

Targeting the X-factor to tackle cardiovascular disease

May 22 2013



New research at The University of Nottingham aimed at preventing harmful blood clots associated with heart disease and stroke has recently received a major funding boost from the British Heart Foundation.

Grants totalling more than £1.2m have been awarded to the University's School of Pharmacy and are aimed at gaining a deeper understanding and selectively targeting coagulation X factors from the blood's contact system.

The contact system recognises foreign surfaces, including bacteria, whereby it then becomes activated triggering a number of processes. These include the release of a peptide bradykinin which can affect changes in blood pressure. Anti-bacterial peptides are also released and blood coagulation is activated.

Recent research in the last five years has shown that inappropriate activation of the contact system can be linked to serious health problems such as heart disease or stroke.

Breakthrough

These new projects focus on proteins termed factor XI and factor XII (X-factors) that contribute to [blood coagulation](#). Factor XI is the 'newest' X factor in evolutionary terms only occurring in mammals but not present in fish, amphibians, reptiles or even mammals that lay eggs (monotremes) such as the platypus.

Professor Jonas Emsley at The University of Nottingham's Centre for Biomolecular Sciences, has previously made a breakthrough by determining the [molecular structures](#) of factor XI and factor XII in studies funded by the British Heart Foundation.

Professor Emsley said: "[Disease models](#) of stroke have shown a significant role for activation of X factors which seem to be central to the pathology of the disease. Thus factor XII and factor XI are of great therapeutic interest in the drive to discover novel anticoagulant therapies to replace heparin and warfarin.

"These currently available treatments target multiple coagulation proteins which have a more central role in healthy blood clotting and hence are more prone to side effects such as bleeding."

The groups of Professor Peter Fischer and Dr Lodewijk Dekker have expertise in drug discovery and have developed a platform for developing new medicines within the School of Pharmacy.

They use drug design methods based on high resolution structures determined using protein crystallography by the group of Jonas Emsley.

They also make use of The University of Nottingham's fully automated state-of-the-art Managed Chemical Compound Collection (MCCC) with more than 80,000 compounds for high through-put screening. This facility is key for identifying lead compounds capable of inhibiting the activity of coagulation factor XII.

New therapies

If crystal structures of lead inhibitors bound to factor XII can be obtained, the observed interactions with the target protein can speed up the process for discovery of new therapies.

This project also benefits from collaboration with Professor Philip Bath (Division of Stroke Medicine, University of Nottingham) who is an expert in clinical trials and the treatment of stroke.

Professor Jeremy Pearson, Associate Medical Director at the BHF said: "Through research like Professor Emsley's we're fighting for every heartbeat, so one day we can put an end to the devastation heart disease brings. This pioneering research project is one of thousands across the UK bringing us a step closer to winning the battle against heart disease.

"We couldn't fund the research team here at The University of Nottingham without your support; donate today so we can fund more projects like this and eradicate [heart disease](#) for good."

Provided by University of Nottingham

Citation: Targeting the X-factor to tackle cardiovascular disease (2013, May 22) retrieved 27 April 2024 from <https://medicalxpress.com/news/2013-05-x-factor-tackle-cardiovascular-disease.html>

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