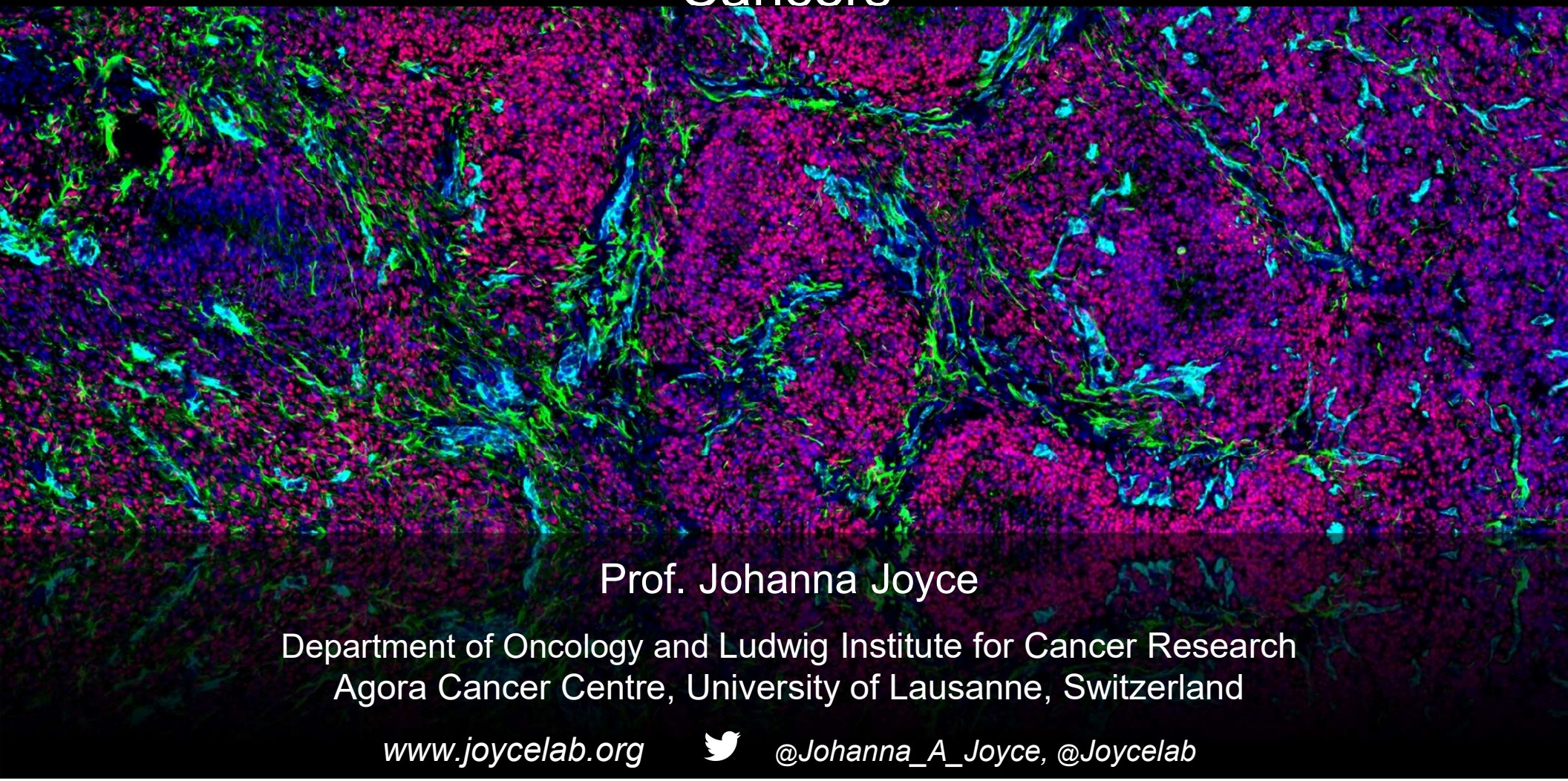
Exploring and Exploiting the Immune Landscape in Brain Cancers



Prof. Johanna Joyce

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Agora Cancer Centre, University of Lausanne, Switzerland

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Disclosure Information (2015-2020)

I have the following disclosures to list:

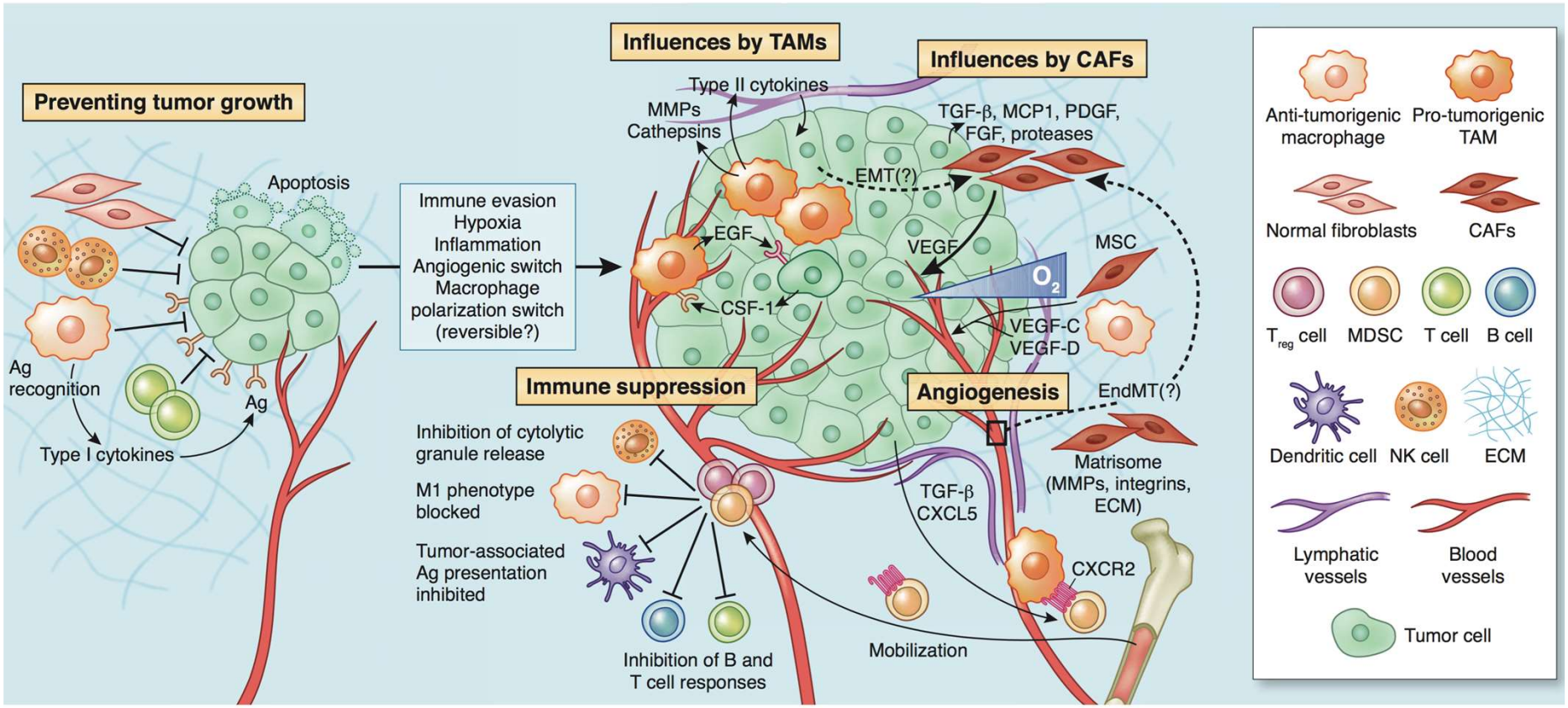
Grant support: Roche (2016-18)

Speaker Honorarium- Novartis (2016)

Speaker Honorarium- Glenmark Pharmaceuticals (2019)

Consulting Honorarium- Ono Pharmaceuticals (2015)

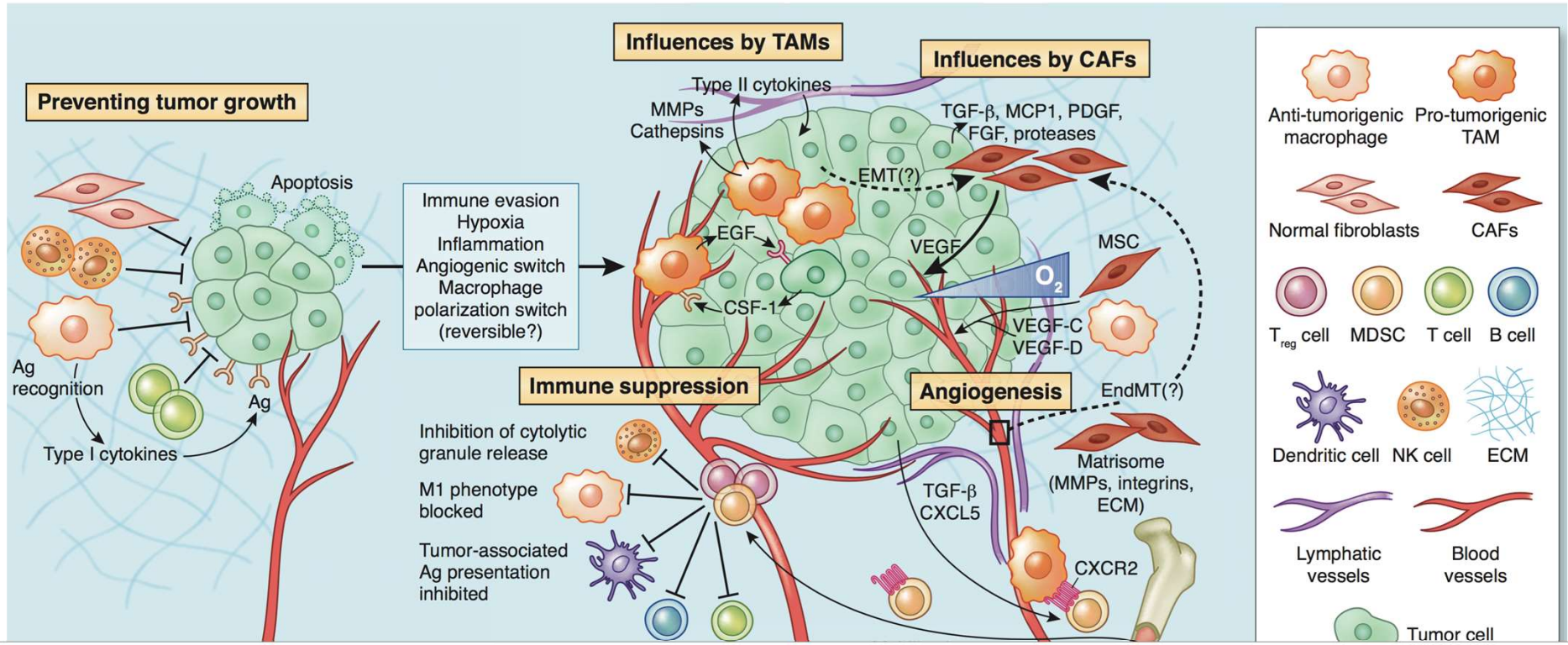
Diverse Cell Types in the Tumor Microenvironment Regulate Cancer Progression



Adapted from:
Quail & Joyce, *Nature Medicine* (2013)
Quail & Joyce, *Nature Reviews Cancer* (2017)

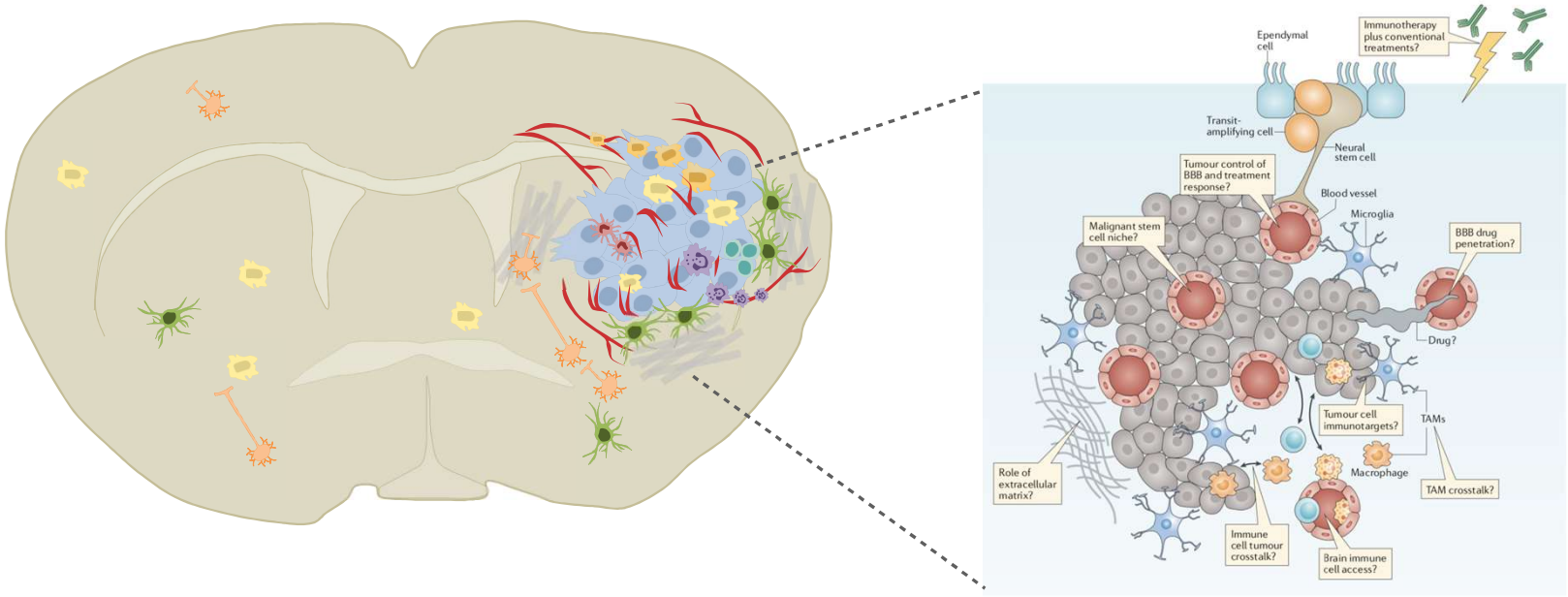
TAM: Tumor-associated macrophage
CAF: Cancer-associated fibroblast

Rationale for Therapeutically Targeting the Tumor Microenvironment



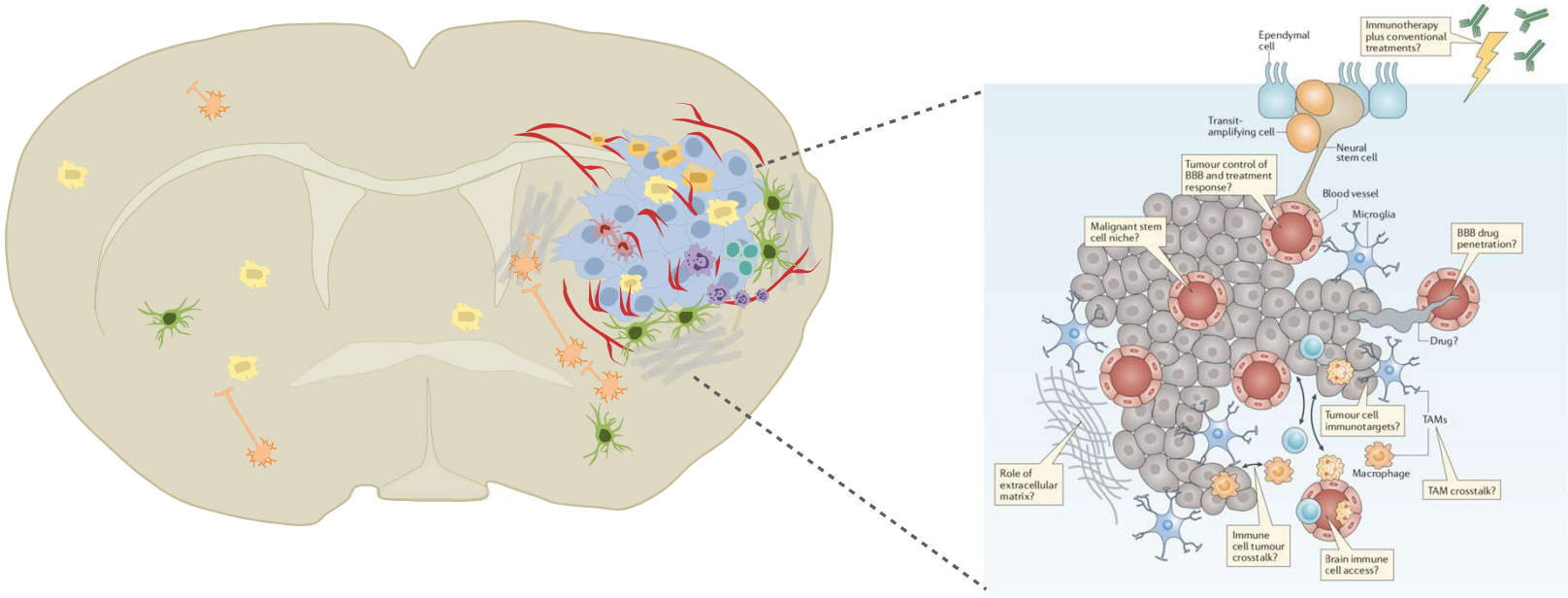
- Normal cells in the tumor microenvironment can be ‘educated’ or converted by cancer cells to promote malignant progression.
- Microenvironment cells represent a comparatively simple target relative to genetically unstable cancer cells, and should not acquire mutations that drive therapeutic resistance.

Exploring and Exploiting the Brain Tumor Microenvironment (TME)



Adapted from:
Quail & Joyce, *Cancer Cell* (2017)
Aldalpe et al, *Nature Reviews Clinical Oncology* (2019)

Exploring and Exploiting the Brain Tumor Microenvironment (TME)

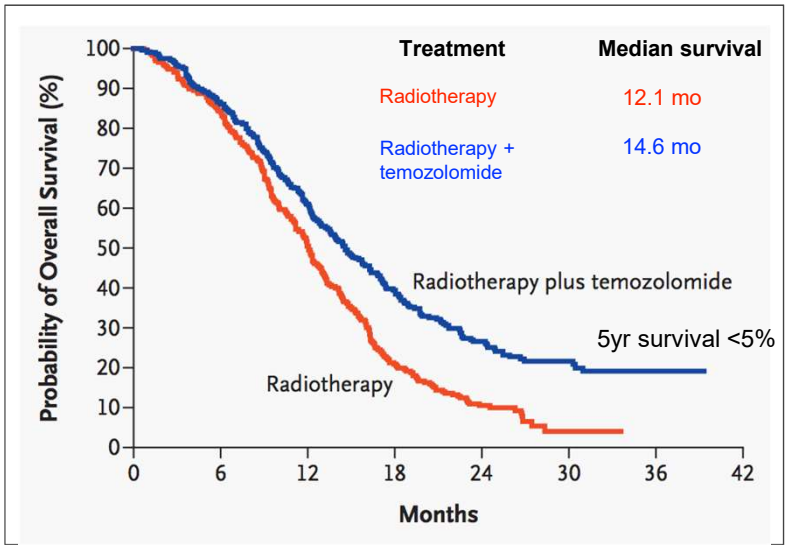


- How does the brain TME evolve with disease progression?
- Is the TME of different brain malignancies sculpted in a disease-specific or tissue-specific manner?
- Do metastases originating from different primary sites sculpt the brain TME through similar or distinct mechanisms?
- How can we overcome the immune-suppressive brain microenvironment?

Brain Malignancies Confer Poor Patient Prognosis

Glioblastoma:

Most lethal primary brain tumor in adults



Stupp et al, *NEJM* (2005)

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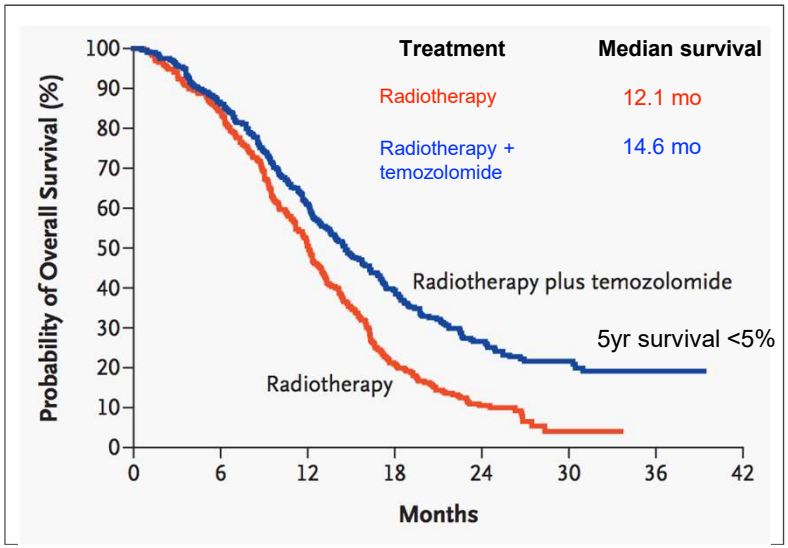
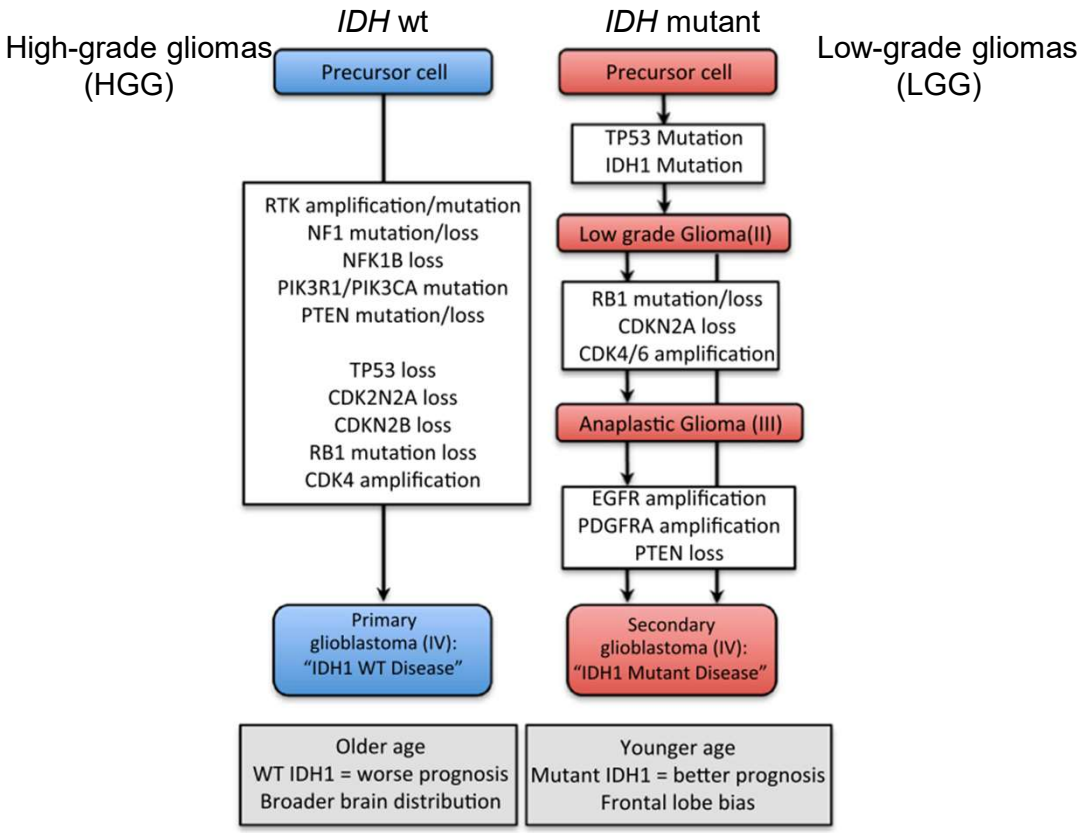


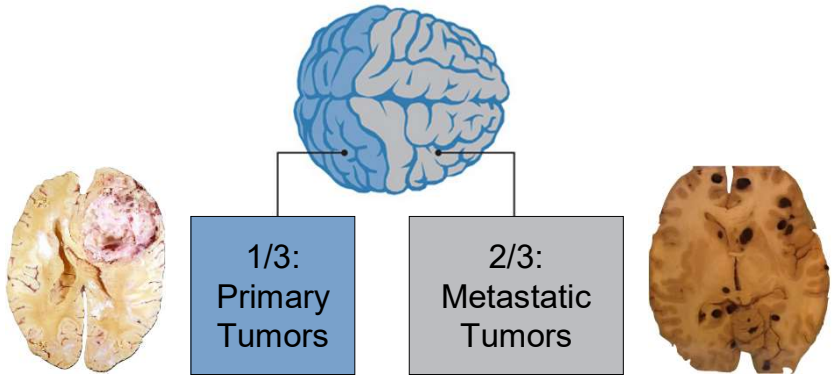
Stupp et al, *NEJM* (2005)

Genetic Alterations in Gliomas



Dunn et al, *Genes Dev* (2012)

Brain Malignancies Confer Poor Patient Prognosis

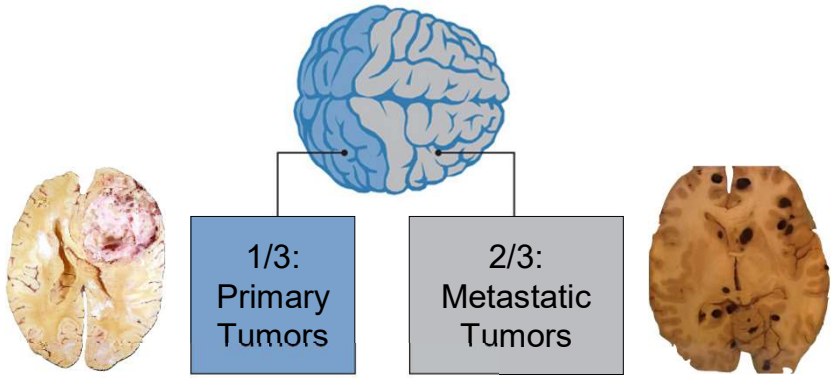


APPROXIMATELY

20-40%

OF ALL OTHER CANCERS LATER
DEVELOP A BRAIN METASTASES

Brain Malignancies Confer Poor Patient Prognosis



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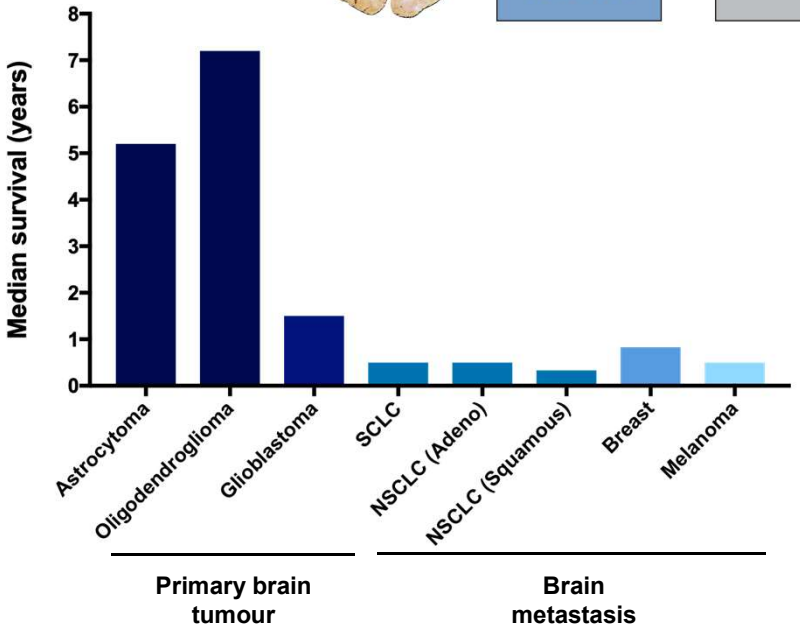
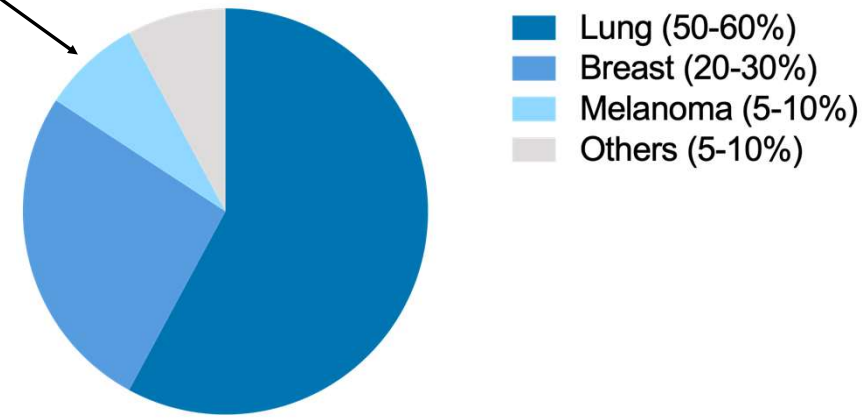
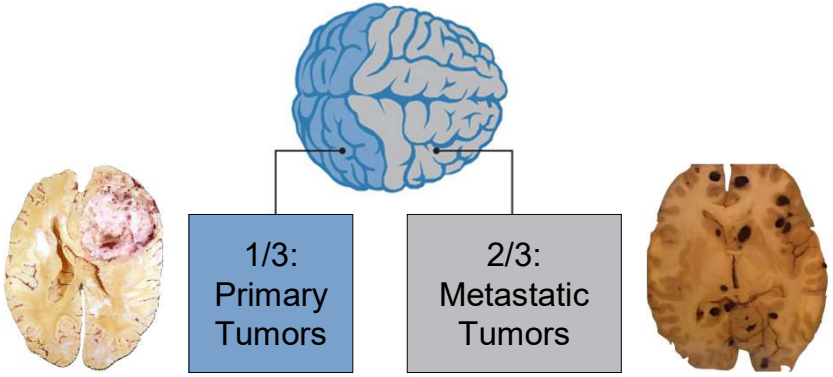




Data summarized from Eichler et al (2011), Cagney et al (2017)

Brain Malignancies Confer Poor Patient Prognosis



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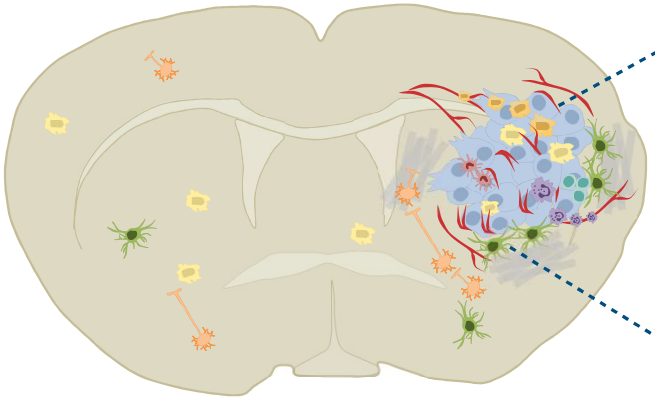
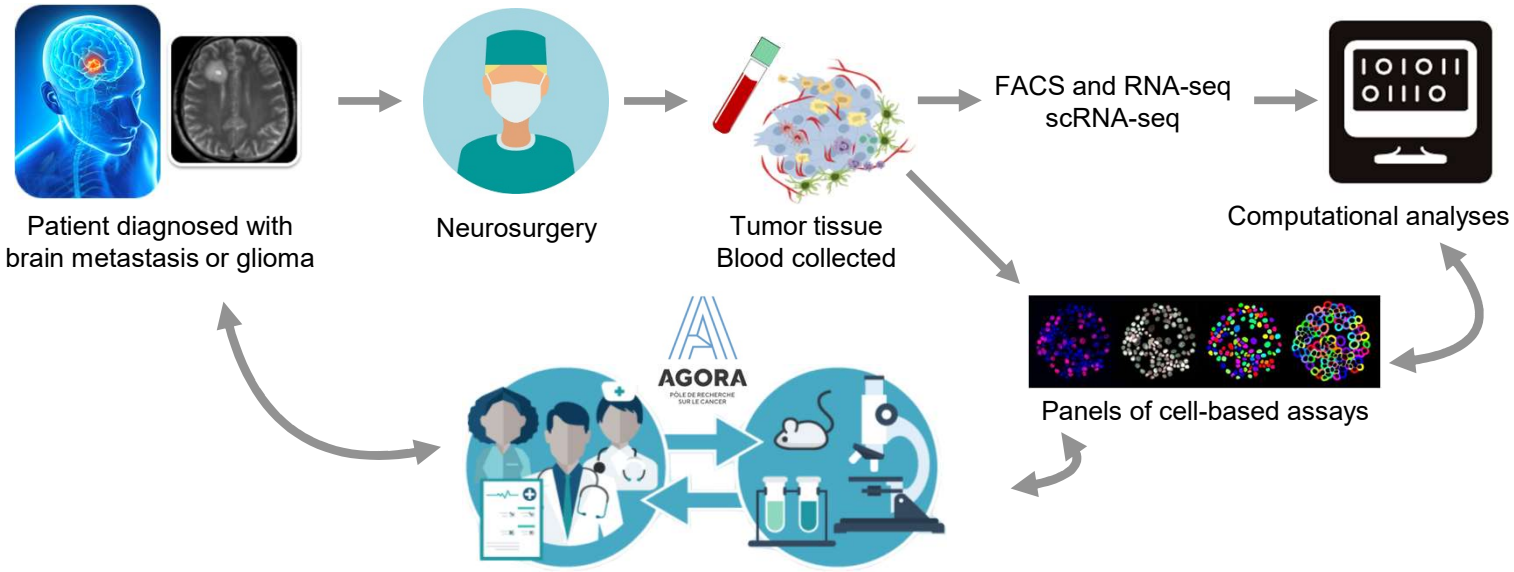


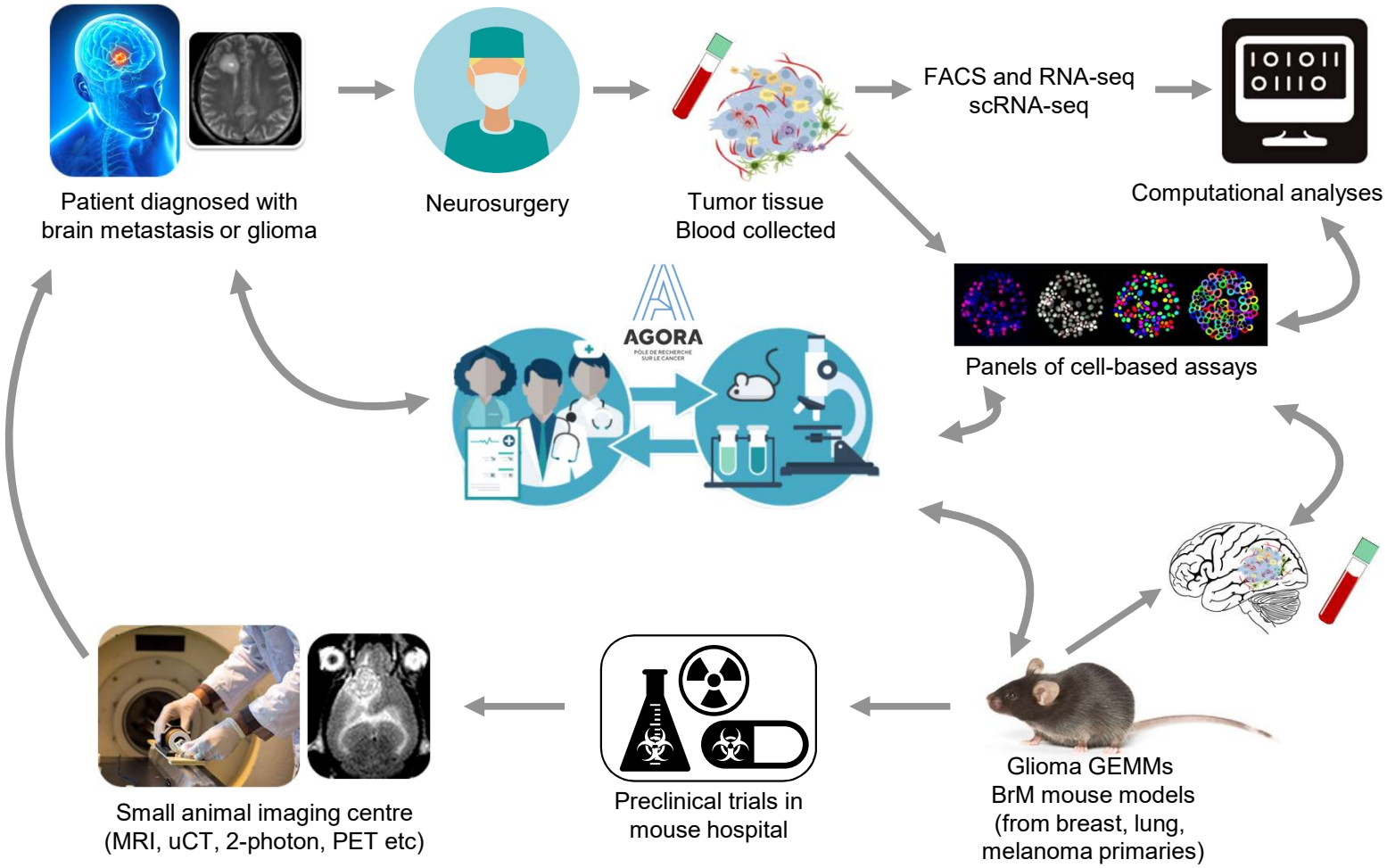
Does the brain microenvironment represent an actionable target?

Which cell types/ pathways should therapeutic interventions be directed towards?

Exploring and Exploiting the Brain Tumor Microenvironment



Exploring and Exploiting the Brain Tumor Microenvironment



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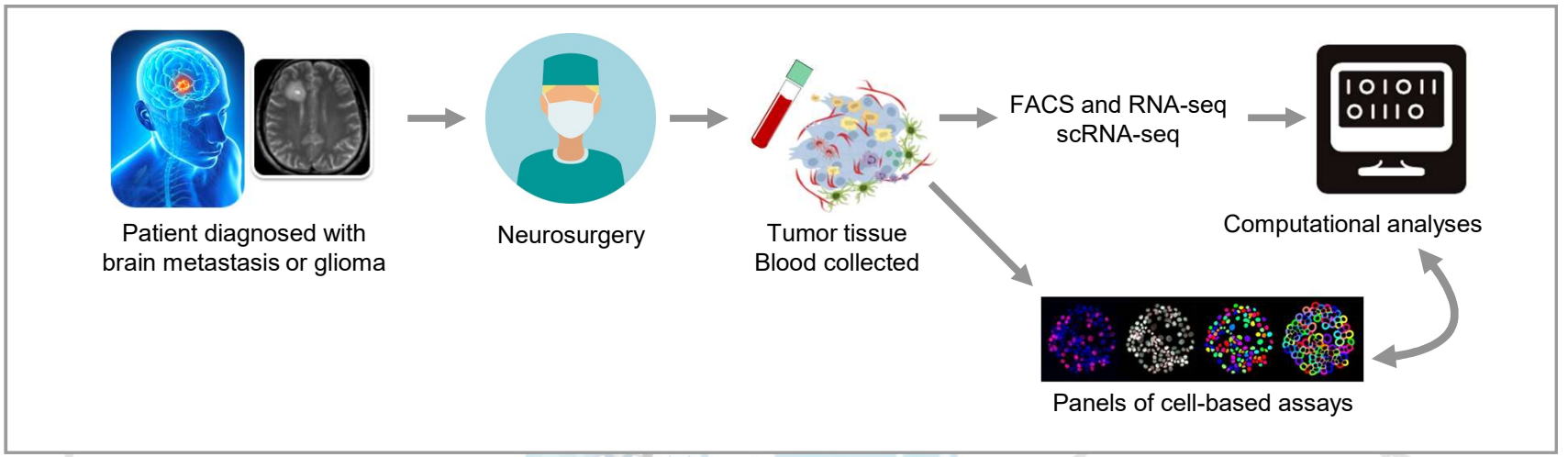
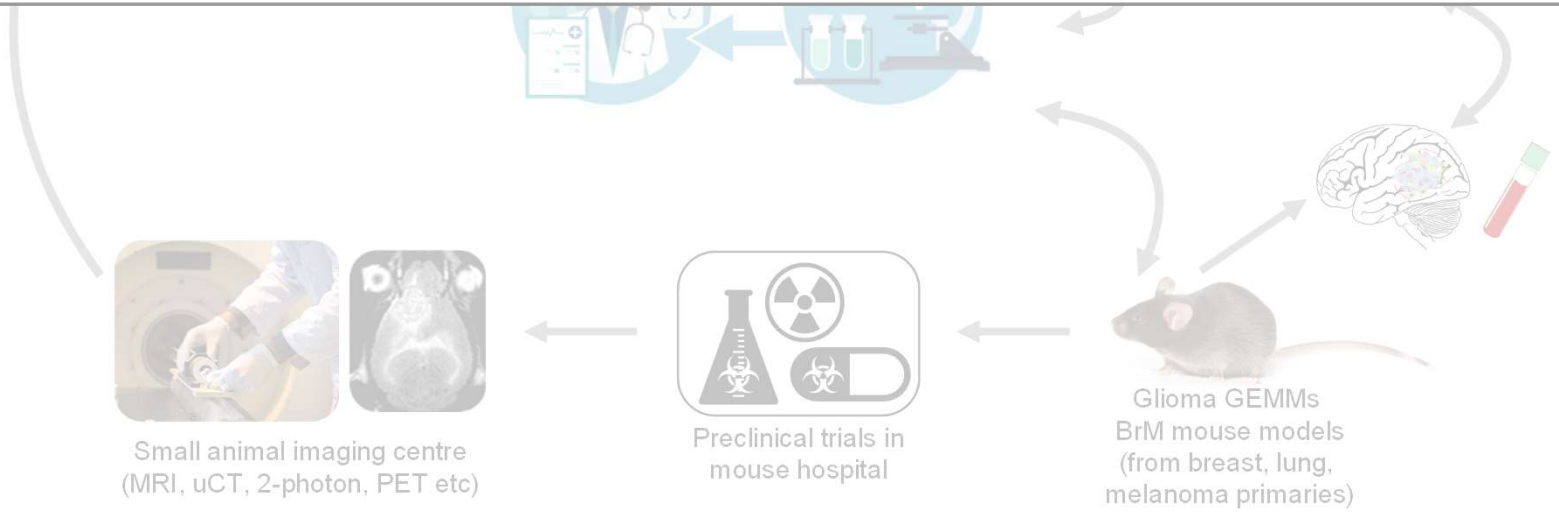
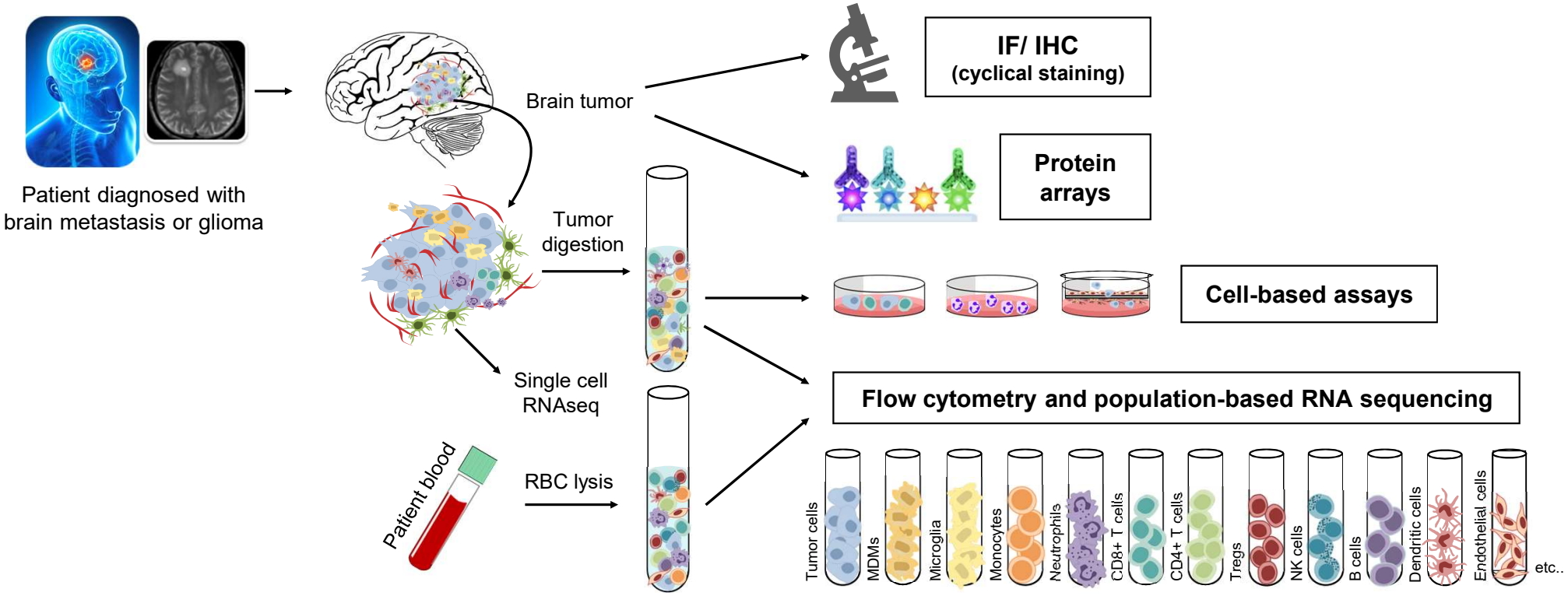




Exploring the Microenvironmental Landscape of Brain Tumors



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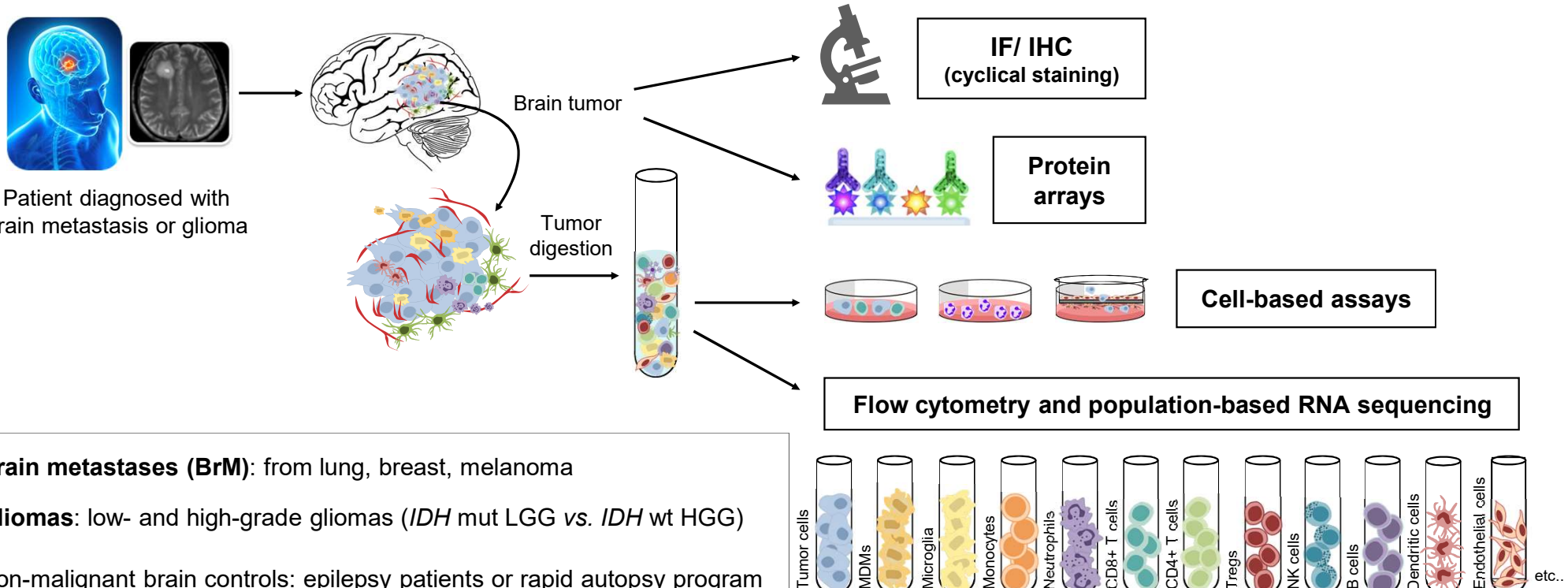


Brain metastases (BrM): from lung, breast, melanoma

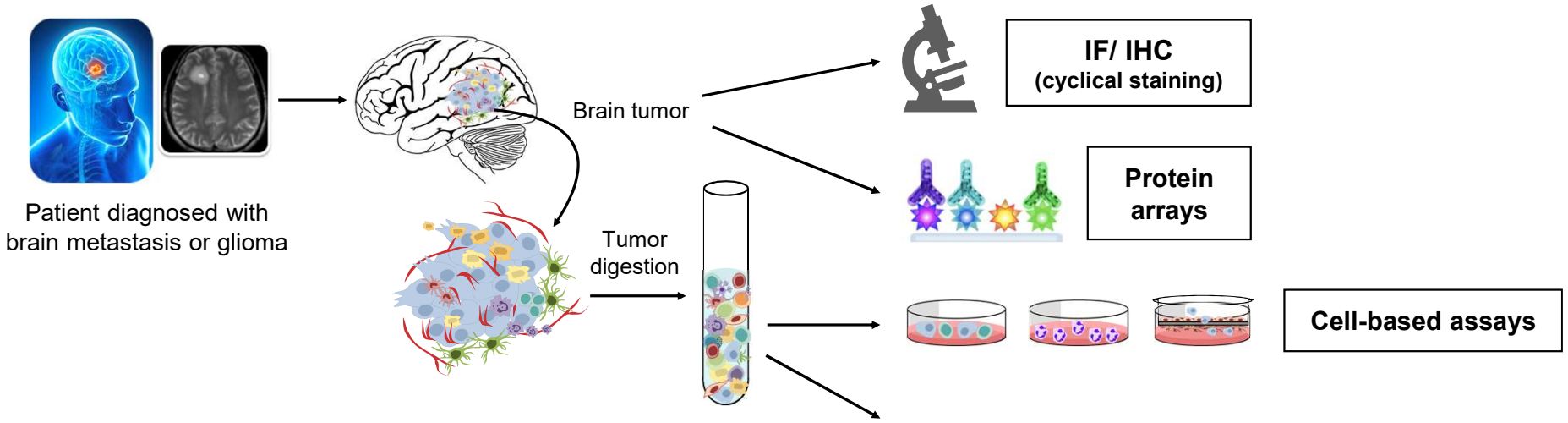
Gliomas: low- and high-grade gliomas (*IDH* mut LGG *vs. IDH* wt HGG)

Non-malignant brain controls: epilepsy patients or rapid autopsy program

Healthy blood controls: healthy volunteers

n > 100 clinical samples

Exploring the Microenvironmental Landscape of Brain Tumors



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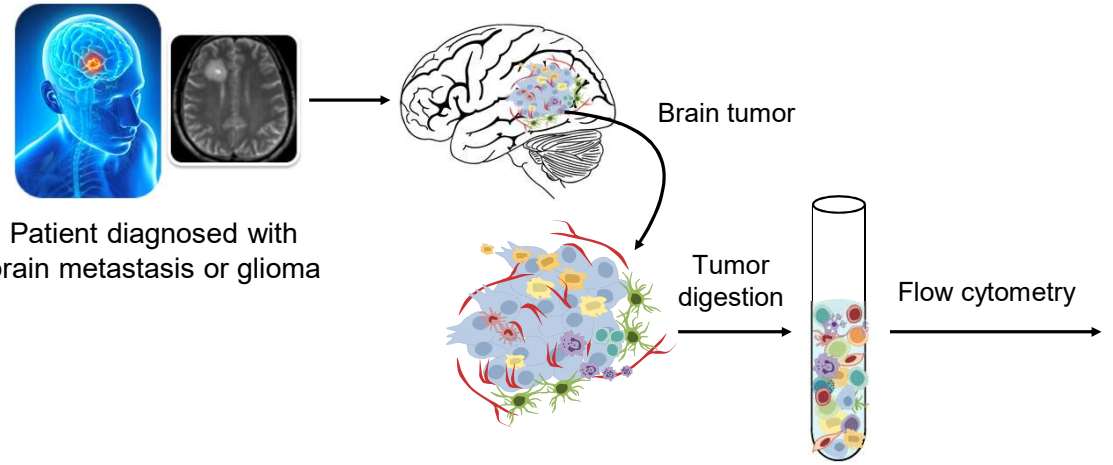
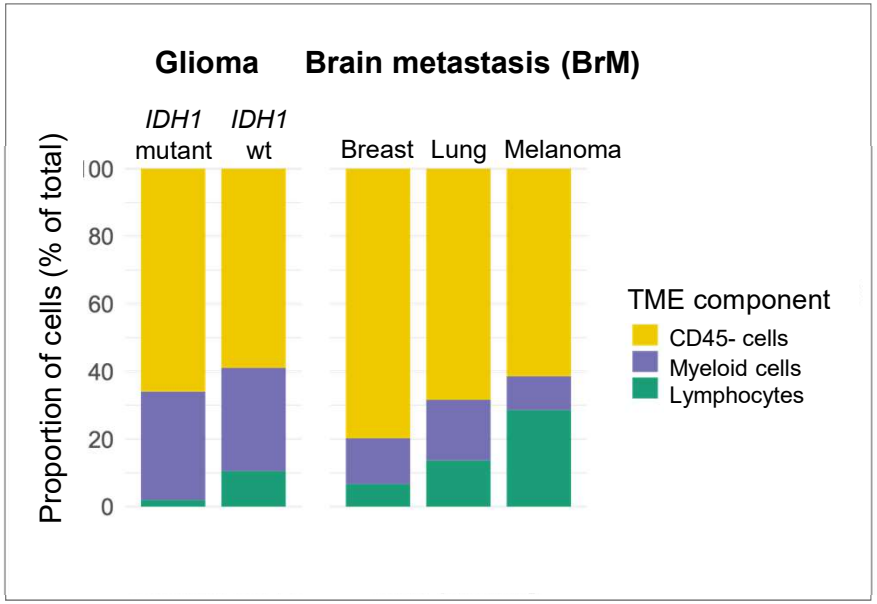
Florian Klemm ***Roeltje Maas*** ***Klara Soukup*** ***Bobby Bowman*** ***Mara Kornete***

Klemm et al, *Cell* (2020);
Maas*, Soukup*, Klemm* et al, ms in preparation

Exploring the Microenvironmental Landscape of Brain Tumors





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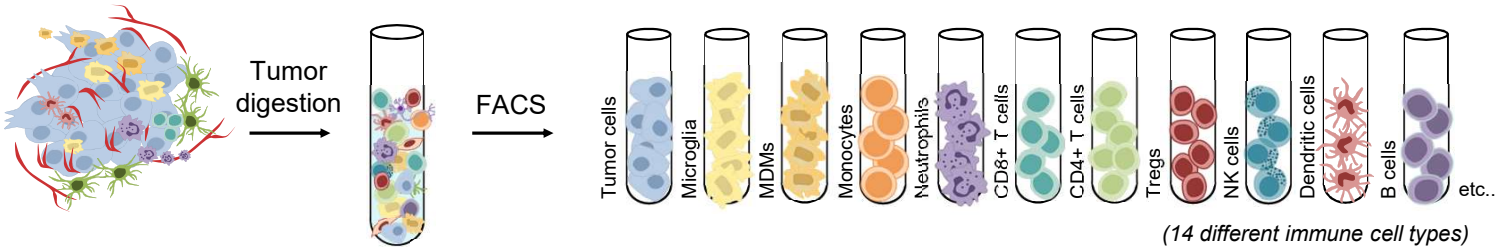
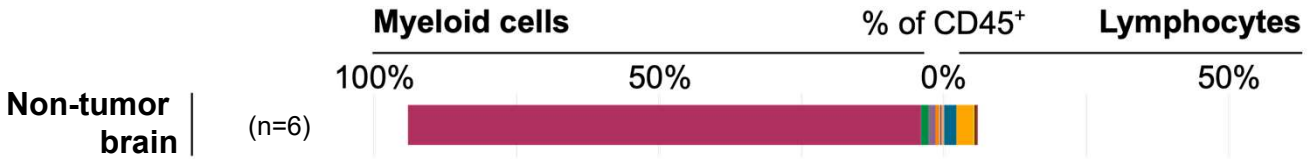
Klemm et al, *Cell* (2020)

Exploring the Immune Landscape of Brain Tumors

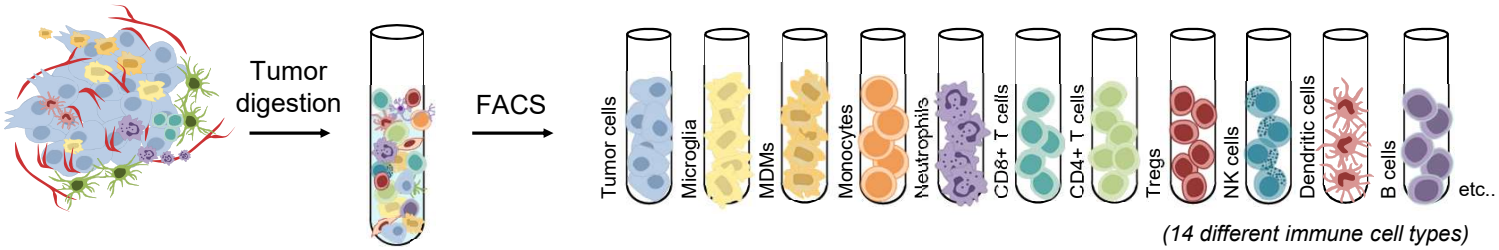


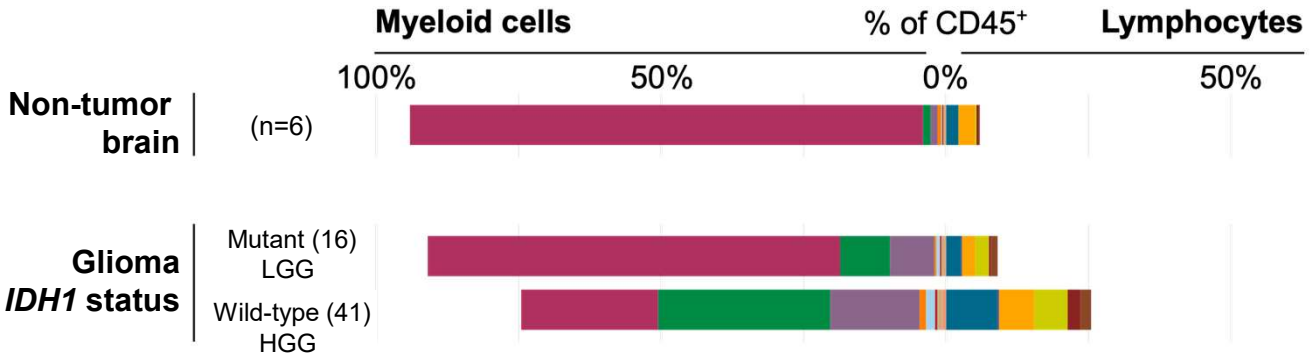


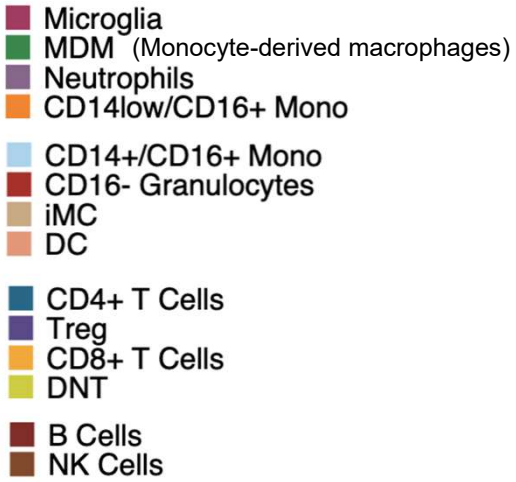
- Microglia
- MDM (Monocyte-derived macrophages)
- Neutrophils
- CD14low/CD16+ Mono
- CD14+/CD16+ Mono
- CD16- Granulocytes
- iMC
- DC
- CD4+ T Cells
- Treg
- CD8+ T Cells
- DNT
- B Cells
- NK Cells

Klemm et al, *Cell* (2020)

Exploring the Immune Landscape of Brain Tumors







Klemm et al, *Cell* (2020)

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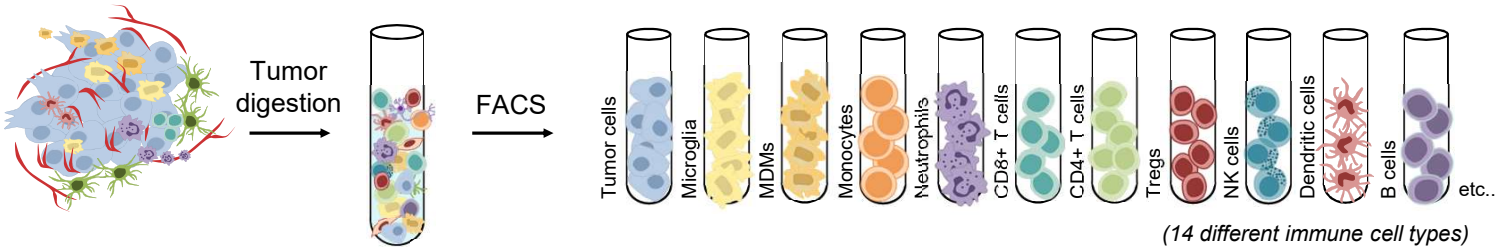
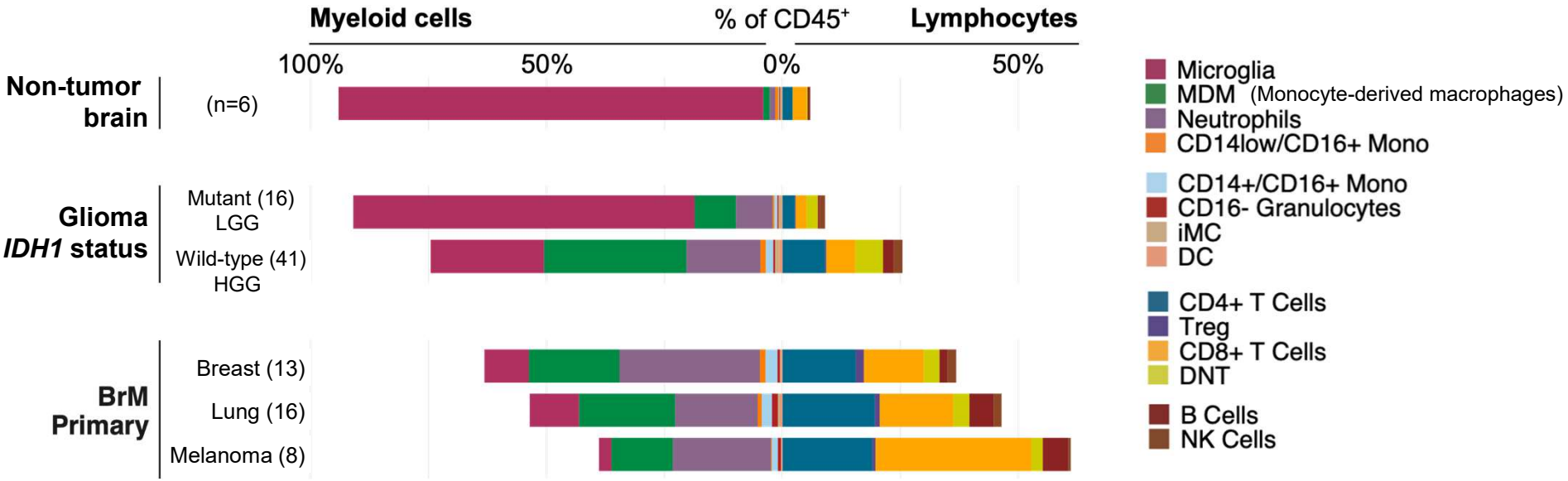
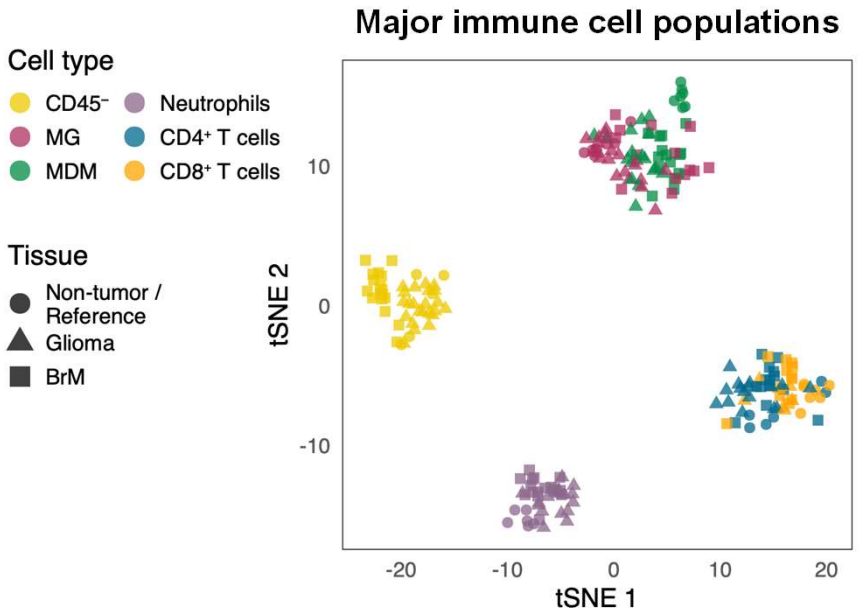




Klemm et al, *Cell* (2020)

Exploring the Immune Landscape of Brain Tumors:
Computational Analyses of RNAseq Data in Different Immune Populations



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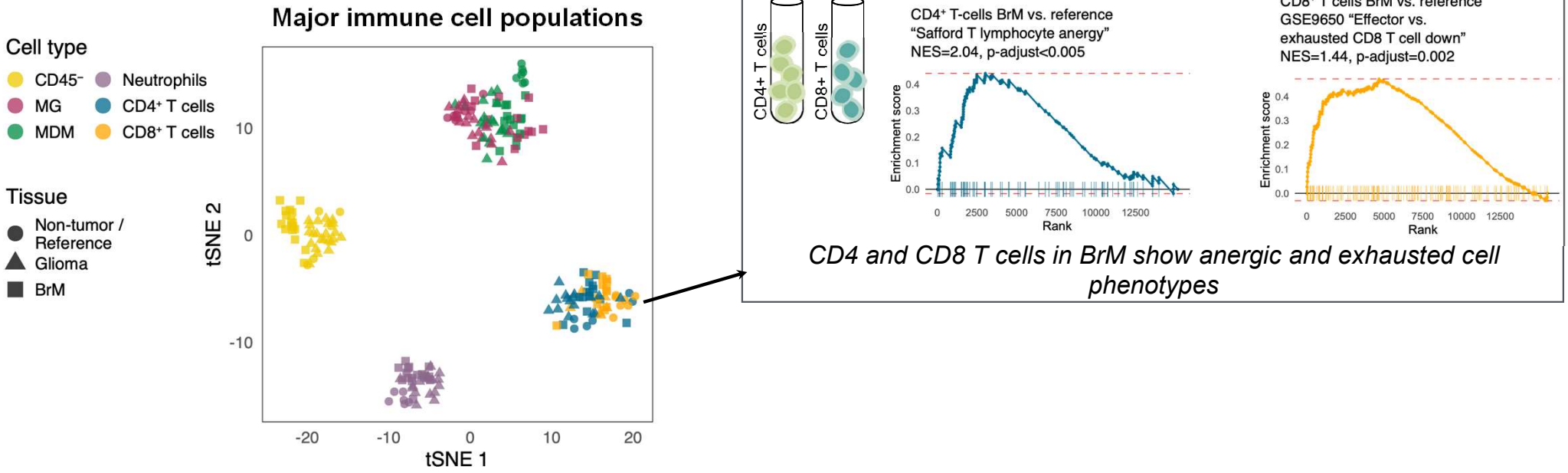

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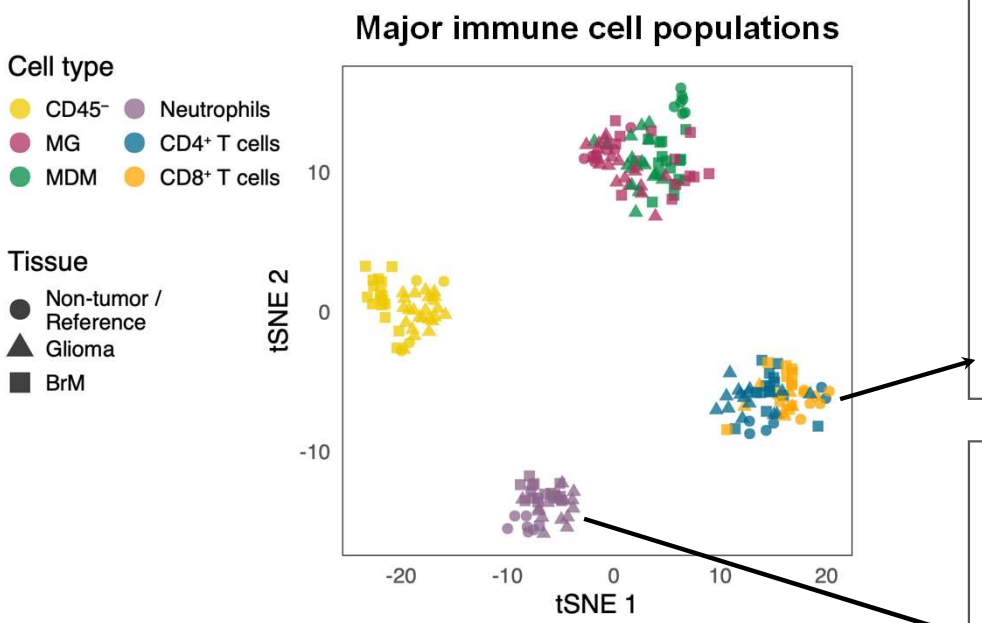
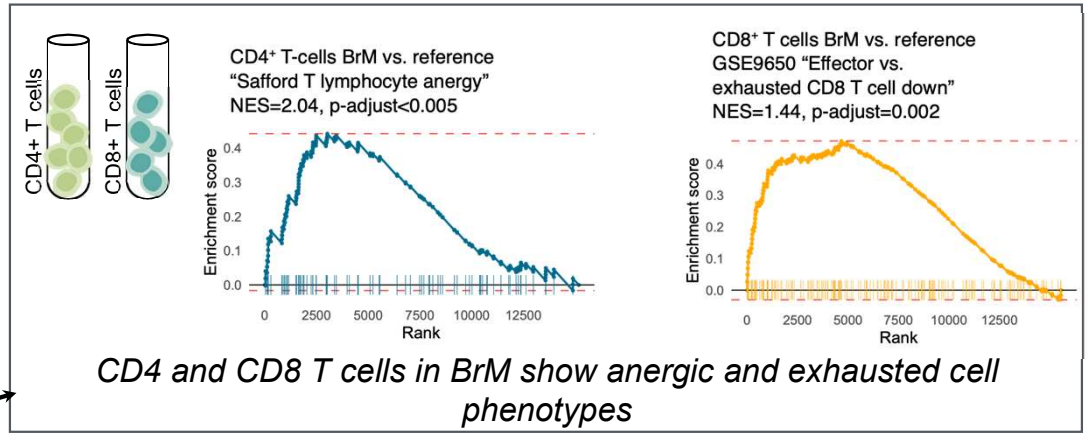
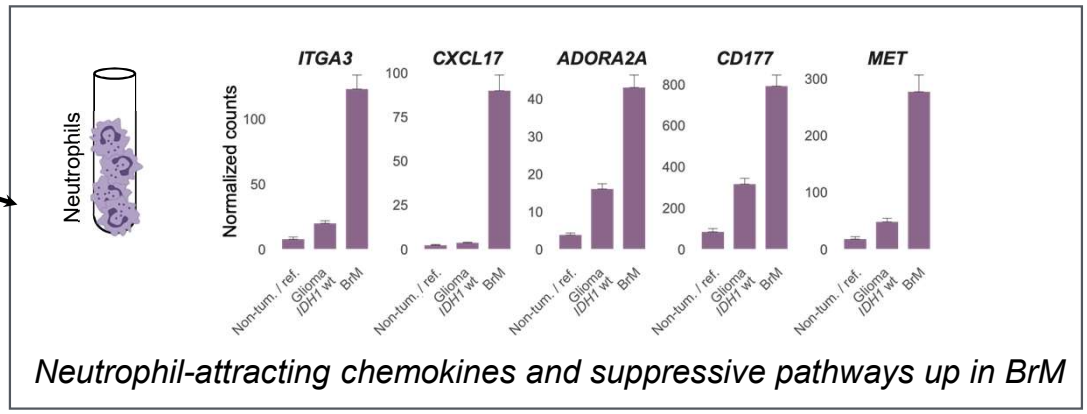




CD4 and CD8 T cells in BrM show anergic and exhausted cell phenotypes



Neutrophil-attracting chemokines and suppressive pathways up in BrM

Klemm et al, *Cell* (2020)

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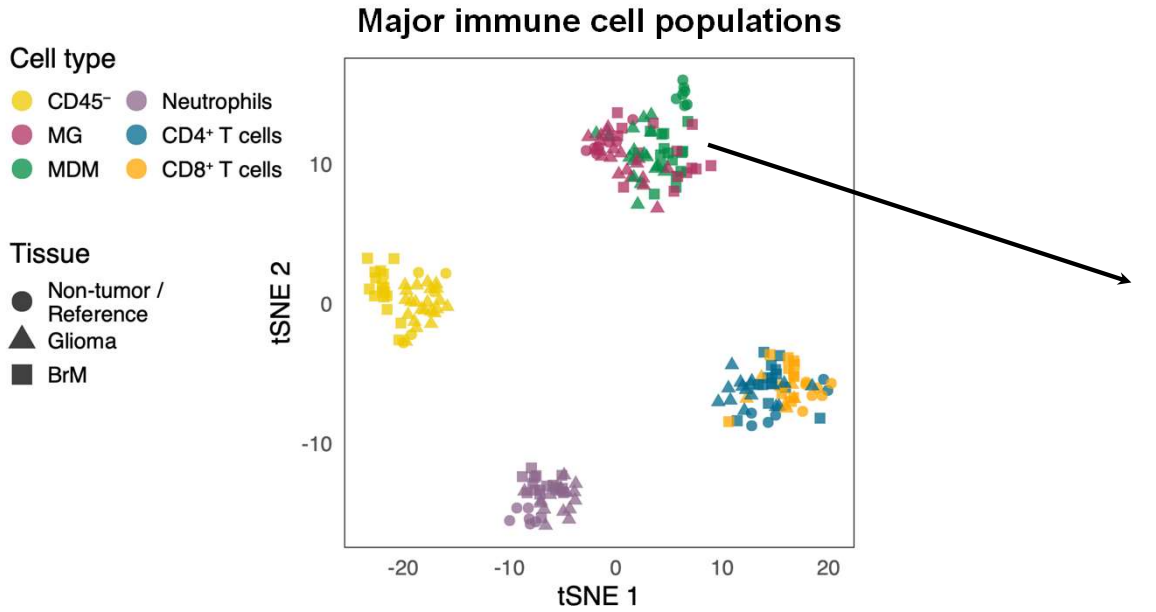
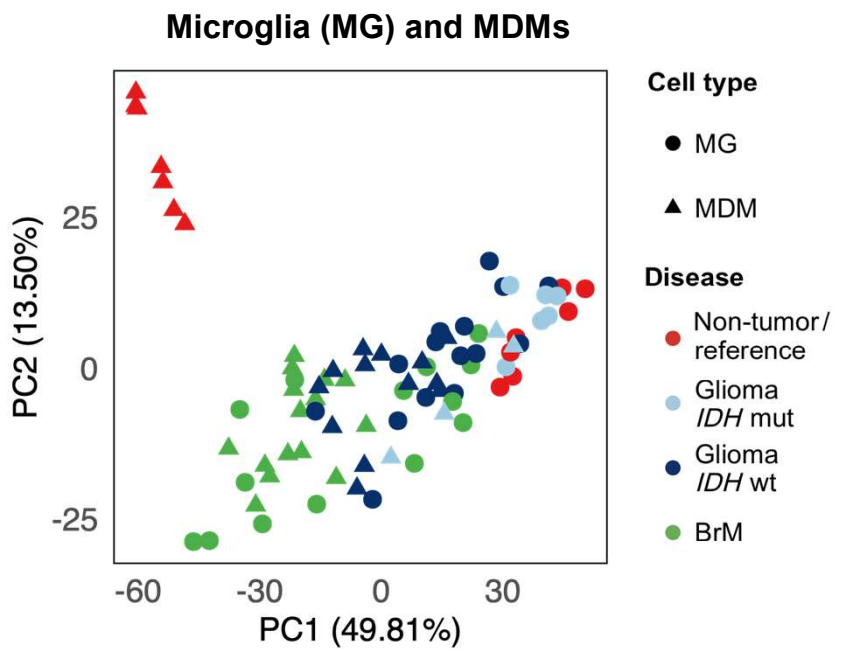




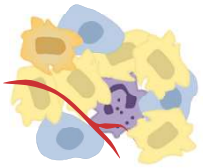
Cell type-specific and disease-specific patterns of TAM 'education' as well as shared pathways between MG & MDMs

Klemm et al, *Cell* (2020)

Unraveling the Complexity of the Immune Landscape in Brain Cancers

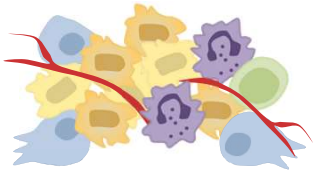
Gliomas

***IDH* mutant** (LGG)



Microglia-rich

***IDH* wt** (HGG)



High accumulation of MDMs
More neutrophils, few T cells

Klemm et al, *Cell* (2020)

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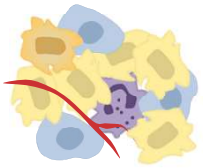

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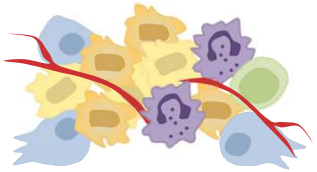

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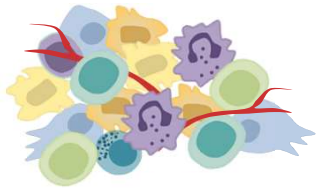
More neutrophils, few T cells

Diverse immune landscapes across different brain cancers

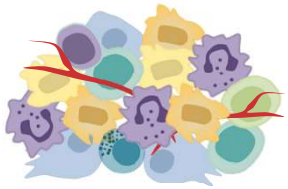
A major driver of TAM phenotypes is the disease of origin

Brain metastases

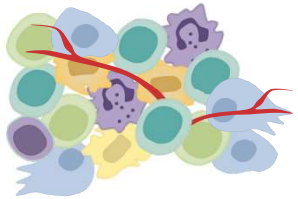
Lung



Breast



Melanoma



Substantial accumulation of cells from the periphery:
T cells, neutrophils, MDMs.
Few NK cells, B cells, Tregs

Very high accumulation of
T cells from the periphery:
CD8+ > CD4+ > neutrophils > MDMs

Klemm et al, *Cell* (2020)

Unraveling the Complexity of the Immune Landscape in Brain Cancers

Gliomas

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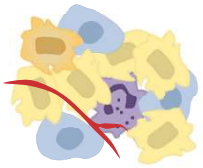

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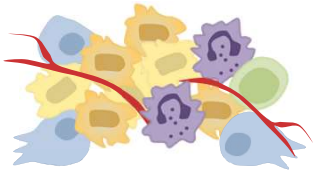

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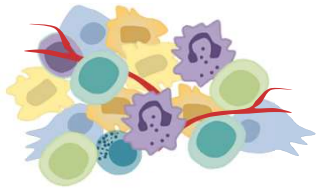

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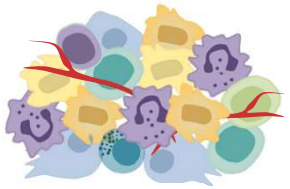
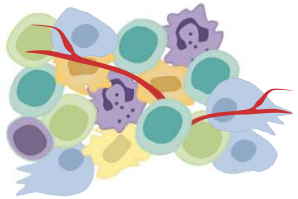


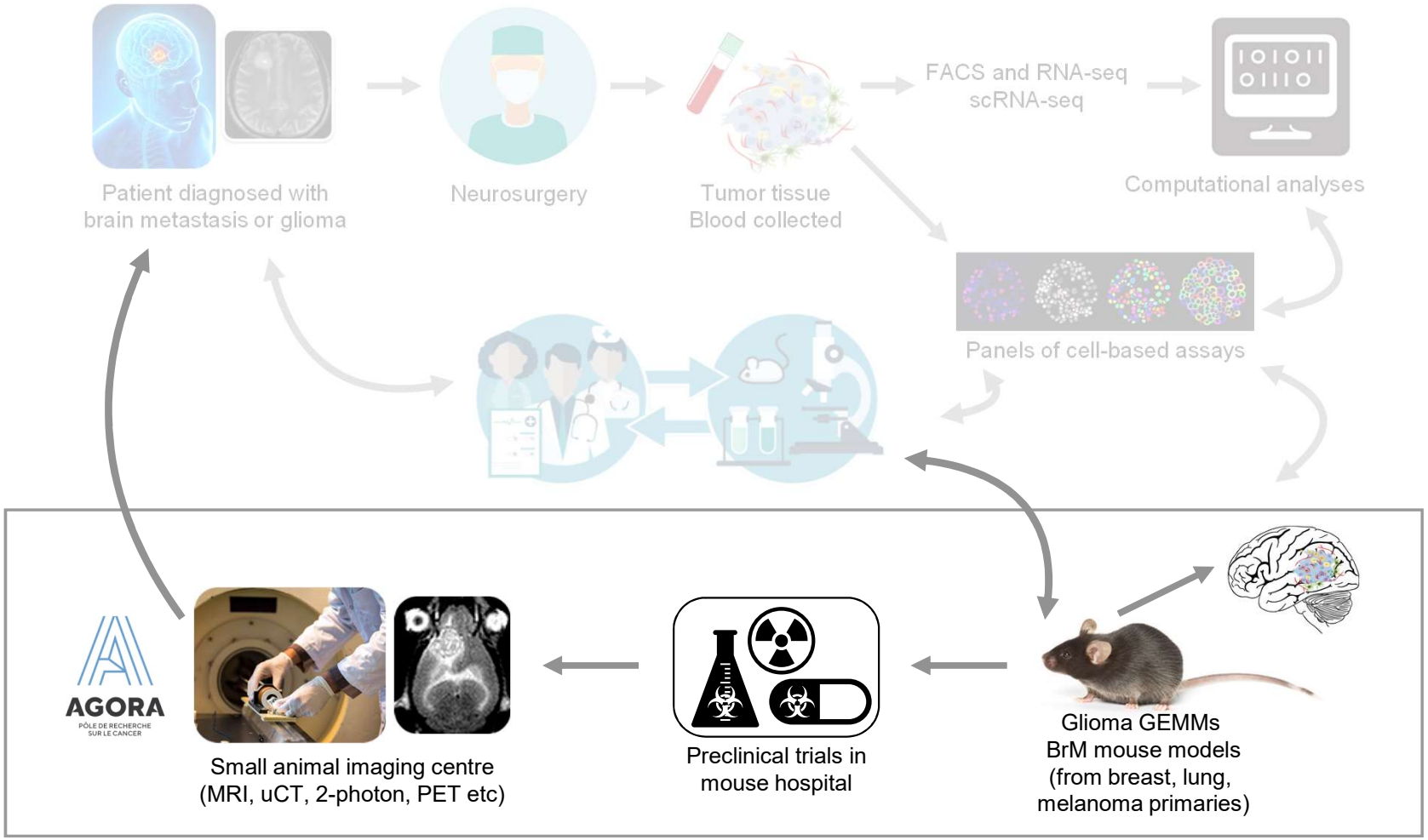
Melanoma



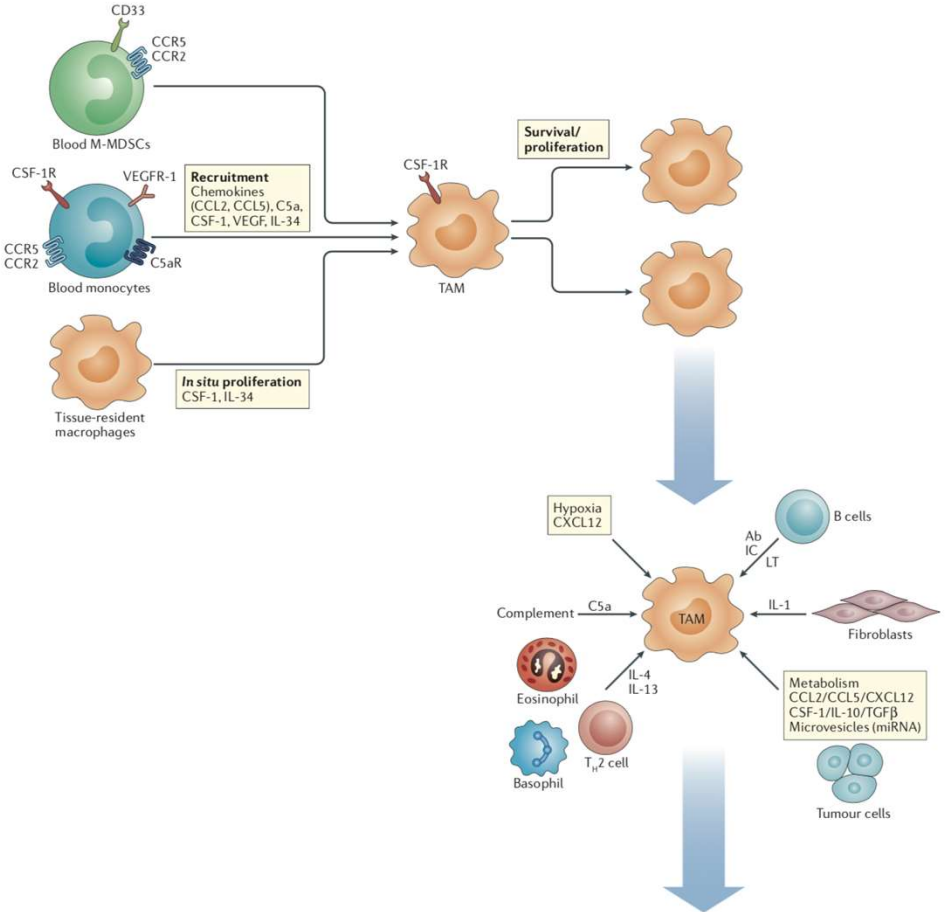
TAMs collectively comprise ~25-80% of immune cells across these brain malignancies

Are they an actionable therapeutic target?

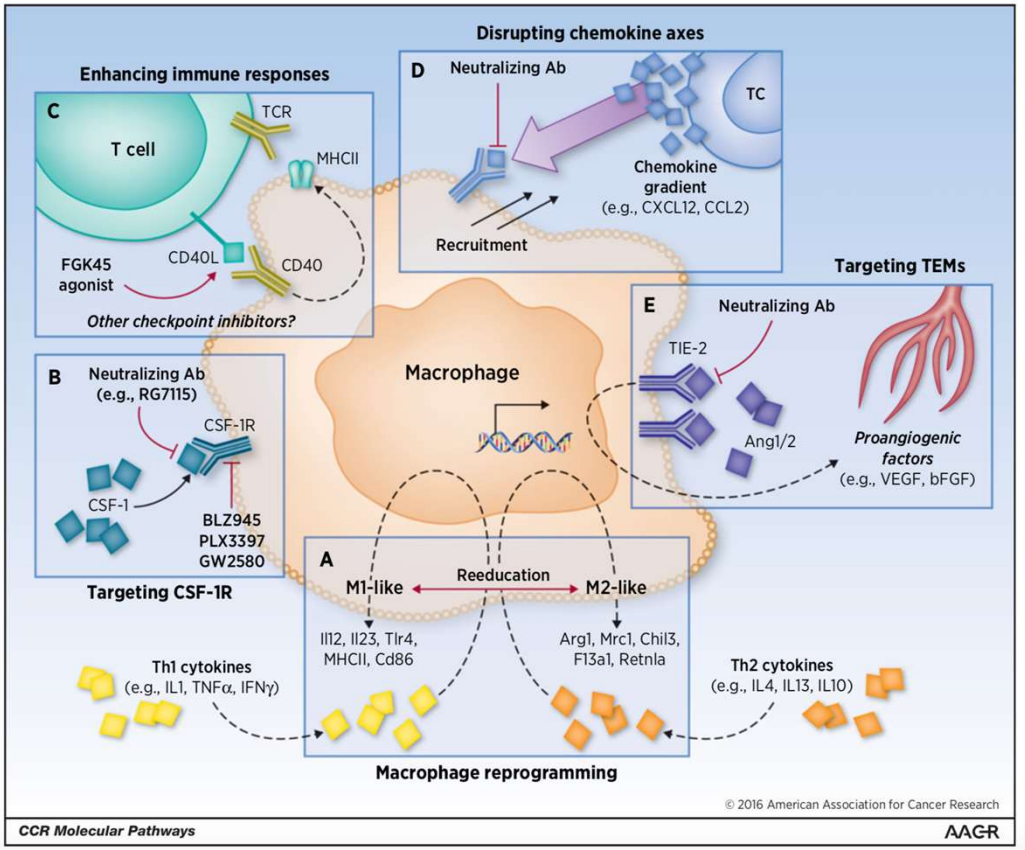
Exploring and Therapeutically Exploiting the Tumor Microenvironment



Diversity of Macrophage Populations, Phenotypes, and Targeting Strategies



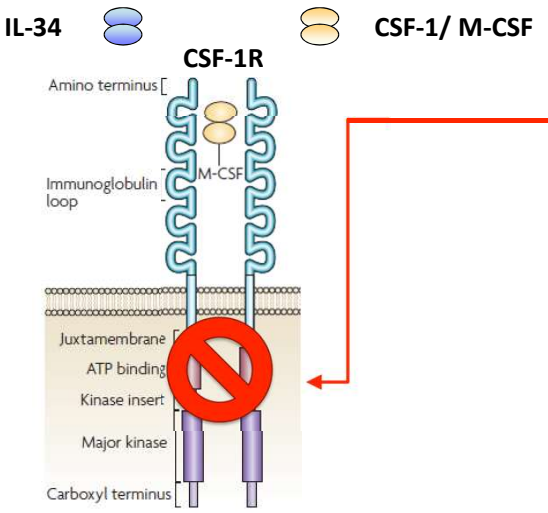
Tumor-modulatory functions
Angiogenesis, Invasion
Metastasis



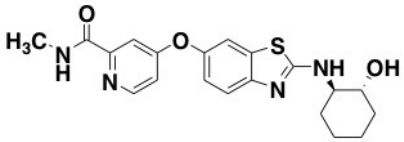
Adapted from: Mantovani et al, *Nat Rev Clinical Oncology* (2017)

Quail & Joyce, *Clinical Cancer Research* (2017)

Targeting TAMs using Inhibitors of Colony Stimulating Factor-1 Receptor (CSF-1R)

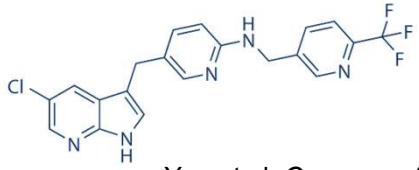


BLZ945 (Novartis)



Pyonteck et al, *Nature Medicine* (2013)
Quail et al, *Science* (2016)
Akkari et al, *Science Translational Medicine* (2020)
Klemm et al, ms in revision

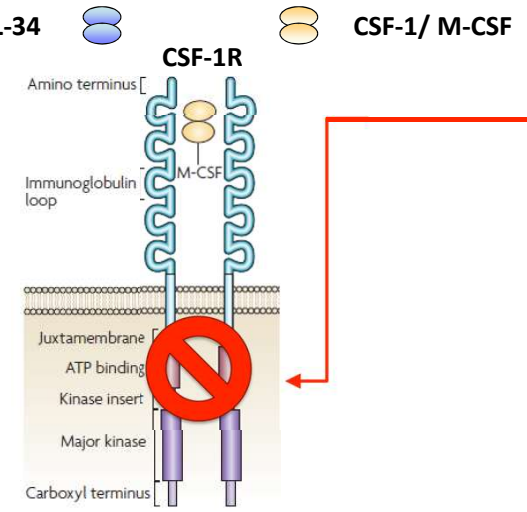
PLX3397 (Plexxikon)



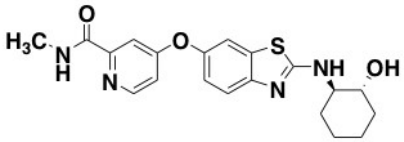
Yan et al, *Oncogene* (2017)

- ATP competitive kinase inhibitors
- Blood-brain barrier permeable
- BLZ945: highly selective for CSF-1R, biochemical IC50 =1nM; PLX3397 IC50 =20nM

Targeting TAMs using Inhibitors of Colony Stimulating Factor-1 Receptor (CSF-1R)



BLZ945 (Novartis)



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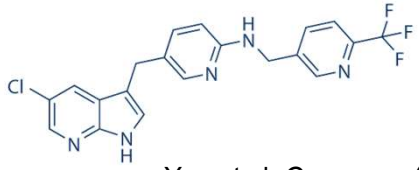

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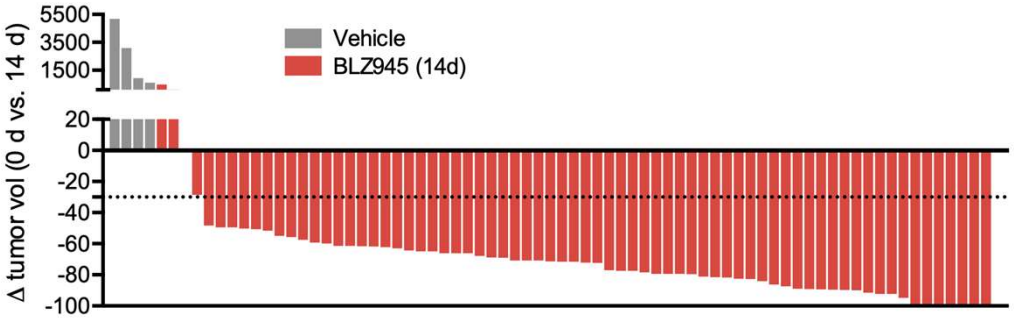
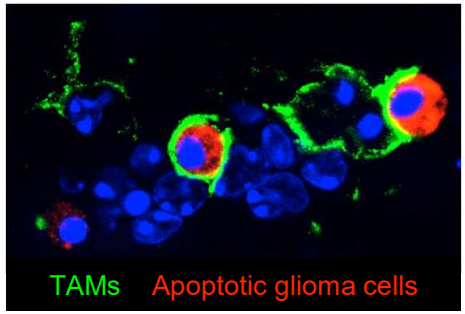
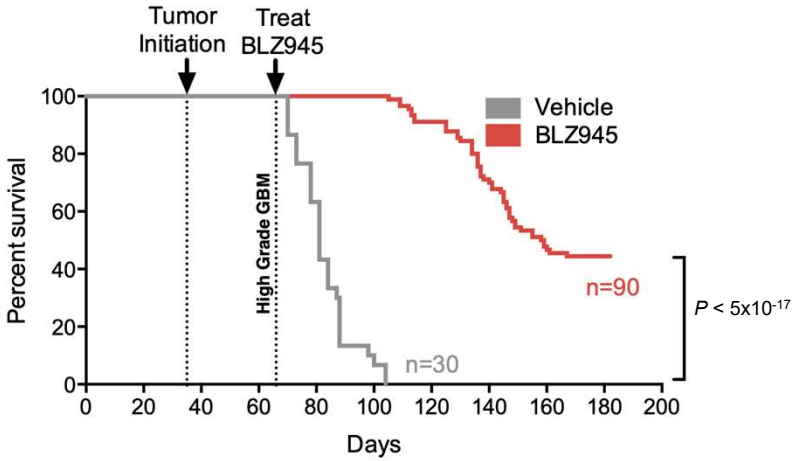
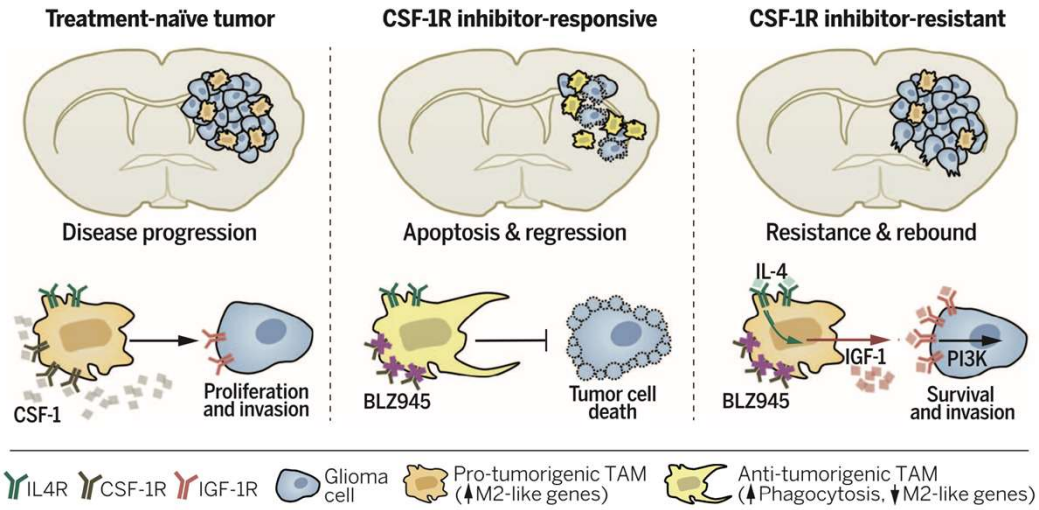
Longitudinal MRI throughout long-term preclinical trial





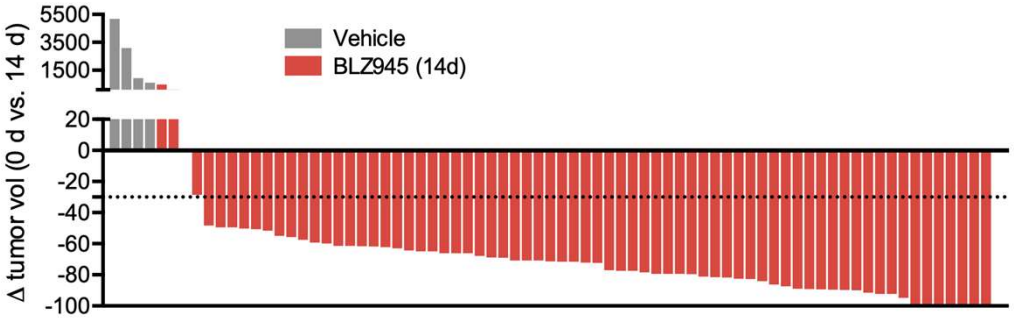
CSF-1R Inhibition Regresses Established High-Grade Preclinical Gliomas

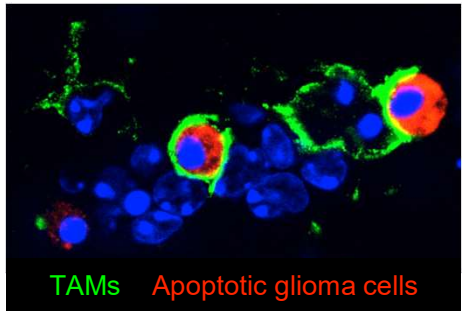




Quail et al, *Science* (2016); Pyonteck et al, *Nature Medicine* (2013)

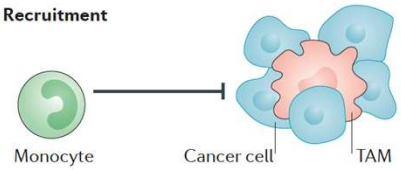
Longitudinal MRI throughout long-term preclinical trial





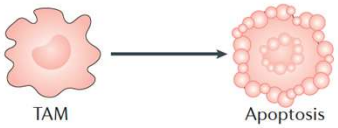
CSF-1R Inhibitors/ TAM-Targeted Therapies in Clinical Development

Recruitment



Drug name	Target	Inhibitor type
Carlumab	CCL2	mAb
PF04136309	CCR2	Small molecule
PLX3397	CSF1R	Small molecule
PLX7486	CSF1R	Small molecule
JNJ-40346527	CSF1R	Small molecule
ARRY-382	CSF1R	Small molecule
BLZ945	CSF1R	Small molecule
IMC-CS4	CSF1R	mAb
R05509554	CSF1R	mAb
RG7155	CSF1R	mAb
FPA008	CSF1R	mAb

Survival



Drug name	Target	Inhibitor type
Clodronate	NA	Small molecule
Zoledronic acid	NA	Small molecule
Trabectedin	Caspase 8	Small molecule
PLX7486	CSF1R	Small molecule
JNJ-40346527	CSF1R	Small molecule
ARRY-382	CSF1R	Small molecule
BLZ945	CSF1R	Small molecule
IMC-CS4	CSF1R	mAb
R05509554	CSF1R	mAb
RG7155	CSF1R	mAb
FPA008	CSF1R	mAb

Reprogramming

Drug name	Target	Inhibitor type
Hu5F9-G4	CD47	mAb
CC-90002	CD47	mAb
TTI-621	SIRPα	Fusion protein
CP-870,893	CD40	Agonistic antibody
RO7009789	CD40	Agonistic antibody
Imiquimod	TLR7	Small molecule
852A	TLR7	Small molecule
IMO-2055	TLR9	Small molecule
BLZ945	CSF1R	Small molecule

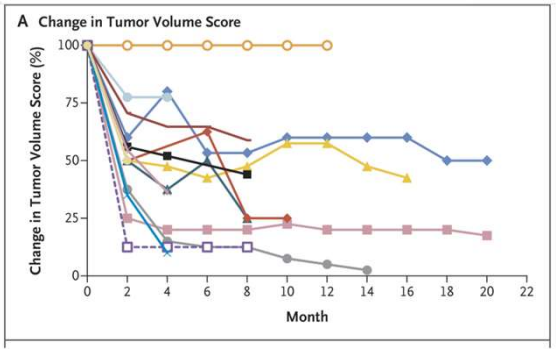
ssetta and Pollard, *Nat Rev Drug Discovery* (2018)

How do standard of care therapies change the TME, including TAMs?

Do these alterations modulate therapeutic efficacy?

Tenosynovial giant cell tumor/ PVNS

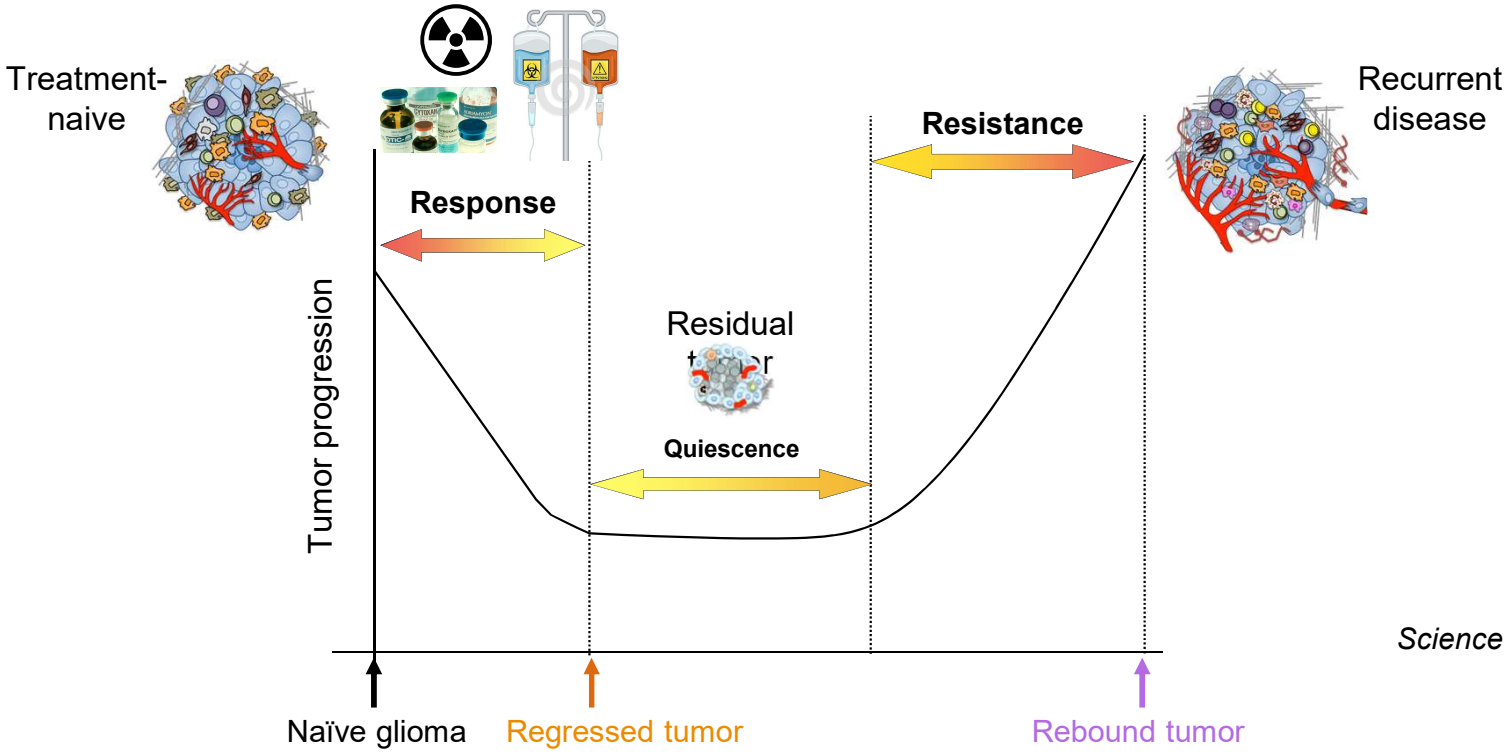
4 mth tumor volume: 85% decrease



Mean decrease: 61%

Tap et al, *NEJM* (2015)

Longitudinal Analyses of TME Alterations Following Therapeutic Intervention



Leila Akkari

Science Translational Medicine (2020)

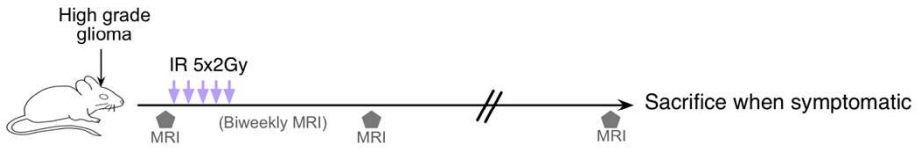
Ink4a/Arf KO; PDGF-B GEMM
p53 KD; PDGF-B GEMM
PDX models

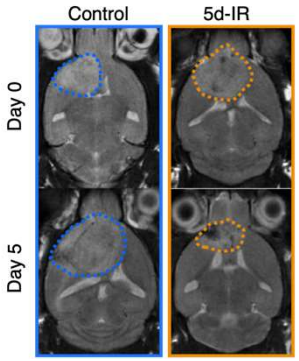
Gene expression of TAM populations

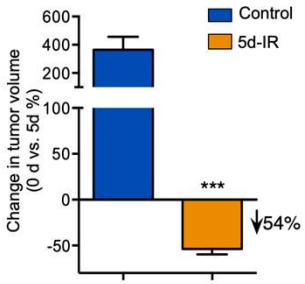
Matched tissue samples

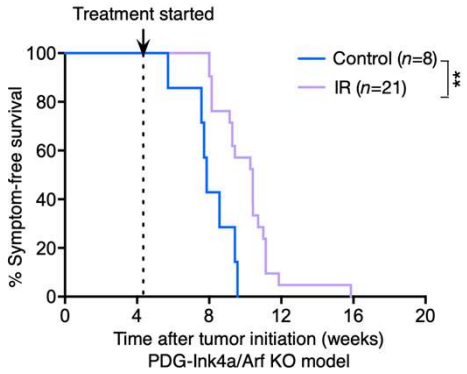
Whole genome expression with computational deconvolution

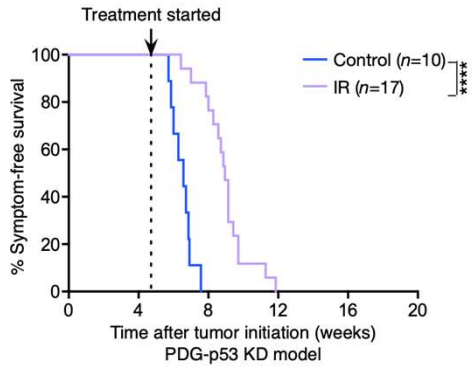
Longitudinal Analyses Following Radiation Therapy: Response and Recurrence



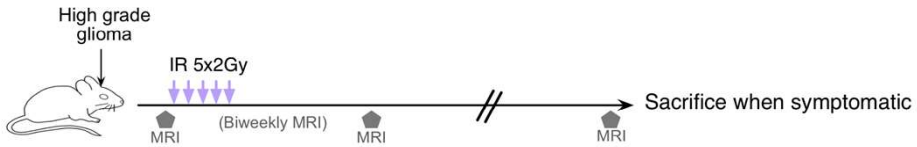


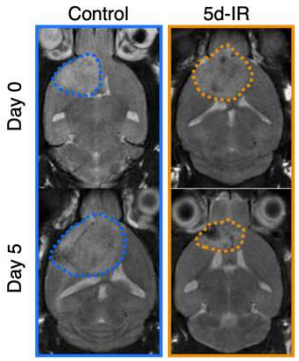


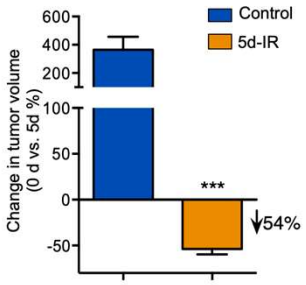


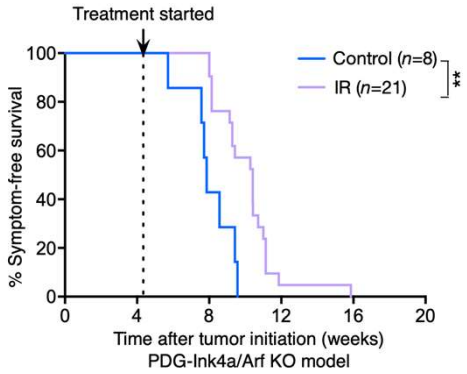


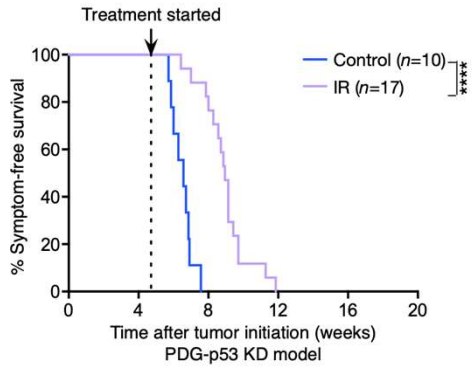
Longitudinal Analyses Following Radiation Therapy: Response and Recurrence

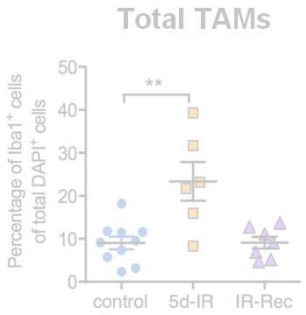


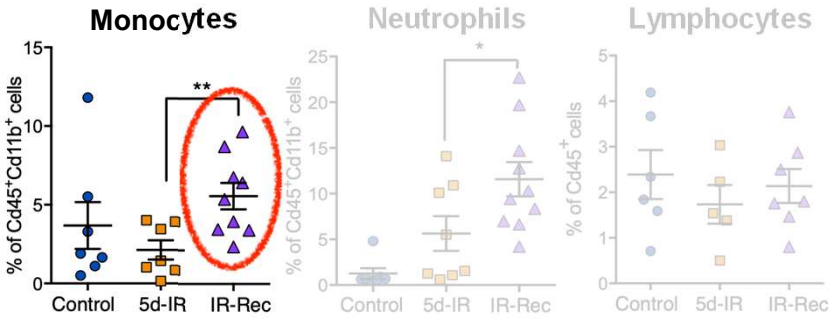


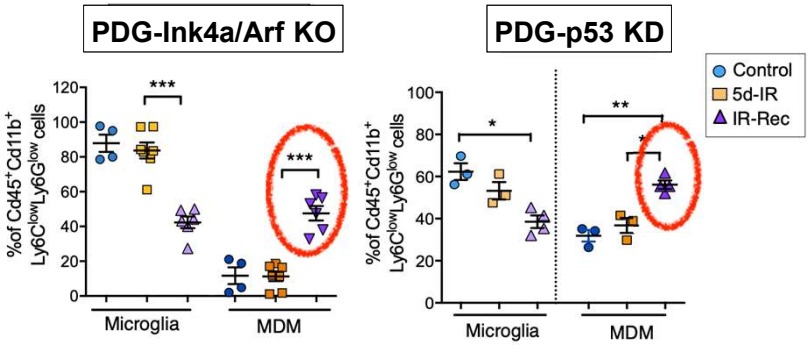




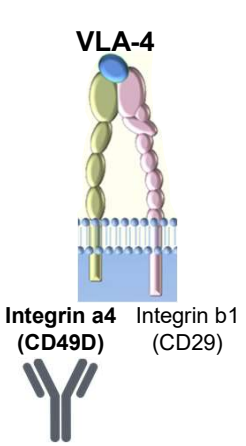


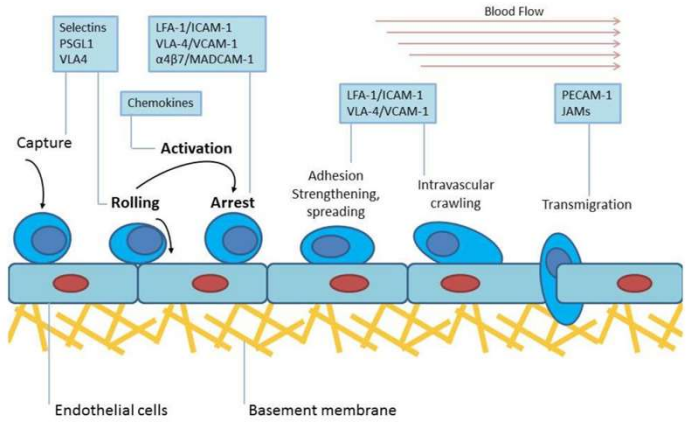




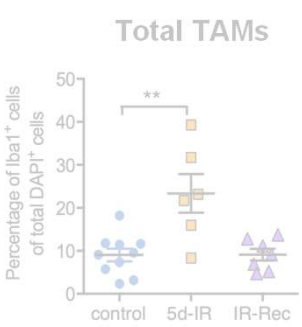


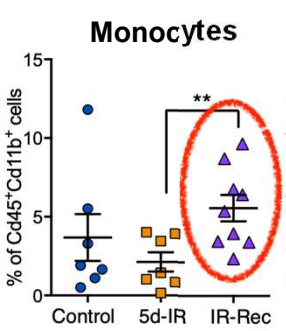
Blocking Infiltration of Monocyte-Derived Macrophages (MDMs) in Gliomas

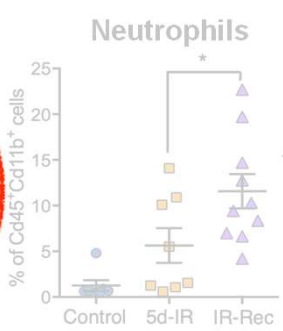


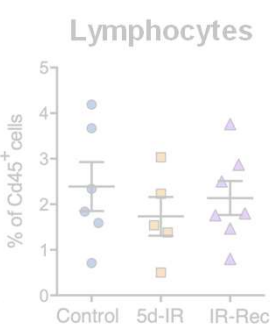


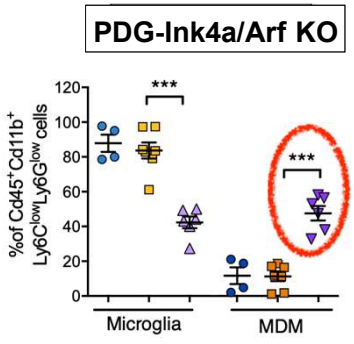
Does blockade of MDM infiltration have an effect on glioma recurrence post-irradiation?

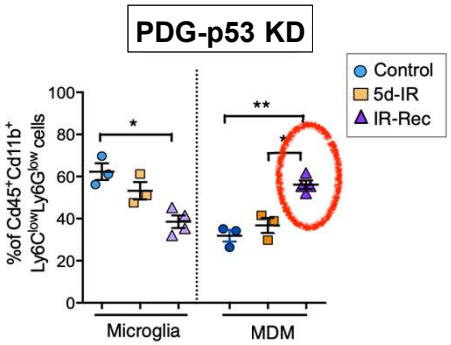




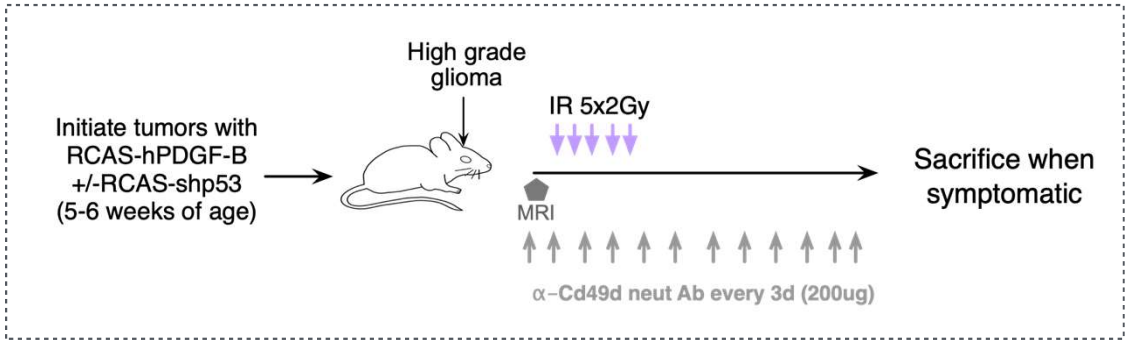


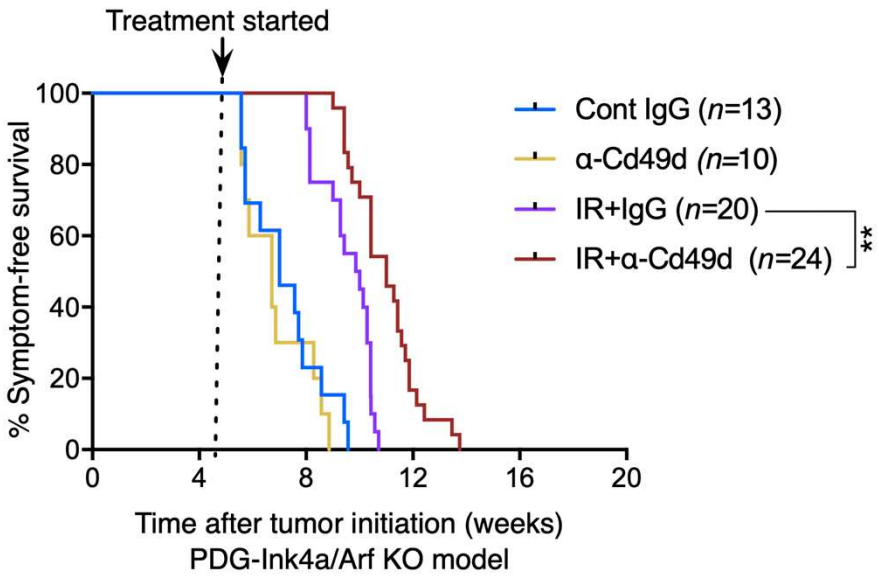


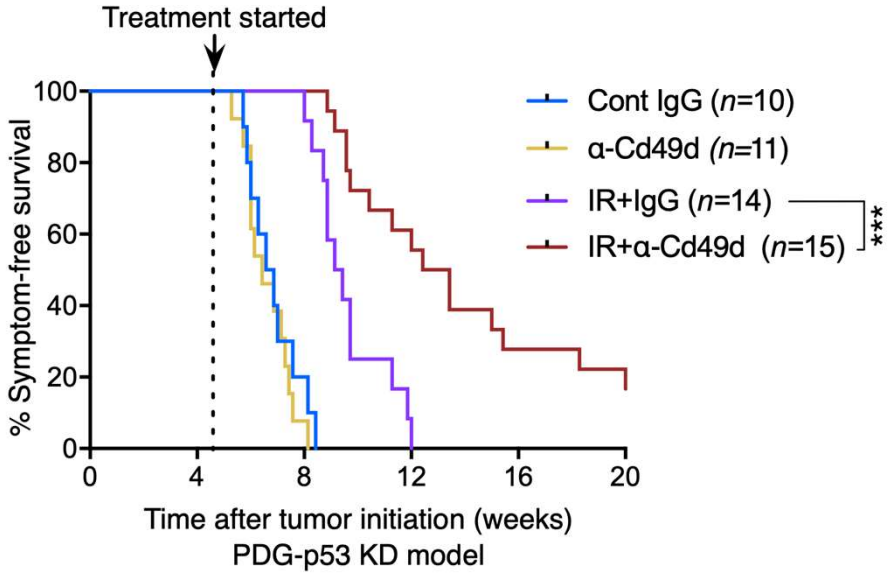




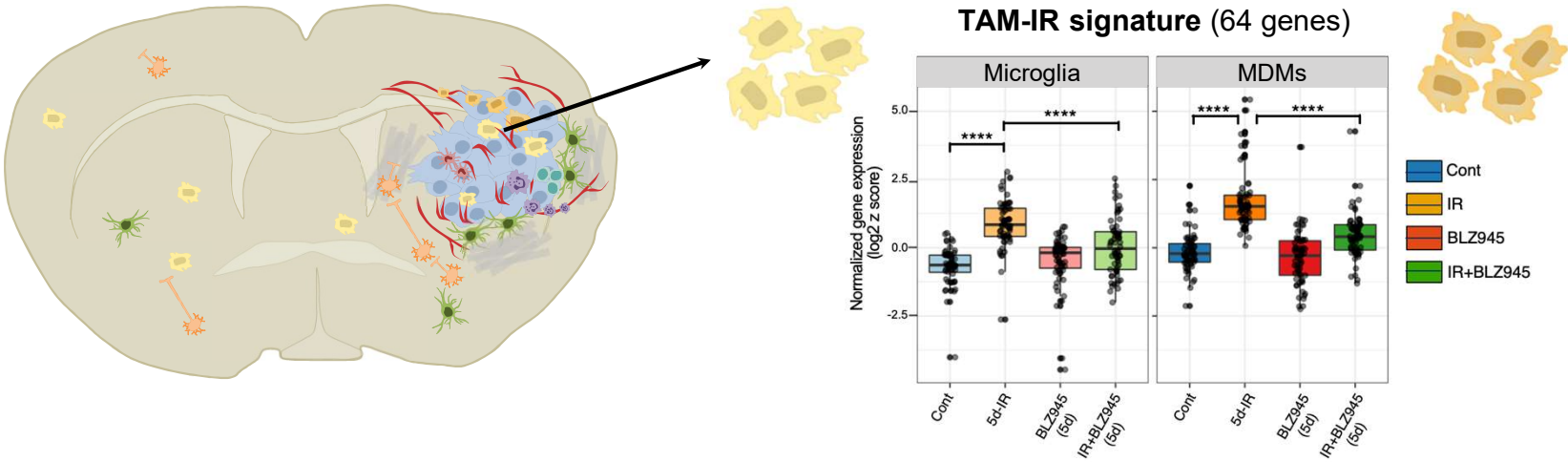
Blocking MDM Infiltration into Gliomas Following Radiation Enhances Survival







Analysis of Phenotypic Alterations in the Irradiated Glioma Microenvironment



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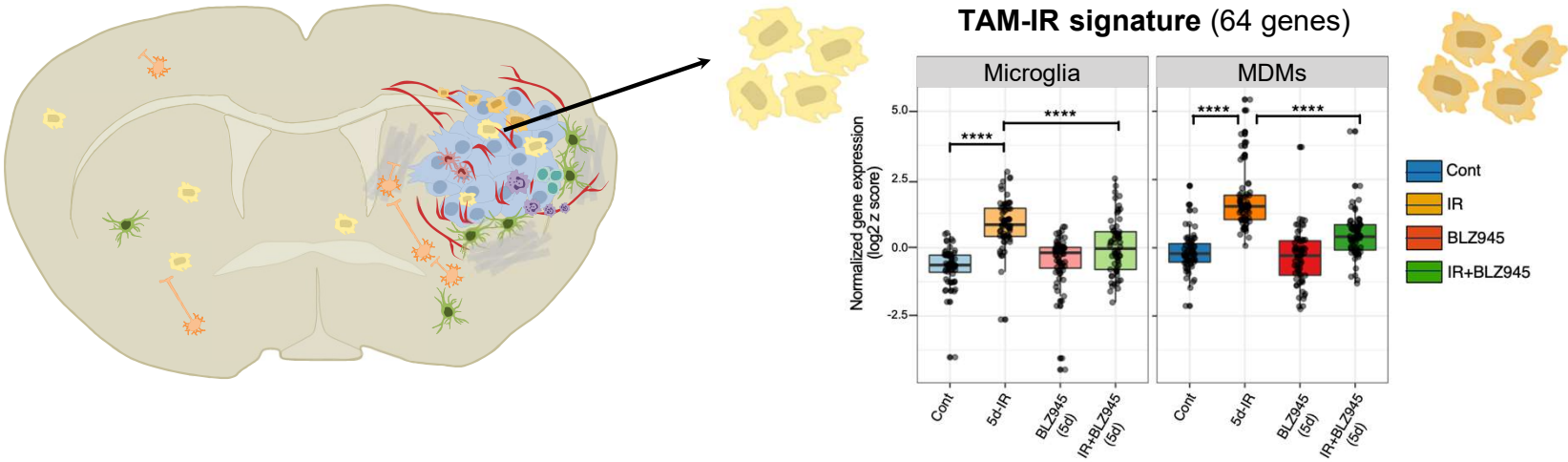
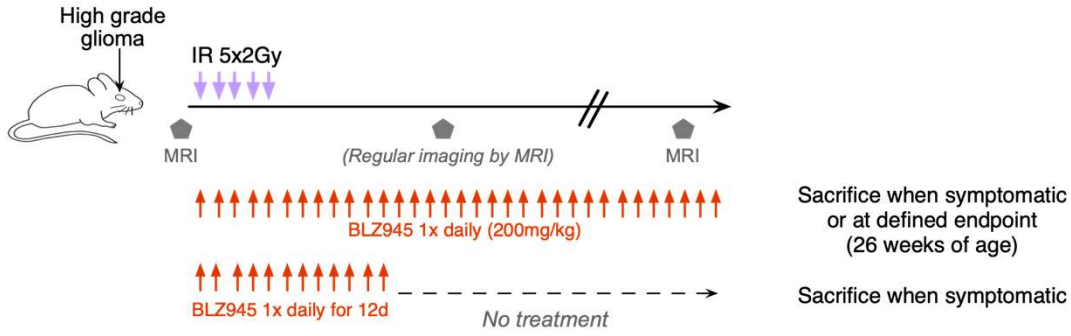
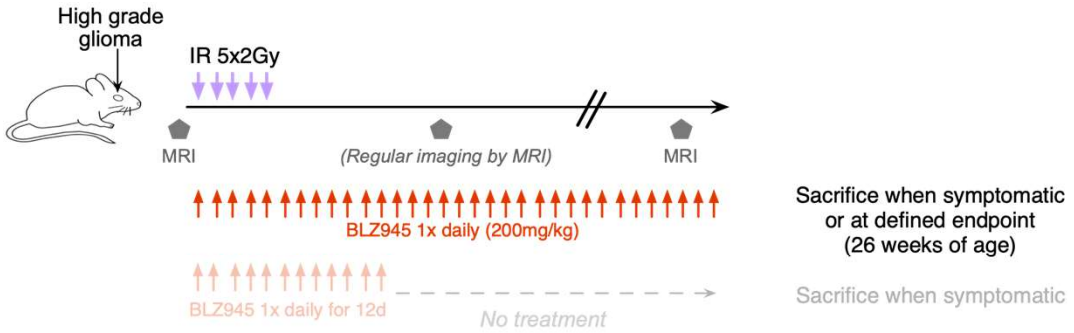
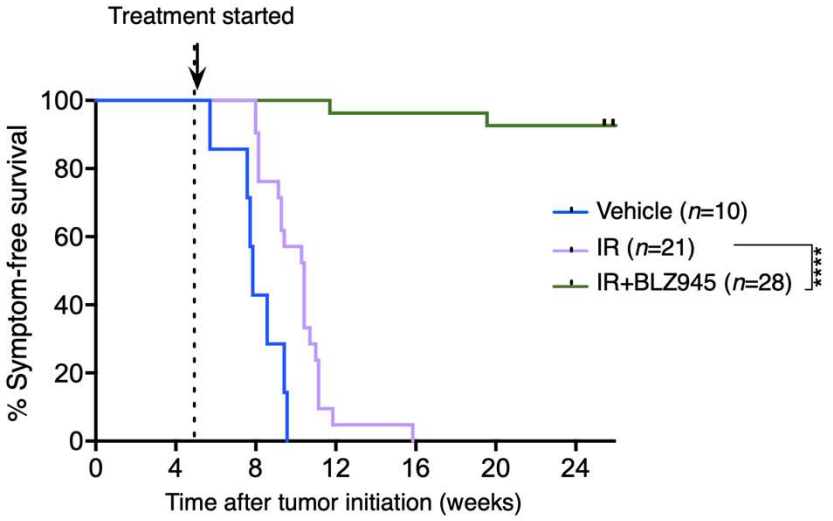


Preclinical Trial Designs Combining CSF-1R Inhibition with Radiotherapy

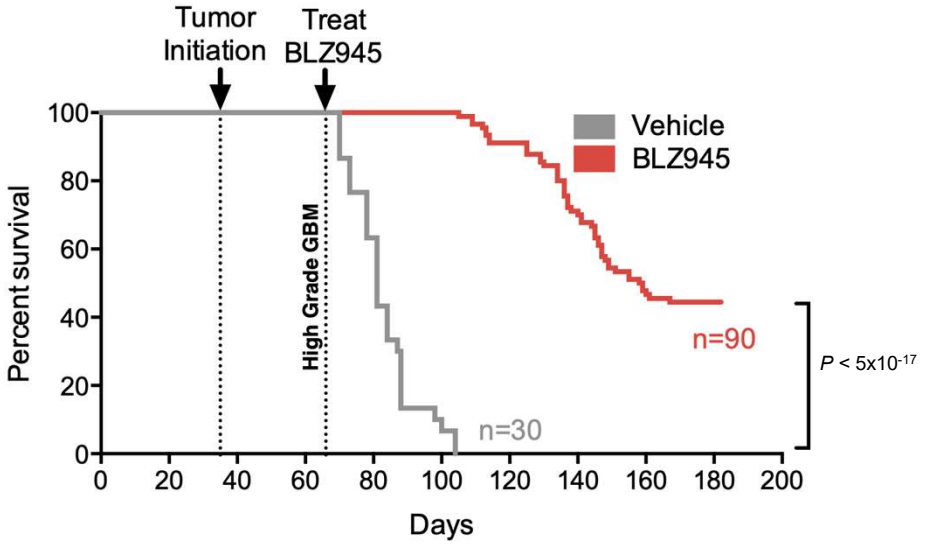


CSF-1R Inhibition in Combination with Radiation Enhances Survival



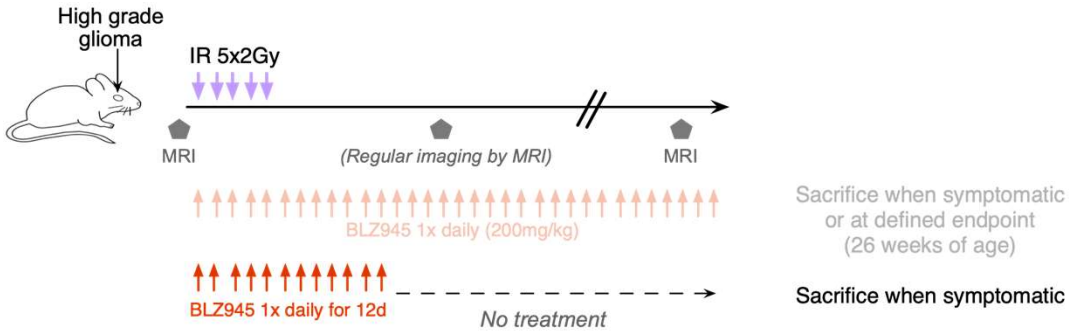


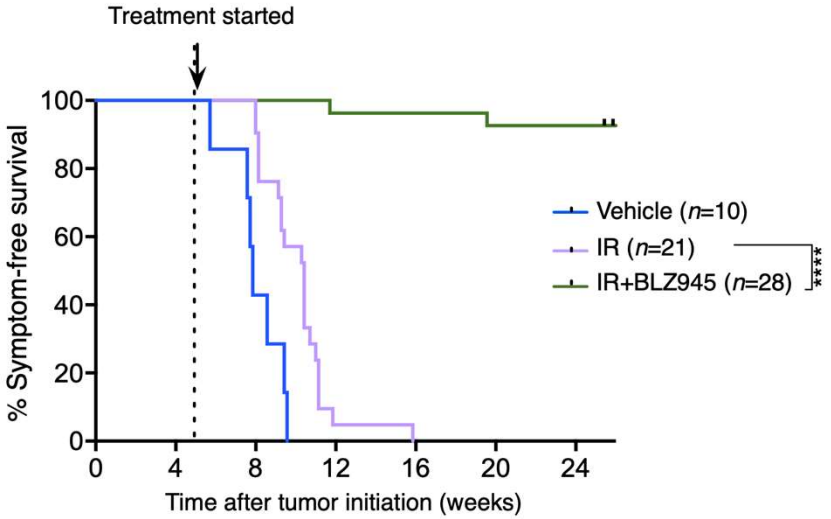
Akkari et al, *Science Translational Medicine* (2020)

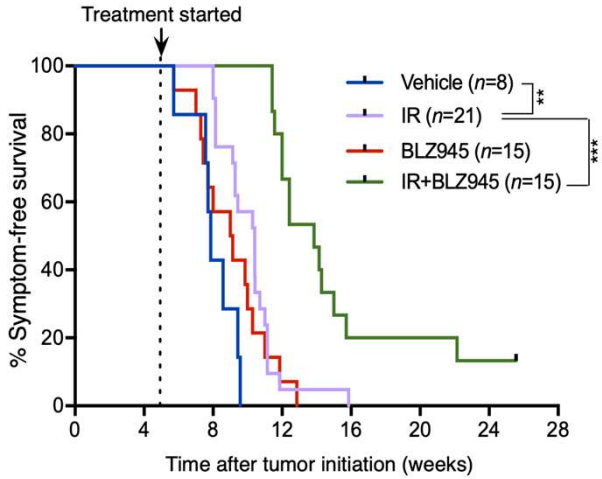


Quail et al, *Science* (2016)

Daily Administration of CSF-1R Inhibitor is Critical for Efficacy

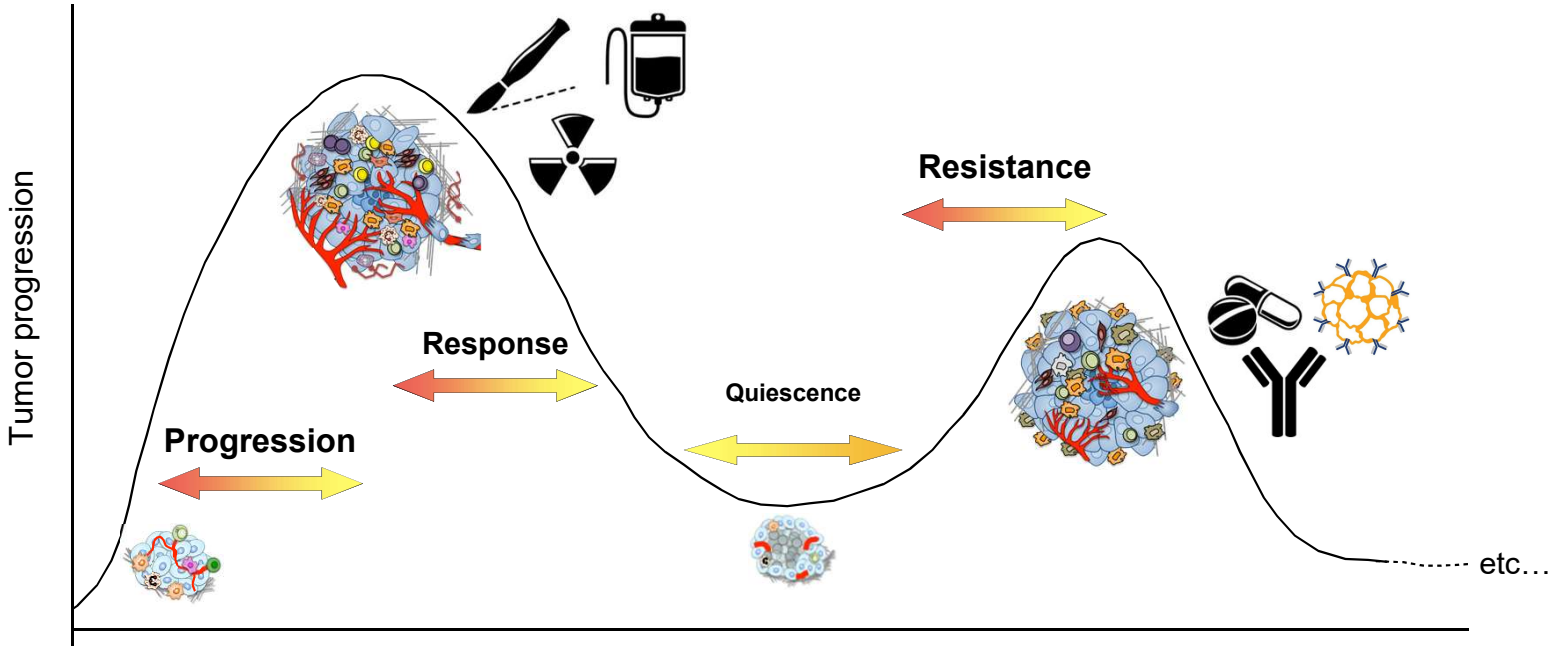






Akkari et al, *Science Translational Medicine* (2020)

Gaining Insights into the *Dynamics* of the Brain Tumor Microenvironment



Longitudinal analyses of patients
- with neurosurgeons, radiation oncologists, neuro-oncologists
@ CHUV Lausanne

In vivo imaging

2-photon/ MRI/ functional probes

Acknowledgements