CDCP1 as a Novel Therapeutic Target for Cancer Therapy

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Technology description

Researchers from Cornell University, Beth Israel Deaconess Medical Center and Pfizer Inc.'s Centers for Therapeutic Innovation (CTI) have invented a technology for the opportunity to develop a potential medicine with a novel mechanism for the treatment of solid tumors. The asset is a fully humanized antibody against CUB Domain Containing Protein-1 (CDCP1) conjugated to a proprietary cytotoxic linker-payload, being developed for the treatment of solid tumors over-expressing CDCP1.

Product Description:

The asset is an antibody drug conjugate (ADC) that specifically targets CDCP1, a single pass transmembrane domain protein, over-expressed in numerous cancers including those of the lung, ovary, and breast (Alajati et al., 2015; He et al., 2016a; Ikeda et al., 2009). An anti-CDCP1-ADC may have activity as a single agent or in combination with current standard of care with the potential to improve efficacy and minimize overlapping toxicities.

Sequential screening of a complex phage library led to the isolation of a fully human antibody that binds human, cynomolgous monkey, and mouse CDCP1. Multiple rounds of engineering produced a final antibody with good target binding affinity and manufacturability characteristics. This antibody was specifically conjugated to a proprietary linker-payload, resulting in a CDCP1-targeting ADC.

The CDCP1-ADC was evaluated in numerous non-clinical patient derived xenograft (PDX) cancer models. PDX models were established by direct implantation of freshly resected human tumor samples in immunocompromised mice and propagated by passaging xenograft fragments into additional animals. Because they are not cultured in vitro, PDX models frequently preserve the genotype and recapitulate the architecture and, importantly, the drug sensitivity of the original human tumor from which they were derived (Tentler et al., 2012). Among the models in which the CDCP1-ADC was examined were: non-small cell lung cancer, small cell lung cancer, head and neck cancer, bladder cancer, breast cancer, and ovarian cancer. In total, more than 40 independent PDX models were examined. Using RECIST criteria, we recorded a complete response in 20%, a partial response in 43%, and stable disease in 18% of the models tested, resulting in an objective response rate of 63%. Of these, non-small cell lung, head and neck, ovarian, and breast cancers were the most responsive while small cell lung and bladder cancers were generally resistant to treatment.

Non-clinical in vivo PK parameters of the CDCP1-ADC were in line with other assets of this class. Non-GLP compliant toxicology studies showed the ADC to be generally well-tolerated with no deaths

observed even at the highest doses. These studies allowed the prediction of clinical dosing that is in line with, or superior to, other assets in the class. The CDCP1 protein is normally expressed at low levels in healthy epithelial tissues, most prominently in lung and colon (Scherl-Mostageer et al., 2001; Hooper et al., 2003). Chronic inhibition/absence of CDCP1 seems to be of little to no consequence as knockout mice lacking it have no reported pathologies (Spassov et al., 2012). This suggests that targeting CDCP1 in diseases such as cancer should pose relatively limited safety risks.

Competitive Landscape:

CDCP1 represents a promising target that has been largely unexplored. Based on publicly available information, there are 5 other assets in preclinical or discovery stages that specifically target CDCP1, with two being ADCs from Alexion Pharma and Bluefin Biomedicine (founded 2016). There has been no development reported on the preclinical asset from Alexion since 2008 and no reports of clinical activity with the Bluefin Biomedicine asset. Hence, the CDCP1-ADC described here may be considered a leader in this class. There are more than a dozen ADCs in various stages of the development cycle for solid tumors. Kadcyla™, targeting Her2 positive breast cancer, is the only ADC currently approved for solid tumors.

Over-expression of CDCP1 has been associated with tumors of the lung, ovary, breast, and kidney among others. In some cases, overexpression has been associated with poorer clinical outcomes (Alajati et al., 2015; Emerling et al., 2015; He et al., 2016a; Ikeda et al., 2009; Turdo et al., 2016). For example, in ovarian clear cell carcinoma, 90% of cases expressed CDCP1 on the surface of malignant cells. In this study, Kaplan-Meir analysis revealed that disease free, as well as overall survival, was significantly improved in CDCP1 non-expressers suggesting a direct role for CDCP1 in malignant progression (He et al., 2016a).

CDCP1 interacts with multiple oncogenic signaling pathways including RAS, EGFR, and Src to promote tumor growth, metastasis, and drug resistance (reviewed in He et al., 2016b). For example, Met receptor signaling drives the physical association of CDCP1 with EGFR in squamous cell carcinoma cell lines, contributing to resistance to the targeted EGFR inhibitor, gefitinib (Gusenbauer et al., 2013). Literature reports further suggest a role for CDCP1 in cell adhesion with its activation by tyrosine phosphorylation on the intracellular domain promoting cell motility and survival in suspension conditions (anoikis resistance) (Uekita et al., 2007). We and others have shown that down-regulation of cell surface CDCP1 through antibody-induced internalization inhibits cell motility, growth in semi- solid medium, and metastasis in vivo (Casar et al., 2012; Fukuchi et al., 2010; Siva et al., 2008).

The tumor inhibitory effects of ADCs are primarily driven by antibody mediated delivery of a toxic payload (Beck et al., 2017). ADCs can also retain the inhibitory properties of their constituent antibodies (Junttila et al., 2011) and therefore affect tumor killing by multiple mechanisms. Antibodies and ADCs targeting CDCP1 have shown tumor growth inhibitory properties in numerous preclinical cancer models (Casar et al., 2012; Fukuchi et al., 2010; He et al., 2016; Kollmorgen et al., 2013; Siva et al., 2008). CDCP1-ADCs have also demonstrated that CDPC1 is internalized upon antibody binding thereby highlighting CDCP1 as an ADC-responsive target (Fukuchi et al., 2010; Kollmorgen et al., 2013; Siva et al., 2008).

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