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Elucidating BBIT20's disruption of the BRCA1/BARD1 interaction: A new therapeutic avenue in pancreatic cancer

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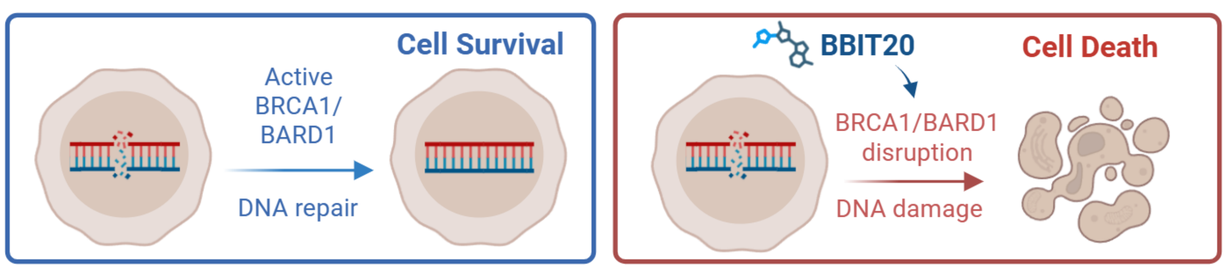
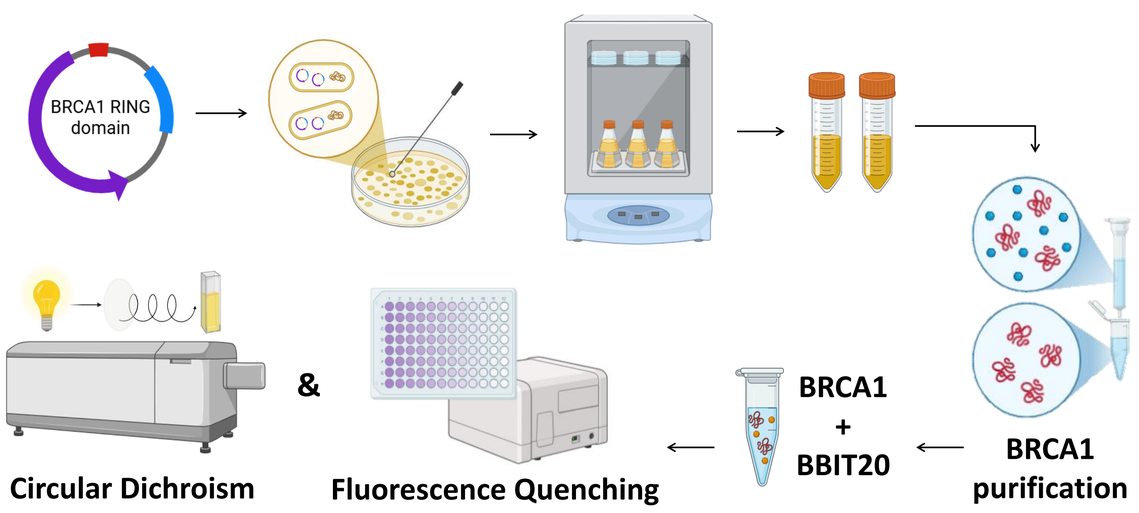
INTRODUCTION & AIM

Pancreatic cancer (PC) remains highly resistant to treatment. Homologous recombination deficient (HRD) tumours are more sensitive to therapies; however, HRD tumours are a minority of PC cases. BBIT20 is an innovative molecule that disrupts HR by inhibiting the BRCA1/BARD1 interaction. *In vitro* and *in vivo* data revealed its potent antitumor activity both as monotherapy and combined with chemotherapy, in PC. *In silico* analyses indicate that the BRCA1 RING domain is the preferential target of BBIT20. This work aims to experimentally define the binding site of BBIT20.



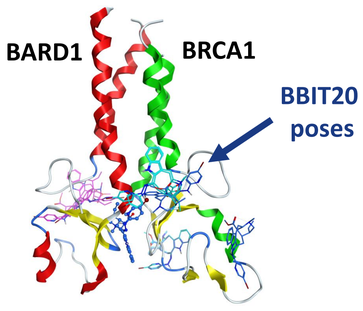
METHOD

Recombinant BRCA1 RING domain was produced and purified from *Escherichia coli* BL21 (DE3). The interaction between BBIT20 and BRCA1 was assessed by fluorescent quenching and far-UV circular dichroism.



RESULTS & DISCUSSION

- **Docking analyses** identified the BRCA1 RING domain as the preferential interaction site for BBIT20 within the BRCA1/BARD1 heterodimer.



- **Circular dichroism** revealed dose-dependent alterations in the secondary structure of BRCA1, consistent with a direct interaction with BBIT20.

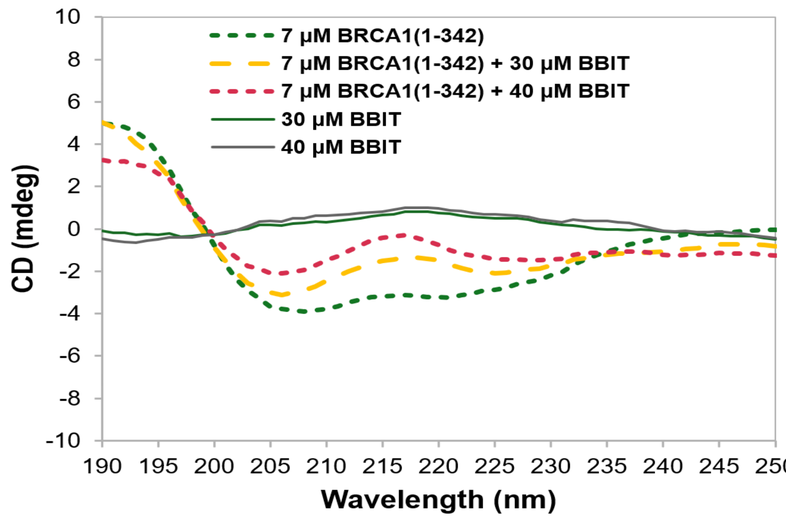


Fig. 1 Far-UV Circular Dichroism (CD) spectra of recombinant BRCA1(1–342) in the absence and presence of BBIT20. To obtain the spectra, 7 µM BRCA1(1–342) in 20 mM potassium phosphate buffer (PB) containing 10 µM Zn, pH 8.0, was incubated with a 1:8 (v/v) mixture of 20 mM PB and 100% ethanol containing BBIT20 at 0, 30, or 40 µM.

- **Fluorescence quenching** confirmed BBIT20 proximity to BRCA1 RING domain. BBIT20 induced a dose-dependent quenching effect in the BRCA1 RING domain (K_{sv} = 8,64*10^4 M^{-1}).

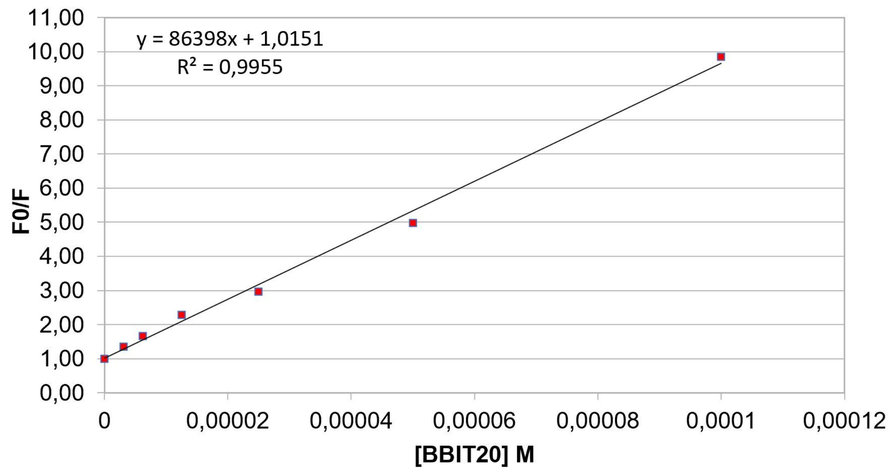


Fig. 2 Fluorescence quenching of recombinant BRCA1(1–342) upon the addition of BBIT20. The Sern-Volmer constant (Ksv) was determined using the Stern-Volmer equation. Fluorescence intensity was measured in 96-well microplates at λex = 290 nm, λem = 340 nm, at 25 ºC. For each well, 180 µL of 5 µM BRCA1(1–342) in 20 mM potassium phosphate buffer (PB) containing 10 µM Zn, pH 8.0, was incubated with 20 µL of a 1:8 (v/v) mixture of 20 mM PB and 100% ethanol containing BBIT20 at a final concentrations of 0, 3.125, 6.25, 12.5, 25, 50, and 100 µM.

CONCLUSIONS

This study indicated that BBIT20 directly interacts with BRCA1 RING domain, inducing structural alterations that hinder formation of the BRCA1/BARD1 heterodimer and ultimately disrupt the HR pathway. Nuclear magnetic resonance (NMR) assays are underway to gain deeper insight into the molecular dynamics of this interaction, which will support the rational design of improved BBIT20 derivatives.

FUTURE WORK/ REFERENCES/ACKNOWLEDGMENT

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