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Physical tissue expansion for nanoscale investigation of clinical specimens in diagnostic pathology and research

Background: In diagnostic pathology and research, investigation of molecular composition and cellular structures using conventional optical microscopy is critical. Expansion Microscopy is a new approach developed by Prof. Edward Boyden's laboratory at MIT. It enables physical magnification and high-resolution imaging of cell and mouse brain tissue sections with diffraction-limited microscopes, by embedding them in a dense swellable polymer and adding water to swell the polymer after the mechanical homogenization (Chen F, Tillberg PW, Boyden ES, Science, 2015). In this study, we aimed to develop a pathology-optimized physical tissue expansion strategy for nanometer imaging & analysis of clinical tissue specimens and show several of its applications in diagnostic pathology and research.

Methods: We have developed a pathology-optimized physical tissue expansion strategy, named Expansion Pathology (ExPath), with clinically optimized labeling, chemistry and imaging methodologies, to enable the expansion and visualization of both human formalin fixed paraffin embedded tissue (FFPE) and frozen clinical tissues. This includes previously unstained or stained, unmounted or mounted, whole tissue slides or tissue microarrays sections, of a large variety of fixed human tissues and pathologies, including breast and ovarian cancer.

Results: Our ExPath protocol enabled expansion of normal and cancer human tissues ~100 times in volume (~4-5x linear dimension expansion) with a post-expansion distortion of about 2-7%. Physical tissue expansion pushes the conventional diffraction-limited microscopes beyond their

resolution limits (currently ~250nm), by enabling for the first time ~80nm resolution imaging of diverse biomolecules in fixed tissue, with an optical microscope. ExPath, enable the diagnosis of certain lesions and pathologies previously diagnosed only with an electron microscope (EM), by using a conventional optical microscope after physical tissue expansion. This strategy facilitates morphological and multiplexed protein investigation of large tissue regions, faster and less expensive. ExPath also enables high-fidelity computational discrimination between early breast neoplastic lesions that to date have challenged human judgement.

Conclusion: ExPath offers a new strategy for the investigation of pathologically important features in human tissue and diseases. ExPath may enable routine use of nanoscale imaging in molecular pathology, diagnostic pathology and research.

Speaker Biography

Octavian Bucur is an Instructor in the Department of Pathology at the Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA. He is developing and applying novel experimental and computational technologies for molecular, diagnostic pathology and personalized medicine. He is also a member of the Ludwig Cancer Center at Harvard Medical School. In collaboration with Prof. Edward Boyden's laboratory at MIT and Prof. Yongin Zhao (now at Carnegie Mellon University), he has developed a pathology-optimized physical tissue expansion method, Expansion Pathology (ExPath), enabling ~100 times three-dimensional expansion of any type of clinical tissue specimen & visualization of 80nm structures with conventional optical microscopes (which are limited to ~250nm resolution). ExPath has the potential of replacing and complementing electron microscopy in diagnosis and investigation of certain diseases (Nature Biotechnology, 2017)

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