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“ADCs have already become a mainstay treatment option across a variety of both hematologic and solid cancers”

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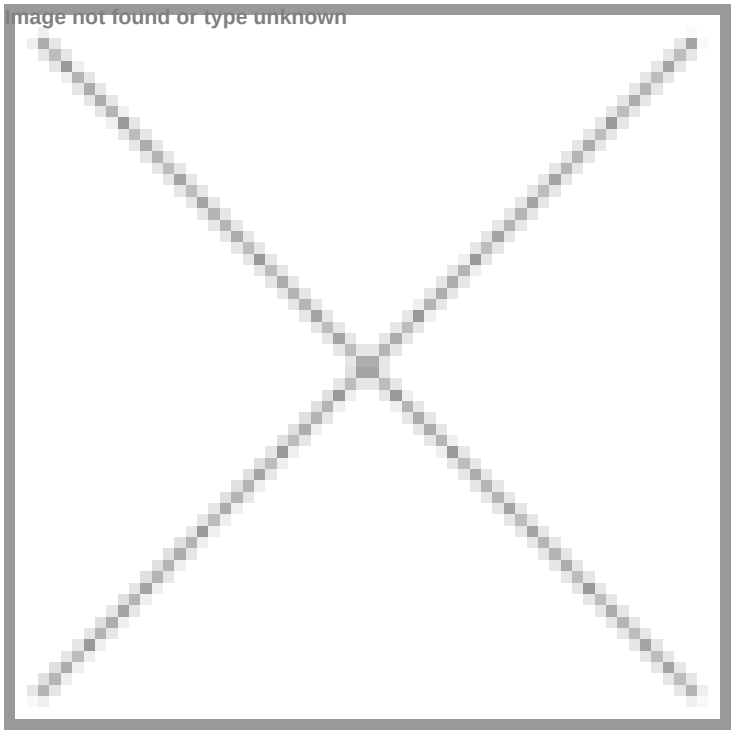
The resurgence of antibody-drug conjugates (ADCs) in cancer therapy signifies a shift towards targeted, highly effective treatments, leveraging the power of monoclonal antibodies to deliver potent cytotoxic payloads directly to cancer cells, minimising harm to healthy tissues. In an interaction with BioSpectrum, Dr Rafael G. Amado, President and Head of Global Research and Development at Zai Lab, discusses the resurgence of ADCs in cancer therapy and explains how ADCs differ from traditional treatments like chemotherapy and biologics. He also highlights the promising ADC candidates in development at Zai Lab and what distinguishes them from other ADCs.



Can you provide an overview of the primary components of ADCs and how they work in general?

Antibody-drug conjugates (ADCs), combine monoclonal antibodies specifically targeted to antigens on the surface of tumour cells with powerful anti-cancer molecules joined by a chemical linker. With the perspective of someone who has worked in cancer research for more than 25 years and helped develop 15 oncology-specific drugs, I view ADCs as a very valuable class of therapeutics. By delivering higher concentrations of cytotoxic agents and reducing off-target side effects, they have potential to deliver a higher benefit to patients than chemotherapy alone with a more limited toxicity profile.

What differentiates ADCs from other categories of cancer therapies such as chemotherapy or biologics? Why would a physician use an ADC vs one of these other categories of therapies?

ADCs deliver chemotherapy in a targeted fashion: the toxic payload is liberated largely in the tumour cell and microenvironment (rather than elsewhere in the body) by taking advantage of a trafficking molecule, generally an antibody, that binds to a tumour-associated antigen. Other differentiators and advantages include the number of toxic molecules on an ADC can be tightly regulated; the pharmacokinetics of the chemotherapy payload on ADCs can be optimised by pairing it with those of the antibody; the nature of the payload on ADCs can be altered to include small molecules, biologically active peptides, protein toxins, enzymes or even radionuclides, to better target specific tumors cells.

Lastly, experimental antibodies can be bispecific or biparatopic, meaning they can bind more than one target in the same cell or in two different cells. This increases the potency of the ADC by heightening the probability that they will bind to and internalise in the cancer cell, even if one of the molecules is not expressed at sufficient levels in a given cell.

There has been a resurgence of ADCs in the past couple of years. Can you tell us more about this and why it's happening? Why is there so much interest and investment in this class of drugs?

It's true that ADCs have undergone a bit of a renaissance. Traditional ADCs had a very narrow therapeutic window. This means that the dose that was effective was very close to the dose that was toxic. This was largely due to lack of specificity of the delivering antibody, lack of ADC internalisation into the cancer cell and ineffective linkers that resulted in the release of a variable number of toxic molecules in the tumor periphery, causing off-target toxicity.

The evolution toward next-generation ADCs has been made possible – in part – by the development of technologies that lead to stronger stabilisation of the ADC's linker and the antibody. These technologies rely primarily on specific methodology for conjugating the linker to specific amino acids in the antibody molecule. These methods generate linkers that release the payload at the target cell or tumor microenvironment under specific conditions (known as cleavable linkers) rather than – as with earlier generation ADCs – releasing linker-payload outside of the tumor and its microenvironment and creating off-target toxicities. Additionally, by enabling targeted release of the payload in the tumor microenvironment, cleavable linkers can create what's known as a bystander effect, delivering toxic payload to neighboring cancer cells even if they do not express the target tumor-associated agent. All but one of the U.S. Food and Drug Administration (FDA) approved ADCs have cleavable linkers.

Zai Lab's investigational compound ZL-1310 is an example of this next generation, because it was intentionally designed to improve upon the earlier ADC compounds. It has a specific linker generated by a technology termed TMALIN (Tumor Microenvironment Activable Linker). This technology binds the linker to three aminoacids in the antibody. It relies on both internalisation into the cancer cell and on the extracellular cleavage via enzymes in the tumor microenvironment. Due to the stability of the linker, ADCs are enriched in the tumour microenvironment, allowing for the incorporation of a high drug-to-antibody ratio (DAR) of payload molecules per ADC. This makes it possible to achieve a strong antitumor effect. ZL-1310 is stable in circulation and its peak concentration is significantly higher than that of the payload, thereby reducing systemic exposure to chemotherapy.

What tumour types seem to be particularly good targets for ADCs?

ADCs have already become a mainstay treatment option across a variety of both hematologic and solid cancers. Zai Lab's pipeline has compounds targeting a wide range of cancers, including many that have proven difficult to treat with standard-of-care therapies. Differential expression of the target in tumour versus normal tissue is critical to achieving selectivity and increasing the therapeutic index.

Can you provide an overview of the promising ADC candidates in development at Zai? What differentiates them from other ADCs and from each other?

Zai Lab is building a portfolio of potential first- and/or best-in-class ADCs to help patients around the world.

ZL-1310 is our investigational, potential first-in-class delta-like ligand 3 (DLL3) ADC. ZL-1310 utilises the TMALIN platform, which enables us to apply more targeted doses of chemotherapy to fight cancer activity. Another key point of differentiation for ZL-1310 is how it's administered

. T-cell engagers must be administered in a hospital setting because of immunological toxicities that are mostly due to interferon release upon T-cell activation. The design of ZL-1310 allows for more flexible administration given its high affinity and half-life. We have seen promising early data utilising ZL-1310 as, for example, a potential treatment for small cell lung cancer (SCLC). We feel this compound could present therapeutic benefits across other neuroendocrine tumours with overactive DLL3-expression such as gastrointestinal tract, prostate, bladder and thyroid cancers.

ZL-6201 is an innovative, potential first-in-class ADC we are developing that targets leucine-rich repeat-containing protein 15 (LRRC15), an appealing target for cancer therapy due to its overexpression in multiple solid tumour types such as sarcoma, glioblastoma and melanoma. ZL-6201 also has potential to target the tumour microenvironment given that the LRRC15 antigen is also expressed in the fibroblasts of the tumour microenvironment, potentially creating a bystander effect even if the antigen is not present in the cancer cells.

What indications is Zai Lab prioritising in its ADC programme and why?

In January 2025, our DLL3-targeted ADC ZL-1310 received an Orphan Drug Designation from the FDA, recognising its potential to treat patients with SCLC. We know SCLC patients urgently need innovative treatment options with improved efficacy, safety and ready access in tertiary care and community settings. As we continue our clinical development and ongoing studies of ZL-1310, we see potential for multiple lines of therapy with indications across a variety of neuroendocrine tumour types.

We are also working to advance ZL-6201 into Investigational New Drug-enabling studies as a potential treatment for patients with sarcoma and other LRRC15-positive solid tumours such as breast cancer and other malignancies where this antigen is enriched in the tumor stroma.

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