Dr. Abby Siegel

Hepatocellular carcinoma (HCC) is one of the most rapidly increasing causes of cancer death in the United States. Sorafenib, an oral tyrosine kinase inhibitor targeted against molecular signaling pathways including RAS and VEGFR, is the only systemic drug to date which has been shown to improve survival in advanced HCC. Biomarkers have not been well-studied in HCC. The goal of this proposal is to identify peripheral predictive and prognostic biomarkers related to DNA methylation in a prospective study of 200 advanced HCC patients, all treated with sorafenib. We will study a surrogate for global hypomethylation (LINE-1), and well as methylation of several gene sites thought to be involved in HCC development and progression.

In particular, methylation of a particular tumor suppressor called RASSF1A has been shown to "turn on" other components of the RAS signaling pathway in HCC. Tumor expression of p-ERK, a downstream target in the RAS pathway, may correlate with better response to sorafenib. We will examine whether methylation of RASSF1A in plasma and tumor tissue correlates with p-ERK expression in tumor tissue. These experiments have the potential to identify simpler and safer ways to predict HCC outcomes. Finally, because of the possibility that folate may affect gene and global methylation levels, we will examine whether folate levels in plasma and red blood cells affect relationships between methylation status and outcome.

Subjects will be recruited from the faculty practices at Columbia University, given an epidemiologic questionnaire, and have blood drawn prior to starting sorafenib. Bloods will be processed and assays will be run in the laboratory of Dr. Regina Santella, who directs the biomarker core facility of the Herbert Irving Comprehensive Cancer Center at Columbia. Folate levels will be processed by our collaborator at Columbia, Dr. Mary Gamble. In a subset of patients from Columbia we will also evaluate pathologic sections of tumor using immunohistochemistry and methylation assays. We will collaborate with both the Cancer Center's pathology core resource, together with Dr. Helen Remotti, an experienced GI pathologist, to complete these studies.

This project will explore relationships between environmental, biological, and treatment-related effects on HCC outcomes in a multidisciplinary way. We believe the results will lead to the development of novel cost-effective predictive and prognostic biomarkers for those with this increasingly deadly disease.
