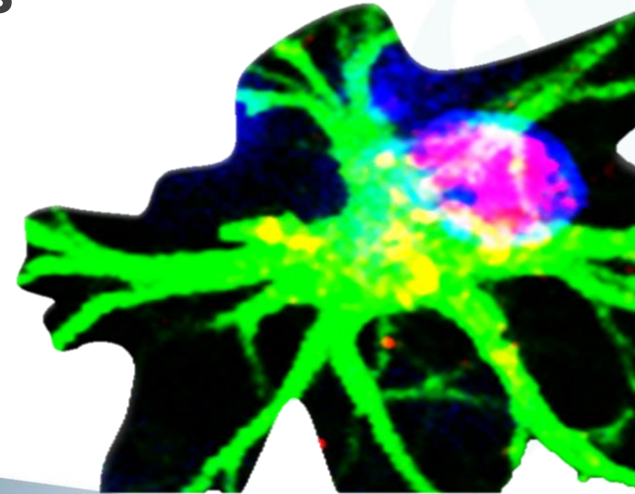


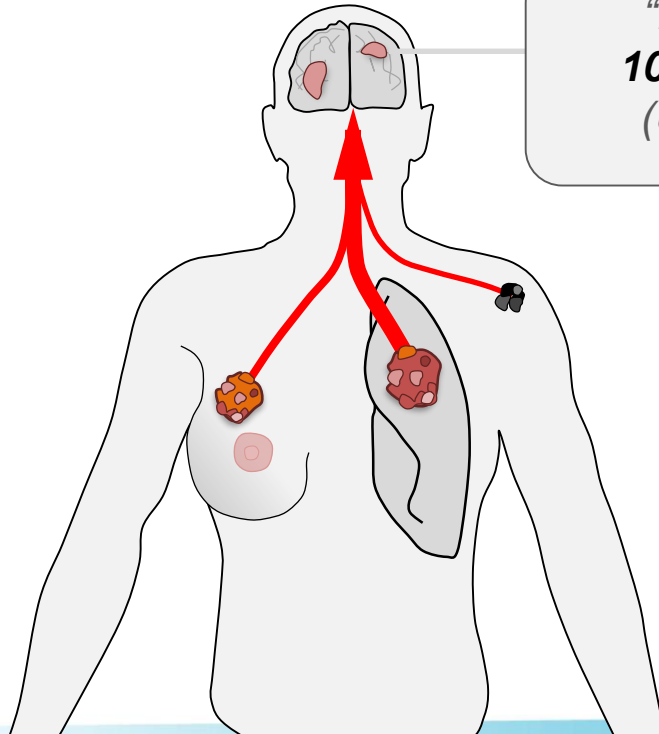
STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis

Neibla Priego
Brain Metastasis Group
Molecular Oncology Programme

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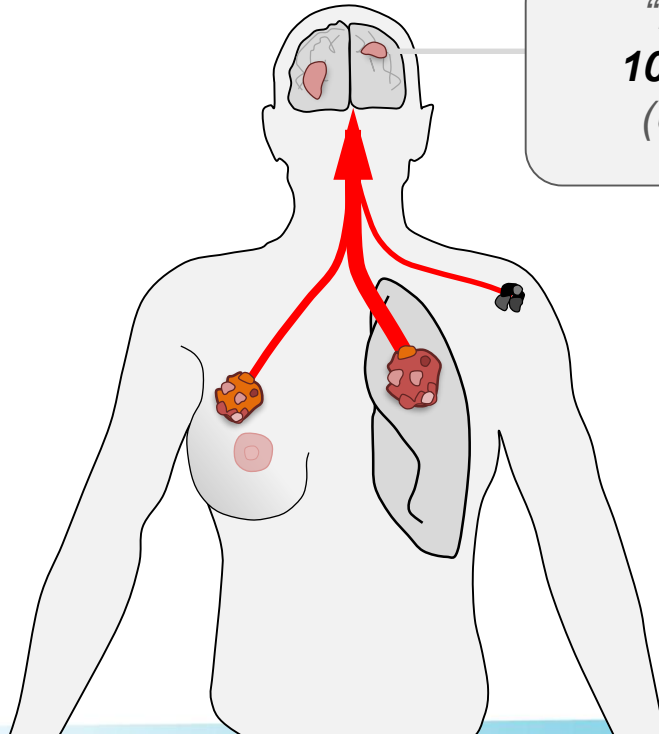


Brain metastases: 2^{ry} brain tumors



*“Brain metastases affect
10-30% of cancer patients”
(Up to 50% in autopsies)*

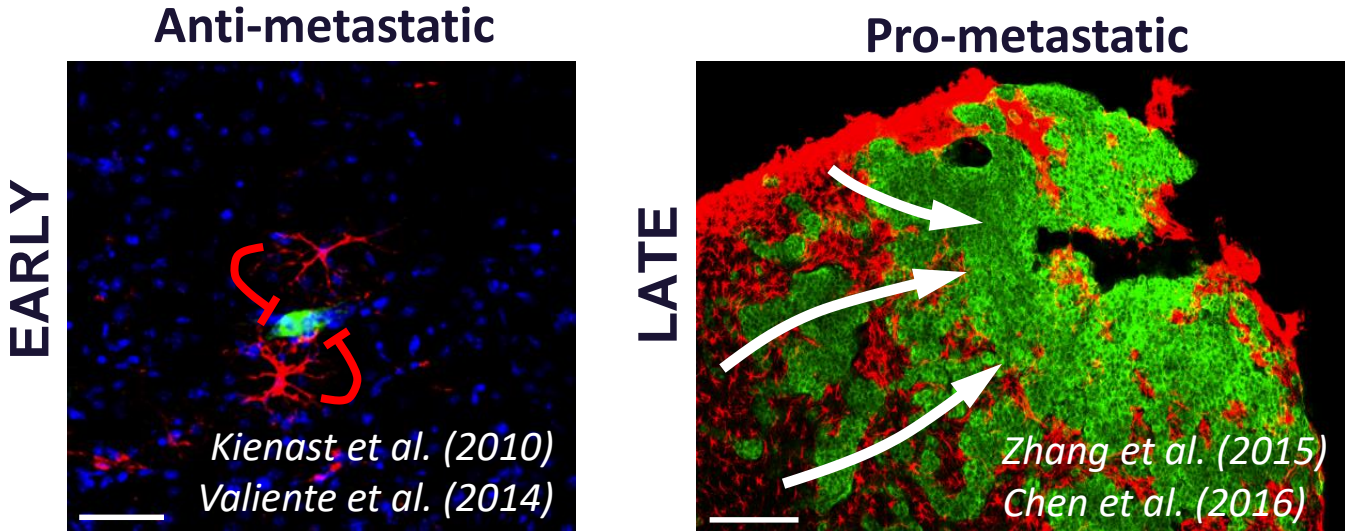
Brain metastases: 2^{ry} brain tumors



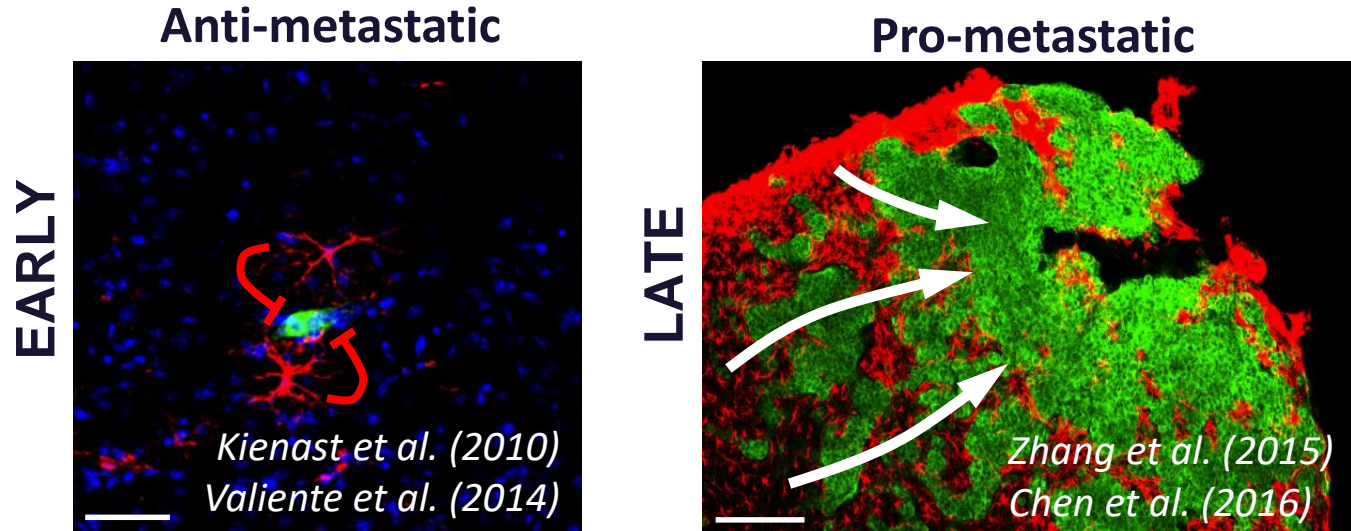
*“Brain metastases affect
10-30% of cancer patients”
(Up to 50% in autopsies)*

- Most **common** cancer in the brain
- **No** effective **treatment**
- Understudied **biology**

Different behavior of the microenvironment during brain colonization in brain metastasis



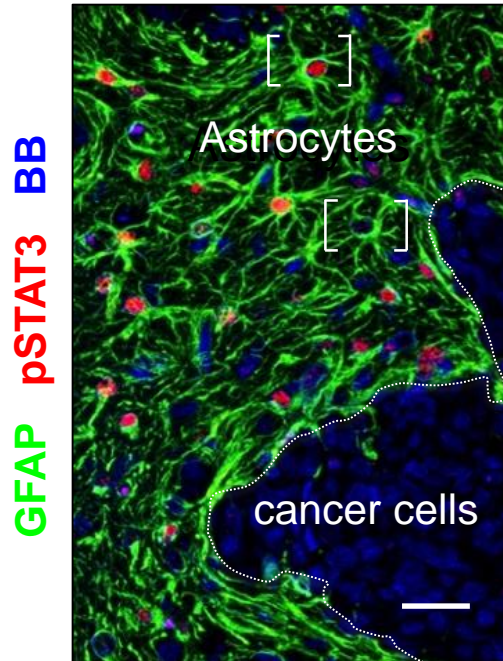
Different behavior of the microenvironment during brain colonization in brain metastasis



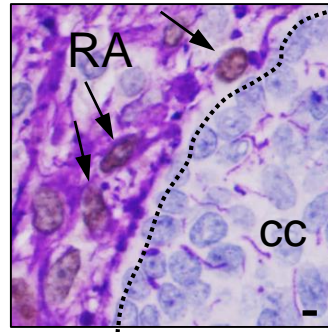
Brain metastatic cells alter molecular patterns in the brain microenvironment creating a permissive niche

pSTAT3+ reactive astrocytes (RA) are present in experimental models and human brain metastasis

H2030-BrM

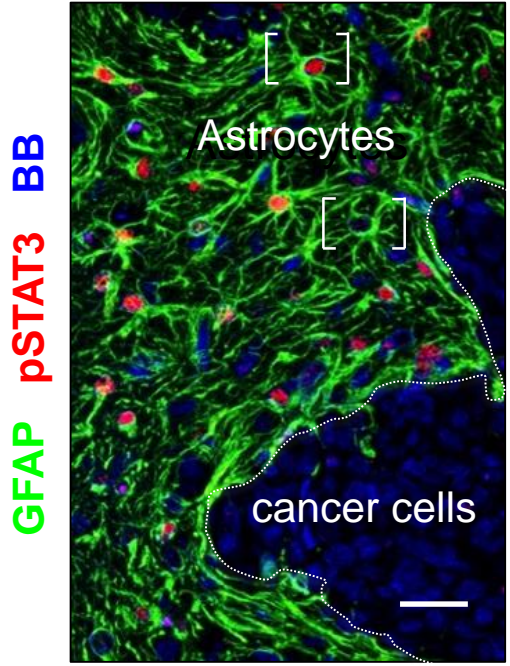


Human brain met.

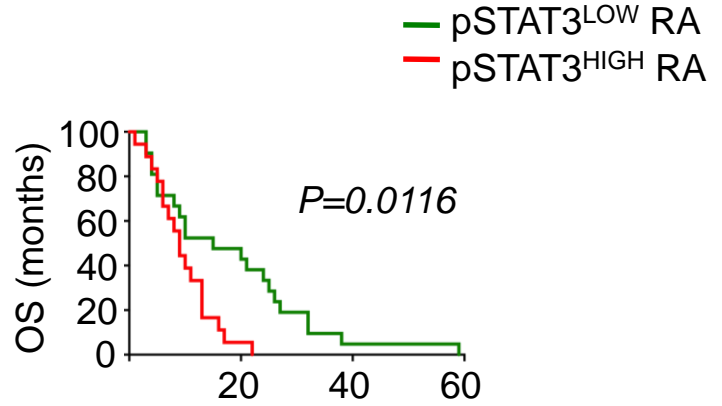
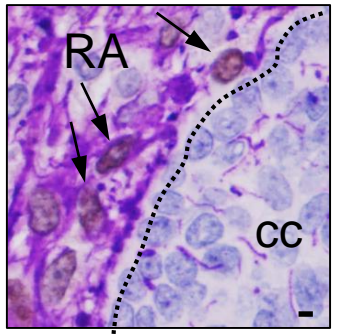


pSTAT3+ reactive astrocytes (RA) are present in experimental models and human brain metastasis

H2030-BrM



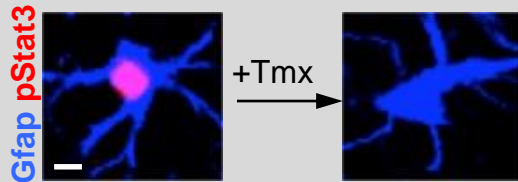
Human brain met.



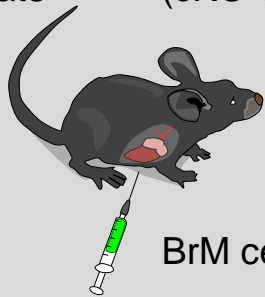
Priego et al. Nat Med.(2018)



GENETIC

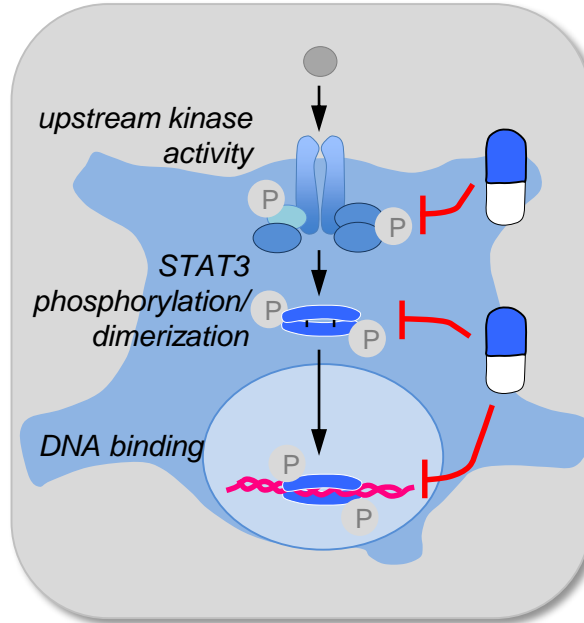


GFAP-CRE/ERT2;
Stat3^{loxP/loxP} (cKO-Stat3)



BrM cells

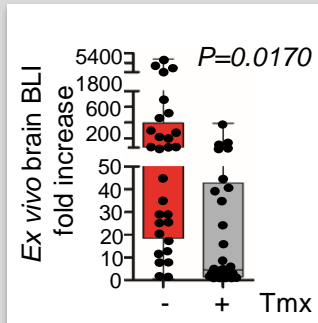
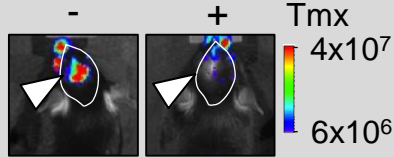
PHARMACOLOGY





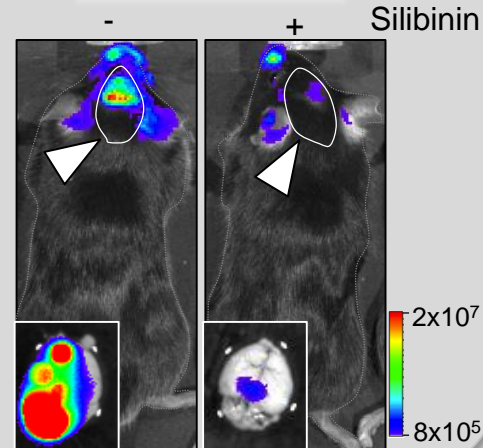
GENETIC

GFAP-CRE/ERT2;
Stat3^{loxP/loxP} (cKO-Stat3)



PHARMACOLOGY

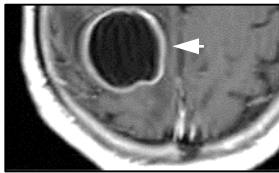
pSTAT3



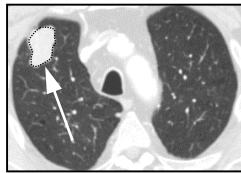
Silibinin treatment in human patients with BrM

18 Stage IV lung cancer
Compassionate use of Silibinin
Other therapies

Pre-Silibinin

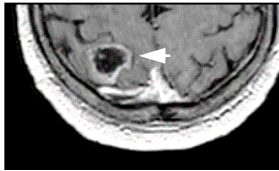


Brain

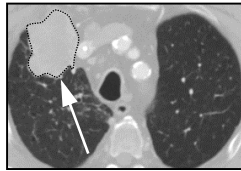


Primary

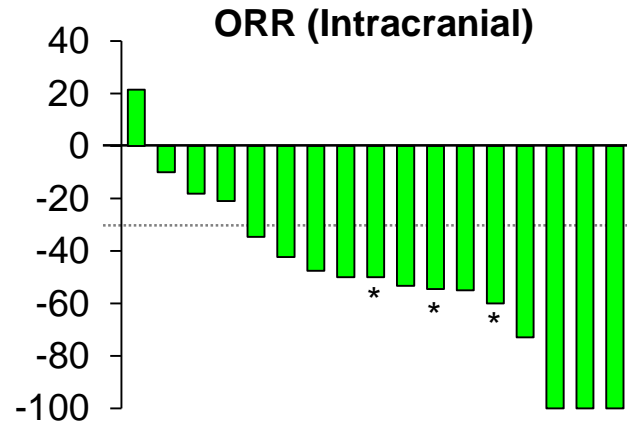
Post-Silibinin (+16m)



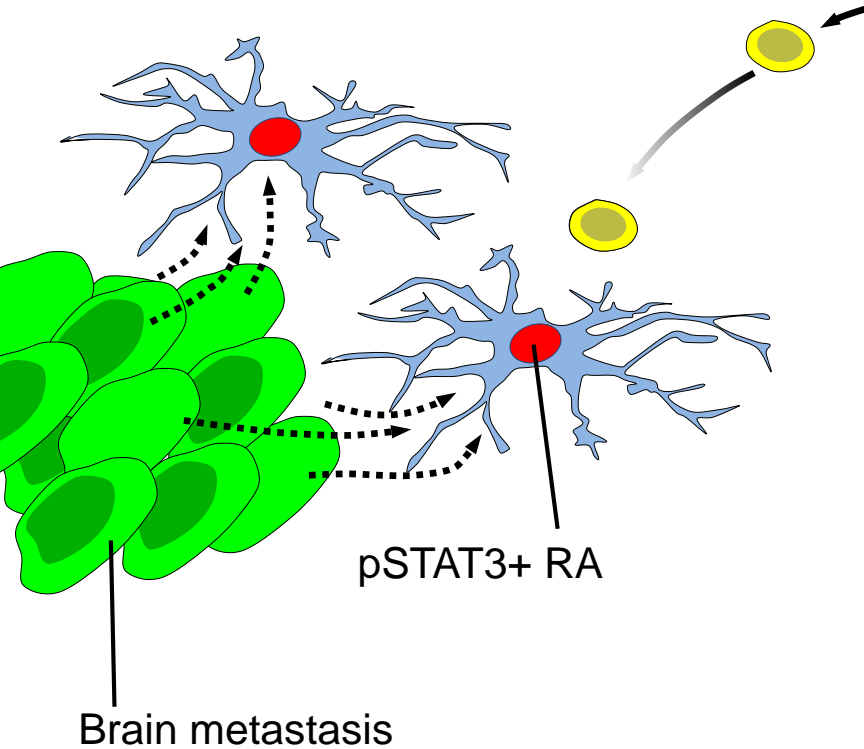
Brain



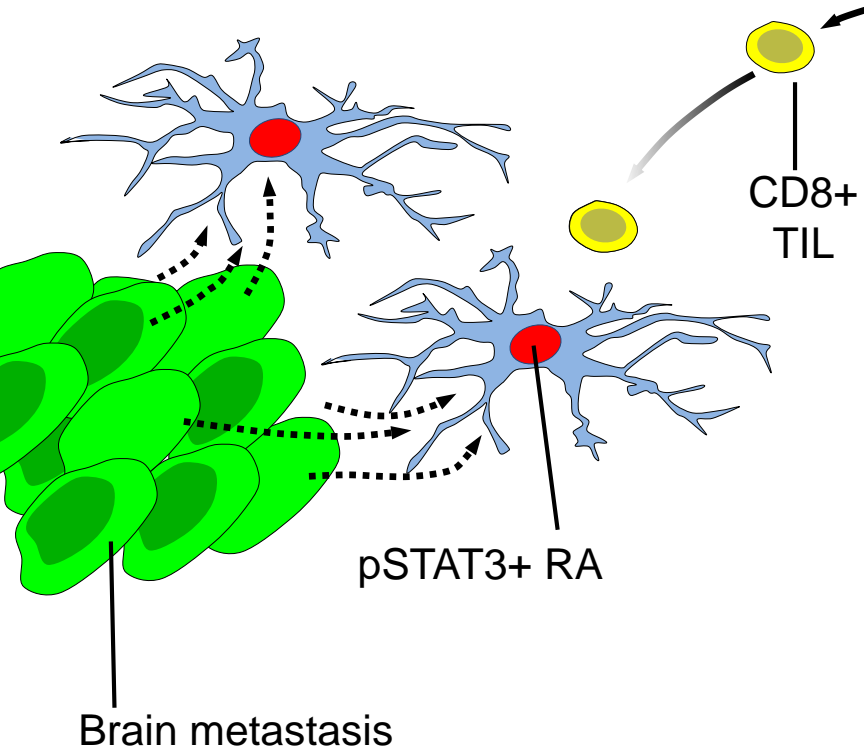
Primary



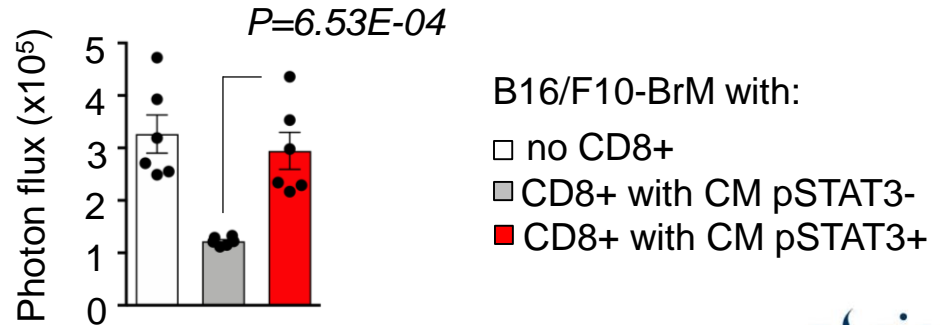
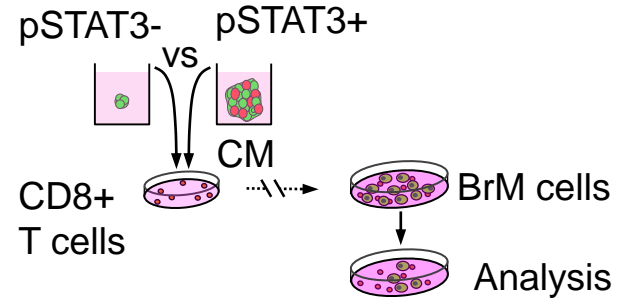
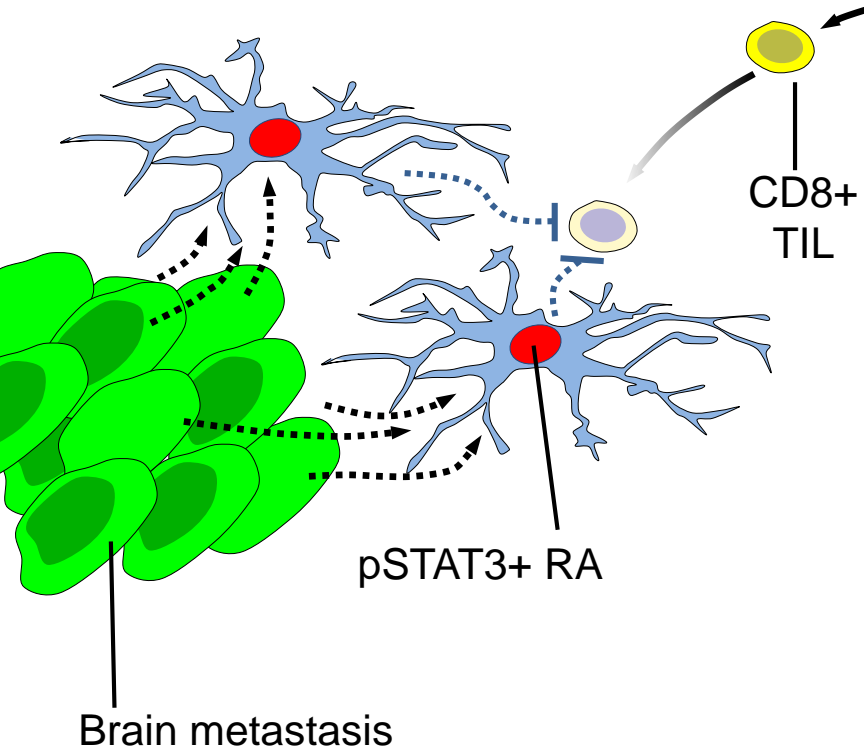
Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?



Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?

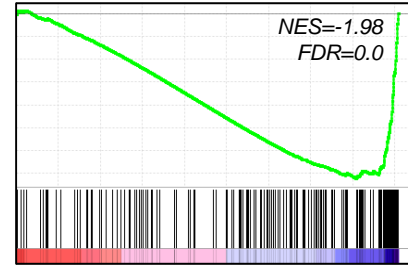
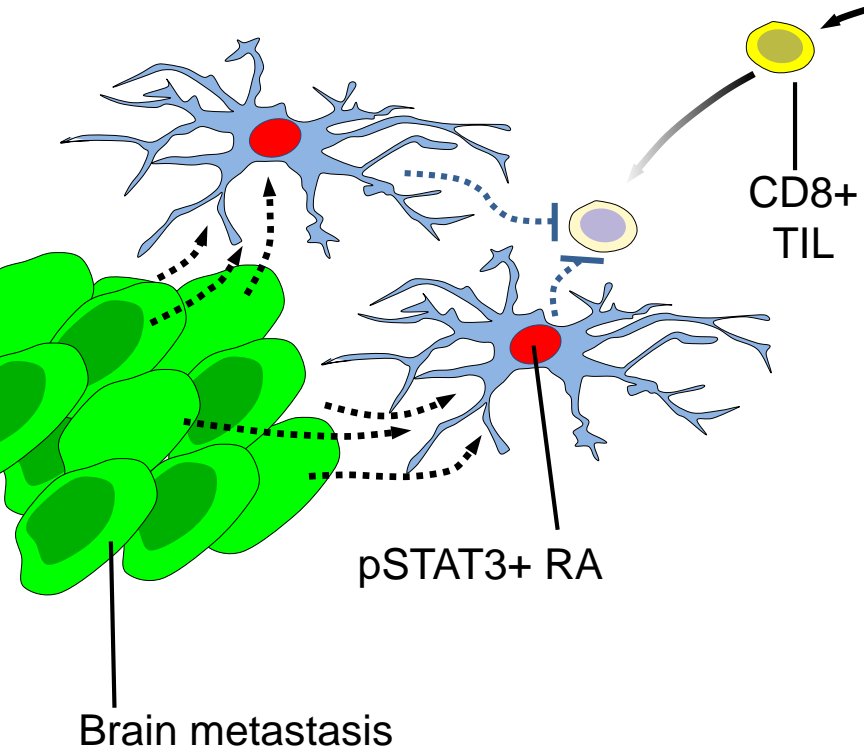


Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?



Priego et al. Nat Med.(2018)

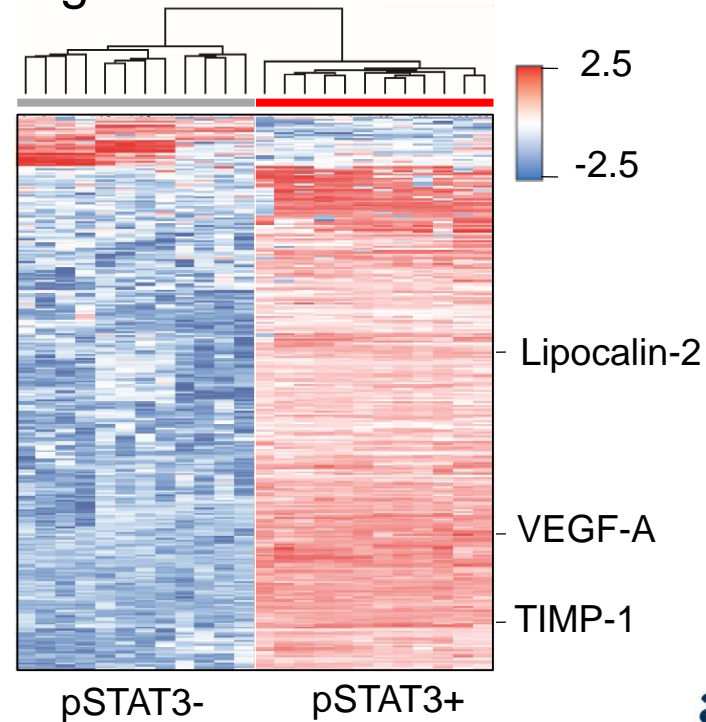
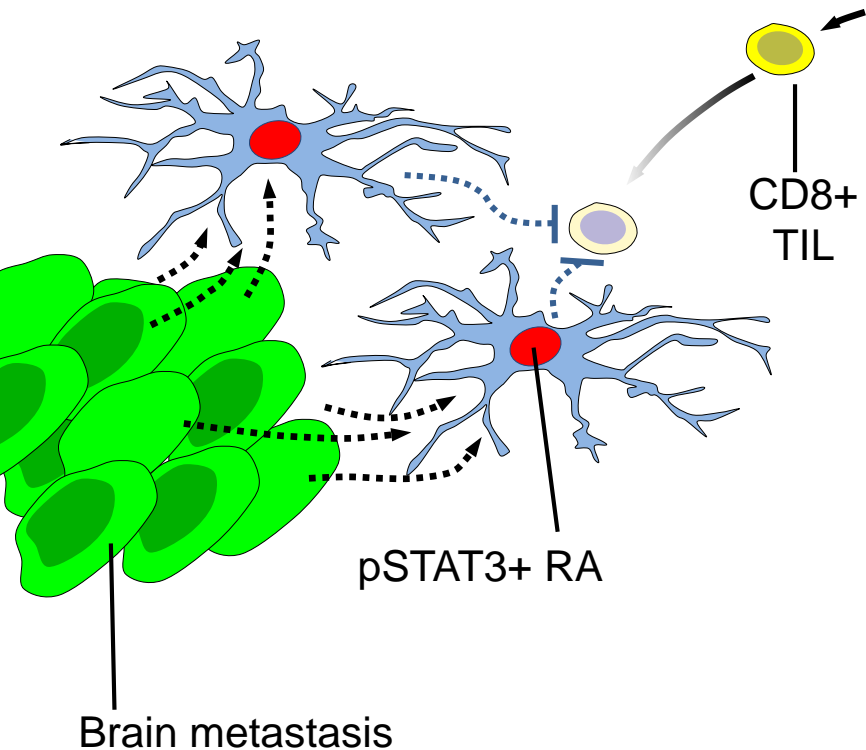
Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?



NAME	NES	p-value	
		NOM	FDR
IMMUNE_RESPONSE	-1.98	0	0
IMMUNE_SYSTEM_PROCESS	-1.88	0	0
HUMORAL_IMMUNE_RESPONSE	-1.84	0	0
ADAPTIVE_IMMUNE_RESPONSE_GO_0002460	-1.63	0.001	0.007
IMMUNE_EFFECTOR_PROCESS	-1.49	0.018	0.065
PROD._OF_MOL._MED._OF_IMMUNE_RESP.	-1.47	0.032	0.072
IMMUNE_SYSTEM_DEVELOPMENT	-1.45	0.018	0.078
REGULATION_OF_IMMUNE_RESPONSE	-1.43	0.044	0.089
POSITIVE_REG._OF_IMMUNE_SYS._PROCESS	-1.36	0.053	0.152
REGULATION_OF_IMMUNE_SYSTEM_PROCESS	-1.35	0.045	0.139
REGULATION_OF_IMMUNE_EFFECTOR_PROCESS	-1.27	0.158	0.246

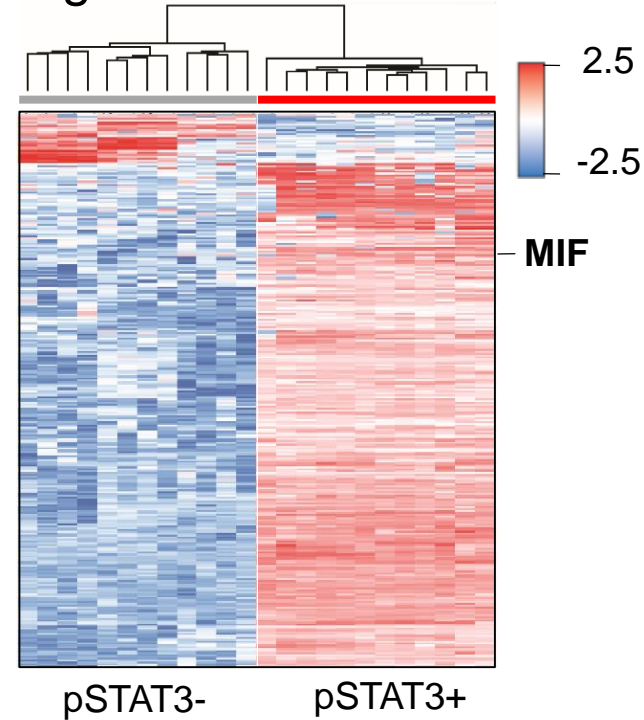
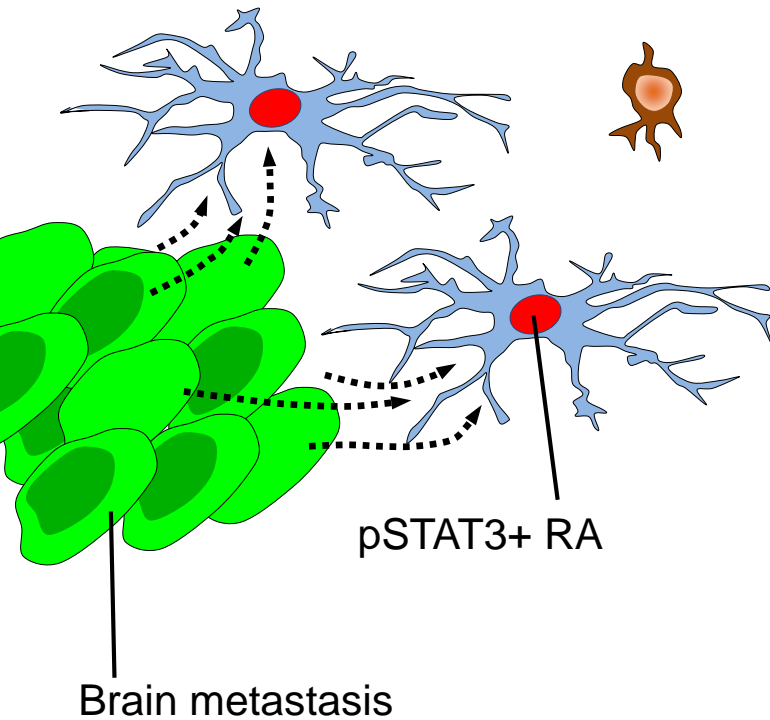
Unpublished data

Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?



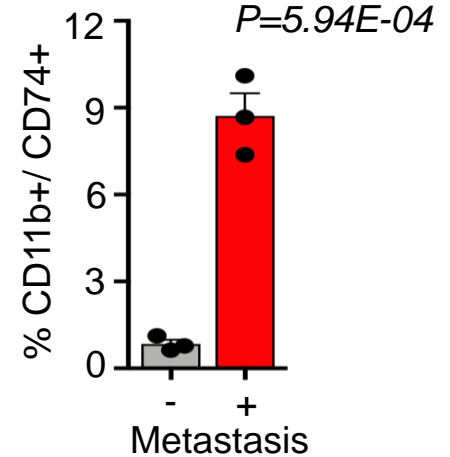
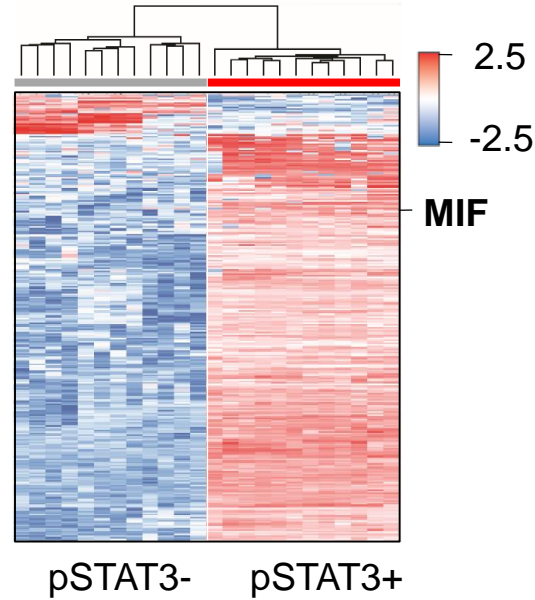
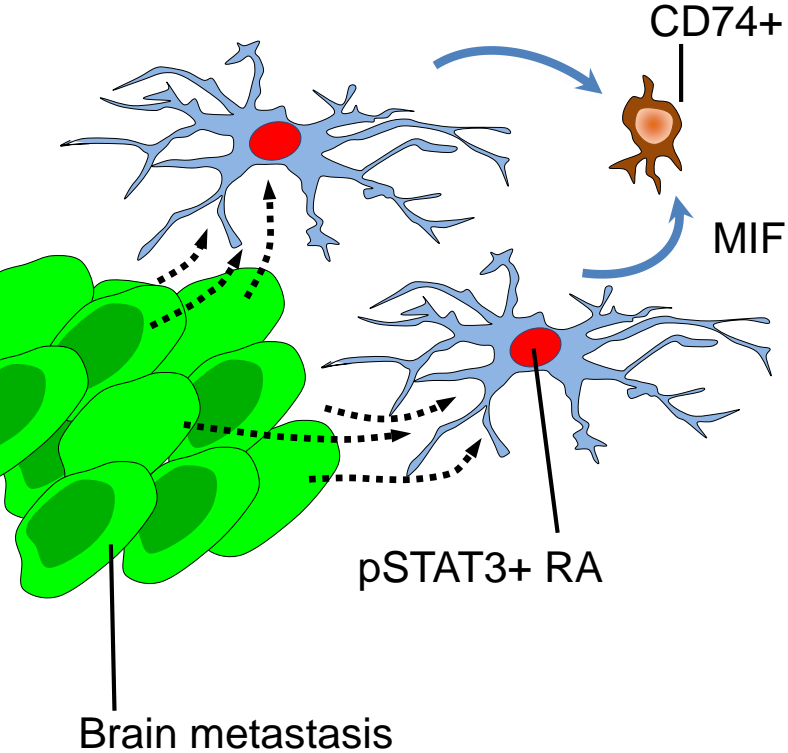
Priego et al. Nat Med. (2018)

Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?



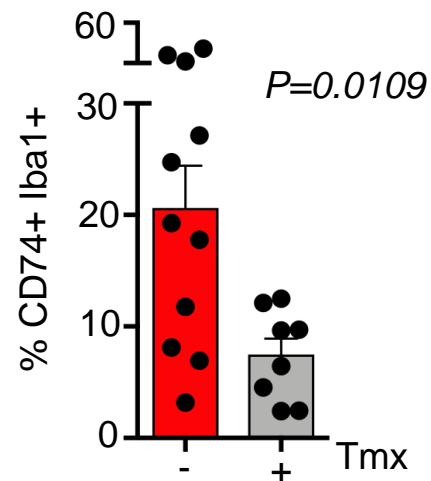
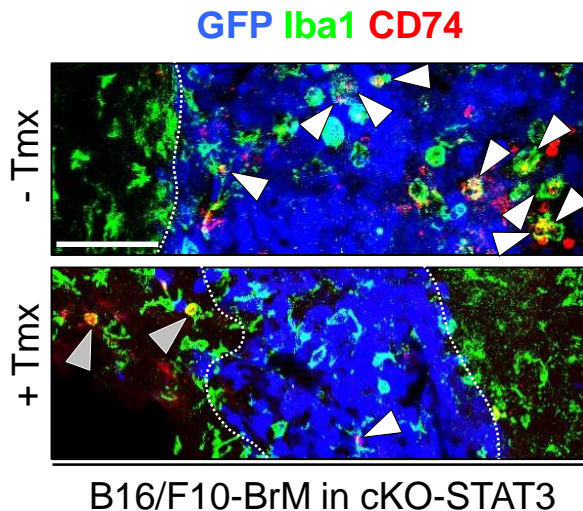
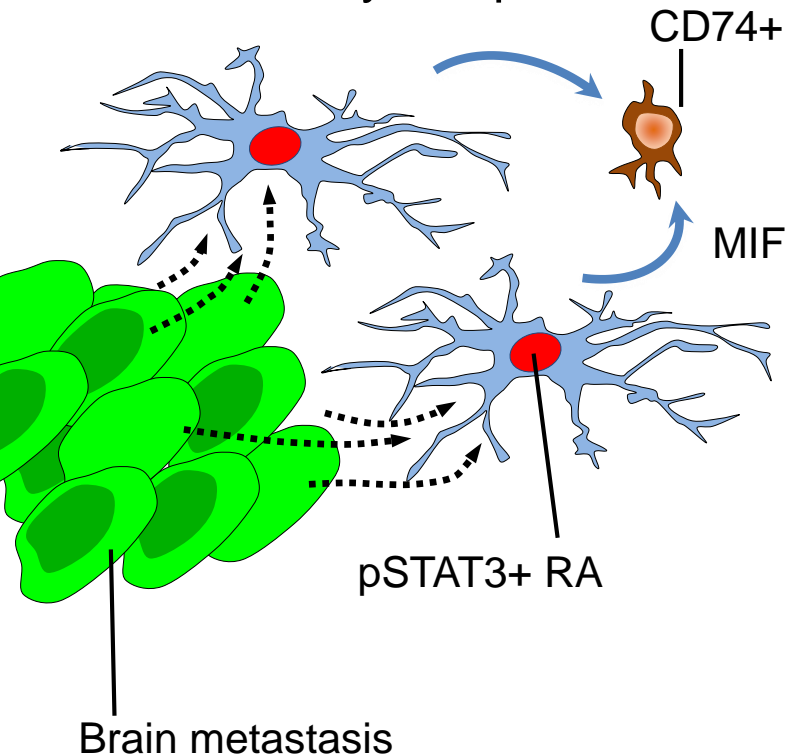
Priego et al. Nat Med.(2018)

Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?

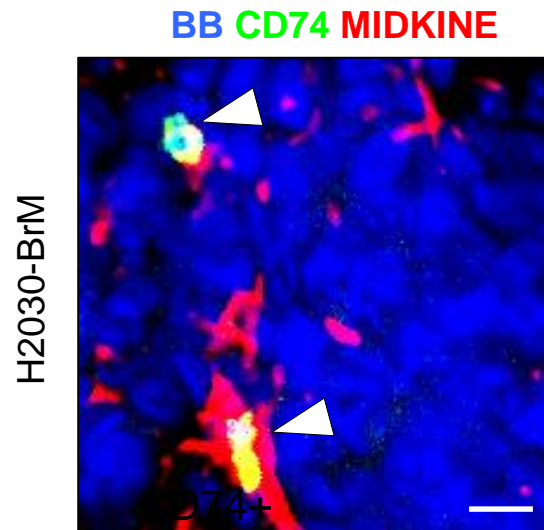
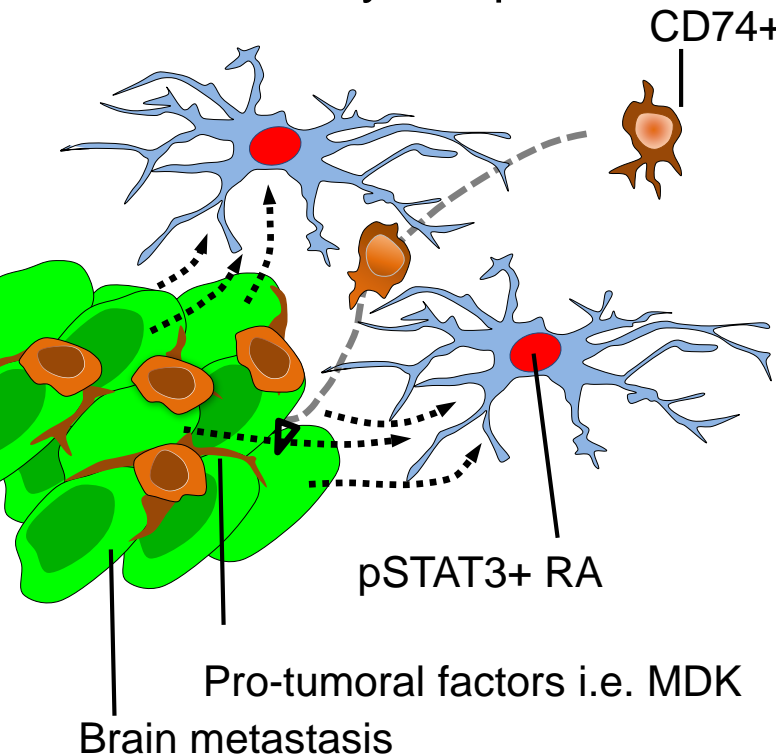


Priego et al. Nat Med.(2018)

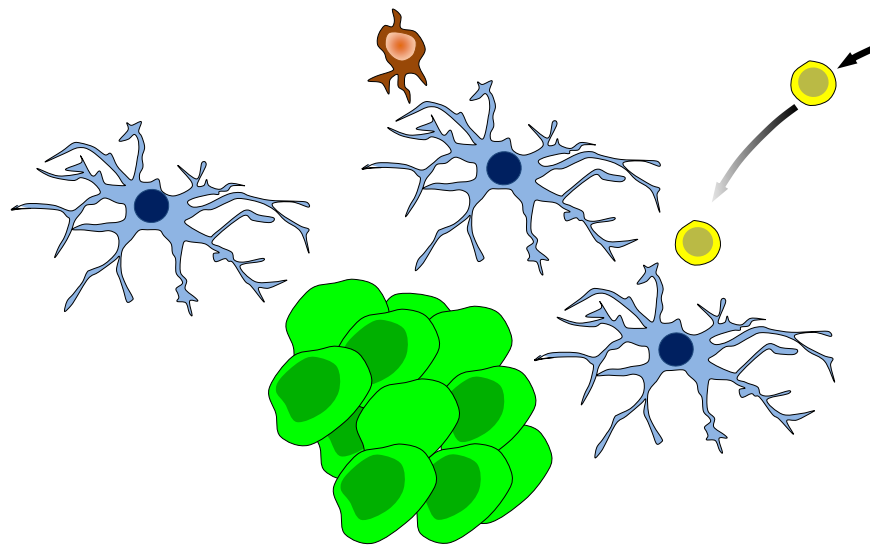
Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?



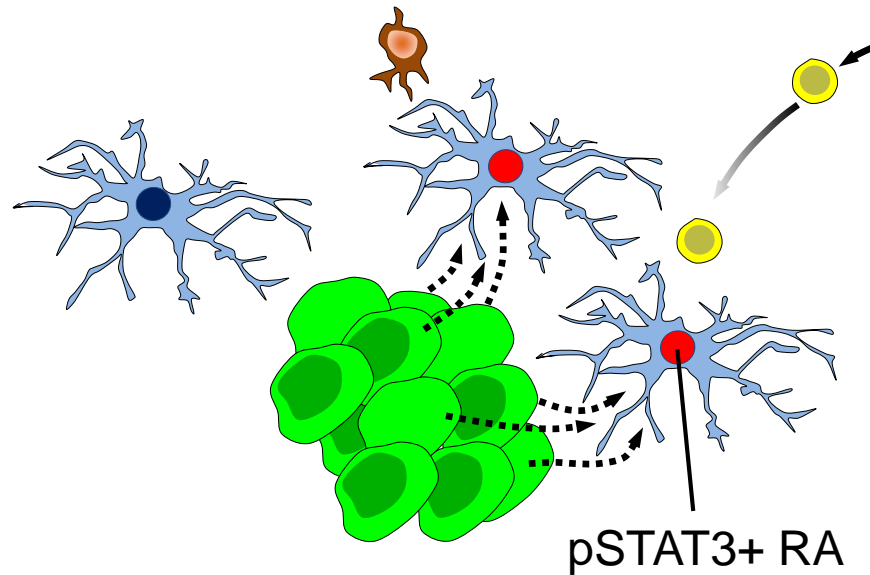
Why are pSTAT3+ RA pro-tumorigenic in brain metastasis?



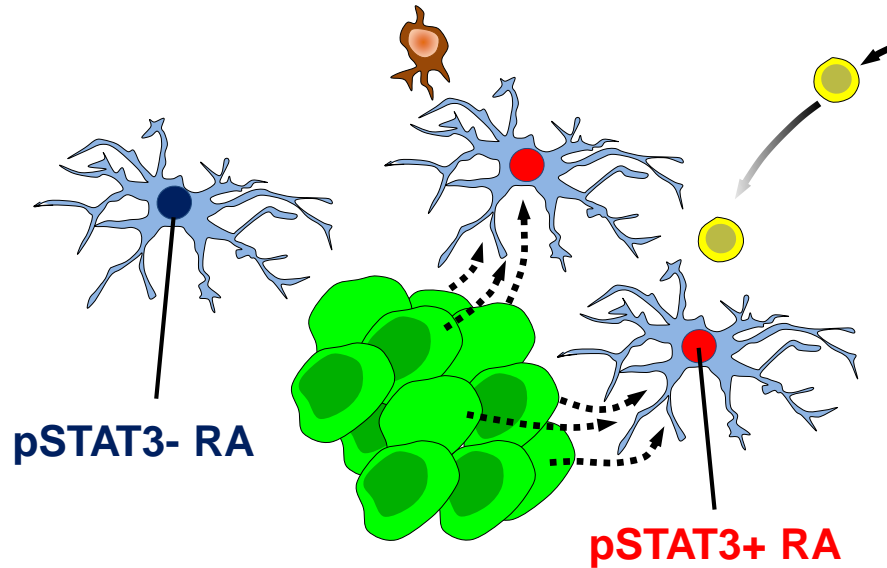
Priego et al. Nat Med.(2018)



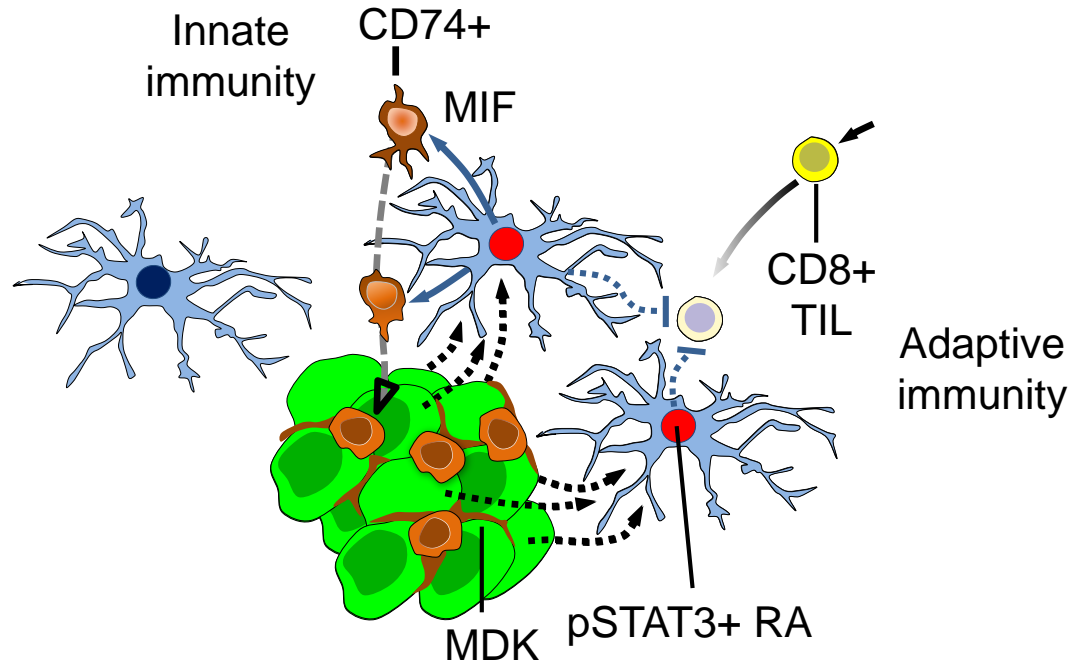
Brain metastatic cells alter molecular patterns in the brain microenvironment



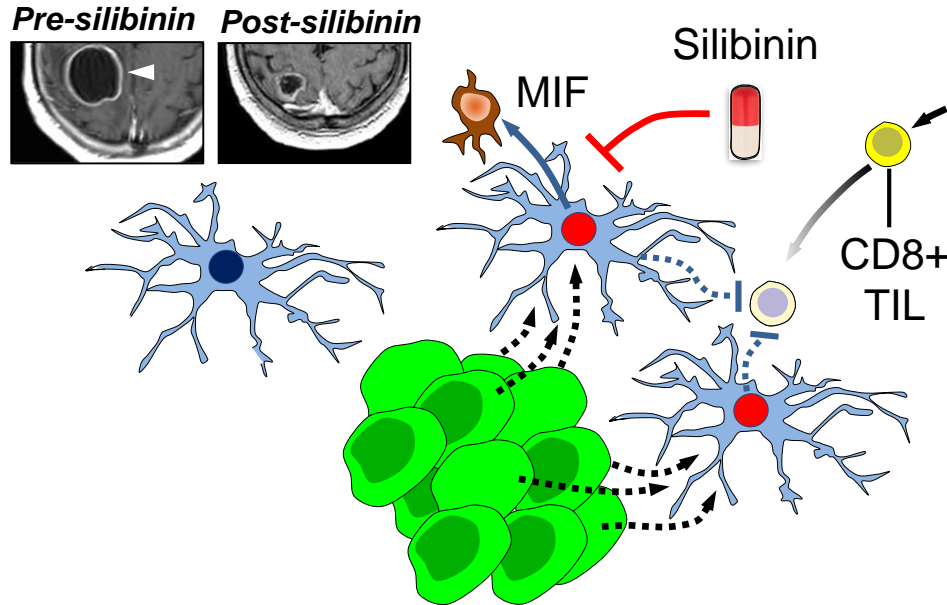
Heterogeneity within the metastasis-associated microenvironment



pSTAT3+ RA act as regulators of local immunosuppression in brain metastasis



Altered signaling pathways in pro-metastatic RA as a novel therapeutic application for brain metastasis





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Cátia Monteiro

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Manuel Pérez

Javier Muñoz

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Isabel Blanco

Fatima Al-Shahrour

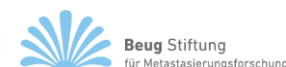
Coral Fustero

Elena Pineiro

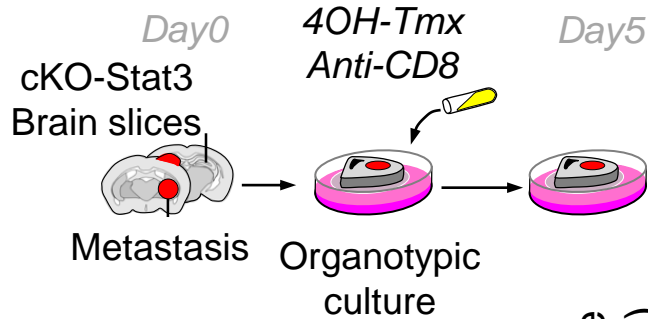


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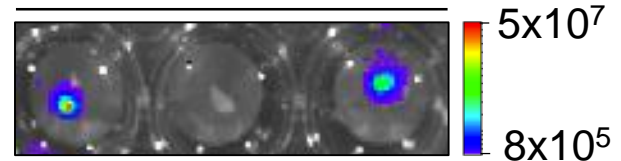
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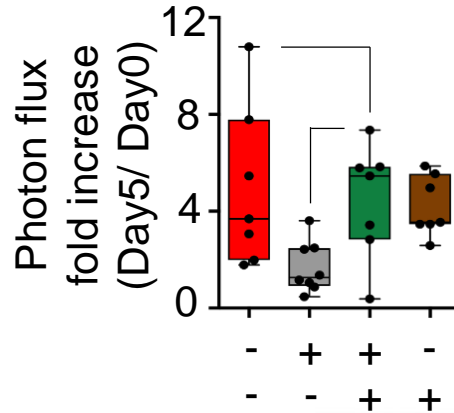
Brain metastasis burden *ex vivo* upon genetic deletion of Stat3 in RA is rescued with anti-CD8 blocking antibody



B16/F10-BrM mets
in cKO-Stat3 br slices

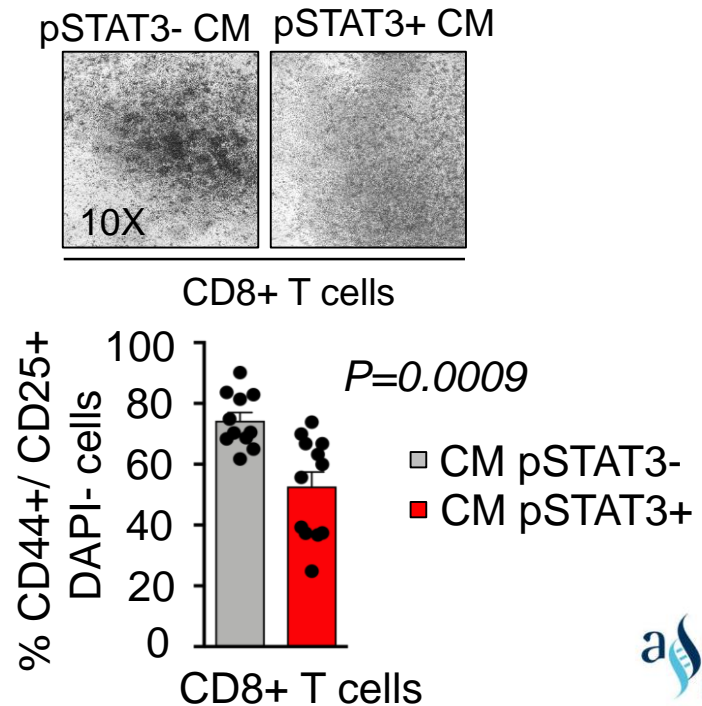
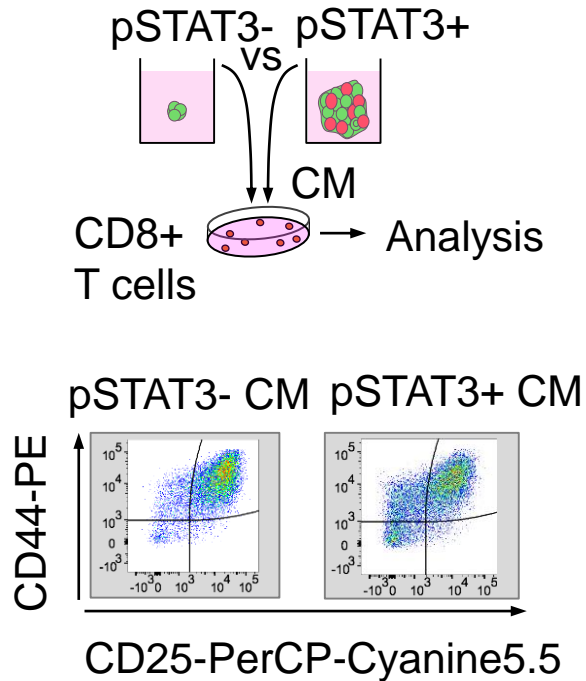


- + + 4OH-Tmx
- - + αCD8+

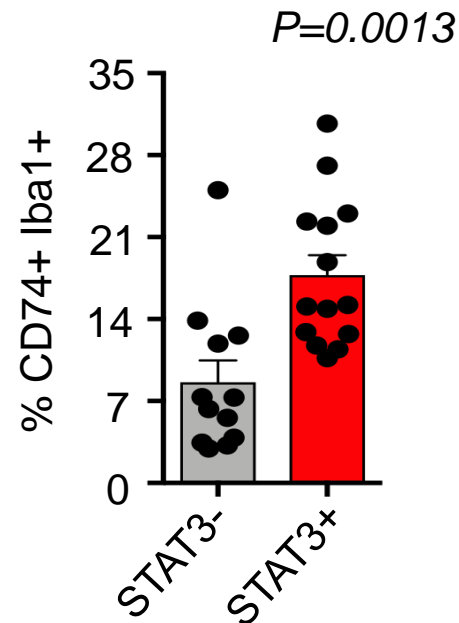
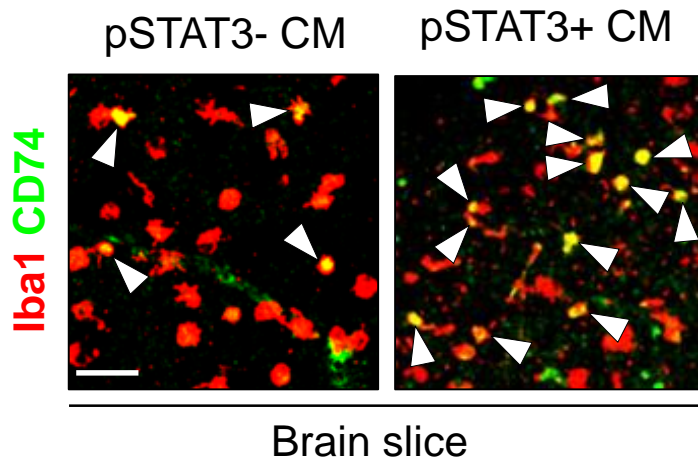
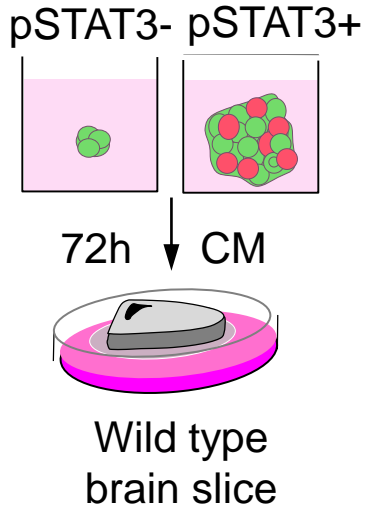


$P=0.7531$
 $P=0.0103$

Secretome of pSTAT3+ RA is sufficient to decrease CD8+ T cell activation *in vitro*

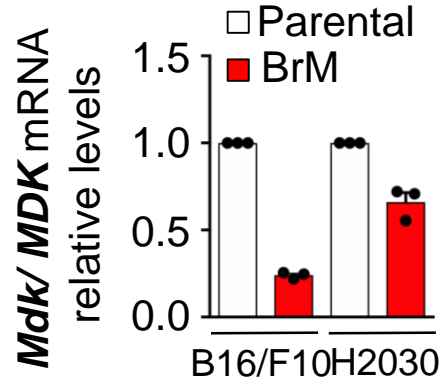


Effect on microglia/macrophages



CD74+/Iba1+ microglia/ macrophage population increases in the presence of conditioned media derived from pSTAT3+ astrospheres

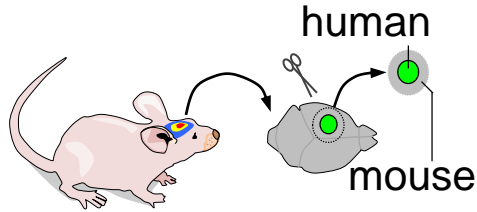
CD74 modulates Midkine expression



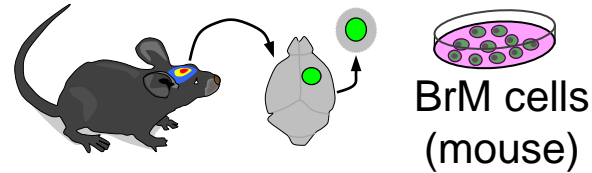
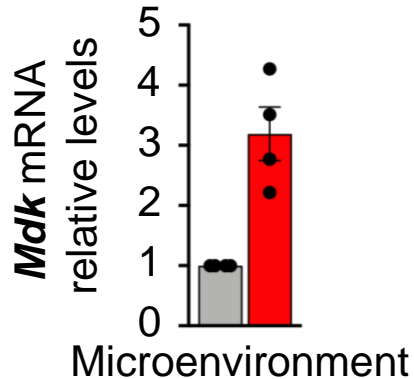
Cancer cells down-regulate Midkine levels in brain metastasis

Are Midkine levels from the **microenvironment** relevant for brain metastasis?

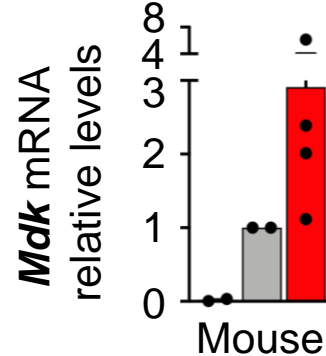
Microglial Midkine is up-regulated in brain metastasis



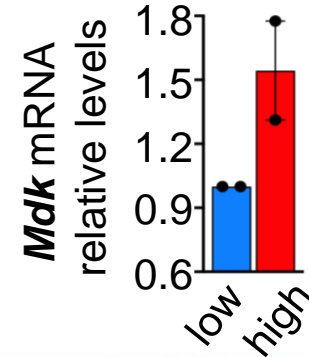
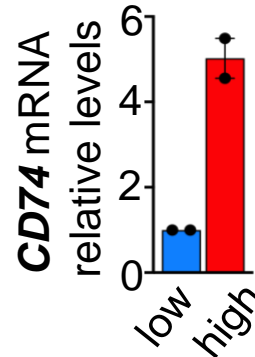
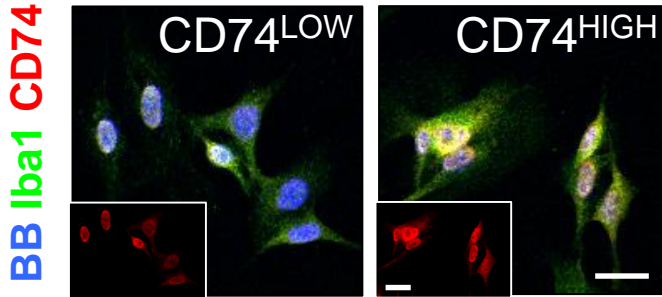
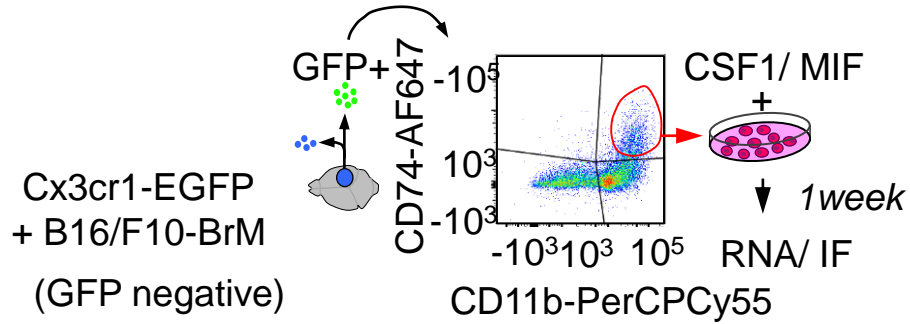
□ No mets.
■ H2030-BrM



■ B16/F10-BrM (*in vitro*)
□ No mets.
■ B16/F10-BrM



Microglial CD74 and Midkine levels correlate in CD74+ cells isolated from a BrM mouse model *in vivo*



Targeting MIF/CD74 axis decreases brain metastasis *ex vivo*

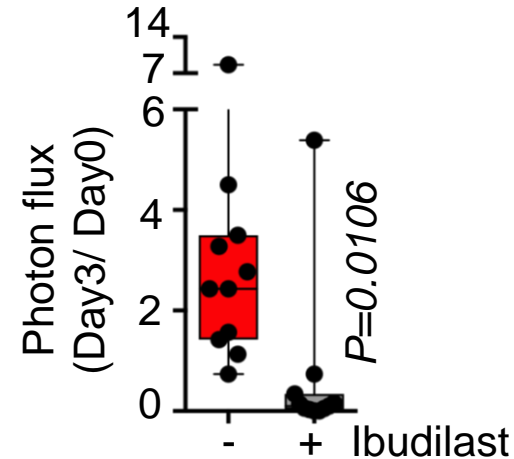
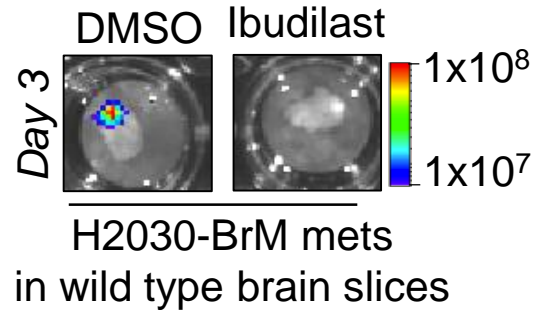
[Neuro Oncol.](#) 2014 Jul; 16(Suppl 3): iii4-iii5.
doi: [10.1093/neuonc/nou206.15](#)

PMCID: PMC4144479

MIF-CD74 GUIDED THERAPEUTIC STRATEGY FOR THE UPFRONT TREATMENT OF GBM PATIENTS WITH AN UNMETHYLATED MGMT PROMOTER

[Kerrie L McDonald](#), PhD, [Wendy Ha](#), and [Hatice Sevim](#)

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Targeting MIF/CD74 axis decreases brain metastasis *ex vivo*

