Targeting solid tumor acidic microenvironment with an alphalex™ PARP inhibitor

#2981

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INTRODUCTION

Poly (ADP-ribose) polymerase inhibitors (PARPi) have shown great promise in the treatment of cancer, however, their current clinical use has been largely limited to monotherapy against homologous recombination-deficient (HRD) tumors. While these drugs are efficacious as monotherapies, durable responses beyond 12 months are uncommon and their activity against HRD-negative tumors is limited. These findings have prompted great interest in combining PARPi's with chemotherapy to increase the duration of response in HRD-positive tumors and expand the activity of these drugs against HRD-negative tumors which comprise >60% of the total number of cancer cases each year. While such combinations are highly active against tumors independent of HRD status, they are also extremely cytotoxic against bone marrow cells. As such, dose reductions ranging from 4- to 40-fold are required when PARPi's are combined with chemotherapy which has resulted in favorable safety profiles but limited efficacy. Tumor-targeting strategies could overcome this efficacy barrier, but the technologies developed thus far are limited by numerous issues, including: (a) lack of universal, non-saturating tumor-targeting mechanisms which limit their use to specific tumor types and their corresponding antigens, (b) inability to deliver therapeutically relevant levels of drug(s) *directly* into tumor cells, and (c) insufficient tumor penetration leading to sub-optimal tumor exposure.

ABSTRACT

Tumor targeting of rucaparib, an FDA-approved PARPi, was achieved using the alphalex™ platform which allows small molecule anti-cancer agents to penetrate cell membranes only at the low pH associated with the tumor microenvironment. *In vitro,* we demonstrated that the alphalex™ conjugate translocates across cancer cell membranes to deliver its cargo directly into the cell. The safety and efficacy of the approach was confirmed *in vivo* using CBX-11 (alphalex™-rucaparib) which was safely administered with cytotoxic chemotherapies to selectively kill both HRD-positive and –negative tumors with significant sparing of the bone marrow. These data highlight an entirely new approach to apply PARPi's against solid tumors independent of HRD status. Furthermore, our approach can be applied to a diverse range of DNA repair inhibitors for potent and selective chemo/radio-sensitization in a tissue-agnostic manner.

RESULTS

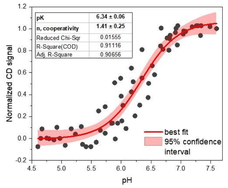
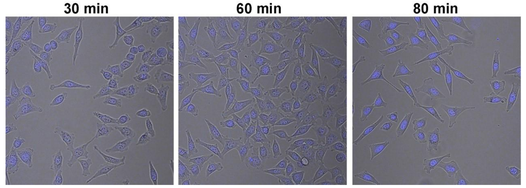
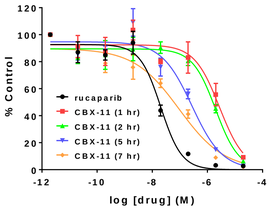


Figure 1. Cybrexa has created several tumor targeting drugs with the alphalex™ platform, including CBX-11. pH sensitivity is shown by circular dichroism (CD) using unilamellar and multilamellar POPC vesicles.

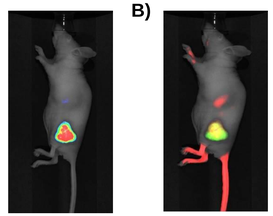
Figure 2. A) Following insertion of CBX-11 into HeLa cells, its rucaparib warhead is translocated into the nucleus within 80 minutes as determined by confocal microscopy.





B) Following administration of rucaparib or CBX-11, the presence of rucaparib in the nucleus is associated with inhibition of PARP enzyme activity in HeLa cells in a time dependent manner. Data are expressed as means ± SEM.

Figure 3. *In vivo*, Licor IR-Dye 800CW-labeled CBX-11 is localized to DLD-1 BRCA2$^{-/-}$ xenograft tumors in mice 8 hours after intraperitoneal administration (A). The signal is also co-localized with a HypoxiSense 680 label (B).



RESULTS

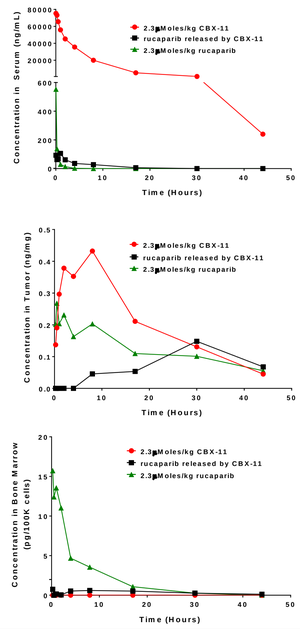


Figure 4. CBX-11 and rucaparib were administrated to mice at equimolar concentrations of 2.3µMoles/kg.

A) Stability of CBX-11 in serum - Following CBX-11 administration, less than 3% of the warhead, rucaparib, is released in serum.

B) CBX-11 insertion and release of rucaparib in tumor occurred in a time dependent fashion.

C) Following CBX-11 dosing, there was limited exposure in bone marrow, whereas much higher concentrations of rucaparib were observed in bone marrow when rucaparib itself was administered.

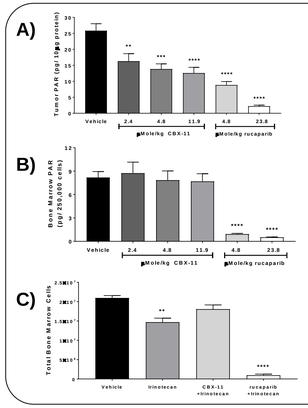
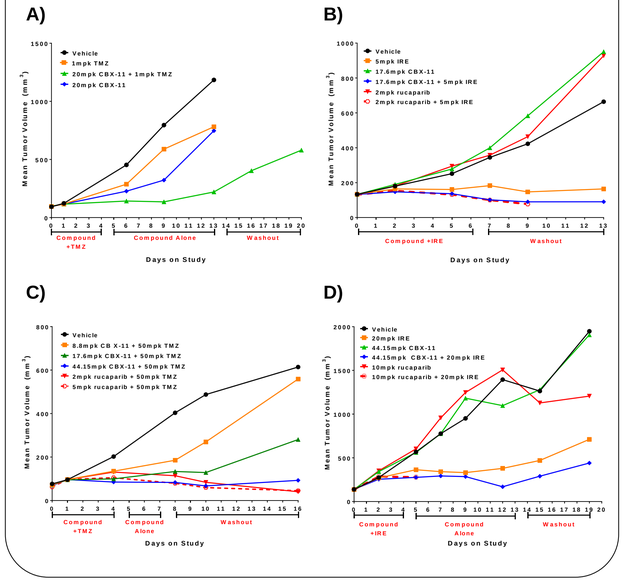


Figure 5. The concentration of CBX-11 compared to rucaparib in the tumor and bone marrow was associated with an inhibition of PARylation in tumor (A) with CBX-11 showing minor effects on PARylation in bone marrow (B). These data are also consistent with the bone marrow cell counts being reduced by treatment with rucaparib and not CBX-11 at efficacious doses (C). Data are expressed as means ± SEM. **p<0.01, ***p<0.001 and ****p<0.0001 significance relative to vehicle.

RESULTS

Figure 6. CBX-11 (alphalex™-rucaparib) shows efficacy against tumor growth in murine A, B) SW620, C) DLD-1 BRCA2$^{-/-}$, and D) DLD-1 wild type xenograft tumor models. Administration of CBX-11 in the presence and absence of other chemotherapeutic agents such as temozolomide (TMZ) or irinotecan (IRE) avoided the toxic effects normally associated with co-administration with PARPi's.



CONCLUSION

These data demonstrate that the alphalex™ platform can selectively deliver PARPi's to tumor tissue and avoid bone marrow toxicity. The tumor selective exposure of CBX-11 (alphalex™-rucaparib) allows full dose co-administration with various chemotherapeutic agents thereby enabling synergistic efficacy in patients without HRD defects.