Lung-targeted lentiviral vector mediates passive immunisation against influenza

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Lentiviral vectors are being investigated for passive immunisation against respiratory pathogens such as Influenza A, which causes >500,000 deaths annually. Current vaccines and prior infection offer no lasting protection against emerging strains and a new global influenza pandemic is anticipated by the World Health Organisation. Broadly neutralising antibodies (bnAbs) isolated from vaccinated volunteers can be used for passive immunisation, but have a relatively short half-life in the circulation and are expensive to manufacture. Delivery of anti-influenza bnAb genes to the lung could provide long-lasting passive immunity to widely divergent strains of influenza. We have utilised lentiviral vectors pseudotyped with the Sendai virus F and HN proteins (rSIV.F/HN) to target lung epithelial cells and the hCEF promoter for long-term lung gene expression. In mice, intranasal delivery of the vector (5e7 TU/mouse) expressing T1-3B (which cross-reacts with multiple Group 1 influenza A strains) resulted in persistent antibody secretion into the serum (340 ng/mL; $p<0.001$ on day 28) and the lung epithelial lining fluid (ELF) (2,300 ng/mL, $p<0.001$). Similar doses also protected mice against a lethal dose of influenza (~15 LD_{50} H1N1 strain A/PR/8/1934) with 50% survival ($p<0.001$). A matched dose of rSIV.F/HN expressing T1-3B from the hCEF promoter was significantly more potent compared with expression from the CMV promoter (0% survival) and the mock treated control group (0% survival). We speculate that expression of broadly neutralising antibodies could be

both time-responsive and cost-effective when deployed as a first line of defence against the next human influenza pandemic.