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CONTRACTING ORGANIZATION: The Wistar Institute, Philadelphia, PA

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14. ABSTRACT

ARID1A encodes a subunit of the SWI/SNF chromatin-remodeling complex and functions as a tumor suppressor. Notably, inactivating mutations in *ARID1A* occur frequently in ovarian clear cell carcinomas (OCCC; >50%) and ovarian endometrioid carcinomas (OEC; >30%). There is an unmet need for effective treatment modalities for *ARID1A*-mutated ovarian cancers. Our preliminary data show that *ARID1A* mutation sensitizes ovarian cancer to anti-PD-L1 treatment. Our recent studies also show that *ARID1A*-mutated ovarian cancer depends on HDAC6 activity. Although most translational studies on HDAC6 inhibitors have focused on their effects on tumor cells, emerging evidence suggests that HDAC6 inhibitors have immunomodulatory effects on various immune cellular subsets. Indeed, our preliminary data suggests that the HDAC6 inhibitor ACY1215 enhances the activation of T cells and suppresses MDSCs in *ARID1A*-mutated OCCCs. They suggest that HDAC6 inhibitors may enhance the anti-PD-L1 therapy in *ARID1A*-mutated ovarian cancers. Our **central hypothesis** is that *ARID1A*-mutated ovarian cancer can be therapeutically eradicated by a combination of clinically applicable HDAC6 inhibitor and anti-PD-L1 immune checkpoint blockade.

15. SUBJECT TERMS
Epithelial ovarian cancer, ovarian clear cell carcinoma, ARID1A, SWI/SNF, HDAC6, Immune checkpoint blockade, anti-PD-L1.

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TABLE OF CONTENTS

	Page
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	11
5. Changes/Problems	12
6. Products	12
7. Participants & Other Collaborating Organizations	14
8. Special Reporting Requirements	15
9. Appendices	15

1. INTRODUCTION:

ARID1A encodes a subunit of the SWI/SNF chromatin-remodeling complex and functions as a tumor suppressor. Notably, inactivating mutations in ARID1A occur frequently in ovarian clear cell carcinomas (OCCC; >50%) and ovarian endometrioid carcinomas (OEC; >30%). There is an unmet need for effective treatment modalities for ARID1A-mutated ovarian cancers. Our preliminary data show that ARID1A mutation sensitizes ovarian cancer to anti-PD-L1 treatment. Our recent studies also show that ARID1A-mutated ovarian cancer depends on HDAC6 activity. Although most translational studies on HDAC6 inhibitors have focused on their effects on tumor cells, emerging evidence suggests that HDAC6 inhibitors have immunomodulatory effects on various immune cellular subsets. Indeed, our preliminary data suggests that the HDAC6 inhibitor ACY1215 enhances the activation of T cells and suppresses MDSCs in ARID1A-mutated OCCCs. They suggest that HDAC6 inhibitors may enhance the anti-PD-L1 therapy in ARID1A-mutated ovarian cancers. Our **central hypothesis** is that ARID1A-mutated ovarian cancer can be therapeutically eradicated by a combination of clinically applicable HDAC6 inhibitor and anti-PD-L1 immune checkpoint blockade.

2. KEYWORDS:

Epithelial ovarian cancer, ovarian clear cell carcinoma, ARID1A, SWI/SNF, HDAC6, Immune checkpoint blockade, anti-PD-L1.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The objective of this proposal is this application is to develop a novel therapeutic strategy for ARID1A-mutated ovarian cancers by combining immune checkpoint anti-PD-L1 and a clinically applicable HDAC6 inhibitor.

Specific Aim 1: To investigate the effects of HDAC6 inhibition and ARID1A status on tumor immune microenvironment.

Specific Aim 2: To develop a novel therapeutic approach for ARID1A-mutated ovarian cancer by combining clinically applicable HDAC6 inhibitor and anti-PD-L1 antibody.

What was accomplished under these goals?

Since the starting of the award, substantial progress has been made toward achieving the goals as outlined in the application.

1) major activities;

The major activities in the first two years are as following:

1. We investigated the mechanism by which ARID1A regulates anti-PD-L1 response
2. We determined the effects of the HDAC6 inhibitor on immune modulating cells in the tumor microenvironment.
3. We determined whether HDAC6 inhibitor and anti-PD-L1 are synergistic in suppressing the growth of ARID1A-inactivated clear cell ovarian carcinoma.

2) specific objectives;

The major objectives in the first two years of funding are as following:

1. To elucidate how ARID1A may regulate expression of CD274 that encodes PD-L1.
2. To prolife how HDAC6 inhibition modulates immune microenvironment in ARID1A inactivated ovarian clear cell carcinomas.

3. To explore the synergy between HDAC6 inhibitor and immune checkpoint blockade in ARID1A inactivated ovarian clear cell carcinomas.

3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative);

CD274 is a direct ARID1A target gene.

ARID1A chromatin immunoprecipitation followed by next generation sequencing (ChIP-seq) analysis revealed that ARID1A was associated with the PD-L1 encoding CD274 gene promoter in ARID1A wildtype OCCC cells [1] (**Figure 1A**). We validated the binding of ARID1A to the Cd274 gene promoter by ChIP in the mouse ovarian ID8-Defb29/Vegf cells (**Figure 1B-C**) in which PD-L1 is implicated [2]. As a negative control, ARID1A binding to the Cd274 promoter was reduced to a level observed in IgG controls in ARID1A knockout ID8-Defb29/Vegf cells (**Figure 1C**). Notably, SNF5, a core subunit of the SWI/SNF complex, was also associated with the Cd274 promoter and its association was reduced by ARID1A knockout (**Figure 1C**). Expression of ARID1B, the mutually exclusive subunit of the SWI/SNF complex with ARID1A, was upregulated in ARID1A knockout ID8-Defb29/Vegf cells (**Figure 1B**) [3]. Although ARID1B was also associated with the Cd274 promoter, ARID1A knockout did not affect the association of ARID1B with the Cd274 promoter (**Figure 1C**). This suggests that ARID1B is unable to compensate for ARID1A loss on the Cd274 promoter. Similar observations were also made in the ARID1A wildtype human OCCC cell lines OVCA429 and RMG1 cells (**Figure 2**), indicating that the association of ARID1A with the CD274 promoter is not a cell line-specific effect. Together, we conclude that CD274 is a direct ARID1A target gene.

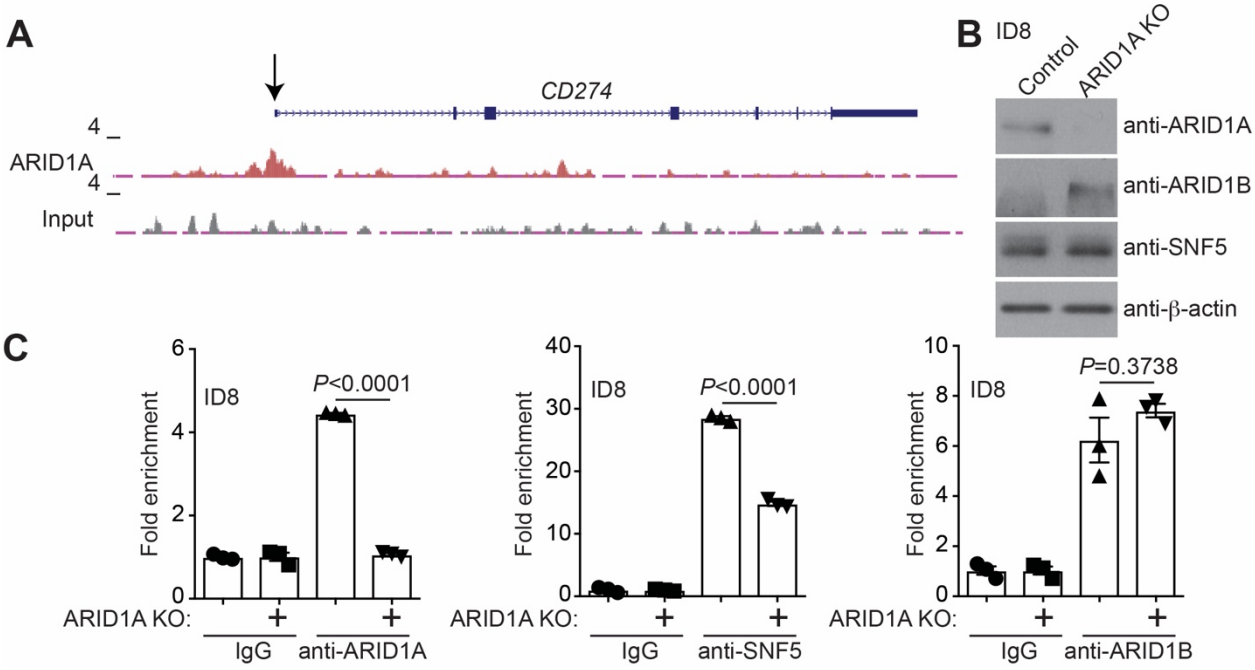

Figure 1. CD274 is a direct ARID1A target gene in mouse ovarian cancer cells.
(**A**) ARID1A ChIP-seq track on the CD274 gene locus in ARID1A wildtype RMG1 cells. (**B**) Expression of ARID1A, ARID1B, SNF5 and □-actin in the ARID1A wildtype control and ARID1A knockout mouse ovarian ID8-Defb29/Vegf cells. (**C**) The indicated ID8-Defb29/Vegf cells were subjected to ChIP analysis for the association of the indicated proteins with the Cd274 gene promoter using the indicated antibodies against ARID1A, SNF5, ARID1B or an isotype-matched IgG control. Error bars represent ± S.E.M. n= 3 independent experiments.

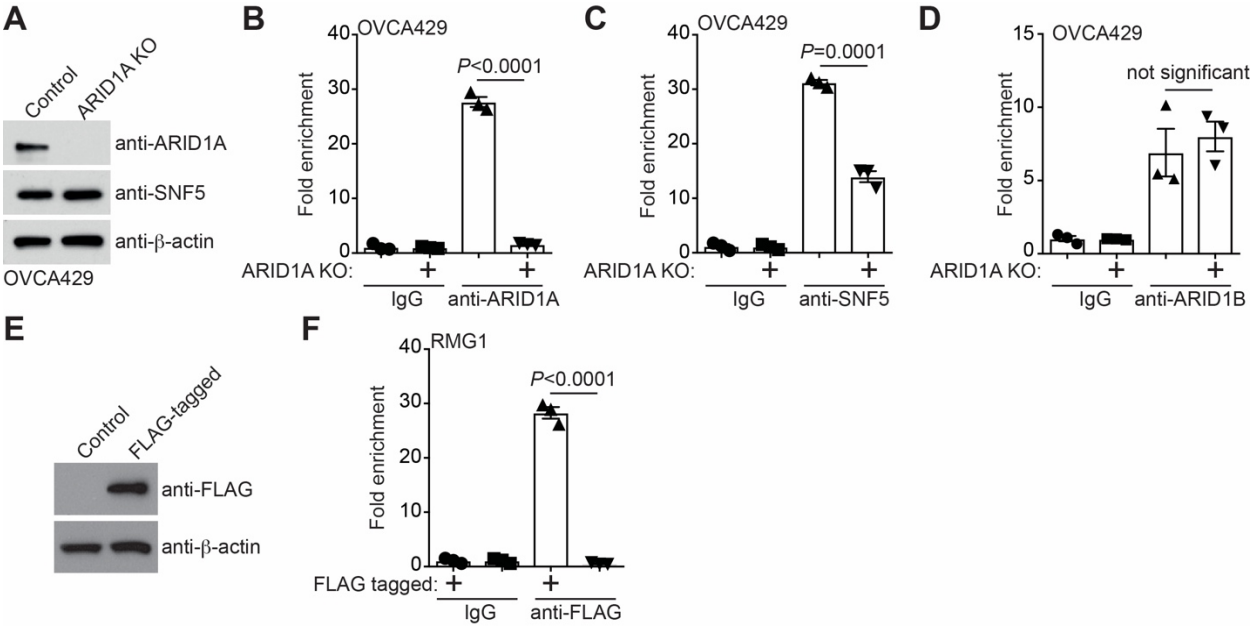

Figure 2. CD274 is a direct ARID1A target gene in human ovarian clear cell ovarian cancer cells.

(**A**) Expression of ARID1A and SNF5 in the ARID1A wildtype control and ARID1A knockout human OVCA429 OCCC cells. □-actin expression was used as a loading control. (**B-D**) ARID1A wildtype control and ARID1A knockout OVCA429 OCCC cells were subjected to analysis for the association of the indicated proteins with the CD274 gene promoter using the indicated antibodies against ARID1A (B) (by CUT & RUN), SNF5 (C) or ARID1B (D) (by ChIP) (C). An isotype-matched IgG was used as a negative control. (**E-F**) Endogenously FLAG-tagged ARID1A wildtype RMG1 OCCC cells were subjected to immunoblot analysis for expression of FLAG (E) or for the association of FLAG-ARID1A with the CD274 gene promoter by ChIP analysis using an anti-FLAG antibody (F). An isotype-matched IgG was used as a negative control. Error bars represent ± S.E.M. n= 3 independent experiments.

ARID1A represses CD274 gene transcription.

We next determined the effect of ARID1A status on changes in Cd274 mRNA and PD-L1 expression. Compared with ARID1A wildtype control ID8-Defb29/Vegf cells, Cd274 mRNA was increased by ARID1A knockout (**Figure 3A**). Consistently, PD-L1 expression measured by both immunoblot and fluorescence-activated cell sorting (FACS) analysis was upregulated upon ARID1A knockout (**Figure 3A**). Interferon-gamma (IFNg) plays a major role in inducing PD-L1 expression [4]. Thus, we examined the effects of ARID1A knockout on IFNg-induced PD-L1 expression. ARID1A knockout significantly enhanced the upregulation of Cd274 mRNA and PD-L1 expression induced by IFNg treatment (**Figure 3A**). Similar findings were made in both ARID1A wildtype mouse ID8-Defb29/Vegf cells and human OVCA429 and RMG1 cells with or without ARID1A knockout (**Figure 4**). We next examined the association of RNA polymerase II (Pol II) and lysine 4 trimethylated histone H3 (H3K4me3), a transcription active promoter epigenetic mark, with the Cd274 promoter. Consistent with changes observed in Cd274 mRNA and PD-L1 expression, ARID1A knockout enhanced the association of Pol II and H3K4me3 with the Cd274 promoter with or without IFNg stimulation (**Figure 3B**). Together, we conclude that ARID1A represses CD274 gene transcription at both the basal levels and in response to IFNg stimulation.

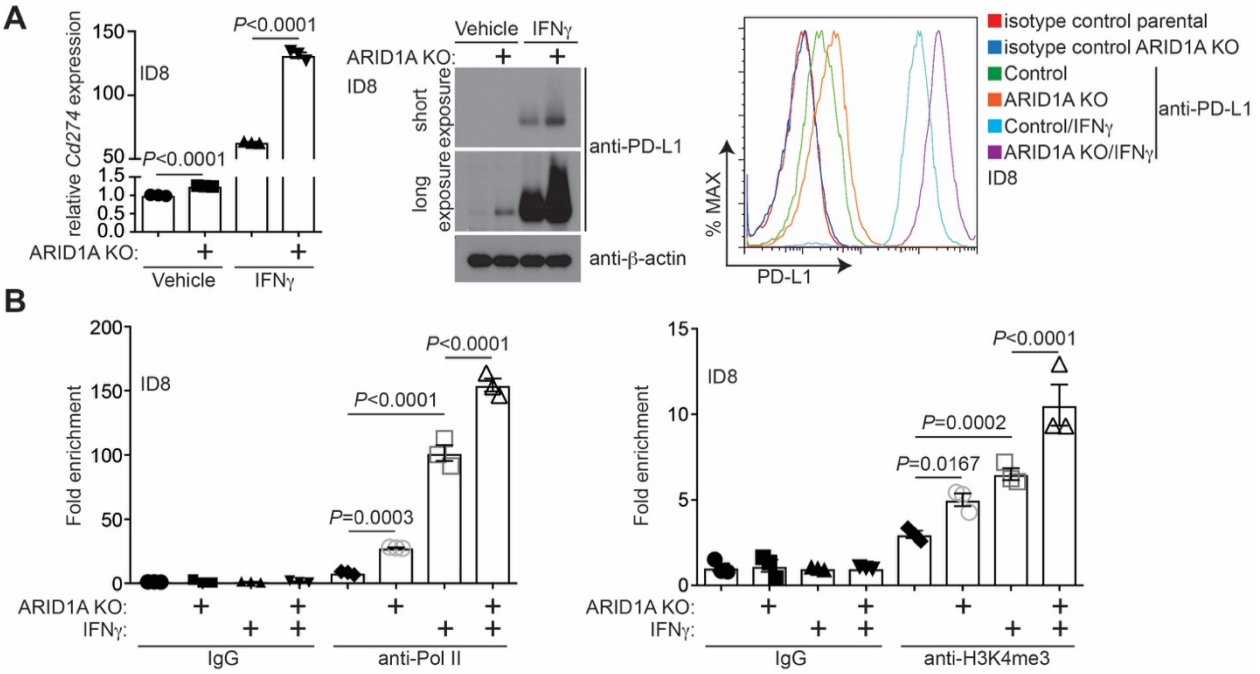

Figure 3. ARID1A transcriptionally represses Cd274 in mouse ovarian cancer cells. (**A**) Expression of Cd274 mRNA and PD-L1 protein in ARID1A wildtype control and ARID1A knockout mouse ovarian ID8-Defb29/Vegf cells treated with or without 20 ng/ml IFNγ determined by qRT-PCR (left) or immunoblot (middle). The cell surface expression of PD-L1 in these cells was determined by flow cytometry analysis (right). (**B**) The indicated ID8-Defb29/Vegf cells treated with or without 20 ng/ml IFNγ cells were subjected to ChIP analysis for the Cd274 gene promoter using the indicated antibodies or an isotype-matched IgG control. Error bars represent ± S.E.M. n= 3 independent experiments.

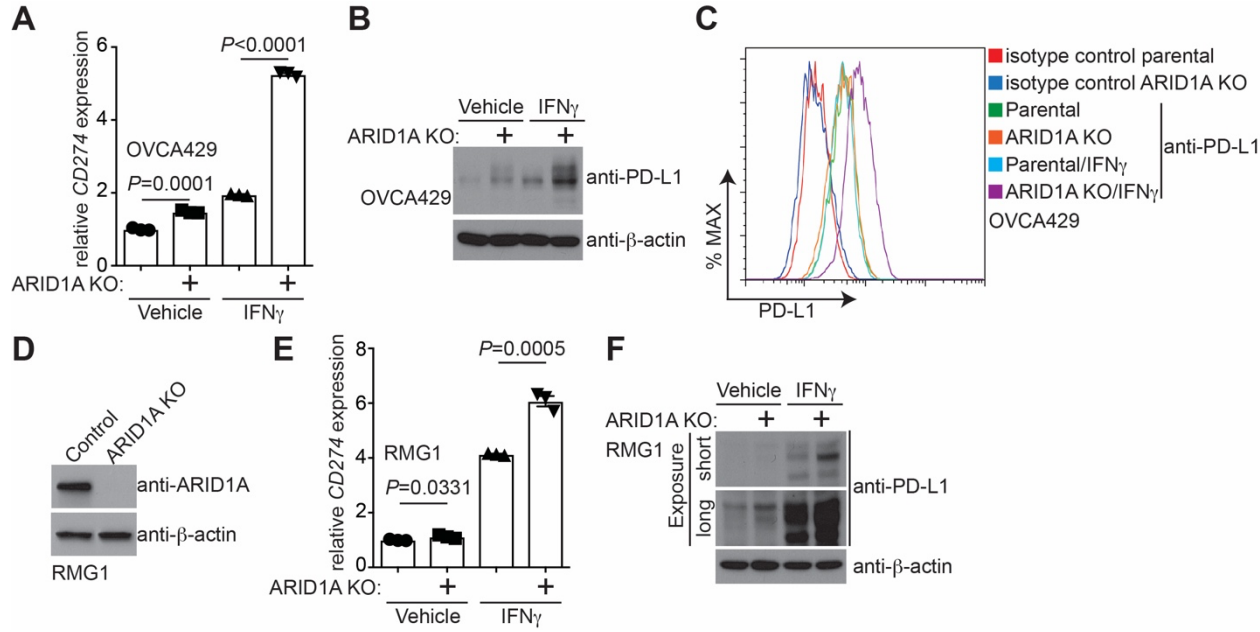

Figure 4. ARID1A represses CD274 transcription in human ovarian clear cell cancer cells.

(**A-B**) Expression of CD274 mRNA (A) and PD-L1 protein (B) in ARID1A wildtype control and ARID1A knockout OVCA429 OCCC cells treated with or without 20 ng/ml IFN determined by qRT-PCR or immunoblot, respectively. (**C**) The cell surface expression of PD-L1 in these cells was determined by flow cytometry analysis. (**E-G**) Validation of ARID1A knockout by immunoblot in RMG1 OCCC cells (E). Expression of CD274 mRNA (F) and PD-L1 protein (G) in ARID1A wildtype control and ARID1A knockout RMG1 OCCC cells treated with or without 20 ng/ml IFN determined by qRT-PCR or immunoblot, respectively. Error bars represent ± S.E.M. n= 3 independent experiments.

HDAC6 inhibitor boosts antitumor immunity.

Given HDAC6 inhibitors' role in immune modulation [5-7], we examined the effects of HDAC6 inhibitor ACY1215 in a conditional genetic ARID1A$^{flox/flox}$/PIK3CA^{H1047R} OCCC mouse model [8, 9] (**Figure 5A**). Notably, HDAC6 inhibitor ACY1215 significantly increased the CD69$^+$ activated CD4 and CD8 T cells in the peritoneal wash (**Figure 5B**). Consistently, IFNg$^+$ CD4 and CD8 T cells were also significantly increased by ACY1215 treatment (**Figure 5A**). In contrast, ACY1215 did not significantly affect Granzyme B$^+$ CD8 T cells or Foxp3$^+$ regulatory T cells (**Figure 5C-D**). These findings suggest that HDAC6 inhibition may boost antitumor immunity.

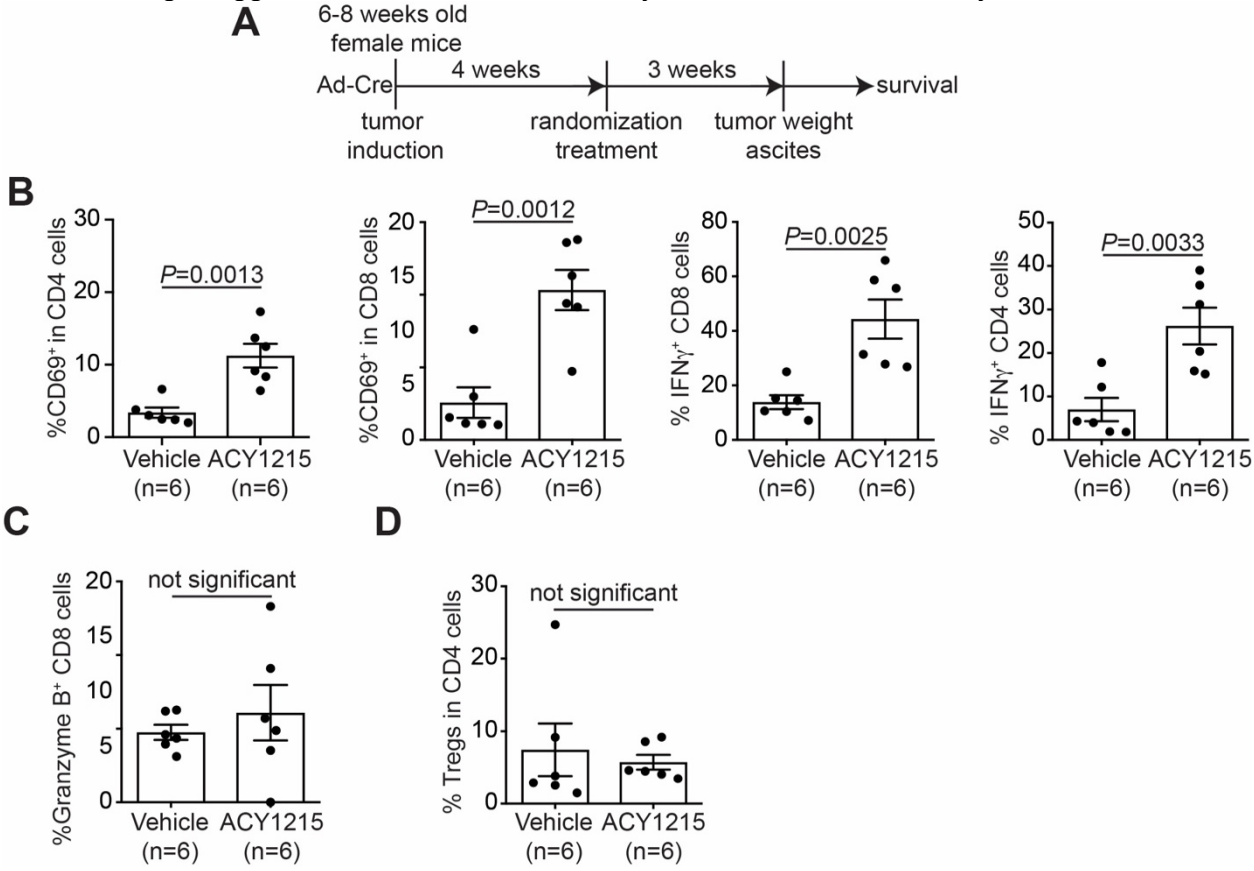

Figure 5. ACY1215 boosts antitumor immunity.
ARID1A$^{flox/flox}$/PIK3CA^{H1047R} OCCCs were induced by intrabursal adenovirus-encoded Cre injection and allowed to establish for four weeks (**A**). The mice were randomized to treat with vehicle control or ACY1215 (50 mg/kg daily by i.p.) for an additional three weeks. At the end of treatment, percentage of CD69 or IFN positive CD8 and CD4 T cells (**B**), Granzyme B$^+$ CD8 T cells (**C**), or Foxp3$^+$ regulatory CD4 T cells (**D**) was assessed by flow cytometry in the peritoneal wash.

Combination of HDAC6 inhibitor and anti-PD-L1 in the ARID1A$^{flox/flox}$/PIK3CA^{H1047R} OCCC mouse model.

Since ARID1A directly represses PD-L1 and HDAC6 inhibition increases T cell activation and activity, we sought to determine the effects of HDAC6 inhibitor ACY1215 and anti-PD-L1 combination in ARID1A-inactivated OCCCs. Toward this goal, we first established OCCCs in 6-8 week old ARID1A$^{flox/flox}$/PIK3CA^{H1047R} female mice by intrabursally injecting adenovirus-Cre [8]. Four weeks after the adenovirus-Cre injection, the mice were randomized into four treatment groups: 1) vehicle and IgG control; 2) ACY1215 (50 mg/kg daily by i.p.) and IgG control; 3) vehicle control and anti-PD-L1 antibody (10 mg/kg twice weekly by i.p.); and 4) ACY1215 and anti-PD-L1 antibody combination for an additional three weeks. At the end of treatment, orthotopic tumors were surgically removed (**Figure 6A**). The tumor weight was measured as a surrogate for tumor burden. As previously reported [8, 10], both anti-PD-L1 antibody and ACY1215 significantly reduced the tumor weight in the OCCC model (**Figure 6A**). We also examined effects of the ACY1215 and anti-PD-L1 combination in reducing ascites produced in the Arid1a$^{flox/flox}$/Pik3ca^{H1047R} OCCC model. Both ACY1215 and anti-PD-L1 single treatment significantly reduced the amount of ascites produced in this model (**Figure 6B**). The reduction in tumor weight and ascites production by ACY1215 or anti-PD-L1 single treatment correlated with an improvement of survival (**Figure 6C**). The HDAC6 inhibitor ACY1215 and anti-PD-L1 combination was synergistic in reducing the tumor burden and improving the survival of tumor-bearing mice (**Figure 6A and C**). Notably, the combination completely eliminated the ascites production (**Figure 6D**). The doses of ACY1215 and anti-PD-L1 used in this study did not significantly affect the body weight of treated mice (**Figure 6E**), suggesting that effective combination doses can be achieved without gross toxicity. Together, we conclude that HDAC6 inhibitor ACY1215 and anti-PD-L1 are synergistic in reducing tumor burden, which correlates with an improvement of survival of mice bearing ARID1A-inactivated OCCCs.

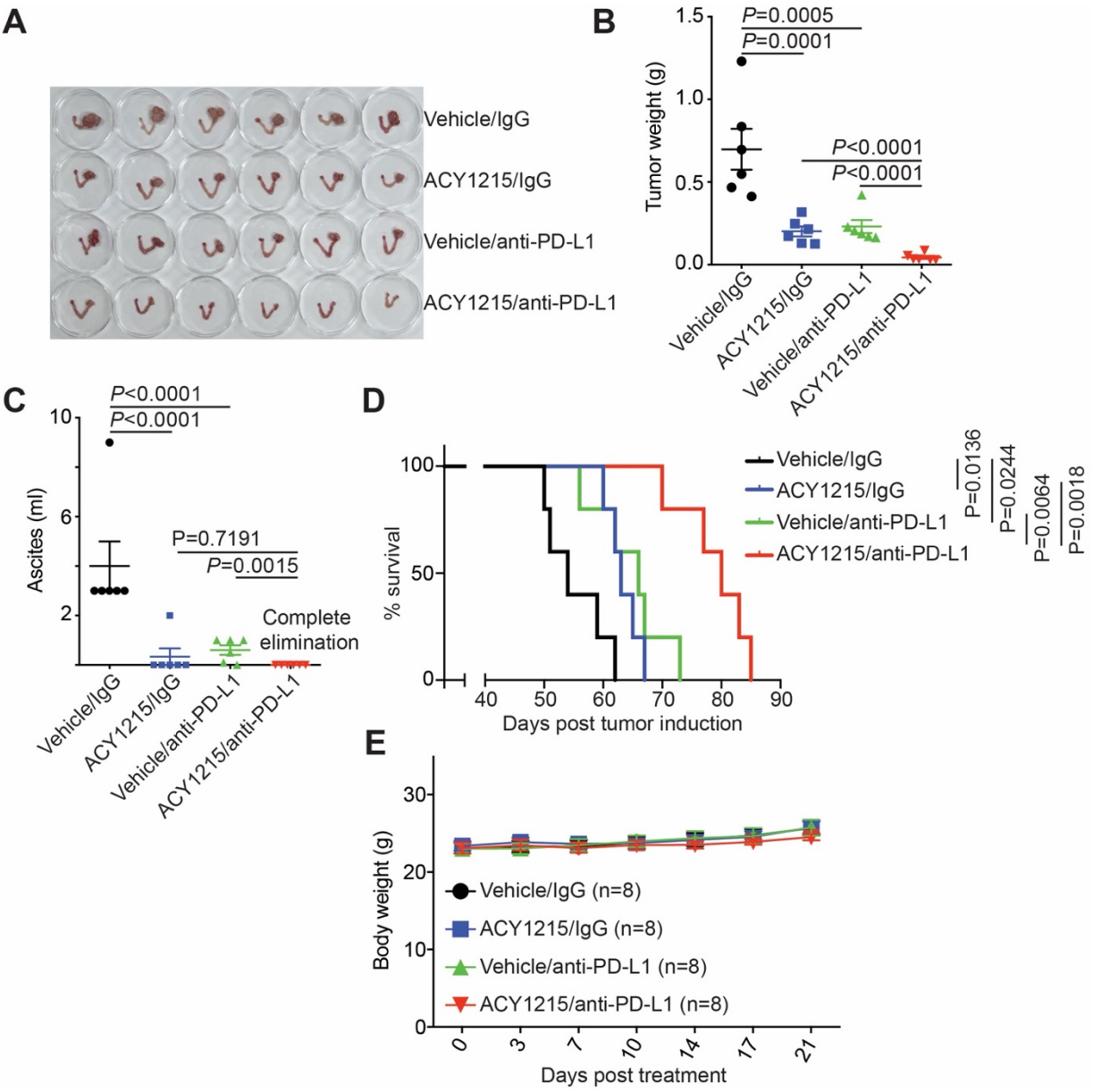

Figure 6. ACY1215 and anti-PD-L1 are synergistic in limiting tumor progression in vivo. (**A**) ARID1A$^{flox/flox}$/PIK3CA^{H1047R} OCCCs were induced by intrabursal adenovirus-encoded Cre injection and allowed to establish for four weeks. The mice were randomized into 4 indicated treatment groups and treated for an additional three weeks. At the end of treatment, 6 mice from each of the indicated groups were euthanized. Images of dissected reproductive tracks with tumors were shown. (**B**) The weights of the dissected tumors were quantified as a surrogate for tumor burden. (**C**) Same as (B), but quantified for the ascites produced. (**D**) After completing treatment, the mice were followed for survival and shown are the Kaplan–Meier survival curves for each of the indicated groups. (**E**) The body weight of mice in the indicated treatment groups during 3 weeks of treatment. Error bars represent ± S.E.M.

We next sought to determine the effects of combination on immune infiltration. Notably, HDAC6 inhibitor ACY1215 significantly increased the CD69^{+} activated CD4 and CD8 T cells in the peritoneal wash (**Figure 7A**). Consistently, IFN□$^{+}$ CD4 and CD8 T cells were also significantly

increased by ACY1215 treatment (**Figure 7B**). In contrast, ACY1215 did not significantly affect Granzyme B^{+} CD8 T cells or Foxp3^{+} regulatory T cells (**Figure 7C**). However, a combination of ACY1215 and anti-PD-L1 treatment only increased IFN□$^{+}$ CD8, but not CD4 T cells (**Figure 7B**). This suggests the implication of CD8 T cells in the combination treatment.

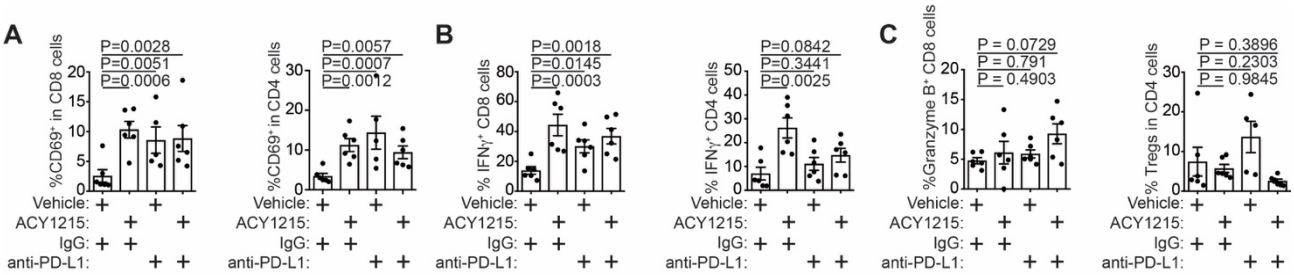

Figure 7. ACY1215 and anti-PD-L1 are synergistic in limiting tumor progression in vivo. (**A**) ARID1A$^{flox/flox}$/PIK3CA^{H1047R} OCCCs were induced by intrabursal adenovirus-encoded Cre injection and allowed to establish for four weeks. The mice were randomized into 4 indicated treatment groups and treated for an additional three weeks. At the end of treatment, percentage of CD69+ CD8 and CD4 T cells (**A**), IFN□ positive CD8 and CD4 T cells (**B**), and Granzyme B positive CD8 cells and intracellular FOXP3 positively stained regulatory CD4 T cells (Treg) (**C**) were assessed by flow cytometry in the peritoneal wash. Error bars represent ± S.E.M.

and/or 4) other achievements.
Nothing to report

What opportunities for training and professional development has the project provided?
Nothing to report

How were the results disseminated to communities of interest?
Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
We plan to do the following during the next reporting period to accomplish the goals:

1. To perform functional studies to characterize the identified changes in the immune modulating cells.
2. To perform loss of function studies to establish whether immune modulating cells contribute to the observed tumor suppressive effects in combination treatment.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report

What was the impact on other disciplines?
Nothing to report

What was the impact on technology transfer?
Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Nothing to report

Changes in approach and reasons for change
Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report

Changes that had a significant impact on expenditures
Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

Significant changes in use or care of human subjects
Nothing to report

Significant changes in use or care of vertebrate animals
Nothing to report

Significant changes in use of biohazards and/or select agents
Nothing to report

6. PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

1. Lin J, Guo D, Liu H, Zhou W, Wang C, Muller I, Kossenkov AK, Drapkin R, Bitler BG, Helin K, Zhang R. SETDB1-TRIM28 complex suppresses antitumor immunity. **Cancer Immunology Research**, under revision.
2. Hao X, Shiromoto Y, Sakurai M, Havas A, Wang L, Berger S, Adams PD, Nishikura K, Kossenkov AV, Liu P, **Zhang R**. ADAR1 downregulation contributes to $p16^{INK4a}$ upregulation independent of RNA editing during cellular senescence and tissue aging. **Nature Cell Biology**, under revision.
3. Zundell J, Fukumoto T, Lin J, Fatkhudinov N, Nacarelli T, Kossenkov AV, Liu Q, Cassel J, Hu CC, Wu S, **Zhang R**. Targeting the IRE1a/XBP1 endoplasmic reticulum stress response pathway in ARID1A-mutant ovarian cancers. **Cancer Research**, in press.
4. Lin J, Fukumoto T, Zundell J, Liu H, Yan Q, Tang CHA, Wu S, Zhou W, Karakashev S, Hu CCA, Sarma K, Kossenkov AV, **Zhang R** (2021). CARM1 determines endoplasmic reticulum stress response by controlling XBP1. **Nature Communications**, 12 (1): 5321. PMCID: PMC8423755.

5. Liu P, Li F, Lin J, Fukumoto T, Nacarelli T, Hao X, Kossenkov AV, Simon MC, **Zhang R** (2021). m^6A independent genome-wide METTL3 and METTL14 redistribution drives senescence-associated secretory phenotype**. Nature Cell Biology**, 23(4): 355-365. PMCID: PMC8035315.
6. Wu S, Fukumoto T, Lin J, Nacarelli T, Wang Y, Ong D, Liu H, Fatkhutdinov N, Zundell JA, Karakashev S, Zhou W, Schwartz LE, Tang HY, Drapkin R, Liu Q, Huntsman DG, Kossenkov AV, Speicher DW, Schug ZT, Dang CV, **Zhang R** (2021). Therapeuitc targeting glutamine dependence in SWI/SNF-inactivated cancers. **Nature Cancer**, 2: 189-200. PMCID: PMC8168620.
7. Kim H, Xu H, George E, Hallberg D, Kumar S, Jagannathan V, Medvedev S, Kinose Y, Devins K, Verma P, Ly K, Wang Y, Greenberg RA, Schwartz L, Johnson N, Scharpf RB, Mills GB, Zhang R, Velculescu VE, Brown EJ, Simpkins F (2020) Combining PARP and ATR inhibition overcomens PARP inhibitor and platinum resistance in ovarian cancer models. **Nature Communications**, 11: 3726. PMCID: PMC7381609.
8. Hashimoto A, Fukumoto T, **Zhang R**, Gabrilovich D (2020) Selective targeting of different populations of myeloid-derived suppressor cells by histone deacetylase inhibitors. **Cancer Immunology and Immunotherapy**, in press.
9. Karakashev S, Fukumoto T, Zhao B, Lin J, Wu S, Fatkhutdinov N, Park PW, Semenova G, Jean S, Gadungog MG, Borowsky ME, Kossenkov AV, Liu Q, **Zhang R** (2020) EZH2 inhibition sensitizes CARM1-high, homologous recombination proficient ovarian cancers to PARP inhibition. **Cancer Cell** 37: 157-167. PMCID: PMC7155421.
10. Zhao B, Liu P, Fukumoto T, Nacarelli T, Fatkhutdinov N, Wu S, Lin J, Aird KM, Tang SY, Liu Q, Speicher DW, **Zhang R** (2020) Topoisomerase 1 cleavage complex enables pattern recongnition and inflammation during senescence. **Nature Communications**, 11: 908. PMCID: PMC7031389.
11. Nacarelli T, Fukumoto T, Zundell JA, Fatkhutdinov N, Jean S, Cadungog MG, Borowsky ME, **Zhang R** (2020) NAMPT inhibition suppresses cancer stem-like cells associated with therapy-induced senescence in ovarian cancer. **Cancer Research** 80: 890-900. PMCID: PMC7024650.
12. Wu S, Fatkhutdinov N, Rosin L, Luppino JM, Iwasaki O, Tanizawa H, Tang HY, Kossenkov AV, Gardini A, Noma KI, Speicher DW, Joyce EF, **Zhang R** (2019) ARID1A spatially partitions interphase chromosomes. **Science Advances** 5: eaaw5294. PMCID: PMC6531001.
13. Fukumoto T, Fatkhutdinov N, Zundell JA, Tcyganov EN, Nacarelli T, Karakashev S, Wu S, Liu Q, Gabrilovich DI, **Zhang R** (2019) HDAC6 inhibition synergizes with anti-PD-L1 therapy in ARID1A-inactivated ovarian cancer. **Cancer Research** 21: 5482-5489. PMCID: PMC6825538.
14. Zhao B, Lin J, Rong L, Wu S, Deng Z, Fatkhutdinov N, Zundell J, Fukumoto T, Liu Q, Kossenkov A, Jean S, Cadungog MG, Borowsky ME, Drapkin R, Lieberman PM, Abate-Shen CT, **Zhang R** (2019) ARID1A promotes genomic stability through protecting telomere cohesion. **Nature Communications** 10: 4067. PMCID: PMC6731242.

Books or other non-periodical, one-time publications.
Nothing to report

Other publications, conference papers and presentations.
Nothing to report

Website(s) or other Internet site(s)
Nothing to report

Technologies or techniques
Nothing to report

Inventions, patent applications, and/or licenses
Nothing to report

Other Products
Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Rugang Zhang
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1 cm
Contribution to Project:	Supervised the study.
Funding Support:	This award

Name:	Dajiang Guo
Project Role:	Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	6 cm
Contribution to Project:	Performed the study.
Funding Support:	This award

Name:	Heng Liu
Project Role:	Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	7 cm
Contribution to Project:	Performed the study.
Funding Support:	This award

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following changes have occurred in other support since the last reporting period:

Dr. Rugang Zhang:

Termination of “Integration of Advanced Genomic & Bioengineering Approaches for Early Detection and Protection of Ovarian Cancer”
Activation of “Metabolic approaches for ARID1A-mutated ovarian cancer”

Dr. Qin Liu:

Termination of “Targeting Neuroblastoma with Armed T Cells”

Termination of “Extracellular DNA in regulation of multiple myeloma”
Termination of “Novel Molecular Therapies of Prostate Cancer”
Termination of “Host Glycomic Determinants of HIV Persistence in vivo”
Termination of “Development of Novel Small-Molecule Rb protein modulator for Ovarian Cancer Immunotherapy”
Termination of “Development and pre-clinical testing of a prophylactic SARS-CoV-2 vaccine”
Activation of “Integration of Biomarker Signatures from Peripheral Blood for Diagnosis, Prognosis, Remission and Recurrence of Lung Cancer – Administrative Supplement”
Activation of “Molecular Mechanism of UV Protection in Cutaneous Melanoma”
Activation of “Metabolic approaches for ARIDIA-mutated ovarian cancer”
Activation of “Define Novel Host Biomarkers and Mechanisms of Post-treatment Control of HIV”
Activation of “BEAT-HIV: Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy”
Activation of “Role of Intestinal Barrier Integrity and Antibody Glycosylation in Long-COVID During HIV-infection”

What other organizations were involved as partners?
Nothing to report

8. SPECIAL REPORTING REQUIREMENTS
Nothing to report

9. APPENDICES:
Nothing to report

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