Inhibition of AXL Signaling with AB801 Augments Anti-Tumor Immune Responses

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Jhansi L. Leslie, Armon Goshayeshi, Ruben Flores, Gonzalo Barajas, Samantha C. Schwager, Enzo Stagnaro, Angelo Kaplan, Janine Kline, Ester Fernandez-Salas, Susan L. Paprcka

Arcus Biosciences, Hayward, CA, USA

ARCUS BIOSCIENCES

Background

- High expression of AXL, a receptor tyrosine kinase, results in drug resistance, attenuated immune responses, and poor prognosis in cancer patients[1,2]
- AXL is expressed in cancer, stromal, and select immune cells. AXL signaling creates an immunosuppressive tumor microenvironment (TME) via both cancer-intrinsic and immune-mediated mechanisms, fostering therapeutic resistance
- Our team has discovered and characterized AB801, a novel highly potent and selective small molecule AXL inhibitor[3]
- AB801 in combination with αPD-1 and chemotherapy overcomes therapeutic resistance and promotes robust anti-tumor responses in murine models

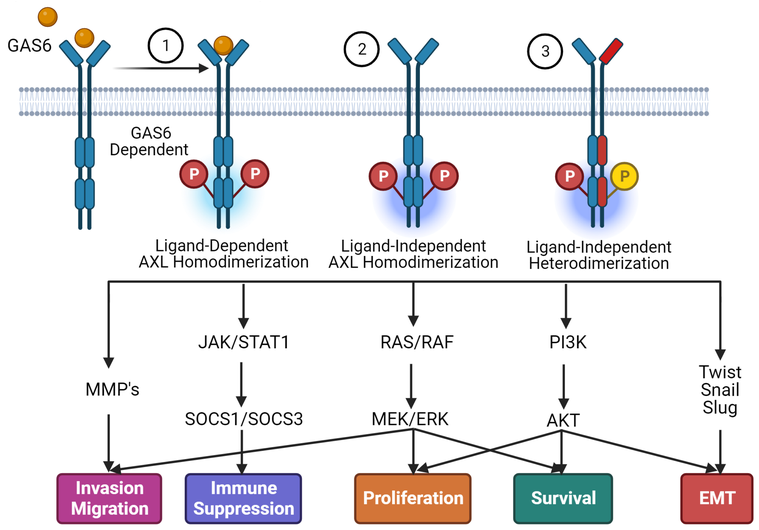


Figure 1. Ligand-dependent AXL signaling is mediated by binding of its ligand, GAS6, leading to receptor dimerization and phosphorylation. Ligand-independent (2)homo- or (3)hetero-dimerization can also occur, resulting in AXL phosphorylation. Phosphorylated AXL signals through various pathways that promote cancer cell survival and proliferation as well as immunosuppression.
Schematic created with Bio Render.com

Cancer Cells & Select Immune Cells Express AXL

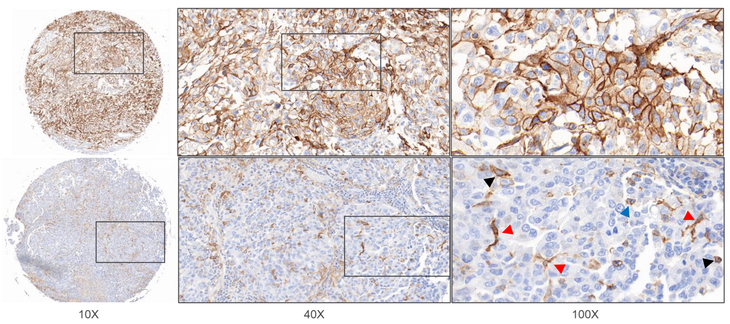


Figure 2. AXL IHC of human NSCLC biopsies demonstrate AXL expression in cancer cells (top panel). Myeloid cells such as MDSC's, monocytes and macrophages (lower panel ▶) and dendritic cells (lower panel ▶), as well as some lymphoid cells (lower panel ▶) also express AXL.

AB801 Sensitizes Cancer Cells to Chemotherapy by Increasing DNA Damage

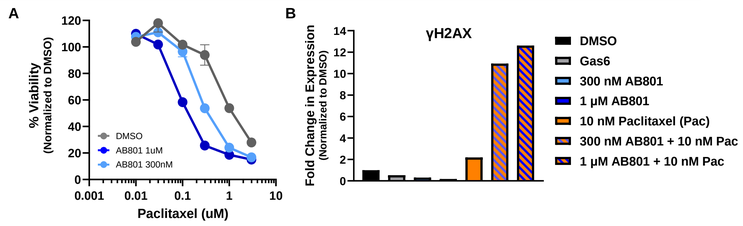


Figure 3. Paclitaxel-resistant HEY-T30 cells were treated with 300 nM or 1 μM AB801 alone or in combination with paclitaxel for 72 h. A) Viability was measured by CellTiter-Glo®. B) γH2AX was quantified by Western blot.

Human Conventional Type 1 Dendritic Cells Increase AXL Expression in Response to Tumor Antigen

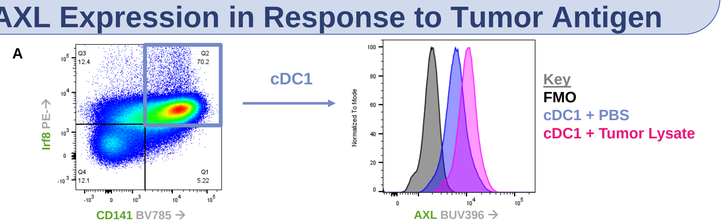


Figure 4. ***In vitro*** **differentiated human cDC1s increase AXL protein expression in response to tumor lysate.** CD34+ HSCs were differentiated into cDC1s by the addition of FLT3L and GM-CSF. cDC1s in the absence of the differentiation cytokines were incubated with PBS or 250 μg of NCIH1299 lysate for 24 hrs and assessed for expression of DC1 markers (IRF8 & CD141) and AXL by flow cytometry.

AXL is Expressed on Cancer Cells & Immune Cells in MC38 Syngeneic Tumors

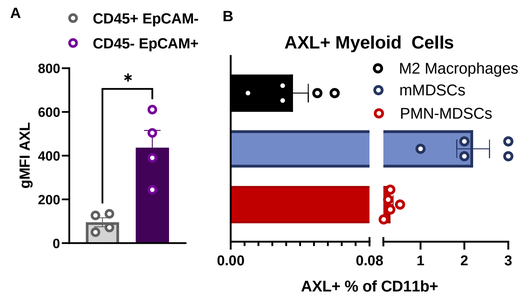
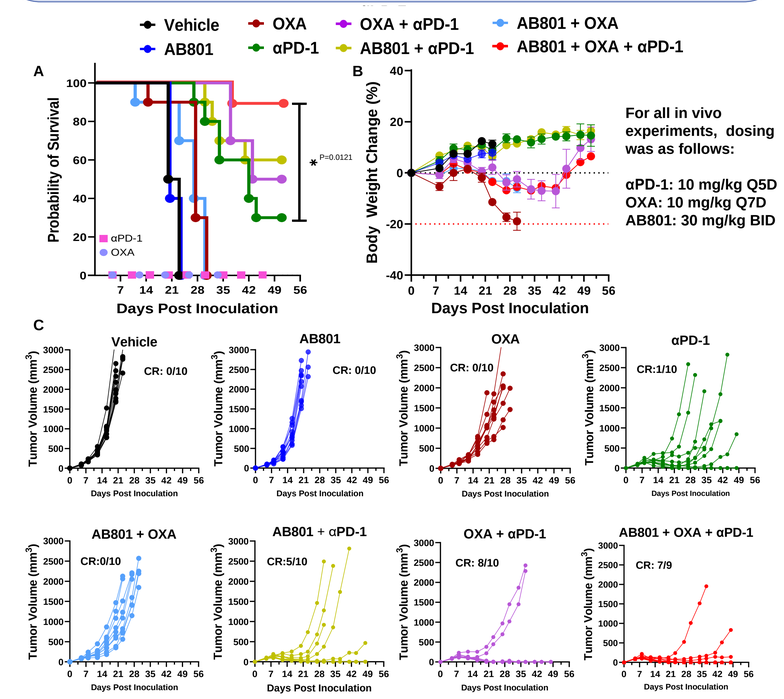


Figure 5. Cancer cells and select myeloid cells express AXL in MC38 tumors grown in C57BL/6 mice. Tumors (~400 mm3) were used to characterize populations expressing AXL. A) AXL is expressed in MC38 cancer cells (CD45-EpCAM+). B) AXL expressing cells in the myeloid compartment (parent gating: Singlets/Live/CD45+/CD11b+) including M2 Macrophages (F4/80+,Ly6C-/CD206+), mMDSCs (Ly6C+,F4/80+ or -), and PMN-MDSCs (Ly6G+ & Ly6Cint).

Combination Therapy with AB801, αPD-1, and Oxaliplatin Results in Greater Tumor Control

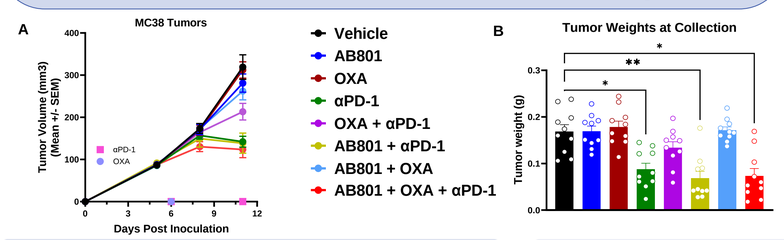


For all in vivo experiments, dosing was as follows:

αPD-1: 10 mg/kg Q5D
OXA: 10 mg/kg Q7D
AB801: 30 mg/kg BID

Figure 6. Efficacy of AB801 in combination with αPD-1 and oxaliplatin in MC38 tumors. A) Survival curves showing improved survival of AB801+ OXA+ αPD-1 therapy vs αPD-1 alone (P=0.012, Mantel-Cox test). Treatment was started when average tumor volume was ~90 mm3 across all groups. B) Change in body weight during treatment. AB801+ αPD-1 resulted in improved survival compared to αPD-1 monotherapy and was better tolerated than OXA + αPD-1 as indicated by the lack of weight loss. C) Plots of individual tumor volumes showing number of complete regressions (CR) per treatment group.

AB801 In Combination with αPD-1 and Oxaliplatin Promotes Greater Anti-Tumor Immune Responses



Triplet Therapy Increases Type 1 Dendritic Cells & Tumor-Specific CD8 T-cells

Decreased Immunosuppressive mMDSCs

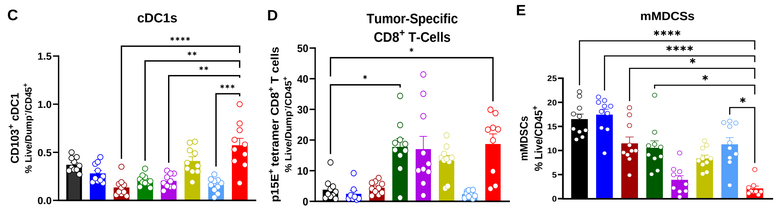


Figure 7. AB801 in combination with αPD-1 and oxaliplatin promotes a pro-inflammatory immune response in the TME. A) Tumor growth kinetics during treatment, showing reduced volume with αPD-1, AB801+ αPD-1, or AB801+ OXA+ αPD-1 therapy. Treatment was started when average tumor volume was ~90 mm3 across all groups. B) Tumor weights at collection showing significantly degreased weight in αPD-1, AB801+ αPD-1 or AB801+ OXA+ αPD-1 treatment groups compared to vehicle (Brown-Forsythe & Welch ANOVA with Dunnett's T3 multiple comparisons test, *, P<0.05, **, P<0.01). C) Frequency of CD103+ DC1s across all treatments D) Frequency of p15e Tetramer+ CD8+ T-cells E) Frequency of mMDSCs. For C-D significance was determined using a Kruskal-Wallis test with Dunn's multiple comparisons test, * P<0.05, ** P< 0.001, **** P<0.0001.

Stk11 KO MC38 Tumors Are Infiltrated with Immunosuppressive Myeloid Cells that Express AXL

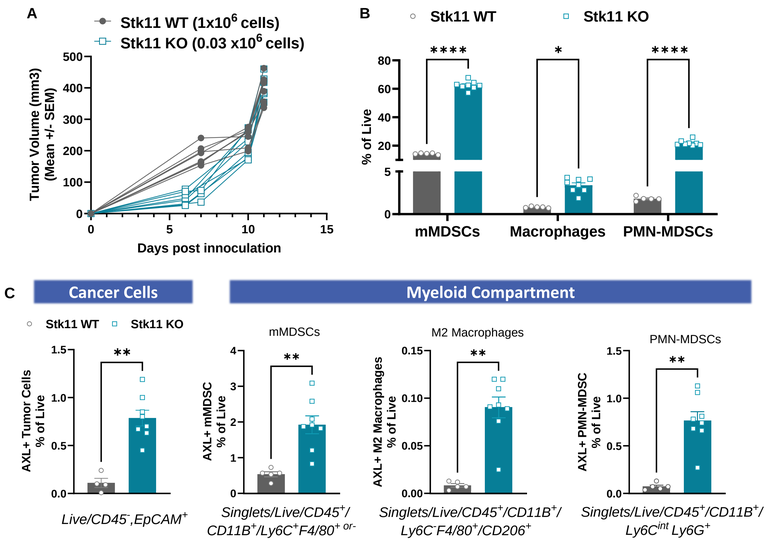


Figure 8. The TME of Stk11 KO tumors is more immunosuppressive with increased suppressive myeloid infiltration and increased AXL expression. A) Stk11 KO tumors have aggressive growth kinetics, therefore 33x less Stk11 KO cells were inoculated to archive similar growth between WT and Stk11 KO tumors. Tumors were collected for TIL when both groups reached ~400 mm3 B) Stk11 KO tumors were more immunosuppressed than WT with increased frequencies of mMDSCs, macrophages, and PMN-MDSCs. C) Increased frequency of AXL+ cancer cells, mMDSCs, M2 macrophages, PMN-MDSCs. * P<0.05, ** P<0.01, *** P< 0.001, **** P<0.0001. Mann-Whiney test.

In Stk11 KO Tumors, AB801 in Combination with αPD-1 and Oxaliplatin Increases Anti-Tumor Efficacy

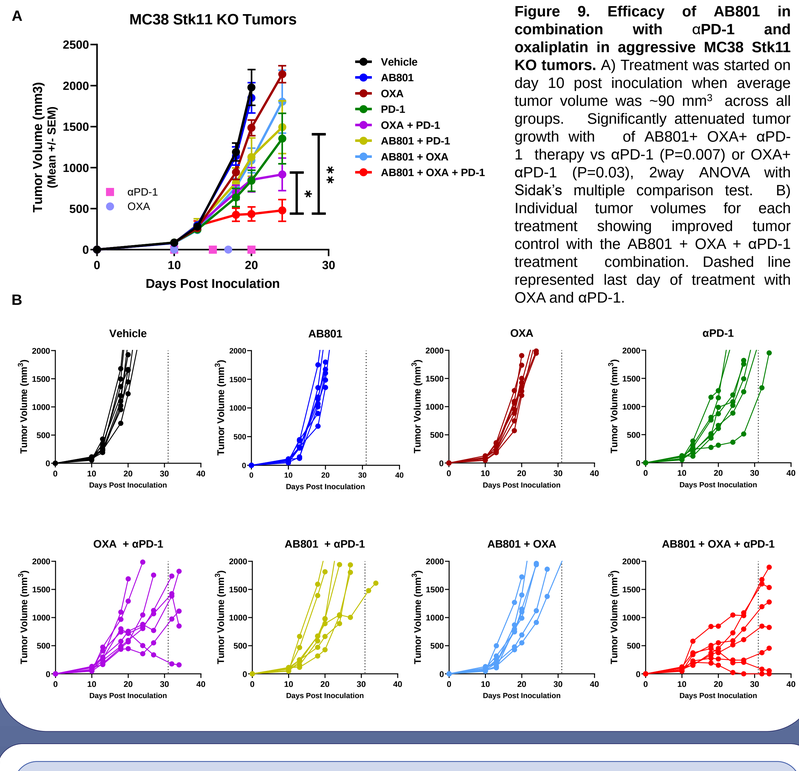


Figure 9. Efficacy of AB801 in combination with αPD-1 and oxaliplatin in aggressive MC38 Stk11 KO tumors. A) Treatment was started on day 10 post inoculation when average tumor volume was ~90 mm3 across all groups. Significantly attenuated tumor growth with of AB801+ OXA+ αPD-1 therapy vs αPD-1 (P=0.007) or OXA+ αPD-1 (P=0.03), 2way ANOVA with Sidak's multiple comparison test. B) Individual tumor volumes for each treatment showing improved tumor control with the AB801 + OXA + αPD-1 treatment combination. Dashed line represented last day of treatment with OXA and αPD-1.

Summary

- AXL is a promising therapeutic target involved in cancer cell-intrinsic and immunomodulatory mechanisms
- The potent and selective AXL inhibitor AB801 reduces immunosuppression in the TME, enables activation of an anti-tumor immune response and renders tumors more susceptible to checkpoint blockade and chemotherapy.
- AB801 in combination with oxaliplatin and αPD-1 improves tumor control in aggressive and immunosuppressed Stk11 KO MC38 tumors.
- AB801 is currently being evaluated in two clinical dose escalation trials one in healthy volunteers (NCT06004921) and one in patients with advanced malignancies (NCT06120075).

References

1) Zhu, C. et al. Mol. Cancer 2019, 18:153.
2) Son, H-Y. et al. Front. Oncol. 2021, 11:756225
3) Miles, D. et al. EORTC-NCI-AACR 2022 Abstract 290, PB070