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Block its recycling system, and cancer kicks the can: study

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All cells have the ability to recycle unwanted or damaged proteins and reuse the building blocks as food. But cancer cells have ramped up the system, called autophagy, and rely on it to escape damage in the face of chemotherapy and other treatments. Now, researchers at the Perelman School of Medicine; the Abramson Cancer Center; and the School of Arts and Sciences, at the University of Pennsylvania, have developed a potent new drug that clogs up the recycling machinery and kills tumor cells in mouse models.

Ravi K. Amaravadi, MD, assistant professor of Medicine, and colleagues showed previously that an old malaria drug, hydroxychloroquine, reduces autophagy in cancer cells and makes them more likely to die when exposed to chemotherapy. The strategy is currently being tested in clinical trials, and preliminary results are promising. The catch, though, is that it's not always possible to give patients a high enough dose of hydroxychloroquine to have an effect on their tumor cells.

Amaravadi teamed up with Jeffrey Winkler, PhD, the Merriam Professor of Chemistry, to design a series of more potent versions of chloroquine. They describe the design, chemical synthesis, and biological evaluation of a highly effective, new compound called Lys05, in the early edition of the Proceedings of the National Academy of Sciences this week.

Unlike hydroxychloroquine, which has little impact on tumor cells when used as a single agent, the new drug, called Lys05, slows tumor growth in

animal models even in the absence of other anti-tumor therapies. What's more, the Lys05 dose that is toxic to cancer cells, which are addicted to recycling and rely on it much more heavily than healthy cells, has little or no effect on healthy cells.

"We see that Lys05 has anti-tumor activity at doses that are non-toxic for the animals," Amaravadi says. "This single-agent anti-tumor activity suggests this drug, or its derivative, may be even more effective in patients than hydroxychloroquine." Remarkably, however, when the investigators increase the dose of Lys05, some animals develop symptoms that mimic a known genetic deficiency in an autophagy gene, ATG16L1, which affects some patients with Crohn's disease . That similarity – technically called a phenocopy – clearly shows that Lys05 works by interfering with the recycling system in cells.

Lys05, and its companion compound Lys01, aren't quite ready for testing in patients, according to Amaravadi. Before that can happen, the molecules need to be optimized and undergo more toxicity testing in animals. Amaravadi and Winkler hope to team up with an industry partner for that portion of the project.

In the meantime, though, Amaravadi says the work illustrates just how important autophagy is to cancer cells, and provides an important new step for future therapies.

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