

Researchers use genomics to identify a molecular-based treatment for a viral skin cancer

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Four years after they discovered the viral roots of a rare skin cancer, researchers at the University of Pittsburgh Cancer Institute (UPCI) and the School of Medicine have now identified a molecule activated by this virus that, in animal studies, could be targeted to selectively kill the tumor cells. The treatment will soon be tested in patients.

Merkel cell carcinoma (MCC), a [skin cancer](#) that is more common among seniors and those with weakened immune systems, could not be readily diagnosed at one time, and it still has a very [poor prognosis](#), said Patrick S. Moore, M.D., M.P.H., and Yuan Chang, M.D., both of the Cancer Virology Program at UPCI and senior authors of a study that appears online today in *Science Translational Medicine*.

"This research effort shows the speed at which genomics can identify molecular causes for cancer and then point the way toward a rational and targeted treatment," Dr. Moore noted. "Since the inception of the 1971 U.S. National Cancer Act, researchers have strived to discover the underlying problems that trigger tumor development."

In 2008, the team first described the new Merkel cell polyomavirus (MCV) in [Merkel cell carcinoma](#). Within a year, they showed it was responsible for [tumor development](#) in most cases of the disease. At least four out of five healthy adults world-wide are infected with MCV, which usually doesn't cause any symptoms.

"The virus remains in the [skin cells](#), and in most cases, no damage is done," Dr. Chang said. "But when mutations occur to this virus, it can cause cancer. Most of the 1,500 new MCC cases per year in the U.S. are caused by MCV infection."

In quick succession, the team devised tests to identify virus-induced MCC, and began unraveling the [biochemical pathways](#) that encourage tumor formation. In their latest project, they "knocked out" a key [viral protein](#) called T antigen and found that MCV directly elevates a [cellular protein](#) called survivin.

Survivin prevents cells from dying and supports cell division, the researchers said. They found that a drug called YM155, which turns off the survivin gene again, was an extremely potent killer of MCC cells in test tubes and was able to suppress the growth of human tumors that had been established in experimental mice. In comparison, 1,360 other drugs—including most of the common chemotherapy drugs—were screened and failed to both kill MCC cells and prevent tumor growth at levels commonly achieved in patients. One of these drugs was able to kill [tumor cells](#) in culture dishes, but made no impact on the MCC tumors in mice. It remains a promising candidate drug since it may have better activity in people and is readily available.

A multicenter clinical trial of YM155, a still-experimental anti-cancer drug that is made by Deerfield, Ill.-based Astellas, is expected to begin in the next six months to determine its effectiveness in MCC patients. The trial will be led locally by Pitt School of Medicine assistant professor Hussein Tawbi, M.D., Ph.D., and professor John Kirkwood, M.D., who also is co-leader of the UPCI Melanoma Program, through the Eastern Cooperative Oncology Group, a multicenter cooperative group supported by the National Cancer Institute (NCI), part of the National Institutes of Health.

Typically, neither the cause of a cancer nor the target for a cancer drug is initially known, so most treatments have developed over decades through trial-and-error. Most therapies affect both healthy tissues and cancer cells, resulting in side effects that limit the drug dose that can safely be given. This study, in contrast, was a "rational" drug study where the underlying cellular defect caused by the virus was first discovered through genetic studies and then a drug targeting this process was tested. Survivin is needed during fetal development, but not in healthy adult cells, and YM155 was not toxic to the mice.

"Scientists can now quickly come up with answers to complex problems, like cancer, using human genetics," Dr. Moore noted. "In less than five years, we have gone from knowing very little about MCC to knowing its exact cause and are devising new, precisely targeted and less-toxic therapies."

Dr. Moore also is a Distinguished Professor and American Cancer Society Professor, Department of Microbiology and Molecular Genetics. Dr. Chang also is a Distinguished Professor and American Cancer Society Professor, Department of Pathology. Last week, they were elected to membership in the prestigious National Academy of Sciences. Prior to their work on MCV, the Chang and Moore lab team discovered another virus, a new human herpesvirus, in 1994 that causes Kaposi's sarcoma, the most common [cancer](#) among AIDS patients.

Provided by University of Pittsburgh Schools of the Health Sciences

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