**ABSTRACT**

**BACKGROUND**: Melanoma represents only 4% of all skin cancers, but nearly 80% of skin cancer deaths. This manuscript applies several new measurement technologies with the purpose of elucidating molecular signatures of melanoma aggressiveness.

**PURPOSE**: We sought to determine whether low-abundant serum proteins related to apoptotic pathways could be measured and correlated with defined melanoma subtypes. Hydrogel core shell nanoparticles, a new technology capable of selectively entrapping low molecular weight proteins and protecting them from enzymatic degradation, were used to capture candidate serum biomarkers. Biomarker levels were correlated with confocal microscopy, thereby representing a combination of new technologies for in vivo histologic documentation.

**RESULTS**: Among a panel of analyzed serum proteins, Bak was differentially expressed between nevi and melanomas. Melanomas with higher Bak serum levels exhibited more pronounced junctional activity on confocal imaging, whereas lesions with 'sparse' dermal nests had weak Bak expression.

**CONCLUSIONS**: Our study links serum proteome analysis with confocal microscopic clinical in vivo histologic classification of melanomas. Bak has not been previously measured in serum. Bak differential expression among melanoma subtypes confirms the importance of the apoptotic pathway as a contributor to melanoma aggressiveness.