The research commercialisation office of the University of Oxford, previously called **Isis Innovation**, has been renamed **Oxford University Innovation**

All documents and other materials will be updated accordingly. In the meantime the remaining content of this Isis Innovation document is still valid.

URLs beginning www.isis-innovation.com/... are automatically redirected to our new domain, www.innovation.ox.ac.uk/...

Phone numbers and email addresses for individual members of staff are unchanged

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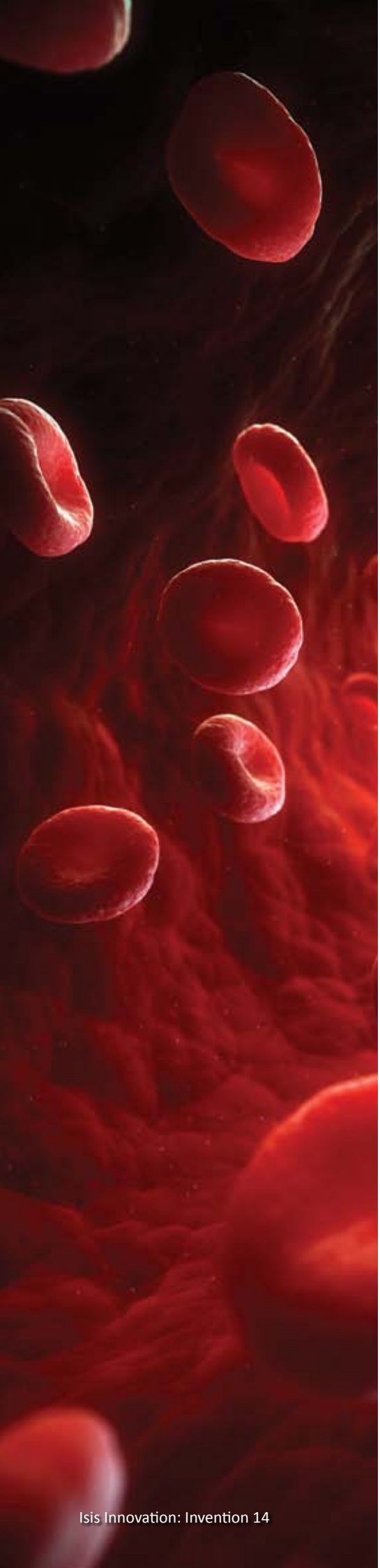


Treating blood clots without the bloodshed

Dr James Groves presents an anti-blood clotting agent, derived from the saliva of the tropical bont tick, which demonstrates high potency without increased bleeding

Blood clotting is a sophisticated physiological cascade, critical for survival by ensuring that minor traumas do not result in life-threatening blood loss. The flipside of the haemostatic coin, however, is that this protection can turn against us. The aberrant formation of a blood clot will block the flow of oxygen and essential nutrients within the vasculature and can result in a range of conditions including myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis.

Narrow therapeutic window

While a number of anticoagulants have been developed, their major limitation is a narrow therapeutic window between clot-busting potency and excessive bleeding. A consequence is that dosing has to be limited, preventing anticoagulants from achieving their full efficacy. In response, significant research efforts have been focused on identifying new molecules that can deliver sufficient anticoagulation without unwanted bleeding.

Learning from the bloodthirsty

Numerous blood-feeding animals, from leeches to vampire bats, have developed an array of specialised salivary proteins that interfere directly with the clotting process, allowing them to feast on an uninterrupted flow of host blood.

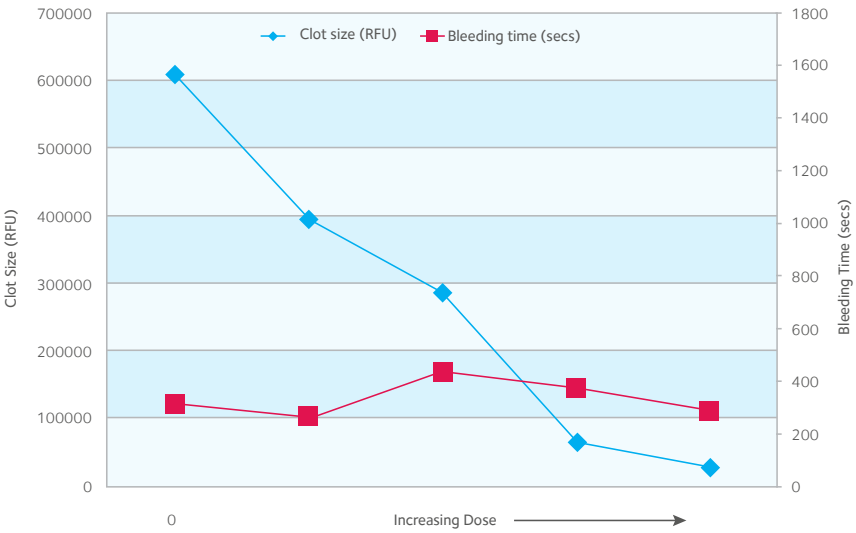
These proteins have been of great value in dissecting the blood clotting cascade, and have led to the development of an array of anticoagulant agents.

Anticoagulation without bleeding

Researchers from the University of Oxford and the National University of Singapore have identified variegin, an anticoagulant extracted from the saliva of the blood-feeding tropical bont tick *(Amblyomma variegatum)*. The team were able to synthesise the small peptide and observe a variety of ideal anticoagulant traits, including specificity, a long duration of action, dose-dependent potency and minimal bleeding *in vivo.* Variegin is a 'first-in-class' anticoagulant that breaks down blood clots by inhibiting thrombin, a key enzyme in the blood clotting cascade. Structural modifications of this protein have generated a suite of derivatives that exhibit a variety of key advantages.

Key advantages

- Unprecedented efficacy: More than 80% inhibition of clot formation
- Reduced side effects: No increase in bleeding time or blood loss
- First-in-class mechanism: Both uncleaved and cleaved peptide inhibit thrombin
- Long lasting: Retained activity of cleaved peptide permits enduring anticoagulation
- Reversible: Anticoagulation can be neutralised by protamine sulphate



Dose-dependent clot inhibition without increased bleeding in a mouse model of thrombosis

Market opportunity

An increasing prevalence of blood clotting disorders is driving investment in identifying improved oral anticoagulants, with revenues expected to be almost $12 billion by 2016 in the US alone. Furthermore, patient safety, particularly in relation to bleeding will drive market share for emerging products (Frost & Sullivan 2011, Analysis of the anticoagulant market). The superior efficacy and side effect profile of variegin, combined with its capacity for structural modification, represents an exciting opportunity to access this market. In addition, the properties of variegin will be of interest to companies engineering heamocompatible coatings for catheters, vascular stents, artificial heart valves and extracorporeal tubing.

"Surgeons want to carry out their work without worrying about their patient bleeding to death. We think we have found a safe anticoagulant, designed by nature, which could allow this happen"

Professor Pat Nuttall OBE, lead inventor, Department of Zoology, University of Oxford.

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