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PureTech Announces Publication of New Preclinical Research from Collaborators that Supports Mesenteric Lymphatic Dysfunction as a Potential Cause of and Therapeutic Target for Obesity and Insulin Resistance

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PureTech Announces Publication of New Preclinical Research from Collaborators that Supports Mesenteric Lymphatic Dysfunction as a Potential Cause of and Therapeutic Target for Obesity and Insulin Resistance

Dysfunction of the mesenteric lymphatics and leakage of pro-inflammatory lymph fluids promoted the accumulation of visceral adipose tissue and insulin resistance in a preclinical model

Treatment with a lymph-targeted COX-2 inhibitor using PureTech's Glyph™ technology platform normalized lymphatic vasculature, blocked weight gain and reversed glucose intolerance and hyperinsulinemia

PureTech Health plc (Nasdaq: PRTC, LSE: PRTC) ("PureTech" or the "Company"), a clinical-stage biotherapeutics company dedicated to discovering, developing and commercializing highly differentiated medicines for devastating diseases, today announced the publication of a research paper in *Nature Metabolism*, which showed for the first time that restoring normal function of the mesenteric lymphatics may reverse insulin resistance and modify obesity-associated metabolic disease. Results from the preclinical study provide further support for the therapeutic potential of PureTech's Glyph technology platform, which is designed to enable the trafficking of small molecule drugs directly into the mesenteric lymphatic system following oral administration. The groundbreaking study was led by PureTech collaborators Natalie Trevaskis, Ph.D., Associate Professor at the Monash Institute of Pharmaceutical Sciences (MIPS) in Australia, Christopher Porter, Ph.D., MIPS Director, and Enyuan Cao, Ph.D., Post-Doctoral Research Fellow at MIPS, in collaboration with PureTech scientists.

The work demonstrates that obesity may be associated with profound and progressive dysfunction of the mesenteric lymphatic system. As shown in preclinical models, a high-fat diet stimulated the formation of new lymphatic vessels, which grew in a highly disorganized pattern. These tortuous, branching vessels tended to leak lymphatic fluid rich in lipid metabolites and pro-inflammatory mediators into the visceral adipose tissue in the abdomen, triggering the promotion of insulin resistance. Results from *ex vivo* experiments using clinical samples suggest that these observations may extend to humans as well.

"We have known for years that the accumulation of fat around the abdomen is correlated with higher rates of diabetes, but the biological reasons remained unclear. This is the first study to identify the profoundly damaging cycle in which the accumulation of abdominal fat leads to dysfunction of the mesenteric lymphatics, which in turn promotes more fat deposition and insulin resistance," said Dr. Trevaskis. "Most exciting of all, we have preclinical evidence that

intervening in this cycle by inhibiting the pathways associated with the lymphatic dysfunction may be a treatment for both obesity and associated metabolic disease. We believe that PureTech's Glyph technology platform is key to this intervention, because it traffics the inhibitors directly where they are needed in the mesenteric lymphatics."

The study also found that inhibition of COX-2 and VEGF-C signaling within the mesenteric lymphatics resulted in a repatterning of the lymphatic vasculature, which in turn led to reduced branching and significantly less leakage of lymphatic fluids rich in lipids and pro-inflammatory mediators. Additionally, targeted inhibition of COX-2 function with a celecoxib prodrug developed using PureTech's lymphatic targeting Glyph technology platform led to a normalization of multiple biomarkers, including VEGF-C concentrations specifically within mesenteric lymph and surrounding adipose tissue, and to levels observed in control animals that were not fed a high-fat diet. This correlated with reduced lymphatic vessel branching and leakage as well as restoration of glycemic control, and weight gain was blocked in the animals fed a high-fat diet. In fact, targeted administration of the celecoxib Glyph prodrug led to a 10-fold greater uptake of celecoxib in mesenteric lymph and more effective restoration of lymphatic function and glycemic control compared to the administration of unmodified celecoxib, which is commercially available.

"What's remarkable about this study is that the COX-2 inhibitor was able to meaningfully repattern the chaotic lymphatic structure in obese mice when it was delivered directly to the mesenteric lymphatics with our Glyph technology platform, and that repatterning was accompanied by a substantial decrease in both weight gain and insulin resistance," said Joseph Bolen, Ph.D., Chief Scientific Officer at PureTech. "We are excited to continue to build off of this pioneering research to identify and advance new potential treatment applications of this platform."

About the GlyphÔ Technology Platform

Glyph is PureTech's synthetic lymphatic-targeting chemistry platform which is designed to employ the body's natural lipid absorption and transport process to orally administer drugs via the lymphatic system. PureTech believes this technology has the potential to (1) enable direct modulation of the immune system via drug targets present in mesenteric lymph nodes and (2) provide a broadly applicable means of enhancing the bioavailability of orally administered drugs that would otherwise become inactive by first-pass liver metabolism. PureTech has demonstrated proof-of-concept by achieving therapeutically relevant plasma levels following oral administration of a neurosteroid, allopregnanolone, in small animal and non-human primate model systems. This and other work has resulted in the generation of PureTech's lead Glyph product candidate, LYT-300 (oral allopregnanolone), which is expected to enter a clinical trial by the end of 2021. The Glyph technology platform is based on the pioneering research of Christopher Porter, Ph.D., and his team at the Monash Institute of Pharmaceutical Sciences at Monash University in Melbourne, which PureTech has exclusively licensed.

About PureTech Health

PureTech is a clinical-stage biotherapeutics company dedicated to discovering, developing and commercializing highly differentiated medicines for devastating diseases, including inflammatory, fibrotic and immunological conditions, intractable cancers, lymphatic and gastrointestinal diseases and neurological and neuropsychological disorders, among others. The Company has created a broad and deep pipeline through the expertise of its experienced research and development team and its extensive network of scientists, clinicians and industry leaders. This pipeline, which is being advanced both internally and through PureTech's Founded Entities, is comprised of 25 therapeutics and therapeutic candidates, including two that have received both U.S. FDA clearance and European marketing authorization, as of the date of PureTech's most recently filed Half Year Report and corresponding Form 6-K. All of the underlying programs and platforms that resulted in this pipeline of therapeutic candidates were initially identified or discovered and then advanced by the PureTech team through key validation points based on the Company's unique insights into the biology of the brain, immune and gut, or BIG, systems and the interface between those systems, referred to as the BIG Axis.

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

Cautionary Note Regarding Forward-Looking Statements

This press release contains statements that are or may be forward-looking statements, including statements that relate to our expectations regarding the GlyphÔ technology platform including the potential for new treatment applications, the applicability of preclinical results to human subjects, and the timing of LYT-300 to enter a clinical trial, our product candidates and approach towards addressing major diseases, and our future prospects, developments, and strategies. The forward-looking statements are based on current expectations and are subject to known and unknown risks and uncertainties that could cause actual results, performance and achievements to differ materially from current expectations, including, but not limited to, those risks and uncertainties described in the risk factors included in the regulatory filings for PureTech Health plc. These forward-looking statements are based on assumptions regarding the present and future business strategies of the Company and the environment in which it will operate in the future. Each forward-looking statement speaks only as at the date of this press release. Except as required by law and regulatory requirements, neither the Company nor any other party intends to update or revise these forward-looking statements, whether as a result of new information, future events or otherwise.

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