Polypeptide-based therapeutics for CNS disorders

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Introduction

Central Nervous System (CNS) drug discovery and development is a challenging task due to the presence of the most impenetrable biological barrier in the human body- the Blood Brain Barrier (BBB). Indeed, only 2 % of small-molecule drugs and almost 0 % of biologic drugs do reach the brain, thus limiting the development of efficient treatments for brain diseases.[1]

Focused on designing non-invasive strategies for brain targeting and active delivery through nanotechnological approaches, we are developing a polymer-based platform for i.v. and also for intranasal delivery using polyglutamates, underpinned on previously established findings of our lab. [2,3]

Results and Discussion

These versatile, biodegradable carriers with controlled architecture and self-assembled behaviour hold several key features. For the i.v. approach they have been modified to target LRP1 receptor overexpressed in early stages of Alzheimer's disease (AD) as well as in the presence of metastasis. We have already validated this approach in an AD model [4] as well as in a Triple negative Breast cancer brain metastasis model (unpublish data). For the intranasal approach. Our systems were crosslinked with reversible disulfide chemistries, prone to disassemble under reductive media to facilitate enhance chemical adsorption to on the mucosa via disulfide interchange with cysteine-rich glycoproteins and also to allow greater diffusion/penetration rates in brain. In parallel, surface modification with targeting motifs has been exploited to improve the ability to cross the mucosal barrier in synergy with the disulfide cross-linking motifs. Screening studies have been performed through mucodiffusion evaluation by NMR techniques and ex vivo permeation assays in a sheep mucosal model. Furthermore, the conjugation of targeting moieties to modulate mucodiffusion and mucoadhesivity and also the conjugate size and shape have demonstrated to be key parameters to enhance mucosa permeation.

Conclusions

We envision that our well-defined polypeptidic system designed will be a suitable therapeutic platform to treat CNS disorders by rationally design any of their components and adapt them to the i.v. or i.n. route of administration.

References

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