Methods for treatment or prevention of pathologic thrombosis or inflammation by PC-TP-mediated inhibition of Protease-Activated Receptor 4 (PAR-4) thrombin receptor

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Human blood platelets mediate pathologic thrombosis, leading to life-threatening conditions such as myocardial infarction and stroke. Thrombi form when circulating platelets become activated and aggregate into a platelet plug at the site of vessel injury. Jefferson researchers have discovered that platelets contain phosphatidylcholine transfer protein (PC-TP), an important activator of platelet aggregation. They have also discovered that small molecule inhibitors of PC-TP inhibit platelet aggregation mediated through the Protease-Activated Receptor 4 (PAR-4) thrombin receptor. This is the first demonstration that PC-TP is present in platelets and is involved in downstream signaling of PAR-4. They have further demonstrated that an inhibitor that blocks PC-TP binding to PAR-4 inhibits platelet activation and subsequent platelet aggregation.

Anti-platelet therapy is a mainstay of managing coronary disease, yet many patients continue to have heart attacks and strokes despite a number of currently marketed anti-platelet agents, all of which target Protease-Activated Receptor 1 (PAR-1). However, platelet activation can be more effectively sustained through PAR-4 inhibition, and therapies that target PAR-4 through PC-TP inhibition may provide enhanced therapeutic benefit over, or in combination with, PAR-1 inhibitors. The significance of this invention is the identification of a novel and specific target for the discovery of new treatments and preventative for platelet-related disorders.

An unexpected aspect of this invention is that platelets from healthy African American (AA) subjects display more rapid aggregation through the PAR-4 thrombin receptor than platelets from healthy European American (EA) subjects, the first demonstration of racial differences in PAR-4-mediated platelet activation, suggesting that PC-TP inhibitors of PAR-4 may have enhanced efficacy in AA patients, a population at two-fold higher risk of coronary heart disease and reduced long-term survival rates. PC-TC-mediated PAR-4 inhibition may also be therapeutic when applied to other, non-thrombotic diseases that occur more commonly or with worse outcomes in AA populations.

The primary applications for the invention are for discovery and development of new therapies for treating heart disease, stroke, peripheral vascular disease and other vascular thromoses. Anti-PC-TP agents may also find uses in the treatment of other PAR-4 mediated diseases, including inflammatory disorders of the liver (hepatitis), lung (pneumonia), and pancreas (diabetes or pancreatitis), thyroiditis, prostatitis and fetal development disorders caused by placental dysfunction. Platelets play a role in cancer metastases and these inhibitors may potentially be useful in cancer treatment.

Business Opportunity:

Methods for treatment or prevention of pathologic thrombosis or inflammation by PC-TP-mediated inhibition of PAR-4 receptor are available for licensing. Drs. Bray and Holinstat are available for collaborative and contract research projects and consulting services related to the invention.

Follow-up:

For further information, please contact Michael Caggiano (michael.caggiano@jefferson.edu, 215-955-6862) in the Office of Technology Transfer and Business Development at TJU citing TJU docket number BRA_PAU.001.