ANTIBODY-DRUG CONJUGATES (ADCS) :

TRANSFORMING TARGETED CANCER THERAPIES

Author: Marie Tautou, Director of Scientific studies

Antibody-drug conjugates (ADCs) represent a major advance in the fight against cancer. These innovative therapies act as veritable “homing missiles”, directly targeting cancer cells while sparing healthy tissue. By combining the specificity of monoclonal antibodies with the potency of cytotoxic agents, ADCs are emerging as one of the most promising forms of targeted therapy, offering patients more effective and less toxic treatment options.At Antineo, we are committed to supporting our customers in demonstrating the efficacy and safety of their ADCs, in order to make cancer treatments more precise and patient-friendly.

In this article, we'll explore the structure of ADCs, their mechanism of action, recent clinical advances, challenges encountered and future prospects in oncology.

What are ADCs ?

ADCs are an innovative class of biomedicines composed of **three essential elements** :

1. **Monoclonal antibody (mAb)** : designed to specifically target antigens overexpressed on the surface of cancer cells

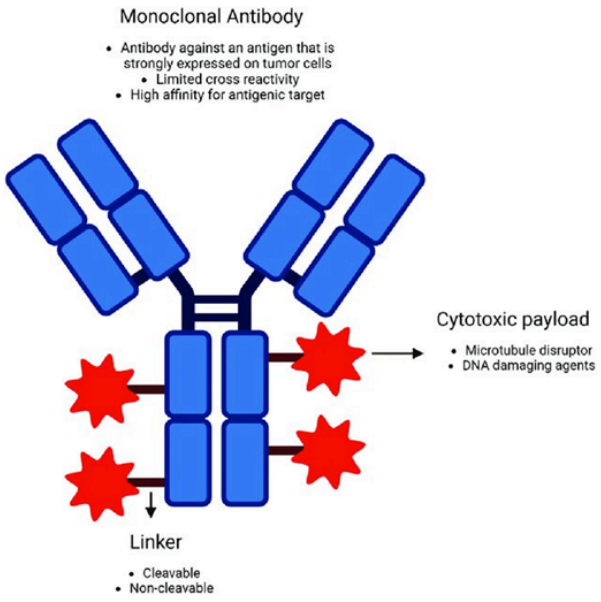
2. **Cytotoxic agent** : a powerful chemotherapeutic agent attached to the antibody, designed to destroy cancer cells

3. **Chemical linker** : this ensures the connection between the antibody and the drug, guaranteeing the stability of the complex in the bloodstream and enabling release of the cytotoxic agent only inside the cancer cell

This approach enables chemotherapy to be administered directly to the tumor, **limiting systemic exposure** and reducing the side effects usually associated with conventional treatments.

ADCs rely on the use of **powerful cytotoxic agents** to eliminate cancer cells. Below are listed the main classes of agents used as ADCs’ payloads :

- **Auristatins** (microtubule inhibitors) : Monomethylauristatin E (MMAE), Monomethylauristatin F (MMAF)
- **Maytansinoids** (microtubule inhibitors) : DM1 (Maytansine derivative), DM4
- **Calicheamycin derivatives** (DNA breakage-inducing agents) : N-acetyl-γ-calicheamycin
- **Camptothecins** (topoisomerase I inhibitors) : SN-38 (active metabolite of irinotecan)
- **Pyrrolobenzodiazepines** (PBDs) (DNA alkylating agents) : PBD dimers
- **Duocarmycins** (DNA alkylating agents) : Duocarmycin derivatives
- **Indolino-benzodiazepines** (DNA intercalating agents) : Tesirine derivatives



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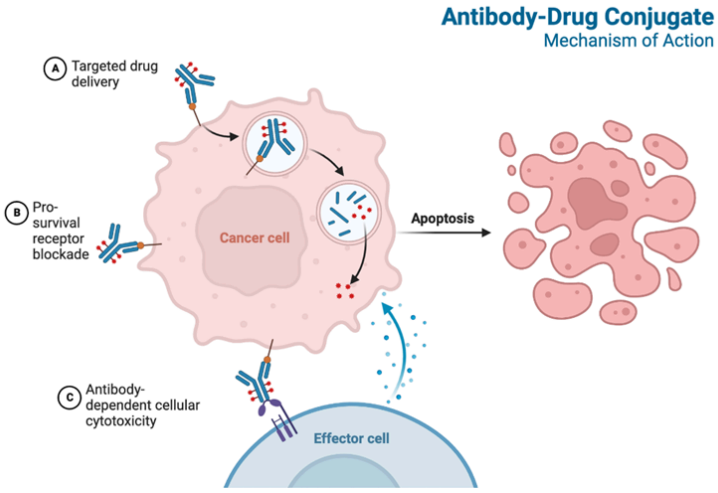
ADCs' mechanism of action

ADCs operate in a targeted, multi-step process :

1. **Recognition and binding :** the ADC monoclonal antibody binds specifically to the tumor antigen present on the surface of cancer cells
2. **Internalization :** Once bound, the ADC is internalized by the cell via endocytosis.
3. **Release of cytotoxic agent :** After internalization, the linker is cleaved, releasing the cytotoxic agent directly into the cell.
4. **Cellular destruction :** The cytotoxic agent interferes with key processes in the cancer cell (DNA replication, cell division), leading to apoptosis (programmed cell death) and tumor shrinkage.



This targeted approach greatly reduces damage to normal, healthy cells, **offering a more selective and effective treatment while minimizing side effects.**

Major ADC approvals - clinical efficacy and safety

Recent clinical trials have led to the **approval of several ADCs revolutionizing cancer treatment** :

- Brentuximab vedotin (Adcetris®) for lymphoma : Targeting the CD30 protein present on the surface of lymphoma cells, this ADC has demonstrated **response rates in excess of 70%** in patients with relapsed or refractory Hodgkin's lymphoma
- Trastuzumab emtansine (Kadcyla®) for HER2+ breast cancer : Combining trastuzumab with the cytotoxic agent emtansine, **it significantly improved survival** in patients who had failed previous treatment.

ADCs already approved show **remarkable clinical efficacy,** with high response rates and increased survival. The most common adverse effects remain manageable (fatigue, neutropenia, mild gastrointestinal disorders), while serious toxicities are rare thanks to the specificity of targeting.

Conclusion - Challenges and future prospects

Despite their potential, ADCs still face multiple challenges :

- **Tumor resistance** : Some cancers develop resistance mechanisms, making ADCs less effective
- **Residual toxicity** : Even with a precise target, some ADCs may exhibit off-target toxicity.
- **Manufacturing difficulties** : The production of ADCs is complex and costly, requiring advanced technologies.

However, the future of ADCs is promising, thanks to technological advances, the development of new therapeutic combinations (with immunotherapies or checkpoint inhibitors), and the extension of their application to solid cancers. **ADCs represent a revolutionary advance in cancer treatment, enabling a more effective and better tolerated targeted approach.**

With a deep understanding of ADCs' structure, mechanism of action, clinical successes, and the current challenges, we at Antineo are committed to help our customers advancing this transformative technology through preclinical phases.

For more information on ADCs and their challenges, please see the following review : Dumontet et al. "Antibody-drug conjugates come of age in oncology." Nature reviews

To discuss collaboration opportunities, visit antineo.fr or contact us directly.