iSN04: A novel nucleic acid drug for the treatment of vascular diseases

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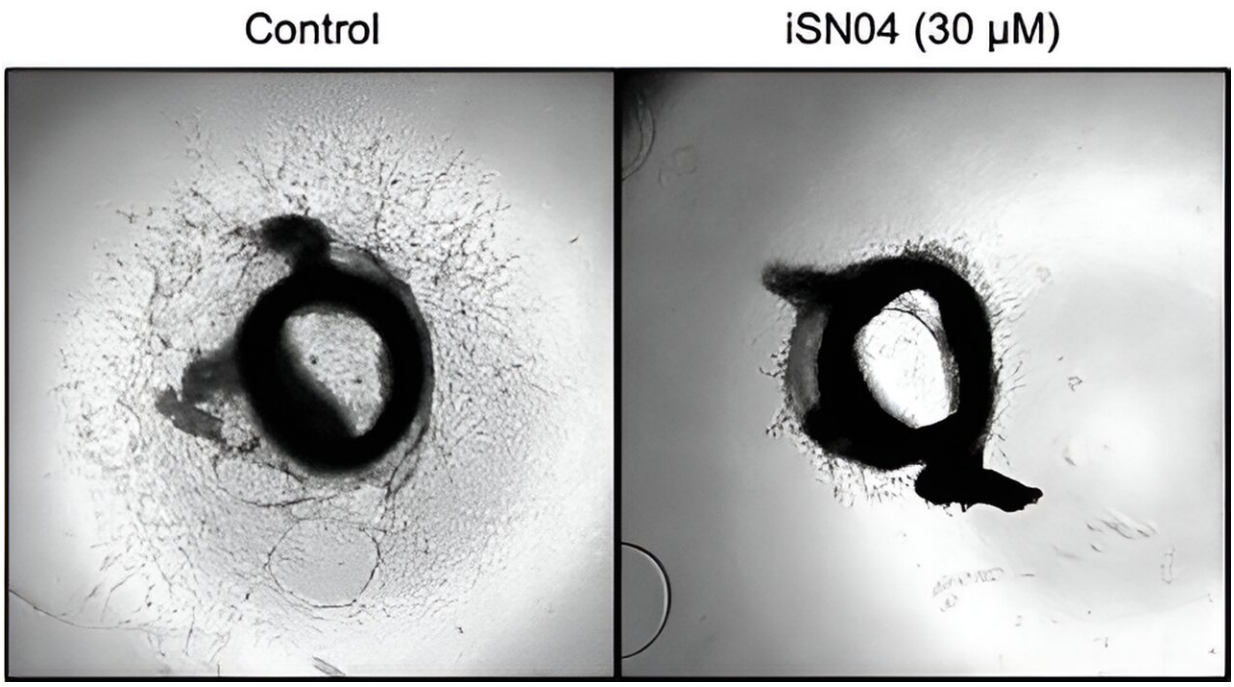

Anti-nucleolin DNA aptamer, iSN04, inhibits angiogenesis. Mouse aortic rings embedded in collagen gel were cultured with or without 30 μM iSN04 for six days. Neovascular sprouting, a model of pathological angiogenesis, was suppressed in the iSN04-treated group. Credit: Tomohide Takaya, Shinshu University

Atherosclerosis, a major cause of mortality worldwide, involves an overgrowth of vascular smooth muscle cells in the blood vessels,

constraining blood flow and potentially causing cardiovascular diseases.

Against this backdrop, researchers from Shinshu University have developed a DNA aptamer called iSN04 that targets and counteracts with the protein nucleolin in smooth muscle cells. This anti-nucleolin aptamer helps maintain smooth muscle cells in a differentiated state, offering new treatment potential for atherosclerosis and other vascular diseases.

Their findings were published on 15 June 2024 in Volume 14 of the journal *Biomolecules*. Ms. Mana Miyoshi, affiliated with the Department of Agriculture, Graduate School of Science and Technology, Shinshu University, contributed to the study as the first author.

Heart diseases and strokes are on the rise worldwide, with atherosclerosis being a leading contributor. Atherosclerosis involves the buildup of plaques—composed of fat, cholesterol, calcium, and other substances found in the blood—inside the arteries.

Over time, this buildup can lead to the hardening and narrowing of the arteries, restricting blood flow. Notably, this condition involves vascular smooth muscle cells (VSMCs) in the arterial walls.

VSMCs can switch between a contractile state (ideal for blood vessel function) and a proliferative state (capable of contributing to plaque formation). During atherosclerosis, the switch from a contractile to a proliferative state can lead to plaque instability and rupture, underscoring the importance of a corresponding therapeutic strategy.

Traditional treatments for atherosclerosis typically focus on lowering cholesterol levels and managing risk factors like high blood pressure. However, a novel approach involves directly targeting VSMCs to stabilize plaques and prevent their rupture.

This innovative strategy has led researchers from Shinshu University, Japan, to develop a novel nucleic acid drug called iSN04. Associate Professor Tomohide Takaya, from the Faculty of Agriculture, Shinshu University led the study.

iSN04 belongs to a group of nucleic acid drugs called DNA aptamer—a short, single-stranded DNA molecule capable of selectively binding to a specific target of interest. iSN04 interacts with a protein called nucleolin in VSMCs.

Nucleolin plays a role in the de-differentiation (loss of specialized function) and proliferation of VSMCs, contributing to plaque formation and instability. By targeting nucleolin with iSN04, the researchers aimed to keep VSMCs in their contractile state, thereby reducing plaque formation and promoting plaque stability.

Interestingly, the same research group laid the groundwork through multiple previous studies for the current study.

Dr. Takaya says, "Our anti-nucleolin DNA aptamer, iSN04, was originally identified as an inducer of skeletal muscle differentiation in 2021. Subsequently, we found that iSN04 also promotes cardiac muscle differentiation in 2023. Therefore, we hypothesized that iSN04 could promote smooth muscle differentiation."

He adds, "This study showed that iSN04 indeed induces vascular smooth muscle cell differentiation, resulting in the inhibition of angiogenesis."

The study showed that iSN04 can help maintain VSMCs in their contractile, differentiated state. The researchers interestingly found that iSN04 can effectively enter VSMCs without any carriers. Once inside, iSN04 reduced VSMC proliferation and increased the levels of a protein marker called α-smooth muscle actin, helping VSMCs in achieving a

contractile state.

Another concern the researchers sought to address was angiogenesis within plaques. Angiogenesis refers to new blood vessel formation within plaques that can lead to their instability and rupture. The study demonstrated that iSN04 could inhibit angiogenesis in an experimental model using mouse aortic rings, indicating its potential to stabilize plaques.

Ms. Miyoshi said, "Given our anti-nucleolin DNA aptamer inhibits angiogenesis by inducing VSMC differentiation, it can find applications as a nucleic acid drug for pathological angiogenesis involved in atherosclerosis, cancer, and retinopathy."

The breakthrough development of iSN04 marks a promising new chapter in the fight against atherosclerosis, and could revolutionize its treatment and improve patient outcomes globally.

More information: Mana Miyoshi et al, Myogenic Anti-Nucleolin Aptamer iSN04 Inhibits Proliferation and Promotes Differentiation of Vascular Smooth Muscle Cells, *Biomolecules* (2024). DOI: 10.3390/biom14060709

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