***Animal Procedures - Treatments.***

*Statement on Animal Care and Use*

All *in vivo* experiments in the macaques were approved by the Animal Care and Use Committee of the University of California and carried out by certified staff at the National Primate Research Center at Davis, California.

*Experimental Groups*

Eight 3-5 months old rhesus macaques were assigned treatments summarized in Condition 1 – Condition 8 in Data Submission excel file. Study group 1, consisting of 4 rhesus macaques (Condition 1, 2, 7, and 8) was designed to evaluate the biodistribution of the intra-tracheally aerosolized fluorescent protein cargo DRI-NLS-Cy5 with shuttle peptide S10 (FS66d2) in the tracheobronchial tree and the lungs, and identify the airway epithelial cell subtypes incorporating the fluorophore. Two of the four monkeys receiving the fluorophore alone served as a control. Study group 2 consisting of another 4 rhesus macaques (Condition 3 – Condition 6) was designed to examine the editing of the CCR5 locus after intra-tracheal aerosolization of the base-editor (Cas9-ABE RNP) and two different shuttle peptides, S10 (one monkey) and FSD315 (two monkeys). One monkey received the base editor alone.

*Animal Experiments – Treatments Administration*

Rhesus monkeys were anesthetized using 2% isoflurane or Telazol IM, and positioned in a dorsal recumbency. Clinical parameters, such as body weight, temperature, respiration rate as well as venous blood were collected. Antero-posterior serial CT images were collected immediately before and after the instillation. Instillation of the solution into the airways was performed using the MADgic laryngo-tracheal mucosal atomizer (Fisher Scientific, Catalog No. NC0924493, Teleflex LLC Madgic Laryngo Tracheal Atomiz MAD700). The atomizer was inserted via the larynx into the trachea with the tip positioned just below the vocal cords. The placement of the atomizer tip was ascertained by the CT imaging. A prefilled syringe containing 1 ml of the instillation solution was connected to the proximal end of the atomizer and the content was expelled to the airways by applying a pressure to the syringe pestle. Additional 400 ul of ambient air was used to complete the instillation of materials left in the atomizer tubing. Atomizer was removed from the airways, and the monkeys remained anesthetized under constant monitoring for additional 1-2 hours followed by the necropsy in the fluorescent protein group, or were allowed to recover from the anesthesia and were euthanized 7 days after the instillation in the gene editor group.