

Layterm Summary

As a result of advances in glioblastoma (GBM) treatment, the current standard-of-care for GBM patients is surgical resection followed by a combination of radiation therapy and chemotherapy with the medication temozolomide. Clinical studies have shown this regimen can provide a significant prolongation of life. Unfortunately, virtually all patients have tumor recurrence despite this treatment and suffer disease progression with ultimately fatal outcomes. Our current research effort has aimed toward understanding the processes underlying this emergent chemoresistance in GBMs. Work from our research group and other groups has led to the proposal that the mismatch repair (MMR) pathway can play a role in GBM chemoresistance. Under the NBTF GBM Grant, we seek to fully characterize the MMR pathway in recurrent GBMs by performing large-scale DNA sequence analysis of MMR genes in patient tumors and immunohistochemical stains of surgical specimens. Should MMR pathway inactivation prove to be a significant component of GBM chemoresistance, specific targeting of the MMR pathway in combination with existing treatments could be synergistic for tumor control. A number of experimental studies have proposed to improve GBM treatment in the future by combination of novel agents with the existing standard-of-care radiation and temozolomide. These efforts will be aided by research such as ours to detail the molecular events in GBM that contribute to chemoresistance.

A note regarding collaborations:

Rebecca A. Betensky, PhD is Associate Professor of Biostatistics at the Harvard School of Public Health with extensive expertise in the field of statistical analysis of large-scale genetic data. We have an ongoing collaboration with Dr. Betensky studying subgroup determination of human glial tumors at the molecular and histopathologic level. This collaboration will continue for analysis of tumor subgroup data generated under the 2006 National Brain Tumor Foundation GBM grant.

Mike Stratton, MB BS, PhD, MRCPATH, FMedSci is Professor of Cancer Genetics at the Institute for Cancer Research and Head of the Cancer Genome Project at the Wellcome Trust Sanger Institute in the United Kingdom has a large collaborative effort seeking to delineate the molecular genetic changes associated with various cancer subtypes. The preliminary data reported in this proposal were collected in collaboration with our research effort examining the molecular genetics of glioblastoma. This collaboration will continue for analysis of MMR-deficient tumors identified as part of the 2006 National Brain Tumor Foundation GBM grant.

Letters of collaboration from Dr. Betensky and Dr. Stratton were omitted due to space limitations – they are available on request.