Towards an integrated multidimensional predictive biomarker for immunotherapy efficacy versus resistance

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Professor in Cancer Immunotherapy
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Disclosures

- Consultant/advisory boards:
  - Roche-Genentech, Merck, Abbvie, Bayer, Aduro, Fog Pharma
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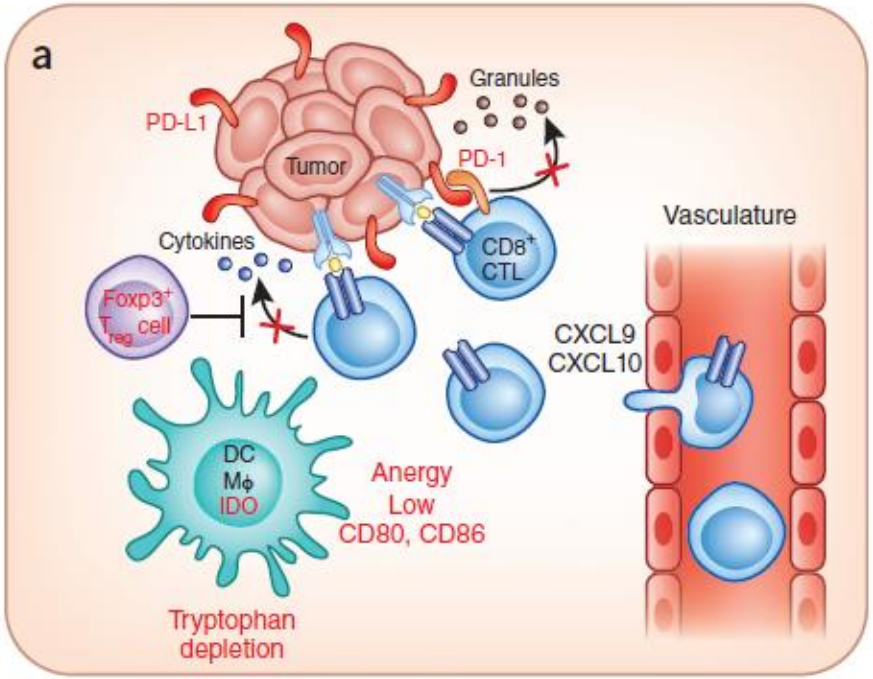
- Cofounder/shareholder
  - Jounce

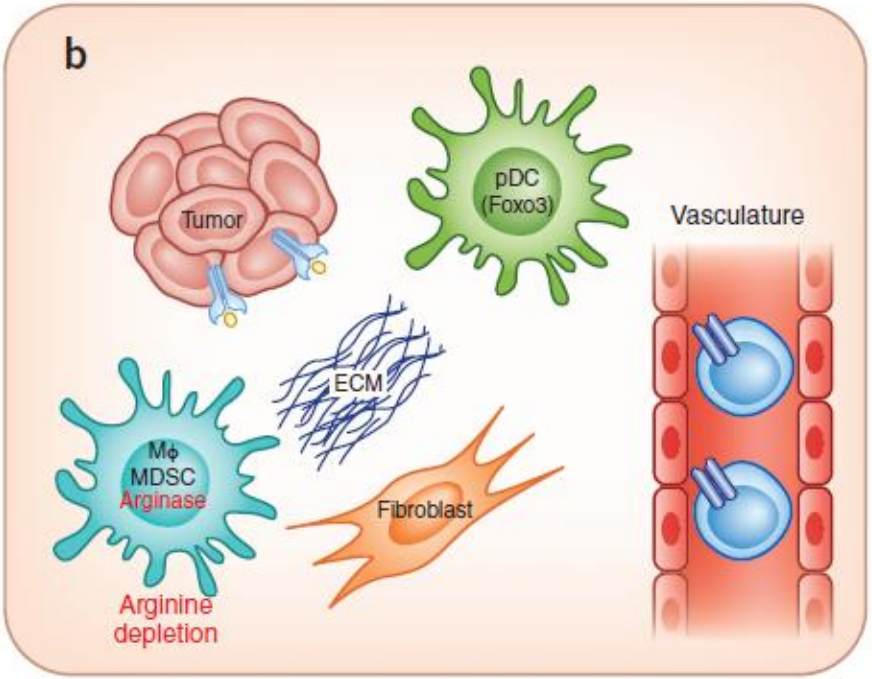
Working model: immunobiology of T cell-inflamed and non-inflamed tumor microenvironment

T cell-inflamed



- Chemokines
- $CD8^+$ T cells
- Type I IFN signature
- Immune escape: Inhibitory pathways
- ***Most immunotherapy responders have this phenotype***

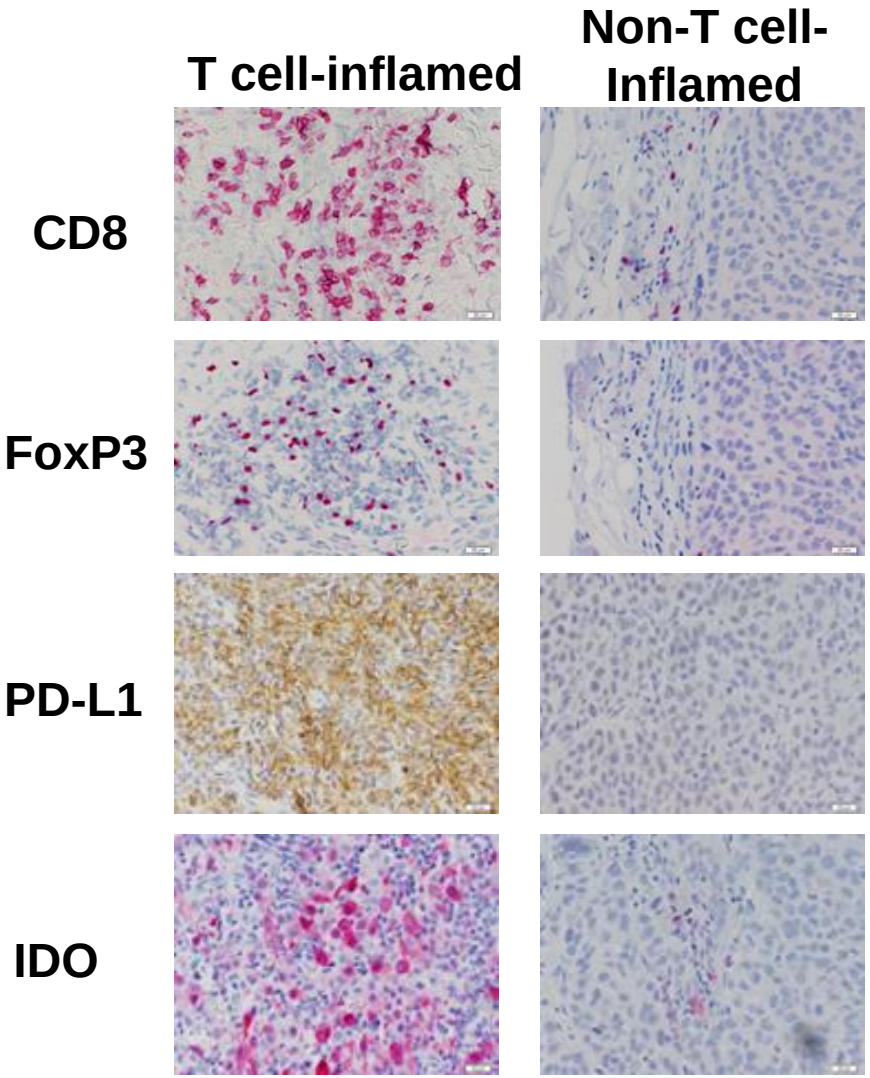
Non-T cell-inflamed

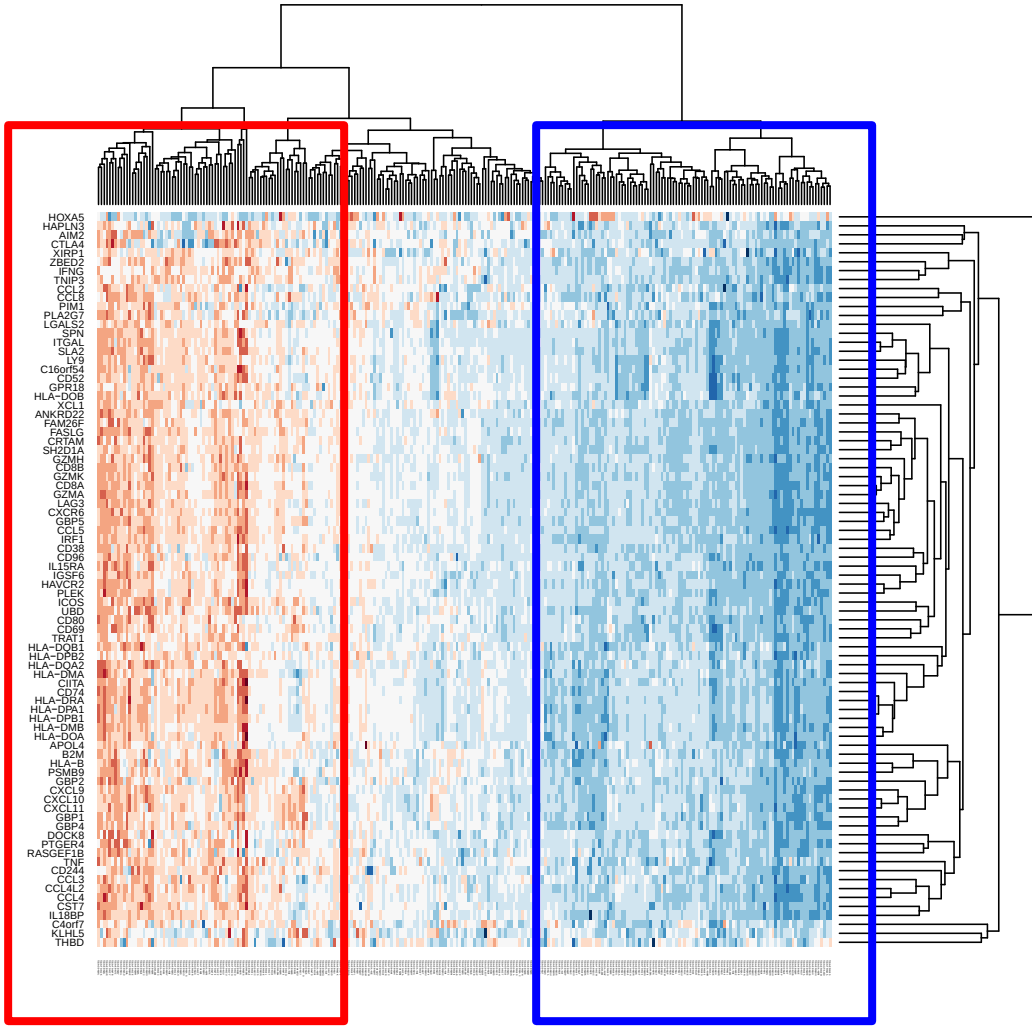


- Low inflammatory signature
- Absent intratumoral $CD8^+$ T cells
- Immune escape: T cell exclusion

Nature Immunol. 2013

Tregs, PD-L1, and IDO are associated with CD8+ T cell infiltration and immune gene signature

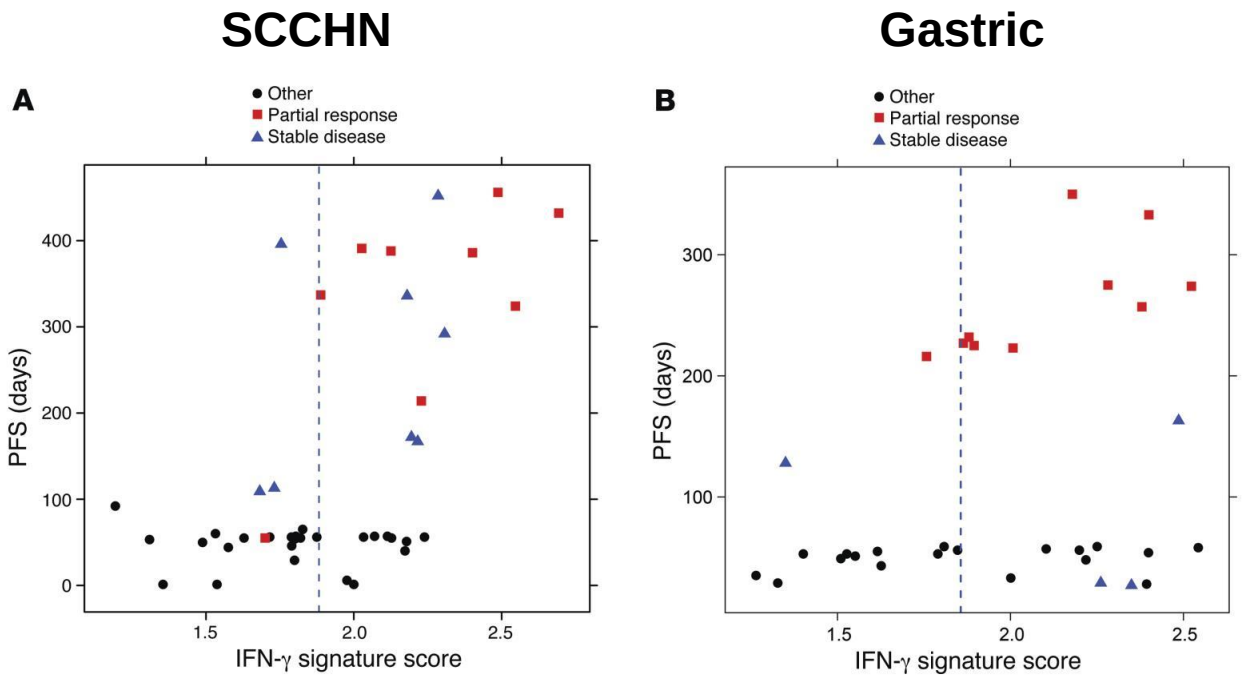




Science Trans. Med. 2013

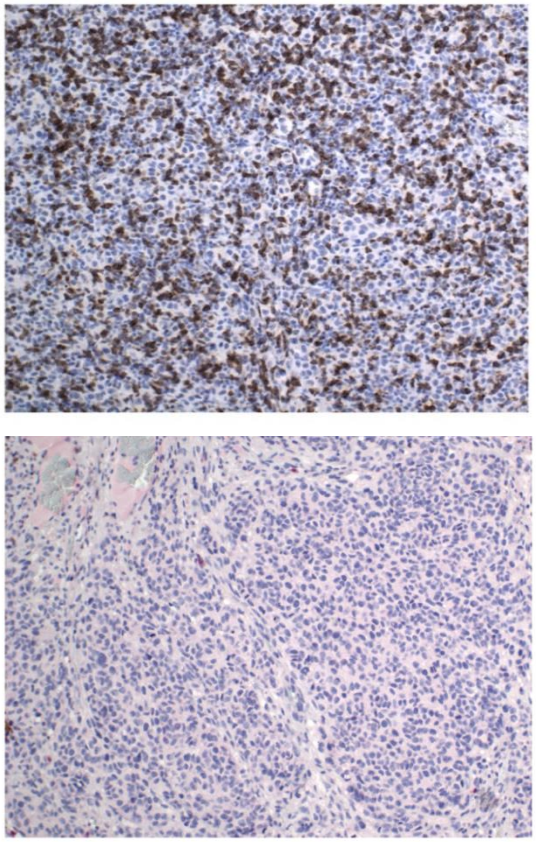
Spranger et al; Nature. 2015

Activity of anti-PD1 in head and neck cancer and gastric cancer is associated with T cell-inflamed tumor microenvironment signature



Ayers…Seiwert et al; JCI, 2017

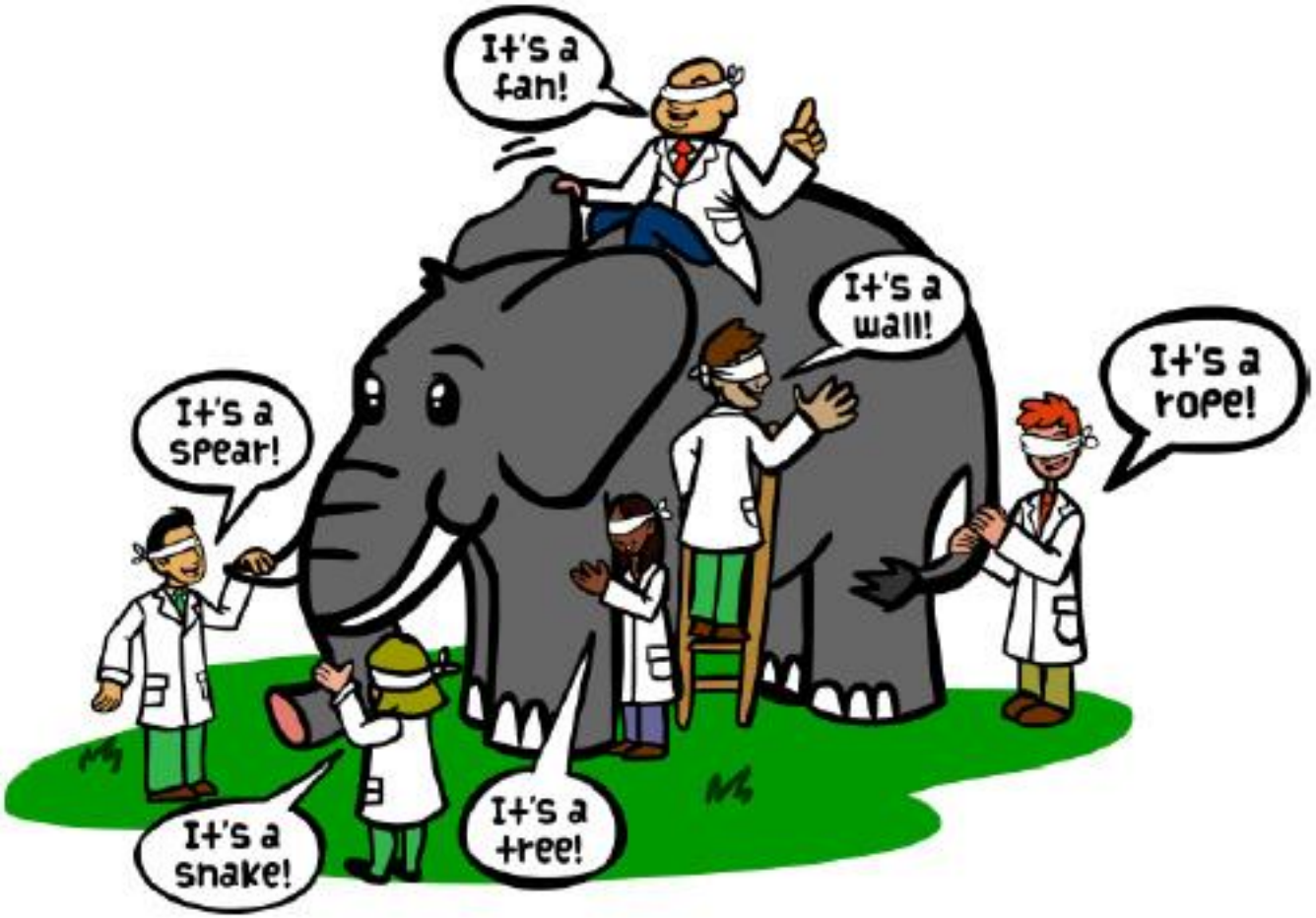
What molecular mechanisms drive the presence or absence of the T cell-inflamed tumor microenvironment?



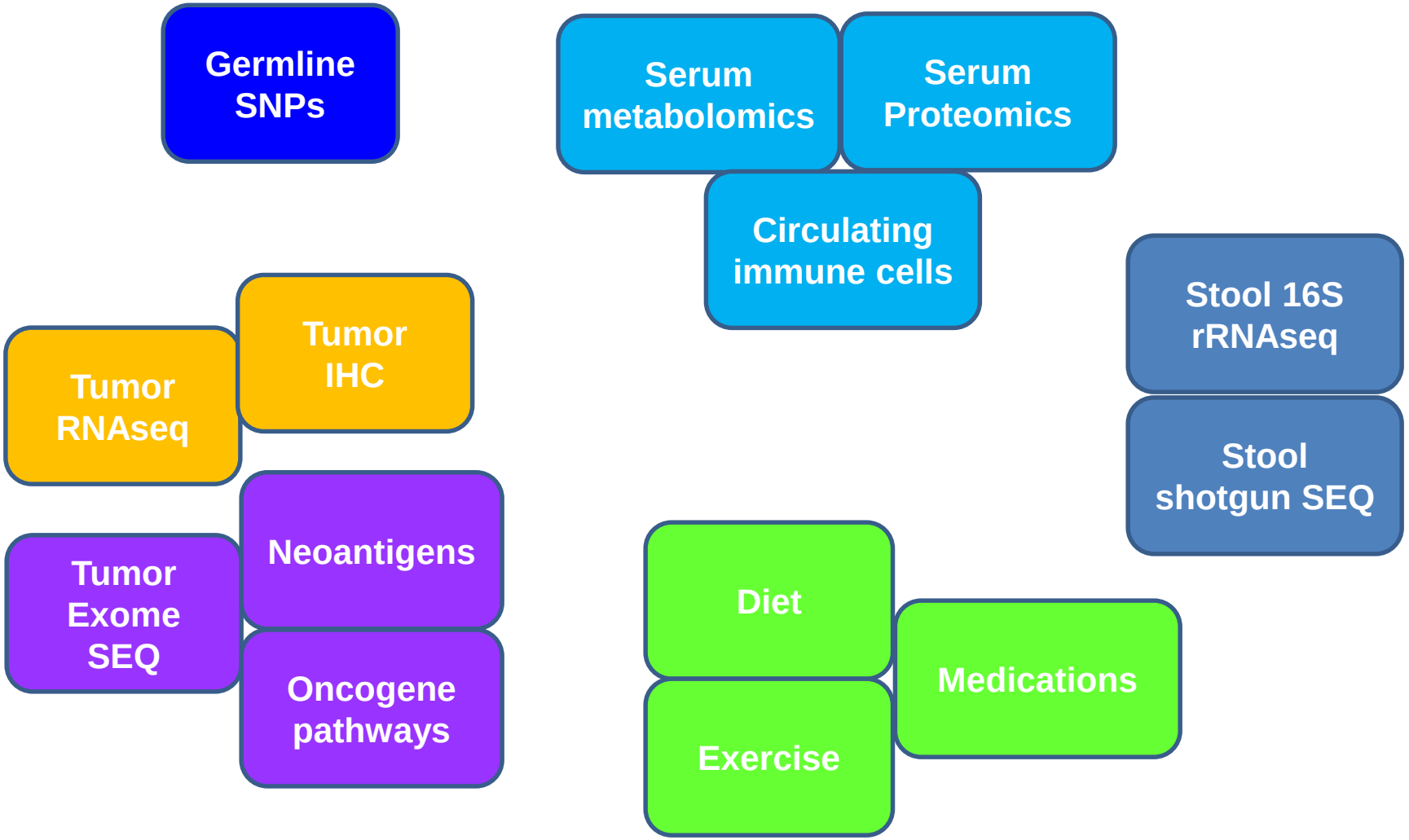
1. Somatic differences at the level of tumor cells
   - Distinct oncogene pathways activated in different patients
   - Mutational landscape and antigenic repertoire
2. Germline genetic differences at the level of the host
   - Polymorphisms in immune regulatory genes
3. Environmental differences
   - Commensal microbiota
   - Immunologic/pathogen exposure history of patients

b**IO**bank protocol: evaluating these parameters in patients treated with anti-PD-1 using multiple genomics platforms

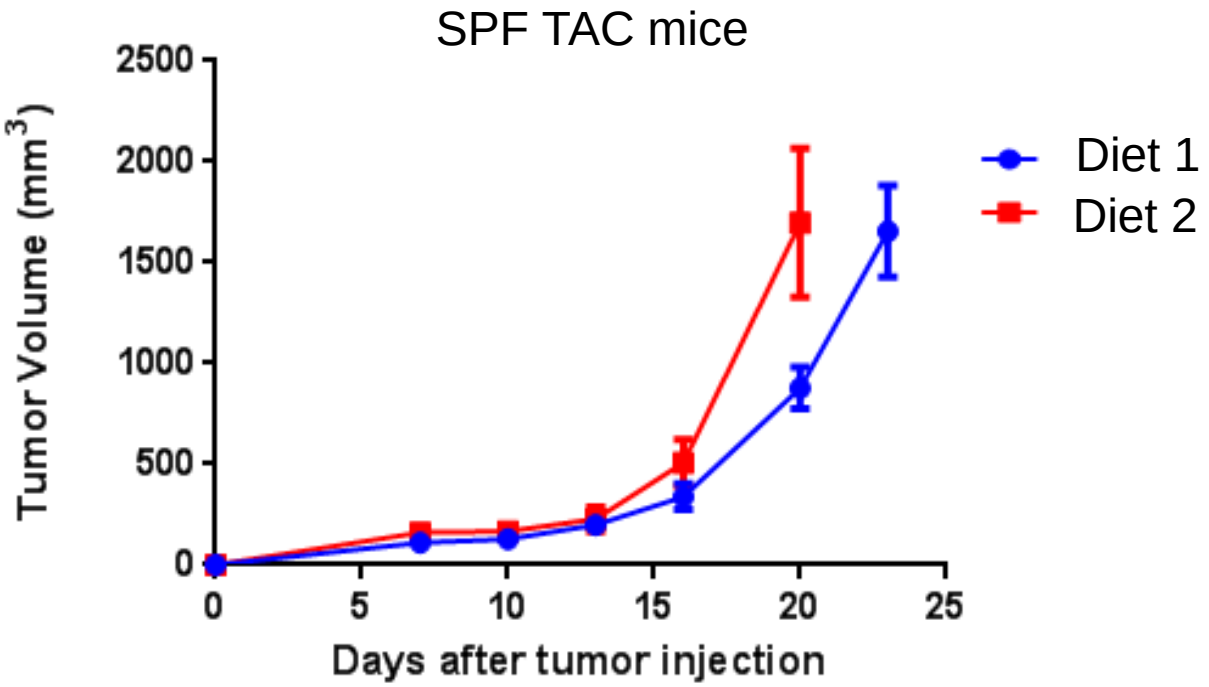
Which dimension of biomarker data is most critical? An integrated approach could be more informative



Multiple tissues and compartments being interrogated in patients



Diet impacts on tumor growth and anti-tumor immunity

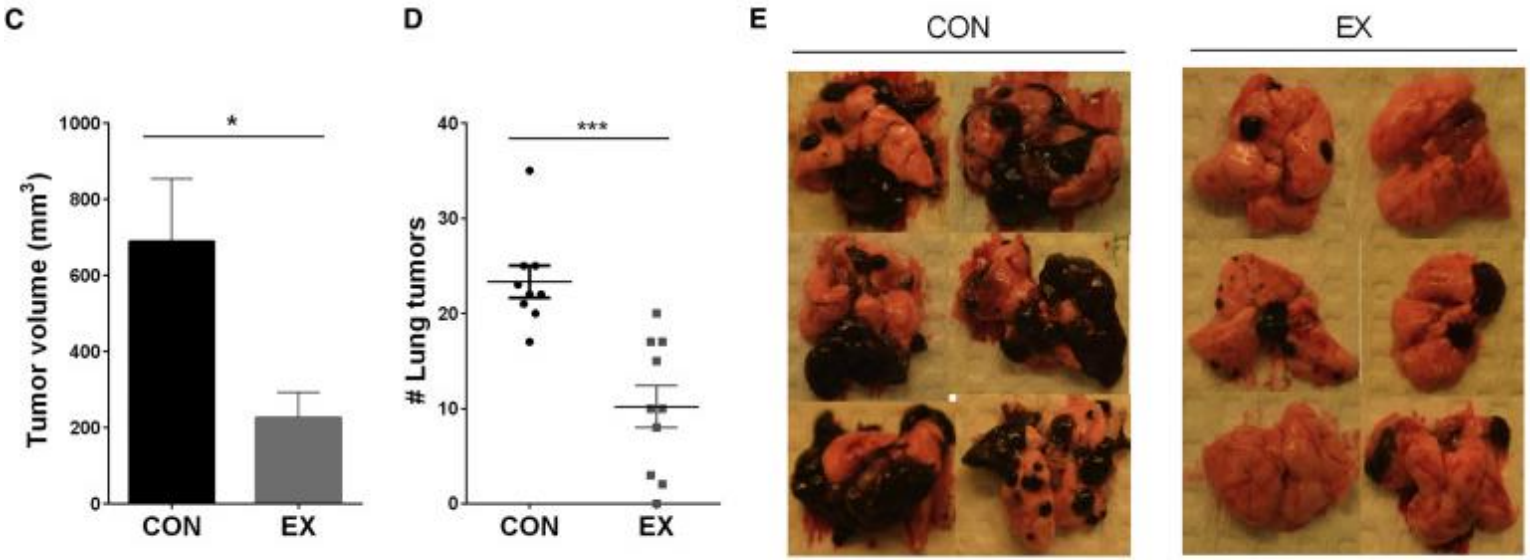


CellPress

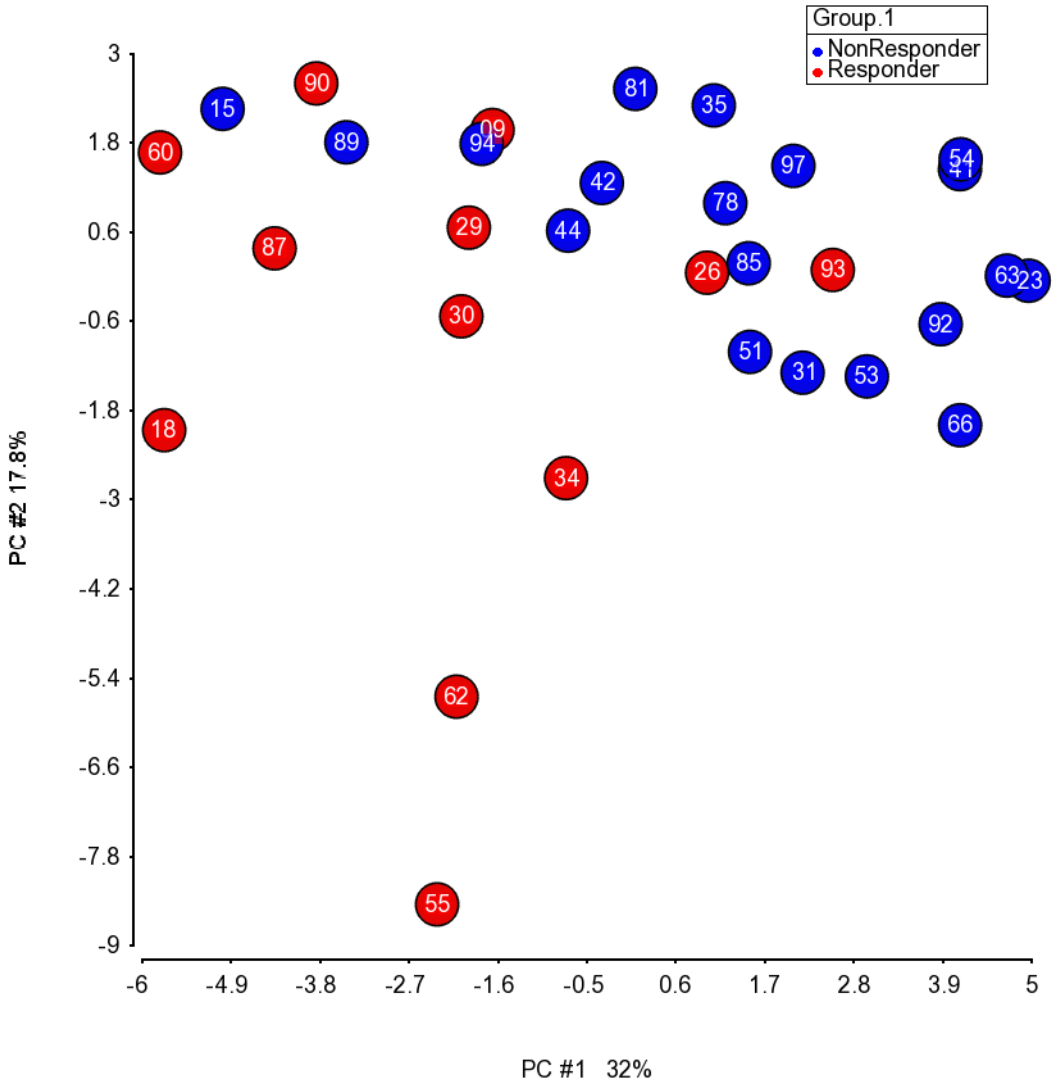
Cell Metabolism
Short Article

Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

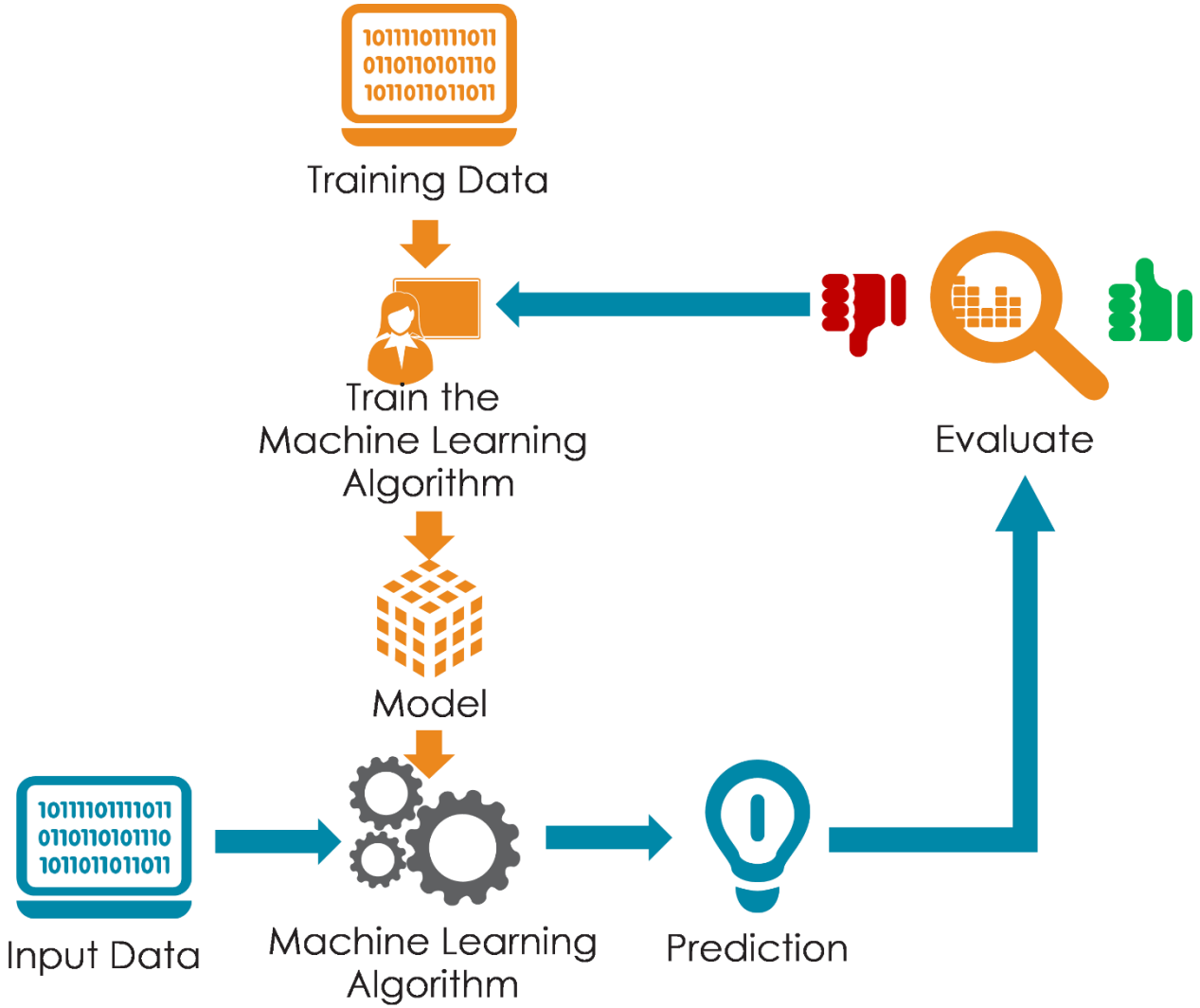
Line Pedersen,[1] Manja Idorn,[2] Gitte H. Olofsson,[2] Britt Lauenborg,[1] Intawat Nookaew,[3,4] Rasmus Hvass Hansen,[5] Helle Hjorth Johannesen,[5] Jürgen C. Becker,[6] Katrine S. Pedersen,[1] Christine Dethlefsen,[1] Jens Nielsen,[3] Julie Gehl,[7] Bente K. Pedersen,[1] Per thor Straten,[2,8] and Pernille Hojman[1,7,*]



Serum metabolites measured by mass spectrometry associated with clinical response to anti-PD-1



Machine learning algorithm approach for identifying combinatorial patterns of biomarkers linked to anti-PD-1 efficacy



Article

Cell

Personalized Nutrition by Prediction of Glycemic Responses

David Zeevi,[1,2,8] Tal Korem,[1,2,8] Niv Zmora,[3,4,5,8] David Israeli,[6,8] Daphna Rothschild,[1,2] Adina Weinberger,[1,2] Orly Ben-Yacov,[1,2] Dar Lador,[1,2] Tali Avnit-Sagi,[1,2] Maya Lotan-Pompan,[1,2] Jotham Suez,[3] Jemal Ali Mahdi,[3] Elad Matot,[1,2] Gal Malka,[1,2] Noa Kosower,[1,2] Michal Rein,[1,2] Gili Zilberman-Schapira,[3] Lenka Dohnalová,[3] Meirav Pevsner-Fischer,[3] Rony Bikovsky,[1,2] Zamir Halpern,[5,7] Eran Elinav,[3,9,*] and Eran Segal[1,2,9,*]

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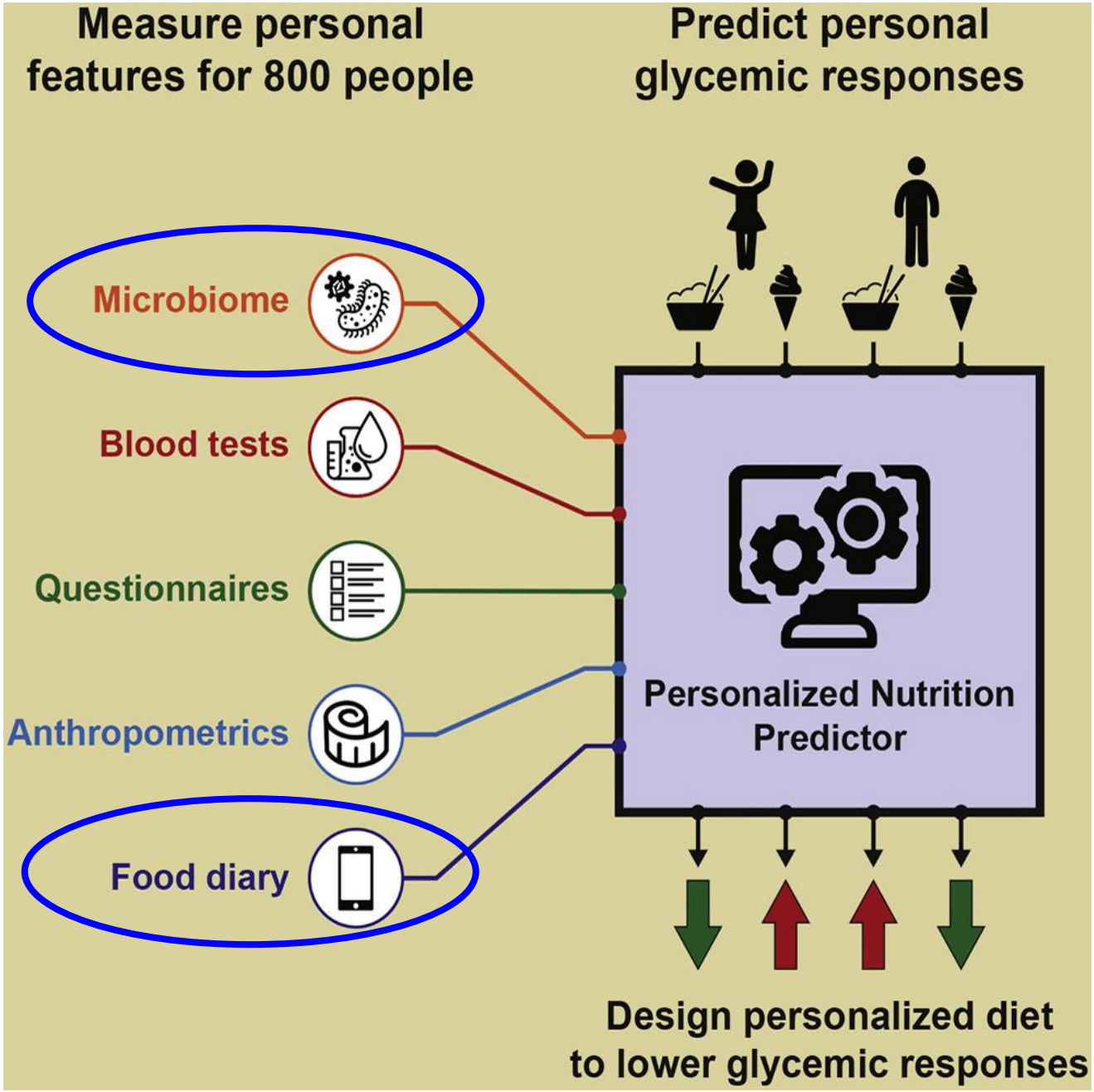
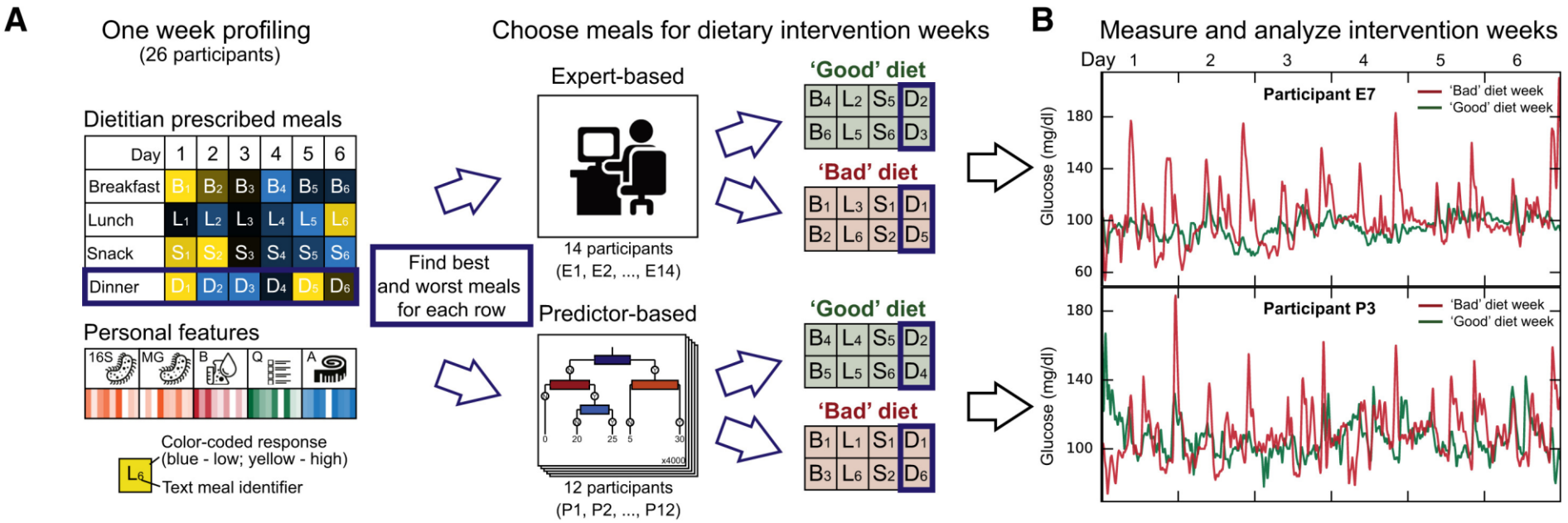
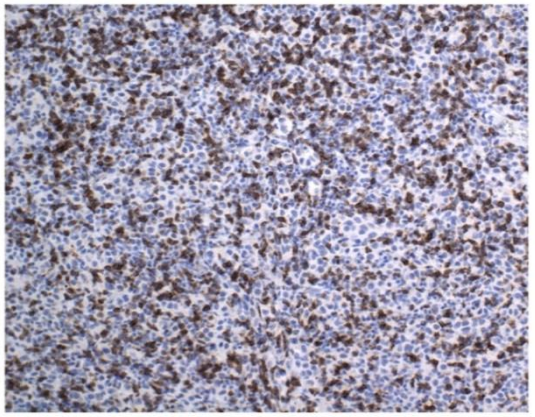
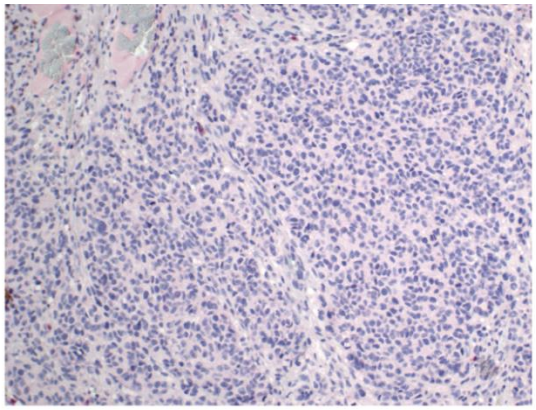

Measure personal features for 800 people
Predict personal glycemic responses
Microbiome
Blood tests
Questionnaires
Anthropometrics
Food diary
Personalized Nutrition Predictor
Design personalized diet to lower glycemic responses

Diet computer-recommended based on specific microbiota and dietary history improves glycemic control



What are the molecular mechanisms that explain the T cell-inflamed versus non-inflamed tumor microenvironments?





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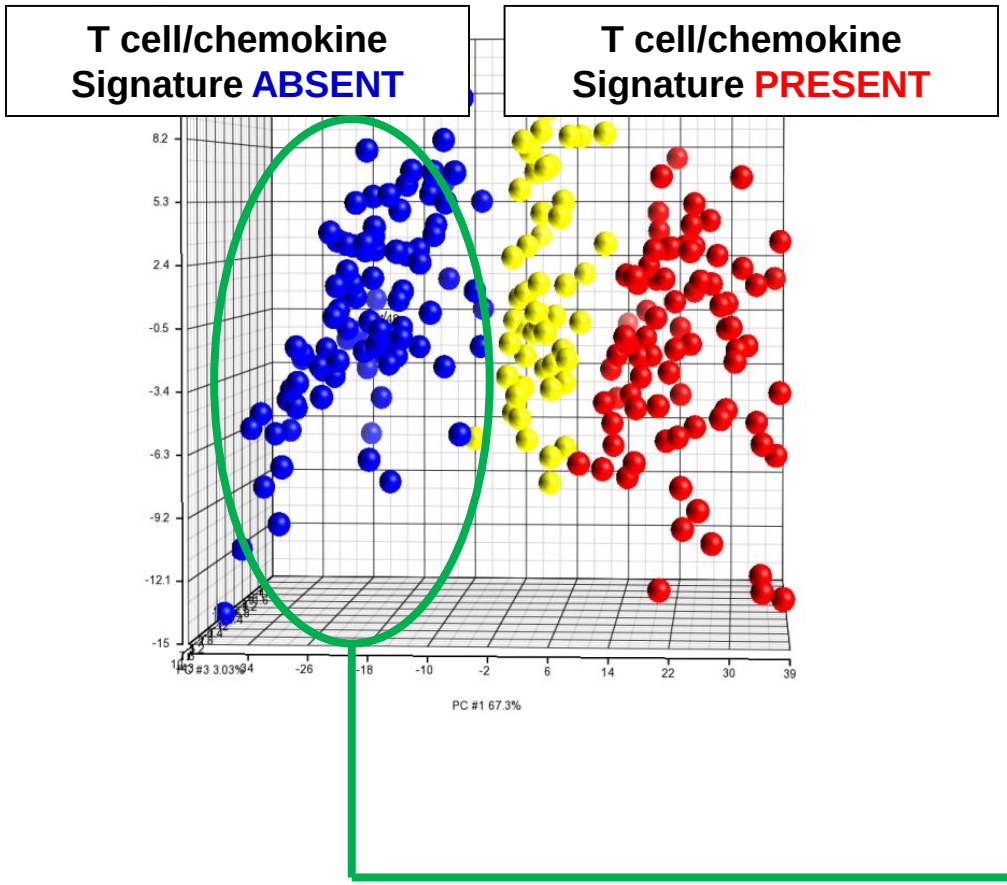
Integrating RNAseq data with exome sequencing data identified pattern: non-T cell inflamed melanomas are enriched for β-catenin signaling

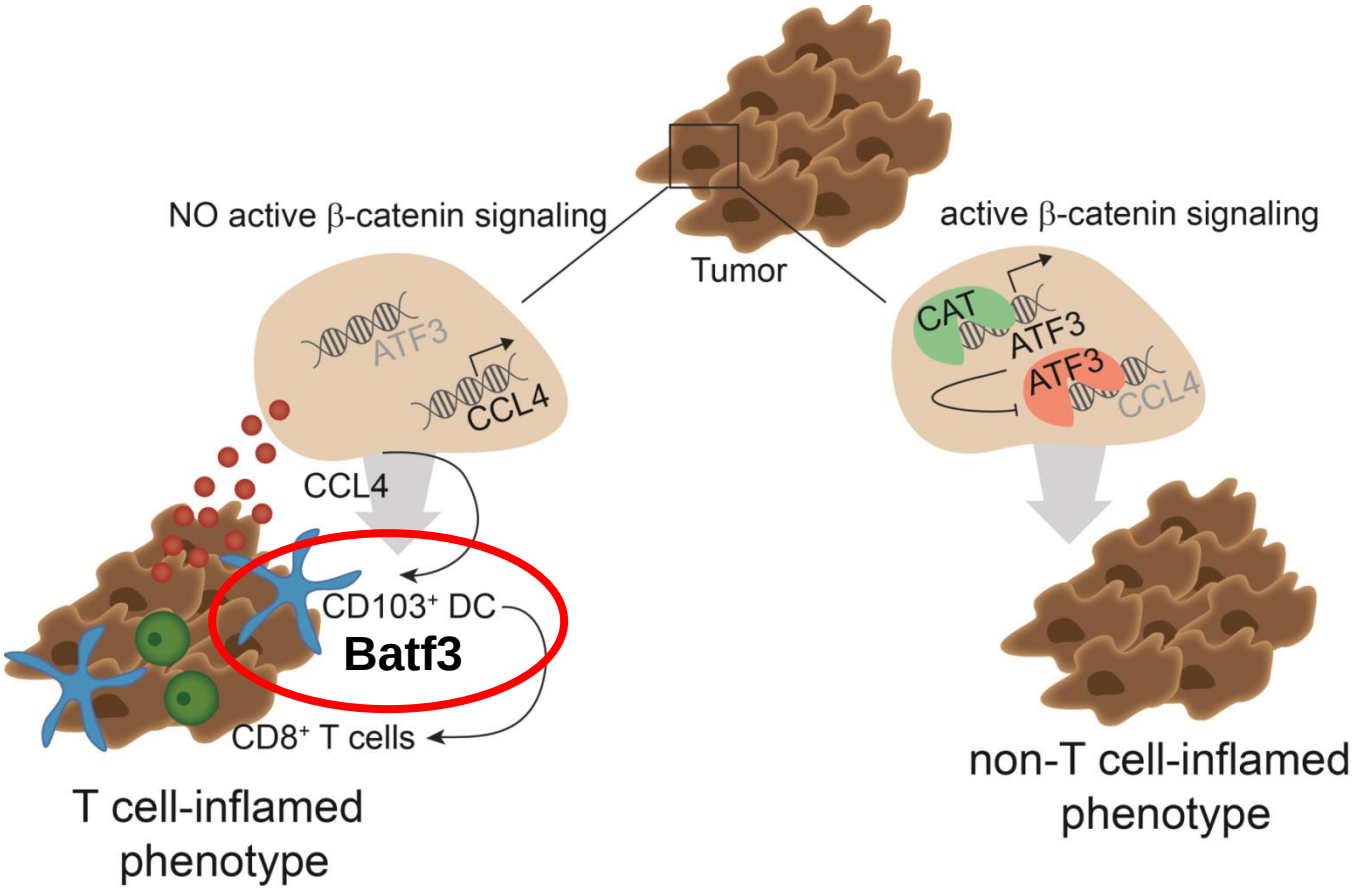


Molecular mechanism for activated β-catenin signaling T cell-signature low patients

8% CTNNB1 GOF mutations
12% LOF mutations in CTNNB1 inhibitors
14% overexpression of Wnt7b
10% overexpression of Fzd3
5% overexpression of CTNNB1

51% no alterations in CTNNB1 pathway

Tumor cell-intrinsic β-catenin activation prevents host anti-tumor immune response by failure to recruit Batf3 DCs



Responsive to Checkpoint blockade

Resistant to Checkpoint blockade

Spranger et al; Nature. 2015

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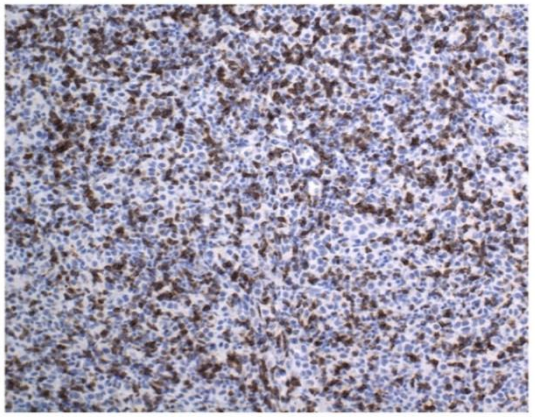

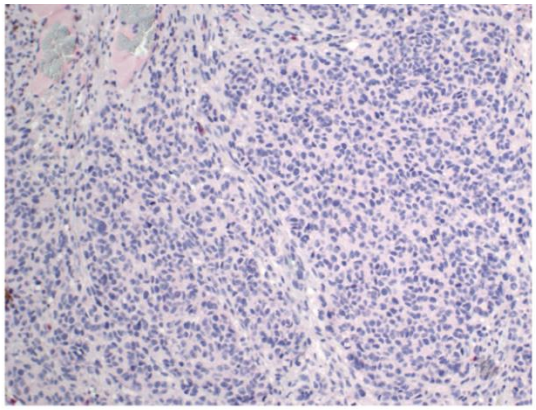

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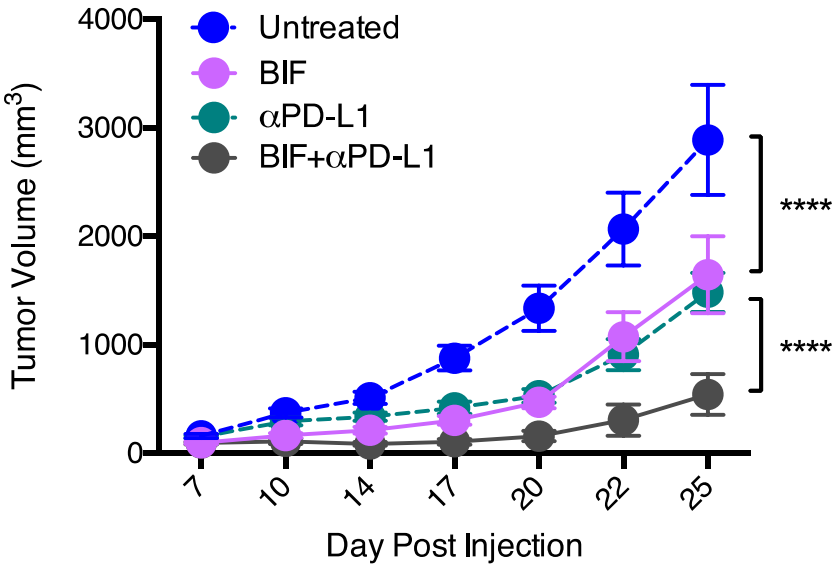
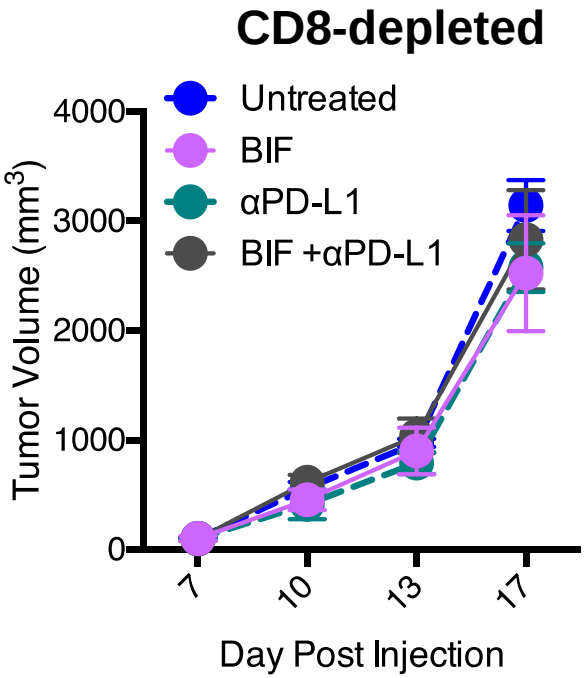
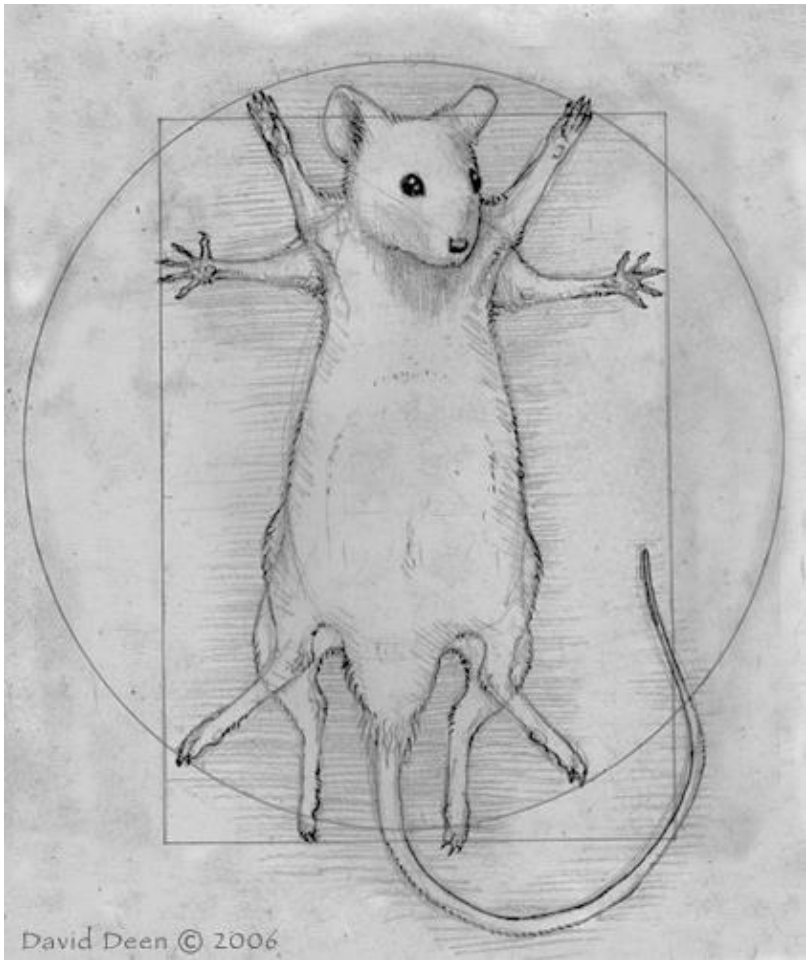
Direct administration of *Bifidobacterium* mix to tumor-bearing TAC recipients improves tumor-specific immunity and response to αPD-L1 mAb

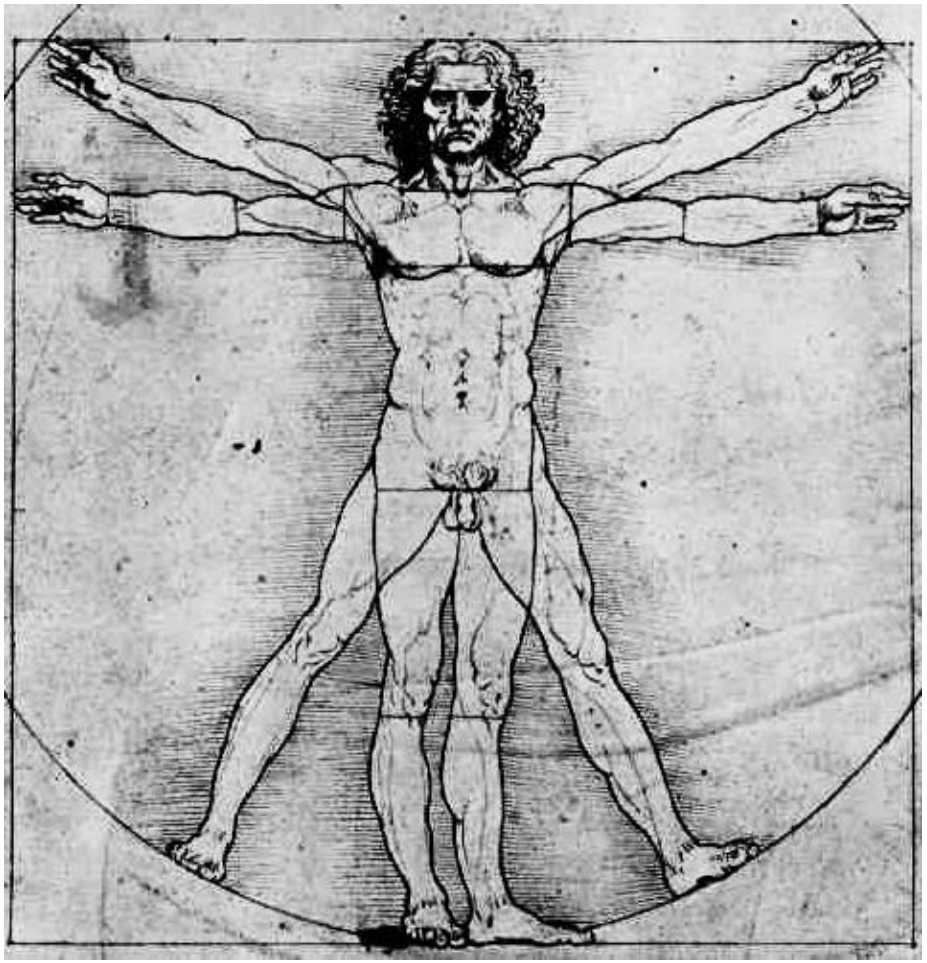




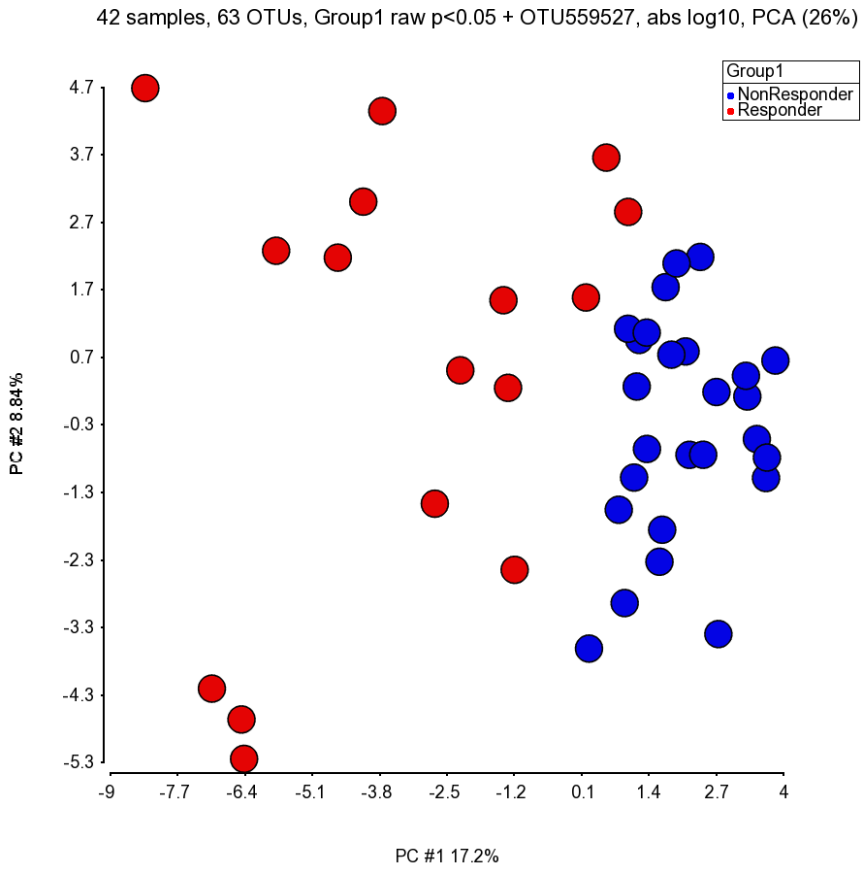
Sivan, Corrales et al; Science. 2015

Does the commensal microbiota impact on anti-tumor immunity carry over to human cancer patients?

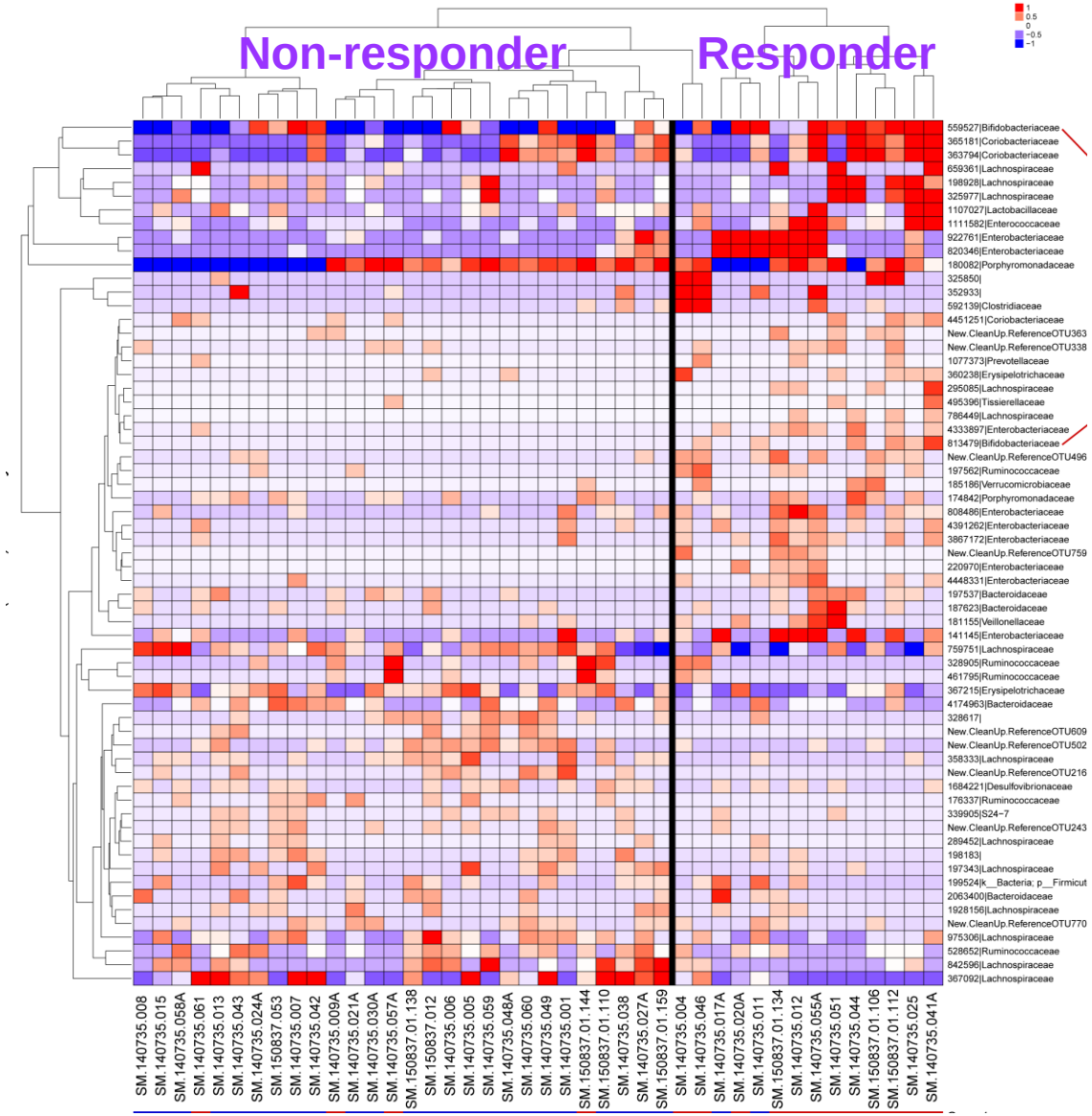




Metastatic melanoma patients: anti-PD-1 responders and non-responders have distinct baseline microbiota

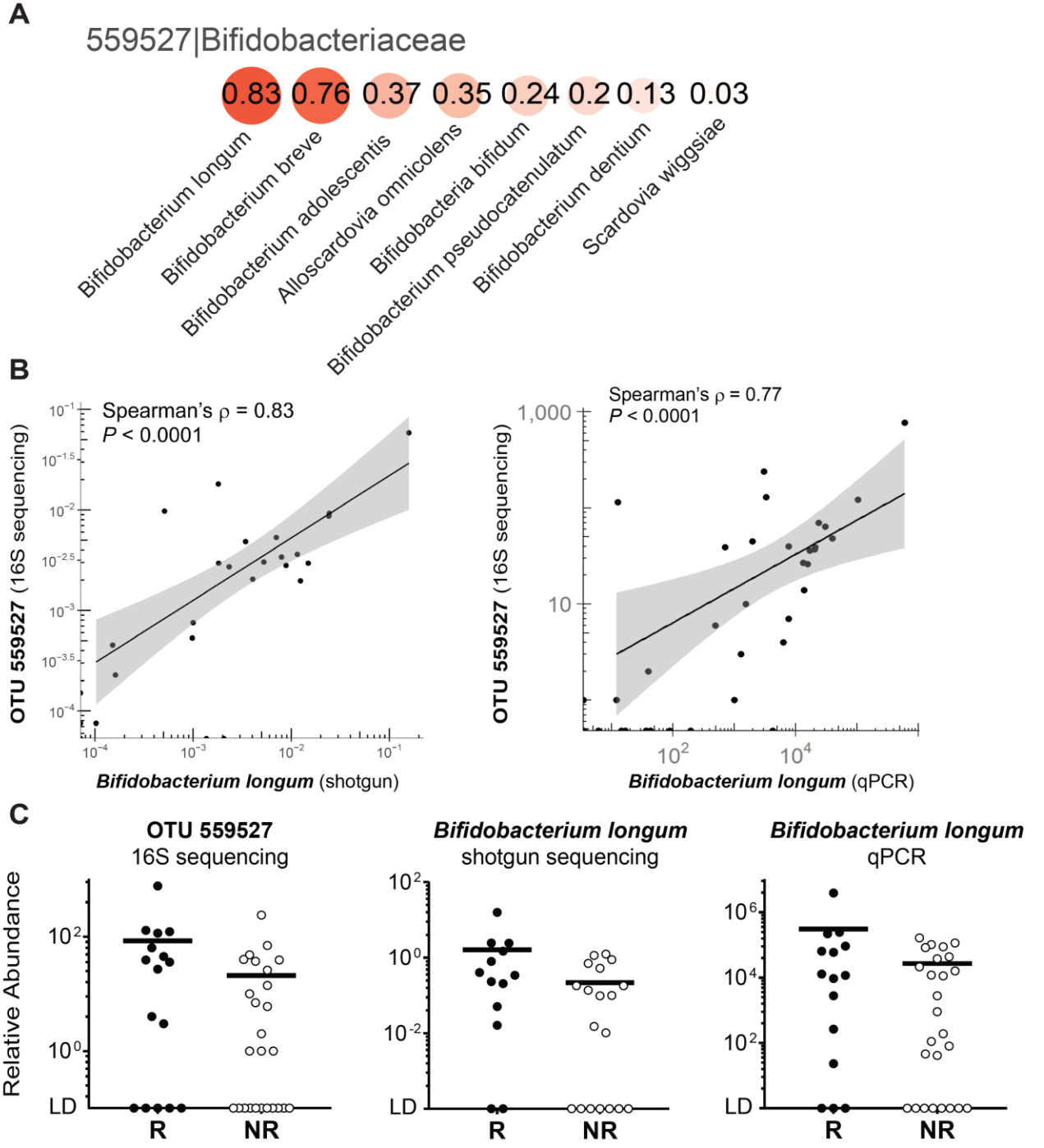


Commensal microbiota associated with clinical response to anti-PD-1 in metastatic melanoma

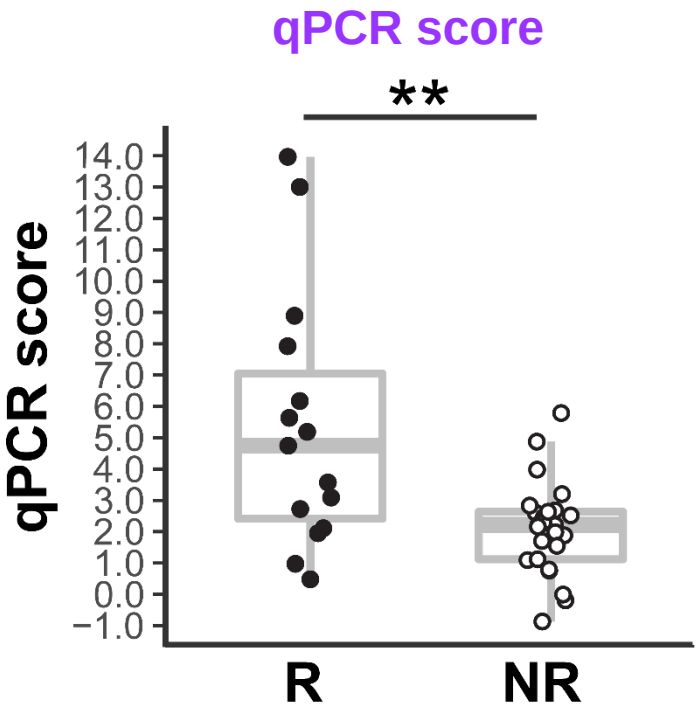


Integration of 16S, shotgun sequencing, and specific-specific PCR: *Bifidobacterium longum* is one species more abundant in responders

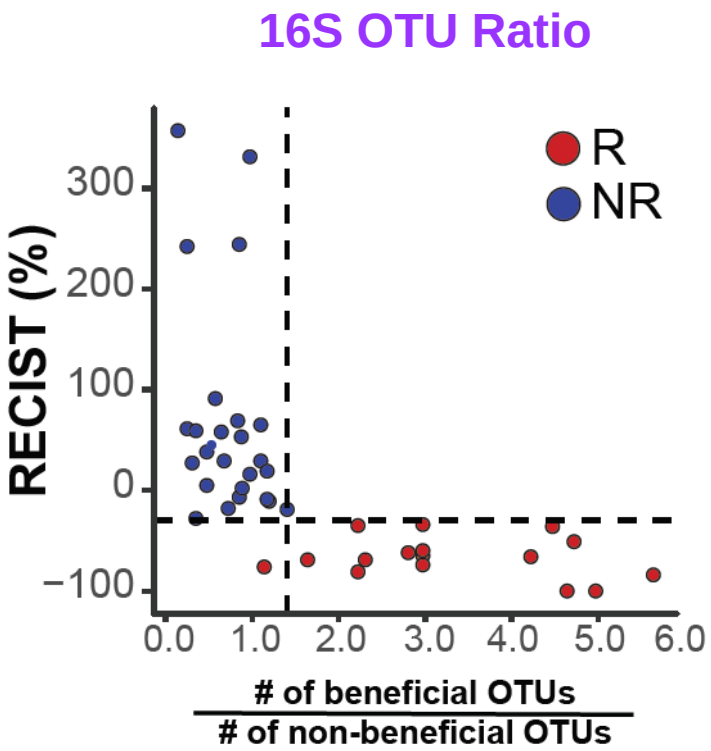
9 additional species confirmed across all three platforms (16S, shotgun, PCR)



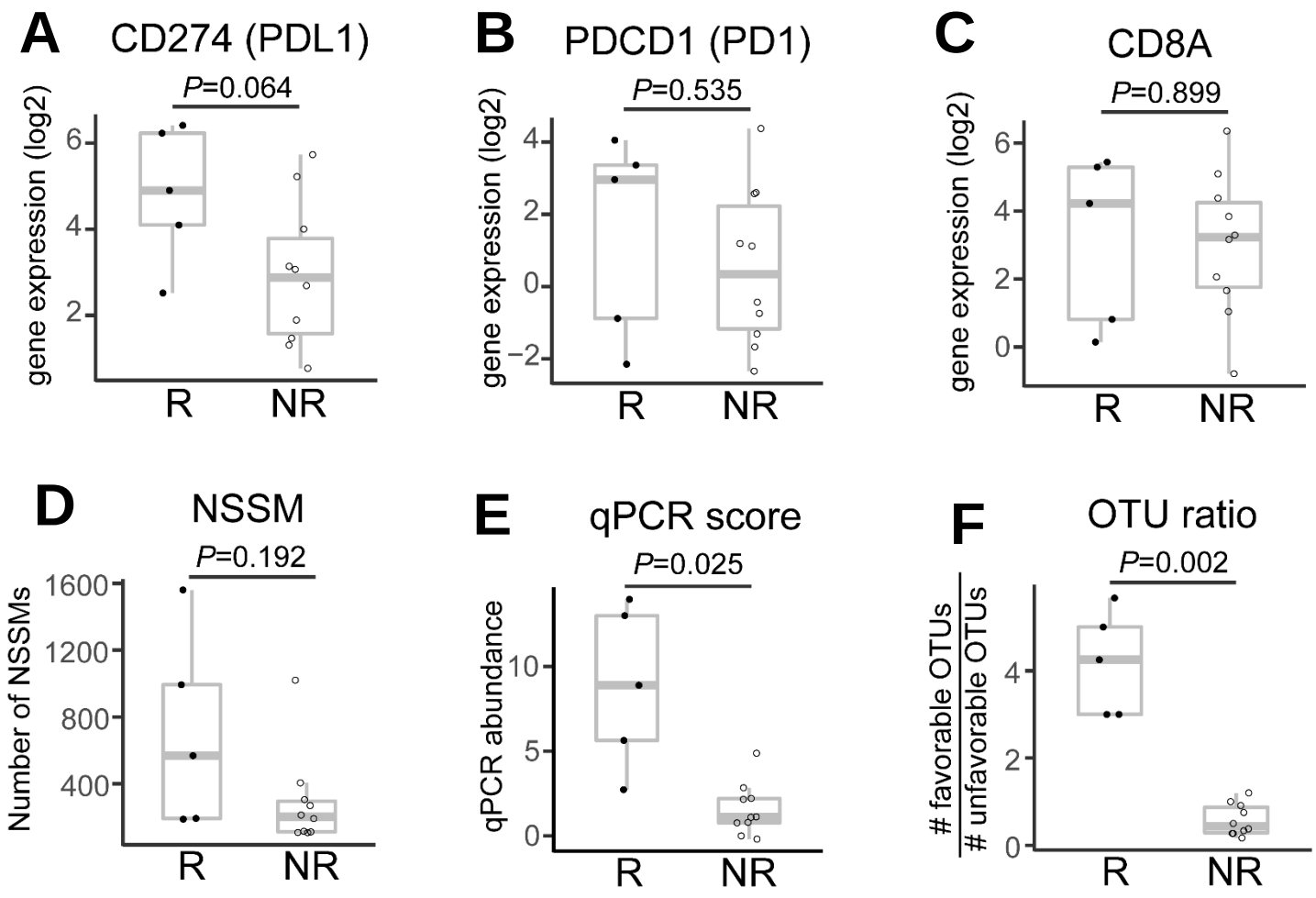
qPCR score and ratio of OTUs as a predictive biomarker for clinical response



10 species total

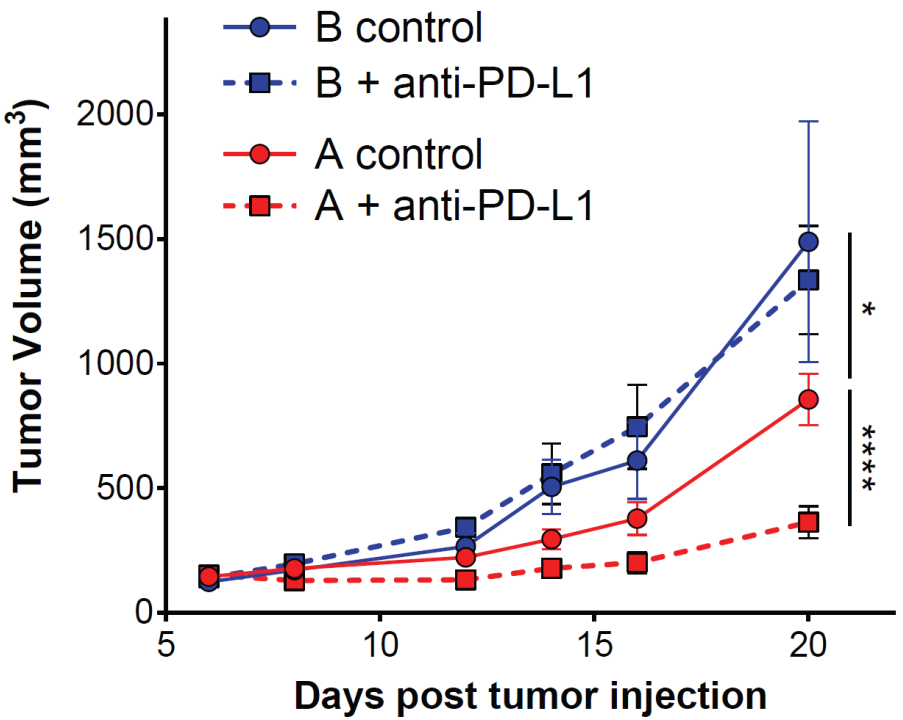


Comparison of biomarkers reveals the high predictive value of microbiota sequencing in this cohort (n=15)



Anti-PD-L1 is effective in GFM that receive responder but not non-responder microbiota

Tumor growth



Matson, Fessler et al;
Manuscript in press

Conclusions

- Multiple tumor and host-derived factors appear to impact on the generation of the T cell-inflamed tumor microenvironment phenotype, and in turn on the efficacy of PD-1-targeted therapy
- Already associated are specific tumor cell-intrinsic oncogene pathways, tumor neoantigen load, specific germline SNPs, serum metabolites, and the composition of the commensal microbiota
- Machine learning approaches are being pursued to identify patterns and potential interactions between dimensions of data
  - Maximize predictive biomarker efficacy
  - Generate new hypotheses about mechanism of effect
  - Develop new therapies to expand therapeutic benefit

Acknowledgments

Uncoupling negative T cell regulation
Stefani Spranger
Brendan Horton
Jason Williams

Anergy/dysfunctional TIL
Jason Williams
Brendan Horton
Yan Zheng

Genetic melanoma models
Stefani Spranger
Michael Leung

Tumor genomics and T cell phenotype
Yuan-yuan Zha
Jason Luke
Riyue Bao
Stefani Spranger
Randy Sweis
Alex Gajewski

Innate immune sensing/ Type I IFNs/STING
Leticia Corrales
Seng-Ryong Woo
Mercedes Fuertes
Aduro (Tom Dubensky)

Germline genetics and T cell phenotype
Kyle Cron
Ayelet Sivan
Ken Onel

Microbiota and anti-tumor immunity
Vyara Matson
Jessica Fessler
Marisa Alegre
Ayelet Sivan
Gene Chang
Bana Jabri
Kevin Lei