

# Efficacy of tumor-targeting *Salmonella typhimurium* A1-R against patient-derived orthotopic xenograft (PDOX) malignant tumor mouse models

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Tumor-targeting *Salmonella typhimurium* (*S. typhimurium*) A1-R, a facultative anaerobe that is an auxotroph of leucine and arginine was developed. The tumor-targeting efficacy of *S. typhimurium* A1-R was demonstrated *in vivo* and *in vitro* using several malignant cell lines including melanoma, sarcoma, glioma, breast, pancreatic, colon, cervical, prostate, and ovarian cancers. Our laboratory, AntiCancer, Inc., also developed a patient-derived orthotopic xenograft (PDOX) model by implanting patient-derived malignant tumor fragments into orthotopic sites in mice. We reviewed studies of *S. typhimurium* A1-R against recalcitrant cancers. *S. typhimurium* A1-R was effective against all PDOX tumor models tested and showed stronger efficacies than chemotherapy or molecular-targeting therapy against some tumors. Furthermore, the synergistic efficacy of *S. typhimurium* A1-R when combined with chemotherapeutic agents, molecular-targeting agents, or recombinant methioninase was also demonstrated. We suggest potential clinical uses of this *S. typhimurium* A1-R treatment.

## [References]

1. Murakami T, Hiroshima Y, Zhang Y, Bouvet M, Chishima T, Tanaka K, Endo I, Hoffman RM. Improved disease-free survival and overall survival after fluorescence-guided surgery of liver metastasis in an orthotopic nude mouse model. *J Surg Oncol*. 2015; 112: 119-24.
2. Murakami T, Hiroshima Y, Zhao M, Zhang Y, Chishima T, Tanaka K, Bouvet M, Endo I, Hoffman RM. Therapeutic efficacy of tumor-targeting *Salmonella typhimurium* A1-R on human colorectal cancer liver metastasis in orthotopic nude-mouse models. *Oncotarget*. 2015; 6: 31368-77.
3. Murakami T, DeLong J, Eilber FC, Zhao M, Zhang Y, Zhang N, et al. Tumor-targeting *Salmonella typhimurium* A1-R in combination with doxorubicin eradicate soft tissue sarcoma in a patient-derived orthotopic xenograft (PDOX) model. *Oncotarget*. 2016; 7: 12783-90.
4. Murakami T, Singh AS, Kiyuna T, Dry SM, Li Y, James AW, et al. Effective molecular targeting of CDK4/6 and IGF-1R in a rare FUS-ERG fusion CDKN2A-deletion doxorubicin-resistant Ewing's sarcoma patient-derived orthotopic xenograft (PDOX) nude-mouse model. *Oncotarget*. 2016; 7: 47556-47564.
5. Murakami T., Homma Y., Matsuyama R., Mori R., Miyake K., Tanaka Y., et al. Neoadjuvant chemoradiotherapy of pancreatic cancer induces a favorable immunogenic tumor microenvironment associated with increased major histocompatibility complex class I-related chain A/B expression. *J Surg Oncol*. 116(3): 416-426. 2017.
6. Murakami T., Hiroshima Y., Zhang Y., Zhao M., Kiyuna T., Hwang H.K., et al. Tumor-Targeting *Salmonella typhimurium* A1-R Promotes Tumoricidal CD8+ T Cell Tumor Infiltration and Arrests Growth and Metastasis in a Syngeneic Pancreatic-Cancer Orthotopic Mouse Model. *J Cell Biochem*. 119:634-639.2018.
7. Murakami T., Hiroshima Y., Miyake K., Hwang H.K., Kiyuna T., DeLong J.C., et al. Color-coded intravital imaging demonstrates a transforming growth factor- $\beta$  (TGF- $\beta$ ) antagonist selectively targets stromal cells in a human pancreatic-cancer orthotopic mouse model. *Cell Cycle*. 16(10): 1008-1014. 2017.
8. Murakami T, Li S, Han Q, Tan Y, Kiyuna T, Igarashi K, et al. Recombinant methioninase effectively targets a Ewing's sarcoma in a patient-derived orthotopic xenograft (PDOX) nude-mouse model. *Oncotarget*. 30;8(22):35630-35638. 2017.
9. Murakami T, Hiroshima Y, Matsuyama R, Homma Y, Hoffman RM, Endo I. Role of the tumor microenvironment in pancreatic cancer. *Ann Gastroenterol Surg*. 2019 Jan 4;3(2):130-137. doi: 10.1002/ags3.12225. eCollection 2019 Mar. Review.
10. Murakami T, Hiroshima Y, Miyake K, Kiyuna T, Endo I, Zhao M, Hoffman RM. Efficacy of Tumor-Targeting *Salmonella typhimurium* A1-R against Malignancies in Patient-Derived Orthotopic Xenograft (PDOX) Murine Models. *Cells*. 2019 Jun 16;8(6). pii: E599. doi: 10.3390/cells8060599. Review.



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