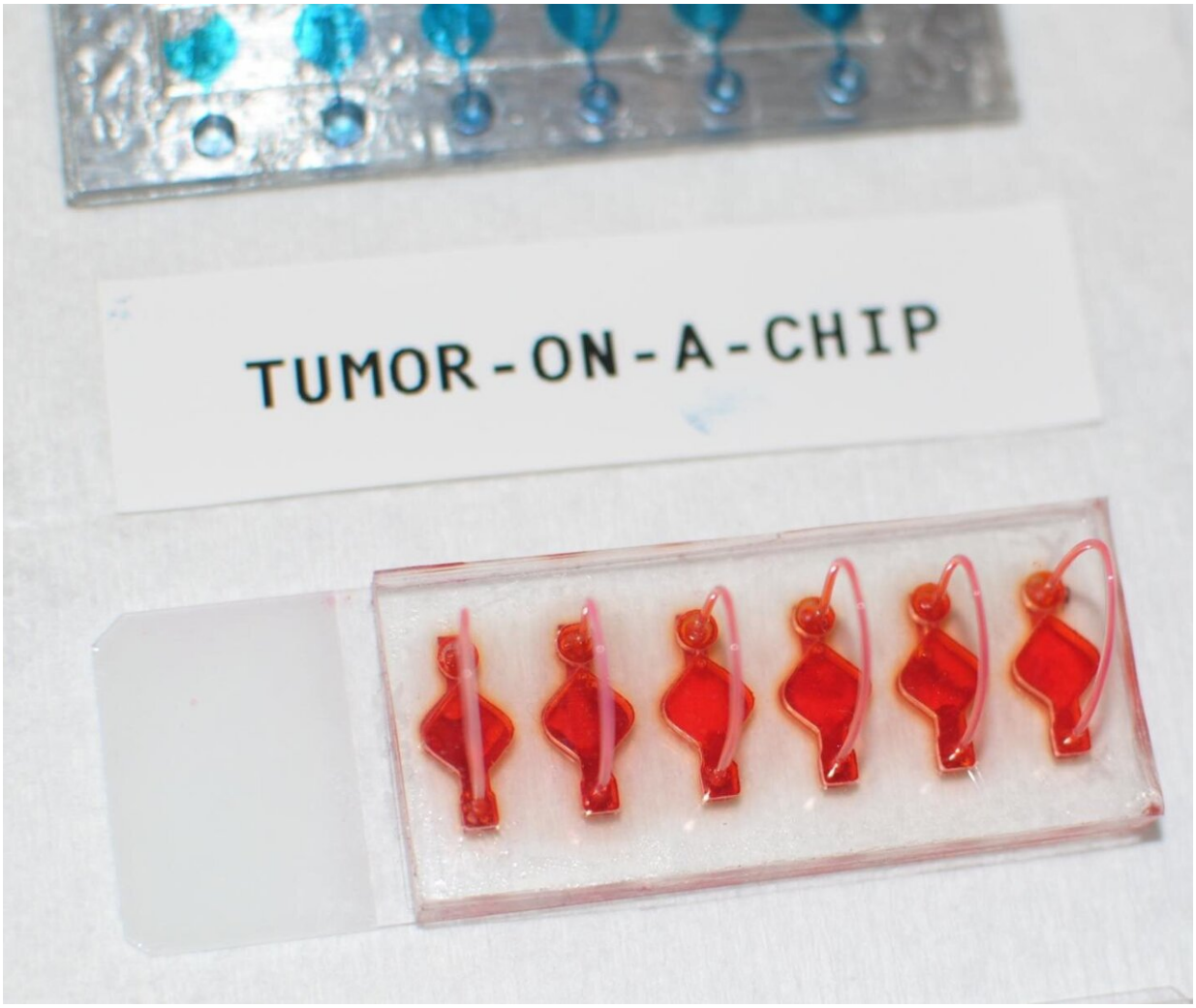
Personalized immunotherapy response studied in body-on-a-chip cancer models

July 19 2021



An example of tumor-on-a-chip, a system used to test drugs on patient-specific tumor organoid models. Credit: WFIRM

Wake Forest researchers and clinicians are using patient-specific tumor 'organoid' models as a preclinical companion platform to better evaluate immunotherapy treatment for appendiceal cancer, one of the rarest cancers affecting only 1 in 100,000 people. Immunotherapies, also known as biologic therapies, activate the body's own immune system to control, and eliminate cancer.

Appendiceal cancer is historically resistant to systemic chemotherapy, and the effect of immunotherapy is essentially unknown because clinical trials are difficult to perform due to lack of adequate patient numbers, resulting in a lack of data and limited research models.

Researchers at the Wake Forest Organoid Research Center (WFORCE), a joint venture between the Wake Forest Institute for Regenerative Medicine (WFIRM), and the Wake Forest Comprehensive Cancer Center, were the first to create appendiceal cancer organoids to use as a predictive model for potential treatment options (published 2018). The Comprehensive Cancer Center is a major high volume center with a global reputation in the treatment of appendiceal cancer.

These cancer organoids are part of WFIRM's 'Body-on-a-Chip' system that allows scientists to engineer the organoids, or human tissue equivalents, that function in a very similar manner as actual human tissues and organs.

In this new study, published in the journal *Clinical Cancer Research*, their results indicate that various types immunotherapies tested on the organoids can potentially support treatment decisions and can achieve personalized results, identifying beneficial treatments while sparing patients from harmful side effects of drugs for which they will obtain no benefit.

"For this study we reconstructed patients' tumors as organoids,

supercharged with a built-in immune system directly obtained from the patient," said senior author Konstantinos I. Votanopoulos, MD, Ph.D., professor of surgery at the Comprehensive Cancer Center and co-director of WFORCE. "In this way we created a personalized interface to study how effective the immunotherapy drugs are in activating a patient's own immune system to kill the cancer. This platform is breaking new ground for appendiceal cancer, and it can also be applied in research for other rare cancers where preclinical models are lacking."

This research study utilizes the WFIRM's "Body-on-a-Chip" system that allows scientists to engineer the organoids, or humanoid tissue equivalents, that function in a very similar manner as actual human organs.

Cells from tumor biopsies from 26 patients were obtained to grow the organoids—tiny, 3-D tissue-like structures, in the lab that that mimic the cancerous tumors. The immune enhanced tumor organoids were treated with one of three immunotherapy drugs and then assessed for responsiveness.

"In the future, by verifying that that the tumor and its organoids behave in the same fashion, we could modify clinical trial design and optimize cost by targeting patients with organoids that have exhibited favorable results," Votanopoulos said.

Current strategies to understand tumor progression center on analyses of the tumor cells in isolation, but do not capture the interactions between a tumor and its surrounding space, known as themicroenvironment or stroma. This leads to inaccuracies in predicting tumor progression and chemotherapy or immunotherapy response. Patient-derived tumor organoids are used as a testing and predicting platform to model diseases, evaluate efficacy and/or toxicity of new and existing drugs, and can be used to test environmental hazards.

Co-author Shay Soker, Ph.D., professor of regenerative medicine who leads tumor organoid research at WFIRM and co-directs WFORCE, said new technologies and biological models that improve prognostication will have a significant effect on patient mortality. "Using the organoids as a preclinical platform can lead to development of novel therapeutics which target and control tumor cells specifically, sparing healthy tissue from the side effects of chemotherapy and immunotherapy treatments," he said. "For rare cancers like appendiceal cancer, this technology can make a difference in overall quality of life for patients."

More information: Erica Lyons et al, Developing Drugs for Prevention of Chemotherapy-Induced Nausea and Vomiting: Draft Guidance from the United States Food and Drug Administration, *Clinical Cancer Research* (2021). DOI: 10.1158/1078-0432.CCR-21-1941

Provided by Wake Forest University Baptist Medical Center