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 immuno-therapy.

REFERENCE

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706 BT7480, A FULLY SYNTHETIC TUMOR-TARGETED IMMUNE CELL AGONIST (TICA™) INDUCES TUMOR LOCALIZED CD137 AGONISM AND MODULATION OF TUMOR IMMUNE MICROENVIRONMENT

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Background After disappointing first clinical experiences with agonistic anti-CD137 (4-IBB) 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 cell co-cultures. BT7480 in vivo activity was determined in human CD137-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.

Ethics Approval The care and use of animals were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of WuXi AppTec and conducted in accordance with the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

REFERENCES

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707 DISCOVERY OF A NOVEL EP2 AND EP4 DUAL ANTAGONIST

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Background Prostaglandin E2 (PGE2) is one of the most abundant prostaglandins, with crucial roles in normal and pathologic physiology. Especially, PGE2 levels are abnormally elevated in many cancers, and high levels of PGE2 are known to be pro-tumorigenic, likely due to the immune suppressive effect in the tumor microenvironment.1–4 There are four types of PGE2 receptors; EP1, EP2, EP3 and EP4. Among them, EP2 and EP4 activate adenylyl cyclase and increase cAMP levels, which induce the cAMP-dependent protein kinase (PKA) signaling pathway. EP2 and EP4 are expressed in various immune cells (e.g. macrophages, dendritic cells, NK cells and CTLs), and genetic and pharmacological inhibition of EP2 and EP4 increases immune activity and suppresses tumor growth.

Methods To evaluate the binding affinity against EP2 and EP4, a radioligand binding assay was conducted using EP2 or EP4 transfected HEK293 cells. Cell membrane homogenates were incubated with [3H]PGE2 in the presence or absence of the test compounds. Following incubation, the samples were filtered rapidly under vacuum through glass fiber filters and rinsed several times with cold Tris-HCI. The filters were dried then counted for radioactivity in a scintillation counter using a scintillation cocktail. The results were expressed as a percent inhibition of the control radioligand specific binding. The antagonistic activity against EP2 and EP4 was assessed via LANCE Ultra cAMP assay (PerkinElmer). HEK293 cells over-expressing EP2 or EP4 were seeded into the plate and treated by PGE2 and compounds. After 30 minutes of incubation, cAMP levels were measured by FRET signal using Variskan plate reader, following the manufacturer’s protocol. Anti-tumor activity of KT-00113 was evaluated using LLC1 syngeneic model. When tumor volume reached approximately 100 mm3, mice were treated PO, QD. Tumor size was measured twice every week.
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 immuno-suppression lifting cancer immunotherapy and may be suitable for further development in a clinical setting.

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APPLICATION OF A NOVEL MSSENS DRUG DELIVERY TECHNOLOGY FOR MRNA THERAPEUTICS

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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 mouse splenocytes using flow cytometry and by the enzyme-linked immunosorbent assay (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 Biopharmaceutical’s IACUC (Institutional Animal Care and Use Committee), approval number SYAU-2027.

REFERENCE


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

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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...