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Illuminating biology at the nanoscale with single-molecule and super-resolution fluorescence microscopy

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Dissecting the inner workings of a cell requires imaging methods with molecular specificity, molecular-scale resolution, and dynamic imaging capability such that molecular interactions inside the cell can be directly visualized. Fluorescence microscopy is a powerful imaging modality for investigating biological systems largely owning to its molecular specificity and dynamic imaging capability. However, the diffraction-limited resolution of light microscopy is substantially larger than molecular length scales in cells, making many sub-cellular structures difficult to resolve. We developed a super-resolution fluorescence microscopy method, stochastic optical reconstruction microscopy (STORM), which overcomes the diffraction limit by using photo-switchable fluorescent probes to temporally separate the spatially overlapping images of individual molecules. This approach has allowed multicolor and three-dimensional imaging of living cells with nanometer-scale resolution and enabled discoveries of novel sub-cellular structures. In this talk, I will present to concept and technological advances of STORM, as well as some of the recent biological discoveries enabled by STORM. I will also describe a new single-cell transcriptome imaging method multiplexed error-robust fluorescent in situ hybridization (MERFISH), which allows numerous RNA species to be imaged and quantified in single cells. This approach enables unique analyses based on copy numbers and spatial distributions of many RNA species within single cells, facilitating the delineation of gene regulatory networks and in situ identification of cell types.