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International Conference and Exhibition on
Pediatric Oncology and Clinical Pediatrics
August 11-13, 2016 Toronto, Canada

PARP1 inhibition sensitizes Ewing sarcoma cells to DNA damage

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Eighty-five percent of all Ewing sarcomas, the fourth most common highly malignant childhood cancer, is defined by a tumor-specific chromosomal translocation t (11; 22) (q24; q12) between the EWSR1 and FLI1 genes. DNA damage induced by expression of EWSR1-FLI1 fusion gene is potentiated by PARP1 inhibition in Ewing cells, where EWSR1-FLI1 genes act in a positive feedback loop to maintain the expression of PARP1. As single agents, PARP1 inhibitors have shown promising activity *in-vitro*, but only modest activity in *in-vivo* models. In our previous work (in PPTP), we showed that low level DNA damage by temozolomide (TMZ) can be potentiated up-to 40-fold through inhibition of PARP1 by talazoparib, leading to dramatic tumor regressions in half of the Ewing sarcoma xeno-graft models. We are currently investigating the biochemical differences between Ewing cell lines where there is synergy in xeno-graft models in mice and those where the combination is inactive; we hypothesize that resistance of Ewing sarcoma xeno-grafts to the synergy of the drug combination is a consequence of intrinsic resistance to either or both talazoparib or TMZ. The combination talazoparib-TMZ in Ewing sarcoma xeno-grafts is the most dramatic synergy between two drugs to be reported. Determining the mechanism(s) of resistance to combination therapy will allow potentially identify biomarkers that will allow identification of patients likely to benefit from such treatment, and spare toxicity for those unlikely to respond.

Biography

Raushan Kurmasheva has completed her PhD at Kazakh State National University and her Post-doctoral studies at University of Arkansas for Medical Sciences and St. Jude Children's Research Hospital. She is an Assistant Professor at the Greehey Children's Cancer Research Institute, UTHSC San Antonio. To date, she has published 46 peer-reviewed papers in reputed journals and has been serving as an *Ad-Hoc* reviewer on *MCT* journal.

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