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Quantification of non-cognate pairs resulting from single cell bispecific antibody assembly using high resolution intact mass measurement

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Bispecific antibodies possess the characteristics and binding specificity of two distinct monoclonal antibodies and as such can bind to two targets or epitopes simultaneously. Generation of a bispecific antibody by co-expression of two light and heavy chains would result in a correctly assembled molecule as well as several mispaired species. While the “knobs-into-holes” technology enables efficient hetero-dimerization of the two heavy chains, the presumed random mispairing of the light chains has not been studied in detail as technologies to readily characterize and quantify the heterodimer species were missing. We employ a combination of analytical approaches for the characterization of co-expressed bispecific antibodies using native and partially denaturing conditions on a high resolution orbital ion trap mass spectrometer. The high mass resolving power of the EMR Orbitrap allows unambiguous identification of all light and heavy chain pairing variants in a mixture of bispecific antibodies randomly assembled *in vivo* upon co-expression and can be accurately quantified down to low levels. We investigate the preferential pairing of one light chain with its cognate heavy chain, and present a high throughput method for quantifying mispairs to direct clone selection during stable cell line generation. Finally, a solution for discriminating between the correctly assembled bispecific and the double light chain mispair is offered through computation and antigen pairing monitored by native MS.

Biography

Wendy Sandoval leads the Applied Proteomics group in Research at Genentech. The group applies a variety of analytical approaches discovery and pipeline projects through collaborations with biologists. In addition to standard bottom-up proteomics platforms, the group has a particular interest in applying native mass and high-resolution mass spectrometry to the study of protein interactions. She studied Chemistry at the University of California at Santa Cruz and has been at Genentech for over twenty years.

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