



Netrin-1 Compounds as Post-MI and Post-Angioplasty Therapeutics as well as for Treating Renal and CNS Reperfusion Injury

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CONTACT

UCLA Technology Development Group  
[ncd@tdg.ucla.edu](mailto:ncd@tdg.ucla.edu)  
tel: 310.794.0558.



INVENTORS

► Cai, Hua Linda

OTHER INFORMATION

KEYWORDS

Therapeutic, netrin-1, peptide drugs, myocardial infarction, MI, ischemia reperfusion, cardioprotection, heart attack, infarct size

CATEGORIZED AS

- Medical
  - Disease: Cardiovascular and Circulatory System
  - New Chemical Entities, Drug Leads
  - Therapeutics

RELATED CASES

2014-526-0

SUMMARY

UCLA researchers have invented a method of decreasing myocardial injury and infarct size through the intravenous administration of the netrin-1 or netrin-1-derived peptides during a cardiac event. These agents have powerful cardioprotective effects and provide a novel and effective therapy for the treatment of myocardial infarction.

BACKGROUND

Netrin-1 is a novel endothelial mitogen that stimulates production of nitric oxide (NO•) which has a well-established role in cardioprotection. In order to develop a viable netrin-1 therapeutic a team at UCLA has developed and optimized a series of novel short peptide derivatives of netrin-1 ranging in length from nine to eleven residues. The compounds have been validated *in vivo* in rodents, and porcine studies are underway.

These lead compounds function at three different mechanistic levels which may lead to three distinct cardiovascular therapeutic product concepts as well as therapeutics for renal reperfusion injury and stroke.

- 1. *Prevention of reperfusion injury*: The first level is acute protection to reduce post-MI infarct size more than 50% when given immediately at the onset of reperfusion or pre-reperfusion. The mechanisms involved include receptor DCC dependent ERK1/2/eNOS phosphorylation and NO• production to directly protect cardiomyocytes against injury. This mechanism may present therapeutic opportunities in renal reperfusion injury and stroke.
- 2. *Prevention of post-MI remodeling and fibrosis*: The second level is inhibition of oxidative stress and autophagy. This may lead to a chronic therapy to prevent post-MI remodeling and fibrosis of the heart and thereby sustain cardiac function and prevent development of post-MI heart failure.
- 3. *Prevention of restenosis*: The third level is inhibition of restenosis/re-occlusions of coronary arteries post angioplasty.In animal models this has been shown to be 100% effective.

INNOVATION

UCLA researchers in the Department of Anesthesiology have identified three novel short netrin-1 derived peptides for the improved treatment of MI. The present technology exerts cardioprotection by exploiting the netrin-1 pathway through binding to its receptor DCC to increase the production of nitric oxide. Treatment of the netrin-1 derivatives in freshly isolated ischemic reperfused hearts reduced infarct size – indicating significant reduction in myocardial injury. The present technology provides three superior short netrin-1 derived peptides for the treatment of MI with improved scalability and fewer adverse side effects. Different combination recipes using the three peptides are additionally beneficial.

APPLICATIONS

Based on the mechanisms of action for these lead compounds, there are at least three different therapeutic concepts for this: (1) acute therapy for treatment of reperfusion injury (post-MI, renal reperfusion injury and stroke), (2) chronic therapy for the prevention of post-MI remodeling and fibrosis to prevent heart failure and (3) post-angioplasty therapeutic to prevent restenosis.

ADVANTAGES

- ▶ All three peptides are small (9-11 amino acids in length) – enabling scalability in production
- ▶ More affordable than full-length netrin-1 peptide
- ▶ Pharmacologically feasible in production, storage and application

STATE OF DEVELOPMENT

*Ex vivo* delivery of the present technology to the heart induced cardioprotection via DCC-dependent activation of ERK1/2 and eNOS.

PATENT STATUS

Country	Type	Number	Dated	Case
Germany	Issued Patent	3125906	11/26/2021	2014-526

France	Issued Patent	3125906	11/26/2021	2014-526
United Kingdom	Issued Patent	3125906	11/26/2021	2014-526
United States Of America	Issued Patent	10,550,163	02/04/2020	2014-526

RELATED MATERIALS

- ▶ [Netrin-1 prevents ischemia/reperfusion-induced myocardial infarction via a DCC/ERK1/2/eNOS s1177/NO/DCC feed-forward mechanism.](#)
- ▶ [Pharmacological postconditioning treatment of myocardial infarction with netrin-1.](#)
- ▶ [Netrin-1 improves post-injury cardiac function in vivo via DCC/NO-dependent preservation of mitochondrial integrity, while attenuating autophagy.](#)
- ▶ [Netrin-1 abrogates ischemia/reperfusion-induced cardiac mitochondrial dysfunction via nitric oxide-dependent attenuation of NOX4 activation and recoupling of NOS.](#)
- ▶ [Central role of SIAH inhibition in DCC-dependent cardioprotection provoked by netrin-1/NO.](#)

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- ▶ [Circulating Biomarker for Early Detection of Post-Operative Cardiac Arrhythmias](#)
- ▶ [A Novel Biomarker for Abdominal Aortic Aneurysm](#)

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UCLA Technology Development Group

10889 Wilshire Blvd., Suite 920, Los Angeles, CA 90095

<https://tdg.ucla.edu>

Tel: 310.794.0558 | Fax: 310.794.0638 | [ncd@tdg.ucla.edu](mailto:ncd@tdg.ucla.edu)

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