

## 'PARP' drug sabotages DNA repair in pre-leukemic cells

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Looking for ways to halt the uncontrolled growth of cancer cells, scientists at Johns Hopkins have found that a new class of drugs, called PARP inhibitors, may block the ability of pre-leukemic cells to repair broken bits of their own DNA, causing these cells to self-destruct. Results of their experiments, expected to be presented at the 53rd Annual Meeting of the American Society of Hematology in San Diego, Dec. 12, have already prompted clinical trials of the drugs in patients with aggressive pre-leukemic conditions, who have few treatment options.

The Johns Hopkins team analyzed the genomes of 144 patients with pre-leukemic conditions, collectively known as myeloproliferative disorders. They found deletions of several [genes](#) that control how [cells](#) repair their DNA. Many DNA repair-related pathways and genes have been linked to both cancer development and interruption of that process.

One of the potential defects identified during Hopkins' [genome](#) scan occurred in the BRCA2 gene, best known for causing hereditary breast cancer and one among many genes in a pathway that regulates DNA repair processes. With mistakes in the BRCA2 gene, pre-cancer and [cancer cells](#) must lean more heavily on other pathways to repair DNA in order to survive.

"To kill pre-cancer and cancer cells, we have to disrupt the other DNA repair pathways that are keeping them alive," says Michael McDevitt, M.D., Ph.D., assistant professor of medicine and oncology at Johns

Hopkins and co-leader of the study.

Some studies indicate BRCA2-mutated cells are sensitive to treatment with "PARP" inhibitors, drugs that block specific DNA–repair proteins. PARP, or poly (ADP-ribose) polymerase, inhibitors are being tested in early clinical trials at Johns Hopkins and elsewhere to treat breast and certain blood cancers.

To test PARP inhibitors' therapeutic potential for pre-leukemias, McDevitt and his colleagues at the Mayo Clinic focused on one particular DNA repair pathway called homologous recombination. Some 15 samples of pre-leukemic cells were irradiated and then tested for their ability to form protein complexes, a first step to repairing the radiation-induced damage. Six of the 15 samples formed no protein complexes, a sign that the homologous recombination pathway was disrupted, and each of the six samples was three to five times more sensitive to PARP inhibitors than were normal cells.

Portions of pre-leukemic cells also were grown in culture and treated with PARP inhibitors to determine whether they could clump together and form colonies, a sign of viable cells. Fewer pre-leukemic cells treated with PARP inhibitors were able to form colonies, an indication that the therapy may be effective for pre-leukemias.

"It's important that PARP drugs target mainly cancer cells while sparing normal cells," says Keith Pratz, M.D., assistant professor of oncology at Johns Hopkins. "Most normal cells may not be affected by PARP inhibitors because they have more than one [DNA repair](#) pathways to rely on."

Pratz and McDevitt are conducting [clinical trials](#) of PARP inhibitors in patients with aggressive myeloproliferative disorders.

"There may be a subset of people with myeloproliferative disorders who can benefit from PARP inhibitors, and we hope that further testing in patients may help define this," says Pratz.

The outlook for patients with myeloproliferative disorders varies. "Some patients can do very well for a long time," says McDevitt. Median survival of patients with a myeloproliferative disorder called myelofibrosis is reportedly five years. Survival times are far shorter – perhaps as short as 15 to 20 months – for many patients with chronic myelomonocytic leukemia, says McDevitt. When a myeloproliferative disorder progresses to acute leukemia, most patients survive only a few months.

Patients with the disorders experience infections, high white blood cell counts, and anemia. No curative treatments, other than bone marrow transplants, are available.

Provided by Johns Hopkins Medical Institutions

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