New pyrimidine compounds may lead to improved treatments for childhood brain cancer

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Src (short for sarcoma) is a family of proto-oncogenic tyrosine kinases active in many cancer tumors, including medulloblastoma, the most common malignant cancer in children. Src represents one of the most promising targets for cancer therapy.

A recent study shows that pyrazolo-[3,4-d]-pyrimidine-derivatives, designed to target Src, may be effective in interfering with the cell cycle and causing cancer cell death in medulloblastoma. The results were published in *FASEB* (The *Journal of the Federation of American Societies for Experimental Biology*) and were funded by the Sbarro Health Research Organization Center for Biotechnology (www.shro.org), a nonprofit group devoted to molecular and genetic research located at the College of Science and Technology at Temple University in Philadelphia, PA and the Human Health Foundation (www.hhfonlus.org), a nonprofit biotechnology research organization located in Terni, Italy.

"Our aim was to investigate the inhibitory effects of new pyrimidine-derivatives," said lead author Antonio Giordano, M.D. PhD, the Founder and Director of the Sbarro Institute for Cancer Research and Molecular Medicine and a 'Chiara fama' Professor at the Department of Human Pathology and Oncology, University of Siena, Siena, Italy. "Our findings show that, in medulloblastoma cells, pyrimidine derivatives can downregulate Src activity and reduce cell proliferation and tumor

progression in vivo. This suggests that pyrimidine derivatives could be an effective therapeutic strategy not only for the treatment of medulloblastomas, but also for other Src expressing tumors."

Although better treatment regimens, including surgery, chemotherapy and radiotherapy have substantially improved survival, medulloblastoma remains incurable in about one third of patients and current treatments can cause toxic neurocognitive side effects.

"Compared with conventional chemotherapeutic agents cisplatin and etoposide that are presently used in medulloblastoma therapy, we found that these pyrimidine derivatives show major inhibitory effects on cell proliferation," said Alessandra Rossi, Ph.D, a co-author of the study, a Research Fellow at the Sbarro Institute. "Using these compounds with radiotherapy could allow the reduction of radiation doses and, consequently, the avoidance of radiotherapy-related cognitive and endocrine toxic effects. Moreover, our findings reveal that the pyrimidine compounds showed synergistic effects when combined with cisplatin and etoposide, suggesting their possible use in association with chemotherapy."

Attempts to further reduce the morbidity and mortality associated with medulloblastoma have been limited by the toxicity of conventional treatments and the low permeability of the blood-brain barrier (BBB), which restricts the entry of hydrophilic and large liphophilic compounds into the brain.

"Other Src inhibitors, currently in clinical trials for the treatment of other pathologies, showed low efficacy in the treatment of metastasis to the brain," said co-author Silvia Schenone, Ph.D, Associate Professor at the University of Genoa, Genoa, Italy, in collaboration with Maurizio Botta, Ph.D, Adjunct Professor at Temple University, Director, Drug Discovery Program, Professor Medical Chemistry and Dean of the

Faculty of Pharmacy at the University of Siena, Siena, Italy. "But our pyrimidine derivatives have liphophilic characteristics, which enable them to pass through the blood brain barrier more easily, representing an other advantage of their use in medulloblastoma therapy."

Besides the possible use of these pyrimidine derivatives in the treatment of medulloblastoma, these compounds could be useful to develop new pharmacologic inhibitors to study the physiological and oncogenic functions of Src.

Provided by Sbarro Health Research Organization