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Society for Immunotherapy of Cancer

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Characteristics of the microbiome of complete responders to Anti-PD1 and healthy individuals: Implications for donor selection and clinical trial design

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Disclosure

- I have no potential disclosure with this presentation

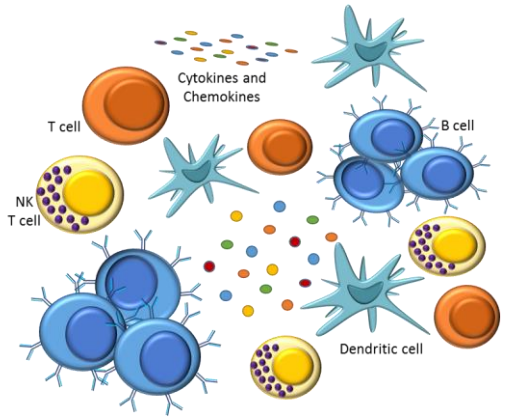
- My PI (Jennifer Wargo) is a co-inventor on patent submitted by The University of Texas MD Anderson Cancer Center to the US Patent and Trademark Office on modulating gut microbes to improve responses to immune checkpoint blockade (Patent # PCT/US1/53717)

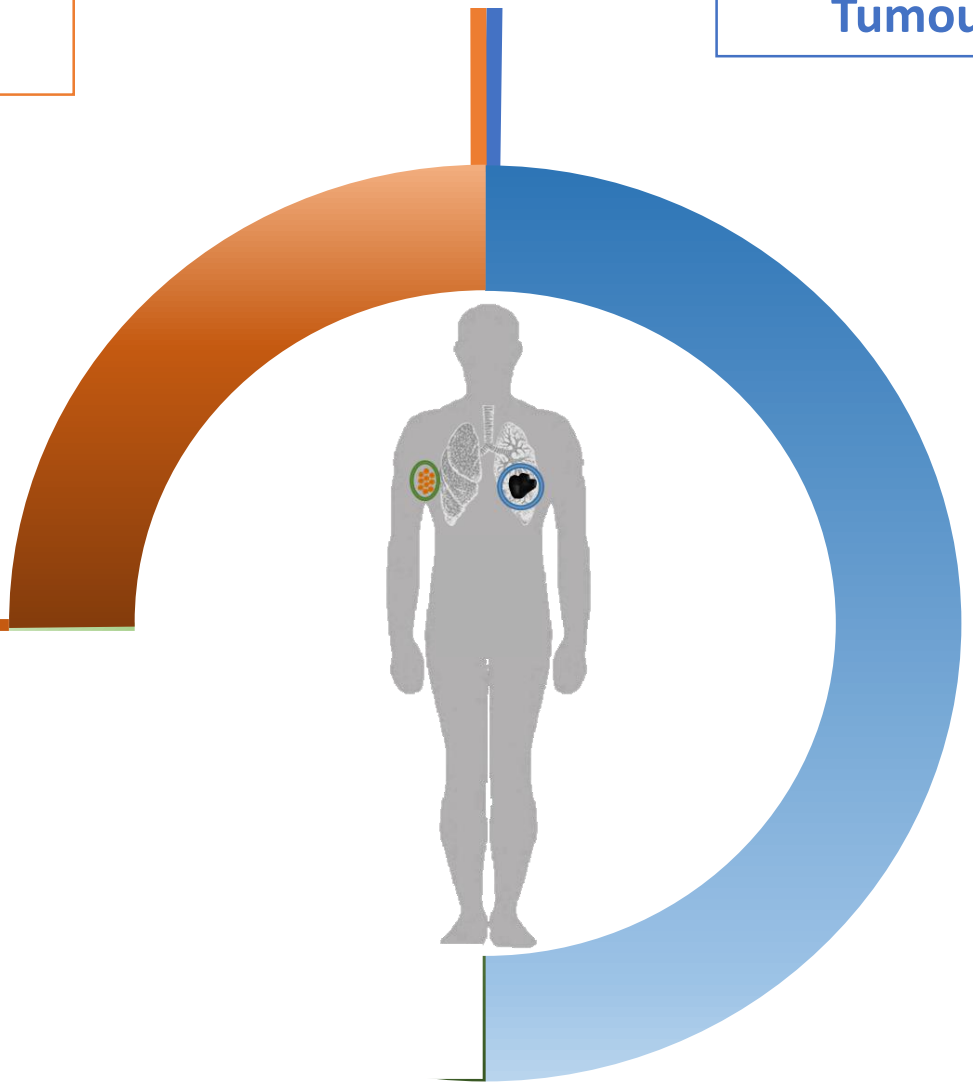
Responses are dependent on factors shaping tumor growth and immunity

Cogdill, Andrews, Wargo - *British Journal of Cancer May 2017*

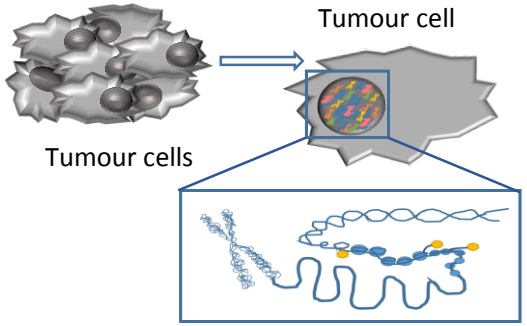
Systemic Immunity

Innate and Adaptive

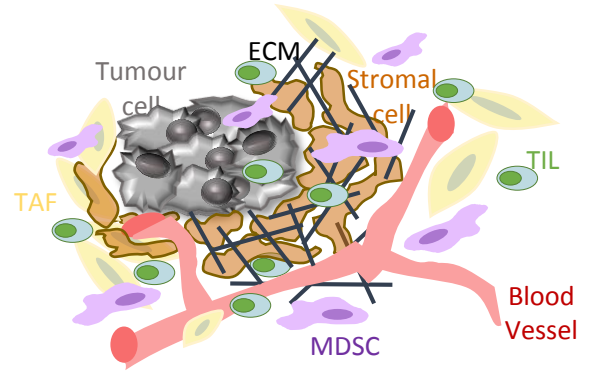




Tumour Genome and Epigenome

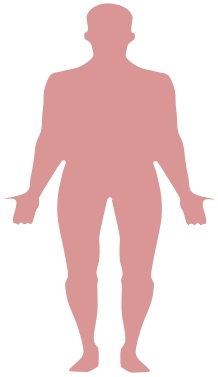


Tumour Microenvironment

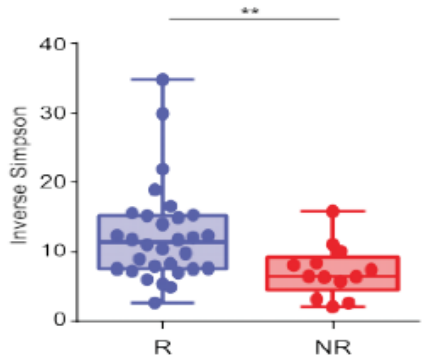


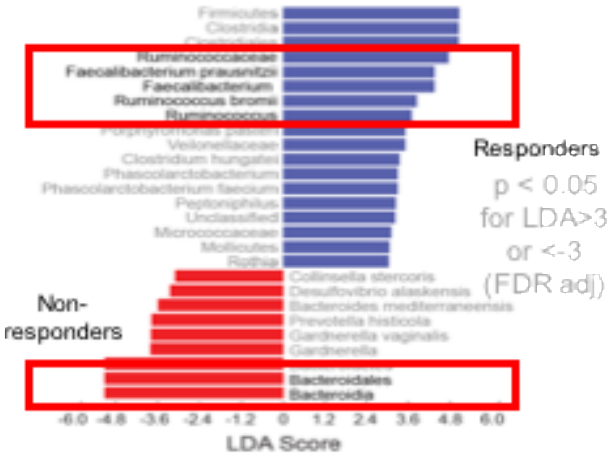
There is a significant microbial contribution to the total makeup of our cellular composition as well as our DNA that dramatically influences our physiology

We studied oral and gut (fecal) microbiome signatures in patients with melanoma

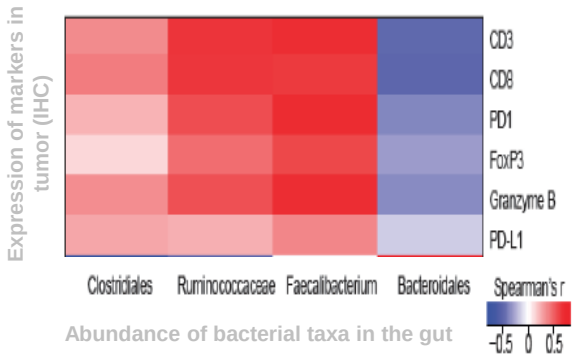


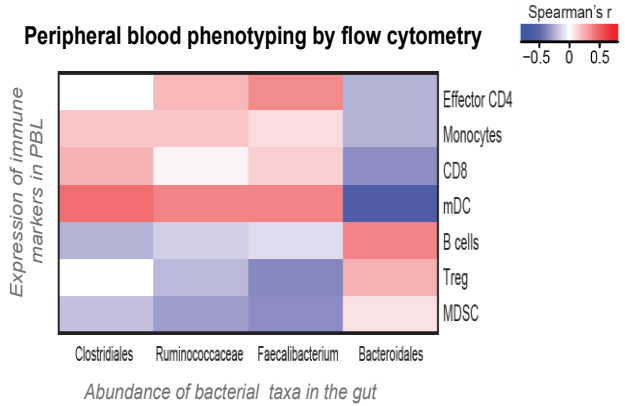
n = 233 patients

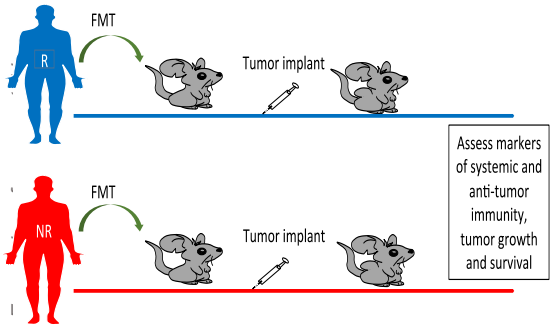


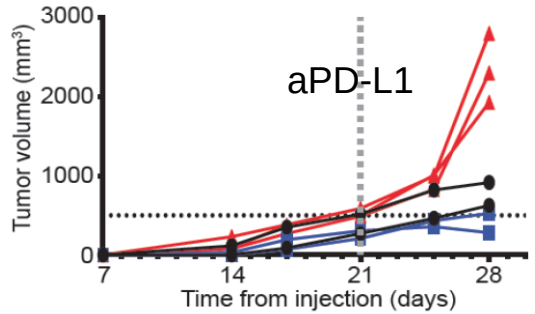


Responders to anti-PD-1 had a higher diversity and differential composition of gut bacteria









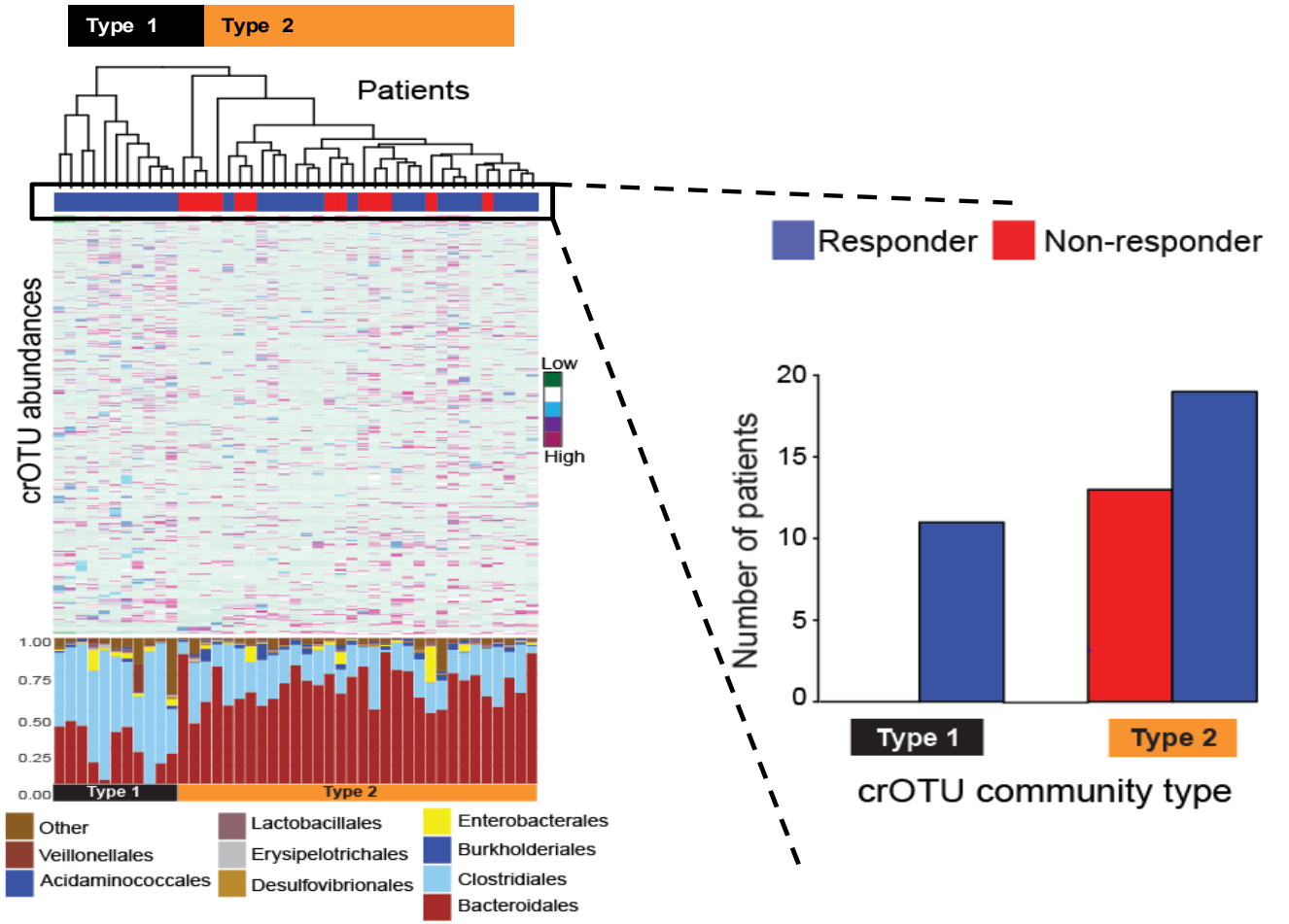
Importantly, these "favorable" signatures in the gut microbiome were associated with better immune profiles in the tumor and in the blood of patients, with validation in murine models

Deepak Gopalakrishnan PhD

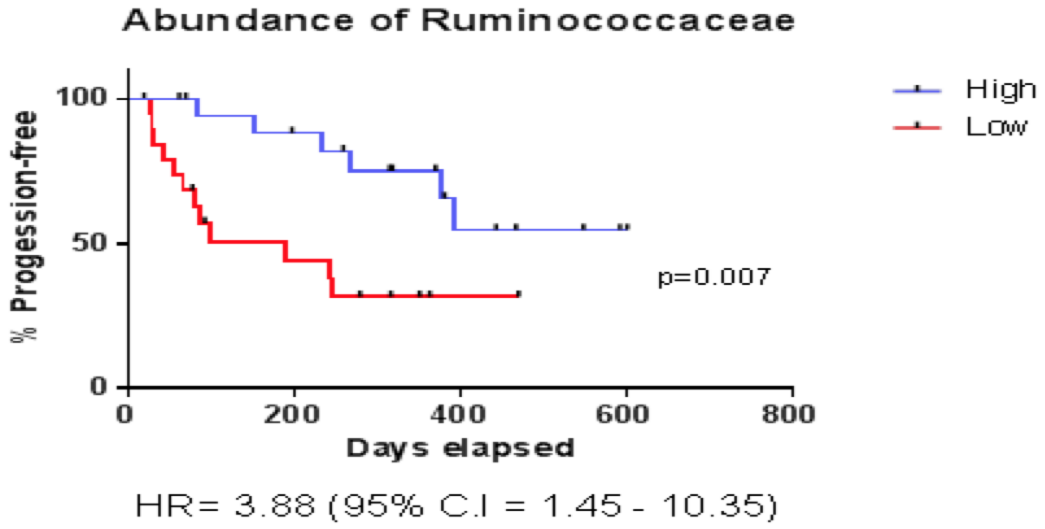
Gopalakrishnan, Spencer et al, Science 2018

Christine Spencer PhD

In our cohort, we identified a gut microbiome “signature” with a high likelihood of response to anti-PD-1 (type I), with subsequent validation in a larger cohort



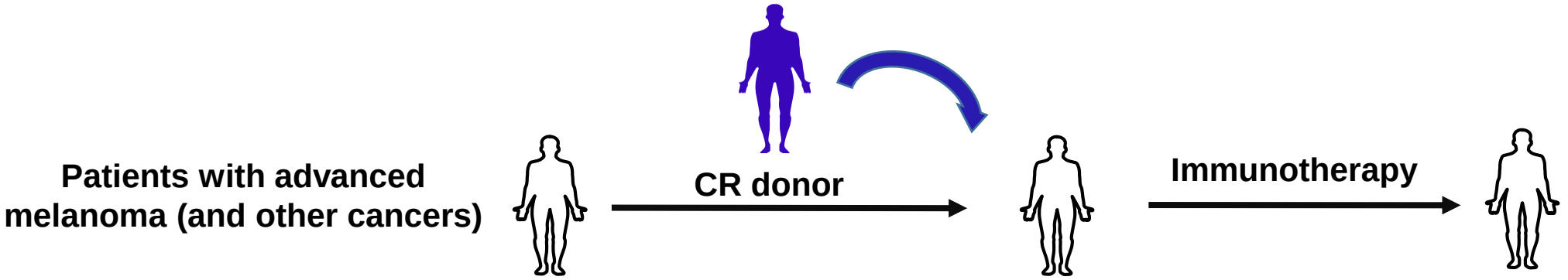
Notably, the relative abundance of Ruminococcaceae was a good surrogate marker for a type I signature, with patients having a high abundance doing better on therapy



*Gopalakrishnan et al, Science 2018 + confidential unpublished data * DO NOT POST **

Based on these findings, studies are underway aiming to modulate the gut microbiome using fecal microbiota transplant (FMT) and other strategies

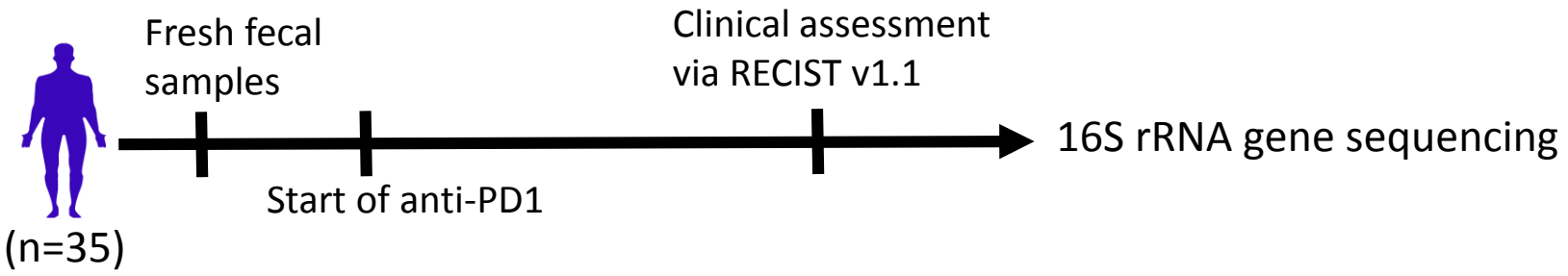
(with some success as recently reported by 2 groups at AACR)



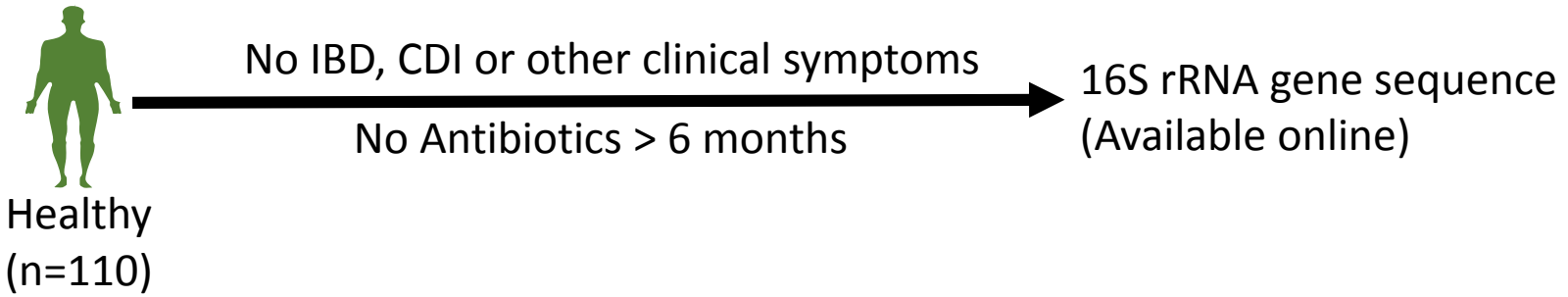
However not all complete responders have what we would consider to be a "favorable" gut microbiome,
And there is the potential to explore the use of FMT from healthy individuals in these types of studies

We studied gut microbiome signatures in complete responders vs. healthy individuals

Complete Responder (CR) cohort: Metastatic melanoma patients on Anti-PD1

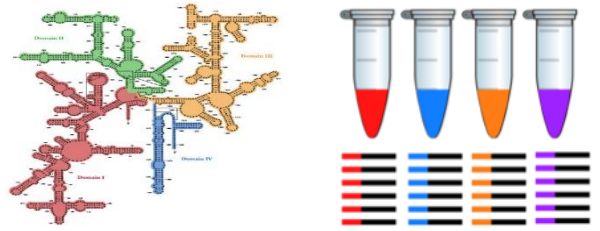


Healthy cohort: sequence data from American Gut Project (McDonald et al. 2018)



16S rRNA: Microbial Taxonomy

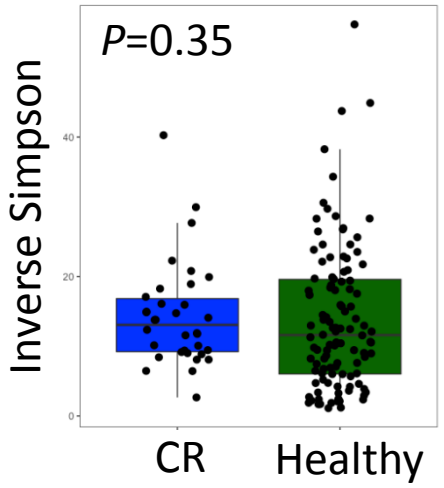
Illumina MiSeq

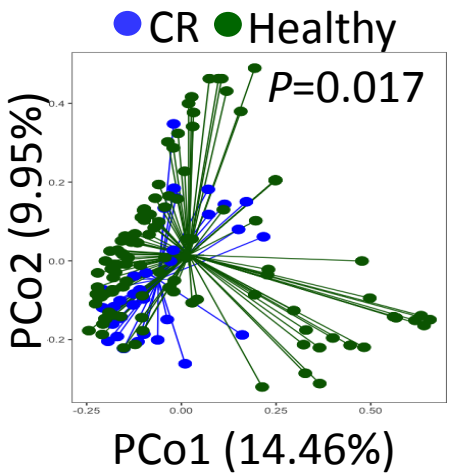


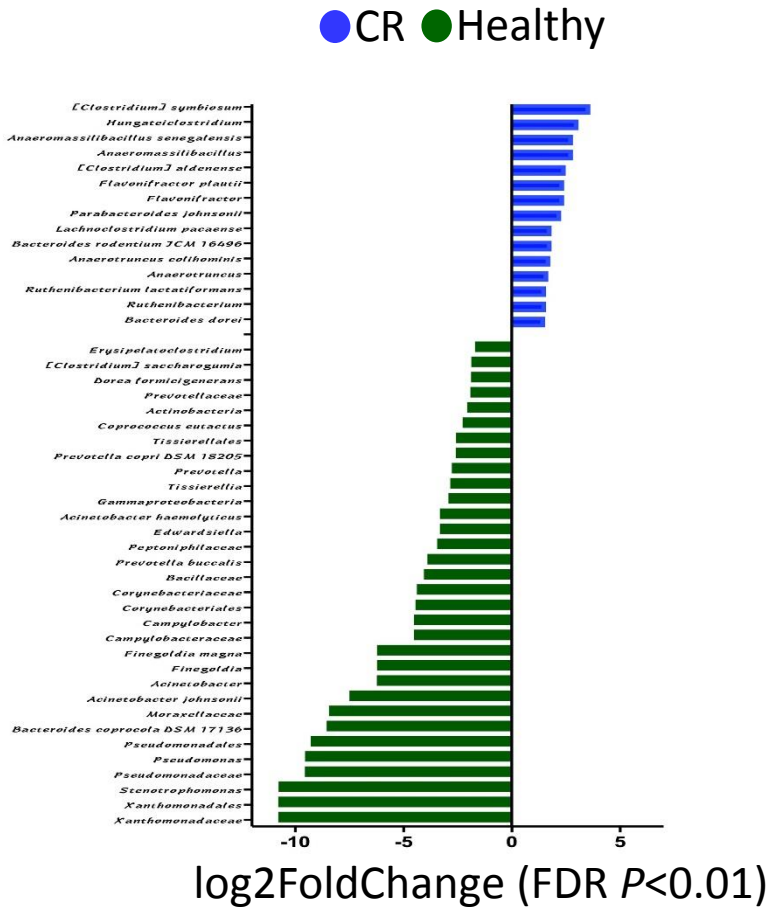
1. V4 region of 16S rRNA gene: Taxonomy by NCBI. Analyzed by QIIME, USEARCH, vsearch, R
2. PICRUSt2 (Douglas et al. 2019): No. of reference genomes 20,000. Functional genes: KEGG. Metabolic pathways: MetaCyc

Murine Melanoma Model

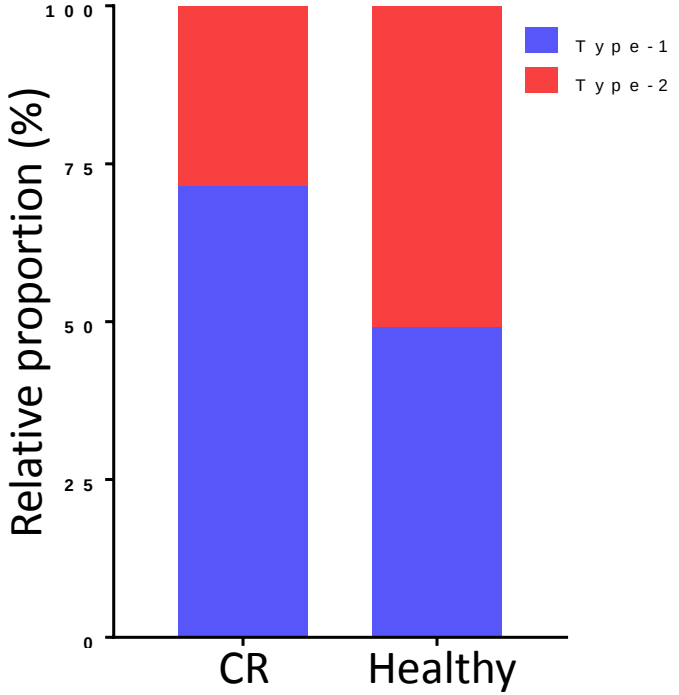
In these studies, CRs and healthy donors had diverse microbiomes overall, with differential composition and proportions of a type I signature between the groups





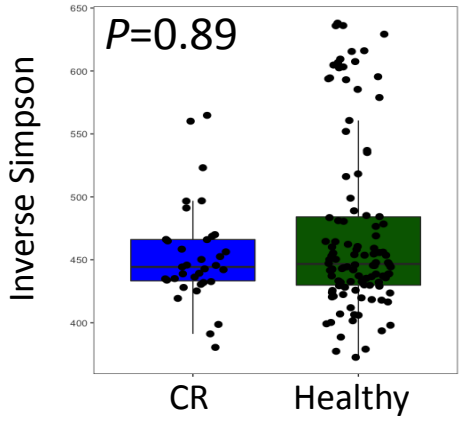


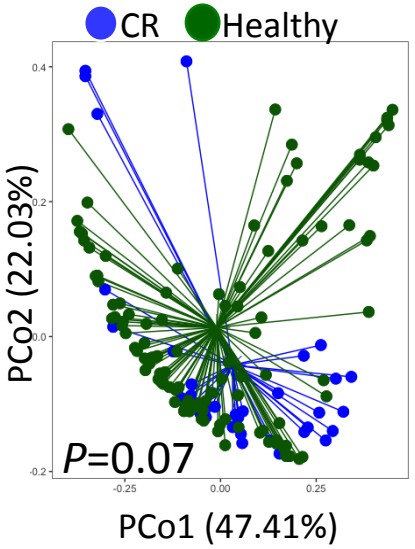
Not all CRs have Type-1 signature

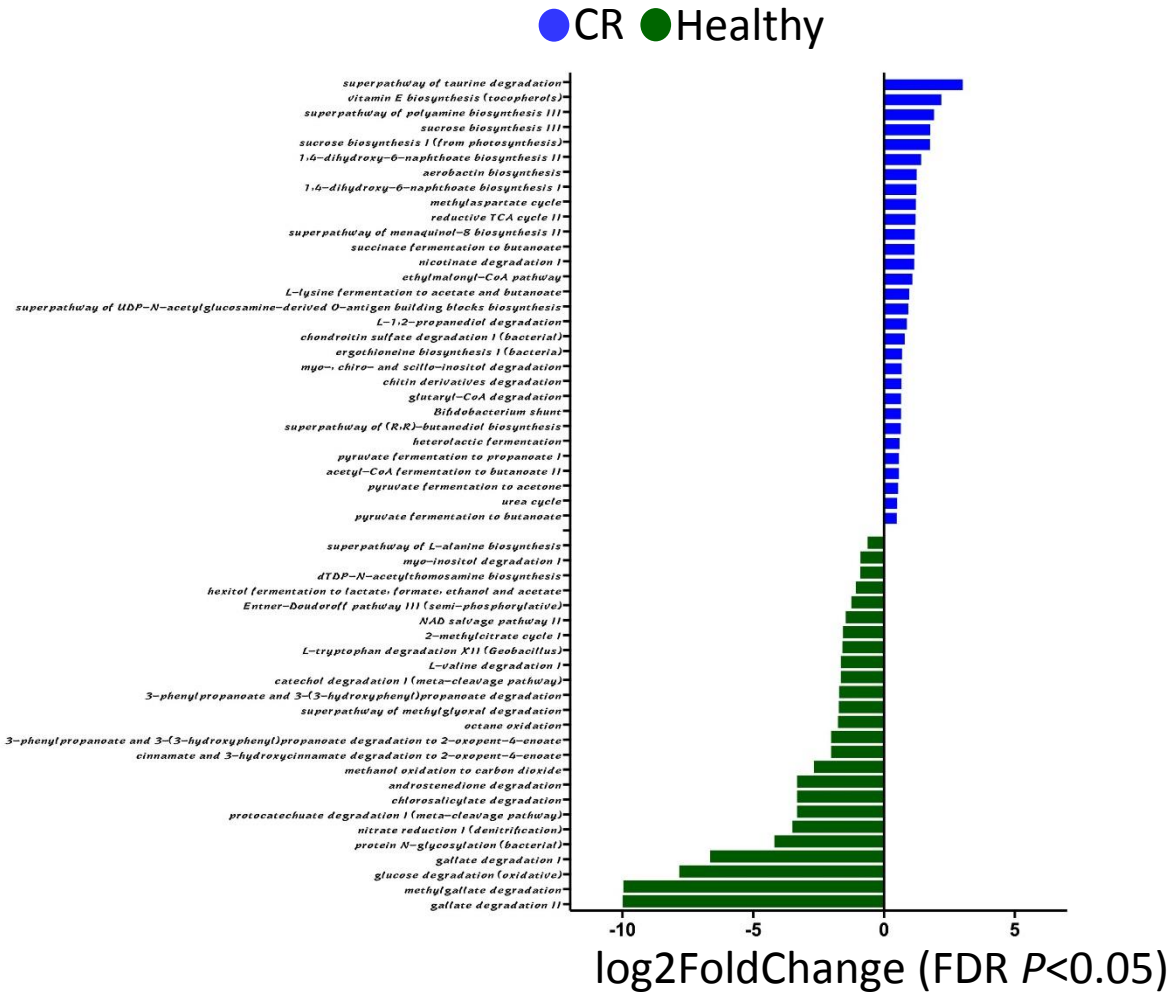


Functional differences between CRs and healthy individuals were also noted, though these need to be interrogated with dedicated metabolomic profiling

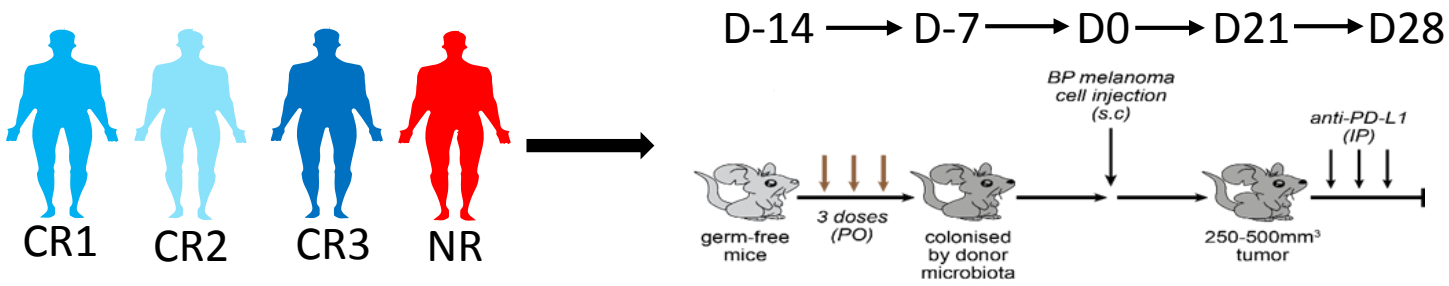
Functional genes diversity

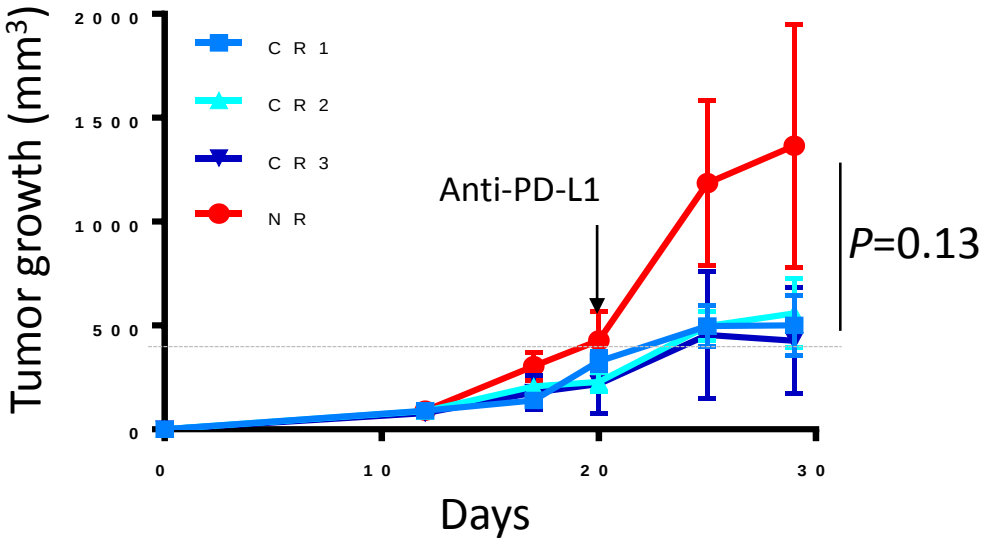


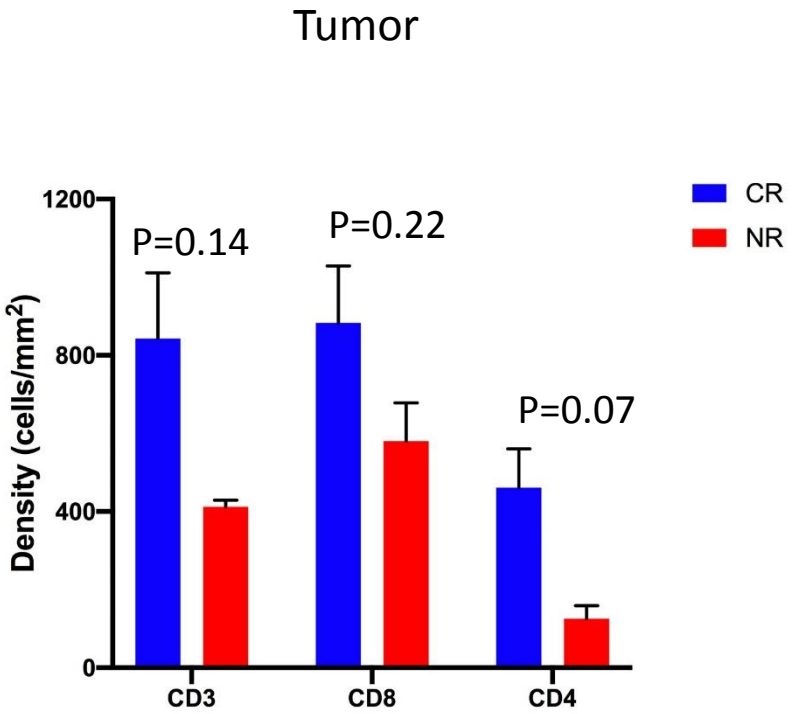




We performed pilot studies in germ-free mouse models, demonstrating good tumor control in mice receiving CR donor FMT (compared to non-responder FMT)







*Confidential unpublished data * DO NOT POST **

Take Home Messages and Next Steps

- There is now strong evidence for the impact of gut microbes in immunotherapy response, though optimal strategies to modulate gut microbes remain incompletely understood
- Treatment with FMT has been associated with responses, however optimal donors remain unknown (and there are some risks associated with FMT)
- Further studies to better understand determinants of enhanced response are needed, and are currently underway (including deeper studies in larger cohorts, and studies using highly selected FMT donors)
- There is still a great deal to learn, and this is best accomplished through collaboration (*and we owe this to our patients*!)

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Extra slide