AWARD NUMBER: W81XWH-19-1-0703

TITLE: Novel Systems Biology Approach to Decoding Actionable Targets to Overcome Resistance in GI Cancer Monotherapies

PRINCIPAL INVESTIGATOR: Nidhi Sahni, Ph.D.

CONTRACTING ORGANIZATION: The University of Texas MD Anderson Cancer Center, Houston, TX

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

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October 2021	Annual	01Sep2020-31Aug2021

4. TITLE AND SUBTITLE

Novel Systems Biology Approach to Decoding Actionable Targets to Overcome Resistance in GI Cancer Monotherapies

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6. AUTHOR(S)

Nidhi Sahni, Ph.D.

E-Mail: nsahni@mdanderson.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 116
Houston, TX 77030-4009

8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Development Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Gastrointestinal (GI) cancer patient responses to treatment are extremely heterogeneous across patient populations, and resistance to current drug therapies often occurs after a short period. Thus, it is urgent to identify new drug combination targets for improving prognosis in a large number of GI cancer patients. GI cancer is more common in military members due to exposure to carcinogens in the field including certain chemicals and ionizing radiation. This type of exposure causes mutations in DNA which increases the rate of cancer development. We have previously shown that heterogeneous cancer mutations potentiate tumor-specific responses through distinct mechanisms and interactome network perturbations. While most of the current methodologies focus on predicting single targets to fight against tumors, few have therapeutic value in designing combination targets. During this reporting period, we have developed a network-based approach integrating functional variomics and synthetic lethality, and identified novel candidate actionable drug combinations for GI cancer. We hypothesize that combination modulation of GI tumors co-treated with MEK and PARP inhibitors will promote reduction of GI tumors compared to single agents alone. The proposed combination therapy, then, is likely to be most effective in military members with GI cancers as their tumors are likely to carry drug-resistant mutations.

15. SUBJECT TERMS

Network model, drug combination, cell lines, patient-derived organoid, xenograft model, KRAS mutation, GI cancer

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
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1. INTRODUCTION:

Although there are many existing tools to predict cancer-causing mutations, it remains challenging to effectively and systematically identify drug combination targets for better CRC therapeutics. The reasons are multi-fold: 1) Most tumors carry multiple driver alterations that trigger diverse oncogenic events that cannot be suppressed with mono-therapies; 2) diverse confounding factors such as intra-tumor and inter-tumor heterogeneity exist across patient populations; and 3) achieving analytical sensitivity often requires generating and analyzing a massive amount of data, which poses an unprecedented computational (big-data) challenge. Our objectives in this application are to devise a network-based framework to discover drug combinations to overcome resistance and conquer cancer progression. Here we propose an integrative approach to predict synergistic drug combinations and experimentally validate their functional effects on CRC using patient-derived tumor models. Together, this application is significant and innovative because it will provide insights in prioritizing drug combination target pairs, and uncovering patient-specific signaling mechanisms, a critical step towards personalized precision medicine in CRC therapy. This work will also experimentally validate several drug combinations in CRC, which stand to not only find their potential cures, but also save more patient lives.

2. KEYWORDS:

Network model, drug combination, cell lines, patient-derived organoid, xenograft model, *KRAS* mutation, GI cancer

3. ACCOMPLISHMENTS:

What were the major goals of the project?.

Specific Aim 1: Discover actionable drug targets to overcome resistance in GI cancer monotherapy via novel network-based approach.		
Major Task 1: Devise a network-based 'functional variomics' pipeline to identify synthetic lethality pairs for combination therapy in CRC	Months	% completion
Subtask 1: Using an integrative 'functional variomics' pipeline to identify driver variants in CRC that confer drug resistance (TCGA and COSMIC)	1-6	100
Subtask 2: Decipher specific signaling perturbations caused by drug-resistant mutations	7-9	100
Subtask 3: Drug combination design based on synthetic lethality and genetic interaction networks	10-12	100
Specific Aim 2: Functionally characterize the effects of actionable drug combinations in GI cancers *in vitro* and *in vivo*.		
Major Task 1: Assess the MEKi and PARPi/XPO1i combinations in CRC cell lines and patient-derived tumor organoid models	Months	% completion

Subtask 1: Submit documents for ACURO approvals	1	100
Subtask 2: Functional characterization of MEKi and PARPi/XPO1i combinations in CRC cell lines	4-24	100
Subtask 3: Functional characterization of MEKi and PARPi/XPO1i combinations in patient-derived tumor organoid (PDO) models	16-24	100
Major Task 2: Assess the MEKi and PARPi/XPO1i combinations in CRC patient-derived xenograft models	Months	% completion
Subtask 1: Submit documents for ACURO approvals	1	100
Subtask 2: Functional characterization of MEKi and PARPi/XPO1i combinations in patient-derived xenograft (PDX) models	14-36	90
Specific Aim 3: Determine molecular mechanisms of overcoming drug resistance mediated by somatic mutations.		
Major Task 1: Transcriptome-wide exploration of gene expression profiling in PDX models upon drug combination treatment using single cell RNA-seq	Months	% completion
Subtask 1: PDX sample preparation and single cell RNA-seq	18-30	100
Subtask 2: Data analysis and integration	20-36	50
Major Task 2: Protein expression profiling in PDX models upon drug combination treatment using Reverse Phase Protein Array (RPPA)	Months	% completion
Subtask 1: PDX sample preparation and RPPA experiment	18-30	100
Subtask 2: Data analysis and integration	20-36	50

What was accomplished under these goals?

Major activities, objectives and results:

We have successfully completed all the proposed work for Years 1 and 2. We are now ahead of schedule, and have performed a part of work proposed for Year 3.

For **Aim 1**, specifically, we have devised a network-based 'functional variomics' pipeline to identify synthetic lethality pairs for combination therapy in colorectal cancer (CRC). We used an integrative framework to discover driver variants in CRC that confer drug resistance, to decipher specific signaling perturbations caused by drug-resistant mutations, and to design drug combinations based on synthetic lethality and genetic interaction networks. To identify the mutations that might perturb signaling pathways, we hypothesized that gene-gene relationships would show perturbations in patients with specific driver mutations. We therefore developed e-MutPath as an open-source R package to identify candidate driver mutations that perturb functional pathways. Three types of omics datasets were integrated, including gene expression, somatic mutations and functional networks or pathways (**Fig. 1**). The output would provide prioritized mutations as well as the perturbed edges in signaling pathways or networks.

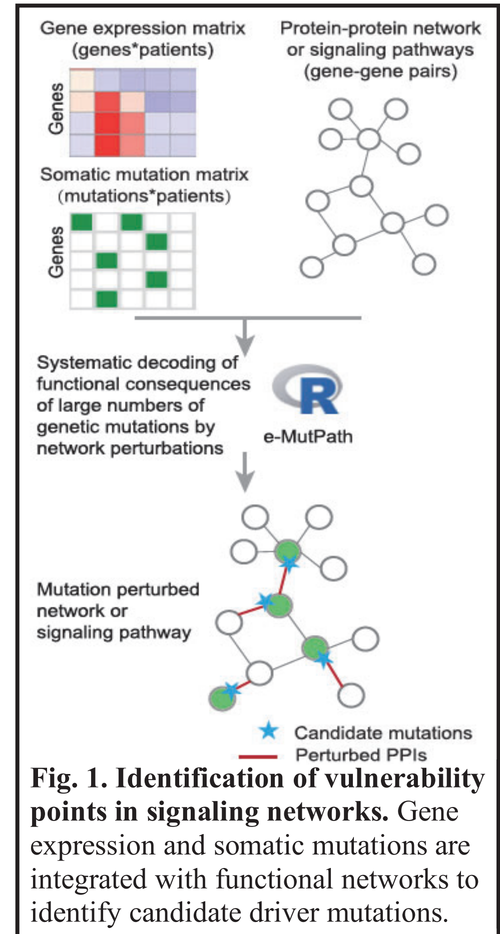

Fig. 1. Identification of vulnerability points in signaling networks. Gene expression and somatic mutations are integrated with functional networks to identify candidate driver mutations.

Specifically, three steps were performed in this computational method in the context of cancer. First, perturbed functional interactions were identified in each cancer patient based on a correlation perturbation analysis of RNA expression (**Fig. 1**, top panel). All the patients were mapped to a two-dimensional plane based on the expression levels of two interacting genes. If a patient showed a significant deviation from a normal gene-gene relationship distribution, the patient would be an outlier in the regression line modeled by all the patients. We used Grubb's test for detecting the outliers. Second, sample-specific interaction perturbation profiles were constructed; if gene expression data in normal samples were present, we also identified the perturbed functional subnetworks or pathways that could distinguish cancer from normal samples (**Fig. 1**, middle panel). Finally, candidate driver mutations in each cancer sample that mediated interaction perturbations were identified by integration of interaction perturbation patterns with mutational profiles (**Fig. 1**, bottom panel). We used Monte Carlo simulation to evaluate whether the patients with specific mutations were significantly overlapped with those showing gene-gene relationship perturbations (**Fig. 2**). The mutations with p-value less than 0.05 were identified as candidate driver edgetic mutations.

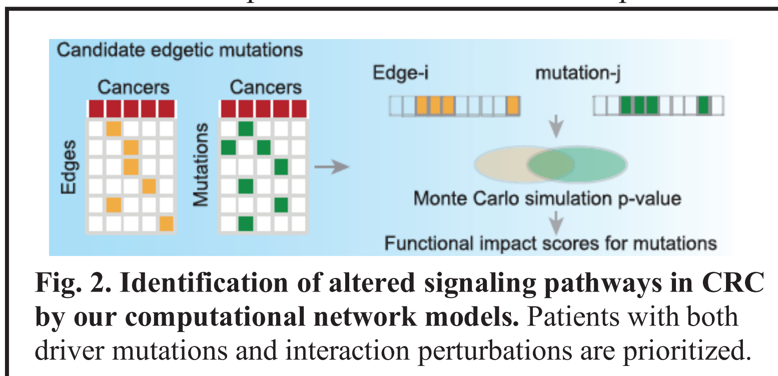

Fig. 2. Identification of altered signaling pathways in CRC by our computational network models. Patients with both driver mutations and interaction perturbations are prioritized.

Having shown e-MutPath could identify mutation-perturbed signaling pathways, we next evaluated its performance in uncovering cancer-related genes in CRC. We first considered the genes from Cancer Gene Census (CGC) and found that our top predictions included a high fraction of CGC genes. To illustrate the power of e-MutPath, we compared its performance with four widely used approaches-SIFT, Polyphen-2, MutationTaster and MutationAssessor. Our result showed that e-MutPath consistently

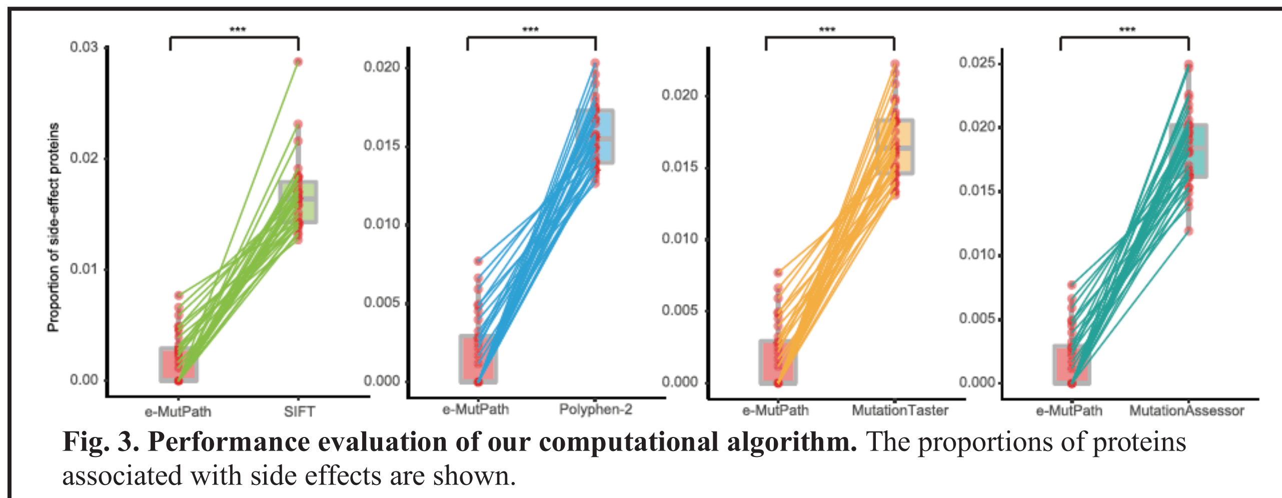

Fig. 3. Performance evaluation of our computational algorithm. The proportions of proteins associated with side effects are shown.

prioritized a larger fraction of cancer genes than other methods, demonstrating the advantage of network integration. We found that while e-MutPath predicted a smaller number of targets, they comprised larger fractions of 'gold standard' cancer genes in CRC. In addition, we obtained known cancer genes from CancerMine, which is a text-mined and routinely updated database of drivers, oncogenes and tumor suppressors. We found that the overall results were consistent for all genes, oncogenes, tumor suppressors and driver genes in CRC. Finally, to evaluate potential targetable and side effects of the predicted genes, we used a list of 151 clinically actionable genes and 237 proteins that are reported to be associated with side effects. We found that e-MutPath predictions exhibited similar fractions of actionable genes but were depleted of side effect-causing proteins across cancer types (**Fig. 3**). Taken together, these results demonstrate significant improvement of e-MutPath over previous state-of-the-art methods in identifying key cancer vulnerability targets. All the tasks for Aim 1 were completed, and resulted in a high-profile publication in 2021 in *Nucleic Acids Research* (PMID: 33211847).

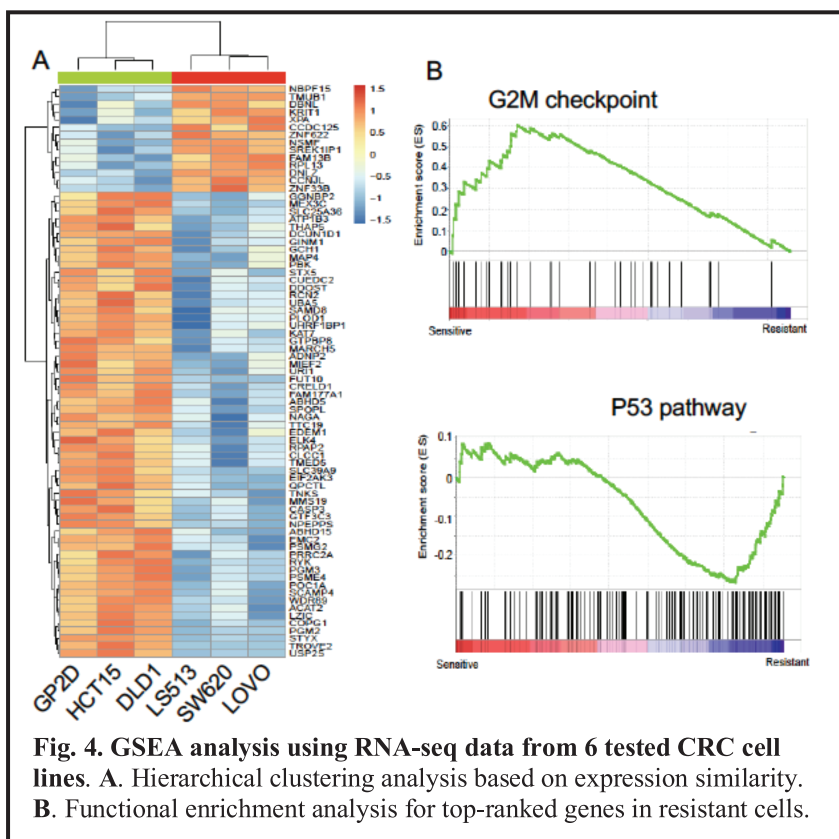

Fig. 4. GSEA analysis using RNA-seq data from 6 tested CRC cell lines. **A**. Hierarchical clustering analysis based on expression similarity. **B**. Functional enrichment analysis for top-ranked genes in resistant cells.

For **Aim 2**, we have assessed the MEKi-based combinations in CRC cell lines. We experimentally determined MEKi sensitive vs resistant CRC cell lines, and performed RNA-seq gene expression to identify signaling

pathways that are altered in different cell lines with distinct drug responses. Our data in 6 CRC cell lines identified 3 lines that are resistant to MEKi (GP2D, DLD1, HCT15), and 3 lines that are sensitive (SW620, CT26, LS513). We also determined their IC50 values. Initial RNA-seq was performed on these cell lines and GSEA analysis indicates that in drug resistant cells, G2M checkpoint (cell cycle) proteins are upregulated, while P53 pathway is downregulated (**Fig. 4**).

As a cross validation, we designed an independent computational method that leverages CRC patient survival (**Fig. 5**). Starting from patient gene expression data, we will identify candidate gene pairs based on (1) elevated expression of both genes in cancer cells, (2) actionability (drug availability); and (3) improved survival in patients with low expression in both genes. For synthetic lethal gene pairs, **we expected** that low expression in both genes offers disadvantage for cancer cell growth, and thus significantly improved survival in corresponding patients, as shown in the Kaplan-Meier plots. **Our results** indicated that CRC patients with reduced expression levels of MEK-gene pairs fare better than their high expression counterparts. We could successfully validate ~20 pairs of e-MutPath generated results so far. MEKi and PARPi/XPO1i combinations are among the top predicted and validated candidates.

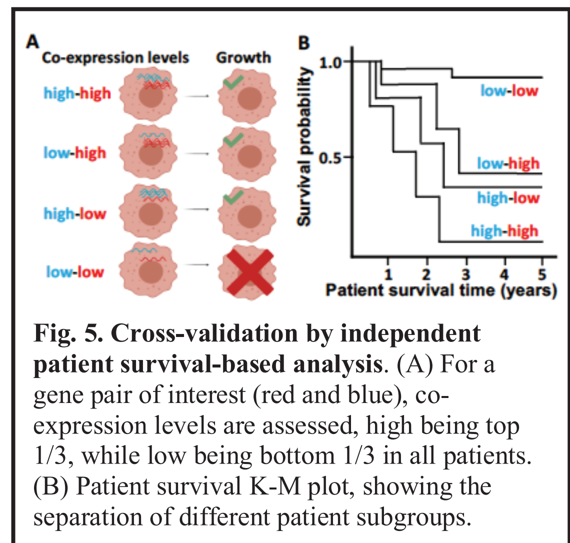

Fig. 5. Cross-validation by independent patient survival-based analysis. (A) For a gene pair of interest (red and blue), co-expression levels are assessed, high being top 1/3, while low being bottom 1/3 in all patients. (B) Patient survival K-M plot, showing the separation of different patient subgroups.

To assess the ability of MEKi and PARPi/XPO1i combination to inhibit cell growth *in vitro*, we tested a panel of 5 colorectal cancer cell lines (LS123, HCT15, DLD1, GP5D and T84) that were previously exposed to increasing concentrations of MEK inhibitors for 72h and exhibited intrinsically resistant (data not shown). These cell lines were tested in as monolayer growth conditions. Cell Titer Glo 2.0 cell viability assays were used to evaluate potential synergy between MEKi alone and in combination with the PARPi (Olaparib) /XPO1i (Eltanexor). Combination Indices were calculated using Calcusyn. We analyzed MAPK and other pathways using Western blot and qRT-PCR analysis. Our data using one resistant line (GP2D) (**Fig. 6**) and one sensitive line (SW620; data not shown) showed much improved synergistic (combination index CI<<1) effect over any single agent. These drug effects were further validated by PARP1-specific and MAP2K1-specific siRNAs (**Fig. 7**).

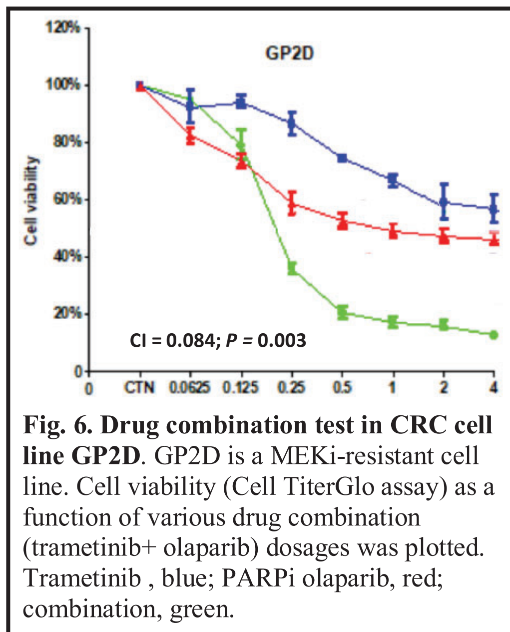

Fig. 6. Drug combination test in CRC cell line GP2D. GP2D is a MEKi-resistant cell line. Cell viability (Cell TiterGlo assay) as a function of various drug combination (trametinib+ olaparib) dosages was plotted. Trametinib , blue; PARPi olaparib, red; combination, green.

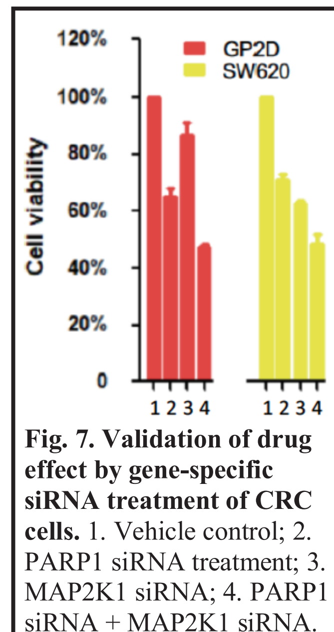

Fig. 7. Validation of drug effect by gene-specific siRNA treatment of CRC cells. 1. Vehicle control; 2. PARP1 siRNA treatment; 3. MAP2K1 siRNA; 4. PARP1 siRNA + MAP2K1 siRNA.

To assess organoid growth, organoids were mechanically disassociated into fragments and plated in 4ul of BME in 96-well plates. After three to four days of growth, organoids were treated with one of 6 groups: 1) control (vehicle); 2) MEKi (trametinib); 3) PARPi (olaparib); 4) MEKi+PARPi combination; 5) XPO1i (eltanexor); 6) MEKi+XPO1i combination. Cell viability was assayed using CellTitre-Glo (Promega). Treatment groups were statistically compared using a one-way ANOVA. Those reaching

statistical significance were compared using the ad-hoc Student's T-test. PDO size and number were measured using high throughput microscopy (using our Nikon HCA system). In both cases, the drug combination therapy appeared to be synergistic and showed great promise over monotherapies. For patient-derived tumor xenograft models, we have completed the test of MEKi-PARPi combination in a few PDX models, which all showed synergy compared to respective control samples. We are in the process of testing more drug combinations resulting from our computational framework, and expect to obtain more promising results soon.

For **Aim 3**, to further dissect molecular mechanisms underlying the effective drug combinations, we have already performed one round of scRNA-seq and RPPA experiments, which is ahead of schedule (originally proposed for Year 3). We are now conducting data analysis and integration. Poly(ADP-ribose) polymerase 1 (PARP-1) and p53 are two key proteins in the DNA-damage response. PARP-1-mediated poly(ADP-ribosyl)ation blocks the interaction between p53 and the nuclear export receptor Crm1, resulting in nuclear accumulation of p53 and preventing genome mutation. Our analysis using western blot (**Fig. 8**) showed that XPO1 inhibition led to an increase in p53 and PARP levels. The survivin protein functions to inhibit caspase activation, thereby leading to negative regulation of apoptosis or programmed cell death, hence is depleted upon XPO1i-MEKi dual blockade (**Fig. 8**). It is also regulated by p53 and the cell cycle. XPO1 inhibitor induces p-ERK and p-AKT (**Fig. 8**), leading to the accumulation of phosphorylated forms of MAPK proteins in the nucleus and cellular growth inhibition. Thus, inhibition of XPO1 induces cytostatic and pro-apoptotic effects in both MEKi-sensitive and MEKi-resistant cell lines at nanomolar concentrations.

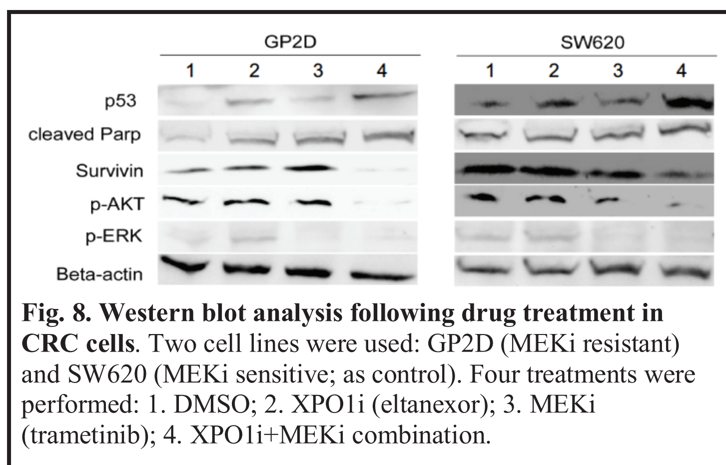

Fig. 8. Western blot analysis following drug treatment in CRC cells. Two cell lines were used: GP2D (MEKi resistant) and SW620 (MEKi sensitive; as control). Four treatments were performed: 1. DMSO; 2. XPO1i (eltanexor); 3. MEKi (trametinib); 4. XPO1i+MEKi combination.

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

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

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

We are indeed ahead of schedule, and have finished some part of work originally planned for Year 3 (such as PDX work). We will carry out the remaining experiments as planned in the SOW, specifically for Specific Aim 3. We intend to determine mode of action for some of our novel predicted MEKi-based drug combinations.

4. IMPACT:
What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

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:

Nothing to Report

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

Some delays occurred during the COVID pandemic. Our research activities were not at full capacity. We are in the process of catching up to carry out the remaining work, which may introduce a delay time during the next reporting period.

Changes that had a significant impact on expenditures

No significant changes.

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

Significant changes in use or care of human subjects
No significant changes.

Significant changes in use or care of vertebrate animals
No significant changes.

Significant changes in use of biohazards and/or select agents
No significant changes.

6. PRODUCTS:

• Publications, conference papers, and presentations

Journal publications.

Li Y, Burgman B, Khatri IS, Pentaparthi SR, Su Z, McGrail DJ, Li Y, Wu E, Eckhardt SG, **Sahni N**[#] and Yi S. e-MutPath: Computational modelling reveals the functional landscape of genetic mutations rewiring interactome networks. ***Nucleic Acids Res.*** 49(1):e2, 1/2021. PMCID: PMC7797045 ([#]**co-corresponding** author).

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

Nothing to report (research in progress).

• Inventions, patent applications, and/or licenses

Nothing to report (research in progress).

• Other Products

Nothing to report (research in progress).

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Nidhi Sahni – 23% in year 2
Scott Kopetz – No Change
Sharad Awasthi – No Change
Alexey Sorokin – No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Grants awarded during the reporting period:

Title: Linking genome variation to transcriptional network dynamics in human B cells

Major Goals: The goal of this proposal is to create a framework for analyzing the causal connections between human genome variation and the regulation of dynamic transcriptional networks in diverse human B cell contexts.

*Status of Support: Active

Project Number: U01HG012041

Name of PD/PI: **Co-PI:** Singh, Harinder; **Sahni, Nidhi**; Das, Jishnu

*Source of Support: National Institutes of Health /NHGRI

*Primary Place of Performance: University of Pittsburg, Pennsylvania

Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/19/21 – 05/31/26

* Total Award Amount (including Indirect Costs): $4,750,000

* Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2021	01.20 calendar
2. 2022	01.20 calendar
3. 2023	01.20 calendar
4. 2024	01.20 calendar
5. 2025	01.20 calendar

Title: INTERCEPT - Colorectal Cancer Research – FP13735

Major Goals: The goal is to find immunotherapy treatments that will be effective as soon as MRD is detected, when the volume of cancer cells is very low and these cells have not had time to build defense mechanisms against patient immune systems.

*Status of Support: Active

Project Number: FP13735

Name of PD/PI: **Kopetz, Scott**

*Source of Support: E.L. and Thelma Gaylord Foundation

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/16/21 – 04/15/26

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2021	00.12 calendar
2. 2022	00.12 calendar
3. 2023	00.12 calendar
4. 2024	00.12 calendar
5. 2025	00.12 calendar

Title: A Randomized Phase 3 Study of MRTX849 in Combination with Cetuximab Versus Chemotherapy in Patients with Advanced Colorectal Cancer with KRAS G12C Mutation with Disease Progression On or After Standard First-Line Therapy (MRTX 849-010)

Major Goals: The goal is to compare the efficacy of MRTX849 administered in combination with cetuximab versus chemotherapy in the second-line treatment setting in patients with CRC with KRAS G12C mutation.

*Status of Support: Active

Project Number: 2020-1348 / PID12524

Name of PD/PI: **Kopetz, Scott**

*Source of Support: Mirati Therapeutics, Inc

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/16/21 – 04/15/28

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2021	00.12 calendar
2. 2022	00.12 calendar
3. 2023	00.12 calendar
4. 2024	00.12 calendar
5. 2025	00.12 calendar
6. 2026	00.12 calendar
7. 2027	00.12 calendar

Title: Tumor Tissue and Apheresis Procurement for Laboratory Research Use. STRATEGIC ALLIANCE: 2019 Research and Development Agreement (TCR-T Program)

Major Goals: The goal is to investigate the frequency and quality of neoantigen-reactive T cells in MD Anderson patients with solid tumors.

*Status of Support: Active

Project Number: 2020-0940 | PID 12481

Name of PD/PI: **Kopetz, Scott**

*Source of Support: Ziopharm Oncology, Inc

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/19/21 – 12/31/26

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2021	00.12 calendar
2. 2022	00.12 calendar
3. 2023	00.12 calendar

4. 2024	00.12 calendar
5. 2025	00.12 calendar

Grants ended during the reporting period:

Title:** ***Novel role of spliceosome in homologous recombination deficiencies in triple negative breast cancer

Major Goals: The major goal is to characterize the functional role of spliceosome genes in homologous recombination and explore rationale combination therapies for breast cancer.

*Status of Support: Completed

Project Number: Young Investigator Grant

Name of PD/PI: **Sahni, Nidhi**

*Source of Support: Breast Cancer Alliance

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/01/19 – 07/31/21

Title:** ***Role of altered enhancer-mediated signaling in liver carcinogenesis

Major Goals: The major goal of this proposal is to study the enhancer-induced alterations in signal transduction in liver cancer.

*Status of Support: Active

Project Number: Pinnacle Research Award

Name of PD/PI: **Sahni, Nidhi**

*Source of Support: American Association for the Study of Liver Diseases

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/01/17 – 08/31/21

***Title:** Evaluating drug combinations, efficacy and adaptive feedback in KRAS inhibition

Major Goals: The major goal is to evaluate novel KRAS inhibitors of KRAS and other mutations to improve CRC outcomes.

*Status of Support: Completed

Project Number: 3U54CA224065-03S1

Name of PD/PI: **Kopetz, Scott**

*Source of Support: NIH/NCI

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/01/20 – 8/31/21

***Title:** University of Texas PDX Development and Trial Center: Project 2 Building Combinatorial Therapies against KRAS-mutant Colorectal and Pancreatic Cancer.

Major Goals: The major goal is to determine the effectiveness of the MEK inhibitor-based combinations through in vivo PDX trials.

*Status of Support: Completed

Project Number: 5U54CA224065-03

Name of PD/PI: **Kopetz, Scott**

*Source of Support: NIH/NCI

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/30/17 – 8/31/21

***Title:** BE GONE Trial: Beans to Enrich the Gut of Obese Colorectal Cancer Survivors

Major Goals: The major goal is to inform recommendations for colorectal cancer survivors, an innovative clinical trial is focusing on a diet modification -the addition of navy beans-and its effect on the gut microbiome.

*Status of Support: Completed

Project Number: RSG-17-049-01-NEC

Name of PD/PI: **Kopetz, Scott**

*Source of Support: ACS

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/30/17 – 06/30/21

***Title:** Tumor Heterogeneity and Acquired Resistance to EGFR Inhibition

Major Goals: The major goal is to understand the mechanisms of resistance of CRC will require a more detailed understanding of the heterogeneity and temporal dynamics of genomic changes, thereby leading to improved biomarkers for benefit and novel strategies to re-challenge tumors with previously effective therapy.

*Status of Support: Completed

Project Number: R01CA184843

Name of PD/PI: **Kopetz, Scott**

*Source of Support: NIH/NCI

*Primary Place of Performance: The University of Texas MD Anderson Cancer Center

Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/13/15 – 01/31/21

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

N/A

QUAD CHARTS:

N/A

9. APPENDICES:

N/A