1930s drug slows tumor growth

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Drugs sometimes have beneficial side effects. A glaucoma treatment causes luscious eyelashes. A blood pressure drug also aids those with a rare genetic disease. The newest surprise discovered by researchers at the Johns Hopkins University School of Medicine is a gonorrhea medication that might help battle cancer.

"Often times we are surprised that a drug known to do something else has another hidden property," says Jun Liu, Ph.D., a professor of pharmacology and molecular sciences at Johns Hopkins and author on the study published Oct. 1 in the Proceedings of the National Academy of Sciences.

In this case, the surprise is a big one. The drug, acriflavine, used in the 1930s for treating gonorrhea, has turned out to have the previously unknown ability to halt the growth of new blood vessels. Preliminary tests showed that mice engineered to develop cancer had no tumor growth if treated with daily injections of acriflavine.

"As cancer cells rapidly divide, they consume considerable amounts of oxygen," says Gregg Semenza, M.D., Ph.D., the C. Michael Armstrong Professor of Pediatrics and director of the vascular program at the Johns Hopkins Institute for Cell Engineering. "To continue growing, a tumor must create new blood vessels to deliver oxygen to the tumor cells."

Acriflavine stops blood vessel growth by inhibiting the function of the protein hypoxia-inducible factor (HIF)-1, which was discovered by Semenza's team in 1992. When HIF-1 senses that the surrounding

environment is low in oxygen, it turns on genes necessary for building new vessels. Though essential for normal tissue growth and wound healing, HIF-1 is also turned on by cancers to obtain the oxygen they need to survive. Most importantly, in order for HIF-1 to work, two subunits must bind together like puzzle pieces.

Most drugs are unable to prevent protein binding because the drug molecules can be much smaller than the proteins they interact with. A medicine must hit just the right spot, a critical domain or pocket on the surface of one protein to stop it from binding to another protein. Even though drugs that stop binding are uncommon, they are such an effective means to stop protein function that Semenza decided to look for one that might block HIF-1. To do that, he turned to the Johns Hopkins Drug Library, a collection of FDA- and internationally approved compounds in that was assembled by Liu.

To visualize protein binding, scientists engineered a cell line so that when the HIF-1 subunits came together, they would cause the cell to light up like a firefly. They then tested each of the more than 3,000 drugs in the drug library in hopes of finding one that would turn out the light. Acriflavine did, andfurther studies confirmed that it was binding directly to HIF-1.

"Mechanistically, this is the first drug of its kind," says Liu. "It is acting in a way that is never seen for this family of proteins."

Liu hopes that acriflavine can one day be incorporated into chemotherapy cocktails, one drug among many that help fight cancer.

Hopkins is seeking even more new uses for old drugs. So far, drugs in the library have been screened for use against malaria, tuberculosis, HIV and the Ebola virus. In the future, Liu expects even more researchers to take advantage of the library, which is continuing to grow as more drugs

are added to the collection.

"In the public domain, Hopkins has the largest drug library," says Liu. "The more drugs you have, the more possibilities, the higher the chance you rediscover something that will help."

Source: Johns Hopkins Medical Institutions