PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

The Parker Institute's Collaborative and Integrated Approach to Immuno-Oncology Biomarkers

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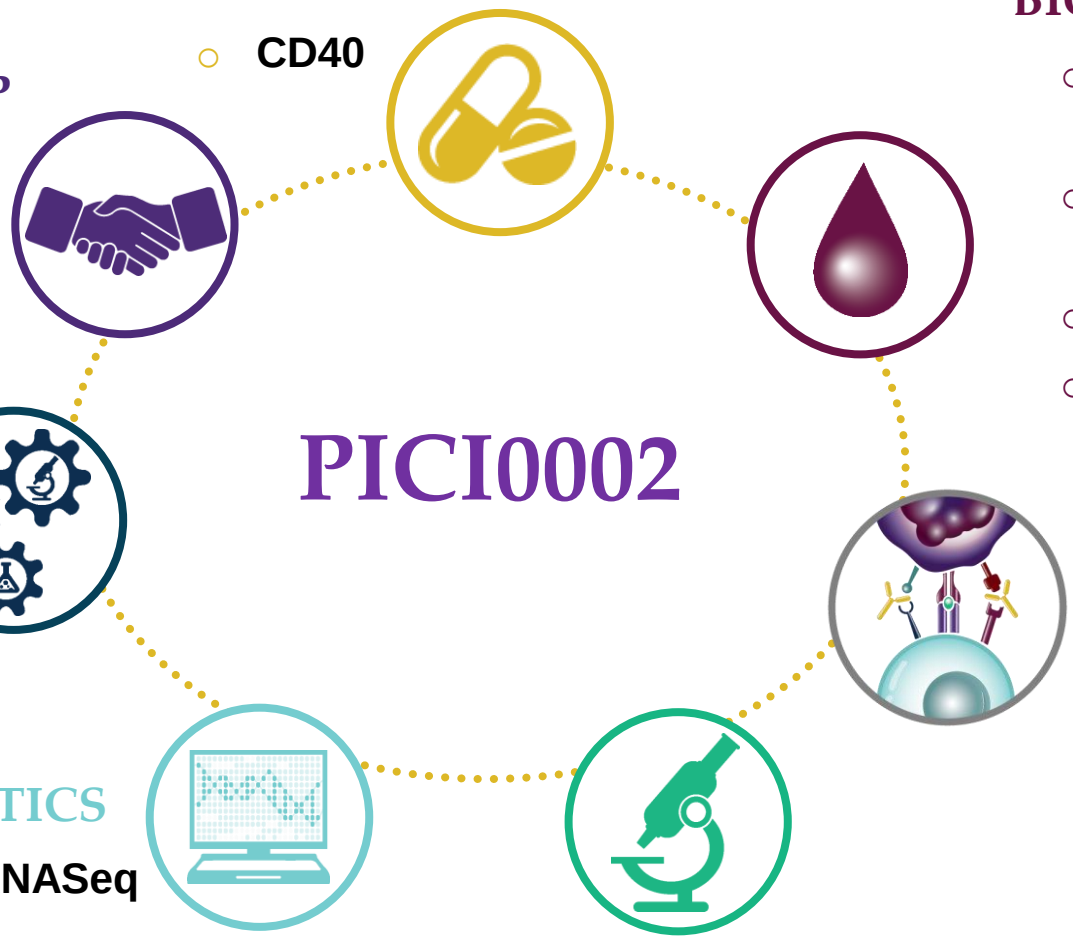
PICI's Approach

- We **bring together the field's top scientists** to conduct big bold research that gets to patients faster
- We **break down barriers** that impede progress so we can do **our most ambitious work**
- We provide the **most innovative tools and resources** to fuel groundbreaking discoveries
- We **foster a culture of trust** to elevate our work and speed up discoveries

PICI Clinical Studies - Deep Immune Profiling



CLINICAL/BD PARTNERSHIP

- BMS
- Apexigen

- Gem/nab-P
- CD40

BIOREPOSITORY

- Pre-tx and on-tx biopsies (when feasible)
- Longitudinal blood samples (PK, PD)
- cfDNA analysis
- Microbiome collections

CLINICAL INFRASTRUCTURE

- IND Sponsor
- Trial design, execution and monitoring
- Data collection/ cleaning/analysis

IMMUNE MONITORING

- CyToF *(PICI Panel)*
- Cytokine profiling

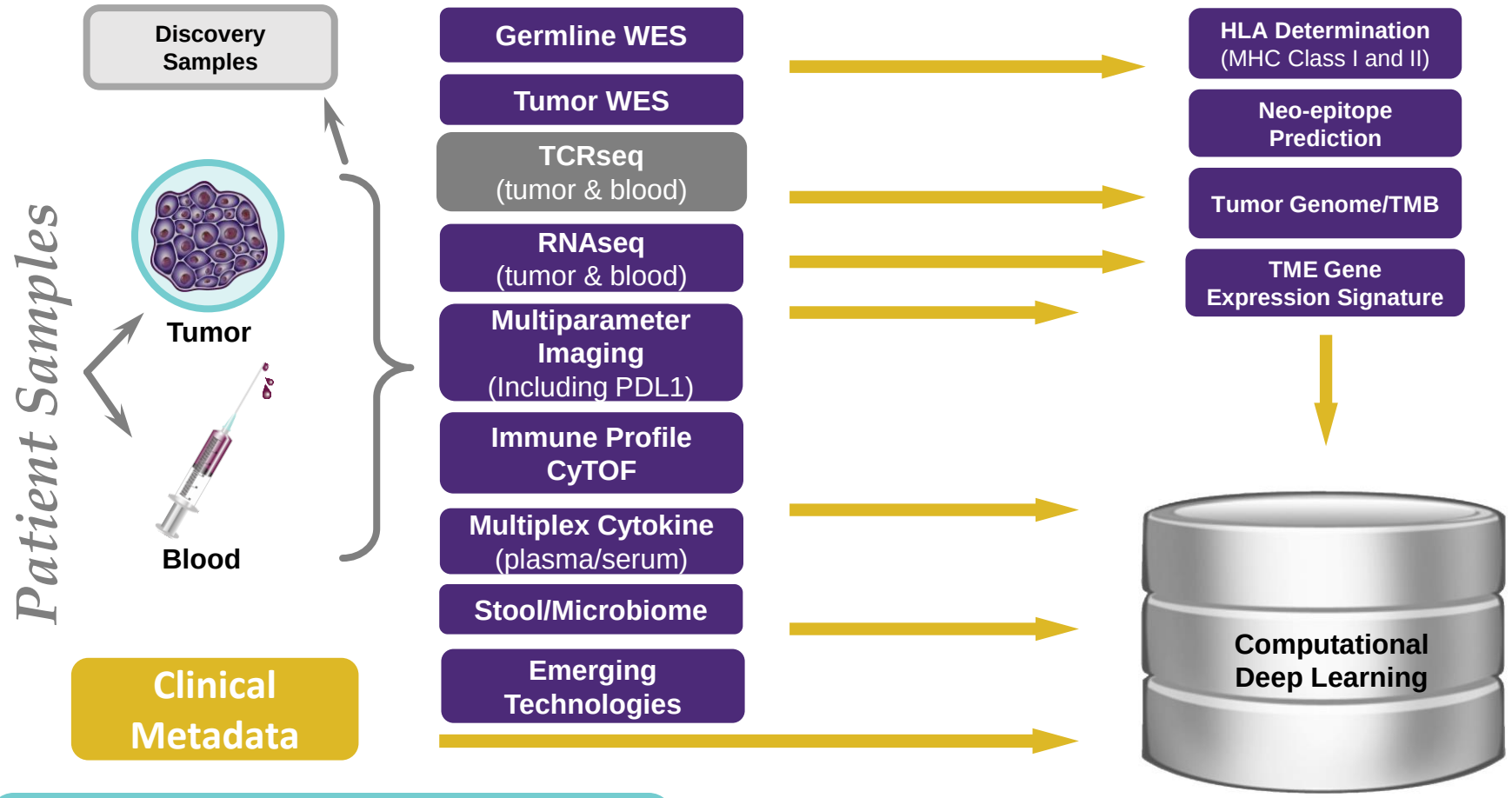
INFORMATICS

- WES/RNASeq
- TMB
- TCR analysis
- Single cell analysis

TISSUE IMAGING

- MIBI
- Vectra Multiplex IHC

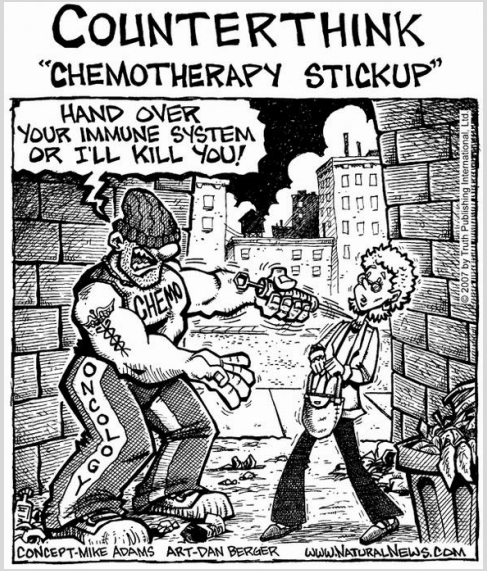
The Parker Translational Suite: Deep Immune Profiling



Harmonized methods of collection and processing at a central biorepository

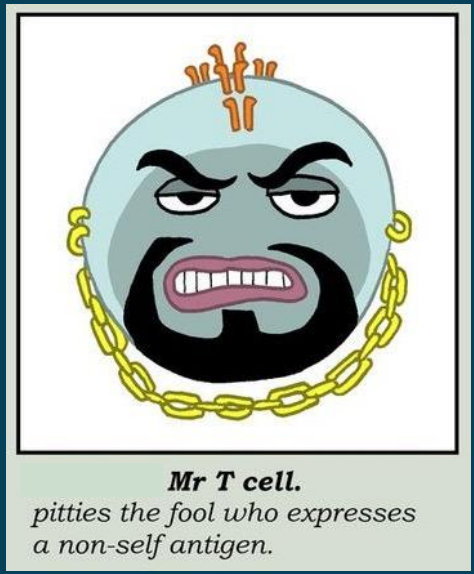
Changing the Paradigm

CHEMO / RADIATION / SURGERY



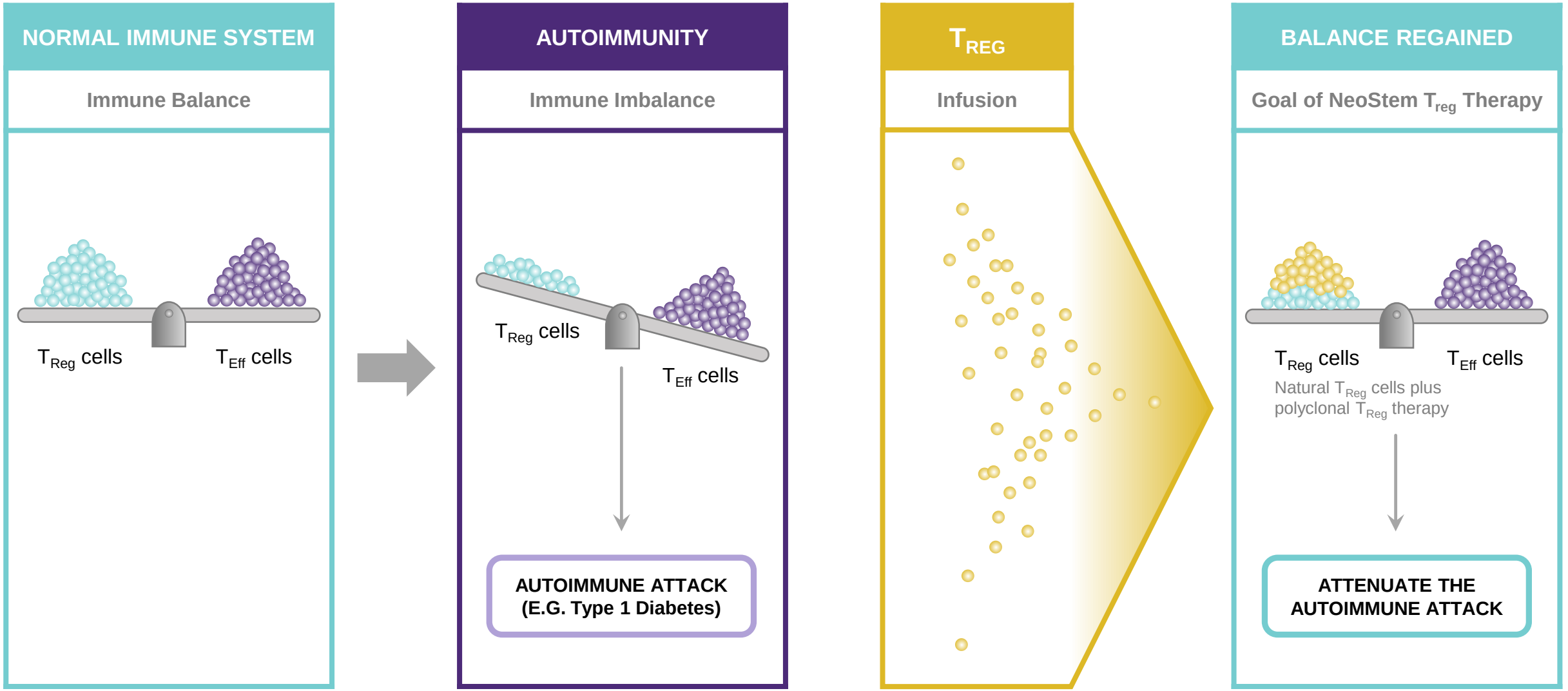
- Cut it out (if possible)
- Poison the tumor
- Wait for escape
- Poison again

IMMUNOTHERAPY



- Re-educate the immune response to treat tumors as **non-self**
- Unleash the immune system brakes and turn on the gas
- Specificity, memory, durability and infectious anti-tumor activity

The Immune System: A Balancing Act



Learning from Infectious Disease Vaccination

Vaccine Strategies – Lessons from Infectious Disease

Confounding variables – what's the intrinsic immune capacity of the individual "Immune Health State"

- Genes, environment, microbiota

Treatment variables – what to dose, how to dose and how much?

- Initiate clinical vaccine trials with multiple technologies
- Determine most effective technology for immunity – Ag design and adjuvants
- Select technologies adaptable to neoantigens – optimal epitope presentation

Immunity readout- define hyporesponsive at baseline and define protective immunity in response to Rx

- Cell mediated immunity
- Ab response
- Type I IFN signatures
- Genetic factors

Collaborate to Advance Personalized Treatments

OPPORTUNITY

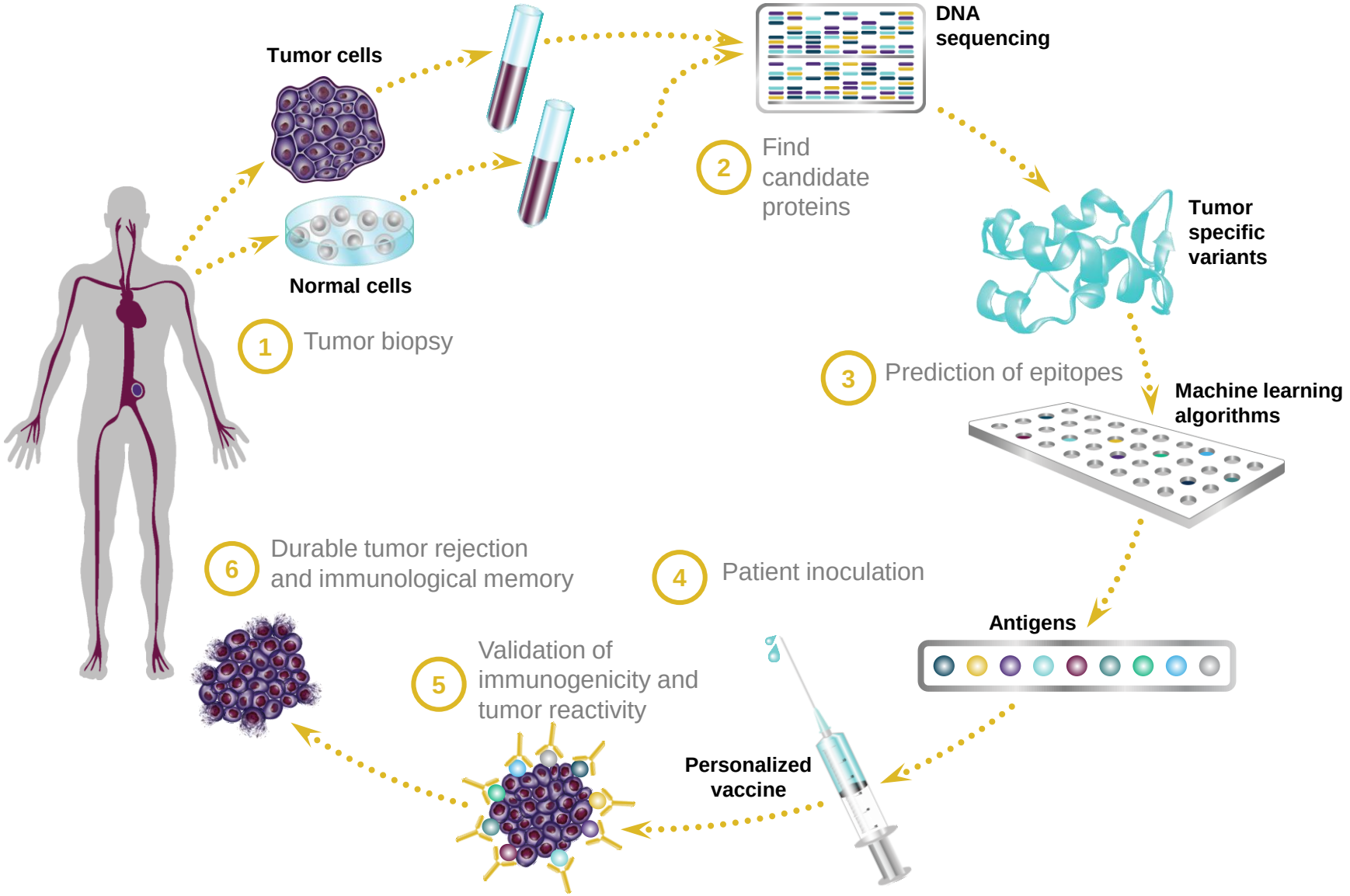
Advance personalized cancer treatments through neoantigen discovery

OUR PROGRESS

Neoantigen Discovery

- Brought together **40 of the world's leading cancer neoantigen research groups**
- Our goal: identify the **best algorithms** to predict which cancer neoantigens can be recognized by and stimulate an immune response
- **Completed first two rounds of predictions** to determine vaccine targets in **melanoma and non-small cell lung cancer**

Tumor Antigen Discovery



Are irAEs Pharmacodynamic Readouts – Autoimmunity?

”

Community Wide Effort to Create a New Response Criteria

Clinical Cancer Research

Cancer Therapy: Clinical

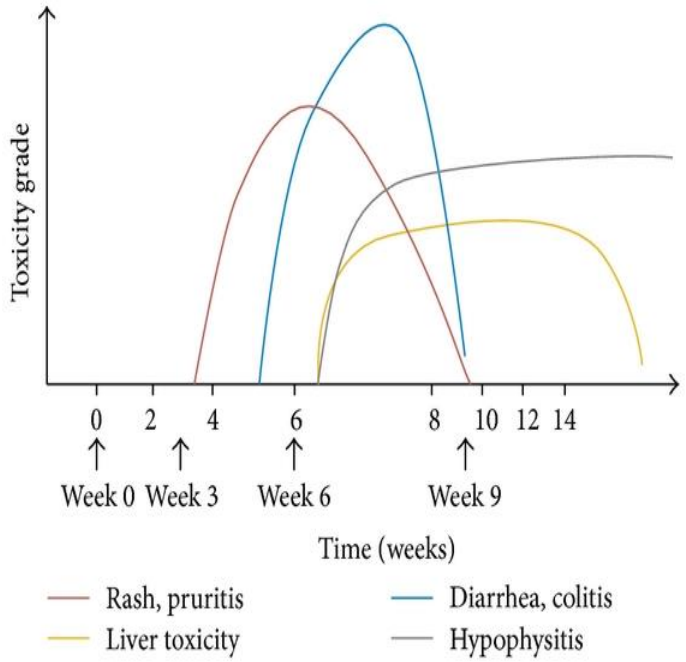
Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok, Axel Hoos, Steven O'Day, Jeffrey S. Weber, Omid Hamid, Celeste Lebbé, Michele Maio, Michael Binder, Oliver Bohnsack, Geoffrey Nichol, Rachel Humphrey, and F. Stephen Hodi

DOI: 10.1158/1078-0432.CCR-09-1624 Published December 2009

Adverse Events are Unique Too: Immune Related Adverse Events irAEs

Immune related adverse events were mostly transient “inflammatory in nature” and reversible with the appropriate intervention



Weber et al. Journal of Clinical Oncology, vol. 30, no. 21, pp. 2691–2697, 2012.

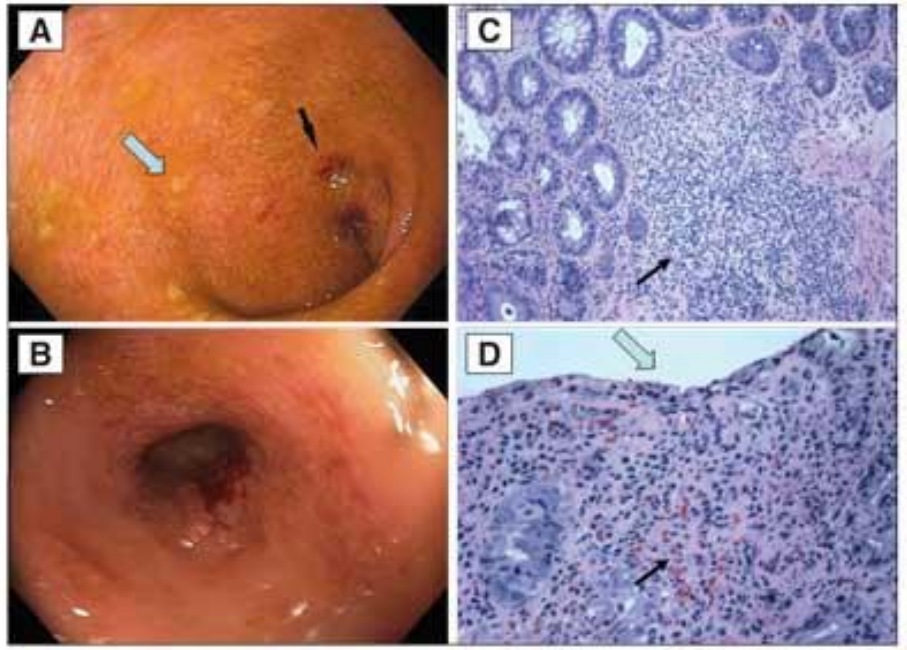
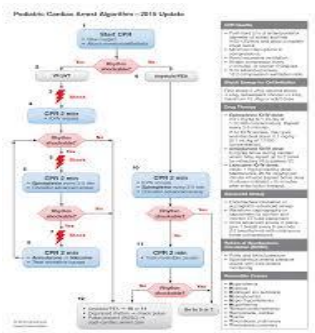
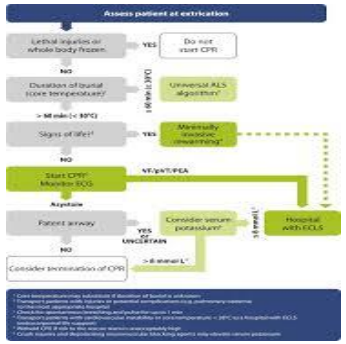
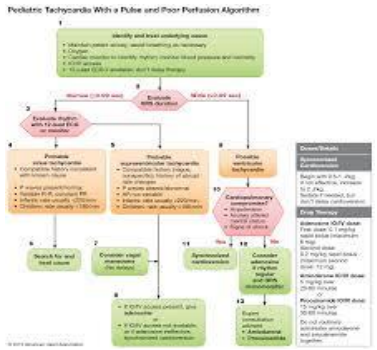


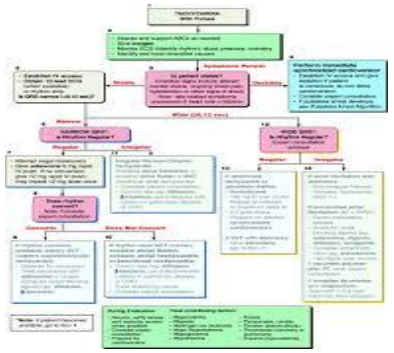
Figure 1: Colonoscopy and Histopathological Findings in an Ipilimumab-Treated Patient With Colitis — The endoscopic appearance of ulcerated **(gray arrow)** and bleeding **(black arrow)** colonic mucosa is shown in **A** and **B**; **C** and **D** show the histological features of ulceration **(gray arrow)** and inflammatory infiltration **(black arrow)** associated with ipilimumab-induced autoimmune colitis.

Development of Toxicity Management Guidelines









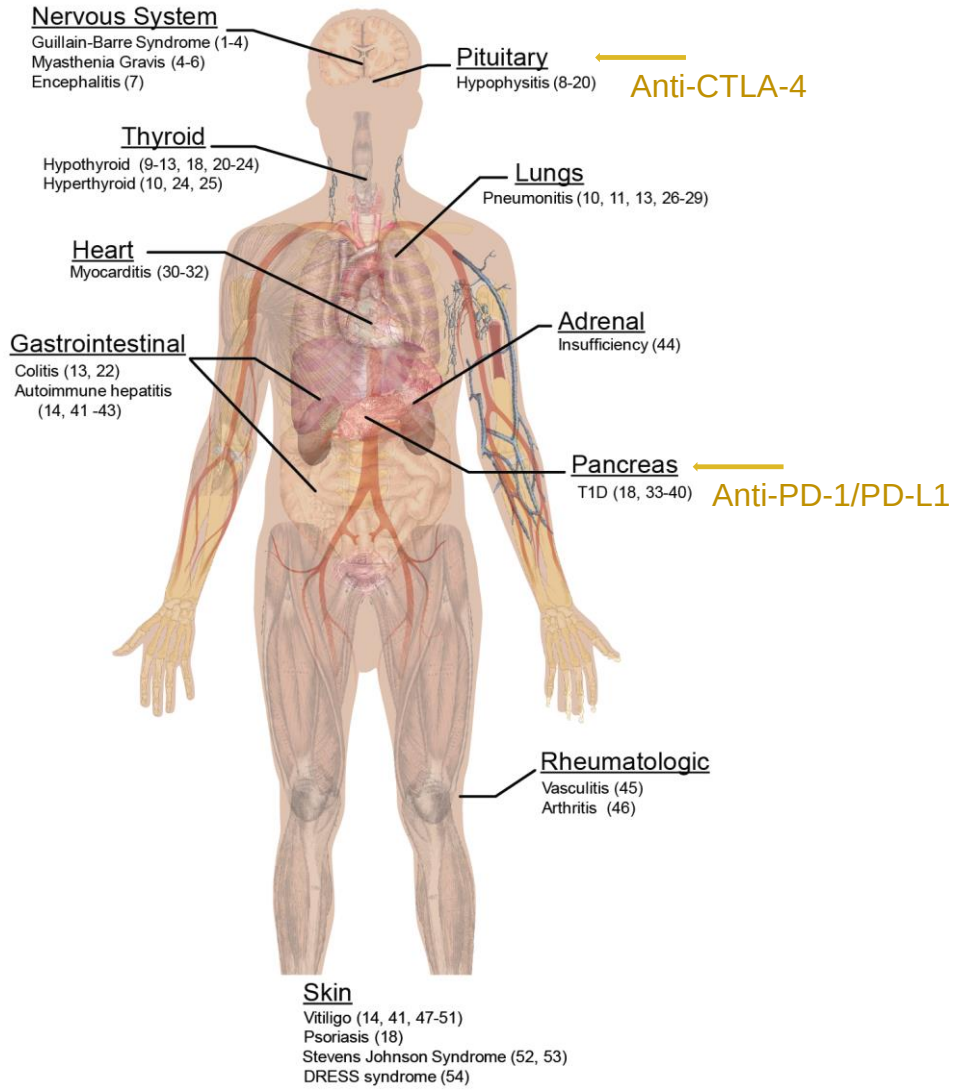
Bottom line:

1. Patient and physician education
2. Early detection and intervention
3. Steroids can reverse most of those events

Oct 2016

Friends and Parker Institute for Cancer Immunotherapy Summit: Optimizing the Use of Immunotherapy

Autoimmune Disorders Associated with Cancer immunotherapy



- Different manifestations depending on checkpoint inhibitor
- Effects can be immediate or long after treatment
- Can multi-organ
- Rarely reversible
- Unknown mechanism
  - Genetic predisposition
  - Epitope-spreading
  - Tumor destruction
  - Breakdown of tolerance
- Limited preclinical models

Autoimmunity and Cancer Program

Purpose

- Generate insight into the mechanisms behind immune-related adverse events (irAEs) following checkpoint inhibition (CPI) in cancer patients
- Identify at-risk patients early and reduce the incidence and/or severity of such events

Status

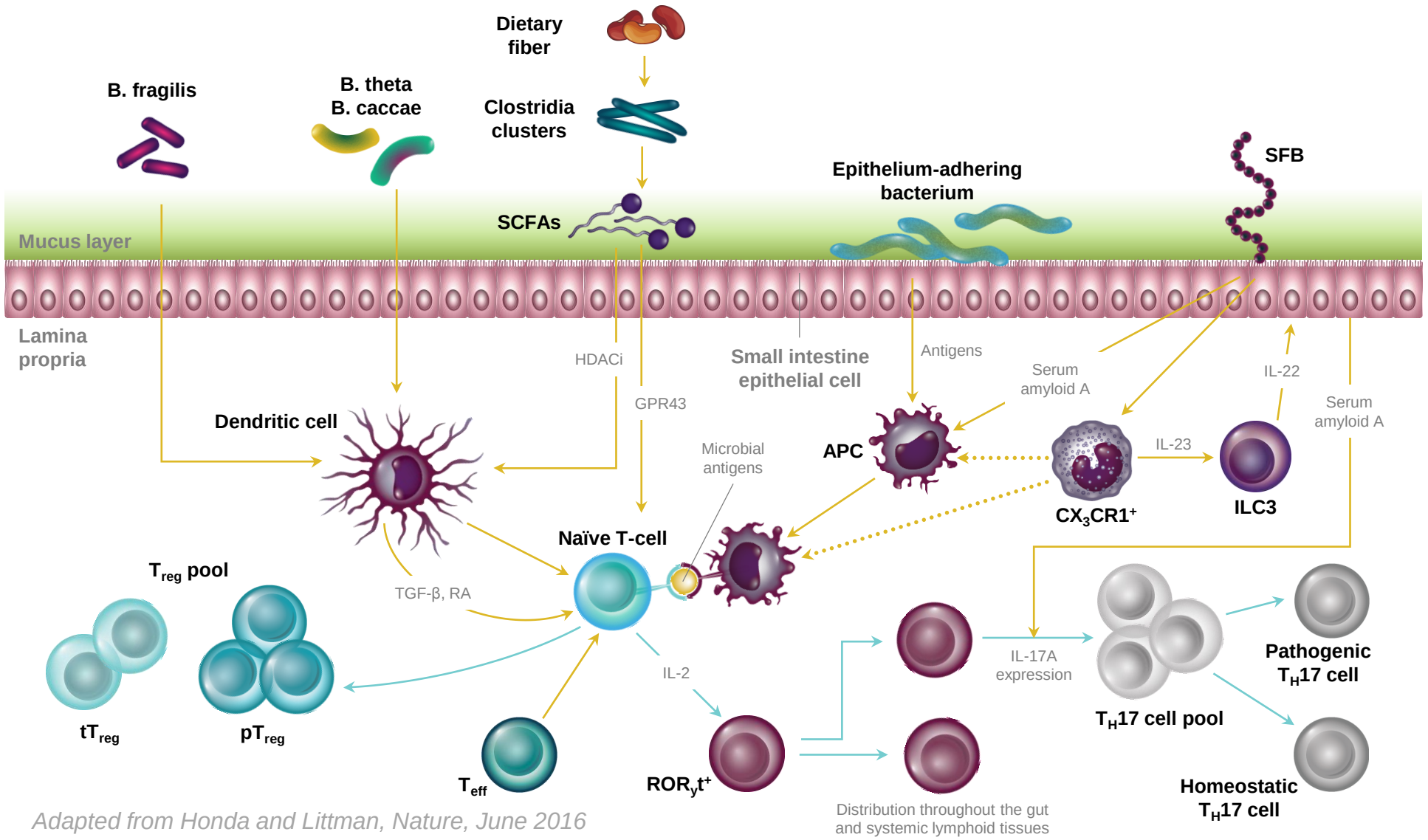
- Four small collaborative projects are being funded
- Larger collaboration with Helmsley Trust/JDRF in discussion
    - Bring together a small group of key opinion leaders from IO and autoimmunity
    - Develop a plan for a more comprehensive project to study irAEs following CPI
- Provided letters of support for member researchers applying for NCI, ACS, etc. grants

What's Next

- PICI is developing a prospective sample collection protocol
- Biobank with prospective sample collections; pre- and post-treatment with CPIs
- Share with collaborators to explore the mechanisms behind CPI-induced irAEs

THE MICROBIOME AND DISEASE

Gut Microbiome-Immune System Interactions



Adapted from Honda and Littman, Nature, June 2016

Microbiota Linked to Disease

Disease	Relevant Finding	Date
Psoriasis	Increased ratio of Firmicutes to Acintobacteria	2008
Reflux esophagitis	Esophageal microbiota dominated by gram-negative anaerobes Gastric microbiota with low or absent *H. pylori*	2002 2008
Obesity	Reduced ratio of Bacteroidetes to Firmicutes	2006
Childhood-onset asthma	Absent gastric *H. pylori* - especially cytotoxin-associated gene (*cagA)* genotype	1996
IBD (colitis)	Increased *Enterobacteriaceae*	2010
Colorectal carcinoma	Increased *Fusobacterium spp.*	2012
Cardiovascular disease	Gut microbiota-dependent metabolism of phosphatidylcholine	2011

Cho and Blaser, "The Human Microbiome: at the interface of health and disease," Nature Reviews Genetics, Mar. 13, 2012

Differences in Gut Microbiome: Anti-PD-1 Responders v. Non-responders

Responders

- More heterogeneous
- More Clostridiales, Faecalibacteria, Ruminococcaceae [ ]

Non-responders

- Less heterogeneous
- More Bacteroidales [ ]

Gopalakrishnan and Wargo et al, AACR 2017, ASCO 2017

Collaborate for Better Responses to Cancer Therapy

OPPORTUNITY

Understand the role the microbiome plays in cancer immunotherapy treatments

OUR PROGRESS

- Launching **first-of-its-kind microbiome-cancer immunotherapy trial** for advanced melanoma patients
- Collaborating with **MD Anderson Cancer Center** and **Seres Therapeutics**
- Based on Dr. Jen Wargo's recent study published in *Science*

PICI Translational and Clinical Analysis PlatformCapabilities – Assess Immune Health and Tumor Immunity