DOXORUBICIN-LOADED NANOPARTICLE BONE CEMENT FOR THE TREATMENT OF METASTATIC SPINE DISEASE

Ateeque Siddique, Mina Aziz, Michael H. Weber, Derek H. Rosenzweig
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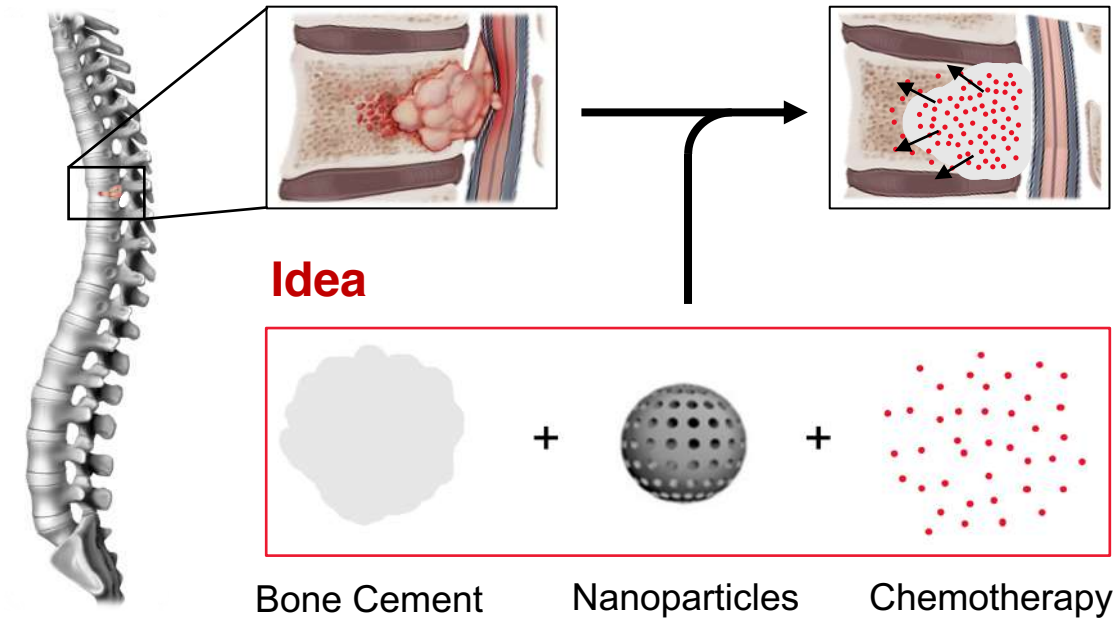
Introduction

The treatment of spinal metastases involves surgical resection followed by reconstruction with bone cement, however, tumor cells can remain hidden and therefore drive recurrence.

Can the standard bone cement be improved by loading it with chemotherapeutics (e.g., doxorubicin) for a sustained local drug release at the surgical site?
Can this cement inhibit tumor growth and prevent recurrence?

By loading mesoporous silica nanoparticles (MSNs) with doxorubicin (DOX) and mixing them into bone cement, a sustained drug release profile is achieved. We show that the augmented cement inhibits breast cancer cell activity in both 2D and 3D cell culture and inhibits cell migration.



C S B 2021 virtual
May 13-15, 2021

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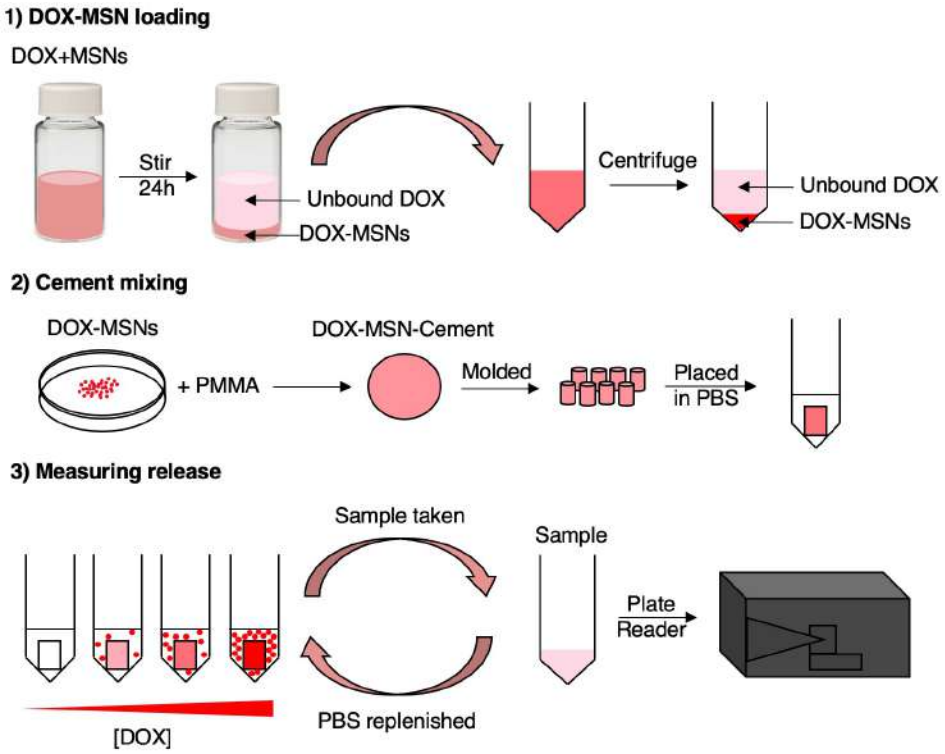
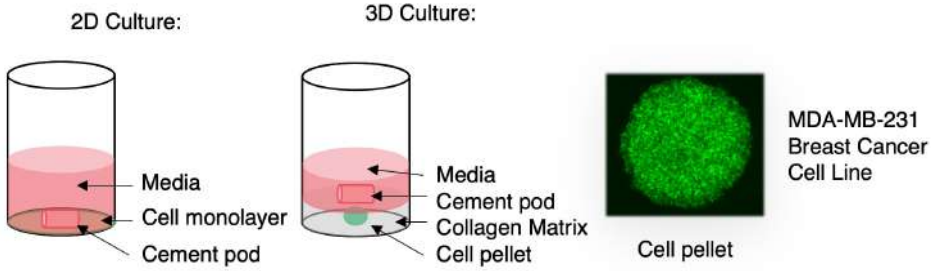
Methods

Nanoparticles were loaded by stirring with concentrated solution of DOX for 24h. The nanoparticles were separated from the unbound DOX by centrifugation and were dried in a 37ºC oven for 24h.

To mix the nanoparticles into bone cement, they were crushed into a fine powder and mixed into the bone cement power. The liquid component of the cement was then added to activate the reaction, and the cement was extruded through a syringe and molded into cylindrical pods.

The cement pods were placed in phosphate-buffered saline (PBS) to measure drug release. At various timepoints, a quantity of PBS was removed to quantify the concentration of DOX using a TECAN plate reader (DOX is auto-fluorescent). The volume of PBS was replenished with fresh PBS.





The *in vitro* efficacy of the DOX-nanoparticle cement was evaluated in both 2D (monolayer) and 3D (pellet) cell culture, where the cement pods were incubated with MDA-MB-231 breast cancer cells for 4-7 days. AlamarBlue assays were done to quantify cell activity. Cell migration was assessed in the 3D culture model by determining the outgrowth area of cells migrating into the collagen matrix. ImageJ software was used for area quantification.

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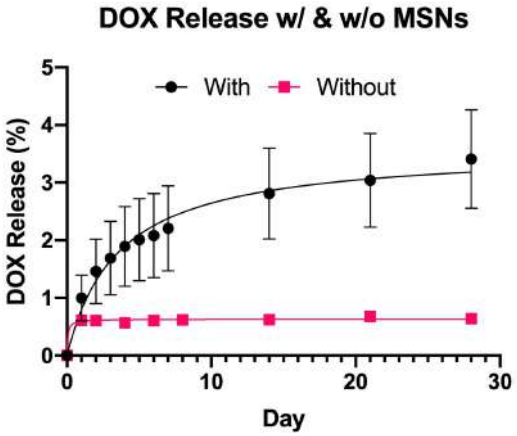
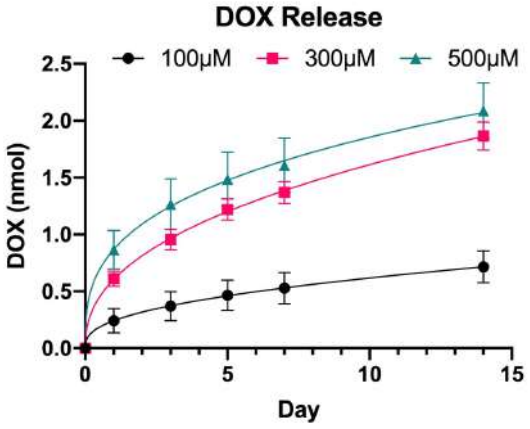
Results

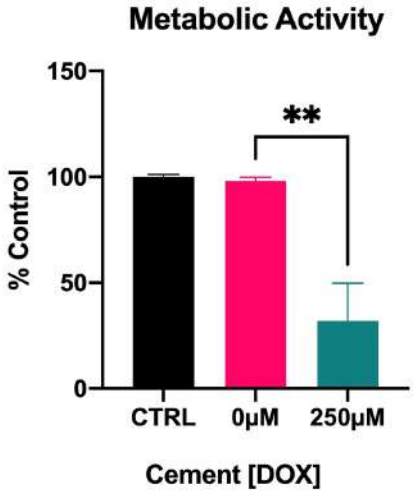
When DOX is mixed into cement without MSNs, the release is limited. When DOX is loaded into MSNs and then mixed into cement, the release is not only gradual, but more of the DOX can diffuse out of the cement.



The release of DOX from MSN-cement can be modified by loading the MSNs with different concentrations of DOX. The drug can diffuse out out of the cement for at least a 14-day period.

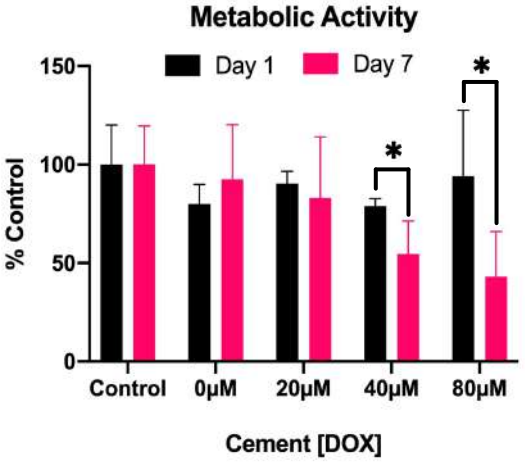


2D:



When the DOX-MSN-cement was incubated with MDA-MB-231 breast cancer cells for 4 days, the cells showed a significant reduction in metabolic activity compared to control ($p < 0.005$).
CTRL = no cement.
0μM = control MSN-cement.
250μM DOX = DOX-MSN-cement.

3D:



DOX-MSN-cement with MSNs loaded with 40μM and 80μM of DOX was effective at inhibiting MDA-MB-231 cell pellet activity at day 7 compared to both the respective day 1 activity and to the control at day 7 ($p < 0.05$).

n = 3
Error bars = SD
* $p < 0.05$
** $p < 0.005$

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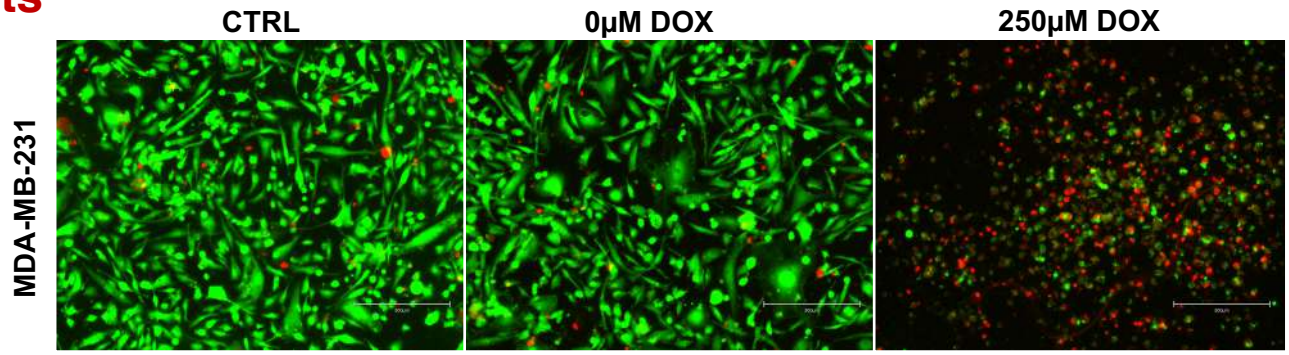
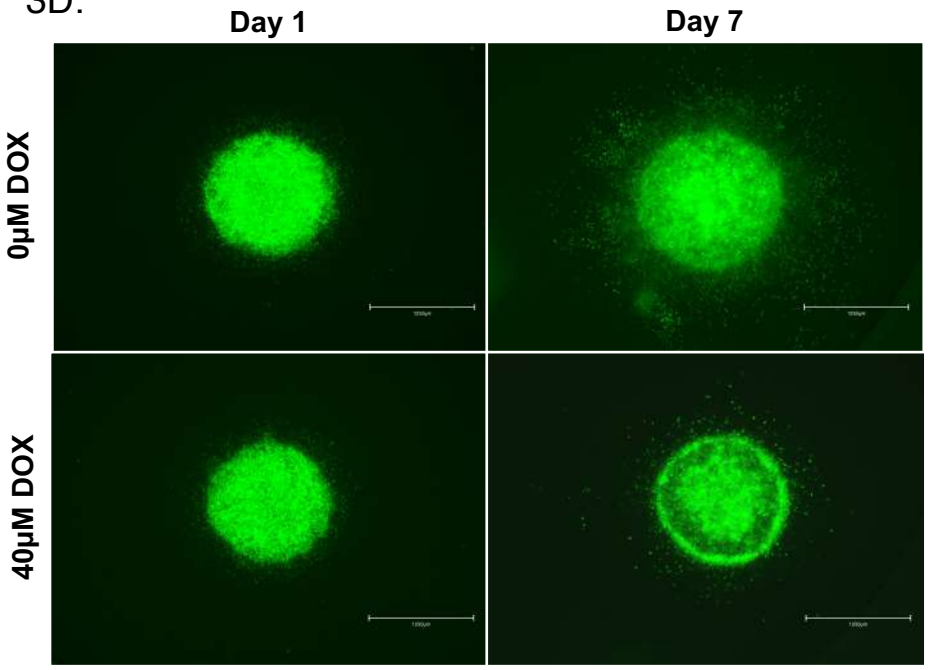
Results

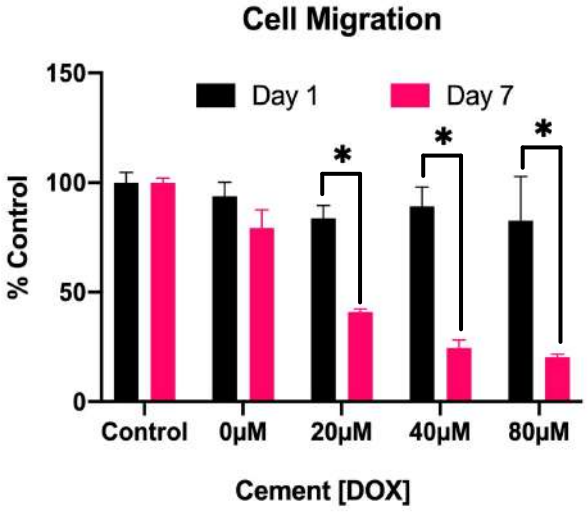
2D:



Live/Dead imaging of MDA-MB-231 cells treated with DOX-MSN-cement for 4 days. CTRL = no cement. 0μM DOX = MSN-cement. 250μM DOX = DOX-MSN-cement.

3D:





n = 3
Error bars = SD
* $p < 0.05$

The 3D MDA-MB-231 cell pellets treated with DOX-MSN-cement showed a significant reduction in cell migration into the collagen matrix at day 7 compared to day 1 of treatment ($p < 0.05$).

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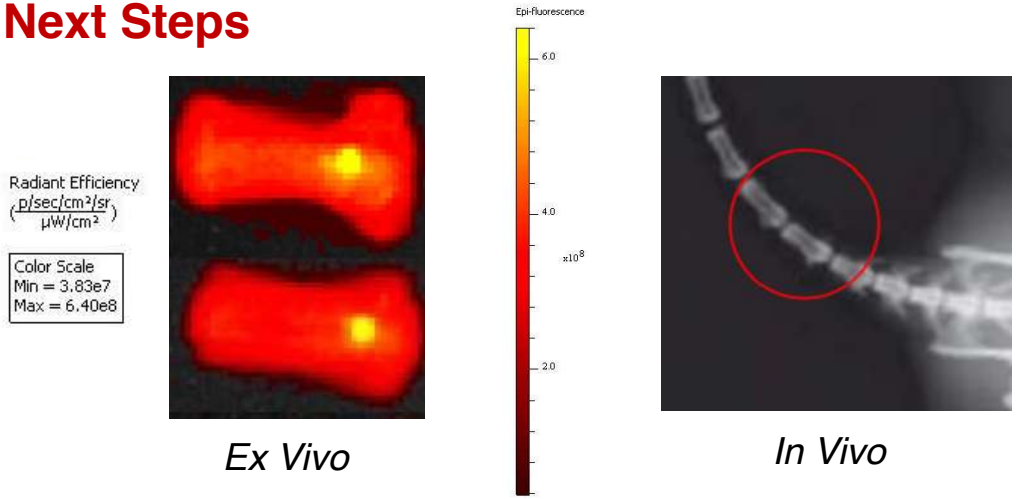
Conclusions

1. Nanoparticles allow for a sustained drug release profile from PMMA bone cement.
2. Drug release profile can be modified by loading different amounts of the drug.
3. DOX-loaded MSN cement is effective at inhibiting breast cancer cell activity *in vitro* in both 2D and 3D cell culture.
4. DOX-loaded MSN cement is effective at inhibiting breast cancer cell migration *in vitro*.

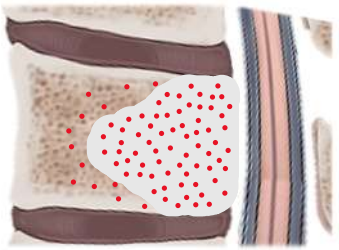
Next Steps



Ex Vivo *In Vivo*

The next steps of this project aim to move towards testing the efficacy of this augment DOX-MSN-cement in *ex vivo* bone and *in vivo* metastasis models.

Goal



Human patients

This project's aim is to develop an improve bone cement to prevent cancer recurrence and improve overall patient quality of life. As cancer therapies improve and patients live longer, it is important to develop such treatments to prevent recurrence and reduce the pain and disability associated with spinal metastases.