Notice of Award

CLINICAL INVESTIGATOR AWARD
Department of Health and Human Services
National Institutes of Health

NATIONAL CANCER INSTITUTE

Federal Award Date: 02/17/2020

Grant Number: 1K08CA241093-01A1
FAIN: K08CA241093

Principal Investigator(s):
Sarah James Hill, MD

Project Title: Targeting molecular vulnerabilities of ovarian cancer

Tina Da Silva
Director of Grants and Contracts
450 Brookline Avenue
Boston, MA 022155450

Award e-mailed to: grantsandcontracts@dfci.harvard.edu

Period Of Performance:
Budget Period: 03/01/2020 – 02/28/2021
Project Period: 03/01/2020 – 02/28/2025

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $253,377 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to DANA-FARBER CANCER INST in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number K08CA241093. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Justin Birken
Grants Management Officer
NATIONAL CANCER INSTITUTE

Additional information follows

SECTION I – AWARD DATA – 1K08CA241093-01A1

Award Calculation (U.S. Dollars)

Salaries and Wages	$144,225
Fringe Benefits	$40,383
Personnel Costs (Subtotal)	$184,608
Other	$50,000
Federal Direct Costs	$234,608
Federal F&A Costs	$18,769
Approved Budget	$253,377
Total Amount of Federal Funds Obligated (Federal Share)	$253,377
TOTAL FEDERAL AWARD AMOUNT	$253,377
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$253,377

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$253,377	$253,377
2	FUTURE COSTS,RECOMMENDED COSTS	
3		
4		
5		

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Cancer Research Manpower
CFDA Number:	93.398
EIN:	1042263040A1
Document Number:	KCA241093A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2020

IC	CAN	2020	2021	2022	2023	2024
CA	8481719	$253,377	FUTURE COSTS,RECOMMENDED COSTS			

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: W9TR / **OC**: 41033 / **Released**: BIRKENJ 02/14/2020
Award Processed: 02/17/2020 12:02:04 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1K08CA241093-01A1

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1K08CA241093-01A1

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget

period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2. As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) K08CA241093. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements

and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.
Treatment of Program Income:
Additional Costs

SECTION IV – CA Special Terms and Conditions – 1K08CA241093-01A1

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

RESTRICTION: National Institutes of Health (NIH) research or training grant funds (both direct costs and associated facilities and administrative costs) released as a result of this Career Development Award may not be retained by the awardee institution without written prior approval of the NIH awarding unit.

REQUIREMENT: This award is contingent upon the adjustment in Dr. Sarah Hill's effort as described in the updated Other Support/Correspondence dated 02/04/2020.

REQUIREMENT: This award is subject to the conditions set forth in PA-19-117, "Mentored Clinical Scientist Research Career Development Award (Parent K08 Independent Clinical Trial Not Allowed)," NIH Guide to Grants and Contracts, 12/20/2018, which are hereby incorporated by reference as special terms and conditions of this award.

Copies of this funding opportunity announcement may be accessed at: http://www.nih.gov/grants/guide/index.html

Copies may also be obtained from the Grants Management Contact indicated in the terms of award.

INFORMATION: Mentored career award recipients are eligible to receive concurrent support in the last two years of the career award. Concurrent support must be in accordance with : NOT-OD-18-157, "Career Award (K) Policy Update: Concurrent Support from a Mentored K Award and a Research Grant."

INFORMATION: This award involves Human Subjects Research. See "Assurance Requirements and Institutional Review Boards" under Part II, Subpart A, Human Subjects, in the NIH Grants Policy Statement, for specific requirements and grantee responsibilities related to the protection of human subjects, which are applicable to and are a term and condition of this award.

This award reflects the National Cancer Institute's acceptance of the certification that all key personnel have completed education on the protection of human subjects, in accordance the NIH Grants Policy Statement, "Education in the Protection of Human Research Subjects."

Any individual involved in the design and conduct of the study that is not included in the certification must satisfy this requirement prior to participating in the project. Failure to comply can result in the suspension and/or termination of this award, withholding of support of the continuation award, audit disallowances, and/or other appropriate action.

INFORMATION: This award, including the budget and the budget period, has been discussed between Justin Birken of the National Cancer Institute and Tina Da Silva on 01/03/2020.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Justin Birken

Email: birkenjg@mail.nih.gov **Phone**: 240-276-6300

Program Official: Susan E Lim
Email: lims@mail.nih.gov **Phone**: 240-276-5630 **Fax**: 240-276-5659

SPREADSHEET SUMMARY
GRANT NUMBER: 1K08CA241093-01A1

INSTITUTION: DANA-FARBER CANCER INST

Budget	Year 1	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$144,225	FUTURE COSTS			
Fringe Benefits	$40,383				
Personnel Costs (Subtotal)	$184,608				
Other	$50,000				
TOTAL FEDERAL DC	$234,608				
TOTAL FEDERAL F&A	$18,769				
TOTAL COST	$253,377				

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	8%	FUTURE COSTS			
F&A Cost Base 1	$234,608				
F&A Costs 1	$18,769				

PI: **Hill, Sarah James**	Title: Targeting molecular vulnerabilities of ovarian cancer	
Received: 07/11/2019	FOA: PA19-117 Clinical Trial:Not Allowed	Council: 01/2020
Competition ID: FORMS-E	FOA Title: Mentored Clinical Scientist Research Career Development Award (Parent K08 Independent Clinical Trial Not Allowed)	
1 K08 CA241093-01A1	Dual:	Accession Number: 4329602
IPF: 1464901	Organization: DANA-FARBER CANCER INST	
Former Number:	Department: Radiation Oncology	
IRG/SRG: NCIJ	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 234,608 Year 2: Year 3: Year 4: Year 5: FUTURE COSTS	Animals: Y Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N HFT: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Sarah Hill	Dana-Farber Cancer Institute	PD/PI
Alan D'Andrea	Dana-Farber Cancer Institute	Other (Specify)-Mentor

Reference Letters

David Livingston	Dana-Farber Cancer Institute/Harvard Medical School	07/11/2019
William Hahn	Dana-Farber Cancer Institute	07/11/2019
Mel Feany	Brigham and Women's Hospital	07/11/2019

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

○ Preapplication ● Application ○ Changed/Corrected Application

4.a. Federal Identifier
CA241093

b. Agency Routing Number

2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number
2019-07-11	2019-1304	

5. APPLICANT INFORMATION **Organizational DUNS*:** 0765807450000

Legal Name*: Dana-Farber Cancer Institute
Department: Radiation Oncology
Division:
Street1*: 450 Brookline Avenue
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5450

Person to be contacted on matters involving this application
Prefix: First Name*: Tina Middle Name: Last Name*: Da Silva Suffix:
Position/Title: Director of Grants and Contracts
Street1*: 450 Brookline Avenue
Street2:
City*: Boston
County: Suffolk
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5450
Phone Number*: 617-632-3940 Fax Number: 617-632-3944 Email: grantsandcontracts@dfci.harvard.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 042263040

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ○ Women Owned ○ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

○ New ● Resubmission
○ Renewal ○ Continuation ○ Revision

If Revision, mark appropriate box(es).
● A. Increase Award ○ B. Decrease Award ○ C. Increase Duration
○ D. Decrease Duration ○ E. Other *(specify)* :

Is this application being submitted to other agencies?* ○Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*	10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
National Institutes of Health	TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Targeting molecular vulnerabilities of ovarian cancer

12. PROPOSED PROJECT		13. CONGRESSIONAL DISTRICTS OF APPLICANT
Start Date*	Ending Date*	MA-007
04/01/2020	03/31/2025	

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Sarah Middle Name: J. Last Name*: Hill Suffix:
Position/Title: Clinical Fellow
Organization Name*: Dana-Farber Cancer Institute
Department: Radiation Oncology
Division:
Street1*: 450 Brookline Avenue
Street2:
City*: Boston
County: Suffolk
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5450
Phone Number*: 617/632-4480 Fax Number: 617/582-8213 Email*: Sarah_Hill@dfci.harvard.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$1,266,885.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$1,266,885.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ● THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
● PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Jean Middle Name: Last Name*: Kane Suffix:
Position/Title*: Assistant Director of Grants & Contracts
Organization Name*: Dana-Farber Cancer Institute
Department: Grants and Contracts
Division:
Street1*: 450 Brookline Avenue, BP322A
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5450
Phone Number*: 617-632-3940 Fax Number: 617-632-3944 Email*: grantsandcontracts@dfci.harvard.edu

Signature of Authorized Representative*
Jean Kane

Date Signed*
07/11/2019

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_Letter.pdf

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

● I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Dana-Farber Cancer Institute
Duns Number:	0765807450000
Street1*:	450 Brookline Avenue
Street2:	
City*:	Boston
County:	
State*:	MA: Massachusetts
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	02215-5450
Project/Performance Site Congressional District*:	MA-007

Additional Location(s) File Name:

Funding Opportunity Number: PA-19-117. Received Date: 2019-07-11T13:42:55.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 00001121

2. Are Vertebrate Animals Used?* ● **Yes** ○ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ● Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number A3023-01

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary.pdf
8. Project Narrative*	Project_Narrative.pdf
9. Bibliography & References Cited	References_Cited.pdf
10.Facilities & Other Resources	Facilities_Other Resources.pdf
11.Equipment	Equipment.pdf
12. Other Attachments	Hill_Full_License.pdf

Funding Opportunity Number: PA-19-117. Received Date: 2019-07-11T13:42:55.000-04:00

PROJECT SUMMARY

Genomic analysis suggests that up to 50% of High Grade Serous Ovarian Cancers (HGSCs) harbor a genomic alteration that might confer a DNA damage repair defect, making therapies that target such defects potential treatment options. There is no method to predict which patients will respond to such therapies, which is a major problem in the field. Preliminary data indicate that patient derived HGSC organoids may be a faithful model system in which to perform functional assays to predict patient therapeutic response. Data from a limited analysis of HGSC organoids suggest that stalled replication fork protection defects are more common than homologous recombination defects in HGSC and that more patients may benefit from the wider array of therapies available to target such defects, including carboplatin, gemcitabine, ATR, WEE1, and CHK1 inhibitors. *The goal of this mentored research career development proposal is to utilize patient derived HGSC organoid cultures to understand the prevalence, mechanisms, and therapeutic relevance of stalled replication fork protection defects in HGSC.* The proposed research studies encompass multiple disciplines including molecular biology, DNA sequencing, and animal modeling which will help investigate the role of stalled replication fork protection defects in HGSC and also provide a well-rounded career development strategy for becoming scientifically independent through execution of the following specific aims:

Specific Aim 1: *Assess the prevalence of fork protection defects in HGSC and whether fork protection defects predicted by HGSC organoid functional assays lead to therapeutic sensitivity to carboplatin and ATR, WEE1, and CHK1 inhibitors.* This will be accomplished by generating organoids from patients being treated with carboplatin and ATR, WEE1, and CHK1 inhibitors, performing functional assays to assess stalled fork protection capacity and therapeutic sensitivity of the organoids in parallel to sequencing analysis, and comparing organoid and patient outcomes.

Specific Aim 2: *Uncover mechanisms leading to fork instability in the organoids and whether different mechanisms of fork protection defects lead to differing sensitivities to the above agents.* This will be accomplished using molecular and cellular biology analysis of specific pathways in the organoids.

Specific Aim 3: *In vivo validation of in vitro mechanisms of stalled replication fork protection defects leading to therapeutic responses in organoid xenograft models of HGSC.* This will be accomplished by generating mouse models using select organoids from aim 2 and testing them for therapeutic responses to agents used in aim 2.

The career development award candidate is an MD/PhD clinically trained in anatomic pathology. The proposed research will occur at Dana-Farber Cancer Institute under the mentorship of Dr. Alan D'Andrea. The candidate will utilize the additional training provided by this award to facilitate her ultimate career goal of becoming an independent physician scientist and leader in the field of ovarian cancer.

PROJECT NARRATIVE

Up to 80% of high grade serous ovarian cancer (HGSC) patients succumb to their disease due to both lack of early detection and limited therapeutic options. Genomic analysis of these tumors has suggested that up to 50% may have difficulty in repairing damage to their DNA which might make them therapeutically sensitive to a variety of available drugs; but there is no functional evaluation of the tumors to determine which, if any, DNA damage repair defects the tumors actually have. The work in this proposal will help to better understand the types and prevalence of the different DNA damage repair defects present in HGSC and how such defects can lead to therapeutic sensitivity to drugs that target DNA damage repair defects.

BIBLIOGRAPHY AND REFERENCES CITED

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8. Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609-15. doi: 10.1038/nature10166. PubMed PMID: 21720365; PMCID: PMC3163504.
9. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov. 2015;5(11):1137-54. doi: 10.1158/2159-8290.CD-15-0714. PubMed PMID: 26463832; PMCID: PMC4631624.
10. Patch AM, Christie EL, Etemadmoghadam D, Garsed DW, George J, Fereday S, Nones K, Cowin P, Alsop K, Bailey PJ, Kassahn KS, Newell F, Quinn MC, Kazakoff S, Quek K, Wilhelm-Benartzi C, Curry E, Leong HS, Australian Ovarian Cancer Study G, Hamilton A, Mileshkin L, Au-Yeung G, Kennedy C, Hung J, Chiew YE, Harnett P, Friedlander M, Quinn M, Pyman J, Cordner S, O'Brien P, Leditschke J, Young G, Strachan K, Waring P, Azar W, Mitchell C, Traficante N, Hendley J, Thorne H, Shackleton M, Miller DK, Arnau GM, Tothill RW, Holloway TP, Semple T, Harliwong I, Nourse C, Nourbakhsh E, Manning S, Idrisoglu S, Bruxner TJ, Christ AN, Poudel B, Holmes O, Anderson M, Leonard C, Lonie A, Hall N, Wood S, Taylor DF, Xu Q, Fink JL, Waddell N, Drapkin R, Stronach E, Gabra H, Brown R, Jewell A, Nagaraj SH, Markham E, Wilson PJ, Ellul J, McNally O, Doyle MA, Vedururu R, Stewart C, Lengyel E, Pearson JV, Waddell N, deFazio A, Grimmond SM, Bowtell DD. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015;521(7553):489-94. doi: 10.1038/nature14410. PubMed PMID: 26017449.
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FACILITIES & OTHER RESOURCES

Dr. Hill will perform the majority of her work in Dr. Alan D'Andrea's laboratory at Dana-Farber Cancer Institute (DFCI). However, for key aspects of the project, she will utilize her clinical department at Brigham and Women's Hospital (BWH) and core facilities at DFCI and the Broad Institute. The available facilities and cores are detailed below.

D'Andrea Laboratory Resources:

Local Environment: The Dana-Farber Cancer Institute (DFCI) and Harvard Medical School (HMS) are centrally located in the Longwood medical area of Boston. Within roughly a 10 by 10 block square, the area also includes the Harvard School of Public Health, Children's Hospital of Boston, The Brigham and Women's Hospital (BWH), and the Beth Israel Deaconess Medical Center. The Dana-Farber Harvard Cancer Center (DF/HCC) area creates an unusually rich environment for both basic science and clinical studies. We have access to numerous experts in almost every field of biological research. The D'Andrea Laboratory is located in the Harvard Institute of Medicine Building on the Harvard Medical School Longwood campus. The building is within one block of Children's Hospital Boston and two blocks of BWH and the main Dana-Farber campus, so there is easy access to all clinical and core facilities to be utilized in this work. In addition, the laboratory is within one block of the Harvard Medical School quadrangle which houses an array of basic science labs and cores that can be called upon for collaboration at any time.

Laboratory: The D'Andrea laboratory consists of five laboratory modules totaling 1,988 square feet in the Department of Radiation Oncology on the second floor of the Harvard Institute of Medicine (HIM) building. We also have 937 square feet of laboratory space on the third floor of the HIM building. The department is fully equipped to complete the proposed work in cell culture, biochemistry, and molecular biology. We also have a Cytogenetics Diagnostic Core Lab run by Lisa Moreau and located adjacent to our laboratory which may become of use if specific DNA damage repair defects need to be assaysed using cytogenetic chromosomal analysis. Dr. Hill has her own bench, desk, freezer, and cold room space. She has access to all of the shared facilities within the DFCI lab. Overall, the D'Andrea laboratory, surrounding Radiation Oncology department, and wider DFCI community offer all of the equipment and resources needed to execute the research in this proposal.

Computers: DFCI facilities for internet, e-mail access, word processing and data storage are available from networked PCs and Macs in the HIM building. Dr. Hill has her own Partners workstation so that she can perform all of her research duties, keep careful watch of the BWH Operating Rooms for any cases of interest, and also perform any emergent clinical duties from afar should the need arise.

Office: There is 854 square feet of office space allocated to Dr. D'Andrea in the HIM building. The offices are located adjacent to the lab rooms. In addition, there are conference rooms located on the second and third floors of the HIM building available for lab, departmental, and collaborative meetings. Both are equipped with projection capabilities. Dr. Hill has full access to the conference rooms for necessary meetings and presentations. The business office is located on the same floor as Dr. D'Andrea's office which gives Dr. Hill immediate access to our grants coordinator as she writes both foundation grants and her upcoming R01.

Dana Farber Harvard Cancer Center (DFHCC) Core Facilities:
The following DF/HCC Core Facilities are available and relevant to this project:

1. The Confocal and Light Microscopy Core Facility is located in the Jimmy Fund Building of DFCI and will be useful for any fluorescent three dimensional imaging of organoids should it be required.
2. The Flow Cytometry Core Facility, located in the Smith Building at DFCI, provides two high-speed cell sorters, and four tabletop analyzers that can be used 24/7. Self-service after-hours sorting is available upon training. This facility can be used to sort tumor and immune cells or sort organoids differentially labeled with fluorescent antibodies or expressing fluorescent markers.
3. The Molecular Biology Core Facility at DFCI provides oligonucleotide synthesis and DNA sequencing services for any cloning needs once the project matures into molecular biology experiments.

4. The MS Proteomics Facility at DFCI, located off-site (approx 10 minutes by shuttle), is fully staffed and provides full protein analysis, including digestion, sample identification, and post-translational modification analysis. It is possible that proteomic analysis of organoids pre- and post- treatment may be useful in exploring mechanisms of stalled replication fork protection defects later in the project.
5. The DFHCC Specialized histopathology core located in the Thorn Building at BWH provides cutting and staining of paraffin embedded organoids and immunohistochemistry staining of organoids with the RAD51 and geminin antibodies to be used in the proposal.

Brigham and Women's Hospital Pathology Department:

Dr. Hill will focus 15% of her time on signing out gynecologic pathology in the BWH Women's and Perinatal Pathology (WPP) Division. The WPP division has a large staff of gynecologic pathologists with varied clinical and research interests who will mentor Dr. Hill in becoming an academic pathologist. The WPP division accessions approximately 13,500 surgical specimens yearly, including approximately 75 prophylactic salpingo-oophorectomies, 200 hysterectomies for benign disorders, 150 ovarian cancer cases, and over 200 benign ovarian conditions allowing for broad clinical exposure and diagnostic training. The WPP division staffs the frozen section room with access to intra-operative specimens in conjunction with the BWH/DFHCC tissue bank, and the divisional gross room where fresh specimens are processed. The frozen section room is a dynamic venue where Dr. Hill will carry out some of her clinical duties and also access fresh tissue for the organoid generation in her proposal. Through her clinical training, she has become an expert at grossly identifying tumor tissue needed for her work and can easily and appropriately allocate tissue for research. In addition, the BWH department of pathology houses a newly renovated morgue where Dr. Hill will conduct rapid autopsies on high grade serous ovarian cancer patients to allocate research tissue for organoid generation and to help clinically understand extent of disease. Overall, the BWH pathology department has a long-standing history of participation in basic and translational research and will offer another avenue of mentorship and support as Dr. Hill transitions to scientific independence.

The Eli and Edythe L. Broad Institute

The Broad Institute is located in Cambridge, MA just a short bus ride from DFCI and houses a Genomics Platform Core facility with equipment for DNA and RNA harvesting from fresh and paraffin embedded human tissue and organoid pellets and whole exome and whole genome sequencing which will be needed in this proposal. The Broad Institute has an online analysis system where all raw data files can be accessed and analyzed. Dr. D'Andrea is an associate member of the Broad Institute which gives Dr. Hill full access to the genomics platform and core facilities as well as to the online analysis Pipeline. In addition, the Broad Institute offers weekly seminars on computation and analysis that will be beneficial to the training in this proposal.

The Belfer Center for Applied Science

The Belfer Center is a core facility that is part of Dana-Farber Cancer Institute and is located in Boston, MA just a few blocks from the D'Andrea laboratory. The center has a fully staffed animal facility with the capacity for generating and appropriately caring for mouse xenograft models, performing drug treatments on the xenografts, monitoring the tumor progression and survival of the animals, and performing detailed analyses of the untreated and post-treatment tumors from the xenograft models. The D'Andrea lab has successfully worked with the Belfer Center for multiple previous xenograft projects and Dr. Hill will utilize the Belfer Center for the work in aim 3 of this proposal.

EQUIPMENT

The majority of the proposed work will take place in Dr. Alan D'Andrea's lab at Dana-Farber Cancer Institute in the Department of Radiation Oncology.

Dana Farber Cancer Institute, D'Andrea Lab (Radiation Oncology): The major equipment available in the D'Andrea Laboratory that is critical to the work in this proposal includes tissue culture hoods and tissue culture incubators critical for organoid generation and culturing, -80° and -120° freezer space critical for tissue sample and organoid culture storage, -20° and 4° freezer/fridge space for reagent and media storage, a Genomic Vision Molecular Combing System critical for the DNA fiber assays, an upright fluorescent microscope with a camera for fiber analysis and other fluorescent microscopy assays, an inverted fluorescent microscope with a camera for analysis of live organoids, cold rooms for molecular assays, warm rooms for tissue digestion and microbiology work, a ClarioStar plate reader for reading chemiluminescence based sensitivity assays, a RadSource RS-2000 Biological System X-Ray source for double strand break induction in the organoids, thermal cyclers for standard PCR and cloning, qPCR machines and interpretation software, a dark room for western blot development, table top centrifuges, standard centrifuges, and ultracentrifuges. This equipment is present in the D'Andrea laboratory and in the adjacent Radiation Oncology core equipment rooms. The laboratory/performance sites are located in the Harvard Institute of Medicine building of the Dana-Farber Cancer Institute. Sharing of facilities among researchers is encouraged, so that a great range of equipment is available within the Dana-Farber Cancer Institute as well as in the Harvard Medical School area in addition to the equipment in the main sites for this research. As the project evolves and new needs arise, there is vast opportunity for collaboration within the Dana-Farber and Harvard Medical School community.

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ARD OF REGISTRATION IN MEDICINE

Established A.D. 1894

This is to certify that

Sarah J. Hill, M.D.

. rvardMedical School in the year 2016 has been duly registered by this board ysician, as provided by the laws of the Commonwealth.

Wakefield, Massachusetts, January 10, 2019

a Sloane, MD

ration in Medicine

hair MD.

77749

Sarah J. Hill M.D.

PERSONAL INFORMATION

PERSONAL INFORMATION

2/21/2019

LICENSE EXPIRATION DATE: [redacted] LICENSE PERSONAL INFORMATION

Dear Dr. Hill :

Thank you for renewing your Massachusetts license to practice medicine and for your continued service to the people of the Commonwealth. A plastic wallet card is enclosed. Please note that your license will expire on [redacted] on PERSONAL INFORMATION

Your next full renewal notice will be sent to the mailing address you provided on your license application. Your renewal notice will be mailed to you at least 60 days before your license expires.

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PERSONAL INFORMATION

Candace Lapidus Sloane, MD

Candace Lapidus Sloane, M.D., Chair
Board of Registration in Medicine

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

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Project Role*: PD/PI Other Project Role Category:

Degree Type: MD/PhD Degree Year: 2016

Attach Biographical Sketch*: File Name: Biosketch_Hill.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT12901467 Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

PROFILE - Senior/Key Person				
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Degree Type: Degree Year:

Attach Biographical Sketch*:	File Name:	Biosketch_DAndrea.pdf
Attach Current & Pending Support:	File Name:	Support_D'Andrea.pdf

BIOGRAPHICAL SKETCH

NAME: Hill, Sarah, J., MD, PhD

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POSITION TITLE: Clinical Fellow

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Harvard College, Cambridge, MA	A.B.	06/2005	Biochemical Sciences
Oxford University, Oxford, UK	M.Sc.	08/2006	Biochemistry
Harvard University, Cambridge, MA	Ph.D.	05/2014	Genetics
Harvard Medical School, Boston, MA	M.D.	05/2016	Medicine
Brigham and Women's Hospital, Boston, MA	Residency	07/2018	Anatomic Pathology
Brigham and Women's Hospital, Boston, MA	Fellowship	07/2019	Women's and Perinatal Pathology

A. Personal Statement: The goal of my research and professional training up to this point has been to prepare me for a career as a physician scientist. **This mentored research career development award will provide the final training needed for me to become scientifically independent.** My research training has been focused on studying mechanisms of human disease most recently with my clinical interest being in ovarian cancer and my paired scientific interest being in the way DNA damage repair defects contribute to the genesis and therapeutic sensitivity of ovarian cancer. Throughout my training, my work has resulted in many first author publications with the most recent in *Cancer Discovery* detailing preliminary discoveries that have given rise to the aims in this proposal.

The goal of the work in this mentored research career development proposal is to understand the prevalence, mechanisms, and therapeutic relevance of stalled replication fork protection defects in high grade serous ovarian cancer (HGSC). This work will utilize patient-derived organoid models and DNA damage repair assays which I have recently established and used to show that more HGSCs harbor stalled replication fork protection defects than defects in the repair of double strand breaks by homologous recombination, which is contrary to the current dogma in the field. The HGSC organoid models will be used to assess the prevalence of fork protection defects in HGSC and also assessed for their predictive capacity for patient response to DNA damage repair defect targeting therapies. The cultures will also be utilized to try to dissect the different mechanisms of stalled fork protection defects that may confer therapeutic sensitivity. Organoid xenograft models will be generated from select cultures to validate *in vitro* findings *in vivo*. The success of this project will require utilization of both my scientific and clinical skills along with mentorship and experimental guidance from my primary mentor and advisory committee.

Most critical to this work is the ability to obtain fresh tumor tissue from which to generate organoid cultures. My training as an anatomic pathologist, and specifically my training as a gynecologic pathologist who has to perform gross analysis of fresh tissue during intraoperative frozen sections, has provided me with the unique expertise of easily being able to identify tumor tissue, no matter how small, in large fresh tissue specimens. Thus, I am able to simultaneously complete my professional duties in the frozen section room, and when extra tissue remains, also identify suitable tumor tissue to be allocated for my own research. My experience over the past 3 years generating organoids concurrent with my pathology training has helped me to understand exactly what is needed for successful organoid generation. Second, this work relies heavily on my ability to execute and analyze specific DNA damage repair assays, perform and analyze DNA sequencing, and perform *in vivo*

validation studies. From my prior training, I have experience in tissue culture and molecular biology techniques. In addition, my primary mentor, Dr. Alan D'Andrea, is a world expert on the DNA damage response and animal modeling of cancer and will be able to help me plan and interpret experiments and decide upon mechanistic avenues of investigation with respect to DNA damage repair as the project progresses. I also have the benefit of the mentorship and expertise in tumor biology (Myles Brown), clinical trials (Ursula Matulonis and Geoffrey Shapiro), immunology and academic pathology (Arlene Sharpe), and DNA and RNA sequencing (Rameen Beroukhim) in the members of my advisory committee whose mentorship will help me execute the work in this proposal and gain valuable new skills, particularly in animal modeling, sequencing analysis, and clinical trials, for my future independence. My personal expertise combined with that of my mentor and advisory committee will give me the perfect combination of resources to complete the proposed work.

Overall, I have the motivation, scientific training, and professional skills to complete this project. Being awarded a mentored research career development grant will offer me the protected time and additional training I need to build upon my prior experience and preliminary data to write an R01 application and become an independent investigator and leader in the field of ovarian carcinogenesis and therapeutic sensitivity.

B. Positions and Honors

Employment:

July 2016-July 2018	Resident in Pathology	Brigham and Women's Hospital
July 2018-July 2019	Women's and Perinatal Pathology Fellow	Brigham and Women's Hospital
July 2016-Present	Clinical Fellow	Harvard Medical School/Dana Farber Cancer Institute
July 2019-Present	Associate Pathologist	Brigham and Women's Hospital

Other Experience and Professional Memberships:

2008-present	American Association for Cancer Research
2008-present	American Association for the Advancement of Science

Honors:

2001-2005	Biochemical Sciences Concentration, Magna Cum Laude with Highest Honors in the Biochemical Sciences AB – Harvard University
2005	Rhodes Scholarship – Elected from District VI for the state of North Dakota and Harvard University
2005	Lawrence J. Henderson Prize "for writing the most meritorious undergraduate thesis in the Biochemical Science concentration at Harvard University for thesis entitled "Characterization of a Novel Chromodomain Protein" based on work conducted in David Livingston's lab at Dana-Farber Cancer Institute from January 2003 – August 2005
2008-2011	DOD Breast Cancer Research Program Pre-Doctoral Traineeship Award (Award W81XWH-08-1-0748)
2012-2016	Ruth L. Kirschstein Individual National Research Service Award Fellowship for MD/PhD students (Award 1F30CA167895-01)
2006-2016	MD Magna Cum Laude in a special field for thesis entitled "Familial ALS proteins function in prevention/repair of transcription-associated DNA damage" Harvard Medical School

No Foreign affiliation.

C. Contributions to Science

1. During my PhD and now in my pathology residency, my research interest has been in the way DNA damage repair defects lead to carcinogenesis and therapeutic vulnerability in women's cancers. I have been fascinated by the fact that, despite genomic analysis suggesting that 50% of high grade serous ovarian cancers (HGSCs) have alterations in DNA damage repair genes, we still have no method of determining what DNA damage repair defects each of these tumors actually harbor and what therapeutic vulnerabilities those defects confer. Thus, I generated culture conditions for patient derived HGSC organoids and established functional assays in the organoids to test the key DNA damage repair pathways thought to be defective in HGSCs. Through analysis of 33 HGSC organoid cultures, I found an unexpected result that challenges the current dogma in the field by demonstrating that not as many HGSCs harbor the expected homologous recombination defects as

expected, rather, more are defective in protection of stalled replication forks. These findings suggest that therapies exacerbating fork protection defects may be more effective for HGSC and that organoids may provide a clinical assay to help assess therapeutic sensitivity and test new therapeutic combinations.

a) **Hill, S. J.**, Decker, B., Roberts, E. A., Horowitz, N. S., Muto, M. G., Worley, M. J., Feltmate, C. M., Nucci, M. R., Swisher, E. M., Nguyen, H., Yang, C., Morizane, R., Kochupurakkal, B., Do, K. T., Konstantinopoulos, P. A., Liu, J. F., Bonventre, J. V., Matulonis, U. A., Shapiro, G. I., Berkowitz, R. S., Crum, C. P., and D'Andrea, A. D. (2018) Prediction of DNA Repair Inhibitor Response in Short Term Patient-Derived Ovarian Cancer Organoids. *Cancer Discovery*. 2018 Sep 13. pii: CD-18-0474. doi: 10.1158/2159-8290.CD-18-0474. [Epub ahead of print]. PMCID:PMC6365285

2. I have also worked to study the mechanisms by which the tumor suppressor BRCA1 functions in DNA damage repair. The major tumor suppressing role of BRCA1 was long thought to be in the repair of double strand DNA breaks by homologous recombination (HR). However, during my graduate work, I was part of multiple studies showing that BRCA1 plays roles in several repair pathways helping to protect the DNA when it is opened up for replication or transcription machinery. I was part of multiple studies highlighting the importance of BRCA1 in protecting stalled replication forks and showing that this function is separate from its role in HR. In addition, I performed a dual yeast two hybrid and mass spectrometry-based screen searching for protein binding partners of BRCA1 and was surprised to find many proteins involved in transcription. This led to the finding that BRCA1 prevents transcription-associated DNA damage such as that caused by R loops or transcriptional pausing at obstacles caused by exogenous UV damage or at transcriptional pause sites. It will be important to understand the disease and therapeutic relevance of these additional functions.

a) Pathania S, Nguyen J, **Hill SJ**, Scully R, Adelmant GO, Marto J, Feunteun J, and Livingston DM. BRCA1 is required for postreplication repair after UV-induced DNA damage. *Mol Cell*. 2011 Oct 21;44(2):235-51. doi: 10.1016/j.molcel.2011.09.002. PMCID:PMC3200447

b) **Hill SJ**, Clark AP, Silver DP, and Livingston, DM. BRCA1 Pathway Function in Basal-Like Breast Cancer Cells. *Mol Cell Biol*. 2014 Oct 15;34 (20):3828-42. doi: 10.1128/MCB.01646-13. PMCID:PMC4187718

c) **Hill SJ**, Rolland T, Adelmant G, Xia X, Owen MS, Dricot A, Zack TI, Sahni N, Jacob Y, Hao T, McKinney KM, Clark AP, Reyon D, Tsai SQ, Joung JK, Gaudet S, Beroukhim R, Marto JA, Vidal M, Hill DE, and Livingston DM. Systematic screening reveals a role for BRCA1 in the response to transcription-associated DNA damage. *Genes Dev*. 2014 Sep 1;28 (17):1957-75. doi: 10.1101/gad.241620.114. PMCID:PMC4197947

d) Hatchi E, Skourti-Stathaki K, Ventz S, Pinello L, Yen A, Kamieniarz-Gdula K, Dimitrov S, Pathania S, McKinney KM, Eaton ML, Kellis M, **Hill SJ**, Parmigiani G, Proudfoot NJ, Livingston DM. BRCA1 Recruitment to Transcriptional Pause Sites Is Required for R-Loop-Driven DNA Damage Repair. *Mol Cell*. 2015 Feb 19;57 (4):636-47. doi: 10.1016/j.molcel.2015.01.011. PMCID:PMC4351672

3. I have also contributed to the understanding of the deleterious effects of DNA damage repair defects in neurodegeneration. During my screening efforts for BRCA1 binding partners, I was surprised to find that an RNA binding protein associated with amyotrophic lateral sclerosis (ALS), called FUS, also associated with BRCA1. This led me to generate the hypothesis that some forms of ALS might be due to DNA damage induced by R-loops which arise during transcription. I tested this hypothesis in both cultured cell lines and motor neurons derived through directed differentiation, and I found that both familial ALS proteins, FUS and TDP43, are important in preventing R-loop and other forms of transcription associated DNA damage which suggests that possibly some forms of ALS may be driven by motor neuron death induced by transcription-associated DNA damage

a) **Hill, S.J.**, Mordes, D.A., Cameron, L.A., Neuberg, D., Landini, S., Eggan, K., and Livingston, D.M. Two Familial ALS proteins function in prevention/repair of transcription-associated DNA damage. *Proc Natl Acad Sci USA*. 2016 Nov 14; Epub ahead of print. doi/10.1073/pnas.1611673113. PMCID:PMC5137757

Complete list of published work in my bibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/1bICajpQhDkEvp/bibliography/56280323/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support:

PRIVATE SUPPORT (Hill, S) 10/01/2018 – 09/30/2019

Stalled replication fork protection defects as a predictor of therapeutic response in high grade serous ovarian cancer

The major goals of this project are to understand the different mechanisms of stalled replication fork protection defects in high grade serous ovarian tumors and how such defects confer sensitivity to different targeted and systemic therapies.

Role: Principal Investigator

PRIVATE SUPPORT (Hill, S) 07/01/2019 – 06/30/2021

Title: Targeting fork protection defects in high grade serous ovarian cancer

Description: The major goals of this project are to use high grade serous ovarian cancer (HGSC) organoids derived in the context of a clinical trial to understand the importance of fork instability in HGSC, uncover mechanisms leading to fork instability, and determine how such functional defects lead to different types of therapeutic sensitivities, including to immune-oncologic (IO) agents.

Role: Principal Investigator

DOD Ovarian Cancer Research Program Pilot Grant (OC180061) (Hill, S) 05/01/2019 – 04/30/2021

Title: Stalled replication fork protection defects as a predictor of therapeutic response

Description: The major goal of this work will be to use high grade serous ovarian cancer (HGSC) organoids to understand the importance of fork instability in HGSC, uncover mechanisms leading to fork instability, and determine how such functional defects lead to different types of therapeutic sensitivities, including to immuno-oncologic agents.

Role: Principal Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: D'Andrea, Alan D.

eRA COMMONS USER NAME (credential, e.g., agency login): eRA COMMONS USER NAME

POSITION TITLE: Professor, Radiation Oncology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	06/1978	Biology
Harvard Medical School, Boston, MA	M.D.	06/1983	Medicine
Children's Hospital of Philadelphia, PA	Residency	07/86	Pediatrics
Whitehead Institute, Cambridge, MA	Postdoctoral Fellow	06/90	Fellowship

A. Personal statement.

Twenty-five years ago, Dr. D'Andrea began to study the molecular pathogenesis of Fanconi Anemia (FA), a human genetic disease characterized by bone marrow failure, leukemia susceptibility, and cellular hypersensitivity to DNA crosslinking agents. Dr. D'Andrea's laboratory contributed significantly to the elucidation of a new DNA repair pathway, the FA/BRCA pathway, and demonstrated that one of the FA genes (FANCD1) is identical to the breast cancer gene, BRCA2. A critical event in the FA pathway is the monoubiquitination of the FANCD2 protein. Interestingly, somatic disruption of genes in the FA/BRCA pathway account for the chromosome instability and drug sensitivity of many solid tumors in the general (non-FA) population including ovarian, breast, leukemia, prostate and prostate cancers. Dr. D'Andrea has expertise in the DNA damage response and how defects in this pathway lead to carcinogenesis and therapeutic sensitivity, especially in high grade serous ovarian cancer. Dr. D'Andrea will serve as the mentor for Dr. Hill's K08 grant. He has already served as a mentor for Dr. Hill's recent work studying DNA damage repair defects in patient-derived high grade serous ovarian cancer organoids which has led to a publication in *Cancer Discovery*. Dr. D'Andrea's extensive professional experience as both a physician and scientist and his previous experience mentoring K08 awardees also make him an ideal career mentor for Dr. Hill.

1. Howlett NG, Taniguchi T, Olson S, Cox B, Waisfisz Q, de Die-Smulders C, Persky N, Grompe M, Joenje H, Pals G, Ikeda H, Fox EA, D'Andrea AD. Biallelic inactivation of BRCA2 in Fanconi Anemia. Science 297:606-609, 2002.
2. Taniguchi T, Tischkowitz M, Ameziane N, Hodgson SV, Mathew CG, Joenje H, Mok SC, D'Andrea AD. Disruption of the Fanconi Anemia/BRCA pathway in cisplatin-sensitive ovarian tumors. Nature Medicine 9:568-74, 2003
3. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov. 2015 Nov;5(11):1137-54. PMCID: PMC4631624
4. Hill SJ, Decker B, Roberts EA, Horowitz NS, Muto MG, Worley MJ, Feltmate CM, Nucci MR, Swisher EM, Nguyen H, Yang C, Morizane R, Kochupurakkal BS, Do KT, Konstantinopoulos PA, Liu JF, Bonventre JV, Matulonis UA, Shapiro GI, Berkowitz RS, Crum CP, D'Andrea AD. Prediction of DNA Repair Inhibitor Response in Short Term Patient-Derived Ovarian Cancer Organoids. Cancer Discov. 2018. Epub 2018/09/15. doi: 10.1158/2159-8290.CD-18-0474. PMCID:PMC6365285 [Available on 2019-11-01]

B. Positions and Honors.

Positions.

1977-78 Research Associate, Laboratory of Dr. William Haseltine, Dana-Farber Cancer Institute, Boston, MA. Project: DNA damage and repair.
1980-83 Research Associate, Laboratory of Dr. Samuel Latt, Children's Hospital, Boston, MA. Project: DNA replication kinetics.
1983-86 Resident in Pediatrics, Children's Hospital of Philadelphia
1986-87 Fellow in Medicine, (Hematology/Oncology), Children's Hospital, Boston
1987-91 Postdoctoral Fellow, Laboratory of Dr. Harvey Lodish, Whitehead Institute, Cambridge, MA. Project: Molecular cloning of the Erythropoietin Receptor.
1991-95 Assistant Professor of Pediatrics, Harvard Medical School
1995-00 Associate Professor of Pediatrics, Harvard Medical School
2000- Professor of Pediatrics, Harvard Medical School, Dana-Farber Cancer Institute
2003-17 Chief, Division of Genomic Stability and DNA Repair, Dana-Farber Cancer Institute
2003- The Fuller-American Cancer Society Professor, Harvard Medical School, Department of Radiation Oncology and Pediatrics
2013- Director: Center for DNA Damage and Repair, Dana-Farber Cancer Institute
2017- Director: Susan F. Smith Center for Women's Cancers, Dana-Farber Cancer Institute

Other Experience and Professional Memberships

1998-02 Member: NIH Hematology 2 Study Section
2003-08 Senior Editor: Molecular Cellular Biology
2004 Editorial Board: Blood Journal
2004 Leukemia and Lymphoma Society (LLS) Scientific Advisory Board
2005 Editorial Board: Journal of Clinical Investigation
2006 Editorial Board: Cancer Research
2012-14 Chairman, NIH Molecular and Cellular Hematology Study Section
2013- External Advisor, Vanderbilt University Cancer Center
2013- Member, Joint Scientific Advisory Committee, AACR Stand Up To Cancer/St. Baldrick's Foundation
2013- Chairman, LLS Career Development (CDP) Review Committee
2013- Member, LLS Medical and Scientific Advisory Board
2013- Associate Member, Broad Institute
2013- External Advisor, Abramson Family Cancer Institute, University of Pennsylvania
2014- Member, External Advisory Board, Malignant Hematopoiesis Program, Mt. Sinai School of Medicine
2014- Member, NCI Board of Scientific Counselors for Basic Sciences
2015- Leader: SU2C-AACR Ovarian Cancer Dream Team, DNA Repair Therapies for Ovarian Cancer

Honors and Awards:

1987 NIH/NHLBI Physician Scientist Award (K08)
1990 March of Dimes Basil O'Connor Scholar Award
1990 Lucille Markey Scholar Award
1995 Elected Member, American Society of Clinical Investigators (ASCI)
1997 The American Academy of Pediatrics Award for Excellence in Pediatric Research
2000 Stohlman Scholar, The Leukemia & Lymphoma Society
2000 Doris Duke Distinguished Clinical Scientist Award
2000 The Ted Williams Senior Investigatorship, Dana-Farber Cancer Institute
2001 E. Mead Johnson Award, Society for Pediatric Research
2003 Award of Merit, The Fanconi Research Fund
2003 Award of Merit, The German Fanconi Anemia Research Fund
2003 Elected Member, American Association of Physicians (AAP)
2004 Merit Award, National Institutes of Health
2004 Speaker, Presidential Symposium, ASH
2005 Keynote Address, MD-PhD Retreat, University of Pennsylvania
2006 The Wilkinson Memorial Lecture, British Society of Hematology

2007 The Abelson Lecture, University of Washington, Seattle, WA.
2008 Chairman, NCI Workshop on DNA Repair and Cancer Therapy
2009 Chairman, Mammalian DNA Repair Gordon Research Conference
2009 Merit Award, National Institutes of Health, NHLBI
2009 Brian P. O'Dell Memorial Research Award, LLS
2010 Keynote Address, International Workshop on Radiation Damage to DNA
2011 Speaker, Presidential Symposium, ASH
2012 AACR G.H.A. Clowes Memorial Award
2012 Fellow, American Association for the Advancement of Science (AAAS)
2014 Plenary Basic Science Speaker, San Antonio Breast Cancer Symposium (SABCS)
2017 Member, National Academy of Medicine (NAM)
2018 Ernest Beutler Lecture and Prize, American Society of Hematology (ASH)

No foreign affiliation.

C. Contribution to Science

1. I have a longstanding interest in hematopoiesis. I cloned the EPO-Receptor as a postdoctoral fellow in Harvey Lodish's laboratory and continued my EPO-Receptor and Cytokinesis Receptor research as a faculty member at the Dana-Farber Cancer Institute. As a hematopoiesis expert, I was invited to chair hematopoiesis study sections at the National Institutes of Health and the Leukemia and Lymphoma Society.
   a. D'Andrea AD, Lodish HF, Wong GG. Expression cloning of the murine erythropoietin receptor. Cell 57:277-285, 1989.
   b. D'Andrea AD, Fasman GD, Lodish HF. Erythropoietin receptor and interleukin-2 receptor beta chain: a new receptor family. Cell 58:1023, 1989.
   c. D'Andrea AD, Cytokine receptors in congenital hematopoietic Disease. N Engl J Med 330:839-846, 1994.
   d. Zhang H, Kozono DE, O'Connor KW, Vidal-Cardenas S, Rousseau A, Hamilton A, Moreau L, Gaudiano EF, Greenberger J, Bagby G, Soulier J, Grompe M, Parmar K, D'Andrea AD. TGF-β Inhibition Rescues Hematopoietic Stem Cell Defects and Bone Marrow Failure in Fanconi Anemia. Cell Stem Cell, 2016 May 5;18(5):668-81. PMCID: PMC4860147

2. In addition to these contributions, I contributed significantly to elucidating the role of protein ubiquitination and deubiquitination in the process of DNA repair. Since these early reports from my laboratory, it has become clear that protein ubiquitination is a critical regulating mechanism in DNA repair.
   a. Huang TT, Nijman S, Mirchandani K, Galardy P, Cohn M, Haas W, Gygi S, Ploegh H, Bernards R, D'Andrea AD. Regulation of Monoubiquitinated PCNA by DUB Autocleavage. Nature Cell Biology 8: 341-347, 2006.
   b. Cohn MA, Kowal P, Yang K, Haas W, Huang T, Gygi SP, D'Andrea AD. A UAF1-containing multisubunit protein complex regulates the Fanconi Anemia Pathway. MolCell 28:786-797, 2007.
   c. Kee, Y., Kim, J. M. & D'Andrea, A. D. Regulated degradation of FANCM in the Fanconi anemia pathway during mitosis. Genes Dev 23, 555-560 (2009). PMCID: PMC2658523
   d. Li H, Lim KS, Kim H, Hinds TR, Jo U, Mao H, Weller CE, Sun J, Chatterjee C, D'Andrea AD, Zheng N. Allosteric Activation of Ubiquitin-Specific Proteases by β-Propeller Proteins UAF1 and WDR20. Mol Cell. 2016 Jul 21;63(2):249-260. PMCID: PMC4958508

3. My laboratory uses the underlying principles of DNA repair biology to predict the drug sensitivity of human leukemias and solid tumors. We have identified DNA repair abnormalities which underlie the cisplatin and PARP inhibitor sensitivities of various solid tumors, including breast and ovarian cancers.
   a. D'Andrea AD. The Fanconi Anemia and Breast Cancer Susceptibility Pathways. 2010 N Engl J Med 362: 1909-1919. PMC3069698
   b. Ceccaldi R, Liu J, Amunugama R, Hajdu I, Primack B, Petalcorin MIR, O'Connor KW, Konstantinopoulos PA, Elledge SJ, Boulton SJ, Yusufzai T, D'Andrea AD. Homologous recombination (HR)-deficient tumors are hyper-dependent on POLQ-mediated repair. Nature. 2015 Feb 12;518(7538):258-62. PMCID: PMC4631624

c. Kim J, Mouw KW, Polak P, Braunstein LZ, Kamburov A, Kwiatkowski DJ, Rosenberg JE, Van Allen EA, D'Andrea AD, Getz G. Somatic ERCC2 Mutations Are Associated with a Distinct Genomic Signature in Urothelial Tumors. Nat Genet. 2016 Jun;48(6):600-6. PMCID: PMC4936490
d. Rondinelli B, Gogola E, Yücel H, Duarte AA, van de Ven M, van der Sluijs R, Konstantinopoulos PA, Jonkers J, Ceccaldi R, Rottenberg S, D'Andrea AD. EZH2 promotes degradation of stalled replication forks by recruiting MUS81 through histone H3 trimethylation. Nat Cell Biol. 2017 Oct 16. doi: 10.1038/ncb3626

Complete list of Published Work
http://www.ncbi.nlm.nih.gov/pubmed?term=D'Andrea%20AD%5BAuthor%5D

D. Research Support.
Ongoing Research Support

5R01HL52725-25 (PI: D'Andrea) 04/15/15 – 03/31/20* NCE
NIH/NHLBI
Molecular Pathogenesis of Fanconi Anemia
This study investigates the molecular pathogenesis of Fanconi Anemia using the recently cloned human Fanconi Anemia Complementation Group C (FACC) cDNA and a newly developed antiserum against the FACC polypeptide.

PRIVATE SUPPORT (D'Andrea) 10/1/11-9/30/19
Extending the use of PARP Inhibitors for Triple Negative Breast Cancer Therapy
Goals/Aims: To determine whether the combination of Velcade plus ABT-888 has enhanced cytotoxic activity for TNBC cell lines *in vitro,* compared to each agent alone; To generate colonies of mice bearing human TNBC orthotopic implants (derived from TNBC cell lines or from TNBC patient biopsies) and to treat these mice with the combination of Velcade plus ABT-888. As a subaim, we will examine the tumors dissected from these mice with numerous pharmacodynamic markers (i.e., immunohistochemistry for pBRCA1, FANCD2-Ub, and RAD51).

5P01HL048546-23 (PI: Grompe)
Pathophysiology and Treatment of Fanconi/Project 2 and Core 9/1/16-5/31/21
NIH
The major goals of this study are 1) determine the mechanism by which TGF-β inhibitors promote FA cellular growth and regulate DNA repair, 2) to determine whether inhibition of TGF-β pathway rescues hematopoietic defects in FA mouse models, and 3) to determine whether inhibition of TGF-β pathway rescues hematopoietic defects in primary bone marrow cells from FA patients.
Role: Project PI

Breast Cancer Research Program: Breakthrough Award (PI: D'Andrea)
DOD 9/1/16-8/31/19
BC151331P1 Dissecting the mechanisms of drug resistance in BRCA ½ mutant breast cancers
The major goal of this study is to identify novel molecular mechanisms of PARPi resistance in *BRCA1/2*-mutated breast cancer.

WITHHELD (PI: D'Andrea) 7/1/16-6/30/20*NCE
PRIVATE SUPPORT
DNA Repair Therapies for Ovarian Cancer
Major goals of this study are to collect and distribute tumor samples, and blood samples, from TNBC (Triple Negative Breast Cancer) and HGSOC (High Grade Serous Ovarian Cancer) patients enrolled in this joint Tesaro/Merck/SU2C clinical trial and to complete the indicated biomarker studies, from multiple industry-sponsored and academic laboratories, and to analyze the collected data.
Role: PI

Richard & Susan Smith Family Foundation (PI: D'Andrea) 9/1/17-8/31/19
Ovarian Tumor Living Biobank

Major goals are to establish the Susan F. Smith Center Living Biobank of recurrent and primary ovarian tumors at Dana-Farber, and to disseminate the knowledge gained from the initiative to investigators with specialties that span multiple cancer types.
Role: PI
Overlap: None

PRIVATE SUPPORT (PI: D'Andrea) 11/1/18/-12/31/19
Exploiting DNA Repair Gene Mutations in Pancreatic Cancer
Major goal of this study is to identify the most potent combinatorial strategy, along with predictive biomarkers, that will inform the design of a clinical trial for PDAC patients.
Role: PI

PRIVATE SUPPORT (PI: D'Andrea) 3/1/19-2/28/21
Nanoparticle-mediated Drug Delivery to Ovarian Cancer Organoid Cultures
Major goal of this study is to understand; 1) the mechanisms that lead to HGSC sensitivity and resistance to various immune and DNA damage repair therapies and 2) what the best method of delivering specific therapies for these defects is.
Role: PI

NIH 1P01CA228696-01A1 (PI: Kantoff) 7/1/19-6/30/24
Project 3: Functional Evaluation and Interpretation of DDR Variants in Prostate Cancer
Major goal of this proposal is to determine whether specific DNA repair gene mutations in prostate cancers are deleterious and vulnerable to targeted therapy.
Role: Project Leader

DF/HCC SPORE in Gastrointestinal Cancer 7/1/19-6/30/24
P50CA127003 (Bass/El-Bardeesy) Project 3
Major goal of this proposal is to define optimal strategies for identifying PDAC patients with DDR deficiency and to conduct innovative PARP inhibitor treatment trials to improve care for these patients.
Role: Co-Project Leader

PRIVATE SUPPORT (D'Andrea/Cubillos-Ruiz) 6/1/19-5/31/2021
Resistance to PARP inhibitor plus anti-PD1 therapy driven by ER stress and bioactive lipids in ovarian cancer
Major goals of this proposal are to evaluate the status of LPA/PERK-controlled signatures in responder vs. non-responder patients, and to determine whether inhibition of LPA-PERK sensitizes OC to Niraparib and Pembrolizumab.
Role: Co-PI

PRIVATE SUPPORT (PI: Sung) 7/1/19-6/30/23
Dissection of BRCA-mediated Tumor Suppression Pathways
Major goals of this study are to evaluate the PARPi and platinum-resistant mechanisms, and to determine their impact on patient drug response.
Role: Specific 4 Project Leader

P50CA168504-06A1 (Winer) 7/01/19 – 06/30/24
NIH/NCI
Dana-Farber/ Harvard Cancer Center SPORE in Breast Cancer – Developmental Research Program
The overall goal of the Developmental Research Program (DRP) is to advance high quality, novel, early-phase research, to foster new ideas in breast cancer research and to move research projects from a pilot stage to a level where external funding for more mature research is possible. A secondary goal of the DRP is to create opportunities for the career development of junior faculty or senior investigators who are interested in transitioning into breast cancer research. The DRP will be co-led by Alan D'Andrea, MD and Nikhil Wagle, MD. They will work with a standing committee made up of SPORE and DF/HCC investigators to review applications.
Role: Co-Director, DRP

Other Grant Support

D'Andrea, A.D.

ACTIVE

5R01HL52725-24 (PI: D'Andrea) 4/15/15-3/31/20 *NCE
NIH $245,000
Molecular Pathogenesis of Fanconi Anemia
Goals/Aims: This study investigates the molecular pathogenesis of Fanconi Anemia using the human Fanconi Anemia Complementation Group C (FACC) cDNA and a newly developed antiserum against the FACC polypeptide.

PRIVATE SUPPORT **(PI: D'Andrea)** 10/1/11-9/30/19
$208,334
Extending the use of PARP Inhibitors for Triple Negative Breast Cancer Therapy
Goals/Aims: To determine whether the combination of Velcade plus ABT-888 has enhanced cytotoxic activity for TNBC cell lines *in vitro,* compared to each agent alone; To generate colonies of mice bearing human TNBC orthotopic implants (derived from TNBC cell lines or from TNBC patient biopsies) and to treat these mice with the combination of Velcade plus ABT-888. As a subaim, we will examine the tumors dissected from these mice with numerous pharmacodynamic markers (i.e., immunohistochemistry for pBRCA1, FANCD2-Ub, and RAD51).

WITHHELD **(PI: D'Andrea)** 7/1/16-6/30/20*NCE
PRIVATE SUPPORT
DNA Repair Therapies for Ovarian Cancer $919,235
Major goals of this study are to collect and distribute tumor samples, and blood samples, from TNBC (Triple Negative Breast Cancer) and HGSOC (High Grade Serous Ovarian Cancer) patients enrolled in this joint Tesaro/Merck/SU2C clinical trial and to complete the indicated biomarker studies, from multiple industry-sponsored and academic laboratories, and to analyze the collected data.
Role: PI

5P01HL048546 (PI: Grompe)
Pathophysiology and Treatment of Fanconi/Project 2 and Core
NIH 9/1/16-5/31/21
$383,000
The major goals of this study are 1) determine the mechanism by which TGF-β inhibitors promote FA cellular growth and regulate DNA repair, 2) to determine whether inhibition of TGF-β pathway rescues hematopoietic defects in FA mouse models, and 3) to determine whether inhibition of TGF-β pathway rescues hematopoietic defects in primary bone marrow cells from FA patients.
Role: Project PI

Breast Cancer Research Program: Breakthrough Award (PI: D'Andrea)
DOD 9/1/16-9/29/19
$166,666
BC151331P1 Dissecting the mechanisms of drug resistance in BRCA ½ mutant breast cancers
The major goal of this study is to identify novel molecular mechanisms of PARPi resistance in *BRCA1/2*-mutated breast cancer.
Role: Partnering PI (Initiating PI – Nussenzweig)

PRIVATE SUPPORT **(PI: D'Andrea)** 9/1/17-8/31/19
$1,379,612
Ovarian Tumor Living Biobank

Major goals are to establish the Susan F. Smith Center Living Biobank of recurrent and primary ovarian tumors at Dana-Farber, and to disseminate the knowledge gained from the initiative to investigators with specialties that span multiple cancer types.
Role: PI

PRIVATE SUPPORT **(PI: D'Andrea)** 3/27/17-3/28/20* NCE
$171,428

Preclinical Study of the CHK1 inhibitor LY2606368 in Combination with the ATR Inhibitor VX-970 in Cell Line and Patient-Derived Xenograft Models of Triple-Negative Breast and Ovarian Cancer
Major goal of this study is to study the combination of the CHK1 inhibitor prexasertib (LY2606368) and the ATR inhibitor VX-970 in preclinical cell line and patient-derived xenograft (PDX) models of TNBC and EOC
Role: PI

PRIVATE SUPPORT **(PI: D'Andrea)** 4/5/18-4/4/20
$168,539

Evaluation of CHK-1 independent homologous recombination-mediated DNA repair as a mechanism of prexasertib resistance
Major goal of this study is to utilize the RAD51 assay to assess the HR status of prexasertib-resistant cell lines developed by members of our laboratory and collaborators at Lilly.

PRIVATE SUPPORT **(TGF beta) (PI: D'Andrea)** 3/25/19-3/24/21
$84,986

Preclinical studies of TGF betaR1- inhibitor LY3200882 in Fanconi Anemia
Major goal of this study is to study the activity of LY3200882 in preclinical models of Fanconi Anemia.

PRIVATE SUPPORT **(PI: D'Andrea)** 11/28/17-11/27/19
$168,539

Preclinical Studies of DNA Repair and Cell Cycle Checkpoint Inhibitors
Major Goal of this study is to systematically evaluate three new drugs from Merck EMD Serono in multiple cancer cell line models and PDX mouse models.

PRIVATE SUPPORT **(PI: D'Andrea)** 11/1/18/-12/31/19
$900,000

Exploiting DNA Repair Gene Mutations in Pancreatic Cancer
Major goal of this study is to identify the most potent combinatorial strategy, along with predictive biomarkers, that will inform the design of a clinical trial for PDAC patients.
Role: PI

PRIVATE SUPPORT **(PI: D'Andrea)** 3/1/19-2/28/21
$165,217

Nanoparticle-mediated Drug Delivery to Ovarian Cancer Organoid Cultures
Major goal of this study is to understand; 1) the mechanisms that lead to HGSC sensitivity and resistance to various immune and DNA damage repair therapies and 2) what the best method of delivering specific therapies for these defects is.
Role: PI

1P01CA228696-01A1(PI: Kantoff) 7/1/19-6/30/24
NIH $156,000
Project 3: Functional Evaluation and Interpretation of DDR Variants in Prostate Cancer
Major goal of this proposal is to determine whether specific DNA repair gene mutations in prostate cancers are deleterious and vulnerable to targeted therapy.
Role: Project Leader

PRIVATE SUPPORT 7/1/19-6/30/24

P50CA127003 (Bass/El-Bardeesy)
NIH $66,666
Project 3
Major goal of this proposal is to define optimal strategies for identifying PDAC patients with DDR deficiency and to conduct innovative PARP inhibitor treatment trials to improve care for these patients.
Role: Co-Project Leader

PRIVATE SUPPORT **(D'Andrea/Cubillos-Ruiz)**
6/1/19-5/31/2021
PRIVATE SUPPORT $125,000 (DFCI portion)
$250,000 (total direct costs including a subcontract)
Resistance to [redacted] inhibitor plus anti-PD1 therapy driven by ER stress and bioactive lipids in ovarian cancer
Major goals of this proposal are to evaluate the status of LPA/PERK-controlled signatures in responder vs. non-responder patients, and to determine whether inhibition of LPA-PERK sensitizes OC to Niraparib and Pembrolizumab.
Role: Co-PI

PRIVATE SUPPORT **(PI: Sung)**
7/1/19-6/30/2023
$213,068
Dissection of BRCA-mediated Tumor Suppression Pathways
Major goals of this study are to evaluate the PARPi and platinum-resistant mechanisms, and to determine their impact on patient drug response.
Role: Specific 4 Project Leader

P50CA168504-06A1 (Winer) 04/01/19 – 03/31/24
NIH/NCI $12,134 (Salary & Fringe only)
Dana-Farber/ Harvard Cancer Center SPORE in Breast Cancer – Developmental Research Program
The overall goal of the Developmental Research Program (DRP) is to advance high quality, novel, early-phase research, to foster new ideas in breast cancer research and to move research projects from a pilot stage to a level where external funding for more mature research is possible. A secondary goal of the DRP is to create opportunities for the career development of junior faculty or senior investigators who are interested in transitioning into breast cancer research. The DRP will be co-led by Alan D'Andrea, MD and Nikhil Wagle, MD. They will work with a standing committee made up of SPORE and DF/HCC investigators to review applications.
Role: Co-Director, DRP

PENDING

PENDING SUPPORT

PENDING SUPPORT

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	B
1.		Sarah	J.	Hill		PD/PI	192,300.00	9			144,225.00	

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fring
Total Number Other Personnel						**Total Othe**

Total Salary, Wages and Fringe Be

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period:** 1

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item **Funds Requested ($)***

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel **Funds Requested ($)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)***

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period:** 1

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Cost	50,000.00
Total Other Direct Costs	**50,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**234,608.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8	234,608.00	18,769.00
		Total Indirect Costs	**18,769.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Ryan McCarthy, 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**253,377.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	253,377.00

L. Budget Justification* File Name: Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	B
1.		Sarah	J.	Hill		PD/PI	192,300.00	9			144,225.00	

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fring
Total Number Other Personnel						**Total Othe**

Total Salary, Wages and Fringe Be

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period:** 2

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
	Total Equipment

Additional Equipment: File Name:

D. Travel **Funds Requested ($)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)***

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period:** 2

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Cost	50,000.00
Total Other Direct Costs	**50,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**234,608.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8	234,608.00	18,769.00
		Total Indirect Costs	**18,769.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Ryan McCarthy, 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**253,377.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	253,377.00

L. Budget Justification* File Name: Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12901467 Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	B
1.		Sarah	J.	Hill		PD/PI	192,300.00	9			144,225.00	

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fring
	Total Number Other Personnel					**Total Othe**

Total Salary, Wages and Fringe Be

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period:** 3

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
	Total Equipment

Additional Equipment: File Name:

D. Travel **Funds Requested ($)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)***

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period:** 3

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Cost	50,000.00
Total Other Direct Costs	**50,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**234,608.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8	234,608.00	18,769.00
		Total Indirect Costs	**18,769.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Ryan McCarthy, 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**253,377.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	253,377.00

L. Budget Justification* File Name: Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12901467 Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period: 4**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	B
1.	Sarah	J.	Hill		PD/PI	192,300.00	9			144,225.00	

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fring

Total Number Other Personnel **Total Othe**

Total Salary, Wages and Fringe Be

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period:** 4

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period:** 4

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Cost	50,000.00
Total Other Direct Costs	**50,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**234,608.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8	234,608.00	18,769.00
		Total Indirect Costs	**18,769.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Ryan McCarthy, 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**253,377.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	253,377.00

L. Budget Justification* File Name: Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	B
1.		Sarah	J.	Hill		PD/PI	192,300.00	9			144,225.00	

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fring
	Total Number Other Personnel					**Total Othe**

Total Salary, Wages and Fringe Be

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period:** 5

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item **Funds Requested ($)***

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel **Funds Requested ($)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)***

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 0765807450000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period:** 5

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Cost	50,000.00
Total Other Direct Costs	**50,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**234,608.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	8	234,608.00	18,769.00
		Total Indirect Costs	**18,769.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Ryan McCarthy, 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**253,377.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	253,377.00

L. Budget Justification* File Name: Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12901467 Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

BUDGET JUSTIFICATION

PERSONNEL:

Sarah J. Hill, M.D., Ph.D., Principal Investigator (calendar months)

Dr. Hill has just completed her Women's and Perinatal Pathology Fellowship at Brigham and Women's Hospital (BWH) on July 1, 2019. She is now an Associate Pathologist at BWH and a clinical fellow at Dana Farber Cancer Institute (DFCI). She will be appointed as an Instructor in Radiation Oncology at DFCI before the end of 2019. Dr. Hill will obtain all tissue/ fluids for organoid generation, genearte all cultures, perform all experiments, interpret all data, and prepare data for publication and presentation for all of the work outlined in the proposal. She will devote the majority of her effort to the research and career development in this proposal (% effort, person months) and will focus on her clinical duties including signing out gynecologic pathology and teaching residents in the BWH pathology department with % of her time (person months). The remaining % of her time (person months) will be devoted to other research projects. Her initial base salary is $ which is comparable to other junior research faculty at DFCI with simialr clinical responsibilities and research training. The fringe benefits rate at DFCI is at 28%.

Alan D'Andrea, M.D., Mentor (0 calendar months)

Dr. D'Andrea is the Fuller-American Cancer Society Professor of Radiation Oncology, Harvard Medical School, and the Director of Susan F. Smith Center for Women's Cancers at the Dana-Farber Cancer Institute. Dr. D'Andrea is an expert in investigating molecular mechanisms of DNA repair. Dr. D'Andrea is also the co-leader of the SU2C Ovarian Cancer Research Team. Dr. D'Andrea will mentor Dr. Hill on the project and in career progression. He will have no measurable effort on the project, and no salary is requested.

RESEARCH-RELATED EXPENSES:

Program-related expenses ($50,000) are requested per year according to the NCI instructions and the following items are requested:

Laboratory Supplies

The supply budget will cover the expense of organoid generation, culture, and functional analysis. The budget will also cover a small portion of the proposed DNA sequencing. Dr. D'Andrea's lab will cover the remaining cost of DNA sequencing and any additional supplies by his discretionary fund.

For organoid culture, the supply budget will include supplies for basic culturing materials (base media, growth factors, matrigel), functional assays such as the DNA fiber assay or drug sensitivity testing, and immunohistochemical analysis of the organoids (cutting paraffin embedded organoids onto slides and performing immunohistochemistry staining for geminin and RAD51). The budget will also cover genomic sequencing in aims 1 and 3.

	Year 1	Year 2	Year 3	Year 4	Year 5
Organoid culture media	$20,000	$15,000	$15,000	$17,000	$24,000
DNA fiber assay reagents	$6,000	$6,000	$6,000	$6,000	$6,000
Antibodies	$1,000	$1,000	$1,000	$1,000	$1,000
DNA damage drugs	$2,000	$2,000	$2,000	$2,000	$2,000
DNA Sequencing	$14,000	$14,000	$4,000	$0	$0
Consumables	$5,000	$5,000	$5,000	$5,000	$15,000
Total:	$48,000	$43,000	$33,000	$31,000	$48,000

Core Facilities:
For murine model generation, maintenance, treatment, and tumor analysis, the core facility at the Belfer Center will be used:

Year 2: $5,000
Year 3: $15,000
Year 4: $17,000

The costs would include purchase of female immune-compromised mice, initial injection of female immune-compromised mice with luciferized organoid cultures for xenograft generation, expansion of xenograft models, drug treatment of xenograft models, subsequent tumor and survival monitoring, maintenance of xenograft models, and necropsy on select animals after experiments are completed. Dr. D'Andrea's lab will cover the remaining cost of murine experiments by his discretionary fund.

Travel: ($2,000/year for years 1-5)

Funds are requested for Dr. Hill to attend three national scientific conferences (AACR Annual Meeting, AACR Ovarian Cancer Meeting, DNA Damage Repair Meeting) per year. The expenses covered include transportation, lodging, all conference fees, and meals.

The requested funds will be used solely for the research and career development activities proposed in this application.

INDIRECT COSTS:

Per PA-19-117 announcement, 8% indirect cost is requested during the funding period.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		923,040.00
Section B, Other Personnel		
Total Number Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)		923,040.00
Section C, Equipment		
Section D, Travel		
1. Domestic		
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		250,000.00
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	250,000.00	
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		1,173,040.00
Section H, Indirect Costs		93,845.00
Section I, Total Direct and Indirect Costs (G + H)		1,266,885.00
Section J, Fee		
Section K, Total Costs and Fee (I + J)		1,266,885.00

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OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ● Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

● Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

● Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount ($) *Source(s)

Tracking Number: GRANT12901467

Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

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3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/ste m_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

☐ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

■ Change of Grantee Institution

*Name of former institution:

Tracking Number: GRANT12901467 Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	Introduction.pdf
Candidate Section	
2. Candidate Information and Goals for Career Development	Candidat e_Section.pdf
Research Plan Section	
3. Specific Aims	Specific_Aims.pdf
4. Research Strategy*	Research_Strategy.pdf
5. Progress Report Publication List (for Renewal applications)	
6. Training in the Responsible Conduct of Research	Training_RCR.pdf
Other Candidate Information Section	
7. Candidate's Plan to Provide Mentoring	
Mentor, Co-Mentor, Consultant, Collaborators Section	
8. Plans and Statements of Mentor and Co-Mentor(s)	Mentor_Statement.pdf
9. Letters of Support from Collaborators, Contributors, and Consultants	LOS.pdf
Environment and Institutional Commitment to Candidate Section	
10. Description of Institutional Environment	Institutional_Environment.pdf
11. Institutional Commitment to Candidate's Research Career Development	Institutional_Commitment.pdf
Other Research Plan Section	
12. Vertebrate Animals	Vertebrate_Animals.pdf
13. Select Agent Research	Select_Agent_Research.pdf
14. Consortium/Contractual Arrangements	
15. Resource Sharing	Resource_Sharin g_Plan.pdf
16. Authentication of Key Biological and/or Chemical Resources	Authentication_Key_Biologic a l Chemica l Resources.pdf
Appendix	
17. Appendix	

Tracking Number: GRANT12901467
Funding Opportunity Number: PA-19-117. Received Date: 2019-07-11T13:42:55.000+04:00

PHS 398 Career Development Award Supplemental Form

Citizenship*:

18. U.S. Citizen or Non-Citizen National?* ● Yes ● No

If no, select most appropriate Non-U.S. Citizen option

- ☐ With a Permanent U.S. Resident Visa
- ■ With a Temporary U.S. Visa
- ☐ Not Residing in the U.S.

If you are a non-U.S. citizen with a temporary visa applying for an award that requires permanent residency status, and expect to be granted a permanent resident visa by the start date of the award, check here: ■

INTRODUCTION TO RESUBMISSION APPLICATION

CRITIQUE,RESPONSE TO CRITIQUE

CANDIDATE INFORMATION AND GOALS FOR CAREER DEVELOPMENT

1) Candidate background

I have a lifelong interest in mechanisms of human disease and am committed to becoming a physician scientist with an independent basic science laboratory. My interest in science and medicine began

PERSONAL INFORMATION

I knew from these experiences that my career goal was to study mechanisms of human disease both to satisfy my fascination with basic biology and to ensure the work I did had a positive clinical impact. Toward this goal, I started at Harvard College as an undergraduate and joined Dr. David Livingston's laboratory at Dana-Farber Cancer Institute (DFCI) where I completed my undergraduate thesis on the localization and function of BMI1 at DNA double strand breaks (1). During this training, I learned about basic science technique and experimental design. I was also fascinated by the way Dr. Livingston used his clinical knowledge to inform and develop the basic science hypotheses he pursued. I was inspired to apply to combined MD/PhD programs in order to train in both science and medicine so that I could execute hypothesis-driven research on mechanisms of disease informed by my own clinical experience.

Before entering medical school, I received a Rhodes Scholarship and completed an MSc in Biochemistry in Dr. Kim Nasmyth's laboratory at Oxford University. This training helped further develop my ability to form a scientific hypothesis and to design controlled experiments. I studied yeast genetics and utilized *S. cerevisiae* to understand the dynamic localization of the cohesin complex on chromosomes during the cell cycle. I was fascinated by the elegant model system and the mechanisms we discovered, but my mind was drawn to the ways our findings might apply to human disease.

Upon returning from Oxford, I entered the MD/PhD program at Harvard Medical School (HMS) and completed my PhD in Dr. David Livingston's laboratory at DFCI. This work focused on mechanisms by which DNA damage repair (DDR) defects contribute to both breast and ovarian carcinogenesis. During my PhD training, I further developed the skills to identify important questions in human disease, generate mechanistic hypotheses, design well controlled experiments, and write papers and grants. I executed an array of molecular biology techniques in human cell lines and conducted yeast two hybrid screens. I worked on three large projects which resulted in a total of five published papers, including three first-author publications (2-6). In the first, I showed that sporadic basal-like breast tumors do not harbor homologous recombination defects, rather they harbor defects in stalled replication fork protection (2). In the second, I discovered a new role for BRCA1 in the prevention and repair of transcription-associated DNA damage, in particular in the prevention of R-loop associated DNA damage and the restart of stalled transcription forks (3, 5). In the third, I discovered that RNA binding proteins associated with amyotrophic lateral sclerosis (ALS), FUS and TDP43, are critical in preventing R-loop-associated DNA damage during transcription suggesting that some forms of ALS might be due to DNA damage induced by R-loops when these proteins are functionally lost (4). I funded my PhD training with both a DOD BCRP and an NCI NIH F30 Pre-Doctoral fellowship. As a result of this work, I was invited to give multiple local and national presentations and received my PhD and MD honors theses. More importantly, I became a disciplined bench scientist with the ability to ask and address clinically important basic science questions and maintained my desire to become an independent investigator.

After defending my PhD, I completed the last two years of medical school. Of all my rotations, I was most drawn to pathology, in particular to gynecologic pathology. I was fascinated by the gross and microscopic pathology of high grade serous ovarian tumors (HGSC). I could tell from the high tumor burden I was seeing after cytoreductions, and the poor therapeutic response of some of the patients I saw in the clinics, that this type of cancer still lacked truly effective therapies and needed better mechanistic understanding. I was also intrigued by the fact that genomic analysis has suggested that up to 50% of HGSCs may have a DDR defect. Given my interest in women's cancers and the DNA damage response from my PhD studies, gynecologic pathology seemed like a natural fit. I applied to anatomic pathology (AP) residencies across the country and was thrilled to be accepted into the program at Brigham and Women's Hospital (BWH) given its rich history of supporting physician scientists and its strong gynecologic pathology division.

Through my AP residency and Women's and Perinatal Pathology (WPP) fellowship, I have built an excellent foundation in gross and microscopic gynecologic diagnostic pathology. However, given my PhD research interests, I wondered about the DDR capacity of the HGSCs I diagnosed every day. I searched for a mentor who shared my combined interests and was excited to find Dr. Alan D'Andrea at DFCI who was actively investigating DDR defects in HGSC. Since joining the D'Andrea laboratory, I have worked to establish culture conditions for patient-derived HGSC organoids using my diagnostic abilities as a pathologist to collect appropriate tumor samples (7). I have established multiple functional assays to test the DDR capacity of these tumors and examine how functional defects lead to sensitivity to therapeutic agents targeting repair defects (7). This work led to a first author publication (7), and to an invitation to speak at the 2018 Rivkin Ovarian Cancer

Research Symposium. More importantly, I have developed key preliminary data and a hypothesis that challenges the current dogma in the field, which is the basis for the work in this mentored research career development award proposal.

In summary, my training to date has focused on studying basic science mechanisms of the genesis and treatment of human disease. From medical school through my clinical fellowship and now as I finish residency and start almost full time in the lab, I have been scientifically productive, publishing basic science papers at every level of training and demonstrating my continued commitment to the physician scientist career path. In my work as a gynecologic pathologist, and my research in DDR defects in HGSC, I have found an ideal way to combine my clinical and scientific interests as I transition to independence. Given my background in hypothesis-driven research and my motivation to become an independent investigator, I believe I have an excellent chance to become a leader and independent physician scientist in the field of ovarian cancer biology.

2) Career goals and objectives

My long-term career goal is to understand the mechanisms by which DDR defects lead to HGSC carcinogenesis and therapeutic sensitivity. Achieving this goal will require careful investigation of the different mechanistic alterations in multiple DDR pathways in tumors and the ways such alterations confer varying therapeutic sensitivities to DDR agents. I will study these defects in the new patient derived HGSC organoid model system described in my preliminary work. As a proof of principle, this work demonstrates my ability to generate HGSC organoids and that I have at least one functional assay to test for defects in each of the two key DNA repair pathways in HGSC. To further understand these repair mechanisms and begin to predict how these repair defects lead to HGSC therapeutic sensitivity, I will need additional training to acquire important new skills. This mentored research career development award offers an extraordinary opportunity to develop these critical skills with the focused mentorship of experts in the intersecting fields around my work. My Mentor and advisory committee have been carefully chosen based on their expertise in areas where I need additional training. I crafted this proposal and training plan with my Mentor and committee members, who are all physician investigators themselves and are deeply invested in my career development, so that I will be poised and ready upon completion of this award to become an independent physician scientist, and ultimately a leader in the field of ovarian cancer.

3) Candidate's plan for career development/training activities during award period

3A) Training program overview: During the award term, I plan to achieve the four training goals below (3B). My research strategy and career development plan include didactic sessions (3C), mentored experiences (3D), conference attendance (3E), and clinical duties relevant to my training goals (3F). During the award period, I will dedicate 75% of my time (9.0 person months) to the research outlined in this proposal, 10% to other research (1.2 person months), and 15% to clinical activities (1.8 person months). Upon completion of this five-year mentored research career development award training plan, I will become an independent physician scientist in the field of ovarian carcinogenesis and therapeutic sensitivity. I will develop the skills to manage my own laboratory focusing on DDR defects in ovarian cancer deploying molecular and cellular biology and genomic techniques on mouse models and human clinical samples, cell lines, and organoid models.

3B) Training Goals (TG):

1) ***To become proficient in analysis of genomic data:***
   Current knowledge/skill gap: I currently have limited experience analyzing whole genome/exome and RNA sequencing data. Sequencing analysis is a key tool in cancer biology, and I will need expertise in the execution and analysis of such experiments for the proposed work and my own independent research program.
2) ***To gain expertise in animal modeling of cancer***:
   Current Knowledge/skill gap: I currently have limited experience with animal models of human disease which allow for *in vivo* validation of *in vitro* findings, and I will need experience in the design, execution, and analysis of animal experiments to complete the work in this proposal and to carry out my own independent research program.
3) ***To gain expertise on the design and execution of clinical trials:***
   Current knowledge/skill gap: I will participate in clinical trials throughout my career both as a pathologist and as a scientist. I currently have limited experience with clinical trials and aim to better understand drug and patient selection, trial design, and trial execution to effectively participate in clinical trials in my future as an independent physician scientist.
4) ***To develop lab and personnel management skills:***
   Current knowledge/skill gap: I will need to acquire new leadership and management skills in order to lead multiple large projects, manage personnel, manage grants and other finances, and coordinate my and my staff's schedules to run my own lab while balancing my continuing clinical duties.

3C) Didactics: I plan to participate in five didactic courses and a longitudinal mentorship program to bolster my

scientific and professional skills. I will also undergo appropriate responsible conduct of research (RCR) training.
1) BMIF 315qc. Computational Statistics for Biomedical Sciences (3 hours per week for 1.5 months Fall Year 1, relevant to TG1-4 and Aims 1-3) This is a graduate level course offered by the Division of Medical Sciences (DMS) at HMS that offers students training in basic statistical analysis of biological data. It will aid me in analyzing data in this proposal and later in my independent work as a scientist and clinician.
2) BMIF 313qc. Computing Skills for Biomedical Sciences (3 hours per week for 1.5 months Fall Year 1, relevant to TG1) This is a graduate level course offered by the DMS at HMS that trains students in basic programming and computational platforms as a gateway to performing more complex genomic analyses.
3) Genetics 390qc: Experimental Approaches in Genetic Analysis (10 days, Winter Year 1, relevant to TG2 and Aim 3): This is a graduate level course offered by the DMS at HMS that provides an intensive two-week course with both lectures and lab experiences in genetically engineered models, including mouse modeling.
4) Clinical Trial & Experimental Design for Researchers (2 hours per week for four weeks, Spring year 2, relevant to TG3): This is a seminar series offered by BWH and led by clinical trialists explaining the different types of trials and how each is designed to educate research scientists who may participate on the translational arm of a trial.
5) *"Leadership Strategies for the Researcher"* (Two days, Spring Year 2, relevant to TG4) This is a workshop at HMS offering strategies for lab and personnel management.
6) *Grant Review And Support Program (GRASP)* (Multiple day-long seminars and mentoring throughout years 1-5, relevant to Aims 1-3 and TG4): This program at HMS offers long term guidance and mentorship to K08-funded early career researchers preparing to submit independent research grant applications (R01s).
3D) Mentored experiences: My mentorship team is led by Dr. Alan D'Andrea (Primary Mentor) who will oversee my training program and coordinate my advisory committee. Dr. D'Andrea has an excellent track record of mentoring researchers and physician scientists at all levels, including multiple K08 recipients, which will be invaluable in my transition to scientific independence. I will present my research and career progress to my individual mentors and committee for constant feedback as outlined in my monitoring plan below.
Mentorship team
1. **Alan D'Andrea, MD** (Primary Mentor): Director: Susan F. Smith Center for Women's Cancers, DFCI, Fuller-ACS Professor, HMS. Dr. D'Andrea has served as the mentor on my preliminary organoid work (7). He is a world expert in the DDR field focusing on the ways in which DDR defects contribute to disease genesis and therapeutic vulnerability with a special interest in HGSC. He is also an expert in mouse modeling of human disease and will help me to design, execute and analyze the *in vivo* validation experiments in Aim 3. He has published extensively in the DDR field and was the leader of the Stand Up To Cancer Ovarian Cancer Dream Team. He will provide experimental guidance regarding the DNA damage response, career mentorship, and additional support to execute the proposed work in all three Aims and all four TGs. In his lab, I will be involved in the hiring and management of a research technician, which will provide me with leadership experience (TG4). We will meet weekly to discuss experimental results, plan for further experiments and publications, and identify necessary external resources and every six months both one-on-one and with my committee for career progress monitoring.
2. Ursula Matulonis, MD (Advisory Committee): Chief, Division of Gynecologic Oncology, DFCI. Dr. Matulonis is a world expert on targeted treatment of HGSC. She will help oversee patient sample acquisition and clinical outcome data for Aim 1. Her mentorship will help me gain experience in the ovarian cancer field through our interactions at local and national gynecologic oncology research meetings, in the design and execution of clinical trials (TG3), and personnel management skills as we work with her team's clinical research coordinators (CRCs) (TG4). We will meet monthly to discuss research progress and every six months with the entire committee.
3. Arlene Sharpe, MD/PhD (Advisory Committee): George Fabyan Professor of Comparative Pathology, Microbiology and Immunobiology, HMS. Dr. Sharpe is an expert on T cell biology and the anti-tumor immune response. She is also an anatomic pathologist and member of the BWH pathology department. She will serve as a mentor for navigating a career in anatomic pathology as a scientist with an independent research program. She will meet with me along with the rest of my committee every six months to navigate progress toward promotion and help navigate academic pathology.
4. Rameen Beroukhim, MD/PhD (Advisory Committee): Assistant Professor of Medicine, DFCI. Dr. Beroukhim is an expert in genomic and transcriptomic analysis of tumors. He will mentor me in the genomic analysis of all tumors and organoids in Aim 1 (TG1). We will meet as needed to discuss experimental design and results and troubleshoot analysis issues. I will have the opportunity to attend his weekly lab meetings and interact with members of his lab to discuss data analysis and troubleshoot computational problems (TG1). He will also meet with me along with my entire committee every six months to monitor overall career and scientific progress.
5. Myles Brown, MD (Advisory Committee): Emil Frei III Professor of Medicine, DFCI. Dr. Brown is an expert in epigenetic regulation of steroid hormone effects and transcriptomic analysis of tumor samples. He has already been an important mentor for my early work with transcriptomic analysis of HGSC organoids, and he will continue to guide me in choosing further hits from my RNA sequencing data to study mechanistically. He is also a

practicing physician scientist and will function as a career advisor in applying for an R01, faculty interviews, and the promotion process. We will meet as needed informally to discuss data, plan future experiments, and discuss my progress toward promotional milestones. He will also participate in all committee meetings to monitor overall career and scientific progress.

6. Geoffrey Shapiro, MD/PhD (Advisory Committee): Director, Early Drug Development Center, DFCI. Dr. Shapiro is a phase I clinical trialist with a special interest in targeting DDR defects in solid tumors. Dr. Shapiro will aid me in the acquisition of specimens and patient outcomes in Aim 1. He will mentor me in clinical trial design (TG 3) and in personnel management as we work with his team's CRCs (TG 4). We will meet monthly to discuss organoid outcomes and every six months with my committee to discuss overall progress.

7. Daphne Haas-Kogan, MD (Chair, Radiation Oncology, DFCI): Professor of Radiation Oncology, HMS. Dr. Haas-Kogan is the chair of my academic department at DFCI, and we will meet every six months to discuss progress toward meeting critical milestones and promotion requirements.

8. Jeffrey Golden, MD (Chair, Pathology, BWH): Ramzi S. Cotran Professor of Pathology, HMS. Dr. Golden is chair of my clinical department at BWH, and we will meet annually to maintain my clinical appointment and discuss career progress.

Research and Career Development Progress Monitoring Plan: In addition to informal and scheduled meetings to discuss experimental design, data analysis, and next experimental steps with each committee member, I will meet with the committee as a group every 6 months. These meetings will include a scientific presentation of my work to allow for discussion of overall progress on all Aims of the research proposal, followed by discussion of my plans for research publication, grant submission, and next steps for faculty promotion. These bi-annual meetings will ensure that I am on track to achieve my career goals. In addition, I will meet separately one-on-one with both Dr. D'Andrea (mentor) and Dr. Haas-Kogan (research department chair), every six months for one hour specifically to discuss progress towards milestones for promotion. For the committee meetings and the individual meetings, I will prepare a list of goals prior to the meeting and record and follow the suggestions and strategies discussed in meeting these goals after the meeting.

3E) Conference attendance: I will attend local and national meetings to gain both clinical and scientific expertise, present and discuss my work, learn about advances in my field, and meet new collaborators. I will attend weekly Gynecologic Oncology Tumor Board meetings at BWH, monthly Gynecologic Oncology Research Meetings alternating between DFCI and Massachusetts General Hospital, and bi-weekly Gynecologic Pathology Interesting Case Conferences at BWH. National Meetings will include the American Association for Cancer Research (AACR) Annual Meeting in April, the annual AACR Ovarian Cancer Research Meeting in September, and one Keystone Symposium or Gordon Research Conference on DDR per year.

3F) Clinical Duties: I completed my residency and fellowship training at BWH and became an Associate Pathologist at BWH on July 1, 2019. I have now begun my clinical responsibilities as an attending Women's and Perinatal Pathologist at BWH (15% or 1.8 person months) which involves signing out on the Women's and Perinatal Pathology biopsy service, teaching residents and fellows gynecologic pathology, and performing occasional rapid autopsies on HGSC patients. These duties will help me become an expert in ovarian cancer pathobiology, stay abreast of developments in the field, and provide access to patient materials for the research in this proposal and my ongoing work in ovarian cancer.

3G) Summary and timeline of Research Strategy and Career Development Plan:

<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th></tr>
<tr><td rowspan="4">Training</td><td colspan="5">Training Goal 1: Develop expertise in analysis of sequencing data</td></tr>
<tr><td colspan="2"></td><td colspan="3">Training Goal 2: Develop expertise in animal modeling</td></tr>
<tr><td colspan="5">Training Goal 3: Develop expertise in clinical trial design</td></tr>
<tr><td colspan="5">Training Goal 4: Develop lab management and leadership skills</td></tr>
<tr><td rowspan="3">Specific Aims</td><td colspan="5">Aim 1: Determine importance of stalled fork defects and organoid predictive capacity in HGSC</td></tr>
<tr><td></td><td colspan="4">Aim 2 A-C: Understand mechanisms of stalled fork defects in HGSC</td></tr>
<tr><td colspan="2"></td><td colspan="3">Aim 3: Validate in vitro findings in vivo</td></tr>
<tr><td rowspan="3">Didactics</td><td>BMIF315qc. BMIF 313qc., Genetics390qc</td><td>Leadership and clinical trial courses</td><td colspan="3"></td></tr>
<tr><td colspan="5">GRASP</td></tr>
<tr><td>RCR</td><td colspan="2"></td><td>RCR</td><td></td></tr>
<tr><td>Meetings</td><td colspan="5">Attend AACR Annual Meeting, AACR Ovarian Cancer Meeting, and one DNA Damage meeting annually</td></tr>
<tr><td>Personnel</td><td colspan="5">Manage Technician</td></tr>
<tr><td>Publications</td><td colspan="2"></td><td>Submit paper on stalled fork prevalence, organoid prediction</td><td colspan="2">Submit paper on mechanisms of stalled fork defects</td></tr>
<tr><td>Funding</td><td colspan="3">Foundation grants</td><td>R01 drafting</td><td>R01 Submission</td></tr>
<tr><td>Clinical</td><td colspan="5">Gynecologic pathology attending and rapid autopsy attending HGSC</td></tr>
</table>

SPECIFIC AIMS

Background: Patients with High Grade Serous Ovarian Cancer (HGSC) have limited therapeutic options. Genomic analysis suggests that up to 50% of HGSCs have genomic alterations that may confer a DNA damage repair defect, making therapies that target repair defects, like carboplatin and PARP, CHK1, WEE1, and ATR inhibitors, important additional options. However, we have no means of predicting which genetic alterations confer specific repair defects and which defects translate to a therapeutic response in the patients.

A model system that allows for functional assays to assess for DNA damage repair defects and prediction of response to therapies targeting such defects is needed. Organoids are three-dimensional structures derived from human tumor tissue that anatomically and functionally mimic the tumor from which they were derived allowing for functional analysis of the parent tumor.

We have generated growth conditions for patient-derived HGSC organoids and have generated a platform of assays in the organoid cultures to test the two major DNA damage response pathways thought to be defective in HGSC, including homologous recombination (HR) repair of DNA double strand breaks and protection of stalled replication forks from degradation or collapse.

Our results thus far indicate that a small number of the cultures tested, specifically those with mutations in DNA repair genes, showed HR defects and sensitivity to PARP inhibitors, which cause cytotoxicity through a synthetic lethal mechanism in cells with HR defects. In contrast, a larger number of organoids from tumors both with and without mutations in known DNA damage repair genes showed stalled replication fork protection defects and sensitivity to agents targeting such defects, such as carboplatin and CHK1 and ATR inhibitors.

Hypothesis: Based on these data, *the hypothesis is* that stalled replication fork protection defects are more prevalent than HR defects in HGSC and that therapies targeting such a defect may offer benefit to a larger patient population. *The major goal of this work will be to* use HGSC organoids to understand the importance of fork instability in HGSC, uncover mechanisms leading to fork instability, and determine how such functional defects lead to different types of therapeutic sensitivities. In addition, this work will offer a well-rounded training program that will enable the investigator to transition to scientific independence.

Specific Aim 1: Assess the prevalence of stalled replication fork protection defects in HGSC and whether fork protection defects predicted by HGSC organoid functional assays lead to therapeutic sensitivity to carboplatin and ATR, WEE1, and CHK1 inhibitors. Generate patient derived HGSC organoid cultures from patients on standard of care therapies and enrolled in clinical trials with specific DNA damage repair agents. Perform HR and stalled fork protection functional assays and sensitivity testing with carboplatin, gemcitabine, and PARP, ATR, WEE1 and CHK1 inhibitors on the organoid cultures in parallel with paired whole genome sequencing of the organoids and tumors to assess the prevalence of each defect in HGSC with respect to the presence or absence of relevant genomic alterations in DNA damage repair genes. Correlate organoid culture sensitivities and functional assay results with patient response to the appropriate agents to assess organoid assay predictive capacity.

Specific Aim 2: Uncover mechanisms leading to fork instability and whether different mechanisms of fork protection defects lead to differing therapeutic sensitivities to the above agents. In a subset of organoid cultures from Aim 1, we will do the following:

A) Perform functional analysis of fork protection in fork stable and unstable organoids after treatment with different combinations of fork stalling agents to assess fork properties in different treatment settings.

B) Perform targeted western blots on fork stable and unstable cultures after treatment with fork stalling agents (used in Aim 2A) looking for alterations in ATR signaling which is involved in stalled fork protection.

C) Assess organoids from Aim 2A for epithelial and mesenchymal markers and for expression and localization of the transcription factor RUNX3, which may be involved in fork protection and prevention of epithelial to mesenchymal transition (EMT). Correlate RUNX3 and EMT status with organoid fork properties and therapeutic sensitivities from Aim 2A to determine if RUNX3 loss correlates with EMT, replication fork stabilization, and therapeutic resistance.

Specific Aim 3: ***In vivo* validation of *in vitro* mechanisms of stalled replication fork protection defects leading to therapeutic responses in organoid xenograft models of HGSC.** Generate four organoid xenograft models by injecting immune compromised mice with one of two representative fork unstable or one of two representative fork stable organoid cultures from 2A in which RUNX3 and EMT status is known. Assess therapeutic response of the four xenografts to vehicle, AZD6738 (ATR inhibitor), gemcitabine, and AZD6738+ gemcitabine. Compare tumor response and overall survival in the mice to organoid functional and sensitivity results with these agents from Aims 1 and 2 to provide preliminary *in vivo* validation of *in vitro* findings.

Impact: This work will use new functional assays (DNA repair) on a novel model system (organoids) to help understand the importance of stalled fork protection defects in treating HGSC. This work may generate a better mechanistic understanding of which stalled fork protection defects lead to therapeutic sensitivities and validate the use of HGSC organoid functional assays as a predictor of therapeutic response.

RESEARCH STRATEGY

Significance: Patients with high grade serous ovarian cancer (HGSC) have limited therapeutic options beyond platinum and paclitaxel-based chemotherapy. Genetic alterations in DNA Damage Repair (DDR) genes including somatic mutations, copy number changes, and methylation changes that may confer defects in repair pathways have been identified in up to 50% of HGSCs (8-10), making therapies that target such defects potential additional options. However, it is unclear if any of these genetic alterations confer functional defects.

Genetic alterations in the BRCA/Fanconi anemia pathway compose the largest number of hereditary and somatic alterations in HGSCs (8, 9). Proteins in these pathways participate in two major DDR pathways including the repair of double strand breaks by homologous recombination (HR) (9) and the protection of stalled replication forks (11). HR is a complex repair process that ensues when a break occurs in both sister chromatids in S-phase of the cell cycle and is repaired in an error-free fashion by a large group of proteins. Without HR, error prone repair mechanisms are used causing genomic instability. Stalled replication forks occur when a cell is trying to replicate its DNA prior to cell division and the replication machinery encounters an obstacle in the DNA. If the stalled fork is not protected, the fork can collapse leading to DNA damage and ultimately genomic instability (11). Although HR and stalled fork protection share some protein partners in the BRCA/Fanconi anemia family, they are ultimately thought to be separate functions (6, 12-14).

It is likely that defects in HR and stalled fork protection are targeted by different therapies. A class of drugs called PARP inhibitors (PARPi), which exert their cytotoxic effects through a synthetic lethal pathway in tumor cells with defects most likely in HR and possibly in the protection of stalled replication forks, have been commonly used to target tumors with purported HR defects (15). In contrast, two classic HGSC agents, the crosslinker carboplatin and the nucleoside analog gemcitabine, and three newer agents ATR, CHK1, and WEE1 inhibitors, are thought to cause replication stress and exacerbate stalled fork protection defects, making them potentially useful in HGSCs with these defects (16-20). We currently have no means of predicting what type of repair defect each tumor has and what kind of therapeutic response each defect will confer.

Until now, detecting a genomic alteration in a DDR gene in HGSC (8-10, 21), without any functional assays to assess the relevance of the alterations, has been used as a predictive marker of an HR defect and response to PARPis. Although clinical trials have suggested that some 'sporadic' HGSC patients respond to PARPis, the strongest responses have been in *BRCA* pathway mutation carriers (21); however not even all of these patients respond, suggesting that genomic status is not enough to predict response and that other pathways such as stalled fork protection defects may be important targets (21). Unfortunately, the prevalence of stalled fork protection defects and their importance to therapeutic sensitivity is not well understood.

To more precisely treat each patient's tumor, functional assays are needed to determine what type of defect is present in each tumor, HR or stalled fork protection defect, and also to decipher which DDR defects confer a response to the various agents targeting each of these defects (22). A model system that allows for functional assays to assess for HR or stalled fork protection defects and prediction of response to therapies targeting such defects is needed. Organoids are three-dimensional structures derived from human normal or tumor tissue that anatomically and functionally mimic the developed human organ (23). Organoids mimicking the parent tumor from which they were derived have aided in the study of multiple tumor types (23, 24). They are inexpensive to generate and easily manipulated.

Preliminary data: We hypothesized that patient derived HGSC organoids would be a rapid (grow in 7-10 days) and inexpensive model system in which to assess the DNA repair capacity of human tumors and determine which repair defects confer sensitivity and resistance to new DDR drugs or drug combinations. With this goal in mind, we generated a robust platform of assays to separately test for both HR and stalled fork protection defects and the therapeutic sensitivities such defects might confer in HGSC organoids compared to genomic profiling of the parent tumor and organoid culture (Hill et al. *Cancer Discovery*. 2018 (7)).

The assays we used included assessing carboplatin and PARP, CHK1, and ATR inhibitor sensitivity; assaying RAD51 focus formation, a surrogate marker for HR capacity, +/- exogenous DNA damage to assess the HR capacity of the tumor (25); and performing a DNA fiber assay (26) after treatment with hydroxyurea, a replication fork stalling agent, to assess stalled fork protection (Figure 1) (7). Organoid generation and the repair assays are highly reproducible by our group and others making the system a robust research tool (27).

The functional assay for HR correlated with PARPi sensitivity/resistance (7). However, in our initial limited HGSC organoid studies, only 6% of cultures showed HR defects and PARPi sensitivity (7), and those cultures were from patients with germline mutations in *RAD51C* and *BRCA2*, both DNA repair genes (9).

The functional assay for replication fork stability correlated with sensitivity to carboplatin, gemcitabine, and CHK1 and ATR inhibitors (7). In contrast to HR, 61% of the 33 HGSC organoid cultures tested, both with and without mutations in DDR genes, had fork protection defects by the fiber assay (7). Although the number of patients assessed was not large enough to achieve statistical significance, these results suggest that fork protection defects are more common than HR defects and that fork protection defects may lead to sensitivity to

Figure 1

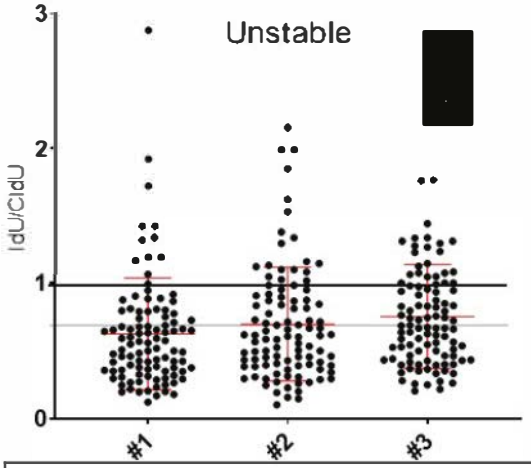

Figure 1. Replication fork stability correlates with drug sensitivity in HGSC organoids. Fiber assay results from 3 biologic replicates for organoid cultures from a sporadic HGSC patient whose cultures were sensitive to carboplatin, prexasertib, VE-822, and gemcitabine, but resistant to Olaparib. For the fiber assay, organoids were sequentially pulsed for equal time periods with two nucleotide analogues, CldU and IdU, followed by exposure to the fork stalling agent hydroxyurea (HU). If the ratio of the track lengths is near one, then the fork was protected during replication stalling. If the ratio of the track lengths is less than one, then the fiber containing the second analogue was degraded, indicating that the tumor cell is unable to protect its stalled forks. The ratio of IdU to CldU in three biologic replicates is shown for organoids treated with HU. A black line marks a ratio of 1 (stable), and a grey line marks the average ratio for this line (unstable). A representative fiber from this line denoting an unstable fork is on top of the panel.

carboplatin, gemcitabine, and CHK1 and ATR inhibitors (7).

Recent data suggest that stalled fork protection defects may be a more important sensitizing factor than HR defects for certain therapies. Platinum based chemotherapy is the current mainstay of HGSC treatment (28), and CHK1 inhibitors have been shown to be effective in HGSC patients (17), both regardless of mutational status. Both agents are suggested to induce lethality in tumors that have stalled replication fork protection defects making the ability to predict a stalled fork protection defect critical in predicting response to a classical and a new therapy (17, 18).

Hypothesis: Based on these data, *the hypothesis is* that stalled fork protection defects are more prevalent than HR defects in HGSC and that therapies targeting such a defect, may offer benefit to a larger patient population not limited to just *BRCA* pathway mutation carriers, unlike with HR and PARPis. Thus, *the major goals of this work will be* to use HGSC organoids to understand the importance of fork instability in HGSC, uncover mechanisms leading to fork instability, and determine how such functional defects lead to different therapeutic sensitivities. These Aims dovetail perfectly with the expertise and current scientific interests of my mentor, Dr. Alan D'Andrea. However, this project, though designed with his guidance, is my independent project which I will utilize to start my own independent research program.

Innovation: The dogma in the HGSC field is that 50% of HGSCs have defects in HR, based solely on genomic analysis of the tumors. This assumption has driven the field to focus heavily on PARPis which target defects in HR, with the expectation that some sporadic HGSCs with somatic genetic alterations will have HR defects. Based on these assumptions, PARPis are being favored both scientifically and in clinical trials, leaving other therapeutic targets less well understood.

Our preliminary data suggest that more HGSCs have defects in protecting stalled replication forks than in HR. The work in this proposal will challenge the dogma that HR is the most common DDR defect in HGSC and instead seek to demonstrate the prevalence of stalled replication fork protection defects in HGSC. We will attempt to understand the different mechanisms of fork protection defects that might contribute to therapeutic response to DNA damage therapies.

This work will utilize a state-of-the-art new model system, patient-derived organoids, which grow rapidly and are inexpensive to generate. It will also utilize novel functional assays (DNA fiber assays) and new targeted therapies (CHK1, WEE1, and ATR inhibitors) which have not been exhaustively studied in HGSC.

Overall, this work may help to generate a better mechanistic understanding of what types of stalled fork protection defects lead to specific therapeutic sensitivities and potentially generate biomarkers of such defects. It may also lead to clinical assays that can be used to predict patient response with proper long-term validation. These findings may help to better specifically target each patient's unique tumor.

Approach:

Scientific Rigor: In all aims of this proposal, strict application of the scientific method will be applied including but not limited to utilizing appropriate controls and careful measurements/analysis to ensure unbiased experimental design and reproducible results. Full transparency will be achieved by making all data supporting the research findings and detailed methods available after the main findings are accepted for publication.

***Specific Aim 1*: Assess the prevalence of fork protection defects in HGSC and whether fork protection defects predicted by HGSC organoid functional assays lead to therapeutic sensitivity to carboplatin and ATR, WEE1, and CHK1 inhibitors.**

Rationale: Preliminary analysis of 33 HGSC organoid cultures revealed that fork instability, indicated by the DNA fiber assay, correlates with sensitivity to carboplatin, prexasertib, and VE-822 (7) in the organoid cultures, suggesting that the DNA fiber assay performed on organoids may be a reasonable biomarker for sensitivity to these agents. This organoid fiber and sensitivity data correlated well with patient outcomes for carboplatin (7). However, this is too small a patient number to generate statistically meaningful results. Thus,

the goal of this Aim is to determine the prevalence of fork protection defects in HGSC and to validate fork instability or other replication fork properties, as read by DNA fiber analysis and drug sensitivity testing in short term organoids, as a biomarker for sensitivity to the above agents. This will be accomplished through DNA fiber analysis and therapeutic sensitivity testing of a larger number of organoids generated from patients who have been or will be treated with carboplatin and possibly newer agents like CHK1, ATR, or WEE1 inhibitors. Using this larger patient number will allow for a more rigorous analysis of our hypothesis than our previous work by helping achieve statistical significance at least in some patient groups (see statistics below) (7).

In addition, since our original work was published, new analysis techniques on our DNA fiber assay will allow us to study two other parameters of replication forks beyond just stability and instability, including replication fork velocity and aberrant origin firing (19). Increased origin firing and slower replication fork velocity or the ability to slow the velocity through therapeutic modulation correlates with response to drugs or drug combinations (11, 19, 29, 30). Thus, in addition to fork instability, we will now also analyze these fork properties to determine which is the best biomarker for specific drug responses.

Methods: Each organoid culture generated in this Aim will be assessed for 1) sensitivity to the HR defect targeting PARPi Olaparib and the replication fork stalling agents carboplatin, gemcitabine, a CHK1 inhibitor (prexasertib), ATR inhibitors (AZD6738 and BAY 1895344), and a WEE1 inhibitor (MK1775); 2) fork stability post hydroxyurea treatment and fork characteristics such as replication fork velocity and origin firing by DNA fiber analysis; and 3) HR capacity by Rad51 focus formation, all of which assays are well established in the laboratory (7). We chose carboplatin and gemcitabine as these are commonly used in HGSC treatment. We chose the CHK1 inhibitor prexasertib, the ATR inhibitors AZD6738 and BAY 1895344, and the WEE1 inhibitor MK1775, because there are active clinical trials with all four of these agents occurring at DFCI from which we can obtain patient material for organoid analysis.

The results of the fiber assay will be assessed 1) to determine the prevalence of fork protection defects or altered fork properties and 2) to determine if fork stability, fork velocity, or aberrant origin firing detected in the fiber assay on organoids can predict sensitivity to any of the classes of drugs we test in the organoids and in the patients in clinical trials with these agents.

In addition to the above assays, with the mentorship of my advisory committee member Dr. Rameen Beroukhim (see committee letter), each organoid culture and matched parent tumor will undergo whole exome sequencing analysis to search for relevant mutations in DDR genes, relevant copy number alterations (i.e. *CCNE1* amplification (31)), and the presence of a homologous recombination defect (HRD) signature which would suggest that the tumor at some point had or currently has a defect in HR (32). Genomic findings will be correlated with functional assay results and patient outcomes to 1) assess the relevance of genomic alterations to actual functional defects and 2) assess the relevance of genomic alterations to therapeutic response.

We will assess the predictive capacity of organoids for different drugs in three different clinical groups. The first group of patients will be patients undergoing laparoscopic biopsy for diagnosis of HGSC prior to neoadjuvant treatment. In collaboration with Drs. Neil Horowitz, Ursula Matulonis, and Christopher Crum (see committee letter and letters of collaboration), we will obtain tumor tissue and generate organoids from these patients, perform the above assays within 10 days of receiving the specimen, and then assess the patient response to carboplatin after neoadjuvant chemotherapy and compare it to the organoid fiber and sensitivity results. We will combine analysis of the tumor marker CA-125, imaging pre- and post- neoadjuvant treatment, and histopathologic analysis of the debulking specimens to determine tumor response to carboplatin and correlate this with the organoid findings. This will allow us to assess the predictive capacity of the organoid assays for carboplatin at the time of interval debulking. We will analyze 50 patients in this group, which is the number needed to provide statistical power as described below. We will also generate organoids from the post-neoadjuvant specimens of these patients when possible and perform the same assays to attempt to understand any molecular and/or functional alterations induced by the treatment.

The second group of patients will be those patients undergoing interval debulking after neoadjuvant chemotherapy with paclitaxel and carboplatin regardless of whether we are able to analyze their pre-treatment sample. Organoid resistance/sensitivity and fiber results from as many tumor sites as possible from the post-neoadjuvant debulking will be compared to patient response to the neoadjuvant chemotherapy and time to recurrence as measured by CA125 levels, histopathologic changes, and imaging to see if carboplatin resistant fork stable organoids correlate with a poor response to neoadjuvant chemotherapy and/or with faster recurrence. We will analyze 50 patients within this group to achieve statistical power as described below.

Finally, we will also generate organoids from patients going on PARP, CHK1, WEE1, and various ATR inhibitor clinical trials ongoing at DFCI, to attempt to analyze organoid predictive capacity for these agents as well. Under the guidance of my committee members, Drs. Geoffrey Shapiro and Ursula Matulonis (see committee letters), we will obtain tumor biopsies and generate organoids from patients during or prior to treatment on the trial, perform the above assays on the organoids and compare the organoid response and fiber results to the

patient response by imaging at the site from which the biopsy was taken for organoid generation. This will determine if any organoid functional assay results correlate with patient response in the tumor site we test. Statistical considerations for this group are dependent on the number of patients enrolling in the trials as described below. We have already successfully matched organoid response and fiber instability to tumor response in three patients treated with prexasertib and one with an ATR inhibitor (7).

Statistical considerations: The primary analysis will be to assess the association between fork stability and treatment sensitivity for organoids (defined to be whether or not the measured IC50 for the culture lies below or above that of the known standard) and for matched patients (defined by imaging, histopathologic, and CA125 measures of response). At 5% significance, we will have 90% power to detect that treatment sensitivity rates are significantly different in fork stable compared to fork unstable patients, under the following scenarios for fork stability prevalence and probability (Pr) of being treatment sensitive (based on observed sensitivity rates of 70% and higher among the fork unstable organoid cultures in preliminary data (7)) and assuming a total of 50 patients each in the untreated and neoadjuvant groups, all receiving carboplatin. Due to limitations in sample size, the association between sensitivity and fork stability in the patients receiving PARP, CHK1, WEE1, and various ATR inhibitors will be considered secondary analyses for hypothesis generation.

Prevalence of fork stability	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
Pr(Sensitive|Stable) when Pr(Sensitive|Unstable)=0.7	0.05	0.17	0.22	0.25	0.26	0.25	0.22	0.17	0.05

Secondary analyses will use univariate logistic regression models to assess the ability of fork velocity or aberrant origin firing detected in the fiber assay to predict treatment sensitivity. We will use log-rank tests and Cox proportional hazard regression models to evaluate whether fork stability, fork velocity, and aberrant origin firing are associated with patient outcomes of time-to-recurrence or time-to-progression.

Potential pitfalls and alternative approaches: One pitfall in this Aim for clinical trials is that we may only be able to analyze one tumor site from each patient. Although the organoid functional assays may predict patient response at that tumor site, patients may progress at other tumor sites not tested. This would be an important finding suggesting that there is heterogeneity in the functional defects present at each tumor site. Obtaining this result would prompt us to perform larger scale studies on multiple sites from each patient in the future to try to understand heterogeneity of functional defects and how best to target such heterogeneity. Another pitfall is that prexasertib has been found to be toxic in patients and is not likely to continue in the clinic. We feel testing a CHK1 inhibitor is important as there may be other drugs in this class in the pipeline. We plan to analyze organoids generated from an ongoing prexasertib trial at DFCI so that we have data assessing organoid predictive capacity on a CHK1 inhibitor which can be compared to any future CHK1 inhibitors.

Summary and benchmarks of success: Overall, the work in this Aim will allow us to assess the prevalence of fork protection defects in HGSC, to begin to validate the use of functional assays in patient-derived organoids as biomarkers for response to one or more of the above therapies, and to assess the relevance of any detected genomic alterations to functional defects and therapeutic sensitivity. Benchmarks of success will include reaching accrual goals of patients from the three groups so that all treatment types can be appropriately assessed. The accrual of these patients, organoid generation, and organoid assays and sequencing will occur over the first three years of the award, and the final benchmark will be submission of a first author manuscript at the end of year three detailing the findings regarding stalled fork protection defect prevalence and predictive capacity of the organoid assays for different therapeutic sensitivities.

Specific Aim 2: Uncover mechanisms leading to fork instability and whether different mechanisms of fork protection defects lead to differing therapeutic sensitivities to the above agents.

Rationale and preliminary data: As described above, preliminary data shows that carboplatin, prexasertib, and VE-822 sensitivity reproducibly correlate with replication fork instability as measured by a DNA fiber assay post hydroxyurea treatment in organoid cultures, making understanding the mechanisms of instability leading to such sensitivity critical (7). However, even though a larger number of patients have fork unstable tumors and do respond to these agents, there is still a significant number who have stable forks and do not respond and who also lack HR defects, making these tumors particularly difficult to treat. This begs the question of what specific fork defects lead to a response and whether such defects can be induced in otherwise fork stable tumors to cause cytotoxicity. Different defects may confer different sensitivities.

With this idea in mind, in our initial analyses of the organoids, in addition to correlating fork instability to certain sensitivities, we sought drug combinations that might lead to fork instability, replication stress, and possibly cytotoxicity even in fork stable organoids. Our initial work had shown that the CHK1 inhibitor prexasertib induced replication stress as shown by increased expression of the replication stress marker phosphorylated RPA (pRPA) and increased phosphorylation of the downstream targets of the replication stress kinase ATR, including phosphorylated KAP1 (pKAP1) and phosphorylated CHK1 (pCHK1), indicating increased ATR activation (Figure 2). However, this increased replication stress alone was not enough to

Figure 2

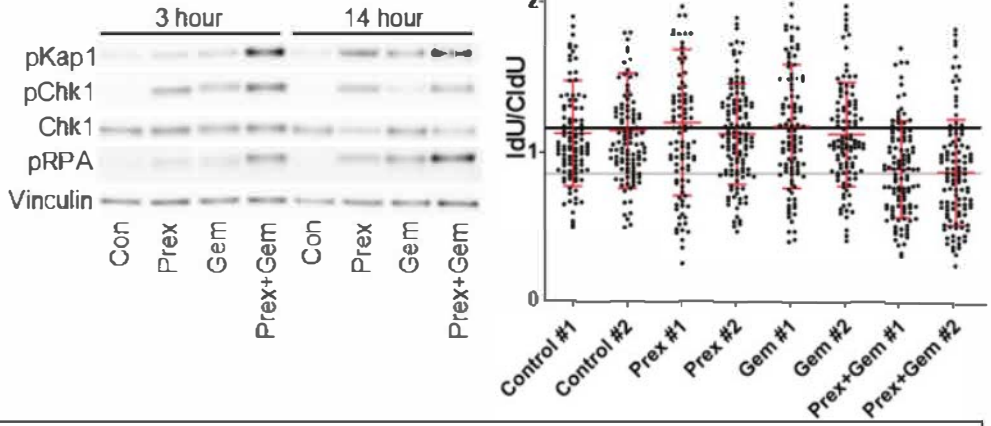

Figure 2. CHK1 inhibitors cause replication stress and confer fork instability in the setting of gemcitabine treatment. On the left is a western blot analyzing a fork stable line 3- and 14-hours post treatment with control (con) media or media containing prexasertib (Prex), gemcitabine (Gem), or prex+gem. On the right is fiber analysis of the same line post-treatment with con, gem, prex, or prex+ gem. For the fibers, a black line marks the average for the stable fibers, and a grey line marks the average drop with instability induced by the combination.

induce fork instability and cytotoxicity in every tumor. Thus, we searched for drugs that could combine with prexasertib to destabilize replication forks even in fork stable tumors. We found that either carboplatin or gemcitabine, when combined with prexasertib, lead to increased replication stress over either carboplatin or gemcitabine alone, as shown by increased pCHK1, pKAP1, and pRPA expression and that these drug combinations lead to fork instability as measured by the DNA fiber assay in a highly reproducible fashion, even in a fork stable line (Figure 2 showing gemcitabine data only). Similar results have now been obtained when combining the ATR inhibitor AZD6738 with carboplatin or gemcitabine (data not shown), and thus AZD6738 will be used for the work in this Aim. These drug combinations may show promise for patients with tumors unresponsive to most common therapies, likely through different methods of fork destabilization.

Based on these findings, the goals of Aim 2 will be to 1) understand how fork instability can be induced in an otherwise fork stable line by combining a CHK1, ATR, or WEE1 inhibitor with various fork destabilizing agents, such as carboplatin or gemcitabine and 2) understand the deeper molecular mechanisms of fork destabilization that lead to sensitivity to a CHK1, WEE1, or ATR inhibitor or carboplatin or gemcitabine either alone or in combination. In this Aim, I will benefit from the guidance of my mentors Drs. D'Andrea and Brown.

A) Perform functional analysis of replication fork properties in fork stable and unstable organoids in the setting of treatment with different combinations of replication stress inducing agents.

Rationale: Based on our preliminary findings in a small set of organoid cultures showing that prexasertib combined with gemcitabine or carboplatin can reproducibly destabilize replication forks in baseline fork stable cultures, we hope to determine if these combinations or others can broadly destabilize replication forks and potentially induce therapeutic sensitivity in baseline fork stable cultures.

Methods: To accomplish this we will assess for fork destabilization with different single drugs as controls and relevant drug combinations in a subset of the fork stable and unstable organoids generated in Aim 1. We will perform drug sensitivity testing in this subset of organoids with these same single agents and drug combinations (some single agent results repeated from Aim 1 as controls in this Aim) in parallel with the fiber assays to determine if replication fork destabilization by combinations correlates with therapeutic sensitivity to drug combinations. Alterations in fork velocity and origin firing will also be assessed to determine if these properties are important for therapeutic sensitivity in the setting of these drug combinations.

Based on preliminary data, we hypothesize that baseline fork unstable cultures will be broadly unstable with and sensitive to combined agents that destabilize stable forks. We will analyze 10 fork unstable carboplatin sensitive cultures from Aim 1 here to confirm this and discern whether any other fork alterations induced by these agents are also important to a therapeutic response in a baseline sensitive culture. In contrast, we hypothesize that only some drug combinations will be able to destabilize replication forks and induce therapeutic sensitivity in baseline fork stable cultures. To achieve statistical power in understanding which combinations can convert stable forks to unstable and induce therapeutic sensitivity, we will analyze 30 fork stable carboplatin resistant cultures from Aim 1 here. The above 40 organoids will be analyzed for fork stability and other fork properties by the DNA fiber assay and therapeutic sensitivity in the setting of vehicle, prexasertib, MK1775, carboplatin, gemcitabine, AZD6738, prexasertib+carboplatin, prexasertib+ gemcitabine, MK1775+carboplatin, MK1775+ gemcitabine, AZD6738+carboplatin, and AZD6738+gemcitabine treatment to assess if fork destabilization and/or other fork property alterations lead to therapeutic sensitivity in the setting of these combinations. Detected differences will help suggest both rational therapeutic combinations for fork stable tumors and molecular pathways for deeper mechanistic analysis of induction of fork instability.

Statistical considerations: In the 30 fork stable patients, the rate of conversion to fork instability will be

estimated for each of the 11 settings. A test of proportions will be performed to determine if the conversion rate is different across the settings. In each setting, we will assess the association between fork stability status after treatment and treatment sensitivity in the baseline fork stable patients. At 5% significance (with a conservative Bonferonni adjustment for multiple testing), we will have 80% power to detect that treatment sensitivity rates are significantly different in fork stable compared to fork unstable, under the following scenarios.

Rates of conversion to instability	**0.5**	**0.6**	**0.7**	**0.8**
Pr(Sensitive|Stable) when Pr(Sensitive|Unstable)=0.7	0.10	0.09	0.07	0.02

We will use univariate logistic regression models to assess the ability of fork velocity or aberrant origin firing to predict treatment sensitivity in each of the 11 settings, regardless of baseline fork stability status.

B) Perform targeted western blots on fork stable and unstable cultures after treatment with replication stress inducing agents looking for up- or down- regulation of the ATR signaling pathway.

Rationale: Once we understand which drug combinations can destabilize forks, the next step will be to decipher which mechanistic pathways are altered to cause fork instability. The ATR signaling pathway is a mechanistically complex pathway with multiple roles critical for dealing with replication stress making it a logical pathway to examine initially (33). We hypothesize that alterations in ATR signaling at different points in the pathway may confer varying therapeutic sensitivities and different post-treatment fork properties. Thus, we will search for alterations in different steps of ATR signaling in our 40 organoid cultures through targeted western analysis of ATR targets +/- drug treatment and correlate any detected alterations with results from 2A.

Methods: With the measures of fork destabilization and sensitivities obtained in Aim 2A in mind, the same 40 organoid cultures will be treated with control media, prexasertib, carboplatin, gemcitabine, MK1775, AZD6738, prexasertib+carboplatin, prexasertib+ gemcitabine, MK1775+carboplatin, MK1775+gemcitabine, AZD6738+carboplatin, or AZD6738+gemcitabine for three or 14 hours and then harvested for targeted western analysis. We will load equal amounts of protein lysate from each culture and treatment in gels to compare protein levels across the lines. We will perform westerns to assess degree of replication stress (pRPA) and degree of induction of different timepoints of the ATR pathway (pKAP1 and pCHK1) post treatment across all the lines which we have successfully done previously (Figure 2) (7).

For fork unstable lines, limited or increased induction of ATR signaling will suggest a mechanism of fork protection defect either before or after the stage of KAP1 phosphorylation in the ATR pathway and suggest testing of up- or down- regulation of further members of the pathway by western analysis including earlier members involved in ATR recruitment and later members involved in preventing fork collapse or initiating fork restart (33). Increased ATR signaling or replication stress induction by select agents in fork stable lines might suggest that the line once had a repair defect but was selected for a resistance mechanism to overcome it, which will prompt further targeted western analysis with up- or down- stream ATR pathway members to assess for resistance mechanisms in such lines. Overall, this work will help determine if ATR pathway alterations lead to any of the fork alterations and sensitivities we observe in Aim 2A.

Statistical considerations: We will use descriptive statistics (means, medians, box and scatter plots) to summarize findings.

Potential pitfalls and alternative approaches: Focusing on ATR signaling, and downstream protein targets is the most logical pathway to study initially in searching for fork defects. However, defects may not be easily discovered in the ATR pathway due to lack of antibodies for western analysis, presence of defects involving proteins not known to be in the ATR pathway at this time, or presence of defects outside the ATR pathway. To overcome these possibilities and cast a wider net to discover other possible mechanistic defects leading to fork instability, I have worked with my committee mentor Myles Brown to perform RNA Sequencing analysis on a select pair of organoid cultures from a single patient which provide the rationale for Aim 2C.

C) Assess for RUNX3 protein alterations in the organoid cultures and for cellular and replication fork alterations induced by RUNX3 loss.

Rationale and preliminary data: We have transcriptionally profiled and compared a pair of organoid cultures from a single patient (data not shown). One culture was generated ***prior*** to the patient receiving neoadjuvant chemotherapy, and the second culture was generated ***after*** that patient received neoadjuvant chemotherapy. Importantly, the pre-treatment culture was platinum sensitive with unstable replication forks, and the post-treatment culture was platinum resistant with stable replication forks (data not shown). We assessed the sequencing data for the most heavily altered hits either involved directly in DDR or involved in controlling the transcriptional profile of the cells in such a way that DDR may be altered. Using these criteria, we have generated a list of our top hits which might be upregulated in the setting of replication stress in a fork unstable tumor or downregulated in a tumor that has been selectively induced to stabilize its replication forks for survival. A top hit was the transcription factor RUNX3, a lymphoid and gastrointestinal specific transcription factor, which has been suggested to have roles in both the DNA damage response and in preventing epithelial

to mesenchymal transition (EMT) in solid tumors (34-36).

Our transcriptional profiling revealed downregulation of RUNX3 in the fork stabilized tumor, and we sought to understand what RUNX3 loss means for replication fork stability. We treated an ovarian cancer cell line with baseline unstable replication forks stably expressing RUNX3 with either control or RUNX3 specific siRNAs, and we then performed DNA fiber analysis on these cells +/- hydroxyurea treatment. RUNX3 depletion led to replication fork stabilization (data not shown). In addition, depletion also led to mild resistance to both carboplatin and gemcitabine (data not shown). These results suggest that RUNX3 depletion leads to therapeutic resistance through replication fork stabilization, which is in line with multiple studies suggesting that RUNX3 protects cells from EMT and prevents a therapeutically resistant tumor phenotype (34, 37). This is also consistent with the finding by another group showing that in mammary epithelial cells with defects in inter-strand crosslink repair, exposure to crosslinking platinum agents leads to EMT in the cells (38, 39). Based on these combined findings, we hypothesize that some HGSCs begin with innate replication fork protection defects. Upon selection with platinum neoadjuvant chemotherapy, the tumors cells develop mechanisms to stabilize their replication forks and transition to a more mesenchymal state, some potentially through down-regulation of RUNX3, and in so doing become carboplatin resistant. To test this hypothesis, we will analyze our profiled organoid cultures from Aim 2A for alterations in RUNX3 and upregulation of mesenchymal markers.

Methods: To ask whether RUNX3 loss leads to replication fork stability, EMT, and drug resistance in ovarian cancer, we will assess RUNX3 status in our cultures from Aim 2A. RUNX3 protein expression is commonly silenced through promoter methylation, but function can also be lost through mis-localization of the protein from the nucleus to the cytoplasm (34). Thus, we will perform western blot analysis of the 40 organoid cultures profiled in Aims 2A and 2B for RUNX3 expression and perform immunofluorescence (IF) analysis on these cultures to assess RUNX3 localization. Cultures with RUNX3 detected by western blot and nuclear localization of RUNX3 by IF will be considered RUNX3 wildtype. Cultures with either RUNX3 loss of expression detected by western blot or RUNX3 localization in the cytoplasm will be considered RUNX3 mutant.

We will next determine if RUNX3 status correlates with epithelial or mesenchymal traits in our cultures. We will perform western blots for the epithelial marker E-Cadherin and the mesenchymal markers N-Cadherin, Slug, and Snail on all of the cultures (40). We will compare RUNX3 status to expression of these markers to determine if loss of RUNX3 leads to upregulation of EMT markers in a subset of our organoid cultures.

Once RUNX3 and EMT status is determined in our cultures, the replication fork properties of these cultures, including stability, velocity, and origin firing after hydroxyurea and all other single or drug combinations, and the therapeutic sensitivity of the cultures to single and drug combinations from Aims 1 and 2A will be compared. This will help us understand how RUNX3 loss and EMT might affect the replication forks and subsequent therapeutic sensitivity or resistance in patient tumors.

In summary, the work in this sub-Aim will help determine if RUNX3 loss leads to a more aggressive phenotype in ovarian cancer through replication fork stabilization which would prompt more analysis of the function of RUNX3 and/or its transcriptional targets in the setting of replication stress.

Pitfalls and solutions: If RUNX3 loss does not correlate with replication fork stabilization, EMT, and therapeutic resistance, other hits from our RNA sequencing analysis will be pursued.

Statistical considerations: We will assess the association between RUNX3 loss and fork stability status, regardless of baseline status, by estimating the odds ratios (odds of having RUNX3 loss in fork stable vs fork unstable) and 95% confidence intervals. Odds ratios significantly greater than 1 indicates greater odds of RUNX3 loss in those with fork stabilization. Similarly, we can assess the association between RUNX3 loss and EMT as well as treatment sensitivity via odds ratios.

Summary and benchmarks of success: Overall, the work in this Aim dissecting different stalled fork protection defects across HGSCs may help to understand which defects in ATR signaling, specific fork properties, or outside of the DNA damage response can lead to different drug sensitivities and also generate unique biomarkers for such defects while at the same time leading to discovery of and understanding of mechanisms of action of relevant drug combinations that can be used in the setting of a lack of fork protection defect. Benchmarks of success will include accrual of appropriate organoid cultures as described above by the end of year two. The fiber and sensitivity analysis described in 2A should be completed by the end of year three, and the targeted western blots, and RUNX3 analyses described in 2B and 2C ongoing through year four. The final benchmark of success will be a manuscript detailing initial findings regarding differing mechanisms of stalled fork protection in HGSC which will be submitted in year four. Mechanistic hypotheses generated by this work will continue to be pursued in years four-five and during independence.

Specific Aim 3: In vivo validation of in vitro mechanisms of stalled replication fork protection defects leading to therapeutic responses in organoid xenograft models of HGSC.

Rationale and preliminary data: Any findings in Aims 1 and 2 that suggest replication fork properties, loss of signaling pathways, or loss of transcription factors may lead to sensitivity or resistance to single or

combination replication stress inducing agents must be validated *in vivo*. Other groups have transplanted patient-derived HGSC organoids into immune compromised mice and generated patient derived xenograft (PDX)-like models of the parent tumors with high tumor take rates (27). We will generate organoid xenograft mice with a select subset of organoid cultures from Aims 1 and 2 and conduct a small series of pilot therapeutic sensitivity tests to generate preliminary *in vivo* data and begin to validate key replication stress findings. My mentor Alan D'Andrea will guide me in this Aim as he has extensive experience with animal models of disease through his work in Fanconi Anemia and ovarian cancer PDX models (41-43).

A) Profile therapeutic sensitivity of organoid xenograft mice to replication stress inducing agents:

Methods: From the 40 organoid cultures in Aim 2, we will select five representative cultures with unstable forks, carboplatin sensitivity, and RUNX3 expression and five organoid cultures with stable forks, carboplatin resistance, and RUNX3 loss. These 10 organoid cultures will be luciferized as previously described (27, 44) to allow bioluminescence imaging of tumors that develop in xenograft models generated from these organoids (27, 43, 44). The luciferized organoid cultures will then be injected intraperitoneally into immuno-compromised female mice (2-5 mice per culture) to generate organoid xenografts. We will select the two fork stable and two fork unstable xenograft models with the best tumor take rates to proceed with validation and drug treatment. In these four models, we will perform whole exome sequencing and histologic analysis of the tumors formed and compare this data to the parent organoids and tumors to validate the models (27, 44). Upon validation, we will expand the four models and conduct therapeutic sensitivity testing with single drugs and combinations of our strongest replication stress inducing agents which are closest to being combined in the clinic. Based on post-treatment induction of replication stress markers by western blot analysis in organoids, gemcitabine and AZD6738 induce the strongest responses either alone or in combination (data not shown), and the combination of AZD6738 with gemcitabine also destabilizes replication forks in organoid cultures (data not shown) and is tolerable *in vivo* (45) making these two drugs the best initial pilot *in vivo* drugs.

The four mouse models will undergo a four-arm single and combination therapeutic sensitivity analysis with vehicle, gemcitabine, AZD6738 (ATR inhibitor), or gemcitabine+AZD6738 to determine if the replication stress and/or sensitivities induced by these single drugs or combination *in vitro* correlates with tumor shrinkage and increased survival *in vivo* (21, 43, 46, 47). Ten mice per model will be treated with vehicle or one of the three drug treatments for three-four weeks in this experiment to achieve statistical power. Mice will be weighed and imaged once per week to follow tumor response compared to untreated controls, and overall survival will be assessed in each setting. Particular attention will be paid to RUNX3 status in these four mouse models, and the tumors formed will be analyzed after necropsies for epithelial or mesenchymal composition which will be correlated with RUNX3 status. Overall, these experiments will show the feasibility of organoid xenograft generation and drug sensitivity testing and the viability of this method for *in vivo* validation of *in vitro* results from Aims 1 and 2. Promising results would prompt a larger study with more xenograft models.

Potential pitfalls and alternative approaches: If we have difficulty generating the organoid xenografts, we will obtain tumor cells to generate organoids from a panel of well characterized HGSC PDX models available in the D'Andrea lab (43, 44). We can perform the same *in vitro* organoid profiling described in Aim 2A on organoids generated from the PDX models. In parallel, we will perform the same *in vivo* therapeutic sensitivity testing described in Aim 3 on the PDX models and match the *in vitro* organoid results to the *in vivo* PDX results we generate. This would provide an alternative method of *in vivo* validation of *in vitro* findings.

Statistical considerations: For each of the mouse models, we will obtain summary measures of weekly tumor size, mouse weight, and survival time across the replicates. For each mouse model, n=10 replicates for each treatment was chosen to provide 90% power to detect a difference of 1.15 standard deviations in tumor growth inhibition at the 5% significance level. For mouse model comparison to organoid results, the association between mouse tumor growth over time and organoid fork stability, treatment sensitivity, RUNX3 loss, fork velocity, and origin firing will be examined for each of the three treatments and the untreated group via spaghetti plots with different colors to discern the groups. Treatments that result in decreasing tumor size will be considered most promising for further study. The median survival time across the replicates in the groups of interest (e.g. fork stable vs unstable) will be used to identify potential trends and agents that increase survival time compared to the untreated group will be considered promising for further study.

Summary and benchmarks of success: Overall, the work in this Aim will serve as a pilot experiment showing that organoid xenografts can be generated and tested for therapeutic sensitivity. The results may begin to validate correlations between *in vitro* organoid functional assay findings and therapeutic sensitivity *in vivo*. As relevant organoids are generated and profiled through years one-three, the key organoid lines will be selected and injected into mice starting at the end of year two and continuing into year three. The drug sensitivity experiments in each of the four models will occur in years three and four. Data obtained will provide preliminary *in vivo* validation of the findings in Aims 1 and 2 and be added to a paper describing mechanisms of replication fork protection defects to be submitted in year 4.

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH

Prior Training: As an MD/PhD student at Harvard Medical School, I took two coursed to fulfill the NIH Training in the Responsible Conduct of Research (RCR) requirements including Medical Sciences 300qc during the first semester of my PhD (Fall 2008) and Medical Sciences 302qc in the Fall 2013 semester which courses in total comprised 21 hours of training in faculty led didactic and small group sessions covering subjects varying from conflict of interest to clinical trials to animal rights.

As I enter this new phase of my training as an Instructor at Dana-Farber Cancer Institute (DFCI), I will fulfill the Responsible Conduct of Research (RCR) requirement with a formal course every four years and with constant discussion with my adviser, Alan D'Andrea, and my advisory committee. For formal coursework, I plan to take the Dana-Farber Cancer Institute Postdoc and Graduate Student Affairs Office Responsible Conduct of Research (RCR) course (please see http://dfcionline.org/departments/pgsao/research/) which is detailed below.

1. **Format:** The course consists of in-person lectures and discussion sessions, independent reading, and online training. Researchers attend six lectures over a one year period by Harvard Faculty, three in the Spring and three in the Fall. Trainees will be given access to a syllabus with required readings and discussion questions, and the topics are addressed in a lecture/discussion format at the faculty lectures. Online training occurs through the Collaborative Institutional Training Initiative (CITI) and consists of four required modules.

2. **Subject Matter:** The subject matter of the RCR course is consistent with the guidelines in NOT-OD-10-019. The curriculum consists of the following topics: Conflict of interest, mentor/mentee responsibilities and relationships, collaborative research, peer review, responsible authorship and publication, industry relationships, data acquisition, research misconduct, responsible authorship, the scientist as a responsible member of society, lab management, and intellectual property considerations. CITI training covers policies regarding human subjects, policies regarding live vertebrate animals, data management, and plagiarism.

3. **Faculty Participation:** Harvard faculty members present six 90 minute lectures over the duration of the course on the range of topics listed in part 2. Participating faculty include Jonathan Marron, MD, Barrett Rollins, MD/PhD, Sonal Jhaveri, PhD, George Demetri, MD, Bruce Johnson, MD, and Qiufu Ma, PhD.

4. **Duration of Instruction:** The course is composed of six 90 minute lectures in addition to individual time reading the assigned articles and completing the four CITI training modules. Over the five year training period, this course would be taken twice for a total of 9 hours per course or 18 total hours of instruction in addition to individual reading time.

5. **Frequency of Instruction:** The RCR instruction will encompass the entirety of the proposed five year training plan. The aforementioned formal RCR course will be taken in year 1 of the training and again in year 4 to fulfill the NIH requirements. The course material will change over time, and the trainee will also mature scientifically allowing for enhanced understanding of the material over time. In addition, the trainee will benefit from constant discussion with mentors and committee members as issues related to RCR occur in the natural progression of the training.

6. **Personal:** I have already had and will continue to have opportunities to discuss RCR topics with my adviser, Alan D'Andrea. As I submitted my first paper from his lab, we had multiple discussions on authorship and confidentiality. We have also frequently discussed lab notebook security and maintenance, grant writing, and human subjects confidentiality as I have navigated between the lab and the clinic obtaining human tissue and performing experiments on it. These topics will continue to be discussed as I maintain my IRB approved tissue protocols and develop new protocols as my research program matures.

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July 8, 2019

Re: Sarah Hill NCI Mentored Clinical Scientist Development Award (K08)

To the Selection Committee,

I am writing to provide my most enthusiastic support to Dr. Sarah Hill's application for an NCI Mentored Clinical Scientist Development Award (K08). Through supervising trainees in my own laboratory and through my position as Director of the Susan F. Smith Center for Women's Cancers (SFSCWC) at the Dana-Farber Cancer Institute (DFCI), I have extensive experience training M.D./Ph.D. physician-scientists. I have also mentored other K08 recipients in my laboratory in the past, including Dr. Steven Margossian, Dr. David Kozono, and Dr. Kent Mouw. Based on her outstanding Ph.D. work and her remarkable accomplishments over the past three years in my laboratory, concurrent with her pathology residency, I rank Dr. Hill in the very top group of physician-scientist trainees I have known. She is on a trajectory to become an independent investigator as accomplished as the very best trainees from our program.

I have worked extensively with Dr. Hill to develop the research project outlined in her proposal—a project that I consider to be the most exciting work in my laboratory. I am committed to continuing to provide her with the day-to-day guidance, supervision, and mentorship necessary to complete her research and transition to a career as a successful independent investigator.

Dr. Hill joined my laboratory shortly after graduating from the Harvard Medical School M.D./Ph.D. program in June 2016 and as she entered the Brigham and Women's Hospital (BWH) Anatomic Pathology Residency Program. By this time, Dr. Hill had acquired a deep interest in ovarian cancer, a disease which is largely rooted in DNA repair abnormalities. Dr. Hill approached me with her plan to set up an ovarian cancer organoid program. While her plan initially seemed overambitious, I was pleased to support this work in my laboratory, given our common interest in DNA repair abnormalities in cancer. By working nights and weekends during her demanding Pathology Residency, Dr. Hill was indeed able to set up a highly successful organoid program, leading to a first author publication and to several national seminar invitations. Based on her organoid work in my lab, Dr Hill was recently awarded a two-year AACR AstraZeneca Ovarian Cancer research fellowship award, a DOD OCRP Pilot Grant, and a one-year internal grant from the "Friends of the Dana-Farber." In short, her work in my laboratory over the last three years has been exceptional.

Graduate work. As described in her accompanying personal statement, Dr. Hill has a longstanding and passionate interest in DNA repair. As an undergraduate at Harvard College, Dr. Hill worked on a DNA repair project with Shridar Ganesan in David Livingston's laboratory at Dana-Farber Cancer Institute (DFCI) and wrote an undergraduate thesis entitled "Characterization of a Novel Chromodomain Protein." Based on this work, and its ultimate publication, Dr. Hill was awarded the Lawrence J. Henderson Prize "for writing the most meritorious undergraduate thesis in the Biochemical Science concentration at Harvard University." She was subsequently awarded a Rhodes Scholarship to study for a year at Oxford University where she received an MSc degree in Biochemistry while working with Dr. Kim Nasmyth, a prominent investigator in the field of cohesin dynamics. On returning from Oxford, Dr. Hill entered the M.D./Ph.D. program at Harvard Medical School. Her Ph.D. research in Dr. David

Livingston's laboratory focused on the following research projects. The work resulted in her publication of five papers, including first-author publications in PNAS, Molecular Cell Biology, and Genes and Development.

In the first project, Dr. Hill systematically evaluated known functions of the BRCA1 protein in basal-like breast cancer cell lines and, at the same time, identified novel BRCA1 functions. She initially found that BRCA1 dysfunction in these tumor lines led to defects in the repair of stalled replication forks as opposed to bonafide HR defects (Hill SJ, Clark AP, Silver DP, and Livingston, DM. BRCA1 Pathway Function in Basal-Like Breast Cancer Cells. Mol Cell Biol. 2014 Oct 15;34 (20):3828-42. doi: 10.1128/MCB.01646-13). Dr. Hill and her collaborators also found that BRCA1 plays a novel role in the restart of transcription after UV damage (Hill SJ, Rolland T, Adelmant G, Xia X, Owen MS, Dricot A, Zack TI, Sahni N, Jacob Y, Hao T, McKinney KM, Clark AP, Reyon D, Tsai SQ, Joung JK, Gaudet S, Beroukhim R, Marto JA, Vidal M, Hill DE, and Livingston DM. Systematic screening reveals a role for BRCA1 in the response to transcription-associated DNA damage. Genes Dev. 2014 Sep 1;28 (17):1957-75. doi: 10.1101/gad.241620.114). For the second project, Dr. Hill and her colleagues evaluated the roles of two proteins which are unrelated to BRCA1. The two proteins, FUS and TDP43, are linked to the disease amyotrophic lateral sclerosis (ALS) and have a known role in RNA processing. Interestingly, Dr. Hill was able to determine that these proteins also play a role in transcription-associated DNA damage. This work was published in PNAS (Hill, S.J., Mordes, D.A., Cameron, L.A., Neuberg, D., Landini, S., Eggan, K., and Livingston, D.M. Two Familial ALS proteins function in prevention/repair of transcription-associated DNA damage. Proc Natl Acad Sci USA. 2016 Nov 14; Epub ahead of print. doi/10.1073/pnas.1611673113).

Current project. Given our shared interest in DNA repair and ovarian cancer pathogenesis and treatment, Dr. Hill developed a platform for generating high grade serous ovarian cancer (HGSC) organoids. To accomplish this goal, Dr. Hill assembled a team of close collaborators, including gynecologic cancer surgeons, medical oncologists, and pathologists. She obtained fresh HGSC tissue directly from the operating room and set up 3D organoid cultures on her own in my laboratory. The organoids grew out in only 7-10 days and closely resembled the primary tumor from which they were derived. Dr. Hill was able to analyze the cultures by multiple assays including drug sensitivity, homologous recombination (HR) function, fork stability, and mutational signature. Importantly, the results of these assays provide a potential predictive tool for drug response in the clinic. I want to stress here that Dr. Hill performed or supervised all of the functional tests on her own, and took the lead in writing her paper (Hill SJ, Decker B, Roberts EA, Horowitz NS, Muto MG, Worley MJ, Feltmate CM, Nucci MR, Swisher EM, Nguyen H, Yang C, Morizane R, Kochupurakkal B, Do KT, Konstantinopoulos PA, Liu JF, Bonventre JV, Matulonis UA, Shapiro GI, Berkowitz RS, Crum CP, D'Andrea AD. Prediction of DNA Repair Inhibitor Response in Short Term Patient-derived Ovarian Cancer Organoids. Cancer Discov. 2018 Sep 13. pii: CD-18-0474. doi: 10.1158/2159-8290.CD-18-0474. PMCID:PMC6365285). Accordingly, her initial work has inspired the aims outlined in her K08 in which the organoids will be an important model system, an application which she wrote entirely on her own. The work described in her application dovetails with my own scientific interests, but the project is hers and she will be able to take it with her and continue working on it independently upon leaving my laboratory.

Research Environment and Funding. I believe that my laboratory is highly suited for Dr. Hill's career development and for the completion of her proposed specific aims. My lab is currently funded by an R01 and a DOD grant, and I also have support from several research foundations. I was the Leader of the Stand Up To Cancer Ovarian Cancer Dream Team which has now ended but was a transformative experience allowing me to establish extensive connections with the national network of ovarian cancer researchers with whom I continue to interact, and which Dr. Hill can benefit from. I currently have funding support from the Ovarian Cancer Research Fund Alliance, the Basser Foundation, the Harvard-MIT Bridge Program, the Breast Cancer Research Foundation, and the Lustgarten Foundation. As the

Director of the Susan F. Smith Center for Women's Cancers (SFSCWC), I also have funding through the endowment of this Center. At least three of these funding sources will extend through the duration of Dr. Hill's K08 and be available to support or supplement her research as needed.

My laboratory currently has eighteen members, including ten postdoctoral fellows, one graduate student, and several PhD staff researchers and technicians. Despite this large number of lab members, I speak with Dr. Hill informally in the lab multiple times per week and formally during one-hour weekly meetings. These interactions will continue, and in addition to discussing her scientific progress at our weekly scheduled meetings, we will also meet one-on-one every six months to discuss her progress toward meeting critical promotion milestones such as publication and grant applications. She will also have regular committee meetings for the duration of her K08 award to allow independent monitoring by her carefully selected committee for career milestone achievement. As I describe in Dr. Hill's training plan below, I believe my laboratory and the SFSCWC will provide an ideal environment for Dr. Hill's training.

Throughout my career, I have trained several academic investigators and physician-scientists who have gone on to have successful independent careers. Dr. Hill ranks favorably among the best postdoctoral fellows to have emerged from my laboratory, including Tony Huang (now an Associate Professor at New York University), Martin Cohn (now an Assistant Professor at Oxford), Clark Chen (now a Professor and Chair of Neurosurgery at University of Minnesota), Gary Kupfer (now the Division Chief of Pediatric Heme/Onc at Yale), Akiko Shimamura (now Professor and the Director of the Bone Marrow Failure and MDS Program at Dana-Farber and Boston Children's Hospital Cancer and Blood Disorders Center), and Hyungjin Kim (now an Assistant Professor at Stony Brook University).

Training plan.
Despite her graduate school and residency training in the area of DNA repair in women's cancers, Dr. Hill will need to continue her training in this challenging field to better grasp the rich mechanistic landscape already deciphered and begin to carve out her own niche within the field. In order to transition to scientific independence in the field of DNA damage repair and ovarian cancer, Dr. Hill will need to develop a new set of professional and scientific skills. The protected time allowed by this K08 award will give her the opportunity for formal coursework and mentored experiences to acquire these skills. I have worked closely with Dr. Hill over the last several months to re-design this training plan which will be accomplished during the five-year K08 funding period and will significantly expand her skill set to that of an independent scientist. Based on reviewer comments, we have dropped one aim and added a different one to make the project more feasible and provide *in vivo* validation of *in vitro* findings. We have also added necessary coursework in areas where Dr. Hill needs additional training and obtained a biostatistics collaborator to aid Dr. Hill in her sample size selection and eventual biostatistical analysis.

Dr. Hill's overall career goal is to understand the mechanisms by which DNA damage repair defects lead to HGSC carcinogenesis and therapeutic sensitivity. The scientific aims of this research plan require expanding Dr. Hill's current knowledge and skills in the DNA repair field to include animal modeling of *in vitro* discoveries, next generation sequencing analysis of cell line, organoid, and tumor samples, and molecularly analyzing the mechanisms of the defects she is detecting in the tumors. Accordingly, she will attend at least one DNA repair conference each year, the AACR Annual Meeting, and the AACR Ovarian Cancer Conference to hear talks on the latest techniques and advances in the field, to foster collaborations, and to present her work. She will regularly attend our weekly D'Andrea lab meetings, which are held jointly with the lab of Dr. Geoffrey Shapiro, a member of Dr. Hill's advisory committee and an expert on DNA repair defects and clinical trials. Dr. Hill will have the opportunity to present her work at these meetings and obtain valuable feedback. As described above and detailed in the research and career development progress monitoring plan below, I will meet informally in the lab

with Dr. Hill multiple times per week and for one-hour one-on-one weekly to discuss her data and plan further experiments. She will also meet regularly with Dr. Shapiro to discuss organoid assay results and the translation of her DNA repair defect findings into the clinic with respect to all aims of the project.

Training Goal 1) To become proficient in analysis of genomic data:

I will supervise Dr. Hill's sequencing analysis along with Drs. Rameen Beroukhim and Myles Brown, both members of Dr. Hill's advisory committee who are experts on the genomic and transcriptomic analysis of tumors respectively and will provide additional experimental and analytic guidance. Drs. Beroukhim and Brown can provide Dr. Hill valuable guidance in sample and control selection, sequencing platform selection, analysis pipeline selection and use, and selection of appropriate hits to further examine mechanistically. Dr. Hill will take a graduate level course on programming and analysis pipelines for large sequencing data sets, BMIF 313qc Computing Skills for Biomedical Sciences, during the fall of her first year in order to gain a better understanding of the analysis of this data. These experiences will help Dr. Hill gain hands on experience with next generation sequencing experimental design and analysis such that she will be able to successfully implement these techniques in aims 1 and 3 of her proposal and more importantly in her independent research program.

Training Goal 2) To gain expertise in animal modeling of cancer:

Dr. Hill will need to validate *in vitro* organoid findings from Aims 1 and 2 *in vivo* as the next step in ushering these findings to the clinic. This will involve injecting immune compromised mice with her tumor organoid cultures, treating these organoid xenografts with various single and drug combinations, and assessing therapeutic response and analyzing the tumors. I will supervise Dr. Hill in all aspects of her animal work. I have extensive experience in modeling human disease in mice from my work in Fanconi anemia and recently through my work analyzing drug responses in high grade serous ovarian cancer patient-derived xenograft models. I have aided Dr. Hill in the design of Aim 3 which will focus on animal modeling of her *in vitro* results, helping her select appropriate numbers of mice to analyze, decide upon relevant outcomes to assess for, and determine how best to analyze the tumors that will be generated in these mice. In addition to this hands-on experience, Dr. Hill will also take a short graduate level didactic course focusing on modeling of human disease including in mice in the winter of year 1, Genetics 390qc: Experimental Approaches in Genetic Analysis. The combined mentored, bench, and didactic work will help Dr. Hill successfully gain experience in modeling cancer in mice, execute aim 3 of her proposal, and prepare her to design and execute such experiments in her independent research program.

Training Goal 3) To gain expertise on the design and execution of clinical trials:

Dr. Hill will participate in clinical trials throughout her career both as a pathologist analyzing histopathologic outcomes clinically, and as a scientist driving rational trial design with her basic science findings and the translational arms of the trials with her organoid models. Dr. Hill's training goal is therefore to better understand drug and patient selection, trial design, and trial execution in order to effectively participate in trials as an independent physician scientist. She will have guidance from her committee members Ursula Matulonis and Geoffrey Shapiro who are expert trialists and participate in a graduate level didactic course, Clinical Trial & Experimental Design for Researchers, in year 2 of her training program. These experiences will help her prepared to participate in clinical trials later in her career as both a physician and scientist.

Training Goal 4) To develop lab and personnel management skills:

Dr. Hill will need to develop leadership and management skills to run her own lab while balancing her continuing clinical duties. All the members of her advisory committee can provide unique insight to sustaining a strong career as an investigator or physician scientist, and Dr. Hill will gain valuable experience in mentorship and personnel management as she will train and supervise a

technician in my lab. She will also take a graduate level didactic course, Leadership Strategies for the Researcher, in year 2 of her training program to learn relevant strategies and procedures for hiring and managing staff in her independent lab. These combined experiences will prepare her to manage her own independent lab in the near future.

Professional Development Goals:

Research and Career Development Progress Monitoring: Dr. Hill will observe and seek guidance regarding leadership, management, publication, and grant writing from myself and the members of her advisory committee Drs. Matulonis, Brown, Sharpe, Shapiro, and Beroukhim and her Radiation Oncology Division head Dr. Haas Kogan who are all active researchers and/or physician-scientists. Dr. Hill will meet separately with myself and Dr. Haas-Kogan for one hour every six months to discuss her progress toward promotion. In addition, she will meet with her advisory committee every six months, during which meetings she will present her scientific progress in a one-hour presentation followed by presenting updates on her progress with grant submission, paper submission, and promotional milestones. The committee will then be able to provide comments and strategies for advancement in all aspects of her career. Prior to each of these meetings with individuals or her committee, Dr. Hill will generate a list of goals for career advancement which she will discuss, and after each meeting Dr. Hill will write down a list of the suggestions for meeting those goals based on the discussion in each setting. In this way, Dr. Hill will have constant individual mentorship and monitoring leading to successful career advancement.

In addition to myself and her committee, Dr. Hill plans to enroll in the Grant Review And Support Program (GRASP) at Harvard Medical School for the duration of this award. GRASP is a program offering guidance and mentorship to early career researchers (and are K award recipients) on grant writing in preparation for submission of a future R01 grant. She also plans to attend a two-day conference at Harvard Medical School on "Leadership Strategies for the Researcher" in Spring 2021, which will outline strategies for lab and personnel management.

Career Advancement Plan: Throughout the five-year award period, 75% of Dr. Hill's time will be dedicated to the scientific research in her proposal, 10% to other research, and 15% to her clinical duties as an anatomic pathologist. She will generate, profile, and sequence the organoid cultures described in aim 1 as relevant clinical trial and standard-of-care samples are accrued, while keeping careful records of patient outcomes over time with the help of her advisors Drs. Matulonis and Shapiro. She will write and submit a first author manuscript describing the prevalence of stalled fork defects and predictive capacity of the organoid system for patient response at the end of year three. Beginning in year two, Dr. Hill will have generated enough organoid cultures to observe variation in therapeutic sensitivities and repair defects and begin to search for differences in stalled fork protection mechanisms. She will perform more detailed fiber analysis after different single and combined drug treatments, targeted western analysis after the same treatments, and analysis of RUNX3 function in a subset of cultures generated in aim 1, as proposed in aims 2a-2c in years 2-4. The organoids generated in aim 1 will feed into aim 3 which will begin at the end of year 2 when she will inject select organoid cultures into immune compromised mice to generate organoid xenograft models of representative fork stable and unstable cultures. She will then carry out therapeutic sensitivity analysis in the organoid xenografts with her best single and combination drugs for inducing replication stress, namely AZD6738 and gemcitabine either alone or in combination. These *in vivo* therapeutic sensitivity experiments will be carried out in years 3 and 4. She will plan to submit a first author manuscript describing initial observations in stalled fork repair mechanisms, possibly relating to RUNX3, in year four with additional *in vivo* validation provided by work in aim 3. As detailed in her career monitoring plan, she will meet every six months with myself and with the chair of Radiation Oncology at DFCI, Daphne Haas-Kogan, to discuss progress toward appointment as Assistant Professor and move toward independence and to talk about strategies in meeting necessary milestones. In year 4, she will use the

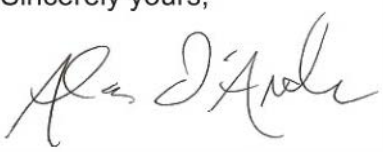
data generated in the first three years to formulate aims and begin to write an R01 application which will be submitted by the end of year 4. During the five-year award period, Dr. Hill will also apply for additional funding opportunities (e.g., DOD, Rivkin Center, and Ovarian Cancer Research Fund Alliance). We expect Dr. Hill will be promoted to Assistant Professor during the K08 award, and she will transition to independence during this period as well. By the end of year five, Dr. Hill will be independent, with her own lab focusing on mechanisms of stalled replication fork defects and how to target them in HGSC, along with new projects related to major problems in ovarian cancer research.

Clinical Development: Dr. Hill finished her pathology residency and clinical fellowship training on July 1, 2019 and is now an associate pathologist in the BWH pathology department. She will now devote 15% of her time to her clinical responsibilities as an attending Women's and Perinatal Pathologist at BWH. She will attend weekly interesting case conferences and gynecologic oncology tumor boards, and she will sign out on the gyn pathology biopsy service. She will meet annually with Dr. Marisa Nucci, the head of the Women's and Perinatal division and Dr. Jeffrey Golden, Chair of Pathology at BWH, to review her clinical performance and career progress. Dr. Hill will continue to perform her mentored laboratory research with me in the remaining 85% or her time, and I will strongly support her candidacy for an independent laboratory research position at the Dana-Farber Cancer Institute thereafter.

As described in the accompanying letter by Daphne Haas-Kogan, the Chair of the Department of Radiation Oncology, Dr. Hill has a unique training plan at the Dana-Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH). Dr. Hill has just completed her residency and clinical fellowship training in anatomic and Women's and Perinatal Pathology respectively on July 1, 2019. She is now an associate pathologist at BWH, and by the end of 2019 she will be appointed Instructor in Radiation Oncology at DFCI where her research activities will occur. Importantly, Dr. Hill will also be working closely with faculty mentors in Medical Oncology at DFCI and Gynecologic Surgery at BWH. Indeed, her recent publication (Hill SJ, Decker B, Roberts EA, Horowitz NS, Muto MG, Worley MJ, Feltmate CM, Nucci MR, Swisher EM, Nguyen H, Yang C, Morizane R, Kochupurakkal B, Do KT, Konstantinopoulos PA, Liu JF, Bonventre JV, Matulonis UA, Shapiro GI, Berkowitz RS, Crum CP, D'Andrea AD. Prediction of DNA Repair Inhibitor Response in Short Term Patient-derived Ovarian Cancer Organoids. Cancer Discov. 2018 Sep 13. pii: CD-18-0474. doi: 10.1158/2159-8290.CD-18-0474. PMCID:PMC6365285) has coauthors from all four of these Departments and is representative of her highly collaborative and interdisciplinary training program.

In summary, Dr. Hill is a remarkable young physician-scientist who is an exceptional candidate for a K08 Award. With her proven publication record and her commitment to ovarian cancer research, I believe she is one of the most talented investigators of her generation and will emerge as a leader in her field.

Sincerely yours,



Alan D. D'Andrea, M.D.

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July 2, 2019

RE: Sarah Hill, M.D., Ph.D.

Dear K08 Review Committee,

I am writing to give my strongest possible support and endorsement for Dr. Sarah Hill's K08 award application entitled "Targeting molecular vulnerabilities of ovarian cancer." I am honored to serve as a member of Dr. Hill's advisory committee and assist her with various aspects of this project for the duration of this K08 award. I am extremely enthusiastic about her scientific and career training plan and feel that she will excel and become a future leader in the field of ovarian cancer research. She is already well on her way.

I am the Chief of the Division of Gynecologic Oncology at the Dana Farber Cancer Institute (DFCI) and a Professor of Medicine at Harvard Medical School. In the Division of Gynecologic Oncology, we are well equipped to assist Dr. Hill with her project, and I am confident this proposal will be executed within the timeframe of the K08 grant. Dr. Hill will be able to carry out the clinical and translational aspects of her grant in our strong multidisciplinary research environment of 10 medical oncologists, 5 gynecologic oncology surgeons, and 2 radiation oncologists all of whom focus solely on the care of gynecologic oncology patients as well as clinical and translational research related to gynecologic cancers. In my role as a medical oncologist, I actively care for ovarian cancer patients, and I am committed to supporting and directing research that will improve therapeutic options for our patients with advanced ovarian cancer. I have been fortunate to have led some of the clinical trials that have led to regulatory approval of PARP inhibitors, which target tumors with defects in DNA damage repair, in both the United States and Europe for patients with ovarian cancer and recognize that Sarah's research has the potential to improve ovarian cancer patient treatment.

I have already worked extensively with Dr. Hill to aid her in obtaining patient consented tumor tissue and assessing patient outcomes for her preliminary work studying the DNA damage repair capacity of high grade serous ovarian cancer in patient-derived organoid cultures; this has led to her recent seminal publication in *Cancer Discovery*. Her preliminary work is *extremely* promising, and I am thrilled that she will now continue this important work and strive for a deeper mechanistic understanding of patient therapeutic response through the work in this K08 application. I plan to mentor her and aid her on her work in multiple ways.

In assisting her with the work in this proposal, I will continue to help her obtain consented tissue and interpret patient outcomes as they relate to the organoid assays for the duration of this K08 and beyond. I am the Principal Investigator of our gynecologic oncology tissue bank (Dana-Farber/Harvard Cancer Center (DF/HCC) study 02-051) which is the main banking study in our Division. This banking study started in 2002 and has over 1000 ovarian cancer samples, many of which also have matching blood samples. Our Division will consent appropriate patients from whom to generate organoid cultures undergoing standard treatment, participating in clinical trials, or wishing to participate in a rapid autopsy program that Dr. Hill has established this year. The Division of Gynecologic Oncology at DFCI and I are committed to giving Dr. Hill the resources and support to carry out her critical research.

Additionally, in my role, I will facilitate other tissue collection protocols that focus on collecting pre- and post- PARP inhibitor treatment (DF/HCC study 18-169) or neoadjuvant chemotherapy (DF/HCC study 15-051) tissue samples. I also direct, along with my colleagues Drs. Joyce Liu, Panagiotis Konstantinopoulos, and Jennifer Veneris, all faculty in the Division of Gynecologic Oncology, multiple clinical trials involving single agent as well as combination studies of PARP, CHK1, WEE1, and ATR inhibitors and immuno-oncologic agents amongst others. I will assure that Sarah is able to collect consented tissue and patient data from our banking efforts and clinical trials so that she can generate organoids from these ovarian cancer patients, compare organoid results to patient outcomes, and fully execute all of the aims in her K08 grant.

I will meet with Sarah frequently in multiple capacities throughout each year of this K08 award. My mentoring philosophy emphasizes frequent face to face meetings, and I always have an open-door policy any time Sarah has a question; we will meet face to face to discuss her progress at least monthly and very likely more often. We will also interact clinically through her work as a gynecologic pathologist and at weekly gynecologic oncology tumor boards. Finally, during my meetings with her, we will also discuss pathways to promotion and progress towards her R01. Her full committee will also meet with her bi-annually as a group to discuss her scientific and career progress, and I will participate in all of those meetings.

I have the utmost confidence that Sarah will be a leader in the field of cancer biology and ovarian cancer research and am committed to supporting Sarah throughout this award as she continues to develop.

independent physician scientist. Her proposed research has the potential for enormous clinical impact in this difficult to treat disease as well as the potential to rapidly result in tangible results for our patients. I give Sarah *and* this proposal my highest possible recommendation

Sincerely yours,

Ursula Matulonis, MD

DANA-FARBER CANCER INSTITUTE | BRIGHAM AND WOMEN'S HOSPITAL

Myles A. Brown, M.D.
Director, Center for Functional Cancer Epigenetics
Dana-Farber Cancer Institute

Emil Frei III Professor of Medicine
Harvard Medical School

Dana-Farber Cancer Institute, D730
450 Brookline Avenue
Boston, Massachusetts 02215

June 26, 2019

Re: Sarah J. Hill, M.D., Ph.D.

Dear Colleagues:

I am writing to offer my strongest possible support for Dr. Sarah Hill's K08 application entitled "Targeting molecular vulnerabilities of ovarian cancer." I have known Sarah since she was a graduate student in David Livingston's lab as I served on her dissertation advisory committee. It will be a great pleasure to serve on Dr. Hill's K08 advisory committee for the duration of the grant to help guide her in both in her career progression and in the analysis of her epigenomic and genomic data. She has developed an exceptional career training plan and a very innovative and impactful research proposal.

I am the Emil Frei III Professor of Medicine at Dana-Farber Cancer Institute and Harvard Medical School. My laboratory focuses on the epigenetic factors that underly the function of steroid hormones and their receptors in cancer, including most recently in ovarian cancer. Together with Shirley Liu, I direct the Center for Functional Cancer Epigenetics at the Dana-Farber Cancer Institute. Our center provides epigenomic and genomic expertise and collaboration to researchers at the Dana-Farber including both data generation platforms as well as computational analysis pipelines and expertise. Our center has been and will continue to be available to assist Dr. Hill with her project. As a physician-scientist who was supported by a K08 early in my own career, I understand the importance of this mechanism. I have had the pleasure of mentoring a number of other K08 awardees who have all gone on to become highly successful independent investigators. I will be able to offer Dr. Hill both scientific and career mentorship. Dr. Hill's research plan focuses on uncovering the role of stalled replication fork protection defects in ovarian carcinogenesis and therapeutic vulnerabilities by utilizing patient-derived organoid models and immortalized cell lines to perform mechanistic and therapeutic analyses. This synergizes with my own interests in steroid hormone signaling and its potential relationship with the DNA damage response in ovarian cancer, and I have already guided Dr. Hill in the performance of the transcriptomic and subsequent bioinformatics analyses on her organoids. I am very experienced in interpreting these types of data, and I helped Dr. Hill analyze her data for meaningful hypotheses. In addition, having been an active physician-scientist throughout my career, I will also be able to help guide her in navigating the difficult balance between these two competing interests and in utilizing her combined clinical and scientific expertise to reach her maximum potential as a physician-scientist.

Dr. Hill will interact frequently in multiple settings for the duration of this K08 award. As a member of her advisory committee, I will attend the formal bi-annual meetings with all of her committee members to monitor her career progress and offer advice in meeting critical milestones for advancement. In addition, we will meet frequently informally when she collaborates with my center to design and analyze any epigenomic experiments. I will also meet with her formally at least bi-annually to discuss mechanistic hypotheses generated through her work and methods or techniques that can be used to further query them, as well as, to discuss maturation of the aims for other grants including an R01 application. I look forward to working on this clinically important project with Dr. Hill and mentoring her as she transitions to scientific independence.

Sincerely,

Myles A. Brown, M.D.

HARVARD MEDICAL SCHOOL
BRIGHAM AND WOMEN'S HOSPITAL

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Arlene H. Sharpe, M.D., Ph.D.
George Fabyan Professor of Comparative Pathology
Co-Chair, Dept. of Microbiology and Immunobiology
Head, Division of Immunology
Co-Director, Evergrande Center for Immunologic Diseases
Director, Transgenic Mouse Core

July 1, 2019

Dear Review Committee,

I am delighted to offer my strongest support for Sarah Hill's K08 application "Targeting Molecular Vulnerabilities of Ovarian Cancer" and willingness to serve on her advisory committee for the duration of this K08 award.

I am the George Fabyan Professor of Comparative Pathology and Co-Chair of the Department of Microbiology and Immunobiology at Harvard Medical School, a member of the Department of Pathology at Brigham and Women's Hospital, an Associate Member at the Broad Institute of MIT and Harvard, and Leader of the Cancer Immunology Program at the Dana-Farber/Harvard Cancer Center. I am a board certified anatomic pathologist and also run my own R01 funded research lab. My lab has a broad focus on T cell co-stimulatory pathways and their immunoregulatory functions. As a physician-scientist focusing on anti-tumor immunity and immunoregulation and who also trained in anatomic pathology at Brigham and Women's Hospital, I will be able to mentor Dr. Hill both clinically and in her career progression. Having trained as an anatomic pathologist as Dr. Hill has done, I will be able to help guide her on becoming an academic pathologist.

I will meet with Dr. Hill in multiple capacities during each year for the duration of this K08 award. Her advisory committee will meet every six months to discuss her research and training plan progress, and I will attend each of those meetings. I also will meet with her as needed to discuss progress in her pathology career. I look forward to fostering Dr. Hill's development as a successful independent investigator and recommend her with my highest possible enthusiasm.

Sincerely,

Arlene Sharpe, M.D., Ph.D.

BROAD INSTITUTE | DANA-FARBER CANCER INSTITUTE | BRIGHAM AND WOMEN'S HOSPITAL | HARVARD MEDICAL SCHOOL

Rameen Beroukhim, MD, PhD
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June 27, 2019

Dear Review Committee,

I am pleased to offer my strongest support for Sarah Hill's K08 application "Targeting Molecular Vulnerabilities of Ovarian Cancer." I would be happy to serve on her advisory committee for the duration of this K08 award and am excited about her clinically important research plan. I have worked with Sarah for many years now, since her time as a graduate student in David Livingston's laboratory, and only have good things to say about Sarah. I am excited to continue working with and mentoring her.

I am an Assistant Professor of Medicine at Harvard Medical School and Dana Farber Cancer Institute, where I both see neuro-oncology patients and run my own R01 funded basic science lab. My lab focuses on understanding the genetic evolution of tumors from primary to metastasis and how such alterations affect the tumor behavior with a particular interest in copy number alterations. We have focused largely on brain cancers but also have an interest in endometrial cancers and in large scale studies of alterations to chromosomal structure across many other cancers. Dr. Hill's functional work and organoid system dovetail beautifully with my own interests as she will be able to functionally

validate and mechanistically explore the genetic alterations we observe. Given my experience as a practicing physician scientist and expertise and genomic analysis, I will be able to offer Dr. Hill mentorship on many levels. Her proposal includes extensive genomic sequencing paired with functional assay analysis both of primary and metastatic tumors. Given my personal expertise with planning, execution, and analysis of such genomic experiments, I will be able to advise her on this work at every stage and offer collaboration as needed or guide her to the right collaborator in some cases. I am excited to see how paired functional and patient outcome analyses aid in interpreting our genomic analysis. In addition, I will mentor Dr. Hill as she tries to balance both her clinical and scientific interests with guidance from my own experience as a practicing physician scientist.

I will interact with Dr. Hill in multiple ways each year for the duration of this K08. As part of her advisory committee, I will meet with her during the bi-annual committee meeting to be held each year to discuss scientific progress and career advancement. In addition, I will be available to discuss scientific issues at any time each year as they arise since we are both based at Dana Farber, and we will meet bi-annually to discuss progress, troubleshoot any genomic issues, and in the later stages of the award begin focusing her R01 aims. Dr. Hill has an exciting research proposal, and I am pleased to mentor her as she transitions to becoming an independent physician scientist.

Sincerely,

Rameen Beroukhim, MD, PhD

DANA-FARBER CANCER INSTITUTE | BWH BRIGHAM AND WOMEN'S HOSPITAL

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June 30, 2019

Dear Review Committee,

I am pleased to write this enthusiastic letter of support for the K08 award application of Dr. Sarah Hill. I have known Sarah for the past two years and will gladly serve as a member of her advisory committee during the period of the K08 award and fully support her research application and career development plan. I have already supported Sarah through her initial development of the high-grade serous ovarian cancer (HGSOC) organoid system and DNA repair functional assays and am committed to providing both career and scientific guidance for this clinically important work as she transitions to independence as a physician-scientist.

I currently serve as Director of Dana-Farber's Early Drug Development Center (EDDC), where a high volume of patients with ovarian cancer are enrolled on early phase trials. I also serve as Clinical Director for the Center for DNA Damage and Repair (CDDR). Additionally, I direct my own NIH-funded independent research lab, which focuses on targeting functional molecular defects, particularly in the DNA damage response and cell cycle, in a variety of solid tumor types. I will be able to act as a career mentor for Sarah as one of the practicing physicians on her committee who has held R01or SPORE funding. I will offer my expertise on assessing and targeting functional defects in solid tumors and will also assist her in the identification of patients who are good candidates for studies in which we will procure biopsies that can be used for organoid generation. I will also be able to provide guidance on compounds that have entered Phase 1 trial and that are of high priority and interest for ovarian cancer, so that organoid and patient responses can be studied in parallel. Currently, the EDDC is conducting several clinical trials open to patients with advanced ovarian cancer with various PARP inhibitors combined with the CHK1 inhibitor prexasertib, the ATR inhibitor VX-970 (M6620), the CDK12 inhibitor dinaciclib, as well as various immunologic agents. It will be of tremendous interest and clinical importance to determine whether the activities of these drugs in organoid cultures predict which DNA damage repair defects confer sensitivity to these agents.

As a member of her committee, I will meet with Sarah regularly during weekly combined D'Andrea/Shapiro laboratory meetings, as well as at weekly meetings of the CDDR, where translational projects are discussed and planned. These meetings will allow us to discuss her results and

review patient outcomes compared to outcomes in the corresponding organoid cultures. I will also make myself available to meet with her any time as needed to discuss scientific issues. Along with the entire committee, I will meet with Sarah bi-annually to monitor research progress and to provide additional feedback and guidance. As she progresses in her training, I will help mentor her on balancing her clinical and laboratory responsibilities and will also help her focus specific aims for her first R01 application.

Sarah's work thus far has been extremely impressive. She has single-handedly developed the ovarian organoid program at the Dana-Farber and has demonstrated tremendous seriousness of purpose, work ethic, ingenuity and technical expertise during the generation of the preliminary data for this K08 award. Sarah has all of the ingredients to successfully emerge as an independent investigator and I anticipate multiple high impact contributions to the ovarian cancer and DNA repair fields.

In summary, I look forward to working with Sarah to determine if more effective treatment regimens can be predicted by the organoid system for patients with ovarian cancer and also to providing mentorship in her transition to scientific independence. She is extremely deserving of a K08 award and I offer my highest recommendation without reservation.

Sincerely,

Geoffrey Shapiro

Geoffrey Shapiro, M.D., Ph.D.

DANA-FARBER
CANCER INSTITUTE

Nabihah Tayob, Ph.D.
Department of Data Sciences
Dana-Farber Cancer Institute

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July 3, 2019

Dear Sarah,

I am writing to confirm my willingness to provide biostatistical support and guidance for your K08 Award Application "Targeting Molecular Vulnerabilities of Ovarian Cancer." I am the lead statistician for the Women's Cancer Program at Dana-Farber Cancer Institute and have extensive experience in analyzing clinical trial and basic science data. I and my staff will have the capacity to help you analyze your results. I was excited by our discussions of the aims of the proposal and have already helped in providing statistical support in selecting sample numbers to appropriately power experiments and in discerning appropriate statistical tests to use for later analysis as you prepared your application. As your work progresses, I will be happy to help analyze correlations and outcomes as you try to assess the predictive capacity of your organoid cultures for patient response. I am excited to see if we can use this model system to better understand how DNA repair targeted therapies work in specific tumors and potentially use it as a clinical tool. I very much hope the grant is given strong consideration.

Sincerely,

Nabihah Tayob

Nabihah Tayob, Ph.D.

BRIGHAM HEALTH

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

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Ross S. Berkowitz, M.D.
Kevin Elias, M.D.
Sarah Feldman, M.D.
Colleen Feltmate, M.D.
Neil S. Horowitz, M.D.
Michael G. Muto, M.D.
Michael J. Worley, Jr., M.D.

June 28, 2019

Dear Sarah,

Thank you for including me in the exciting research planned in your K08 Award application "Targeting molecular vulnerabilities of ovarian cancer." As you know, my colleagues and I have a very busy gynecologic oncology practice with over a 100 patients per year who present for surgery and chemotherapy for newly diagnosed ovarian cancer. It has been a pleasure helping you identify patients and get fresh tissue for your work thus far, and I am more than happy to continue our fruitful collaboration. The results of your organoid work are quite exciting so my colleagues and I want to help support you in your efforts however we can.
As a group we have discussed changing the paradigm for how we will manage women who present with advanced stage ovarian cancer. We now plan to do laparoscopic assessment for cytoreduction. This will give us more opportunity to obtain tissue pre and post neoadjuvant chemotherapy. Having these paired samples hopefully will allow you to rapidly test the predictive capacity of the organoids which ultimately will be very valuable clinical information. In addition to providing tissue, we have our patient registry from which we can obtain clinical data (surgical outcomes, response to therapy, etc) to support your efforts as well.

Thank you again for all your efforts thus far and for including us in your research. I look forward to working with you as you transition to scientific independence and seeing where this work leads and whether or not it will help us predict cytoreducibility and chemotherapeutic response in the future.

Sincerely,

Neil S. Horowitz, M.D.
Assistant Prof. of Obstetrics, Gynecology and Reproductive Medicine, Director of Clinical Research

Harvard Medical School

Brigham and Women's Hospital

Christopher P. Crum, MD
Professor of Pathology

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June 24, 2019

Dear Sarah,

I am writing to offer my strongest support for your K08 award application "Targeting molecular vulnerabilities of ovarian cancer." It has been my pleasure working with you to ensure that your access to tissues and opportunity to exploit your high grade serous ovarian cancer organoid system. As you know from experience, our division sees a high volume of tumor material but more important, we have a special relationship with everyone in the Dana-Farber Cancer Institute (DFCI)-Brigham and Women's Hospital (BWH) network including close collaboration in our human investigation protocols. Your unique position within this group has been instrumental to your success and will give you access to all of the human material you need. We will work with the you and the DFCI to maximize your support at all levels. Best of luck and please contact me at any time if you need any assistance.

Christopher P Crum, MD

DESCRIPTION OF INSTITUTIONAL ENVIRONMENT

Dana-Farber Cancer Institute (DFCI): The majority of my work will occur at DFCI which is one of the top cancer centers in the country and houses in-patient clinics, innumerable independent research labs offering opportunities for collaboration in any field, and multiple research core facilities including flow cytometry, sequencing, and microscopy cores, all of which will be utilized in this training program. DFCI is also home to the Belfer Center, which houses a fully staffed mouse model generation and experimentation facility, which will be used in Aim 3 of this proposal. DFCI also houses one of the busiest gynecologic oncology programs in the country which is led by my advisory committee member Ursula Matulonis and whose clinical members I interact with daily both in clinical and research capacities. My primary academic appointment at DFCI will be in the Department of Radiation Oncology which houses a group of researchers with a strong focus on DNA damage repair including Dr. Dipanjan Chowdhury, who also focuses on ovarian cancer, and my mentor Dr. Alan D'Andrea, and has affiliations with my advisory committee member Dr. Geoffrey Shapiro. Due to the department's long-standing interest in the DNA damage response, I will have access to all equipment needed for DNA damage repair assays within my immediate research building. In addition, the Department of Radiation Oncology fosters an excellent environment for young physician scientists housing multiple junior investigators including Drs. Joseph Mancias, Kent Mouw, and Alexander Spektor, who have recently transitioned to independent positions and will be excellent sources of advice. Within DFCI, I will have multiple opportunities to attend research seminars given by world class scientists including the Radiation Oncology and Cancer Biology seminars, where I will also have the opportunity to present my own work to get insight and feedback from senior staff.

Aside from my department, I will also have access to the resources of the DFCI Office for Faculty Development (OFD). This office provides a consultation service for early career faculty to be mentored by and receive career advice from later career faculty on career advancement and building relationships with mentors and institutional leadership, along with many other topics. The OFD also offers a variety of dinners, seminars, and bootcamps which provide mentorship on career advancement and opportunities to interact with other early career faculty members. These events include DFCI sponsored faculty dinners allowing for early career DFCI faculty members to go to dinner together and discuss their shared experiences, a Leadership Bootcamp which consists of a half day seminar led by senior DFCI members for early career faculty providing mentorship on the challenges of leadership and difficult decision making, and short seminars on various topics as such as preparing a CV for a job search or what job search committees look for in candidates.

Overall DFCI provides a very rich research and mentorship environment that has successfully generated many world class scientists and will be an ideal training environment for me.

Brigham and Women's Hospital (BWH): The BWH pathology department will be the location of my clinical appointment as associate pathologist and it is connected to DFCI by a bridge, making the transition between my clinical and scientific duties very easy. It is one of the highest volume pathology departments in the country for every subspecialty, meaning I will see ample cases to hone my diagnostic abilities. The gynecologic pathology division has a large faculty with varied interests who will be sources of advice for navigating a career in academic pathology. In addition, the department has a strong academic background in both basic and translational research which has generated many independent physician scientists, including my advisory committee member Dr. Arlene Sharpe and one of my long-term career advisers Dr. Mel Feany. The department hosts weekly Grand Rounds where I will be given the opportunity to present my work.

Harvard Medical School (HMS): HMS houses world class researchers ranging from early to late career and also houses the Harvard School of Public Health (HSPH) and is located within a block of DFCI. HMS offers graduate level courses on biostatistics and computational biology, amongst other topics, in which I will participate. There are opportunities to interact with senior scientists interested in DNA damage repair, such as Dr. Stephen Elledge, and ovarian cancer, such as Dr. Joan Brugge, who both actively collaborate with the D'Andrea lab. HMS is also home to the Harvard Catalyst program which provides mentorship and learning opportunities both on scientific topics, such as deep sequencing analysis, and lab management, such as various leadership seminars. HSPH offers monthly journal clubs and seminars on cancer genomics and data analysis. I plan to attend seminars at both HMS and HSPH when relevant to my work.

The Eli and Edythe L. Broad Institute of MIT and Harvard: The Broad Institute is located a short bus ride away from the DFCI campus. My mentor Alan D'Andrea is an associate member and I am a post-doctoral affiliate. The Broad Institute offers an enormous array of sequencing platforms and data analysis tools which I am able to utilize for my work. In addition, it offers weekly analysis seminars and office hours to help me perform analysis on the data I generate.

Overall, DFCI and its surrounding environment provide ample opportunities for mentorship, teaching, and collaboration that will help me gain the skills I need to transition to scientific independence. I will take advantage of as many opportunities as possible.

DANA-FARBER CANCER INSTITUTE | BRIGHAM AND WOMEN'S HOSPITAL | Boston Children's Hospital

Daphne Haas-Kogan, M.D.
Professor and Chair
Department of Radiation Oncology
Dana-Farber Cancer Institute
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Boston Children's Hospital
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July 7, 2019

To Whom It May Concern:

As Chair of the Department of Radiation Oncology at Dana Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH), I am pleased to write this letter in support of the application of Dr. Sarah Hill, M.D., Ph.D. for a Mentored Clinical Scientist Research Career Development (K08) Award.

Dr. Hill will be appointed as an Instructor in Radiation Oncology at Dana-Farber Cancer Institute/Harvard Medical School (July 2019). Her clinical training in pathology and scientific training in genomics, molecular biology of DNA damage repair, and human model generation dovetails with our Department's interest in investigating the contribution of DNA damage repair defects to human carcinogenesis and therapeutic sensitivity. She will be a major contributor to modeling human tumors within our Department. As Chair of our Department, I guarantee that Dr. Hill will have 75% of her time protected to devote to the research in this proposal for the duration of this K award.

As evidenced by the signature of Dr. Jeffrey Golden, Chair of the Department of Pathology at Brigham and Women's Hospital, Dr. Hill will also be appointed as an Associate Pathologist on the Gynecological Pathology service. For the duration of the K award, her clinical activity, which will consist of signing out gynecologic pathology and conducting rapid autopsies on selected gynecologic malignancy patients, would constitute no more that 15% of her total time. Her clinical work will provide her with a translational clinical context that is highly synergistic with her research interests and enables her to be actively engaged in the instruction of clinical residents and fellows.

Dr. Hill's proposal is well-strategized and builds on preliminary findings generated in her recent publication Hill et al, "Prediction of DNA Repair Inhibitor Response in Short Term Patient-Derived Ovarian Cancer Organoids," *Cancer Discovery*, 2018. She will benefit greatly from continuing to work with her mentor Dr. Alan D'Andrea who is a member of the Department of Radiation Oncology and who has a longstanding interest in DNA repair and cancer. Dr. Hill has also established an advisory committee of preeminent investigators and physician scientists to help mentor her on all aspects of this project, including Drs. Ursula Matulonis, Myles Brown, Arlene Sharpe, Geoffrey Shapiro, and Rameen Beroukhim. Each of her mentors is uniquely suited to advise her on navigating the competing interests of science and medicine and to offer personalized expertise on the many facets of her work.

As Chair of our Department, I am in full support of Dr. Hill's research career advancement. I will work with Dr. D'Andrea and Dr. Golden to follow her career development and will be involved in the bi-annual review of her progress. I will work with Dr. D'Andrea to ensure that Dr. Hill has the necessary research and financial resources to pursue the aims of her proposal. The combined goal of our Department, her pathology mentors, and her advisory committee is to help Dr. Hill achieve scientific independence. Our commitment to Dr. Hill's career development is not contingent on her receipt of this award.

Based on Dr. Hill's research and clinical accomplishments, the continued support of her research mentor and advisory committee, the strong commitment from her clinical department, and the unwavering commitment from our Department, we are certain that Dr. Hill will successfully transition to scientific independence. The protected time and continued mentored experience that this K08 award will provide her will give her the needed time and resources to focus on developing her own research program and maturing the necessary skills to be an independent investigator.

Sincerely,

D. Haas-Kogan

Daphne Haas-Kogan, M.D.
Chair, Radiation Oncology

Jeffrey Golden, M.D.
Chair, Pathology

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ● No
Is the Project Exempt from Federal regulations?	● Yes ● No
Exemption Number	■ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	02-051 Collection of Tissue and Blood Specimens and Clinical Data in Patients with Suspected Gynecological Neoplasms, and Patients with Gynecological Cancers	No
2	15-051 Pilot study of serial tissue collection in patients with ovarian, fallopian tube, and peritoneal cancer receiving neoadjuvant chemotherapy	No
3	18-169 Tissue collection from women undergoing treatment with PARP-inhibitor therapy for recurrent epithelial ovarian cancer	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 03/31/2020

1.1. Study Title *

02-051 Collection of Tissue and Blood Specimens and Clinical Data in Patients with Suspected Gynecological Neoplasms, and Patients with Gynecological Cancers

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ☐ 1 ☐ 2 ☐ 3 ■ 4 ☐ 5 ☐ 6 ■ 7 ■ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	● No
1.4.b. Are the participants prospectively assigned to an intervention?	○ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	○ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	○ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Ovarian Neoplasms
- Fallopian Tube Neoplasms

2.2. Eligibility Criteria

Diagnosis of suspected gynecological neoplasms
Diagnosis of a gynecological cancer
Subjects diagnosed with a recurrent gynecological cancer

2.3. Age Limits	Min Age: 18 Years	Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	Inclusion_WomenMinorities.pdf	
2.5. Recruitment and Retention Plan	02-051_Recruitment_Retention.pdf	
2.6. Recruitment Status	Recruiting	
2.7. Study Timeline	Study_Timeline.pdf	
2.8. Enrollment of First Subject	08/14/2002	Actual

02-051 Tissue Collection Protocol

2.4 INCLUSION OF WOMEN, MINORITIES AND CHILDREN

1. Inclusion of Women and Minorities

Planned Distribution of Subjects

Accrual of women and minorities to trials in the DF/HCC generally reflects the population of the state of Massachusetts and New England. DF/HCC has a large primary service area, with the majority of its patients coming from southern Massachusetts, although it also draws patients throughout New England and beyond. The primary service area is overwhelmingly White.

In accordance with NCI definitions, the catchment area for DF/HCC is Boston, Massachusetts (Suffolk County). Within Massachusetts, the metropolis of Boston is geographically much smaller than most major cities in the United States and has a relatively small population of 617,594 (US Census 2010). Of the total population in Boston, 53.9% are White, 24.4% Black or African American, 8.9% Asian, <1% Native Hawaiian or Pacific Islander, and 17.5% Hispanic or Latino. Within Boston there are a substantial number of Italian Americans, Irish Americans, and Asian Americans. In addition, the population of Mexican, Central American, and South American residents is increasing over time. Lastly, there is a sizeable Russian and Eastern European population in the city. Across all disease areas, 56% of non-White adult cancer patients in Boston are treated by one of the four DF/HCC institutions (DFCI/BWH/MGH/BIDMC) and 83% of Hispanic adult residents who have cancer are treated by one of the four DF/HCC institutions.

As reported in the 2016 DF/HCC Cancer Center Support Grant, renewed in 2016, DF/HCC accruals to therapeutic trials in 2014 included 53.5% women and 11.1% minorities. For our catchment area, 52.9% of accruals were women, while 12.2% were minorities. African Americans comprised 7.5% and 7.1% of total and catchment area accruals, respectively. Therefore, DF/HCC accruals reflect the burden of minority populations in our catchment area. Accordingly, the targeted/planned enrollment of subjects in the 02-051 tissue collection protocol similarly reflects the demographic distribution of minorities in our catchment area.

Subject Selection Criteria

For the 02-051 tissue collection protocol, subjects considered for enrollment will be evaluated solely on the basis of protocol eligibility criteria; subjects who meet eligibility criteria and who provide informed consent will be enrolled, regardless of race. This study targets patients with gynecologic neoplasms, the demographics of which largely resemble the general population. Dana-Farber provides clinical care to cancer patients regardless of gender or racial/ethnic origin, and clinical research protocols adhere to this guideline. Consistent with NIH policy, investigators are required to include minorities in study populations so that the research findings can benefit all persons at risk.

Outreach Programs

Recruitment of minorities to clinical trials continues to be a national challenge. This is a challenge that many Comprehensive Cancer Centers face, and is particularly acute in a city like Boston that has a relatively small population and few minority cancer patients. Although DF/HCC partner institutions have a deep commitment to providing services to a diverse community, such as cancer screening services (e.g. mobile mammography, prostate screening, and skin cancer screening programs), many patients reached through these mechanisms receive their primary care elsewhere. DF/HCC has a long-standing institutional policy that it will not redirect screened patients needing additional care or cancer treatment to a DF/HCC institution unless patients independently request information about treatment at our facilities.

Respect of these boundaries has adversely affected our minority accrual, but is critical to maintaining strong ties with the community, ensuring continuity of health care, and continuing to receive community support of our outreach screening efforts.

Members of the Gynecologic Oncology Program participate in a multi-faceted approach to address the challenge of cancer disparities called the DF/HCC Initiative to Eliminate Cancer Disparities (IECD, http://www.dfhcc.harvard.edu/research/cancer-disparities/about-iecd/). The IECD is led by Dr. Bruce Chabner, a faculty member at Massachusetts General Hospital and Harvard Medical School, and a leading researcher with extensive portfolio in racial and ethnic disparities research that impact cancer care. We work closely with Dr. Chabner to ensure that we are participating in all of the mechanisms developed through the Initiative to support efforts to enhance diversity in accrual and to address cancer disparities, including:

A. Workforce Diversity. Diversity offices and policies have been established at DF/HCC, with a key goal of increasing the diversity of clinical research staff. We work with this/these office(s) to maximize the diversity of our research support team. The IECD also has a strong partnership with University of Massachusetts – Boston, a minority-serving institution that has very strong programs in science and nursing. Through this partnership, mechanisms have been developed to recruit their students and graduates, a large percentage of whom are from underrepresented backgrounds. We will take advantage of these mechanisms in filling any available staff positions.

B. Community Education and Engagement. The IECD has established a dynamic Community Engagement Committee (CEC) which facilitates and coordinate a wide array of community education activities. The CEC is currently engaged in an extensive effort to increase knowledge and awareness of cancer clinical trials in the Boston community. In addition, presentations have been provided to health care providers within local community health centers. Members of the Gynecologic Oncology Program will participate in the trainings and provide information on relevant trials as appropriate.

The CEC has also developed a strong and growing partnership with faith-based institutions focused on cancer education. The Faith-Based Cancer Disparities Network represents nine congregations with over 12,500 congregants. Collectively, the participants represent the leadership of their respective health ministers who are passionate and committed to ensuring a healthy congregation. To support these activities, a toolkit has been developed for health ministers that provide extensive 'select and use' materials (e.g. bulletin inserts, bible bookmarks, educational materials) and information on ongoing clinical trials open for recruitment. We will provide materials for the toolkit related to ovarian cancer, and will also provide staffing for community education speaking engagements as requested.

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C. Cultural Competency and Addressing Barriers to Care. The Patient Navigation Network formed in 2007 is comprised of all navigators across DF/HCC institutions and other Boston hospitals. The primary purpose is to provide educational sessions and opportunities to learn best practices. One particular focus has been on identifying best practice and barriers related to patient navigation for black, non-Hispanic breast cancer patients in the Boston area.

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Addressing Bias in Clinical Trial Design
Because eligibility criteria can inherently exclude minorities from participating in trials, specific questions on the inclusivity/exclusivity of minorities and children have been added to the protocol application form used at DF/HCC and are used by the Scientific Review Committee to evaluate eligibility criteria. Efforts are made to avoid heteronormative and gender binary language in the protocol and consent. These efforts help to ensure that investigators consider inherent bias in trial design and helps to emphasize the importance of inclusivity.

Proposed Exclusions
There is no proposed exclusion of any racial/ethnic group. Women of childbearing potential are not excluded from enrollment. In the geographical location at which these studies will be conducted, limited numbers, if any, American Indians, Alaska Natives, Native Hawaiians, or other Pacific Islanders will be eligible for the trial. However, these groups are not excluded from enrollment. Ovarian cancer is a disease that only affects patients with female genitalia, however, patients with ovarian cancer who identify as genders other than female are not excluded.

Sources
1. Massachusetts Department of Public Health (MDPH) MassCHIP (Community Health Information Profile)
2. Cancer Incidence and Mortality in Massachusetts 2010-2014 (report of the MDPH, published August 2017)
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2. Inclusion Across the Lifespan
The minimum eligible patient age for the 02-051 tissue collection protocol is 18. Individuals under the age of 18 are excluded, as ovarian cancer is extremely rare for patients under the age

of 18. Separate, age-specific and cancer-specific studies in children are preferable to ovarian cancer in this population.

02-051 Tissue Collection Protocol

2.5 Recruitment and Retention

Patients recruited to the 02-051 tissue collection protocol will be among those referred to the Gynecologic Oncology Program at the participating hospitals. Consent will be sought and obtained by the study team. The written IRB-approved informed consent document will be provided to all prospective subjects. These documents include sections explaining why the study is being done, what other options exist, what is logistically involved in the study, and risks of the study procedures. The consent form also discusses costs and confidentiality and provides contact numbers for questions regarding the study. Patients will be given 24-hour contact information to reach their study physician.

02-051 Tissue Collection Protocol

2.7 Study Timeline

The 02-051 tissue collection protocol is an ongoing tissue collection protocol open in the Gynecologic Oncology Program at Dana Farber/Harvard Cancer Center. Enrollment is anticipated to remain open throughout the extent of the K08 grant.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	DFCI

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ● Yes ○ No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): DFCI

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	0	0	0	0	0

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	3	0	0	0	0	0	0	0	0	3
Asian	88	0	0	0	0	0	6	0	0	94
Native Hawaiian or Other Pacific Islander	1	0	0	1	0	0	0	0	0	2
Black or African American	146	0	0	2	0	0	10	0	0	158
White	3574	0	0	25	0	0	233	0	0	3832
More than One Race	32	0	0	24	0	0	0	0	0	56
Unknown or Not Reported	32	0	0	43	0	0	90	0	0	165
Total	3876	0	0	95	0	0	339	0	0	4310

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	02-051_Protection_Subjects.pdf

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site? ○ Yes ● No ○ N/A

If yes, describe the single IRB plan

3.3. Data and Safety Monitoring Plan

3.4. Will a Data and Safety Monitoring Board be appointed for this study? ○ Yes ● No

3.5. Overall structure of the study team

02-051 Tissue Collection Protocol

3.1 Protection of Human Subjects

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

The 02-051 Tissue Collection Protocol allows for the collection of identified clinical samples from women with confirmed or suspected gynecologic neoplasms for use in research. Participants also consent to research-related collection of blood (up to once a year). The protocol allows for collection of archival samples or for obtaining fresh tissue that would otherwise be discarded from surgical procedures, paracenteses, or thoracenteses after all necessary clinical studies have been performed. Clinical data are collected from the medical records or from publically available databases. Research procedures performed on available samples may involve molecular characterization, including expression analyses or next generation sequencing, or tissue culture, organoid, or PDX generation. Participants are enrolled at one of the Dana-Farber/Harvard Cancer Center participating hospitals. The Dana-Farber Cancer Institute serves as the coordinating site and is responsible for the overall management, reporting and protection of data.

b. Study Procedures, Materials and Potential Risks

Research procedures.

Clinical samples will be obtained from eligible and consenting women with confirmed or suspected gynecologic neoplasms, either as archival samples, or as fresh specimens at the time of a clinically indicated procedure (e.g., surgery, paracentesis, thoracentesis). Research-related blood collection (up to once a year) may be performed. No other research-related procedures would be performed on participants. Collected samples will be utilized for organoid and PDX model generation.

Biospecimens, Data and Records.

Data and records to be collected about participants include name, date of birth, medical history, oncologic and treatment history. The specimen bank and clinical data bank will be catalogued in a computerized, password-protected, linked database file. Patient-derived material will be linked to patient clinical information using a numerical identifier, which will be coded using internal tissue bank code number identifiers to ensure patient confidentiality.

Potential Risks.

Potential risks of participation in the 02-051 Tissue Collection Protocol include potential complications from blood collection procedures, including pain, infection, or bleeding. There is also a risk of loss of confidentiality.

Alternative treatments and procedures.

Potential subjects for the 02-051 Tissue Collection Protocol will have the option of not enrolling in the protocol. The patient's treatment plan would not be affected by their choice to enroll or not to enroll in this tissue collection protocol.

2. Adequacy of protection against risks

a. Informed Consent

Patients recruited to the study will be among those referred to Gynecologic Oncology Programs at the participating hospitals. Consent will be sought and obtained by the study team. The written IRB-approved informed consent document will be provided to all prospective subjects. These documents include sections explaining why the study is being done, what other options

exist, what is logistically involved in the study, risks of the study procedures, and description of other required tests. The consent form also discusses costs and confidentiality and provides contact numbers for questions regarding the study.

b. Protections against risk
All procedures will be conducted by trained personnel. Blood samples will be drawn by experienced phlebotomists or infusion room nurses who work at participating centers.

The informed consent process at DF/HCC provides potential subjects with an extensive discussion of confidentiality in accordance with HIPAA guidelines. Results obtained from any research studies will not be placed in the subject's medical record, and publication of results will be done in a way that will not identify subjects. Subjects will be informed that their records may be inspected by study sponsors and that the results of the study may be published or used for teaching purposes. DF/HCC uses all reasonable efforts to protect subject privacy and the confidentiality of medical information. To protect against potential loss of confidentiality, all participant information will be stored in a password-protected file. Additionally, any patient-derived material will be identified with a numerical identifier only, with the link to patient clinical information restricted to a password-protected file.

3. Potential Benefits of the Proposed Research to Research Participants and Others
Participants are unlikely to benefit directly from participation in this research. Participation in this research will allow for greater insight into biology of ovarian cancer. This could result in new treatments and significant clinical benefit for women with this disease.

4. Importance of Knowledge to Be Gained
Clinical samples obtained from this protocol will support research into understanding the biology of ovarian cancer. This knowledge will be important to develop novel treatments in this disease.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ○ Yes ● No

4.2.e. Intervention Model

4.2.f. Masking ○ Yes ● No

❑ Participant ■ Care Provider ■ Investigator ■ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ○ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Section 1 - Basic Information (Study 2)

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 03/31/2020

1.1. Study Title *

15-051 Pilot study of serial tissue collection in patients with ovarian, fallopian tube, and peritoneal cancer receiving neoadjuvant chemotherapy

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ☐ 1 ☐ 2 ☐ 3 ■ 4 ☐ 5 ☐ 6 ■ 7 ■ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	○ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	○ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	○ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 2)

2.1. Conditions or Focus of Study

- Ovarian Neoplasms
- Fallopian Tube Neoplasms

2.2. Eligibility Criteria

INCLUSION CRITERIA

Participants must have clinically advanced stage (defined as disease outside of the pelvis) suspected or confiirmed epithelial ovarian, fallopian tube or peritoneal cancer.

Participant's treatment plan includes neoadjuvant chemotherapy (past, present, or future) with a platinum-based chemotherapy regimen selected by the treating physician. Single agent carboplatin is allowed, No prior drug therapy for this malignancy is permitted (except for patients who enroll after the initiation of neoadjuvant chemotherapy.

Patients must be seen and evaluated by a gynecologic oncologist at the time of treatment planning. The treating physician will determine, based on standard practice, if the patient is a candidate for neoadjvant chemotherapy, and upon completion of 2-4 cycles, if the patient's response is such that an attempt at cytoreductive surgery is appropriate.

Patients must have the ability to understand and the willingness to sign a written informed consent document.

Patients must be willing to undergo research-related genetic sequencing)somatic and germline) and data management, including the deposition of de-identified genetic sequencing data in NIH central data repositories.

EXCLUSION CRITERIA

Participants who had prior chemotherapy, radiotherapy or cytoreductive surgery for their current diagnosis of ovarian, fallopian tube, or peritoneal cancer will not be eligible for Cohort 1. Participants participating in Cohort 2 may have already received neoadjuvant chemotherapy.

Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirement.

Participants with any condition, which in the opinion of the patient's treating oncologist, or the physician performing the biopsy procedure, would make participation in this protocol unreasonably hazardous for the patient.

Additionaly, patients with the following medical contraindications to a biopsy procedure would be excluded from enrolling in Cohort 1.

Therapeutic anticoagulation that cannot be safely interrupted for a procedure.

History of serious or life-threatening allergic reaction to local anesthetics (i.e. lidocaine, xylocaine).

Active cardiac or pulmonary disease, defined as history of uncontrolled or symptomatic angina, history of arrhythmias requiring medications, or clinically significant myocardial infarction greater than months from study entry, uncontrolled or symptomatic congestive heart failure, uncontrolled chronic obsyructive pulmonary disease with increased anesthesia risk, other cardiac or pulmonary condition, which in the opinion of the treating physician would make this protocol unreasonably hazardous for the patient.

2.3. Age Limits	Min Age: 18 Years	Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	15-051_Women_Minorities.pdf	
2.5. Recruitment and Retention Plan	05-051_Recruitment_Retention.pdf	
2.6. Recruitment Status	Recruiting	
2.7. Study Timeline	15-051_Study_Timeline.pdf	
2.8. Enrollment of First Subject	08/24/2015	Actual

15-051 Tissue Collection Protocol

2.4 INCLUSION OF WOMEN, MINORITIES AND CHILDREN

1. Inclusion of Women and Minorities

Planned Distribution of Subjects

Accrual of women and minorities to trials in the DF/HCC generally reflects the population of the state of Massachusetts and New England. DF/HCC has a large primary service area, with the majority of its patients coming from southern Massachusetts, although it also draws patients throughout New England and beyond. The primary service area is overwhelmingly White.

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15-051 Tissue Collection Protocol

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15-051 Tissue Collection Protocol

2.7 Study Timeline

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IER ID#	Enrollment Location Type	Enrollment Location
Study 2, IER 1	Domestic	DFCI

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ● Yes ○ No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): DFCI

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
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Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	0	0	0	0	0

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	2	0	0	0	0	0	0	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	44	0	0	0	0	0	1	0	0	45
More than One Race	0	0	0	2	0	0	0	0	0	2
Unknown or Not Reported	0	0	0	0	0	0	1	0	0	1
Total	46	0	0	2	0	0	2	0	0	50

Section 3 - Protection and Monitoring Plans (Study 2)

3.1. Protection of Human Subjects — 02-0215Protection5Subjects._pf

3.d. Is this a multi-site stupy that will use the same _rotocol to conpuct non-exem_t human subjects research at more than one pomestic site? ○ Yes ● No ○ N/A

If yes, describe the single IRB plan

3.3. Data anp Safety Monitoring Plan

3.4. Will a Data anp Safety Monitoring Boarp be a__ointep for this stupy? ○ Yes ● No

3.2. Overall structure of the stupy team

15-051 Tissue Collection Protocol

3.1 Protection of Human Subjects

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

The 15-051 Tissue Collection Protocol allows for the collection of pre- and post-chemotherapy samples for women with newly diagnosed suspected ovarian cancer who are undergoing neoadjuvant chemotherapy for use in research.

At DF/HCC, women with newly diagnosed suspected ovarian cancer typically undergo a diagnostic biopsy (either via interventional radiology or by laparoscopy) to establish the diagnosis. For participants in this protocol who enroll after this diagnostic biopsy has been performed, an archival sample of this biopsy will be requested. For participants in this protocol who enroll prior to a diagnostic biopsy has been performed, a fresh research specimen will be collected at the time of the biopsy. At the time of interval cytoreductive surgery, a fresh surgical specimen will be allocated to research after confirmation that all tissue necessary for clinical diagnosis and treatment has been allocated. Additionally, blood samples for research testing will be collected at 5 timepoints in the participant's clinical course (at diagnosis; at completion of neaodjuvant chemotherapy prior to cytoreductive surgery; at the time of cytoreductive surgery; at completion of adjuvant chemotherapy; at time of first disease progression following initial therapy) for analysis of cell-free DNA (cfDNA). Should circumstances allow, the protocol also allows for collection of fresh tissue that would otherwise be discarded from surgical procedures, paracenteses, or thoracenteses after all necessary clinical studies have been performed. Clinical data are collected from the medical records or from publicly available databases. Research procedures performed on available samples may involve molecular characterization, including expression analyses or next generation sequencing, or tissue culture, organoid, or PDX generation. Participants are enrolled at one of the Dana-Farber/Harvard Cancer Center participating hospitals. The Dana-Farber Cancer Institute serves as the coordinating site and is responsible for the overall management, reporting and protection of data.

b. Study Procedures, Materials and Potential Risks

Research procedures.

Participating woman who have not yet undergone a diagnostic biopsy will have additional material allocated for research purposes at the time of their diagnostic biopsy. Additional clinical samples will be obtained at the time of interval cytoreductive surgery. Clinical samples may also be obtained at the time of a clinically indicated procedure (e.g., additional surgery, paracentesis, thoracentesis). Research-related blood collection will be collected at 5 timepoints during the participant's clinical course. Collected samples will be utilized for organoid and PDX model generation. Blood samples will be analyzed for cfDNA.

Biospecimens, Data and Records.

Data and records to be collected about participants include name, date of birth, medical history, oncologic and treatment history. The specimen bank and clinical data bank will be catalogued in a computerized, password-protected, linked database file. Patient-derived material will be linked to patient clinical information using a numerical identifier, which will be coded using internal tissue bank code number identifiers to ensure patient confidentiality.

Potential Risks.

Potential risks of participation in the 15-051 Tissue Collection Protocol include potential complications from biopsy or blood collection procedures, including pain, infection, or bleeding. There is also a risk of loss of confidentiality.

Alternative treatments and procedures.
Potential subjects for the 15-051 Tissue Collection Protocol will have the option of not enrolling in the protocol. The patient's treatment plan would not be affected by their choice to enroll or not to enroll in this tissue collection protocol.

2. Adequacy of protection against risks
a. Informed Consent
Patients recruited to the study will be among those referred to Gynecologic Oncology Programs at the participating hospitals. Consent will be sought and obtained by medical oncologists who are study investigators. The written IRB-approved informed consent document will be provided to all prospective subjects. These documents include sections explaining why the study is being done, what other options exist, what is logistically involved in the study, risks of the study procedures, and description of other required tests, including biopsies. The consent form also discusses costs and confidentiality and provides contact numbers for questions regarding the study.

b. Protections against risk
All procedures will be conducted by trained personnel. Blood samples will be drawn by experienced phlebotomists or infusion room nurses who work at participating centers. Patients who undergo tumor biopsies will be monitored directly after these procedures to ensure that no ill side effects occurred. Radiologic-guided biopsies will be performed under the supervision of experienced surgeons or interventional radiologists at the participating sites.

The informed consent process at DF/HCC provides potential subjects with an extensive discussion of confidentiality in accordance with HIPAA guidelines. Results obtained from any research studies will not be placed in the subject's medical record, and publication of results will be done in a way that will not identify subjects. Subjects will be informed that their records may be inspected by study sponsors and that the results of the study may be published or used for teaching purposes. DF/HCC uses all reasonable efforts to protect subject privacy and the confidentiality of medical information. To protect against potential loss of confidentiality, all participant information will be stored in a password-protected file. Additionally, any patient-derived material will be identified with a numerical identifier only, with the link to patient clinical information restricted to a password-protected file.

3. Potential Benefits of the Proposed Research to Research Participants and Others
Participants are unlikely to benefit directly from participation in this research. Participation in this research will allow for greater insight into biology of ovarian cancer and mechanisms of resistance to platinum/taxane chemotherapy. This could result in new treatments and significant clinical benefit for women with this disease.

4. Importance of Knowledge to Be Gained
Clinical samples obtained from this protocol will support research into understanding the biology of ovarian cancer and possible mechanisms of resistance to platinum/taxane chemotherapy. This knowledge will be important to develop novel treatments in this disease.

Section 4 - Protocol Synopsis (Study 2)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ○ Yes ● No

4.2.e. Intervention Model

4.2.f. Masking ○ Yes ● No

❑ Participant ■ Care Provider ■ Investigator ■ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ○ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Section 1 - Basic Information (Study 3)

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 03/31/2020

1.1. Study Title *

18-169 Tissue collection from women undergoing treatment with PARP-inhibitor therapy for recurrent epithelial ovarian cancer

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ☐ 1 ☐ 2 ☐ 3 ■ 4 ☐ 5 ☐ 6 ■ 7 ■ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	○ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	○ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	○ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 3)

2.1. Conditions or Focus of Study

- Ovarian Neoplasms
- Fallopian Tube Neoplasms

2.2. Eligibility Criteria

INCLUSION CRITERIA
Participants must have confirmed, advance epithelial ovarian, fallopian tube or peritoneal cancer.
Participant's treatment plan must have included chemotherapy with a platinum-based chemotherapy regimen. There is no limit on the amount of prior platinum the patient may have received.
Cohort 1: Must be planning to start treatment with PARPi.
Cohort 2: Must be currently on treatment with PARPi, or have stopped treatment with a PARP inhibitor within 3 months due to disease progression and not have started another chemotherapeutic agent.
NOTE: Patients who are receiving PARPi either as monotherapy or in combination will be eligible for this protocol. For patients receiving PARPi on a separate interventional protocol, protocol assessments and procedures from the interventional protocol take precedence over this protocol.
Age is greater than 18 years
Patients must have the ability to understand and the willingness to sign a written informed consent document.
Patients must be willing to undergo research-related genetic sequencing (somatic and germline) and data management, including the deposition of de-identified genetic sequencing data in NIH central data respositories.

EXCLUSION CRITERIA
Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestitve heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness.social situations that would limit compliance with study requirement.
Participants with any condition, which in the opinion of the patient's treating oncologist, or the physician performing the biopsy procedure, would make participation in this protocol unreasonably hazardous for the patient.
Participants with either an active infection with or known history of: Hepatitis B, Hepatitis C, HIV, Tuberculosis.
Lung biopsies not allowed on this protocol due to procedual risks.
Biopsies requiring general anesthesia are not allowed for research.

2.3. Age Limits	Min Age: 18 Years	Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	18-169_Women_Minorities.pdf	
2.5. Recruitment and Retention Plan	18-169_Recruitment.pdf	
2.6. Recruitment Status	Recruiting	
2.7. Study Timeline	18-169_Study_Timeline.pdf	
2.8. Enrollment of First Subject	05/06/2018	Actual

18-169 Tissue Collection Protocol

2.4 INCLUSION OF WOMEN, MINORITIES AND CHILDREN

1. Inclusion of Women and Minorities

Planned Distribution of Subjects

Accrual of women and minorities to trials in the DF/HCC generally reflects the population of the state of Massachusetts and New England. DF/HCC has a large primary service area, with the majority of its patients coming from southern Massachusetts, although it also draws patients throughout New England and beyond. The primary service area is overwhelmingly White.

In accordance with NCI definitions, the catchment area for DF/HCC is Boston, Massachusetts (Suffolk County). Within Massachusetts, the metropolis of Boston is geographically much smaller than most major cities in the United States and has a relatively small population of 617,594 (US Census 2010). Of the total population in Boston, 53.9% are White, 24.4% Black or African American, 8.9% Asian, <1% Native Hawaiian or Pacific Islander, and 17.5% Hispanic or Latino. Within Boston there are a substantial number of Italian Americans, Irish Americans, and Asian Americans. In addition, the population of Mexican, Central American, and South American residents is increasing over time. Lastly, there is a sizeable Russian and Eastern European population in the city. Across all disease areas, 56% of non-White adult cancer patients in Boston are treated by one of the four DF/HCC institutions (DFCI/BWH/MGH/BIDMC) and 83% of Hispanic adult residents who have cancer are treated by one of the four DF/HCC institutions.

As reported in the 2016 DF/HCC Cancer Center Support Grant, renewed in 2016, DF/HCC accruals to therapeutic trials in 2014 included 53.5% women and 11.1% minorities. For our catchment area, 52.9% of accruals were women, while 12.2% were minorities. African Americans comprised 7.5% and 7.1% of total and catchment area accruals, respectively. Therefore, DF/HCC accruals reflect the burden of minority populations in our catchment area. Accordingly, the targeted/planned enrollment of subjects in the 18-169 tissue collection protocol similarly reflects the demographic distribution of minorities in our catchment area.

Subject Selection Criteria

For the 18-169 tissue collection protocol, subjects considered for enrollment will be evaluated solely on the basis of protocol eligibility criteria; subjects who meet eligibility criteria and who provide informed consent will be enrolled, regardless of race. This study targets patients with gynecologic neoplasms, the demographics of which largely resemble the general population. Dana-Farber provides clinical care to cancer patients regardless of gender or racial/ethnic origin, and clinical research protocols adhere to this guideline. Consistent with NIH policy, investigators are required to include minorities in study populations so that the research findings can benefit all persons at risk.

Outreach Programs

Recruitment of minorities to clinical trials continues to be a national challenge. This is a challenge that many Comprehensive Cancer Centers face, and is particularly acute in a city like Boston that has a relatively small population and few minority cancer patients. Although DF/HCC partner institutions have a deep commitment to providing services to a diverse community, such as cancer screening services (e.g. mobile mammography, prostate screening, and skin cancer screening programs), many patients reached through these mechanisms receive their primary care elsewhere. DF/HCC has a long-standing institutional policy that it will not redirect screened patients needing additional care or cancer treatment to a DF/HCC institution unless patients independently request information about treatment at our facilities.

Respect of these boundaries has adversely affected our minority accrual, but is critical to maintaining strong ties with the community, ensuring continuity of health care, and continuing to receive community support of our outreach screening efforts.

Members of the Gynecologic Oncology Program participate in a multi-faceted approach to address the challenge of cancer disparities called the DF/HCC Initiative to Eliminate Cancer Disparities (IECD, http://www.dfhcc.harvard.edu/research/cancer-disparities/about-iecd/). The IECD is led by Dr. Bruce Chabner, a faculty member at Massachusetts General Hospital and Harvard Medical School, and a leading researcher with extensive portfolio in racial and ethnic disparities research that impact cancer care. We work closely with Dr. Chabner to ensure that we are participating in all of the mechanisms developed through the Initiative to support efforts to enhance diversity in accrual and to address cancer disparities, including:

A. Workforce Diversity. Diversity offices and policies have been established at DF/HCC, with a key goal of increasing the diversity of clinical research staff. We work with this/these office(s) to maximize the diversity of our research support team. The IECD also has a strong partnership with University of Massachusetts – Boston, a minority-serving institution that has very strong programs in science and nursing. Through this partnership, mechanisms have been developed to recruit their students and graduates, a large percentage of whom are from underrepresented backgrounds. We will take advantage of these mechanisms in filling any available staff positions.

B. Community Education and Engagement. The IECD has established a dynamic Community Engagement Committee (CEC) which facilitates and coordinate a wide array of community education activities. The CEC is currently engaged in an extensive effort to increase knowledge and awareness of cancer clinical trials in the Boston community. In addition, presentations have been provided to health care providers within local community health centers. Members of the Gynecologic Oncology Program will participate in the trainings and provide information on relevant trials as appropriate.

The CEC has also developed a strong and growing partnership with faith-based institutions focused on cancer education. The Faith-Based Cancer Disparities Network represents nine congregations with over 12,500 congregants. Collectively, the participants represent the leadership of their respective health ministers who are passionate and committed to ensuring a healthy congregation. To support these activities, a toolkit has been developed for health ministers that provide extensive 'select and use' materials (e.g. bulletin inserts, bible bookmarks, educational materials) and information on ongoing clinical trials open for recruitment. We will provide materials for the toolkit related to ovarian cancer, and will also provide staffing for community education speaking engagements as requested.

The CEC also sponsors a wide range of community events for National Minority Cancer Awareness Week. Members of this research team make themselves available to provide community talks throughout the year, and have provided resource material related to ovarian cancer for use in the on-going outreach efforts. The CEC has also created several cancer education displays one of which is called "The Choice is Yours" – a cancer prevention-focused poster display as part of a collaboration with local libraries. Launched in 2008, for a period of 2-4 weeks, a display of these six posters along with brochures and books are showcased at branches of the Boston Public libraries in recognition of National Minority Cancer Awareness. With over 6000 visitors to these libraries during this period, this is an excellent mechanism to reach a broad and diverse population. The display is made available to the other branch offices within the Boston Library network, and continues to be a centerpiece of the Cancer Center's

National Minority Cancer Awareness. We will work with the CEC to include information about ovarian cancer clinical trials in the next iteration of the library outreach program.

DF/HCC institutions have a strong portfolio of community-based research in cancer prevention. These research teams are highly engaged with Boston's communities of color, and provide an important portal into our cancer treatment and research programs. The IECD has trained community-based research field staff regarding DF/HCC's clinical research activities, and how to most effectively connect patients when requested. There will be specific information provided on ovarian cancer.

C. Cultural Competency and Addressing Barriers to Care. The Patient Navigation Network formed in 2007 is comprised of all navigators across DF/HCC institutions and other Boston hospitals. The primary purpose is to provide educational sessions and opportunities to learn best practices. One particular focus has been on identifying best practice and barriers related to patient navigation for black, non-Hispanic breast cancer patients in the Boston area.

DF/HCC has access and provides a wide array of cultural and language appropriate clinical trials and tissue banking materials and resources. Information about these resources is incorporated into the CEC's outreach education materials, and community-based research staff is trained on providing this information to community members in need of cancer treatment information.

Addressing Bias in Clinical Trial Design
Because eligibility criteria can inherently exclude minorities from participating in trials, specific questions on the inclusivity/exclusivity of minorities and children have been added to the protocol application form used at DF/HCC and are used by the Scientific Review Committee to evaluate eligibility criteria. Efforts are made to avoid heteronormative and gender binary language in the protocol and consent. These efforts help to ensure that investigators consider inherent bias in trial design and helps to emphasize the importance of inclusivity.

Proposed Exclusions
There is no proposed exclusion of any racial/ethnic group. Women of childbearing potential are not excluded from enrollment. In the geographical location at which these studies will be conducted, limited numbers, if any, American Indians, Alaska Natives, Native Hawaiians, or other Pacific Islanders will be eligible for the trial. However, these groups are not excluded from enrollment. Ovarian cancer is a disease that only affects patients with female genitalia, however, patients with ovarian cancer who identify as genders other than female are not excluded.

Sources
1. Massachusetts Department of Public Health (MDPH) MassCHIP (Community Health Information Profile)
2. Cancer Incidence and Mortality in Massachusetts 2010-2014 (report of the MDPH, published August 2017)
3. Boston Public Health Commission
4. US Census 2010

2. Inclusion Across the Lifespan
The minimum eligible patient age for the 18-169 tissue collection protocol is 18. Individuals under the age of 18 are excluded, as ovarian cancer is extremely rare for patients under the age

of 18. Separate, age-specific and cancer-specific studies in children are preferable to ovarian cancer in this population.

18-169 Tissue Collection Protocol

2.5 Recruitment and Retention

Patients recruited to the 18-169 tissue collection protocol will be among those referred to the Gynecologic Oncology Program at the participating hospitals. Consent will be sought and obtained by the study team. The written IRB-approved informed consent document will be provided to all prospective subjects. These documents include sections explaining why the study is being done, what other options exist, what is logistically involved in the study, and risks of the study procedures, including biopsies. The consent form also discusses costs and confidentiality and provides contact numbers for questions regarding the study. Patients will be given 24-hour contact information to reach their study physician.

18-169 Tissue Collection Protocol

2.7 Study Timeline

The 18-169 tissue collection protocol is an ongoing tissue collection protocol open in the Gynecologic Oncology Program at Dana Farber/Harvard Cancer Center. Enrollment is anticipated to remain open throughout the extent of the K08 grant.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 3, IER 1	Domestic	DFCI

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ● Yes ○ No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): DFCI

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	0	0	0	0	0

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	1	0	0	0	0	0	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	1	0	0	0	0	0	0	0	0	1
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	2	0	0	0	0	0	0	0	0	2

Section 3 - Protection and Monitoring Plans (Study 3)

3.1. Protection of Human Subjects	18-169_Protection_Subjects.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ● No
3.5. Overall structure of the study team	

18-169 Tissue Collection Protocol

3.1 Protection of Human Subjects

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

The 18-169 Tissue Collection Protocol collects pre- and post-treatment research biopsies from women who are undergoing or have progressed on treatment with PARP inhibitors. Research blood collection also occurs every 2 months.

Participants in this protocol will be enrolled into one of two cohorts: Cohort 1, which will enroll women who were planned to initiate PARP inhibitor therapy, and Cohort 2, which will enroll women who are undergoing or who have progressed on treatment with PARP inhibitors, but who have not received an intervening therapy. For participants in Cohort 1, a pre-treatment research biopsy will be performed and a pre-treatment blood sample will be collected. The participant will then initiate PARP inhibitor treatment as prescribed by their treating oncologist. During the time they are on treatment, participants undergo blood collection every 2 months. At the time of progression, participants will undergo a post-progression biopsy as well as a post-progression blood collection. For participant in Cohort 2, blood collection will occur every 2 months if they remain actively on PARP inhibitor therapy. At the time of progression, a post-progression biopsy and post-progression blood collection will be performed. Archival tumor will be collected from all participants. Clinical data are collected from the medical records or from publically available databases. Research procedures performed on available samples may involve molecular characterization, including expression analyses or next generation sequencing, or tissue culture, organoid, or PDX generation. Participants are enrolled at one of the Dana-Farber/Harvard Cancer Center participating hospitals. The Dana-Farber Cancer Institute serves as the coordinating site and is responsible for the overall management, reporting and protection of data.

b. Study Procedures, Materials and Potential Risks

Research procedures.

Participating women in Cohort 1 will receive pre-treatment and post-progression research biopsies and will also have research blood collection at baseline (pre-treatment), every 2 months while on PARP inhibitor therapy, and post-progression. Participating women in Cohort 2 will undergo a post-progression research biopsy and have research blood collection every 2 months while on PARP inhibitor therapy and post-progression. Collected samples will be utilized for organoid and PDX model generation. Blood samples will be analyzed for cfDNA.

Biospecimens, Data and Records.

Data and records to be collected about participants include name, date of birth, medical history, oncologic and treatment history. The specimen bank and clinical data bank will be catalogued in a computerized, password-protected, linked database file. Patient-derived material will be linked to patient clinical information using a numerical identifier, which will be coded using internal tissue bank code number identifiers to ensure patient confidentiality.

Potential Risks.

Potential risks of participation in the 18-169 Tissue Collection Protocol include potential complications from biopsy or blood collection procedures, including pain, infection, or bleeding. There is also a risk of loss of confidentiality.

Alternative treatments and procedures.

Potential subjects for the 18-169 Tissue Collection Protocol will have the option of not enrolling in the protocol. The patient's treatment plan will not be affected by their choice to enroll or not to enroll in this tissue collection protocol.

2. Adequacy of protection against risks

a. Informed Consent

Patients recruited to the study will be among those referred to Gynecologic Oncology Programs at the participating hospitals. Consent will be sought and obtained by medical oncologists who are study investigators. The written IRB-approved informed consent document will be provided to all prospective subjects. These documents include sections explaining why the study is being done, what other options exist, what is logistically involved in the study, risks of the study procedures, and description of other required tests, including biopsies. The consent form also discusses costs and confidentiality and provides contact numbers for questions regarding the study.

b. Protections against risk

All procedures will be conducted by trained personnel. Blood samples will be drawn by experienced phlebotomists or infusion room nurses who work at participating centers. Patients who undergo tumor biopsies will be monitored directly after these procedures to ensure that no ill side effects occurred. Radiologic-guided biopsies will be performed under the supervision of experienced surgeons or interventional radiologists at the participating sites.

The informed consent process at DF/HCC provides potential subjects with an extensive discussion of confidentiality in accordance with HIPAA guidelines. Results obtained from any research studies will not be placed in the subject's medical record, and publication of results will be done in a way that will not identify subjects. Subjects will be informed that their records may be inspected by study sponsors and that the results of the study may be published or used for teaching purposes. DF/HCC uses all reasonable efforts to protect subject privacy and the confidentiality of medical information. To protect against potential loss of confidentiality, all participant information will be stored in a password-protected file. Additionally, any patient-derived material will be identified with a numerical identifier only, with the link to patient clinical information restricted to a password-protected file.

3. Potential Benefits of the Proposed Research to Research Participants and Others

Participants are unlikely to benefit directly from participation in this research. Participation in this research will allow for greater insight into clinical mechanisms of drug (including PARP inhibitor) resistance and exploration of methods of overcoming clinical drug resistance. This could result in new treatments and significant clinical benefit for women with drug-resistant ovarian cancer.

4. Importance of Knowledge to Be Gained

Clinical samples obtained from this study will support research into the mechanisms of drug resistance development and provide insights into how to overcome drug resistance. This knowledge will be important to develop novel treatments to overcome drug-resistant ovarian cancer.

Section 4 - Protocol Synopsis (Study 3)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ○ Yes ● No

4.2.e. Intervention Model

4.2.f. Masking ○ Yes ● No

❑ Participant ■ Care Provider ■ Investigator ■ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ○ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

VERTEBRATE ANIMALS

The objective of Specific Aim 3 "*In vivo* validation of *in vitro* mechanisms of stalled replication fork protection defects leading to therapeutic responses in organoid xenograft models of HGSC" is to generate preliminary *in vivo* data to help validate *in vitro* findings from Aims 1 and 2. Immune compromised mice will be injected with luciferized versions of four separate organoid cultures as described in Kopper et al., *Nature Medicine* 2019 PMID: 31011202 to generate "organoid mice" for therapeutic testing. Successful xenograft generation and therapeutic sensitivity detection matching *in vitro* organoid responses with specific agents in the series of pilot experiments described in Aim 3 would prompt a larger study with more organoid mouse models focusing in on specific single drugs or combinations to provide statistically meaningful validation.

1. Description of Procedures

"Organoid xenograft mice" will be generated as follows. Approximately 8-to 10-week old female NSG (NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ) mice will be used for all the organoid xenograft experiments involving establishment of the new organoid xenograft models as well as drug treatments. The mice will be purchased from the Jackson laboratory, Bar Harbor, ME (stock number- 005557). The specific use of these mice is described in detail in the Approach section in Aim 3.

As described in the preliminary data section, Hans Clevers' group has already generated organoid xenograft ovarian cancer models successfully (Kopper et al., Nature Medicine 2019 PMID: 31011202). Our group has previously generated luciferized patient derived xenograft models (Liu JF et al, Clinical Cancer Research, 2017;23(5):1263-73). We will utilize both protocols to generate luciferized xenograft models with four of our organoid cultures, and these mouse models will be maintained at the Belfer Institute at the Dana-Farber Cancer Institute (DFCI). The therapeutic sensitivity studies to be conducted on these models, as described in Aim 3, will be conducted at the Belfer Institute and will be overseen by Dr. Sarah Hill the PI and her mentor Dr. Alan D'Andrea.

Establishment of organoid xenograft models: Ovarian cancer organoid xenografts will be established by implanting the luciferized patient-derived organoid cultures intraperitoneally in NSG mice as described previously (Kopper et al., Nature Medicine 2019 PMID: 31011202 where orthotopic transplantation was used). For model generation, 10 different luciferized organoid cultures will be implanted intraperitoneally into 2-5 NSG mice per organoid culture with the goal of establishing at least four different models. To assess for tumor development, mice will be examined three times each week for abdominal distention or palpable tumor. If mice develop any signs of morbidity or ascites, fail to develop tumors after a period of one year, or undergo a bodyweight gain of 40%, the mice will be euthanized. Mice will undergo necropsies after euthanasia, and major organs and ascites (if available) will be collected for histopathologic analysis. We plan to establish four new organoid xenograft models from the four models with the best tumor take rates (two fork stable and two fork unstable). We will therefore need approximately 50 nude mice to establish the new organoid xenograft models. Models will then be histologically and genetically validated and then expanded for drug testing.

Therapeutic sensitivity studies in organoid xenograft models: We will use the organoid xenograft models described above to evaluate a small subset of the single drugs and drug combinations described in Aims 1 and 2. These experiments are described in Aim 3. The four organoid xenograft models generated above will be implanted in NSG mice by intraperitoneal injections of approximately 5 x 10^6 cells/mouse. Tumor growth will be measured by bioluminescence imaging (BLI). One-three weeks after tumor cell injections, tumor-bearing animals will be randomized according to mean BLI counts to treatment groups (vehicle, single drugs or combination of drugs). For each group, efficacy and survival will be assessed (n=10 mice/group). The drugs will be administered for three-four weeks and tumor growth will be monitored at weekly intervals by both mouse weight and by bioluminescence imaging (BLI) and compared between the vehicle and drug-treated groups. The drugs will be administered at maximum tolerated doses (MTDs). For example, AZD6738 (ATR inhibitor), will be administered at 30 mg/kg either days one-three or four of every seven days by oral gavage. For the combination studies, two drugs will be administered concurrently, and if toxicity becomes an issue administration will be sequential. In the efficacy study, mice will be euthanized promptly when they reach experimental endpoints. The surviving mice will be euthanized at approximately 100 days after the drug treatments. The animals will be euthanized by CO_2 asphyxiation.

For bioluminescence imaging, a Xenogen system will be used. Briefly, the animals will be anesthetized by isoflurane using a precision vaporizer with an induction chamber connected to the IVIS Lumina II BLI instrument (Perkin Elmer) and then transferred to individual nose cones within the imaging chamber. The Firefly luciferase substrate, D-Luciferin (Fisher Scientific), will be injected intraperitoneally (150 µl of D-Luciferin in PBS 15mg/ml) before imaging. Image acquisition will take up to 20 minutes. Mice will be monitored for full recovery and will be placed back in the housing facility.

We plan to test two individual drugs (gemcitabine and AZD6738) and one drug combination (AZD6738+ gemcitabine) compared to vehicle in our 4 organoid xenograft models in a 4-arm experiment. Therefore, we will need approximately 160 NSG mice.

2. Justifications

Mouse models have proven to be an important tool in unraveling many aspects of cancer. Importantly, mouse models have served to aid the discovery of many therapeutic and diagnostic approaches that have translated into clinical benefit for patients. In particular, primary human tumors can be propagated in immunocompromised mice without rejection and patient-derived xenograft (PDX) or organoid xenograft models can be established. The PDX and organoid xenograft models mostly retain the principal histological and genetic characteristics of their donor tumor and remain stable across passages. The PDX and organoid xenograft models have been shown to be predictive of clinical outcomes and are being used for preclinical drug evaluation, biomarker identification, biological studies, and personalized medicine strategies. Specifically, for this project, organoid xenograft models of ovarian cancer will allow testing of sensitivity to drugs such as ATR inhibitors and gemcitabine both as monotherapies and in combination in cancer cells that preserve the genomic background of patients' tumors. Moreover, noninvasive imaging of tumor-bearing mice also allows continuous monitoring of the disease. Thus, mice represent a standard experimental model for xenograft tumors.

The parent organoid models and matched organoid xenografts used in the studies are unique with specific genomic changes such as a CCNE1 amplification. We plan to study specific models of replication fork stable and fork unstable tumors to try to understand how destabilizing replication forks can lead to therapeutic responses. The work will help understand how combinatorial approaches may yield therapeutic benefit across a variety of replication fork stable or unstable backgrounds. Multiple studies from the literature (Burger AM, Anticancer Drug Development 2002; Suggitt M, Clin Canc Res 2005) have highlighted the need for studying cancer drug resistance in a physiologically relevant setting such as a mouse model.

Furthermore, these mouse models are an essential step in the preclinical drug development pipeline (Tentler JJ, Nat Rev Clin Oncol 2012). Experiments in these *in vivo* models will yield important information about tolerability and scheduling of drug combinations that cannot be obtained from artificial *in vitro* systems or computational methods. The studies in mouse models will allow us to confirm biomarkers for patient stratification such as DNA fiber assays, as well as additional targets for further study. Thus, our research goals cannot be accomplished without use of the organoid xenograft mouse models. Sample sizes are minimized to utilize only the required number of animals to produce preliminary results. For each mouse model, n=10 replicates for each treatment was chosen to provide 90% power to detect a difference of 1.15 standard deviations in tumor growth inhibition at the 5% significance level.

3. Minimization of Pain and Distress

Veterinary care:
The animals will be housed (5 to a cage) and cared for at the Animal Resource Facility in the Longwood Center at the Dana-Farber Cancer Institute, Boston, MA. This animal facility is barrier-maintained, with HEPA-filtered air, isolator cages, and reverse osmosis water. Mice will be housed in an autoclaved cage set-up and provided with irradiated rodent diet and reverse Osmosis filtered water. The mice will be under the supervision of the Facility's veterinarian. Animals will be regularly screened for pathogens and have negative serum titers for sendai, PVM, HMV, GD-7, REO-3, LCFM, GDVII and mycoplasma pneumonia. The facility includes an area for

animal procedures such as injections and bleeding. All animal procedures with the exception of irradiation are conducted in a room adjacent to the animal suite. Irradiation is conducted on the same floor in a room in close proximity to the animal suite. The Animal Resources Facility animal management program is ACCREDITED by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) meeting or exceeding all the standards for animal care and use. There is peer review by the Dana-Farber Cancer Institute Animal Care and Use Committee (IACUC) for all experimental protocols. During the course of these studies, any animals displaying any behavior indicative of compromised health, disease or signs of discomfort (e.g. difficulty obtaining food or water, diarrhea, progressive dermatitis, hair coat abnormalities) before reaching an experimental endpoint will be euthanized and subjected to an autopsy.

Tumor-bearing animals will be observed daily for any sign of sickness. Behavior of mice will be monitored and inspected for evaluation of pain and distress. If any animal displays a hunched posture, bloated or cramped abdomen, or weight loss of greater than 15% of its body weight or remains motionless even when the cage has been moved will be considered to be in distress. Impaired breathing, sunken eyes, matted fur and anorexia will also be considered to be a sign of discomfort. Any mice with visible tumors will be monitored carefully on a daily basis for signs of discomfort and distress. We will adhere to our institutional policy and ensure that tumor burden does not exceed 2 cm in diameter. Tumors will not be allowed to become ulcerated or necrotic. Additionally, tumors will not be allowed to significantly interfere with the movements of the animal, especially its ability to obtain food and water, bear its own weight or regain normal posture if placed on its back. Any animal judged to be in distress will be euthanized before reaching an experimental endpoint. If required, we will provide mice with supportive (palliative) care when needed. For palliative care, warm saline will be injected subcutaneously once a day (1 ml/mouse) or twice a day (0.5 ml/mouse). The DFCI mouse protocols (# 08-036 and #11-044) describing the proposed studies have been reviewed and approved by our IACUC. We will strictly adhere to the IACUC policies and follow the guidelines for humane endpoints as approved in our protocol.

Procedures for ensuring the limited pain, discomfort and injury to the animals:

Limitation of animal discomfort: The maintenance and surveillance of the animals will involve a high standard of humane care at a level above recommendations set forth in the NIH publication "Guide for the Care and Use of Laboratory Animals" (DHHS Publication No. 86-23, Revised 1996). The principle investigators on this project are kept informed of recent issues regarding the use of animals in experimental research. No animal will be allowed to die on the proposed project but will be frequently observed by our staff or animal care staff and euthanized whenever considered to be in distress or pain. Invasive procedures will be carried out under anesthesia, as described below.

Methods of anesthesia: For procedures involving bioluminescence imaging, inhalation anesthesia will be induced by brief inhalation of isoflurane (2-5%). The depth of anesthesia will be monitored by spontaneous motion, respiratory rate, eye-blink, and response to stimulation. Properly anesthetized mice are unresponsive to stimuli but recover fully within a few minutes. Animals will be closely monitored until they recover from anesthesia. Mice will be closely followed on a daily basis and euthanasia will be performed on animals displaying irreversible signs of discomfort.

SELECT AGENT RESEARCH

The work in this proposal does not utilize any agents defined as select agents by HHS or the USDA.

RESOURCE SHARING PLAN

Organoid Line Sharing

The proposal will generate organoid cultures of patient tumors. Some will be short term and not necessarily used to generate organoid lines, but for those cultures that do grow in the long term, the cultures will be shared by request after publication in a de-identified fashion to protect patient privacy. Instructions for making requests of any published cultures will be included in all publications of the work and all requests will be filled as quickly as possible. Material transfers will be executed in accordance with the Partners and DFCI IRB approved protocols under which all patient material for organoid generation was obtained and should not be more restrictive than a simple letter agreement (SLA) or uniform biological materials transfer agreement (UBMTA).

Organoid Xenograft Sharing

The proposal will generate mouse xenograft models using select organoid cultures of patient tumors. The xenograft models will be shared by request after publication in a de-identified fashion to protect patient privacy. Instructions for making requests of any published models will be included in all publications of the work and all requests will be filled as quickly as possible. Material transfers will be executed in accordance with the Partners and DFCI IRB approved protocols under which all patient material for organoid and xenograft generation was obtained and should not be more restrictive than a simple letter agreement (SLA) or uniform biological materials transfer agreement (UBMTA).

Data and Genomic Data Sharing

All genomic and/or other data will be shared according to the Dana-Farber policies described below and in accordance with all NIH and CDMRP policies.

Data Sharing Policy for Publicly-Funded Research
This submission will comply with the following data sharing policy. The Dana-Farber Cancer Institute is in agreement with NIH policies on data sharing and is striving to expedite translation of research results into knowledge, products and procedures to improve human health.

In agreement with the NIH Data Sharing Policy and Implementation Guidance (March 5, 2003), the Principal Investigator (PI) will:
a) Share and make available to the public; results and accomplishments of publicly-funded research, and
b) Ensure that the privacy and confidentiality of patient data is protected

Investigators who want access to data must make a formal request to the PI, who will review and sign-off on the request before access to the data is provided. The PI will review and sign-off requests for publication of data in literature, databases, data repositories, and web-accessible locations.

Data sharing will involve timely publication of research final data in: scientific and clinical literature, supplementary data accompanying literature, public databases, data repositories (such as dbGaP for genomic or transcriptomic data), or direct data exchange with other parties. The final research data will be published no later than the acceptance for publication of the main findings from the final data. Final data will be preserved for a minimum of seven years from the date of publication or until it becomes obsolete.

Data sharing and protection will be in accordance with the listed guides below
- The Guide to Human Research Activities of Dana-Farber/Harvard Cancer Center (November 2014)
- Final NIH Statement on Sharing Research Data (February 26, 2003)
- Confidentiality, Data Security, and Cancer Research: Perspectives from the National Cancer Institute (March 23, 1999)

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

Organoid cultures: All organoid lines generated will undergo whole exome or whole genome sequencing along with a matched adjacent section of the parent tumor from which they were derived to validate the line as having come from the same patient and matching the mutational burden of the parent tumor from which it was derived. For these lines, multiple frozen aliquots are generated after acquisition and used for no more than 4 months after thawing.

Organoid xenograft models: Tumors from all organoid xenograft models generated will undergo whole exome or whole genome sequencing along with a matched adjacent section of the parent tumor from which the organoids used to generate the mouse were derived to validate the model as having come from the same patient and matching the mutational burden of the parent tumor from which it was derived.

Cell Lines: All cell lines which might be used for biologic experiments have been purchased from ATCC and have been genetically sequenced by the Broad Institute for validation.

Antibodies: Antibodies are used in the proposal for multiple purposes including Western blot and immunohistochemistry. For each application, we use siRNA-mediated knockdown to determine specificity in the desired application.

Drugs: Prexasertib is obtained from the company which makes this drug for clinical studies under specific MTAs with the participating institutions. Carboplatin and Paclitaxel are purchased from the Dana-Farber Cancer Institute Pharmacy. VE-822, AZD6738, BAY 1895344, Gemcitabine, and MK1775 are purchased from Selleck Chemicals.

The authentication of all key biological and chemical resources will be transparently reported in publications, which will be deposited into PubMed Central. No other key biological or chemical resources will be generated with NIH funds and all other reagents used will be standard laboratory reagents.

THE COMMONWEALTH OF MASSACHUSETTS

BOARD OF REGISTRATION IN MEDICINE

Established A.D. 1894

This is to certify that

Sarah J. Hill, M.D.

a graduate of Harvard Medical School in the year 2016 has been duly registered by this board as a qualified physician, as provided by the laws of the Commonwealth.

Wakefield, Massachusetts, January 10, 2019

Candace Lapidus Sloane, MD

Chair, Board of Registration in Medicine

Robert S. Rubin MD.

Secretary

Certificate No. 277749

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project O Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Sarah	J.	Hill		PD/PI	CAL. MONTHS.INST. BASE SALARY				144,225.00	40,383.00	184,608.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **184,608.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*

Total Number Other Personnel **Total Other Personnel**

Total Salary, Wages and Fringe Benefits (A+B) **184,608.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

OMB Number: 4040-0001
ExpirationDate: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period:** 2

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.	Sarah	J.	Hill		PD/PI	CAL. MONTHS.INST. BASE SALARY				144,225.00	40,383.00	184,608.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **184,608.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*

Total Number Other Personnel **Total Other Personnel**

Total Salary, Wages and Fringe Benefits (A+B) **184,608.00**

RESEARCH & RELATED Budget (A-B) (Funds Requested)

Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0765807460000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period:** 3

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Sarah	J.	Hill		PD/PI	CAL. MONTHS.INST. BASE SALARY				144,225.00	40,383.00	184,608.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person 184,608.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*

Total Number Other Personnel

Total Other Personnel

Total Salary, Wages and Fringe Benefits (A+B) 184,608.00

RESEARCH & RELATED Budget (A-B) (Funds Requested)

Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period:** 4

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.	Sarah	J.	Hill		PD/PI	CAL. MONTHS.INST. BASE SALARY				144,225.00	40,383.00	184,608.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **184,608.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*

Total Number Other Personnel **Total Other Personnel**

Total Salary, Wages and Fringe Benefits (A+B) **184,608.00**

RESEARCH & RELATED Budget (A-B) (Funds Requested)

Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0765807450000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Dana-Farber Cancer Institute

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period:** 5

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		Sarah	J.	Hill		PD/PI	CAL. MONTHS.INST. BASE SALARY				144,225.00	40,383.00	184,608.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person 184,608.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*

Total Number Other Personnel **Total Other Personnel**

Total Salary, Wages and Fringe Benefits (A+B) 184,608.00

RESEARCH & RELATED Budget (A-B) (Funds Requested)

Funding Opportunity Number: PA-19-117 . Received Date: 2019-07-11T13:42:55.000-04:00