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ABT-888, an oral poly(ADP-ribose) polymerase (PARP) inhibitor, enhances chemotherapy and radiation against pediatric brain tumors

Poly(ADP-ribose) polymerase (PARP) is a critical enzyme for repairing DNA breaks in human cells. While this is an indispensable mechanism for protecting normal tissue against genetic damages and mutations, tumor cells also use this enzyme to protect themselves from DNA breaks caused by chemotherapy and radiation. We therefore hypothesize that inhibition of PARP in tumors cells would overcome their resistance to chemotherapy and radiation. We first demonstrated that the PARP enzyme is highly expressed in more than 85% of the pediatric medulloblastomas and glioblastoma multiforme examined, and we are currently studying PARP expression in ependymomas as well. We also showed that PARP is expressed at a low level in normal developing brain, and this finding is suggestive that inhibiting the PARP enzyme may have minimal side effect on the normal brain in children. We then implanted pediatric medulloblastoma and glioblastoma multiforme inside mice's brains, and we showed that adding ABT-888, an oral drug that inhibits the PARP enzyme, increased tumors' sensitivity to temozolomide, a chemotherapy drug that is active against several pediatric brain tumors. ABT-888 inhibited tumor PARP activity by more than 95%, and this drug preferentially accumulated in the implanted tumors at 10-20 times the levels in adjacent normal brains. In a monkey model, about 40% of the ABT-888 in the blood entered the spinal fluid, confirming that this drug crosses the blood-brain-barrier and is worthy of further investigation as a novel drug for brain tumors.

Other investigators have also shown that ABT-888 increases the effectiveness of additional chemotherapy drugs, including cisplatin and irinotecan, two agents also active against pediatric brain tumors. We have preliminary results showing that ABT-888 inhibits key enzymes responsible for repairing DNA damages caused by radiation, and our animal experiment to confirm that ABT-888 increases tumor sensitivity to radiation therapy is ongoing. We are optimistic that PARP inhibition by ABT-888 will be a successful novel strategy for overcoming chemotherapy and radiation resistance in pediatric brain tumors. Our proposal for a clinical trial to study the combination of ABT-888 and temozolomide in children with recurrent brain tumors has been approved by the Pediatric Brain Tumor Consortium, and we will be submitting this study to the Cancer Therapy Evaluation Program at the National Cancer Institute for review shortly.