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MD Anderson Cancer Center
Making Cancer History®

Microbiome, Lifestyle, and Melanoma

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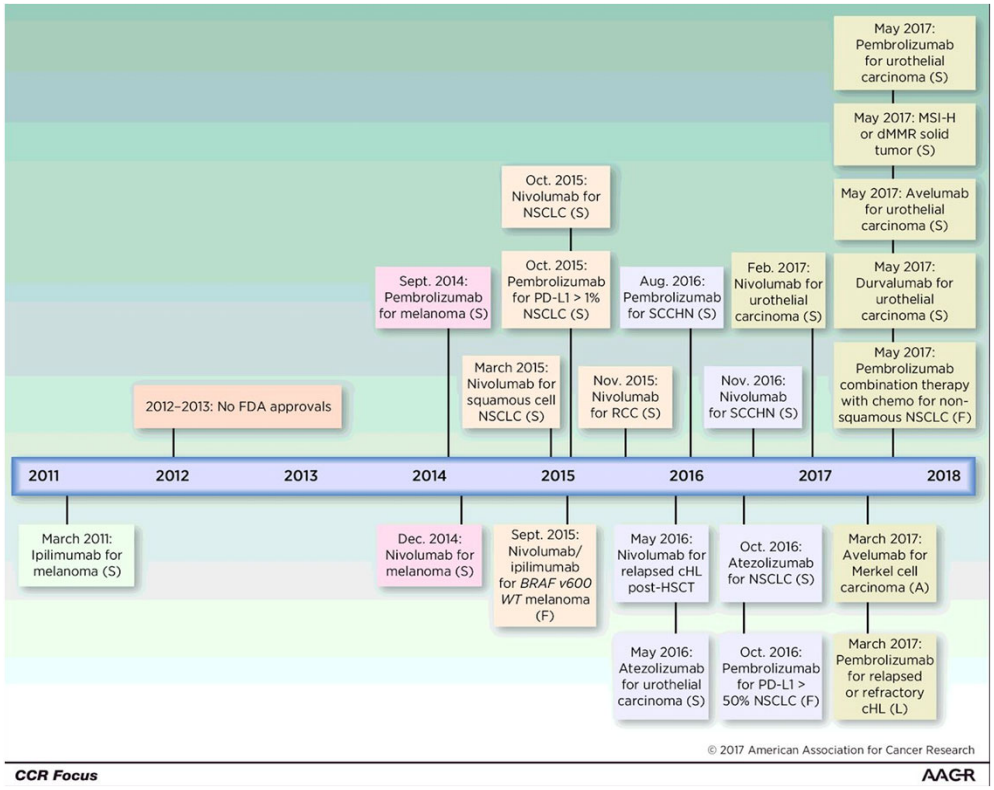
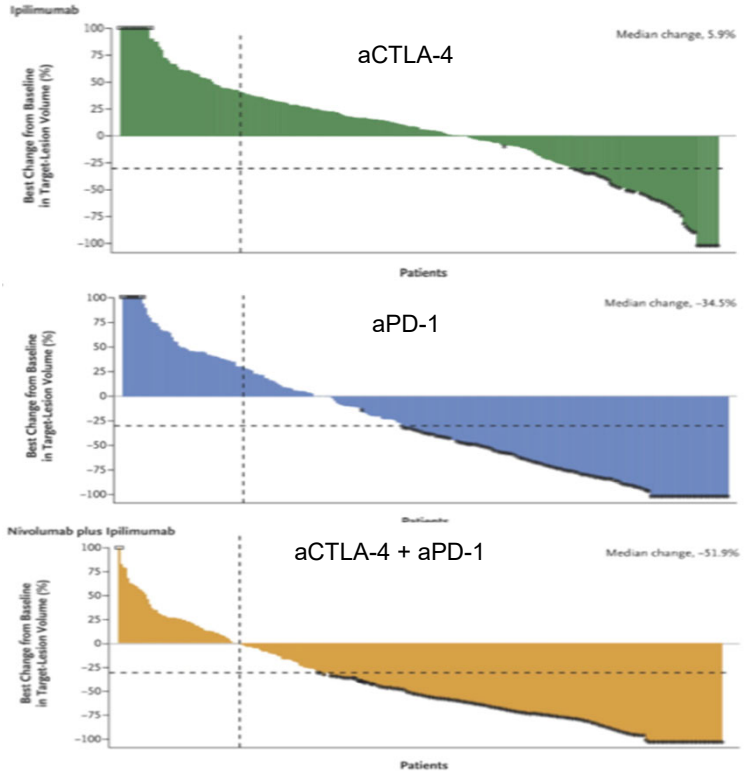
UT, MD Anderson Cancer Center

The Art and Science of Managing the New Melanoma Landscape
The University of Texas MD Anderson Cancer Center

October 17, 2020

We have made tremendous advances in cancer treatment with the use of immunotherapy, but not all patients benefit and toxicity can be an issue

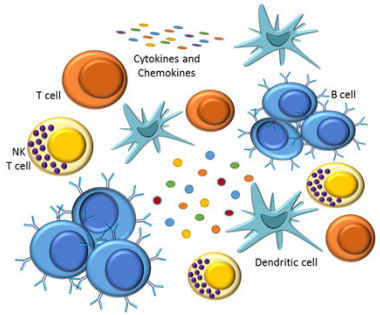


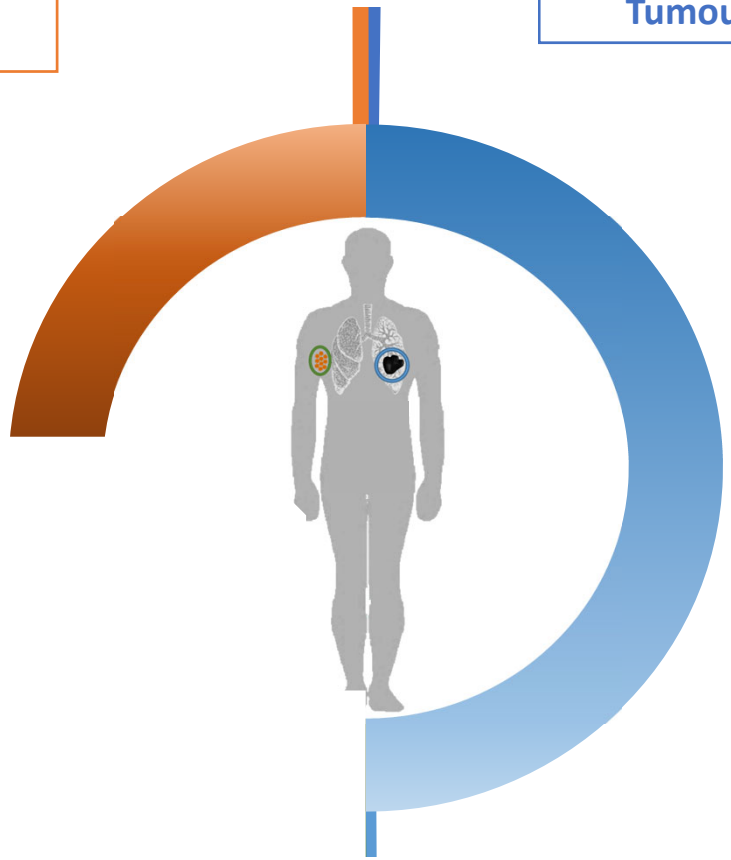


There is a critical need to better understand who will benefit from these agents, as well as proper timing, sequence, and combination regimens

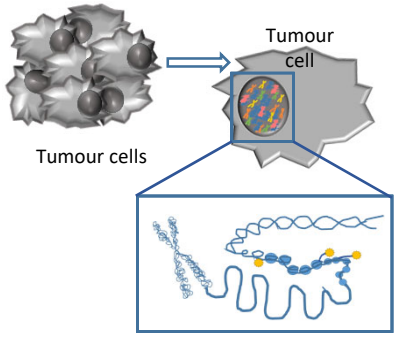
Responses are dependent on factors shaping tumor growth and immunity

Systemic Immunity
Innate and Adaptive

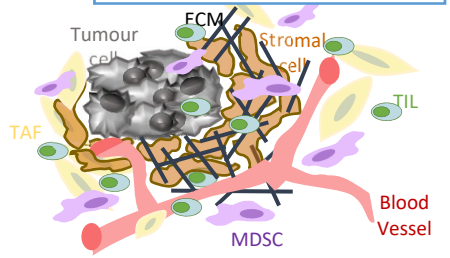




Tumour Genome and Epigenome



Tumour Microenvironment



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

Why should we study the microbiome?

There are more genes in the human microbiome than there are stars in the galaxy

There is an increasing appreciation of the role of the microbiome in health and disease

DOI: 10.1093/jnci/djs003
Advance Access publication on January 23, 2012.
Published by Oxford University Press 2012.

BRIEF COMMUNICATION

Fifteen-Year Effects of *Helicobacter pylori*, Garlic, and Vitamin Treatments on Gastric Cancer Incidence and Mortality

Jun-Ling Ma, Lian Zhang, Linda M. Brown, Ji-You Li, ...
Wei-Dong Liu, Yuanreng Hu, ...
David Pee, William ...

New written informed consents were obtained for the extended follow-up phase from May 2, 2003, to August 1, 2010. Data from 3365 eligible ...

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Immunoproliferative Small Intestinal Disease Associated with *Campylobacter jejuni*

Report

LETTER

Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth

doi:10.1038/nature11465

Sergei I. Grivennikov[1*], Kepeng Wang[1,2*], Daniel Mucida[3,4], C. Andrew Stewart[5], Bernd Schnabl[6], Dominik Jauch[1], Koji Taniguchi[1,7], Guann-Yi Yu[1], Christoph H. Österreicher[1,8], Kenneth E. Hung[9], Christian Datz[10], Ying Feng[11], Eric R. Fearon[11], Mohamed Oukka[12], Lino Tessarollo[13], Vincenzo Coppola[14], Felix Yarovinsky[15], Hilde Cheroutre[3], Lars Eckmann[6], Giorgio Trinchieri[5] & Michael Karin[1]

Proinflammatory CD4$^+$CD45RB^{hi} Lymphocytes Promo... and Intestinal Carcinogenesis in *Apc*$^{Min/+}$ Mice

... Zhongming Ge,[1] Prashant R. Namb...

MyD88 inhibition amplifies de... cell capacity to promote pancreatic carcinogenesis via Th2 cells

Atsuo Ochi,[1] Andrew H. Nguyen,[2] Andrea S. Bedrosian,[1] Harry M. Mushlin,[2] Saman Zarbakhsh,[1] Rocky Barilla,[1] Constantinos P. Zambirinis,[1] Nina C. Fallon,[1] Adeel Rehman,[1] Yuliya Pylayeva-Gupta,[3] Sana Badar,[1] Cristina H. Hajdu,[4] Alan B. Frey,[2] Dafna Bar-Sagi,[3] and George Miller[1,2]

Cell PRESS

Promotion of Hepatocellular Carcinoma by the Intestinal Microbiota and TLR4

Dianne H. Dapito,[1,2,10] Ali Mencin,[3,10] Geum-Youn Gwak,[1,7,10] Jean-Philippe Pradere,[1,10] Myoung-Kuk Jang,[1] ... Adebowale Adeyemi,[3] Ramon Bataller,[8] ... Hossein Khiabanian,[4,5] ... Raul Rabadan,[4,5]

Grace Y. Chen,[1,3] Michael H. Shaw,[2,3] Gloria Redondo,[2,3] and Gabriel Núñez[2,3]
Division of Hematology and Oncology, Department ...
Cancer Center, Univ...

Intestinal Neoplasia in the *Apc*^{Min} Mouse: Independence from the Microbial and Natural Killer (*beige* Locus) Status[1]

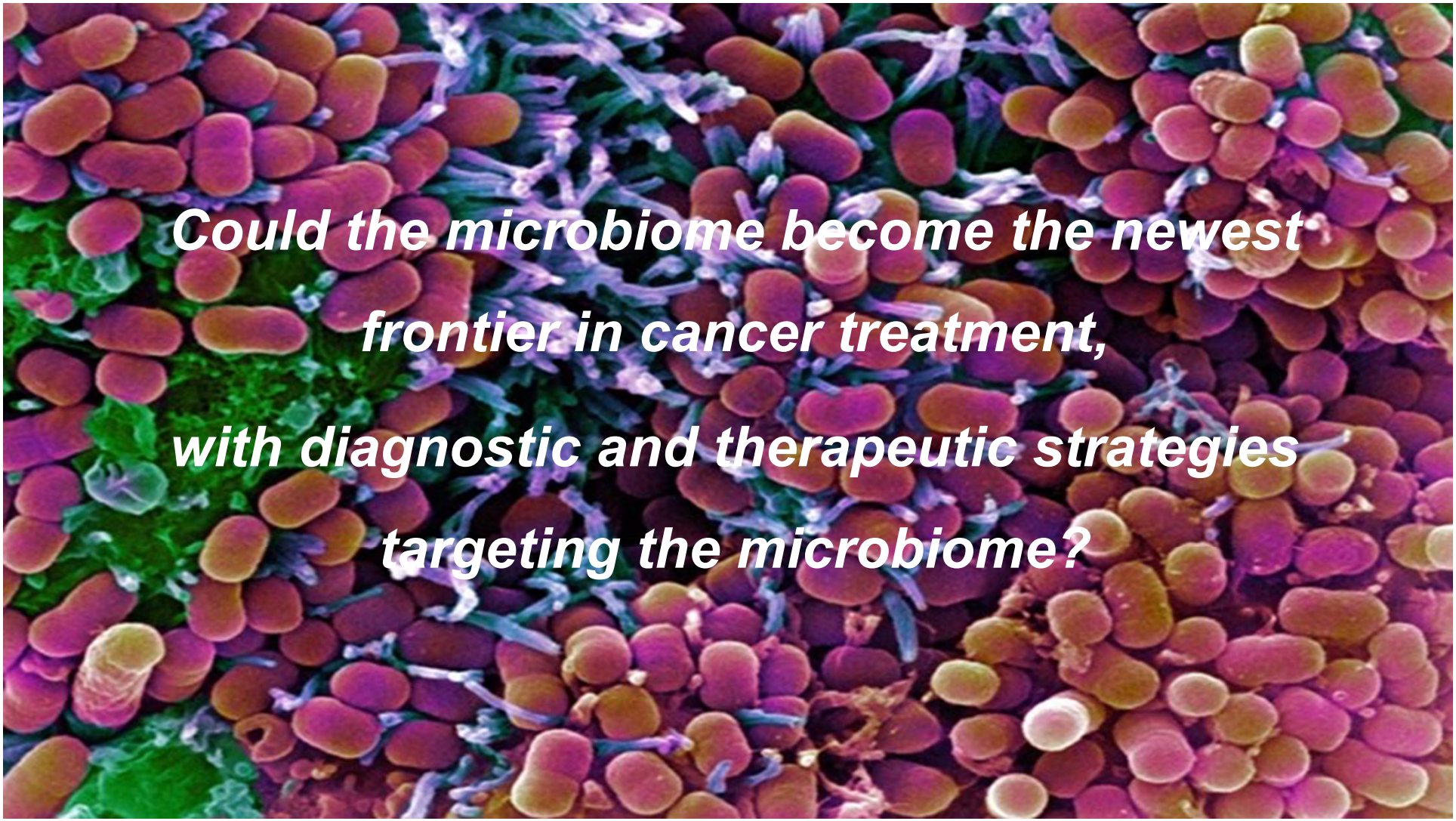
William F. Dove,[2] Linda Clipson, Karen A. Gould,[3] Cindy Luongo,[4] David J. Marshall, Amy R. Moser,[5] Michael A. Newton, and Russell F. Jacoby

McArdle Laboratory for Cancer Research [L. C., A. R. M.] and Laboratory of Genetics [W. F. D., K. A. G., C. L.], University of Wisconsin, Madison, Wisconsin 53706; Department of Medicine, Division of Gastroenterology [D. J. M., R. F. J.] and Department of Biostatistics, Comprehensive Cancer Center [M. A. N.], University of Wisconsin, Madison, Wisconsin 53792

Chronic Active Hepatitis and Associated Liver Tumors in Mice Caused by a Persistent Bacterial Infection With a Novel *Helicobacter* Species

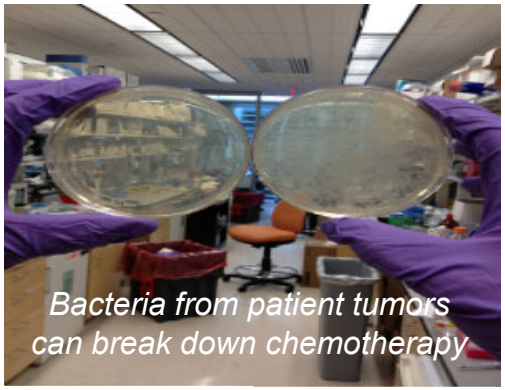
Jerrold M. Ward, James G. Fox, Miriam R. Anver, Diana C. Haines, Cathi V. George, Michael J. Collins, Jr., Peter L. Gorelick, Kunio Nagashima, Matthew A. Gonda, Raymond V. Gilden, Joseph G. Tully, Robert J. Russell, Raoul E. Benveniste, Bruce J. Paster, Floyd E. Dewhirst, John C. Donovan, Lucy M. Anderson, Jerry M. Rice*

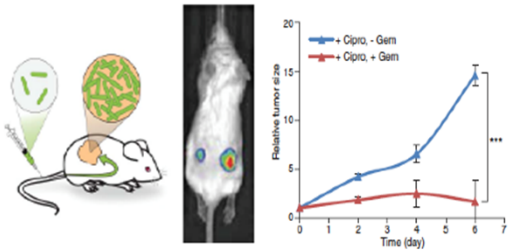
There is a significant microbial contribution to the total makeup of our cellular composition as well as our DNA that dramatically influences our physiology


Could the microbiome become the newest
frontier in cancer treatment,
with diagnostic and therapeutic strategies
targeting the microbiome?

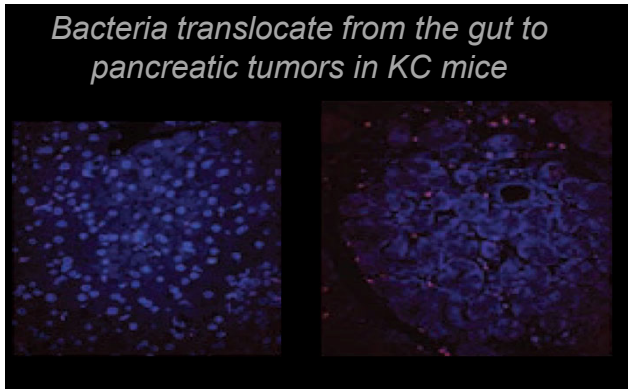
Microbes have been identified in human tumors for over a century, and more than 16% of human cancers are currently felt to be related to microbes

Bacteria within pancreatic tumors can negatively impact responses to chemotherapy and immunotherapy

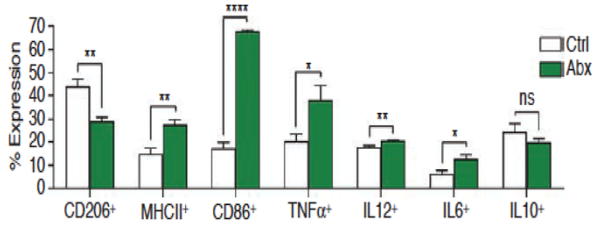




Geller et al, Science 2017

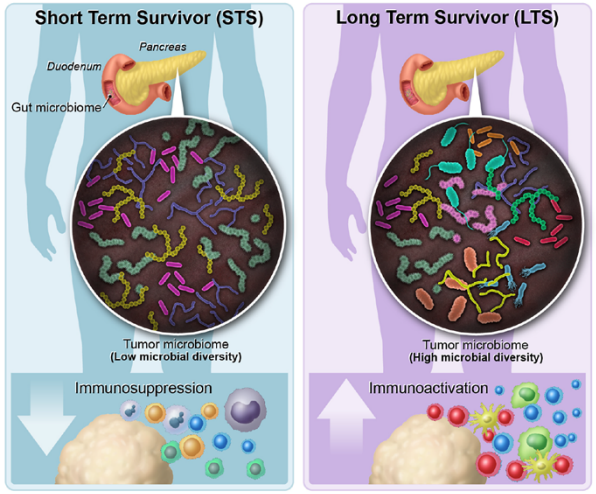


Ablation of bacteria with antibiotics was associated with enhanced immune function



Pushulkar et al, Cancer Discovery 2018

However not all microbes are bad, as the presence of some microbes within tumors is associated with better long-term outcomes



Riquelme et al, Cell 2019

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

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

Decreased MHC Class I expression

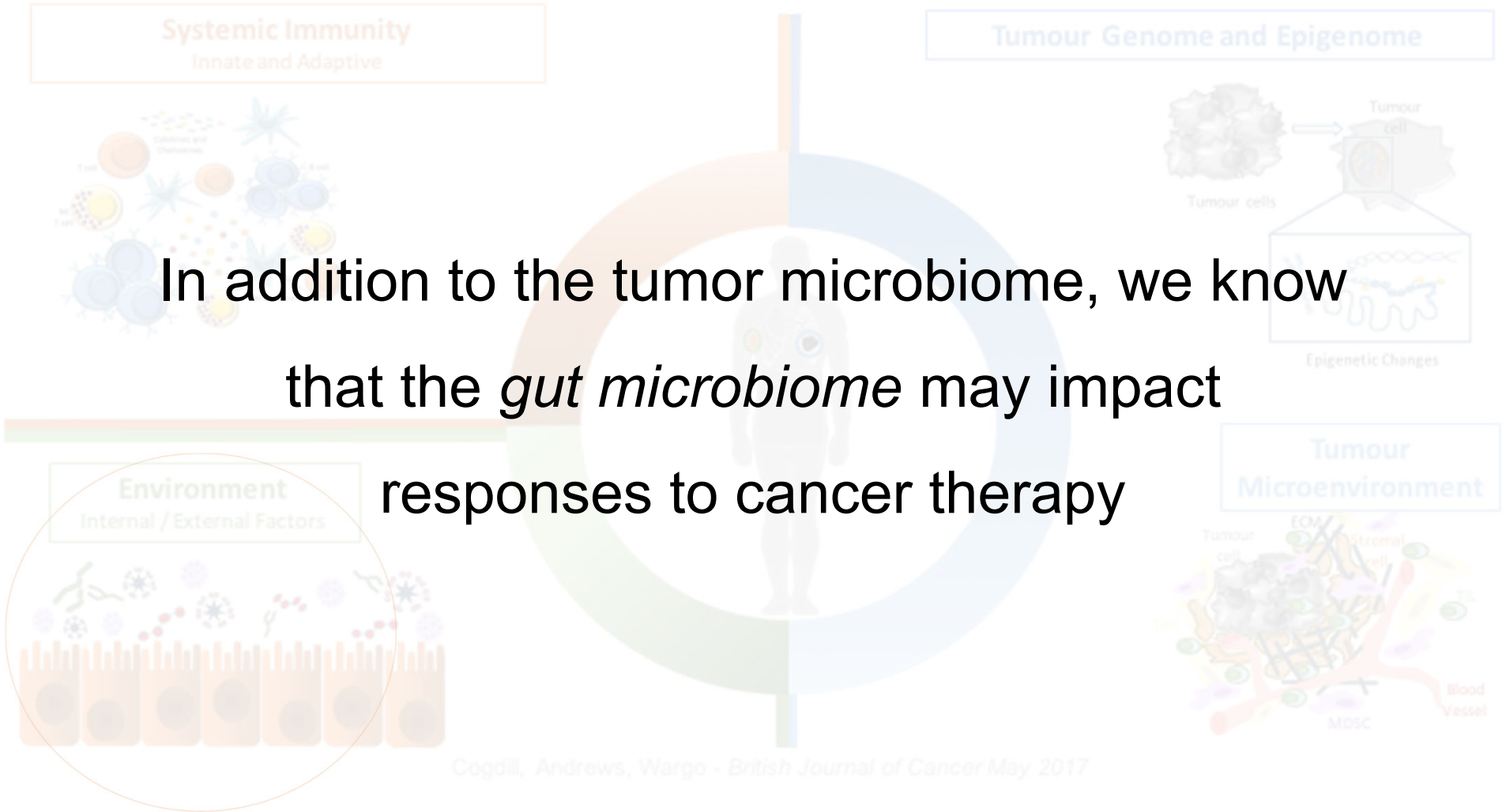
Increased production of anti-inflammatory cytokines

it clonal
n of
lymphocytes

Induction of alternative immune checkpoints (eg TIGIT)

Confer resistance to and potentiate toxicity of chemotherapeutic agents

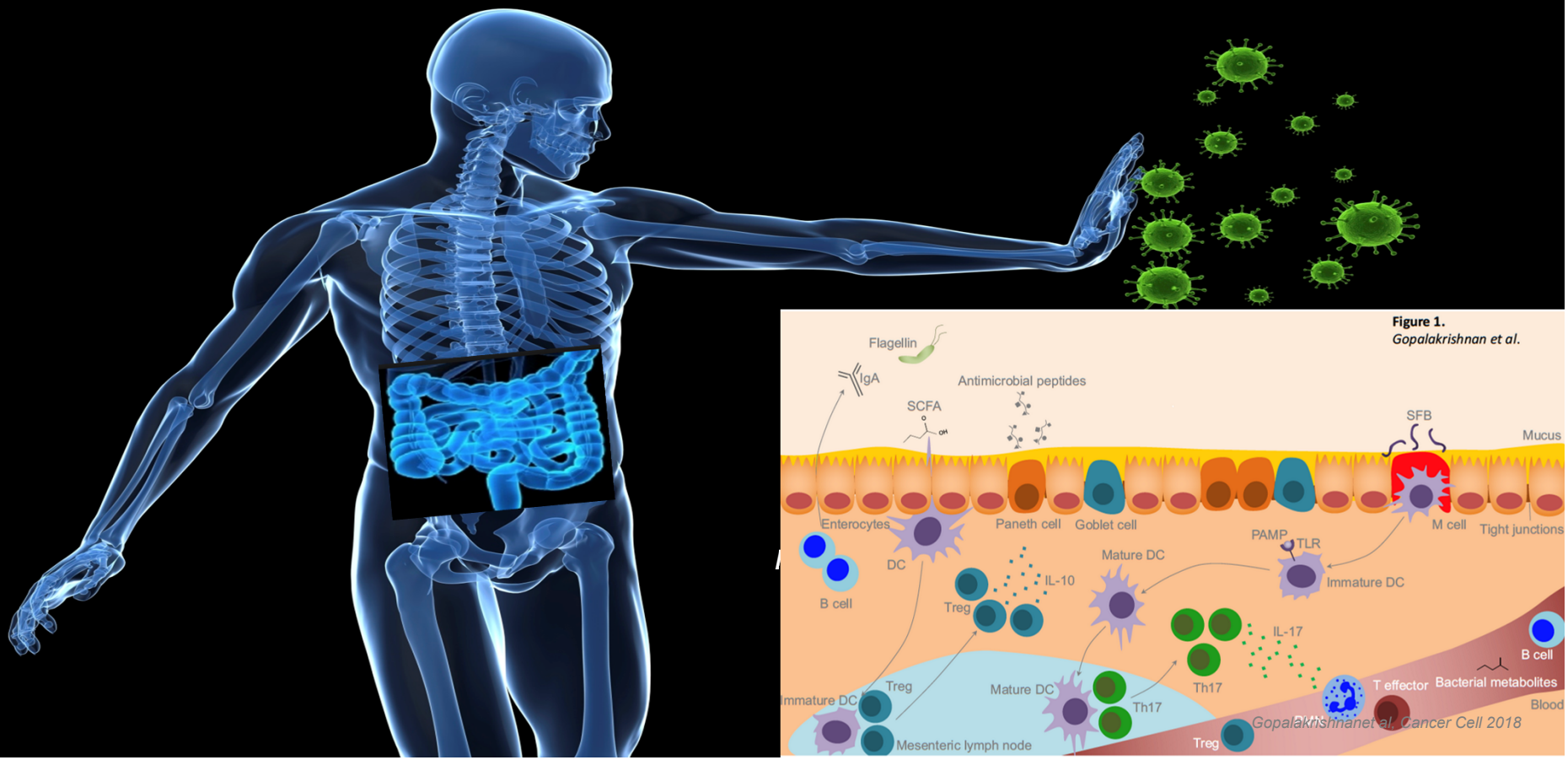
Adapted from Cogdill et al, Trends in Immunology 2018



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

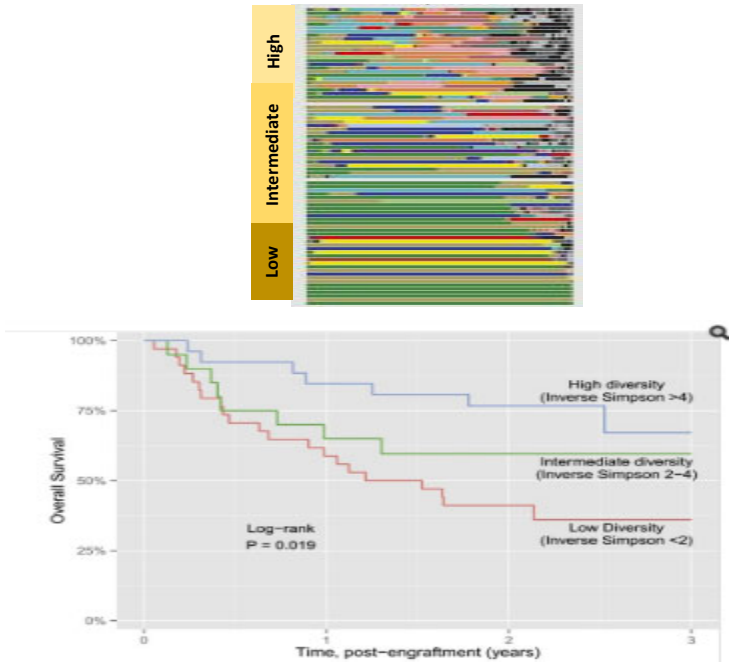
Cogdill, Andrews, Wargo - *British Journal of Cancer* May 2017

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



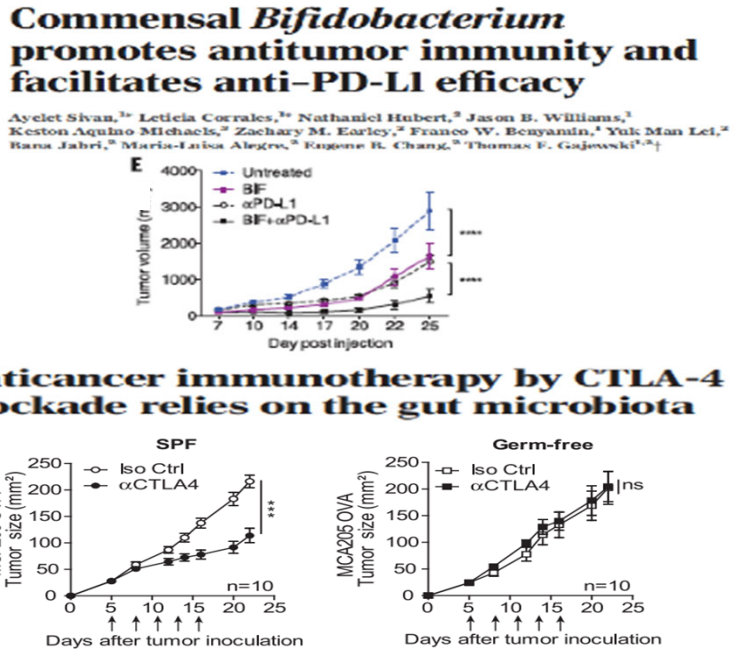
Landmark studies were performed several years ago demonstrating that gut microbes could influence response to cancer immunotherapy (and checkpoint blockade in mice)

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



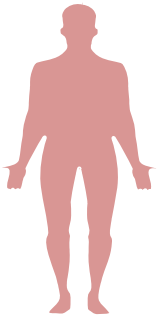
Taur…Pamer Blood 2014

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

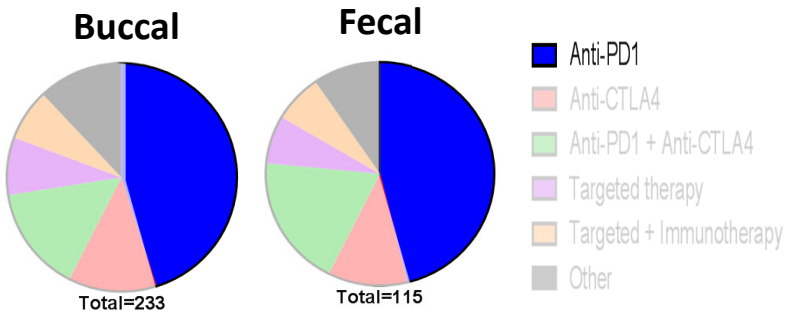


Sivan…Gajewski Science 2015, Vetizou…Zitvogel Science 2015

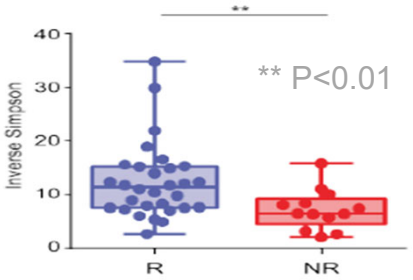
We studied oral and gut (fecal) microbiome in a large cohort of patients with metastatic melanoma going onto systemic therapy

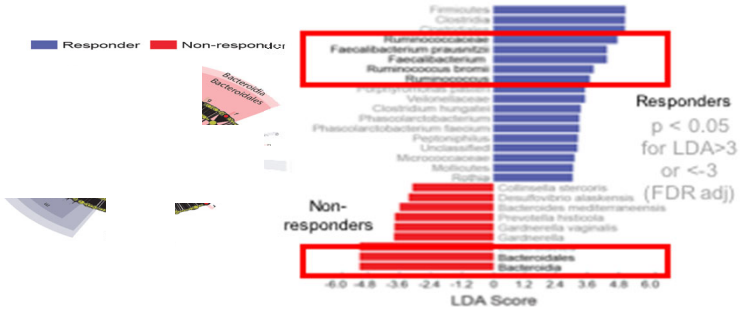


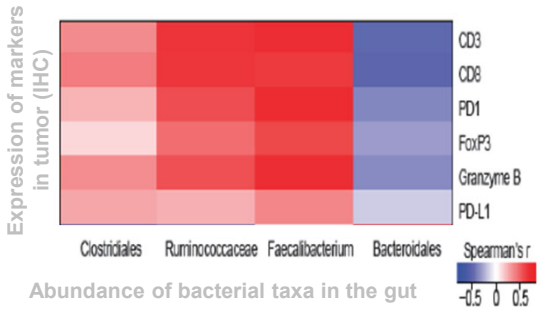
n = 233 patients



Microbiome sequencing & immune profiling was performed







Responders to anti-PD-1 had a higher diversity of gut bacteria along with additional compositional differences, which was associated with more favorable immune profiles in the tumor microenvironment

Deepak Gopalakrishnan PhD

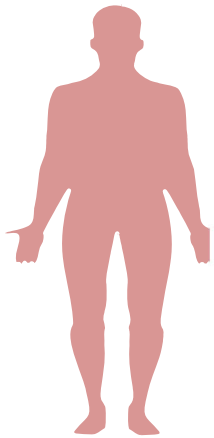
Gopalakrishnan et al, Science 2018

Chris Spencer PhD

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

YES!

Numerous studies are now underway incorporating modulation of the gut microbiome in combination with response to 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

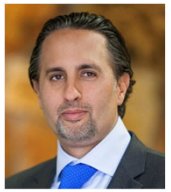
By **Jocelyn Kaiser** | Apr. 5, 2019 , 1:45 PM

apy
ebo)

Ongoing

In preparation

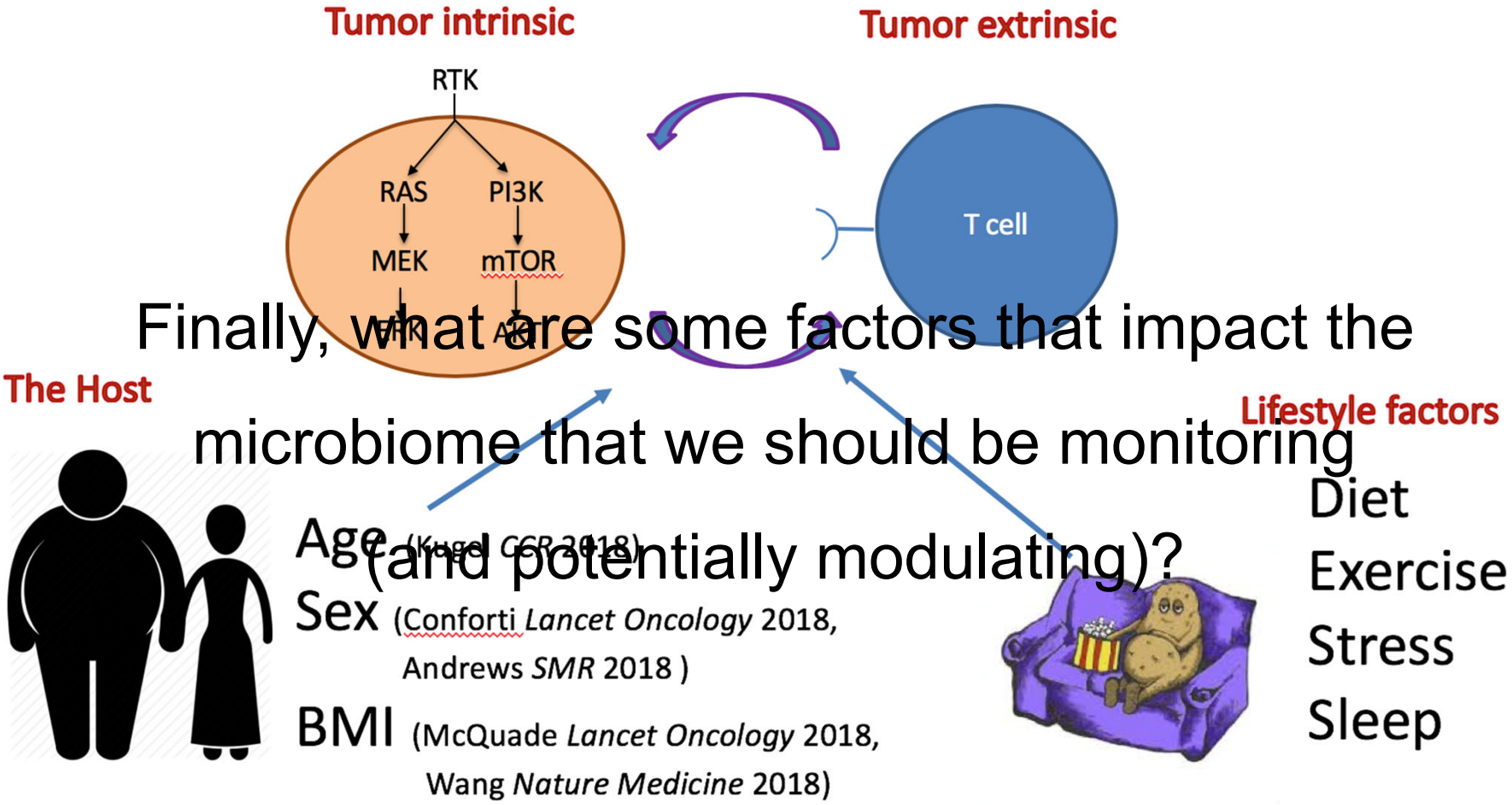
Promising data from 2 ongoing clinical trials was presented at AACR Annual Meeting (March 2019)



MDACC PIs: Tawbi & Glitza

Angeles Clinic PI: Hamid

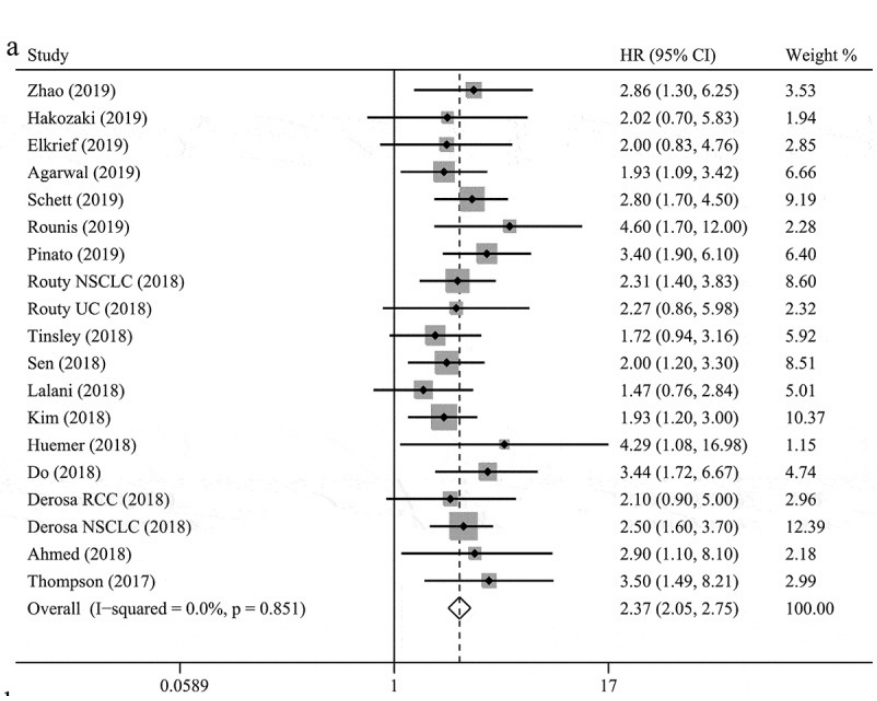
Finally, what are some factors that impact the microbiome that we should be monitoring (and potentially modulating)?



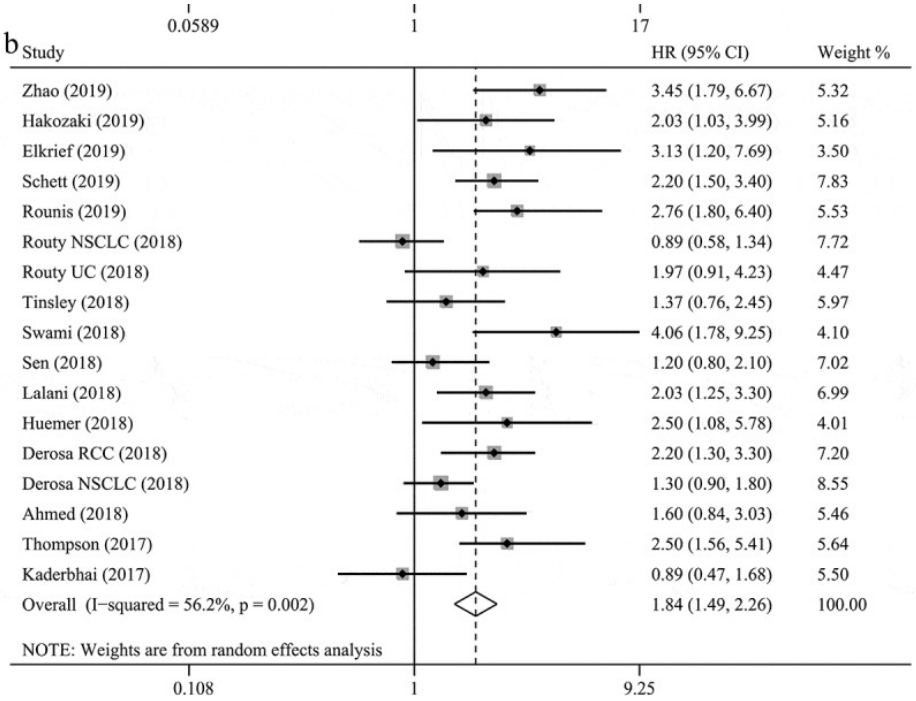
Slide adapted from Jen McQuade MD MDACC

Antibiotics have been shown to negative impact response to checkpoint blockade

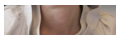
Overall survival



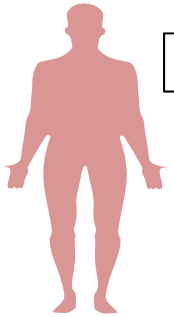
Progression free survival

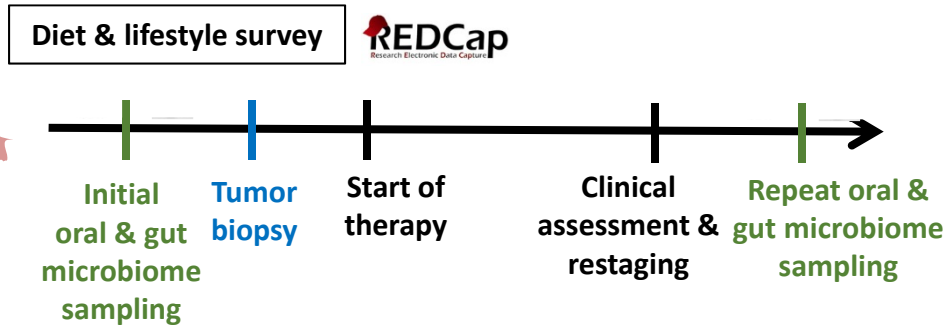


Huang XZ et al., Oncoimmunology 2019 Sept



In our cohort, we also studied the influence of diet and lifestyle factors (as well as OTC probiotic use) on the microbiome and response





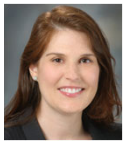
Christine Spencer PhD

Lorenzo Cohen PhD

Patients with a high fiber diet had higher diversity in the gut microbiome, higher abundance of response-associated bacteria, and higher response to PD-1 (~5x)

When integrated with a “favorable” microbiome signature (type I), diet still matters (high fiber is better)

Having a good gut microbiome signature is not enough, you need to “feed it” the right things



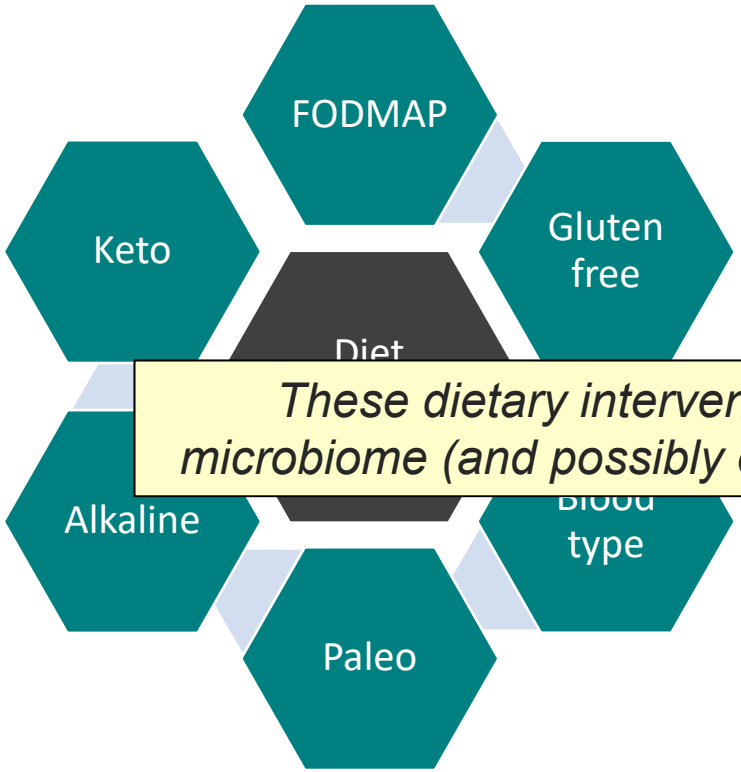
Carrie Daniel MacDougall PhD

*Spencer et al, confidential unpublished data * PLEASE DO NOT POST**

Jen McQuade MD

Why should we continue to profile and study the impact of diet on microbiota & cancer?

Cancer patients are independently exploring different dietary strategies



These dietary interventions are likely impacting the gut microbiome (and possibly even tumor / other metabolic profiles)

- No secret formula or evidence-based dietary guidelines for cancer patients.
- Lack of dietary data collection in many / most trials and clinical cohorts
- The best we can do is extrapolate from evidence-based cancer *prevention* guidelines (AICR, ACS)

*Personal communication MD Anderson Clinical Nutrition

Slide courtesy of Carrie Daniel-MacDougall PhD MPH

Testing diet as a precision intervention in cancer:

Carrie Daniel PhD MPH and Jen McQuade MD

Hypothesis: *A whole foods-based, fiber-rich diet will modulate the microbiome and enhance systemic and anti-tumor immunity*

Phase I NED melanoma patients — In-progress
- Feasibility

Phase II Biomarkers in the context of anti-PD1 therapy
- Changes in microbiome
- Changes in immunity

Phase III Behavioral intervention diet studies
- Disease outcomes

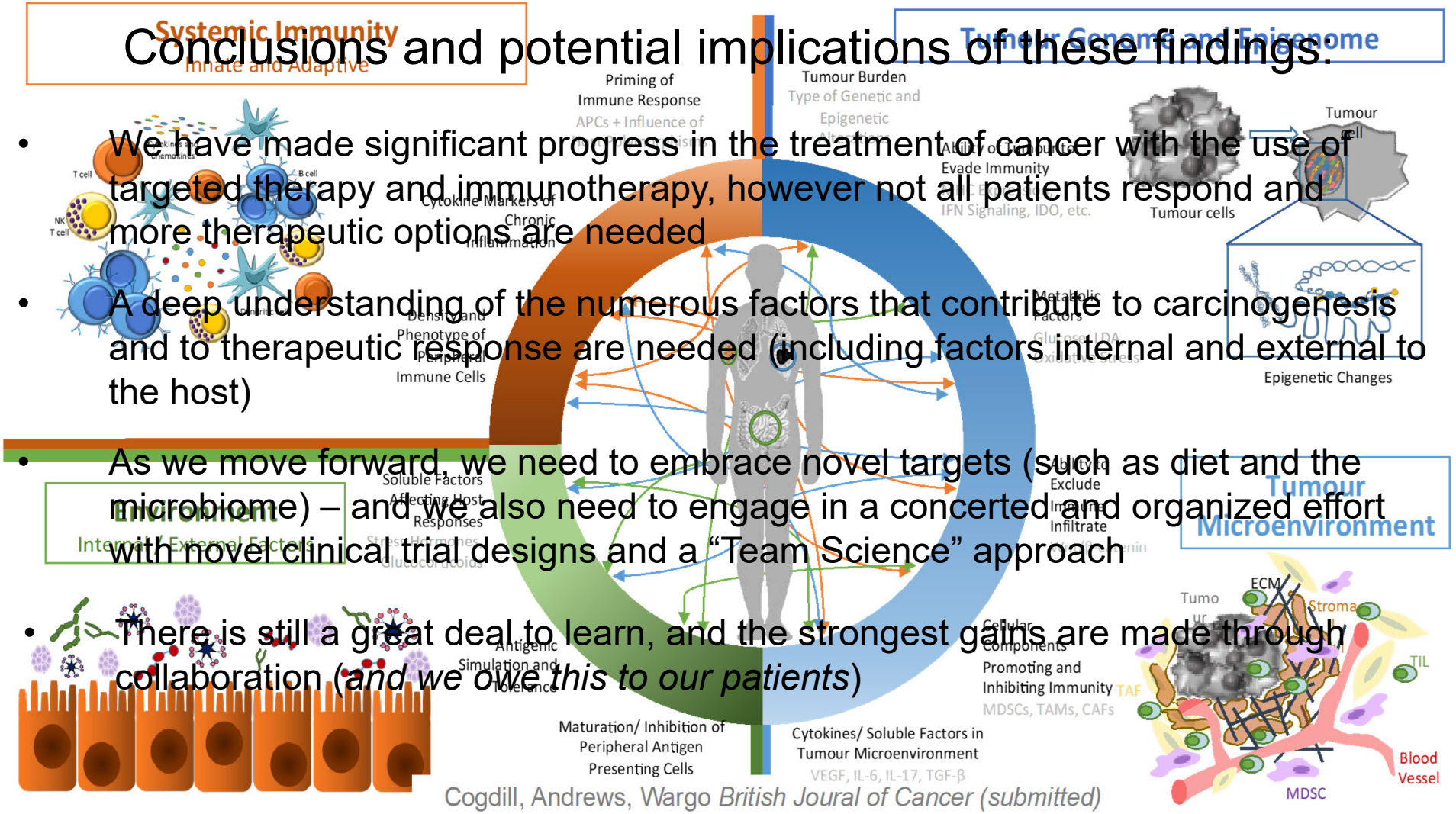
SEERAVE FOUNDATION · Melanoma Research Alliance · The University of Texas MD Anderson Cancer Center, Making Cancer History® · The Mark Foundation for Cancer Research · Rising Tide Foundation

Controlled feeding study:

All calorie-containing food and beverages prepared and provided to patients

Conclusions and potential implications of these findings:

- We have made significant progress in the treatment of cancer with the use of targeted therapy and 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 targets (such as diet and 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)*

Acknowledgements

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Conference organizers, faculty / staff, attendees

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  - **Nadim Ajami PhD, Scientific Research Director**
  - **Christine Miller Diaz, Program Manager**

Laboratory Investigation (Wargo Lab Members)

Alexandria P. Cogdill MS (PhD candidate)
Robert Szczepaniak-Sloane BS (PhD candidate)
MD Abdul Wadud Khan, Post Doctoral Fellow
Sarah Johnson, Research Investigator
Gabriel Ologun, T32 Post Doctoral Fellow
Jingjing Wang, Post Doctoral Fellow
Golnaz Morad, PhD, Post Doctoral Fellow

- **MDA Alumni** - Christine Spencer PhD, Vancheswaran Gopalakrishnan PhD, Zachary A. Cooper PhD, Luigi Nezi PhD, Sangeetha Reddy MD PhD, Miles Andrews MD PhD, Peter Prieto, MD MPH, Wei-Shen Chen, MD PhD, Pierre Oliver Gaudreau, MD

Other key collaborators

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

MDACC Collaborators

- **Liz Burton MBA – Dir., Research Planning & Dev., Surgical Onc**
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- **Michael Davies MD PhD, Jeff Gershenwald MD**
- **Hussein Tawbi MD PhD, Bella Glitza MD**
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- **and other Surg Onc Faculty / Staff**
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Baylor CMMR

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