On-Demand Inhibition of Thrombin with a Cooperative Supramolecular Drug

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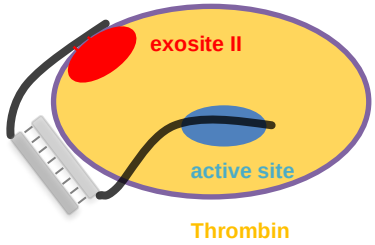
Globally, 1 in 4 adults will suffer from a stroke in their lifetime, however, treatment options are limited. Thrombin is one of the most important enzymes involved in blood clotting, the key process in the occurrence of stroke. One of the therapeutic challenges in addressing blot clotting is that excessive or irreversible inhibition is equally dangerous[1].



Inspired by natural proteins from blood-sucking insects that rely on thrombin inhibition to access their meal[2, 3], we have developed a supramolecular inhibitor that works by cooperative interactions between two binding sites on thrombin. This drug is made of two distinct molecules, one that binds to Thrombin's active site and the other exosite 2. Both molecules contain a PNA sequence which provides a reversible and dynamic link. Neither of the molecules by themselves is sufficient for potent thrombin inhibition but when brought together, they result in potent inhibition of clotting. Thus, controlling the link between the two components allows a tight control of the anti-clotting activity and we demonstrate that we could unlink the two components with a fast-acting antidote. To the best of our knowledge, this is the first supramolecular drug to function *in vivo*.

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2. Agten, S.M., et al., *Potent Trivalent Inhibitors of Thrombin through Hybridization of Salivary Sulfopeptides from Hematophagous Arthropods.* Angewandte Chemie International Edition, 2021. **60**(10): p. 5348-5356.
3. Watson, E.E., et al., *Rapid assembly and profiling of an anticoagulant sulfoprotein library.* Proceedings of the National Academy of Sciences, 2019. **116**(28): p. 13873-13878.