Bloodstream scavenger inhibits clotting without increased bleeding

July 23 2012

A compound that mops up debris of damaged cells from the bloodstream may be the first in a new class of drugs designed to address one of medicine's most difficult challenges -- stopping the formation of blood clots without triggering equally threatening bleeding.

In a mouse study published online July 23, 2012, in the journal Proceedings of the National Academy of Sciences, Duke University Medical Center scientists report that the experimental compound called PAMAM G-3 actually prevents activation of the process that leads to the formation of dangerous blood clots, while avoiding any impact on the factors that are essential to normal blood clot formation.

"In the thrombosis (clotting) space, the holy grail has been to make something anti-thrombotic that doesn't significantly increase your chance of hemorrhage or bleeding," said Bruce A. Sullenger, Ph.D., director of the Duke Translational Research Institute and senior author of the study. "We think this is a promising example of a type of compound that could do that. If it can be clinically developed and exhibit the same properties in humans, clearly that would improve safety and outcome of treating patients who have thrombotic disease."

Thrombosis, the formation of blood clots in the circulatory system that form blockages, is a major cause of death in the Western world, contributing to the mortality associated with leading killers such as myocardial infarctions, stroke, and even cancer.

"If you can control thrombosis without greatly increasing hemorrhage or bleeding risk, you would address a major unmet medical need," Sullenger said. "It would have potentially major clinical implications."

The thrombosis study builds upon previous work by Sullenger and his group, which showed that the compounds called nucleic acid-binding polymers or NABPs, which include PAMAM G-3, have potent anti-inflammatory properties. Work published last year by Sullenger's lab demonstrated the polymer's potential to interrupt the inflammatory response that is the hallmark of auto-immune disorders such as lupus and multiple sclerosis.

It had been shown previously that dying and diseased cells spill nucleic acids into the bloodstream at high levels — rogue bits of DNA and RNA that trigger an inflammatory immune response. Noting that any circulating nucleic acids or inorganic polyphosphates also seem to trigger the coagulation response, the researchers hypothesized that NBAPs might also be effective anti-coagulants. In test tube-based assays and experiments in two mouse models of thrombosis, the NABPs proved to be potent inhibitors of thrombosis without simultaneously triggering abnormal bleeding.

After screening several of the NABPs, which were originally developed for other biomedical applications, the team settled on PAMAM G-3 due to its combination of anticoagulant potency and low toxicity.

"We found that other [NABP] compounds were more toxic, but this particular compound, PAMAM G-3, had been purported to be less toxic in mouse models, so that's why we chose it for our further studies," said Shashank Jain, Ph.D, the study's lead author and a post-doctoral associate at Duke.

The researchers plan further work to better understand how the nucleic

acids and polyphosphates are mediating the coagulation response. They will also engineer additional NABP compounds to improve potency, safety and tolerability. And of course they have their sights set on the clinic, but that is a few years away.

"Clearly we want to think about other animal models and then translating it eventually into human studies," Sullenger said. "In a variety of the major diseases, thrombosis is an important clinical problem, and the challenge is always, how do you treat it without causing bleeding problems? If you can address that critical issue, it would be a significant advance."

Provided by Duke University Medical Center