Bioengineering exosomes to enhance brain targeting in a mouse traumatic brain injury model

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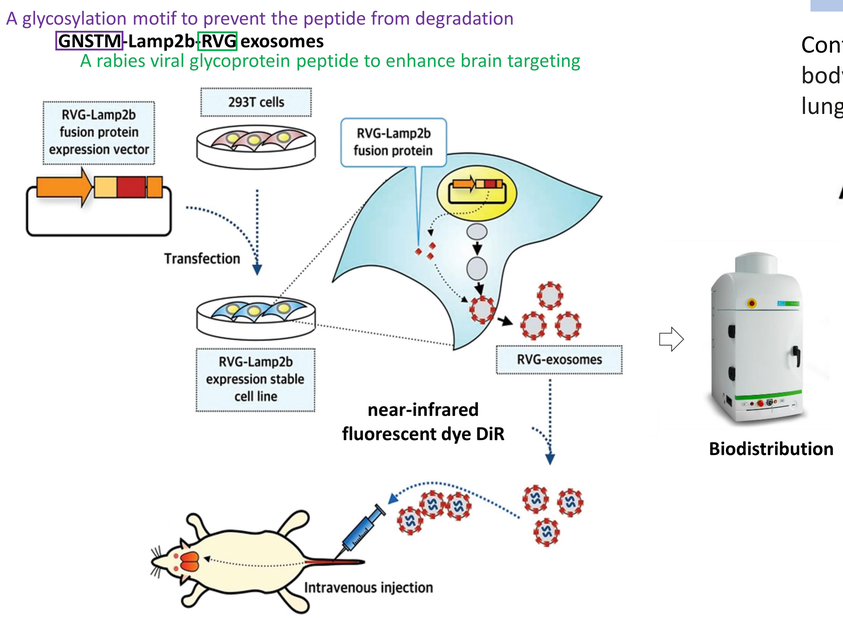
Introduction

This study generated a stable cell line for producing exosomes with a peptide, Rabies Virus Glycoprotein (RVG), attached to a membrane protein, Lamp2b, to enhance brain delivery capacity (Nat Commun. 2018 Apr 3;9(1):1305). Studies were conducted to compare the uptake of native and bioengineered exosomes (RVG-exosomes) by human neuroblastoma cells and their brain distribution in a mouse traumatic brain injury (TBI) model.

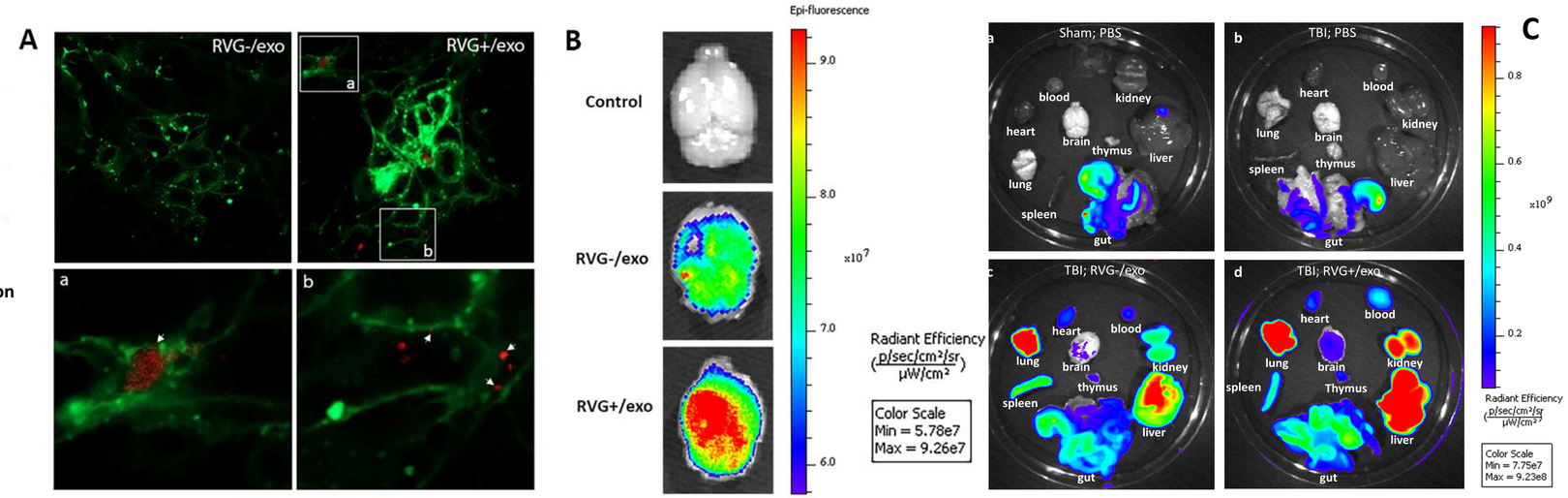
Methods and Materials

HEK293T cells were transfected with pcDNA GNSTM-3-RVG-10-Lamp2b-HA (Addgene) to generate a stable cell line. Native and RVG-exosomes were concentrated using the Tangential Flow Filtration system (Pall Corporation). DiO-stained SH-SY5Y cells (0.5×10^5 cells/well) were incubated with DiR-labelled native or RVG-exosomes for 2 hours before they were fixed and imaged using a confocal microscope (× 60 magnification). Adult CD1 mice were subjected to a severe unilateral cortical contusion by compressing the cortex to a depth of 2.0 mm at a velocity of 5 m/s and 100 ms duration. Within 15 min post-TBI, mice were given native or RVG-exosomes (9×10^{10} particles/mouse, i.v.) labelled with CellMask™ Deep Red Plasma Membrane Stain (Thermofisher). Sham-operated mice received equal volumes of vehicle (PBS). Bio-distribution and brain delivery were examined using *in vivo* optical fluorescent imaging (IVIS® Spectrum *in vivo* imaging system) 2 hours after injection.



Results

Confocal images in **A,** showed cell uptake of RVG-exosomes (red) by SH-SY5Y cells (green) and the presence of RVG-exosomes along the membrane of the cell body (a) and neurites (b). Optical images (**B & C**) demonstrated high uptake of both native exosomes and RVG-exosomes in the liver, spleen, GI tract, and lungs. The RVG-exosome treatment increased signal in the brain, with an average radiant efficiency 41% higher than for native exosome treatment.



Conclusion

The expression of Lamp2b-RVG increases the uptake of exosomes by neuroblastoma cells and the accumulation of exosomes in the brain after systemic administration.