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MAIN FIELDS OF RESEARCH; ABSTRACT

Ewing sarcoma is an aggressive pediatric bone and soft tissue tumor driven by the expression of a fusion oncoprotein named EWS-FLI1, which acts as an oncogenic transcription factor. Tumor cells are strictly dependent on continuous expression of the fusion protein, since downregulation of EWS-FLI1 inhibits tumor growth.
We demonstrated that EWS-FLI1 is predominantly a proteasomal substrate with a high turnover rate which is mediated by poly-ubiquitination at one specific site. Interference with the fusion protein turnover is critical for the modulation of tumor cell proliferation and survival.
This study provided novel insights into the crucial importance of targeting the stability of EWS-FLI1 as novel strategy for the treatment of Ewing sarcoma.
Hence, we aimed at identifying compounds that destabilize EWS-FLI1 with subsequent reduction of tumor cell growth and proliferation by performing a screen of 2'486 FDA-Approved drugs and 204 novel targeted compounds in a Ewing sarcoma cell line. We adopted a Global Protein Stability approach as novel read-out (Global Protein Stability Profiling in mammalian cells, Science, 2008), which relies on a reporter construct expressing two fluorescent dyes to monitor changes in stability of EWS-FLI1 by high-throughput flow cytometry. Next, we aim to validate the results of the screen and characterize the mechanism of action of the most promising drug candidates.

We conclude that the study of EWS-FLI1 turnover represents a novel approach to identify new effective drugs that can be used as monotherapy or in combination with other drugs as novel treatment opportunities in Ewing sarcoma.

SPECIAL TECHNIQUES AND EQUIPMENT

Flow Cytometry, FACS, compound screen, lentiviral transduction, primary cell culture, xenograft.