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Sonnet BioTherapeutics Announces Results of Biodistribution Studies Demonstrating Solid Tumor Targeting Using the FHAB Technology

- ***Two independent radiolabeling studies showed a 2.5- to 4.7-fold increase in tumor tissue with mIL12-F_HAB, the mouse version of SON-1010, compared with mIL-12 alone***
- ***Accumulation was observed in tumors compared to normal mice, and was expectedly transient in liver and kidney***
- ***The model shows that the F_HAB technology provides tumor targeting and retention, as well as extended half-life, that importantly complements results from the human clinical studies***

PRINCETON, NJ / ACCESSWIRE / September 20, 2023 /Sonnet BioTherapeutics Holdings, Inc. (NASDAQ:SONN), a clinical-stage company developing targeted immunotherapeutic drugs, announced data from two radiolabeling studies that validate the tumor targeting attributes associated with albumin binding by the F_HAB technology.

Sonnet performed two independent *in vivo* proof-of-concept (POC) studies to show the biodistribution of interleukin-F_HAB molecules to the tumor microenvironment (TME), using labs with expertise in radiolabeling biologics and *in vivo* biodistribution analysis. The labs employed different radiolabeling methodologies (^{99m}Tc or ^{89}Zr) for mIL-12 and mIL12-F_HAB, either with or without a polyhistidine tag (His-Tag). The two studies were completed using the B16F10 mouse melanoma model for measuring the accumulation of radiolabeled product and tumor volume inhibition over various time points. The key findings from both studies indicated that mIL12-F_HAB had significantly higher tumor accumulation, 2.5-4.7 times higher on average at the longer time points, and increased retention when compared to mIL-12. Accumulation was demonstrated in tumors compared to normal mice, and was transient in liver, kidney, and other organs, as expected. Importantly, radiolabeled mIL12-F_HAB also demonstrated measurable accumulation in the draining lymph nodes. Overall, these findings have important implications for therapeutic applications of any mono- (ILx-F_HAB) or bi-functional (ILx-F_HAB-ILy) molecules demonstrating enhanced tumor targeting and accumulation, as well as the potential for improved efficacy that could lead to a variety of drug candidates.

"In addition to the previous multiple data sets that have highlighted the extended pharmacokinetic properties of the F_HAB technology along with improved activity relative to wild-type IL-12, this is the first formal evidence of tumor targeting, which I believe supports our best-in-class cancer drug development platform", commented Pankaj Mohan, Ph.D.,

Founder and CEO of Sonnet. "Furthermore, these characteristics should enable a broader therapeutic window, potentially allowing the use of lower doses at longer intervals."

Sonnet previously compared three constructs, the F_HAB, an anti-TGF-β scFv, and an anti-TGF-β-F_HAB fusion protein, to evaluate the generic potential for *in vivo* accumulation and retention in tumors by F_HAB-albumin complexes using a 4T1 tumor-bearing mouse model, which has tumors that over-express TGF-β. Accumulation and retention profiles were characterized over a 24-hour period by Western blot analysis of tumor extracts taken at 30 minutes, then at 4-, 12-, and 24-hours after dosing of each construct. The comparative data showed that the F_HAB domain exhibited superior accumulation and retention in the tumor at all time points. In contrast, the anti-TGF-β molecule, which lacked the F_HAB domain, exhibited a rapid decline in abundance at 4 hours and was not detectable at 12 or 24 hours, thus exhibiting poor accumulation and retention in the tumor. By comparison, fusion of the F_HAB domain to anti-TGF-β, which created the anti-TGF-β-F_HAB fusion protein, restored the accumulation and retention profile in the tumor extracts tested at all time points, thus proving that the F_HAB-albumin complex is driving anti-TGF-β into the tumor, while the anti-TGF-β molecule without F_HAB did not. In summary, these early findings highlighted the importance of the F_HAB domain's binding to albumin, which in turn facilitated the targeted delivery and retention of various fusion constructs within the tumor tissue, making F_HAB a promising technology for the innovation of biologic therapeutics.

John Cini, Ph.D., Co-Founder and Chief Scientific Officer, said "I am very excited to establish *in vivo* proof-of-concept involving F_HAB binding to albumin as a unique approach for cytokine-based drug development that can target tumors by binding to FcRn and GP60 receptors, promote retention in the TME by binding to SPARC, and ultimately potentiate a strong immune response. This is indeed a promising approach in cancer immunotherapy."

Richard Kenney, M.D., Chief Medical Officer, commented that "the F_HAB technology's key differentiating characteristics of tumor targeting due to albumin binding with SPARC and extended half-life may translate into the demonstration of clinical benefit in Sonnet's human studies with SON-1010."

About Sonnet BioTherapeutics Holdings, Inc.

Sonnet BioTherapeutics is an oncology-focused biotechnology company with a proprietary platform for innovating biologic drugs of single or bispecific 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 Section21E of the Securities ExchangeAct of

1934 and Private Securities Litigation Reform Act, as amended, including those relating to the timing of an IND submission, 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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