INVITED SPEAKER

NMR INPUT IN THE CHARACTERIZATION OF THERAPEUTICAL MABS

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Monoclonal antibodies (mAbs) are biotherapeutics products that have achieved outstanding success in treating many life-threatening and chronic diseases. Structural biology and biophysical tools are used all over the R&D pipeline from early stages of research to the release of clinical batches. One the one hand, structural methods such as X-ray Crystallography and cryo-EM are routinely used to characterize biotherapeutics structural properties with the obtention of 3-D structures that will help a candidate selection. On the other hand, biophysical tools are used to characterize stability, structural integrity and biological activity of the biotherapeutics along the R&D pipeline. The higher order structure (HOS) is unique to Biologics and is the combination of the primary/secondary/tertiary and quaternary structures of proteins. HOS of monoclonal antibodies (mAbs) directly dictate their ability to bind either antigen via their Fab domains or effector cells via their Fc region. As a result, the HOS of a protein links primary structure modification to the biological activity and is directly related to the function of the molecule as it impacts potency and immunogenicity. Degradations and modifications, routinely encountered during development, production and long-term storage of mAbs, can potentially affect HOS and cause extensive damage on therapeutics efficacy. To date, HOS evaluation of mAbs during development has been carried out using low-to-moderate resolution biophysical methods which are not efficient to detect subtle changes that could origin observed potency loss. CH3-2D-NMR fingerprinting has been recently introduced to meet this challenge and can generate a well-resolved spectral map offering a comprehensive atomic-level fingerprint of the primary to quaternary structures of a mAb. Studies conducted by Sanofi clearly demonstrate the added value of CH3-2D-NMR when combined with chemometric tools to identify structural differences linked to batches variations occurring during the manufacturing process of therapeutical mAbs that could so far only be indirectly suspected.