Developing an Engineered Exosome Therapeutic Platform for Immuno-Oncology

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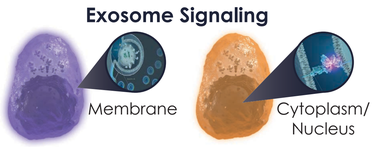
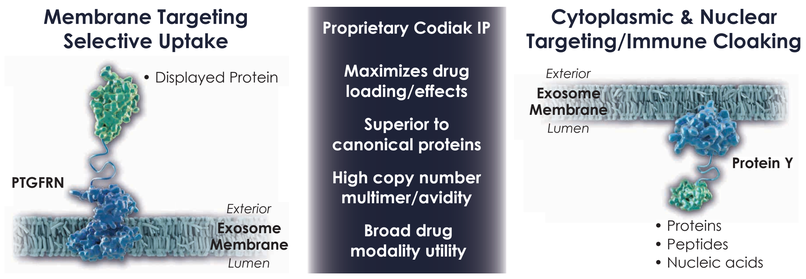
What are Exosomes?

- Exosomes are extracellular vesicles (30-200 nm) that convey complex molecules and biological signals between cells[1]



  - » Convey and protect complex macromolecules that alter the function of recipient cells
  - » Intrinsically non-immunogenic

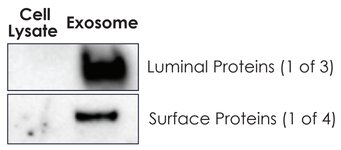
- Codiak BioSciences is developing a therapeutic platform utilizing exosome biology, known as engEX™

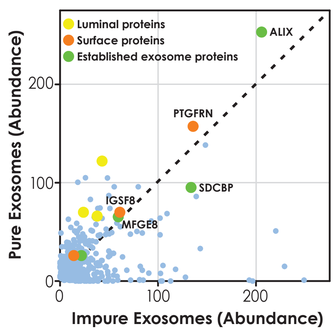


- Exosomes can be engineered to carry specific biologically active entities, including small molecules, proteins, antibodies, peptides and nucleic acids, individually or in combination, on the exosome surface, in the lumen, or both
- We believe our ability to alter tropism by precisely modifying the exosome surface may allow us to target many cell types in the immune system

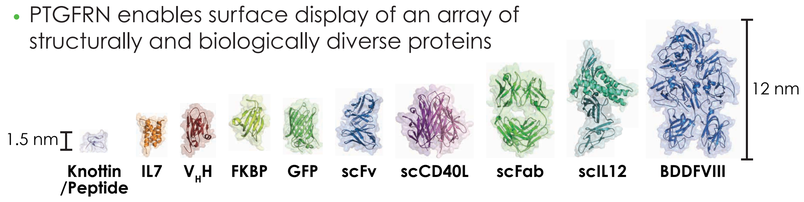
Identifying Proprietary Exosome Scaffold Proteins

- Proteomic analysis led to the identification of several scaffolds, including the exosome-specific protein transmembrane glycoprotein (PTGFRN, immunoglobulin super family)

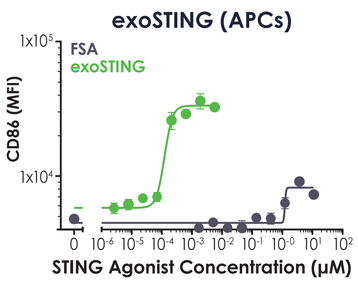




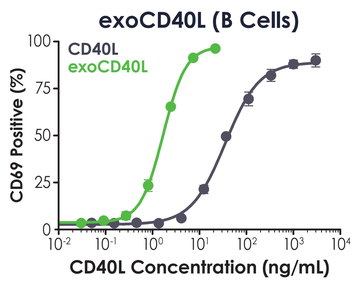
- PTGFRN enables surface display of an array of structurally and biologically diverse proteins



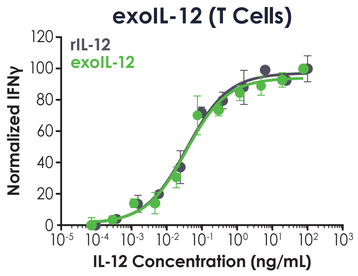
- The engEX™ platform currently allows us to engineer exosomes to precisely target a wide range of immune cell types, including Antigen Presenting cells (APCs), B cells, T cells, Macrophages, and NK cells*



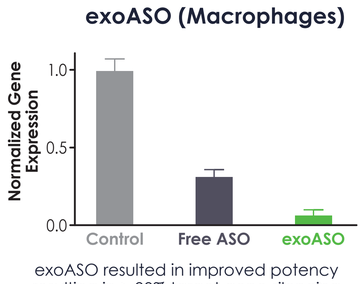
exoSTING improved APC activation by >10,000 fold vs. free STING agonist (FSA)



exoCD40L improved B-cell activation by ~15 fold vs. recombinant CD40L when expressed on exosome surface



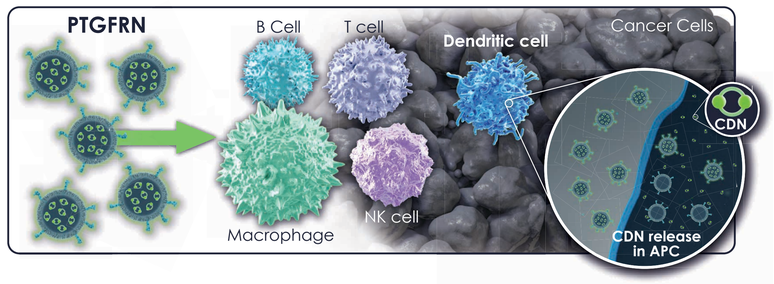
exoIL-12 retained similar potency to rIL-12 when displayed on exosome surface



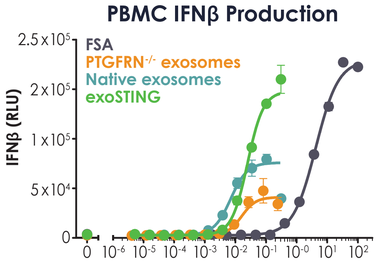
exoASO resulted in improved potency resulting in > 90% target gene silencing

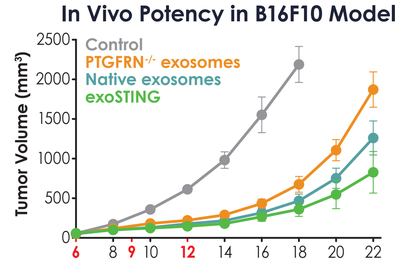
*Data from preclinical models

exoSTING is a Novel Therapeutic Candidate Targeting Cancer



- Exosomes containing damaged dsDNA following chemo- or radiation therapy can activate the Stimulator of Interferon Genes (STING) pathway and reinforce anti-tumor immunity[1]
- exoSTING is composed of exosomes overexpressing PTGFRN and loaded with a cyclic dinucleotide (CDN) small molecule STING agonist
- In preclinical models, the addition of PTGFRN to exosomes loaded with STING agonist resulted in significantly higher IFNβ production vs. exosomes without it
- Exosomes overexpressing PTGFRN demonstrated the most anti-tumor activity in checkpoint refractory B16F10 tumors

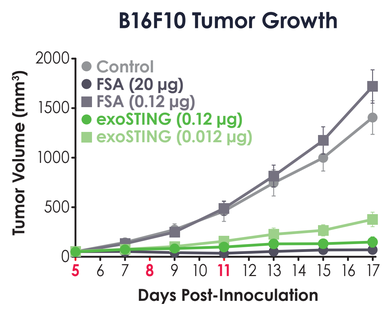




(Left Panel) Dose-response in human PBMCs treated with free STING agonist (FSA) or exosomes with overexpression of PTGFRN (exoSTING), native expression of PTGFRN, or exosomes devoid of PTGFRN$^{-/-}$ loaded with STING agonist. The IFNβ production was diminished in PTGFRN knockout (-/-) STING exosomes vs. PTGFRN overexpressed exoSTING, *p < 0.05 by 1-way ANOVA.
(Right Panel) Potency of STING-loaded exosomes with PTGFRN variants; treatment on Days 6, 9, and 12, indicated in red, with a minimally efficacious dose of STING agonist (0.02 μg).

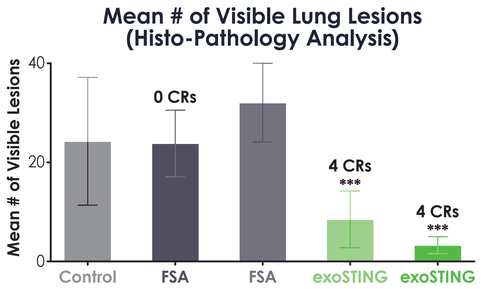
exoSTING Showed Superior Anti-tumor Activity in Preclinical models

- exoSTING showed robust potency in hard-to-treat cold B16F10 tumors at a 1000-fold lower dose than an FSA

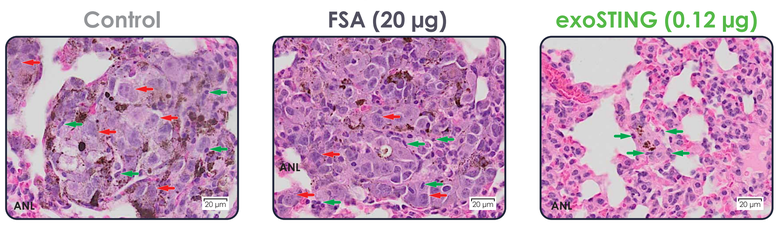


B16F10 cells inoculated SC and IV. Mean volumes for SC tumors, with treatment on Days 5, 8, and 11, indicated in red.

- Statistically significant reduction (p < 0.05) in visible lesions in mice treated with exoSTING compared to FSA



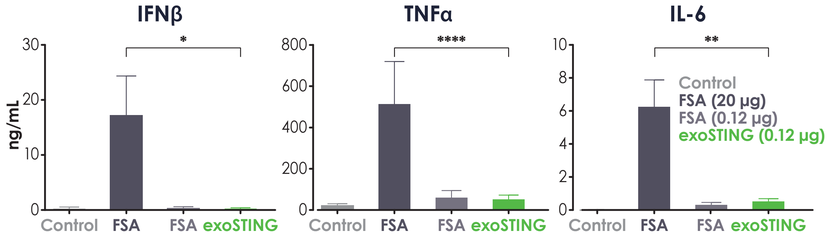
- 50% cure rate in animals treated with exoSTING
- Complete remission in distal lung tumor lesion with exoSTING



Representative images of histopathology analysis of lung tumors on Day 17
Tumor cells Immune cells ANL: Adjacent Normal Lung

exoSTING Delivers Potency without Systemic Inflammation

- Statistically significant reduction of serum cytokines compared to efficacious dose of free STING agonist, suggesting cytokine responses are limited to the tumor

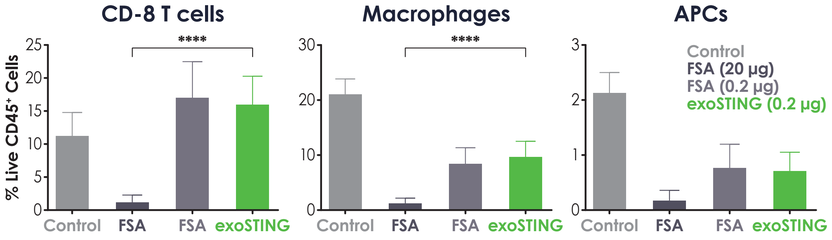


Mice bearing SC 50-70 mm^3 B16-F10 tumors received IT injections of exoSTING or free STING agonist; 4 h post injection, serum assayed for indicated cytokines. * p<0.05; ** p<0.005; **** p<0.0005 . Significance per 1-way ANOVA.

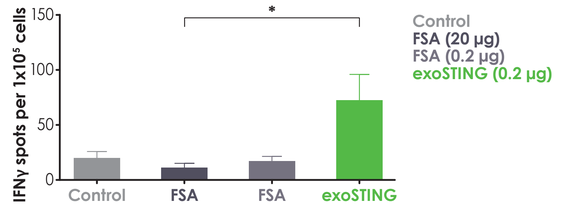
exoSTING Preserves Immune Cell Viability

- exoSTING preserved tumor resident T cells, macrophages, and APCs, resulting in better systemic immunity than the free STING agonist

Preserves Effector T cells and APCs in the Tumor



Better Systemic Immunity / Antigen-specific T-cell Response

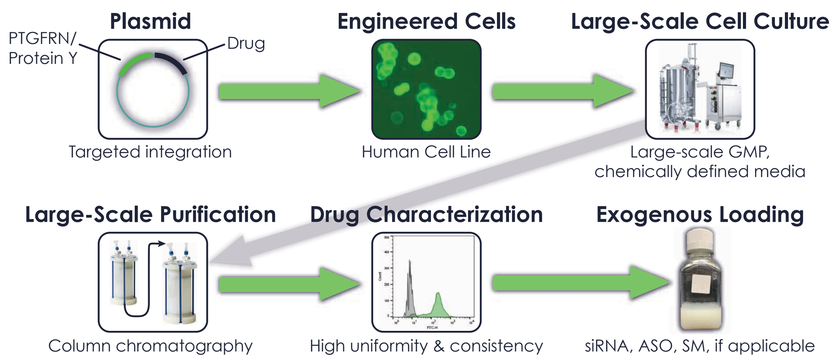


Analysis of TIL and spleen subsets by flow cytometry 24 hours after a second dose of exoSTING or FSA. * p<0.05; **** p<0.0005, Significance per 1-way ANOVA

exoSTING Summary: A Promising New Therapeutic Candidate

- exoSTING, based on the engEX™ platform, is being developed as a novel therapeutic candidate targeting cancer
- Utilizing a high-density PTGFRN surface display, exoSTING is loaded with a proprietary STING agonist
- exoSTING provided anticancer potency at doses 1000-fold lower than a free STING agonist
- In preclinical models, at potent doses, exoSTING resulted in low levels of serum systemic cytokines vs. a free STING agonist, suggesting the potential for a wide therapeutic index
- In preclinical models, exoSTING preserved effector T cells and APCs in the tumor, with better systemic immunity than a free STING agonist
- IND and CTA-enabling studies are ongoing, with a potential filling in the first half of 2020

Proprietary and Scalable Production Process Established



Reference: 1) Kitai et al. DNA-Containing Exosomes Derived from Cancer Cells Treated with Topotecan Activate a STING-Dependent Pathway and Reinforce Antitumor Immunity. *J Immunol* 2017; 198:1649-1659.