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Multi-step High-throughput Conjugation Platform for the Development of Antibody-Drug Conjugates

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HighlightsComplete multi-step protein conjugation process on liquid handling station

- Reagent removal by automated intermediate buffer exchange step
- Automated intermediate protein quantification with process feedback
- Case studies demonstrating efficiency and comparability

1. Introduction

Antibody-drug conjugates (ADCs) constitute a class of therapeutic molecules inspiring high hopes for patients as well as pharmaceutical companies on the basis of their potential for cancer treatment. Around 60 ADCs in clinical trials in the beginning of 2017 (Beck et al., 2017) indicate the amount of resources that is currently and has previously been invested in their development. Until 2017, the only two ADCs on the market were Seattle Genetics's brentuximab vedotin (Adcetris) and Genentech and Immunogen's trastuzumab emtansine (Kadcyla), approved in 2011 and 2013, respectively. In August 2017, inotuzumab ozogamicin (Besponsa) by Pfizer was approved for relapsed or refractory B-cell precursor acute lymphoblastic leukemia. The highly complex compounds consist of three components: a monoclonal antibody (mAb), a cytotoxic drug and a linker between the two. The intention is to combine the specificity of the mAb and the cell-killing capacity of the small molecule drug in one compound, potentially widening the therapeutic window compared to the individual cytotoxic drug.

Induced by the currently limited success of conjugation procedures where random lysines or hinge cysteines are targeted, a generation of more homogeneous ADCs with site-specific conjugation strategies is currently in development. These strategies enable control of drug-to-antibody ratio (DAR) and conjugation site, both of which heavily influence efficacy, stability and pharmacokinetics (Drake et al., 2014; Lhospice et al., 2015; Pillow et al., 2014; Shen et al., 2012; Strop et al., 2013). Site-specific conjugation to engineered cysteines instead of hinge cysteines has been shown to improve the therapeutic index (Junutula et al., 2008). To pave the way for this third generation of ADCs more than 40 site-specific drug conjugate technologies have been developed, often in combination with