Drug mitigates toxic effects of radiation in mice

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While radiation has therapeutic uses, too much radiation is damaging to cells. The most important acute side effect of radiation poisoning is damage to the bone marrow. The bone marrow produces all the normal blood cells, and therefore a high dose of radiation can lead to low blood counts of red cells, platelets and white blood cells. Humans that receive a lethal dose of radiation as in the setting of an accidental exposure die of bone marrow failure. While there are a few drugs that will decrease toxicity when given before exposure to radiation ("radioprotectants"); currently, no effective therapy exists to mitigate bone marrow toxicity of radiation when given after radiation exposure ("radiomitigants"). The identification of successful human radiomitigants is a top research priority of the U.S. Department of Homeland Security and National Institutes of Health.

In a study published today in the Journal of Clinical Investigation, a team led by UNC Lineberger Associate Director for Translational Research, Norman Sharpless, MD, provides a first example of successful radiomitigation in mammals. The investigators found that oral treatment of mice with a drug that inhibits enzymes involved in cell division caused certain groups of bone marrow cells to temporarily stop dividing (which they termed 'pharmacological quiescence' or PQ). Several decades of work have shown that cells which are not dividing are resistant to agents that damage DNA, like radiation. Workers in the Sharpless lab were then able to show that the induction of PQ immediately before or up to 20 hours after radiation exposure were able to protect mice from a lethal dose of radiation. PQ protected all the

normal cells of blood, including platelets, red cells and white cells.

"We believe this study is really exciting. We have identified a simple, non-toxic pill that decreases radiation toxicity even when given after radiation exposure. We believe this approach could be of use in humans who are accidentally or intentionally exposed to lethal doses of radiation," said Sharpless, who is an associate professor of medicine and genetics at UNC's School of Medicine.

PQ relies on the use of potent and selective inhibitors of cellular enzymes called CDK4 and CDK6. Related drugs have been used extensively in humans with cancer, and CDK4/6 inhibitors are currently being tested in humans. Importantly, these drugs can be given as a pill, are chemically stable and have little toxicity. Therefore, such compounds could be stockpiled for use in the setting of an unexpected radiological disaster. The group showed that structurally different versions CDK4/6 inhibitors provided protection from radiation, whereas other types of kinase inhibitors did not.

Sharpless believe PQ may have a role in treating patients with cancer. Radiation is used in cancer therapy, and therefore PQ might benefit such patients. Also, several commonly used chemotherapy drugs cause bone marrow toxicity by damaging DNA, and therefore PQ might protect from chemotherapy toxicity in addition to radiation toxicity. A concern is that PQ might also protect a patient's tumor from the toxicity of therapeutic DNA damaging agents, but the Sharpless group showed that at least some types of cancer were not protected by inhibitors of CDK4/6. Bone marrow protection is a major issue in medical oncology, with billions of dollars of growth factors used annually in the US alone for this problem. In particular, PQ protects platelets and red cells, which are largely unmet needs in current clinical oncology.