# Xencor Presents Data from Multiple Preclinical XmAb® Bispecific Antibody and Cytokine Programs at the AACR Annual Meeting 2021

April 10, 2021

MONROVIA, Calif.--(BUSINESS WIRE)--Apr. 10, 2021-- Xencor, Inc. (NASDAQ:XNCR), a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies and cytokines for the treatment of cancer and autoimmune diseases, today announced the presentation of new data from multiple preclinical XmAb® bispecific antibody programs and its preclinical IL-12-Fc cytokine program at the American Association for Cancer Research (AACR) Annual Meeting, being held virtually April 10-15, 2021.

"Xencor's XmAb bispecific Fc domains enable the rapid design and simplified development of Fc-containing protein structures and are being used to create new platforms, a wide range of multi-specific antibodies and engineered cytokines. At AACR, we are presenting emerging preclinical data from early-stage programs that highlight the potential of our CD28 platform and XmAb 2+1 bispecific antibody format, as well as our more advanced IL-12 cytokine, which builds off our prior work with IL-15 and IL-2," said John Desjarlais, Ph.D., senior vice president and chief scientific officer at Xencor. "In 2021, we anticipate submitting an IND for XmAb819, our lead XmAb 2+1 CD3 bispecific antibody targeting ENPP3, and initiating a Phase 1 study in early 2022. We are also advancing through preclinical development our wholly owned lead CD28 candidate, a B7-H3 x CD28 bispecific antibody designed to be evaluated for the treatment of patients with a range of solid tumors."

Poster presentations will be archived under "Events & Presentations" in the Investors section of the Company's website located at www.xencor.com.

XmAb Engineered Cytokine Platform

- Abstract 1743, "IL12 heterodimeric Fc-fusions engineered for reduced potency exhibit strong anti-tumor activity and improved therapeutic index compared to native IL12 agents"

IL-12 is a potent proinflammatory cytokine produced by activated antigen-presenting cells, and it leads to proliferation of T cells and NK cells and increased cytotoxicity through high levels of interferon gamma signaling. As a potent immune stimulating protein, IL-12 can have a significant effect on shrinking tumors; however, prior clinical studies have demonstrated it to have a narrow therapeutic window, limiting potential response rates.

Xencor's IL-12-Fc cytokine program builds on the Company's prior work with IL-15-Fc cytokines in oncology, where reduced potency led to improved pharmacokinetics, pharmacodynamics and tolerability in preclinical studies. IL-12-Fc fusions were engineered with reduced potency in order to improve potential tolerability, slow receptor-mediated clearance and prolong the molecules' half-lives, compared to native IL-12. The potency-reduced IL-12-Fc fusions demonstrated significant anti-tumor activity *in vivo* concurrent with activation and proliferation of CD8+ T cells and increased levels of interferon gamma in serum. In non-human primates, the engineered cytokines had an improved pharmacokinetic profile and therapeutic window compared to a native cytokine-Fc fusion, with superior exposure, a more gradual dose response and similar levels of cytokine production in serum.

XmAb CD28 Bispecific Antibody Platform

T cells in the tumor microenvironment require both T cell receptor (TCR) and co-stimulatory receptor engagement to achieve full activation. CD28 is a key immune co-stimulatory receptor on T cells; however, the ligands that activate T cells through CD28 are usually not expressed on tumor cells. Targeted CD28 bispecific antibodies, a new class of T cell engager, may provide conditional co-stimulation of T cells, for example, to T cells recognizing neoantigens or in concert with CD3 T-cell engaging bispecific antibodies.

- Abstract: 1880, "PDL1-targeted CD28 costimulatory bispecific antibodies enhance T cell activation in solid tumors"

Xencor engineered PD-L1 x CD28 bispecific antibodies to provide conditional co-stimulation of T cells, activating them when bound to tumor cells. PD-L1, which is expressed on many types of tumors, suppresses anti-tumor responses by the immune system and has been shown to directly inhibit CD28 co-stimulation. A PD-L1 x CD28 bispecific antibody, therefore, may promote CD28 co-stimulation and simultaneously block CD28's suppression by PD-L1.

*In vitro*, the combination of the PD-L1 x CD28 and a CD3 T cell engager enhanced T cell activation and proliferation compared to the CD3 bispecific alone, as designed. PD-L1 x CD28 also enhanced the interaction between T cells and antigen presenting cells and exhibited strong CD28-dependent anti-tumor activity in mice. PD-L1 x CD28 was well tolerated in non-human primates and exhibited favorable pharmacokinetics.

XmAb 2+1 Bispecific Antibody Format

Xencor's XmAb 2+1 bispecific antibodies are a type of CD3 T cell engager, with two tumor binding domains and one CD3 binding domain. The affinities for tumor binding are tuned, allowing for selective killing of high antigen-expressing tumor cells, potentially sparing low antigen-expressing

normal cells. The XmAb 2+1 format may be especially beneficial when developing bispecific antibodies that target solid tumors, where tumor-associated antigens are often expressed on a range of normal tissues, including critical organs.

- Abstract: 1860, "Bispecific claudin-6 x CD3 antibodies in a 2+1 format demonstrate selectivity and activity on human ovarian cancer cells"

Claudin-6 (CLDN6) is a tumor-associated antigen overexpressed in ovarian cancer and other solid tumors, and its differential expression in cancerous tissue makes CLDN6 an intriguing target for CD3 bispecific antibodies. Many members of the claudin family, which are small transmembrane proteins, have high sequence identity, which complicates selectivity among claudins. CLDN6 x CD3 bispecific antibodies were engineered in the XmAb 2+1 format, and the tumor binding domain was further engineered for improved selectivity of CLDN6 over similar claudin family members, such as CLDN9. In preclinical models, CLDN6 x CD3 bound more preferentially to tumor cells compared to cell lines with normal tissue CLDN9 expression levels. Lead candidates demonstrated reversal of tumor growth in human-cell engrafted mouse models of ovarian cancer. Further data from non-human primate studies demonstrated the candidates were well-tolerated with favorable pharmacokinetic profiles.

- Abstract: 1831, "Affinity tuned XmAb® 2+1 GPC3 x CD3 bispecific antibodies demonstrate selective activity in liver cancer models"

GPC3 is an antigen associated with hepatocellular carcinoma, squamous cell carcinoma of the lung and other cancers. Under certain conditions, GPC3 can trigger Wnt signaling and promote tumor proliferation. Despite a favorable expression profile, unfavorable tolerability has been reported from multiple clinical studies evaluating CAR-T therapy and T cell engaging bispecific antibodies that target GPC3. GPC3 x CD3 bispecific antibodies in the XmAb 2+1 format selectively recruited T cells to kill high GPC3-expressing cancer cells and avoided cytotoxicity to a low GP3C-expressing cell line. A comparison of GPC3 x CD3 bispecific antibodies with the XmAb 2+1 format and first-generation T cell engagers demonstrated similar anti-tumor activity and immune cell proliferation *in vitro*.

**About Xencor, Inc.**

Xencor is a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies and cytokines for the treatment of cancer and autoimmune diseases. Currently, 20 candidates engineered with Xencor's XmAb® technology are in clinical development internally and with partners. Xencor's XmAb antibody engineering technology enables small changes to the structure of proteins resulting in new mechanisms of therapeutic action. For more information, please visit www.xencor.com.

**Forward-Looking Statements**

Certain statements contained in this press release may constitute forward-looking statements within the meaning of applicable securities laws. Forward-looking statements include statements that are not purely statements of historical fact, and can generally be identified by our use of words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “seek,” “look forward,” “believe,” “committed,” “investigational,” and similar terms, or by express or implied discussions relating to the quotations from Xencor's senior vice president and chief scientific officer, any expectations relating to future product candidates, research and development programs and other statements that are not purely statements of historical fact. Such statements are made on the basis of the current beliefs, expectations, and assumptions of the management of Xencor and are subject to significant known and unknown risks, uncertainties and other factors that may cause actual results, performance or achievements and the timing of events to be materially different from those implied by such statements, and therefore these statements should not be read as guarantees of future performance or results. Such risks include, without limitation, the risks associated with the process of discovering, developing, manufacturing and commercializing drugs that are safe and effective for use as human therapeutics and other risks described in Xencor's public securities filings. For a discussion of these and other factors, please refer to Xencor's annual report on Form 10-K for the year ended December 31, 2020 as well as Xencor's subsequent filings with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended to date. All forward-looking statements are qualified in their entirety by this cautionary statement and Xencor undertakes no obligation to revise or update this press release to reflect events or circumstances after the date hereof, except as required by law.

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