

## **Targeting the DNA Repair Defects of BRCA1 and BRCA2 Mutant Tumours**

**Nicholas Turner, Institute of Cancer Research**

### **Summary**

BRCA1 and BRCA2 proteins are required for the homologous recombination DNA repair pathway. Lack of this pathway sensitises BRCA1/2 mutant tumour cells to interstrand cross linking agents, such as carboplatin. A clinical trial is currently examining tailored treatment for BRCA1/2 mutation carriers with carboplatin. Current research into developing new therapies for BRCA mutant tumours, including the use of PARP inhibitors, is also described.

### **Mutations in BRCA1/2**

BRCA1 and BRCA2 are very large proteins which bear little resemblance to each other and have a wide range of different functions. However both share a role in DNA repair and this is thought to be important in underlying their predisposition to cancer.

BRCA1/2 mutation carriers are heterozygous for the mutant allele in normal cells. The wild type allele expresses the BRCA1/2 protein and therefore cells have relatively normal BRCA1/2 function. In tumours the wild type allele is lost which means only the mutant protein is expressed. The goal of this research is to identify therapies that are toxic to tumour cells but not harmful to normal cells with BRCA1/2 function.

### **Outline of DNA repair mechanism**

Double stranded breaks (DSB) are the most toxic kind of DNA lesion. There are two main repair pathways for these breaks. BRCA1/2 proteins are required for homologous recombination repair (HR), which is the least error prone. DSB that arise at stalled or blocked replication forks are especially reliant on HR for repair. Without the HR repair pathway, tumour cells lacking BRCA1/2 use alternative repair pathways which leads to errors, genomic instability and eventual cell death.

### **BRCA1/2 mutation clinical trial**

BRCA2 null cells and normal cells were treated with a variety of chemotherapy drugs to see if there were differences in levels of cell death between the two groups. The BRCA2 null cells were extremely sensitive to interstrand cross linking agents such as cisplatin. The DNA damage caused by these drugs is dependent upon BRCA2 for repair and therefore at clinically viable doses of the drug BRCA2 null cells were unable to survive whilst wild type cells were essentially unaffected.

The first clinical trial aimed at providing tailored treatment for BRCA1/2 mutation carriers has been established to address in vivo if these individuals are particularly sensitive to platinum salts and if their normal tissue is also more sensitive (since these cells are heterozygous for the mutant gene). Information on the trial can be found at:

[http://www.breakthrough.org.uk/researchcentre/clinical\\_trials/brca\\_trial/index.html](http://www.breakthrough.org.uk/researchcentre/clinical_trials/brca_trial/index.html)

The trial is only open to known BRCA1/2 mutation carriers in 1<sup>st</sup> metastatic relapse. It is in relatively early stages of recruitment with an aim to recruiting 74 BRCA1 and 74 BRCA2 mutation carriers from national and international centres by 2008.

### **Developing new therapies for BRCA mutant tumours**

As described above, BRCA1/2 mutation carriers are deficient in the homologous recombination repair pathway. Using the concept of synthetic lethality, it was hypothesised that if an additional repair pathway (in this case the base excision repair pathway) was removed from a cell then normal cells would be able to survive but in BRCA1/2 mutant cells the loss of two repair mechanisms would be lethal.

The PARP enzyme is critical for base excision repair. PARP inhibitors developed by KUDOS pharmaceuticals were used to treat BRCA2 null and wild type cells. The inhibitors were highly

toxic to BRCA2 null cells. In addition heterozygous cells (equivalent to normal somatic cells in mutation carriers) are no more sensitive to PARP inhibitors than wild type cells. This result was replicated in a BRCA2 tumour cells lines and also in BRCA1 null cells.

There is currently a Phase 1 clinical trial of PARP inhibitors taking place in the UK which is not specifically for BRCA1/2 mutation carriers but there is interest in recruiting these individuals. A Phase 2 study using a different PARP inhibitor compound is planned in metastatic carriers.

### **Extension of results**

It is hoped these results can be extended to develop therapies for non-familial breast cancer and other types of cancer. For example:

- Sporadic ovarian cancers very commonly have a defect in the BRCA1/2 pathways and platinum drugs (such as cisplatin) are used effectively in treatment of these cancer.
- The inhibition of other breast cancer susceptibility genes including Chek2 and ATM has been shown to increase cell sensitivity to PARP inhibitors. Therefore cells with mutations in these genes may also be candidates for treatment with this class of drug.