Pactamycin analogs offer new, gentler approach to cancer treatment

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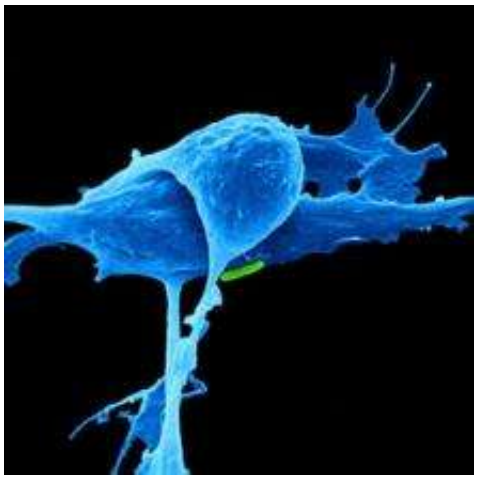

Researchers at Oregon State University are pursuing a new concept in treatment of epithelial cancer, especially head and neck cancer, by using two promising "analogs" of an old compound that was once studied as a potent anti-tumor agent, but long ago abandoned because it was too toxic.

The analogs are more highly selective than the parent compound, pactamycin, which originally was found to kill all cells, from bacteria to mammals, by inhibiting their protein synthesis.

The pactamycin analogs, which were developed with biosynthetic engineering, also offer a different approach toward cancer therapy—an effort to essentially put cancer cells to sleep, instead of killing them. If successful, this trend may herald a new future in "kinder and gentler" cancer treatments.

Findings on this promising approach to cancer were just published in *PLOS One*, in work supported by the National Institute of Health and other agencies.

The effects of the pactamycin analogs, called TM-025 and TM-026, were characterized in head and neck cancer cell lines, which cause the eighth most common cancer in the world. But they may have applications to a wider range of cancers, the researchers said, particularly melanoma.

"A traditional view of chemotherapy is that you try to completely kill cancer cells and destroy tumors," said Arup Indra, an associate professor in the OSU College of Pharmacy and one of the lead authors on the study. "Sometimes this is effective, sometimes not as much. An alternative approach is to cause rapid cell aging and induce premature senescence, which we believe could become a new frontier in cancer drug development."

A senescent cancer cell, Indra said, doesn't usually die, but the growth of it and the larger tumor is slowed or stops, and it continues to live in a vegetative state, almost like being asleep. Such an approach can be an alternative way to control cancer without completely killing it, which may help reduce problems with resistance that can quickly develop to chemotherapeutic drugs. And it also avoids some of the most toxic and debilitating side effects of cancer chemotherapies, which are often caused by cell death.

The new findings showed that these analogs of pactamycin largely stopped cancer cell proliferation and growth, causing cells to age and lose their ability to divide and grow. These effects are partly mediated by tumor suppressor p53, which is frequently mutated in human cancers. They do not yet form the basis for a therapy, researchers said, because methods must still be perfected to get them more selectively into the cancer cells.

"With further research we hope to create a nontoxic nanocarrier that could provide targeted delivery of the TM-025 and TM-026 analogs specifically to cancer cells," said Gitali Indra, an OSU assistant professor and also a lead and corresponding author

on the study. "In some cases, such as oral cancer, it may also be possible to use topical treatments. But this approach should have significant promise if we can develop techniques to adequately target the cancer cells."

More information: Guha G, Lu W, Li S, Liang X, Kulesz-Martin MF, Mahmud T, et al. (2015) Novel Pactamycin Analogs Induce p53 Dependent Cell-Cycle Arrest at S-Phase in Human Head and Neck Squamous Cell Carcinoma (HNSCC) Cells. *PLoS ONE* 10(5): e0125322. DOI: 10.1371/journal.pone.0125322

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