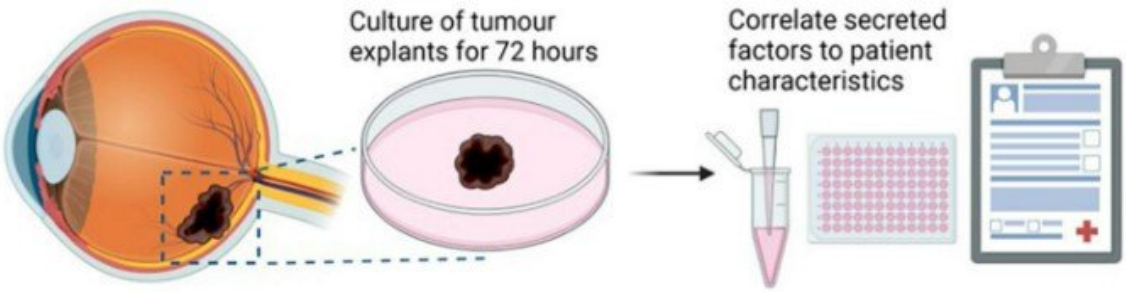
New tools to manage rare eye cancer

February 2 2023



Tumor secretion of IL-6, IL-13, VEGF-A, and PlGF correlate with clinical characteristics in ex vivo, control-treated, primary UM patient tumors. (A) Schematic of the explant culture protocol with vehicle control. Following 72 h of culture, the secretion levels of 10 inflammatory and 7 angiogenic analytes were compared in n = 11 freshly isolated UM tumors treated with vehicle control, to determine if correlations existed between secretions in TCM and patients' clinical parameters. Credit: *Frontiers in Medicine* (2023). DOI: 10.3389/fmed.2022.1036322

Findings from an international research study involving Irish and Spanish patients reveal a candidate drug and biomarker that could be used to manage uveal melanoma.

Uveal melanoma (UM) is a rare eye cancer that begins in melanocytes—the pigment producing cells that give eyes their color and that are also found in the back of the eye.

Ireland has the one of the highest incidence rates in the world of this rare eye cancer, which is associated with risk factors such as fair complexion, pale eyes and higher risk of burning on sun exposure.

One current eye treatment option for UM patients involves the complete removal of the eye while other patients receive radiotherapy directly on the eye. Despite this treatment, the tumor will spread (metastasize), usually to the liver, in 1 out of every 2 patients. Many patients will undergo this life-altering surgery or local radiotherapy but will still be anxious about their risk of metastatic disease.

There are limited treatment options once the disease spreads to the liver with as few as 8% of patients surviving beyond two years. New ways to identify or predict patients whose cancer has spread, and new treatments for metastatic UM are needed to improve patient outcomes.

This research initially focused on molecules called cysteinyl leukotriene (CysLT) receptors to investigate their potential as biomarkers and drug targets to treat UM. Biomarkers help to identify the patients most likely to develop metastatic UM. CysLT are involved in inflammation and known for playing a role in allergic diseases such as asthma. More recently, they have been implicated in a wide range of diseases including central nervous system diseases and cancer.

Led by Professor Breandán Kennedy, UCD School of Biomolecular & Biomedical Science and Fellow, UCD Conway Institute in University College Dublin, this team used patient samples and experimental models to see if levels of these molecules, CysLT receptors, are linked to patient survival and what effect the candidate drug, (1,4-dihydroxy quininib) has on them.

Dr. Kayleigh Slater, postdoctoral fellow and first author on this study said, "This research builds on our previous work evaluating compounds

that can interfere with CysLT receptors in UM cells in the laboratory.

"We developed a laboratory model of primary UM from patient samples and a preclinical model of metastatic UM. Then, we used biochemical and pharmacological tests to gather a range of data. This preclinical data shows us firstly that higher CysLT receptor levels in primary UM tumors is an indication of poor prognosis. Secondly, our candidate drug effects the molecular hallmarks of the disease that enable the cancer to grow and spread in UM models. Thirdly, we identified a biomarker that appears to predict which patients will not develop metastatic disease."

Professor Breandán Kennedy said, "These are positive findings using an Irish cohort of patient samples in a disease that is the primary cause of eye cancer in Ireland. We have shown that this candidate drug can act on the tumor and that the biomarkers could be valuable prognostic tools for clinicians to assess which patients are unlikely to develop metastatic disease. We are immensely grateful to the clinical team in the Royal Eye and Ear Hospital Dublin and the patients who agreed to partake in this study at a very difficult time in their lives."

Mr. Noel Horgan, consultant ophthalmologist, Royal Victoria Eye & Ear Hospital and St Vincent's University Hospital said, "Uveal melanoma, although uncommon, occurs more often in Ireland than in other parts of the world. Unfortunately, effective treatment for advanced stage (metastatic) uveal melanoma remains elusive in many cases. Research continues to advance our understanding of this type of melanoma. Our team are delighted to collaborate with the research team at UCD in their efforts to make progress in the search for new and more effective treatments for this disease."

The research team have embedded patient involvement in their work from the start. Melody Buckley, a member of the patient support group, Ocular Melanoma Ireland with a family member who is a uveal

melanoma patient said, "I am delighted that Irish researchers have published novel research that may lead to a future cure for this rare and deadly eye cancer."

Their study, in collaboration with researchers from Spain and the U.K., is particularly valuable because it suggests potential treatments in cases where the cancer has spread to the liver. Such treatments are critically needed especially for patients for whom life-prolonging alternatives such as KIMMTRAK are unsuitable.

More information: Kayleigh Slater et al, 1,4-dihydroxy quininib modulates the secretome of uveal melanoma tumour explants and a marker of oxidative phosphorylation in a metastatic xenograft model, *Frontiers in Medicine* (2023). DOI: 10.3389/fmed.2022.1036322

Provided by University College Dublin