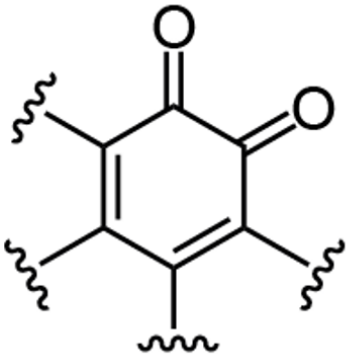
CAMBRIDGE | Enterprise

Ortho-quinone prodrug strategy (self-immolative linkers)

Background



The para-quinones doxorubicin (Adriamycin), geldanamycin, mitoxantrone and mitomycin C have lower redox-cycling rates than ortho-quinones and are successfully used in the clinic. Despite ortho-quinones displaying wide anti-proliferative effects, they display dose-limiting toxicity (leading to anaemia and methaemoglobinemia) which has hampered their development and use.

Current 'prodrug' approaches do not overcome the dose-limiting toxicity as they are too labile under physiological conditions (esters and hydrazones) or not sufficiently labile in tumours (ketals).

Technology overview

A novel chemistry for controlled masking and targeted release of ortho-quinones (e.g. β-lapachone, 1, 3-hydroxy-β-lapachone, dunnione and cryptotanshinone) that illustrates improvements over other pro-drug approaches.

Key features

- Novel chemistry with pH-dependent elimination enables release of hydroxyquinone
- A highly modular technology that can be adapted for numerous trigger

Reference number: Ber-7195-19

functionalities & targeting approaches

- Prodrugs of β-lapachone show:
    - ono redox cycling of the masked drug
    - ono methaemoglobin formation
    - lower ohaemolysis of haemoglobin (related to anaemic side effects)

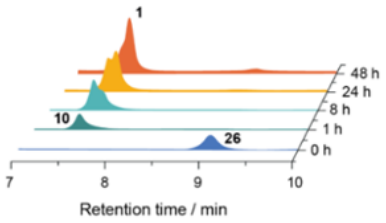
Potential applications

- Generation of novel prodrugs of ortho-quinones for therapeutic use or diagnosis
- Generation of novel antibody prodrug conjugates (APDCs) for therapeutic use or diagnosis

Opportunity

We are seeking a commercial partner for collaboration and/or licensing of this technology, which is protected by patent application.

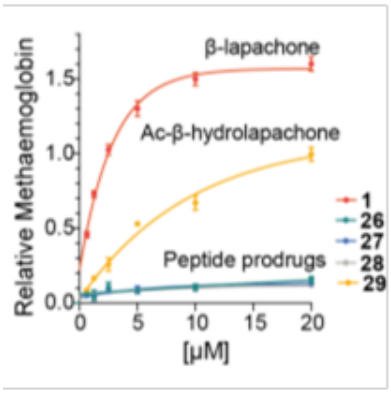
Release of β-lapachone from peptide prodrug



- Release of β-lapachone 1 from peptide prodrug 26 at 254 nm after in vitro dipeptide cleavage by protease cathepsin B (MES 20 mM buffer, pH 5)
- Peaks for the intermediate 10 and β-lapachone 1 overlap

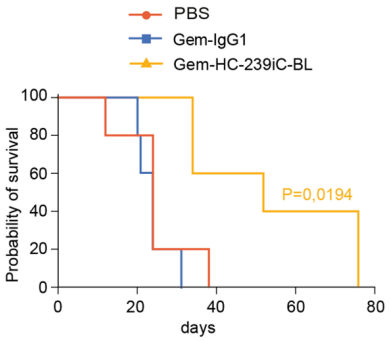
Concentration-dependent methaemoglobin generation

- Concentration-dependent methaemoglobin generation by dipeptide prodrugs after 4 h incubation in ovine blood
- Methaemoglobin was measured by absorbance at 630 nm following treatment with compounds relative to DMSO control
- Data shows mean ± SEM from one representative experiment (n=3)



Gem-HC-239iC-BL has an effect on subcutaneous AML tumour growth and prolongs survival of mice

- NOD-SCID immunocompromised mice were inoculated with HEL cells to induce tumour growth and were treated intravenously with either ADC Gem-HC-239iC-BL, the native antibody Gem-IgG1 or PBS (2 doses administered at 7.5mg/Kg)
- Overall survival over time (n= 5)
- Log rank test indicates a statistically significant difference between DAR-2 ADC Gem-HC-239iC-BL treatment versus PBS and versus native antibody Gem-IgG1 treatment (P= 0.0194)



Self-immolative linkers for protection and controlled release of ortho-quinones

- New C–C bond-cleaving elimination that is pH dependent
- Elimination releases hydroxyquinone
- Highly modular and adaptable for numerous trigger functionalities & targeting approaches

Inventors

Professor Gonçalo Bernardes (right) and colleagues

Professor Gonçalo Bernardes is Professor of Chemical Biology at the Yusuf Hamied Department of Chemistry, University of Cambridge; a Royal Society University Research Fellow and a Fellow of Trinity Hall College, Cambridge.

Publication

Controlled masking and targeted release of redox-cycling ortho-quinones via a C–C bond-cleaving 1,6-elimination, Nat Chem. 2022; 14(7): 754–765

Want to know more?

To learn more, please make an enquiry.