

# Gas-Phase Structural Biology: New Technologies for the Rapid Assessment of Protein Complex Sequence, Structure, and Stability

**Brandon T. Ruotolo**

*University of Michigan, Department of Chemistry, 930 N. University Ave., Ann Arbor MI, 48109, USA.*

Within each living organism proteins are at work, carrying out activities which impact every aspect of cellular function from synthesis to cell death. The next generation of medicines will rely heavily upon our ability to quickly assess the structures and stabilities of such complex macromolecular machines, as well as the influence of large libraries of conformationally-selective small molecule binders and protein-based biotherapeutics. Such endeavours are nearly insurmountable with current tools. In this presentation, I will discuss recent developments surrounding the activation of gas-phase protein complex ions aimed at bridging this gap in basic technology. One such development is collision induced unfolding (CIU), which uses ion mobility-mass spectrometry (IM-MS) to measure the stability and unfolding pathways of gas-phase proteins, without the need for covalent labels or tagging, and consuming 10-100 times less sample than almost any other label-free technology. In parallel with this approach, my lab are pursuing chemical modification strategies aimed at the improved liberation of sequence informative peptide fragments from intact protein complex precursor ions during collision induced dissociation (CID), enabling the assessment of protein quaternary structure and sequence simultaneously. Recent developments in understanding the mechanisms of protein CIU and CID, the ability of these tools to differentiate therapeutic antibodies and enable the discovery of conformationally-selective inhibitors, will be discussed.