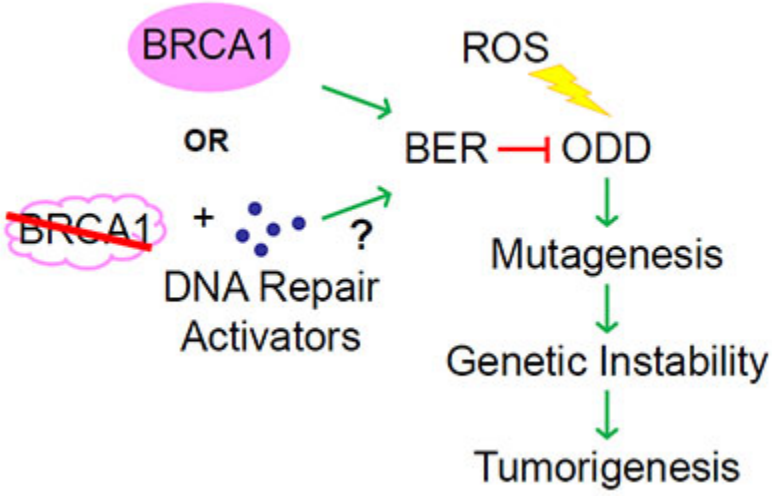
Docket #: S10-253

DNA Repair Compounds to Prevent Cancer

Stanford researchers have identified small molecules that can intercept cancerous or pre-cancerous cells by activating DNA repair in cells damaged by oxidative stress. These compounds could be used as chemopreventive or chemotherapeutic agents to prevent malignancy or metastasis in patients with impaired DNA base-excision repair (BER) due to BRCA1 mutations or other factors. This approach may prove more effective than current chemoprevention agents because BRCA1-associated cancers rarely express the estrogen receptor (the target for tamoxifen or raloxifene). Because the BER-activating compounds have been approved for use in humans for other indications, they have a known safety profile and are candidates for drug repositioning.



BRCA1- mediated Tumorigenesis and Prevention. *Oxidative DNA damage (ODD) is induced by reactive oxygen species (ROS) and removed by the base-excision DNA repair pathway (BER). ODD, if left unrepaired, leads to mutagenesis, genetic instability, and tumorigenesis. BRCA1 activates BER, reduces levels of ODD, and thus, has been implicated in preventing tumorigenic events. When BRCA1 is*

mutated, DNA repair-activating drugs may enhance BER and prevent tumorigenesis.

Stage of Research
The inventors have demonstrated direct BER activation with benserazide and acetohexamide in the presence of mutant BRCA1 in vitro. In further studies, benserazide was superior to tamoxifen in preventing in vitro tumorigenesis of BRCA1-mutated cells and it delayed in vivo tumorigenesis of BRCA1-mutant breast cancer cells.

Applications

- **Chemoprevention** - prophylactic treatment for patients with a predisposition for cancer due to oxidative DNA damage (e.g. patients with BRCA mutations)
- **Cancer therapeutic** - prevent or delay metastasis by activating DNA repair
- **Drug repositioning** - small molecule drugs with DNA repair activity (such as bensearzide or acetohexamide) could be developed for cancer indications

Advantages

- **Known safety profile** for existing compounds found to have DNA repair activity
- **Specificity** for BRCA1-associated malignancies compared to current chemoprevention agents which target the estrogen receptor
- Chemoprevention approach **reduces need for prophylactic surgery**

Publications

- U.S. Published Patent Application 20160038444, "MODULATON OF CELLULAR DNA REPAIR ACTIVITY TO INTERCEPT MALIGNANCY".
- Alli E, Ford JM, BRCA1: a movement toward cancer prevention, Mol Cell Oncol. 2015 Jan 21;2(3):e979685. doi: 10.4161/23723556.2014.979685. eCollection 2015 Jul-Sep.
- Alli E, Ford JM, BRCA1: Beyond double-strand break repair, DNA Repair (Amst). 2015 Aug;32:165-71. doi: 10.1016/j.dnarep.2015.04.028. Epub 2015 May 1.

- Alli E, Solow-Cordero D, Casey SC, Ford JM, Therapeutic targeting of BRCA1-mutated breast cancers with agents that activate DNA repair, Cancer Res. 2014 Nov 1;74(21):6205-15. doi: 10.1158/0008-5472.CAN-14-1716. Epub 2014 Sep 12.
- PCT Published Patent Application WO/2014/164730, "MODULATION OF CELLULAR DNA REPAIR ACTIVITY TO INTERCEPT MALIGNANCY".

Patents

- Published Application: WO2014164730
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