Phase separation and small molecule interference with aggregation: treatment options for neurodegeneration

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Phase separation of polymers is well known for synthetic polymers but was recently discovered to be functionally important also for biopolymers forming liquid liquid phase separated compartments without membranes. Results on a system, relevant in B cells will be presented that relies on phase separation of three components, lipid vesicles and two scaffolding proteins that are largely intrinsically disordered, namely SLP65 and CIN85.

While phase separation of biopolymers occurs that keep the rotational correlation time in the one digit nanosecond range, other biopolymers aggregate forming finally fibrils. We have studied the process of aggregation of α-synuclein and other proteins involved in neurodegeneration on membranes *in vitro* and identified key time points in the aggregation process, that enable targeted isolation of a so called intermediate I and the fibrillar endpoint (2). Intermediate I has the characteristics of a toxic oligomer. In addition, we determined the structure of anle138b, a clinical drug candidate (3) bound to fibrils that were grown in the presence of lipids (4) that are doped with anle138b (5). Anle138b is not only clinically relevant but changes the organization of the aggregates regarding density and particle size which we try to understand by studying the structure of these aggregates.

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