Docket #: S22-303

Ballistic microscopy (BAM): High-throughput cytoplasm spatio-temporal pico-sampling from live-single cells for omic studies using particle bombardment

Researchers from Stanford University have developed a technique coined Ballistic Microscopy (BaM) which enables non-destructive sampling of pico-liters or less of biological components from live cells with high spatial and temporal resolution. The sample collection can be coupled with structural, mass spectrometry and/or sequencing-based pipelines for untargeted spatio-temporal identification of cellular components.

Living cells contain millions of heterogenous components that work together to perform biological functions. Deciphering the roles of each of these components across space and time remains a major challenge. Traditional label-based light microscopy experiments allow for dynamic imaging of living cells and tissues, but require prior knowledge of the biomolecules observed. Conversely, in Mass Spectrometry Imaging (MSI), untargeted studies provide information on the location and identity of molecular species in biological samples by coupling spatial distributions to mass-based omics analyses. These studies can be high throughput and high resolution, but they typically rely on sample preparation and ionization methods that preclude their use in dynamic imaging of living cells or tissues. The technology described here, BaM, combines the untargeted and high throughput sample collection for omics-level analyses (similar to MSI) with the advantages of light microscopy, namely compatibility with longitudinal data collection on living samples.

The key advance provided by BaM is the ability to collect small amounts of biological material from living cells without destruction of the cell. This is achieved by using micro-and nano-particles that travel through the sample at ballistic speeds and collect a pico- or femto-liter amount of cellular material in their flight path. Due to the high velocity and small size of the particles, the cells remain intact and alive. The thousands to millions of particles sent through the sample are then captured within a hydrogel to record both spatial and temporal information. Coupling the sample collection with standard omics and/or structural techniques for either later or in-line analysis completes the method by identification of the cellular components at each spatiotemporal data point. This combination of high spatio-temporal resolution with omics and structural level analysis provides an unprecedented level of detail in the observation of cellular heterogeneity and offers broad application to fundamental studies of biological function.

Stage of Development
Prototype

Applications

- Instrumentation to enable fundamental studies of cellular and tissue function
- Coupling to mass spectrometry, next generation sequencing, and electron microscopy instrumentation and pipelines

Advantages

- **Omics-level analysis** of biological components is **extended to dynamic and live-cell experiments**, which is not possible using current microscopy techniques.
- Sample collection can be coupled with a variety of omics-level pipelines (e.g. proteomics, DNA/RNA sequencing) to identify heterogenous biological molecules, as well as for structural studies via electron microscopy techniques (e.g. TEM, cryo-EM).
- Compatible with all cell and tissue types
- Penetration depth can be tuned from 10 to 500 ?m, providing compatibility with a variety of tissue thicknesses.

- **High spatial and temporal resolution** – sampling from each nanometer to micrometer spatial location at up to 1 microsecond time points.

Patents

- Published Application: WO2024044276
- Published Application: 20260049976

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