A nanoscience-based approach to protein condensation diseases

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Understanding interparticle interactions in protein solutions is of central importance to gain insight into the origin of protein condensation diseases such as Creutzfeldt Jakob, Alzheimer, Parkinson or cataract, the leading cause of blindness worldwide (1). Here I will demonstrate how we can use a nanoparticle-based approach to understanding protein stability and aggregation/phase separation. I will discuss in particular the system eye lens and show that the eye lens proteins (alpha-, beta- and gamma-crystallin) are ideally suited for an attempt to use well-defined analogies to nanoparticles in suspension in order to understand the molecular origins of cataract formation (2). The approach that we follow in our work is schematically shown in Figure 1.

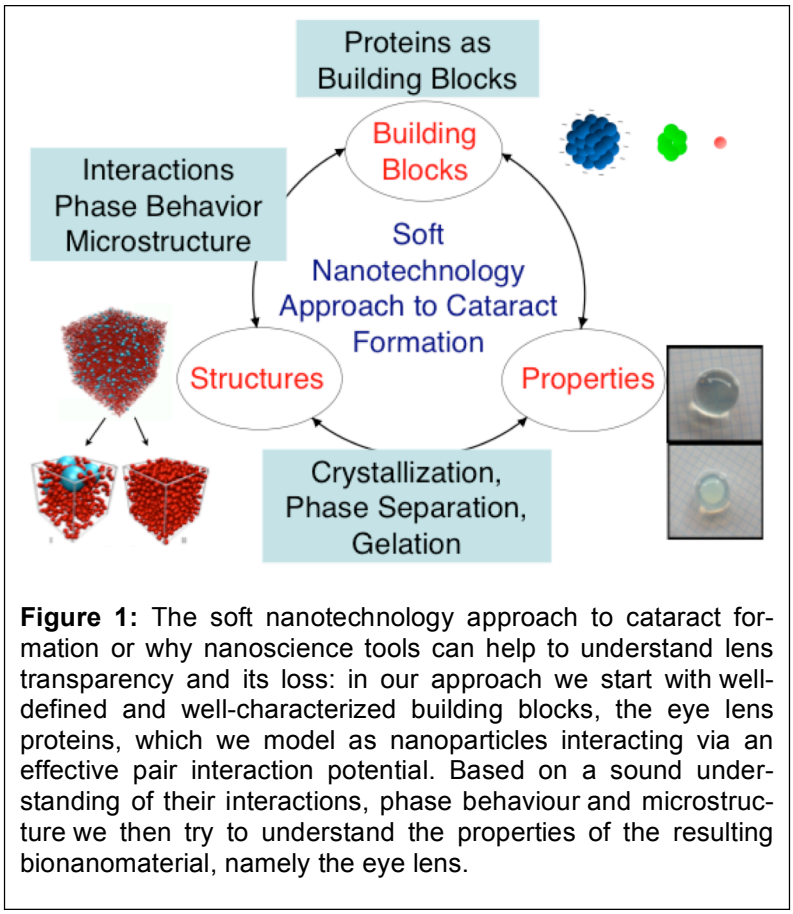

Figure 1: The soft nanotechnology approach to cataract formation or why nanoscience tools can help to understand lens transparency and its loss: in our approach we start with well-defined and well-characterized building blocks, the eye lens proteins, which we model as nanoparticles interacting via an effective pair interaction potential. Based on a sound understanding of their interactions, phase behaviour and microstructure we then try to understand the properties of the resulting bionanomaterial, namely the eye lens.

I will present results from a study of the structural and dynamic properties of individual lens protein solutions and mixtures up to concentrations corresponding to those found in the eye lens using small-angle neutron (SANS) and X-ray scattering (SAXS) combined with light scattering, rheological measurements, molecular dynamics simulations and statistical physics (3-5).

We discuss the results in the context of simple models from colloid science and demonstrate that they indeed allow us to interpret the complex protein phase diagrams. The nanoparticle-based approach and an example for the results thus obtained are shown in Figure 2.

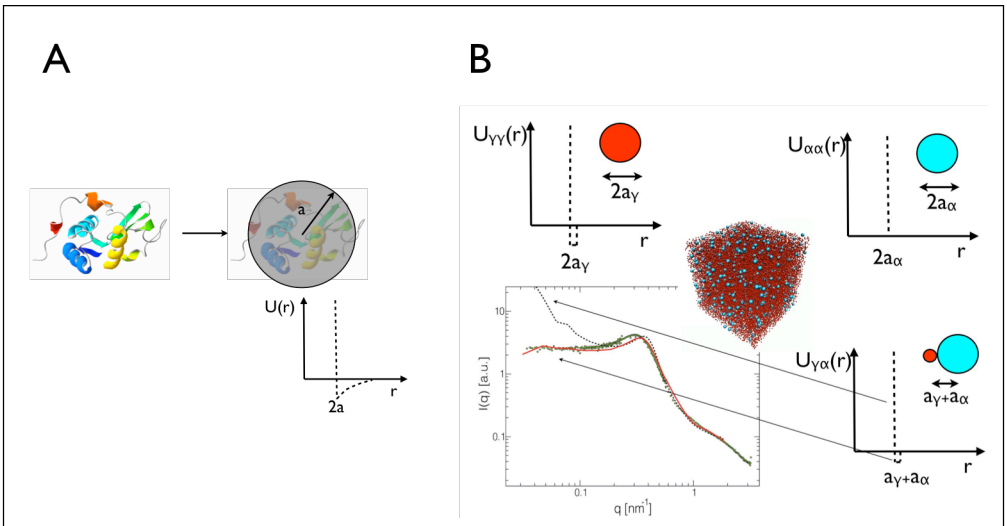

Figure 2: A) Schematic representation of the coarse-grained view of a protein, where the exact three-dimensional structure of a protein is replaced with a globular particle that then interacts with other proteins via an effective pair potential. B) SANS data obtained with a concentrated γ-α-crystallin mixture together with the theoretical prediction for either a hard sphere repulsion (dashed line) or a weak mutual attraction (red solid line) between γ- and α-crystallins (see [3] for details).

I will show that a subtle balance of interactions between the individual proteins controls transparency of lens protein mixtures at high concentrations, comparable to those in the living eye lens. In particular I will demonstrate that the stability of lens protein mixtures is greatly enhanced by weak, short-range attractions between two of the prevalent mammalian crystallins, alpha- and gamma-crystallin. Provided they are not too strong, such mutual attractions considerably decrease the critical temperature and the related opacity due to light scattering in the vicinity of the critical point, and are thus essential for lens transparency.

References:

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