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TITLE:	Endoplasmin: A Novel Therapeutic Target and Potential Marker of Chemoresistance
PRINCIPAL INVESTIGATOR:	Selvendiran Karuppaiyah, PhD
CONTRACTING ORGANIZATION:	The Ohio State University
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our proposed study is to identify endoplasmin protein expression as a predictive marker associated with OC chemoresistance and identification of these pathways as potential therapeutic targets. Utilizing an endoplasmin small molecule inhibitor we plan to assess chemotherapy treatment using in vitro and in vivo studies with mice models. Our proposed research has the potential to identify novel the mechanisms of endoplasmin-mediated chemoresistance and targeting ENPL might serve to revert tumors to a chemosensitive state on a cellular level, therefore, improving treatment effect and prognosis/overall survival.

15. SUBJECT TERMS

Cancer Biology, Target Therapy and Biomarkers

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1. INTRODUCTION

Mortality rates from ovarian cancer (OC) are the highest among all gynecologic cancers and current therapies to treat the disease have failed to improve survival rates. Thus, there is a *critical need* to identify novel targets for alternative therapies for OC to improve outcomes. To effectively treat OC, it is important to: (i) Identify predictive markers associated with chemoresistance and (ii) elucidate the pathways involved in intrinsic chemoresistance to identify novel therapeutic targets. With these targets objectives in mind, we propose to identify the association of endoplasmin (ENPL) with platinum-resistant OC. ENPL is a member of a family of adenosine triphosphate (ATP)-metabolizing molecular chaperones that have roles in stabilizing and folding other proteins localized to melanosomes and the endoplasmic reticulum (ER). While ENPL expression has been demonstrated to play a critical role in immune modulation, cancer, and chemoresistance, the exact molecular pathways by which it acts remain unknown. Our current preliminary study demonstrated that ENPL expression in the membrane fraction is highly elevated in platinum resistant OC cell lines and patient samples. The hypothesize of our proposed study is that overexpression of endoplasmin contributes to chemo-resistance and that targeting endoplasmin using novel small molecule compounds will facilitate more successful treatment of the disease. To test this hypotheses, the following specific aims are proposed:

Specific Aim 1: To identify the role of ENPL expression in chemosresistance and progression OC. Our *working hypothesis is that* OC cells expressing ENPL expel carboplatin through exosome secretion and that OC cells with high levels of ENPL will be resistant to platinum treatment.

Specific Aim 2: To evaluate the effects of inhibiting ENPL on the efficacy of carboplatin treatment using *in vitro and in vivo* mouse models. Our *working hypothesis* is that inhibiting ENPL by small molecule inhibitors (DAP-1 or DAP-2) will significantly increase the efficacy of carboplatin (CP).

2. KEY WORDS

Ovarian Cancer

Platinum resistance

Endoplasmin

Exosomes

Small molecule inhibitor (DAP-1)

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goal of this study is to evaluate a novel protein, Endoplasmin, as a potential therapeutic target in chemoresistant ovarian cancer

What was accomplished under these goals?

We have identified the significance of key findings in SA1

(i) ENPL plays a key role in chemo-resistant;
(ii) Developed a MFD chip for exosome isolation in cancer cells;
(iii) Exosomes are highly elevated in platinum resistant OC cells;
(iv) Identified the ENPL expression is highly elevated in chemoresistant OC

Specific Aim 1: To identify the role of endoplasmin (ENPL) expression in chemosresistance and progression OC.
1a) Prepare forms for approval of Animals use and protocols involved.
Milestone # 1 Animal use approval (Year 1: month1-2): **Completed 100%.**

1b) Prepare IRB forms for approval of human sample use and protocols involved.

Milestone # 1 human sample use approval (Year 1: month1-3): **Completed 100%**

Approach 1. To determine the role of ENPL in OC cell survival, proliferation, and drug resistance.

Milestone # 1. Confirm and correlate the ENPL expression to Platinum resistance by ENPL knockdown (KD) or overexpression (OE) in chemo resistant cells and sensitive ovarian cancer cell lines (Year 1: 1 to 4 months). **Completed 75%**

Approach 2. To determine the mechanism of OC chemoresistance by ENPL. **Approach 1**: Assessment of cells' sensitivity to carboplatin expressing wild type, knock down and over expression ENPL or MRP2 in OC sensitive or resistant cell lines.

Milestone # 2. Depletion of ENPL in WT chemoresistant cells impacts the MRP2 expression, analyze the carboplatin sensitivity in either ENPL or MRP KD cells (Year 1: 4 to 6 months). **Completed 50%**

Approach 3 & **4.** To determine if ENPL regulates exosome secretion through MRP2 in OC cells.

Milestone # 3 Confirm the role of ENPL-mediated exosome secretion through MRP2 in OC and further identify ENPL, carried in exosomes, can confer cisplatin resistance to a cisplatin sensitive background (Year 1: 5 to 8 months). **Completed 25%**

Approach 5. To evaluate the clinical significance of ENPL expression as a marker of platinum resistance and survival in OC patient samples.

Milestone # 4. This study will confirm the prognostic value of ENPL as a biomarker for chemoresistance, disease progression, and prediction of potential treatment response (Year 1: months 7 to 12). **Completed 75%**

What opportunities for training and professional development has the project provided?

We have training for Gynecology Oncology Clinical fellows in this proposed project in vitro study.

Publication: **Draft 1 is preparing based on SA1 proposed study and being currently finalizing the results.**

RESULTS

1. ENPL knockdown inhibits cell survival, proliferation and migration/invasion: We propose to identify the association of endoplasmin (ENPL) with platinum-resistant OC. ENPL is a member of a family of adenosine triphosphate (ATP)-metabolizing molecular chaperones that have roles in stabilizing and folding other proteins localized to melanosomes and the endoplasmic reticulum (ER). While ENPL expression has been demonstrated to play a critical role in immune modulation, cancer, and chemoresistance, the exact molecular pathways by which it acts remain unknown. We have identified that expression of pENPL, and ENPL proteins are highly elevated in platinum resistant patient samples and OC cells. To determine if ENPL regulates cell survival, proliferation, migration, and invasion in platinum resistant cells, we analyzed it in ENPL knockdown (KD) OC cells. Our results confirm a significant decrease in OC platinum resistant cell survival and proliferation in ENPL knockdown (KD) OV8 cells under hypoxia (**Fig.**). Additionally, we labeled the exosomes with exo-glow green, and confirmed internalization of the labeled ENPL KD or hypoxic exosomes by co-culturing them with OV4 cells (**Fig. 8D**). We observed a significant impact on cellular migration/invasion with co-culture of hypoxic OV4 cells with 20µg of secreted exosomes for 48h (**Fig. 8E & F**) compared to OV4 cells co-cultured with ENPL KD exosomes. Overall these results suggest a role for ENPL in platinum resistant in OC cells and collectively, these data indicate that highly expression of ENPL plays a key role in OC cell proliferation migration and invasion in OC chemo-resistant microenvironments.

2. Development of microfluidics device (MFD) for the isolation of exosomes and validation. Exosomes are nano-sized (30 -120 nm) vesicles released by a variety of cells and are generated within the endosomal system Within the tumor microenvironment exosomes are considered to be a potential mediator of tumor progression and chemoresistance. Exosomes are key factors contributing to platinum resistance via enhanced efflux of platinum from cancer cells. Our study overcomes the limitations and problems associated with conventional methods of isolating exosomes. Conventional methods of isolating exosomes in research laboratories are technically challenging, involve laborious ultracentrifugation, require a large sample volume, and are time consuming. Moreover, commercial kits are costly and are non-specific. In addition, previous microfluidic chips developed on the microfluidic platform employ the use of smooth channels for the isolation of exosomes, which were then processed for further analysis on a chip. This is an important limitation as it decreases the surface area and quality of the chip due to the existence of contaminating proteins, which ultimately compromises the quantity of the sample. Our novel, microfluidic-based approach, allows for exosomal isolation from a small sample volume and provides a greater yield of high-quality exosomes compared to traditional techniques. Also, commercial kits are costly and non-specific. Using our novel microfluidics device (**Fig. 4A**), we have isolated exosomes from both platinum-sensitive and resistant cell lines. Vesicle size was confirmed by transmission electron microscopy (TEM) (**Fig. 4B**). We will address both technical and biological reproducibility of ENPL mediated exosome secretion, which carry oncogenic proteins and potential prognostic biomarkers, using different technologies and methods in different collaborators' or core laboratories by sharing the cell lines, exosomes, patient ascites cells and serum samples. We validated exosome secretion levels in different OC cells, patient ascites samples and pO2 measurements using two different mouse models (**Fig. 1 & 2**). Exosome isolation and purification was validated using a microfluidics device in PI and Dr. Hansford's laboratories (**Fig. 3 & 4**) and were compared with other standard methods (ultracentrifugation and commercial kit, **Fig. 5**).

3. Exosome secretion levels are high in chemoresistant OC cells. Although there is evidence that exosome secretion is a key factor for platinum resistance (28) and our preliminary study showed that exosome secretion contributes to chemoresistance in cancer, it is still unknown if endoplasmin-mediated exosome secretion is elevated in ovarian tumor microenvironments and involved in chemoresistance, or if expression of exosomal ENPL or its target proteins is associated with OC chemoresistance. To determine if exosomes play a role in

chemoresistance, we first compared the secretion of exosomes from chemoresistant to chemosensitive OC cells. Our preliminary data showed that the chemoresistant cell lines, TR-127, TR-182 and primary ovarian cancer cells isolated from patient ascites (POCC-1), had a 4-8-fold increase in exosome release when compared to chemosensitive cell lines (OVCAR-3 and OVCAR-8), normalized to their cell counts (**Fig. 5A-C**). This suggests that increased exosomes release could contribute to chemoresistance

4. Knockdown of ENPL inhibits exosome secretion, increases drug accumulation, and has cytotoxic effect in OC. After we identified that OC chemoresistant cells and patient samples demonstrate characteristic constitutive expression of ENPL and high levels of exosome secretion, we created a model to test the effect of knockdown of ENPL. To determine if ENPL regulates exosome secretion, we analyzed exosome secretion, CP accumulation in cell lysates and exosome in ENPL knockdown (KD) OC cells. Our results show that ENPL KD in TR-127 or OVITOKO cells, significantly decreases the concentration of exosomes (**Fig. 6A-B).** After CP treatment, cells were collected for inductively-coupled plasma mass spectrometry (ICP-MS) analysis. Note that CP accumulation is increased in OC cell lysates and decreased in exosomes following TMEM knockdown as quantified via ICP-MS (**Fig. 6C**) and nuclear localization by Immuno-fluorescence (**Fig. 6D**). Additionally, we confirmed that knockdown of ENPL expression significantly sensitized cells to CP toxicity (**Fig. 6E**). These results suggest that ENPL expression plays a key role in the chemo-resistance of OC through exosome secretion. The precision of the knockdown will be reconfirmed by overexpression of ENPL in OV or TR127-TMSi cells by transfection with an overexpression plasmid. Rescue of ENPL knockdown effects, in OV or TR127 TM Si cells, will further establish ENPL-mediated chemo-resistance in OC.

5. ENPL expression is highly elevated in chemoresistant OC. Membrane proteins are amongst the first members to sense any change in the event of pathological conditions. This easy accessibility renders them as perfect candidates for potential disease biomarkers with both diagnostic and prognostic potential. ENPL is one such membrane protein whose upregulation is associated with platinum resistance. Our *working hypothesis* is that the presence of ENPL in serum exosomes can serve as biomarkers for this resistance. To determine whether ENPL is most strongly associated with chemoresistance, we will evaluate the differential expression of ENPL in serum samples derived from OC patients using an ELISA in human OC serum samples were performed which revealed highly elevated ENPL expression in the chemo-resistant OC patient samples but absent or lower ENPL expression in the chemosensitive and control serum samples (**Fig. 9A & B**). ENPL expression levels are 8-25 fold higher in chemo-resistant OC serum samples when compared with sensitive samples. This indicates that ENPL expression is very specific to OC chemoresistant tissues and serum compared with benign or chemosensitive tissues and serum. We further validated this expression in a different set of benign, OC patients samples and demonstrated a high expression of ENPL and CD1B when analyzed using ELISA (**Fig. 10A & B**). This supports its potential as a biomarker as well as a therapeutic target.

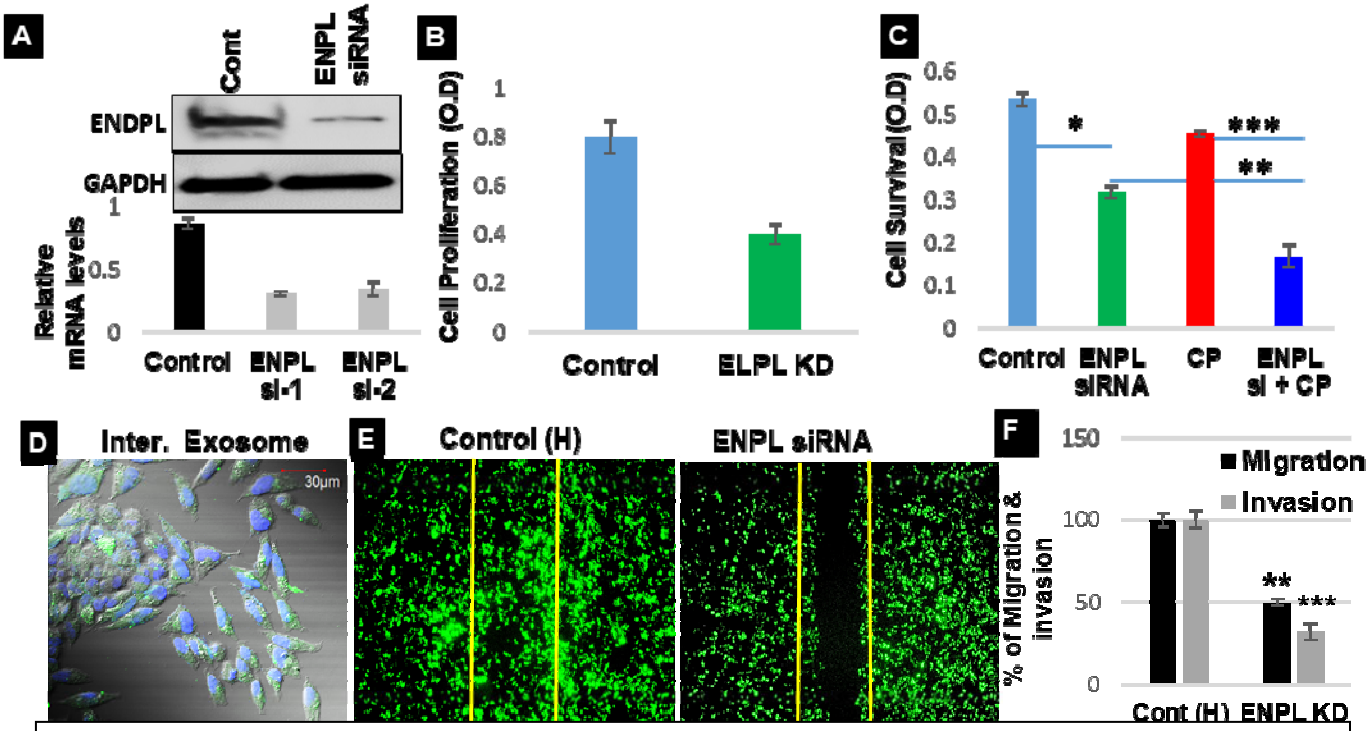

Fig. 1. ENPL contributes to OC cell survival, proliferation migration & invasion: A. ENPL KD in OV4 was confirmed (two different clones si1 and si2) by WB & RT-PCR. **B & C)** Effect of ENPL KD significantly inhibits cell proliferation and cell survival in OC cells by AntiBrDu and SRB assays (n=5,*p < 0.001). **D)** OV4 wt and kd cells exosomes were labelled with exo-glow-green, which labels the proteins inside the exosomes, and co-cultured with Wt OV4 cells in conditioned medium. Exosome internalization was confirmed by microscopy. The differential contrast image (DIC Green) shows that exosomes are internalized. **E** & F**)** decreased migration and invasive potential in OV4 treated with ENPL kd exosomes compared to without ENPL kd cells exosomes (n=4; p<0.002, or 0.01)

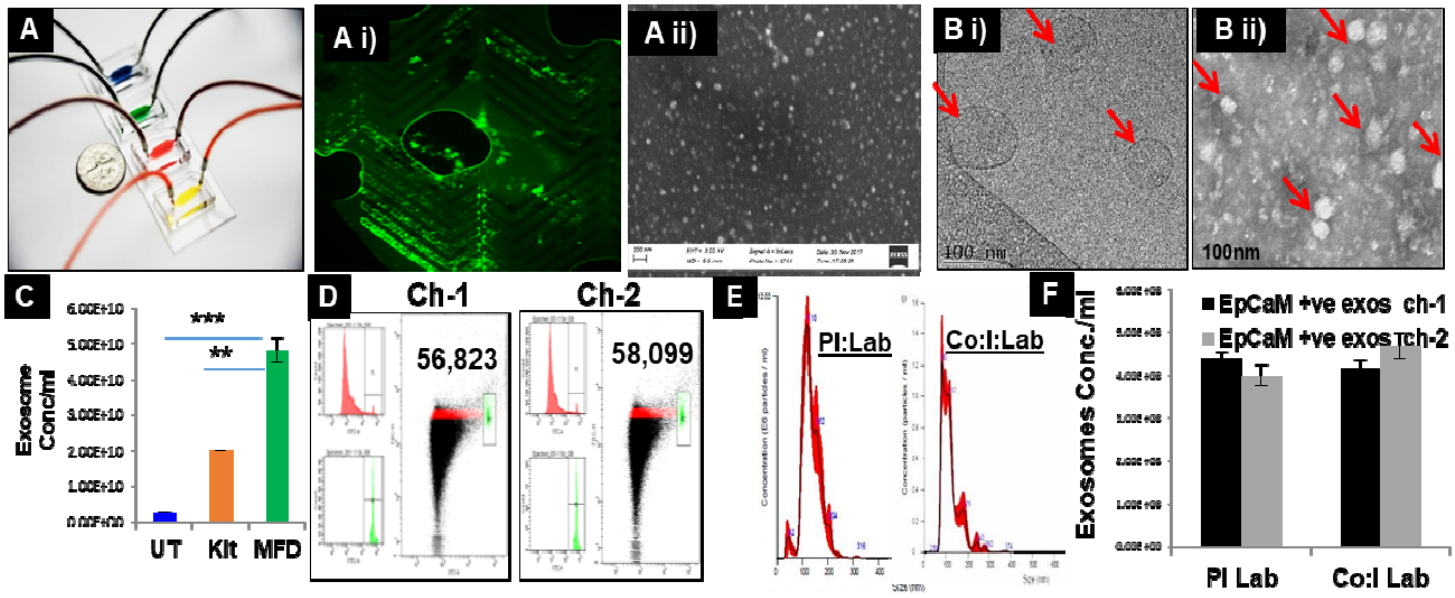

Figure 2. Exosome isolation by MFD and characterization. **A)** Microfluidic "catch and release" device, PDMS channels functionalized with CD9 and CD63 antibodies in MFD, fhe flow is shown in different colors. **A-i**), Labelled Exosome (green) capture in MFD channels; A-**ii**) SEM images of captured exosomes on the MFD channels. **B)** Morphological characterization and size measurement of exosomes (indicated by red arrows) by (**i**) Cryo and (**ii**) classical transmission electron microscope (TEM). **C)** Quantity of CD9 and CD63 positive exosomes obtained by device. Microfluidic device had greater yield than ultracentrifugation and commercial kits (n=10, ***p<0.0001 and**p<0.005, respectively). D). Exosome particles confirmed in two different channels by flow cytometry (the bar surrounding green color indicates exosome count) **E)** NTA for exosome quantification, isolated by microfluidic chip in PI and Co-I labs showing reproducible results (n=5)**. F)** Quantification of Exosomes by NTA in benign, control & HGSOC serum samples (n=5, p < 0.0001).

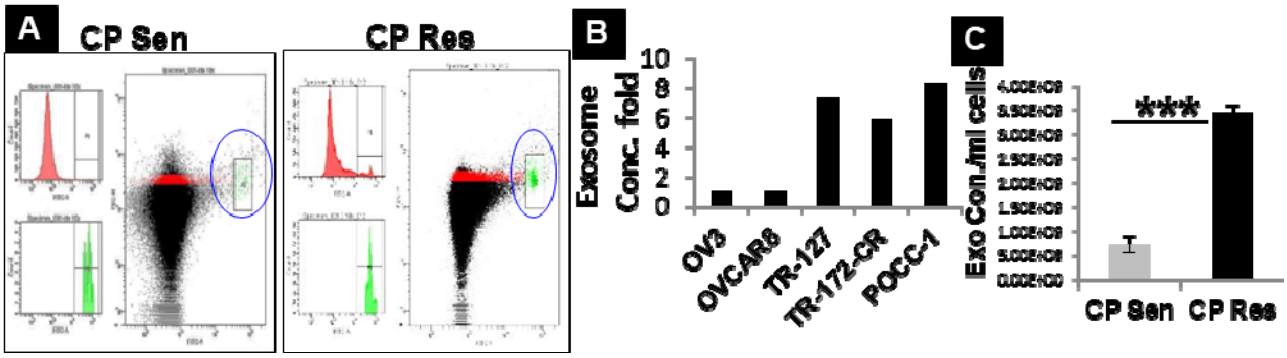

Fig. 3. Exosome secretion in OC cells: **A**) Exosome secretion in OC cells as quantified by image stream flow-cytometry (ISF). **B-C)** Exosome secretion levels are higher in OC chemoresistant cells (CP Res) than chemosensitive cells (CP Sen) (n=5, $p<0.0001$).

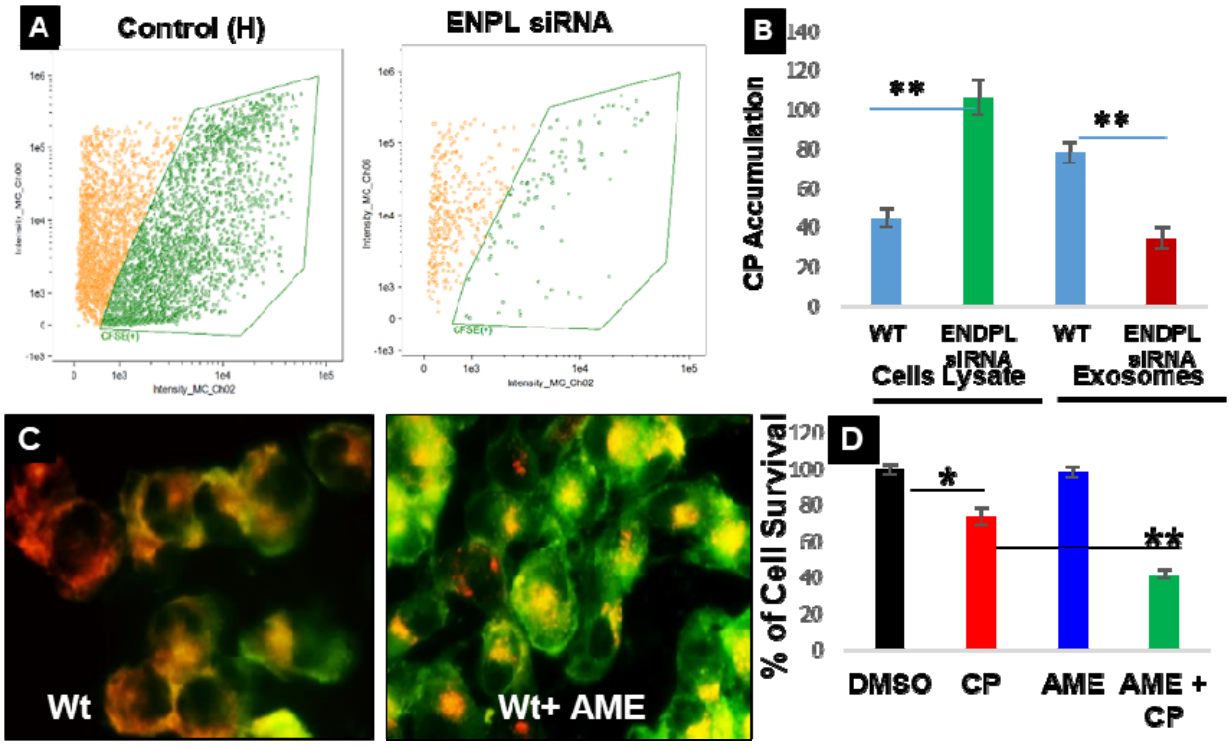

Figure 4. ENPL involvement in OC chemoresistance: **A)** ENPL KD in OV4 was confirmed (two different clones si1 and si2) by WB & RT-PCR. **C)** Effect of ENPL KD significantly reduced exosome secretion in the hypoxic OC cells by NTA (n=5,*p < 0.001. **B) ENPL** KD and WT cells were treated with CP (10μM) for 6 hours and cell-lysates and exosomes were subjected to ICP-MS for CP accumulation, (n-5, p<0.001). **C)** When treated with GFP-labeled CP, the OV cells showed CP localized on the outer membranes of the cells (green color) while the OV ENPL Si or AME exosome inhibitor treated cells clearly show CP accumulation in the nuclei (counterstained with red plasma membrane stain). **E)** Decreased cell survival potential in OV4 treated with ENPL kd or exosome inhibitor AME compared to control or single treatment with cisplatin (n=7; p<0.002 or 0.05).

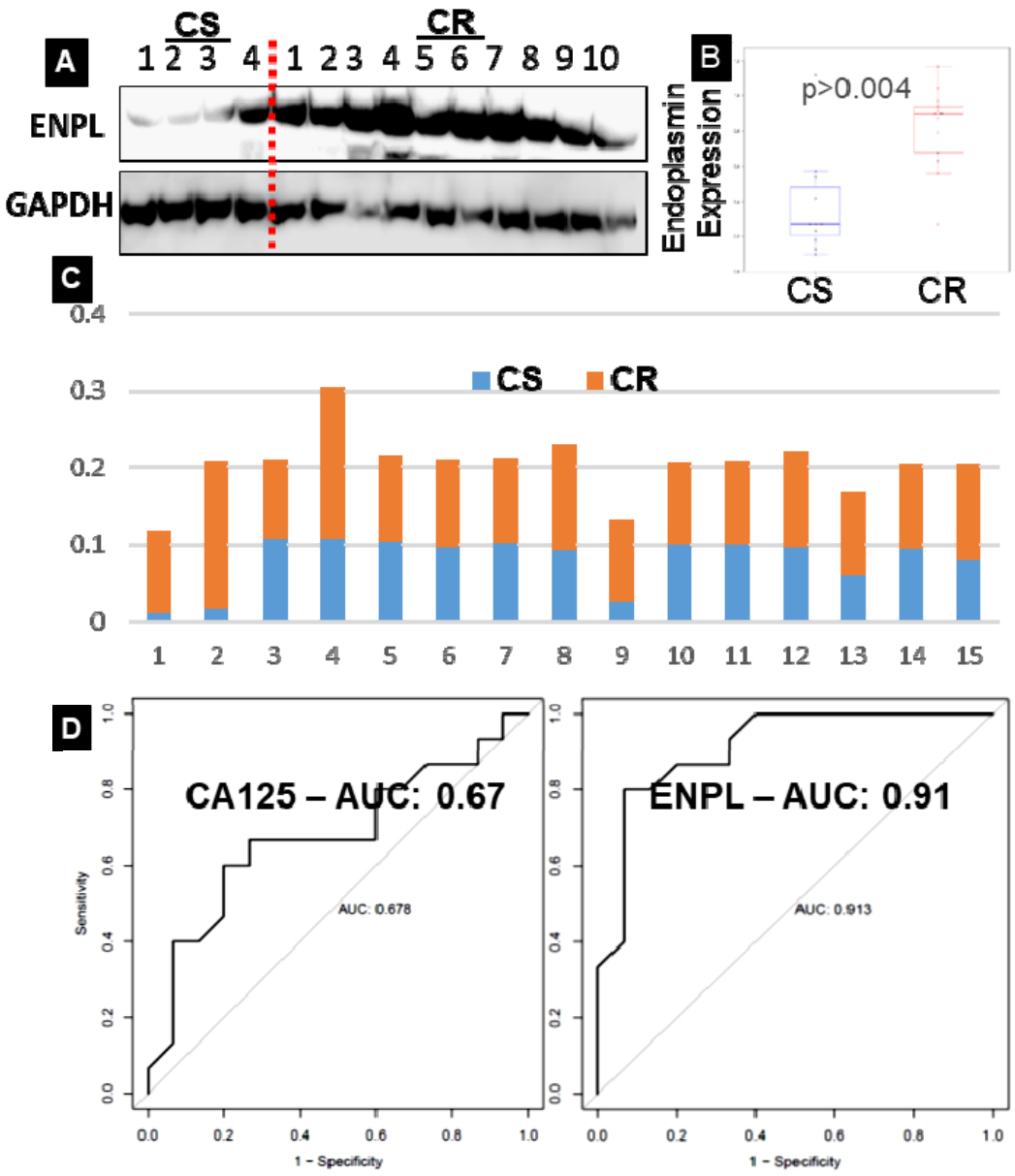

Figure 5. ENPL expression in OC patients: A & B) ENPL expression is highly elevated in OC platinum resistant patient serum or tissues than platinum sensitive (n=10 for WB; n=4 for IHC); **C)** High ENPL in OC patient serum samples than OC platinum sensitive serum exosomes samples (n-18); **D)** ROC curves of CA125, and ENPL based on ELISA results from exosomes isolated from platinum sensitive and resistant disease of OC serum samples. ENPL had an AUC of greater than 0.91, compared to CA125 0.67 (aka MUC16) analyzed (n=16).

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?

Currently we are finalizing the manuscript describing the data presented in the report and plan to submit it in July end.

For year 2, we plan to complete our proposed experiments from Aim 1, To determine if ENPL regulates exosome secretion through MRP2 in OC cells and Does ENPL associate with exosomes to mediate OC chemo-resistance?. Currently we have preliminary data that is under analysis state.

Initiate experiments from Aim 2 July middle.

4. IMPACT

1. Impact on the development of the principal discipline (ovarian cancer) of the project: Identifying the role of endoplasmin in the development of platinum-resistance of OC: Our preliminary results showing that ENPL could play a role in in promoting OC progression and chemoresistance through the exosome secretion payways. Based on these findings, we will evaluate novel mechanisms linking ENPL with exosomal secretion, including, how ENPL expression plays a role in exosome release and contributes to OC chemoresistance through the MRP2 activation in OC in SA1 and SA2. This finding will potentially lead to the identification of novel biomarkers and therapeutic targets for chemoresistant OC.

2. Impact on the development of other disciplines: Our study can have impact on all other solid tumors. By identifying the role of ENPL and combining the approaches of blocking exosome secretion with cisplatin treatment approaches, the outcome of combination thearpy can me enhanced and made for successful for the patient.

3. Impact of the technology transfer: Translational Technology - Microfluidics device: We have developed a novel microfluidics based device to isolate intact exosomes with greater purity and quality in a shorter time that will allow for downstream processing. These factors are critical for moving forward in clinical translation and be directly applicable for exosome-based biomarker screening in patient serum samples.

4. Impact on society beyond science and technology: nothing to report.

5. CHANGES & PROBLEMS

Changes: Nothing to report

Problems: Approximately 3 months prior, we faced a problem with our ENPL KO in different OC cells. It appeared that our ENPL siRNA clone contaminated or cells got mixed with the different siRNA clone or control siRNA. This significantly delayed our mechanistic study experiments. We solved the problems within a month, selected ENPL siRNA clone, and confirm the knockdown in different OC cells.

- **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**
  Role of ENPL mediated platinum resistant in ovarian cancer. Dorayappan KDP, Gardner, M, Colin H, Zingarelli R, Smith BQ, Lightfood M, Flannery M, Hays J, Hansford D, Freitas M, Zhanf Y, Cohn DE, **Selvendiran K**. *Manuscript under preparation for Molecular cancer research 2021.*

- **Journal publications.**
  Nothing to report

- **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**
  We have developed a novel microfluidics based device to isolate intact exosomes with greater purity and quality in a shorter time that will allow for downstream processing. These factors are critical for moving forward in clinical translation and be directly applicable for exosome-based biomarker screening in patient serum samples.

- **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: Selvendiran Karuppaiyah
Project Role: PI
No Change

Name: David Cohn
Project Role: Co-I
No Change

Name: Jing Zhao
Project Role: Biostatistician
No Change

Name: Kalpana Deepa Priya Dorayappan
Project Role: Post Doc Fellow
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?

Active Support Changes:

Selvendiran Karuppaiyah (PI)

Now Active / Awarded:
DOD FY20 Ovarian Cancer Research Program - Clinical Translational Research
Award W81XWH2110427 Total Costs: 06/15/2021 – 06/14/2023 3 calendar months

Jing Zhao (Biostatistician)

Active / Awarded:
DOD FY20 Ovarian Cancer Research Program - Clinical Translational Research
Award W81XWH2110427 Total Costs: 06/15/2021 – 06/14/2023 0.6 calendar months

Active / Awarded:
Role: **Biostatistician**
Nat In. Arthritis & Muscoskeletal & Skin
Title: Skeletal muscle in rheumatoid arthritis
K23AR068450 Total Costs: 09/012020 – 08/31/2021 2.4 calendar months

Active / Awarded:
Role: Biostatistician
National Institute of Neurological Disorders and Stroke
Title: Reducing infection susceptibility by immune function restoration in spinal cord injury
R01NS118200 Total Costs: 07/01/2020 – 06/30/2022 0.6 calendar months

Active / Awarded:
Role: Biostatistician
National Institute of Neurological Disorders and Stroke
Title: Implementation of machine learning workflows in primary brain tumor diagnostics R03NS116334 Total Costs: 06/01/2020 – 11/30/2021 0.6 calendar months

Active / Awarded:
Role: Biostatistician
NCI
Title: The translational regulation of pro-apoptotic genes R01CA251753 Total Costs: 07/14/2020 – 06/30/2025 1.2 calendar months

Active / Awarded:
Role: Biostatistician
National Heart, Lung and Blood Institute
Title: ISGylation regulates lung endothelial inflammation
R01HL157164 Total Costs: 04/20/2021 – 03/31/2025 1.2 calendar months

Active / Awarded:
Role: Biostatistician
NCI
Title: Validating urine derived cancer cells (UDCC) – non-invasive and living liquid biopsies – in bladder cancer clinics
R33CA258016 Total Costs: 05/01/2021 – 04/30/2024 0.60 calendar months

What other organizations were involved as partners:

1. Additional OC platinum resistant and sensitive serum samples was provided by **Dr. Larry Maxwell, MD** at **Inova Schar Cancer Center** for evaluate the clinical significance of ENPL expression as a marker of platinum resistance and survival in OC patient samples.

Nothing to report on any other personnel's and relationships.

8. Special Reporting Requirements

Nothing to report

9. APPENDICES

Award Chart

W81XWH-20-1-0361: Endoplasmin: A Novel Therapeutic Target and Potential Marker of Chemoresistance

PI: Selvendiran Karuppaiyah The Ohio State University, Ohio **Budget:** $389,881

Topic Area: OCRP **Mechanism:** FY 19 OCRP Pilot Award OCRP PA

Research Area(s): SCS Coding **Award Status:** 06/01/2020 – 05/31/2021

Study Goals: The goal of this study is to evaluate a novel protein, Endoplasmin, as a potential therapeutic target in chemoresistant ovarian cancer

Specific Aims:

SA.1: To identify the role of ENPL expression in chemosresistance and progression of OC.
SA.2: To evaluate the effect of inhibiting ENPL on the efficacy of carboplatin treatment using in vitro and in vivo OC mouse models.

Key Accomplishments and Outcomes:

Publications: none to date
Patents: none to date
Funding Obtained: none to date