ASM

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The interaction between the human gut microbiome and pancreatic ductal adenocarcinoma (PDAC): Microbial influence on patient response to anti-cancer treatment.

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Background

Emerging research suggests that the human gut microbiome may contribute to the development and progression of pancreatic cancer, and influence patient response to anti-cancer therapy.

An altered microbiome composition, or dysbiosis, can lead to inflammation of the gut, which increases intestinal permeability and affects immune function both locally and systemically. Pro-inflammatory bacteria can then potentially migrate from the intestinal tract through the compromised intestinal barrier and enter the bloodstream, where, once in circulation, can travel to distant organs. This infiltration of bacteria can promote genomic damage, facilitate the malignant transformation of tumour cells and cellular proliferation, and potentially drive tumour progression.

Due to the proximity and anatomical continuity of the pancreas and the intestinal tract, research has suggested the existence of a gut microbiota-pancreas axis, in which bacteria can migrate between the pancreas and the gut. This would potentially allow bacteria to make molecular alterations to the tumour's microenvironment, metabolism, and sensitivity to drugs.

Aim and Objectives

Aim:
This study seeks to prospectively explore the relationship between the gut microbiome and patient response to anti-cancer therapy.

Objectives:
1. Analyse the relative abundance of the four main bacterial phyla present in stool samples, focusing on *Firmicutes* and *Proteobacteria*).
2. Determine the changes in bacterial composition over the course of anti-cancer treatment.
3. Determine participant response to treatment according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 guidelines and serum CA19-9 levels.

Rationale

The two most significant bacterial phyla associated with PDAC treatment response are *Firmicutes* and *Proteobacteria*. Patients with advanced PDAC show lower levels of *Firmicutes,* and higher levels of *Proteobacteria*, which has been linked to a reduced treatment response, progression-free survival (PFS) and overall survival (OS).

Many bacteria within the *Firmicutes* phylum produce butyrate, a short-chain fatty acid with several anti-cancer properties. In vitro studies have shown butyrate to have anti-proliferative, anti-invasive, pro-differentiating and pro-apoptotic effects. Additionally, these studies have also shown butyrate to increase the sensitivity of PDAC cell lines to chemotherapy.

Gammaproteobacteria, a class of bacteria that belongs to the *Proteobacteria* phylum, has been shown to attenuate gemcitabine efficacy. *Gammaproteobacteria* produce the enzyme cytidine deaminase, which metabolises gemcitabine into its inactive isoform. This could potentially lead to the degradation of gemcitabine, and consequently, resistance to chemotherapy.

Method

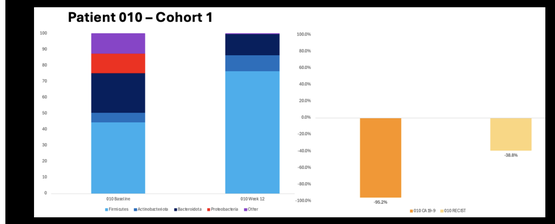
This study was conducted as a single-centre, phase 1 trial at St. John of God Subiaco Hospital in Western Australia. Thus far, 14 participants have undergone microbiome analysis. Eligible participants had histologically confirmed, locally advanced PDAC, with at least 1 lesion measurable by radiological imaging, and detectable levels of CA19-9.

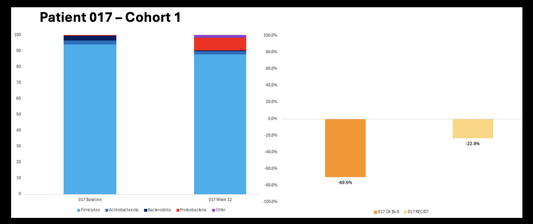
Participants were randomly assigned to one of three cohorts, and received combinations of Gemcitabine and Nab-Paclitaxel, the tumour-penetrating peptide LSTA-1, and the immunotherapy agent durvalumab.

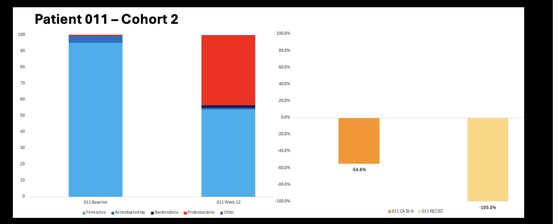
To determine participant response to treatment, tumours were assessed every 8 weeks according to RECIST v1.1 guidelines, and CA19-9 levels were analysed monthly.

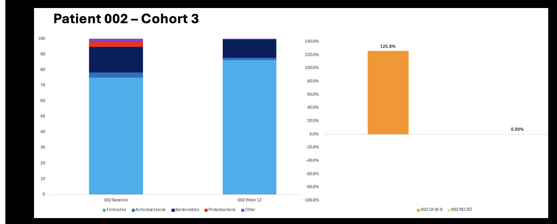
Microbiome samples were obtained via stool collection pre-treatment and 12 weeks into treatment, with microbial profiling completed using 16S rRNA sequencing. This allowed us to evaluate the correlation between microbiome composition and treatment response.

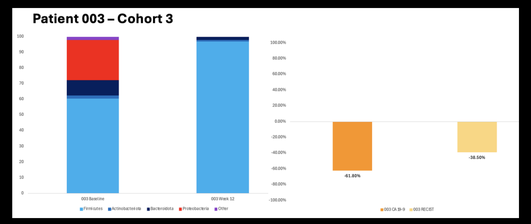
Microbiome Composition and Treatment Response

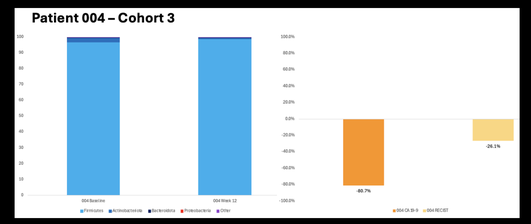


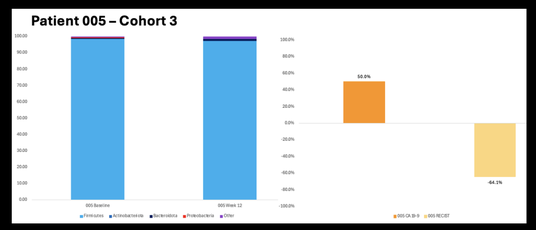


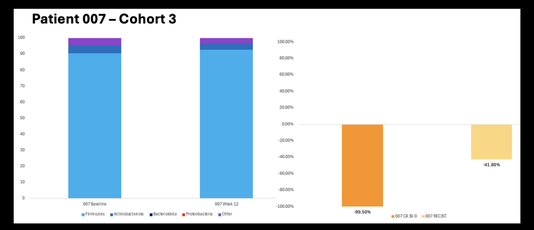


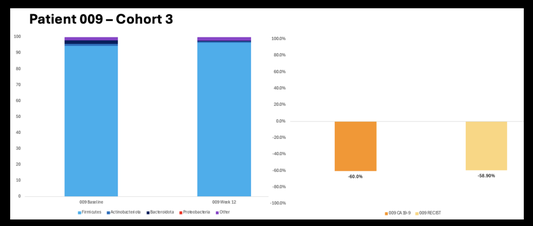


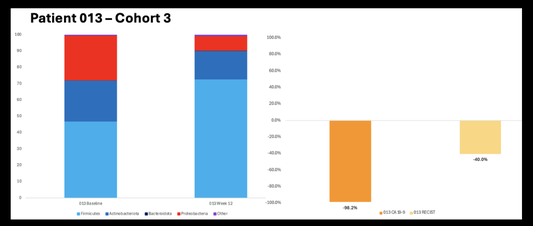


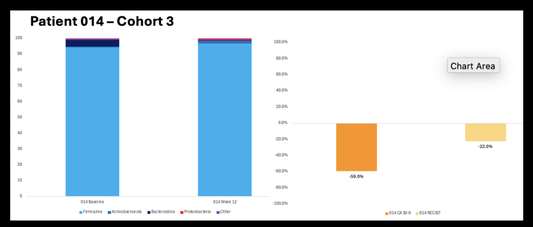


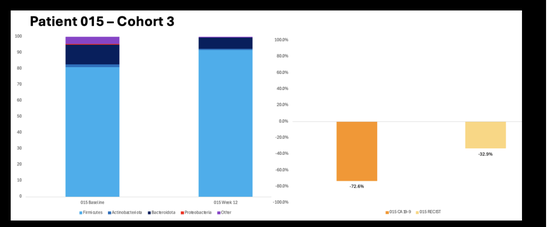


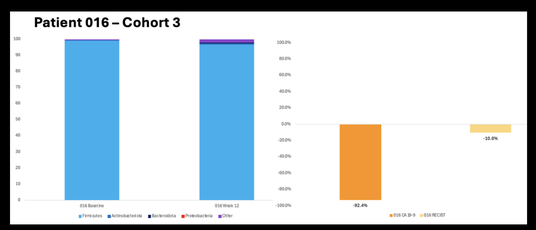


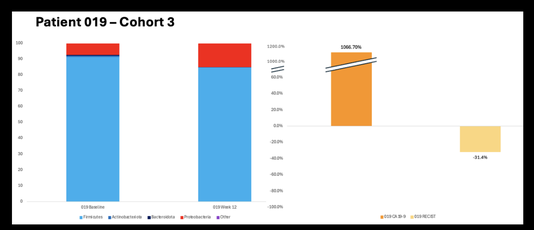


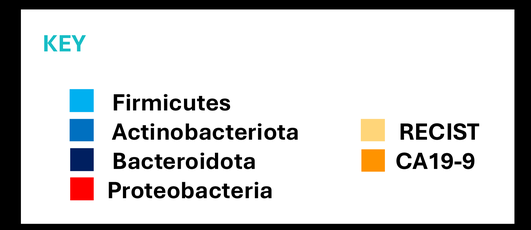












Results

Our analysis was centred on the four primary bacterial phyla within the gut microbiome: *Firmicutes*, *Actinobacteriota*, *Bacteroidota*, and *Proteobacteria.*

There were 4 patients (007, 009, 011 and 015) who demonstrated a notable response to treatment, including a RECIST partial response, and at least a 50% decrease in CA19-9 levels. These patients had a high relative abundance of *Firmicutes* (greater than 80%), a high abundance of *Actinobacteriota* and *Bacteroidota*, as well as very low levels of *Proteobacteria* (less than 0.54%).

5 patients (004, 005, 014, 016 and 017) displayed a promising treatment response, with high levels of *Firmicutes* (greater than 94%), and low levels of *Proteobacteria* (less than 0.39%). These patients demonstrated a decrease in CA19-9 levels and a decrease in tumour size of at least 10%. Due to these patients' having a favourable microbiome composition and treatment response thus far, these patients are expected to achieve a RECIST partial response.

There were 4 patients in this study who showed disease progression (002, 003, 010 and 013). All 4 of these patients demonstrated the highest baseline levels of *Proteobacteria* (up to 27%), and the lowest baseline levels of *Firmicutes* (as low as 44%).

Another patient (019) initially responded to treatment, achieving a RECIST partial response, but later experienced a significant increase in CA19-9 levels. Microbiome analysis revealed low levels of *Firmicutes,* and a significant increase in *Proteobacteria* during treatment, suggesting likely disease progression.

Changes in Bacteria

After 12 weeks of treatment, we observed notable shifts in microbiome composition.

9/14 patients demonstrated an increase in their relative abundance of *Firmicutes*, with 8 of these patients being in cohort 3, meaning they were treated with chemotherapy, the LSTA-1 peptide and immunotherapy.

Additionally, 10/14 patients demonstrated a decrease in their relative abundance of *Proteobacteria*, with 9 of these patients belonging to cohort 3.

Finally, 8/14 participants showed both an increase in their abundance of *Firmicutes* and a decrease in *Proteobacteria*. 7 of these 8 patients once again belonged to cohort 3.

These shifts suggest that the addition of immunotherapy to treatment regimens may have a potentially favourable impact on microbiome composition, which could have implications for future treatment approaches.

Summary

In conclusion, our findings provide evidence of a relationship between the gut microbiome and treatment response in PDAC patients. We believe that this is the first prospective study to show association between the gut microbiome and treatment response in PDAC patients.

Additionally, these insights may inform personalised treatment strategies, in which microbiome composition could serve as a biomarker to guide therapy selection. This also raises the potential to manipulate the microbiome using appropriate anti-microbial and probiotic therapies. This is a rising area of interest in GI cancer research that we believe offers exciting opportunities for future collaboration.

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