

Sonnet BioTherapeutics Announces the Generation and Characterization of Two Novel Immunotherapeutic Pipeline Drug Candidates, SON-1411 and SON-1400, Each Containing a Variant IL-18 Domain

- Sonnet discovered and characterized a modified version of Interleukin-18 (IL-18^{BPR} Binding Protein Resistant or IL-18^{BPR}) that exhibits wild-type binding to the IL-18 receptor (IL-18Rc), coupled with undetectable binding to the inhibitory IL-18 Binding Protein (IL-18BP)
- IL-18^{BPR} was linked to Sonnet's proprietary tumor targeting F_HAB platform, with or without single-chain wild-type IL-12
- The bifunctional SON-1411 molecule is manufactured in Chinese Hamster Ovary (CHO) cells, while the monofunctional SON-1400 molecule is made in *E. coli*; both have been highly purified and were bioactive in the receptor binding assays
- IL-18^{BPR} and IL-12 could be combined for broad applications in oncology and cell-based therapies

PRINCETON, N.J., June 13, 2024 (GLOBE NEWSWIRE) -- Sonnet BioTherapeutics Holdings, Inc. (NASDAQ:SONN) (the "Company" or "Sonnet"), a clinical-stage company developing targeted immunotherapeutic drugs, announced today the generation and *in vitro* characterization of two novel drug candidates, SON-1411 (IL18^{BPR}-F_HAB-IL12) and SON-1400 (IL18^{BPR}-F_HAB), each containing a modified version of recombinant human interleukin-18 (IL-18^{BPR}). SON-1411 is a proprietary bifunctional fusion protein consisting of IL-18^{BPR} combined with single-chain wild-type IL-12, linked to Sonnet's Fully Human Albumin Binding (F_HAB[®]) platform, which will replace SON-1410 as a development target. SON-1400 is a monofunctional fusion protein comprising the same IL-18^{BPR} domain linked to the F_HAB. F_HAB extends the half-life and biological activity of linked molecules by binding native albumin in the serum and targets the tumor microenvironment (TME) through high affinity binding to glycoprotein 60 (gp60) and the Secreted Protein Acidic and Rich in Cysteine (SPARC).

IL-18 can regulate both innate and adaptive immune responses through its effects on natural killer (NK) cells, monocytes, dendritic cells, T cells, and B cells. IL-18 acts synergistically with other pro-inflammatory cytokines to promote interferon-γ (IFN-γ) production by NK cells and T cells. Systemic administration of IL-18 has been shown to have anti-tumor activity in several animal models. Moreover, tumor-infiltrating lymphocytes (TILs) express more IL-18 receptors than other T cells. However, IL-18 clinical trials have shown that, although it is well

tolerated, IL-18 has poor efficacy in the treatment of cancers, most likely due in large part to the high co-expression of IL-18 binding protein (IL-18BP) in the TME. In particular, IL-18BP serves as a “decoy receptor” that binds to IL-18 with higher affinity, compared with the IL-18Rc complex, thereby causing a negative feedback loop with IL-18 and inhibiting IL-18-mediated TIL activation. Thus, there exists a potential for the discovery of IL-18 variant compositions that could harness the therapeutic potential of IL-18 for the treatment of cancers.

Sonnet’s strategy for amino acid modifications to rIL-18 was based on a compilation of literature review, 3D X-ray crystallography structures, and computer modeling analysis. Subsequently, certain IL-18 variant sequences were synthesized, engineered into expression constructs and manufactured at small scale in either CHO cell culture or *E. coli*. Highly purified milligram quantities of SON-1411 or SON-1400 were analyzed *in vitro* for IL-18Rc or IL-18BP binding activities, respectively, using the HEK-Blue™ and Bright-Glo Luciferase™ IL-18Rc reporter assays. *In vitro* results for at least one variant of IL-18 showed equivalent binding to the IL-18 Rc, compared to the wild-type IL-18 reference molecule, concomitant with no or reduced binding to IL-18BP.

“The development of a modified IL-18 has been a challenging scientific achievement. IL-18 is a key cytokine that, when combined synergistically with IL-12, has the potential to be an important therapeutic asset for oncology and cell-based therapy. We believe that these novel molecules combined with our proprietary F_HAB platform are expected to demonstrate tumor targeting and longer half-lives, which in turn are expected to allow a therapeutic window for commercialization of these important oncology candidates,” said Pankaj Mohan, Ph.D., Sonnet Founder and Chief Executive Officer.

“The known MOA of IL-18 inhibition by IL-18BP is reviving the importance of clinical applications of IL-18. IL-18BP has been shown to be elevated in cancer patients, thus negating the clinical use of IL-18. Sonnet is excited about the development of a novel bifunctional cytokine molecule, IL18^{BPR}-F_HAB-IL12, which contains a unique IL18 domain that does not bind the inhibitor IL-18BP but still maintains full IL-18 and IL-12 bioactivity. The clinical application of this bifunctional fusion protein could potentially expand immunotherapy applications for cancer patients,” commented John Cini, Ph.D., Sonnet Chief Scientific Officer.

About SON-1411

SON-1411 is a candidate immunotherapeutic recombinant drug that is closely related to and will replace SON-1410, which links an unmodified single-chain human IL18 and an unmodified IL-12 with the albumin-binding domain of the single-chain antibody fragment A10m3. The only difference between SON-1410 and SON-1411 is that in the latter, the IL-18 domain has been modified via mutagenesis to retain wildtype binding to the IL-18 receptor (IL-18 Rc) while inhibiting or abolishing binding to the IL-18 binding protein (IL-18 BP). The A10m3 scFv was selected to bind both at normal pH, as well as at the acidic pH that is typically found in the TME. The F_HAB technology targets tumor and lymphatic tissue, providing a mechanism for dose sparing and an opportunity to improve the safety and efficacy profile of IL-18 and IL-12, as well as a variety of potent immunomodulators that can be added using the platform. Interleukin-12 can orchestrate a robust immune response to many cancers and pathogens. Given the types of proteins induced in the TME, such as

SPARC and gp60, several types of cancer such as non-small cell lung cancer, melanoma, head and neck cancer, sarcoma, and some gynecological cancers are particularly relevant for this approach. SON-1411 is designed to deliver IL-18^{BPR} and IL-12 to local tumor tissue, turning 'cold' tumors 'hot' by stimulating IFN γ , which activates innate and adaptive immune cell responses and increases the production of Programed Death Ligand 1 (PD-L1) on tumor cells.

About Sonnet BioTherapeutics Holdings, Inc.

Sonnet BioTherapeutics is an oncology-focused biotechnology company with a proprietary platform for innovating biologic drugs of single or bifunctional action. Known as F_HAB (Fully Human Albumin Binding), the technology utilizes a fully human single chain antibody fragment (scFv) that binds to and "hitch-hikes" on human serum albumin (HSA) for transport to target tissues. Sonnet's F_HAB was designed to specifically target tumor and lymphatic tissue, with an improved therapeutic window for optimizing the safety and efficacy of immune modulating biologic drugs. F_HAB is the foundation of a modular, plug-and-play construct for potentiating a range of large molecule therapeutic classes, including cytokines, peptides, antibodies, and vaccines.

Forward-Looking Statements

This press release contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the outcome of the Company's clinical trials, the Company's cash runway, the Company's product development, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statements that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the Securities and Exchange Commission. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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