# Generating Artificial Targets to Deliver Therapies Specifically to the Brain

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Treatment of neurological disorders such as Alzheimer's disease is hindered by the presence of the blood-brain barrier (BBB), a protective barrier composed of the specialized endothelial cells lining the brain vasculature. To overcome the BBB, current brain-delivery strategies bind nanoparticles to target proteins on the brain vasculature. However, such strategies have inherent brain-specificity limitations, as the target proteins are also found in the peripheral vasculature, leading to off-target nanoparticle delivery to organs like the lungs and liver.

Here, we present a novel delivery strategy[1] which exploits the specialization of the BBB to generate 'artificial' targets selectively on brain endothelial cells (BEC) (figure 1), thereby boosting brain specificity. We demonstrate the low-endocytic rate of BEC *vs.* peripheral EC[2] may be harnessed to selectively retain free ligands on the surface of the brain vasculature, thereby acting as targets to direct nanoparticles towards the brain with no increased accumulation in peripheral organs.

In addition, we outline a novel selection paradigm to identify brain-targeting ligands based on probing the endocytic internalization rates of individual cell-membrane components across different endothelial phenotypes. We identify peptides selectively retained on the surface of BEC (fig. 2) to generate artificial targets for the delivery of proteins to the brain. Hence, this selection paradigm identifies peptides for brain-targeting which would have been overlooked by conventional screening procedures, thereby increasing the repertoire of cell-membrane components able to be exploited for targeting nanoparticles to the brain.

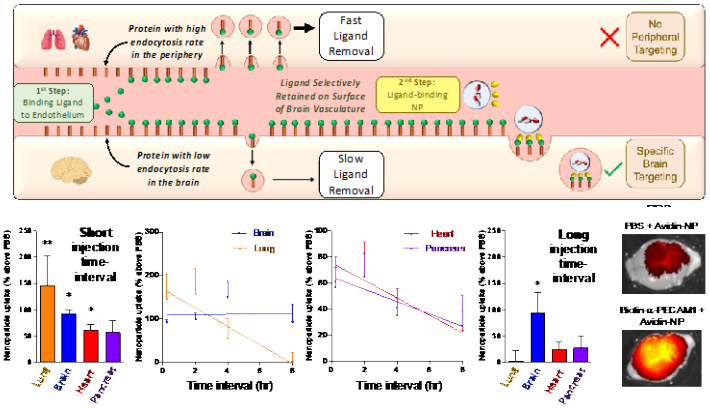


**Figure 1.** Generation of artificial brain targets by exploiting the low endocytic rate of brain endothelial cells.

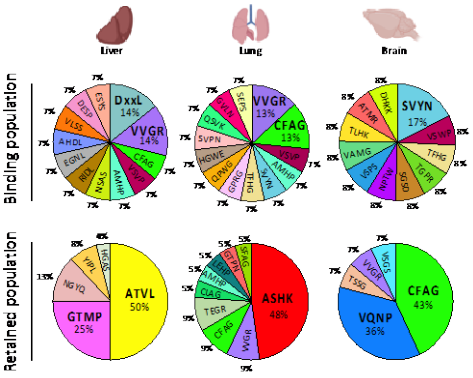


**Figure 2.** Identification of peptides binding to, or retained on the surface of liver, lung or brain endothelial cells.

**References**:

[1] Gonzalez-Carter *et al.*, *Proc Natl Acad Sci USA*, **2020**, *117 (32)*, 19141-19150
2 Ben-Zvi *et al.*, *Nature*, **2014**, *509 (7501)*, 507-11