APPLICATION OF A NOVEL MSSENS 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))-specific T cell responses were assessed by immunophenotyping and serum PGE2 levels with vitamin D receptor and serum 25(OH)2D3 levels in breast and ovarian cancer. Anticancer Res 2012;32:351-357.

Results Systematic structure-activity relationship (SAR) investigation identified novel EP2 and EP4 dual antagonists. The most promising compound KT-00113 possesses high potency against both EP2 and EP4, while maintaining high selectivity over other prostanoid receptors. In vitro and in vivo ADMET studies show that KT-00113 has a favorable profile, apt for further examination in in vivo cancer models and immune cell function in tumors.

Conclusions KT-00113, a highly potent and selective EP2/4 dual antagonist has strong potential to become the best-in-class immune suppression lifting cancer immunotherapy and may be suitable for further development in a clinical setting.

REFERENCES

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 Mahinkar, Tong Zi, Ke Xu, Kevin Dooley, Su Chul Jang, Bryan Choi, Andrew Grube, Christine McCoy, Jorge Sanchez-Salazar, Michael Doherty, Scott Estes, Kyniakos Economides, Douglas Williams, Sriram Sathyanaayan. Codia 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
DEVELOPMENT OF IL-33 AS A NOVEL IMMUNOTHERAPY OF CANCER

Joshua Zhong*, Runzi Sun, Binfeng Lu. 1Carlmont High School, Belmont, CA, USA; 2University of Pittsburgh, Pittsburgh, PA, USA

Background Immune-checkpoint-blockade (ICB) therapy has produced unprecedented survival benefits for cancer patients but such therapy has been limited by low response rates in most cancer. One major obstacle for ICB therapy is the reduced immunogenicity of tumor tissues due to genetically driven down-regulation of epithelial tissue cytokines. IL-33 is a member of the IL-1 gene family and its level is downregulated in many advanced carcinomas such as lung cancer, breast cancer and pancreatic cancer. It has recently been shown that IL-33 plays an important role in mediating cancer immune therapy. In addition, transgenic expression of the active form of IL-33 in tumor cells or administration of the recombinant IL-33 exerts strong antitumor effects. Mechanistically, IL-33 enhances the function of Th1 and CD8+ T cells in vitro and immune memory without systemic IL-12 exposure and thereby create a therapeutic window for this potent cytokine.

Ethics Approval All animals were maintained and treated at the animal care facility of Codia Biosciences in accordance with the regulations and guidelines of the Institutional Animal Care and Use Committee (CB2017-001).

REFERENCES


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