# Precision drugs could unmask cancers to immune system and boost effects of immunotherapy

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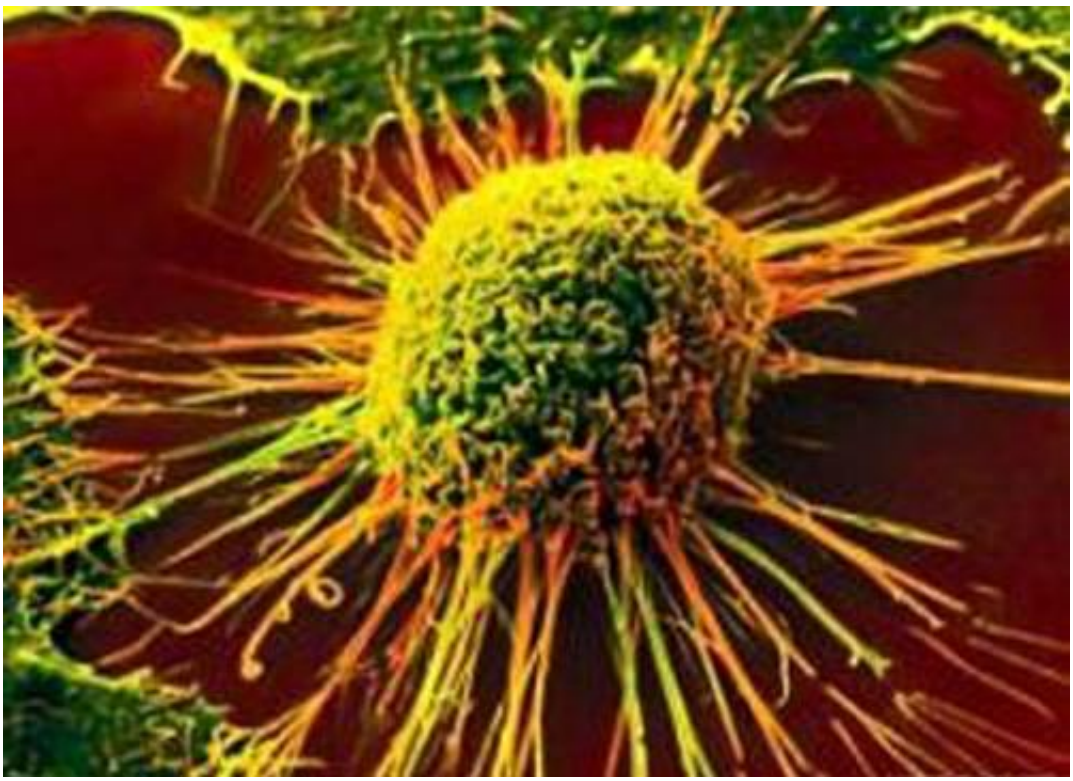

Precision cancer drugs called PARP inhibitors have a previously unknown ability to boost the immune system, and could help many more patients benefit from immunotherapy, a new study reveals.

Scientists found that PARP inhibitors sparked a powerful immune response when used against cancer cells with weaknesses in repairing their DNA.

The study changes our understanding of how PARP inhibitors work—and suggests they could be used alongside immunotherapies to boost their effectiveness. Clinical trials have already started to assess this combination.

Some patients have benefited dramatically from a new generation of immunotherapies—but often only between 10 and 20 per cent of patients will respond, with many others' cancers able to hide from the immune system.

Scientists at The Institute of Cancer Research, London, and the Institut Gustave Roussy, France, led by Professor Chris Lord and Dr. Sophie Postal-Vinay, found that PARP inhibitors could unmask some of these cancers that can currently evade detection by immune cells.

Their study is published in the *Journal of Clinical Investigation* and was funded by Breast Cancer Now and Cancer Research UK.

PARP inhibitors such as olaparib block one of the systems which cells use to repair their DNA. They are designed to attack tumours that are already defective at DNA repair, especially ovarian and breast cancers in women with inherited BRCA mutations.

The researchers looked at lung tumours taken from patients, and found those with deficiencies in their DNA repair contained significantly more immune cells within the tumours, compared with tumours in patients with a functioning DNA repair system. This suggested that the DNA repair mutations were stimulating an immune response against the tumours.

They also studied cancer cells from non-small cell lung cancers and triple-negative breast cancers with mutations in DNA repair genes such as ERCC1 or BRCA, to assess whether PARP inhibitors could increase this immune response.

When cancer cells with defective repair systems are treated with PARP inhibitors to block their remaining system of DNA repair, they can no longer repair any DNA damage so accumulate more and more DNA mutations until they die.

The researchers found that the accumulation of DNA damage in cancer cells treated with PARP inhibitors triggered the release of various molecular signals that have the potential to attract immune cells to the tumour, suggesting that treatment with PARP inhibitors could enhance the immune response against these cancer cells.

In one ERCC1-deficient cancer cell line, 24 out of the 50 signalling pathways that were activated after exposure to PARP inhibitors were related to the immune system.

The scientists found that PARP inhibitors could potentially be used to treat lung cancers with faults in their DNA repair genes, in part because of these newly discovered effects on the immune system. By using PARP inhibitors alongside immunotherapy, this immune response could be further enhanced to kill the cancer cells more effectively.

As 30 to 50 per cent of patients with non-small cell lung cancer have a deficiency in the ERCC1 DNA repair system, this could open up a new, more effective ways of treating a large proportion of non-small cell lung cancer patients.

Study leader Professor Chris Lord, Professor of Cancer Genomics at The Institute of Cancer Research, London, said:

"The findings of this study substantially change our understanding of how PARP inhibitors work. We now know that they not only kill tumours by damaging their DNA, but also by attracting immune cells to attack them—acting as a sort of double-pronged attack.

"Immunotherapy is a genuinely brilliant cancer treatment but generally only for the 10 to 20 per cent of people who respond to it. Finding the tumour is half of the battle in immunotherapy so by attracting the immune cells to the tumour, PARP inhibitors could enable the immunotherapy drug to target their attack."

Study co-leader Dr. Sophie Postel-Vinay, Clinician Scientist and Medical Oncologist at Gustave Roussy, France, and The Institute of Cancer Research, London, said:

"Our study found that PARP inhibitors enlist immune cells to aid in the killing of cancer cells. This provides a rationale for using PARP inhibitors alongside immunotherapies to further stimulate the immune response to cancer cells with DNA repair defects and enhance the therapeutic benefit of the treatment."

"This will be evaluated in a clinical trial of lung, prostate and bladder cancers, which is starting later this year."

Dr. Ian Walker, Director of Clinical Research at Cancer Research UK, said:

"This study highlights the important role that research in the lab plays in helping us devise new clinical trials. Identifying new combinations that make cancer drugs more effective could open up many new treatment options for patients with cancers that are hard-to-treat, like lung cancer. This is an exciting development and we look forward to seeing if PARP inhibitors can improve survival for these patients."

Dr. Kotryna Temcinaite, Research Communications Manager at Breast Cancer Now, said:

"These are really promising findings that show once more just how important PARP inhibitors could be in treating a number of cancers. Not only do these drugs interfere with tumour cells' ability to repair DNA but this study suggests they may have additional effects in initiating an immune response, which could then be exploited using other treatments.

"Activating the immune system to attack tumours is an exciting approach that is beginning to show promise in breast cancer. We now look forward to seeing how the combination of PARP inhibitors and checkpoint inhibitors may work in clinical trials for breast cancer patients."

**More information:** Roman M. Chabanon et al, PARP inhibition enhances tumor cell–intrinsic immunity in ERCC1-deficient non–small cell lung cancer, *Journal of Clinical Investigation* (2018). DOI: 10.1172/JCI123319

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