

Proton therapy induces biologic response to attack treatment-resistant cancers

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Mayo Clinic researchers have developed a novel proton therapy technique to more specifically target cancer cells that resist other forms of treatment. The technique is called LEAP, an acronym for "biologically enhanced particle therapy." The findings are published today in *Cancer Research*, the journal of the American Association for Cancer Research.

"The [human body](#) receives tens of thousands of DNA lesions per day from a variety of internal and external sources," says Robert Mutter, M.D., a [radiation oncologist](#) at Mayo Clinic and co-principal investigator of the study. "Therefore, cells have evolved complex repair pathways to efficiently

repair damaged DNA. Defects in these repair pathways can lead to the development of diseases, including [cancer](#), says Dr. Mutter.

"Defects in the ATM-BRCA1-BRCA2 DNA repair pathway are commonly observed in cancer," says Dr. Mutter. "And breast and ovarian cancer mutations in BRCA1 and BRCA2 repair genes are the most common cause."

Dr. Mutter; Zhenkun Lou, Ph.D., co-principal investigator of the study; and their colleagues studied a novel method of delivering proton therapy to target tumors with inherent defects in the ATM-BRCA1-BRCA2 DNA repair pathway.

"We compared the effects of delivering the same amount of energy or dose into [cancer cells](#) using a dense energy deposition pattern with LEAP versus spreading out the same energy more diffusely, which is typical of conventional photon and proton therapy," says Dr. Mutter. "Surprisingly, we discovered that cancers with inherent defects in the ATM-BRCA1-BRCA2 pathway are exquisitely sensitive to a new concentrated proton technique."

Dr. Lou says surrounding normal tissues were spared, and their full complement of DNA repair elements remained intact. "We also found that we could rewire the DNA repair machinery pharmacologically by co-administration of an ATM inhibitor, a regulator of the body's response to DNA damage, to make repair-proficient cells exquisitely sensitive to LEAP," says Dr. Lou.

Dr. Mutter says the distinct physical characteristics of protons allow [radiation](#) oncologists to spare nearby normal tissues with superior accuracy, compared to conventional photon-based radiation therapy. "LEAP is a [paradigm shift](#) in treatment, whereby newly discovered biologic responses, induced when proton energy deposition is concentrated in cancer cells using novel radiation planning techniques, may enable the

personalization of radiotherapy based on a patient's tumor biology," says Dr. Mutter.

Drs. Mutter and Lou say their findings are the product of several years of preclinical development through collaboration with experts in physics, radiation biology and mechanisms of DNA repair. Dr. Mutter and the radiation oncology team at Mayo Clinic are developing clinical trials to test the safety and efficacy of LEAP in multiple tumor types.

More information: Qin Zhou et al. Inhibition of ATM induces hypersensitivity to proton irradiation by upregulating toxic end joining, *Cancer Research* (2021). DOI: [10.1158/0008-5472.CAN-20-2960](https://doi.org/10.1158/0008-5472.CAN-20-2960)

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