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### **The Role of Multivalent Counterions in Protein Crystallization<sup>1</sup>**

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In this talk, I will give an overview of our recent studies on the phase behavior of model globular proteins in solution in the presence of multivalent counterions. We have shown that negatively charged globular proteins at neutral pH in the presence of multivalent counterions undergo a “reentrant condensation (RC)” phase behavior [1,2], i.e. a phase-separated regime occurs in between two critical salt concentrations,  $c^* < c^{**}$ , giving a metastable liquid-liquid phase separation (LLPS) [3]. This reentrant phase behavior corresponds to an effective charge inversion of proteins as confirmed by zeta-potential measurements and supported by Monte Carlo simulations [1,2]. Crystallization from the condensed regime follows different mechanisms. Near  $c^*$ , crystals grow following a classic nucleation and growth mechanism; near  $c^{**}$ , the crystallization follows a two-step mechanism, i.e, crystals growth follows a metastable LLPS [3,4]. Nucleation rate is faster from the protein-poor phase than that from the protein-rich phase, which cannot be explained by the recent theories. SAXS measurements demonstrate that protein clusters act as precursors for crystal growth, which reduce the energy barrier of nucleation [4]. X-ray diffraction analyses on the high quality single crystals provide direct evidence of the crystal structure and cation binding sites [3]. The bridging effect of the metal cations explains the cluster formation.

[1] Zhang, F.; et al. *Phys. Rev. Lett.* **2008**, 101, 148101.

[2] Zhang, F.; et al. *Proteins* **2010**, 78, 3450.

[3] Zhang, F.; et al. *J. Appl. Cryst.* **2011**, 44, 755.

[4] Zhang, F.; et al. In preparation.

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