MedicalXpress

Human microbiome-derived bacterial strains with antitumor activity

January 24 2019

Vedanta Biosciences, a clinical-stage company developing a new category of therapies for immune-mediated diseases based on rationally defined consortia of human microbiome-derived bacteria, today announced a publication in *Nature* reporting a newly discovered mechanism underlying antitumor immunity that involves human microbiota-driven induction of interferon-gamma-producing (IFNγ+) CD8+ T cell accumulation in the gut and tumors. Led by Vedanta's scientific co-founder Kenya Honda, M.D., Ph.D., of Keio University School of Medicine, the research also led to the identification and selection of a defined consortium of human microbiome-derived bacterial strains that harnesses this mechanism of antitumor activity and cooperatively potentiates responses to checkpoint inhibitor therapies and immune challenges in general. Based on this research, Vedanta is advancing VE800, a proprietary clinical candidate designed to enhance immune responses against cancer. Vedanta plans to initiate clinical studies in 2019 to evaluate VE800 in combination with Bristol-Myers Squibb's checkpoint inhibitor OPDIVO (nivolumab).

"This research demonstrates that specific, human microbiome-derived bacteria assembled rationally into consortia can cooperatively enhance the responses to immune checkpoint inhibitors, which supports our hypothesis that modulating the gut microbiota could be a powerful tool for potentiating immune responses that help fight cancer and infection," said Bernat Olle, Ph.D., Chief Executive Officer of Vedanta Biosciences. "This work also builds upon Dr. Honda's previous groundbreaking research on the role of the human microbiome in

modulating a range of immune responses and provides a robust scientific foundation for our proprietary lead cancer candidate, VE800."

The authors of the *Nature* paper sought to understand the previously poorly characterized relationship between the human microbiota and intestinal IFNy+ CD8 T cells, which are critical to innate and adaptive immune responses. In preclinical models, they were able to establish that the number and frequency of these immune cells in the gut depend on the presence of a gut microbiota and are plastic, with specific members of the microbiota promoting their intestinal accumulation in an inducible and reversible manner. The authors went on to identify specific commensal bacterial strains from healthy human donors that spurred the production of IFNy+ CD8+ T cells.

Through rigorous selection, the authors isolated a defined consortium of commensal bacteria derived from the human microbiome that proved most effective at inducing rapid and persistent accumulation of IFNy+ CD8+ T cells. Mice colonized with the defined bacterial consortium demonstrated enhanced therapeutic efficacy in a range of tumor models when given in conjunction with PD-1 or CTLA4 immune checkpoint inhibitors. The strains identified are primarily rare, low-abundance components of the human microbiome, representing a significant opportunity for amplification as a therapeutic strategy.

The research demonstrates for the first time that human microbiome-derived bacterial consortia that cooperatively enhance the responses of immune checkpoint inhibitors can be identified. The authors addressed the challenge of reducing a complex community of human microbiome bacteria down to a few, rationally defined members that can induce a robust immune potentiation response necessary for an effective cancer immune therapy, and directly linking their activity to pathways that promote antitumor immunity.

The *Nature* paper also found that human stool samples showed considerable variability in their ability to induce colonic IFNy+ CD8+ T cells. Vedanta's development process is designed to bypass this variability by using pure, clonal cell banks of well-characterized bacterial strains isolated from healthy humans to produce defined consortia of uniform composition. This eliminates the need to rely on direct sourcing of fecal donor material of inconsistent composition. Vedanta sources bacteria from a vast, extensively characterized collection of 80,000 bacterial isolates obtained from human donors from four continents, which is believed to be the largest collection of human-gut associated bacteria. It then designs high-throughput assays to screen product candidates against a given disease target.

VE800 is Vedanta Biosciences' proprietary oral immuno-oncology product candidate. It consists of a rationally defined bacterial consortium that activates cytotoxic CD8+ T cells, a type of white blood cell that is the predominant effector in cancer immunotherapy. In preclinical studies, VE800 has been shown to enhance the ability of these T cells to infiltrate tumors, thereby promoting suppression of tumor growth and enhancing survival. Data also suggest that VE800 may enhance the effects of checkpoint inhibitors. Vedanta is evaluating VE800 alone and in combination with checkpoint inhibitors as a potential treatment for patients with advanced or metastatic cancers. In December 2018, Vedanta entered into a clinical trial collaboration to evaluate Bristol-Myers Squibb's programmed death-1 (PD-1) immune checkpoint inhibitor OPDIVO (nivolumab) in combination with Vedanta's VE800, in patients with advanced or metastatic cancers. Clinical trials are expected to begin in 2019.

More information: Takeshi Tanoue et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity, *Nature* (2019). DOI: 10.1038/s41586-019-0878-z

Provided by Vedanta Biosciences