

High field MRI characterization of tumor growth kinetics, vascularity and cellularity in a PDGF-driven *tv-a* mouse model of glioma



Patrick McConville¹, Jonathan B. Moody¹, Richard J. Lister¹, Alicia Kreger¹, Erin Trachet¹, William L. Elliott¹, Brian D. Ross², Alnawaz Rehemtulla², Eric C. Holland³ and W. R. Leopold¹

¹Molecular Imaging Research, Inc. (MIR), ²University of Michigan and ³Memorial Sloan-Kettering Cancer Center

MOTIVATION

1. RCAS/*tv-a* technology provides a promising new platform for development of tissue-, and oncogenic pathway-specific mouse tumor models.
2. These models may facilitate elucidation of the mechanisms of neoplastic transformation, and development of targeted treatments.
3. MRI has unique capabilities in characterization of tumor appearance, growth, heterogeneity, cellularity and vascularity in *in vivo* models.

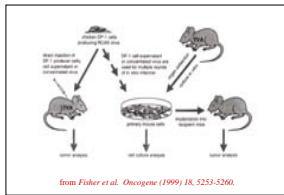
AIMS

1. To use high field (7T) MRI to characterize tumor appearance, heterogeneity and growth.
2. To characterize vascularity (with contrast enhanced MRI), tumor cellularity (diffusion MRI).
3. To correlate MRI findings with histology.

BACKGROUND

METHODS

RESULTS AND CONCLUSIONS



Conventional Transgenics

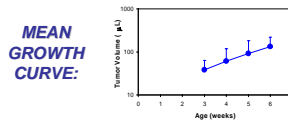
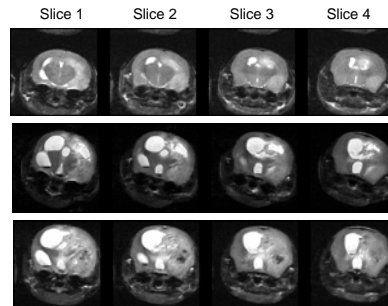
- Multi-gene defects require complex breeding patterns
- Germ line mutations often lethal to developing animal
- Organ specificity difficult to control

T-va 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

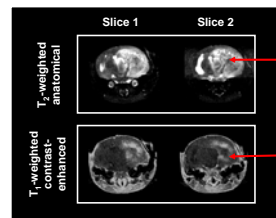
- Mice expressing *tv-a* under the control of the nestin promoter expressed in glial-progenitors (*Ntv-a* mouse) [1] were bred.
- 40 *Ntv-a* mice that had developed tumors following intracranial injection with PDGF-encoding RCAS virus [2] underwent weekly MRI to characterize tumor growth and development.
- 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.
- 10 *Ntv-a* mice were used in a pilot studying the effect of Temozolamide in this model, as determined by the above MRI methods.

Tumor Growth in a *Ntv-a* Mouse High Grade Glioma



Mean Doubling Time = 11.1 ± 2.7 days

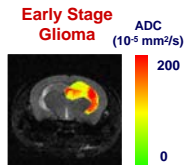
Vascularity in a *Ntv-a* Mouse High Grade Glioma



Dark regions indicate necrosis, typical of high grade glioma

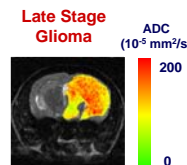
Ring enhancement pattern is typical of high grade glioma and identifies regions with abnormal vasculature

Tumor Cellularity: Diffusion MRI in the *Ntv-a* Mouse



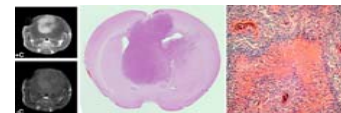
- the water apparent diffusion coefficient (ADC) is inversely proportional to tumor cellularity

⇒ higher cellularity (lower ADC) in the tumor margins



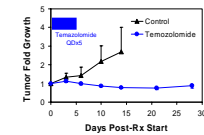
- lower cellularity (higher ADC) in the tumor core and ventricular regions

Histology

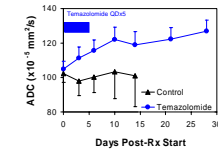


- histology confirms the high cellularity typical of glioblastoma multiforme, and correlates well with anatomical and contrast-enhanced MRI (left panels)

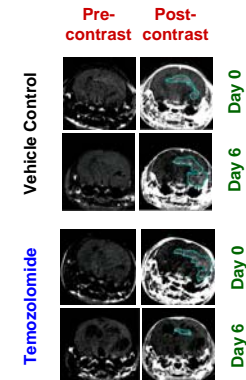
Treatment Response with Temozolamide



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



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



- a decrease in the contrast-enhancing volume is observed following treatment with Temozolamide, compared with vehicle control mice.

- this indicates a decrease in the volume of tissue with abnormal, 'leaky' vasculature

[1] Hesselager G, Holland EC. *Neurosurgery*. 2003 Sep;53(3):685-94
[2] Shih, et al. *Cancer Res*. 2004 Jul; 64(14):4783-9