Staff Writer
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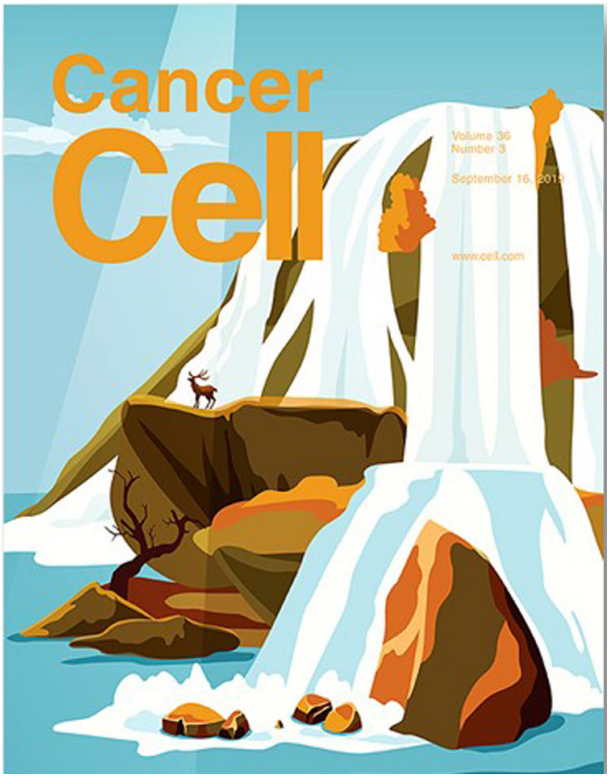
Sylvester Researchers Uncover Why PARP Inhibitors Could Be a New Treatment for a Common Lymphoma

A study looking at PARP inhibition in diffuse large B cell lymphoma opens the door to a new way to treat this common type of cancer, according to study author Izidore S. Lossos, M.D., endowed director of the Lymphoma Program at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine, and head of the Hematological Malignancies Site Disease Group.



Findings by Dr. Lossos and his team published in *Cancer Cell* suggest that PARPi and chemotherapy could work well together to inhibit LMO2-positive diffuse large B cell lymphoma tumor growth.

“Diffuse large B cell lymphoma is common, accounting for about 30% of all the non-Hodgkin lymphomas,” Dr. Lossos said. “While these patients’ survival has improved in recent years, it still stands at approximately 60%. That means 40% of patients continue to die from this cancer, so we need to improve outcomes with new and better treatment options.”

Diffuse large B cell lymphomas expressing LMO2 protein have deficient homologous recombination DNA repair, and tumors expressing the protein are sensitive to poly (ADP-ribose) polymerase inhibitors (PARPis). LMO2 was first described as an oncogene in acute lymphoblastic leukemia, and LMO2 expression is known to be one of the best prognostic biomarkers for the outcome of diffuse large B cell lymphoma patients, according to Dr. Lossos, who started research in this area about 16 years ago.

“We’ve shown that this gene is specifically expressed in normal lymphocytes in germinal centers – an area in the lymph nodes that usually appears as part of an immune response to any pathogen,” he said. “But because this area tends to have high proliferation and high mutational activity, it’s also a very frequent site of where lymphomas originate.”

In this paper, the first looking at PARP inhibition in diffuse large B-cell lymphoma, Dr. Lossos and study coauthor Ramiro E. Verdun, Ph.D., demonstrated a new function of LMO2: It is a protein that regulates the choice between different DNA repair pathways.

“Our bodies often have double-strand breaks in the DNA that are repaired by the cells. In certain cells, like those in the germinal centers, they need to have a double stranded break in

order to allow mutation of the immunoglobulin gene, so the body can produce antibodies. But this process needs to be very well controlled," Dr. Lossos said. "We demonstrated that, while in the cell, LMO2 regulates the choice between error-free and error-prone DNA repair pathways, allowing the introduction of normal B cell mutation."

Dr. Lossos and coauthors wrote: "Considering the essential role of the homologous recombination in repairing double strand breaks during DNA replication, it is likely that the higher accumulation of double strand breaks observed in LMO2 diffuse large B cell lymphoma is due to this LMO2-dependent homologous recombination dysfunction."

They went on to discover the potential role for PARPis, which can be used to impair specific DNA repair mechanisms or pathways, according to Dr. Lossos and Dr. Verdun.

"PARP inhibitors are currently used in treatment of solid tumors," Dr. Lossos said. "They're used in patients with breast cancer that have BRCA deficiency, and they're used in patients with prostate cancer and sarcomas, usually after detection of some abnormality in the DNA repair pathway.

"It was shown that cells in which homologous recombination is inhibited cannot tolerate the presence of PARPi and they die. So, PARPi can induce cell death in cells that express high levels of LMO2," he said. "We also demonstrated that if you combine PARPi with chemotherapy, you further increase cell death."

The research suggests a new way to treat diffuse large B cell lymphoma patients. The findings identify a biomarker which can

alert providers as to which patients will respond to treatment with a PARP inhibitor. Dr. Lossos and colleagues also generated a specific monoclonal antibody that can be used to identify which patients' tumors express LMO2.

"Our findings may lead to therapeutic approaches in a variety of LMO2 expressing tumors. Whereas the precise molecular mechanisms by which LMO2 mediates homologous recombination dysfunction need further investigation, our data provide a sound mechanistic basis for employing LMO2 expression as a biomarker for homologous recombination dysfunction that will help to stratify diffuse large B cell lymphoma patients for therapy with PARPi in clinical trials."