JOSHUA C. BLACK, PH.D., UNIVERSITY OF COLORADO SCHOOL OF MEDICINE

INVESTIGATOR BIOGRAPHY
Dr. Black is an assistant professor in the Department of Pharmacology at the University of Colorado School of Medicine, Anschutz Medical Campus. He studied cancer epigenetics as a postdoctoral fellow at the Massachusetts General Hospital/Harvard Medical School and earned his Ph.D. in Molecular Biology at the University of California, Los Angeles.

SELECT HONORS
Dr. Black has been the recipient of a Tosteson Postdoctoral Fellowship from the Massachusetts General Hospital Executive Committee on Research, an Amgen Molecular Biology Institute Dissertation Year Award, a UCLA Dissertation Year Fellowship, an institutional Ruth L. Kirschstein National Research Service Award Cell and Molecular Biology Training Grant, and numerous research-related undergraduate honors. He has also been a Jane Coffin Childs Memorial Fund Fellow.

MEDICAL FOCUS
Chromosomal structural abnormalities, variation in the copy number of genes and aberrant DNA replication contribute to instability of the genome, cancer risk and associated drug resistance. Aggressive, drug-resistant cancer is associated with aberrant duplication of specific regions of the genome that often harbor genes and oncogenes involved in cell survival. For example, duplications in a region of the genome called cytoband 1q21 are affiliated with increased oncogene expression, drug resistance and poor outcomes in cancer. These so-called “somatic copy-number variations” are often thought of as integrated and inherited genetic events within tumors; however, recent studies suggest some heterogeneity may not be stably inherited. Identifying the factors and mechanisms that influence genome stability and drug resistance will help us understand how amplifications of specific regions emerge, contribute to the development of cancer, and are inherited as tumor cells propagate. Such knowledge has the potential to impact our understanding of these difficult-to-treat tumors.

RESEARCH PROPOSAL
Dr. Black’s previous work identified alterations in chromatin states that promote re-replication and copy number gains of specific regions of the genome, as well as associated resistance to specific chemotherapeutic treatments. Altering the chromatin structure, or epigenetic state, directly generates transient site-specific copy gains (TSSGs) of regions affiliated with drug resistance. Dr. Black’s work suggests a new paradigm in cancer genetics: that some genomic alterations may not be inherited genetic changes, but instead represent a dynamic, regulated heterogeneity. While this could provide tumors an adaptive response to chemotherapy, it may also be exploited to overcome drug resistant cancers. Dr. Black’s proposal will test the hypothesis that DNA methylation acts to suppress TSSG and that loss of TSSG suppression causes drug resistance. Aim 1 will identify the components of the DNA methylation machinery that suppress TSSG and identify novel regions that undergo TSSG in response to DNA hypomethylation. Aim 2 will use an acute myeloid leukemia (AML) model to determine if TSSG occurs in vivo and if regions that undergo TSSG are amplified in human AML patients. The data generated in this proposal will shed light on how tumors acquire heterogeneity and begin to establish new targets and pathways to treat patients with drug resistance that may have arisen through TSSG.