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Developing Photo Activated Localization Microscopy

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Photo Activated Localization Microscopy, PALM, acquires super-resolution images by activating a subset of activatable fluorescent labels and estimating the center of the each molecular label to sub-diffractive accuracy. When this process is repeated thousands of times for different subsets of molecules, then an image can be rendered from all the center coordinates of the molecules. I will describe the circuitous story of its development that began with another super-resolution technique, NSOM, developed by my colleague Eric Betzig, who imaged single molecules at room temperature, and later we spectrally resolved individual luminescent centers of quantum wells. These two observations inspired a generalized path to localization microscopy, but that path was abandoned because no really useful fluorescent labels were available. After a decade of nonacademic industrial pursuits and the subsequent freedom of unemployment, we came across a class of genetically expressible fluorescent proteins that were switchable or convertible that enabled the concept to be implemented and be biologically promising. The past ten years have been very active with many groups exploring applications and enhancements of this concept. Demonstrating significant biological relevance will be the metric if its success.