Microbiome as Predictor of Benefit and Toxicity in Cancer Immunotherapy

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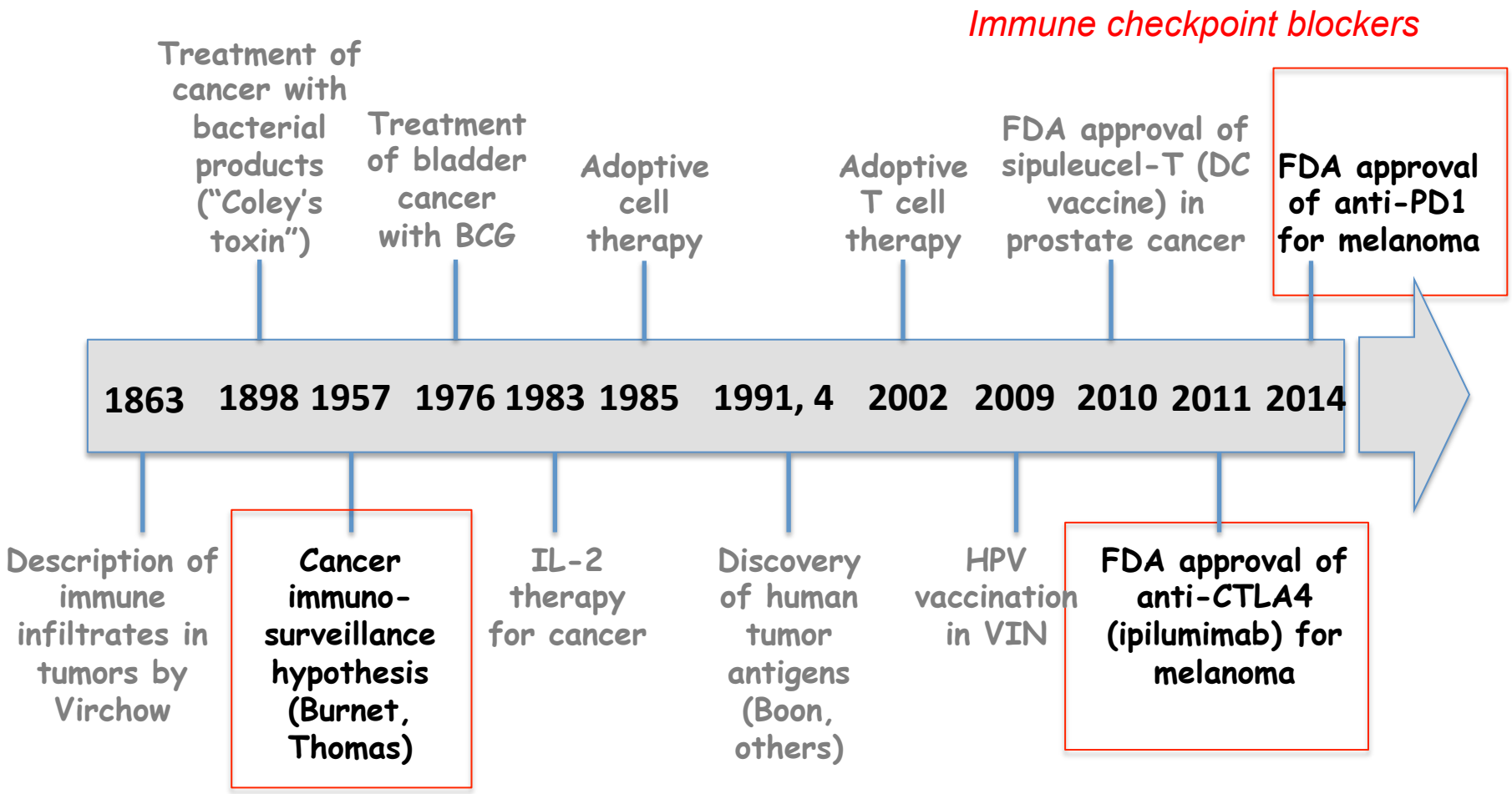
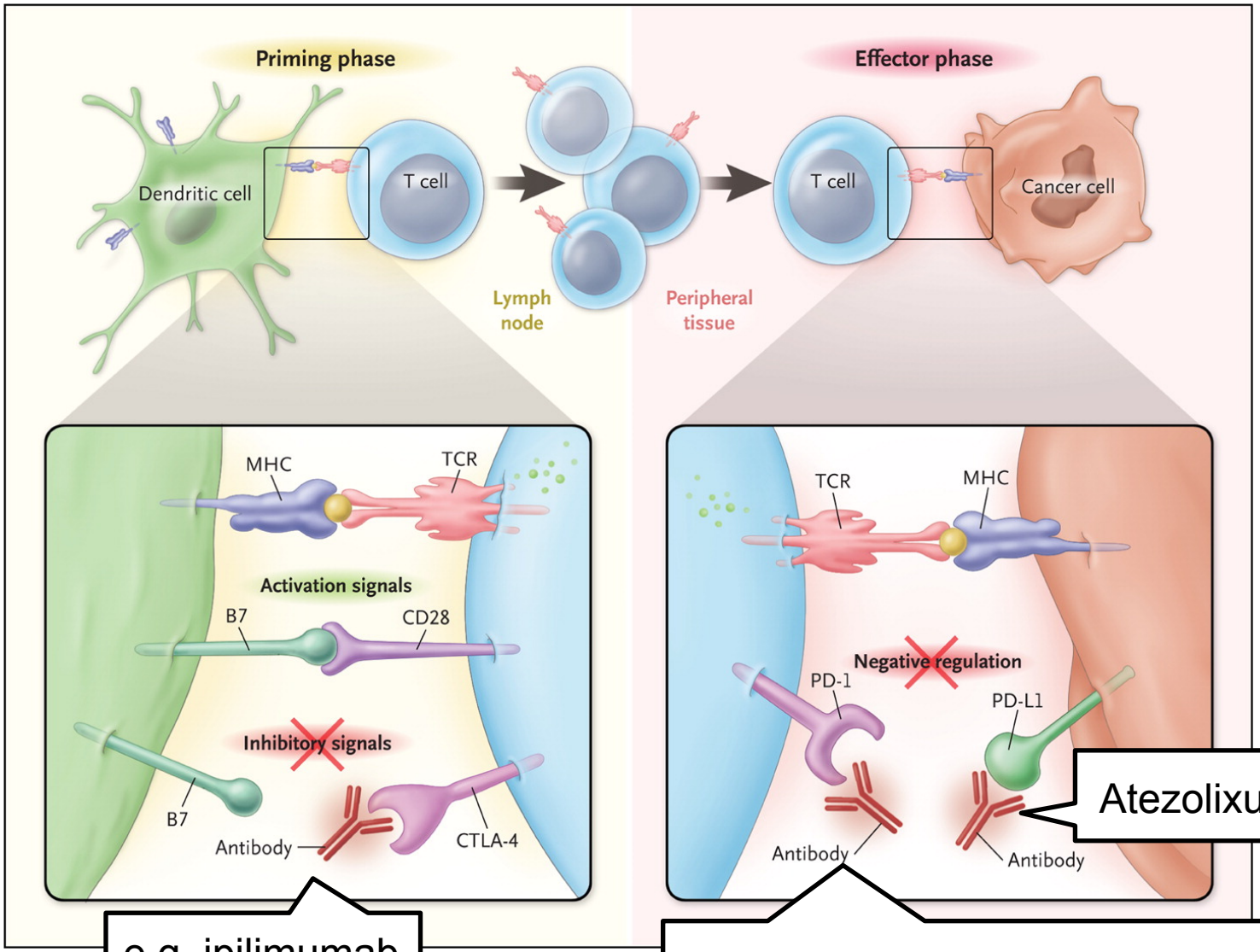
Optimizing Immunotherapy
New Approaches, Biomarkers, Sequences and Combinations
PRBB Auditorium, Barcelona
October 20th 2017

Cancer Immunotherapy

Cancer Immunotherapy is defined as the approach to treat the tumor by either inducing de novo or reactivating tumor specific immune responses

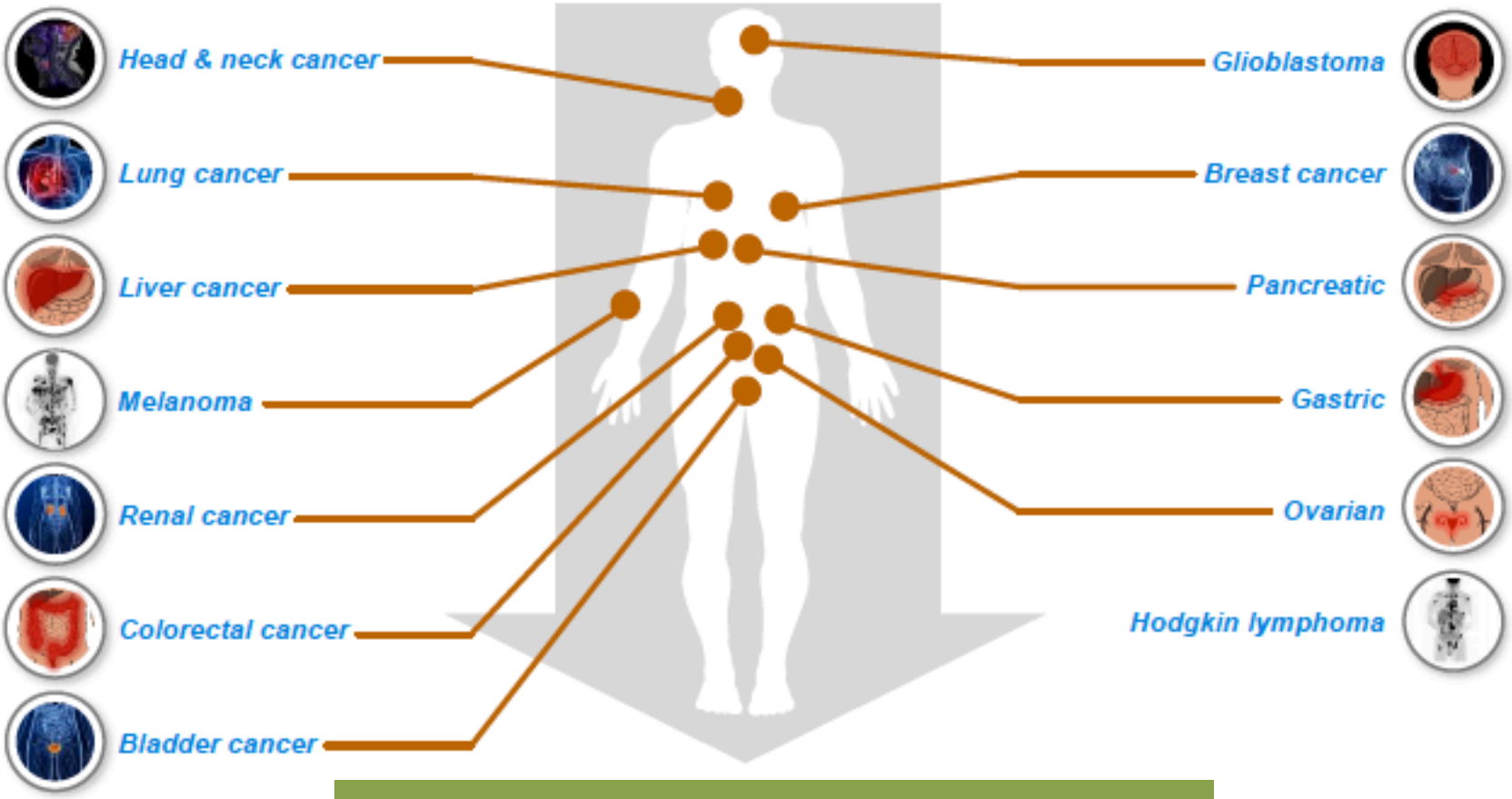


Immune Checkpoint Blockers (ICB)



Ribas A. N Engl J Med 2012;366:2517-2519.

Despite the Clinical Success in a Variety of Cancers only a Subset of patients Exhibits Durable Responses



Broad Activity but only a subset of patients exhibits durable responses: 15-40 %

Factors Contributing to Anti Cancer Immunity: The Role of The Microbiota

Immunotherapy Not Working? Check Your Microbiota

Nathan R. West[1] and Fiona Powrie[1,2,*]
[1]Kennedy Institute of Rheumatology, University of Oxford, Oxford OX3 7LF, UK
[2]Translational Gastroenterology Unit, Experimental Medicine Division, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK
*Correspondence: fiona.powrie@kennedy.ox.ac.uk
http://dx.doi.org/10.1016/j.ccell.2015.11.010

Immunity
Review
CellPress

Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors

Microbiota: a key orchestrator of cancer therapy

Soumen Roy and Giorgio Trinchieri

NATURE REVIEWS | CANCER VOLUME 17 | MAY 2017 | 271

CA CANCER J CLIN 2017;67:326–344

The Role of the Microbiome in Cancer Development and Therapy

Aadra P. Bhatt, PhD[1]; Matthew R. Redinbo, PhD[2,3,4]; Scott J. Bultman, PhD[5,6]

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 5), pp: 8890-8899

Review

Cross-talk between microbiota and immune fitness to steer and control response to anti PD-1/PDL-1 treatment

Cell

Leading Edge
Perspective

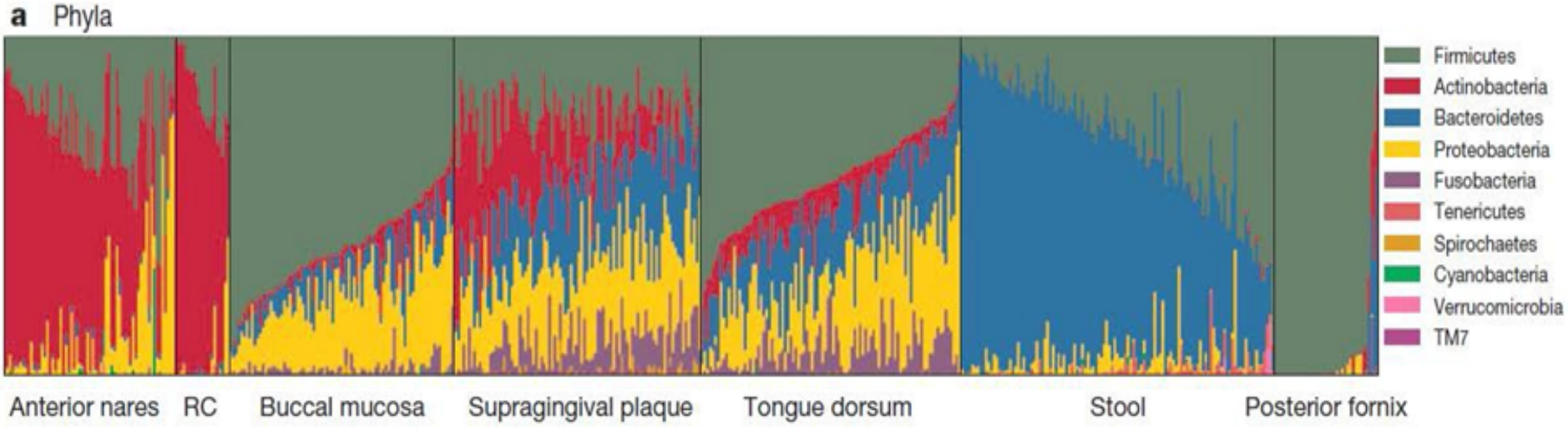
Microbiome and Anticancer Immunosurveillance

The Human Microbiota

- The human microbiota is the ensemble of bacteria and other microorganisms (such as archaea, fungi, protozoa and virus) that inhabit the epithelial surface of our body
- Most of these microorganisms reside in the gastrointestinal tract (10-100 trillions bacteria in the human intestine)

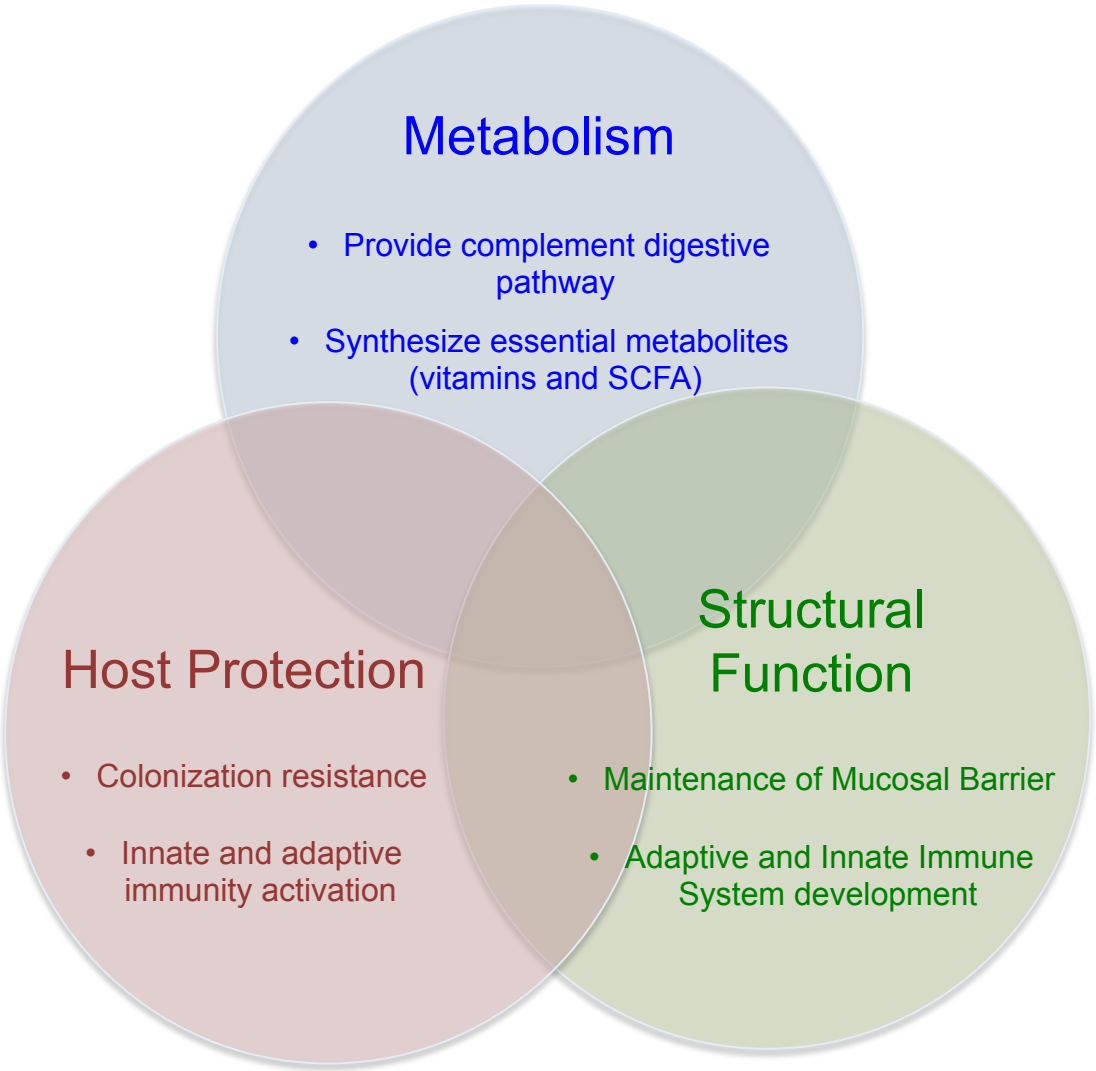
These microorganisms are not just passenger but actively participate in many physiological processes

Human Microbiome Complexity



- Our microbiome is dominated by 4 large groups of bacteria phyla: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria
- In the human body each site is different in terms of its predominant microbial types
- There is considerable variation in microbial composition among healthy individuals
- Several factors can affect microbiota composition (environmental factors, age,life's style, disease, disease treatment)
- Loss of microbial complexity and stability can have detrimental effect to human health

Role of Gut Microbiota



Microbiota and Cancer Immunotherapy

- The gut microbiota represents a significant source of human genetic and metabolic diversity
- Distinct bacteria, or bacterial products can promote alteration in both innate and adaptive immune responses

The microbiota can determine the immune fitness of an individuals and this has consequence in the outcome of therapies that are involving the immune system (toxicity and benefit)

Microbiota and ICB Therapy

Science

CANCER IMMUNOTHERAPY

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

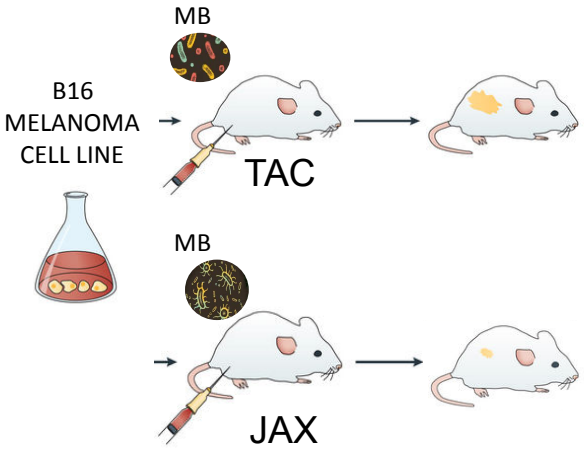
Ayelet Sivan,[1*] Leticia Corrales,[1*] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2]†

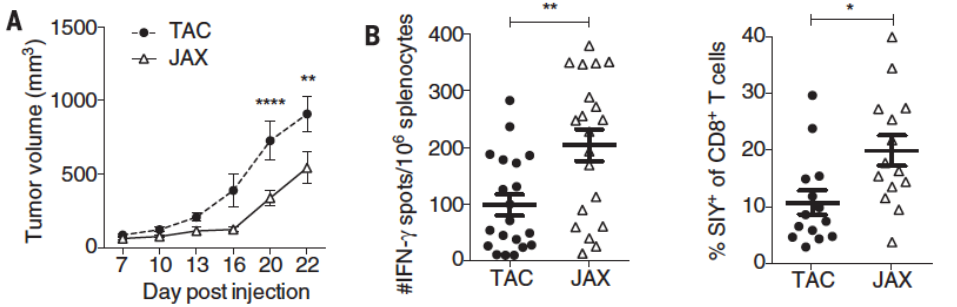
CANCER IMMUNOTHERAPY

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

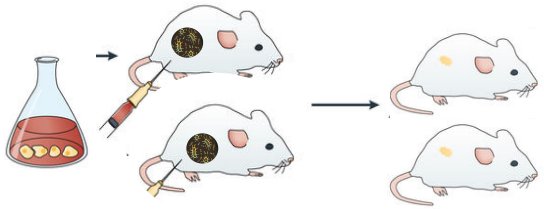
Marie Vétizou,[1,2,3] Jonathan M. Pitt,[1,2,3] Romain Daillère,[1,2,3] Patricia Lepage,[4] Nadine Waldschmitt,[5] Caroline Flament,[1,2,6] Sylvie Rusakiewicz,[1,2,6] Bertrand Routy,[1,2,3,6] Maria P. Roberti,[1,2,6] Connie P. M. Duong,[1,2,6] Vichnou Poirier-Colame,[1,2,6] Antoine Roux,[1,2,7] Sonia Becharef,[1,2,6] Silvia Formenti,[8] Encouse Golden,[8] Sascha Cording,[9] Gerard Eberl,[9] Andreas Schlitzer,[10] Florent Ginhoux,[10] Sridhar Mani,[11] Takahiro Yamazaki,[1,2,6] Nicolas Jacquelot,[1,2,3] David P. Enot,[1,7,12] Marion Bérard,[13] Jérôme Nigou,[14,15] Paule Opolon,[1] Alexander Eggermont,[1,2,16] Paul-Louis Woerther,[17] Elisabeth Chachaty,[17] Nathalie Chaput,[1,18] Caroline Robert,[1,16,19] Christina Mateus,[1,16] Guido Kroemer,[7,12,20,21,22] Didier Raoult,[23] Ivo Gomperts Boneca,[24,25*] Franck Carbonnel,[3,26*] Mathias Chamaillard,[5*] Laurence Zitvogel[1,2,3,6]†

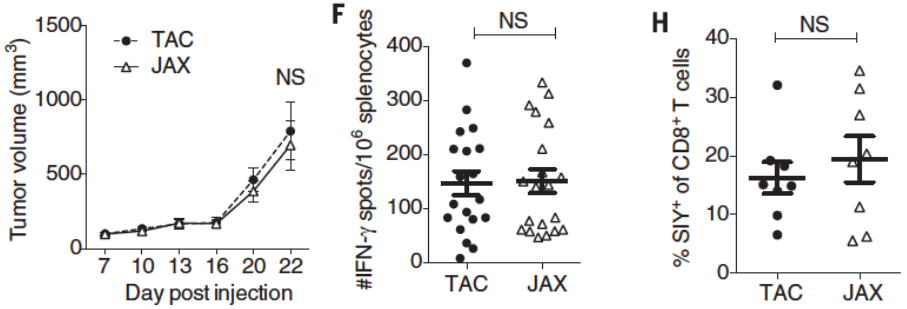
Microbiota Influences Anti-PDL1 Immunotherapy

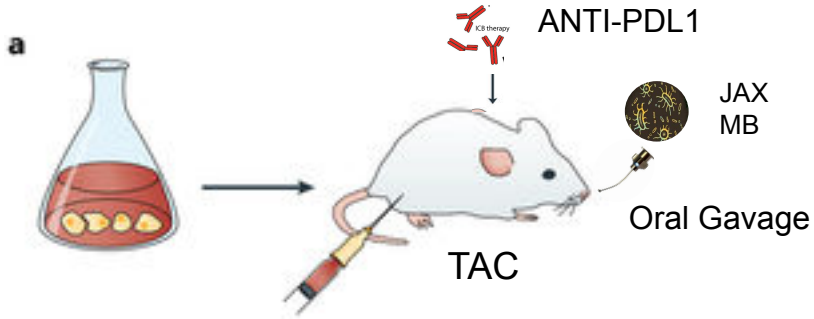


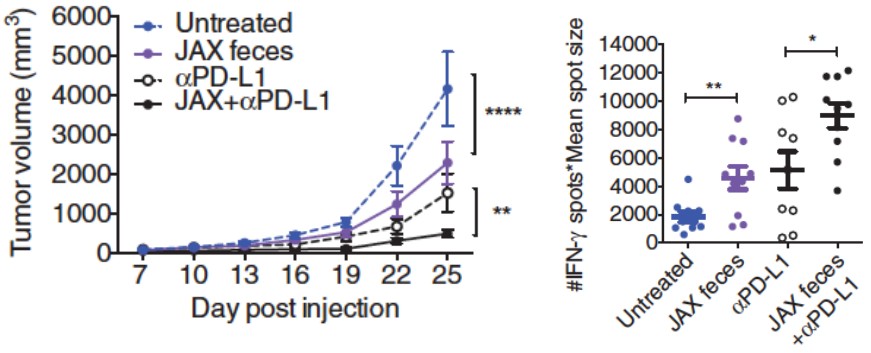


CO-HOUSING: hybrid Microbiota



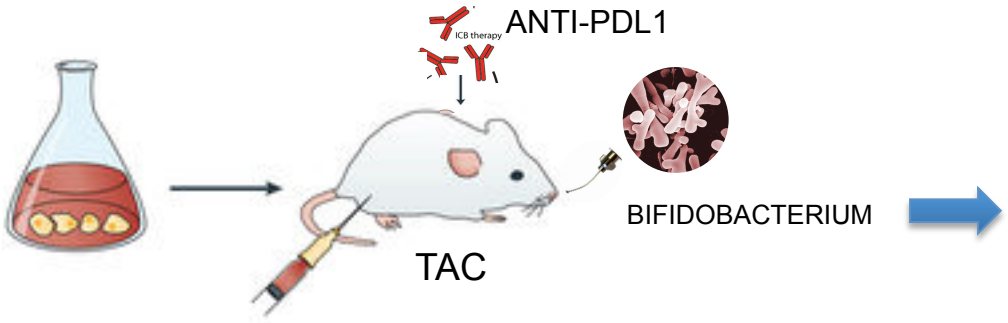




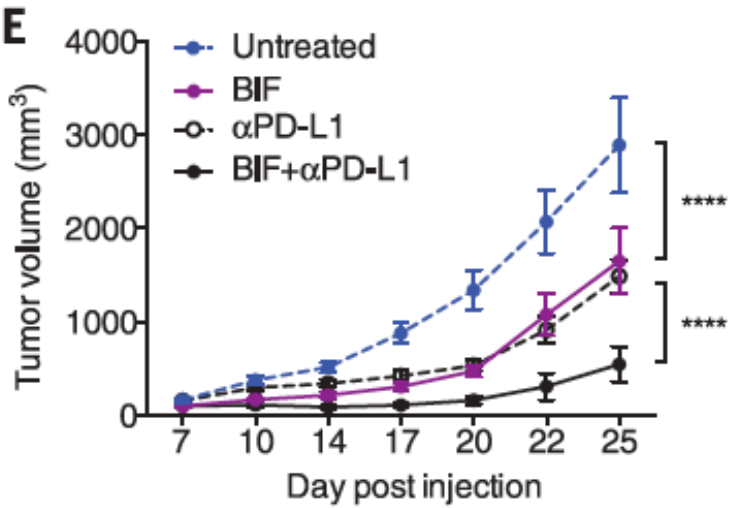


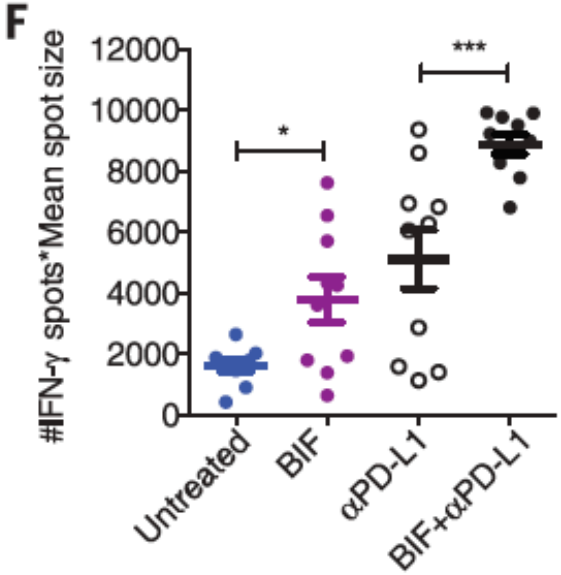
Sivan et Al. Science 2015

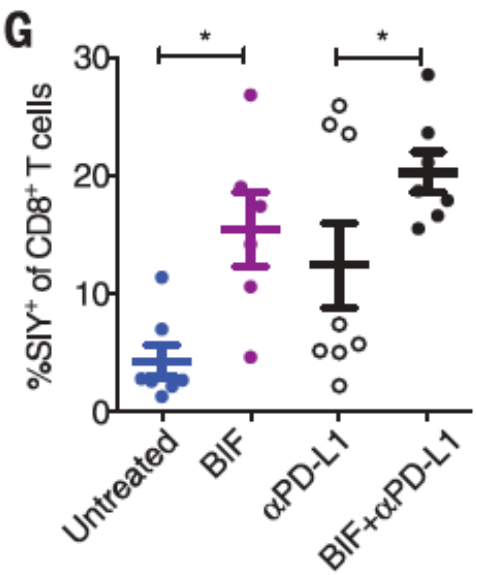
Bifidobacterium facilitates anti PD-L1 efficacy



Induces augmented DC function and enhanced $CD8^+$ T cell priming

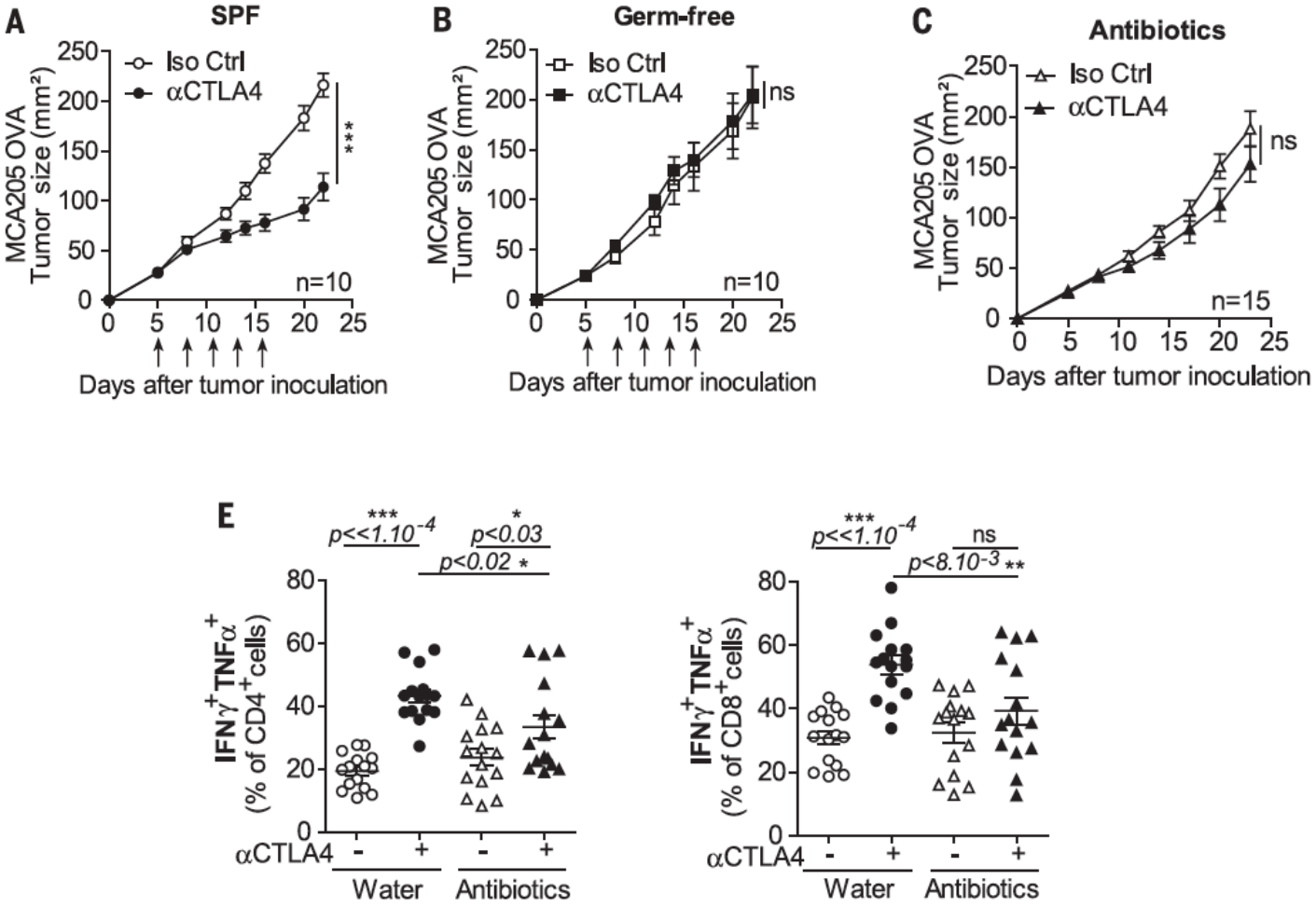






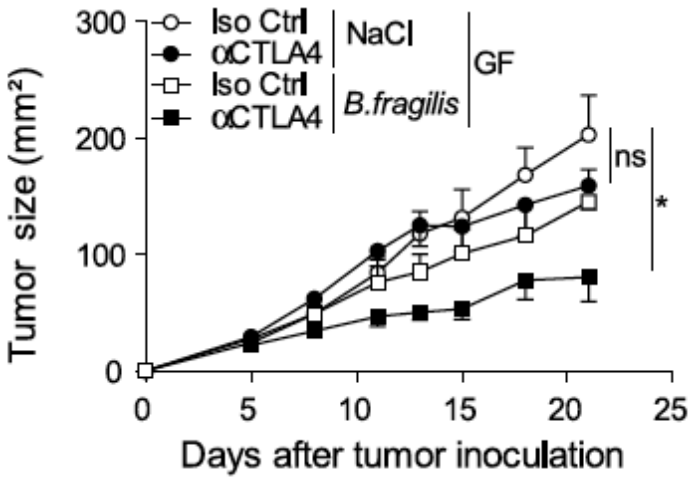
Sivan et Al. Science 2015

Microbiota is Required for the Immunomodulatory Effect of Anti CTLA-4

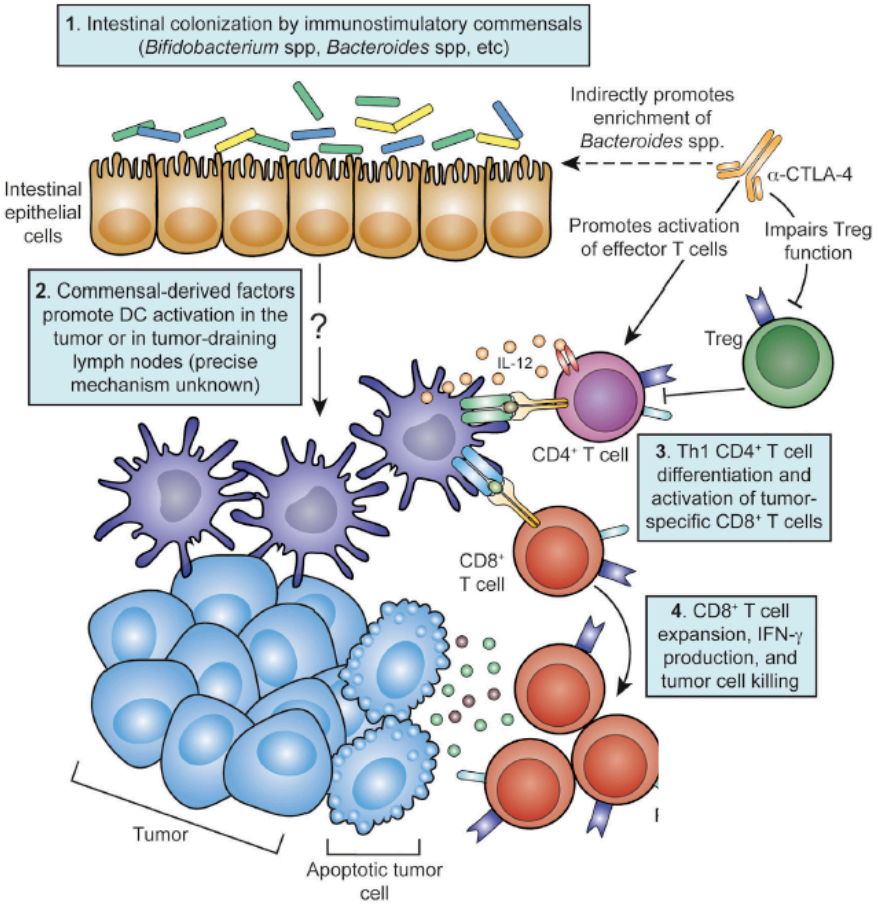


Vetizou et Al. Science 2015

Anti CTLA-4 favours the Overgrowth of *Bacteroides Fragilis* that Boosts anti Cancer Immunity



Colonization of germ free mice with B. Fragilis improved the anti tumoral response of anti CTLA-4 therapy



Vetizou et Al. Science 2015

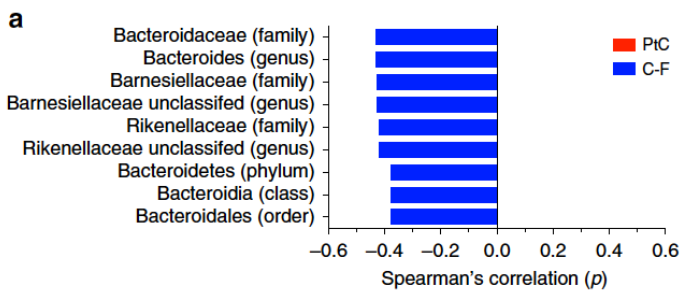
Human Studies

nature COMMUNICATIONS

Received 11 Nov 2015 | Accepted 7 Dec 2015 | Published 2 Feb 2016

Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis

Krista Dubin[1,2,3], Margaret K. Callahan[4,5], Boyu Ren[6], Raya Khanin[7], Agnes Viale[8], Lilan Ling[2], Daniel No[2], Asia Gobourne[2], Eric Littmann[2], Curtis Huttenhower[6,9], Eric G. Pamer[1,2,10,*] & Jedd D. Wolchok[4,5,10,11,*]



ASCO-SITC
CLINICAL IMMUNO-ONCOLOGY SYMPOSIUM
January 25-27, 2018 | San Francisco Marriott Marquis | San Francisco, CA | #ImmunoOnc18

DEVELOPMENTAL THERAPEUTICS—IMMUNOTHERAPY

Association of the diversity and composition of the gut microbiome with responses and survival (PFS) in metastatic melanoma (MM) patients (pts) on anti-PD-1 therapy.

Jennifer Ann Wargo, Vancheswaran Gopalakrishnan, Christine Spencer, Tatiana Karpinets, Alexandre Reuben, Miles Cameron Andrews,

Analysis of 113 fecal samples of patients with MM treated with anti PD-1

- ❑ The gut microbiota of responders had a greater diversity
- ❑ Responders had increased abundance of Clostridiales (specifically the Ruminoccocaceae family)
- ❑ No association between oral microbiome and response to therapy

Future Directions: Microbiota as Biomarkers

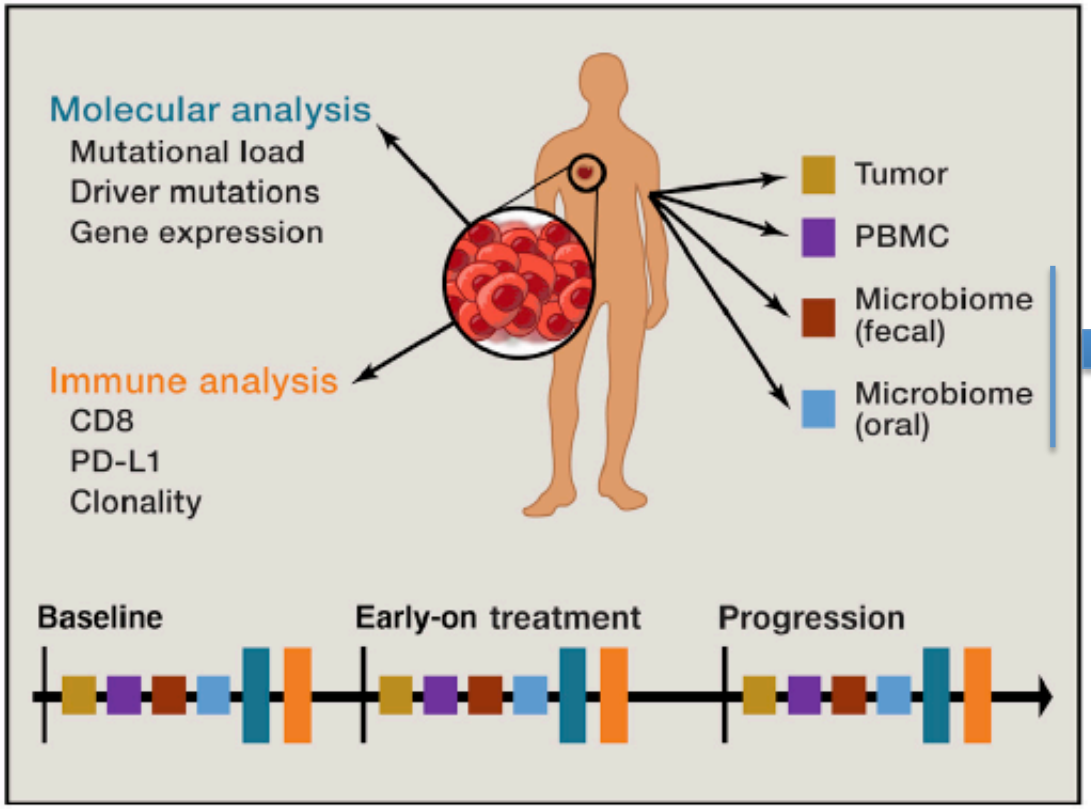
Leading Edge
Review

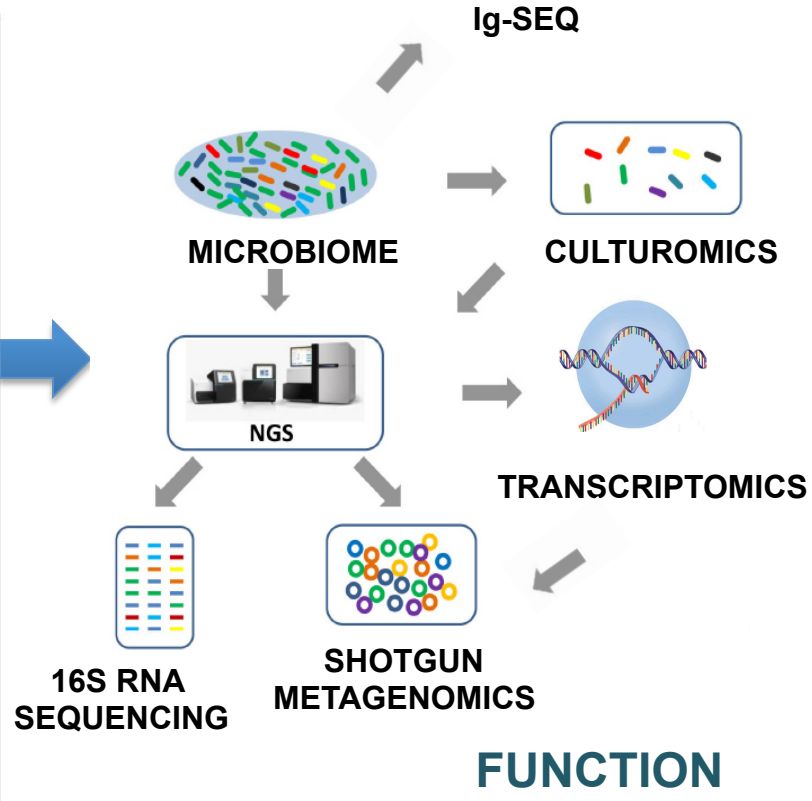
Cell

Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy

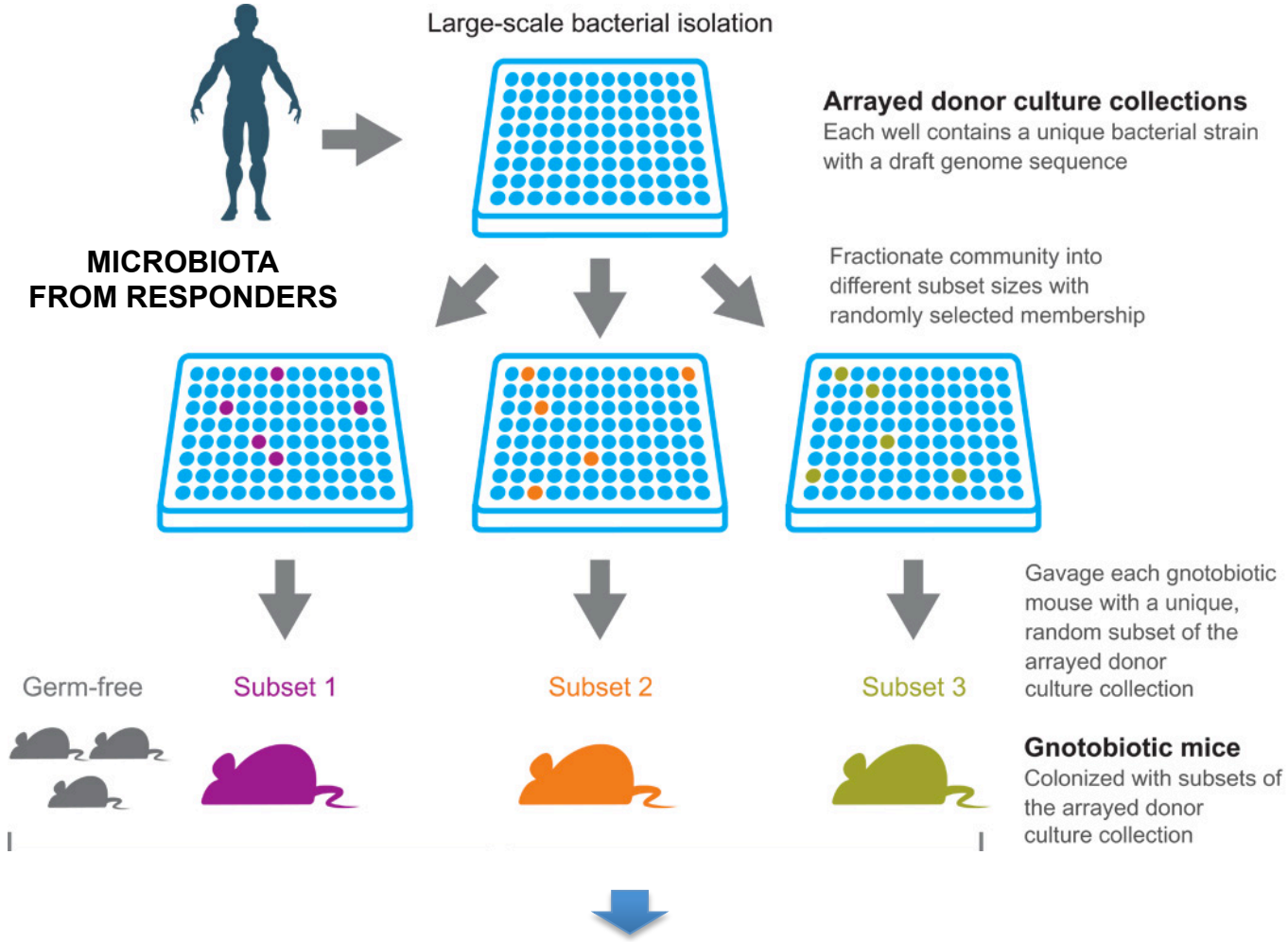
Padmanee Sharma,[1,*] Siwen Hu-Lieskovan,[2] Jennifer A. Wargo,[3] and Antoni Ribas[2,*]

Cell *168*, February 9, 2017 © 2017 Elsevier Inc.

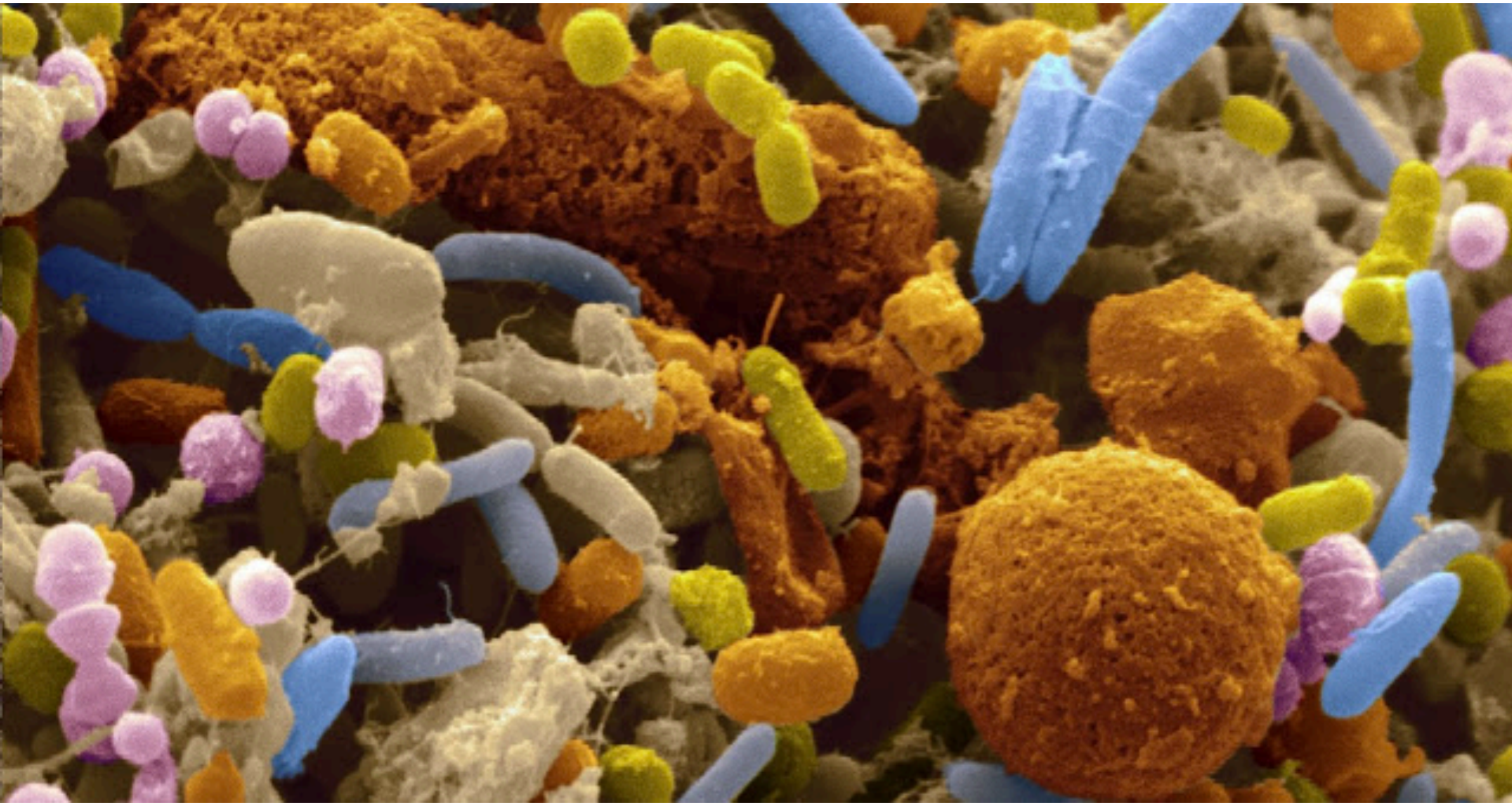




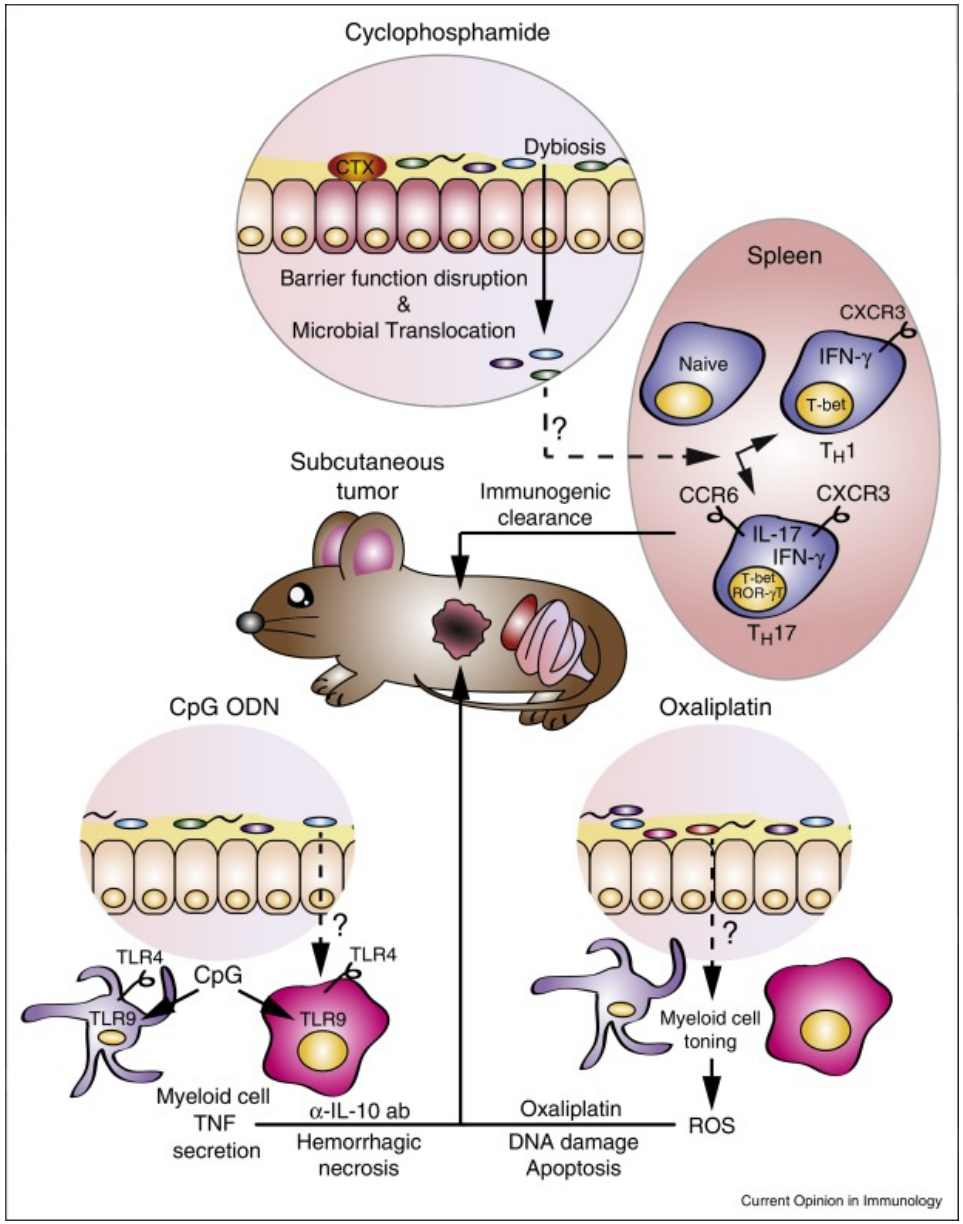
Future Directions: Probiotics



TEST EFFICACY IN MODULATING CANCER IMMUNOTHERAPY IN MOUSE MODELS



Thank you for Your Attention

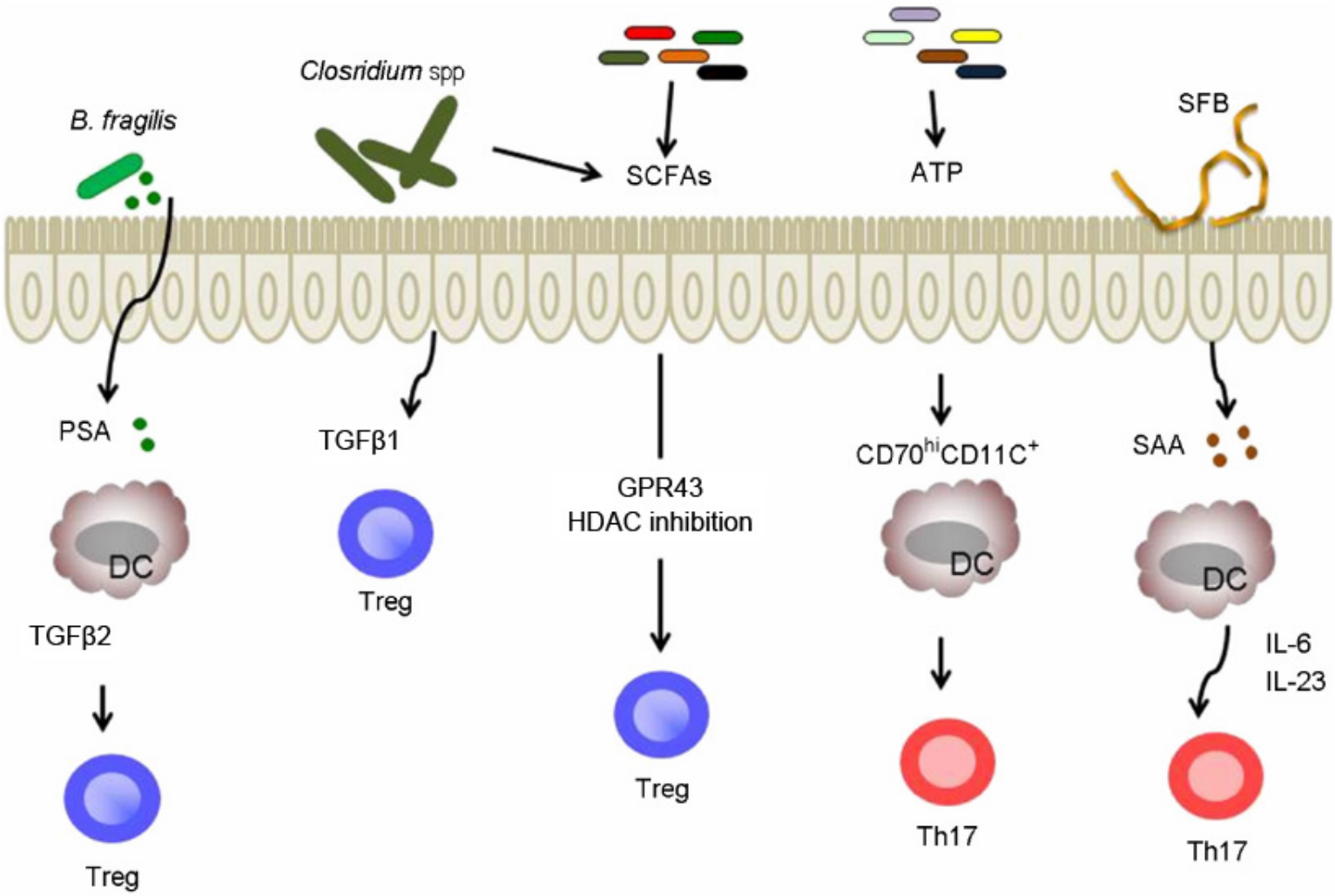


MICE GERM FREE OR ANTIBIOTIC TREATED MICE BEARING SUBCUTANEUS SYNGENIC TUMOURS DO NOT RESPOND TO CHEMOTHERAPIES (OXALIPLATIN AND CYCLOPHOSPHAMIDE) AS WELL AS THEIR MICROBIOTA SUFFICIENT COUNTERPARTS.

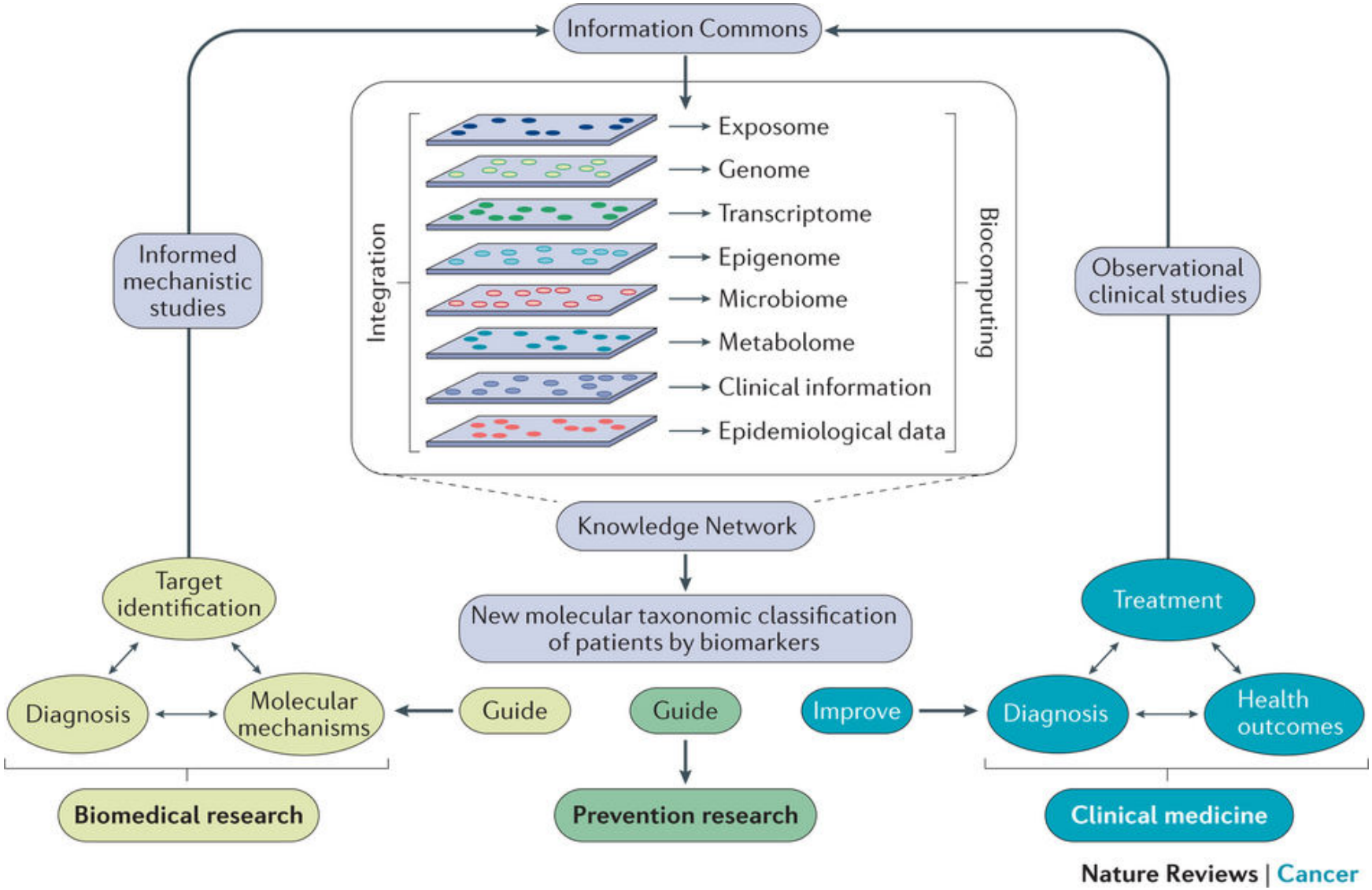
CTX->TRASLOCATION OF DISTINCT GRAM+ BACTERIA (ENTEROCCOCCUS HIRAE LACTOBACILLUS JOHNSONII) FROM THE GUT TO SECONDARY LYMPHOID ORGANS→ INDUCTION OF TH17 TH1 EFFECTOR T CELLS THAT CONTRIBUTE TO THE ANTI-TUMOUR EFFICACY OF CTX

OXALIPLATIN- HEALTHY MICROBIOTA IS NECESSARY FOR THE TUMOR INFILTRATION OF MIELOID CELLS WHICH PROMOTE TUMOR REGRESSION BY PRODUCTION OF OXIGEN REACTIVE SPECIES.

Influence of the Microbiota on T cells



Future Directions



Nature Reviews Cancer **16**, 525–537 (2016)