MRI Characterization of Tumor Development in a *tv-a* Transgenic Mouse Model of Glioma

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INTRODUCTION: RCAS/*tv-a* technology (1,2) provides a promising new platform for development of tissue-, and oncogenic pathway-specific mouse tumor models, for elucidation of mechanisms of neoplatistic transformation, and for development of targeted treatments. The technology relies on somatic gene transfer through infection by RCAS viral vectors derived from the avian retrovirus (ALV-A) in mice expressing the gene for the RCAS receptor (*tv-a*). We characterized tumor appearance, growth and heterogeneity using high field MRI in a mouse that expresses *tv-a* under the control of the nestin promoter expressed in glial-progenitors (*Ntv-a* mouse).

METHODS: 19 *Ntv-a* mice that had developed tumors following intracranial injection with ALV virus encoding PDGF at 3 weeks of age (as determined by MRI) underwent weekly brain MRI to characterize tumor growth and development, until they reached a moribund state and were sacrificed. T2-weighted fast spin-echo MRI was used (3 minute images). At multiple time points, tumors were also evaluated using T1-weighted spin-echo MRI (3 minute images), pre- and post-contrast agent injection, 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.

RESULTS AND DISCUSSION: The mean time for tumor appearance was 3.3 ± 0.4 weeks. After appearance, the tumors grew rapidly (2 week doubling time) and invasively, invading one or both ventricles (see Figure). Tumor cellularity was higher at the outer margins, with ADC similar to that which has been measured in implanted glioma xenografts (~100-120 cm^2/s). Early stage tumors showed little enhancing after contrast injection, but localized enhancing regions were evident in late stage tumors (See Figure). Histologic sections correlated well with T2-weighted contrast and ADC, confirming localized regions of high cellularity.

CONCLUSION: We have characterized tumor growth, heterogeneity, vasculature and cellularity using high field, high-throughput MRI for the first time in the PDGF-driven *Ntv-a* mouse model. The MRI-measured tumor characteristics were very similar to those measured clinically in oligodendroglioma, with late stage tumors showing contrast-enhancing regions typical of malignant tissue. This study demonstrates the unique capabilities of MRI in the *Ntv-a* model, for following tumor appearance and development, showing its potential for pre-clinical efficacy studies in this model. Future use of high field MRI in other *tv-a* models will further highlight this potential.

REFERENCES: 1. Holland and Varmis (1998), PNAS, **95:**1218
2. Xu et al. (2003) Magn Reson Med **49(3):**551-7