

INVITED LECTURE H1

New approaches to cancer biomarker discovery

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Although our understanding of the molecular pathogenesis of common types of cancers has improved considerably, the development of effective strategies for cancer diagnosis and treatment have lagged behind. The vast dynamic range of protein abundance in plasma and the likely occurrence of tumor derived proteins in the lower range of protein abundance represent a major challenge in applying a proteomic based strategy for their identification. A combination of innovative strategies promises to overcome these challenges. Recent experience in comprehensive profiling of plasma proteins indicates that low abundance proteins may be identified and quantified with high confidence following extensive plasma fractionation and with the use of protein tagging procedures and high-resolution mass spectrometry. From an experimental design point of view, most cancer biomarker studies, including those aimed at identifying markers for early detection, are initiated with analysis of specimens from newly diagnosed subjects. The discovered candidate markers are subsequently investigated for their utility for early cancer diagnosis. A preferred approach for discovery of such markers is to utilize plasma obtained at a pre-clinical stage, prior to the diagnosis of cancer. Yet this approach has been rarely if ever implemented. One implementation of this approach is through the use of mouse models of cancer that potentially represent an efficient means for uncovering diagnostic markers because of the ability to engineer mice that harbor genetic alterations known to be associated with tumors in humans, and because of the limited heterogeneity among mice bred under uniform conditions and the ability to sample blood in a standardized manner, at defined stages of tumor development. Another implementation of this approach is to utilize plasma obtained at a pre-clinical stage, prior to the diagnosis of cancer thereby avoiding confounding factors such as inflammation and metabolic disturbances and bias due to differential specimen handling between cases and controls will be presented. Novel studies of epithelial tumors using mouse models and studies based on the use of pre-diagnostic human plasma will be presented.