Medications developed for other uses show potential to curb cervical cancer

December 16 2013, by Rob Forman

Two existing drugs – one the active ingredient in an anti-fungal medication and the other now used to control iron levels in the blood – both show promise as potential treatments for cervical cancer, according to newly published research by scientists at Rutgers New Jersey Medical School.

Cervical cancer is the third most common gynecologic cancer in the United States, and takes the life of one of every three women diagnosed with it.

"Cervical cancer still takes a terrible toll, despite advances in prevention, detection and treatment," says Michael Mathews, the senior member of the research team. Their article, whose first author is Elisabeth Mémin, has been published online by the journal *Cancer Research*.

"Early stage disease is curable," adds co-author Bernadette Cracchiolo, director of gynecologic oncology at the school, "but late stage and recurrent disease have limited treatment options. We need novel concepts, novel agents that can save lives in those cases, especially for African-American women, whose death rate is twice that of Caucasians. We believe our new research offers those."

The research demonstrates how the two drugs, ciclopirox (anti-fungal) and deferiprone (blood treatment), effectively inhibit an enzyme called deoxyhypusine hydroxylase (DOHH). The enzyme is believed to be essential to the molecular chain of events that leads to cervical cancer.

The researchers performed lab experiments on cells derived from a cervical cancer and found that when DOHH is blocked, a protein known as eIF5A fails to mature. That, in turn, alters the expression of genes that without the medications would cause cancer cells to proliferate. "Some gene products go down and others go up, because mature eIF5A has more than one biochemical action inside cells," Mathews explains. "For cell proliferation, each drug's dual action is like both easing off the accelerator and depressing the brake pedal."

For Mathews and his Rutgers colleague Hartmut Hanauske-Abel, this is the second significant success announced within a matter of weeks involving these two medications. In September, a research team they led published similarly exciting findings in the journal *PLOS ONE* about HIV – evidence that the same two drugs eradicated the virus from infected cells examined in lab cultures.

The drugs had two separate effects on HIV. First, both medications prevented the virus from reproducing within cells. Second, by disturbing the function of the mitochondria, the cells' power stations, the drugs caused HIV-infected cells to self-destruct while sparing healthy cells. Once the medications were discontinued, HIV infection did not return. If these promising results are corroborated in clinical trials, they would represent a major advance over current treatments, which patients must take as long as they live. Existing antiretroviral drugs don't eliminate HIV but only inhibit its multiplication. If current cocktails of drugs are discontinued, the disease returns.

So what made Mathews and Hanauske-Abel decide that ciclopirox and deferiprone could act against both HIV and cervical cancer? The key is contained in the two drugs' molecular structures, according to Mathews.

"While ciclopirox and deferiprone were developed for unrelated uses, Hartmut's knowledge of enzymes and pharmacology suggested that both drugs could influence some of the most basic processes that occur within human cells," he says. "We then designed experiments that could help us take advantage of those properties, and our predictions were validated."

An essential aspect of the research team's work with these medications is that both are approved by the Food and Drug Administration for their originally intended uses, which means they are considered safe for use by human patients. Repurposing the medications to treat cervical cancer and HIV creates a potentially huge shortcut to approval if the drugs prove their worth.

"A drug produced from scratch needs to be proven both safe and effective before the FDA will permit its use, and that is a painstaking and expensive process requiring extensive animal experiments," Hanauske-Abel says. "If we start with an existing drug, FDA-approved for an 'old' indication, its safety is already established and the innovation

process becomes much shorter."

More information: Hanauske-Abel HM, Saxena D, Palumbo PE, Hanauske A-R, Luchessi AD, et al. (2013) Drug-Induced Reactivation of Apoptosis Abrogates HIV-1 Infection. *PLoS ONE* 8(9): e74414. DOI: 10.1371/journal.pone.0074414