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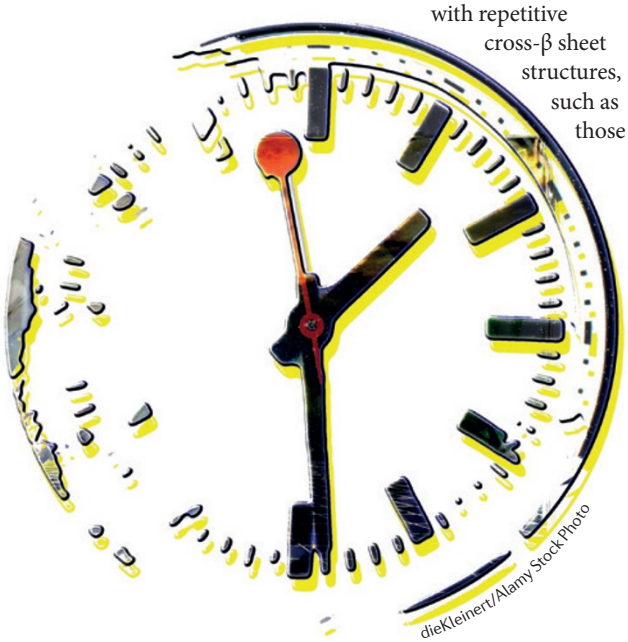
PRION DISEASES

Polythiophenes delay prion-induced neurodegeneration

Transmissible spongiform encephalopathies (TSEs) are caused by an infectious abnormally folded prion protein (PrP^{Sc}) — known as a seed — which propagates by inducing the misfolding and aggregation of native cellular prion protein (PrP^{C}), resulting in progressive neurodegeneration. Although several therapeutic approaches have been investigated for TSEs, there are currently no drugs available for these disorders. Now, writing in *Science Translational Medicine*, Herrmann and colleagues report the design of novel polythiophene-based compounds that attenuate neurodegeneration and prolong survival in prion-infected mice.

Luminescent conjugated polythiophenes (LCPs) are polymeric thiophene-based fluorescent molecules that bind to protein aggregates with repetitive cross-β sheet structures, such as those formed by PrP^{Sc}, and can be used to stain various amyloids in tissues. Previously, LCP treatment of prion-infected brain homogenates from mice and of cultured cerebellar slices has been shown to reduce prion infectivity. Given this, Herrmann and colleagues set out to assess the prophylactic and therapeutic potential of LCPs in a mouse model of prion disease.



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First, they administered four chemically diverse LCPs by intraventricular infusion into the brains of mice one week prior to infection with the RML6 prion. Although two of the compounds were ineffective, LIN5001 and LIN7002 prolonged survival by 16.7% and 36.4%, respectively. Importantly, LIN5001 treatment also similarly extended survival when treatment was started 20 days following infection. Misfolded-protein assays and fractionation experiments indicated that LIN5001 was probably acting to stabilize small PrP^{Sc} aggregates, inhibiting the positive feedback loop in protein aggregation that generates new prion seeds through fragmentation.

Next, the authors performed a series of structure–activity relationship studies, nuclear magnetic resonance experiments and solvent molecular dynamics simulations to extract a set of rules that predicted the binding and activity of LCPs. They discovered that the backbone must contain at least five thiophene or selenophene moieties, that therapeutic efficacy requires charged side groups (carboxylic and acetic acids) and that anionic side groups must be linked to the terminal thiophene rings.

Using this structural information, Herrmann and colleagues designed a new set of LCPs. Based on *in silico* properties, the authors selected six of the new LCPs and prophylactically administered them to mice infected with RML6 prions. As predicted, LIN5044, which showed the strongest binding to aggregates, exhibited the most potent anti-prion activity, prolonging survival by 87.5% compared with vehicle-treated mice.

Levels of PrP^{Sc} and protein aggregation in brain homogenates from RML6-infected mice were reduced by treatment with the stronger binders, which correlated with anti-prion activity. Furthermore, histological analyses of the brains of mice treated with LIN5044 revealed an overall reduction in spongiosis, PrP deposition and astrogliosis at the terminal stage of the disease, indicating attenuation of the neurodegenerative process.

Notably, intraventricular or intraperitoneal administration of LIN5044 to RML6 prion-infected mice was effective even when the disease had already progressed to the symptomatic phase, with the LCP significantly improving motor performance and prolonging survival.

These findings support further investigation of LCPs in the treatment of TSEs. Given that LCPs are active against many amyloids, this strategy has the potential to be extended to proteinopathies beyond prion diseases.

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ORIGINAL RESEARCH PAPER Herrmann, U. *et al.* Structure-based drug design identifies polythiophenes as antiprion compounds. *Sci. Transl. Med.* **7**, 299ra123 (2015)