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TITLE: Gut Microbiome as a Predictor of Response to Chemotherapy in Metastatic Colorectal Cancer

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CONTRACTING ORGANIZATION: UNIVERSITY OF MIAMI,
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13. SUPPLEMENTARY NOTES

14. ABSTRACT: Despite decades of research, a combination of cytotoxic chemotherapies continues to be the first line treatment for metastatic colon and rectal cancer (CRC). Patients typically respond variably to chemotherapy with ~20-30% experiencing only disease stability and up to 30% progressing despite chemotherapy. Currently there are no known and validated predictors of response to cytotoxic chemotherapy. Furthermore, whether there are any patient related factors, which predict response to chemotherapy, is not known. Recent years have seen an increase in our understanding of the role of gut microbiome in health as well as in the pathogenesis of various diseases. Recent research from our group and others have shown that gut microbiota supports growth of colon, pancreatic and many other cancers. Our preliminary studies also suggest that not all the bacterial communities in gut microbiome promote tumor growth as selective gut microbiome modulation by individual antibiotics like vancomycin or metronidazole has similar effects Interestingly, our preliminary data in animal models suggest that gut microbiome can modulate response of cancer to various therapeutic strategies including chemotherapy and immunotherapy. This interaction of gut microbiome and chemotherapy in the treatment of colon cancer has been observed by other groups as well. For instance, it has been observed that in the absence of gut microbiome the efficacy of Oxaliplatin is reduced and this may be due partially to an impaired ROS production by myeloid cells. Based on literature as well as our preliminary studies we have proposed a novel hypothesis: Gut microbiome composition can predict response of patients with metastatic colorectal cancer to standard of care chemotherapy. Selective gut microbiome modulation could emerge as novel therapeutic strategy to improve response to standard of care chemotherapy immunotherapy. This hypothesis will be tested through an observational clinical study with an interventional animal study component.

15. SUBJECT TERMS
NONE LISTED

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1. INTRODUCTION:

Despite decades of research, a combination of cytotoxic chemotherapies continues to be the first line treatment for metastatic colon and rectal cancer (CRC). Patients typically respond variably to chemotherapy with ~20-30% experiencing only disease stability and up to 30% progressing despite chemotherapy. Currently there are no known and validated predictors of response to cytotoxic chemotherapy. Furthermore, whether there are any patient related factors, which predict response to chemotherapy, is not known.

Recent years have seen an increase in our understanding of the role of gut microbiome in health as well as in the pathogenesis of various diseases. Recent research from our group and others have shown that gut microbiota supports growth of colon, pancreatic and many other cancers. Our preliminary studies also suggest that not all the bacterial communities in gut microbiome promote tumor growth as selective gut microbiome modulation by individual antibiotics like vancomycin or metronidazole has similar effects Interestingly, our preliminary data in animal models suggest that gut microbiome can modulate response of cancer to various therapeutic strategies including chemotherapy and immunotherapy. This interaction of gut microbiome and chemotherapy in the treatment of colon cancer has been observed by other groups as well. For instance, it has been observed that in the absence of gut microbiome the efficacy of Oxaliplatin is reduced and this may be due partially to an impaired ROS production by myeloid cells. Based on literature as well as our preliminary studies we have proposed a novel hypothesis: *Gut microbiome composition can predict response of patients with metastatic colorectal cancer to standard of care chemotherapy. Selective gut microbiome modulation could emerge as novel therapeutic strategy to improve response to standard of care chemotherapy and/or immunotherapy.* This hypothesis will be tested through an observational clinical study with an interventional animal study component.

2. KEYWORDS:

Colorectal Cancer, Metastasis, Pancreatic Cancer, Gut, Microbiome, Chemotherapy, Antibiotics, Immunotherapy.

3. ACCOMPLISHMENTS:

- **Major goals of the project:**

  Specific aim 1- Does Gut Microbiome composition predicts response to chemotherapy?

  Major Task: Recruitment of 1st 30 Subjects, baseline imaging, gut microbiome collection, initiation of chemotherapy in 1st 30 subjects, completion of 4 months of chemotherapy on recruited subjects, collection of post chemotherapy samples of gut microbiome. Contributor: Vikas Dudeja (PI) & Nipun Merchant (Co-PI).

  Specific aim 2- Does modulation of gut microbiome modify response to chemotherapy?

  Major task: Generation of human gut microbiome avatar mice by transplanting stool from 10 responders, 10 patients with stable disease and 10 patients with progressive disease into germ free mice. Implantation of colon cancer cell lines subcutaneously in human gut microbiome avatar mice. Contributor: Vikas Dudeja (PI) & Ashok Saluja (Co-PI).

- **Accomplishment under these goals:**

  For Aim 1, we have acquired IRB approval at University of Miami. However, based on recommendations by the HRPO, we are awaiting conversion of our IRB to a single site IRB to be initiated by UAB. We have submitted our documents to UAB for final approval. Personnel for recruitment of specimens is right now in place.

For Aim 2, we have obtained IACUC approval as well as ACUR approval. We are waiting on IRB and HRPO approval so that we can collect gut microbiome specimens, which will be used for generation of Human Gut Microbiome AVATAR mice.

- **Opportunities for training and professional development:** Nothing to report

- **Dissemination of results to community of interest:** Nothing to report

- **Plan to do during next reporting period to accomplish the goals:**
  As soon as we receive this single site IRB approval, we will recruit patients with metastatic colorectal cancer and collect stool for gut microbiome analysis. Subsequently, these patients will receive will recruit patients with metastatic colorectal cancer and collected stool for gut microbiome. Subsequently, these patients received chemotherapy FOLFOX and Avastin for 4 months. After 4 months, treatment response was evaluated by cross sectional imaging and stool will again be collected for gut microbiome analysis and used for the second aim of the grant (PI: Dudeja and Saluja).

4. IMPACT:

- **Impact on the development of the principal discipline(s) of the project:** Nothing to report

- **Impact on other disciplines:** Nothing to report

- **Impact on technology transfer:** Nothing to report

- **Impact on society beyond science and technology:** Nothing to report

5. CHANGES/PROBLEMS: Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations:**
  Journal Publications: Nothing to report
  Book or other non-periodical, one-time publications: Nothing to report
  Other publications, conference papers, and presentations: Nothing to report

- **Website(s) or other internet sites(s):** Nothing to report

- **Technologies and techniques:** Nothing to report

- **Inventions, patent applications, and/or licenses:** Nothing to report

- **Other products:** Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

- **Individuals worked on the project:**

Name:	Nipun Merchant, MD
Project Role:	Co-PI

Researcher Identifier:	
Nearest person month worked:	6
Contribution to Project:	Aim 1: Does Gut Microbiome Composition Predict Response to Chemotherapy?
Funding Support:	Not applicable

- **Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period:** Nothing to report

- **Other organizations involved as partners:** Nothing to report

8. SPECIAL REPORTING REQUIREMENTS:

Collaborative Awards: Nothing to report

Quad Charts: Nothing to report

9. APPENDICES: Nothing to report