Biomarkers identified in preclinical studies evaluating the BRG1/BRM ATPase inhibitor FHD-286 in uveal melanoma

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Abstract

The BRG/Brahma-associated factors (BAF) family of chromatin remodeling complexes (also referred to as the mSWI/SNF complex) regulates chromatin accessibility and gene expression through its ATP-dependent remodeling activity. Phenotypic screening of cancer cell lines demonstrated that uveal melanoma (UM) is exquisitely sensitive to inhibition of the ATPase components of the BAF complex, BRG1 and BRM (also called SMARCA4 and SMARCA2, respectively). Sensitivity was further confirmed in vivo, with strong responses in both primary and metastatic cell line and patient-derived xenograft models. FHD-286, a BRG1/BRM ATPase inhibitor, is currently under evaluation in a Phase I dose escalation in subjects with metastatic uveal melanoma. Preclinical studies show BRG1/BRM inhibition impacts melanocyte biology including the lineage-specific transcription factors MITF and SOX10 and their downstream targets. We also show a decrease in proliferation readouts and positive change in clinically-established markers predicative of poor prognosis in uveal melanoma. This suggests that inhibition of the BAF complex may be epigenetically reprogramming the cells to a less aggressive phenotype. Herein, we describe our findings of biomarkers that offer promising readouts of on-target BRG1/BRM ATPase engagement and clinical impact on metastatic uveal melanoma.

Uveal melanoma cell lines are sensitive to BRG1/BRM ATPase inhibition

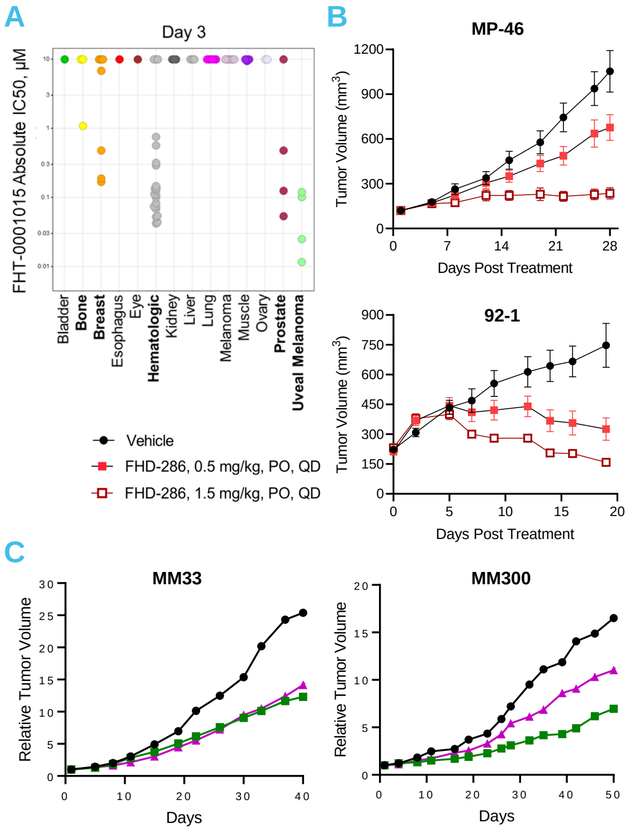

Figure 1. Uveal melanoma (UM) tumors are responders *in vitro* and *in vivo* to BRG1/BRM ATPase inhibitors (tool compounds FHT-1015 and FHT-2256; clinical-stage compound FHD-286). (A) Cell lines were treated for 3 days with a dose titration of FHT-1015 and relative viability was measured using Cell-Titer Glo. **(B)** Dose-dependent tumor growth inhibition with FHD-286 in UM cell line-derived xenograft (CDX) models. MP-46 (BAP1 null) and 92-1 (BAP1 intact) were derived from primary tumors. **(C)** Tumor growth inhibition with FHT-2256 in UM patient-derived xenograft (PDX) models. Mice were dosed QD or BID on a 4 days on, 3 days off schedule. MM33 and MM300 (SF3B1 mutant) were derived from metastatic tumors.

BRG1/BRM inhibition downregulates the MITF/SOX10 pathway

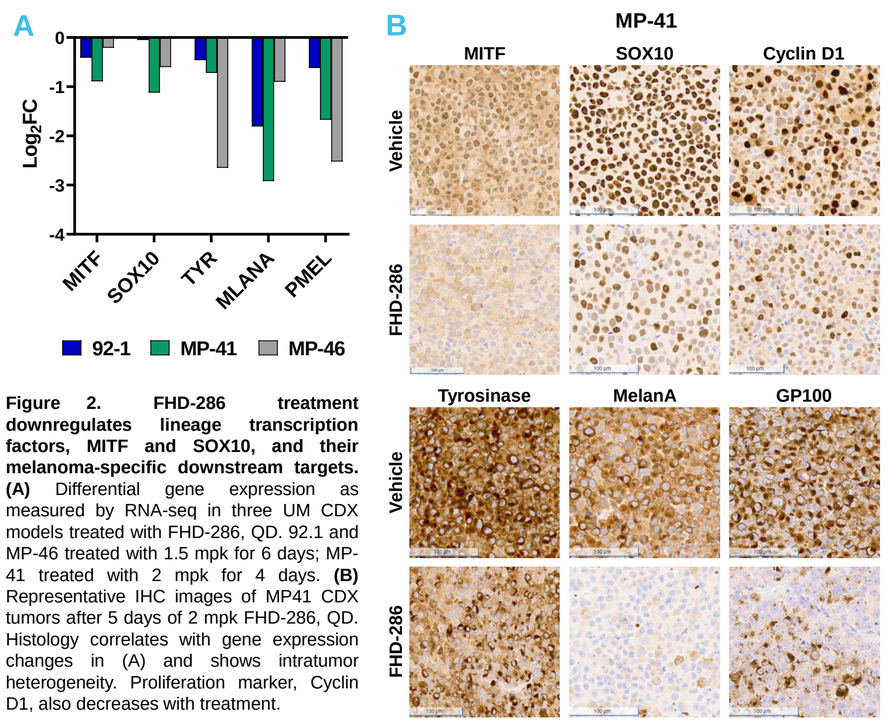

Figure 2. FHD-286 treatment downregulates lineage transcription factors, MITF and SOX10, and their melanoma-specific downstream targets. (A) Differential gene expression as measured by RNA-seq in three UM CDX models treated with FHD-286, QD. 92.1 and MP-46 treated with 1.5 mpk for 6 days; MP-41 treated with 2 mpk for 4 days. **(B)** Representative IHC images of MP41 CDX tumors after 5 days of 2 mpk FHD-286, QD. Histology correlates with gene expression changes in (A) and shows intratumor heterogeneity. Proliferation marker, Cyclin D1, also decreases with treatment.

FHD-286 has a positive impact on clinically-relevant markers associated with poor prognosis

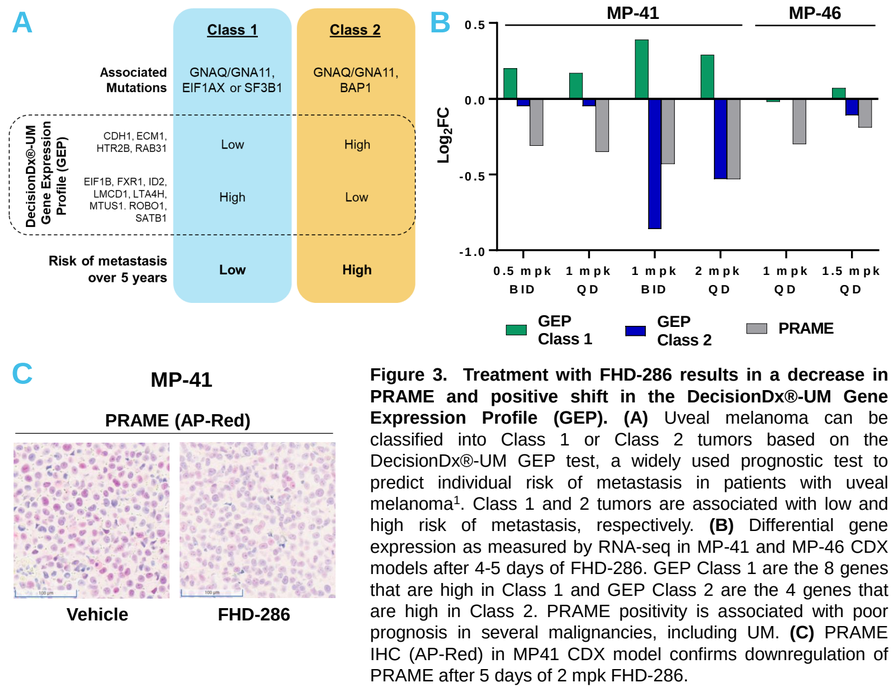

Figure 3. Treatment with FHD-286 results in a decrease in PRAME and positive shift in the DecisionDx®-UM Gene Expression Profile (GEP). (A) Uveal melanoma can be classified into Class 1 or Class 2 tumors based on the DecisionDx®-UM GEP test, a widely used prognostic test to predict individual risk of metastasis in patients with uveal melanoma[1]. Class 1 and 2 tumors are associated with low and high risk of metastasis, respectively. **(B)** Differential gene expression as measured by RNA-seq in MP-41 and MP-46 CDX models after 4-5 days of FHD-286. GEP Class 1 are the 8 genes that are high in Class 1 and GEP Class 2 are the 4 genes that are high in Class 2. PRAME positivity is associated with poor prognosis in several malignancies, including UM. **(C)** PRAME IHC (AP-Red) in MP41 CDX model confirms downregulation of PRAME after 5 days of 2 mpk FHD-286.

BRG1/BRM inhibition may lead to a less suppressive tumor microenvironment in uveal melanoma

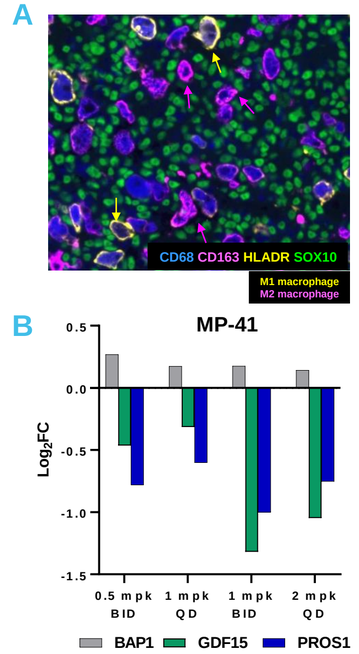

Figure 4. FHD-286 leads to positive changes associated with immunosuppressive M2 macrophage polarization in aggressive UM tumors. (A) Representative immunofluorescence image of a metastatic uveal melanoma biopsy. Tumor cell (SOX10+); M1 macrophage (CD68+/CD163-/HLADR+); M2 macrophage (CD68+/CD163+/HLADR-). Anti-inflammatory M2 macrophages are in proximity to tumor cells and more abundant than pro-inflammatory M1 macrophages. **(B)** Differential gene expression as measured by RNA-seq in MP-41, a BAP1 intact but aggressive model, after 4-5 days of FHD-286. Treatment leads to subtle upregulation of BAP1 and dose-dependent downregulation of two genes found to be upregulated with BAP1 loss. PROS1 has been mechanistically linked to immunosuppressive macrophage polarization in UM in preclinical studies[2].

Conclusions

- FHD-286, a first in class, selective, oral allosteric inhibitor of BRM/BRG1, is efficacious in multiple uveal melanoma models.
- Melanoma-specific markers downstream of MITF/SOX10 signaling are promising markers of target engagement.
- Downregulation of PRAME and a positive change in the uveal melanoma prognostic gene expression profile suggests FHD-286 may be shifting tumor cells to a less aggressive phenotype.
- We propose that through BAP1, FHD-286 may also support the transition towards a less suppressive tumor microenvironment associated with M2 macrophage polarization.
- Ph1 studies are ongoing with FHD-286.

References / Acknowledgements

1. DecisionDx®-UM is a registered trademark of Castle Biosciences Inc.

2. Kaler CJ, Dollar JJ, Cruz AM, Kuznetsoff JN, Sanchez MI, Decatur CL, Licht JD, Smalley KSM, Correa ZM, Kurtenbach S, Harbour JW. BAP1 Loss Promotes Suppressive Tumor Immune Microenvironment via Upregulation of PROS1 in Class 2 Uveal Melanomas. Cancers (Basel). 2022 Jul 28;14(15):3678.