Tumor Immune Microenvironment: A Holistic Approach Workshop

April 21-22, 2022 • San Diego and Virtually

#SITCworkshop

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Society for Immunotherapy of Cancer

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

Jennifer Wargo MD, MMSc – R. Lee Clark Professor of Surgical Oncology & Genomic Medicine
University of Texas, MD Anderson Cancer Center – Houston TX, USA

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

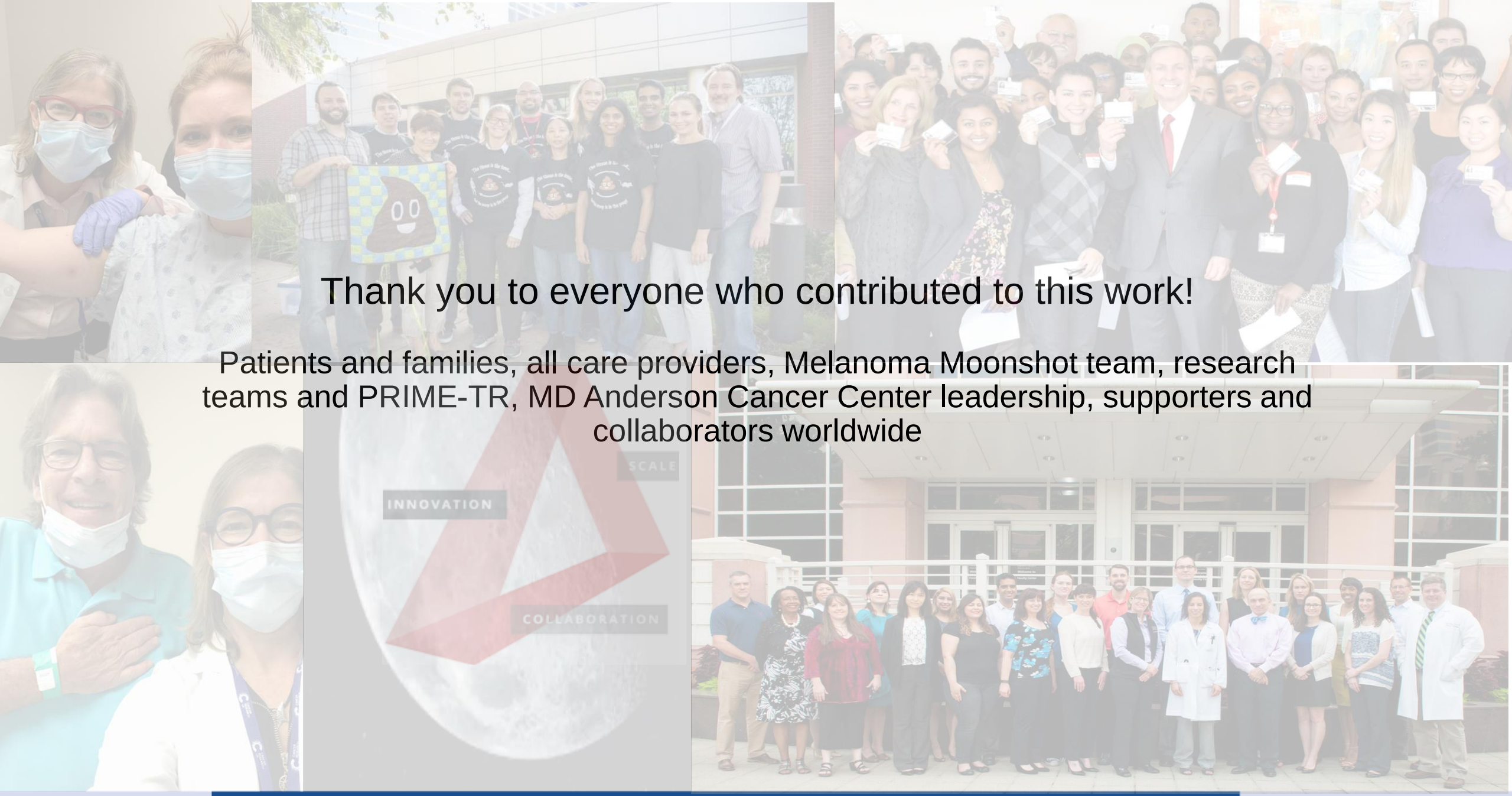
Jen Wargo

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"

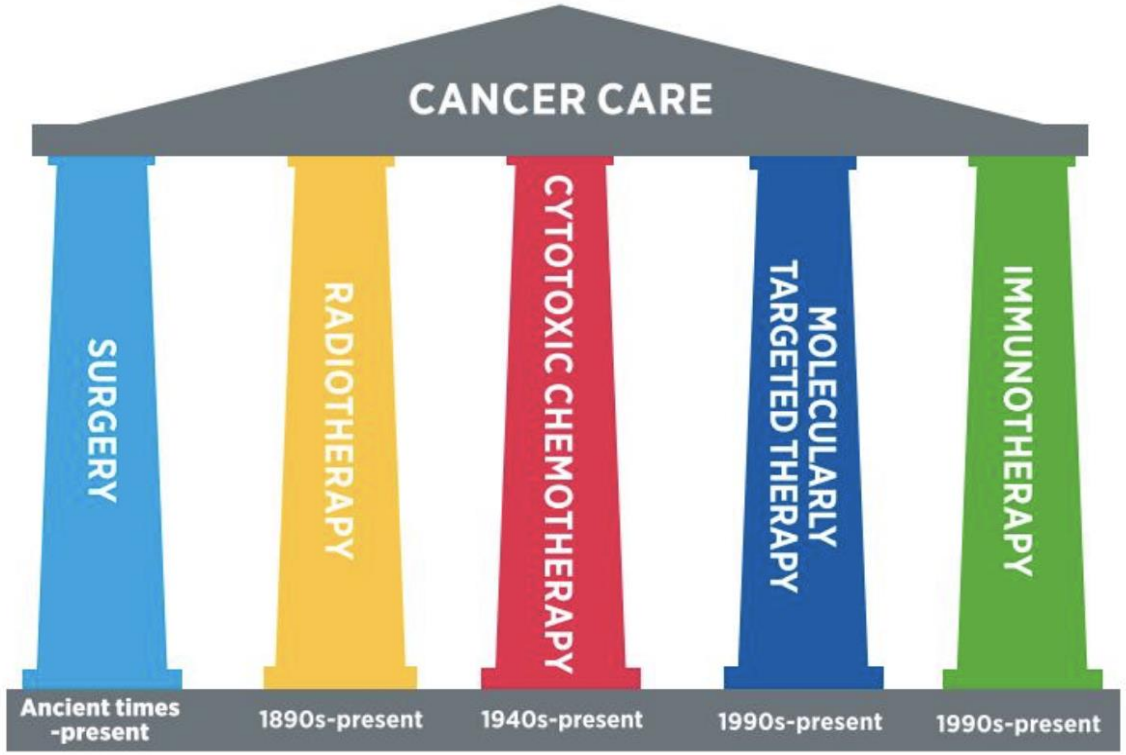
II. Understanding factors that influence the TME and gut microbes in health and disease

"You are what you eat"

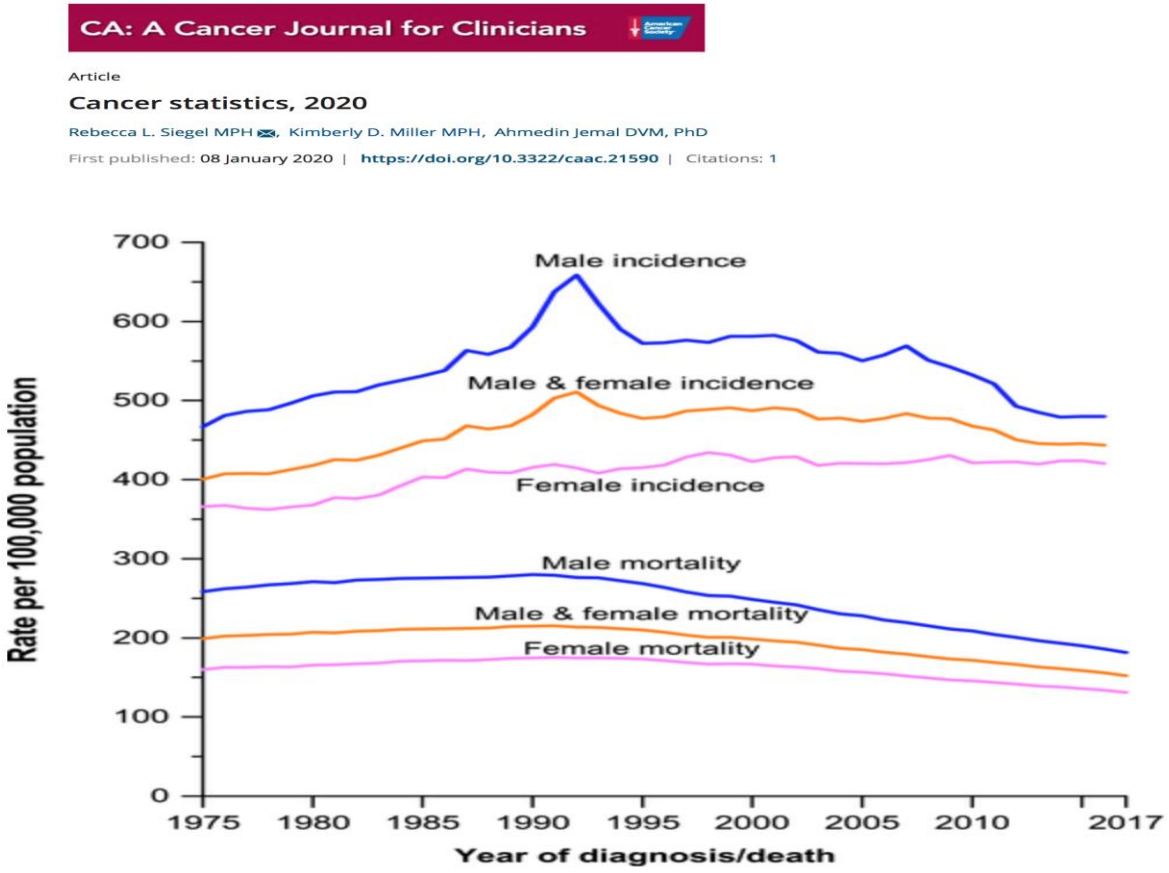
III. Targeting tissue, tumor, and gut-based microbes to intercept / prevent cancer and to promote overall health

"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



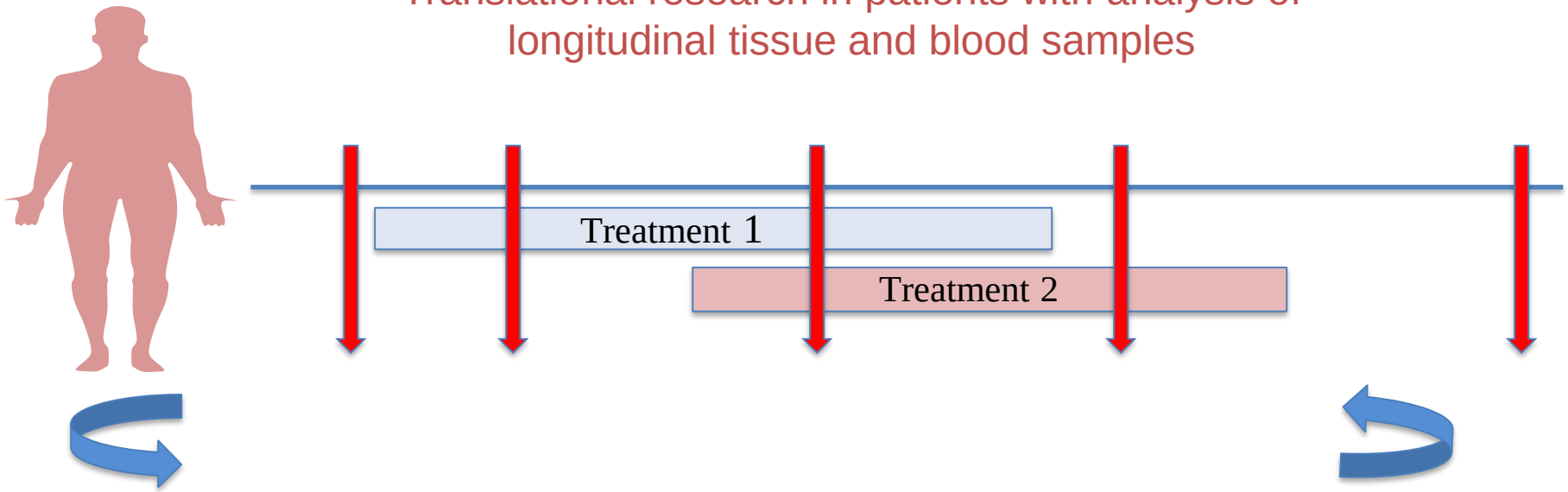
From AACR Cancer Progress Report



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

Translational research in patients with analysis of longitudinal tissue and blood samples



Murine models
(GEMM, PDX, etc)

Control

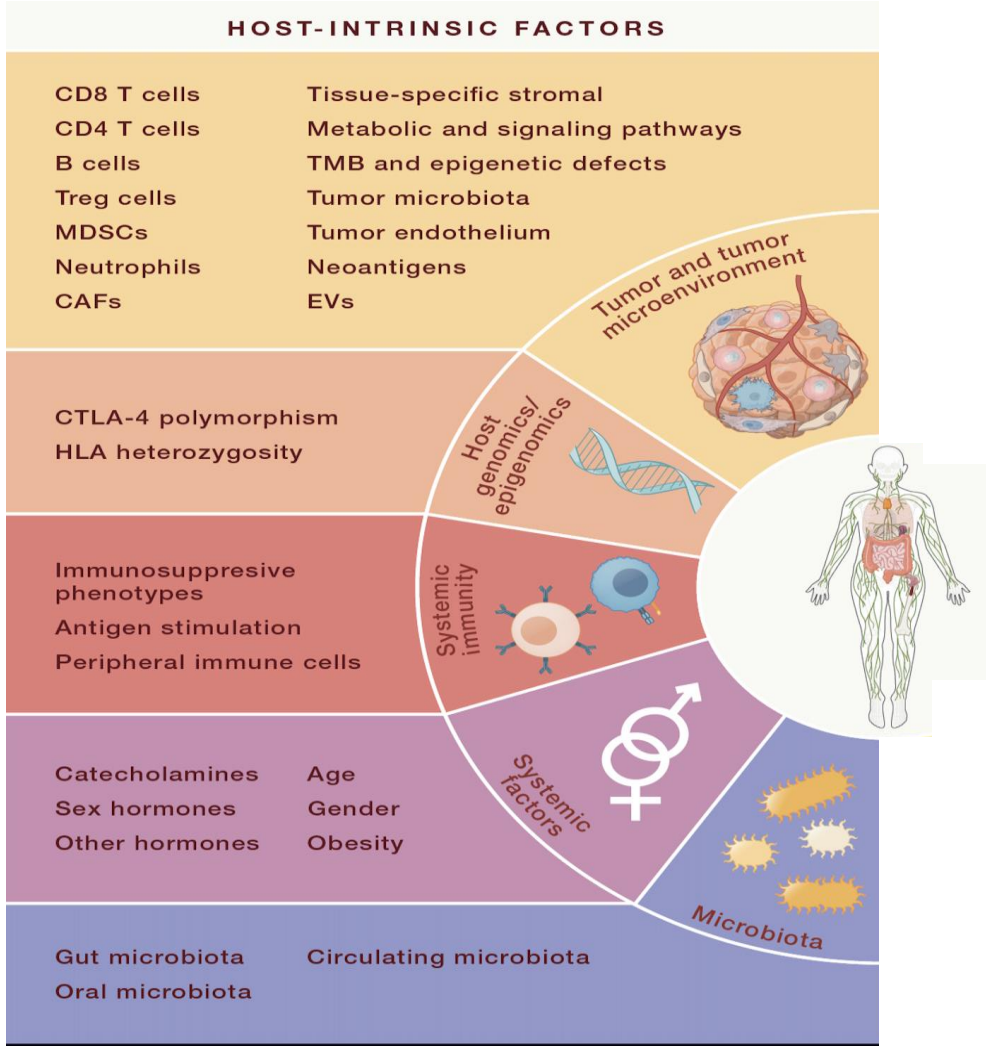
Treatment 1

Treatment 2

Treatment 1 + Treatment 2

Mechanistic studies and therapeutic optimization in murine models

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



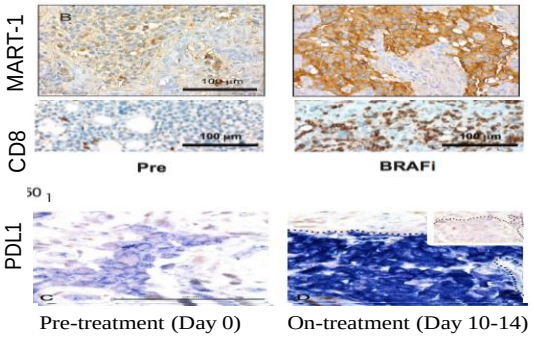
Morad et al, *Cell 2021*

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)*



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

Paolo Antonio Ascierto, Pier Francesco Ferrucci, Rosalie Fisher, Michele Del Vecchio, Victoria Atkinson, Henrik Schmidt, Jacob Schachter, Paola Queirolo, Georgina V. Long, Anna Maria Di Giacomo, Inge Marie Svane, Michal Lotem, Gil Bar-Sela, Felix Couture, Bijoyesh Mookerjee, Razi Ghori, Nageatte Ibrahim, Blanca Homet Moreno and Antoni Ribas

Atezolizumab plus cobimetinib and vemurafenib in *BRAF*-mutated melanoma patients

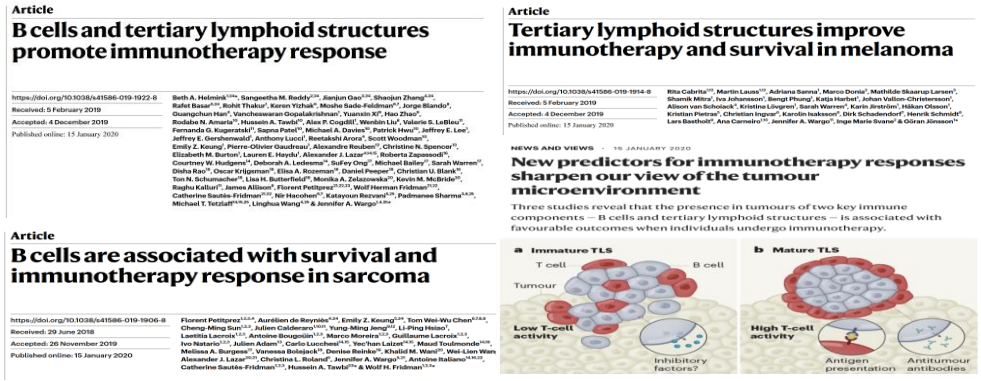
Ryan J. Sullivan, Omid Hamid, Rene Gonzalez, Jeffrey R. Infante, Manish R. Patel, F. Stephen Hodi, Karl D. Lewis, Hussein A. Tawbi, Genevieve Hernandez, Matthew J. Wongchenko, YiMeng Chang, Louise Roberts, Marcus Ballinger, Yibing Yan, Edward Cha and Patrick Hwu

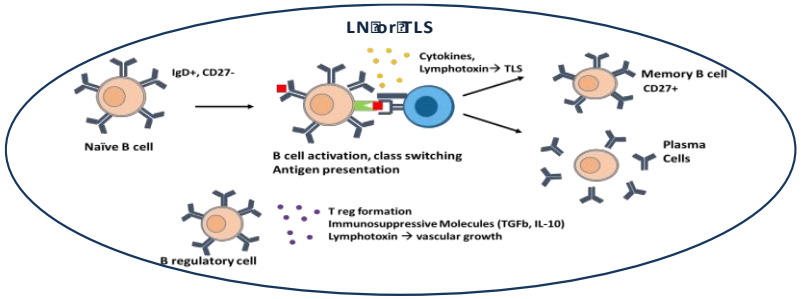
Combined BRAF and MEK inhibition with PD-1 blockade immunotherapy in *BRAF*-mutant melanoma

Antoni Ribas, Donald Lawrence, Victoria Atkinson, Sachin Agarwal, Wilson H. Miller Jr, Matteo S. Carlino, Rosalie Fisher, Georgina V. Long, F. Stephen Hodi, Jennifer Tsoi, Catherine S. Grasso, Bijoyesh Mookerjee, Qing Zhao, Razi Ghori, Blanca Homet Moreno, Nageatte Ibrahim and Omid Hamid

Frederick et al, CCR 2013, Ascierto et al, Ribas et al, Sullivan et al *Nature Med* 2019

In addition to this, we and others have identified tissue-based biomarkers of response to immune checkpoint blockade, with opportunities to target these therapeutically to improve responses





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

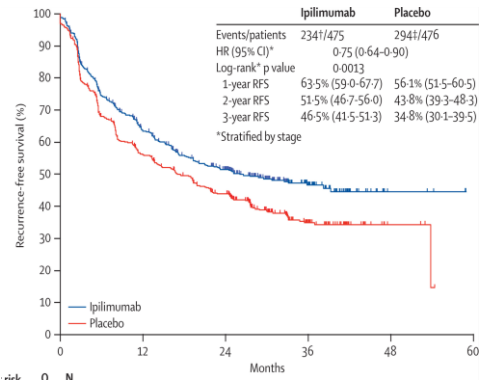
Sangeetha Reddy MD MS to discuss "Targeting the interaction of oncogenic signaling with immunity in breast cancer" Session IV: 4:40 pm on 4/21

Abigail Overacre-Delgoffe PhD to discuss "Microbiota-specific T follicular helper cells support tertiary lymphoid structure formation and anti-tumor immunity in colorectal cancer"

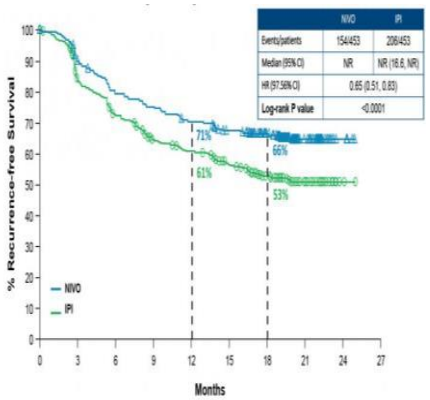
Importantly, treatment with immunotherapy and other strategies are being used in patients with earlier stage disease, and tissue +/- blood-based analyses are critical

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

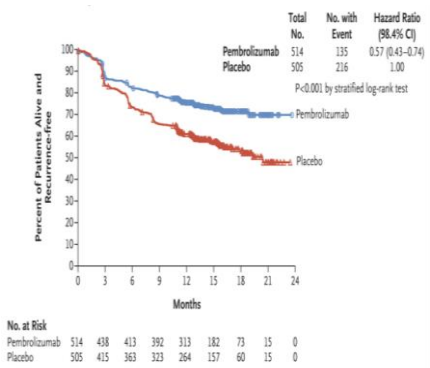
EORTC 1871



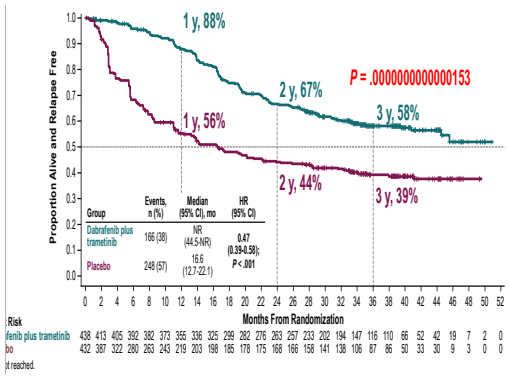
Checkmate 238

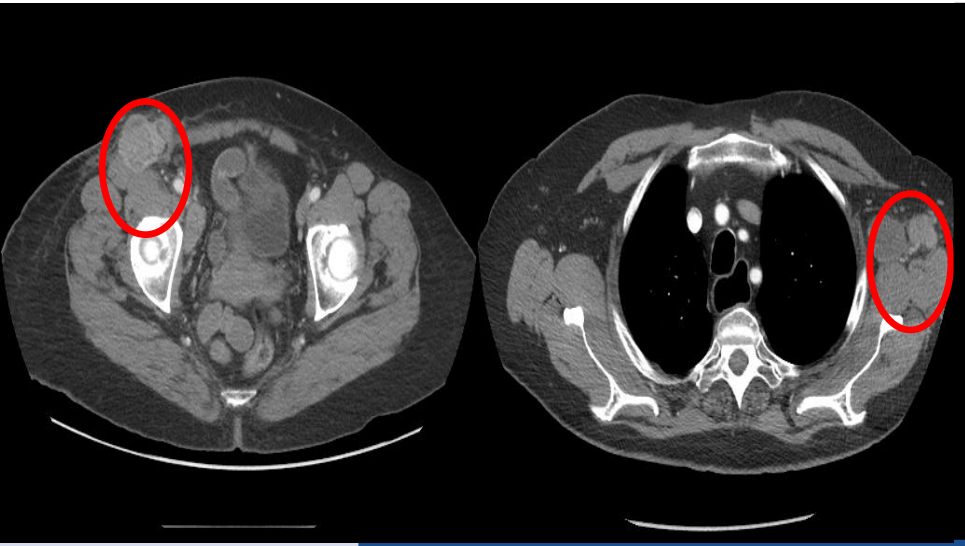


Keynote 054

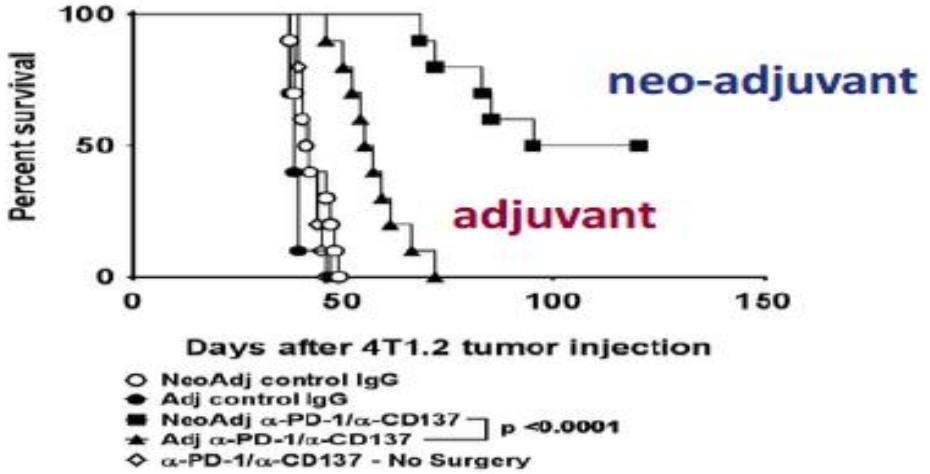


COMBI-AD





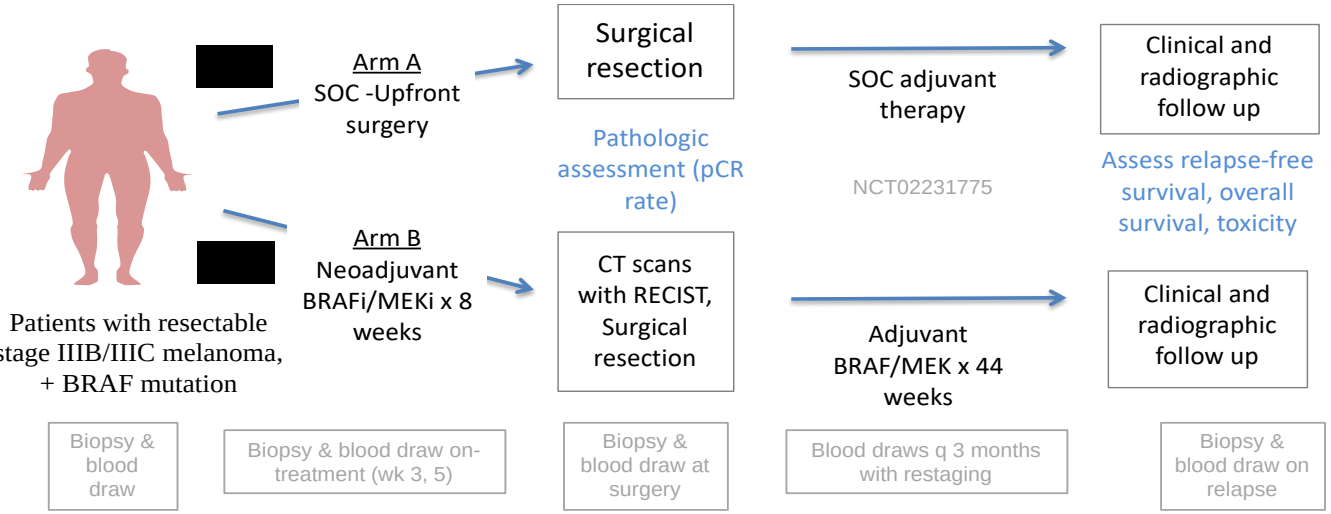
Upfront surgery is currently the standard of care for these patients,
but up to 70% of patients treated in this manner will relapse (at least before the use of adjuvant targeted therapy and immune checkpoint blockade)

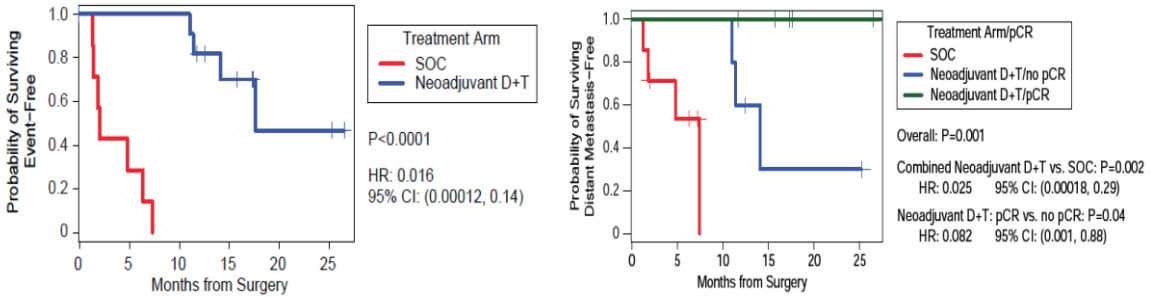


Liu, et al., Cancer Discovery 2016

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

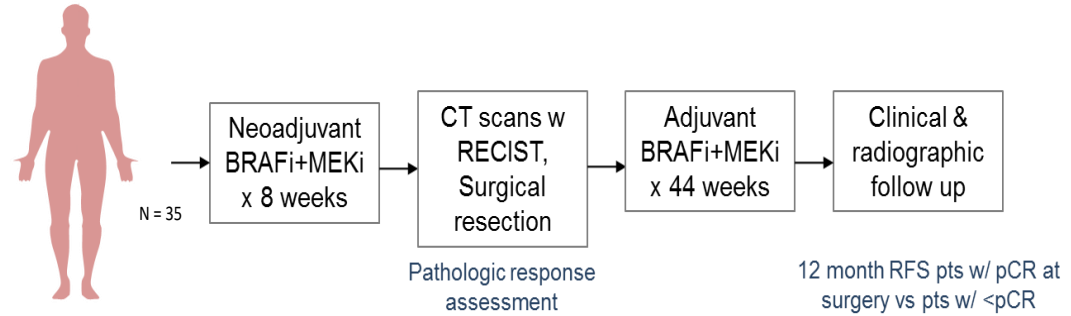
Demonstrating improved survival over SOC upfront surgery, with pathologic complete response (pCR) and other markers predictive of long-term benefit (RECIST response rate 85%, pCR rate 58%)

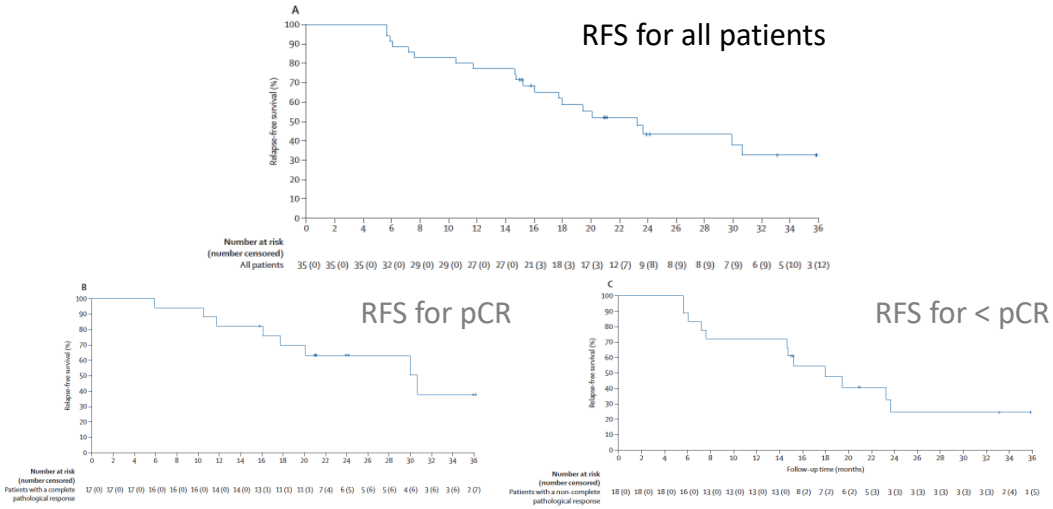




Amaria, Prieto et al, Lancet Oncology 2018

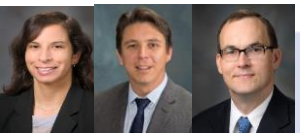
Notably, other groups have observed similar findings, though relapse rates were higher than observed in our trial





Long, et al Lancet Oncology 2019

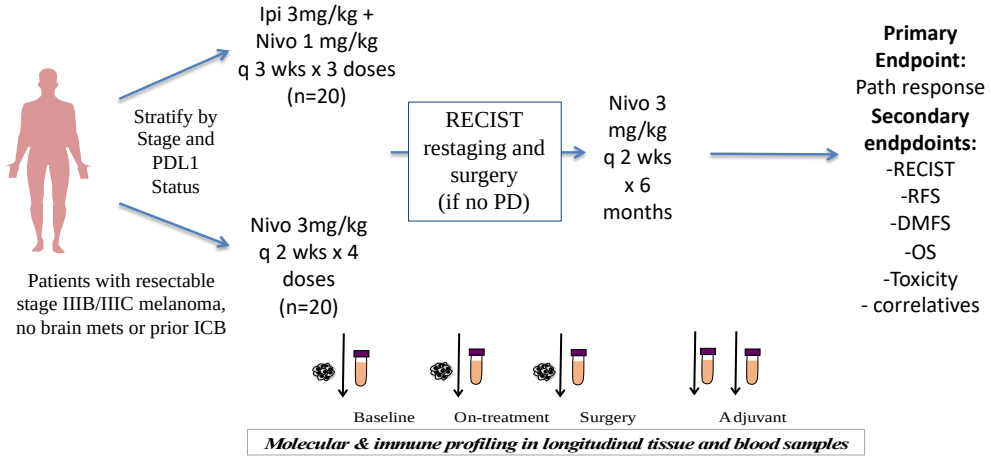
Georgina Long MD

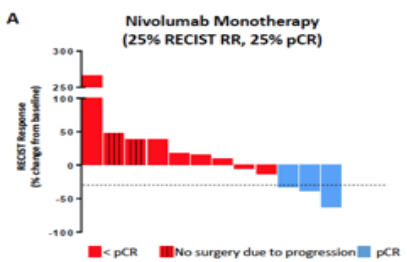


Roda Amaria MD
Peter Prieto MD MPH
Michael Tetzlaff MD PhD

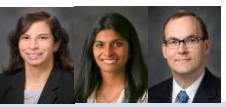
We next studied the use of neoadjuvant immune checkpoint blockade in patients with high-risk resectable metastatic melanoma

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)





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
Fevers/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
Hyperthyroidism	8	0	27	9
Hypothyroidism	0	0	36	0
Myositis/myalgias	8	0	18	9
Pain	25	8	27	0



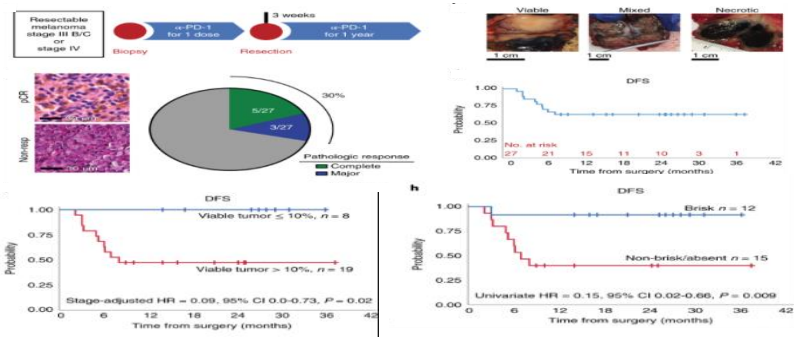
Roda Amaria MD
Sangeetha Reddy MD
Michael Tetzlaff MD PhD

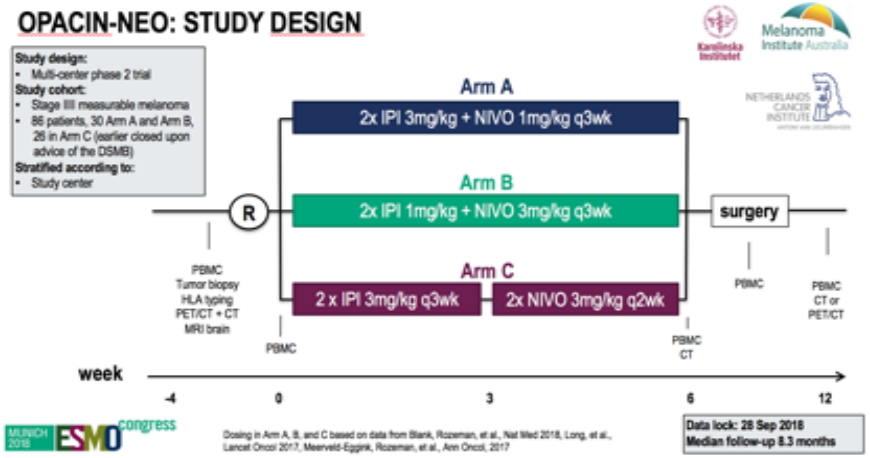
Amaria, Reddy et al
Nature Medicine 2018

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

Tara Mitchell MD, E. John Wherry MD PhD, Giorgios Karakousis MD

Penn





Huang. Et. Al 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)

INTERNATIONAL NEOADJUVANT MELANOMA CONSORTIUM
INMC

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. Messina[3], J. E. Stein[4], X. Xu[5], R. N. Amaria[6], C. U. Blank[7], B. A. van de Wiel[7], P. M. Ferguson[8], R. V. Rawson[8], M. I. Ross[9], A. J. Spillane[10], J. E. Gershenwald[8,11], R. P. M. Saw[8], A. C. J. van Akkooi[7], W. J. van Houdt[12], T. C. Mitchell[1,2], A. M. Menzies[10], G. V. Long[13], J. A. Wargo[9,14], M. A. Davies[2,6,15], V. G. Prieto[1,16], J. M. Taube[#] & R. A. Scolyer[#]

Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy226
Published online 25 June 2018

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

Rodabe N Amaria*, Alexander M Menzies*, Elizabeth M Burton*, Richard A Scolyer*, Michael T Tetzlaff*, Robert Antdbacka, Charlotte Ariyan, Roland Bassett, Brett Carter, Adil Daud, Mark Faries, Leslie A Fecher, Keith Flaherty, Jeffrey E Gershenwald, Omid Hamid, Angela Hong, John Kirkwood, Serigne Lo, Kim Margolin, Jane Messina, Michael Postow, Helen Rizos, Merrick I Ross, Elisa A Rozeman, Robyn P M Saw, Vernon Sondak, Ryan J Sullivan, Janis M Taube, John F Thompson, Bart A van de Wiel, Alexander M Eggermont, Michael A Davies, The International Neoadjuvant Melanoma Consortium members†, Paolo A Ascierto†, Andrew J Spillane†, Alexander C J van Akkooi†, Jennifer A Wargo†, Christian U Blank†, Hussein A Tawbi†, Georgina V Long†

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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

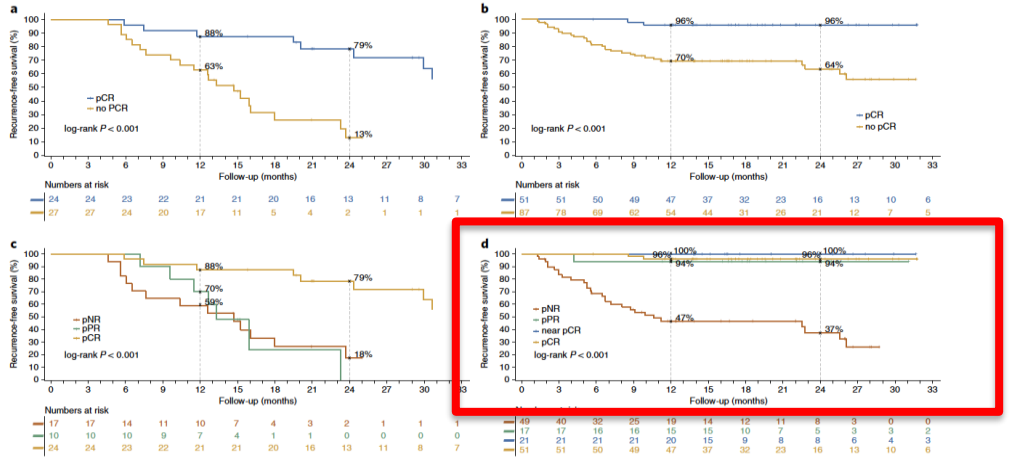
DOI: 10.1158/1078-0432.CCR-20-3285 Published January 2021 Check for updates

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

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

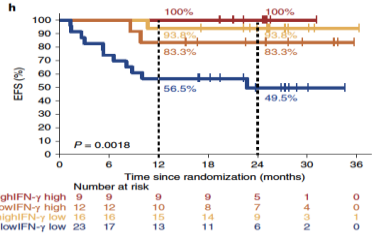
Alexander M. Menzies[1,2,3,12], Rodabe N. Amaria[4,12], Elisa A. Rozeman[5,12], Alexander C. Huang[6,7,12], Michael T. Tetzlaff[8,12], Bart A. van de Wiel[5,12], Serigne Lo[1,2,12], Ahmad A. Tarhini[8], Elizabeth M. Burton[4], Thomas E. Pennington[1,2,9], Robyn P. M. Saw[1,2,9], Xiaowei Xu[6], Giorgos C. Karakousis[6], Paolo A. Ascierto[10], Andrew J. Spillane[1,2,3], Alexander C. J. van Akkooi[5], Michael A. Davies[4,13], Tara C. Mitchell[6,13], Hussein A. Tawbi[4,13], Richard A. Scolyer[1,2,11,13], Jennifer A. Wargo[4,13], Christian U. Blank[5,13] and Georgina V. Long[1,2,3,13]



nature medicine LETTERS
https://doi.org/10.1038/s41591-020-01211-7

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

E. A. Rozeman[1], E. P. Hoefsmit[2,17], I. L. M. Reijers[1,17], R. P. M. Saw[3,4,5], J. M. Versluis[1], O. Krijgsman[2,6], P. Dimitriadis[2], K. Sikorska[2], B. A. van de Wiel[6], H. Eriksson[6,16], M. Gonzalez[1], A. Torres Acosta[7], L. G. Grijpink-Ongering[7], K. Shannon[2,5], J. B. A. G. Haanen[3,4], J. Stretch[3,4,5], S. Ch'ng[3,4,5], O. E. Nieweg[3,4,5], H. A. Mallo[1], S. Adriaansz[1], R. M. Kerkhoven[18], S. Cornelissen[19], A. Broeks[19], W. M. C. Klop[19], C. L. Zuur[19], W. J. van Houdt[19], D. S. Peeper[2,6], A. J. Spillane[3,4,14], A. C. J. van Akkooi[20], R. A. Scolyer[3,15], T. N. M. Schumacher[2,6], A. M. Menzies[3,20], G. V. Long[3,20] and C. U. Blank[1,2]



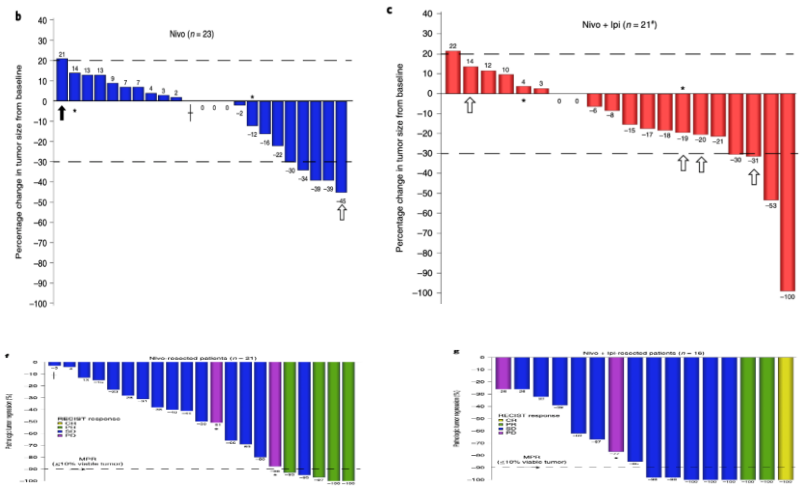
Menzies et al, Rozeman et al, Nature Medicine 2021

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

nature medicine ARTICLES
https://doi.org/10.1038/s41591-020-01224-2

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

Tina Cascone[1✉2], William N. William Jr[1,15], Annikka Weissferdt[2,3], Cheuk H. Leung[4], Heather Y. Lin[4], Apar Pataer[3], Myrna C. B. Godoy[5], Brett W. Carter[5], Lorenzo Federico[6], Alexandre Reuben[1], Md Abdul Wadud Khan[7], Hitoshi Dejima[8,16], Alejandro Francisco-Cruz[8], Edwin R. Parra[8], Luisa M. Solis[8], Junya Fujimoto[9], Hai T. Tran[1], Neda Kalhor[2], Frank V. Fossella[1], Frank E. Mott[1], Anne S. Tsao[1], George Blumenschein Jr[1], Xiuning Le[1], Jianjun Zhang[1], Ferdinandos Skoulidis[1], Jonathan M. Kurie[1], Mehmet Altan[1], Charles Lu[1], Bonnie S. Glisson[1], Lauren Averett Byers[1], Yasir Y. Elamin[1], Reza J. Mehran[3], David C. Rice[3], Garrett L. Walsh[3], Wayne L. Hofstetter[3], Jack A. Roth[3], Mara B. Antonoff[3], Humam Kadara[8], Cara Haymaker[8], Chantale Bernatchez[6,8], Nadim J. Ajami[9], Robert R. Jenq[9,10,11], Padmanee Sharma[12,13], James P. Allison[13], Andrew Futreal[9], Jennifer A. Wargo[7], Ignacio I. Wistuba[1,8], Stephen G. Swisher[3], J. Jack Lee[4], Don L. Gibbons[1], Ara A. Vaporciyan[3], John V. Heymach[1,14,17] and Boris Sepesi[3,17]



Tina Cascone MD
Boris Sepesi MD

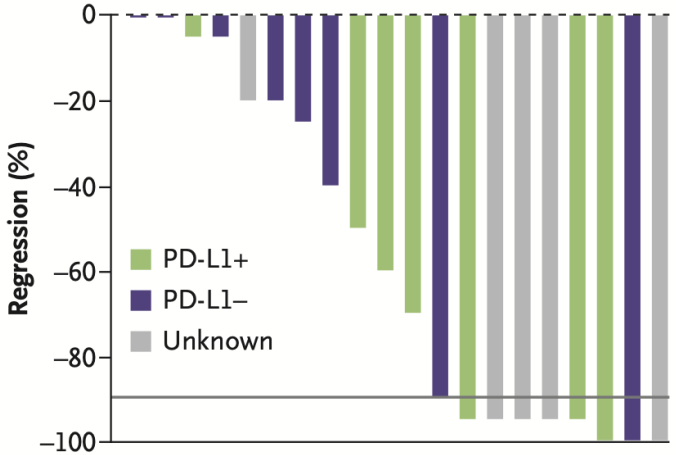
Cascone et al, Nature Medicine 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

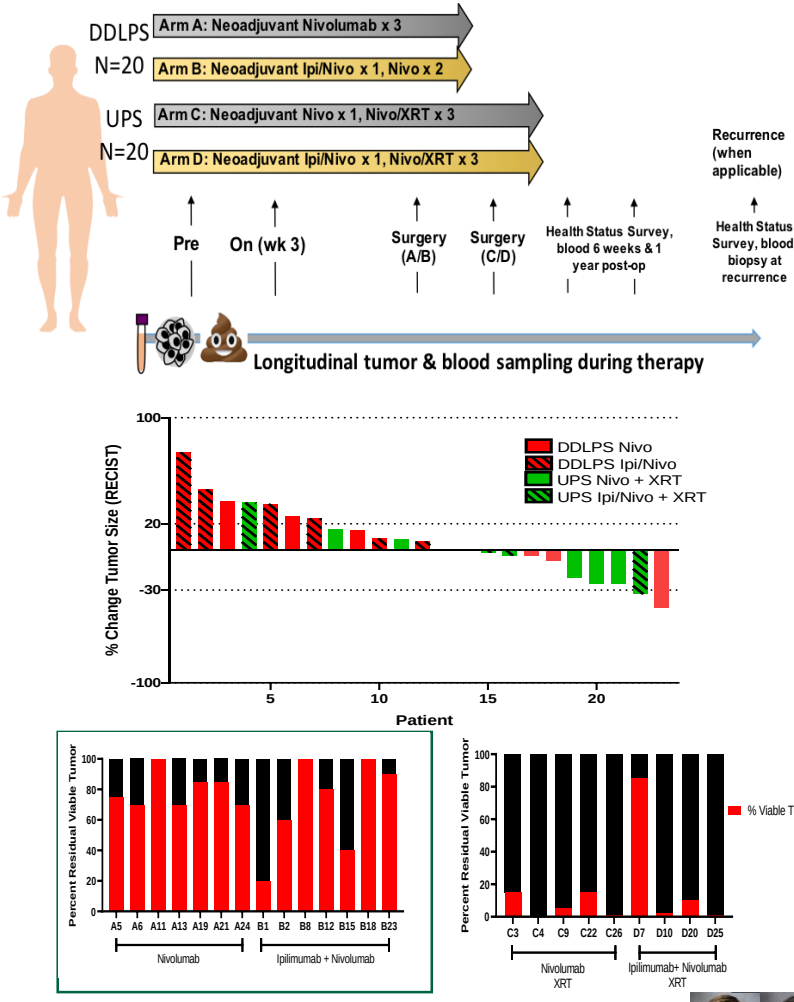
Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

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



Forde et al, NEJM 2018

Patrick Forde MD



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

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**

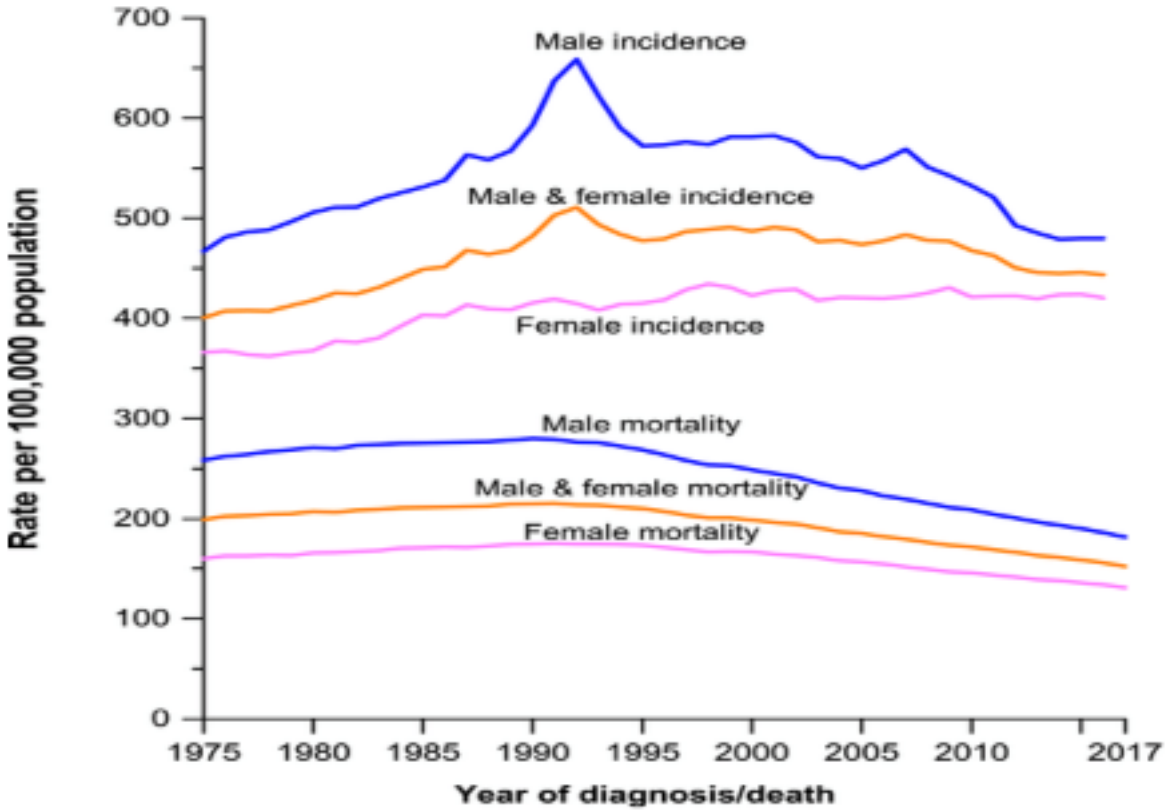
LUNG, HEAD and NECK, ESOPHAGEAL and GASTRIC, BREAST, GBM

Alexander Eggermont MD PhD

From PeerView presentation SSO 2021

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

sex matters!



VOLUME 36 · NUMBER 26 · SEPTEMBER 10, 2018

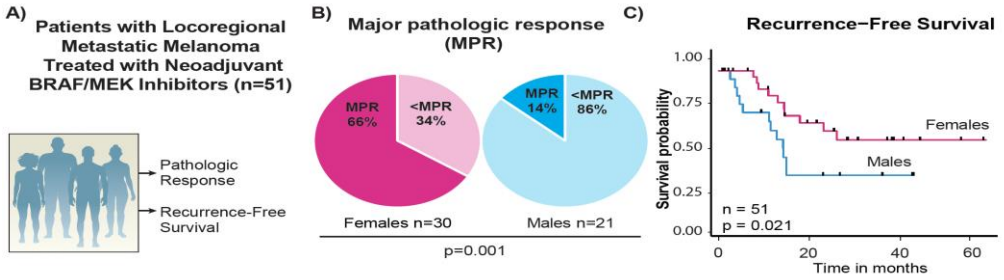
JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology

Berna C. Özdemir, *Lausanne University Hospital; and International Cancer Prevention Institute, Lausanne, Switzerland*
Chantal Csajka, *Lausanne University Hospital; and University of Lausanne, Lausanne, Switzerland*
Gian-Paolo Dotto, *International Cancer Prevention Institute; University of Lausanne, Lausanne, Switzerland; and Massachusetts General Hospital, Charlestown, MA*
Anna Dorothea Wagner, *Lausanne University Hospital, Lausanne, Switzerland*

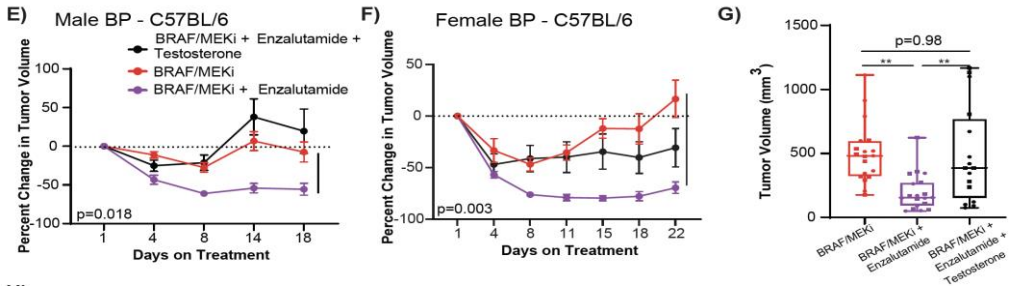
In one of our neoadjuvant studies, we noted a strong sexual dimorphism in response to therapy (which was confirmed in additional cohorts)

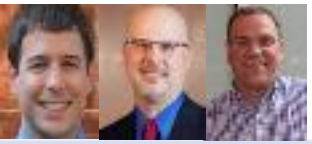
Patients who achieved a complete resposne to neoadjuvant targeted therapy had long-term benefit *(and the majority of these patients were female)*



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)

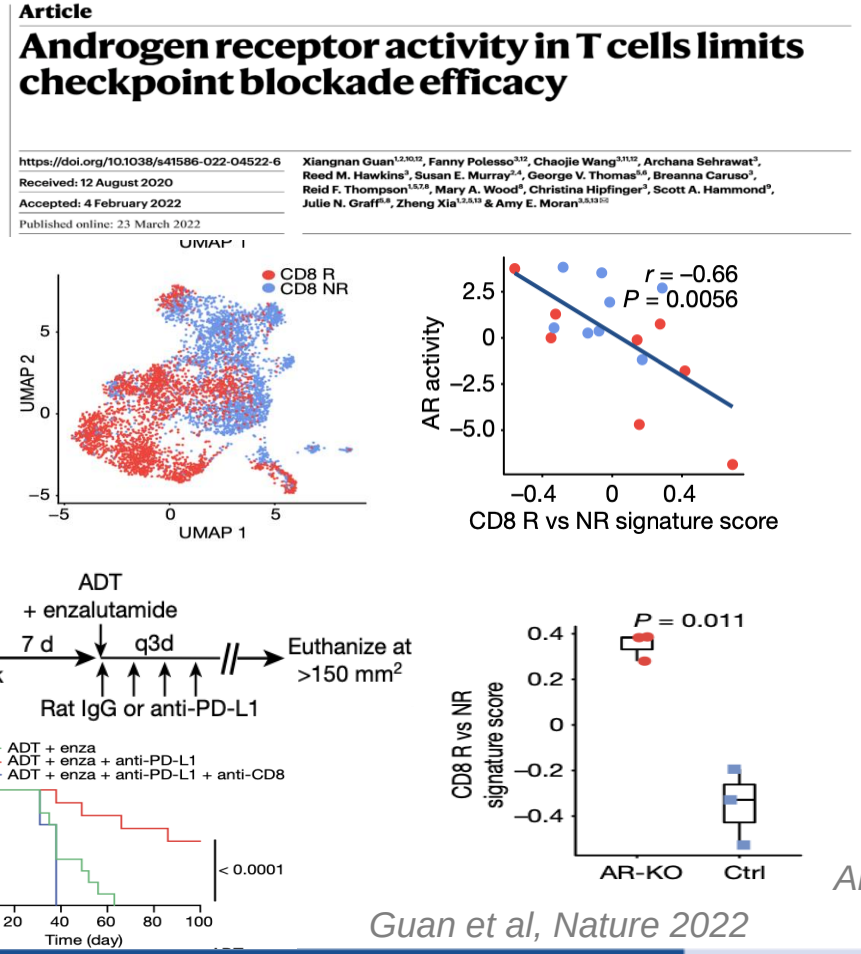




Chris Vellano PhD
Joe Marszalek PhD
Tim Heffernan PhD

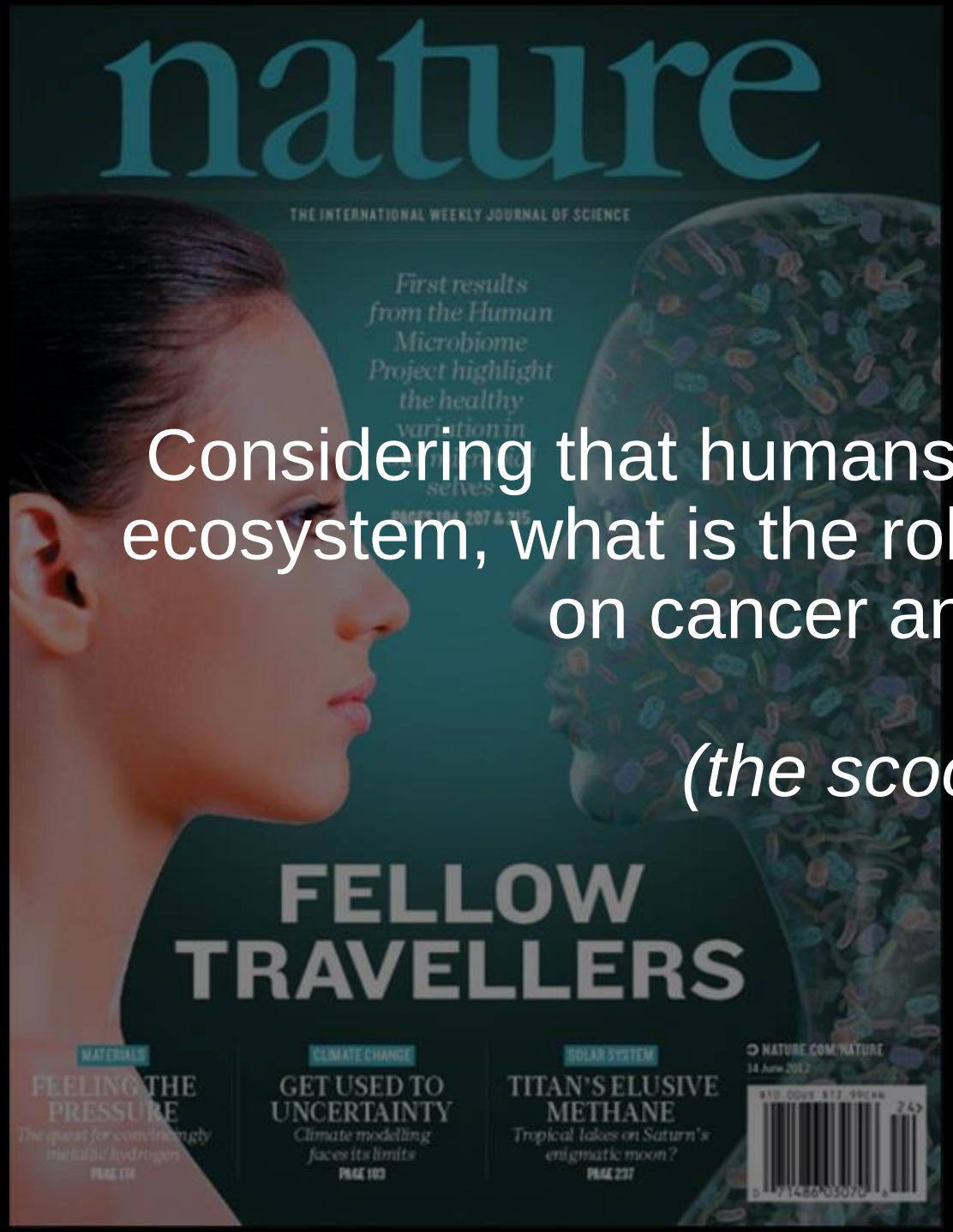
Vellano et al, accepted for publication

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)



Guan et al, Nature 2022

Amy Moran PhD



Considering that humans / organisms represent a complex ecosystem, what is the role of microbes that co-exist with us on cancer and therapy response?

(the scoop is in the poop)

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%

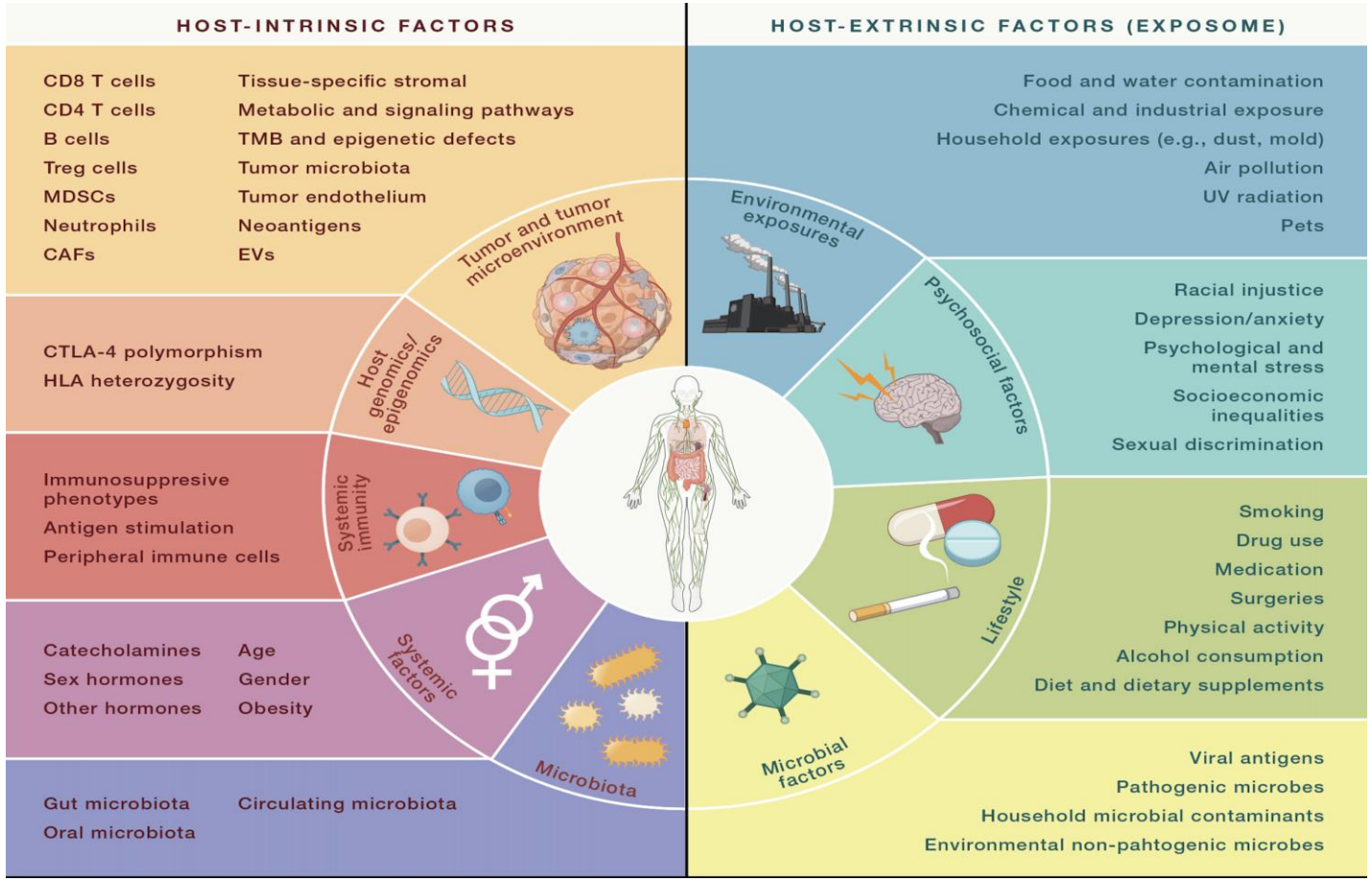
2-20 million microbial genes in an individual

99%

inherently modifiable

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

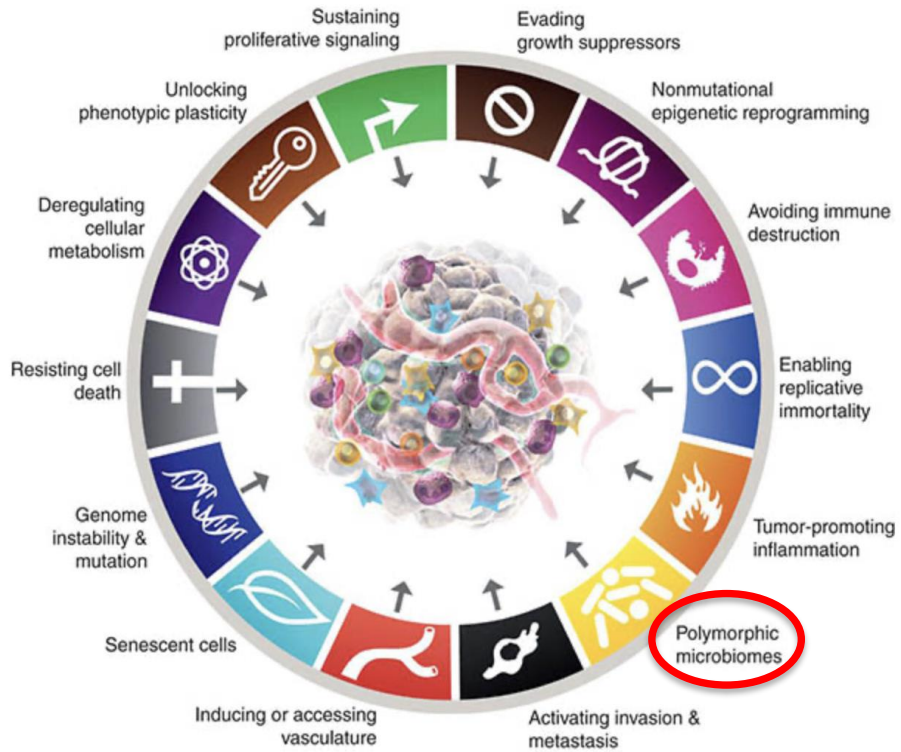
Microbes (along with other factors) can profoundly influence our physiology, cancer, and other disease states



Golnaz Morad PhD

Morad et al, *Cell 2021*

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

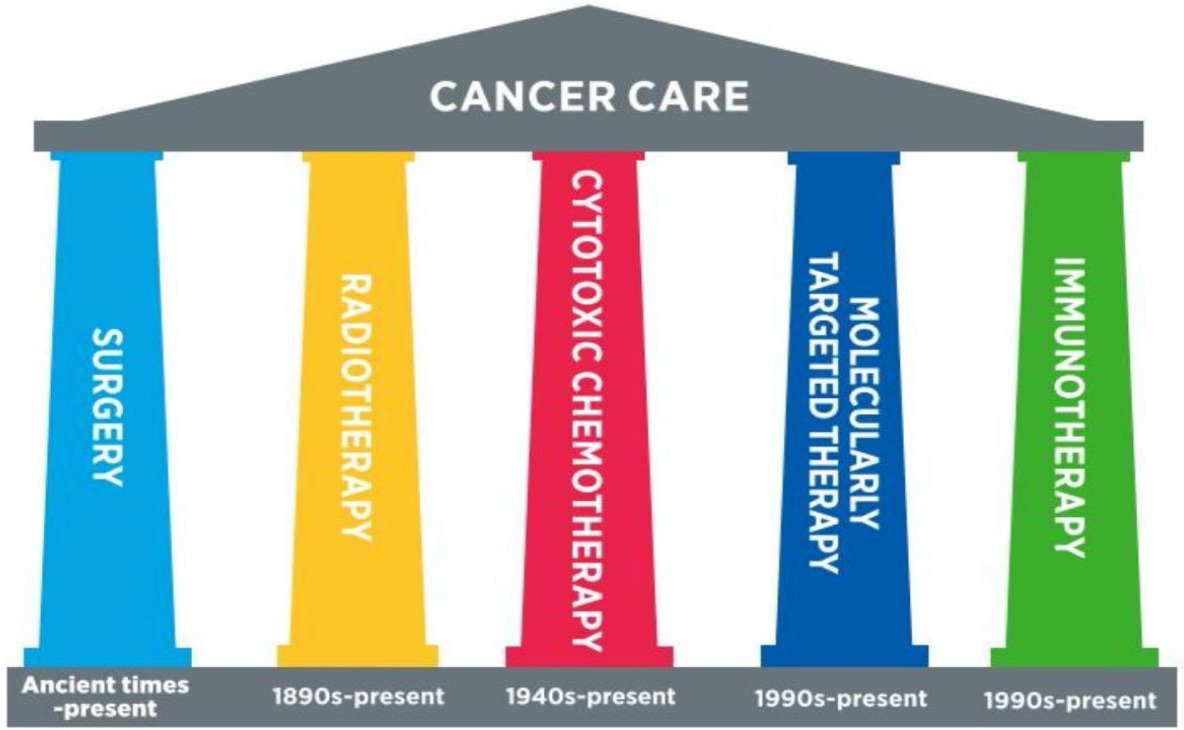


"Hallmarks of Cancer: New Dimensions" provides an update to the landmark "Hallmarks of Cancer" series. Graphic from Cancer Discovery.

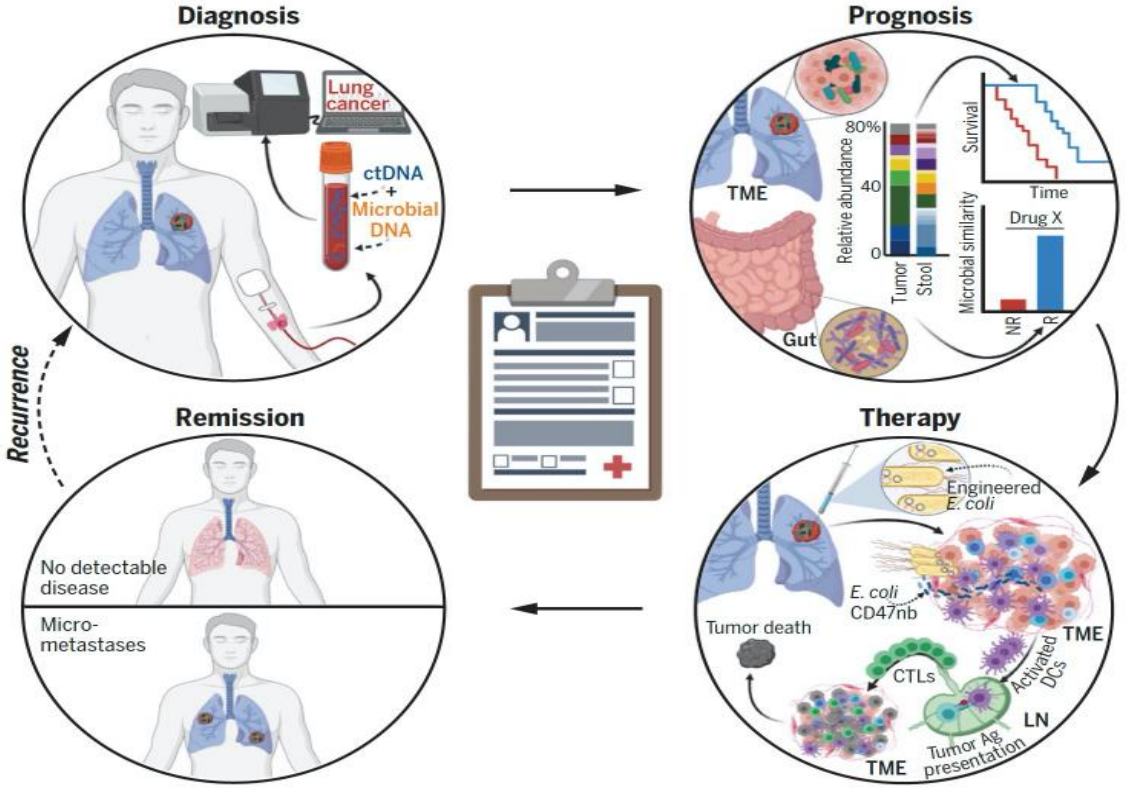
Hanahan, *Cancer Discovery 2022*

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?

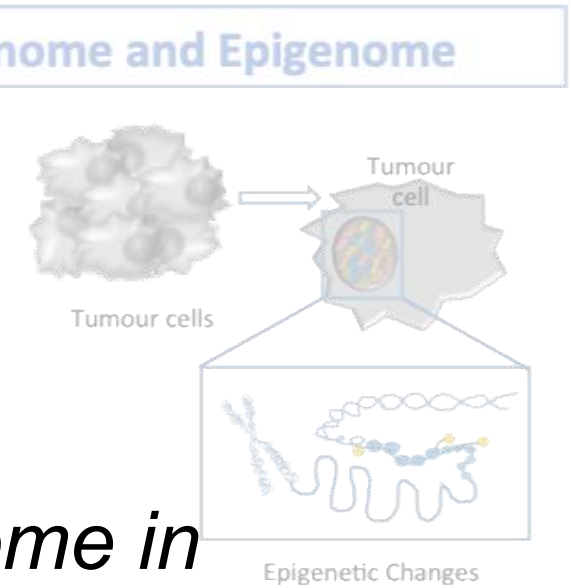


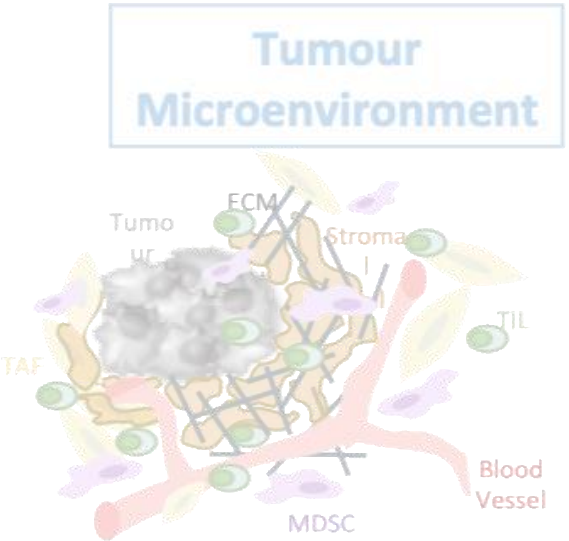
From AACR Cancer Progress Report



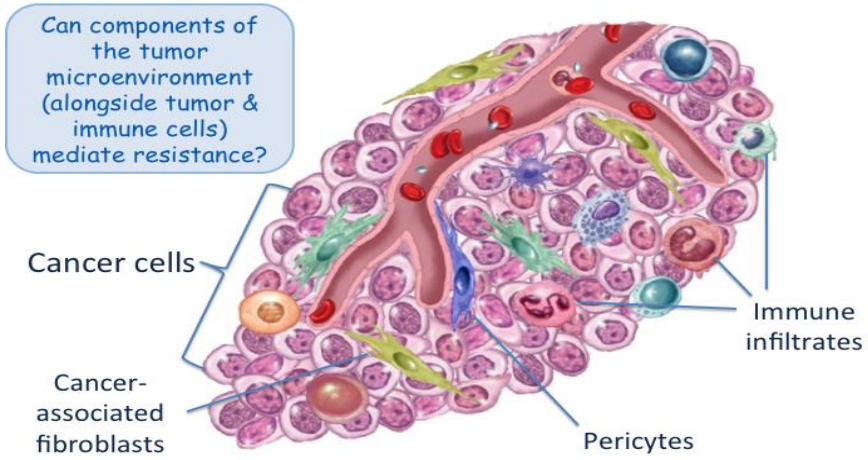
Sepich-Poore et al, Science 2021

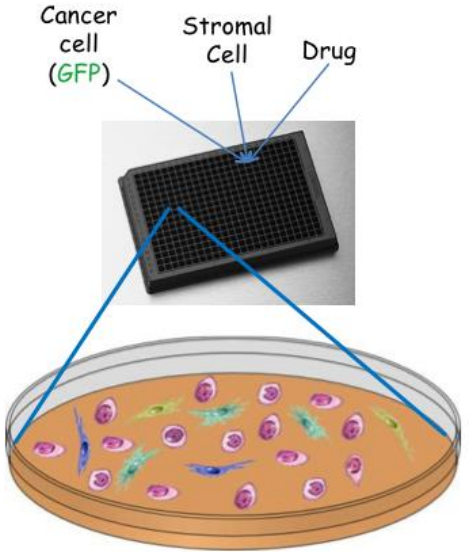
We first studied the role of the microbiome in cancer, but did it serendipitously

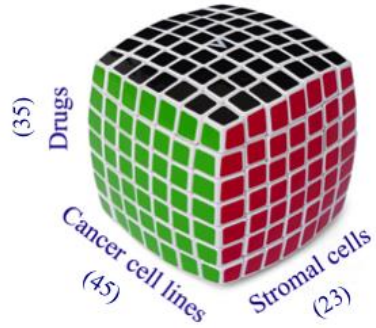




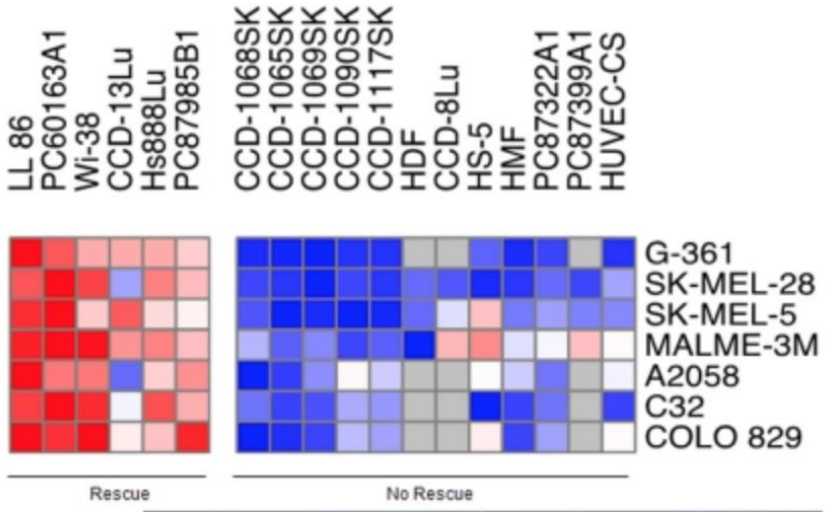
We used a model to study stromal-mediated resistance in melanoma







Certain stromal cells were capable of mediating resistance to targeted therapy



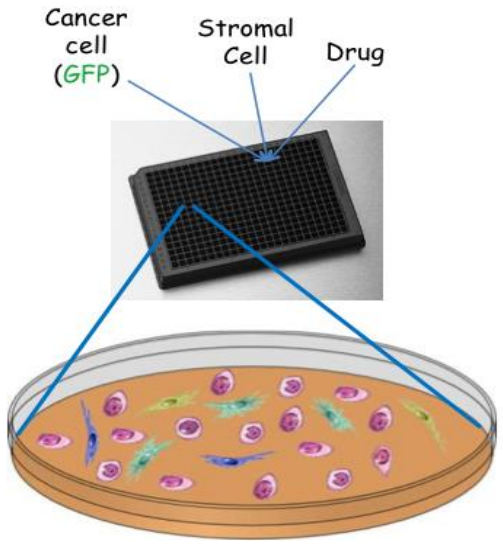
Tumor microenvironment induces innate RAF-inhibitor resistance through HGF secretion

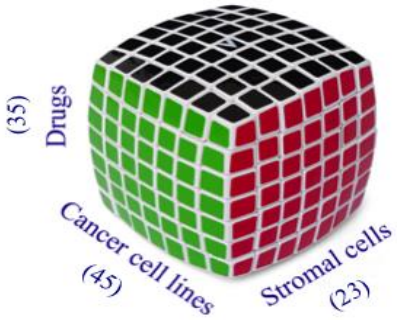
Ravid Straussman[1], Teppei Morikawa[2], Kevin Shee[1], Michal Barzily-Rokni[1], Zhi Rong Qian[2], Jinyan Du[1], Ashli Davis[1], Margaret M. Mongare[1], Joshua Gould[1], Dennie T. Frederick[3], Zachary A. Cooper[3], Paul B. Chapman[4], David B. Solit[4,5], Antoni Ribas[6,7], Roger S. Lo[7,8], Keith T.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

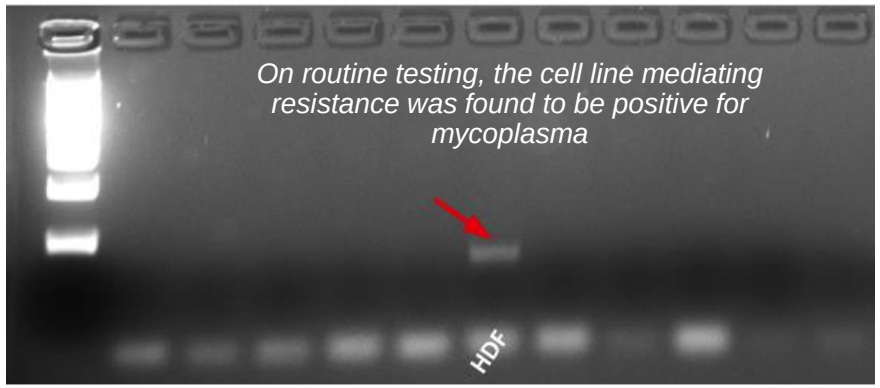
Straussman et al, Nature 2012

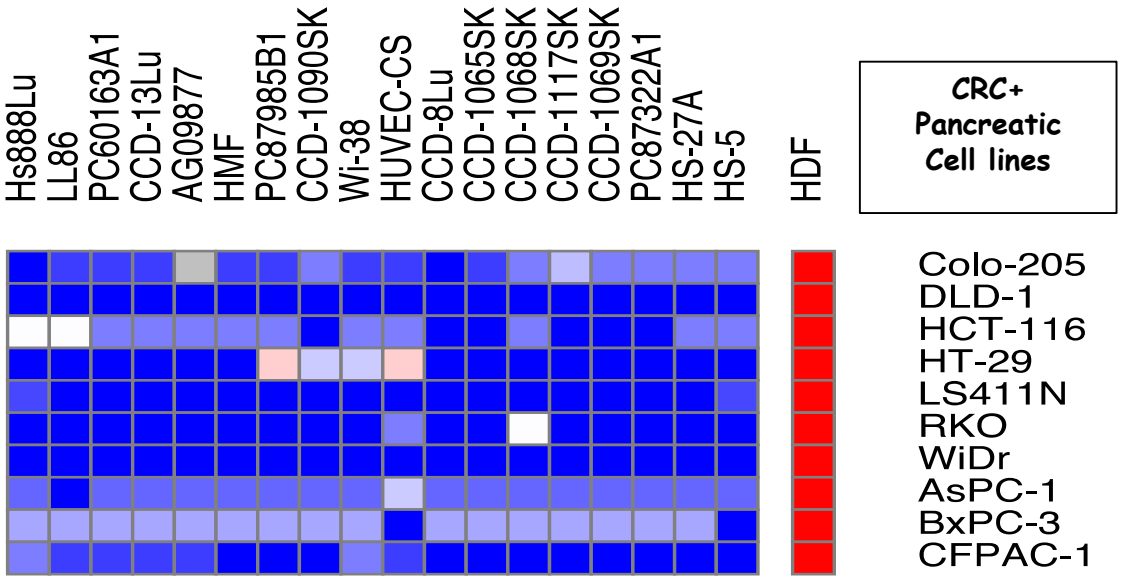
We used the model to study stromal resistance in other cancers *(with a twist)*

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







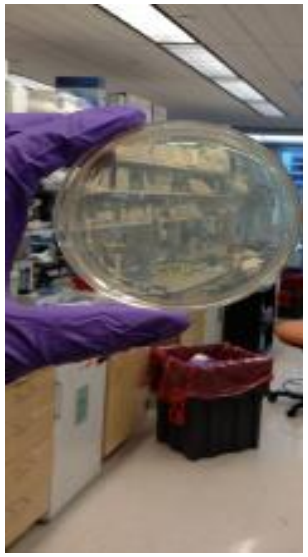


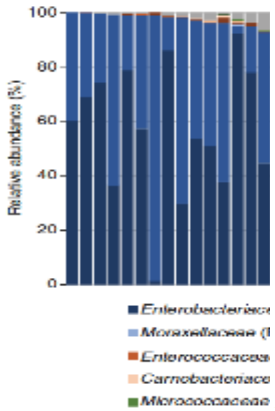
In these studies, one cell line rescued cancer cells from gemictabine

Mycoplasma is responsible for rescue from Gemcitabine:

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

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

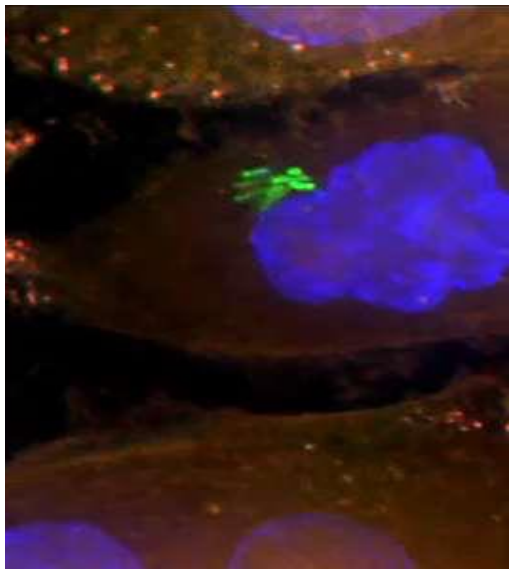


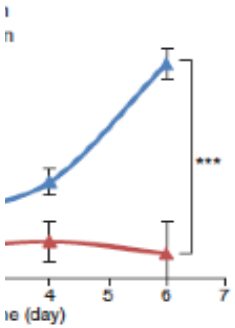


CANCER

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]‖¶

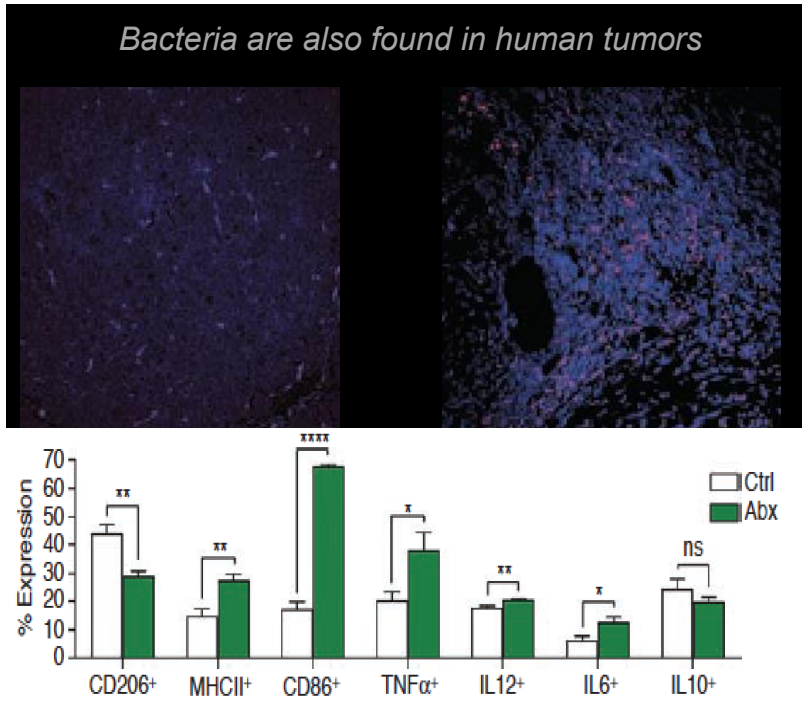




With Ravid Straussman Todd Golub, Matt Katz, Anirban Maitra, Mike Kim, and others… Science 2017

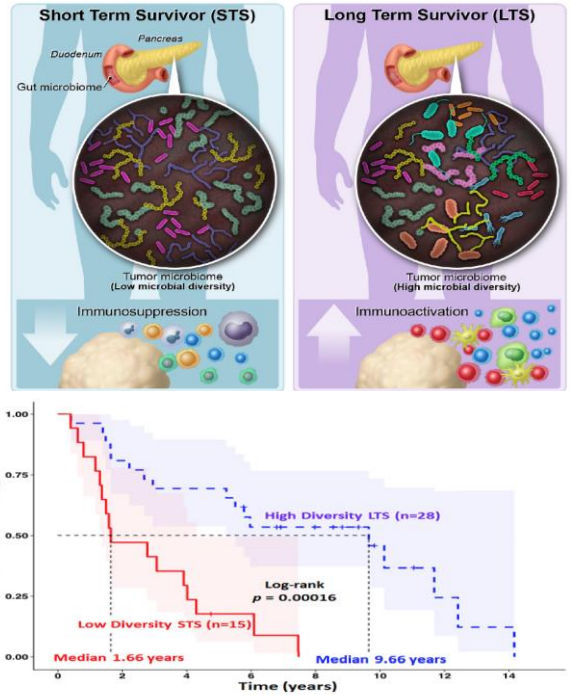
Intra-tumoral microbes may also impact anti-tumor immunity, with some intra-tumoral microbes negatively impacting it, while others promote immunity *(even via neoantigens)*

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



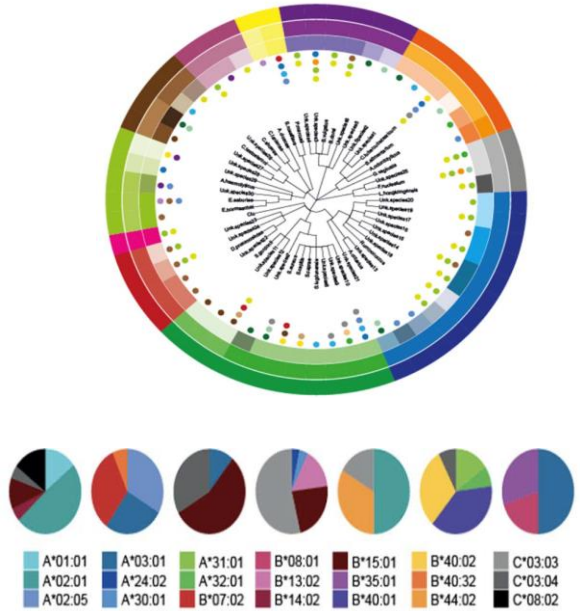
Pushulkar et al, Cancer Discovery 2018

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)

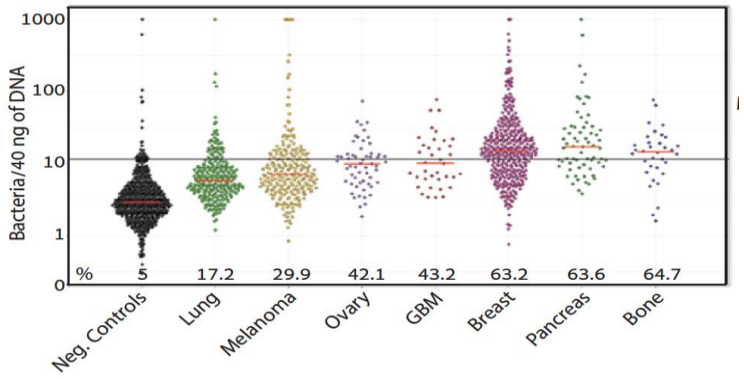


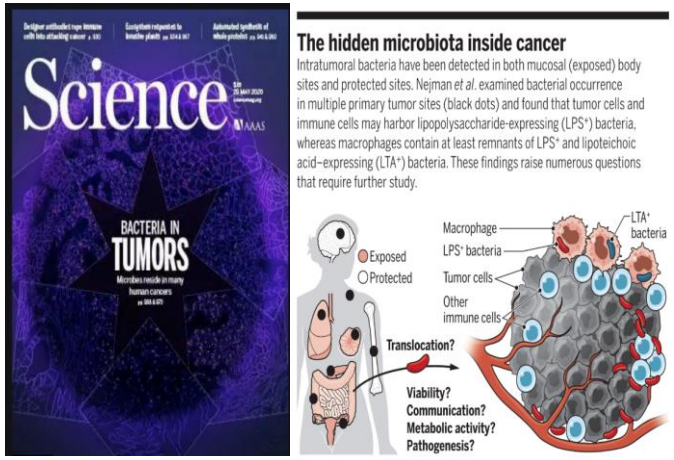
Kalaora, Nagler et al, Nature 2021

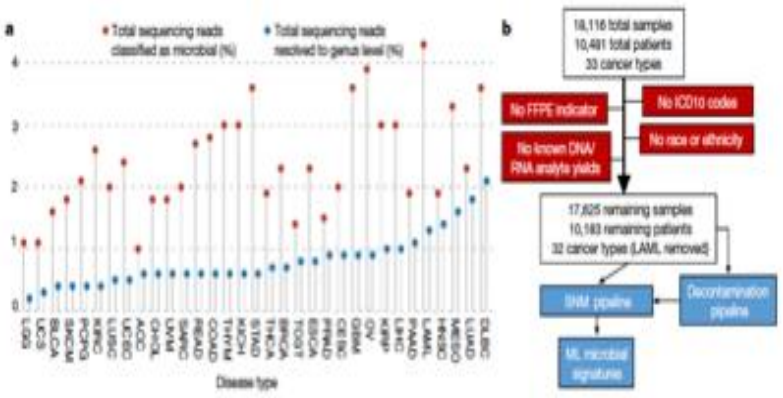
Yardena Samuels PhD

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

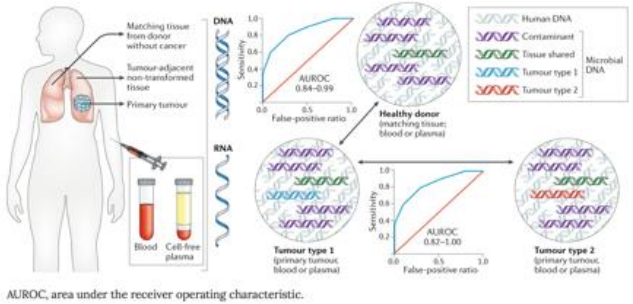
Intra-tumoral bacteria were identified in all tumor types, though composition differed depending on histology







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



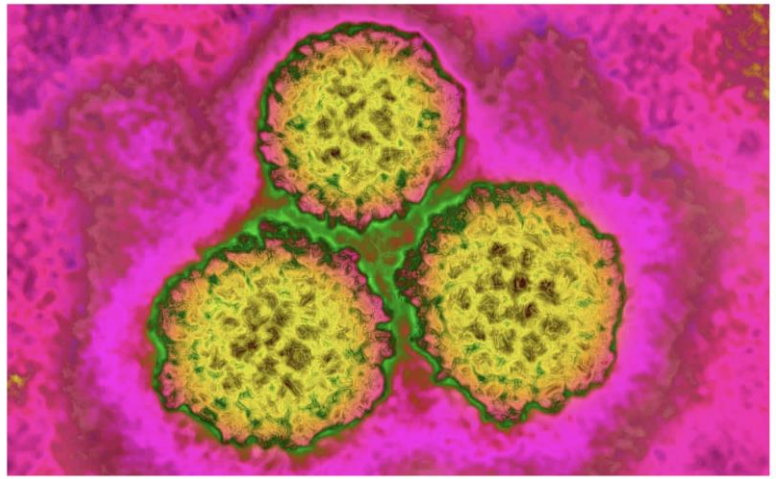
Trinchieri Nat Rev Clin Oncology 2020

Ravid Straussman MD PhD

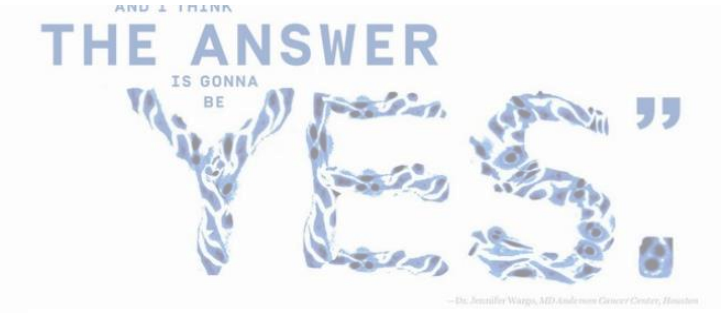
Rob Knight PhD *Nejman et al Science 2020, Poore et al, Nature 2020*

‘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



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

PRIME-TR
PROGRAM FOR INNOVATIVE MICROBIOME & TRANSLATIONAL RESEARCH
BUILD.INNOVATE.CURE.

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Co-Director


Rob Jenq, MD
Co-Director

DATA SCIENCE


Matt Wong, BSc
Sr. Scientific App. Specialist


Aditya Mishra, PhD
Computational Scientist


Ashish Damania, BSc
Assoc. Computational Scientist

CLINICAL TRANSLATION


Pranoti Sahasrabhojane, MSc
Clin. Studies Supervisor

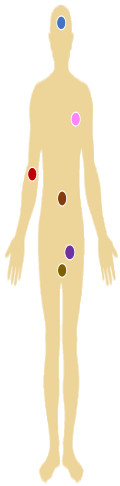

Khalel Imanbayev, MD
Rsrch. Data Coordinator

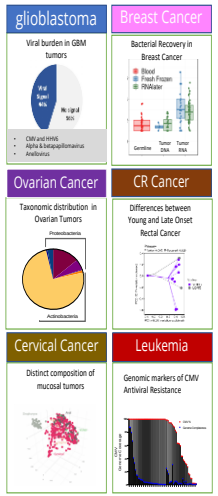

Yasmine Hoballah, MSc
Rsrch. Asst. II

Microbiome Data Mining

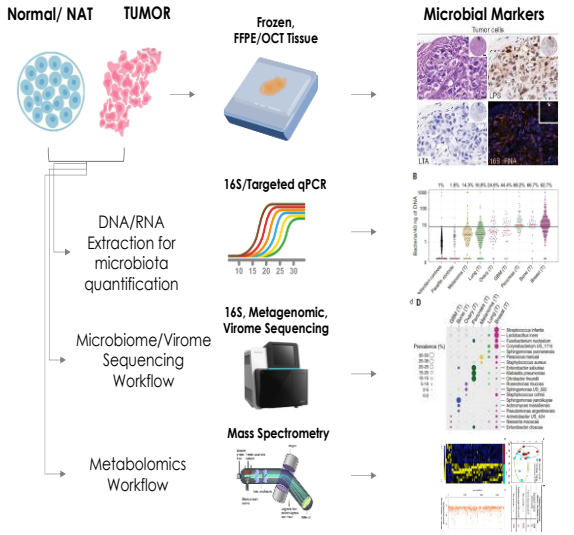
PRIME-TR Microbiome-dedicated bioinformatic resources

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





TISSUE MICROBIOME PROFILING



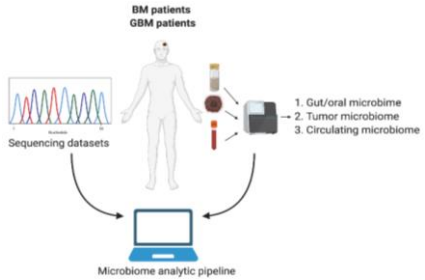
Evidence of presence of intact/live bacteria (bacterial components) in tissue - localization

Quantification of bacterial signal in tumor and normal tissue

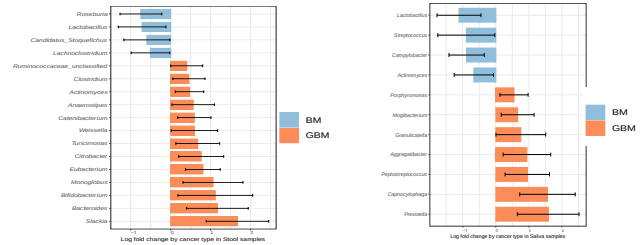
Taxonomic profiling of microbial signals

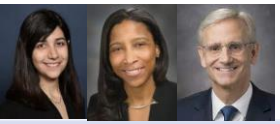
Metabolomic profiling of microbial signals

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



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

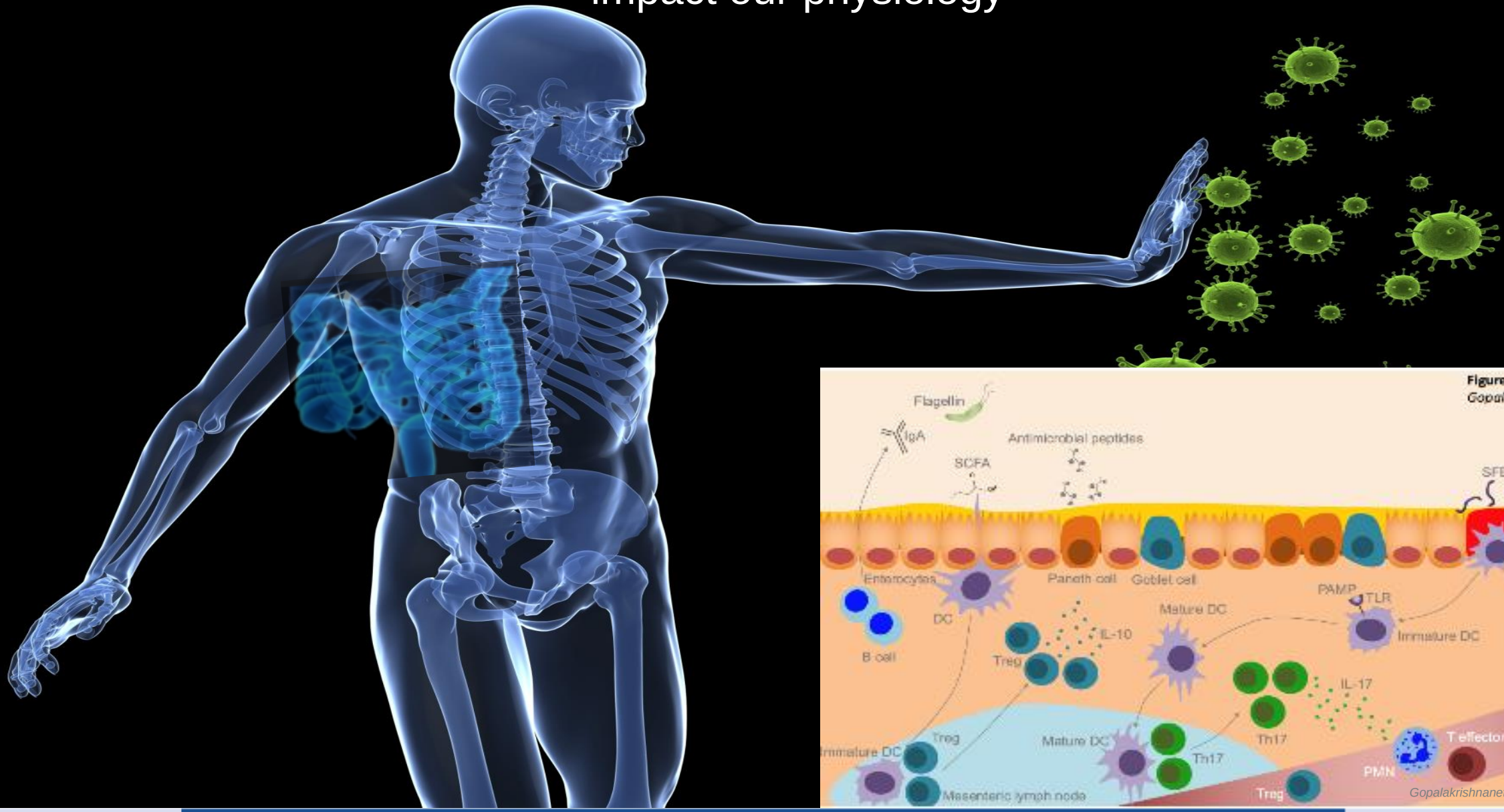




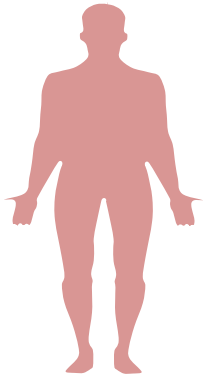
Golnaz Morad PhD
Sherise Ferguson MD
Fred Lang MD

*Confidential unpublished data * DO NOT POST **

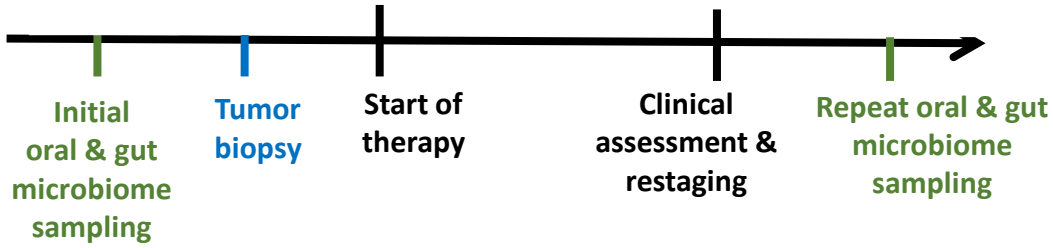
In addition to microbes within tumors, we know that microbes within the gut profoundly impact our physiology

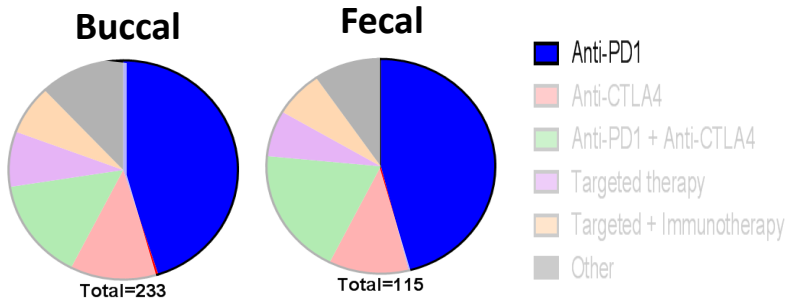


We studied oral and gut (fecal) microbiome in a large cohort of patients with metastatic melanoma going onto systemic therapy

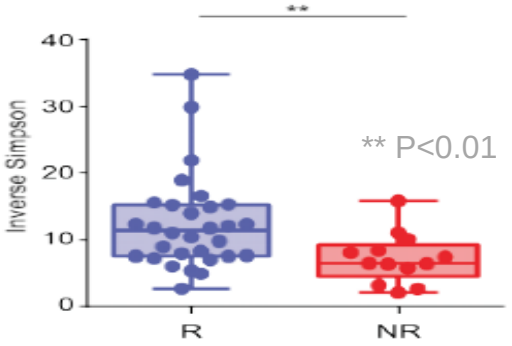


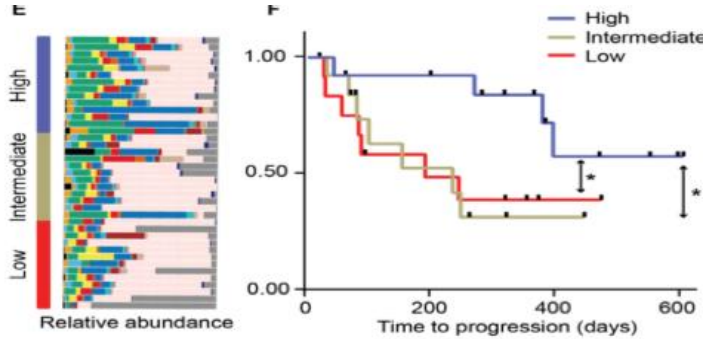
n = 233 patients

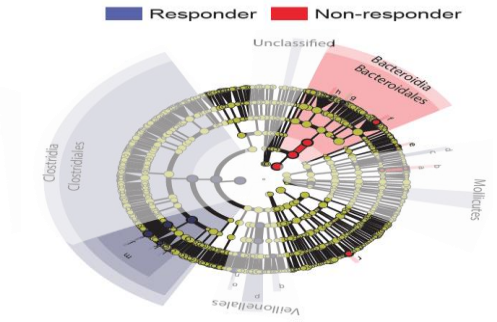


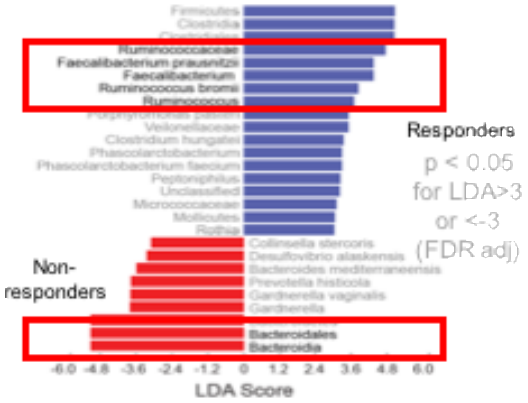


Microbiome sequencing & immune profiling was performed









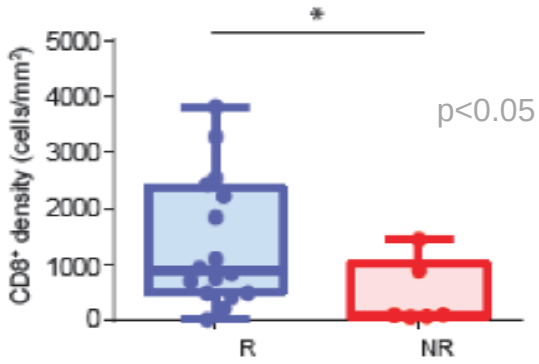
Responders to anti-PD-1 had a higher diversity of gut bacteria associated with prolonged PFS (along with additional compositional differences)

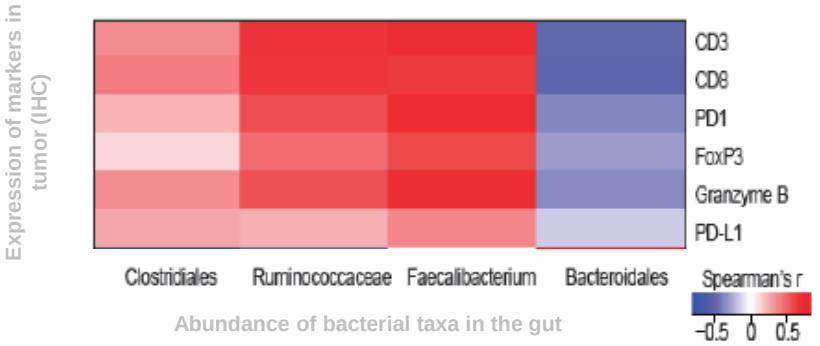
Deepak Gopalakrishnan PhD

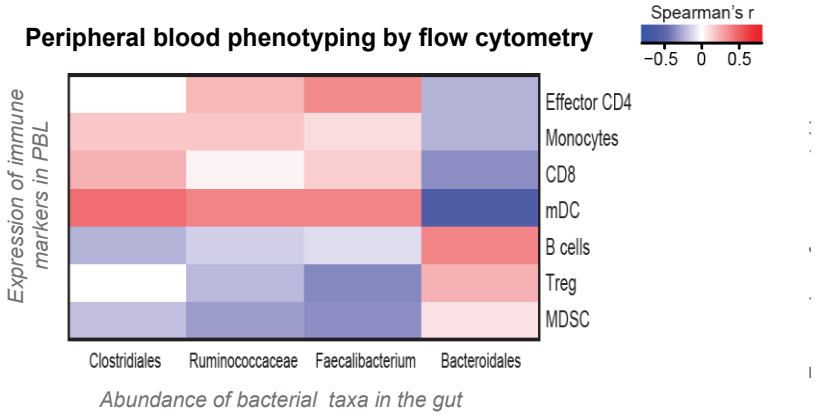
Gopalakrishnan et al, Science 2018

Christine Spencer PhD

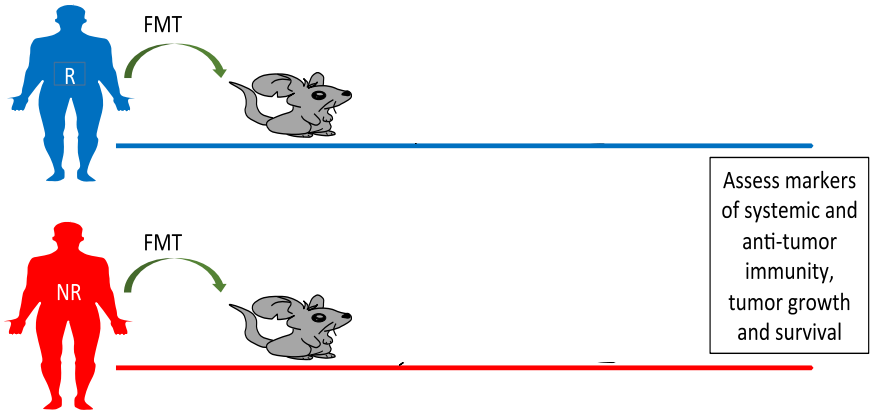
Importantly, “favorable” signatures in the gut microbiome were associated with enhanced immune responses in the tumor microenvironment

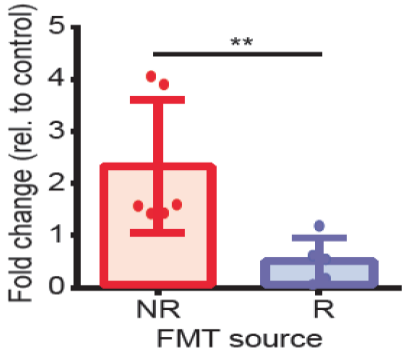


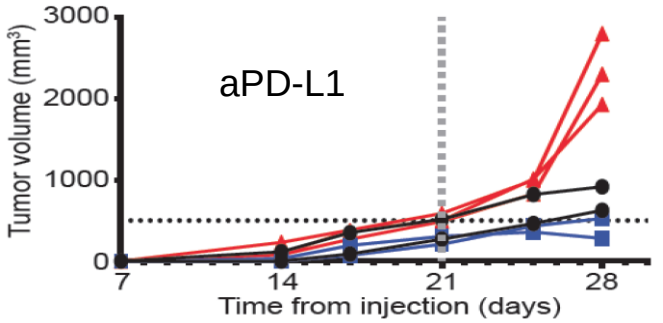




And mechanistic studies in germ free mice showed that fecal transplant could recapitulate the phenotype







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

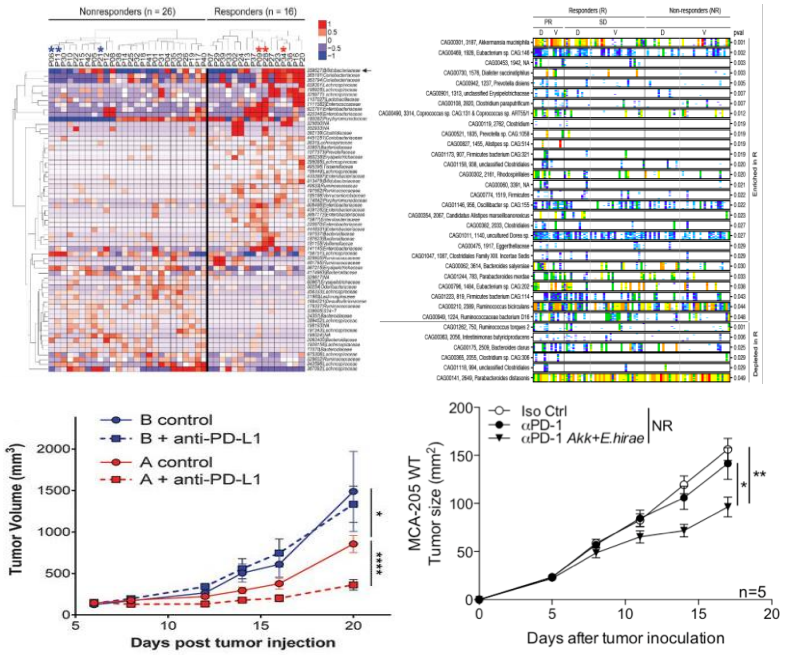
Luigi Nezi PhD

Gopalakrishnan et al, Science 2018

Alex Cogdill PhD

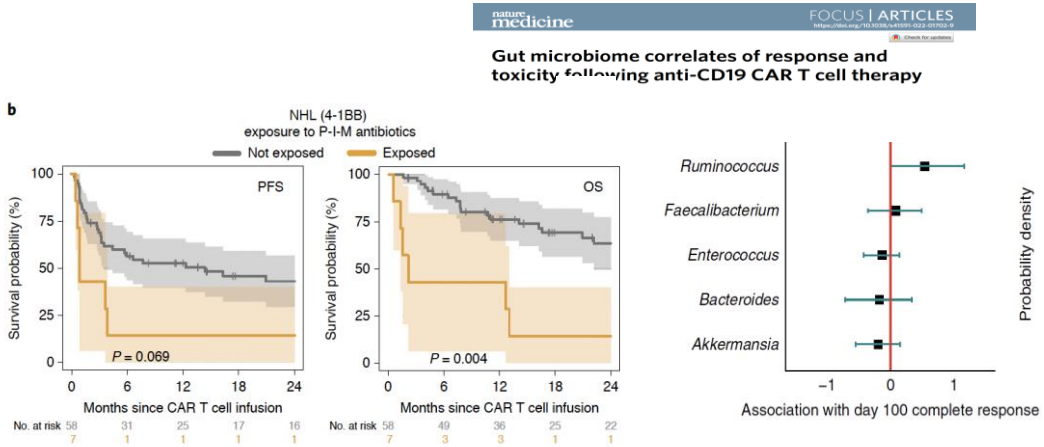
Numerous studies in human cohorts now support a link between the microbiome and response (and toxicity) to cancer therapy

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)

McCulloch et al, Nature Medicine 2022

Lee et al, Nature Medicine 2022

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

(and/or to abrogate toxicity)

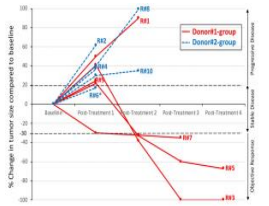
Efforts to target gut microbes to improve response to cancer treatment are proving to be effective

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

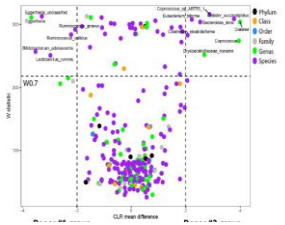
CLINICAL TRIALS

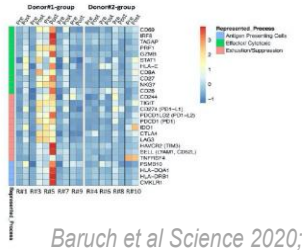
Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients

Erez N. Baruch[1,2*†], Ilan Youngster[3,4], Guy Ben-Betzalel[1], Rona Ortenberg[1], Adi Lahat[5], Lior Katz[6], Katerina Adler[7], Daniela Dick-Necula[8], Stephen Raskin[4,9], Naamah Bloch[10], Daniil Rotin[8], Liat Anafi[8], Camila Avivi[8], Jenny Melnichenko[1], Yael Steinberg-Silman[1], Ronac Mamtani[11], Hagit Harati[1], Nethanel Asher[1], Ronnie Shapira-Frommer[1], Tal Brosh-Nissimov[12], Yael Eshet[4,8,13], Shira Ben-Simon[10], Oren Ziv[10], Md Abdul Wadud Khan[14], Moran Amit[15], Nadim J. Ajami[14], Iris Barshack[4,8], Jacob Schachter[1,4], Jennifer A. Wargo[14,16], Omry Koren[10], Gal Markel[1,2,17*†], Ben Boursi[4,18,19†]



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

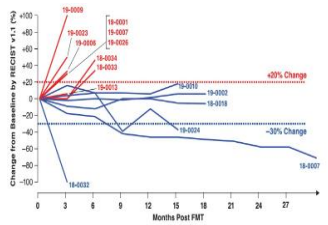




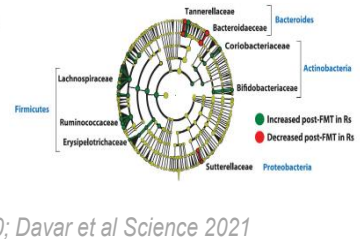
CLINICAL TRIALS

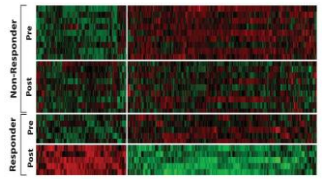
Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients

Diwakar Davar[1*], Amiran K. Dzutsev[2*], John A. McCulloch[2], Richard R. Rodrigues[2,3], Joe-Marc Chauvin[1], Robert M. Morrison[1], Richelle N. Deblasio[1], Carmine Menna[1], Quanquan Ding[1], Ornella Pagliano[1], Bochra Zidi[1], Shuowen Zhang[1†], Jonathan H. Badger[2], Marie Vetizou[2], Alicia M. Cole[2], Miriam R. Fernandes[2], Stephanie Prescott[2], Raquel G. F. Costa[2], Ascharya K. Balaji[2], Andrey Morgun[4], Ivan Vujkovic-Cvijin[5], Hong Wang[6], Amir A. Borhani[7], Marc B. Schwartz[8], Howard M. Dubner[8], Scarlett J. Ernst[1], Amy Rose[1], Yana G. Najjar[1], Yasmine Belkaid[5], John M. Kirkwood[1], Giorgio Trinchieri[2‡§], Hassane M. Zarour[1,9‡§]



- 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

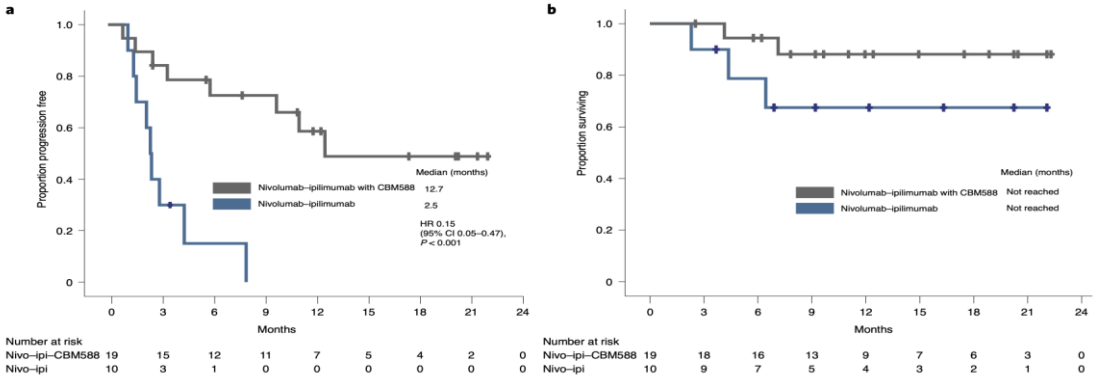
A recent clinical trial published in *Nature Medicine* demonstrated that treatment with a live bacterial product (CBM588) in combination with CTLA-4 and PD-1 blockade was effective in treating patients with metastatic renal cell carcinoma

nature medicine
FOCUS | ARTICLES
https://doi.org/10.1038/s41591-022-01694-6

OPEN

Check for updates

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



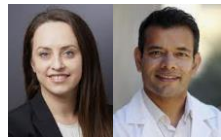
Dizman et al Nature Medicine 2022

Erez Baruch MD PhD

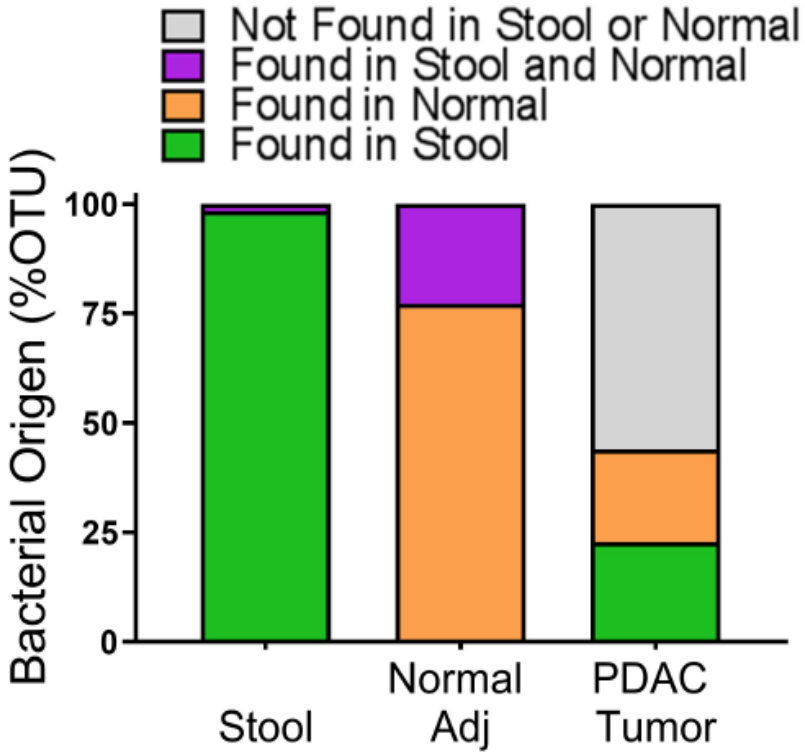
Diwakar Davar MD

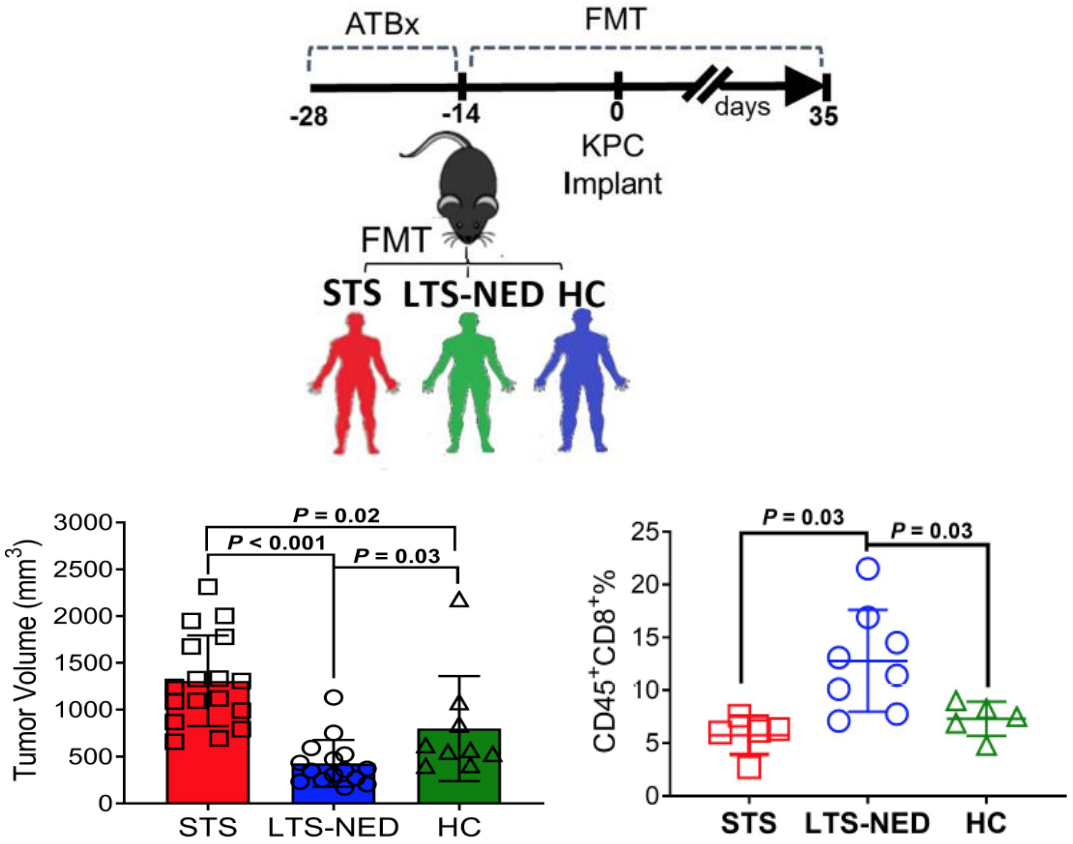
Nazli Dizman MD

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



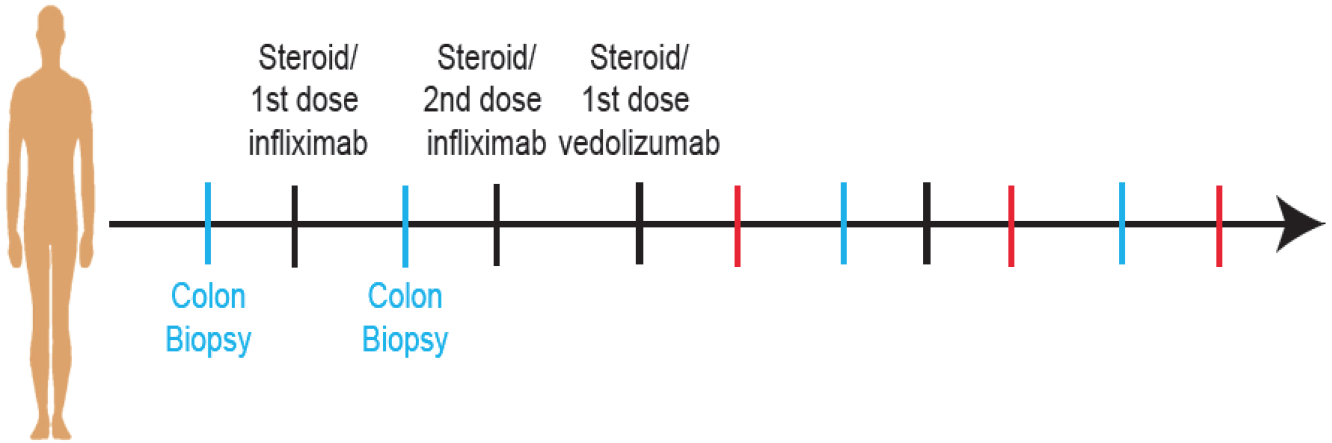


Clinical trials are underway using gut microbiome modulation (in patients with pancreatic cancer and colorectal cancer (PIs – McAllister, Overman)

Florencia McAllister MD PhD

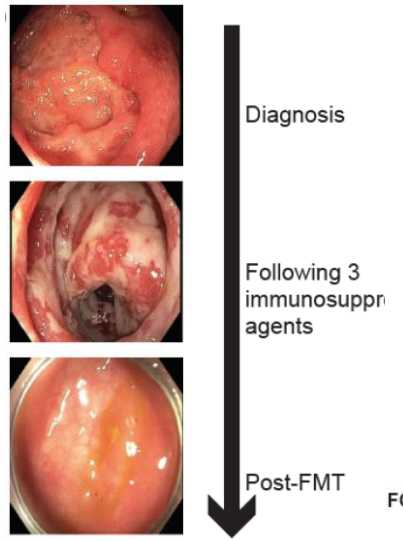
Riquelme et al, Cell 2019

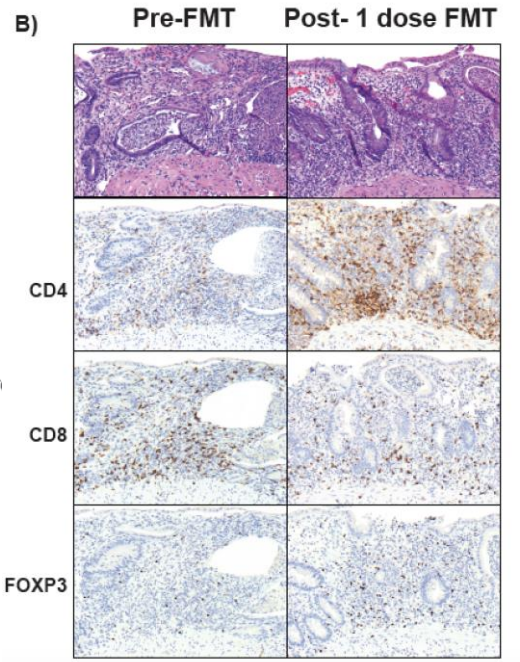
These approaches may also be helpful in treating immunotherapy toxicity

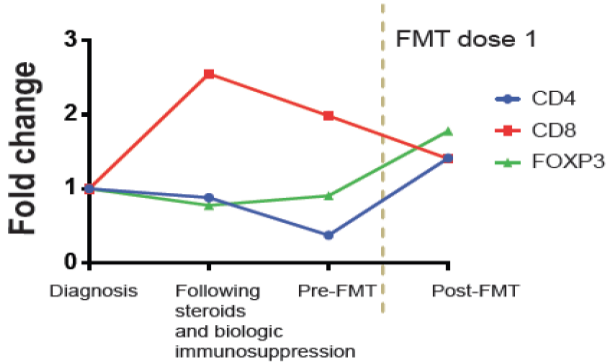


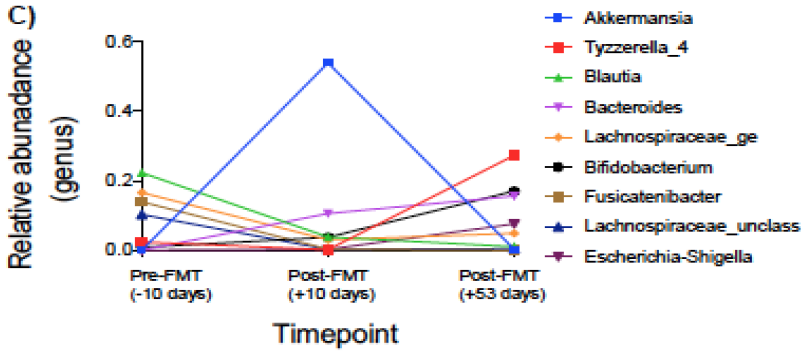
She was treated with FMT from a healthy donor and had complete resolution of all symptoms

50 yo female with metastatic urothelial cancer was treated with aCTLA-4 + a PD-1 and developed colitis refra...ry 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

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

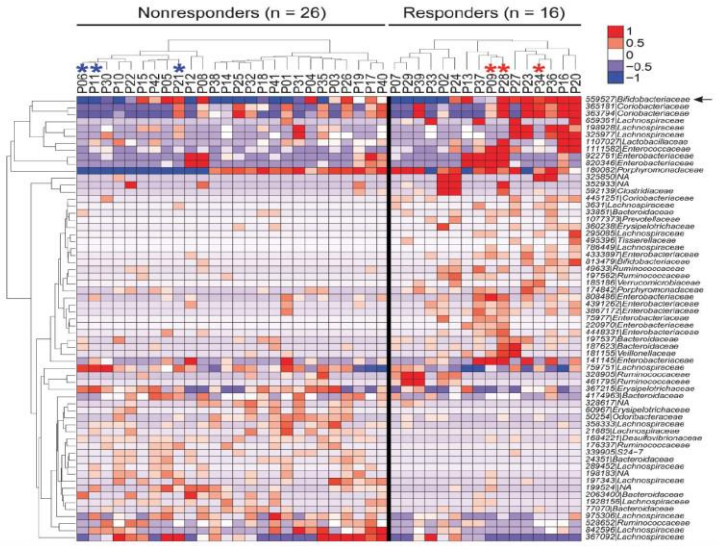
Content current as of:
06/13/2019

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

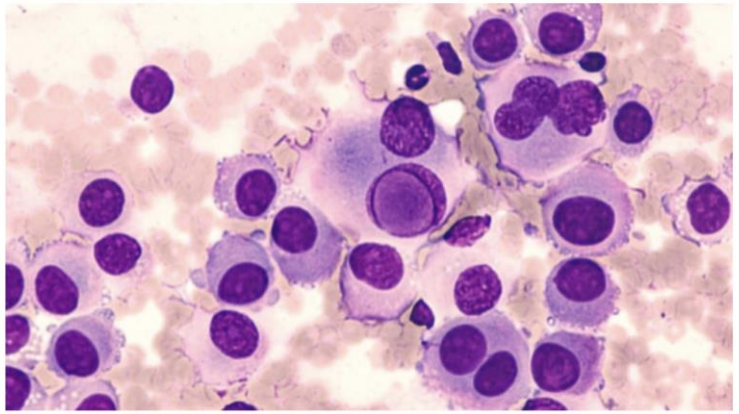
Vyara Matson,[1*] Jessica Fessler,[1*] Riyue Bao,[2,3*] Tara Chongsuwat,[4] Yuanyuan Zha,[4] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4†]



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.

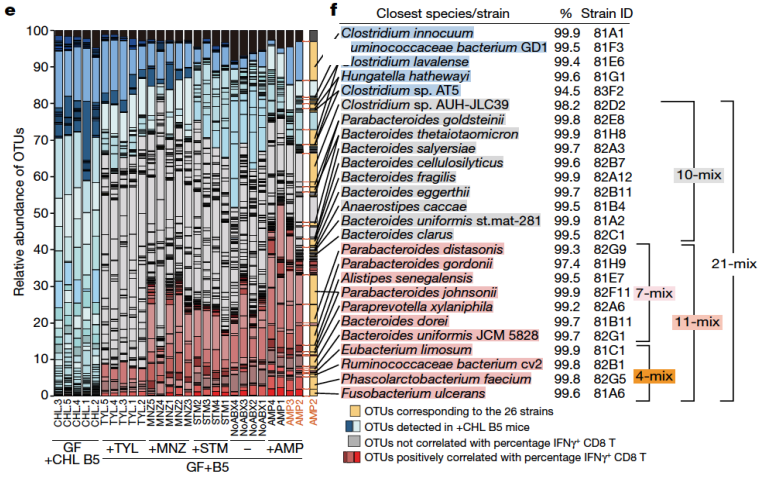
The company said it was motivated both by the challenges of patient enrollment during the COVID-19 pandemic and the progress of other candidates in its preclinical pipeline.

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. Plichta[4], Ashwin N. Skelly[1], Wataru Suda[3,5,6], Yuki Sugiura[7], Seiko Narushima[1,3], Hera Vlamakis[4], Iori Motoo[3], Kayoko Sugita[1], Atsushi Shiota[1,7], Kozue Takeshita[1], Keiko Yasuma-Mitobe[1], Dieter Riethmacher[8], Tsuneyasu Kaisho[9], Jason M. Norman[10], Daniel Mucida[11], Makoto Suematsu[7], Tomonori Yaguchi[12], Vanni Bucci[13], Takashi Inoue[14], Yutaka Kawakami[12], Bernat Olle[10], Bruce Roberts[10], Masahira Hattori[3,5,6], Ramnik J. Xavier[4,15], Koji Atarashi[1,2,3] & Kenya Honda[1,2,3]✉

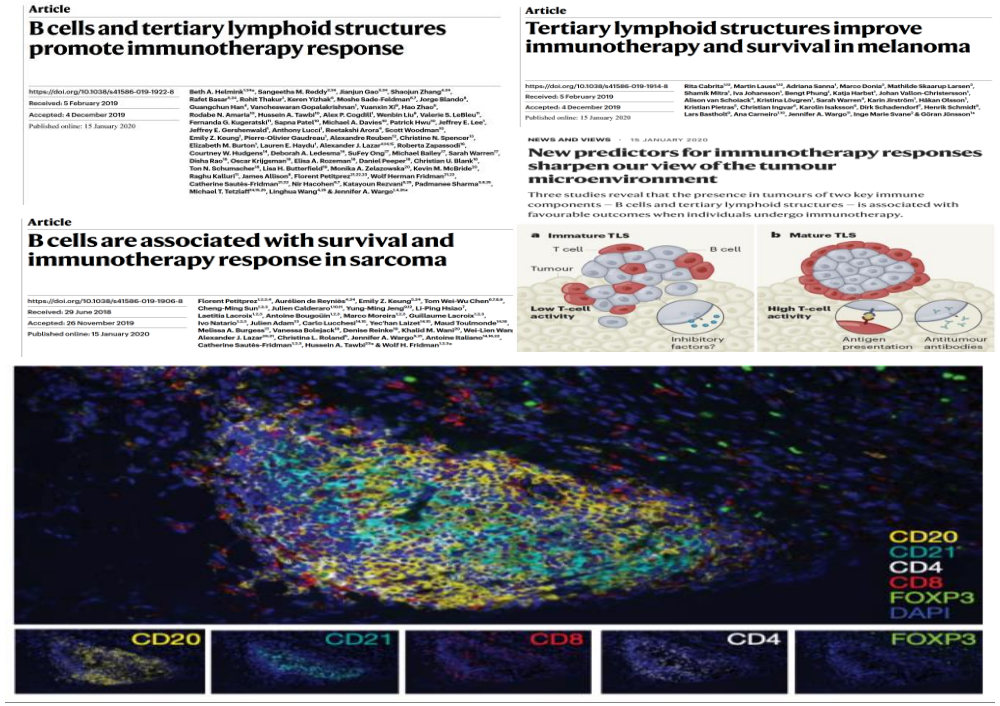


Tanoue et al, Nature 2019

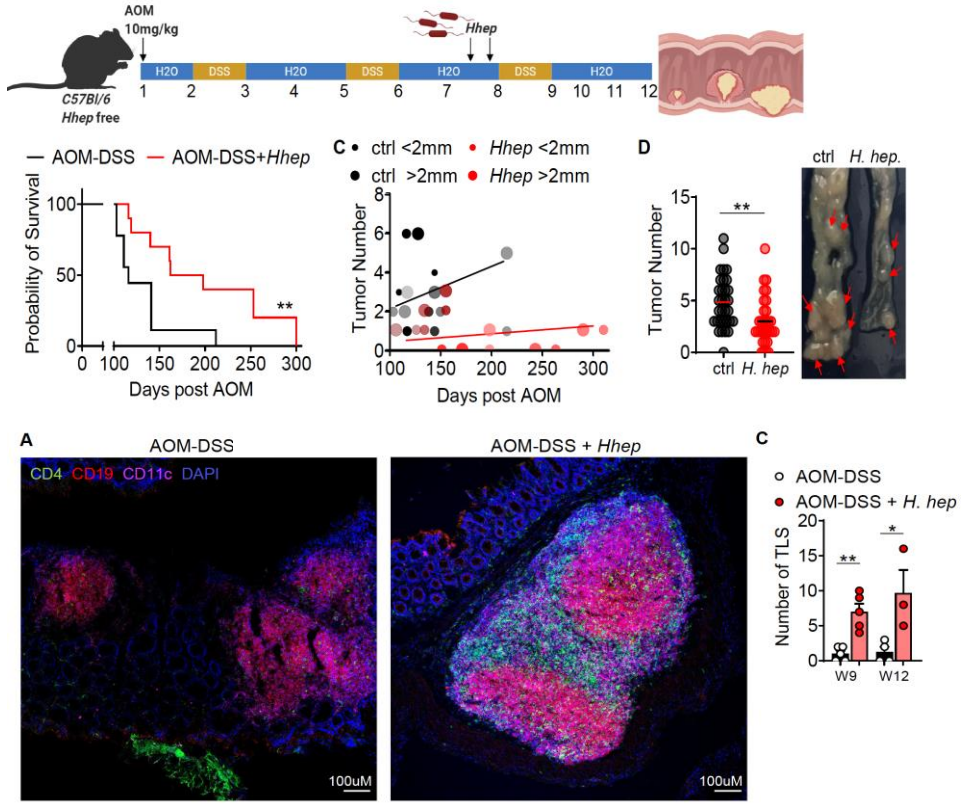
Clinical trials are now in progress based on insights gained from these & other studies…

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

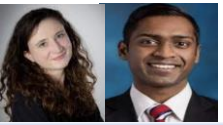


Helmink et al, Cabrita et al, Petiprez et al, Bruno T. Nature 2020



Overacre-Delgoffe, et al. Immunity 2021

Endeavor
The Mark Foundation for Cancer Research
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)

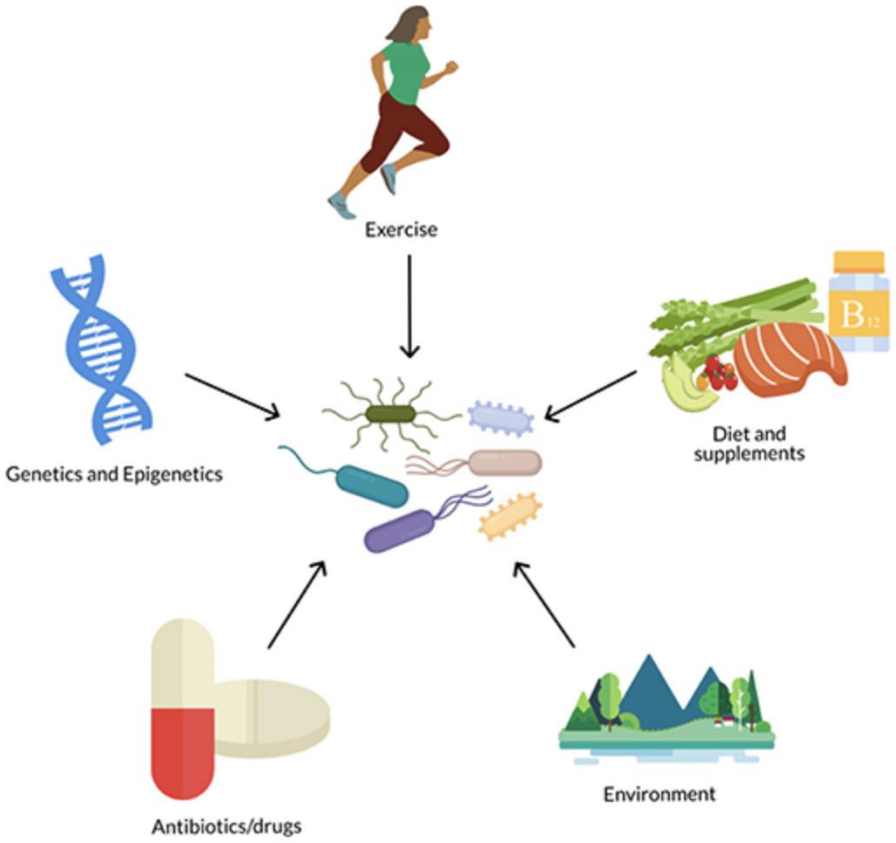
Data to be presented at ASCO 2022

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

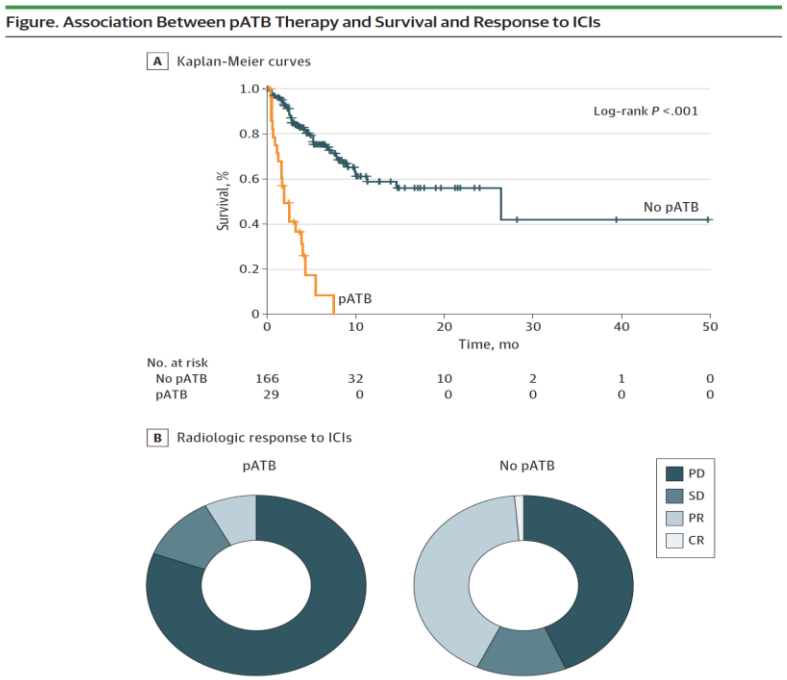
You are what you eat!

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



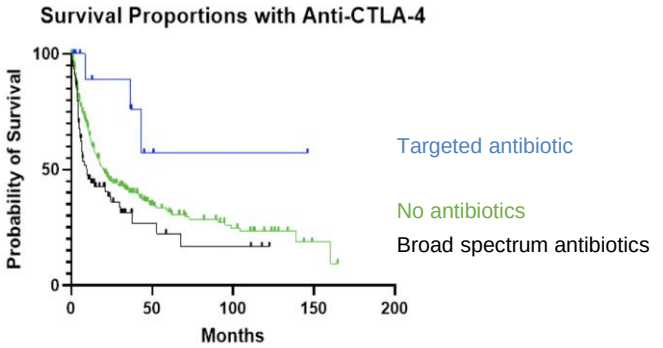
Hughes Frontiers in Nutrition 2020

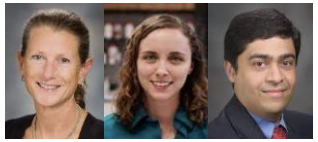
Numerous studies have shown that patients receiving antibiotics before treatment with immune checkpoint blockade (ICB) have worse outcomes (response and survival)



Pinato et al, *JAMA Oncology* 2019

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

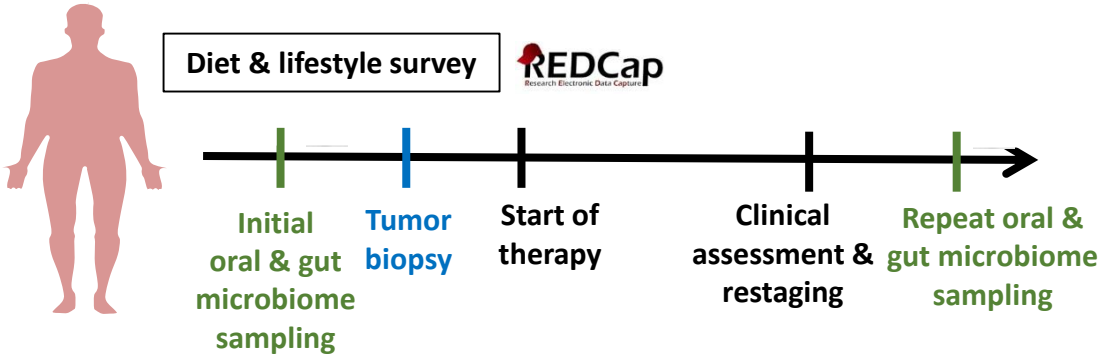




Stephanie Watowich PhD
Liz Park PhD
Vivek Subbiah MD

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

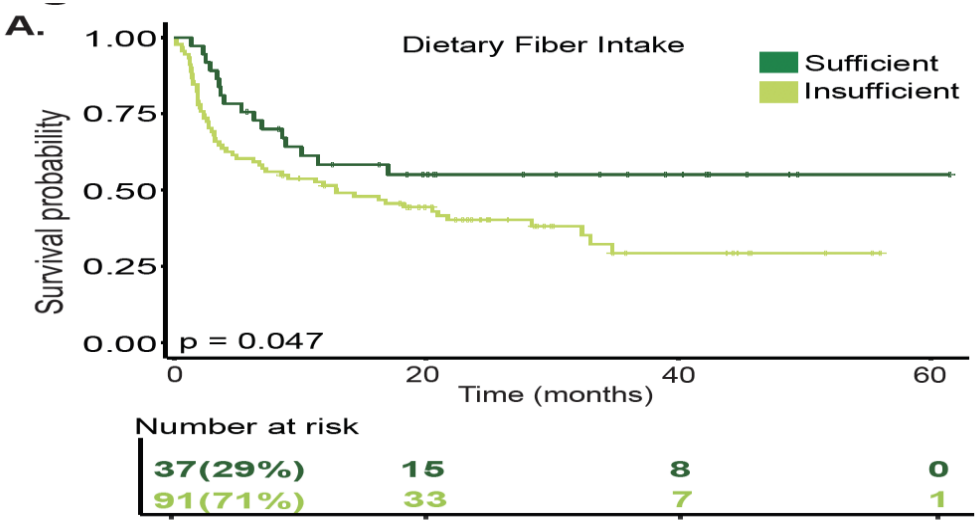
In our cohort, we also studied the influence of diet and lifestyle factors on the microbiome and response to immune checkpoint blockade



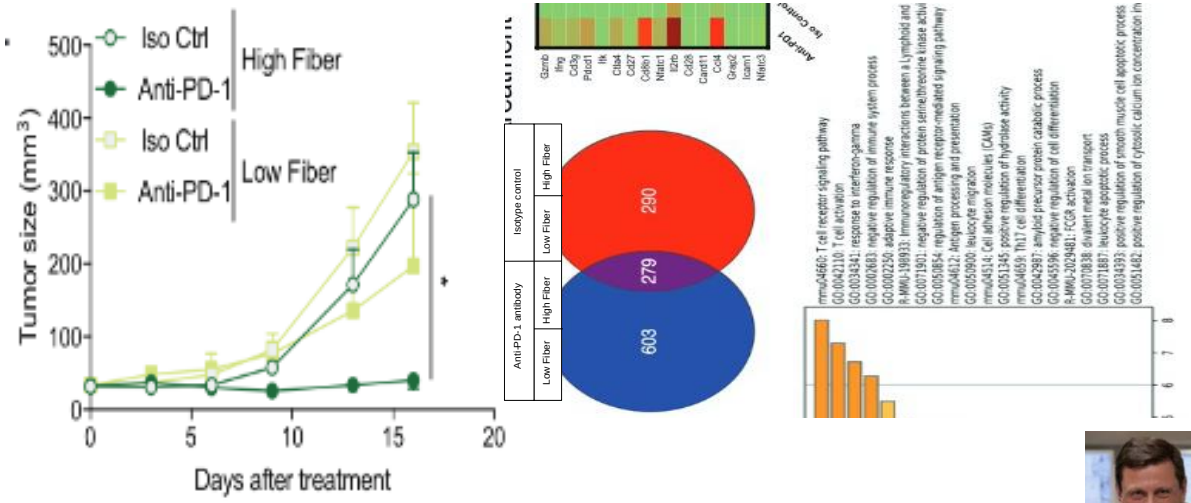
Christine Spencer PhD

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

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

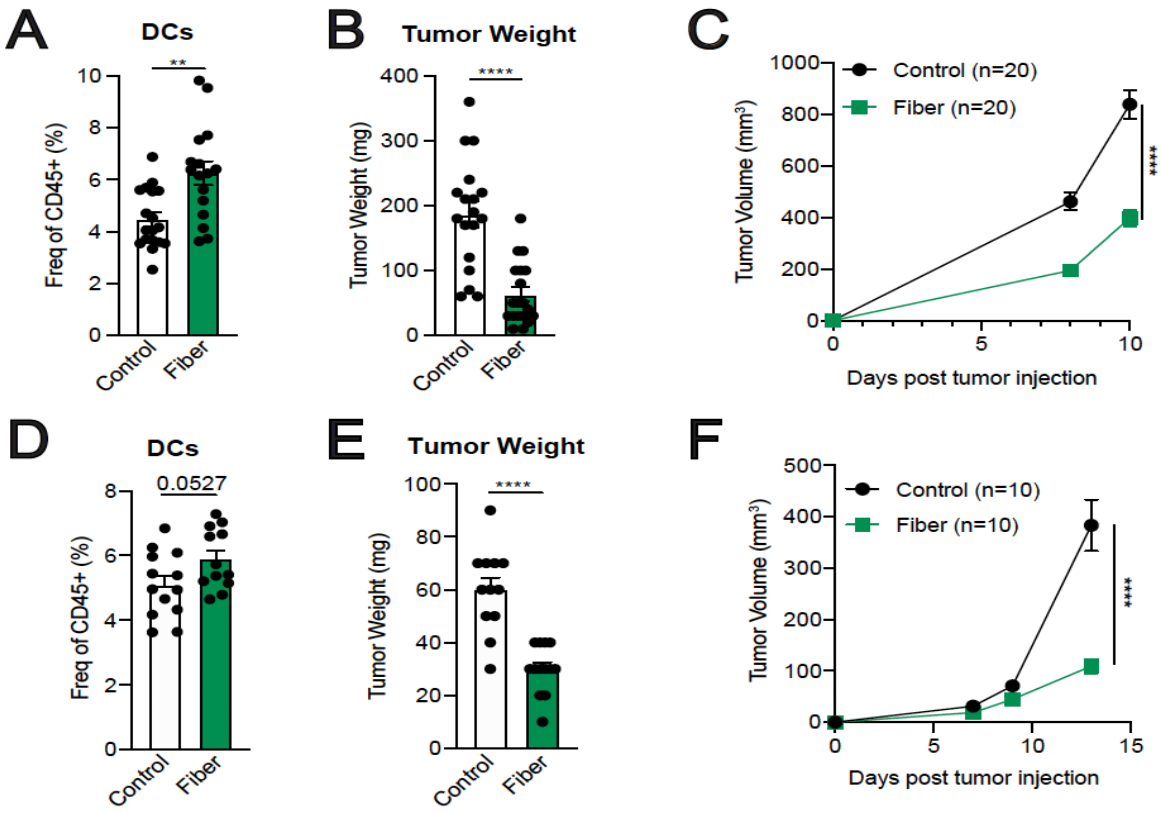
Carrie Daniel MacDougall PhD

Spencer et al, Science 2021

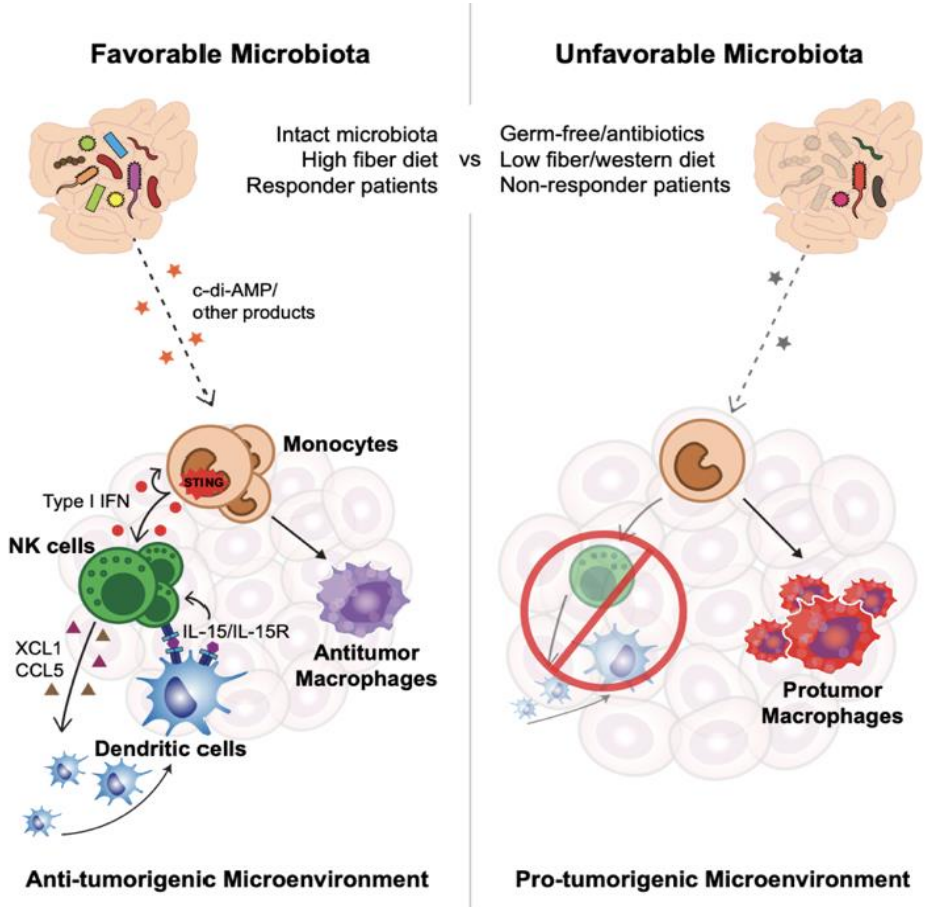
Giorgio Trinchieri PhD

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



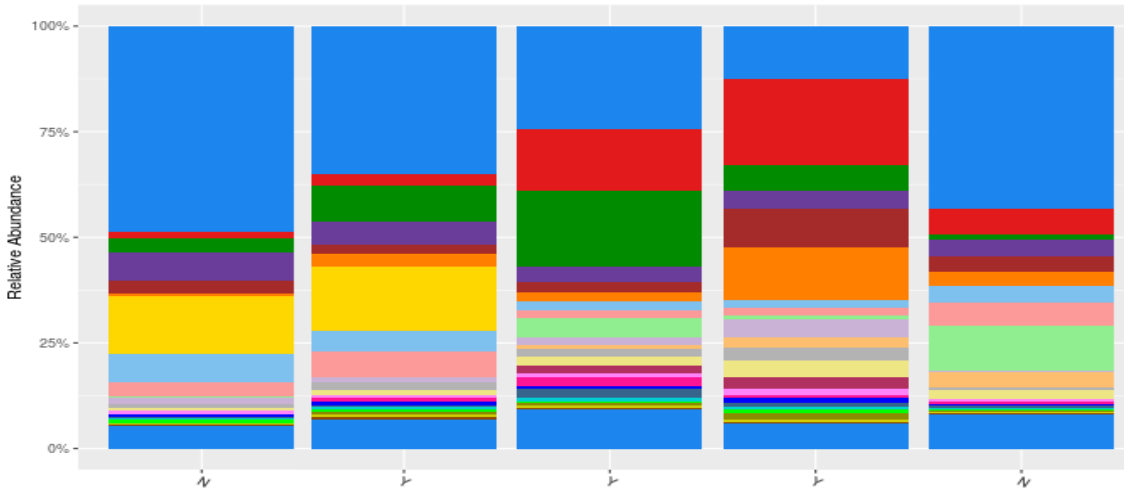
Gut microbiota and dietary fiber shape the TME in part via monocyte reprogramming by STING-mediated IFN signaling

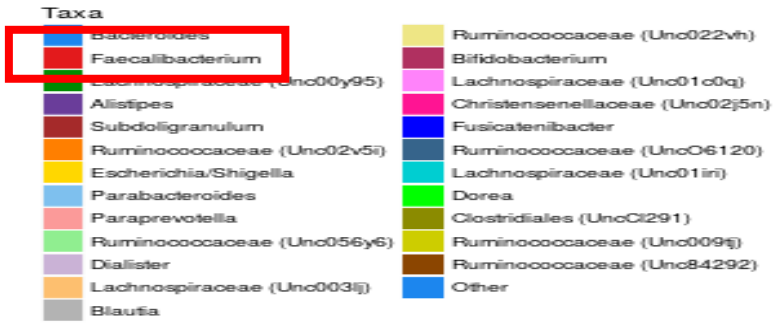


Lam et al, Cell 2021

Romina Goldszmid, PhD

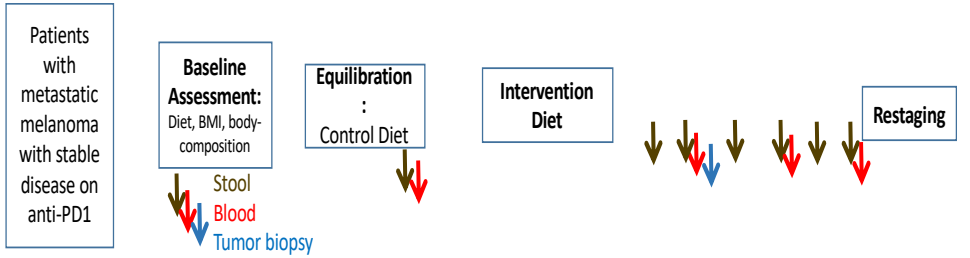
There is evidence that changes in diet can have an impact on gut microbes and associated physiology in a short time frame





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*

Phase I — NED melanoma patients — In-progress
- Feasibility

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

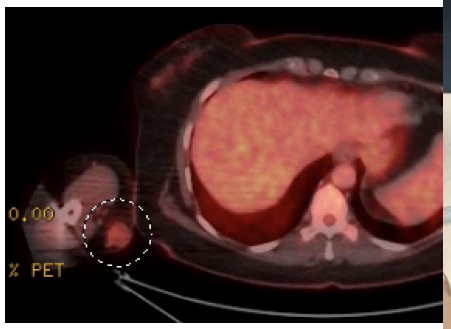
Phase III — Behavioral intervention diet studies
- Disease outcomes

DIET (Diet and Immune Effects Trial):

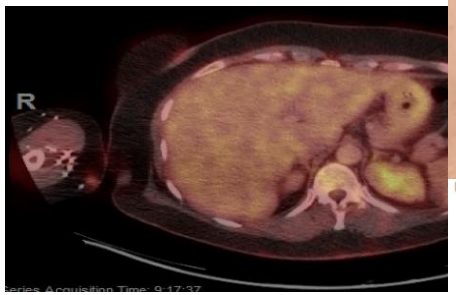
All calorie-containing food and beverages prepared and provided to patients

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 tran



Received immune checkpo and high fiber diet on trial

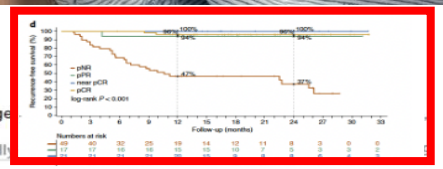


Diagnosis

A: Skin, right distal arm melanoma, ellipse :
Skin and subcutis with healing surgical wound/scar.
Margins have been evaluated; and are free of melanoma.

B: Skin, right upper arm in transit metastasis, ellipse:
Skin and subcutis with healing surgical wound/scar and adjacent necrosis, hemorrhage
viable tumor not identified. See comment.

Electronicall



Comment

B. These histologic featuresa are consistent with a melanoma lesion (clinically a satellite) with 0% viable tumor, 60% fibrosis, 1% pigmentation. The rest of the lesion is composed of a mixed lymphohistocytic infiltrate. An immunohistochemical study on paraffin sections with anti-Mart 1 and anti-SOX-10 fails to reveal viable melanoma cells in the dermis.

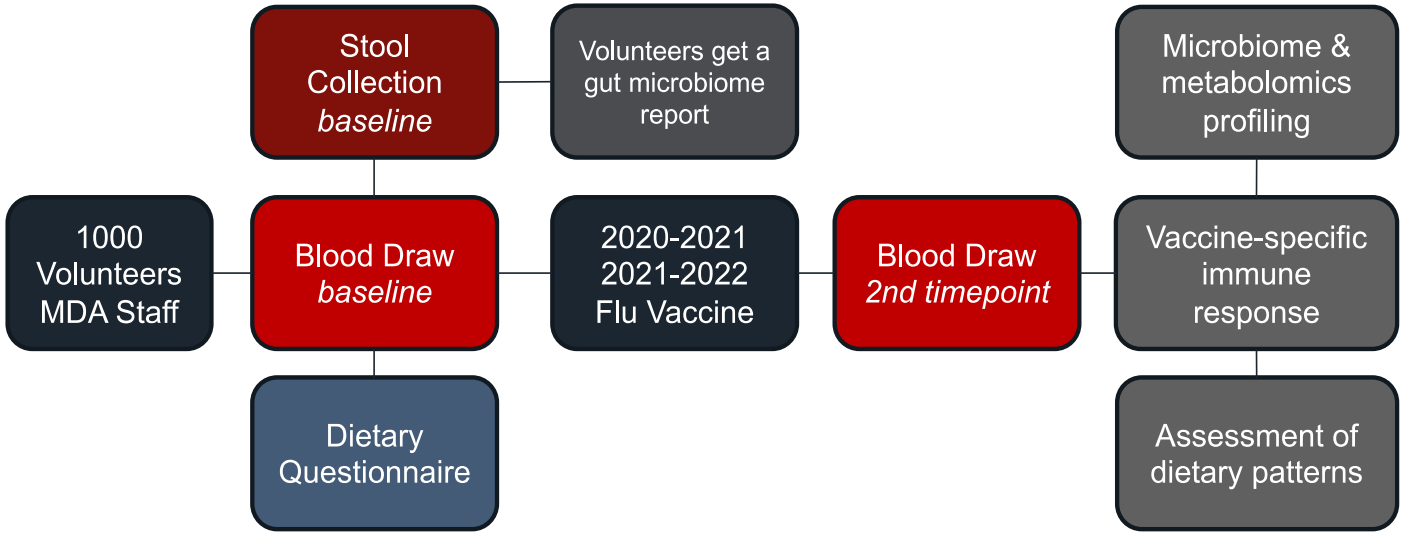
Jen McQuade MD

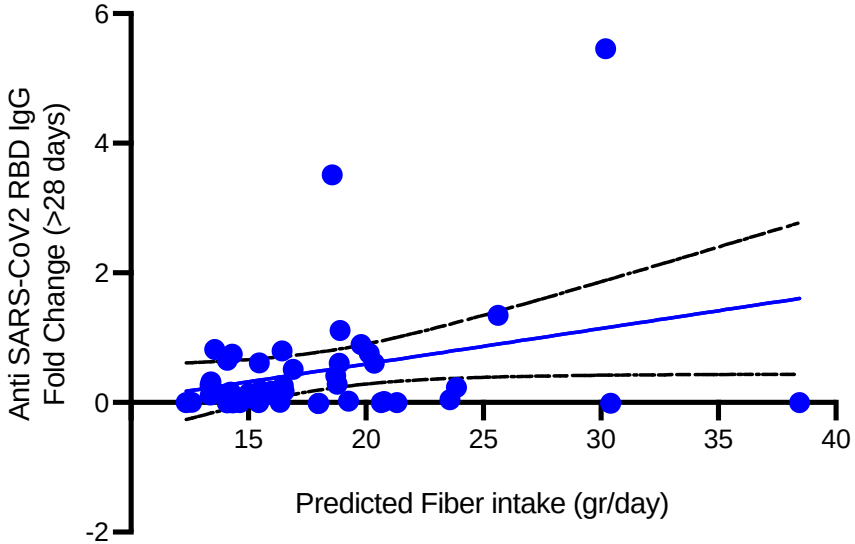
Confidential unpublished data * DO NOT POST *

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?

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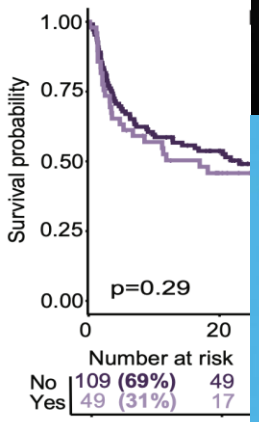

31% of our p
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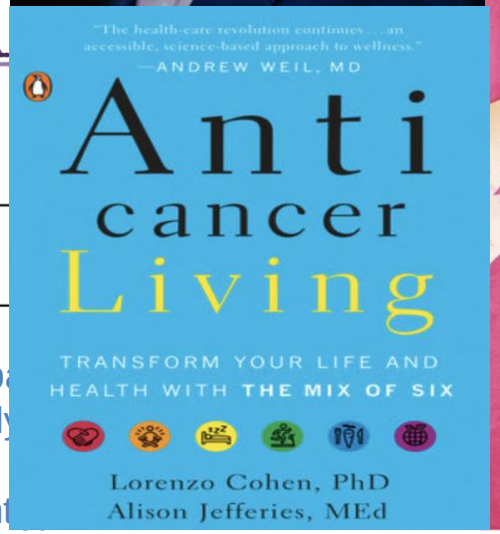
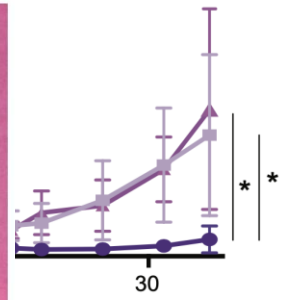
and had a
significant
nonetheless this was intriguing

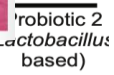


LIFE & ARTS | IDEAS | ESSAY

Those Probiotics May Actually Be Hurting Your 'Gut Health'

obiotics had
anti-PD-1,
t microbes,
ti-tumor

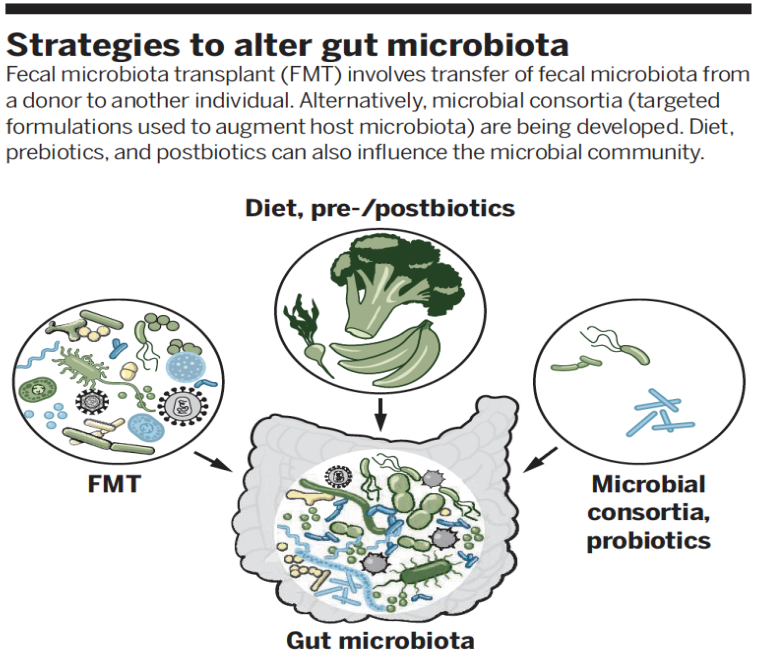




Probiotic 2
(*Lactobacillus*
based)

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



Prior to treatment	During therapy	Assessing impact	Long-term effects
Patients - What patient population to treat? Treatment naïve or refractory? - Should the microbiome be profiled to stratify / select patients? **Pre-conditioning regimen** - Do we need to pre-treat the gut with antibiotics to facilitate engraftment? **How should we optimally modulate the gut microbiota?** - 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?** - Immune checkpoint blockade (anti-PD-1)? - Other forms of immunotherapy? - Other therapy? **How do we optimally monitor patients during therapy?** - Microbiome analyses to assess engrafment / function? - Immune profiling? - Peripheral blood - Tumor **How can we facilitate stable engraftment?** - Should we recommend dietary changes? - Any medications to avoid?	**What are appropriate primary endpoints for such studies?** - Safety and tolerability - Engraftment - Others? **What are appropriate secondary endpoints?** - 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** - 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** - What is impact on overall and disease-specific survival? **Toxicity** - Can we uncouple toxicity and response to immunotherapy? **Other transplanted traits with FMT?** - Obesity? - Depression? - Any potentially favorable traits?

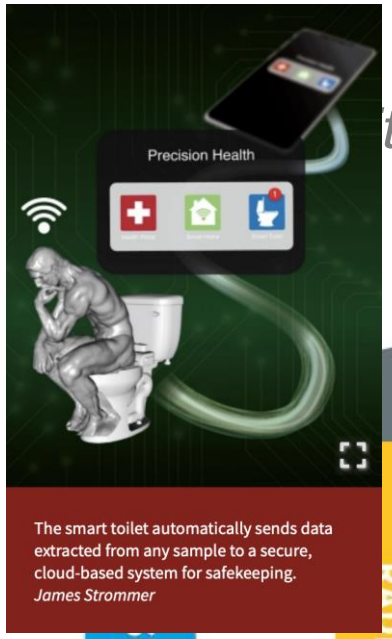
Adapted from McQuade et al, Lancet Oncology 2019

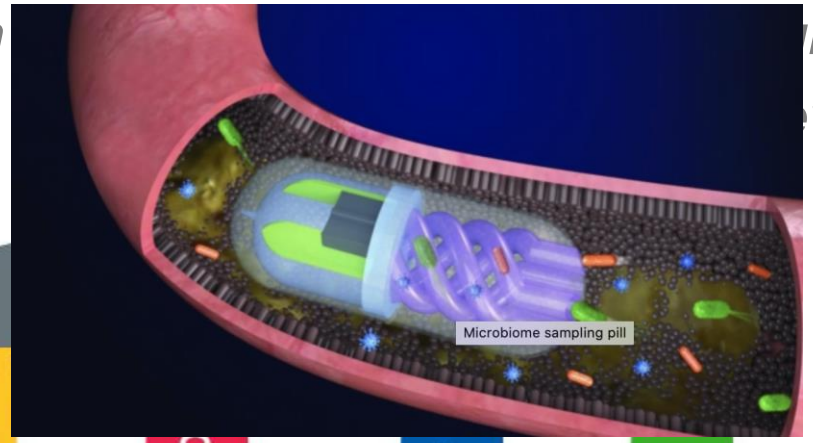
Wargo Science 2020; McQuade et al Lancet Oncology. 2019

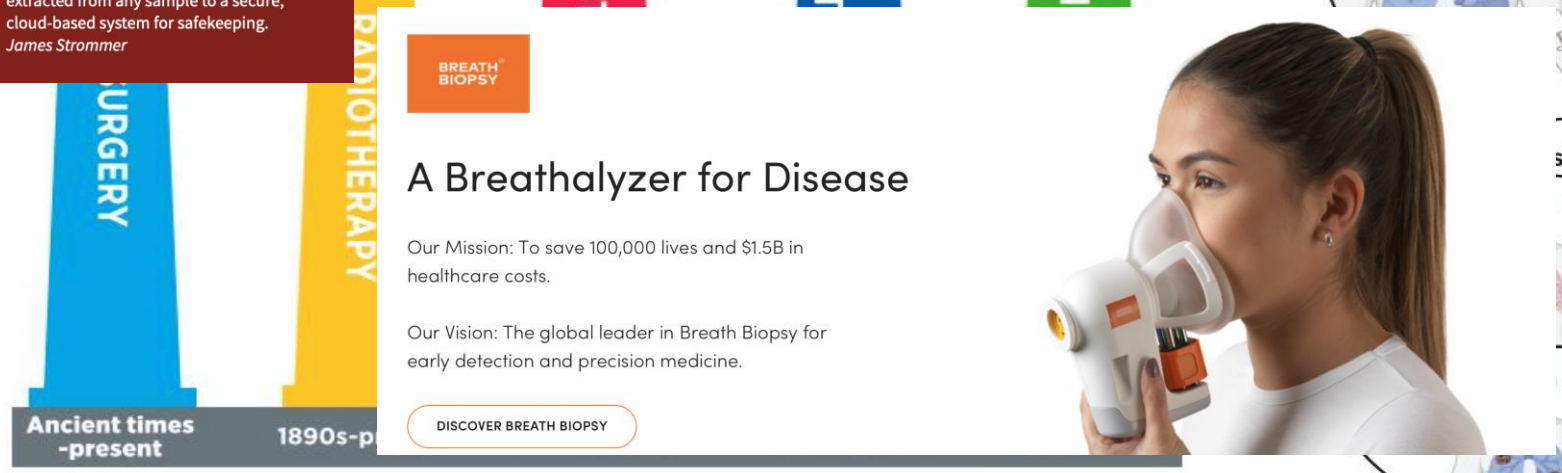
Could microbiome targeting become the next “pillar” of cancer care?

...th ...late the microbi...

...event cancer alto...







Diet–microbiota interactions and personalized nutrition

*Aleksandra A. Kolodziejczyk[1,4], Danping Zheng[1,2,4] and Eran Elinav[1,3]**

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

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

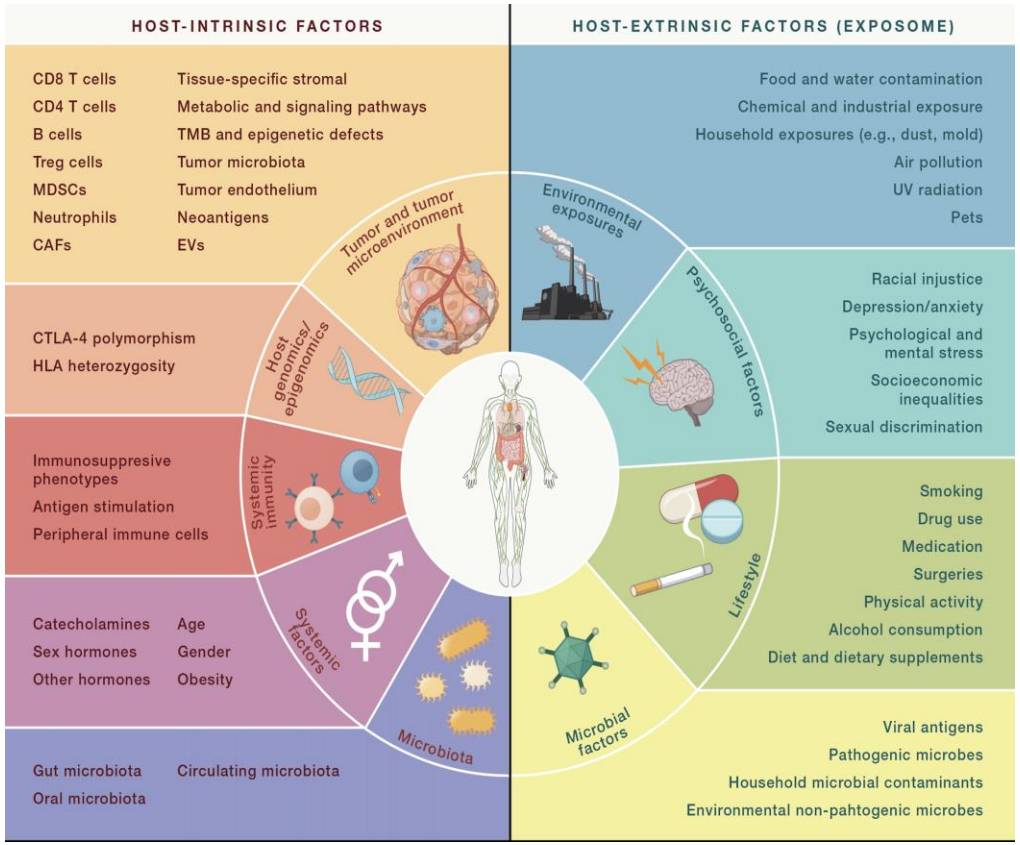
Markham Heid Feb 3 · 7 min read ★

From AACR Cancer Progress Report

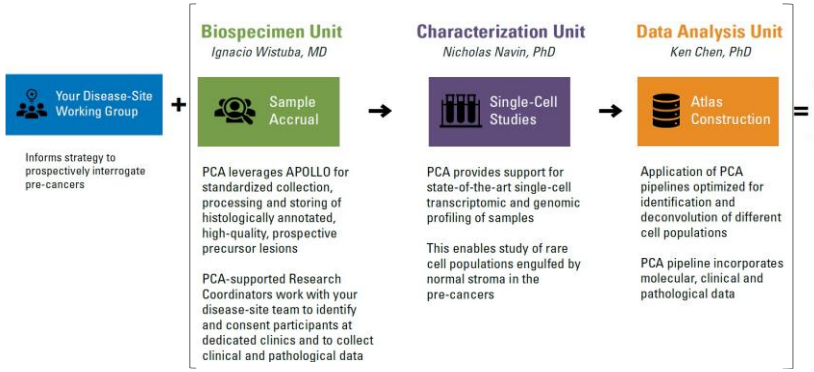
III. Targeting tissue, tumor, and gut-based microbes to intercept / prevent cancer and to promote overall health

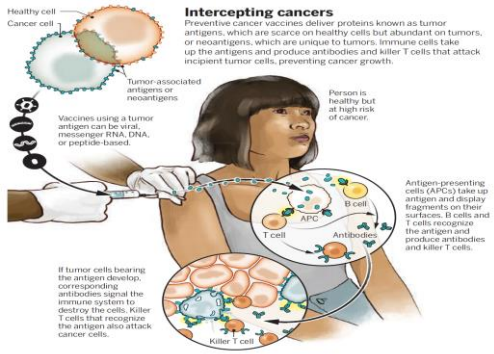
“An ounce of prevention is worth a pound of cure”

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



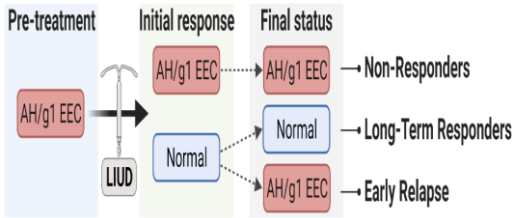
MDA Pre-Cancer Atlas: Structure & Expertise

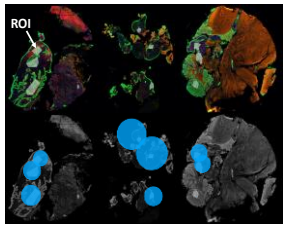




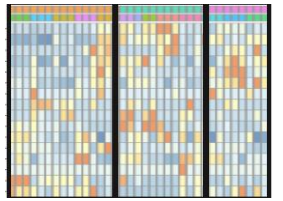
Kaiser, Science 2022

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



Cancer and immune cell deconvolution

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

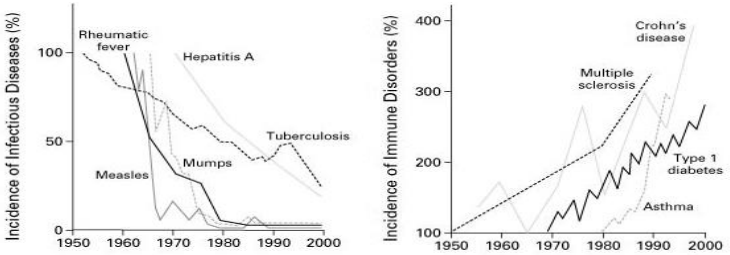
What is driving increased cancer and disease rates in younger individuals, and how can we prevent it?

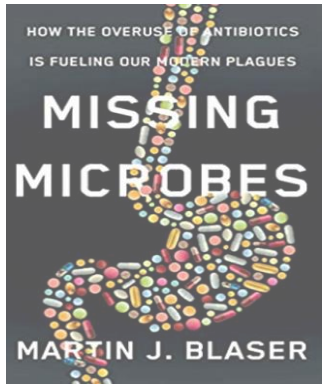
Could exposure to antibiotics and other factors that disrupt the microbiome be contributing to higher rates of disease and cancer? And can we target the gut microbiome in cancer prevention?

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

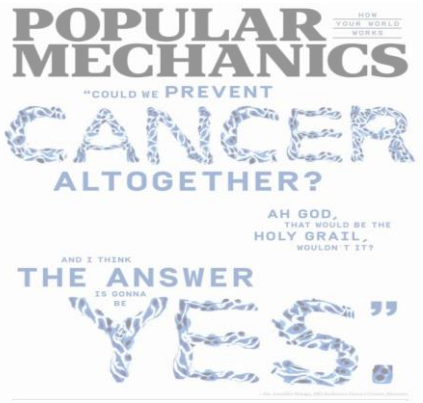


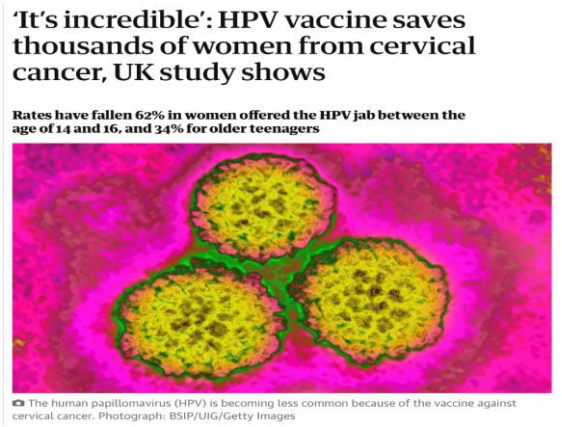


Marty Blaser MD
Prof of Medicine & Microbiology, Rutgers University

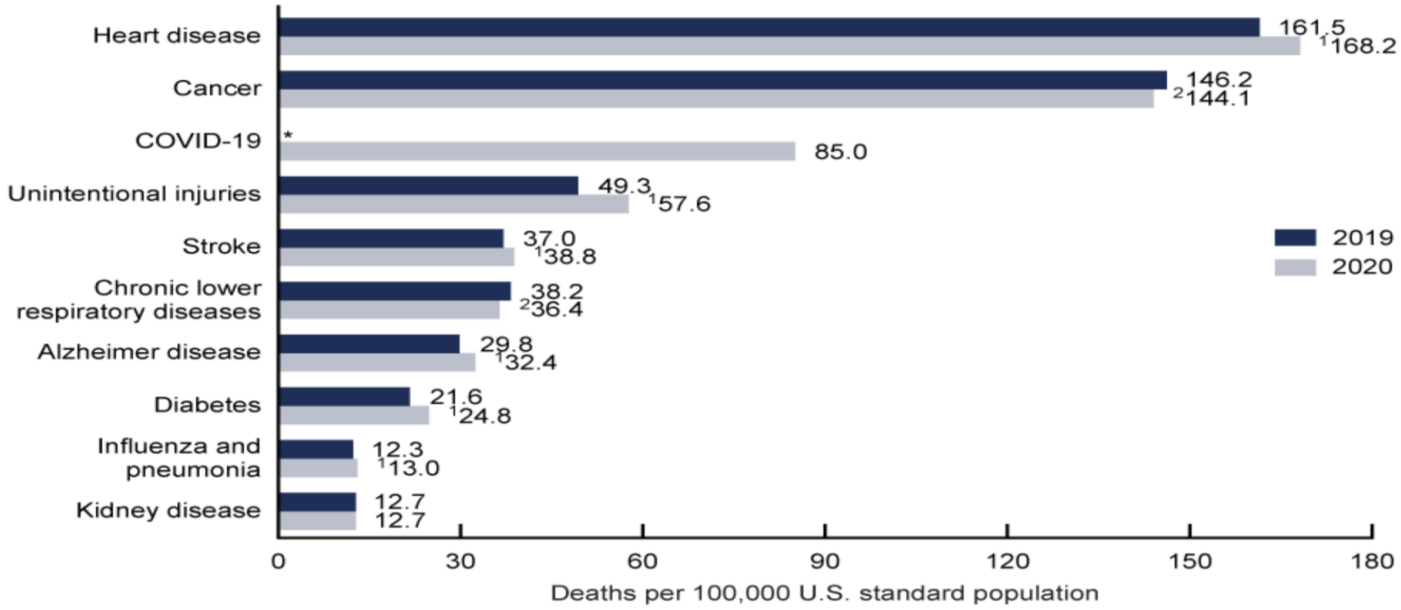
Other factors contributing to cancer risk (and that impact the microbiome) include diet, geography ("Z"NA), and physical inactivity and stress – can we promote overall health and reduce cancer risk by addressing these factors, including disparities?

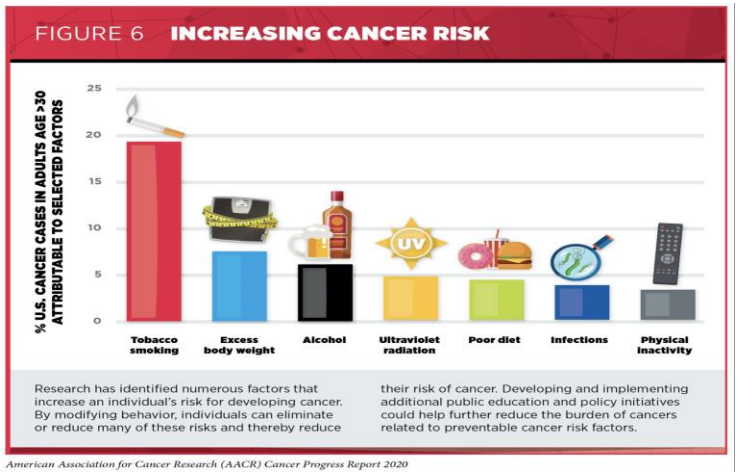
We know that microbes can contribute to cancer development (such as HPV and *H. pylori*). Can we study cancer and pre-malignant tissues to learn how to prevent cancer altogether?





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





Bolte et al, Gut 2021

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

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 Traweek MD – Postdoctoral T32 Fellows

- **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, Alexandria P. Cogill PhD, Robert Szczepaniak Sloane PhD, Beth Helmink MD PhD, Pei-Ling Chen MD PhD; Rohit Thakur PhD

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**
- **Patrick Hwu MD, and other Melanoma Med Onc Faculty / Staff**
- **Merrick Ross MD, Emily Keung MD, Crisy Roland MD**
- **and other Surg Onc Faculty / Staff**
- **Michael Tetzlaff MD PhD, Alex Lazar MD, Stephanie Watowich PhD**
- **Andry Futreal, MD, Chair, Robert Jenq MD PhD, and other Genomic faculty / staff**
- **Amir Jazaeri MD, Shannon Westin MD MPH, Karen Lu MD, Melinda Yates PhD, Anil Sood MD, Sanghoon Lee PhD, Mikayla Waters (MD/PhD candidate), and many others in gyn oncology!**

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**

Philanthropic/Grant Support

- **NIH/NCI, MRA, BSF, AACR-SU2C, PICI, Sabin Family Foundation**
- **Melanoma Moon Shot Program**

Industry Sponsors/Collaborators

Thank you for all that you do in this world…

Any questions?