Finding existing drugs potentially active against *BRCA*-mutated breast cancers: a literature-based approach

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Background

- Mutations in the *BRCA* genes predispose to developing breast, ovarian and other cancers.
- Poly (ADP-ribose) polymerase (PARP) inhibitors represent one treatment option in the treatment of *BRCA*-mutated cancers. Platinum salts have been proposed as another option since they induce DNA breaks that then require proficient BRCA for repair. Next to this 'soft' repurposing – using an anticancer drug to treat another cancer – **we sought to identify 'hard' repurposing opportunities – using non-cancer drugs, here in *BRCA*-mutated tumors**.

Materials & Methods

- A PubMed search was performed on 15 July 2019 to identify which of the **293 ReDO (Repurposing Drugs in Oncology) drugs** had evidence of interaction with *BRCA* or PARP. A **dataset of abstracts and meta-data from PubMed was generated**.
- Each abstract was assessed for relevance, evidence (preclinical, clinical) and biological effect (single agent activity in *BRCA*-mutated cancer, association with PARP inhibitors).
- For relevant drugs, additional data were gathered from clinical trial registries to assess whether trials in *BRCA*-mutated cancers or with PARP-inhibitors were ongoing.

Results

- From the 293 ReDO drugs, 147 (50%) had at least one article reporting an effect related to BRCA or PARP, for a total of 1,364 abstracts. **73 drugs (25%) were considered to have a possibly beneficial interaction with *BRCA* or PARP**. Based on the abstracts, 15 drugs (5%) were selected but after reading the full articles, 4 drugs were then excluded because the data were still reconsidered too preliminary.
- **11 drugs (4%) were considered worthy of further research in breast cancer (Table 1).**
- Five of these 11 drugs (aspirin, metformin, mifepristone, sirolimus and vitamin D3) are trialed in the preoperative, adjuvant, neoadjuvant and advanced breast cancer settings.
- Whereas 3 trials investigate the role of vitamin D3, metformin or mifepristone as chemo-preventive agents in high-risk patients (incl. *BRCA* patients), none of the 11 drugs is investigated therapeutically in *BRCA*-mutated cancer patients or in combination with PARP inhibitors.

Table 1: selection of non-anticancer drugs that could interact with *BRCA* or with PARP inhibitors

Drug *Main indication*	**Rationale**	**Main reference(s)**	**Clinical Trials in BC** (last update Feb 2020) *Inc. trials with PARPi or in BRCA pop.*
Aspirin *Analgesia*	• Associated with reduction of breast cancer incidence in *BRCA* mutation carriers • Inhibits increased glycolysis induced by *BRCA1* mutation	Kehm 2019 Breast Cancer Res Chiyoda 2017 Cancer Prev Res Wang 2019 Cancer	**11 trials (chemoprev., preoperative, adjuvant, neoadjuvant, advanced …)** *None*
Artesunate *Malaria*	• Induces DNA double-strand breaks. More potent in cells defective in homologous recombination	Li 2008 Cancer Res	**None** *None*
Chloroquine *Malaria*	• Enhances cisplatin effect on *BRCA*-deficient ovarian cancer cells. • Augments carboplatin efficacy in TNBC cells by preventing repair of double-stranded DNA breaks	Wan 2018 Endoc Relat Cancer Liang 2016 Cancer Lett	**3 trials** *None*
Metformin *Type 2 diabetes*	• Reverses resistance mechanisms induced by PARPi in TNBC • Synergizes with denosumab by targeting RANKL, which is overexpressed in *BRCA*-mutated basal-like BC cells • Inhibits metabolic 'reprogramming' induced by *BRCA1* loss • Reduced gene expression of *BRCA1* in a window BC trial	Han 2019 Am J Cancer Res Cuyàs 2017 Cell Cycle Cuyàs 2016 Cell Cycle Cuyàs 2016 Oncotarget Hadad 2011 Breast Cancer Res Treat	**40+ trials (chemoprev., preoperative, adjuvant, neoadjuvant, advanced …)** *1 trial (chemoprev., ongoing)*
Mifepristone *Abortion*	• Cytotoxic to *BRCA*-mutant ovarian cancer cells • Prevents BC in a *BRCA*-deficient mice model	Ponandai 2019 Acta Obstet Gynecol Scand Skor 2013 Clinc Cancer Res Poole 2006 Science	**8 trials (chemoprev., preoperative & advanced)** *1 trial (chemoprev., ongoing)*
Minocycline *Bacterial infection*	• Is a potent PARP inhibitor • Suppresses 5-FU-induced PARP-1 activity, increases 5-FU efficacy and reduces 5-FU toxicity in a colon cancer model	Alano 2006 PNAS Huang 2009 Biochem Biophys Res Commun	**2 trials (prev. of neuropathy, prevention of anxiety-depression)** *None*
Nicotinamide *Vit B3 deficiency*	• Is a potent PARP inhibitor and a chemo- & radio-sensitizing agent regardless of the *BRCA* status in BC	Domínguez-Gómez 2015 Oncol Res Chen 1993 Cancer Chemother Pharmacol	**1 trial (prev. of neuropathy)** *None*
Pyrvinium Pamoate *Pinworm infection*	• Re-sensitizes PARPi-resistant cancer cells to PARPi in vivo, through inhibition of hyperactivation of Wnt signaling induced by PARPi.	Xu 2013 PloS One Yamamoto 2019 Mol Carcinog	**None** *None*
Sirolimus *Prevention of transplant rejection*	• In *BRCA*-mutated BC models, synergizes with PARPi through inhibition of homologous recombination (Rac51) & with through ribosomal protein S6 inhibition • Restores sensitivity to PARPi in PARPi-resistant *BRCA*-deficient BC cells in vivo, through ribosomal protein S6 inhibition • Radio-sensitizes through suppression of homologous recombination by impairing recruitment of BRCA1 and Rad51 in BC cells	Osoegawa 2017 Oncotarget Vassilopoulos 2014 J Biol Chem Sun 2014 Oncotarget Chen 2011 Radiat Res	**None (all done with new mTOR inhibitors but not with sirolimus)** *None*
Spironolactone *Hypertension*	• Synergizes with both PARPi and cisplatin in vitro through inhibition of homology directed repair by impairing Rad51 foci formation	Shahar 2014 Nucleic Acids Res	**None** *None*
Vitamin D3 *Vitamin D3 deficiency*	• Vit D receptor expression is a good prognostic factor in *BRCA*+ BC • Vit D upregulates *BRCA1* in BC cells • Vit D sensitizes BC cells to PARPi, radiation and chemotherapy through interactions with DNA repair (several mechanisms reported)	Heublein 2017 J Exp Clin Cancer Res Campbell 2000 Oncogene Graziano 2016 Oncogene Pickholtz 2014 Oncotarget Gonzalo 2014 J Steroid Biochem Mol Biol Hershberger 2001 Clin Cancer Res Bao 2014 Int J Mol Med	**50+ trials (chemoprev., biomarkers, preoperative, adjuvant, neoadjuvant, advanced, supportive care…)** *1 trial (chemoprev., reported at ASCO 2018, no effect on mammographic density)*

5-FU: 5-fluorouracil; BC: breast cancer; BRCA: breast cancer gene; CMV: cytomegalovirus; DNA: deoxyribonucleic acid; PARP: poly (ADP-ribose) polymerase; PARPi: PARP inhibitor; RANKL: receptor activator of nuclear factor kappa-B ligand; TNBC: triple-negative breast cancer;

Conclusion

- **We identified 11 non-cancer drugs that deserve further research in *BRCA*-mutated cancers or in combination with PARP-inhibitors.**
- Further studies are necessary to select which drugs could be repurposed as single agent, in combination with PARP inhibitors, or in combination with other treatments in patients with *BRCA*-mutated cancers.
- Since those drugs have well-known clinical features, **window of opportunity trials with biological endpoints represent an option to study their role with PARP inhibitors or in *BRCA*-mutated cancers**.
- The role of drugs widely used such as aspirin or metformin could also be investigated in retrospective datasets of patients with *BRCA*-mutated cancers or treated with PARP inhibitors.

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