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14. ABSTRACT During the fourth year of this award, all objectives outlined in the original application in support of this virtual training program, in support of early career investigators, were completed. These include: i) oversight and review of all training program members' research progress, ii) initiation of cooperative research projects, continuation of monthly webinar series, consisting of research reports, career development, leadership training, and team science project planning. iii) expansion of an Academy website, iv) engagement of Academy members with advocacy community, v) promotion of Academy members in national networks, on review committees, and as meeting presenters, v) designed and implemented an annual workshop, including the development of a leadership curriculum, vi) Implemented metrics for program evaluation; measured these metrics during the fourth year; distributed base line and year four instruments; collected and analyzed data from base line responses and year one, and collected data from all participants through end of year 4 (data analysis ongoing).					
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1. INTRODUCTION

The failure to make meaningful progress toward the timely diagnosis and treatment of epithelial ovarian cancer has as much to do with the culture of biomedical research as it does with the complexity of this disease. The recognition of these complexities, as well as of the unusually small number of scientists committed to a career studying ovarian cancer, provided the basis for the inspired call by the DOD OCRP Integration Panel in 2009 to establish an innovative new virtual Ovarian Cancer Academy. In the context of this award, we have designed a training program to help Early Career Investigators (ECIs) work smarter, not harder, to experience and appreciate the value of ‘team-based science,’ and to find ways to value and incorporate, in real time, the ideas and energy of consumer advocates into the ovarian cancer research process. We also propose to institute methods of both trainee and program evaluation at this early stage in the development of this virtual Academy. This will not only to document the potential benefits of this new way of approaching investigator training, but also generate the data necessary to continuously shape the future of this Academy into the most high impact and cost-, time-, and energy-efficient training program it can be.

2. KEYWORDS

Provide a brief list of keywords (limit to 20 words).

Ovarian cancer; early-career investigator; career development; mentorship; research training; leadership training; consumer advocate; patient advocate; professional development; virtual; team-based science.

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1: Facilitate communication and collaboration among all of the ECIs, designated mentors, ovarian cancer research and patient advocacy communities.

Major Task 1: Manage overall research and career progress of Ovarian Cancer Academy Early Career Investigators

Subtask 1: Oversee and manage ongoing and new Ovarian Cancer Academy research, for existing and to-be-added Ovarian Cancer Academy Early Career Investigators and evaluate the progress of research projects with the goal of advancing the research. This would include reviewing, assessing and providing substantive suggestions for: Research progress and future directions, Manuscripts for publication, Development of grant applications for future funding, Presentations at national and other scientific meetings.

Subtask 2: Develop and design a cooperative research project during monthly virtual meetings and during annual workshops

Subtask 3: Arrange for monthly virtual meetings with appropriate telecommunications technology. Dr. Levine will be responsible for the technical and logistic aspects of the meetings. Drs. Maihle and Levine will share the responsibility of creating monthly agendas and moderating the conferences.

Milestone #1: Monthly meetings running successfully

Major Task 2: Facilitate communication and collaboration external to the Academy, which includes creating an Academy website and making it available in the public domain, this will be coordinated with the DoD OCRP

Subtask 1: Create an Academy website

Milestone #2: Website available in the public domain and was revised and updated during the past year’s award period. Updating/editing is ongoing.

Subtask 2: Maintain and expand the Academy website

Subtask 3: Engage Academy members with advocacy community

Subtask 4: Position the Academy members in national networks as committee members, reviewers, and speakers

Milestone #3: ECIs have national roles in science and medicine

Specific Aim 2: Design and implement an annual workshop and develop and administer a leadership curriculum.

Major Task 3: Develop annual workshops and leadership curriculum

Subtask 1: Prepare logistics for workshops

Subtask 2: Create agendas and materials for workshops

Milestone #4: First workshop successfully completed

Subtask 3: Improve leadership skills of the ECIs (beginning at end of year 1)

Specific Aim 3: Develop and measure metrics to determine the success of this training program through program evaluation studies.

Major Task 4: Develop metrics for program evaluation

Subtask 1: Assemble program evaluation team

Subtask 2: Identify or create instruments for evaluation

Milestone #5: Evaluation instruments available (beginning at end of year 1)

Major Task 5: Perform program evaluation (beginning at and of year 1)

Subtask 1: Evaluate ECIs in scientific and leadership development (beginning at end of year 2)

Milestone #6: Program evaluation reports generated (beginning at end of year 2)

Subtask 2: Evaluate the Academy as a program (beginning at end of year 1)

What was accomplished under these goals?

AIM 1/TASK 1/Subtask 1: Oversee and manage ongoing and new Ovarian Cancer Academy research, for existing and to be added Ovarian Cancer Academy Early Career Investigators; evaluate the progress of research project with the goal of advancing the research.

This task has largely been accomplished, and continues on an ongoing, iterative basis through the evaluation of Academy Scholar research progress by the Academy leadership, peers, and assigned primary and secondary mentors, during the monthly webinars, as well as during site visits to Scholar's home institutions and/or meetings with Scholars during the annual Workshop. During the past year the Dean and Assistant Dean have provided ongoing career and professional advice to one of the OCA's Scholars, Dr. Wa Xian. Dr. Xian had some professional discord with her supervisor at her institution. Through numerous conversations by email, telephone, and teleconference, the Deans provided advice and guidance regarding conflict resolution. The advice was generally appreciated and followed, in part. Ultimately, Dr. Xian decided to leave her current position and seek additional employment within the local area. After one opportunity fell through, she was able to find a full time position at the University of Houston. Her DOD award is nearing conclusion and will not be transferred to her new institution.

Additional site visits are planned by the Dean and Assistant Dean during this fifth year of the OCA award. The goal of the Dean/Assistant Dean is to visit as many Scholar's programs as possible in accordance with the Scholar's schedules. The leadership also continues to monitor research progress through presentation of Scholar's research during monthly webinars, as well as through review of slide presentations for national/regional meetings, and also by participating in a mock study section held as a component of the annual OCA Workshop. The leadership also provides written feedback to scholars on drafts of manuscripts, as well as through individual interactions during other regional/national meetings.

AIM 1/ TASK 1/Subtask 2: Develop and design a cooperative research project during monthly virtual meetings and during annual workshops.

Several presentations regarding cooperative research have occurred during this reporting period. A portion of the 2019 Academy's Annual Workshop was devoted to revising/renewing team commitments to various teams or team projects. One team project has proceeded very nicely. The investigators have been meeting on a regular basis and have submitted two R01 applications. In the first R01, Dr. Mehta was the contact PI, and Drs. Yang

and Zamarin are co-PIs. In the second application, Dr. Yang is contact PI, Dr. Mehta is a co-investigator, and Dr. Tushir-Singh is a key collaborator. Dr. Cho, who is an OCA mentor, provided a letter of support. Regulatory documents have also been completed and materials and methods have been transferred between institutions. The Assistant Dean has helped coordinate these efforts and has provided research support for this team science experiential project. Specifically, the Assistant Dean has performed single cell sequencing for the team's exploratory project. Patient cancer cells were collected by Dr. Zamarin at MSKCC. They were then cultured by Dr. Mehta at the University of Michigan using her hanging drop assay and treated with carboplatin chemotherapy. Dr. Yang at Yale prepared single cell libraries for RNA sequencing and quality control testing. The Assistant Dean then performed additional quality control testing and single cell sequencing at NYU. Data analysis is ongoing. This experience has had multiple positive interactions for the Scholars including, but not limited to, real scientific exchange across junior and senior Academy members.

AIM 1/TASK 1/Subtask 3: Arrange for monthly virtual meetings with the appropriate telecommunications technology.

Monthly Webex-based webinars continued to provide the basis for monthly research updates during year 4, as well as professional development sessions (see topics/speakers list in Appendix A). The past year's format for these webinars continued our changes based on input from the Scholars' and webinar evaluation data. The goal in making these changes was for the monthly Scholar research presentations to become less 'perfunctory,' and critically more interactive, which is one of the challenges with using any virtual communication format. The format that is now adopted for all webinars is as follows: i) provision of the presenter's slides at least one day *prior* to the next day's webinar, ii) inclusion of a list of discussion questions that the Scholar wishes to solicit feedback on in one of those slides; iii) reduction in the number of slides presented (typically no more than 5-10). This change in format has resulted in greater satisfaction by the Scholars. The OCA Leadership has observed more frequent and longer discussions among the Scholars/mentors following these presentations and generally 'richer' content during these discussions. Rare technical challenges continue to occur, but overall, the Scholars (and leadership) have become very comfortable using this technology. All participants are asked to comment (via survey links sent out the same day as the webinar is held), but often we only get feedback if a problem has occurred. The Dean and Assistant Dean work collaboratively (biweekly conference calls) to develop new and stimulating professional skills development programming, and also to review each month's performance by each Scholar (research progress, presentation skills, mentor's engagement, etc.).

AIM 1/TASK 2/Subtask 1: Create an Academy website.

The new Ovarian Cancer Academy website has been completed: www.ovariancanceracademy.org. This website has been live since September 15, 2016.

Subtask 2: Maintain and expand the Academy website.

During Summer 2018, this website was updated. The challenge of maintaining up-to-date and accurate information of this website is ongoing. One future goal may be to turn to a 'self service' model of maintenance (by the Scholars) in addition to expanding its content. There are continual updates with Scholar publications and archiving of select presentations. The website is due for an overhaul in the next 12-18 months.

Subtask 3: Engage Academy members with advocacy community.

Academy members were engaged with the advocacy community through six different activities during Year 4. During the annual workshop, the Academy met with community leaders from the Centers for Disease Control and learned about their outreach efforts and public education regarding ovarian cancer prevention and early detection. There were a number of speakers including representation from clinical translation, scientific support, policy, and epidemiology. The evening concluded with a talk from local advocate Ms. Amy Breitmann, who founded Lydia's Project. Lydia's Project provides free services to women and girls anywhere facing any type of cancer. This support includes ongoing correspondence and encouragement every month for at least twelve

months. They fund rent, utility, medical supplies, and prescription assistance to women who are unable to afford these basic expenses while undergoing cancer treatment and who reside in Georgia. There were also lectures from the American Cancer Society highlighting the public face of interactions between cancer research, support services and patients/advocates.

Scholars were paired with senior research experts (matched to their research interests) during a ‘Meet the Expert’ roundtable discussion at the 2019 AACR Advances in Ovarian Cancer Research Meeting held in Atlanta, GA. These were well attended sessions, covering diverse topics in the field of ovarian cancer research (e.g., ‘Early Detection’) and were particularly appreciated by the large number of consumer advocates in attendance. In the coming year, the Assistant Dean is one of the co-chairs of the 2020 Rivkin Symposium and will be well-positioned to include Academy Scholars in various aspects of interactions with advocates and scientific leaders.

Subtask 4: Position the Academy members in national networks as committee members, reviewers, and speakers.

All 2018 Scholars participated in, and were recognized in the program for their participation on, the Program Planning Committee for the 2018 Rivkin Annual Ovarian Cancer Research Symposium, held in Seattle, WA in Sept., 2018. These Scholars have written a meeting report that was published in a special issue of the *International Journal of Gynecological Cancer* in 2019. One advocate also had an independent article that was included in this publication (Appendix C). The Scholars have also served as grant reviewers, study section members, and journal reviewers. They have been invited to speak at various national and international symposia, including four current Scholars and two Academy alumni giving oral presentations at the 2019 AACR Advances in Ovarian Cancer Research Meeting held in Atlanta, GA. Academy members participate on NRG Oncology committees serving as members and vice-chairs.

AIM 2/TASK 3/Subtask 1: Prepare annual OCA Workshop

The fourth Annual OCA Workshop was efficiently planned and completed. The workshop was held Sept. 12-13, 2019 in Atlanta, GA. This year’s workshop was planned as a doorstep meeting in conjunction with the 2019 AACR Advances in Ovarian Cancer Research Meeting, also held in Atlanta, GA, to provide time efficiency and economy for all OCA participants.

Subtask 2: Create agenda and material for annual OCA Workshop.

The Fourth Annual Academy Workshop agenda (Appendix B) was designed by the OCA Leadership, in consultation with their Science Officer, to focus on four specific areas: 1) Our Academic Partners at the Centers for Disease Control and Prevention; 2) Effective advocacy; 3) Interacting with other key cancer organizations; and 4) Building Your Research Network through grant applications and team science. One highlight of this year’s Workshop was the visit to the CDC. We spent the entire afternoon interacting with members of the ovarian cancer CDC team, culminating with tours of the national HPV virology laboratory (in the same building as the coronavirus laboratory) and a visit to the Emergency Operations Center. This Workshop was successfully completed on September 13, 2018 in Atlanta, GA, and informal (written) feedback from all participants (mentors and Scholars) was that this continues to be a valuable and enjoyable experience.

Subtask 3: Improve leadership skills of the ECIs (beginning at end of year 1)

In the fourth year of the award, several monthly webinars included programming geared toward leadership developed (see Teleconference List – Appendix A). In the early part of the year, we covered topics related to translational research and working with industry. We had representatives from Big Pharma, NCI NCTN, and FDA. In the later part of the year, we focused on personal growth and wellness with talks on happiness and organization. The fiscal year concluded with our first session on communication, which will be the theme for

the upcoming semester. During these sessions on translational research, Scholars learned how to take research from the lab into the clinic with options to include investigator-initiated trials with Big Pharma, committee approval through the NCTN cooperative group mechanisms, and what sort of criteria the FDA is concerned with during various aspects of drug development. Part of being a good leader is being resilient through difficult challenges that arise during the course of scientific research. The sessions on happiness and organization will be personally beneficial to the Scholars and also provide them with skills to disseminate through their research groups and interactions. Communication skills will make their research travel more broadly and position them for additional peer review funding.

AIM 3/TASK 4/Subtask 1: Assemble program evaluation team and coordinate ongoing evaluation tasks.

The personnel identified in the original application, Drs. Lara Stepleman and N. Maihle worked together during Year 4 of this award (including a team of evaluators, Ms. Sarah Egan and Dr. Tasha Wyatt) to conduct the performance evaluation tasks. Monthly meetings were held to review evaluation needs/tasks, to review monthly (anonymized) webinar data, workshop data, and to plan for future evaluation tasks, as well as to complete the ongoing requirements associated with the Medical College of Georgia IRB protocol associated with this award in support of these observational studies. Evaluation data for the program during the past year of this award are being evaluated and will be included as a component of the final progress report.

Subtask 2: Identify or create instruments for evaluation

Validated instruments have been developed, IRB approval has been granted, and annual survey data collection are ongoing (3 collection points per year: Entry, 6 mos, and 12 mos). These assessments include: a baseline instrument for assessment of skills and attitudes before the implementation of this new training program, an instrument for a 6 month evaluation of performance, and a 12 month evaluation. In addition, a smaller instrument has been developed to obtain ongoing feedback (anonymously) regarding the utility and content of the monthly webinars on a real time (monthly) basis to facilitate continuous improvement of this programming. To date, our program evaluation data has shown no ‘improvement’ in Scholar aptitudes across a wide range of metrics. For this reason, the Dean consulted with an expert in the evaluation of federally-funded training programs to discuss these interim program evaluation data and options for corrections going forward. Two suggestions were proposed which we plan to implement going forward. First, it is apparent that we are working with a selected pool of investigators who (self) score very highly during their baseline assessment in most categories being evaluated; hence, there is little ‘room for increase’, especially over a short time frame (e.g. 2-3 years). Second, the instruments being used have a significant level of duplicative information being collected (at 3 different time points each year, from all participants); as a result, sometimes data are incomplete because surveys are started but not completed (average time for completion for each time point exceeds 30 min per session).

AIM 3/ Task 5: Perform program evaluation

The three instruments scheduled for development and distribution during Year 4 have been distributed. Data from all three time points has been collected, and data analysis is ongoing. As described above, we will continue and complete the quantitative analyses originally proposed for evaluation of this program, making only minor changes to the instruments being used to ensure completion of each survey and hence the collection of complete data sets for each time point.

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

All components of this training program are geared, at some level, toward training and professional development.

How were the results disseminated to communities of interest?

OCA's external-facing website has been developed and is updated on an ongoing basis. In addition, a 'Meet the Expert' table was fielded by Academy trainees in partnership with senior scientists matched to a given Scholar's research area/expertise during the 2019 AACR Ovarian Cancer Research Meeting. This provided both advocates and other (ovarian cancer) investigators the opportunity to learn more about ovarian cancer research and, importantly, about the Ovarian Cancer Academy. Drs. Maihle and Levine also show OCA slides (recruitment and informational) during various research presentations nationally to educate and promote the activities of the Academy to other interested academics as well as to prospective trainees.

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

See outline of remaining Aims/Tasks, above, and as originally outlined in the Statement of Work for schedule. All tasks have been completed and are ongoing due to the administrative and mentoring nature of this award.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Scholars continue to communicate a real sense of 'pride' during their attendance of the annual workshop and research symposium – pride at being a part of such a prestigious group of Scholars! Academy Scholars continue to publish papers in high impact journals and compete for federal funding. These observations support the notion that, during the short time since its inception, the Ovarian Cancer Academy has had an impact on the Scholars in terms of their leadership abilities (and confidence), and a strong sense of cooperativity and collaboration, as opposed to competitiveness. In addition, the OCA has increased the numbers of and enhanced the visibility of these Scholars – and hence, the field of ovarian cancer– throughout the country. In fact, some of our Scholars have been invited presenters at international symposia. Their national and international scientific presentations have led to interactions within the Academy, as well as with senior leaders within the ovarian cancer research community. Moreover, the mentors – similarly, expressed strong feelings toward their pride in participating in this important forum, during our feedback session at the Annual Workshop. They themselves enjoy the opportunity to participate together in training the next generation as well as to network with each other.

In Major Task 1, we aimed to facilitate communication and collaboration within the Academy. Our monthly webinars and the annual workshop allowed early career investigators to comment on and improve each other's research projects, as well as to receive criticisms and suggestions from the mentors. In Major Task 3, we completed the fourth annual workshop that had a major component on interactions with external ovarian cancer communities as it related to both leadership development and team building. These activities impact the management styles of the principal investigators, making them aware of the value of differences in perspectives, whether they are among peers or among the participating advocacy community. Over time, this Workshop and other activities of the OCA have enhanced Scholar success in competing for research funding. We predict all of these leadership and professional development activities will impact the successful conduct of individual ovarian cancer research projects well into the future, which will in turn result in improvements in ovarian cancer patient survivorship and quality of life.

The Scholars have been highly successful in a collaborative team science project, based on their planning during the monthly webinars, as well as during the Annual Workshop (Major task 1, subtask 2). This project is being conducted in the context of career development presentations to make the Scholars aware of the benefits of conducting team science, including their ability to leverage the various skill sets of all participants within the Academy to create a synergistic project that will ultimately compete for external funding while incorporating the perspectives of consumer advocates. We predict these interactions will lead to lifelong relationships among Academy participants that will result in the sharing of data, resources, and expertise. This will promote not only the future success of all Academy participants but also, over time, will result in the more effective translation of

what is learned in the laboratory into clinical practice. We further predict that these collaborative interactions will result in new ways of approaching scientific investigation among the Scholars, as well as the development of intangible support between investigators.

What was the impact on other disciplines?

During the past year the OCA Dean was contacted by an NCI Training Branch Program Director, as well as an NIH GM Program Officer, to inquire about the design and function of the OCA, and these interactions are ongoing. In addition, the Dean consulted on the development of a second DOD-sponsored virtual training program in the area of Kidney Cancer; that Academy came into existence in FY20. There is clear interest in this still relatively new approach to biomedical research training and particular interest in the way it breaks down previously 'permanent' silos within the cancer research and research training industry. The existing silos are geographic proximity, single institution training programs, and also barriers to inter-professional and interdisciplinary training (e.g., Dr. Nabel's work is funded by NASA, and he spoke to us during the 2019 OCA Workshop about the probability of the existence of 'extra-terrestrial life').

This interest speaks in support of the early favorable impressions among leaders in the cancer research and biomedical research communities regarding the OCA's methods regarding leadership and professional development training for early career investigators across disciplines. There is interest in how the OCA's approach to 'virtual' training might impact other cancer researchers in other disease sites through dissemination of the OCA's methods and best practices. For example, our grantsmanship training has already provided the OCA Scholars a competitive advantage in obtaining research funding during an exceptionally competitive period for research funding. More importantly than such successful competition for limited resources, however, is that OCA Scholars are clearly beginning to think more deeply about what it means to be a scientist, such as their responsibilities as burgeoning leaders not only in the field of ovarian cancer research, but also in the biomedical research enterprise, as well as in their respective institutions. They are learning to turn to each other with a growing sense of the importance of peer mentorship, as well as cooperation and collaboration in science. The biomedical research enterprise and the institutions that conduct research are very different than they were ten years ago, and these young leaders will, of necessity, need to be pioneers in what it means to maintain integrity while simultaneously advancing the field in addition to their own careers, while supporting each other and their patients.

The Assistant Dean was appointed as Chair of the NCI Cancer Biomarkers Study Section during FY19. This will allow his efforts as part of the Academy to be shared with peer reviewers of funding applications, and though he will not influence any review criteria for NIH scoring, he will be in contact with leaders in the field of biomarker research throughout the country.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

The activities of this growing 'community of scholars' have begun to influence the patient community and the public in general. The early success of the OCA and its participants has stimulated the thinking of not only consumer advocates, but the public as well. At a time when cynicism in our country, and particularly cynicism regarding government programs and all things medically related (based on the press as well as often negative personal experiences), is rapidly increasing, the OCA has provided a forum for young altruistic scholars to be encouraged to think philosophically about the scientific community and its responsibilities. These responsibilities are to our patients, to medicine, to the research community, and to the greater public good. Currently, scientific literacy and the importance of evidence-based decision making are experiencing insecurities. To combat that, we are training leaders who are not only confident in the importance of working together to ensure our country expands its interest in and commitment to biomedical research, but also its

understanding of the research enterprise, of fundamental scientific tenets, and particularly of data-driven decision making. While simultaneously, these serious young scholars also exemplify the ‘fun’ and ‘success’ to be gained while doing so! These outcomes, in addition to the contributions of these young scholars to the encouragement and sometimes tangible benefits we can offer ovarian cancer patients, are just the beginning signs of the impact that this new program is likely to have over the longer term. They are effectively changing the culture of science, slowly but surely, away from the long tradition of success through ‘rugged individualism’ and toward the synergy and joy that can be found by working cooperatively and creatively together. The Ovarian Cancer Academy website, discussed below, provides public knowledge about the research activities of the early career investigators as well as general knowledge regarding the Academy composition and purpose to the public-at-large. By demonstrating the way in which scientists can and should collaborate – with respect across disciplines, backgrounds, and perspectives – the Academy may reshape the pervasive public perception and attitude that scientific research occurs in silos without interaction between investigators. The perception of the lack of interaction among scientists also implies limiting the communication of discoveries (or the discovery process) to the public and with limiting the recognition of the invaluable contributions that can be made by working in synergy with the consumer advocacy community.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

During the last year, the Dean relocated her research program from the Medical College of Georgia, where she was serving as Associate Director of the Georgia Cancer Center, to the University of Mississippi Medical Center’s Cancer Center and Research Institute (UMMC), where she will also serve as Associate Cancer Center Director. Her new leadership appointment was effective October 22, 2018. Her new Center Director, Dr. John Ruckdeschel (founding director of the Moffitt Cancer Center) is pleased not only with her recruitment, but also at the prospect of serving as the ‘host’ institution for this prestigious and important new training program, and in doing so, piloting an entirely new way of preparing the next generation of ovarian cancer investigators.

Because of this transition, a few modest changes are being proposed in the evaluation component (Aim 3) during the coming year of this award. All of the original aims of this proposal will still be completed within the scope of the budget as awarded. However, we propose to replace Dr. Stepleman’s effort (5%) with a consulting contract for her services in support of this training program. Dr. Stepleman will remain the PI of the IRB protocol that supports the observational studies associated with this program through the end of this award. Dr. Stepleman has enjoyed her interactions with this program’s leadership and plans to remain engaged in this collaboration as a consultant for the duration of this award, including publication of our evaluation results. Her invaluable insights during the development of this program as well as her continued interest in and support for this training program are recognized and appreciated.

Dr. Maihle is in the process of requesting the transfer of this DOD award which supports the activities of the Academy. Augusta University has agreed to relinquish these funds; similarly, UMMC has agreed to accept the transfer of this award. We emphasize that this move will not affect the conduct of any of the proposed objectives or the scope of the work to be performed, as outlined in the Statement of Work or the objectives of this Award, or the proposed budget supporting these activities.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
None.

6. PRODUCTS

• Publications, conference papers, and presentations

A manuscript by the OCA trainees, in collaboration with Dr. Deborah Armstrong and the Academy Deans, reviewing the proceedings of the 2018 Rivkin Ovarian Cancer Symposium, has been published during this reporting period in the *International Journal of Gynecologic Cancers*. Appropriate acknowledgement of the DOD OCRP awards supporting these OCA trainees who are co-authors, as well as the award supporting the OCA’s programmatic activities, have been made in this manuscript.

• Website(s) or other Internet site(s)

As previously described, in year 1 of this award, a new website for the Ovarian Cancer Academy was created and can be found at www.ovariancanceracademy.org. The website went live on or about September 15, 2016. The website serves the following two purposes: 1. To disseminate information about the Ovarian Cancer Academy to the public and 2. To provide a resource for communication within the Academy. As a public facing website, it contains general information about the Academy, how to apply, and information regarding current awardees. It also highlights research awards, publications, and other accomplishments of the Academy early career investigators. As a resource for internal communication, the website houses recording of most of year 1’s monthly webinars as well as an archive of slide sets/presentations regarding professional development. In year 2, the website was indexed in major search engines. During Year 3, information related to the OCA was updated, and continued updates to both the inward and outward facing interfaces are anticipated, as proposed in our original application. These updates will include information on all Academy members, consistent with the original goals outlined of this program.

• Technologies or techniques

Nothing to Report

• Inventions, patent applications, and/or licenses

Nothing to Report

• Other Products

Nothing to Report.

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

The leadership of the Academy during year 4 of this award has remained Dr. Nita Maihle, Academy Dean, and Dr. Douglas Levine, Assistant Academy Dean. They have been supported in their activities by Dr. Christina Jordan, Project Coordinator (UMMC), and Ms. Maureen Soltren, Project Manager (NYU).

The table, below, summarizes the participating early career investigators, as well as their primary and secondary mentors:

ECI	PRIMARY MENTOR	SECONDARY MENTOR
1. Arend, Rebecca	Michael Birrer	Kunle Odunsi
2. Mehta, Geeta	Ronald Buckanovich	Kenneth Nephew
3. Johnson, Neil	Jeff Boyd	
4. Liao, John	Mary L. (Nora) Disis	Jonathan Berek
5. Yang-Hartwich, Yang	Melinda Irwin	Alessandro Santin
6. Mitra, Anirban	Kenneth Nephew	Ronald Buckanovich
7. McLean, Karen	Kathy Cho	
8. Rankin, Erinn	Jonathan Berek	Mary L. (Nora) Disis
9. Zamarin, Dmitriy	Carol Aghajanian	
10. Cubillos-Ruiz, Juan	Jose Conejo-Garcia	
11. Wa Xian	Christopher Crum	

12. Pepin, David	Patricia Donahoe	
13. George, Sophia	Brian Slomovitz	Ie-Ming Shih
14. Salvatore Condello	Daniela Matei	Kenneth Nephew
15. Rachel Vogel	Melisa Geller	Heather Nelson
16. Jogender Tushir-Singh	Sharon Stack	Charles Landen

Changes in active other support of the PI's or key personnel?

There have been no changes in Other Support for Dr. Maihle, or for the key personnel during the period of this award. Dr. Levine has received a DOD Omics Consortium Development Award: The DoD Omics Consortium to Study the Origins of Ovarian Cancer. The award dates are: 6/15/2019 – 6/14/2021 and effort is 0.6 calendar months. Dr. Levine also received a renewal award from the Honorable Tina Brozman Foundation for Clinical Development of an Implantable Nanosensor for Early-Stage Ovarian Cancer Detection. This will also have 0.6 calendar months of effort and the award dates are 01/01/19-12/31/20.

Name: American Association for Cancer Research

Address: 615 Chestnut St., 17th Floor, Philadelphia, PA 19106-4404 USA

Name: American Cancer Society

Address: 250 Williams Street NW, Atlanta, GA 30303

Name: Centers for Disease Control and Prevention (CDC)

Address: 1600 Clifton Rd. Atlanta, GA 30329-4027

Partner's contribution to the project: During the period of this award, the OCA collaborated with the American Cancer Society and the Center for Disease Control to provide programming for the Scholars during the Annual OCA Workshop, held in Atlanta, GA. The AACR also provided opportunities for OCA Scholars to participate in roundtable discussions with assigned senior faculty.

In addition, the Assistant Dean was an invited speaker at the 2019 AACR Ovarian Cancer Research Meeting. Many other OCA Scholars, Mentors, and Alumni participated as invited speakers as well. Furthermore, all of the Academy Scholars had posters during this conference. The AACR contributions to the Academy included: no financial support, no in kind support, no facilities, or personnel exchanges. Invited speakers participating in this symposium's presentations, including the Academy Scholars, were remunerated for their participation in this meeting by deferral of their meeting registration fee and reimbursement for their travel expenses. Hence, no financial contribution was made to any Academy member that was not made to any other conference presenter or organizer. The AACR also facilitated meeting space for the Academy workshop.

The CDCs contributions to the Academy included: no financial support, no in kind support, no facilities, or personnel exchanges. Representatives from the CDC participated in Day 1 of the Academy Workshop by providing meeting space for the Academy on the CDC grounds.

The ACS contributions to the Academy included: no financial support, no in kind support, no facilities, or personnel exchanges. Representatives from the ACS participated in Day 2 of the Academy Workshop and supported their own local travel expenses.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

The following items are contained in the Appendix, in support of this Annual Report:

- A. Listing of Monthly Webinars Dates, Speakers, and Topics (FY 2019)
- B. Fourth Annual Ovarian Cancer Academy Workshop Agenda (2019)
- C. *International Journal of Gynecological Cancer* Supplement (2019)

APPENDIX A: Listing of Monthly Webinars – Dates, Speakers, and Topics **(FY 2019)**

January 2019

RESEARCH PRESENTATION: Yang

Biotech stories - Paul Haluska M.D., Ph.D.; Global Director of Scientific Affairs, Oncology; Merck Research Laboratories

February 2019

RESEARCH PRESENTATION: Cubillos-Ruiz

Introduction to NRG Oncology – Mike Birrer M.D., Ph.D.; DOD Academy Mentor and Director, UAB Comprehensive Cancer Center

March 2019

RESEARCH PRESENTATION: Mitra

GOG/NRG biospecimen resources – Heather Lankes PhD, MPH; Director, Translational Research Operations

April 2018 (AACR Meeting in Atlanta, GA – OCA dinner for attendees)

May 2019

Understanding NCI Clinical Trials Programs: **Elise Kohn**, Head, Gynecologic Cancer Therapeutics, Clinical Investigations Branch, Cancer Therapy Evaluation Program, NCI

June 2019

Working with the FDA: Sanjeeve Balasubramaniam, MD, MPH, Medical Officer, FDA

July 2019

RESEARCH PRESENTATION: Liao

RESEARCH PRESENTATION: Mehta

PREPARATION FOR ANNUAL WORKSHOP – BRIEFING and SUGGESTIONS

(August 2018 - Summer Break)

September 12-13, 2019 – Annual OCA Workshop (Atlanta, GA)

October 2019

RESEARCH PRESENTATION: Tushir-Singh

Making it all Fit...Strategies to Promote Meaningful Growth and Development in Medicine: Richard M. Wardrop

November 2019

RESEARCH PRESENTATION: VOGEL

Happiness & Human Flourishing – Daniel L. Benkendorf, PhD

December 2019

RESEARCH PRESENTATION: Condello

SYMPOSIUM DEBRIEF/REVIEW PLANNING, WEBINAR SCHEDULES AND OTHER DISCUSSION

January 2020

Powerful Presentations: Tools for Filtering Details and Telling a Story: Melissa Marshall

APPENDIX B: Fourth Annual Ovarian Cancer Academy Workshop Agenda
(FY 2019)



2019 Ovarian Cancer Academy Annual Workshop

**The Westin Peachtree Plaza
210 Peachtree Street Northwest
Atlanta, GA 30303**

09/12/2019 – 9/13/2019

Leadership: Nita J. Maihle, Ph.D. & Doug Levine, M.D.

CDMRP Science Officer: Karen Wylie, Ph.D.

Thursday, September 12, 2018 Centers for Disease Control

EARLY CAREER INVESTIGATORS ONLY

- | | |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11:00am | Depart from The Westin Peachtree Plaza
210 Peachtree Street Northwest |
| 11:30pm | Arrive at the Centers for Disease Control
1600 Clifton Road, Atlanta, Georgia 30333
Proceed through security |
| 12:00-1:15pm | Welcome Luncheon at the CDC
Introductions & Purpose of the Meeting
<i>Nita J. Maihle, PhD and Douglas A. Levine, MD</i>
Overview of CDC/NCCDPHP/DCPC
<i>Kimberly E. Smith, MBA, MHA, Policy Team Lead, Division of Cancer Prevention and Control (DCPC), Centers for Disease Control and Prevention</i> |
| SESSION 1: COLLABORATIONS WITH CDC | |
| 1:15- 1:45pm | Overview of the Ovarian Cancer Academy
<i>Nita J. Maihle, PhD and Douglas A. Levine, MD</i> |
| 1:45 – 2:15pm | Overview of the CDC Ovarian Cancer Research Program and Activities
<i>Sherri Stewart-Querec, PhD, Scientific Support and Clinical Translation Team Lead, Division of Cancer Prevention and Control (DCPC), Centers for Disease Control and Prevention</i> |
| 2:15 – 3:00pm | Cross-Collaboration/CDC Datasets and Resources |

Sherri Stewart-Querec, PhD, Scientific Support and Clinical Translation Team Lead, Division of Cancer Prevention and Control (DCPC), Centers for Disease Control and Prevention

Sun Hee Rim, PhD, MPH, Epidemiologist, Division of Cancer Prevention and Control (DCPC), Centers for Disease Control and Prevention

Mary Puckett, PhD, Health Scientist, Division of Cancer Prevention and Control (DCPC), Centers for Disease Control and Prevention

3:00 – 3:15pm

Group Summary/Next Steps and Discussion

Kimberly E. Smith, MBA, MHA, Policy Team Lead, Division of Cancer Prevention and Control (DCPC), Centers for Disease Control and Prevention

Vikram Mohan, JD, Policy Analyst, Division of Cancer Prevention and Control (DCPC), Centers for Disease Control and Prevention

3:15 – 3:30pm

Break - Move to tour buildings

3:30 – 4:00pm

Tour buildings (Labs and Emergency Operations Center)

4:00pm

Depart from the Centers for Disease Control

4:30pm

Arrive at The Westin Peachtree Plaza

4:30 – 6:30pm

Check in to hotel – Break on your own

SESSION 2: NETWORKING WITH ALUMNI & PERSPECTIVES IN ADVOCACY

ALL ACADEMY MEMBERS

6:30 – 7:00pm

Networking Reception with OCA Alumni at White Oak Kitchen & Cocktails

7:00 – 9:00pm

**Dinner and Presentation –
White Oak Kitchen & Cocktails
270 Peachtree St NW, 100, Atlanta, GA 30303**

***Guest Advocate, Ms. Amy Breitmann, Augusta, GA
Founder ‘Lydia’s Project’***

Friday, September 13, 2018

The Westin Peachtree Plaza

7:30-8:00am

Continental Breakfast - Chastain Room
Coffee and Refreshments served

SESSION 3: GRANTSPERSONSHIP

8:00-8:30am

Opening Remarks and Moment of Silence
Karen Wylie, PhD, CDMRP Science Officer

8:30 -10:00am

OCA Mock Study Section
Scientific Review Panel (OCA Mentors/Advocates)

10:00 – 10:15am

Break

10:15 – 11:00am

Team Science

SESSION 34: REGIONAL NETWORKING

11:00 – 11:45am

Ovarian Cancer Research and Opportunities in Greater Atlanta area
Invited Guest Scientists

11:45-1:00pm

Networking Luncheon at the Chastain Room
*Keynote Speaker: Dr. William Phelps, Senior Vice President,
Extramural Research, American Cancer Society, Atlanta, GA*

***PLEASE COMPLETE YOUR WRITTEN EVALUATIONS BEFORE LEAVING-
WE WELCOME YOUR FEEDBACK!!!***

(AACR SYMPOSIUM – KEYNOTE SPEAKER – 6PM)

*(*The flyer below was distributed at the 2019 AACR Ovarian Cancer Symposium)*



DoD-Sponsored Ovarian Cancer Academy: 10 Years of Empowering Early Career Cancer Investigators*

Our ability to truly impact the lives of women diagnosed with ovarian cancer is dependent on our ability to discover new ways of diagnosing and treating this disease. Our slow progress on this front has as much to do with the culture of biomedical research as it does with the complexity of this disease. Recognizing the need for innovation in this area, in 2009 the DoD's Ovarian Cancer Research Program initiated a virtual training platform, intended to transcend geographic and institutional barriers, to support the career development of early career investigators committed to the study of this disease. Since that time, 18 new investigators have participated in the DoD-sponsored Ovarian Cancer Academy (OCA) – a novel training program designed to build a community of practice among scientists and physicians who have acquired the skills necessary to effectively collaborate - working toward the common goal of eradicating this disease. OCA Scholars work in solidarity with ovarian cancer survivors so that the patient's important perspective can be incorporated into the research process - sharing their ideas and passion toward the common goal of overcoming this disease. Please read more about this training program at: <http://www.ovariancanceracademy.org>.

The **leadership** of this year's OCA (Nita J. Maihle, Dean, Douglas A. Levine, Assistant Dean, Karen Wylie, Science Officer), the **OCA Scholars** (Rebecca Arend, Salvatore Condello, Juan Cubillos-Ruiz, Sophia George, Yang Yang Hartwich, Neil Johnson, John Liao, Karen McLean, Geeta Mehta, Anirban Mitra, David Pepin, Erinn Rankin, Jogender Tushir-Singh, Rachel Vogel, Wa Xian, and Dmitriy Zamarin), and their **OCA Mentors** (Carol Aghajanian, Mike Birrer, Jeff Boyd, Ron Buckanovich, Jonathan Berek, Kathy Cho, Jose Conejo-Garcia, Chris Crum, Nora Disis, Patricia Donohoe, Melissa Geller, Melinda Irwin, Chip Landon, Daniela Matei, Heather Nelson, Ken Nephew, Alessandro Santin, Sharon Stack, and Brian Slomowitz) are grateful to the Ovarian Cancer Working Group of the DCPC for the opportunity provided to the OCA Scholar's to site visit the CDC and learn more about their work. We look forward to continued interactions with this Group.

APPENDIX C: International Journal of Gynecological Cancer
Supplement (FY 2019)

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Introduction

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Introduction

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- s7** Genomics and molecular mechanisms of high grade serous ovarian cancer: the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium
E B Rankin

- s22** Survivor advocacy: I speak for those who can't
S S Powell



OPEN ACCESS

Introduction: the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium

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ABSTRACT

In September 2018, the 12th Biennial Ovarian Cancer Research Symposium was presented by the Rivkin Center for Ovarian Cancer and the American Association for Cancer Research, in Seattle, WA, USA. The 2018 Symposium focused on four broad areas of research: Detection and Prevention of Ovarian Cancer, Genomics and Molecular Mechanisms of Ovarian Cancer, Tumor Microenvironment and Immunology of Ovarian Cancer, and Novel Therapeutics: Response and Resistance of Ovarian Cancer. In addition, a special panel on the 'Role of Advocates in Ovarian Cancer Research' was featured.

In September 2018, the 12th Biennial Ovarian Cancer Research Symposium was presented by the Rivkin Center for Ovarian Cancer and the American Association for Cancer Research (AACR). The goal of this Symposium was to bring together clinicians and researchers from across disciplines and institutions worldwide to share new knowledge to advance the field of ovarian cancer research. The conference sought to enhance our understanding of this disease, with the intent of using this information to improve the prevention, early detection, and treatment of ovarian cancer.

A particular focus of this Symposium was the inclusion of early-career investigators during the planning process. During this year's Symposium, established scientists partnered with early-career investigators to facilitate each session. The 2018 Symposium focused on four broad areas of research: Detection and Prevention of Ovarian Cancer, Genomics and Molecular Mechanisms of Ovarian Cancer, Tumor Microenvironment and Immunology of Ovarian Cancer, and Novel Therapeutics: Response and Resistance of Ovarian Cancer.

The abstracts¹ from each of these research areas will be published in *Clinical Cancer Research*² and are reviewed in this supplement to the *International Journal of Gynecological Cancer*. Reflecting a priority of the Rivkin Center, to encourage and support young investigators in the field of ovarian cancer research, these reviews are authored by early-career investigators who are scholars in the Department of Defense-sponsored Ovarian Cancer Academy (OCA) (<http://www.ovariancanceracademy.org>). OCA members compete for these mentored awards through the Department of Defense's Congressionally Directed Medical Research Programme (<https://cdmrp.army.mil/ocrp/>).

The Rivkin Center (www.rivkin.org) was founded in 1996 by Swedish Cancer Institute medical oncologist Saul E Rivkin, MD (now retired), in memory of his wife, Marsha,

who lost her life to ovarian cancer. The organization provides seed funding for researchers exploring promising new areas of investigation in the field of ovarian cancer. Areas of priority include innovative research pilot studies, scientific scholar awards for new investigators, and bridge funding awards. To date, the Rivkin Center has awarded more than \$13 million in scientific research awards and has a goal to continue to increase its research funding annually. A major focus of the Rivkin Center has been the biennial meetings, held now for more than 20 years, to promote educational and intellectual interactions and collaborations across the spectrum of ovarian cancer clinical and basic science research.

In 2014, the Rivkin Center partnered with the AACR to broaden the scope of research opportunities and information sharing for investigators focused on the study of ovarian cancer. The AACR now organizes biennial fall research symposia alternating with the Rivkin meetings. This fruitful partnership has served to expand the range of clinical, translational, and basic science collaborations in the field of ovarian cancer research, as reflected in the spectrum of abstracts reviewed in the research summaries presented in this supplement. In addition to these summaries, a representative of the patient advocacy community has highlighted perspectives shared during the panel discussion on emerging roles for consumer advocates as medicine and biomedical research become more patient-centric.

Contributors This introduction was written by NJM and DKA, with contributions from DAL and KD.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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ReFeRenCeS

1. Symposium abstract book pdf. Available: <https://www.rivkin.org/wp-content/uploads/2018/09/2018-Ovarian-Cancer-Research-Symposium-Program.pdf>
2. Available: http://aacrjournals.org/site/Meetings/meeting_abs.xhtml



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Meeting report from the 2018 12th Biennial Ovarian Cancer Research Symposium detection and prevention of ovarian cancer

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Received 11 April 2019

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ABSTRACT

The objective of this review is to summarize recent research advances in the detection and prevention of ovarian cancer and discuss the experts' opinions of future directions. The 12th Biennial Ovarian Cancer Research Symposium was held in Seattle, Washington, in September 2018. At this meeting, experts in ovarian cancer research gathered to present and discuss recent breakthroughs and their visions of future ovarian cancer research. Session 1 of the symposium focused on the detection and prevention of ovarian cancer. It included two invited oral presentations from Ranjit Manchanda, MD, PhD (Barts Cancer Institute) and Rosana Risques, PhD (University of Washington). Another eight oral presentations were selected from abstract submissions. Fifteen abstracts were presented in poster format. These presentations covered topics including cellular origin of high-grade serous cancer, risk factors for ovarian cancer, new methods for early detection of ovarian cancer, mechanisms underlying ovarian cancer development, and new therapeutic approaches for preventing ovarian cancer from forming or progressing. In conclusion, a clear understanding of the cellular origin and molecular mechanisms underlying the initiation of high-grade serous cancer is essential for developing effective means for early detection and prevention of this most devastating type of ovarian cancer. Recognizing the complexity of ovarian cancer and appreciating that ovarian cancer is not a single disease will help us to generate proper models, design rational experiments, and collect and analyze patient data in a meaningful way. A concerted effort in the field will help to bridge the basic science and clinical applications and lead to more precise and effective detection and treatment.

Epithelial ovarian cancer is a disease with poor prognosis. It is the fifth most common cause of death from cancer in women, and is the most lethal of all gynecological cancers. The lifetime risk of a woman developing ovarian cancer is 1 in 71, and 1 in 200 women will develop ovarian cancer between their 50th and 70th birthday. Worldwide, 224 747 new cases of ovarian cancer are diagnosed annually and there are an estimated 140 163 disease-related deaths.¹ Ninety percent of all deaths from ovarian cancer are due to high-grade serous cancer, and this cancer sub-type accounts for 75% of all cases.² Despite recognition of the importance of early detection and rapid

progress in our understanding of the cellular origin of high-grade serous cancer, only 2% of cases can be identified at stage I.³ As a consequence, up to 80% of women present with stages III/IV disease, and the 5-year survival rate is just 30%. This severe mortality and poor survival rates have not changed much since the 1930s.⁴ Therefore, there is an urgent and unmet medical need for precise diagnosis and effective treatment for this disease at earlier stages, where the survival rate is >90%, as we have achieved in cervical cancer and breast cancer⁵ after the biology/origin of these two women's cancers were unraveled.

At the 12th Ovarian Cancer Research Symposium at the Rivkin Center for Ovarian Cancer in Seattle, Washington, one session focused on the detection and prevention of ovarian cancer. Diverse topics were covered in this session, including basic biological questions such as the cellular origin of high-grade serous cancer and clinical applications such as diagnostic markers for early detection. Dr Ranjit Manchanda (Barts Cancer Institute) presented a population-based test for ovarian cancer gene mutations. He discussed the limitations associated with the current system of genetic testing, based on clinical criteria/family history, and presented data supporting the promising outcome of population-based *BRCA* testing in the Jewish population. Dr Manchanda further extended the testing for established cancer genes in non-Jewish women and suggested surgical prevention is a cost-effective approach in women at high risk identified by this test.

Dr Rosana Risques (University of Washington) also presented her recent research on using ultra-sensitive sequencing tools for detection of ovarian cancer. The presentation by Dr Risque centered on deep sequencing of genital tract fluids for *TP53* mutations using techniques to identify very small numbers of affected cells. They demonstrated the presence of *TP53* mutations in these fluids in women with ovarian cancer and also in 100% of controls. These findings underline the fact that cells containing *TP53* mutations are present in the peritoneal or other genital tract fluids of virtually all women, increasing with age and in keeping with a 'pre-malignant mutation background' discussed in their previous paper.⁶ Interestingly, it complements the model proposed by Soong



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et al in a subsequent presentation, in which genetically altered but non-malignant precursor cells escape from the fallopian tubes and, in some instances, culminate in high-grade serous cancer in the peritoneal cavity.⁷ The two studies superimposed on prior work attest to both the frequency of *TP53* mutations in the fallopian tube and the likelihood that such cells commonly exist in the peritoneal fluid. The mechanism(s) by which malignancy occurs and who is at risk for a rare occurrence of malignant transformation remains to be determined.

In addition, Ms Heydrich and colleagues (Color Genomics) presented their studies in Texas supporting the benefit of providing broad access to genetic testing in the obstetrics and gynecology care setting. Using a next-generation, sequencing-based assessment of 30 genes associated with hereditary cancer risk, they identified 90 patients with increased risk for cancer among 1113 people included in this study. Significantly, 70 of the 90 identified as at increased risk had no significant family history of ovarian cancer and would not have been obvious candidates for screening. This finding suggests that broader genetic testing would be beneficial in identifying a larger set of patients at risk.

Developing rational and effective screening and cancer preventive strategies for ovarian cancer, particularly high-grade serous cancer, requires a better understanding of the origin of this disease. During the past decade, clinical and molecular evidence has increasingly suggested that many, if not all, cases of high-grade serous cancer arise from the fallopian tube.⁸ In the original serous carcinogenesis model, high-grade serous cancer was thought to arise through dissemination of tumor cells from serous tubal intra-epithelial carcinomas.⁹ However, many cases are found not to be associated with serous tubal intra-epithelial carcinomas. Drs Thing Rinda Soong and Christopher Crum (University of Washington and Harvard Medical School, respectively) presented data to support a new alternative model termed 'precursor escape'. In this model, a pre-cancerous lesion termed 'early serous proliferation' bearing *p53* mutations is found in the distal fallopian tube of patients with high-grade serous cancer.¹⁰ Their study indicates for the first time a lineage continuity between early serous proliferation in the distal tube and some metastatic high-grade serous cancer via shared, site-specific *TP53* mutations, explaining the apparent sudden onset of cancers without co-existing serous tubal intra-epithelial carcinomas. This new pre-cancer–cancer paradigm for high-grade serous cancer suggests that precursor initiation and progression to malignancy are separated spatially and temporally.

The study presented by Dr Burdette (University of Illinois, Chicago) explained why the ovary is the primary metastasis site for tumors derived from the fallopian tube. Using imaging mass spectrometry, Dr Burdette and colleagues found that norepinephrine and a series of new molecules may facilitate the colonization of fallopian tube-derived tumor cells on the ovarian surface. Therapeutic intervention blocking ovarian metastasis can be developed targeting pathways activated by these molecules.

Using genetic mouse models, Drs Shuang Zhang and Benjamin Neel (New York University-Langone Medical Center) showed that *PAX8*+ fallopian tube cells can be transformed in the presence of combined retinoblastoma inactivation and *TP53* mutations and give rise to serous cancer. Dr Zhang and colleagues also claimed that under the same conditions, ovarian epithelial cells can be transformed to form serous-like tumors. It is important to notice that

the serous-like tumors generated from transformed ovarian surface epithelial cells do not express *PAX8*, a hallmark of high-grade serous cancer, whereas the tumors generated from transformed fallopian tube epithelial cells express all the hallmarks of this cancer as shown in publications from various laboratories.^{11 12} A presentation given by Dr Sophia George (University of Miami) further investigated the fallopian tube as the site of origin of high-grade serous cancer by performing RNAseq analysis of fallopian tube from patients with and without *BRCA* mutations. The women carrying a deleterious mutation in the *BRCA1/2* genes have an increased risk of this cancer of up to 40%. Dr George and colleagues found that the fallopian tube epithelium of a *BRCA1/2* carrier shows distinct unique pre-neoplastic processes, such as increased metabolic activity and aberrant regulation of DNA repair pathways. Their study using a *BRCA* model may provide new insights into the early development of ovarian cancer.

Kendall Greening from Dr David Huntsman's laboratory (University of British Columbia) presented preliminary data suggesting that 42% of post-menopausal women had *p53* lesions in the fallopian tube. They plan to study the effect of the use of oral contraceptive pills and its association with >40% reduction in the risk of high-grade serous cancer by studying *p53* lesions in the fallopian tubes. Their study may disclose the impact of oral contraceptive pills on the earliest known precursors of serous cancer. Dr Angela Russo and colleagues (University of Illinois at Chicago) presented their work on the effect of loss of *PAX2* and *PTEN* in the fallopian tube epithelium.¹³ Their data suggested that loss of *PTEN* or *PAX2* mediated a cancer stem cell phenotype that initiates formation of high-grade serous cancer. These findings may help to define early events of carcinogenesis and help to refine the strategies of targeted therapeutics or marker discovery for early detection of serous cancer. Dr Kara Bernstein and colleagues (University of Pittsburgh) presented their work on characterization of cancer-associated mutations in the *RAD51* paralogs on homologous recombination proficiency. This may help us to develop more effective predictive models of targeted therapies, such as poly-ADP-ribose polymerase inhibitors. Using yeast 2/3-hybrid assays, they found that mutations in *RAD51* disrupted the interaction between *RAD51* and *XRCC2*, a protein required for the early response of *RAD51* to DNA damage,¹⁴ and subsequently affect homologous recombination proficiency.

Several presentations mentioned recent progress with tools to deal with the unmet clinical need for early detection of ovarian cancer. The recent discovery of fallopian tube as the site of origin of high-grade serous cancer has re-shaped strategies of early detection.¹⁵ For instance, Dr Jennifer Barton (University of Arizona) presented her work on a second-generation falloposcope for minimally invasive imaging of the fallopian tube. They propose to use this imaging test as an adjunct confirmatory test after an initial positive or suspicious blood test with known or recently uncovered markers for serous tubal intra-epithelial carcinoma lesions in their laboratory. Their continuous work on identifying sensitive and specific serum protein markers and optimizing the falloposcope may create a reliable and efficient detection method for general screening of the general population for early epithelial ovarian cancer.

Dr Amy Skubitz (University of Minnesota) and colleagues presented their work using Proseek Multiplex Oncology II plates to simultaneously measure the expression of 92 cancer-related

proteins in serum in order to bypass the inability of CA125 and HE4 screening of the general population to identify early-stage disease. Their analysis of women with advanced serous cancer compared with age-matched healthy women showed that CA125 alone achieved a sensitivity of 93.4%, but by adding five proteins to CA125, they increased sensitivity to 98.4%. They hope that this Proseek technology will help to identify biomarkers to improve the sensitivity and specificity of detection methods for early stages of high-grade serous cancer.

Dr Karen Belkic (Karolinska Institution) summarized the key achievement of the fast Pade transform in magnetic resonance spectroscopy for diagnosis of early ovarian cancer. Their meta-analysis showed that cancerous and benign ovarian lesions are inadequately distinguished via fast Fourier transform-based magnetic resonance spectroscopy. In contrast, the high-order, non-parametric fast Pade transform has clear display with identification and exact quantification of key metabolic transformation, including the ovarian cancer biomarker phosphocholine. Their next step is pursuing this strategy in vivo for diagnosis of ovarian cancer. Dr Kristin Boylan and colleagues from the University of Minnesota, also used mass spectrometry-based proteomics methods for early detection. They hypothesized that ovarian cancer cells can be detected during a routine Pap test performed for cervical cancer prevention. Given the convincing data supporting the fallopian tube as the site of origin of ovarian cancer, they think it is likely that ovarian cancer protein can be found in the lower genital tract, perhaps even in the early stages. Using the extract from patient's tumor tissue run on 2D-liquid chromatography tandem mass spectrometry, followed by bioinformatics integration, they identified thousands of protein markers shared by several patients, including well-known markers of ovarian cancer such as CA125. Their further analysis using patient-matched normal tissues will help to uncover cancer-specific markers that could be used for the quantification of proteins from Pap test fixatives and cervical swabs for ovarian cancer protection.

Dr Naoko Sasamoto (Brigham and Women's Hospital) and colleagues presented their efforts on improving the efficiency and accuracy of using CA125 as a prediction method. They hypothesized that the distinct personal characteristics among individuals contributed to the low specificity of CA125 as an ovarian cancer screening biomarker. Thus they proposed to identify personal characteristics that influence CA125 levels in order to create personalized thresholds for CA125, thereby improving its performance as an ovarian cancer screening biomarker. They conducted internal and external validation of two prediction models (linear and dichotomous) of circulating CA125 among post-menopausal women using 28 842 controls without ovarian cancer in four large population-based studies. Although both models appeared to provide some improvement to the CA125 method, a further fine-tuning of these models is required to increase the predictive ability of these models.

Estrogen-induced DNA damage may contribute to the early development of ovarian cancer.¹⁶ To overcome the technical challenges in detecting and analyzing the variety of different DNA lesions that are formed by estrogen compounds, Dr Kaushlendra Tripathi (University of Alabama) and colleagues have developed a new method. They used biotinylated estrogens to allow immunodetection of estrogen-induced DNA adducts by slot-blot and single-cell molecular cloning and proximity ligation assays. Using

this method, they quantitatively detected these adducts on DNA and showed that estrogen activates replication-associated DNA damage response and induces chromosomal instability. Thus, the biotin-labeled estrogens could be used as a tool to detect the early stage of ovarian carcinogenesis.

Several research groups presented their work on identifying risk factors for the development of ovarian cancer that might reduce its burden. Dr Kara Michels (National Cancer Institute) presented a study examining the association between metabolic dysregulation and development of ovarian cancer by a case-control study within the Surveillance, Epidemiology and End Results Medicare linked database. Their results suggest that individual components of metabolic syndrome, rather than the syndrome itself, are associated with ovarian cancer. Thus high levels of triglycerides are associated with an increased risk of high-grade serous cancer, whereas a high level of fasting glucose is linked with a reduced risks for this cancer.

Dr Holly Harris (Fred Hutchinson Cancer Research Center) and colleagues presented their work on the use of Mendelian randomization to examine the association between polycystic ovary syndrome and ovarian cancer. They evaluated the single nucleotide polymorphisms associated with polycystic ovary syndrome using publicly available data from genome-wide association studies. Based on seven associated single nucleotide polymorphisms, they found an inverse association between genetically predicted polycystic ovary syndrome and high-grade serous cancer and endometrioid tumors.

As full-term births have been known to be protective for ovarian cancer,¹⁷ Dr Alice Lee (California State University) and colleagues presented their work on incomplete pregnancies and risk of ovarian cancer based on the pooled epidemiologic data from 16 population-based, case-control studies from the Ovarian Cancer Association Consortium. They found that both incomplete and complete pregnancies are protective against ovarian carcinogenesis, although full births are more protective. The protective association is strongest for clear cell ovarian cancer and less apparent for high-grade serous cancer and mucinous ovarian cancers. Randomized trials and recent meta-analysis have shown better survival for women who took hormone therapy after their diagnosis in comparison with women who did not.¹⁸ Dr Celeste Pearce from the same research group (California State University) presented their study on the relationship between use of hormone therapy before ovarian cancer diagnosis. They analyzed 4700 patients with ovarian cancer recorded in the Ovarian Cancer Association Consortium and found that women who used hormone therapy before diagnosis had an 11% decreased risk of death compared with those who did not. It appears that the longer duration confers better survival in both serous and mucinous ovarian cancer.

Other factors linked with reduced ovarian cancer risks are higher parity and oral contraceptive use.¹⁹ In order to understand the association between the lifetime number of ovulatory cycles and ovarian cancer risk, Dr Britton Trabert and colleagues (National Cancer Institute) analyzed 3866 cases of ovarian cancer collected by the Ovarian Cancer Cohort Consortium. In this large prospective analysis of pooled cohort study data, they observed a positive association between increased risk of ovarian cancer of several histotypes, including serous, endometrioid, and clear cell tumors, but not mucinous tumors. Their data suggest that a DNA damage-rich

environment created by ovulation at the ovary surface and within the fallopian tube increases the risk of ovarian carcinogenesis.

Dr Faina Linkov (University of Pittsburgh) presented their study of 1840 patients with ovarian cancer at the University of Pittsburgh Medical Center facilities and concluded that intra-peritoneal chemotherapy showed enhanced long-term survival of patients. Since intra-peritoneal chemotherapy has not been widely used outside specialty hospitals, increasing its use in clinical practice for the treatment of patients with ovarian cancer may improve outcomes.

Christina Clarke (Kaiser Permanente Colorado) and colleagues presented a retrospective observational study of high-grade serous cancer to explore predictors of long-term survival, using data from five participating health plans in the Cancer Research Network. They confirmed that younger age, lower stage, and receipt of chemotherapy were statistically significantly associated with long-term survival.

In this session, a few researchers also presented their findings for the development of new approaches for early treatment. Tiffany Lam and colleagues (University of Minnesota) hypothesized that some tumor cells can evade initial chemotherapy treatment by entering a dormant state. They used a silica gel encapsulation platform to capture the subset of cells capable of dormancy. They observed a connection between cells' ability to enter dormancy and chemoresistance in ovarian cancer. Therefore they suggest that silica gel technology might be used as a predictive clinical tool to identify patients at risk of early recurrence or serve as a research tool to study the mechanisms underlying dormancy, chemoresistance, and recurrence.

Dr Chang Li (University of Washington) and colleagues presented their attempts to develop preventive approaches for patients with ovarian cancer at high-risk of disease recurrence or patients with cancer-predisposing inherited mutations. Their approach is based on in vivo genetic modification of hematopoietic stem cells.²⁰ By microRNAseq and microRNA arrays, these researchers identified microRNAs that were absent in tumor-associated leukocytes, allowing for tumor-restricted therapeutic transgene expressions by inserting these microRNAs in the 3' untranslated region of the transgenes. They hypothesized that these genetically engineered tumor-associated neutrophils and macrophages can overcome the immunosuppressive tumor environment allowing effector T-lymphocyte cells to stop tumor growth at an early stage. They are using oncogene-transgenic mice that develop spontaneous tumors to test this hypothesis.

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The American Cancer Society describes the 'signs' of ovarian cancer as 'bloating, abdominal pain, a feeling of fullness'—clearly all indications of late-stage disease. Indeed markers such as CA125 and imaging by transvaginal ultrasound also report frank cancer which, if not cured by surgery, represents a largely protracted medical struggle with limited odds of success.²¹ It would seem that the future should include early detection afforded by the large period of time presented by most pre-cancerous lesions and non-invasive cancer form of other organs. A molecular analysis of an early lesion that could be tied to high-grade serous cancer would provide an

array of targets that are either secreted by these cells or presented on the cell surface, with potential screening and therapeutic value, respectively. Monoclonal antibodies to secreted proteins have the potential to form the basis of population-wide screening methods from blood or cervical fluid for those at risk who might benefit from salpingectomy. Monoclonal antibodies to surface proteins of the cells in these lesions might assist in alternative detection via imaging technologies through the fallopian tube isthmus, similar to the confocal endoscopy performed today with Barrett's esophagus. They might also provide potentially non-invasive means of eradicating these early lesions through cytotoxic effects. While it seems that imaging technologies akin to the endoscopy and colonoscopy employed are not yet available for monitoring the fallopian tube, it would seem with the rapid pace of development that the fallopian tube will soon be within range of these modalities.

One goal of all cancer therapy is to provide early screening and pre-emptive intervention to avoid the challenges presented by highly metastatic cancers. Thus, the stages of cancer have a huge influence on the outcome. Early diagnosis of cancer will fundamentally affect the management of these tumors. The Ovarian Cancer Research Society has started to explore the current hypothesis that the fallopian tube is the origin of high-grade serous cancer and aims to develop new, sophisticated and yet simple strategies to detect the cancer in its earliest stage: the pre-cancerous lesion. If successful, we would have filled an important unmet medical need that has been troubling the medical profession for decades. Continuously developing new knowledge in this field is essential for us to develop medical diagnostic technologies that might save lives and improve the quality of global healthcare.

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Genomics and molecular mechanisms of high grade serous ovarian cancer: the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium

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ABSTRACT

Objective The aim of this study was to review current research efforts in genomics and molecular mechanisms of high grade serous ovarian cancer, presented at the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium, held at the University of Washington.

Methods The 12th Biennial Rivkin Center Ovarian Cancer Research Symposium brought together leaders in the field to discuss recent advances in ovarian cancer research and therapy.

Results The genomics and molecular mechanisms of ovarian cancer session featured invited speaker presentations by Dr Alan D' Andrea on 'Deoxyribonucleic acid (DNA) repair in ovarian cancer' and Dr Kathleen Cho on 'Modeling the genomics of high grade serous carcinoma in the mouse'. Eight additional oral presentations and 46 poster presentations were selected from the submitted abstracts that highlighted current research efforts in p53, DNA repair, genomic instability and modeling disease in mice, and organoids in high grade serous ovarian cancer. **Conclusions** New technologies utilizing clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (CAS9) approaches in mice, organoids, and cell based screens continue to advance our knowledge of key molecular drivers of ovarian cancer initiation, progression, and drug resistance. Improved understanding of the mechanisms of poly ADP ribose polymerase inhibitor resistance may lead to new therapeutic strategies to enhance outcomes in women with high grade serous ovarian cancer.

INTRODUCTION

Ovarian cancer is a heterogeneous disease with multiple subtypes that are classified based on distinct histological and genetic features. The most common and lethal subtype of ovarian cancer is high grade serous ovarian cancer. Approximately 70% of women diagnosed with high grade serous ovarian cancer present with advanced disease where the tumor has disseminated beyond the ovaries and pelvic organs to the peritoneum and abdominal organs, including the diaphragm, stomach, omentum, liver, and intestines.^{1,2} Common mutations associated with the development of high grade serous ovarian cancer include *TP53* mutations and *BRCA1/2* mutations.³ At

the genomic level, high grade serous ovarian cancer is also characterized by recurrent deoxyribonucleic acid (DNA) copy number alterations, making this cancer genomically unstable.⁴ These clinical findings suggest an important role for p53, DNA repair, and genomic instability in the pathogenesis of high grade serous ovarian cancer, and were a focus of the research presented at the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium during the session on genomics and molecular mechanisms of ovarian cancer.

Here we will summarize the key topics discussed in this session that was held on September 13–15, 2018, at the University of Washington.

p53 And HIGH GRADE SEROUS OVARIAN CANCER

The tumor suppressor p53 is known as the guardian of the genome due to its central role in regulating DNA damage responses. A variety of stimuli, including DNA damage, nutrient starvation, and oncogenic signaling, activate p53 signaling to modulate cell cycle arrest, apoptosis, ferroptosis, senescence, oncogenic signaling, metabolic reprogramming, differentiation, invasion, and signaling within the tumor microenvironment (for a recent review see Mello and Attardi⁵). Mutations in *TP53* are found in 96% of cases of high grade serous ovarian cancer, making p53 a critical tumor suppressor for ovarian cancer.³ *TP53* mutations are found within early serous tubal intraepithelial lesions found in the fallopian tube, suggesting that p53 loss is an early event in the pathogenesis of high grade serous ovarian cancer (for an recent review see Soong et al⁶). In the genomic and molecular mechanisms of ovarian cancer session, Dr Kathy Cho presented data from murine models of ovarian cancer demonstrating that recombination of *Trp53* inactivation along with *Brca1* and *Rb1* inactivation in fallopian tube epithelium utilizing Cre-lox technology requires a latency period of more than a year for early serous tubal intraepithelial carcinoma lesions to progress to high grade serous ovarian cancer, suggesting that tumor initiation and progression require additional events.^{7,8}



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Dr Rong Wu presented on new technologies utilizing clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (CAS9) mediated somatic gene editing in fallopian tube epithelium to model gynecologic cancers in mice. Importantly, he reported that the Cre-CRISPR/Cas9 sgRNA system could recapitulate morphology and immunophenotypic characteristics of *Apc-Pten* or *Brca1-Trp53-Rb1-Nf1* endometrioid carcinomas and high grade serous ovarian cancer produced by Cre-lox technology. Within the Rivkin Symposium, we also learnt of additional research efforts utilizing CRISPR-Cas9 mediated gene targeting in organoid cultures derived from mouse oviduct and ovarian surface epithelium to identify gene combinations that result in tumor formation in transplantation studies.⁹ Future work utilizing these technologies and model systems will expedite the identification of genetic events that work in concert with p53 mutations to promote high grade serous ovarian cancer formation and metastasis within murine models.

Similar to most cancers, the majority of *TP53* mutations in high grade serous ovarian cancer are missense mutations that reside within the DNA binding domain. Mutant p53 proteins result in loss of wild type p53 function through multiple mechanisms, including loss of DNA binding and protein structural mutations. *TP53* mutations can facilitate p53 protein aggregation leading to loss of p53 function, dominant negative effects, and gain of function activities. Previous studies have shown that R248 and R280 mutant p53 proteins stimulate p53 protein aggregation *in vitro* and enhance p53 protein aggregates within the nucleus of cancer cells to inactivate p53 function.¹⁰ Dr Nicole Heinzl discussed the development of an enzyme linked immunosorbent assay recently published by Maritschnegg et al¹¹ that may be utilized to detect p53 protein aggregates in high grade serous ovarian cancer patient specimens. Ongoing studies are focused on determining whether p53 aggregates correlate with patient survival and/or response to platinum based chemotherapy in high grade serous ovarian cancer.

There are likely multiple mechanisms by which p53 mediates its tumor suppressor functions in ovarian cancer. One target that may contribute to the pathogenesis of high grade serous ovarian cancer is forkhead box protein M1 (FOXM1). FOXM1 is a forkhead box transcription factor that controls cell cycle progression and cell proliferation in normal cells through activation of G2 specific genes.^{12,13} In cancer cells, FOXM1 has additional functions in controlling apoptosis, angiogenesis, invasion, genomic instability, inflammation, and metabolism.¹² In ovarian cancer, aberrant activation of FOXM1 has been shown to promote tumor migration, invasion, chemoresistance, and poly ADP ribose polymerase inhibitor resistance.^{14–16} The FOXM1 transcription factor network is overexpressed at the messenger ribonucleic acid (RNA) level in 87% of high grade serous ovarian cancer.³ FOXM1 is a repressed p53 target, indicating that p53 loss may contribute to enhanced FOXM1 signaling in high grade serous ovarian cancer.¹⁷ In support of this notion, FOXM1 expression is increased in p53 and Rb deficient murine ovarian surface epithelial cells and tumors compared with p53 and Rb wild type cells.¹⁸ Dr Carter Barger recently demonstrated that FOXM1 is highly expressed in human cancers with p53 inactivation and Rb-E2F deregulation. Moreover, FOXM1 expression was associated with genomic instability.¹⁸ Overall, these studies suggest that FOXM1 may be an important therapeutic target for the treatment of high grade serous ovarian cancer.

dnA RepAIR In HIGH GRAdE SeROuS OvARIAn CANCeR

Defective homologous recombination plays an important role in the pathogenesis and therapeutic response of high grade serous ovarian cancer. It has been estimated that approximately 50% of high grade serous ovarian cancers have defects in DNA repair and homologous recombination. Most notably, 20% of high grade serous ovarian cancers exhibit germline or somatic mutations in the homologous recombination proteins BRCA1/2 and an additional 11% of high grade serous ovarian cancers lose BRCA1 expression through promoter methylation. Additional genomic changes within genes such as EMSY, PTEN, RAD51, ATM, recombination plays, and Fanconi anemia also result in defective homologous recombination in 25% of high grade serous ovarian cancer tumors.³

The homologous recombination pathway plays an important role in repairing DNA double strand breaks that occur during DNA replication. Defects in homologous recombination result in the accumulation of chromatid breaks.¹⁹ If chromatid breaks are not repaired, the cells become dependent on alternative end joining double strand break repair for survival. Alternative end joining will repair the breaks by joining the double strand breaks, resulting in chromosomal rearrangements and genomic instability.²⁰ Homologous recombination deficient tumors are particularly sensitive to intrastrand and interstrand crosslinks induced by platinum based chemotherapeutic agents.²¹

In addition to chemotherapy, homologous recombination deficient high grade serous ovarian cancers are also particularly sensitive to poly ADP ribose polymerase inhibitors. In 2014, olaparib was first approved by the Food and Drug Administration for the treatment of BRCA1/2 mutant epithelial ovarian cancer for those who have received three or more chemotherapy regimens.²² Subsequently, rucaparib was approved for women with advanced ovarian cancer who have been treated with two or more chemotherapies and have germline or somatic BRCA mutations.²³ Niraparib was the first approved poly ADP ribose polymerase inhibitor for maintenance therapy in recurrent ovarian cancer patients who are in complete or partial response to platinum based chemotherapy, regardless of BRCA mutation status.²⁴ Currently, olaparib, niraparib, and rucaparib are approved by the Food and Drug Administration for maintenance therapy in patients with recurrent epithelial ovarian cancer who are in complete or partial response to platinum based chemotherapy.²⁵ There are a number of ongoing combination studies evaluating the safety and efficacy of poly ADP ribose polymerase inhibitors with chemotherapy, radiation therapy, immunotherapy, antiangiogenic agents, PI3K pathway inhibitors, and inhibitors of DNA damage repair.²⁶ Phase II clinical trials combining olaparib with paclitaxel in BRCA mutated cancers have reported improved clinical responses compared with single agent platinum or topoisomerase inhibitors.²⁷ However, significant myelosuppression limits the combination of poly ADP ribose polymerase inhibitors with standard doses of platinum and topoisomerase inhibitors.^{28,29}

A recent study by Drs Sarah Hill and Alan D'Andrea demonstrated that independent of DNA repair gene mutational status, high grade serous ovarian cancer patient organoids with a functional defect in homologous recombination, as determined by defective RAD51 foci assembly following irradiation, correlates with response to poly ADP ribose polymerase inhibition.³⁰ These studies highlight the importance of homologous recombination deficiency in mediating

poly ADP ribose polymerase inhibitor response in high grade serous ovarian cancer and suggest that functional testing of homologous recombination activity may be most effective to predict which patients may respond to poly ADP ribose polymerase inhibitors. There are multiple mechanisms by which homologous recombination defective tumors are sensitive to poly ADP ribose polymerase inhibition. First, poly ADP ribose polymerase is a single strand DNA repair protein. If single strand breaks are not repaired by poly ADP ribose polymerase, they are converted into double strand breaks during replication that are repaired by RAD51 and homologous recombination.^{20 31} Additional mechanisms for poly ADP ribose polymerase inhibitor mediated sensitivity of homologous recombination deficient high grade serous ovarian cancer cells may also include activation of classic non-homologous end joining and inhibition of DNA repair mediated by the accumulation of poly ADP ribose polymerase1-DNA complexes.³²

Despite the enthusiasm for the addition of poly ADP ribose polymerase inhibitors to the clinical landscape of high grade serous ovarian cancer, many patients who initially respond to poly ADP ribose polymerase inhibitors develop resistance. There are multiple mechanisms by which high grade serous ovarian cancers develop resistance to poly ADP ribose polymerase inhibitors. Dr Alan D'Andrea, an invited speaker at the Rivkin Symposium, spoke about the current research efforts investigating mechanisms that drive sensitivity and resistance to poly ADP ribose polymerase inhibitors. In BRCA1/2 deficient tumors, a common mechanism driving poly ADP ribose polymerase inhibitor resistance is the restoration of BRCA1 or BRCA2 protein activity through genetic or epigenetic events.³² Loss of poly ADP ribose polymerase1 expression, the target of poly ADP ribose polymerase inhibitors, has also been linked to poly ADP ribose polymerase inhibitor resistance in human cancer cell lines.³³ In addition to loss of poly ADP ribose polymerase1 expression, mutations within poly ADP ribose polymerase1 that prevent poly ADP ribose polymerase trapping by poly ADP ribose polymerase inhibitors at sites of DNA damage can also contribute to drug resistance.³⁴ Recent studies have utilized unbiased screening methods to identify novel mediators of poly ADP ribose polymerase inhibitor resistance.

Screening for factors that mediate resistance of BRCA1 deficient tumors to poly ADP ribose polymerase inhibitors identified mitotic arrest deficient 2 like 2 (REV7) and tumor protein p53 binding protein 1 (53BP1).³⁵ 53BP1 is a chromatin binding protein that is rapidly recruited to double strand breaks where it regulates DNA repair choices by inhibiting DNA end resection and homologous recombination and promotes non-homologous end joining.³⁶ During homologous recombination, BRCA1 promotes the displacement of 53BP1 from chromatin near double strand breaks to activate DNA end resection.^{37 38} Loss of 53BP1 in a *Brca1* deficient setting is sufficient to promote homologous recombination and confer poly ADP ribose polymerase inhibitor resistance.^{36 39 40} REV7 has recently been identified as a component of the shieldin complex, a downstream effector of 53BP1 in DNA double strand break repair.^{32 35 41} Dr Yizhou He presented data on another CRISPR mediated screen for genes that mediate poly ADP ribose polymerase inhibitor response where the multifunctional homodimeric protein hub dynein light chain LC8-type I (DYNLL1) was identified as an another important factor mediating poly ADP ribose polymerase inhibitor sensitivity. Studies revealed DYNLL1 loss resulted in poly

ADP ribose polymerase inhibitor resistance. In these studies, He et al found that DYNLL1 is a negative regulator of DNA end resection.⁴² These findings are consistent with a recent report demonstrating that DYNLL1 acts to regulate 53BP1 non-homologous end joining by promoting 53BP1 oligomerization and chromatin interactions.⁴³ Overall, these findings highlight the importance of the p53BP1 pathway in poly ADP ribose polymerase inhibitor resistance and have revealed novel mechanisms governing the DNA damage response.

In addition to the p53BP1 pathway, Dr Jeremy Chien presented work ongoing in his laboratory that has identified the TP53 induced glycolysis regulatory phosphatase TIGAR as an important mediator of poly ADP ribose polymerase inhibitor response. Knockdown of TIGAR enhanced responses to olaparib in ovarian cancer cells *in vitro*. Moreover, TIGAR expression is amplified and correlates with poor overall survival in high grade serous ovarian cancer, suggesting that TIGAR may be an important therapeutic target for ovarian cancer. Overall, these data demonstrate that there are multiple mechanisms that may drive poly ADP ribose polymerase1 resistance, suggesting that analysis of each individual patient may be necessary to inform treatment strategies for these patients. Dr Elizabeth Stover performed a near genome CRISPR/Cas9 screen in BRCA2 mutant high grade serous ovarian cancer cell lines to identify genes that mediate survival to platinum based chemotherapy. In this screen, overexpression of the proapoptotic genes BCL-like 1 (BCL-XL), BCL2 apoptosis regulator (BCL-2), and MCL1 apoptosis regulator mediated resistance to platinum based chemotherapy. In preliminary studies, antiapoptotic inhibitors against BCL-XL, MCL1, or BCL2/BCL-XL synergized with cisplatin or paclitaxel, suggesting that antiapoptotic targets such as BCL-XL and MCL1 may be additional therapeutic targets driving chemotherapy resistance in high grade serous ovarian cancer. Moreover, BCL-XL, MCL1, or BCL2/BCL-XL inhibitors also synergized with the poly ADP ribose polymerase inhibitor olaparib, suggesting that BCL-XL and MCL1 may be therapeutic targets to use in combination with DNA damaging agents.

GenOMIC InStABILITY Of HIGH GRADe SeROuS OvARIAN CAncer

High grade serous ovarian cancer ranks among the top cancers with chromosome structural variants.^{1 4} In addition to recurrent mutations in *TP53* and the homologous recombination pathway, high grade serous ovarian cancer exhibits a high degree of somatic copy number alterations. Dr James Brenton presented work from his laboratory where they utilized copy number signatures derived from whole genome sequencing of core biopsies as a novel approach to identify mutational processes in high grade serous ovarian cancer. Their study identified seven distinct copy number signatures that are present in high grade serous ovarian cancer patient specimens at the time of diagnosis. Importantly, a copy number signature associated with oncogenic RAS signaling (neurofibromin 1, NF1; KRAS proto-oncogene GTPase, KRAS; and NRAS proto-oncogene GTPase, NRAS) predicts platinum resistant relapse and poor survival in high grade serous ovarian cancer patients. Moreover, they identified a copy number signature associated with BRCA1/2 related homologous recombination defects

that is associated with improved patient survival.⁴⁴ Their study also reveals the majority of high grade serous ovarian cancer patients have a mixture of copy number signatures, suggesting multiple mutational processes may coevolve during the pathogenesis of high grade serous ovarian cancer.⁴⁴ These studies reveal new information regarding mutational processes that occur during the evolution of high grade serous ovarian cancer and have important therapeutic implications in the use of copy number signatures for patient stratification to targeted therapies in high grade serous ovarian cancer.

eMeRGIInG AReAS wthIn HIGH GRAdE SeROuS OvARIAn CAnCeR

The analysis and identification of driver non-coding somatic mutations in epithelial ovarian cancer is an emerging area of research in the ovarian cancer field. Whole genome sequencing studies within epithelial ovarian cancer have identified thousands of non-coding somatic mutations.⁴⁵ Dr Rosario Corona presented ongoing work in the Lawrenson laboratory analyzing non-coding somatic mutations in epithelial ovarian cancer to distinguish between driver and passenger non-coding mutations. They hypothesized that driver non-coding mutations may localize to regulatory elements (promoters, enhancers) of genes known to be involved in the pathogenesis of ovarian cancer. They utilized genome wide histone 3 methylates Lys27 (H3K27) acetylation ChIP-sequencing of fresh primary ovarian cancer tissue samples from each major ovarian cancer histotype combined with RNA sequencing to identify common active regulatory elements across all histotypes. They then integrated these data with whole genome sequencing data to identify common non-coding mutations within active regulatory elements in ovarian cancer. Preliminary data identify several commonly mutated regulatory elements within each ovarian cancer histotype, including RNA polymerase III subunit E (POLR3E) and coiled-coil-helix-coiled-coil-helix (CHCHD6) for high grade serous ovarian cancer. Future studies are needed to further explore the identification and validation of these novel non-coding somatic mutation in epithelial ovarian cancer.

SuMMARy

In summary, new technologies utilizing CRISPR-CAS9 approaches in mice, organoids, and cell based screens continue to advance our knowledge of key molecular drivers of ovarian cancer initiation, progression, and drug resistance. Poly ADP ribose polymerase inhibitors, targeting homologous recombination defects in high grade serous ovarian cancer, have significantly altered the clinical management of ovarian cancer. However, resistance to these agents has emerged as an important clinical challenge. The development of predictive biomarkers for single agent poly ADP ribose polymerase inhibitors are needed for patient stratification. Additionally, improved understanding of the mechanisms of poly ADP ribose polymerase inhibitor resistance may lead to new therapeutic strategies to enhance outcomes in women with high grade serous ovarian cancer.

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Tumor microenvironment and immunology of ovarian cancer: 12th Biennial Rivkin Center Ovarian Cancer Research Symposium

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ABSTRACT

The 12th Biennial Ovarian Cancer Research Symposium organized by the Rivkin Center for Ovarian Cancer and the American Association for Cancer Research held on September 13–15, 2018 covered cutting edge and relevant research topics in ovarian cancer biology and therapy. Sessions included detection and prevention, genomics and molecular mechanisms, tumor microenvironment and immunology, novel therapeutics, and an education session. In this article we provide an overview of the key findings presented in the tumor microenvironment and immunology session.

INTRODUCTION

Ovarian cancer is the most lethal gynecologic malignancy and the fifth leading cause of cancer-related deaths among women in the USA.^{1,2} Recent developments in the field of ovarian cancer biology have uncovered several key findings that help us understand the disease better and provide us with new directions for improving patient outcome.³ Tumor microenvironment (TME) has emerged as an important area of interest. The TME includes the blood vessels, fibroblasts, immune cells, extracellular matrix (ECM), and all the signaling molecules surrounding the tumor.⁴ TME closely interacts with the tumor and mediates its initiation, progression, and metastasis.^{4–6} The vital TME components have become new therapeutic targets since they can profoundly affect patients' responses to treatments.⁷ Accumulating evidence suggests that the efficacy of chemotherapy and the promising technique of immunotherapy can be improved through the modulation of TME.⁸ Therefore, research interest in understanding the complexity and diversity of TME has exponentially increased in recent years. This aspect of ovarian cancer research was well represented in the 'Tumor Microenvironment and Immunology of Ovarian Cancer' session of the 12th Biennial Ovarian Cancer Research Symposium.

TumOR micROenviROnment And ImmunOIlogy SeSSion

The session included two invited speaker presentations followed by eight talks from selected abstracts. The first invited talk by **dr Frances Balkwill** from

Barts Cancer Institute presented her laboratory's efforts to better understand ovarian cancer metastasis by first deconstructing metastasis in patient tumors and then developing experimental models based on the knowledge gained to accurately study the mechanism of regulation of metastatic colonization of the omentum. Using biopsies of metastasis from high-grade serous ovarian cancer (HGSOC) patients representing a spectrum of disease progression from marginal to aggressive, they profiled the dynamic interactions and changes in the tumor and stroma as the metastasis progressed. Extensive studies were performed using the same biopsy samples including gene expression, matrisome, ECM organization, biomechanical properties, cytokine/chemokine levels, and cellular profiles. The matrisome in humans consists of about 300 proteins that form the ECM, growth factors associated with the ECM, proteases and other ECM-modifying enzymes, and other ECM-associated proteins.⁹ Changes in the matrisome was a key feature identified, which could be correlated with prognosis and immune cell signatures that can themselves affect patient outcome. Through the reorganization of fibrillar collagens and the expression of glycoproteins and proteoglycans, the matrisome signature also determined the stiffness of the tumors. Moreover, there was a strong association between the number of α -smooth muscle actin and α -fibroblast-activated protein (FAP)-positive cancer associated fibroblasts (CAFs) and metastasis progression. Combining multiple different types of analysis on the same biopsies, and utilizing biopsies from patients exhibiting different extents of metastatic tumor progression, Dr Balkwill's group provided a comprehensive picture of the process. This complements the data from primary tumors provided by The Cancer Genome Atlas Program and can effectively form a platform for launching detailed studies deciphering the mechanism of metastatic progression in HGSOC as well as provide novel therapeutic targets to treat metastasis.

Dr Balkwill proceeded to describe her group's efforts to reconstruct the omentum in a petri dish to provide effective models to further study the mechanisms of the key factors identified by their multi-parameter analysis of ovarian cancer metastasis. Using



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HGSOC cells, fibroblasts, and adipocytes embedded in a collagen I gel, her group has developed tri-cultures representing the omental metastasis. Similarly, they have generated a quadri-culture model by including omental mesothelial cells. These models have been characterized for the expression of the matrix proteins identified in the deconstruction experiments, and transforming growth factor beta (TGF- β) was found to be a regulator of five of the six matrix molecules identified in the matrisome signature. Dr Balkwill also presented their characterization of mouse HGSOC models and presented data pointing towards the similarities in the ECM and immune subsets in the mouse and human tumors. Taken together, the models presented provide unique opportunities to study detailed mechanisms of metastatic colonization as well as drug discovery.

In the next invited talk, **dr ernst Lengyel** from the University of Chicago reported his group's recent findings on the role of cancer/testis antigen 45 (CT45) in increasing chemosensitivity of ovarian tumors. To study the role of the metastatic tumor proteome on the HGSOC patient outcome following chemotherapy, his group collaborated with Matthias Mann from the Max Planck Institute of Biochemistry. They developed a high-sensitivity, label-free proteomic mass spectrometry-based work-flow to analyze the proteome from formalin-fixed paraffin-embedded (FFPE) tumors. Using this approach they quantified more than 9000 proteins in chemosensitive and chemoresistant tumors. CT45 was the most upregulated in the chemosensitive tumors. It was found to affect DNA damage repair pathways by regulating protein phosphatase 4. The expression of CT45 is suppressed in the normal ovary by DNA methylation and is significantly upregulated in ovarian tumors through the loss of methylation. By combining immunopeptidomics and mass spectrometry, Dr Lengyel identified the role of CT45 as a cancer antigen presented on human leucocyte antigen class I receptors. These CT45 peptides were found to be potent in activating patient-derived cytotoxic T cells and inducing cancer cell killing. This novel comprehensive proteomics strategy incorporating proteome quantification, phosphoproteomics, interactome studies, and immunopeptidomics was effective in analyzing achieved FFPE tumor samples and identifying a unique biomarker, which is particularly relevant to long-term patient survival and immunotherapy.

Dr Lengyel also described the reciprocal signaling between CAFs and ovarian cancer cells identified by quantitative label-free mass spectrometry-based phosphoproteomics in co-cultures of CAFs and ovarian cancer cells. His group had previously shown that the metastasizing ovarian cancer cells utilized lipids released from the adipocytes in the omentum to drive their growth. His present findings demonstrate that the reciprocal signaling between CAFs and the cancer cells help the cancer cells switch their metabolism towards utilizing glycogen once the fat reserves are depleted. The activation of p38 mitogen-activated protein kinase signaling in the CAFs by the cancer cells resulted in the increased secretion of the cytokines interleukin 6 (IL-6), C-X-C motif chemokine ligand 10 (CXCL10), and C-C motif chemokine ligand 5 (CCL5). The secreted cytokines activated glycogenolysis in the cancer cells in a paracrine manner by activating phosphoglucomutase 1. Glycogen phosphorylase inhibition reduced metastasis in mice indicating that blocking glycogen mobilization could be a potentially effective therapeutic strategy to treat metastasis.

dr laurie Ailles from the University of Toronto presented her group's recent findings on the differential gene expression profiles

of ovarian cancer CAFs and cancer cells. CAFs could be subdivided into two groups based on the expression levels of FAP. FAP high and FAP low CAFs had distinct transcriptional programs, and analysis of The Cancer Genome Atlas data demonstrated a shorter progression-free and overall survival in FAP high patients. FAP high CAFs were functionally distinct from FAP low CAFs, with the FAP high CAFs having a greater ability to promote cancer cell invasion in vitro and tumor growth in mice. It would be interesting to analyze the matrisome signature described by Dr Balkwill in these FAP high and FAP low CAFs. The heterogeneity and potential functions of the subsets of CAFs would be relevant in future strategies involving targeting of the tumor stroma. **dr Katherine Fuh** from Washington University presented her group's findings on the role of discoidin domain receptor 2 (DDR2) expression in fibroblasts in promoting ovarian cancer metastasis. Inhibition or silencing DDR2 in fibroblasts decreased cancer invasion and mesothelial cell clearance as well as decreased collagen staining (trichrome) intensity and quantity in tumors. This suggests the possibility of targeting the stromal DDR2 as a potential therapeutic option, and again calls for the analysis of the secretome of the fibroblasts and the cancer cells regulated by DDR2. **dr Sara Zanivan** from the University of Glasgow reported the role of oxidoreductase chloride intracellular channel protein 3 (CLIC3) as a secreted factor and key contributor of tumor-stromal interaction. Through the mass spectrometry-proteomic comparative analysis of CAFs and their normal counterparts, CLIC3 was identified as the most upregulated and the most deposited in ECM. Further analysis revealed that the abundant CLIC3 in tumors was secreted by both stromal and cancer cells and could activate tissue transglutaminase-2 to promote blood vessel growth and increase tumor invasiveness. Their findings suggest a new mechanism of TME factor-mediated tumor invasion.

Understanding the complexity and diversity of immune cells in the TME has become critical for maximizing the clinical benefits from immunotherapy. **dr Alan d'Andrea's** group at Harvard Medical School applied a novel high-multiplex tissue cyclic immunofluorescence (t-CycIF) platform to understanding the dynamics between DNA damage in cancer cells and the immune context in HGSOC TME. This platform quantifies the expression of 60 antigens at single cell resolution. Data from over 10^6 cells showed distinct cell compositions in the TME of BRCA1/2 mutant and homologous recombination wild-type HGSOCs. On one hand, tumors with high programmed cell death protein 1 (PD-1) and its ligand (PD-L1) expression have high infiltration of CD1c+dendritic cells, which indicates the suppression of antigen presenting pathway and that these tumors are likely to respond to immune checkpoint blockade. Conversely, a subset of tumors with high levels of DNA damage show active interferon signaling and high CD8+ cytotoxic T-cell infiltration suggesting an immunogenic phenotype in this subset of HGSOCs. The application of new technologies like t-CycIF will contribute to the development of rational combination therapies and predictive biomarkers for DNA damaging agents and immune checkpoint blockade. **dr Pamela Kreeger's** group at the University of Wisconsin-Madison analyzed the secretome of macrophages and identified fms-related tyrosine kinase 3 ligand, heparin-binding epidermal growth factor, IL-6, IL-8, and leptin to be associated with tumor spheroid spreading in a macrophage-HGSOC spheroid co-culture using a 35-cytokine-multiplex assay. Although each ovarian cancer cell line (eg, OVCAR3, OVCA433, and OV90) responded to a different

set of cytokines secreted by macrophages, they utilized a common signaling pathway to regulate spheroid spreading, which is the Janus kinase 2/signal transducers and activators of transcription 3 (JAK2/STAT3) activation leading to matrix metalloproteinase-9 (MMP-9)-promoted tumor spreading. These findings suggest that multiple macrophage-secreted factors drive the tumor metastasis in HGSOC patients. However, they may share the same downstream signaling pathways, such as JAK2/STAT3/MMP-9. The identification of this molecular mechanism indicates the possibility of controlling tumor metastasis in a broad group of patients by targeting the main common signaling pathways for macrophage-tumor interaction. **dr Ronny drapkin's** group at the University of Pennsylvania revealed the role of ring finger protein 20 (RNF20)/histone H2B monoubiquitylation (H2Bub1) loss as an early event in HGSOC that modulate the immune signaling pathways during tumor initiation. H2Bub1 is an epigenetic regulator and tumor suppressor that is lost in serous tubal intraepithelial carcinomas (STICs) and HGSOCs. Ubiquitin ligase RNF20 catalyzes H2Bub1. Their data demonstrated that the inhibition of RNF20 altered immune signaling pathways and led to increased cell migration and clonogenic growth. The loss of RNF20/H2Bub1 functions is possibly responsible for the early oncogenic phenotype in STICs.

Angiogenesis is another important therapeutic target in the TME. **dr Anil Sood's** group in the University of Texas MD Anderson Cancer Center identified a new target for overcoming the resistance to anti-angiogenic therapy. p130cas (Crk-associated substrate) is a central regulator of focal adhesion kinase (FAK)/Src-mediated angiogenesis. Their data showed that p130cas was highly expressed in the tumor-associated vascular endothelium. Ablation of p130cas gene or inhibition of its expression in mouse models of ovarian cancer increased the sensitivity to anti-vascular endothelial growth factor antibody treatment and inhibited tumor growth through autophagy-regulated cell death in endothelial cells. They have generated nanoparticle-delivered peptide antagonist to p130cas as a targeted therapeutic agent. The antagonist's clinical efficacy and mechanism of action are under evaluation.

It is also very exciting that new imaging technologies have been applied to the quantitative assessment of the architectural features in the TME of ovarian cancer. **dr Paul Campagnola's** group at the University of Wisconsin-Madison used collagen-specific sensitive second harmonic generation imaging microscopy, 3D texture analysis, and machine learning to extract textural features and build models of the ECM in the ovarian cancer TME. They generated models for normal stroma, high-risk stroma, benign tumor, high-grade serous, low-grade serous, and endometrioid carcinoma. By examining the collagen alterations, they developed quantitative biomarkers for assessing the increased collagen concentration and the changes of alignment of collagen molecules within fibrils and fibers. Their data indicate that combining macro/supramolecular probes and the fiber morphology classification improves our understanding of TME evolution in ovarian cancer and the role of ECM alteration in disease etiology. This novel approach has the potential to be developed into new prognostic and diagnostic methods.

The poster session included very interesting presentations covering epigenetic modulators, non-coding RNAs, tumor immunology, in vitro models, cancer stem cells, novel therapeutics, and so on. Coffman reported that ovarian cancer cells mediate EZH2 induction and epigenetic reprogramming to convert mesenchymal

stem cells into carcinoma-associated mesenchymal stem cells. Zhang demonstrated that a combination of histone deacetylase 6 inhibition with PD-L1 checkpoint blockade could be a potential strategy to treat ARID1A-mutated clear cell ovarian cancer. Inhibition of nuclear factor- κ B activity in macrophages and potentially other cells in the ovarian TME was shown to inhibit tumor progression by Yull. Other studies included association of decreased let-7 with stemness, the role of long non-coding RNAs in metabolism, autophagy, or immune response, and a glycosylation-dependent mechanism involving Sox2 that drives a cancer stem cell phenotype. Posters covering tumor immunology demonstrated that the inositol-requiring enzyme 1/Xbox binding protein 1 arm of the endoplasmic reticulum stress response pathway in dendritic cells was necessary for accelerated ovarian cancer progression, that neuropilin-1 promotes survival and suppressive function of T_{reg}, and included a study providing new insights into the metabolic pathways that regulate T cell anti-tumor responses in ovarian cancer. Another study demonstrated that ovarian cancer patient monocytes are more tumoricidal when cultured with interferons than monocytes from matched controls, supporting a novel, innate, immune-based approach to immunotherapy of ovarian cancer.

In vitro models were represented by a 3D cell culture model for predicting the response to standard carboplatin chemotherapy, a 3D perfused bioreactor that allows the study of tumor biology and anti-tumor drug testing under physiological conditions, and models mimicking shear forces to improve our fundamental understanding of peritoneal metastasis and mechanotransduction. Therapeutics targeting ovarian cancer included the use of myxoma virus (MYXV) as a poxvirus that synergized with chemotherapy, aldehyde dehydrogenase 1A inhibitors increased LKB1 phosphorylation leading to AMP-activated protein kinase phosphorylation. McLean showed that the combination of inhibiting IL-6/LIF signaling with ruxolitinib with anti-estrogen therapy resulted in a synergistic decrease in ovarian cancer tumor cell viability. A new two-step targeting approach was presented that introduces non-natural targets (azide functional groups) in the tumors followed by the delivery of drug-loaded polymeric nanoparticles that are surface modified to have high affinity for these synthetic targets. Other pathways covered in the abstract session included apelin/APJ pathway in omental metastasis, role of TGF β 1/protein kinase C α /Twist1 signaling pathway in ovarian cancer metastasis, and the induction of insulin-like growth factor signaling by follicular fluid in fimbrial cells causing stemness, clonal expansion, and transformation. Yang-Hartwich presented data supporting the role of mutant p53 in promoting the initiation of HGSOC from fallopian tube precursors, while Rankin demonstrated that tumor-associated mesothelial cells promoted tumor invasion by increasing collagen deposition and remodeling.

CONCLUSIONS

The TME contributes to the 'hallmarks' of cancer and also shapes therapeutic responses and chemoresistance.^{4 6 10} It provides potential prognostic markers and therapeutic opportunities. Significant advances have been made in our understanding of the various components of the TME, including the cellular and acellular constituents. The 12th Biennial Ovarian Cancer Research Symposium reflected the increasing interest in the

TME of ovarian cancer and provided an excellent overview of the cutting-edge research going on in the ovarian cancer TME field, which provides renewed hope for our collective efforts to understand and eventually cure ovarian cancer. The identification of targetable molecular and cellular components in the TME will lead to the development of combination therapies that can simultaneously modulate TME and eliminate cancer cells to treat ovarian cancer more efficiently and effectively.¹¹ The new breakthroughs in the field of ovarian cancer TME that were presented at this meeting are leading the way in our fight against this deadly disease.

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Novel therapeutics: response and resistance in ovarian cancer

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Abstract

Here we review the latest pre-clinical and clinical developments for treatment of ovarian cancer, presented at the American Association of Cancer Research/Rivkin Center Ovarian Cancer Research Symposium held at the University of Washington in September 2018. Abstracts and presentations pertaining to the 'Novel Therapeutics' session were reviewed and are summarized here. The session featured a keynote presentation from Dr Ursula Matulonis, who summarized the current state of the art of treatment of ovarian cancer, including recent clinical trials incorporating the use of novel agents, including poly-ADP-ribose polymerase (PARP) inhibitors, other DNA-damaging agents, vascular endothelial growth factor receptor inhibitors, mirvetuximab soravtansine, and immune checkpoint blockade. Dr Jung-Min Lee then summarized the rationale and the results of early studies for targeting cell cycle checkpoint kinases for anti-cancer therapy. Eight submissions were selected for oral presentations, and 36 abstracts were presented as posters. The topics covered a range of clinical and pre-clinical strategies and biomarkers, including immunotherapy, mechanisms of chemotherapy, and PARP inhibitor resistance, DNA-damaging agents, and other novel therapeutic strategies. Key studies have highlighted that resistance to chemotherapy and PARP inhibitors remain a major challenge in therapy of ovarian cancer. Cancer stem cells represent an important mechanism of chemoresistance and strategies to target these cells may be a pathway to prevention of ovarian cancer relapse. Advancement of novel therapeutics targeting DNA damage, cell metabolism, and endoplasmic reticulum present some of the novel strategies in the pipeline. Emerging compelling pre-clinical data with novel antibody-drug conjugates targeting various surface receptors in ovarian cancer alone and in combination with immune checkpoint blockade generate a strong enthusiasm for rapid translation of these strategies to clinic.

Introduction

Since the last symposium in 2016, we have seen a series of developments in ovarian cancer, with approval of several poly-ADP-ribose polymerase (PARP) inhibitors in different treatment settings as well new clinical trials using agents targeting DNA repair, oncogenic pathways, and the immune system. The Novel Therapeutics session focused on the studies that aim to delineate the mechanisms of

resistance to existing agents, identify novel targets, and develop new treatment combinations.

Current state of therapy of ovarian cancer and novel combinations in clinical trials

Dr Ursula Matulonis gave a keynote lecture in this session, summarizing the state of the art of treatment of ovarian cancer and the results of recent clinical trials. Given the advances with PARP inhibitor development in ovarian cancer, she highlighted the multiple ongoing trials using PARP inhibitors in combination with other agents. These include PARP inhibitors in combination with agents targeting other mechanisms of homologous DNA repair, vascular endothelial growth factor and vascular endothelial growth factor receptor inhibitors, such as cediranib and bevacizumab, phosphatidylinositol-3-kinase inhibitors, and programmed cell death protein 1 (PD-1) inhibitors, some of which have demonstrated signals of activity in early clinical trials.^{1–3} She further summarized clinical data with folate receptor-targeting antibody drug conjugate mirvetuximab soravtansine, with a single agent response rate of 39% in non-heavily pre-treated patients.⁴ Combinations of mirvetuximab soravtansine with other agents, such as pembrolizumab, chemotherapy, and bevacizumab are ongoing. The responses appear to be enriched in the patients with medium/high folate receptor α expression, which will serve as a biomarker for future patient selection.

Targeting Cell Cycle Checkpoints and DNA repair mechanisms

Cell cycle checkpoint kinases represent another target for therapy in ovarian cancer, particularly those cancers not carrying inactivating BRCA mutations. Dr Jung-Min Lee summarized the pre-clinical data and early clinical data behind prexasertib, an inhibitor of checkpoint kinase 1/2 in non-BRCA-mutant ovarian cancer. In pre-clinical models, the drug demonstrates synergistic activity when used in combination with olaparib in non-BRCA-mutant cell lines, probably through inhibition of RAD51-mediated homologous DNA repair.⁵ A phase I/II trial in 28 patients with advanced platinum-resistant non-BRCA-mutant ovarian cancer demonstrated a promising response



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rate of 33%.⁶ Grade 3/4 neutropenia was the most common adverse event, which interestingly was transient. Dr Lee further discussed other ongoing studies targeting DNA checkpoints alone or in combination, including combinations of checkpoint kinase 1 inhibitor and mammalian target of rapamycin inhibitors, and checkpoint kinase 1 inhibitors with PARP inhibitors, which are ongoing. Finally, she presented early clinical data with combinations of carboplatin with Wee1 inhibitors, demonstrating a promising response rate of 43% with 5.3 months' median progression-free survival.

pArpInhibitors: reCeNt fInDIngs, meChANIsms of resIstANCe, ANd Novel CombINAtIOns

Dr Kathleen Moore and colleagues presented results of the QUADRA study, which evaluated single agent niraparib at 300 mg daily in patients with high-grade serous ovarian cancer and three or more prior lines of therapy. A total of 463 patients were treated in the study and the results were assessed according to platinum sensitivity, BRCA status, and homologous recombination deficiency status. In 456 patients with measurable disease, the disease control rate was 49%. In the primary efficacy population, defined as homologous recombination deficiency positive, the overall response rate was 29%, with a disease control rate of 71%. The most commonly observed grade 3 and higher adverse events were anemia (26.3%) and thrombocytopenia (20.5%). Niraparib thus demonstrated promising activity in this heavily pre-treated population, including platinum-resistant patients and some non-BRCA-mutant patients (NT-101).

Despite the promising response rate, this trial highlights the sad reality that PARP inhibition is not an option for the majority of patients, particularly those with platinum-resistant disease and BRCA wild-type status. Identification of biomarkers of primary and acquired resistance and strategies to minimize toxicity thus remain a high priority for further development of this class of agents.

Nanoparticles present an innovative and attractive strategy for drug delivery to tumors as a means of minimizing systemic toxicity.⁷ Dr Paige Baldwin and colleagues explored nanoparticle encapsulation of talazoparib, followed by intraperitoneal delivery, to minimize systemic toxicities of PARP inhibition. The resultant drug formulation was more efficient in suppressing tumor growth than the parental drug, with no obvious signs of toxicity (NT-87).

A number of studies uncovered several new mechanisms of PARP inhibitor resistance.⁸ Dr Neil Johnson presented an oral abstract describing a novel mechanism responsible for acquired PARP inhibitor resistance. BRCA1 mutations in the BRCA1 C-terminal domain normally lead to protein misfolding and degradation, promoting sensitivity to PARP inhibitors. Dr Johnson and colleagues have uncovered a mechanism, whereby retention of intron in a BRCA1 gene containing mutation in the BRCT domain results in intron translation and loss of BRCA1 C-terminal domain. This led to robust BRCA1 C-terminal expression and resistance to chemotherapy. Dr Lu Liu and colleagues demonstrated that short-term and chronic PARP inhibition can drive aldehyde dehydrogenase 1A1 expression, thus conferring stemness to the cancer cells,⁹ which eventually drives adaptive resistance to PARP inhibitors (NT-100). Finally, Dr Anniina Färkkilä used *in vitro* exposure to PARP inhibitors to characterize the mechanisms of PARP inhibitor resistance

in BRCA1 mutant cells. The resultant resistance to PARP inhibitors was mediated by several mechanisms in different clones, highlighting the potential for heterogeneity in resistance on PARPi treatment (NT-92).

With identification of PARP inhibitor resistance mechanisms comes the rationale for combination therapies to overcome the resistance. Dr Marilyne Labrie and colleagues implemented a "window of opportunity" trial to study adaptive resistance to PARP inhibitors. Using reverse-phase protein array analysis, measuring the expression of over 300 proteins in pre- and post-treatment samples, the authors were able to develop an algorithm that could suggest potential combination partners for PARP inhibition in specific patients (NT-098).

Targeting DNA damage through several targets is a rational strategy to overcome PARP inhibitor resistance.¹⁰ Dr Erin George presented an oral abstract on the potential utility of ataxia telangiectasia and Rad3-related protein (ATR) inhibitors in combination with PARP inhibitors. They identified constitutive activation of the ATR/checkpoint kinase 1 pathway in PARP inhibitor and carboplatin-resistant cell lines. Treatment of such cell lines with an ATR inhibitor in combination with an ataxia-telangiectasia mutated inhibitor was synergistic both *in vitro* and *in vivo*. Interestingly, this approach was also effective in CCNE-amplified tumors, which are known to be highly resistant to therapy. Dr Anne Steino and colleagues have explored VAL-083 as a strategy to overcome platinum and PARP resistance. VAL-083 is a first-in-class DNA-damaging agent, which induces inter-strand DNA crosslinks leading to double-stranded DNA breaks. The authors examined VAL-083 in combination with PARP inhibitors both in homologous recombination-proficient and homologous recombination-deficient cell lines and demonstrated synergistic activity in both settings (NT-109). Dr Ludmila Szabova and colleagues evaluated another example of a DNA-damaging agent—non-camptothecin topoisomerase I inhibitors—in ovarian cancer. BRCA1/2- and PALB2-deficient cell lines were highly sensitive to the new compounds. Moreover, combination between the new compounds and olaparib was synergistic (NT-110). Dr Amber Yasmeeen and colleagues explored poly-ADP-ribose glycohydrolase (PARG) as a potential strategy to sensitize ovarian cancer cells to DNA-damaging agents. PARG is responsible for poly-ADP-ribose catabolism which is synthesized by PARP.¹¹ Faulty poly-ADP-ribose formation or disintegration inhibits single-strand break repair. The authors demonstrate that PARG is expressed in 30% of ovarian cancers in The Cancer Genome Atlas. Inhibition of PARG in ovarian cancer cell lines resulted in reduced cellular proliferation and migration and sensitized the cells to PARP inhibitors and cisplatin (NT-117). Dr Rashid Gabbasov and colleagues focused on targeting heat shock protein 90, which plays a role in mediating maturation and stability of several key proteins required for DNA damage response.¹² They demonstrate that targeted inhibition of heat shock protein 90 with ganetespib sensitizes BRCA1-null cell lines to the effects of talazoparib (NT-094).

A number of studies looked at other signaling pathways that might be targeted in combination with PARP inhibition. Dr Alicia Beeghly-Fadiel and colleagues have demonstrated that nuclear orphan receptor NR4A1/TR3 plays an important pro-growth and pro-survival role in ovarian cancer.^{13,14} Inhibition of NR4A1 using a chemical antagonist or small interfering RNA knockdown resulted in tumor growth inhibition, and was synergistic with PARP inhibitor therapy (NT-88). Dr Takeshi Fukumoto and colleagues have shown that up-regulation

of Wnt/ β -catenin pathway in BRCA-mutant cancer cells results in PARP resistance.¹⁵ Interestingly, activation of the Wnt pathway was secondary to N6-methyladenosine modification of FZD10 mRNA. PARP inhibition and Wnt/ β -catenin inhibitor showed synergistic suppression of growth of PARP inhibitor-resistant cancer both *in vitro* and *in vivo* in a xenograft ovarian cancer mouse model (NT-93).

overComINg ChemotherApy resistANCe

A number of studies have focused on the mechanisms of resistance to chemotherapy and potential strategies to overcome it. Dr Wa Xian and colleagues used ovarian cancer resection specimens to generate libraries of ovarian cancer stem cells. The authors showed that while the majority of these cells are killed by chemotherapy, a number of clones are resistant to treatment. The resistant clones were characterized by a gene expression profile that was distinct from that of the sensitive clones. A broad screen of small molecules against the resistant clones proved that these cells are also resistant to other chemotherapy drugs. However, a number of compounds were either directly cytotoxic or cytotoxic in combination with paclitaxel, presenting a potential strategy to eliminate the resistant clones with upfront therapy and prevent cancer recurrence (NT-115). Dr Allison Sharrow and colleagues explored ovarian cancer stem cells as a potential mechanism of chemotherapy resistance.⁹ Using aldehyde dehydrogenase 1 (ALDH1) as a marker of stemness in ovarian cancer cell lines, they demonstrated the increased resistance of populations with high levels of ALDH1 to chemotherapy. The authors further used gene expression analyses in these populations and identified several up-regulated pathways, including mTOR, FGF18, and CD47, which could be explored therapeutically (NT-107). In support of these findings, Dr Nuzhat Ahmed presented an oral abstract summarizing a proteomic analysis of chemo-naïve and chemo-experienced ovarian cancer cells isolated from patients, demonstrating that chemotherapy results in enrichment of markers of cancer stem cells as well as alterations in pathways involved in DNA repair, immune recognition, cell cycle, and metabolism. This study provided important findings about potential mechanisms of chemotherapy resistance that may lead to a relapse in ovarian cancer and generated a rationale for potential novel combinations.

Dr Alex Cole and colleagues presented an oral abstract summarizing data on a new mechanism of chemotherapy resistance mediated by nuclear factor of activated T cells 3 (NFAT3), which is over-expressed in cancer stem cells.¹⁶ They showed that over-expression of NFAT3 promotes quiescent phenotype with G0 arrest. While *in vivo* this results in tumor growth arrest, it also leads to chemoresistance. These data thus highlight the possibility that NFAT3 might be a potential mechanism of chemotherapy targeting and presents an attractive therapeutic target to be used in combination with chemotherapy.

Tumor hypoxia results in a number of biologic changes in the tumor cells and microenvironment.¹⁷ Dr Andrea Nieto-Velozá demonstrated that chemical induction of hypoxia in ovarian cancer cell line results in paclitaxel resistance, although no effect is seen on sensitivity to cisplatin (NT-102). These findings highlight that hypoxia-mediated chemotherapy resistance does not occur with all agents.

Several groups employed new compounds in combination with chemotherapy as potential chemotherapy sensitizers. Dr Amber Yasmeen and colleagues explored whether differential sequencing of

PARP inhibitors and chemotherapy might improve efficacy. Regardless of BRCA mutational status, exposure to PARP inhibition before chemotherapy resulted in efficient induction of apoptosis *in vitro* (NT-118). Dr Vermont Dia presented a potential strategy to overcome chemoresistance induced by transforming growth factor β 1 using BG-4. BG-4 is a bioactive peptide isolated from the seeds of *Momordica charantia* and exhibits anti-cancer properties.¹⁸ While addition of transforming growth factor β 1 to ovarian cancer cell lines in the presence of paclitaxel and cisplatin resulted in chemotherapy resistance, the resistance was ameliorated by addition of BG-4. This was accompanied by reversal of transforming growth factor β 1-induced epithelial to mesenchymal transition, suggesting a possible mechanism of BG-4 action (NT-91). Dr John Giannios presented a strategy of targeting chemoresistant ovarian cancer cells through the use of paired guide RNAs targeting microRNA-221/222, which are known to inhibit apoptosis.¹⁹ By encapsulating paired guide RNAs into pegylated nanosomes tagged with anti-EphA2 antibodies, the authors were able to deliver the RNAs into EphA2-expressing ovarian cancer cells. This strategy led to inhibition of microRNA-221/222 biogenesis and downstream pathways, resulting in reversal of chemoresistance (NT-95).

tArgetINg eNdoplAsmIC retICulum stress pAthwAy

Cancer cells are characterized by endoplasmic reticulum stress and unfolded protein response, which contributes to cancer cell survival and resistance to stress caused by chemotherapy, hypoxia, and nutrient deprivation.²⁰ Dr Carlos Telleria and colleagues explored endoplasmic reticulum stress as a potential mechanism to target ovarian cancer cells. Treatment with anti-progestin mifepristone or HIV protease inhibitor induced endoplasmic reticulum stress in ovarian cancer cell lines. Combination of these drugs with the proteasome inhibitor bortezomib resulted in enhanced ovarian cancer cell death (NT-111). Similarly, Dr Yang Yang-Hartwich and colleagues explored the unfolded protein response pathway as a potential target for overcoming chemoresistance in ovarian cancer. Using a novel sulfonamide SF-Y3, the authors demonstrated inhibition of proliferation and induction of apoptosis in ovarian cancer cells. This effect was primarily seen in cancer cells with high levels of Bip1, a key chaperone protein in the endoplasmic reticulum, implicating its role in SF-Y3-induced unfolded protein response (NT-116).

tArgetINg metAboliC pAthwAys

Advances in understanding of metabolism and biosynthetic pathway alterations in cancer cells are the rationale for selective targeting of these pathways as a means to improve the efficacy of standard therapies. Dr Adegbite Emmanuel and colleagues revealed preliminary results of *in silico* screening of inhibitors of lactate dehydrogenase, which plays a role in ovarian cancer metabolism²¹ (NT-86). Dr Manish Patankar and colleagues explored the use of oxidative phosphorylation inhibitors in ovarian cancer, given the mounting evidence that the mitochondrial pathway can also contribute to cancer cell metabolism. They showed that atovaquone is an efficient inhibitor of electron transport in ovarian cancer cells and leads to tumor growth inhibition in an ID8 tumor model. The authors highlighted several mechanisms of action of atovaquone, including production of free radicals and

inhibition of ion transport resulting in loss of mitochondrial membrane potential (NT-103).

Antibody drug Conjugates

Targeting of ovarian cancer surface molecules using antibody drug conjugates is a viable therapeutic strategy, best supported by the initial data from the phase I trial of mirvetuximab soravtansine, a folate receptor-targeting antibody drug conjugate, which demonstrated a 26% response rate in a heavily pre-treated patient population and a 39% response rate in patients with three or fewer lines of therapy.⁴ This generates a strong rationale for evaluation of analogous strategies targeting other surface molecules and for further optimization of folate receptor α targeting. Dr Venita De Almeida presented pre-clinical data with STRO-002, a novel antibody drug conjugate targeting folate receptor α , which was optimized by selection of the antibody, drug linker, conjugation site, and drug-antibody ratio that conferred the best pharmacological properties. The resultant drug exhibited high potency *in vitro* and *in vivo*, while exhibiting a high safety profile in toxicology studies (NT-90). Dr Chunsheng Li and colleagues presented an antibody drug conjugate strategy targeting CD248, which is expressed by over 90% of ovarian cancers. In pre-clinical models, the antibody was cytotoxic to cancer cells both *in vitro* and *in vivo* and induced infiltration of lymphocytes into tumors, highlighting a potential dual mechanism of action of this strategy with rationale for combination with immune checkpoint blockade (NT-99). Finally, Dr Wolf Wiedemeyer and colleagues explored SC-003, another antibody drug conjugate targeting dipeptidase 3. By screening a patient-derived xenograft bank of ovarian cancers, the authors identified dipeptidase 3 as a common target in tumor-initiating cells. Treatment of dipeptidase 3 + patient-derived xenograft models with SC-003 resulted in efficient tumor regression. By using dipeptidase 3-expressing syngeneic mouse cells, the authors further showed that such a strategy can synergize with systemic programmed cell death protein 1 (PD-1) blockade (NT-113).

ImmunoTherapy

Treatment with immune checkpoint blockade has been evaluated in epithelial ovarian cancer, but with disappointing response rates to date.^{22–25} These findings necessitate the development of rational combinations and identification of biomarkers that might predict response to PD-1/PD-L1 blockade. Dr Dmitriy Zamarin presented an oral abstract discussing the results of a phase II clinical trial evaluating the use of the PD-L1 inhibitor durvalumab in combination with folate receptor α vaccine TPIV200 in 27 patients with heavily pre-treated platinum resistant/refractory ovarian cancer. While the overall response rate was 4%, similar to previously observed results with single agent PD-1/PD-L1 inhibitors, the study demonstrated a median overall survival of 21 months, which is better than the expected overall survival of <1 year in this patient population.²⁶ There was evidence of potentially enhanced clinical benefit from subsequent chemotherapy in the patients after completion of immunotherapy, highlighting the rationale for the use of chemotherapy in combination with immune checkpoint blockade in this patient population. Dr Denise Cecile presented pre-clinical findings of insulin growth factor binding protein 2 vaccine in ID8-luciferase

tumor models. The authors also employed a new method of anti-tumor assessment using multi-view multi-spectral imaging, allowing for more accurate tumor volume assessment. The study was able to demonstrate heterogeneity in metastatic tumor distribution and response, suggesting that this strategy may be a useful tool for evaluation of inter-tumoral heterogeneity in animal models.

Other Therapeutic Strategies

A number of abstracts discussed other novel targets and therapeutic modalities with potential application to ovarian cancer. Dr Karen Levy presented an oral abstract discussing pre-clinical data behind the use of a new radiation approach termed FLASH, which consists of short pulses of ultra-high dose radiation given in a single fraction.²⁷ In a peritoneal model of ID8 ovarian cancer, this approach was effective in controlling tumors, while having no significant toxicity in comparison with conventional radiation. Dr Varatharasa Thivyanathan and colleagues developed single-stranded nucleic acid aptamers with ability to recognize and bind ovarian cancer endothelial cells through annexin A2. Using this technology, the authors made an RNA/DNA nanoparticle capable of delivering doxorubicin to cancer cells in animal models. This strategy presents a potential mechanism for delivering drugs directly to the tumors while avoiding systemic toxicity (NT-112).

Several studies focused on the alterations common to high-grade serous ovarian cancer and other histologies. Missense mutations in p53 are the most common genetic alterations in ovarian cancer.²⁸ Dr Satish Kumar Ramraj and colleagues used the p53 reactivator drug PRIMA-1^{MET} in combination with SHetA2, a small molecule that inhibits mortalin (mitochondrial heat shock protein 70).²⁹ The combination was synergistic in ovarian cancer cell lines with mutant and wild-type p53 and showed additive activity in p53-null cell lines (NT-104).

Clear cell carcinoma of the ovary represents a highly chemoresistant sub-type of ovarian carcinoma and frequently harbors mutations in ARID1A.³⁰ Dr Shogo Shigeta and colleagues performed small interfering RNA screens against two ovarian clear cell carcinoma cell lines. A number of genes were identified as potential targets, including bromodomain BET family proteins BRD2 and BRD3. Knockdown of these proteins using RNA interference resulted in tumor growth inhibition (NT-108). Dr Shuai Wu and colleagues explored the mechanisms of acquired resistance to enhancer of zeste homolog 2 (EZH2) inhibition. In ARID1A-mutated cancer cells, the switch of the SWI/SNF catalytic sub-unit from SMARCA4 to SMARCA2 was the primary mechanism of resistance, leading to induction of anti-apoptotic genes such as BCL2. Use of BCL2 inhibitor ABT263 was able to overcome EZH2 inhibitor resistance and was synergistic with EZH2 inhibition *in vivo* (NT-114).

Epithelial to mesenchymal transition contributes to ovarian tumor metastasis and chemoresistance.³¹ Dr Junming Yue and colleagues demonstrated that knockout of the metal regulatory transcription factor 1 results in inhibition of this transition, leading to reduced cell proliferation, migration, and invasion (NT-120). Dr Carmela Ricciardelli and colleagues explored all-trans retinoic acid as a means of inhibiting the annexin A2-S100A10 signaling pathway, which plays a role in ovarian cancer invasion and metastasis.³² Treatment of ovarian cancer cells with all-trans retinoic acid led to reduced cell

survival, proliferation, and invasion, although the mechanism was not always S100A10-dependent (NT-105). Dr Flavio Rizzolio and colleagues demonstrated that targeting of peptidyl prolyl cis-trans isomerase (Pin1), which controls different oncogenes and tumor suppressors, can inhibit tumor growth in mouse ovarian cancer model.³³ Chemical or short hairpin RNA inhibition of Pin1 in ovarian cancer cell lines sensitized the cells to the effect of carboplatin (NT-106).

Several studies have characterized new compounds whose mechanisms of action are not yet fully understood. Dr Alexandra Young and colleagues explored synthetic analogs of phyllanthusmin for cytotoxic activity in ovarian cancer cell lines.³⁴ The most potent analog, PHY34, has nanomolar potency in high-grade serous ovarian carcinoma cell lines *in vitro* and displayed cytotoxic activity through late-stage autophagy inhibition and activation of apoptosis. The analog was also effective with intra-peritoneal administration in xenograft models (NT-119). Dr Arvinder Kapur and colleagues used fabclavine, a metabolite of *Xenorhabdus budapestensis*, and demonstrated that the compound inhibited ovarian cancer cell line proliferation and induced apoptotic cell killing at nanomolar concentrations (NT-096). Dr Powel Crosley and colleagues generated a TRAIL-expressing recombinant vaccinia virus and demonstrated its activity against granulosa cell tumor cell lines. Combination of the recombinant virus with procaspase-activating compound 1 resulted in further potentiation of lytic activity (NT-89). Dr David Pepin presented the results of the effects of Mullerian inhibiting substance on ovarian cancer cells isolated from ascites.³⁵ Using single cell RNA sequencing, their study uncovered a high degree of heterogeneity of expression of known and novel markers related to epithelial–mesenchymal states and stemness, both across patients and within patient samples. In addition, they uncovered some unexpected effects of Mullerian inhibiting substance on the immune cells in ascites. These findings will be important in understanding responses to this substance as it progresses through clinical development.

Finally, several groups presented early data on identification of novel compounds and pathways for targeting in ovarian cancer. Dr Hilary Kenny and colleagues used high throughput screening of small molecules against an ovarian cancer organotypic model that recapitulates features of ovarian cancer stroma. They identified three compounds—two targeting tyrosine kinases—which inhibited ovarian cancer adhesion, invasion, and growth (NT-97). Dr Einav Zmora and colleagues analyzed endothelial growth factor-like ligands from ascites of 43 patients with ovarian cancer and found that 86% of them expressed high levels of amphiregulin, which is a cytokine playing a role in tissue repair and inflammation.³⁶ The authors generated an antibody against amphiregulin and evaluated it in animal tumor models. Treatment with anti-amphiregulin resulted in significant prolongation of survival of mice bearing cancer xenografts (NT-121).

CoNCludINg remArks

In summary, the symposium presented a rich influx of information, highlighting novel mechanisms of primary and acquired resistance to chemotherapy and PARP inhibition. The revolving theme of combination therapy to overcome or prevent resistance resonates

throughout all studies. Potential combination partners include other agents inhibiting DNA repair, agents targeting cellular checkpoints, and drugs effective against cancer stem cells. Immune checkpoint inhibitors, while effective in a small subset of patients, unfortunately demonstrate limited single-agent activity in ovarian cancer and rational combinations with other immunotherapies, PARP inhibitors, and standard chemotherapy are currently underway. Other novel therapeutic strategies focusing on endoplasmic reticulum stress response, epithelial to mesenchymal transition, and targeting of surface molecules using novel antibody drug conjugates demonstrate compelling evidence of anti-tumor activity in pre-clinical models and generate a strong rationale for evaluation in clinic.

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Survivor advocacy: I speak for those who can't

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AbStrACT

The 12th Biennial Ovarian Cancer Research Symposium held on September 13–15, 2018, brought together ovarian cancer scientists, clinicians, survivors, and advocates in Seattle, Washington. The Symposium featured a panel on 'The role of advocates in ovarian cancer research' aimed at facilitating discussion between scientists and patient advocates to enable a more patient-centric approach to ovarian cancer research. Here we describe learnings from panelists that included seasoned research scientists and patient advocates.

I attended the panel discussion on 'The role of advocates in ovarian cancer research' during the 12th Biennial Ovarian Cancer Research Symposium and I learnt something new that I have actually known all along: *there aren't many ovarian cancer survivors; therefore, there aren't many ovarian cancer survivor advocates*. Ovarian cancer accounts for only 2.5% of cancer diagnoses in women, and the survival rate is much lower than that of other cancers. Of those who survive, some will not be well enough to advocate or have the mental energy to act. Therefore, I—an ovarian cancer survivor—am one of a relatively small number of people with the experience, ability, and interest to be a survivor advocate.

Survivor advocates are people who have navigated a diagnosis of cancer and its subsequent treatment, and who share the knowledge gained through their personal experience with a broader audience. The goal in disseminating the panel's collective wisdom on the topic of advocates in research is to bridge the gap between the advocate who wants to make an impact on a disease that affected them personally, and the scientist who spends their career trying to affect the same disease but without the perspective of one who has lived through it. Hopefully, by explaining some of the possible ways that advocates and scientists can interact, ovarian cancer scientists will be inspired to incorporate patients' perspectives into all aspects of their studies.

The panel emphasized that survivor advocates can and should be involved in every step along the cancer research path. Advocates bring the patient perspective to researchers for use in grant proposals to get research support. Advocates can play a critical role by posing questions to the scientists to help them better frame the topics to be examined,

and to question their assumptions. Advocates can provide feedback about the layperson's summary in grant abstracts and in clinical protocols. Advocates can also help to publicize clinical trials or spread other information through their close-knit network of survivors/friends. And, of course, they can advocate for legislative action and additional research funding. Through the process, advocates, by their very presence, emphasize the needs of the patient and the related need for urgency, paving the way to patient-centric healthcare.

There are many ways to get started in advocacy. To gain a better understanding, advocates can attend cancer research conferences to learn about the current state of research and meet those involved in it. The conferences also provide an excellent opportunity to meet other survivor advocates and scientists; that network can lead to advocacy opportunities. Additionally, several organizations, such as SHARE Cancer Support, the Research Advocacy Network, and the Ovarian Cancer Research Alliance, provide training, including online courses, and conferences specifically for those interested in advocacy. The training in basic medical research terminology and scientific concepts provides advocates with the necessary information to advocate knowledgeably. Some groups also provide advocate mentorship, pairing new advocates with those with experience. Even organizations that are not cancer-specific can provide relevant advocacy information and training.

Advocates can also contact local healthcare institutions and research centers in their area to determine whether there are existing advocacy programmes they can join. These entities may have advisory boards, advocacy networks, or survivor support groups with openings for advocates, or may welcome advocates to share their stories in educational settings. Regional and national organizations such as the National Institutes of Health and the National Cancer Institute (NCI) also have advocacy opportunities through their advisory boards or other programmes. For example, NCI's Office of Advocacy Relations specifically works to connect survivors with NCI to improve cancer research. And finally, organizations that allocate research funds, such as the Department of Defense Ovarian Cancer Research Program, use survivor advocates to review grant applications and clinical trial approvals.



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Review Article

Several simple steps can be taken by advocates at the grass-roots level. Those interested in policy adjustments or funding enhancement can write to their congressional representatives to encourage change, especially by emphasizing the amount of money that comes into their districts as a result of the funds they allocate to cancer research. Advocates can themselves raise funds for research through numerous fundraising activities. They can post their survivor status on social media; spreading the word about survivorship status can help lead to advocacy opportunities. Advocates can also use social media to disseminate information about medical research, such as clinical trials, to their networks of survivors/friends. Finally, advocates can simply ask relevant organizations: "What can I do to help?"

From their experience, survivor advocates gain the opportunity to give back to the scientists who pioneered their life-saving treatment, and to give their survival a purpose. In return for their service, advocates ask only that scientists use their collective voice to inform Congress by contacting their representatives at key times and exercising their right to vote. Advocates also appreciate it when the scientists can cover their out-of-pocket expenses by including those expenses in the grant proposals.

Like the survivor advocates on the panel, *I keep losing my friends*. Once I disclosed my ovarian cancer diagnosis I became a magnet for anyone who knew someone with a similar diagnosis. Suddenly, I knew many women with ovarian cancer, who I now count among my friends. But as ovarian cancer continues its insidious attack I also have more friends who have succumbed to its assault. As a result, I have become even more passionate about advocating. *I am the voice of those who can no longer speak for themselves*.

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