Codiak Presents Data at AACR 2021 Demonstrating Potential of Engineered Exosomes to Enhance the Therapeutic Index of Well-Validated Cancer Immunotherapy Pathways

April 10, 2021

– exoASO™-STAT6 mediated genetic reprogramming of tumor associated macrophages results in potent single-agent anti-tumor activity in multiple preclinical models; IND submission planned for H2 2021 –

– exoIL-12™ produces local and prolonged immune activation without detectable systemic exposure to IL-12 or INF-γ and no treatment-related AEs in healthy volunteers; patient data readout expected by YE 2021 –

CAMBRIDGE, Mass., April 10, 2021 (GLOBE NEWSWIRE) -- Codiak BioSciences, Inc. (Nasdaq: CDAK), a clinical-stage biopharmaceutical company focused on pioneering the development of exosome-based therapeutics as a new class of medicines, today reported new preclinical evidence from Codiak's exoASO-STAT6 program and clinical results from the healthy volunteer portion of the ongoing Phase 1 trial of Codiak's exoIL-12 program at the virtual American Association for Cancer Research (AACR) Annual Meeting 2021. These data illustrate the potential of engineered exosomes to target previously undruggable but well-validated pathways in cancer immunotherapy and generate potent single-agent activity.

"We now have a growing body of preclinical and clinical evidence across our pipeline programs demonstrating that engineering exosomes to deliver potent drug molecules enhances the therapeutic index of pathways known to drive the immune response to fighting tumors," said Douglas E. Williams, Ph.D., President and Chief Executive Officer of Codiak. "In particular, data from multiple *in vitro* and *in vivo* studies of engineered exosomes incorporating an antisense oligonucleotide demonstrate potent single-agent and highly selective genetic reprogramming of tumor associated macrophages, which is unique among macrophage targeting strategies. We look forward to advancing our exoASO-STAT6 candidate into clinical trials following our Investigational New Drug application (IND) filing anticipated later this year."

Both exoASO-STAT6 and exoIL-12 were developed via Codiak's proprietary engEx™ Platform, which enables the company to engineer exosomes – naturally occurring, extracellular vesicles – with distinct properties, load them with various therapeutic molecules and alter tropism so they reach specific cellular targets. exoIL-12 is currently being evaluated in a Phase 1 clinical trial in patients with cutaneous T cell lymphoma (CTCL) and is one of two Codiak programs in human clinical testing.

exoASO-STAT6 Results in Potent Single-Agent Complete Anti-Tumor Response in Multiple Preclinical Models
M2 phenotype macrophages promote tumor growth by creating a highly immunosuppressive environment in the tumor. exoASO-STAT6 is a novel therapeutic candidate designed to deliver antisense oligonucleotides (ASOs) to selectively target STAT6, a key immunosuppressive transcription factor in tumor associated macrophages (TAMs). Codiak plans to focus clinical development of exoASO-STAT6 initially in myeloid rich cancers such as colorectal cancer, hepatocellular carcinoma (HCC) and others.

Results from multiple *in vitro* and *in vivo* studies demonstrate that exoASO-STAT6 effectively reprograms macrophages to a pro-inflammatory M1 phenotype, resulting in potent single-agent anti-tumor activity. exoASO-STAT6 exhibits a selective tropism for myeloid cells and delivered up to 12-fold more ASO to M2 macrophages *in vivo* than ASO administration without an exosome (e.g., "free").

In vivo studies with exoASO-STAT6 in two syngeneic tumor models (CT26 and Hepa 1-6) consistently demonstrated potent single-agent activity. Monotherapy with exoASO-STAT6 resulted in 60% complete tumor remission in CT26 tumors. Notably, free STAT6 ASO showed no anti-tumor activity at the same dose, highlighting the enhancement in ASO therapeutic efficacy conferred by exosomes. Intravenous administration of exoASO-STAT6 in mice bearing Hepa1-6 orthotopic HCC tumors also resulted in profound reduction (62%) of tumor burden. In contrast, anti-CSF1R or anti-PD1 therapy as a comparator did not result in any measurable effects on tumor growth in either model.

In both tumor models, monotherapy activity of exoASO-STAT6 is accompanied by a substantial remodeling of the tumor microenvironment (TME), as evidenced by marked increase in pro-inflammatory markers such as iNOS positive monocyte/macrophages, one of the hallmarks of effective M1 macrophage reprogramming, and reduction in immunosuppressive markers such as CD163. Subsequent genetic and histology analyses confirmed remodeling of the TME to a pro-inflammatory M1-like phenotype induced by exoASO-STAT6 therapy.

exoIL-12 Demonstrates Local Pharmacology, Tolerability and Absence of Systemic IL-12 Exposure in Healthy Volunteers
IL-12 is a potent anti-tumor cytokine; however, translating IL-12 into a drug in the clinic has generally been hindered by significant safety and tolerability concerns. To overcome these limitations, exoIL-12 was designed to facilitate dose control of IL-12 and limit systemic exposure and associated toxicity by localizing IL-12 in the TME to potentially expand the therapeutic index.

Previously reported pharmacokinetic and pharmacodynamic data from the randomized, placebo controlled, double-blind Phase 1 study showed that administration of exoIL-12 in healthy volunteers resulted in a favorable safety and tolerability profile and prolonged pharmacodynamic effect with no local or systemic treatment-related adverse events and no detectable systemic exposure of IL-12. In particular, a subcutaneously administered single ascending dose of exoIL-12 demonstrated no systemic exposure across the dose range (0.3-12.0 µg), which is in direct contrast to previous clinical studies with recombinant IL-12. New pharmacodynamic data presented at AACR 2021 show no systemic IFN-γ production, which may further explain the favorable safety and tolerability of exoIL-12.

Pharmacodynamic data from skin punch biopsies showed detectable levels of exoIL-12 in the skin at the 6.0 µg dose as much as 24 hours post injection, indicating retention at the injection site and prolonged activation of the IL-12 signaling cascade. Based on these findings, the 6.0 µg dose level has been selected for the second portion of the Phase 1 trial currently underway, where the safety and efficacy of exoIL-12 will be evaluated following repeat doses into the lesions of patients with early-stage CTCL.

About exoASO™-STAT6
exoASO-STAT6 is an exosome engineered to deliver antisense oligonucleotides and selectively target uptake in M2 polarized tumor-associated macrophages via overexpression of the exosomal protein, PTGFRN. Targeting STAT6 acts as a potent switch of the polarization of tumor-associated macrophages from an M2 tumor permissive/anti-inflammatory phenotype to an M1 T cell attractive, anti-tumor/inflammatory phenotype. Codiak plans to initially develop exoASO-STAT6 for primary and metastatic cancers of the liver, such as hepatocellular carcinoma, pancreatic ductal adenocarcinoma, colorectal carcinoma, lung adenocarcinoma, uveal melanoma, glioma, thyroid cancer and ovarian cancer.

About exoIL-12™
exoIL-12 is Codiak's exosome therapeutic candidate engineered to display fully active IL-12 on the surface of the exosome, using the exosomal protein, PTGFRN, as a scaffold, and designed to facilitate potent local pharmacology at the injection site with precisely quantified doses. By limiting systemic exposure of IL-12 and associated toxicity, Codiak hopes to enhance the therapeutic index with exoIL-12, delivering a more robust tumor response, dose control and an improved safety profile.

Codiak intends to focus development of exoIL-12 on tumors that have, in previous clinical testing, shown clinical responses to recombinant IL-12 used as a monotherapy. This list includes CTCL, melanoma, Merkel cell carcinoma, Kaposi sarcoma, glioblastoma multiforme, triple negative breast cancer, among others.

About Codiak BioSciences
Codiak is a clinical-stage biopharmaceutical company focused on pioneering the development of exosome-based therapeutics, a new class of medicines with the potential to transform the treatment of a wide spectrum of diseases with high unmet medical need. By leveraging the biology of exosomes as natural intercellular transfer mechanisms, Codiak has developed its proprietary engEx Platform to expand upon the innate properties of exosomes to design, engineer and manufacture novel exosome therapeutic candidates. Codiak has utilized its engEx Platform to generate a deep pipeline of engineered exosomes aimed at treating a broad range of disease areas, spanning oncology, neuro-oncology, neurology, neuromuscular disease and infectious disease.

Forward-Looking Statements
This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including, among other things, statements concerning the development and therapeutic potential of exoIL-12 and exoASO-STAT6, including future development plans and regulatory filings and timing with respect thereto. Any forward-looking statements in this press release are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. For a discussion of these risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in Codiak's Annual Report on Form 10-K for the year ended December 31, 2020, and in subsequent filings with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties and other important factors in Codiak's subsequent filings with the Securities and Exchange Commission. All information in this press release is current as of the date of this report, and Codiak undertakes no duty to update this information unless required by law.

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