The Louis laboratory studies the biological basis of human brain tumors in order to understand which molecules go awry in the formation of brain tumors. Understanding the molecular basis of human brain tumors enables improved diagnosis, better assessment of patient prognosis, more precise prediction of response to existing therapies, greater understanding of resistance to current chemotherapies, and design of novel treatments. For example, our studies showing that molecular genetic alterations are powerful predictors of therapeutic response and survival in patients with anaplastic oligodendrogliomas and other oligodendroglial tumors have led to changes in diagnostic protocols worldwide for these tumors.

Our laboratory investigates the molecular genetic basis of human brain tumors. Brain tumors are the second most frequent malignancy of childhood, and their incidence in adults increases with advancing age. These tumors are also among the most devastating of human malignancies, affecting the organ that defines the “self,” often severely compromising quality of life. Malignant gliomas of the cerebral hemispheres in adults are the most common brain tumors and are the focus of our laboratory efforts. Elucidating the molecular basis of glioma formation may impact both diagnostic and therapeutic aspects of clinical neuro-oncology. We have demonstrated alterations characteristic of specific glioma subtypes and grades. We originally demonstrated that molecular genetic analysis could be used to define clinicopathologically relevant subsets of glioblastomas (e.g., those with TP53 mutations and those with EGFR amplification). Glioblastomas with TP53 mutations are often so-called secondary glioblastomas, meaning the glioblastoma has arisen in a prior lower-grade astrocytoma; this scenario typically occurs in younger adult patients. TP53 mutations are also common in glioblastomas having many giant cells. EGFR gene amplification, on the other hand, typically occurs in so-called primary (or de novo) glioblastomas, which appear to arise more rapidly in older adult patients, as well as in small-cell glioblastomas.

We have also shown that molecular genetic alterations are powerful predictors of therapeutic response and survival in patients with anaplastic oligodendrogliomas and in patients with other oligodendroglial tumors. Those patients, whose tumors have 1p loss, essentially always respond to therapy, and those with combined 1p and 19q loss that lack other detectable alterations have durable responses and long survival times (i.e., more than 10 years). In contrast, those patients whose tumors lack these genetic alterations but harbor others, such as EGFR amplification, rarely respond to chemotherapy in a durable manner and have short survivals (i.e., fewer than two years). These findings have already led to incorporation of molecular diagnostic testing around the world for these parameters.

We have also investigated whether gene expression profiling could be used to classify high-grade gliomas in a manner more objective, explicit and consistent than
Standard pathology. Our data have suggested that class prediction models, based on defined molecular profiles, classify diagnostically challenging malignant gliomas in a manner that better correlates with clinical outcome than does standard pathology.

Most recently, we have demonstrated that glioblastomas treated with the alkylating agent temozolomide (which is now the standard of care for such cases) frequently inactivate mismatch repair genes, leading to more rapid growth during therapy and to therapeutic resistance. The data in patients has been complemented by a series of in vitro experiments demonstrated a role for MSH6 inactivation in temozolomide resistance. We are studying novel mechanisms for temozolomide resistance as well as screening libraries to identify compounds that therapeutically target temozolomide-resistant glioblastomas.

Selected Publications:


Molecular diagnostic applications in glioma management. From Jansen et al., Lancet Neurology 2010.