The role of the microbiome in response and toxicity to cancer therapy

Jennifer A. Wargo MD MMSc
Professor, Departments of Genomic Medicine & Surgical Oncology
UT, MD Anderson Cancer Center

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Disclosure information
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- I have the following financial relationships to disclose:

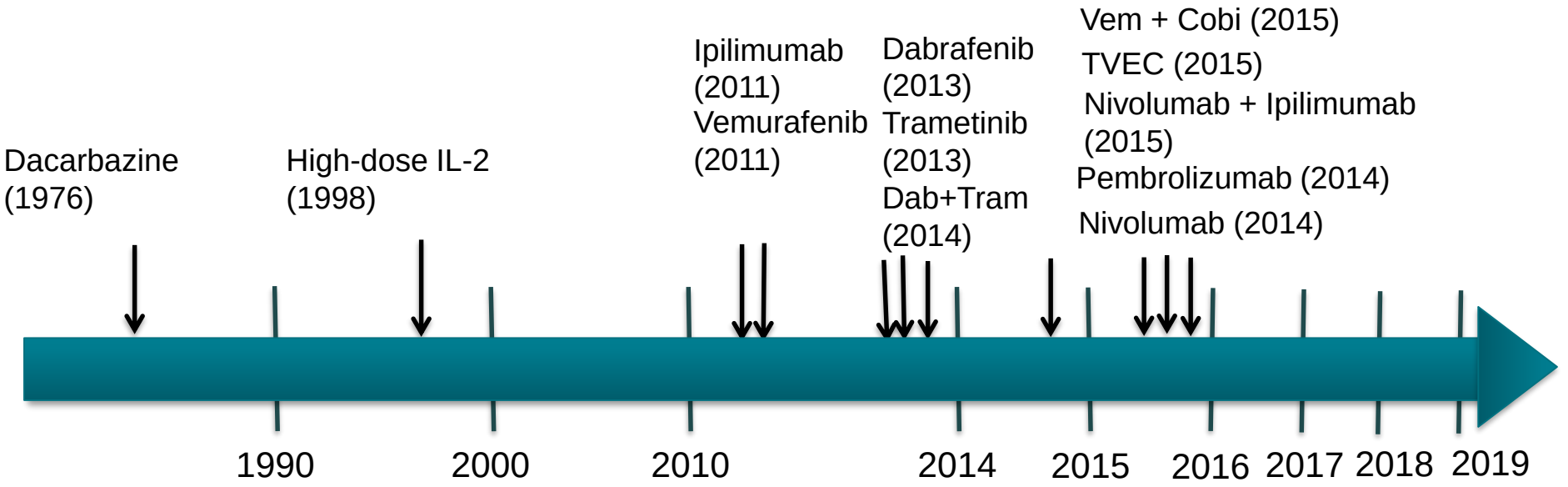
- Speaker's bureau: Imedex, Dava, Omniprex, Illumina, BMS
- Advisory board member: Roche - Genentech, GSK, Novartis, Astra-Zeneca
- Clinical trial support: Roche - Genentech, GSK, BMS, Novartis

- I am a scientific advisor to Microbiome DX

- *I am co –Inventor on patent submitted by The University of Texas MD Anderson Cancer Center to the US Patent and Trademark Office based on this work (Patent # PCT/US1/53717)*

We have made major advances in the treatment of melanoma and other cancers through the use of targeted therapy and immunotherapy

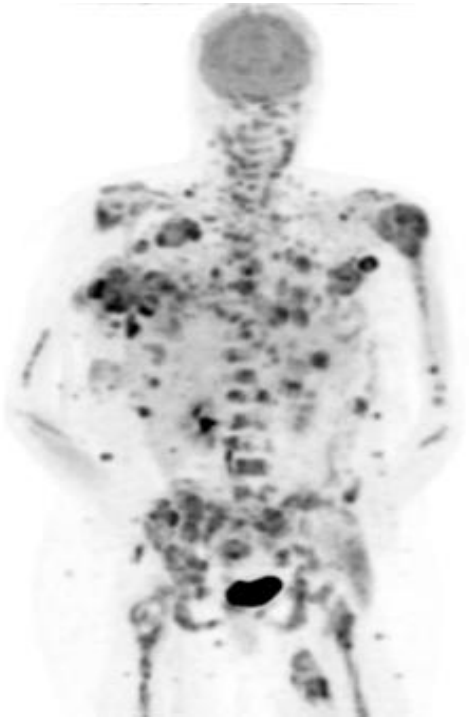
FDA-approved agents for stage IV melanoma



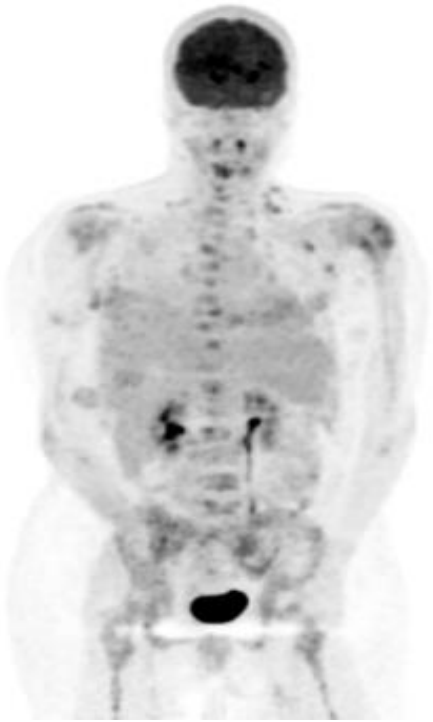
These agents are now being used successfully across cancer types and across the spectrum of disease (alone or in combination with other therapies)

Dab, dabrafenib; FDA, Food and Drug Administration; IL-2, interleukin 2; Tram, trametinib – www.FDA.gov

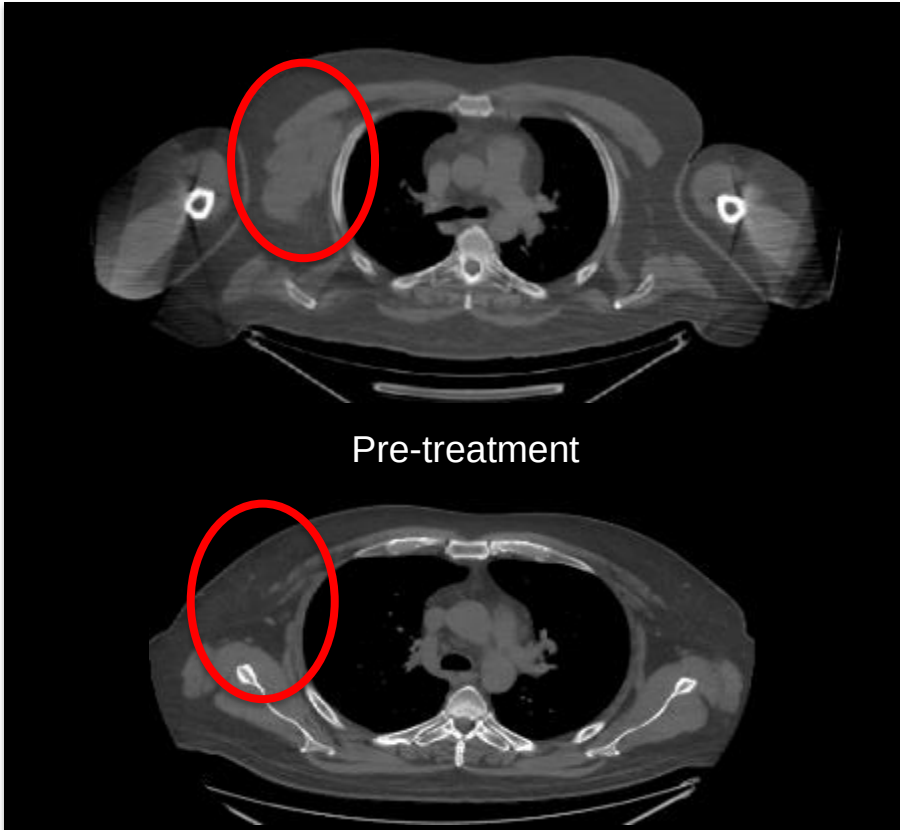
Treatment with these therapies can result in rapid tumor regression



Before starting targeted therapy (BRAF)

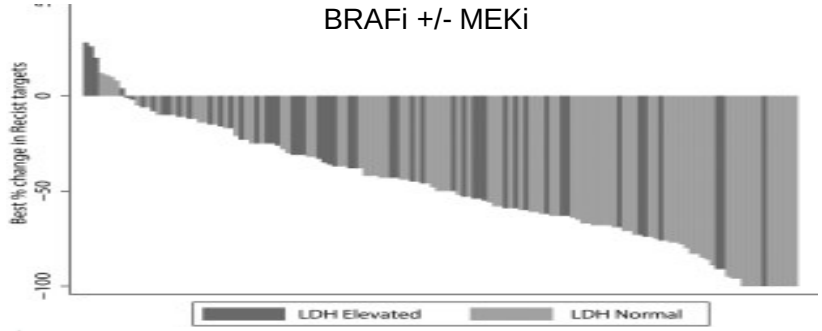


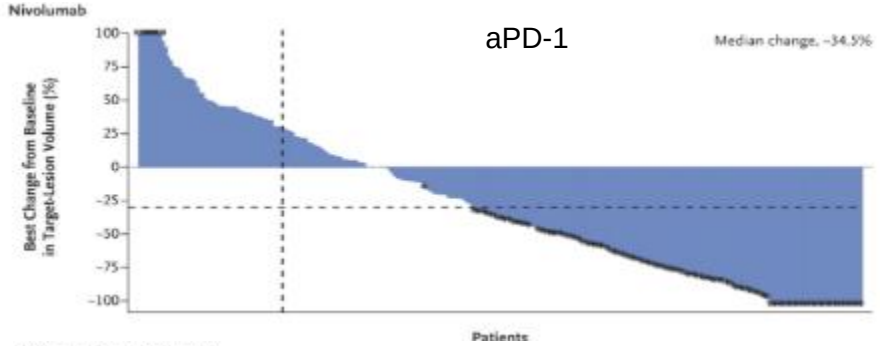
2 weeks later

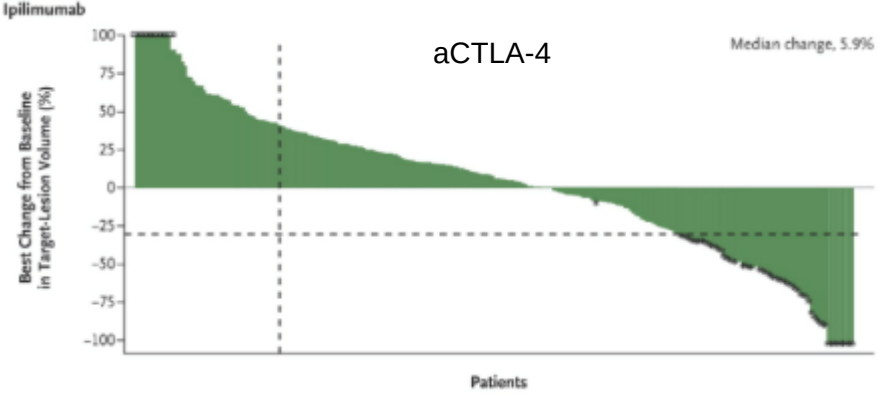


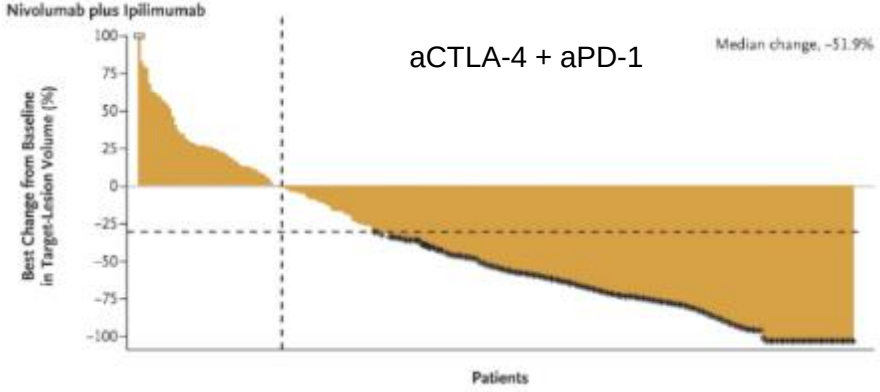
After treatment with combined PD-1 and CTLA-4 blockade

Despite these advances responses are heterogeneous and are not always durable, and toxicity can be an issue…







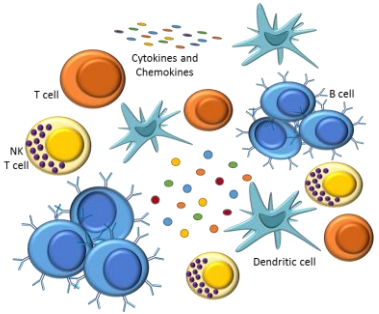


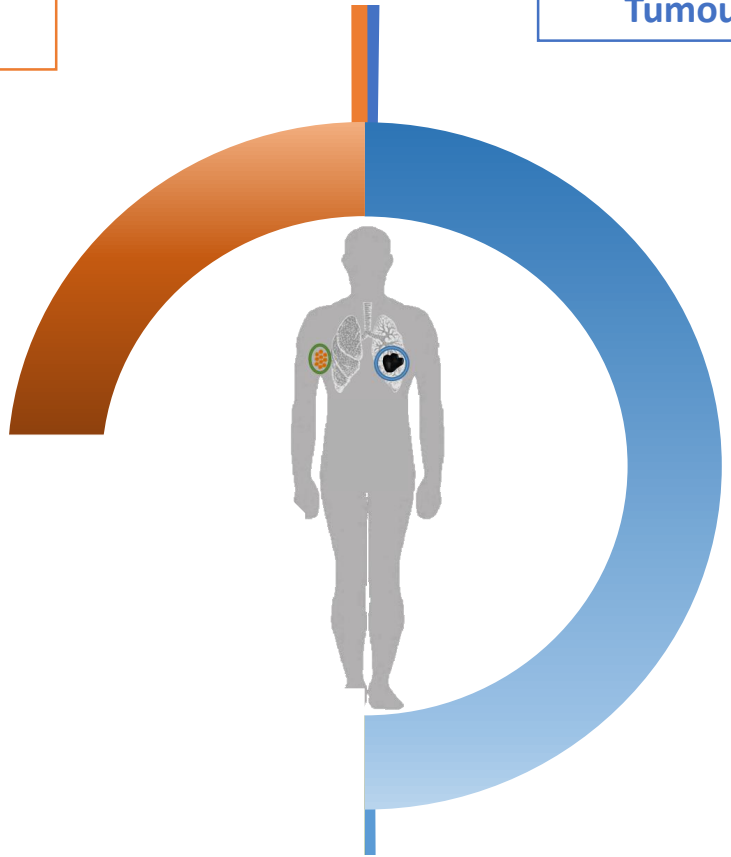
There is a critical need to better understand who will benefit from therapy, as well as proper timing, sequence and combination of different therapeutic agents

Menzies Cancer 2015; Larkin NEJM 2015

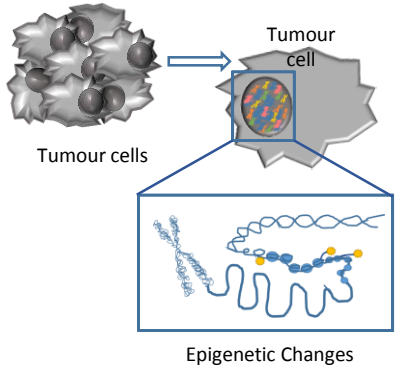
Responses are dependent on factors shaping tumor growth and immunity

Systemic Immunity
Innate and Adaptive

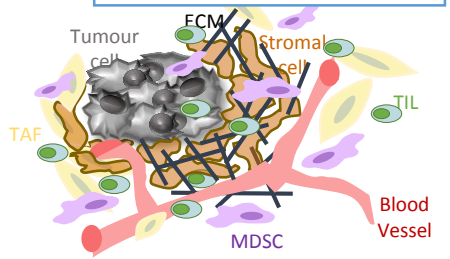




Tumour Genome and Epigenome



Tumour Microenvironment

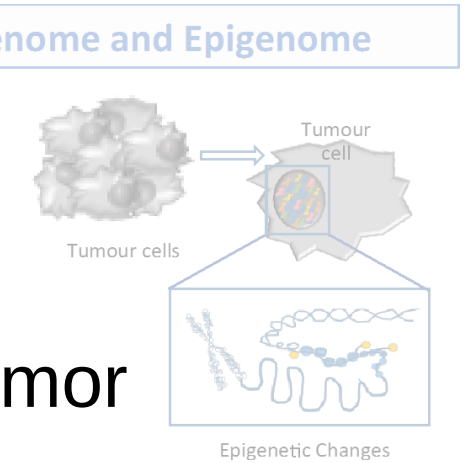


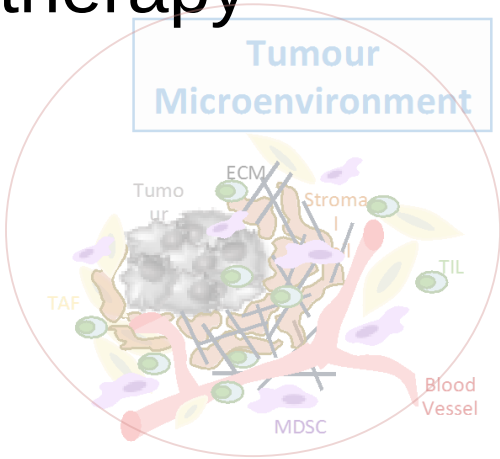
Cogdill, Andrews, Wargo - *British Journal of Cancer May 2017*

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

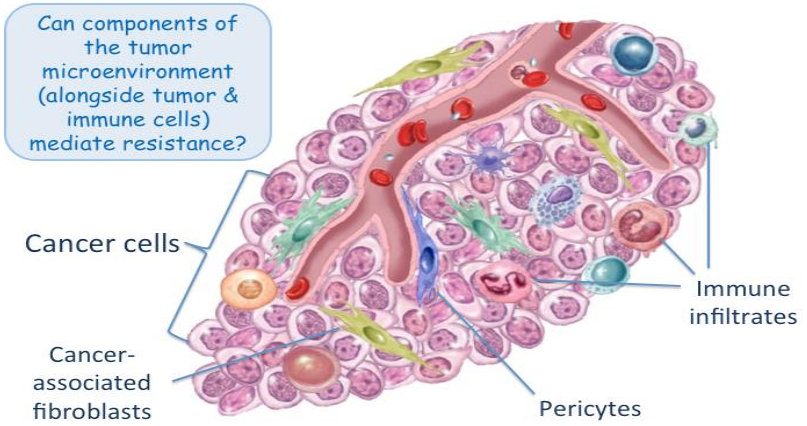
We first studied the role of the tumor microbiome in response to cancer therapy

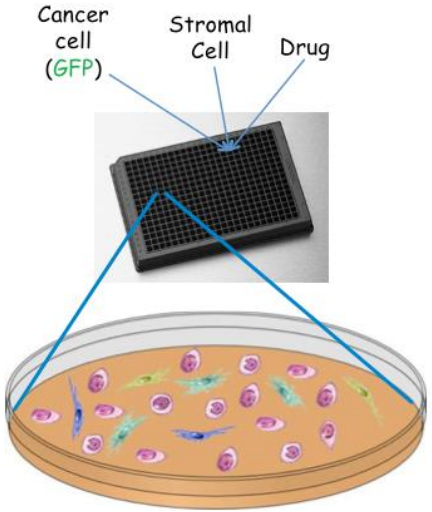
(serendipitously)

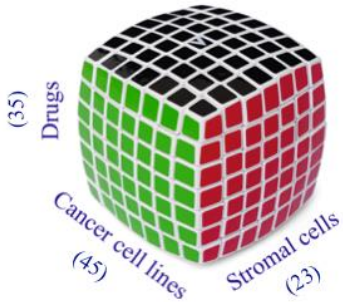




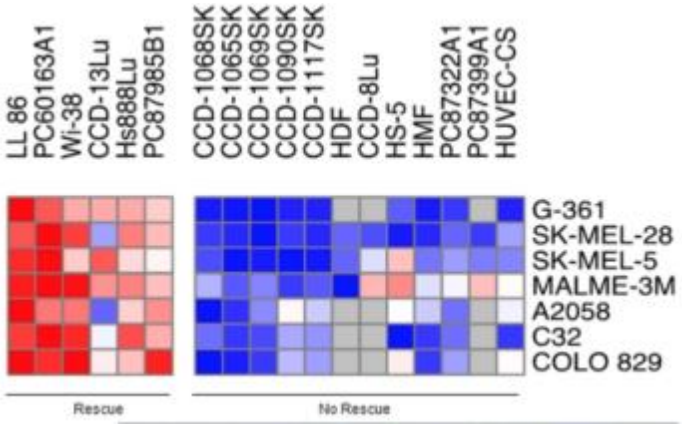
We used a model to study stromal-mediated resistance in melanoma







Certain stromal cells were capable of mediating resistance to targeted therapy



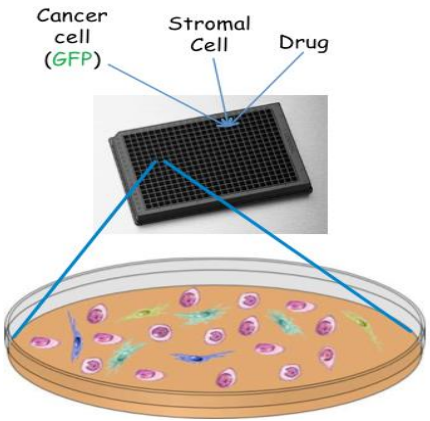
Tumor microenvironment induces innate RAF-inhibitor resistance through HGF secretion

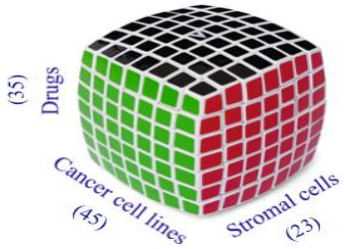
Ravid Straussman[1], Teppei Morikawa[2], Kevin Shee[1], Michal Barzily-Rokni[1], Zhi Rong Qian[2], Jinyan Du[1], Ashli Davis[1], Margaret M. Mongare[1], Joshua Gould[1], Dennie T. Frederick[3], Zachary A. Cooper[3], Paul B. Chapman[4], David B. Solit[4,5], Antoni Ribas[6,7], Roger S. Lo[7,8], Keith T. Flaherty[3], Shuji Ogino[2,9], Jennifer A. Wargo[3], and Todd R. Golub[1,10,11,12,*]

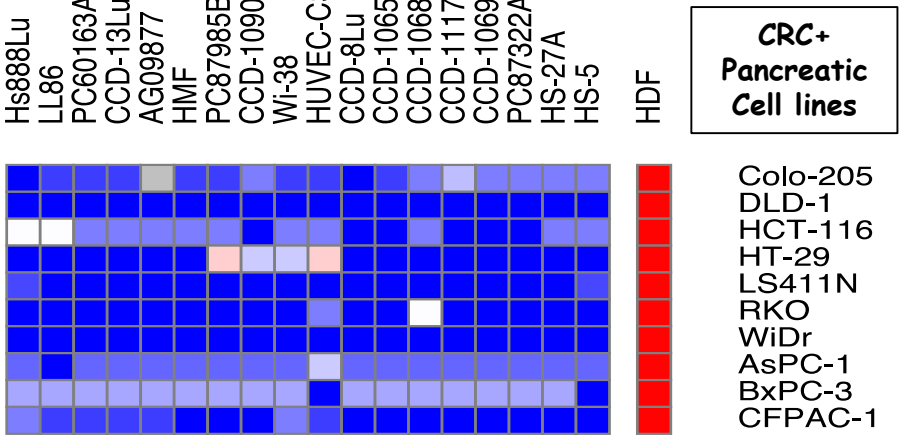
Straussman et al, Nature 2012

We studied the role of tumor stroma in resistance to therapy, and identified bacteria within cell lines derived from cancer patients that could confer resistance to therapy

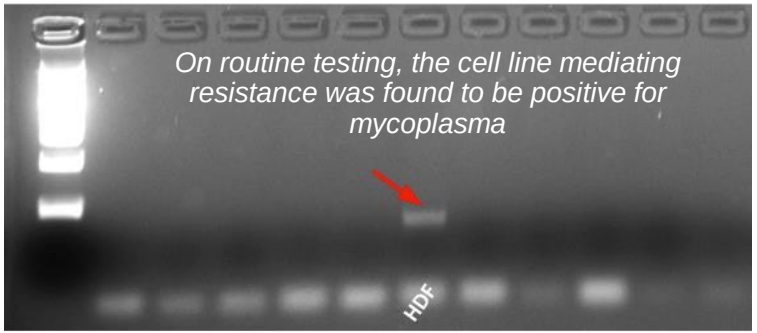
We worked with a team from MIT / the Broad to study resistance to chemotherapy in colorectal cancer and pancreatic cancer







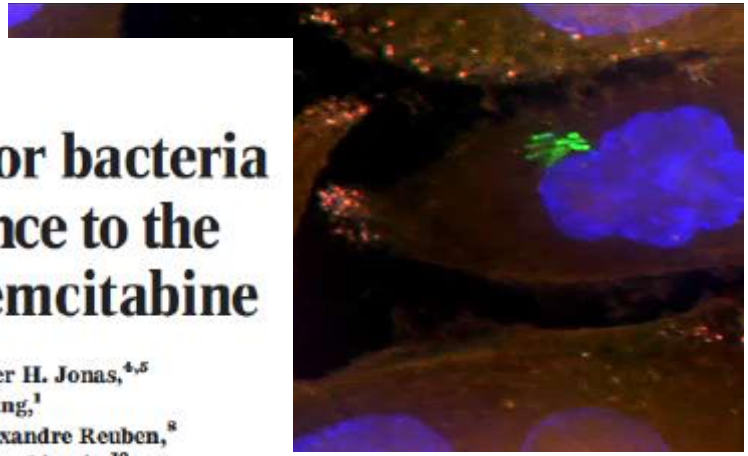
In these studies, one cell line rescued cancer cells from gemictabine



Mycoplasma is responsible for rescue from Gemcitabine:

- Eradication of mycoplamsa → no rescue
- Infection of another cell line → rescue
- WGS of HDF-pre-conditioned media → mycoplasma
- Bacteria were breaking down gemcitabine into inactive form

We validated these findings in patient samples, and showed that targeting co-targeting the bacteria and the cancer cells was associated with improved survival in mice

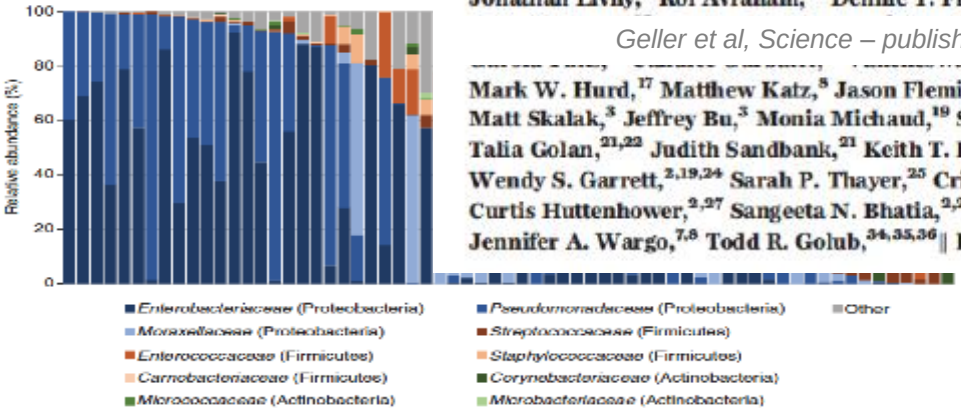


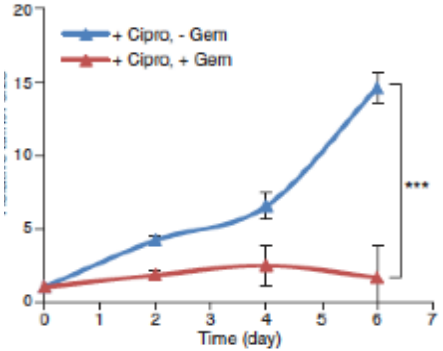
CANCER

Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine

Leore T. Geller,[1†] Michal Barzily-Rokni,[2*] Tal Danino,[3†] Oliver H. Jonas,[4,5] Noam Shental,[6] Deborah Nejman,[1] Nancy Gavert,[1] Yaara Zwang,[1] Zachary A. Cooper,[7,8‡] Kevin Shee,[2] Christoph A. Thaiss,[9] Alexandre Reuben,[8] Jonathan Livny,[2] Roi Avraham,[10] Dennie T. Frederick,[11] Matteo Ligorio,[12] Mark W. Hurd,[17] Matthew Katz,[5] Jason Fleming,[5] Anirban Maitra,[15] David A. Smith,[2] Matt Skalak,[3] Jeffrey Bu,[3] Monia Michaud,[19] Sunia A. Trauger,[13] Iris Barshack,[20,21] Talia Golan,[21,22] Judith Sandbank,[21] Keith T. Flaherty,[12] Anna Mandinova,[2,23] Wendy S. Garrett,[2,19,24] Sarah P. Thayer,[25] Cristina R. Ferrone,[26] Curtis Huttenhower,[2,27] Sangeeta N. Bhatia,[2,28,29,30,31,32,33] Dirk Gevers,[2§] Jennifer A. Wargo,[7,8] Todd R. Golub,[34,35,36]‖ Ravid Straussman[1]‖¶

Geller et al, Science – published September 15, 2017

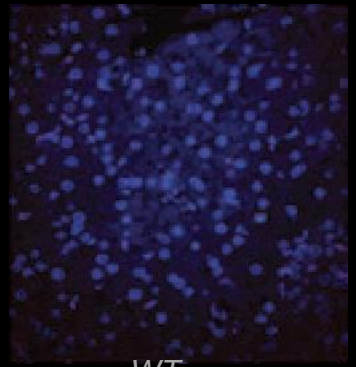


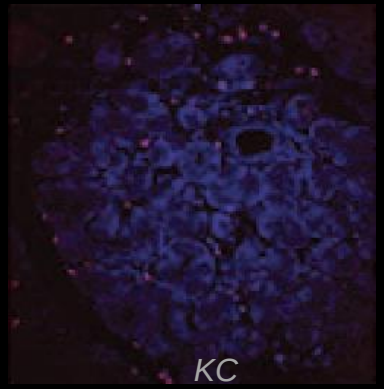


With Ravid Straussman Todd Golub, Keith Flaherty, Dirk Gevers, Curtis Huttenhower et al

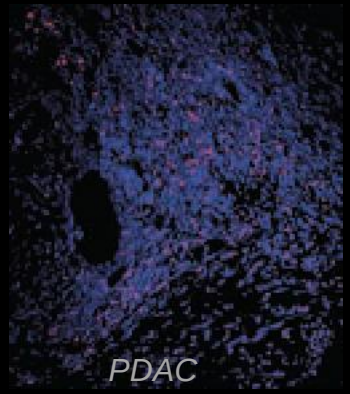
We now know from the work of others that intra-tumoral bacteria may also negatively impact anti-tumor immunity

Bacteria translocate from the gut to pancreatic tumors in KC mice

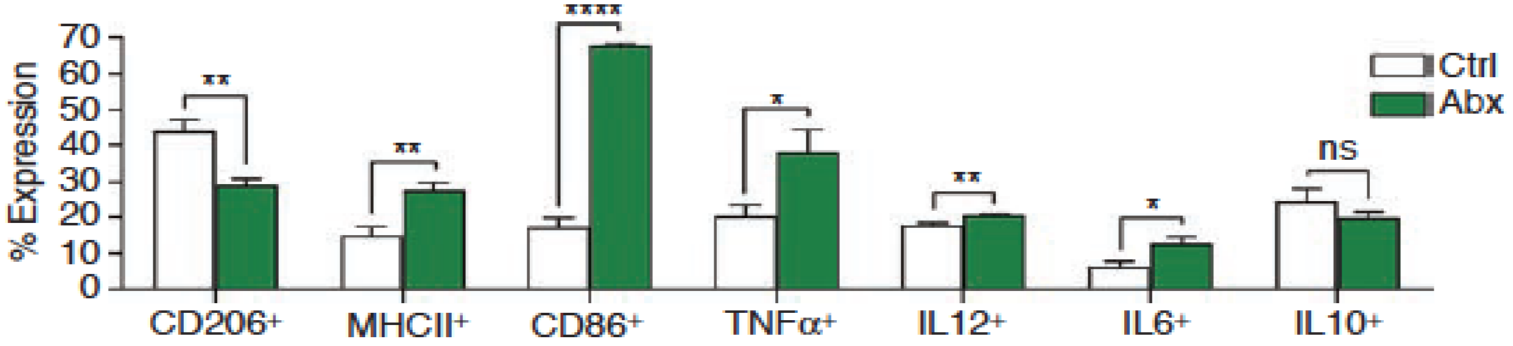




Bacteria are also found in human tumors

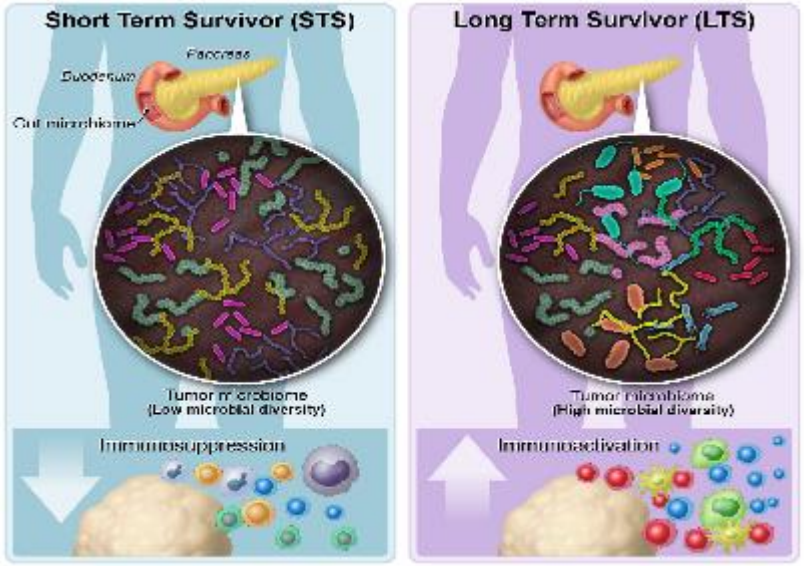


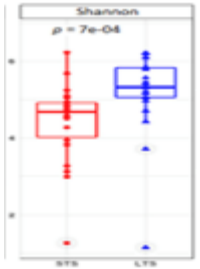
Ablation of bacteria with antibiotics was associated with less immunosuppressive TAMs and enhanced immune function

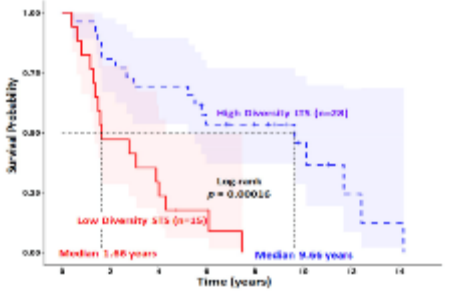


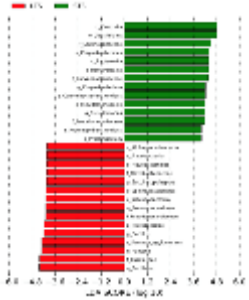
Pushalkar et al, Cancer Discovery 2018

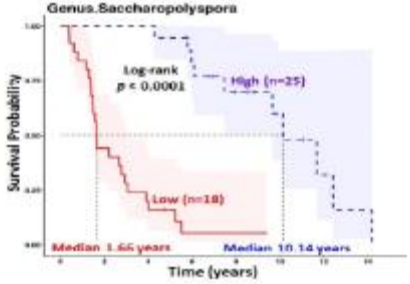
However these intra-tumoral microbes may also may positively influence response, and may be influenced by the gut microbiome

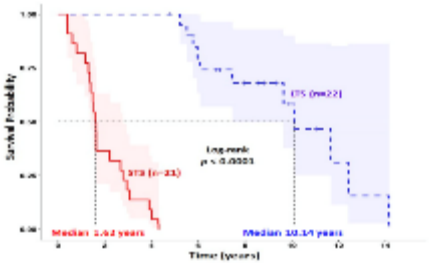


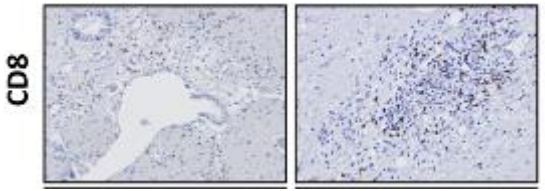




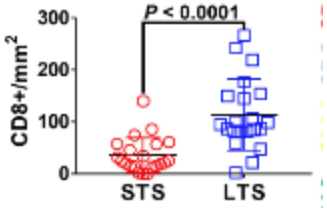








STS LTS



Florencia McAllister MD PhD

Riquelme et al, Cell 2019

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This suggests a “yin and yang” of intra-tumoral microbes, with some contributing to cancer development / resistance, while others help responses

Positive impact on therapy response

Negative impact on therapy response

Potentiation of acute IFNγ responses by bacterial vesicles

Direct engagement of innate immunity

Increased prod
pro-inflammato

Molecular mimicry

Increased expression of checkpoint molecules

Direct recognition of the virus by the TCR in adoptive T cell therapies and vaccines

Decreased MHC Class I expression

Increased production of anti-inflammatory cytokines

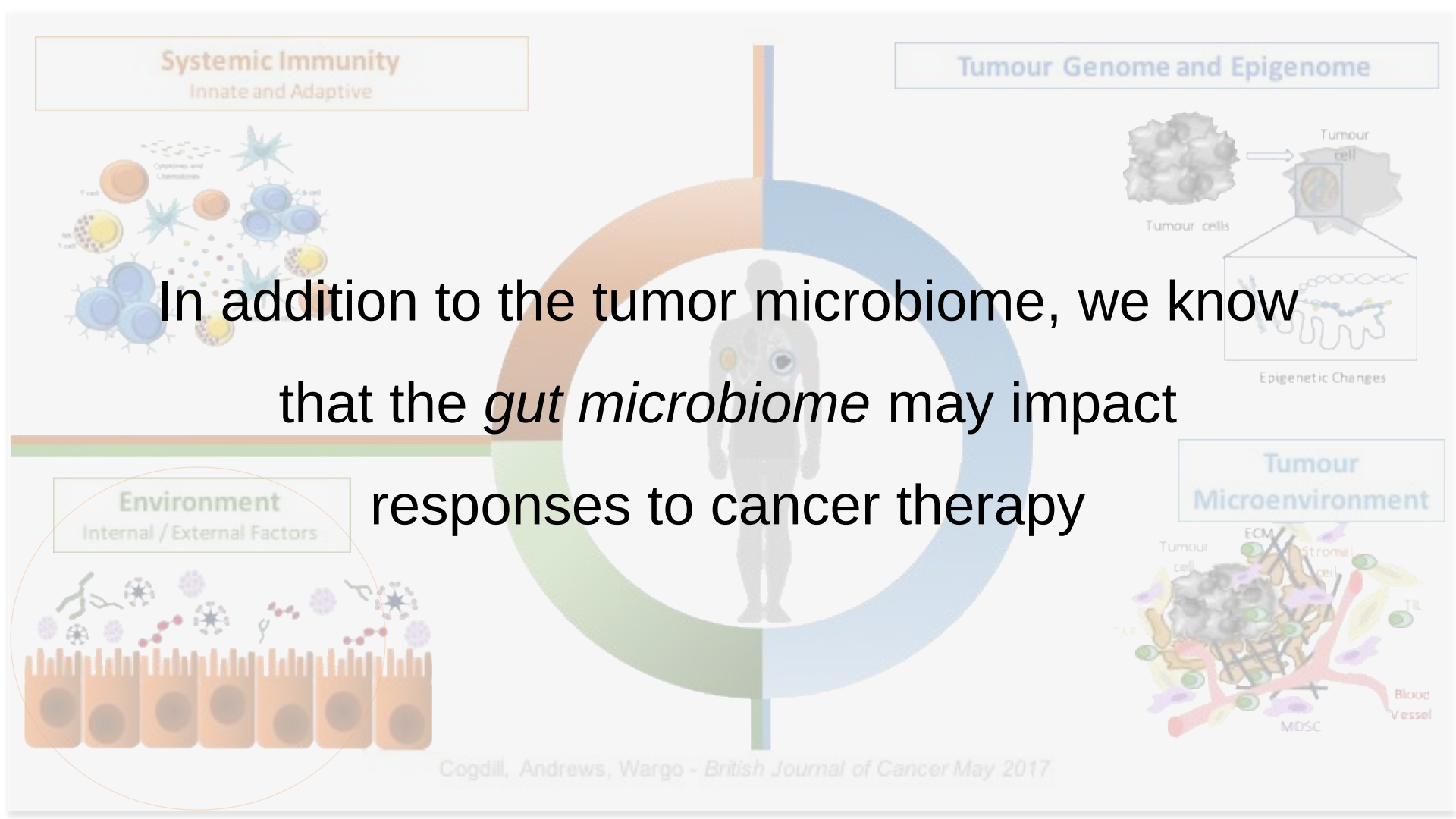
it clonal
n of
lymphocytes

Induction of alternative immune checkpoints (eg TIGIT)

Confer resistance to and potentiate toxicity of chemotherapeutic agents

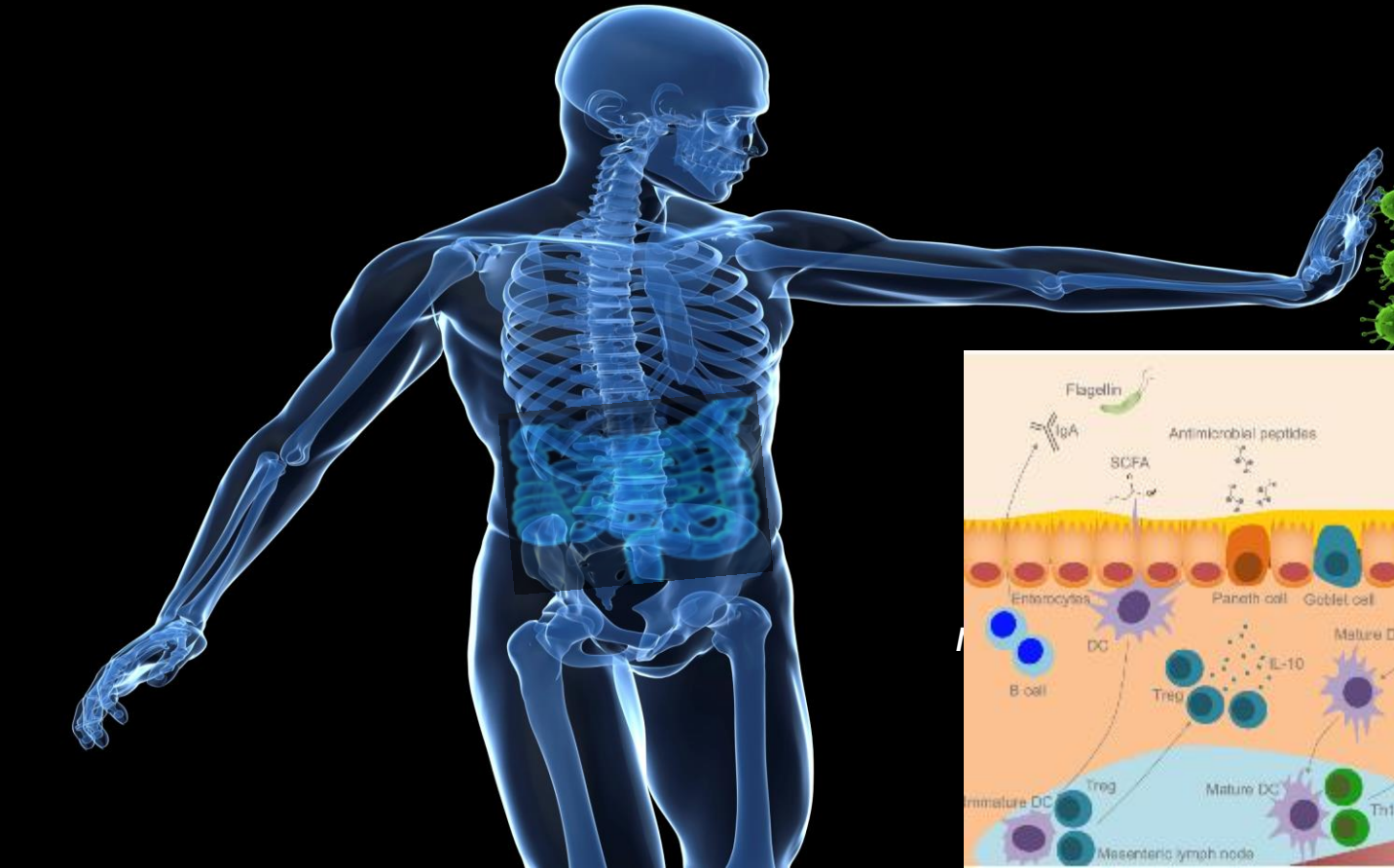
These intra-tumoral microbes may serve as important biomarkers (and potentially even as therapeutic targets)

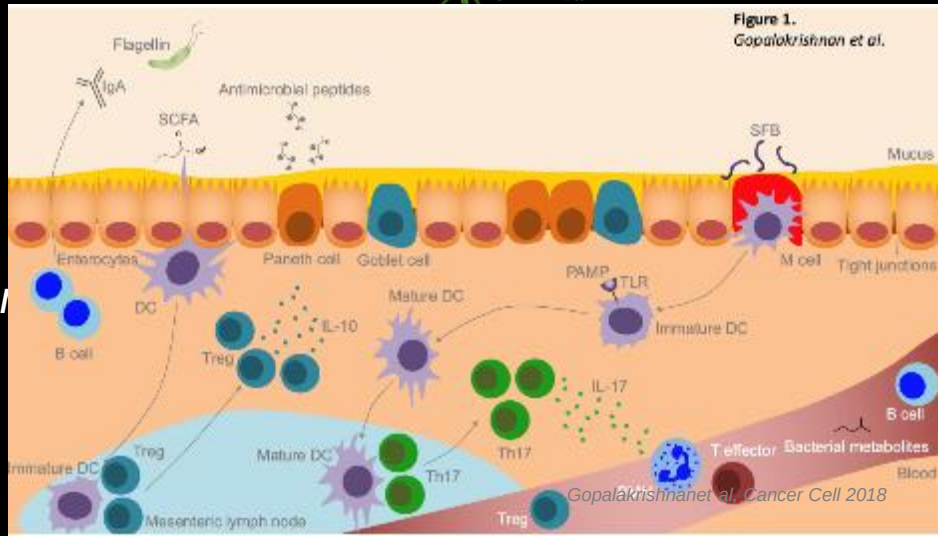
Adapted from Cogdill et al, Trends in Immunology 2018



In addition to the tumor microbiome, we know that the *gut microbiome* may impact responses to cancer therapy

However we knew from the elegant work of others that gut microbes can also modulate overall immunity (as well as anti-tumor immunity)

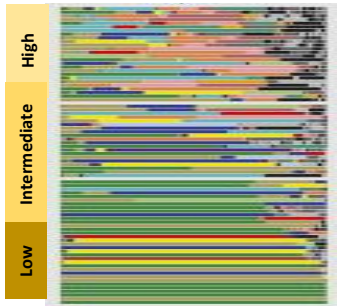


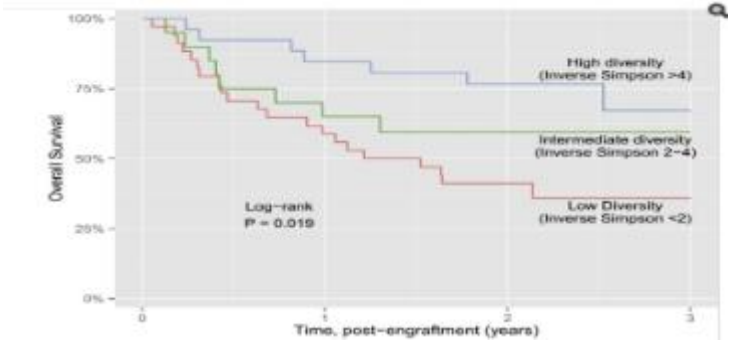


Gopalakrishnan et al. Cancer Cell 2018

Landmark studies were performed several years ago demonstrating that gut microbes could influence response to cancer immunotherapy (and checkpoint blockade in mice)

Diversity of the gut microbiome is associated with differential outcomes in the setting of stem cell transplant in patients with AML



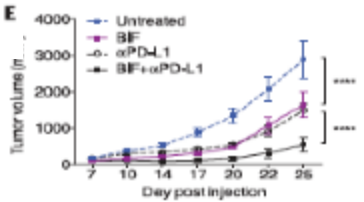


Taur…Pamer Blood 2014

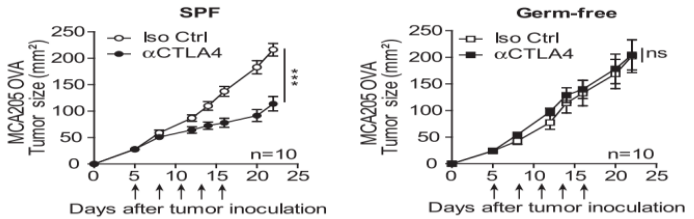
Composition of the gut microbiome is associated with differential responses to checkpoint blockade in murine models

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

Aycket Sivan,[1*] Leticia Corrales,[1*] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[2] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Rana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2]†

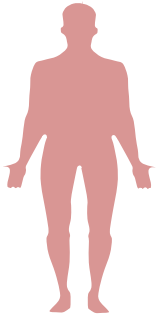


Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

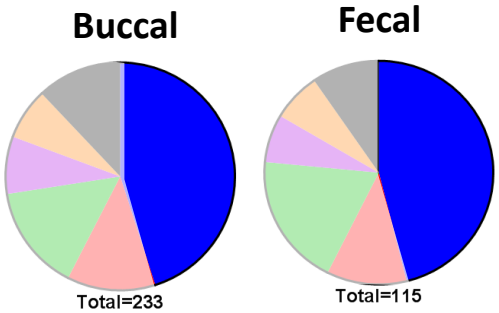


Sivan…Gajewski Science 2015, Vetizou…Zitvogel Science 2015

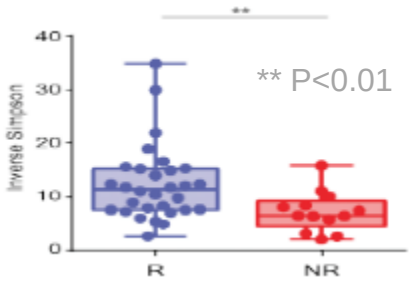
We studied oral and gut (fecal) microbiome in a large cohort of patients with metastatic melanoma going onto systemic therapy

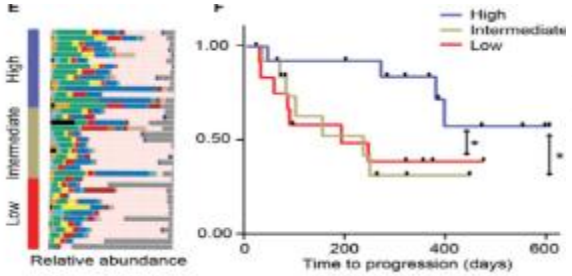


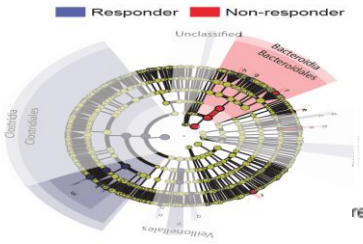
n = 233 patients

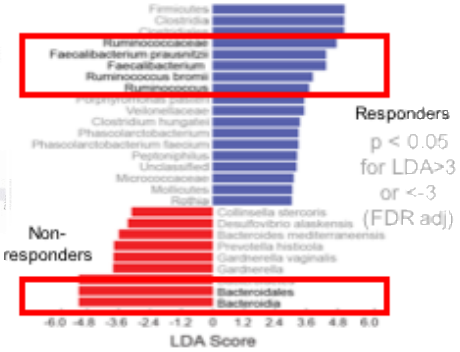


Microbiome sequencing & immune profiling was performed









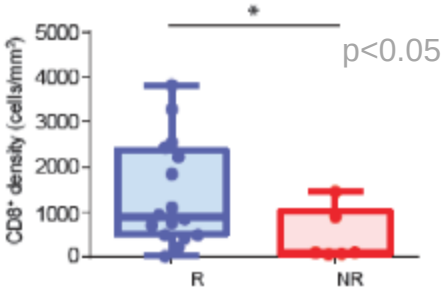
Responders to anti-PD-1 had a higher diversity of gut bacteria associated with prolonged PFS (along with additional compositional differences)

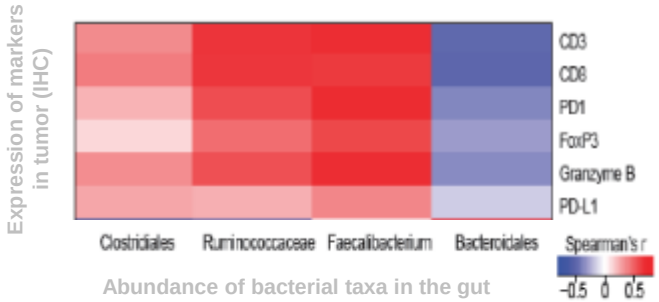
Deepak Gopalakrishnan PhD

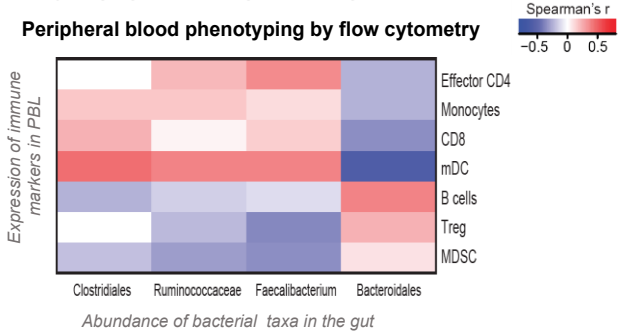
Gopalakrishnan et al, Science 2018

Christine Spencer PhD

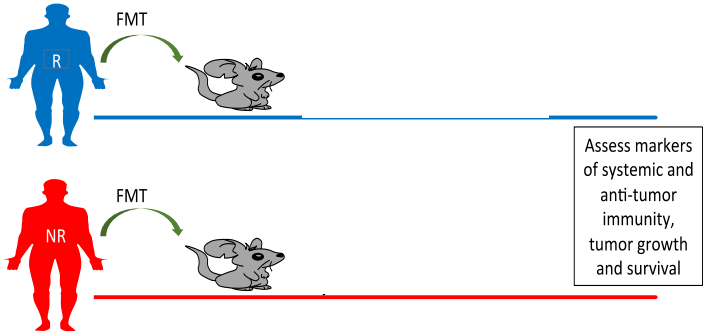
Importantly, “favorable” signatures in the gut microbiome were associated with enhanced immune responses in the tumor microenvironment

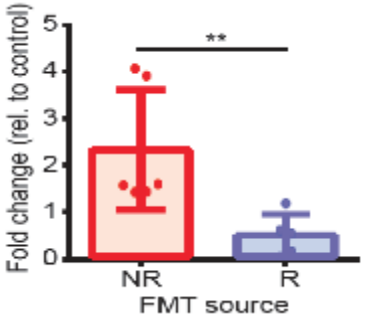


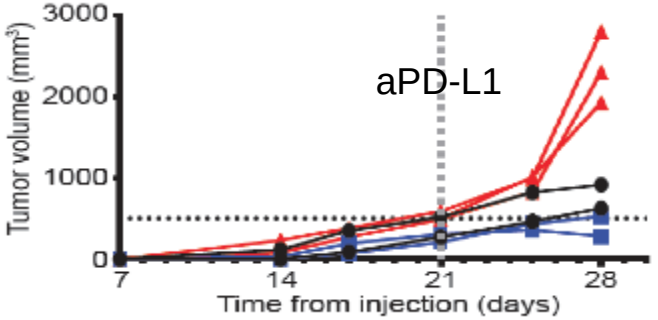




And mechanistic studies in germ free mice showed that fecal transplant could recapitulate the phenotype







Mechanistic insights suggest that this is mediated both at the level of the gut and mesenteric lymph node, and also potentially via metabolites produced by gut microbes potentially mediating distant effects

Luigi Nezi PhD

Gopalakrishnan et al, Science 2018

Alex Cogdill MS (PhD candidate)

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Several important questions arise given this data:

1) *Can the microbiome be used as a biomarker for response?*
2) *Can we modulate the microbiome to enhance response (and / or abrogate toxicity) to immunotherapy?*

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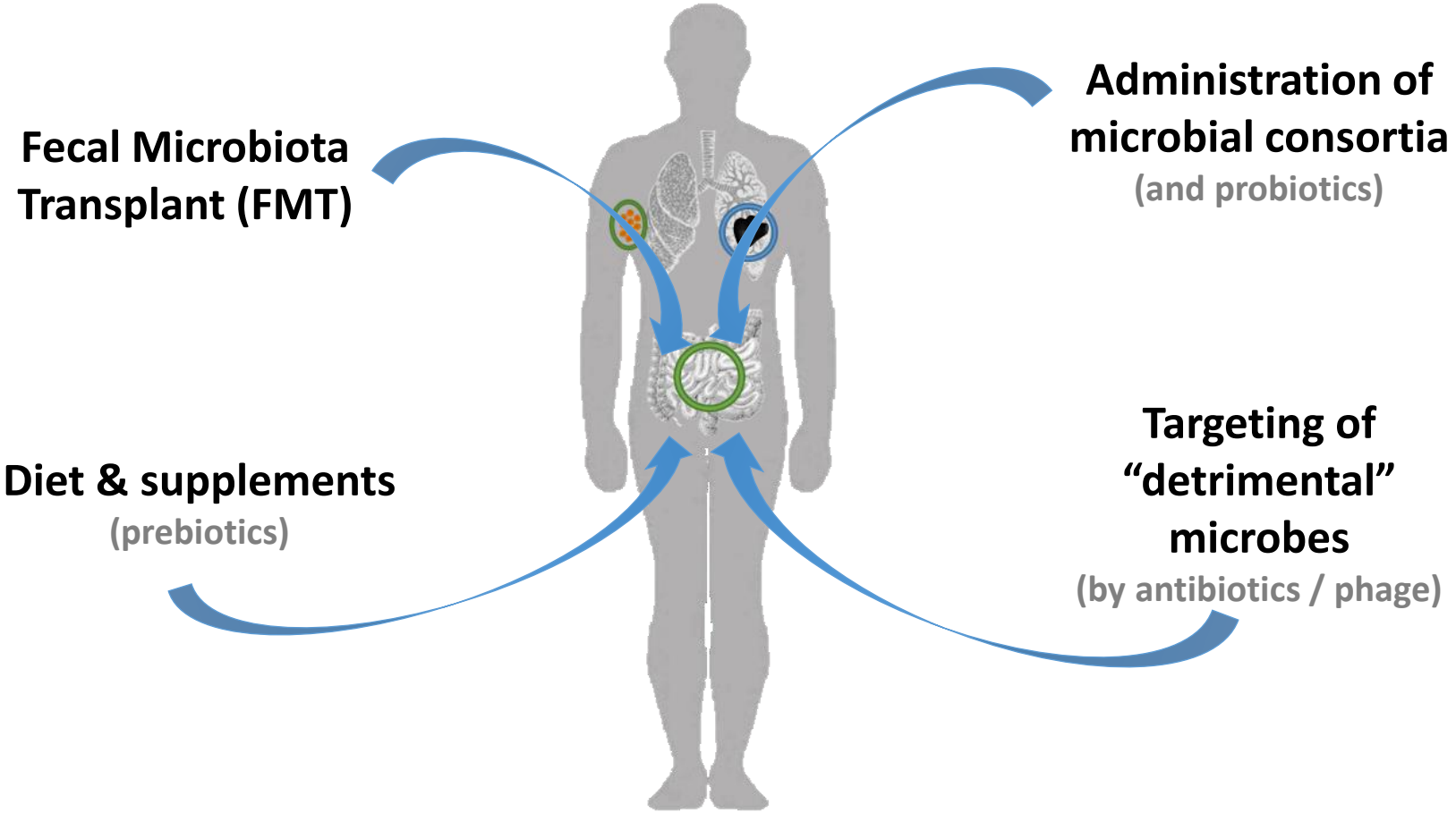
Can we modulate the gut microbiome to enhance responses to immunotherapy?

(and/or to abrogate toxicity)

YES!

Several different strategies may be used to modulate the gut microbiota



We are running a clinical trial using microbiome modulation with a consortia versus with FMT in patients with metastatic melanoma going onto immune checkpoint blockade

Clinical studies are testing whether cancer immunotherapy drugs work better when patients receive a fecal transplant. JEFF MCINTOSH/THE CANADIAN PRESS/AP PHOTO

Fecal transplants could help patients on cancer immunotherapy drugs

By **Jocelyn Kaiser** | Apr. 5, 2019 , 1:45 PM

apy
ebo)

Ongoing

In preparation

Promising data from 2 ongoing clinical trials was presented at AACR Annual Meeting (March 2019)

MDACC PIs: Tawbi & Glitza

Angeles Clinic PI: Hamid

This includes a trial studying use of FMT in patients with metastatic melanoma who progressed on anti-PD-1, with encouraging results (NCT 03353402)

TEL AVIV UNIVERSITY אוניברסיטת תל אביב

Ella Lemelbaum Institute for Immuno-Oncology
Sheba Medical Center

Native microbiota depletion phase: Antibiotics and PEG-based diarrhea solution

↓

FMT - Colonoscopy followed by orally ingested capsules

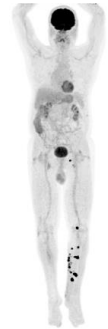
↓

Re-induction of anti-PD-1 therapy (Nivolumab, every 14 days)
+
Maintenance FMTs – orally ingested stool capsules in conjunction to each anti-PD-1 dose

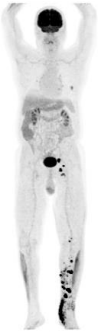
↓

After completion of 6 combined cycles (three months) – treatment continues as anti-PD-1 monotherapy

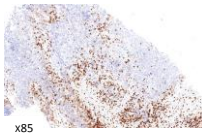
Notably, clinical responses were seen (even in the setting of prior progression on anti-PD-1) and were associated with an increase in immune infiltrate from baseline to post-FMT

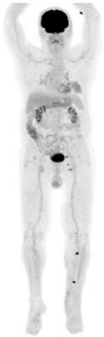


Pre-treatment



Day 67





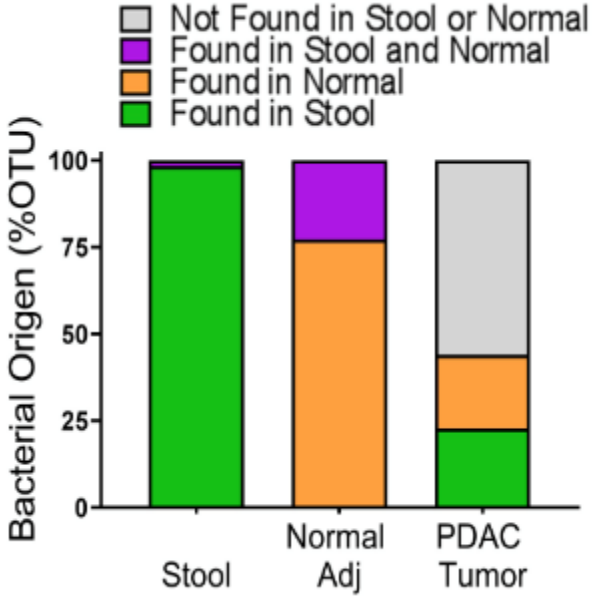
Day 111

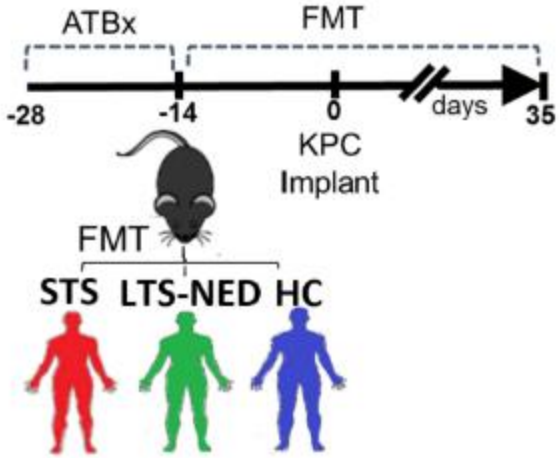
Confidential unpublished data **DO NOT POST****

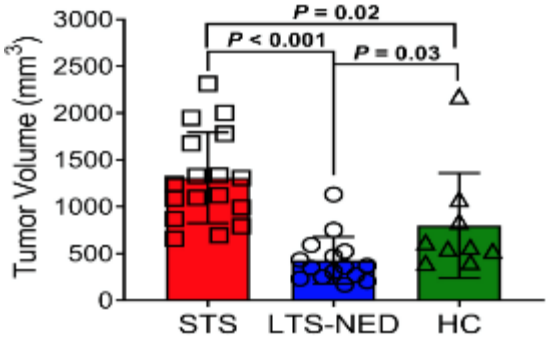
First author: Erez Baruch

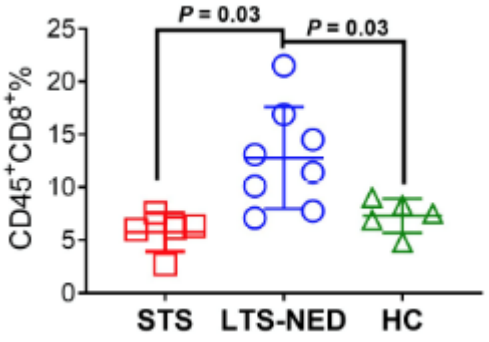
Senior authors: Gal Markel, Ben Boursi

There is “cross-talk” between the gut and tumor microbiome, substantiating the rationale for FMT and other microbiome modulation strategies in other cancers









Florencia McAllister MD PhD

Riquelme et al, Cell 2019

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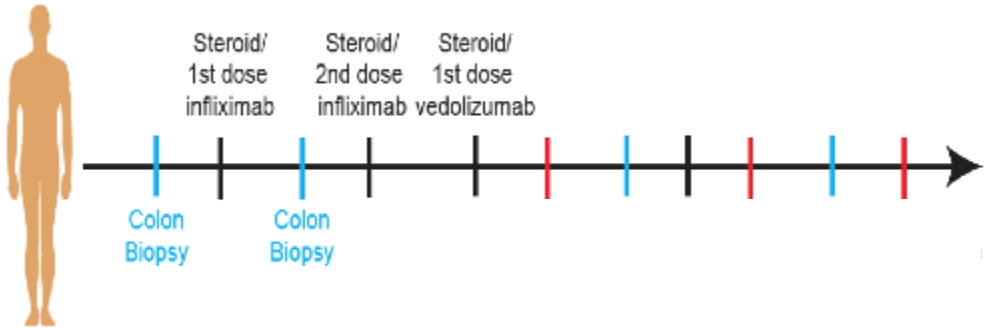
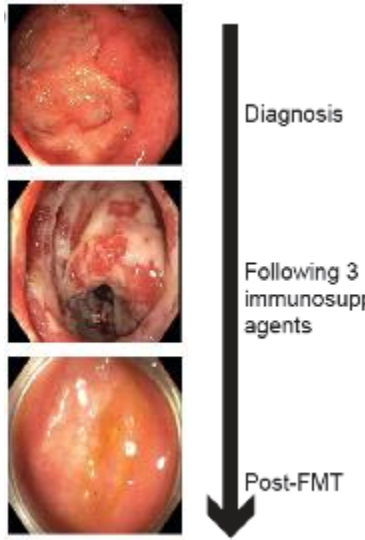
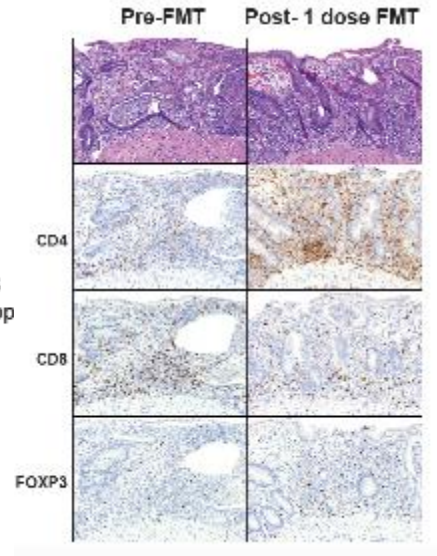
We have evidence that FMT may be helpful in treating immunotherapy toxicity

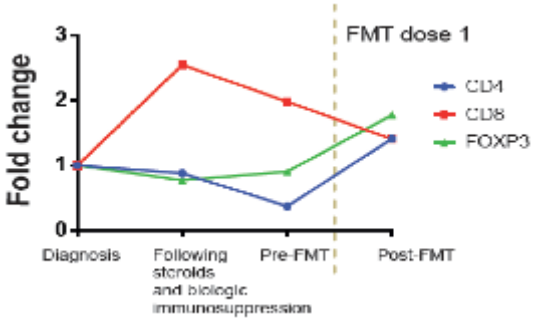


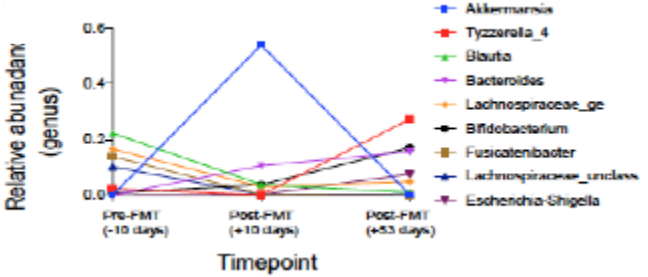
50 yo female with metastatic urothelial cancer was treated with aCTLA-4 + a PD-1 and developed colitis refractory to steroids and aTNF

She was treated with FMT from a healthy donor and had complete resolution of all symptoms









Mimi Wang MD PhD

Wang et al, Nature Medicine 2018

Rob Jenq MD

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant

Zachariah DeFilipp, M.D., Patricia P. Bloom, M.D., Mariam Torres Soto, M.A., Michael K. Mansour, M.D., Ph.D., Mohamad R.A. Sater, Ph.D., Miriam H. Huntley, Ph.D., Sarah Turbett, M.D., Raymond T. Chung, M.D., Yi-Bin Chen, M.D., and Elizabeth L. Hohmann, M.D.

SUMMARY

Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory *Clostridioides difficile* infection and is being actively investigated for other conditions. We describe two patients in whom extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* bacteremia occurred after they had undergone FMT in two independent clinical trials; both cases were linked to the same stool donor by means of genomic sequencing. One of the patients died. Enhanced donor screening to limit the transmission of microorganisms that could lead to adverse infectious events and continued vigilance to define the benefits and risks of FMT across different patient populations are warranted.

Based on published data and on results from upcoming FMT trials, can we identify an optimal consortia of microbes that will enhance responses to immunotherapy?

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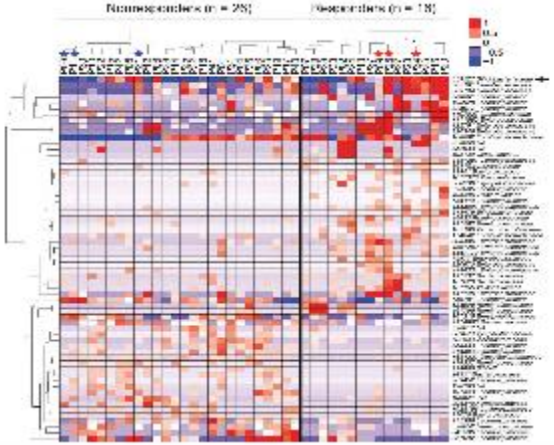
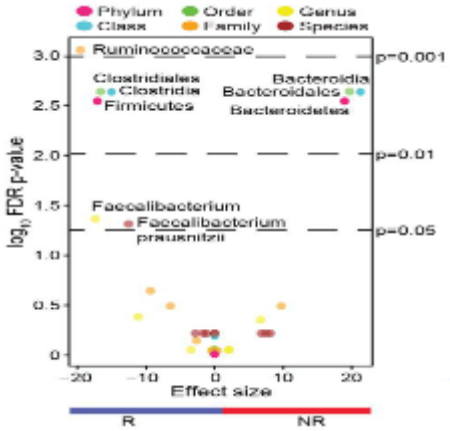
Groups are working hard to identify optimal consortia to enhance immune responses, with promising work in pre-clinical models

The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients



Matson…Gajewski et al, Science 2018

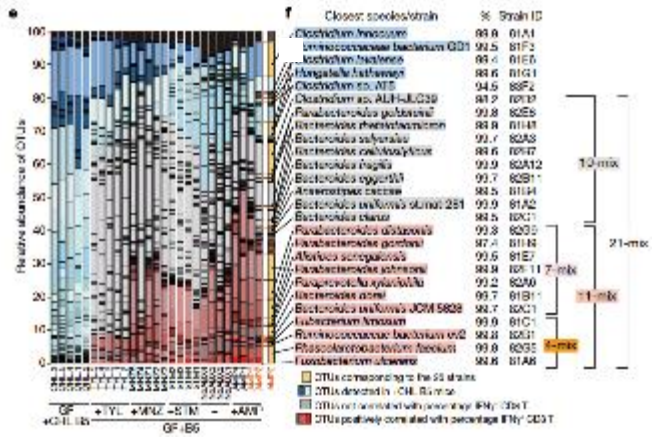
Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients



Gopalakrishnan…Wargo et al, Science 2018

ARTICLE

A defined commensal consortium elicits CD8 T cells and anti-cancer immunity



Tanoue…Honda et al, Nature 2019

Clinical trials are now in progress based on insights gained from these & other studies…

Tumor intrinsic

Tumor extrinsic

RTK

RAS

PI3K

MEK

mTOR

T cell

The Host

Lifestyle factors

Finally, what are some other factors that impact the microbiome that should be considered?

Age (Kugel *CCR* 2018)

Sex (Conforti *Lancet Oncology* 2018, Andrews *SMR* 2018)

BMI (McQuade *Lancet Oncology* 2018, Wang *Nature Medicine* 2018)

Diet

Exercise

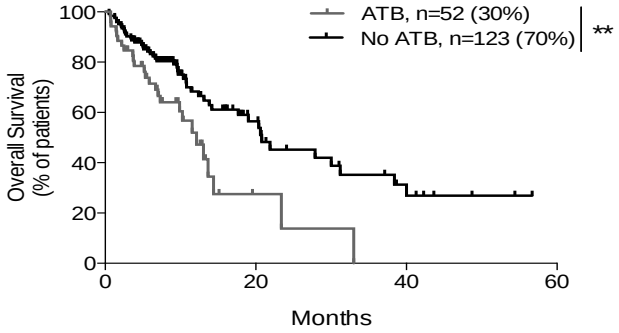
Stress

Sleep

Slide adapted from Jen McQuade MD MDACC

Antibiotics have been shown to negative impact response to checkpoint blockade

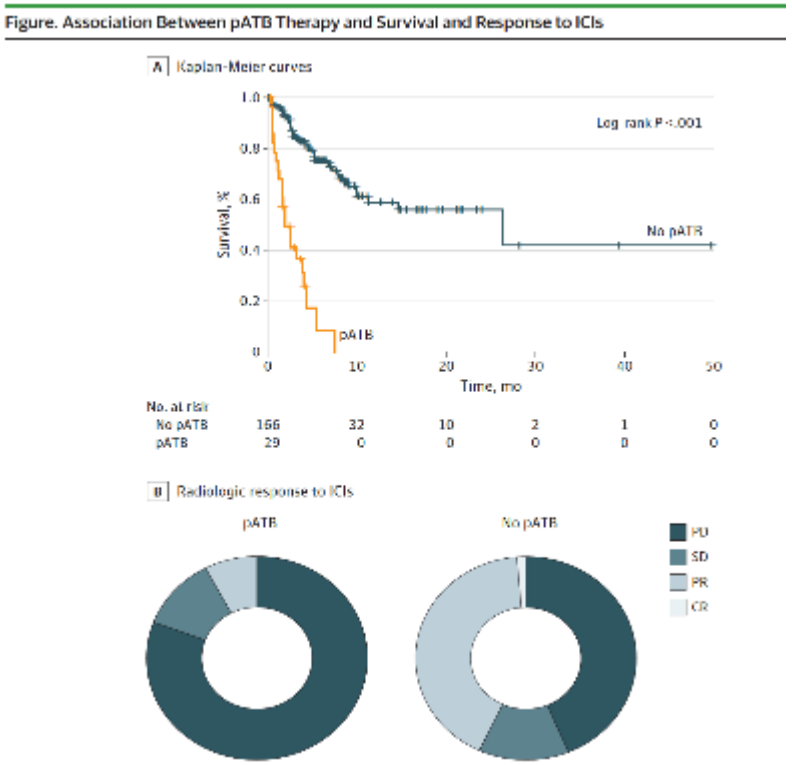
Antibiotics (ATB) taken 2 months before and/or 1 month after the 1st administration of aPD1 Ab or aPD-L1 Ab.



n=175

Median OS ATB: 12.1 months
Median OS No ATB: 20.8 months

Routy et al, Science 2018



Pinato et al, *JAMA Oncology* 2019

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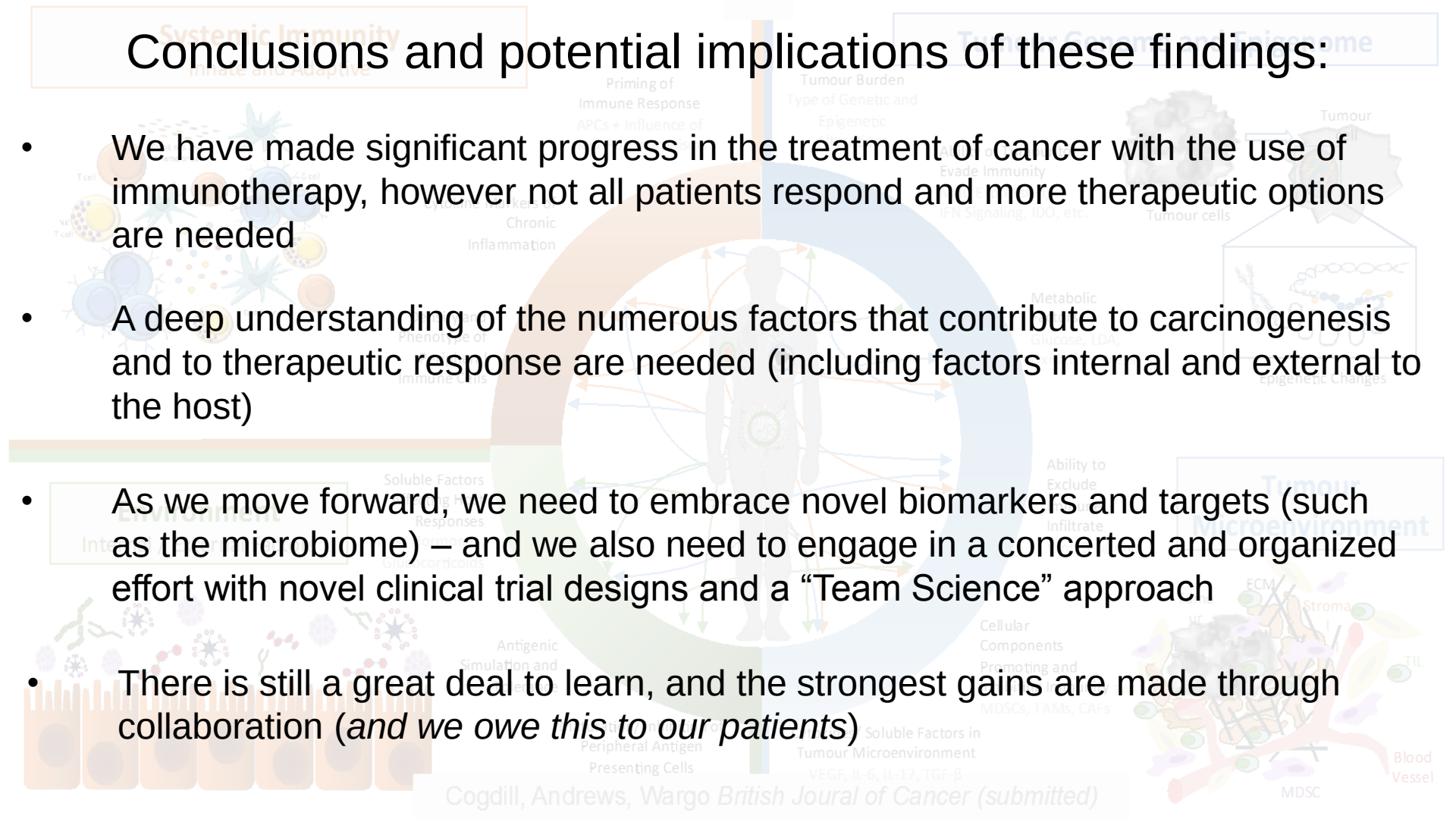
Conclusions and potential implications of these findings:

- We have made significant progress in the treatment of cancer with the use of immunotherapy, however not all patients respond and more therapeutic options are needed
- A deep understanding of the numerous factors that contribute to carcinogenesis and to therapeutic response are needed (including factors internal and external to the host)
- As we move forward, we need to embrace novel biomarkers and targets (such as the microbiome) – and we also need to engage in a concerted and organized effort with novel clinical trial designs and a “Team Science” approach
- There is still a great deal to learn, and the strongest gains are made through collaboration (*and we owe this to our patients*)



Cogdill, Andrews, Wargo *British Journal of Cancer (submitted)*

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Conference organizers, faculty / staff, attendees

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- **Zachary A. Cooper PhD (alumni)**
- **Alexandria P. Cogdill MS (PhD candidate)**
- Robert Szczepaniak-Sloane BS (PhD candidate)
- Rohit Thakur PhD
- Wei-Shen Chen, MD PhD
- Sangeetha Reddy MD PhD
- Liz Burton MBA

Other key collaborators

- **Laurence Zitvogel MD PhD, Giorgio Trinchieri PhD**
- **Ravid Straussman MD PhD**

MDACC Collaborators

- **Jim Allison PhD, Pam Sharma MD PhD**
- **Michael Davies MD PhD, Jeff Gershenwald MD**
- **Hussein Tawbi MD PhD, Bella Glitza MD**
- **Patrick Hwu MD, other Melanoma Med Onc Facutly / Staff**
- Jeff Lee MD, Merrick Ross MD, other Surg Onc Faculty / Staff
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- Robert Jenq MD PhD, other MDACC faculty / staff

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Baylor CMMR

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