Novel DNA Analogues of duocarmycins as new toxins for antibody-drug conjugates (ADCs)

Newly synthesised analoguitys s t (3)5 an (3)t (6)4 (1 4(5)u5 o(3 u5

Background

Antibody-drug conjugates (ADCs) are a therapeutic strategy utilising the selectivity of an antibody to deliver an active small molecule to antigen-presenting cells.

The majority of ADCs employ toxic payloads that interfere with microtubules. DNA minor groove alkylating agents are a suitable alternative, offering extreme cytotoxic potency while being insensitive to many cellular resistance mechanisms.

Duocarmycins are a small group of antitumour and antibiotic natural products with extreme cytotoxicity. Currently, some analogues of these compounds have been synthesised to arm antitumour antibodies but are highly lipophilic.

Technology

Lipophilic payloads cause aggregation and lead to a reduction of the achievable drug-antibody ratio, as well as faster clearance of the resulting ADC. This reduces overall exposure, limiting the therapeutic response.

Three different and novel variations of the alkylating subunit have been prepared and incorporated into duocarmycin analogues with demonstrated decreases in lipophilicity and bs(o)TJEMC ang (en-US)MD 2sikyl1co 2sikyl1co 2sikyl1co 2sikyier

Limiting the aggregation minimises the threats of in vivo immune response, unexpected toxicity and decreased therapeutic effect.

Applications

ADCs are a rapidly emerging class of cancer treatment. Therefore, with modified potency, efficacy, and stability, duocarmycins could be integrated into existing or future modes of therapy for enhanced ameliorative outcomes.

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