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TITLE: The development of novel therapies involving DNA as a target

ABSTRACT: Drugs that produce DNA interstrand cross-links e.g. the nitrogen mustards and platinum drugs remain important and widely used cancer chemotherapeutic agents. They are, however, not targeted agents, DNA interstrand cross-links account for only a small proportion of the DNA damage produced, and DNA repair plays an important role in determining inherent sensitivity and acquired resistance. In an attempt to produce more selective agents, we have utilised the tricyclic natural product pyrrolobenzodiazepine (PBD) structure. PBD monomers exert their biological activity by binding and covalently bonding in the minor groove of DNA. An important development in the history of the PBDs was the synthesis of non-natural PBD dimers that have the ability to efficiently and selectively form highly cytotoxic DNA interstrand cross-links. Rational structural modification can produce PBD dimers with exquisite potency making them ideal candidates for the 'warhead' component of antibody drug conjugates. Two different sites on PBD dimers have been utilised to attach linkers; N10 and C2, and antibody-PBD conjugates (APCs) of both types have shown impressive *in vitro* and *in vivo* activity against both haematological malignancies and solid tumours. Twelve APCs have now progressed into the clinic including vadastuximab talirine and rovalpituzumab tesirine.
ADCs delivering PBD dimer payloads represent a novel mode of action in the antibody-drug conjugate area. An important feature of the highly cytotoxic DNA interstrand cross-links produced by the PBD dimers is their persistence in cells. This contributes to their potency and also to their ability to affect slowly proliferating target cells, including cancer stem cells. The PBD dimers are a highly flexible platform with many advantages over existing payloads. These include the ability to target low copy number antigens and to exploit low drug antibody ratios due to the high warhead potency. APCs are active in tumour types inherently resistant to other warhead classes and against multidrug resistant tumours.