



Tumor Immune Microenvironment: A Holistic Approach Workshop

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Society for Immunotherapy of Cancer

Targeting the Tissue and Tumor Microenvironment and Microbiome to Promote Health and End Cancer

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Society for Immunotherapy of Cancer
Tumor Immune Microenvironment: A Holistic Approach Workshop
Opening Keynote Address
April 21, 2022

Disclosure information

SITC Tumor Immune Microenvironment: A Holistic Approach Workshop

Thursday April 21, 2022

Targeting the Tissue and Tumor Microenvironment and Microbiome to Promote Health and End Cancer

Jen Wargo

I have the following financial relationships to disclose:

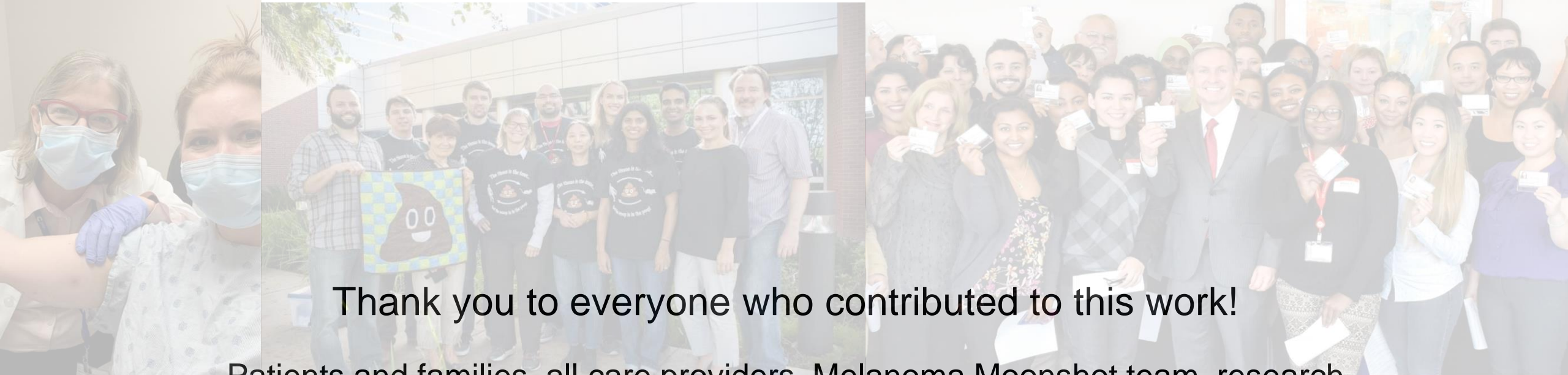
Speaker's bureau / advisory boards: Imedex, Dava, Omniprex, Illumina, BMS, Roche –
Genentech, GSK, Novartis, Astra-Zeneca, PeerView, Micronoma, Ella Therapeutics, Gilead
Stock options: Micronoma

-and-

I will discuss the following off label use and/or investigational use in my presentation:

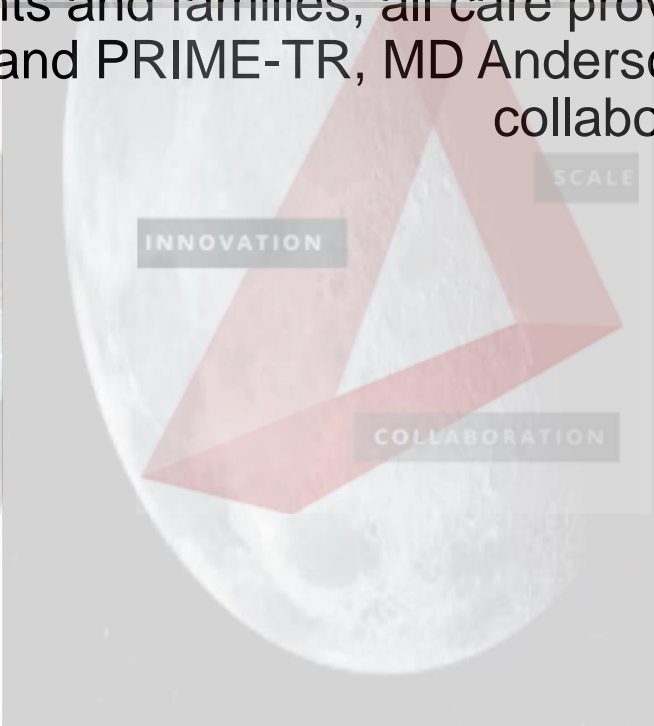
Microbiome modulation strategies

Androgen receptor blockade



Thank you to everyone who contributed to this work!

Patients and families, all care providers, Melanoma Moonshot team, research teams and PRIME-TR, MD Anderson Cancer Center leadership, supporters and collaborators worldwide



Targeting the Tissue and Tumor Microenvironment and Microbiome to Promote Health and End Cancer

- I. Insights from studies of the tumor microenvironment (TME) and gut microbiome in cancer

“The tissue is the issue, the scoop is in the poop, and sex matters”

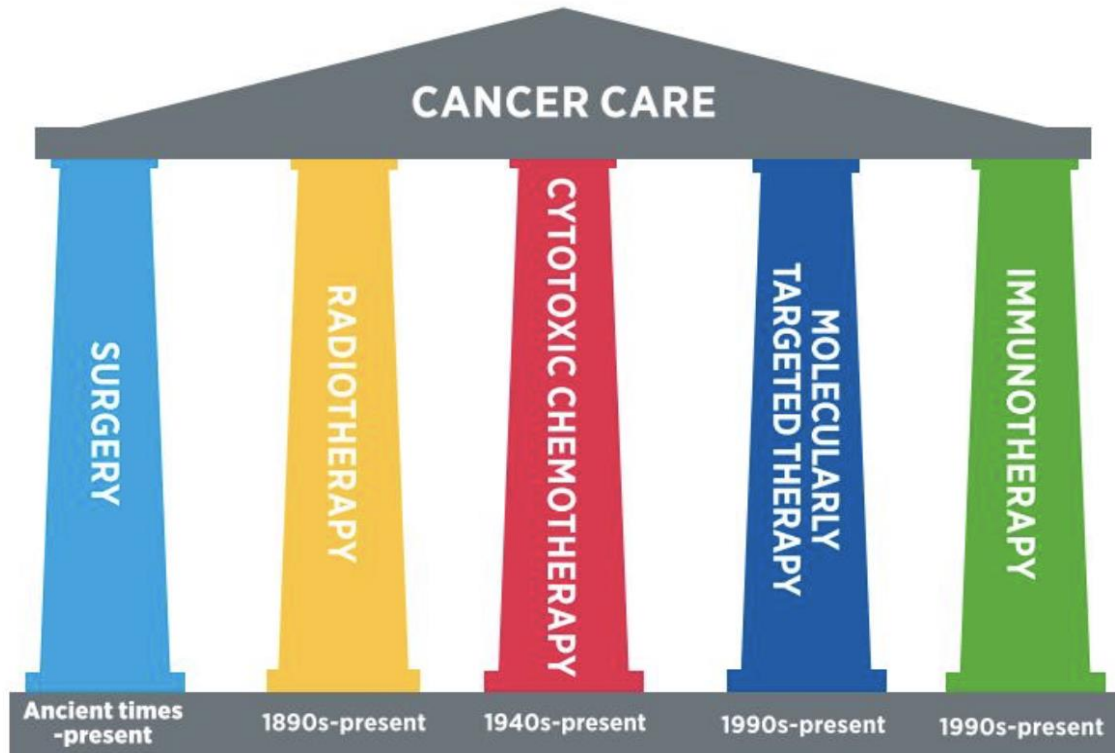
- II. Understanding factors that influence the TME and gut microbes in health and disease

“You are what you eat”

- III. Targeting tissue, tumor, and gut-based microbes to intercept / prevent cancer and to promote overall health

“An ounce of prevention is worth a pound of cure”

We have made major advances in cancer treatment with the use of immunotherapy and other approaches, with an overall decline in cancer-related mortality



From AACR Cancer Progress Report

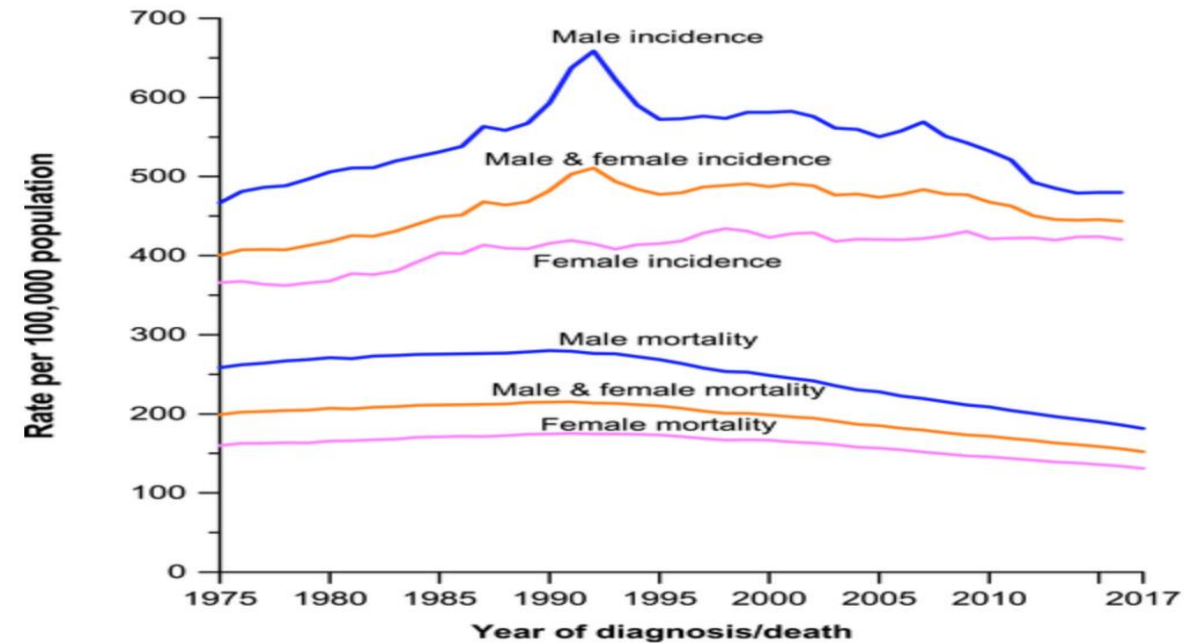
CA: A Cancer Journal for Clinicians

Article

Cancer statistics, 2020

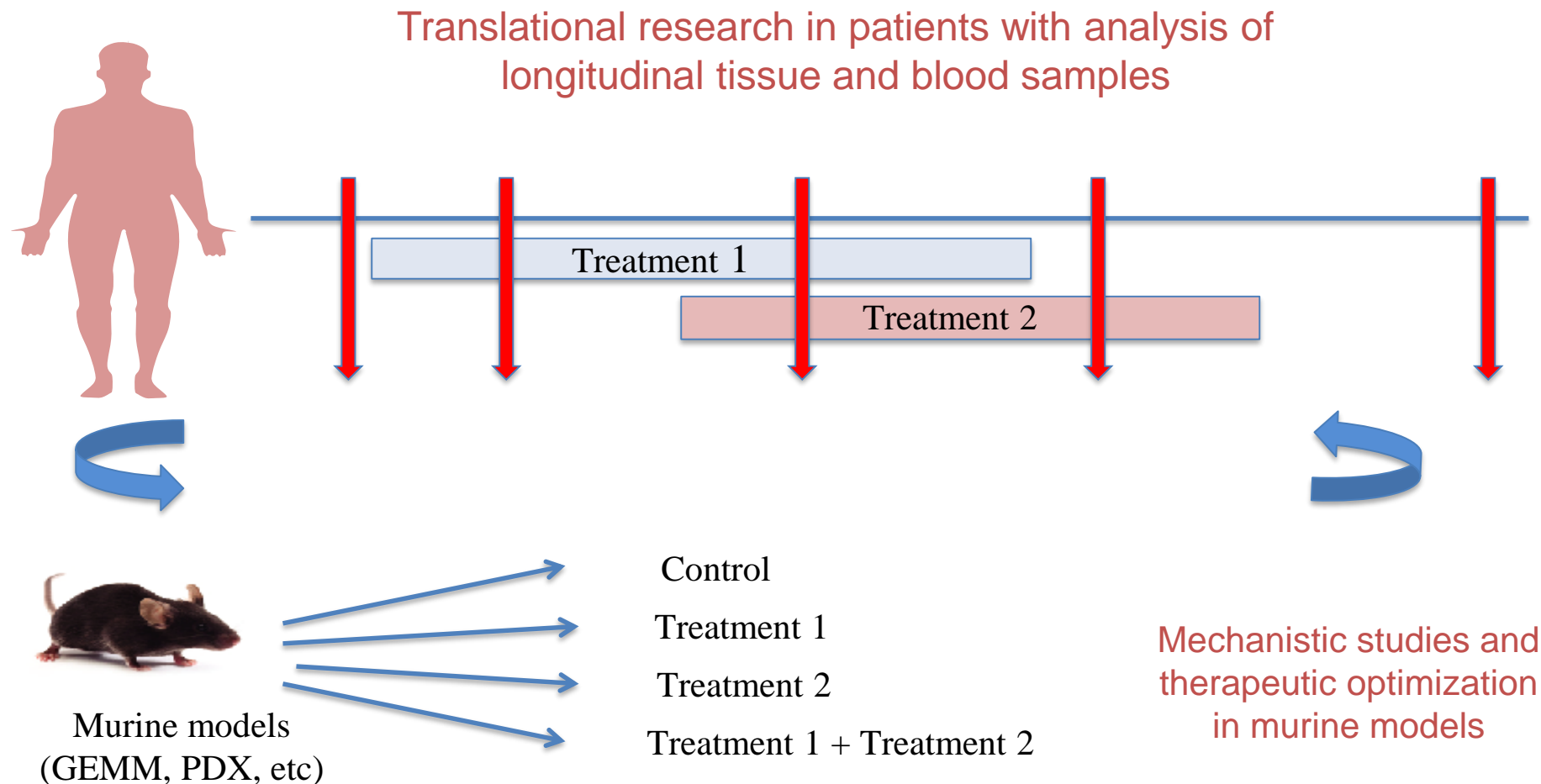
Rebecca L. Siegel MPH, Kimberly D. Miller MPH, Ahmedin Jemal DVM, PhD

First published: 08 January 2020 | <https://doi.org/10.3322/caac.21590> | Citations: 1

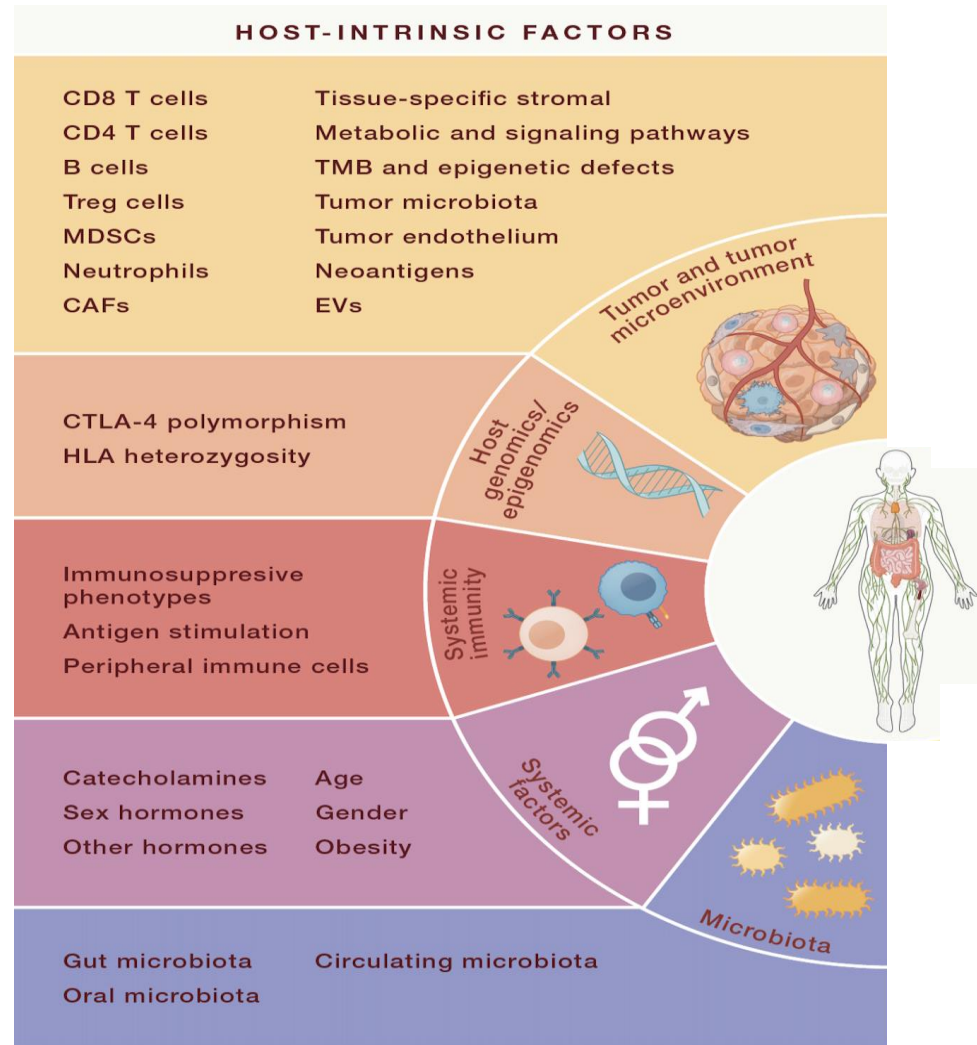


There is a still a critical need to improve responses to cancer therapy (and limit toxicity) in patients with established cancer, and opportunities to prevent cancer altogether

A powerful way to better understand response (and toxicity) to cancer treatment is via “reverse translation” – where findings go from bedside to bench, and back again



Through these types of approaches, we have identified a number of factors that impact tumor growth and response to cancer treatment that may be targeted



Morad et al, *Cell* 2021

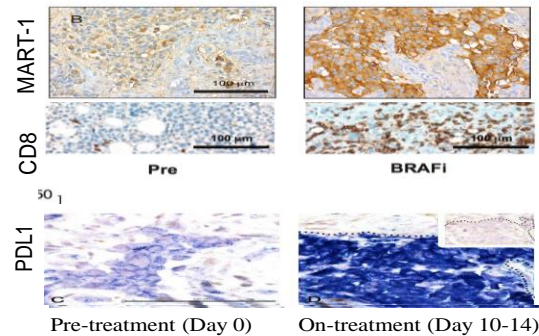


I. Insights from studies of the tumor microenvironment (TME) and gut microbiome in cancer

“The tissue is the issue, the scoop is in the poop, and sex matters”

Tissue-based analyses have helped us understand how oncogenic mutations impact anti-tumor immunity, as well as biomarkers of response to immune checkpoint blockade

Targeting oncogenic BRAF impacts anti-tumor immunity, providing the rationale for combined treatment with molecularly-targeted therapy and immunotherapy in melanoma (*and in other cancers*)



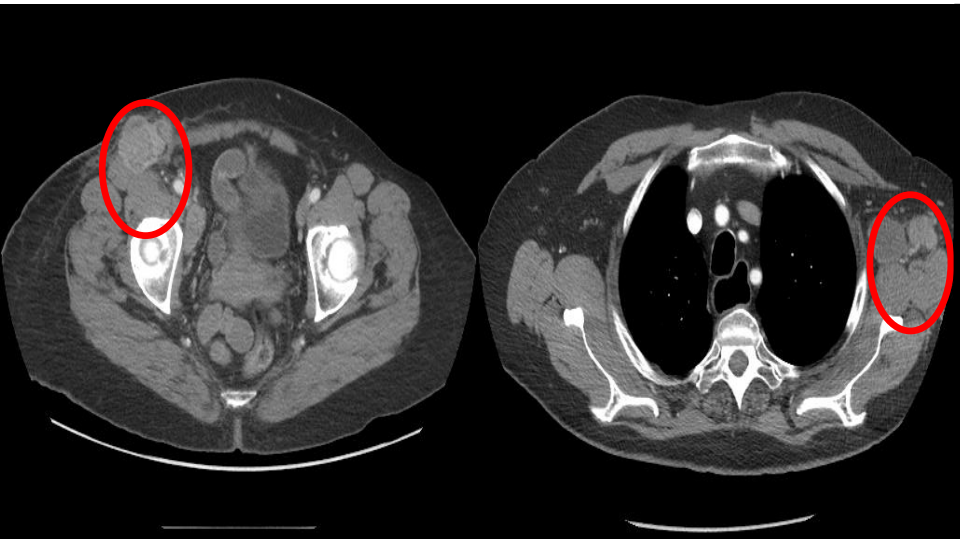
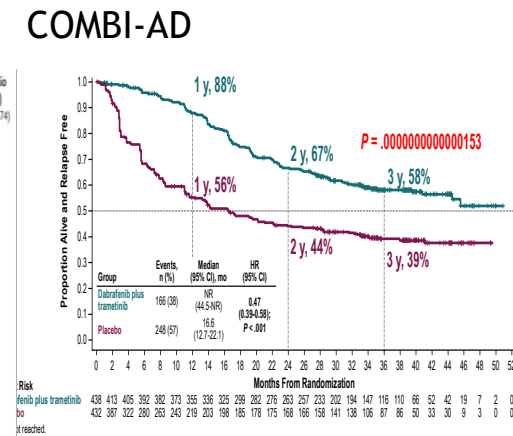
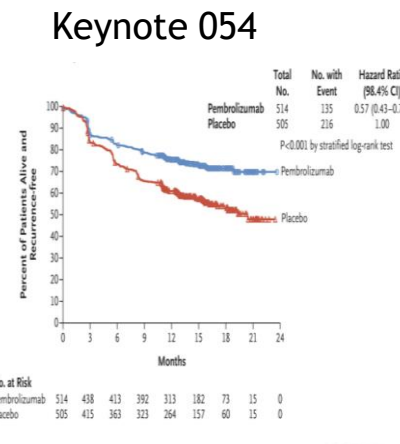
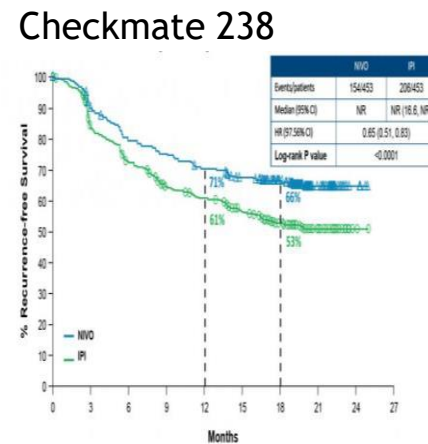
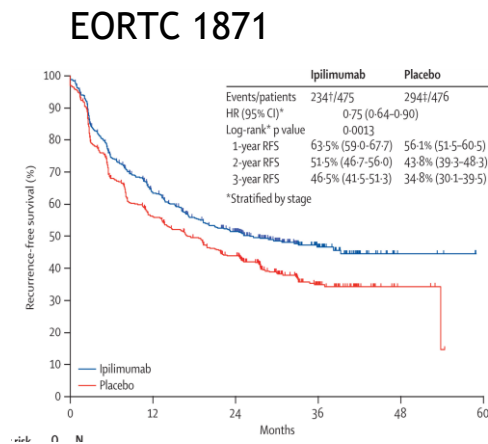
LETTERS
nature
medicine

Dabrafenib, trametinib and pembrolizumab or placebo in *BRAF*-mutant melanoma

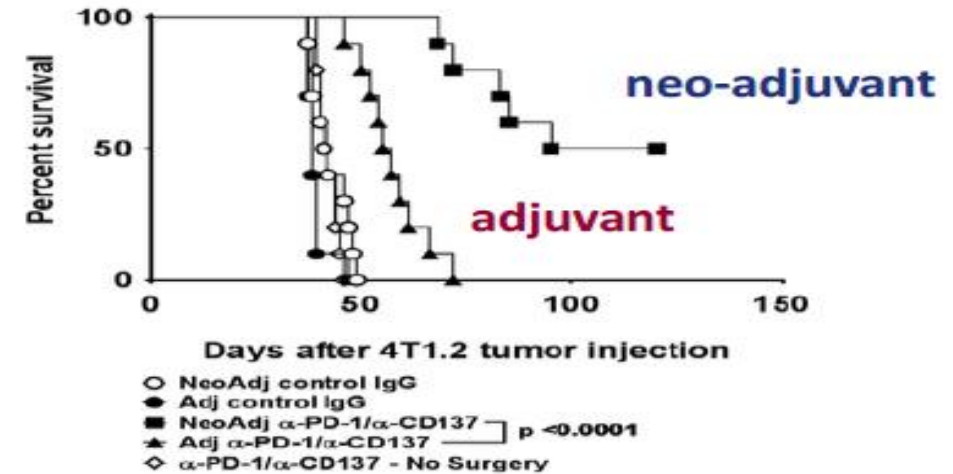
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Importantly, treatment with immunotherapy and other strategies are being used in patients with earlier stage disease, and tissue +/- blood-based analyses are critical

In addition, there is a strong rationale to use these in the neoadjuvant (pre-surgical) setting



Upfront surgery is currently the standard of care for these patients, but up to 70% of patients treated in this manner will relapse (at least before the use of adjuvant targeted therapy and immune checkpoint blockade)

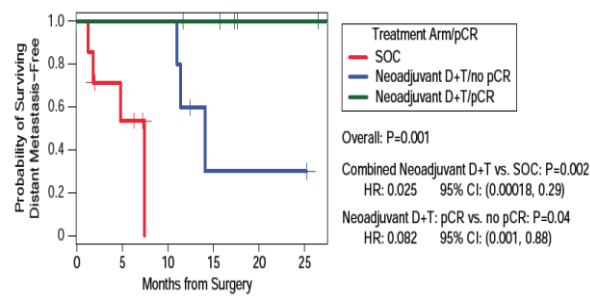
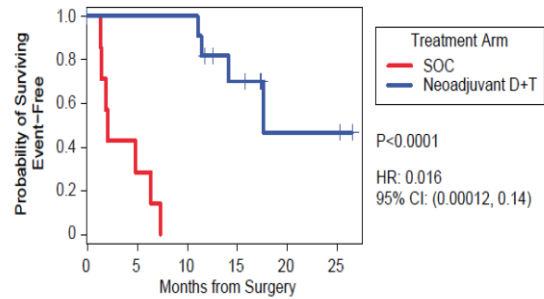
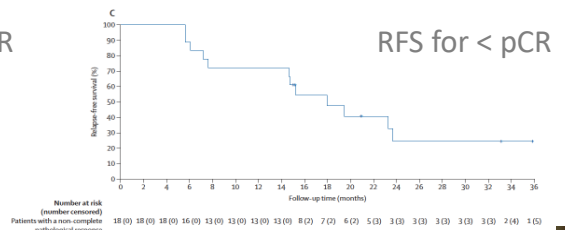
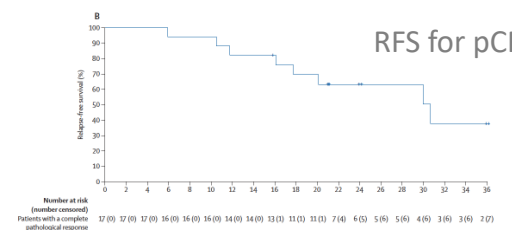
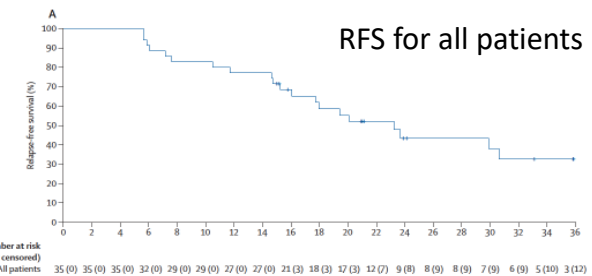
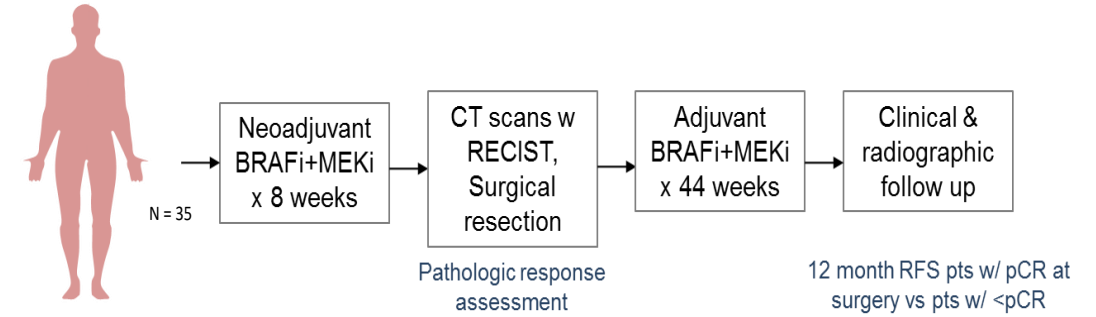
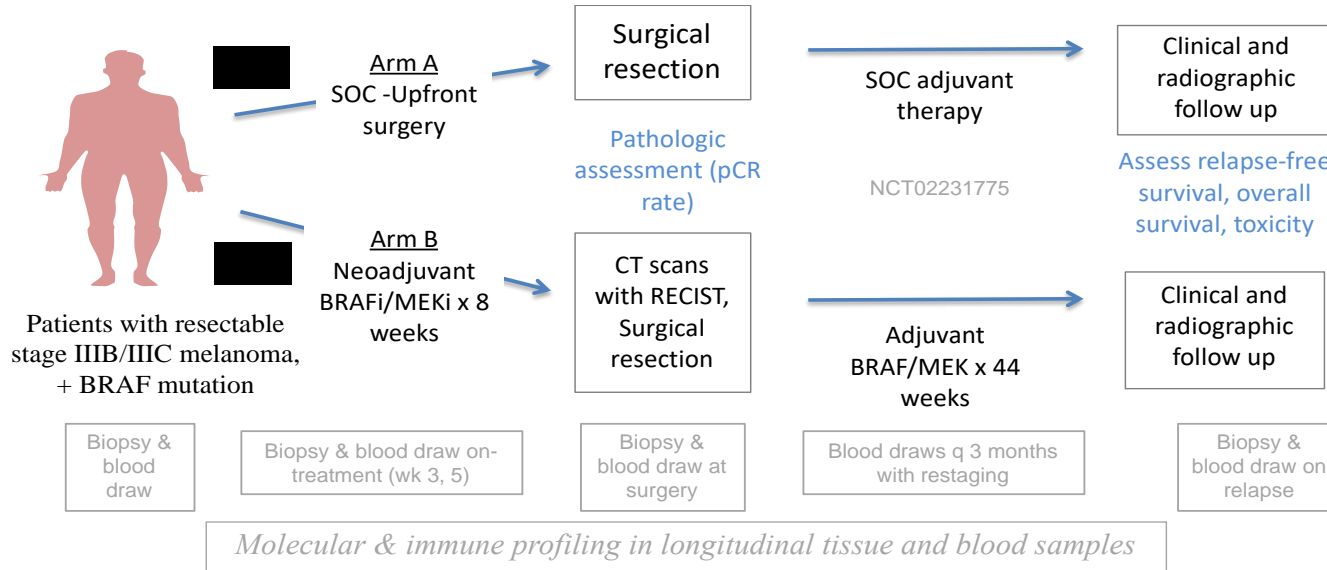


Liu, et al., Cancer Discovery 2016

We first studied the use of neoadjuvant targeted therapy vs. standard-of-care upfront surgery for patients with high-risk resectable metastatic melanoma

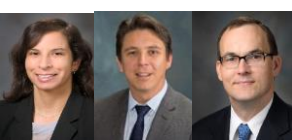
Demonstrating improved survival over SOC upfront surgery, with pathologic complete response (pCR) and other markers predictive of long-term benefit (RECIST response rate 85%, pCR rate 58%)

Notably, other groups have observed similar findings, though relapse rates were higher than observed in our trial



Long, et al Lancet Oncology 2019

Georgina Long MD



Roda Amaria MD

Peter Prieto MD MPH

Michael Tetzlaff MD PhD

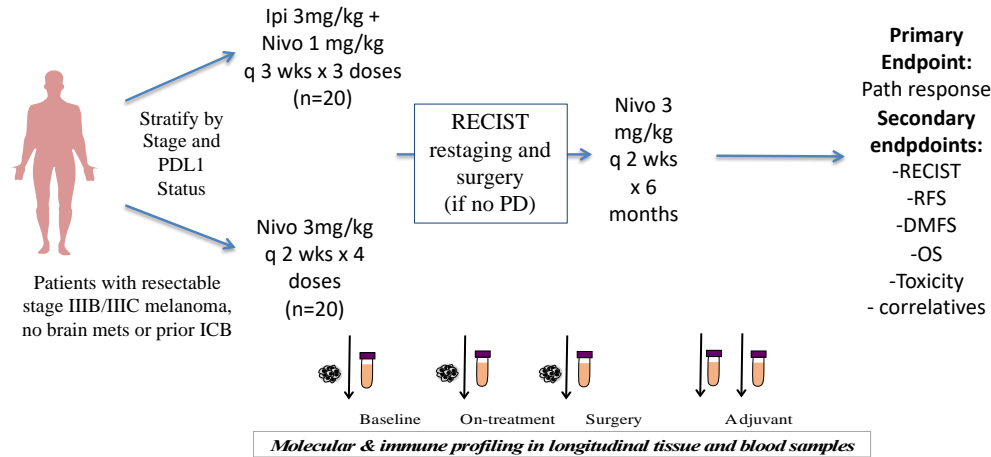
Amaria, Prieto et al, Lancet Oncology 2018

A Holistic Approach Workshop

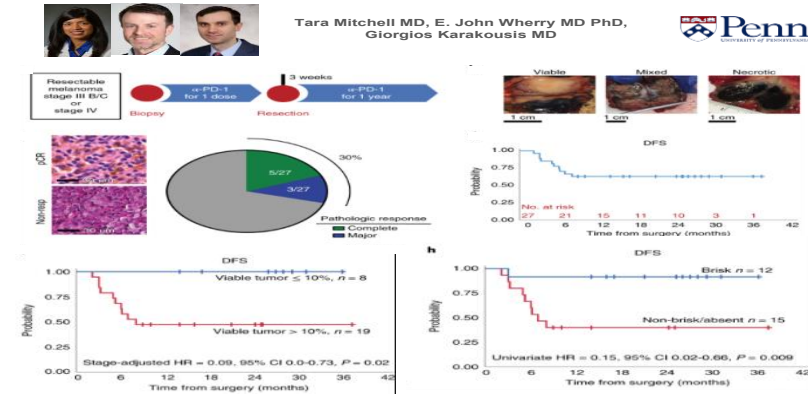
#SITCworkshop

We next studied the use of neoadjuvant immune checkpoint blockade in patients with high-risk resectable metastatic melanoma

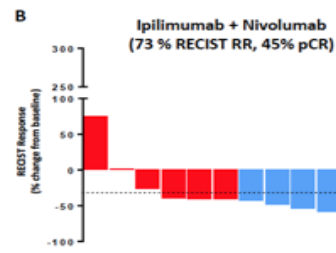
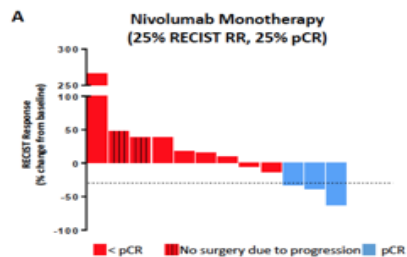
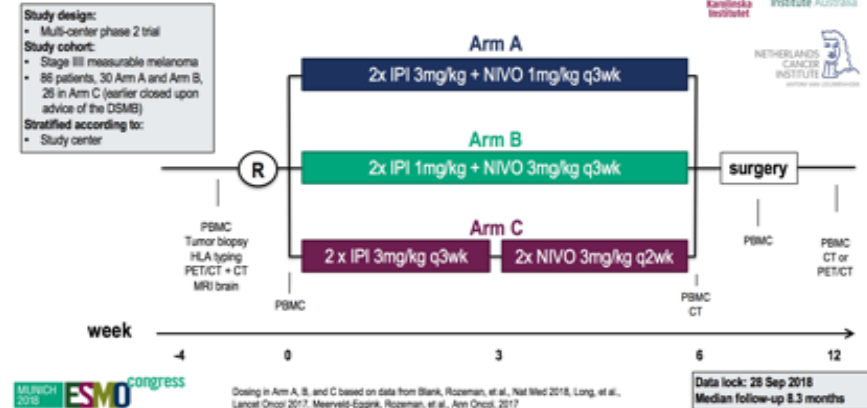
Demonstrating improved RECIST response and pCR rates in patients receiving combined immune checkpoint blockade (aCTLA-4 + aPD-1) BUT with much higher rates of toxicity (Ipi 3 / Nivo 1)



Importantly we have been working with others on neoadjuvant strategies, helping to define optimal strategies



OPACIN-NEO: STUDY DESIGN



Select Treatment Related Adverse Events During Neoadjuvant Treatment	Nivolumab (n=12)		Ipilimumab + Nivolumab (n=11)	
	Any Grade, %	Grade 3-4, %	Any Grade, %	Grade 3-4, %
Any Treatment Related Adverse Events	92	8	91	73
Fatigue	67	0	55	0
Rash	17	0	73	0
Fatigue/chills/flu like	8	0	64	0
Weight loss/anorexia	17	0	27	0
Transaminitis	17	0	55	27
Colitis/diarrhea	17	0	64	18
Hypothyroidism	8	0	27	9
Hypothyroidism	0	0	36	0
Myositis/myalgias	8	0	18	9
Pain	25	8	27	0



Roda Amaria MD
 Sangeetha Reddy MD
 Michael Tetzlaff MD PhD

Amaria, Reddy et al
 Nature Medicine 2018

Huang. Et. AI Nature Med 2018
 Rozemann, et al Lancet Oncology 2019

Christian Blank MD



We are working with the MRA, FDA, industry, investigators and other key stakeholders to build on findings and improve patient outcomes (including with tissue-based analyses)



Who We Are

- >240 International Members
- Pharma engagement
- Multidisciplinary
- Pooled analyses
- White papers & guidelines

Our Goals

1. Consistent trial design across international sites
2. Align translational plans and efforts to understand biology of response and resistance
3. Develop a platform for rapid drug development
4. Determine if neoadjuvant therapy is superior to adjuvant therapy

ESMO

ORIGINAL ARTICLE

Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

M. T. Tetzlaff^{1,2*}, J. L. Messina³, J. E. Stein⁴, X. Xu⁵, R. N. Amaral⁶, C. U. Blank⁷, B. A. van de Wiele⁸, P. M. Feghian⁹, R. V. Rawson¹⁰, M. L. Bass¹¹, A. J. Spillane¹², J. E. Gershenwald¹³, R. P. M. Saw¹⁴, A. C. J. van Akkooi¹⁵, W. J. van Houdt¹⁶, T. C. Mitchell¹⁷, A. M. Menzies¹⁸, G. V. Long¹⁹, J. A. Wargo²⁰, M. A. Davies^{21,15}, V. G. Prieto¹⁶, J. M. Taube²² & R. A. Scolyer²³

Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium

Rodolfo N. Amaral¹, Alexander M. Menzies², Elizabeth M. Burton³, Richard A. Scolyer⁴, Michael T. Tetzlaff⁵, Robert Andriakha⁶, Charlotte Ariyan⁷, Roland Bassett⁸, Brett Carter⁹, Adil Daud¹⁰, Mark Faries¹¹, Leslie A. Fisher¹², Keith Flaherty¹³, Jeffrey G. Gershenwald¹⁴, Omid Hamid¹⁵, Angela Hong¹⁶, John Kirkwood¹⁷, Sergie Lo¹⁸, Kim Margolin¹⁹, Jane Messina²⁰, Michael Postow²¹, Helen Rizos²², Merrick I. Ross²³, Elisa A. Rozeman²⁴, Robyn P. M. Saw²⁵, Vernon Sondak²⁶, Ryan J. Sullivan²⁷, Janis M. Taube²⁸, John F. Thompson²⁹, Bart A. van de Wiele³⁰, Alexander M. Eggemann³¹, Michael A. Davies³², The International Neoadjuvant Melanoma Consortium members¹⁻³³, Paolo A. Ascierto³⁴, Andrew J. Spillane³⁵, Alexander C. J. van Akkooi³⁶, Jennifer A. Wargo³⁷, Christian U. Blank³⁸, Hussein A. Tawbi³⁹, Georgina V. Long⁴⁰

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Reviews

Neoadjuvant Therapy for Melanoma: A U.S. Food and Drug Administration—Melanoma Research Alliance Public Workshop

Kristen L. Mueller, Marc R. Theoret, Steven J. Lemery, Laleh Amiri-Kordestani, Charlotte E. Ariyan, Michael B. Atkins, Donald A. Berry, Christian U. Blank, Angela M. DeMichele, Patrick M. Forde, Nageatte Ibrahim, Patricia Keegan, Tara C. Mitchell, Rebecca A. Moss, Caroline Robert, Rajeshwari Sridhara, Janis M. Taube, Michael T. Tetzlaff, Jennifer A. Wargo, Keith T. Flaherty, Michael J. Kaplan, Suzanne L. Topalian, Ashley F. Ward, and Marc S. Hurlbert

DOI: 10.1158/1078-0432.CCR-20-3285 Published January 2021

Tetzlaff et al Ann Onc 2018, Amaria et al, Lancet Oncology 2019; Mueller et al CCR 2021

nature medicine

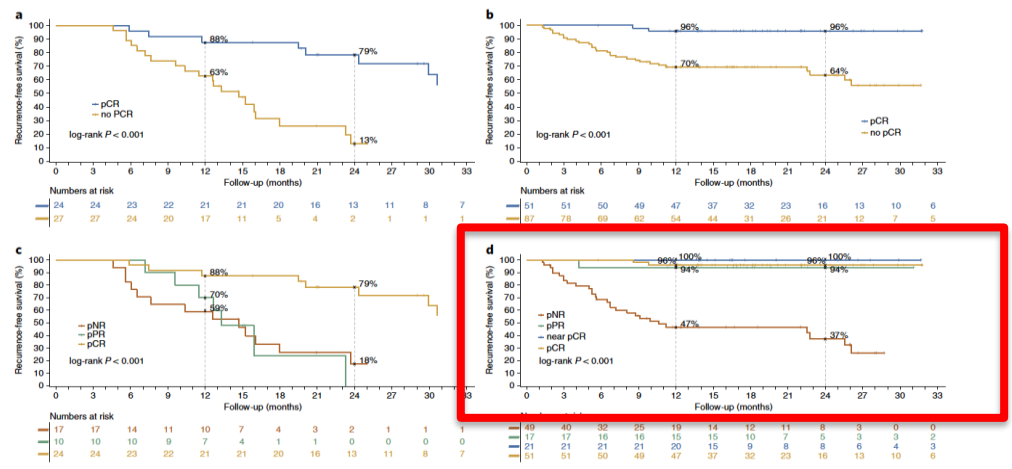
ARTICLES

https://doi.org/10.1038/s41591-020-01188-3

Check for updates

Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC)

Alexander M. Menzies^{1,2,3,12}, Rodolfo N. Amaral^{4,12}, Elisa A. Rozeman^{5,12}, Alexander C. Huang^{6,7,12}, Michael T. Tetzlaff^{8,12}, Bart A. van de Wiele^{9,12}, Sergie Lo^{10,12}, Ahmad A. Tahrini¹¹, Elizabeth M. Burton¹², Thomas E. Pennington^{1,2,9}, Robyn P. M. Saw^{1,2,9}, Xiaowei Xu¹², Giorgos C. Karakousis¹², Paolo A. Ascierto¹⁰, Andrew J. Spillane^{1,2,3}, Alexander C. J. van Akkooi¹², Michael A. Davies^{4,13}, Tara C. Mitchell^{6,13}, Hussein A. Tawbi^{4,13}, Richard A. Scolyer^{12,13,13}, Jennifer A. Wargo^{4,13}, Christian U. Blank^{5,13} and Georgina V. Long^{12,13,13}



nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-05211-7

Check for updates

Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma

E. A. Rozeman¹, E. P. Hoefsmit^{2,3}, L. L. M. Reijers^{4,5}, R. P. M. Saw^{6,7,8}, J. M. Verschuik⁹, O. Krizgsman¹⁰, P. Dimitriadis¹¹, K. Sikorska¹², B. A. van de Wiele¹³, H. Eriksson^{14,15}, M. Gonzalez¹⁶, A. Torres Acosta¹⁷, L. G. Griplink-Ongering¹⁸, K. Shannon^{19,20}, J. B. A. G. Haanen^{21,22}, J. Stretch^{23,24}, S. Chng^{25,26}, O. E. Nieweg^{27,28}, H. A. Maitlo²⁹, S. Adriaensz³⁰, R. M. Kerkhoven³¹, S. Cornelissen³², A. Broeks³³, W. M. C. Klep³⁴, C. L. Zuur³⁵, W. J. van Houdt³⁶, D. S. Peeser^{37,38}, A. J. Spillane^{39,40}, A. C. J. van Akkooi⁴¹, R. A. Scolyer^{42,43}, T. N. M. Schumacher^{44,45}, A. M. Menzies⁴⁶, G. V. Long⁴⁷ and C. U. Blank^{48,49}

Menzies et al, Rozeman et al, Nature Medicine 2021



Tumor Immune Microenvironment: A Holistic Approach Workshop

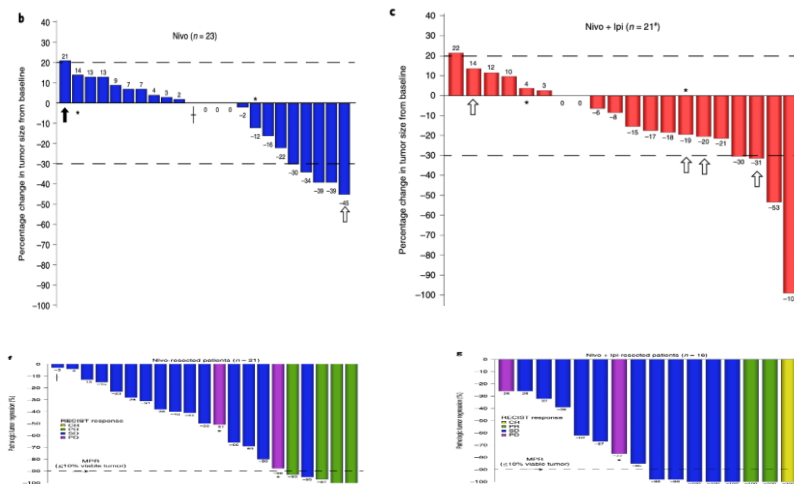
#SITCworkshop

Importantly, treatment with neoadjuvant immune checkpoint blockade is being used in other cancer types with success



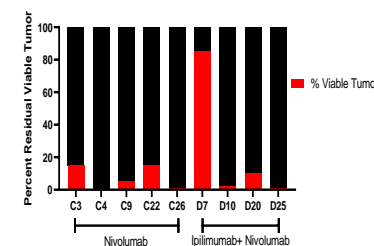
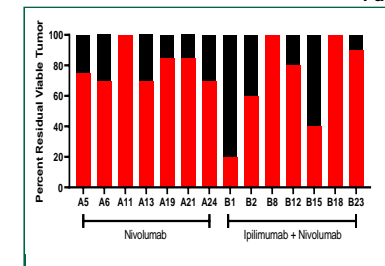
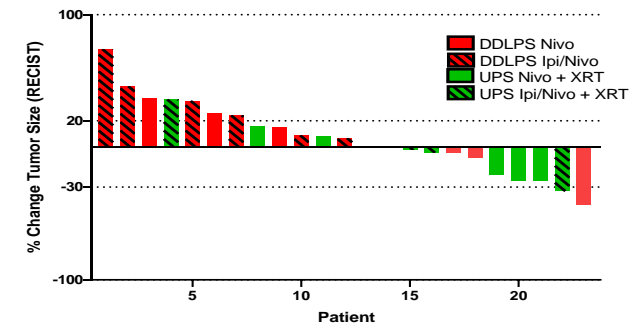
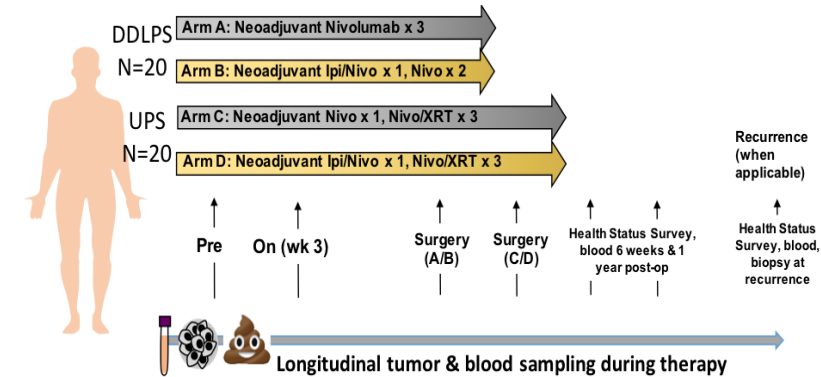
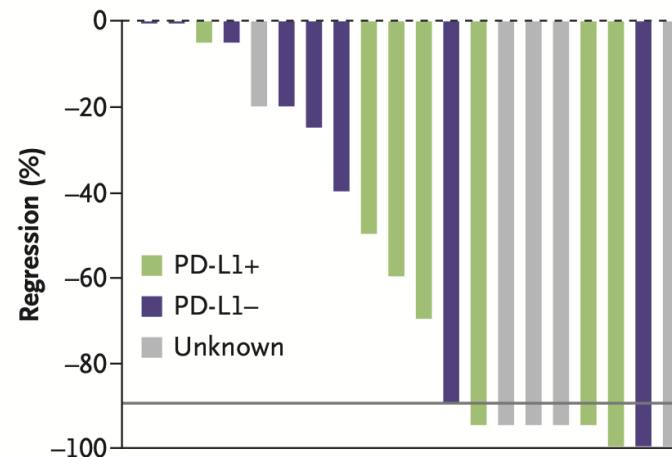
Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial

Tina Cascone^{1,5*}, William N. William Jr^{1,5}, Annika Weissferdt^{2,3}, Cheuk H. Leung⁴, Heather Y. Lin⁴, Apar Pataer³, Myrna C. B. Godoy⁵, Brett W. Carter², Lorenzo Federico⁶, Alexandre Reuben¹, Md Abdul Wadud Khan⁷, Hitoshi Dejima^{8,16}, Alejandro Francisco-Cruz⁹, Edwin R. Parra⁸, Luisa M. Solis⁸, Junya Fujimoto⁸, Hai T. Tran¹, Neda Kalhor², Frank V. Fossella¹, Frank E. Mott¹, Anne S. Tsao¹, George Blumenschein Jr¹, Xiuning Le¹, Jianjun Zhang¹, Ferdinando Skoulidis¹, Jonathan M. Kurie¹, Mehmet Altan¹, Charles Lu¹, Bonnie S. Glisson¹, Lauren Averett Byers¹, Yasir Y. Elamin¹, Reza J. Mehran³, David C. Rice³, Garrett L. Walsh³, Wayne L. Hofstetter³, Jack A. Roth³, Mara B. Antonoff³, Humam Kadara⁸, Cara Haymaker⁸, Chantale Bernatchez^{6,8}, Nadim J. Ajami⁹, Robert R. Jenq^{9,10,11}, Padmanee Sharma^{12,13}, James P. Allison¹³, Andrew Futreal⁹, Jennifer A. Wargo⁹, Ignacio I. Wistuba^{1,8}, Stephen G. Swisher³, J. Jack Lee⁴, Don L. Gibbons³, Ara A. Vaporciyan³, John V. Heymach^{1,14,17} and Boris Sepesi^{3,17}



Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll



Tina Cascone MD
Boris Sepesi MD

Cascone et al, Nature
Medicine 2021

Forde et al,
NEJM 2018



Patrick Forde MD

Crisy Roland MD (ASCO 2020)
Emily Keung MD (SITC 2021)



Tumor Immune Microenvironment: A Holistic Approach Workshop

#SITCworkshop

THE #1 NEOADJUVANT IMMUNOTHERAPY TOPIC IN THE NEXT 5 YEARS: *More Cures—Less Surgery!*

MELANOMA palpable lymph nodes

- Nivolumab 3 + ipilimumab 1: 70% pathologic CR!!
- **No more TLND in >50%** of patients with palpable nodes in 5 years

BLADDER CANCER

- 50% pCR for T3 bladder cancers: wait and see
- Reduction cystectomies

MSI COLORECTAL CANCER

- 19/20 pCR for MSI CRC! (Haanen et al. *Nature Medicine*. 2020)
- In future in case of pCR: **NO surgery, but endoscopy + MRI**

LUNG, HEAD and NECK, ESOPHAGEAL and GASTRIC, BREAST, GBM

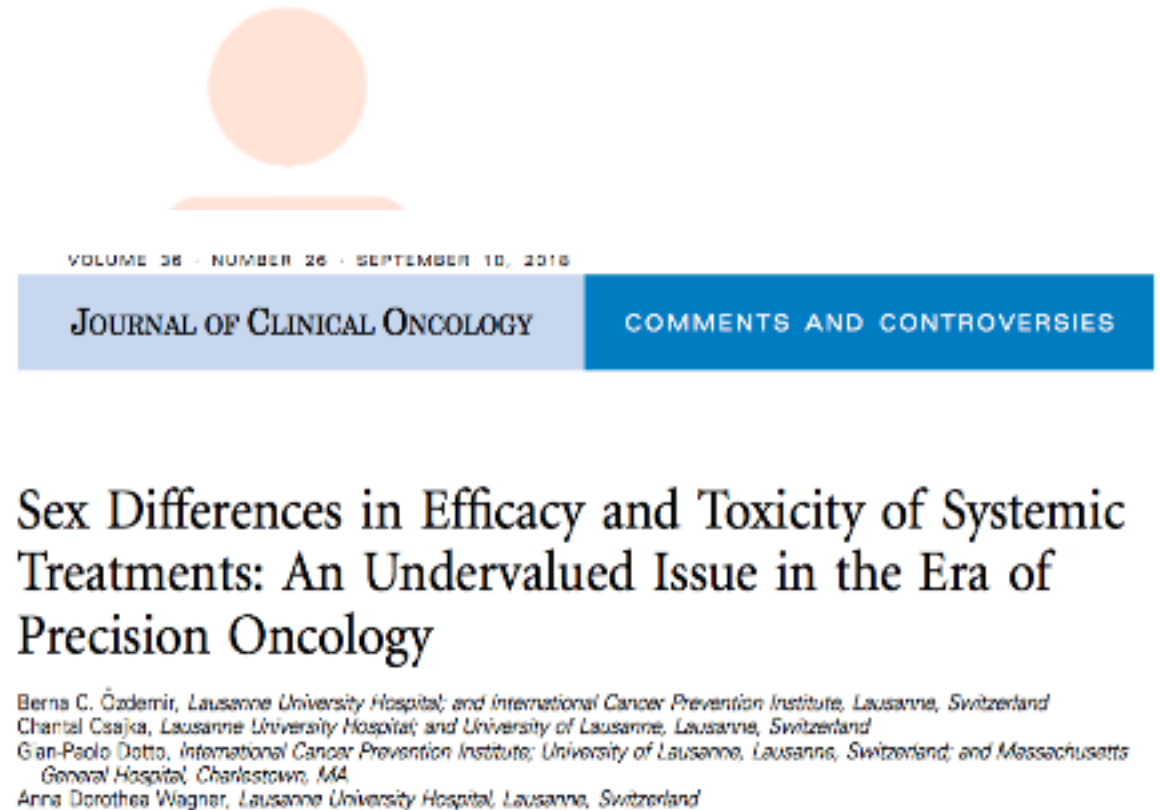
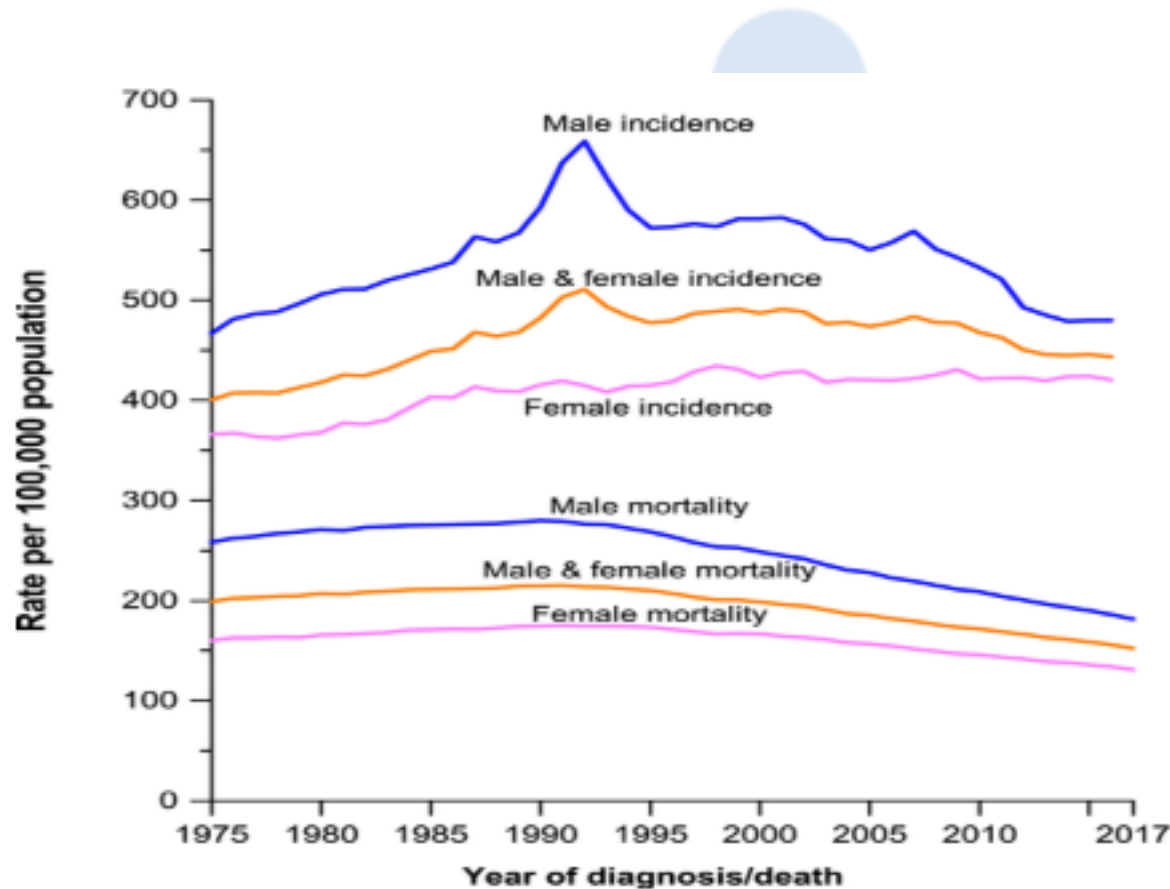


Alexander Eggermont MD PhD

From PeerView presentation SSO 2021

What about the role of gender / sex hormones on cancer & therapy response?

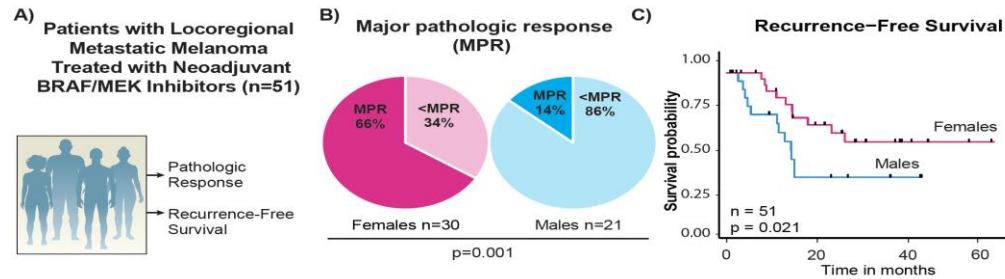
sex matters!



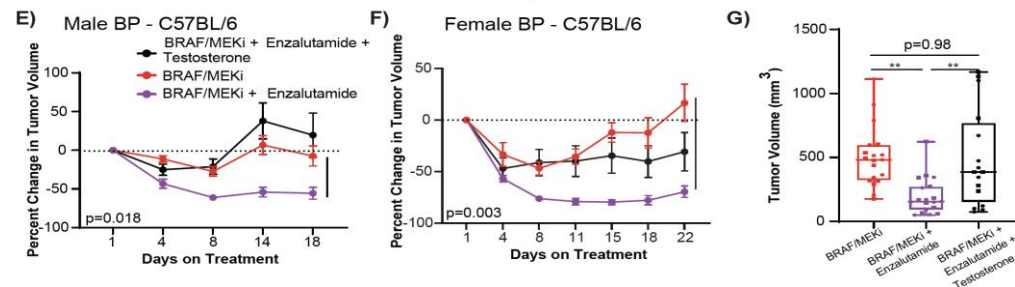
In one of our neoadjuvant studies, we noted a strong sexual dimorphism in response to therapy (which was confirmed in additional cohorts)

Patients who achieved a complete response to neoadjuvant targeted therapy had long-term benefit *(and the majority of these patients were female)*

Sex-specific differences are also noted in immunity and may impact response to immunotherapy, and AR blockade enhances response to immunotherapy (and enhances T cell function)



We validated these findings in a murine model (and showed that by blocking AR we can improve response to BRAF/MEKi in both males and females)

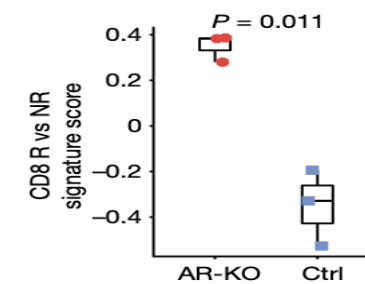
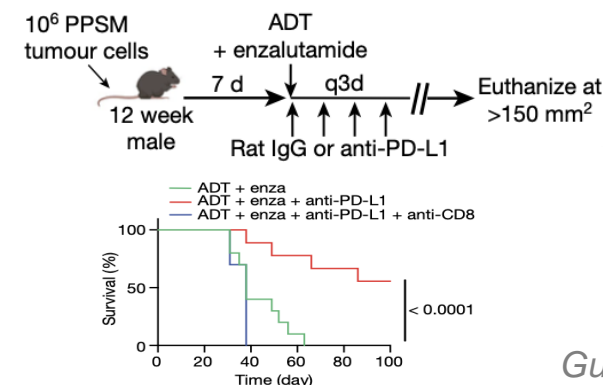
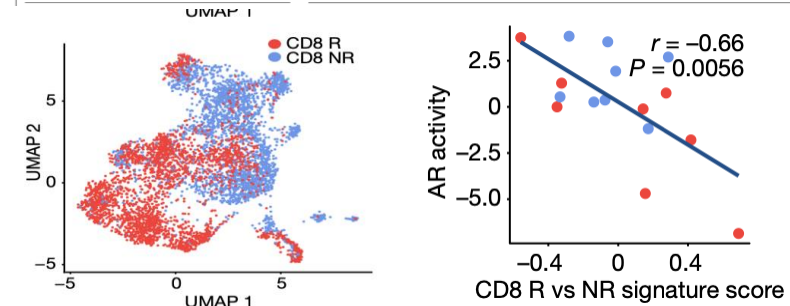


Chris Vellano PhD
Joe Marszalek PhD
Tim Heffernan PhD

Vellano et al, accepted for publication

Article
Androgen receptor activity in T cells limits checkpoint blockade efficacy
<https://doi.org/10.1038/s41586-022-04522-6>
Received: 12 August 2020
Accepted: 4 February 2022
Published online: 23 March 2022

Xiangnan Guan^{1,2,3,10,12}, Fanny Polesso^{3,12}, Chaojie Wang^{3,12}, Archana Sehrawat³, Reed M. Hawkins³, Susan E. Murray^{3,4}, George V. Thomas^{5,6}, Breanna Caruso³, Reid F. Thompson^{1,5,7,8}, Mary A. Wood⁹, Christina Hipfinger⁷, Scott A. Hammond⁹, Julie N. Graff⁸, Zheng Xia^{1,3,10} & Amy E. Moran^{3,12,13}



Guan et al, Nature 2022

Amy Moran PhD



nature

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

First results
from the Human
Microbiome
Project highlight
the healthy
variation in
ourselves

PAGES 194, 207 & 215

FELLOW TRAVELLERS

MATERIALS

FEELING THE
PRESSURE

The quest for convincingly
metallic hydrogen

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CLIMATE CHANGE

GET USED TO
UNCERTAINTY

Climate modelling
faces its limits

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SOLAR SYSTEM

TITAN'S ELUSIVE
METHANE

Tropical lakes on Saturn's
enigmatic moon?

PAGE 237

NATURE.COM/NATURE

14 June 2012

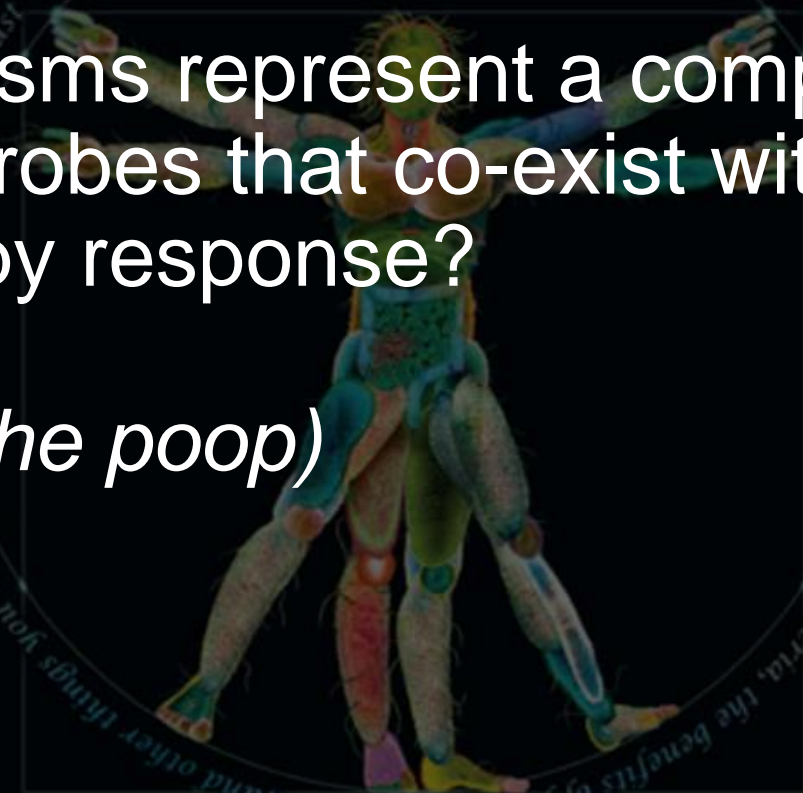


The Economist

AUGUST 18TH-24TH 2012

Economist.com

Microbes maketh man





**3.5 billion years ago,
microbes helped to shape the earth for future forms of life...**

**3.5 billion years later,
it is now clear that microbes are pervasive in our environment
(and within living organisms)**

20,000 human
genes in an
individual

1%

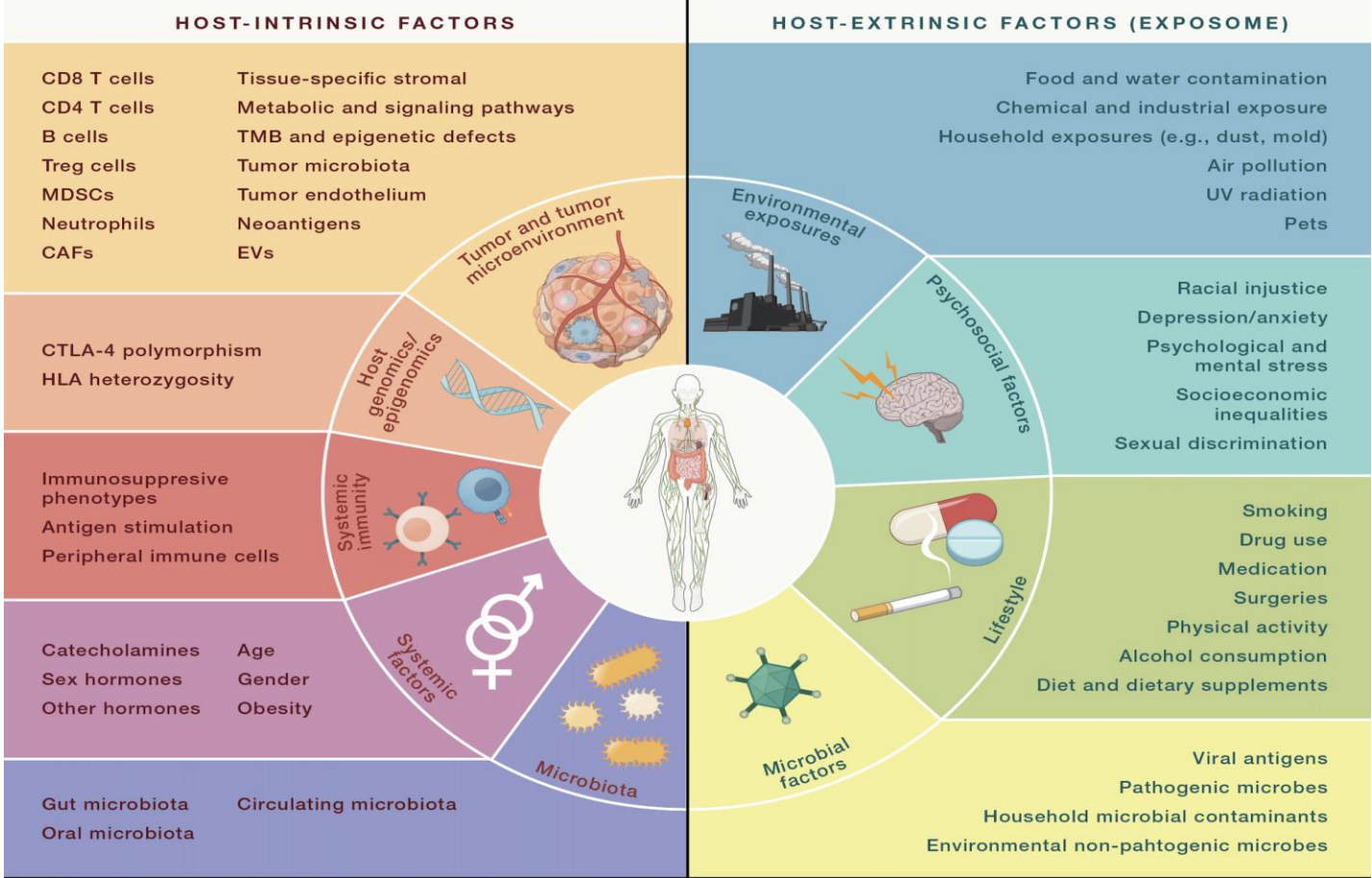


2-20 million
microbial genes in
an individual

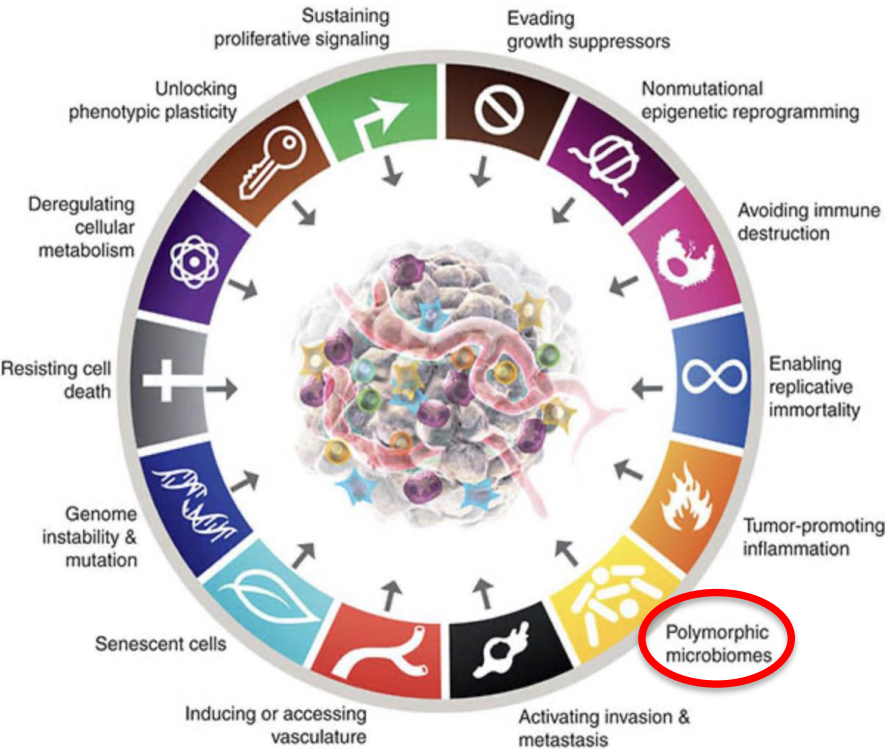
99%
*inherently
modifiable*

Advances in next-generation sequencing have allowed us to better understand these microbes

Microbes (along with other factors) can profoundly influence our physiology, cancer, and other disease states



The microbiome has now been recognized as one of the emerging Hallmarks and Enabling Characteristics in the Hallmarks of Cancer



"Hallmarks of Cancer: New Dimensions" provides an update to the landmark "Hallmarks of Cancer" series. Graphic from Cancer Discovery.



Golnaz Morad PhD

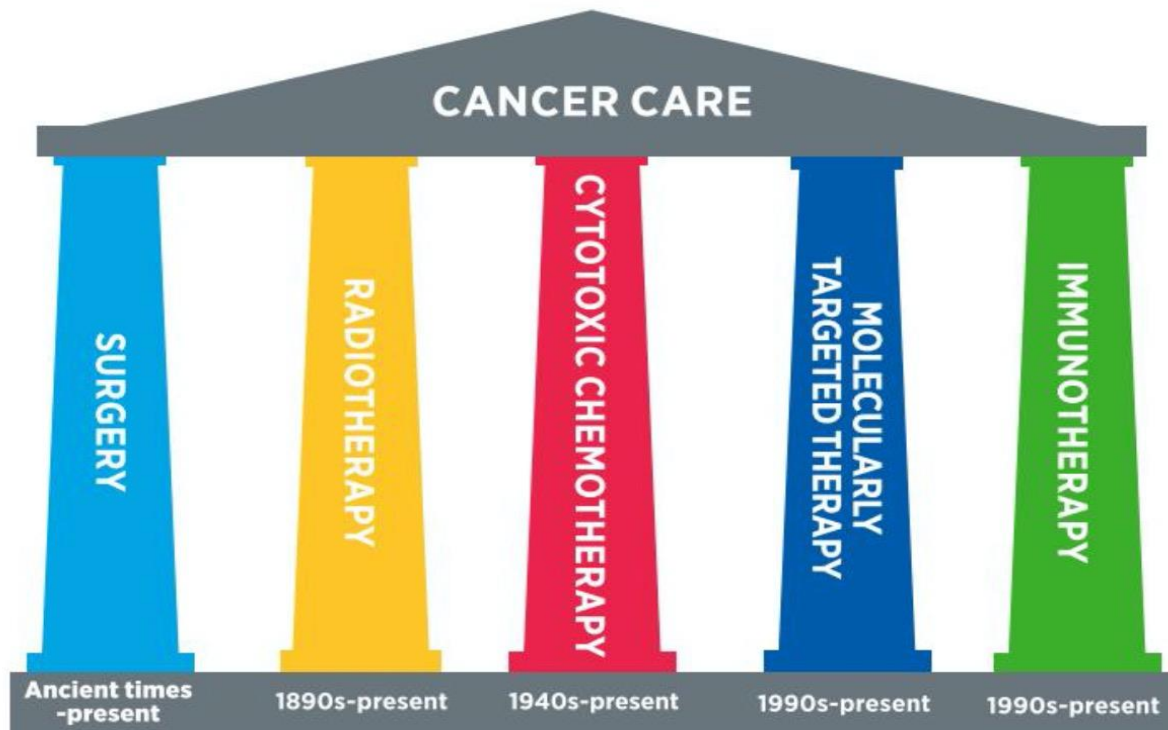
Morad et al, *Cell* 2021



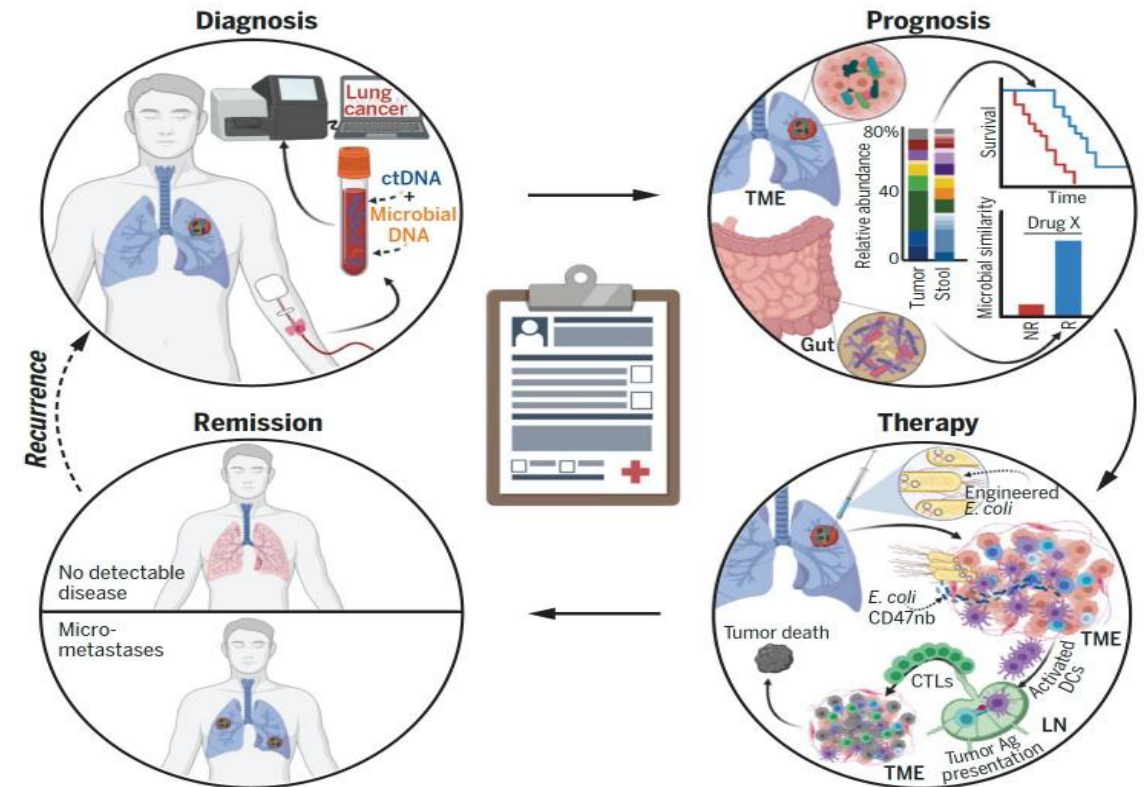
Hanahan, *Cancer Discovery* 2022

Could microbiome targeting become the next “pillar” of cancer care?

With strategies to monitor and modulate the microbiome to treat, intercept, and perhaps even prevent cancer altogether?

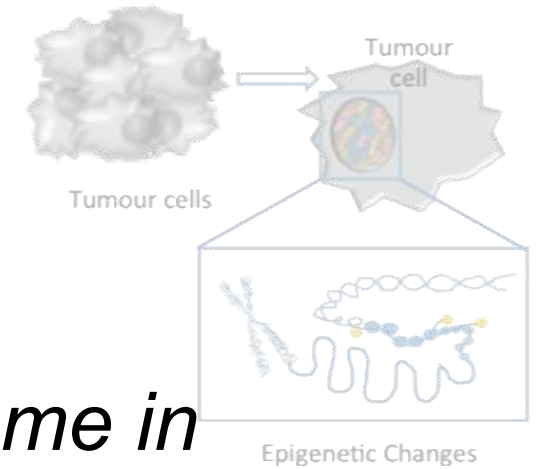


From AACR Cancer Progress Report



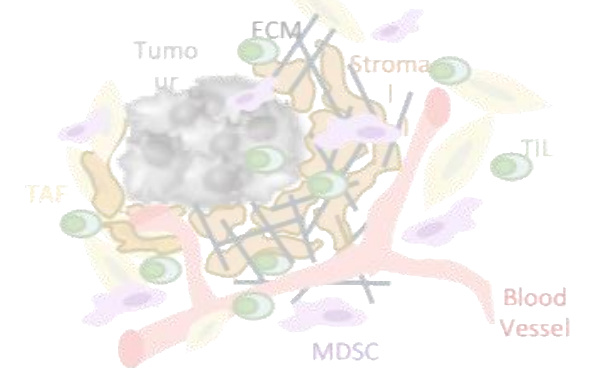
Sepich-Poore et al, Science 2021

Tumour Genome and Epigenome

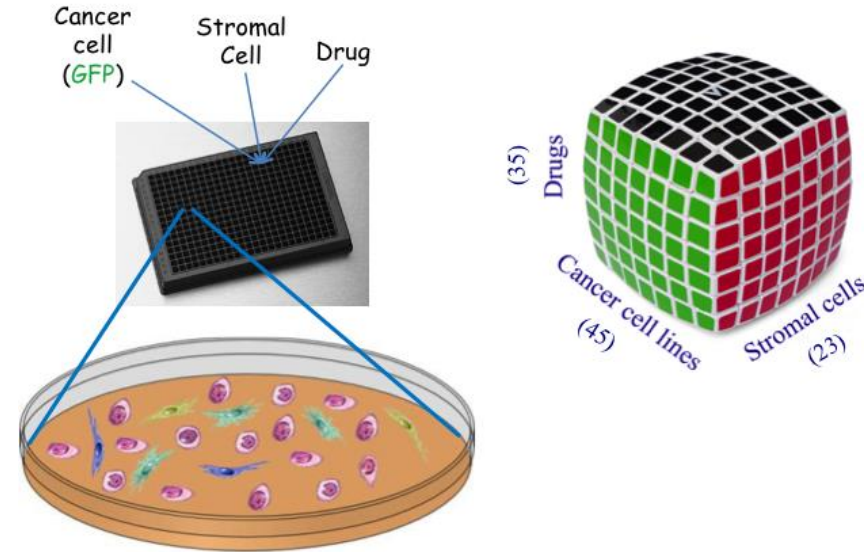
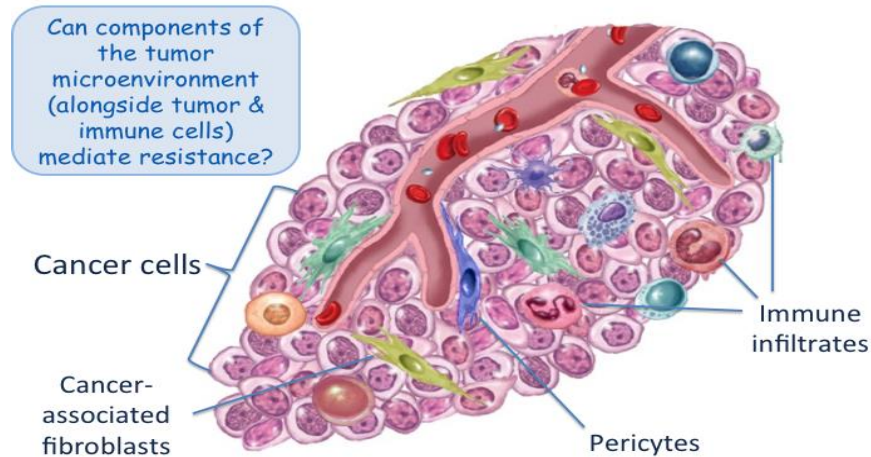


We first studied the role of the microbiome in cancer, but did it serendipitously

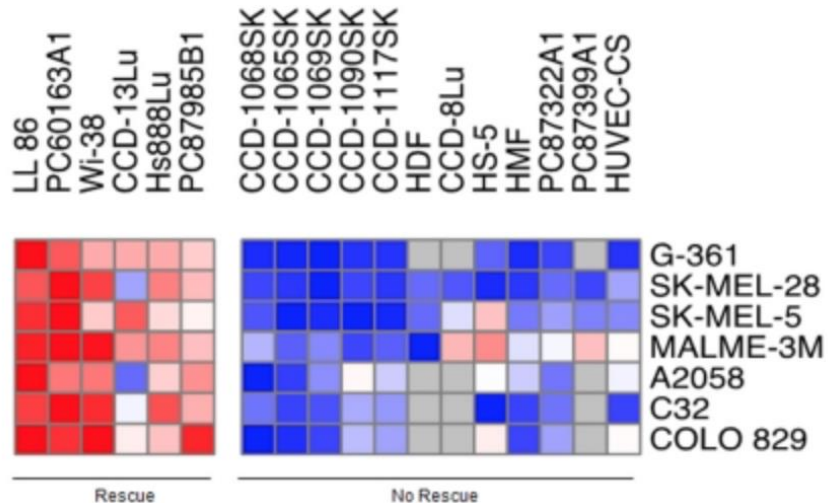
Tumour Microenvironment



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



Certain stromal cells were capable of mediating resistance to targeted therapy



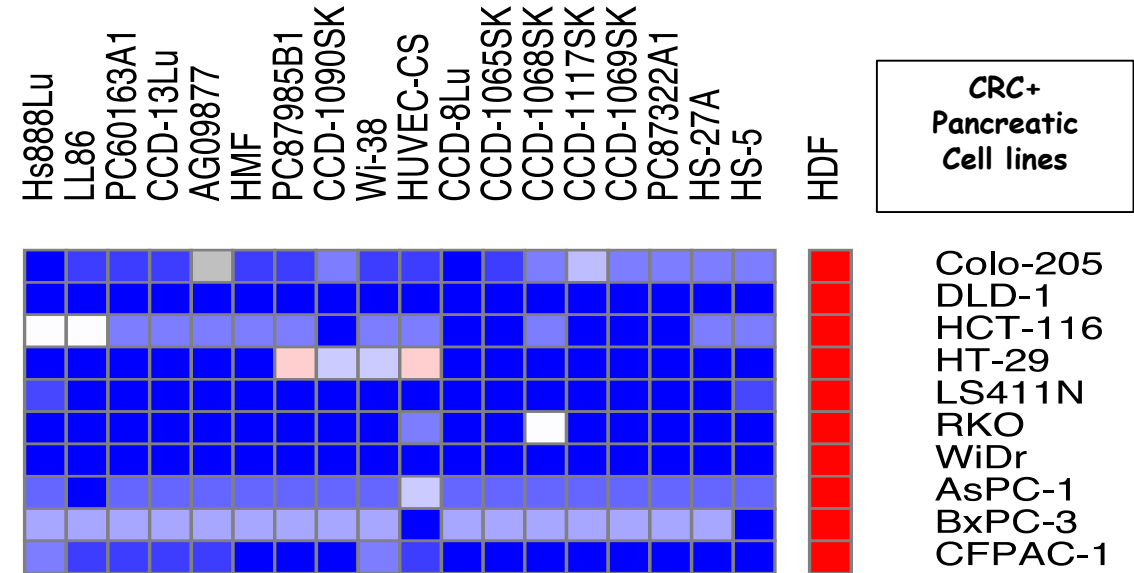
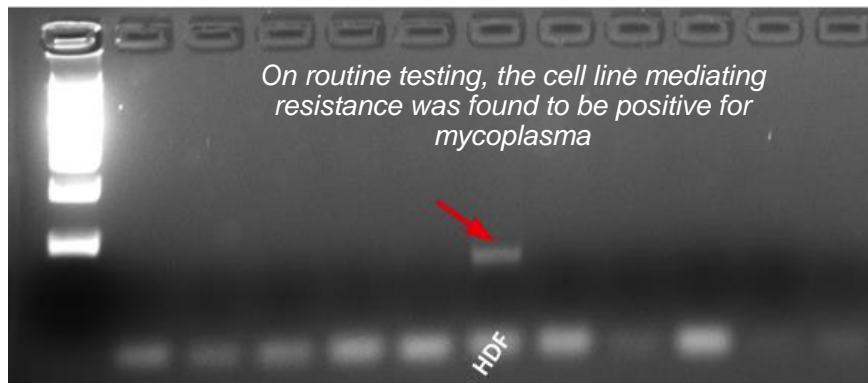
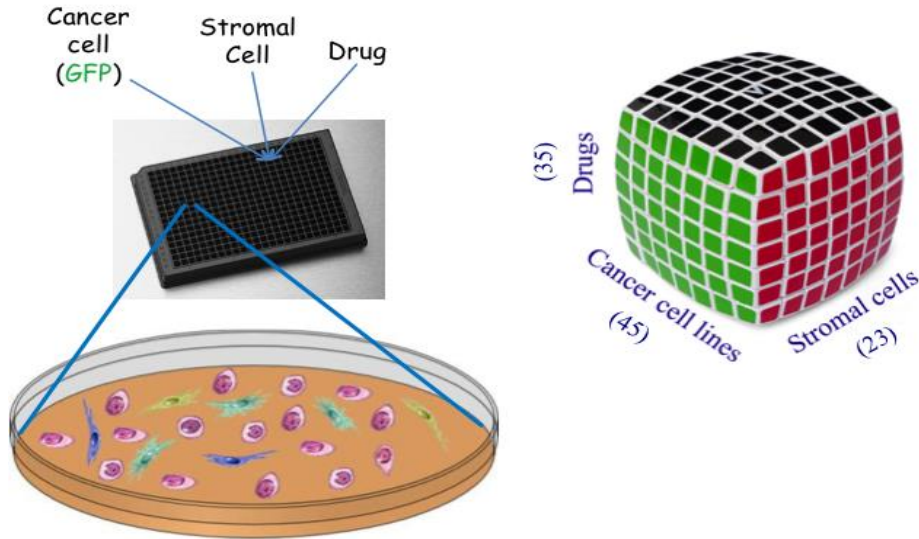
Tumor microenvironment induces innate RAF-inhibitor resistance through HGF secretion

Ravid Straussman¹, Teppei Morikawa², Kevin Shee¹, Michal Barzily-Rokni¹, Zhi Rong Qian², Jinyan Du¹, Ashli Davis¹, Margaret M. Mongare¹, Joshua Gould¹, Dennie T. Frederick³, Zachary A. Cooper³, Paul B. Chapman⁴, David B. Solit^{4,5}, Antoni Ribas^{6,7}, Roger S. Lo^{7,8}, Keith T. Flaherty³, Shuji Ogino^{2,9}, Jennifer A. Wargo³, and Todd R. Golub^{1,10,11,12,*}

Straussman et al, Nature 2012

We used the model to study stromal resistance in other cancers (*with a twist*)

The same strategy was employed to study resistance to chemotherapy in colorectal cancer and pancreatic cancer



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

Mycoplasma is responsible for rescue from Gemcitabine:

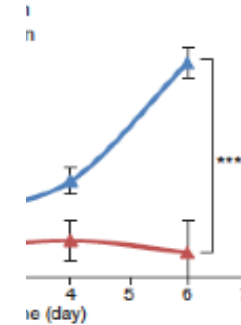
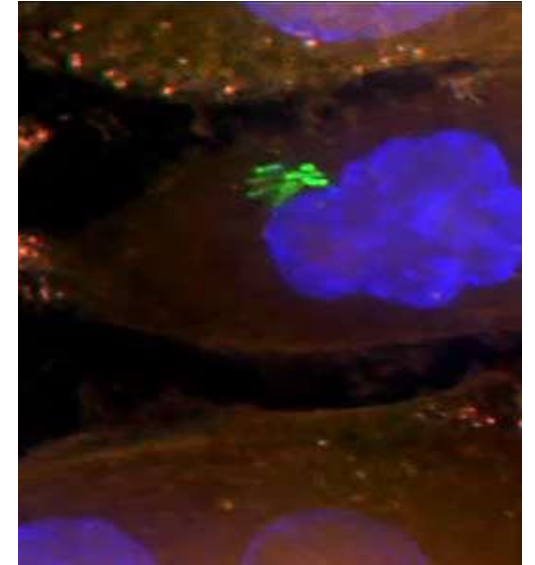
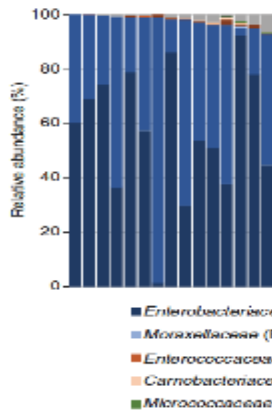
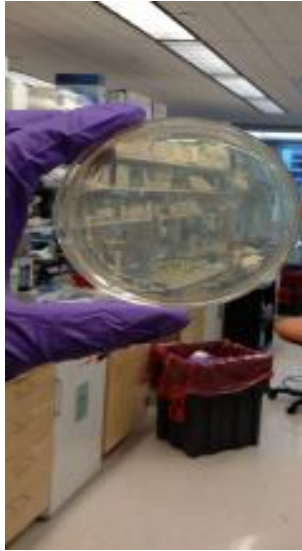
- Eradication of mycoplasma → no rescue
- Infection of another cell line → rescue
- WGS of HDF-pre-conditioned media → mycoplasma
- Bacteria were breaking down gemcitabine into inactive form

We validated findings in human samples and mouse models, suggesting that intra-tumoral bacteria may mediate resistance to chemotherapy

CANCER

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

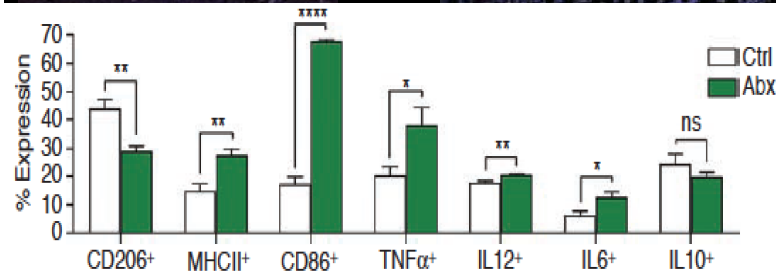
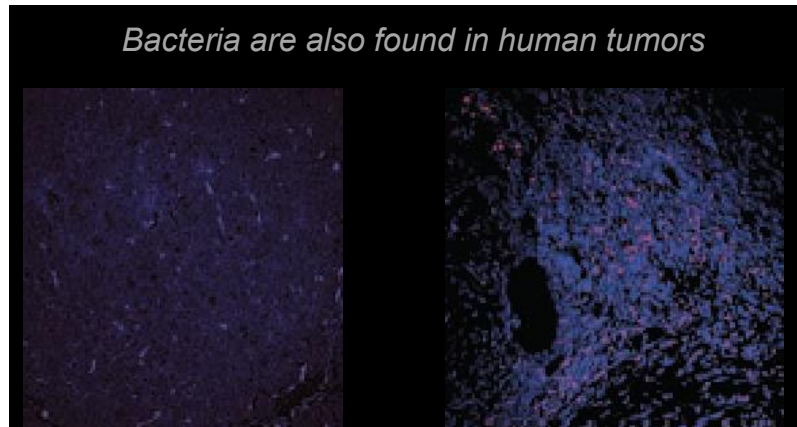
Leore T. Geller,^{1*} Michal Barzily-Rokni,^{2*} Tal Danino,^{3†} Oliver H. Jonas,^{4,5} Noam Shental,⁶ Deborah Nejman,¹ Nancy Gavert,¹ Yaara Zwang,¹ Zachary A. Cooper,^{7,8‡} Kevin Shee,² Christoph A. Thaiss,⁹ Alexandre Reuben,⁸ Jonathan Livny,² Roi Avraham,¹⁰ Dennie T. Frederick,¹¹ Matteo Ligorio,¹² Kelly Chatman,¹³ Stephen E. Johnston,² Carrie M. Mosher,² Alexander Brandis,¹⁴ Garold Fuks,¹⁵ Candice Gurbatri,¹⁶ Vancheswaran Gopalakrishnan,⁸ Michael Kim,⁸ Mark W. Hurd,¹⁷ Matthew Katz,⁸ Jason Fleming,⁸ Anirban Maitra,¹⁸ 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||¶}



With Ravid Straussman Todd Golub, Matt Katz, Anirban Maitra, Mike Kim, and others... Science 2017

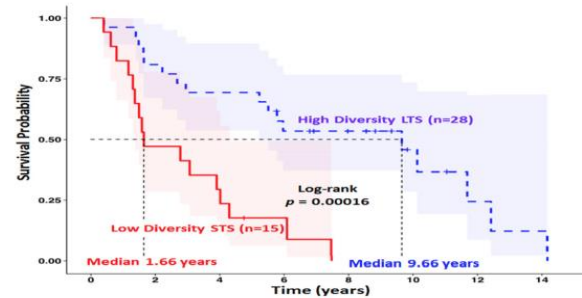
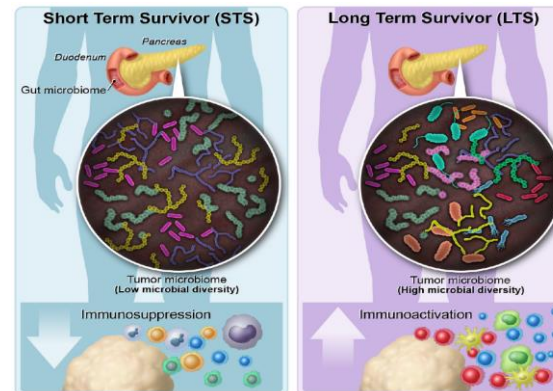
Intra-tumoral microbes may also impact anti-tumor immunity, with some intra-tumoral microbes negatively impacting it, while others promote immunity (*even via neoantigens*)

Bacteria are found in patient tumors and in GEMM of pancreatic cancer, and are associated with a more immunosuppressive tumor microenvironment in some cases



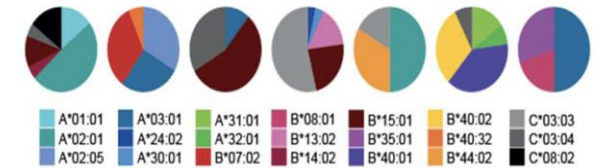
Pushulkar et al, Cancer Discovery 2018

However in other cohorts, a more diverse tumor microbiome is associated with improved survival, and an enhanced immune infiltrate



Riquelme et al, Cell 2019

Microbes are identified in melanoma tumors, and microbial neoantigens are processed and presented (and recognized by T cells)



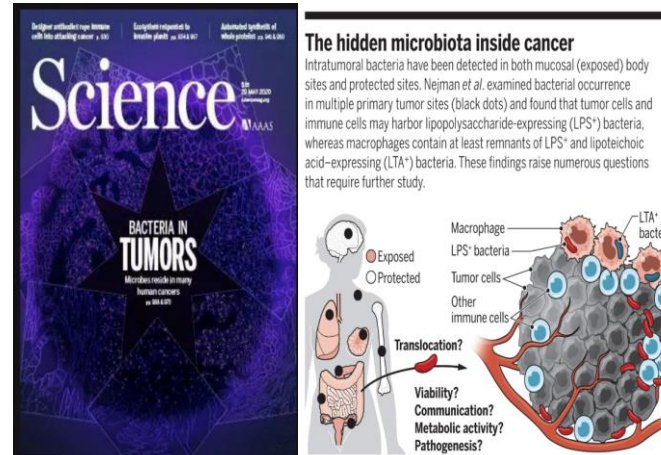
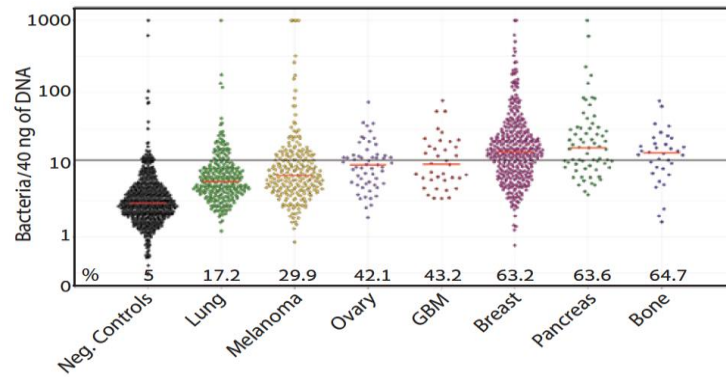
Kalaora, Nagler et al, Nature 2021

Yardena Samuels PhD

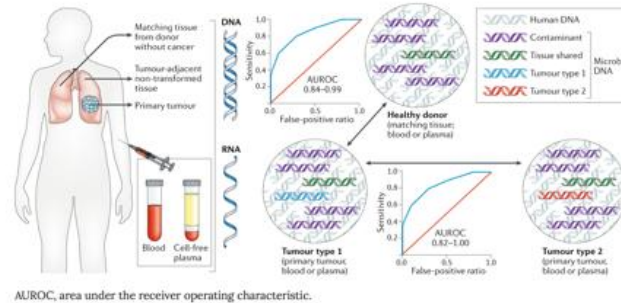
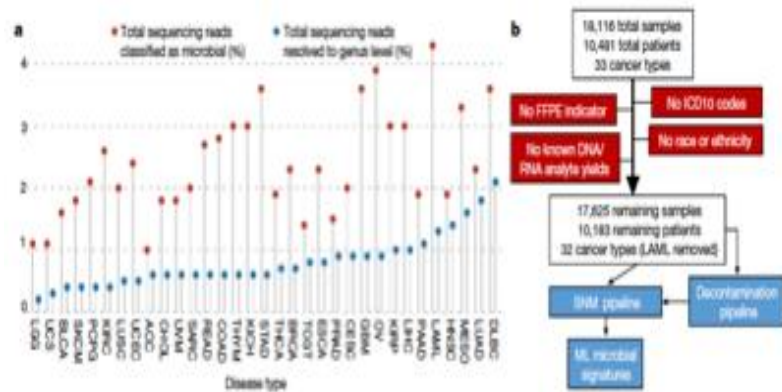


Microbial signatures are now being identified across all tumor types, with opportunities to target them to improve outcomes (*and even prevent cancer*)

Intra-tumoral bacteria were identified in all tumor types, though composition differed depending on histology

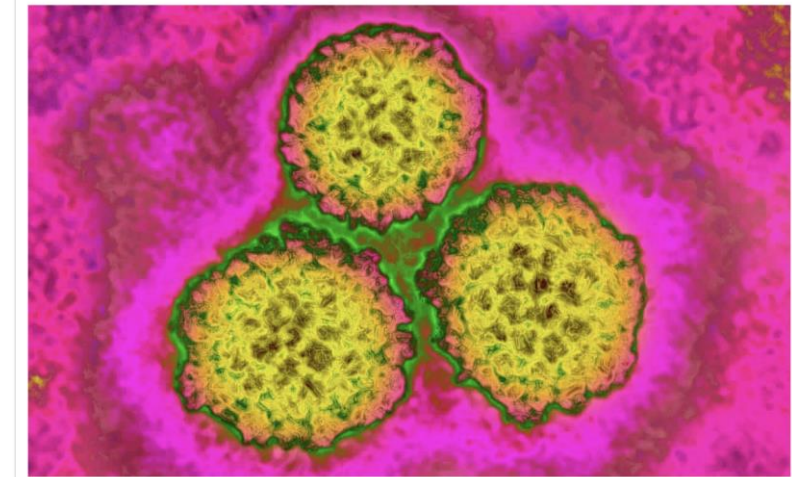


Mining of TCGA data also reveals microbial signatures in tumors (and in blood) of patients with cancer



'It's incredible': HPV vaccine saves thousands of women from cervical cancer, UK study shows

Rates have fallen 62% in women offered the HPV jab between the age of 14 and 16, and 34% for older teenagers



The human papillomavirus (HPV) is becoming less common because of the vaccine against cervical cancer. Photograph: BSIP/UiG/Getty Images

AND A THING
THE ANSWER
IS GONNA
BE
YES

— Dr. Jonathan Wargo, MD, Dana-Farber Cancer Center, Boston



Ravid Straussman MD PhD

Rob Knight PhD Neiman et al Science 2020, Poore et al, Nature 2020

Trinchieri Nat Rev Clin Oncology 2020

Investigators are now interrogating the tumor (& gut) microbiome across cancer types, with promising results



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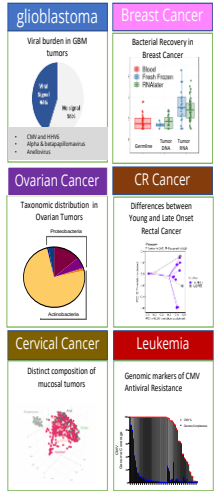
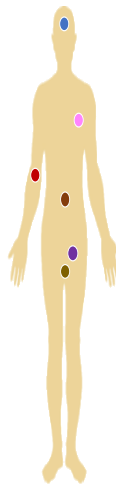
Khalel Imanbayev, MD
Rsrch. Data Coordinator

Yasmine Hoballah, MSc
Rsrch. Asst. II

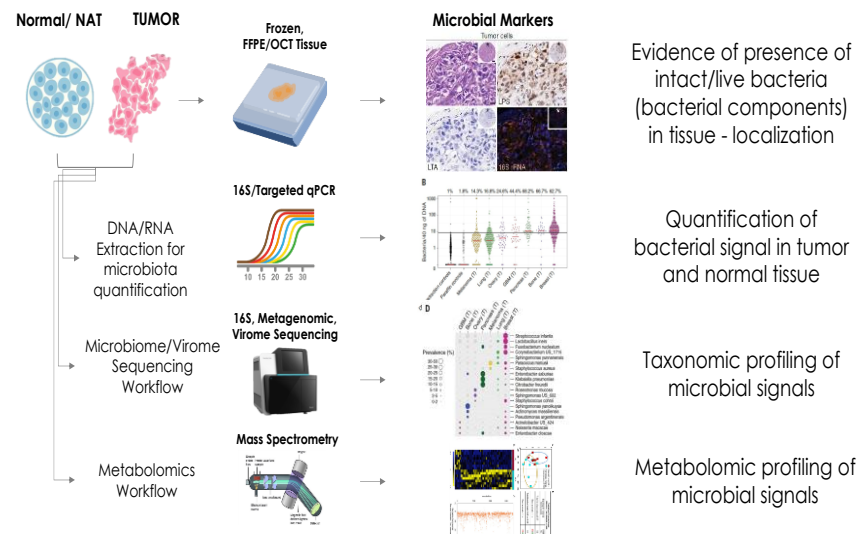
Microbiome Data Mining

PRIME-TR Microbiome-dedicated bioinformatic resources

INPUT	METHOD	OUTPUT
WGS	VirMAP	• Feature tables
WXS/WES	• DNA and RNA eukaryotic viruses, endogenous retroviruses, and bacteriophages	• Genomic reconstructions
Bulk RNASeq	BacMAP	• Genomic annotation
fastq files	• Decontamination engine	
bam files	• Primer/Probe Design	• Oligos for targeted identification and imaging
	• Feature Selection	• Discovery analysis



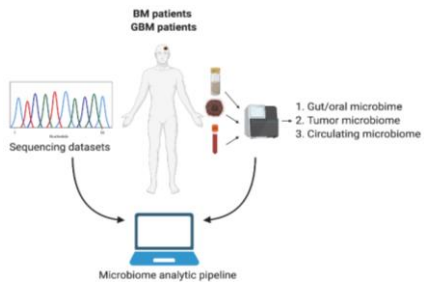
TISSUE MICROBIOME PROFILING



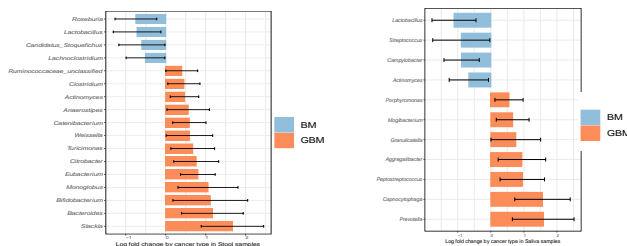
We have some very interesting findings across cancer types, including data that will be presented at this meeting by Dr. Golnaz Morad and others, who are interrogating the tumor (and gut / oral) microbiome in patients (and in pre-clinical models) of brain tumors



Golnaz Morad PhD
Sherise Ferguson MD
Fred Lang MD



Differential signatures observed in the gut and oral microbiome of patients with brain metastases (BM) versus GBM



Confidential unpublished data * DO NOT POST *

In addition to microbes within tumors, we know that microbes within the gut profoundly impact our physiology

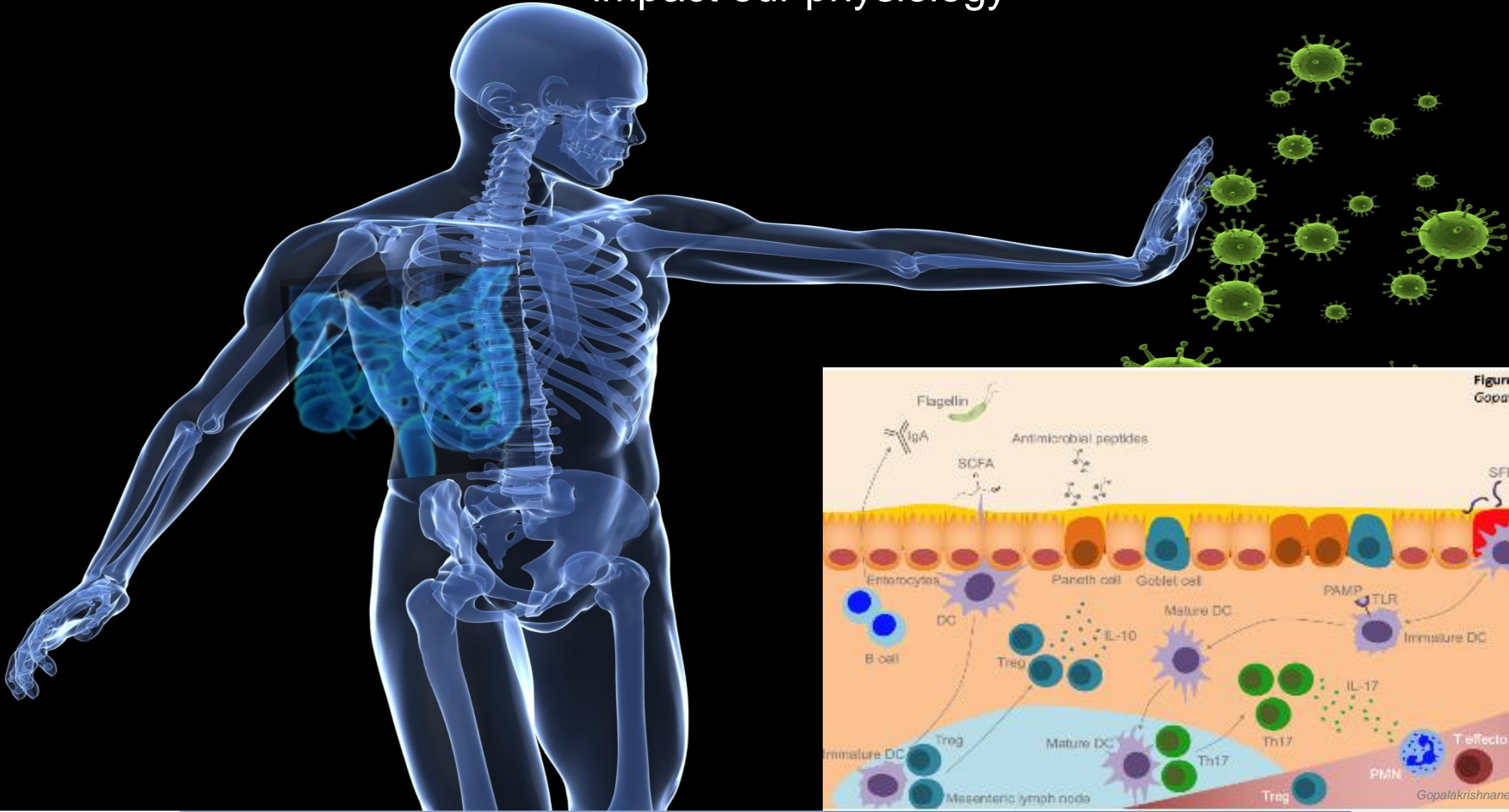
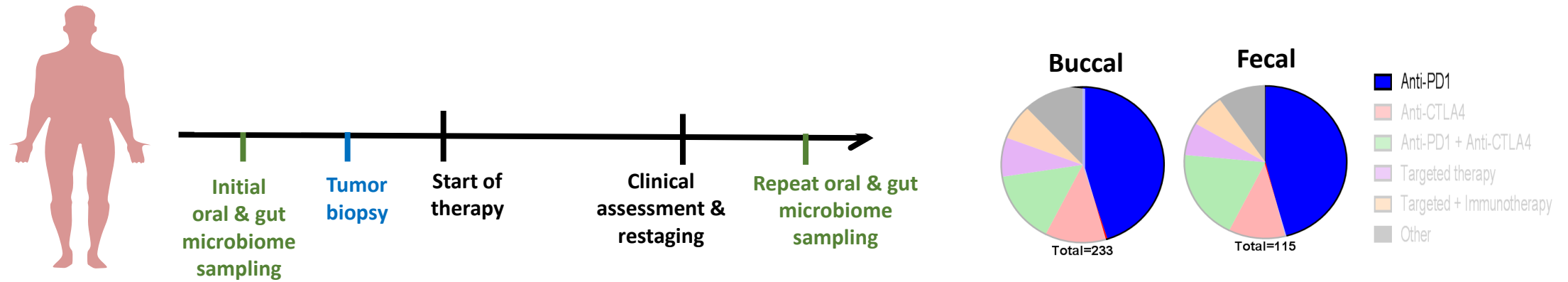


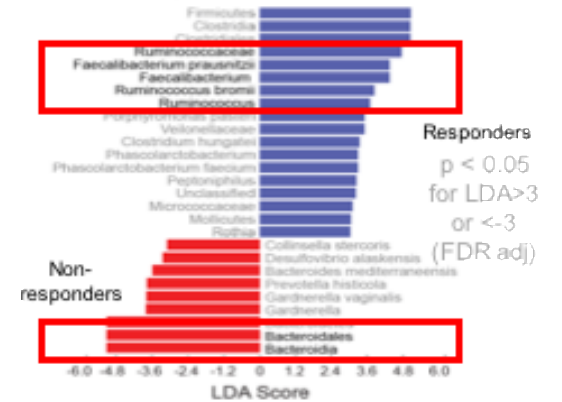
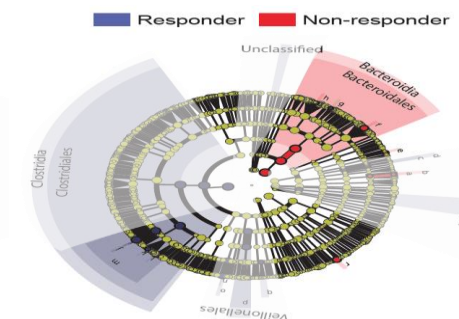
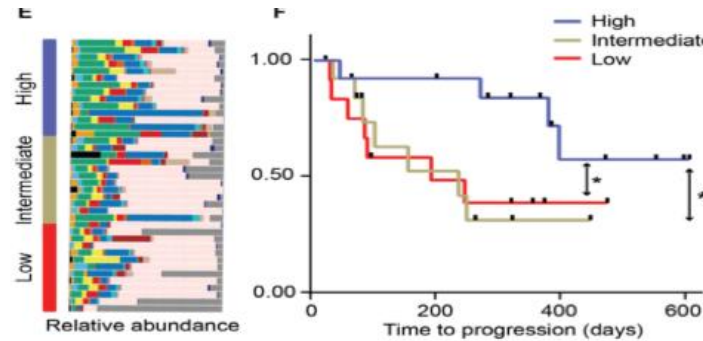
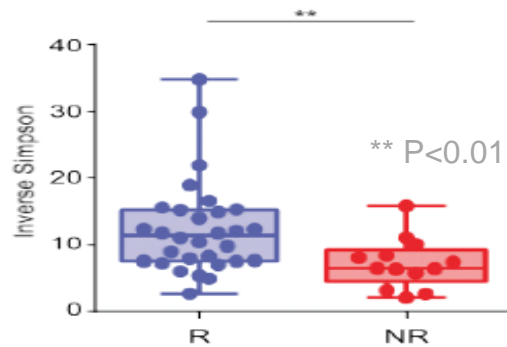
Figure 1.
Gopalakrishnan et al.

Gopalakrishnan et al, Cancer Cell 2018

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



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)



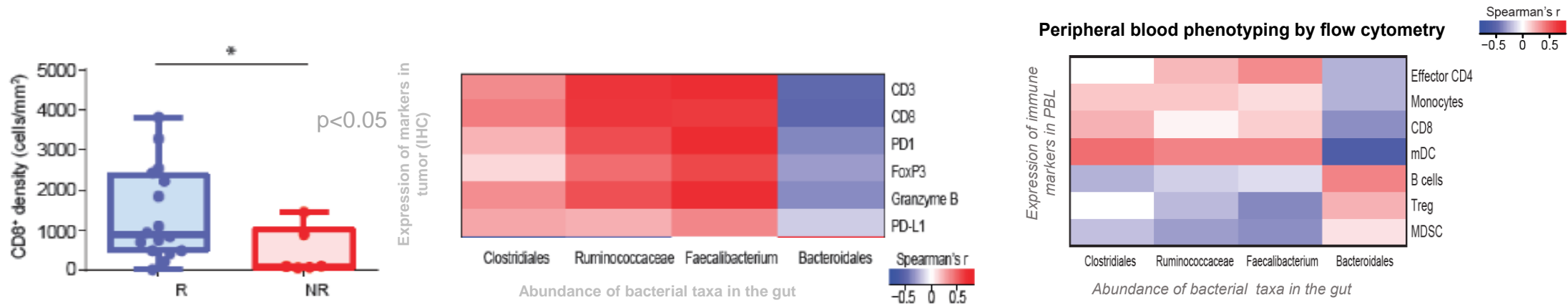
Deepak Gopalakrishnan PhD

Gopalakrishnan et al, Science 2018

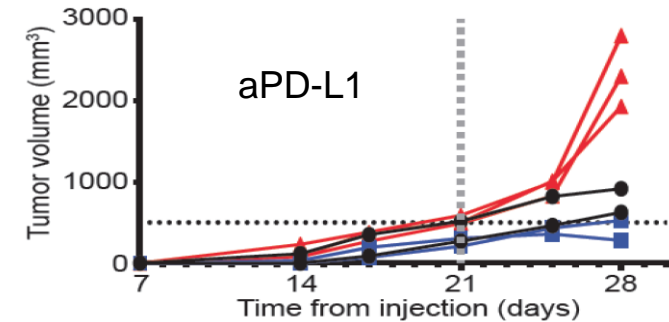
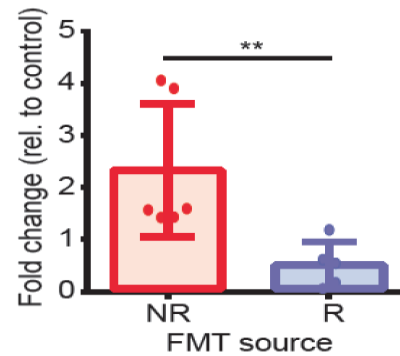
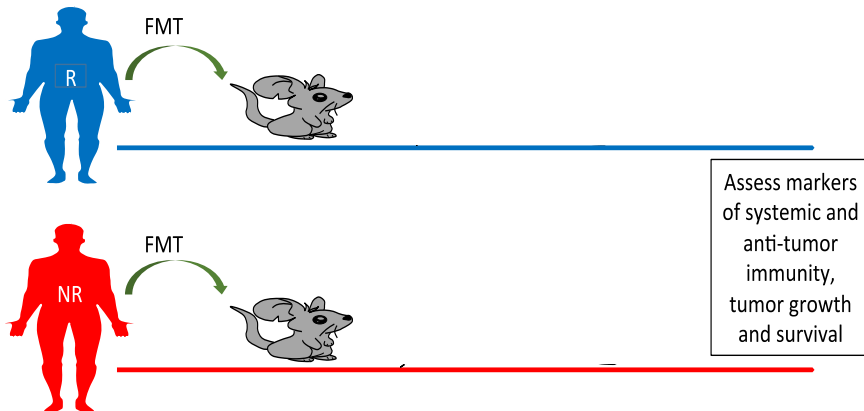


Christine Spencer PhD

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

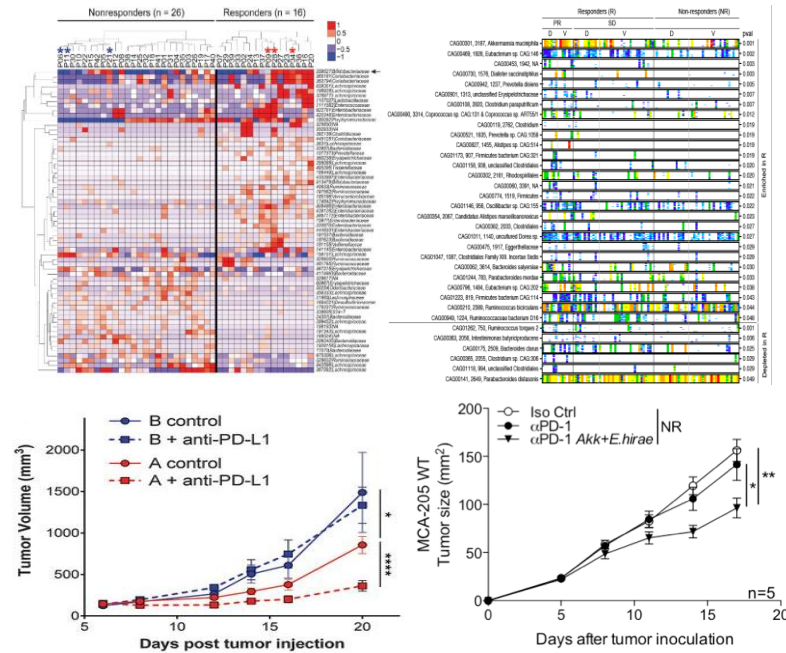
Gopalakrishnan et al, Science 2018



Alex Cogdill PhD

Numerous studies in human cohorts now support a link between the microbiome and response (and toxicity) to cancer therapy

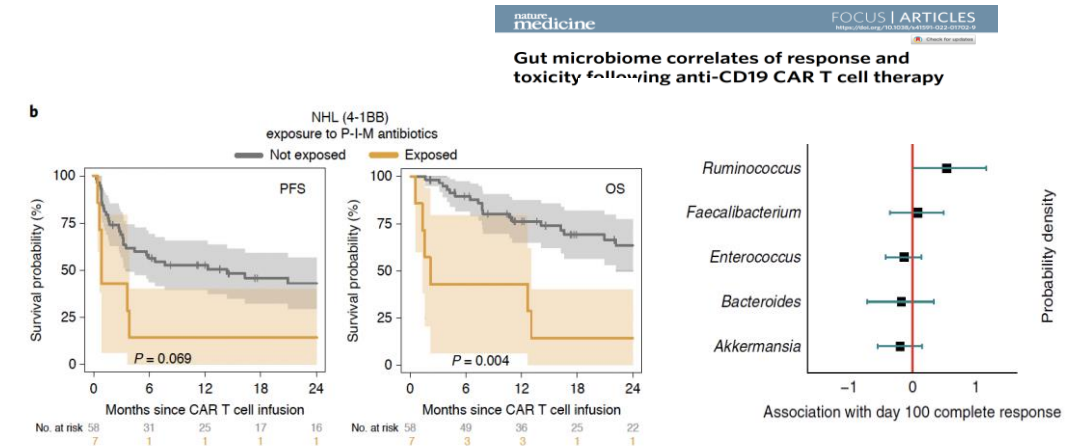
Studies in patients with melanoma, RCC, and NSCLC demonstrate differential "signatures" in R vs NR to ICB



Matson et al, Routy et al, Science 2018



Gut microbes are also strongly associated with response and toxicity to CAR-T therapy, with patients receiving antibiotics demonstrating shorter survival and higher toxicity, and specific taxa in the gut microbiome associated with prolonged survival and lower toxicity



Smith et al, Nature Medicine 2022

However, complexities exist - as taxa associated with response and lower toxicity are not congruent across all cohorts (though some unifying functional aspects exist)

Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1

McCulloch et al, Nature Medicine 2022

Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma

Lee et al, Nature Medicine 2022

Can we modulate the gut microbiome to enhance
responses to immunotherapy?
(and/or to abrogate toxicity)

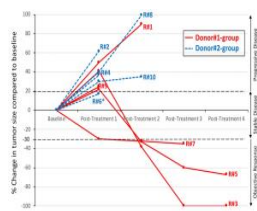
Efforts to target gut microbes to improve response to cancer treatment are proving to be effective

Clinical trials published in *Science* in 2021 demonstrate that treatment with fecal microbiota transplant (FMT) can overcome resistance to immunotherapy in patients with metastatic melanoma

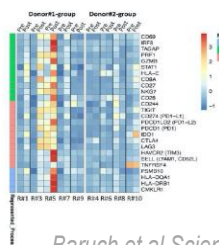
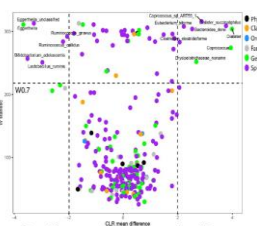
CLINICAL TRIALS

Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients

Erez N. Baruch^{1,2,3,4}, Ilan Youngster^{3,4}, Guy Ben-Betzalel¹, Rona Ortenberg¹, Adi Lahat⁵, Lior Katz⁶, Katerina Adler⁷, Daniela Dick-Necula⁸, Stephen Raskin^{4,9}, Naamah Bloch¹⁰, Daniil Rotin⁸, Liat Anaf⁸, Camila Avivi⁸, Jenny Melnichenko¹, Yael Steinberg-Silman¹, Ronac Mamtani¹¹, Hagit Harati¹, Nethanel Asher¹, Ronnie Shapira-Frommer¹, Tal Brosh-Nissimov¹², Yael Eshet^{4,8,13}, Shira Ben-Simon¹⁰, Oren Ziv¹⁰, Md Abdul Wadud Khan¹⁴, Moran Amit¹⁵, Nadim J. Ajami¹⁴, Iris Barshack^{4,8}, Jacob Schachter^{1,4}, Jennifer A. Wargo^{14,16}, Omry Koren¹⁰, Gal Markel^{1,2,17,18}, Ben Boursi^{4,18,19,20}



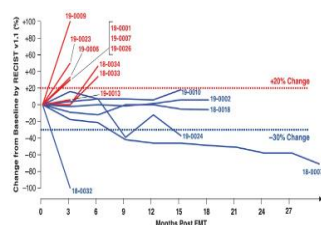
- 10 patients treated
- Had progressed on multiple therapies
- 2 donors (both CR)
- 3 patients responded
- Changes in microbiome and immune infiltrates noted



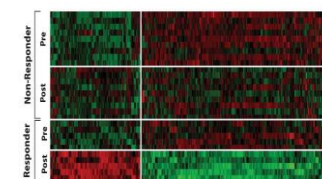
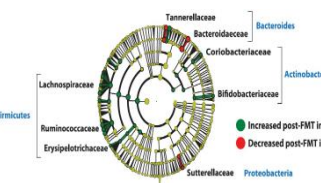
CLINICAL TRIALS

Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients

Diwakar Davar^{1,2}, Amiran K. Dzutsev^{2,3}, John A. McCulloch², Richard R. Rodrigues^{2,3}, Joe-Marc Chauvin¹, Robert M. Morrison¹, Richelle N. Deblasio¹, Carmine Menna¹, Quanquan Ding¹, Ornella Pagliano¹, Bochra Zidi¹, Shuowen Zhang¹, Jonathan H. Badger², Marie Vetzizou², Alicia M. Cole², Miriam R. Fernandes², Stephanie Prescott², Raquel G. F. Costa², Ascharya K. Balaji², Andrey Morgun⁴, Ivan Vujkovic-Cvijin⁵, Hong Wang⁶, Amir A. Borhani⁷, Marc B. Schwartz⁸, Howard M. Dubner⁸, Scarlett J. Ernst¹, Amy Rose¹, Yana G. Najjar¹, Yasmine Belkaid⁵, John M. Kirkwood¹, Giorgio Trinchieri^{2,5}, Hassane M. Zarour^{1,9,10,11}



- 15 patients treated
- Had progressed on prior anti-PD-1
- 7 donors (4 CR, 3. PR)
- 6 patients with clinical benefit
- Changes in microbiome and immune infiltrates noted, and serum metabolites



Baruch et al Science 2020; Davar et al Science 2021

A recent clinical trial published in *Nature Medicine* demonstrated that treatment with a live bacterial product (CBM588) in combination with CTLA-4 and PD-1 blockade was effective in treating patients with metastatic renal cell carcinoma

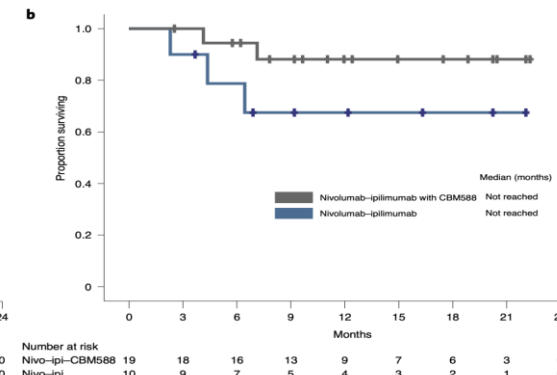
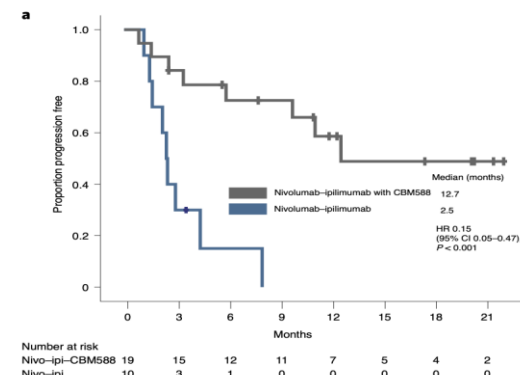
nature
medicine

FOCUS | ARTICLES
<https://doi.org/10.1038/s41591-022-01694-6>

Check for updates

OPEN

Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial

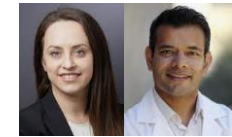


Dizman et al Nature Medicine 2022



Erez Baruch MD PhD

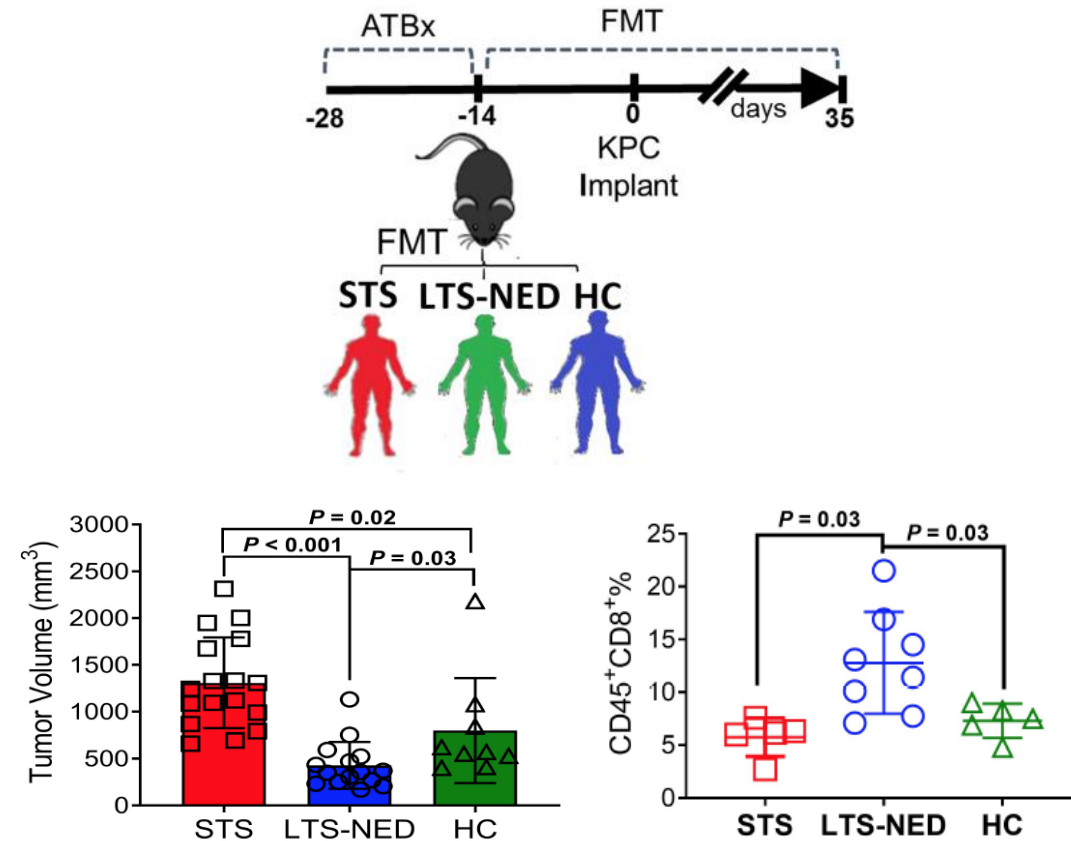
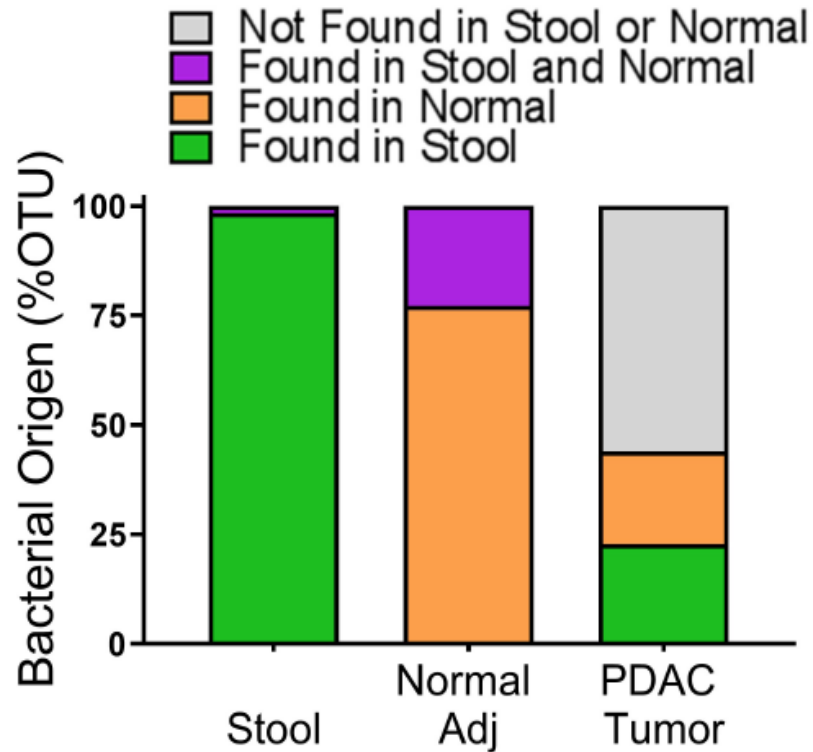
Diwakar Davar MD



Nazli Dizman MD

Sumanta Pal, MD

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

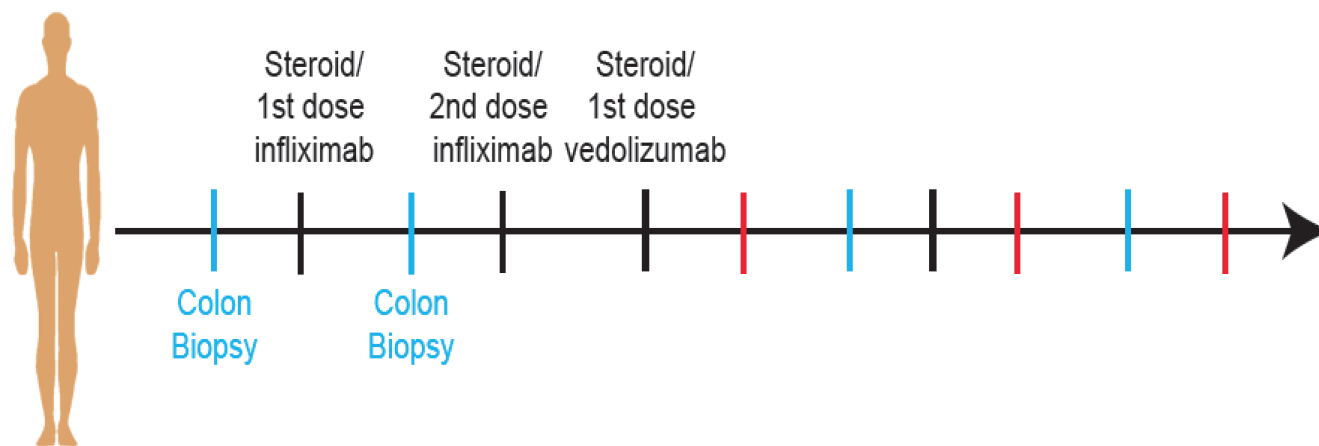


Florencia McAllister MD PhD

Clinical trials are underway using gut microbiome modulation (in patients with pancreatic cancer and colorectal cancer (PIs – McAllister, Overman)

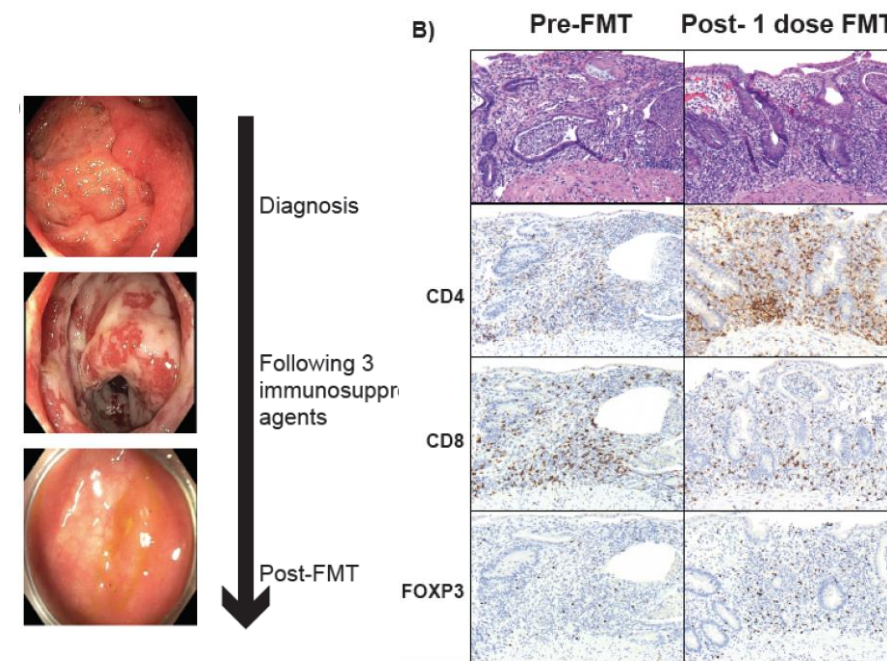
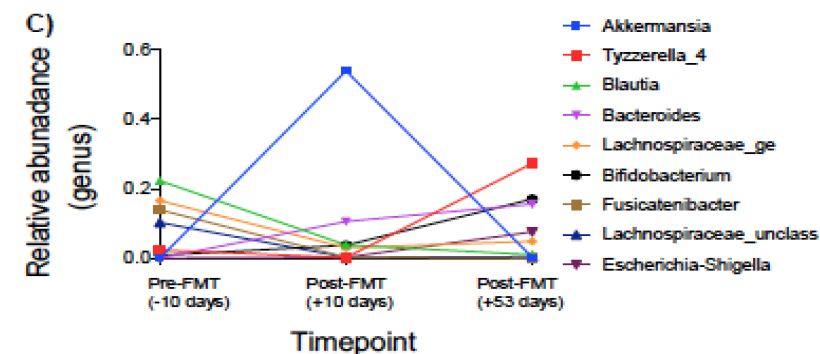
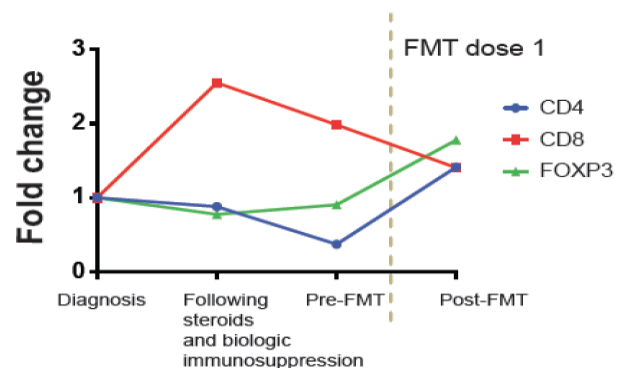
Riquelme et al, Cell 2019

These approaches may also be helpful in treating immunotherapy toxicity



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

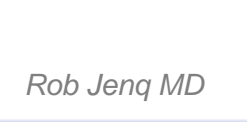
50 yo female with metastatic urothelial cancer was treated with aCTLA-4 + a PD-1 and developed colitis refractory to steroids and aTNF



Mimi Wang MD PhD



Wang et al, Nature Medicine 2018



Rob Jenq MD

Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms

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Safety & Availability (Biologics)

[Biologic Product
Security](#)

[Blood Safety &
Availability](#)

June 13, 2019

The Food and Drug Administration (FDA) is informing health care providers and patients of the potential risk of serious or life-threatening infections with the use of fecal microbiota for transplantation (FMT). The agency is now aware of bacterial infections caused by multi-drug resistant organisms (MDROs) that have occurred due to transmission of a MDRO from use of investigational FMT.

Summary of the Issue

Content current as

of:

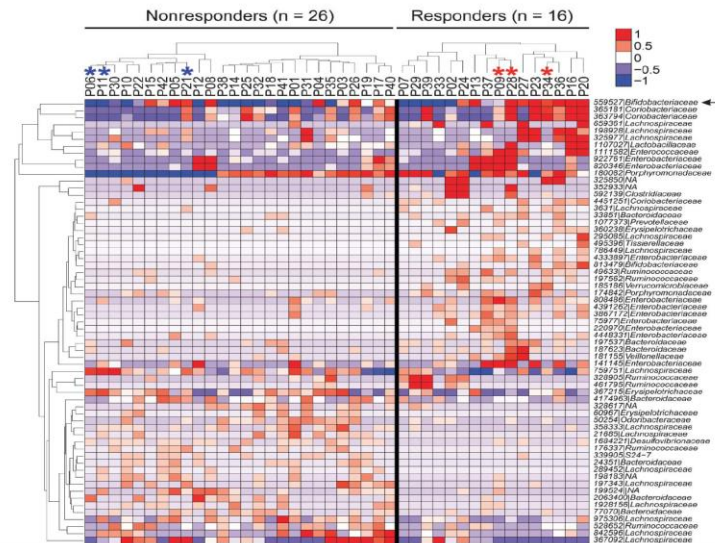
06/13/2019

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?

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

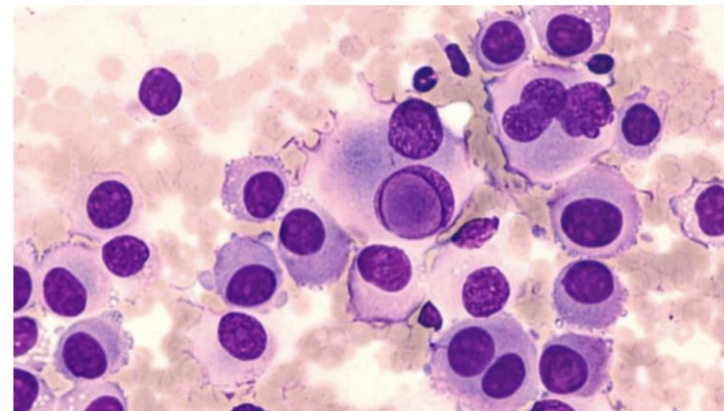
Vyara Matson,^{1*} Jessica Fessler,^{1*} Rilyue Bao,^{2,3*} Tara Chongsawat,⁴ Yuanyuan Zha,⁴ Maria-Luisa Alegre,⁴ Jason J. Luke,⁴ Thomas F. Gajewski^{1,4,†}



Matson et al, Science 2018

Seres to Discontinue Microbiome Cancer Clinical Program

Published: Mar 08, 2021 | By Mark Zipkin



Microbiome company **Seres Therapeutics** announced the discontinuation of its Phase Ib trial of SER-401, an orally delivered consortia of bacteria that was intended to boost the efficacy of checkpoint inhibitors in patients with metastatic melanoma.

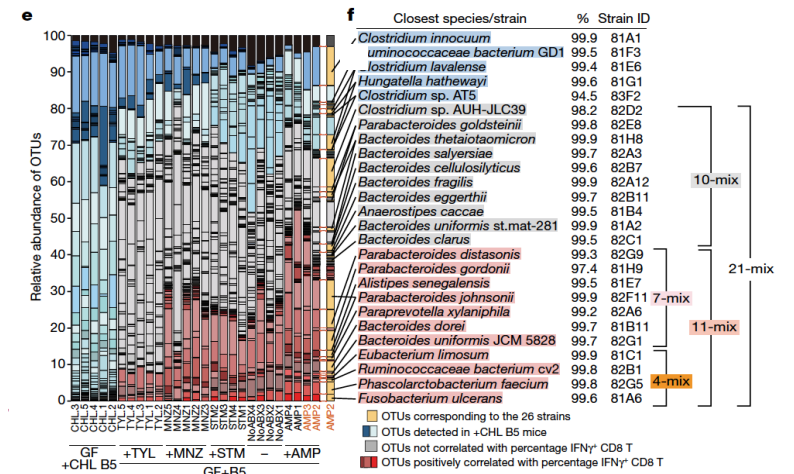
The company said it was motivated both by the challenges of patient enrollment during the COVID-19 pandemic and the progress of other candidates in its preclinical pipeline.

ARTICLE

<https://doi.org/10.1038/s41586-019-0878-z>

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

Takeshi Tanoue^{1,2,3,16}, Satoru Morita^{1,16}, Damian R. Plichta⁴, Ashwin N. Skelly¹, Wataru Suda^{2,5,6}, Yuki Sugiyama⁷, Seiko Narushima^{1,3}, Hera Vlamakis⁴, Iori Motoo³, Kayoko Sugita¹, Atsushi Shiohara^{1,2}, Kozue Takeshita¹, Keiko Yasuma-Mitobe¹, Dieter Riethmacher⁴, Tsuneyasu Kaisho⁸, Jason M. Norman¹⁰, Daniel Mucida¹¹, Makoto Suematsu⁷, Tomonori Yaguchi¹², Vanni Bucchi¹³, Takashi Inoue¹⁴, Yutaka Kawakami¹⁵, Bernat Olle¹⁶, Bruce Roberts¹⁰, Masahira Hattori^{1,5,6}, Ramin J. Xavier^{4,15}, Koji Atarashi^{1,2,3,16} & Kenya Honda^{1,2,3,16}

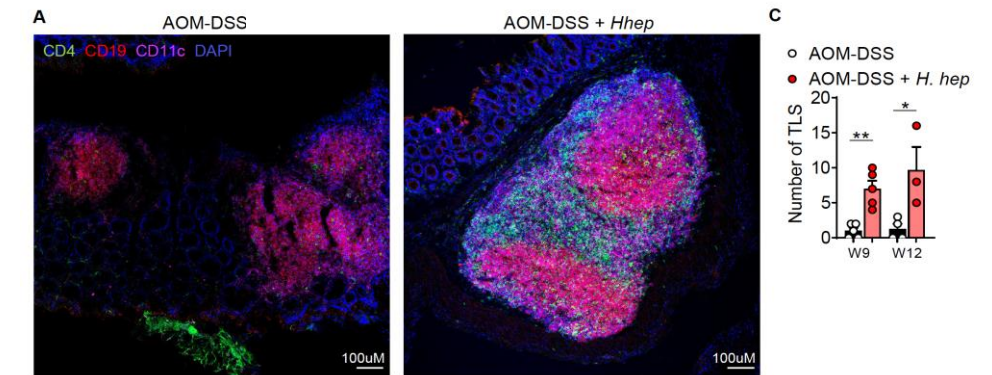
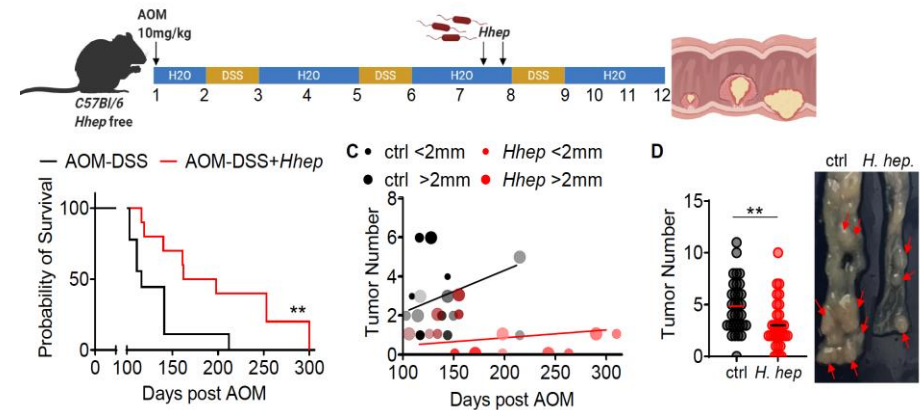


Tanoue et al, Nature 2019

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

Targeted microbial intervention in the gut (and/or tumor) may improve anti-tumor immunity through TLS / B cells

B cells and tertiary lymphoid structures (TLS) are associated with improved anti-tumor immunity, ICB response

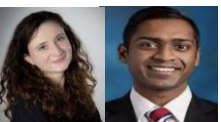


Helmink et al, Cabrita et al, Petiprez et al, Bruno T. Nature 2020

Overacre-Delgoffe, et al. Immunity 2021



Thank you to the Mark Foundation for supporting studies of TLS / B cells



Elise Nassif MD PhD
Manoj Chelvanambi PhD

Unifying signatures in the gut microbiota are found in patients with TLS in the TME (IO responders)

Data to be presented at ASCO 2022



Tumor Immune Microenvironment: A Holistic Approach Workshop

#SITCworkshop

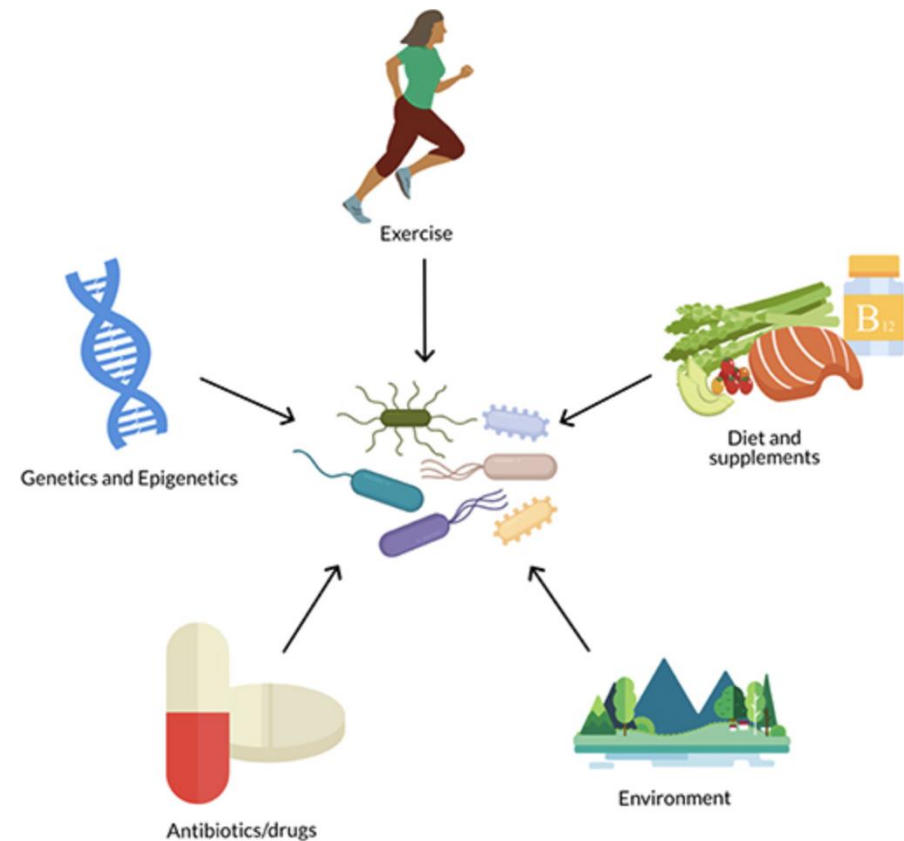


Given the critical role of the gut microbiome, what is the role of diet (and other factors) in response to cancer treatment?

II. Understanding factors that influence the TME and gut microbes in health and disease

You are what you eat!

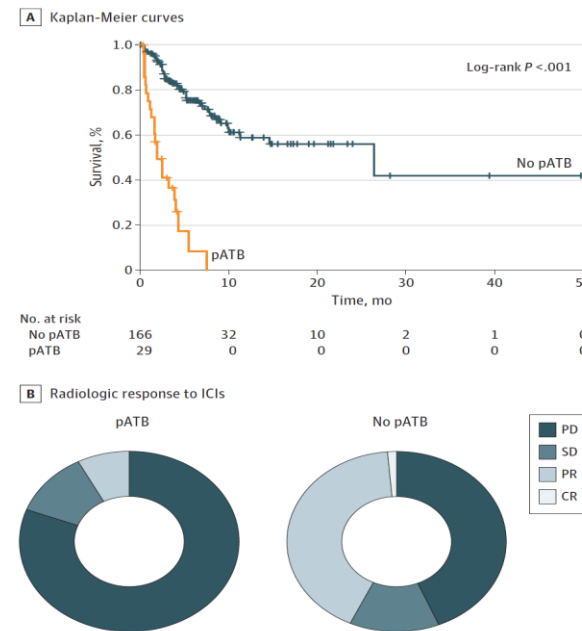
Microbes in the gut are influenced by a number of features including diet, antibiotics, and environmental factors



Hughes *Frontiers in Nutrition* 2020

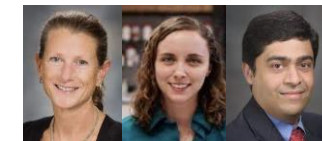
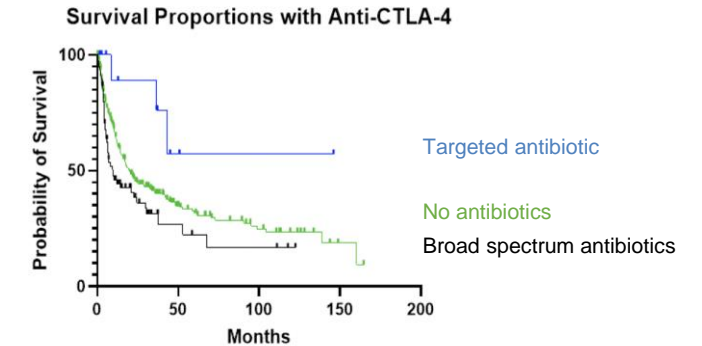
Numerous studies have shown that patients receiving antibiotics before treatment with immune checkpoint blockade (ICB) have worse outcomes (response and survival)

Figure. Association Between pATB Therapy and Survival and Response to ICIs



Pinato et al, *JAMA Oncology* 2019

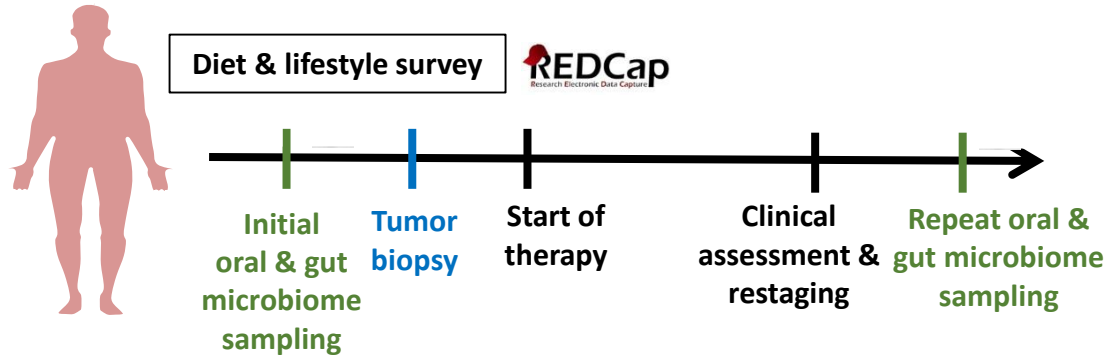
However, some targeted antibiotic approaches may actually enhance response to ICB



Stephanie Watowich PhD
Liz Park PhD
Vivek Subbiah MD

These results have potential implications for patients with earlier stage disease, and implications far beyond cancer

In our cohort, we also studied the influence of diet and lifestyle factors on the microbiome and response to immune checkpoint blockade

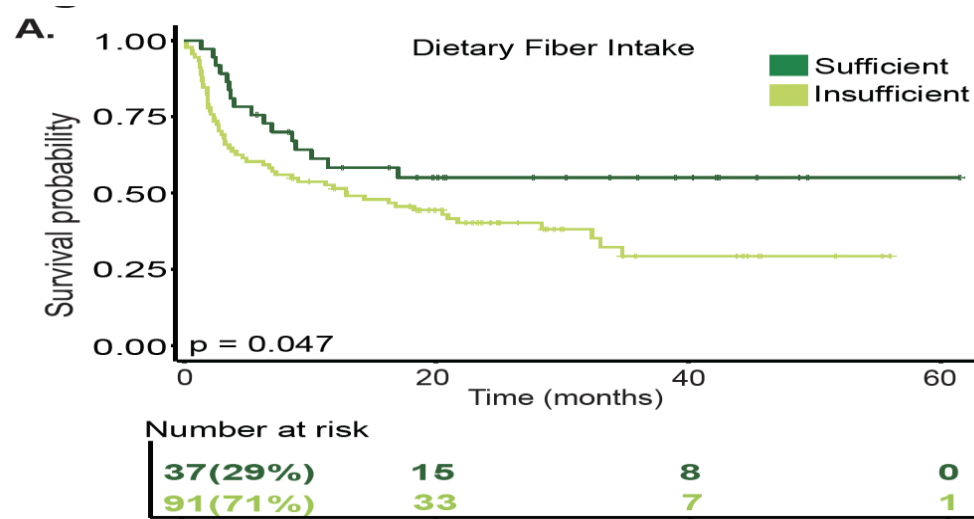


Patients reporting sufficient fiber intake (>20gm/day) have better outcomes on ICB

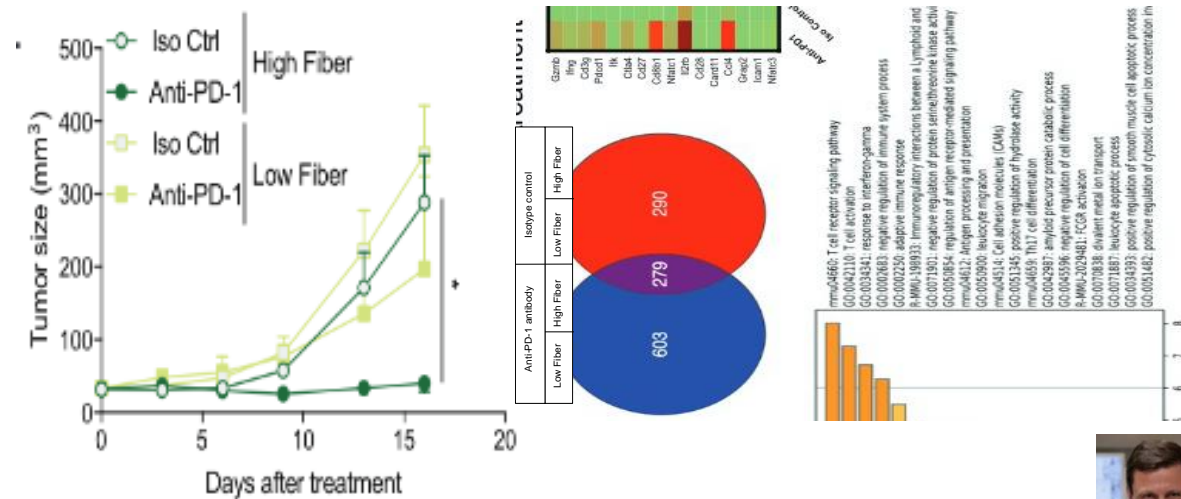
Christine Spencer PhD



Lorenzo Cohen PhD



These findings were recapitulated in pre-clinical models, demonstrating that mice given a low fiber fail to respond, and fail to activate T cell signaling pathways in the TME on treatment with anti-PD-1



Jen McQuade MD

Carrie Daniel MacDougall PhD

Spencer et al, Science 2021

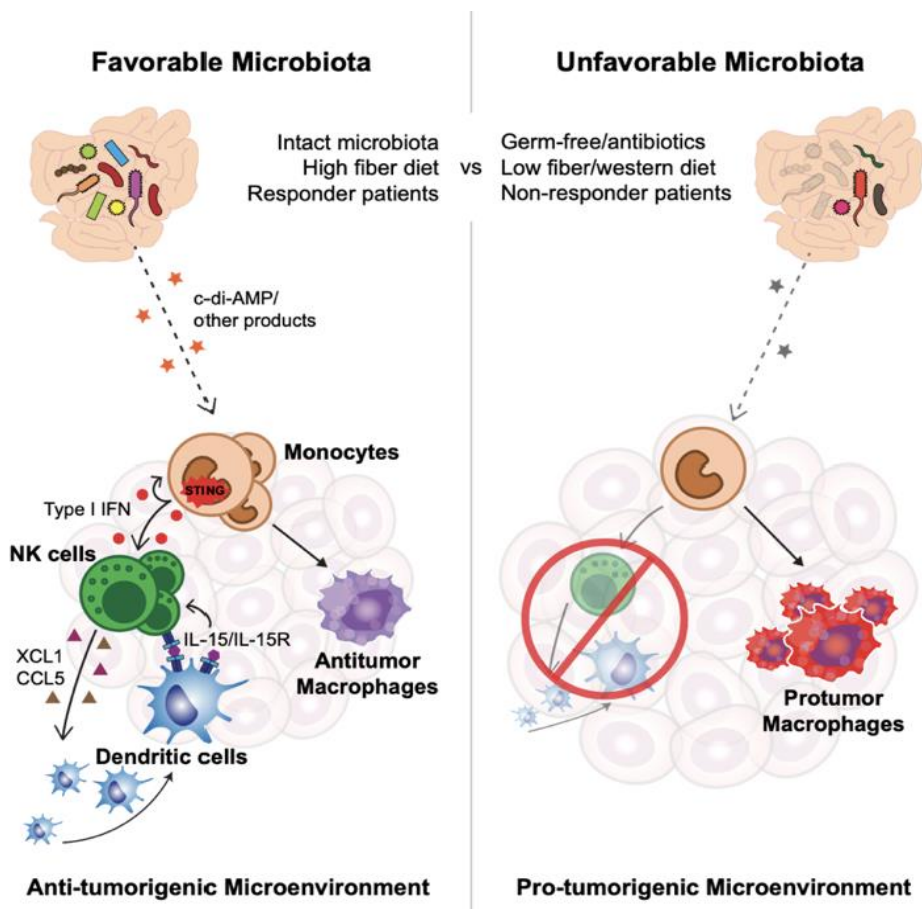
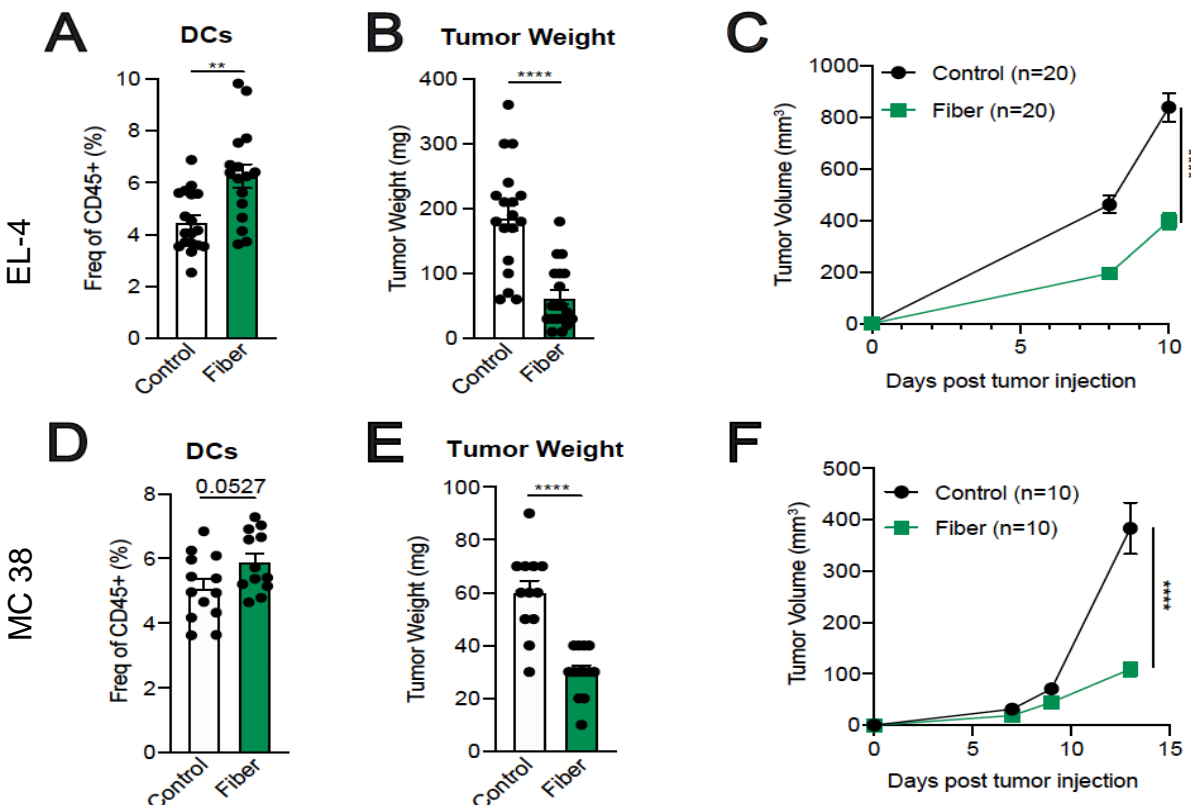
Giorgio Trinchieri PhD



This data is galvanized by data from others that high dietary fiber intake promotes anti-tumor immunity

Mice treated with a high fiber diet have delayed tumor outgrowth and more DCs

Gut microbiota and dietary fiber shape the TME in part via monocyte reprogramming by STING-mediated IFN signaling

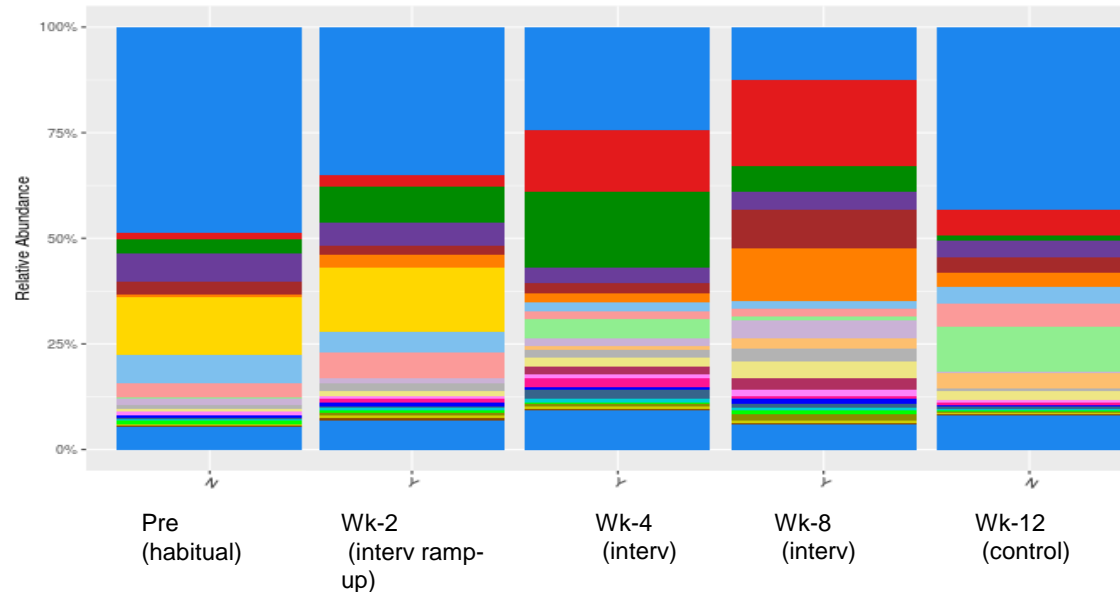


Lam et al, Cell 2021

Romina Goldszmid, PhD



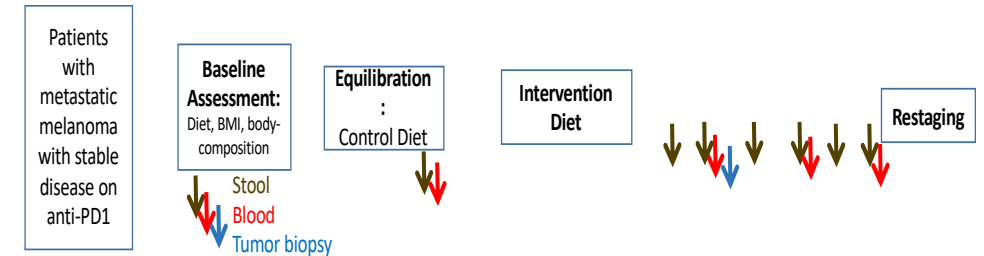
There is evidence that changes in diet can have an impact on gut microbes and associated physiology in a short time frame



Daniel et al, confidential unpublished data DO NOT POST

We are now running dietary intervention trials in combination with checkpoint blockade (funded by Seerave and other foundations)

Carrie Daniel, Jen McQuade, et al

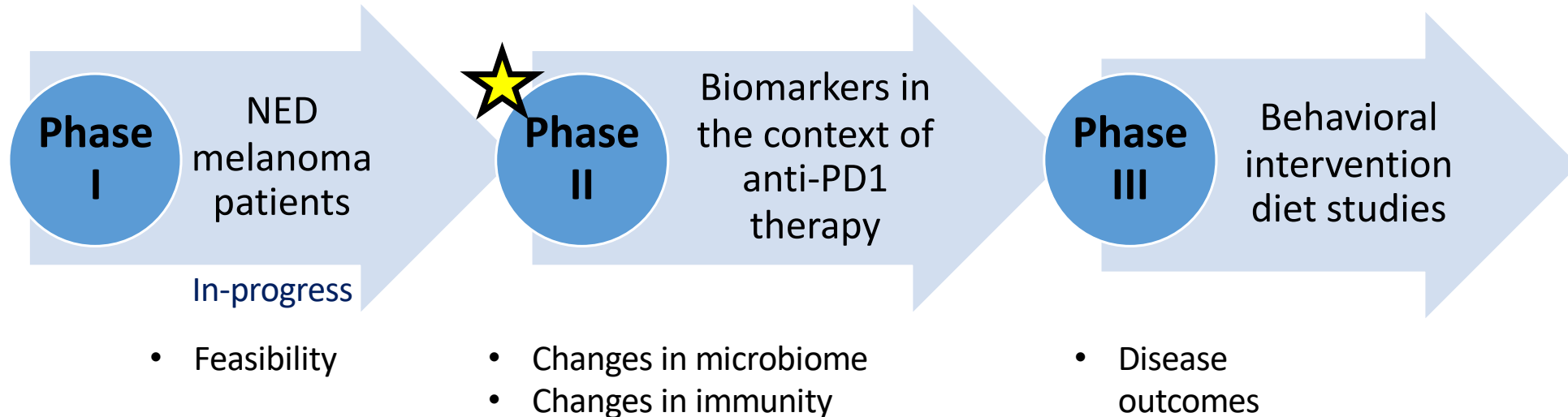


Testing diet as a precision intervention in cancer:



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*



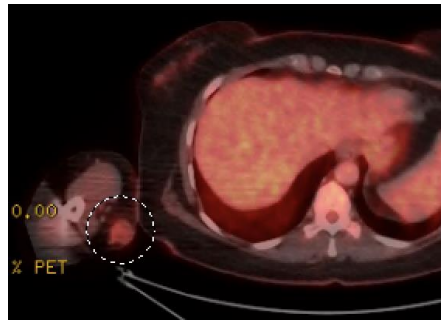
DIET (Diet and Immune Effects Trial):

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

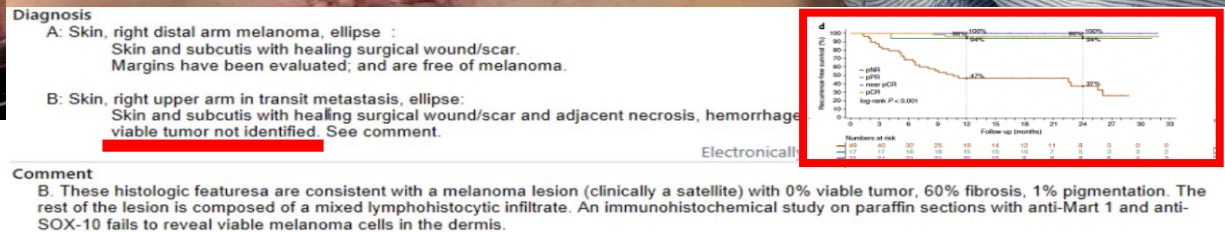


We are seeing encouraging results in this trial, and we are working with others to run similar dietary intervention studies

43 year old female with metastatic melanoma (right arm in transit)



Received immune checkpoint and high fiber diet on trial



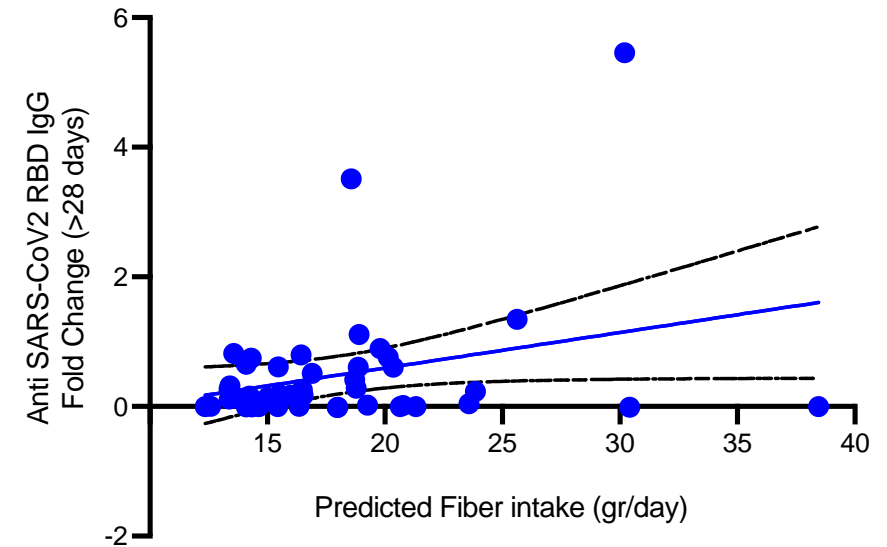
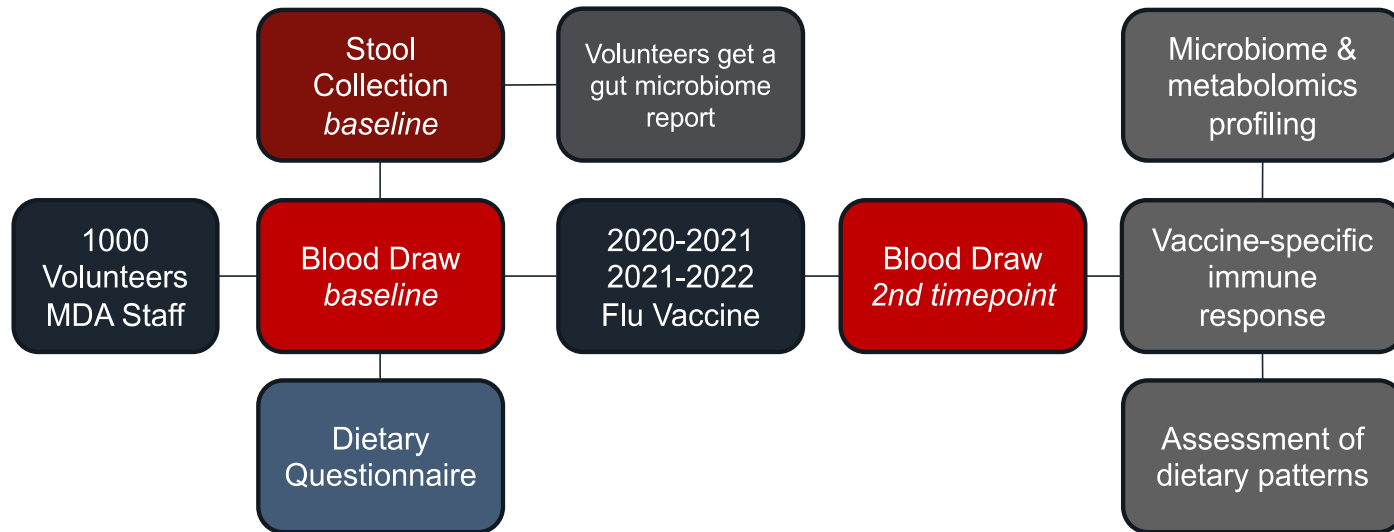
Jen McQuade MD

Confidential unpublished data * DO NOT POST *

We are also assessing the gut microbiome and dietary patterns in “healthy” individuals receiving vaccines for flu and SARS-CoV-2

ENDVR Trial – Environmental Determinants of Vaccine Response

MD Anderson Annual Flu Vaccine Campaign, 97% Employee Coverage



*Confidential unpublished data * DO NOT POST **

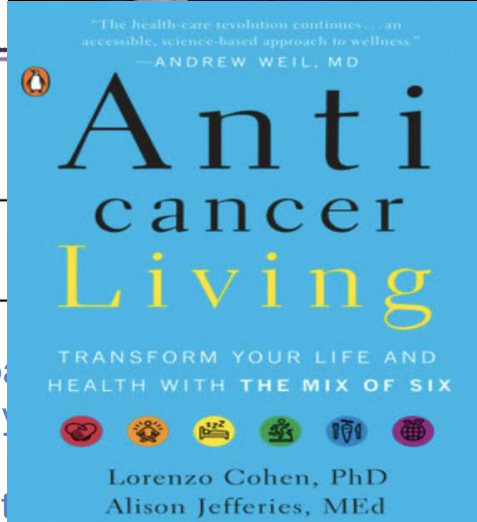
Our goal is to have a dietary intervention trial open this year to improve vaccine response with an eye on next-generation strategies to modulate gut microbes to improve immunity

Nadim
Ajami
PhD

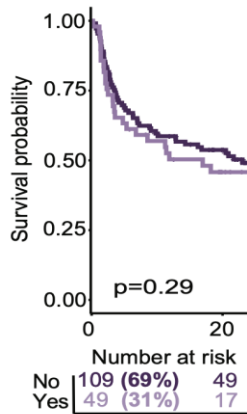


How do commercially-available probiotics influence the gut microbiome and therapeutic response?

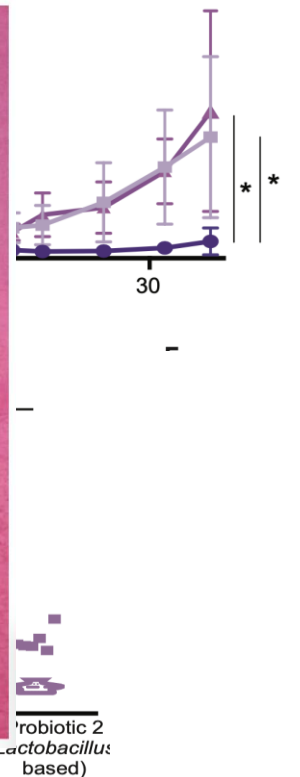
An unintended consequence of giving probiotics to patients is that they may alter their own microbiome, so using commercially available probiotics may have unintended consequences.



Probiotics had anti-PD-1, it microbes, ti-tumor



31% of our patients who were given commercially available probiotics and had a significant improvement in response, nonetheless this was intriguing

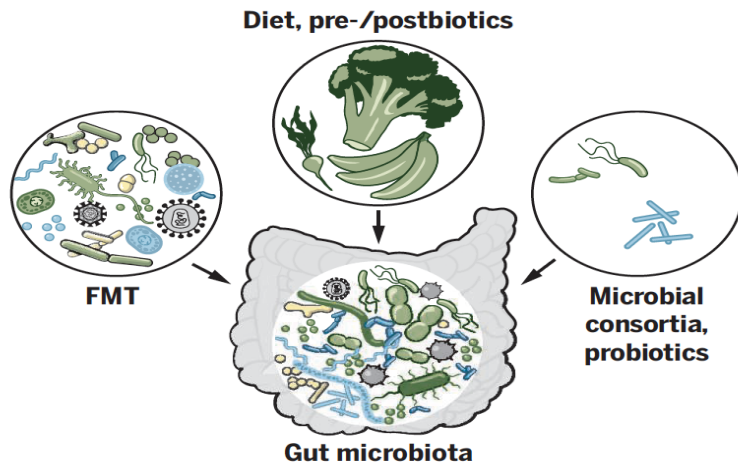


Spencer et al, Science 2021

Strategies to alter gut microbiota to improve responses (and to reduce toxicity) are currently underway, but numerous considerations exist as we use these approaches

Strategies to alter gut microbiota

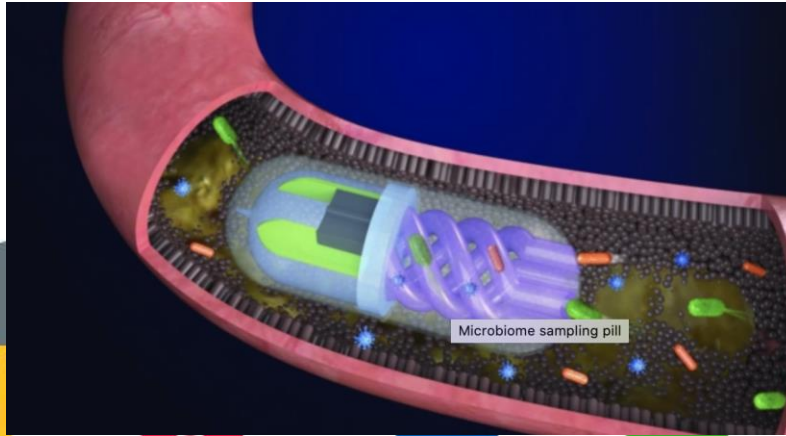
Fecal microbiota transplant (FMT) involves transfer of fecal microbiota from a donor to another individual. Alternatively, microbial consortia (targeted formulations used to augment host microbiota) are being developed. Diet, prebiotics, and postbiotics can also influence the microbial community.



Prior to treatment	During therapy	Assessing impact	Long-term effects
Patients <ul style="list-style-type: none"> - What patient population to treat? Treatment naïve or refractory? - Should the microbiome be profiled to stratify / select patients? Pre-conditioning regimen <ul style="list-style-type: none"> - Do we need to pre-treat the gut with antibiotics to facilitate engraftment? How should we optimally modulate the gut microbiota? <ul style="list-style-type: none"> - FMT? - How should FMT be administered? - How do we select donors? - Should patient fecal material be “banked” for later auto-FMT? - Diet, Designer Consortia? - Phage / antibiotics / other? 	What therapy should we combine with modulation of the gut microbiome? <ul style="list-style-type: none"> - Immune checkpoint blockade (anti-PD-1)? - Other forms of immunotherapy? - Other therapy? How do we optimally monitor patients during therapy? <ul style="list-style-type: none"> - Microbiome analyses to assess engraftment / function? - Immune profiling? - Peripheral blood - Tumor How can we facilitate stable engraftment? <ul style="list-style-type: none"> - Should we recommend dietary changes? - Any medications to avoid? 	What are appropriate primary endpoints for such studies? <ul style="list-style-type: none"> - Safety and tolerability - Engraftment - Others? What are appropriate secondary endpoints? <ul style="list-style-type: none"> - Response / Toxicity? - Radiographic (RECIST and / or irRC) - Rate of complete responses - Pathologic response (on biopsy or after neoadjuvant therapy) - Novel markers (ctDNA, immunophenotyping) 	Durability of engraftment <ul style="list-style-type: none"> - How durable is engraftment? - What microbes / functional phenotypes in gut microbiota are associated with responses? And can these be used to design consortia? Overall responses <ul style="list-style-type: none"> - What is impact on overall and disease-specific survival? Toxicity <ul style="list-style-type: none"> - Can we uncouple toxicity and response to immunotherapy? Other transplanted traits with FMT? <ul style="list-style-type: none"> - Obesity? - Depression? - Any potentially favorable traits?

Wargo Science 2020; McQuade et al Lancet Oncology. 2019

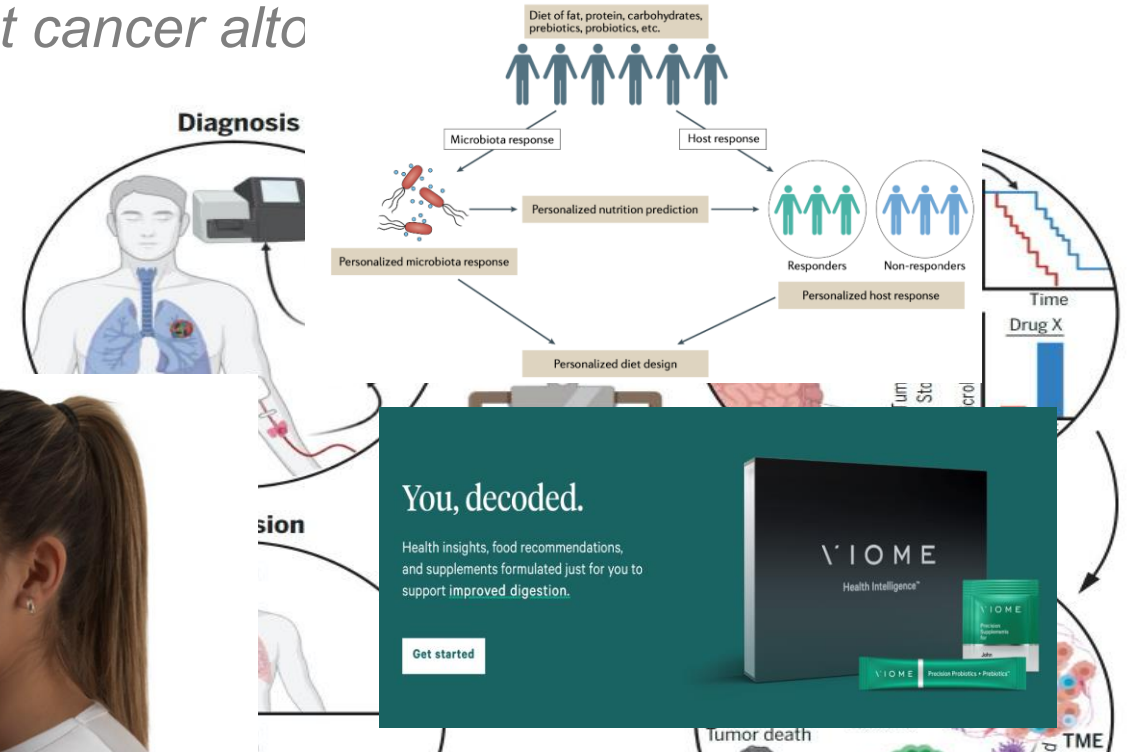
Could microbiome targeting become the next “pillar” of cancer care?



...ulate the microbial
...vent cancer alto

Diet–microbiota interactions and personalized nutrition

Aleksandra A. Kolodziejczyk^{1,4}, Danping Zheng^{1,2,4} and Eran Elinav^{1,3*}



URGERY

ANCIENT TIMES - PRESENT

1890s-P

BREATH BIOPSY

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Our Mission: To save 100,000 lives and \$1.5B in healthcare costs.

Our Vision: The global leader in Breath Biopsy for early detection and precision medicine.

DISCOVER BREATH BIOPSY



You, decoded.

Health insights, food recommendations, and supplements formulated just for you to support improved digestion.

Get started



Your Microbiome Could Play a Role in Your Covid-19 Response

Gut health could be an important piece in the Covid-19 puzzle

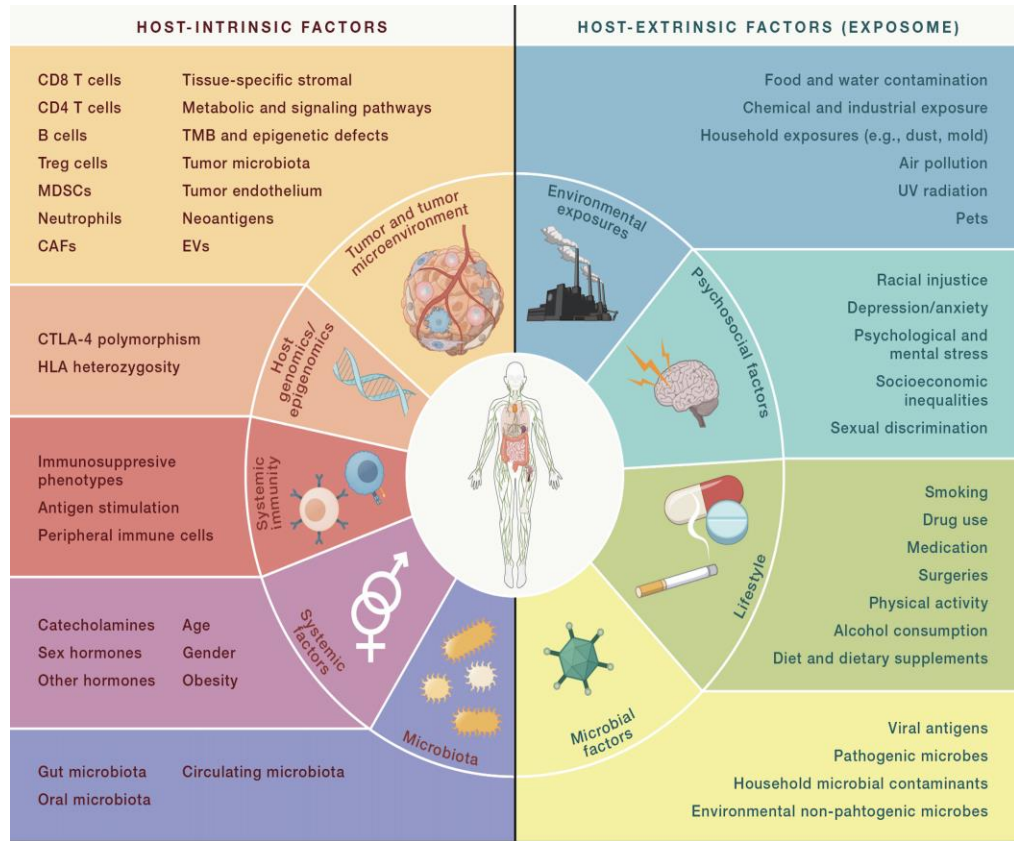
Markham Heid Feb 3 · 7 min read



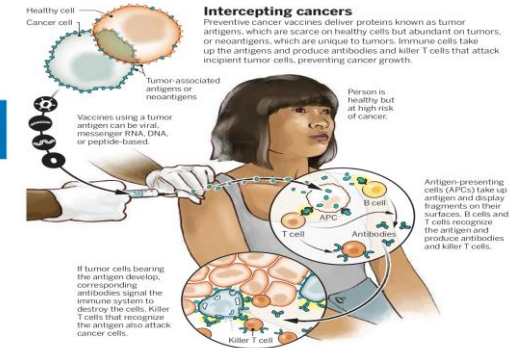
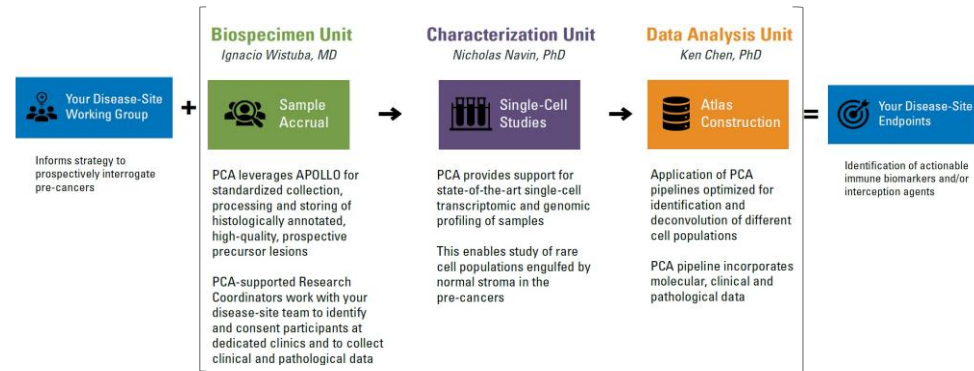
III. Targeting tissue, tumor, and gut-based microbes to intercept / prevent cancer and to promote overall health

“An ounce of prevention is worth a pound of cure”

Cancer and other diseases are occurring in people at younger ages, with opportunities for interception & prevention

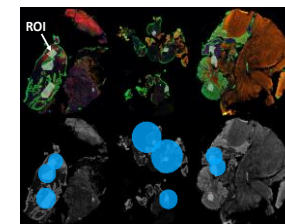
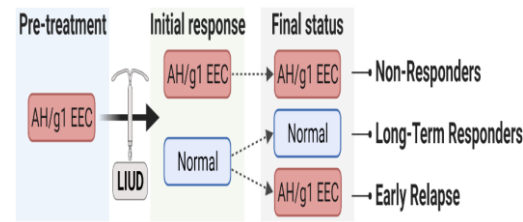


MDA Pre-Cancer Atlas: Structure & Expertise

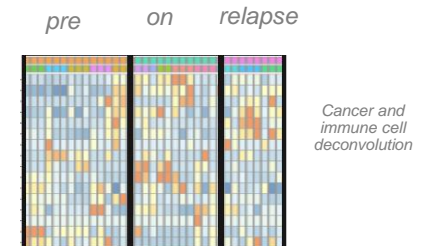


Kaiser, Science 2022

Investigators are also using novel approaches (spatial transcriptomics) in the interception of endometrial cancer (thank you to Nanostring GeoMX, Pam Sharma, Jim Allison)



DNA
PanCK
CD45
CD10



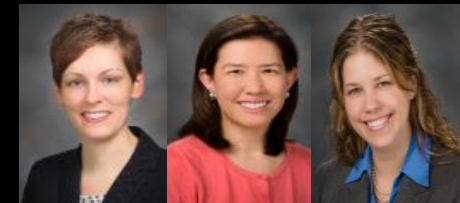
Confidential unpublished data, DO NOT POST



Educardo Vilar Sanchez MD PhD
Anirban Maitra MBBS

Congratulations to Dr. Karen Lu for her award from the Victoria's Secret Global Fund for Women's Cancers 2022!

Melinda Yates PhD
Karen Lu MD
Shannon Westin MD MPH



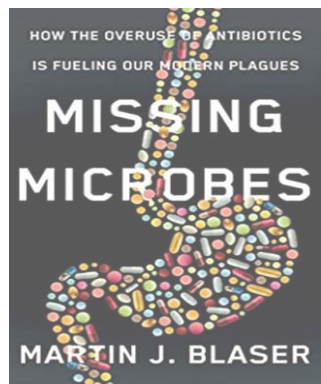
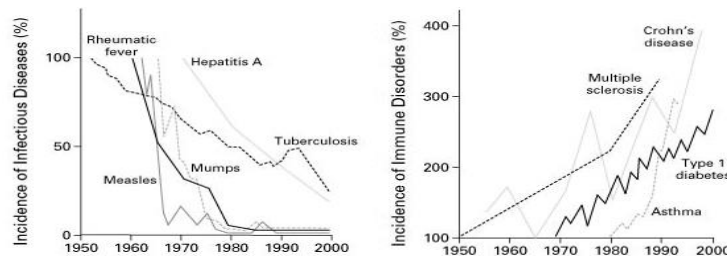
What is driving increased cancer and disease rates in younger individuals, and how can we prevent it?

Could exposure to antibiotics and other factors that disrupt the microbiome be contributing to higher rates of disease and cancer? And can we target the gut microbiome in cancer prevention?

The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases

Jean-François Bach, M.D., D.Sc.

N Engl J Med 2002; 347:911-920 | September 19, 2002 | DOI: 10.1056/NEJMra020100

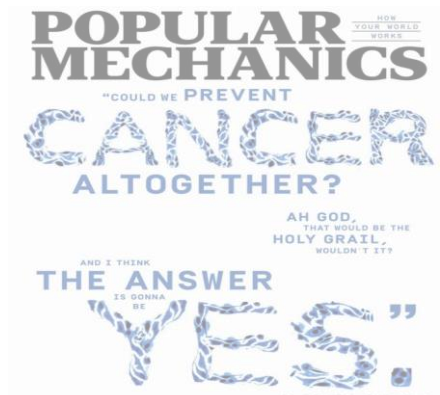


Marty Blaser MD
Prof of Medicine &
Microbiology, Rutgers
University

Other factors contributing to cancer risk (and that impact the microbiome) include diet, geography ("Z"NA), and physical inactivity and stress – can we promote overall health and reduce cancer risk by addressing these factors, including disparities?

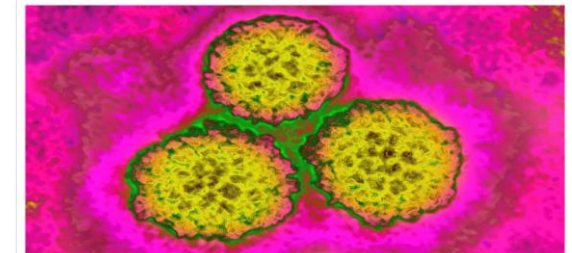


We know that microbes can contribute to cancer development (such as HPV and *H. pylori*). Can we study cancer and pre-malignant tissues to learn how to prevent cancer altogether?



'It's incredible': HPV vaccine saves thousands of women from cervical cancer, UK study shows

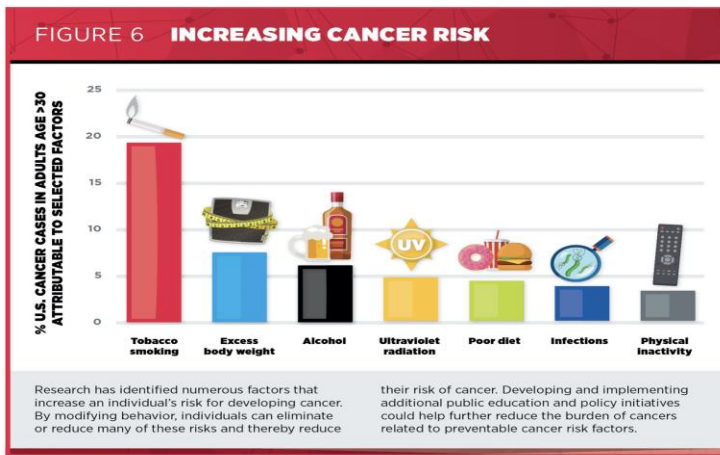
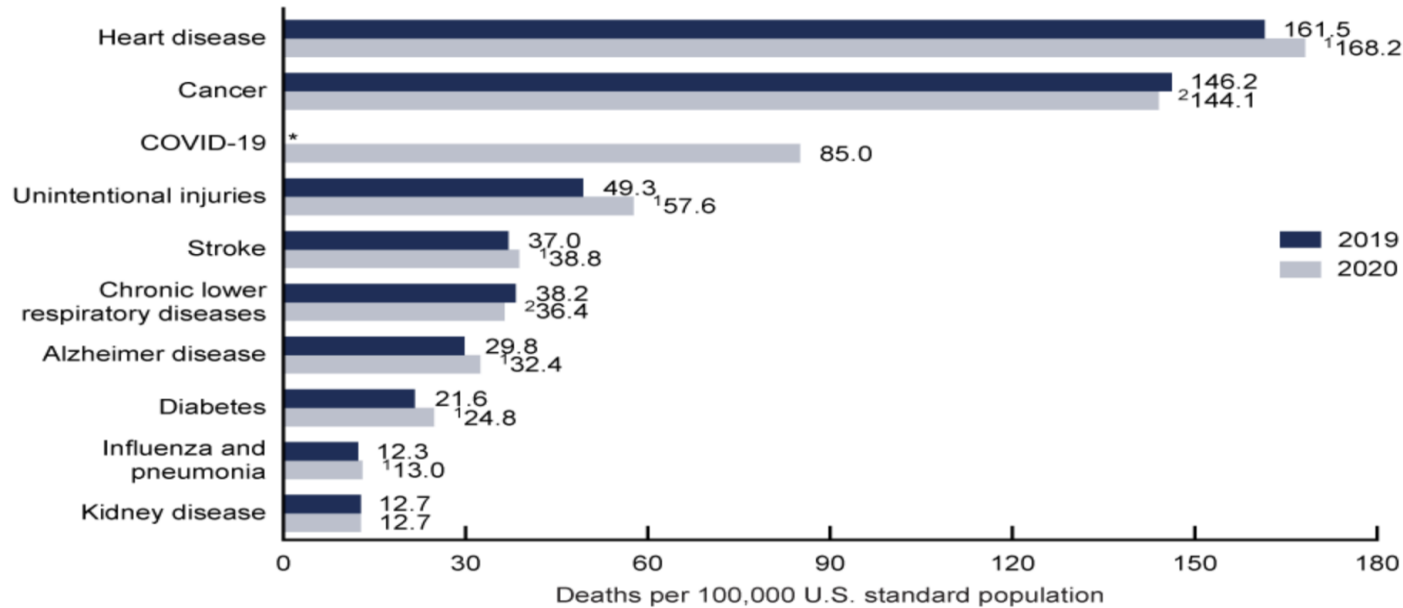
Rates have fallen 62% in women offered the HPV jab between the age of 14 and 16, and 34% for older teenagers



The human papillomavirus (HPV) is becoming less common because of the vaccine against cervical cancer. Photograph: BSIP/UG/Getty Images

These same factors are influencing other diseases, and we can work together to make changes to promote overall health

Can we monitor and modulate gut microbes, diet, and other variables in cancer treatment, and to promote overall health?



Bolte et al, Gut 2021



We can help address these issues on a global scale and also as individuals



The choices that we make every day have a tremendous impact on our microbiome and on our physiology - and also on our planet

Conclusions and potential implications of these findings:

- We have made significant progress in the treatment of melanoma and other cancers with the use of multi-modality therapy, 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)
- Multidisciplinary teams (involving patients, families, clinicians, basic & translational researchers, foundations / funding bodies, pharma) are all key in advancing the field, and we can learn a lot from each other to push the field forward faster
- There is still a great deal to learn, but the future is bright

Acknowledgements

Patients and their families

University of California Irvine – 19th Annual Immunology Fair

- **PRIME TR (Program for Innovative Microbiome & Translational Research)**
 - Nadim Ajami PhD, Executive Director
 - Jillian Losh PhD, Program Manager; Andreeka Lewis, Senior AA
 - Matt Wong MS, Senior Application Specialist
 - Clinical & bioinformatics teams (Pranoti, Khalel, Yasmine, Adi, Ashish)

Laboratory Investigation (Wargo Lab Members)

Sarah Johnson MS, Laboratory Manager

Golnaz Morad PhD, Post Doctoral Fellow

Manoj Chelvanambi, PhD, Post Doctoral Fellow

Elizabeth Park PhD, Post Doctoral CPRIT TRIUMPH Fellow

Mike White MD, Post Doctoral T32 Fellow

Matt Lastrapes, PhD candidate; Anik Banerjee PhD candidate

Russell Witt MD, Post-doctoral T32 Fellow

Sam Cass MD, Raymond Traweck MD – Postdoctoral T32 Fellows

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Other key collaborators

- Laurence Zitvogel MD PhD, Giorgio Trinchieri PhD
- Ravid Straussman MD PhD, Yardena Samuels PhD
- Wendy Garrett MD PhD, Curtis Huttenhower PhD

MDACC Collaborators

- Steve Swisher MD, Jeff Lee MD, Carin Hagberg MD
- Jim Allison PhD, Pam Sharma MD PhD
- Michael Davies MD PhD, Jeff Gershenwald MD, Jen McQuade MD
- Hussein Tawbi MD PhD, Bella Glitza MD, Carrie Daniel PhD
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- and other Surg Onc Faculty / Staff
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Prior Mentors

- Toni Ribas MD PhD, Steve Rosenberg MD PhD
- Lisa Butterfield PhD, Keith Flaherty MD, Arlene Sharpe MD PhD

Baylor CMMR

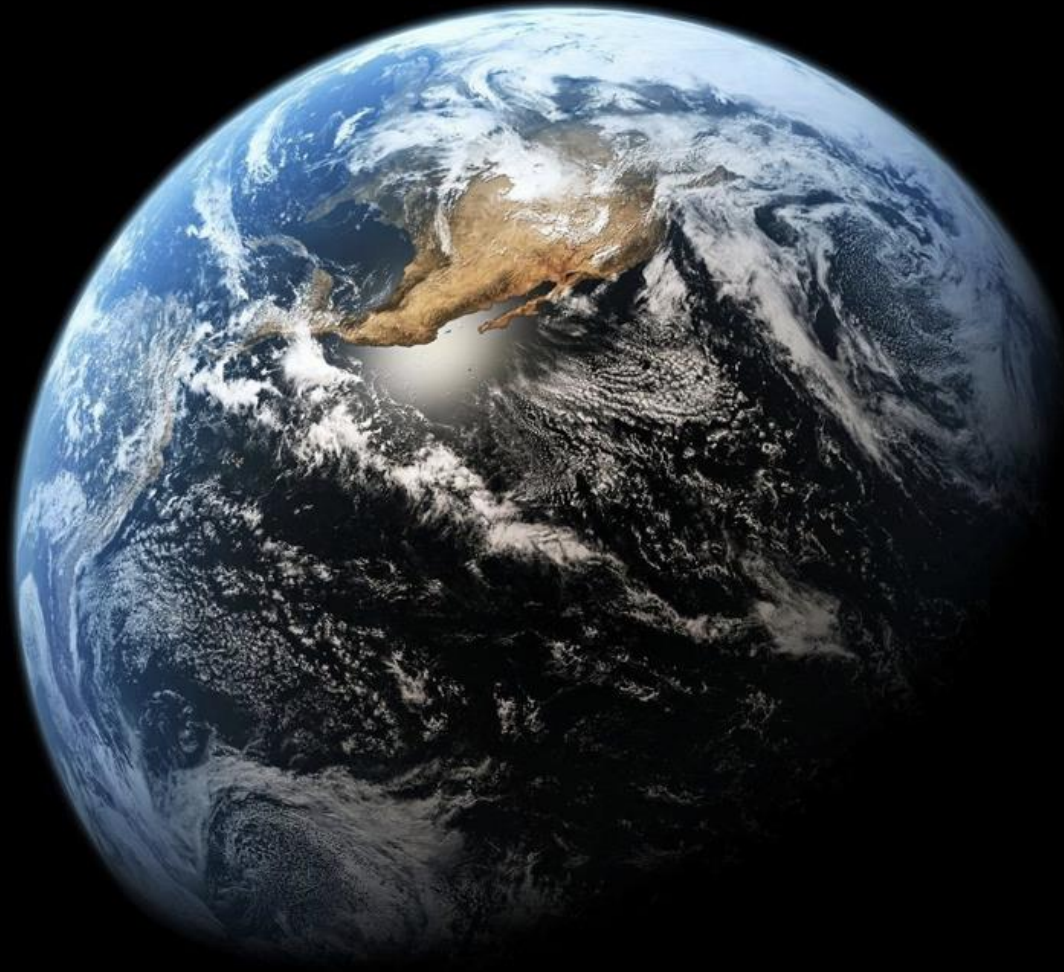
- Joe Petrosino PhD, Diane Hutchinson PhD

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- Melanoma Moon Shot Program

Industry Sponsors/Collaborators

Thank you for all that you do in this world...



Any questions?