New drug may overcome treatment resistance in a high-risk children's cancer

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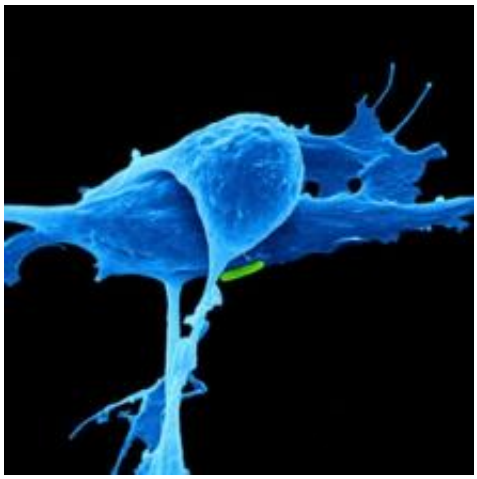

Pediatric oncologists from The Children's Hospital of Philadelphia (CHOP) have reported their latest results in devising new treatments for stubbornly deadly forms of the childhood cancer neuroblastoma.

Building on their previous experiences in treating some refractory subtypes of neuroblastoma with the anticancer drug crizotinib, the researchers have identified a powerful new drug with "unparalleled" strength against forms of the cancer that resist crizotinib.

"Our preclinical results provide a strong rationale for fast-tracking this drug into clinical trials in children with neuroblastoma," said study leader Yael P. Mossé, M.D., a pediatric oncologist at The Children's Hospital of Philadelphia. "We expect to begin a clinical trial early this year."

Mossé collaborated with Mark A. Lemmon, Ph.D., previously at the Perelman School of Medicine at the University of Pennsylvania, and currently at Yale University.

The study appeared Jan. 8 in the print edition of *Cancer Discovery*.

Usually appearing as a solid tumor in the chest or abdomen, neuroblastoma accounts for a disproportionate share of cancer deaths in children, despite many recent improvements in therapy. Neuroblastoma is particularly complex, with a bewildering variety of types and subtypes caused by separate and interacting gene mutations.

Mossé and colleagues have long studied how mutations in the anaplastic lymphoma kinase (ALK) gene cause types of neuroblastoma, stemming from their original 2008 discovery of the gene's role in most cases of rare, inherited neuroblastoma. Subsequent research has showed that abnormal ALK changes drive approximately 14 percent of high-risk forms of neuroblastoma.

Based on this knowledge, Mossé and other scientists in the multicenter Children's Oncology Group were able to repurpose crizotinib, an ALK inhibitor, in clinical trials of children with neuroblastoma. Crizotinib was already approved by the FDA to treat adults with a subtype of lung cancer caused by abnormalities in the ALK gene.

In children with neuroblastoma, different mutations within the ALK gene respond differently to crizotinib. One particular mutation, labelled F1174L, resisted crizotinib, so Mossé's team sought a new-generation, more effective ALK inhibitor.

They tested numerous next-generation ALK inhibitors, and their data allowed them to pursue for further investigation an agent called PF-06463922, currently being tested in a phase 1/2 clinical trial of an ALK-driven subtype of lung cancer in adults. That agent binds more tightly than crizotinib to the signaling kinases that drive cancer.

In the current study, PF-06463922 was more powerful than crizotinib in both neuroblastoma

tumor cell cultures and in animal models—mice with implanted neuroblastoma tumors derived directly from human patients. Mossé, Lemmon, and colleagues showed that PF-06463922 showed more profound inhibition of ALK than crizotinib, and at far lower concentrations. The tumors in the animals showed rapid, complete and sustained regression.

"The responses we saw in animals were unprecedented in models of ALK-driven neuroblastoma, and bolsters the case for clinical development of this agent for treating children with this subtype of neuroblastoma," said Mossé. "The drug had very broad potency against a range of ALK mutations, so this could become the ALK inhibitor that is prioritized for frontline therapy in patients with ALK-driven neuroblastoma."

More information: N. R. Infarinato et al. The ALK/ROS1 Inhibitor PF-06463922 Overcomes Primary Resistance to Crizotinib in ALK-Driven Neuroblastoma, *Cancer Discovery* (2015). DOI: 10.1158/2159-8290.CD-15-1056

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