The tumor microbiome associates with features of the tumor microenvironment, treatment outcomes, and histologies; a national collaboration of the exORIEN Consortium

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Background

- A tumor microbiome has recently been established as present in many cancer types. Further study is needed to define the scope of its role in cancer tumorigenesis, progression, and treatment outcomes.
- The Oncology Research Information Exchange Network (ORIEN) established a collaboration among eight member institutions to study the tumor microbiome and clinical features across several cancers

Methods

- We evaluated RNAseq data from n =2,892 tumors using the tool {exotic}.
- Matched cancers from the Cancer Genome Atlas were processed by the same method (n= 2,720 samples).
- Clinical data, including treatment information, lab values, detailed histology, and long-term follow-up, were collected and harmonized across sites.

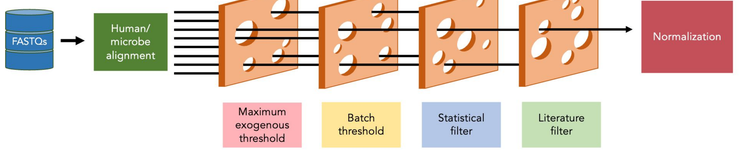

Figure 1. The {exotic} pipeline schema

N = 2892		Cancer (Primary Location) cont.	
Cancer (Primary Location)		SKCM	138 (4.8)
COAD	500 (17.3)	Rectum	1 (0.72)
Cecum	38 (7.6)	Skin	121 (87.7)
Colon	428 (85.6)	Soft Tissue	1 (0.72)
Rectum	34 (6.8)	Other	15 (10.9)
LUAD	261 (9.0)	THCA	539 (18.6)
Lung	260 (99.6)	Thyroid	539 (100)
Other	1 (0.38)	Other CR	39 (1.3)
LUSC	127 (4.4)	Cecum	8 (20.5)
Lung	126 (99.2)	Colon	27 (69.2)
Other	1 (0.79)	Rectum	4 (10.3)
PAAD	156 (5.4)	Other Lung	104 (3.6)
Pancreas	156 (100)	Lung	103 (99.0)
READ	95 (3.3)	Other	1 (0.96)
Rectum	95 (100)	Other Pancreatic	216 (7.5)
SARC	691 (23.9)	Pancreas	216 (100)
Abdomen	17 (2.46)		
Bone	45 (6.51)	**Sex (%)**	
Colon	4 (0.58)	Male	1418 (49.0)
Intestine	25 (3.62)	Female	1474 (51.0)
Lung	7 (1.01)		
Pancreas	2 (0.29)	**Age (%)**	
Rectum	2 (0.29)	10-19	15 (0.5)
Retroperitoneum	95 (13.7)	20-29	120 (4.1)
Skin	2 (0.29)	30-39	207 (7.2)
Soft Tissue	316 (45.7)	40-49	397 (13.7)
Stomach	56 (8.10)	50-59	691 (23.9)
Uterus	28 (4.05)	60-69	794 (27.5)
Other	92 (13.3)	70-79	530 (18.3)
SCLC	26 (0.9)	80-89	128 (4.4)
Lung	25 (96.2)	90+	10 (0.3)
Other	1 (3.84)		

N = 2720		Cancer (Primary Location) cont.	
Cancer (Primary Location)		SARC	259 (9.5)
COAD	478 (17.6)	Bone	2 (0.8)
Cecum	87 (18.2)	Colon	1 (0.4)
Colon	382 (79.9)	Retroperitoneum	98 (37.8)
Rectum	7 (1.5)	Soft Tissue	117 (45.2)
Other	2 (0.4)	Stomach	2 (0.8)
LUAD	533 (19.6)	Uterus	29 (11.2)
Lung	531 (99.6)	Other	10 (3.9)
Other	2 (0.4)	SKCM	
LUSC	502 (18.5)	Skin	103 (100)
Lung	495 (98.6)	THCA	502 (18.5)
Other	7 (1.4)	Thyroid	502 (100)
PAAD	177 (6.5)		
Pancreas	177 (100)	**Age (%)**	
READ	166 (6.1)	10-19	12 (0.4)
Colon	6 (3.6)	20-29	62 (2.3)
Rectum	156 (94.0)	30-39	157 (5.9)
Other	2 (1.2)	40-49	262 (9.8)
		50-59	510 (19.1)
Sex (%)		60-69	762 (28.5
Male	1371 (50.5)	70-79	695 (26.0)
Female	1349 (49.5)	80-89	210 (7.9)

Table 1. Patient Demographics. Reads that did not align to the human reference genome were filtered of (1) common laboratory contaminants, (2) taxa that inversely correlate with input RNA quantity, and (3) taxa commonly found in the negative control of microbiome experiments.

Results

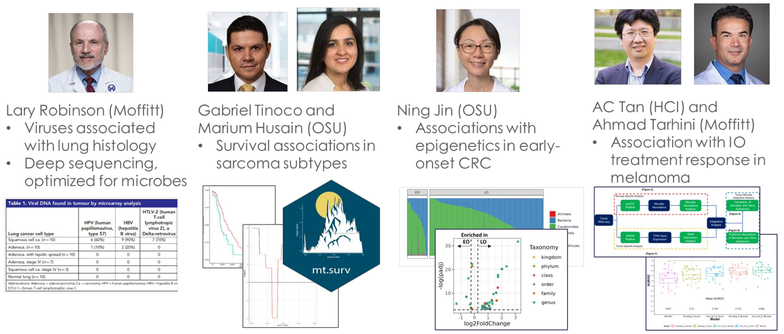

Figure 2. The eight manuscripts planned for co-submission as the exORIEN Consortium set. Additional details from one manuscript, led by Nic Denko at OSU, are shown as an example. **A)** Hypoxia is associated with shorter overall survival in colorectal cancer patients treated with radiation. **B)** Several microbes, including Fusobacterium, show a significant interaction with hypoxia for overall survival. **C)** Follow-up mouse experiments tested the effects of hypoxia and the immune system in a mouse model of colorectal cancer. **D)** Both BALB/c and nude mice (lacking T-cells) show differences in tumor hypoxia following atovaquone treatment. **E)** The differences the tumor microbiomes are more strongly affected by the immune system than hypoxia. **F)** However, some microbes are present in both high and low hypoxia tumors and alter their expression in each condition, shown here for *Cutibacterium*.

- Microbes were found in all tumors and associated with treatment outcomes for all modalities tested, including radiation in colorectal cancer, chemotherapy in pancreatic cancer, and immunotherapy in melanoma.
- In the case of radiation treatment in colorectal cancer, the microbes also affected outcomes in preclinical model systems and were modified by altering hypoxia levels with the drug atovaquone.
- Virus prevalence associated with histological subtypes in lung cancer.
- Similar microbes in ORIEN and TCGA tumors associated with overall survival in subtypes of sarcoma (dedifferentiated liposarcoma, leiomyosarcoma, and others).
- Finally, microbes associated with expression-based indicators of the tumor microenvironment across cancer types.

Conclusions

- These results suggest that the tumor microbiome may have broad clinical utility as a biomarker of treatment outcomes and as a target for rational manipulation.

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