Design of high-affinity, conformation-specific ligands for pharmacotherapy of prion protein-related diseases

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During prion diseases, the cellular prion protein, PrPC, is induced to convert its conformation into an infectious form, PrPSc, which subse- quently forms insoluble amyloid fibrils, and microscopically visible plaques. Here, the development of compounds that specifically interact with soluble conformations of the prion protein is proposed. The aims comprise stabilization of PrP against the pathogenic conformational transitions and the ability to manipulate conformational states of the prion protein with small molecule ligands. A cyclic approach of in- creasing and refining the affinity of candidate ligand molecules is hy projected: By means of various biophysical techniques and with empha- sis on nuclear magnetic resonance (NMR) spectroscopy, the interaction of potential drug molecules and peptides with prion protein will be mapped at high resolution. Novel ligands will be designed such as to fit into these mapped interaction sites, synthesized, and validated in a cell model of prion disease. For the parallel synthesis of focused compound libraries, a solid phase supported methodology especially ex- ploiting click reactions will be employed. Ultimately, this iterative approach is expected to yield high-affinity ligands that specifically bind to soluble prion protein, stabilize its conformation, and prevent conversion into a pathogenic conformation. The results from this pro- ject are also expected to provide fundamental insights into drug dis- covery for related conformational, i.e. neurodegenerative diseases, such as Parkinson's or Alzheimer's disease.

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