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Peering into Cells One Molecule at a Time: Single-molecule and plasmon-enhanced fluorescence super-resolution imaging

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Single-molecule fluorescence brings the resolution of optical microscopy down to the nanometer scale, allowing us to unlock the mysteries of how biomolecules work together to achieve the complexity that is a cell. This high-resolution, non-destructive method for examining subcellular events has opened up an exciting new frontier: the study of macromolecular localization and dynamics in living cells. We have developed methods for single-molecule investigations of live bacterial cells, and have used these techniques to investigate three important prokaryotic systems: membrane-bound transcription activation in *Vibrio cholerae*, carbohydrate catabolism in *Bacteroides thetaiotaomicron*, and DNA mismatch repair in *Bacillus subtilis*. Each system presents unique challenges, and we will discuss the important methods developed for each system. Furthermore, we use the plasmon modes of bio-compatible metal nanoparticles to enhance the emissivity of single-molecule fluorophores. The resolution of single-molecule imaging in cells is generally limited to 20-40 nm, far worse than the 1.5-nm localization accuracies which have been attained *in vitro*. We use plasmonics to improve the brightness and stability of single-molecule probes, and in particular fluorescent proteins, which are widely used for bio-imaging. We find that gold-coupled fluorophores demonstrate brighter, longer-lived emission, yielding an overall enhancement in total photons detected. Ultimately, this results in increased localization accuracy for single-molecule imaging. Furthermore, since fluorescence intensity is proportional to local electromagnetic field intensity, these changes in decay intensity and rate serve as a nm-scale read-out of the field intensity. Our work indicates that plasmonic substrates are uniquely advantageous for super-resolution imaging, and that plasmon-enhanced imaging is a promising technique for improving live cell single-molecule microscopy.