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Design, synthesis and biological activity of novel molecules designed to target PARP and DNA

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ABSTRACT

In order to enhance the cytotoxic potential of poly(ADP-ribose) polymerase (PARP) inhibitors in *BRCA1* or *2* deficient tumours, we designed a series of molecules containing a 1,2,3-triazene moiety tethered to a PARP targeting scaffold. A cell-based selectivity assay involving a *BRCA2*-deficient Chinese hamster cell line and its corresponding *BRCA2* wild type transfectant, was used to predict the PARP targeting potential of the latter agents. The results showed that adding a DNA damaging function to the PARP inhibitors decreased but did not abrogate the selective targeting of the *BRCA2*-deficient cells. The DNA damaging moiety augmented the potency in *BRCA2* deficient cells by 2-20 fold. The most selective dual PARP-DNA targeting agent **14b** was found to possess dual DNA and PARP targeting properties.

The past five years have seen significant development in the field of DNA repair inhibitors.[1] In this context, a cellular condition termed "synthetic lethality" is being targeted for selective chemotherapeutic intervention against solid tumours of the breast, ovary and pancreas. Synthetic lethality arises when one of two genes "A" or "B" is mutated and the functions of a non-mutated gene "A" or "B" are required to rescue the cells from the dysfunction of the mutated one.[2,3] Therefore, in cells in which gene "A" is mutated, blockade or dysfunction of gene product "B", leads to cell death. As an example, one such occurrence is the mutation of the *BRCA1* or *2* genes,[4] which are tumor suppressor genes involved in homologous recombination repair.[5] In the context of homologous recombination repair, *BRCA1* and *2* form a complex with PALB2[6] and RAD51 that relocates to the site of damage.[7] Mutation of *BRCA1* and *2* leads to loss of CtIP and PALB2 recruitment and RAD51 activation respectively.[8,9] This subsequently leads to loss of DNA repair function. An alternative to this deficiency is the expression of the *PARP* gene product commonly referred to as poly(ADP-ribose) polymerase (PARP).[10] The latter is responsible for the recruitment of DNA polymerase and XRCC1 via poly(ADP-ribose) chains, leading to a base excision repair (BER) mechanism.[11] Activation of BER can compensate for the loss of homologous recombination repair functions. Since this is the only alternative for rescuing the cells in *BRCA1* or *2* mutant cells, blockade of PARP creates a synthetic lethality condition that ultimately leads to cell death.[12] This confers to PARP inhibitors the unique ability to selectively induce cell death in *BRCA1* or *2* mutated tumours.[13]

The first generations of PARP inhibitors, including nicotinamide, 3-aminobenzamide and 2-methylquinazolin-4-[3H]-one were rather weak, with IC_{50} for PARP inhibition ranging from 120 μM to 5 μM.[14,15] While the later generations of PARP inhibitors (e.g. 5-aminoisoquinolinone and 4-amino-1,8-naphthalimide), were more potent,[15] it was not until 2014 that the first PARP inhibitor, olaparib, was approved for the treatment of ovarian cancer.[16] Despite being considered to be a selective cancer targeting approach, the overall survival obtained with PARP inhibitors as single agents in patients with *BRCA1* or *2* mutations has been disappointing.[17] Furthermore, mechanisms of resistance to the synthetic lethality condition brought on by PARP inhibition in *BRCA1* and *2* mutated tumors have emerged *in vivo*.[18] Some observed mechanisms include: reactivation of *BRCA1* and *2*,[19] spontaneous mutation of the *TP53BP1* gene and p-glycoprotein 1 upregulation.[20] Thus, strategies directed at augmenting the potency of PARP inhibitors are under evaluation.[21] To enhance therapeutic potency, combinations of PARP inhibitors with DNA damaging agents are currently being investigated in clinical trials to overcome drug resistance.[22-24]

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