Conclusions These data support an immune-mediated anti-tumor effect of IL4I1 inhibition by CB-668, and suggest inhibition of IL4I1 represents a novel strategy for cancer immunotherapy.

REFERENCE

BT7480, A FULLY SYNTHETIC TUMOR-TARGETED IMMUNE CELL AGONIST (TICA™) INDUCES TUMOR LOCALIZED CD137 AGONISM AND MODULATION OF TUMOR IMMUNE MICROENVIRONMENT
Punit Upadhyaya, Kristen Hurov, Jessica Kublin, Jun Ma, Elizabeth Repash, Nicholas Keen. Bicycle Therapeutics, Lexington, MA, USA

Background After disappointing first clinical experiences with agonistic anti-CD137 (4-1BB) antibodies, a new generation of both systemic and targeted CD137 agonists is entering clinical development.1-3 These strategies rely on biologic agents with suboptimal properties for CD137 agonism due to their relatively large sizes and long circulating half-lives. These properties may limit their tissue penetration and cause sustained agonism resulting in overstimulation and activation-induced cell death of lymphocytes due to continuous exposure. Fully synthetic constrained bicyclic peptides (Bicycles™) with antibody-like affinities and target selectivity are uniquely suited to circumvent the above barriers to optimal targeted CD137 agonistic therapeutics. BT7480 is a tumor-targeted immune cell agonist (TICA) designed to deliver a highly potent CD137 agonist to Nectin-4 overexpressing tumor tissue with a flexible dosing schedule maximizing anti-tumor activity while circumventing the need for continuous systemic exposure.

Methods BT7480 functional activity in vitro was analyzed by measuring IL-2 and IFN gamma production from primary human PBMC/tumor cell co-cultures. BT7480 in vivo activity was determined in huCD137 syngeneic tumor models using tumor immune cell and transcriptional profiling by FACS, IHC, and Nanostring as well as tumor growth kinetics as read-outs.

Results BT7480 binds potently and simultaneously to Nectin-4 and CD137 as assessed biochemically and caused Nectin-4-dependent CD137 agonism in primary human PBMC/tumor co-cultures. BT7480 in vivo activity was determined in huCD137 syngeneic tumor models using tumor immune cell and transcriptional profiling by FACS, IHC, and Nanostring as well as tumor growth kinetics as read-outs.

Conclusions BT7480 is a highly potent Nectin-4 expression dependent CD137 agonist with optimal target binding, pharmacologic, and pharmacokinetic properties that enable intermittent dosing for curative effect through modulation of tumor immune microenvironment in syngeneic mouse tumor models. BT7480 is currently being evaluated in IND-enabling safety studies.

REFERENCES
APPLICATION OF A NOVEL MSENS DRUG DELIVERY TECHNOLOGY FOR MRNA THERAPEUTICS

Sojin Lee*, Joon Young Park, Goo-Young Kim, Sang Woo Jo, Minhyuk Yun, Hye Yeong Nam, Helen Cho. Samyang Biopharmaceuticals Corporation, Gyeonggi-do, Korea, Republic of Korea.

Background Successful clinical translation of mRNA therapeutics requires an appropriate delivery strategy to overcome instability of mRNA and facilitate cellular uptake into the cells. Several lipid based nanoparticle approaches that encapsulate mRNA, notably lipid nanoparticle (LNP), have been developed, but their efficiency for delivery to certain target tissues and toxicity profiles still have room for improvement.

The application of a novel polymer based nanoparticle technology platform, so called Stability Enhanced Nano Shells (SENS) for mRNA (mSENS) as a mRNA delivery platform for a cancer vaccine was demonstrated.

Methods The physicochemical properties of mSENS formulation, particle size and encapsulation efficiency, were characterized using dynamic light scattering (DLS) and gel retardation assay. Using luciferase-encoding mRNA, the protein expression levels in vitro and in vivo were evaluated by luciferase assay or bioluminescence imaging (BLI), respectively. For cancer vaccine studies, antigen (tyrosinase-related protein 2 (Trp-2)) expression in patients with functional and non-functional pituitary adenomas. BMC Endocr Disord 2020;20:39.


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EXOSOME SURFACE DISPLAY OF IL-12 RESULTS IN TUMOR-RETAINED PHARMACOLOGY WITH SUPERIOR POTENCY AND LIMITED SYSTEMIC EXPOSURE

Nuruddeen Lewis*, Chang Ling Sia, Katherine Kirwin, Sonya Haupt, Gauri Mahimkar, Tong Zi, Ke Xu, Kevin Dooley, Su Chul Jang, Bryan Choi, Andrew Grube, Christine McCoy, Jorge Sanchez-Salazar, Michael Doherty, Scott Estes, Kyriakos Economides, Douglas Williams, Srijam Sathyarayanan. Codiak BiSciences, Andover, MA, USA.

Background The promise of Interleukin-12 as a cancer treatment has yet to be fulfilled with multiple tested approaches being limited by unwanted systemic exposure and unpredictable pharmacology. To address these limitations, we generated exoIL-12™, a novel, engineered-exosome therapeutic that displays functional IL-12 on the surface of an exosome.

Methods IL-12 exosomal surface expression was achieved via fusion to the abundant exosomal surface protein PTGFRN. Potency was assessed in vitro using human PBMCs or murine splenocytes and in vivo using mouse subcutaneous tumor models. Local versus systemic pharmacology was determined with intratumoral injection in mice and subcutaneous injection in monkeys. All studies were benchmarked against recombinant IL-12 (rIL-12).

Results Exosomes engineered to express either murine or human IL-12 had equivalent potency in vitro to rIL-12 as