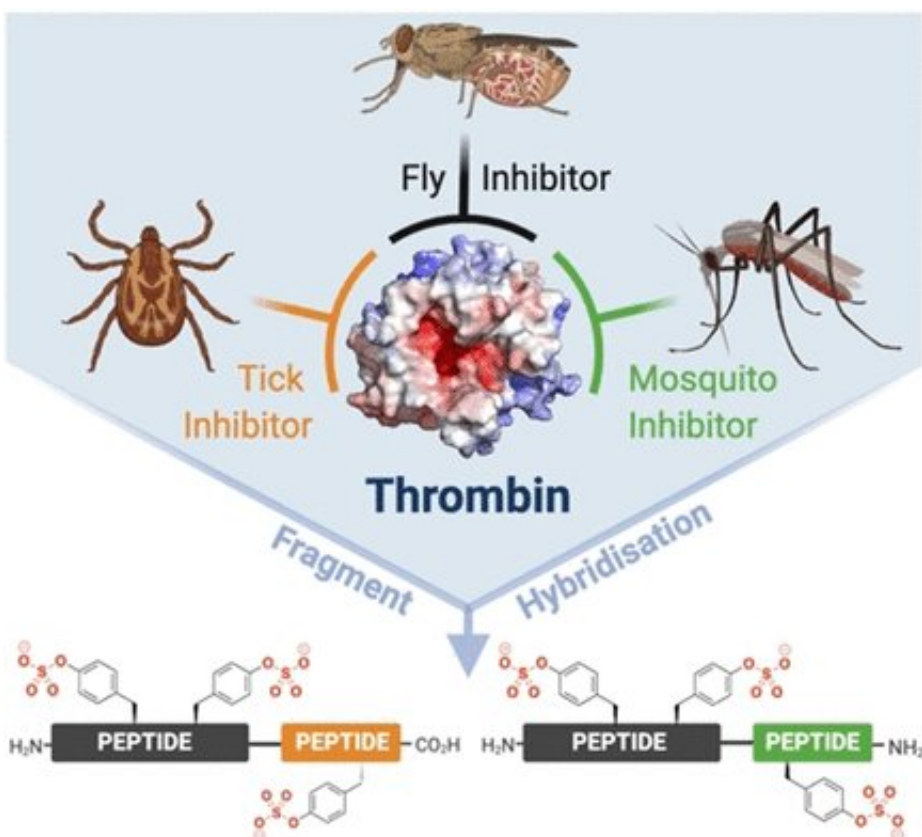


Potent trivalent inhibitors of thrombin from anticoagulation peptides in insect saliva

January 29 2021



Credit: Angewandte Chemie International Edition

Thrombosis, the clogging of blood vessels, is a major cause of heart attacks and embolism. Scientists have now engineered the first inhibitors of thrombin, a protease promoting thrombosis, that is three-fold efficient. In a study published in the journal Angewandte Chemie, the

authors demonstrate that attacking three sites of the thrombin molecule is more efficient than attacking only two sites, which is the mode of action of many natural agents.

Soon after an injury, [thrombin](#) appears at the site of the wound, promoting platelet coagulation and fibrin development to clog the wound and grow new tissue. Unfortunately, inside [blood vessels](#) uncontrolled thrombin activity may lead to clogged pathways causing fatal outcomes for patients. Thrombosis has come into focus recently when it appeared that it was one of the major complications of severe COVID-19.

Many biting and blood-sucking insects carry natural anti-thrombosis factors to keep the blood in a wound liquid. Some of these natural inhibitors have been turned into medicine. The most applied thrombin inhibitor is hirudin, a peptide isolated from leeches.

In their quest to optimize thrombin inhibition, Richard J. Payne from the University of Sydney, Australia, in collaboration with an international team of scientists, scrutinized the way the inhibitors act. Most thrombin inhibitors from insects block two sites on thrombin. Usually, they attack the [active site](#) (the substrate-cleaving site) plus one of two other regions on the surface of the enzyme, which are important for regulating coagulation.

To cover all three sites with one drug, the researchers chose three natural inhibitors, which were then patched together. They connected the tsetse thrombin inhibitor, or TTI, from the [tsetse fly](#) with either an inhibitor peptide called variegins from a tropical tick or the inhibitor anophelin from the malaria mosquito *Anopheles*. The resulting hybrid peptides were designed to span all three binding sites of thrombin.

This design proved to be efficient. According to the authors, the "constructs from both hybrid series exhibited exquisitely potent

thrombin inhibitory activities." The scientists reported up to 385-fold inhibition for the hybrid involving the peptides from tsetse fly and *Anopheles* mosquito. For the other hybrids, the improvements were still two- to 10-fold. Notably, in human plasma all hybrids inhibited thrombin generation and platelet aggregation.

To test the constructs in a live body, the researchers applied one of the hybrids to a mouse model. Here, it made a thrombus shrink at least with the same efficiency as hirudin, and it reduced fibrin accumulation. The authors hope that this work will not only lead to efficient anticoagulation drugs, but will also help in the design of other peptide-based agents.

More information: Stijn M. Agten et al. Potent Trivalent Inhibitors of Thrombin through Hybridization of Salivary Sulfopeptides from Hematophagous Arthropods, *Angewandte Chemie International Edition* (2020). [DOI: 10.1002/anie.202015127](https://doi.org/10.1002/anie.202015127)

Provided by Wiley

Citation: Potent trivalent inhibitors of thrombin from anticoagulation peptides in insect saliva (2021, January 29) retrieved 24 April 2024 from <https://phys.org/news/2021-01-potent-trivalent-inhibitors-thrombin-anticoagulation.html>

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