Changing cancer care, one organoid at a time

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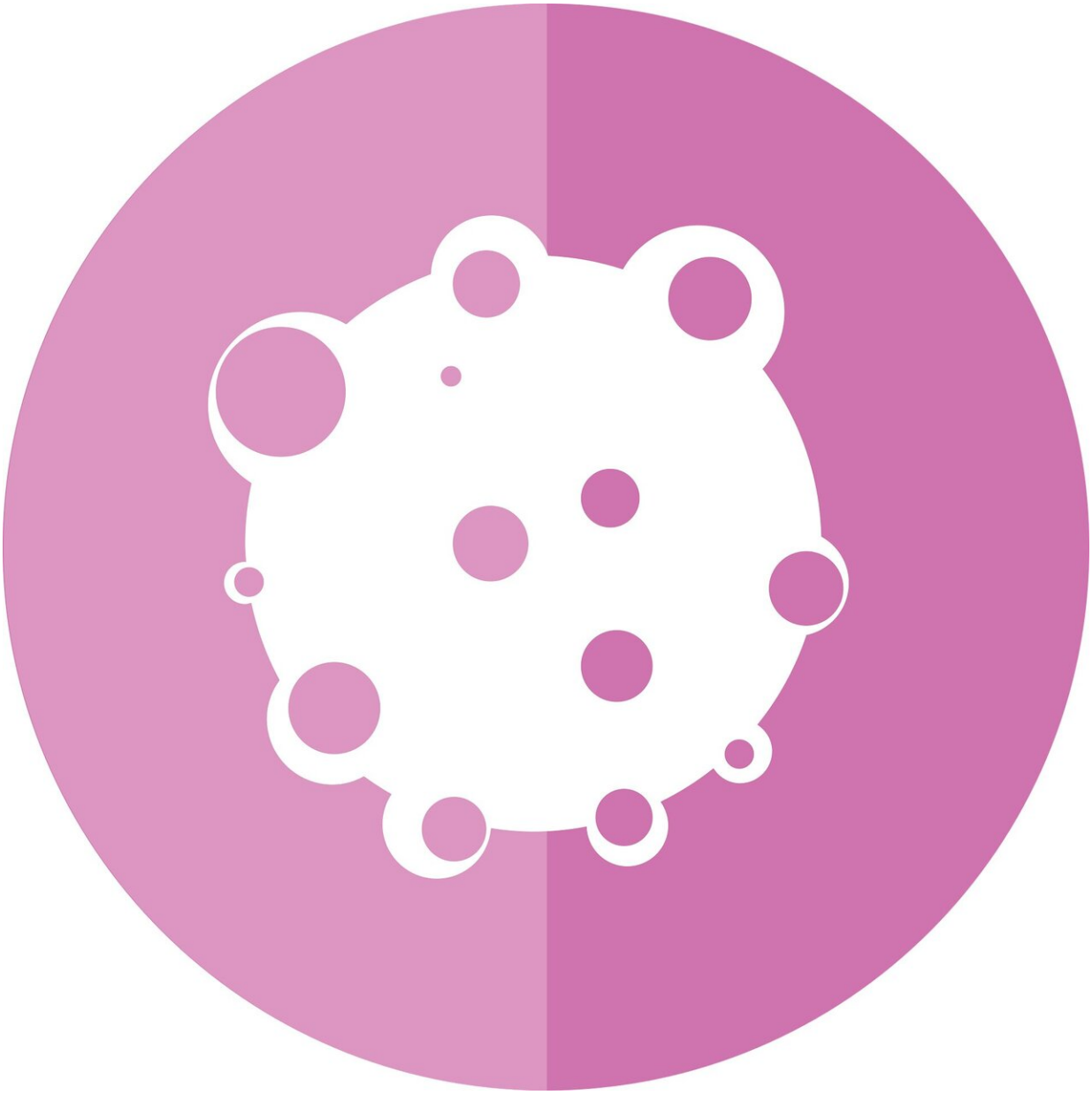

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A patient-specific tumor organoid platform developed by Wake Forest Institute for Regenerative Medicine (WFIRM) researchers and their cancer center colleagues could someday take the guessing game out of immunotherapy treatments. The hope is that, one day, these tumor organoids will be used to personalize patients' treatments, to focus on those that will best help them fight their own cancer.

"Immunotherapy drugs are not inexpensive, and it is not uncommon for the cost of therapy to be measured in millions of dollars per patient," said senior author Aleks Skardal, Ph.D., who was an assistant professor at WFIRM at the time of the study. "This bioengineered patient-specific tumor model opens the door to speedier drug screening to get the best therapy to patients as soon as possible and rationalize the use of immunotherapy drugs to the patients that will show a clinical response."

The work is detailed in a paper published recently in the journal *Annals of Surgical Oncology*.

For this study, the researchers were able to combine melanoma cells and white blood cells from the patients' peripheral blood and lymph nodes, and create patient-specific, immune-active tumor organoids to test their response to immunotherapy treatment. For many cancers, immune response is only possible after appropriate exposure of the specific immune cells, T-cells, to tumor antigens. However, tumor cells develop mechanisms to evade the immune system and go unnoticed. Immunotherapy allows these T-cells to re-detect tumor cells and eventually kill them.

"These constructs will potentially allow us to predict immunotherapy effectiveness and generate adaptive immunity at the level of the individual patient," said leading author Konstantinos Votanopoulos, MD,

Ph.D., associate professor of surgical oncology at the Wake Forest Comprehensive Cancer Center (WFCCC) and co-director of the Wake Forest Organoid Research Center (WFORCE). "Our team has previously co-cultured lymph nodes and tumor from the same patient for screening purposes, but this is the first time we have used this platform to train the immune system of the patient to directly recognize and kill their own tumor without the use of drugs. Creating such a clinically relevant model has the potential to revolutionize the way we approach both cancer research and cancer care."

Organoids are tiny, 3-D tissue-like structures created in the laboratory that mimic the function of human tissues and organs such as the heart, liver, lung, blood vessels, as well as cancer. The organoids are used as a testing and predicting platform to model diseases, evaluate efficacy and/or toxicity of new and existing drugs, and can also be used to test environmental hazards.

To construct the platforms, tumor cells and lymph node biospecimens were surgically obtained from eight patients with stage III and IV melanoma and co-cultured to create the organoids. From the biospecimens received, an average of 75 to 100 organoids were created in each instance and were typically split into equal numbers of patient tumor organoids and immune-enhanced patient tumor organoids. Immunotherapy testing was initiated on day 7 and the organoids were incubated under these conditions for 72 hours. This allowed the researchers to demonstrate that immunotherapy treatment was effective in killing of the tumor only in the immune-enhanced patient tumor organoids, where the organoids without immune cells experienced no tumor death.

The technique for growing organoids has rapidly improved since the early 2010s and WFIRM has been at the forefront of this technology, said Shay Soker, Ph.D., a professor of regenerative medicine who leads

the organoid biofabrication core at WFIRM.

"WFIRM scientists have successfully created organoids replicating most of the main organs of the body such as the liver, heart, brain and lung to screen drugs and model diseases, which can eliminate the need for animal testing," Soker said. "This method generates a 100 percent human experimental platform that recreates the interaction between host, tumor and immune system within 24 hours of obtaining the tissue specimen. It allows us to track the evolution of disease within the patient and potentially adjust the treatment based on the way the cancer changes over time."

WFIRM has partnered with the Comprehensive Cancer Center to establish the Wake Forest Organoid Research Center (WFORCE), a joint effort that brings together researchers and clinicians, like Soker and Votanopoulos, who co-direct the effort and are working side by side, to leverage the use of tissue organoid technologies for the benefit of patients.

The organoid platforms are a disruptive technology that could potentially save lives while also saving billions of dollars of taxpayer money and effect policy design. In 2017, the cost of health care in the US reached $3.5 trillion and is projected by the Centers for Medicare & Medicaid Services to reach $6 trillion by 2027. A portion of this cost is allocated in treating side effects from drugs that quite often have no meaningful activity for the patient.

More information: Konstantinos I. Votanopoulos et al, Model of Patient-Specific Immune-Enhanced Organoids for Immunotherapy Screening: Feasibility Study, *Annals of Surgical Oncology* (2019). DOI: 10.1245/s10434-019-08143-8