

Novel murine models of immune competent spontaneously-arising heterogeneous gliomas for evaluating the new classes of chemo-immunotherapeutics

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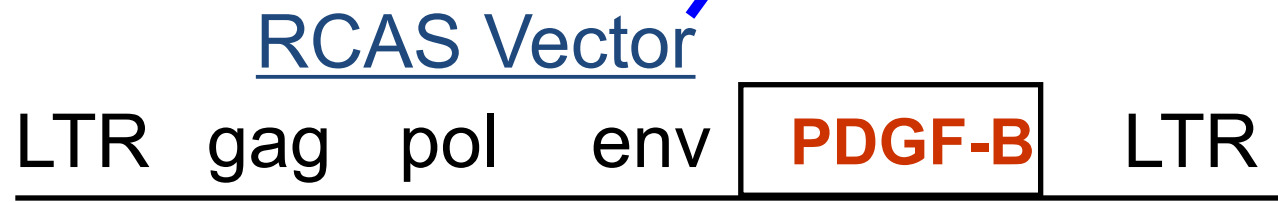
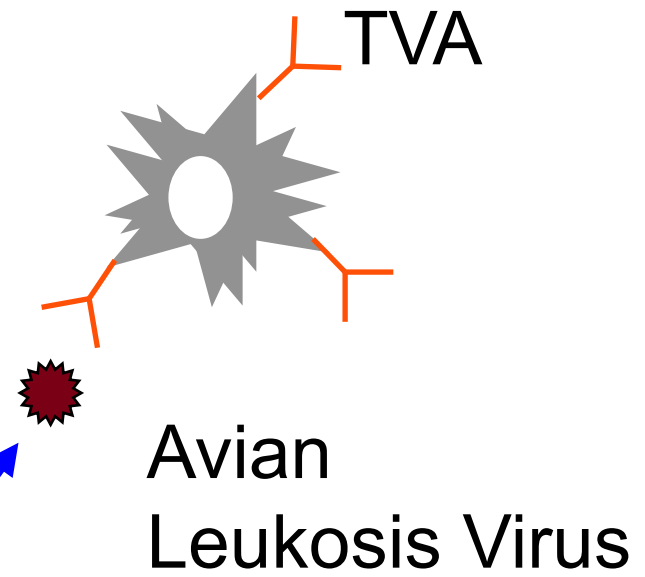
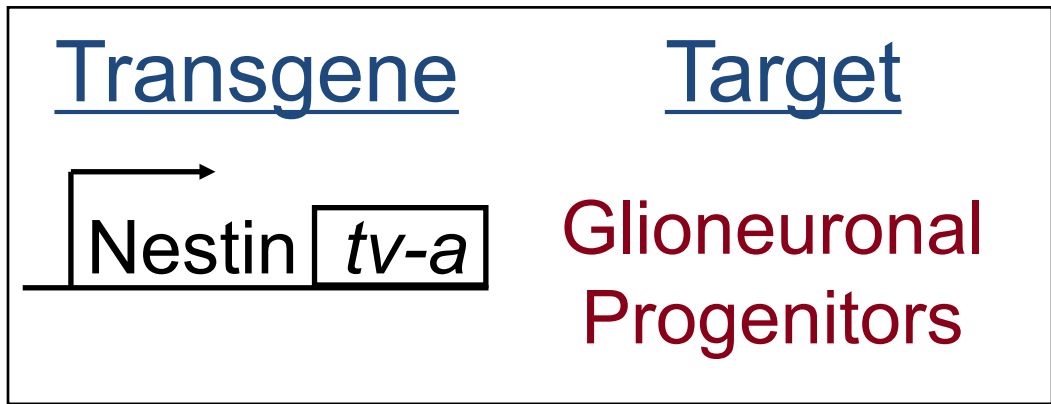
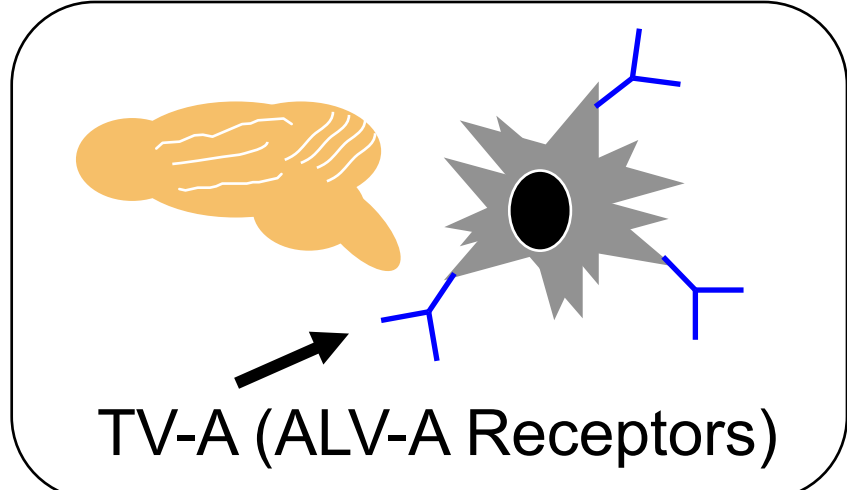
Limitations of current in vivo models for testing immune therapeutics

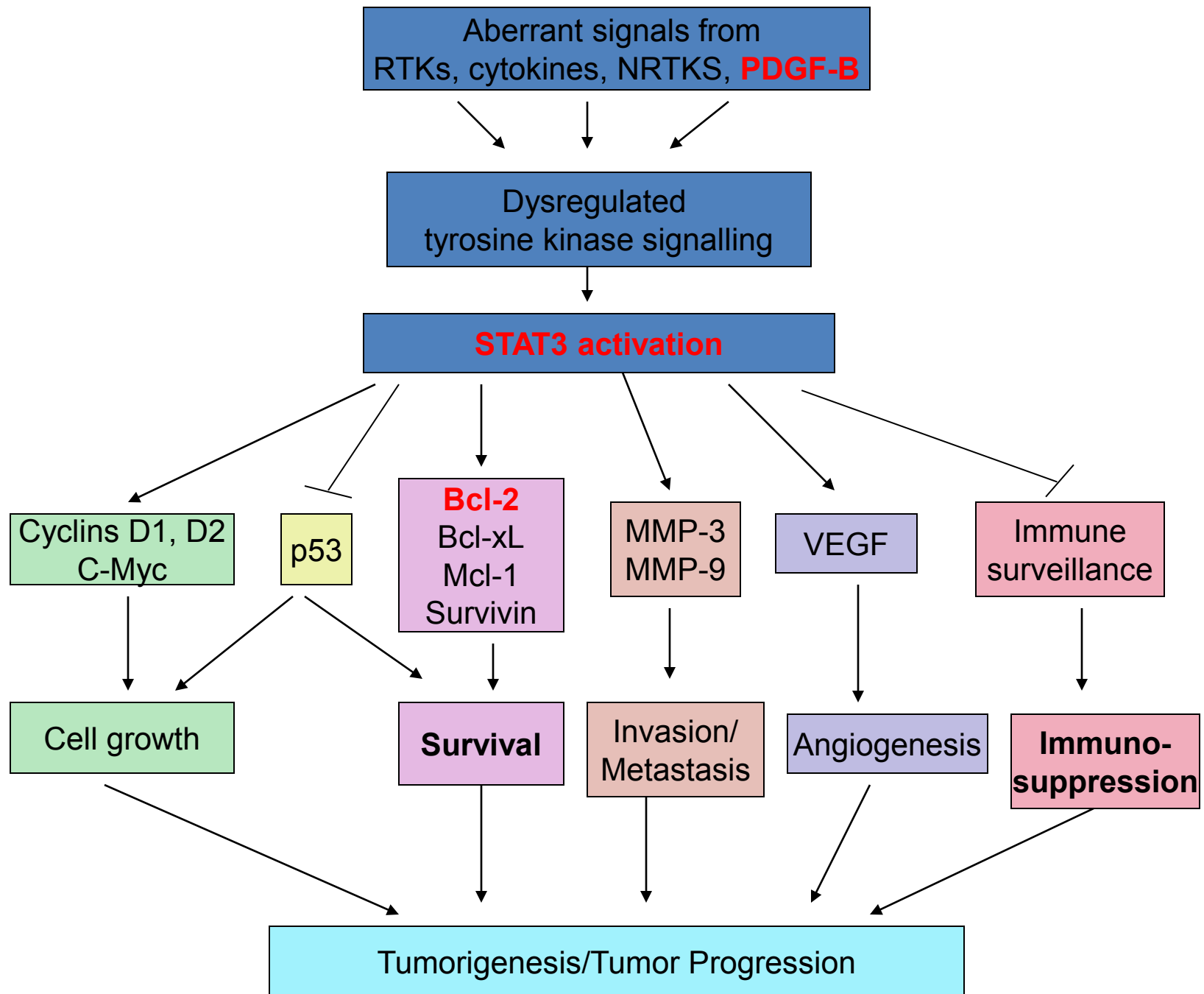
- **Not immune competent.**
- **Cloned cell lines do not recapitulate the heterogeneous nature of intrinsic glioma.**
- **Cell lines perpetuated *in vitro* have significantly reduced immune suppression.**

Therefore, models of spontaneously-arising heterogeneous tumors in immune competent animals are needed for the pre-clinical assessment of immune therapeutics.

The RCAS/*tv-a* System

(Holland, et al, Genes Dev.15:1913, 2001)



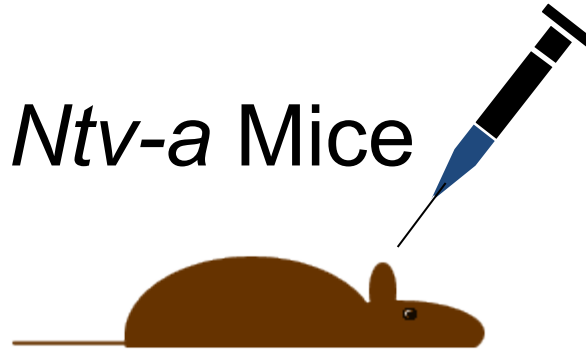


Hypothesis

- (1) STAT3 and Bcl2 enhance tumor formation and grade in a PDGF-B dependent model of glioma.**
- (2) The gliomas formed in Ntv-a mice are immunosuppressive, and high-grade gliomas are more immunosuppressive relative to low-grade gliomas.**
- (3) Endogenously arising malignant gliomas can be used to test chemo-immunotherapeutics, such as the STAT3 inhibitor WP1066.**

Experimental Protocol

Ntv-a Mice



Inject RCAS vectors *
into frontal lobe



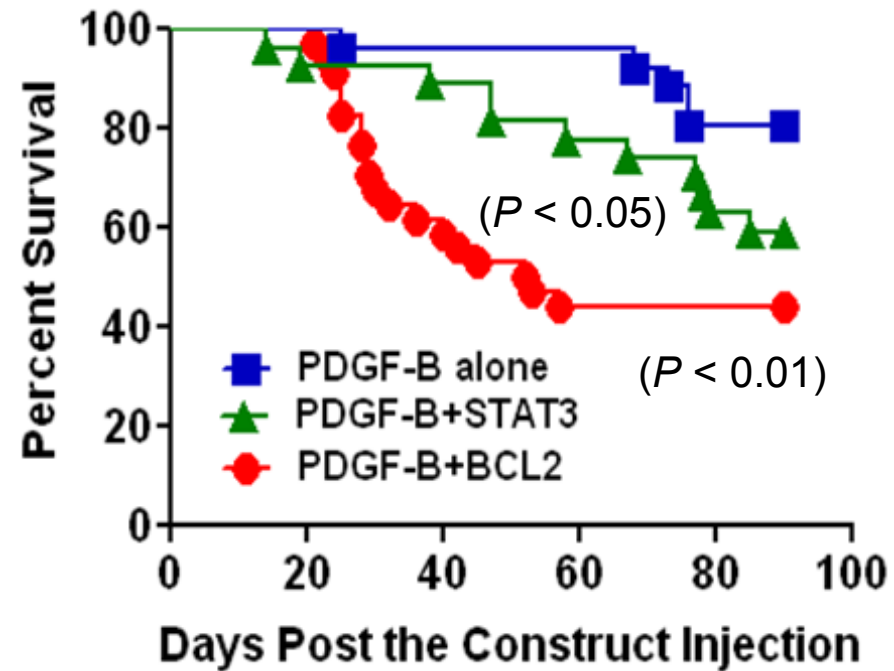
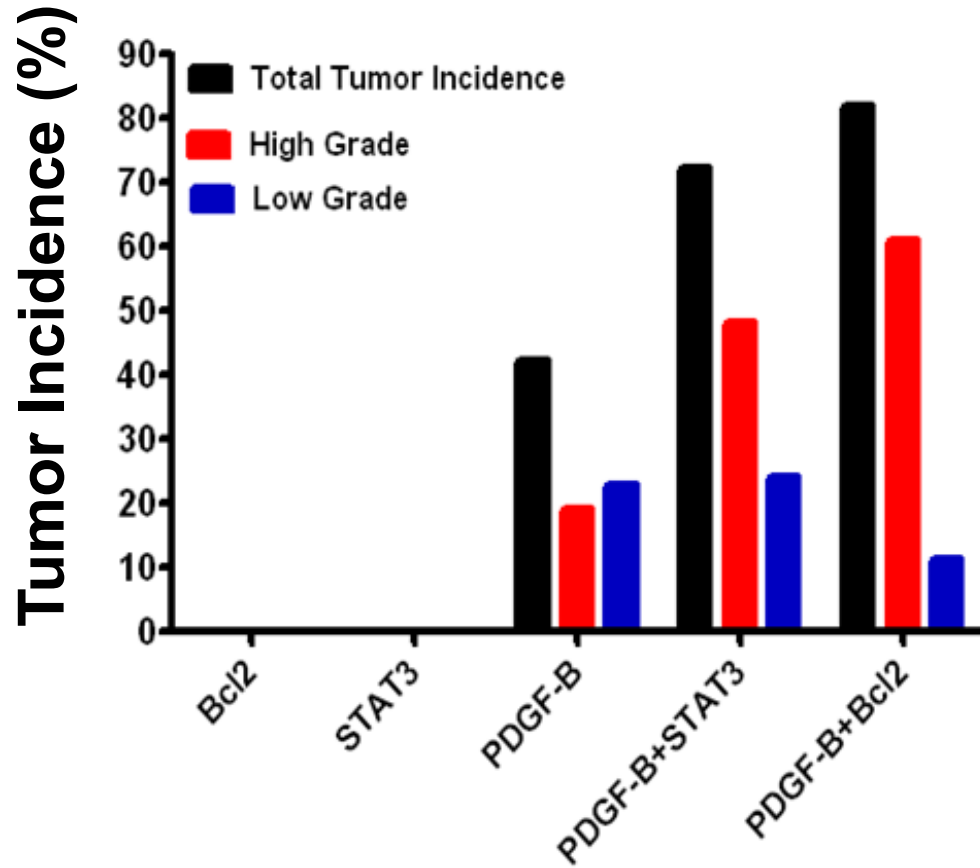
90 day observation; experiment terminated



Histopathological & Immunological Analysis

* PDGF-B, Bcl2, STAT3, PDGF-B + Bcl2, or PDGF-B + STAT3

STAT3 and Bcl2 promote tumor formation, tumor grade, and increase mortality



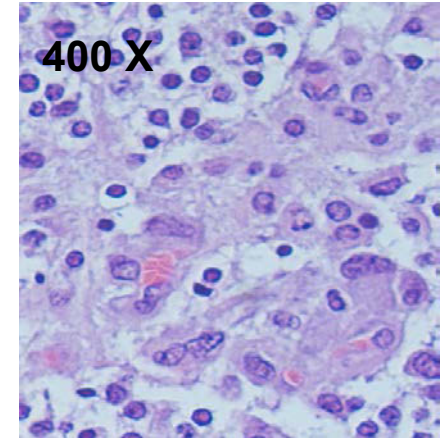
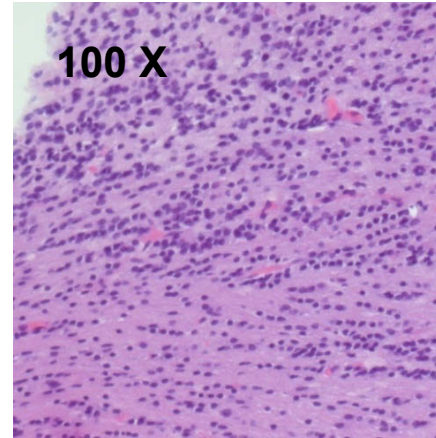
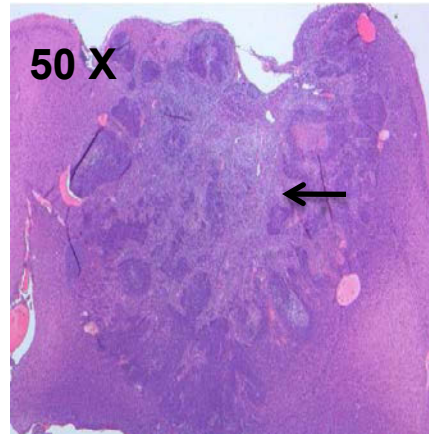
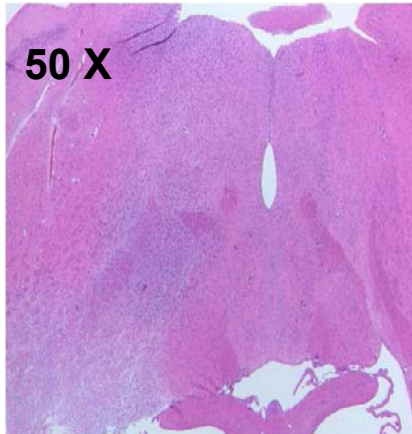
Phenotypic features of *de novo* malignant glioma in a PDGF-B + Bcl2 mouse

Low-grade

High-grade

Infiltration

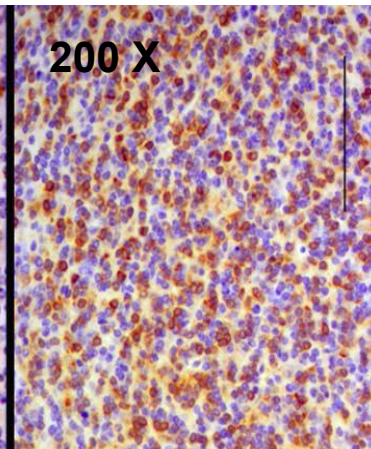
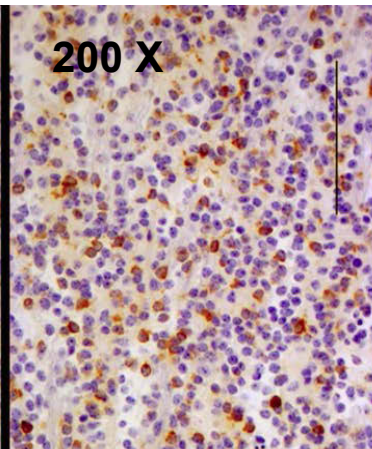
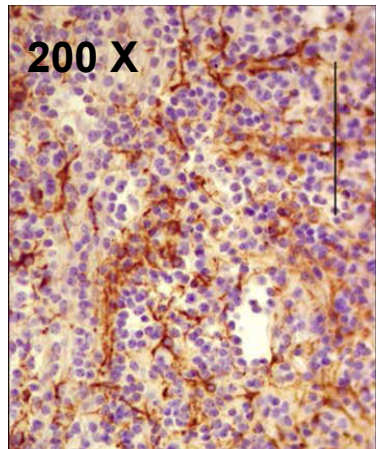
Vascular proliferation



GFAP

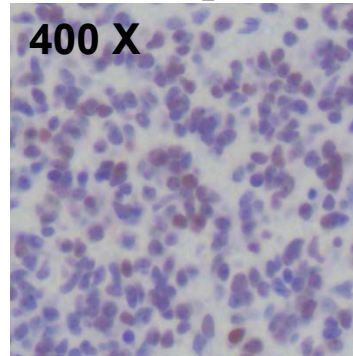
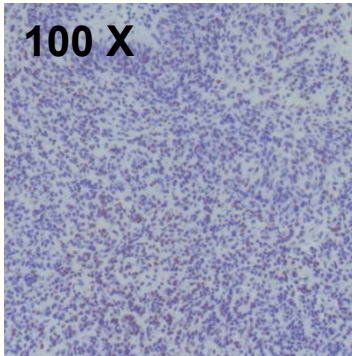
PDGF-B

Bcl-2

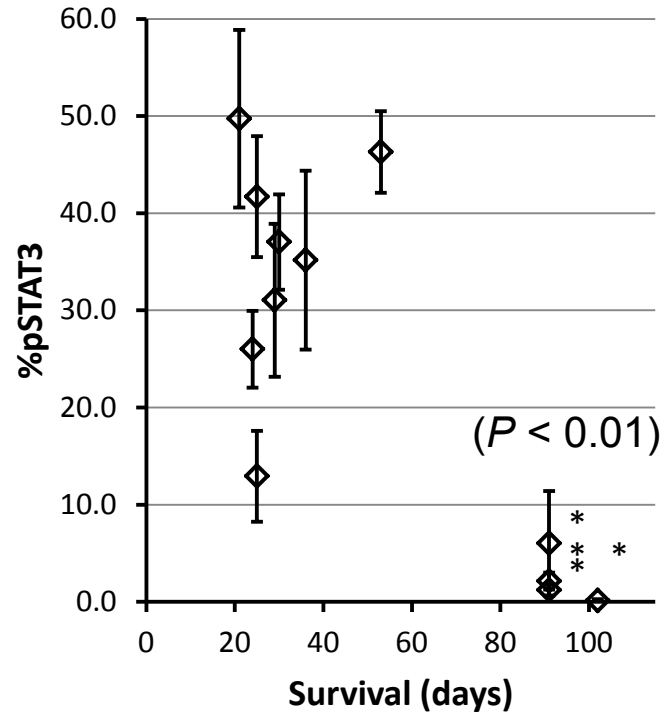
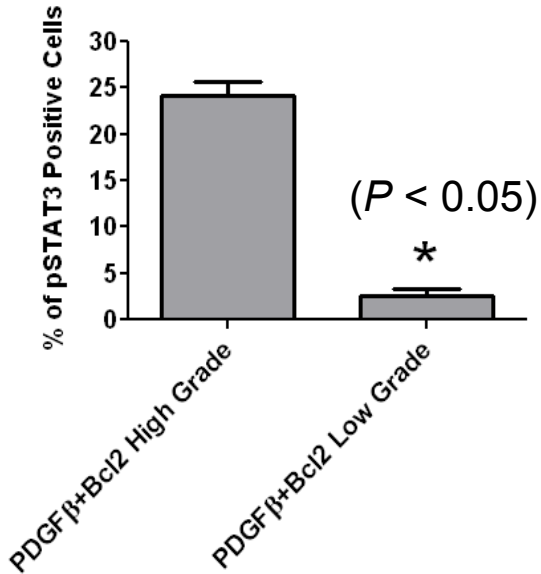
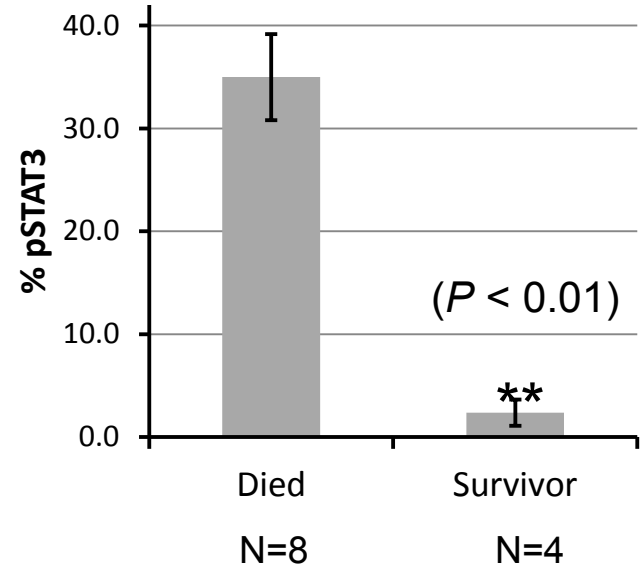
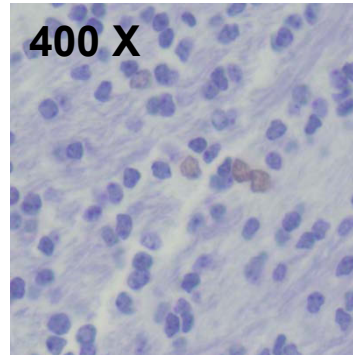
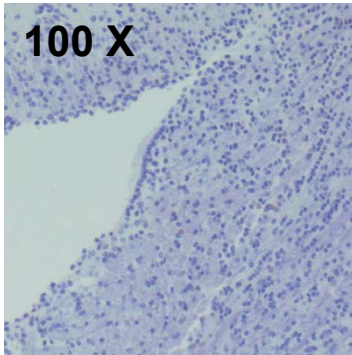


Intratumoral pSTAT3 Expression

High-grade

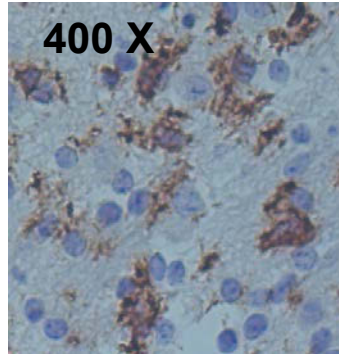
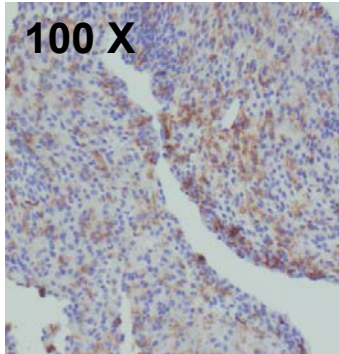


Low-grade

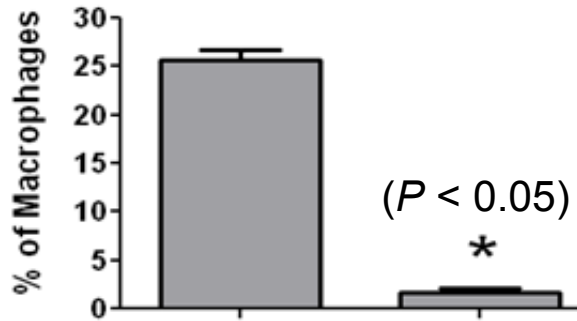
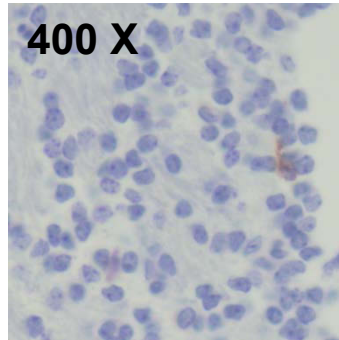
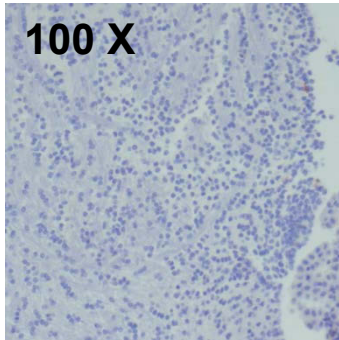


Intratumoral Macrophage Infiltration

High-grade

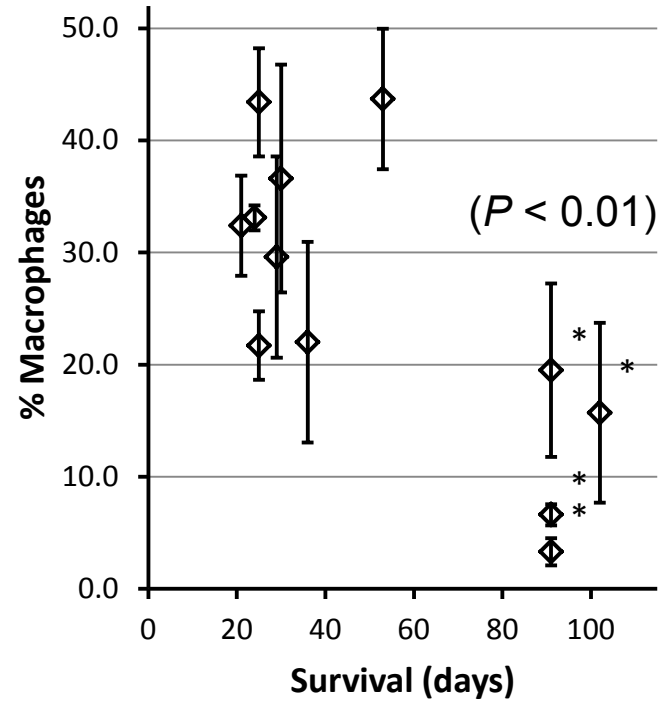
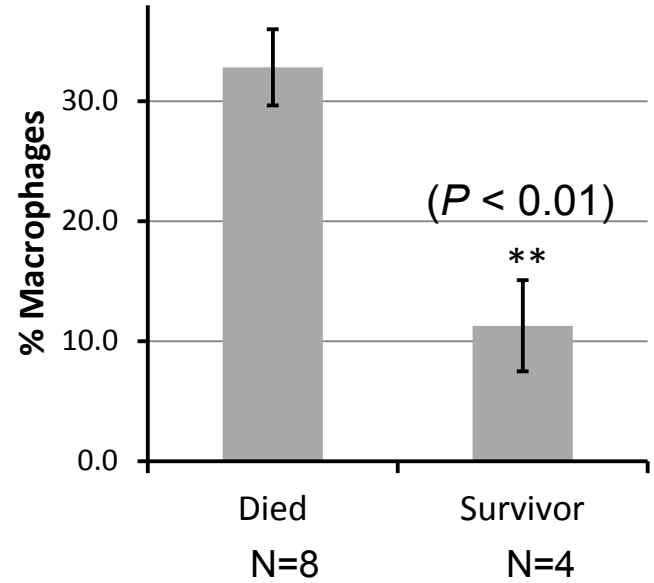


Low-grade

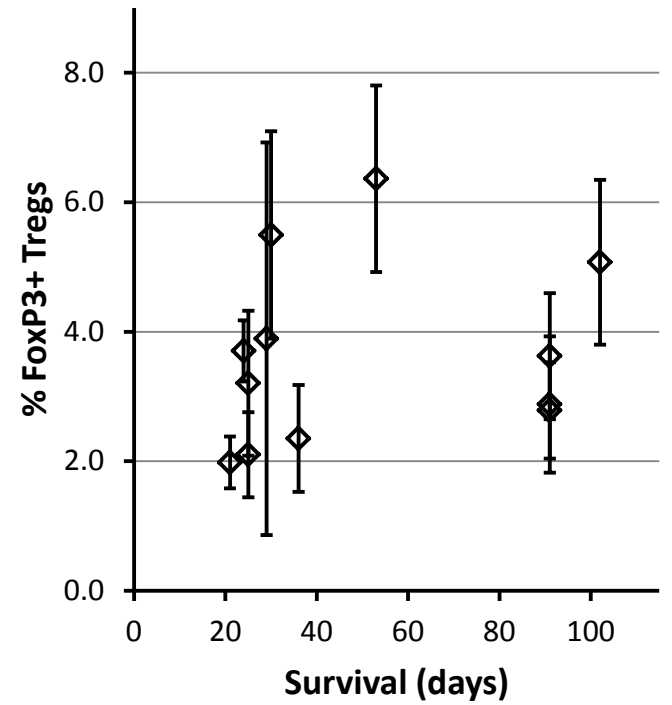
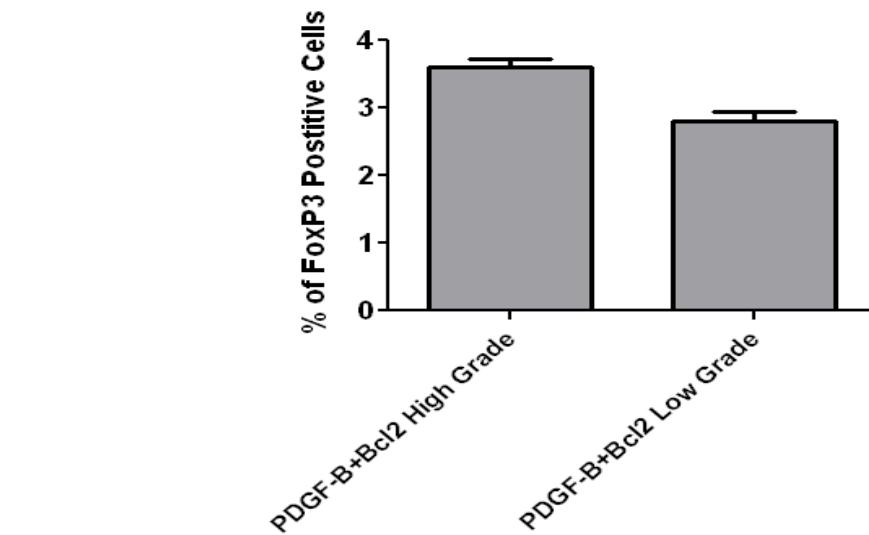
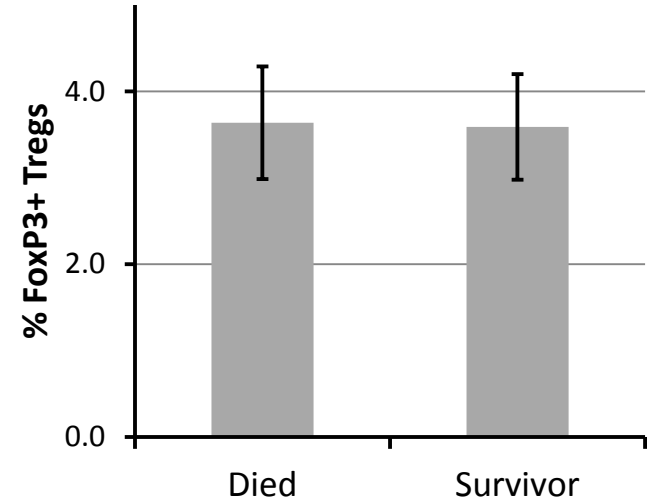
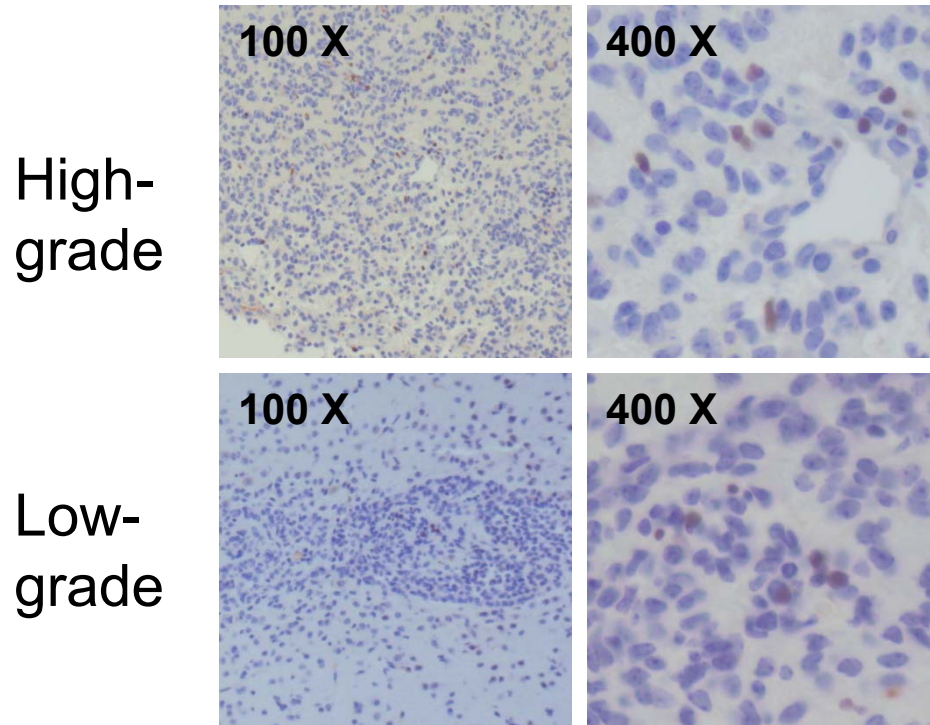


PDGF-B+Bcl2 High Grade

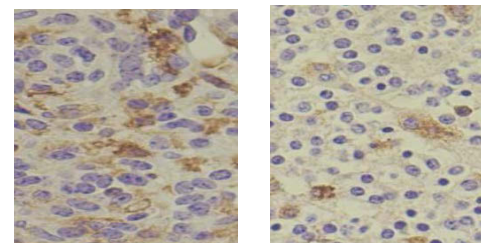
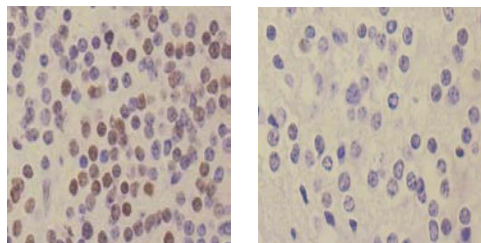
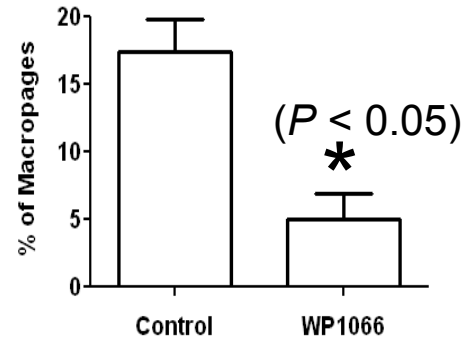
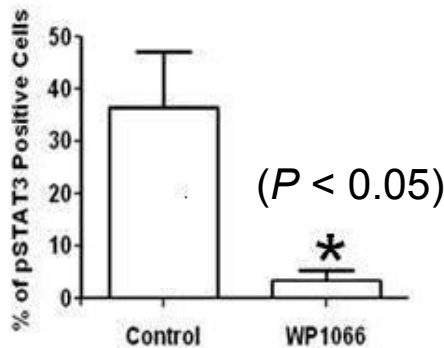
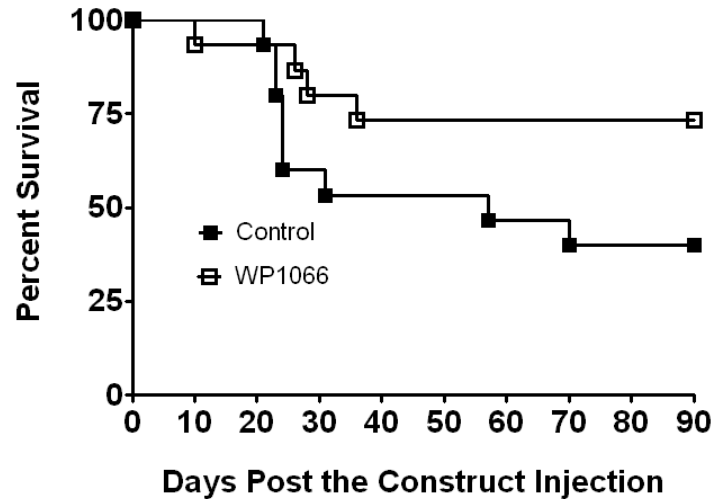
PDGF-B+Bcl2 Low Grade



Intratumoral FoxP3+ Treg Infiltration



The utility of testing immunotherapeutics in heterogeneous immunocompetent model



Summary

- **STAT3 and Bcl2 significantly enhanced tumor formation and grade in a PDGF-B dependent murine model of glioma.**
- **Intratumoral STAT3 expression and macrophage infiltration correlated with tumor grade and have prognostic significance, similar to studies of human gliomas.**
- **The STAT3 inhibitor WP1066 decreased both intratumoral STAT3 expression and macrophage infiltration, which correlated with increased survival.**

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