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Impeding Pathogenic Dimerization in a Misfolded Light Chain Through the Design of an Inhibitory Peptide

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AL amyloidosis is a condition associated with the aggregation and deposition of immunoglobulin light chains in diverse tissues resulting in organ failure. The high susceptibility of antibodies to mutations makes AL amyloidosis strongly patient-specific. Therefore, understanding the assembly mechanisms is crucial to achieving prompt diagnoses and designing personalized therapeutics. Here, we focus on a particular patient-derived light chain, previously experimentally characterized.

We studied the early phases of aggregation through extensive all-atom MD simulations on the germ-line non-aggregating monomer and on its mutant aggregation-prone counterpart. The simulations hinted at misfolding in the mutant structure. We then considered the dimerization process through docking on the misfolded monomer. With further MD simulations, we were able to propose the structure of a putative pathogenic dimer.

We analyzed the interface of the dimer to detect the most relevant interacting residues and selected an aminoacidic chain that we optimized via mutagenesis to design a competitive peptide, possibly suitable for dimerization hindrance.

Altogether, the results obtained could pave the way to investigate the ensuing phases of the aggregation. This could enhance the development of patient-specific drugs suited for preventing early-stage protein aggregation.