A WORD WITH...

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WHICH ARE THE TRENDS THAT WILL CHARACTERIZE THE ANTIBODY-DRUG CONJUGATES (ADCS) SECTOR?

ADCs are advanced chemotherapy treatments in which the cytotoxic payload targets the tumor cell by means of an antibody. The specificity and affinity of the antibody molecule combined is the key to the safe delivery of the toxic payload into the cell overexpressing a certain tumor -associated antigen at its surface. The previous generation of ADC payloads (dominated by Auristatins and Maytansinoids) is now being superseded by new classes of toxins that are more potent than those currently available (with a potency in the picomolar range or lower) and will help to further reduce doses.
As a CDMO, Cerbios-Pharma SA (hereinafter "CERBIOS") is already experiencing this change as it works with molecules that are becoming more potent every day. Significant new manufacturing challenges are associated with next-generation payloads and CDMOs need to be ready to provide suitable processing solutions. The linkers, which connect the payload to the antibody, are a key component of an ADC that controls the release of the payload inside the target cell. Both further improvements to existing linkers and newly invented ones will allow an optimization of drug release and the control of the bystander effect in which the neighbor cells are also hit, regardless of the antigen expression level. From a conjugation point-of-view, whereas first-generation ADCs were based on stochastic conjugation approaches that generated heterogeneous products, the new products under development allow better product homogeneity. This means that the Drug Antibody Ratio (DAR) is controlled through the insertion of specific conjugation sites into the antibody molecule by means of protein engineering.

PEOPLE ARE TALKING ABOUT THE "ADC REVOLUTION": WHAT WILL THE NEXT-GENERATION ADCS BE LIKE? WHAT APPROACHES WILL MANUFACTURERS HAVE TO ADOPT IN TERMS OF PROCESS AND DEVELOPMENT?

One of the drawbacks of the monoclonal antibodies used to treat solid tumors is their poor tissue penetration and the consequent ineffective delivery of the cytotoxic payload. One way to overcome this problem is to reduce the size of the antibody. A number of new approaches are being adopted, such as antibody fragments reduced to the minimum antigen recognition domain or other engineered protein molecules that, although they do not belong to the antibody family, are capable of selectively recognizing the tumor epitope; or even fully synthetic small molecules that bind with the tumor antigen and are easily internalized, thereby maximizing payload delivery. In this latter case, the anti-tumor product will be entirely derived from chemical synthesis.
On the other hand, payloads will continue to evolve and new classes of payloads will be used. As ADC producers and developers deal with increasingly potent payloads, improved containment measures will be required in order to guarantee the safety of the personnel involved in development and manufacturing activities; we can expect a greater use of disposable equipment in order to simplify cleaning procedures and validation obligations and campaign changeover on multi-purpose production lines.
At CERBIOS, we believe that it is important to keep ahead of new requirements and maintain a state-of-the-art setup. On the protein side, the new monoclonal antibodies engineered to become ADCs, are being designed to withstand the demanding conditions of the conjugation process and therefore reduce aggregation or fragmentation events. This could make some process parameters less critical than they are now, leading to more robust and reproducible processes, which is just as important for ADC manufacturers as for all others.

It is remarkable how, in ADCs, the two main components (payload and protein) generate significant increases in overall manufacturing costs, which is prompting CDMOs to develop a more efficient process, by switching the focus from the final product to the conjugation process. Consequently, the process development approach we are using follows the principles of Quality by Design (QbD) accompanied by Design of Experiments (DOE) and the implementation of Process Analytical Technologies that are now a regular part of good practices and have even been incorporated into current guidelines.
Finally, and consequently, supply chain integration could be an essential step towards further reducing manufacturing and development costs: a solution that CERBIOS makes available through the PROVEO® alliance, where protein scaffolds for the ADCs will need to be provided directly in conditions that are suitable for the conjugation step, including as the final step of the Fill-and-finish of the conjugate either in liquid or lyophilized form.

LET'S TALK ABOUT THE PRECLINICAL VALIDATION OF ADCS: WHICH ARE THE CHALLENGES THAT THE MANUFACTURERS OF SITE-SPECIFIC ADCS NEED TO FACE?

The ADC development arena is moving extremely fast. Recent developments in the field have provided a number of different approaches for site-specific conjugation.
These include protein engineering with the addition of new cysteines, the preferred amino acid for conjugation or cell engineering leading to modified cell systems, in which the introduction of non-natural amino acids allow the use of unique conjugation chemistries.
Other systems include the enzymatic approach, with the addition of specific protein tags at the level of the antibody sequence or modifying the glycan moiety.
All these systems are leading to the formation of new conjugation sites that are favorable for click chemistry conjugation.
We can expect that new conjugation methods will become available in the near future.

Manufacturers therefore need to keep up to date and in contact with technology developers, in order to adopt the new approaches for ADC development and manufacture properly. At CERBIOS, for example, we are working with startups or small biotech companies from the proof-of- concept stage, supporting them in the preclinical phase and through the early clinical studies. In these phases, it is our job, after the initial tech transfer, to support the development of the conjugation and manufacturing activities, in order to generate a robust, consistent and scalable process, which we will apply for commercial supplies and in compliance with all applicable regulatory requirements. The approach is definitely more biological than chemical. Indeed, ADC size is dominated by the large monoclonal and, therefore, the main analytical developments are biological.

THE PRODUCTION OF HIGHLY POTENT TOXINS AND THEIR CONJUGATION WITH PROTEINS REPRESENTS AN EXAMPLE OF "CROSS-CONTAMINATION" BETWEEN CHEMISTRY AND BIOLOGY. WHAT ARE YOUR THOUGHTS ON THIS, IMAGINING A SWOT ANALYSIS WITHIN THIS PRODUCTION SETTING?

Yes, ADCs bring a unique kind of challenge, in that they are generated in a process that has chemical and biological requirements. The strength of CERBIOS, lies precisely in the coexistence of these worlds: for 40 years it has housed under the same roof both a Chemical Division (for the production of folates, vitamin D derivatives and HPAI) and a Biological Division (for recombinant proteins and probiotics). At CERBIOS, ADCs mean applying both its expertise in the development and manufacturing of HPAIs and its experience and know how in the production and manipulation of recombinant proteins, on the same site in Lugano (a very unique setup).
The continuous growth of the ADCs currently in the development and early clinical phases, associated with the high added value of these products, represents an excellent opportunity for CERBIOS as a CDMO.