PRESS RELEASE

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NUS Medicine cardiovascular research team develops anticoagulant drugs with high anticlotting efficacy and minimal bleeding

Singapore, 6 December 2021- A team lead by Research Assistant Professor Koh Cho Yeow from the Cardiovascular Diseases Translational Research Programme at Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine) and Cardiovascular Research Institute, Associate Professor Mark Chan, from the Department of Medicine, NUS Medicine, who is also the Deputy Director (Clinical Research Matters) from the Cardiovascular Research Institute and National University Heart Centre, as well as, Professor R. Manjunatha Kini from the Department of Biological Sciences at NUS, developed a series of thrombin inhibitors to be powerful anticoagulants, commonly known as blood thinners or anticlotting medications.

The NUS Medicine research team searched tick saliva for novel anticlotting proteins and then modified the amino acid sequences of these proteins to produce next-generation anticoagulants with high anticlotting efficacy but minimal bleeding in small and large animal models of blood vessel clotting.

Blood-feeding animals rely on specific molecules in their saliva to overcome defence mechanisms of their mammalian hosts for successful survival. For example, tick saliva contains molecules that can stop blood from clotting, and suppress inflammation or immune response to enable continuous feeding on the same bite site for days, sometimes undetected by the host. The harmful effects of these parasites can actually be harnessed for medical treatments.

The paper titled **"Efficacy and safety of next-generation tick transcriptome-derived direct thrombin inhibitors"**, which was first published in *Nature Communications* end November 2021, explained how the team developed a series of thrombin inhibitors to be potent anticoagulants based on sequences of inhibitors of blood coagulation enzyme thrombin found in the tropical *bont tick Amblyomma variegatum*. Anticoagulants are used in conditions where there is an increased propensity to form blood clots in our body depriving blood supplies to important tissues and organs, otherwise known as thrombosis. These medications are needed in many diseases caused by blood clots including heart attacks, strokes, deep vein thrombosis, pulmonary embolism and even some severe complications caused by SARS-CoV-2 infection.

In certain conditions where the likelihood of thrombosis is extremely strong, doctors may even combine anticoagulants with antiplatelets such as aspirin. The reverse side of such treatment is the danger of excessive suppression of clotting ability, resulting in bleeding. Therefore, there is a need for the development of safer anticoagulants with lower tendency to cause excessive bleeding.

The team has tested two inhibitors, *variegin* (a first-generation thrombin inhibitor that the team previously discovered) and *ultravariegin* (a second-generation thrombin inhibitor that the team recently designed). Both molecules are extremely potent, with *ultravariegin* inhibiting thrombin 445-fold better than *bivalirudin* (an anticoagulant currently used in human during coronary stenting). Yet, despite their much greater anticlotting efficacy, these two molecules caused much less bleeding than commonly-used anticoagulants. The lower tendency of *variegin* & *ultravariegin* to cause excessive bleeding is especially clear if anticoagulants: *variegin, ultravariegin, heparin* or *bivalirudin* were used in combination with another class of anticlotting medications -antiplatelet medications such as *aspirin* and *ticagrelor*, resulting in a 5 to 7-fold lower bleeding risk. To further enhance the safety of *ultravariegin*, the team discovered an additional molecule that could potentially be used as an antidote to *ultravariegin*, which acts as an instantaneous reversal of the anticoagulant action in the event of bleeding

“This is a collaborative effort of researchers from Singapore and other countries, playing various critical roles in the study. It is also a good demonstration of how nature continues to provide inspiration in drug discovery and development,” said Dr Koh.

Assoc Prof Chan added, “It is truly amazing what new treatments you can find from the tiniest insects if you look hard enough.”

These next-generation anticoagulants will now need to be tested in human trials to determine if they can effectively counteract clotting without the bleeding side effects of currently available anticoagulants.

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, 30 university-level research institutes, research centres of excellence and corporate labs focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research and cybersecurity.

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Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is Asia's leading medical school and ranks among the best in the world (Times Higher Education World University Rankings 2022 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2021).

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