Role of TWIST1 in GBM Tumorigenicity

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Background

- Glioblastoma (GBM)
  - Invasive phenotype
    → difficult to treat
  - Avg. survival < 1 year
- TWIST1
  - bHLH transcription factor
  - Central regulator of mesenchymal change (EMT) in carcinoma
  - Up-regulated in malignant gliomas
  - Enhances invasion and proliferation

→ Hypothesis: TWIST1 is necessary for GMB tumorigenesis.

Experimental Paradigm

NPC's extracted

Transformed with Akt1 and Ha-RasV12

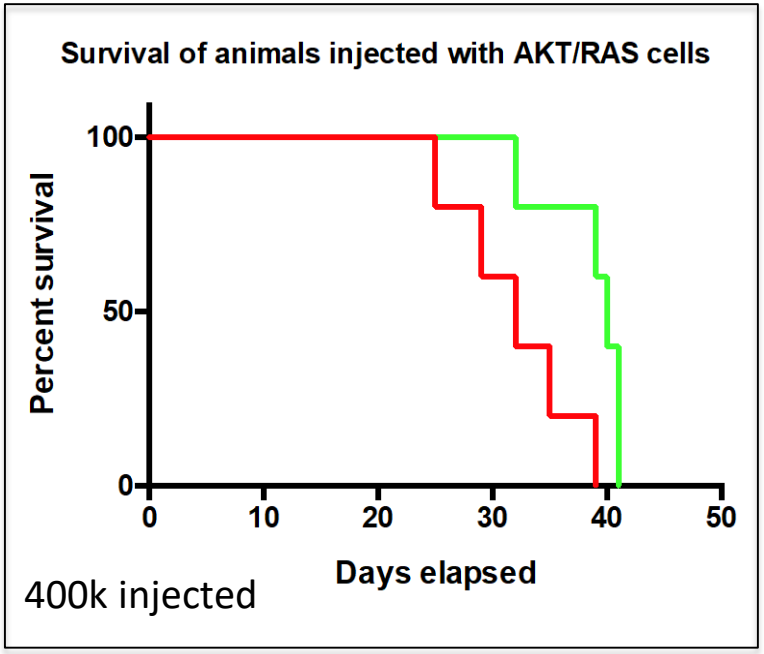
Oncogenic TW +/+

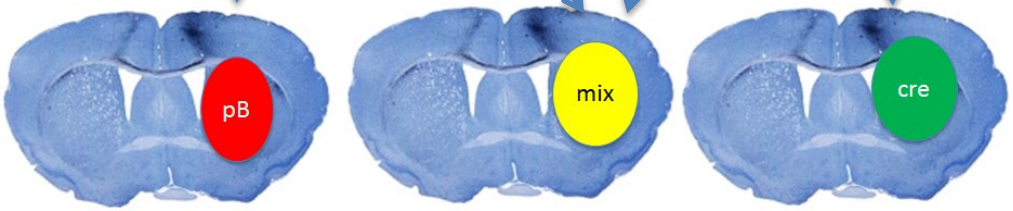
Cre recombinase

FACS sorting showed 99.5% green cells

Oncogenic TW -/-

Oncogenic TW +/+



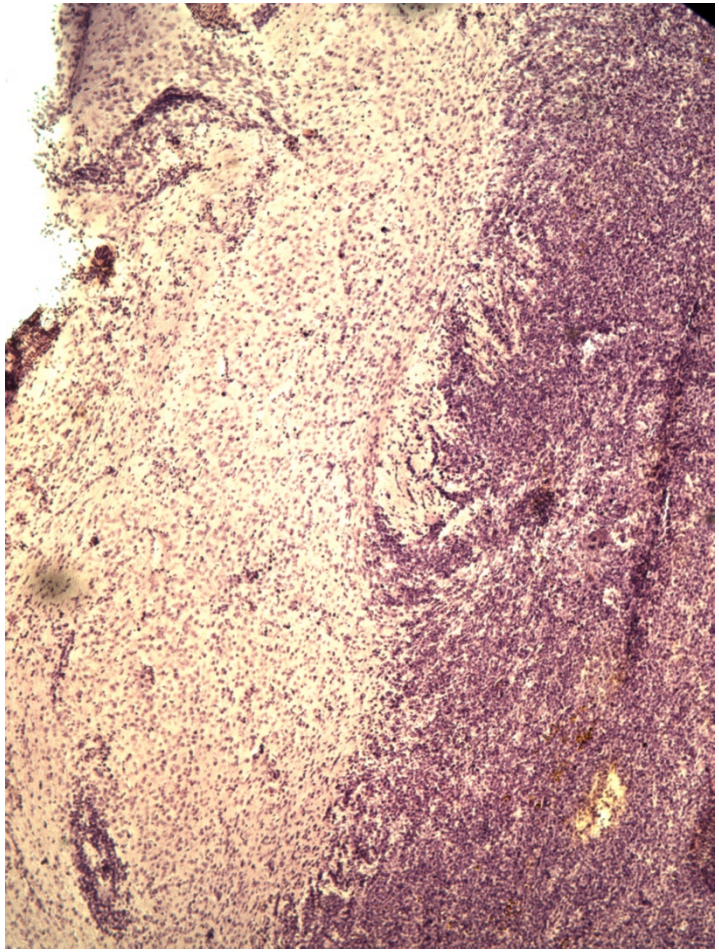


pB TW +/+

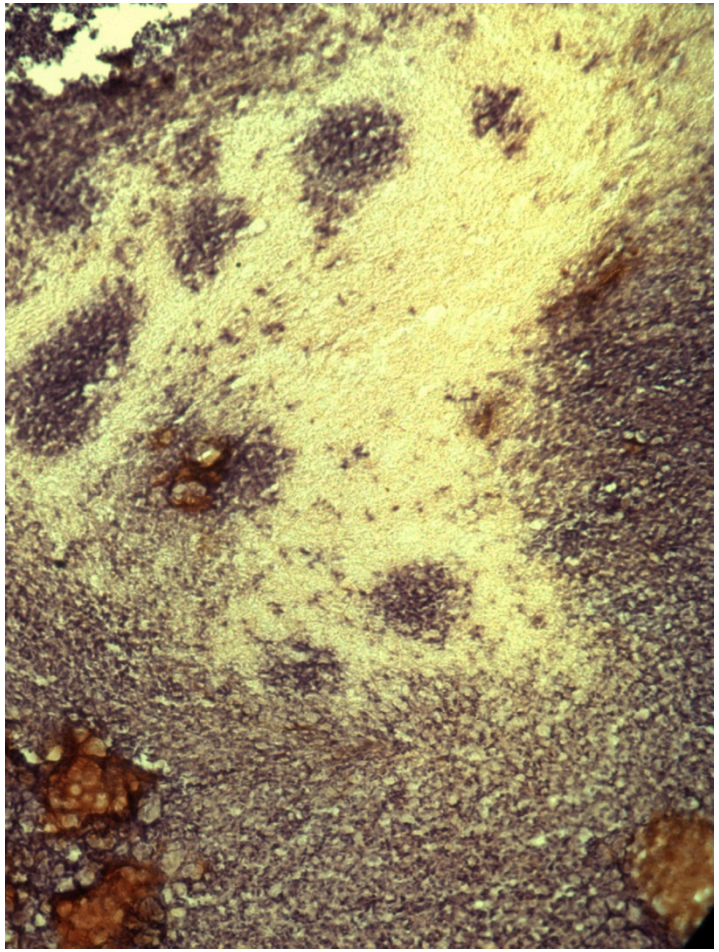
pB TW +/+ + cre TW -/-

cre TW -/-

H&E Staining of 400K Survival Models



47 pB TW +/+



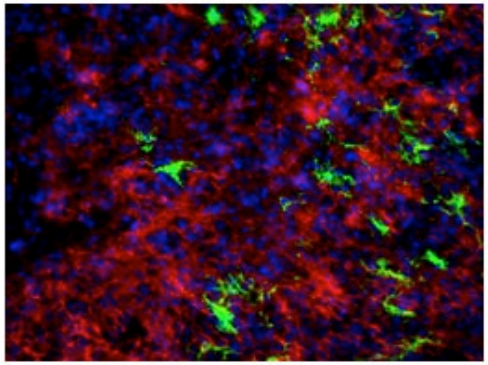
84 cre TW -/-

Survival Tumor Data

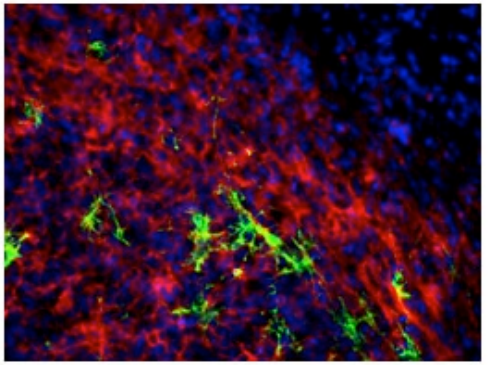
Animal	Cell Type	Cell Number	Tumor
65	AKT pB TW +/+	400K	RED
47	AKT pB TW +/+	400K	RED
70	AKT pB TW +/+	400K	RED
92	AKT pB TW +/+	400K	RED
84	AKT cre TW -/-	400K	RED + green
38	AKT cre TW -/-	400K	RED + green

50/50 co-injections

A30



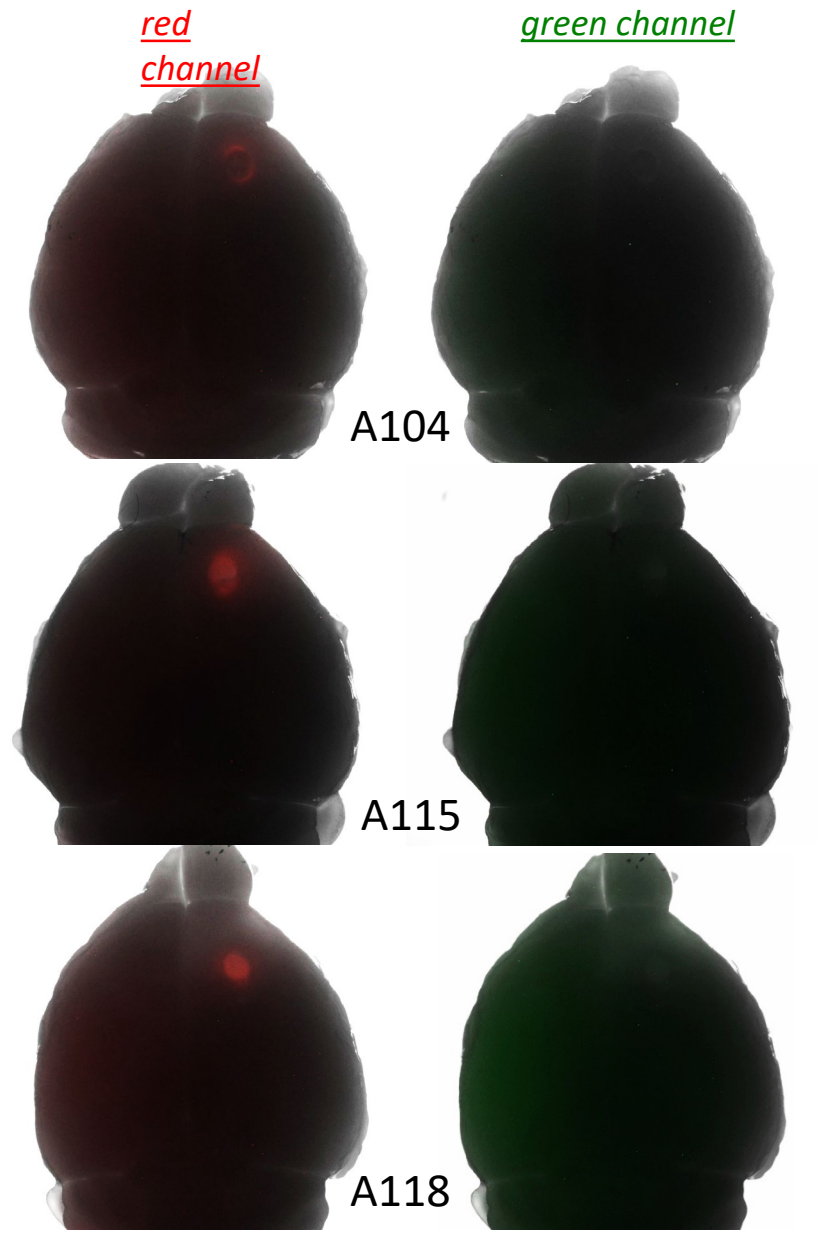
A12



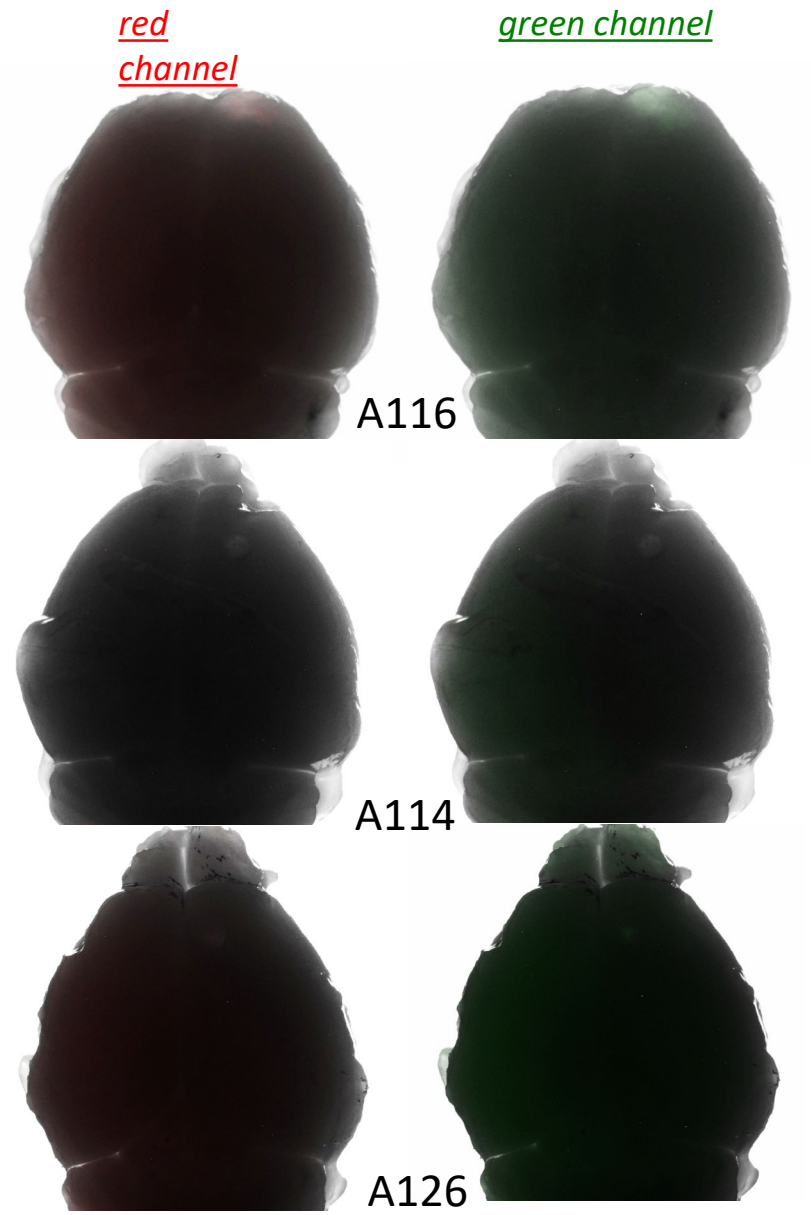
pB TW +/+ cells: red

cre TW -/- cells: green

200K/10d AR pB TW +/+



200K/10d AR cre TW -/-



200K/20d AR pB TW +/+

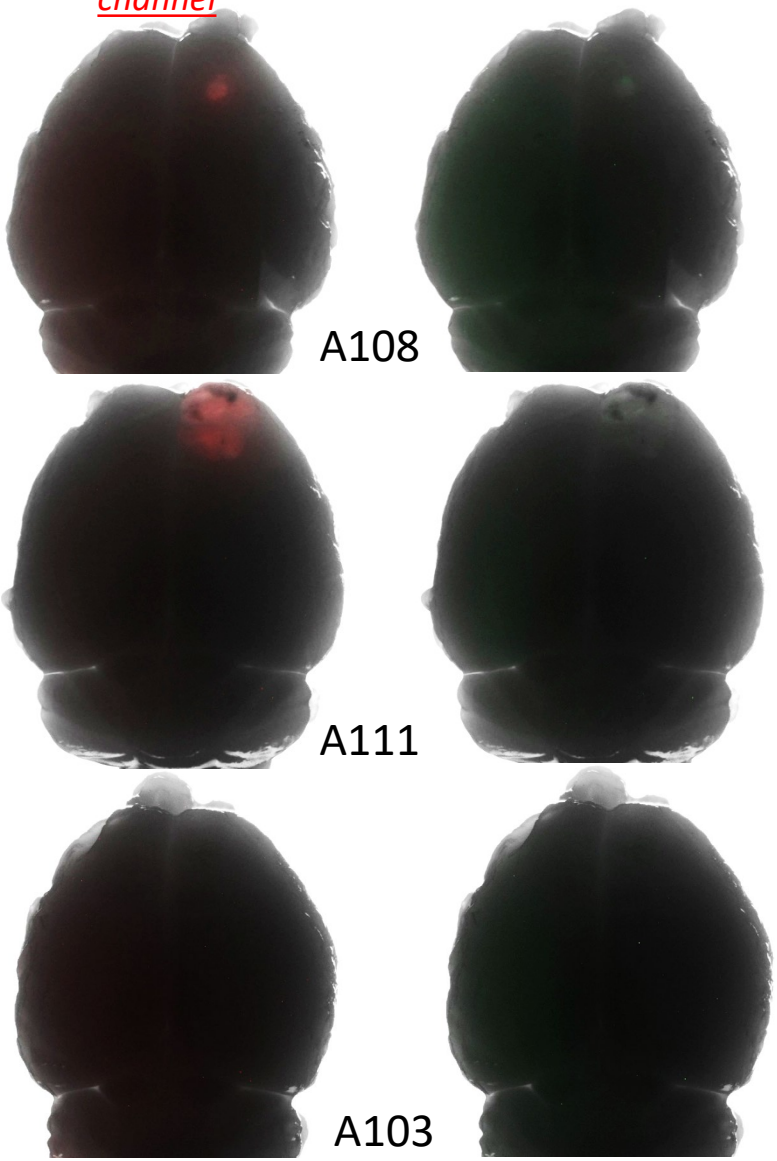
red channel

green channel

200K/20d AR cre TW -/-

red channel

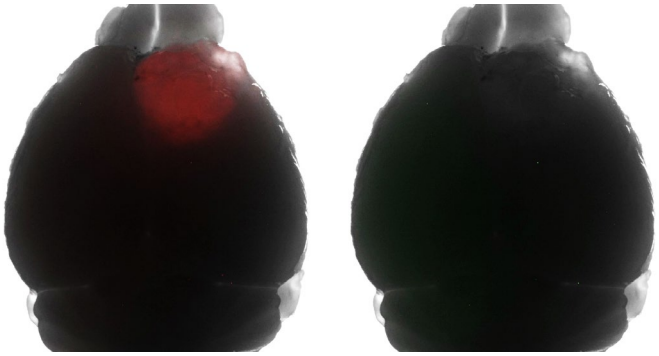
green channel



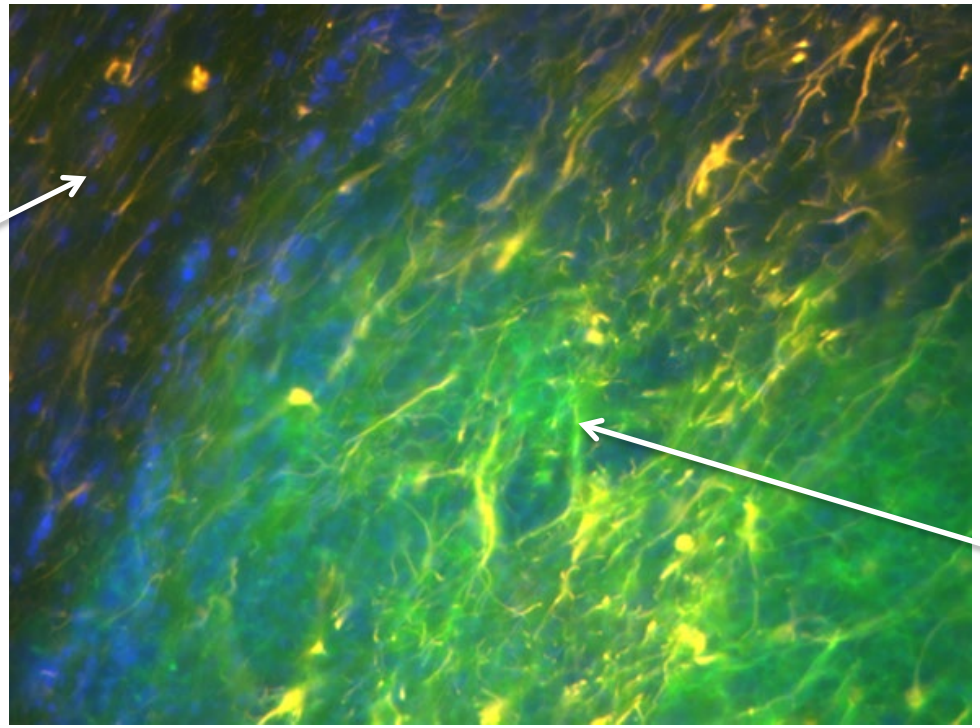
A122

200K/20d

pB TW +/+



pB TW +/+ cells: green GFAP: red



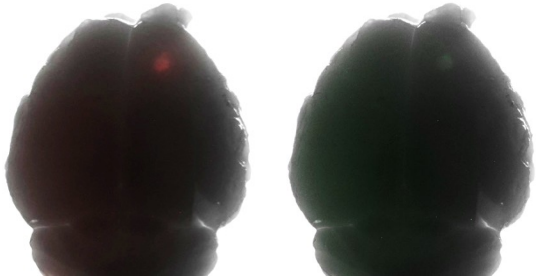
Normal brain

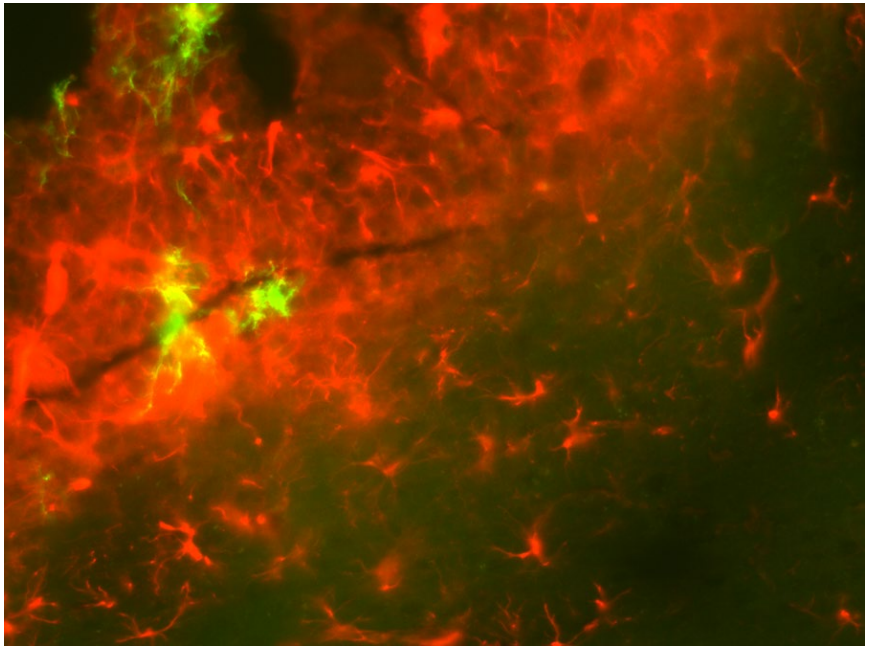
Tumor

A108

200K/20d

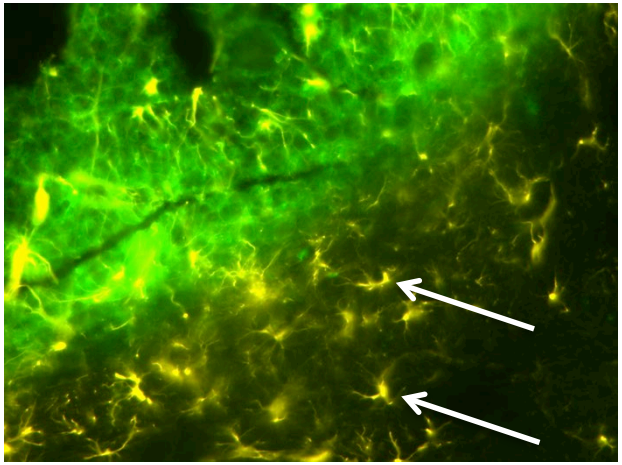
cre TW -/-



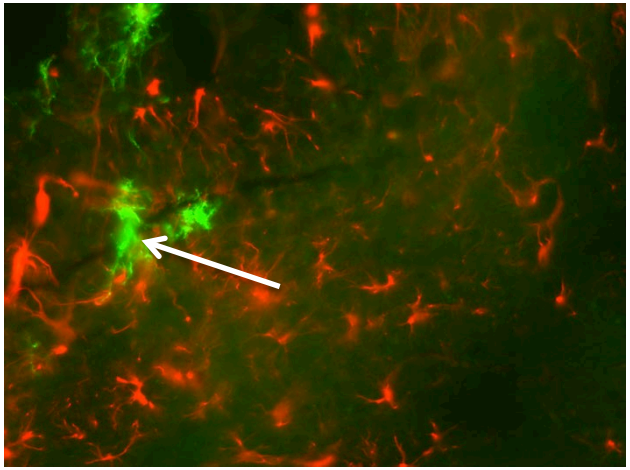


pB TW +/+
cells: red
cre TW -/-
cells: green

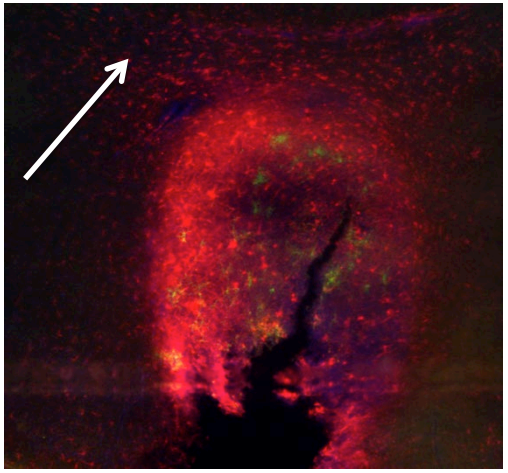
pB TW +/+ cells: green
GFAP: red



cre TW -/- cells: green
GFAP: red



pB TW +/+ cells: red
cre TW -/- cells: green



Conclusions:

- Small minority of TW+ cells can support tumorigenesis (<1% w/ FACS)
- Supports prior indications that TWIST1 promotes invasion and proliferation
- TWIST1 may regulate neural differentiation
- Future studies: Further staining (i.e. Ki67 for proliferation)

THANK YOU!

Dr. Rostomily

Dr. Mikheev

Christina Buckman

Jim Pridgeon

Dr. Ellenbogen

Donors