Supplementary Material -1

Oligomerization of FVFLM peptides and their ability to inhibit beta amyloid peptides aggregation: consideration as a possible model

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Experimental background behind the theoretical formulation

Prior to our investigation there has been no report of protein misfolding associated with PE. We have been pointed in this direction during our earlier proteomics study when we found that PE women excrete a panel of non-random fragments of SERPINA1 and albumin. In particular, presence of fragments corresponding to the 21 and 22 amino acid C-terminus sequences highly associated with clinically severe disease(*1*). Their conspicuous serrated peak aspect at mass spectrometry (Fig. S1), resulted from the various oxidized states of the two Met residues, a finding consistent with fragmentation of SERPINA1 *in vivo* in the context of oxidative stress. Analyzing our observed cleavage pattern, we deduced that the two cleavages generating these fragments occurred within a stretch of five hydrophobic aminoacids (381FVF↓L↓M385, with ↓ indicating the cleavage sites) which by definition is an aggregation "hot spot"(*2, 3*). Additionally, this site is the recognition sequence for the hepatic serpin-enzyme complex (SEC) receptor which removes circulating SERPINA1-enzyme complexes(*4*). Sequence motifs bearing homology with this pentapeptide are also found in Aβ peptide which was shown to compete for binding to SEC receptor(*5*). The analogous "hot-spot" in Aβ sequence (16KLVFF20) harbors the α-secretase site which is cleaved during physiological (non-amyloidogneic) processing of APP. Cleavage of APP by β-secretase (amyloidogenic processing) results in this sequence remaining intact, a phenomenon germane to Ab polymerization and fibril formation(*6*). Short pentapeptide hydrophobic sequences with same or analogous aminoacids are now explored therapeutically as inhibitors of Aβ fibrilization

and toxicity. Although we did not specifically know if the enzymes of the secretory pathway could be responsible for generation of our conspicuous C-terminus SERPINA1 fragments in PE urine, we knew from *in vitro* studies of other proteins that L↓M represents a major and preferred cleavage site for β-secretase (*7, 8*). This premise would be consistent with the established roles of SERPINA1 as suicide antiprotease and endogenous inhibitor of Aβ aggregation (*9*). Moreover, it would explain the consistent finding of SERPINA1 co-deposited with aggregated Aβ in both AD plaques (*10*) and vascular atherosclerotic lesions (*11*).

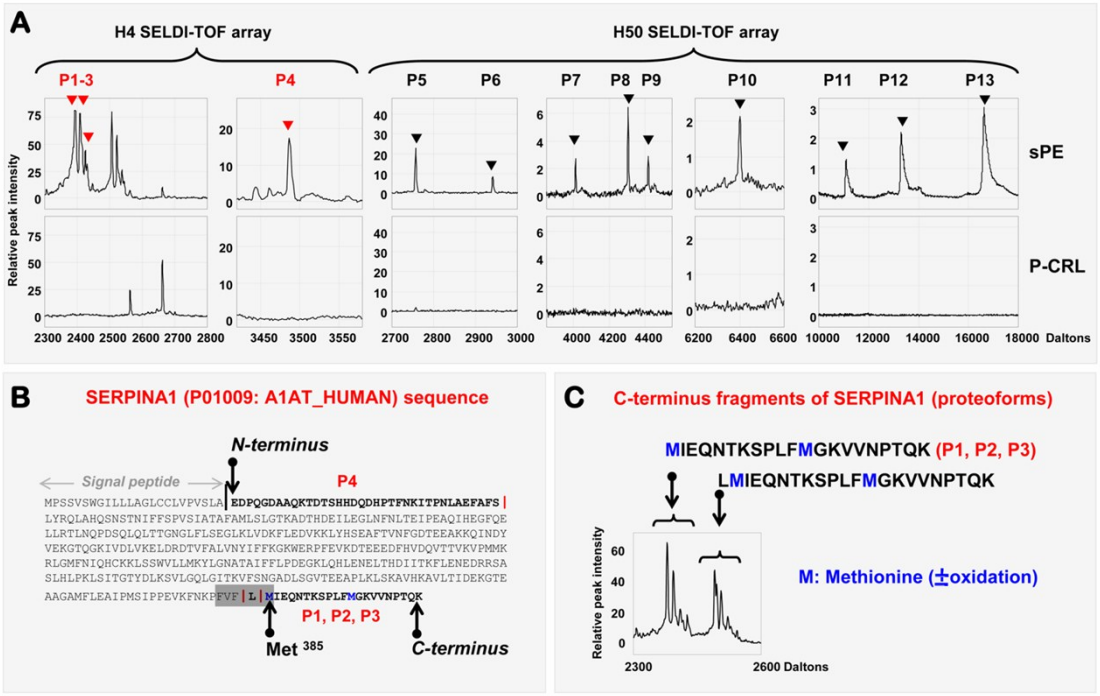

Figure S1 The urine proteomics profile of preeclampsia with biomarkers mapping to SERPINA1 sequence

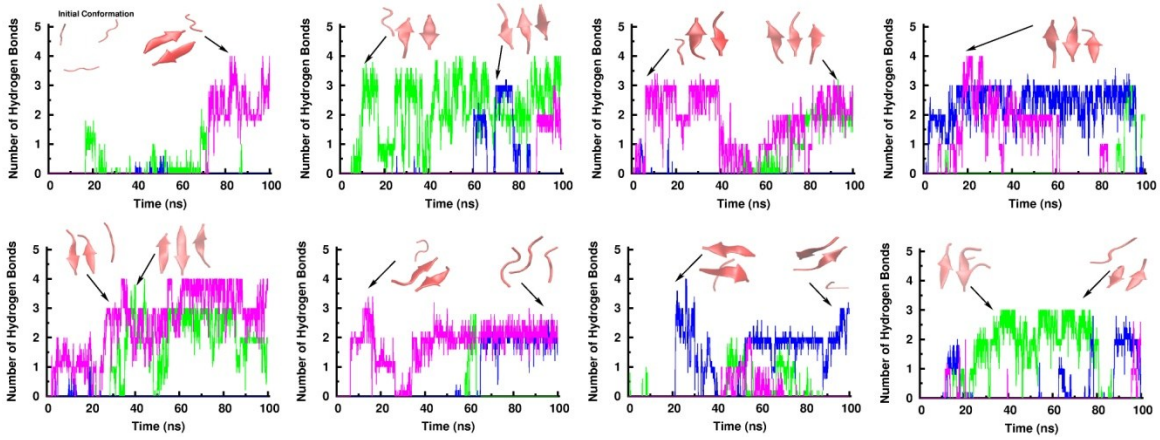

Figure S2 The time dependence of number of backbone hydrogen bonds between monomers KLVFF. Green, blue, magenta curves represents number of hydrogen bonds between peptide 1 and peptide 2, peptide 1 and peptide 3, peptide 2 and peptide 3, respectively.

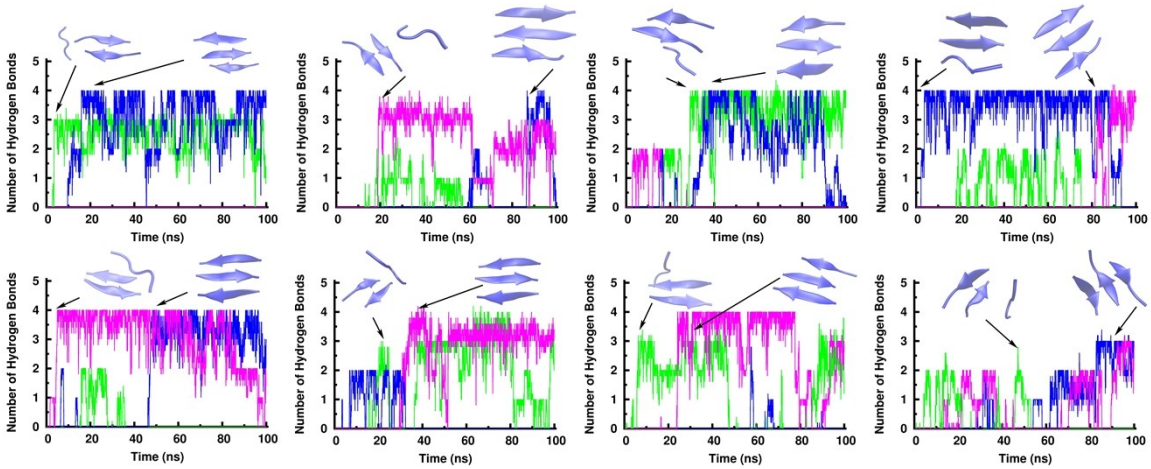

Figure S3 The time dependence of number of backbone hydrogen bonds between monomers FVFLM for Trajectories 9 to 16 of the FVFLM trimer system. Green, blue, magenta curves as in Figure S2.

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