PROJECT SUMMARY (See instructions):

Characterizing oncogenic mutations led to major discoveries that were translated into patient care in several cancers. Both primary and metastatic brain tumors have universally poor prognosis and there is a pressing need for development of new therapies. Multicenter efforts such as The Cancer Genome Atlas led to identification of molecular alterations such as mutations in *IDH1*, *IDH2*, *EGFR*, *BRAF*, which can be targeted with therapies.However, mutation analysis is not always feasible due to lack of available tumor tissue and tumor biopsies are difficult to perform. Cell-free (cf) DNA detected in the cerebral spinal fluid (CSF) and perhaps in plasma from patients with brain tumors can offer material for mutation analysis, which can be obtained using less invasive approaches than surgery. We hypothesize that CSF and circulating sources of tumor DNA reflect the mutation profile of the tumor and therefore can be used to detect molecular changes in the tumor. To test this hypothesis, the results from mutation analyses of CSF and plasma cfDNA will be compared to the results of mutation analyses of tumor tissue. The ultimate clinical-translational goal is to use this approach as an alternative to mutation analysis of tumor tissue samples for diagnosis, monitoring response to treatment and evaluating changes in the molecular profile in brain tumors over time. The following **Specific Aims** have been formulated**: (1) Determine the concordance between CSF and plasma sources of DNA relative to tumor. To assess concordance of mutation testing in CSF derived cfDNA, plasma cfDNA, and tumor DNA samples in 40 patients with gliomas in: a. Temporally concordant sampling in 20 patients undergoing tumor resection with concurrent CSF and plasma collection. b. Temporally discordant sampling in 20 patients with available FFPE archival tumor samples and CSF and plasma collection at different time points. (2) Identify the molecular changes through longitudinal sampling of CSF and plasma sources of DNA. To monitor mutation profile in longitudinal samples of plasma and CSF cfDNA from 20 patients with advanced cancers and radiological evidence of leptomeningeal involvement.** Mutation analysis will be performed using droplet digital PCR system QX200 (Bioarad, Pleasanton, CA), Idylla™ Molecular Diagnostic platform (Biocartis, Mechelen, Belgium), targeted next-generation sequencing (IonTorrent, Life Technologies, Carlsbad, CA) and other relevant technologies.

RELEVANCE (See instructions):

Significant progress in genomic technologies helped to expand our understanding of the molecular landscape of brain tumors. Coordinated multicenter initiatives such as The Cancer Genome Atlas (TCGA) led to identification of molecular alterations such as mutations in *IDH1*, *IDH2*, *EGFR*, *BRAF* genes, which can be targeted with cancer therapies and improve so far dissatisfying treatment outcomes. In order to translate these advances into clinical practice we need new tools such as liquid biopsies to allow for molecular testing in brain tumors especially when availability of tumor tissue is limited due to inherent challenges in getting access to brain tumor tissue. CSF or plasma derived cfDNA can provide such accessible material for mutation analysis, which can be used in lieu of tumor tissue and extend availability of oncogenic mutation testing to patients without available tissue.