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Bispecific antibodies: Strategies, considerations and challenges

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BISPECIFIC ANTIBODIES: STRATEGIES, CONSIDERATIONS AND CHALLENGES

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Bispecific antibodies (BsAbs) are moving mainstream as therapeutics with currently two bispecific antibodies approved and about 30 in clinical development. The idea of using a BsAb as a therapeutic has been around for almost as long as its monospecific counterpart, however during this time over 40 MAbs were approved but only two BsAbs. One of the main reasons why BsAbs lag behind is that they are far more complex to produce.
The co-expression of the two different heavy chains and two different light chains results in up to nine unwanted species in addition to the BsAb. Although a BsAb molecule can be made this way, it results in low yield and it is difficult to purify away the unwanted species. One solution to this pairing problem is to purify individual half-antibodies, combine and finally purify the bispecific antibody.
The presentation will discuss novel approaches to overcome the pairing challenge and enable production in a single cell. Heavy chain mispairing is prevented by the previously established knobs-into-holes technology, while novel mutations in the antibody heavy and light chain Fab region now facilitate orthogonal pairing of the light chains.
In addition, strategies to screen for the best bispecific antibody will be discussed. This includes considerations for designing bispecifics to match the proposed mechanism of action and intended clinical application.