Microfluidic Platform for Investigation of Mechanoregulation of Breast Cancer Bone Metastasis

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INTRODUCTION

Breast Cancer Bone Metastasis

Approximately 70% of advanced breast cancer patients experience bone metastasis (1). Bone is a dynamic organ that is constantly degraded by osteoclasts and built by osteoblasts. **Metastasized breast cancer cells (BCCs) reduce bone quality** by upregulating normal osteoclast activity and disrupting the normal bone remodeling process (Figure 1).

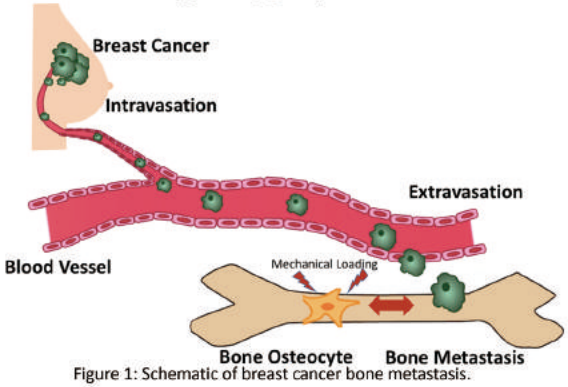

Figure 1: Schematic of breast cancer bone metastasis.

Bone Osteocyte

Osteocytes are the **mechanosensory bone cells** that sense the shear stress generated by oscillatory interstitial fluid flow due to physical activities. Mechanically stimulated osteocytes signal to other bone cells, more specifically downregulate osteoclasts' bone resorption. Therefore, **exercise, a common cancer intervention strategy**, can regulate bone remodeling, and thus potentially affect BCC metastasis to bone through mechanotransduction of osteocytes.

Microfluidic Platform

Our recent *in vitro* studies showed that mechanically stimulated osteocytes can regulate BCC migration and modify endothelial cells (2). However, a more physiologically relevant platform with **3D culturing environment, real-time cell signalling and direct stimulatory flow** is needed.

OBJECTIVES

1. **To develop a microfluidic model for studying mechanoregulation of breast cancer bone metastasis.**
2. **To determine the effects of physiologically-relevant mechanical loading on osteocytes' regulation of breast cancer bone metastasis.**

ACKNOWLEDGEMENT

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MICROFLUIDIC PLATFORM DESIGN

Highly metastatic MDA-MB-231 human BCCs were cultured inside a cylindrical lumen lined with human umbilical vein endothelial cells (HUVECs) (3), which is adjacent to a population of either static or mechanically-stimulated osteocyte-like MLO-Y4 cells (Figure 2). A customized pump was used to produce physiologically relevant oscillatory fluid flow (1 Pa, 1 Hz) (4). Soluble factors were diffused through hydrogel-filled side channels to instigate intercellular communication between MLO-Y4 cells and BCCs over 3 days.

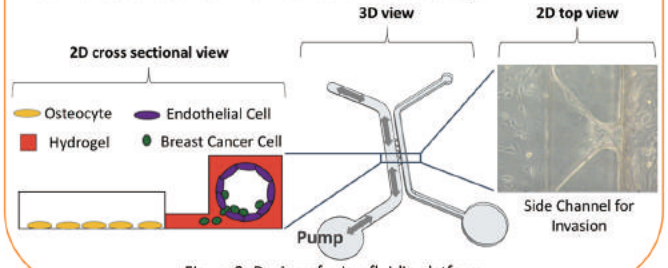
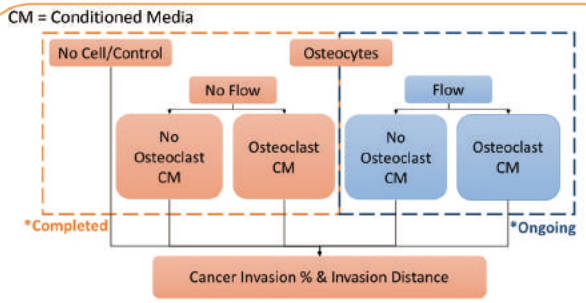


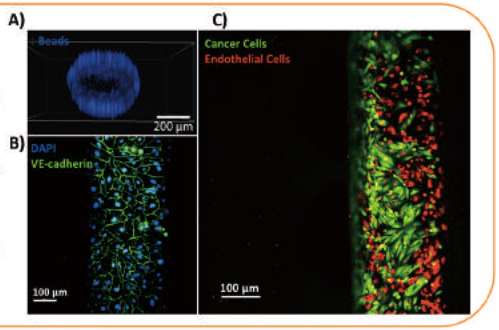
Figure 2: Design of microfluidic platform.

EXPERIMENTAL CONDITION



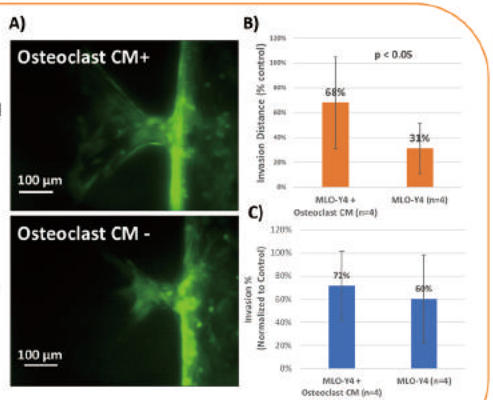
ARRESTED CANCER LUMEN ESTABLISHMENT

Figure 3: Lumen formation. A)Hydrogel lumen formation validated with fluorescent beads, B)HUVEC inside hydrogel lumen, C)Arrested MDA-MB-231 in HUVEC lumen.



RESULT FROM STATIC EXPERIMENT

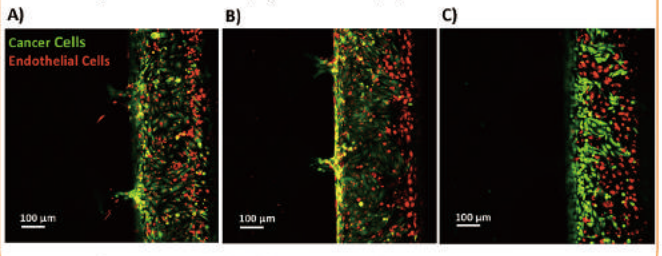
Figure 4: MDA-MB-231 transendothelial invasion towards static MLO-Y4 with or without osteoclast CM. A)MDA-MB-231 stained with CellTracker green, B)Invasion distance, C)Invasion percentage.



➢ **Breast cancer cells invaded further toward osteocytes with osteoclast CM**

PRELIMINARY RESULT FROM FLOW EXPERIMENT

Figure 5: MDA-MB-231 transendothelial invasion towards static or flow stimulated MLO-Y4. A)Control with no cell, B)Static MLO-Y4, C)Flow stimulated MLO-Y4.



➢ **Mechanically loaded osteocytes decreased breast cancer transendothelial invasion**

CONCLUSION AND FUTURE STEPS

✓**Enabled real-time signaling between different cell populations**
✓**Integrated physiological relevant oscillatory flow**
✓**Provided a new platform**

❑ **Elucidate the effects of bone mechanical loading on breast cancer bone metastasis**
❑ **Determine the key mechanisms involved in osteocyte regulation**

REFERENCES

(1) Hagberg. Cancer Epidemiology. 2013. (2) Ma. J. Cell Biochem. 2018. (3) Bischel. Biomaterials. 2013. (4) Middleton. ORS 2017 Annual Meeting.