PROJECT TITLE

Developing small-molecule inhibitors to inhibit DNA damage repair in BRCA-mutant cancers

PRINCIPAL INVESTIGATOR

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PROJECT SUMMARY

Background/context to the research: Breast and ovarian cancers are among the most prevalent causes of cancer deaths worldwide. These cancers can be caused by mutations in genes called BRCA1 and BRCA2 (BRCA), which are essential for repairing DNA. Breaks in DNA occur regularly and are repaired quickly in healthy cells. Without BRCA, cancer cells rely on other error prone ways to fix broken DNA. Blocking those back-up repair mechanisms can cause too much DNA damage in cancer cells, leading to their death.

Description of the current standard of care: Currently, BRCA-mutant breast and ovarian cancers are treated with drugs that cause additional DNA damage: platinum therapy and PARP inhibitors. Because cancer cells cannot repair damaged DNA the way healthy cells can, they are preferentially killed.

Research question or problem to be solved: It is common for breast and ovarian tumors associated with defects in BRCA genes to develop resistance to the current clinically approved drugs, which can cause disease relapse. There is an urgent need for new drugs that target alternate DNA repair pathways to kill cancer cells and improve the sensitivity of cancer cells current therapeutic options. We have discovered that reducing levels of a lesser-known protein involved in DNA repair causes a build-up of DNA damage and kills cancer cells. This protein must bind to it's partner protein to fix breaks in DNA. We hypothesize that a drug that blocks the binding of these two proteins could be used to treat BRCA-mutant associated cancers.

Thorough description of proposed research/method(s): We want to develop a specialized procedure for testing thousands of molecules to find ones that disrupt the interaction between the specific DNA repair protein and its partner. We will attach each protein to a special molecule called a fluorophore. These fluorophores will produce a certain color of light when the two proteins are bound together. We will test ~25K molecules to find the ones that reduce light production, indicating that they block the interaction between the two proteins. We will then test these molecules on BRCA-mutant cancer cells that are resistant to PARP inhibitors.

Potential benefit to patients/impact on the field: Molecules that block the function of the DNA repair protein we study would allow us to better understand the role of this protein in BRCA-mutant cancers. Eventually, drugs targeting this protein could be used to treat breast and ovarian cancer patients, especially those who have developed resistance to the current chemotherapies.