

Microbiome – The Gut Brain

Longitudinal Studies with Open Access to Metadata

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Microbiome – The forgotten Organ

- The gut microbiome is a potent modulator of the immune system
- Pre-clinical studies by Gajewsky¹ and Zitvogel² et al. have reported that the gut microbiota modulates the efficacy of immune checkpoint blockade therapy.
- Pamer and Wolchok³ et al. demonstrated that gut microbiota could predict ipilimumab-induced colitis in melanoma patients.
- Wargo⁴ et al. suggested a signature of gut microbiota composition may predict response of melanoma patients to checkpoint blockade.

Microbiome – the hidden Treasure

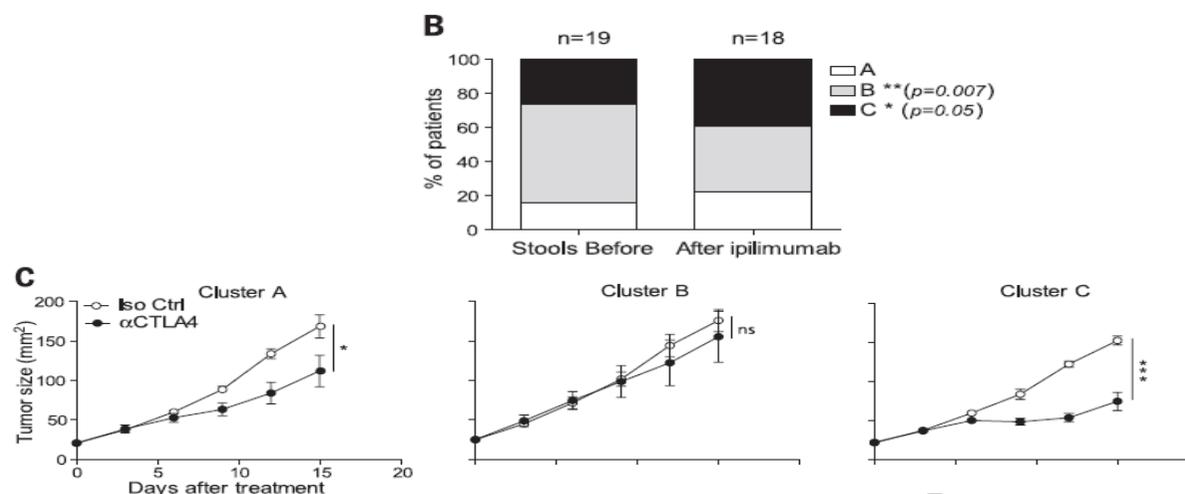
1. The host microbiota plays an important role in shaping systemic immune responses
2. Recent studies suggest possible roles of host microbiota in affecting the responses to IO therapies
3. The microbiota-immunity field is still at an early stage. This presents an opportunity for industry and academia to explore and potentially leapfrog the regular development timelines

CANCER IMMUNOTHERAPY

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

CANCER IMMUNOTHERAPY

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



Marie Vetizou... Laurence Zitvogel, Science NOV 27, 2015; Ayelet Sivan...Thomas F Gajewski, Science Nov 27, 2015

We know what we don't know.....

- What is a “normal” microbiome?
 - Lifestyle, lifestyle changes, vaccinations
- How is the microbiome influenced by diet, probiotics, smoking,....
- Pre-analytical conditions?
 - How to collect
 - How to ship
- How and what to analyze
 - Bacteria
 - Virus
 - Yeast
- Bioinformatics - clustering of the data

Great Potential of the Microbiome Initiative

Multiple shots on goal

- **Microbiome as a therapeutic target**
 - Influencing the microbiome to prevent diseases
 - Changing the microbiome to augment treatment outcomes
 - Functional food
 - Probiotics or contra-biotics
- **Microbiome as Biomarker**
 - Predict response to therapy – IO or TT (pre-treatment signatures)
 - Prognostic for therapeutic response
- **Microbiome as monitoring tool**
 - Longitudinal changes during therapy (on-treatment signatures)
- **Data drive future drug design based on functional ecological networks**

Working Hypothesis

- Derive robust microbial-composition signatures and corresponding microbial-functional-pathway signatures that correlate with tumor response to IO and / or TT
- Develop a pretreatment signatures into a predictive biomarker of response
- On-treatment samples will be informative of temporal changes that occur in microbiota composition or metabolites in responders vs non-responders upon treatment → designing consortia of bacteria for use as therapies.
- Functional pathway analysis
 - SCFA (i.e. butyrate) associated with increased Treg populations and as a consequence might be associated with less response⁵

Path to Win

- Analyze host microbiota in I-O and TT trials/treatments to correlate microbiota makeup and abundance to clinical outcome.
 - Host microbiota as one of the patient/indication selection criteria for I-O and TT trials/treatments
- Augment host baseline microbiota for I-O and TT trials through microbiome reconstitution.
- Facilitate new drug discovery programs based on the understanding of microbiota and immune modulation.
- Combined microbiome analysis with molecular markers of the host (e.g. cytokines for autoimmune diseases).
- Longitudinal studies should start as soon as possible (before birth, pregnant mothers).
- Involve consumers and not only patients (educational efforts).
- Open access to metadata

Strategy to address Microbiome Research

- **Cross SGG Initiative**
 - Technical issues, data standards, sample collecting / sampling standards
 - “normal’ Microbiome
 - Microbiota changes under supplements, probiotics etc.
- **SGG Oncology Project**
 - Microbiome as response predictor / biomarker
 - Microbiome as enrichment strategy
- **Other SGG projects**
 - Ongoing efforts in Diabetes
 - Planned efforts in Infection Control and autoimmune disorders

Microbiome –Key Deliverables

- **Create (stool) databank** incl all relevant patient information to analyze correlations between the composition of the gut microbiome and to be defined physiological and pathophysiological conditions
- Define or **identify groups/clusters/strains** of bacteria which have a **prognostic/predictive value** in terms of the wellness of an individual patient under different physiological and pathophysiological conditions
- Develop strategies to **influence the microbiome** e.g. an appropriate diet or medication to positively impact the composition of the microbiome as a pre- or co-treatment of cancer patients under chemo- or immunotherapy **to enhance response or duration of response**

Discussion

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