Immunome Res 2018,Volume:14
DOI: 10.4172/1745-7580-C3-021

Delivering results: synthetic delivery materials created *via* engineering design criteria for self-replicating replicon mRNA vaccines

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To combat with orphaned indications, sudden outbreaks, evolving pathogens and biosecurity threats, Tiba Biotech has developed a fully synthetic replicon mRNA platform for the rapid design and scalable manufacture of vaccines that generate protective cellular (T cell) and humoral (antibody) responses against a range of diseases. The technology consists of two major components: an engineered antigen-expressing replicon mRNA payload capable of finite and controlled self-replication that induces potent interferon responses, and a chemically-defined modified dendrimer-based delivery material. The engineering advances embodied in this vaccine platform delivery technology include: (1) thermostable components that facilitate a straightforward self-assembly process. This capability reproducibly yields synthetic adjuvant-free mRNA nanoparticles of uniform size and shape, thus enabling rapid formulation of the drug product; (2) creation of stable nanoparticles that do not expose or release the replicon mRNA extracellularly, which would prematurely activate innate immunity and shut down the ability to express the exogenous mRNA; (3) a large, flexible payload capacity for multiplexing, which is the co-delivery of multiple large nucleic acid molecules in a single nanoparticle, thus enabling the simultaneous transport of complex or multiple subunit antigens and potentially the induction of cross-protective immunity to multiple strain sequences; and (4) an ionizable nature to prevent cytotoxicity and a systemic increase in inflammatory cytokines. Demonstrative of this platform's broad utility, it has been used to generate protective immunity in multiple lethal challenge models, including Ebola virus, Venezuelan equine encephalitis, H1N1, *Toxoplasma gondii* and HPV-induced cancer. Additionally, candidate vaccines have been developed against Zika virus and parasitic flatworms. Furthermore, early delivery material safety studies in nonhuman primates and livestock animals showed no reactogenicity, highlighting its tolerability and potential for both clinical translation and animal health.

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