FLUORESCENTLY LABELED SILICA COATED GOLD NANOPARTICLES AS FIDUCIALS FOR CORRELATIVE MICROSCOPY

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The field of correlative microscopy where, for example, light and electron microscopy are combined has been growing very quickly in recent years. In order to gain additional information from combining these two techniques, it is very important to properly overlay (or register) the images obtained with the two modalities. A fiducial marker that is clearly visible in both modalities improves the speed and accuracy of this process [1].

Such a fiducial marker would need to be a particle or nanocomposite that provides us with high contrast for electron microscopy. Furthermore, it is important that the particle is bright and photostable for light microscopy. For an integrated approach the fluorescence has to be preserved even under the vacuum (and cryo) conditions of an electron microscope. A final and very important requirement is the size of the particle. As a simple fiducial marker, a large particle diameter of 50-100 nm would be acceptable. However, if we also want to be able to use the particles for immunolabeling the total diameter should be as small as possible, ideally below 50 nm.

In this work, gold nanoparticles coated with a thin layer of fluorescently labeled silica, are presented as fiducial markers. The metallic core provides the electron contrast while the fluorophores embedded in the silica shell provide the fluorescence signal. Proof of principle experiments are conducted demonstrating that we can successfully use this type of particles as fiducial markers for image registration in typical biological samples.

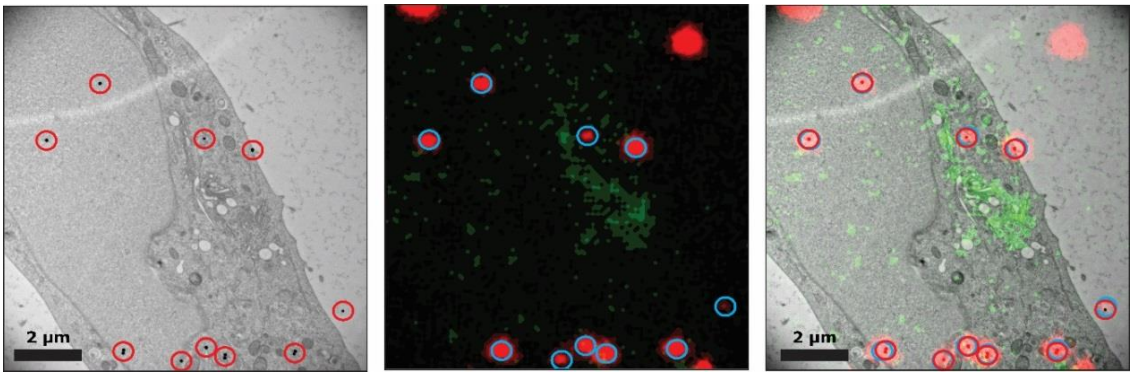

Figure 1: CLEM images of the fiducials drop casted on a section of resin embedded HeLa cells. In the TEM picture (left) and in the fluorescent image (middle) the fiducials are encircled. The positions of the fiducials are used to register the two images (right).

[1] W. Kukulski *et al.*, "Correlated fluorescence and 3D electron microscopy with high sensitivity and spatial precision," The *Journal of Cell Biology.*, **192(1)**, 111-119 (2011)