AWARD NUMBER: **W81XWH-16-1-0468**

TITLE: **Targeting BRCAness in Gastric Cancer**

PRINCIPAL INVESTIGATOR: **Eric Collisson, MD**

CONTRACTING ORGANIZATION: **The Regents of the University of California, San Francisco**
San Francisco, CA 94143

REPORT DATE: **October 2018**

TYPE OF REPORT: **ANNUAL**

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2018	ANNUAL	09/15/2017-09/14/2018

4. TITLE AND SUBTITLE
Targeting BRCAness in Gastric Cancer

5a. CONTRACT NUMBER
W81XWH-16-1-0468

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
1855 FOLSOM ST STE 425
SAN FRANCISCO CA 94103-4249

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

In the past year, we have made substantial progress in the project's goals. We have set up a system (described below) to interrogate gastric cancer cells with ATR and PARP inhibitors. This screening platform is now up and running and we are prosecuting preliminary hits. Over the next year, we will validate hits generated here and further the interrogation of clinical samples.

15. SUBJECT TERMS
Gastric cancer, BRCAness, DNA repair, DNA damage, PARP inhibitor, MEK inhibitor

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	15	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. Introduction

Inactivating germline and somatic mutations affecting genes involved in DNA damage repair are features of upper gastrointestinal malignancies, but we do not know how common these lesions are. Genes encoding for proteins important for mismatch, base-excision, and homologous recombination (HR) repair are affected in subsets of these tumors. For example, mutations in the HR genes *BRCA1* and *BRCA2* have been found in some gastric cancers. Loss of BRCA1 protein expression has been found in 21% of gastric cancers and was associated with diffuse-type histology and poor survival. PARP1 (polyADP ribose polymerase 1) is an enzyme essential for base-excision repair, a complementary DNA repair pathway to the HR repair pathway inactivated by mutations in *BRCA1* and *BRCA2*. Inactivation of PARP1 enzymatic activity, and thereby base-excision repair, can produce a synthetic lethality in cells lacking HR function. Clinical activity of single agent PARP inhibitors has been observed in patients with germ-line *BRCA1/2* mutations as well as tumors displaying "BRCAness", which is characterized by genomic instability and susceptibility to PARP inhibitors in the absence of *BRCA1/2* mutations. Mutations conferring BRCAness have been identified in a number of genes involved in the DNA damage response, including *RAD51C, ATM, ATR, MDC1, MRE11A, PALB2, CHK1/2, RAD50,* and components of the Fanconi's anemia repair pathway but the disease-specific relevance of these mutations is not known. Oncogenic signal transduction pathways, such as PI3K as well as RAF-MEK-ERK pathways may be involved in the regulation of the DNA repair machinery.

The purpose of this research is to elucidate a) whether GI malignancies with mutations in genes conferring BRCAness will be sensitive to PARP inhibition, in particular in combination with inhibitors of oncogenic signal transduction pathways (MEK, PI3K, TGFb, WNT, Notch, Hedghog, JAK-STAT) or with chemotherapy; b) whether mutations conferring BRCAness provoke an immune response that could be enhanced pharmacologically; c) whether there is a DNA signature predictive of PARP inhibitor sensitivity or combinatorial therapies. Addressing these questions will set the stage for development of increasingly efficient treatment strategies for GI cancers involving PARP inhibitors.

2. Keywords.

Gastric cancer, BRCAness, DNA repair, DNA damage, PARP inhibitor, MEK inhibitor.

3. Accomplishments

What were the major goals of the project?

1. Obtain clinical samples from PARP inhibitor treated gastric cancers.
2. Apply genomic signatures of "BRCAness" to gastric cancer clinical samples.
3. Identify genes that drive resistance or sensitivity to PARP and ATR inhibition in gastric cancer cells.
4. Validation studies and analysis of archival tissue.

What was accomplished under these goals?

Goal 1. Obtain clinical samples from PARP inhibitor treated gastric cancers.

The clinical trial originally proposed is not being carried out due to financial priorities at the company originally proposed to sponsor these studies. To make up for this change in plans we have taken steps to a) open a different clinical trial using PARPi in gastric cancer here at UCSF and b) obtain samples from this trial from collaborators at Yale.

The UCSF IRB approved our ramicirumab olabarib protocol in April 2018. An Approval letter was sent to DoD PO under separate cover. We are waiting on Central IRB approval, but Dr. Dhawan's CTEP profile has not been

approved and she has started maternity leave. We are working around this by changing the PI to Dr. Munster as she already has an account set up. Once this change in PI has been made, the study should activate relatively quickly, we anticipate within the next two to three weeks.

A material transfer agreement with Yale University has been successfully negotiated in September 2018.

Goal 2. Apply genomic signatures of "BRCAness" to gastric cancer clinical samples.

Computational infrastructure has been built to successfully achieve the aims. In the last year, a group led by Michael Stratton from the United Kingdom published a new algorithm to assess the degree of homologous recombination deficiency (HRD) present in a given cancer genome (Davies, H et al., Nat. Med. 2017). This work demonstrated that both mutational signature profiles and genome structural alterations provided information relevant to assessing HRD in breast tumors. To determine the applicability of these observations to another type solid tumor where DNA damage repair genes are frequently mutated, we assessed the presence of genomic scars resulting from HRD in 101 metastatic prostate cancer tumor samples using whole genome and transcriptome analysis (Quigley D. *et al.*, Cell, 2018). We developed methods to computationally identify deletions with flanking microhomology, and applied methods for mutation signature detection. Our analysis showed that while both previously published mutational signatures associated with HRD and the presence of deletions bearing flanking homology were associated with biallelic inactivation of the HR gene *BRCA2*, elevated microhomology frequency was most consistently associated with HRD (**Figure 1**). To extend this analysis to gastric cancer, we have gained access to and are now downloading ~50 whole genome low pass sequences published by our collaborators (Cancer Genome Atlas Research, Nature, 2014; Camargo MC et al., The Cancer Genome Atlas, Gastric Cancer, 2016) For exploratory analysis, we have analyzed exome sequence data from 166 gastric tumors sequenced by the TCGA. We quantified the total number of mutations in each tumor (**Figure 2**) and applied mutation signature analysis to these gastric tumors, identifying signatures associated with known etiologies of DNA damage including tumors with strong signals associated with microsatellite instability and more modest signatures associated with HR defects (**Figure 3**). As a positive control for this analysis, we analyzed ovarian cancer with known BRCA mutation status as a gold standard. Our preliminary analysis indicated that gastric tumors do not appear to manifest a mutational signature consistent with HRD, at least in the cohort analyzed here. We are making efforts to obtain samples of patients with HR-deficient gastric cancer to assess them for presence of a genomic scar in the coming months.

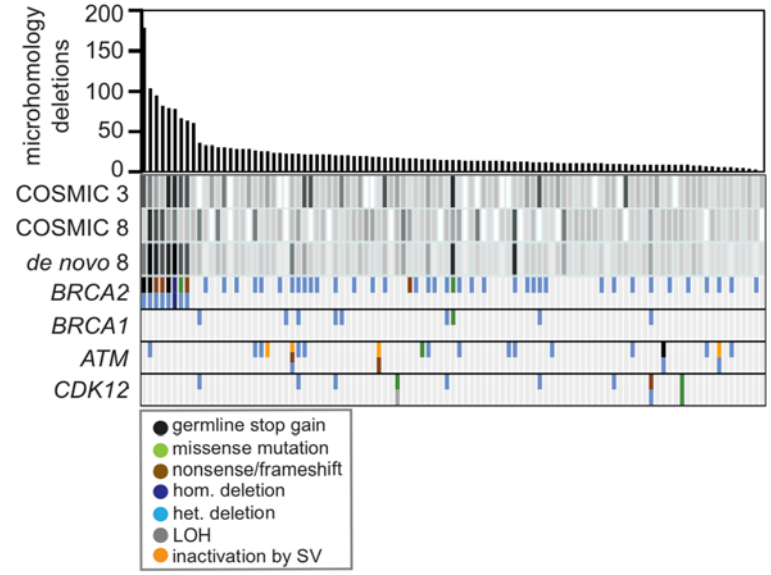

Figure 1: Genomic features associated with the presence of HRD, assessed in 101 metastatic prostate tumors. From top to bottom: the frequency of deletions bearing two or more nucleotides of microhomology (MH deletions); fit of mutation signatures COSMIC 3 and 8 and *de novo* 8; alterations associated with DNA repair by homologous recombination.

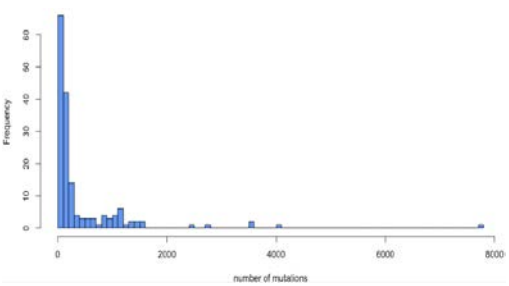

Figure 2: Somatic mutation frequency in TCGA gastric cancer. The median number of mutations is 139.5 in each tumor.

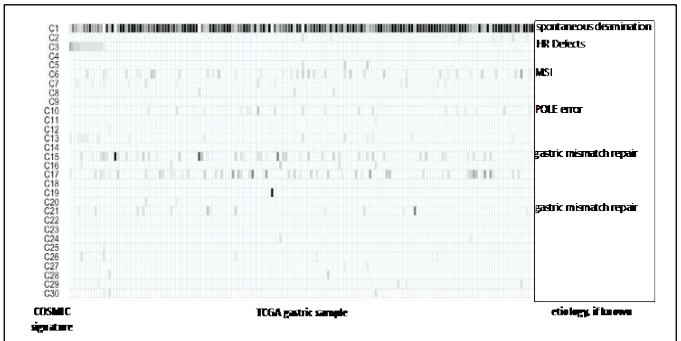

Figure 3: The detection of mutational signatures in TCGA gastric cancer.

Goal 3: Identify genes that drive resistance or sensitivity to PARP and ATR inhibition in gastric cancer cells.

In prior reports, we described the generation of gastric cancer cell lines suitable for large scale CRISPRi screening. We generated AGS, MKN7 and KATOIII cell lines stably expressing dCas9-KRAB, a fused protein used for CRISPRi transcriptional repression. We validated these cells by infection with a construct expressing a sgRNA targeting the cell surface protein, CD59, and showed successful depletion of CD59 by FACS. These validated cell lines were therefore considered suitable for large scale CRISPRi pooled sgRNA screening. We also described our drug sensitivity screening studies across various gastric cancer cell lines (AGS, KATOIII, MKN7 and NCI-N87) to determine the drug response to PARP inhibitors and the ATR inhibitor, AZD6738. AGS cell lines were sensitive to ATR inhibition, while MKN7 cells were resistant. Due to their sensitivity to ATRi, we selected AGS cells for our proposed CRISPRi screen to identify genes involved in resistance to ATR inhibition. **Figure 1A** shows the workflow for our experiment. The screen had two arms, treating the cells with a DMSO control or a highly toxic concentration (0.5uM) of the ATR inhibitor, AZD6738. The libraries we transduced contain 5 sgRNAs targeting each of 8000 genes; those selected are potential drug targets, kinases, phosphatases, apoptosis and cancer-related genes.

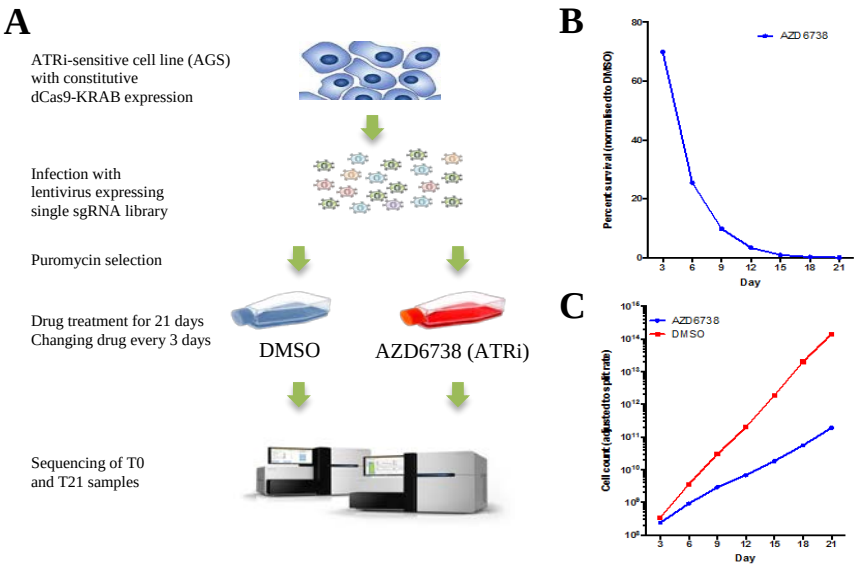

Figure 1: (A) CRISPRi screen workflow. (B) Dose response curve of AGS cells treated with AZD6738. (C) Cell counts for DMSO and AZD6738-treated arms

Our screen lasted three weeks and cells were passaged every three days. At each split, we confirmed BFP expression, counted cells and reseeded 45 million cells per arm in fresh drug or vehicle. BFP coverage in each arm remained above 90% throughout the experiment (data not shown). Extrapolating the growth rate using the cell counts (and seeding rate) and compared the DMSO to AZD6738 arms, we showed that after 21 days of treatment, 0.134% of the cells had survived in the AZD6738 arm (**Figure 1B).** To ensure adequate sgRNA

coverage, we maintained a minimum of $45x10^6$ cells in each arm and froze down aliquots of approximately 30 million cells from T0, $T21^{AZD}$ and $T21^{DMSO}$. After collecting DNA from these samples, we carried out PCR to enrich the sgRNA amplicon and add ligation adaptors, SPRI-purification for PCR product cleanup (**Figure 2A** and QC analysis using the Bioanlayzer **(Figure 2B)** where we see that final product is around an expected ~278bp. We then used the HiSeq4000 to sequence the sgRNAs to sufficient depth.

The QC analysis met the expected criteria. The median read counts across the 3 samples, known as T0, $T21^{DMSO}$ ('untreated') $T21^{AZD}$ (treated)), were 2506, 1946 and 1974 reads, respectively **(Figure 3A)**, far above the minimum 250 reads generally aimed for. The phenotypes of all sgRNAs targeting the gene are ranked by absolute value, and the top 3 are averaged to obtain a gene-level phenotype, and the Mann-Whitney p-value compares the phenotypes of all sgRNAs targeting the gene to all negative control sgRNAs. In **Figure 3B**, the negative controls are distributed around the 0 phenotype as expected, along with the majority of the sgRNAs. Throughout these results, 'gamma' refers to the growth phenotype (untreated/T0), while 'rho' refers to the resistance phenotype (treated/untreated). When plotting the reads count for 'gamma' (growth) scatter plot, we have the expected tail of hits leading towards the T0 axis. In the 'rho' (resistance) scatter plot, we see the majority of hits leading towards the treated axis **(Figure 3C**), as expected for a resistance screen.

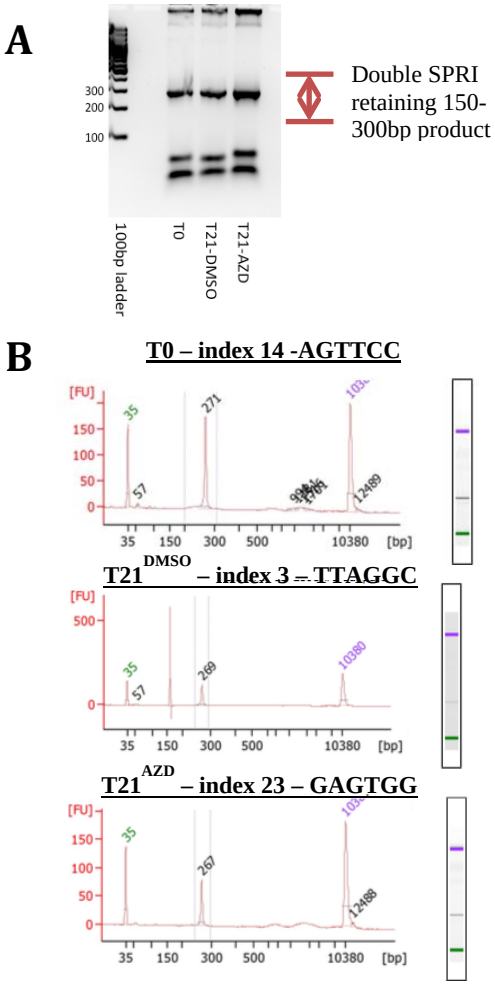

Figure 2: (A) Enrichment and SPRI purification of sgRNA amplicons for T0, $T21^{AZD}$ and $T21^{DMSO}$ samples. (B) Bioanalyzer analysis of SPRI-selected fragments for each sample.

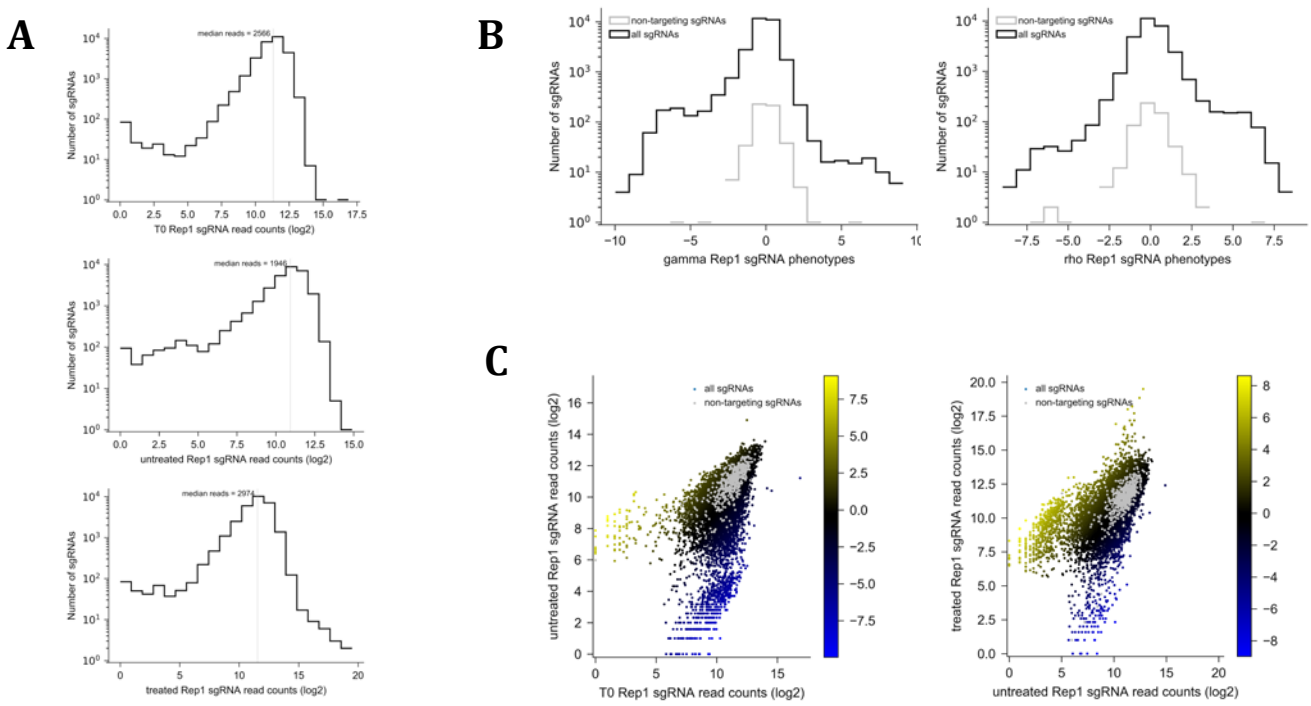

Figure 3: (A) QC plots showing high median read counts for T0, $T21^{AZD}$ and $T21^{DMSO}$ samples. (B) QC plots demonstrating that non-targeting controls have no phenotype. (C) Growth (left) and resistance (right) read counts

When we dissect the essential hits from the 'gamma' comparison, we see many of the expected genes on our list, such as TERT and ABCE1 **(Figure 4A)**. Perhaps unsurprisingly, ATR itself also come up as an essential hit in this ATR inhibitor-sensitive cell line.

We used the following criteria to select resistance hits:

- Focus primarily on the **resistance** hits, as we treated with a toxic concentration of inhibitor on a sensitive cell line
- **Impact** on drug response: select genes with average 'rho' phenotype values above or below 2.0/-2.0 and 'rho' p-values below 0.05
- **Essential** genes: avoid genes with a 'gamma' phenotypes below -2.0

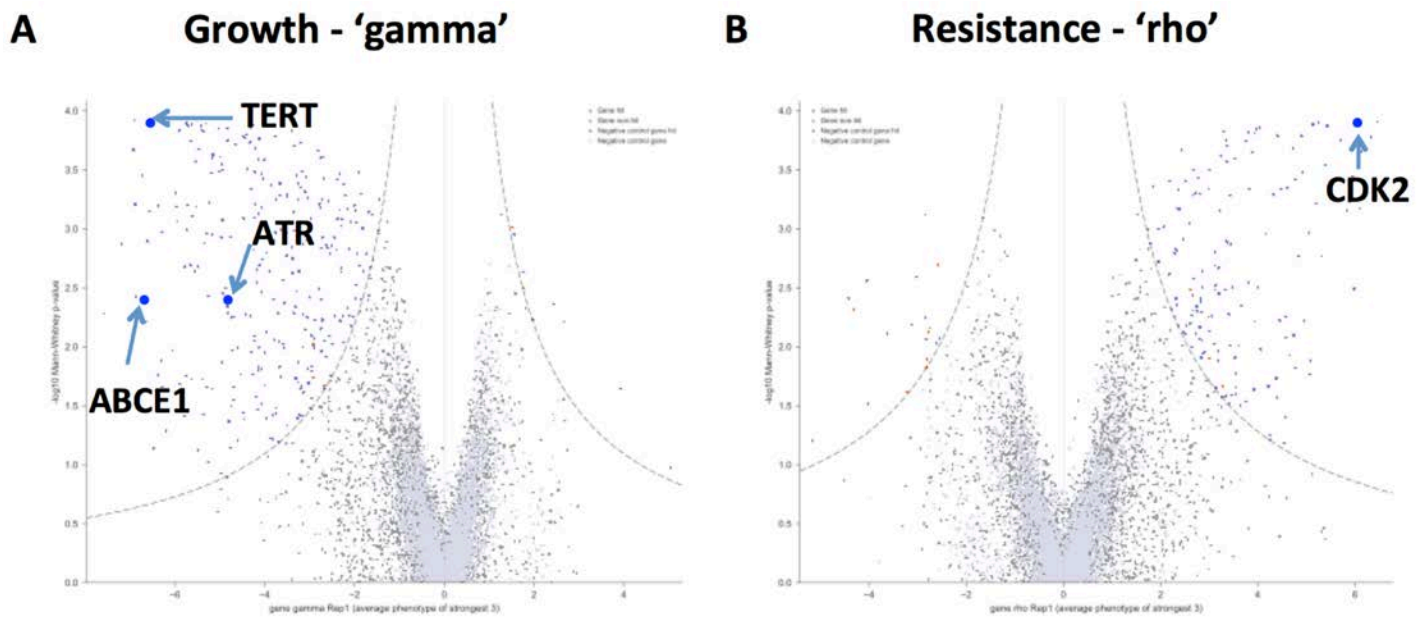

Figure 4: Volcano plots showing the effect of CRISPRi knockdown of genes on (A) growth and (B) ATRi sensitivity. Each spot is the average of the top 3 sgRNAs for each gene. Genes known to affect growth and sensitivity are highlighted on each graph.

Our criteria generated a list of 57 potential genes whose knockdown associated with ATRi resistance **(Figure 4B)**. CRISPRi-mediated knockdown of CDK2 was the strongest inducer of resistance to AZD6738, and promisingly, this hit was previously identified by our lab as an important mediator of ATRi resistance. CDK2 will be one of positive controls for induction of resistance to ATR inhibition. We have selected 7 additional candidate genes for validation, and have included these in the construction of a smaller targeted validation screen. Several additional control sgRNAs are also included in that group, and these are described in **Table 1**.

Table 1: Control sgRNAs included on our validation screen

Type	Gene	Purpose
Test	CDK2	sgRNA leads to resistance in screen previously published by our lab
Control	ATR	Target gene
Control	PLK1	Essential gene
Control	*ARID1A*	Synthetically lethal partner with ATR inhibtior
Control	*TP53*	ATR inhibition is synthetically lethal in *TP53* mutant CLL cells
Control	*SLFN11*	Schlafen-11 inhibits RNA synthesis. Involved in PARPi resistance
Control	*CDC25A*	CDC25A a major determinant of sensitivity to ATR inhibition

For our validation screen, we will use the complementary gene-editing tool, Cas9 RNPs, in a multi-well high throughput format **(Figure 5)**. Three unique crRNAs targeting each gene along with non-targeting controls will be complexed with a tracrRNA and Cas9 protein to form a RNP. Using the Lonza Amaxa 96-well shuttle electroporator, we will electroporate these RNPs into nuclear-tagged AGS cells, which are then seeded into multiple 384 well plates. We will extract genomic DNA from each of these samples too for later PCR, sequencing and knockout analysis. 24 hours later, these cells are treated with DMSO control or AZD6784 (concentrations = SF50, SF25, SF5). We will assess the growth of these cells twice daily for 7 days using the Incucyte Live-Cell Analysis System.

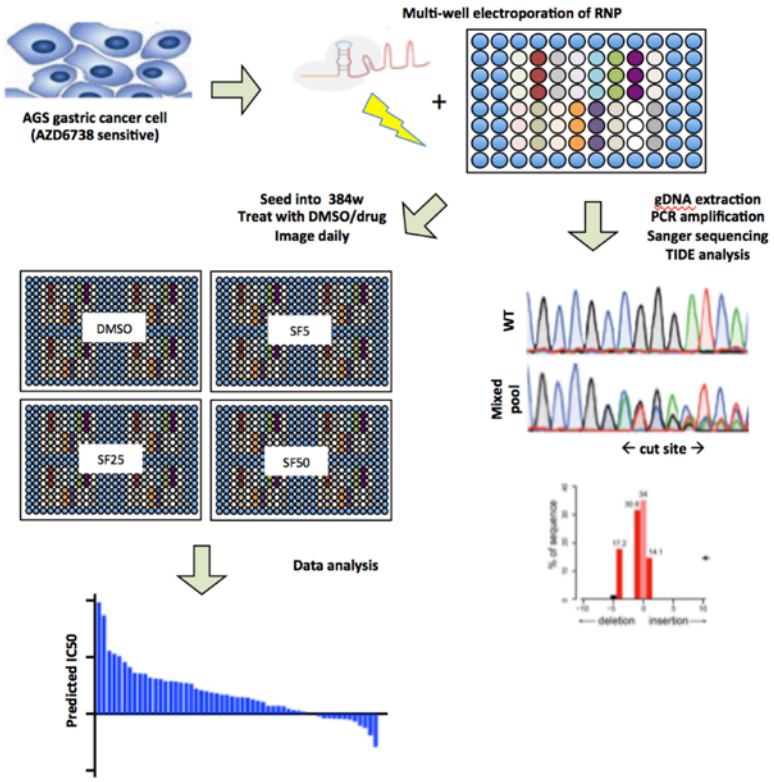

Figure 5: Workflow for RNP mini-screen to validate candidate ATRi resistance genes in AGS cells.

Goal 5. Validation studies and analysis of archival tissue (Janjigian et al Cancer Discovery 2018)

All tumors were prospectively reviewed to confirm histologic subtype, Lauren classification, and to estimate tumor content. We integrated genomic data with clinical characteristics, treatment history, response, and survival data. Overall survival (OS) time was measured from the date of diagnosis of Stage IV disease until the date of death or last follow-up. Progression-free survival (PFS) and OS on first-line platinum therapy and first-line chemotherapy with trastuzumab and immune checkpoint inhibitors in chemotherapy-refractory patients was calculated from the date of start of treatment to the date of radiographic disease progression, death or last evaluation.

The MSK-IMPACT assay was performed in a CLIA-certified laboratory, initially using a 341 and more recently 410 and 468 gene panels, as previously described, with results reported in the electronic medical record (1,2). The assay is capable of detecting mutations, small insertions and deletions, copy number alterations and select structural rearrangements.

To identify potential biomarkers of response to systemic chemotherapy in an unbiased manner, we correlated the genomic findings with treatment response and patient outcomes in the 187 patients with HER2-negative disease treated with first-line fluoropyrimidine/platinum. In this setting, the median PFS was similar to the published literature (6.9 vs 5.3 months), with favorable OS (26.3 months vs 10.17 months) (15). In this analysis, no single mutant allele or gene, including those with a role in DNA repair pathways, such as BRCA1/2, were significantly associated with treatment response (**Figure 6A**).

As an association between defects in homologous recombination deficiency (HRD) and response to platinum-based chemotherapy has been identified in other cancer types, we inferred a surrogate marker for HRD from the

copy-number data (large-scale state transitions, LST (3,4) and correlated the results with overall response and duration of treatment with chemotherapy. LST score was not predictive of progression free survival (HR=0.99, p=0.947, log-rank test) and was not higher in patients with responses to first line therapy lasting over 24 months (P=0.6, two-tailed t-test; **Figure 6B**). Notably, the majority of patients with prolonged response to platinum-based combination chemotherapy, including the two patients with the longest outlier responses (68 and 104 months, respectively), harbored no somatic alterations in known HR genes.

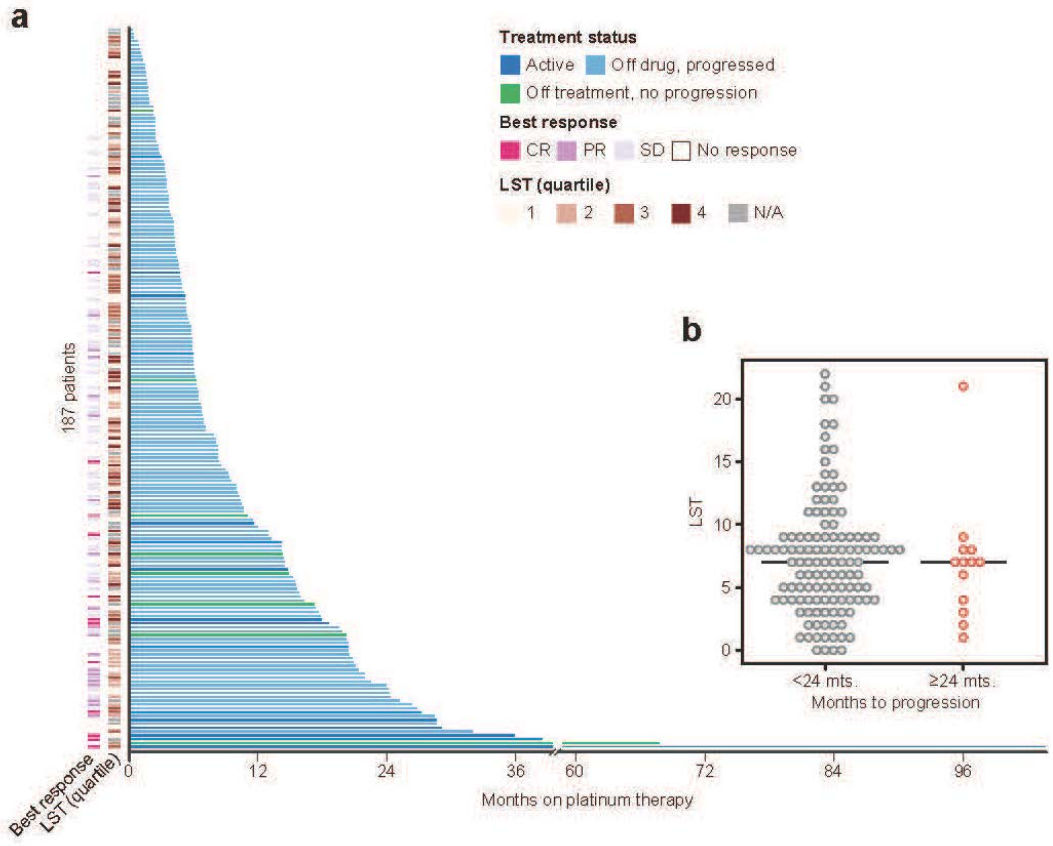

Figure 6. Genomic determinants of response to platinum cytotoxic chemotherapy. A, Swimmer's plot showing months on first-line platinum-based therapy for 185 patients with metastatic, HER2-negative esophageal cancer. The annotation tracks on the left of the y-axis indicate the patient's best response to platinum and the estimated LST score. The color of individual bars indicate the current status of the patient on this line of treatment. B, Distribution of LST scores in patients that progressed on platinum treatment before 24 months compared to patients with prolonged response (>24 months). Horizontal bars represent the median by group.

Major task 2 : Establish PDXs (Janjigian)—we implanted 35 PDXs over the course of two years (17 PDXs in year 1 and 18 PDXs in year 2) .

Major task 3
NGS analyses of the established PDX models (Janjigian)
The sequecing of matched samples from the parent tumors and the esablished PDXs demostrated that these models accurately reflect the genomic profiles of the patient samples.

4. Impact

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

Reflecting her academic and research achievements, in 2018, Dr. Janjigian was appointed Chief of MSK's Gastrointestinal Oncology Service. This service is one of the largest at MSKCC and Dr. Janjigian's selection as its leader after an international search is a testament to her remarkable accomplishments.

How were the results disseminated to communities of interest?
National meetings and manuscript published in Cancer Discovery 2018 Jan;8(1):49-58. doi: 10.1158/2159-8290.CD-17-0787. Epub 2017 Nov 9. PMID: 29122777

A second manuscript outlining the rapid autopsy data is in re-submitted for second review to Cancer Discovery

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

We will keep expanding the cohort of PDX to better reflect our diverse patient population.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. Changes/Problems

Changes in approach and reasons for change

None

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report

Changes that had a significant impact on expenditures

Nothing to report

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

Nothing to report

6. Products

• **Publications, conference papers, and presentations**

published in Cancer Discovery 2018 Jan;8(1):49-58. doi: 10.1158/2159-8290.CD-17-0787. Epub 2017 Nov 9.PMID: 29122777

A second manuscript outlining the rapid autopsy data is in re-submitted for second review to Cancer Discovery

Books or other non-periodical, one-time publications.
Nothing to report

Other publications, conference papers, and presentations

Nothing to report

• Website(s) or other Internet site(s)
Nothing to report

• Technologies or techniques

Improved efficacy of tumor implantation to immune deficient mice
1. Dissect human tumor to 100mm3 pieces
2. With blunt edge of scissors, scrape off soft/whitish necrotic tissue
3. Cut the fragment to 20-30mm3 pieces by removing non-viable tissue
4. Implant these 20-30mm3 pieces in bilateral flank of immune deficient mice as described anywhere

• Inventions, patent applications, and/or licenses
Nothing to report

• Other Products
Nothing to report

8. Special Reporting Requirements
Nothing to report

9. Appendices

Yale University **MTO.20445**

UBMTA Implementing Letter

The purpose of this letter is to provide a record of the biological material transfer, to memorialize the agreement between the PROVIDER SCIENTIST (identified below) and the RECIPIENT SCIENTIST (identified below) to abide by all terms and conditions of the Uniform Biological Material Transfer Agreement ("UBMTA") March 8, 1995, and to certify that the RECIPIENT (identified below) organization has accepted and signed an unmodified copy of the UBMTA. The RECIPIENT organization's Authorized Official also will sign this letter if the RECIPIENT SCIENTIST is not authorized to certify on behalf of the RECIPIENT organization. The RECIPIENT SCIENTIST (and the Authorized Official of RECIPIENT, if necessary) should sign both copies of this letter and return one signed copy to the PROVIDER. The PROVIDER SCIENTIST will forward the material to the RECIPIENT SCIENTIST upon receipt of the signed copy from the RECIPIENT organization.

1. PROVIDER Organization: **Yale University**
Address: 25 Science Park – 3rd Floor, 150 Munson Street, New Haven, CT 06511 U.S.A.

2. RECIPIENT Organization: **The Regents of the University of California on behalf of its San Francisco Campus**
Address: 3333 California St, S-11, San Francisco, CA 94143-1209 (94118 for courier services)

3. ORIGINAL MATERIAL: **Deidentified human formalin fixed paraffin embedded tumor tissue slides, (Up to 5 slides)**

NOTE: The ORIGINAL MATERIAL was collected under PROVIDER IRB Protocol Nr. HIC-2000021407 and is subject to the Additional Binding Terms per Addendum 1 which is incorporated into this Implementing Letter.

4. Termination date for this letter: N/A

5. Transmittal Fee to reimburse the PROVIDER for preparation and distribution costs. Amount: N/A

This Implementing Letter is effective when signed by all parties. The parties executing this Implementing Letter certify that their respective organizations have accepted and signed an unmodified copy of the UBMTA, and further agree to be bound by its terms, for the transfer specified above.

PROVIDER SCIENTIST
Name: **Michael Cecchini, M.D.**
Title: Assistant Professor of Medicine (Medical Oncology)
Signature: _____ Date: 8/31/18

PROVIDER ORGANIZATION AUTHORIZATION
Authorized Official: Donald B. Wiggin
Title: Contract (MTA) Manager, Office of Sponsored Projects
Signature: _____ Date: *05 September 2018*

RECIPIENT SCIENTIST
Name: **Eric Collisson, M.D.**
Title: Associate Professor of Medicine
Signature: DocuSigned by: Eric Collisson 85BB34D21EDF4FC... Date: 8/28/2018

RECIPIENT ORGANIZATION CERTIFICATION
Certification: I hereby certify that the RECIPIENT organization has accepted and signed an unmodified copy of the UBMTA:
Authorized Official: Mora Fisher Mattingly
Title: Assistant Director, Industry Contracts
Signature: Mora Fisher Mattingly Date: 28 August 2018

Addendum 1. – Additional Binding Terms

The ORIGINAL MATERIAL are samples obtained or derived from human subjects ("HUMAN MATERIAL"), and the following terms also apply:

a. NO PROTECTED HEALTH INFORMATION WILL BE PROVIDED WITH THE HUMAN MATERIAL.

b. The PROVIDER represents that the collection, use, and distribution of HUMAN MATERIAL, collected under approved PROVIDER IRB Protocols, as described in this UBMTA has been reviewed and approved as necessary and as required by law.

c. The RECIPIENT represents that it has all necessary licenses, authorizations, and approvals to receive and use the HUMAN MATERIAL as described in this UBMTA.

d. The RECIPIENT represents that it will not attempt to discover, nor in any way retain, the identity of the natural person(s) from whom the HUMAN MATERIAL was originally obtained.

e. The RECIPIENT shall handle the HUMAN MATERIAL in accordance with all applicable guidelines, law, and regulations, including national biosafety guidelines promulgated by the National Institutes of Health. PROVIDER makes no representations that the HUMAN MATERIAL is free of any specific biohazardous agents.

f. Subjects from whom HUMAN MATERIAL has been derived and provided to PROVIDER may decide to withdraw consent for use of the HUMAN MATERIAL. If PROVIDER is notified that consent to use any particular HUMAN MATERIAL has been withdrawn and that the applicable sample(s) should be destroyed, PROVIDER will then notify the RECIPIENT of the HUMAN MATERIAL for which consent has been withdrawn and request that the RECIPIENT shall destroy the HUMAN MATERIAL,and shall promptly provide PROVIDER with certification that the same has been destroyed.

g. These Additional Binding Terms shall survive termination or expiration of this Implementing Letter.

h. In the event of any conflict between the terms of the UBMTA and any Additional Binding Terms set forth herein, such Additional Binding Terms shall govern.