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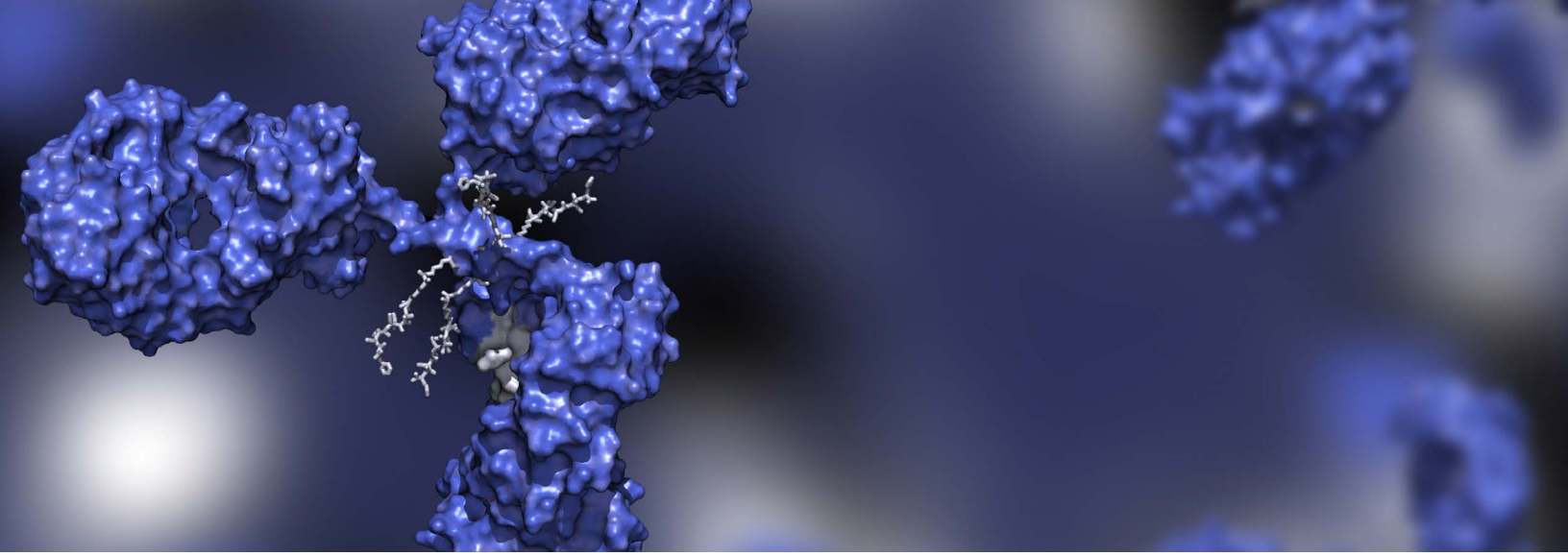

ADCs: Surmountable Challenges Ahead Of A Brighter Future

Andreas Dreps
Senior Vice President, Drug Development Services, ICON Biotech

There are several core challenges facing the development of ADCs, however the sector is rapidly evolving and adapting new ideas and techniques.

Antibody drug conjugates (ADCs), a group of agents created by covalently linking cytotoxic substances to monoclonal antibodies (mAbs) and capable of specifically targeting tumor tissues, offer great oncological potential.

However, developing them is exceptionally difficult. As of November 2023, there were 15 US Food and Drug Administration (FDA)-approved ADCs, but over 90 other candidates failed during clinical testing in recent years. More than 150 more are still in development.

Some examples of failed ADCs include Genentech's Vadastuximab talirine, AstraZeneca/MedImmun's MEDI4276, and AbbVie's Rovalpituzumab Tesirine, which failed due to fatal side effects, payload-associated toxicities, and lack of efficacy, respectively.

As a drug class, ADCs have been 'in development' for a long time. Andreas Dreps, Senior VP and Global Head of ICON's Drug Development Unit, notes that the original idea for ADCs was theorized by the pioneering chemist Paul Ehrlich in 1904, shortly after antibodies were first discovered by Emil von Behring and Kitasato Shibasaburo in 1890.

"ADCs are all about identifying an antigen expressed by a tumor, developing or discovering a suitable antibody, and binding this antibody to a cytotoxic," says Dreps. "Theoretically, it's a wonderful idea, but it comes with several challenges."

Systemic Barriers

The first major challenge facing those wishing to develop an effective ADC is tumor heterogeneity.

If you were to excise a tumor and take a cross-sectional view of it, multiple different tissues would be present. As well as being functionally different, these groups of cells would also be genetically or phenotypically different, and thus would have different antigen expressions.

In effect, any delivered ADC would therefore only be able to kill some of the tumor cells present, leaving the rest alive, a state from which they would multiply – allowing the cancer to 'escape' the drug.

Heterogeneity can increase over time, too, explains Dreps. "All of the sudden, the cells might mutate, meaning that your target antigen sites no longer exist."

Tumor cells also work to develop mechanisms of resistance. According to Dreps, the internalization of ADCs and subsequent cleavage, which releases the cytotoxic and requires certain conditions to occur, is an incredibly sensitive process, and one that tumor cells can adapt to mitigate.

"We've known for many years with simple chemotherapeutic agents that tumor cells have the ability to develop mechanisms of resistance," he says. "It could be that they express the same antigen as before, and that they internalize the drug properly, releasing the payload, but unfortunately [resistance has been developed.]"

Off-target effects are another major issue facing the development of ADCs. Dreps outlines several key components.

The first is simply due to healthy tissues expressing the same antigens as the target tumor. HER2 is a perfect example. While it is overexpressed in around 20% of breast cancers, offering a valuable avenue for targeted treatment – it is also expressed by tissues in the nervous system and epithelial cells. Therefore, when a HER2-targeting treatment is delivered, some healthy tissues are damaged.

Off-target effects also occur due to the relatively unstable nature of ADCs. Made of three highly-specific components – the antibody, the cytotoxic and the linker – ADCs are delicate structures.

"Once delivered to the blood stream, many factors come into play," says Dreps. "First, the immune system might recognize these antibodies as not originating from inside the body [a factor that can has previously led to near-fatal cytokine storms in patients]. Also, antigens constantly shed off the surface of tumors … you end up with parts of these antigens in the bloodstream and these are, of course, targets for the antibodies."

This second factor also makes combining radiotherapy with ADCs difficult: by destroying tumor cells with radiation, huge volumes of antigen enter the blood stream. Dreps says that, typically, ADCs would not be delivered for at least three weeks after radiotherapy.

The manufacture of ADCs is another barrier to clinical success. Rounding back on the unstable linker chemistry which joins the cytotoxic to the antibody, Dreps explains that any ADC formulation "must be stable during preparation, must be stable during storage, and must be stable when circulating in the bloodstream." Currently, many simply are not.

He also points out that, between batches, the ratio of antibody to cytotoxic can be highly variable, and that both viral and bacterial contaminants are relatively common, underpinning the need for highly refined manufacturing protocols.

Recent Advances and Future Potentials

In more recent years, there have been several major advances in how we both develop and think about ADCs.

Dreps believes the most major advance is in our understanding of linker chemistry which, he says, "was not really well understood a decade ago." This has allowed scientists to develop a new class of linkers that cleave only under specific conditions found in tumor microenvironments, reducing off-target effects. Advances in how we design and manufacture mAbs, with particular focus on their binding specificities, affinities, and pharmacokinetics, have been made too.

"In the '90s and up until 2001, the production costs of mAbs were very high. The ability to find a site to produce them was incredibly limited, too. Thankfully, this has changed, and we now have capabilities to produce them in small batches with small costs," says Dreps.

> "Despite the challenges facing those looking to develop ADCs, these advances mean the future of the drug class looks bright."

Improvements to production methods are also occurring. Traditional methods, which typically utilize bioreactors that must be cleaned between batches, come with a high risk of contamination. The sector is now moving away from these and towards using pre-sterilized, disposable, component-based toolsets, which not only reduce these risks but allow for faster, more flexible, production.

Despite the challenges facing those looking to develop ADCs, these advances mean the future of the drug class looks bright.

It is almost certain that a healthy number of the 150-plus still-in-development cohort of ADCs makes it to the clinic, and Dreps believes that, as their use becomes more widespread and the associated base of research grows, new treatment pathways may flourish.

“Right now, ADCs are a systemic treatment used in those suffering from metastatic cancer. Maybe, in the future, they could be used in the earlier stages – as a neoadjuvant therapy,” he explains.

“The cosmetic outcome, especially for breast cancer patients, could be improved,” says Dreps. “We could use ADCs as a neoadjuvant eight to ten weeks before surgery to shrink the tumor and get a better outcome.”

> “ADCs are a wonderful idea with a real future – it’s just about solving the problems along the way.”

Advances in adjuvant use are likely, too. By delivering ADCs alongside surgery – a process in which typically most, but not all, tumor cells are removed – “significant clinical benefit” can be derived.

“Particularly in tumors where we know the ‘preferred’ metastases are in the liver or kidneys, ADC use could be investigated in the future,” continues Dreps.

“ADCs are a wonderful idea with a real future – it’s just about solving the problems along the way.”

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