Docket #: S20-234

Method and composition of matter for blocking production of respiratory viruses in virus-infected human cells

Stanford researchers have invented a method and developed compositions of matter to reduce the production of infectious viruses in cells that line the respiratory tract. The invention enables the use of gene-silencing approaches to prevent and treat viral infections.

The invented method leverages use of a micro-vesicle called ARMMS, which is produced by direct outward budding of the plasma membrane in cells that produce arrestin-like cellular protein, ARRDC1 (PNAS:109,4146). ARRDC1 localizes to the plasma membrane and recruits another protein (TSG101) to the site, which in turn causes the plasma membrane to bud outward and form a micro-vesicle. RNAs that are physically attached to ARRDC1, are transferred into the vesicle along with ARRDC1. Following ARMMS release, they can fuse with plasma membranes of other cells and discharge their cargo directly into the cytoplasm of those cells, evading degradation by extracellular enzymes, and hence overcoming a major challenge in delivering RNA therapeutics.

A fruitful application of the technology is prophylaxis and treatment of COVID-19. The technology can be used to attack coronavirus replication protein RdRP (RNA-dependent RNA polymerase), a major molecular target, at multiple evolutionarily-conserved sites---limiting drug resistance by virus mutation.

Stage of Development
In vitro data

Applications

- Delivery of any prodrug RNA: siRNA, RNAi, miRNA, stRNA, dsRNA, shRNA etc.

- Delivery to any cell type: viral, mammalian etc.
- Therapeutic for COVID-19, SARS, MERS, Cancer, Genetic Diseases, Metabolic Diseases

Advantages

- Delivery to any target cell: viral, mammalian etc.
- Intranasal method of delivery
- Delivery of undegraded prodrug RNA by evading degradation via:
  - extracellular enzymes (proteases and nucleases) by ARMMS packaging
  - DICER by genetic alteration of ARMMS-producing cells to inactivate DICER genes
  - endocytosis mechanisms by direct cargo delivery to target cell cytoplasm
- Limits drug resistance by virus mutation

Publications

- Nabhan, J. F., Hu, R.,et al. (2012). Formation and release of arrestin domain-containing protein 1-mediated microvesicles (armms) at plasma membrane by recruitment of TSG101 protein. PNAS 109(11), 4146–4151.

Patents

- Published Application: WO2022046711
- Published Application: 20230304005
- Issued: 12,815,906 (USA)

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