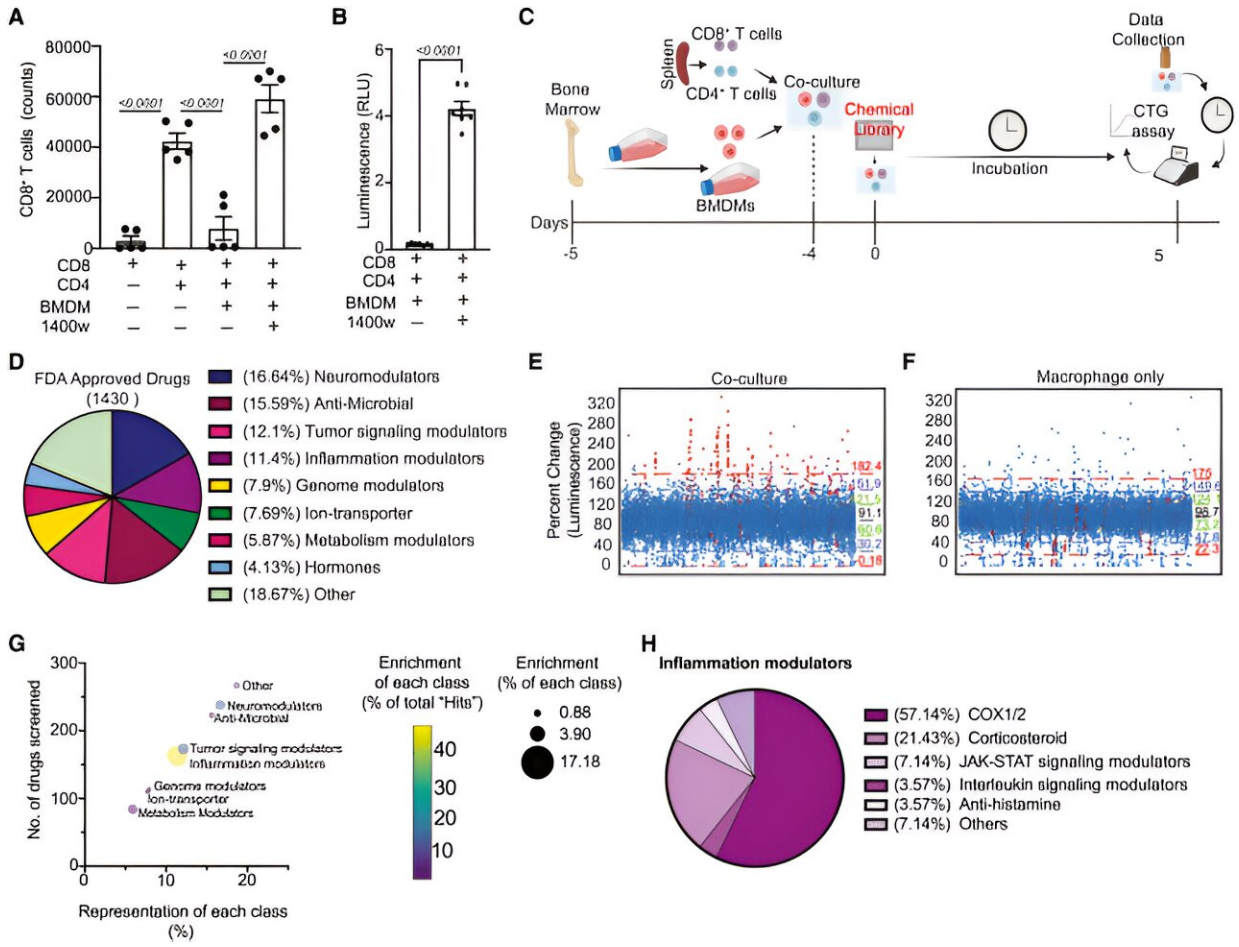
New drug combinations could improve therapies for breast cancer, other aggressive cancers

August 27 2024, by Angela Yeager



Quantification of $CD8^+$ T cells by multispectral flow cytometry in an ex vivo co-culture assay. Credit: *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101698

Oregon Health & Science University researchers have identified a combination of treatments that show promise in slowing the progression of cancer and reducing tumor growth. Their research lays the groundwork for developing more effective treatments for triple negative breast cancers and mesotheliomas—both aggressive forms of cancer that are difficult to treat.

The new study was published Friday in *Cell Reports Medicine*.

"Current immune therapies are effective for only a small percentage of patients with these types of cancer," said Sanjay V. Malhotra, Ph.D., co-senior author on the study. Malhotra is the Sheila Edwards-Lienhart Endowed Chair in Cancer Research, a professor of cell, developmental and cancer biology, and the co-director of the Center for Experimental Therapeutics in the OHSU Knight Cancer Institute. "This is a serious gap in treatment, and new medicines are needed."

Solid tumors—like triple-negative breast cancers, known as TNBC, and mesothelioma, cancer that forms in the internal organs—are often not responsive to chemotherapy or certain immune therapies, such as checkpoint inhibitors, which are drugs that block checkpoint proteins to boost the body's immune system so it can fight cancer.

"Only a subset of patients, about 20% to 40%, with advanced solid tumors derive clinical benefit, and of those, a substantial portion progress over time," said Shivaani Kummar, M.D., an author on the paper. She is a professor and head of the Division of Hematology and Medical Oncology in the OHSU School of Medicine, co-director of the Center for Experimental Therapeutics and co-deputy director for Clinical & Translational Research in the OHSU Knight Cancer Institute.

"The ability to do combination immunotherapy-based screens and quickly move promising combinations forward for clinical development

could provide more effective therapies for patients with a variety of cancers," she said.

Successful combination

The research team developed a cell-based assay, or test, to identify molecules in macrophages, a type of white blood cell that patrols the body for invading organisms. The researchers used the assay to screen 1,430 Food and Drug Administration-approved small-molecule drugs to test combinations with checkpoint inhibitor immune therapy. The top candidates that improved response to checkpoint inhibitors were then tested in animal models of TNBC to identify those that slowed breast cancer growth.

"The combination worked on other subtypes of breast cancer in addition to TNBC," Malhotra said. "The drugs not only slowed progression of the cancer, but also led to cancer regression, which is highly exciting to say the least."

The successful combination that slowed and reduced the cancer in animal models involved standard-of-care chemotherapy, combined with a checkpoint inhibitor and the drug Indomethacin, a non-steroidal anti-inflammatory medication.

Lisa Coussens, Ph.D., chair of the Department of Cell, Developmental and Cancer Biology in the OHSU School of Medicine and co-deputy director for Basic and Translational Research at the OHSU Knight Cancer Institute, is a co-senior author on the study and an expert on the role of immune cells in regulating various aspects of solid tumor development.

"The study recognized the critical importance of macrophages that not only enhance tumor progression directly, but that also suppress the

activity of anti-tumor T cells," she said. "Identifying these cells will lead to new targeted therapies to quell the T cell-suppressive activities of macrophages in solid tumors. This approach can be combined with checkpoint inhibitors and chemotherapy to improve outcomes for patients with some solid cancers."

Going forward, the collaborative team will test the other drug combinations from their screening with chemotherapy and checkpoint inhibitors on different types of hard-to-treat solid tumors, such as mesotheliomas, pancreatic tumors and melanomas.

"Our approach opens an under-explored area for studying immune therapy with new combinations of drugs," Malhotra said. "Given adequate resources, these new treatments could be brought forward for evaluation in clinical trials in 18 to 24 months."

Other contributors to this study included OHSU researchers Sushil Kumar, Ph.D., Dhanir Tailor, Ph.D., Arpit Dheeraj, Ph.D., Wenqi Li, M.S., Kirsten Stefan, Ph.D., Jee Min Lee, M.S., and Pepper Schedin, Ph.D., as well as Dylan Nelson, M.S., and Bailey Keefe, M.S. with Oregon State University.

More information: Sushil Kumar et al, Uncovering therapeutic targets for macrophage-mediated T cell suppression and PD-L1 therapy sensitization, *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101698

Provided by Oregon Health & Science University