Anthos Therapeutics, Inc.
www.anthostherapeutics.com

Anthos: Solving the thrombosis dilemma with a hemostasis-sparing anticoagulant

Anthos is developing a pioneering phase 2 monoclonal antibody, abelacimab, as an effective anticoagulant that aims to provide treatment by inhibiting Factor XI to avoid severe bleeding.

Thrombosis is a major unmet need. Globally more than one in four people die from thromboembolic events. Many more suffer morbidity due to complications. These events occur despite the availability of anticoagulants, which, while effective, bring risk of severe or fatal bleeding. These risks lead physicians and patients to underutilize, underdose and prematurely discontinue these drugs. Anthos Therapeutics wants to end the compromise between prescribing an effective anticoagulant and exposing patients to the risk of severe bleeding.

More than 5 million people a year die of stroke, and the need for a new treatment is clear. Venous thromboembolism is the largest cause of preventable hospital deaths and the second leading cause of death in people with cancer. With the right drug, these deaths are preventable.

Although an improvement over warfarin, a forerunner, direct-acting oral anticoagulants (DOACs) are only given to around half of the patients who need them most. DOACs are used in 50% of outpatients at high risk of stroke and 42% of surgical inpatients at risk of venous thromboembolism. Data on DOAC use in other at-risk groups show similar findings.

These figures reflect fears about the risk of major bleeding. The annual rate of major bleeding with DOACs is approximately 2% to 5%, and one-in-five people die within three months of suffering a major bleed. Other patients, such as frail, elderly people with comorbidities, never receive an effective DOAC dose because the associated risk of bleeding is perceived to be too great.

Uncoupling thrombosis and hemostasis

The need for physicians to walk a tightrope between preventing thromboembolic events and causing major bleeds is due to DOACs' mechanism of action. All existing anticoagulants act on a pathway that is common to pathological thrombosis and physiological hemostasis. It is impossible to reduce thromboembolic events without affecting normal hemostasis and increasing the risk of major bleeds, giving DOACs a narrow therapeutic window.

Evidence of why DOACs cause bleeds led researchers to look for drug targets that could uncouple pathological thrombosis and physiological hemostasis. Armed with such targets, researchers could design drugs that prevent thromboembolic events without raising bleeding risk.

That thinking led researchers to hypothesize that Factor XI, a coagulation factor that appears to play a major role in pathological thrombosis, but little to no role in physiological hemostasis, could change the treatment paradigm. While DOACs or warfarin affect coagulation factors that act on both hemostasis and thrombosis, evidence suggests inhibiting Factor XI and XIa may effectively prevent pathological thrombosis without a simultaneous elevation in bleeding risk (Fig. 1).

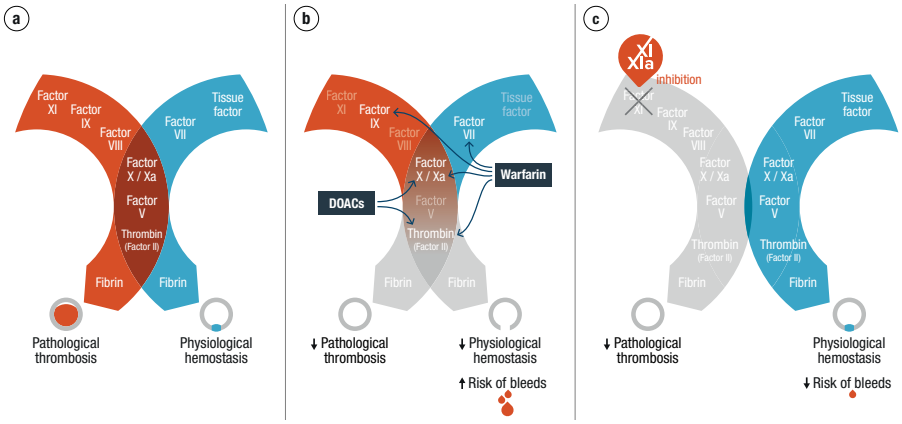

Fig. 1 | A new paradigm: distinguishing thrombosis from hemostasis. The coagulation factors involved in pathological thrombosis can be separated from the factors important for physiologic hemostasis (a), DOACs or warfarin affect coagulation factors that act on both hemostasis and thrombosis (b), inhibiting Factor XI and XIa with abelacimab may prevent pathological thrombosis without increasing the risk of bleeding (c). DOAC, direct-acting oral anticoagulants.

The hypothesis is supported by real-world evidence in people with genetic Factor XI deficiency, who are at reduced risk of thromboembolic events and suffer little to no spontaneous bleeding. Other genetic, epidemiological, clinical and animal model data also support the hypothesis.

Anthos is developing abelacimab, also known as MAA868, to validate the hypothesis. The monoclonal antibody is the only 'dual activity' Factor XI inhibitor which targets both the inactive zymogen, Factor XI, and the active form, Factor XIa. By acting on both forms, Anthos achieves >99% inhibition of the target compared to the 60% to 80% levels of inhibition attained by other drug candidates.

As a monoclonal antibody, abelacimab is free from other problems linked to DOACs. A significant minority of atrial fibrillation patients are contraindicated to oral anticoagulants or are unable to adhere to lifelong daily or twice daily dosing. Other patients experience heightened bleeding risk as slight impairments to renal function suddenly push their drug levels up. In contrast, abelacimab is given once a month and not impacted by renal function, liver disease or other drugs.

Validating abelacimab in the clinic

A phase 2b trial of abelacimab in patients undergoing total knee arthroplasty is underway. The study, which is due to read out in the first half of 2021, will demonstrate the effect of abelacimab on Factor XI and XIa inhibition, clotting in patients after surgery and the incidence of adverse events. Anthos is initiating a second phase 2 study in patients with atrial fibrillation that will directly compare abelacimab to a DOAC in addition to preparing registration trials.

The studies will show whether Factor XI inhibition is the transformative hemostasis-sparing approach to anticoagulation. If Factor XI inhibition lives up to that potential, the approach will provide protection from thromboembolic events without raising the risk of significant bleeding. In doing so, Anthos stands to give physicians the confidence to prevent and treat thrombosis, thereby addressing one of the biggest unmet medical needs.

CONTACT
Jonathan Freeman, COO
Anthos Therapeutics, Inc.
Cambridge, MA, USA
Tel: +1-617-430-6940
Email: jonathan.f@anthostherapeutics.com