Acoustically-stimulated drug carriers for targeted drug release and bone fracture repair

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INTRODUCTION

- Impaired fracture healing has a crippling effect physically, mentally and financially for healthcare systems.
- Systemic application of treatments such as osteoinductive molecules (eg 6-bromoindirubin-3'-oxime (BIO)), has been limited by pharmacokinetic issues, side effects and costs. We aim to overcome these limitations by developing a targeted drug delivery system using acoustically-stimulated, nanodroplets (NDs) with a phase-transitioning liquid perfluorocarbon (PFC) core, which vaporise into microbubbles (MBs) upon ultrasound (US) stimulation. Acoustically stimulated NDs combine the benefit of a nanoscale vehicle, with the biological effects of cavitating MBs, enhancing drug delivery, release and uptake.

HYPOTHESIS

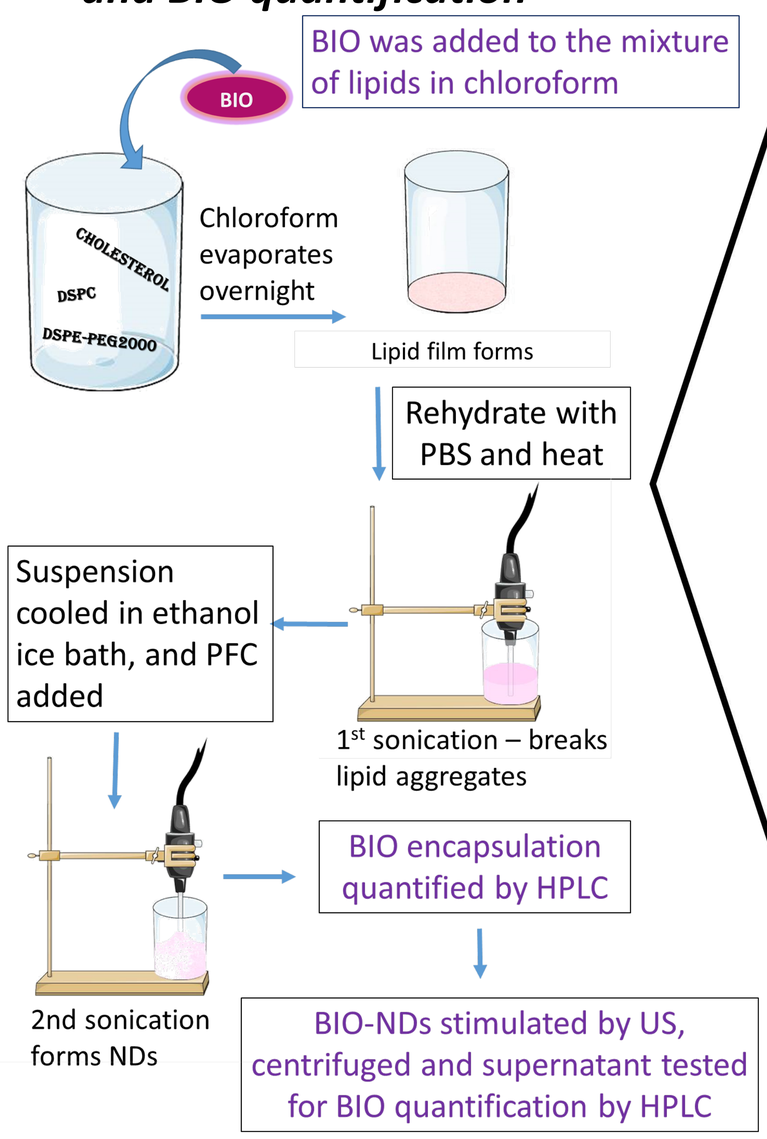
i) ND preparations are non-toxic to human bone marrow stromal cells (BMSCs)

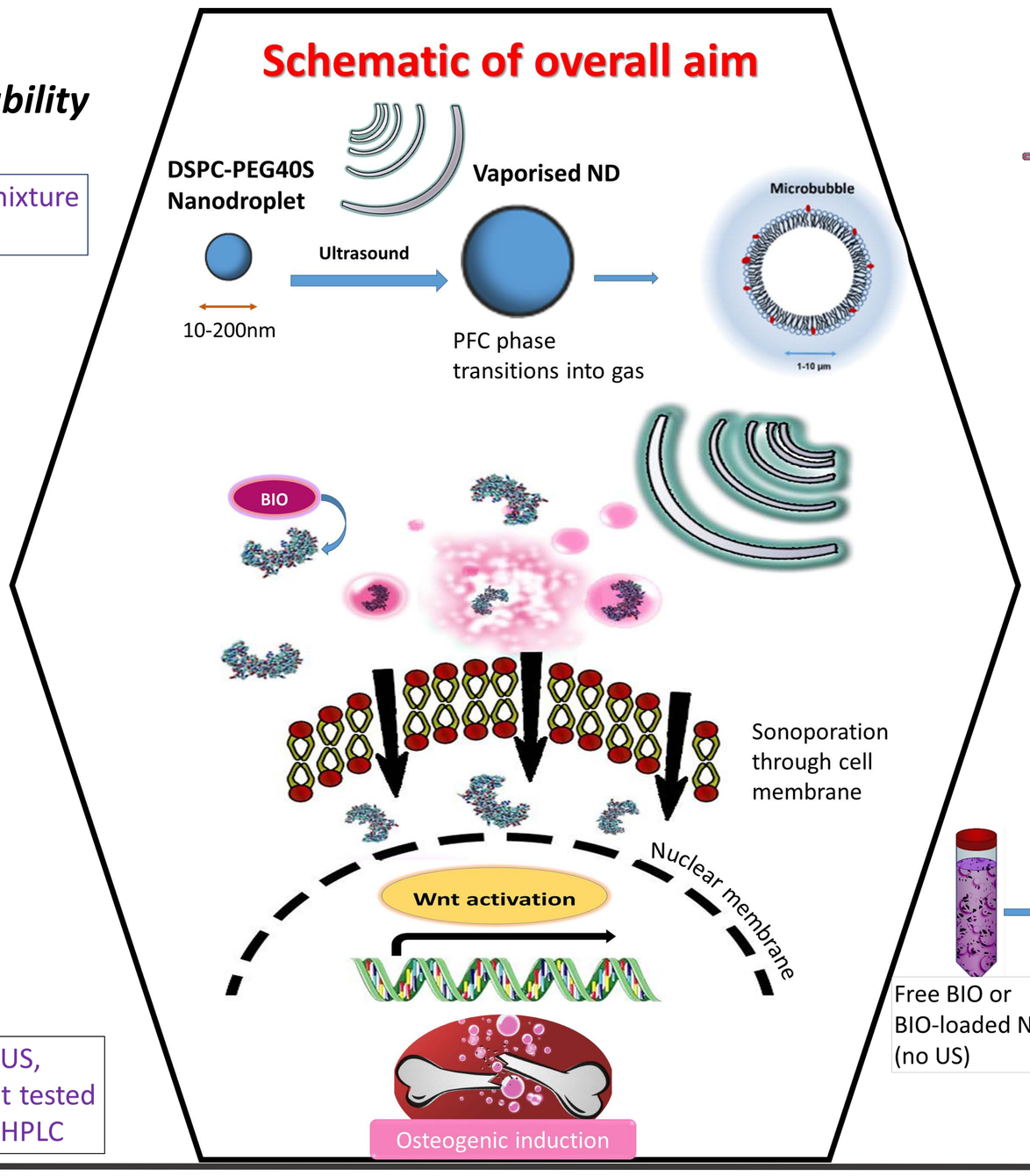
ii) They encapsulate BIO osteogenic agent efficiently and release BIO upon US stimulation

iii) BIO loaded NDs can induce Wnt expression associated with osteogenic differentiation

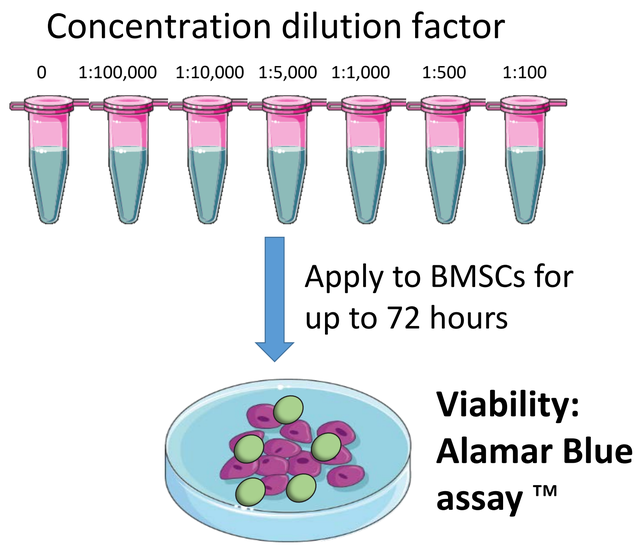
METHODS

i) Nanodroplet fabrication, stability and BIO quantification

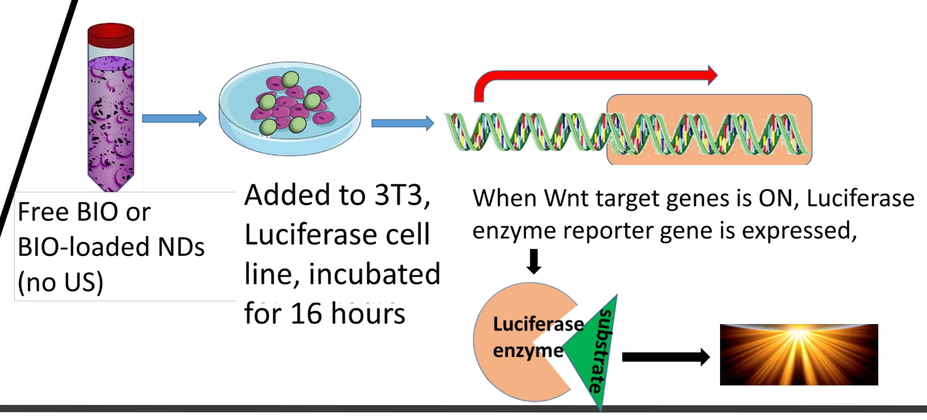




ii) Cytotoxicity assay

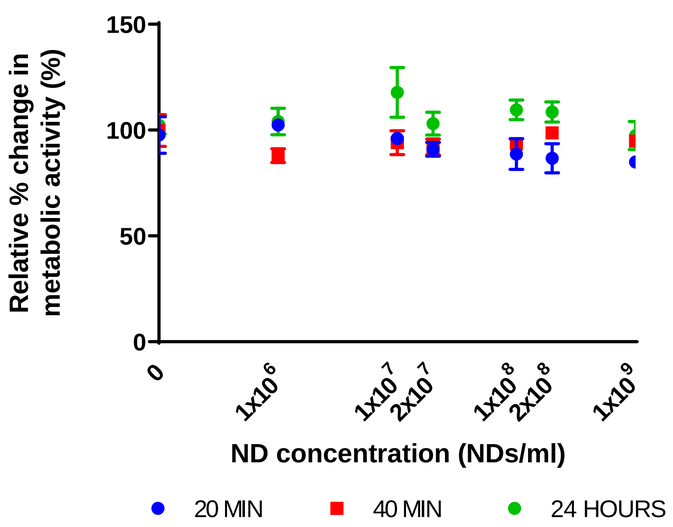


iv) Luciferase assay – Wnt activation without US



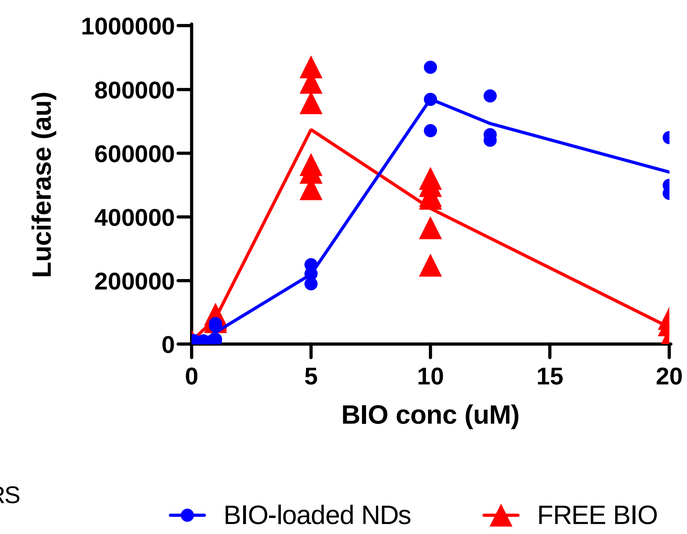
RESULTS & DISCUSSION

Cytotoxicity



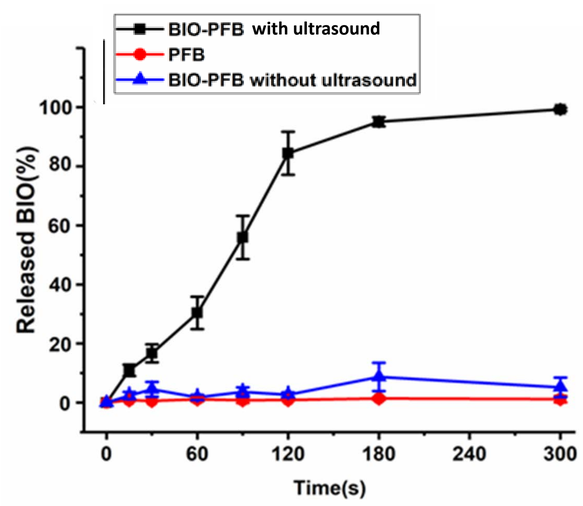
- No safety concerns when NDs were incubated with BMSCs for up to 24h

Bioactivity assay

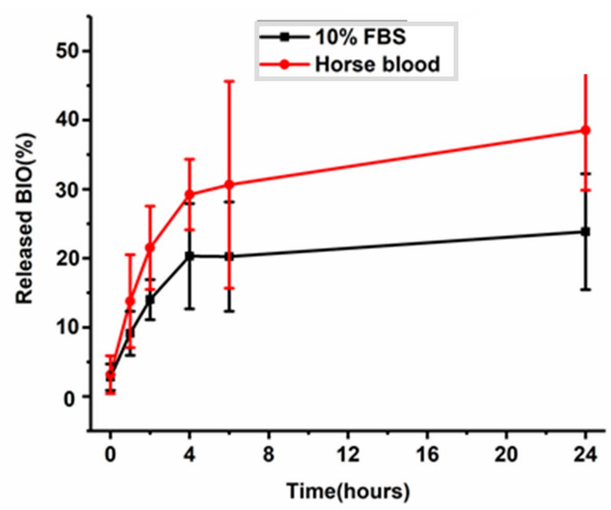


- Free BIO peak activity = 5 μM
- BIO-NDs, induce 70% less activity at 5 μM

BIO release and encapsulation stability



- BIO loaded NDs in PBS (37 °C) remain stable with no release
- US activation causes 100% BIO release



- BIO loaded NDs in FBS (37 °C) release 20% of BIO within 4h
- BIO loaded NDs in horse blood (37 °C) release 30% of BIO within 4h

CONCLUSION

- These experiments indicated that NDs are a safe vehicle which encapsulate BIO in a stable manner and release 100% of their load upon US activation.
- BIO can stimulate Wnt signalling pathways , involved in osteogenic differentiation and NDs retain 70% of BIO activity in vitro.
- Therefore BIO-loaded NDs have shown potential for use a targeted drug delivery vehicle.

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