In this issue of *Clinical Cancer Research*, Landreville and colleagues (1) report the effect of histone deacetylase inhibitors to shift uveal melanoma cells toward a more differentiated state, to cause cell-cycle arrest, and to inhibit tumor growth. These same researchers recently showed that inactivating mutations in the ubiquitin carboxy-terminal hydrolase *BAP1* gene are associated with uveal melanoma cell metastasis (2), and in the current report, they show that histone deacetylase inhibitors (HDACi) counter the effect of *H2A* monoubiquitin accumulation in the setting of *BAP1* loss.

Despite effective therapies (radio-plaque, proton beam, enucleation) to eradicate and prevent local recurrence of primary uveal melanoma, nearly half of patients with primary uveal melanoma ultimately develop metastatic disease (3). Few patients have detectable metastases at the time of primary disease diagnosis, indicating that micro-metastatic spread occurs early in the disease. Metastatic uveal melanomas typically have a long latency period and, once evident, are recalcitrant to the chemotherapeutic and biologic therapies that have been used to date. Upon evidence of metastatic disease, the median survival of patients is 6 to 9 months.

The presence of aberrations in chromosome 3 (e.g., monosomy 3) has long been known to be a key feature of most primary uveal melanoma tumors that metastasize. The identification of inactivating mutations in the *BAP1* gene, localized on chromosome 3p21, in the majority of tumors with monosomy 3 indicates that loss of heterozygosity or other mechanisms that result in *BAP1* loss play a critical role in the uveal melanoma metastatic process (2). Beyond monosomy 3 status, gene expression profiling of primary uveal melanoma tumors is suggested to provide even greater prognostic risk of metastatic disease (class 1, very low metastatic risk; class 2, high metastatic risk; ref. 4). *BAP1* loss is highly correlated with class 2 tumor status (2).

Stemming from the observation that class 2 uveal melanoma tumors lose morphologic features of melanocytic differentiation and that their gene expression signature is enriched for genes expressed in primitive neuroectodermal cells, Landreville and colleagues sought to identify compounds that would shift cells toward a more class 1–like (more differentiated) gene expression profile. They used Gene Set Enrichment and Connectivity Mapping analysis. Comparing the most differentially expressed genes between class 1 and class 2 tumors with sets of genes altered by particular chemotherapeutic agents revealed multiple HDACis to best match the differentially expressed class 1 versus class 2 genes. This result is consistent with the fact that HDACis were identified from synthetic library screens for their capacity to drive cancer cell differentiation and have been used in clinical trials with this intent (5).

Consistent with its role in cellular differentiation, *BAP1* was recently identified as a homolog of the *Drosophila* calypso gene. Scheuermann and colleagues showed that calypso forms a polycomb group (PcG) complex with ASX termed the polycomb repressive deubiquitinase (PR-DUB). The PR-DUB complex binds at PcG target genes and removes monoubiquitin from histone H2A, and loss of the PR-DUB complex results in elevated levels of monoubiquitinated H2A (6). The deubiquitination of H2A mediated by *BAP1* as part of the PR-DUB complex is countered by the monoubiquitinatating activity of the polycomb repressive complex 1 (PRC1).

Thus, at least one mechanism for HDACi efficacy in uveal melanoma cells with *BAP1* loss may be the reduction in monoubiquitination of H2A after HDACi treatment. As suggested by Landreville and colleagues, this could possibly be due to HDACi inhibition of BMI1, an important PRC1 complex protein that drives monoubiquitination of histone H2A (7), although this specific mechanism in uveal melanoma has not been verified. In addition, it is clear that HDACi treatment resulted in a
more 'class 1-like' phenotype in uveal melanoma cells with intact BAP1, suggesting that the effect of HDACis is pleotropic. Likewise, the varying effects of different HDACis on cell cycle, growth, and viability are consistent with differential inhibition of histone deacetylases and/or other HDACi targets. As there are a variety of cellular effects mediated by HDACis (e.g., apoptosis, autophagy, cell cycle arrest, antiangiogenesis, anti-invasion) and multiple processes in which BAP1 may function (e.g., regulation of cell cycle and/or growth, epigenetic modulation, DNA damage response), future research will likely reveal more than one mechanism by which HDACis alter uveal melanoma cell function (Fig. 1).

Given the robust molecular prognostic markers of metastatic risk and the well-characterized latency period of metastases, uveal melanoma is a clear candidate for adjuvant therapy intervention. The difficulty historically has been to identify an agent with a good biologic rationale and acceptable toxicity. The study by Landreville and colleagues would suggest that HDACis may have activity in uveal melanoma. Future clinical trials treating uveal melanoma patients with HDACis in both the metastatic and adjuvant setting are warranted.

BAP1 mutations have also recently been discovered in 23% of sporadic mesotheliomas (8). In addition, 3 different groups have recently identified BAP1 germline mutations in multiple families with a high propensity for different cancers (uveal melanoma, cutaneous melanoma, mesothelioma, lung adenocarcinoma, meningioma; refs. 9–11). Thus, the initial characterization of BAP1 as a tumor suppressor gene has gained significant validity.

A phase I clinical trial in which 13 patients with advanced mesothelioma were treated with the HDACi suberoylanilide hydroxamic acid (SAHA) showed 4 patients to complete ≥6 cycles and 2 patients to have a partial response (12). A phase III clinical trial is currently testing SAHA in advanced mesothelioma (13). It will be of great interest to know whether the cellular changes observed in the preclinical studies with HDACis in uveal melanoma cells are observed in BAP1 mutant mesothelioma and correlate with clinical response.

The identification of BAP1 as a functional tumor suppressor in multiple cancers provides an important clue toward understanding what ultimately drives these tumor types. Significant questions remain about the relationship between particular exposures, for example, UV radiation or asbestos, and BAP1 gene alterations. Do different types of mutations in different locations of the BAP1 gene result in different functional outcomes, or is loss of significant expression sufficient to drive metastasis? How does loss of BAP1 manifest itself molecularly in different cancer cell backgrounds with distinct sets of other molecular aberrations? In the case of germline BAP1 mutations, do distinct syndromes emerge given the genetic background of each family that harbors a BAP1 mutation?

The preclinical studies of Landreville and colleagues present an intriguing first glimpse into the possibility

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**Figure 1.** The multiple functions of histone deacetylase inhibitors (HDACi): cell-cycle inhibition, cell death, and epigenetic regulation, as well as antiangiogenesis (not shown) and anti-invasion (not shown). Ub, ubiquitin.

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of therapeutically countering uveal melanoma in general and, specifically, uveal melanomas with BAP1 tumor suppressor loss. As more is discovered about the molecular alterations that drive uveal melanoma, HDAC-Cis could serve as a first-step therapeutic approach upon which to build.

Disclosure of Potential Conflicts of Interest

S.E. Woodman: research grant awards, GlaxoSmithKline and Bristol-Myers Squibb.

Received November 8, 2011; accepted November 11, 2011; published OnlineFirst December 2, 2011.

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BAP1tism of a Tumor Suppressor
Scott E. Woodman

*Clin Cancer Res* Published OnlineFirst December 2, 2011.

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Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-2870

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