

Heparin derivative suppresses neuroblastoma tumor growth

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Researchers at Duke Medicine have identified a new strategy for treating neuroblastoma using a modified version of heparin, a century-old injectable drug that thins the blood to prevent clots from forming.

The study, conducted in mice and published June 17, 2014, in the *Journal of Clinical Investigation*, found that when [heparin](#) is altered to remove its blood-thinning properties, it can suppress and shrink neuroblastoma tumors without causing severe bleeding.

"Our research translates mechanistic insights about heparin into a potential new therapy for neuroblastoma, and possibly other cancers," said senior author Gerard C. Blobe, M.D., Ph.D., professor of medicine, pharmacology and cancer biology at Duke.

Neuroblastoma is a cancer that arises in nerve tissue, and is typically seen in infants and children. While neuroblastoma is rare overall – 700 new cases in the United States each year, according to the American Cancer Society – it is the most common cancer in infants.

Despite numerous treatment options for neuroblastoma, survival rates in children with advanced cancer are less than 40 percent due to disease recurrence and the persistence of residual cancerous cells after chemotherapy. However, one difference between neuroblastoma and other solid tumors is the function of the stroma, or [connective tissue](#) around the tumor.

"Most of the time we think of stroma in [solid tumors](#) as a bad thing that helps cancers become more invasive. In neuroblastoma, it's the opposite: having a lot of connective tissue around the tumor does something favorable for patients," Blobe said.

Studying the stroma's biology, the researchers determined that the connective tissue produces and releases receptors involved in nervous system signaling called heparan sulfate proteoglycans. The heparan sulfate proteoglycans had a differentiating effect on the [cancer cells](#), making immature cancer cells act more like mature neurons and keeping them from proliferating.

Heparan sulfate proteoglycans are structurally similar to the anticoagulant heparin, which led the researchers to hypothesize that heparin might recreate the function naturally occurring in the stroma. They administered heparin to human neuroblastoma cells in laboratory cultures as well as to mice with neuroblastoma, and found that it could differentiate cancer cells and cause tumors to regress in mice. However, the heparin caused severe bleeding, rendering it an unusable treatment.

"That's what caused the 'eureka' moment. Heparin was effective, but caused serious bleeding," said Erik H. Knelson, an M.D./Ph.D. candidate at Duke University School of Medicine and the study's lead author. "If we could find a modified heparin that still promoted differentiation but did not cause anticoagulation, we might have a successful treatment."

The researchers studied the structure of heparin, and determined that although certain properties were necessary for anticoagulation, only some were important for the signaling that promoted differentiation. Using this finding, they identified a derivative of heparin that would still allow for differentiation but not cause anticoagulation.

When tested in lab cultures, the heparin derivative suppressed

[neuroblastoma](#) growth. In mice, it slowed the cancer's progression, shrunk the tumors and extended the animals' lives.

"The study illustrates the benefit of listening to the cancer and its biology," Knelson said. "We started out with an investigation of tumor stroma and its mechanism, and designed a potential therapy using this new understanding."

The team is now working to move the research into clinical trials in humans to determine whether the heparin derivative offers the same benefit in humans as it did in mice.

"We want to repurpose a drug that's already out there for the benefit of patients," Blobe said. "What's exciting about that is there are other tumors in which differentiation is useful, so there's the potential to apply these insights to other cancers."

Provided by Duke University Medical Center

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