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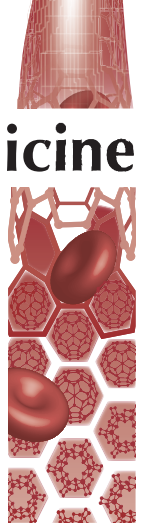
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# Mitochondria-targeted nanomedicines for cardiovascular applications

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“Mitochondria-targeted nanomedicines will enable novel and emerging applications, such as the regulation of mitophagy for mitochondrial quality control, modulation of mitochondrial calcium and the delivery of genetic material such as mitochondrial microRNAs”

**Tweetable abstract:** Mitochondria are increasingly a target for drug delivery in cardiovascular diseases. This editorial describes how a nanomedicine approach may improve drug potency and efficacy in a safe and controlled manner.

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## What do mitochondria do in the cardiovascular system?

The heart must continuously perform work to meet the perfusion demands of all tissues and this requires a great deal of energy in the form of adenosine triphosphate (ATP). For this reason, cardiomyocytes are packed with mitochondria, around 30% by cell volume, collectively capable of generating ~6 kg of ATP per day by oxidative phosphorylation via the electron transport chain (ETC) [1]. A natural by-product of this process is the generation of reactive oxygen species (ROS), which are scavenged by endogenous mitochondrial antioxidants [2]. However, mitochondria are not just cellular ‘powerhouses’, but also contribute to calcium homeostasis, biosynthesis of macromolecules and intracellular signaling [3].

## Why are mitochondria considered a therapeutic target?

Mitochondrial dysfunction is increasingly recognized as a feature of multiple cardiovascular disorders. For example, impaired ATP availability may reflect changes in fuel utilization and energy buffering in the failing heart [1]. Excessive production of ROS can lead to oxidative damage, particularly when endogenous antioxidants are depleted, which contributes to heart failure, but is also implicated in the dysfunction of vascular endothelial cells leading to hypertension and atherosclerosis [4].

Of critical importance, is the role that mitochondria play in determining cell fate, as exemplified by ischemia–reperfusion (I/R) injury following myocardial infarction (MI). During ischemia, the lack of ATP via oxidative phosphorylation leads to energy depletion and ionic dysregulation, thereby changing pH and elevating levels of calcium and succinate. Revascularization results in the oxidation of succinate, which generates a huge burst of ROS via reverse electron transport at complex I [5]. The combination of these conditions is a potent trigger for the formation of the mitochondrial permeability transition pore (mPTP), which dissipates the mitochondrial membrane potential leading to proinflammatory necrotic cell death [5]. Hence, inhibition of complex I during early reperfusion or inhibition of the mPTP are therapeutic targets for I/R injury. The mPTP is also a therapeutic target in heart failure, where elevated ROS and  $\text{Ca}^{2+}$ , along with ATP depletion increase the probability of pore opening. This contributes to the loss of cardiomyocytes, with replacement fibrosis and inflammatory cell activation [6].

### Are there examples of drugs that target mitochondria?

Mitochondria-targeted antioxidants have the potential to reduce ROS and prevent the deleterious effects of oxidative stress. A key example is coenzyme Q10 (CoQ10), a lipid-soluble antioxidant that is an essential cofactor in the ETC and acts to reduce ROS and regenerate other antioxidants [7]. In a double-blind clinical trial, CoQ10 supplementation has been shown to improve symptoms and reduce major adverse cardiovascular events in patients with chronic heart failure [8]. To overcome variable bioavailability, CoQ10 has been linked to the lipophilic cation, triphenylphosphonium (TPP<sup>+</sup>), which promotes uptake across lipid membranes driven by the negative membrane potential, resulting in greatly enhanced cellular, and even higher mitochondrial, accumulation [5]. The resulting mitoquinone compound (MitoQ) has been shown to attenuate the development of high blood pressure and cardiac hypertrophy in hypertensive rats by reducing oxidative stress in vascular endothelial cells [4].

Elamipretide (Bendavia, SS31, MTP-131) is a positively charged synthetic tetra-peptide, which accumulates at the inner mitochondria membrane due to electrostatic and hydrophobic interactions, where it has antioxidant effects and interacts with cardiolipin to improve mitochondrial function [7]. Promising results have been obtained in preclinical studies, for example, reversing mitochondrial dysfunction and improving cardiac function in dogs with heart failure [9]. However, subsequent clinical trials have been equivocal, with elamipretide well tolerated, but showing no benefit after 4 weeks in heart failure patients [10]. Longer duration studies or improved drug delivery may be required.

MitoSNO has been designed as a nitric oxide (NO) donor targeted to the mitochondria by conjugation with TPP<sup>+</sup>. The release of NO upon reperfusion temporarily inhibits complex I and reduces myocardial I/R injury in mice [11]. Cyclosporine A (CsA) inhibits cyclophilin D to prevent mPTP opening and pilot studies observed a small reduction in infarct size when intravenous CsA was given to patients immediately before revascularization [12], however, a recent meta-analysis found no long-term benefits on cardiac function or mortality [13]. It is unclear whether this represents intrinsically poor efficacy in humans or a problem of rapid drug delivery to the inner mitochondrial membrane.

### How can nanoparticles help target mitochondria?

Drug-delivery systems based on nanoparticles (NPs) offer advantages by altering the biodistribution of therapeutic molecules through targeted delivery, controlled release and tuning to the unique molecular properties of diseased tissues. This has the potential to increase drug potency at the site of action, thereby improving efficacy with fewer off-target effects.

Mitochondria-targeted nanomedicines have primarily been exploited for the treatment of cancer, albeit with different intended outcomes for cell survival [14]. The challenges for uptake and targeting are similar, including delivery to hypoxic or poorly perfused tissues. Effective delivery to tumors is aided by the enhanced permeability and retention (EPR) effect, whereby fenestrated blood vessels (i.e., small vessels that are sparsely lined with endothelial cells) are permissive to extravasation thereby overcoming the endothelial barrier [15]. The EPR effect is also present in cardiovascular disease, to varying degrees, most likely with acute injury (e.g., post-MI) and to a lesser extent in chronic heart failure [16]. Active targeting can also be deployed by conjugating NPs with DNA, peptides or antibodies that recognize specific molecular targets [17]. These could recognize markers that are unique or overexpressed in the injured tissue or cell providing disease specificity [16].

Targeting the cardiovascular system with NPs has additional problems to overcome, for example, the high flow rates and shear forces in major arteries minimize contact with the vessel wall thereby limiting uptake. Rational NP design can help overcome this, for example, a neutral surface charge prolongs time in the circulation, while non-spherical geometry optimizes contact with the vessel wall due to a tumbling effect. These properties, in combination with particle size, determine the relative biodistribution in different tissues (reviewed in [15]). The parameters may also be tuned to favor particular conditions within the diseased tissue, for example, by making them pH, temperature or redox-sensitive [16].

For mitochondrial targeting, NPs can, of course, be functionalized using the same techniques as described earlier (TPP<sup>+</sup>, SS31 or fusogenic lipid moieties). For example, MITO-Porter is a liposome-based nanocarrier functionalized with an octa-arginine peptide, which can deliver cargos into the mitochondrial matrix via membrane fusion, including CoQ10 in cultured fibroblasts [18] and is under investigation for mitochondrial gene delivery [17].

Liposomes in particular have been widely studied for drug-delivery purposes owing to their potential for subcellular delivery, controlled release of drugs, excellent biocompatibility and targeting efficacy [17]. Indeed, a number of liposomal NP drugs have been clinically approved by the US FDA including the COVID-19 mRNA

vaccines. Polymeric NPs represent another promising approach, which has good biocompatibility, while offering higher stability and better controlled release than liposomes [17]. For example, polylactic/glycolic acid (PLGA) NPs have been studied as a carrier for CsA, where it was found to be cardioprotective by inhibiting mPTP opening in a murine I/R model *in vivo* [19]. However, the adsorption of plasma proteins onto PLGA is a major drawback since this acts as a flag for removal by phagocytosis [15]. Conjugation with polyethylene glycol (PEG) prolongs circulation time by counteracting this effect, while also improving solubility and protecting from protein degradation. PEG-functionalized PLGA NPs have been reported for the delivery of the ROS scavenger, resveratrol, in a rat model of I/R injury, where it was found to diminish mitochondrial ROS and mPTP opening, resulting in smaller infarct sizes [20].

In conclusion, the use of mitochondrial-targeted nanomedicines for cardiovascular disease remains in its infancy, with most research at the preclinical proof-of-principle stage. The basic toolkit exists, but a great deal of work remains to optimize circulation times and uptake across multiple membranes, while escaping phagocytic and lysosomal capture. For I/R injury, uptake needs to happen extremely rapidly, which represents an additional challenge, while long-term safety and clearance pathways will require special attention for chronic diseases such as heart failure. Progress will depend on multidisciplinary expertise bridging materials science, chemistry, pharmacology and cardiovascular medicine. The prize is a new generation of targeted therapeutics that can potentially rejuvenate borderline therapies by improving efficacy via accumulation at the specific site of injury. Mitochondria-targeted nanomedicines will enable novel and emerging applications, such as the regulation of mitophagy for mitochondrial quality control, modulation of mitochondrial calcium and the delivery of genetic material such as mitochondrial microRNAs [2].

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