Therapeutic Implications of the Emerging Molecular Biology of Uveal Melanoma

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Statement of Translational Relevance

Uveal melanoma is a unique clinical and molecular subtype of melanoma that has no known effective therapy in the metastatic setting. Significant advances in our understanding of the biology of this disease, combined with the growing availability of agents which can be used to rationally target these findings, have led to the development of a number of clinical trials testing various treatment strategies for advanced disease. Herein, we present an overview of the current knowledge of the molecular biology of uveal melanoma, with particular attention paid to tumor specific aberrations which can be exploited for therapeutic benefit. We discuss the pathogenic roles of GNAQ/11, PTEN, IGF/IGF1R, MET, BAP1, and other key molecules, review potential therapeutic strategies, and review the next generation of recently initiated clinical trials for the treatment of advanced uveal melanoma.
Abstract

Uveal melanoma represents the most common primary intraocular malignancy in adults. Although uveal and cutaneous melanoma both arise from melanocytes, uveal melanoma is clinically and biologically distinct from its more common cutaneous counterpart. Metastasis occurs frequently in this disease, and, once distant spread occurs, outcomes are poor. No effective systemic therapies are currently available; however, recent advances in our understanding of the biology of this rare and devastating disease, combined with the growing availability of targeted agents which can be used to rationally exploit these findings, hold the promise for novel and effective therapies in the foreseeable future. Herein, we review our rapidly growing understanding of the molecular biology of uveal melanoma, including the pathogenic roles of GNAQ/11, PTEN, IGF/IGF1R, MET, BAP1, and other key molecules, potential therapeutic strategies derived from this emerging biology, and the next generation of recently initiated clinical trials for the treatment of advanced uveal melanoma.
Introduction

Although uveal melanoma represents only 5% of all melanomas, this disease is the most common primary intraocular malignancy of the adult eye, affecting six individuals per million per year (1, 2). These tumors arise from melanocytes within the uveal tract, which consists of the iris, ciliary body, and choroid of the eye. Several features of the primary tumor have been associated with poor prognosis, including location in the ciliary body or choroid (as opposed to the iris), diffuse configuration, and larger size (3-6). Histologically, uveal melanomas with epithelioid morphology fare worse than those with spindle cells (7), as do those with higher mitotic activity, extrascleral invasion, or the presence of microvascular networks (3, 8, 9). Genetic features, including monosomy of chromosome 3 and amplification of chromosome 8q, have also been identified as poor prognostic indicators (10, 11). Two independent groups have identified microarray gene expression profiles which accurately segregate uveal melanomas into two tumor classes by risk of metastasis (12-15). Class I tumors appear to have a low-risk of metastasis while class II tumors are more aggressive, correspond with monosomy in chromosome 3, and are associated with a higher rate of metastatic death.

The natural history of uveal melanoma is characterized by the frequent development of metastases, with over 50% of patients developing metastatic disease at any time from the initial diagnosis of the primary to several decades later (2, 16-21). A broad spectrum of therapies, including systemic therapies (22), hepatic artery infusion of chemotherapy, hepatic embolization, metastasectomy, and others, have been used to treat patients with metastatic uveal melanoma. However, a recent meta-analysis demonstrated no compelling evidence that these interventions confer any survival benefit (23). Although a recently completed phase III trial which randomized 93 patients with hepatic metastases from uveal (n = 82) or cutaneous (n = 11) melanoma to percutaneous hepatic perfusion with melphalan to standard of care met its primary endpoint of hepatic progression-free survival, no survival advantage was observed (24).

Due to the lack of effective therapies for this disease, prognosis after the development of metastasis is poor. In the largest published series of patients with uveal melanoma,
the median survival after diagnosis of metastatic disease was 3.6 months, with a 5-year cumulative survival of less than 1% (16). In this series, only 39% of patients received treatment for metastatic disease. In contrast, a smaller single institutional series of 119 cases treated at Memorial Sloan-Kettering Cancer Center demonstrated a 22% five year survival for patients with metastatic uveal melanoma (13, 18). In this study, 81% of patients received treatment for stage IV disease, including 20% who underwent complete surgical metastatectomy. Factors relating to improved outcomes included female gender, age younger than sixty, longer time from treatment for the primary uveal melanoma to the development of metastases, surgical resection of metastases, and lung or soft tissue as sole site of metastasis.

Given these unsatisfactory outcomes, there is a compelling need for novel and effective therapeutic strategies for the management of metastatic uveal melanoma. As current treatment for localized disease often leads to visual loss, whether due to enucleation or the local effects of radiation within the eye, the identification of active pharmacologic agents may obviate the necessity for these locally destructive therapies. Innovation in pharmacotherapy depends largely upon elucidating the molecular mechanisms underlying uveal melanoma pathogenesis. Recent advances in our understanding of the biology of this rare and devastating disease, combined with the growing availability of targeted agents which can be used to rationally exploit these findings, hold the promise for novel and effective therapies in the foreseeable future. Herein, we review recent developments in our understanding of the pathogenesis of uveal melanoma, as well as the associated potential therapeutic implications.

I. MAPK Pathway

Eighty-six percent of primary uveal melanoma tissue exhibits activation of the mitogen-activated protein kinase (MAPK) pathway (25). In this signaling pathway, ligand binding to cell surface tyrosine kinase receptors leads to exchange of GDP for GTP on Ras. Activated in its GTP-bound state, Ras activates Raf, which subsequently activates MAPK/extracellular signal-related kinase kinase (MEK). MEK phosphorylates and activates extracellular signal-related kinase (ERK), which dimerizes and translocates to
the nucleus, where it mediates cell proliferation, survival, differentiation, and apoptosis. Preclinical studies demonstrate that inhibition of the MAPK pathway in uveal melanoma cell lines results in decreased cell proliferation (26, 27), suggesting that several key molecules in this pathway, including BRAF, GNAQ/11, and MEK, may serve as potential therapeutic targets.

**BRAF as a Therapeutic Target.** Cutaneous and uveal melanomas differ in many ways, including pattern of spread and responsiveness to chemotherapy; however, given their common melanocytic origin and the significantly larger body of knowledge about cutaneous melanoma, observations made in cutaneous melanoma have served to guide investigation into the molecular biology of uveal melanoma. BRAF has been shown to be of great significance in cutaneous melanoma, with up to 62% of cases harboring activating mutations in *BRAF* (28). Ninety-five percent of such cases result in a V600E mutation which involves a valine to glutamic acid substitution at position 600.

Based upon these findings in cutaneous melanoma, several groups have investigated the mutational status of *BRAF* in primary uveal melanomas (29-32), as well as in liver metastases of uveal melanoma (25). These studies have been overwhelmingly negative, with only one case harboring a BRAF V600E mutation (30). Several groups, however, have posited that uveal melanoma exhibits significant intra-tumoral heterogeneity and that conventional PCR techniques are insufficiently sensitive to identify *BRAF* mutations that may be present in a small subset of cells within a tumor. Using nested PCR and pyrophosphorylysis-activated polymerization techniques, these groups demonstrated that subsets of tumor tissue, but not the entire tumor, harbor a BRAF mutation (33, 34). This observation, in part, may explain the identification of several uveal melanoma cell lines that harbor a *BRAF* mutation (29, 33, 35-37). Interestingly, Calipel et al. demonstrated that uveal melanoma cell lines exhibit similar MAPK pathway activation and proliferation regardless of *BRAF* mutational status, indicating that other mechanisms of MAPK pathway activation are present in uveal melanoma (35).
Preclinical studies have demonstrated that sorafenib, a small molecule inhibitor of the Raf family of kinases, PDGFR-β, VEGFR-2 and -3, and KIT, inhibits MAPK signaling and decreases proliferation, even in BRAF wild-type cell lines. Interestingly, studies of PLX4270, an inhibitor with relative selectivity for V600E BRAF, in uveal melanoma cell lines demonstrated that only the BRAF mutant lines exhibited decreased cell viability with therapy, while no effect was observed in the wild-type cells (unpublished data). This is consistent with recent data indicating that effective RAF inhibition in BRAF wild-type cells may activate rather than inhibit MAPK pathway signaling (38-40), and that, although both BRAF mutant and wild-type uveal melanomas may require MAPK signaling for growth, inhibition of this pathway likely has different consequences depending upon the genetic background of the cell.

To date, there are a number of clinical trials evaluating various BRAF inhibitors such as PLX4032 (RO5185426, also known as RG7204), XL281, and GSK2118436 in melanoma (Table 1). Several of these have enrolled patients with uveal melanoma, and one trial of the combination of carboplatin, paclitaxel, and sorafenib is specifically enrolling patients with ocular melanoma. The ongoing phase I study of XL281 in patients with advanced solid tumors included 1 patient with uveal melanoma who achieved a confirmed partial response lasting 4 months (41). It will be critical to carefully assess any clinical benefit observed in patients treated on these trials in relationship to tumor mutational status to optimally assess the role and future of BRAF inhibition as a therapeutic strategy for the treatment of uveal melanoma.

**GNAQ/11 as Therapeutic Targets.** Despite the absence of BRAF mutations, 86% of primary uveal melanomas exhibit activation of the MAPK pathway as evidenced by activation of phospho-ERK.(26-32) In cutaneous melanoma, MAPK pathway activation has also shown to be mediated by mutations in NRAS (42); however, these mutations have not been found in uveal melanoma (29). Thus, while uveal melanoma, like cutaneous melanoma, is characterized by MAPK activation, the mechanism of MAPK activation differs between these two unique subtypes of melanoma.
Recent studies have identified G-proteins as potential drivers of MAPK activation in uveal melanoma. Genetic screens have demonstrated that 46% to 53% of uveal melanoma exhibit mutations in GNAQ (26, 43-45). These mutations are not associated with clinical, pathological, immunohistochemical, or genetic factors associated with advanced uveal melanoma, indicating that this alteration may represent an early event in disease pathogenesis (43). Recent data suggest that over half of uveal melanomas lacking a mutation in GNAQ exhibit a mutation in GNA11 (44). GNAQ is a q class G-protein α-subunit. G proteins are a family of heterotrimeric proteins (Gαβγ) coupled to cell surface, seven-transmembrane spanning receptors. Upon ligand binding to these receptors, the GDP bound to the Gα subunit of Gαβγ is exchanged for GTP, resulting in a conformational change and the subsequent dissociation of the Gα from the Gβγ subunits. These two subunits are then able to regulate various second messengers. Gα activation is terminated by a GTPase intrinsic to the Gα subunit. The q class Gα (Gqα) mediates its activity through stimulation of phospholipase Cβ, which cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol triphosphate (IP3) and diacyl glycerol (DAG). DAG goes on to activate protein kinase C, which ultimately activates downstream pathways including the MAPK signaling pathway.

Van Raamsdonk et al. demonstrated that transfection of GNAQ Q209L in human melanocytes results in anchorage-independent growth, with cells able to grow in the absence of the DAG analog 12-O-tetradecanoyl phorbol-13-acetate, presumably due to high levels of DAG production by constitutively activated phospholipase Cβ. GNAQ Q290L transfected melanocytes have increased ERK activation, as compared to melanocytes with wild-type GNAQ. Interestingly, small interfering RNA (siRNA) targeting Gnaq normalizes phospo-ERK levels, increases the number of resting cells, decreases cell number, and decreases anchorage-independent growth. Injection of nude mice with melanocytes harboring GNAQ Q209L, but not wild-type GNAQ melanocytes, leads to the development of pigmented tumors at the injection site (26). GNA11 has similarly been validated as an oncogene that results in MAPK activation, comparable to that achieved with GNAQ (44).
The somatic GNAQ exon 5 Q209L and Q209P mutations most commonly identified lead to a glutamine to lysine and glutamine to proline substitution, respectively, at position 209, which lies in the Ras-like domain of GNAQ. The GNA11 exon 5 mutation most commonly observed results in a Q209L substitution that is analogous to the Q209L substitution observed in GNAQ. Mutations at this site cause loss of the intrinsic GTPase activity, similar to that seen in Ras family members (46). Since Gα inactivation is mediated by this intrinsic GTPase, such mutations lead to constitutive Gα activation and downstream signaling. Exon 4 mutations in GNAQ and GNA11 have also been identified in 4.8% of uveal melanomas that lead to alterations at arginine 183 (R183) (44). In all but one of the tumors tested, exon 5 Q209 and exon 4 R183 mutations were mutually exclusive. Interestingly, tumors characterized by these mutations display distinct biologic activity. Injection of GNA11 Q209L transfected melanoma cells in immunocompromised mice produced rapidly growing tumors at all injection sites, whereas injection of R183C transfected cells produced tumor growth at only one half of injection sites with a longer latent period. Furthermore, while all mice injected with the GNA11 Q209L variant developed visceral metastases, this was not observed with melan-a cells transfected with GNAQ Q209L, supporting the hypothesis that GNA11 Q209 mutations are more oncogenic than the GNAQ Q209 variant. Indeed, a recent study demonstrated an inverse relationship of the frequency of GNAQ mutations and GNA11 mutations when comparing blue nevi, uveal melanoma, and uveal melanoma metastases. While GNA11 mutations were observed in 7% of blue nevi, 32% of uveal melanoma, and 57% of uveal melanoma metastases, GNAQ mutations were present in 55% of blue nevi, 45% of uveal melanoma and 22% of uveal melanoma metastases. This also suggests that mutations in GNA11 connote a greater risk of distant metastasis in uveal melanoma than GNAQ mutations.

Thus, in vitro and in vivo studies support the hypothesis that GNAQ/11 mutations result in MAPK activation and play an essential role in the development of uveal melanomas. There is currently significant interest in investigating inhibition of the GNAQ/11 pathway for the treatment of uveal melanoma; however, whether inhibition of this pathway will be an effective strategy is yet to be determined. Importantly, it is also not known whether
pathway inhibition at the level of GNAQ/11 or further downstream will be optimal. Currently, there are no clinically available specific inhibitors of GNAQ/11, phospholipase Cβ or the various PKC isoforms with which to investigate these critical questions.

**MEK as a Therapeutic Target.** An alternative therapeutic strategy for these patients is the targeting, not of GNAQ/11, but rather of the downstream effector MEK. Treatment of uveal melanoma cell lines bearing GNAQ mutations with U0126, a small molecule inhibitor of MEK, leads to a decrease in phospho-ERK and cell number, a loss of anchorage-independent growth, and an increase in the sub-G0/G1 subpopulation. Moreover, in these cell lines, U0126 results in lower cell numbers than siRNA-mediated knockdown of GNAQ, suggesting that targeting the downstream target MEK may be more effective than inhibiting GNAQ itself (26). Additional *in vitro* studies indicate that uveal melanoma cell lines bearing the GNAQ Q209L mutation are sensitive to MEK inhibition with AZD6244, another potent, selective, orally-available, and non-ATP competitive small molecule inhibitor of MEK1/2 (47). MEK inhibition in these cells is associated with decreased signaling through both the MAPK and PI3K pathways, as demonstrated by inhibition of phospho-ERK and phospho-AKT. Although these effects are not observed in cells wild-type for GNAQ or BRAF, transfection of GNAQ wild-type cell lines resistant to AZD6244 with GNAQ Q209L leads to the induction of sensitivity to AZD6244 in terms of both ERK inhibition and decreased proliferation.

We have observed clinical efficacy of MEK inhibition in subset analysis of patients with metastatic uveal melanoma treated with AZD6244 on 3 completed trials (48-50). On a randomized phase II study of AZD6244 versus temozolomide for patients with melanoma, of the 20 patients with uveal melanoma, 17 received AZD6244 during the study: 7 received AZD6244 upfront while 10 received AZD6244 following progression on temozolomide (49). The progression-free survival (PFS) hazard ratio (HR) was 0.76 (80% CI, 0.38 - 1.53) in favor of AZD6244, with a median PFS of 50 days for those randomized to temozolomide (80%CI = 43 days, 83 days; 12 events/13 patients) and 114 days for those randomized to AZD6244 (80%CI = 70 days, 202 days; 5 events/7 patients). Insufficient numbers of patients have been treated thus far with AZD6244 to
conclude a benefit over chemotherapy and to assess whether GNAQ/11 status is predictive of response; however, these questions are currently being assessed in a randomized phase II trial of temozolomide versus AZD6244 in patients with advanced uveal melanoma, with patients stratified by GNAQ/11 mutational status (Table 2). This study is powered to test the hypothesis that AZD6244 will decrease the 4 month progression rate by 40% when compared with temozolomide in the GNAQ/11 mutant patient population who are temozolomide/DTIC naive. This study will also assess the efficacy of AZD6244 in temozolomide/DTIC naive patients regardless of genetic background, as well as patients with tumor characterized by a GNAQ/11 mutation who have previously been treated with temozolomide/DTIC.

II. PI3K/Akt Pathway
Phosphoinositide 3-kinase (PI3K) signaling is also implicated in uveal melanoma. PI3K is activated by G-protein coupled receptors and by receptor tyrosine kinases. Upon activation, PI3K catalyzes the conversion of phosphatidylinositol (3,4)-bisphosphate (PIP2) to phosphatidylinositol(3,4,5)-triphosphate (PIP3). PIP3 mediates translocation of Akt (also known as protein kinase B) to the cell membrane, where it is activated. Akt mediates several key proliferation and cell survival pathways. PI3K signaling is antagonized by phosphatase and tensin homolog (PTEN), a protein that stimulates conversion of PIP3 to PIP2, and, thus, decreases Akt activation.

A relative decrease in PTEN expression in aggressive primary uveal melanomas compared with less aggressive tumors was previously reported, with either decreased or complete loss of PTEN expression as measured by immunohistochemistry observed in 58.7% of cases evaluated (51). Loss of PTEN was associated with a less favorable profile for patients presenting with primary uveal melanoma, where patients with a total loss of PTEN have a median survival of 60 months compared with more than 120 months for patients with normal or nearly normal PTEN expression.

**PI3K and Akt as Therapeutic Targets.** Several uveal melanoma cell lines exhibit PI3K activation (51-53). A few of these cell lines exhibit submicroscopic chromosomal
deletions leading to loss of expression of PTEN, representing one mechanism of pathway activation (51). Inhibition of PI3K with LY294002 in uveal melanoma cell lines results in decreased proliferation that is observed even in cell lines harboring a BRAF mutation (53, 54). While LY294002 and the related nonreversible PI3K inhibitor Wortmannin have limited clinical utility due to their poor solubility and high toxicity, more tolerable PI3K inhibitors such as XL147 are currently undergoing clinical investigation. In addition, inhibition of the PI3K/Akt pathway at the level of Akt is currently being investigated with agents such as perifosine, GSK2141795, GSK690693, and MK2206 now in clinical trials (Table 1).

**mTOR as a Therapeutic Target.** Mammalian target of rapamycin (mTOR) is a downstream effector of the PI3K pathway that stimulates cell proliferation through translational control of cell cycle progression regulators. There exist two structurally and functionally distinct mTOR complexes: mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2 rapamycin insensitive) (55). mTORC1 is activated mainly via the PI3K pathway through AKT and the tuberous sclerosis complex (56). Activated AKT phosphorylates TSC2, which leads to dissociation of the TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP-bound state and activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1 (57, 58).

Several mTOR inhibitors, including everolimus and temsirolimus, are being evaluated in clinical trials for melanoma, and a new class of compounds targeting both TORC1/2 is also under investigation for advanced cancers (Table 1). No significant single agent activity has thus far been demonstrated in melanoma (59). Of significant clinical relevance, treatment of uveal melanoma cell lines with the mTOR inhibitor rapamycin at levels that inhibit downstream mTOR signaling by 100% results in only 9% to 21% inhibition of cell proliferation (53). This phenomenon is explained, in part, by the finding that mTOR inhibition induces Akt activation through loss of the mTOR pathway-dependent inhibition of insulin-like growth factor-1 receptor (IGF-1R) signaling.
IGF-1R blockade abrogates mTOR inhibition-mediated Akt activation and confers sensitivity to mTOR inhibition in cancer cells (60). Thus, IGF-1R-mediated feedback activation of PI3K signaling appears to confer resistance to mTOR inhibitors, and mTOR inhibition alone is likely insufficient for the successful treatment of uveal melanoma. Interestingly, it has been demonstrated that activation of Akt due to mTOR blockade can be inhibited in vitro by pretreatment with an IGF-1R antibody (61, 62), suggesting that combination therapy targeting both mTOR and the IGF-1R pathway may produce more favorable results than mTOR inhibition alone.

III. Therapeutic Targets Upstream of the MAPK and PI3K/Akt Pathways

Preclinical data demonstrate that simultaneous inhibition of both the MAPK and PI3K/Akt pathways result in the synergistic inhibition of cell proliferation (53), suggesting that dual-pathway inhibition may be necessary for the optimal management of uveal melanoma. Such inhibition may be achieved by combining two or more inhibitors targeting components of both pathways. Alternatively, as several key cell-surface receptors activate both pathways simultaneously, effective inhibition of such receptors may serve as an alternative therapeutic strategy.

KIT as a Therapeutic Target. A member of the platelet derived growth factor receptor (PDGFR) family of kinases, KIT is a receptor tyrosine kinase that mediates growth differentiation, as well as attachment, migration, and proliferation of cells. Binding of the KIT ligand stem cell-derived factor (SCF) results in receptor dimerization and autophosphorylation. Docking sites for several Src homology-2 signaling proteins such as those mediating PI3K, MAPK, and JAK/STAT pathway activation are subsequently revealed.

KIT expression has been identified in up to 87% of primary uveal melanomas by immunohistochemistry; however, less than 40% exhibit strong staining (63-65). Uveal melanoma cell lines as well as normal uveal melanocytes produce SCF; however, only uveal melanoma cell lines secrete SCF, suggesting the presence of a relevant autocrine
loop in the setting of malignancy (66). Stimulation of normal uveal melanocytes with SCF results in activation of both ERK1/2 and Akt; however, in a KIT expressing uveal melanoma cell line, stimulation led to MAPK pathway activation only (65). Inhibition of KIT, using both imatinib mesylate, a small molecule inhibitor of several receptor tyrosine kinases, including ABL, KIT, and PDGFR, as well as siRNA techniques, leads to a reduction in proliferation of uveal melanoma cell lines expressing the target. This effect was not observed in KIT negative cell lines or in normal uveal melanocytes (63, 65, 66). Treatment with imatinib abrogates both the MAPK and PI3K/Akt pathways in normal uveal melanocytes. In KIT expressing uveal melanoma, treatment with imatinib decreased the SCF-induced MAPK activation and resulted in decreased invasion by uveal cell melanoma lines as determined by penetration through a Matrigel-coated membrane (65). Interestingly, inhibition of MEK in the uveal melanoma cell line using UO126 decreased SCF-induced cell proliferation by 92% to 98%, but Akt inhibition had no significant effect, suggesting that the proliferative effects of the SCF/KIT autocrine loop in uveal melanoma likely funnel primarily through the MAPK pathway (66).

There are currently several clinical trials investigating various KIT inhibitors, including imatinib, nilotinib, dasatinib, and others, in patients with advanced melanoma (Table 1). Despite promising preclinical data, results observed in patients with uveal melanoma treated on these studies have been underwhelming (67). In a phase II study of imatinib in 13 patients with uveal melanoma metastatic to the liver, one patient achieved stable disease for 5 months; however, no objective responses were observed (68). In a phase II study of sunitinib, a tyrosine kinase inhibitor of c-kit, PDGFR, vascular endothelial growth factor (VEGF) receptor, and fms-related tyrosine kinase 3 (FLT-3), of 18 evaluable patients with advanced uveal melanoma, one patient achieved a partial response and 12 achieved stable disease (69). The median overall and progression-free survivals were 8.2 months and 4.0 months, respectively. As the lack of the response observed in these studies might reflect treatment of patients with absent or very low KIT expression, Hoffman et al. hypothesized that more consistent responses might be achieved in a patient population with high tumor expression levels; however, in another study of 12 patients with metastatic uveal melanoma characterized by high KIT
expression by immunohistochemistry treated with imatinib, no significant responses were observed (70).

The results observed in these clinical trials are disappointing but consistent with what has been observed in trials of KIT inhibition in cutaneous melanoma. The “oncogene addiction” hypothesis is based upon the hypothesis that tumorigenesis is dependent upon dysregulation of a gene or gene product. Protein expression is not indicative of such dysregulation in all cases and cannot be reliably used to guide drug development. Indeed, no difference in survival is observed between patients with uveal melanoma characterized by high KIT expression and those with disease characterized by low KIT expression (63). Rather than simple expression, activation of KIT via a mutation or amplification in may be required to connote sensitivity to KIT inhibition as has been observed in tumors such as gastrointestinal stromal tumors and, more recently, in melanoma (71). While such alterations have been associated with melanomas arising from acral, mucosal, and chronically sun-damaged surfaces (72, 73), thus far, no activating mutations have been identified in primary uveal melanoma samples (63, 64, 70).

**IGF-1R as a Therapeutic Target.** The insulin-like growth factor (IGF) signaling pathway is implicated in both MAPK and PI3K signaling and appears to play a role in cell-cell adhesion as well as tumor invasiveness (74, 75). IGF-1 binds IGF-1R, leading to activation of the intrinsic receptor tyrosine kinase activity and phosphorylation of insulin receptor substrate (IRS). IGF-1R is expressed on primary uveal melanomas (76). Although melanoma cells do not secrete or express IGF-1 (76), this ligand is produced by the liver, the predominant metastatic site in uveal melanoma. It has been demonstrated that inhibition of IGF-1R in uveal melanoma cell lines results in decreased proliferation (77, 78), and the IGF-1 signaling axis is implicated, not only in proliferation of uveal melanoma cells, but also in their metastatic potential (79, 80).

In a study of 36 patients with uveal melanoma, ten of 18 patients (56%) who died of advanced disease bore tumors with high IGF-1R expression. In contrast, only five of 18
patients (28%) who survived more than fifteen years following primary surgical enucleation had tumors with high levels of IGR-1R expression (77). This association between IGF-IR expression and melanoma-specific mortality was also suggested in a subsequent study of 132 patients with uveal melanoma, where 24 of 42 patients (57%) with high expression of IGF-1R died of metastatic disease, while only 31 of 90 patients (34%) succumbed to metastatic uveal melanoma (80).

Treatment of uveal melanoma cell lines with picropodophyllin (PPP), a specific inhibitor of IGF-1R, results in decreased IGF-1R expression, decreased IGF-1R phosphorylation, decreased downstream MAPK and PI3K signaling, and a 60% to 90% decrease in cell survival (81, 82). PPP has a lower IC50 in uveal melanoma cell lines when compared with cisplatin, 5-FU, and doxorubicin, and has variable synergistic effects when used with chemotherapy. In vivo xenograft studies using a uveal melanoma cell line in SCID mice demonstrated that intraperitoneal, intravitreal, and oral treatment with PPP leads to tumor regression, decreased liver micrometastases, decreased IGF-1R phosphorylation, decreased PI3K and MAPK signaling, decreased MMP-2 expression, and increased apoptosis in tumor cells (81, 83). Interestingly, xenografts lacking IGF-1R exhibit no such response to PPP (82).

To date, there are several monoclonal antibodies and small molecule agents targeting IGF-1R in clinical development for advanced solid cancers. Several of these agents are being combined with agents targeting mTOR in an effort to overcome the feedback dis-inhibition observed with mTOR blockade alone discussed above (Table 1). Whether such a therapeutic strategy will be effective in uveal melanoma will be addressed in an upcoming phase II study of IMC-A12, the anti-IGF-1R monoclonal antibody, in patients with this disease (Table 2).

**IGF-1 as a Therapeutic Target.** An alternative strategy to directly targeting IGF-1R for the inhibition of the IGF pathway is suppression of the ligand, IGF-1. Basal serum IGF-1 levels have been associated with locally advanced disease as well as the development of liver metastases (84).
Octreotide is a somatostatin analogue that binds primarily to somatostatin receptor subtype sst2 and has been demonstrated to suppress IGF-I plasma levels in patients with solid tumors (85, 86). Octreotide has been further demonstrated to decrease tyrosine phosphorylation levels of p85, the PI3K regulatory subunit, leading to dephosphorylation of phosphosinositide-dependent kinase 1 (PDK1) and Akt, without affecting PTEN, total PDK1 levels, or total Akt levels (87-89). Pasireotide (SOM230) is a novel, multi-receptor, somatostatin analog that binds with nanomolar affinity to somatostatin receptor subtypes sst1, sst2, sst3, and sst5, and potently suppresses GH, IGF-I, and ACTH secretion (90). Pasireotide has been demonstrated to significantly suppress IGF-I plasma levels to a greater extent than that achieved with octreotide. Administration of pasireotide 1 µg/kg/h and 10 µg/kg/h to male Lewis rats significantly decreased plasma IGF-1 levels by 68% and 98%, respectively, on day 2 of therapy (91-93). This suppression is achieved primarily via the reduction of pituitary GH secretion, although peripheral inhibitory effects of pasireotide on IGF-I action has been demonstrated as well (94).

In addition to affecting IGF-1 plasma levels, both octreotide and pasireotide may have direct affects upon uveal melanoma cells, as somatostatin receptors are known to be expressed on melanoma cells. One study demonstrated that 96% of cutaneous melanomas tested expressed the somatostatin receptor sst1, 83% expressed sst2, 61% expressed sst3, 57% expressed sst4, and 9% expressed sst5 (95). Of 25 clinical uveal melanoma samples tested, all demonstrated expression of sst2, 7 (28%) expressed sst3, and 14 (56%) expressed sst5 (96). Interestingly, octreotide or vapreotide demonstrated dose dependent inhibitory effects on cell proliferation in three uveal melanoma cell lines (OMM2.3, OCM3 and Mel270) tested (96).

The combination of the mTOR inhibitor RAD001 with pasireotide is being tested in an on-going phase I trial, and with the recommended phase II dose has been identified. A phase II study of this combination testing the hypothesis that mTOR inhibition in
combination with inhibition of the IGF-1R pathway is an effective therapy for uveal melanoma is on-going (Table 2).

**c-MET as a Therapeutic Target.** The c-MET proto-oncogene encodes a tyrosine kinase receptor responsible for biological functions as diverse as cell motility, proliferation and survival (97-100). Hepatocyte growth factor/scatter factor (HGF) is a plasminogen-like protein which acts as the endogenous ligand for this receptor, binding of which leads to autophosphorylation of tyrosine residues within the receptor's activation loop, activation of kinase activity, and to phosphorylation of additional tyrosine residues adjacent to the carboxyl terminus which form a docking site for intracellular adaptors of downstream signaling (97, 100, 101). Signaling in this pathway is primarily mediated by Grb2, phosphatidylinositol 3-kinase (PI3K), Src, Gab1, STAT3, phospholipase C-gamma (PLCγ), Shc, Shp2, and Shp1 (100).

HGF acts as a mitogen to melanocytes, and c-MET overexpression correlates with the invasive growth phase of melanoma (102). Melanoma cells, but not melanocytes, express HGF, leading to a potential autocrine positive feedback loop in the development of melanoma (102). Although uveal melanomas overexpress c-MET, activating mutations or genetic amplifications of c-MET do not appear to play a significant role in this disease (103). Hendrix et. al. first reported in 1998 the expression of c-MET by the more invasive interconverted phenotype of uveal melanoma cell lines, and subsequently demonstrated a motogenic response to HGF by c-Met expressing cells, but not by those who failed to express c-Met (104). Cell migration capacity appears to be enhanced by HGF via activation of phospho-AKT and the downregulation of the cell adhesion molecules e-cadherin and beta-catenin in a dose dependent fashion (105). Both c-MET inhibition and AKT inhibition independently inhibited the downregulation of adhesion molecules by HGF and completely abolished the migration of these two cell lines, suggesting that activation of p-AKT via the HGF/c-MET axis is involved in HGF-induced uveal melanoma cell migration (105, 106). c-MET blockade using the small molecule SU11274 significantly inhibited both cell proliferation and migration in all uveal melanoma cell lines tested (103).
HGF and its receptor tyrosine kinase c-Met play essential roles in the processes of liver embryogenesis and in hepatic regeneration following injury in the adult state, emphasizing their role in as both morphogen and mitogen for this organ (98, 106). As uveal melanoma metastases preferentially involve the liver, the question arises as to whether local factors within the hepatic environment such as HGF or IGF-1 are responsible for the dominant pattern of metastases seen at this site, and whether inhibition of this pathway could decrease the risk of developing metastastic disease (107). In a series of 60 patients with resected uveal melanoma, higher levels of c-MET expression were associated with a significantly higher risk of death from metastatic disease (79); however, another series of 132 patients with uveal melanoma demonstrated that while expression of both c-MET and IGF-1R were predictive of poor prognosis in univariate analysis, the presence of c-MET alone was not predictive for decreased overall survival (108).

Work further exploring the role of c-MET in the pathogenesis of uveal melanoma is ongoing. While there is great interest in targeting the HGF/c-MET pathway for the treatment of this disease, with a number of relevant agents currently in clinical development (Table 1), the efficacy of this strategy remains to be determined.

IV. Emerging Insights into the Biology of Advanced Uveal Melanoma
As discussed in the introduction, prior studies indicate that uveal melanomas segregate into two tumor classes based upon microarray gene expression profiles. Class I tumors have low rates of metastasis, while class II tumors are more aggressive and associated with a higher rate of death from metastatic disease (12-15). Harbour et. al. interrogated a sample of 31 class II uveal melanoma metastatic samples and identified an 84% incidence of somatic mutations in the ubiquitin carboxy-terminal hydrolase BRCA1 associated protein-1 (BAP1) (109), a component of the ubiquitin proteasome system that has been implicated in cancers such as lung, breast, and renal cell carcinoma (110-113). BAP1 is a deubiquinating enzyme (DUB) which interacts with the breast cancer susceptibility gene, BRCA1, via its RING finger domain, but does not appear to function
as a deubiquinato of BRCA (114, 115). Unlike other members of the ubiquitin carboxyl hydrolase family, BAP1 possesses a large C-terminal domain which is predicted to coordinate the selective association with potential substrates or regulatory components (116). BAP1 participates in the assembly of multiprotein complexes containing numerous transcription factors and cofactors, and activates transcription in an enzymatic-activity-dependent manner, thereby regulating the expression of a variety of genes involved in various cellular processes (117).

Mutations, deletions and rearrangements of *BAP1* on chromosome 3p21.3 have been detected in lung and lung cancer cell lines, and in sporadic breast tumors (114, 118). Depletion of BAP1 resulted in altered expression of 249 genes, including key mediators of cell cycle progression, DNA replication and repair, cell metabolism, survival and apoptosis (117). BAP1 has tumor suppressor activity both *in vitro* and *in vivo* (119, 120). Expression of wild-type BAP1 significantly abolished tumorigenicity of a human non-small cell lung cancer cell line in nude mice, while expression of mutant BAP1 that lacks either deubiquitinating activity or nuclear localization did not suppress tumorigenicity, implying that both deubiquitinating activity and nuclear localization are necessary for the tumor suppressive activity (119). Suppression of BAP1 by RNA interference has also been demonstrated to inhibit cellular proliferation (120-122).

Microarray analysis comparing 92.1 uveal melanoma cells characterized by a wild-type BAP1 transfected with either control or BAP1 siRNA indicated that the gene expression profile of the BAP1 siRNA treated cells shifted towards a class 2 tumor profile versus the class 1 profile observed in the control treated cells, indicating a dominant role for BAP1 in the regulation of expression of these genes (109). mRNA levels of CDH1 and c-Kit were increased, whereas those for ROBO1, a neural crest differentiation gene, and the melanocyte differentiation genes CTNNb1, EDNRB, and SOX10 were down-regulated. More work is required to elucidate the molecular mechanisms governing the function of BAP1 in uveal melanoma and to assess potential treatment strategies derived from these studies.
Summary

As there are no effective systemic therapies for uveal melanoma, prognosis after the development of metastatic disease remains dismal. Recent studies have brought to light several key signaling cascades that are implicated in the development and progression of uveal melanoma, some of which serve as potential therapeutic targets. It is becoming increasingly clear that, like many cancers, uveal melanomas comprise a heterogenous group of disease, each with distinct molecular features. Each molecular subtype may have unique clinical characteristics and may respond best to a specific therapeutic strategy. The identification of effective therapies for uveal melanoma will depend upon our ability to develop clinical trials with this possibility in mind.
 References


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Legend:

**Figure 1. Major signaling pathways in uveal melanoma.**

The MAPK, PI3K, mTOR, and IGF1-R pathways intersect significantly in uveal melanoma pathogenesis. Briefly, stimulation of GPCR results in replacement of GDP for GTP on the G\(\alpha\) subunit. G\(\alpha\)-GTP is the active form and mediates activation of PLC\(\beta\), which promotes cleavage of PIP2 to IP3 and DAG. DAG goes on to activate PKC, which stimulates the MAPK signaling pathway. MAPK signaling leads to tumor growth and proliferation. The GNAQ Q209L mutation inactivates the intrinsic phosphatase of the G\(\alpha\) protein, thus preventing hydrolysis of GTP to GDP and enabling constitutive downstream MAPK signaling. PI3K mediates phosphorylation of PIP2 to PIP3, and PTEN antagonizes this process. PIP3 activates Akt, which promotes tumor growth and proliferation. Both ERK and Akt also activate the mTOR signaling pathway, which also mediates tumor growth and proliferation. IGF-1 simulation of IGF1-R leads to dimerization and auto-phosphorylation of the receptor, resulting in recruitment and activation of IRS, which can then activate both the PI3K and MAPK pathways. mTOR also exerts inhibitory effects on IGF-1R, such that mTOR blockade disinhibits IGF-1R signaling to paradoxically promote tumor proliferation. There are numerous points at which these pathways can be manipulated, including inhibition of IGF-1 levels with somatostatin analogs or IGF1-R signaling by PPP, PI3K inhibition by LY294002 or Wortmannin, mTOR inhibition by rapamycin, everolimus, or temsorilimus, or MAPK pathway inhibition with BAY-439006, AZD6244, U0126, 17-AAG, or 17-DMAG.

Table 1. Receptor tyrosine kinase inhibitors and inhibitors of the MAP kinase and PI3K/Akt pathways of interest in uveal melanoma.

<table>
<thead>
<tr>
<th>Signaling Pathway</th>
<th>Target</th>
<th>Agent</th>
<th>Development Stage</th>
<th>Trial Status</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP Kinase</td>
<td>BRAF</td>
<td>PLX4032 (RO5185426)</td>
<td>Phase III trial in cutaneous melanoma</td>
<td>Accrual completed</td>
<td>NCT01006980</td>
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<td></td>
<td></td>
<td>XL281</td>
<td>Phase I trial in solid tumors</td>
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<td>NCT00451880</td>
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<tr>
<td></td>
<td></td>
<td>Sorafenib (BAY 43-9006)</td>
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<td>NCT01143402</td>
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<td></td>
<td>GSK1120212</td>
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<td></td>
<td>MSC19363698</td>
<td>Phase I trial in solid tumors</td>
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<td>PI3K/Akt</td>
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<td></td>
<td>Temsirolimus</td>
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<td>Everolimus (RAD001)</td>
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<td>Ridaforolimus (AP23573)</td>
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<td>TORC1/2</td>
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<td>Receptor Tyrosine Kinases</td>
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<td><strong>IGF-1R</strong></td>
<td>IMC-A12</td>
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<td>CP-751,871</td>
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<td>AXL1717</td>
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<td><strong>c-Kit</strong></td>
<td>Imatinib</td>
<td>Phase II in metastatic uveal melanoma</td>
<td>Ongoing</td>
<td>NCT00421317</td>
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<td>Dasatinib</td>
<td>Phase I with bevacizumab in metastatic solid tumors</td>
<td>Ongoing</td>
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<td>Ongoing</td>
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<td><strong>c-Met</strong></td>
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<td>Phase I in solid tumors other than NSCLC</td>
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<td></td>
<td>ARQ 197</td>
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<td>PRO143966</td>
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Table 2. Currently accruing clinical trials for advanced uveal melanoma.

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<td>NCT01034787</td>
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<td>Alberta Health Services</td>
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<td>NCT00506142</td>
<td>Liposomal vincristine</td>
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<td>Genasense, Carboplatin &amp; Paclitaxel</td>
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<td>M.D. Anderson Cancer Center</td>
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<td>II</td>
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<td>III</td>
<td>EORTC</td>
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<td>NCT00168870</td>
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<td>Charite University, Berlin, Germany</td>
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<td>NCT01200238</td>
<td>STA-9090</td>
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<td>Dana-Farber Cancer Institute</td>
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<td>Imatinib</td>
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<td>Centre Oscar Lambret</td>
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<td>NCT01252251</td>
<td>SOM230 &amp; RAD001</td>
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<td>pending</td>
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Tumor growth and proliferation

IP3

mTOR

MEK

ERK

17-AAG

Rapamycin

Perifosine

AZD6244

GNAQ Q209L

DAG

IP3

PI3K

PP2

PTEN

ERK

Raf

GPCR

Gɑ, Gβγ

GTP, GDP

PPP

IGF1–R

IGF1

EC

EC

IC

IRS

Akt

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