Development of tumor-targeted PARP inhibitors for the treatment of solid cancers

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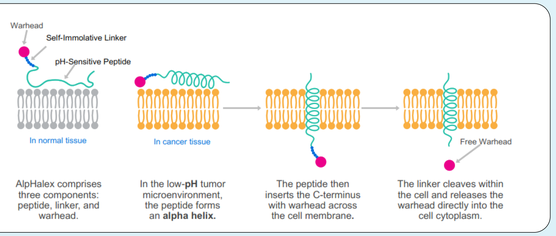
ABSTRACT

Monotherapy poly (ADP-ribose) polymerase inhibitors (PARPi's) have demonstrated efficacy against metastatic solid tumors, with the greatest activity observed in homologous recombination-defective (HRD) cancers. However, resistance occurs rapidly, and there is limited activity against non-HRD cancers. Pre-clinical studies indicate the potential for exquisite synergy between PARPi's and chemotherapy. However, bone marrow suppression is a major barrier to treatment efficacy with these combinations. As such, there is a great unmet need to enable safer and more effective means to combine PARPi's with chemotherapy.

METHODS

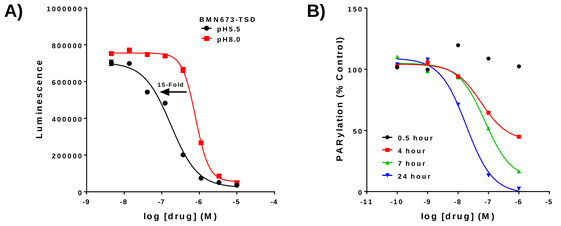
We sought to develop a new class of tumor-targeted PARPi's (TSDs) which will address the issues of off-target toxicity and increase treatment efficacy against both HRD and non-HRD cancers when used in combination with chemotherapy. Tumor targeting was achieved by attaching BMN673, a best-in-class PARP-trapping PARPi [1, 2], to a novel peptide which is triggered by low pH to insert its C-terminus across the cell membrane into the cytosol where it is released upon intracellular linker cleavage. BMN673 was chosen because it had attachment points that were considered compatible for immediate conjugation to the low pH dependent peptide. BMN673 attached to this peptide (BMN673-TSD) was tested for its targeting and delivery into cancer cells based on the acidity of the tumor microenvironment.



RESULTS

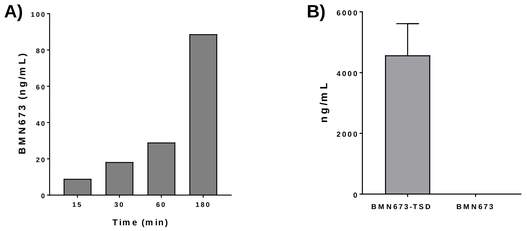
Using our novel TSD platform, we have successfully conjugated BMN673 to a low pH dependent peptide and demonstrated the following: (1) pH-dependent delivery of functional BMN673 into tumor cells *in vitro*; (2) sustained and selective *in vivo* tumor localization of BMN673; (3) target engagement by BMN673 specifically in tumor tissue; (4) prevention of bone marrow toxicity when combined with chemotherapy, again compared with unconjugated drug; and (5) selective tumor cell killing in both non-HRD and HRD xenografts, including patient-derived xenografts (PDXs).

Figure 1. pH and Time Dependence.



A) Cellular PARylation inhibition by BMN673-TSD was determined in DLD-1 wildtype cells incubated at pH 5.5 and pH 8; B) Time dependent PARylation inhibition in DLD-1 BRCA2$^{-/-}$ cells was determined by a chemiluminescent ELISA following incubation with BMN673-TSD at time points indicated.

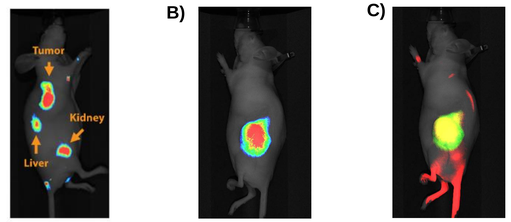
Figure 2. Cellular Uptake and Plasma Stability.



A) Detection of BMN673 in DLD-1 BRCA2$^{-/-}$ cells treated with BMN673-TSD; B) Detection of only BMN673-TSD not BMN673 in systemic circulation in mice.

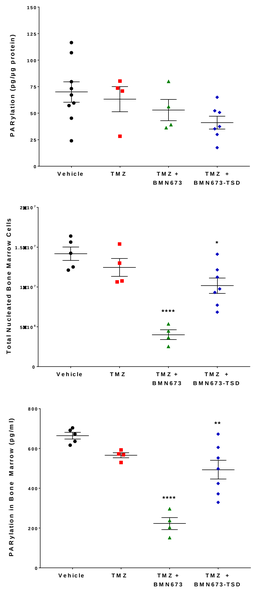
RESULTS

Figure 3. Tumor Localization.



DLD-1 BRCA2$^{-/-}$ xenografts were grown in the flank or shoulder of mice which were administered intravenous (A) or intraperitoneal (B,C) doses of 1mg/kg Licor IR Dye 800CW-labeled BMN673-TSD. C) HypoxiSense™ 680 fluorescent imaging agent (2nmol) was used to detect hypoxic regions of the tumors.

Figure 4. Target Engagement in Xenografts and Bone Marrow.



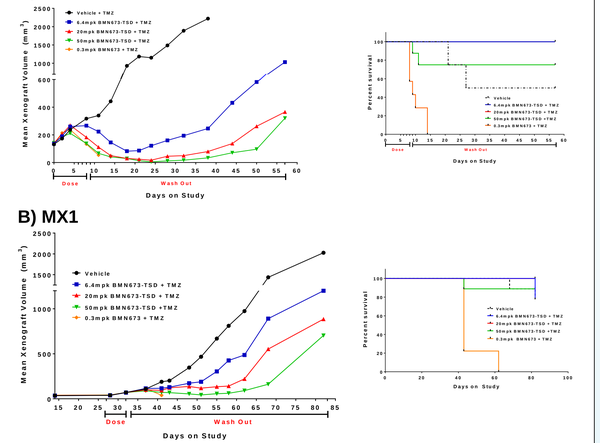
A) PARylation inhibition in DLD-1 BRCA2$^{-/-}$ xenografts following IV dosing of 10mg/kg BMN673-TSD + 50mg/kg TMZ for 2 days

B) Oral dosing of 0.3mg/kg BMN673 + 50mg/kg TMZ induces a significant reduction in bone marrow cell count which is not seen with IV dosing of 10mg/kg BMN673-TSD. *p<0.05, ****p<0.0001 significance relative to vehicle.

C) Oral dosing of 0.3mg/kg BMN673 + 50mg/kg TMZ induces a significant reduction in bone marrow cell PARylation. **p<0.01, ****p<0.0001 significance relative to vehicle.

RESULTS

Figure 5. Selectivity in HRD Xenografts



Mean DLD-1 BRCA2$^{-/-}$ (A) or MX1 (B) xenograft growth following intraperitoneal dosing of 6.4, 20 or 50mg/kg BMN673-TSD or oral dosing of 0.3mg/kg BMN673 for 8 days (A), or 5 days (B), respectively. All mice were orally dosed with 10mg/kg TMZ. (Insets) Kaplan-Meier analysis of survival rate based on death or removal from study when body weight loss exceeded 20% from initial body weight.

CONCLUSION

This approach increases the safety and efficacy of PARPi's in combination with chemotherapy and will expand their use into a wider range of HRD and non-HRD solid tumor types. The TSD platform can be applied to other DNA repair inhibitors in the future, and it will allow safe and effective combinations with other systemic therapies, including immunotherapy.

REFERENCES

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