PureTech's Vedanta Biosciences Publishes Seminal Research in Leading Scientific Journal for its Immuno-oncology Candidate, VE800

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PureTech Health plc (LSE: PRTC) ("PureTech Health"), an advanced biopharmaceutical company developing novel medicines for dysfunctions of the Brain-Immune-Gut (BIG) Axis, is pleased to note that its affiliate Vedanta Biosciences today announced the publication of important research in one of the top scientific journals, *Nature,* that underlies Vedanta's proprietary oral immuno-oncology product candidate, VE800.

The research revealed a new mechanism by which human microbiota induce an important immune cell that is key to the body's ability to generate antitumor immunity. It also identified a proprietary consortium of bacterial strains that harnesses this mechanism, VE800, which Vedanta Biosciences expects to enter the clinic in 2019 in combination with Bristol-Myers Squibb's checkpoint inhibitor OPDIVO® (nivolumab).

Bharatt Chowrira, JD, PhD, President and Chief of Business and Strategy at PureTech Health, said: "This *Nature* publication reveals – for the first time – that human microbiome-derived bacterial consortia have the potential to enhance and broaden the responses to immune checkpoint inhibitors. The research also led to the selection of VE800, which we believe has tremendous therapeutic potential to treat a broad range of cancers. We look forward to Vedanta's clinical trials of VE800 in combination with Bristol-Myers Squibb's Opdivo (nivolumab), which are planned for 2019."

The full text announcement from Vedanta Biosciences is as follows:

Vedanta Biosciences Announces Publication in Nature of Seminal Research Revealing A New Mechanism of Human Microbiota-Driven Antitumor Immunity Involving Induction of IFNγ+ CD8+ T Cell Accumulation in the Gut and Tumours

Research also identified a rationally-defined consortium of human commensal bacteria (VE800) that robustly induces IFNγ+ CD8+ T cells and enhances antitumor immunity

Vedanta's clinical candidate VE800 is expected to enter clinical studies in 2019 in combination with Bristol-Myers Squibb's checkpoint inhibitor OPDIVO® (nivolumab)

CAMBRIDGE, Mass., Jan. 23, 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* that revealed 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 tumours. Led by Vedanta's scientific co-founder Kenya Honda, MD, PhD, 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, PhD, 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-characterised relationship between the human microbiota and intestinal IFNγ+ 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 IFNγ+ 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 IFNγ+ CD8+ T cells. Mice colonised with the defined bacterial consortium demonstrated enhanced therapeutic efficacy in a range of tumour 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 IFNγ+ CD8+ T cells. Vedanta's development process is designed to bypass this variability by using pure, clonal cell banks of well-characterised bacterial strains isolated from healthy humans to produce defined consortia of uniform composition. This eliminates the need to rely on direct sourcing of faecal donor material of inconsistent composition. Vedanta sources bacteria from a vast, extensively characterised 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.

About VE800

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 tumours, thereby promoting suppression of tumour 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.

About Vedanta Biosciences

Vedanta Biosciences is a clinical-stage company developing a new category of therapies for immune-mediated diseases based on rationally-defined consortia of human microbiome-derived bacteria. Vedanta Biosciences is a leader in the microbiome field with capabilities and deep expertise to discover, develop, and manufacture live bacteria drugs. These include what is believed to be the largest collection of human-gut associated bacteria, a suite of proprietary assays to select pharmacologically potent strains, vast proprietary datasets from human interventional studies, and facilities for cGMP-compliant manufacturing of rationally-defined bacterial consortia in powder form. Vedanta Biosciences' pioneering work, in collaboration with its scientific co-founders, has led to the identification of human commensal bacteria that induce a range of immune responses – including induction of regulatory T cells, CD8+ T cells, and Th17 cells, among others. These advances have been published in leading peer-reviewed journals, including *Science* (multiple), *Nature* (multiple), *Cell,* and *Nature Immunology*. Vedanta Biosciences has harnessed these biological insights and its capabilities to generate a pipeline of programs in infectious disease, autoimmune disease, allergy, and immuno-oncology.

Vedanta Biosciences was founded by PureTech Health (LSE.PRTC). Its scientific co-founders are world-renowned experts in immunology and microbiology who have pioneered the fields of innate immunity, Th17 and regulatory T cell biology, and include Ruslan Medzhitov, PhD, (Yale and Howard Hughes Medical Institute (HHMI)), Brett Finlay, PhD, (University of British Columbia and HHMI), Kenya Honda, PhD, (inventor of Vedanta Biosciences' lead product candidate; Keio University and RIKEN), Dan Littman, PhD, (New York University and HHMI), Alexander Rudensky, PhD, (Sloan Kettering and HHMI), and Jeremiah Faith, PhD, (Mount Sinai School of Medicine).

About PureTech Health

PureTech Health (LSE: PRTC) is an advanced biopharmaceutical company developing novel medicines for dysfunctions of the Brain-Immune-Gut (BIG) Axis. The Company has developed deep insights into the connection between these systems and the resulting role in diseases that have proven resistant to established therapeutic approaches. By harnessing this emerging field of human biology, PureTech Health is developing new categories of medicines with the potential to have great impact on people with serious diseases.

PureTech Health is advancing a rich pipeline of innovative therapies across two divisions: its Affiliates and its Internal labs. PureTech's Affiliates include seven clinical-stage platforms with two product candidates that have been filed with the US Food and Drug Administration (FDA) for review and other novel pre-clinical programmes. These affiliates are developing ground-breaking platforms and therapeutic candidates in collaboration with some of the world's leading experts.

PureTech's Internal research and development is centred on tissue-selective immunomodulation for the treatment of oncology, autoimmune, and CNS-related disorders, with a near-term focus on targeting newly-discovered, foundational immunosuppressive mechanisms in oncology and novel approaches that harness the lymphatic infrastructure.

For more information, visit www.puretechhealth.com or connect with us on Twitter @puretechh.