Correlative Light Electron Microscopy: 1 + 1 = 3

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Correlative Light Electron Microscopy combines the strengths of light and electron microscopy in one experiment and the sum of such an experiment should provide more data / insight than each technique alone (1 + 1 = 3). There are many ways to perform a CLEM experiment and a variety of microscopy modalities can be combined. I will discuss 3 processing techniques based on light microscopy in conjunction with Transmission Electron Microscopy, each with its specific application and its advantages and challenges.

1. The first is based on the use of coverslips with an embossed finder pattern. Importantly, it allows for live cell imaging and captures an event of interest using chemical fixation. This is possibly one of the technically easiest CLEM techniques but retracing the same object in the light and electron microscope remains a challenge.

2. A second uses the Tokuyasu cryo immuno labelling technique to trace back objects of interest. This allows for relatively high immuno labelling efficiencies but is almost impossible in combination with live cell imaging.

3. The third is based on cryo-fixation to obtain best possible preservation of ultrastructure. This allows us to capture events that would be lost because of chemical fixation, e.g. membrane tubules. It allows for live cell imaging but immuno labelling options are limited.