Quantitative characterization of tissue structure and function across spatial scales remains one of the most challenging problems in Biomedical Imaging. Field of view, depth of interrogation, and resolution are critical features that dramatically impact image quality and information content. Optical methods can potentially provide a single platform for imaging biological tissues with resolution and depth sensitivity ranging from microns to centimeters. This lecture will review the development of near-infrared methods for quantitatively characterizing thick tissues with scalable resolution and depth based on fundamental light-tissue interaction mechanisms. Emphasis will be placed on intrinsic signal imaging of structure and biochemical composition, and multi-modality image co-registration. Examples will be provided that highlight the sensitivity of optical methods to alterations in cellular metabolism, extracellular matrix, and vasculature.