



The microbiome and personalized immunotherapy

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THE UNIVERSITY OF TEXAS

**MDAnderson
Cancer Center**

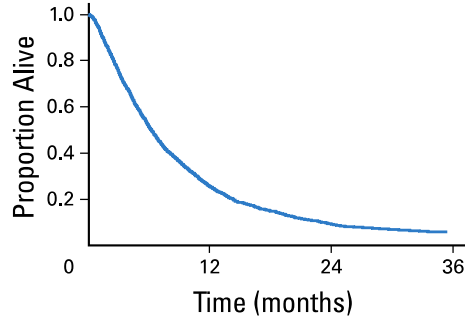
Making Cancer History®

Disclosures

- Advisory Board: BMS
- Consulting: Merck

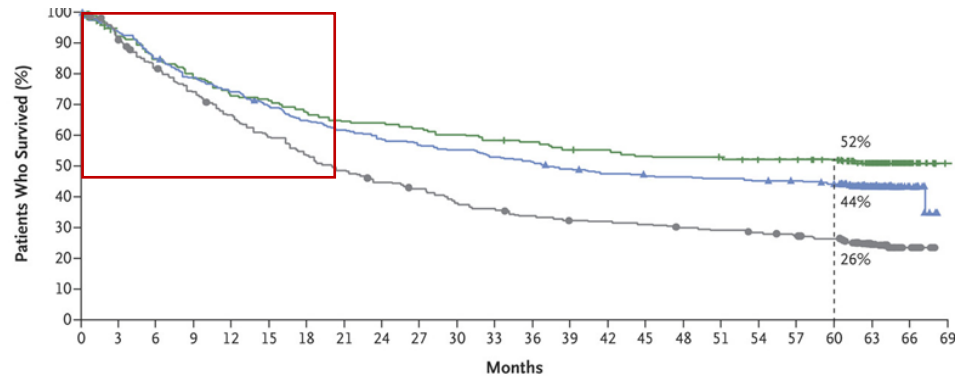
We have made tremendous advances in the treatment of cancer with immune checkpoint inhibitors, but responses are heterogeneous

Historic metastatic melanoma long-term survival <10%

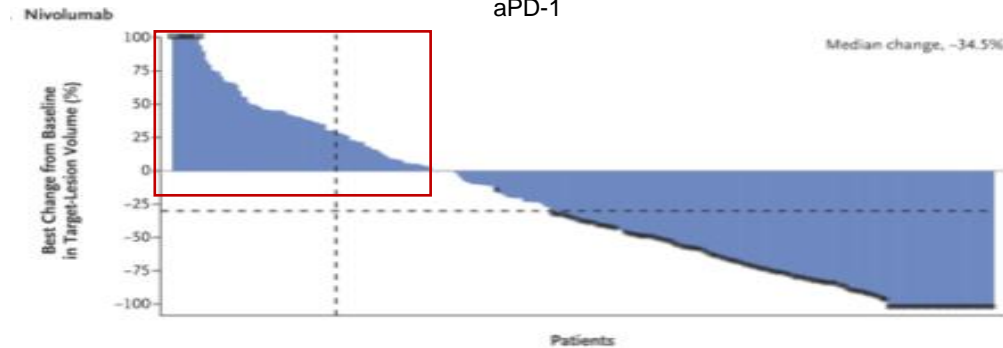


Korn JCO 2009

Metastatic melanoma long-term survival >50%

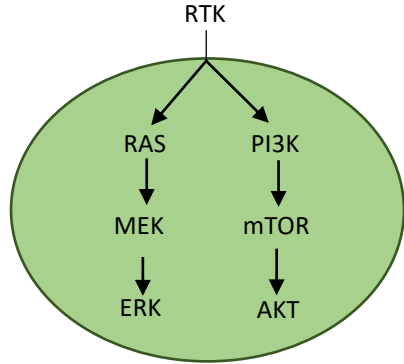


Wolchock NEJM 2019

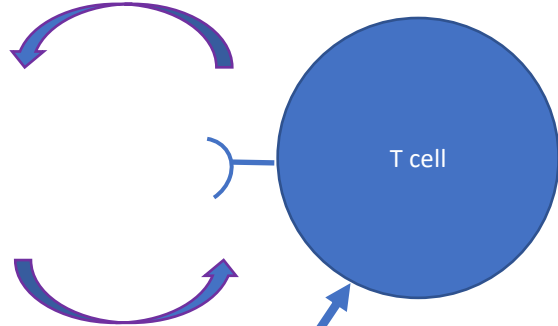


What factors determine response vs resistance?

Tumor intrinsic



Tumor extrinsic



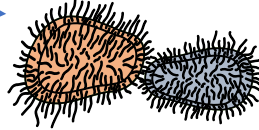
Host factors



Age (Kugel *CCR* 2018, Reijers *ESMO* 2019, Thakur *SITC* 2019)

Sex (Conforti *Lancet Oncology* 2018, Andrews *SMR* 2018, Wang *Cancer Medicine* 2019)

Microbiome



Modifiable factors

Obesity

(McQuade *Lancet Oncology* 2018, Wang *Nature Medicine* 2018, Richtig *PLOS One* 2018, Cortellini *JITC* 2019, Naik *JITC* 2019)

Diet?

Exercise?

Stress?

Sleep?

The Human Microbiome


100 trillion
microbes

3% human body
mass

1-10X microbes :
human cells

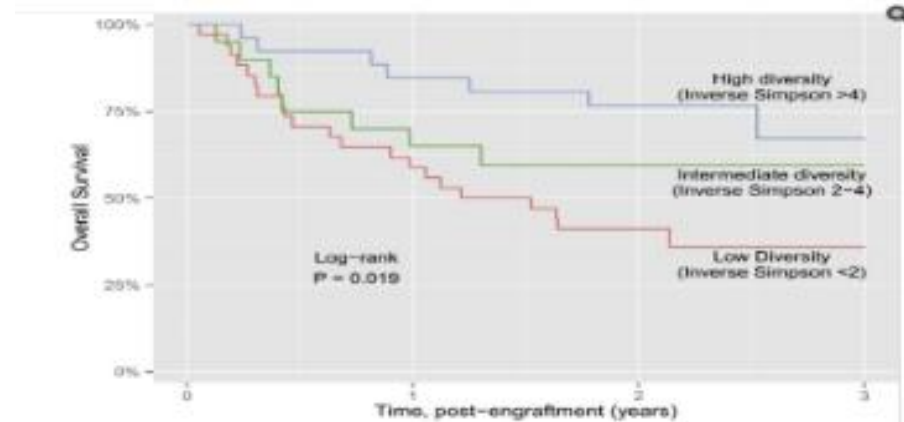
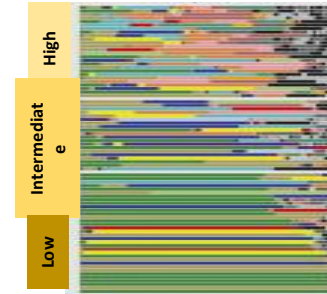
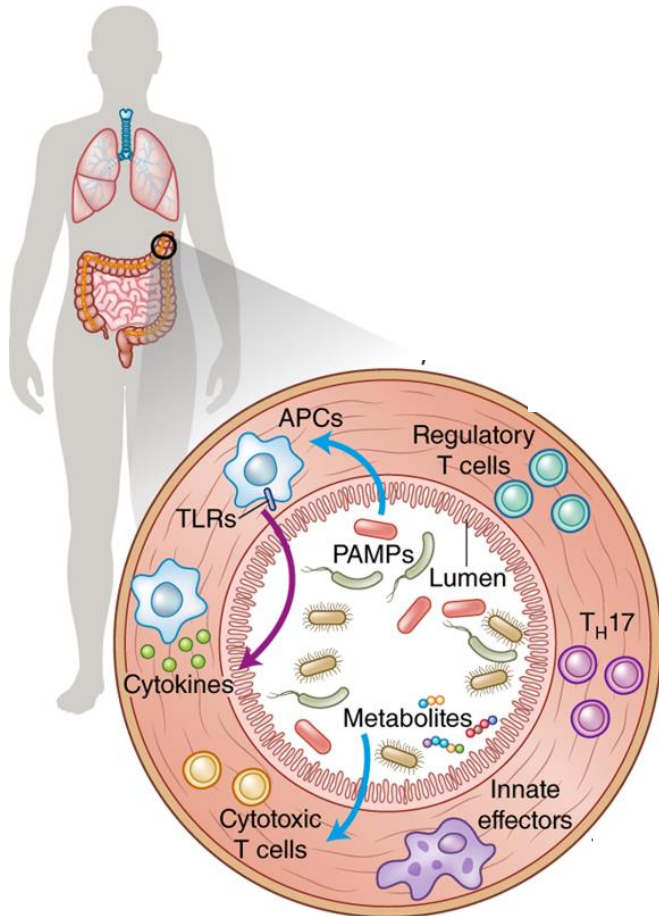
10-100X microbial :
human genes

largest # microbes
– GI tract

- 
- Obesity
 - Diabetes
 - Inflammatory Bowel Disease
 - Cancer
 - Eczema
 - Allergies
 - Asthma
 - Depression

Intimate relationship between gut microbiome & immune system

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



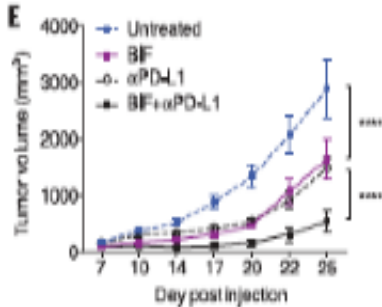
Landmark studies demonstrated that gut microbes could influence response to immunotherapy in mice



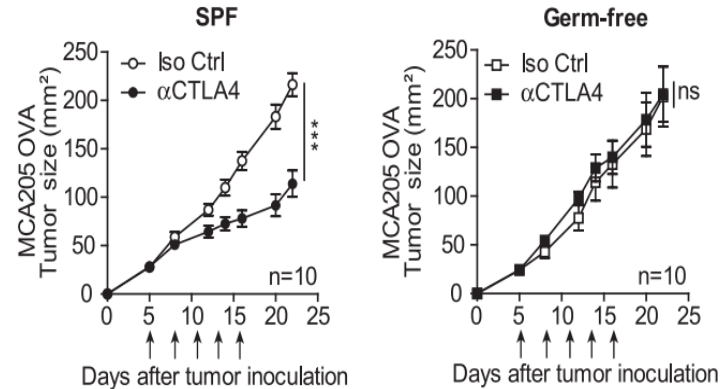
Gut microbiome and anticancer immune response: really hot Sh*t!

S Viaud^{1,2}, R Daillère^{1,2}, IG Boneca^{3,4}, P Lepage^{5,6}, P Langella^{5,6}, M Chamailard^{7,8,9,10}, MJ Pittet¹¹, F Ghiringhelli^{12,13,14}, G Trinchieri¹⁵, R Goldszmid¹⁵ and L Zitvogel^{1,2,16}

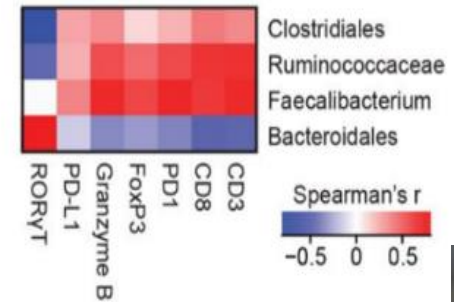
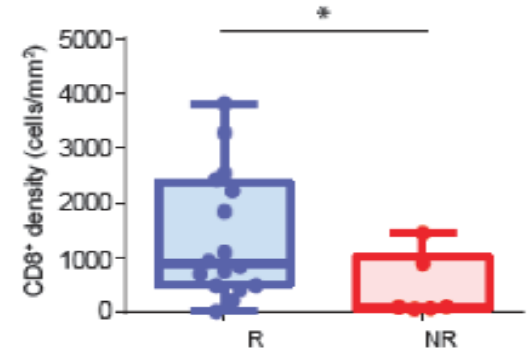
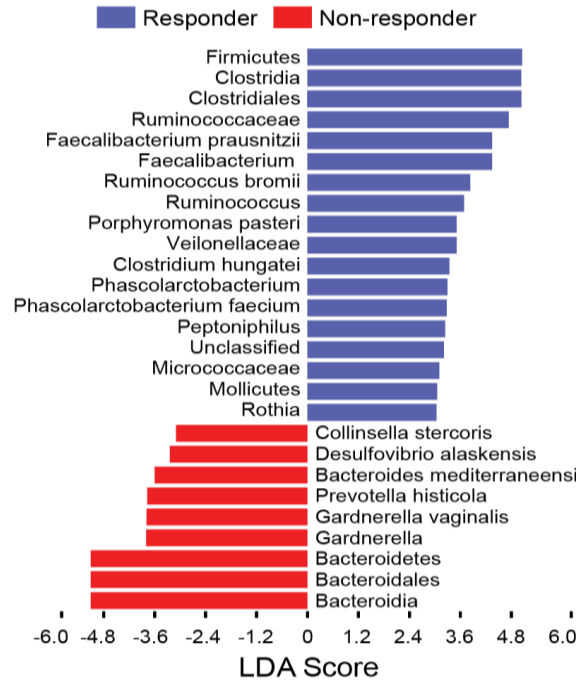
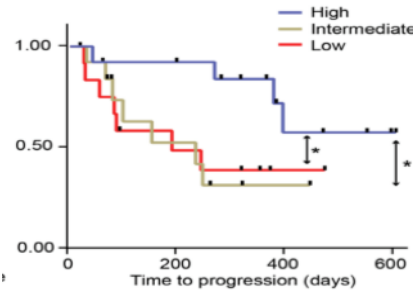
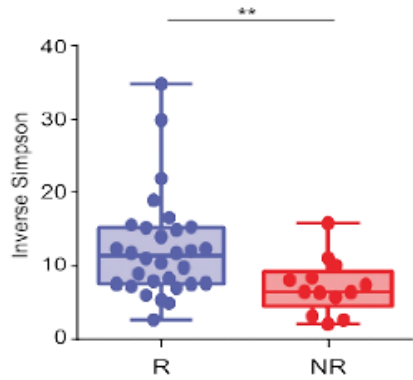
Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy



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



In human cohorts: The gut microbiome of responders to immunotherapy is distinct from that of non-responders

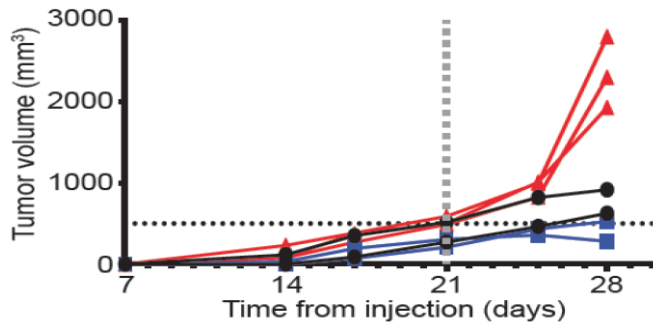
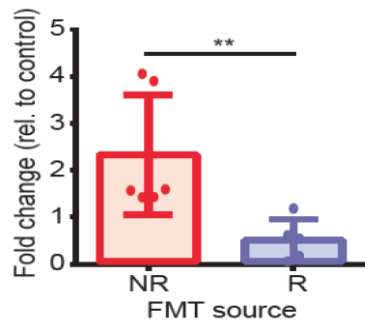
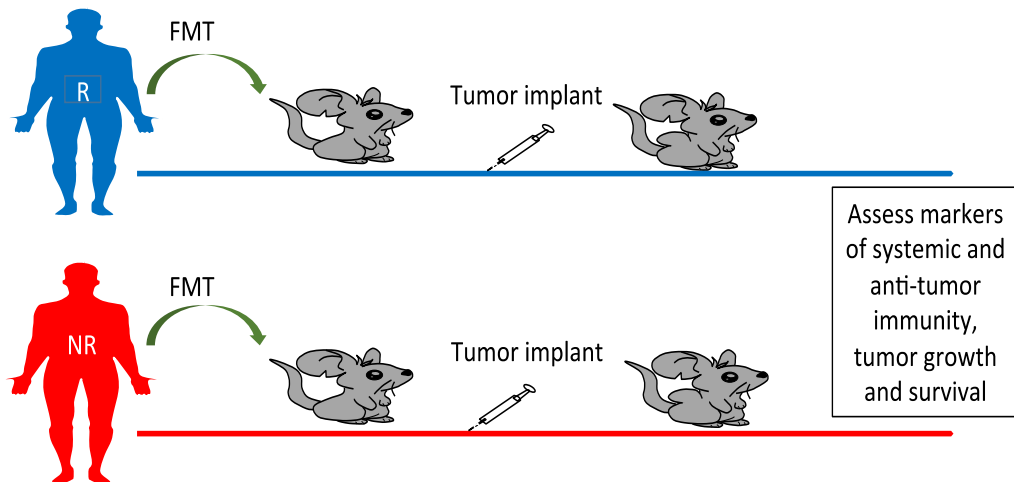


Gopalakrishnan Spencer



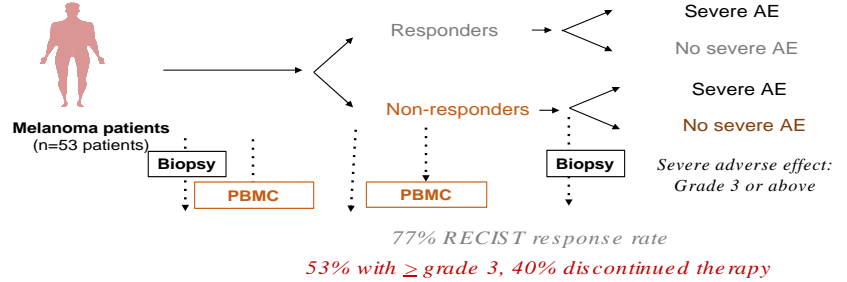
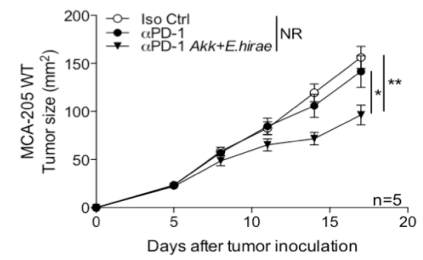
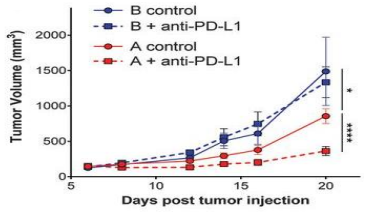
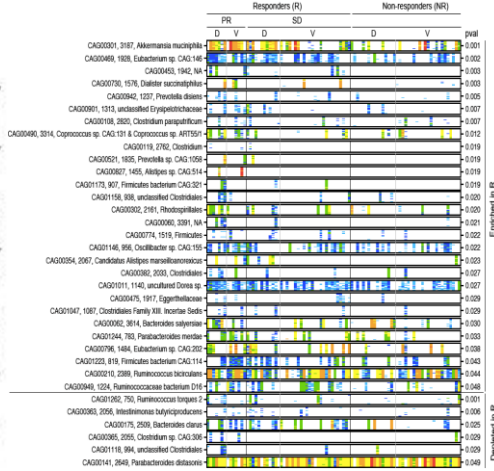
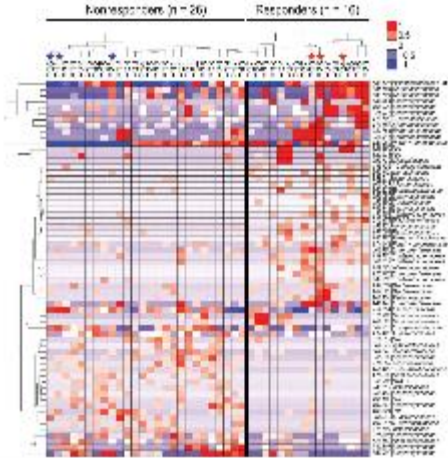
Wargo

Responsiveness to immunotherapy can be transmitted via microbiota transplant!



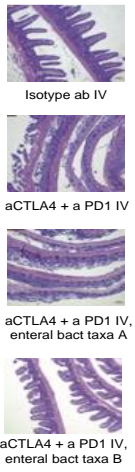
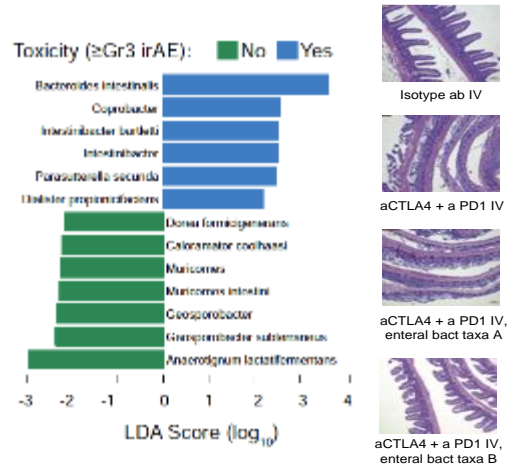
Numerous studies in human cohorts now support a link between the microbiome and response and toxicity to cancer therapy

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



77% RECIST response rate
53% with ≥ grade 3, 40% discontinued therapy

Patients with ≥ Gr3 adverse events had a higher abundance of *B. intestinalis* in baseline microbiome samples, with validation in animal models (Zitvogel lab)

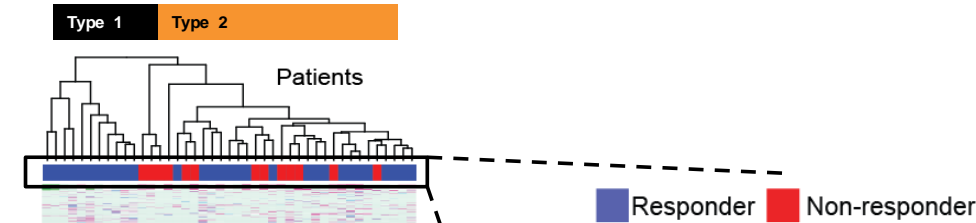


Andrews et al (Wargo & Zitvogel lab collaboration), confidential unpublished data *PLEASE DO NOT POST*

slide courtesy of Jen Wargo

Microbiome as a predictive biomarker

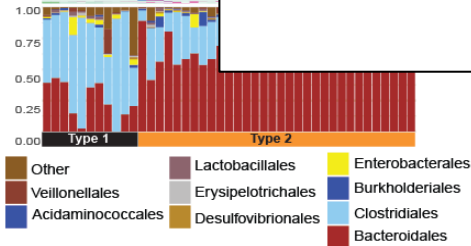
In MDACC cohort a gut microbiome “signature” with a high likelihood of response to anti-PD-1 was identified



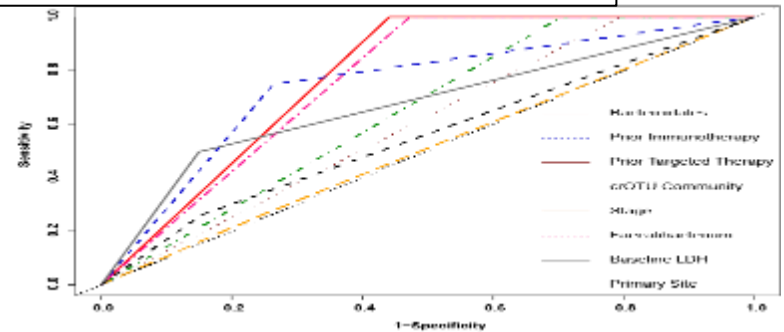
Suggesting that the gut microbiome could be used as a biomarker of response to immune checkpoint blockade, with patients with a “type 1” respond

Can we use gut microbiome signatures as a biomarker for response to immunotherapy?

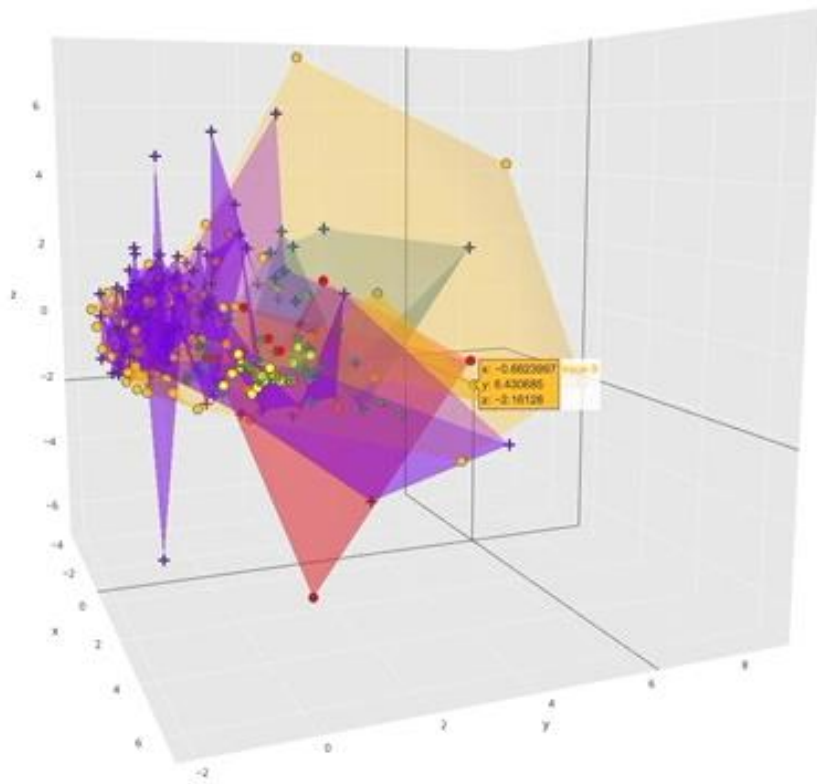
- *What assay should be used? (should be rapid, accurate and cost-effective)*
- *Can we develop strategies to monitor gut microbes and their function for overall precision health?*



Type 1 Type 2
crOTU community type



However, there is only modest overlap between pro-response bacteria identified in distinct cohorts



- ✚ Wargo R
- Wargo NR
- Gajewski NR
- ✚ Gajewski R
- Zitvogel NR
- ✚ Zitvogel R

Several factors may account for these differences:

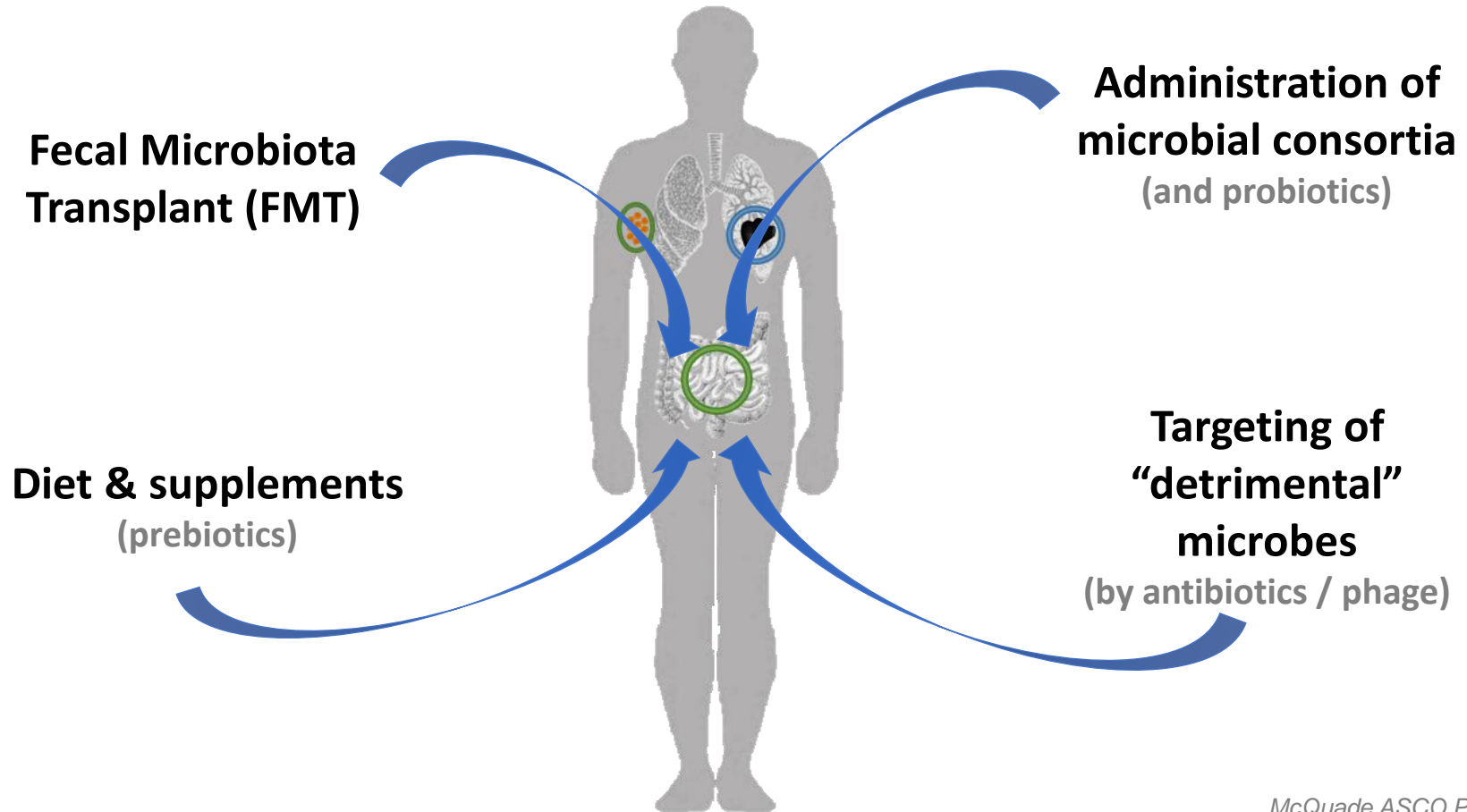
- *Different methods of analysis*
- *Regional and dietary influences*

And function may be more important than phylogeny

Nonetheless results from additional cohorts and trials will help to inform the composition as will preclinical screening

Microbiome as a therapeutic target

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



Prior to treatment

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 administered?

How do we select donors?

- Diet?

- Designer Consortia?

- Phage / antibiotics / other?



During therapy

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 engraftment / function?
 - Immune profiling?
 - Peripheral blood
 - Tumor

How can we facilitate stable engraftment?

- Should we recommend dietary changes?
- Any medications to avoid?

Assessing impact

What are appropriate primary endpoints for such studies?

- Safety and tolerability
- Engraftment
- Others?

What are appropriate secondary endpoints?

- Response
- Radiographic (RECIST and / or irRC)
- Rate of complete responses
- Pathologic response (on biopsy or after neoadjuvant therapy)
 - Toxicity
- Novel markers (ctDNA, immunophenotyping)

Long-term effects

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?

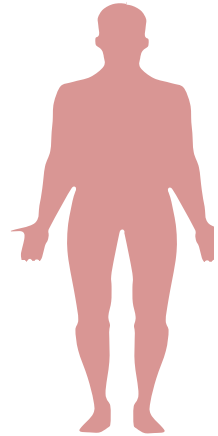
Toxicity

- Can we uncouple toxicity and response to immunotherapy?

Other transplanted traits with FMT?

- Obesity?
- Depression?
- Any potentially favorable traits?

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



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

Fecal transplants could help patients on cancer immunotherapy drugs

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

apy
:bo)

Ongoing

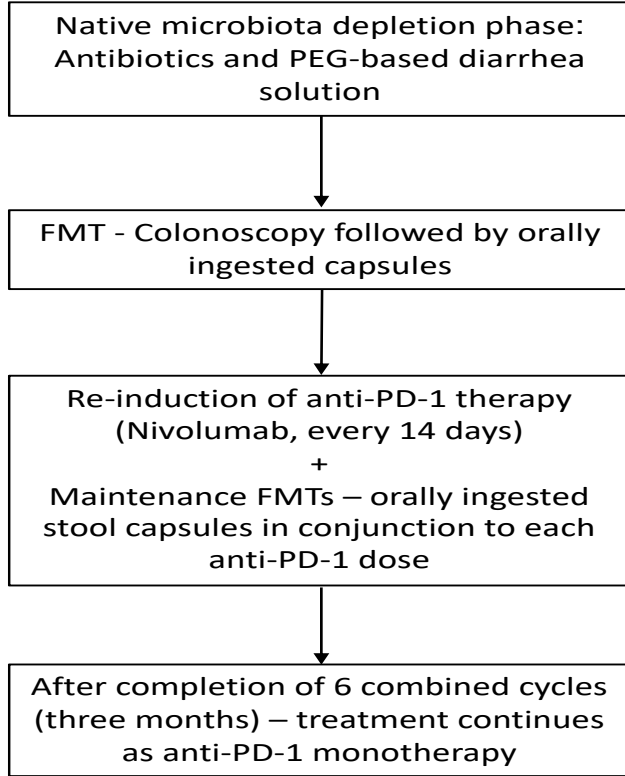
In preparation



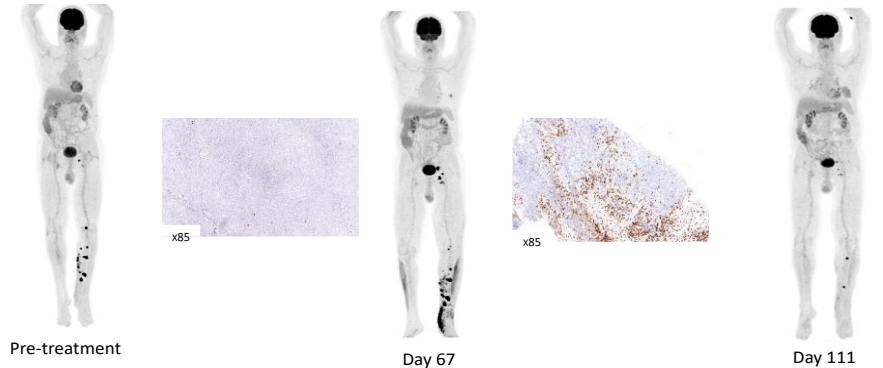
Promising data from 2 ongoing clinical trials was presented at AACR Annual Meeting (March 2019)



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



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



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

First author: Erez Baruch

Senior authors: Gal Markel, Ben Boursi

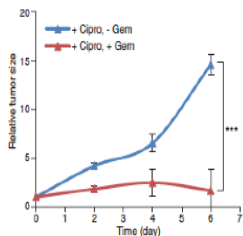
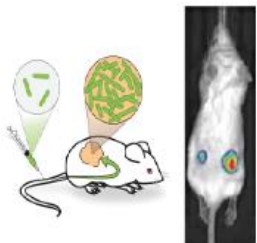


Intra-tumoral microbiome

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

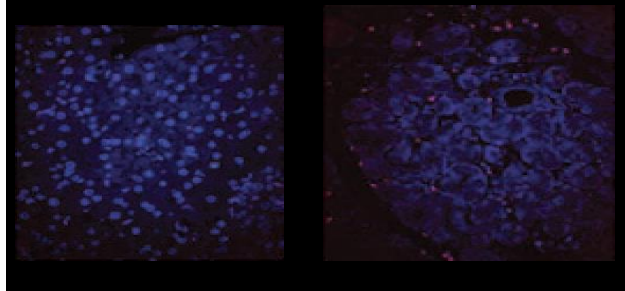


Bacteria from patient tumors can break down chemotherapy

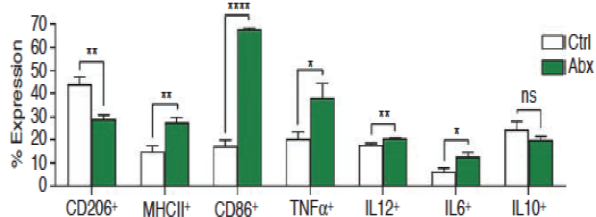


Geller et al, Science 2017

Bacteria translocate from the gut to pancreatic tumors in KC mice

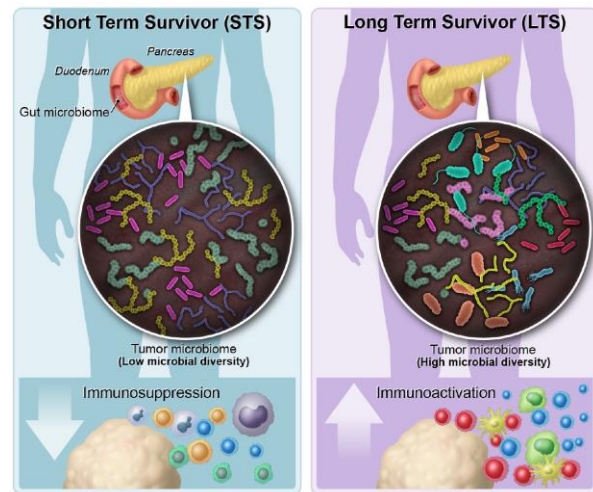


Ablation of bacteria with antibiotics was associated with enhanced immune function



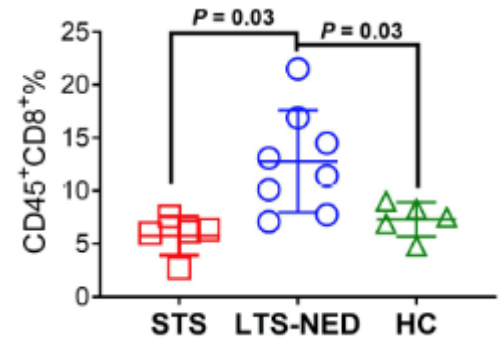
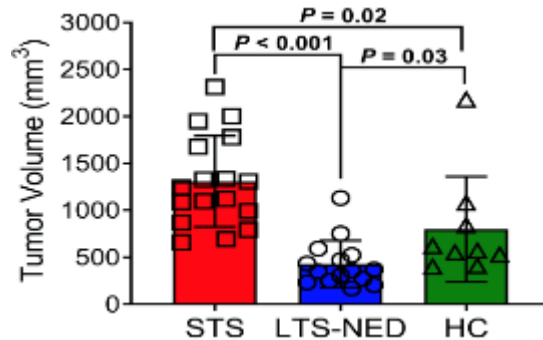
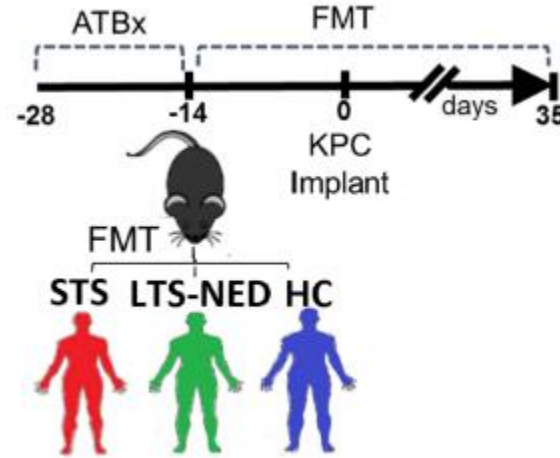
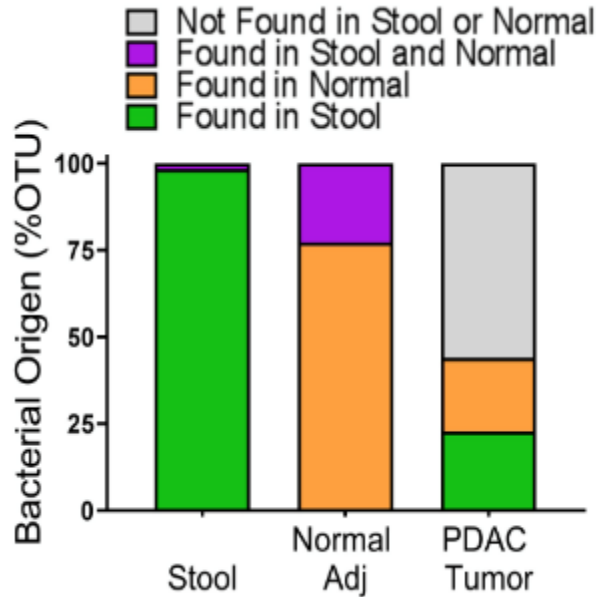
Pushulkar et al, Cancer Discovery 2018

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



Riquelme et al, Cell 2019

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

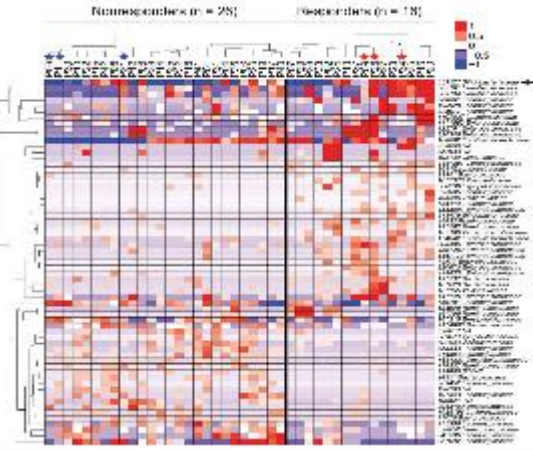


Can we identify defined consortia of
microbes to enhance response to
immunotherapy?

Defining optimal consortia based on pro-response bacteria from cohort studies vs *in vitro* screens and/or *in vivo* validation

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

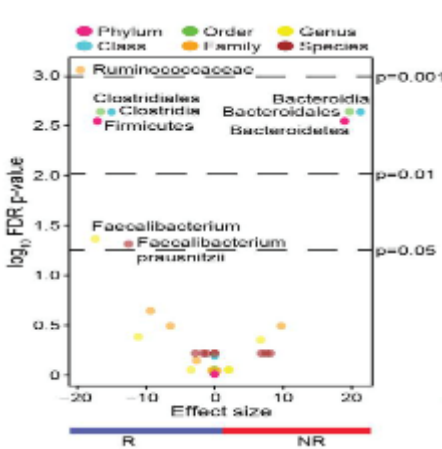
Vivara Matson,¹ Jessica Feeler,¹ Rhyne Bao,^{2,3} Tara Chongwut,⁴ Yuanyuan Zhu,⁴ Maria Luisa Alegre,⁴ Jason J. Lako,⁴ Thomas F. Gajewski^{1,5}



Matson...Gajewski et al, Science 2018

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

V. Gopalakrishnan,^{1,2} C. N. Spencer,^{1,2} L. Neel,^{1,2} A. Benben,¹ M. C. Andrews,¹ T. V. Karpitskiy,¹ P. A. Prieto,^{1,2} D. Viciento,¹ K. Hoffman,¹ S. C. Wei,¹ A. P. Cappilli,¹ L. Zhao,¹ C. W. Hudgens,¹ D. S. Hutchinson,¹ T. Manne,¹ M. Pelaez-de-Macedo,¹ T. Cotichini,¹ T. Kumar,¹ W. S. Chen,¹ S. M. Reddy,¹ B. Szczepanski-Sloane,¹ J. Galloway-Pena,¹ H. Jiang,¹ P. L. Chen,¹ E. Z. Shigali,¹ K. Ravindra,¹ A. M. Akinci,¹ R. F. Chinnai,¹ S. Nishikawa,¹ L. M. Venzor,¹ P. C. Okunuga,¹ V. B. Jones,¹ A. G. Novaresi,¹ F. McAllister,¹ F. Maveco Riquelme Sanchez,¹ Y. Zhang,¹ L. La Chetler,¹ L. Zivogol,¹ N. Posa,¹ J. L. Austin-Ireneman,¹ L. E. Hayden,¹ F. M. Bartlett,¹ J. M. Gardner,¹ E. Brennan,¹ J. Ma,¹ P. A. Lazarus,¹ T. Tsujihara,¹ A. Bhak,¹ H. Yoshida,¹ I. C. Gilboa,¹ W. J. Ihm,¹ S. P. Patel,¹ S. E. Woodman,¹ B. N. Amaral,¹ M. A. Davies,¹ J. E. Gershenwald,¹ P. Han,¹ J. P. Lee,¹ J. Zhang,¹ L. M. Cavoski,¹ Z. A. Cooper,¹ F. A. Fataoui,¹ R. Hussain,¹ N. J. Ajami,¹ J. F. Petrosino,¹ M. T. Tetzlaff,¹ P. Sharma,^{1,2} J. P. Allison,¹ R. R. Jena,¹ J. A. Wargo,^{1,2,3,4}

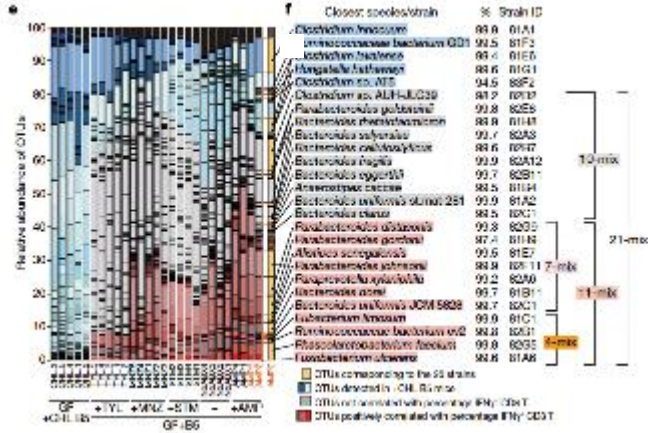


Gopalakrishnan...Wargo et al, Science 2018

ARTICLE

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

Tanoue T, Honda M, Tanoue K, Honda T, Honda K, Honda S, Honda Y, Honda Z, Honda A, Honda B, Honda C, Honda D, Honda E, Honda F, Honda G, Honda H, Honda I, Honda J, Honda K, Honda L, Honda M, Honda N, Honda O, Honda P, Honda Q, Honda R, Honda S, Honda T, Honda U, Honda V, Honda W, Honda X, Honda Y, Honda Z, Honda AA, Honda AB, Honda AC, Honda AD, Honda AE, Honda AF, Honda AG, Honda AH, Honda AI, Honda AJ, Honda AK, Honda AL, Honda AM, Honda AN, Honda AO, Honda AP, Honda AQ, Honda AR, Honda AS, Honda AT, Honda AU, Honda AV, Honda AW, Honda AX, Honda AY, Honda AZ, Honda BA, Honda BB, Honda BC, Honda BD, Honda BE, Honda BF, Honda BG, Honda BH, Honda BI, Honda BJ, Honda BK, Honda BL, Honda BM, Honda BN, Honda BO, Honda BP, Honda BQ, Honda BR, Honda BS, Honda BT, Honda BU, Honda BV, Honda BW, Honda BX, Honda BY, Honda BZ, Honda CA, Honda CB, Honda CC, Honda CD, Honda CE, Honda CF, Honda CG, Honda CH, Honda CI, Honda CJ, Honda CK, Honda CL, Honda CM, Honda CN, Honda CO, Honda CP, Honda CQ, Honda CR, Honda CS, Honda CT, Honda CU, Honda CV, Honda CW, Honda CX, Honda CY, Honda CZ, Honda DA, Honda DB, Honda DC, Honda DD, Honda DE, Honda DF, Honda DG, Honda DH, Honda DI, Honda DJ, Honda DK, Honda DL, Honda DM, Honda DN, Honda DO, Honda DP, Honda DQ, Honda DR, Honda DS, Honda DT, Honda DU, Honda DV, Honda DW, Honda DX, Honda DY, Honda DZ, Honda EA, Honda EB, Honda EC, Honda ED, Honda EE, Honda EF, Honda EG, Honda EH, Honda EI, Honda EJ, Honda EK, Honda EL, Honda EM, Honda EN, Honda EO, Honda EP, Honda EQ, Honda ER, Honda ES, Honda ET, Honda EU, Honda EV, Honda EW, Honda EX, Honda EY, Honda EZ, Honda FA, Honda FB, Honda FC, Honda FD, Honda FE, Honda FF, Honda FG, Honda FH, Honda FI, Honda FJ, Honda FK, Honda FL, Honda FM, Honda FN, Honda FO, Honda FP, Honda FQ, Honda FR, Honda FS, Honda FT, Honda FU, Honda FV, Honda FW, Honda FX, Honda FY, Honda FZ, Honda GA, Honda GB, Honda GC, Honda GD, Honda GE, Honda GF, Honda GG, Honda GH, Honda GI, Honda GJ, Honda GK, Honda GL, Honda GM, Honda GN, Honda GO, Honda GP, Honda GQ, Honda GR, Honda GS, Honda GT, Honda GU, Honda GV, Honda GW, Honda GX, Honda GY, Honda GZ, Honda HA, Honda HB, Honda HC, Honda HD, Honda HE, Honda HF, Honda HG, Honda HH, Honda HI, Honda HJ, Honda HK, Honda HL, Honda HM, Honda HN, Honda HO, Honda HP, Honda HQ, Honda HR, Honda HS, Honda HT, Honda HU, Honda HV, Honda HW, Honda HX, Honda HY, Honda HZ, Honda IA, Honda IB, Honda IC, Honda ID, Honda IE, Honda IF, Honda IG, Honda IH, Honda II, Honda IJ, Honda IK, Honda IL, Honda IM, Honda IN, Honda IO, Honda IP, Honda IQ, Honda IR, Honda IS, Honda IT, Honda IU, Honda IV, Honda IW, Honda IX, Honda IY, Honda IZ, Honda JA, Honda JB, Honda JC, Honda JD, Honda JE, Honda JF, Honda JG, Honda JH, Honda JI, Honda JJ, Honda JK, Honda JL, Honda JM, Honda JN, Honda JO, Honda JP, Honda JQ, Honda JR, Honda JS, Honda JT, Honda JU, Honda JV, Honda JW, Honda JX, Honda JY, Honda JZ, Honda KA, Honda KB, Honda KC, Honda KD, Honda KE, Honda KF, Honda KG, Honda KH, Honda KI, 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Honda SB, Honda SC, Honda SD, Honda SE, Honda SF, Honda SG, Honda SH, Honda SI, Honda SJ, Honda SK, Honda SL, Honda SM, Honda SN, Honda SO, Honda SP, Honda SQ, Honda SR, Honda SS, Honda ST, Honda SU, Honda SV, Honda SW, Honda SX, Honda SY, Honda SZ, Honda TA, Honda TB, Honda TC, Honda TD, Honda TE, Honda TF, Honda TG, Honda TH, Honda TI, Honda TJ, Honda TK, Honda TL, Honda TM, Honda TN, Honda TO, Honda TP, Honda TQ, Honda TR, Honda TS, Honda TT, Honda TU, Honda TV, Honda TW, Honda TX, Honda TY, Honda TZ, Honda UA, Honda UB, Honda UC, Honda UD, Honda UE, Honda UF, Honda UG, Honda UH, Honda UI, Honda UJ, Honda UK, Honda UL, Honda UM, Honda UN, Honda UO, Honda UP, Honda UQ, Honda UR, Honda US, Honda UT, Honda UU, Honda UV, Honda UW, Honda UX, Honda UY, Honda UZ, Honda VA, Honda VB, Honda VC, Honda VD, Honda VE, Honda VF, Honda VG, Honda VH, Honda VI, Honda VJ, Honda VK, Honda VL, Honda VM, Honda VN, Honda VO, Honda VP, Honda VQ, Honda VR, Honda VS, Honda VT, Honda VU, Honda VV, Honda VW, Honda VX, Honda VY, Honda VZ, Honda WA, Honda WB, Honda WC, Honda WD, Honda WE, Honda WF, Honda WG, Honda WH, Honda WI, Honda WJ, Honda WK, Honda WL, Honda WM, Honda WN, Honda WO, Honda WP, Honda WQ, Honda WR, Honda WS, Honda WT, Honda WU, Honda WV, Honda WW, Honda WX, Honda WY, Honda WZ, Honda XA, Honda XB, Honda XC, Honda XD, Honda XE, Honda XF, Honda XG, Honda XH, Honda XI, Honda XJ, Honda XK, Honda XL, Honda XM, Honda XN, Honda XO, Honda XP, Honda XQ, Honda XR, Honda XS, Honda XT, Honda XU, Honda XV, Honda XW, Honda XX, Honda XY, Honda XZ, Honda YA, Honda YB, Honda YC, Honda YD, Honda YE, Honda YF, Honda YG, Honda YH, Honda YI, Honda YJ, Honda YK, Honda YL, Honda YM, Honda YN, Honda YO, Honda YP, Honda YQ, Honda YR, Honda YS, Honda YT, Honda YU, Honda YV, Honda YW, Honda YX, Honda YY, Honda YZ, Honda ZA, Honda ZB, Honda ZC, Honda ZD, Honda ZE, Honda ZF, Honda ZG, Honda ZH, Honda ZI, Honda ZJ, Honda ZK, Honda ZL, Honda ZM, Honda ZN, Honda ZO, Honda ZP, Honda ZQ, Honda ZR, Honda ZS, Honda ZT, Honda ZU, Honda ZV, Honda ZW, Honda ZX, Honda ZY, Honda ZZ.



Tanoue...Honda et al, Nature 2019

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

Can patient choices impact the microbiome?

How do known determinants of the gut microbiome contribute?

External factors (modifiable)

Medications

(antibiotics, probiotics, PPIs, metformin, anti-depressants)

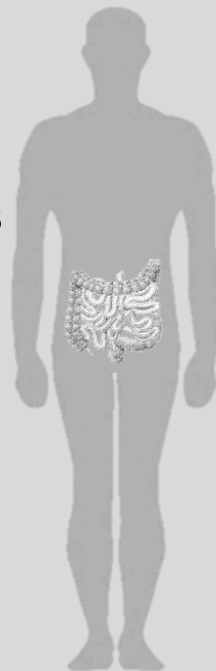
Diet

(fiber rich plant-based diet vs. "Western" diet)

Host factors (cannot be modified)

Demographics
(age, sex)

Host Genomics
(HLA, other factors)



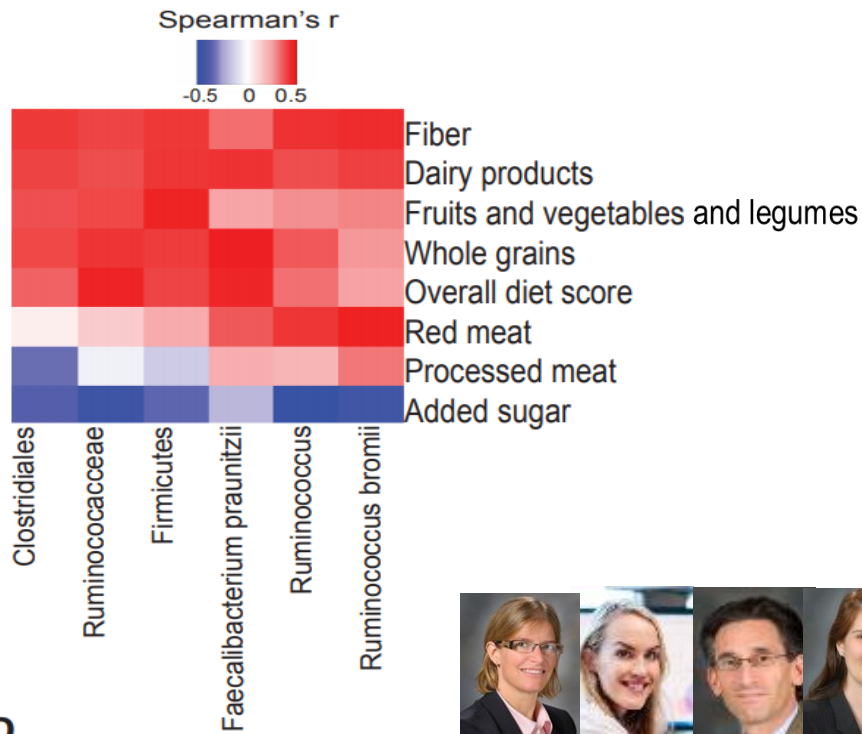
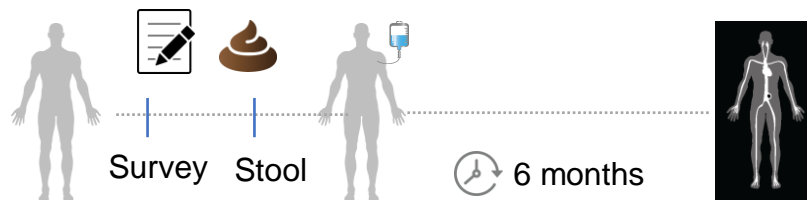
Anthropometrics
(BMI)

Geography

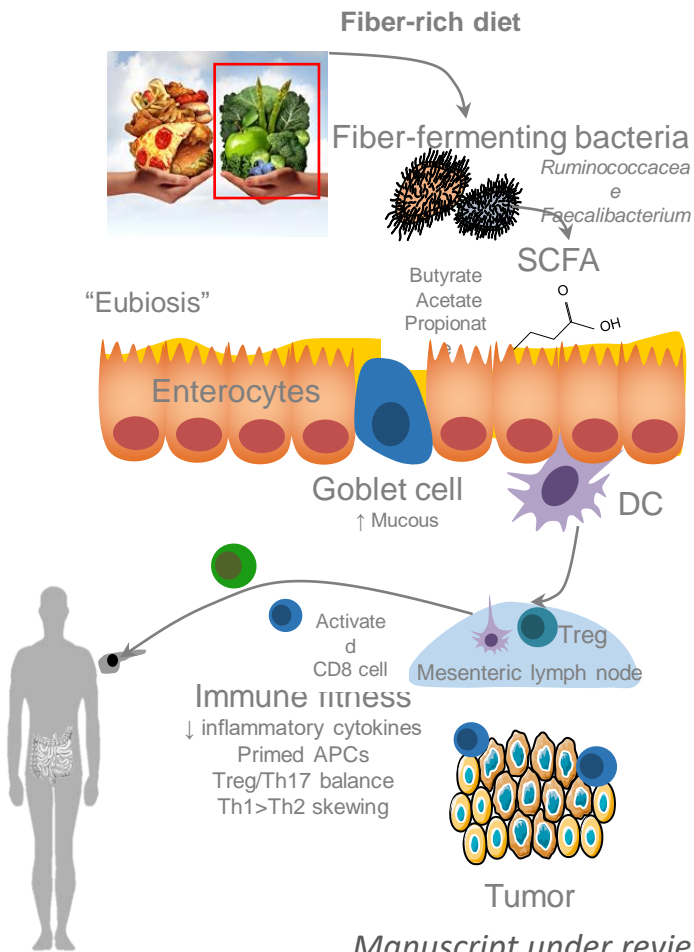
Psychological Factors
(depression, stress, etc.)

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

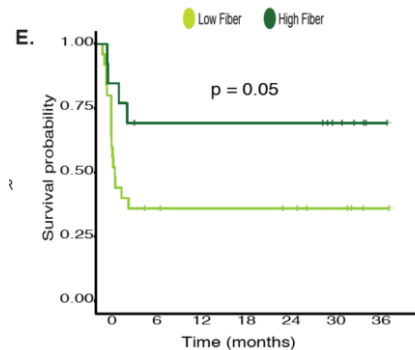
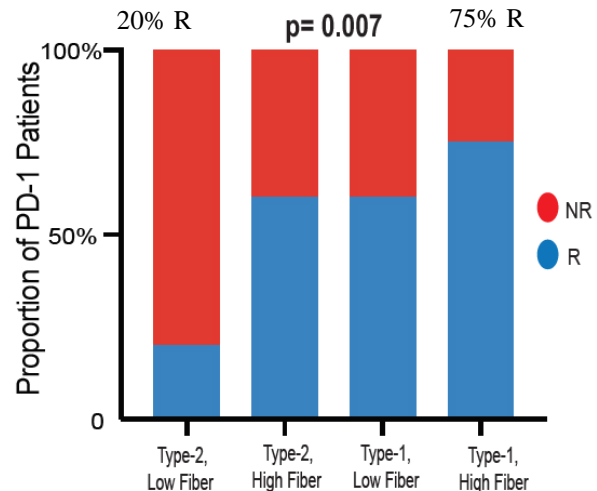
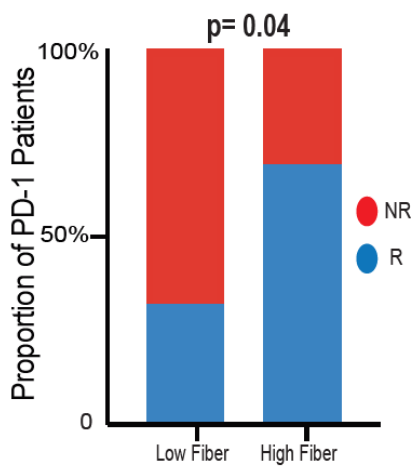
Dietary components	Microbial metabolites	Potential microbes involved
Fiber-rich plant foods legumes cruciferous/other veg	Short-chain fatty acids (e.g., butyrate, propionate, acetate)	<i>Faecalibacterium prausnitzii</i> <i>Eubacterium rectale</i> <i>Roseburia intestinalis</i>
berries/apples/pears/citrus/ other whole fruits whole grains		<i>Ruminococcus spp.</i> <i>Clostridium spp.</i>
Polyphenols from soy, cruciferous vegetables, berries, coffee, wine, chocolate, nuts	Phenolic compounds (e.g., urolithin)	<i>Akkermansia muciniphila</i> <i>Bacteroides</i> <i>thetaiotaomicron</i> <i>Bacteroides vulgatus</i> <i>Bifidobacterium spp.</i>
Red and processed meats, animal products high in saturated fat and cholesterol	N-nitroso compounds 2° bile acids [e.g., deoxycholic acid (DCA)] Trimethylamine (TMA)	<i>Peptostreptococcaceae</i> <i>Clostridium spp.</i> <i>Fusobacterium nucleatum</i> <i>Pseudomonas spp.</i> <i>Desulfovibrio desulfuricans</i>



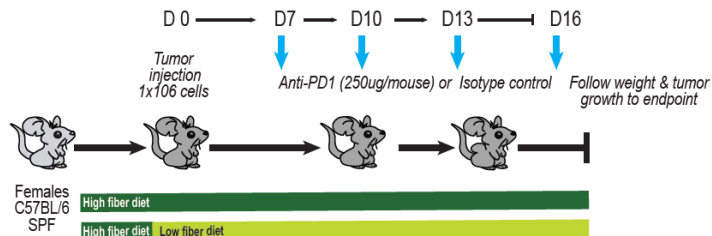
Dietary fiber intake is associated with response to immunotherapy



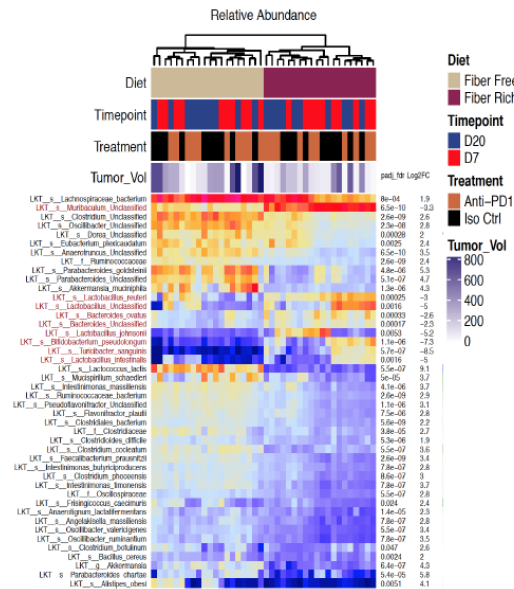
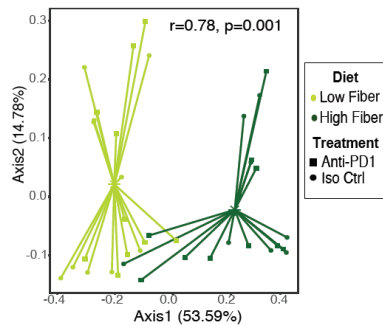
OR of response: high vs. low-fiber
 4.8 (1.1-20.3)



Dietary fiber impacts anti-tumor immunity *in vivo*

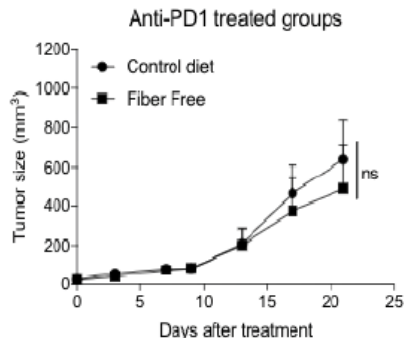
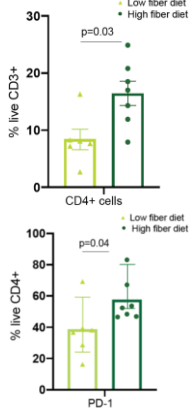
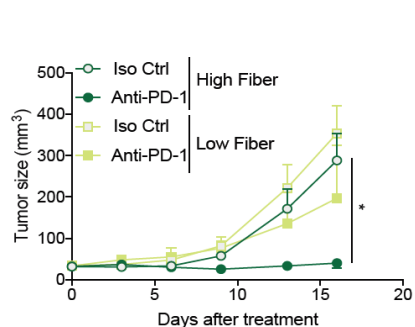


Dietary fiber deprivation rapidly shifts gut microbiome



Dietary fiber impacts anti-tumor immunity

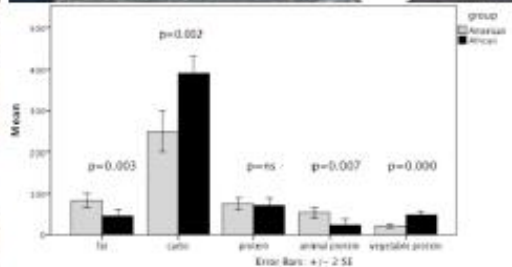
Impact of dietary fiber on response to PD1 NOT seen in germ-free mice -> microbiome mediated?



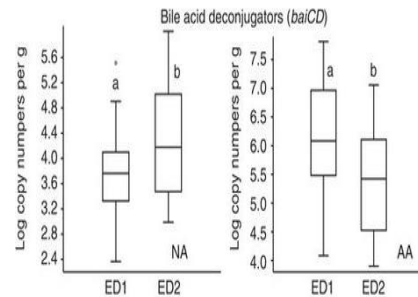
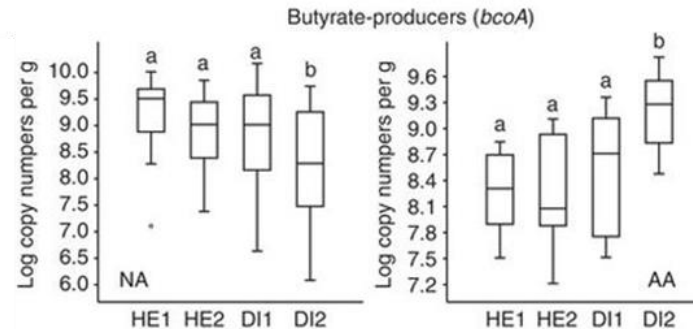
M. Vetzou, NCI | J. McCulloch, NCI | G. Trinchieri, NCI

There is evidence that changes in diet can have a profound impact on the microbiome in a short time frame

Two week controlled feeding study of “swapping”
Northern African and African American diet



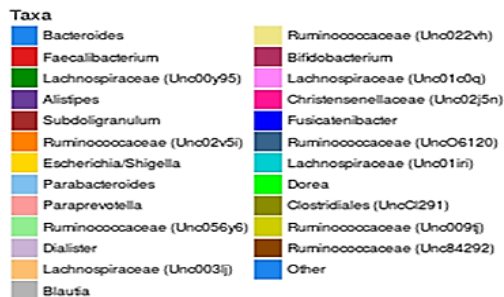
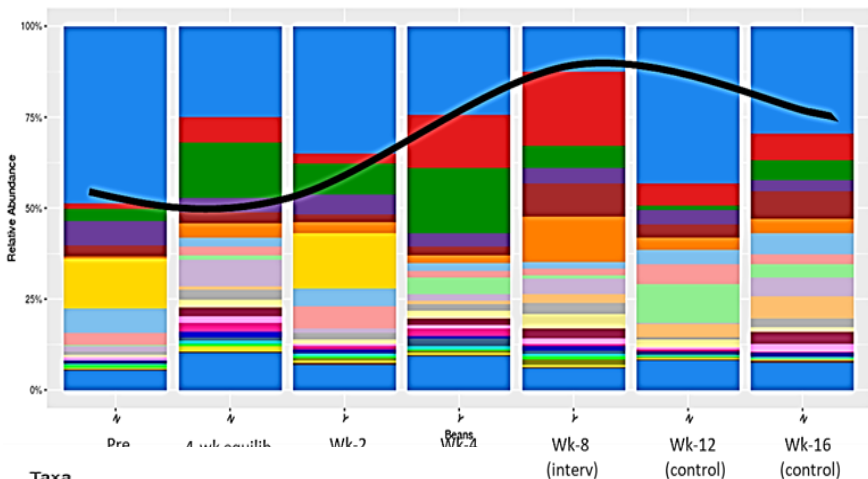
<20 g/fiber per day-> >50 g



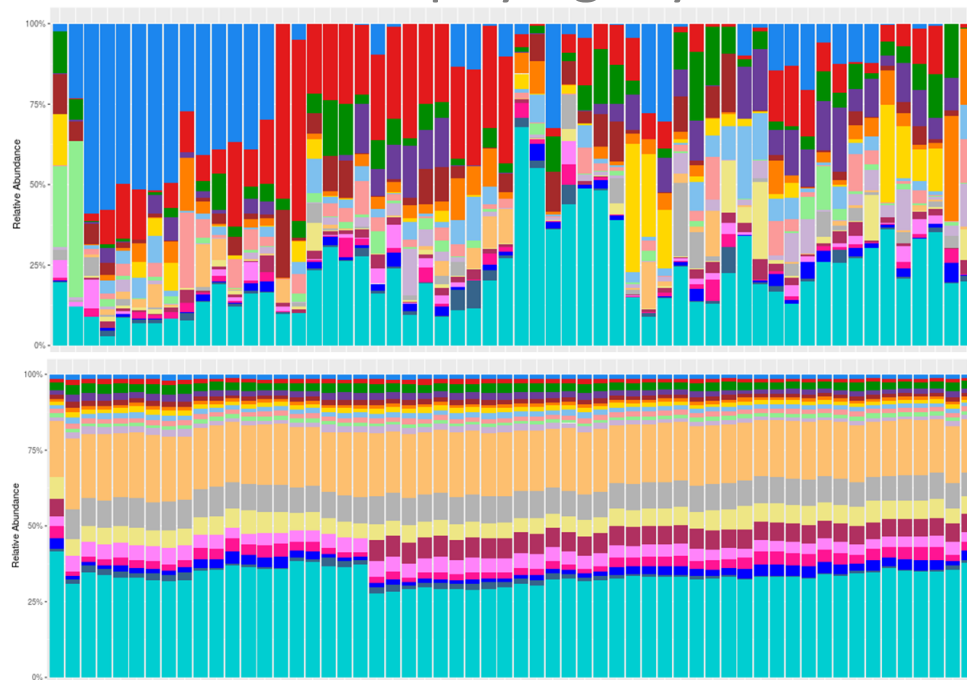
BEGONE study: What have we learned?



Crossover study of addition of 16 g fiber/day via beans to usual diet of colorectal cancer patient survivors



Function over phylogeny

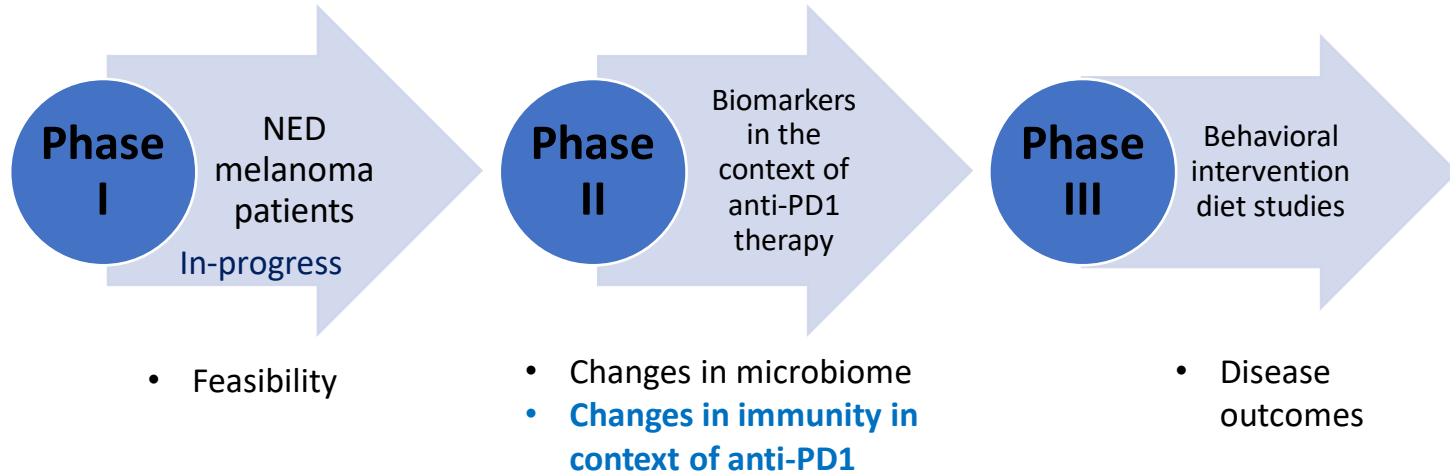


Daniel CR Unpublished data- Please do not post

Testing diet as a precision intervention in cancer:

Hypothesis:

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



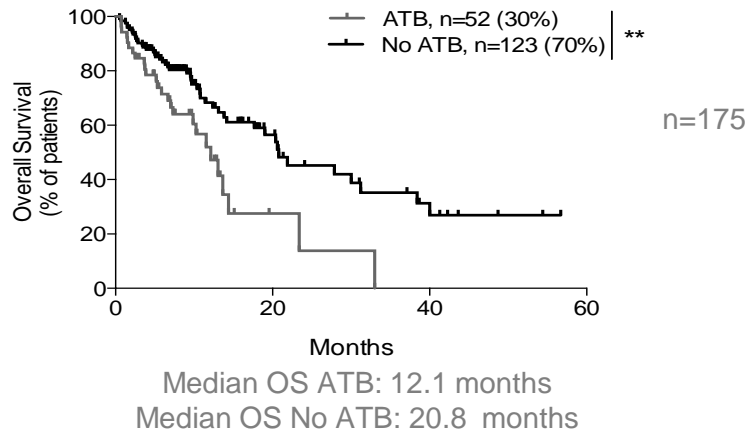
Controlled feeding study:

All calorie-containing food and beverages prepared and provided to patients by MDACC Bionutrition Research Core and/or Savor Health



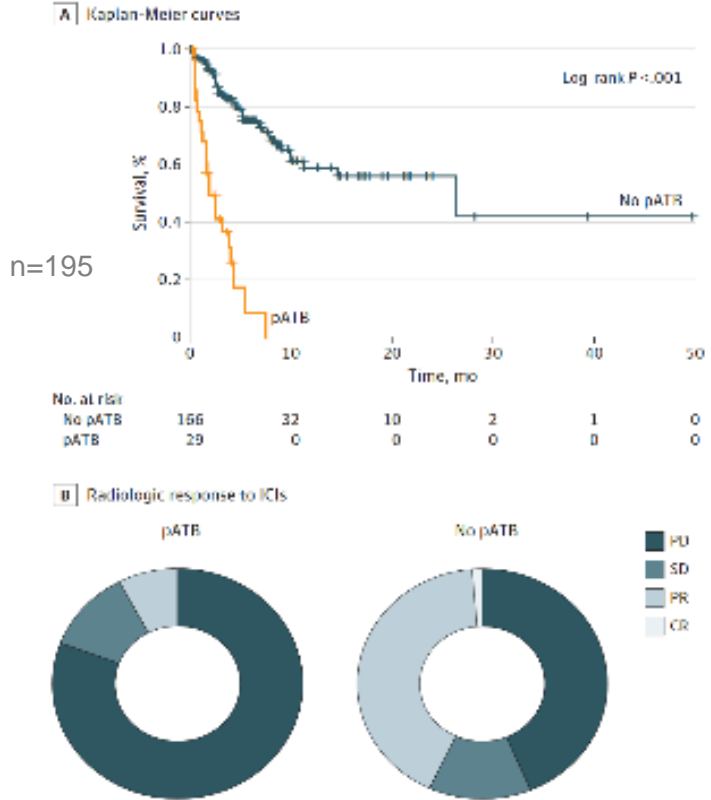
Antibiotics have been shown to negatively impact response to ICB

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



Routy et al, Science 2018

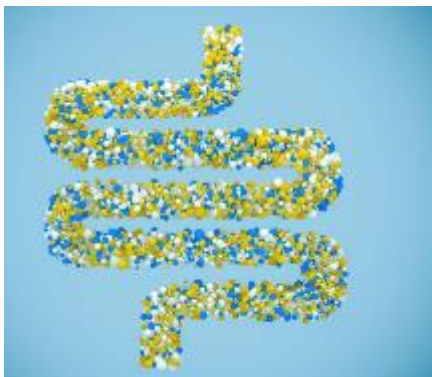
Figure. Association Between pATB Therapy and Survival and Response to ICB



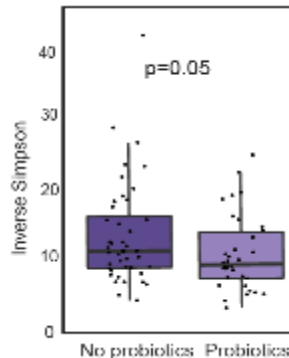
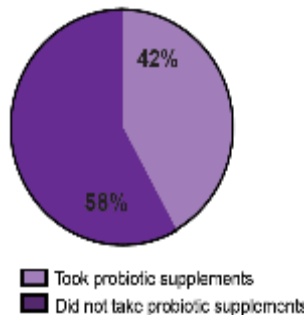
Pinato et al, JAMA Oncology 2019

Wouldn't it be easier to just take a pill?

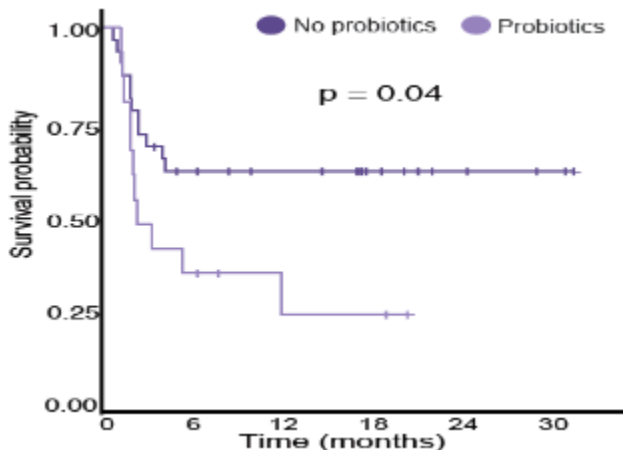
An unintended consequence of groups publishing this work is that patients now want to modulate their microbiome (and will do so using things such as over the counter probiotics)



Melanoma patients



42% of our patients reported taking OTC probiotics, which was associated with a lower diversity of the gut microbiome



Patients who reported taking OTC probiotics were also less likely to respond to anti-PD-1 therapy

Conclusions

- Gut microbiome is distinct between responders and non-responders to immunotherapy and responsiveness to immunotherapy can be transferred via FMT in mice
- Gut microbiome may be both a biomarker and a therapeutic target
- Diet and “biotics” are key determinants of the gut microbiome and may influence response to immunotherapy
- Multiple studies of different approaches to gut microbiome modulation to enhance immune response in cancer are currently underway with promising early data from FMT studies

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Savor Health



MD Anderson Physician Scientist Program