

## ***KEAP1* aberrant methylation is a novel marker of patients outcome in malignant gliomas**

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The Keap1 (Kelch-like ECH-associated protein 1) protein tightly regulates the functions of Nrf2 (nuclear factor-erythroid 2-related factor 2) which plays a pivotal role in the cellular response to oxidative stress. We determined whether *KEAP1* gene is epigenetically regulated in malignant gliomas and if promoter aberrant methylation may impact patient's outcome. We developed a QMSP assay to analyze 86 malignant gliomas and 20 normal brain tissues. The discriminatory power of the assay was assessed by ROC curve analysis. The AUC value of the curve was 0.823 (95%CI: 0.764-0.883) with an optimal cut off value of 0.133 yielding a 74% sensitivity (95%CI: 63%-82%) and an 85% specificity (95%CI: 64%-95%). Bisulfite sequencing analysis confirmed QMSP results and demonstrated a direct correlation between percentage of methylated CpGs and methylation levels (Spearman's Rho 0.929, P=0.003). Remarkably, a strong inverse correlation was observed between methylation levels and *KEAP1* mRNA transcript in tumour tissue (Spearman's Rho -0.656 P=0.0001) and in a cell line before and after treatment with 2-deoxy-5 Azacytidine (P=0.003). RECPAM multivariate statistical analysis studying the interaction between *MGMT* and *KEAP1* methylation in subjects treated with radiotherapy and temozolomide (n=70), identified three prognostic classes of glioma patients at different risk to progress. While simultaneous methylation of *MGMT* and *KEAP1* promoters was associated with the lowest risk to progress, patients showing only *MGMT* methylation were the subgroup at the higher risk (HR 5.54, 95% CI 1.35-22.74). Our results strongly indicate that aberrant *KEAP1* methylation may represent a novel predictor of outcome in glioma patients.

### **Biography**

Paola Parrella received the Medical Doctor degree (summa cum laude) in 1993. From 1998 to 2002 she was a Post Doctoral Fellow at the Division of Head and Neck Cancer Research at The Johns Hopkins University, Baltimore USA. Since 2002 she is Staff Scientist at the Laboratory of Oncology, IRCCS Casa Sollievo della Sofferenza (FG), Italy. Dr. Parrella is the author of more than 40 peer reviewed publication and Principal Investigator and co-investigator of several grants related to cancer biomarkers development.