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Single Fluorescent Molecules as Nano-Illuminators for Biological Structure and Function

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Since the first optical detection and spectroscopy of a single molecule in a solid (Phys. Rev. Lett. **62**, 2535 (1989)), much has been learned about the ability of single molecules to probe local nanoenvironments and individual behavior in biological and nonbiological materials in the absence of ensemble averaging that can obscure heterogeneity. Because each single fluorophore acts a light source roughly 1 nm in size, microscopic imaging of individual fluorophores leads naturally to superlocalization, or determination of the position of the molecule with precision beyond the optical diffraction limit, simply by digitization of the point-spread function from the single emitter. For example, the shape of single filaments in a living cell can be extracted simply by allowing a single molecule to move through the filament (PNAS **103**, 10929 (2006)). The addition of photoinduced control of single-molecule emission allows imaging beyond the diffraction limit (super-resolution) and a new array of acronyms (PALM, STORM, F-PALM etc.) and advances have appeared. We have used the native blinking and switching of a common yellow-emitting variant of green fluorescent protein (EYFP) reported more than a decade ago (Nature **388**, 355 (1997)) to achieve sub-40 nm super-resolution imaging of several protein structures in the bacterium *Caulobacter crescentus*: the quasi-helix of the actin-like protein MreB (Nat. Meth. **5**, 947 (2008)), the cellular distribution of the DNA binding protein HU (submitted), and the recently discovered division spindle composed of ParA filaments (Nat. Cell Biol. **12**, 791 (2010)). Even with these advances, better emitters would provide more photons and improved resolution, and a new photoactivatable small-molecule emitter has recently been synthesized and targeted to specific structures in living cells to provide super-resolution images (JACS **132**, 15099 (2010)). Finally, a new optical method for extracting three-dimensional position information based on a double-helix point spread function enables quantitative tracking of single mRNA particles in living yeast cells with 15 ms time resolution and 25-50 nm spatial precision (PNAS **107**, 17864 (2010)). These examples illustrate the power of single-molecule optical imaging in extracting new structural and functional information in living cells.