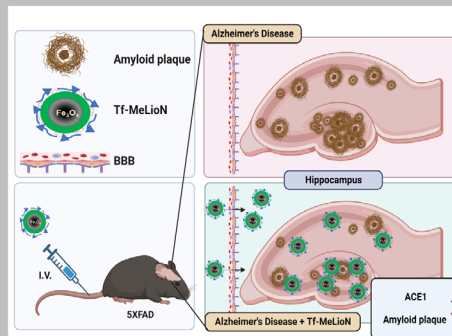


Abstract

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases and a major contributor to dementia. Although the cause of this condition has been identified long ago as aberrant aggregations of amyloid and tau proteins, effective therapies for it remain elusive. The complexities of drug development for AD treatment are often compounded by the impermeable blood-brain barrier and low-yield brain delivery. In addition, the use of high drug concentrations to overcome this challenge may entail side effects. To address these challenges and enhance the precision of delivery into brain regions affected by amyloid aggregation, we proposed a transferrin-conjugated nanoparticle-based drug delivery system. The transferrin-conjugated melittin-loaded L-arginine-coated iron oxide nanoparticles (TF-MeLiONs) developed in this study successfully mitigated melittin-induced cytotoxicity and hemolysis in the cell culture system. In the 5XFAD mouse brain, TF-MeLiONs remarkably reduced amyloid plaque accumulation, particularly in the hippocampus.

This study suggested TF-MeLiONs as a potential drug delivery platform and TF-MeLiONs as a candidate for therapeutic drug targeting of amyloid plaques in AD. These findings provide a foundation for further exploration and advancement in AD therapeutics.

Graphical summary



Conclusion

This study demonstrated that TF-MeLiONs have the potential to prevent AD development by reducing the A burden in the hippocampus of 5XFAD mice. TF-MeLiONs successfully mitigated the melittin-induced cytotoxicity and hemolysis in an *in vitro* cell culture. In the 5XFAD mouse brain, TF-MeLiONs were delivered across the BBB and remarkably reduced amyloid plaque accumulation, particularly in the hippocampus. This study suggested the potential of TF-MeLiONs as a delivery platform and that of TF-MeLiONs for ameliorating amyloid-related pathologies in AD and provides a foundation for the use of TF-MeLiONs as a promising AD treatment strategy.

Funding

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Results

Figure 1. Synthesis and characterization of TF-MeLiONs.

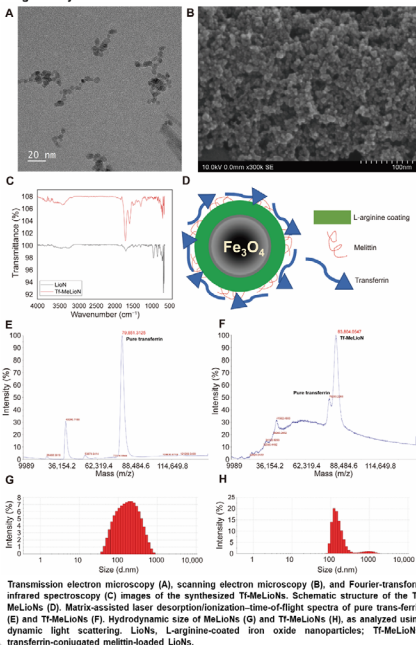


Figure 2. Biosafety profile of TF-MeLiONs in vitro.

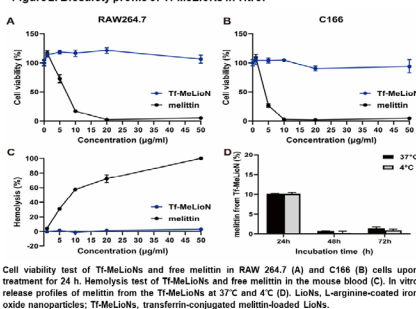


Figure 3. Brain delivery of TF-MeLiONs to 5XFAD mice.

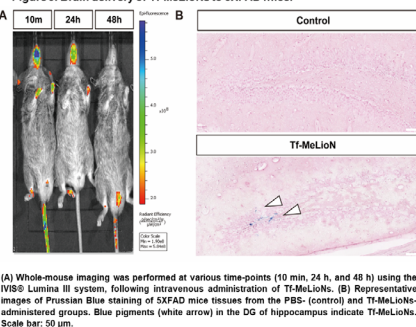


Figure 4. Biosafety profile of TF-MeLiONs in vivo.

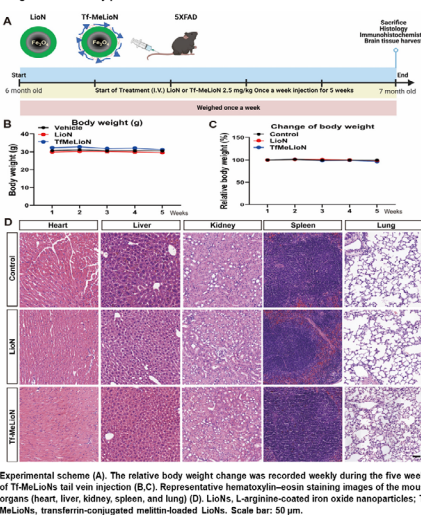


Figure 5. Effects of TF-MeLiONs treatment on the density of amyloid plaques in the 5XFAD mice.

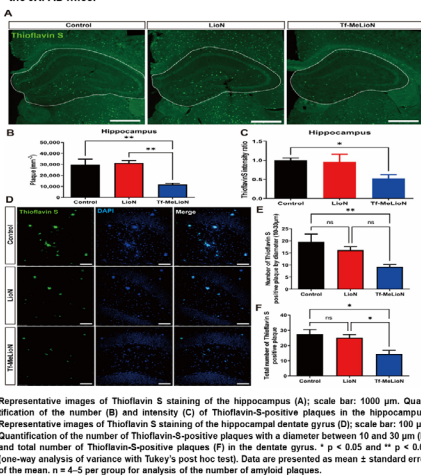


Figure 6. Effects of TF-MeLiONs treatment on the number of amyloid plaques in the early stage of 5XFAD mice.

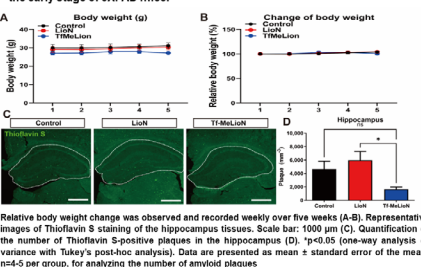
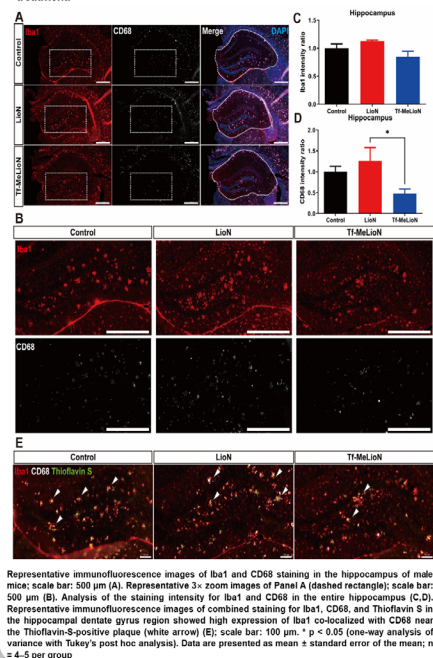


Figure 7. Analysis of microglial activation in the hippocampus upon TF-MeLiONs treatment.

Figure 8. Mechanism of β -amyloid regulation in the hippocampus.