NBE-Therapeutics Ltd
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NBE therapeutics
Innovating medicines

Destroying cancer cells and providing antitumor immunity

NBE-Therapeutics is developing a novel class of immune-stimulatory antibody drug conjugates (iADCs) that not only target and destroy cancer cells, but also trigger long-lasting antitumor immunity.

NBE-Therapeutics' immune-stimulatory antibody drug conjugates (iADCs) have a novel mode of action that makes them uniquely well-equipped to fight cancer. iADCs target and destroy cancer cells, while at the same time eliciting long-lasting antitumor immunity that prevents relapse in preclinical models. The iADCs also synergize with immune checkpoint inhibitors to improve antitumor activity.

NBE-Therapeutics, a private biotech based in Basel, Switzerland, is creating iADCs using a suite of proprietary technologies. These technologies facilitate NBE-Therapeutics' mission to develop safer, more effective next-generation iADCs through the design of candidates with best-in-class properties. Preclinical pharmacological and toxicology models predict that these drugs will have exquisite therapeutic indices.

If the development candidates live up to the potential they have shown in preclinical models, NBE-Therapeutics will have a pipeline of prospects that address long-standing difficulties of ADC development.

Why ADC development has stalled

ADCs could hold the key to the targeted delivery of strong cytotoxic drugs to tumor cells. The idea is to link the cytotoxic drug to a tumor-antigen-specific antibody, thereby ensuring that the therapeutic payload is delivered to cancer cells, not to healthy tissues.

However, since Wyeth, now part of Pfizer, won approval for the first ADC in 2000, the field has suffered far more setbacks than successes. To date, the US Food and Drug Administration has only approved four anticancer ADCs since Wyeth's Mylotarg came to market almost 20 years ago.

The travails of the ADC sector can be partly explained by difficulties relating to the quality of the target and the properties of the targeting antibody. However, this explanation misses a critical point. The success of ADCs also requires stability of the linker that connects the toxin to the antibody and dictates the pharmacokinetic (PK) properties.

Classical ADCs generated by chemical conjugation suffer from a variety of liabilities, including product heterogeneity, weak linkers and variable PK properties. These shortcomings translate into drugs with narrow therapeutic windows. Unstable linkers also prohibit the use of very potent toxins because they result in ADCs that are liable to release the payload before engaging with tumor cells, resulting in significant side effects.

These shortcomings have made it hard to develop safe and effective ADCs.

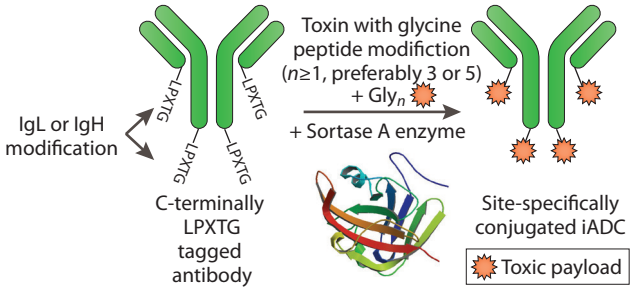

Fig. 1 | NBE's SMAC technology for site-specific conjugation. This is a highly efficient conjugation technology, which routinely achieves more than 97% conjugation efficiencies. It is also highly selective and causes no stress on the antibody and even works on semi-purified mAbs.

How NBE-Therapeutics is improving ADCs

NBE-Therapeutics has solutions to the key challenges in ADC development. First, NBE-Therapeutics leverages its own discovery and optimization platform to develop novel antibodies against any relevant tumor target. The Transpo-mAb Display platform is based on mammalian cell display of full-length immunoglobulin G libraries expressed by stable DNA transposition.

As the antibodies are expressed in B lymphocytes, the platform selects for well-expressed and well-behaved candidates with favorable developability and PK profiles. These antibodies are an important part of iADCs with favourable PK properties.

Second, NBE-Therapeutics has developed a proprietary enzyme-based conjugation platform, called SMAC-technology. The platform uses a unique class of sortase transpeptidase enzymes that catalyze the formation of stable peptide bonds at specific pentapeptide substrates incorporated into the antibody sequence. SMAC-technology conjugation is highly selective, site-specific and efficient and occurs under physiological conditions with minimal stress on the antibody molecule during conjugation (**Fig. 1**).

Third, NBE-Therapeutics is leveraging its site-specific SMAC-technology to generate homogenous iADCs with ultrapotent proprietary anthracycline-based toxins conjugated to antibodies via stable peptide bonds.

The combination of these technologies results in iADCs with excellent pharmacological and PK properties, long serum half-lives and high serum stability. These characteristics translate into a predicted favorable therapeutic index.

The therapeutic potential of iADCs

NBE-Therapeutics has demonstrated in preclinical models that iADCs eradicate tumor cells through effective targeting and elicit strong, long-lasting antitumor immunity. This immunity even prevents tumor regrowth if the iADC-cured animals are rechallenged with the same tumor type.

If this performance translates into humans, iADCs will transform cancer care by both wiping out tumors and by activating the immune system against residual tumor cells.

The immune-stimulatory function of iADCs also suggests the drugs will combine effectively with checkpoint inhibitors. Suboptimal dosing of both iADCs and checkpoint inhibitors has shown strong synergistic antitumor responses beyond those achievable by either drug individually.

NBE-Therapeutics has recently selected its first iADC development program targeting the tumor-associated antigen receptor tyrosine kinase-like orphan receptor 1 (ROR1). The planned clinical development program will initially target triple-negative breast cancer and lung adenocarcinoma, indications in which a significant fraction of patients express ROR1.

Anti-ROR1 iADC NBE-002, the first and presumably best-in-class ROR1-targeted ADC therapy, will serve as a proving ground for NBE-Therapeutics' technologies. NBE-002 could mark the beginning of the end for ADC development difficulties, leading to better drugs for patients with a range of cancers.

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