Microfluidic cryo-fixation – a game changer in correlative microscopy

A team of researchers at the Centre for Advanced Molecular Imaging are developing a novel microfluidic platform that will enable correlative light and electron microscopy to visualise molecular structure information in dynamic processes.

Benefits over existing technologies:

- Potential to develop 'First in Class' solution to revolutionise correlative microscopy
- Correlate high resolution optical microscopy with atomic resolution electron microscopy
- On demand cryofixation in real-time with seamless sample transfer

Background

Light and electron microscopy are complementary techniques that provide different information about the same specimen. In biological systems, light microscopy allows for live cells to be imaged in real-time whereas electron microscopy can provide a static, but higher resolution picture regarding molecular structure. Recent advances in optical super-resolution techniques have started to bring the resolution of optical microscopy closer to that of electron microscopy.

The ability to combine the dynamic information provided by optical microscopy with the molecular structure information provided by electron microscopy will be a major breakthrough in biological microscopy[1-3]. The key to achieving this goal is to be able to fix the biological sample being studied on demand and in real-time in a manner that is compatible with electron microscopy.

Cryofixation is generally considered the gold standard in fixation techniques because it preserves the sample in a state as close to its natural state as possible. Currently all correlative imaging protocols based on cryofixation require a transfer step from the optical microscopy to a high pressure freezer or a plunge freezing device.

Whilst such protocols have been shown to be effective, there is an inherent time delay between optical observation and cryofixation, and there is a risk of perturbing the sample during the transfer process.

The ideal solution would be to cryo-freeze the sample whilst it is being imaged on the optical microscope platform.

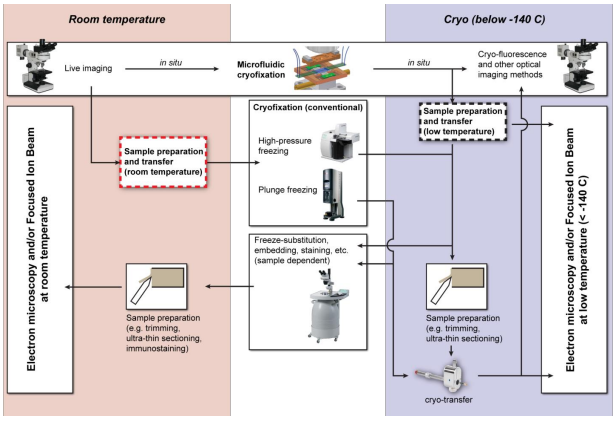

Illustration of the correlative light and electron microscopy workflow (Ref. 4).

The opportunity

A microfluidic concept for cryofixation has been demonstrated recently[4]. Whilst this device demonstrates the ability to cryo-freeze a sample whilst it is being imaged in an optical microscope, the device still suffers from a lack of resolution in optical imaging, and the sample transfer mechanism is not addressed.

Our team is looking to develop a novel microfluidic platform, based on the concepts that have been demonstrated thus far, that simplifies the microfluidic design to allow for higher resolution optical imaging and seamless sample transfer across optical and electron microscopy.

The Centre for Advanced Molecular Imaging is seeking partners to help us with the design and prototyping of a microfluidic cryofixation platform for correlative microscopy. Our team has broad expertise across optical microscopy, including construction of bespoke microscope components, electron microscopy as well as high impact biological systems to apply this technology. We also have strong working relationships with several major microscopy manufacturers to ensure compatibility across microscope platforms.

1. Smith, C. (2012) Microscopy: Two microscopes are better than one. *Nature* 492, 293-297.

2. Kukulski, W. et al. (2011) Correlated fluorescence and 3D electron microscopy with high sensitivity and spatial precision. *J. Cell Biol.* 192, 111-119.

3. Spiegelhalter, C. et al. (2010) From Dynamic Live Cell Imaging to 3D Ultrastructure: Novel Integrated Methods for High Pressure Freezing and Correlative Light-Electron Microscopy. *PLoS One* 5, e9014.

4. Mejia Y. X. et al. (2014) Microfluidic cryofixation for correlative microscopy. *Lab on a Chip* 14, 3281-3284.

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