TARGETING THE VESSEL WALL DURING VASCULAR INTERVENTION WITH SB-030 PREVENTS PLATELET ACTIVATION AND SUBSEQUENT NEOINTIMAL HYPERPLASIA

John Paderi, Kate Stuart, Julia Chen, Sharmi Saha, Harsha Kabra, Andrew Woolley, Taylor Skurnac, Alyssa Panitch, Nathan Bachtell
Symic Bio, Emeryville, CA

PURPOSE

After plates were incubated at 37°C for 24 hours, PRP was inactivated and spun down to quantify platelet inhibition with SB-030. SB-030 was rinsed, and flow cells were exposed to whole blood under flow at arterial shear rates of 1000 s⁻¹ for 10 minutes. Blood was pretreated with calcine-AM so bound platelets and leukocytes could be imaged by fluorescence microscopy. Images were subsequently quantified using ImageJ software to calculate the platelet adhesion percentage.

Animal model of neointimal hyperplasia

Angioplasty was performed in the study rabbits using a Fogarty balloon placed near the internal femoral branch, inflated, and dragged to the iliac bifurcation (repeated twice). Following denudation, with the inflated balloon still in place, either 2 mL of SB-030 or saline control was delivered through the lumen of the balloon to the site of denudation. After either 2 hours or 28 days post procedure, rabbits were euthanized and the artery sections of interest were isolated. Platelet deposition and neointimal hyperplasia were assessed.

In vivo inhibition of platelet binding

Positive staining of platelets was performed using an antibody to CD41/62. Platelet inhibition was quantified after subtracting non-specific background and determining the area of positive staining in saline- (control) and SB-030-treated arteries.

In vivo inhibition of neointimal hyperplasia

Neointimal tissue was assessed in artery cross sections stained with Verhoffe Van Gieson. Thickness and area of the neointimal tissue were measured using ImageJ software.

METHODS

In vitro assessment of platelet activation and inflammatory factor release

Fibrillar collagen was treated with SB-030, and plates were subsequently treated with varying concentrations of SB-030. SB-030 is a novel matrix regulating molecule that binds specifically to subendothelial collagen that is exposed during vascular intervention or surgical procedures. It is composed of collagen-binding peptides covalently attached to a heparin backbone. The collagen-binding peptides are derived from a platelet receptor to collagen and thus directly compete for platelet-collagen binding sites.

The heparin backbone has pleiotropic functionality, both providing a hydrophilic barrier and binding growth factors that promote a healthy healing response with reduced neointimal hyperplasia in a rabbit vessel injury model.

Vessel occlusion caused by atherosclerosis can be treated with various procedures, including peripheral bypass surgery, angioplasty, and stenting.

Each of these procedures, however, cause damage to the vessel endothelium, exposing the underlying tissue matrix.

Platelets are the first cells to recognize exposed matrix as an injury, binding to collagen within the matrix and becoming activated.

Activated platelets both release chemicals that cause vessel restriction (vasoconstriction) and recruit inflammatory cells that activate smooth muscle cells, leading to neointimal hyperplasia.

In this study, SB-030 was evaluated both in vitro and in vivo to determine its effect on inhibiting platelet-extracellular matrix interactions and subsequent neointimal hyperplasia.

RESULTS

SB-030 inhibits in vitro platelet-collagen binding from whole blood under flow

SB-030 treatment inhibited collagen-mediated platelet binding by approximately 86% as observed and quantified from flow cell imaging.

SB-030 inhibits in vitro platelet-collagen binding from whole blood under flow

SB-030 is a novel matrix regulating molecule that improves vessel patency in a rabbit model by targeting the upstream platelet response at the vessel wall following injury.

This approach does not systematically compromise platelet function and is unique from current approaches for improving patency, in which cytostatic or cytotoxic agents are employed.

SB-030 has wide application in vascular intervention including bypass surgery, angioplasty, or stenting.

A clinical trial, called SHIELD, is underway to evaluate SB-030 in peripheral artery disease.

DECLARATION OF INTEREST

All authors are employees and shareholders of Symic Bio.

This study was sponsored by Symic Bio.

ACKNOWLEDGEMENTS

The authors thank Swati Jagannar of Symic Bio for her in vitro assay design input, CVPath for conduct of the in vivo assays, and Jennifer Klein, PhD of Klein Medical Communications for medical writing contributions.