SOCIÉTÉ CHIMIQUE DE GENÈVE

# Cutting-edge Analytical and Structural Methods for the Characterization of Antibodies and Antibody-Drug Conjugates


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Antibody–drug conjugates (ADCs) are one of the fastest growing classes of oncology therapeutics. After half a century of research, the approvals of brentuximab vedotin (2011) trastuzumab emtansine (2013) and more recently of inotuzumab ozogamicin (2017) have paved the way for ongoing clinical trials that are evaluating more than 60 further ADC candidates. The limited success of first-generation ADCs informed strategies to bring second-generation ADCs to the market, which have higher levels of cytotoxic drug conjugation, lower levels of naked antibodies and more-stable linkers between the drug and the antibody. Furthermore, lessons learned during the past decade are now being used in the development of third-generation. ADCs are more complex than naked mAbs, as the heterogeneity of the conjugates adds to the inherent microvariability of the biomolecules. The development and optimization of ADCs rely on improving their analytical and bioanalytical characterization by assessing several critical quality attributes, namely the distribution and position of the drug, the amount of naked antibody, the average drug to antibody ratio, and the residual drug-linker and related product proportions. Because of the hybrid nature of ADCs, product quality attributes for both the biological component and the smallmolecule components must be considered. Therefore, early-developability assessment requires state-of-the-art analytical and structural methods, such as native and ion mobility mass spectrometry, two-dimensional liquid chromatography and capillary electrophoresis coupled to mass spectrometry. These emerging methods allow a deep insight into important structural features that are related to ADC functions as well as allowing understanding of ADC biotransformations in vivo.



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