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Nanoparticle-mediated brain delivery of a tetracationic porphyrin with potent anti-prion activities

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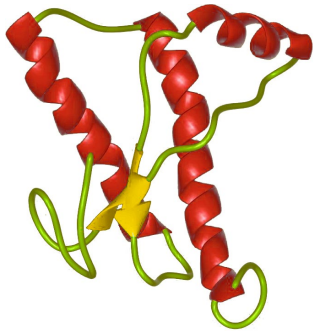
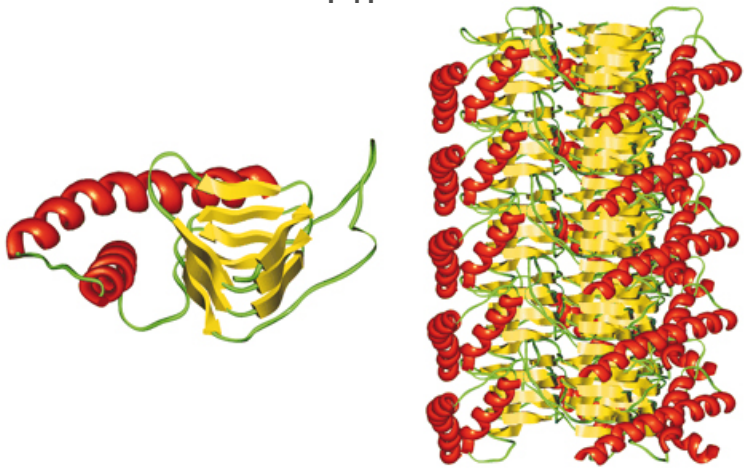
Conversion of PrP^{C} into PrP^{Sc} is the key pathogenic event in prion diseases

PrP^{C}



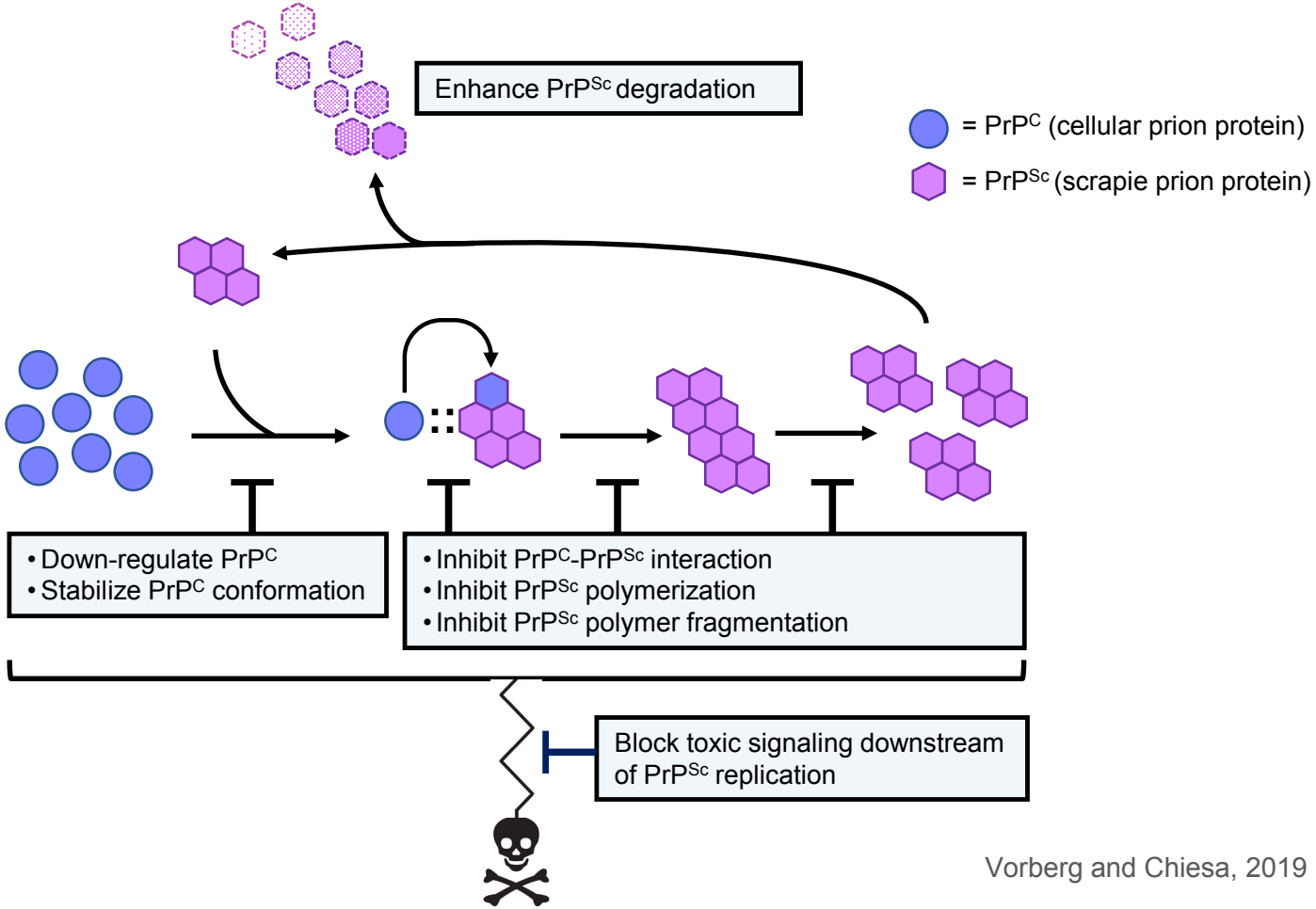
PrP^{Sc}



- Cellular protein
- Soluble
- Protease-sensitive
- 43% α-helix, 3% β-sheet
- NMR structure

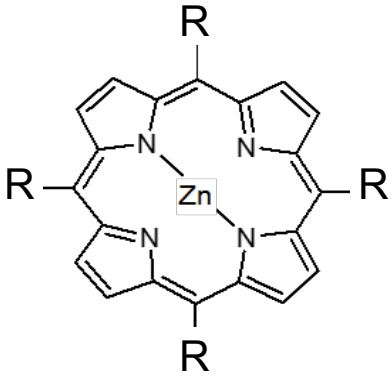
- Disease-specific protein
- Insoluble/aggregated
- Partially protease-resistant
- 30% α-helix, 43% β-sheet
- 3D structure unknown

Possible therapeutic strategies for prion diseases

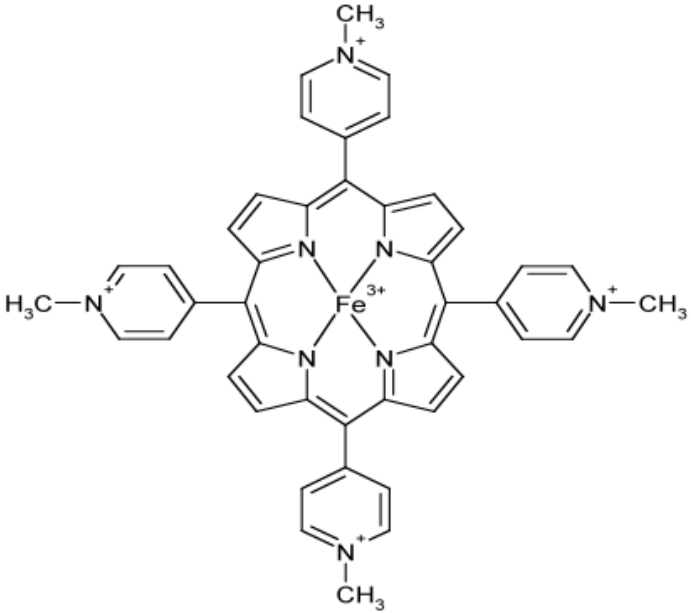


Vorberg and Chiesa, 2019

VA01: a porphyrin with potent anti-prion activity



VA01



Fe(III)TM-PyP

Caughey et al.,1998
Priola et al., 2000

17610–17615 | PNAS | October 12, 2010 | vol. 107 | no. 41

Pharmacological chaperone for the structured domain of human prion protein

Andrew J. Nicoll[a,1], Clare R. Trevitt[b,1], M. Howard Tattum[b], Emmanuel Risse[a], Emma Quarterman[a], Amaurys Avila Ibarra[c], Connor Wright[a], Graham S. Jackson[b], Richard B. Sessions[c], Mark Farrow[a], Jonathan P. Waltho[d], Anthony R. Clarke[b,c], and John Collinge[a,b,2]

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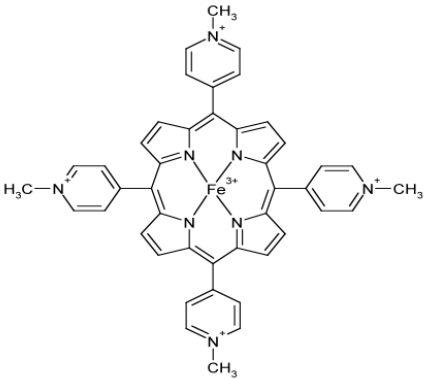
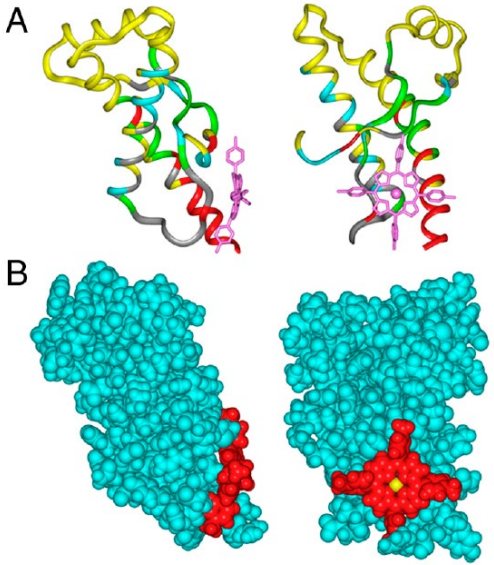
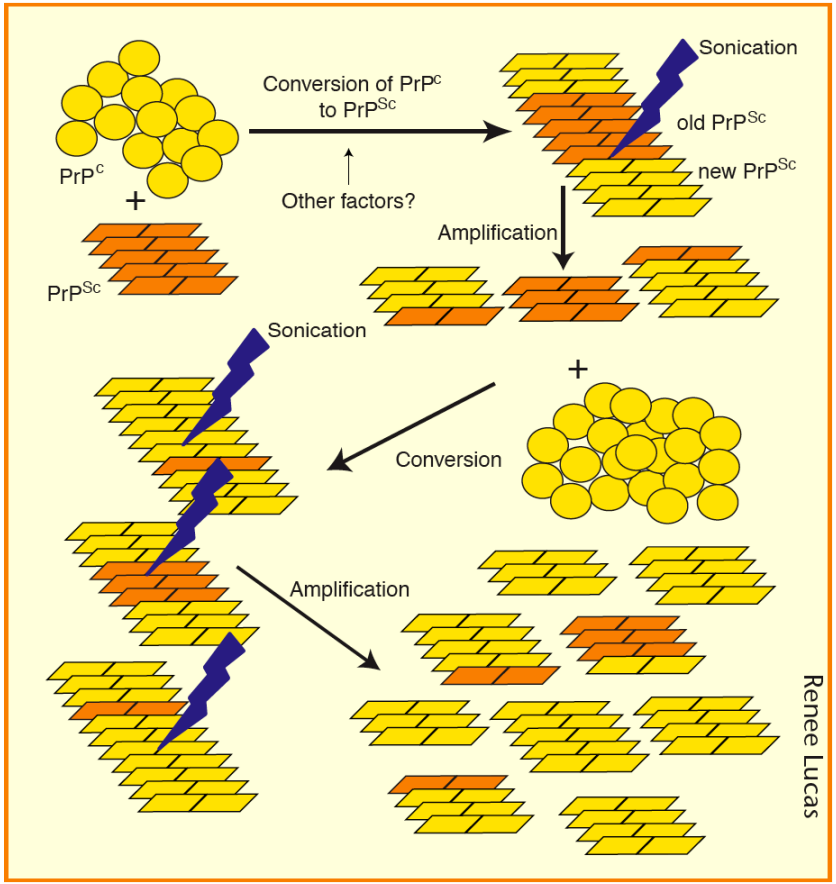


Fe(III)TM-PyP

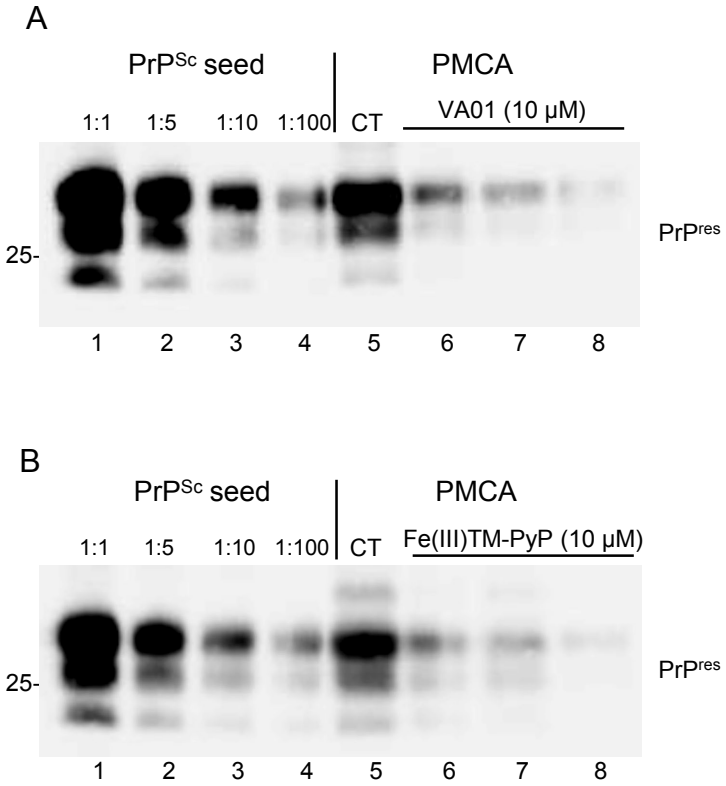


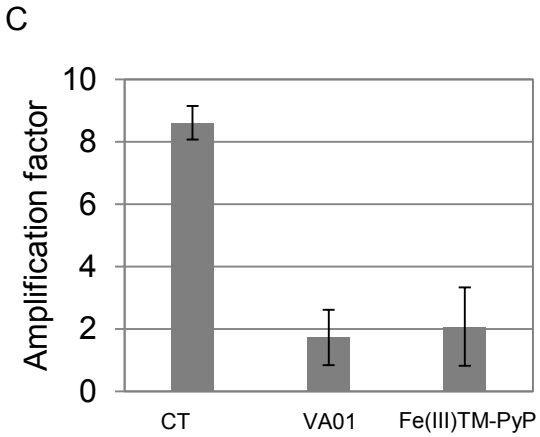
A cell-free PrP^{Sc} conversion assay (Protein Misfolding Cyclic Amplification, PMCA)



Saborio et al., 2001

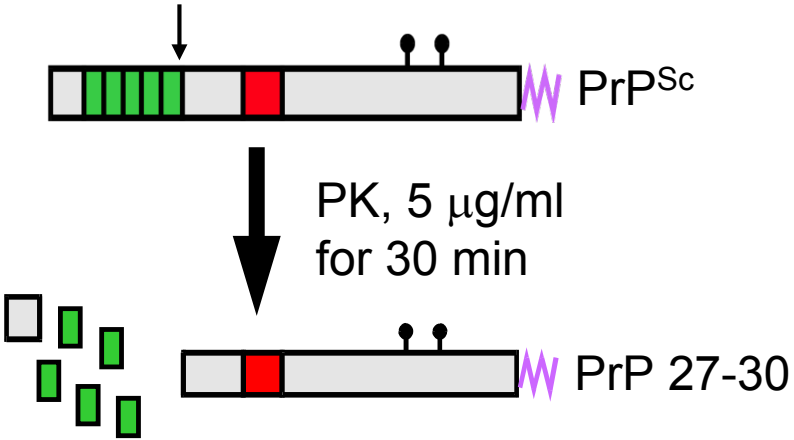
VA01 inhibits PrP^{Sc} replication in PMCA

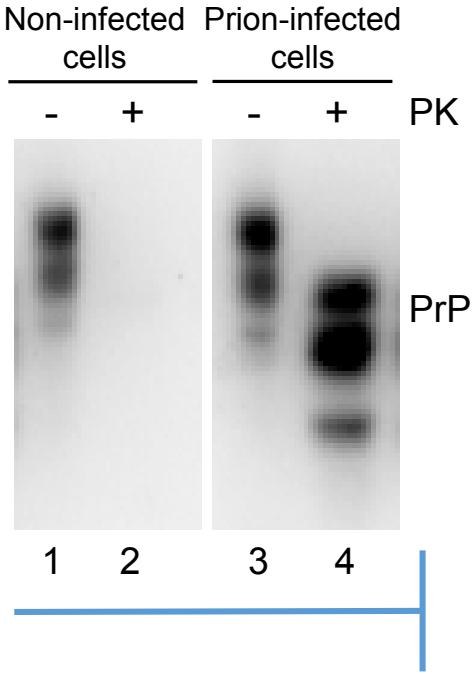




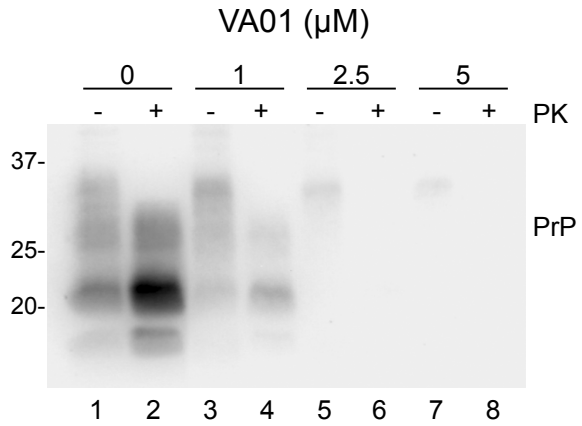
A cell assay for analysis of anti-prion activity

Cultures of prion-infected N2a cells (ScN2a-22L)

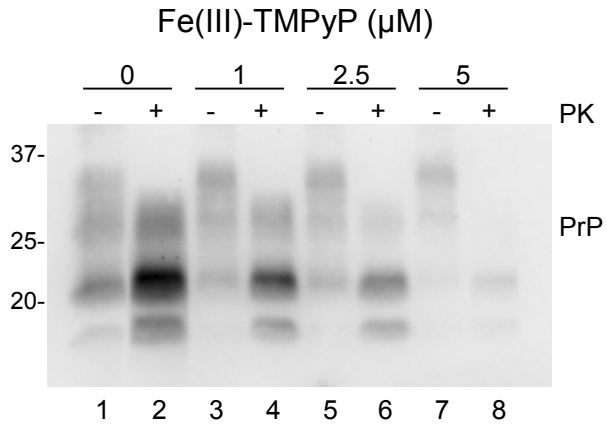




VA01 is more potent than Fe(III)TM-PyP in clearing prions from cells

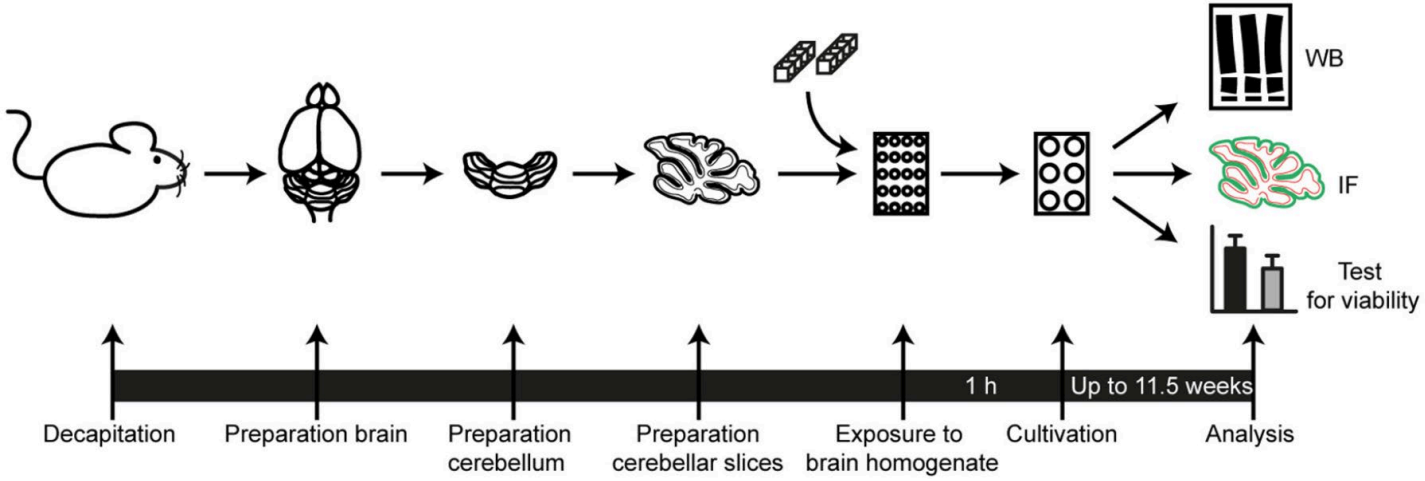


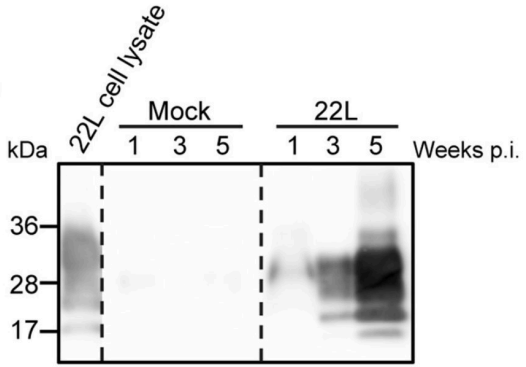
IC_{50} = 0.68 μM



IC_{50} = 1.293 μM

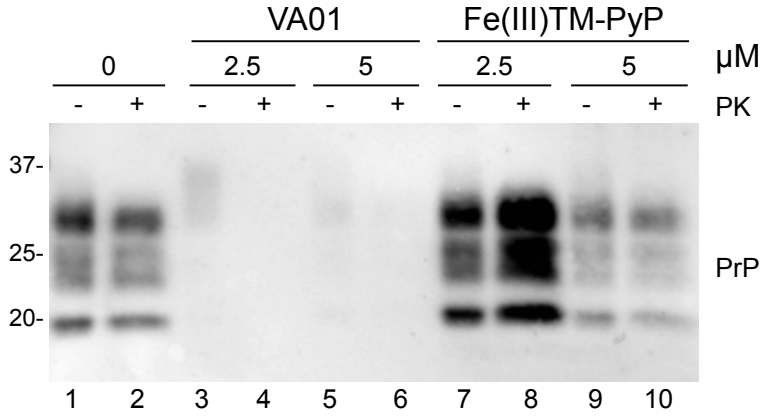
The prion-infected cerebellar organotypic cultures (COCS)





Wolf et al., 2015

VA01 is more potent than Fe(III)TM-PyP in the prion-infected COCS assay

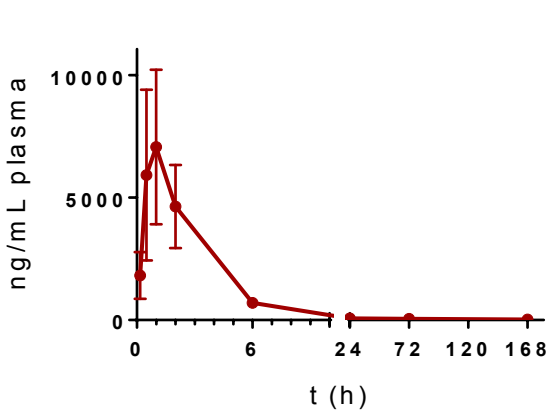


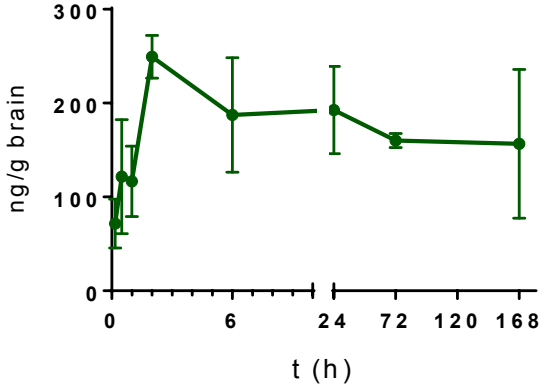
22L-infected COCS, treated for 1 week

Does VA01 reach the brain?

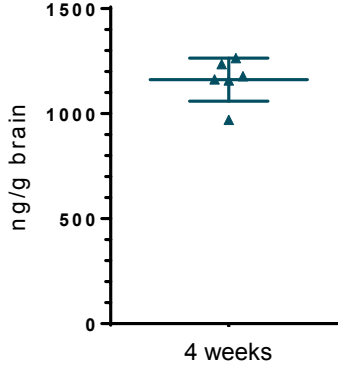
VA01 pharmacokinetics

10 mg/kg, i.p., single dose





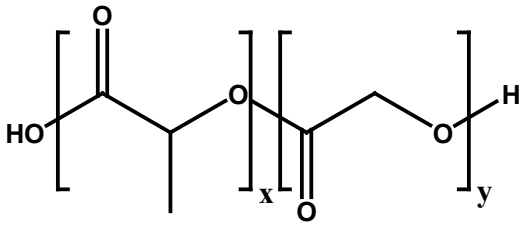
10 mg/kg, i.p., chronic treatment

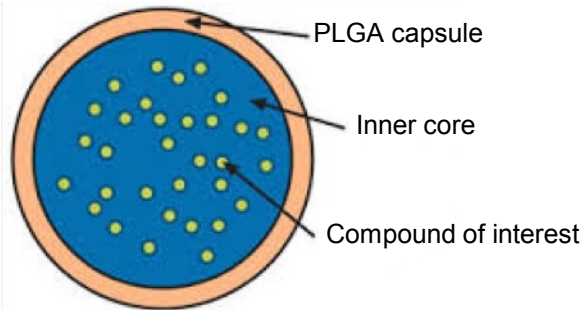


How can we boost the brain delivery of VA01?

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles

- PLGA



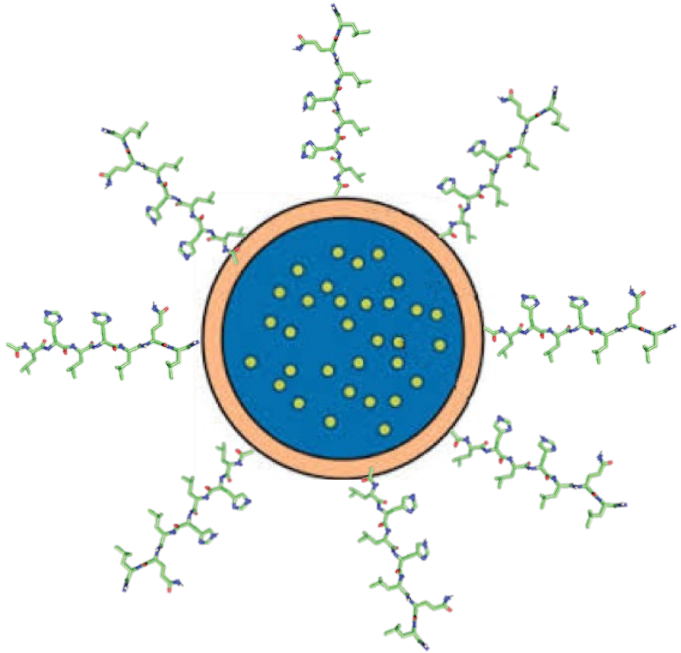


- Safe (FDA approved)
- Relatively inexpensive
- Amenable to chemical modification
- Forms nanoparticles
  - 100-200 nm
  - -20/-40 mv charge
  - can be loaded with various molecules

The g7 peptide improves brain delivery of PLGA nanoparticles

The g7 peptide

- Synthetic opioid-like glycopeptide modified to avoid opioid effects
- Crosses the BBB through receptor-mediated endocytosis
- Can be linked to PLGA
- g7-PLGA forms nanoparticles like PLGA



Costantino et al., 2005

g7-PLGA NPs have been successfully used in mouse models of brain diseases

EMBO Molecular Medicine Vol 7 | No 12 | 2015

Research Article

Cholesterol-loaded nanoparticles ameliorate synaptic and cognitive function in Huntington's disease mice

Marta Valenza[1,†], Jane Y Chen[2,†], Eleonora Di Paolo[1,‡], Barbara Ruozi[3,‡], Daniela Belletti[3], Costanza Ferrari Bardile[1], Valerio Leoni[4,5], Claudio Caccia[4], Elisa Brilli[1], Stefano Di Donato[4,§], Marina M Boido[6], Alessandro Vercelli[6], Maria A Vandelli[3], Flavio Forni[3], Carlos Cepeda[2], Michael S Levine[2], Giovanni Tosi[3] & Elena Cattaneo[1,*]

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Reduced plaque size and inflammation in the APP23 mouse model for Alzheimer's disease after chronic application of polymeric nanoparticles for CNS targeted zinc delivery

Antonietta Vilella[a,1], Daniela Belletti[b,1], Ann Katrin Sauer[c,d], Simone Hagmeyer[c,e], Tasnuva Sarowar[c,e], Martina Masoni[c,e], Natalia Stasiak[a], John J.E. Mulvihill[f,h], Barbara Ruozi[b], Flavio Forni[b], Maria Angela Vandelli[b], Giovanni Tosi[b,*], Michele Zoli[a,*], Andreas M. Grabrucker[d,g,h,*]

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International Journal of Molecular Sciences

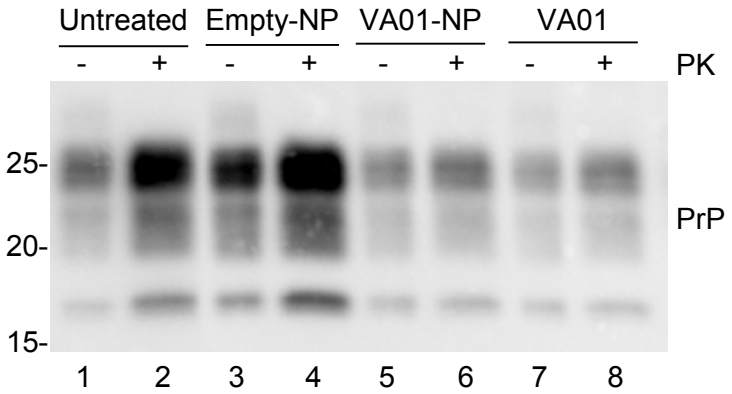
MDPI

Article

Targeting Brain Disease in MPSII: Preclinical Evaluation of IDS-Loaded PLGA Nanoparticles

Laura Rigon [1,2,†], Marika Salvalaio [2,3,†], Francesca Pederzoli [2,4], Elisa Legnini [1,2], Jason Thomas Duskey [4], Francesca D'Avanzo [1,2], Concetta De Filippis [1,2], Barbara Ruozi [4], Oriano Marin [5], Maria Angela Vandelli [4], Ilaria Ottonelli [4], Maurizio Scarpa [1,2], Giovanni Tosi [4] and Rosella Tomanin [1,2,*]

VA01-loaded g7-NPs reduce PrP^{Sc} levels in prion-infected COCS



22L-infected COCS, single treatment, analyzed after 48h

Summary

- VA01 inhibits PrP^{Sc} replication in PMCA, N2a cells and COCS
- VA01 is more potent than Fe(III)TM-PyP
- A fraction of VA01 reaches the brain after systemic administration but its biological activity in the brain is variable
- Functionalized nanoparticles (g7-NPs) improve brain delivery of drugs
- VA01 can be efficiently loaded in g7-NPs maintaining its anti-prion activity *in vitro*

Conclusions

- VA01 is a promising therapeutic molecule for prion diseases
- Before testing the therapeutic efficacy of VA01 in preclinical models, we need to improve its brain penetration
- VA01-loaded g7-NPs are active *in vitro*
- We are now testing the brain delivery of VA01 loaded in g7-NPs

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