Super-Resolution Microscopy with Mechanosensitive Membrane Tension Probes

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The mechanical properties of cells are key parameters that regulate some of their functions and therefore, dysregulation in sensing their environment have implications in various diseases. Although it is generally accepted that membrane tension is a key parameter to many different cellular processes such as cell adhesion, endocytosis, exocytosis, phagocytosis, intracellular membrane trafficking and cell division, measuring in vivo forces like tension remains technically challenging. Newly designed oligothiophenes fluorescent probes displaying ground-state planarization at room temperature have led to the development of push-pull probes as mechanosensitive molecules, called "flippers"[1,2]. These probes insert easily into lipid membranes, where they display red-shifted absorption and a much stronger fluorescence emission in the liquid ordered (L_o) lipid phase than in the liquid disordered (L_d) phase due to the forces imposing a planarization of the chromophore already in its ground state. In this contribution, we evaluate different flipper derivatives for single-molecule localization microscopy imaging and report for the first time imaging below the diffraction limit with several mechanosensitive probes using the PAINT method (Point Accumulation for Imaging in Nanoscale Tomography)[3,4]. This work paves the way to the imaging of local forces with nanometric precision in cell biology.

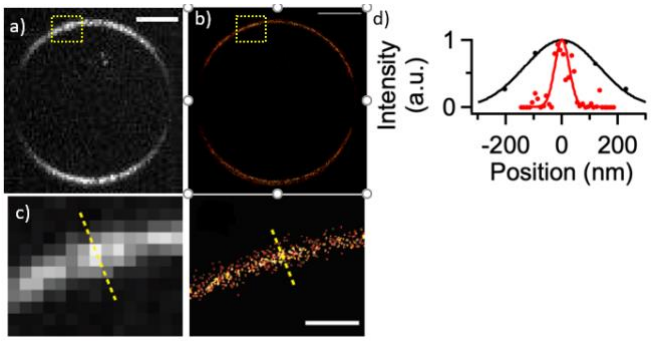

Figure 1. *a) Diffraction limited image of a GUV made of lipids in the L_o phase. b) PAINT super-resolution image of the same GUV. c) Magnified view of regions in boxes in b) and c). d) Cross-sections of the GUV membrane indicated by a line in d). Scale bars: a), b), c): 2 µm; d): 500 nm.*

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(2) Fin, A.; Vargas Jentzsch, A.; Sakai, N.; Matile, S. Oligothiophene Amphiphiles as Planarizable and Polarizable Fluorescent Membrane Probes. *Angew. Chem. Int. Ed Engl.* **2012**, *51* (51), 12736–12739.

(3) Garcia-Calvo, J.; Maillard, J.; Fureraj, I.; Strakova, K.; Colom, A.; Mercier, V.; Roux, A.; Vauthey, E.; Sakai, N.; Fürstenberg, A.; Matile, S. Fluorescent Membrane Tension Probes for Super-Resolution Microscopy: Combining Mechanosensitive Cascade Switching with Dynamic-Covalent Ketone Chemistry. *J. Am. Chem. Soc.* **2020,** *142* (28), 12034-12038.

(4) Maillard, J.; Drab, E.; Garcia, J.; Silaghi, M.; Matile, S.; Fürstenberg, A. *In preparation*.