New compounds may aid in development of targeted therapies for a rare pediatric cancer

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Two recently discovered compounds have shown promise in preclinical studies for treating Ewing sarcoma, a rare cancer that predominantly affects children and adolescents.

Both compounds suppress the activity of EWS-FLI1, which belongs to a class of molecules called transcription factors that play key roles in gene regulation. In Ewing sarcoma, EWS-FLI1 switches certain genes "on" or "off" incorrectly, leading to uncontrolled cellular proliferation and, ultimately, tumors. Although they are difficult to target for drug treatment because of their structure, transcription factors offer significant opportunities for developing more precise therapies that perform better and have fewer side effects.

"Our current approach—a combination of chemotherapy, radiation and surgery—is a tough road and isn't extremely effective in patients whose cancer has spread or relapsed," said senior author Patrick Grohar, M.D., Ph.D., an associate professor at Van Andel Research Institute and a pediatric oncologist at Spectrum Health Helen DeVos Children's Hospital. "EWS-FLI1 is unique to Ewing sarcoma and is present in the majority of cases, which offers an excellent opportunity for developing precise therapies that combat cancer cells with less chance of affecting normal, healthy cells. At the same time, these findings lay the groundwork for devising ways to target transcription factors in other cancers, which historically has been challenging."

The new compounds are derived from mithramycin, a drug previously investigated as a potential therapy for Ewing sarcoma. Not only do they suppress EWS-FLI1 activity more effectively than mithramycin, but the new compounds also demonstrate far less toxicity, making them attractive candidates for further studies.

"Although we are hopeful our findings will lead to new, more effective therapies for Ewing sarcoma, we also believe they serve as a precedent for targeting transcription factors in other tumor types," Grohar said. "We're excited to complete the preclinical work, which will help us prioritize one of the compounds for translation into a clinical trial."

More information: C. L. Osgood et al. Identification of mithramycin analogs with improved targeting of the EWS-FLI1 transcription factor, *Clinical Cancer Research* (2016). DOI: 10.1158/1078-0432.CCR-15-2624

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