Okayama University Medical Research Updates （OU-MRU） 2021.08 Vol.93

Source: Okayama University (JAPAN), Public Relations Division

For immediate release: 3 August 2021

Okayama University research: Repurposing cancer drugs: An innovative therapeutic strategy to fight bone cancer.

(Okayama, 3 August) **In a study reported in the journal *Molecular Cancer Therapeutics*, researchers from Okayama University describe the effects of pexidartinib, a drug targeting macrophages infiltrating into a tumor, for bone and soft-tissue malignancies.**

Sarcoma is a rare form of cancer that often originates within bones and then spreads to other organs. A distinct feature of cancer and sarcoma is the presence of tumor-associated macrophages (TAMs). These are usually healthy blood cells which have been converted by cancer cells to turn against the body and help their perpetrators spread. Now, in a collaboration between Okayama University and the Memorial Sloan Kettering Cancer Center, a research team has shown that PLX3397 (pexidartinib), a drug that can inhibit the formation of TAMs, is effective in mitigating the spread of sarcoma.

Colony stimulating factor 1 (CSF-1) is a cytokine secreted by cancer cells which oversees the creation of TAMs. PLX3397 is known to effectively inhibit CSF-1/CSF-1 receptor (CSF-1R) on TAMs. Now, in this study the researchers investigated whether this ability of PLX3397 could be leveraged in sarcoma too.

Sarcoma cells were first analyzed to confirm that they secreted CSF-1. Next, blood cells were extracted from mice and grown in the same environment as these sarcoma cells. Subsequently, the blood cells started proliferating faster and showing TAM-like tendencies. When the genetic makeup of these nascent TAMs was assessed, the team found showed that they had transformed into M2-like macrophages, a subtype that indeed promotes tumor growth. The mixture of cells was then treated with varying doses of PLX3397 to find that the drug curbed the transformation, growth, and movement of TAMs.

Next, the effects of PLX3397 in a mouse model of bone cancer were examined. Sarcoma cells were transplanted into the tibial bones of mice and monitored for a few weeks. By the end of 3 weeks, the cancer had grown and spread into the lungs of these mice. However, mice who had been treated with high doses of PLX3397 not only showed smaller tumors within their bones, but also displayed no signs of cancer within their lungs. Lastly, the team extracted tumor tissues from these mice to study the cancer cells closely. It was found that PLX3397 also increased the presence of cancer-fighting immune cells, CD8 T cells, within these tumors. PLX3397 thus showed an effective inhibition of sarcoma in cellular and animal models.

“Our preclinical results show that PLX3397 has strong macrophage- and T cell-modulating effects that may translate into cancer immunotherapy for bone and soft tissue sarcomas,”

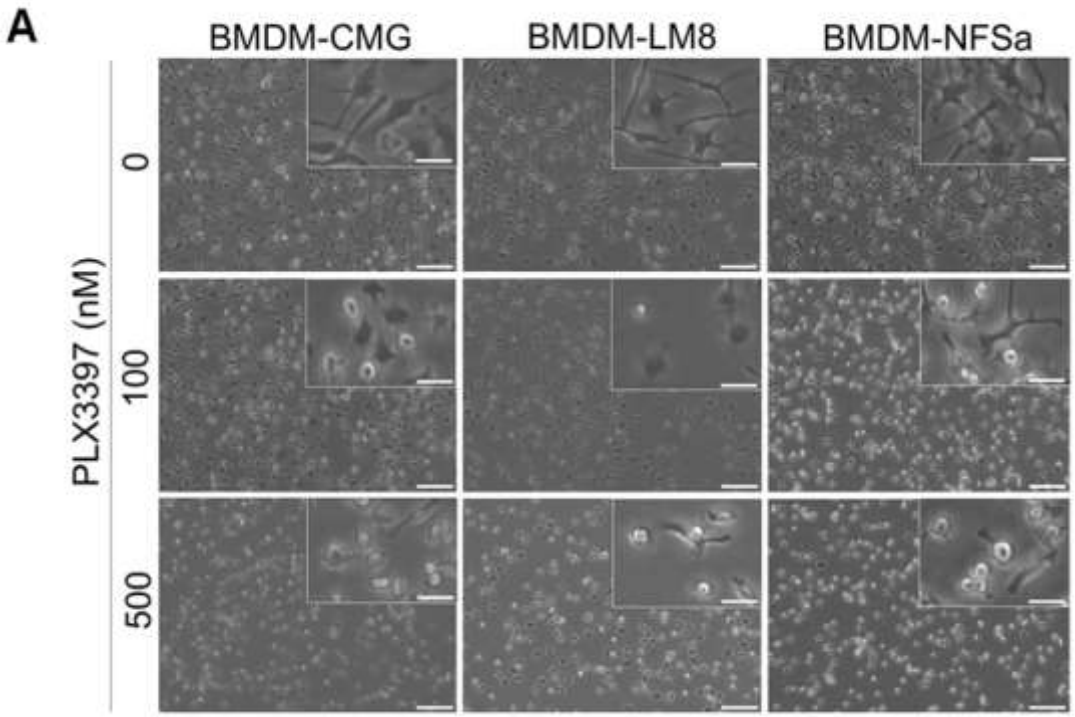
conclude the researchers. Although successful results still need to be shown in human clinical trials, this study paves the way for an effective new way to tackle sarcoma.

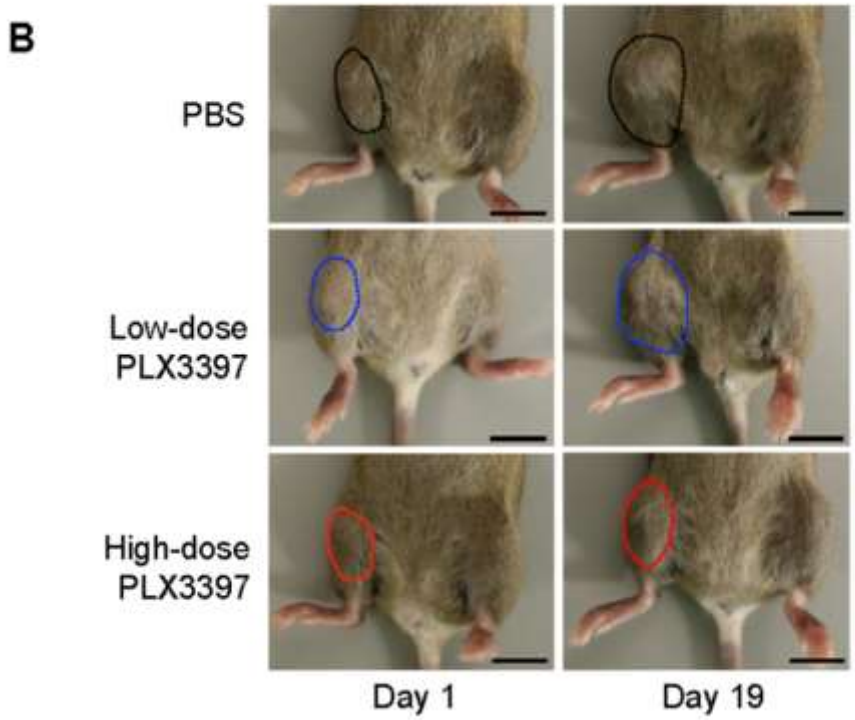
Background

Sarcoma: Sarcoma is a form of cancer that originates within bone tissue or soft tissues such as the muscles, fat, or tendons. The former type, osteosarcoma, is the most common subtype of bone cancer and affects mostly teens and young adults. Sarcomas have a high potential of spread to distant organs, predominantly to the lungs.

At present, nearly a third of patients respond very poorly to the available therapies for sarcoma. Thus, development of targeted therapies and/or immunotherapies for bone and soft-tissue sarcomas is crucial.

Tumor-associated macrophages (TAMs): In certain forms of cancer, innocuous blood cells are recruited by cancerous ones and converted into specialized immune cells called TAMs. Under usual circumstances, macrophages help the body ward off invaders and combat infection (M1-like macrophages). However, the CSF-1 secreted by cancer cells within the tumor milieu generates macrophages which promote the growth and progression of tumors (M2-like macrophages). Owing to this property, inhibition of CSF-1/CSF-1R is being investigated as a therapeutic target against TAMs in the different cancerous tissues.





Caption

A. The growth of TAMs was curbed with increasing doses of PLX3397 treatment.
B. The growth of tumors at the site of transplantation (circled) was greatly contained with high doses of PLX3397 compared to the control (PBS).

Reference

Tomohiro Fujiwara, Mohamed A. Yakoub, Andrew Chandler, Alexander B. Christ, Guangli Yang, Ouathek Ouerfelli, Vinagolu K. Rajasekhar, Aki Yoshida, Hiroya Kondo, Toshiaki Hata, Hiroshi Tazawa, Yildirim Dogan, Malcom A.S. Moore, Toshiyoshi Fujiwara, Toshifumi Ozaki, Ed Purdue, John H. Healey. CSF-1/CSF-1R Signaling Inhibitor Pexidartinib (PLX3397) Reprograms Tumor-Associated Macrophages and Stimulates T-Cell Infiltration in the Sarcoma Microenvironment. *Molecular Cancer Therapeutics*, 2021 Jun 4;molcanther.0591.2020.
DOI: 10.1158/1535-7163.MCT-20-0591
https://mct.aacrjournals.org/content/early/2021/06/04/1535-7163.MCT-20-0591

Correspondence to

Assistant Professor FUJIWARA Tomohiro, M.D.,Ph.D.
Department of Orthopaedic Surgery,
Graduate School of Medicine, Dentistry and Pharmaceutical Science,
Okayama University, 2-5-1 Shikata-cho, Kita-ku,
Okayama 700-8558, Japan
E-mail: tomomedvn@okayama-u.ac.jp


Assistant Professor
FUJIWARA Tomohiro

Further information
Okayama University
1-1-1 Tsushima-naka , Kita-ku , Okayama 700-8530, Japan
Public Relations Division
E-mail: www-adm@adm.okayama-u.ac.jp
Website: http://www.okayama-u.ac.jp/index_e.html
Okayama Univ. e-Bulletin: http://www.okayama-u.ac.jp/user/kouhou/ebulletin/
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OKAYAMA University
1-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530 Japan

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OKAYAMA University
1-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530 Japan

◆About Okayama University

Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

Website: http://www.okayama-u.ac.jp/index_e.html

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Hirofumi Makino, M.D., Ph.D.
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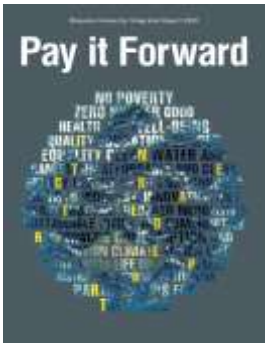

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An integrated report is intended to explain how an organization creates value over time through an organic integration of the vision and the combination of financial information and other information. Through this report we hope to promote greater interest in Okayama University among readers everywhere. In order to help us make improvements in future editions, we encourage you to contact us with any comments and suggestions you may have.

OKAYAMA University
1-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530 Japan