



Ultra-resolution in the cell nucleus with single molecule expansion microscopy

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Over the past two decades, super-resolution (SR) microscopy methods have pushed through the diffraction limit of light and are now delivering insights and discoveries, particularly when applied inside cells. However, even with the best resolution gains – up to an order of magnitude with single molecule (SM) methods – much detail of the sub-cellular environment remains obscured. Expansion microscopy (ExM) is a new imaging modality that provides sub-diffraction information by expanding samples so that previously unresolvable detail can be visualised directly without specialised optics or photophysical manipulation.[1] Because ExM is achieved purely through the sample, combination with other SR techniques is readily achievable with essentially cumulative resolution gains. When combined with SM-SR methods, ultra-resolution – imaging at sub 10 nm – becomes possible.[2]

In this talk, I will discuss our recent work on developing ultra-resolution methods to visualise key cellular structures focussing on application of super-resolution and ExM inside the cell nucleus.[3] In this endeavour, we have applied the SR technique of *d*STORM to visualise epigenetic histone modifications in T cells and have established the nuclear lamin as a suitable reference structure for quantification of these (Fig 1). We have demonstrated that expansion of T cell nuclei preserves the distributional features observed in unexpanded nuclei opening the way to investigate the nucleus at near single biomolecule resolution.

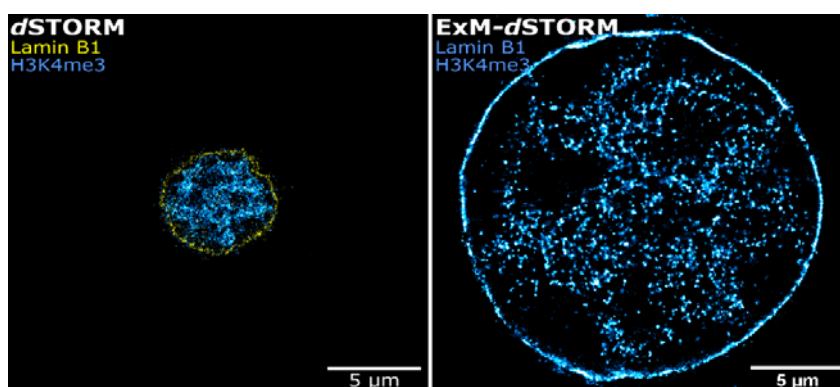


Figure 1. Single molecule super-resolution (left) and ultra-resolution (right) imaging of Lamin B1 and the histone modification H3K4me3 in T cells.

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2. FU Zwettler, S Reinhard, D Gambarotto, TDM Bell, V Hamel, P Guichard, M Sauer, Molecular resolution imaging by post-labeling expansion single-molecule localization microscopy (Ex-SMLM). *Nat. Comms*, 2020, **11**, 3388.
3. AM Rozario, A Morey, C Elliott, B Russ, DR Whelan, SJ Turner, TDM Bell, 3D single molecule super-resolution of whole nuclear lamina. *Front. Chem.* 2022, **10**, 863610.