De novo generation of infectious prions in vitro produces a new disease phenotype

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Prions are the proteinaceous infectious agents responsible for Transmissible Spongiform Encephalopathies. Compelling evidence supports the hypothesis that prions are composed exclusively of a misfolded version of the prion protein (PrPSc) that replicates in the body in the absence of nucleic acids by inducing the misfolding of the cellular prion protein (PrP C). The most common form of human prion disease is sporadic, which appears to have its origin in a low frequency event of spontaneous misfolding to generate the first PrPSc particle that then propagates as in the infectious form of the disease. The main goal of this study was to mimic an early event in the etiology of sporadic disease by attempting de novo generation of infectious PrPSc in vitro. For this purpose we analyzed in detail the possibility of spontaneous generation of PrPSc by the protein misfolding cyclic amplification (PMCA) procedure. Under standard PMCA conditions, and taking precautions to avoid cross-contamination,