The Avidity Paradox: Optimising T7-Polymersome Valency for Enhanced Blood-Brain Barrier Transcytosis

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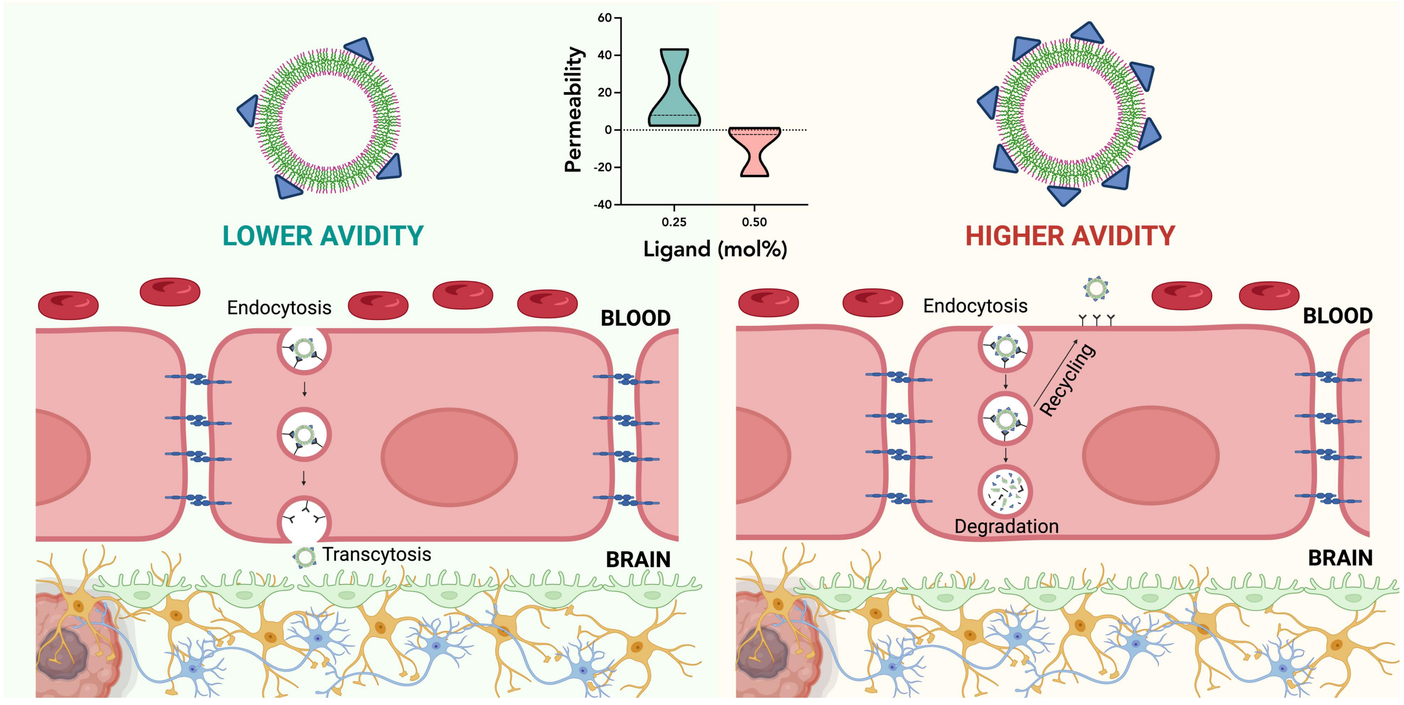
Drug Delivery to the Brain

Over the past decade, roughly 10% of new FDA-approved drugs targeted central nervous system (CNS) disorders, while it has been estimated that 98% of small-molecule drugs and nearly all large molecule therapeutics are unable to cross the blood–brain barrier (BBB). There is a clear need for novel therapeutic modalities that promote receptor-mediated transcytosis modulation and efficiently deliver drugs to the brain.

Aim of the Project

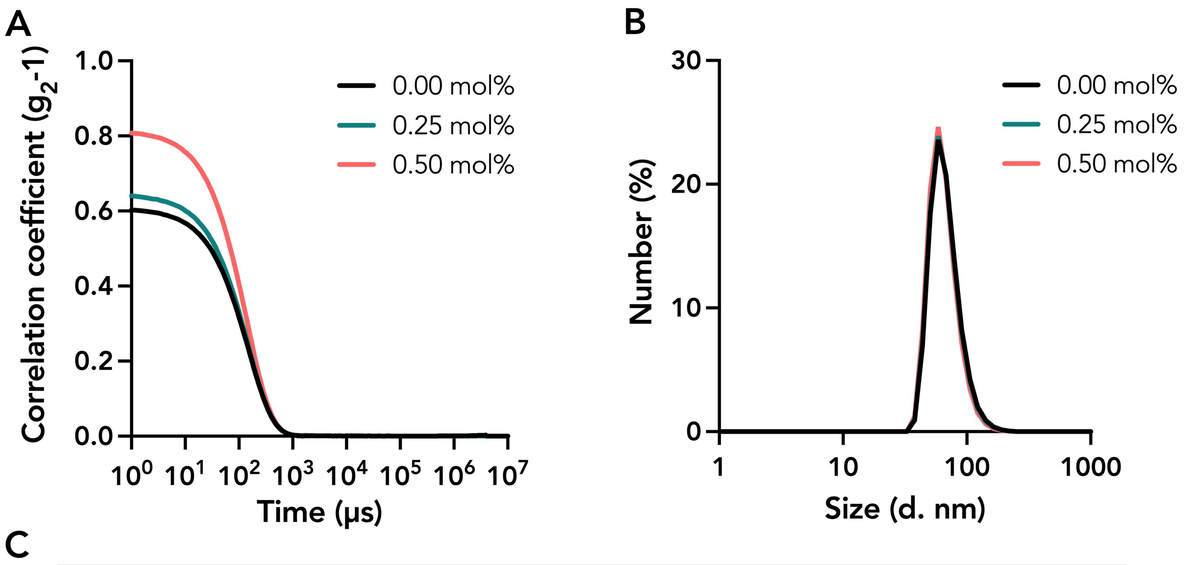
Traditional targeted nanomedicines focus on using high affinity ligands that selectively bind to cell receptors, such as the transferrin receptor (TfR) in the endothelial cells of the BBB. Here, we aim to understand whether avidity also plays a role on the capacity of nanoparticles to cross such barriers.



Methods

We synthesised poly(ethylene glycol)-*b*-poly(lactic acid) (PEG-*b*-PLA) polymersomes and functionalised them with the T7 (His-Ala-Ile-Tyr-Pro-Arg-His) heptapeptide, which exhibits high affinity to the to human TfR, via copper-catalysed alkyne-azide cycloaddition. Formulations were prepared with low (0.25 mol%) and high (0.50 mol%) T7 valencies and characterised by dynamic light scattering (DLS) and transmission electron microscopy (TEM). To evaluate BBB crossing, we used a two-dimensional in vitro model consisting of bEnd.3 mouse brain endothelial cells in a transwell system.

Results



C

Formulation	T7 (mol%)	Mean diameter (nm) ± SD
Pristine	0.00	103.2 ± 20.8
Low valency	0.25	101.7 ± 20.4
High valency	0.50	95.9 ± 18.8

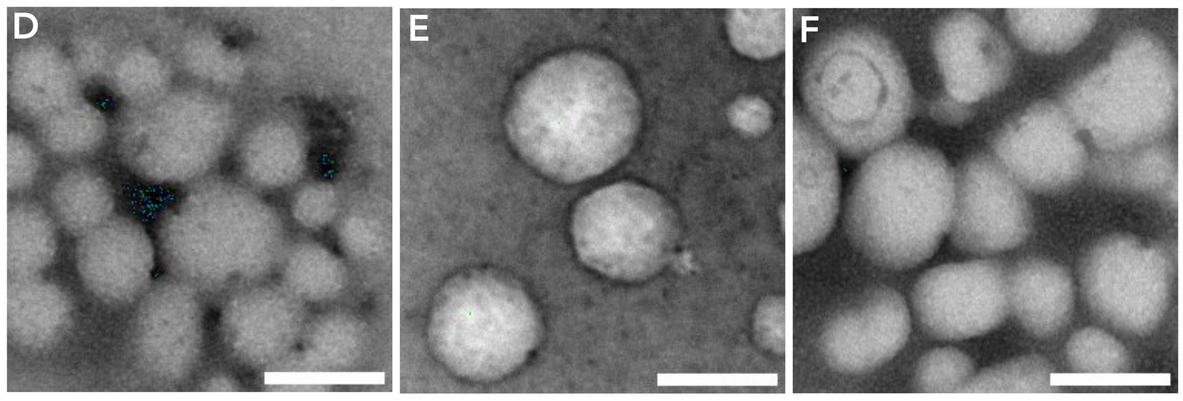


Fig 1. Characterisation of polymersomes in terms of size and morphology. Dynamic light scattering (DLS) autocorrelation function data **(A)** and size distribution by number **(B)** of pristine and T7-decorated PEG-b-PLA polymersomes. Summary table of size distribution results **(C)** showing a similar peak diameter for both nanoparticle types (n = 3). SD, standard deviation. Representative transmission electron micrographs (TEM) of pristine polymersomes **(D)**, low T7 valency (0.25 mol%) **(E)**, and high T7 valency (0.50 mol%) polymersomes **(F)**. Scale bar: 100 nm.

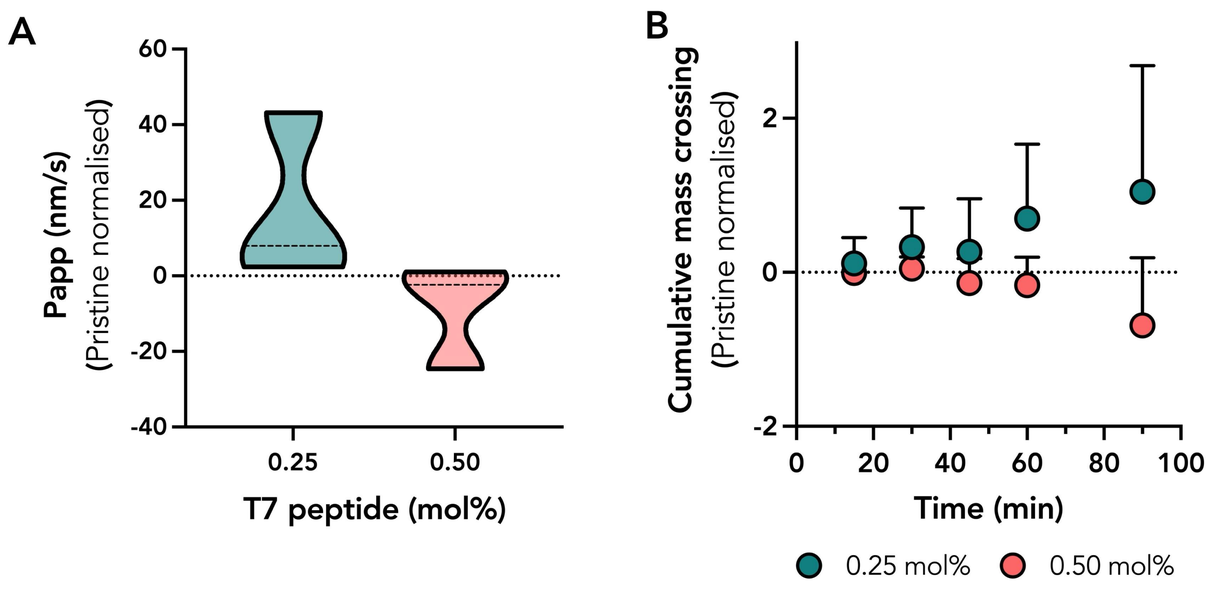


Fig 2. Blood–brain barrier transcytosis. Apparent permeability coefficients (Papp) for low (0.25 mol%) and high (0.50 mol%) T7 valency polymersomes **(A)**. Truncated violin plots depict the data distribution for each group. The non-specific TfR transport was removed by subtracting the Papp values of pristine polymersomes (n = 3). Cumulative mass crossing of polymersomes across the in vitro BBB model over a 90-minute period **(B)**. Data is normalised to pristine polymersomes to isolate the effect of the T7 peptide on BBB permeability (n = 3).

Proof-of-concept

We have shown that targeted PEG-*b*-PLA polymersomes can safely transport drugs across the BBB, with low ligand valency formulations showing superior BBB permeation compared to high-valency designs.

Full Paper

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