Docket #: S13-106

Multiplexed Ion Beam Imaging: High-resolution, High-sensitivity, Quantitative Tissue Imaging

Stanford researchers developed and patented a multiplexed immunohistochemistry method called multiplexed ion beam imaging (MIBI), which uses antibodies tagged with non-biological elemental isotopes (e.g. rare earth elements) and secondary ion mass spectroscopy. (See figure 1). While conventional IHC qualitatively detects only 1-3 antigens in tissue samples, this new technique measures 50-100 targets in a tissue specimen simultaneously with virtually no signal interference between channels. The dynamic range of the technique is on the order of 105, exceeding that of conventional immunofluorescence and clinical IHC methods by nearly 1000 fold. Specimens are prepared using conventional IHC methods, compatible with formalin fixed paraffin embedded tissue blocks (FFPE), and are stable indefinitely. MIBI can be expanded to other detection reagents (e.g. aptamers, nucleic acid probes) to perform analogous assays (e.g. in situ hybridization). This technique provides multiplexed, quantitative, single-cell analysis in solid tissue specimens that was previously possible only in cell suspensions compatible with flow cytometry, and significantly advances clinical diagnostics and research applications.

Stage of Development
The Angelo Lab applies their Multiplexed Ion Beam Imaging method to cancer biology, infectious diseases, immune tolerance, allergy, and the maternal-fetal interface research.

Figure

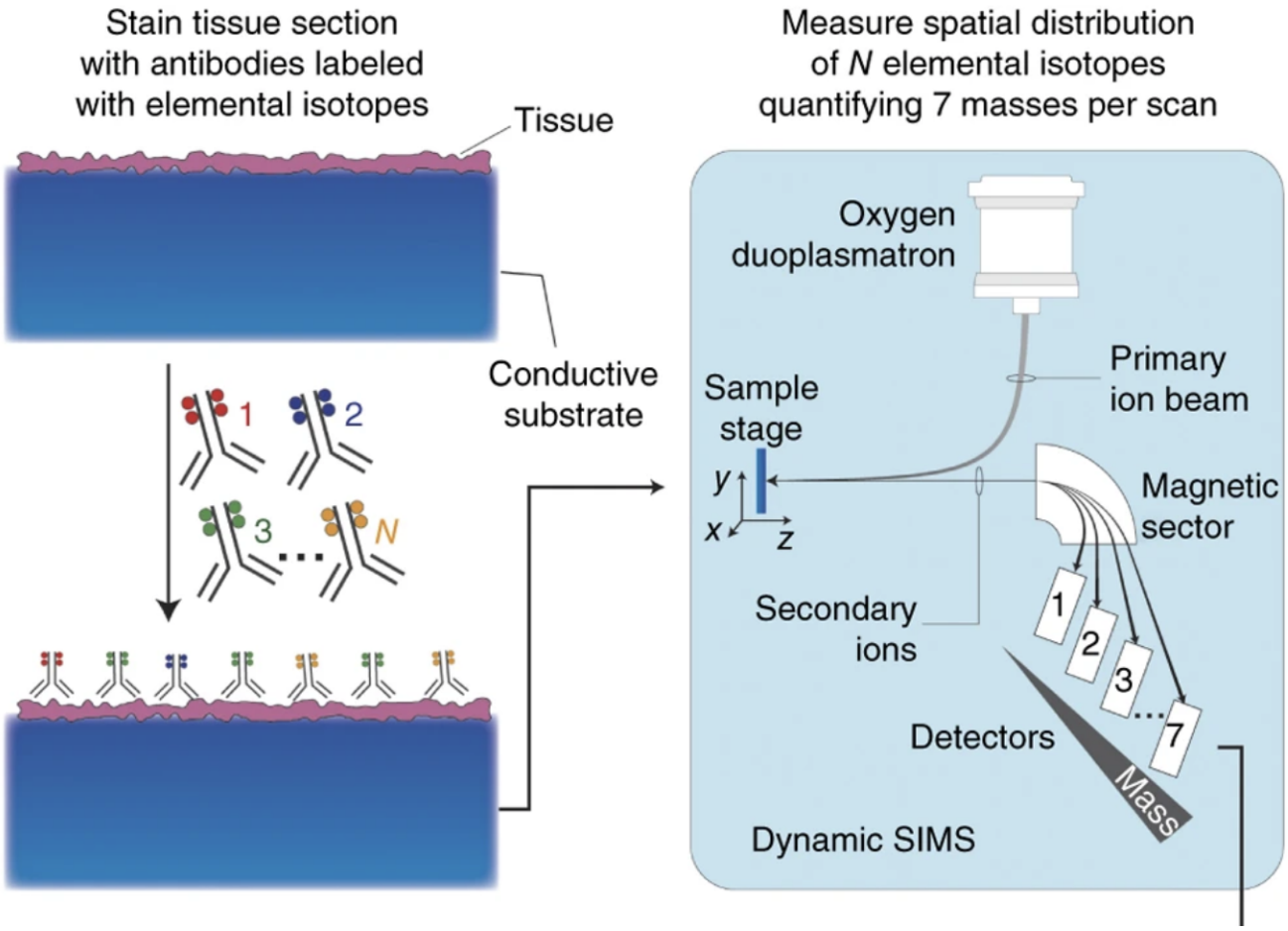


Figure Description: Multiplexed ion beam imaging multiplexed immunohistochemistry workflow (Image courtesy: The Angelo Lab).

Applications

- Clinical Assays
  - Cancer diagnostics and classification
  - Precision medicine
  - Clinical trials
  - Pathology workflows
- Research Tool
  - Tumor microenvironment studies
  - Immunology research
  - Biomarker discovery
  - Systems biology

Advantages

- Sensitive, quantitatively accurate, multiplexed assays
  - Simultaneous measurement of 50-100 targets with quantitative precision
  - 1,000-fold greater dynamic range (105) compared to conventional methods
  - Virtually no signal interference between detection channels
- Expandable to other detection reagents like aptamers and nucleic acid probes
- Single-cell spatial proteomics - flow cytometry-like analysis with preserved tissue architecture
- Stable specimen and archival tissue analysis, compatible with standard IHC preparation techniques and repositories

Publications

- Angelo, M., Bendall, S. C., Finck, R., Hale, M. B., Hitzman, C., Borowsky, A. D., Levenson, R. M., Lowe, J. B., Liu, S. D. , Zhao, S., Natkunam, Y., & Nolan, G. P. (2014). Multiplexed ion beam imaging of human breast tumors. Nature medicine, 20(4), 436-442.
- Levenson, R. M., Borowsky, A. D., & Angelo, M. (2015). Immunohistochemistry and mass spectrometry for highly multiplexed cellular molecular imaging. Laboratory Investigation, 95(4), 397-405. DOI: 10.1038/labinvest.2015.2
- Keren, L., Bosse, M., Thompson, S., Risom, T., Vijayaragavan, K., McCaffrey, E., ... & Angelo, M. (2019). MIBI-TOF: A multiplexed imaging platform relates cellular phenotypes and tissue structure. Science advances, 5(10), eaax5851. DOI: 10.1126/sciadv.aax5851
- Lomeli, G., Bosse, M., Bendall, S. C., Angelo, M., & Herr, A. E. (2021). Multiplexed ion beam imaging readout of single-cell immunoblotting. Analytical chemistry, 93(24), 8517-8525.
- Liu, C. C., McCaffrey, E. F., Greenwald, N. F., Soon, E., Risom, T., Vijayaragavan, K., ... & Angelo, M. (2022). Multiplexed ion beam imaging: insights into pathobiology. Annual Review of Pathology: Mechanisms of Disease, 17(1), 403-423.
- Liu, C. C., Bosse, M., Kong, A., Kagel, A., Kinders, R., Hewitt, S. M., ... & Angelo, M. (2022). Reproducible, high-dimensional imaging in archival human tissue by

multiplexed ion beam imaging by time-of-flight (MIBI-TOF). Laboratory Investigation, 102(7), 762-770.

Patents

- Published Application: WO2015038784
- Published Application: 20150080233
- Published Application: 20190162729
- Issued: 10,041,949 (USA)

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