



FIRST EVIDENCE OF NEW 'DRUGGABLE' DNA REPAIR TARGET TO DESTROY CANCER CELLS

BLOCKING a key DNA damage repair enzyme, called APE1, could provide a new way to kill cancer cells containing faulty BRCA genes, according to research presented at the National Cancer Research Institute (NCRI) Cancer Conference in Liverpool, today (Monday).

Researchers at The University of Nottingham have developed small molecules that block APE1. They tested the ability of these molecules to stop the enzyme from repairing DNA damage in breast, pancreatic and cervical cancer cells containing faults in BRCA1 or BRCA2 genes.

The BRCA genes control a separate, major DNA repair pathway. Cells with damaged BRCA1 or BRCA2 have a faulty 'repair kit'. This allows damaged cells to accumulate faults and multiply out of control – which increases the risk of developing cancer, especially ovarian and breast cancer.

But too much damage can lead to cell death. Blocking APE1 in these BRCA-deficient cells effectively blocks two repair routes at once, killing the cancer cells.

This technique of blocking two repair routes is already being used with a new class of drugs called PARP inhibitors. These prevent cells fixing faults in BRCA-deficient cells by blocking PARP, a key enzyme in the same repair pathway as APE1.

APE1, like PARP, is essential for carrying out a type of DNA damage repair – removing and correcting faulty DNA components – but has a more specific role in this repair process compared to the PARP enzymes.

The research suggests that APE1 could provide an additional drug target to PARP.

Dr Srinivasan Madhusudan, clinical senior lecturer and consultant in medical oncology, who is leading the APE1 drug discovery research programme at The University of Nottingham, said: "This important study provides the first evidence that APE1 is an important new target for personalised cancer treatment.

"Not only could these molecules provide a basis for new drugs to treat cancers with faulty BRCA genes – especially breast and ovarian cancer – but they could help 'soften up' cells from many cancer types to boost the effect of radiotherapy and chemotherapy."

Professor Steve Jackson, a DNA damage repair expert, said: "Destroying cancer cells by knocking out two repair mechanisms simultaneously is emerging as an important way to treat the disease. We've already made strides in developing treatments that do this, and this new research builds on that work.

"This promising new target may lead to even more specific drugs capable of delivering a knock-out double blow to cancer cells, leaving healthy cells unharmed - so potentially causing fewer side effects.

"It also brings fresh hope for the development of new drugs which can be prescribed when patients become resistant to conventional treatments. We'll look forward to further development of potential new drugs to block this very specific target with great interest."

Baroness Delyth Morgan, Chief Executive of Breast Cancer Campaign, which part-funded the research, said: "With up to ten per cent of all breast cancers thought to result from faulty BRCA1 and/or 2 genes, new treatments for these patients could possibly help up to 4,800 of the women diagnosed with the disease in the UK each year. Currently there are limited options available to them and this potential new treatment, although at an early stage could provide a real lifeline and a better chance of survival, which can only be good news."

ENDS

For media enquiries please contact Simon Shears in the NCRI press office on 0151 239 6043, or the London press office on 020 3469 8300, or, out-of-hours, the duty press officer on 07050 264 059.

Notes to Editors:

A novel synthetic lethality approach targeting human apurinic/apyrimidinic endonuclease (APE1) in cells deficient in double strand break repair.

View the conference abstract here <http://www.ncri.org.uk/ncriconference/2011abstracts/abstracts/A186.html>

About PARP inhibitors

PARP inhibitors block PARP, a protein which is part of DNA's 'emergency repair kit' in cells - it prevents mistakes being passed on when cells grow and divide. An alternative 'repair kit' is also controlled by the BRCA1 and BRCA2 genes - these genes are faulty in some cancer cells. When both copies of the BRCA1 or BRCA2 genes are faulty, the cells rely on the PARP pathway to repair damaged DNA. By blocking PARP with drugs, cancer cells which have lost BRCA1 or BRCA2 can no longer repair DNA damage and they die. This is why PARP inhibitors are effective in treating the small percentage of cancers in which BRCA1 or BRCA2 is faulty.

Because cancer treatments such as radiotherapy and chemotherapy kill cells by damaging DNA, PARP inhibitors also have the potential to increase the effectiveness of some of these treatments, even in cancers that do not have mutations in BRCA1 or BRCA2.

Breast Cancer Campaign

- The Breast Cancer Campaign Tissue Bank, the UK's first ever national breast cancer tissue bank is a unique collaboration with four leading research institutions to create a vital resource of breast cancer tissue

www.ncri.org.uk/ncriconference

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for researchers across the UK and Ireland. Visit www.breastcancer-tissuebank.org

- Breast Cancer Campaign aims to beat breast cancer by funding innovative world-class research to understand how breast cancer develops, leading to improved diagnosis, treatment, prevention and cure
- The charity currently funds 105 projects worth over £17.3 million in 31 locations across the UK and Ireland
- Breast cancer is the most common cancer in the UK and accounts for nearly one in three of all cancers in women
- In the UK, around 48,000 new cases of breast cancer are diagnosed each year - that's 130 a day
- Visit breastcancercampaign.org or follow us at twitter.com/bccampaign

The University of Nottingham

The University of Nottingham, described by The Sunday Times University Guide 2011 as 'the embodiment of the modern international university', has award-winning campuses in the United Kingdom, China and Malaysia. It is ranked in the UK's Top 10 and the World's Top 75 universities by the Shanghai Jiao Tong (SJTU) and the QS World University Rankings. It was named 'Europe's greenest university' in the UI GreenMetric World University Ranking, a league table of the world's most environmentally-friendly higher education institutions, which ranked Nottingham second in the world overall.

The University is committed to providing a truly international education for its 40,000 students, producing world-leading research and benefiting the communities around its campuses in the UK and Asia.

More than 90 per cent of research at The University of Nottingham is of international quality, according to the most recent Research Assessment Exercise, with almost 60 per cent of all research defined as 'world-leading' or 'internationally excellent'. Research Fortnight analysis of RAE 2008 ranked the University 7th in the UK by research power. The University's vision is to be recognised around the world for its signature contributions, especially in global food security, energy & sustainability, and health.

About the NCRI Cancer Conference

The National Cancer Research Institute (NCRI) Cancer Conference is the UK's major forum for showcasing the best British and international cancer research. The Conference offers unique opportunities for networking and sharing knowledge by bringing together world leading experts from all cancer research disciplines. The seventh annual NCRI Cancer Conference is taking place from the 6-9 November 2011 at the BT Convention Centre in Liverpool. For more information visit www.ncri.org.uk/ncriconference

About the NCRI

The National Cancer Research Institute (NCRI) was established in April 2001. It is a UK-wide partnership between the government, charity and industry which promotes co-operation in cancer research among the 22 member organisations for the benefit of patients, the public and the scientific community. For more information visit www.ncri.org.uk

NCRI members are: the Association of the British Pharmaceutical Industry (ABPI); Association for International Cancer Research; Biotechnology and Biological Sciences Research Council; Breakthrough Breast Cancer; Breast Cancer Campaign; Cancer Research UK; CHILDREN with CANCER UK, Department of Health; Economic and Social Research Council; Leukaemia & Lymphoma Research; Ludwig Institute for Cancer Research; Macmillan Cancer Support; Marie Curie Cancer Care; Medical Research Council; Northern Ireland Health and Social Care (Research & Development Office); Roy Castle Lung Cancer Foundation; Scottish Government Health Directorates (Chief Scientist Office); Tenovus; The Prostate Cancer Charity; Welsh Government (National Institute for Social Care and Health Research); The Wellcome Trust; and Yorkshire Cancer Research.

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