Recent Advances in the Antibody-Drug Conjugate Clinical Pipeline

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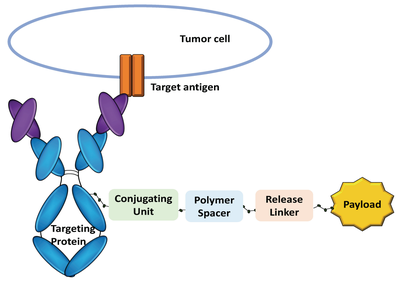
Introduction

Antibody-drug conjugates (ADCs) are a complex class of biotherapeutics that utilizes monoclonal antibodies to selectively deliver potent cytotoxic agents to the tumor site. The design of these products gives promise to a targeted therapy that only affects tumor cells and spares healthy tissues [1].

Figure 1. ADC Design. ADCs are composed of a monoclonal antibody, cytotoxic payload, and a chemical release linker joined through a conjugating unit. Depending on certain characteristics of these components, additional spacers may be employed to enhance stability. ADCs are designed to recognize a target antigen on the surface of tumor cells resulting in internalization, release of the payload, and execution of cell death.



As of April 2021, the U.S. Food and Drug Administration (FDA) has approved ten ADCs. More ADCs are entering clinical trials, against numerous targets and employing a wide range of payloads. The industry is also gradually shifting from utilizing conventional technologies to newer and more robust approaches to conjugate such complex biomolecules. This poster highlights recent efforts in ADC development to overcome challenges often observed with ADCs. Here, novel targets, cytotoxic payloads, linker chemistries, and bioconjugation techniques are surveyed in ADCs under clinical evaluation to outline the current tends in the ADC framework and provide perspective on the future directions of this class of targeted therapeutics.

ADC Components and Considerations

The clinical success of ADCs hinges on the design, including target selection, the monoclonal antibody, payload, linker, additional spacers, and the conjugation method of the ADC [2].

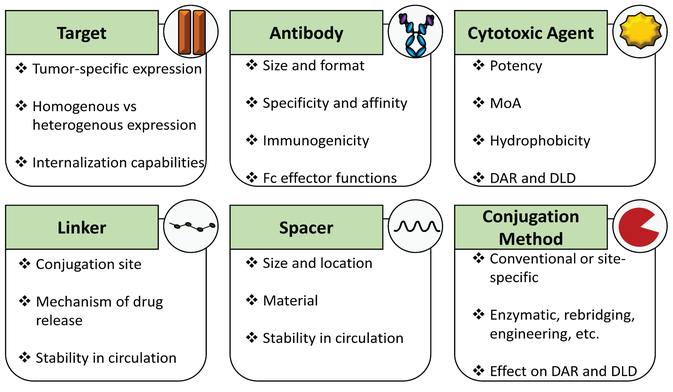


Figure 2. ADC Components. Each component of the ADC design plays a significant role in ADC performance both. Various properties relating to the stability and mechanism of action impact the success of ADCs in targeting tumor-associated antigens and eliciting cell death.

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Methods

We utilized Clinicaltrials.gov database to identify active clinical ADC studies. Search items included "antibody drug conjugate" and "cancer" with exclusion criteria: Trials for marketed ADCs, ADCs for non-oncological indications, and trials of terminated, withdrawn, completed, and unknown status.

Inclusion Criteria	Exclusion Criteria
Keywords: "antibody drug conjugate" and "cancer"	Marketed ADCs and antibody dye conjugates in search results
Status: • Not yet recruiting • Recruiting • Enrolling by invitation • Active, not recruiting • Suspended	Status: • Terminated • Completed • Withdrawn • Unknown Status

Table 1. Summary of the Methods.

Clinical Investigation of ADCs

There are currently 76 novel ADCs in 148 active clinical trials. Most of the ADCs are currently under investigation in phase 1 trials, while a small percentage has advanced to phase 3. More than 80% of ongoing trials are evaluating ADC safety and efficacy in solid tumors, an increase compared to those approved.

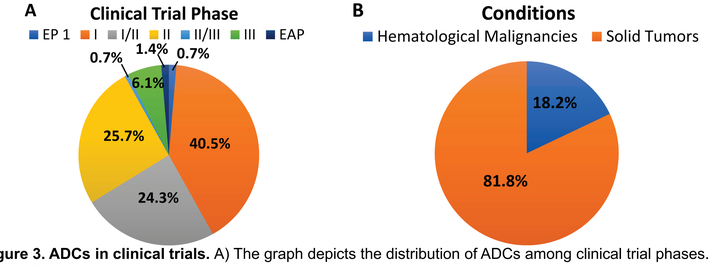
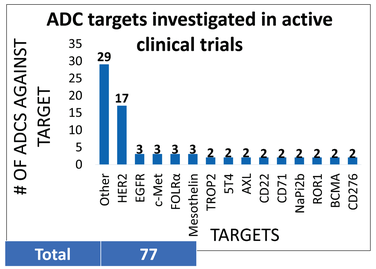


Figure 3. ADCs in clinical trials. A) The graph depicts the distribution of ADCs among clinical trial phases. B) Most ADCs are under investigation for solid tumors with a small percentage targeting hematological malignancies. Early phase 1 (EP 1); Early Access Program (EAP).

ADC Targets

There are 43 disclosed targets organized here by the number of ADCs designed to recognize them. HER2 is currently the most popular target, likely due to its high expression across a wide range of tumor types. Targeting HER2 could broaden the number of indications an ADC is approved for. Additionally, while nearly all ADCs recognize only one target, we found one bispecific ADC against EGFR and MUC16.

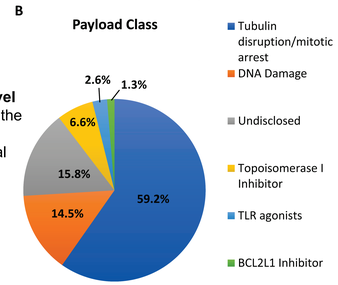
Figure 4. Targets of Novel ADCs. The graph includes targets of ADCs in which more than two products are designed to recognize the proteins. "Other" refers to targets where there is only one ADC designed to recognize it in clinical trials or the target is undisclosed.



Payloads

Payload classes have diversified since early ADC approvals. While most still employ tubulin disruptors, there is an increase in those using DNA damaging agents. More notable, new classes have emerged, including topoisomerase inhibitors, as seen in recent approvals, Toll-like receptor (TLR) agonists to induce immune mediated toxicity, and apoptotic agents.

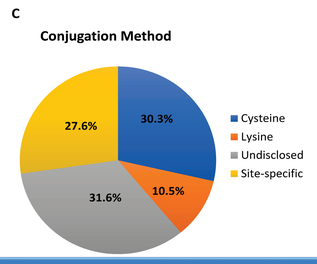
Figure 5. Payloads of Novel ADCs. The graph includes the different payload classes employed by developmental ADCs.



Conjugation

All approved ADCs utilize conventional conjugation such as through surface exposed lysine residues or free cysteines of reduced interchain disulfide bonds. However, strategies to optimize conjugation technologies to improve stability and allow for conjugation of higher potent payloads are emerging. This includes chemoenzymatic conjugation to engineered residues of the antibody, and mechanisms that may only release the payload under certain physiological conditions specific to the tumor environment.

Figure 6. Conjugation Methods of Novel ADCs. The graph includes the different conjugation methods employed by developmental ADCs.



The Future of ADCs

ADCs hold the promise of providing better therapies in oncology. Advancements continue in the optimization of ADC components and conjugation technique with unique formats emerging to combat potential drawbacks of the conventional ADC design. Recent updates in ADCs within the clinical pipeline revealed the emergence of several novel formats to address the drawbacks of conventional ADCs including new targets and more ADCs against targets relevant to multiple indications, new toxic payloads, and site-specific conjugation platforms. More unique developments are likely underway towards the aim of optimizing ADC design for clinical applications

References

1. Nejadmoghaddam, Mohammad-Reza et al. "Antibody-Drug Conjugates: Possibilities and Challenges." *Avicenna journal of medical biotechnology* vol. 11,1 (2019): 3-23.
2. Bxk, Alain et al. ·Strategies and challenges for the next generation of antibody–drug conjugates." *Nature Reviews Drug Discovery* vol. 16, (2017): 315-337.