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Researchers develop first patient-derived cells to study leptomeningeal disease

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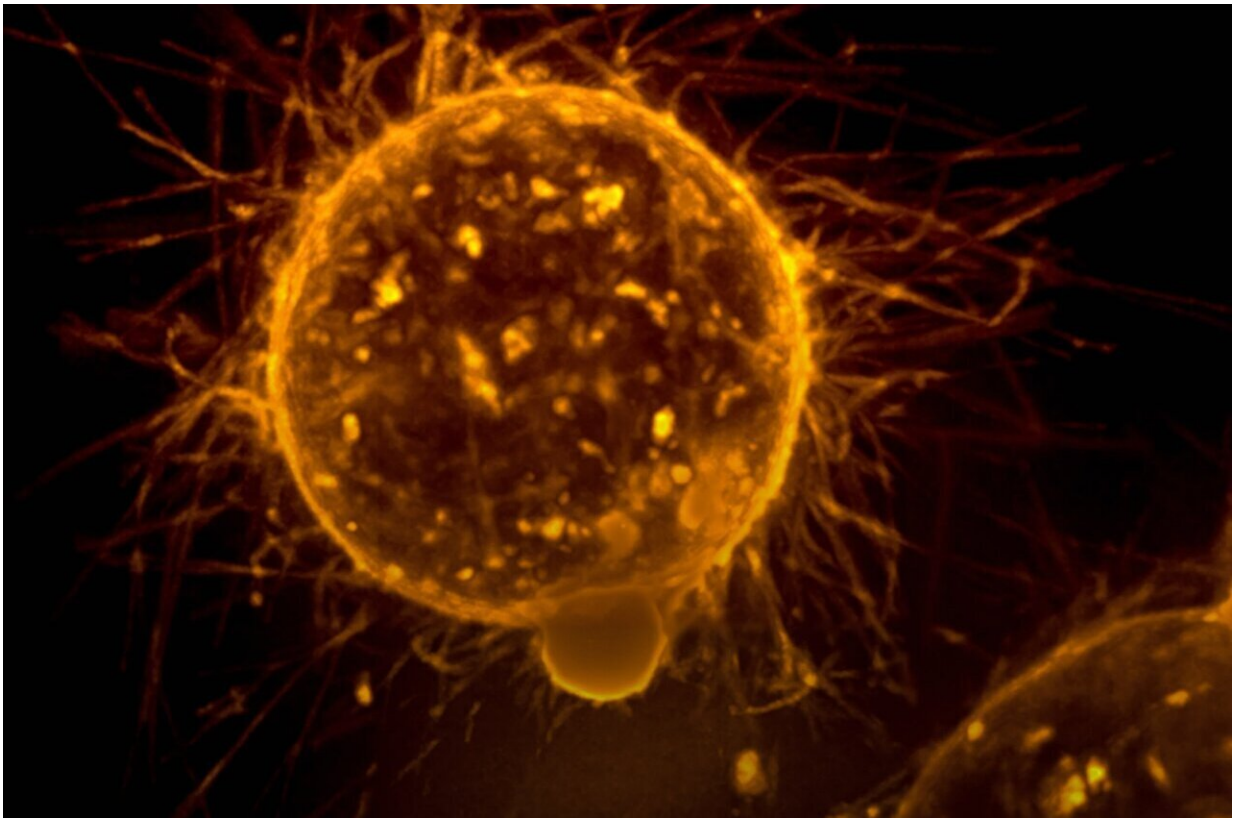

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Leptomeningeal disease is a rare complication of several different types of cancer, including melanoma. It occurs when tumor cells migrate to the cerebrospinal fluid and the tissue that surrounds the brain and spinal

column known as the meninges. Patients who develop leptomeningeal disease have a very poor prognosis and typically survive only three to six months after diagnosis. These poor outcomes are partly due to the lack of model systems to study the disease in a laboratory. In a new article published in *Neuro-Oncology,* Moffitt Cancer Center researchers showed for the first time that patient-derived circulating tumor cells can be cultured from the cerebrospinal fluid of patients with leptomeningeal disease, and that those cells could be used to identify potential drug targets.

Leptomeningeal disease occurs in less than 8% of cancer patients and often presents during the very late stages of the disease. Patients who develop leptomeningeal disease have no effective treatment options, and physicians' primary goals are to alleviate symptoms and improve quality of life while limiting toxicity as much as possible. Due to these poor outcomes, there is a great unmet need for improved therapies. However, until now scientists have been unable to culture leptomeningeal disease cells from patients to assist with their studies.

A team of Moffitt researchers led by Peter Forsyth, M.D., chair of the Department of Neuro-Oncology, and Keiran Smalley, Ph.D., director of the Donald A. Adam Melanoma and Skin Cancer Center of Excellence, has been able to add an important resource to study leptomeningeal disease by successfully growing and culturing circulating tumor cells derived from the cerebrospinal fluid of patients with melanoma leptomeningeal disease. Importantly, the researchers showed that the culturing process did not significantly change the gene expression pattern of the cultured cells compared to the original patient cells.

"Culturing these cells was an extremely difficult process. There was a lot of trial and error until we found the precise mix of growth factor supplements and culture conditions to be successful," said Forsyth.

With their success of growing the cells, the researcher team wanted to confirm their utility in laboratory experiments to study leptomeningeal disease and identify new drug targets. They compared gene expression patterns of the cultured cells to normal nontumorigenic cells from the same patient and discovered that the cultured tumor cells had enriched expression of genes in the insulin-like growth factor signaling pathway, including IGFBP2 and IGF1R, which control many processes involved in cancer development.

The researchers assessed whether the cells could be used as a tool for therapeutic experiments and focused on targeting IGF1R. They reported that treating the cells with the IGF1R inhibitor ceritinib inhibited growth of the tumor cells in cell culture and in mice, and combination treatment with ceritinib and the MEK inhibitor trametinib resulted in greater inhibition than either agent alone.

"Collectively, our results showed that cerebrospinal fluid-circulating tumor cell expansion was possible. These findings also provide support that these patient derived cells are impactful tools for better understanding leptomeningeal disease pathology and testing the efficacy of targeted therapies," said Vincent Law, lead author and a research associate in Forsyth's lab.

More information: Vincent Law et al, A preclinical model of patient-derived cerebrospinal fluid circulating tumor cells for experimental therapeutics in leptomeningeal disease from melanoma, *Neuro-Oncology* (2022). DOI: 10.1093/neuonc/noac054

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