

Scientists uncover novel therapeutic targets and candidate biomarkers in childhood cancers

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Researchers at the Children's Cancer Institute (Instituto do Câncer Infantil, ICI), the Federal University of Rio Grande do Sul (UFRGS), the Cancer and Neurobiology Laboratory, and the Pediatric Oncology Service at the university hospital (Hospital de Clínicas de Porto Alegre, HCPA) have obtained evidence suggesting that proteins known to regulate neuronal development and plasticity may be useful biomarkers and therapeutic targets in childhood cancers. These proteins, called neurotrophins, are well-known signaling molecules in normal brain development and function. The neurotrophin family of proteins, which includes brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), activate the Trk family of cell-surface protein receptors. There is growing interest in investigating how overexpression of neurotrophins and Trk receptors in tumors can stimulate cancer growth and contribute to chemotherapeutic resistance.

Ewing sarcoma is a highly aggressive pediatric cancer that occurs in bone or nearby soft tissue and is characterized by small round blue cells. It appears to arise from neural crest or mesenchymal cells. The biological alterations underlying Ewing sarcoma typically include gene fusions involving the EWS and FLI-1 genes. Advances in multimodality therapy, in which cytotoxic chemotherapy is combined with surgery or radiotherapy, have improved clinical outcomes. However, survival rates remain unsatisfactory, with 5-year survival rates currently being approximately 70% overall, but only 56% among older teens, and just

15-30% if overt metastasis has already occurred before starting treatment.

In a study published in the journal *Oncotarget*, Tiago Heinen and colleagues showed that Trks are expressed in Ewing tumors from patients. When the researchers used selective inhibitors to block TrkA and TrkB (receptors for NGF and BDNF, respectively) in cultured Ewing sarcoma, tumor cell growth and survival were inhibited, with stronger inhibition being observed when both receptors were inhibited simultaneously. Furthermore, Trk inhibition also made the tumor cells more susceptible to chemotherapeutic drugs currently used to treat patients with Ewing sarcoma, even when cells were conditioned to become resistant to chemotherapy. Notably, levels of beta-III tubulin, a protein involved in tumor aggressiveness, were reduced in cells treated with Trk inhibitors.

In a previous study by the same group, published in the *Journal of Molecular Neuroscience*, Amanda Thomaz and colleagues found that TrkB inhibition reduced the viability and survival of medulloblastoma cells. Currently, one third of patients with medulloblastoma, the most common form of pediatric brain cancer, have a low chance of being cured. Survivors often suffer from long-term neurological disabilities due to the adverse effects of chemotherapeutics, radiotherapy, and surgery.

"These studies provide the first evidence that inhibiting neurotrophin signaling can yield anticancer effects on Ewing sarcoma and medulloblastoma. The findings may lead to improvements in treatment effectiveness", says UFRGS professor and senior author of the studies, Dr. Rafael Roesler.

In addition to being drug targets, neurotrophins may also serve as biomarkers of childhood cancers. In a study involving 71 children

(including adolescents) with acute myeloid leukemia or acute lymphoid leukemia and 44 healthy controls, Julia Portich, Mirela Gil, and colleagues found that BDNF levels in the plasma or blood marrow of leukemia patients were significantly reduced during active stages of the disease (diagnosis and relapse), and returned to normal during remission. Importantly, BDNF levels at the time of diagnosis were significantly lower in patients who ultimately died than in those who survived. "Our findings suggest that measuring blood levels of BDNF at diagnosis may provide information about disease activity and risk of death that would be helpful for guiding therapeutic decisions", says Dr. Caroline Brunetto de Farias, Head of Cellular and Molecular Research at ICI and senior author of the biomarker study, which was presented at the European Cancer Congress in Vienna, Austria in September 2015. ICI President Dr. Algemir Brunetto says, "By fostering this type of research, we aim to increasingly support basic science informed by clinical needs in the field of pediatric oncology in South America."

More information: Tiago Elias Heinen et al, Trk inhibition reduces cell proliferation and potentiates the effects of chemotherapeutic agents in Ewing sarcoma, *Oncotarget* (2014). [DOI: 10.18632/oncotarget.8992](https://doi.org/10.18632/oncotarget.8992)

Amanda Thomaz et al. BDNF/TrkB Signaling as a Potential Novel Target in Pediatric Brain Tumors: Anticancer Activity of Selective TrkB Inhibition in Medulloblastoma Cells, *Journal of Molecular Neuroscience* (2015). [DOI: 10.1007/s12031-015-0689-0](https://doi.org/10.1007/s12031-015-0689-0)

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