Use of Thrombin Mutant to Reverse the Effect of Direct Thrombin Inhibitors

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Technology description

Technical Summary

Direct thrombin inhibitors (DTIs) are a relatively new class of agents which specifically bind to and inactivate one or more of the active sites on the thrombin molecule. These drugs exhibit a number of advantages that make them uniquely attractive as potential therapeutic agents. Such advantages include the fact that Antithrombin III is not required as a cofactor, they can inhibit clot-bound thrombin, circulating inhibitors do not inhibit their function, and they do not appreciably bind to plasma proteins. With all of their advantages, however, problems remain for patients requiring the use of DTIs. Current antidote principles for DTI's (such as DFP thrombin, benzoyl thrombin, meizothrombin, etc.) have been too toxic or are not effective in fluid phase. Furthermore, DTIs have a propensity to cause hepatotoxicity and hemorrhage. The invention is a mutant thrombin that has a high affinity for thrombin inhibitors, but a low affinity for prothrombotic thrombin substrates such as fibrinogen. Consequently, the mutant thrombin can serve as an antidote for synthetic DTIs without many of the side effects associated with failed approaches.

The current estimate of patients treated with anticoagulants for atrial fibrillation (AF), deep vein thrombosis/pulmonary embolism (DVT/PE), acute ischemic stroke (IS), and unstable angina (UA) approaches 65 million. The market for anticoagulant agents in AF, DVT/PE, acute IS, and UA has been estimated at $5 billion.

Application area

The thrombin mutant provides a quick and powerful antidote to synthetic direct thrombin inhibitors.

Institution

Emory University

Inventors

Stephen Hanson
Professor

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com