

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

Newly synthesised analogues of duocarmycin utilised as an optimised toxic payload in ADCs for cancer treatment.

## 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 favourable properties of the derived ADCs.

## Major advantages

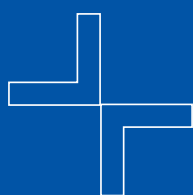
- Cytotoxic at all phases of the cell cycle and insensitive to drug resistance mechanisms.
- Decreased lipophilicity minimises issues with protein conjugation and faster clearance.
- Limiting the aggregation minimises the threats of in vivo immune response, unexpected toxicity and decreased therapeutic 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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## UniServices by the numbers

Total external research funding:

**\$261.3M**

(35% increase over 2020)

**45**

companies started in the past five years

**\$1.25BN**

Total market capitalisation of companies formed

**\$73.5M**

Net asset value of the University of Auckland Inventors' Fund

**17,335** Covid-19 vaccinators trained by the Immunisation Advisory Centre in 2021

**1,700**

New Zealand teachers reskilled and upskilled through Tui Tuia | Learning Circle professional learning and development in 2021

**3,000**

clinical staff at 22 DHBs trained through teamwork-based acute care simulations designed by NetworkZ in the past five years

**14,391** times that child and youth mental health workers attended Whāraurau e-modules, trainings and workshops in 2021

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### Contact



**Aran Sisley**  
Commercialisation Manager  
+64 21 2626 707  
[a.sisley@auckland.ac.nz](mailto:a.sisley@auckland.ac.nz)



**Kent Lee**  
Senior Commercialisation Manager  
+64 22 687 9007  
[kent.lee@auckland.ac.nz](mailto:kent.lee@auckland.ac.nz)

### UniServices

Level 10, 49 Symonds Street,  
Private Bag 92019,  
Victoria Street West,  
Auckland 1142, New Zealand  
+64 9 373 7522 [uniservices.co.nz](http://uniservices.co.nz)

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