

Ischemic Stroke Treatment That is Not Pharmaceutical

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DESCRIPTION

Drug Nanotechnology in biomedicine has opened up previously unheard-of possibilities for precise drug delivery. Improved inferior physicochemical properties, longer blood circulation times, less off-target body distribution, and easier site-specific drug release in blood clots are some of the shortcomings of antithrombotic drugs that can be effectively addressed by rational design of nanomedicines. However, despite these significant advantages, inefficient drug loading, premature drug leakage, and biosafety risks related to carrier materials still significantly impede the clinical translation of nanomedicines. Due to off-target distribution and early drug leakage prior to thrombus lesions, conventional nanocarrier encapsulation of thrombolytic drugs falls short of expectations as a solution for effective thrombolysis with low bleeding risk. In addition, the majority of drugs and nanomedicines had short tissue penetration distances and were positioned on the superficial surface of blood clots or ischemia regions, resulting in inadequate therapeutic effects.

The secondary recurrence of thrombus following treatment has significantly increased as a significant obstacle for thrombus therapy. Antithrombotic nanomedicines have therefore not been approved for clinical use. In recent years, nonpharmaceutical techniques like Photothermal Therapy (PT) and mechanotherapy have emerged as promising antithrombotic methods. It is important to note that photothermal photosensitizers can be used for image-guided hyperthermal thrombolysis and effectively encourage the drug's deep penetration into the thrombi. However, PTT alone cannot eliminate thrombuses and is associated with high thrombosis recurrence rates. Micro/nanomotors (MNM)-driven mechanotherapy, which has shown clear advantages in breaking through multiple biological barriers by mechanical motion *in vivo*, has received a lot of attention alongside PTT as an intelligent and controllable nonpharmaceutical modality. Due to their excellent biocompatibility with Nitric Oxide (NO), Oxygen (O₂), and Hydrogen (H₂), gas bubble-driven

nanomotors have sparked a lot of interest in biomedical applications research. Notably, some gases have the potential to act as biological mediators and driving forces within the body.

NO-driven nanomotors are of great interest in the treatment of cerebro-cardiovascular diseases because NO improves endothelial function and reduces oxidative stress, both of which contribute to thrombosis prevention and neuroprotection. However, the clinical application of conventional NO-driven nanomotors was hampered by numerous flaws. The majority of Janus nanomotors with asymmetric nanostructures, on the other hand, are typically easily phagocytized by the Reticuloendothelial System (RES) and eliminated from the body following intravenous injection.

The majority of NO-driven nanomotors, on the other hand, were constructed by embedding NO donors in nanocarriers, which resulted in inefficient fuel loading, NO production, and autonomous motion. The heterogeneity of pathological microenvironments, such as L-arginine, DETANONOate, and S-nitrosothiols (RSNOs), can also have an effect on the motion efficiency of nanomotors made up of endogenous stimuli-activatable NO donors. By meticulously engineering a carrier-free, self-assembled nanomotor with a photothermal photosensitizer and a photothermally activated NO donor, this study proposed a precision nonpharmaceutical modality. In three animal models of thrombotic diseases, it outperformed Lumbrokinase (LBK, a clinical first-line thrombolytic drug) in terms of therapeutic efficacy and safety, as anticipated.

By improving the microvasculature network surrounding the lesions, restoring blood flow to ischemic regions, and increasing cyclic Guanosine Monophosphate (GMP), the NO released from the nano-penetrator contributes to thrombosis recurrence prevention and ischemic stroke relief. Based on the intriguing molecular nanoassembly of a fuel pair, this is the first attempt to construct a carrier-free photothermal nanomotor, according to our knowledge. Gas-driven nanomotors take a conceptual leap forward thanks to this adaptable nano-penetrator.

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