AWARD NUMBER: W81XWH-20-1-0190

TITLE: Multimodal Treatment Consisting of Ferroptotic Agent and Chimeric TRAIL as a Second-Line Therapy for Ovarian Peritoneal Carcinomatosis

PRINCIPAL INVESTIGATOR: M. Haroon A. Choudry

CONTRACTING ORGANIZATION: University of Pittsburgh, Pittsburgh, PA

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Fort Detrick, Maryland 21702-5012

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Multimodal Treatment Consisting of Ferroptotic Agent and Chimeric TRAIL as a Second-Line Therapy for Ovarian Peritoneal Carcinomatosis

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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14. ABSTRACT

Ovarian cancer is the most common cause of death among all gynecological neoplasms. Ovarian peritoneal carcinomatosis (OPC) is a frequent terminal evolution of ovarian cancer and is regarded as a lethal condition. In the past, OPC was considered a terminal disease stage, but over the past two decades, the therapeutic techniques of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC) have been developed. However, although CRS treated with HIPEC has been associated with an increased response rate, complete responses have been rare and recurrences are common. In this grant application, we are developing a multimodal treatment consisting of the FDA-approved ferroptotic agent artesunate and TRAIL as a second-line therapy. Currently, we are establishing tumoroids of OPC and investigate the mechanism of the synergistic induction of apoptosis caused by the integration of signal transduction pathways in organoids of OPC. Although ferroptosis is considered a distinctive form of cell death compared to other types of death such as apoptosis and it is known to result from iron-dependent accumulation of lipid peroxides rather than caspase activation, our studies have shown that ferroptosis interplays with apoptosis. In this grant period,

15. SUBJECT TERMS
Ferroptosis, apoptosis, crosstalk between death signals, synergistic interaction

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
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TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

In this grant application, we propose developing a humanized patient-derived xenograft (PDX) mouse model and tumoroids to assess the preclinical efficacy of chimeric TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)-based ferroptotic agent artesunate therapy to be used in addition to conventional hyperthermic intraperitoneal chemotherapy to treat OPC patients after cytoreductive surgery.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Ferroptosis artesunate Apoptosis chimeric TRAIL Synergistic interaction integration death signals humanized patient derived xenograft (PDX) mouse model tumoroids

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The specific aims of this project are to: (1) investigate the mechanism of the synergistic induction of cytotoxicity caused by the interplay between apoptosis and ferroptosis during the combined treatment, and (2) examine genetic signatures of tumor tissues from ovarian peritoneal carcinomatosis (OPC) patients and examine the preclinical efficacy of the multimodal approach (Fc-TRAIL + ferroptotic agent) in a humanized patient-derived xenograft (PDX) mouse model of OPC.

Major Task 1: Identify mutation status and transcriptional signatures of genes (3-18 months)
Subtask 1: Determine the status of biomarkers in OPC tumor tissues

Major Task 2: Establish PDX tumors and determine the growth and regression of PDX tumors during multimodal treatment (3-20 months) Subtask 1: Establish PDX tumors with humanized mice
Subtask 2: Examine preclinical efficacy of combinatorial treatment on PDX tumors Subtask 3: Statistical analysis of data

Major Task 3: Investigate mechanism of synergistic interaction between ferroptosis and apoptosis (3-24 month)—100% completion in June 2023.
Subtask 1 Establish OPC tumoroid cultures
Subtask 2: Examine cytotoxicity of combinatorial treatment in tumoroid cultures
Subtask 3: Investigate interaction between ferroptosis and apoptosis in tumoroid cultures

What was accomplished under these goals? *For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings,*

Establishment of tumoroids: Tumor tissues from patients were used to establish 3-dimensional tumoroid culture. Tumor tissue fragments were washed and incubated in chelating solution supplemented with EDTA. After incubation, tissues were washed with basal culture medium and resuspended in Basement Membrane Matrix. The Basement Membrane Matrix was overlaid with Human Stem Cell medium.

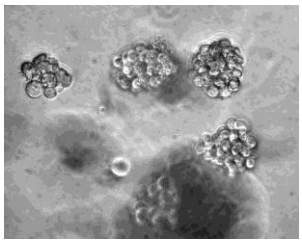

Figure 1. *Ex vivo* primary tumoroid cultures

Cytotoxicity: Tumoroids were treated with TRAIL and cytotoxicity was determined using PI staining assay as shown below. TRAIL induced cytotoxicity which was detected by DNA fragmentation**.**

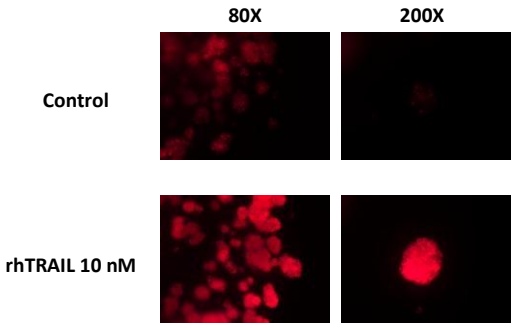

Figure 2. Cytotoxic effect of TRAIL on tumoroids. Tumoroids were grown for 14 days in Matrigel and then treated with 10 nM rhTRAIL for 24 h. The tumoroids were stained with propidium iodide (PI) and fluorescent images were detected.

Interaction between artesunate and TRAIL: We previously showed that the combinatorial treatment of ferroptotic agent sorafenib (SRF)/artesunate (ART) and apoptotic agent TRAIL markedly enhances TRAIL-induced apoptosis (**Fig. 3**), but not ferroptosis (data not shown). These synergistic effects were due to increased activation (cleavage) of caspases, which resulted in increased PARP cleavage, the hallmark feature of apoptosis.

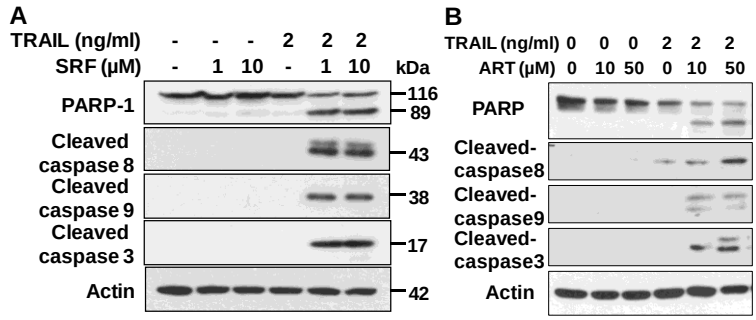

Figure 3. Effect of SRF/ART on TRAIL-induced apoptosis. Human colorectal carcinoma HCT116 cells (**A**) and human ovarian adenocarcinoma OVCAR3 cells (**B**) were pretreated with SRF/ART for 20 h and treated with TRAIL for 4 h in the presence of SRF and ART, respectively. The cleavage of caspase-8, caspase-9, caspase-3, and PARP was detected using immunoblotting. Actin was used as a protein loading control in each lane.

To examine the role of Bid in the combinatorial treatment of ferroptotic agent erastin (ERA) and artesunate (ART), and TRAIL-induced synergistic apoptosis was assessed using Bid knockdown OVCAR-3 cells. OVCAR-3 cells transfected with either negative control siRNA or Bid siRNA were treated with ERA and TRAIL. The amount of Bid protein was reduced by 40% in siRNA-transfected cells and synergistic apoptosis was also reduced in siRNA-transfected cells (**Figure 4b**). These

results demonstrated that Bid plays an important role in the synergistic apoptosis of OVCAR-3 cells during treatment with ERA and TRAIL.

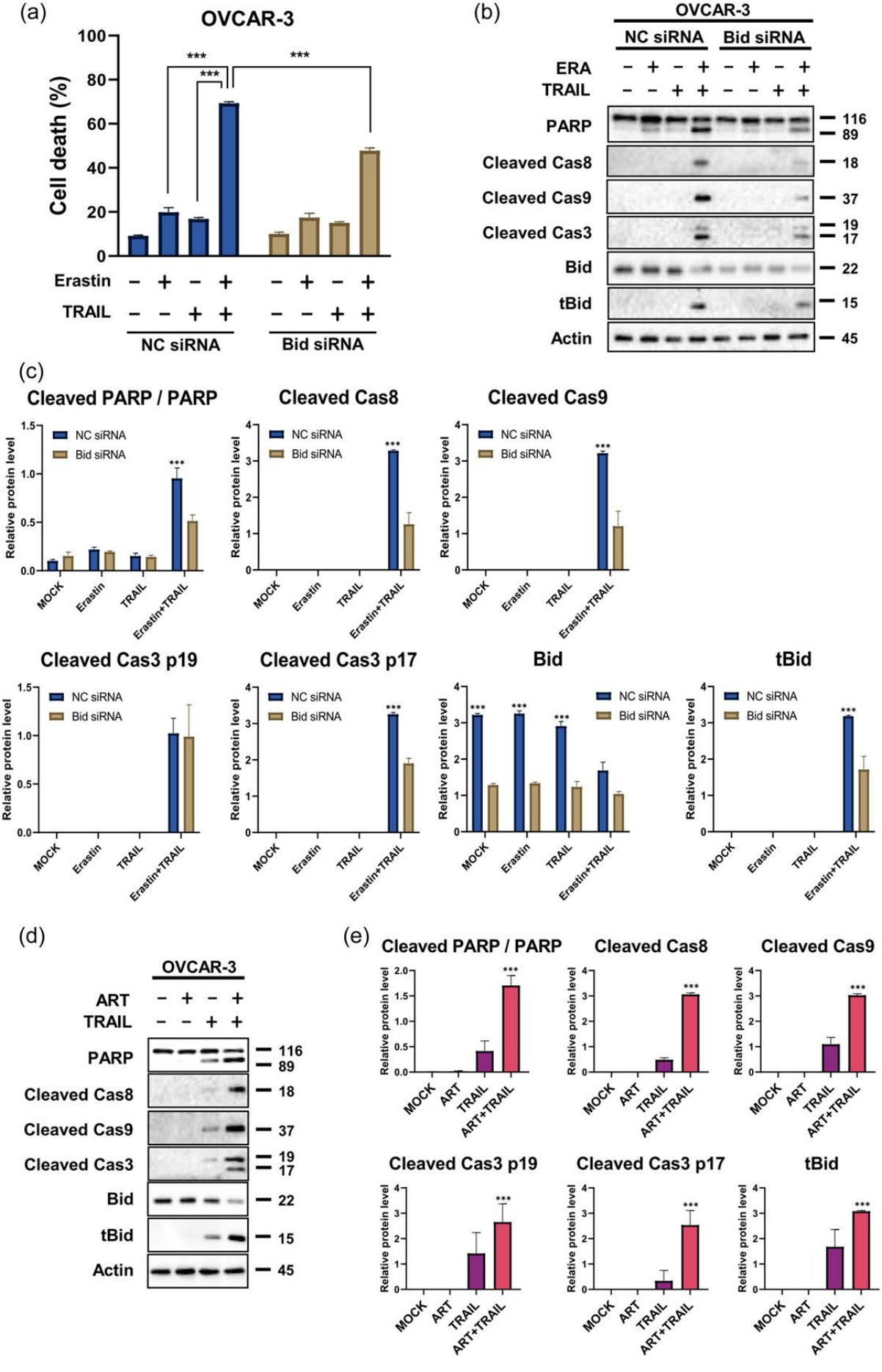

Figure 4. Role of Bid (BH3-interacting domain death agonist) in the synergistic interaction between ERA/ART and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in OVCAR-3 cells. Human ovarian adenocarcinoma OVCAR-3 cells were transfected with negative control small interfering RNA (siRNA) and Bid siRNA for 24 h. The transfected cells were pretreated with ERA (50 μM) for 20 h and then exposed to human recombinant TRAIL (50 ng/ml) for an additional 4 h. (a) Cell death was determined using a trypan blue exclusion assay. Error bars represent the mean± SD from triplicate experiments. For statistical analysis, two-way analysis of variance (ANOVA), followed by Tukey's post hoc test was used. ***$p < 0.001$. (b) Whole-cell extracts were analyzed with the immunoblotting assay using indicated antibodies. (c) Densitometry analysis of the bands from the western blot was performed. Error bars represent the mean ± SD from triplicate experiments. For statistical analysis, two-way ANOVA, followed by Tukey's post hoc test was used. ***$p < 0.001$ versus the Bid siRNA group. OVCAR-3 wild-type cells were pretreated with ART (50 μM) for 20 h and then exposed to human recombinant TRAIL (50 ng/ml) for an additional 4 h. (d) Whole-cell extracts were analyzed with an immunoblotting assay using indicated antibodies. (e) Densitometry analysis of the bands from the western blot was performed. Error bars represent the mean ± SD from triplicate experiments. For statistical analysis, one-way ANOVA was used. ***$p < 0.001$ versus the MOCK group. PARP, poly (ADP-ribose) polymerase; tBid, truncated Bid.

We further extended our studies the role of tBid in the synergistic interaction between ferroptotic agent and TRAIL. Previous studies showed that cleavage of Bid is a prerequisite to link death receptor-mediated intrinsic apoptosis. Unlike wild-type (WT) and Bid/Bid knockout (KO) cells, Bid G94E/Bid KO cells did not show apoptosis, as assessed by PARP cleavage (**Fig. 5**).

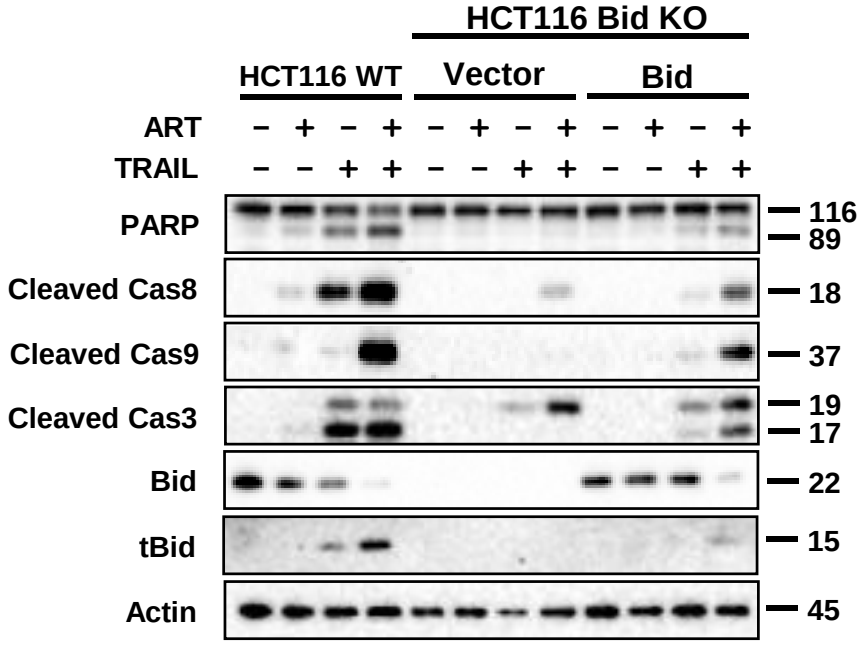

Figure 5. Role of Bid in the synergistic interaction between ART and TRAIL. HCT116 wild-type (WT) or Bid knockout (KO) cells stably expressing control vector and Bid were pretreated with artesunate (ART) (50 μM) for 20 h and then exposed to human recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (2 ng/ml) for an additional 4 h. Cell lysates were analyzed with an immunoblotting assay using indicated antibodies.

Cleaved caspase-9 signaling mediated by mitochondria-dependent apoptosis was also blocked in Bid G94E/Bid KO cells (**Fig. 6**). Data from the immunoblotting assay for mitochondria isolation show that tBid was produced in HCT116 WT, Bid/Bid KO, and Bid G94E/Bid KO cells and moved into mitochondria during the combinatorial treatment (**Figure 6**). These results suggest that truncation of Bid leads to translocation of tBid into the mitochondrial outer membrane. However, it is not enough to form MOMP and induce the mitochondria-dependent apoptosis pathway without the functional BH3 domain of Bid in Bid G94E/Bid KO cells.

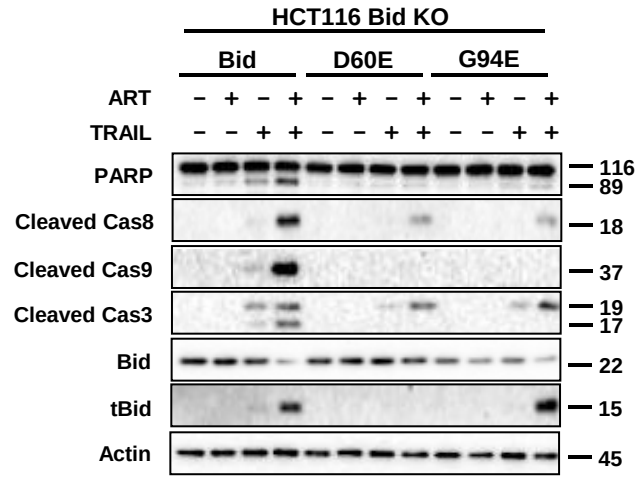

Figure 6. Employment of Bid (BH3-interacting domain death agonist) mutants for investigating the role of Bid in the synergistic apoptosis. HCT116 Bid knockout (KO) cells stably expressing Bid, Bid D60E, or Bid G94E were pretreated with ART (50 μM) for 20 h and then exposed to TRAIL (2 ng/ml) for an additional 4 h. Cell lysates were analyzed with an immunoblotting assay using indicated antibodies.

Our previous studies demonstrated that ferroptosis-inducing agents lead to activation of the endoplasmic reticulum stress (ER) response and the PERK-eIF2α-ATF4-CHOP signaling pathway, which results in the upregulation of PUMA and DR5. To examine the hierarchical profiles of ER stress response signaling pathways and cell death networks, we employed HCT116 WT and HCT116 Bid KO cells and then investigated the level of CHOP and DR5 expression during the combinatorial treatment. The level of CHOP was upregulated during treatment with ART alone or combined ART and TRAIL, but not TRAIL alone. The upregulation of CHOP occurred regardless of Bid status (deficient or mutant) or in the presence of a caspase-8 inhibitor. These results suggest that since caspase-8 activation and Bid cleavage are downstream of DR5, an inhibitor of caspase-8 cannot block the ART-induced elevation of DR5 level. However, it can block ART-promoted TRAIL-induced apoptosis through inhibition of caspase-8 activity and Bid cleavage. To examine the role of CHOP in the cleavage of Bid during combined treatment of ART and TRAIL, we employed MEF WT and MEF CHOP KO cells. When these cells were treated with ART and TRAIL, Bid cleavage was observed in MEF WT cells, but not in MEF CHOP KO cells (**Figure 7**). These data suggest that CHOP plays an important role in the promotion of Bid truncation.

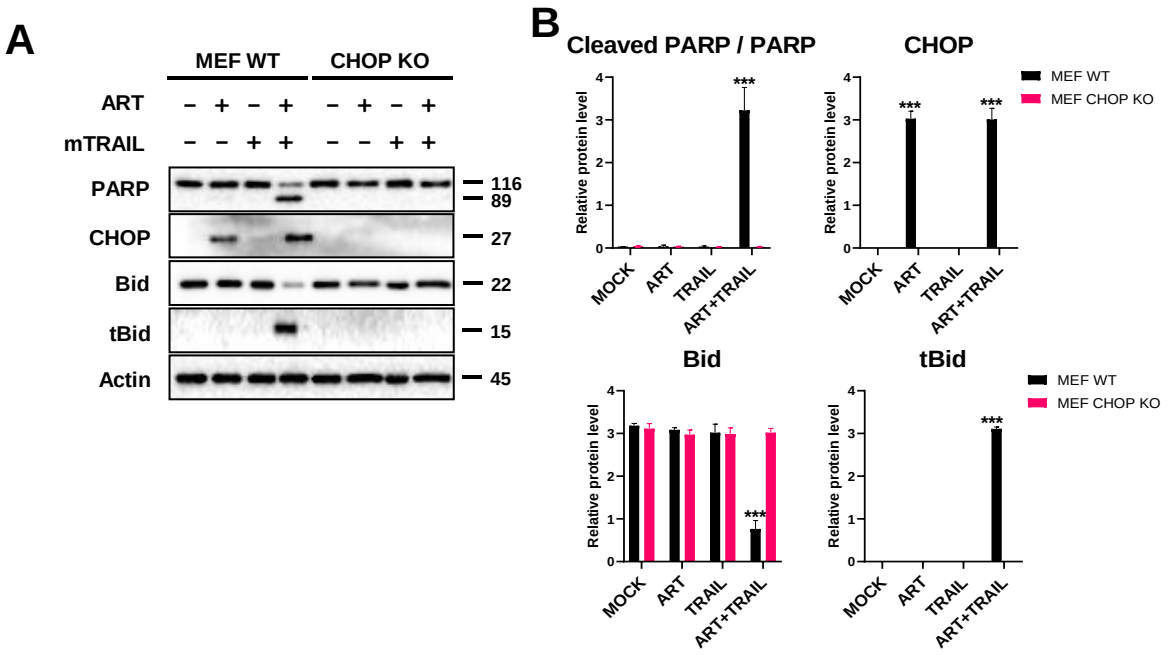

Figure 7. Truncation of Bid (BH3-interacting domain death agonist) in CHOP (CCAAT-enhancer-binding protein homologous protein)-deficient cells. mouse embryonic fibroblast (MEF) wild-type (WT) and CHOP knockout (KO) cells were pretreated with artesunate (ART) (50 μM) for 20 h and then exposed to mouse recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (100 ng/ml) for an additional 4 h. (A) Whole-cell extracts were analyzed with an immunoblotting assay using indicated antibodies. (B) Densitometry analysis of the bands from the western blot was performed. Error bars represent the mean ± SD from triplicate experiments. For statistical analysis, two-way analysis of variance, followed by Tukey's post hoc test was used. ***$p < 0.001$ versus the CHOP KO group. PARP, poly (ADP-ribose) polymerase; tBid, truncated Bid.

In conclusion:

Our results indicate that Bid plays a critical role in the crosstalk between the ferroptotic agent-induced ER stress response and TRAIL-induced apoptosis.

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

N/A

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

***4.* IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project? *If there is nothing significant to report during this reporting period, state "Nothing to Report."*

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report.

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

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: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

1. Dilly AK, Honick BD, **Lee YJ**, Bartlett DL, Choudry HA. Rational application of targeted therapeutics in mucinous colon/appendix cancers with positive predictive factors. Cancer Med. 9:1753-1767, 2020. PMID 31958897

2. Lee YS, Kalimuthu K, Park YS, Makala H, Watkins SC, Choudry MHA, Bartlett, DL, Kwon YT, and **Lee YJ**. Ferroptotic Agent-induced Endoplasmic Reticulum Stress Response Plays a Pivotal Role in the Autophagic Process Outcome. J Cell Physiol, 2020;10.1002/jcp.29571 PMID 31985039

3. Lee YS, Kalimuthu K, Park YS, Choudry MHA, Bartlett, DL, and **Lee YJ**. BAXdependent mitochondrial pathway mediates the crosstalk between ferroptosis and apoptosis. Apoptosis, 2020; doi: 10.1007/s10495-020-01627-z. PMID: 32737652

4. Dilly AK, Honick BD, **Lee YJ**, Bartlett DL, Choudry HA. Synergistic apoptosis following endoplasmic reticulum stress aggravation in mucinous colon cancer. Orphanet J Rare Dis. 15:211, 2020. PMID: 32811515

5. **Lee YJ**. The interplay between apoptosis and ferroptosis mediated by ER stress. Apoptosis, 25:783, 2020. PMID: 33140179

6. Dilly AK, Honick B, Frederick R, Elapavaluru A, Velankar S, Makala H, Hitchens K, Foley L, Guo J, Beumer J, Rigatti L, **Lee Y**, Bartlett D, Choudry HA. Improved chemosensitivity following mucolytic therapy in patient-derived models of mucinous appendix cancer. Translational Research, 229:100-114, 2021. PMID: 33164812

7. Kalimuthu K, Kim JH, Park YS, Luo X, Zhang L, Ku JL, Choudry HA, **Lee YJ.** Glucose deprivation-induced endoplasmic reticulum stress response plays a pivotal role in enhancement of TRAIL cytotoxicity. J Cell Physiol., 236:6666-6677. doi: 10.1002/jcp.30329, 2021. PMID: 33586156

8. Xi Y, Li Y, Xu P, Liu Z, Sihan Li, Tung H, Cai X, Wang J, Xu M, Ren S, Zhang M, **Lee YJ**, Huang L, Yang D, He J, Huang Z, Xie W. The anti-fibrotic drug pirfenidone inhibits liver fibrosis by targeting the small oxidoreductase glutaredoxin-1. Science Advances, 7(36):eabg9241. doi: 10.1126/sciadv.abg9241, 2021. PMID: 34516906

9. Kalimuthu K, Keerthana CK, Mohan M, Arivalagan J, Christyraj JRSS, Firer MA, M. Choudry HA, Anto RJ, **Lee YJ**. Emerging Role of Selenium in the Metabolic Pathways: New Therapeutic Targets for Cancer. J Cell Biochem., 123:532-542, 2022. PMID: 34935169.

10. Kim JH, Li J, Luo X, Choudry MHA, **Lee YJ**. Involvement of Bid in the crosstalk between ferroptotic agent-induced ER stress and TRAIL-induced apoptosis. J Cell. Physiol., 237:4180-4196, 2022. PMID: 35994698

11. Liu W, Chen H, Zhu Z, Liu Z, Ma C, **Lee YJ**, Bartlett DL, Gu ZS. Ferroptosis inducer improves the efficacy of oncolytic virus-mediated cancer immunotherapy. Biomedicines, 10:1425, 2022. PMID: 35740445

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention,

diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions; • new business creation; and*
- *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Yong J. Lee—PI: 2020-2022
Name: Haroon Choudry—PI: 2022-2023
Name: Reetesh Pai—No change
Name: Yongli Shuai—No change

Name: Theresa Whiteside—No change Kalishwaralal Kalimuthu---postdoc fellow was terminated
Jin Hong Kim— postdoc fellow was terminated
Xiangwei Wu—No change

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

PI: Choudry

Active:

National Institutes of Health NIH R21CA263468 (PI: Choudry) 8/01/21-7/31/23 0.6 Calendar Months

NIH/NCI

Title: Application of mucus modulating multipurpose bromelain nanoparticles to overcome the mucus barrier in appendiceal pseudomyxoma peritonei

The major goal is to employ bromelain nanoparticles to treat pseudomyxoma peritonei.

Role: PI

National Institutes of Health NIH R21CA273630 (PI: Choudry) 9/01/22-8/31/24 0.6 Calendar Months

NIH/NCI

Title: Application of mucus modulating multipurpose trypsin nanoparticles to overcome the mucus barrier nd deliver mitochondria-targeted anticancer drugs in mucinous carcinoma peritoneeibromelain nanoparticles to overcome the mucus barrier in appendiceal pseudomyxoma peritonei

The major goal is to employ trypsin nanoparticles to treat pseudomyxoma peritonei.

Role: PI

PI: Lee
Active:

National Institutes of Health R21CA259243 (PI: Lee) 12/01/21-11/30/23 0.6 Calendar Months
NIH/NCI
Title: Application of in vivo humanized PDX mouse model and ex vivo organoid model to assess the therapeutic efficacy of combinatorial therapy for pseudomyxoma peritonei
The major goal is to develop a combinatorial therapy to treat pseudomyxoma peritonei.
Role: Principal Investigator

RA210084 (PI: Lee) 08/01/2022-07/31/2023 0.6 Calendar Months
DOD W81XWH-21-RCRP-CA
Title: Assessing the preclinical efficacy of combined ferroptotic agent and secretory TRAIL-armed NK cells for pseudomyxoma peritonei
Role: Principal Investigator

R01 CA265827A1 (PI: Lee) 7/01/2023 - 6/30/2028 2.4 Calendar Months
NIH/NCI
Title: Assessment of hyperthermia-based multimodal approach for hepatic colorectal metastases
Role: Principal Investigator

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)
- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*

- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

A collaborator—Dr. Xu Luo, an Associate Professor at University of Nebraska, join as a collaborator.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*