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# Immune checkpoint inhibitors and the union of bugs against cancer

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In 2011, the first immune checkpoint inhibitor (ICI) therapeutic antibody was approved by the US Food and Drug Administration for the treatment of advanced melanoma. Based on Phase III trials, 6 different ICI agents are now approved for the treatment of a range of tumors, including renal cell carcinoma, and, most recently, for any solid tumor with genetic instability (Table 1). These agents act by unleashing the power of the immune system via targeting of inhibitory T-cell immune checkpoint pathways, including the receptor programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) system, and the related CTLA-4 costimulation pathway. By pharmacologic blockade of these pathways, suppressive influences are removed, unleashing active immune responses mediated by T cells and other cells that in health are responsible for antitumor immune surveillance. Dozens of additional ICI agents are currently in development.

At present, clinical responses to ICI therapy are quite heterogeneous and of variable durability. In most trials, although only a subset of participants display clinical responses, the benefits can be remarkable. Yet >60% of all patients display primary resistance to ICI treatment, which has been linked to a number of factors intrinsic to the tumor (i.e., low mutational burden and poor antigenicity of tumor cells), to the host immune response (i.e., defective antigen presentation or exhaustion of the tumor-infiltrating lymphocytes), or arising from their functional interactions (i.e., local immunosuppression by extracellular metabolites).[1] Following a 2015 report on clinical responses in patients receiving anti-CTLA-4 ICI,[2] in early 2018 a flurry of reports has further highlighted the influences of a previously unsuspected internal universe on ICI responsiveness. These studies, including 3 studies published concurrently in *Science*,[3–5] provide evidence that ICI responsiveness may be determined by the community of commensal bacteria that reside within the intestine, referred to as the gut microbiome.

Our immune systems evolved in the presence of microbes that individually, or in combination, serve a number of functions indispensable to host survival. Indeed, the gut microbiome is essential for (i) modulation of the availability of nutrients for metabolism, (ii) the degradation of medications and availability of a range of immunomodulatory factors, and (iii) the priming of innate and adaptive immune cells that determines triggering thresholds

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DISCLOSURE

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for immune responses. In some animal models of inflammatory and autoimmune diseases, individual gut bacterial species, which in health are commensals or sym*bionts* with the host, have been shown to affect disease susceptibility, acting akin to opportunistic *patho*gens, hence the term *pathobiont*. In other models, individual microbial species may instead display antiinflammatory influences by directly or indirectly mediating the expansion of immune cells including regulatory T cells (Tregs), which may be induced by gut resident dendritic cells. Although Tregs have been shown to protect against autoimmunity and inflammatory conditions, in solid tumor models Treg expansion is associated with disease progression and worse clinical outcomes. Most importantly, preclinical mouse models with orthotopic tumor transplants suggest that responsiveness to cancer immunotherapy is affected by the composition of the microbiome.[6]

In health, the gut microbiome is a complex and dynamic community, generally composed of >1000 phylogenetically distinct taxa. To survey the landscape within these complex communities, culture-independent technologies have been developed that are based on taxonomic profiling by 16S ribosomal RNA gene sequence analysis. In randomized controlled trials of patients with advanced malignancies, including renal cell carcinoma,[3] analyses of prospectively collected fecal samples demonstrated that patients nonresponsive to ICI treatment often have significantly contracted gut microbial communities, with reduced diversity of distinct identifiable species or taxa. These contracted gut communities were often linked to recent oral antibiotic treatments for dental, urinary, and pulmonary infections that are common in patients with malignancy.[3]

Based on 16S rRNA analyses, ICI non-responsiveness was also found to be correlated with imbalances within gut microbiome communities, termed dysbiosis, characterized by overrepresentation of specific bacterial species, such as within the Bacteriodiales order.[5] In contrast, responder status was associated with expansions of other anaerobic taxa, such as from the Clostridiales family[5] or from common anaerobic commensals.[4] However, the particular species that was identified differed between reports,[3–5] and it is currently unclear whether these differences derive from variance inherent to the patient populations under investigation or nuances between the different analytic methods applied. Clinical improvement was correlated with enhanced *in vitro* T-cell response to individual candidate bacterial species[4] and, in another report,[7] with decreased frequency of peripherally derived colonic Tregs, increased frequencies of dendritic cell subsets associated with antitumor immune responses, and greater responses from T helper cell (Th1) and/or $CD8^+$ T-cell subsets.

To assess the influences of the gut microbiome in a particular donor, fecal microbiota transplants were given to recipient mice raised germ-free or with drastically reduced gut communities from broad-spectrum antibiotics. In the current studies, only certain donor samples were found to restore antitumor benefits of ICI treatment[4]; in particular, fecal microbiota transplants from mice obtained from 2 different vendors had different effects. Although immune-mediated tumor control was not associated with fecal microbiota transplants from mice obtained from Taconic Biosciences (Rensselaer, NY), fecal microbiota transplants from mice obtained from The Jackson Laboratory (Bar Harbor, ME) conveyed antitumor benefits.[6] These findings contrasted with an earlier report that Taconic

mice harbor a pathobiont commensal species, which was required to evoke a severe form of genetically linked autoantibody-associated inflammatory arthritis in predisposed murine hosts.[8]

However, our current focus on the contributions of individual taxa to biases in global immune set points may not always be relevant, as gut communities are generally quite complex and the life cycles of individual taxa are often interdependent. Moreover, as experimental monocolonization by an individual species does not have a physiological analogue, the experimental focus is now shifting to transfers of mixed commensal communities and to defining the molecular mechanisms by which microbes may affect the efficacy of ICI treatments.[6]

In summary, the current state of the art suggests that the clinical miracles imparted by ICI agents to some patients with malignancy may be directly or indirectly linked to the influence of pathobionts within the gut microbiome. It is interesting to speculate that differences in the gut microbial composition may also influence the risk of immunemediated adverse events, including interstitial nephritis and immune-complex glomerulonephritis, which have been reported with ICI therapy. In the future, enhanced clinical benefits may be conveyed by improved ICI formulations and combination regimens, but there may also be clinical opportunities to optimize the internal commensal communities that appear to be fundamental determinants of the clinical response to ICI.

From a wider perspective, we should also ponder whether the increasing frequencies of advanced malignancies may have origins akin to those implicated in the current epidemics of autoimmune and allergic disease. To variable degrees, the rising occurrence of all of these conditions could be, in part, an unforeseen consequence of our habitual overuse of antibiotics and excessive hyper hygiene, which reduce the complexity and result in the loss of keystone species in our inner commensal universe.[9]

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**Table 1 |**

Approved immune checkpoint inhibitors and indications

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| **Currently approved immune checkpoint inhibitors** |
| *PD-1 inhibitors* |
| Pembrolizumab (Keytruda) |
| Nivolumab (Opdivo) |
| *PD-ligand 1 inhibitors* |
| Atezolizumab (Tecentriq) |
| Avelumab (Bavencio) |
| Durvalumab (Imfinzi) |
| *CTLA-4 inhibitor* |
| Ipilimumab (Yervoy) |
| **Currently approved indications** |
| Renal cell carcinoma |
| Urothelial cell carcinoma |
| Non-small cell carcinoma |
| Metastatic melanoma |
| Hodgkin’s lymphoma |
| Head and neck cancer |
| Hepatocellular cancer |
| Stomach cancer |
| Merkel cell carcinoma |
| Any solid tumor with positive biomarkers (i.e., microsatellite and genetic instability) |