Assessment of Metal Organic Framework as Potential Drug Carriers in Cardiovascular Diseases

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Introduction

Cardiovascular diseases (CVDs) are considered the major cause of death worldwide. Therapeutic delivery to the cardiovascular system may play an important role in the successful treatment of a variety of CVDs, including atherosclerosis, ischemic-reperfusion injury, and microvascular diseases. Despite their clinical benefits, current therapeutic drugs are hindered by their short half-life and systemic side effects. This limitation could be overcome using controlled drug release with the potential for targeted drug delivery using a nanomedicine approach. In the current study, we have assessed the use of a highly porous nano-sized preparation of iron-based Metal-organic Framework (MOF) commonly referred to as nanoMIL-89 as potential drug carriers in the cardiovascular system.

Objectives

i. To assess the effect of nanoMIL-89 on the viability and cytotoxicity of human vascular cells and the cellular uptake *in vitro*

ii. To evaluate the organ-system toxicity of nanoMIL-89 *in vivo* using the Zebrafish model.

Methodology

In vitro

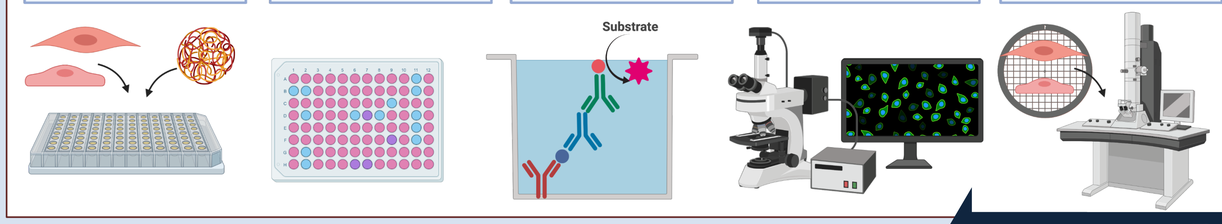
i. PAECs and PASMCs seeding and treatment with nanoMIL-89 (0 – 100 µg/mL)

ii. Viability assay using AlamarBlue and cytotoxicity using LDH assay

iii. Anti-inflammatory effect tested by measuring CXCL8 release using ELISA

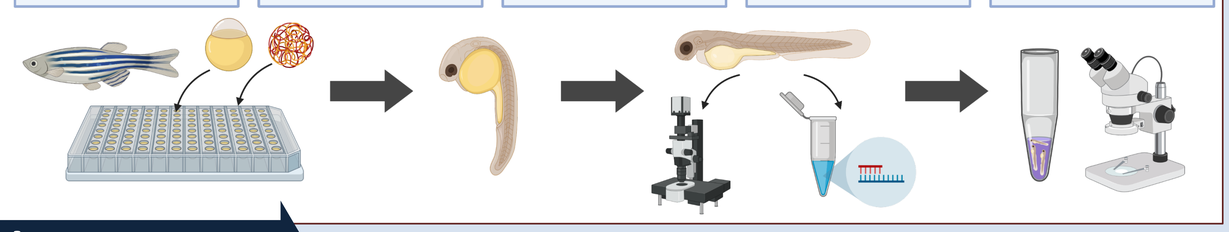
iv. Cellular uptake of nanoMIL-89 using light and confocal microscopes

v. Cellular internalization of MIL-89 using transmission electron microscope and energy dispersive spectroscopy



In vivo

0 hpf	24 hpf	48 hpf	72 hpf	96 hpf
Culturing Zebrafish embryos (AB) and treatment with nanoMIL-89 (0-300µM)	Viability and tail-flicking assessments	Viability and hatching rate	Heart and blood flow analysis + viability and hatching rate	Locomotion assessment and Prussian blue staining



Results

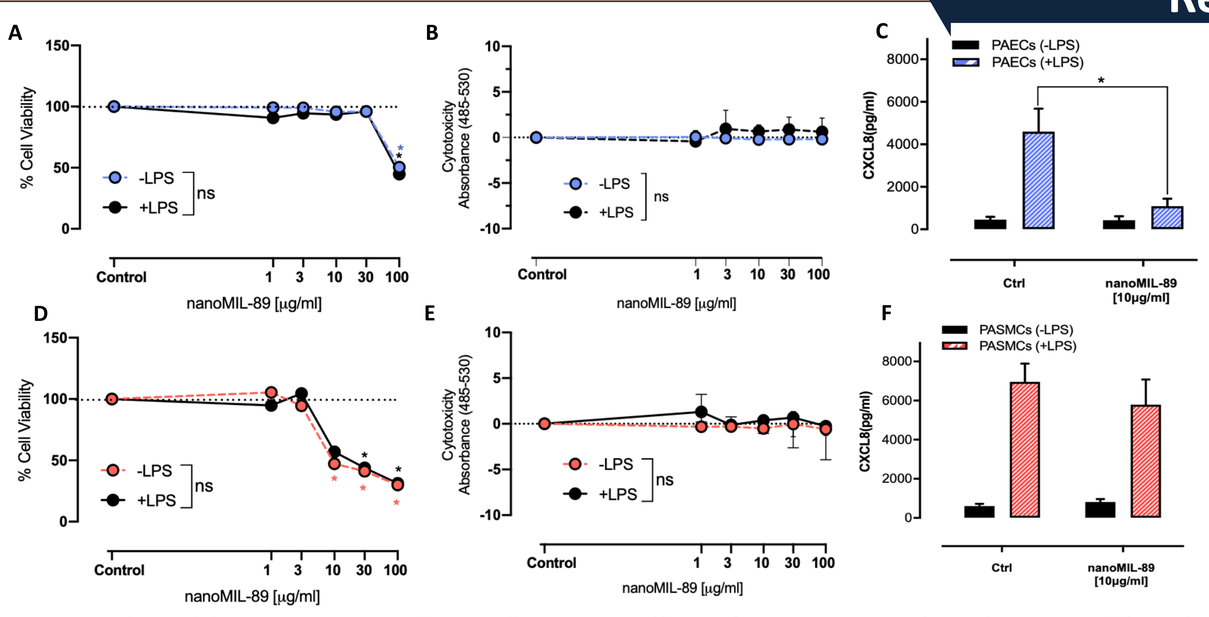


Figure 1. The viability, cytotoxicity and anti-inflammatory effects of nanoMIL-89 on **(A,B,C)** PAECs and **(E,D,F)** PASMCs using AlamarBlue® ,LDH and ELISA. Data are mean ± SEM; n=3. (*p<0.05).

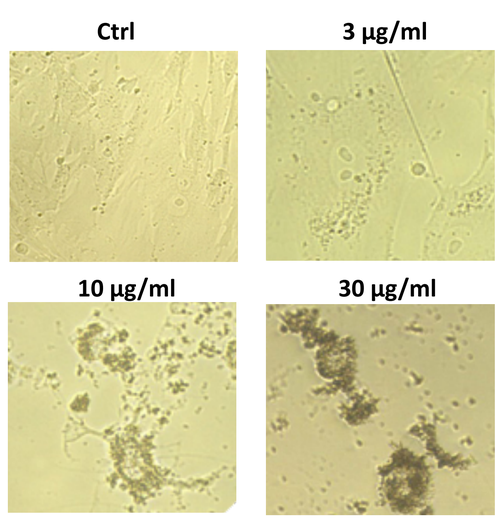


Figure 2. Light microscope images (20X) showing the cellular uptake of nanoMIL-89 by PASMCs at 72 hours post treatment.

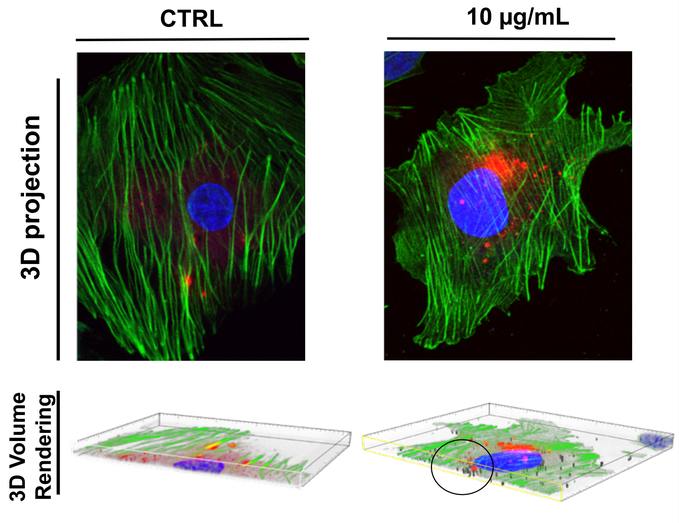


Figure 3. Z-stacked confocal images of PAECs (ctrl), **(B)** PAECs treated with 10µg/mL of nanoMIL-89 indicate the cellular up take of nanoMIL-89 in the cytoplasm. Channels used: Green; cytoskeleton, Red; cytoplasm, Blue; nucleus.

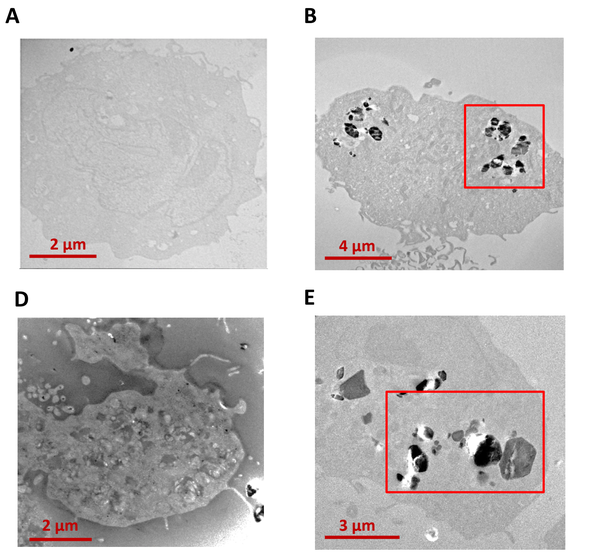


Figure 4. Scanning Transmission electron microscope images of (A,D) untreated PAECs and PASMCs sections. (B,E)PAECs and PASMCs treated with 5µg/mL nanoMIL-89 show the cellular internalization of nanoparticles. (C,F) Energy dispersive spectroscopy elemental mapping showing iron distribution of nanoMIL-89 in both cell types.

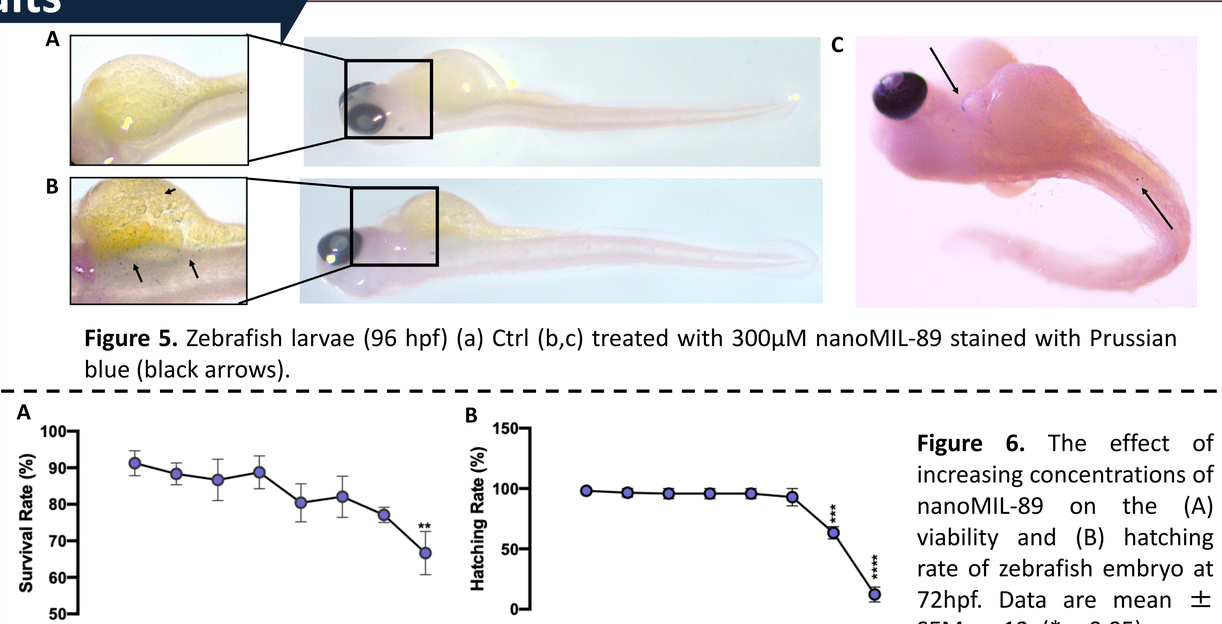


Figure 5. Zebrafish larvae (96 hpf) (a) Ctrl (b,c) treated with 300µM nanoMIL-89 stained with Prussian blue (black arrows).

Figure 6. The effect of increasing concentrations of nanoMIL-89 on the (A) viability and (B) hatching rate of zebrafish embryo at 72hpf. Data are mean ± SEM; n=12. (*p<0.05).

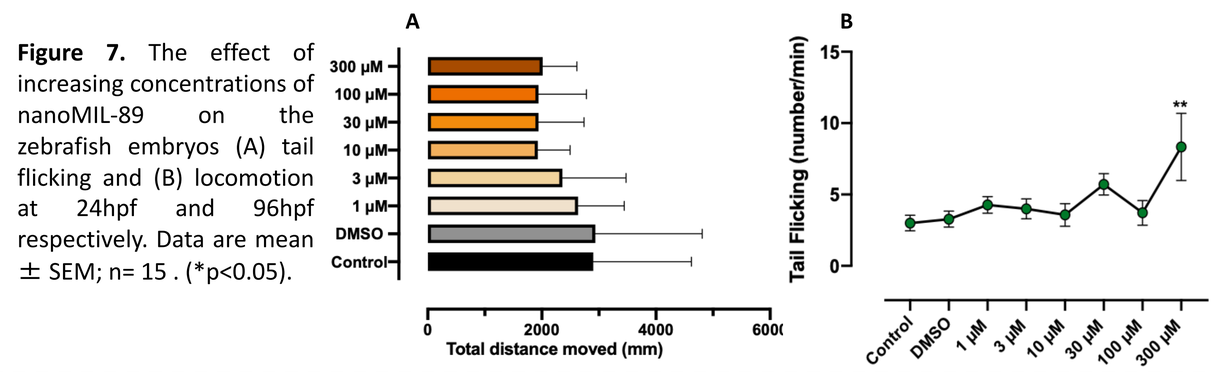


Figure 7. The effect of increasing concentrations of nanoMIL-89 on the zebrafish embryos (A) tail flicking and (B) locomotion at 24hpf and 96hpf respectively. Data are mean ± SEM; n= 15 . (*p<0.05).

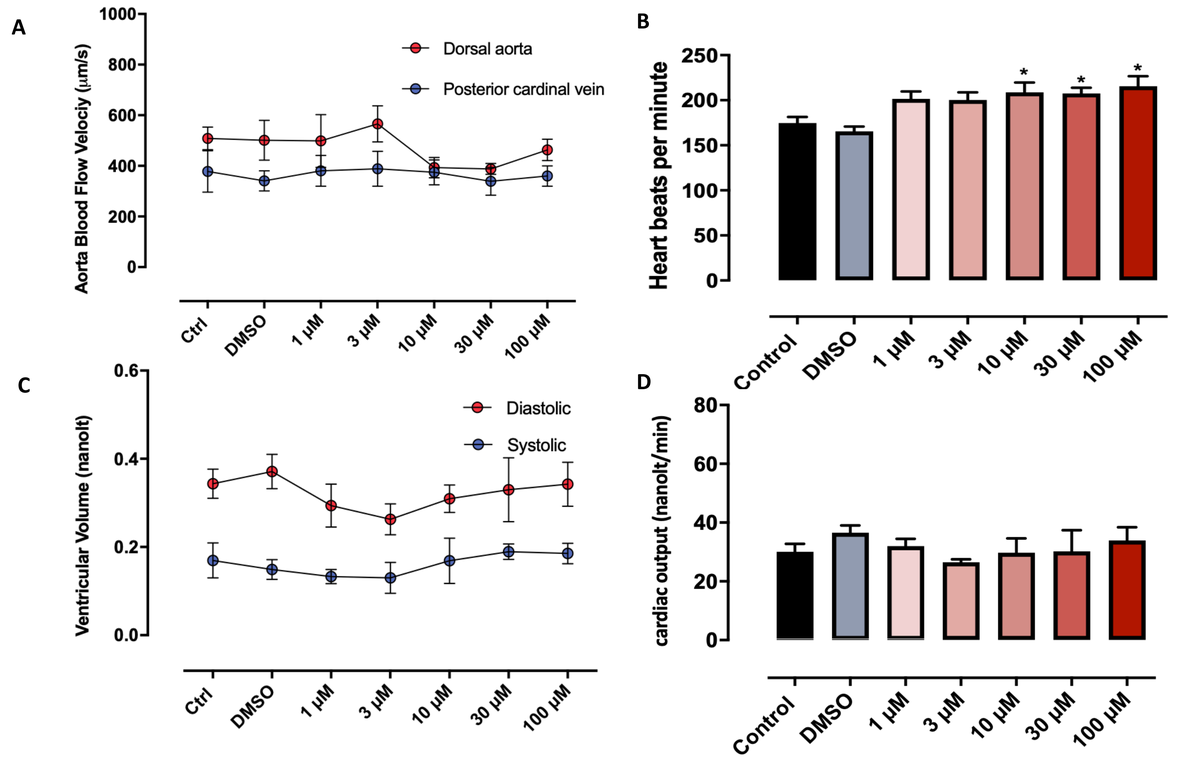


Figure 7. The effect of increasing concentrations of nanoMIL-89 on zebrafish embryos (A) blood flow, (B) heartbeats (C) ventricular volume and (D) cardiac output at 72hpf. Data are mean ± SEM; n=4-6. (*p<0.05).

Conclusion

- nanoMIL-89 have no toxic effects on PAECs and PASMCs.
- nanoMIL-89 have anti-inflammatory effects as it significantly decreased the release of CXCL8 from PAECs and PASMCs.
- Confocal and TEM images showed high cellular uptake of nanoMIL-89 in PAECs and PASMCs.
- At concentrations ≤30µM, nanoMIL-89 are relatively safe with no significant toxicity effect on Zebrafish embryos development.
- High concentrations (>100µM) of nanoMIL-89 were observed to delay zebrafish hatching, increase their tail flicking activity at (24hpf) and may cause heart deformation which is currently under investigation using cardiotoxicity markers.
- nanoMIL-89 is a promising nanoparticle prototype for drug delivery in the cardiovascular system. Further investigations of MOFs, including diseased models and drug- loaded formulation is required.

Acknowledgment

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