Exploring Novel Peptide-Based Natural Products as a Payload for the Generation of Antibody and Peptide-Assisted Targeted Cancer Therapy

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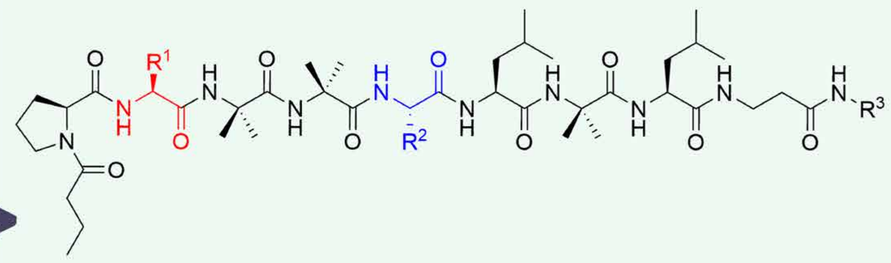
Background

- Targeted cancer therapy is a growing field in research due to its improvements to reducing adverse effects by widening the therapeutic index of cytotoxic payloads
- Antibody-drug conjugates (ADCs) are a leading field in targeted cancer therapy with 12 FDA-approved ADCs
- However, among these 12, there are 7 different types of payloads used representing 3 unique mechanisms of action (microtubule inhibitors, topoisomerase I inhibitors, or DNA-damage)
- This ultimately leads to an issue of **drug resistance**

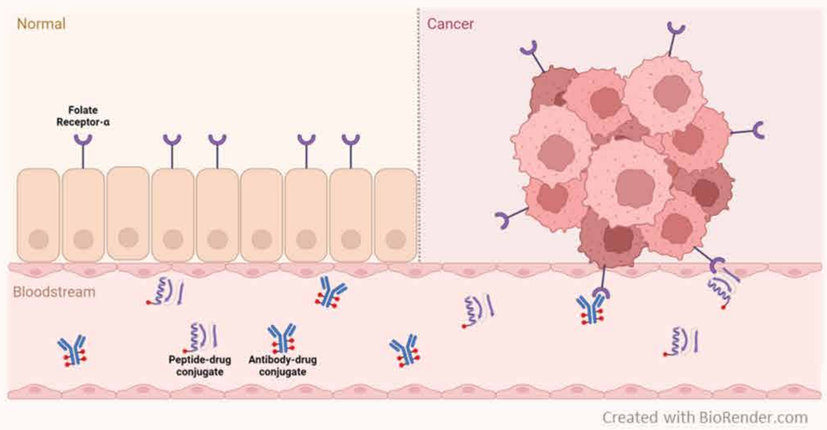
MoA: Inhibition of oxidative phosphorylation

Aminolipopeptides: An Attractive Anticancer Drug

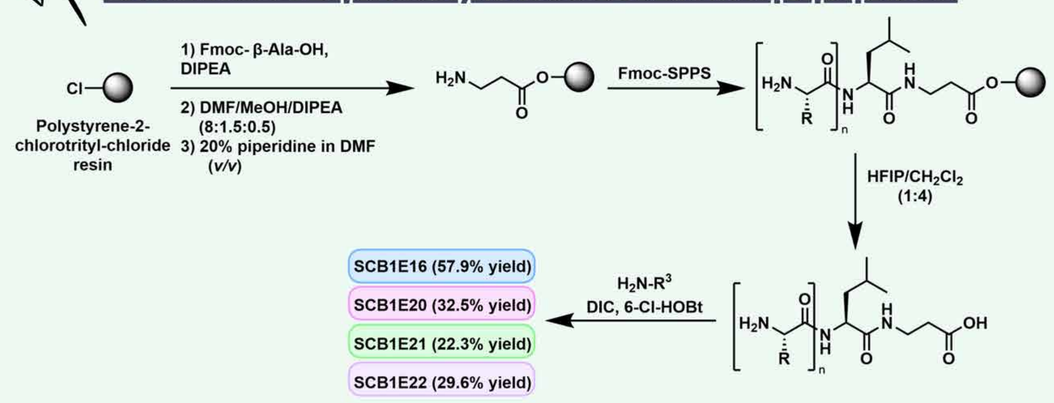


Folate Receptor-α (FRα): The Ideal Target

- Glycosyl-phosphatidylinositol (GPI) anchored cell-surface protein
- Normal tissues:
  - Minimal role post-embryogenesis
  - Low expression
  - Restricted to apical surface
- Cancer cells:
  - Exposed to blood circulation
  - Overexpressed in many cancer types including endometrial carcinoma, **ovarian**, and lung cancer



Solid Phase Peptide Synthesis of Aminolipopeptides



Biological Evaluation of Aminolipopeptide Analogues in Ovarian Cancer Cell Lines

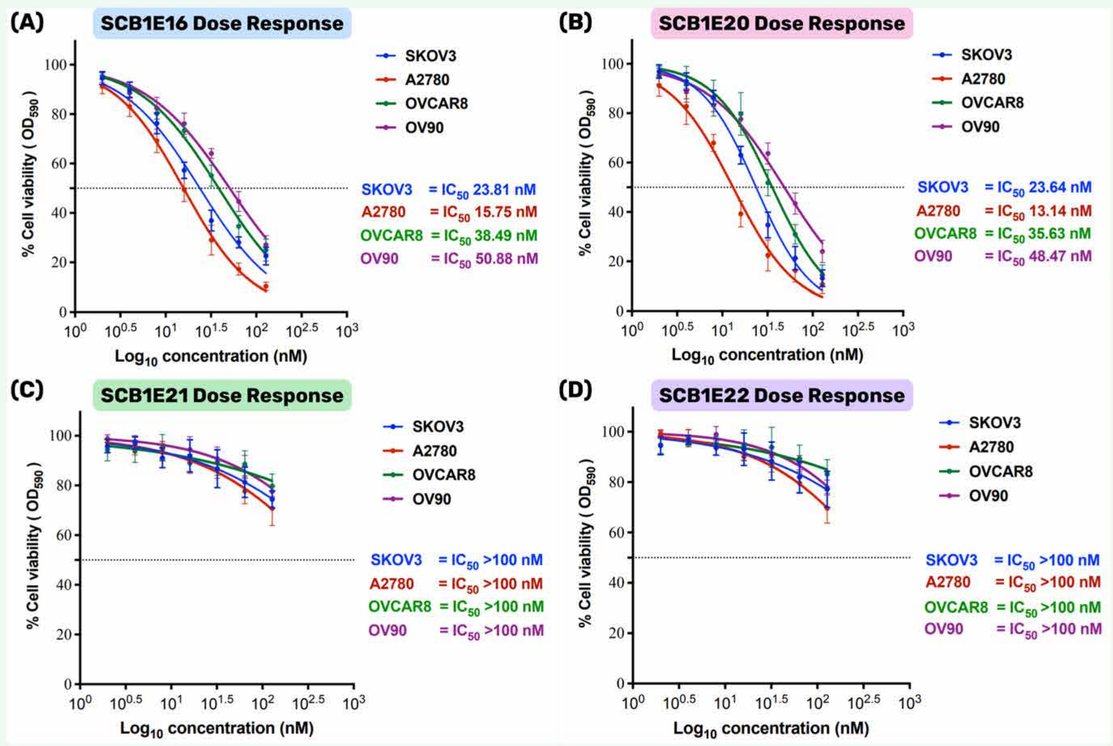


Figure 1. Cell viability (%) as evaluated by Crystal Violet assay after 48 h incubation of SKOV3 (FRα +ve, EGFR -ve), A2780 (FRα -ve), OVCAR8 (FRα +ve, EGFR -ve), and OV90 (EGFR -ve) cells with Compounds (A) SCB1E16, (B) SCB1E20, (C) SCB1E21, and (D) SCB1E22

FRα-Binding Peptides

Molecular Modelling

- Molecular models and predicted free binding energy of analogues of the C7 peptide and the binding site of FRα gave insight as to which peptides would have the best selectivity for FRα

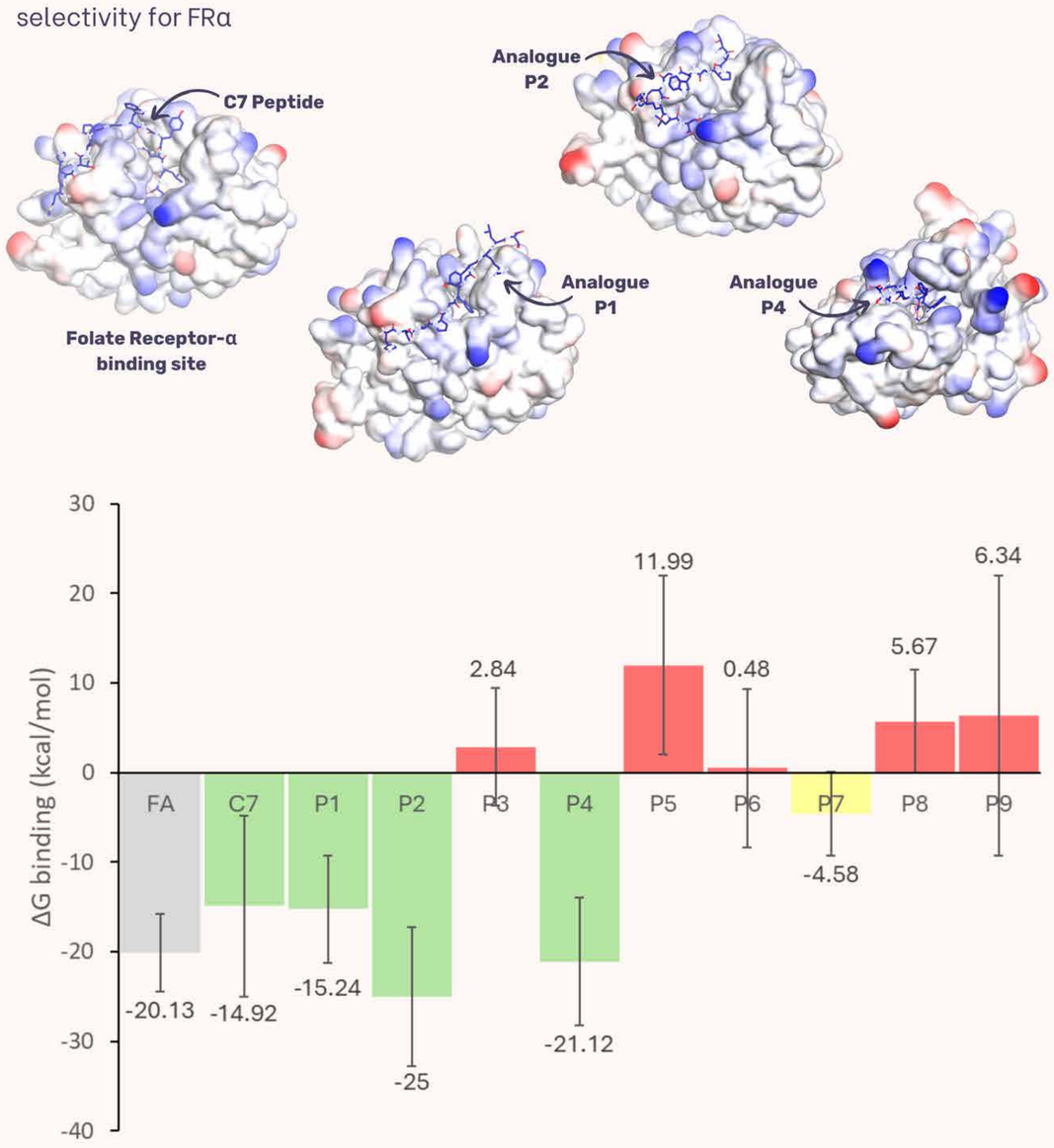
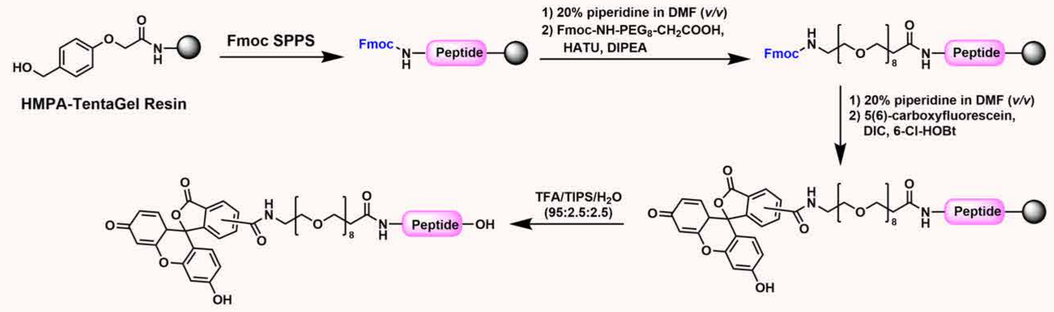


Figure 2. Predicted free binding energy of the modelled FRα-binding peptide C7, its analogues P1-9, and the native ligand folic acid (FA)

Synthesis of FRα-binding Peptides for Internalisation Studies

- 5(6)-carboxyfluorescein (5(6)-FAM) for visualisation inside cells
- PEG_8 spacer to prevent interference of 5(6)-FAM with peptide binding



Future Work

- Conjugate SCB1E20 to the most selective FRα binding peptide to form a peptide-drug conjugate (PDC)
- Conjugate SCB1E20 to an anti-FRα antibody to give an antibody-drug conjugate (ADC)
- Biologically evaluate the PDC and ADC for selective toxicity of ovarian cancer cells expressing FRα

SCAN ME

Key References:

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