

An antibody–drug conjugate (ADC) comprises an antibody covalently attached to highly potent drugs using a bioconjugation technology. As therapeutics, they combine the exquisite specificity of antibodies, enabling discrimination between healthy and diseased tissue, with the cell-killing ability of cytotoxic drugs.

The concept of targeted toxic payload delivery to cancer cells dates all the way back to 1913 when Paul Ehrlich described a 'haptophore' that can deliver a 'toxophore' selectively to a tumour. It took several decades before such a species was created in the form of an ADC with, in the 1970s, ADCs being tested on animals. Following this, a decade or so later, tests on humans showed encouraging results. In the 1990s, the first ADCs based on humanized and chimaeric monoclonal antibodies (mAbs) were reported with greater payload potency and superior target selection achieved throughout the decade. These advances, amongst others, led to ADC gemtuzumab ozogamicin (trade name, Mylotarg) being approved by the US Food and Drug Administration (FDA) in 2001. However, despite encouraging preliminary results, Mylotarg was voluntarily withdrawn from the market in 2010 as post-approval clinical trials for patients with acute myeloid leukaemia (AML) showed the ADC to offer no clinical benefit over classical chemotherapy. Notwithstanding this disappointment in the field, ADCs showed considerable promise in following years with two further ADCs gaining FDA approval — brentuximab vedotin (trade name, Adcetris) in 2011 and trastuzumab emtansine (trade name, Kadcyla) in 2013. Most recently, in 2017, Mylotarg was re-introduced into the US market for treatment of CD33-positive AML, and inotuzumab ozogamicin (trade name, Besponsa) was approved for treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Thus there are four ADCs currently on the market, and with an estimated ca. 80 ADCs currently in the clinic, it is predicted that the market for ADCs will grow rapidly in coming years.

However, and perhaps most importantly, many lessons have been learned from both ADC success and failure stories. For example, ADCs that exist as heterogeneous mixtures often have a relatively narrow therapeutic window compared to homogeneous (or near homogeneous) ADCs and these mixtures can also lead to major negative pharmacokinetic implications. There have also been issues related to the potency of the toxin being either too potent or not potent enough, and the specific site of modification on an antibody has been shown to be critical to down-stream in vivo consequences, amongst many other findings. An explosion of interest and research has also been observed in the use of bispecific antibodies, antibody fragment platforms, new drug types and antibody–nanoparticle conjugates as alternatives to classical ADCs. It is thus an exciting time to be working in the field and it is clear that in order for ADCs to deliver their full potential, advancements in various areas of research are needed.

This Special Issue highlights: (i) leading strategies currently used for the site-specific construction of ADCs (i.e. disulfide and enzymatic-based modification strategies) and how to avoid the retro-Michael instability of classical maleimide bioconjugates; (ii) non-classical approaches to antibody lysine modification; (iii) alternatives to classical ADCs in the format of antibody fragments, antibody–nanoparticle conjugates and bispecifics; (iv) new toxins in the form of amanitins and the latest developments in the field of

pyrrolobenzodiazepines (PBDs) as well as related covalent-binding DNA-interactive molecules; and (v) how technologies developed for ADCs can be used for site-specific chelator–antibody conjugation for imaging with radiometals. It then concludes with an overview on drawing lessons from the clinical development of antibody–drug conjugates.