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Bacteria shed light on new drug targets for inherited cancers

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Cancer Research UK scientists have succeeded in purifying a protein found in bacteria that could reveal new drug targets for inherited breast and ovarian cancers - and other cancers linked to DNA repair faults. The study is published in the journal *Nature* yesterday.

The team, based at Cancer Research UK's Paterson Institute in Manchester, are the first to decipher the structure of a protein called PARG – which plays an important role in DNA repair and acts in the same pathway as PARP.

PARP inhibitors have been showing great promise in clinical trials for patients with breast, ovarian and prostate cancers caused by mutations in genes called BRCA1 and BRCA2. They work by blocking the action of PARP – a protein that chemically tags areas of DNA damage to highlight them to the cell's DNA repair machinery.

PARG removes these chemical tags after the DNA damage has been repaired. So the researchers believe that, similar to PARP inhibitors, drugs designed to block the action of PARG could be effective in treating cancer.

Lead author Dr. Ivan Ahel, based at Cancer Research UK's Paterson Institute in Manchester, said: "For decades scientists have wanted to find out the structure of PARG, but its large size makes it very hard to produce in the lab. By studying a smaller version of PARG found in bacteria, we've been able to create a '3D map' that researchers can use to

understand more about how PARG works. The next step will be to investigate whether drugs that block its activity might be an effective way of treating cancers driven by faults in DNA repair genes."

Dr. Julie Sharp, senior science information manager at Cancer Research UK, said: "This discovery shows that bacteria and humans share similarities in the cellular machinery they use to repair damaged DNA. Importantly, knowing the structure of PARG in bacteria could help researchers design targeted treatments that are also effective in cancer patients. We hope this will lead to further treatment options for patients with a range of cancers in the future."

More information: Slade et al, The structure and catalytic mechanism of a poly(ADP-ribose) glycohydrolase, *Nature* (2011). dx.doi.org/10.1038/nature10404

Provided by Cancer Research UK