Understanding responses to cancer immunotherapy: the tissue is the issue, but the scoop is in the poop

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Understanding responses to cancer immunotherapy:
The tissue is the issue, but the scoop is in the poop
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• I have the following financial relationships to disclose:
  - Speaker’s bureau: Imedex, Dava, Omniprex, Illumina, BMS
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  • I am an advisor to Microbiome DX
• I am co-Inventor on patent submitted by The University of Texas MD Anderson Cancer Center to the US Patent and Trademark Office based on this work (Patent # PCT/US1/53717)
Despite these advances responses are heterogeneous and are not always durable, and toxicity can be an issue...

There is a critical need to better understand who will benefit from therapy, as well as proper timing, sequence and combination of different therapeutic agents.
How can we better understand responses to therapy and optimize treatment regimens?
Responses are dependent on factors shaping tumor growth and immunity.
Translational research in tumors of patients on checkpoint blockade reveals molecular and immune mechanisms of response & resistance.

Molecular and immune profiling performed in longitudinal tumor samples during therapy.

Mechanisms of resistance were identified, with defects in IFN signaling & antigen processing / presentation, as well as a high burden of copy number loss.

These studies also revealed that adaptive immune signatures in early on-treatment biopsies are highly predictive of response.

With Jim Allison, Pam Sharma, Andy Futreal, Lynda Chin, Arlene Sharpe, and others.

Chen et al, Cancer Discovery 2016
Roh et al, Science Translational Medicine 2017
Translational research in novel clinical trials is also providing insights into mechanisms of response and resistance to checkpoint blockade.

**Inclusion Criteria**
- Resectable stage IIIB/IIIC, oligometastatic stage IV melanoma
- >1 site amenable to biopsy

**Exclusion Criteria**
- Brain, bone mets, LMD
- Active, known autoimmune disease
- Systemic steroid use (>10 mg prednisone daily)
- Prior anti-PD1/PD-L1, CTLA-4 treatment

**Study Design**
- **Ipi 3mg/kg + Nivo 1 mg/kg**
  - q 3 wks x 3 doses (n=20)
- **Nivo 3mg/kg**
  - q 2 wks x 4 doses (n=20)

**Primary Endpoint:**
Path CR rate at surgical resection

**Secondary Endpoints:**
- RFS
- DMFS
- OS
- Toxicity
- Immune Monitoring

**Molecular & immune profiling in longitudinal tissue and blood samples**

**Presidents: Rodabe Amaria & Jennifer Wargo**

**Presented by Dr. Sangeetha M. Reddy at the Presidential Session of The Annual Meeting of the Society of the Immunotherapy of Cancer**

**Presidential award nominee**
Environmental factors (such as the **microbiome**) may also impact responses.

THE HUMAN MICROBIOME

100 trillion microbes

3% human body mass

1-10X microbes : human cells

10-100X microbial : human genes

largest # microbes – GI tract

Slide credit: Ami Bhatt and Robert Jenq
There Human Microbiome Project (HMP) helped to define the composition of the microbiome in healthy individuals.
Disturbances of the gut microbiome (dysbiosis) are implicated in a large number of diseases.
Could the microbiome become the newest frontier in the fight against cancer, with “single cell techniques” employed in diagnostic and therapeutic strategies?
How can we characterize the microbiome?
16s and whole genome shotgun sequencing (WGS) are useful tools in characterizing the microbiome.

**Metrics:**

- **Diversity:** elucidates distribution and assembly patterns of microbial communities.
- **Types of diversity**
  - $\alpha$ - intra-sample
  - $\beta$ - inter-sample
- **Relative abundance:** bacterial communities analyzed as discrete OTUs, and frequency of an OTU relative to all others is quantified.
What is the role of the microbiome in cancer?
There is a growing appreciation of the role of the microbiome in cancer
Bacteria in tumors of cancer patients may mediate resistance to therapy

Geller et al, Science – published September 15, 2017

With Ravid Straussman Todd Golub, Keith Flaherty, Curtis Huttenhower et al
There is also strong evidence that bacteria in the gut may influence responses to cancer therapy (particularly immunotherapy).
The gut microbiome may influence responses to SCT and checkpoint blockade

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

Composition of the gut microbiome is associated with differential responses to checkpoint blockade in murine models

Sivan...Gajewski Science 2015, Vetizou...Zitvogel Science 2015
Based on this evidence, we wanted to better understand the role of the gut microbiome in response to checkpoint blockade in patients with melanoma.
Hypothesis

• Differential bacterial “signatures” exist in responders versus non-responders to immune checkpoint blockade

• Favorable signatures will be associated with an enhanced anti-tumor immune response (with increased CD8+ T cells, as well as evidence of an enhanced innate immune response)

• Insights gained could lead to strategies to enhance responses to therapy (through modulation of the microbiome)
We studied oral and gut (fecal) microbiome in a large cohort of patients with metastatic melanoma going onto systemic therapy.
Is there an association between the diversity of the microbiome and response to anti-PD-1 in patients with metastatic melanoma?
The diversity of the oral and gut microbiome were analyzed in responders versus non-responders to PD-1 blockade.

Patients with metastatic melanoma going onto aPD-1 were enrolled onto protocol and microbiomes were profiled (n=105). “Responders” CR, PR, SD for at least 6 months. “Non-responders” PD. PFS also assessed.

Restaging scans performed at week 12 & RECIST responses were measured.

Responders to anti-PD-1 therapy had a higher diversity in their gut microbiome than non-responders (with no differences noted in the oral microbiome).

Higher diversity of the gut microbiome is associated with improved PFS on melanoma patients on anti-PD-1 therapy (no difference in oral microbiome).

Is there an association between the *composition* of the microbiome and response to anti-PD-1 in patients with metastatic melanoma?
Patients with metastatic melanoma going onto aPD-1 were enrolled onto our microbiome protocol.

"Responders" CR, PR, SD for at least 6 months

"Non-responders" PD

Restaging scans performed at week 12 & RECIST responses were measured

Significant differences were noted in composition in the gut microbiome of responders vs non-responders

No substantial differences were noted in composition in the oral microbiome of responders vs non-responders

What is the relationship between the gut microbiome and anti-tumor immunity in this cohort?
Anti-tumor immune responses were assessed and were compared to the composition of the gut (fecal) microbiome in patients on anti-PD-1.

High abundance of Ruminococcus & Faecalibacteria in the gut was associated with cytotoxic T cells in TME.

Differences in composition of the gut microbiome were associated with differences in PFS on aPD-1.

What is the mechanism through which a “favorable” gut microbiome may enhance responses to checkpoint blockade?
We are gaining insight into how the gut microbiome influences responses to checkpoint blockade.

Mice with a “favorable” gut microbiome and enhanced response to checkpoint blockade had more functional antigen-presenting cells (DCs) capable of priming an antigen-specific T cell response.

Differences in the metabolic profiles of gut bacteria in responders versus non-responders to anti-PD-1 were noted in our cohort.

Similar findings in our patients treated with anti-PD-1 (multiplex IHC panel developed by Lisa Coussens PhD, Staining performed by Alex Reuben PhD)

Sivan…Gajewski Science 2015

Zitvogel et al, Cell 2016

We are now building on these studies to further investigate the mechanism and to test strategies to enhance therapeutic responses.

Germ-free mice receiving FMT from responders have delayed tumor growth and enhanced response to aPD-L1.

Presented by Dr. Vancheswaran (Deepak) Gopalakrishnan at the Annual Meeting of the Society of the Immunotherapy of Cancer.

Importantly, other groups have made similar observations in other cancer types

**Routy B., L. Zitvogel. Gut microbiota determines efficacy of PD-1 blockade against lung and renal carcinoma.**

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

**Ruminococcaceae and Akkermansia muciniphila contrasted responders from NR**

(shotgun MG in 107 pts)

Other studies are emerging on gut microbiome and response to checkpoint blockade in patients…

Combination immunotherapy approaches through understanding the tumor, host, and the microbiota

(Gajewski – AACR Annual Meeting 2017)

Metagenomic shotgun sequencing to identify specific human gut microbes associated with immune checkpoint therapy efficacy in melanoma patients (Koh Neoplasia 2017)

Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab – Chaput et al, Annals of Oncology 2017

FMT from NSCLC pts in GF mice predicted response to aPD-1, and oral gavage of specific bacteria (A. muciniphila) restored sensitiviy to aPD-1

Cancer and the Microbiome
Does your gut hold the key to your cancer?
Can we modulate the gut microbiome to enhance responses to immunotherapy?

YES!
We are working with the Parker Institute for Cancer Immunotherapy and others to implement a clinical trial to test the hypothesis that modulation of the gut microbiome will enhance responses (using FMT and other strategies).
Conclusions and potential implications of these findings:

• There is increasing evidence for the role of the microbiome in health and disease, and evidence that the gut microbiome may influence responses to cancer therapy.

• This raises important questions in the context of immunotherapy:
  - should we be profiling the microbiome of patients going onto therapy?
  - should we also be limiting (or closely monitoring) antibiotic use in these patients?
  - do we need to consider diet / pro-biotic intake in these patients?
  - do we also need to consider the role of the microbiome in pre-clinical models?

• There is also now strong evidence to suggest that modulation of the microbiome can enhance responses to immune checkpoint blockade and other forms of immunotherapy, though this needs to be tested carefully in the context of clinical trials.

• There is still a great deal to learn, and the strongest gains are made through collaboration (and we owe this to our patients).
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