Scientists find cancer weak spots for new targeted drugs

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New drugs could attack cells that have defective DNA-repair processes - a hallmark of a cancer cell.

A major computational analysis by scientists at the University of Sussex and The Institute of Cancer Research, London, has found a number of potential targets for drugs that exploit the inherent weaknesses of cancer cells.

The findings could lead to personalised medicine that 'reads' a cancer patient's DNA and only attacks defective cells – in contrast to the scattergun approach of conventional chemotherapy, which attacks all dividing cells, including healthy ones.

The study is published today (Tuesday 24 February 2015) in the journal *Nature Reviews Cancer*.

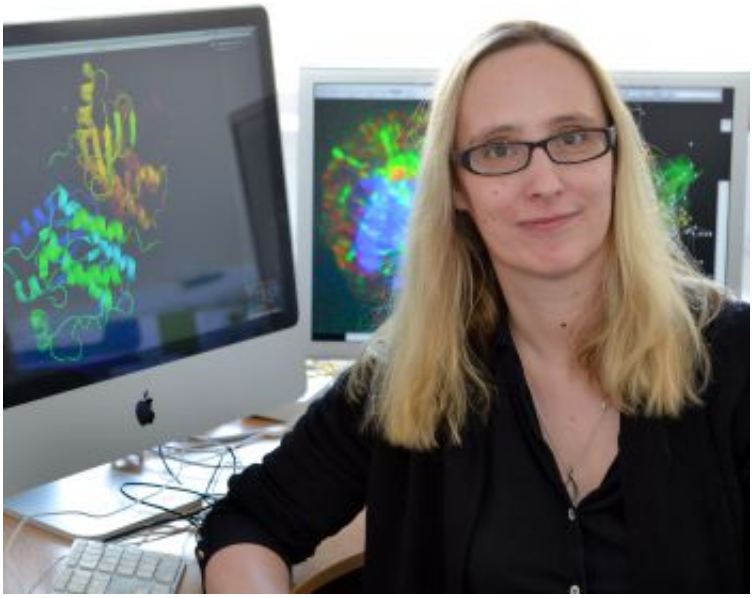
Scientists from the University of Sussex and The Institute of Cancer Research (ICR) analysed the patterns of mutations found in the DNA sequences of tumours from more than 5,000 cancer patients.

The team, jointly led by Dr Frances Pearl (Sussex) and Dr Bissan Al-Lazikani (ICR), focused on the 'DNA repair' systems that protect the genetic information of the cell, and are mutated in almost all cancers. Breaking these systems for DNA repair allows cancer cells to divide uncontrollably and generate even more mutations – helping them become resistant to chemotherapy and radiation treatments.

"Knowing which DNA repair processes are defective in an individual tumour allows us to target new drugs that are only toxic to cells with a particular pattern of mutations – ie cancer cells," said Dr Pearl, who heads the Bioinformatics Research Group at Sussex.

One class of drug called PARP inhibitors already target DNA repair systems. They are being used in clinical trials to treat women with breast or ovarian cancers that have mutations in BRCA genes, and one of the class, olaparib, has recently been licensed for women with ovarian cancer in Europe and the US.

But the development of new targeted drugs like these relies on identifying good targets. It is only because of huge advances in technology that such a large-scale analysis is now possible.



Dr Frances Pearl, Bioinformatics Academic Research Manager at the University of Sussex

By using cutting edge computing techniques, the team have been able to examine much larger data sets than ever before. Dr Pearl said: "This analysis shows that there are many other cancers where new targeted drugs could selectively kill tumours with DNA repair defects.

"This potentially means thousands more cancer patients could be saved from the horrible side-effects of chemotherapy by receiving precision medicine, which doesn't kill the body's healthy cells."

Study co-leader Dr Bissan Al-Lazikani, Team Leader in Cancer Therapeutics at The Institute of Cancer Research, London, said:

"Only a small fraction of the proteins involved in cancer are targeted by current drugs, and we urgently need drugs that hit new targets. DNA repair proteins hold particular promise as new drug targets, and there are

already some drugs coming through that exploit cancer's inherent weaknesses in DNA repair.

"Using 'big data' analysis, our study has identified untargeted DNA repair proteins that look especially promising as the targets for new anti-cancer drugs. Such drugs would not only prove useful in their own right, but also potentially in combination with radiotherapy or other drugs to overcome treatment resistance. We hope this study will help speed up the development of new personalised cancer treatments."

The University of Sussex is home to the world-leading Genome Damage and Stability Centre, one of the largest concentrations of scientists studying DNA repair in the world. Centre Director Professor Tony Carr said: "Understanding the responses of cells to genome damage is critical in our fight to beat cancer and other life-threatening diseases.

"The University of Sussex is playing a vital role in this war against cancer, not just through cutting edge scientific discovery but through the work of our drug discovery colleagues at Sussex and ICR who are creating new medicines that have a real impact in the treatment and diagnosis of major human diseases.

"The more we discover, the more intelligent our weapons against cancer become, and the closer we get to the day when cures for this major killer will be found."

The Institute of Cancer Research, London, discovers more new cancer drugs than any other academic centre in the world. Since 2005, the Institute of Cancer Research (ICR) has successfully discovered 17 drug candidates, and progressed seven drugs discovered at the ICR into clinical trials.

Professor Paul Workman, Chief Executive of The Institute of Cancer

Research, London, said:

"It is faults in their DNA repair systems that allow cancer cells to accumulate mutations so rapidly, and to evolve in ways that make them hard to treat. But these deficiencies in DNA repair can also leave cancers vulnerable to attack, and this analysis shows how we could design drugs to further weaken cancer cells' repair systems - and drive them to their deaths."

Professor Laurence Pearl, Head of the School of Life Sciences at the University of Sussex, and a co-author of the research, commented: "I am particularly delighted with the burgeoning collaboration between world-class research groups at Sussex and ICR which will be critical to bringing forward a new class of anti-cancer drugs to target the DNA damage response."

More information: "Therapeutic opportunities within the DNA damage response" *Nature Reviews Cancer* 15, 166–180 (2015) DOI: 10.1038/nrc3891

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