isaiah Osei-Gyening  
Branavan Manoranjan  
Seogho Son



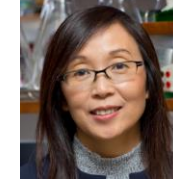
Dana  
Pe'er



Ronan  
Chaligne



Mara  
Monetti



Li  
Gan

### **Current Support:**

Alan and Sandra Gerry Metastasis and Ecosystems Center  
Break Through Cancer  
Canadian Institutes of Health Research  
Druckenmiller Center for Lung Cancer Research  
Experimental Therapeutics Center MSKCC  
Geoffrey Beene Foundation  
Karla Bookman  
Mary Kay Ashley Foundation  
Melanoma Research Alliance  
National Cancer Institute

### **Past Support:**

American Brain Tumor Association  
Anna Fuller Foundation  
Baker Foundation  
Brown Foundation  
Damon Runyon Cancer Research Foundation  
F.M. Kirby Foundation

MSKCC Brain Tumor Center  
Pershing Square Sohn Cancer Research Alliance  
Pew Charitable Trusts  
Society of MSKCC  
Starr Cancer Consortium  
W.M. Keck Foundation