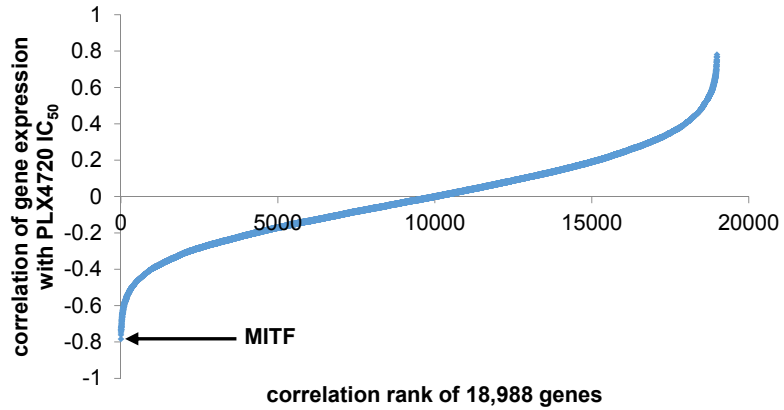
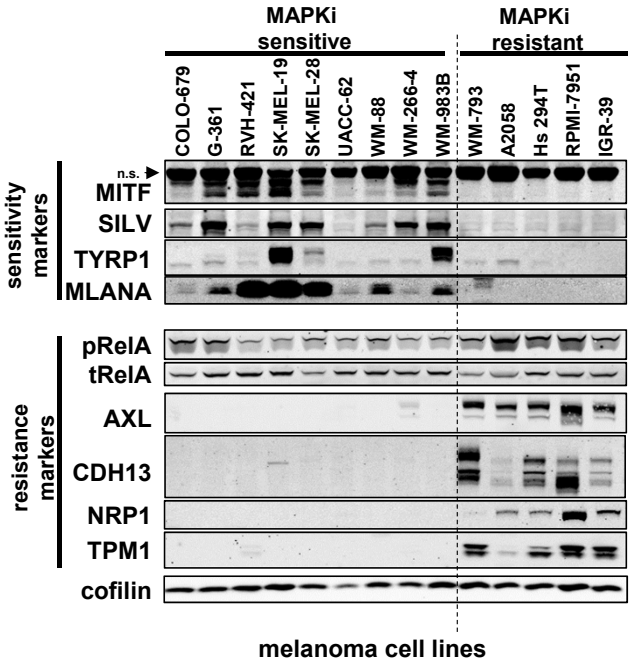
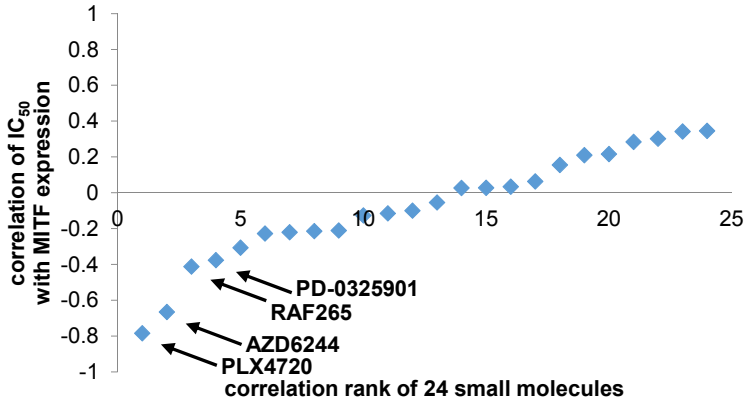
Supplementary Figure S1. Correlation of MITF expression with RAF-inhibitor sensitivity.
Using a panel of 29 $BRAF^{V600}$-mutant melanoma cell lines, Pearson correlation (r) was calculated between gene expression and PLX4720 IC_{50} values. Correlation was then plotted relative to correlation rank.



Supplementary Figure S2. Transcriptional class distinction in BRAF^{V600}-mutant melanoma cell lines. Expression of selected markers by Western blot. Cell lines were plated at densities (specified in Materials and Methods) to achieve approximately 75-90% confluence 5 days after plating and then harvested. n.s.: non-specific band.

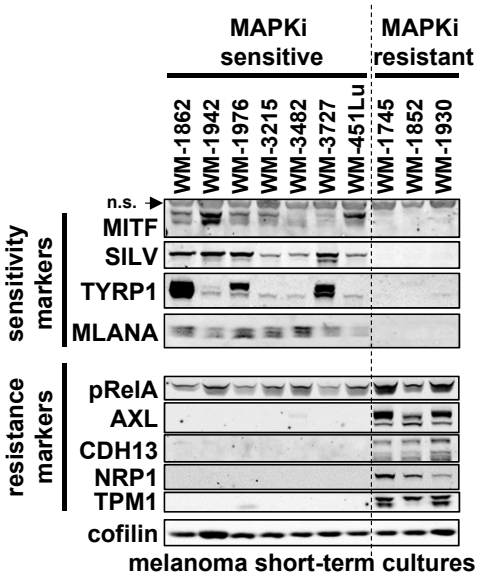


Supplementary Figure S3. Correlation of MITF expression with MAPK pathway inhibitor sensitivity. Using a panel of 24 targeted and cytotoxic small molecule cancer therapeutics, Pearson correlation (r) was calculated between IC_{50} value and MITF gene expression levels across the same 29 cell lines used in (a). Correlation was then plotted relative to correlation rank. This set of small molecules included four MAPK pathway inhibitors: PLX4720 (BRAFi), AZD6244 (MEKi), RAF265 (RAFi), and PD-0325901 (MEKi).



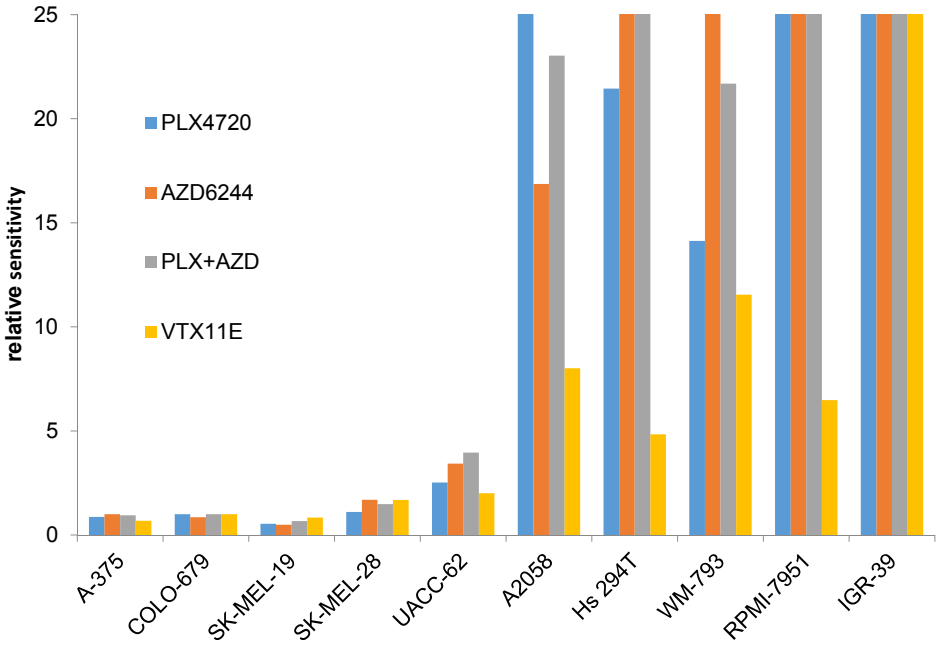
Supplementary Figure S4. Transcriptional class distinction in BRAF^{V600}-mutant melanoma short-term cultures.

Expression of selected markers by Western blot. Short-term cultures were plated at densities (specified in Materials and Methods) to achieve approximately 75-90% confluence 5 days after plating and then harvested. n.s.: non-specific band.



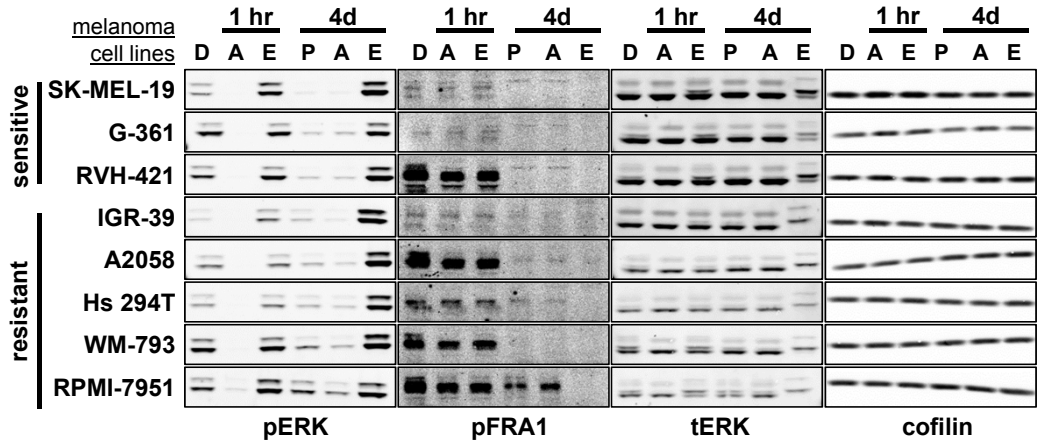
Supplementary Figure S5. MITF-low/NF-κB-high melanomas are resistant to inhibition of RAF, MEK, RAF/MEK, and ERK.

Sensitivity profile of selected melanoma cell lines to inhibition of BRAF (PLX7420), MEK (AZD6244), RAF/MEK (PLX+AZD), and ERK (VTX11E). Following four-day drug treatment, viability was read out and relative sensitivity calculated as described in Materials and Methods.



Supplementary Figure S6. Effects of MAPK pathway inhibitors on levels of pERK and pFRA1 in sensitive and resistant cell lines.

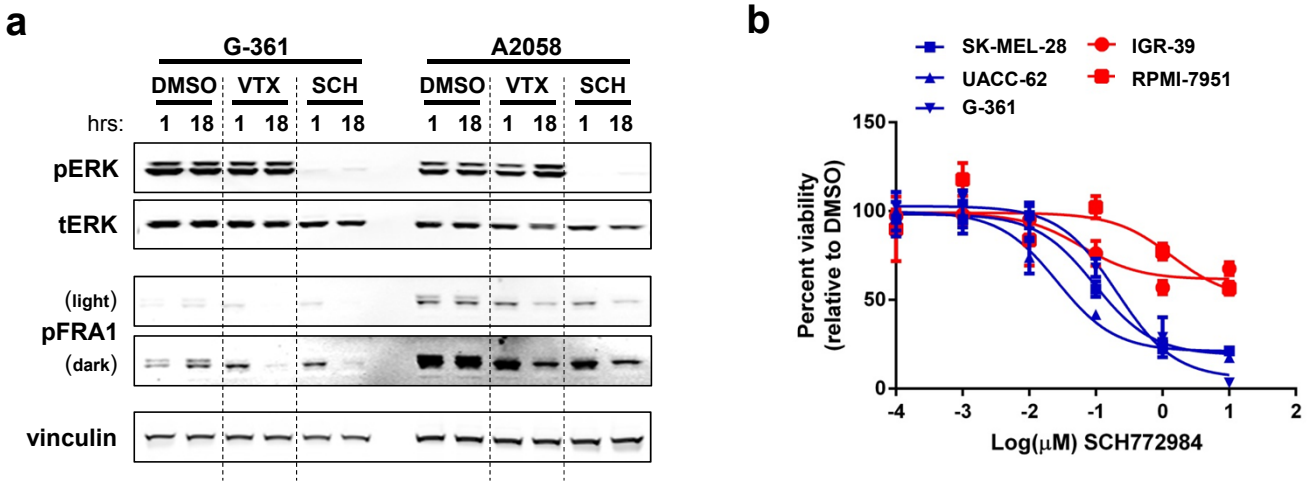
All cells were seeded in parallel and allowed to proliferate for 5 days, with indicated drugs added for the indicated lengths of time prior to simultaneous final harvest. DMSO control was treated for 4 days.
D, DMSO; P, 2 μM PLX4720; A, 200 nM AZD6244; E, VTX11E, 2 μM.



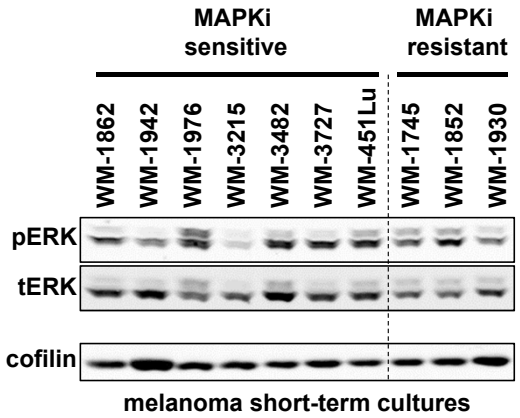
Supplementary Figure S7. MITF-low/NF-κB-high melanomas are resistant to inhibition of RAF, MEK, RAF/MEK, and ERK.

(**a**) Effects of ERK inhibitors VTX11E (VTX) and SCH772984 (SCH) on phosphorylation of ERK and the ERK substrate FRA1.

(**b**) Comparative sensitivity profiles of the ERK inhibitor SCH772984.

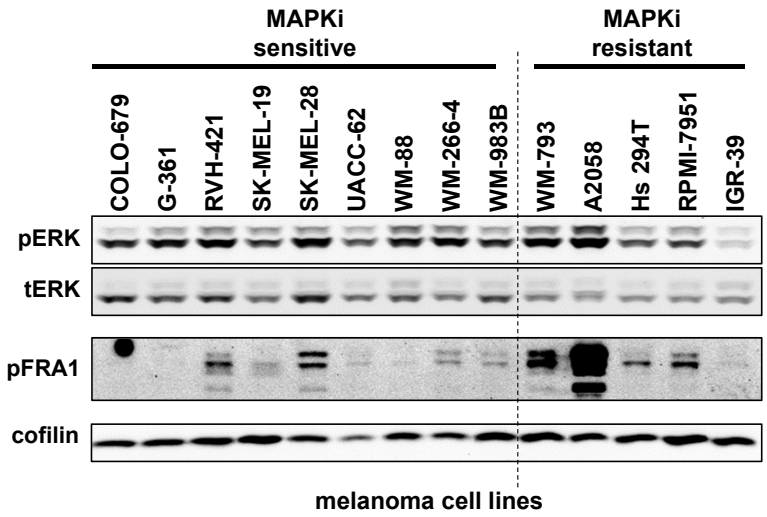


Supplementary Figure S8. Comparable steady-state MAPK pathway activity in sensitive and resistant melanoma short-term cultures.
Short-term cultures were harvested 5 days after plating and blotted for pERK as a readout of MAPK pathway activity.



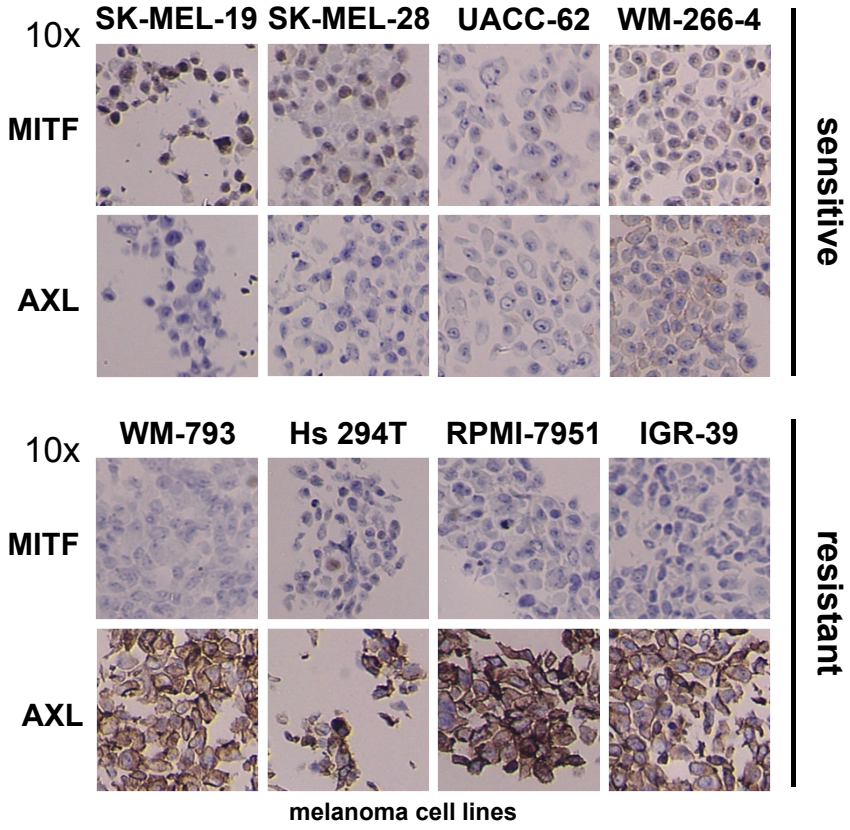
Supplementary Figure S9. Comparable steady-state MAPK pathway activity in sensitive and resistant melanoma cell lines.

Cell lines were harvested 5 days after plating and blotted for pERK and pFRA1 as readouts of MAPK pathway activity.

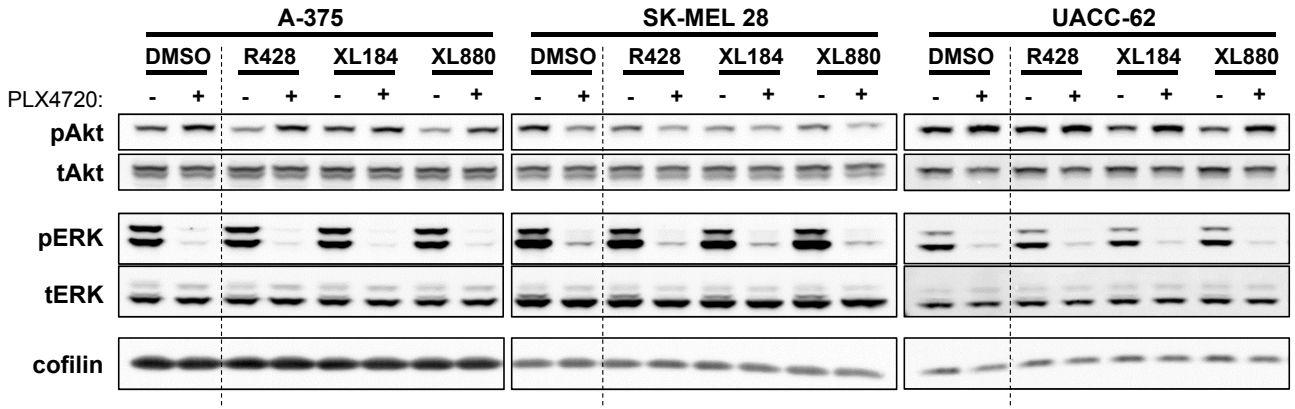


Supplementary Figure S10. Staining of MITF and AXL in known MITF-expressing and AXL-expressing cell lines.

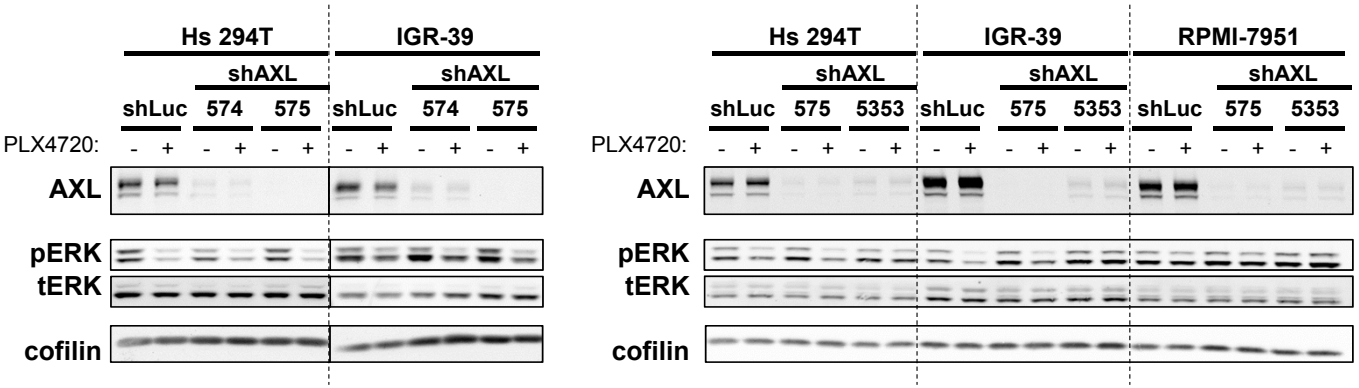
MAPK pathway inhibitor sensitive and resistant melanoma cell lines were fixed, embedded, and stained for MITF and AXL expression.



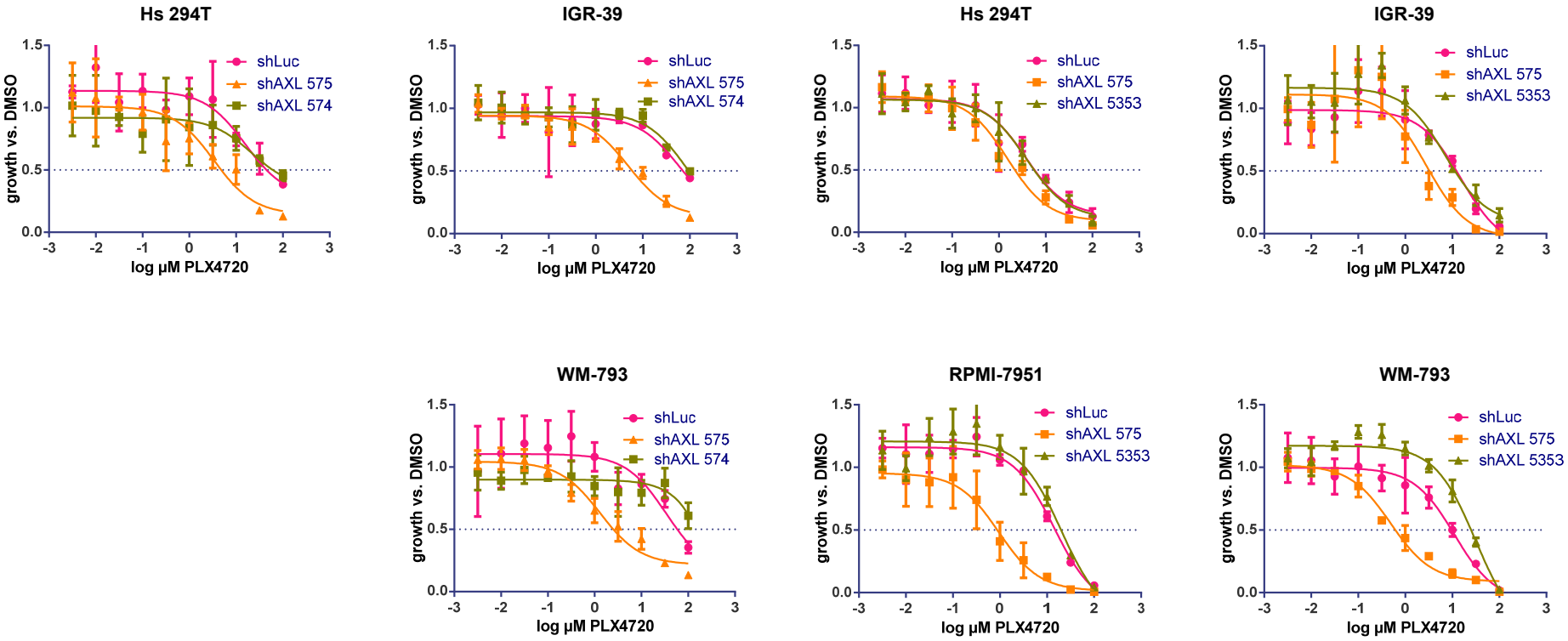
Supplementary Figure S11. Lack of effect of AXL inhibitors on pERK and pAkt levels in sensitive cells lines not exogenously overexpressing AXL.
Cells were treated overnight with the indicated AXL inhibitors in the presence or absence of PLX4720 (2 μM) prior to harvest.



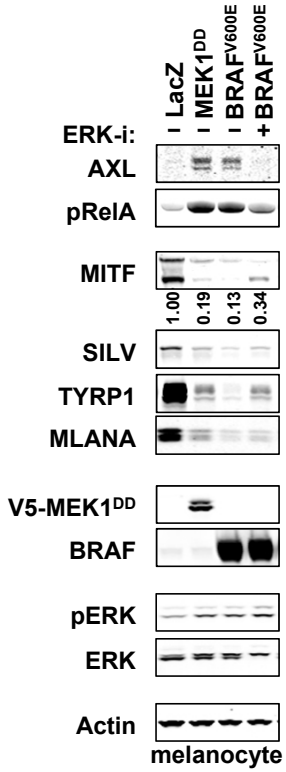
Supplementary Figure S12. Lack of effect of AXL knockdown on pERK levels in intrinsically resistant lines. Following infection with the indicated shRNAs, cells were treated overnight with PLX4720 (2 μM) prior to harvest.



Supplementary Figure S13. Lack of consistent sensitization to PLX4720 following AXL knockdown in intrinsically resistant lines.
Following infection with the indicated shRNAs, cells were seeded for 4-day treatment with PLX4720 prior to viability readout.

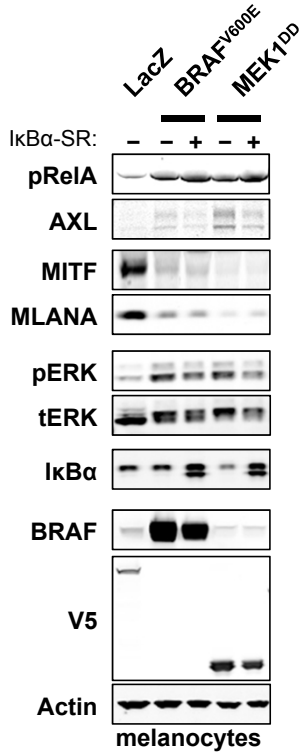


Supplementary Figure S14. MAPK pathway activation alters melanocyte transcriptional state.
Effects of aberrant MAPK pathway activation on markers of the MITF-high and NF-κB-high classes. Melanocytes were infected with constitutively active MEK1^{DD} or BRAF^{V600E} and treated with an ERK inhibitor (VTX11E) or control. Cells were subsequently lysed for Western blot analysis of the indicated markers. MITF expression levels are quantified and normalized to LacZ-expressing cells treated with DMSO.



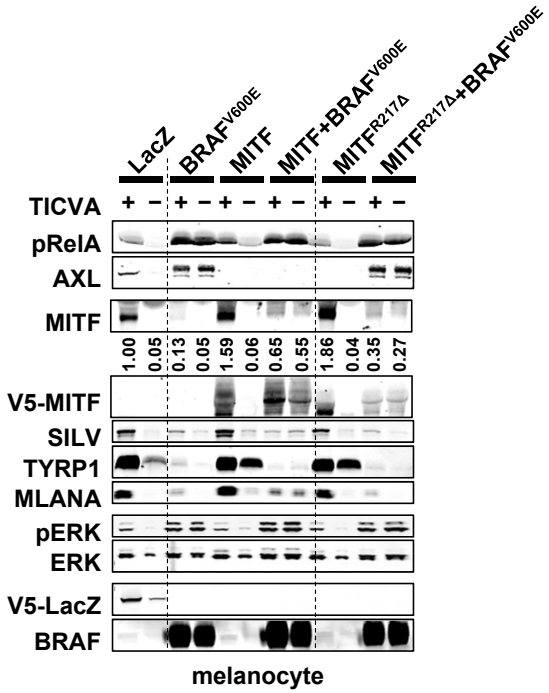
Supplementary Figure S15. NF-κB pathway activity is required for maximal AXL induction, but not MITF suppression, following MAPK pathway activation in melanocytes.

Melanocytes were infected with $BRAF^{V600E}$ or $MEK1^{DD}$, in the presence or absence of the IκBα super-repressor, harvested, and blotted for the indicated markers.

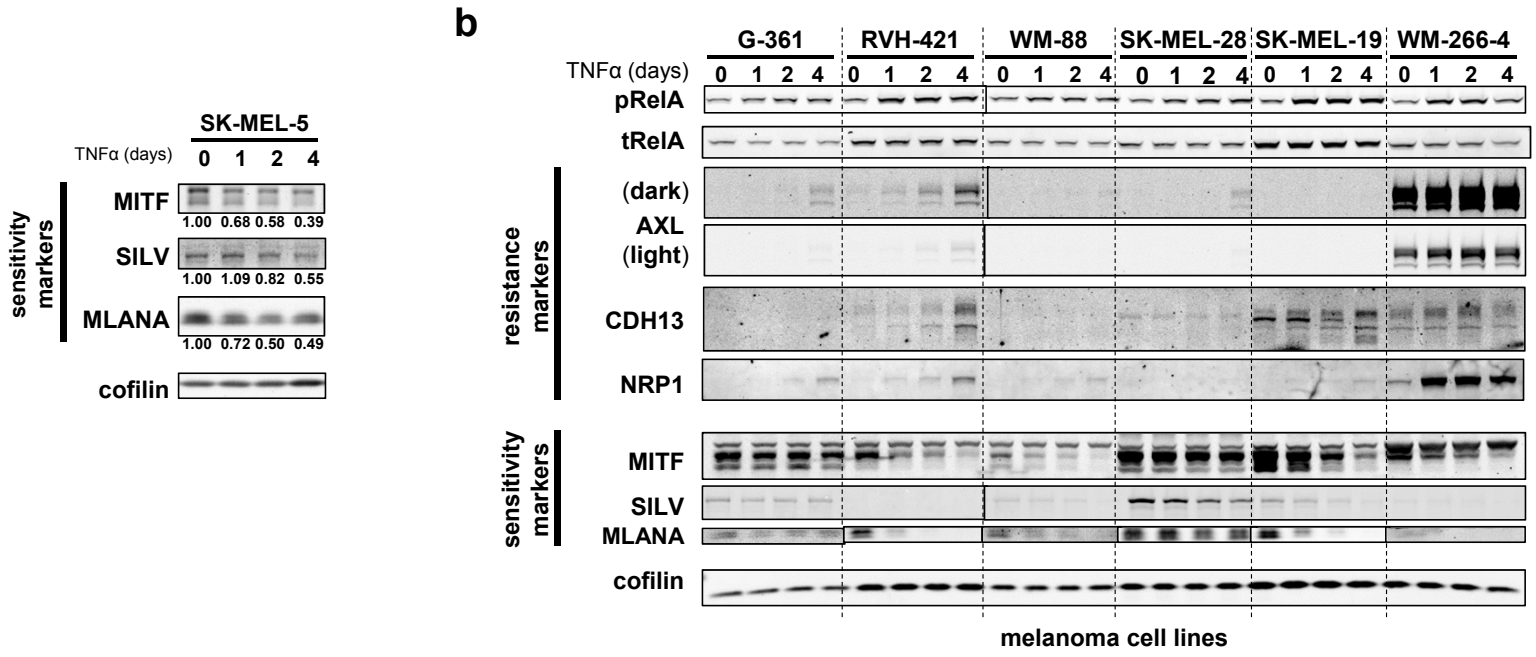


Supplementary Figure S16. The balance of MITF and MAPK pathway activity governs melanocyte transcriptional state.

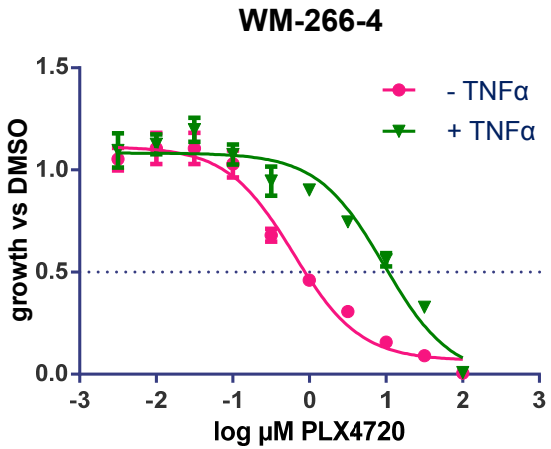
Expression of wild-type MITF, but not a DNA-binding impaired MITF (R217Δ), can prevent the induction of AXL by aberrant MAPK pathway activity. Melanocytes were infected with indicated constructs and harvested for Western blot analysis. MITF expression levels are quantified and normalized to LacZ-expressing cells cultured in TICVA medium.



Supplementary Figure S17. NF-κB pathway activation induces the NF-κB-high/MITF-low state.
(a) Parental SK-MEL-5 cells were seeded in parallel allowed to proliferate for 5 days, with TNFα (25 ng/mL final) added for the indicated lengths of time prior to simultaneous final harvest. Levels of MITF and MITF target gene (MLANA, SILV) expression were quantified.
(b) Cells were seeded in parallel and allowed to proliferate for 5 days, with TNFα (25 ng/mL final) added for the indicated lengths of time prior to simultaneous final harvest. Lysates were blotted for the indicated markers of NF-κB and MITF transcriptional states.



Supplementary Figure S18. NF-κB activation confers resistance to MAPK pathway inhibition.
Following overnight pretreatment with TNFα (25 ng/mL final) or vehicle control, cells were treated with PLX4720 for 4 days prior to viability read-out.



Supplementary Figure S19. Cultured-to-resistance lines exhibit resistance to inhibition of RAF, MEK, RAF/MEK, and, in some cases, ERK.

Four-day drug sensitivity characterization of parental and cultured-to-resistant melanoma cell lines. COLO-679-PR1 required PLX4720 for continued growth and therefore could not be returned to DMSO to undergo GI50 assessment.