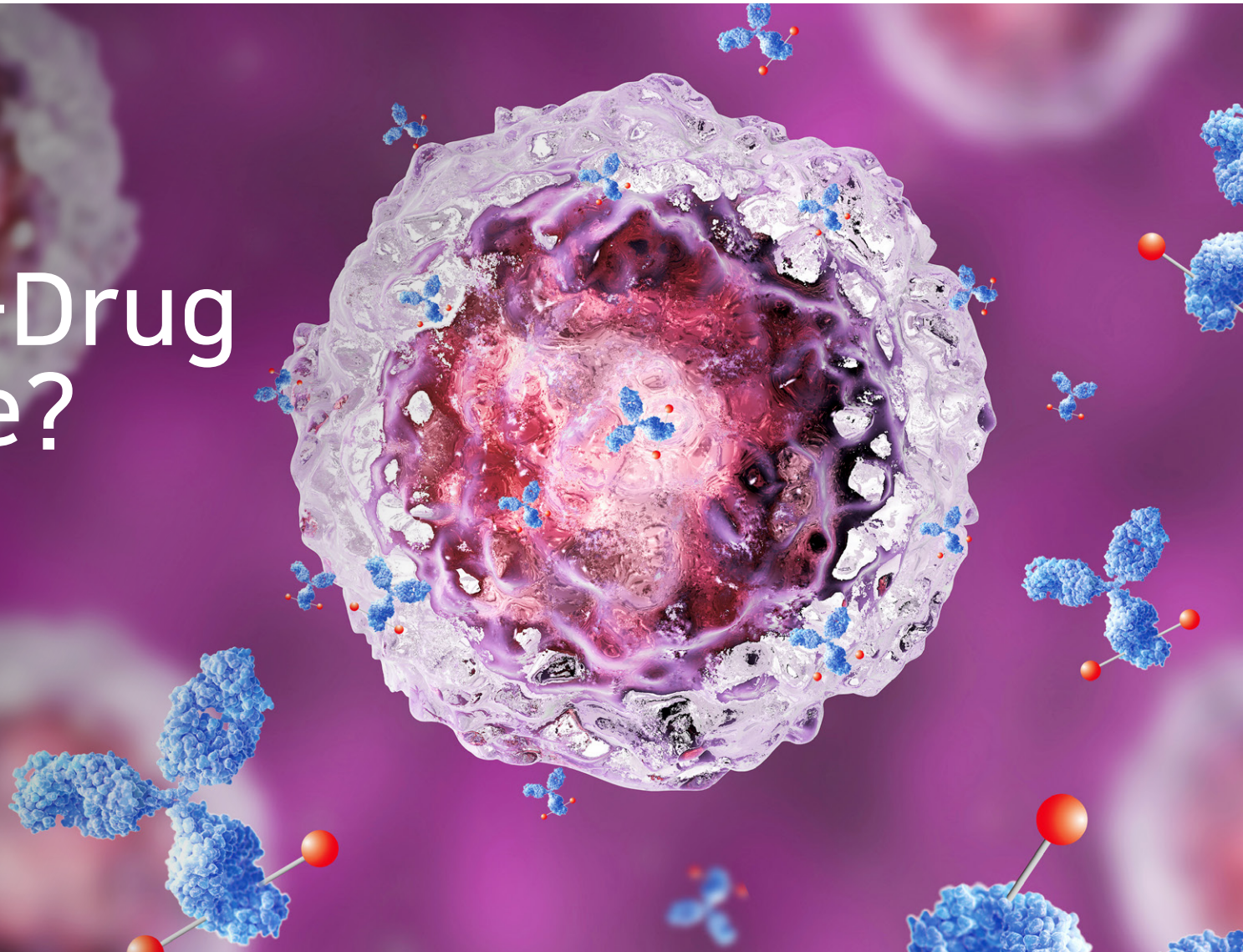


# What is Antibody-Drug Conjugate?



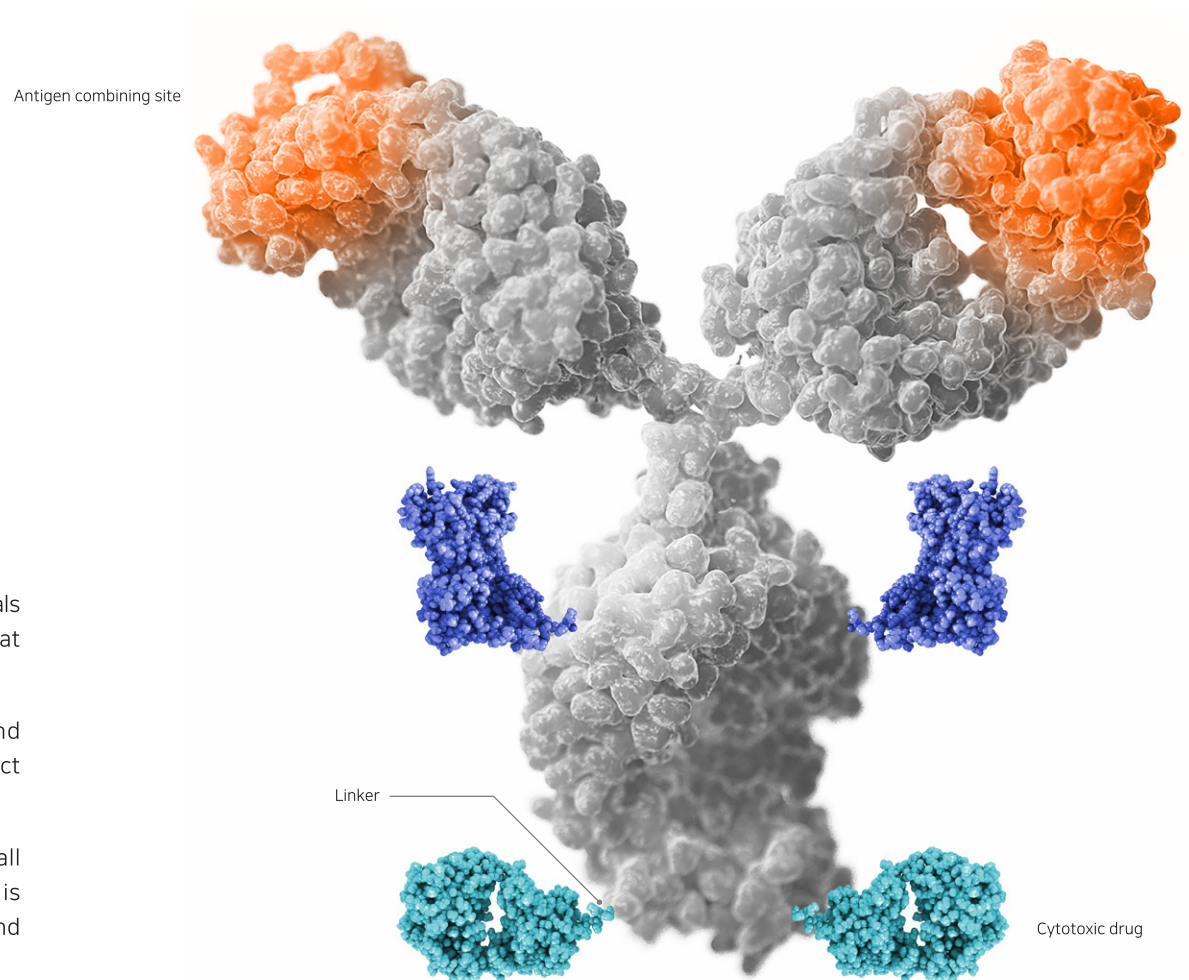
# About Antibody-Drug Conjugate

Antibody-Drug Conjugates (ADCs) are highly targeted biopharmaceuticals built by combining a potent small molecule drug with an antibody that binds to specific types of antigens.

Cytotoxic agents and other chemical drugs for curing cancer and incurable diseases are extremely effective, yet their toxicity may affect normal cells as well and cause side effects.

ADCs, on the other hand, are capable of delivering cytotoxic small molecules to target lesion without damaging normal tissues, as it is a combination of tumor-specific targeted monoclonal antibodies and potent chemical drugs.

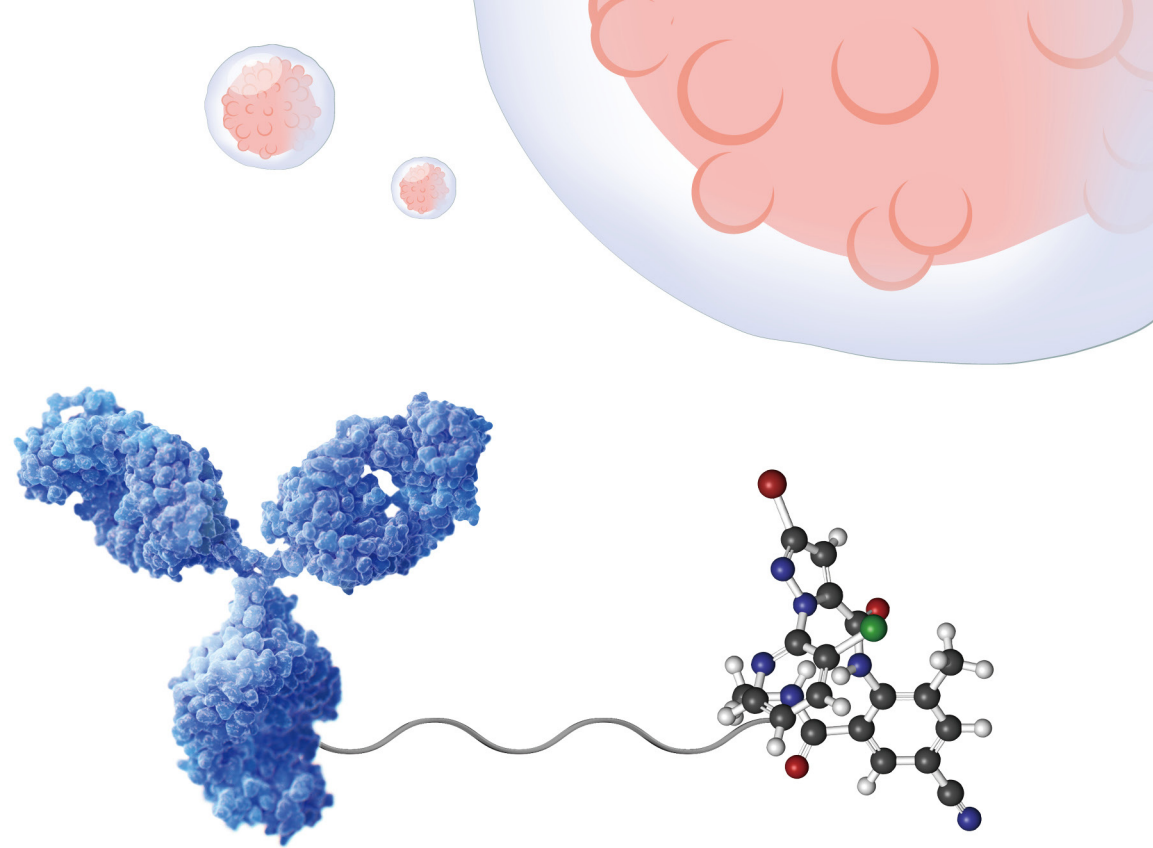
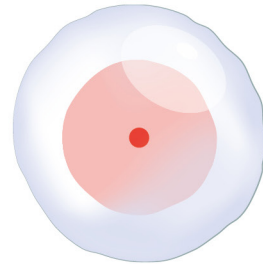
Thanks to its enhanced efficiency and safety, research and development of ADC-based therapies are surging recently, particularly in cancer treatments with high toxic anticancer chemotherapy.



**Antibody-Drug Conjugate**



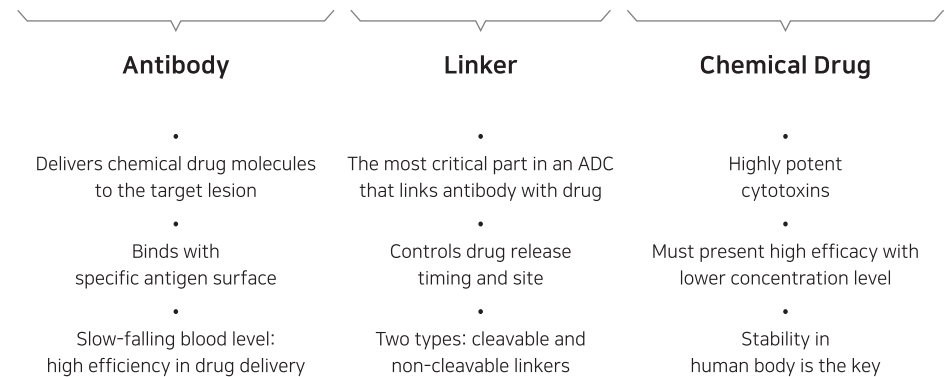
# Structure of ADC



ADCs are composed of monoclonal antibodies and cytotoxic drug molecules tied up with specialized chemical linkers. The antibody delivers the attached chemical molecules to the target antigens. Thus the antibody has to be developed in a way to detect and attach to specific antigen only found on target cells.

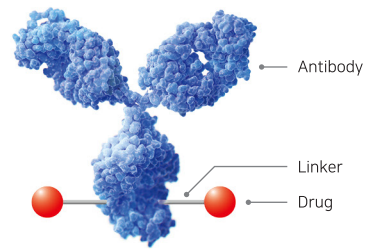
The chemical drug that is attached to antibody is the key element in cancer treatment. However, as the number of molecules that each conjugate can carry is limited, the substance must be capable of killing cancer cells even in lower concentration levels. Furthermore, because it must maintain a certain level of stability after circulating through patient's body, a vast range of research is in progress to develop chemical drugs that satisfy these demanding conditions.

The linkers, a structure that combines antibody and drug, is the most critical and also the most complicated part of a conjugate, as a slightest fluctuation in linker force can result in reduced treatment efficiency or damage in normal cells. There are two types of linkers: "cleavable linkers" that are cut in response to pH, protease or concentration level, and "non-cleavable linkers" that release drug through degradation of the antibody.



A visual representation of ADC structure

# Mechanism of ADC



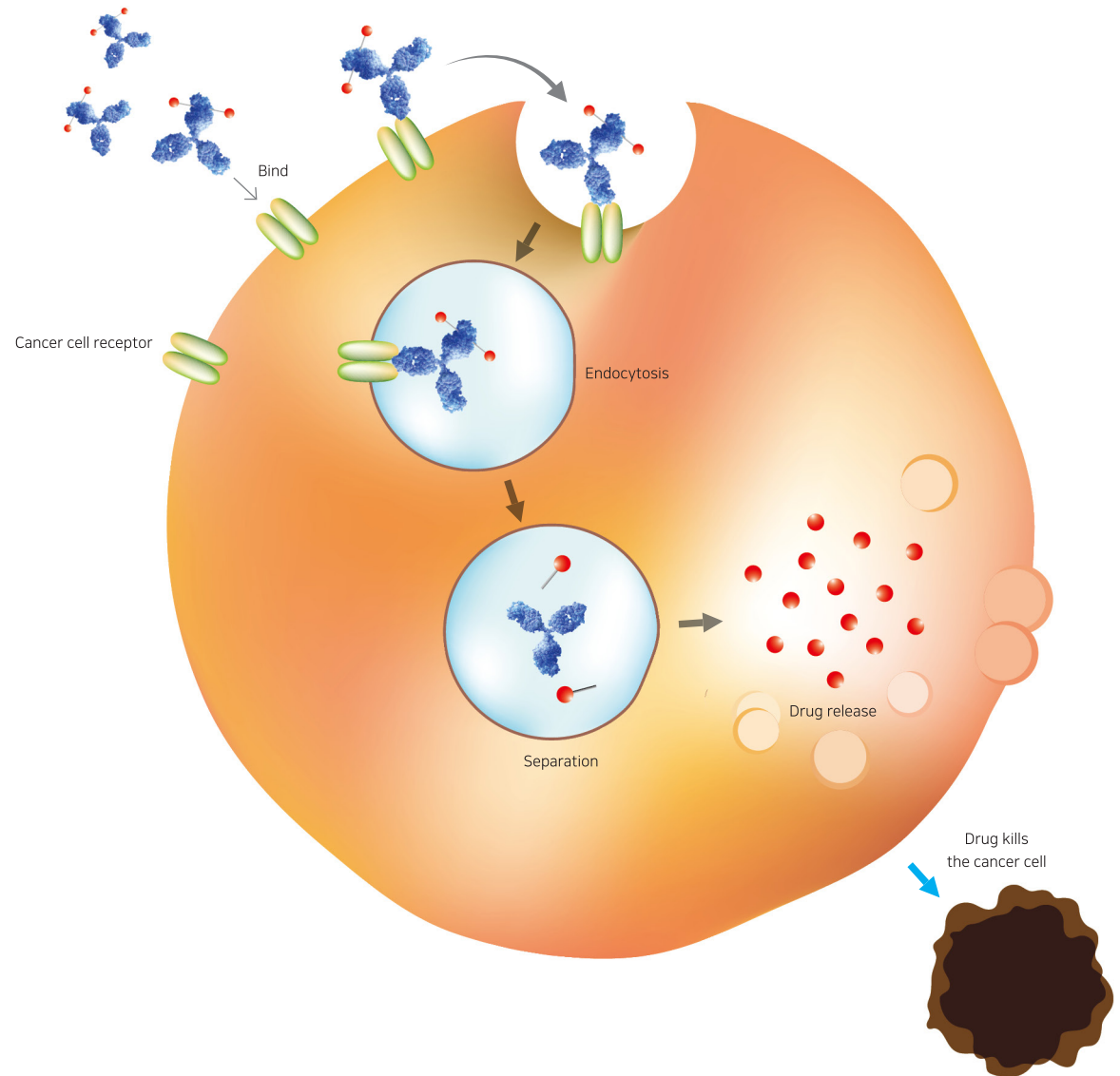
Antibody-Drug Conjugate

The basic concept of ADCs is to combine highly potent chemical drugs with antibodies that bind only with targeted antigens, to maximize the delivery of drugs to the lesion with minimum side effect.

Cytotoxic drug molecule is linked to an antibody by a connection called a "linker." When this complete ADCs are injected into a patient body, they travel through circulation system and approach the lesion to attach to the target antigen.

Upon binding, the cancer cell engulfs the ADC, and the drug is released by either broken linkers (by pH, protease, or concentration level) or degradation of antibody.

This mechanism of action is highly efficient in killing cancer cells without damaging normal tissues, minimizing adverse effects.



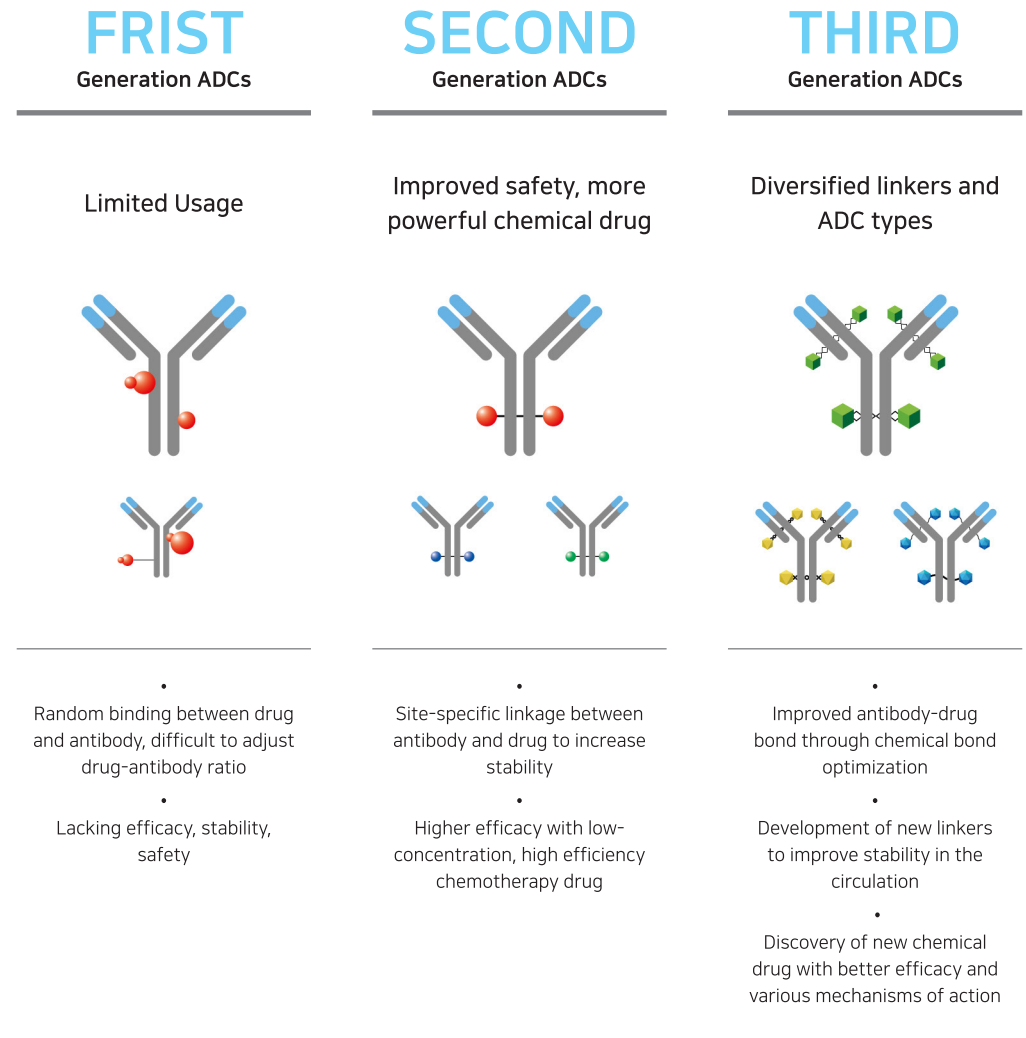
Mechanism of ADCs

# Status of ADC Technology Development

The Antibody-Drug Conjugate technology provides new and innovative therapies so that patients can be treated with improved safety and efficacy. The first generation ADC drugs, the research of which started as early as in the 1950s, were unable to pinpoint the linker position—the drug molecules tend to randomly attach on the surface of an antibody, making the production difficult and heightening the possibility of adverse event. As these ADCs were only at the very early stage of technological innovation, they demonstrated only limited potency in clinical trials.

To improve this, the second generation ADC therapies that are currently in use adopted site-specific approaches and introduced amino acid substitution or unnatural amino acids to enhance drug stability and efficacy. Discovery of more powerful chemical drugs have played an important role in upgrading the potency of the ADCs, too.

The key to the Third-generation ADC drugs, that are under development, is to ensure clear drug-antibody ratio (DAR) without affecting target antigen. Also a new generation of linkers are being developed to maintain more stable binding between antibody and drug in the circulation system.

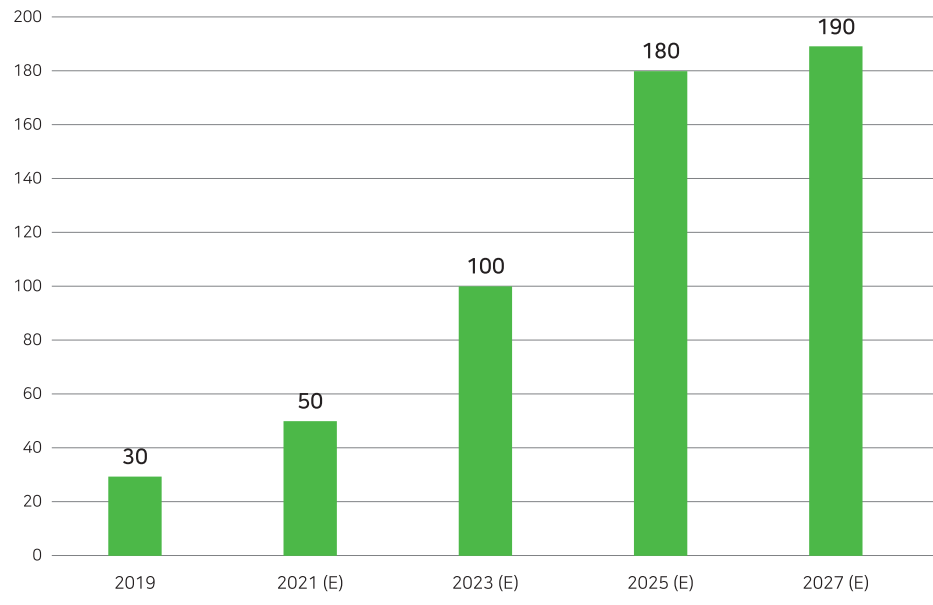


# Marketability of ADC

The ADCs already yielded significant results in the anticancer field, proving their marketability. As of 2021, a total of eleven anticancer ADCs have been approved by US FDA. The global market size is about 5 billion dollars, which is expected to reach 1.8 billion by 2025.

ADC therapeutics for various cancer indications such as breast cancer, Hodgkin's lymphoma, acute lymphocytic leukemia, and multiple myeloma are continue to be developed. Pfizer, Genentech, and GSK and other global pharmaceutical players have succeeded in developing ADCs, adding momentum to the growth of the market. Currently, more than 100 ADC drugs are under development.

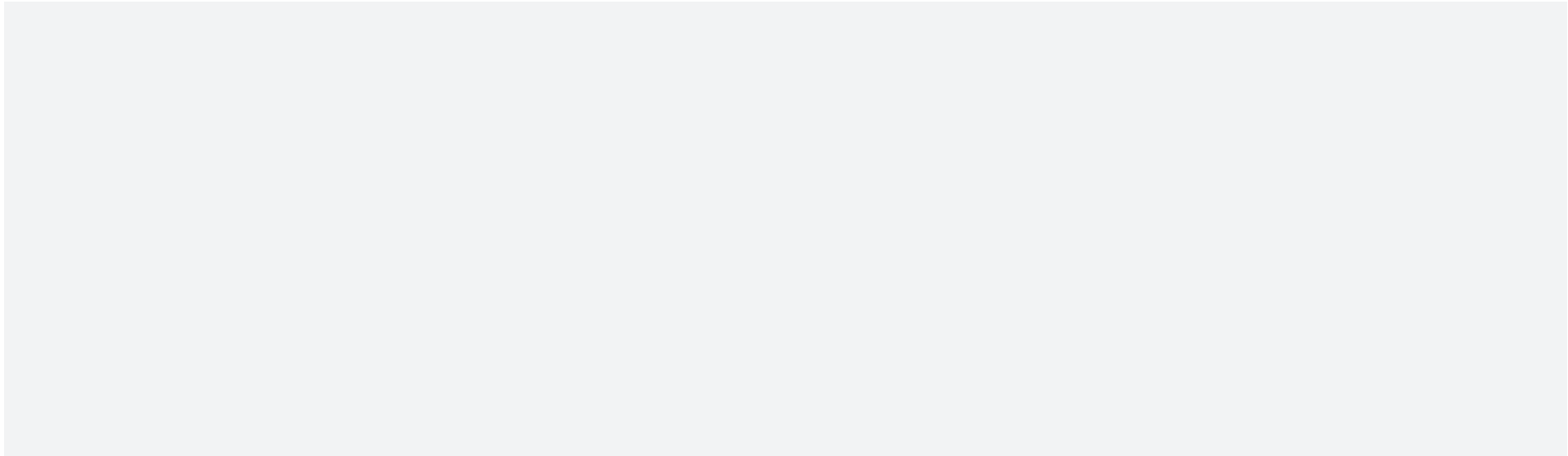
Global ADC market projection (Unit: USD 1,00 million)



Source: Cortellis

FDA-approved ADC anticancer therapeutics (2021)

Active Ingredient (antibody + chemical)	Company (approved year)	Linker	Indications
Gemtuzumab ozogamicin	Pfizer (2000, 2017)	pH-sensitive linkers	Acute myeloid leukemia
Brentuximab vedotin	Seattle Genetics (2011)	Protease-cleavable linkers	Hodgkin's Lymphoma
Trastuzumab emtansine	Genentech (2013, 2019)	Non-cleavable linkers	Breast cancer and HER2-positive breast cancer
Inotuzumab ozogamicin	Pfizer (2017)	pH-sensitive linkers	Acute lymphocytic leukemia
Polatuzumab vedotin	Genentech (2019)	Protease-cleavable linkers	B-cell lymphoma
Enfortumab vedotin	Astellas Pharma (2019)	Protease-cleavable linkers	Urothelial cancer
Trastuzumab deruxtecan	Daiichi Sankyo (2019)	Protease-cleavable linkers	HER2-positive breast cancer
Sacituzumab govitecan	Immunomedics (2020)	Protease-cleavable linkers	Triple-negative breast cancer
Belantamab mafodotin	GSK (2020)	Non-cleavable linkers	Myeloma
Loncastuximab tesirine	ADC Therapeutics (2021)	Protease-cleavable linkers	B-cell lymphoma
Tisotumab vedotin	Seattle Genetics (2021)	Protease-cleavable linkers	Cervical cancer



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