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TITLE: Analisa Difeo/Project Title: Identification of miRNA Signatures Associated with Epithelial Ovarian Cancer Chemoresistance with Further Biological and Functional Validation of Identified Key miRNAS

PRINCIPAL INVESTIGATOR: **Analisa DiFeo**

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14. ABSTRACT

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy in the United States. One major obstacle in the clinical management of the disease is the high incidence of recurrence after cytotoxic chemotherapy and the development of platinum resistance. Given the crucial importance to overcome chemotherapy resistance to platinum therapy, we hypothesize that miRNA profiling in EOC cell lines and surgical specimens with varying chemosensitivities will uncover a potential predictive "fingerprint" for individualized therapy, while further biological validation of these miRNAs signatures will allow for the development of novel therapeutic strategies to enhance chemosensitivity. Through mircoarray analysis of miRNAs differentially expressed in an *in vitro* model of acquired carboplatin resistance consisting of EOC cell lines sensitive to carboplatin, A2780, and its resistant variants, CP20 (moderately resistant) and CP70 (resistant), we identified a panel of miRNAs that correlate with carboplatin response. We uncovered four miRNAs (miR-23b, miR-132, miR-183. miR-181a and miR-203) that are significantly upregulated in both platinum-resistant cell lines. Additionally, we found that miR-181a was also correlated with several clinical parameters in a cohort of ovarian tumor specimens from women diagnosed with stage III, grade 3, papillary serous adenocarcinoma all treated with platinum-based chemotherapy. Furthermore, we uncovered the biological relevance of this miRNA. We found that miR-181a induced platinum-resistance through the maintenance of cancer stem cells via the regulation for TGFb and Wnt signaling pathway. In summary, through the funding provided by the CDMRP we were able uncover several miRNAs that correlate with patient outcome and platinum resistance (Task 1), reveal the functional relevance of miR—181a (Task 2) and confirm that targeting this miRNA as a novel therapeutic option in ovarian cancer (Task 3).

15. SUBJECT TERMS

microRNA, ovarian cancer, platinum resistance

16. SECURITY CLASSIFICATION OF:			**17. LIMITATIO**	**18. NUMBER**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	UU	13	**19b. TELEPHONE NUMBER** *(include area code)*

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Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy. Platinum and taxane-based drugs are used in combination as first-line chemotherapeutics for women newly diagnosed with EOC, unfortunately approximately 20% do not respond to this treatment and have very poor outcomes due to chemoresistance, making advanced ovarian cancer particularly difficult to eradicate. Given the crucial importance to overcome chemotherapy resistance to platinum therapy, we hypothesize that miRNA profiling in EOC cell lines and surgical specimens with varying chemosensitivities will uncover a potential predictive "fingerprint" for individualized therapy, while further biological validation of these miRNAs signatures will allow for the development of novel therapeutic strategies to enhance chemosensitivity. The overarching goal of this project is to identify miRNAs involved in the development of ovarian cancer chemoresistance and ascertain their biological relevance using both *in vitro* and *in vivo* models of ovarian adenocarcinoma. To test our hypothesis, we propose to: 1) Validate the clinical relevance of the miRNA signature we identified in our *in vitro* model of chemosensitivity using a well-defined clinical cohort of ovarian cancer specimens; 2) determine the biological and functional relevance of the miRNAs that correlate with chemotherapeutic response**;** 3) explore whether *in vivo* targeting of miRNAs that are overexpressed in chemoresistant cancer cells can sensitize chemoresistant ovarian tumors to platinum treatment and inhibit ovarian cancer dissemination in a pre-clinical ovarian cancer mouse model. Our study, if successful, will identify key miRNAs involved in the regulation of chemoresistance in EOC and significantly contribute to the understanding of their biology and function *in vitro* and *in vivo*. Those miRNAs may also serve as predictive markers for tailored therapy. Furthermore, targeting these miRNAs using *in vivo* will provide a new paradigm for overcoming chemotherapy resistance clinically and thus improve survival in late stage disease.

KEYWORDS: ovarian cancer, platinum-resistance, microRNA, metastasis, cancer stem cells

ACCOMPLISHMENTS:

What were the major goals of the project?

Given the crucial importance to overcome tumor resistance to first-line agents such as carboplatin, we hypothesize that miRNA profiling in EOC cell lines and surgical specimens with varying chemosensitivities will uncover potential predictive markers for individualized therapy, while further biological validation of these miRNAs signatures will allow for the development of novel therapeutic strategies. Thus, the overarching goal of this proposal was to identify selected miRNAs involved in the development of ovarian cancer chemoresistance and ascertain their biological relevance using both *in vitro* and *in vivo* models of ovarian adenocarcinoma.

Task 1: Validate the clinical relevance of the panel of miRNA's identified in our *in vitro* model of chemosensitivity using a well-defined clinical cohort of ovarian cancer specimens.

Task 2: Determine the biological and functional relevance of the miRNAs that correlate with chemotherapeutic response.)

Task 3: Explore whether *in vivo* targeting of miR-183 which is overexpressed in chemoresistant cancer cells can sensitize chemoresistant ovarian tumors to cisplatin treatment and inhibit ovarian cancer dissemination in a pre-clinical ovarian cancer mouse model

What was accomplished under these goals?

Through miRNA array analysis of an *in vitro* model of acquired platinum resistance consisting of an OvCa cell line sensitive to carboplatin, A2780, and its resistant variants, CP20 (moderately resistant) and CP70 (resistant) which, we have identified a panel of miRNAs that are correlated with carboplatin response (**Tables 1 and 2**). Interestingly, the majority of miRNAs were upregulated in the platinum resistant variants compared to the parental sensitive cell line. Well-known miRNA clusters such as the miR-17-92 and the let7 family were some the most significantly altered miRNAs. Additionally, we both the moderately resistant and resistant cell lines had many of the same dysregulated miRNAs with only a few miRNA that were exclusively changed in each cell line alone (**Figure 1**).

Table 1: miRNAs downregulated in platinum resistant ovarian cancer cells

Mature ID	FC (CP20/ A2780)	p-value	FC (CP70/A2780)	p-value
miR-92a	0.44	0.008	0.23	0.0005
miR-18a	0.79	0.04	0.19	0.00009
miR-210	0.25	0.004	0.41	0.01
miR-124	0.3	0.008	0.2	0.004
miR-125b	0.45	0.01	0.14	0.003
miR-363	0.11	0.02	0.13	0.03
miR-130a	0.4	0.002	0.73	0.08
miR-193a-5p	0.5	0.08	0.8	0.36
miR-20a	0.56	0.06	0.15	0.005
miR-19a	0.57	0.07	0.15	0.008
miR-17	0.61	0.11	0.16	0.01

Figure 1

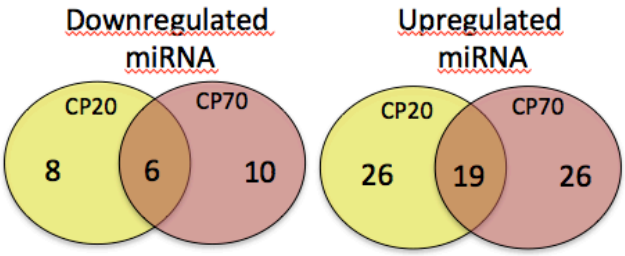
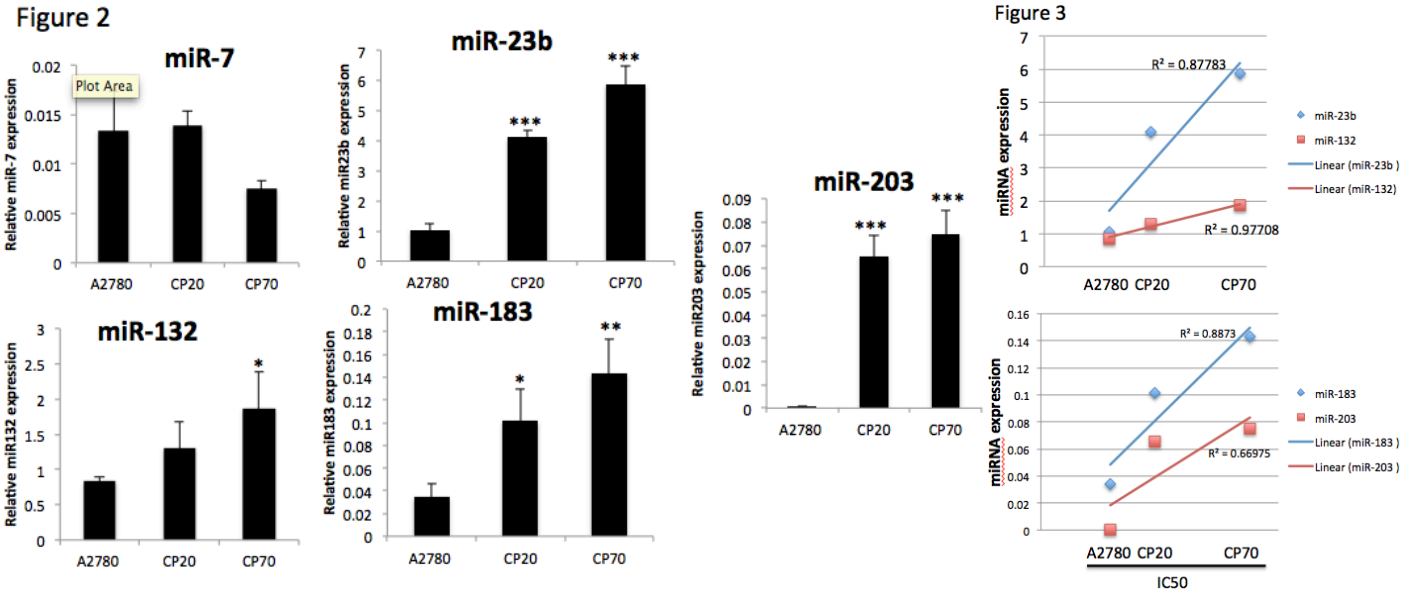


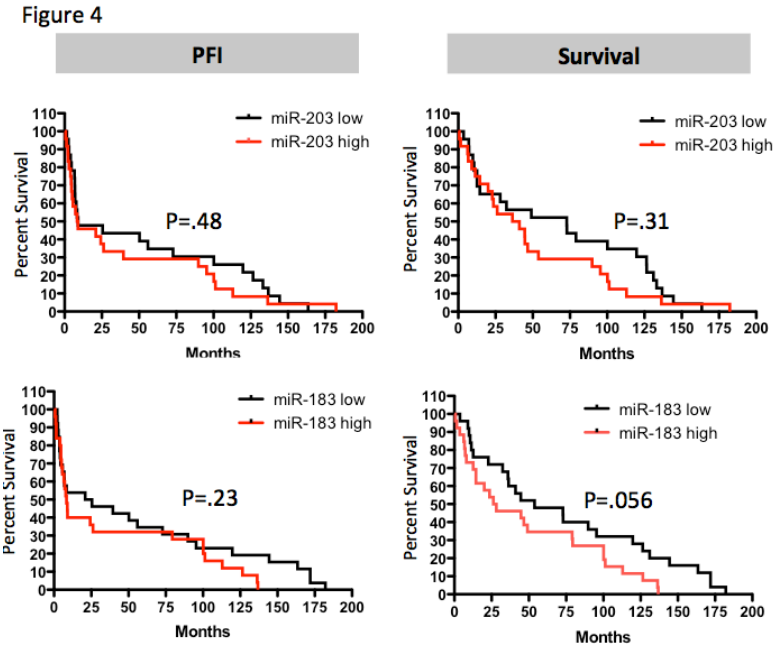
Table 2: miRNAs upregulated in platinum resistant ovarian cancer cells

Mature ID	FC (CP20/ A2780)	p-value	FC (CP70/ A2780)	p-value
let-7g	26.32	0.000026	50.97	0.000021
let-7b	6.11	0.000046	23.4	0.000568
let-7i	2.9	0.000078	7.74	0.000072
let-7e	8.18	0.001984	15.91	0.000152
let-7a	6.42	0.003078	13.72	0.002556
miR-132	**15.73**	**0.000028**	**9.33**	**0.000391**
miR-23b	**15.94**	**0.000037**	**10.69**	**0.000328**
miR-9	**36.04**	**0.00003**	**38.54**	**0.000007**
miR-148a	8.64	0.000251	7.97	0.000083
miR-7	9.57	0.000011	3.18	0.003136
miR-27b	8.03	0.001567	3.92	0.001501
miR-148b	3.19	0.001814	3.69	0.005809
miR-30c	3.23	0.001991	2.21	0.010526
miR-200c	7.79	0.002082	5.74	0.002728
miR-183	**6.64**	**0.003117**	**9.07**	**0.000999**
miR-146b-5p	9.44	0.004059	4.52	0.020673
miR-196a	3.87	0.007077	3.45	0.005725
miR-193b	4.81	0.010541	4.93	0.010036
miR-128	3.86	0.016774	4.56	0.01578
miR-181c	2.81	0.006823	2	0.111084
miR-214	**3.81**	**0.025935**	**2.18**	**0.361897**
miR-181a	**1.97**	**0.048522**	**1.54**	**0.127733**
miR-181d	**2.03**	**0.048564**	**1.08**	**0.953417**
miR-181b	**1.59**	**0.053891**	**1**	**0.89711**
miR-199a-3p	2.2	0.000754	1.01	0.973468
miR-21	2.51	0.002247	1.2	0.15501
miR-126	1.65	0.053338	3.32	0.000606
miR-125a-5p	1.84	0.077812	2.05	0.041421
miR-100	3.03	0.08162	4.13	0.013408
miR-191	1.46	0.210084	1.83	0.034618
miR-29a	0.87	0.519884	1.86	0.032717
miR-15b	1.64	0.000377	2.79	0.000285
let-7d	2.21	0.477048	6.13	0.008461

We next sought to confirm our array findings and validate the clinical relevance of the panel of miRNA's identified using a well-defined clinical cohort of ovarian cancer specimens. Firstly, in order to confirm the miRNA array results several of the significantly upregulated miRNAs which have not been previously associated with chemotherapy response were analyzed in the panel of platinum-resistant ovarian cancer cell lines. Taqman PCR analysis confirmed that 4 (miR-203, -183, -23b and -132) of the 5 (miR-203, -183, -23b, -132 and -7) miRNAs analyzed were significantly upregulated in the platinum-resistant cells (**Figure 2**). In addition, rather then comparing two distinct groups (i.e., sensitive vs. resistant), we directly correlated the level of each miRNA expression with the IC50 of each cell lines which is a measure of the effectiveness of platinum in inducing apoptosis. As shown in **Figure 3**, the expression of miR-203, -183, -23b and -132 reveal a positive linear correlation with cell resistance. Strikingly, miR-132 expression displays an almost perfect correlation with cell resistance ($R^2 > 0.98$).

Next, in order to assess the clinical relevance of these miRNA we ascertained whether there was a correlation between miRNA expression and several clinical parameters including progression-free survival and

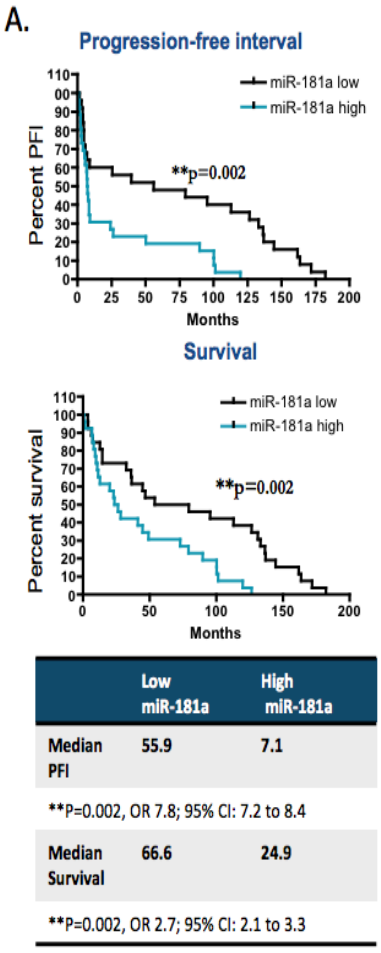




overall survival. Total RNA was extracted using RecoverAll Total Nucleic Acid isolation kit (Ambion) from a well annotated clinical cohort of 53 stage III serous adenocarcinoma patient samples all treated with platinum therapy. Using the median expression value for each miRNA as a cut-point, the cohort was dichotomized into miRNA-high or miRNA-low expressing tumors. Interestingly, only miR-183 showed a trend towards significance with survival, high expression of miR-183 correlated with poor overall survival (**Figure 4**). Specifically, tumors with high expression of miR-183 had a median survival of 27.2 months whereas those patients who has low expression the median survival was 53.8 months (p=0.056, 95% CI 1.4-2.6).

Given that none of these preliminary miRNAs correlated with outcome we continued to expand our clinical cohort and examine the expression of other miRNAs that correlated with platinum-resistance (Table 1&2) Upon expansion of our clinical cohort we uncovered a novel miRNA, miR-181a, which was shown to be significantly induced in platinum-resistant cells (**Table 2**), correlated with patient outcome and tumor recurrence (**Figure 5A & B**). MicroRNA-181a expression dichotomized into miR-181a-high or miR-181a-low expressing tumors based on median expression in a

clinically annotated patient cohort of high-grade stage III primary papillary serous ovarian cancer, revealed significant differences in the median progression-free survival (PFS) (59.9 months) for patients with low miR-181a expression, compared to 7.1 months in patients with high miR-181a expression (**Figure 5A**, *P*=0.002, OR 7.8; CI: 7.2-8.4). Furthermore, patients with low miR-181a levels exhibited a median overall survival (OS) of 66.6 months in contrast to a median OS of 24.9 months in patients with high miR-181a expression (**Figure 5A**, P=0.002, OR 2.7; CI: 2.1-3.3). Additionally, given that a major contributor to the overall poor survival of patients with high-grade serous ovarian cancer is tumor recurrence, we also assessed whether miR-181a was differentially expressed in recurrent tumors compared to matched-primary tumors. The expression of miR-181a was assessed in patient-matched tumor biopsies that were taken at primary surgery (PS-O: chemotherapy naïve ovarian tumor) and at secondary surgery (SCR: after tumor has recurred after at least two lines of chemotherapy). In the SCR tumors, miR-181a expression was upregulated 2.51-fold compared to PS-O (*P*=0.0006) (**Figure 5B**).



	Low miR-181a	High miR-181a
Median PFI	55.9	7.1
**P=0.002, OR 7.8; 95% CI: 7.2 to 8.4		
Median Survival	66.6	24.9
**P=0.002, OR 2.7; 95% CI: 2.1 to 3.3		

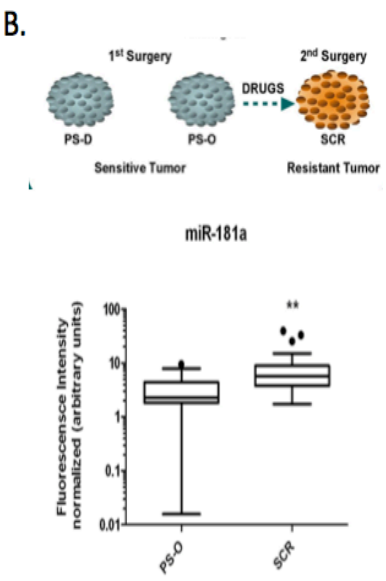


Figure 5: miR-181a levels are associated poor outcome and shorter time to recurrence in HGSOC. **(A)** Kaplan-Meier curves for progression-free survival (PFS) (top) and overall survival (OS) (bottom) according to relative expression levels of miR-181a (dichotomized at the median). **(B.)** Box plot diagrams showing the expression analysis of miR-181a in a cohort of patient matched tumor specimens from **PS-O**, primary surgery, ovary and **SCR,** secondary surgery.

Given the crucial importance of miRNAs in the regulation of global gene expression and cancer-relevant signaling pathways, our initial hypothesis was that a number of miRNAs play a yet unappreciated role in HGSOC development and chemotherapy resistance.

The other main goal of this proposal was to systemically validate the biological and functional consequences of dysregulated miRNAs that correlate with patient outcome in relevant HGSOC cell culture and in vivo models. Through these studies, we found that miR-181a can affect key biological processes including tumor cell survival, chemotherapy response, cellular migration and invasion, and cancer cell dissemination *in vivo*. Specifically, through the use of both intraperitoneal and intrabursal mouse models of ovarian cancer, we validated the functional relevance of miR-181a in ovarian cancer dissemination and progression in disease relevant in vivo models (**Figure 6**). Mice implanted with miR-181a expressing cells had increased overall tumor burden and a significantly higher incidence of metastatic nodules in the peritoneum (**Figure 6A**). Importantly, mRNA and IHC analyses of these tumors showed the maintenance of EMT *in vivo* (**Figure 6B**).

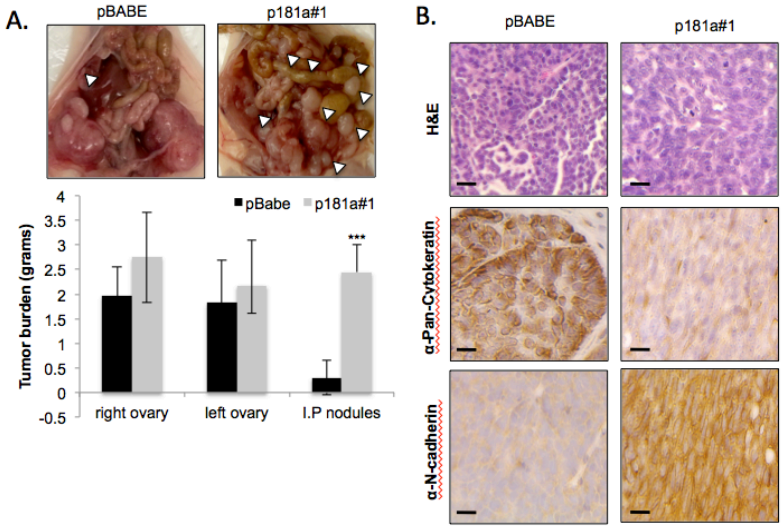


Figure 6. miR-181a regulates EMT and increases metastasis *in vivo*. **(a)** Gross images of metastatic nodules after intrabursal injection of ovarian cancer cells expressing pBABE control or pmiR-181a cells (top; white arrows). Ovarian tumors have been removed from the p181a#1 mouse in order to observe the extensive dissemination of tumor nodules throughout the abdomen. Total tumor burden in pBABE (n=5) vs. p181a-injected mice (n=7) at 3 weeks post-intraperitoneal injection ($2x10^6$ cells) (bottom). B. H&E and IHC staining(s) for pan-cytokeratin and N-cadherin in representative pBABE and p181a#1 tumors.

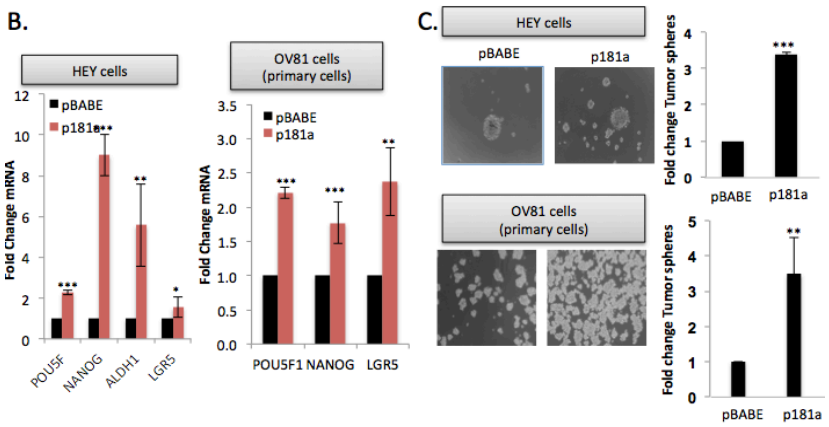
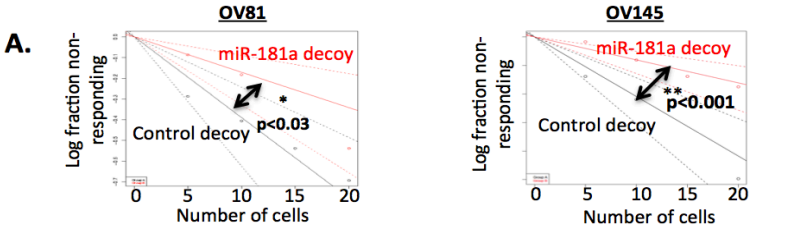


Figure 7: Enhanced miR-181a promotes EMT and contributes to the maintenance of CICs. **(B.)** qtRT-PCR of CIC markers in primary and established cells expressing miR-181a or control. **(C)** Tumor sphere assays in miR-181a and control cells. (tumor spheres were quantified using METAMORPH software and 100 random fields in 10x were counted).



	Average stem cell frequency	Confidence Interval
Control Decoy	1:25.7	16.0 to 41.1
miR-181a decoy	1:58.5	30.4 to 112.4

	Average stem cell frequency	Confidence Interval
Control Decoy	1:9.6	6.6 to 14.0
miR-181a decoy	1:24.9	15.6 to 39.6

B.

# tumor cells injected	# mice with tumors	
	p001	p181a
100,000	5/ 5	5/5
10,000	3/5	5/5*
1,000	1/5	5/5**

Figure 8: miR-181a contributes to the CICs. **(A)** ELDA and quantification of stem cell frequency in primary cells following control or miR-181a inhibition. **(B)** *In vivo* limiting dilution assay demonstrating increased tumor formation in nu/nu mice for p181a-expressing cells.

Following those studies we have also found that miR-181a overexpression also enhances the stem-like features of HGSOC cells that are not driven by the TGFβ signaling pathway (**Figure 7**). We found that miR-181a expressing cells have increased expression of stem cell markers (**Figure 7B**). In addition, tumor sphere assays which allow for the assessment of whether a single cell harbors the potential to both initiate and maintain tumors in the absence of cellular interaction and adhesion, revealed that enhanced miR-181a expression significantly increased CICs (**Figure 7C**).

Furthermore, we have now performed Extreme Limited Dilution Analysis [ELDA] in cells with targeted inhibition of miR-181a (miR-181a decoy) in order to assess miR-181a's direct effects on stem cell frequency. One, five, ten or twenty cells/ were sorted and placed directly into 96 well ultra-low attachment plates. After 7 days, the numbers of wells with tumor spheres were counted and the data was analyzed by ELDA platform. We found that miR-181a inhibition significantly decreased the stem cell frequency (**Figure 8A**). Lastly, we have also completed *in vivo* limiting dilution assays (LDA) and determined that miR-181a increased the tumor initiating properties of primary cells (**Figure 8B**).

Given that uncovering the molecular factors that contribute to the emergence of CICs is a critical component to understanding HGSOC drug resistance and recurrence we next sought to determine the mechanism by which miR-181a was regulating the emergence of these CICs.

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

How were the results disseminated to communities of interest? A manuscript detailing some of these findings was published in Nature Communications and was featured in *FierceDiagnostics (01/14); EurekAlert (01/14); ScienceDaily (01/14) and The ASCO Post (02/14).* In addition, Dr. DiFeo (PI) has presented this data at several scientific meetings as well as at gynecological cancer survivor groups at local hospitals.

What do you plan to do during the next reporting period to accomplish the goals? Nothing to report

IMPACT

What was the impact on the development of the principal discipline(s) of the project?
A greater understanding of the molecular alterations driving ovarian cancer treatment resistance will allow for the development of rationally designed targeted molecular therapies to treat the underlying drivers of the disease. Clinically, 80% of women diagnosed with advanced ovarian cancer initially respond to the combination of taxane- and platinum-based chemotherapy; however, the majority of them relapses after one year and respond poorly to additional chemotherapy due to the development of drug resistance. Thus, circumventing chemoresistance to commonly use first-line agents requires innovative strategies that could ultimately improve the outcome of adjuvant therapy and result in prolonged disease-free interval and survival. This study which focused on the identification and functional assessment of key miRNAs that are involved in ovarian cancer chemoresistance lead several important findings that expand our knowledge on miRNA biology, uncovers a novel miRNA that could be used as a prognostic biomarker as well as a therapeutic target. The miRNA signature we uncovered may eventually help predict patients' response to clinically available first-line agents and thus provide guidance for the selection of tailored chemotherapeutic regimens in order to decrease the incidence of recurrence. Lastly, uncovering that one of the miRNAs, miR-181a, drives chemotherapy resistance through the maintenance of cancer stem cells also strengthens the rationale to uncover compounds that inhibit this miRNA.

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.*

What was the impact on technology transfer?
Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

CHANGES/PROBLEMS
Nothing to Report

PRODUCTS

Manuscripts:

1. Fishman D, Wang F, DiFeo A and Narla G Quantitative PCR array identification of microRNA clusters associated with epithelial ovarian cancer chemoresistance. Gynecologic Oncology 120 (2011) S2–S133
2. Nagaraj A, Joseph PL, DiFeo A miRNAs as Prognostic and Therapeutic Tools in Epithelial Ovarian Cancer. Biomark Med. 2015 Mar;9(3):241-57.
3. Parikh A, Lee C, Joseph P, Marchini S, Baccarini A, Kolev V, Fruscio R, Shah H, Mullokandov, Fishman D, Romualdi C, D'Incalci M, Rahaman J, Kalir T, Redline RW, Brown BD, Narla G, and **DiFeo A.** miR-181a induces TGF-β-mediated epithelial-to-mesenchymal transition and promotes epithelial ovarian cancer progression. *Nat Commun*. 2014;5:2977. doi: 10.1038/ncomms3977.
4. Nagaraj A, Joseph PL, Kovalenko O, Singh S, Resnick K, Zanotti K, Waggoner S, **DiFeo A** Wnt/β-catenin signaling regulates platinum resistance in ovarian cancer. Oncotarget. 2015 Jun 29.
5. Enrica C, Paracchini L, Fruscio R, **DiFeo A**, Ravaggi A, Clivio L, Katsaros D, D'incalci M, Marchini S, Romualdi C Integrated analysis to identify regulatory networks associated to patients survival with stage I epithelial ovarian cancer *JCO* (under review)

Employment:

1) Received an Impact Score of 15 which was in the 1st percentile on an R01 application based on preliminary data obtained from the grant.

2) Promoted to a tenure-tracked Assistant Professor at the Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH in 2012

3) Received Norma C. and Albert I. Geller Designated Professor In Ovarian Cancer Research in 2013

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	*Analisa DiFeo*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	0000-0001-8319-6763
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:	Analisa DiFeo
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-8319-6763
Nearest person month worked:	12
Contribution to Project:	Dr. DiFeo oversaw all experiments and interpreted the results. She guided the progress of the project.
Funding Support:	Mary Kay Foundation and Ovarian Cancer Research Fund-Liz Tilberis Award

Name:	*Peronne Joseph*
Project Role:	*Research technician*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*12*
Contribution to Project:	Peronne performed all the experiments outlined in the grant proposal including the miRNA qPCR array on the key miRNAs that have been identified in the cell culture resistance model using 384-well customized qPCR array in the RNA samples obtained from the clinical cohort of patient specimens. She will also perform data analysis to correlate those miRNAs expression with patient response to cisplatin and other clinicopathological parameters. She also ascertained the biological relevance of each miRNAs. Peronne Joseph was responsible for data analysis, the preparation of scientific reports and manuscripts for publications.
Funding Support:	

Name:	*Anil Belur Nagaraj*
Project Role:	Post-doctoral Fellow
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3*
Contribution to Project:	Anil was responsible for the experimental design and data evaluation related to the lentiviral-based miRNA sponge/decoy vectors and pre-clinical mouse model experiments. He also helped with the preparation of manuscripts and presentations related to the overall project.
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report

What other organizations were involved as partners?
Nothing to Report