Nanoscale Refractive Index Measurement via Near-field Scanning Optical Microscopy

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The laboratory of Professor Vadim Backman at Northwestern University is exploring a novel backscattering microscopic technique for detection of early-stage cancers of the colon, pancreas, and lung: partial-wave spectroscopy (PWS). Currently, this technique is being applied in preclinical trials of cancer screening involving several hundred patients, and has shown sufficient promise to merit extensive funding support. The hypothesis underlying PWS is that the degree of disorder of nanometer-scale optical refractive index (RI) fluctuations within a cell serves as a sensitive measure of cellular changes indicative of early-stage cancer. To validate the PWS hypothesis and thereby place this promising diagnostic technique upon a firm foundation, we require direct RI measurements within cells with unprecedented nanometer-scale spatial resolution. However, such nanoscale RI fluctuations are invisible to conventional optical microscopy. Furthermore, a comprehensive literature search reveals that no method currently exists to directly measure the RI within biological cells at the required nanometer spatial resolution, which is much finer than the Abbe diffraction limit. However, my current research has established the feasibility of such measurements using a novel application of the near-field scanning optical microscope (NSOM). While NSOM is a proven technique for scanning nanometer-scale surface features of structures, the key innovation of the present research is the use of the NSOM probe to *penetrate* materials such as biological cells to map out internal features. To date, collected data for liquids of known RI indicate that there exists a linear relationship (to a correlation factor $R^2 = 0.9863$) between the mean NSOM photon frequency and the RI of a sample over the range $n_D = 1.3000$ to $n_D = 1.6000$ for a 50 nm diameter probe. This RI range encompasses and exceeds the biological range of interest. Furthermore, the z-axis spatial resolution of this technique for this probe diameter has been measured to be approximately 25 nm. In addition to permitting rigorous, direct testing of the fundamental hypothesis underlying PWS, observation of specific nanometer-scale changes within biological cells will add to the current basic-science knowledge of malignancy progression, thereby providing a springboard for future research.