In vitro and *in silico* approaches to screen and select prototype compounds for prion disease´s therapy

Yraima Cordeiro

Laboratório de Biologia Molecular Estrutural, Faculdade de Farmácia, UFRJ

Transmissible spongiform encephalopathies (TSEs) are infectious neurodegenerative disorders for which symptomatic, curative, or prophylactic treatments are not available. TSEs arise as a consequence of the conversion of soluble cellular prion protein (PrP^{C}) into the scrapie isoform (PrP^{Sc}), which aggregates and accumulates in the central nervous system. Diverse therapeutic strategies have been proposed, including blocking the conversion of PrP^{C} to PrP^{Sc}, increasing PrP^{Sc} clearance, and/or stabilizing PrP^{C}. While several compounds have been effective *in vitro* and in animal models, none have proven effective in clinical studies to date. Besides, substantial toxicity and the lack of permeability of the selected compounds across the blood–brain barrier have been observed. Thus, our group is applying multiple approaches for the screening and evaluation of organic compounds for anti-prion activity, including initial screening in prion-infected cell cultures, *in silico* prediction of pharmacokinetic and physicochemical properties, *ex vivo* evaluation of cellular toxicity, and *in vitro* assays using purified recombinant prion protein. We propose that a combination of *in vitro* and *in silico* approaches would be useful for the rapid identification of novel anti-prion drug candidates with suitable pharmacokinetic and pharmacodynamic properties that would support their use as drugs.