



Patrick McConville¹, Jonathan B. Moody¹, Alicia Kreger¹, Erin Trachet¹, Richard J. Lister¹, William L. Elliott¹, W. R. Leopold¹ and Eric C. Holland²

¹Molecular Imaging Research, Inc. (MIR) and ²Memorial Sloan-Kettering Cancer Center

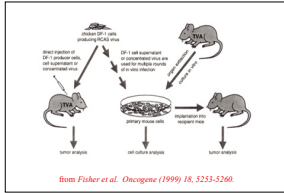
MOTIVATION

1. The Nestin *tv-a* mouse provides a promising model for glioma, driven by specific oncogenes.
2. These models may provide an means for testing novel targeted therapies, and an efficient way of optimizing new combination strategies.
3. A response to Temozolamide has never been characterized in the *Ntv-a* mouse.

AIMS

1. To use T2-weighted MRI to measure *tv-a* glioma growth, response to Temozolamide.
2. To use diffusion MRI to measure *tv-a* glioma cellularity/cell kill response to Temozolamide.
3. To use contrast-enhanced T1-weighted MRI to measure *tv-a* glioma vascular response to Temozolamide.

BACKGROUND



Conventional Transgenics

- Multi-gene defects require complex breeding patterns
- Germ line mutations often lethal to developing animal
- Organ specificity difficult to control

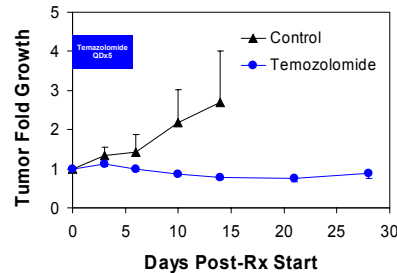
Tv-a Transgenics

- Control/introduction of multiple genetic defects in same model possible
- Somatic gene changes in adult animals
- Timing of defects more easily controlled
 - Simultaneous
 - Sequential
- Organ specificity controlled at multiple levels
 - Tissue specific promoters
 - Direct tissue virus infection
- One transgenic mouse for models of multiple genetic defects
 - Simplified breeding efforts

METHODS

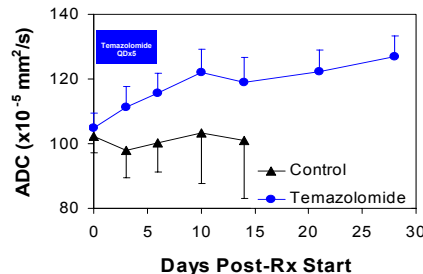
- Mice expressing *tv-a* under the control of the nestin promoter expressed in glial-progenitors (*Ntv-a* mouse) [1] were bred.
- Ntv-a* mice that had developed tumors following intracranial injection with PDGF-encoding RCAS virus [2] were divided into 2 groups (vehicle control, n=5 and Temozolamide treated, n=5).
- T2-weighted fast spin-echo MRI was used to evaluate tumor growth.
- T1-weighted spin-echo MRI pre- and post-contrast agent injection, was used to delineate regions of dense and/or 'leaky' microvasculature.
- Tumor cellularity was also evaluated during the course of the study by diffusion-MRI measurement of the apparent diffusion coefficient (ADC).
- When signs of illness were apparent, animals were sacrificed, and the brains harvested for histology.

Tumor Growth Response



⇒ growth inhibition and regression in the Temozolamide treated group (n=5), compared with a vehicle control group (n=4)

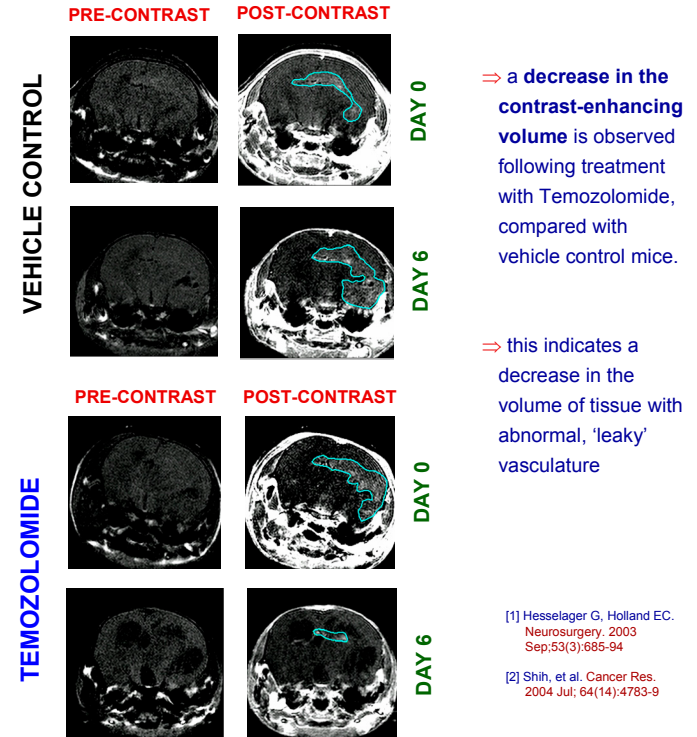
Diffusion Response



⇒ early increase in ADC in the Temozolamide treated group, compared with treated control ADC, indicating efficacy.

RESULTS AND CONCLUSIONS

Contrast-enhancement Decrease



[1] Hesselager G, Holland EC. *Neurosurgery*. 2003 Sep;53(3):685-94

[2] Shih, et al. *Cancer Res*. 2004 Jul; 64(14):4783-9