ASBMR 2022 ANNUAL MEETING
ASBMR The American Society for Bone and Mineral Research
SEPTEMBER 9-12, 2022
AUSTIN, TX, UNITED STATES
+ONLINE EXPERIENCE

Evaluating the Efficacy of an Acidic Oligopeptide-Radioisotope Chelator Conjugate to Target and Deliver Radioactive Agents to Bone Cancers

L. JUNG[1] and P. LOW[1, 2]
1 Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette, IN
2 Department of Chemistry, Purdue University, West Lafayette, IN

PURDUE UNIVERSITY
PURDUE INSTITUTE FOR DRUG DISCOVERY

INTRODUCTION

In United States, 20~30% of breast cancer and prostate cancer patients are diagnosed with bone metastases, and the likelihood of bone metastases development increases up to 80% in metastatic tumors (1, 2, 4). The five-year survival rate for both types of bone metastases is less than 20~30%, and this disease is still considered as incurable (1, 2). Therefore, there is an urgent need to develop a bone-targeted radiotherapy to improve the poor prognosis.

HYPOTHESIS

When cancer cells metastasize to a bone, they disrupt bone homeostasis, and in this process, hydroxyapatites, calcium phosphate crystals that structure bones, become exposed to blood vessels and can be targeted (3, 4). **In this project, we hypothesize that an oligoaspartic acid can target and deliver imaging and therapeutic agents to hydroxyapatites exposed in breast and prostate tumor bearing bones.**

METHOD

To validate the hypothesis, subjects were first challenged with breast or prostate cancer in their legs. After confirming tumor growth and bone lesion development, mice were injected with oligoaspartic acid-fluorescent dye conjugate and were imaged to visualize the biodistribution of the conjugates. Once diseased-bone localization of the targeting moiety was confirmed, mice were injected with oligoaspartic acid-radioactive agent conjugate and were imaged at different timepoints to 1. confirm tumor-bearing bone localization and 2. assess any off-site localization. **(Figure 1)**

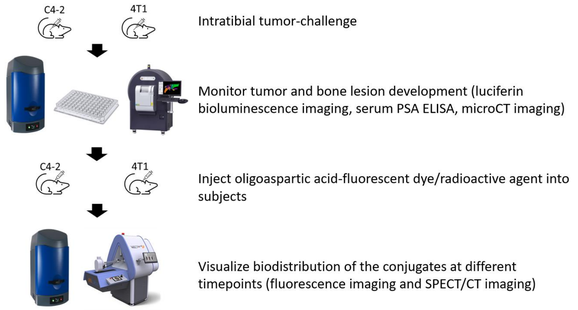

Figure 1.

RESULTS

Oligoaspartic acid-fluorescence dye conjugate localization to bone lesions

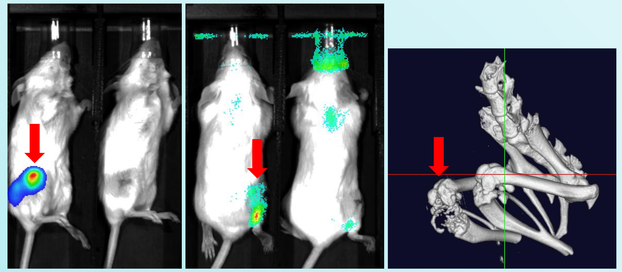

Figure 2 (left). Luciferin bioluminescence image of 4T1 tumor bearing (left; red arrow) and non-tumor bearing (right) mice.
Figure 3 (middle). Fluorescence image of 4T1 tumor bearing (left; red arrow) and non-tumor bearing (right) mice.
Figure 4 (right). MicroCT image of 4T1 tumor (red arrow) bearing mouse.

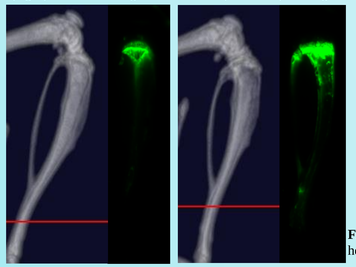

Figure 5. MicroCT image and fluorescence image of healthy (left) and C4-2 tumor bearing (right) mouse.

Comparison between healthy tibia and tumor bearing tibia have demonstrated that our bone-targeted imaging agent can target and deliver imaging agents to both osteolytic and osteoblastic lesions induced by 4T1 or C4-2 cells, respectively. In both cancer models, minimal offsite localization to healthy tissue was noted, and no obvious toxicity was identified.

Oligoaspartic-radioisotope chelator conjugate localization to bone lesions

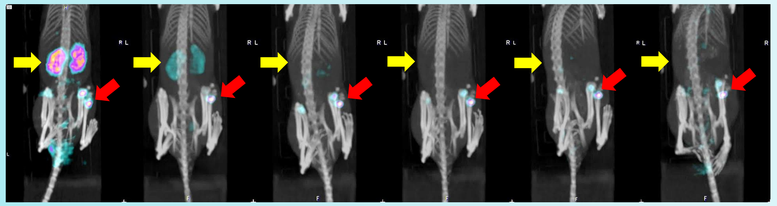

Figure 6. SPECT/CT images of a 4T1 tibial tumor bearing mouse injected with low dosage of oligoaspartic acid-Lu177 chelated agent conjugate. From left and right, images were obtained at 3 hrs, 24 hrs, 72 hrs, 96 hrs, 120 hrs, and 168 hrs post radiotherapeutic agent injection. Yellow arrow indicates kidneys and red arrow indicates tumor bearing tibia.

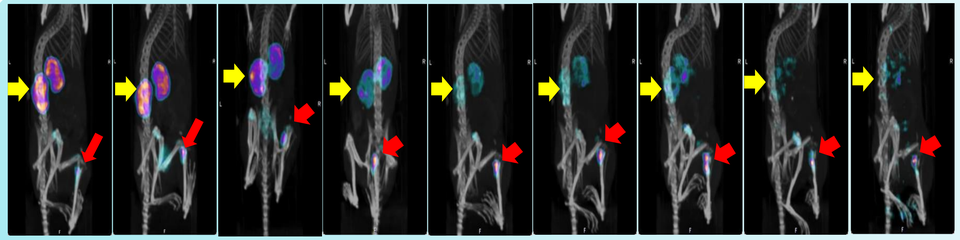

Figure 7. SPECT/CT images of a 4T1 tibial tumor bearing mouse injected with high dosage of oligoaspartic acid-Lu177 chelated agent conjugate. From left to right, images were obtained at 2 hrs, 12 hrs, 24 hrs, 48 hrs, 72 hrs, 96 hrs, 144 hrs, 196 hrs, and 240 hrs post radiotherapeutic agent injection. Yellow arrow indicates kidneys and red arrow indicates tumor bearing tibia.

SPECT/CT scans have revealed that radioactive conjugates do localize specifically to tumor bearing tibias and were retained in the diseased bone even at 2 weeks post-injection. Renal excretion was rapid in both dosages: in low dosage, majority were excreted within 24 hours and in high dosage, most were excreted within 48 to 72 hours. Offsite concentration at other healthy tissue was minimal, and no body weight reduction associated with the radioactive conjugate was observed.

CONCLUSIONS

In conclusion, we have confirmed that our targeting moiety can localize to hydroxyapatites exposed in both osteolytic and osteoblastic lesions and can selectively deliver both fluorescent dye and radioisotope-chelated agents without obvious offsite localization. High tumor-bearing bone specificity, minimal offsite localization, rapid renal excretion, and long bone retention all emphasize that the radioactive oligoaspartic acid conjugate has potential to be a potent radio-therapy against bone cancers.

Currently we are assessing therapeutic potency of the radioactive oligoaspartic acid conjugates in both breast and prostate cancer growth in bones in murine models.

REFERENCES

1. Marazzi, F. et al. “Diagnosis and Treatment of Bone Metastases in Breast Cancer: Local Approach and Systemic Therapy in a Guide for Clinicians.” *Cancers*. 2020, 12: 2390.
2. Hernandez, R. et al. “Incidence of bone metastases in patients with solid tumors: analysis of oncology electronic medical records in the United States.” *BMC Cancer*. 2018, 18:44.
3. Stapleton, M. et al. “Development of Bone Targeting Drugs.” *Int. J. Mol. Sci.* 2017, 18: 1345.
4. Vinay, R. and KusumDevi, V. “Potential of Targeted Drug Delivery System for the Treatment of Bone Metastasis.” *Drug Deliv*. 2016, 23: 21-29.

ACKNOWLEDGEMENTS

We thank the Purdue Imaging Facility for assistance with data collection. We also thank Quince Therapeutics for funding the research.

QUINCE THERAPEUTICS

CONTACT INFORMATION

Losha Dasol Jung—jung280@purdue.edu 3342246330
Philip Low—plow@purdue.edu