

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

1. Cordes T, Hoellen F, Dittmer C, Salehin D, Kummel S, Friedrich M, Koster F, Becker S, Diedrich K, Thill M. Correlation of prostaglandin metabolizing enzymes and serum PGE2 levels with vitamin D receptor and serum 25(OH)2D3 levels in breast and ovarian cancer. *Anticancer Res*; **32** (2012):351–357.
2. Diakowska D, Markocka-Maczka K, Nienartowicz M, Lewandowski A, Grabowski K. Increased level of serum prostaglandin-2 in early stage of esophageal squamous cell carcinoma. *Arch Med Sci* (2014); **10**:956–961.
3. Akbari N, Ghorbani M, Salimi V, Alimohammadi A, Khamseh ME, Akbari H, Nourbakhsh M, Sheikh A, Taghavi SF, Tavakoli-Yaraki M. Cyclooxygenase enzyme and PGE2 expression in patients with functional and non-functional pituitary adenomas. *BMC Endocr Disord* 2020; **20**:39.
4. Gomes RN, Felipe da Costa S, Colquhoun A. Eicosanoids and cancer. *Clinics (Sao Paulo)*, **73** (2018) e530s.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0707>

708

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*

Background Successful clinical translation of mRNA therapeutics requires an appropriate delivery strategy to overcome instability of mRNA and facilitate cellular uptake into the cells.¹ 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 mouse splenocytes using flow cytometry and by the enzyme-linked immunosorbent spot (ELISPOT) assay. The anti-tumor efficacy was studied in B16F10 lung tumor model in C57BL/6 mice. Liver and systemic toxicity of mSENS treated mice was evaluated through blood chemistry and complete blood count (CBC) tests.

Results A library of mSENS formulations complexed with luciferase-encoding mRNA, were characterized for their particle

size, surface charge, encapsulation efficiency, colloidal stability, and in vitro and in vivo luciferase protein expression level. Upon systemic administration in mice, varying biodistribution profiles were observed, implicating the potential for tailored delivery to target tissues. Particularly, cancer vaccine application was further developed leveraging the formulation with preferential spleen delivery. Following vaccination with Trp-2 mRNA encapsulated with mSENS (Trp-2 mRNA-mSENS) in B16F10 tumor bearing mice, strong Trp-2 antigen-specific IFN- γ T-cell responses were observed. Generated anti-tumor immunity also marked suppression of B16F10 lung tumors were observed in Trp-2-mSENS immunized mice compared to non-immunized controls, demonstrating the potential of mSENS as a mRNA delivery platform for the application for vaccine.

Conclusions Proprietary biodegradable polymer based-mSENS platform offers an attractive delivery strategy for mRNA by tailoring to specific therapeutic applications. Depending on the application, whether it's a vaccine or protein replacement, a rationally designed mSENS formulation can efficiently distribute mRNA to specific tissues. In particular, application of a splenic mSENS formulation for a cancer vaccine has been demonstrated in murine tumor model. In summary, mRNA delivery through mSENS platform is expected to provide significant opportunities in clinical development for mRNA therapeutics.

Ethics Approval The study was approved by Samyang Biopharmaceuticals' IACUC (Institutional Animal Care and Use Committee), approval number SYAU-2027.

REFERENCE

1. Piotr S. Kowalski, Arnab Rudra, Lei Miao, and Daniel G. Anderson, delivering the messenger: advances in technologies for therapeutic mRNA delivery. *Molecular Therapy* Vol. 27 No 4 April 2019.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0708>

709

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, Sriram Sathyanarayanan. *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-12TM, 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