Small Molecule NMMHC IIA Inhibitors

Targeting NMMHC IIA to Prevent Thrombosis

Overview

Drug Name	Compoud-006 and compound-011
Description	The compounds targeting non-muscular myosin heavy chain IIA (NMMHC IIA) were screened out through *in vitro* experiments (compounds binding rate to NMMHC IIA, cytotoxicity, and the protective effect for cellular oxygen–glucose deprivation/reoxygenation injury). Concluded from thrombosis animal models, compound-006 was effective at reducing arterial thrombosis and compound-011 could significantly inhibit the deep vein thrombosis.
Target	NMMHC IIA
Drug Modality	Small molecule
Indication	Thrombosis
Product Category	Inhibitors
Mechanism of Action	Inhibiting NMMHC IIA to impede thrombosis
Status	Preclinical
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for compoud-006 and compound-011. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

Non-muscle Myosin Heavy Chain IIA (NMMHC IIA)

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Introduction	NMMHC-IIA is a protein encoded by the MYH9 gene, which contains an IQ domain and a myosin head-like domain. NMMHC-IIA is expressed in most cells and tissues where it is involved in several important functions, including cytokinesis, cell motility, and maintenance of cell shape.
Approved Name	Myosin heavy chain 9
Official Symbol	MYH9
Gene Type	Protein coding
Synonyms	MHA; FTNS; EPSTS; BDPLT6; DFNA17; MATINS; NMMHCA; NMHC-II-A; NMMHC-IIA
Ensembl	ENSG00000100345
Gene ID	4627
mRNA Refseq	NM_002473
Protein Refseq	NP_002464
OMIM	160775
UniProt ID	P35579
Chromosome Location	22q12.3

Clinical Resources

Gene Function	Mutations in MYH9 cause a Mendelian autosomal-dominant disorder known as MYH9-related disease (MYH9-RD). All affected individuals present congenital hematological alterations consisting in thrombocytopenia, platelet macrocytosis, and inclusions of the MYH9 protein in the cytoplasm of granulocytes. Most patients develop one or more non-congenital manifestations, including sensorineural deafness, kidney damage, presenile cataracts, and/or elevation of liver enzymes.
Pathway	Akt/GSK3β-NF-κB signaling pathways; caspase-3/ROCK1/MLC pathway
Major Conditions	Non-syndromic sensorineural deafness autosomal dominant type 17; epstein syndrome; alport syndrome; sebastian syndrome; fechtner syndrome; macrothrombocytopenia.

Drug Modality

Small Molecule

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Compound-006 and compound-011 are two small molecule lead compounds targeting NMMHC IIA with high affinity and non-cytotoxicity.

Indication

Thrombosis

Thrombosis is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system. Venous thrombosis leads to congestion of the affected part of the body, while arterial thrombosis affects the blood supply and leads to damage of the tissue supplied by that artery, such as ischemia and necrosis. A piece of either an arterial or a venous thrombus can break off as an embolus which can travel through the circulation and lodge somewhere else as an embolism.

Thromboembolic conditions have been estimated to account for 1 in 4 deaths worldwide in 2010 and taken together, thrombosis, as the common underlying mechanism of myocardial infarction, ischemic stroke, and venous thromboembolism, is the leading global cause of mortality.

The treatment for thrombosis depends on whether it is in a vein or an artery, the impact on the person, and the risk of complications from treatment. Commonly used medications include anticoagulants, thrombolytic agents, and antiplatelet agents.

Mechanism of Action

Inhibiting NMMHC IIA to Impede Thrombosis

NMMHC IIA has important roles in cytokinesis and cell plasticity and is involved significantly in thrombosis regulation. Its deficiency leads to platelet aggregation and thrombosis formation. Previous studies have reported that the inhibition of NMMHCIIA activity could reduce thrombosis development and inflammatory reaction by preventing tissue factor expression and activity. Compound-006 and compound-011, both are NMMHCIIA inhibitors, showed inhibitory effects on venous thrombosis and arterial thrombosis, respectively, from *in vivo* tests.

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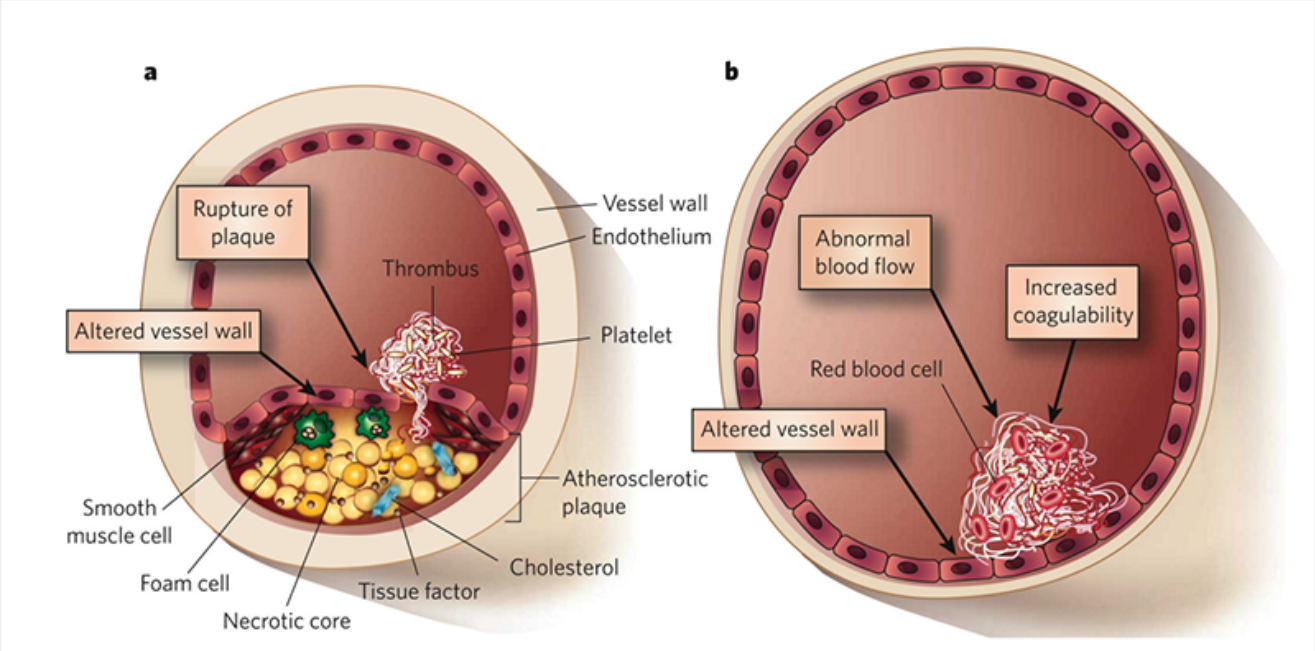


Figure. Triggers of arterial and venous thrombosis
From Nature. 2008 February 21; 451(7181): 914–918.

Status

The Status of Compound-006 and Compound-011

Efficacy test on compound-006 and compound-011 in mice thrombosis models have been completed after the two compounds were screened out.

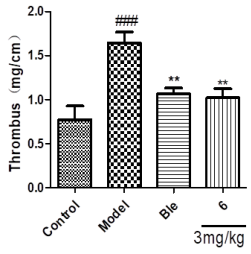
	Discovery/Optimization	Pre-clinical	Phase I	PhaseII	PhaseIII
NMMHC IIA Inhibitors					

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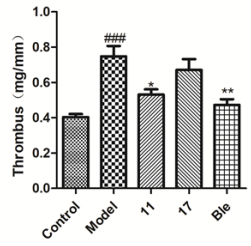
Data



* The size of thrombus was quantified as mg/cm.

Compound-006 Suppressed Arterial Thrombosis in Mice Carotid Artery Thrombosis Model

In mice with carotid artery thrombosis induced by ferric chloride, thrombosis was observed and the arterial walls were greatly thickened. Compared to the control, compound-006 significantly reduced ferric chloride induced arterial thrombosis.



* The size of thrombus was quantified as mg/cm.

Compound-011 Alleviated Thrombus Formation in Mice Deep Venous Thrombosis (DVT) Model

Compound-011 reduced the mass of thrombus in DVT mice compared to the control, demonstrating its inhibitory effect on the formation of DVT.

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