Docket #: S23-281

Selective Organ and Cell-type in vivo Delivery of RNA Using GSer-CARTs

Stanford scientists have discovered that Guanidinylated Serinol Charge-altering Releasable Transporters (GSer-CARTs) can be tuned for selective mRNA delivery to the lung and spleen in a predictable fashion. Selective in vivo RNA delivery can enhance on-target efficacy and reduce off-target toxicity of RNA therapeutics.

RNA-based technologies have emerged as a versatile and successful method for many biomedical applications such as COVID-19 vaccines, cancer immunotherapy, and genome editing. Contemporary delivery of RNA therapeutics has been enabled by lipid nanoparticles (LNPs) that are capable of complexing, protecting, and delivering mRNA into cells where they are released for translation. But, while some clinical success has been demonstrated with the use of LNPs, their innate propensity for trafficking to the liver greatly limits their biomedical applications. Accordingly, enhancing on-target efficacy and reducing off-target toxicity remain a grand challenge in the field of RNA-based technologies.

Unlike the vast majority of lipidated ammonium-based delivery systems, GSer-CARTs are novel guanidinium-based transporters that enable efficient mRNA delivery and, after a unique charge cancellation to neutral byproducts, release their RNA cargo for intracellular translation. Importantly, through systematic investigation, GSer-CARTs have been identified that upon IV administration are highly selective for uptake into the the lung (up to 96%) and spleen (up to 98%) in mice. In addition, GSer-CARTs enable the selective transfection of splenic macrophages (up to 80%) without the use of targeting ligands. GSer-CARTs work with a variety of cargoes including circRNA. They are also readily prepared and tuned, stable upon storage and well-tolerated. Consequently, GSer-CARTs have the potential to become a leading delivery system for a variety of RNA therapeutics due to their ease of synthesis, stability, tolerability and on-target efficacy without a targeting ligand.

Stage of Development:
Research – *in-vivo* data

Applications

- Specific *in vivo* delivery of mRNA to the lung and/or spleen
- Enhance on-target efficacy and reduce off-target toxicity of RNA therapeutics
- Selective delivery to various cell-types such as splenic macrophages and lung cells

Advantages

- Step-economically (two steps) prepared, scalable and storable
- Readily tunable and predictable delivery to organs *in vivo*
- Well tolerated
- Efficient mRNA release and delivery to cells
- Selective cell-type delivery without the use of targeting ligands

Publications

- Zhijian Li, Laura Amaya, Aloysius Ee, Sean K. Wang, Alok Ranjan, Robert M. Waymouth, Howard Y. Chang, and Paul A. Wender. Organ- and Cell-Selective Delivery of mRNA In Vivo Using Guanidinylated Serinol Charge-Altering Releasable Transporters. *Journal of the American Chemical Society* 2024. 146 (21), 14785-14798.

Patents

- Published Application: WO2025072271

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