



Single Molecule, Microfluidic and Genetically Encoded Chemical Tools to Study Protein Structure and Dynamics

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Abstract:

In any complex biological system, a mosaic of molecular states and reaction pathways exist in parallel. Conventional ensemble experiments measure only the average behavior of these systems, discounting coexisting populations and rare events. Ignoring such information can easily lead to generation of false or insufficient models, which may further impede our understanding of the biological process. A powerful approach to overcome these limitations is direct observation at the single molecule level, which probes the distribution of behaviors rather than just the average. However, the strength of single molecule techniques to monitor bimolecular structure and function is largely hampered by the requirement to label biomolecules in a non-perturbing fashion with suitable fluorescent dyes. I will present how genetically encoding unnatural amino acids can overcome this bottleneck by serving as biocompatible chemical handles. In particular, I will demonstrate the development of a new “click” based technology that holds the potential to facilitate installing suitable photostable dyes with single amino acid precision in vitro and in vivo.¹ Furthermore, I will present microfluidic technologies that enable ultrafast kinetic studies in single molecule experiments, and experiments with extremely high photo stability utilizing a built-in “rapid gas exchange technology”.² En route with describing these tools the relevance of single molecule studies for biology will be highlighted by presenting data that allows for a better understanding of α synuclein structure and dynamics, a protein linked to Parkinson and Alzheimer’s.³

References:

- (1) Plass T, Milles SM, Koehler C, Schultz C, Lemke EA. *Angewandte Chem Int Ed* **2011**, *50(17)*, 3878--81.
- (2) Lemke EA, Gambin Y, Vandelinder V, Brustad EM, Liu HW, Schultz PG, Groisman A, Deniz AA. *J Am Chem Soc* **2009**, *131*, 13610-2.
- (3) Gambin Y, Vandelinder V, Ferreon ACM, Lemke EA Groisman A, Deniz AA. *Nature Methods* **2011**, *8(3)*, 239-41.

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