Lentiviral-mediated expression of monoclonal antibodies in the lung to protect against influenza

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Protein based therapeutics, such as monoclonal antibodies and enzyme replacement therapies, have had dramatic clinical impact in chronic diseases, but these therapies can be associated with high treatment burden (e.g. multiple inhalations or injections). Delivery of lentiviral and AAV vectors to organs such as the liver and muscle can generate 'protein factories' in the body. The secretion of therapeutic proteins into the circulation from a single administration of vector can result in persistent, stable levels without the fluctuating 'peak and trough' concentrations observed with multiple (often weekly) injections. We are investigating the expression of monoclonal antibodies in the lung to protect against respiratory pathogens, including broadly neutralising antibodies for long-lasting passive immunity to widely divergent and emerging strains of influenza. Our preferred vector is based on a third-generation, self-inactivating simian immunodeficiency virus (SIV), which has been pseudotyped with the F and HN proteins from Sendai virus (rSIV.F/HN) for efficient cell targeting in the lungs (Thorax 2017;72:137-147). We constructed rSIV.F/HN vectors using the hCEF promoter to express luciferase and EGFP reporter genes, as well as vectors expressing the broadly neutralizing antibody T1-3B, which was isolated from vaccinated volunteers (V_H1-69 germline family), and is able to cross-react with multiple group 1 influenza A strains. Intranasal delivery of rSIV.F/HN hCEF Lux (5E7 Transducing Units (TU)) to BALB/c mice (n=4) resulted in robust luciferase expression in both the nose (~1E6 p/s/cm^2/sr) and lung (~5E5 p/s/cm^2/sr) that was maintained for at least 150 days post-delivery ($p>0.15$). Visualisation of lung sections from mice dosed with rSIV.F/HN expressing EGFP (1E8 TU), showed fluorescence in multiple cell types including airway epithelial and parenchymal cells, as confirmed with co-localisation of β-tubulin (ciliated) or Surfactant protein C (Alveolar Type II) cell markers with native EGFP. Intranasal delivery of rSIV.F/HN expressing T1-3B (5E7 TU) resulted in expression of antibody in both the serum (~0.1 μg/mL) and Bronchoalveolar Lavage Fluid (BALF) (~0.1 μg/mL) that was significantly higher than naive or irrelevant vector treatment ($p<0.05$ for all). Using the murine influenza challenge model, we showed that intranasal delivery of 1E8 and 2.7E8 TU of the vector could protect mice against the highly lethal influenza strain A/PR/8 H1N1 (10 LD50), resulting in 83% ($p<0.01$) and 100% survival ($p<0.01$), respectively. We have also shown protection in mice against the 2009 pandemic H1N1 virus (A/California/7/2009) (10 LD50), in which 1E7 TU and 1E8 TU of the vector resulted in 67% ($p<0.001$) and 100% ($p<0.001$) survival, respectively. We speculate that during the next human influenza pandemic, prophylaxis provided by lung gene transfer may be more cost-effective and time-responsive than traditional, vaccines or parenteral administration of therapeutic antibody, offering an important first line of defence for essential health workers.